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Rationale and Design of the Multicenter Catheter Ablation of Ventricular Tachycardia Before Transcatheter Pulmonary Valve Replacement in Repaired Tetralogy of Fallot Study

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Patients with repaired tetralogy of Fallot are at elevated risk for ventricular arrhythmia and sudden cardiac death. Over the past decade, the pathogenesis and natural history of ventricular tachycardia has become increasingly understood, and catheter ablation has emerged as an effective treatment modality. Concurrently, there has been great progress in the development of a versatile array of transcatheter valves that can be placed in the native right ventricular outflow tract for the treatment of long-standing pulmonary regurgitation. Although such valve platforms may eliminate the need for repeat cardiac operations, they may also impede catheter access to the myocardial substrates responsible for sustained macro-reentrant ventricular tachycardia. This manuscript provides the rationale and design of a recently devised multicenter study that will examine the clinical outcomes of a uniform, preemptive strategy to eliminate ventricular tachycardia substrates before transcatheter pulmonary valve implantation in patients with tetralogy of Fallot.
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Intracardiac repair of tetralogy of Fallot (TOF), first performed over a half-century ago, is associated with an elevated risk for sustained ventricular tachycardia (VT) and sudden cardiac death (SCD). Historically, implantable cardioverter defibrillator (ICD) placement was the preferred management strategy for both primary and secondary prevention of sustained VT and SCD in this population. However, more recently, improved understanding of the electrophysiologic basis for monomorphic VT in TOF has thrust catheter ablation to the forefront as a therapeutic

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See page 20 for Declaration of Competing Interest.

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modality for this problem in select, low-risk patients.[1] With the advent of both balloon-inflatable and now larger self-expanding transcatheter pulmonary valves (TPVs) for the treatment of pulmonary regurgitation in TOF, there is now concern that culprit VT substrates may become electrically shielded from future catheter ablation attempts and render this therapy potentially ineffective.[2] The present manuscript provides the rationale and design of the multicenter CATAPULT-TOF (Catheter Ablation of ventricular Tachycardia before transcatheter PULmonary valve replacement in repaired Tetralogy Of Fallot) study, which intends to explore the outcomes of a uniform, preemptive VT catheter ablation approach.

Patients with TOF experience a series of surgical insults to the right ventricular (RV) myocardium at the time of initial cardiac repair, consisting of RV outflow tract (RVOT) muscle bundle resection, patch closure of the ventricular septal defect, and variable placement of a transannular patch that extends onto the anterior RV free wall or (historically) a ventriculotomy incision. Electrically inert by themselves, surgical incisions and patches invariably become surrounded by regions of interstitial and subendocardial fibrosis, the extent of which is associated with the duration of time after intracardiac repair. Both direct electrophysiologic assessment (catheter-based measurement of myocardial voltage) and contrast-enhanced cardiac magnetic resonance imaging studies report strong associations between the duration of time after intracardiac repair and the size and burden of myocardial scar, suggesting that progressive and degenerative remodeling occurs surrounding these surgical sites.[3,4] Similarly, electrocardiographic abnormalities such as prolongation and fragmentation of the QRS complex are increasingly observed in older cohorts of patients with TOF, reflecting these underlying myocardial changes.[5] The most abnormal areas are principally situated in the RVOT, immediately subjacent to the pulmonary annulus and at the anticipated, and even unintended, location of native RVOT TPV placement.[6] Consistent with the concept of progressive degenerative remodeling, longitudinal follow-up for patients with TOF demonstrates an incremental and mounting risk for sustained monomorphic VT and SCD over the decades after intracardiac repair, with conservative lifetime estimates that exceed 10%. Most studies report a period of relative quiescence in childhood, followed by a twofold to threefold increase in risk in young adult life.[7,8] The majority of events are sustained monomorphic VT after TOF repair.[9]

Several observational studies have been performed to predict the risk for ventricular arrhythmia (VA) in patients with repaired TOF. Historically, such studies intended to capture the manifestations of VA that could be effectively managed by ICD placement, with measurable outcomes that included a composite of SCD, aborted cardiac arrest, appropriate ICD therapies, and sustained monomorphic VT.[9−13] Given that clinical sustained monomorphic VT (now a realistic therapeutic target in the modern era) is but one of the components of the composite outcome in the existing risk prediction tools, the existing models were not intended or designed to predict future risk of sustained VT in the context of TPVs in repaired TOF. Additional concerns related to the application of existing risk scores for the identification of sustained monomorphic VT before TPV placement include different characteristics of the target populations and the absence of external validation (for all but a single model).[9,14−16] Importantly, the reported median follow-up duration of ≤3.7 years for such studies[9−12] is also a major limitation, given the established pattern of unremitting risk over a lifetime that may follow TPV implantation. Therefore, the noninvasive prediction of future sustained monomorphic VT is currently imperfect for the purpose of guiding peri-TPV management decisions for long-term VT risk reduction in repaired TOF. Conversely, recent work has highlighted the importance of slowly conducting anatomical isthmuses (SCAIs) for the prediction of future sustained monomorphic VT.[17] The detection of abnormal wave front propagation through regions of diseased myocardium between surgical scars and nearby fixed, anatomical structures provides the essential requirements for ventricular macro-reentry. Specifically, a conduction velocity ≤0.5 m/s has been reported as the optimal discriminator between patients with and without inducible or clinically sustained monomorphic VT.[17] Assessment of the presence of therefore represents a form of personalized medicine for repaired TOF, and SCAIs are relatively unique among patients with congenital heart disease (Figure 1).

Preoperative electrophysiologic assessment and catheter ablation for TOF is comparable with other conditions in the fields of pediatric and congenital electrophysiology in which preemptive electrophysiologic evaluation and catheter ablation are routinely recommended. For example, for Ebstein's anomaly, existing guidelines note that preoperative assessment and catheter ablation of latent substrates are reasonable, given the concern for reduced efficacy after tricuspid valve operations.[18] Not unlike the scenario in TOF and native RVOT transcatheter valves, postoperative catheter ablation has been shown to be particularly suboptimal when a bioprosthetic valve has been sewn to the tricuspid position, yielding poor outcomes even at experienced centers.[19] Preoperative electrophysiology study and catheter ablation have therefore been advocated before tricuspid valve replacement for patients with Ebstein's anomaly.[19] An analogy also exists for the Wolff-Parkinson-White pattern, where the lifetime incidence of SCD is approximately 3% to 4%, and noninvasive risk assessment is imperfect. The demonstration of bidirectional block through an accessory pathway translates to a negligible risk of future SCD. Accordingly, universal electrophysiology study and catheter ablation (without attempts to employ noninvasive risk stratification) are now endorsed by most practicing pediatric electrophysiologists.[20] These 2 examples highlight the shared rationale for universal screening and catheter ablation for both repaired TOF and other common arrhythmia syndromes.

There are currently 2 TPV options that are approved by the Food and Drug Administration in the United States for the native RVOT and one with a CE mark in Europe. The Harmony valve (Medtronic Inc. Minneapolis, Minnesota) is a self-expanding platform designed to accommodate a wide variety of oversized and distorted RVOT anatomies. The ensemble consists of either 22 or 25 mm porcine pericardial valves that are mounted on a nitinol frame, sewn to a polyester knit fabric, and range between 55 and 51 mm in

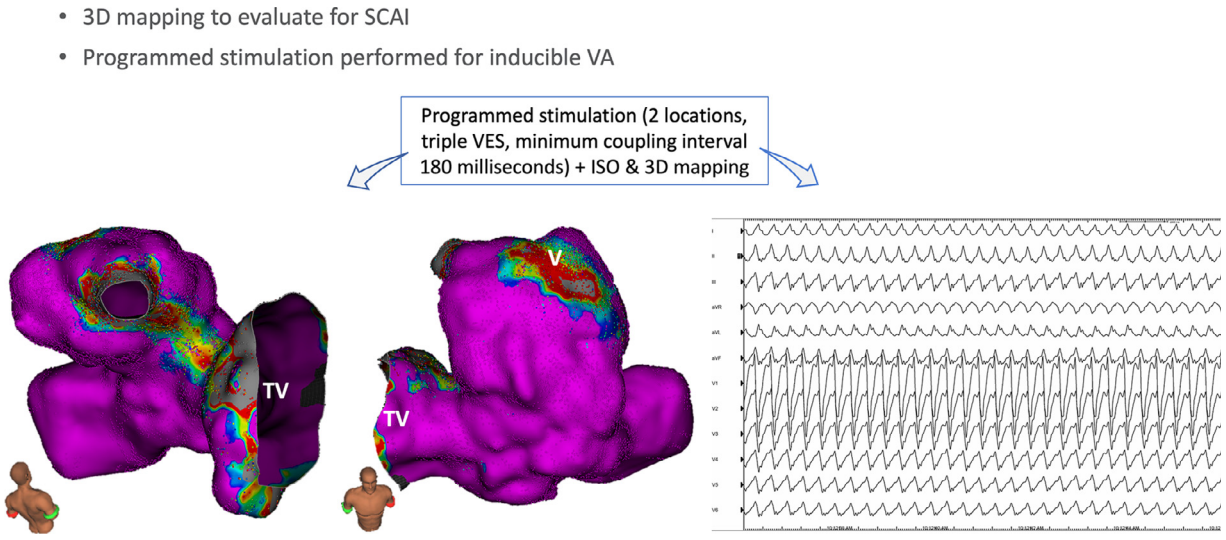

Figure 1. Approach to ventricular tachycardia substrate assessment for repaired tetralogy of Fallot. Both three-dimensional mapping to detect the presence of slowly conducting anatomical isthmuses (SCAIs) and programed ventricular stimulation to determine the inducibility of sustained monomorphic VT are performed as part of a comprehensive electrophysiologic evaluation. 3D = three-dimensional; ISO = isoproterenol; ms = millisecond; VES = ventricular extrastimuli.

length. Systolic and diastolic electrocardiogram-gated computed tomographic angiography with comprehensive post-processing and 3-dimensional multiplanar reconstructions are performed to fully evaluate patient anatomy and guide appropriate device selection. The device is manufactured in 2 sizes depending on the patient's RVOT anatomy. Similarly, the Alterra Adaptive Prestent (Edwards LifeSciences, Irvine, CA) is a self-expanding nitinol device that is partially covered by polyethylene terephalate fabric that serves to downsize the RVOT for a standard conventional TPV (29 mm Sapien S3) and measures 48 mm in length. The device is symmetrical, with a central valve seating location, and is available in a single size. Finally, the Venus P—valve, another self-expanding platform that consists of a nitinol frame covered by bovine pericardium and manufactured in progressive 2-mm valve size increments (ranging from 28 to 36 mm). was recently introduced. Preliminary data confirm that native RVOT valves cover greater proportions of anatomical isthmuses for VT in TOF compared with conventional transcatheter valves (12.9 vs 6.2 cm^2), supporting the view that the valve platforms can impede access to the VT substrate among patients with TOF.[21] Full TPV specifications are provided in Table 1.

These and other existing TPV platforms may ultimately pose an insurmountable challenge to lesion delivery after implantation. Fabrics used in the construction of these valve platforms are effectively industrial plastics. Their high electrical resistivity can result in a loss of current density and absence of tissue heating at intended sub-annular target sites. In contrast, nitinol, which is an excellent electrical conductor, permits shunting of radiofrequency energy, manifested as a low electrical impedance and attenuation of energy delivery during attempted catheter ablation (Figure 2). Similarly, newer and emerging catheter ablation

Table 1
Specifications of FDA approved and CE mark native right ventricular outflow transcatheter pulmonary valves and right ventricular outflow tract reducers

Transcatheter valve	Fabric	Frame	Valve	Outflow diameter, mm	Valve housing, mm	Inflow diameter, mm	Length, mm
Harmony TPV 22	Polyester	Nitinol	Porcine pericardium	32	22	41	55
Harmony TPV 25	Polyester	Nitinol	Porcine pericardium	43	25	54	51
Alterra Adaptive Pre-stent/Sapien S3	Dacron	Nitinol	Bovine pericardium	47	27	47	48
Venus P - Valve	Porcine pericardium	Nitinol	Porcine pericardium				
L28P				38	28	38	60
L30P				40	30	40	60
L32P				42	32	42	65
L34P				44	34	44	67
L36P				46	36	46	67

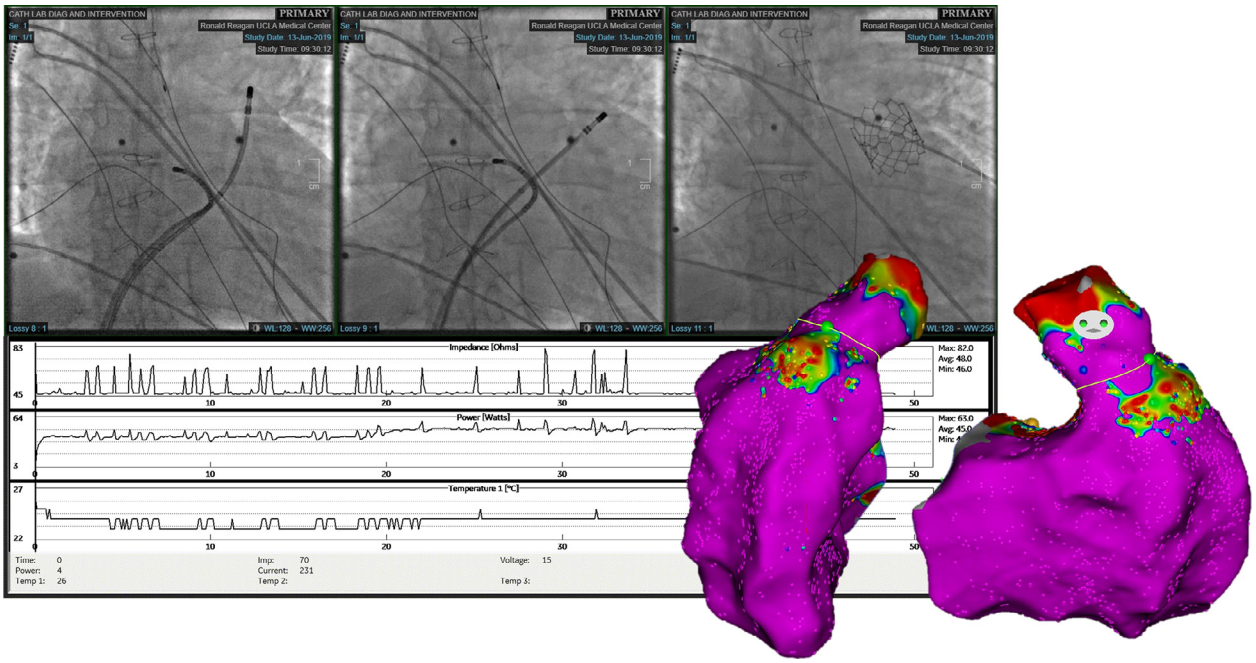

Figure 2. Example of unsuccessful catheter ablation after TPV placement in a patient with tetralogy of Fallot. Before TPV placement, a slowly conducting anatomical conduction isthmus was identified between the pulmonary annulus and a ventriculotomy incision and was associated with easily inducible sustained monomorphic ventricular tachycardia. After TPV placement, this isthmus became inaccessible to catheter placement, and attempted ablation at the TPV site was associated with erratic impedance values and ineffective lesion delivery. The patient subsequently had implantable cardioverter-defibrillator placement. Green dot and yellow circumferential line indicate the lower extent of the TPV.

energy sources may be equally ineffective in the context of self-expanding TPVs. For instance, previous reports suggest that nitinol can sufficiently disrupt the voltage gradient associated with pulsed field ablation to render this modality unsafe.[22] Stereotactic radiotherapy for the ablation of VT substrates is, in its current state, insufficiently circumscribed as an energy source to be delivered safely at the common septal substrate adjacent to the conduction system for repaired TOF. Finally, preliminary evidence suggests a relatively high rate of damage to the neighboring semilunar valve with this modality.[23] Whether other future energy sources will be able to safely overcome the inherent biophysical challenges of catheter ablation after TPV placement is currently unknown.

The safety and efficacy of catheter ablation for monomorphic VT after repaired TOF is increasingly recognized and suggests favorable expectations for a preemptive approach. Complications reported at the time of VT ablation for patients with TOF are exceptionally rare, with a single instance (femoral pseudoaneurysm that was managed conservatively) reported to date.[17,24,25] Catheter ablation is now recognized as an effective therapeutic modality for the treatment of sustained monomorphic VT after repaired TOF in appropriately identified candidates.[2] Acute success after catheter ablation of clinical VT for patients with repaired TOF has been reported to range from 69% to 81%[17,24] and for patients who underwent a uniform preemptive strategy before either TPV placement or surgical pulmonary valve replacement, reported acute success is higher at 94%.[25] Importantly, confirmation of bidirectional block is a prerequisite; empiric placement of intraoperative lesions without such confirmation has been shown to yield suboptimal outcomes.[26] Accordingly, in a recent study of 97 patients before pulmonary valve replacement, in the absence of SCAIs (either at baseline or with catheter ablation) and with proved bidirectional block, no clinical VT recurrence was observed up to 14 years of follow-up, attesting to the durability of this approach.[27] The risk-benefit profile of the alternative (ICD therapy) for repaired TOF lies in stark contrast to catheter ablation. ICD placement is associated with substantial morbidity for the TOF population, with a cumulative risk of major complications approaching 50% at 10 years.[28]

Studies of VT ablation surrounding TPVs for TOF patients with native RVOT are scarce. To date, there are no dedicated investigations reporting the outcomes of routine VT assessment before planned TPV placement. In contrast, case studies have reported the outcomes of catheter ablation after smaller balloon-expandable TPV placement, typically within bioprosthetic valves or conduits. As noted, these earlier iterations of TPVs are significantly less likely to cover large portions of RVOT myocardium, given their dimensions and implantation technique. Even after the placement of these smaller balloon-expandable valves, catheter ablation has been reported to be extremely challenging.[29]

It is in the context of these considerations that the CATAPULT-TOF was conceptualized. The study will involve a collaboration between the Pediatric and Congenital Electrophysiology Society and the International Society of Adult Congenital Heart Disease and will aim to determine the outcomes of a uniform, preemptive approach. It is hypothesized that in patients with repaired

TOF and VT substrates, catheter ablation surrounding the TPV procedure can be performed safely and effectively, with very low risk for recurrence of SCAIs or inducible VA at follow-up evaluation. Similarly, the study will aim to assess for the evidence of proarrhythmia related to this approach in a large multicenter population of TOF. Finally, it is hypothesized that a combination of successful catheter ablation and subsequent TPV placement will result in a substantial reduction in a conventional SCD risk score calculation (and consequently, fewer patients meeting criteria for primary prevention ICD placement), owing to a combination of VT circuit elimination and favorable RV remodeling after TPV placement.

Methods

The primary aim of the study will be to compare a commonly used SCD risk score before and after a combined strategy of TPV + electrophysiologic study and catheter ablation of VT for patients with TOF. It is hypothesized that an algorithmic, tailored approach to VT ablation before transcatheter TPV placement will result in a decrease in calculated conventional risk scores for patients with TOF after TPV placement compared with pre-TPV electrophysiology evaluation. The primary outcome will consist of a comparison of the numerical risk score at the time of the pre- and post-TPV electrophysiologic studies. The secondary aim will be to assess the safety, acute efficacy, and durability of VT ablation associated with TPVs in TOF. It is hypothesized that given the advances in mapping and ablation technologies, catheter ablation of VT is safe and effective for durable elimination of inducible VT for TOF in the modern era. Secondary outcomes will consist of the number of acute complications, the proportion of patients with acute VT ablation success, VT noninducibility at 6 months, and adverse cardiac events at the last follow-up. Finally, the impact of surgical era on catheter ablation outcomes will be assessed.

Patients will be included if they have a diagnosis of TOF or TOF-related variants, are aged $\geq$18 years, and have a planned TPV placement in native RVOT. Patients will be excluded if they have a non-TOF congenital heart disease (i.e., isolated pulmonary stenosis) and TOF-related variants without a concomitant native RVOT requiring TPV placement (i.e., pulmonary atresia with intact ventricular septum, TOF-pulmonary atresia, and so on) or previous catheter or surgically attempted ablation of monomorphic VT.

This will be a prospective, multicenter study evaluating the outcomes of an algorithmic approach to VT ablation before TPV placement. Local ethics approval will be obtained at all participating centers, and patient consent to prospectively collect clinical data will be obtained before study data collection. Centers will transmit the de-identified data to the principal investigators at the coordinating center (University of California at Los Angeles) for adjudication and statistical analysis. A standardized, suggested management plan will be provided to the participating centers (Figure 3). However, each center will provide individualized care as judged appropriate by the treating physician(s) and medical team. Patients referred for TPV placement will undergo baseline comprehensive diagnostic workup followed by invasive electrophysiology evaluation with catheter ablation for inducible sustained VT and/or SCAIs, as appropriate. SCD risk scores will be calculated at the time of the electrophysiology study before catheter ablation (Table 2). The perceived SCD risk after the procedure will be managed by the treating physician according to accepted guidelines. For patients who will undergo catheter ablation at the index procedure, repeat noninvasive diagnostic evaluation and invasive electrophysiology testing with cardiac catheterization will be performed 6 ± 3 months after catheter ablation, at which point risk score calculation will be repeated. All components of the risk score will be assessed at both time points.

Descriptive statistics, including means, SDs, and ranges for continuous variables and percentages and frequencies for categorical variables will be provided to describe the study sample, procedural characteristics, and clinical outcomes (e.g., ICD placement and clinical VA) during follow-up. The anticipated SCD risk score[9] calculated at the time of the pre-TPV electrophysiology evaluation, assuming VA inducibility in 40% of the population and risk factor prevalence as previously reported, is 2.95 ± 3.4.[26] It is anticipated that at least 80% of patients will be rendered noninducible for VA at the follow-up electrophysiology study and that the covariates left ventricular end-diastolic pressure and non-sustained ventricular tachycardia used in the risk calculation will also decrease after a successful combination of VT ablation and TPV placement, such that the mean follow-up score will be 1.4 ± 3.4. Risk scores before and after the combination of VT ablation + TPV will be compared by means of the Wilcoxon signed rank test. Using an alpha cut-point of 0.05, the probability of avoiding a type II error is 0.8 when including a minimum of 75 patients who will undergo follow-up electrophysiology study. As it is anticipated that the proportion of patients with inducible VT at the pre-TPV electrophysiology study is 0.4, a total of 188 patients are required to satisfy the primary aim. Descriptive statistics will be used for the secondary aims of quantifying acutely successful VT ablation, noninducibility at follow-up electrophysiology study and complications or adverse cardiovascular events during follow-up. All statistical analyses will be completed with JMP version 14.0 (SAS Corp., Cary, North Carolina).

Discussion

The multicenter Catheter Ablation of ventricular Tachycardia before transcatheter PULmonary valve replacement in repaired Tetralogy Of Fallot (CATAPULT-TOF) Study has been endorsed by the Pediatric and Congenital Electrophysiology Society/the International Society of Adult Congenital Heart Disease Research Collaborative and aims to assess the clinical outcomes of an algorithmic, tailored approach to VT ablation before transcatheter TPV placement. The present study is based on a rapid evolution in our understanding in the pathophysiologic basis, detection, and treatment of monomorphic VT for patients with repaired TOF. The optimal timing, approach to catheter ablation, and yield of the proposed preemptive strategy are ultimately unknown. Moreover, inheritable arrhythmia and acquired disease substrates may contribute to ventricular

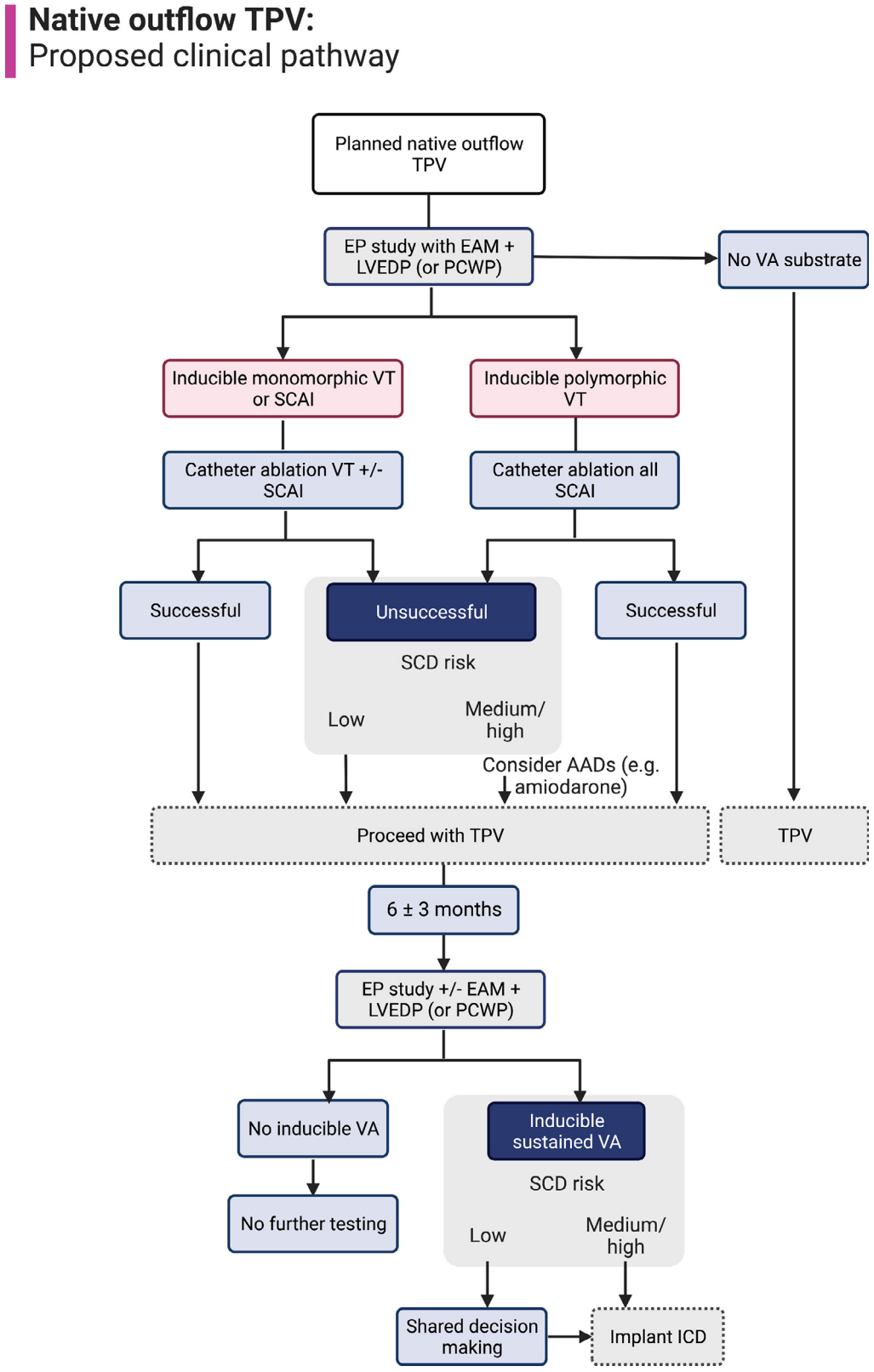

Figure 3. Flow Chart of the suggested electrophysiology management algorithm for patients with tetralogy of Fallot who undergo transcatheter pulmonary valve placement. AAD = antiarrhythmic drug; EP = electrophysiology; PCWP = pulmonary capillary wedge pressure.

Table 2
Risk score used for the primary aim.[9]

Variable	Points Attributed
Prior palliative shunt	2
Inducible sustained ventricular tachycardia	2
QRS duration ≥ 180 ms	1
Ventriculotomy incision	2
Nonsustained ventricular tachycardia	2
LVEDP ≥ 12 mm Hg	3
Total points	0−12

arrhythmogenesis despite successful catheter ablation.[30] Such disease entities are outside the scope of the present investigation. Nevertheless, the results of the present study are expected to improve our understanding for the clinical management of monomorphic VT for future generations of repaired TOF who undergo TPV placement.

Declaration of Competing Interest

Drs. Aboulhosn and Levi report a relation with Edwards Lifesciences Corp. that includes consulting or advisory and with Medtronic Inc. that includes consulting or advisory. The remaining authors have no competing interests to declare.

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