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Review

Risk Stratification for Sudden Cardiac Death in Repaired Tetralogy of Fallot

Jayant Kakarla, MBBS, Nathan C. Denham, BM, PhD, Ayako Ishikita, MD, PhD, Erwin Oechslin, MD, Rafael Alonso-Gonzalez, MD, and Krishnakumar Nair, MD

University Health Network Toronto, Peter Munk Cardiac Centre, Toronto Adult Congenital Heart Disease Program, and University of Toronto, Toronto, Ontario, Canada

ABSTRACT

There has been significant progress in the prevention of sudden cardiac death in repaired tetralogy of Fallot. Contemporary cohorts report greater survival attributable to improved surgical techniques, heart failure management, and proactive strategies for risk stratification and management of ventricular arrhythmias including defibrillator implantation and ablation technology. Over the last 25 years, our understanding of predictive risk factors has also improved from invasive and more limited measures to individualized risk prediction scores based on extensive demographic, imaging, electrophysiological, and functional data. Although each of these contemporary scoring systems improves prediction, there are important differences between the study cohorts, included risk factors, and imaging modalities that can significantly affect interpretation and implementation for the individual patient. In addition, accurate phenotyping of disease complexity and anatomic repair substantially modulates this risk and the mechanism of sudden death. Routine implementation of risk stratification within repaired tetralogy of Fallot management is important and directly informs primary prevention defibrillator implantation as well as consideration for proactive invasive strategies including ventricular tachycardia ablation and pulmonary valve replacement. Assessment and risk stratification by a multidisciplinary team of experts in adult congenital heart disease are crucial and critical. Although we have increased understanding, reconciliation of these complex factors for the individual patient remains challenging and often requires careful consideration and discussion with multidisciplinary teams, patients, and their families.

RÉSUMÉ

De grands progrès ont été réalisés pour prévenir la mort subite d'origine cardiaque chez les patients ayant une tétralogie de Fallot réparée (TFr). Dans les cohortes contemporaines, l'amélioration du taux de survie peut être attribuée à l'évolution des techniques chirurgicales, à la prise en charge de l'insuffisance cardiaque et à la mise en place de stratégies proactives pour la stratification du risque d'arythmies ventriculaires et pour leur prise en charge, notamment par l'implantation de défibrillateurs et l'ablation. Au cours de 25 dernières années, les moyens utilisés pour caractériser les facteurs de risque à valeur prédictive sont passés de mesures limitées et invasives à l'établissement de scores individualisés basés sur de grands corpus de données démographiques, électrophysiologiques, fonctionnelles et d'autres issues de l'imagerie. Bien que chacun de ces systèmes contemporains d'évaluation du risque permette de raffiner notre capacité prédictive, des différences importantes entre les cohortes à l'étude, les facteurs de risque considérés et les modalités d'imagerie peuvent influencer l'interprétation des scores et les soins prodigués à un patient en particulier. De plus, la description phénotypique exacte de la complexité de la maladie et de la réparation anatomique permet de moduler la stratification du risque de mort subite d'origine cardiaque et son mécanisme possible. Il importe que la stratification du risque fasse partie intégrante de la prise en charge de la TFr puisqu'elle oriente directement le choix de mettre ou non en place un défibrillateur en prévention primaire, et qu'elle fasse partie de l'équation lorsque des stratégies invasives proactives, comme l'ablation de la tachycardie ventriculaire ou le remplacement de la valve pulmonaire, sont envisagées. La mesure et la stratification du risque par une équipe multidisciplinaire d'experts en cardiopathies congénitales sont donc des étapes cruciales. Même si les connaissances se sont affinées au fil du temps, il peut être difficile de faire la synthèse de ces facteurs complexes dans le cas d'un patient en particulier. C'est pourquoi il faut bien souvent se tourner vers l'équipe multidisciplinaire, le patient et ses proches pour évaluer rigoureusement les options.

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Corresponding author: Dr Krishnakumar Nair, 3rd Floor, GW 3-552, Peter Munk Cardiac Centre, Toronto General Hospital, University of Toronto, 200 Elizabeth St, Toronto, Ontario M5G 2C4, Canada. Tel.: +1-647-993-6247; fax: +1-416-595-1811.

E-mail: Krishnakumar.Nair@uhn.ca

Tetralogy of Fallot (TOF) is the commonest cyanotic congenital heart defect and has undergone disease changing progress in management and survival over the last 8 decades. The advances in imaging modalities and evolution in catheter-based and surgical techniques, electrophysiology, heart failure

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management, and surveillance strategies have led to substantial progress in long-term survival with patients routinely living into their fifth or sixth decade.[1] However, late mortality from sudden death has been concerning since its recognition in the 1970s.[2] Ventricular arrhythmias and heart failure are the presumed principal etiologies; however, other mechanisms may be contributory.[3] Although our ability to prevent, detect, and treat these triggers has improved significantly, sudden cardiac death (SCD) remains among the commonest mechanism of mortality.[4,5] Historical cohorts report an 8.3% risk of death in patients over 35 years,[6] 20 times the general population, with contemporary cohorts showing a 0.9% annual risk.[7,8] This is an area of ongoing concern to the clinical community with regular literature reviews and ever emerging strategies to improve the prediction and management of arrhythmia substrates.[9] More recently, formal scoring criteria have been developed to better identify those believed to be at highest risk for life-threatening arrhythmias and SCD.[10–12] The purpose of this article is to review the current understanding of risk stratification and the role of invasive intervention and device therapies in reducing this risk. Finally, we will consider additional, important, etiologies of sudden death in this population.

Risk Stratification

Disease severity

Late mortality for repaired TOF (rTOF) has been reported across a broad range from 10% to 22% over 30 years,[5,13] with an annual incidence of sudden death ranging from 0.9% to 3%.[6,7] The variation reported between study cohorts is inherited by the retrospective design of the studies of different institutions and attributable to heterogeneity in anatomy, electrophysiological features, surgical substrate, and surgical technique that fall under the broad phenotype of rTOF. Cohort studies have demonstrated a variety of potential high-risk features that have been summarized in recent reviews and statements of scientific authorities (listed in Table 1).[9,14] However, given the clinical heterogeneity, it is important to exercise caution before extrapolating the impact of every risk factor to an individual patient as their clinical phenotype may be dramatically different from the study population. The impact of this effect is highlighted by a multicentre analysis demonstrating that increasing complexity of defects, within rTOF, independently confers a higher burden of sudden death.[10,11] "Complex" repairs, such as those with pulmonary atresia or a double outlet right ventricle (RV), have 4 times the risk of sudden death compared with conventional anatomy (0.05 vs 0.20 incidence of SCD over 20 years).[10] Similarly, the INDICATOR multicentre cohort study found that repair with a conduit has a higher risk of death when associated with right ventricular remodelling and hypertrophy compared with patients with native outflow tracts.[15] On the other end of the spectrum, significant right ventricular outflow tract (RVOT) obstruction with an intact ventricular septum, irrespective of the method of repair, has a very low risk of sudden death with an incidence of <0.01 over 20 years.[10] Clearly, applying universal risk factors to all patients may detrimentally underestimate or unnecessarily overestimate risk for the individual. The cost of this misidentification is high with potential premature death or inappropriate implantable cardiac defibrillator (ICD) implantation, which carries a high morbidity in this population.[16]

Risk factors

No single risk factor sufficiently stratifies sudden death with the presence of multiple risk factors conferring a more accurate risk prediction of vulnerable patients.[6] The early multicentre studies showed that the strongest risk factors were right or left ventricular (LV) systolic impairment, a late age of repair, a broad QRS ($\geq$180 milliseconds), and a transannular patch repair.[6] A recent meta-analysis of 15 studies between 2008 and 2018, encompassing over 7000 patients with rTOF, demonstrated the consistent effect of age, older age of repair, QRS duration, previous palliative shunts, ventricular dysfunction (of either ventricle), and atrial arrhythmias on the overall risk of sudden death.[14]

As with acquired cardiomyopathy, the presence of significant LV systolic dysfunction may be sufficient to warrant intervention with a primary prevention ICD although this is not universally accepted[17,18] and does not predict appropriate ICD therapy by itself.[19] Similarly, in contrast to historic studies, right-sided valve dysfunction has not consistently been shown to affect the risk of sudden death although the cohorts reporting these risk factors were comparatively small.[14]

In addition, it is also apparent that there is incremental risk with continuous variables such as age, QRS duration, and ventricular ejection fraction, and these should be considered with granularity rather than using absolute thresholds.[14] Important qualities within each risk factor as well, such as the degree of QRS fragmentation, more specific for myocardial fibrosis, confer incremental independent risk prediction of sudden death and appropriate ICD shocks over QRS duration alone.[14,19–21]

Finally, patients with genetic syndromes, particularly 22q11 microdeletion syndrome associated with rTOF and pulmonary atresia, are at increased risk for premature mortality and up to 5 times risk of sudden death.[22,23] However, there may be confounding factors including greater LV systolic dysfunction and effects from extra cardiac lesions in these patients.[24]

Khairy score

Beyond noninvasive markers, a landmark analysis by Khairy et al.[25] demonstrated that inducible monomorphic or polymorphic ventricular tachycardia (VT) from a rigorous programmed ventricular stimulation incrementally increased the odds ratio of sudden death by 5-fold over established noninvasive risk factors alone. In contrast, noninducibility was found to be associated with a good prognosis of an 89% 10-year survival. Based on these results, alongside a retrospective analysis of rTOF patients with ICDs, the Khairy score[26] was published in 2008 to better predict appropriate ICD therapy. This inaugural risk score continues to inform guidelines for primary prevention ICD implantation in this cohort.[27–29] Widespread adoption has invariably afforded significant benefit; however, there are important pitfalls in application with contemporary management. First, invasive measures are not routinely taken, necessitating the use of a "noninvasive" modification with loss in predictive value.[12] Secondly, the study cohorts excluded high complexity lesions (Rastelli

Table 1. Anatomic, clinical, and electrophysiological risk factors

Risk factors	Characteristics	Additional considerations	References
Anatomy	Defect complexity	DORV, pulmonary atresia, truncus arteriosus confer a higher risk	Oliver et al. 2021[10]
	Conduit repair	Higher risk seen with an increased RV mass	Valente et al. 2014,[15] Bokma et al. 2023[8]
Genetics	22q11 deletion syndrome trisomy 21	Confers higher risk of late mortality and sudden death	Van Mil et al. 2020,[22] Kauw et al. 2020,[23] Blais et al. 2021[82]
Age	Older age		Gatzoulis et al. 2000,[6] Bokma et al. 2017,[20] Possner et al. 2020[14]
	Older age of repair	In historic cohorts (pre-1980s) younger age of repair conferred a higher risk	
Type of repair	Initial palliative shunt Ventriculotomy Transannular patch		Gatzoulis et al. 2000,[6] Khairy et al. 2004,[25] 2008,[26] Possner et al. 2020[14]
	Multiple repairs	Multiple thoracotomies	
Ventricular assessment	RV function	Moderate or worse function	Oliver et al. 2021,[10] Vehmeijer et al. 2021,[11] Ghonim et al. 2022,[12] Possner et al. 2020[14]
	LV function	Abnormal function, diastolic dysfunction, or raised LVEDP	Ghai et al. 2002,[83] Ghonim et al. 2022,[12] Vehmeiier et al. 2021,[11] Oliver et al. 2021,[10] Possner et al. 2020,[14] Khairy et al. 2008[26]
	Degree of RV LGE Presence of LV LGE	Extent of LGE burden	Babu-Narayan et al. 2006,[84] Ghonim et al. 2022[12]
Arrhythmias	NSVT	Symptomatic. Inconsistent independent effect across studies	Khairy et al. 2008,[26] Koyak et al. 2013,[85] Bokma et al. 2023,[8] Ghonim et al. 2022[12]
	IART	Symptomatic or sustained (>30 s)	Vehmeijer et al. 2021,[11] Ghonim et al. 2022,[12] Bokma et al. 2023,[8] Possner et al. 2020[14]
	Inducible VT on PES	Sustained monomorphic or polymorphic VT with aggressive stimulation protocol (3 extra stimuli from 2 sites including isoprenaline)	Khairy et al. 2004[25]
QRS	Increasing duration of QRS	Initially stratified by greater than 180 ms; contemporary analysis suggests interpreting risk with QRS as a continuous variable	Gatzoulis et al. 2000,[6] Bokma et al. 2017,[20] Oliver et al. 2021,[10] Possner et al. 2020[14]
	Presence and degree of fragmentation	Greatest risk with >3 fragmented signals in 2 or more continuous anterior leads	Bokma et al. 2017,[20] Egbe et al. 2018,[86] Vehmeijer et al. 2018,[21] Possner et al. 2020[14]
Ischemic heart disease	Coronary disease	Symptomatic ischemic disease in one study and presence of coronary disease in another study	Vehmeijer et al. 2018,[21] Oliver et al. 2021[10]
Symptoms	Symptomatic heart failure	NYHA II/III symptoms	Vehmeijer et al. 2018[21]
	Syncope	Unexplained or presumed arrhythmia	Khairy et al. 2004,[25] Oliver et al. 2021[10]
Biomarkers	Raised BNP	BNP $\geq$ 127	Ghonim et al. 2022[12]
Functional assessment	Low VO_2 max	VO_2 max as assessed by CPET less than 17 mL/kg/m^2	Müller et al. 2015,[87] Ghonim et al. 2022[12]

Risk factors for SCD or sustained VT with corresponding criteria and limitations. This list is not exhaustive with several, unlisted, risk factors that have not been systemically reproduced.

BNP, B natriuretic peptide; CPET, cardiopulmonary exercise testing; DORV, double outlet right ventricle; IART, intra-atrial re-entrant tachycardia; LGE, late gadolinium enhancement; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association heart failure classification; PES, invasive programmed extra stimulation; RV, right ventricle; SCD, sudden cardiac death; VT, ventricular tachycardia.

repair, double outlet RV, or pulmonary atresia) and, as demonstrated by more recent studies, application of this criterion may underestimate the risk in these specific groups.[10] Thirdly, despite exclusion of high-risk anatomic groups, the cohort was still highly comorbid by current standards, with a late age of repair (4.5 years), half requiring palliative shunts before definitive repair, a quarter having syncope, and 17% having documented sustained VT.[25] It is possible that the historic surgical strategy alongside a longer duration of cyanotic unrepaired circulation in childhood will have resulted in greater myocardial fibrosis. This likely leads to a greater substrate for arrhythmia and a higher risk of sudden death than we may see in a contemporary cohort. It is thus not surprising that a recent reanalysis of the score demonstrated a suboptimal C-statistic of 0.6 in prediction of sudden death[10] and indiscriminate application to triage contemporary patients may not be suitable.

Contemporary risk scores

Three large multicentre analyses have produced 3 different risk scores with a higher sensitivity and specificity for sudden death prediction. We describe the risk factors used in each score in Table 2.

Table 2. Contemporary risk scores

Score	Components	Risk categories	Predictive values (C-statistic)
Khairy et al. 2008[26] and Bokma et al. 2017[88] modifications	*Original 12-point risk score*: LVEDP (3) NSVT (2) Ventriculotomy (2) Inducible VT/VF on PES (2) Prior palliative shunt (2) QRS > 180 ms (1) Non-invasive score excludes inducible VT/VF on PES Bokma et al.[88] modification excludes inducible VT/VF on PES and includes CMR assessed RV and LV function	*Annual risk of ICD therapy:* 0-2: low risk (<1%) 3-5: moderate risk (1-11.5%) >5: high risk (>11.5%)	0.6 Without invasive data: 0.56 Bokma et al.[88] modification: 0.75
PACES/HRS guidelines (Khairy et al. 2014)[29]	LV dysfunction NSVT QRS > 180 ms Extensive ventricular scarring Inducible VT/VF on PES	Risk of SCD sufficiently high to consider primary prevention ICD if "multiple risk factors"	0.66-0.73[21]
Spanish ACHD (Oliver et al. 2021)[10]	*Odds ratio per risk:* Lesion specific risk: Low (3.4) Moderate (3.9) High (9.8) Age (0.98) Male (1.8) Syncope (4.1) Symptomatic heart disease (8) NSVT (5.3) QRS duration (1.02) Moderate-severe ventricular dysfunction (RV or LV) (3.7) Systemic (3.8) or subpulmonary ventricular hypertrophy (2.7)	Composite risk calculator of predicted risk of SCD over 5 y: (http://cardioim.iisgmsai.org:48080/calc/) Risk classified as: Very low (<1%) Low (1%-4%) Moderate (4%-12%) High (>12%)	For all ACHD: 0.91 For rTOF: 0.83
Prevention ACHD (Vehmeijer et al. 2021)[11]	*7-point risk score:* Coronary artery disease (1) NYHA II/III symptoms (1) IART (1) Moderate LV impairment (1) Moderate RV impairment (1) QRS duration >120 ms (1) QT dispersion >70 ms (1)	*Annual risk of SCD for rTOF:* 1-2 : <1% 3: 1% 4: 3% 5: 6% 6: 14% 7: >25%	0.81
Ghonim et al. 2022[12]	*100 point risk score:* RV LGE (0-40) LV LGE (0-6) RV systolic dysfunction (4-10) LV systolic dysfunction (4-12) Peak VO_2 uptake ≤17 mL/kg/min^2 (6) BNP ≥127 ng/L (12) IART (8) Age over 50 (6)	*Annual risk of SCD:* 0-20: 0.2% 21-50: 0.7% ≥51: 4.4%	0.87

The AiTOR model[30] is an additional scoring system, as described in this review, validated to predict a composite end point rather than solely sudden death and/or VT and has not been included in the table.

ACHD, adult congenital heart disease; BNP, B natriuretic peptide; CMR, cardiac MRI; ICD, implantable cardiac defibrillator; IART, intra-atrial re-entrant tachycardia; LGE, late gadolinium enhancement; LV, left ventricle; LVEDP, left ventricular end diastolic pressure; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association heart failure classification; PES, programmed electrical stimulation; peak VO_2, peak VO_2 uptake during cardiopulmonary exercise testing; rTOF, repaired tetralogy of Fallot; RV, right ventricle; SCD, sudden cardiac death; VT, ventricular arrhythmias.

The Spanish adult congenital heart disease (ACHD) multicentre network, which studied a spectrum of congenital heart disease (including 360 patients with rTOF of variable disease complexity), created a risk score with a high sensitivity for sudden death (C-statistic 0.91) without significant loss of specificity.[10] Alongside the PREVENTION-ACHD risk score, which also analysed a broad spectrum of congenital heart disease (including 138 patients with rTOF), ischemic heart disease was highlighted as a novel and important contributing risk factor for sudden death by increasing the odds by between 4- and 8-fold.[10,11] Although these risk scores underwent validation with internal bootstrap analysis and a subsequent prospective analysis with an independent cohort for the PREVENTION-ACHD study, they are derived from all types of congenital heart diseases. There are strengths to this approach, with a high specificity and sensitivity for sudden death across disparate congenital disease lesions; however, it is unknown if their predictive value is maintained specifically within the rTOF group itself. Also, it is plausible that specific risk factors for rTOF would have been excluded as they are not applicable to other congenital heart defects.

Most recently, a prospective risk score incorporating detailed cardiac magnetic resonance imaging and late gadolinium enhancement (LGE) burden based on a large cohort of 550 patients with rTOF demonstrated a high ability to predict sudden death.[12] The score, comprising 8 risk factors, relies heavily on cardiac MRI metrics (68 out of 100 points) and particularly on the extent of RV LGE enhancement (40 out of 100 points). Those identified as highest risk (4.4% annual mortality) had a 36% mortality at 10 years compared with those in the lowest risk group (<0.2% annual mortality) with a 10-year mortality of 1%.

Interestingly, after accounting for the degree of LGE, QRS duration, characteristics of surgical repair, and nonsustained VT were no longer independent predictors reflecting the interplay of these parameters as surrogate markers of myocardial fibrosis. It is important to note, however, that accurate quantification of LGE within the RV requires a high level of experience and expertise for reproducibility. Given the heavy weighting of this value on the risk score, it is pertinent to consider the ability of each centre to accurately deliver these CMR-derived metrics before inappropriate extrapolation to their cohort.[12]

A fourth scoring criterion, published earlier this year, was developed using a machine-learning algorithm incorporating 57 variables from rTOF patients' electronic records to predict a composite outcome of death, heart failure admission, resuscitated sudden death, or VT.[30] After development, a refined model of the 10 strongest variables, labelled "AiTOR," was validated in an independent cohort of 411 patients with a C-statistic comparable to the other contemporary risk scores (Table 2). The model highlighted the impact of functional metrics from cardiopulmonary exercise testing as well as routinely derived CMR measurements on predicting adverse outcomes. Unfortunately, LGE was only formally qualified in a small group (4%), perhaps reflective of routine clinical practice, and was not powered for inclusion in the final model. It is important to note that the model predicted a composite of outcomes, and there were very few sudden deaths or VT in the development (<3% and 3%, respectively). Although all the outcomes are clinically highly relevant, it is unclear if the risk score remains robust in prediction of sudden death or VT specifically.[30]

It is important to appreciate that these scores, as within any high-risk cohort, do not comprehensively include all those who will experience SCD. Even with sensitivity approaching 95%,[10,12] the very lowest risk patients remain with a small risk of ventricular arrhythmias and sudden death (approximately 0.2% a year).[12] It remains to be seen whether complimentary approaches using continuous monitoring, such as wearable biosensors,[31,32] contemporary multidisciplinary clinical surveillance, and earlier intervention for structural and electrophysiology abnormalities, will further mitigate this remaining risk.[33]

Overall, considering our broader understanding of the extent and granularity in risk factors, the spectrum of disease, and the evolution of rTOF cohorts, existing guidelines[27,34] are too crude to precisely follow for an accurate assessment of the risk of sudden death (Fig. 1). In practice, however, decision-making is often challenging given the heterogeneity of the rTOF population from different surgical eras and inconsistent estimates of SCD from historical and contemporary risk scoring criteria.

For example, in our follow-up, we have a 30-year-old woman with complex rTOF (pulmonary atresia with RV to pulmonary artery conduit repair), which was repaired early in infancy. She currently has a dilated RV (RV end-diastolic volume index 152 mL/m^2), with an RV ejection fraction of 40% and a mildly impaired LV systolic function (left ventricular ejection fraction 47%). She has no LV LGE and mild RV LGE burden in the base of the RVOT and around the ventricular septal defect (VSD) patch. Her electrocardiogram (ECG) shows a right bundle branch block with a QRS duration of 188 milliseconds, fractionated QRS, and no significant QTc dispersion. Her ambulatory ECG monitoring shows short, asymptomatic runs of nonsustained VT and short runs of asymptomatic intra-atrial re-entrant flutter for which she previously had a successful ablation. Recent assessment revealed New York Heart Association class II symptoms with a peak VO_2 of 12 mL/kg/m^2 (32% predicted), B natriuretic peptide of 201 pg/mL, and no coronary disease. By Heart Rhythm Society/Pediatric and Congenital Electrophysiology Society guidelines, her risk of SCD would qualify her for consideration of a primary prevention ICD,[29] whereas European Society of Cardiology ACHD guidelines would not,[27] and European Society of Cardiology ventricular arrhythmias guidelines would instead advocate a programmed ventricular stimulation study for further stratification.[35] Using contemporary risk scoring, her predicted risk of SCD would vary from 0.7%/y[12] to 3%/y[11] to 35% over 5 years.[10] As illustrated, practical reconciliation of this uncertainty for individual patients in clinical practice is unresolved and of great relevance as it directly informs primary prevention ICD implantation and structural and electrophysiology intervention of proarrhythmic substrates.

Reducing the Risk of Sudden Death

The majority of risk factors and risk scores in rTOF are heavily weighted towards predicting the risk of ventricular arrhythmias. The value in this approach is epidemiologic; it is among the most likely etiologies of sudden death in rTOF[6,15]

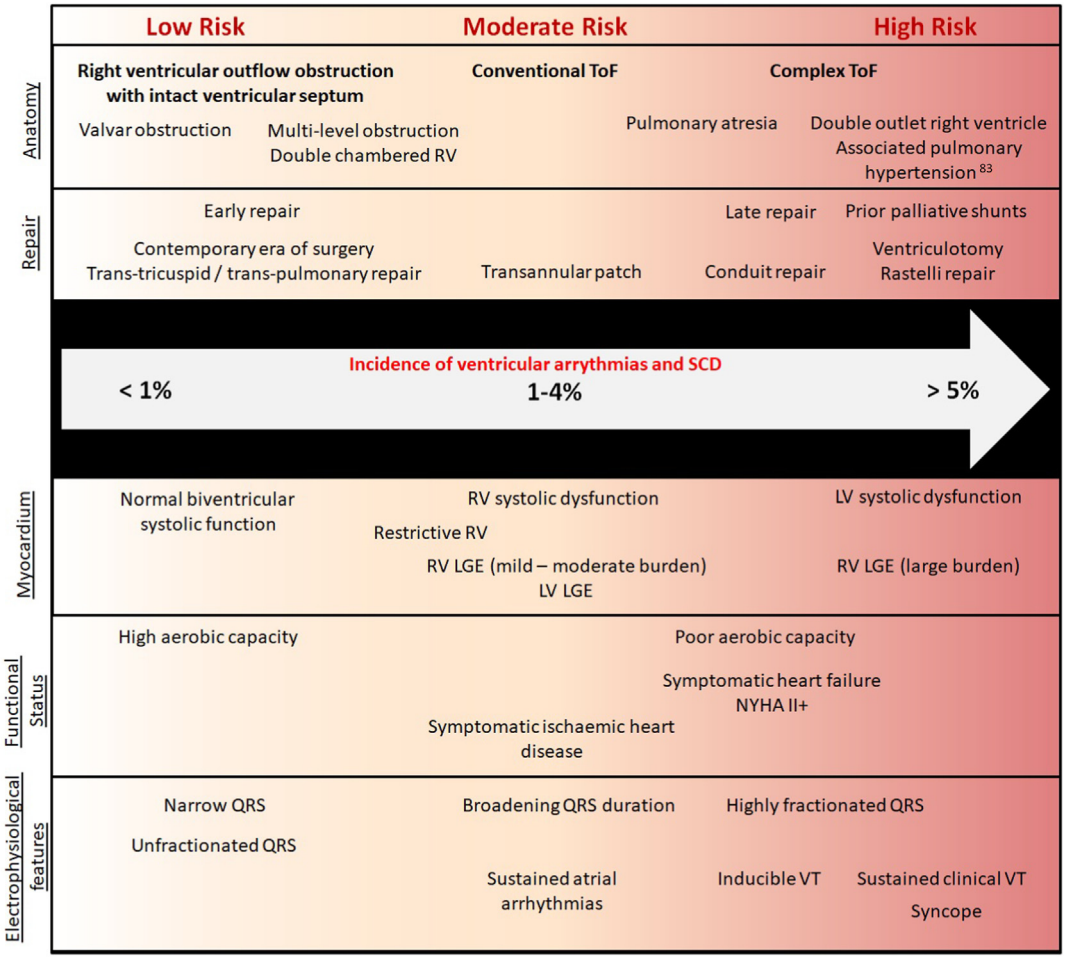

Figure 1. Schematic representation of the most important risk factors and their value to predict ventricular arrhythmia and SCD in rTOF. LGE, late gadolinium enhancement; LV, left ventricle; NYHA, New York Heart Association heart failure classification; rTOF, repaired tetralogy of Fallot; RV, right ventricle; SCD, sudden cardiac death; VT, ventricular arrhythmias.

and permits identification of patients who will benefit from specific interventions to mitigate the risk. Both ICDs and VT ablation are potentially effective strategies in reducing arrhythmic events and death. However, beyond ventricular arrhythmias, there are also important and under-recognized causes of SCD attributable to bradyarrhythmia and heart failure, which may also be avoidable with early intervention.

Medical therapy for heart failure

Heart failure is an increasingly recognized direct contributor to sudden death in population with rTOF. The causes are multifactorial but closely overlap with the risk factors for arrhythmic death identified in the described scoring systems including increasing age, LV dysfunction, and atrial tachyarrhythmia alongside haemodynamically significant valve disease.[36] Whether "conventional" medical therapy such as renin-angiotensin system inhibitors, β-blockers, newer agents (such as SGLT2 inhibitors), and cardiac resynchronization therapy reduces mortality and sudden death in rTOF patients with heart failure is uncertain, although they might play a role in patients with LV dysfunction.[37–40]

Implantable cardiac defibrillators

Aside from secondary prevention indications after aborted sudden death or sustained ventricular arrhythmias, international guidelines also support ICD implantation, with a class IIa recommendation, for the primary prevention of SCD in rTOF patients with multiple risk factors. The included risk factors vary depending on the guideline but generally include LV systolic dysfunction, right ventricular systolic dysfunction, nonsustained symptomatic VT, a QRS duration of ≥180 milliseconds, extensive right ventricular scarring, and inducible sustained VT at an electrophysiology study.[27,34] At present, guidelines do not reference the recently published risk scoring criteria that are likely to offer more accurate and precise estimation of an individual patient's risk. Increased granularity with such scores may also benefit physician, patient, and family discussions on individual risk as routinely occurs with other high-risk patient groups such as hypertrophic cardiomyopathy.[41] This process is of great value given that patients are frequently young with implications on lifestyle, occupation, driving, and long-term psychosocial well-being.[42,43]

For patients suitable for ICD implantation, the 2 currently available strategies are transvenous and subcutaneous defibrillators. Transvenous systems provide the additional useful functionality of antitachycardia pacing (which can be tailored in those with a secondary indication)[44] and bradycardia pacing for pre-existing conduction disease. Most transvenous devices can be implanted conventionally on the left side; however, right-sided implants are occasionally required for anatomic or vascular access reasons. Although more technically challenging, right-sided implantation, when clinically required, is not associated with poorer outcomes, complications, worse parameters, or suboptimal defibrillation thresholds.[45]

The entirely subcutaneous device is an attractive alternative when there is no pacing requirement, as it preserves venous access in young patients and may avoid the high rate of transvenous lead-related complications.[46–48] There is currently limited data to compare the long-term outcomes of subcutaneous devices; however, complication rates in appropriately screened patients appear to be low.[19,49,50] The primary barrier to implantation relates to ineligibility, in as many as 40%, due to T-wave oversensing in the context of a typically wide QRS and right bundle branch block morphology associated with rTOF. Right sternal screening and implantation has higher success rates of up to 75% in 1 case series; however, screening failure correlates closely with increasing QRS duration, which is frequently seen in this cohort.[51–53]

Patients with rTOF have a high rate of appropriate shocks in the region of 5%-10% per annum, with no difference in rates between primary or secondary indication implants.[26,54] This is unfortunately accompanied by a high rate of device-related complications, reported to be 6% within 30 days of implant and 43% by a median of 7 years in a large French registry.[19] The commonest complication affecting 1 in 4 patients is an inappropriate shock (most commonly due to atrial arrhythmia), followed by lead dysfunction, infection, and bleeding.[46–48] Our centre recently reported similar complication rates, with those at highest risk having a greater anatomic and device complexity.[16] In conjunction with aggressive atrial arrhythmia management, careful device programming of detection zones, long detection times, and SVT discrimination algorithms are clearly of paramount importance to reduce this high rate of inappropriate therapy. It is therefore strongly recommended that implantation and surveillance are performed at centres experienced in congenital electrophysiology with the resources and the expertise to manage the frequent implant-related complications and offer prompt management of arrhythmias.

Catheter ablation of ventricular tachycardia

The majority of ventricular arrhythmias identified in rTOF are monomorphic VT[26] using a macro re-entrant circuit based on discrete pathways of slow conduction within the RV (Fig. 2B). The 4 commonest isthmuses are well characterized and defined by their anatomic boundaries:[55]

Isthmus 1: between the tricuspid annulus and tract RVOT patch/incision

Isthmus 2: between the pulmonary annulus and the RVOT incision

Isthmus 3: between the pulmonary annulus and the VSD patch

Isthmus 4: between the tricuspid annulus and the VSD patch

Targeted radiofrequency catheter ablation to block 1 or more of these isthmuses has been demonstrated in several studies to reduce the risk of future ventricular arrhythmia, ICD shocks, and sudden death in patients with sustained VT.[56–60] In a minority of patients, there is an alternative source of VT including the conduction bundles or focal sites in the right or left outflow tract, which are also amenable to ablation.[60] Ablation outcomes are generally good with acute success rates of 70%-80%[57] limited predominantly by inaccessible tissue, due to prosthetic material such as patches or prosthetic valves, or hypertrophied myocardium.[61] In contrast, there is a paucity of data on the outcomes of antiarrhythmic drugs either as an alternative to or in conjunction with ablation, with only a single study showing benefit from amiodarone in 6 patients after failed ablation.[62]

Patients who present with a slower, haemodynamically tolerated VT can undergo more extensive electroanatomic mapping to better localize VT circuits; however, it is unclear if this translates to superior outcomes. Faster poorly tolerated VT, however, represents half of the VT seen in this population.[63] Although this presents technical limitations for ablation, acute success rates using substrate-based approaches are acceptable if the conduction block is achieved across targeted isthmuses.[58,61] This faster VT cohort, however, are more likely to have recurrent fast VT with worse outcomes and potentially higher mortality and thus remain with a long-term ICD indication in the longer term.[63] Particularly in the well-tolerated VT group, there is great interest whether an "up front" first-line VT ablation may avoid the need for an ICD[63] after achieving satisfactory ablation end points.[58,61] This has a class IIb indication in international guidelines;[27,34] however, robust outcome data are limited and further long-term surveillance of these cohorts is warranted before translation to routine practice.

Pulmonary valve replacement

Haemodynamically significant pulmonary regurgitation is common after rTOF and results in longstanding volume overload or the RV with adverse remodelling (dilatation and systolic dysfunction) predisposing to ventricular arrhythmias and sudden death.[6,64] Although pulmonary valve replacement (PVR) improves symptoms and right ventricular parameters (positive remodelling of the RV), it is unclear whether it significantly reduces the risk of future ventricular arrhythmias, ICD therapies, and sudden death.[65–69] Heterogeneity in study outcomes may be partly attributable to variability in the timing and indications for PVR between cohorts, which may have resulted in different degrees of right ventricular arrhythmic burden and reversible substrate. A large cohort study did demonstrate a reduction in ICD therapies after PVR,[67] but there was no effect on medium-term recurrent sustained VT or sudden death in a propensity score–adjusted analysis of clinical outcomes in multicentre, international registry.[66] Very recently, longer term outcomes were reported from this cohort, over a median of 8 years, that did reveal a significant reduction in sustained VT and sudden death (hazard ratio 0.4) if specific RV volumetric and functional criteria for intervention were met.[8]

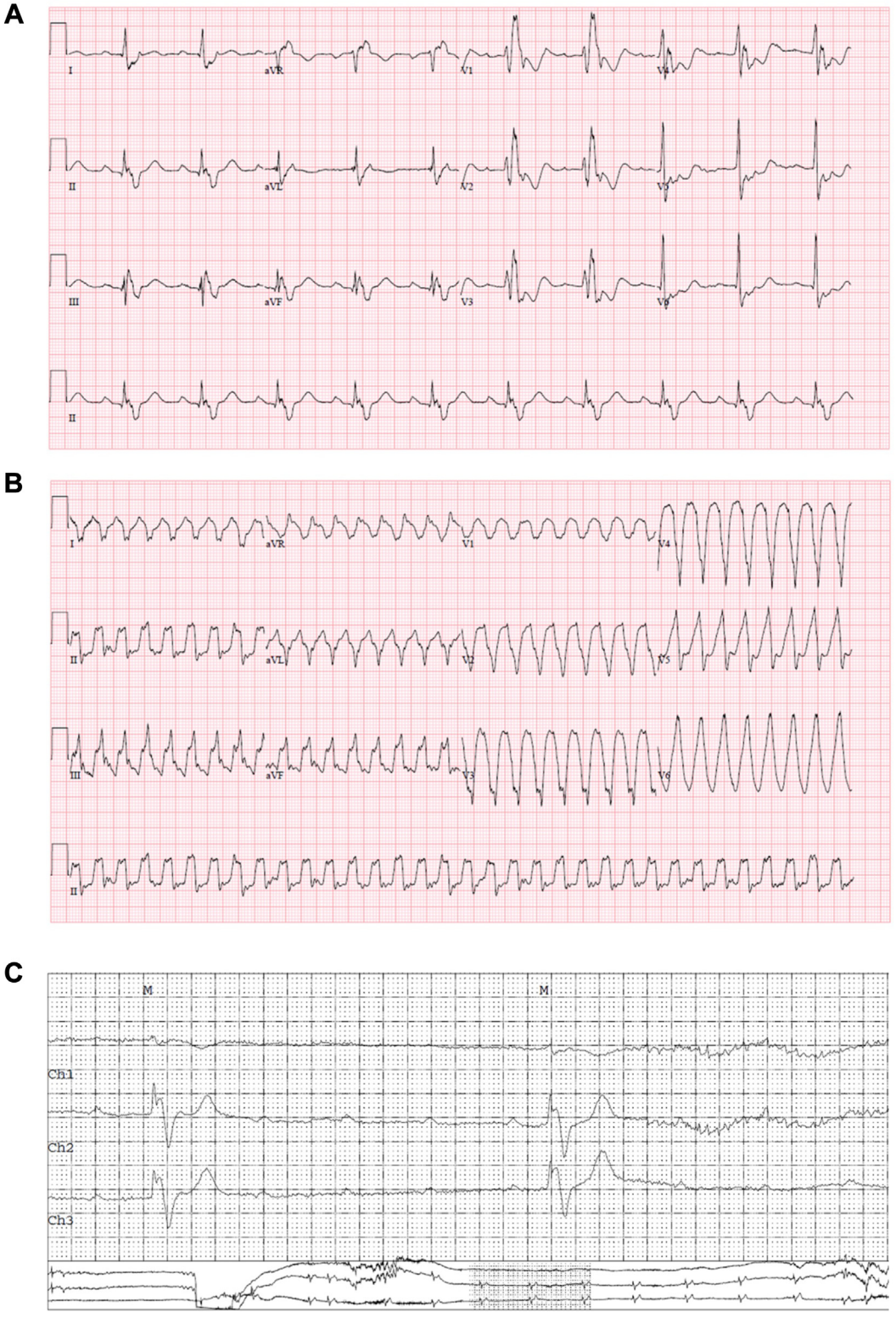

Figure 2. The spectrum of electrographic markers associated with sudden cardiac death. (**A**) A 12-lead ECG from a 57-year-old with recurrent heart failure admissions before a cardiac resynchronization therapy implant. This demonstrates several risk factors associated with SCD including a broad (190 milliseconds) and fractionated QRS complex. As part of a comprehensive risk assessment, he was offered a primary prevention defibrillator. (**B**) An ECG from a 55-year-old demonstrating monomorphic ventricular tachycardia with a left bundle appearance in V1, a QRS transition in V5, and a rightward inferior axis typical for an RVOT exit site seen in rTOF. Following electrical cardioversion, he underwent VT ablation and secondary prevention ICD implantation. (**C**) A 3-channel ambulatory rhythm monitor recording from a 41-year-old with syncope demonstrating high-grade AV block, evidenced by P waves with a dissociated broad QRS escape of approximately 20 beats per minute. She had a pre-existing secondary prevention S-ICD and underwent a transvenous ICD implantation for bradycardia pacing support. AV, atrioventricular; ECG, electrocardiogram; ICD, implantable cardiac defibrillator; rTOF, repaired tetralogy of Fallot; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; S-ICD, subcutaenous ICD; VT, ventricular tachycardia.

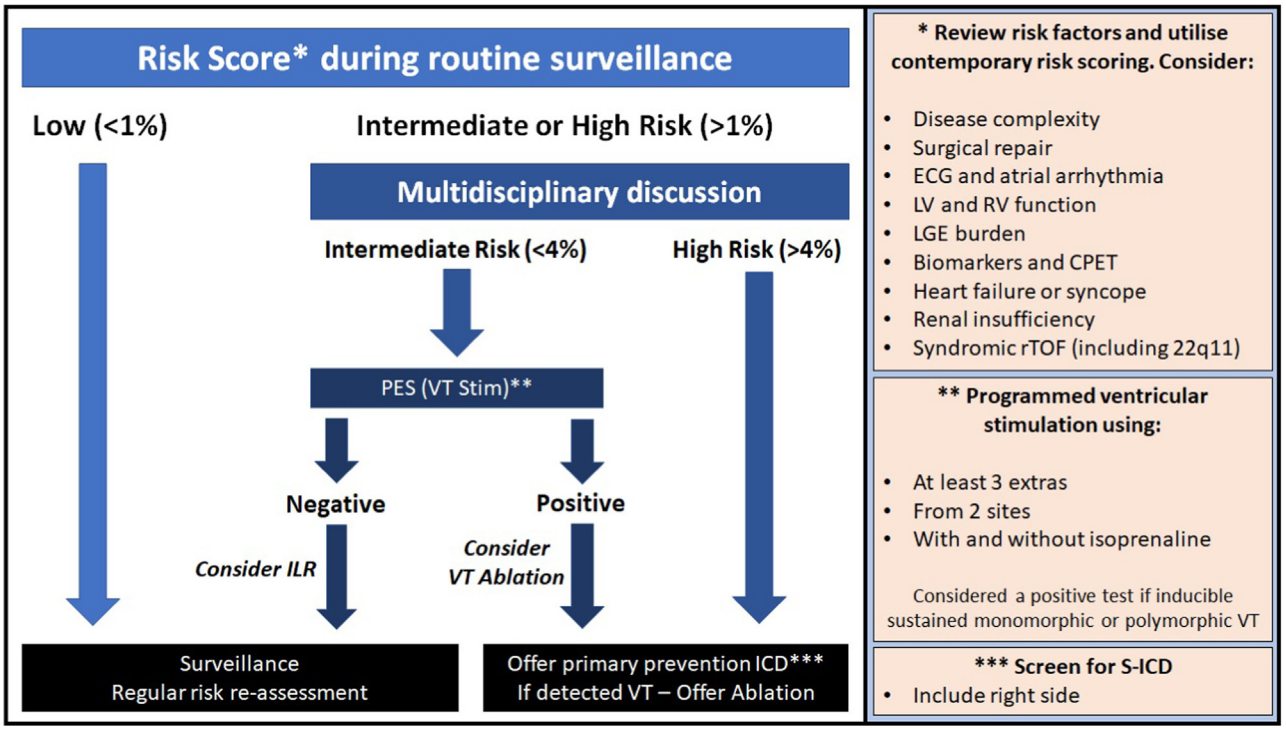

Figure 3. Risk stratification algorithm for SCD in patients with rTOF. Many additional scenarios, including the presence of haemodynamic lesions, an indication for PVR, detected ventricular arrhythmia, and bradyarrhythmia, have distinct considerations. CPET, cardiopulmonary exercise testing; ECG, electrocardiogram; ICD, implantable cardiac defibrillator; ILR, implantable loop recorder; LGE, late gadolinium enhancement; LV, left ventricle; PES (VT Stim), programmed ventricular stimulation; RV, right ventricle; S-ICD, subcutaneous ICD; VT, ventricular tachycardia.

Decision-making in PVR intervention is further complicated by evidence that supplementing PVR with concomitant ablation of anatomic isthmuses may independently reduce ventricular arrhythmic events and the need for an ICD in patients at high risk of VT or inducible VT preoperatively.[68–73] However, empiric concomitant cryoablation, at the time of PVR, has a high rate of failure of isthmus block.[71] Consequently, although VT burdens may be reduced, up to half remain with inducible VT at a post-PVR electrophysiology study and therefore still warrant consideration of ICD implantation.[70,71] More targeted surgical cryoablation of specific isthmus guided by preprocedure electroanatomic mapping and catheter ablation appears to have superior outcomes with greater freedom from ventricular arrhythmias, sudden death, and potentially ICD implantation.[72,73] Overall, despite conflicting data, it is reasonable to offer selected patients undergoing PVR preoperative risk stratification with a VT simulation study and electroanatomic guided ablation for those with induced VT.[9,34] This decision should be supported by a consensus of a multidisciplinary ACHD team in an expert centre.

Bradyarrhythmia

It is assumed that most sudden deaths in rTOF are related to ventricular tachyarrhythmia and heart failure.[6] However, late onset of high-grade atrioventricular (AV) block is well documented in this population and strongly associated with sudden death.[74,75] The incidence has been reported at 1%, with similar numbers undergoing permanent pacing implantation in a large US-based epidemiologic analysis.[76] This incidence is rising, perhaps related to greater patient surveillance in an ageing population who already have significantly delayed conduction in their His-Purkinje system.[77,78]

There are several published case reports of late AV block, most of which presented with syncope and/or cardiac arrest often without a clear trigger or recent change in ECG characteristics.[79,80] Risk factors include, as in degenerative conduction disease, an increasingly prolonging PR interval, bifascicular block, and left fascicular disease.[77,80] In addition, late recovery of postoperative AV block after the initial repair (beyond day 3) is independently associated with a 6 times risk of sudden death over a 30-year follow-up.[77] These findings do, however, reflect a cohort undergoing a historic surgical approach for repair, and there may be many other unaccounted confounders that contribute to sudden death.

Risk stratification for late AV block remains challenging with limited data and no prospective studies of screening strategies. It remains to be seen whether prolonged invasive or noninvasive rhythm monitoring, as is increasingly adopted in other high-risk cohorts, will detect occult conduction disease before sudden death. Lastly, the value of invasive electrophysiology assessment of conduction intervals to risk stratify selected patients also remains unknown.[81]

Conclusions

Late sudden death after repair of TOF remains a concern; however, substantial progress has been made in risk

stratification in recent years. Contemporary multimodal assessment by a multidisciplinary team of experts at ACHD centres to inform risk scores appears to identify the majority of patients who would benefit from primary prevention ICDs and/or ventricular substrate ablation and/or pulmonary valve intervention. However, many patients continue to fall within an intermediate risk category or have conflicting risk estimates. Multidisciplinary team discussions of each case alongside the patients and their family are paramount to navigate this uncertainty (Fig. 3). It remains to be seen whether the adjunctive long-term rhythm surveillance, improvements in device technology, and ablation strategies will bring more certainty and fewer complications and mitigate sudden death in this cohort.

Ethics Statement

The authors confirm the research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a review article and commentary without patient identifiable information. The IRB did not require consent for the purposes of this article.

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Disclosures

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