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Updates on inherited arrhythmia syndromes (Brugada syndrome, long QT syndrome, CPVT, ARVC)

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ABSTRACT

The inherited arrhythmia (IA) syndromes are a group of rare and complex conditions that may predispose individuals to ventricular arrhythmias and sudden cardiac death. Our understanding of the genetic architecture underlying these syndromes has evolved, with recent reappraisals of variant pathogenicity and quantification of polygenic influences. The IA population includes an increasing proportion of low-risk patients, often identified via familial screening; avoiding over-treatment in these patients is an important consideration. Conversely, high-risk patients have an expanding armamentarium of targeted therapeutic interventions available beyond the ICD, with many emerging novel therapies. Refined risk stratification in the intermediate risk group is critical, utilising novel risk factors, genotype and multiparametric risk scores. Artificial intelligence will almost certainly play a role in diagnosis and risk stratification moving forward. Durable phenotype correction with gene therapy (or precision ablation) is an ultimate goal. This review will focus on updates in pathophysiology, diagnosis, risk stratification and management of Brugada syndrome, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia and arrhythmogenic right ventricular cardiomyopathy.

Introduction

The inherited arrhythmia (IA) syndromes are a group of rare and complex conditions that may predispose individuals to ventricular arrhythmias and sudden cardiac death. The phenotypic spectrum of IA patients includes an expanding population of asymptomatic and low risk individuals, in the context of family screening, genetic testing and increased awareness in the referring community. Recent reappraisals of variant pathogenicity and polygenic influences have informed our understanding of the genetic architecture underlying these syndromes. Diagnostic criteria now consider clinical features, probabilistic provocation tests and advanced imaging modalities in those syndromes with structural changes; artificial intelligence is likely to play an ancillary diagnostic role in the near future. Avoidance of over-treatment in low-risk patients is an important consideration. Conversely, high-risk patients have an expanding armamentarium of targeted therapeutic interventions available beyond the ICD, with many emerging novel therapies. Refined risk stratification in the intermediate risk group is critical, utilising novel risk factors, genotype, multiparametric risk scores and potentially artificial intelligence. Durable phenotype correction with gene therapy (or precision ablation) is an ultimate goal. This review will focus on updates in pathophysiology, diagnosis, risk stratification and management of Brugada syndrome (BrS), long QT syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT) and arrhythmogenic right ventricular cardiomyopathy(ARVC) (Central Illustration). Other less common IA syndromes such as short coupled ventricular fibrillation, early repolarization, short QT syndrome and left dominant arrhythmogenic cardiomyopathy fall outside the

Abbreviations: ACM, arrhythmogenic cardiomyopathy; AI, artificial intelligence; ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; BrS, Brugada syndrome; CMRI, cardiac magnetic resonance imaging; CPVT, catecholaminergic polymorphic ventricular tachycardia; CRDS, calcium release deficiency syndrome; DSP, desmoplakin; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; IA, inherited arrhythmia; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; LCSD, left cardiac sympathetic denervation; LGE, late gadolinium enhancement; LV, left ventricular; MAE, major arrhythmic events; MET, metabolic equivalent of task; NSVT, non sustained ventricular tachycardia; PET, positron emission tomography; PVC, premature ventricular contraction; PVS, programmed ventricular simulation; RV, right ventricular; RVOT, right ventricular outflow tract; SCA, sudden cardiac arrest; SCB, sodium channel blockade; SCD, sudden cardiac death; TdP, torsade de pointes; TFC, Task Force Criteria; VA, ventricular arrhythmia; VT, ventricular tachycardia; VF, ventricular fibrillation.

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scope.

Brugada syndrome

BrS is an IA syndrome with the hallmark finding of J point elevation associated with a coved ST segment and T wave inversion in the right precordial leads (Fig. 1).[1] Affected individuals have a predisposition to ventricular fibrillation (VF), mostly during sleep. There is a male predominance with phenotypic expression influenced by age, usually presenting after adolescence. Prevalence is ~1: 2000, although ethnicity and sex markedly influence this estimate.[2]

Genetics and pathophysiology

BrS is one of the most polygenic IA syndromes, with Mendelian autosomal dominant inheritance demonstrated in only 20 %.[3] The only definitive disease-causing variants result in loss of function of Nav1.5 encoded *SCN5A* (Table 1).[3] Genome-wide association studies have identified multiple risk loci (single nucleotide polymorphisms), with subsequent development of a polygenic risk score, that may account for the BrS phenotype in a significant proportion of patients.[4,5] At present, the polygenic risk score requires additional validation before routine use in clinical practice.

Our understanding of the pathophysiology of BrS is evolving; historically, the condition was regarded as a pure channelopathy, with relative contributions of abnormal depolarisation and abnormal repolarisation debated.[6] Mounting evidence, however, supports "concealed" structural right ventricular outflow tract (RVOT) abnormalities in a significant proportion of patients, leading to conduction delay and perhaps more in keeping with a primary disturbance of depolarisation.[7–9] Histopathological studies have reported increased collagen and fibrosis with a propensity for the epicardial RVOT, associated with reduced connexin-43.[7–9] Autopsies of 28 hearts in patients with SCD due to BrS and 29 controls demonstrated diffusely increased fibrosis irrespective of biopsy site in the BrS hearts, albeit with the highest burden in the RVOT.[7] An inflammatory component is supported by both inflammatory cell infiltrates on histopathology and autoantibodies to cardiac proteins in the sera of BrS patients (specifically alpha cardiac actin, alpha skeletal actin, keratin and connexin-43)[8–10]; further validation of these findings is required. RVOT substrate may manifest as low voltage and fractionated signals on epicardial electroanatomic mapping, with ablation of this abnormal tissue able to "correct" the Brugada phenotype.[11,12] A proposed summation of BrS pathophysiology is a "reduced RVOT conduction reserve", with a predilection for the epicardium, that is at least in part genetically mediated.[13]

Diagnosis

Until 2016, a type 1 ECG was considered diagnostic of BrS. The J wave consensus statement recognised the potential for overdiagnosis with a drug-induced type 1 ECG, and proposed the requirement of additional clinical factors in these patients, quantified in the Shanghai score (Table 2).[6] A spontaneous type 1 ECG was still considered diagnostic. Fundamentally, this acknowledges the imperfect specificity of sodium channel blockade (SCB) and lack of a gold standard for BrS diagnosis. Sensitivity and specificity vary by SCB agent used, with ajmaline six times more likely to induce a type 1 pattern than procainamide[14]; it is unclear whether this represents more false positives with ajmaline, false negatives with procainamide, or a combination of both. Ajmaline-induced type 1 ECGs are concerningly not uncommon in patients with no suspicion of BrS, such as healthy controls or patients with AV nodal reentrant tachycardia.[15] A head-to-head comparison in at risk patients and healthy controls would be valuable to refine the relative sensitivity and specificity of each agent. SCB challenge may be considered in patients with suspicion for BrS based upon clinical and/or family history (e.g. cardiac syncope and non-diagnostic T2/3 Brugada ECG pattern, or family history of unexplained premature SCD), in the absence of a spontaneous type 1 pattern. Prior to considering performing a SCB challenge, artificial intelligence (AI) may play an increasing role in screening for BrS, and directing subsequent testing. A deep learning model demonstrated cardiologist-level accuracy in identifying a type 1 pattern on standard ECGs and Holter monitors, in patients with procainamide-induced or suspected BrS.[16]

Risk stratification

Consensus exists that BrS patients with prior cardiac arrest or sustained ventricular arrhythmia (VA) are at high risk and warrant ICD implantation (I), and that patients with cardiac syncope (particularly in the setting of a spontaneous type 1 ECG) are at relatively high risk and ICD implantation should be considered (IIa).[6] Consensus also typically exists that asymptomatic drug-induced type 1 patients are very low risk (< 0.3 % per annum risk of cardiac arrest or SCD).[17–19] The more challenging and controversial group are those at intermediate risk – specifically the asymptomatic spontaneous type 1 patients. These patients are at low, but not negligible, risk (0.4–1.2 % per annum).[17–19] In these patients, consideration of other risk factors or modifiers may be useful. Risk attenuates with advancing age, with patients over 60 years

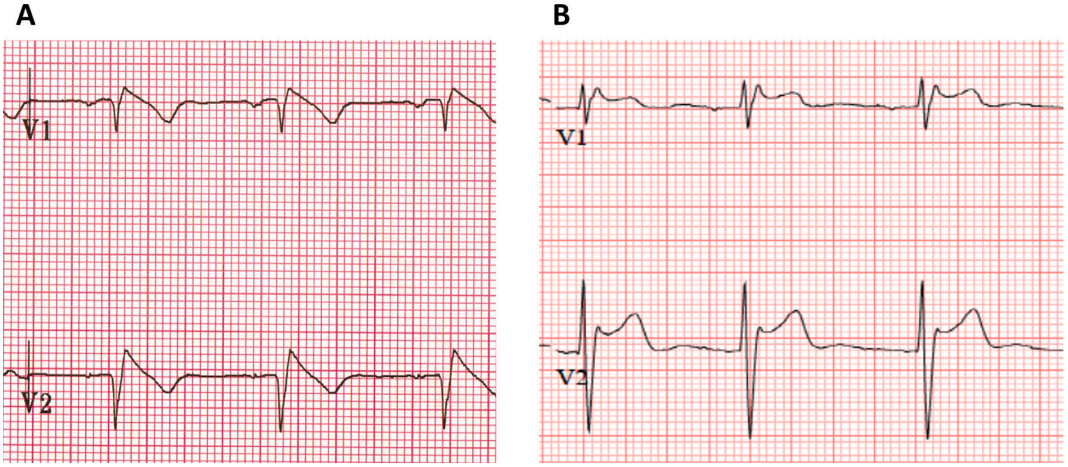


Fig. 1. Brugada pattern electrocardiograms.
Panel A demonstrates a type 1 Brugada pattern ECG with high lead placement of V1 and V2. Panel B demonstrates a type 2 (non-diagnostic) Brugada pattern ECG with standard lead placement.

Table 1
Pathogenic variants in inherited arrhythmia syndromes.

Variant	Inheritance	Level of evidence	Variant	Inheritance	Level of evidence
Brugada	Yield~20 %		**LQTS**	Yield~70–80 %	
SCN5A (LOF)	AD	Definitive	KCNQ1	AD	Definitive
			KCNH2	AD	Definitive
CPVT	Yield~70–80 %		SCN5A (GOF)	AD	Definitive
RYR2 (GOF)	AD	Definitive	CACNA1C	AD	Moderate
CASQ2	AR	Definitive	CALM1	AD	Definitive
	AD	Moderate	CALM2	AD	Definitive
TRDN	AR	Definitive	CALM3	AD	Definitive
TECRL	AR	Definitive	TRDN	AR	Strong
CALM1	AD	Moderate			
CALM2	AD	Moderate	**ARVC**	Yield~66 %	
CALM3	AD	Moderate	PKP2	AD	Definitive
			DSP	AD/AR	Definitive
CRDS			DSG2	AD/AR	Definitive
RYR2 (LOF)	AD		DSC2	AD/AR	Definitive
			JUP	AR	Definitive
			TMEM43	AD	Definitive
			PLN	AD	Moderate
			DES	AD	Moderate

Level of evidence compiled from ClinGen Gene Curation Framework reappraisals.[3,41,79,108] Only variants with moderate, strong or definitive evidence for pathogenicity listed. Note LQTS and CPVT phenotypic overlap for CALM1–3 and TRDN. AD = autosomal dominant, AR = autosomal recessive, LOF = loss of function, GOF = gain of function, LQTS = long QT syndrome, CPVT = catecholaminergic polymorphic ventricular tachycardia, CRDS = calcium release deficiency syndrome, ARVC = arrhythmogenic right ventricular cardiomyopathy.

Table 2
Shanghai score for diagnosis of Brugada syndrome.

	Points
ECG findings[a,b]	
A. Spontaneous type 1 Brugada ECG pattern	3.5
B. Fever-induced type 1 ECG	3
C. Type 2/3 ECG that converts to type 1 with SCB provocation	2
Clinical history[a]	
A. Unexplained cardiac arrest or documented VF/PMVT	3
B. Nocturnal agonal respiration	2
C. Suspected arrhythmic syncope	2
D. Syncope of unclear etiology	1
E. AF/flutter <30 y without clear etiology	0.5
Family history[a]	
A. First or second degree relative with definite BrS	2
B. Suspicious SCD (fever, nocturnal, Brugada-aggravating drug) in a first or second degree relative	1
C. Unexplained SCD age < 45 y in first or second degree relative with negative autopsy	0.5
Genetic testing	
A. Probable pathogenic mutation in BrS susceptibility gene	0.5
Score (requires at least 1 ECG finding)	
≥ 3.5 points: Probable/definite BrS	
2–3 points: Possible BrS	
<2 points: Nondiagnostic	

SCB = sodium-channel blockade, VF = ventricular fibrillation, PMVT = polymorphic ventricular tachycardia, AF = atrial fibrillation, BrS = Brugada syndrome, SCD = sudden cardiac death. Adapted from Antzelevitch et al., 2017.

[a] Only award points once for highest score in category.

[b] Testing at both standard and high leads.

old in particular at low risk.[20] Family history of SCD is an inconsistent risk factor in the literature, although several studies including a recent meta-analysis have reported increased major arrhythmic events (MAEs = SCD, cardiac arrest, VF, VT or ICD discharge) in patients with early familial SCD (< 35–40 y).[21,22] Loss of function *SCN5A* variants are also an inconsistently reported risk factor.[19,23,24] In 200 BrS patients deemed to be "high risk", a loss of function variant in *SCN5A* was associated with both a more aggressive clinical phenotype and more pronounced electrical abnormalities on substrate mapping.[24] A greater quantifiable abnormal electrical substrate on ECG appears to confer proportionate risk. A systematic review identified 12 ECG markers of risk, including peripheral lead type 1 pattern (leads II, III, aVF, V5, V6, I, aVL), first degree AV block, atrial fibrillation, fragmented QRS, QRS > 120 ms, R wave in aVR, S wave in I, early repolarisation in inferolateral leads, ST segment depression, T wave alternans, dispersion of repolarisation and Tzou criteria (V1R > 0.15 mV, V6S > 0.15 mV, V6 S:*R* > 0.2).[25] Furthermore, the burden of type 1 pattern over time correlates with risk, and cardiac events may be temporally associated with periods of spontaneous type 1 pattern.[26,27]

The role of programmed ventricular stimulation (PVS) in risk stratification remains controversial; easily inducible VF or VT (with 1–2 extrastimuli) has been correlated with MAEs in several studies predominantly from the same cohort of patients,[11,17,28] but was not corroborated in two large prospective registries.[19,29] Recently, Gaita et al. found PVS inducibility was significantly associated with arrhythmic events in asymptomatic spontaneous type 1 patients (7/103 in PVS positive versus 4/236 in PVS negative groups; 0.7 % versus 0.2 % per year), but this represents very small numbers in an overall low risk population.[17] The authors do not routinely advocate PVS, particularly as non-invasive risk modifiers may be better discriminators. The yield of implantable loop recorders (ILRs) has been considered in low-intermediate risk BrS patients with non-specific symptoms, including palpitations, syncope of unclear aetiology and presyncope.[30] VA was only detected in a single patient (fast non-sustained VT, subsequently offered an ICD), although 20 % of patients were found to have actionable supraventricular arrhythmias or bradyarrhythmias.

Risk scores have attempted to amalgamate proposed risk factors, but these have been hampered by poor discrimination in intermediate risk patients.[31] BRUGADA-RISK attempted to improve discrimination with a multicentre study of 16 risk factors in 1110 patients; probable arrhythmic syncope, spontaneous type 1 ECG, early repolarisation and type 1 pattern in the peripheral leads were associated with arrhythmic events,[18] with reasonable discrimination on external validation.[17] The PAT score was devised from a systematic review of 67 studies and 7538 patients, with 15/23 risk factors evaluated found to be significant (Table 3)[32]; this requires additional validation. Multiparametric scores may incrementally improve our intermediate risk group stratification, though it is conceivable that AI with access to electronic medical records will supersede these scores.

Table 3
Risk factors included in the PAT score and BRUGADA-RISK score for risk stratification in Brugada syndrome.

PAT score		BRUGADA-RISK	
Risk factor	Score	Risk factor	Score
History of MAEs	7		
Unexplained syncope	5		
Arrhythmic syncope	5	Probable arrhythmic syncope	12
T-peak T-end ≥100 ms	5		
PR ≥ 200 ms	4		
MAEs during drug challenge	4		
Fragmented QRS	3		
Type-1 in peripheral leads	3	Type-1 in peripheral leads	12
aVR sign	3		
Early repolarization	3	ER in peripheral leads	9
FHx SCD of age < 40	2		
Positive EP study	2		
Atrial fibrillation	2		
Spontaneous type-1 ECG	2	Spontaneous type-1 ECG	14
Positive SCN5A	1		
Incidence MAEs per 100 person years		5 year risk of VA/SCD	
Score 0–4: 0.00 %		Score ≥ 12: 4.9 %	
Score 5–9: 0.18 %		Score ≥ 21: 11.5 %	
Score 10–14: 5.42 %		Score ≥ 24: > 15 %	
Score ≥ 15: 6.59 %			

MAE (major arrhythmic events) defined as sudden cardiac death, sudden cardiac arrest, sustained ventricular tachycardia, ventricular fibrillation or appropriate ICD therapy. FHx = family history, EP = electrophysiology, ER = early repolarization, VA = ventricular arrhythmia, SCD = sudden cardiac death. Adapted with permission from Rattanwong et al., 2023 and Honarbakhsh et al., 2021.

An approach to risk stratification and management in BrS is depicted in Fig. 2.

Management

Low risk patients require lifestyle advice only and reassurance (avoid drugs listed on brugadadrugs.org, treat fever, avoid excess alcohol consumption, avoid cocaine). The evidence supporting a pro-arrhythmic effect of cocaine and alcohol in BrS is limited to case reports or small series at best.[33,34] Mechanistically, cocaine has SCB properties, whereas proarrhythmic effects of alcohol in BrS are poorly understood. Prescription drugs to be avoided have sodium channel blocking properties and will not be encountered by *most* young patients in their everyday lives. These drugs should be considered carefully, however, in those who are hospitalized or undergoing surgery, and in those who require antiarrhythmic, psychotropic or antiepileptic therapy. Traditionally, high risk patients have been managed with an ICD +/− quinidine, but these are not disease-specific interventions and have significant associated morbidities.[35,36] Quinidine is a complex class Ia antiarrhythmic with uniquely potent I_{to} inhibition properties, thought to be important for VA suppression in BrS.[36,37] Indications include recurrent ICD therapies or high-risk patients who do not undergo ICD implantation (e.g. refused or contraindicated). Dose-dependent gastroenterological and neurological side effects are common, and availability is limited globally. Low dose initiation (200-600 mg daily), evening administration and cholestyramine may improve tolerability. In those with an ICD indication, the subcutaneous ICD may be considered. Up to 15 % of BrS patients may fail screening (compared to 7–8 % screening failure in the general population), mostly due to T wave oversensing in the setting of

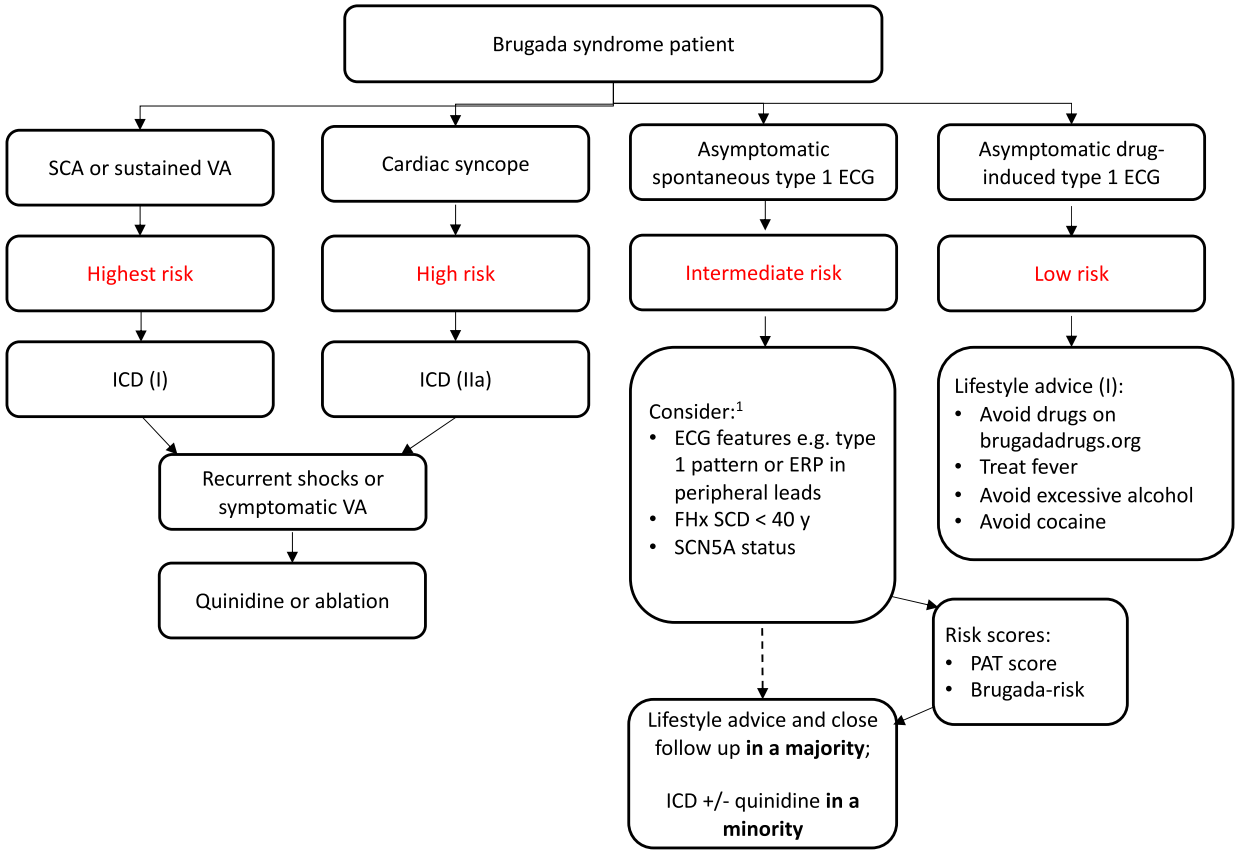


Fig. 2. Risk stratification and management of Brugada syndrome patients.
Guideline recommendations from Priori et al.,[37] [1]The authors do not routinely perform PVS in this group, but note that guidelines allow consideration of PVS for easily inducible VT/VF for additional risk stratification. SCA = sudden cardiac arrest, VA = ventricular arrhythmia, ICD = implantable cardioverter-defibrillator, ERP = early repolarisation pattern, FHx = family history, SCD = sudden cardiac death.

intermittent type 1 pattern and dynamic repolarization abnormalities.[38,39] Lead complications appear to be reduced with the subcutaneous ICD, with a possible trend to increased inappropriate shocks in the ATLAS trial.[39] Isoproterenol is indicated for VF storm; the proposed mechanism is augmentation of L-type calcium channel current and restoration of repolarization homogeneity.[40]

Ablation of epicardial RVOT substrate has increasing evidence as a useful adjunct in patients with breakthrough events; abnormal low voltage and fractionated signals are targeted with the procedural endpoint being resolution of type 1 changes despite SCB.[11,12,41] The long-term BRAVO results in patients with spontaneous VF reported a 96 % freedom from VF (allowing for multiple procedures) at a mean follow up of 4 years, with a 2.5 % acute hemopericardium rate.[12] As epicardial ablation techniques become safer (e.g. CO_2 insufflation) there may be a role for prophylactic ablation in intermediate-high risk patients, akin to accessory pathway ablation in Wolff-Parkinson-White syndrome; this approach remains theoretical for the present time.

Long QT syndrome

LQTS is a group of inherited channelopathies with the hallmark finding of QT prolongation on ECG, in the absence of structural heart disease or predisposing factors. Affected individuals have a predisposition to SCD and ventricular arrhythmias, in particular torsade de pointes (TdP). Prevalence is approximately 1: 2500.[42]

Genetics and pathophysiology

LQTS inheritance is typically autosomal dominant, with a pathogenic variant identified in up to 80 % of patients.[43] The significant majority of these are in 3 genes – *KCNQ1* (LQT1), *KCNH2* (LQT2) and *SCN5A* (LQT3). A reappraisal of 17 genes reported to cause LQTS determined only 8 had moderate, strong or definitive evidence (Table 1); the remainder were limited or disputed in their evidence base.[44] Genome wide association studies have identified multiple susceptibility single nucleotide polymorphisms, with a polygenic risk score devised that was higher in patients with genotype negative, compared to genotype positive, LQTS.[45] Polygenic risk scores are not yet in routine clinical use. Several rare LQTS syndromes warrant consideration; compound heterozygous variants in *KCNQ1* or *KCNE1* result in the autosomal recessive Jervell and Lange-Nielsen syndrome, associated with sensorineural deafness and an increased risk of SCD. Timothy syndrome may present as a multisystem disorder or "cardiac only" LQTS phenotype, due to variants in *CACNA1C*. Other overlap syndromes between LQTS and CPVT typically demonstrate autosomal recessive inheritance and have unique clinical features (e.g. variants in triadin and calmodulin).

The classical arrhythmia in LQTS is TdP. Initiation often follows a short-long-short sequence due to a premature ventricular contraction (PVC), but may also occur without this sequence, particularly in LQT1.[46] TdP onset may occur at faster heart rates in LQT1, potentially related to the failure of physiological IK_s augmentation that usually occurs with increased sympathetic drive, with delayed afterdepolarisation triggers.[47] Interestingly, in an anatomic human ventricle tissue model of polymorphic VT, the initiating PVC always originated from the steep repolarisation gradient region and manifested as R on T; the authors proposed the term "R from T" was more mechanistically accurate.[48] An alternative conceptualisation of arrhythmogenicity in LQTS involves electromechanical reciprocity, whereby electrical repolarisation outlasts mechanical systole, creating a sensitised environment for arrhythmic triggers.[49]

Diagnosis

The diagnosis of LQTS requires careful evaluation of clinical history, family history, baseline ECG (including QTc and T wave morphology) and exercise-provoked ECG changes, in the absence of a QT prolonging agent or precipitant.[40,43,50,51] Measuring the QTc accurately with the tangent method and U wave exclusion is critically important.[52] Whilst certain drugs and electrolyte derangements are well described to cause QT prolongation, a recent report suggested athlete's heart can also be associated with QT prolongation.[53] Apparent acquired LQTS may also represent concealed congenital LQTS "unmasked" by a secondary QT prolonging factor, with up to 25 % of these patients genotype positive.[54] Genotype-specific triggers for arrhythmic syncope and SCA are well-described in LQT1–3[43]; these include exercise (particularly swimming) in LQT1, auditory stimuli and the postpartum period in LQT2, during sleep or rest (without arousal) in LQT3 and emotional stress in LQT1–3.

An inherent challenge in LQTS diagnosis is the significant overlap of upper limit of normal QTc in the healthy population with LQTS patients; up to 40 % of genotype positive LQTS patients may have a normal baseline QTc (i.e. concealed), with a further 30 % demonstrating borderline QT intervals.[55] Exercise testing is useful in this scenario, with the 4-min recovery QTc demonstrating the greatest sensitivity and specificity.[55,56] Sex-specific cut-offs with the best discrimination for diagnosis in LQT1 and LQT2 patients were 440 ms for males and 450 ms for females.[56] The probability of LQTS may be quantified using the modified LQTS diagnostic score (Table 4) or the online calculator available at www.qtcalculator.org.[50,52] Genotyping is useful to confirm the diagnosis of LQTS, and may be especially valuable in borderline diagnostic cases. The critical advance in the concealed or borderline LQTS population may come from AI – deep learning augmented ECG analysis outperformed QTc alone in differentiating LQTS patients from healthy subjects, and predicting genotype.[57,58] In an evaluation of patients referred to the Mayo clinic for whom a presumed diagnosis of LQTS was dismissed, the 5 leading culprits were a prolonged QTc secondary to vasovagal syncope, positive LQTS gene that was deemed not significant, positive family history of SCD deemed unrelated to LQTS, transient QT prolongation and misinterpretation of the QTc due to U wave inclusion.[59]

Table 4
LQTS diagnostic score.

	Points
ECG findings[a]	
A. QTc interval[b], ms	
≥ 480	3
460–479	2
450–459 (male)	1
QTc[b] 4th minute recovery of EST ≥ 480 ms	1
B. Torsades de pointes[c]	2
C. T wave alternans	1
D. Notched T wave in 3 leads	1
E. Low heart rate for age[d]	0.5
Clinical history	
A. Syncope[c]	
With stress	2
Without stress	1
B. Congenital deafness	0.5
Family history[e]	
A. Family members with definite LQTS	1
B. Unexplained SCD below age 30 among immediate family members	0.5
Score ≤ 1: low probability of LQTS, 1.5–3: intermediate probability, ≥ 3.5 high probability.	

[a] In the absence of medications or disorders known to affect these electrocardiographic features.
[b] QTc calculated by Bazett's formula $QTc = QT/\sqrt{RR}$.
[c] Mutually exclusive.
[d] Resting heart rate below the 2nd percentile for age.
[e] The same family member cannot be counted in A and B. Reproduced with permission from Schwartz et al. 2012.

An approach to LQTS diagnosis is depicted in Fig. 3.

Risk stratification

LQTS patients with a history of cardiac arrest or sustained VA are at the highest risk and warrant ICD implantation.[40] Those with syncope on beta blockers are also at high risk, and an ICD should be considered.[40] In asymptomatic patients, risk is related to QTc linearly and genotype, with sex modification.[60–62] LQT2 and LQT3 are higher risk than LQT1. ICD implantation may be considered in a select minority of asymptomatic patients, based upon QTc, sex, genotype and specific variant location. The 1–2-3 LQTS risk score considers QTc and genotype to give a 5-year risk estimate for life-threatening arrhythmic events, via an algorithm.[63] Several nuances in risk assessment are not considered in 1–2-3 LQTS, however – the first being the effect of specific variants within each genotype. Transmembrane pore variants are typically considered highest risk, followed by variants in other transmembrane domains, with variants in the N or C terminus lowest risk.[64,65] Furthermore, an age-dependent sex interaction with risk is evident in LQTS, with males at increased risk until early adolescence and females in adulthood.[62] Presumably this relates to sex hormone effects on K channels; testosterone potentiates IK_s (reduces QTc) and estrogen inhibits IK_r (increases QTc). Two risk models from the Rochester LQTS registry considered sex, age, symptoms, QTc and specific variants within genotypes.[66,67] In females 15–60 years old, the highest risk groups were LQT2 with a non-pore variant and QTc > 500 ms, and LQT2 with a pore variant and QTc > 460 ms.[66] In male adolescents 10–20 years old, the highest risk groups were LQT1 with a C-loop variant and either QTc ≥ 500 ms or prior syncope, and LQT2 with a pore loop variant and both QTc ≥ 500 ms and prior syncope.[67]

An approach to risk stratification and management in LQTS is depicted in Fig. 4.

Management

All patients with LQTS should avoid QT prolonging drugs and triggers. Triggers are often genotype-specific, and may include swimming in LQT1 and auditory stimuli (such as alarm clocks) in LQT2. This may be the only intervention required in a selected very low risk group (asymptomatic, normal QTc, genotype positive, older than 18 years at diagnosis), in a strategy termed "intentional non-therapy".[68] An up-to-date list of drugs which can cause QT prolongation may be found at www.crediblemeds.org or the related smartphone app. Historically restrictive guidelines with respect to sport have been relaxed as risk of sports-related events appears to be low.[69,70] Sports participation is reasonable if patients have been appropriately assessed, treated and educated, with the possible exception of swimming in LQT1,[69] particularly in open water or swimming alone. Beta blockers significantly ameliorate arrhythmic risk in LQTS. Non-selective beta blockers (nadolol and propranolol) are preferred[71]; bisoprolol is a possible alternative in low risk patients and may be better tolerated.[72] There are conflicting data for beta blocker efficacy in LQT3,[60,73] with one study only demonstrating a risk reduction in females.[74] Beta blockers in LQTS are indicated in patients with a QTc ≥ 470 ms and are reasonable in those with QTc < 470 ms.[40] Mexiletine appears beneficial in LQT3,[75] and possibly LQT2.[76]

An ICD is recommended for secondary prevention, with the possible exception of treatment naive LQT1 patients post cardiac arrest, due to the marked efficacy of beta blockers and left cardiac sympathetic denervation (LCSD) in this genotype.[40] An ICD should be considered in patients with syncope on beta blocker and in a select minority of high-risk asymptomatic patients considering age, sex, QTc and specific variant. In a retrospective analysis of over 3000 patients in the LQTS registry, ICD therapy resulted in a reduction in mortality in patients with non-fatal cardiac arrest, syncope on beta blocker and those with QTc ≥ 500 ms plus syncope off beta blocker.[77] LCSD may be considered in patients with breakthrough events on beta blockers, if an ICD is

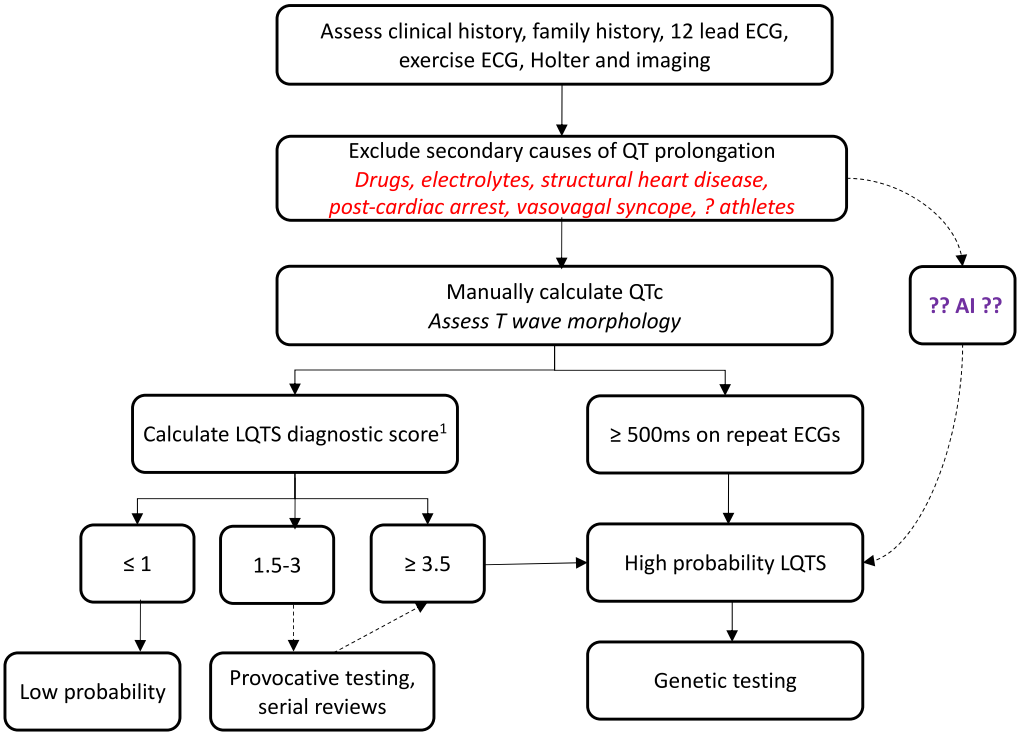


Fig. 3. Approach to diagnosis of long QT syndrome.
Modified with permission from Wilde et al.,[48] [1]The LQTS diagnostic score (i.e. Schwartz score[40]), confers a points-based probability of LQTS, whereby ≤1 is low probability of LQTS, 1.5–3 is intermediate probability and ≥ 3.5 is high probability (Table 4). The score considers ECG findings, clinical history and family history. AI = artificial intelligence.

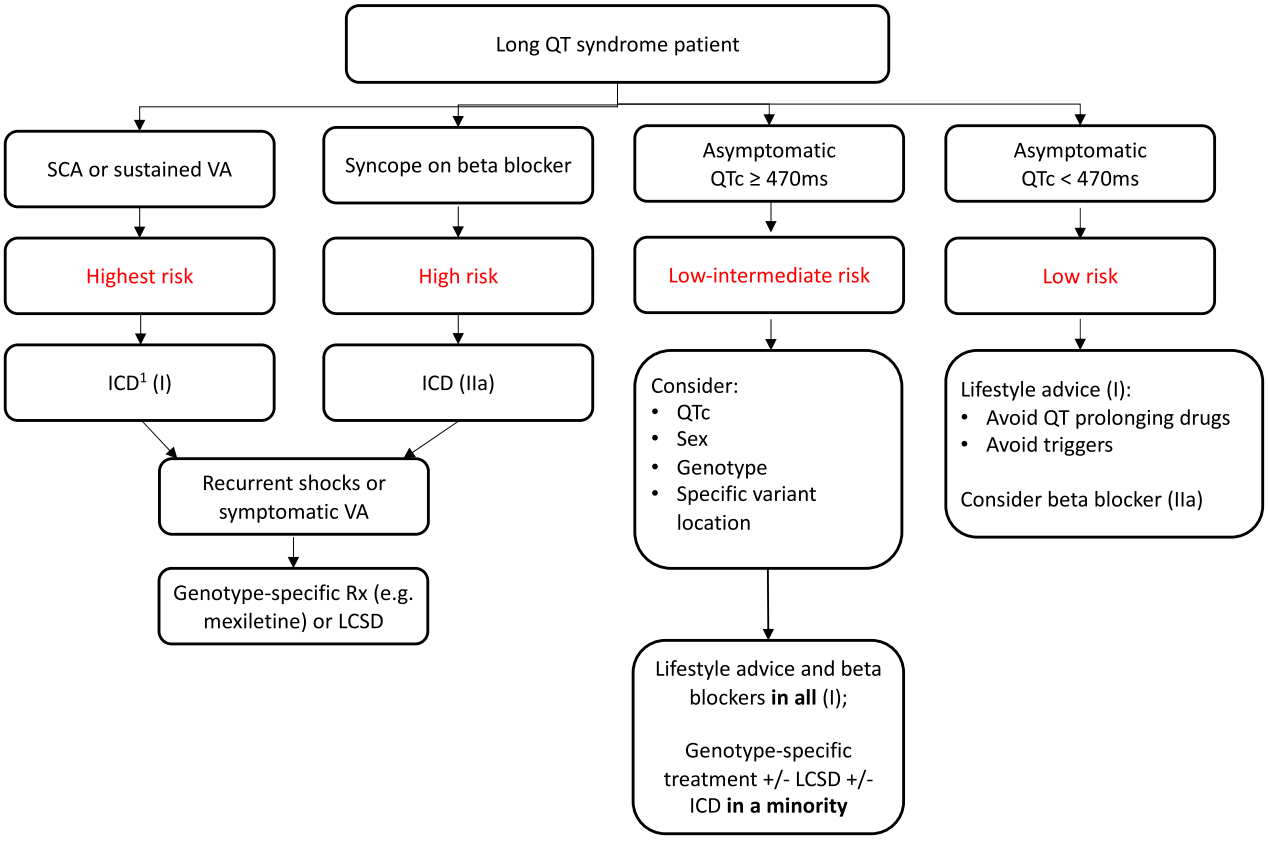


Fig. 4. Risk stratification and management of long QT syndrome patients.
Guideline recommendations from Priori et al.,[37] [1]Beta blocker +/− LCSD, without ICD, may be considered in treatment naive LQT1 patients post SCA or sustained VA. SCA = sudden cardiac arrest, VA = ventricular arrhythmia, ICD = implantable cardioverter-defibrillator, LCSD = left cardiac sympathetic denervation.

contraindicated or refused or if beta blockers are ineffective or not tolerated in high-risk patients.[40] The efficacy of LCSD was demonstrated in a single center experience of 125 patients followed for a mean of 13 years – an 86 % reduction in annual cardiac event rate was reported, noting only a small minority of patients had LQT3.[78] A QTc < 500 ms at 6 months postoperatively predicted excellent outcomes. The procedure was relatively safe with no major complications, with 2.4 % developing permanent left eye ptosis.

In the realm of precision medicine, lumacaftor + ivacaftor has been shown to shorten QTc in both a cellular LQT2 model and in two LQT2 patients with a hERG trafficking defect.[79,80] Lumacaftor (initially developed for the treatment of cystic fibrosis) acts as a small molecule chaperone, assisting trafficking of deficient hERG potassium ion channel proteins to the cell membrane; ivacaftor potentiates the action of lumacaftor. A dual component "suppression and replacement gene therapy vector" has successfully rescued the *KCNQ1* phenotype in a stem cell model.[81] Further study is required before clinical application of these approaches, with gene therapy a near term prospect.

Catecholaminergic polymorphic ventricular tachycardia

CPVT is an inherited disorder of intracellular calcium handling, resulting in catecholamine triggered episodes of VA. Genetic variants typically encode regulatory channels or proteins in the sarcoplasmic reticulum.[82] Prevalence is effectively unknown, but the figure ~1: 10000 has been postulated without supporting data.[40,83] Age at presentation is usually shortly before or early in adolescence.

Genetics and pathophysiology

A causative genetic variant is identified in 70–80 % of CPVT patients.[82,84] *RYR2* gain of function with autosomal dominant inheritance accounts for almost all gene positive CPVT cases; careful assessment of phenotype is critical, as *RYR2* is a large gene with a 3 % background rate of rare benign variants in the normal population.[85] *CASQ2* CPVT (~5 % cases) was historically considered autosomal recessive, but an autosomal dominant heterozygous form with variable penetrance has now been described.[86] A review of 11 published causative genes for CPVT determined that 7 had moderate to definitive evidence (Table 1), including the rare variants *CALM1–3*, *TRDN* and *TECRL*.[82] In CPVT, dysregulation of intracellular calcium leads to a net increase in intracellular calcium, sodium influx via the sodium-calcium exchanger and delayed after depolarisations; these may trigger VAs.[84] Activation of calcium / calmodulin dependent PKII mediated phosphorylation of *RYR2* appears to be a critical event in arrhythmogenesis.[87]

Diagnosis

The classical presentation of CPVT is syncope or cardiac arrest in the context of adrenergic stress, although up to 25 % of patients may develop symptoms in the setting of normal daily activities.[83,88] The pathognomonic feature for diagnosis is exercise induced polymorphic and/or bidirectional ventricular arrhythmia (bigeminy, couplets, bidirectional VT).[88] Induced VAs are often stereotypical and are moderately reproducible on repeat exercise stress testing, with a typical threshold heart rate of 100-130 bpm to unmask arrhythmia.[89] Modifying the exercise test protocol may aide in diagnosis, with some utility for a sprint-like "burst" protocol in incompletely penetrant patients.[90]

Risk stratification

CPVT patients with prior cardiac arrest or sustained VA are at the highest risk.[40] In patients without this history, proband status and syncope appear to increase risk.[91,92] Furthermore, C-terminal domain variants in *RYR2* have been associated with beta blocker failure.[92] Complexity of VA on therapy is likely also a marker of risk and represents a practical risk marker to follow over time.

An approach to risk stratification and management in CPVT is depicted in Fig. 5.

Management

Akin to LQTS, in CPVT historically restrictive guidelines with respect to exercise have been relaxed with evidence that cardiac events are uncommon with ongoing athletic participation in appropriately assessed and optimally treated patients.[70,93] Genotype positive phenotype negative patients in particular appear to be at low risk with this approach. Beta blockers remain the mainstay of therapy in CPVT and should be prescribed to all with a phenotype, and strongly considered even in those with concealed CPVT.[40,92] The non-selective beta blockers nadolol and propranolol are preferred.[92] In a multicentre crossover study of 247 CPVT patients, adding flecainide to beta blockers reduced arrhythmic events in symptomatic patients (particularly those with breakthrough events).[94] Flecainide should be considered as an adjunctive therapy to beta blockers if breakthrough events occur or complex ventricular arrhythmia remains inducible on exercise stress testing.[40] Initial combination therapy with nadolol and flecainide in survivors of cardiac arrest is also a strong consideration. Conversely, in lower risk patients who are intolerant to beta blockers, flecainide as monotherapy may be reasonable.[95]

LCSD is effective and is typically the first invasive treatment strategy considered in CPVT; indications include breakthrough events on medical therapy, intolerance to medications, and potential use in high-risk individuals as an adjunct to medical therapy.[40,96,97] The role of the ICD, however, remains controversial; complication rates are high, and shocks may be ineffective or even proarrhythmic due to increased adrenergic drive.[98,99] Implantation is reasonable for secondary prevention in patients on optimized medical therapy (considering concurrent LCSD), but is generally not recommended for primary prevention.[40] Shared decision making is essential in untreated patients who present with cardiac arrest – medical therapy +/− LCSD may be more appropriate given the efficacy of these interventions and greater risk of ICD complications in this population. Observational studies have reported conflicting evidence on mortality and SCD risk post secondary prevention ICD in previously untreated patients.[92,98] In a recent international multicenter study of 235 symptomatic children with CPVT, SCD only occurred in those without an ICD (3 %, typically in the setting of medication non-compliance), with high rates of appropriate shocks, inappropriate shocks and device-related complications in those with an ICD (43 %, 25 % and 29 % respectively).[100] When an ICD is implanted, a delayed detection single VF zone should be programmed to avoid unnecessary shocks.

Gene therapies represent an exciting and emerging field in CPVT. Adenovirus associated viral vector serotype-9 mediated delivery of the CaMKII peptide inhibitor has reversed molecular changes and phenotype in both murine and stem cell models of CPVT.[101] Several other gene therapy strategies demonstrate promise in pre-clinical trials, including gene transfer, allele silencing, gene editing and modulation of signalling pathways.[84]

Rare CPVT syndromes and calcium-release deficiency syndrome

Typical CPVT is due to *RYR2* or *CASQ2* variants, with stereotypical exercise-induced VA and beta blocker responsiveness. Rare genotypes such as *TRDN*, *TECRL* and *CALM1–3* often have a more severe phenotype and LQTS overlap, without the stereotypical exercise stress test response and with a less predictable response to medical therapy (Table 5).[84,102,103] This supports a genotype driven classification for these rare CPVT overlap syndromes.

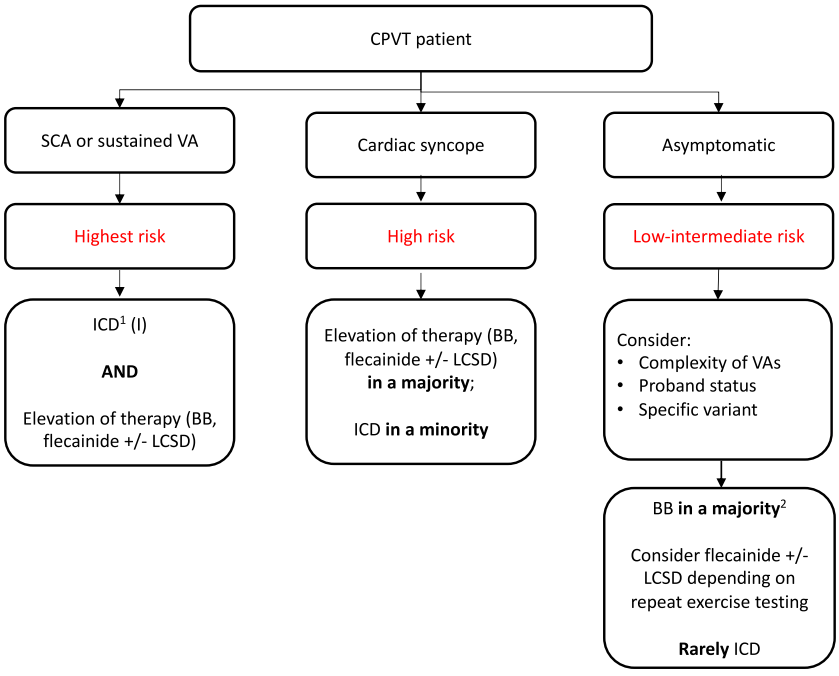
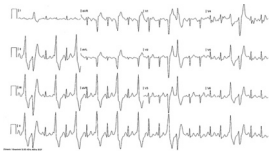
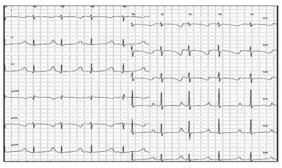
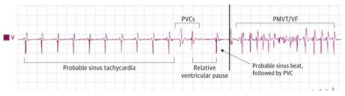


Fig. 5. Risk stratification and management of CPVT patients.
Guideline recommendations from Priori et al.,[37] [1]Beta blocker +/− LCSD, without ICD, may be considered in treatment naive CPVT patients post SCA or sustained VA. [2]Beta blockers may be considered (not mandatory) in genotype positive phenotype negative CPVT patients. CPVT = catecholaminergic polymorphic ventricular tachycardia, SCA = sudden cardiac arrest, VA = ventricular arrhythmia, ICD = implantable cardioverter-defibrillator, LCSD = left cardiac sympathetic denervation, BB = beta blockers.

Table 5
Typical CPVT, atypical CPVT and CRDS phenotypes.

Gene variant	Phenotype	
Typical CPVT		
RYR2 (GOF) CASQ2	Catecholamine associated VAs Stereotypical EST response Beta blocker responsive	
Atypical CPVT		
CALM1–3 TRDN TECRL	More severe phenotype LQTS overlap Absence of typical EST response ↑ beta blocker breakthrough TRDN – mild skeletal myopathy	
CRDS		
RYR2 (LOF)	Often present with SCD or SCA Absence of typical EST response LBLPS initiation Beta blocker efficacy unclear	

Typical CPVT ECG demonstrates exercise-induced frequent ventricular ectopy and bidirectional couplets. Atypical CPVT ECG demonstrates a CALM-1 female at 2 years of age with marked QT prolongation (courtesy of Crotti et al.[99]). CRDS device electrograms demonstrate a LPLPS initiation (courtesy of Roston et al.[101]). CPVT = catecholaminergic polymorphic ventricular tachycardia, GOF = gain of function, VAs = ventricular arrhythmias, EST = exercise stress test, LOF = loss of function, SCD = sudden cardiac death, SCA = sudden cardiac arrest, LBLPS = long burst long pause short coupled ventricular extrastimulus.

The recently described calcium release deficiency syndrome (CRDS) is due to *loss of function RYR2* variants, and is a distinctly separate syndrome from CPVT.[104,105] CRDS may present with familial SCD or cardiac arrest without typical exercise induced arrhythmia. Long burst, long pause short coupled ventricular extrastimuli often induce arrhythmic events, and may represent a unique diagnostic protocol.[104] Beta blocker efficacy in CRDS is unclear; flecainide may be beneficial.[105]

Arrhythmogenic right ventricular cardiomyopathy

ARVC is an inherited arrhythmogenic cardiomyopathy characterised by fibrofatty replacement of the right ventricle, accompanied by electrical instability with a predisposition to VAs and SCD. LV dominant forms are now well recognised, with a potential shift to either "arrhythmogenic cardiomyopathy (ACM)" as the overarching term, or to genotype-specific nomenclature.[106–108] As previously stated, this review will focus on "classic" right ventricular dominant forms. Prevalence is 1: 2000 to 1: 5000 with autosomal dominant inheritance and age-dependent penetrance, with most cases diagnosed between the second and fourth decades of life.[109,110]

Genetics and pathophysiology

A pathogenic variant is identified with genetic testing in approximately 2/3 of those who fulfill Task Force Criteria (TFC) for ARVC, with 8 genes deemed to have moderate or definitive evidence on reappraisal of 26 reported ARVC genes (Table 1).[111] Five of these disease-causing variants are desmosomal and 3 non-desmosomal. Notably a "pathogenic variant" is found in 0.5 % of the general population who do not meet diagnostic criteria.[112] Recent evidence may support cadherin-2 pathogenicity in addition to these 8 genes.[113]

The classical "triangle of dysplasia" in the right ventricle involves the inflow, outflow and apex, although the posterolateral left ventricle is often involved before the RV apex.[114] Substrate usually progresses epicardial to endocardial, with relative septal sparing.[115] A subset of patients demonstrate active inflammatory changes on cardiac MRI (CMRI) and histopathology.[116,117] This may be in keeping with the discovery of anti-heart and anti-intercalated disc antibodies at increased levels in ARVC probands and relatives compared to controls – further prospective studies are required to determine the clinical application of antibody testing.[118]

Diagnosis

The 2010 TFC consider global or regional dysfunction on imaging, histopathology, depolarisation and repolarisation abnormalities on ECG, VAs, family history and genotype to confer a definite, borderline or possible diagnosis of ARVC.[119] A typical *PKP-2* ARVC phenotype is demonstrated in Fig. 6. When considering the original TFC diagnostic contributors, the role of myocardial biopsy is currently limited due to its invasive nature and the increasing availability of high-quality CMRI. Nevertheless, electroanatomic mapping guided biopsy in particular may be useful in cases of diagnostic uncertainty and is safe in experienced centers.[116] Having said that, biopsy is rarely performed in the current era. Importantly, the TFC only apply to classical ARVC, and not to biventricular or LV dominant forms. These are often different genotypes with unique pathophysiology and natural histories.[107,108] For example, desmoplakin (*DSP*) cardiomyopathy often presents with episodic myocardial injury (mimicking myocarditis in young patients) with a characteristic late gadolinium enhancement (LGE) pattern of sub-epicardial ring-like LV enhancement.[120]

Several additional unique diagnostic challenges warrant consideration in ARVC. Sarcoidosis may fulfill TFC - factors favouring sarcoidosis include prolonged PR interval, advanced AV block, longer QRS duration, RV apical involvement, reduced LV ejection fraction and positive ^{18}F-FDG PET, whereas factors favouring ARVC include larger RVOT dimensions, subtricuspid involvement and peripheral T wave inversion.[121] Electroanatomic mapping (potentially with guided biopsy) may provide further guidance – basal septal involvement with equivalent bipolar and unipolar voltage reductions suggests sarcoid, whereas disproportionate unipolar voltage reduction (i.e. suggesting more epicardial substrate) may suggest ARVC.[122] Athlete's heart may mimic ARVC in some cases.[123] In athletes, regional RV dysfunction is usually absent, RV function is usually preserved and scarring is usually absent. Misdiagnosis of ARVC is relatively common, with 50 % of suspected cases referred to Johns Hopkins ARVC Center ruled out, mostly due to CMRI misinterpretation.[124]

The optimal approach to surveillance in family members of ARVC probands is not clearly established. First degree relatives of probands followed in the Netherlands ACM registry (who did not have a diagnosis of "definite ARVC" at initial assessment) were more likely to receive a diagnosis of "definite ARVC" during follow up if they had symptoms at initial review, were aged 20–30 years or had borderline ARVC.[125] In a systematic review, concealed genotype positive relatives were more likely to manifest a phenotype during follow up than relatives of genotype-elusive probands.[126] These clinical and genetic findings may inform both frequency of follow up intervals (e.g. 1–2 yearly versus 3–5 yearly) and duration of follow up.

Risk stratification

Prior cardiac arrest, sustained VT and severe RV or LV dysfunction all significantly increase risk of VA in ARVC.[106,127] Other risk factors include younger age, male sex, prior cardiogenic syncope, number of

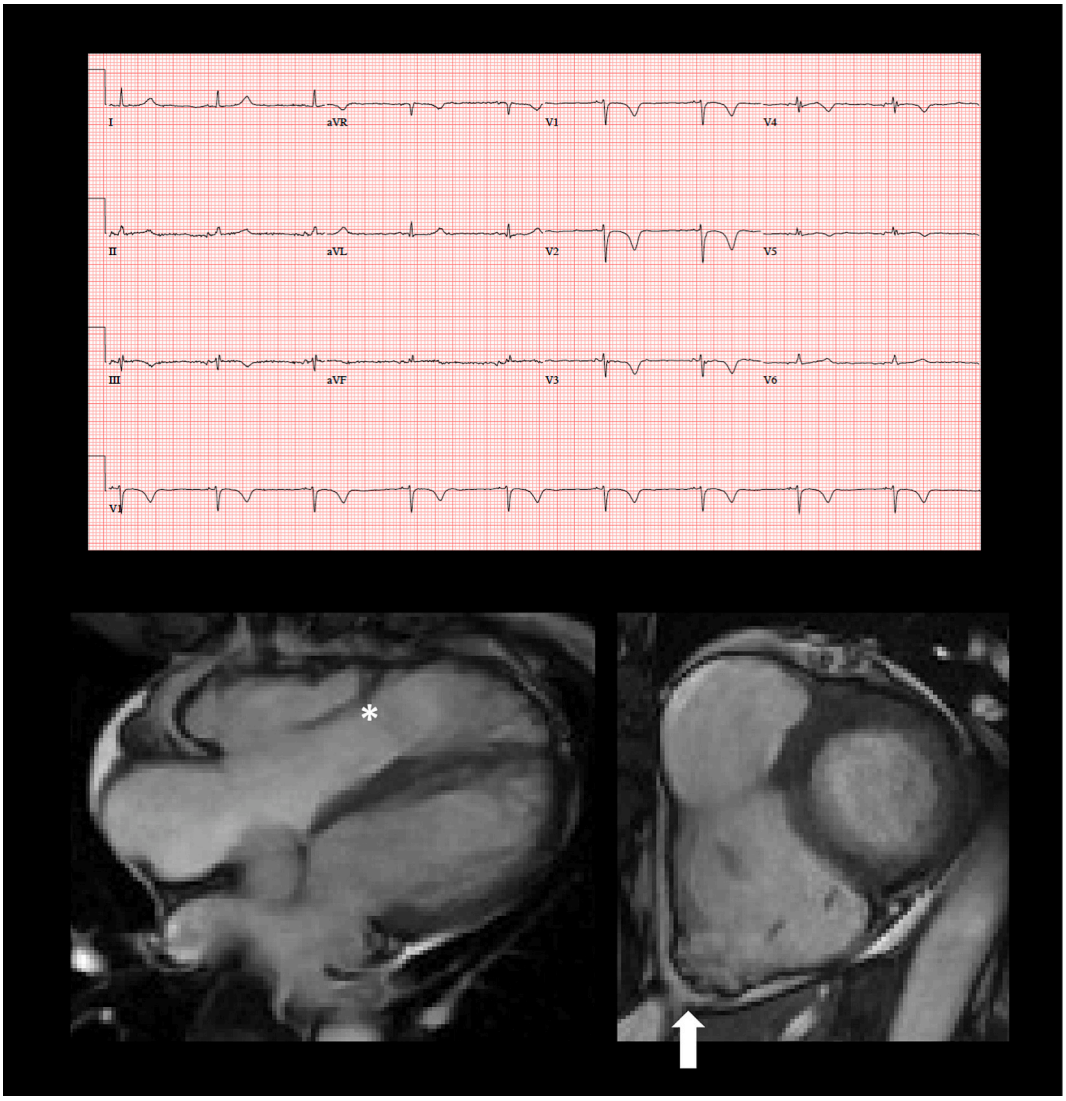


Fig. 6. Plakophilin-2 ARVC phenotype.
Note T wave inversion V1–5 and low amplitude QRS complexes on ECG. Cardiac MRI displays RV dilatation (white asterisk) and focal aneurysmal outpouching of the RV free wall (white arrow).

leads with T wave inversion, fragmented QRS, late potentials, scar burden, PVC burden, NSVT and inducibility of VA.[106,110,127] Existing guidelines consider major and minor risk factors in their relative strength of recommendations for ICD implantation.[106,128]

In 2019, a risk calculator for ARVC was devised from an international multicenter cohort of 529 patients with no history of SCD or sustained VA, with a 27.7 % event rate during follow up.[127] The calculator provides a 5-year estimated risk of sustained VA and is available at www.arvcrisk.com. Subsequently, the model was expanded to provide a 5-year risk of fast VA (>250 bpm), given the imperfect correlation of "any VA" (particularly ICD therapy) with SCD or cardiac arrest.[129] External validation demonstrated improved discrimination compared to consensus-based risk factor algorithms.[130] A second external validation also demonstrated reasonable discrimination, albeit with a tendency to overestimation of risk, but performance was genotype dependent.[131] Best discrimination was observed in *PKP2* variant patients (the dominant genotype), with less impressive performance in genotype-elusive and *DSP* variant patients. *DSP* variant patients appear to have unique risk factors with LV ejection fraction <55 %, frequent PVCs and LGE all associated with severe VAs.[120] Patients with *TMEM43* p.S358L variants represent a uniquely high-risk group, who should all receive primary prevention ICDs (males post puberty, and females by their late 20s to early 30s).[132] A revised risk score incorporating genotype is under development.[133]

PVS inducibility may be useful in intermediate risk patients, with 76 % sensitivity and 68 % specificity for VAs.[134] Inducibility was added to the ARVC risk calculator as an optional risk modifier following this study, though it is not performed often given its invasive nature. Additional studies suggest abnormal deformation on CMRI or echocardiography adds prognostic value.[135,136] Anti-heart and anti-intercalated disc antibodies may also be prognostic, but require further validation.[118]

An approach to risk stratification and ICD indications is depicted in Fig. 7.

Management

Moderation of exercise is important in ARVC given a dose-response relationship with disease progression particularly for *PKP2* patients.[106,128] The extent of restriction is unclear and should be balanced against the physical and mental health benefits of regular exercise. The authors suggest <650 MET-hours per year (~ 30 mins of brisk walking per day in addition to usual daily activities), with evidence of phenotype

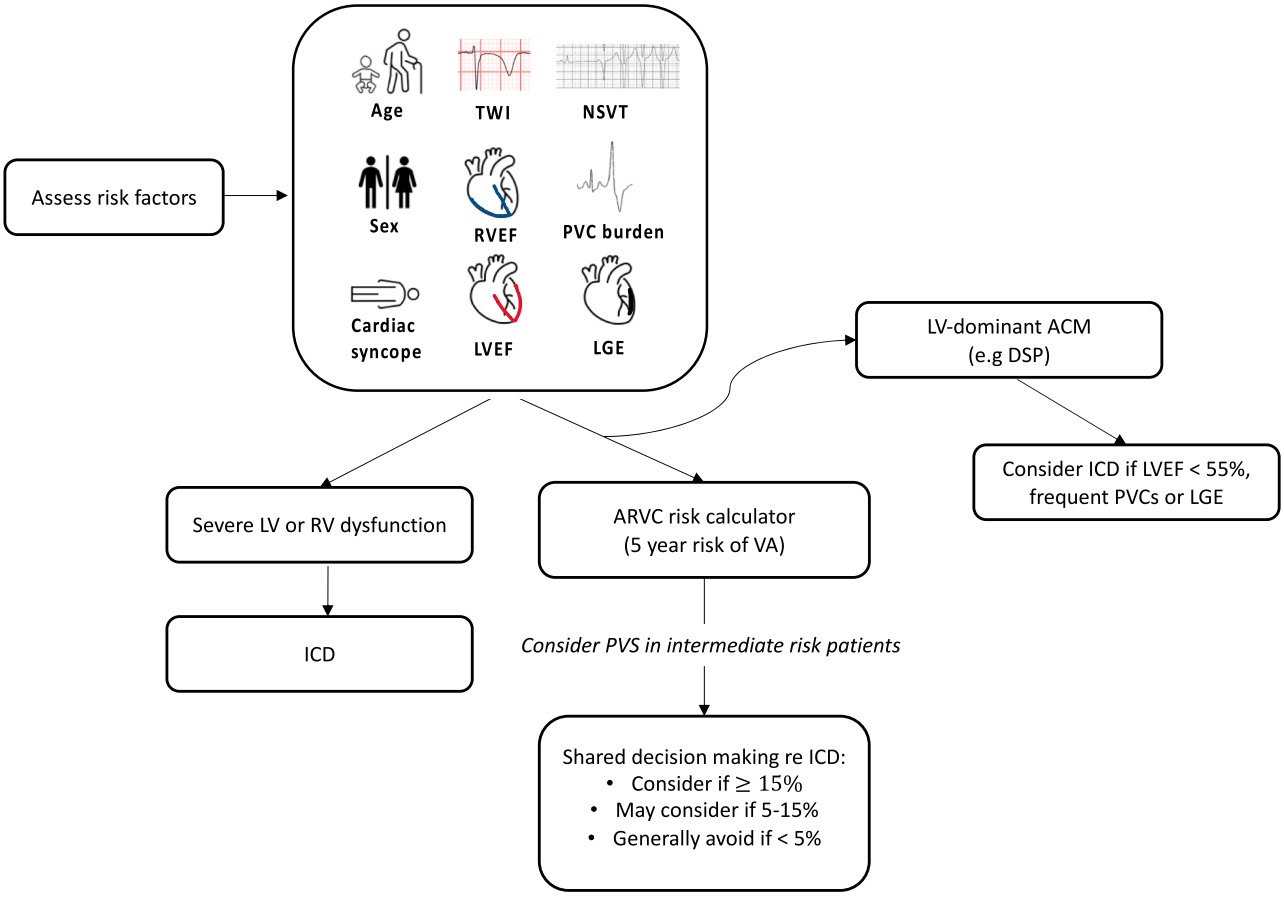


Fig. 7. Approach to risk stratification and management of primary prevention ARVC patients.
TWI = T wave inversion, NSVT = non sustained ventricular tachycardia, RVEF = right ventricular ejection fraction, PVC = premature ventricular contraction, LVEF = left ventricular ejection fraction, LGE = late gadolinium enhancement, LV = left ventricle, RV = right ventricle, ICD = implantable cardioverter-defibrillator, VA = ventricular arrhythmia, PVS = programmed ventricular stimulation, ACM = arrhythmogenic cardiomyopathy, DSP = desmoplakin cardiomyopathy.

progression beyond this threshold.[137] Most of these data applies to *PKP2* patients – it is less clear if LV dominant ACM demonstrates phenotype progression with exercise. There is a paucity of data for pharmacotherapy in ARVC; beta blockers are recommended for VAs given both exercise and isoproterenol are known to induce arrhythmia.[106,128] Other antiarrhythmic medications are prescribed empirically as required.

ICD implantation is recommended for secondary prevention as well as for primary prevention in patients with severe LV or RV dysfunction.[106,128] In other patients, we suggest application of the risk calculator, accepting that the appropriate risk threshold for ICD implantation is not established, and that sustained VA does not equate to SCD risk. Risk thresholds will differ from hypertrophic cardiomyopathy, given most events in HCM are SCD or cardiac arrest, whereas most events in ARVC are ICD treated VAs and sustained VT.[127,138] The authors consider an ICD if estimated 5-year risk exceeds 15 %, may consider an ICD with 5–15 % risk and generally avoid ICD implantation if risk is <5 %. An ICD may need to be considered earlier in the course with LV dominant forms (e.g. *DSP* variant). Shared decision making is important. The subcutaneous ICD appears to be a safe and effective option in ARVC, although the inability to deliver anti tachycardia pacing (particularly for treatment of slower VTs) should be carefully considered.[139] The transvenous ICD may have sensing issues over time due to progression of disease. North American ARVC patients are more likely to receive an ICD than European patients for any given risk level, without an increased risk of VAs in European patients without ICDs.[140] This likely reflects a combination of regional practices and differing patient populations, but remains an interesting observation.

Ablation is an effective option for breakthrough arrhythmia with 70 % of patients VT free at 5 years, allowing for multiple procedures.[141] A combined epicardial and endocardial approach may be required. Cardiac transplant is most often indicated for severe RV dysfunction and heart failure, but may be considered for refractory VA in suitable patients.[106,128] Moving forward, adeno-associated virus mediated restoration of *PKP2* in murine and stem cell models shows promise in rescuing the ARVC phenotype.[142]

Conclusion

The phenotypic spectrum of IA patients includes an expanding population of asymptomatic and low risk patients. Family screening, genetic testing and community awareness have influenced this trend, with AI diagnosis likely to further modify population phenotype. Careful minimalism is required in these patients (e.g. concealed LQTS or CPVT, asymptomatic drug-induced BrS) to avoid harms of therapy. Indeed, critical appraisal of evidence for variant pathogenicity and of diagnostic criteria will reduce unnecessary labelling of healthy individuals with a medical condition. Refined risk stratification will guide management of intermediate risk patients, utilising novel risk factors, genotype, multiparametric risk scores and eventually AI. Appropriate risk thresholds for intervention then need to be further defined. High risk patients have an expanding armamentarium of therapeutic interventions available beyond the ICD, including targeted pharmacotherapy, ablation and LCSD. An ultimate goal is phenotype correction with gene based or molecular therapies, or potentially ablation in the case of BrS – the clinical application of these approaches will almost certainly expand in the not too distant future.

Declaration of competing interest

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed to the manuscript as written. The authors have no conflicts of interest to declare.

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