2. Long QT Syndrome (LQTS) *Expert Consensus Recommendations on* ***LQTS Diagnosis***

1. LQTS is diagnosed:
   a. In the presence of an LQTS risk score ≥3.5 in the absence of a secondary cause for QT prolongation *and/or*
   b. In the presence of an unequivocally pathogenic mutation in one of the LQTS genes *or*
   c. In the presence of a QT interval corrected for heart rate using Bazett's formula (QTc) ≥500 ms in repeated 12-lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation.
2. LQTS can be diagnosed in the presence of a QTc between 480–499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.

Expert Consensus Recommendations on ***LQTS Therapeutic Interventions***

Class I	1. The following lifestyle changes **are recommended** in all patients with a diagnosis of LQTS: a) Avoidance of QT-prolonging drugs (www.qtdrugs.org) b) Identification and correction of electrolyte abnormalities that may occur during diarrhea, vomiting, metabolic conditions or imbalanced diets for weight loss. 2. Beta-blockers **are recommended** for patients with a diagnosis of LQTS who are: a) Asymptomatic with QTc ≥470 ms *and/or* b) Symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF). 3. Left cardiac sympathetic denervation (LCSD) **is recommended** for high-risk patients with a diagnosis of LQTS in whom: a) Implantable cardioverter defibrillator (ICD) therapy is contraindicated or refused *and/or* b) Beta-blockers are either not effective in preventing syncope/arrhythmias, not tolerated, not accepted or contraindicated. 4. ICD implantation **is recommended** for patients with a diagnosis of LQTS who are survivors of a cardiac arrest. 5. All LQTS patients who wish to engage in competitive sports **should be** referred to a clinical expert for evaluation of risk.
Class IIa	6. Beta-blockers **can be useful** in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤470 ms. 7. ICD implantation **can be useful** in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy. 8. LCSD **can be useful** in patients with a diagnosis of LQTS who experience breakthrough events while on therapy with beta-blockers/ICD. 9. Sodium channel blockers **can be useful**, as add-on therapy, for LQT3 patients with a QTc >500 ms who shorten their QTc by >40 ms following an acute oral drug test with one of these compounds.
Class III	10. Except under special circumstances, ICD implantation **is not indicated** in asymptomatic LQTS patients who have not been tried on beta-blocker therapy.

Epidemiology

Patients affected by the long QT syndrome (LQTS) have been identified all over the world and in all ethnic groups. A possible exception is represented by a paucity of cases identified among black Africans and among African-Americans. Among Caucasians, the prevalence of LQTS has been established by a prospective ECG study, complemented by molecular screening, performed on over 44,000 infants at age 15–25 days.[5] LQTS disease-causing mutations were identified in 43% and 29% of the infants with a QTc exceeding 470 and 460 milliseconds (ms), respectively. These findings demonstrate a prevalence of about 1:2000 apparently healthy live births (95% CI, 1:1583 to 1:4350). This prevalence reflects only infants with an abnormally long QTc and does not take into account the significant number of "concealed mutation-positive patients."

Genetic variants

Since 1995, when the first three genes responsible for LQTS were identified,[6–8] molecular genetic studies have revealed a total of 13 genetic forms of congenital LQTS caused by mutations in genes encoding potassium-channel proteins, sodium-channel proteins, calcium channel-related factors, and membrane adaptor proteins. Patients with *LQT1*, *LQT2*, and *LQT3* genotypes with mutations involving *KCNQ1*, *KCNH2*, and *SCN5A* make up over 92% of patients with genetically confirmed LQTS. Up to 15%–20% of patients with LQTS remain genetically elusive.[1] Mutations in auxiliary β-subunits to *KCNQ1* (*KCNE1*, *LQT5*) and *KCNH2* (*KCNE2*, *LQT6*) are infrequent, but they result in clinical phenotypes similar to patients with mutations in their associated α-subunits of *KCNQ1* and *KCNH2*. A recessive form of LQTS, the Jervell and Lange-Nielsen syndrome, involves the same (homozygous) or different (compound heterozygous) *KCNQ1*

mutations from both parents, is more virulent and is associated with deafness. Mutations in *KCNJ2* (*Kir2.1, LQT7*) result in the neurologic musculoskeletal Andersen-Tawil syndrome with associated QT prolongation. The remaining LQTS genotypes (*LQT4* and *LQT8-13*) have each been identified in just a few families or in single individuals.

Common variants in the LQTS genes (single nucleotide polymorphisms [SNPs]), and in some cases unrelated genes, are thought to contribute to the variable penetrance of LQTS within affected family members having the same gene mutation.[9]

Clinical manifestations

The clinical manifestations of LQTS fall under two main categories: the arrhythmic events and the electrocardiographic (ECG) aspects.

The arrhythmic events are due to runs of torsades de pointes VT, which, according to its duration, produces syncope, cardiac arrest, and—when it deteriorates into VF—sudden death. Among untreated patients, the natural history is represented by the occurrence of a number of syncopal episodes, eventually leading to sudden death. Sudden death as a first manifestation represents the main rationale for the treatment of asymptomatic patients. Atrial arrhythmias, specifically atrial fibrillation, are more frequent in LQTS patients compared to controls.[10,11]

The conditions associated with arrhythmic events are, to a large extent, gene-specific,[12] with most arrhythmic events occurring during physical or emotional stress in *LQT1*, at rest or in association with sudden noises in *LQT2* patients, and at rest or during sleep in *LQT3* patients.

The ECG alterations are important and numerous. While the prolongation of the QT interval is the hallmark of LQTS, it is not always present. Indeed, between 10% (*LQT3*) and 37% (*LQT1*) of genotype-positive patients have a QT interval within normal limits at rest.[13] Ventricular repolarization is not only prolonged but often presents bizarre morphologic alterations, some of which tend to be gene-specific.[14] Macroscopic T-wave alternans[15] is perhaps the most distinctive ECG pattern of LQTS, and is a marker of high cardiac electrical instability. Notches on the T-wave are rather typical for *LQT2* and their presence is associated with a higher risk for arrhythmic events.[16] Long sinus pauses are not infrequent among *LQT3* patients.

Diagnosis

The diagnosis of LQTS is mainly based on measurement of the QT interval corrected for heart rate (QTc) using Bazett's formula. When using a prolonged QTc to diagnose LQTS, one must exclude secondary causes of QTc prolongation that can occur with drugs, acquired cardiac conditions, electrolyte imbalance, and unbalanced diets. A scoring system has been established, which takes into account the age of the patient, medical and family history, symptoms, and QTc and provides a probability of the diagnosis of LQTS.[17,18]

Approximately 20%–25% of patients with LQTS confirmed by the presence of an LQTS gene mutation may have a normal range QTc.[13,19] The use of provocative tests for QT measurement during change from a supine to standing position,[20] in the recovery phase of exercise testing,[21,22] or during infusion of epinephrine[23,24] has been proposed - to unmask LQTS patients with normal QTc at resting ECG. These tests may be considered in uncertain cases. However, the clinical use of this test requires more extensive validation.

Risk stratification

Individuals at the extremes of the curve, those at very high or at very low risk, are easy to identify. For the larger group, in the gray area, risk stratification is difficult and can be fraught with errors in either direction. There are genetic and clinical clues that facilitate risk assessment.

Specific genetic variants, such as the Jervell and Lange-Nielsen syndrome[25] and the extremely rare Timothy syndrome (*LQT8*)[26] are highly malignant, manifest with major arrhythmic events very early, and respond poorly to therapies. Within the most common genetic groups, specific locations, types of mutations, and degree of mutation dysfunction are associated with different risks. Mutations in the cytoplasmic loops of *LQT1*,[27,28] *LQT1* mutations with dominant-negative ion current effects,[29] and mutations in the pore region of *LQT2*[29,30] are associated with higher risk, and the same is true even for some specific mutations with an apparently mild electrophysiological effect.[31] By contrast, mutations in the C-terminal region tend to be associated with a mild phenotype.[32]

Clinically, there are several patterns and groups associated with differential risk. High risk is present whenever QTc >500 ms[13,33] and becomes extremely high whenever QTc >600 ms. Patients with a diagnosis of LQTS who are identified by genetic testing as having two unequivocally pathogenic variants and a QTc >500 ms (including homozygous mutations as seen in patients with Jervell and Lange-Nielsen syndrome) are also at high risk, in particular when they are symptomatic. The presence of overt T-wave alternans, especially when evident despite proper therapy, is a direct sign of electrical instability and calls for preventive measures. Patients with syncope or cardiac arrest before age 7 have a higher probability of recurrence of arrhythmic events while on beta-blockers.[34] Patients who have syncope or cardiac arrest in the first year of life are at high risk for lethal events and may not be fully protected by the traditional therapies.[35,36] Patients who suffer arrhythmic events despite being on full medical therapy are at higher risk.

By contrast, it also is possible to identify patients at lower risk. Concealed mutation-positive patients are at low, but not zero, risk for spontaneous arrhythmic events. The risk for an arrhythmic event in this group has been estimated around 10% between birth and age 40 in the absence of therapy.[13] A major risk factor for patients with asymptomatic genetically diagnosed LQTS comes from drugs that block the I_{Kr} current and by conditions that lower their plasma potassium level.

Among genotyped patients, *LQT1* males, who are asymptomatic at a young age,[37] are at low risk of becoming symptomatic later on in life, while females, and especially *LQT2* females, remain at risk even after age 40.

Management

The aggressiveness to manage patients with LQTS is related in part to the risk for life-threatening arrhythmic events, as highlighted in Section 2.5. The AHA/ACC/ESC Guidelines for LQTS Therapy, published in 2006, are still relevant in 2012.[2] Life-style modifications such as avoidance of strenuous exercise, especially swimming, without supervision in *LQT1* patients, reduction in exposure to abrupt loud noises (alarm clock, phone ringing, etc) in *LQT2* patients, and avoidance of drugs that prolong QT interval in all LQTS patients, should be routine. Participation of LQTS patients in competitive sports is still a matter of debate among the experts. Recently available retrospective data suggest that participation in competitive sports of some patients with LQTS may be safe.[38] Based on these data,[38] which still need confirmation, low-risk patients, with genetically confirmed LQTS but with borderline QTc prolongation, no history of cardiac symptoms, and no family history of multiple sudden cardiac deaths (SCD), may be allowed to participate in competitive sports in special cases after full clinical evaluation, utilization of appropriate LQTS therapy and when competitive activity is performed where automated external defibrillators are available and personnel trained in basic life support.[38] This applies especially to patients genotyped as non-LQT1. In all patients with a high perceived risk (see Section 2.5) and in patients with exercise-induced symptoms, competitive sport should be avoided. Specific therapies available for patients with LQTS and indications for their use are described below.

Beta-blockers

Beta-blockers are clinically indicated in LQTS, including those with a genetic diagnosis and normal QTc, unless there is a contraindication such as active asthma.[34,35] Presently, there is no substantial evidence to favor cardioselective or noncardioselective beta-blockers; however, the former is preferred in those patients who suffer from asthma. Long-acting beta-blockers such as nadolol or sustained-release propranolol should be preferred as these medications can be given once or twice a day with avoidance of wide fluctuations in blood levels. Recent data also suggest that, particularly in symptomatic patients, these drugs may perform better than, for example, metoprolol.[39] While studies are not available to define the most effective dosage, full dosing for age and weight, if tolerated, is recommended. Abrupt discontinuation of beta-blockers should be avoided as this may increase the risk of exacerbation.

Implantable Cardioverter-Defibrillator (ICD) (Figure 1)

ICD therapy is indicated in LQTS patients who are resuscitated from cardiac arrest.[40] ICD is often favored in patients with LQTS-related syncope who also receive beta-blockers.[41] Prophylactic ICD therapy should be considered in very-high-risk patients such as symptomatic patients with two or more gene mutations, including those with the Jervell and Lange-Nielsen variant with congenital deafness.[25] ICD therapy has life-time implications. Complications are not infrequent, especially in the younger age group, and risk/benefit considerations should be carefully considered before initiating this invasive therapy.[42,43] Accordingly, *LQT1* patients who experience a cardiac arrest while not receiving beta-blockers may only be treated with beta-blockers or with LCSD (see below) in settings when the implant of an ICD is likely to be associated with high risk, such as in infants and pediatric patients.[44,45] LQTS-related sudden death in one family member is not an indication for ICD in surviving affected family members unless they have an individual profile of high risk for arrhythmic events.[46]

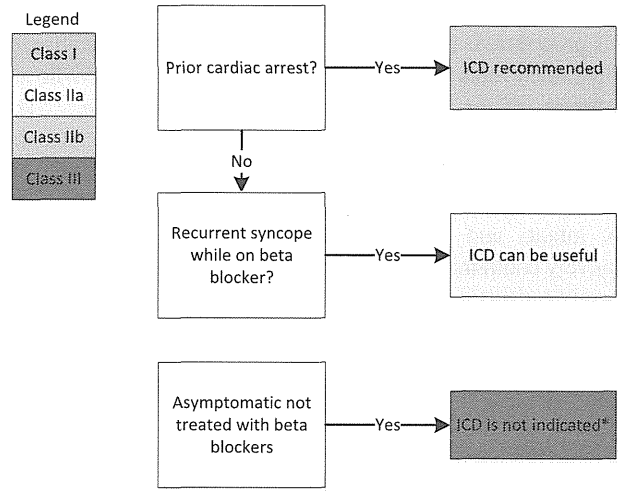

Figure 1 Consensus recommendations for ICDs in patients diagnosed with long QT syndrome.

Considering the potential complications associated with the implantation of an ICD in young individuals, we recommend caution when using a device in asymptomatic patients. We suggest that ICD therapy not be used as first-line therapy in an asymptomatic LQTS patient; beta-blockers remain the first-line therapy in LQTS patients. However, an ICD may be considered in those patients who are deemed to be at very high risk, especially those with a contraindication to beta-blocker therapy. A decision to have an ICD implanted should be made only after a careful consideration of (1) risk of sudden death; (2) the short- and long-term risks of ICD implantation; and (3) values and preferences of the patient. The physician must discuss the risks and benefits of ICD therapy with the patient, and patient's values and preferences are important in this decision.

Whenever ICD therapy is chosen, thoughtful programming (in particular to prevent inappropriate shocks) is pertinent and usually requires a VF-only zone, with a cutoff rate greater than 220–240 bpm.

Left Cardiac Sympathetic Denervation (LCSD)
This procedure is often effective in reducing the probability for arrhythmic events in high-risk patients, including those who are intolerant of or refractory to beta-blockers alone.[47] The procedure can be done surgically through a left supraclavicular incision[48–50] or as a minimally invasive procedure in experienced centers.[51] This procedure is frequently used in very-high-risk infants and children in whom ICD therapy may be relatively contraindicated due to the physical size of the patient, in some patients with syncope despite beta-blocker therapy, and in patients with asthma or who are intolerant of beta-blockers.

Other therapies: Gene-specific LQTS therapies including oral mexiletine,[52] flecainide,[53] and ranolazine[54] have been utilized to a limited extent in high-risk LQTS patients refractory to beta-blockers or in patients with recurrent events despite ICD and LCSD therapies. The use of these sodium channel blockers has generally been limited to LQT3 patients. In brief, the use of these agents is usually carried out on an observational trial basis, with, occasionally, some dramatic results for individual subjects. Follow-up experience with these therapies is limited. No general recommendations can be made at this time in the use of gene-specific therapies.

3. Brugada Syndrome (BrS) *Expert Consensus Recommendations on* ***Brugada Syndrome Diagnosis***

1. BrS *is diagnosed* in patients with ST-segment elevation with type 1 morphology ≥2 mm in ≥1 lead among the right precordial leads V_1, V_2, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously *or* after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.
2. BrS ***is diagnosed*** in patients with type 2 or type 3 ST-segment elevation in ≥1 lead among the right precordial leads V_1, V_2 positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a **type I** ECG morphology.

Expert Consensus Recommendations on ***Brugada Syndrome Therapeutic Interventions***

Class I	1. The following lifestyle changes ***are recommended*** in all patients with diagnosis of BrS: a) Avoidance of drugs that may induce or aggravate ST-segment elevation in right precordial leads (for example, visit Brugadadrugs.org), b) Avoidance of excessive alcohol intake. c) Immediate treatment of fever with antipyretic drugs. 2. ICD implantation ***is recommended*** in patients with a diagnosis of BrS who: a) Are survivors of a cardiac arrest and/or b) Have documented spontaneous sustained VT with or without syncope.
Class IIa	3. ICD implantation ***can be useful*** in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias. 4. Quinidine ***can be useful*** in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24 hours. 5. Quinidine ***can be useful*** in patients with a diagnosis of BrS: a) Who qualify for an ICD but present a contraindication to the ICD or refuse it *and/or* b) Have a history of documented supraventricular arrhythmias that require treatment. 6. Isoproterenol infusion **can be useful** in suppressing arrhythmic storms in BrS patients.
Class IIb	7. ICD implantation ***may be considered*** in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients). 8. Quinidine ***may be considered*** in asymptomatic patients with a diagnosis of BrS with a spontaneous **type I** ECG. 9. Catheter ablation ***may be considered*** in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks.
Class III	10. ICD implantation **is not indicated** in asymptomatic BrS patients with a drug-induced **type I** ECG and on the basis of a family history of SCD alone.

Epidemiology

No precise data are available on the epidemiology of BrS. However, its prevalence is much higher in Asian and Southeast Asian countries, especially Thailand, Philippines and Japan, reaching 0.5–1 per 1000.[55] In some part of Asia, BrS seems to be the most common cause of natural death in men younger than 50 years. BrS is known as Lai Tai (Thailand), Bangungut (Philippines), and Pokkuri (Japan). The reason for this higher prevalence in Asia is unknown. However, it has been speculated that it may be in part related to an Asian-specific sequence in the promoter region of *SCN5A*.[56]

BrS is 8–10 times more prevalent in males than in females.[55] The presence of a more prominent transient outward current (I_{to}) in males may contribute to the male predominance of the syndrome.[57] Higher testosterone levels also may have a significant role in the male predominance.[58]

Genetic basis

Inheritance of BrS occurs via an autosomal dominant mode of transmission. Twelve responsible genes have been reported so far.[59] In all 12 genotypes, either a decrease in the inward sodium or calcium current or an increase in one of the outward potassium currents has been shown to be associated with the BrS phenotype. Genetic abnormalities are found in one third of genotyped BrS patients. *SCN5A*, the gene that encodes for the α subunit of the cardiac sodium channel, account for less than 30% of clinically diagnosed BrS patients. Genetic testing is not recommended in the absence of a diagnostic ECG. Genetic testing may be useful otherwise and is recommended for family members of a successfully genotyped proband.[1]

Clinical manifestations

Symptoms associated with BrS include:

1. VF or aborted SCD (more often at night than during the day)
2. Syncope
3. Nocturnal agonal respiration
4. Palpitations
5. Chest discomfort

These symptoms often occur during rest or sleep, during a febrile state or with vagotonic conditions, but rarely during exercise. The syndrome typically manifests during adulthood, with a mean age of sudden death of 41 ± 15 years.[55] BrS is associated with no clearly apparent structural heart diseases; however, several clinical studies have reported mild right and left ventricular structural abnormalities.[60,61]

Diagnosis

Diagnostic criteria from the Report of the Second Consensus Conference in 2005 have been used for the diagnosis of BrS.[55] Since some clinical studies on the sensitivity and the specificity of the ECG diagnosis of BrS have been reported, new diagnostic criteria of BrS are proposed here. BrS is definitively diagnosed when a **type I** ST-segment elevation is observed either spontaneously or after intravenous administration of a sodium channel blocking agent (ajmaline, flecainide, pilsicainide, or procainamide) in at least one right precordial lead (V_1 and V_2),[62] which are placed in a standard or a superior position (up to the 2nd intercostal space).[63,64]

The differential diagnosis includes a number of diseases and conditions that can lead to Brugada-like ECG abnormality, including atypical right bundle branch block (RBBB), left ventricular hypertrophy, early repolarization, acute pericarditis, acute myocardial ischemia or infarction, acute stroke, pulmonary embolism, Prinzmetal angina, dissecting aortic aneurysm, various central and autonomic nervous system abnormalities, Duchenne muscular dystrophy, thiamine deficiency, hyperkalemia, hypercalcemia, arrhythmogenic right ventricular cardiomyopathy (ARVC), pectus excavatum, hypothermia, and mechanical compression of the right ventricular outflow tract (RVOT) as occurs in mediastinal tumor or hemopericardium.[55,65]

Many subjects displaying a **type I** ECG, spontaneous or drug-induced, are asymptomatic. In asymptomatic patients, the following findings are considered supportive for the diagnosis of BrS:

1. Attenuation of ST-segment elevation at peak of exercise stress test followed by its appearance during recovery phase.[66,67] It should be noted, however, that in selected BrS patients, usually *SCN5A* mutation-positive patients, it has been observed that ST-segment elevation might become more evident during exercise.[66]
2. Presence of first-degree atrioventricular (AV) block and left-axis deviation of the QRS
3. Presence of atrial fibrillation
4. Signal-averaged ECG; late potentials[68]
5. Fragmented QRS[69,70]
6. ST-T alternans, spontaneous left bundle branch block (LBBB) ventricular premature beats (VPB) during prolonged ECG recording
7. Ventricular effective refractory period (ERP) <200 ms recorded during electrophysiological study (EPS)[70,71] and HV interval >60 ms
8. Absence of structural heart disease including myocardial ischemia

Prognosis and risk stratification

Since the first reporting, the reported annual rate of events has decreased.[70,72–78] The change probably reflects the inherent bias during the first years following the description of a novel disease, in which particularly severe forms of the disease are most likely to be diagnosed.

Several clinical variables have been demonstrated to predict a worse outcome in patients with BrS. Little controversy exists on the high risk of recurrence of cardiac arrest among patients who have survived a first VF. There is general agreement that these patients should be protected with an ICD, irrespective of the presence of other risk factors.[55]

Most studies have concurrently agreed on the evidence that the presence of syncopal episodes in patients with a spontaneous **type I** ECG at baseline (without conditions known to unmask the signature sign, i.e., drugs and fever) have high risk of cardiac arrhythmic events at follow-up.[70,72–80]

Among other risk stratification indicators, the presence of fragmented QRS[69,70] and an effective refractory period below <200 ms[70,71] have been recently proposed. Male gender has consistently been shown to be associated with more arrhythmic events.[81] Spontaneous AF, which can appear in 10% to 53% of

cases, has been shown to have prognostic significance and has been associated with a higher incidence of syncopal episodes and documented VF.[82,83]

The risk of lethal or near-lethal arrhythmic episodes among previously asymptomatic patients with BrS varies according to the series: 8% event rate at 33 ± 39 months of follow-up reported by Brugada et al[73]; 6% event rate at 34 ± 44 months by Priori et al[70]; 1% event rate after 40 ± 50 months and 30 ± 21 months of follow-up, respectively, by Eckardt et al[76] and Giustetto et al,[84] and, finally, Probst et al[85] reported a 1.5% event rate at 31 months of follow-up.

Although large registries agree that EPS inducibility is greatest among BrS patients with previous sudden death or syncope,[75,76] there is no consensus on the value of the EPS in predicting outcome. The results published by Brugada et al[73] indicate that inducibility during EPS is an independent predictor for arrhythmic events, and Giustetto et al[84] stressed the negative predictive value (none of the patients with a negative EPS developed arrhythmic events vs 15% of patients with a positive EPS result during 30 ± 21 months of follow-up), while the rest of the registries failed to demonstrate this.[75,76,85] The PRELUDE (PRogrammed ELectrical stimuLation preDictive valuE) registry failed to support the view that lack of inducibility has negative predictive value in BrS.[70] The FINGER (France, Italy, Netherlands, GERmany) registry, the largest series of BrS patients published so far, found that inducibility of sustained ventricular arrhythmias was significantly associated with a shorter time to first arrhythmic event in the univariate analysis, but in the multivariate analysis, inducibility did not predict arrhythmic events.[85] These results were confirmed in a recent prospective study in previously asymptomatic patients.[70] Neither a positive family history of sudden death nor a *SCN5A* mutation has proven to be a risk marker in any of the large studies.[75,76,81] However, some specific types of mutations, such as those that result in a truncated protein, or some common SNPs, might have prognostic significance.[86–89]

Therapeutic options and recommendations for BrS patients

ICD (Figure 2)

To date, the only proven effective therapeutic strategy for the prevention of SCD in BrS patients is the ICD. It is important to remark that ICDs are not free from several disadvantages, especially in the group of patients who are active young individuals, who will require multiple device replacements during their life-time. Some series have reported low rates of appropriate shocks (8%–15%, median follow-up 45 months) and high rates of complications, mainly inappropriate shocks (20%–36% at 21–47 months follow-up).[2,90,91] Asymptomatic BrS patients do not qualify for an ICD as their risk for life-threatening events is very low.[59] In this group of patients, individual assessment of associated risk factors (gender, age, baseline ECG, inducibility) should be performed.

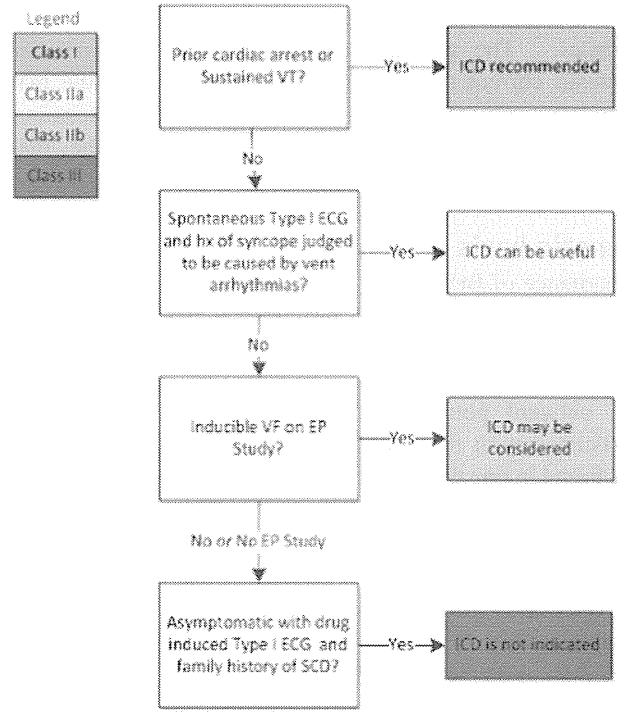

Figure 2 Consensus recommendations for ICDs in patients diagnosed with Brugada syndrome.

Pharmacological Treatment in BrS

With the objective of rebalancing the ionic currents affected in BrS during the cardiac action potential, drugs that inhibit the transient outward potassium current (I_{to}) or increase the sodium$^+$ and calcium currents have been tested in BrS:

- Isoproterenol (which increases the L-type calcium current), has proved to be useful for treatment of electrical storm in BrS,[92] but controlled data on its therapeutic role are not available.
- Quinidine, a Class Ia antiarrhythmic drug with I_{to} and I_{Kr} blocker effects, has been shown to prevent induction of VF and suppress spontaneous ventricular arrhythmias in a clinical setting. Quinidine is currently being used in (1) patients with ICD and multiple shocks; (2) cases in which ICD implantation is contraindicated; or (3) for the treatment of supraventricular arrhythmias.[93] It has been suggested that quinidine could also be useful in children with BrS, as a bridge to ICD or as an alternative to it.[94,95] Randomized studies on the use of quinidine, however, have not been performed.

Radiofrequency Catheter Ablation in BrS

After the demonstration that VF events were triggered by ventricular ectopy of similar morphology, radiofrequency ablation of ventricular ectopy has been postulated as a therapeutic approach in BrS patients. Few anecdotal cases in high-risk BrS implanted with an ICD have shown no short-term recurrence of VF, syncope or SCD.[96–99] Nademanee et al[100] have presented the first series showing that electrical

epicardial substrate ablation in the RVOT can prevent VF inducibility in a high-risk population. However, randomized data on the effect of catheter ablation on spontaneous arrhythmic events are lacking.

4. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) *Expert Consensus Recommendations on CPVT Diagnosis*

1. CPVT ***is diagnosed*** in the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats or VT in an individual <40 years of age.
2. CPVT ***is diagnosed*** in patients (index case or family member) who have a pathogenic mutation.
3. CPVT ***is diagnosed*** in family members of a CPVT index case with a normal heart who manifest exercise-induced premature ventricular contractions (PVCs) or bidirectional/polymorphic VT.
4. CPVT ***can be diagnosed*** in the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats or VT in an individual >40 years of age.

Expert Consensus Recommendations on ***CPVT Therapeutic Interventions***

Class I	1. The following lifestyle changes ***are recommended*** in all patients with diagnosis of CPVT: a) Limit/avoid competitive sports, b) Limit/avoid strenuous exercise, c) Limit exposure to stressful environments. 2. Beta-blockers ***are recommended*** in all symptomatic patients with a diagnosis of CPVT. 3. ICD implantation ***is recommended*** in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope or polymorphic/bidirectional VT despite optimal medical management, and/or LCSD.
Class IIa	4. Flecainide ***can be a useful*** addition to beta-blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers. 5. Beta-blockers ***can be useful*** in carriers of a pathogenic CPVT mutation without clinical manifestations of CPVT (concealed mutation-positive patients).
Class IIb	6. LCSD ***may be considered*** in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT/several appropriate ICD shocks while on beta-blockers and in patients who are intolerant or with contraindication to beta-blockers.
Class III	7. ICD as a standalone therapy ***is not indicated*** in an asymptomatic patient with a diagnosis of CPVT. 8. Programmed electrical stimulation ***is not indicated*** in CPVT patients.

Introduction

CPVT is a rare arrhythmogenic disorder characterized by adrenergic-induced bidirectional and polymorphic VT.[101,102]

Epidemiology

The prevalence of the disease could be as high as 0.1:1000. However, the number is a rough estimate and is not derived from a systematic assessment in the population. Given that the resting ECG is normal in CPVT patients and cardiac imaging is also unremarkable, it is not easy to evaluate the prevalence of the disease in the population. As a result, the real prevalence of the disease is unknown.

Genetic variants

Two types of CPVT have been identified: an autosomal dominant form, due to mutations in the gene encoding for the cardiac ryanodine receptor (*RyR2*)[103,104] known as CPVT1, and a less common autosomal recessive form, resulting from mutations in the gene for cardiac calsequestrin (*CASQ2*),[105,106] now known as CPVT2. Altogether mutations in *RyR2*[107] and *CASQ2* are found in only 60% of the CPVT patients,[1] suggesting that other genes may be involved in CPVT.

Mutations in the *KCNJ2* gene encoding the cardiac inward rectifier K channel are known to cause the Andersen-Tawil syndrome, also known as *LQT7*. Mutations in this gene have recently been found in patients with adrenergically mediated bidirectional VT. It is currently unknown whether these cases should be regarded as variants of *LQT7* that phenocopy CPVT or whether specific mutations in the *KCNJ2* gene cause a novel variant of CPVT.[108] In 2007 a consanguineous Arab family with an early-onset lethal form of recessive CPVT was linked to a new locus on chromosome 7p1422-p22; until now, however, no gene has been identified.[109]

Mutations in the *Ank2* gene are known to cause LQT4. Recently, mutations in this gene have also been described in a patient with bidirectional VT.[110] In analogy to the discussion about the mutations in the *KCNJ2* gene, it is unclear whether *Ank2* should be regarded as a CPVT gene or whether *LQT4* may phenocopy CPVT. Three mutations with recessive inheritance were recently identified in two families with cardiac arrhythmias and sudden death.[111] However, more data are required before it becomes established whether *TRDN*, which encodes triadin, is a gene for this novel form of recessive CPVT. Finally, a mutation in the *CALM1* gene encoding for calmodulin kinase has been observed co-segregating with adrenergically mediated arrhythmias in one large family, and a second mutation in the same gene was found in a sporadic patient with CPVT diagnosis.[112]

Clinical manifestations

The first clinical episode often manifests in the first or second decade of life and is usually prompted by physical activity or emotional stress.[102,113,114] When the fainting episode is associated with seizure-like activity it may be attributed to a neurologic diagnosis, thus causing delay in the diagnosis of CPVT. A family history of exercise-related syncope, seizure or sudden death is reported in 30% of the patients and may help directing diagnosis toward CPVT.

Diagnosis

CPVT patients present a normal resting ECG, occasionally with a lower than normal heart rate.[102,115] When patients start exercising ventricular ectopy develops, increasing in complexity as the heart rate increases. Indeed, initially monomorphic VPBs appear and they may be followed by polymorphic VPBs and bidirectional or polymorphic VT. Holter monitoring, exercise stress test or implantable loop recorders are therefore pivotal investigations for establishing the diagnosis of CPVT. Adrenergically mediated atrial arrhythmias (premature atrial beats, atrial tachycardias and atrial fibrillation) are also common manifestations of the disease.

Programmed electrical stimulation has no diagnostic or prognostic value in CPVT as either bidirectional or polymorphic VT is not inducible. Drug challenge with epinephrine or isoproterenol may elicit arrhythmias and is useful in patients who are unable to exercise (for example, after resuscitation or because of young age). Exercise-induced atrial arrhythmias, including atrial fibrillation, are part of the clinical phenotype of CPVT.[116,117]

Risk stratification

There are not many indicators of risk of adverse outcome in CPVT. The occurrence of cardiac arrest before diagnosis, but not the occurrence of syncope, is associated with higher risk of arrhythmic episodes at follow-up.[115] Similarly, diagnosis in childhood is a predictor of adverse outcome. After diagnosis, the lack of beta-blocker therapy and the use of beta-blockers other than nadolol are independent predictors for arrhythmic events.[115] Also, the persistence of complex ectopy in exercise tests is a marker for worse outcome.[115] Initial evidence of genotype–phenotype correlations are emerging in CPVT patients. Relatives with a RYR2 mutation in the C-terminal channel-forming domain showed an increased odds of nonsustained VT (odds ratio, 4.1; 95% CI, 1.5–11.5; $P = .007$) compared with N-terminal domain.[118] In the recessive form of CPVT, affected individuals carry homozygous or compound heterozygous mutations; the carriers of a single *CASQ2* mutation are healthy.[119] Nevertheless, several clinical investigations suggested that a single *CASQ2* mutation could represent a potential susceptibility factor for ventricular arrhythmias.[120–122]

Management

Beta-blockers

The first-line therapeutic option for patients with CPVT is beta-blockers without intrinsic sympathomimetic activity combined with exercise restriction.

Nadolol, being a long-acting drug, is preferred for prophylactic therapy and has been found to be clinically effective. The dosage used is usually high (1–2 mg/kg) with the necessity of a faultless compliance to the therapy. The annual rate of arrhythmic events on beta-blockers ranges between 11% per year to 3% per year (27% over 8 years).[115] Larger groups of CPVT probands are needed to address the issue of beta-blocker efficacy in CPVT. As nadolol is not available in several countries it may be suggested that other nonselective beta-blockers are equally effective (i.e., propranolol). Holter recordings and exercise tests should be repeated periodically to assure that the degree of sinus tachycardia that precedes onset of arrhythmias is known so that in daily life it can be avoided as much as possible. Moreover, to prevent noncompliance-related SCD, it is crucial to alert the patients of the importance of adherence to therapy to preempt life-threatening events.

Asymptomatic VPBs usually persist on Holter recordings (and exercise tests) with an unmodified threshold of appearance. Complete suppression of asymptomatic VPBs does not seem to be mandatory. The presence of couplets or more successive VPBs during exercise testing seems significantly associated with future arrhythmic events, suggesting intensifying the treatment in these patients.[115]

ICD

An ICD should be considered in CPVT patients who do not respond to an optimal medical management and when LCSD is not possible. All efforts should be made to ensure that patients with an ICD have also an optimal medical treatment.[123,124] In patients who have experienced an aborted cardiac arrest before initiation of therapy, beta-blockers, or beta-blockers and flecainide, should be started and ICD implanted.

Implantation of an ICD is a technical challenge in pediatric patients, and problems such as inappropriate shocks, proarrhythmic effects of the ICD and the need for a life-time protection requiring multiple reinterventions should be

addressed when the decision is taken. Painful shocks by ICD can increase the sympathetic tone and trigger further arrhythmias leading to a malignant cycle of ICD shocks and even death. Because of this the ICD should be programmed with long delays before shock delivery and high cutoff rates.

Verapamil

Verapamil has been shown to be beneficial in some CPVT patients by reducing the ventricular arrhythmia burden on top of beta-blocker therapy during a short-term follow-up period,[125,126] though its long-term effect remains controversial.

Flecainide

Flecainide reduces significantly the ventricular arrhythmia burden in a limited number of CPVT patients.[127,128] A larger study is required to fully elucidate the effect of the drug, but flecainide should now be regarded as the first addition to beta-blockers when control of arrhythmias seems incomplete.

Left Cardiac Sympathetic Denervation (LCSD)

Small series have been published reporting significant results of LCSD on arrhythmic events.[50,51,129–133] Although the short-term results seem encouraging, more data with a long-term follow-up are needed. LCSD is not available in many centers all over the world as it requires a very well-trained surgeon and dedicated techniques. Therefore, the place of LCSD in the therapeutic management of CPVT patients resistant to optimal pharmacological therapy remains to be proven but seems very promising.

Catheter Ablation

Catheter ablation of the bidirectional VPBs that trigger VF may become an adjunctive therapy in patients with refractory CPVT. However, the published experience is very limited and therefore is not discussed in the recommendation.[134]

Evaluation of family members

Family screening (siblings and parents) by clinical evaluation and genetic testing (when a mutation has been detected) is mandatory to identify undiagnosed patients and asymptomatic carriers who are at risk of arrhythmic events and should be treated. It is suggested that genetically positive family members should receive beta-blockers even after a negative exercise test.[115,118]

5. Short QT Syndrome (SQTS) *Expert Consensus Recommendations on* ***Short QT Syndrome Diagnosis***

1. SQTS ***is diagnosed*** in the presence of a QTc ≤330 ms.
2. SQTS ***can be diagnosed*** in the presence of a QTc <360 ms and one or more of the following: a pathogenic mutation, family history of SQTS, family history of sudden death at age ≤40, survival of a VT/VF episode in the absence of heart disease.

Expert Consensus Recommendations on ***Short QT Syndrome Therapeutic Interventions***

Class I	1. ICD implantation ***is recommended*** in symptomatic patients with a diagnosis of SQTS who a. Are survivors of a cardiac arrest *and/or* b. Have documented spontaneous sustained VT with or without syncope.
Class IIb	2. ICD implantation ***may be considered*** in asymptomatic patients with a diagnosis of SQTS and a family history of SCD. 3. Quinidine ***may be considered*** in asymptomatic patients with a diagnosis of SQTS and a family history of SCD. 4. Sotalol ***may be considered*** in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.

Epidemiology and genetic bases

One of the rarer cardiac channelopathies is the short QT syndrome (SQTS). As the terminology implies the signature sign of this disease entity is a short QT interval. Gussak et al[135] were the first to suggest an association with atrial and ventricular fibrillation (i.e., SCD). With more case reports halfway through the first decade of this century this association became clearer,[136–138] but more than 10 years after the first description, the largest series described contain at most 60 cases, underlining the fact that the disease entity is rare indeed.[139] Until now DNA variants in 3 potassium channel genes (*KCNH2, KCNQ1, KCNJ2*) have been described to associate with SQTS[137,138,140]; interestingly mutations in these three genes are also linked with three variants of LQTS (*LQT1, LQT2,* and *LQT7,* respectively). While mutations found in the three genes in LQTS patients cause a loss of the protein function, the mutations found in SQTS patients cause a gain of function. Mutations in the genes encoding alpha- and beta-subunits of the L-type cardiac calcium channel (*CACNA1C* and *CACNB2*) have been identified in patients with short QT interval. Often patients with mutations in these genes present a type I Brugada syndrome ECG either spontaneously or in response to drug challenge with Class I antiarrhythmic agents.[141]

Clinical diagnosis

The diagnosis of SQTS is still a matter of debate. A major point of discussion in the definition of diagnostic criteria is represented by the cutoff value at the lower end of the QTc that should be used to diagnose the disease. QTc should be calculated avoiding tachycardia and bradycardia to prevent

the use Bazett's formula at rates in which its correction is not linear and may lead to underestimation or overestimation of QTc values.

The proposed diagnostic scoring scheme that has been put forward by Gollob et al,[142] has not been accepted unanimously.[143,144] In analogy to the Schwartz score for the LQTS the score uses a number of clinical criteria with a gradual score for the QTc interval and a significant role for clinical and genetic criteria.

This group has reached a consensus that a cutoff value ≤330 ms should be used for the diagnosis. Gollob et al[142] in their "diagnostic score" also used 330 ms as the cutoff with the heaviest weight. This QTc value is well below the 2 standard deviations (±350 ms in males and ±365 ms in females).[145–147] In the Finnish cohort reported by Anttonen et al[148] only 0.4% of individuals had a QTc <340 ms and 0.1% of the population had a QTc <320 ms.

Risk stratification and treatment

Therapeutic management using ICDs is undisputed in SQTS patients who have experienced sustained VT/VF episodes.[139] Appropriate programming of the ICD is needed to prevent inappropriate ICD shocks from T-wave oversensing due to tall T waves. Quinidine seems an effective alternative due to the QT-prolonging action. However, it has been reported that the QTc-prolonging effect of quinidine is particularly prominent in patients with a *KCNH2* mutation (SQTS **type II**).[139,149] Other drugs, including Class III drugs, such as sotalol, are not effective in prolonging the QTc interval in SQT1 patients[149] but may be effective in the other subtypes.

The optimal strategy for primary prevention of cardiac arrest in SQTS is not clear given the lack of independent risk factors, including syncope, for cardiac arrest. Although intuitively it might seem reasonable to suggest that patients with the shortest QTc values are at highest risk, clinical data do not support this hypothesis.[139] However, in a combined symptomatic and asymptomatic group (QTc <360 ms) QTc was the only risk factor for arrhythmic events.[139]

Quinidine might have a role in primary prevention of cardiac arrest, but data are very preliminary and require confirmation in larger cohorts of patients. There are certainly no data to support the implantation of an ICD in asymptomatic patients with SQTS. A study from Finland revealed that individuals with short (<340 ms) and very short (<320 ms) QTc values had no documented arrhythmic events after an average follow-up of 29 years.[148] Data from Japan and the US seem to support these findings.[145,150] An ICD might be considered in SQTS patients with a strong family history of SCD and evidence for abbreviated QTc in at least some of the victims.

6. Early Repolarization (ER) *Expert Consensus Recommendations on* ***Early Repolarization Diagnosis***

1. ER ***syndrome is diagnosed*** in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT
2. ER syndrome ***can be diagnosed*** in an SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
3. ER pattern ***can be diagnosed*** in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG

Expert Consensus Recommendations on ***Early Repolarization Therapeutic Interventions***

Class I	1. ICD implantation ***is recommended*** in patients with a diagnosis of ER syndrome who have survived a cardiac arrest.
Class IIa	2. Isoproterenol infusion ***can be useful*** in suppressing electrical storms in patients with a diagnosis of ER syndrome. 3. Quinidine in addition to an ICD ***can be useful*** for secondary prevention of VF in patients with a diagnosis of ER syndrome.
Class IIb	4. ICD implantation ***may be considered*** in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST-segment elevation >1 mm in 2 or more inferior or lateral leads. 5. ICD implantation ***may be considered*** in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J-wave amplitude, horizontal/descending ST segment) in the presence of a strong family history of juvenile unexplained sudden death with or without a pathogenic mutation.
Class III	6. ICD implantation ***is not recommended*** asymptomatic patients with an isolated ER ECG pattern.

Definition and epidemiology

In 1953, Osborn described the classic J wave in experimental hypothermia.[151] Dogs subjected to hypothermia developed spontaneous VF that was preceded by the development of J waves.[151] The J wave, which was attributed to a current of injury (hence the term "J") was later termed the Osborn wave. Further experiments demonstrated that hypothermic J waves are presumably the ECG reflection of increased dispersion of repolarization caused by a disproportionate abbreviation of the epicardial action potential compared to the endocardium.[152]

ER is a common ECG pattern characterized by J-point and ST-segment elevation in 2 or more contiguous leads. The presence of ER pattern in the precordial leads has been considered a benign phenomenon, but recently its presence in