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HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

Developed in partnership with the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology, and the Asia Pacific Heart Rhythm Society (APHRS); and in collaboration with the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the Pediatric and Congenital Electrophysiology Society (PACES) and the Association for European Pediatric and Congenital Cardiology (AEPC).

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1 Introduction

This international consensus statement is the collaborative effort of three medical societies representing electrophysiology in North America, Europe and Asian-Pacific area: the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA) and the Asia Pacific Heart Rhythm Society. The objective of the consensus document is to provide clinical guidance

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for diagnosis, risk stratification and management of patients affected by inherited primary arrhythmia syndromes. It summarizes the opinion of the international writing group members based on their own experience and on a general review of the literature with respect to the clinical data on patients affected by channelopathies.

This document does not address the indications of genetic testing in patients affected by inherited arrhythmias and their family members. Diagnostic, prognostic, and therapeutic implications of the results of genetic testing also are not included in this document because this topic has been covered by a recent publication [1] coauthored by some of the contributors of this consensus document, and it remains the reference text on this topic. Guidance for the evaluation of patients with Idiopathic Ventricular Fibrillation, Sudden Arrhythmic Death Syndrome and Sudden Unexplained Death in Infancy, which includes genetic testing, are provided as these topics were not covered in the previous consensus statement.

Developing guidance for genetic diseases requires adaptation of the methodology adopted to prepare guidelines for clinical practice. Documents produced by other medical societies have acknowledged the need to define the criteria used to rank the strength of recommendation for genetic diseases [2].

The most obvious difference encountered for inherited diseases is that randomized and/or blinded studies do not exist in this field. Therefore most of the available data derive from registries that have followed patients and recorded outcome information. As a consequence, all consensus recommendations are level of evidence (LOE) C (i.e., based on experts' opinions).

The consensus recommendations in this document use the commonly used Class I, IIa, IIb and III classification and the corresponding language; "is recommended" for Class I consensus recommendation; "can be useful" for a Class IIa consensus recommendation; "may be considered" to signify a Class IIb consensus recommendation; "should not" or "is not recommended" for a Class III consensus recommendation (failure to provide any additional benefit and may be harmful).

Definitions of special terms used in the document

In the consensus document, the following terms will be defined as:

- **Syncope:** in the context of inherited arrhythmogenic disorders, the occurrence of "syncope" is an important indicator of arrhythmic risk. Although there is no definition to differentiate a syncopal episode caused by ventricular arrhythmias from an otherwise unexplained syncope, in the context of this document, the term "syncope" implies the

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exclusion of events that are likely due to vasovagal events such as those occurring during abrupt postural changes, exposure to heat and dehydration, emotional reactions to events such as blood drawing, etc. We refer to the guidelines of ESC and AHA/ACCF for the differential diagnoses of syncope [3, 4].

- **Symptomatic individuals:** the term "symptomatic" refers to individuals who have experienced ventricular arrhythmias (usually ventricular tachycardia or resuscitated ventricular fibrillation), or syncopal episodes (see definition above). The presence of symptoms is, in some of the channelopathies, an independent predictor of cardiac arrest at follow up.
- **Arrhythmic events:** the term refers to the occurrence of symptomatic or asymptomatic sustained or nonsustained spontaneous ventricular tachycardia, or unexplained syncope/resuscitated cardiac arrest.
- **Concealed mutation-positive patients:** this term is used to refer to individuals without clinical symptoms or phenotype of a channelopathy who carry the genetic defect present in clinically affected members of the family.

Methodological aspects and instructions for the consultation of the document

When considering the guidance from this document, it is important to remember that there are no absolutes governing many clinical situations. The final judgment regarding care of a particular patient must be made by the health care provider and the patient in light of all relevant circumstances. Recommendations are based on consensus of the writing group following the Heart Rhythm Society's established consensus process. It is recognized that consensus does not mean unanimous agreement among all writing group members. We identified the aspects of patients' care for which a true consensus could be found. Surveys of the entire writing group were used. The authors received an agreement that was equal to or greater than 84% on all recommendations; most recommendations received agreement of 94% or higher.

This statement is directed to all health care professionals who are involved in the management of 1) individuals who survived a cardiac arrest at a young age (usually defined as <40 years) in the absence of a clinical diagnosis of cardiac disease, despite extensive clinical assessment; 2) family members of individuals who died suddenly at young age with a negative autopsy; 3) in patients and family members in whom the diagnosis of a channelopathy is clinically possible, likely, or established, and 4) young patients with unexplained syncope.

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All members of this document writing group provided disclosure statements of all relationships that might present real or perceived conflicts of interest. Disclosures for all members of the writing group are published in Appendix A.

List of Abbreviations:

ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy
AV: Atrio-ventricular
BrS: Brugada Syndrome
CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia
ECG: Electrocardiogram
EPS: Electrophysiological Study
ERP: Effective Refractory Period
HUT: Head-up Tilt Test
ICD: Implantable Cardioverter Defibrillator
ICD-Codes: International Classification of Diseases Codes
IVF: Idiopathic Ventricular Fibrillation
LBBB: Left Bundle Branch Block
LCSD: Left Cardiac Sympathetic Denervation
LQTS: Long QT Syndrome
LQT1, 2, 3 etc.: subtypes based on the underlying gene defect
MRI: Magnetic Resonance Imaging
PCCD: Progressive Cardiac Conduction Disease
PVC: Premature Ventricular Contraction
QTc: QT interval **c**orrected for heart rate using Bazett's formula
RBBB: Right Bundle Branch Block
RV: Right Ventricle
RVOT: Right Ventricular Outflow Tract
SADS: Sudden Arrhythmic Death Syndrome
SCA: Sudden Cardiac Arrest
SCD: Sudden Cardiac Death

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SIDS: Sudden Infant Death Syndrome

SNP: Single Nucleotide Polymorphism

SQTS: Short QT Syndrome

SUDI: Sudden Unexplained Death in Infancy

SUDS: Sudden Unexplained Death Syndrome

VPB: Ventricular Premature Beat

VT: Ventricular Tachycardia

VF: Ventricular Fibrillation

2 Long QT Syndrome

*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 QTc≥ 500 ms in repeated 12-lead 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 VT/VF. 3. Left cardiac sympathetic denervation (LCSD) **is recommended** for high-risk patients with a diagnosis of LQTS in whom: a) 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 ≤ 470ms.

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	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 <u>not</u> indicated** in asymptomatic LQTS patients who have not been tried on beta-blocker therapy.

2.1 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 in 29% of the infants with a QTc exceeding respectively 470 and 460 ms. These findings demonstrate a prevalence of about 1:2,000 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".

2.2 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 and is more virulent and associated with deafness. Mutations in *KCNJ2* (*Kir2.1, LQT7*) result in the neurologic musculo-skeletal

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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 or 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].

2.3 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.

2.4 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

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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.

2.5 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 milliseconds (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

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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 which 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.

2.6 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 of this chapter. 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 suggests 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 above, 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.

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2.6.1 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 non-cardioselective 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.

2.6.2 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].

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

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only after a careful consideration of 1) risk of sudden death; 2) the short and long term risks of ICD implantation; 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 cut off rate greater than 220-240 beats per minute.

2.6.3 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 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. Nogeneral 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 V1,V2, 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 V1,V2 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 1 ECG morphology

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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 1 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 1 ECG and on the basis of a family history of SCD alone.

3.1 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].

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3.2 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].

3.3 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].

3.4 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 1 ST-segment elevation is observed either spontaneously or after intravenous administration of a sodium channel blocking agent (ajmaline, flecainide, pilsicainde, or procainamide) in at least one right precordial lead (V1 and V2) [62], which are placed in a standard or a superior position (up to the 2nd intercostal space) [63, 64].

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The differential diagnosis includes a number of diseases and conditions that can lead to Brugada-like ECG abnormality, including atypical 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 1 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 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 LBBB Ventricular Premature Beats (VPB) during prolonged ECG recording
7. Ventricular ERP < 200 ms recorded during EPS [70, 71] and HV interval > 60 msec
8. Absence of structural heart disease including myocardial ischemia

3.5 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].

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Most studies have concurrently agreed on the evidence that the presence of syncopal episodes in patients with a spontaneous type 1 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 msec [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 have proven to be risk markers 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].

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3.6 Therapeutic options and recommendations for BrS patients

3.6.1 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 lifetime. 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.

3.6.2 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. Quindine 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 quindine 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.

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3.6.3 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 have presented the first series showing that electrical epicardial substrate ablation in the RVOT can prevent VF inducibility in a high risk population [100]. 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 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.

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4.1 Introduction

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

4.2 Epidemiology

The prevalence of the disease could be as high as 0.1:1,000. 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.

4.3 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*, that encodes triadin, is a gene for this novel form of recessive CPVT. Finally, a mutation in the

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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].

4.4 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.

4.5 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 CVPT. 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 nor prognostic value in CPVT as either bidirectional or polymorphic VT are 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].

4.6 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

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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=0.007), 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].

4.7 Management

4.7.1 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 non-selective 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 non-compliance 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].

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4.7.2 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, pro-arrhythmic effects of the ICD and the need for a life-time protection requiring multiple re-interventions 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 cut-off rates.

4.7.3 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.

4.7.4 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.

4.7.5 Left cardiac sympathetic denervation

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.

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4.7.6 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].

4.8 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.

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5.1 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 were the first to suggest an association with atrial and ventricular fibrillation (i.e. SCD) [135]. 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, 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].

5.2 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 formula at rates in which its correction is not linear and may lead to underestimation or overestimation of QTc values.

A first attempt to come to a diagnostic scheme has been proposed by Gollob et al [142], but this score is not 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 cut-off value of $\leq$330 ms should be used for the diagnosis. Gollob et al, in their "diagnostic score" also used 330 ms as the cut-off with the heaviest weight [142]. 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 Antonnen et al. only 0.4% of individuals had a QTc <340 ms and 0.1% of the population had a QTc <320 ms [148].

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5.3 Risk stratification and Treatment

Therapeutic management using ICD's 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 type1) [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 <360msec) 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 a 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 a 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

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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 >1mm 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

6.1 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 the inferior and/or lateral leads has been associated with idiopathic VF in case-control studies (ER syndrome) [153-158]. Furthermore, the ER ECG pattern is associated with an increased risk of arrhythmic death and mortality in epidemiological studies, either as a primary cause of sudden death or in conjunction with concurrent cardiac disease [159-162].

Numerous cases of patients with idiopathic VF who have the ER pattern in the inferior and/or lateral ECG leads have now been described. At least five case-control studies assessing the presence of ER among patients with idiopathic VF, involving more than 300 patients, have been published [153-158].

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ER ECG pattern (> 1 mm) in the inferior/lateral leads occurs in 1-13% of the general population and in 15-70% of idiopathic VF cases [153-161]. In the pediatric age group it is even more prevalent. Male sex is strongly associated with ER ECG pattern, since over 70% of subjects with ER are males. The prevalence of the ER ECG pattern declines in males from early adulthood until middle-age which suggests a hormonal influence on the presence of ER [163]. The ER pattern is more common in young physically active individuals, athletes, and African-Americans [164]. There is an increased prevalence of ER reported in South-East Asians [161]. The ER pattern is associated with high vagal tone, as well as hypothermia and hypercalcemia. ECG features of bradycardia, prolonged QRS duration, short QT interval, and left ventricular hypertrophy assessed by the Sokolow-Lyon index, are also associated with ER [163]. There also is some overlap between the BrS and ER syndrome, since an ER pattern in the inferior or lateral leads is found in 11-15% of the BrS patients [165]. ER pattern also is frequently observed in patients with short QT syndrome, and many patients with an ER pattern or ER syndrome have a relatively short QT interval without frank short QT syndrome [166].

6.2 Clinical Diagnosis

Given the high prevalence of the ECG pattern of ER, we recommend a conservative approach in establishing the diagnosis of this condition. Patients with the ER pattern on the 12-lead ECG who have been resuscitated from an ECG-documented episode of idiopathic VF and/or Polymorphic VT are those diagnosed with the ER syndrome. Similarly, SCD victims with a negative autopsy with an archived ECG showing the ER pattern also are diagnosed with ER syndrome when evidence of other diagnoses such as BrS have been excluded.

At this stage of our understanding of early repolarization, there is an unusual dilemma in which the ECG pattern is highly prevalent, the inheritance is not clearly monogenic in most cases and the genetic substrate is not clearly defined. For this reason, we have chosen not to label family members with the ER pattern as ER syndrome patients pending a better understanding of their risk. High risk features including extent of family history of SCD, arrhythmic syncope and amplitude and morphology of the ER pattern may lead to consideration of a prophylactic ICD in conjunction with review by an expert center with a focus on inherited arrhythmias. Asymptomatic individuals with the ER pattern on ECG with a mutation considered pathogenic for ER as well as family members of a patient diagnosed with ER syndrome who present with a diagnostic ECG may be affected by the disease.

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6.3 Genetic Variants

Genetic contributions to ER are suggested by anecdotal observations of a common familial history of SCD of subjects with ER and idiopathic VF [167]. Familial ER has been reported to have an autosomal dominant inheritance pattern with incomplete penetrance. Two independent population-based studies also have suggested some degree of inheritance of the ER patterns in the general population [163, 168], but the familial inheritance of malignant ER patterns has not been clearly demonstrated [153]. A candidate gene approach in idiopathic VF patients with ER has identified a mutation in *KCNJ8*, which encodes a pore-forming subunit of the ATP-sensitive potassium channel [169, 170]. Mutations in the L-type calcium channel genes, including *CACNA1C, CACNB2B,* and *CACNA2D1* [171] as well as loss-of-function mutations in *SCN5A* [172] have also been associated with idiopathic VF with ER. Given the high prevalence of ER in the general population, ER likely has a polygenic basis that also is influenced by non-genetic factors. A recent genome-wide association meta-analysis in three independent populations of European ancestry found eight loci associated with ER, the strongest association being found with SNPs located at the *KCND3* genes, that encodes the transient outward potassium channel Ito (*Kv4.3*) coding gene [173]. However, replication studies could not confirm these observations in other populations so far.

6.4 Clinical manifestations

Life-threatening arrhythmias are often the first and unexpected manifestation of ER syndrome. An increase in the amplitude of ER has been described before the onset of VF in ER syndrome patients, and VF is usually triggered by short-long-short sequence in which a short coupled extrasystolic beat is followed by a pause and the next extrasystolic beat falls on the T wave of the preceding beat and initiate the arrhythmic episode [156]. The majority of population-based studies have shown that subjects with ER in the inferior leads are at a higher risk of all-cause mortality, cardiac mortality, and especially unexpected sudden death [159-162], though some exceptions have been reported [174]. In the studies of middle-aged subjects, the mortality curves of subjects with and without ER begin to diverge after age 50 [159, 160], suggesting that the presence of the ER pattern may increase the risk of arrhythmic death in the presence of additional triggers, such as acute ischemic events.

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6.5 Diagnosis

In survivors of VF and in patients with polymorphic VT, clinical evaluation including echocardiogram, coronary angiography, magnetic resonance imaging (MRI), and selected endocardial biopsies should be performed to exclude other causes of VF. Consideration should be given to provocative drug infusion with epinephrine and with a sodium channel blocker, such as ajmaline or flecainide, to unmask latent inherited causes of cardiac arrest, such as BrS and LQTS[157]. The presence of short QT syndrome also should be noted. There are no validated techniques to provoke the ER pattern, although 12-lead Holter monitoring to detect evidence of the ER pattern during bradycardia is warranted.

6.6 Risk stratification

The magnitude of the J-point elevation may have prognostic significance. Either slurred or notched J-point elevation ≥0.2 mV is relatively rare in the general population, but appears to be associated with an increased risk [159]. Furthermore, J point elevation in idiopathic VF patients is of greater amplitude and ECG lead distribution compared to those with an established cause of cardiac arrest [157]. The available data also suggest that transient changes in the presence and amplitude of J-point elevation portends a higher risk for VF [153]. A horizontal or descending ST-segment following J-point elevation is associated with a worse outcome in the general population [175]. This observation has been very helpful in distinguishing idiopathic VF patients from matched controls, and is a key aid in clinical decision making [176].

6.7 Management

The clinical implications of the observation of an ER pattern in the ECG of an asymptomatic subject are not clear. The presence of ER is associated with 3 times the risk of developing VF, but the overall risk is still negligible considering the rarity of VF in the general population[158, 177]. Because the presence of ER may increase the vulnerability to sudden death during an acute ischemic event, a plausible implication stemming from the population studies is that middle-aged subjects with the ER pattern in the ECG, especially those with a high amplitude of J-point elevation and horizontal/downsloping ST segment, should target a reduction in their long-term risk for acute coronary events in accordance with current practice guidelines.

Electrical storm is relatively common after ICD implantation in patients with the ER syndrome [178, 179]. Case series evidence supports the acute use of isoproterenol for

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suppression of recurrent VF, and quinidine for long-term suppression [178, 179]. Isoproterenol is typically initiated at 1.0 µg/minute, targeting a 20% increase in heart rate or an absolute heart rate > 90 bpm, titrated to hemodynamic response and suppression of recurrent ventricular arrhythmia.

6.8 Screening of family members

No recommendations can be given to screen the families of individuals with asymptomatic ER pattern. There are no established provocative tests to diagnose concealed ER in family members of ER syndrome patients, although preliminary observation suggest that the Valsalva maneuver may assist in identifying concealed ER cases. Therapeutic recommendation 5 uses the term strong family history. There is no clear definition of this term, but it is typically chosen when more than one family member is affected, deaths occur at an early age and a first-degree relative is affected.

7 Progressive Cardiac Conduction Disease (PCCD)

Expert Consensus Recommendations on Progressive Cardiac Conduction Disease Diagnosis

1. Progressive Cardiac Conduction Disease (PCCD) ***is diagnosed*** in the presence of unexplained progressive conduction abnormalities in young (<50 years) individuals with structurally normal hearts in the absence of skeletal myopathies especially if there is a family history of PCCD.

Expert Consensus Recommendations on Progressive Cardiac Conduction Disease Therapeutic Interventions

Class I	1. Pacemaker implantation ***is recommended*** in patients with a diagnosis of PCCD and the presence of: a) Intermittent or permanent third degree or high-grade AV block or b) Symptomatic Mobitz I or II second degree AV block.
Class IIa	2. Pacemaker implantation ***can be useful*** in patients with a diagnosis of PCCD and the presence of bifascicular block with or without first degree AV block. 3. ICD implantation ***can be useful*** in adult patients diagnosed with PCCD with a mutation in the Lamin A/C gene with left ventricular dysfunction and/ or non-sustained VT.

7.1 Introduction

Progressive cardiac conduction disease (PCCD) is a heterogeneous disorder of unclear etiology, which can be serious and potentially life-threatening. Its underlying mechanism can be either functional or structural or there can be overlap between these two mechanisms [180]. The most frequent form of PCCD is a degenerative form called Lenègre-Lev disease. The

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mechanism of PCCD with structural abnormality is considered as a primary degenerative disease or an exaggerated aging process, with sclerosis principally affecting the conduction tissue [181]. Aging itself is suggested to play a critical role in PCCD, meaning that at every age conduction abnormalities are more outspoken than expected based on age alone.

Both familial PCCD with either a structurally normal heart (hereby defined as "Isolated PCCD") and familial PCCD associated with dilated cardiomyopathy will be discussed.

7.2 Epidemiology

No systematic clinical data are available on the age of onset and course of symptoms in affected individuals. When genetically mediated, the majority of PCCD patients have an autosomal dominant mode of inheritance [1].

7.3 Genetic variants

The discovery of gene mutations that are causally involved in inherited PCCD is relatively recent [180]. Common PCCD-associated genes (defined as genes with causative mutation in >5% of affected individuals [1]) are *SCN5A* and *TRPM4* for PCCD occurring in the structurally intact heart [182] and *LMNA* for PCCD associated with heart failure [1].

7.4 PCCD and structurally normal heart

Mutations in the *SCN5A* gene cause the majority of familial PCCD and often causes a combined phenotype with Brugada syndrome [181]. Subtle structural abnormalities, mainly fibrosis, are present in *SCN5A* mutation positive subjects. Recently, mutations in the transient receptor potential channel, subfamily M(elastatine), member 4 (*TRPM4*) *Ca^{2+}-activated* channel gene were reported in patients with PCCD [183] and are estimated to account for a significant portion of inherited forms of RBBB (25%) or AV block (10%) [1].

7.5 PCCD and structurally abnormal heart

When PCCD is accompanied by the presence of concomitant congenital heart disease, mutations in early cardiac transcription factor genes such as *Nkx2.5* or *GATA4* are more likely.

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Mutations in the *Nkx2.5* or *TBX5*, genes involved in the regulation of heart development, are associated with structural congenital heart defects such as septal defects [181].

PCCD also may precede development of dilated cardiomyopathy. Mutations in the *LMNA* gene encoding Lamin A/C were found to be causally involved in Emery–Dreifus muscular dystrophy as well as in families with dilated cardiomyopathies and severe PCCD without skeletal muscle involvement [180, 181, 184].

In a small percentage of cases, Wolff-Parkinson-White syndrome is familial and associated with cardiac hypertrophy, presenting as a hypertrophic cardiomyopathy phenocopy. Mutations in the *PRKAG2* gene and other glycogen storage diseases may also display abnormal electrical AV connections. Patients with mutations in the *PRKAG2* gene have a variable combination of glycogen storage cardiomyopathy, PCCD including sinus bradycardia and AV block, ventricular pre-excitation, arrhythmias, and sudden death. [185]. Most authors would classify the phenotype of *PRKAG2* mutations as a hypertrophic cardiomyopathy with conduction defects rather than a PCCD with hypertrophy.

7.6 Clinical manifestations

PCCD can be seen by a prolonged P wave duration, PR interval and QRS widening with axis deviation on the surface ECG, which may progress over time as an age-dependent penetrance. In isolated forms of PCCD, there are typically no extra-cardiac manifestations. In non-isolated forms of PCCD, congenital heart disease, cardiomyopathy, or extra-cardiac manifestations are present. Phenotypic expression of mutations may vary from individual to individual and has, among others an age-dependent onset [1].

In patients with mutations in the *LMNA* gene and PCCD, the AV node and specialized conduction system are progressively replaced by fibrofatty tissue and patients are at risk for premature SCD [184, 185]. In addition to conduction abnormalities, most adult patients with *LMNA* mutations have AV conduction disturbances, atrial and ventricular arrhythmias [186]. *LMNA* mutations are also found at frequencies of 6-8% among patient populations with idiopathic or familial dilated cardiomyopathy. Heart failure is a common phenotypic feature in families with cardiac manifestations of *LMNA* disease [187, 188]. Because of the limited information and the low number of patients in many of the clinical reports, a statement about the incidence of arrhythmias in relation to structural or functional PCCD is precarious. The occurrence of tachyarrhythmia and sudden death is expected to be more frequent in PCCD patients that carry loss-of-function *SCN5A* mutations, a disease entity comparable with *SCN5A*-

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associated BrS [180]. Interestingly, overlapping phenotypes of BrS1, LQTS, and inherited conduction system defects have been reported in some families [185].

7.7 Diagnosis

The diagnosis of PCCD in an index patient is based on clinical data including history, family history, and 12-lead ECG. The potential presence of congenital heart disease and/or cardiomyopathy must be investigated by 2-D echocardiography or other imaging modalities, such as cardiac MRI. Early-onset PCCD in the absence of structural heart disease should prompt consideration of PCCD genetic testing, particularly if there is a positive family history of conduction abnormalities, pacemaker implants, or sudden death [1].

(Targeted) genetic testing may be considered as part of the diagnostic evaluation for patients with either isolated PCCD or PCCD with concomitant structural heart disease, especially when there is documentation of a positive family history of PCCD [1].

7.8 Risk stratification

Screening for underlying cardiovascular manifestations with a resting 12-lead ECG, Holter, or 2-D echocardiogram is recommended, independent of symptom status. Patients with first-degree AV block in association with bifascicular block and symptomatic, advanced AV block have a substantial incidence of sudden death. In the presence of permanent or transient third-degree AV block, syncope is associated with an increased incidence of sudden death regardless of EPS results [189]. Based on this evidence in patients with PCCD diagnosis, pacemaker implant may be indicated even in individuals with bifascicular block and first degree AV block and thus representing an exception to the recommendation set by international guidelines for patients who have this phenotype in all the other clinical conditions.

There is no genotype-based risk stratification for patients with PCCD. Some mutations may be associated with development of heart failure and/or extracardiac features, such as skeletal myopathy, that can be diagnosed, followed and treated after having PCCD classified as a genetic entity [1]. Patients with *LMNA* mutations may experience malignant arrhythmias and SCD despite pacemaker implantation [184]. ICD therapy is therefore warranted at an early stage; a risk stratification scheme has recently been proposed [190].

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7.9 Management

Once cardiac involvement occurs, particularly with the muscular dystrophies, the clinician should maintain a low threshold for investigating symptoms or ECG findings to determine the need for EPS, pacemaker or ICD implantation. Screening for underlying cardiovascular manifestations with a resting 12-lead ECG or 2-D echocardiogram to determine cardiac involvement should be part of the routine clinical assessment, independent of symptom status [2]. Asymptomatic family members who are positive for the family's PCCD-associated mutation should be prospectively followed for the early development of PCCD-related symptoms, deterioration of cardiac conduction, and beginning signs and symptoms of heart failure. In addition, medications with conduction slowing properties should be restricted, and fever, an aggravating trigger in individuals with *SCN5A* mutations, should be preemptively treated [1].

7.10 Screening of family members

Cascade family screening is useful in families with mutation-positive PCCD. When a clinical diagnosis of PCCD is established in an index case, a careful clinical investigation of first-degree family members is necessary. Genotyping of family relatives is done after mutation identification in the index cases and may be useful to exclude presence or development of PCCD. Taken together, a comprehensive clinical and genetic evaluation of family members is generally recommended to detect inherited forms of PCCD disease and other cardiac and non-cardiac disease features [1].

8 Unexplained cardiac arrest: Idiopathic VF

Expert Consensus Recommendations on Idiopathic Ventricular Fibrillation Diagnosis

1. IVF ***is defined*** as a resuscitated cardiac arrest victim, preferably with documentation of VF, in whom known cardiac, respiratory, metabolic and toxicological etiologies have been excluded through clinical evaluation.

Expert Consensus Recommendations on Idiopathic Ventricular Fibrillation Evaluation

Class IIa	1. Genetic testing in IVF ***can be useful*** when there is a suspicion of a specific genetic disease following clinical evaluation of the IVF patient and/or family members.
Class III	2. Genetic screening of a large panel of genes in IVF patients in whom there is no suspicion of an inherited arrhythmogenic disease after clinical evaluation ***should not be performed.***

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Expert Consensus Recommendations on Idiopathic Ventricular Fibrillation Therapeutic Interventions

Class I	1. ICD implantation ***is recommended*** in patients with the diagnosis of IVF.
Class IIb	2. Antiarrhythmic therapy with quinidine, PES guided or empirical, ***may be considered*** in patients with a diagnosis of IVF in conjunction with ICD implantation or when ICD implantation is contraindicated or refused. 3. Ablation of Purkinje potentials ***may be considered*** in patients with a diagnosis of IVF presenting with uniform morphology PVCs in conjunction with ICD implantation or when ICD implantation is contraindicated or refused. 4. If a first degree relative of an IVF victim presents with unexplained syncope and no identifiable phenotype following thorough investigation, then after careful counseling an ICD implant ***may be considered***.

Expert Consensus Recommendations on Idiopathic Ventricular Fibrillation Evaluation of Family Members

Class I	1. Evaluation of first degree relatives of all IVF victims with resting ECG, exercise stress testing and echocardiography ***is recommended***. Assessment of first degree relatives with history of palpitations, arrhythmias or syncope should be prioritized. 2. Follow up clinical assessment ***is indicated*** in young family members of IVF victims who may manifest symptoms and /or signs of the disease at an older age and in all family members whenever additional SUDS or SUDI events occur.
Class IIa	3. Evaluation of first degree relatives of IVF victims with Holter and signal averaged ECGs, cardiac MRI and provocative testing with Class Ic antiarrhythmic drugs ***can be useful***.
Class IIb	4. Evaluation of first degree relatives of IVF victims with epinephrine infusion ***may be considered.***

8.1 Definition

When individuals survive a cardiac arrest we are able to investigate and treat them for the underlying cause. The term idiopathic ventricular fibrillation (IVF) is used when the cardiac arrest remains unexplained despite this investigation. In 1992, when discovery of the genetic basis of cardiac channelopathies was in its infancy, the hypothesis was advanced that concealed forms of arrhythmogenic disorders could underlie these cases representing subclinical “electrical abnormalities” of the heart [191]. A subsequent expert consensus statement [192] defined IVF as “the terminology that best acknowledges our current inability to identify a causal relationship between the clinical circumstance and the arrhythmia.” In the same article, the minimal requirements for the diagnosis of IVF were also defined [192]. It is therefore expected that the proportion of cardiac arrests defined as IVF is destined to decrease as we identify more conditions that may lead to life-threatening arrhythmias in the absence of overt cardiac abnormalities.

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8.2 Epidemiology

In the CASPER registry of cardiac arrest survivors, in whom overt coronary and structural disease had already been excluded, 44% remained without a diagnosis after further comprehensive evaluation (see below) [193]. There is little other systematic data on the prevalence of IVF as an entity.

8.3 Diagnosis

IVF is diagnosed by the exclusion by clinical evaluation of known cardiac, respiratory, metabolic and toxicological etiologies that may lead to cardiac arrest. Ideally VF should be documented. The most recent consensus document defining the minimal requirements for diagnosis of IVF dates back to 1997. Data from the CASPER registry [193], suggest that careful clinical assessment of patients surviving a cardiac arrest in the absence of structural cardiac abnormalities (normal cardiac function on echocardiogram, no evidence of coronary artery disease, and a normal ECG) can lead to diagnosis of a disease in more than half of cases. A staged cascade screening approach was associated with an incremental diagnostic yield in this cohort: 1) ECG, signal averaged ECG, telemetry 2) Imaging (MRI with and without contrast); 3) Provocative tests (exercise stress test, epinephrine infusion, procainamide); 4) EPS and voltage map; 5) Ventricular biopsy; 6) Targeted genetic testing. A similar yield has been observed with thorough evaluation of Sudden Unexplained Death Syndrome (SUDS) cases and their relatives [194, 195].

Genetic diagnostic testing in IVF cases may be considered when clinical evaluation is either inconclusive or suggests that a 'forme fruste' of a channelopathy might be present. Several factors may generate such a suspicion: 1) age, 2) gender, 3) activity at the time of cardiac arrest (for example rest, exercise, emotion or auditory stimuli). A family history of premature sudden death may also strengthen the possibility of a genetic substrate. The yield of genetic screening of IVF patients is heterogeneous. Krahn et. al. identified mutations in 47% of patients with suspected IVF by using targeted genetic testing led by clinical diagnostic testing [193]. However, Bai et al [196], reported that the yield of genetic screening in IVF patients and family members of SCD victims is very low in the absence of a clinical suspicion to guide testing. The cost of screening a large number of genes responsible for many different diseases is too expensive at this stage to be recommended, particularly as a negative result does not rule them out as potential the causes of IVF.

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8.4 Management

In IVF, as there is by definition no evidence for pathogenesis, management is empirical and most patients are advised to undergo an ICD implant. Unfortunately, the natural history of IVF is poorly defined. Data collected in a small series of patients by Crijns et al suggested that at 2.8 years of follow up only 1/10 patients had a recurrence of VT but none experienced ICD shock or death [197]. Similarly, Belhassen et al[198] reported a multicenter experience on 26 IVF patients studied with programmed electrical stimulation (PES) to test VF inducibility (81% of inducible patients). PES was repeated after administration of quinidine or a combination of quinidine and amiodarone to test suppression of inducibility. At follow-up ranging between 14 and 216 months no VF or fatalities occurred. Remme et al reported a 43% recurrent event rate in a long-term follow-up of 37 IVF patients (77±41 months) [199]. Knecht et al [200] reported their experience in which IVF patients with recurrent and troublesome VF underwent catheterization and ablation of Purkinje potentials responsible for VPBs that initiated the arrhythmia. By far the majority (36/38) were free of VF at 52 months of follow up. This represents a specific subset of IVF patients presenting with frequent ventricular arrhythmias; most IVF patients do not suffer such a storm after initial resuscitation from cardiac arrest.

8.5 Screening of family members

Experience of investigating blood relatives of IVF survivors is limited but supports the possibility of incompletely penetrant disease being more evident in family members than in the index case, particularly if only limited investigation is possible due to a poor neurological outcome post-arrest [193]. A similar predominantly non-invasive diagnostic protocol to that utilized in SUDS families may be employed (see chapter 9). As with families of SUDS victims, it is reasonable that relatives of IVF survivors who are obligate carriers or have ominous symptoms such as cardiac syncope should be prioritized for evaluation. In families with IVF young family members may require periodic re-assessment even if the initial assessment is normal as young patients may only become cognizant of symptoms at an older age, and certain diseases have age-related penetrance. Repeated evaluations should occur if family members become symptomatic or additional suspicious sudden deaths are identified in the family. There are no data on appropriate interventions for a first degree relative of an IVF victim who presents with unexplained cardiogenic syncope without an identifiable phenotype despite thorough

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investigation. Consideration should be given to monitoring with an implantable loop recorder, or after careful counseling the possibility of an ICD implant.

9 Unexplained sudden cardiac death: the Sudden Unexplained Death Syndrome(SUDS) and Sudden Unexplained Death in Infancy(SUDI)

Expert Consensus Recommendations on Sudden Unexplained Death Syndrome Diagnosis

1.	It **is recommended** that an unexplained sudden death occurring in an individual older than 1 year of age is known as "sudden unexplained death syndrome" (SUDS).
2.	It **is recommended** that a SUDS death with negative pathological and toxicological assessment is termed "sudden arrhythmic death syndrome" (SADS).

Expert Consensus Recommendations on Sudden Unexplained Death Syndrome Evaluation

Class I	1. It **is recommended** that personal/family history and circumstances of the sudden death are collected for all SUDS victims. 2. It **is recommended** that all sudden death victims diagnosed as SUDS undergo expert cardiac pathology to rule out the presence of microscopic indicators of structural heart disease. 3. Collection of blood and/or suitable tissue for molecular autopsy/post-mortem genetic testing **is recommended** in all SUDS victims.
Class IIa	4. An arrhythmia syndrome focused molecular autopsy/postmortem genetic testing **can be useful** for all SUDS victims.

Expert Consensus Recommendations on Sudden Unexplained Death Syndrome Therapeutic Interventions

Class I	1. Genetic screening of the first degree relatives of a SUDS victim ***is recommended*** whenever a pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDS victim. 2. Evaluation of first degree blood relatives of all SUDS victims with resting ECG with high right ventricular leads, exercise stress testing and echocardiography ***is recommended***. Assessment of obligate carriers and relatives with a history of palpitations, arrhythmias or syncope should be prioritized. 3. Follow up clinical assessment ***is indicated*** in young family members of SUDS victims who may manifest symptoms and /or sign of the disease at an older age and in all family members whenever additional SUDS or SUDI events occur.
Class IIa	**4.** Evaluation of first degree relatives of SUDS victims with ambulatory and signal averaged ECGs, cardiac MRI and provocative testing with Class Ic antiarrhythmic drugs ***can be useful*.**
Class IIb	5. Evaluation of first degree relatives of SUDS victims with epinephrine infusion ***may be considered.***

Expert Consensus Recommendations on Sudden Unexplained Death in Infancy Diagnosis

1.	It ***is recommended*** that unexplained sudden death occurring in an individual younger than 1 year of

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age with negative pathological and toxicological assessment is termed "sudden unexplained death in infancy" (SUDI).

Expert Consensus Recommendations on Sudden Unexplained Death in Infancy Evaluation

Class I	1. It ***is recommended*** that personal/family history and circumstances of the sudden death are collected for all SUDI victims. 2. Collection of blood and/or suitable tissue for molecular autopsy ***is recommended*** in all SUDI victims.
Class IIa	3. An arrhythmia syndrome focused molecular autopsy/postmortem genetic testing ***can be useful*** for all SUDI victims.
Class IIb	4. Sudden death victims diagnosed as SUDI at autopsy ***may be considered*** for assessment by an expert cardiac pathologist to rule out the presence of microscopic indicators of structural heart disease.

Expert Consensus Recommendations on Sudden Unexplained Death in Infancy Therapeutic Interventions

Class I	1. Genetic screening of the first degree relatives of a SUDI victim ***is recommended*** whenever a pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDI victim. Obligate mutations carriers should be prioritized
Class IIa	2. Evaluation of first degree relatives of SUDI victims with a family history of inherited heart disease or other SUDS or SUDI deaths with resting ECG and exercise stress testing and additional tests as indicated ***can be useful***. Assessment of first degree relatives with history of arrhythmias or syncope should be prioritized. 3. Follow up clinical assessment ***can be useful*** in young family members of SUDI victims with a family history of inherited heart disease or other SUDS or SUDI death who may manifest symptoms and /or signs of the disease at an older age and in all family members whenever additional SUDS or SUDI events occur.
Class IIb	4. Evaluation of first degree relatives of SUDI victims with resting ECG and exercise stress testing ***may be considered.***

9.1 Definitions

SCD is a common outcome of "acquired" cardiac diseases such as acute myocardial ischemia and ischemic dilated cardiomyopathy where the cause is readily determined [201]. An unexplained SCD, however, is a pathological diagnosis of exclusion that covers a number of possible etiologies. A commonly used term is "sudden arrhythmic death syndrome" (SADS) that describes a SCD where an autopsy and toxicology have been undertaken, non-cardiac etiologies excluded and the heart found to be morphologically normal [202, 203]. Another similar descriptor "sudden *adult* death syndrome" [204], has been termed to describe non-pediatric cases. In Southeast Asia, cases of young male sudden deaths have been attributed to "sudden *unexpected* or *unexplained* death syndrome" (SUDS) as well as "sudden unexpected nocturnal

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death syndrome" (SUNDS). These have, however, been directly related to BrS as an etiology, have been used interchangeably and do not necessarily imply a through pathological evaluation [205]. The terms "sudden infant death syndrome" (SIDS) or "sudden unexpected death in infancy" (SUDI) are used in cases under 1 year of age when the cause of death remains unexplained although SIDS implies a more stringent circumstantial and forensic investigation. These are discussed further below [206].

The definitions utilized for unexplained SCD have varied. The timing of unwitnessed deaths (less than 1 hour to less than 24 hours) is one factor [202, 203, 207, 208]. Another is the limited or even absence of access to autopsy in some countries and a histopathological examination may be the exception rather than the rule [207, 209, 210]. If an autopsy has not been undertaken or considered inadequate then the death remains unexplained but other etiologies, genetic and acquired should be considered and a broader diagnostic view needs to be considered. Consistent use of the descriptors SUDS and SADS would be similar to the use of SUDI and SIDS and will help reduce confusion over terminology. This will ensure that familial evaluation is guided towards the diagnosis of likely etiologies such as arrhythmia syndromes.

When individuals survive a cardiac arrest we are able to investigate and treat them for the underlying cause. The term idiopathic ventricular fibrillation (IVF) is used when the cardiac arrest remains unexplained despite this investigation. In 1992, when discovery of the genetic basis of cardiac channelopathies was in its infancy, the hypothesis was advanced that concealed forms of arrhythmogenic disorders could underlie these cases representing subclinical "electrical abnormalities" of the heart [191]. A subsequent expert consensus statement [192] defined IVF as "the terminology that best acknowledges our current inability to identify a causal relationship between the clinical circumstance and the arrhythmia." In the same article, the minimal requirements for the diagnosis of IVF were also defined [192]. Therefore, it is expected that the proportion of cardiac arrests defined as IVF is destined to decrease as we identify more conditions that may lead to life-threatening arrhythmias in the absence of overt cardiac abnormalities.

9.2 Epidemiology

It is clear that the relevant International Classification of Diseases Codes (ICD-codes) for unexplained SCD underestimate significantly its true frequency [203]. The incidence and prevalence of unexplained SCD depends, however, upon the population studied and the investigators. Autopsies for unexplained sudden death are mandatory in the UK. The incidence of unexplained SCD amongst the general population aged 4 to 64 years has been estimated to

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be up to 1.34/100,000 per annum [203] with 4.1% of SCD in the 16 to 64 age group being unexplained [204]. A recent Irish study reported an incidence of unexplained SCD of 0.76/100,000 year in subjects aged 14 to 35 years old accounting for 27% of the total incidence of SCD[211]. Danish data are limited by a 75% autopsy rate but supports an incidence of at least 0.8/100,000 per annum amongst 1 to 35 year olds with 43% of autopsied cases being unexplained [207]. Not only is the proportion of SCD that remains unexplained apparently higher in the young but victims are more commonly young men who die suddenly in their sleep or at rest [203]. Amongst predominantly male US military recruits aged 18 to 35 years old the unexplained SCD rates is as high as 4.5/100,000 per annum, accounting for 35% of all SCD in this group [212]. A regional Australian study of SCD in the 5 to 35 year old confirms a 29% proportion as unexplained [213]. An autopsy series of the general population in the Veneto region of Italy has, however, suggested that normal hearts are present in only 6% of SCD cases [208] while a US series of sudden deaths amongst athletes found only a 3% prevalence [214]. Conversely, sudden deaths amongst British athletes contained a 26% prevalence of morphologically normal hearts [215]. There is therefore remarkable variation and discrepancy.

The incidence of unexplained sudden death below 1 year of age (SIDS and SUDI) is well defined and exceeds the incidence of SCD in young adults or in children over 1 year of age by an order of magnitude. A recent national study from Ireland revealed a sudden death rate of 1.4/100,000 among children age 1-4 years compared to 59/100,000 under 1 year [216]. A population based-study in the US revealed similar rates with an annual incidence of SCD of 3/100,000 for children age 1-4, and 80/100,000 for children < 1 year [217]. It should be noted that campaigns to avoid modifiable risk factors (predominantly avoiding the prone sleeping position) have resulted in significant declines in SIDS rates around the world. However, these have plateaued and the current rate of SIDS in the US is 53/100,000 [218].

In the CASPER registry of cardiac arrest survivors, in whom overt coronary and structural disease had already been excluded, 44% remained without a diagnosis after further comprehensive evaluation (see below) [193]. There are little other systematic data on the prevalence of IVF as an entity.

9.3 Diagnosis

The diagnosis of an unexplained SCD ideally relies upon an autopsy and toxicological studies being undertaken to exclude non-cardiac etiologies. Further pathological evaluation of the heart is then necessary with detailed histopathological examination to exclude clear causes for SCD

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[219]. This may identify structural cardiac genetic disease such as hypertrophic cardiomyopathy that would indicate the need for familial evaluation and the retention of tissue suitable for DNA extraction and targeted genetic testing. This examination is best undertaken with the support of an expert cardiac pathologist to improve the accuracy of diagnosis and guide familial evaluation [210]. In a number of cases pathological findings may be equivocal as to the cause of death: for example idiopathic left ventricular hypertrophy without histological disarray; bicuspid aortic valve; anomalous coronary artery without evidence for ischemia. These should be considered unexplained as familial evaluation can still uncover a significant burden of arrhythmia syndromes in these cases [220]. If the death remains unexplained, then additional investigations may prove helpful. Collection of any available antemortem history or cardiac investigation may provide clues but a normal antemortem ECG does not exclude an underlying cardiac genetic cause, particularly when BrS has been diagnosed in the family [221]. Retention of tissue suitable for DNA extraction permits a molecular autopsy to either confirm a genetic diagnosis or even make the diagnosis in up to 35% of cases [222]. This may also prove helpful in the event of a SUDI death as post-mortem genetic testing reveals mutations in cardiac channelopathy genes in an estimated 10% of SIDS cases [222].

9.4 Management

Once a diagnosis of SUDS has been made, further management revolves around evaluating family members.

9.5 Screening of family members

When first degree relatives of victims of SADS or premature (less than 50 years old) unexplained sudden death undergo cardiac assessment, up to half of families reveal cardiac genetic diseases such as the arrhythmia syndromes (LQTS, BrS and CPVT in particular) and occasionally subtle and difficult to detect forms of cardiomyopathy (ARVC in particular) [202, 209, 223, 224]. If an autopsy has not been undertaken then additional etiologies diagnosed in families include cardiomyopathies in general and familial hypercholesterolemia [209, 223]. The strategy for evaluation often is staged with less invasive investigations first and then more invasive tests if a diagnosis is not made (Figure 3). Family members who are more likely to be affected include those with symptoms of concern such as syncope or seizure; and obligate carriers [224]. The investigative protocol may include: personal history; family history and history of sudden death victim; resting, exercise, signal averaged and ambulatory 24 hour ECG;

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echocardiography; provocation testing with sodium channel blocker and/or epinephrine and cardiac MRI as required [202, 209, 223, 224]. Signal averaged and ambulatory ECGs are least effective in making a clinical diagnosis [209, 224]. Resting and exercise ECG, Class I drug challenge and cardiac imaging offer most diagnostic value consistently across studies [209, 224]. A retrospective revision of an autopsy diagnosis by an expert pathologist may also support a diagnosis in a family [209].

The investigation of family members of cases of SUDI deaths often occurs on an ad hoc basis yet there are little data on its yield. Molecular autopsy identifies a lower burden of ion channel disease in SIDS compared to SUDS and there is a greater likelihood of sporadic genetic disease as a cause of sudden death in infancy. It is therefore likely that the yield of clinical evaluation of first degree relatives will be significantly lower than in SUDS. Nonetheless if there is a positive molecular autopsy result, a family history of other cases of SUDI, SUDS or premature unexplained sudden death or of inherited heart disease then the yield is likely to be greater and familial evaluation more worthwhile.

As with families of SUDS victims, it is reasonable that relatives of SUDI deaths who are obligate carriers or have ominous symptoms such as cardiac syncope should be prioritized for evaluation. In families with SUDS deaths young family members may require periodic re-assessment even if the initial assessment is normal as young patients may only become cognizant of symptoms at an older age, and certain diseases have age-related penetrance. Repeated evaluations should occur if family members become symptomatic or additional suspicious sudden deaths are identified in the family.

10 Inherited Arrhythmia Clinics

Table 11: Inherited Arrhythmia Clinic Expert Consensus Recommendation

Class I	Patients (probands) and first-degree relatives with a diagnosed or suspected inherited cardiovascular disease as a potential cause of SCD (SUDS/SUDI) ***should be evaluated*** in a dedicated clinic with appropriately trained staff

The evaluation and treatment of families suspected of having inherited arrhythmias requires a multidisciplinary team and approach. The presentation often is that of a proband or family member who has experienced a life-threatening arrhythmia, sudden cardiac arrest or SCD. In the usual circumstance, there are profound and far-reaching medical and psychosocial implications of both presentation of the inherited arrhythmia and genetic testing on patients and families [1, 2]. The presence of an inherited arrhythmia or a positive genetic test can

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dramatically change the life of a patient and questions related to transmissibility of disease to one's children, participation in athletics, insurability and prohibited types of employment are among the common questions patients and families face. Perhaps the most important role of the inherited arrhythmia clinic in the case of the sudden death of a proband is to provide support, expert evaluation, advice and treatment to surviving family members.

Recent evidence suggests that a structured inherited arrhythmia (or inherited cardiovascular disease) clinic improves the likelihood of making a diagnosis in suspected cases of inherited arrhythmias and SCD [196, 209, 224-227]. The promise of an appropriately resourced, structured clinic is that of a comprehensive evaluation of patients and families, more efficient use of diagnostic testing and therapy and ready access to a broad range of medical, genetics and psychosocial expertise in managing families afflicted by inherited arrhythmias. An inherited cardiovascular disease clinic is an invaluable resource to patients and families not only at the time of the initial evaluation but in an ongoing fashion as medical, genetic and social questions relevant to the inherited heart disease arise.

There are different operational models for inherited arrhythmia clinics; the choice may be determined by the health system or the regulations that exist in a given country. However, the linchpins of a successful inherited heart disease clinic include not only medical, nursing and genetics proficiency but a dedicated staff with operational and logistic expertise who have ready access to all team members. Each member of the team has key roles to play in the optimal evaluation of families suspected of having inherited arrhythmias. The personnel and workflow in an ideal inherited arrhythmia clinic is illustrated in the schematic in Figure 4. The key personnel include a clinic coordinator who is responsible for patient intake, collection and collation of medical records, scheduling appointments for patients and family members and assisting with questions relating to insurance coverage. The initial evaluation of patients and family members may be performed by a nurse specialist and genetics counselor [228]. This requires not only review of medical records, but pedigree development, collection and collation of medical testing such as imaging studies, pathological specimens, autopsy reports and results of previously performed genetic testing. In the ideal situation, the results of testing on the patient or family members are reviewed by the physicians, nurses and counselors prior to the clinic visit. The physicians are typically a clinical cardiologist / electrophysiologist with expertise in inherited arrhythmias and medical genetics or a medical geneticist with an interest in cardiac arrhythmias partnering with a clinical electrophysiologist. In some countries, only a geneticist is permitted to order and/or discuss genetic test results with patients. It is important to bear in mind that many

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presentations that suggest an inherited arrhythmia may be the result of acquired disease or an inherited cardiomyopathy. If the inherited arrhythmia clinic is part of a larger program in inherited heart disease experts in cardiomyopathy will likely be available, otherwise access to such experts is essential. The team of physicians will perform the general medical evaluation of the patient, review of the records, interpretation of test results and development of diagnostic and identify the treatment plans. In some cases evaluation of a family includes post mortem review of a family member and the opinion of a cardiac pathologist often is useful in making the proper diagnosis.

The increasing complexity and demands of the proper diagnosis and management of patients with inherited cardiovascular disease creates an opportunity for the development of specialized training for clinical electrophysiologists interested in the care of patients with inherited arrhythmias [229]. Such a specialty track would consolidate aspects of care involving indications and interpretation of genetic test results and pharmacological and device therapy.

The management of patients with inherited arrhythmias includes expert judgment regarding the indications, type and interpretation of genetic testing. In collaboration with a genetic counselor, patients and families should be properly prepared regarding expectations and outcomes of genetic testing. The role of genetic testing may vary depending upon the exact inherited arrhythmia being considered and the particular mutation may have an impact on specific therapeutic recommendations. Arguably the most important part of the testing procedure is reviewing the test results and implications with patient and family, being prepared to discuss the implications for other family members, the meaning of variants of uncertain significance (VUS), mosaicism and issues related to paternity and consanguinity. The genetic counselor is an essential [228] and in some countries legally mandated provider in this aspect of the care of patients and families with suspected inherited arrhythmias.

The genetic test only is part of the management of a patient with an inherited arrhythmia. The treatment of patients with inherited arrhythmias may vary from medication therapy and lifestyle modification to device implantation to LCSD. Patients may require invasive EPS and treatment with pacemakers or ICDs. In some cases surgical or thoracoscopic cardiac sympathetic denervation are required for cardiac rhythm control and SCD prevention. In general patients will require adjustment to both the underlying disease and therapy which could be assisted by access to psychologists with an interest in patients with heart disease.

Patients in an inherited arrhythmia clinic may be survivors of SCA. The management of the recovery of these patients from their index event may require the expertise of psychologists,

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psychiatrists and the intervention of physical and occupational therapists. Moreover, the diagnosis of an inherited disease of any kind, particularly one that carries with it the risk of significant morbidity and premature mortality is often associated with significant emotional distress that at times will require referral of patients and families [230-236].

A structured inherited arrhythmia (or heart disease) clinic provides the platform for optimized, multidisciplinary evaluation and management of patients and families with suspected inherited heart disease. The collective efforts of the core staff and access to a variety of experts in related disciplines will result in improved quality of care [224, 226, 233, 237-242], patient satisfaction [233] and improvement in appropriate use of diagnostic testing [196, 209] and therapeutic intervention. The promise of such a clinic structure is lower overall cost and improvement in patient outcomes.

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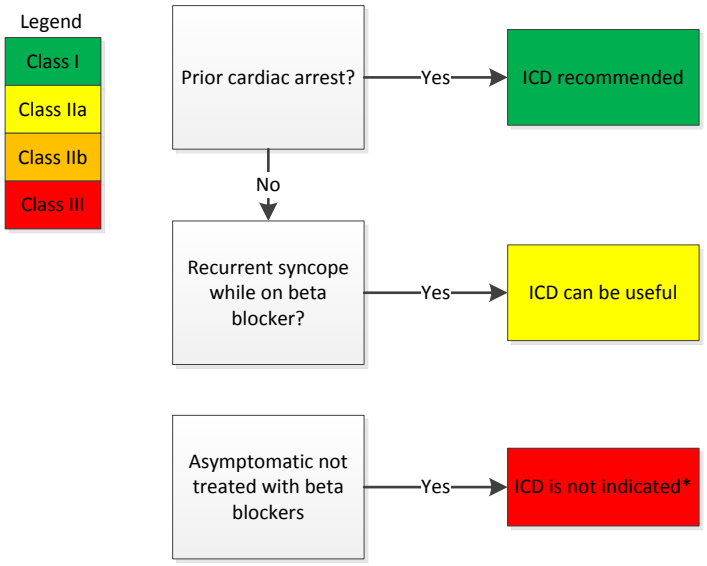
Figure 1: Consensus Recommendations for ICDs in Patients Diagnosed with Long QT Syndrome



*Except under special circumstances, ICD implantation is not indicated in asymptomatic patients who have not been tried on beta-blocker therapy

Figure 2. Consensus Recommendations for ICDs in Patients Diagnosed with Brugada Syndrome

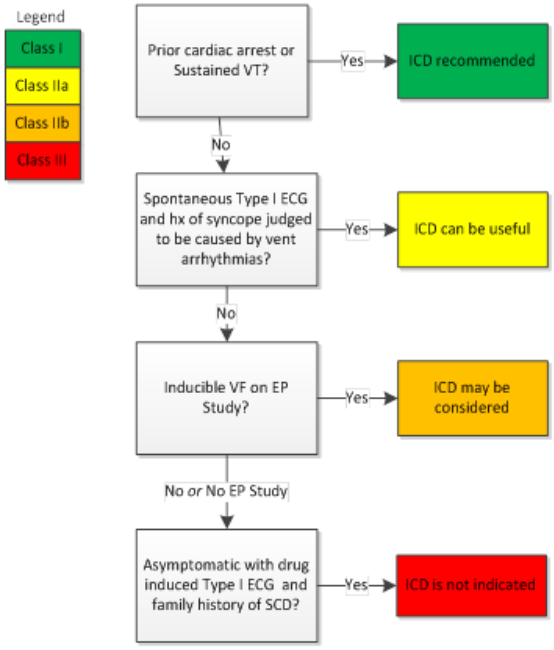
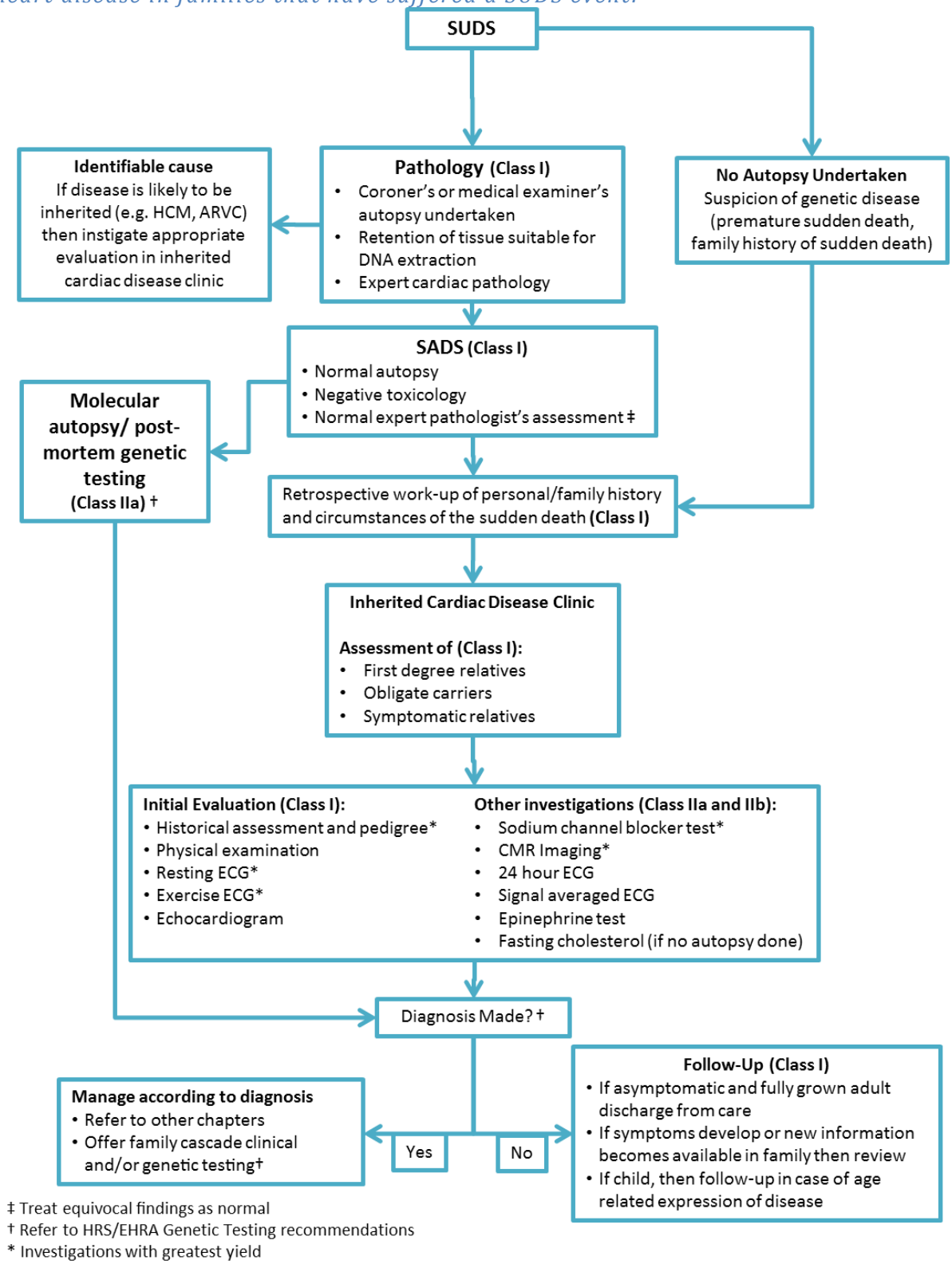
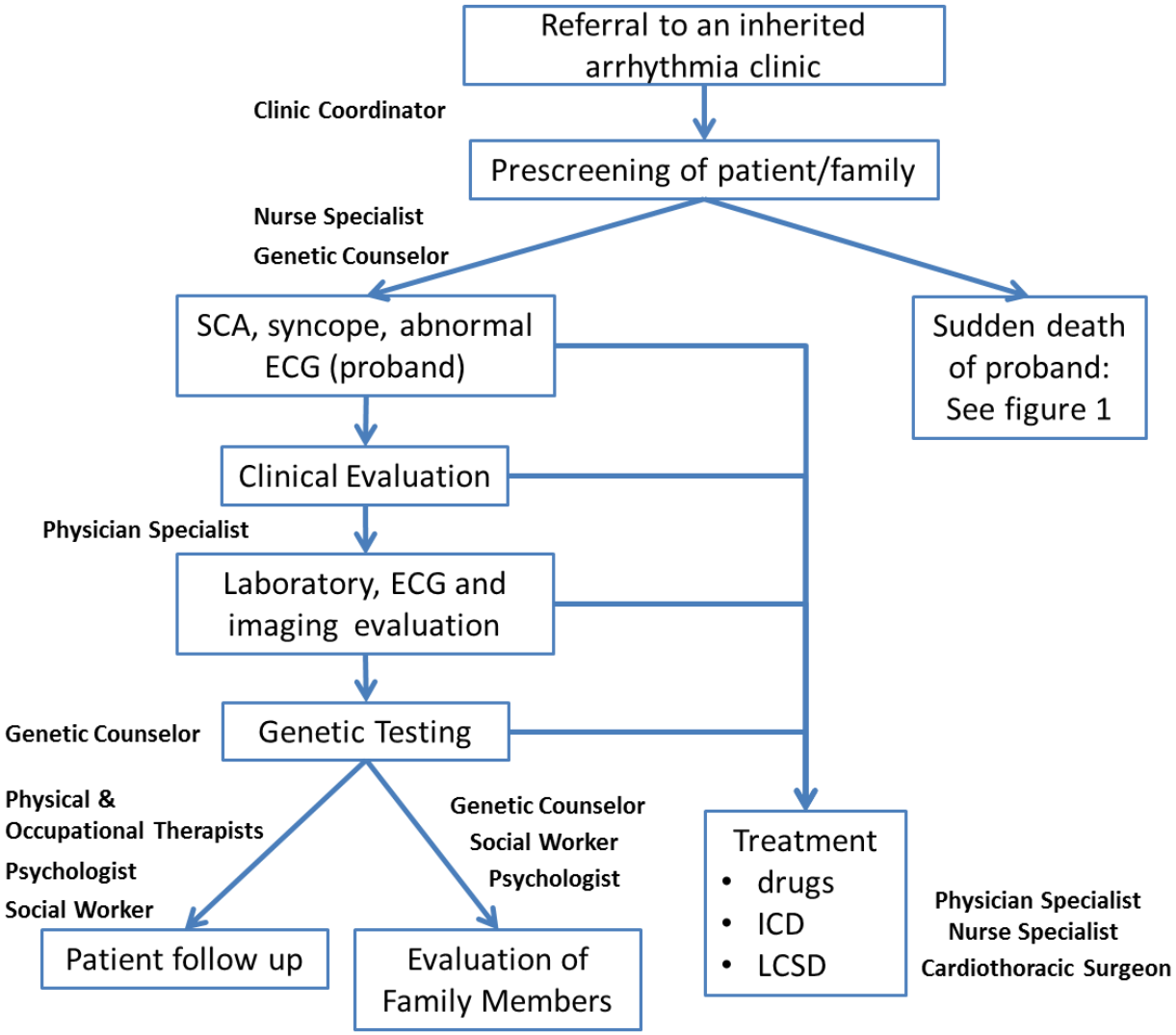


Figure 3: Algorithm to describe the investigative strategy for identification of inherited heart disease in families that have suffered a SUDS event.



‡ Treat equivocal findings as normal
† Refer to HRS/EHRA Genetic Testing recommendations
* Investigations with greatest yield

Figure 4. Workflow and personnel in the evaluation of patients and families with inherited arrhythmias



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Elijah R. Behr, MA, MBBS, MD, FRCP	Cardiovascular Sciences Research Centre, St. Georges University of London, London, UNITED KINGDOM	None	None	Biotronik	British Heart Foundation (f) Boston Scientific-shared with colleague (f) St. Jude Medical-shared with colleague (f) Cardiac Risk in the Young (f)	None	EU-FP7 research project (f) St. Jude Medical-consumables for research (b) British Heart Foundation-Research Grants (f)
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Minoru Horie, MD, PhD	Shiga University of Medical Sciences, Department of Cardiology, Otsu, JAPAN	Daiichi-sankyo (b) Sanofi-Aventis (b) Boelinger Japan (b) Takeda Pharma (b)	None	None	None	None	None
Heikki Huikuri, MD	Oulu University Central Hospital, Division of Cardiology Medicine, Oulu, FINLAND	Sanofi Winthrop (b) Bohringer Ingelheim (b) Bayer (b) Merck (b)	None	Daiichi Sankyo Pharma Dev. (d)	None	None	None
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Andrew D. Krahn, MD, FHRS	University of Western Ontario, University Hospital, London, CANADA	Medtronic (b)	None	Medtronic (f) St Jude Medical (f) Boston Scientific (f)	Medtronic (d) St Jude Medical (c)	None	None
Antoine Leenhardt, MD	AP-HP, Bichat Hospital, Service de Cardiologie et Centre de Référence des Maladies Cardiaques Héréditaires, Paris, France	Servier (b); Sanofi (b); MEDA Pharma (b); Bayer (b);St. Jude Medical (b); MSD (b); Boston Scientific (b); Medtronic (b); Biotronik (b); Boehringer Ingelheim (b) Genzyme (b)	*None*	*None*	*None*	*None*	*None*

(a) = $0; (b) = < $10,000; (c) = >$10,000 to < $25,000; (d) = >$25,000 to <$50,000; (e) = >$50,000 to < $100,000; (f) = >$100,000

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(a) = $0; (b) = < $10,000; (c) = >$10,000 to < $25,000; (d) = >$25,000 to <$50,000; (e) = >$50,000 to < $100,000; (f) = >$100,000

Peer Reviewer Disclosure Table

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Bernard Belhassen, MD	Tel Aviv Medical Center, Tel Aviv, ISRAEL	None	None	None	None	None	None
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Eric Schulze-Bahr, MD, PhD	University of Munster, Munster, GERMANY	None	None	None	None	None	None
Christian Wolpert, MD	University Hospital Mannheim, Ludwigsburg, GERMANY	1; Medtronic Inc., St. Jude Medical, Bard Electrophysiology, Sorin Group	None	None	None	None	None

Peer Reviewer Disclosure Table

Peer Review	Employment	Consultant/ Advisory Board	Speakers' Bureau/ Honoraria	Research Grant	Fellowship Support	Board Mbs/Stock Options/Partner	Others
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Robert M. Campbell, MD	Sibley Heart Center, Emory University School of Medicine, Atlanta, GA, USA	None	None	None	None	None	None
Edward T. Martin, MD	Oklahoma Heart Institute, Tulsa, OK, USA	1; Lantheus, Siemens,	None	None	None	None	None
Swee Chye Quek, MD	National Univeristy of Singapore, SINGAPORE	None	None	None	None	None	None

NUMBER	VALUE
0 =	$0
1 =	< $10,000
2 =	> $10,001 to < $25,000
3 =	> $25,001 to < $50,000
4 =	> $50,001 to < 100,000
5 =	> $100,001