Heart Rhythm UK position statement on clinical indications for implantable cardioverter defibrillators in adult patients with familial sudden cardiac death syndromes

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Whilst the decision regarding defibrillator implantation in a patient with a familial sudden cardiac death syndrome is likely to be most significant for any particular individual, the clinical decision-making process itself is complex and requires interpretation and extrapolation of information from a number of different sources. This document provides recommendations for adult patients with the congenital Long QT syndromes, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. Although these specific conditions differ in terms of clinical features and prognosis, it is possible and logical to take an approach to determining a threshold for implantable cardioverter-defibrillator implantation that is common to all of the familial sudden cardiac death syndromes based on estimates of absolute risk of sudden death.

Keywords
Sudden cardiac death syndromes • Consensus document • Implantable cardioverter defibrillator

The sudden unexpected death of a young or relatively young person can have profound implications for the surviving family members beyond those associated with bereavement and the immediate sense of loss. Among these other sequelae may be a concern that the sudden death was caused by a genetic condition and that other family members may suffer the same fate. This increased awareness of the role of inherited conditions in the development of malignant ventricular arrhythmias and sudden death of young individuals has been accompanied by widespread acceptance of the implantable cardioverter defibrillator (ICD) as an important potential means of preventing sudden death in these circumstances.

Although the decision regarding defibrillator implantation is likely to be one of the most significant for any particular individual, the clinical decision-making process itself is complex and requires interpretation and extrapolation of information from a number of different sources. The relative rarity of the individual conditions seriously limits the amount and quality of the data upon which the clinician can draw in making a recommendation. It is not unusual for different members of the same family to receive different recommendations regarding ICD therapy from their (different) respective cardiologists despite little or no difference in their clinical circumstances. Patients can find this situation both difficult to...
understand and frustrating. International and national clinical guidelines have an important role in this process. The purpose of the current document is to focus particularly on the indications for ICD implantation in adult patients (16 years and over) with the familial sudden death syndromes, specifically the ion channelopathies (long QT syndromes (LQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT)), hypertrophic cardiomyopathy (HCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). All patients with (or suspected of having) one of these familial sudden cardiac death (SCD) syndromes should be assessed by a clinician with considerable experience in the management of these conditions. This document does not aim to provide recommendations for ICD implantation for children with these syndromes.

The ACC/AHA/ESC 2006 guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

The ACC/AHA/ESC guidelines (2006) reflect a consensus of international expert opinion on the management of patients with ventricular arrhythmias and others considered at risk of sudden death. Specific sections of this document address ventricular arrhythmias associated with 'genetic arrhythmia syndromes' and cardiomyopathies. These guidelines are intended to assist health care providers in clinical decision-making by 'describing a range of generally acceptable approaches for the diagnosis and management of specific diseases or conditions.' They attempt to 'define practices that meet the needs of most patients in most circumstances.'

With regard to ICD implantation in the familial sudden death syndromes, the recommendations are very broad in terms of what can be considered acceptable practice. For instance, class I indications (ICDs definitely indicated) are largely restricted to patients who have already demonstrated a propensity for malignant ventricular arrhythmias or sudden death. No class III indications (ICDs contraindicated) are suggested by these guidelines. As a consequence, the 2006 guidelines reflect the uncertainties and broad range of current clinical practice internationally. In the current document, we aim to provide a more detailed discussion of the approach to clinical decision-making regarding ICD implantation in the adult patient population, with an emphasis on (i) establishing a correct clinical diagnosis, (ii) assessment of absolute risk of sudden death within specific clinical and genetic subgroups where possible, and (iii) published experience of ICDs in these patients. Details of molecular genetics, pathophysiology, and wider management aspects are not described in detail but are discussed where necessary in order to put the issues relevant to ICD implantation in perspective. The specific recommendations in this document are based on a unified consensus-based approach to determining appropriate thresholds for ICD implantation across the range of familial SCD syndromes. The target users of this position statement include all healthcare professionals involved in the management of this group of patients.

Development of the position statement

(i) The decision to recommend implantation of an ICD is dependent upon a balance between perceived risks of sudden death in an individual patient (often expressed in terms of per cent risk of death/year) and the morbidity/mortality associated with lifelong ICD therapy, which is not easy to quantify. A survey of UK electrophysiologists was undertaken to examine an overall threshold for ICD implantation in terms of percentage risk of sudden death per year. We postulated that heart rhythm specialists with the experience of ICD implantation and follow-up would be well placed to put the risks of ICDs in context, particularly if they were to imagine themselves in the position of the patient. The following question was emailed to 71 electrophysiologists/ICD implanters in the UK: 'If you personally had a cardiac condition with a quantifiable risk of sudden death, and the only treatment was an ICD, what level of risk (in terms of percentage risk of death/year) would prompt you to have an ICD implanted? The question refers to your current age and it is assumed that this level of risk remains constant with time.' Of the 50 respondents, the most common response (42% of respondents) received regarding the ICD threshold was 1% risk of sudden death/year, with a mean value of 2.47%/year. Implanters >45 years had a significantly higher threshold for implantation (3.06 ± 1.38%/year) than younger implanters (1.64 ± 1.08%/year, P < 0.05).

(ii) Consensus process. A statement development group was selected by the Council of Heart Rhythm UK, consisting of cardiac electrophysiologists, cardiac nurses, patient representatives, and specialists in heart muscle disease. An initial meeting of the group was held at which the need for a specific document addressing a unified approach to ICD implantation in the familial SCD syndromes was agreed and the results of the survey of UK implanters regarding thresholds for ICD implantation were presented. Subsequently, a comprehensive review of evidence in English language publications relating to diagnostic criteria, risk assessment, and ICD implantation in the syndromes was undertaken by specified group members. Specific attention was directed to studies in which absolute risks of sudden death (rather than relative risks of cardiac events) were quoted or could be calculated. A draft document was produced according to a pre-specified format common to the individual conditions addressed.

The congenital long QT syndromes

The congenital LQTS are caused by genetically determined disturbances of ion channel function leading to prolonged repolarization in ventricular myocytes. LQT1 is caused by mutations in the gene KCNQ1, which encodes for the potassium channel that, when co-expressed with other subunits, produces the k_s current. LQT2 is caused by mutations in KCNH2, the gene encoding the potassium channel that carries the k_n current. Mutations in the cardiac sodium channel gene SCN5A cause LQT3. Although a
number of rarer forms of the syndrome exist, LQT 1, 2, and 3 comprise the majority of genotyped patients.\textsuperscript{8,9}

**Current ACC/AHA/ESC guidelines for implantable cardioverter defibrillator prescription in long QT syndromes**

The classes of ICD indications as defined by the ACC/AHA/ESC Writing Committee can be summarized as follows and refer to individuals who otherwise have reasonable expectation of survival with a good functional status for $\geq 1$ year.

**Class I.** Implantation of an ICD along with the use of beta-blockers is recommended for LQTS patients with previous cardiac arrest (level of evidence: A).

**Class IIa.** Implantation of an ICD with continued use of beta-blockers may be effective to reduce SCD in LQTS patients experiencing syncope and/or VT while receiving beta-blockers (level of evidence: B).

**Class IIb.** Implantation of an ICD with the use of beta-blockers may be considered for prophylaxis of SCD for patients in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3 (level of evidence: B).

**Establishing a clinical diagnosis**

**Classical findings**

The classical clinical presentation of the condition is with syncope or cardiac arrest in a child or adolescent, associated with a family history of similar presentations and with a prolonged QT interval on the surface electrocardiogram (ECG). The original syndrome described by Jervell and Lange-Neilsen is associated with congenital deafness (autosomal recessive), with the autosomal dominant form (Romano-Ward) being associated with normal hearing. Triggers for syncope/cardiac arrest differ in the three commonest forms of autosomal dominant disease. In LQT1, cardiac events occur typically in the setting of physical exertion, including swimming. LQT2 arrhythmias are classically associated with sudden auditory stimuli like alarm bells and telephone rings. LQT3 is best known for death or syncpe during sleep.

**Electrocardiographic features**

The typical electrocardiographic features of severely affected individuals include marked prolongation of the QT interval (often in excess of 500 ms) and significant T wave abnormalities including T wave alternans and intermittent marked T wave inversion. Since the advent of genetic testing, it has become clear that characteristic T wave shapes correlate with specific genotypes although there is considerable overlap. Patients with LQT1 tend to have a broad and pronounced T wave or late onset of a normal appearing T wave. Patients with LQT2 have low-amplitude T waves or bifid T waves and those with LQT3 have the latest appearing T waves that are peaked and/or bifid or are asymmetrical with a steep downslope.

**Lesser degrees of QT prolongation**

It is increasingly acknowledged that, in addition to the classical presentation, symptomatic individuals may present with lesser degrees of QT prolongation or even borderline or normal corrected QT intervals. The QT interval is defined as the interval from the onset of the QRS complex to the point at which the T wave ends.\textsuperscript{10} When the QT interval is measured in individual leads, the lead showing the longest QT should be used (usually V2 or V3). However, if this measurement differs by $\geq 40$ ms from that in other leads, the measurement may be in error and measurements from adjacent leads should be considered. The QT interval is considered prolonged when it exceeds 450 ms in males and 460 ms in females following correction for heart rate.\textsuperscript{10} Many medications and other cardiac conditions can give rise to prolonged QT intervals and this should be taken into consideration when the diagnosis of congenital LQTS is being suggested. Some authors recommend the use of provocative epinephrine tests\textsuperscript{11} if the syndrome is suspected but the QT interval or normal or borderline. These provocative tests have been evaluated only in selected subgroups, however, and are not foolproof even in these groups. The decision to perform epinephrine provocative testing should be taken in the context of the clinical and family history and the likely effect on patient management that would result from a ‘positive’ or ‘negative’ result; currently they are not recommended as part of routine clinical practice.\textsuperscript{12}

Conventional electrophysiological testing does not have a role in the diagnosis of LQTS.

**Genetic testing**

The advent of genetic testing for mutations associated with the congenital LQTS has raised the possibility of a “genetic diagnosis” for suspected cases.\textsuperscript{13} Although the specificity of a positive result is very high, the diagnostic yield (sensitivity) of current genetic testing is relatively modest. In patients with classical clinical presentations, the pick-up rate varies between 70 and 90% (depending upon the laboratory involved) but in patients with borderline QT interval prolongation, the diagnostic yield is significantly less than this, perhaps 20–30%. For this reason, and the fact that a ‘negative’ result does not exclude the diagnosis, widespread genetic testing of individuals presenting with normal/borderline QT intervals, no other clinical features and no family history of the syndrome has a very limited role as a means of diagnosis.

**Risk of sudden death within specific clinical and genetic subgroups**

The overall population-based risk of the LQTS with expressed phenotypic evidence of disease is low\textsuperscript{14} when receiving appropriate treatment most usually with beta-blockers.\textsuperscript{15} Evidence from the international LQT registry indicates an $\approx 4\%$ risk of mortality over 40 years,\textsuperscript{14,16} i.e. 0.1%/year and this observation is further supported by their most recent data.\textsuperscript{17}

Indicators of high relative risk of sudden death include a personal history of aborted SCD or syncope and QT prolongation $\geq 500$ ms. Recent syncope (within the last 2 years) is a stronger predictor of aborted cardiac arrest/death than is a more remote history of syncope.\textsuperscript{17} Gender and age also play significant roles in influencing the clinical course of LQTS in that cardiac events tend to occur more frequently in children, with males having an increased risk of events during pre-adolescence and females having higher event rates in adolescence and beyond.\textsuperscript{18} Although it is often assumed that sudden death of a sibling is a risk factor
for death in LQTS patients, there is little evidence to support this. Kaufman et al.\textsuperscript{19} have specifically examined this question among relatives of probands entered into the International Long QT Registry between 1979 and 2006. Clinical and ECG criteria were obtained at enrolment and updated annually. Of the 1915 subjects, there were 270 who had a sibling who had died. In a multivariate analysis, QTc $>0.53$ s and a personal history of syncope were associated with an increased risk of aborted cardiac arrest or death but death of a sibling was not. The authors concluded that severe symptoms in a close relative cannot be used as an indicator of personal risk for those family members affected by the same pathogenic substrate; rather, that incomplete penetrance and variable expressivity that are such consistent findings in LQTS preclude predicting severity of symptoms even in siblings. In contrast, an individual’s own QTc and history of syncope were strong predictors of risk. Unusually for a study of this type, the authors also examined absolute risk of aborted cardiac arrest/death for asymptomatic individuals on beta-blockade who had had a sibling die. No aborted cardiac arrest/deaths occurred in 50 such individuals over a 5-year period.

**Patients presenting with aborted cardiac arrest**

Although there are no prospective studies available on the risk of recurrent cardiac arrest in LQTS patients presenting with aborted sudden death and not treated with ICDs, such individuals are thought very likely to suffer subsequent events and it is for this reason that this form of presentation is considered an AHA/ACC/ESC class 1 indication for ICD implantation. Zareba et al.\textsuperscript{20} described a group of such patients, used as historical controls for comparison with a matched group undergoing ICD implantation. Twenty-seven of 89 patients died or had recurrent cardiac arrest during a 9-year follow-up, i.e. an absolute risk of death of 3.37%/year. As a consequence of the retrospective nature of the data collection in this study,\textsuperscript{21} it is likely that this figure represents an upper estimate of the true risk of sudden death in these patients. Many of the ’controls’ died within the first month after identification, suggesting that they may have died as a result of complications of the original cardiac arrest and that their deaths may not have been sudden or preventable by ICD therapy. Indeed more recent studies\textsuperscript{22} suggest that outcomes of LQTS patients presenting with cardiac arrest maybe good if appropriately treated with beta-blockade. Nevertheless, in LQTS patients presenting with aborted cardiac arrest, the consequences of a recurrence of malignant ventricular arrhythmias (for instance due to drug non-compliance or other reason) are such that ICD implantation is recommended in this group.

Recommendation: Long QT syndrome patients presenting with ventricular fibrillation/cardiac arrest without reversible precipitant should undergo ICD implantation in addition to oral beta-blockade.

**Patients presenting with syncope despite beta-blockade**

The same study\textsuperscript{20} also described a historical control group consisting of LQTS patients with continuing syncope despite beta-blockade. Eleven of 72 patients died or had recurrent cardiac arrest during a 7-year follow-up, i.e. 2.18%/year.

Although the same reservations regarding the retrospective nature of this and similar studies still apply,\textsuperscript{21} given the likely high absolute risk of sudden death in this patient group, ICD implantation is certainly a reasonable approach. It is important to recognize however that left cardiac sympathetic denervation (LCSD) is an underused option and should be considered in patients with syncopal symptoms persisting despite full beta-blockade, those with asthma or other intolerance of beta-blockers, and those with shocks who already have an ICD in place. Left cardiac sympathetic denervation is associated with significant reduction in the incidence of aborted cardiac arrest and syncope in high-risk LQTS patients, although it does not confer complete protection.\textsuperscript{23} Although this procedure, either via a video-assisted thoracoscopic procedure\textsuperscript{24,25} or using the traditional surgical approach, cannot completely abolish the risk of subsequent arrhythmic events and sudden death, it does offer a reasonable alternative to ICD particularly in the paediatric population when the co-morbidity associated with ICD treatment can be high.\textsuperscript{26}

In terms of beta-blocker therapy, the particular agent may well be relevant in terms of efficacy in the LQTS, with many clinicians preferring propranolol or nadolol based on the long-term experience with these agents that block both beta-1 and beta-2 adrenergic receptors.\textsuperscript{27} The European experience indicates success with these drugs when properly used, leading to low residual SCD rates.\textsuperscript{15,28} Available data from numerous studies indicate excellent symptom suppression and almost zero mortality in LQT1 patients treated with these drugs long-term,\textsuperscript{15,28} non-compliance and the use of QT-prolonging drugs being responsible for almost all life-threatening "beta-blocker failures."\textsuperscript{22}

LQT2 patients are also best treated with beta-blockers as the first line of management. In this group, syncope suppression is not so good as in LQT1 but the Italian experience would again suggest an excellent impact on prognosis.\textsuperscript{15} Recent data taken from adolescents from the International LQT registry would also support that view.\textsuperscript{17}

LQT3 patients have mutations in SCN5A and are relatively uncommon\textsuperscript{7} with less published experience of the outcome when treated with beta-blockers.\textsuperscript{15} LQT3 patients are less likely to present with warning symptoms, with the first event potentially being SCD and this may have provoked the concern physicians express in the management of these patients.\textsuperscript{19} More recent reports of the outcome of LQT3 patients\textsuperscript{29} suggest that although infants who suffer cardiac events during their first year of life suffer from a highly malignant form of the disease, most LQT3 patients can do well and for a long period of time with the current therapies. Beta-blockers will often be prescribed in the first instance before the genotype is available unless the clinician is absolutely certain regarding an LQT3 diagnosis based on the ECG. It seems likely that beta-blockers will remain the initial treatment for many LQT3 patients and there is evidence that LCSD can be very effective in their management.\textsuperscript{29} Potentially valuable (but unproven) drug options such as flecainide, mexiletine, and calcium channel blockers are likely to be reserved for patients with ICDs in situ and continuing symptoms.

Recommendation: Long QT syndrome patients experiencing continuing syncope despite beta-blockade or LCSD (when VT/VF has not been excluded as the cause of syncope) should undergo ICD implantation.
Patients without symptoms

Priori et al. examined lifetime cardiac event rates (syncope and sudden death) in initially asymptomatic patients. There were statistically significant differences in the rates of cardiac events and cardiac arrest/sudden death depending on the underlying genotype, with patients with LQT2 or LQT3 having a higher risk than those with LQT1; hence the class Ib indication for ICD implantation in the ACC/AHA/ESC guidelines (LQT2 or LQT3). With regard to the key endpoint of SCD, absolute event rates according to genotype were as follows:

- LQT1: 0.3%/year (males 0.33%, females 0.28%);
- LQT2: 0.6%/year (males 0.46%, females 0.82%);
- LQT3: 0.56%/year (males 0.96%, females 0.30%).

So with regard to asymptomatic patients even with the highest risk genotype, risk of death was <1%/year, suggesting that the indication for ICD implantation is not particularly strong in any of these groups. The reported risk in a study looking at beta-blockers in different genotypes would also support a good prognosis with four sudden deaths occurring in an average 5-year follow-up in 335 patients. These data do not support the current class Ib recommendation for ICD implantation in asymptomatic individuals based purely on genotype.

If one were to try and identify specific high-risk features among asymptomatic patients with LQTS, then QT duration would seem a much better candidate than genotype. The major factor contributing to an increased risk of cardiac events (syncope, aborted cardiac arrest, or LQTS-related death) during childhood or adolescence is a QTc interval >500 ms. Sauer et al. studied adults presenting after age 18 in the International Long QT Syndrome Registry and looked at aborted cardiac arrest/LQTS death, endpoints particularly relevant to ICD therapy. Potential lethality of LQTS in adulthood, measured by aborted cardiac arrest or LQTS-related sudden death was related to female gender, QT duration >500 ms, and internim syncope after age 18. These all supercede genotype in terms of predictive power. QTc was particularly relevant, with a QTc of 500–549 ms (vs. <499 ms) associated with an HR of 3.34, and a QTc interval of >550 ms (vs. <499) contributed an HR of 6.35. Moreover, any QTc interval <499 ms was found not to contribute independently to an increased risk of a lethal event (compared with a QTc interval <493 ms). These risk factors held true for asymptomatic as well as symptomatic patients. The frequency of ACA before age 18 and the frequency of ACA/LQTS-related death after age 18 were similar among the three genotypes.

Recommendation: The identification of an LQT2 or LQT3 genotype should not by itself constitute an indication for ICD implantation.

Electrophysiological studies

Conventional invasive electrophysiological testing using programmed stimulation protocols designed for other applications is not helpful in terms of defining the risk of SCD. There may be a role for invasive phenotyping although prospective evidence of benefit is needed.

Brugada syndrome

The Brugada syndrome is an inherited condition that is characterized by ventricular arrhythmias, syncope, or sudden death in the presence of a specific ECG pattern: coved ST elevation and J-point elevation of at least 2 mm in at least two of the right precordial ECG leads in the absence of cardiac structural disease. Altered function of the ion currents fK1, ICaL, or IKur are thought to be possible mechanisms for this syndrome. To date, the great majority of identified disease-causing mutations have been located in the SCN5A gene encoding the alpha subunit of the human voltage-gated sodium channel.

Current ACC/AHA/ESC guidelines for implantable cardioverter defibrillator prescription in Brugada syndrome

The classes of ICD indications as defined by the ACC/AHA/ESC Writing Committee can be summarized as follows and refer to individuals who otherwise have reasonable expectation of survival with a good functional status for >1 year.

- **Class I.** An ICD is indicated for Brugada syndrome patients with previous cardiac arrest.
- **Class Ia.** An ICD is reasonable for Brugada syndrome patients with spontaneous ST segment elevation in V1, V2, or V3 who have had syncope; an ICD is reasonable for Brugada syndrome patients with documented VT that has not resulted in cardiac arrest.
- **Class Ib.** EP testing may be considered for risk stratification in asymptomatic Brugada syndrome patients with spontaneous ST elevation.

Establishing a clinical diagnosis

The diagnosis of the syndrome in an individual requires the presence of the type 1 Brugada ECG pattern with at least one of the other recognized diagnostic criteria from the 2005 consensus document: syncope, prior cardiac arrest, documented or inducible polymorphic ventricular tachycardia or ventricular fibrillation, a family history of sudden death <45 years old, or nocturnal agonal respiration. As part of the diagnostic process, it is important to exclude other conditions that may mimic the Brugada ECG pattern. These include structural disease that may be hereditary (ARVC) or acquired (for example, acute myocardial infarction or ischaemia of the right heart or pulmonary embolism) and similar ECG patterns in normal hearts (early repolarization syndrome or hypothermia). These are separate clinical entities and have different pathophysiology and prognoses.

The ECG pattern can be dynamic and therefore intermittently present. In some cases, the ECG pattern may be associated with fever, electrolyte abnormality, or drug exposure. It can also be incompletely expressed in a family. Known or suspected mutation carriers can have a normal ECG or a non-diagnostic Brugada pattern of a saddle-shaped ST segment with or without elevation: the type 2 and 3 ECG patterns, respectively. In these cases, a diagnostic challenge with a sodium channel blocker such as ajmaline, flecainide, propafenone, and procainamide may
induce the typical type 1 ECG pattern and support the diagnosis in a family member.\textsuperscript{37}

It has become apparent that sporadic cases of type 1 ECGs without a family history or other diagnostic features of the condition may occur, some being revealed by exposure to drugs with sodium channel-blocking effects. Only a small proportion of these drug-induced cases are associated with ventricular arrhythmias and could hence be described as the Brugada syndrome.\textsuperscript{38,39} It is not clear whether these sporadic cases have an underlying genetic predisposition, and whether they represent latent Brugada syndrome has not been clearly established.

**Genetic testing**
Genetic testing has a very low sensitivity for the Brugada syndrome, with a ‘positive’ test being found in only $\approx 30\%$ of those with clear evidence of the clinical syndrome. As a consequence, the value of genetic testing for diagnostic purposes is limited.

**Risk of sudden death within specific clinical and genetic subgroups**

The understanding of the risk of sudden death in the Brugada syndrome has been informed by reports from a few different series of patients. The Brugada group, who originally described the syndrome in 1992, hold a registry with a large number of individuals collected from across Europe and the USA.\textsuperscript{36,40–43} There are other separate cohorts from an Italian group led by Priori et al.\textsuperscript{44,45}, a joint European venture led by Wilde and Eckardt and colleagues\textsuperscript{46–48} and the Japanese Idiopathic Ventricular Fibrillation Study Investigators.\textsuperscript{49} Franco-Japanese\textsuperscript{50} and Belgian\textsuperscript{51} groups have reported their experiences of ICD implantation in Brugada syndrome, the latter for primary prevention and from the Brugada group.

Indicators of high relative risk of sudden death associated with the syndrome include a personal history of aborted SCD or syncope (RR 3.51), the spontaneous presence of a type 1 ECG pattern (as opposed to a drug-induced type 1 pattern) (RR 4.65), male gender (RR 3.47), and South-East Asian origin. A family history of sudden death and SCN5A mutation status do not carry an increased risk of sudden death.

**Patients presenting with aborted cardiac arrest**

Table 1 describes these data according to patient presentations with the diagnostic type 1 Brugada ECG and sudden death rates or appropriate ICD shock rates. Despite some variation in terms of absolute rates of SCD, it is clear that patients presenting with the Brugada ECG and aborted cardiac arrest have a very high risk of subsequent similar events and there is widespread agreement that an ICD is indicated in these patients.

**Recommendation:** Brugada syndrome patients presenting with ventricular fibrillation/cardiac arrest without reversible precipitant should undergo ICD implantation.

**Patients presenting with syncope**

Absolute rates of potentially lethal events are also high in Brugada patients presenting with syncope (Table 1) and are very similar to those associated with LQTS patients experiencing syncope despite beta-blockade; all studies show rates considerably higher than 1% per year.

**Recommendation:** Brugada syndrome patients with syncope (when VT/VF has not been excluded as the cause of syncope) should undergo ICD implantation.

**Spontaneous type 1 electrocardiogram in the absence of symptoms**

There is considerable controversy concerning the management of the asymptomatic Brugada syndrome with a spontaneous type 1 ECG abnormality. In a subgroup analysis of a larger series, Brugada et al.\textsuperscript{51,42} reported event rates in 547 patients who had not suffered a previous cardiac arrest, 423 (77%) of whom were asymptomatic and 55% of whom had a family history of SCD. The overall risk of sudden death or ventricular fibrillation was 8% over 24 months of follow-up (4% per year) and this was greatest among individuals with spontaneous type 1 ECG patterns, syncope, and sustained ventricular arrhythmia inducible at EP studies. Asymptomatic carriers with and without spontaneous ECG abnormalities were also found to be at higher risk if they were inducible at EPS.

Contemporaneously, Priori et al.\textsuperscript{45} had published a cohort of 200 patients with a longer mean follow-up time (34 ± 44 months) in which EP studies had a low positive predictive value for cardiac events and sudden death. Patients with spontaneous ECG abnormalities and syncope were at highest risk (hazard ratio 6.4). Those without syncope but a spontaneous type 1 ECG pattern (41%) were at an intermediate risk (hazard ratio 2.1), whereas a negative baseline ECG, with or without syncope, was considered low risk.

**Table 1** Cardiac event rates per annum from different study populations for different clinical presentations of Brugada syndrome calculated from available data

<table>
<thead>
<tr>
<th></th>
<th>Brugada et al.\textsuperscript{41}</th>
<th>Sacher et al.\textsuperscript{50}</th>
<th>Takagi et al.\textsuperscript{49}</th>
<th>Sarkozy et al.\textsuperscript{51}</th>
<th>Probst et al.\textsuperscript{48}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patient numbers</td>
<td>334</td>
<td>220</td>
<td>188</td>
<td>47</td>
<td>1029</td>
</tr>
<tr>
<td>Prior cardiac arrest</td>
<td>13.8%</td>
<td>10.7%</td>
<td>9.8%</td>
<td>Not studied</td>
<td>7.7%</td>
</tr>
<tr>
<td>Previous syncope</td>
<td>8.8%</td>
<td>3.15%</td>
<td>1.9%</td>
<td>2.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>(72% FH) 3.74%</td>
<td>(54% FH) 1.7%</td>
<td>(10% FH) 0%</td>
<td>(57% FH) 4.8%</td>
<td>(37% FH ) 0.5%</td>
</tr>
<tr>
<td>Asymptomatic spontaneous type 1 ECG</td>
<td>6.4%</td>
<td>2.54%</td>
<td>0%</td>
<td>Unavailable</td>
<td>0.81%</td>
</tr>
<tr>
<td>Asymptomatic drug-induced type 1 ECG</td>
<td>0%</td>
<td>0.73%</td>
<td>0%</td>
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<td>0.35%</td>
</tr>
</tbody>
</table>

Event rates are rates per annum of sudden cardiac death, ventricular fibrillation, or (in patients with ICDs) appropriate shocks per annum.
This conflict has been repeated when the other studies in Table 1, apart from Sarkozy et al., are compared with the Brugada group data. They have generally demonstrated lower event rates, particularly among asymptomatic individuals, a lower proportion of individuals with a family history of SCD, possibly indicating less penetrant and therefore less severe disease, and a failure of positive predictive value for EP studies, probably because of the lower event rate. The argument has focused on two main characteristics of the cohorts being studied: whether Brugada syndrome had been sufficiently and accurately diagnosed on the basis of the presence of type 1 ECGs in the non-Brugada series; and whether the Brugada registry was subject to a referral bias towards more severe cases, a trend commonly seen in early registry data for many relatively uncommon conditions.

The publication of two meta-analyses has informed the debate further regarding the role of electrophysiology. In both meta-analyses, a discrepancy was detected between the Brugada series and other studies, with little positive predictive value being found by the latter group. It was suggested that the early referrals to the registry, ‘the founders’ effect’ may be causing selection bias. There was agreement however concerning the high negative predictive value of EPS in asymptomatic patients, which is consistent whether the higher risk Brugada series is considered or the other studies described by Paul et al.

The controversy over the role of EPS may be resolved by further systematic long-term prospective studies in the USA and Europe. In the meantime, there are methodological concerns about EP studies: the greater inducibility of Brugada syndrome patients compared with normal individuals; the ‘false positive rate’ in normal subjects; the reproducibility of findings; and the relevance to a dynamic and varying substrate. In summary, the value of EP studies to predict sudden death in asymptomatic patients is unclear and unresolved. They may provide some reassurance if negative in asymptomatic patients, but the risk of inconclusive positive results must be appreciated.

A firm recommendation regarding ICD implantation in this group (spontaneous type 1 ECG without symptoms) cannot be made at this time; either a conservative strategy or ICD implantation based on results of EP testing can be supported by different series.

Asymptomatic patients who require drug-provocation to reveal the Brugada pattern

In contrast to the controversy discussed above, there is widespread agreement that asymptomatic patients who require drug-provocation to reveal the Brugada pattern are at very low risk of sudden death (Table 1).

Recommendation: Asymptomatic individuals who require a drug to induce the type 1 ECG pattern are at low risk of sudden death and the risks of ICD therapy are likely to outweigh the benefits in this group.

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic VT is an uncommon arrhythmogenic disorder characterized by life-threatening ventricular arrhythmias associated with physical or emotional stress in the absence of structural heart disease. The autosomal dominant form is caused (in up to 60% of cases) by mutations in the cardiac ryanodine receptor gene RyR2. This gene encodes the cardiac ryanodine receptor, the major calcium release channel on the sarcoplasmic reticulum in cardiac myocytes. A rarer autosomal recessive form has been found to be associated with mutations in the cardiac calsequestrin gene CASQ2, which encodes the SR Ca²⁺-binding buffer protein CASQ2. It is thought that the resulting defective calcium handling predisposes to malignant ventricular arrhythmias via delayed afterdepolarization-induced extrasystolic activity under conditions of exercise or other catecholaminergic stimuli.

Current ACC/AHA/ESC guidelines for implantable cardioverter defibrillator prescription in catecholaminergic polymorphic ventricular tachycardia

The classes of ICD indications as defined by the ACC/AHA/ESC Writing Committee can be summarized as follows and refer to individuals who otherwise have reasonable expectation of survival with a good functional status for >1 year.

Class I.

- Implantation of an ICD along with the use of beta-blockers is recommended for patients with CPVT who are survivors of cardiac arrest (level of evidence C).

Class IIa.

- Implantation of an ICD along with the use of beta-blockers can be effective for affected patients with CPVT with syncope and/or documented sustained VT while receiving beta-blockers (level of evidence C).

Establishing a clinical diagnosis

Classical features

Patients are usually children, adolescents, or young adults presenting with syncope due to bidirectional ventricular tachycardia (beat-to-beat alternation of the QRS axis), polymorphic ventricular tachycardia, or idiopathic ventricular fibrillation occurring during physical exercise or emotion. There may be a family history of sudden death at an early age, and extensive investigation usually reveals no evidence of structural heart disease.

Electrocardiographic features

The resting ECG is usually normal or shows sinus bradycardia, and these patients not infrequently are given a diagnosis of LQTS with normal QT. Exercise electrocardiography or intravenous catecholamine infusion is the key investigation in terms of clinical diagnosis, with a high yield of exercise-induced ventricular salvos in this condition. Ambulatory electrocardiography can also play a role in identifying exercise-induced ventricular arrhythmias as a cause of symptoms, although in less controlled circumstances. Although exercise-induced bidirectional VT has been considered the hallmark of this condition, this arrhythmia has been known to occur occasionally in other channelopathies such as Andersen syndrome and LQTS. In the latter conditions, however, the resting ECG is very likely to show QT and T-wave abnormalities.
**Genetic tests**

Although the diagnostic yield (sensitivity) from genetic testing is relatively high (~80%) in patients with typical clinical features, a negative test does not exclude the diagnosis. A positive genetic test is of great value for the individual patient given the prognostic implications and for screening family members.

**Electrophysiology studies**

Electrophysiology studies have a low sensitivity and specificity for inducing ‘clinical’ arrhythmias in patients with CPVT, with or without catecholamine infusion.65

**Risk of sudden death within specific clinical and genetic subgroups**

The recent discovery and relative rarity of CPVT is such that the available evidence concerning risk of SCD is based on considerable fewer patients than either LQTS or the Brugada syndrome and absolute risks of sudden death in clinical subgroups are much less well-defined.

It is said that high lethality is a particular feature of both RyR2 CPVT and non-genotyped CPVT and that the protection afforded by beta-blockade is less than in the LQTS.65,66 This is difficult to measure in any objective way given that CPVT is a much more recently discovered condition and, as has been the case for LQTS, Brugada syndrome and HCM, it is likely that lethality will be overestimated if based on initial series comprising the most severely affected individuals. Nevertheless, the fact that in the largest study of CPVT patients reported to date66 the fatal/near-fatal event rate was as high in family members as in probands does support the possibility that gene mutations in this condition are highly penetrant.

As a consequence, oral beta-blockade (1 to 2 mg/kg per day nadolol, 3 to 4 mg/kg per day propranolol) is recommended for all mutation carriers even in the absence of symptoms. There have been a number of small clinical studies reporting the follow-up of CPVT patients taking beta-blockade. Leenhardt et al.60 reported two deaths among 21 French patients over 7 years, i.e. an incidence of sudden death of 1.36%/year. Priori et al.66 in a study of 30 European probands and 9 affected relatives reported no deaths on beta-blockade after a mean follow-up of 46 months; ~50% of patients had arrhythmia recurrence on drugs, however, and 6 of 12 patients with ICDs had appropriate shocks for ventricular arrhythmias; it is, of course, unclear whether these patients would have died without these shocks. In a study of 21 Japanese patients,67 4 of 21 patients died over 6.8 year follow-up, i.e. sudden death incidence of 2.8%/year, and a more recent study of 12 European probands and 38 affected relatives suggested a sudden death rate of 1%/year (1 of 50 patients died over a 2-year follow-up).68 In the largest study of CPVT patients reported to date,66 the incidence of fatal or near-fatal events in those patients prescribed beta-blockade was 1.2% per year. These ‘beta-blocker failures’ may be attributed in part but not completely to non-compliance or lose dosage of medication.

Although the studies discussed above suggest ‘beta-blocker failures’ may be more common in CPVT than in LQTS, there are particular downsides to the use of the ICD in the CPVT population that are very relevant to the decision whether or not to implant a device. Defibrillator shocks have the potential to trigger a ventricular arrhythmia ‘storm’ in these patients secondary to a pain- and anxiety-induced catecholamine surge. Failures of the ICD to prevent ventricular arrhythmia-related deaths have been reported under these circumstances.69

Patients with CPVT are at higher risk in the absence of beta-blockade, with a 3.1%/year risk of fatal or near-fatal events under these circumstances.66 As with LQTS, other options exist if beta-blockade cannot be tolerated. Initial experience with LCSD in patients with CPVT has been encouraging70 and provides a logical form of treatment for patients with this condition who are unable to take full dose-beta blockade or continue to have symptoms despite medication.

**Recommendation**: Catecholaminergic polymorphic ventricular tachycardia patients presenting with ventricular fibrillation/cardiac arrest without reversible precipitant should undergo ICD implantation in addition to oral beta-blockade or LCSD.

**Patients presenting with aborted cardiac arrest**

There are no data available on the absolute risk of death in patients with CPVT presenting with aborted cardiac arrest, although this presentation has been shown to be an independent predictor for subsequent fatal or near-fatal events66 in an overall population that carries a 1.2% per year risk of death on beta-blockade. As a consequence, it is very likely that the risk/benefit equation in this group favours ICD implantation. Conversely, patients presenting with syncope rather than aborted cardiac arrest did not have a higher fatal or near-fatal event rate during follow-up.

**Recommendation**: Catecholaminergic polymorphic ventricular tachycardia patients presenting with ventricular fibrillation/cardiac arrest without reversible precipitant should undergo ICD implantation.

**Patients with documented sustained VT or syncope despite beta-blockade and/or left cardiac sympathetic denervation**

The absolute risk of CPVT patients with syncope despite beta-blockade (or after LCSD) is unknown but clearly additional treatment will be required under these circumstances. Some preliminary studies have suggested beneficial effects of other drugs such as flecainide71 or verapamil but certainly ICD treatment should be considered in these cases.

**Recommendation**: Catecholaminergic polymorphic ventricular tachycardia patients experiencing sustained VT or syncope (when VT/VF has not been excluded as the cause) despite beta-blockade or LCSD should be considered for ICD implantation.

In contrast to the LQTS, in CPVT there is an opportunity to test the efficacy of beta-blockade to prevent malignant ventricular arrhythmias by means of provocative testing (exercise electrocardiography or catecholamine infusion). Some authors have indicated that beta-blockade should be titrated in order to ensure a maximum sinus rate on exercise of 110 bpm, based on effectiveness in suppressing ventricular arrhythmias. Results of exercise stress tests during follow-up are significantly associated with future cardiac events,66 but sensitivity and specificity of the test are not high.

**Recommendation**: Catecholaminergic polymorphic ventricular tachycardia patients experiencing exercise-induced sustained VT despite beta-blockade or LCSD should be considered for ICD implantation.
Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is usually inherited as an autosomal dominant trait with variable clinical penetrance and clinical expression. In most patients, HCM is caused by mutations in genes that encode cardiac sarcomeric proteins, but it is also associated with syndromes such as Noonan syndrome and inherited metabolic disorders.2,7,3 Pathologically, HCM is characterized by myocardial hypertrophy, typically affecting the interventricular septum more than other myocardial segments, disorganization (‘disarray’) of cardiac myocytes and myofibrils, myocardial fibrosis, and small vessel disease.74 This myocardial disorganization is thought to be the basis for ventricular arrhythmias and sudden death associated with the syndrome.

Current ACC/AHA/ESC guidelines for implantable cardioverter defibrillator prescription in hypertrophic cardiomyopathy

The classes of ICD indications as defined by the ACC/AHA/ESC Writing Committee can be summarized as follows and refer to individuals who are receiving chronic optimal medical therapy and otherwise have reasonable expectation of survival with a good functional status for >1 year.

Class I. Implantable cardioverter defibrillator therapy should be used for treatment in patients with HCM who have sustained VT and/or VF (level of evidence: B).

Class IIa. Implantable cardioverter defibrillator implantation can be effective for primary prophylaxis against SCD in patients with HCM who have one or more major risk factor (Table 2) for SCD (level of evidence: C).

Class IIb. EP testing may be considered for risk assessment for SCD in patients with HCM (level of evidence: C).

Establishing a clinical diagnosis

Classical descriptions of the condition include symptoms of chest pain (rest or with exercise), shortness of breath, or syncope on exertion together with the presence of a systolic murmur. The ECG is frequently abnormal in affected individuals and may include criteria for left ventricular hypertrophy associated with repolarization changes, isolated repolarization changes with moderate-to-severe T wave inversion, and the presence of deep Q waves. The current diagnosis of HCM rests, in the great majority of cases, on the two-dimensional echocardiographic identification of one or more segments of abnormally increased wall thickness (>15 mm in adults) in a non-dilated left ventricle in the absence of any other cardiac or systemic disease that could account for hypertrophy.75 Borderline LV wall thicknesses of 13 or 14 mm in an adult patient may constitute evidence of HCM, but in the setting of systemic hypertension or sustained athletic activity the diagnosis cannot be made on clinical grounds alone. Magnetic resonance imaging maybe useful in selected patients or family members, particularly when echocardiographic studies are technically suboptimal or when segmental hypertrophy is confined to unusual locations such as the anterolateral LV free wall or apex.76

Although LV hypertrophy may emerge in young children, the onset of hypertrophy is typically in adolescence (13–17 years) and often complete by the time full growth and maturation are achieved (18 to 21 years). LV outflow tract geometry is changed with accelerated body growth during this time and systolic anterior motion of the mitral valve causing dynamic obstruction to LV outflow may develop. Delayed late-onset hypertrophy is currently thought to be rare but is increasingly recognized; patients may develop the first echocardiographic evidence of hypertrophy during middle age.

It is evident from genetic studies that there is no true minimum LV wall thickness diagnostic or pathognomonic for HCM and indeed normal wall thickness is compatible with the presence of an HCM-causing gene mutation. In the context of a family history of HCM, otherwise unexplained mild electrocardiographic or echocardiographic abnormalities will have a much higher probability of being an expression of a gene abnormality than in individuals without such a history. With this in mind, specific less demanding criteria have been suggested for the diagnosis in adult members of affected families, based on specific ‘major and minor’ electrocardiographic and echocardiographic features.77

In recent years, mutations in the genes encoding contractile proteins have been identified as the cause of HCM. It is therefore likely that that molecular genetic techniques and criteria will ultimately become the tools for the classification of this disease. Currently, however, the diagnostic yield (sensitivity) of genetic testing in clinical cases of clear familial HCM is in the region of 60%;78 the yield is dependent upon patient selection falling to significantly lower levels if familial selection is not confirmed;79 i.e. a negative result is common and does not exclude the diagnosis. The successful identification of a disease-causing mutation does, of course, allow rapid and accurate screening of family members.80

<table>
<thead>
<tr>
<th>Table 2 Risk factors for sudden cardiac death in hypertrophic cardiomyopathy</th>
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<tr>
<td><strong>Major risk factors</strong></td>
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<tr>
<td>Cardiac arrest (VF)</td>
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<tr>
<td>Spontaneous sustained VT</td>
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<tr>
<td>Family history of SCD</td>
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<tr>
<td>Unexplained syncope</td>
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<tr>
<td>LV thickness ≥ 30 mm</td>
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<tr>
<td>Abnormal exercise BP</td>
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<td>Non-sustained spontaneous VT</td>
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Risk of sudden death within specific clinical and genetic subgroups

The reported annual incidence of SCD in patients with HCM has declined from between 2 and 4% to 1% or less per year, a reflection, perhaps, more of the identification of patients with milder disease than the impact of modern treatment in high-risk patients.81 Sudden cardiac death occurs throughout life with a maximum incidence in adolescence and young adulthood, often without warning signs or symptoms.82 Although there is an excess of deaths during
or after strenuous exertion (see below), most occur during mild exertion or sedentary activities. The mechanism underlying most SCDs is thought to be ventricular tachyarrhythmia, but conduction disease and thrombo-embolism may account for some cases. Rapid atrial fibrillation (AF) and myocardial ischaemia appear to be important triggers for sudden ventricular arrhythmia.

Although sudden death rates in HCM populations are generally low, the fact that sudden death frequently occurs without warning in young and at most mildly symptomatic people provides a powerful stimulus to pre-emptively screen patients in order to identify those at greatest risk. There are, however, several major challenges, not least the fact that the disease is relatively uncommon making it difficult to collate large patient cohorts on which to base robust risk algorithms. Heterogeneity in causation and clinical phenotype also make group comparisons problematic and the substrate for sudden death may change during the long natural history so that patients’ risk changes with time. The current approach to risk stratification is based on an evaluation of a small number of readily determined clinical parameters that have been considered to be the most predictive of risk.

Patients presenting with aborted cardiac arrest or sustained VT
The easiest high-risk group to define are those (relatively rare) patients who have already declared their propensity for fatal ventricular arrhythmia by surviving an episode of sustained ventricular tachycardia or ventricular fibrillation (Table 2). Cumulative survival (death or ICD discharge) in this group is 59% at 5 years. Sustained monomorphic ventricular tachycardia is rarely documented prior to death, but is sometimes associated with apical left ventricular aneurysms. It is not known whether haemodynamically tolerated sustained ventricular tachycardia is associated with the same adverse prognosis as syncopal ventricular arrhythmia. Multi-centre registry data report yearly discharge rates of 10–11% for secondary prevention in patients with a history of successfully resuscitated ventricular tachycardia or ventricular fibrillation.

Recommendation: Patients with HCM presenting with ventricular fibrillation/cardiac arrest or sustained VT without reversible precipitant should undergo ICD implantation.

Patients with one or more recognized major risk factors for sudden cardiac death
The clinical features used to determine sudden death risk in HCM are essentially surrogate markers of the severity of the underlying myocardial disease, as direct functional assessment of the underlying disease process is currently not possible. In spite of the fact that there is very little evidence that (with the exception of prior cardiac arrest) any one risk factor is more predictive than another, in the current AHA/ACC/ESC guidelines for the prevention of SCD, risk factors are sub-classified into ‘major’ and ‘possible’.

Unexplained or recurrent syncope
Patients with HCM can experience syncope at rest and during all grades of exertion. Many mechanisms are responsible including left ventricular outflow tract obstruction, arrhythmia, and abnormal vascular reflexes. It is generally agreed that syncope should always prompt a search for a mechanism and that should no treatable cause be identified, it should be considered a risk factor for sudden death. Data on the association between syncope and sudden death risk are few and contradictory, but in a recent study, unprovoked syncope was associated with a relative risk of 2.27 for SCD.

Family history of sudden cardiac death
Clinical and genetic studies have shown that some families with HCM undoubtedly have a high risk of sudden death at a young age. However, in a recent systematic review of the published literature, most published studies did not demonstrate a significant relationship between a family history of SCD and cardiac death or SCD. Only three studies demonstrated that family history of SCD was an independent predictor of SCD, but it was relatively weak with an average reported hazard ratio of only 1.27 (95% CI 1.16–1.38). This apparently counterintuitive observation can be explained by different definitions of a positive family history, variable clinical expression between individuals from the same family, and the inherent difficulties in modelling family history as a risk factor. For example, the cause of death in a relative is frequently unknown and it is difficult to determine how the number of sudden deaths in a family relates to the number of individuals at risk. At present, therefore, the management of an individual with an adverse family as their only risk factor is largely empiric and often determined by psychological and social considerations.

Non-sustained ventricular tachycardia
In most studies, the prevalence of non-sustained ventricular tachycardia (NSVT) during ambulatory electrocardiography varies between 20 and 30%. Its frequency increases with age and the duration of electrocardiographic recording. The association between NSVT and sudden death risk also varies between studies, but the majority reports a relative risk in excess of 2.5. There is very little evidence that the duration, frequency, or rate of runs influences the prognostic significance of NSVT (defined by a minimum rate of 120 bpm), but age does appear to be an important modifier, with a relative risk of 4 in patients <30 years of age.

Left ventricular hypertrophy
In two studies, the risk of sudden death in patients with a maximum wall thickness >30 mm (or 25 mm in two or more segments) was approximately four-fold. In a third study, age appeared to modify the risk, with an annual sudden death rate of 17% in patients with severe hypertrophy aged <18 years compared with 0% in older patients.

Exercise blood pressure responses
Upright exercise testing can be safely performed in the overwhelming majority of patients with HCM (including those with left ventricular outflow tract obstruction). Several studies have shown that a failure of blood pressure to rise appropriately, i.e. by >20–30 mmHg from baseline, is associated with an increased cardiovascular mortality with a relative risk ranging from 2.4 to 9.6. In younger patients (age 40–50 years or less), the presence of an abnormal blood pressure response during exercise is...
associated with a higher relative risk than in older patients. Several mechanisms are responsible for the abnormal response, including inappropriate vasodilatation in non-exercising muscles, splanchic venous pooling, poor augmentation of cardiac output, and possibly sub-endocardial myocardial ischaemia due to microvascular dysfunction.

When assessing blood pressure responses for the purpose of determining risk, several caveats apply.

(i) It is normal for children and young adolescents to have a flat blood pressure response during exercise.
(ii) Concomitant medication (beta-blockers, verapamil) may blunt the blood pressure response.
(iii) Data on exercise blood pressure assume that maximum exercise has been performed. Early cessation of exercise due to poor effort or technical reasons needs to be considered when assessing blood pressure response.

Left ventricular outflow tract obstruction
Dynamic left ventricular outflow tract obstruction causes dyspnoea, chest pain, syncope and predisposes to the development of atrial arrhythmias and stroke. At least three studies have shown that outflow tract obstruction is associated with an increased risk of sudden death. There is general agreement that all patients with symptomatic outflow obstruction should initially receive medical therapy (beta-blockers, verapamil, disopyramide). If symptoms persist, then patients should be considered for invasive gradient reduction (surgery or alcohol septal ablation). There are currently no data to support septal reduction for risk in asymptomatic (or medically controlled) outflow tract obstruction.

Atrial fibrillation
Paroxysmal supraventricular arrhythmias occur during ambulatory electrocardiographic monitoring in 30–50% of patients. Sustained AF is present in 5% of patients at diagnosis, and develops in a further 10% in the subsequent 5 years. In a large study of 480 consecutive HCM patients, patients with AF had increased risk for HCM-related death (OR 3.7) because of excess heart failure-related mortality but not SCD. The risk associated with AF was substantially greater in patients with outflow obstruction or with earlier development of AF (<50 years of age).

High-risk mutation
As the large majority of patients with HCM have inherited disease, all patients with HCM should be counselled on the implications of the diagnosis for their families. Cascade screening, particularly when guided by direct DNA testing, can identify asymptomatic individuals at risk and can reassure relatives who are not at risk of inheriting the disease. In patients with disease caused by mutations in sarcomeric protein genes, some studies have reported associations between particular mutations and a high risk of SCD. Most notable are some families with cardiac troponin T mutations that in spite of mild hypertrophy have a 50% mortality before the age of 40 years. However, most of these studies are limited by the small size of patient cohorts. Further, most HCM-causing mutations are individually rare, making it difficult to establish with confidence how a particular variant relates to risk of SCD in an adequate number of patients. For these reasons, the presence of a ‘high risk’ mutation is not currently regarded as sufficient reason to implant an ICD in the absence of other clinical risk factors.

Intense physical exertion
As 40% of HCM sudden deaths occur following moderate-to-severe exertion, current guidelines recommend that young patients with HCM should not participate in competitive sports. However, the increase in the relative risk of sudden death incurred by regular participation in vigorous exercise is unknown, and it is unclear how the inclusion of intense physical exercise as a possible risk factor in the AHA/ACC/ESC guidelines impacts on the decision to implant an ICD.

Recommendations for ICD implantation in patients with HCM are based not on randomized trials but on observational data. The approach to risk stratification recommended in the AHA/ACC/ESC consensus guidelines is based on the concept of global risk burden, whereby treatment decisions are determined by the presence of a small number of risk factors. The presence of two or more risk factors identifies a cohort of patients with an annual sudden death risk of ~3%, whereas the presence of any single risk factor is associated with an annual risk of ~1%. The ACC/AHA/ESC guidelines state that ICD implantation ‘can be effective’ (a class IIa recommendation) in patients with one or more of the recommended risk factors.

Single-risk factor patients: the ‘grey’ area
The advice to consider ICD for primary prevention in patients with multiple risk factors appears straightforward and not controversial. However, the inclusion of HCM patients with a single risk factor could result in ICD implantation in 25% of patients. ICD implantation carries significant life-long morbidity and mortality risks that may be particularly great in this young patient population; the risk of harm may outweigh the benefit in a group with a <1% per annum risk of SCD or less. The AHA/ACC/ESC guidelines reflect a concern that a recommendation to implant an ICD only in patients with multiple risk factors would result in a failure to treat individuals with solitary risk factors that may be sufficiently concerning to warrant intervention (e.g. multiple sudden deaths in a family or recurrent unexplained syncope). Although this concern is understandable, it does mean that the recommendations for ICD implantation are loosely defined, reflecting large differences in clinical practice, influenced as much by the biases of individual clinicians and the perceived medico-legal consequences of inaction as by the clinical characteristics of individual patients. Importantly, although we support the rationale of stating that ICD implantation can be appropriate in the single-risk factor patient, we do not support an interpretation that implantation should be the norm in this setting.

Recommendations: Patients with HCM and two or more recognized risk factors for SCD should be considered for ICD implantation. Patients with HCM and a single recognized risk factor for SCD may, according to individual circumstances, be considered for ICD implantation.
Electrophysiological testing
The AHA/ACC/ESC guidelines suggest that electrophysiological testing might have a role in some borderline cases (class IIb indication). Thirty six per cent of patients have inducible sustained ventricular tachycardia when using protocols consisting of three premature stimuli delivered during three drive pacing cycle lengths in the left and/or right ventricle. Ventricular tachycardia induced by such aggressive protocols is associated with a higher risk of cardiac events (defined as sudden death, cardiac arrest, or syncope accompanied by ICD discharge), but the predictive accuracy for sudden death is very low. For these reasons, we would not support the routine use of electrophysiology testing in this setting.

Conventional ventricular stimulation studies have been shown to have low accuracy in predicting sudden death in HCM. There is evidence however that a distinct electrophysiological abnormality, paced ventricular electrogram fractionation, may have greater value for predicting SCD than conventional invasive criteria or the non-invasive criteria discussed above. Ventricular electrogram fractionation is provoked using an invasive electrophysiological technique in which ventricular extrastimuli are introduced at progressively shorter intervals at four separate sites in the right ventricle. In a prospective study of 185 patients with an unequivocal diagnosis of HCM followed for 4.3 years, abnormal fractionation was shown to have greater positive predictive value for a sudden death event than the use of single or combined conventional risk factors in patients with at least one risk factor. The exact role of this technique in the selection of patients with HCM for ICDs awaits further study in larger populations.

| Table 3 |

Arrhythmogenic right ventricular cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy is a familial cardiomyopathy that may result in arrhythmia, heart failure, and sudden death. It is characterized pathologically by progressive myocyte loss and fibrofatty replacement, with a predilection for the right ventricle. Familial disease is common, with autosomal dominant inheritance and incomplete penetrance; a recessive form has also been described. The finding of disease-causing mutations in genes encoding cell adhesion proteins (e.g. plakoglobin and desmoplakin) provides the basis for the hypothesis that ARVC is a disease of the cell-to-cell junction. The inverse relation between wall stress and wall thickness may explain the increased susceptibility of the thin-walled right ventricle, and the predilection of early disease for its thinnest portions, represented by the ‘triangle of dysplasia’ (diaphragmatic, infundibular, and apical right ventricular regions as well as in the left ventricle). These structural changes disrupt the normal pattern of electrical activity across the ventricular myocardium, leading to the potential for abnormal electrical circuits and the generation of re-entrant ventricular arrhythmias and ventricular fibrillation. The condition is, in general, a progressive one and clinical features are rare below the early teenage years.

The classes of ICD indications as defined by the ACC/AHA/ESC Writing Committee can be summarized as follows and refer to individuals who are receiving chronic optimal medical therapy and otherwise have reasonable expectation of survival with a good functional status for > 1 year.

Class I. Implantable cardioverter defibrillator implantation is recommended for the prevention of SCD in patients with ARVC with documented sustained VT or VF (level of evidence: B).

Class IIa. Implantable cardioverter defibrillator implantation can be effective for the prevention of SCD in patients with ARVC with extensive disease, including those with LV involvement, one or more affected family members with SCD, or undiagnosed syncope when VT or VF has not been excluded as the cause of syncope (level of evidence: C).

Class IIb. EP testing might be useful for the risk assessment of SCD in patients with ARVC (level of evidence: C).

Establishing a clinical diagnosis
Classical features
Clinical presentation usually occurs during adolescence or in the twenties with symptoms of palpitation, syncope, or sudden death. The ECG at rest shows inverted T waves in the right pre-cordial leads (V1–3) with or without incomplete right bundle branch block. Occasionally distinct waves occur after the end of the QRS complex, suggesting delayed activation of some portions of the right ventricular wall (‘epsilon wave’). The ECG during symptoms demonstrates the presence of sustained monomorphic ventricular tachycardia with a left bundle branch block pattern or bursts of ventricular ectopic activity. In late phases of the disease, ARVC may be considered a differential diagnosis in patients presenting with heart failure, particularly if this has predominantly right-sided features.

Pre-clinical or concealed phase
Although diagnosis is not difficult in those patients with typical features, patients with pre-clinical or mild disease pose much more of a problem. Imaging (with echocardiography or magnetic resonance imaging) during this phase may be negative because the disease often involves only patchy and small areas of abnormal myocardium in the ‘triangle of dysplasia’. A combination of multiple views and imaging modalities are required for full assessment. A particular problem is the interpretation of small right ventricular motion abnormalities which may be responsible for false positive interpretation. Caution should be taken in the interpretation of RV apical motion due to trabeculations and mid-apical lateral wall motion due to the insertion of the moderator band. There is no ‘gold standard’ clinical or imaging test for the condition, and as a consequence a scoring system based on the overall clinical picture has been devised to assist in the diagnosis and standardize reporting of clinical trials (1994 Task Force criteria). Clinical features are subdivided into major and minor. The diagnosis is fulfilled by the presence of two major criteria, one major criterion plus two minor criteria or four minor criteria from different groups. The majority of studies reporting outcomes have used this diagnostic scoring system. These have recently been updated and include more quantitative criteria, and abnormalities are defined on the basis of comparison with normal subject data (Table 3). In the recently modified version, the presence of inverted T waves in V1–3 is considered a major
<table>
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<tr>
<th>Original Task Force criteria</th>
<th>Revised Task Force criteria</th>
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<tr>
<td>I. Global or regional dysfunction and structural alterations* Major</td>
<td>By 2D echo Regional RV akinesia, dyskinesia, or aneurysm and one of the following (end diastole): PLAX RVOT $\geq 32$ mm [corrected for body size (PLAX/BSA) $\geq 19$ mm/m$^2$] or PSAX RVOT $\geq 36$ mm [corrected for body size (PSAX/BSA) $\geq 21$ mm/m$^2$] or fractional area change $\leq 33%$</td>
</tr>
<tr>
<td>Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment</td>
<td>By MRI Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: Ratio of RV end-diastolic volume to BSA $\geq 110$ mL/m$^2$ (male) or $\geq 100$ mL/m$^2$ (female) or RV ejection fraction $\leq 40%$</td>
</tr>
<tr>
<td>Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging)</td>
<td>By RV angiography Regional RV akinesia, dyskinesia, or aneurysm</td>
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<tr>
<td>Severe segmental dilatation of the RV</td>
<td>Minor</td>
</tr>
<tr>
<td>By 2D echo Mild global RV dilatation and/or ejection fraction reduction with normal LV</td>
<td>Regional RV akinesia or dyskinesia and one of the following (end diastole): PLAX RVOT $\geq 29$ to $&lt; 32$ mm [corrected for body size (PLAX/BSA) $\geq 16$ to $&lt; 19$ mm/m$^2$] or PSAX RVOT $\geq 32$ to $&lt; 36$ mm [corrected for body size (PSAX/BSA) $\geq 18$ to $&lt; 21$ mm/m$^2$] or fractional area change $&gt;33%$ to $\leq 40%$</td>
</tr>
<tr>
<td>Mild segmental dilatation of the RV</td>
<td>By MRI Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and one of the following: Ratio of RV end-diastolic volume to BSA $\geq 100$ to $&lt; 110$ mL/m$^2$ (male) or $\geq 90$ to $&lt; 100$ mL/m$^2$ (female) or RV ejection fraction $&gt;40%$ to $\leq 45%$</td>
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<tr>
<td>Regional RV hypokinesia</td>
<td>II. Tissue characterization of wall Major</td>
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<tr>
<td>Fibrofatty replacement of myocardium on endomyocardial biopsy</td>
<td>Residual myocytes $&lt; 60%$ by morphometric analysis (or $&lt; 50%$ if estimated), with fibrous replacement of the RV free wall myocardium in one or more sample, with or without fatty replacement of tissue on endomyocardial biopsy</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
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<tr>
<td>----------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>III. Repolarization abnormalities</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td></td>
</tr>
<tr>
<td>Inverted T waves in right precordial leads (V₁, V₂, and V₃) or beyond in individuals &gt;14 years of age (in the absence of complete right bundle-branch block) or in V₄, V₅, or V₆</td>
<td></td>
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<tr>
<td>IV. Depolarization/conduction abnormalities</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>Epsilon waves or localized prolongation (&gt;110 ms) of the QRS complex in right precordial leads (V₁ to V₃)</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td></td>
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<tr>
<td>Late potentials (SAECG)</td>
<td></td>
</tr>
<tr>
<td>Filtered QRS duration (fQRS) ≥ 114 ms</td>
<td></td>
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<tr>
<td>Duration of terminal QRS &lt; 40 μV (low-amplitude signal duration) ≥ 38 ms</td>
<td></td>
</tr>
<tr>
<td>Root-mean-square voltage of terminal 40 ms &lt; 20 μV</td>
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<tr>
<td>Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R’, in V₁, V₂, or V₃, in the absence of complete right bundle-branch block</td>
<td></td>
</tr>
<tr>
<td>V. Arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>Non-sustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td></td>
</tr>
<tr>
<td>Left bundle-branch block-type ventricular tachycardia (sustained and non-sustained) (ECG, Holter, exercise)</td>
<td></td>
</tr>
<tr>
<td>Frequent ventricular extra-systoles (&gt;1000 per 24 h) (Holter)</td>
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<tr>
<td>VI. Family history</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>Familial disease confirmed at necropsy or surgery</td>
<td></td>
</tr>
<tr>
<td>ARVC/D confirmed in a first-degree relative who meets current Task Force criteria</td>
<td></td>
</tr>
<tr>
<td>ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative</td>
<td></td>
</tr>
<tr>
<td>Identification of a pathogenic mutation categorizes as associated or probably associated with ARVC/D in the patient under evaluation</td>
<td></td>
</tr>
</tbody>
</table>

Continued
Table 3

<table>
<thead>
<tr>
<th>Original Task Force criteria</th>
<th>Revised Task Force criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minor</strong></td>
<td><strong>Revised</strong></td>
</tr>
<tr>
<td>Familial history (clinical diagnosis based on present criteria)</td>
<td>ARVC/D confirmed pathologically or by current Task Force criteria in a second-degree relative</td>
</tr>
<tr>
<td>Premature sudden death (&lt;35 years of age) due to suspected ARVC/D in a first-degree relative</td>
<td>ARVC/D confirmed pathologically or by current Task Force criteria in a second-degree relative</td>
</tr>
<tr>
<td><strong>Familial history (clinical diagnosis based on present criteria)</strong></td>
<td><strong>Familial history (clinical diagnosis based on present criteria)</strong></td>
</tr>
<tr>
<td>Familial history (clinical diagnosis based on present criteria)</td>
<td>Familial history (clinical diagnosis based on present criteria)</td>
</tr>
</tbody>
</table>

**PLAX, parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; aVL, augmented voltage unipolar left arm lead.**

**Diagnostic terminology for original criteria:** This diagnosis is fulfilled by the presence of two major, or one major plus four minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: two major or one major and two minor criteria or four minor from different categories; borderline: one major and one minor or three minor criteria from different categories; possible: one major or two minor criteria from different categories.

109 Table reproduced with permission from Marcus et al.

**most cases of ARVC are thought to be caused by autosomal dominantly inherited mutations in genes encoding different proteins of the desmosome of cardiomyocytes.** The diagnostic yield (or sensitivity; a positive result in established cases) for the commonest (the *PKP2* gene) is 30% or less, so the value of genetic testing in a purely diagnostic role is limited.

### Risk of sudden death within specific clinical and genetic subgroups

#### Patients presenting with ventricular arrhythmias

The risk of sudden death associated with ARVC patients presenting with ventricular arrhythmias has been addressed by the study of Corrado et al. They reported a multicentre observational study of the outcomes of 132 ARVC patients who had undergone ICD implantation because of a history of cardiac arrest (10% of total implants), sustained ventricular tachycardia (62% of implants), or syncope without electrocardiographic documentation (16%). All patients had an ‘unequivocal’ diagnosis of ARVC, fulfilling either two major or one major plus two minor diagnostic criteria recommended by the 1994 Task Force of the European Society of Cardiology. No patient with only minor criteria entered the study. Analysis of projected survival was based on appropriate defibrillator shocks for sustained ventricular fibrillation or flutter recorded on stored electrograms, rather than shocks triggered by ventricular tachycardia that may not have been life-threatening. Patients who had ICDs implanted because of presentation with cardiac arrest had a risk of subsequent sudden death or ‘life-saving’ shock of 21%/year. The corresponding appropriate shock rates for the other clinical groups were as follows: poorly tolerated VT 9%/year, syncope without ECG documentation 8%/year, and well-tolerated VT of 1%/year. Multivariate analysis revealed that, in addition to presentation with cardiac arrest or poorly tolerated VT, left ventricular involvement was an independent predictor of potentially lethal ventricular arrhythmias.

The largest series of US patients with ARVC was described by Dalal et al. from the Johns Hopkins ARVC registry. The authors reported the details of ICD therapy in the Johns Hopkins registry in a separate report. Forty-four of the 67 patients with ICDs received appropriate device therapies during a mean follow-up of 4.4 years. An appropriate shock does not, of course, equate to a life saved; the authors described life-saving therapy as that delivered in response to a ventricular arrhythmia with a rate greater than 240 bpm; on these criteria, 14 patients fulfilled these criteria, i.e. an overall incidence of ‘life-saving’ shock of 5%/year.

**Recommendation:** Arrhythmogenic right ventricular cardiomyopathic patients presenting with ventricular fibrillation/cardiac arrest or poorly tolerated VT should undergo ICD implantation. Arrhythmogenic right ventricular cardiomyopathic patients presenting with
syncope (when VT/VF has not been excluded as the cause of syncope) should undergo ICD implantation.

Additional insight into predictors of sudden death is provided by the study of Hulot et al.\textsuperscript{113} who described outcomes of 130 patients who fulfilled Task Force criteria. In this study, most (78\%) had suffered at least one episode of ventricular tachycardia and over half had evidence of gross RV dilation and dysfunction. After a mean follow-up of 8 years, there were 7 SCDS and 14 deaths as a result of progressive heart failure. All patients who died of a cardiovascular cause had at least one episode of left bundle branch block VT. Multivariate analysis showed that after the adjustment for history of syncope, ventricular tachycardia, and QRS dispersion, clinical signs of right ventricular failure and left ventricular dysfunction both remained independently associated with cardiovascular mortality.

Recommendation: Arrhythmogenic right ventricular cardiomyopathic patients presenting with ventricular arrhythmias and severe structural disease should be considered for ICD implantation.

**Asymptomatic patients with mild disease**

The largest systematic study of ARVC in family members of sudden death victims over a long period is that of Nava et al.\textsuperscript{114} who described the outcome of 151 affected individuals from 37 families with a mean follow-up of 8.5 years. The 37 probands presented with either autopsy findings (19 individuals) or ventricular arrhythmias. Patients had to fulfill 1994 Task Force criteria to be considered affected. Most had mild echocardiographic abnormalities (64\% mild, 30\% moderate, and 6\% severe) and all were advised to avoid physical exercise and sports activity, but only two patients underwent ICD implantation. During a mean follow-up period of 8.5 years, only one family member died suddenly (mortality rate of 0.08\%/year). The authors suggested that the apparent contrast between a malignant family history and the relatively benign follow-up in their series could be explained by early diagnosis, exercise restriction, and anti-arrhythmic therapy. The most commonly used drugs were beta-blockade and amiodarone. By comparing available clinical data in probands who died suddenly and in affected living patients, only a history of syncope was predictive of sudden death. Thus, the risk of an ICD (particularly in thin-walled right ventricles) must be weighed against the small risk of sudden death in these patients.

Recommendation: Arrhythmogenic right ventricular cardiomyopathic patients who are asymptomatic with mild disease are at low risk of sudden death, and the risks of ICD therapy may outweigh the benefits in this group.

**Electrophysiological testing**

The electrophysiological study is of limited value in identifying patients at risk of lethal ventricular arrhythmias. Programmed ventricular stimulation has a low predictive accuracy,\textsuperscript{115} with ~50\% of both false positive and false negative results. This finding is in keeping with the limited predictive value of electrophysiological study in conditions other than ischaemic heart disease, such as hypertrophic and dilated cardiomyopathy. Electrophysiological testing was of limited practical value in predicting appropriate shocks.\textsuperscript{116} All of the patients with a history of spontaneous sustained VT had inducible arrhythmias at electrophysiology study, but among those patients with other presentations inducible VT did not predict subsequent ICD shocks.

**Complications of implantable cardioverter defibrillators in familial sudden death syndromes**

Although the ICD can, without doubt, be a life-prolonging therapy in the familial SCD syndromes, there are significant negatives in terms of both morbidity and, occasionally, mortality associated with these devices.

Two relatively large series in adult patients with LQTS have been reported: the first from the US\textsuperscript{117} was considered by some to have exaggerated the likely benefit of ICD therapy,\textsuperscript{21} with the second from Germany possibly having more relevance to practice in the UK.\textsuperscript{115} In this second group of 27 patients implanted between 1994 and 2003, 37\% of the patients had 178 ‘appropriate’ shocks, although the authors acknowledge these episodes may have represented potentially self-terminating tordes de pointes in many cases. Twenty per cent of the patients had electrical storms, and there was also a 30\% incidence of ‘inappropriate’ shocks in these relatively young patients. Patients with Brugada syndrome suffer a similarly high rate of device complications. The ongoing risk of complications (8.9\% per annum) and the high frequency of inappropriate shocks (2.5 times higher than appropriate) in an asymptomatic and young age group are of concern.\textsuperscript{116}

Implantation of ICDs is not without the risk of death as well as morbidity. In a study of 132 patients with ARVC,\textsuperscript{110} five patients required an additional pacing lead during the follow-up period of 39 months because of undersensing or pacing failure, and one patient died from endocarditis secondary to device infection. Several other published series have confirmed the relatively high incidence of device-related complications in ARVC patients. Wichter et al.\textsuperscript{117} described a 37\% lead-related complication rate at 7 years post-implant. More recently, Lin et al.\textsuperscript{118} have described similarly high rates of device complications and inappropriate shocks in patients with HCM. These findings (in particular the risk of death associated with device implantation) reinforce the need to weigh carefully the relative risks and benefits of ICD implantation in specific patients rather than take an approach of recommending an ICD whenever a possible risk of sudden death associated with a familial syndrome has been identified.

**Special considerations concerning implantable cardioverter defibrillators in children**

The recommendations in this document refer to the adult population. Clinical decision-making with regard to the use of ICDs in children with familial SCD syndromes is particularly challenging. Clinical diagnosis can be much more difficult in this patient group and the phenotype is very likely to change with periods of rapid growth. Evidence regarding the assessment of risk of sudden death in children is significantly more limited than that available for the adult population. Implantable cardioverter defibrillator implantation in children is
associated with complex challenges in terms of implantation, programming, and follow-up. The decision to implant an ICD in a child carries a commitment to long-term therapy with the likelihood of multiple device replacements. In comparison with adults, children have a high rate of lead failure and both appropriate and inappropriate shocks. Despite these problems, there is evidence that some children with familial sudden death syndromes can cope well with an implantable defibrillator and have a significant survival benefit. As a consequence, the balance between risk of sudden death and risk associated with ICD implantation is very difficult to judge but likely to be different from that in the adult population. It will differ depending upon the age, emotional maturity, and size of the child. This having been said, presentation with life-threatening ventricular arrhythmias/cardiac arrest without a reversible precipitant will usually constitute an appropriate indication for an ICD in children as well as adults.

In view of the higher rate of ICD complications in children than adults, alternative treatment options are often considered (particularly in very young children) in an attempt to delay ICD implantation. In small children (<20 kg) with symptomatic LQTS, for instance, LCSD is more likely to be considered. In young patients with HCM, there is evidence that high-dose beta-blocker therapy may improve survival. A recent study reported the outcome of ICD implantation in children (>7 years) with conventional ‘adult’ indicators of high risk of sudden death. This confirmed the feasibility of risk stratification in children and the efficacy of defibrillator implantation although associated with an increased risk of infection and frequency of discharges.

**Summary and conclusions**

Although the decision regarding defibrillator implantation in a patient with a familial syndrome is likely to be one of the most significant for any particular individual, the clinical decision-making process itself is complex and requires interpretation and extrapolation of information from a number of different sources. Although the specific conditions described in this document differ in terms of clinical features and prognosis, it is possible and logical to take an approach to determining a threshold for ICD implantation that is common to all of the familial SCD syndromes.

**Conflict of interest:** A.J.C. is an advisor/speaker for Medtronic and Boston Scientific, a speaker for Biotronik, and has received research funds from St Jude.

**Patients attitudes towards implantable cardioverter defibrillator therapy**

In this paper, we have focused on the physician/device implanters’ views of the relative balance between risks of sudden death and those of device implantation in patients with familial sudden death syndromes, although with an attempt to place themselves in the position of a patient. The key role of the physician in the decision-making process is to provide the patient (or their parents) with a recommendation, together with a discussion of the reasons behind that recommendation and possible alternative options. This discussion should, of course, be targeted on the particular circumstances of that patient and it is important that the patient’s views and attitudes towards their disease and ICDs are taken into account. For instance, the physician may have identified clear evidence of mild disease in a sibling of a sudden death victim shown at post-mortem to have ARVC. The physician may have explained that long-term follow-up studies have indicated a good prognosis in this situation, with an estimated risk of sudden death of <1% per year and that the risks of an ICD might well outweigh the benefits in this situation. However, the long-term anxiety associated with the unheralded death of a sibling from the same disease may be such that an ICD confers considerable psychological benefit over and above any survival benefit; under these circumstances implantation of an ICD may be the best course of action.

**References**


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