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STATE OF THE ART REVIEW
Arrhythmias

Implantable defibrillators in primary prevention of genetic arrhythmias. A shocking choice?

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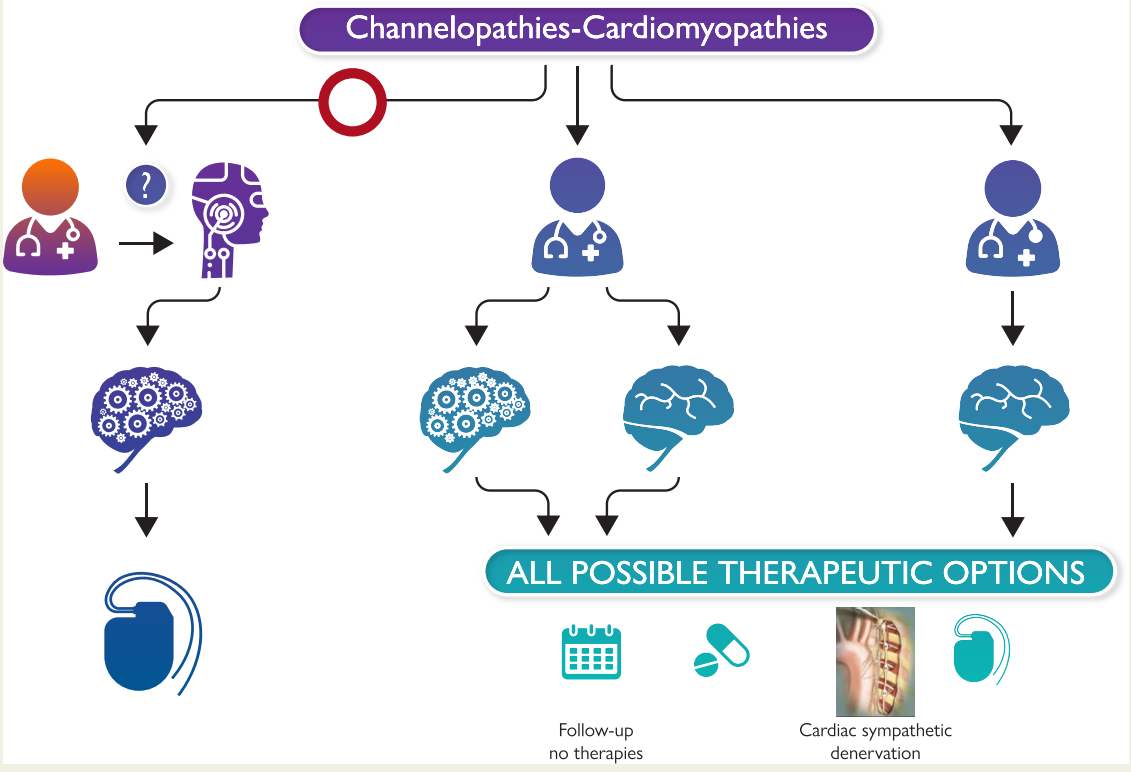
Graphical Abstract



This figure illustrates three different approaches to the management of cardiomyopathies and of channelopathies. The first approach, on the left, reflects a currently growing trend and relies on the semi-passive acceptance of algorithms originated by 'electronic risk calculators' and 'risk

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scores': in this situation a non-expert physician, instead of deciding on his/her own, turns to and fully relies on the algorithm and this automated response predominantly favours the choice of ICD implant over alternative therapies. The second approach, in the middle, represents the wise combination of an experienced cardiologist using also the data from an electronic risk calculator and thereby considering all possible reasonable choices. The third approach, on the right, is the traditional one, based on the personal choice by an expert clinician who first integrates the specific characteristics of each patient and then makes an unbiased choice among the different therapeutic options available. The second and third approaches are equally valid; we wish to underscore that the third one implies that the 'true expert' does not need electronic risk calculators. By contrast, we regard as potentially dangerous the situation in which a doctor without specific expertise in uncommon and life-threatening disorders decides essentially on the sole basis of the algorithm. In all three approaches the final decision must be shared with the patient. Finally, after installing the initial therapy, risk stratification for SCD should be re-assessed on a regular basis during follow-up because the risk of SCD may change over time either increasing, due to the disease progression, or decreasing when the therapies are effective. The panel illustrating "Cardiac sympathetic denervation" is reproduced with permission from Collura *et al.*[147]

Abstract

Many previously unexplained life-threatening ventricular arrhythmias and sudden cardiac deaths (SCDs) in young individuals are now recognized to be genetic in nature and are ascribed to a growing number of distinct inherited arrhythmogenic diseases. These include hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy, long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (VT), and short QT syndrome. Because of their lower frequency compared to coronary disease, risk factors for SCD are not very precise in patients with inherited arrhythmogenic diseases. As randomized studies are generally non-feasible and may even be ethically unjustifiable, especially in the presence of effective therapies, the risk assessment of malignant arrhythmic events such as SCD, cardiac arrest due to ventricular fibrillation (VF), appropriate implantable cardioverter defibrillator (ICD) interventions, or ICD therapy on fast VT/VF to guide ICD implantation is based on observational data and expert consensus. In this document, we review risk factors for SCD and indications for ICD implantation and additional therapies. What emerges is that, allowing for some important differences between cardiomyopathies and channelopathies, there is a growing and disquieting trend to create, and then use, semi-automated systems (risk scores, risk calculators, and, to some extent, even guidelines) which then dictate therapeutic choices. Their common denominator is a tendency to favour ICD implantation, sometime with reason, sometime without it. This contrasts with the time-honoured approach of selecting, among the available therapies, the best option (ICDs included) based on the clinical judgement for the specific patient and after having assessed the protection provided by optimal medical treatment.

Keywords Implantable cardioverter defibrillator • Hypertrophic cardiomyopathy • Arrhythmogenic cardiomyopathy • Long QT syndrome • Brugada syndrome • Catecholaminergic polymorphic ventricular tachycardia

Introduction

Many previously unexplained life-threatening ventricular arrhythmias and sudden cardiac deaths (SCDs) in young individuals are now recognized to be genetic in nature and are ascribed to a growing number of distinct inherited arrhythmogenic diseases. Genetic arrhythmias are mostly linked to either inherited cardiomyopathies (CMPs), such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic cardiomyopathy (ACM) or to cardiac ion channel diseases, henceforth channelopathies, including long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and short QT syndrome (SQTS).[1] The definition, classification, genetics, clinical manifestation, and diagnostic criteria of these inherited CMPs and channelopathies at risk of SCD have been reported in detail elsewhere.[2–6]

Traditionally, enhanced ventricular arrhythmogenicity in genetic CMPs has been ascribed to morpho-functional ventricular and structural myocardial substrates, respectively, including hypertrophy and disarray, microvascular ischaemia, and intramyocardial fibrosis in HCM and fibro-fatty myocardial replacement, ventricular dilatation/dysfunction, and aneurysms in ACM.[7,8] Conversely, the arrhythmogenic pathways of genetic channelopathies occur at molecular and cellular level and rely on functional changes of cardiac channels and receptors.[1] However, emerging translational research studies support the concept that malignant genetic tachyarrhythmias can be triggered by the complex interplay of arrhythmogenic mechanisms related to both structural myocardial abnormalities and cellular electrical current disturbances.[9,10]

The implantable cardioverter defibrillator (ICD) is the most effective therapy for prevention of SCD.[2,11–17] Given the protection afforded by ICD against arrhythmic SCD, young patients with inherited CMPs and channelopathies, who have a predominantly arrhythmia-related prognosis, may survive for many decades with nearly normal life expectancy, as opposed to older patients with either ischaemic or non-ischaemic dilated CMP in whom the concurrent ventricular dysfunction leading to heart failure and often progressive decline in ventricular dysfunction limits longevity. However, the survival benefits offered by ICD therapy are paralleled, especially in channelopathies,[1] by a significant incidence over time of inappropriate discharges and lead-related complications which may increase long-term morbidity and mortality.[18–20] This increases the need for accurate selection of patients for ICD therapy, by balancing the risk of life-threatening arrhythmias against that of dangerous and disabling side-effects, as the importance of quality of life is

increasingly recognized.[21–23] The availability of the subcutaneous ICD (S-ICD), which allows the avoidance of intravascular lead failure and/or endocardial infection, now provides a valuable alternative to conventional transvenous ICD[24,25] (despite its numerous limitations, e.g. T-wave oversensing and arrhythmic storms requiring multiple shocks). There is a general consensus that patients who survive an episode of arrhythmic cardiac arrest need protection by an ICD to abort arrhythmia relapses (secondary prevention); however, indications for prophylactic device implantation in patients without spontaneous life-threatening ventricular tachyarrhythmias (primary prevention) are often less certain.[23,26,27]

Here, we present our views on how to address arrhythmic risk stratification and treatment of young individuals with inherited CMPs and channelopathies, with a specific focus on what should be considered the appropriate role of ICD therapy in the primary prevention of SCD.

Risk stratification

In channelopathies and possibly for CMPs, randomized trials are generally non-feasible and may even be ethically unjustifiable in young individuals with relatively rare genetic arrhythmogenic conditions. Thus, the stratification of risk for arrhythmic cardiac arrest and SCD is largely based on observational data and expert consensus.[22,23] In addition, the variety of etiologies for inherited CMPs leading to different phenotypic variants, genetic penetrance and outcomes, makes a cause-specific prediction of the arrhythmic risk necessary.

Recently, to assist the clinician in the risk assessment, algorithms have been developed which result in risk scores, often designed as electronic calculators, whose clinical utility remains to be established.[28–30] Studies proving that the use of risk calculators for CMPs and channelopathies results in improved outcomes compared to 'single risk factor' based approaches are currently lacking.

As the arrhythmic substrate may worsen over time according to late or progressive phenotypic expression, it is not sufficient to perform risk stratification for SCD in patients with genetic arrhythmias at their initial evaluation but it is necessary to re-assess it on a regular basis during follow-up. Most important, the effect of treatment is not generally considered by risk scores. Algorithms evaluate the baseline arrhythmic risk to predict future malignant events, without accounting for changes in the risk resulting from proper treatment either present at the time of first evaluation or subsequently started during follow-up. While quantitative figures are not available, pharmacological treatment (for instance with β-blockers) is expected to substantially modify the basal arrhythmic risk of patients with CMP (HCM or ACM) and channelopathies (LQTS or CPVT) and, thus, to alter the predictive power of risk scores. *Failure to adjust for the effects of treatment may cause risk scores to overestimate the predicted risk and lead to inappropriate therapy including ICD implantation* (*Graphical Abstract*). *Table 1* summarizes the current risk stratification of patients with major genetic CMPs and channelopathies, based on recognized risk predictors of malignant arrhythmic outcome.

Hypertrophic cardiomyopathy

Traditionally, risk stratification for SCD in patients with HCM is based on clinical risk markers identified by retrospective observational studies.[31–40] The evolving knowledge of the disease prognosis has allowed to identify new risk markers and to develop prediction models for guiding prophylactic ICD. However, risk stratification remains imprecise, likely because of the heterogeneity of the disease, and is associated with a high number of patients that need to be treated in order to prevent one SCD.[12,41] The available risk prediction strategies include the 2014 European Society of Cardiology (ESC) calculator and the 2020 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for the management of HCM.[22,27] They share many predictors of increased risk of SCD such as family history of SCD, syncope, severity of left ventricular (LV) hypertrophy and non-sustained ventricular tachycardia (NSVT). Of note, LV wall thickness is a linear parameter in the ESC calculator, while it is binary ($<$30 ms or $\geq$ 30 mm) in the AHA/ACC guidelines. The ESC calculator includes age (as an inverse predictor), left atrial diameter and LV outflow tract gradient, whereas it does not take into account emerging prognostic factors such as LV systolic dysfunction, apical aneurysm, and late gadolinium enhancement that are considered important for prediction of SCD by the AHA/ACC guidelines. Direct comparison between the two risk prediction algorithms is difficult and they should be viewed as complementary rather than alternative to guide ICD therapy.

HCM patients with pathogenic or likely pathogenic sarcomere gene mutations appear to have an earlier and more severe phenotypic expression and a worse outcome with increased risk of ventricular arrhythmias and SCD, greater incidence of atrial fibrillation, heart failure, and overall mortality than sarcomere mutation negative HCM patients.[42] However, the prognostic role of the genetic background is limited by the high variability of the clinical relevance of the same genetic variant, either within or between families. Hence, at present, despite some suggestion for inclusion of a positive sarcomere gene in SCD prediction, results of genotyping are not generally used for risk stratification of SCD and therapy decision-making, with particular reference to ICD implantation.[22]

Recent studies demonstrated the limited predictive value in children of some adult risk markers for SCD.[43] While unexplained syncope, NSVT, LV hypertrophy, and left atrial enlargement show similar risk prediction in children as in adults, the association between SCD risk and age, family history, resting LV outflow tract gradient, amount of late gadolinium enhancement, LV systolic dysfunction and apical aneurysms in the paediatric population with HCM remains to be established. Although prediction models for paediatric patients are available, they are not yet systematically used for risk stratification in clinical practice.[44]

Arrhythmogenic cardiomyopathy

The natural history of ACM is predominantly related to ventricular electrical instability which may lead to arrhythmic cardiac arrest any time during the disease course.[45,46] Individual risk assessment of ACM is traditionally based on the severity of ventricular arrhythmias and ventricular systolic dysfunction.[4,14,16,23,46–53] Patients who have experienced sustained VT or VF have a high rate of recurrences. Unexplained syncope and dilation/dysfunction of right ventricle, LV, or both have been identified as major predictors of malignant arrhythmic events. A number of minor clinical predictors of arrhythmic outcome have been reported. Of importance, the largest multicentre outcome studies demonstrated that the electrophysiologic

Table 1 Current risk stratification of major cardiomyopathies and channelopathies

	HCM	ACM	LQTS	BrS
High risk category	• Cardiac arrest • Sustained VT	• Cardiac arrest • Sustained VT • Severe RV and/or LV systolic dysfunction	• Cardiac arrest • Malignant genetics • Events in the first year of life	• Cardiac arrest • Sustained VT
Intermediate-high risk category	• Recent syncope • Family history for SCD (due to HCM) • Massive LVH • LV apical aneurysm • LV systolic dysfunction	• Unexplained syncope • Non-sustained VT • Moderate systolic dysfunction of RV, LV, or both	• Syncope and/or TdP (despite β-blocker therapy) • T wave alternans • QTc >500 ms	• History of syncope • Spontaneous type I ECG
Intermediate-low risk category	• Amount of LGE • Non-sustained VT	• Male sex • Young age (at diagnosis) • Compound genotype • Proband status • Low QRS amplitude • Extent of T-wave inversion • Number of PVBs/24 h • Amount of LGE • Inducibility of PVS	• LQT2 women • Syncope off β-blockers	• Inducibility at PVS
Low risk category	• No risk factors • G+/Ph- individuals	• No risk factors • G+/Ph- individuals	• No risk factors • G+/Ph- individuals	• No risk factors • G+/Ph- individuals

G+/Ph-, genotype positive-phenotype negative; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; LVH, left ventricular hypertrophy; PVBs, premature ventricular beats; PVS, programmed ventricular stimulation; RV, right ventricular; SCD, sudden cardiac death; TdP, torsades de pointes; VT, ventricular tachycardia.

study with programmed ventricular stimulation is of limited value in identifying patients at risk of arrhythmic cardiac arrest because of its low predictive accuracy.[14–16]

A gene-specific risk stratification of ACM is still a matter of debate. Among carriers of desmosomal gene defects, available data indicate that multiple desmosomal gene mutations are likely to have a more severe phenotypic expression and an increased lifetime risk of malignant arrhythmias and SCD.[50] Single truncating mutations in the DSP gene have also been associated with a worse arrhythmic prognosis.[51] With regard to non-desmosomal gene defects, the TMEM43 p.S358L founder mutation, identified almost exclusively in Newfoundland, is almost fully penetrant and highly lethal among male carriers so to be considered by itself an indication to prophylactic ICD.[54]

Other non-desmosomal gene defects mostly responsible for biventricular or left-dominant ACM, which include mutations of the genes encoding filamin C, lamin A/C, desmin, RNA binding motif protein 20, and phospholamban (PLN), have been associated with a distinctively higher risk of SCD.[55]

Novel biomarkers are currently emerging as useful tools for risk prediction of the original predominant-right variant of ACM [i.e. arrhythmogenic right ventricular cardiomyopathy (ARVC)]. Testosterone, plasma bridging integrator 1, soluble ST2, miRNAs, anti-DSG2 antibodies, correlate with disease severity and arrhythmias incidence.[56,57] The risk of SCD in patients with left-sided disease variant [i.e. arrhythmogenic left ventricular cardiomyopathy (ALVC)] remains to be established. Emerging risk predictors include moderate LV systolic dysfunction (ejection fraction <45%), the amount of myocardial fibrosis, and a series of scar-related electrical features such as T-wave inversion in the lateral leads, low QRS voltages and frequent/complex ventricular arrhythmias.[58,59]

A calculator to predict the arrhythmic outcome of the classic ARVC phenotype has been proposed. It incorporates a number of disease-related features into a logistic regression equation aimed to provide estimates of the 5- and 10-year risk.[29] However, this prediction model suffers from biases due to the inhomogeneous study population, which includes both patients with and those without an ICD and the combined end-point used for the assessment of the arrhythmic outcome, which includes appropriate ICD intervention for VT/VF. Appropriate ICD intervention is a poor surrogate of arrhythmic cardiac arrest: indeed, most VT episodes treated by ICD are expected to be self-terminating and even short episodes of fast (>180/min) VT hemodynamically could be well tolerated and asymptomatic, because the LV systolic function in most ARVC patients is preserved or only slightly depressed. Since appropriate ICD interventions accounted for more than 70% of the study outcomes, *the model likely overestimates the true risk of SCD and benefit of an ICD*. Of note, as only one fourth of the total study population had an ICD, 60% of the study patients (without an ICD) were prevented from experiencing an appropriate ICD intervention. Hence, these outcome data, which are inhomogeneous and unbalanced in favour of ICD recipients, may be misleading and lead to ICD overtreatment of asymptomatic patients (*Figure 1*).

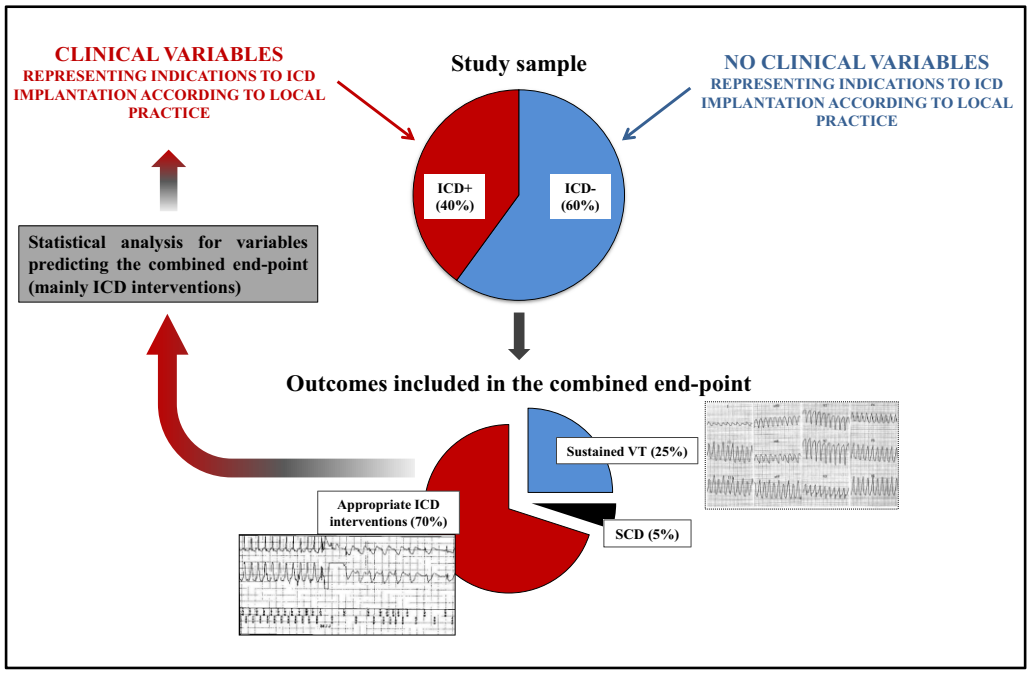

Figure 1 The figure illustrates the limited reliability of risk scores and calculators based on data obtained by heterogeneous study cohorts, including both implantable cardioverter defibrillator recipients and non-implantable cardioverter defibrillator recipients, and study design with a composite endpoint, including appropriate implantable cardioverter defibrillator intervention. In this representative example, although the mixed arrhythmogenic right ventricular cardiomyopathy study population predominantly comprises non-implantable cardioverter defibrillator patients (60%), outcomes mostly consist of appropriate implantable cardioverter defibrillator intervention (70%), which is an endpoint achievable exclusively by implantable cardioverter defibrillator recipients. Because the vast majority of outcomes in the arrhythmogenic right ventricular cardiomyopathy mixed population study are implantable cardioverter defibrillator interventions and the pre-determinate variables entered into the prediction model are those arrhythmic risk factors, that have been previously identified by implantable cardioverter defibrillator studies and represent current indication to implantable cardioverter defibrillator therapy for primary prevention of sudden cardiac death, the predictors identified by the statistical analysis coincides with the clinical variables used to guide implantable cardioverter defibrillator implantation. As a consequence, the study does allow to identify specific predictors of less frequent arrhythmic outcomes, other than appropriate implantable cardioverter defibrillator intervention, such as sustained ventricular tachycardia and cardiac arrest form ventricular fibrillation, which almost exclusively occur in the larger population of patients at lower risk and, thus, without indication to implantable cardioverter defibrillator implantation (non-implantable cardioverter defibrillator recipients). Most important, since appropriate implantable cardioverter defibrillator intervention is a recognized poor surrogate of arrhythmic sudden cardiac death, the use of risk scores and calculators based on risk predictors of appropriate implantable cardioverter defibrillator intervention may a misleading guide to implantable cardioverter defibrillator therapy for prevention of sudden cardiac death. Homogeneous study cohorts with regard to baseline treatment (particularly implantable cardioverter defibrillator therapy) are needed to make outcome studies more scientifically rigorous and to avoid that potentially misleading risk stratification scores are incorporated into calculators, which, in turn, may lead inexpert physicians to improperly implant an implantable cardioverter defibrillator for primary prevention of sudden cardiac death in young patients with genetic arrhythmias. ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death; VT, ventricular tachycardia.

A more specific calculator for prediction of life-threatening ventricular arrhythmias (i.e. fast VT/VF, or sudden cardiac arrest), using the same study design and database, has been recently proposed.[60] Surprisingly, traditionally recognized and clinically validated major risk factors such as a history of NSVT, syncope and the severity of ventricular systolic dysfunction did not predict the occurrence of life-threatening ventricular arrhythmias. Conversely, malignant arrhythmic events were associated with younger age, male sex, the burden of ectopic ventricular beats and the extent of T-wave inversion in the inferior and precordial leads, which are common disease features. *Because the available calculators for risk assessment of either VT or VF are based on outcome data that are inhomogeneous and unbalanced in favour of ICD recipients, they are potentially misleading with overestimation of the arrhythmic risk, which translates into overtreatment with ICD of asymptomatic ACM patients, a disquieting current trend.* Before these calculators can be recommended for clinical use, rigorous external validation studies are needed to assess their effective role in the prediction of SCD among ACM patients from community setting and from different geographic areas, with a diversity of ethnic backgrounds and genotypes, as it has been done in HCM patients.[61]

Long QT syndrome

Whereas in the 1970s and 1980s it was thought that the natural history of LQTS was usually represented by episodes of syncope which, in the absence of therapy, could be followed by a lethal one, over the years it became evident that almost two-thirds of SCDs in LQTS are

the sentinel event.[62] This realization changed how we thought about the immediate start of therapy, once the diagnosis was made. Thus, with few exceptions (see below), every LQTS patient should be promptly treated with full-dose β-blockers (preferably, nadolol or propranolol); then, individual risk stratification will guide, if necessary, 'treatment intensification' with either left cardiac sympathetic denervation (LCSD), mexiletine, or ICD implant.

The understanding of risk stratification in LQTS has evolved significantly during the last 50 years.[6,63] The early studies, in 1985[64] and in 1991,[65] identified the following factors as being associated with high risk: congenital deafness, female gender, a previous syncope, a markedly prolonged QT interval, and to be a proband (first patient identified in a family). A turning point in risk stratification for LQTS, ground-breaking also for other diseases of genetic origin, came only when genetic data began to be used to complement the clinical phenotype[66–68] and when the objective became to identify the risk factors for a first cardiac event. Conceptually, another major step forward came with the realization that cardiac events occurring in the first year of life identify a subgroup at extremely high risk and difficult to protect;[69,70] by extension, it has become evident that lumping together patients with different characteristics, just to increase numbers, is misleading and self-defeating.

Two large studies, both based on almost 700 genotyped patients, have improved risk stratification. One provided the unexpected evidence that the triggers for lethal events were gene-specific; this led to gene-specific management.[68] The other showed that a QTc ≥500 ms represents a clear dividing line above which risk was significantly higher, and gene-specific differences became evident.[67] Currently, we have identified several groups of patients at high risk for life-threatening events and also some at relatively low risk. The first group includes patients with two mutations,[71,72] with events in the first year of life,[69,70] with pore mutations especially in *KCNH2*,[73] with mutations in the S6 region of *KCNQ1*,[74] with mutations on the Calmodulin genes[75,76] or causing either the Jervell and Lange-Nielsen (J-LN)[77] or the Timothy syndrome,[6,78] or simply with a QTc >500 ms.[6,67] Conversely, a lower risk is present among LQT1 males without symptoms off therapy by age 25–30[79] and among the J-LN patients with both mutations on the *KCNE1* gene.[77] Risk stratification for LQTS is now being complicated, and refined at the same time, by the necessary attention to the presence of modifier genes[80] which act by either increasing[81–83] or decreasing[84,85] arrhythmic risk.

A risk calculator has been proposed also for LQTS,[30,86] following the concept proposed for HCM. The risk for potentially lethal events is calculated on the baseline data of genotype and QTc. If such risk exceeds 5% in 5 years, then an ICD would be recommended. The main issue with this approach is that, as well known in Medicine, any risk decreases when a patient is treated with effective therapies. It follows that before recommending an ICD, the baseline risk for LQTS patients should be reassessed after having implemented the 'optimal medical treatment' available and this, for LQTS, is represented by the combination of β-blockers with LCSD, with the possible addition of mexiletine for LQT3 and LQT2. Unfortunately, the proponents of the calculator have omitted to consider how much lower the risk would be for a patient receiving "optimal medical treatment" which, for LQTS, is the one mentioned above, as already recommended by two American guidelines.[87,88] *The acceptance of this 'risk calculator' would obviously and disquietingly cause a number of asymptomatic LQTS patients to be implanted with an ICD.* Along the same lines, a recent study[89] suggested that ICDs are effective in all subgroups of LQTS patients enrolled in a registry and followed by a variety of physicians with limited specific experience; however, this 'real-world' study provided results quite different from those obtained in the referral centres providing optimal medical treatment[90,91] which show that the need of an ICD is limited to a small minority of LQTS patients.

Catecholaminergic polymorphic ventricular tachycardia

Risk stratification for the occurrence of cardiac events in CPVT patients is still very imprecise. A history of cardiac arrest, absence of β-blocker therapy, younger age at the time of diagnosis, and proband status, are all independent predictors for cardiac events.[92,93] NSVT during an exercise stress test has been correlated with a worse outcome but cardiac arrest has been reported also in subjects without arrhythmias during the exercise stress test.[94] Genotype–phenotype correlations have been searched for in CPVT but, so far, nothing clinically useful has emerged that would help identify the patients at risk for aborted cardiac arrest/SCD.

Short QT syndrome

SQTS is definitely very rare and thus understandably the only accepted risk factor at this time is a history of cardiac arrest or documented spontaneous sustained VT. For asymptomatic patients there is simply no validated strategy for risk stratification. Neither electrophysiological studies nor genetic screening help in risk assessment.[95,96] Genetic screening does not help in risk assessment. A score to predict the risk for life-threatening arrhythmias in asymptomatic patients was tentatively proposed[97] but when it was tested in an independent cohort[96] the incidence of cardiac arrest was similar in the high and low risk groups.

Brugada syndrome

The modest but definite risk for SCD and the absence of an agreed upon effective pharmacological therapy, make risk stratification particularly daunting when dealing with asymptomatic subjects with BrS. Patients with aborted cardiac arrest or documented spontaneous sustained VT are clearly at high risk for SCD and for them an ICD indication is clear.[98] It has also been reported that the presence of *SCN5A* mutations are associated with increased clinical severity.[99] Conversely, asymptomatic patients without a spontaneous diagnostic electrocardiographic (ECG) pattern are at low risk and, for them, little more than regular follow-up visits are indicated.[98]

The difficulty concerns asymptomatic patients with a spontaneous type 1 ECG pattern. Their risk appears to be between 0.5% and 1% per year,[100] but a relatively low annual risk may translate, for young patients, into a relatively high risk over time.

In the absence of better data, the debate on risk stratification has largely centred on the role of the electrophysiologic study (EPS) with the result of an endless debate between one group[101,102] which considers inducibility at EPS as a major predictor for SCD/VF and other groups[103,104] finding a low positive predictive value of EPS. A meta-analysis reported an increased risk with two ventricular

extrastimuli but not with one or three.[105] Considering the limitations in EPS reproducibility, and the fact that a negative EPS cannot exclude further arrhythmias, the place of an EPS in risk stratification still appears to be controversial, and it should not be used as the only variable to define the management of the patient, according to the group led by Probst on the basis of a study on over 1600 patients.[106] They essentially confirmed the suggestions for risk stratification coming from Sieira *et al.*[107] for the patients with a high or low scores. However, the conclusion also was that for patients with an intermediate score the clinical usefulness of these scores was limited, and that the correctness of the clinical decision on whether or not to implant an ICD was superior to that strictly based on the existing scores. We share a recent analysis on risk stratification for BrS, written by a BrS expert, which concludes that while the Sieira *et al.*[107] and Shanghai scores[108] are useful for clinical decisions, they cannot substitute the experience-based clinical approach and that physicians' management strategies cannot be replaced by a calculating machine.[109]

Implantable cardioverter defibrillator therapy

Multiple randomized controlled studies consistently demonstrated that ICD implantation is the most effective therapy for interrupting life-threatening ventricular tachyarrhythmia and preventing SCD in patients with ischaemic and non-ischaemic heart disease.[26] An ICD is increasingly implanted in young people with genetic CMPs and channelopathies for either primary and secondary prevention of SCD.[18,19] According to current guidelines, there is general consensus that ICD therapy for secondary prevention in patients who survived an episode of spontaneous VF or sustained VT (high risk category) is recommended, because of the high recurrence rate of lethal arrhythmic events (*Table 1*). However, the indication of ICD implantation for primary prevention in patients without prior spontaneous life-threatening ventricular arrhythmias is still debated because the prediction of arrhythmic cardiac arrest based on clinical risk factors may not be sufficiently accurate to justify a device implant (intermediate risk category). And, indeed, the available risk stratification algorithms show a low positive predictive value leading to a disquietingly high rate of unnecessary ICD implantation, largely in a young population.[18,20] The implantation of an ICD is considered reasonable in patients with major risk factors (intermediate-high risk category). Of note, a syncopal episode is considered a very alarming symptom in all patients with genetic arrhythmias, because it may share the same arrhythmic mechanism with cardiac arrest and SCD. However, in these patients a potentially malignant syncope needs to be accurately differentiated from a neurally mediated (vaso-vagal) syncope that is benign and frequently observed in young individuals. In this regard, an implantable loop recorder may be indicated in patients presenting with unexplained syncope to identify the mechanism, either arrhythmic or non-arrhythmic, over long-term monitoring. Although the device may also provide a better characterization of the arrhythmia burden, its role to improve the arrhythmic risk stratification in asymptomatic patients remains to be established.[110]

Table 2 Complications of transvenous implantable cardioverter defibrillator

Acute complications
Venous access:
Pneumothorax, haemothorax
Air embolism
Perforation of the central vein
Inadvertent arterial entry
Lead placement:
Perforation of the heart or vein with pericardial effusion/ tamponade
Damage of heart valve
Generator:
Pocket haematoma requiring intervention
Improper or inadequate lead connection
Long-term complications
Lead-related:
Upper extremity vein thrombosis
Pulmonary embolism
Superior vena cava obstruction
Lead dislodgement requiring repositioning
Infection, endocarditis
Lead failure (malfunction or fracture)
Perforation, pericarditis
Tricuspid valve regurgitation
Generator-related:
Skin erosion
Pocket infection
Migration
Damage from electric shock, radiation, traumatic chest contusion
Therapy-related:
Inappropriate shock[a]
Acceleration of VT/degeneration into VF
Underdetection of VT/VF

[a]Due to either supraventricular tachycardia or abnormal sensing (i.e. ventricular oversensing due to T-or P-wave oversensing, lead fracture of electromagnetic interference).
ICD, implantable cardioverter defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

An ICD may be indicated in selected patients with minor risk factors (intermediate-low risk category). In these patients, the decision to implant an ICD should be made on individual basis, by assessing the overall clinical profile, the age, the strength of the risk factor(s)

identified, the level of SCD risk that is acceptable to the patient, and, most important, the potential risk of inappropriate interventions and complications. Indeed, young and active patients with genetic conditions have a greater probability to experience complications (>25% at 5 years),[18] such as inappropriate shocks and, most important, intravascular lead failure or infection requiring surgical intervention, which significantly impact the quality of life and may increase morbidity and mortality because of the many decades of life expectancy (*Table 2*).[19,20] Most important, implantation of an ICD is not generally indicated in asymptomatic patients with no risk factors and healthy mutation carriers who have a low risk of malignant ventricular arrhythmias.

Of note, indications for ICD implantation may vary in different countries as a consequence of several non-clinical factors such as cultural background, socio-economic conditions, healthcare system, availability of advanced technology, cost–benefit considerations, and liability. Compared with the conservative approach of many European countries, the current threshold for decision to implant an ICD in the USA is lower.[111]

Hypertrophic cardiomyopathy

Current AHA/ACC guidelines recommend that the decision to insert an ICD in patients with HCM relies on a traditional single risk factor approach, which is believed by general consensus to be more accurate for reaching a clinically reasoned and personalized decision.[22] Because risk stratification is imprecise, shared decision making between an educated patient and a physician with HCM experience plays an important role. According to the 2020 AHA/ACC guidelines,[22] the prespecified thresholds of SCD risk provided by the ESC calculator are not recommended as the only arbiter for reaching a decision to insert an ICD, though they may help patients with HCM to understand a quantified estimate of the 5-year risk of SCD during shared decision-making discussions.[22,27] In the paediatric population it should be considered that some single risk factors may have a lower predictive value and that the accuracy of risk assessment increases with multiple risk markers.[43,44,112,113] In children, the estimated risk of SCD should be accurately balanced with the expected high incidence of electrode and device related morbidity and mortality during long-term ICD therapy.

Arrhythmogenic cardiomyopathy

The performance of the 2015 International Task Force Consensus (ITFC) algorithm to guide ICD implantation in patients with ARVC was validated by the study of Orgeron *et al.*[114] The algorithm accurately differentiated survival from any sustained VT/VF among the different ICD class indications. The observed incidence rate was slightly higher than estimated for patients with Class I and Class IIa indications (observed versus expected incidence 30% vs. >10%/year for Class I and 15% vs. 1% to 10%/year for Class IIa), while it was as predicted for patients with Class IIb and III ICD indications (observed vs. expected 2.4% vs. 1% to 10% for Class IIb and 0% vs. <1% for Class III). The algorithm performed well also in the patient subgroup without a previous history of sustained ventricular arrhythmias, with a good prediction of ICD intervention by class indications on either VT/VF or VF/ventricular flutter, although there was limited differentiation of risk between patients with Class I and IIa indications. Recently, the comparison of the clinical performance of current algorithms for ICD implantation in ARVC confirmed that both the 2015 ITFC and the modified ITFC recommendations provide the highest ICD protection rates.[114,115] The 2015 ITFC remain the best performing algorithm to indicate an ICD in ARVC, if one considers a threshold of >6% 5-year risk (similar to the threshold for HCM patients) of fast VT.[115]

Channelopathies

An immediate distinction needs to be made between those channelopathies, such as LQTS and CPVT, in which adrenergic triggers are important and those, such as BrS and SQTS, in which they are not. The reason for this necessary separation is twofold. First, ICD shocks are painful and frightening; as a consequence they produce a major release of norepinephrine which, in LQTS and CPVT patients, often initiates an arrhythmic storm with immediate recurrence of VT/VF and a sequence of multiple shocks which, besides being psychologically devastating for the patients and their families, can lead to the exhaustion of therapies and to the patient's death.[116,117] Second, for BrS and for SQTS—besides the still uncertain evidence for the protective effect of quinidine[118]—the therapeutic options are essentially an ICD or no therapy[1]; whereas for both LQTS[6,90,119–121] and CPVT[92,121–123] there are very effective therapies which, even without providing 100% protection, are associated with excellent clinical results and good quality of life.[21,124]

Subcutaneous implantable cardioverter defibrillator

ICD therapy in patients with CMPs and channelopathies may lead to considerable morbidity, because many patients experience ICD-related adverse events and inappropriate interventions over time.[18,20] The lead system constitutes the most common malfunction and, consequently, is the most vulnerable part of the ICD system. Lead failure/fracture requiring lead extraction is the most frequent and potentially life-threatening adverse event, which increases with the age of the lead, and thus young patients with a long life prediction are the most vulnerable. The recent availability of subcutaneous, leadless ICD (S-ICD) that maintains protection from SCD while minimizing the risks of intravascular lead failure or infection has offered an alternative to the traditional transvenous ICD in young patients with genetic CMPs and channelopathies[24,25,125] (*Figure 2*). However, the S-ICD is not without its risks and shortcomings. These include potential oversensing of electrical signals; inability to provide anti-bradycardia, anti-tachycardia or cardiac resynchronization pacing; inability to extend the number of VT beats preceding the shock, which is a major issue with LQTS where episodes of torsades-de-pointes VT often terminate spontaneously after 15–30 s; and exhaustion of therapies with arrhythmic storms which are not rare especially in CPVT.[116,117] Strategies that may increase S-ICD eligibility and reduce inappropriate shocks include proper pre-implantation ECG testing, new implantation techniques, device programming (single-zone vs. dual-zone programming), and software upgrading including the 'SMART Pass', which is a recently introduced filter that should reduce oversensing.[125,126] Because the main objective of ICD therapy is the prevention of SCD (not the interruption of VT), without exposing the patient to

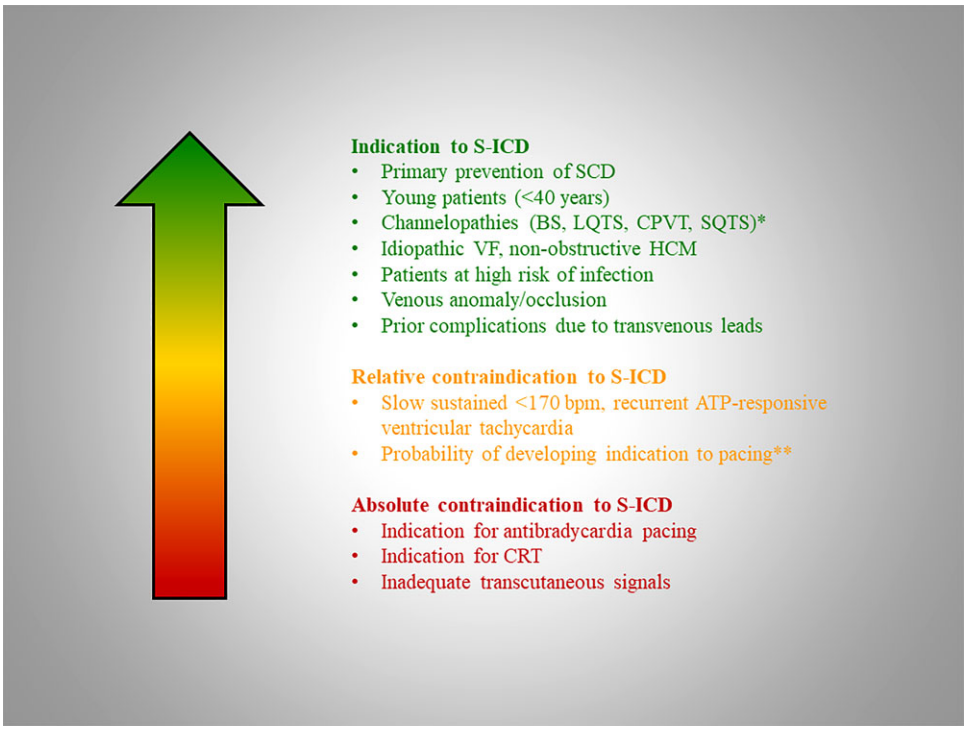

Figure 2 Indications and contraindications, either relative or absolute, to implant a subcutaneous implantable cardioverter defibrillator. All patients with an indication to implantable cardioverter defibrillatorimplantation may be eligible to subcutaneous implantable cardioverter defibrillator, if there is no need for pacing. Accordingly, a subcutaneous implantable cardioverter defibrillator is contraindicated in patients requiring pacing for bradycardia, cardiac resynchronization therapy or antitachycardia pacing. Also, a transvenous implantable cardioverter defibrillator may be prudentially preferred in some patients with a greater probability of developing the need for pacing over follow-up. subcutaneous implantable cardioverter defibrillator is particularly indicated in young patients who have a greater chance to experience lead failures requiring surgical revision and/or extraction because of their many decades of life expectancy. The implantation of a subcutaneous implantable cardioverter defibrillator is particularly justified in young patients affected by hypertrophic cardiomyopathy or channelopathies, in whom polymorphic ventricular tachycardia and ventricular fibrillation, typically unresponsive to anti-tachycardia pacing, are the predominant arrhythmic events that trigger shock therapy. In these patients eligibility may be limited by T-wave oversensing with R- and T-wave double-counting, leading to inappropriate shocks. Suitability of subcutaneous implantable cardioverter defibrillator may be improved by means of proper pre-implantation electrocardiograph testing, device programming (single-zone vs. dual-zone programming), and the use of electronic sensing filter such as the SMART pass filter. *There are significant limitations for the use of subcutaneous implantable cardioverter defibrillator for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia. The main ones are the inability to provide pacing, the lack of flexibility to increase the delay to shock, the limited number of therapies available in case of electrical storms. **Examples of conditions associated with a greater probability of developing future indications to pacing include: first degree atrio-ventricular (AV) block with PR interval >300 ms; bi-/tri-fascicular block; left bundle branch block with a reduced left ventricular ejection fraction; the need of β-blocker therapy in patients with the tendency to sinus bradycardia; and heart disease at high risk of sinus node dysfunction or AV block (e.g. cardiac sarcoidosis, laminopathies). ATP, anti-tachycardia pacing; BS, Brugada syndrome; CRT, cardiac resynchronization therapy; HCM, hypertrophic cardiomyopathy.

potentially lethal complications, all efforts should be made to implant a life-saving device which reduces the risk of electrode and device-related side-effects.

Non-shocking therapeutic options

Hypertrophic cardiomyopathy

Despite a 70-year experience in treating HCM, no effective medical therapies to prevent SCD have been identified. β-blockers are frequently used, but there is no evidence that they prevent SCD, as is also true for amiodarone.[22] No randomized clinical trials of β-blockers or amiodarone have been performed in HCM, with one single recent exception.[127] Retrospective studies found that HCM patients who had undergone septal myectomy to relieve outflow tract obstruction and severe symptoms had a lower rate of appropriate ICD discharges and risk for SCD, as compared with non-myectomy HCM patients. However, because the evidence is still incomplete and the impact of surgical myectomy debated, lowering the arrhythmic risk in asymptomatic patients is not a primary indication to this intervention.[128,129] It is noteworthy that alcohol septal

ablation, although it creates a potentially arrhythmic scar, does not appear to increase the risk of SCD.[130]

Prior studies identified HCM as a leading cause of SCD among competitive athletes, though recent longitudinal studies provided discordant findings. According to current guidelines, physical activity and competitive sport of mild/moderate intensity is allowed in adult HCM patients with a low-risk profile.[131]

Arrhythmogenic cardiomyopathy

Restriction from intense sports activity is regarded as an important preventive tool for both healthy mutation carriers and clinically affected persons in order to protect them from the risk of exercise-related malignant arrhythmic events and disease development or progression.[23,132,133] β-blockers are essential drugs to be offered in all clinically affected individuals, for both prevention of arrhythmias and reduction of right ventricular wall stress. Antiarrhythmic drug therapy offers the potential to ameliorate symptoms in ACM patients with ventricular arrhythmias, although there is no proof that it confers protection against SCD. Amiodarone, alone or in association with β-blockers, and sotalol are the most effective drugs, combining the synergistic effects of class III antiarrhythmic properties and of β-adrenergic blockade.[134] The potential for serious cumulative toxic effects often precludes long-term therapy with amiodarone, especially in younger patients. Catheter ablation has emerged as a valuable treatment in patients with sustained monomorphic VT, when antiarrhythmic drug therapy is either ineffective or non-tolerated.[135–137] The epicardial location of some VT reentry circuits, which reflects the propensity of lesions to originate and progress from the epicardium, may explain the limited success of endocardial catheter ablation. Several studies have shown the feasibility and long-term efficacy of epicardial catheter ablation for patients in whom one or more endocardial procedures have been unsuccessful.[137] However, catheter ablation of VT remains a symptomatic therapy in ACM patients and should not be looked upon as an alternative to ICD therapy for prevention of SCD.

Channelopathies

Long QT syndrome

LQTS is unquestionably the channelopathy with the best data from which to draw conclusions that are both clinically meaningful and scientifically reliable, and indeed this is perhaps the first disease in which precision medicine is beginning to play a role.[138] This is the consequence of four factors: (i) large numbers of patients; (ii) few referral centres worldwide which allowed uniform data collection; (iii) long follow-up because data have been carefully collected for almost 50 years;[139] (iv) the early institution of professionally managed international registries which have provided data for well over 25 years.[140,141]

There are three main modes of therapy for LQTS patients, independent of the ICD. β-blockers are the mainstay of therapy since the mid-70s[63] and nadolol and propranolol are the drugs of choice.[6,87,142] Mexiletine was introduced in 1995 for LQT3[143] patients and in 2019 for LQT2[144] patients (but only 2/3 respond well). LCSD was first used in the early 70s[145,146] and, following two large studies[119,120] and a simpler surgical approach,[147–149] its efficacy has become evident beyond doubt, and it is currently recommended (IA) by the American guidelines.[87,88]

Catecholaminergic polymorphic ventricular tachycardia

β-blockers represent the mainstay of therapy for CPVT.[87,98] Data with flecainide appear encouraging but are far from definitive.[150] LCSD is being used since 2008[122] in its management and, in addition to β-blockers when necessary, given the positive results of large studies[92,123,151] it has now become the preferred approach for therapy intensification whenever β-blockers appear insufficient.[152] This is also the reflection of the fact that an in-depth analysis of the effect of ICD implants in 136 CPVT patients has shown that not only an ICD was not associated with improved survival but that, instead, ICDs were associated with a high rate of inappropriate shocks along with other device-related complications and concluded that the use of ICDs should be limited as much as possible and LCSD should be favoured.[152]

Short QT syndrome

The very small number of patients with SQTS who have been treated and followed for a reasonable amount of time has limited the reliability of the available studies. Accordingly, the only pharmacological therapy that leads to QTc lengthening and reduction of arrhythmic events is quinidine. It has been recommended that quinidine be considered on a case-by-case basis in patients with increased risk of SCD and strong family history of SCD as a primary prevention (class IIb, level of evidence C).[26] In patients with SQTS and recurrent ICD shocks, quinidine has been shown to prevent further ICD discharges.[95]

Brugada syndrome

Despite the fact that BrS is much more common than SQTS, the data for pharmacological therapy are similarly very limited and the only drug that has received significant interest so far, and on which multiple retrospective studies have yielded encouraging reports, is quinidine.[118,153] Among non-pharmacological therapy options, epicardial ablation of the arrhythmogenic substrate (the areas that generate fractionated ECG) in the right ventricular outflow tract area has been proposed and was first performed in nine severely symptomatic patients; after ablation of an area with abnormal low amplitude QRS voltages and late to very late (>200 ms) fractionated activity, in eight patients the ECG normalized, and recurrence of arrhythmic events was successfully prevented.[154] For such patients this procedure may be useful. However, this epicardial approach has been extended also to asymptomatic patients, in whom the typical ECG patterns can disappear after the procedure and are reported to be no longer elicited by ajmaline or flecainide exposure.[155] The exact role for epicardial ablation remains to be established but there is a growing consensus that, given the potential complications (e.g. tamponade or damage to the coronary arteries) and the relatively low event rate in asymptomatic patients with BrS with a type 1 ECG, a prophylactic epicardial ablation in asymptomatic patients raises ethical questions and should be discouraged at present.[156]

Left cardiac sympathetic denervation

The mechanisms of action of LCSD have been repeatedly described.[90,157] By preventing the release of norepinephrine in the ventricles, LCSD significantly increases the threshold for VF,[158] thus

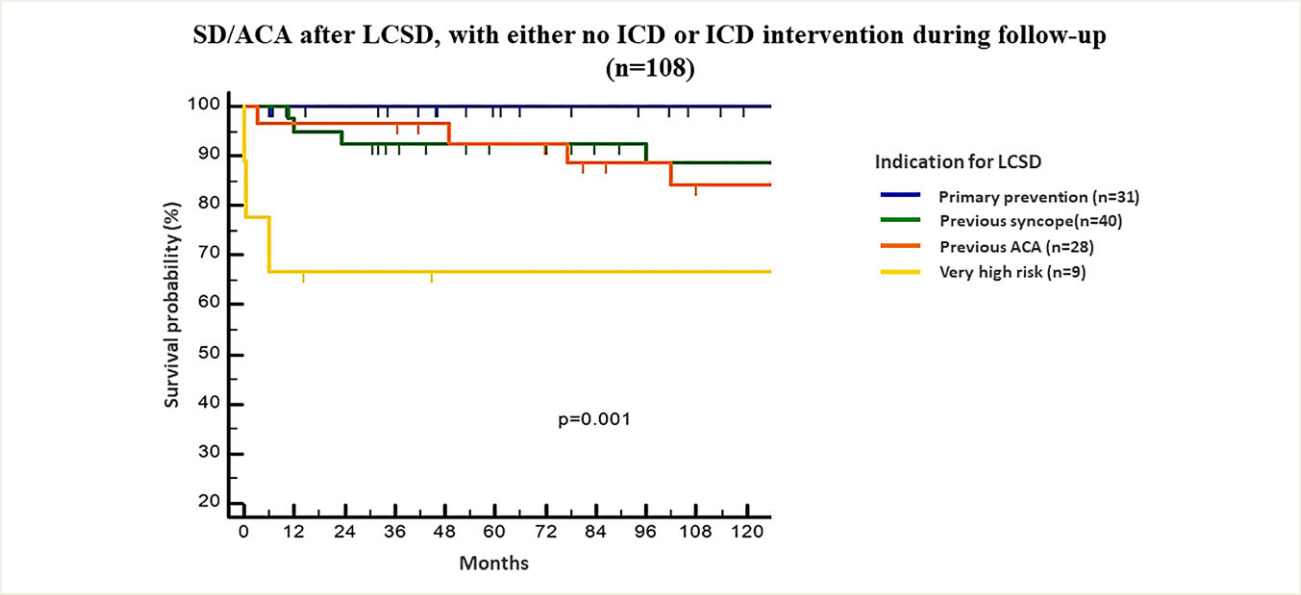

Figure 3 On treatment, Kaplan–Meier curves of cumulative survival free from aborted cardiac arrest/sudden death in long QT syndrome patients with either no implantable cardioverter defibrillator at the time of their first aborted cardiac arrest/sudden death after left cardiac sympathetic denervation or no implantable cardioverter defibrillator interventions during a 10-year follow-up. It is evident that for the 'very high risk group', which comprises extremely malignant genotypes and events in the first year of life, left cardiac sympathetic denervation is often not sufficient and an implantable cardioverter defibrillator implant is probably necessary. Conversely, all patients in primary prevention remained without symptoms. Importantly, patients with either syncope on β-blocker therapy or cardiac arrest did rather well as out of 68 patients only 1 (1.4%) died over a 10-year period. *Modified from reference Dusi et al.*[90] *with permission.* ACA, aborted cardiac arrest.

making more difficult for a heart to fibrillate. Also, ventricular refractoriness is prolonged[159] without impairing cardiac performance.[160] The capability of coronary bed to dilate is also increased,[161] and there is no reinnervation because this is a preganglionic denervation, without post-denervation supersensitivity.[162]

The efficacy of LCSD has been repeatedly and convincingly demonstrated in numerous studies in patients with both LQTS[90,119–121] and CPVT.[92,121–123,151] The efficacy of cardiac sympathetic denervation is not limited to channelopathies as shown by the data from the Shivkumar's group in patients with structural heart disease[163,164] (at variance with us, they favour bilateral cardiac sympathetic denervation at outset, but the principle remains the same), and in a few patients with ARVC.[165,166]

Some recent data[90] are especially relevant to situations in which too many cardiologists still recommend ICD implantation without considering to first perform LCSD. *Figure 3* shows the occurrence of either sudden death or aborted cardiac arrest after LCSD among LQTS patients with either no ICD or ICD interventions during follow-up. At 10 years after LCSD the survival free from sudden death/aborted cardiac arrest is between 85% and 90% for patients with previous aborted cardiac arrest or syncope. Of note, among the patients with events after surgery none had aborted cardiac arrest or sudden death as first event, but only syncope. Given that LCSD shortens QTc by approximately 60 ms in more than half of the patients with a QTc >500 ms at baseline, it was important to observe that among the patients with a QTc <500 ms at 6 months post LCSD the survival free from aborted cardiac arrest/sudden death was 100%. Finally, two studies[90,120] provided data on the impact of LCSD in the unfortunate patients with multiple ICD shocks; in five

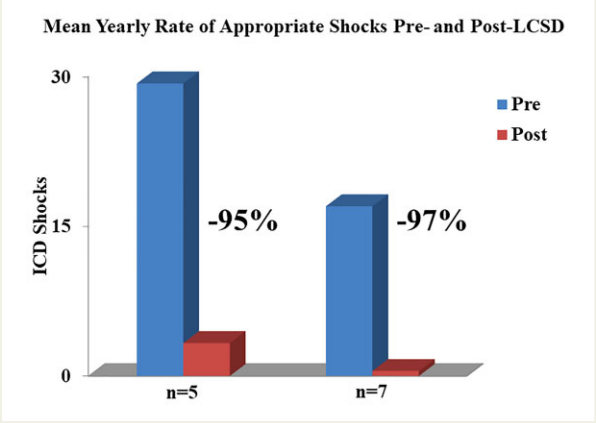

Figure 4 Long QT syndrome patients with electrical storms and multiple implantable cardioverter defibrillator shocks who, for this reason, underwent left cardiac sympathetic denervation. Two studies,[90,120] and different patients. It is evident that left cardiac sympathetic denervation was followed by a striking reduction in the number of shocks. In this case left cardiac sympathetic denervation did not save the life of the patients, which was taken care of by the implantable cardioverter defibrillator, but produced a major and dramatic change in the quality of life of the patients and of their parents.

patients, the mean yearly rate fell after surgery by 95% from 29.3 to 3.3 ($P = 0.02$), while in seven patients the reduction was by 97% from 17 to 0.5 (*Figure 4*). This dramatic reduction has a major effect

on the quality of life of the patients and of their families and should be always considered for patients implanted with an ICD.

The strength of these data is such that, when patients are not fully protected by β-blockers, it is no longer justifiable that they receive the indication for ICD implant without being offered the option of LCSD. The violation of this right to be fully informed may carry consequences.[167]

Sports in implantable cardioverter defibrillator recipients with genetic arrhythmias

Cardiologists are frequently asked to evaluate sports eligibility and to design recreational exercise programmes in asymptomatic young ICD recipients with genetic CMPs and channelopathies, who aspire to a physically active lifestyle and to take advantage of the many established benefits of exercise. Although patients with an ICD are traditionally considered not eligible to engage in competitive sports,[168] the available evidence indicates that ICD may provide a reasonable protection against SCD in athletes. A prospective, multinational registry which recruited 372 athletes with an ICD from the USA and Europe, including patients with CMPs and channelopathies, demonstrated that over a median follow-up of 31 months there were no arrhythmic deaths, resuscitated cardiac arrests or shock-related injuries, although sports activity increased the chance of experiencing life-threatening ventricular arrhythmia (appropriate shocks in 8% of participants during exercise versus in 3% at rest), which required multiple ICD shocks in 2% of the total population.[169] Moreover, the new S-ICD system appears as a promising therapeutic option aimed at avoiding the risk of sports-related lead damage over time. Of concern, systematic and intense athletic training in young CMP patients with a prophylactic ICD may increase over time not only the risk of SCD but also may favour the progression of the underlying heart muscle disease.[133,134] Accordingly, competitive and leisure sports activity may be allowed in selected athletes with an ICD, taking into account the specific patient's risk profile, with particular reference to the underlying arrhythmogenic cardiac disease.[131] Finally, ICD implantation is not justified when the only objective is to allow patients with genetic arrhythmias to participate in competitive sports.

Conclusions

ICDs represent a formidable weapon in our armamentarium for preventing SCD, and their careful and appropriate use saves lives. Unfortunately, they come with a cost. Especially in the young, the hasty and often incorrect decision to implant an ICD can become a nightmare for patients exposed to frequent inappropriate, rather than life-saving, shocks. It has to be sadly recognized that the choice for an ICD sometimes represents defensive medicine, but those defended are the doctors, not the patients.

There is a growing trend for the design of methods (risk scores, electronic calculators, and even guidelines) that dictate whether an ICD is indicated or not, instead of giving priority to the thoughtful clinical decision by clinicians with specific expertise in CMPs and channelopathies. Rarely, the decision to implant an ICD in asymptomatic patients is warranted, but this is always in the presence of an experience-based clinical assessment of imminent risk of cardiac arrest. *We are concerned with an ongoing disquieting trend, which results in an excessive and inappropriate number of ICD implants in patients with CMPs and channelopathies*. There are no substitutes for the complex process of a thorough clinical assessment based on specific expertise.

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