Consensus Statement on Primary and Secondary Prevention of Sudden Death. Argentine Society of Cardiology – Uruguayan Society of Cardiology (with the collaboration of the CONAREC)

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INTRODUCTION

Prevention of sudden death is a major challenging task for the overall medical community, and it makes a great responsibility for the specialists on the subject matter. Following this spirit of commitment, we have created a working group through the Scientific Societies to discuss and establish consensus for the most relevant aspects of this subject.

Sudden death (SD) is defined as natural death, from cardiovascular causes, which occurs unexpectedly, within a short gap from the onset of triggering symptoms, usually less than an hour or during sleep.

SD is a problem of serious magnitude, since it stands for half of the cardiovascular deaths, and 25% of the total deaths in adults. About half the times, it may occur in individuals with no previous heart disease, as a first episode.

While, in absolute values, SD occurs mostly in healthy individuals, its incidence in the overall population is low, and it increases as more severe subpopulations are selected. These patients with high risk factors for SD represent a minority in epidemiological terms. This analysis suggests two possible scenarios:

1. In the population with no clear markers of risk for SD, the core of treatment are the management of coronary risk factors, early consultation for suspected symptoms of heart disease, training in assisting a cardiopulmonary arrest, and availability of automatic defibrillators in areas with high concentration of people.
2. For the highest risk subgroups, prevention justifies the adoption of active and possibly costly measures to prevent SD. As a result, such therapies are only applicable to a small percentage of the overall population who will be exposed to it.

Structural and/or inflammatory heart disease is the main substrate in the pathopysiology of SD. However, about 5% of the episodes of SD occur among subjects without determinate heart disease, particularly among younger population. There is a great variety of "primary" electrophysiological abnormalities that contribute to SD in patients without structural heart disease. The importance of recognizing these cases is that, if a possible recurrence of arrhythmia can be prevented so that it does not result in cardiac arrest and sudden death, then the long-term prognosis is excellent due to absence of structural heart disease.

This Consensus is the result of the collaborative effort of the Area of Standardizations and Consensus, the Electrophysiology Council of the Argentine Society of Cardiology, and an outstanding group of experts from the Uruguayan Society of Cardiology. In addition to the chapters about SD prevention for the different (hypertrophic, idiopathic, ischemic) cardiomyopathies, we have developed other specific topics of the specialty, such as prolonged QT syndrome, Brugada syndrome, and right ventricular (RV) arrhythmogenic dysplasia. We have also intended to formulate recommendations on a particularly interesting topic because it affects our region, as is the case of Chagas disease. Moreover, and for the first time, we dared to propose recommendations to prevent SD in pediatric population, despite the complexity and relevance of this issue to pediatric clinical practice.

The goal is to deliver a document that physicians (cardiologist, clinician, pediatrician, or electrophysiologist) can use as a tool to find the necessary information to make decisions. Colleagues will also find guidelines so as to choose the best strategy in risk stratification and therapeutic recommendations for appropriate prevention of SD.

The kind of recommendation is detailed in each of the topics of this Consensus according to the following classification:

- **Class I:** conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
- **Class II:** conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment.
  Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy.
  Class IIb: usefulness/efficacy is less well established by evidence/opinion.
- **Class III:** conditions for which there is evidence and/or general agreement that a procedure or treatment is not useful/effective, and may even be harmful in some cases.

Also, while no proper literature is available for many of the topics, there is reference to the level of evidence which the agreed recommendation is based on, in accordance with the following schema for classification:

– **Level of Evidence A:** strong data derived from randomized clinical trials or meta-analysis. Assessment of several groups of populations at risk (3-5). Overall consistency in the target and magnitude of the effect.
– **Level of Evidence B:** data derived from a single randomized clinical trial or major non-randomized studies. Assessment of small groups (2-3) of populations at risk.
– **Level of Evidence C:** consensus or opinions from experts and/or small trials, retrospective studies, registries.

As for what has been discussed so far, we hope that this complete Consensus will indeed become a reference text for all cardiologists and a guide for their decision-making.

CHAPTER 1
LONG AND SHORT QT INTERVAL SYNDROME
Hereditary long QT interval syndromes

Hereditary long QT interval (LQT) syndromes are channelopahties that prolong ventricular repolarization and predispose to syncope and/or SD. (1) Syncopes are due to a peculiar variety of polymorphic ventricular tachycardia (VT), whose electrocardiographic configuration was given the name of torsade de pointes. (2)

These arrhythmias are usually self-limited, but can sometimes degenerate into ventricular fibrillation and cause the patient's SD. They are triggered by physical or mental stress and by swimming, and it may occur at rest or during sleep in some families. (3)

In physiological conditions, QT interval duration depends on age and sex (4) (Table 1).

Three syndromes typically describe the hereditary long QT interval:

1. The Jervell and Lange-Nielsen (JLN) syndrome

In 1957, Jervell and Lange-Nielsen described a family with six very young children with congenital deafness, four with recurrent syncopes, three of whom died suddenly and their ECGs showed a very long QT interval. (5)

2. The Romano-Ward syndrome

The Romano-Ward syndrome is observed more frequently than the above syndrome, and is different in that hearing is normal and, in general, there is dominant autosomal heredity. (6) However, the proportion of women affected is higher; one of the reasons would be that mothers carrying genetic mutations most often transmit the disease to their daughters. (7)

The Romano-Ward syndrome described 12 chromosomal mutations which involve ion channels or cell membrane proteins that regulate the exchange of sodium, potassium, and calcium. (3)

Its incidence is estimated at one case per 2,500-5,000 individuals from the overall population, and it causes between 3,000 and 4,000 deaths annually in children and adolescents. (6)

3. Sporadic variety

Known genetic mutations cannot be identified in 25-30% of the cases with LQT syndrome phenotype and normal hearing, and they lack easily identifiable familial characteristics. (6)

Diagnostic recommendations

Diagnosis of hereditary LQT syndromes (7)

Class I

1. Positive genetic mapping. (Level of Evidence A.)
2. Criteria by Schwartz et al, score ≥ 4. (Level of Evidence B.)

The certainty of the diagnosis is confirmed by demonstrating, with the genetic study, the responsible chromosomal abnormality. However, to date, known mutations are found only in 70-85% of the cases with positive phenotype. (8) Negative genetic screening in family members of patients with well-known chromosomal mutations rules out the diagnosis of this condition. (9) When there is no genetic study available, the set of diagnostic criteria proposed by Schwartz et al (10) are used, which are based on ECG, clinical and familial findings, in addition to the length of the QTc interval (Table 2).

To obtain the total score, syncopes must be excluded when torsade de pointes are considered, and only one criterium from the family history must be taken into account. This way, the maximum score is 9 points.

If the score is ≥ 4, diagnostic likelihood for this syndrome is high, with a sensitivity of 24% and a

Table 1. Length of QTc interval (sec) by age and sex

	Both sexes 1-12 years	> 12 years Male	> 12 years Female
Normal	≥ 0.39 < 0.45	≥ 0.39 < 0.45	≥ 0.39 < 0.46
Long	≥ 0.45	≥ 0.45	≥ 0.46

specificity of 99%. (3)

Some authors prefer Keating's criteria, (11) who diagnoses hereditary familial LQT syndrome in symptomatic patients when the interval is ≥ 450 msec, and in asymptomatic patients, when QTc interval is ≥470 msec, with a sensitivity of 36% and a specificity of 99%.

Another fact to point out is the need to perform several measurements due to spontaneous fluctuations observed in the QTc interval. (3)

FAMILIES WITH LONG QT INTERVAL SYNDROME AND RISK FOR SUDDEN DEATH

Patients with LQT syndrome may have arrhythmic heart events regardless of the QTc interval length and the involved chromosomal abnormality. Moreover, there are additional genetic modifiers such as polymorphism in the NOS1AP gene, which would have a key role in the arrhythmic risk for carriers of the disease. (12)

The risk is considered as very high, high, intermediate, or low. (7)

Very high risk

1. Patients who recovered from a cardiac arrest.
2. Jervell and Lange-Nielsen syndrome.
3. QTc ≥ 0.60 sec.
4. Patients with recurrent syncopes despite beta-blockers.

High risk

1. Patients with LQT 2 or 3 and QTc ≤ 500 msec.
2. Carriers of polymorphism in the NOS1AP gene.
3. LQT 2 with mutations in the pore region.

Intermediate risk

1. QTL 1 with beta-blockers, asymptomatic, and QTc ≥ 500 msec.

Table 2. ECG, clinical and familial criteria for the diagnosis of hereditary long QT interval syndromes

Criteria	Points
1. ECG findings	
A: Prolongation of QTc interval (msec)	
≥ 480	3
460-479	2
450-459 (in males)	1
B: Torsade de pointes	2
C: T-wave alternans	1
D: Notched T wave (in three leads)	1
E: Low heart rate for age	0.5
2. Clinical history	
A: Syncope with stress	2
B: Syncope without stress	1
C: Congenital deafness	0.5
3. Family history	
A: Family members with long QT interval	1
B: Sudden death in family members < 30 years of age	0.5

Low risk

1. Asymptomatic patients with QTc ≥ 500 msec, and with beta-blockers.

Therapeutic recommendations

Acute treatment of the torsade de pointes

The torsade de pointes episodes that cause syncope and/or cardio-circulatory arrest should be treated with (13):

Class I

A. Immediate electric cardioversion. (Level of Evidence A.)

Class IIa

A. Correct and/or remove any other intercurrent factor that may worsen the condition (hypokalemia, drugs, etc.). (Level of Evidence B.)
B. Magnesium sulfate, 2 grams IV. (Level of Evidence B.)

Class IIb

A. Transient ventricular pacing. (Level of Evidence C.)

Chronic treatment

Management of hereditary long QT interval syndromes is based on a mainstay of palliative therapy aimed at preventing malignant ventricular arrhythmias and SD. (3-7)

Class I

A. Changes in lifestyle. (Level of Evidence B.)
B. Beta-blocking agents. (Level of Evidence A.)
C. Beta-blocking agents + ICD in patients recovered from cardiac arrest. (Level of Evidence A.)

Class IIa

A. Beta-blocking agents + ICD in patients with recurrent syncopes despite beta-blockers. (Level of Evidence B.)

Class IIb

A. Beta-blocking agents + ICD in high risk patients. (Level of Evidence B.)
B. DDD pacemaker. (Level of Evidence B.)
C. Left cardiac sympathetic denervation. (Level of Evidence B.)

Beta-blocking agents are particularly effective in carriers of mutations that involve potassium channels and, primarily, those whose increased adrenergic tone triggers arrythmic events. Propranolol (3 to 10 mg/kg body weight) and nadolol (80 to 160 mg/day) are the beta-blockers of choice. Metropolol may be used for patients with breathing conditions. The ICD is recommended for subjects with a family history of SD, in those who recovered from cardiopulmonary arrest due to ventricular fibrillation and/or VT whose causes are not transient and/or reversible. In those who continue having syncopes due to episodes of polymorphic VT or ventricular fibrillation, despite the therapy with proper doses of beta-blockers. (14) When beta-blockers are not well tolerated and/or cause symptomatic sinus bradycardia or stimulate bradycardia-dependent torsade de pointes episodes ("sodium variant"), the implantation of a permanent

pacemaker is required. In patients with hereditary LQT interval syndrome, DDD pacemaker implantation is advised in those who have sustained pause-dependent VT or in those whose tachyarrhythmias are recurrent despite their medication. (15) The pacemaker of choice is the one with dual chamber, and stimulation pacing should be regulated (in general, > 80 bpm) to maintain QTc interval values ≤ 0.44 seconds; the 100 bpm at baseline should not be exceeded in order to avoid tachycardia cardiomyopathy.

Follow-up of patients with long QT interval syndrome

Patients should be periodically monitored with stress tests and 24-hour ambulatory ECG (Holter). Competitive physical activity should not be allowed in most cases.

CHAPTER 2
BRUGADA SYNDROME

Brugada syndrome (BS) is a genetic disease characterized by a typical ECG pattern of right precordial ST-segment elevation in the right precordial leads associated with high risk of sudden death (SD) secondary to ventricular arrhythmia, in the absence of structural heart disease documented by conventional diagnostic studies. (16) Known genetic defects are located in the chromosome 3 and affect the gene which codes for the sodium channel (SCN5A). (17, 18) Susceptibility for the development of arrhythmias is secondary to a marked transmural dispersion of repolarization, with the emergence of a vulnerable window in which a premature impulse can initiate reentrant arrhythmias.

The estimated prevalence is lower than 5 in 10,000, and it is highly predominant in males (8:1), although the dynamic nature of ECG findings conspires against knowing the true prevalence of the disease. It is the most common cause of SD in subjects under 50 years old in the absence of heart disease. The typical ECG (type 1) shows J point and ST-segment elevation in right precordial leads (> 0.2 mV) followed by negative T-waves. Definitive diagnosis of BS is obtained with the presence of the type-1 ECG pattern in one precordial lead of V1 to V3, associated with some of the following findings: documented ventricular fibrillation, polymorphic VT, family history of sudden death in subjects under 45 years old, type-1 ECG pattern in family members, VT induction with programmed stimulation or nocturnal agonal respiration. When type-1 ECG pattern is unclear, the diagnosis can be made by placing the precordial lead two intercostal spaces above the normal position. Type-2 ECG pattern, characterized by ST-segment elevation ≥ 2 mm at baseline, a fall with ST ≥ 1 mm, followed by a positive or biphasic T, and type-3 ECG pattern, similar to types 1 and 2 but with ST-segment elevation < 1 mm, are not diagnoses of BS. The finding of any of these patterns is important, mainly in patients with symptoms and/or family history, since induction of a type-1 ECG pattern through pharmacologic maneuvers (ajmaline, flecainide, among others) confirms the diagnosis in suspicious patients. (19) In patients with type-1 ECG pattern, performing these tests does not provide additional information, and may be dangerous. The test should be performed by experienced staff and in a safe setting.

Follow-up studies have shown that symptomatic patients with typical ECG pattern and family history of SD (FHSD) have a high risk for SD. Conversely, asymptomatic patients without FHSD have a low risk for arrhythmic events. Risk stratification and therapeutic approach in these patients are still controversial.

Finally, different drugs have shown to induce type-1 ECG pattern associated with BS and ventricular arrhythmia. For this reason, BS patients should be warned of the use of certain medications due to their potential harmful effect and, if taken, medication should be controlled. (20)

Therapeutic recommendations

Class I

1. An implantable cardioverter defibrillator (ICD) should be indicated in patients with BS and history of a SD episode with no other apparent cause. (Level of Evidence C.)
2. An ICD should be indicated for BS patients with spontaneous T-ST segment elevation in V1, V2, or V3, and with a history of syncope of cardiac origin. (Level of Evidence C.)
3. An ICD should be indicated for BS patients with documented VT not causing SD. (Level of Evidence C.)

Class IIa

1. ICD implantation is reasonable in BS patients with T-ST segment elevation induced by drugs and a history of syncope of cardiac origin. (Level of Evidence C.)
2. ICD implantation is reasonable in asymptomatic BS patients with spontaneous T-ST segment elevation and with tachycardia or ventricular fibrillation induced during an electrophysiologic study (EPS); patients should be informed about the treatment risk and probable benefits. (Level of Evidence C.)
3. Isoproterenol and quinidine may be useful for the treatment of electrical storms in patients with BS. Quindine can also be used for the chronic treatment of symptomatic patients, in areas where an ICD is unavailable. (Level of Evidence C.)

Class IIb

1. ICD implantation is reasonable in asymptomatic BS patients with induced T-ST segment elevation and a family history of SD and with tachycardia or ventricular fibrillation induced during an EPS. (Level of Evidence C.)

Class III

1. Type Ic antiarrhythmic agents (for example, flecainide and propafenone), and those of type Ia, except for quinidine (for example, procainamide or ajmaline), are contraindicated in patients with BS. (Level of Evidence C.)

Recommendations for the clinical management of patients with Brugada syndrome

Class I

1. The patient carrier of the BS pattern should be informed about the effect of drugs that may promote arrhythmias. (Level of Evidence C.)

Class IIa

1. Performing a programmed EPS with ventricular stimulation could be useful to stratify the risk in asymptomatic patients with a spontaneous type-1 Brugada pattern. (Level of Evidence C.)
2. It is reasonable to strictly monitor a spontaneous ST-segment elevation in patiens with ST elevation induced by drugs. (Level of Evidence C.)

Class IIb

1. Performing a programmed EPS with ventricular stimulation could be useful to stratify the risk in asymptomatic patients with a type-1 Brugada pattern induced by drugs, and with a family history of SD. (Level of Evidence C.)

CHAPTER 3
ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA

The arrhythmogenic right ventricular dysplasia (ARVD) is a cardiomyopathy characterized by a progressive –partial or massive – replacement of the RV myocardium by adipose or fibroadipose tissue.

Worldwide prevalence of this disease is calculated in 1/2,000 to 1/10,000 depending on the population studied; it is more common in some regions of Italy, such as the Veneto Region. The ARVD is the most common cause of sudden death (SD) among Italian athletes, and up to 20% of SD might correspond to young adults. (21) In other countries, such as United States, SD would correspond to 5% of patients under 65 years old. (22) Progressive structural abnormalities, which consist of fibroadipose replacement, would be the arrythmogenic substrate of this disease. The responsible tachyarrhythmias would be generated as a result of reentry originating from the RV. These tachycardias are typically very fast, paroxysmal, and have frequent recurrences.

Some authors have demonstrated that carriers of the disease have a high risk of SD. In a series of necropsies on young subjects who died suddenly, a high incidence of ARVD was observed; (23) however, other authors have observed a low risk of SD in the long-term follow-up. (24) Annual mortality rate with no treatment is 2.5-3%, and for individuals under treatment, 1%. (25)

Therapy for this condition is intended primarily to prevent lethal effects. The ICD improves survival rate of patients in secondary prevention and of those at increased risk for SD; therefore it is recommended for this type of patients. However, baseline treatment usually consists of beta-blockers; if these agents are ineffective to manage the symptoms or prevent VT recurrence, other antiarrhythmic agents will be necessary, such as sotalol and amiodarone, (26) particularly useful if they are able to supress inducible arrhythmias. (27)

There is little experience on ablation, and preliminary outcomes show it seems to be ineffective; however, recent studies based on three-dimensional mapping methods are more optimistic and provide better outcomes, so it would be an option to consider in cases of recurrence despite the use of antiarrhythmic drugs, or cases with multiple ICD shocks, or in subjects who cannot receive an ICD. (28)

Secondary prevention

Recent multicenter studies have consistently shown a high frequency of appropriate shocks and a very low rate of arrhythmic death in patients with ARVD treated with ICD, (29) which turns it into the therapy of choice in these cases. While there are no prospective randomized trials that assess drug therapy versus ICD for secondary prevention of SD in these patients, non-randomized studies and the experts' opinions support the use of the devices over the use of drugs.

Primary prevention

Some authors suggest that patients who meet the diagnostic criteria for ARVD have a high risk for SD and an ICD indication would be enough; however, further studies are required to confirm this argument. (30)

When thinking of primary prevention, one should bear in mind that there are no well-defined markers of clinical risk in ARVD, since the studies on survival with ICD and primary prevention about this condition are quite limited.

In high-risk patients, the rate of appropriate ICD shocks is 10% per year, while in low-risk patients, the rate is much lower. For that reason, patients diagnosed with ARVD in association with high risk for SD should be considered for ICD therapy. Some experts have proposed the use of ICD based on the presence of risk factors for SD, such as (31-37):

1. Evidence of extensive RV damage.
2. Involvement of the left ventricle (LV).
3. Aneurysms of the RV.
4. Dysplasia associated with a locus of the chromosome genotype 1q42-43.

Other identified risk factors for clinical usefulness are the following:

– Male subjects.
– Unsustained VT detection in non-invasive monitoring.
– Severe RV.dilation.
– VT induction during EPS.

This last factor is controversial, with dissimilar results. Corrado et al (29) showed that the number

of appropriate ICD discharges did not differ between patients who were VT induced and patients who were not at EPS, while Witcher et al (24) evidenced that VT or VF induction at EPS showed a tendency to a larger number of appropriate shocks. Similarly, Roguin et al (33) considered that VT induction was the main independent predictor of appropriate ICD shocks.

The importance of identifying high risk subgroups with indication of ICD lies in the optimization of the risk-benefit relationship, since –in addition to the general undesirable side effects by the use of ICD, such as infections or spurious shocks– two very important issues are to be considered:

1. The fatty infiltration could make it difficult to obtain proper thresholds, particularly the possibility of good sensing, which results in the lack of detecting potentially lethal arrhythmias.
2. The RV is thinned and non-contractile, so, while it is a rare complication, there is the risk of cardiac perforation and tamponade during catheterization.

Recommendations

Class I

1. ICD implantation is recommended to prevent SD in ARVD patients with sustained VT, documented VF or syncope of arrhythmic origin, whose life expectancy is > 1 year. (Level of Evidence B.)

Class IIa

1. ICD implantation may be effective to prevent SD in ARVD patients with risk factors for SD whose life expectancy is > 1 year. (Level of Evidence C.)
2. Drug therapy with beta-blockers and/or antiarrhythmic agents (sotalol or amiodarone) would be indicated in ARVD patients with no risk factors for SD, or in ARVD patients with risk factors for SD whom ICD implantation is not possible. (Level of Evidence C.)
3. Ablation may be useful as an adjuvant therapy in patients with ARVD and recurrent VT, despite optimal antiarrhythmic therapy. It would be indicated due to incessant VT, frequent ICD discharges or impossibility to receive an ICD or drugs. (Level of Evidence C.)

Class IIb

1. The EPS could be useful for risk stratification of SD in patients with ARVD. (Level of Evidence C.)

CHAPTER 4
HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a condition characterized by the presence of left ventricular hypertrophy not attributed to other causes, such as valve disease or hypertension. (38)

It is the most common genetic heart disease (1/500 births) of dominant autosomal transmission, with significant intragenic diversity; more than 600 mutations have been identified in different genes which encode sarcomere proteins. (39) Moreover, there are also other diseases in which genetic and metabolic causes interact and present a similar phenotypic manifestation (phenocopies), as is the case of the Anderson-Fabry disease, the glycogen storage disease, and some mytochondrial diseases. (39)

Many patients are diagnosed during routine tests and in some cases SD may be the first manifestation of the disease. Common symptoms are dyspnea on exertion, angina, presyncope, and syncope. Diastolic dysfunction is predominant in these patients, and they often have LV outflow tract obstruction. (38) During progression of the disease, some patients may have progression of symptoms, atrial fibrillation, embolic phenomena, and –in a very low percentage– heart failure due to systolic dysfunction. It should also be pointed out that this population is at higher risk for developing infective endocarditis, particularly in subjects with obstruction and in those with implanted endocardial devices such as ICD and/or pacemakers. (38)

Assessment of risk for sudden death

Our great challenge is to be able to identify the patients at highest risk for a SD episode. The incidence of SD in HCM is almost 6% in tertiary care centers, and below 1% in non-selected populations. HCM is the main cause of SD for those who practice competitive athletics and, while it is more common in young people, it may occur at any age. (38)

Below is a summary of the main major risk factors of SD that were included in the International Consensus on HCM published in 2003; in the "minor factors" section, we have also added other predictors, on the basis of the different publications from 2003 to date. (38-40)

Major risk factors

- Cardiac arrest due to documented ventricular fibrillation.
- Spontaneous sustained VT.
- Family history of premature SD
- Recent unexplained syncope.
- Extreme ventricular hypertrophy (≥ 30 mm).
- Non-sustained VT (repetitive or prolonged with HR ≥ 120 bpm).

Minor risk factors (possible in individual patients)

- Atrial fibrillation.
- Myocardial ischemia.
- LV outflow tract obstruction (> 30 mm Hg).
- Genetic high-risk mutations.
- Young patients.
- Abnormal response of blood pressure during physical exercise.
- Systolic dysfunction with ejection fraction < 50%.
- Associated coronary heart disease.
- Muscular bridges.
- Patients who underwent septal alcohol ablation.
- Evidence of myocardial fibrosis.

It should be pointed out that EPS for induction of

ventricular tachyarrhythmias is not a criterium and should not be used as a risk marker.

Therapeutic alternatives for patients with hypertrophic cardiomyopathy and high risk for sudden death

Many drugs have been evaluated to prevent SD in patients with HCM, but none of them has proved to be effective in reducing its risk. (38) Although it has been reported that 25% of the patients who had appropriate shocks due to ICD received amiodarone, such therapy is considered when the ICD is not available or is rejected by the patient. (41) ICD is the only treatment that proved to be effective to prevent SD in highest risk patients.

ICD indications in hypertrophic cardiomyopathy

Secondary prevention

In patients resuscitated from SD and in those who are symptomatic due to VT and/or syncope associated with ventricular arrhythmia. (38-41)

Primary prevention

The indication of ICD as primary prevention is substantially different depending on the country of origin, health care system, availability of devices, and opinions of different experts. (40) One of the most controversial issues today is whether only one risk factor is enough to indicate an ICD, or whether patients should have two or more factors. (40, 41) The first posture is predominant among authors from United States, who argue that only one risk factor can be enough to recommend ICD implantation as primary prevention in certain patients, and they consider that there is no relationship between the number of risk predictors and SD. They also demonstrated that the period of time between ICD implantation and the first appropriate shock can reach up to 10 years, and that one third of the patients in primary prevention who received appropriate shocks had only one risk factor. (40) However, it is important to highlight that, in some of the studies on which such strategy is based, patients did not undergo routine Holter monitoring.

In turn, European authors affirm that prognosis is more ominous when two or more factors are combined. According to the evidence and recommendations from different experts, we have taken the most important elements of the two main postures at international level and have developed a guideline for selecting patients who can benefit the most from this therapy (Table 3).

CHAPTER 5
ISCHEMIC CARDIOPATHY

Primary prevention

Several studies have assessed the usefulness of ICD in primary mortality prevention in patients with ischemic cardiopathy. Table 4 summarizes the most relevant aspects of these studies.

The MADIT I study (42) was the first one to show the utility of these devices in primary prevention. It recruited post-infarction patients with LVEF < 36% and unsustained VT, without indication for revascularization. These patients were taken to EPS and, if induced sustained ventricular arrhythmias were not supressed with procainamide, they were implanted an ICD or they followed a conventional treatment. A total of 196 patients were recruited (95 ICD and 101 conventional treatment) and, for a median follow-up of 27 months, ICD therapy was associated with a significant reduction of mortality, 54% (15 deaths in the ICD group and 39 in the conventional treatment group; p = 0.009). The MADIT study was highly criticized (small number of patients, long follow-up period, and differences between groups in the treatment used); however, it was a pioneering study in primary prevention.

The CABG-PATCH trial (43) assessed the effect of an epicardial ICD implantation at the time of coronary-artery bypass surgery in patients with LVEF ≤ 35% and abnormalities in the signal-averaged ECG. After 4 years of follow up, no benefit was observed with the ICD therapy.

The MUSTT study (44) included patients similar to those of the MADIT; one group was assigned to receive EPS-guided antiarrhythmic therapy, and the other received no therapy. The follow up was 60 months. The risk for cardiac arrest or death from arrhythmia was lower among the patients assigned to the EPS-guided therapy at 24 and at 60 months of follow up. This benefit was attributed to the use of ICD, which was implanted in 58% of these patients. The MUSTT registry (45) showed a high mortality rate at 5 years in patients without inducible ventricular arrhythmia, which was slightly lower than that in inducible patients but significantly higher than that in the ICD group. It suggests that those patients could have benefited from ICD, and that programmed ventricular stimulation is bad risk stratification for this type of patients.

The MADIT II trial (46) was a prospective study that enrolled patients with a prior AMI and a LVEF ≤30% more than a month before. An arm was assigned to ICD, and the other to conventional therapy in a 3:2 ratio. Death from any cause was the primary end point. A total of 1,232 patients were enrolled, who were assessed during an average follow-up of 20 months. The study was suspended prematurely because it reached its ICD efficacy objective, with a total mortality rate of 14.2% in the ICD group versus 19.8% in the conventional therapy group (HR 0.69, CI 95% 0.51-0.93; p = 0.016).

The DINAMIT trial (47) assessed the early ICD implantation after an acute myocardial infarction (6-40 days, mean of 18 days). While there was a significant reduction of death due to arrhythmia with the ICD (HR 0.42; p = 0.009), total mortality was similar in

	Recommendation	Level of Evidence
Secondary prevention		
ICD		
a) HCM patient resuscitated from SD or syncope with SVT and/or documented VF.	I	B
Amiodarone		
a) The same indications as those for ICD, when the latter is unavailable or its indication is rejected by the patient.	IIa	C
Primary prevention		
ICD		
a) HCM with two or more major risk factors, or one major and two minor risk factors		
b) Indication for an ICD with only one major criterium may be considered for patients under 40 years of age, except for cases of abnormal blood pressure response during exercise with low positive predictive value in isolation, but its value increases when associated with troponin T mutations	IIa	C
c) Since SD is relatively less common in the elderly, ICD should not be indicated for this age group with only one risk factor.		
Amiodarone		
The same indications as those for ICD, when the latter is unavailable or its indication is rejected by the patient.	IIb	C

HCM: Hypertrophic cardiomyopathy. SVT: Sustained ventricular tachycardia. VF: Ventricular fibrillation. ICD: Implantable cardioverter-defibrillator. SD: Sudden death.

Table 3. Guideline for ICD implantation in patients with hypertrophic cardiomyopathy

Table 4. Relevant aspects of the studies that evaoluated the usefulness of ICD in primary prevention of mortality in patients with ischemic heart disease

	MADIT	CABG-PATCH	MUSTT	MADIT II	DINAMIT	SCD-HEFT
Year of publication	1996	1997	1999	2002	2004	2005
n	196	900	704	1232	674	2521
Inclusion criteria	- 25 < age > 80 y. - AMI > 3 months - EF ≤ 35% - NSVT - Inducible sustained VT, not suppressible.	- Candidate to CABG - < 80 years - EF ≤ 35% - Abnormal SAECG	- Coronary heart disease - EF ≤ 40% - NSVT - Inducible sustained VT	- Age > 21 years - AMI ≥ 1 month - EF ≤ 30%	- 18 < age > 80 y. - AMI between 6 and 40 d. - EF ≤ 35% - HR ≥ 80 in Holter	- Age > 18 years - Heart failure FC II-III - EF ≤ 35%
EF endpoint (%)	≤ 35	≤ 35	≤ 40	≤ 30	≤ 35	≤ 35
Follow up (months)	27	48	60	24	30	60
Mortality controls (%)	39	24	55	22	19	36
ICD mortality (%)	16	27	24	16	17	29
Relative mortality reduction (%)	59	___	56	28	___	23
Absolutemortality reduction (%)	23	___	31	6	___	7
NNT	4.3	___	3.2	17	___	14.3

both treatment groups (p = 0.66). This was due to a significant increase of death from nonarrhythmic causes (HR 1.75; p = 0.02).

The SCD-HeFT trial (48) enrolled 2,521 patients with left ventricular dysfunction (LVEF ≤ 35%) of ischemic and non-ischemic etiology, with class I or II CHF, despite receiving optimal medical therapy. Patients were randomly assigned to three treatment groups: shock-only, single-lead ICD (n = 829), amiodarone (n = 845), and placebo (n = 847). After a follow-up period of 45 months, 666 patients (26.4%) reached the primary end point (total mortality): 244 patients in the placebo group (29%), 240 in the amiodarone group (28%), and 182 in the ICD group (22%). Compared with placebo, ICD therapy was associated with a relatively significant reduction of mortality rate, 23% (HR 0.77; CI 95% 0.62-0.96; p = 0.007), whereas the amiodarone therapy provided no clinical benefit. In the subgroup with ischemic and non-ischemic etiology, ICD therapy was associated with a decreased risk for death, and it was centered in patients with HF FC II and in those with LVEF ≤ 30%.

Conclusions

The MADIT II and SCD-HeFT primary prevention studies on ischemic cardiopathy have shown a total mortality reduction in that population. The simplicity of the inclusion criteria, basically ejection fraction and prior AMI, has led to enhance substantially the indication of a high-cost therapy such ad ICD implantation. However, some authors have questionned its outcomes and emphasized the need to identify subgroups in which the benefit is greater, as well as to recognize those patients with higher nonarrhythmic mortality whose survival rate does not improve with the device. This way, the cost-benefit equation would be optimized. (49, 50) The authors of the MADIT II trial published a score for which they selected five risk markers: age > 70 years, QRS > 120 msec, AF or HR > II, and BUN between 26 and 50 mg/dl. The ICD was only beneficial to those who had one or two variables (51) (Table 5).

The data from MADIT I and MUSTT studies, despite the important methodological differences, are coincidental with the therapeutic benefit from ICD for patients with high risk criteria, such as severe LV dysfunction, NSVT, and positive VT induction.

Regarding the cost-effectiveness relationship of the indication for an ICD in primary prevention of SD, there is a pubished model available, which is based on the outcomes of the MADIT II trial. (52) This study shows an inappropriate cost-effectiveness relationship, with an average ratio estimation of the incremental cost-effectiveness of about 235,000 dollars per year of life saved, which is clearly outside the acceptable range. This unfavorable result was particularly due to the fact that the estimated increase in life expectancy for these patients with ICD implantation was only 2 months throughout the study (3.5 years); according to this model, only a reasonable cost-effectiveness value for the parameters of United States would be obtained, in the event that mortality reduction with ICD is maintained for 12 years. Although data of this kind have not been published in our country, Argentina, it is unlikely that (in the overall group of patients studied) the cost-effectiveness relationship be appropriate in our country since, in general, the lower the GDP per capita of a country, the less money is available to invest in health, and the more restrictive the cut-off points of cost-effectiveness. Thus, a therapy that may not be cost-effective in the United States will most likely be too expensive for use in Argentina. However, it is possible to consider that cost-effectiveness would be appropriate in our country in those cases in which the estimated efficacy of ICD was greater, since it has been demonstrated that its efficacy is the most important variable to determine its cost-effectiveness. (53) That way, selection of patients in which a greater benefit from ICD is expected could generate an appropriate indication for ICD in Argentina, in terms of cost-effectiveness.

In the light of what has been mentioned, in the post-AMI population of our country it is necessary to select higher-risk groups in whom this valuable therapeutic resource can be utilized.

Thus, the opinion of this Consensus is that taking into account only the ejection fraction and the time as parameters is not enough to indicate an ICD to all the post-AMI population. Therefore, the recommendation of an ICD in "similar MADIT II" patients will be of class IIa.

Yet, we point out that, within this population, the indication is more precise in the subgroups with a score 1-2 of the MADIT II, in which the cost-effectiveness will be more appropriate. In this regard, QRS complex duration > 120 msec is a stable and easy to obtain variable and the one linked to greater benefit for patients with ICD in the MADIT II and SCD HeFT studies.

We also emphasize that subgroups with severe comorbidities are not good candidates, especially those with moderate to severe renal dysfunction and with a score of 3 or above of the MADIT II due to the high nonarrhythmic mortality rate in these patients.

Table 5. Risk variables of the score elaborated with the data provided by the MADIT II trial

Risk factors	HR	CI 95%	p
FC > II	1.87	1.23-2.86	0.004
AF	1.87	1.06-3.22	0.034
QRS > 120 msec	1.65	1.08-2.51	0.02
> 70 years	1.57	1.02-2.41	0.042
BUN > 25 < 50 mg/dl	1.56	1.00-2.42	0.048

Recommendations in primary prevention

Class IIa

1. Patients with > 40 days post-AMI, EF < 30%, FC I or asymptomatic, under optimal medical therapy, with a life expectancy > 1 year. (Level of Evidence A.)
2. Patients with > 40 days post-AMI, EF < 35%, FC II-III, under optimal medical therapy, with a life expectancy > 1 year. (Level of Evidence A.)

Class IIb

1. Patients with unexplained syncope, structural heart disease, EF ≥ 35%, and negative VT induction. (Level of Evidence C.)

Class III

1. Patients with < 40 days post-AMI. (Level of Evidence A.)
2. Patients in FC IV with no concomitant indication for resynchronization or who are on organ transplant waiting list. (Level of Evidence C.)
3. Patients who will undergo artery bypass surgery or have already undergone it within the last 3 months. (Level of Evidence C.)
4. Patients with serious comorbidities such as severe COPD, severe renal failure, serious psychiatric disorders or life expectancy with acceptable quality of life < 1 year. (Level of Evidence C.)

Secondary prevention

The population of patients who have suffered a resuscitated sudden cardiac death from non-reversible cause constitutes a high-risk group due to its increased likelihood of a recurrent new episode. Secondary prevention of SD refers to the treatment used to avoid or treat the recurrence of new major arrhythmic events, such as ventricular fibrillation and sustained VT, threatening arrhythmias to life.

A prospective and randomized study on secondary prevention that recruited 1,016 patients compared the ICD therapy versus antiarrhythmic drugs class III (mainly empiric amiodarone) and showed improved survival in patients with ICD. (54) This study reported a significant estimated reduction of the relative risk (RRR) of 39% (CI 95% 19-59%) in the ICD group at 1 year, of 27% (CI 95% 6-48%) at 2 years, and of 31% (CI 95% 10-52%) at 3 years. Other two prospective randomized studies on a group of patients with a history of SD showed similar results (Table 6). (55, 56) In a meta-analysis of the studies mentioned above, the ICD was associated with significant RRR, of 50% in arrhythmic death and 25% in all-cause mortality. (57)

Most patients included in the prospective randomized studies on patients resuscitated from SD (AVID, CIDS, CASH) had coronary heart disease. The mean left ventricular ejection fraction (LVEF) ranged between 32 and 45%. Current evidence is robust and strongly supports the benefit in survival of the use of ICD versus therapy with antiarrhythmic agents in this group of patients.

Recommendations in secondary prevention

Class I

1. ICD therapy is indicated in patients who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes. (Level of Evidence A.)
2. ICD therapy is indicated in patients with coronary heart disease, LVEF ≤ 40% and spontaneous sustained VT, whether hemodynamically stable or unstable. (Level of Evidence B.)
3. ICD therapy is indicated in patients with syncope of undetermined origin, coronary heart disease with LVEF ≤ 40%, EPS-induced ventricular fibrillation or hemodynamically unstable sustained VT. (Level of Evidence B.)

Class IIa

1. ICD implantation is reasonable for patients with coronary heart disease, sustained VT and normal or near-normal ventricular function. (Level of Evidence C.)

Class III

1. ICD therapy is not indicated for patients who have no reasonable expectancy for survival, even if they meet the implantation criteria specified above. (Level of Evidence C.)
2. ICD therapy is not indicated for patients with incessant ventricular fibrillation or tachycardia. (Level of Evidence C.)
3. ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. (Level of Evidence C.)
4. ICD therapy is not indicated for patients in FC IV of the NYHA refractory to drug therapy and for those who are not candidates to cardiac resynchronization therapy or heart transplantation. (Level of Evidence C.)
5. ICD therapy is noy indicated when VT is amenable to surgical or catheter ablation (for example, right ventricular or left ventricular outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). (Level of Evidence C.)

CHAPTER 6
IDIOPATHIC DILATED CARDIOMYOPATHY

Idiopathic dilated cardiomyopathy (DCM) is the second cause of death after ischemic cardiopathy in patients with heart failure. Mortality rate in these patients at 5 years is estimated in approximately 20%, and about 30% correspond to SD.

Treatment with ACE inhibitors and beta-blockers has reduced mortality in this group of patients with significant LV dysfunction, and has also decreased the number of hospitalizations. The association with other drugs, such as loop diuretics or aldosterone antagonists, has proved to reduce mortality even more

Table 6. Results of prospective and randomized studies on secondary prevention of ischemic cardiomyopathy

Study	AVID	CASH	CIDS
Year of publication	1997	2000	2000
N	1,016	197	659
Inclusion criteria	Aborted of SD due to VF, SVT with syncope, SVT with EF ≤ 40% and symptoms of hemodynamic deterioration	Aborted of SD due to VF or documented SVT	Aborted of SD due to VF or SVT, VT and syncope, SVT with EF < 35%, syncope with SVT inducible at EPS
EF (%)	≤ 40	-	≤ 35
Follow up (months)	18 ± 12	57 ± 34	36
Mortality controls (%)	24	44.4	29.6
ICD mortality (%)	15.8	36.4	25.3
Relative mortality reduction (%)	39	23	20
Absolute mortality reduction (%)	8.2	8	4.3
NNT	12.2	12.5	23.2

in this group of patients when they are symptomatic with heart failure (HF) in FC III-IV. Despite the optimal medical therapy for these patients, there is still an increased risk for SD. In most of the large-scale randomized studies, more than half of the patients included are carriers of dilated cardiomyopathy secondary to coronary heart disease, and the ICD in them was associated with improved survival compared with the use of antiarrhythmic agents. This has been demonstrated both in primary and secondary prevention.

There are few studies on idiopathic DCM. Among them, the AMIOVIRT trial and the CAT registry did not show ICD benefits related to the use of amiodarone or control in this group of patients. (58, 59) Both trials included a small number of patients and a population with a lower than expected mortality rate, therefore they were stopped early. The DEFINITE trial enrolled 458 patients with idiopathic DCM, EF < 35% and ventricular arrhythmia. (60) The ICD implantation significantly reduced the risk for SD. In the SCD-HeFT study, patients were assigned to three arms: placebo, amiodarone or ICD. (48) In this study, 48% of the patients were carriers of idiopathic DCM, and a 23% reduction of total mortality (p = 0.07) was found in the ICD group.

When selecting individual patients for ICD implantation, we should take into account clinical factors and associated comorbidities. Age older than 80 years, history of atrial fibrillation, FC III-IV, and creatinine values > 1.8 mg/dl are some of the variables associated with increased mortality at one year of ICD implantation. (51) Mortality increases from 0.4% to 21% in patients with less or more than two of these variables, respectively.

Recommendations

Class I

1. In patients with idiopathic DCM who have had sustained VT or VF, with syncope or SD, ICD implantation should be performed. (Level of Evidence A.)
2. In patients with branch to branch VT and in those who are presumed to have idiopathic VT, EPS and possible ablation should be considered. (Level of Evidence C.)

Class IIa

1. In patients with idiopathic DCM, EF ≤ 35%, FC II-III of the NYHA, stable over the past 3 years, with optimal treatment and life expectancy > 1 year, an ICD should be implanted. (Level of Evidence A.)
2. In patients with idiopathic DCM, EF > 35% and sustained VT refractory to antiarrhythmic agents, ICD implantation should be considered. (Level of Evidence C.)
3. In patients with unexplained syncope, idiopathic DCM and significant deterioration of the EF, an ICD implantation should be considered. (Level of Evidence C.)
4. In patients with idiopathic DCM who have had tachycardia with wide QRS, it would be appropriate to perform an EPS for diagnostic purposes. (Level of Evidence C.)
5. Patients with idiopathic DCM, EF > 35% and asymptomatic unsustained ventricular arrhythmia, a therapy with antiarrhythmic agents of the II or III group would be possible. (Level of Evidence C.)
6. In patients who have had multiple ICD shocks by VT despite complete medical treatment, a catheter ablation should be considered. (Level of Evidence C.)

Class IIb

1. In patients with idiopathic DCM, EF ≤ 35%, FC I of the NYHA, optimal treatment, and life expectancy > 1 year, ICD implantation may be considered. (Level of Evidence C.)
2. In patients with idiopathic DCM, EF > 35% and sustained VT, the use of amiodarone may be considered. (Level of Evidence C.)

CHAPTER 7
CHAGAS DISEASE

Chagasic cardiomyopathy is one of the main causes of morbidity in Latin America, and particularly in

our country, Argentina. It is estimated that this condition is present in 25-30% of the patients with positive serology. (61) Typically, it causes conduction disorders and abnormal automaticy, abnormalities in ventricular wall motion, heart failure, thromboembolic events, and what primarily concerns us in this issue: ventricular arrhythmias and SD. It is estimated that SD is responsible for about 55-65% of the deaths due to this condition, and not always it is associated with traditional mortality markers, such as deterioration of the ventricular function. (62)

Epidemiology

The percentage of infected individuals who develop chronic cardiac lesions varies depending on location, age, time of exposure in an endemic area, number of reinfestations, socio-economic status, period of infection evolution, and nutritional status. (63) Mortality range depends on the stage of the disease. In the series by Viotti et al (64), it was observed that 50% of the total deaths in patients without heart failure occurred suddenly. This group showed a total mortality of 0.5% in patients without ECG changes, 2.8% in those with ECG changes only, and 14% in patients with signs of asymptomatic ventricular dysfunction (increased diameters in echocardiography and/or cardiomegaly in chest X-ray). A mortality rate of 50% during the first year and SD of 44% due to VT and or VF as the most common causes were observed in patients on dilated stage with congestive heart failure. (61) A relevant and common observation is that patients who have sustained ventricular arrhythmias or resuscitated SD episodes have no evidence of ventricular dysfunction and required ICD implantation for secondary prevention. In recent series which analyzed total mortality characteristics and predictors, 15-28% of the patients studied with those characteristics did not have ventricular dysfunction. (65, 66)

Risk stratification

The main problems we have to face when making decisions could be summarized in two main issues: the lack of clinical trials including chagasic patients to validate the ICD implantation, and the difficulty to detect a high-risk subgroup among patients without symptomatic heart failure.

Regarding the first problem, different publications of observational studies have shown that impaired left ventricular function, FC III-IV, cardiomegalia, and non-sustained VT are bad prognostic indicators of chronic Chagas disease. (67-69) These findings would suggest that the behavior of chagasic cardiomyopathy in the presence of ventricular dysfunction would not be different from the dilated cardiomyopathies of ischemic-necrosis or idiopathic etiology.

In some studies, what calls the attention is the high percentage of appropriate ICD discharges in the follow-up of chagasic populations, with a 42% at one year and a short period between implantation and first shock. (65, 70)

Patients without clinical evidence of ventricular dysfunction, with abnormal ECG due to intraventricular conduction disorders with or without complex ventricular arrhythmia are a major challenge, as well as those who have not yet undergone events that justify secondary prevention. For that reason, different ways to stratify risk by evaluating different variables as combined or independent clinical predictors have been tried to be determined. In this direction, Rassi et al (70) developed a risk score based on six independent prognostic factors, assigning them a number of points proportional to their regression coefficient: FC III-IV 5 points; cardiomegaly evidence in chest X ray, 5 points; systolic dysfunction in ECG, 3 points; NSVT in Holter, 3 points; low-voltage QRS (< 0.5 mV), 2 points; and male sex, 2 points. Three risk groups were defined: low risk, 0-6 points; intermediate risk, 7-11 points; and high risk, 12-20 points. Mortality for those groups was 10%, 44%, and 84%, respectively.

Primary prevention

It is known that direct homologation of the indications of international guidelines to this disease is not possible, since no chagasic patients were recruited in the randomized trials of reference; therefore, it is unikely that ICD therapy for primary prevention be accepted, defined only by variables of ventricular function. Our recommendation for patients with ventricular dysfunction associated with syncope or non-sustained VT is to perform an EPS and, in case they have inducible VT/VF (regardless of the tolerance), implantation of ICD is advisable.

In cases of syncope or non-sustained VT without evidence of ventricular dysfunction, we recommend performing an EPS; in case of induction of VT/VF, regardless of the tolerance, implantation of ICD is advisable.

Indications for electrophysiologic study

Class I

1. An EPS is indicated for VT/VF induction in patients with ventricular dysfunction or parietal dyskinesias associated with syncope of unkown origin. (Level of Evidence B.)

Class IIa

1. An EPS is indicated in patients with syncope of unknown origin and/or NSVT without evidence of ventricular dysfunction. (Level of Evidence C.)
2. An EPS is indicated for VT/VF induction in patients with ventricular dysfunction associated with NSVT. (Level of Evidence B.)

Indications for ICD implantation

Primary prevention

Class I

1. An ICD is indicated in patients with ventricular dysfunction or parietal dyskinesias associated with

syncopes of unknown origin with inducible VT/VF at EPS, regardless of hemodynamic tolerance. (Level of Evidence B.)

Class IIa

1. ICD implantation is reasonable in patients with syncope of unkown origin and with significant ventricular dyskinesia or dysfunction. (Level of Evidence C.)

Secondary prevention

In cases of secondary prevention, we prefer to homologate the indications of the international guidelines; therefore, we accept the following:

Class I

1. An ICD implantation is indicated in survivors of a cardiac arrest secondary to ventricular fibrillation or VT with poor hemodynamic tolerance after identifying the cause of the episode and discard reversible causes. (Level of Evidence A.)
2. An ICD implantation is indicated in patients with spontaneous VT and ventricular dysfunction (or associated parietal dyskinesias), regardless of hemodynamic tolerance. (Level of Evidence B.)

Class IIb

1. An ICD implantation is reasonable in patients with sustained VT and normal ventricular function. (Level of Evidence C.)

CHAPTER 8
SUDDEN DEATH IN PEDIATRICS

The incidence of cardiac sudden death (SD) due to cardiovascular diseases in pediatric age is significantly lower than in adult population. The event rate in children and adolescents is between 1.3 and 8.5 deaths per 100,000 patients per year, whereas in adults older than 35 years, it is 100 deaths per 100,000 patients per year. (72)

Given the low incidence of events, there are no randomized clinical trials to define the risk stratification of SD for pediatric population, nor has the role of primary prevention therapies been defined. Therefore, the level of evidence for most of the recommendations in pediatric patients is level C.

Despite these limitations, several groups of young patients with increased risk for SD have been identified, compared with the overall population, including carriers of primary electrical diseases such as congenital long QT syndrome (CLQTS), cardiomyopathies, and congenital heart diseases. (73)

In young individuals, the "reversible" causes of SD include Wolff-Parkinson-White syndrome, acute myocarditis, and some cases of LQTS induced by drugs. In many patients with monomorphic VT in patients with "apparently normal" heart, further tests such as contrast-enhanced MR coronary angiography or endomyocardial biopsy can detect subclinical evidences of structural heart disease, of which ARVD and myocarditis are the most common findings that often pass unnoticed with the usual non-invasive methods. (74)

Cases of VT that are triggered by exercise have poor prognosis, and this association is a sensitive marker of an abnormal heart. (75) Some patients with catecholaminergic polymorphic VT (CPVT) may be asymptomatic but yet at risk for SD. (76) Symptomatic ventricular arrhythmia can also be the early sign of some cardiomyopathies.

There is still discussion about sudden infant death syndrome (SIDS) and the potential role of cardiac arrhythmias as the cause of some of those deaths. The causes of SIDS are under ongoing research. While apneas associated with inadequate breathing regulation are the main cause, there are also evidences which indicate that cardiac etiology could explain the 5% of the SIDS (autonomic dysfunction and genetic arrhythmias). (77)

Congenital heart diseases (CHD) represent a diverse spectrum of anatomical and functional defects, and therefore differences are significant with respect to natural progress, presurgical and post-surgical physiology, as well as the risk for arrhythmias and SD for each of them. During childhood and adolescence, more than 75% of deaths in patients with CHD are intrahospital events, which occur in the perioperative period. After 20 years of age, there is a progressive increase of SD incidence and total cardiac mortality for those with operated CHDs.

The CHDs at higher risk of late SD are the tetralogy of Fallot, D- and L- transposition of the great vessels (D-TGV and L-TGV), aortic stenosis, Ebstein's anomaly, and the different types of single anatomic or functional ventricle. Patients with tetralogy of Fallot constitute the largest subgroup, in which the risk for SD seems to depend on time. The longer the follow-up time, the higher the risk for SD, which increases if there are also hemodynamically significant, residual lesions and/or ventricular dysfunction. Surgical (or hemodynamic) solution of these residual defects is a priority, and it should be considered before starting any other type of antiarrhythmic therapy.

In general, patients with CHD who have syncope of unknown origin or aborted cardiac arrest should be carefully stratified. A positive outcome of EPS can identify patients at high risk for late SD. (78) The possible existence of paroxysmal AV block should also be considered, particularly in those conditions that evolve spontaneously to it, such as L-TGV and the AV channel, and in patients with a history of temporary AV block during immediate postoperative period.

Coronary anomalies deserve a special mention, since they cause effort syncope and SD in older children and in young individuals without cardiovascular history and often normal ECG. The most common one is the anomalous origin of the left coronary artery from the right sinus of Valsalva. Angulation of the coronary ostium, or compression of the left coronary artery coursing between the aorta and the pulmonary artery during vigorous exercise,

may cause myocardial ischemia and development of VT or VF. Definitive diagnosis is performed by mutlislice CT or by selective coronary angiography, and the indication is coronary artery bypass surgery. Coronary involvement may occur in isolation (fistulas, anomalies in implantation, origin or path) or associated with CHD, such as pulmonary atresia with intact septum or LV hypoplasia. Aneurysms, expansions, or stenosis secondary to inflammatory diseases are rare (Kawasaki, Takayasu, polyarteritis nodosa) or early atherosclerosis in familial dyslipidemias, malignant hypertension, and heart transplant. In these pathologies, although antiarrhythmic agents with coronary vasodilation action may be effective, the therapy should target to definitely solve the heart condition through angioplasty or coronary artery bypass surgery.

The risk for SD in young individuals with severe ventricular dysfunction has been considered lower than risk in adults with similar LV involvement. However, in a study of ICD in young patients on a waiting list for a heart transplant, 46% showed appropriate therapies on a mean follow-up of 7 months. (79) Until there are no conclusive data for this age group, ICD implantation for primary prevention should be extrapolated from randomized clinical trials on adult population for similar patients. The decision to implant an ICD for primary prevention in pediatric population at increased risk due to family history of SD is often raised in conditions such as MPAR, CQTLS, and CPVT, and the Brugada syndrome. Risk factors, although known, have not yet been validated in follow-up clinical trials. The risk for SD in children with CQTLS and MPAR is 2% and 3% per year, respectively. (80, 81) On the other hand, it has been reported that the risk at 1 and 3 years for recurrent events (appropriate shock of ICD) is 30% and 55% respectively in pediatric survivors of SD. (82)

Recommendations

Class I

1. ICD therapy is indicated in any pediatric survivor of cardiac arrest after having excluded any reversible causes, provided the patient receives optimal medical treatment and has a life expectancy > 1 year. (Level of Evidence B and C.)
2. ICD implantation is indicated for pediatric patients with sustained VT in association with CHD, with hemodynamic repercussion (ablation or heart surgery), and with a life expectancy > 1 year. (Level of Evidence B and C.)
3. ICD therapy is indicated for patients at high risk of SD or severe ventricular arrhythmias in association with congenital heart diseases (channelopathies or cardiomyopathies) who cannot be adequately protected by other methods (drugs, catheter ablation, surgical repair, pacemarker, left stellectomy, etc.). (Level of Evidence B and C.)
4. Hemodynamic evaluation with cardiac catheterization and/or MRI and/or EPS should be performed in pediatric patients with sustained VT to discard subclinical heart involvement. (Level of Evidence C.)
5. Investigation of pediatric patients' relatives suspected of genetic alterations should include clinical evaluation, ECG, echocardiography, Holter monitoring, stress test –if age permitted–, and possibly, pharmacological tests. (Level of Evidence C.)

Class IIa

1. ICD therapy is reasonable for pediatric patients with spontaneous sustained ventricular arrhythmia associated with severe systemic ventricular dysfunction, provided they are undergoing appropriate medical treatment and have a life expectancy > 1 year. (Level of Evidence B.)
2. ICD therapy together with medical/surgical treatment is reasonable for patients at high risk for SD or sustained ventricular arrhythmias in association with genetic involvement (channelopathies or cardiomyopathies) or with CHD. (Level of Evidence C.)
3. ICD therapy is reasonable for patients with CHD with syncope of undetermined origin in the presence of either severe ventricular dysfunction or inducible, sustained ventricular arrhythmias, in the absence of reversible causes, provided they receive optimal medical-surgical treatment and have a life expectancy > 1 year. (Level of Evidence B.)
4. Hemodynamic evaluation with cardiac catheterization and/or MRI and/or EPS is reasonable in patients with CHD and sustained VT. (Level of Evidence C.)
5. Invasive hemodynamic evaluation with cardiac catheterism and/or MRI and/or EPS is reasonable in patients with CHD in association with syncope of undetermined origin and/or ventricular dysfunction. (Level of Evidence B.)

Class IIb

1. EPS may be considered for patients with CHD and ventricular couplets or NSVT to determine the risk for sustained ventricular arrhythmia. (Level of Evidence C.)
2. Catheter ablation may be considered for children and adolescents with idiopathic, monomorphic, repetitive, non-sustained VT refractory to medical treatment, even if it is asymptomatic or there is no ventricular dysfunction. (Level of Evidence C.)
3. Catheter ablation may be considered in refractory patients with VT/VF, whose VPB causing the event always has the same morphology. (Level of Evidence C.)

Class III

1. Antiarrhythmic therapy is not indicated for asymptomatic pediatric patients with simple, monomorphic VPBs, without determinate heart

disease. (Level of Evidence C.)
2. Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with CHD and simple, isolated VPBs. (Level of Evidence C.)

CHAPTER 9
OTHER CONDITIONS

Left ventricular non-compaction

Left ventricular non-compaction (LVNC) is a rare heart condition of genetic origin, included in non-classified cardiomyopathies, also known as spongiform cardiomyopathy. (83)

Characteristics

Disorder of the left ventricular myocardium structure, with prominent trabeculation and intertrabecular recesses, forming compacted and non-compacted myocardium layers. (84) Sometimes, it may be associated with coronary fistulas and congenital heart disorders, such as Ebstein's anomaly, bicuspid aortic valve, corrected transposition of the great vessels, and interventricular septal defects. (85) It may be due to a fetal cardiac malformation during intrauterine stage, with persistent fetal trabecular pattern, changing the regulation of cell proliferation, differentiation, and maturation. They would be transferred mainly in an autosomal format dominated by mutations of the Tafazzin genes, dystrobrevin-alpha genes (DTNA), and sarcomere protein genes. (86, 87)

Diagnosis

Electrocardiography: in general, findings shown are common to cardiomyopathies, with conduction disorders, bundle branch block image, and primary repolarization changes.

Echocardiography: there are various diagnostic criteria; the most common ones include:

a) In typical and advanced stages, there are two defined myocardial layers, a thin epicardial layer, and a thick endocardial layer with several and prominent trabeculations in a compaction/non-compaction relation > 2:1 at the end-systolic period.
b) Doppler flow in the intertrabecular recesses.
c) Prominent trabecular meshwork in the apex or in the inferomedial and lateral segments. (88)

Cardiac magnetic resonance imaging: presence of hypertrabeculation in the apex, in the lateral and inferior walls of the LV, with a relation of compaction/non-compaction layers >2.3, measured during diastolic period. (89)

Prognosis

Its mid-term morbidity and mortality is high in symptomatic patients, determined by the possible progression to manifestations of refractory heart failure due to systolic dysfunction, stroke with or without atrial fibrillation, and occurrence of SD, which is the main cause of death due to its association with malignant ventricular arrhythmias, justifying the implantation of an ICD. For that reason, evaluation for heart transplant is also common.

Secondary prevention

Class I

1. ICD implantation is indicated in survivors of SD due to ventricular fibrillation or hemodynamically unstable sustained VT, in the absence of reversible causes. (Level of Evidence A.)

Primary prevention

Class I

1. ICD implantation is indicated in patients with structural heart disease and spontaneous VT, whether hemodynamically stable or unstable. (Level of Evidence B.)

Class IIb

1. ICD implantation may be considered in patients with LVNC and history of syncope, NSVT, EF ≤ 35% or family history of SD. (Level of Evidence C.)
2. ICD implantation may be considered for patients with LVNC in association with family history of SD. (Level of Evidence C.)

Idiopathic ventricular fibrillation

At present, the diagnosis of idiopathic ventricular fibrillation (IVF), also known as primary electrical disease, is by exclusion. These are patients with ventricular fibrillation but no evidence of structural heart disease in echocardiogram, no coronary artery disease detected by coronary angiography or stress test, no ECG repolarization changes, and normal MRI. Therefore, carriers of long or short QT syndrome, Brugada syndrome or catecholaminergic VT are excluded from this definition. It is estimated that this disease is responsible of up to 5% of the cases of SD. (90)

Electrocardiography: in general, the ECG is morphologically standard, as well as the QTc interval at baseline, with some exceptions. Patients with a history of syncope and SD have shown J-wave and early ventricular repolarization in lateral and inferior walls; however, there are still no conclusive data about this association. (91, 92) Occasionally, ventricular fibrillation is triggered by ventricular premature beats with left bundle branch block pattern and righ axis deviation with very short coupling interval (ventricular premature beats originating from the Prkinje system or right ventricular outflow tract). In general, its most common presentation is as sustained or non-sustained polymorphic VT that shortly turns into ventricular fibrillation.

Electrophysiology: both AH and HV intervals and refractory periods are normal. Induction of sustained polymorphic tachyarrhytmias is a very bad prognostic marker for patients who have had IVF and, in general, this response is subsided with antiarrhythmic drugs Class Ia. With aggressive protocols, inducibility is

positive in up to 89% of the cases with IVF, whereas in normal subjects, it may reach up to 9%. (93)

Prognosis and treatment: Recurrence of IVF is estimated in about 22% and 37% in the next 2 and 4 years after the first episode, respectively. (93) Given the absence of structural heart disease, prognosis is quite good if the arrhythmic episodes are subsided or controlled. The possible alternatives include: ICD, radiofrequency ablation and antiarrhythmic drugs (quinidine), not as monotherapy but as combined therapy. Existing reports about this rare condition are enough to indicate ICD as secondary prevention of SD in survivors.

Radiofrequency ablation of triggering premature beats has been used for healing purposes and for reducing the discharge frequency of ICD. (94) Occassionally, ventricular arrhythmias from the right ventricular outflow tract may be found in patients with IVF or malignant polymorphic VT. Radiofrequency ablation is a valid alternative for this entity. (95)

Secondary prevention

Class I

1. ICD implantation is indicated in survivors of SD due to ventricular fibrillation or hemodynamically unstable sustained VT, after excluding reversible causes. (Level of Evidence A.)

Primary prevention

Class I

1. ICD implantation is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or ventricular fibrillation induced at EPS. (Level of Evidence B.)

Catecholaminergic polymorphic ventricular tachycardia

Characteristics of the catecholaminergic polymorphic ventricular tachycardia (CPVT) include DVT induced by emotional stress or physical activity, in the absence of structural heart disease. It is also known as familial CPVT because of its hereditary genetic origin, although it may appear as de novo mutation in patients with no family history of CPVT. Syncopal sustained polymorphic ventricular tachycardia or ventricular fibrillation is often the main symptom of this disease.

Genetics

Mutations in two genes are reported to be responsible for CPVT:

1. Ryanodine receptor (R and R2) or calcium sarcoplasmic calcium release channel. Activation of this channel through exercise or beta-adrenergic stimulation would increase intracellular calcium release, triggering DVT occurrence. It would have an autosomal dominant transmission associated with the chromosome 1q42-q43.
2. Calsequestrin-2 (CASQ2); this mutation would be of recessive autosomal type. It would cause a change in the cellular dynamics of calsequestrin-2, a protein acting as reservoir of intracellular calcium. (96, 97)

Electrocardiography

At baseline, ECG is standard, with no repolarization changes and with normal QT interval. The overall complexity of the arrhythmia is related to the levels of exercise; at the beginning of the exercise, sinus tachycardia, frequent, supraventricular and ventricular premature beats occur and then follow polymorphic VT triggered by a VPB that progresses to sustained or non-sustained forms. Two-directional VT is also frequent in this condition.

Electrophysiological study

Electrophysiological intervals are normal, and inducibility of VT or VF is negative. The mechanism of the arrhythmia would be associated with late micro reentry and post-potential circuits dependent upon calcium and/or variants of the autonomic tone.

Prognosis

It is not possible to perform a proper prognostic stratification because it is a low-prevalence condition; however, it is accepted that the risk for SD without treatment is high in symptomatic young patients due to syncope or hemodynamically unstable VT. In general, beta-blocking therapy is usually effective in most patients. The worst prognostic marker would be the recurrence of ventricular tachycardia in patients treated with beta-blocking agents. (98)

Treatment

Physical exercise

Class I

1. Restricting physical exercise is mandatory.

Beta-blockers

Their utilization is effective in preventing recurrence of arrhythmias and syncope, with some exceptions and considerations. An almost 100% adherence to therapy is necessary to prevent suppression of drug syndrome and occurrence of ventricular arrhythmias. It does not completely deny the induction of supraventricular or ventricular arrhythmias as a result of exercise. It is mandatory to administrate them in all the cases with genetic diagnosis at an early age.

Class I

1. Beta-blockers are indicated in carriers of genetic alterations of the CPVT, diagnosed at an early age, and spontaneous arrhythmias induced by exercise. (Level of Evidence C.)

Class IIa

1. Beta-blockers are indicated in asymptomatic carriers of genetic alterations of the CPVT, diagnosed at an early age. (Level of Evidence C.)

Class IIb

1. Beta-blockers are indicated in asymptomatic carriers of genetic alterations of the CPVT, diagnosed at adult age. (Level of Evidence C.)

Cardiodefibrillator

There is agreement on its utilization in symptomatic patients under treatment with beta-blockers, resuscitated patients, and carriers of the gene with familial history of SD. (99)

Secondary prevention

Class I

1. ICD implantation and beta-blocking therapy are indicated in patients with CPVT, survivors of SD and with a life expectancy > 1 year. (Level of Evidence C.)

Primary prevention

Class IIa

1. ICD implantation is recommendable for patients with CPVT who have had syncope or sustained ventricular tachycardia under beta-blocking therapy. (Level of Evidence C.)

BIBLIOGRAPHY

1. Schwartz PJ, Periti M, Melliani A. The long Q-T syndrome. Am Heart J 1975;89:378-90.
2. Dessertenne F. Ventricular tachycardia with 2 variable opposing foci. Arch Mal Coeur 1966;59:263-7.
3. Acunzo RS. Las taquicardias ventriculares multiformes en pacientes con intervalo QT prolongado. En: Elizari MV, Chiale PA, editores. Arritmias cardíacas. Bases celulares, diagnóstico y tratamiento. Editorial Propulsora Literaria 1998; cap. 20, p. 395-413.
4. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. AHA/ACCF/HRS. Recommendations for the standardization and interpretation of the electrocardiogram. Part IV: The ST Segment, T and U Waves, and the QT Interval. J Am Coll Cardiol 2009;53:982-91.
5. Jervell A, Lange-Nielsen F. Congenital deaf mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J 1957;54:59-68.
6. Lu JT, Kass RS. Recent progress in congenital long QT syndrome. Curr Opin Cardiol 2010;25:216-21.
7. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. ACC/AHA/ESC Europace 2006;8:746-837.
8. Medeiros-Domingo A, Iturralde-Torres P, Ackerman MJ. Clínica y genética en el síndrome de QT largo. Rev Esp Cardiol 2007;60:739-52.
9. Shimuzu W. The long QT syndrome: Therapeutic implications of a genetic diagnosis. Cardiovasc Res 2005;67:347-56.
10. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long Q-T syndrome: An update. Circulation 1993;88:782-4.
11. Imboden M, Swan H, Denjoy I, Van Langen IM, Latinen-Forsblom PJ, Napolitano C, et al. Female predominance and transmission distortion in long QT syndrome. N Engl J Med 2006;355:2744-51.
12. Tomás M, Napolitano C, De Giuli L, Bloise R, Subirana I, Malovini A, et al. Polymorphisms in the NOS1AP gene modulate QT interval duration and risk of arrhythmias in the long QT syndrome. J Am Coll Cardiol 2010;55:2745-52.
13. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, et al. Prevention of torsade de pointes in hospital settings. AHA/ACCF. Circulation 2010;121:1047-60.
14. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Europace 2006;8:746-837.
15. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al. ACC/AHA/HRS Guidelines for device-based therapy of cardiac rhythm abnormalities. Circulation 2008;117:350-408.
16. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391-6.
17. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, et al. Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome. Eur Heart J 2002;23:1648-54.
18. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Brignole M, et al. Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome: a prospective evaluation of 52 families. Circulation 2000;102:2509-15.
19. Belhassen B, Viskin S, Fish R, Glick A, Setbon I, Eldar M. Effects of electrophysiologic-guided therapy with Class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol 1999;10:1301-12.
20. Postema P, Wolpert C, Amin A, Probst V, Borggrefe M, Roden D, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). Heart Rhythm 2009;6:1335-41.
21. Corrado D, Thiene G, Nava A, Rossi L, Pennelli N. Sudden death in young competitive athletes: clinicopathologic correlations in 22 cases. Am J Med 1990;89:588-96.
22. Peters S, Peters H, Thierfelder L. Risk stratification of sudden cardiac death and malignant ventricular arrhythmias in right ventricular dysplasia-cardiomyopathy. Int J Cardiol 1999;71:243-50.
23. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med 1988;318:129-33.
24. Wichter T, Borggrefe M, Haverkamp W, Chen X, Breithardt G. Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease. Results in patients with inducible and noninducible ventricular tachycardia. Circulation 1992;86:29-37.
25. Roberts R, Schwartz K. Myocardial diseases. Circulation 2000;102:34-9.
26. Marcus GM, Glidden DV, Polonsky B, Zareba W, Smith LM, Cannom DS, et al. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. J Am Coll Cardiol 2009;54:609-15.
27. Calkins H, Marcus F. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: an update. Curr Cardiol Rep 2008;10:367-75.
28. Arbelo E, Josephson ME. Ablation of ventricular arrhythmias in arrhythmogenic right ventricular dysplasia. J Cardiovasc Electrophysiol 2010;21:473-86.
29. Corrado D, Leoni L, Link MS, Della Bella P, Gaita F, Curnis A, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation 2003;108:3084-91.
30. Gillis AM, Sheldon RS, Wyse DG, Duff HJ, Cassidy MR, Mitchell LB. Clinical and electrophysiologic predictors of ventricular tachyarrhythmia recurrence in patients with implantable cardioverter defibrillators. J Cardiovasc Electrophysiol 2003;14:492-8.
31. Hodgkinson KA, Parfrey PS, Bassett AS, Kupprion C, Drenckhahn J, Norman MW, et al. The impact of implantable cardioverter-defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). J Am Coll Cardiol 2005;45:400-8.
32. Pezawas T, Stix G, Kastner J, Schneider B, Wolzt M, Schmidinger H. Ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy: clinical presentation, risk stratification and results of long-term follow-up. Int J Cardiol 2006;107:360-8.
33. Roguin A, Bomma CS, Nasir K, Tandri H, Tichnell C, James C, et al. Implantable cardioverter-defibrillators in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol 2004;43:1843-52.

34. Tavernier R, Gevaert S, De SJ, De Clercq A, Rottiers H, Jordaens L, et al. Long term results of cardioverter-defibrillator implantation in patients with right ventricular dysplasia and malignant ventricular tachyarrhythmias. Heart 2001;85:53-6.
35. Wichter T, Paul M, Wollmann C, Acil T, Gerdes P, Ashraf O, et al. Implantable cardioverter/defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy: single-center experience of long-term follow-up and complications in 60 patients. Circulation 2004;109:1503-8.
36. Piccini JP, Dalal D, Roguin A Bomma C, Cheng A, Prakasa K, et al. Predictors of appropriate implantable defibrillator therapies in patients with arrhythmogenic right ventricular dysplasia. Heart Rhythm 2005;11:1188-94.
37. Wichter T, Breithardt G. Implantable cardioverter-defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy: a role for genotyping in decision-making? J Am Coll Cardiol 2005;45:409-11.
38. Maron BJ, McKenna WJ, Danielson GK, Kappenbergr LJ, Kuhn HJ, Seidman CE, et al. ACC/ESC clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines (Committee to Develop an Expert Consensus Document on Hypertrophic Cardiomyopathy). Eur Heart J 2003;21:1965-91.
39. Konno T, Chang S, Seidman JG; Seidman CE. Genetics of hypertrophic cardiomyopathy. Curr Opin Cardiol 2010;25:205-9.
40. Casabé JH, Acunzo R, Fernández A, Gabay J, Galizio N; Hita A, et al. Consenso Argentino de Miocardiopatía Hipertrófica. Rev Argent Cardiol 2009;77:151-66.
41. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac abnormalities. Circulation 2008;117:350-408.
42. Moss AJ, Hall WJ, Cannon DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996;335:1933-40.
43. Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary artery bypass graft surgery. Coronary artery bypass graft (CABG) patch trial investigators. N Engl J Med 1997;337:1569-75.
44. Buxton AE, Lee KL, Fischer JD, Josephson ME, Prystowsky EN, Hafley H. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882-90.
45. Buxton AE, Lee KL, DiCarlo L, Gold MR, Greer GS, Prystowsky EN, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. N Engl J Med 2000;342:1937-45.
46. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.
47. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic Use of an Implantable Cardioverter-Defibrillator after Acute Myocardial Infarction. N Engl J Med 2004;351:2481-8.
48. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37.
49. Myerburg RJ. Implantable cardioverter defibrillators alter myocardial infarction. N Engl J Med 2008;359:2245-53.
50. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter defibrillators for the prevention of sudden cardiac death. J Am Coll Cardiol 2008;52:1111-21.
51. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, Zareba W, et al. Risk Stratification for primary implantation of a cardiac defibrillators in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;51:288-96.
52. Zwanziger J, Hall WJ, Dick AW, Zhao H, Muschlin A, Hahn RM, et al. The cost effectiveness of implantable cardioverter defibrillators. Results from MADIT II. J Am Coll Cardiol 2006;47:2310-8.
53. Cowie M, Marshall D, Drummond M, Ferko N, Maschio M, Ekman M, et al. Lifetime cost-effectiveness of prophylactic implantation of a cardioverter defibrillator in patients with reduced left ventricular systolic function: results of Markov modelling in an European population. Europace 2009;11:716-26.
54. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-83.
55. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation 2000;102:748-54.
56. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297-302.
57. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J 2000;21:2071-8.
58. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic non sustained ventricular tachycardia - AMIOVIRT. J Am Coll Cardiol 2003;41:1707-12.
59. Bänsch D, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: The Cardiomyopathy Trial (CAT). Circulation 2002;105:1453-8.
60. Kadish A, Dyer A, Levine J, Quigg R, Estes NA, Anderson KP, et al. Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy (DEFINITIVE). N Engl J Med 2004;350:2151-8.
61. Consenso de Arritmias Ventriculares. Consejo de Electrocardiografía, Electrofisiología, Arritmias y Marcapasos "Dr. Antonio Batro". Rev Argent Cardiol 2002;70(Supl 4).
62. Rassi A Jr. Implantable Cardioverter-Defibrillators in patients with Chagas heart disease: misperceptions, many questions and the urgent need for a randomized clinical trial. J Cardiovasc Electrophysiol 2007;18:1241-3.
63. Consenso de Enfermedad de Chagas, Consejo de Enfermedad de Chagas y Miocardiopatías Infecciosas "Dr. Salvador Mazza". Rev Argent Cardiol 2002;70(Supl 1):1-87.
64. Viotti R, Vigliano C, Lococo B, Petti M, Bertocchi G, Álvarez MG, et al. Indicadores clínicos de progresión de la miocarditis chagásica crónica. Rev Esp Cardiol 2005;58:1037-44.
65. Cardinalli-Neto A, Greco O, Bestetti R. Automatic Implantable Cardioverter-Defibrillators in Chagas' Heart Disease Patients with Malignant Ventricular Arrhythmias. Pacing Electrophysiol 2006;29:467-70.
66. Cardinelli-Neto A, Bestetti R, Cordeiro J, Rodrigues V. Predictors of all-cause mortality for patients with chronic Chagas' heart disease receiving implantable cardioverter defibrillator therapy. J Cardiovasc Electrophysiol 2007;18:1236-40.
67. Rassi A Jr, Rassi A, Rassi S. Predictors of mortality in chronic Chagas disease. A systematic review of observational studies. Circulation 2007;115:1101-8.
68. Dubner S, Valero E, Pesce R, Zuelgaray JG, Mateos JC, Filho SG, et al. A Latin American registry of implantable cardioverter defibrillators: the ICD-LABOR study. Ann Noninvasive Electrocardiol 2005;10:420-8.
69. Muratore C, Batista L, Chiale P, Eloy R, Tentori MC, Escudero J, et al. Implantable cardioverter defibrillators and Chagas' disease: results of the ICD Registry Latin America. Europace 2009;11:164-8.
70. Murature C, Rabinovich R, Iglesias R, González M, Darú V, Sosa Liprandi A. Implantable cardioverter defibrillators in patients with Chagas' disease: are they different from patients with coronary disease? Pacing Electrophysiol 1997;20:194-7.
71. Rassi A Jr, Rassi A, Little W, Xavier S, Rassi S, Rassi AG, et al. Development and validation of a risk score for predicting death in Chagas' heart disease. N Engl J Med 2006;355:799-808.
72. Wren C, O'Sullivan JJ, Wright C. Sudden death in children and adolescents .Heart 2000;83:410-3.
73. Silka MJ, Kron J, Dunnigan A, Dick M 2nd. Sudden cardiac death and the use of implantable cardioverter-defibrillators in pediatric patients. The Pediatric Electrophysiology Society. Circulation 1993;87:800-7.

74. Strain JE, Grose RM, Factor SM, Fisher JD. Results of endomyocardial biopsy in patients with spontaneous ventricular tachycardia but without apparent structural heart disease. Circulation 1983;68:1171-81.
75. Ryujin Y, Arakaki Y, Takahashi O, Kamiya T. Ventricular arrhythmias in children: the validity of exercise stress tests for their diagnosis and management. Jpn Circ J 1984;48:1393-8.
76. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation 2002;106:69-74.
77. Schwartz PJ, Stramba-Badiale M, Segantini A, Austoni P, Bosi G, Giorgetti R, et al. Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med 1998;338:1709-14.
78. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomized trials. Lancet 1997;350:1417-24.
79. Dubin AM, Berul CI, Bevilacqua LM, Cillins KK, Etherigde SP, Fenrich AL, et al. The use of implantable cardioverter-defibrillators in pediatric patients awaiting heart transplantation. J Card Fail 2003;9:375-9.
80. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348:1866-74.
81. McKenna WJ, Behr ER. Hypertrophic cardiomyopathy: management, risk stratification, and prevention of sudden death. Heart 2002;87:169-76.
82. Alexander ME, Cecchin F, Walsh EP, Triedman JK, Bevilacqua LM, Berul CI. Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. J Cardiovasc Electrophysiol 2004;15:72-6.
83. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from European Society of Cardiology working group on myocardial and pericardial diseases. Eur Heart J 2008;29:270-6.
84. Pignatelli RH, McMahon CJ, Dreyer WJ, Denfield SW, Price J, Belmont JW, et al. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. Circulation 2003;108:2672-8.
85. Lilje C, Rázek V, Joyce JJ, Rau T, Finckh BF, Weiss F, et al. Complications of non-compaction of the left ventricular myocardium in a paediatric population: a prospective study. Eur Heart J 2006;27:1855-60.
86. Henderson DJ, Anderson RH. The development and structure of the ventricles in the human heart. Pediatr Cardiol 2009;30:588-96.
87. Klaassen S, Probst S, Oechslin E, Gerull B, Krings G, Schuler P, et al. Mutations in sarcomere protein genes in left ventricular noncompaction. Circulation 2008;117:2893-901.
88. Jenni R, Oechnlin E, Schneider J, Jost CA, Kaufman PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart 2001;86:666-71.
89. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol 2005;46:101-5.
90. Consensus Statement of the Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States: survivors of out-of-hospital cardiac arrest with apparently normal heart. Need for definition and standardized clinical evaluation. Circulation 1997;95:265-72.
91. Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016-23.
92. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2009;361:2529-37.
93. Morady F, DiCarlo L, Baerman J, de Buitleir M. Comparison of coupling intervals that induce clinical and nonclinical forms of ventricular tachycardia during programmed stimulation. Am J Cardiol 1986;57:1269-73.
94. Haissaguerre M, Shoda M, Jais P, Nogami A, Shah DC, Kautzner J, et al. Mapping and ablation of idiopathic ventricular fibrillation. Circulation 2002;106:962-7.
95. Noda T, Shimizu W, Taguchi A, Aiba T, Satomi K, Suyama K, et al. Malignant entity of idiopathic ventricular fibrillation and polymorphic ventricular tachycardia initiated by premature extrasystoles originating from the right ventricular outflow tract. J Am Coll Cardiol 2005;46:1288-94.
96. Lahat H, Pras E, Eldar M. RYR2 and CASQ2 mutations in patients suffering from catecholaminergic polymorphic ventricular tachycardia. Circulation 2003;107:29.
97. Laitinen PJ, Brown KM, Piippo K, Swan H, Devaney JM, Brahmbhatt B, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. Circulation 2001;103:485-90.
98. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation 2002;106:69-74.
99. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-Year follow-up of 21 patients. Circulation 1995;91:1512-9.