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# Sudden Death in Ischemic Heart Disease

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## 1. Introduction

Sudden cardiac death (SCD) is defined by the death from unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within one hour of the onset of symptoms [1].

It is a major health problem worldwide, with a prevalence estimated in the range of 300 000 to 350 000 cases per year in the United States [2]. Event rates in Europe are similar to those in United States [3].

Coronary heart disease (CHD) is the leading cause of SCD explaining approximately 80% of cases [4]; cardiomyopathies and primary electrical abnormalities account for most of the remainder. Approximately 50% to 70% of these deaths are related to ventricular tachyarrhythmias (ventricular fibrillation/ tachycardia) [5].

Available medical therapies, such as beta-blockers [6] or antiarrhythmic drugs including amiodarone, failed to abolish the occurrence of SCD after a myocardial infarction (MI) [7], [8].

Implantable cardioverter defibrillators (ICD) are devices currently available capable of abort life-threatening ventricular tachyarrhythmias and therefore prevent SCD.

Although it is not possible to prevent all cases of SCD in the general population, the main issue is the identification of individuals at increased risk that may benefit from ICD implantation.

The highest risk of SCD in various heart diseases, either genetic or acquired, is related with the previous occurrence of ventricular arrhythmias [9]. In secondary prevention, predominantly three randomized clinical trials have established the criteria for ICD implantation.

The antiarrhythmics versus Implantable Defibrillators (AVID) trial showed mortality reduction with ICD among survivors of ventricular fibrillation or sustained ventricular tachycar-

dia causing severe symptoms [10]. The Canadian Implantable Defibrillator Study (CIDS) trial showed a 20% relative risk reduction in mortality with ICD therapy compared to amiodarone [11], although not statistically significant. The Cardiac Arrest Study Hamburg (CASH) trial confirm, though not with a statistical level of significance, the beneficial role of ICD therapy in the treatment of cardiac arrest survivors during long-term follow-up [12]. A meta-analysis of these trials showed a 28% reduction in mortality due predominantly to a reduction in arrhythmic death [13].

Thus, patients with ventricular tachyarrhythmias (VT or VF), not secondary to a transient or reversible cause, meet a Class I indication for ICD therapy. In addition, patients with syncope and significant documented VT/VF also meet indications for ICD therapy (Level of Evidence A) [14].

However it is worth noting that, in most centers, the deployment of an ICD for primary prevention far exceeds the number of devices placed for secondary prevention.

Compared to optimal medical therapy, the use of ICDs in recent trials for primary prophylaxis in CHD population was associated with a reduction in 5-year all-cause mortality of 23% to 36% and a reduction in absolute mortality of 1.5% to 3% per year.

## 2. Clinical parameters

Coronary disease is the main etiology of heart disease in Western countries and the major cause of heart failure and SCD. It is defined by the presence of significant coronary stenosis in a main coronary vessel or by the demonstration of previous MI.

Sudden death associated with CHD may occur in the acute context or months to years after MI. At least 50% of all SCDs due to CHD occur as a first clinical event and among subgroups of patients thought to be at relatively low risk for SCD [15].

SCD risk is associated with the conventional risk factors for coronary atherosclerosis [16] including obesity, smoking [17], genetic predisposition [18], [19], ECG pattern of LVH or LBBB, certain angiographic parameters or heart rate profile during exercise [20].

The rhythm most often recorded at the time of sudden cardiac arrest is VT or VF [21]. The pathophysiological mechanism underlying the arrhythmias can be variable and multifactorial.

Transient factors may interact with a fixed substrate that, in ischemic heart disease, is attributed to scar-based re-entry.

In chronic stage of CHD, the occurrence of SCD has an inverse relation with EF of left ventricle and, at present, this is the parameter most widely used to categorize "high risk" patients for SCD.

Other factors that have been demonstrated to contribute to the risk for SCD after MI include the presence of non-sustained ventricular tachycardia (nsVT), inducible VT by EP testing

[22] or symptomatic heart failure (HF). Premature ventricular complexes (PVC) predict an increased risk of SCD during long-term follow-up, especially if  $\geq 10$  PVC per hour. The presence of frequent PVCs during or after exercise has been associated with greater risk for serious cardiovascular events but not specifically SCD.

Several other parameters are considered predictors of sudden death, but all with low or moderate predictive values, whose sensitivity and specificity have not yet been studied in detail in large patient populations.

Different noninvasive exams that allow quantification of ischemia (cardiac SPECT) [23], characterization of longitudinal strain abnormalities (echocardiography) [24] or MI scar (Cardiac Magnetic Resonance) [25], T wave alternant (ECG) or the presence and extent of sympathetic denervation (cardiac  $^{123}\text{I}$ -MIBG imaging) were used in order to improve risk stratification of sudden death in ischemic cardiomyopathy [26], [27].

### 3. Primary prevention trials

To date, seven multicenter studies were essential for defining the criteria and timing for ICD implantation in ischemic heart disease: Multicenter Automatic Defibrillator Implantation Trial (MADIT [28]), Coronary Artery Bypass Graft Patch (CABG-Patch) [29], Multicenter Unsustained Tachycardia Trial (MUSTT) [30], MADIT II [31], Defibrillators In Acute Myocardial Infarction Trial (DINAMIT) [32], Sudden Cardiac Death in Heart Failure (SCD-HeFT)<sup>8</sup> and Immediate Risk Stratification Improves Survival (IRIS) [33].

Low LV ejection fraction (up to 30 to 40%) was the inclusion criterion similar in all of these studies.

Specific criteria in each of the studies were the presence of non sustained ventricular tachycardia and electrophysiological study showing inducible VT (MADIT and MUSTT), recent coronary revascularization and abnormal signal-averaged ECG (CABG-Patch), recent MI (DINAMIT, IRIS) and heart failure (SCD-HeFT).

Based on these trials, the American College of Cardiology, American Heart Association and the European Society of Cardiology guidelines recommend the implementation of ICDs in all patients with an ejection fraction inferior or equal to 30%, as well as patients with EF less than 35% with heart failure New York Heart Association (NYHA) class II or III. ICD can be considered in postinfarction patients with EF to 40% who have sustained ventricular arrhythmias inducible during electrophysiology study [14].

As a rule, ICD implantation is not indicated in patients recovering from an acute MI (less than 40 days) or CABG surgery (within 90 days) or in patients with NYHA class IV.

The Number needed to treat (NNT) of ICD implantation is quite different between the trials depending on the severity of the patients evaluated and varied between 4 in MUSTT and 14 in SCD-HeFT [34].

There is still a controversy regarding the effect of Cardiac Resynchronization Therapy (CRT) on the risk of ventricular tachyarrhythmias, specially in patients at higher risk of heart failure [36]. Some studies suggested that epicardial activation in CRT may cause dispersion of depolarization and prolongation of QT interval [37].

Recently, MADIT-CRT trial showed an inverse association between reverse remodeling and the risk of subsequent ventricular tachyarrhythmias: in high responders to resynchronization therapy (defined as  $\geq 25\%$  reduction in LVESD), there was a 55% lower risk of arrhythmias at 1-year post-implantation.

It seems that reverse remodeling had a dual effect of both heart failure and arrhythmia risk reduction [38].

#### 4. ECG measurements

Classically, the presence of Left Bundle Branch Block (LBBB) was considered of major prognostic importance, associated with the occurrence of sudden death in patients with ischemic heart disease. This was based on earlier studies, most of them performed before the era of percutaneous coronary revascularization [39].

In more recent investigations, especially those resulting from secondary analyses of MUSTT and MADIT-II trials, it has become clear that QRS prolongation is related with mortality after MI, although the magnitude of the relationship between abnormal intraventricular conduction and SCD in CHD remains unclear [40].

In an analysis of MUSTT trial, the authors noted that patients with LBBB had lower ejection fractions and higher incidence of symptomatic heart failure, suggesting that the increase in overall mortality was probably due to a sicker population [41].

In the MADIT-II cohort with prolonged QRS its duration (QRSd) was found to be an independent predictor of SCD in medically managed patients (HR 2.12) but not in ICD-treated patients (HR 0.77). This was attributed to the fact that ICD-treated MADIT II patients died predominantly of non-sudden HF, and QRSd would not predict HF mortality [42].

In the cardiac resynchronization therapy trial (MADIT-CRT), CRT dramatically reduces the progression of HF in patients with a low ejection fraction and a wide QRS complex. QRS duration and morphology was considered an important prognostic factor indicating more advanced cardiac pathology [43].

Other electrocardiographic parameters in which the prognostic value was evaluated were T-wave alternant (MTWA), the signal-averaged ECG (SAECG) and QT parameters and dynamics [44].

One of the parameters with more consistent results was MTWA. TWA consist of a fluctuation of the amplitude or morphology of the T wave every other beat assessed during exercise testing or atria pacing [45].

A positive MTWA determined an approximately 2.5-fold higher risk of cardiac death and life-threatening arrhythmia and showed a very high negative predictive value both in ischemic [46] and no ischemic patients. According to guidelines, it is a recommendation class IIa the use of TWA to improve the diagnosis and risk stratification of patients with ventricular arrhythmias [14].

In a small study in patients post-MI and EF less than or equal to 30%, microvolt TWA was better than QRS duration at identifying a high-risk group and also a low-risk group unlikely to benefit from ICD therapy [47].

SAECG permits the identification of low-amplitude signals (microvolt level) at the end of the QRS complex referred to as late potentials. These indicate regions of abnormal myocardium with slow conduction believed to serve as markers of the substrate for reentrant ventricular tachyarrhythmias [48]. It has a high negative predictive value but its value is lower after coronary revascularization. [49]

## 5. Autonomic variables

The main variables studied included the autonomic heart rate variability (HRV)/turbulence and the baroreceptor sensitivity.

HRV corresponds to a beat-to-beat variance in cardiac cycle length resulting from the sympatho-vagal influence on the sinus node. HRV is a term that encompasses a large number of different measures derived from 24-h Holter recordings.

In general, if such measures are extremely low, it is considered that there is autonomic dysfunction and this has been shown to independently predict the risk of SCD in post-infarct patients [50].

Methods based on non-linear dynamics and HR turbulence seems to provide better prognostic information than the traditional ones [51], [52].

Several studies have evaluated the prognostic value of heart rate variability in patients with ischemic heart disease [53]. In the randomized defibrillator in AMI trial (DYNAMIT), which used reduced SDNN combined with reduced left ventricular ejection fraction measured early (within 2weeks) after AMI as an inclusion criterion, there was no mortality benefit from ICD therapy in these presumably high risk patients [32].

On the contrary, in the cardiac arrhythmias and risk stratification after myocardial infarction (CARISMA) study, reduced HR variability measured at 6weeks after AMI, particularly the very-low frequency spectral component, was a powerful index in predicting arrhythmic events. The REFINE trial (Risk estimation after infarction, non-invasive evaluation) confirmed that HRV and HR turbulence yield more powerful prognostic information for arrhythmic events when measured later (6–10weeks) after AMI [54].

Despite these promising results, further prospective studies are needed to determine the usefulness of these parameters in clinical practice.



Reduced baroreflex sensitivity, a quantitative index of primarily vagal reflexes, evaluated by the phenylephrine method or by a non-invasive measurement [55], is also useful in assessing the risk of SCD [56, 57].

## 6. Autonomic imaging

There is evidence that regional and global sympathetic denervation could predispose to ventricular arrhythmias in post-MI patients. The denervated but viable myocardium could be hyperresponsive to circulating catecholamines [58, 59].

Using imaging methods for the evaluation of the sympathetic system in vivo, in human and animal models, such as [ $^{123}\text{I}$ -mIBG cardiac imaging, it has been reported that the mismatch between sympathetic innervation and perfusion could be associated with increased risk of ventricular arrhythmias.

The extent of sympathetic denervation measured at 4-Hour delayed  $^{123}\text{I}$ -mIBG SPECT imaging has been correlated with inducibility of ventricular arrhythmias in electrophysiological testing [60]. In another study including patients with advanced heart failure, late [ $^{123}\text{I}$ -mIBG SPECT defect score was also an independent predictor for ventricular arrhythmias causing appropriate ICD therapy (primary end point) as well as the composite of appropriate ICD therapy or cardiac death (secondary end point) [27]

More studies are required to determine the role of autonomic imaging in post-MI patients, possibly detailing their correlation with CMR findings.

## 7. Electrophysiological testing

Patients after MI have the highest induction rates in electrophysiological study and the presence of ejection fraction less than 40% and asymptomatic NSVT is associated with a inducibility of 20-40% [22], [61].

Programmed ventricular stimulation identifies most patients at risk for sustained monomorphic ventricular tachycardia associated with reentrant circuits that result of the healing process after infarction [22].

Electrophysiological study was required in MADIT, MUSTT, BEST-ICD [62], but not in MADIT -II and SCD-HeFT trials.

Based on these trials, electrophysiological testing is not required before ICD implantation. It is recommended (class I) for diagnostic evaluation of symptoms suggestive of tachyarrhythmias, to guide VT ablation and for differential diagnosis of a wide-QRS-complex tachycardias of unclear mechanism [14].

Electrophysiological study is also reasonable for risk stratification in patients with NSVT, and LVEF equal or less than 40% (Class IIa). Inducibility of VT in patients with NSVT is as-

sociated with a high risk for VT/FV and the characteristics of NSVT could not predict the inducibility [63].

## 8. Echocardiographic parameters

The echocardiogram is a fundamental exam for the identification of candidates for ICD implantation. Although an LVEF of  $<40\%$  is commonly used for stratification of patients at risk for ventricular arrhythmias, it does not allow accurate discrimination of patients with or without sudden arrhythmic death. Moreover, sudden arrhythmic death also occurs in patients with an LVEF of  $\geq 40\%$  [64].

The technical advances in echocardiography will probably allow exploring the appraisal value of new variables beyond the ejection fraction of the left ventricle in the risk stratification.

In a unicenter study a greater involvement of peri-infarct zone longitudinal strain was independently associated with an increased risk of having an appropriate ICD therapy on follow-up. In such study the odds of dying in a patient with a peri-infarct zone strain value of  $-6\%$  was approximately 11.5 times that of a patient with a peri-infarct zone strain value of  $-17\%$  [65].

## 9. Cardiac magnetic resonance

Cardiac MRI allows characterization of cardiac morphology in patients with poor echocardiographic window and provides an estimate of the location and amount of intramyocardial fibrosis.

The presence of myocardial scar or fibrosis as measured by delayed enhancement after administration of gadolinium has been recently associated with post-infarct arrhythmic death [66], [67] suggesting that contrast-enhanced MRI may enable better risk stratification for ICD implantation among patients with prior MI compared with traditional variables such as LVEF and NYHA class.

Roes S et al identified infarct tissue heterogeneity on contrast-enhanced MRI as a strong predictor of spontaneous ventricular arrhythmia in ICD therapy recipients [68]. In a more recent study from a tertiary center which included the monitoring of 52 patients, it was identified a relationship between the transmural extent of infarction and the occurrence of spontaneous ventricular arrhythmias in patients with chronic ischemic cardiopathy [69].

## 10. Conclusion

Ischemic heart disease is the heart disease in which most often there is indication for an ICD implantation. However, after placed, these devices are used in a minority of patients in the context of primary prevention.



Left ventricular dysfunction remains the most robust parameter in the decision to implant an ICD. All therapeutic measures that can accelerate or improve myocardial reperfusion by contributing to the preservation of ventricular function are undoubtedly the best strategies to reduce costs associated with ICDs.

In recent years numerous studies have been performed using non-invasive methods for diagnosis of autonomic dysfunction or anatomic-functional abnormalities but it remains a need for a proper validation of predictors of arrhythmic death.

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