PRIMARY AND SECONDARY PREVENTION OF SUDDEN CARDIAC DEATH: WHO SHOULD GET AN ICD?

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Despite numerous efforts in recent years, anticipating and preventing sudden cardiac death (SCD) still remains an important “gamble” for modern cardiology. It remains one of the most important causes of death in the industrialised countries. No exact data on the real incidence of cardiac arrest exist, and reported values vary between 0.36–1.28/1000 population per year.¹ This variability can be explained by the different methods used to gather data and by the difficulty in classifying sudden death. In the USA an incidence of 1–2/1000 inhabitants per year (0.1–0.2%) has been estimated, with an absolute number of SCD ranging between 300 000–400 000/year.² Two thirds of these deaths occur out of hospital, and out-of-hospital cardiac arrest accounts for 60–70% of cardiac mortality from all causes. The rhythm observed in victims of out-of-hospital cardiac arrest depends on the time elapsed between collapse and the first ECG recording, and ventricular fibrillation (VF) accounts for 95% of cardiac arrests if this interval is <4 min.³ If the time elapsed is not known, VF represents the first rhythm identified in 40% of the cases, asystole in 40%, electromechanical dissociation in 20% and a ventricular tachycardia (VT) in <1% of the cases.

MAIN CAUSES OF SUDDEN CARDIAC DEATH

In most cases, SCD occurs in patients with structural heart disease. Coronary artery disease (CAD) undoubtedly represents the most frequent cause of cardiac arrest, responsible for 80% of the cases. About 20% of CAD have cardiac arrest as the first clinical manifestation which otherwise can occur during the course of the patient's clinical history. In particular, patients with a preceding myocardial infarction (MI) represent a category of patients at particularly high risk. At 2.5 year follow up after MI the incidence of arrhythmic mortality was 2%. The most important independent predictive factor for SCD in these patients is left ventricular dysfunction.⁴ If SCD is analysed in terms of number of events per year, the highest risk subgroup of patients (patients with a reduced ejection fraction, a clinical history of heart failure or survivors from cardiac arrest) is responsible for a small percentage of the events. In these patients the incidence of sudden death is high but the absolute number of events is low. It is therefore necessary to identify markers of SCD risk which can be applied to the lower risk population who account for the majority of yearly events.

An important group of patients accounting for a proportion of yearly SCD events are those who do not have ischaemic cardiomyopathy and sometimes have apparently normal hearts; in these patients SCD often occurs in young age. They include patients with genetically determined structural cardiomyopathies (hypertrophic and dilated cardiomyopathy, right ventricular arrhythmogenic dysplasia) and with channelopathies, such as long QT syndrome, short QT syndrome and Brugada syndrome.

Major research efforts have been focused on primary and secondary prevention of SCD. Various trials have failed to confirm the hypothesis of a prophylactic role for antiarrhythmic drugs in the prevention of SCD. Class I antiarrhythmic drugs in the CAST (Cardiac Arrhythmia Suppression Trial) study, despite been able to reduce ventricular arrhythmias, paradoxically increased SCD and all cause mortality. In the SWORD (Survival With Oral d-sotalol) trial, sotalol had a negative effect on mortality. In other trials amiodarone has not increased mortality but on the other hand has not increased survival. Trials examining the role of implantable cardioverter-defibrillators (ICDs) in primary and secondary prevention of SCD have shown benefit.

The strength of most of the ICD trials, which have shown benefit of this treatment in primary and secondary prevention of SCD, is that all cause mortality has been used as the primary end point. This underlines the positive effect of this therapeutic approach, not only in reducing arrhythmic death but also in improving survival.

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SECONDARY PREVENTION

Patients resuscitated from cardiac arrest are at very high risk of SCD, with a mortality rate of 45% at 2 years. In the 1980s, ICD therapy was used with caution because there was some concern that the ICD would simply change the mode of death without modifying survival. Trials subsequently demonstrated the superiority of ICDs with respect to standard medical treatment in reducing both SCD and total mortality.

The first trial to investigate the use of ICDs in secondary prevention was the DUTCH study⁵ which began to enroll patients in 1983 and was concluded in 1993. It included 60 patients who survived SCD following a documented VT/VF; they were randomised to either conventional drug treatment or ICD therapy. A 63% reduction of mortality was observed in the group of patients treated with an ICD. The enrolment in another secondary prevention trial, CASH (Cardiac Arrest Study Hamburg),⁶ began in 1987. Patients who had survived cardiac arrest caused by a documented ventricular arrhythmia were randomised to receive either an ICD or one of the three drugs considered the most effective in prevention of SCD—propafenone, metoprolol and amiodarone. The primary end point was all cause mortality, and the secondary end points were SCD and cardiac arrest. After 5 years the surveillance committee of the study recommended the interruption of the propafenone arm because of significant excess of mortality (29%) and cardiac arrests compared to the ICD arm. The results demonstrated that in patients treated with an ICD there was a 23% reduction of total mortality at 2 years with respect to patients treated with metoprolol or amiodarone (statistically borderline). The secondary end point of freedom from SCD was significantly greater in patients assigned to ICD therapy than in those assigned to drug treatment, with a 61% reduction of SCD in the ICD group.

CIDS (Canadian Implantable Defibrillator Study)⁷ enrolled patients with cardiac arrest caused by VF; it also included patients with sustained VT causing syncope, patients with poorly tolerated VT and left ventricular ejection fraction (LVEF) <40%, and patients with syncope and inducible or monitored VT. A total of 659 patients were enrolled and randomised to ICD or amiodarone treatment. The results showed a 20% relative risk reduction of all cause mortality and a 33% reduction of arrhythmic mortality with ICD therapy compared to amiodarone treatment; this reduction did not reach statistical significance but it came very close ($p = 0.09$). The analysis of the cause specific mortality in this study supports the presumed mechanism of action of ICD therapy which is to prevent deaths caused by ventricular arrhythmia. A multivariate analysis of the CIDS data was carried out in order to identify those patients who would most likely benefit from treatment with an ICD. Considering the three variables which were significant predictors of all cause mortality in the amiodarone treated group (increasing age, decreasing LVEF, and New York Heart Association (NYHA) functional class), patients were divided into four equally sized quartiles of ascending risk of death. The principal finding of this analysis was that patients most likely to benefit from ICD therapy are those at highest risk of death, with at least two of the following characteristics: age ≥ 70 years, LVEF $\leq 35\%$, and presence of NYHA class III or IV. In this group of patients ICD determined a 50% relative risk reduction of mortality.⁸

The biggest trial on secondary prevention of SCD, comparing ICD and drug treatment (amiodarone, sotalol) is the AVID (Antiarrhythmics Versus Implantable Defibrillators) trial⁹ which enrolled 1016 patients. It included patients with cardiac arrest caused by VF/VT, patients with VT and syncope, and patients with VT and LVEF $\leq 40\%$. After a mean (SD) follow up of 18.2 (12.2) months, the study was interrupted prematurely because of a significant reduction of mortality in the ICD arm (39% at 1 year). Again, the greatest benefit was observed in patients with low ejection fractions (LVEF $\leq 35\%$) whereas similar benefits were observed in patients with either VF or VT as index arrhythmia. Further data were obtained from the AVID registry¹⁰ which included all 4595 patients screened and registered, regardless of whether they were randomised or not. Of the patients screened, only those with a reasonable likelihood of being eligible to receive antiarrhythmic drug treatment, ICD therapy or both were registered. The registered patients were divided into six groups according to the presenting arrhythmia: VF, VT with syncope, symptomatic VT, asymptomatic VT, VT/VF of transient/correctable cause, and unexplained syncope with inducible VT. A high mortality rate was noted for all six groups, with 2 year survival rates ranging from 76% in patients presenting with syncopal VT to 84% in patients with unexplained syncope. The surprisingly high and similar mortality across the arrhythmia subgroups were not explained by multivariate analysis looking at baseline risk predictors, such as ejection fraction or antiarrhythmic treatment.

Another analysis of the AVID registry compared patients with stable ventricular tachycardia, who were felt to be at low risk and not subsequently randomised in the AVID trial, with patients with unstable VT. The mortality in 440 patients with stable VT tended to be greater than that observed in 1029 patients presenting with unstable VT (33.6% vs 27.6% at 3 years; relative risk (RR) 1.22; $p = 0.97$). After adjustment for baseline and treatment differences, the relative risk was little changed (RR = 1.25, $p = 0.06$). These data suggest that also patients with stable VT are still at high risk for SCD and may benefit from ICD therapy.

The main clinical trials on secondary prevention of SCD are summarised in table 1. All of these trials demonstrated the effectiveness of ICD therapy in secondary prevention of SCD. As a consequence, ICD therapy is a class I (evidence level A) indication for patients surviving cardiac arrest caused by VF/VT or with sustained haemodynamically stable VT not due to transient or reversible causes according to the American College of Cardiology/American Heart Association (ACC/AHA) 1998 guidelines.

PRIMARY PREVENTION

In the mid 1990s, the idea that the ICD could be effective in the primary prevention of SCD in carefully selected patients was investigated. MADIT (Multicenter Automatic Defibrillator Implantation Trial)¹¹ was the first trial to demonstrate a prophylactic role for ICD therapy in patients with CAD, selected on the basis of episode of spontaneous non-sustained VT on Holter monitoring and inducible, non-suppressible VT/VF at electrophysiologic study. ICD therapy reduced the incidence of cardiac death to 3% at 1 year and to 17% at 3 years versus 23% and 46%, respectively, in the group treated with conventional

Table 1 Secondary prevention trials of sudden cardiac death

Trial	Year	No. patients	Enrolment criteria	Aim	Results
AVID	1997	1016	Survived VT/VF cardiac arrest or VT with syncope or VT with LVEF $\leq 40\%$	Antiarrhythmic treatment vs ICD	31% reduction of mortality with ICD at 3 years
DUTCH	1995	60	Survived cardiac arrest due to VF/VT and old MI (>4 weeks) and inducible VT at EPS	ICD as first choice therapy vs conventional therapeutic strategy (antiarrhythmic drugs and then eventual ICD)	ICD as first choice therapy reduces primary end points (death, recurrent cardiac arrest and cardiac transplantation)
CASH	2000	288	Cardiac arrest due to VF or VT	ICD vs antiarrhythmic agents	23% reduction of all cause mortality with ICD
CIDS	2000	659	Cardiac arrest due to VF or sustained VT and syncope or poor tolerated VT and LVEF $<40\%$ or syncope and inducible or monitored VT	ICD vs amiodarone	20% reduction of all cause mortality with ICD

AVID, Antiarrhythmic Versus Implantable Defibrillators; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

therapy. The results of this study resulted in a modification of the ACC/AHA guidelines to include implantation of ICD in MADIT criteria patients as a class I recommendation (level of evidence B) for primary prevention of SCD.

These results were confirmed by the larger MUSTT (Multicenter Unsustained Tachycardia Trial),¹² in which more than 700 patients with CAD, LVEF $\leq 40\%$, spontaneous non-sustained VT and inducible VT at electrophysiological study were enrolled. They were randomly assigned to receive either antiarrhythmic treatment, including drugs and ICD, as indicated by the results of electrophysiologic study, or no antiarrhythmic treatment. Mortality was lower in the group of patients assigned to electrophysiologically guided therapy. Of those patients assigned to electrophysiologic guided therapy, only those who actually received an ICD had improved survival. Patients assigned to electrophysiologically guided therapy who received drugs and not defibrillators performed worse than those assigned to no antiarrhythmic treatment. The authors concluded that electrophysiologically guided therapy with ICD, but not with antiarrhythmic drugs, reduces the risk of sudden death in high risk patients with CAD.

In the CABG-Patch¹³ trial patients with CAD, reduced LVEF ($<36\%$), and abnormalities on signal averaged ECGs, scheduled for elective coronary artery bypass graft surgery (CABG), were enrolled. They were randomly assigned to treatment with an ICD or to the control group. The results indicated no difference in survival between the two groups. There are several reasons to explain these apparently discordant results. The first is that revascularisation may have significantly improved left ventricular function after surgery in many patients, so reducing the risk level of these patients. Secondly, signal averaged ECGs used for patient selection is probably a worse risk predictor for SCD than inducible VT.

These trials and others began to demonstrate that LVEF was the best predictor for SCD, with the electrophysiological study and the autonomic indexes appearing less important. In the MADIT II trial,¹⁴ published in 2002, 1232 patients with coronary artery disease and LVEF $\leq 30\%$ were randomised to standard treatment or ICD implantation. In the latter group of patients a reduction of 31% of all cause mortality was observed. LVEF alone in these patients seemed to be sufficient for risk stratification. As a result of this study the European Society of Cardiology included ICD therapy for MADIT II type patients as a class IIA (level of evidence B) recommendation. The

committee did not include this indication as a class I recommendation, agreeing that it was necessary that concordant results had to be obtained in at least another study addressing the same issue. The indication was then upgraded to a class I recommendation in the guidelines for the diagnosis and treatment of chronic heart failure updated in 2005, after the publication of the more recent studies, discussed below. It must be kept in mind that in these primary prevention studies, as well as in secondary prevention studies, the primary end point is expressed as relative risk reduction of all cause mortality. This means that the overall clinical impact of ICD implantation is less impressive than that suggested by the relative risk reduction. However, we should not forget that the patients enrolled in these studies are patients with advanced cardiomyopathy with poor survival, independent of any therapeutic approach.

Early primary prevention studies demonstrated the benefits of ICD therapy in CAD patients implanted late after MI. But the optimal timing for implantation of prophylactic ICD in post-MI patients was examined in a subanalysis of the MADIT II.¹⁵ Patients were divided into two groups: those who had MI <18 months and ≥ 18 months before enrolment in the study. Patients with remote MI showed more benefit from ICD implantation compared with patients with recent MI, although the difference did not reach statistical significance.

The question of whether patients with recent MI could benefit from early ICD implantation was addressed in DINAMIT (Defibrillator in Acute Myocardial Infarction Trial).¹⁶ The patients enrolled in this study had recent MI (6–40 days), reduced LVEF ($\leq 35\%$), and impaired cardiac autonomic function. At 30 month follow up no difference was observed in overall mortality between ICD and pharmacological treatment. ICD therapy reduced death from VF but there was an increase in the rate of deaths from non-arrhythmic causes. From these results it was concluded that patients with a recent MI do not benefit from ICD.

The DEFINITE (Defibrillators in Non Ischemic Cardiomyopathy Treatment Evaluation) trial in 2004 investigated whether patients with non-ischaemic dilated cardiomyopathy, LVEF $\leq 35\%$, premature ventricular beats or non-sustained VT would benefit from ICD implantation by randomising them to standard drug treatment versus standard drug treatment and ICD. Standard treatment and ICD resulted in a reduction in the risk of death from any cause that

Table 2 Primary prevention trials of sudden cardiac death

Trial	Year	No. patients	Enrolment criteria	Aim	Results
MADIT	1996	196	LVEF $\leq$ 35%; prior MI; asymptomatic NSVT; NYHA class I–III; inducible VT refractory to intravenous procainamide on EP study	ICD vs standard medical treatment	54% reduction in total mortality with ICD therapy
CABG-Patch	1997	900	LVEF $\leq$ 35%; patients scheduled for CABG; positive SAECG results	ICD vs no ICD	No reduction in total mortality with ICD therapy
MUSTT	1999	704	LVEF $\leq$ 40%; CAD; NSVT; inducible VT on EP study	Electrophysiologically guided therapy (antiarrhythmic or ICD) vs standard therapy	51% reduction of total mortality with ICD therapy
MADIT II	2002	1232	EF $\leq$ 30%, prior MI	Conventional therapy vs ICD	31% reduction of all cause mortality with ICD
DEFINITE	2004	229	EF $\leq$ 36%; non-ischaemic dilated cardiomyopathy; NSVT or PVCs at Holter monitoring	Conventional therapy vs conventional therapy and ICD	ICD reduced rate of death from any cause (7.9% vs 14.4% at 2 years)
DINAMIT	2004	674	EF $\leq$ 35%, recent MI (within 4–40 days); impaired cardiac autonomic modulation (HR variability)	Conventional therapy vs ICD	No reduction in death from any cause with ICD therapy ($p=0.66$); reduction of arrhythmic deaths with ICD ($p=0.009$)
COMPANION	2004	1520	NYHA class III–IV due to ischaemic and non-ischaemic cardiomyopathy, QRS $\geq$ 120 ms	Conventional therapy vs conventional therapy and CRT with PMK or PMK-ICD	CRT with PMK and ICD was associated with a 36% reduction of risk of death from any cause
SCD-HeFT	2005	2521	EF $\leq$ 35%, NYHA class II–III (ischaemic and non-ischaemic)	Conventional therapy + placebo vs conventional therapy + amiodarone vs conventional therapy + ICD	23% reduction of overall mortality with ICD

CABG-Patch, Coronary Artery Bypass Graft Patch; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT, cardiac resynchronisation therapy; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; EF, ejection fraction; EPS, electrophysiological study; HR, heart rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PMK, pacemaker; PVCs, premature ventricular contractions; SAECG, signal averaged electrocardiogram; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; VF, ventricular fibrillation; VT, ventricular tachycardia.

approached but did not reach statistical significance ($p = 0.08$), probably because an insufficient number of patients were enrolled (458). The more recently published trial, SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial),¹⁷ enrolled 2521 patients with ischaemic (1311) and non-ischaemic (1210) heart disease, heart failure and LVEF $\leq$ 35%. The patients were randomised either to placebo or amiodarone or ICD implantation. ICD therapy was associated with a significant (23%) reduction of all cause mortality both in patients with ischaemic heart disease and in those with non-ischaemic heart disease.

The COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial¹⁸ evaluated cardiac resynchronisation therapy (CRT) in combination with ICD. COMPANION enrolled 1520 patients with ischaemic and non-ischaemic advanced heart failure and intraventricular conduction delay. The patients were randomised to optimal drug treatment alone or in association with biventricular pacing with or without ICD. The results showed that CRT decreases the combined risk of death from any cause or first hospitalisation and when combined with an ICD significantly reduces mortality. Although the COMPANION trial was designed to evaluate the effect of CRT on heart failure, it has also demonstrated an improvement of prognosis in patients who underwent CRT and ICD implantation. This seems to confirm the results obtained from the preceding trials and seems to suggest that all patients treated with CRT would also benefit from an ICD.

Table 2 summarises the main clinical trials on primary prevention of SCD.

In spite of the meaningful results of ICD trials, the optimal stratification of patients at risk for SCD is still open to debate.

To date, the best predictor of mortality risk has been shown to be the LVEF. This parameter alone or in association with other indicators has been used in all SCD trials. It cannot, however, be considered a sufficient parameter, because although in the group of patients with reduced LVEF there is a high rate of SCD, absolute numbers of SCD in this group are low compared to the general population because of the differences in the population sizes. Among the potential predictors, heart rate variability, T wave alternans (TWA), signal averaged ECG, baroreflex sensitivity, electrophysiological testing, and QRS duration have been considered but to date the results have been disappointing. Among these indexes, those which appear more promising are QRS duration and TWA. A potential role of TWA in the risk stratification of MADIT II like patients is supported by a recently published study¹⁹ in which 129 post-MI patients with LVEF $< 30\%$ were enrolled. TWA testing was prospectively assessed in all patients. At 24 months of follow up no SCD was observed in TWA negative patients, whereas a 15.6% rate of SCD was observed in the remaining patients. Another study²⁰ evaluated the role of microvolt TWA in identifying MADIT II criteria heart failure patients at high and low risk of death. The study included 177 patients of whom 32% had a QRS duration > 120 ms and 68% had an abnormal TWA test. At 2 years, the mortality rate was lower among patients with a normal TWA test. Interestingly in this study, the TWA test was a better predictor than QRS complex duration. Although TWA and QRS duration have been shown to be good indexes for risk stratification in patients already considered a high risk on the basis of reduced LVEF, there are not sufficient data regarding their possible role in patients with preserved or moderately depressed ventricular function. More studies and data are needed in this setting.

GENETIC CARDIOMYOPATHIES

Arrhythmogenic cardiomyopathies with a genetic basis can be divided into two groups:

- ▶ Structural arrhythmogenic cardiomyopathies with macroscopic alterations of the heart, including the idiopathic dilated and hypertrophic cardiomyopathies and right ventricular arrhythmogenic dysplasia
- ▶ Disorders of the cellular membrane ionic channels. In this group there are no structural heart abnormalities and they are, therefore, considered primarily electrical disorders. They generally manifest exclusively with arrhythmias and are responsible for SCD in apparently normal hearts. They include the Brugada syndrome, the long QT syndrome, catecholaminergic polymorphic VT, and the short QT syndrome.

For all of these disorders, ICD implantation is definitely recommended for secondary prevention. Indications for primary prevention is still a matter of debate and risk stratification has been proposed for each condition along the following lines:

- ▶ *Idiopathic dilated cardiomyopathy*—risk factors for SCD include familial history of SCD (>2 relatives who died from SCD at young age), non-vasovagal syncope, non-sustained ventricular tachycardia, LVEF $\leq 35\%$.
- ▶ *Hypertrophic cardiomyopathy*—major risk factors for SCD include familial history of SCD, syncope, hypotension during exercise, interventricular septum ≥ 30 mm. Minor risk factors include non-sustained VT. The presence of one major risk factor should suggest ICD implantation.
- ▶ *Right ventricular arrhythmogenic dysplasia (RVAD)*—the most important risk factors for SCD are unexplained syncope, stable and monomorphic VT, dilatation of the right ventricle with severe dysfunction and involvement of the left ventricle. ICD therapy is always indicated in patients with RVAD and unexplained syncope, when neurally mediated syncope has been excluded.
- ▶ *Brugada syndrome*—risk stratification in these patients is still ongoing and no definite guidelines have been drawn. The most important risk factors appear to be familial history of SCD, unexplained syncope, the presence of typical Brugada morphology on a standard ECG (coved ST elevation in V1–V2), and inducibility of VT/VF at the electrophysiological study.
- ▶ *Long QT syndrome*—in this group of patients ICD therapy in primary prevention should be limited to patients with familial history of SCD or syncope, regardless of β -blocker treatment.

CONCLUSIONS: “WHO SHOULD GET AN ICD?”

The answer to this question is continuously changing as evidence is published and defined. Practice guidelines need to be updated periodically. At present, considering the results of the clinical trials and based on our clinical experience, we suggest the following indications for ICD implantation. These recommendations are at variance with the current National Institute for Health and Clinical Excellence (NICE) guidelines for ICD implantation.

In our opinion ICD implantation is:

- ▶ definitely indicated as class I recommendation in
 - (1) patients in need of secondary prevention, regardless of the cardiomyopathy

- (2) patients with prior MI and LVEF $\leq 30\%$
- (3) patients with non-ischaemic dilated cardiomyopathy and LVEF $\leq 30\%$
- (4) patients with genetic cardiomyopathy at high risk
 - ▶ probably indicated as class II recommendation in
 - (1) patients with prior MI and LVEF $\leq 35\%$
 - (2) patients with non-ischaemic dilated cardiomyopathy and LVEF $\leq 35\%$
 - (3) patients who are candidates for cardiac resynchronisation therapy and LVEF $\geq 30\%$

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