ARRHYTHMIAS

Sudden death: managing the patient who survives

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Sudden cardiac death (SCD) is defined as an unexpected death due to cardiac causes occurring within 1 h of symptom onset in a person without any prior condition that would appear to be fatal. It represents a major public health problem affecting more than 500 000 patients annually in the USA, and accounts for approximately 50% of deaths from cardiovascular causes. The most common electrical mechanism leading to SCD is the interaction of a triggering event and an abnormal substrate that induces ventricular tachycardia (VT) degenerating (or not) into ventricular fibrillation (VF). Less frequently, SCD is initiated directly by VF or polymorphic VT. SCD associated with bradyarrhythmias or asystole, frequently expressing electromechanical dissociation, are less frequent, and usually occur in the setting of advanced heart failure[1] (figure 1).

Cardiac arrest (CA) events can sometimes be resolved by resuscitating manoeuvres, thus preventing what would have been an SCD. Although strictly speaking this should be referred to as a CA episode, some refer to this as aborted SCD or simply as an SCD event. The vast majority of SCDs are due to a first arrhythmic event, although 10–15% of them are due to recurrent events. The prevention of a life threatening arrhythmic event in patients who survive a CA is referred to as 'secondary prevention'. However, since sustained VT can also be lethal, prevention of SCD in patients who already had sustained VT (even if the VT did not cause the CA) are also included in the concept of secondary prevention of SCD and in some of the so-called 'secondary prevention trials', as discussed below. This article discusses the causes, risk stratification, and management of patients who have already survived a CA.

It is important to recognise that, although much of the recent emphasis has been on risk stratification and primary prevention of SCD, when a patient has already had a CA event, risk stratification is simpler and totally different. The main questions become: What was the cause and what was the mechanism of the CA? This can be called the cause/mechanism approach to CA survivors (table 1). The importance of this approach is as follows: If the mechanism can be identified and the cause of the CA is transient or can be prevented, our therapeutic efforts should be directed towards abolishing such a cause and its resultant deleterious mechanism. Otherwise, the risk of recurrence is high regardless of how we treat the underlying heart disease and we have to protect the patient from the expected reappearance of the causative mechanism.

Since the majority of patients have either structural heart disease or a primary electrical disease that can be arrhythmogenic, we will briefly review them (box 1). We will then consider a general evaluation of the CA survivor, followed by the therapeutic approach to these patients.

CARDIAC CAUSES OF SUDDEN DEATH

Primary structural disease

Coronary artery disease

Approximately 65–70% of SCDs are attributed to ischaemic heart disease, thus demonstrating that coronary artery disease (CAD) is the most frequent substrate underlying SCD. A classical issue that has been the subject of controversy for more than two decades, and still remains unresolved, is whether the 'cause' of SCD in CAD is myocardial ischaemia or the late consequences of CAD, such as scarring resulting from previous myocardial infarction and/or structural remodelling. The incidence of VT/VF in the first hours of an acute ST elevation is approximately 10%. Most deaths are associated with acute occlusion of the left coronary circulation and usually occur within the first hour of symptom onset, with half occurring out of hospital. Obviously, this proves that acute ischaemia can cause CA. In addition, classical studies have shown that surgical revascularisation decreases the risk of SCD. However, it is also clear that life threatening ventricular arrhythmias and SCD can occur in patients with CAD in the absence of acute ischaemia. Sustained monomorphic VT can be initiated by programmed electrical stimulation with the patient resting or even sedated, obviously in the absence of acute ischaemia, and on many occasions the induced VT is identical to the spontaneous one[2] (figure 2). In the CABG Patch trial, which included only patients with low ejection fraction and candidates for revascularisation, the incidence of SCD was as high as 7% in the conventional group. This incidence decreased to 4% in the implantable cardioverter-defibrillator (ICD) group,[3] suggesting that even the best protection against ischaemia (in patients with left ventricular dysfunction, ie, presumed extensive scarring) does not offer good protection against SCD. A complementary finding showed good protection against

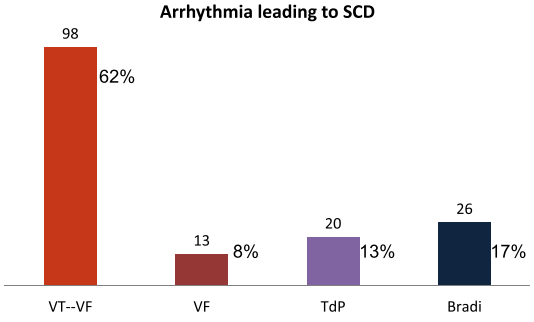

Figure 1 Distribution of terminal arrhythmia leading to sudden cardiac death (SCD) in patients with ambulatory electrocardiographic monitoring. Numbers represent absolute number of patients in each category. Bradi, bradyarrhythmias; TdP, torsades des pointes; VF, ventricular fibrillation; VT, ventricular tachycardia. Modified from Bayes de Luna *et al*.[1]

SCD by revascularisation in CA survivors with extensive CAD but preserved ejection fraction.[4]

In summary, both acute ischaemia and scar tissue (and even the two of them together) can be the substrate for malignant ventricular arrhythmias and SCD in patients with CAD. Severe multivessel disease is the marker for the former and chronic scar manifested by left ventricular dysfunction for the latter. However, sometimes it may be difficult to distinguish which mechanism is more likely to be operative.

Non-ischaemic cardiomyopathy

Patients with cardiomyopathy are the second largest group who present with SCD.

Non-ischaemic dilated cardiomyopathy

Dilated cardiomyopathy (DCM) can be due to non-ischaemic causes (viral, autoimmune, genetic, alcohol related, etc). Regardless of aetiology, the prognosis is poor, as the presence of heart failure increases overall mortality and the incidence of SCD, which represents approximately 10% of all SCDs. VT degenerating into VF is the predominant mechanism of death, although bradycardia and pulseless electrical activity is responsible for one third of cases. The presence of unexplained syncope in patients with DCM, especially in those with poor New York Heart Association (NYHA) functional class, should be taken into consideration, as non-sustained VT could be the underlying cause.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic heart muscle disease with a prevalence of 1:500 in adults; it is the most common cause of SCD in young people, accounting for more than one third of unexplained SCD among athletes. The mechanism of SCD in HCM is not well understood, but myocardial scar has been found only in hypertrophic regions, and this scarring provides the substrate for lethal arrhythmia. The main clinical markers considered to have predictive value for SCD include family history of SCD, unexplained syncope, left ventricular thickness ≥30 mm, hypotension with exercise, and prior VT.

Arrhythmogenic right ventricular cardiomyopathy

Also called arrhythmogenic right ventricular dysplasia (ARVD), this is a chronic disease characterised by progressive fibrofatty infiltration of the right ventricular wall. About 30% of cases are familiar. Several genetic defects have been postulated; the most common gene identified is the plakophilin mutant, which can be found in 25% of patients. The desmoplakin gene, the first gene identified in the autosomal dominant form, has also been correlated with SCD. The plakoglobin gene, located in chromosome 17p, is associated with the autosomal recessive form (Naxos disease), a less common disorder reported in Mediterranean countries and usually associated with skin disorders. The identified mutations are in genes coding proteins involved in cellular adhesion.

Patients may present with signs of right ventricular dilatation, palpitations, and syncope; in some cases, SCD is the first manifestation. The most common arrhythmia is sustained VT originating from the right ventricle, typically with left bundle branch block morphology.

Diagnosis of ARVD is challenging, as the cardiac imaging techniques (ventriculography, cardiac MRI, and echocardiography) can be insensitive. Electroanatomic mapping is a useful tool, as it may show an abnormal right ventricular voltage map. As is often the case, however, the simplest diagnostic tool can provide the necessary clue: 90% of patients with ARVD have some ECG abnormality. The most common, but also unspecific, is the presence of T wave inversion in leads V1 to V3. A more specific finding is the epsilon wave, described as a terminal notch in the QRS complex, that can be present in 23% of patients after the first VT event.

Primary electrophysiologic abnormalities

SCD can occur in patients with apparently no structural disease. However, it is well recognised that unexplained sudden death is mainly due to primary cardiac arrhythmia.

Long QT syndrome (LQTS)

Congenital LQTS

Hereditary LQTS is a genetic channelopathy characterised by an increased risk of polymorphic VT (torsade de pointes) and SCD. Nine different genes have been implicated in this syndrome, all of them affecting cardiac repolarisation. At least three autosomal dominant genetic abnormalities have been described: (1) LQTS1 associated with gene

Table 1 Summary of steps of the cause/mechanism approach for cardiac arrest (CA) survivors

Step 1. Identify cause of CA as:	Step 2. Identify mechanism of CA as:	Step 3. Assign therapy. Most likely:
Transient	Ventricular fibrillation	Temporary monitoring
Correctable	Sustained ventricular tachycardia	Ablation
Not transient nor correctable	Bradycardia	Revascularisation
	Electromechanical dissociation	Pacemaker
		ICD

ICD, implantable cardioverter-defibrillator.

Box 1 Main causes of sudden cardiac death

- Metabolic disturbances
- Primary structural disease
  - Coronary artery disease
  - Non-ischaemic cardiomyopathy
    - Non-ischaemic dilated cardiomyopathy
    - Hypertrophic cardiomyopathy
    - Arrhythmogenic right ventricular cardiomyopathy
- Primary electrophysiologic abnormalities
  - Long QT syndrome
  - Short QT syndrome
  - Brugada syndrome
  - Catecholaminergic polymorphic ventricular tachycardia
  - Idiopathic ventricular fibrillation

KVLQT1 in chromosome 11, controlling the slow inactivating potassium channel (IKs); (2) LQTS2 associated with gene *HERG* in chromosome 7, which controls the rapidly inactivating potassium channel (IKr); and (3) LQTS3, described as a defect in the gene *SCN5A* (chromosome 5) which controls the sodium channel. LQTS1 is influenced by catecholamines, LQTS2 is adrenergic dependent, and patients with LQTS3 usually have arrhythmias during slow heart rates, frequently during sleep. This suggests that patients with LQTS1 are very responsive to β-blockers, while for those with LQTS3 β-blockers may worsen their condition.

Acquired LQTS

The congenital and acquired forms of LQTS are very different. The acquired form is usually due to electrolyte disbalance (hypokalaemia, hypomagnesaemia, hypocalcaemia) or drug treatment. Drugs are by far the most common cause of this syndrome, particular antiarrhythmics, antipsychotics, certain antibiotics, and antihistamines.

Short QT syndrome

This is a newly recognised syndrome, first described in 1999. This disorder is characterised by a short corrected QT interval (QTc) <300 ms, tall and narrow T waves, an autosomal dominant pattern of inheritance, increased risk of SCD, paroxysmal atrial fibrillation, and short atrial and ventricular refractory periods at electrophysiology study. Gain-of-function mutations in genes that encode potassium channels (*HERG*, *KCNQ1*, and *KCNJ2*) have been identified. The optimal treatment for this disorder is still unknown. Antiarrhythmic agents that prolong the QT interval, such as sotalol or class IA agents, may be beneficial. However, despite the risk of T wave oversensing, ICD placement is first line therapy in SCD survivors.

Brugada syndrome

In the 1990s Brugada and Brugada described a syndrome of a specific ECG pattern of labile ST segment elevation and T wave inversion without structural abnormality of the heart that was associated with SCD. This syndrome is genetically determined, and transmission is autosomal dominant with variable penetration. In 25–30% of these patients a mutation in the cardiac sodium channel gene, *SCN5A*, is detected. The population prevalence of the disease is unknown, but a Brugada-like ECG pattern may be present in 1 per 1000 adults. The Brugada pattern is dynamic, and sometimes not found on a routine ECG. When clinical suspicion is high, a drug challenge with sodium channel blocking drugs may be diagnostic by reproducing the type 1 ECG pattern.

Catecholaminergic polymorphic VT

This is a familiar disorder characterised by bidirectional VT. The typical presentation is syncope, VT, or VF in children and adolescents characteristically induced by emotional or physical stress. One third of the cases are familiar, and the remaining are presumably due to new mutations. Two genetic

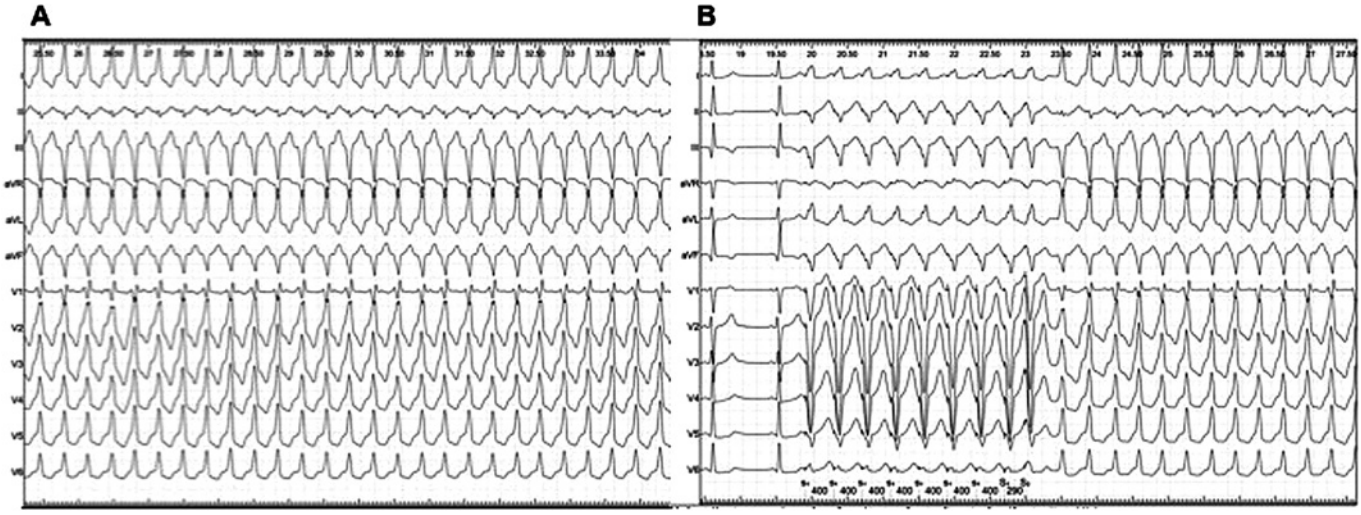

Figure 2 (A) Clinical monomorphic ventricular tachycardia in a patient with healed myocardial infarction. (B) Induction of morphologically identical ventricular tachycardia by programmed electrical stimulation in the electrophysiology laboratory.

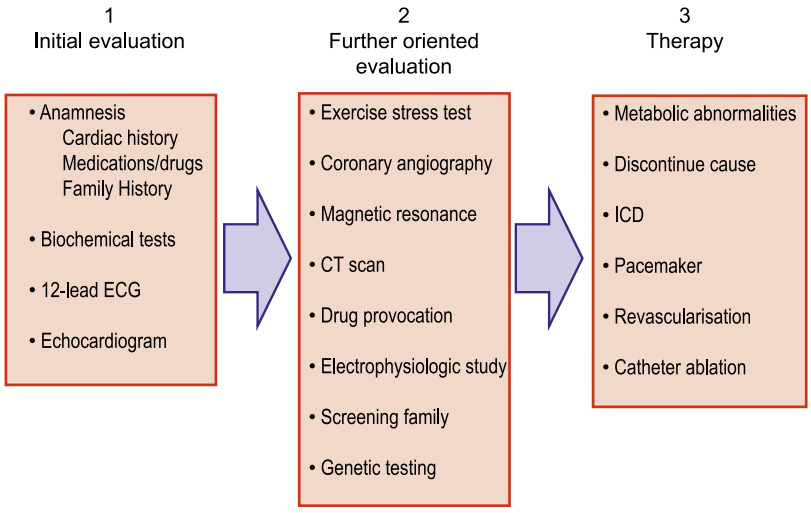

Figure 3 Main steps for evaluation and treatment. Note that although all the tests in the initial evaluation should be performed for all patients, tests in the second step should be individually oriented, performing only the necessary tests required for each patient to establish final diagnosis and treatment. ICD, implantable cardioverter-defibrillator.

forms have been recognised: an autosomal dominant form linked to mutations in the cardiac ryanodine receptor; and an autosomal recessive form caused by mutations in the calsquestrin-2 gene. These proteins are implicated in the control of intracellular calcium release, so the mechanism of this arrhythmia is supposed to be triggered activity caused by delayed after depolarisations. Patients diagnosed in life usually present with symptoms (usually syncope) before the age of 10 years. When untreated, the prognosis of this syndrome is very poor, with an estimated mortality of 30–50% by the age of 30 years.

Idiopathic ventricular fibrillation

This entity is a diagnosis of exclusion after the above disorders are carefully excluded. It is estimated to account for 5–10% of survivors of SCD. Recent data suggest the role of triggering premature beats, and the benefit of radiofrequency catheter ablation of those triggers.[5] However, the mainstay of treatment is ICD implantation.

EVALUATION OF CA SURVIVORS

The evaluation of survivors of CA begins immediately after resuscitation (figure 3). First of all, it is important to establish any obvious provoking factors that may have led to the event and which need to be corrected to prevent an immediate recurrence. After this, it is essential that the patient undergoes a complete cardiac examination to establish the existence of underlying heart disease. In the absence of apparent heart disease, an evaluation for primary electrical disease should be undertaken. Finally, in selected patients, the evaluation of family members is necessary. Table 2 provides typical examples of the causes of CA according to mechanism, and classified as transient, correctable, or not transient nor correctable.

Initial evaluation

The patient and/or the family should be interrogated about prior diagnoses of heart disease, the use of any medication (especially antiarrhythmic drugs, diuretics, and those that prolong the QT interval), the use of an illicit drug such as cocaine, and the presence of symptoms before the event (especially chest pain).

Standard laboratory testing can identify metabolic disturbances (hypokalaemia, hypomagnesaemia, acidosis, etc), which can lead to SCD. But we have to bear in mind that a laboratory abnormality by itself almost never leads to a fatal arrhythmia. The proarrhythmic effects of electrolyte abnormalities are often increased by myocardial ischaemia or LQTS.

The ECG—a simple test with relatively minimal cost—often provides the diagnosis, so it must be done in the immediate evaluation and should be repeated as often as the cardiologist considers necessary. The ECG should be evaluated for the evidence of acute or chronic ischaemia, conduction system disease, prolonged QT interval, Brugada syndrome pattern, signs of ventricular hypertrophy, ventricular ectopy or epsilon wave suggesting ARVD, or pre-excitation syndrome.

Evaluation of primary structural disease

Ascertaining the aetiology and extent of the underlying heart disease is important for management and prognostic reasons.

Coronary angiography

As CAD is the most common underlying disease (except for the very young), cardiac catheterisation with coronary angiography is necessary in most cases. Coronary angiography must be performed for both managing an acute coronary syndrome and for the diagnosis of chronic coronary heart disease.

Role of imaging in diagnosis

Recent advances in cardiac imaging have substantially improved the ability to diagnose the cause and extent of many heart diseases. The most common cardiac imaging modalities include two dimensional echocardiography, MRI, and CT. Echocardiography can detect many of the potential

Table 2 The cause/mechanism approach for cardiac arrest survivors: typical examples

Mechanism	VF	VT	Bradycardia	EMD
Cause				
Transient	Acute MI	Drug induced torsades	Acute inferior MI	
Correctable	WPW with AF leading to VF	Digitalis intoxication with VT	Drug intoxication	Pericardial tamponade
Not transient nor correctable	Chronic LV dysfunction	LV aneurism	Degenerative disease	End stage heart failure

AF, atrial fibrillation; EMD, electromechanical dissociation; LV, left ventricle; MI, myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

causes of SCD, including left ventricular dysfunction, which is one of the most important predictors of future arrhythmic events, HCM or DCM, and ARVD. When two dimensional echocardiography does not establish an accurate diagnosis, cardiac MRI can be extremely useful; this is because MRI has the ability to provide tissue characterisation in addition to functional information, becoming the first option (after initial echocardiography) for further assessment of cardiomyopathies, myocarditis, and coronary anomalies. Although cardiac MRI has the advantage of imaging without radiation exposure or the use contrast containing iodine, sometimes it is not possible to perform due to claustrophobia or other contraindications. In these cases, CT is a good option, and is also superior to cardiac MRI for visualising the coronary arteries.

Electrophysiologic study

In patients with sustained and non-sustained VT, the electrophysiologic (EP) study may provide useful information concerning both mechanism and treatment. Although the results of MADIT[6] and MUSTT[7] suggest that in patients with coronary heart disease and low ejection fraction (<40%) the induction of sustained monomorphic VT predicts an increased risk of SCD and total mortality, recent trials including MADIT-II[8] and SCD-HeFT[9] have further reduced the need for an EP study. In addition, in cases in which an ablation procedure is indicated, an EP study will obviously be performed.

Evaluation of primary electrical disease

SCD in the absence of structural heart disease is the most discouraging and complex manifestation of sudden death and its mechanisms are poorly understood. In autopsy series,[10] this group represents 5% of all SCD cases, and in up to 50% of cases SCD was the first manifestation of disease. An important percentage of these patients have some structural or functional derangement that has not been diagnosed. After exhaustive heart examination with detailed review of the clinical history, it is possible to elucidate the SCD mechanism in >50% of cases.

Although an ICD is indicated in survivors of SCD without a correctable cause, the identification of a primary electrical disorder is useful in directing medical treatment to prevent arrhythmia recurrence and in guiding the screening of family members.

The CASPER trial,[11] published in 2009, showed how systematic testing resulted in unmasking of the cause of apparently unexplained CA in >50% of patients. Sixty-three CA survivors with no evident cardiac disease (defined as normal ECG, normal cardiac function on two dimensional echocardiogram, and no coronary disease) were enrolled. After systematic evaluation that included cardiac MRI, signal averaged ECG, exercise testing, drug provocation test, and selective electrophysiological testing, a diagnosis was obtained in 35 of the patients: LQTS in eight, catecholaminergic polymorphic VT in eight, ARVD in six, early repolarisation in five, coronary spasm in four, Brugada syndrome in three, and myocarditis in one. Genetic testing was also done and identified disease-causing mutations in 47% of the patients. Screening of family members of these patients identified 24% affected individuals, who were then treated. When cardiac causes and mechanisms of CA and genetic conditions are identified, they can be treated and lives are saved.

TREATMENT

Table 3 and figure 3 summarises a general approach to treatment of the CA survivor.

ICD implantation

Following resuscitation from SCD, ICD implantation is supposed to be an effective strategy for the prevention of recurrent episodes. Although the device does not prevent the arrhythmia leading to SCD, it reverses the arrhythmia promptly when it occurs. Three prospective, randomised trials, the Anti-arrhythmics versus Implantable Defibrillators (AVID) study,[12] the Canadian Implantable Defibrillator Study,[13] and the Cardiac Arrest Study Hamburg,[14] compared ICD implantation versus pharmacologic therapy in the secondary prevention of SCD. The largest of these trials, AVID, enrolled 1016 patients who had been resuscitated from VF, sustained VT producing syncope, or VT without syncope but with left ventricular ejection fraction ≤40% and serious cardiac symptoms. Treatment was randomised for patients to receive either an ICD or antiarrhythmic drugs (sotalol or amiodarone). The primary end point was overall mortality. Overall survival was greater with the ICD, with unadjusted survivals for the ICD versus antiarrhythmic drug treatment groups of 89% vs 82% at 1 year, 82% vs 75% at 2 years, and 75% vs 65% at 3 years ($p<0.02$). The ICD group experienced a 39% reduction in deaths in the first year, with a 27% and 31% reduction in years 2 and 3, respectively. A subanalysis of the AVID study[15]

Table 3 The cause/mechanism approach for cardiac arrest (CA) survivors: treatment

Mechanism	VF	VT	Bradycardia	EMD
Cause				
Transient	Monitoring + support	Monitoring + support	Monitoring	Extensive work-up
Correctable	Treat cause Evaluate need for therapy of underlying HD	Treat cause Evaluate need for therapy of underlying HD	Transient PM support if necessary	Correct underlying cause
None	ICD	ICD, consider additional ablation	PM	Heart transplant?

EMD, electromechanical dissociation; HD, heart disease; ICD, implantable cardioverter-defibrillator; PM, pacemaker; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 4 Analysis of secondary prevention trials

Study	Patient population	Randomisation	Follow-up (months)	Mortality medical therapy arm	Mortality ICD arm	RR (95% CI)	Conclusion
AVID	1016 patients with life threatening sustained VT/VF	ICD versus empiric amiodarone or sotalol (mainly amiodarone)	18	55/509	24/507	0.44 (0.28 to 0.7)	Survival benefit with ICD
CASH	288 survivors of SCD	ICD versus empiric amiodarone, metoprolol or propafenone	12	64/189	13/99	0.39 (0.22 to 0.67)	Survival benefit with ICD
CIDS	659 patients with sustained VT/VF	ICD versus empiric amiodarone	18	43/331	30/328	0.70 (0.45 to 1.09)	Trend towards survival benefit with ICD

ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

showed that the ICD was more effective than antiarrhythmic drugs in reducing arrhythmic cardiac death, while there was no significant difference in non-arrhythmic death. Thus, ICD implantation is superior to antiarrhythmic drug treatment after life threatening arrhythmias.

The Cardiac Arrest Study Hamburg trial was a German randomised trial of ICD versus amiodarone, metoprolol or propafenone in patients resuscitated from SCD secondary to documented VT/VF unrelated to myocardial infarction. After a 2 year follow-up, the SCD rate was lower in the ICD group versus amiodarone or metoprolol groups. However, there was no statistically significant difference in total mortality.

The Canadian ICD Study enrolled a total of 659 patients with resuscitated VF, VT or syncope deemed to be secondary to arrhythmia. They were randomised to receive treatment with either an ICD or amiodarone. At the 5 year follow-up, the total mortality and arrhythmic mortality with ICD therapy was reduced compared to amiodarone, but this reduction did not reach statistical significance.

A systematic review of these three trials[16] concluded that ICD implantation for secondary prevention was efficacious in preventing SCD (RR 0.5) and resulted in a significant reduction in total mortality (RR 0.76). Another meta-analysis found a 7% absolute reduction (statistically significant) in all cause mortality with ICD compared to amiodarone[17] (number needed to treat: 15). Another recent meta-analysis using individual patient data from these three randomised trials confirmed the superiority of ICD versus amiodarone, showing a 28% reduction in the relative risk of death with the ICD that was due to a 50% reduction in arrhythmic death.[18] A summary of data from the secondary prevention trials is given in table 4.

Antiarrhythmic drugs, catheter ablation, and surgery

As previously mentioned, antiarrhythmic drugs confer less protection than an ICD for secondary prevention of SCD. However, adjunctive therapies are frequently needed for patients with an ICD when the patient has numerous ICD shocks or they are symptomatic owing to arrhythmic episodes. That is due to the fact that the device is useful for terminating arrhythmias but it does not prevent them. Amiodarone and sotalol are the preferred antiarrhythmic drugs to use in the setting of patients with ICDs, amiodarone being even more effective in reducing the arrhythmic episodes.[19] The use of antiarrhythmic drugs may be beneficial not only for reducing the frequency of ventricular arrhythmias but also for suppressing other arrhythmias (supraventricular arrhythmias) causing inappropriate shocks, or for lowering the rate of VT, improving the clinical tolerance or even making it more amenable to terminate by antitachycardia pacing or catheter ablation.

Except for those patients with the Wolf-Parkinson-White syndrome in whom catheter ablation may be curative, for patients at risk from SCD, ablation is often used along with an ICD. Catheter ablation has been shown to be a useful therapy not only for patients with recurrent arrhythmic episodes but also for patients with electrical storms.[20] In experienced centres, surgical techniques for ventricular tachyarrhythmias may also be beneficial to reduce the burden of arrhythmia. The role of catheter ablation as a primary prevention therapy of malignant ventricular arrhythmias at the time of ICD implantation in patients with a chronic myocardial infarction is still a controversial issue because, despite the proven reduction in arrhythmic episodes and ICD shocks, a reduction in mortality or improvements in quality of life have not been demonstrated.[21 22]

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