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Sudden Cardiac Death - A Review

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WAN: ***Sudden Cardiac Death - A Review.*** *Each year, more than 300,000 people in the United States suffer from sudden cardiac death. It may be due to a combination of both structural and functional elements whereby a structural substrate is destabilized by functional elements to trigger the life-threatening arrhythmia. Common underlying aetiologies for sudden cardiac death include coronary artery diseases, myocardial diseases like hypertrophic and dilated cardiomyopathies, electrophysiological disorders like congenital and acquired long-QT syndrome, Wolff-Parkinson-White and Brugada syndrome. The management strategies, risk stratification, primary and secondary prevention of sudden cardiac death are reviewed. However, not only patients with high risk estimated by current predictors are prone to sudden cardiac death, most such deaths occur in the general population currently considered not to be at high risk. Thus, in order to make a significant impact on the public health, we should focus on developing effective risk markers and devising broader strategies to prevent sudden cardiac death in the general population. (J HK Coll Cardiol 1999;7:18-31)*

摘要

在美國，每年有30萬以上發生心臟猝死。可能是由於結構與功能元素相結合作用的結果。功能元素使結構本質去穩定從而觸發威脅生命的心律失常。常見的心臟猝死因包括心病、肥厚及擴張心肌病、失天及獲得長QT綜合征WPW及Brugada 綜合征等電生理紊亂。對心臟猝死的處理策略、危險分級、一級及二級預防作了復習。然而，不只是目前預測因素估計的高危者具布猝死傾向，大部分這類猝死發生在目前認為不是高危者的普通人口。因此，為了對公眾衛生產生顯著影響，我們應注意發現有效的危險標誌並設計較為廣泛的策略以預防普通人口的心臟猝死。

1. Introduction

Sudden cardiac death is defined as unexpected death due to cardiac causes that occurs within one hour of acute symptoms. There is the sudden, abrupt loss of heart function (i.e. cardiac arrest) in a person who may or may not have diagnosed heart disease. Cardiac arrhythmias (e.g. ventricular fibrillation), sudden pump failure (e.g. acute myocardial infarction), acute circulatory obstruction (e.g. pulmonary embolism) and cardiac rupture are some of the commonest causes. Sudden cardiac death due to ventricular arrhythmias is a significant cause of mortality in patients with coronary artery and structural heart diseases.

Each year, more than 300,000 people in the United States and 100,000 people in the United Kingdom suffer from sudden cardiac death. Sudden death can strike people of any age and sex but it typically occurs in males with an average age of 65 years and more than 80% have coronary heart diseases. In around 20% of cases, sudden death is the first manifestation of disease.

In the past 30 years, advances in the ability to identify and modify risk factors associated with sudden cardiac death, prompt resuscitation and defibrillation, appropriate surgical and medical treatments with drugs like aspirin, beta blockers, antiarrhythmics and thrombolytics, and more recently, implantation of antiarrhythmia devices results in the reduction of age-adjusted sudden cardiac death mortality rates. However, sudden cardiac death remains a common clinical problem that all physicians are likely to encounter.

In the present essay, the evaluation, management, primary and secondary prevention of sudden cardiac death are reviewed.

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2. Pathophysiology and Aetiology

A proposed pathophysiological model for sudden cardiac death combines both a structural and functional elements whereby a structural substrate is destabilized by functional elements to trigger the life-threatening arrhythmia. This interaction may convert premature ventricular complexes into triggering events for ventricular tachycardia (VT) and ventricular fibrillation (VF) resulting in circulatory collapse, cerebral hypoperfusion, loss of consciousness, respiratory arrest and then death. Figure 1 showed the various contributing factors for sudden cardiac death[1].

The most common triggering factors are acute myocardial infarction (AMI) or coronary ischaemia (chronic or acute spasm), previous myocardial infarction (MI) with scarring and aneurysm formation. Other structural risk factors includes hypertrophic and dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, myocarditis, infiltrative myocardial diseases, Wolff-Parkinson-White syndrome with fast conducting antegrade accessory pathways, valvular heart disease and mitral valve prolapse.

Electrical abnormalities which predispose to sudden cardiac death include congenital and acquired long QT syndrome, the Brugada syndrome, systemic factors (hypoxia, acidosis and electrolyte disturbance) and proarrhythmia due to various drugs.

The observation of a circadian variability in the incidence of sudden cardiac death with a prominent peak in the early morning hours provides evidence that transient disturbances in the autonomic tone can predispose the heart to increased electrical vulnerability. Analysis of heart rate variability (HRV) provides further evidence of reduced vagal and elevated sympathetic tone during the morning hours particularly in patients with compromised left ventricular function. Diurnal variations in ventricular repolarization as indicated by QT interval changes in the surface ECG also support the concept of triggering factors in the genesis of sudden cardiac death[2,3].

Most episodes of sudden cardiac death are thought to be due to VF. VF may be "primary" when it is not resulting from the consequence of haemodynamic deterioration or "secondary" when it is precipitated by such event. Occasionally, VF may be due to degeneration from a sustained VT.

In some cases of sudden cardiac death, bradycardia, asystole or electromechanical dissociation may be the underlying rhythm. This can be a primary event seen commonly in patients with end stage heart failure or terminal illness or a secondary event seen in patients as a result of delay rescue from ventricular fibrillation.

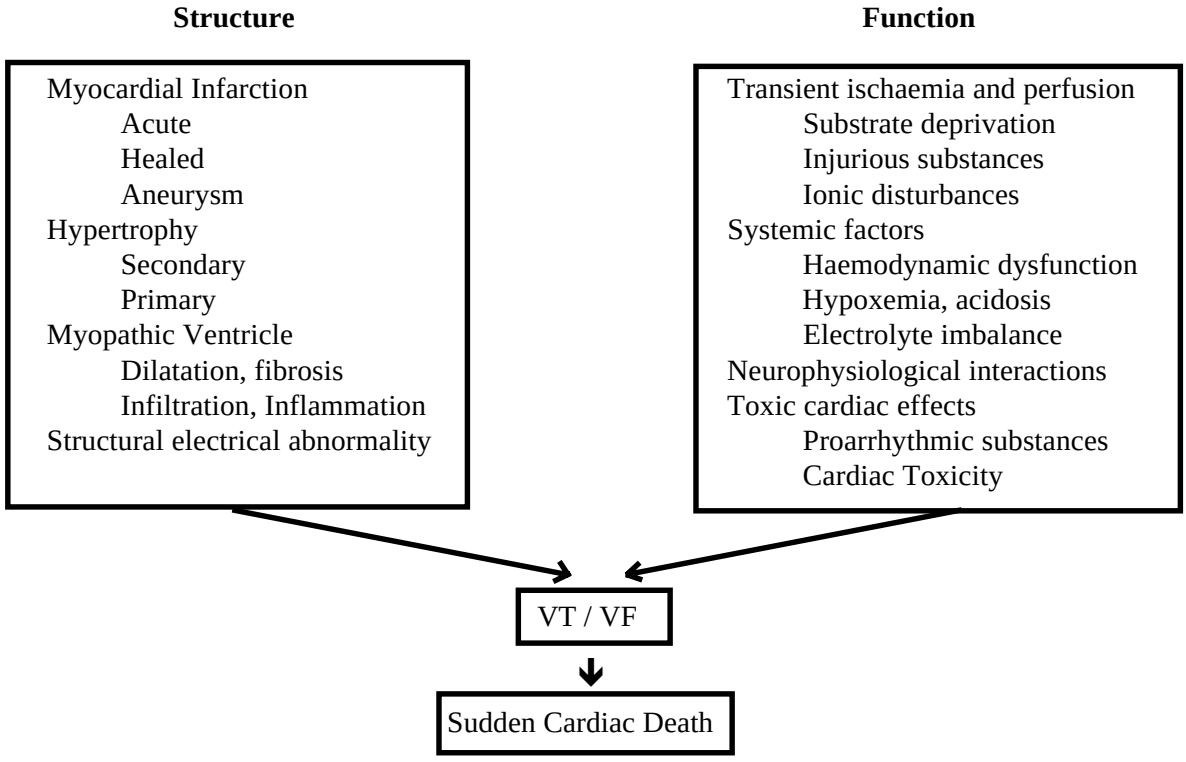

Figure 1. *Structure, function and the pathogenesis of sudden cardiac death*

2.1 Coronary Artery Diseases

In the United States and Europe, coronary artery disease is the most common diagnosis in sudden cardiac death. Autopsy and clinical studies have shown that 80% of patients with sudden cardiac death have atherosclerotic coronary artery disease and coronary thrombi may be detected in up to 50% of sudden death victims. But only about 25% of patients resuscitated from an out-of-hospital cardiac arrest will develop new Q wave infarction with another 25% of patients showing enzymatic evidence of necrosis.

Several mechanisms have been proposed as causes of potential fatal arrhythmias. In a patient with acute myocardial infarction, the sudden occlusion of a coronary vessel due to rupture of artherosclerotic plaque will result in acute ischaemia and ventricular fibrillation. Patients with known coronary artery disease or history of MI with scarring of the related myocardium will have an anatomical substrate consisting of intercalating fibrosis and normal myocytes. This will produce areas of slow conduction and block of normal electrical propagation resulting in re-entry circuit formation and ventricular tachyarrhythmias. In other cases, a combination of ischaemia, reperfusion, electrolyte disturbance, autonomic dysfunction or drug toxicity contribute to the generation of ventricular tachyarrhythmias. Arrhythmogenic mechanisms in such cases include re-entry, enhanced automaticity and early afterdepolarizations.

Other causes of cardiac death related to the coronary arteries include coronary artery spasm (e.g. substance abuse with cocaine), anomalous coronary anatomy (e.g. congenital anomalous origin or course of coronary artery), embolism, trauma or arteritis.

2.2 Myocardial Diseases

2.2.1 Hypertrophic Cardiomyopathy

Myocardial hypertrophy has been defined as a risk factor of sudden cardiac death. The hypertrophy can be primary like in cases of hypertrophic cardiomyopathy or secondary as in cases of hypertension. In hypertrophic cardiomyopathy (HOCM), sudden death tends to occur in young adults especially during vigorous exercise. It accounts for around 5-10% of sudden cardiac deaths. Risk factors include significant symptoms of heart failure, family history of sudden death and nonsustained ventricular tachycardia. Unfortunately, the underlying electrophysiological abnormality from individual mutations are not understood though polymorphic ventricular tachycardia or ventricular fibrillation is thought to be the initial event at the time of cardiac arrest[4]. In some cases, AV block with asystole or rapid supraventricular tachycardia is the initial event.

2.2.2 Dilated Cardiomyopathy

Non-ischaemic dilated cardiomyopathy contributed to about 10% of resuscitated cardiac arrest victims and sudden death accounts for about 50% of all deaths in this group of patients. Sudden death usually occurs late in the course of disease compared with patients suffering from hypertrophic cardiomyopathy. In this group of patients, monomorphic or polymorphic ventricular tachycardias are usually implicated as the cause of sudden cardiac death. Amonomorphic ventricular tachycardia involving marco-reentry using the His-Purkinje system has been reported in some patients with dilated cardiomyopathy.

Histology of the myocardium indicates myocyte death and replacement by fibrous tissue as well as hypertrophy of remaining myocytes. Systemic factors such as haemodynamic dysfunction in congestive heart failure, hypoxemia, acidosis, electrolyte disturbances like hypokalaemia and neurophysiological interactions contribute to the cardiac electrical instability. In patients with advance heart failure, bradyarrhythmias may account for more than 50% of sudden cardiac deaths.

2.2.3 Miscellaneous

Left or right ventricular dysfunction due to various heart diseases like rheumatic heart diseases, congenital heart disease, arrhythmogenic right ventricular dysplasia (ARVD), infiltrative and inflammatory myopathic diseases (e.g. myocarditis) can predispose to sudden cardiac death.

In ARVD, there is a regional myopathy of predominantly the right ventricle with the affected myocardium infiltrated with fatty vacuolization and fibrosis. Patients with ARVD are subjected to recurrent episodes of sustained monomorphic ventricular tachycardia or even polymorphic ventricular tachycardia with left bundle branch block pattern and multiple QRS morphologies.

Patients with corrected congenital heart diseases like Fallot's tetralogy may develop arrhythmias originating from the right ventriculotomy or septal repair sites.

2.3 Electrophysiological Disorders

Electrophysiological disorders can result in sudden cardiac death. These include congenital and acquired long-QT syndrome, Brugada Syndrome and Wolff-Parkinson-White Syndrome (WPW).

2.3.1 Congenital long-QT syndrome

In congenital long-QT syndrome (LQTS), a family history of sudden cardiac death is often present although sporadic cases had been reported. Mortality rates in untreated symptomatic patients with congenital LQTS are 26%, 35% and 53% at 3, 5 and 15 years respectively[5]. Sudden cardiac death is usually precipitated by adrenergic triggers like stress or exercise.

Molecular biology underlying the syndrome involves link to chromosome 3 (SCN5A sodium channel gene), 4, 7 (HERG potassium channel gene) and 11 (KVLQT1 gene) for LQT3, LQT4, LQT2 and LQT1 respectively. Slowly (I_{Ks}) or rapidly (I_{Kr}) activating component of the delayed rectifier or the cardiac sodium channel (I_{Na}) are involved[6].

The QT intervals in patients with congenital LQTS and their family (gene carriers) are usually prolonged but can be normal in about 5 to 10% cases. Another important feature is that the QTc value in a patient with LQTS may be variable and may be normal at times. Therefore, the diagnosis include ECG findings (prolonged QTc, torsade de pointes, T wave alternans), clinical history (syncope, congenital deafness) and family history of unexplained sudden death. With the recent advances in molecular genetics, it is hoped that the condition can be diagnosed accurately prior to the occurrence of any life-threatening arrhythmias[5].

2.3.2 Acquired long-QT syndrome

In acquired long-QT syndrome, prolong QT interval is commonly associated with electrolyte disturbances or various drugs as shown on Table 1. The electrophysiological mechanism is due to early afterdepolarization (EAD) resulting in torsades de pointes (TdP) type of polymorphic ventricular tachycardia. The initiation of TdP can be pause dependent, associated with a long-short sequence, short-long sequence or cascade phenomenon. Premature depolarization generates a post-extrasystolic pause, the sinus complex that followed shows marked TU changes and a subsequent ventricular extrasystole originates. This generates a new pause, followed by more bizarre TU changes from which progressive longer and faster runs of polymorphic ventricular tachycardia originate[5].

Table 1. Causes of acquired long-QT syndrome

Hypokalaemia
Hypomagnesaemia
Hypocalcaemia
Quinidine (other Class Ia antiarrhythmic drugs)
Amiodarone and sotalol (other Class III antiarrhythmic drugs)
Amitriptyline (other tricyclic antidepressants)
Chlorpromazine (other phenothiazine drugs)
Terfenadine and astemizole
Erythromycin
Cisapride
Pentamidine
Organophosphate insecticides
Cocaine
Probucol

2.3.3 Bradyarrhythmias

Bradyarrhythmias can also cause sudden cardiac death. For patients with congenital heart block, the escape pacemaker may deteriorate in time with ventricular arrhythmias appearing as the patient's bradycardia becomes more and more inappropriate.

2.3.4 Wolff-Parkinson-White Syndrome

Supraventricular ventricular tachycardia with very rapid ventricular rates can cause haemodynamic collapse. Atrial fibrillation in patient with Wolff-Parkinson-White Syndrome (WPW) may result in very rapid conduction via the accessory pathway down to the ventricle, thus producing ventricular tachycardia and fibrillation.

2.3.5 Brugada Syndrome

Recently, Brugada reported data on a group of patients with electrocardiographic (ECG) findings of right bundle branch block pattern and persistent ST segment elevation in lead V1 to V3 and sudden cardiac death. Structural heart disease or coronary artery disease had been excluded in this group of patients. They have a mean age of 40 with a male to female ratio of 8:1. The prodromal symptoms of nocturnal sudden death are seizures or syncope. In the recent report by Brugada in February, 1998, during a mean follow up of 34 months in 63 patients, an arrhythmic event occurred in 14 symptomatic patients (34%) and 6 asymptomatic patients (27%) suggesting that these patients have a relatively high risk of sudden death[7].

The high take-off ST segment elevation is either the coved or saddle-back type. There are several proposed underlying mechanism for the ST segment elevation in Brugada syndrome, including intraventricular conduction disturbance, early ventricular repolarization, local ventricular depolarization and sympathetic imbalance[8,9]. Mutations in the cardiac sodium channel gene, SCN5A, causing either an acceleration of the recovery of the sodium

channel (missense mutation) or nonfunctional sodium channels (insertion and deletion mutations) had been reported recently in early 1998[10]. Diagnosis involves programmed ventricular stimulation to induce ventricular tachyarrhythmias and the use of drugs like ajmaline, flecainade and procainamide to augment the ST segment elevation.

The author has recently encountered a 28 years old gentleman who might be the first reported case of Brugada syndrome in Hong Kong. He had no history of drug abuse but there was family history of syncope attacks. He was admitted to Tuen Mun Hospital because of syncope and convulsion. Cardiac monitoring during the convulsive attack showed polymorphic VT (with absent central pulses) which reverted to sinus rhythm spontaneously. The baseline ECG showed the typical high take-off ST segment elevation in V2. Further investigations including serum electrolytes, cardiac enzyme, toxicology screening, echocardiogram, angiography, left ventriculography and magnetic resonance imaging of the heart (to rule out ARVD) were all normal. Programmed ventricular stimulation showed inducible ventricular fibrillation with 2 or 3 extrastimuli in the right ventricular apex or outflow tract. After intravenous infusion of procainamide, the ST segment elevation was augmented in V2 and aVL as shown in Figure 2.

Some patients with structurally normal hearts, who survive sudden cardiac death, exhibit none of the above discussed characteristics and the precise underlying causes cannot be defined. Their electrophysiological studies and Holter monitoring results are often normal.

3. Management Strategies

The management strategies of sudden cardiac death involves immediate resuscitation with defibrillation, identification and prompt correction of reversible underlying precipitating factors, risk stratification, drug therapy, device implantation, follow up and prevention of recurrence. Under this section, management strategies will be discussed with respect to primary and secondary prevention. Risk stratification is discussed under Section 4.

3.1 Immediate Response and Automated External Defibrillators (AEDs)

With the development of community based cardiopulmonary resuscitation (CPR) programmes, more and more people are trained for immediate CPR. Figures from the United States have shown that approximately 40-50% of patients can be stabilized in the field and transferred to the emergency department and 24% successfully discharged. The timing from cardiac arrest to the initiation of CPR and prompt defibrillation is crucial for the survival of the sudden cardiac arrest victim. The chances of survival drop by 10% for every 1 minute delay, thus, after around 10-12 minutes, the survival rate is less than 20%. A half-year study carried out by the Hong Kong Ambulance

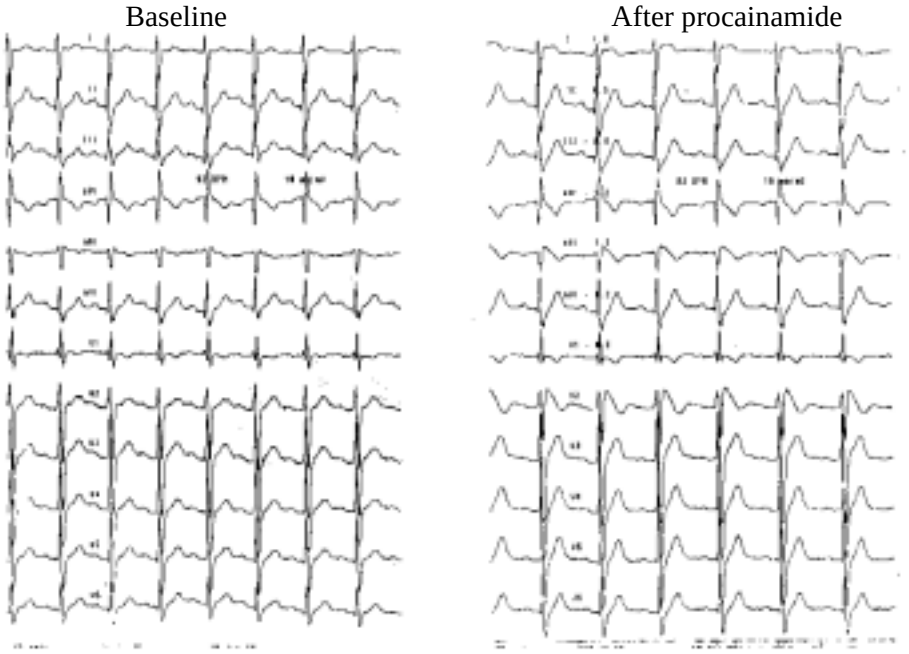

Figure 2. Augmentation of ST segment elevation after procainamide in the 28 years old gentleman

Services showed that only 8.9% (66 out of 744 arrests) of cardiac arrest victims received bystander CPR and the arrest to first shock interval was a significant factor related to survival. However, only 1.6% of these victims were discharged alive which was below the world standard. Therefore, the author concluded that in order to improve survival rates of out-of-hospital arrests, arrest to shock interval must be reduced and the frequency of bystander CPR increased[11].

The American Heart Association has supported the concept of the need of the "chain of survival" to rescue the person who suffers cardiac arrest in the community. The chain consists of: 1). Early Access 2). Early CPR 3). Early Defibrillation 4). Early Advanced Care (Figure 3).[12]

Figure 3. The Chain of Survival[12]

The development of the Automated External Defibrillator (AED) in the community to provide early and prompt defibrillation improves the chance of survival of cardiac arrest patients. The device is designed to recognize many variations of ventricular arrhythmias while at the same time ensuring that it does not inappropriately detect other rhythms. Most AED manufacturers have exceeded the AHA requirement for the specificity and sensitivity.

In Hong Kong, most ambulances and all St. John's ambulances have installed the AED. This device can automatically detect and analyze the cardiac rhythm, deliver the external defibrillation using biphasic energy shock and give voice alert and command to the medical personnel.

With the further development of the AED, personnel training and the collaboration of different parties e.g. Fire Services Department, Heath Services Department and private corporations, it is hope that the device can be installed in all international airlines, large corporations, shopping malls and even in the home of patients with high risk of sudden cardiac death. Much coordination and communication work is still awaited to achieve this goal.

3.2 Acute Management

Upon arrival at the Accident and Emergency Department, advanced cardiac life support should be instituted immediately. This includes securing the airway, intubation with oxygenation, defibrillation, CPR, intravenous access, cardiac drugs (e.g. adrenaline, lignocaine, procainamide, bretylium, etc.), and correction of electrolyte and acid-base disturbance. In cardiac arrest patients with asystole, bradycardia or heart block, an external or transvenous cardiac pacemaker can be placed. In cases of electromechanical dissociation, underlying causes like hypovolemia, tamponade, hypoxemia, tension pneumothorax, acidosis, hyperkalaemia and massive pulmonary embolism should be treated.

Magnesium, isoprenaline and overdrive pacing are particularly useful in cases of TdP type of polymorphic ventricular tachycardia occurring in patients with acquired long-QT syndrome.

The management of AMI and acute coronary syndrome involve standard treatments like aspirin, thrombolytics, angioplasty (PTCA), heparin, beta blockers, angiotensin converting enzyme inhibitors (ACEI) and antiarrhythmics. For AMI, early ventricular fibrillation or ventricular tachycardia within 48 hours of the initial event do not portend a poor long term prognosis, and the management of these patients is therefore that of the acute infarction itself.

Other investigations include electrocardiography (to document AMI, acute ischaemia, WPW syndrome, long-QT syndrome, Brugada syndrome), echocardiography (to document regional myocardial function, valvular and anatomical abnormalities, pericardial effusions), cardiac catheterization (will be discuss later under Section 3.5), myocardial biopsy (for myocarditis) and magnetic resonance imaging (for ARVD).

3.3 Antiarrhythmic Drug Therapy

Previously, class I antiarrhythmic agents, beta blockers and class III antiarrhythmic agents were used to treat complex ventricular arrhythmias hoping to prevent sudden cardiac death[13].

Concerning the use of antiarrhythmics for primary prevention of sudden cardiac death, there were several randomised studies. Based on the publication of the Cardiac Arrhythmia Suppression Trial (CAST) and CAST II[14,15] showing excessive mortality with the use of class IC agents (flecainide, encainide and moricizine) in post infarction patient, these agents are

not recommended. Results from the Electrophysiologic Study Versus Electrocariographic Monitoring (ESVEM) trial[16], the Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE)[17] and several smaller studies (Basel Antiarrhythmic Study & Infarct Survival BASIS[18] and Polish Amiodarone Trial PAT[19]) showed that amiodarone and sotalol are more effective than other antiarrhythmic agents in the prevention of recurrent sustained ventricular tachycardia and the sympathetic inhibition component of these drugs do contribute to mortality reduction.

However, the development of a so-called pure class III antiarrhythmic agents had been hampered by the Survival With Oral d-Sotalol (SWORD) Trial[20] which showed increased mortality among patients assigned to d-sotalol. This trial intended to show that a pure potassium-channel blocking action could reduce all-cause mortality in patients with previous myocardial infarction and left ventricular dysfunction but was prematurely terminated when an interim analysis showed the increased mortality.

Beta-blockers are associated with highly significant reductions in risk of death in post-infarction patients (56 trials, 53,521 patients: OR 0.81; 95% CI 0.75 to 0.87, P < 0.00001). The survival benefit appears to be mediated by both a reduction in arrhythmia-related death (25-30%) and recurrent infarction. Recent interest in use of carvedilol, a beta blocker with antioxidant and a-adrenergic blocking activity in congestive heart failure requires further exploration. Carvedilol has been shown to decrease incidence of resuscitated VT or VF, unexplained syncope and sudden death in patients with congestive heart failure from 25% to 9%[21].

The European Myocardial Infarction Amiodarone Trial (EMIAT)[22] had shown that amiodarone has no impact on overall survival (all cause mortality 11.3% in the amiodarone group versus 12.1% in the placebo group) despite some improvement in sudden death survival in patients with depressed left ventricular function following MI (arrhythmic death 5.6% in amiodarone group and 8.2% in the placebo group). The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)[23] recruited survivors of recent MI (within the last 6 to 45 days), and randomized them to either amiodarone or placebo. The protocol required patients to have complex ventricular ectopy, defined as more than or equal to 10 ventricular premature depolarizations per hour or nonsustained ventricular tachycardia (NSVT). There was a statistically significant reduction in the primary endpoint of VF or arrhythmic death in patients assigned to the amiodarone group. However, there was a non-statistical trend toward decreased all-cause mortality in patients randomly assigned to amiodarone. Using efficacy analysis, there was a 21.2% reduction in total mortality with amiodarone (37% versus 50%, P=0.136). Using intention-to-treat analysis, there was a statistically non-significant 18.3% reduction in all-cause mortality (57% versus 68%, P>0.15).

For primary prevention of sudden cardiac death in patients with congestive heart failure, the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA)[24] study showed that amiodarone treated patients with advanced stable heart failure had lower mortality than the control group (33.5% versus 41.4% P=0.024). There were also reductions in sudden death and death from progressive heart failure. The Veterans Affairs Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy (CHF STAT)[25] had shown that amiodarone treated patients with ejection fraction ≤40% and asymptomatic but frequent and complex ventricular arrhythmias had a trend towards reduction in hospitalizations and cardiac death combined, which is significant in patients with non-ischaemic aetiology.

Overall data from the amiodarone trials on high risk patients (post-infarction, congestive heart failure or survivors of cardiac arrest) suggest that this agent is effective in reducing the risk of death (14 trials, 5713 patients: OR 0.83; 95% CI 0.72 to 0.95, P = 0.01).

In summary, for the primary prevention of sudden cardiac death, beta blockers are shown to be particularly effective in post infarction patients, sotalol and amiodarone are effective for high risk patients and carvedilol is promising in patients with congestive heart failure. For the routine prophylactic use of amiodarone and sotalol in post MI patients, evidences suggested that they only have a limited role at the present moment[26]. Discontinuation of these antiarrhythmic drugs is high due to intolerance or adverse effects. Nevertheless, as the group of patients with increased risk of recurrent ventricular tachyarrhythmias were heterogeneous, further randomized trials are needed to clarify the present controversies in choosing the best antiarrhythmic drug in particular subgroups of patients in different clinical settings.

Holter or electrophysiological study guided antiarrhythmic therapy have been advocated. Suppression of arrhythmias guided by these methods was associated with a good clinical outcome. The ESVEM study showed that while Holter monitoring led to predictions of antiarrhythmic drug efficacy more often than the electrophysiological study, there was no statistical significant difference in the clinical success of drug therapy as selected by the two

methods[16].

In secondary prevention of sudden cardiac death (i.e. in survivors of cardiac arrest), several recently published randomized studies had shown that the implantable cardioverter defibrillator (ICD) is the treatment of choice when transient or reversible causes are excluded (discussed under Section 3.7). Nevertheless, antiarrhythmic drugs remain useful in patients not suitable or not indicated for ICD implantation, as well as for acute control of arrhythmias and as adjunctive treatment to ICD (decreasing the frequency of shocks, slowing ventricular tachycardia rate to within the antitachycardia pacing window, treating atrial arrhythmias, etc.)[27]

3.4 Radiofrequency Catheter Ablation

In recent years, the development of catheter based radiofrequency ablation technique has allowed a safe and effective treatment of cardiac arrhythmias. The success rate is greater than 90% for supraventricular ventricular tachycardias involving accessory pathways or nodal re-entry.

In patients with WPW syndrome and atrial fibrillation, ablation of the atrioventricular accessory pathway will be curative and prevent the recurrence of rapid ventricular tachycardia (VT) and fibrillation.

This ablation technique is also very effective in treating VTs in structurally normal hearts. The two major group of VTs arise from the right ventricular outflow tract (VT with left bundle branch block pattern and right axis deviation) and the posterior fascicle of the left ventricle (verapamil-sensitive fascicular VT with right bundle branch block pattern and left axis deviation) respectively. Bundle branch reentrant VT is also amenable to catheter ablation.

At present, radiofrequency catheter ablation of post-MI or ischaemic VT has only a limited role and is time consuming. The clinical ventricular tachycardia must be reliably reproducible in the electrophysiological laboratory, well tolerated clinically and sustained enough to be mappable. Due to the intrinsic limitation of radiofrequency current, the reentry pathway, if based on circus movement, must be relatively subendocardial. However, de Bakker et al found that the earliest and latest endocardial sites of activation were connected through scar tissue by bands of surviving myocardial fibers that could run subendocardially, intramurally and even epicardially[28]. The patient should have limited number of morphologically distinct ventricular tachycardia patterns. Ablation will be difficult and the end point uncertain if nonclinical tachycardia is induced during electrophysiological study.

The method of ablating the tachycardia rests on endocardial catheter electrode mapping of the earliest site of activation, pace mapping, concealed entrainment and identification of mid-diastolic potentials. The definition of the endpoint of ablation has not been fully resolved. Where ventricular tachycardia was difficult to induce and to reproduce, the predictive value of permanent success may be diminished.

Finally, remodelling of the myocardium is a progressive process and previously stable substrates can become arrhythmogenic with time. As a result, the major use of catheter ablation in cardiac arrest or ischaemic heart patients is as an adjunct treatment to lessen the frequency of arrhythmias after ICD implantation and thus decrease the number of shocks.

In future, with the development of new ablation and mapping techniques (e.g. 3D mapping with CARTO-system[29], microwave or transmural ablation, etc.), it is hoped that the clinical application of radiofrequency ablation in ischaemic VT will be greater.

3.5 Angioplasty and Coronary Bypass Surgery

Cardiac catheterization provides the most complete assessment of the structure, function and coronary arteries of the heart. It should be performed in virtually all survivors of cardiac arrest. Angioplasty should be performed in patients with evidence of ischaemia and significant critical stenosis. Studies have shown that an open infarct-related artery may prevent the development of the abnormal electrophysiological reentrant circuit by allowing a more homogenous area of infarcted tissue to form. However, its exact role in the prevention of sudden cardiac death awaits further prospective controlled trials.

In patients with ischaemic heart disease and angina, surgical coronary revascularization decrease sudden death rates, with greatest benefits observed in patients with depressed left ventricular function and multiple vessel disease. Among cardiac arrest survivors, revascularization is indicated in patients with evidence of ischaemia. Although it is uncertain whether revascularization will alter the frequency of spontaneous episodes of arrhythmia, it may improve the patient's ability to tolerate an episode of VT and may also inhibit the development of new arrhythmias.

3.6 Other Surgical Therapies

Other surgical therapies play important roles in the management of both cardiac arrest survivors and patients at risk of sudden cardiac death.

Direct surgical approach to eliminate or ablate the VT focus arising from the scarred or aneurysmal tissue have been developed. These techniques employed epicardial and/or endocardial mapping and programmed

ventricular stimulation to locate the presumed site of origin of the VTs followed by surgical resection or ablation (e.g. using cryothermia or laser). The major drawback of arrhythmia surgery is the operative morbidity and mortality (5% to >20%), thus this option is limited for use in selected patients and experienced centers.

Surgical therapy can also be effective in certain group of patients with risk of sudden cardiac death. Examples include left cervicothoracic sympathectomy in patients with congenital long-QT syndrome who failed medical therapy and septal myotomy in patients with hypertrophic obstructive cardiomyopathy.

Orthotopic heart transplantation has emerged as an acceptable therapeutic alternative for selected patients with end stage heart failure and resistant ventricular arrhythmias.

3.7 Implantable Cardioverter Defibrillator (ICD)

The concept of an ICD was developed by Michel Mirowski in 1966-7. Since the first human implant of ICD in 1980, significant interest and enthusiasm has developed all over the world for the use of ICDs for patients with life-threatening ventricular tachyarrhythmias. More than 10,000 ICDs have subsequently been implanted worldwide.

As rapid technical advancement continues, the ICD has evolved from a short-lived, large-size, non-programmable device requiring a thoracotomy for lead insertion into a multiprogrammable, small-size, antiarrhythmia device inserted almost exclusively without thoracotomy, now capable of treating bradycardia, VT and VF. These devices are capable of correctly sensing the arrhythmia (facilitate by using rate, onset, stability criteria and atrial sensing), delivering antitachycardia pacing (ATP), low energy shock, achieving a lower defibrillation threshold (by using biphasic shock), storing intracardiac electrocardiograms, extensive diagnostics, backup pacing and transvenous implantation.

Recently, defibrillators incorporating an atrial lead have become available, such device not only provide dual-chamber pacing but also use the pattern of sensed atrial depolarization to distinguish supraventricular from ventricular arrhythmias. Over the years, ICDs have achieved low sudden cardiac death recurrence rates (average 1% to 2% annually) and a high percentage of appropriate ICD therapy (> 98% of successful reversion of VT with circulatory collapse or VF).

In the context of secondary prevention of sudden cardiac death, several trials are recently published. The randomized Antiarrhythmics Versus Implantable Defibrillators (AVID) trial[30] showed that in survivors of ventricular fibrillation or sustained ventricular tachycardia causing significant haemodynamic compromise, the ICD was superior to antiarrhythmic drugs for increasing overall survival (patients who received an ICD had a 39% reduction in total mortality at 1 year, a 27% reduction at two years, and a 31% reduction at three years compared to patients in the conventional therapy group $P < 0.02$).

The Cardiac Arrest Study Hamburg (CASH) trial[31] aimed to test the hypothesis that ICD therapy would significantly reduce 2-year mortality when compared to treatment with amiodarone, propafenone, or metoprolol in survivors of cardiac arrest. Patients assigned to the ICD arm before July, 1990, underwent device placement by open thoracotomy. Those assigned after that date received transvenous systems. Patients in the medical treatment arm received an average of amiodarone 300mg per day, propafenone 600mg per day, or metoprolol 100mg per day. The primary endpoint of the study was all-cause mortality. Secondary endpoints included recurrent cardiac arrest requiring cardiopulmonary resuscitation and SCD. There was a 37% reduction in overall mortality among those assigned to the ICD treatment arm (12.1% versus 19. 6%) when compared to those receiving amiodarone or metoprolol ($P = 0.047$). The mortality data comparing amiodarone and metoprolol were similar. There was a significant decrease in SCD in patients treated with ICD when compared to medical management (2% versus 11%, $P < 0.001$).

The randomised, multicentre Canadian Implantable Defibrillator Study (CIDS)[32] compared ICD with amiodarone therapy in patients with cardiac arrest or haemodynamically unstable ventricular tachycardia and left ventricular ejection fraction ≤35%. After 3 years of follow up, patients randomized to the ICD group had a 19.6% relative risk reduction in the primary endpoint of all-cause mortality compared to the amiodarone group, a difference approaching statistical significance (25% mortality in ICD group versus 30% mortality in the amiodarone group, $P = 0.072$).

In summary, these multicentre, randomized clinical trials (AVID, CASH, CIDS) have shown the superiority of ICD over antiarrhythmic medical therapy in secondary prevention of sudden cardiac death and reducing total mortality in certain groups of high risk patients.

For trials examining the outcome of ICD implantation on primary prevention of sudden cardiac death, the prospective, randomized, multicentre Automatic Defibrillator Implantation Trial (MADIT)[33]

showed improved survival with the ICD implantation in post-infarction patients with low ejection fraction (EF ¢G 0.35) and inducible non-suppressible ventricular tachycardias (54% reduction in all-cause mortality in the ICD group relative to conventional treatment P = 0. 009). The cardiac mortality was also significantly higher in the conventional treatment group than the ICD group (27% vs 12%). In view of this result, this group of patients have been included in the AHA/ACC indications for ICD implantation (Appendix 1).

The Coronary Artery Bypass Graft Surgery CABG-Patch trial[34] enrolled patients with coronary artery disease scheduled for elective CABG who also had a LVEF less than 30% and an abnormal signal-averaged electrocardiogram (SAECG). Nine hundred patients were randomized to receive either an ICD at the time of CABG or usual care. There was no significant difference in the primary endpoint of total mortality at 30 days and a mean of 32 months. Therefore, ICD implantation is not recommended in this group of patients.

With the evidences available so far, the American College of Cardiology and the American Heart Association had published the indications for ICD implantation in 1998 as listed in Appendix 1[35].

The interaction between the ICD and antiarrhythmic agents is important. Beneficial interactions are slowing of ventricular tachycardia which yields improved haemodynamic tolerance, improved ATP and low energy cardioversion success (less battery drain from the ICD), limiting the number of recurrence of arrhythmia which minimizes patient discomfort and prolongs ICD battery life, preventing or slowing supraventricular tachycardias which reduce the number of false shocks from the ICD. The disadvantages of combining pharmacological therapy with the ICD are the cost and side effects of both therapies, slowing of the ventricular tachycardia which may result in failure to detect the arrhythmia, increased defibrillation and pacing thresholds, worsened haemodynamic intolerance to ventricular tachycardia. As a result, repeated electrophysiological testing and a meticulous follow up programme is necessary in a patient implanted with an ICD.

An ICD is easily justifiable in those high risk patients but unfortunately most sudden cardiac deaths occur in a large population of patients with a rather low risk for sudden death. The decision to implant an ICD has major economic, social and political implications. The cost of an ICD device and implantation is currently expensive. The price of an ICD is around HK$150,000-250,000 excluding other associated costs such as hospitalization, operation, follow up and replacement. A cost-effectiveness analysis of the MADIT trial (MADIT/CES) found the ICD to have a cost-effectiveness ratio of US$22,000-31,000 per life-year gained comparable to the widely accepted non-cardiac therapies such as renal dialysis (US$30,000 to 50,000 per year of life saved)[36,37]. However, the cost-effectiveness ratio and direct costs are expected to come down as the technology is improved and mass production is achieved.

In the future, it is expected that there will be an increasing trend for the implantation of ICDs and newer models equipped with better detection and therapy algorithms, haemodynamic sensors will be available.

4. Identification of Patients at Risk

Risk stratification for arrhythmogenic events and sudden death in patients with organic heart disease, particularly those with coronary heart disease and a history of MI, continues to be one of the major tasks of cardiologists, although advanced management strategies including thrombolysis, acute PTCA and surgery dramatically reduced the percentage of sudden deaths following infarction. Non-invasive testing like echocardiography and radionuclide studies, 24 hour Holter monitoring, signal-averaged electrocardiogram (SAECG), heart rate variability (HRV), QT dispersion, as well as, invasive techniques such as electrophysiological study with programmed ventricular stimulation (VT induction) are being used.

4.1 Non-invasive testing

4.1.1 Echocardiography and Radionuclide studies

Left ventricular ejection (LVEF) has been identified as probably the most important predictor of total mortality and morbidity following AMI and mortality increase exponentially as LVEF decrease from 0.40 to 0.30[26]. LVEF can be measured by radionuclide cardiography or estimated by echocardiography. These methods seem to be equal in terms of predicting total mortality. However, in terms of arrhythmic death prediction, studies have shown that LVEF is not a very sensitive marker. Therefore, a combination of LVEF and another method (e.g. SAECG, HRV, etc.) appears promising in identifying patients at high risk of sudden death[38].

4.1.2 Holter monitoring and Heart Rate Variability (HRV)

Post MI or heart failure patients with frequent non-sustained ventricular tachycardia or complex

ventricular ectopic beats during Holter monitoring were shown to have higher risk of sudden death in various studies. With the publication of the results from the MADIT study[33] (discussed under Section 3.7), the documentation of nonsustained ventricular tachycardia in post MI patients could be accepted as indication for invasive studies.

Heart Rate Variability (HRV) reflects the sympathicovagal activity at the sinoatrial node. Both sympathovagal imbalance at the cost of parasympathetic tone and a change in the circadian rhythm of HRV are known to be independent risk factors for arrhythmic events (in both the pre-thrombolytic and thrombolytic era). HRV can be assessed from 24 hour Holter monitoring by calculation of indices which are based on statistical operations on RR intervals (time-domain analysis). Compared to assessment of LVEF as a risk marker, HRV is superior with respect to prediction of arrhythmic events and sudden death whereas both parameters yield comparative power for prediction of total mortality[39]. Four year survival was 90% for patients with a normal standard deviation of normal-to-normal intervals (SDNN > 100msec), while survival was only 60% in patients with depressed HRV (SDNN < 50msec). Another study, the ATRAMI study showed that 2-year survival in post MI patients was > 98% in patients with SDNN > 105msec and 90% for those with SDNN < 70msec ($P < 0.0001$)[39,40].

Since the predictive power of either Holter monitoring or HRV alone is relatively low, the combined use with other traditional risk markers like SAECG or LVEF will result in improved risk stratification.

4.1.3 Signal-averaged ECG (SAECG)

SAECG detecting abnormal delays of ventricular activation by demonstrating late potentials (low amplitude, high frequency components in the terminal QRS complex) is a useful tool to screen out patients who will have higher risk of developing malignant ventricular arrhythmias. A normal SAECG will give more than 95% confidence that the patient (post-infarction) will not have significant ventricular tachyarrhythmias in the future. Use of the SAECG as one of the methods for risk stratification after infarction seems well founded. When combined with other risk indicators (e.g. LVEF), the efficacy could be increased[41].

In patients with ARVD, SAECG can identify those with more extensive right ventricular involvement and of inducible VT during programmed stimulation[42]. In patients with dilated cardiomyopathy, SAECG might prove useful in predicting spontaneous VT[43]. In patients with HOCM, the role of SAECG is still controversial[44].

4.1.4 Miscellaneous

QT interval dispersion as a measure of interlead variations of QT interval duration in the surface 12-lead ECG is believed to reflect regional differences in repolarization heterogeneity and thus, may provide an indirect marker of arrhythmogenicity. However, the use of QT dispersion as risk stratification in post infarct, heart failure and HOCM patients still remains controversial[45].

Other non-invasive markers of patients at risk of sudden death include T wave alternans and baroreflex sensitivity (BRS) measurement. The ATRAMI study[40] showed that BRS is a strong and independent risk factors for post-infarction mortality demonstrating the usefulness of autonomic markers.

4.2 Invasive testing - Electrophysiological Studies (EPS) and Programmed Ventricular Stimulation

Inducible sustained ventricular tachycardia during EPS has been shown to confer 20-30% yearly recurrence rate of the tachyarrhythmia in post MI patients[46-58]. While the VT induction protocols differ among different centres, commonly used protocols include using 2 different basic drive train cycle lengths with up to 3 extra stimuli given in a tandem fashion in 2 sites (right ventricular apex and outflow tract) or using a basic drive train cycle length of 400ms with delivery of up to 4 extrastimulus only once in the right ventricular apex (as described by Lee and the author)[59]. In the latter study, we compared prospectively three different stimulation protocols to examine the influence of a short basic drive train cycle length and repetition of extrastimuli on induction of ventricular tachycardia in 30 consecutive patients who had documented ventricular tachycardia or fibrillation based on underlying coronary artery disease. Protocol A used a basic drive train cycle length of 400ms with each extrastimulus coupling interval delivered only once. Protocol B used the same basic drive train cycle length, but with each extrastimulus coupling interval repeated 3 times before decrementing. Protocol C used 300ms as the cycle length of basic drive trains without repetition of extrastimuli. A total of 90 inductions were performed. The results showed that there was no clinical benefit for repetition of extrastimuli and a short basic cycle length of 300ms was not superior to 400ms for induction of ventricular tachyarrhythmias[59].

VT induction is particularly useful for risk stratification in certain group of high risk patients like the MADIT population described earlier (Section 3.7)[33]. EPS guided therapy (either drug or defibrillator) can minimize the risk of sudden cardiac death in patients

with coronary artery disease, post MI and NSVT[60]. Risk stratification using EPS in patients with NSVT and coronary artery disease and no history of MI has been more controversial. In patients with a poor LVEF (≤ 0.35), a negative VT induction study did not preclude a substantial risk of sudden death. Some centres even advocate routine VT induction in all post MI patients thought to be at high risk from either a low ejection fraction or frequent or complex spontaneous ventricular ectopia[61]. However, without conclusive data, routine stimulation of such patients cannot be recommended.

The value of programmed ventricular stimulation in diseases other than MI remains to be clarified. In patients with dilated cardiomyopathy, induction of sustained monomorphic VT did not reliably predict future arrhythmic events or sudden death[62]. In patients with HOCM, data had been conflicting[63].

In summary, non-invasive tests like echocardiography, Holter, HRV, SAECG are important methods for risk stratification in post MI patients. Patients with normal non-invasive test results do have good prognosis (and thus further EPS is not justified). EPS with electrical stimulation seems to be the clinically most valuable single method to predict arrhythmic events. However, as an invasive procedure it is not suitable as a screening test for a large cohort. The stepwise approach for risk stratification using first non-invasive followed by invasive procedures seem to be the most suitable and effective approach at the present moment[64].

For the screening of asymptomatic and apparently healthy individuals in the general public, one must consider whether the screening method is financially and practically possible. As coronary artery disease remains the most common cause of sudden cardiac death, an effective, inexpensive and non-invasive screening method to obtain sufficient information on potential ischaemia is awaited. At the mean time, the best we can do is to educate the general public to reduce risk factors for coronary artery disease. For noncoronary causes of sudden cardiac death, screening at school or before starting competitive sports can help identify those individuals with asymptomatic structural heart or electrical diseases such as HOCM, WPW and long QT syndromes[65].

5. Conclusion

In the past 30 years, we have gained much knowledge on the epidemiology, pathophysiology, management, primary and secondary prevention of sudden cardiac death. Many large clinical trials on the prevention of this disease are in progress. At the same time, recent advances in treating patients with coronary artery diseases (e.g. aspirin, thrombolytics, beta blockers, ACEI, PTCA, bypass surgery, etc.) have significantly reduce the mortality. Risk stratification and identification of patients at risk remain a challenge to the physician and the available data from the published clinical trials apply only to several selected groups of patients. At the extreme, one could identify a small group of patients with multiple high risk predictors having a high probability of death, which only accounts for a small fraction of the total deaths. It should be remembered, however, that even though the actual rates are comparatively low, most sudden deaths occurs in the very large segment of the general population not thought to be at high risk.

In order to have an impact on the public health, we should aim at developing cost-effective means to identify effective risk markers and devise broader strategies to prevent sudden death in the general population.

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Appendix 1. ACC/AHA Guidelines for Implantation of Antiarrhythmia Devices

Since 1980, the American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of guidelines in the area of cardiovascular disease. The ACC/AHA Guidelines for Implantation of Antiarrhythmia Devices was published in the April 7, 1998 issue of Circulation and in the April 1998 issue of the Journal of American College of Cardiology35.

Indications for ICD Therapy

Class I

1. Cardiac arrest due to VF or VT not due to a transient or reversible cause.
2. Spontaneous sustained VT.
3. Syncope of undetermined origin with clinically relevant, haemodynamically significant sustained VT or VF induced at electrophysiological study when drug therapy is ineffective, not tolerated, or not preferred.
4. Nonsustained VT with coronary disease, prior MI, LV dysfunction, and inducible VF or sustained VT at electrophysiological study that is not suppressible by a Class I antiarrhythmic drug.

Class IIa

None.

Class IIb

1. Cardiac arrest presumed to be due to VF when electrophysiological testing is precluded by other medical conditions.
2. Severe symptoms attributable to sustained ventricular tachyarrhythmias while awaiting cardiac transplantation.
3. Familial or inherited conditions with a high risk for life-threatening ventricular tachyarrhythmias such as long QT syndrome or hypertrophic cardiomyopathy.
4. Nonsustained VT with coronary artery disease, prior MI, and LV dysfunction, and inducible sustained VT or VF at electrophysiological study.
5. Recurrent syncope of undetermined aetiology in the presence of ventricular dysfunction and inducible ventricular arrhythmias at electrophysiological study when other causes of syncope have been excluded.

Class III

1. Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias.
2. Incessant VT or VF.
3. VF or VT resulting from arrhythmias amenable to surgical or catheter ablation; for example, atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, right ventricular outflow tract VT, idiopathic left ventricular tachycardia, or fascicular VT.
4. Ventricular tachyarrhythmias due to a transient or reversible disorder (e.g. AMI, electrolyte imbalance, drugs, trauma).
5. Significant psychiatric illnesses that may be aggravated by device implantation or may preclude systematic follow-up.
6. Terminal illnesses with projected life expectancy 6 months.
7. Patients with coronary artery disease with LV dysfunction and prolonged QRS duration in the absence of spontaneous or inducible sustained or nonsustained VT who are undergoing coronary bypass surgery.
8. NYHA Class IV drug-refractory congestive heart failure in patients who are not candidates for cardiac transplantation.