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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Introduction

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Over the past decade, there has been a marked increase in the number of well designed, adequately powered clinical trials undertaken to answer key questions related to the management of patients with ventricular arrhythmia and/or at risk for arrhythmic death. These trials have addressed several important questions, including what is the best way manage the patient with a cardiac arrest, what is the role of prophylactic antiarrhythmic therapy in high risk patients, and what is the effect of suppression of premature ventricular depolarizations on mortality. In addition, some of these trials included important analyses related to quality of life and to cost of treatment. Although many other ongoing trials are addressing important questions related to sudden death prevention, there was widespread agreement among Canadian arrhythmia specialists that it would be appropriate to consolidate our current state of knowledge by means of a Canadian Cardiovascular Society (CCS) consensus conference. The Executive Committee of the CCS agreed with this and approved a primary panel of Canadian cardiologists to prepare 10 chapters pertaining to this subject. Primary panel members wrote an initial draft of their chapters with recommendations, and then met in April 1999 to review and modify their work. The resulting revised chapters were then sent out to a secondary panel for review. Revisions were made based on these reviews, and the updated document was then presented to the CCS general membership during the annual scientific meeting held in October 1999. Final revisions were then made based on feedback from these presentations before submission of the present document for publication in *The Canadian Journal of Cardiology*.

The goals of this statement are to provide the health care community with a good summary of the current state of knowledge in the area of prevention of sudden death from ventricular arrhythmia. In addition, recommendations flowing from this data base have been formulated by consensus panel members. Although many of these recommendations are based on evidence from randomized clinical trials, there are a number of areas where clinical trial evidence is not available. One may have considered basing recommendations only on the results of randomized trials, but this would not have provided guidance to the practising clinician in a number of important areas. A number of relatively uncommon conditions place patients at risk for cardiac arrhythmic death. It is unlikely that clinical trials will ever be performed because of the low rate of occurrence of these diseases. It is, therefore, appropriate to base recommendations about the management of these conditions on the opinion of experts in the area.

All recommendations have been graded according to the level of evidence available in support of the recommendation. The strongest recommendations are Grade A, which are based on the results of randomized clinical trials. Where the randomized trial data are less robust, because of either a small number of patients or conflicting results from multiple trials, Grade B recommendations have been made. Recommendations that are not based on data from randomized clinical trials are all considered to be Grade C.

Levels of evidence and grading of recommendations

Level of evidence	Grade
Level I: Large randomized trials or meta-analysis with clearcut results (and low risk of error)	A
Level II: Small randomized trials or meta-analysis with uncertain results	B
Level III: Nonrandomized contemporaneous controls	C
Level IV: Nonrandomized historical controls	C
Level V: No controls, case series	C

Some of the major recommendations of this consensus statement relating to the use of the implantable cardioverter defibrillator (ICD) merit comment. On the basis of the results of three recently completed randomized clinical trials, a Grade A recommendation was made to use the ICD in patients who have survived either a cardiac arrest or severe symptomatic sustained ventricular tachycardia. It is now clear from these trials that the ICD reduces mortality in these patients compared with treatment with amiodarone alone. The committee did not find that the clinical trial evidence supporting prophylactic ICD use was as compelling as that in support of ICD use in survivors of cardiac arrest. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) showed a substantial and statistically significant benefit of the ICD in patients with ischemic heart disease with severe left ventricular dysfunction and nonsustained ventricular tachycardia, shown to have inducible sustained ventricular arrhythmia. The MADIT study is rather small and by itself not very convincing. The committee was, rather, influenced by the recent results from the Multicenter Unsustained Tachycardia Trial (MUSTT), which provides additional support of the use of prophylactic ICD in patients with an inducible sustained ventricular arrhythmia and ischemic heart disease. The Grade B recommendation to perform electrophysiological testing in many patients with ischemic heart disease and left ventricular dysfunction, with a view to ICD implantation in those with inducible ventricular tachycardia or ventricular fibrillation, is a considerable departure from current Canadian practice. This is a direct result of the recent clinical trial data that are now available.

The cost implications of widespread use of ICD therapy cannot be ignored. Most of the major ICD trials have had detailed economic analyses associated with them, and these have been reviewed by the consensus panel. Preliminary reports from the Canadian Implantable Defibrillator Study (CIDS) and Antiarrhythmics Versus Implantable Defibrillators (AVID) study indicate that the cost of ICD therapy is high. Both studies report that the cost per year of life saved by ICD therapy in survivors of cardiac arrest is in excess of $100,000. This makes ICD therapy in cardiac arrest survivors one of the more expensive therapies used in Canada. The medical evidence that ICD therapy is beneficial cannot be separated from its economic implications. Nonetheless, the decisions about whether we can afford ICD therapy, and in which patients it is too expensive, are questions of great social importance. The approach to

these questions must include the input of physicians and health economists. However, ultimately they cannot be answered from a medical or economic perspective alone. The ethical implications of rationing expensive medical care are beyond the scope of this consensus conference but clearly are worthy of further consideration by the CCS.

This consensus conference cannot in any way be considered the final document. There are many unresolved questions and other issues that panel members could not agree upon for lack of firm results from clinical research. Ongoing studies to be published within the coming years will clearly change our view of many of these questions.

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Chapter 1: Epidemiology

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Sudden death claims 35,000 to 40,000 Canadians each year and is thus a major public health problem. Studies reporting on sudden death have used multiple definitions, making comparisons difficult. The most common and widely accepted definition is death within 1 h of the onset of symptoms without previous known disease or disease expected to be lethal, or unwitnessed death with the victim known to be alive less than 24 h earlier. In the general adult population, the incidence is 0.1% to 0.2%/year (1), with approximately 18% of all deaths being sudden. Most sudden deaths are cardiac in origin (SCD), but there are also neurological (intracranial disasters such as bleeding as well as status epilepticus) and vascular causes (dissection of a major vessel and massive pulmonary embolus). Cardiac causes are usually electrical and involve either bradycardia (usually asystole) or tachycardias (usually ventricular tachycardia [VT] or fibrillation [VF]). Forty to fifty per cent of all cardiovascular deaths are sudden, with the majority of these having underlying coronary artery disease (2). In one-half to two-thirds of patients, sudden death is the first manifestation of the underlying coronary artery disease (3).

PATHOPHYSIOLOGY

The pathophysiology of sudden death is difficult to determine because few sudden death events occur under monitored conditions. In one study of sudden death in a defined population (4), the initial rhythm documented by emergency response personnel was VF in 120 of 220

(55%), sustained VT in eight (4%) and bradycardia or asystole in 92 (42%). Another study found 65% to be VF, 10% VT and 25% bradycardia (5).

The anatomical substrate responsible for SCD is age dependant. In those under 35 years of age, congenital heart disease predominates (6). In those over 35 years of age, ischemic heart disease is by far the most common cardiac abnormality, accounting for up to 80% of cases, followed by various cardiomyopathies in 10% to 15% (7) - mainly dilated, hypertrophic and arrhythmogenic right ventricular cardiomyopathies. Uncommon causes of SCD in the mature adult population include various valvular, inflammatory and infective disorders of the heart as well as the more recently recognized ion channel abnormalities such as long QT interval syndromes, Brugada syndrome (8) and those precipitated by drugs or toxins.

The electrophysiological mechanisms of malignant ventricular arrhythmias are multiple and are related to complex and as yet not completely understood interactions among the anatomical substrate, triggering arrhythmias (eg, premature ventricular complexes, nonsustained VT and bradycardia) and neurohormonal or other modulating factors (9). Transient acute myocardial ischemia is a major potential trigger for polymorphic VT and VF, and one autopsy series reported that 48% of patients dying suddenly from a supposed cardiac cause had acute complete coronary occlusion
(10). Reperfusion acutely can also be proarrhythmic due to rapid and heterogeneous changes in ventricular refractoriness.

The anatomical abnormalities can be influenced by many neurological/autonomic, hormonal, metabolic and pharmacological factors, both acutely and chronically. Many systemic factors such as hypoxia, acidosis and electrolyte abnormalities can alter the electrophysiological environment. Autonomic factors are increasingly recognized to be important, with altered heart rate variability indicating increased sympathetic tone - a well defined risk factor for SCD (11).

Recent genetic and molecular discoveries suggest that there may be genetic predispositions to SCD that exist either without environmental provocation or occur much more readily when the

appropriate environmental conditions are met (eg, ischemia, drugs/toxins, metabolic abnormalities) (7). The genes responsible for SCD in a number of clinical conditions code for proteins in cellular ion channels, and have been isolated in long QTand Brugada syndromes (8). It is possible that in the future a genetic predisposition to VT postmyocardial infarction (MI) and VF secondary to scar with or without ischemia will be identified, and general screening techniques will be made available.

POPULATION STUDIES

In the general population, the risk factors for sudden death are overwhelmingly those of coronary artery disease. The Framingham study (1) reported a 10-fold difference in incidence of sudden death, depending on risk factors including age, hypertension, cigarette smoking, serum cholesterol level, glucose intolerance, electrocardiographic abnormalities and prior congestive heart failure. The risk in some populations also varies over time. In the post-MI population, for example, the risk is highest immediately following the event and falls progressively over the next 12 to 24 months.

No risk factors specific for sudden death have been identified. Approximately half the victims of sudden death have had no symptoms of heart disease before the event (4). Of those reporting symptoms, one-third report previous chest pain and a very small number complain of palpitations. This makes identification of potential victims difficult.

A number of population studies have been reported, with the largest and most complete being from Framingham (1) and Yugoslavia (2). The Framingham study showed an incidence of sudden death of 0.3/1000 men/year in the absence of any risk factors. This increased to 5.9/1000 men/year with multiple risks. In the Yugoslavia Cardiovascular Disease study, the highest risk group had an incidence of 11.7/1000 men/year. In the Framingham study, the rates in women were half those in men with otherwise equal risk factors. The incidence of sudden death is markedly increased with certain types of underlying heart disease. The two most common are ischemic heart disease and heart failure, discussed here, with the less common forms discussed in later chapters.

SPECIFIC HEART DISEASES

The incidence of out-of-hospital sudden death occurring in the setting of acute MI (AMI) remains unclear because of the uncertainty of diagnosis. It has been estimated that up to half of the patients with an AMI or an acute ischemic episode die suddenly before hospital admission (3). For those presenting with AMI, several large trials have provided data on sudden deaths and major complications that may lead to sudden death. Pooled published data from the Second International Study of Infarct Survival (ISIS-2) (12), the Third International Study of Infarct Survival (ISIS-3) (13), the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) (14) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI -2) (15,16) indicate that the prevalence of VF, asystole and cardiac arrest was 9.2% during the first few weeks of the AMI. The European and Canadian trials of amiodarone in survivors of AMI reported on the prevalence of arrhythmic death according to defined criteria. In the European Myocardial Infarct Amiodarone Trial (EMIAT) (17), the prevalence of arrhythmic death was 3.2%/year (total mortality was 7.8%/year). Similar rates were reported in the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT): sudden death 2.6%/year and total mortality 5.8%/ year (18). Sudden death in heart failure is substantial and forms about 50% of cardiac mortality. Pooled data from a number of small studies in the 1980s on 1057 patients with coronary artery disease or primary myocardial disease (19-27) gives a one-year mortality of 43%. Of this, 42% was due to sudden death. Sudden death in patients with dilated cardiomyopathy was examined in 14 small studies on a total of 1432 patients followed for an average of 3.6 years (28). Sudden death was reported to be 12%. Most clinical trials of therapies in congestive heart failure have reported on the prevalence of sudden death. In the Studies Of Left Ventricular Dysfunction (SOLVD) treatment trial, sudden death during the 3.5 years of follow-up was 8.5%, with total mortality of 37.4% (29). In the Veterans Administration Heart Failure Trial II (V-HeFT II), during 2.5 years of follow-up, sudden death was 18.5% and total mortality was 35.4% (30).

Mortality in heart failure trials from the 1990s reported similar results. In a trial of a positive inotropic agent, sudden death was 6.0% and total mortality was 22.2% during 0.97 years of follow-up (31). Two trials of amiodarone in congestive heart failure reported data on sudden death. In one trial with a follow-up of 13 months, sudden death was 13.8% and total mortality

37.4% (32). In the other trial, with an average follow-up of 45 months, sudden death was 20.6% and total mortality was 40.7% (33). An observation that can be made is that, while total mortality in congestive heart failure is dependent on disease severity, sudden death rates run parallel to, and form a substantial proportion of, the total mortality. Overall, the incidence of sudden death in patients with heart failure is between 6% and 18%/year.

CONCLUSION

The risk of sudden death rises with certain risk factors and in the presence of underlying heart disease. While the risk of SCD increases with disease severity, the relative percentage of deaths that are sudden decreases as the mortality risk due to other competing causes of death increases. Thus, in the group of patients with the highest overall mortality risk, interventions to decrease sudden death would have a lesser impact on overall mortality. Patients who have survived an episode of VF or VT in the absence of a reversible cause are at highest risk. Without effective therapy, the one-and two-year probabilities of VT/VF recurrence or death are 30% and 50%, respectively (34).

While higher risks increase the rate of SCD, the absolute number of sudden deaths is greater in the much larger low risk population. To begin to have an impact on the problem and to develop preventive strategies (primary and secondary), the incidence, causes and circumstances surrounding sudden death must be better known. A major challenge will be to identify persons at high risk in the low risk populations where specific interventions may have a greater overall impact.

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Chapter 2: The appropriate evaluation of the patient at risk for sudden death from ventricular arrhythmias

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This chapter reviews the various ways in which patients at risk for sudden cardiac death (SCD) may present to medical attention. Recommendations are made regarding the appropriate investigation of such patients in order to stratify further their risk of SCD.

PATIENT PRESENTATIONS

The patient presumed to be at risk of SCD may present to the physician in a number of ways. The patient may have known heart disease, suspected heart disease, a family history of heart disease or SCD, or may just exhibit risk factors for heart disease. This chapter addresses some of these patient presentations, especially those involving structural heart dis-ease.

The patient with structural heart disease: Because of the strong association between left ventricular (LV) dysfunction and SCD, risk stratification for SCD is considered most frequently in patients with known structural heart disease, especially following myocardial infarction (MI), and in patients with congestive heart failure (CHF) (1,2).

Post-MI patient: In the post-MI patient, the strongest predictor of total mortality and, indeed, a strong predictor of SCD is the presence of severe LV dysfunction (1,3). LV ejection fraction (LVEF) less than 35% post-MI is a strong predictor of total mortality as well as arrhythmic mortality. Furthermore, post-MI studies have clearly shown the benefits of angiotensin-

converting enzyme inhibition in patients with LVEF 0.35 or less post-MI. For these reasons, it is recommended that all patients post-MI have an objective determination of LV function (by echocardiography, radionuclide angiography or LV angiogram) (**Level I, Grade A**).

In addition, because residual ischemia post-MI is a predictor of subsequent mortality, some form of ischemia detection with treadmill testing, pharmacological stress or perfusion imaging should be considered (4,5).

Because ventricular arrhythmia post-MI has been shown to be a risk factor, especially when combined with a low ejection fraction, several interventional studies have been performed to assess the value of antiarrhythmic agents in post-MI patients with ventricular arrhythmia (see Chapter 7). It is clear that beta-blockers reduce mortality in this population, and class I agents have been shown to increase mortality (6-9). Amiodarone has been shown in a meta-analysis to result in a modest reduction in arrhythmic mortality (10). The results of these trials are discussed in detail in Chapter 7. Because the role of treatment of ventricular ectopy for mortality reduction post-MI is still unclear, the use of Holter monitoring for routine risk stratification post-MI is not recommended at this time.

Other forms of risk stratification post-MI have been proposed, including signal-averaged electrocardiography (ECG), T wave alternans, heart rate variability and baro-receptor sensitivity (11-19). For these to be recommended for risk stratification in routine clinical practice, we would need evidence that therapeutic measures can reduce mortality when aimed specifically at patient populations showing these prognostic markers. However, no large trials have been performed showing that therapy reduces mortality in these patient subsets and, therefore, routine use of these tests is not recommended.

CHF: The patient with CHF from prior MI or from dilated cardiomyopathy is at significant risk of cardiac death, with SCD contributing 30% to 40% of all mortality in patients with New York Heart Association functional class II to III CHF (20). For this reason, considerable attention has been given to risk stratification in patients with severe LV dys-function. Two major studies have now assessed the value of electrophysiological (EP) testing and implantable cardioverter

defibrillator (ICD) implantation in patients with severe LVdysfunction (21). These studies are discussed in detail in Chapter 6.

The value of routine Holter monitoring in patients with heart failure and coronary artery disease is not established. Many of the post-MI patients included in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT) had nonsustained ventricular tachycardia (VT) documented by other means including prolonged telemetric monitoring following admission for CHF. In patients with CHF due to idiopathic dilated cardiomyopathy, recent studies have shown no value of Holter monitoring in predicting SCD
(22). Therefore, routine Holter monitoring is not recommended in this patient population.

Patient referred for nonsustained VT: Occasionally, patients are found to have nonsustained VT during monitoring for other reasons. Nonsustained VT has been shown to be a risk factor for SCD only in patient populations with significant LV dysfunction. For this reason, LV function should be assessed in patients referred for nonsustained VT (**Grade C**). Patients with LVEF 0.35 or less would then be assessed as outlined in Chapter 6.

The patient referred because of an abnormal ECG: Patients may be referred for evaluation because of an abnormal ECG. Because asymptomatic pre-excitation patients are at low risk of sudden death, routine EP testing is not recommended (23). In patients who have had symptoms of rapid palpitations, presyncope or syncope, or those whose occupations demand further risk stratification, EP testing should be performed. In patients referred because of an ECG showing a long QT interval, investigation should proceed as discussed in Chapter 8. **The patient who has had sustained VT/ventricular fibrillation:** Further investigation is almost always necessary in patients who have already had an episode of sustained VT or ventricular fibrillation (VF). Because ischemia may frequently play a role in cardiac arrest, heart catheterization with coronary angiography should be strongly considered in most patients presenting with polymorphic VT, VF or cardiac arrest (**Grade C**). In patients presenting with wide complex tachycardia, EP testing should be considered for diagnostic purposes to differentiate VT from sustained VT and to rule out causes of VT that may be curable with

catheter ablation therapy, eg, bundle branch re-entrant VT (**Grade C**). Patients who have suffered cardiac arrest in the absence of a reversible cause are candidates for ICD therapy, as discussed in Chapters 4 and 5. EP testing is not generally recommended in such patients before ICD implantation. In patients with VF in whom an ischemic cause is suspected based on coronary angiography and noninvasive evidence of reversible ischemia, revascularization therapy is generally recommended. Although some members of the consensus panel felt that such patients should undergo EP testing following revascularization, there is no published evidence to support this view. Most panel members felt that EP testing need not be considered following revascularization when LV function is good (LVEF 0.40 or greater).

The patient presenting with syncope: In patients referred because of syncope, the prognosis generally depends on the presence of structural heart disease. In the Framingham study, isolated syncope was not associated with excessive mortality including sudden death (24). However, in patients with severe LV dysfunction, syncope carries an ominous prognosis. Middlekauff et al (25) showed in a population referred for syncope that LVEF 0.30 or less was the only independent predictor of sudden death. More than 50% of patients who had syncope and LVEF 0.30 or less had SCD over an average of two years of follow-up. On the other hand, in patients with preserved LV function, the actuarial risk of sudden death was extremely low. Furthermore, the total mortality was high in this population regardless of the mechanism of syncope (26). Therefore, the patient presenting with syncope, especially in the presence of structural heart disease or history of MI, should undergo assessment of LV function if not already performed.

In patients with LV dysfunction, inducible VT or VF at EP testing has previously been shown to be a risk factor in long term outcome (21). In addition, in the Canadian Implantable Defibrillator Study (CIDS), patients presenting with syncope but who had a low ejection fraction and inducible VT were at a risk of death similar to that of patients who had presented with sustained VT and VF. For these reasons, it is recommended that, in patients with significant LV dysfunction (LVEF 0.35 or less), EP testing be performed to determine whether sustained VT or VF is inducible (**Grade C**).

SUMMARY OF RECOMMENDATIONS

A. The patient with structural heart disease:

1. Post-MI patients should have objective determination of LV function (**Level I, Grade A**).
2. Post-MI patients should have noninvasive testing for residual ischemia (**Level V, Grade C**).

B. The patient referred for nonsustained VT:

1. Patients referred for nonsustained VT should have objective assessment of LV function (echocardiography, radionuclide angiography or LV angiogram) (**Level I, Grade A**).
2. Patients with LVEF 0.35 or less and prior MI who would be suitable candidates for an ICD should undergo EP testing to determine whether sustained VT or VF is inducible (**Level II, Grade B**).
3. Patients with LVEF 0.35 or less and prior MI who would not be suitable candidates for an ICD should not undergo an EP study but should instead be considered for empirical amiodarone therapy (**Level IV, Grade C**).

C. The patient referred because of an abnormal ECG:

1. Patients with Wolff-Parkinson-White syndrome and symptoms of rapid palpitation, syncope or presyncope should have EP testing (**Level V, Grade C**).

D. The patient who has had sustained VT/VF:

1. Such patients should be considered for coronary angiography (**Level V, Grade C**).
2. Patients with sustained wide complex tachycardia should undergo diagnostic EP testing (**Level V, Grade C**).

E. The patient presenting with unexplained syncope:

1. The patient with unexplained syncope should have determination of LV and right ventricular function (**Level V, Grade C**).
2. In patients with significant LV dysfunction post-MI LVEF 0.35 or less), EP testing should be performed to determine whether sustained VT or VF is inducible (**Level V, Grade C**).

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Chapter 3: The management of acute ventricular tachycardia or fibrillation

Paul Dorian MD MSc, François Philippon MD

Ventricular tachycardia (VT), usually defined as more than three consecutive electrocardiographic (ECG) complexes of ventricular origin at a mean rate of more than 100 beats/min, varies widely in severity and potential clinical consequences. This chapter deals with *sustained* VT, usually defined as tachycardia lasting longer than 30 s or requiring immediate treatment because of hemodynamic compromise.

All patients with sustained VT require immediate stabilization and basic life support if necessary. This includes cardiopulmonary resuscitation, artificial ventilation and immediate cardioversion if the patient is unconscious or pulseless, or if there is severe hemodynamic compromise.

If the clinical circumstances permit, a 12-lead ECG should be performed. Serum electrolytes, including potassium and magnesium concentrations, should be measured. A brief history and physical examination should be performed, considering in particular the possible presence of myocardial ischemia or acute myocardial infarction (MI). A complete drug history should be taken, and prior history of cardiac dis-ease and the circumstances surrounding the onset of the clinical arrhythmia should be assessed.

DIAGNOSIS OF VT

The vast majority of patients with wide complex tachycardia and coexisting structural heart disease have VT. However, in occasional patients the diagnosis of the cause of tachycardia remains uncertain even after obtaining a history and examining the 12-lead ECG. In such patients, administration of intravenous adenosine to obtain atrioventricular block and 'uncover' the underlying atrial rhythm may be considered but should not delay definitive therapy of the unstable patient.

Of note, most wide complex tachycardias of uncertain origin are due to VT rather than to supraventricular tachycardia (SVT) with aberrancy, particularly in older patients and in those with structural heart disease. Because administration of adenosine as a diagnostic test to differentiate VT from SVT has risks, including delay of definitive treatment, transient hypotension (1) or tachycardia acceleration in the case of ventricular pre-excitation (Wolff-Parkinson-White syndrome), its use in this setting is discouraged. Verapamil, which has been used occasionally to treat wide complex tachycardia believed to be SVT, may cause serious or life-threatening hypotension if the arrhythmia is actually VT, and intravenous verapamil is strongly discouraged unless the arrhythmia is known with certainty to be due to SVT and to be using the atrioventricular node as a necessary portion of the re-entry circuit.

It is important to note that VT may have diverse etiologies and that the appropriate treatment may depend on the specific etiology of the arrhythmia, if the latter can be established. The following sections deal with specific clinical syndromes of ventricular tachyarrhythmias according to clinical and ECG presentation.

MANAGEMENT OF TORSADE DE POINTES VT

Torsade de pointes polymorphic VT occurring in the presence of prolonged repolarization (prolonged QT interval), usually manifesting as nonsustained or sustained polymorphic runs of a VT that begin after a pause ('pause-dependent' or 'bradycardia-dependent' polymorphic VT), is best treated with intravenous magnesium, and by increasing the heart rate with temporary transvenous pacing and, in some cases, intravenous isoproterenol (2) (**Level IV, Grade**

C). In addition, correction of hypokalemia and discontinuation of any agent responsible for QT prolongation is essential.

TREATMENT OF ARRHYTHMIAS IN ACUTE MI

Patients in whom VT occurs during MI (usually manifesting as polymorphic VT beginning with a closely coupled premature ventricular complex) should be treated in the same way as patients with acute MI without sustained arrhythmias (as outlined in the Canadian Consensus Conference on the treatment of acute myocardial infarction) (3,4). Although there are no controlled data evaluating beta-blockers *after* sustained VT or ventricular fibrillation (VF) in acute myocardial infarct, intravenous beta-blockers during myocardial infarct reduce the risk of death (RR=0.87, CI 0.77 to 0.98)
(5) and may reduce the incidence of VT or VF (6,7). Intravenous beta-blockers are recommended in all patients following acute MI unless contraindications exist; this recommendation also applies to patients who develop VT or VF during the acute phase (**Level I, Grade A**).

There are no large scale, randomized clinical trials assessing the efficacy of any antiarrhythmic therapy in the prevention of *recurrence* of polymorphic VT (or VF) in acute MI, and in particular there is no evidence from controlled clinical trials that lidocaine is useful as secondary prophylaxis of VT in the setting of acute MI. There is evidence that intra-venous lidocaine, used as *primary prophylaxis* for the prevention of VF in acute MI, can reduce the incidence of VF (5). However, meta-analyses of randomized, blinded intravenous lidocaine trials for this indication show a statistically significant 62% increase in mortality over placebo (8,9), and thus the use of lidocaine for secondary or primary prophylaxis of VT in the setting of acute MI is not recommended.

MONOMORPHIC VT WITH MODERATE OR LITTLE HEMODYNAMIC COMPROMISE

In a patient with symptomatic, nonsyncopal, monomorphic VT, intravenous antiarrhythmic drug therapy or immediate cardioversion may be used. It is the consensus of the panel that

immediate synchronized cardioversion with appropriate anaesthesia is extremely effective and is often the best first line therapy for this arrhythmia. Many physicians choose to use intravenous antiarrhythmic drugs to achieve chemical cardioversion and to reduce the likelihood of recurrent VT.

If time and circumstances permit, and the expertise and equipment are available, temporary overdrive pacing can frequently terminate VT. This can be accomplished by using a temporary transvenous pacemaker and, rarely, transcutaneous overdrive pacing for very slow VT.

The risk of immediate recurrence of sustained VT is usually low to intermediate, and intravenous antiarrhythmic therapy is not obligatory after electrical cardioversion. However, in cases of hemodynamically tolerated sustained VT, it may be appropriate to administer intravenous antiarrhythmic therapy to terminate VT and to prevent early recur-rences. Drugs available for this use include intravenous lidocaine, procainamide, quinidine, bretylium and amiodarone.

With respect to the use of intravenous antiarrhythmic drugs to terminate ongoing VT, there are very few randomized controlled studies in this setting. In a small, randomized clinical trial of 29 patients with sustained VT (cycle length 379±65 ms), procainamide was substantially superior to lido-caine in restoring sinus rhythm (70% chemical conversion with procainamide versus 20% chemical conversion with lidocaine) (10). Larger, observational trials of intravenous lidocaine in VT suggest an efficacy rate between 10% and 20% in converting tachycardia to sinus rhythm (11-14). Similar open label trials of procainamide suggest a 70% to 80% conversion rate (10). Although intravenous quinidine, bretylium and amiodarone have all been used during ongoing sustained VT, there are no randomized or large scale, well documented, observational trials of any of these therapies. However, a large, multicentre, blinded, randomized trial comparing bretylium with amiodarone at standard doses and with amiodarone at doses expected to be ineffective (125 mg intravenously), in patients with recurrent sustained VT or VF resistant to lidocaine and procainamide, showed equal efficacy of standard dose amiodarone and bretylium, with a recurrence rate of 42% of VT at 24 h in a population with two or more episodes in the previous 12 h (15).

Intravenous procainamide is recommended for the treatment of monomorphic sustained VT with moderate or little hemodynamic compromise (**Level II, Grade B**).

TREATMENT OF VF

It is universally accepted that VF should be treated with immediate direct current defibrillation shocks. In addition, it is accepted that the elements comprising basic and advanced cardiac life support, including cardiopulmonary resuscitation, artificial ventilation and establishment of intravenous access, are required for all cases of VF. Discussion of other nonantiarrhythmic treatments such as adrenalin administration in this setting is beyond the scope of this document. Providing early defibrillation in addition to basic and advanced cardiac life support, and providing all elements in the 'chain of survival' as promptly as possible are strongly endorsed.

With specific reference to antiarrhythmic drugs, they either may be used during ongoing VF that is resistant to defibrillation or may be administered after successful restoration of a perfusing rhythm to prevent the recurrence of VF.

Drugs that have been advocated and studied in this setting include intravenous lidocaine, bretylium and amiodarone. Intravenous procainamide and quinidine have been little studied and are not recommended.

With respect to lidocaine, there are no randomized controlled studies that support the use of lidocaine in ongoing VF or in the secondary prophylaxis of VF. Two small randomized studies showed that lidocaine and bretylium were equivalent in the primary result of restoration of spontaneous circulation in out-of-hospital cardiac arrest (16,17). One retrospective, uncontrolled study suggested that survival improved after lidocaine compared with historical controls
(18). A larger retrospective study suggested that the use of lidocaine was associated with a lower chance of resuscitation than nonuse in in-hospital cardiac arrest, even after controlling for variables known to influence resuscitation success (19). Arandomized study of lidocaine versus adrenalin in VF resistant to one shock showed no significant difference in resuscitation

or survival rates, but showed greater incidence of asystole following defibrillation in the lidocaine group (25% after lidocaine versus 7% after adrenalin, P<0.02) (20).

Both in animals and in humans, lidocaine increases defibrillation thresholds (21,22). When used as primary prophylaxis in acute MI, the use of lidocaine is associated with an increase in mortality over that of placebo (8). Although lidocaine is advocated as first line treatment in VF by the European Resuscitation Council and the American Heart Association Committee on Resuscitation (23,24), these recommendations are not based on evidence from randomized clinical trials.

Likewise, there is no clear evidence that bretylium is effective in the treatment of shock refractory VF. As noted above, two studies showed no difference in outcome between lidocaine and bretylium treatment in cardiac arrest (16,17). One cohort study showed a worse short term outcome in bretylium recipients than in controls (19). A randomized, blinded, controlled study of bretylium in recurrent VT/VF showed a significantly higher adverse event rate than with amiodarone (15).

Intravenous amiodarone was compared with intravenous lidocaine in ongoing shock-resistant VF in a small, randomized preliminary study (n=20 patients), which showed statistically significant improvement in resuscitation rates with amiodarone versus lidocaine (25). In a recently completed large trial (the Amiodarone and Out of Hospital Resuscitation of Refractory Sustained Ventricular Tachycardia [ARREST] trial) (26), intravenous amiodarone (300 mg intravenous push) was superior to a placebo in a randomized, blinded, controlled clinical trial of 504 patients with outof-hospital VF resistant to defibrillation. The primary endpoint of survival to hospital admission was significantly higher in the amiodarone arm (44%) than in the placebo arm (34%) (P<0.05). In the subgroup of patients with transient return of pulse during the resuscitation and subsequent recurrence of VF, the survival to hospital rates were 64% in the amiodarone versus 41% in the placebo arm (26). Although this study did not show improved survival to hospital discharge following amiodarone, it is the only study to show the value of any pharmacological therapy in a randomized, blinded comparison with placebo or an alternative therapy. In view of this trial, patients with VF resistant to defibrillation should be treated with intravenous amiodarone (**Level II, Grade B**).

ELECTRICAL STORM

'Electrical storm' is usually defined as frequent recur-rences of hemodynamically unstable sustained VT or VF within a short period of time, usually two or more episodes within a 24 h period. Most patients suffering from high frequency, life-threatening arrhythmias have substantial left ventricular dysfunction, myocardial ischemia, heart failure or all of the above. Case series suggest that lidocaine and procainamide are relatively ineffective at preventing recur-rences of ventricular arrhythmias in this setting (15). One large study, partially detailed above, compared intravenous amiodarone with intravenous bretylium in patients with two or more (mean 4.93) episodes of sustained VT or VF in the previous 24 h. In this blinded, randomized study, the use of either drug at standard doses was associated with an approximately 50% recurrence rate of arrhythmia within the first 24 h. The median number of events within the first 12 h was
0.0 following amiodarone 1.0 g/24 h, 1.92 following bretylium 2510 mg/24 h and 1.92 following amiodarone 125 mg/24 h (15). Although bretylium and amiodarone were equally effective in the blinded intention-to-treat analysis in this study, significantly more patients on bretylium had serious adverse effects (58% versus 42%, P=0.01).

Patients with electrical storm (two or more episodes of sustained VT or VF within 24 h) may be treated with intra-venous amiodarone or intravenous bretylium (**Level II, Grade B**), although amiodarone is most likely to be tolerated.

SUMMARY

The treatment of VT and VF is complex. The etiology, severity and long term prognosis of patients with varying forms of VT and VF differ substantially. In addition to the immediate stabilization and cardioversion/defibrillation of patients with substantial hemodynamic compromise, a thorough review of possible causative or contributing factors to ventricular tachyarrhythmia and therapy directed at the underlying cause, if possible, is important. If no specific treatable causes are found, antiarrhythmic drug therapy can be useful. Selection of a particular drug should depend on the clinical trial evidence, if available, that supports drug

efficacy. Importantly, physicians need to monitor patients carefully for adverse effects and inefficacy, and stop therapy if these are observed.

THE MANAGEMENT OF ACUTE VT OR VF RECOMMENDATIONS

A. Patients with polymorphic VT and QT prolongation:

These patients should be treated with intravenous magnesium, temporary pacing or intravenous isoproterenol (**Level IV, Grade C**).

B. Patients with VT or VF complicating acute MI:

Intravenous beta-blockers are recommended in all patients following acute MI unless contraindications exist; this recommendation also applies to patients who develop VT or VF during the acute phase (**Level I, Grade A**).

C. Patients with hemodynamically tolerated sustained monomorphic VT:

Intravenous procainamide is recommended for the treatment of monomorphic sustained VT with moderate or little hemodynamic compromise (**Level II, Grade B**).

D. Patients with shock-resistant VF:

Patients with VF resistant to defibrillation should be treated with intravenous amiodarone (**Level II, Grade B**).

E. Patients with electrical storm:

Patients with electrical storm (two or more episodes of sustained VT or VF within 24 h) may be treated with intravenous amiodarone or intravenous bretylium (**Level II, Grade B**).

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Chapter 4: Long term management of the survivor of ventricular fibrillation or sustained ventricular tachycardia

Stuart J Connolly MD, Andrew Krahn MD, George Klein MD

It has been widely accepted for many years that patients who survive ventricular fibrillation (VF) or sustained monomorphic ventricular tachycardia (VT) are at high risk for sudden death due to a recurrence of one of these arrhythmias. Cohort follow-up studies from the 1970s indicate that these patients have a risk of death in the range of 10% to 15%/year (1). The risk of subsequent death is considerably less in those who have had recent myocardial infarction (MI) than in those who have not had acute MI at the time of their cardiac arrest. It is accepted that patients who have survived a cardiac arrest or sustained VT who do not have recent MI should be treated because the risk of recurrence is high. For this reason, no placebo controlled trials have been performed in these patients. The major clinical question addressed by clinical trials is the relative merit of different treatment strategies, in particular, comparison of the implantable cardioverter defibrillator (ICD) and antiarrhythmic drug therapy.

Although there are many causes of cardiac arrest and sustained VT, the vast majority of patients presenting with these arrhythmias have ischemic heart disease and prior MI. The remaining patients usually manifest some other form of myocardial disease. Rarely, patients have structurally normal hearts. The patient surviving VF or sustained VT typically has multivessel coronary artery disease and reduced left ventricular function. Comorbid noncardiovascular conditions such as diabetes, chronic lung disease and cerebral vascular accident are not uncommon. Thus, although these patients are at high risk for recurrence of arrhythmia, there are also significant competing risks for death from nonar-rhythmic causes.

TRIALS OF ANTIARRHYTHMIC DRUG THERAPY

One randomized trial has compared two antiarrhythmic drug strategies in cardiac arrest survivors. The Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) enrolled 228 patients with cardiac arrest who were randomized to receive either amiodarone therapy or a therapeutic strategy that consisted primarily of Vaughan-Williams class I antiarrhythmic drug therapy guided by serial ambulatory electrocardiographic monitoring or electrophysiological testing (2). Half-way through the study, all patients also received an ICD in addition to randomized therapy. The risk of the primary outcome, a composite of cardiac death, sustained VT/VF or syncopal ICD shock, was significantly reduced by amiodarone. At four years of follow-up, event-free survival was 52% for amiodarone and 36% for the conventional arm, a 44% increase. Cardiac death and all-cause mortality rates were also lower with amiodarone. Although this is a small study, it does provide some support for a benefit of amiodarone over Vaughan-Williams class I antiarrhythmic drugs.

There is other evidence that amiodarone may be a useful antiarrhythmic drug for the prevention of VT or VF. Thirteen randomized, controlled trials of amiodarone were performed in patients with recent MI or congestive heart failure. These trials were designed to determine whether amiodarone could reduce mortality in these high risk populations. Some of these trials did show a reduction in mortality, but several others failed to demonstrate convincingly that amiodarone was beneficial. A meta-analysis of all 13 of these trials, however, showed that there was a 29% reduction in arrhythmic death with little effect on other causes of death (P=0.003) (3). There was a 13% reduction in all-cause mortality (P=0.03). This meta-analysis provides moderate support for the notion that amiodarone is an effective antiar-rhythmic agent. In addition, there is considerable clinical experience in many countries supporting the idea that amiodarone is an effective drug for suppressing VT and VF.

The ICD was developed in the 1970s and introduced in the early 1980s. Since that time, it has evolved from a rather crude, inflexible instrument capable of delivering shocks for tachycardia into a highly sophisticated, multiprogrammable device that can be implanted by means of a

simple operation requiring little more than local anesthesia. There is a vast amount of direct evidence that the ICD terminates VT and VF, not only in the controlled setting of the operating room or the electrophysiology laboratory, but also in patients experiencing spontaneous arrhythmias. The internal data storage capability of modern ICDs amply demonstrates that these devices can terminate what in all likelihood would be lethal ventricular arrhythmias. Notwithstanding this direct information, there was considerable concern that ICD therapy may not prolong life compared with antiarrhythmic drug therapy, not only because antiarrhythmic therapy alone likely is effective against these arrhythmias, but also because of the substantial competing risk of death from nonarrhythmic causes that the typical cardiac arrest survivors faces. In other words, the benefit of the ICD may be rather small because ICD patients surviving a subsequent cardiac arrest may go on to die from ongoing left ventricular dysfunction or recurrent ischemia.

For these reasons, three randomized, controlled trials were performed comparing medical therapy with ICD therapy. In the Canadian Implantable Defibrillator Study (CIDS), the ICD was compared with amiodarone (4). In the Cardiac Arrest Study Hamburg (CASH), the ICD was compared with three medical approaches: the class I antiarrhythmic drug propafenone; the beta-blocker metoprolol; and amiodarone (5). In the Antiarrhythmics Versus Implantable Defibrillators (AVID) Study, the ICD was compared with 'best medical therapy', which was either guided sotalol therapy or amiodarone (6). However, only 2% of patients in the treatment arm actually received sotalol at discharge in the AVID study. Thus, it was essentially a comparison of ICD with amiodarone. The AVID study enrolled 1016 patients, CIDS enrolled 659 patients, and CASH enrolled 191 into the amiodarone versus ICD comparison. The AVID study was terminated early because of a greater than expected reduction in mortality with the ICD. At two years, there was a reduction in mortality of 27±21% ($P<0.02$). In CIDS there was a nonsignificant reduction of risk of death with the ICD from 10.2%/year to 8.3%/year (19.7% relative risk reduction, $P=0.142$). In CASH there was a similar nonsignificant relative risk reduction in overall mortality with the ICD compared with either amiodarone or metoprolol. The propafenone arm of CASH was terminated prematurely because of excessive mortality in this group.

In a meta-analysis of the three trials of the ICD versus amiodarone (unpublished data), 934 patients were randomized to ICD and 932 to amiodarone. Patients were a mean age of 64 years, and 81% were male. The mean left ventricular ejection fraction (LVEF) of the ICD patients was 34% compared with 33% of the amiodarone patients; 81% of both groups had coronary artery disease. Fifty per cent of patients presented with VF, and the remainder presented with either VT or unmonitored syncope. Eight per cent of patients had an epicardial ICD, and the remainder had a nonthoracotomy implant. In the meta-analysis, there was a highly significant mortality reduction with the ICD with a hazard ratio 0.73 (95% CI 0.59 to 0.89, P=0.003). The three studies were internally consistent. There was an even greater effect on the outcome of arrhythmic death, with an overall hazard ratio in favour of the ICD of 0.48 (95% CI 0.32 to 0.73, P=0.0005). The fact that most of the ICD benefit occurs by means of a reduction in death from arrhythmia, with little change in other causes of death, lends biological plausibility to the results of these trials.

In CIDS and AVID, there was an imbalance in the use of beta-blockers, with ICD patients significantly more likely to receive a drug of this class than patients randomized to amiodarone. It is thus possible that some of the beneficial effect of the ICD in these studies was due to increased use of a beta-blocker. Subgroup analysis from the meta-analysis indicates, however, that the ICD treatment effect is not significantly different for patients on, or not on, beta-blockers at baseline. Furthermore, the CASH study did not experience this beta-blocker imbalance but observed a benefit of ICD therapy over amiodarone that is similar to that of CIDS and the AVID study. These two considerations suggest that the beta-blocker imbalance is a minor factor in these trials.

Meta-analysis indicates a 27% reduction in mortality with the ICD over a mean follow-up period of 2.3 years. The ICD extended life on average by 4.4 months at six years of follow-up. The annual mortality rate on amiodarone was
12.3%, and this was reduced to 8.7% with the ICD. Therefore, implanting an ICD in 10 patients, rather than using amiodarone alone, prevents one death over the first three years of follow-up.

In summary, there is convincing evidence that the ICD is superior to amiodarone in patients who have had VF or symptomatic sustained VT. There is a 25% to 30% reduction in mortality, which is almost entirely due to a 50% reduction in deaths related to ventricular arrhythmia. Because there are substantial competing risks of nonarrhythmic death in these patients, the magnitude of the benefit of the ICD is only moderate. Nonetheless, on the basis of the clear evidence of ICD superiority from randomized controlled trials, it is the recommendation of the consensus conference that, in general, the typical patient with VF or sustained VT not related to acute MI or other correctable cause should receive an ICD as their primary mode of management for the prevention of death due to recurrent arrhythmia (**Level I, Grade A**).

There are many gradations of VT presentation. The most severe cases present with cardiac arrest or syncopal episode. Some VT patients maintain consciousness but have varying degrees of symptoms. The CIDS and AVID studies included patients whose VT episode caused cardiac arrest or syncope, and those in whom LVEF was less than 35%. Therefore, the recommendation of the consensus conference for management of sustained VT applies only to patients with VT causing cardiac arrest or syncope, or with LVEF less than 35%. The benefit of the ICD over amiodarone on survival in patients with well tolerated VT is not defined by clinical trials, but is likely minimal.

Some patient subgroups were not well represented in these randomized trials. Patients with cardiac arrest who are found to have severe coronary stenosis and normal left ventricular function are not common and were not well represented in the ICD trials. Coronary bypass graft surgery without ICD implantation would be a reasonable therapy in VF survivors with critical coronary artery stenosis and well preserved left ventricular function. It is also reasonable that therapy be individualized in patients with severe comorbidity or in the very elderly.

RECOMMENDATIONS

A. Patients surviving cardiac arrest or symptomatic sustained VT (not within three days of acute MI and not associated with correctable cause):

1. Patients with VF should receive an ICD (**Level I, Grade A**).
2. Patients with VT causing syncope should receive an ICD (**Level I, Grade A**).
3. Patients with minimally symptomatic VT with LVEF 35% should receive an ICD (**Level I, Grade A**).
4. Patients with minimally symptomatic VT and LVEF greater than 35% should receive either pharmacological therapy or an ICD (**Level V, Grade C**).

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Chapter 5: Treatment approaches for patients with sustained VT/VF

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Over the years, treatments that have been proposed for the prevention of ventricular tachycardia/ventricular fibrillation (VT/VF) and sudden death in patients with a known propensity to VT/VF have included empirical antiar-rhythmic drug therapy (1), individualized antiarrhythmic drug therapy selected by a noninvasive approach (Holter monitoring) (2,3), individualized antiarrhythmic drug therapy selected by an invasive approach (electrophysiological testing) (4-6), empirical amiodarone therapy (7,8), empirical beta-blocking drug therapy (9), coronary revascularization with or without blind aneurysmectomy (10), catheter ablation or electrosurgical therapy (11,12), and implantable cardioverter defibrillator (ICD) therapy (13,14). In this chapter, we discuss each of these approaches and briefly comment on their roles in contemporary VT/VF therapy. Subsequent chapters will discuss the results of direct comparisons of these approaches. As will be highlighted then, the approaches to VT/VF therapy other than the use of an ICD are reserved for patients with relative contraindications to ICD placement and for patients with hemodynamically well tolerated VT who are at lower risk of sudden death.

EMPIRICAL ANTIARRHYTHMIC DRUG THERAPY

The first treatment proposed for the prevention of VT/VF was the empirical use of antiarrhythmic drugs. With the exception of amiodarone (see below), the follow-up probabilities of VT/VF recurrence or sudden death in patient populations treated with an empirically chosen

antiarrhythmic drug from class I or class III are no better than those of untreated historical controls. Indeed, in some instances, the follow-up VT/VF recurrence or sudden death probabilities may actually have been worsened by empirical standard anti-arrhythmic drug therapy by virtue of antiarrhythmic drug proarrhythmia (15). Accordingly, patients with VT/VF should not be treated with empirical antiarrhythmic drug therapy other than amiodarone.

INDIVIDUALIZED ANTIARRHYTHMIC DRUG THERAPY

To date, two approaches to individualized antiarrhythmic drug therapy for patients with VT/VF have been described. The noninvasive approach (2,3) uses spontaneous ventricular arrhythmias as an index of electrical instability. Therapy is then predicted to be effective in long term use if it sufficiently suppresses this index. When this approach is used, a therapy that is predicted to be effective can be found for 80% of VT/VF patients (15). The invasive approach (4-6) uses inducible VT/VF at a catheter electrophysiological study as the index of electrical instability. Therapy is then predicted to be effective in long term use if it suppresses VT/VF inducibility. When this approach is used, a therapy that is predicted to be effective in long term use is found for only 45% of VT/VF patients (15). Comparisons of the outcomes of patients treated with individualized antiarrhythmic drug therapy that is predicted to be effective versus those of patients treated with individualized antiarrhythmic drug therapy that is predicted to be ineffective suggest either that predictedeffective drug therapy prevents arrhythmia recurrence and sudden death or that predicted-ineffective drug therapy increases the probability of arrhythmia recurrence and sudden death (3,6). In the absence of a concurrent untreated control group, historical controls have been used to support the first of these two possibilities. Although the first randomized clinical trial of these two approaches to individualized anti-arrhythmic drug therapy selection found the invasive approach to be superior to the noninvasive approach (16), a later trial found the two approaches to be equivalent (17). A randomized trial of the efficacy of various antiarrhythmic drugs undergoing assessment by these approaches to individualized antiarrhythmic drug therapy indicated that sotalol therapy was more likely than other therapies to be predicted to be effective and then to prove to be effective in long term use (18). Accordingly, selected patients with VT/VF may be treated with

individualized standard antiarrhythmic drug therapy selected by either the noninvasive or the invasive approaches. In contemporary practice, the patients most often treated in this fashion are those with well preserved left ventricular function whose arrhythmia is well tolerated VT. In such patients, many practitioners prescribe sotalol therapy if it is predicted to be effective by the invasive approach.

EMPIRICAL AMIODARONE THERAPY

Empirical amiodarone was first suggested for VT/VF patients when no effective standard antiarrhythmic drug therapy could be found (7,8). At that point, amiodarone was being used in patients for whom there were no other treatment alternatives where a prediction of amiodarone failure had no clinical utility. Because the outcomes of patents treated with empirical amiodarone therapy were good, with a low two-year probability of VT/VF recurrence, the practice of prescribing amiodarone therapy empirically became firmly established. Accordingly, empirical amiodarone is appropriate therapy for selected patients with VT/VF.

EMPIRICAL BETA-BLOCKING DRUG THERAPY

Empirical beta-blocking drug therapy has been suggested to be a treatment alternative for some patients with VT/VF. Specific VT/VF populations suggested to respond to beta-blocking drug therapy include those without identifiable structural heart disease, those with some forms of the long QT interval syndrome, those with reversible myocardial ischemia, those with mitral valve prolapse, those with idiopathic right ventricular outflow tract VT and those whose VT/VF has an exercise trigger. Some investigators have also suggested empirical beta-blocking drug therapy for the more common forms of VT/VF that occur in patients with structural heart disease (9). At the very least, there is substantial evidence of the importance of beta-blocking therapy as an adjunctive treatment in VT/VF patients (19). Accordingly, patients with VT/VF and structural heart disease should not be treated with empirical beta-blocking drug therapy alone. Nevertheless, combining beta-blocking drug therapy with the other specific forms of antiarrhythmic therapy is advisable.

REVASCULARIZATION THERAPY

Coronary artery bypass grafting with or without left ventricular aneurysmectomy was the first nonpharmacological approach to VT/VF prevention (10). Although some success was reported, the probability of recurrent VT/VF in patients so treated remained high. Nevertheless, coronary revascularization remains an important adjunctive treatment for patients with VT/VF in the setting of atherosclerotic heart disease, by removing ischemia as a VT/VF trigger and by enhancing the efficacy of specific antiarrhythmic therapy. Revascularization is only a primary antiarrhythmic treatment for the prevention of VT/VF that is clearly ischemic in origin. Patients with coronary artery disease whose VT/VF occurs in association with strong symptomatic or electrocardiographic evidence of reversible myocardial ischemia, those whose VT/VF is reproducibly precipitated by exercise testing and those whose VT/VF occurred during a critical life experience may be considered to be in this category. The vast majority of patients in this category present with rapid polymorphic VT or VF rather than with slower monomorphic VT. These very carefully selected patients with VT/VF may be treated by coronary revascularization alone. Whether the efficacy of revascularization therapy for this purpose can be adequately predicted by a postoperative electrophysiological study remains controversial.

ABLATION/ISOLATION OF THE ARRHYTHMOGENIC SUBSTRATE

Electrosurgical or transcatheter ablation therapies are alternatives for patients with a focal origin for their VT/VF (11,12). These procedures are designed to destroy the focal origin of the tachyarrhythmia or to isolate it from the rest of the ventricular myocardium. Given our understanding of the mechanisms of VT/VF, these approaches are limited to patients with monomorphic VT. The best candidates for trans-catheter ablation procedures are those with VT in the absence of underlying structural heart disease. Such patients include those with idiopathic right ventricular outflow tract VT (20) or idiopathic left septal VT (21). Bundle branch re-entrant VT (22), which can occur with dilated cardiomyopathy, is also very well treated in this way. Patients with atherosclerotic heart disease, a single prior myocardial infarction, preserved left ventricular systolic function, monomorphic VTs with a limited number of morphologies and an independent indication for cardiac surgery are the best candidates for

electrosurgical treatment. Most centres offering this option use map-guided approaches to target the ablation or isolation surgical procedure. Accordingly, electrosurgical or transcatheter ablation/isolation of the arrhythmogenic substrate is an appropriate therapy for selected patients with VT.

THE ICD

The most recent nonpharmacological approach to the treatment of VT/VF is the ICD (13,14). The components of present-generation devices can usually be limited to the impulse generator, and a single lead with a pacing/sensing pair and a high voltage coil for direct current shock delivery implanted in the same way as a VVI pacemaker. The clear superiority of the biphasic shock waveform, with reversal of shock polarity midway along a truncated exponential waveform, has made it the industry standard. This simple system provides adequate defibrillation safety margins for over 90% of patients. More recently, dual-chamber ICDs have been approved for use. All of these devices are capable of dual chamber sensing/pacing, and some are also capable of dual chamber arrhythmia detection and treatment. In their present form, these devices do not prevent VT/VF. Instead, the ICD awaits the spontaneous occurrence of VT/VF and then reacts automatically to terminate the VT/VF. Current generations of the ICD provide a tiered therapy response that allows different ICD responses for VT/VF with different characteristics, using painless pacing algorithms to terminate slower, organized VT while reserving painful direct current shocks for faster, disorganized VT or VF. The major criterion used by an ICD to identify the presence of VT/VF is the ventricular rate sensed by the ventricular sensing electrode pair. Accordingly, without supplemental criteria, the ICD may have difficulty differentiating supraventricular tachyarrhythmias, especially sinus tachycardia and atrial fibrillation, from VT/VF. The supplemental criteria available in single-lead ICDs include suddenness of onset (to prevent ICD treatments for sinus tachycardia) and ventricular regularity (to prevent ICD treatments for atrial fibrillation). Newer, dual-chamber ICDs also evaluate the relationships between atrial and ventricular activation sequences to discriminate further between atrial and ventricular tachyarrhythmias. Accordingly, the ICD is appropriate therapy for selected patients with VT/VF.

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Chapter 6: The role of prophylactic implantable cardioverter defibrillators to prevent sudden cardiac death

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As discussed in Chapter 1, sudden cardiac death is a major public health problem affecting thousands of Canadians each year. Although the underlying mechanism of death is a sustained ventricular arrhythmia in most, the majority of patients with cardiac arrests have no prior history of ventricular arrhythmia. Unfortunately, resuscitation rates for cardiac arrest are extremely poor (fewer than 5% of victims survive hospital discharge [1,2]). As a result, although survivors of cardiac arrest have a high subsequent risk of sudden death, these patients account for a very small proportion of all patients who ultimately die from a ventricular arrhythmia (3).

Thus, the current strategy of implantable cardioverter defibrillator (ICD) implantation in patients with a prior history of sustained ventricular arrhythmias (discussed in Chapter 4), while having a major effect on individual health, has little effect on the health of the general population. If resuscitation rates remain low and if the number of patients with underlying structural heart disease who are at risk for sudden death remains high, then a prophylactic strategy is needed to decrease the incidence of sudden death in the general population.

POTENTIAL TARGET POPULATIONS

The incidence of sudden death in the general population is too low, and the financial and social implications are too high at present to consider the use of prophylactic ICDs in large

populations. Instead, these devices should be considered in specific populations where the risk of sudden death is high and clinical studies have demonstrated that ICDs decrease risk.

A number of risk factors for sudden death have been evaluated in different populations (Chapters 2, 7 and 8). These include a family history of sudden death in patients with a genetically transmitted cardiac disease, and the presence of left ventricular (LV) dysfunction, ventricular ectopy, nonsustained ventricular tachycardia (VT), inducible VT, abnormal heart rate variability, ventricular late potentials and T wave alternans, among others. However, of these, only the presence of late potentials, LV dysfunction, inducible VT and nonsustained VT have been evaluated in therapeutic trials involving the prophylactic use of ICDs. The role of prophylactic ICDs in asymptomatic patients with a genetically transmitted cardiac disease is discussed in Chapter 8.

TABLE 1

Prophylactic implantable cardioverter defibrillator trials - Clinical characteristics

	MADIT	MUSST	CABG Patch
Number	196	704	900
Male (%)	94	90	84
Left ventricular ejection fraction (average %)	26	29	27
New York Heart Association functional class II or III (%)	65	64	73
Positive signal-averaged electrocardiogram (%)	67	Unknown	100
Nonsustained ventricular tachycardia (%)	100	100	Unknown
Inducible ventricular tachycardia (%)	100	100	Unknown

CABG Coronary artery bypass grafting; MADIT The Multicenter Automatic Defibrillator Implantation Trial; MUSST The Multicenter Unsustained Tachycardia Trial

TABLE 2

Prophylactic implantable cardioverter defibrillator (ICD) trials - Effect of ICD on outcome

	MADIT	MUSST*	CABG Patch
Average follow-up (months)	27	39	32
Actuarial mortality			
Follow-up time (years)	4	5	4
Control group (%)	51	48	24
ICD group (%)	29	24	27
Number of lives saved/1000 patients treated	220	240	0

**Nonrandomized comparison. CABG Coronary artery bypass grafting; MADIT The Multicenter Automatic Defibrillator Implantation Trial; MUSST The Multicenter Unsustained Tachycardia Trial*

CLINICAL STUDIES TO DATE

Three studies have evaluated the use of ICDs for prophylactic indications (Tables 1,2). The Multicenter Automatic Defibrillator Implantation Trial (MADIT) recruited 196 patients with a prior myocardial infarction (MI), LV dysfunction (ejection fraction [EF] 35% or less) and spontaneous asymptomatic nonsustained VT (4). Once identified, all patients had to have inducible sustained VT during programmed ventricular stimulation. In addition, this VT remained inducible after intravenous administration of procainamide. These patients were randomized to a therapeutic strategy that included ICD implantation versus one in which medical therapy alone was employed. After a mean follow-up of 27 months, 15 of 95 patients assigned to receive a defibrillator died versus 39 of 101 patients receiving medical therapy alone. This 54% reduction in total mortality was highly statistically significant.

The Coronary Artery Bypass Grafting (CABG) Patch trial recruited 900 patients with LV dysfunction (EF 35% or less) and an abnormal signal-averaged electrocardiogram scheduled

to undergo coronary artery bypass surgery (5). Patients were randomized to receive a prophylactic ICD versus standard care without specific antiarrhythmic therapy. No differences in mortality between groups were noted after a mean follow-up of 32 months (101 deaths in 446 ICD patients versus 95 deaths in 454 control patients). In a subsequent analysis, arrhythmic deaths accounted for 30% of all deaths. ICD therapy significantly reduced the risk of ar-rhythmic death (6).

The Multicenter Unsustained Tachycardia Trial (MUSTT) evaluated 2202 patients with asymptomatic nonsustained VT, coronary artery disease and LVEF 40% or less (7). All patients underwent programmed electrical stimulation, and 767 (35%) had inducible sustained VT. Of these, 704 agreed to be randomized to electrophysiologically (EP) guided therapy versus no antiarrhythmic therapy. After a median follow-up of 39 months, the primary endpoint of ar-rhythmic death or resuscitation from a cardiac arrest was reduced by 27% in inducible patients assigned to EP-guided therapy (P=0.043). This was also associated with a trend toward reduced mortality (20% reduction, P=0.06).

Subsequent analysis of MUSTT revealed that the reduction in arrhythmic death and total mortality occurred exclusively in patients in whom EP testing showed that antiarrhythmic therapy would not be effective and who received an ICD. Total mortality after five years was 55% in patients treated medically with antiarrhythmic drugs (a rate similar to that in patients randomized to no antiarrhythmic therapy) versus only 24% in patients receiving an ICD. In addition, ICD use was identified as a strong predictor of survival independent of all available clinical factors in a Cox proportional hazards model.

In summary, the two studies in which coronary patients with LV dysfunction and asymptomatic nonsustained VT were studied have demonstrated improved survival with a treatment strategy that included the use of the ICD. Both studies included patients with severely depressed EF (the average EF in MADIT and MUSTT was 26% and 29%, respectively) and had a high mortality rate in the absence of ICD therapy (approximately 50% after five years) (Table 2). This mortality rate is similar to that observed in patients after resuscitation after a cardiac arrest

(see Chapter 4). In addition, spontaneous nonsustained VT and inducible sustained VT were prerequisites for ICD use in both studies. Lack of VT suppression by procainamide was mandatory for inclusion in MADIT but was not incorporated into the EP protocol used in MUSTT. Because suppression of inducible VT by procain-amide occurs in a minority of cases and because both studies had similar outcomes, repeat testing after procainamide does not appear to be essential to identify a group at high risk for sudden death. In contrast, the CABG Patch trial, which was negative, only included patients undergoing revascularization and had no requirement for either spontaneous or inducible arrhythmia. Of note, control group mortality in CABG Patch was much lower (24% after four years) than in either MADIT or MUSTT.

One key issue that has not been addressed adequately by these studies is whether routine Holter monitoring should be used in coronary patients with LV dysfunction. As discussed in Chapter 2, no systematic screening strategy was used to identify patients eligible for MADIT or MUSTT. Thus, the applicability of these results to a population in which nonsustained VT is found by routine screening strategy is not certain.

The absolute magnitude of the mortality benefit observed in MADIT and MUSTT was relatively high (Table 2). According to the data from MADIT, approximately 220 lives would be saved after four years for every 1000 patients treated, whereas MUSTT data suggest that the magnitude of benefit would be approximately 240 lives saved for every 1000 patients treated with an ICD for five years.

However, it should be noted that there was no randomized comparison of ICD use in MUSTT. Nonetheless, differences between control and EP-guided arms were magnified in centres where ICD use was high and in all centres during the later stages of the trial as ICD use became more popular in patients randomized to EP-guided therapy. MADIT was a relatively small study with a number of limitations. In particular, beta-blockers were underprescribed in the medical arm, and there was no true control group without antiar-rhythmic therapy. In addition, only one-half of the patients in the medical arm were receiving amiodarone by the end of the trial. Both MUSTT and MADIT excluded patients in whom severe concurrent noncardiac disease limited expected survival. In addition, patients over the age of 80 years were excluded

from MUSTT, and both studies excluded patients with class IV heart failure. Thus, the benefit of EP testing and ICD therapy in these very ill patients remains unproven.

In light of the results of MADIT and MUSTT, an EP study is recommended in coronary patients with asymptomatic nonsustained VT (three or more consecutive beats at a rate greater than 100 beats/min) and LVEF 35% or less. Patients undergoing an EP study for this indication and in whom a sustained ventricular arrhythmia is induced should receive a prophylactic ICD. In view of the limitations of these studies noted above, these recommendations were categorized as Grade B by the consensus conference based on Level II evidence. Patients in whom an ICD is judged to be inappropriate (eg, class IV congestive heart failure [CHF]) should not undergo EP testing and should be considered for amiodarone therapy (see Chapter 7).

ONGOING AND FUTURE STUDIES

The present data suggest that the ICD is beneficial in coronary patients with LV dysfunction, spontaneous nonsustained VT and inducible sustained VT. However, the risk of sudden death is substantial in other patient groups. There are ongoing studies with less restrictive entrance criteria:

MADIT II, which is randomizing 1200 patients with an old MI and EF 30% or less to receive an ICD or to receive usual therapy (8);

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), with 2500 patients with class II and III CHF and EF 35% or less randomized to best CHF therapy (including angiotensin-converting enzyme inhibitor and beta-blocker, if possible), best CHF therapy and an ICD, or best CHF therapy and amiodarone (9);

Defibrillators in Acute Myocardial Infarction Trial (DINAMIT), a study of 525 patients after a recent MI with LV dysfunction and low heart rate variability who are randomized to receive or not receive an ICD;

The Beta-blocker Strategy plus ICD (BEST-ICD) trial, which is recruiting 1200 patients early after MI with LV dysfunction and more than nine premature ventricular complexes/h, decreased heart rate variability or an abnormal signal-averaged

electrocardiogram (10). Patients must tolerate beta-blocker therapy and are randomized to EP-guided therapy or to no antiarrhythmic therapy.

RECOMMENDATIONS

1. Patients who have had previous MI with LV dysfunction (EF 35% or less) and asymptomatic spontaneous nonsustained VT who would be suitable candidates for an ICD should undergo an invasive EP study to determine the inducibility of VT or ventricular fibrillation. If sustained VT or ventricular fibrillation is induced, the patient should receive an ICD (**Level II, Grade B**).

2. Patients with LVEF 35% or less and prior MI who would not be suitable candidates for an ICD should not undergo an invasive EP study, but should instead be considered for empirical amiodarone therapy (see Chapter 7) (**Level V, Grade C**).

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Chapter 7: Antiarrhythmic therapy for the prevention of sudden cardiac death

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Heart disease, most often coronary artery disease, accounts for approximately 40% of deaths in western societies (1). Of deaths among those with coronary artery disease, about half may be described as sudden, occurring within 1 h of the onset of the symptoms of the fatal event in a patient who would have otherwise been expected to survive for some months. Heart failure may be defined as a condition in which the heart is unable to generate sufficient cardiac output to supply the body's oxygen demands, while maintaining normal ventricular volumes and end-diastolic pressures. Congestive heart failure (CHF) occurs most commonly as a result of coronary artery disease but may be caused by a variety of other cardiac conditions. Approximately 50% of deaths among patients with CHF are sudden (2). Although the exact mechanism of death in patients who die suddenly is not always clear, careful community studies suggest that ventricular arrhythmias, usually ventricular tachycardia (VT) or ventricular fibrillation (VF), are the immediate cause of death in most and are usually precipitated by an acute ischemic event (3-5).

Coronary care units were first established in the 1960s with the identification of VF as the etiology of most early deaths in acute myocardial infarction (AMI). Development of the cardiac monitor, the techniques of cardiopulmonary resuscitation and the external defibrillator allowed the early detection and effective treatment of VF. Intravenous anti-arrhythmic drugs, initially used to treat life-threatening ventricular arrhythmias, were recommended for prophylaxis

against VF, initially to suppress warning arrhythmias and eventually for prophylaxis against VF for most patients during the acute phase of myocardial infarction (MI). Experiences with management in the coronary care unit of patients with AMI generated a rationale for the use of long term oral antiarrhythmic therapy as prophylaxis against life-threatening ventricular arrhythmias among hospital survivors of MI.

POST-AMI TRIALS

Six randomized trials of class I antiarrhythmic drugs were reported during the 1970s and 1980s (6). No study demonstrated a benefit of therapy, and there was a negative trend in four of the six trials. Eventually, Furburg (6) raised concerns about small sample size, the failure to select high risk patients and the use of drugs of relatively low antiarrhythmic potency.

A series of observational cohort studies reported during the 1980s delineated the mortality rates and predictive factors among survivors of AMI. These studies generally found that the occurrence of premature ventricular complexes (PVCs) among survivors of MI was a predictive factor for subsequent death, and the risk increased with the frequency and complexity of PVCs (7). Later studies showed that left ventricular (LV) dysfunction was the most powerful predictor of subsequent mortality, but that both LV dysfunction and PVCs contributed independently to mortality risks (8,9). The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI-2) study (10), in which all patients received either streptokinase or tissue-type plasminogen activator, showed that overall hospital and follow-up mortality had dropped sharply from the prethrombolytic era, but that LV dysfunction and PVCs continued to be independent predictors of subsequent mortality among survivors of AMI.

The Cardiac Arrhythmia Suppression Trial (CAST) (11) was designed to overcome deficiencies in the earlier trials of prophylactic antiarrhythmic therapy. The key underlying strategies were the selection of higher risk patients and the demonstration of marked PVC suppression as a predictor of drug efficacy for mortality reduction. The trial was conducted among survivors of recent MI with LV dysfunction and frequent PVCs demonstrated on Holter monitor. A prior pilot

study allowed the selection of three new antiar-rhythmic drugs (encainide, flecainide and moricizine) that very effectively suppressed PVCs, and were well tolerated and apparently safe (12). Each patient was evaluated for PVC suppression, which had to be achieved with one of the three drugs, before randomization to that drug or placebo, and follow-up was planned for up to two years. The trial had to be interrupted early after a mean follow-up of only 10 months because of a marked excess of all-cause mortality and arrhythmic death with both encainide and flecainide. It became apparent that the study protocol had led to the selection of a relatively low risk cohort.

The investigators carried on with CAST II (13), with some important changes: evaluating only moricizine versus placebo, lowering the LV ejection fraction (LVEF) criteria to 40% or less, including patients with VT runs of 15 beats or more but lasting 30 s or less, and limiting pre-entry Holter monitoring to no more than 90 days. This trial was also terminated early because of excess mortality with moricizine during the initial 14 days of treatment ($P<0.02$) and the unlikelihood that any advantage of moricizine would appear with continuation of the study.

A definitive meta-analysis of antiarrhythmic drug therapy among survivors of AMI summarized the results of all randomized trials of class I agents (14). Among patients randomized in trials of class I agents, there was a consistent trend toward harm in trials of class IA, IB and IC drugs, with a 14% excess in overall mortality ($P=0.03$).

The inefficacy of class I agents led investigators to evaluate drugs with class III activity, particularly amiodarone, which also has class I, II and IV actions (15). By the late 1980s, amiodarone was increasingly widely regarded as the most effective drug for the prevention of life-threatening ventricular arrhythmias, and was the most commonly used agent to treat patients at high risk for VT and VF when an invasive electrophysiological study (EPS) had failed to identify a drug that prevented arrhythmia induction. Several factors prompted the initiation of amiodarone trials, including increasing recognition of its efficacy, development of rational approaches to limiting its potentially harmful side effects, increasing and consistent data for the high mortality risk among survivors of AMI with LV dysfunction and/or asymptomatic frequent or repetitive PVCs, and the failure and even harmful effects of other drug regimens.

The Basel Antiarrhythmic Study of Infarct Survival (BASIS) (16) was the first to demonstrate a statistically significant benefit of prophylactic antiarrhythmic drug therapy among survivors of AMI. Over the mean follow-up of one year, all-cause mortality rates were for amiodarone 5%, for individual antiarrhythmic therapy (mostly quinidine or mexiletine) 10% and for control 13% (P=0.048 amiodarone versus control). Long term follow-up showed no re-bound of events in spite of discontinuing amiodarone at one year (17).

The Polish Arrhythmia Trial (18) randomized 613 survivors of recent MI who had a contraindication to beta-blocker therapy (presumably LV dysfunction in most instances). During a one-year follow-up, cardiac mortality was 6.2% with amiodarone and 10.7% with placebo (P=0.048), and all-cause mortality was 6.9% with amiodarone and 10.7% with placebo (P=0.095). Lown grade IV arrhythmia was seen in 7.5% of amiodarone patients and 19.5% of placebo patients (P<0.001). The Spanish Study of Sudden Death (SSSD) (19) enrolled 368 patients with recent MI and EF 20% to 45%, plus three or more PVCs/h, couplets or VT consisting of fewer than 15 beats. During a mean follow-up of 2.8 years, all-cause mortality was for amiodarone 3.5%, for metoprolol 15.4% (P=0.006) and control 7.7% (P=0.19 amiodarone versus control).

The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) (20,21) was a randomized, placebo controlled, double-blind trial of amiodarone among patients with frequent or repetitive PVCs (10 or more/h, or one or more runs of VT) detected six to 45 days after MI. Patients received amiodarone 10 mg/kg for two weeks and then, depending on body weight and age, 300 to 400 mg/day to four months, and subsequent Holter-guided dose reductions to 200 to 300 mg/day to eight months and 200 mg five to seven days/week for up to two years.

The study was powered to detect a 50% reduction of the principal outcome of a composite of resuscitated VF or ar-rhythmic death among patients who had not been off amiodarone for more than three months. This outcome was reduced 48.5% by amiodarone (P=0.016). All-cause mortality by intention-to-treat analysis was reduced 18.3% by amiodarone (P=0.129). Absolute risk reductions were greatest among the patients with CHF or a history of prior MI. Serious side effects were uncommon, and none was fatal.

The European Myocardial Infarct Amiodarone Trial (EMIAT) (22,23) was conducted contemporaneously with CAMIAT. Eligibility among survivors of AMI was based on LVEF less than 40%, rather than the presence of ventricular arrhythmias, although all patients had baseline Holter monitoring. Amiodarone was given in a dose of 800 mg/day for two weeks, 400 mg/day for three and a half months, and 200 mg/day subsequently. The principal outcome of all-cause mortality by intention-to-treat analysis was nearly identical in the amiodarone and placebo groups. Although all-cause mortality in the placebo group was higher than in CAMIAT (21), reflecting a higher risk cohort, the study was underpowered to detect a significant difference in all-cause mortality. The composite of resuscitated VF or arrhythmic death determined by an on-treatment (efficacy) analysis was reduced about 50% (P=0.008), almost identical to that observed in CAMIAT. There were three deaths from pulmonary fibrosis in the amiodarone group.

There was a significant reduction of the composite out-come of resuscitated VF or arrhythmic death in each trial (21,23). The greatest benefits occurred among patients with both LV dysfunction and frequent or repetitive PVCs. Neither trial showed a significant reduction of all-cause mortality. It is not possible to say, from these two trials alone, whether the failure to detect a reduction of this outcome was due to inadequate power or, alternatively, to competing harmful effects of amiodarone on nonarrhythmic outcomes. The Amiodarone Trials Meta-Analysis (ATMA) (24) investigators carried out a cooperative prospective meta-analysis of all randomized trials of prophylactic amiodarone therapy to obtain more reliable efficacy and toxicity data. Thirteen trials were assessed (eight post-MI and five among patients with CHF). Among the 6553 patients, there was a reduction of all-cause mortality of 13% (P=0.030) and of ar-rhythmic death of 29% (P=0.003). These reductions were more marked in an on-treatment analysis (18% mortality reduction, P=0.0003, and 35% reduction of arrhythmic death, P=0.0006). In the eight post-MI trials, the annual mortality was 8.7% in the control group and fell 8% with amiodarone, while in the five CHF trials the control mortality was 24.3%/year and fell 17% with amiodarone. The most reliable data on the prevalence and severity of amiodarone side effects come from the six large double-blind, randomized trials of amiodarone reviewed in the ATMA collaboration (24). Hypothyroidism was the most common serious

adverse experience, occurring with an absolute excess of 5.9%. Amiodarone caused excess rates of peripheral neuropathy (0.3%), lung infiltrates (1.1%), bradycardia (1.6%) and hepatic dysfunction (0.6%) during a mean follow-up of 1.1 years.

The promise of class III agents also prompted the Survival With Oral *d*-Sotalol (SWORD) (25) trial, which tested the pure class III agent *d*-sotalol among patients with prior MI and LV dysfunction. The trial had to be terminated early after a mean follow-up of only five months because of excess all-cause mortality with *d*-sotalol (5%) versus placebo (3%) (P=0.006). Most of the excess deaths were arrhythmic. The baseline risk was lower than anticipated and may have precluded demonstration of benefit.

Dofetilide, another class III agent, was assessed in the Danish Investigation of Arrhythmias and Mortality on Dofetilide (DIAMOND) (26). Survivors of recent MI with LVEF 35% or less were randomized to dofetilide or placebo. There was no significant difference in mortality.

Azimilide, yet another class III agent, is being evaluated in the Azimilide Post-Infarction Survival Evaluation (ALIVE) (27). Survivors of AMI with EF 15% to 35% are randomized to azimilide 75 or 100 mg/day versus placebo. The principal outcome is all-cause mortality among patients with low heart rate variability. Enrolment is nearly complete at about 3500 patients.

NONSUSTAINED VT TRIALS

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) (28) was initiated at a time when serial drug testing with invasive EPS was more prevalent than it is now. Patients with prior Q-wave MI, at least one episode of asymptomatic unsustained VT and EF 35% or less who had undergone a standard EPS protocol and failed to suppress induced VT or VF with intravenous procainamide (or equivalent) were randomized to implantable cardioverter defibrillator (ICD) or conventional antiarrhythmic therapy (amiodarone in 80%). MADIT II has been initiated by the same investigators, using less complex entry criteria (survivors of AMI with EF 35% or less) and a treatment protocol more reflective of current thinking (ICD versus no antiar-rhythmic therapy).

The Multicenter Unsustained Tachycardia Trial (MUSTT) (29) was also initiated in the era of serial drug testing during invasive EPS. Patients with coronary artery disease confirmed by cardiac catheterization, LVEF 40% or less, and nonsustained VT within six months of enrolment and 48 h or more after their last MI or revascularization were enrolled. Such patients underwent EPS and, if VT was inducible, they were randomized to no antiarrhythmic therapy or to electrophysiologically guided therapy (drug suppression or ICD for failure of at least three drugs). Details of these protocols, results and implications for practice are discussed in Chapter 6.

CHF TRIALS

Amiodarone is the only antiarrhythmic agent that has been evaluated in sizeable randomized trials among patients with CHF because of its effectiveness against severe ventricular arrhythmias and its lack of negative inotropic effects. The first such major trial was that of the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) (30). Eligible patients had severe chronic CHF and objective criteria of LV dysfunction but were free of symptomatic ventricular arrhythmias. After a mean follow-up of 13 months, all-cause mortality was 41.4% in control and 33.5% with amiodarone (P=0.024), and the secondary outcome of death or hospital admission for CHF fell from 58.2% to 48.5% (P=0.0024). A smaller trial, the Estudio Piloto Argentino de Meurte Subite y Amiodarone (EPAMSA) (31), randomized patients with CHF and asymptomatic complex ventricular arrhythmias. After a mean follow-up of 12 months, all-cause mortality fell from 28.6% to 10.5% (P=0.02) with amiodarone. The emerging picture of substantial efficacy was confused by the results of the Veterans Administration Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (VA-STATCHF) (32). Patients with a documented history of CHF plus 10 or more PVCs/h were randomized to amiodarone or placebo. After 45 months of follow-up, there was no difference in the incidence of all-cause mortality (placebo 42%, amiodarone 39%, P=0.60) or of sudden death (placebo 52%, amiodarone 49%, P=0.43). These results were surprising in light of the dramatic benefits observed in GESICA and led to subgroup analyses. In GESICA, 71% of patients had nonischemic CHF, versus only 28.5% of patients in VA-STATCHF. In the latter trial, there was a trend toward reduced mortality in favour of amiodarone among the nonischemic patients (P=0.07).

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (33) was begun in 1997. Up to 3000 patients will receive conventional antifailure treatment (angiotensinconverting enzyme [ACE] inhibitor, digoxin, diuretics, beta-blockers and warfarin and/or acetylsalicylic acid [ASA]) and are being randomly allocated to therapy with amiodarone, placebo or ICD.

Patients with a variety of other predictors of high risk of arrhythmic sudden cardiac death (hypertrophic obstructive cardiomyopathy, LV hypertrophy, long QT syndromes, arrhythmogenic right ventricular dysplasia and Wolff-Parkinson-White syndrome) are discussed in Chapter 8.

RECOMMENDATIONS

These recommendations are placed in the context of a hierarchy of patients at increasing risk of sudden cardiac death. There is a focus on the prevention and reduction of risk in patients with coronary artery disease because most sudden deaths in western countries occur in such people.

A. Patients at low risk of sudden cardiac death:

1. Public education and medical advice should be directed toward the prevention of coronary artery disease. People with one or more risk factors for coronary artery disease should have medical guidance for modification of any risk factors (levels of evidence and grades of recommendation are detailed in a prior Canadian Cardiovascular Society [CCS] consensus conference [34]).

B. Patients at higher risk of sudden cardiac death:

1. Survivors of AMI
    a. All patients:
        i. Risk factor management should be as detailed in a prior CCS consensus conference (35).

ii. ASA should be prescribed for all patients without clear contraindications, commencing immediately on presentation and continuing indefinitely (**Level I, Grade A**) (35-38).

iii. Beta-blockers should be prescribed to all patients without contraindications, commencing early in the hospital stay and continuing indefinitely (**Level I, Grade A**) (35,39,40).

iv. Class I antiarrhythmic agents increase mortality and are contraindicated (**Level I, Grade A**) (14).

v. An objective measure of LV function (echocardiography, radionuclide angiography or LV angiogram) is indicated if LV dysfunction is suspected, yet is not obvious from the clinical history or state of the patient (**Level I, Grade A**).

b. Patients with LV dysfunction (LVEF 35% or less):

i. If PVCs are infrequent, not repetitive, then amiodarone should be considered but is of uncertain value and is not recommended for routine use (**Level II, Grade B**) (23,24,41).

ii. For frequent or repetitive PVCs, amiodarone significantly reduces the incidence of arrhythmic death and resuscitated VF, but there is uncertainty about whether it reduces all-cause mortality in such patients (21,23,24,41). Accordingly, amiodarone may be prescribed if the risk associated with the arrhythmia appears to be particularly high (**Level II, Grade B**) (28,29).

iii. For nonsustained VT:

- patients who would be suitable candidates for an ICD should undergo an invasive EPS to determine the inducibility of VT or VF. If sustained VT or VF is induced, the patient should receive a prophylactic ICD (**Level II, Grade B**) (28,29).

- patients who would not be suitable candidates for an ICD should not undergo an EPS, but should instead be considered for empirical amiodarone therapy (**Level V, Grade C**).

2. Patients with heart failure not associated with recent MI
    a. All patients should have maximum utilization of proven therapies including ACE inhibitors and beta-blockers, and digoxin and diuretics (CCS consensus conference) (42).
    b. Amiodarone has been shown to reduce mortality (24,30,31), but it has not been rigorously evaluated in patients receiving beta-blocker therapy and it may be less efficacious among patients with ischemic ventricular dysfunction (32). The drug should be considered for use in all patients with heart failure (**Level II, Grade C**).

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Chapter 8: Unusual causes of sudden cardiac death due to ventricular tachyarrhythmias

Anne M Gillis MD FRCPC, Robert M Hamilton MD FRCPC, Catherine A LeFeuvre MD FRCPC

Sudden cardiac death (SCD) is most commonly due to ventricular tachyarrhythmias in the setting of coronary artery disease or other forms of structural heart disease. However, SCD secondary to ventricular tachycardia (VT) or ventricular fibrillation (VF) may occur in younger persons with primary electrical disease and in patients with less common forms of heart disease including arrhythmogenic right ventricular dysplasia (ARVD), hypertrophic cardiomyopathy (HCM) or other congenital anomalies. The prevalence of these disorders is low and, hence, rigorous prospective trials on management have not been conducted. Therefore, the recommendations related to the investigation and management of SCD in these settings reflect a consensus opinion of cardiologists.

PRIMARY ELECTRICAL DISEASE

Idiopathic VF is believed to account for 3% to 9% of outof- hospital episodes of VF that are unrelated to myocardial ischemia (1). The long QT syndrome (LQTS) and the Brugada syndrome are caused by defects in ion channel genes and are characterized by phenotypic electrocardiographic (ECG) abnormalities (2-5). Increased dispersion of ventricular repolarization is believed to provide the electro-physiological substrate for VF in these two disorders. Idiopathic right ventricular outflow tract (RVOT) VT and idiopathic left ventricular VT are usually catecholamine or calcium sensitive and are thought to be due to enhanced automaticity or triggered activity (6,7).

THE CONGENITAL LQTSs

The congenital LQTSs are inherited conditions characterized by QT interval prolongation (QT interval corrected for heart rate [QTc] greater than 440 ms), increased QT interval dispersion and a high risk of SCD (2,3,8-10). The prevalence of LQTSs is estimated to be one in 10,000 (11). The risk of SCD is less than 1%/year, although some phenotypes are associated with increased risk (10). Congenital LQTSs were first described in 1957 by Jervell and Lange-Nielsen (12) (autosomal recessive transmission associated with sensorineural deafness) and in 1963 and 1964 by Romano et al (13) and Ward (14), respectively (autosomal dominant transmission). A number of mutations have been identified (Table 1) (15-21). However, the genes and proteins responsible for this disorder remain unidentified in approximately 40% of patients. Patients with LQTS frequently demonstrate alterations in sinus node function including mild bradycardia compared with their unaffected siblings (22).

TABLE 1
Mutations in long QT (LQT) syndrome

Syndrome	Chromosome	Gene product	Current affected
LQT1	11	KV LQT1 minK	I_{Ks}
LQT2	7	HERG	I_{Kr}
LQT3	3	SCN5A	I_{Na}
LQT4	?	?	?
LQT5	21	minK	I_{Ks}

Recent studies (albeit in a small number of families) suggest that penetrance for nonlethal symptoms or QT interval prolongation may be as low as 25%, rather than the suggested 90% (23). However, persons carrying a nonpenetrant gene may still be at significant risk (6% to 11%) for sudden death (24,25).

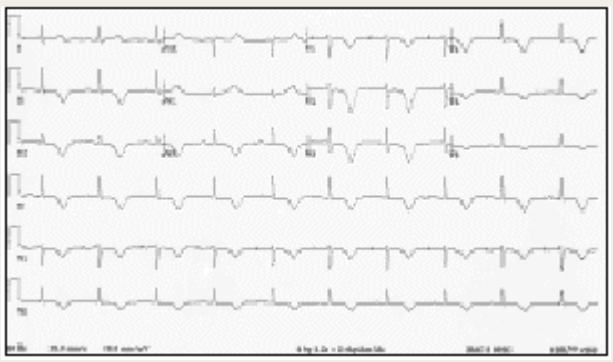

Figure 1) *Example of an electrocardiogram from a patient with long QT syndrome due to mutation of KVLQT1. The patient is paced AAI, rate 60 beats/min. The inverted T waves in the precordium developed following DDD pacing, lower rate 80 beats/min. Courtesy of Dr A Gillis*

Risk stratification: Most patients present in their teenage years with a history of syncope or seizures. The diagnosis is made if the QTc is greater than 440 ms in males and greater than 460 ms in females in the absence of an apparent cause for QT prolongation (eg, electrolyte abnormality, QT prolonging drugs, heart disease) (2,3,8) **(Figure 1)**.

Family members should be screened for LQTSs by careful history, 12-lead ECG and exercise treadmill test if the QTc is in the upper limits of normal or if T wave/U wave morphology is suggestive of LQTS. **The ECG phenotype fails to identify up to one-third of affected family members.** Genotyping is likely to be of potential benefit to screen family members with known mutations in the near future. The standard electrophysiological study (EPS) is not of value in identifying patients at risk of SCD.

Therapy of the LQTSs: Beta-blockers are the initial therapy for the treatment of the LQTSs (26) followed by insertion of an atrial-based pacemaker (27,28) and continued beta-blocker therapy or left stellate ganglionectomy (29) if syncope recurs. Because beta-blocker therapy may precipitate 2° atrioventricular block and a long ventricular pause, atrioventricular sequential pacing is probably the ideal pacing modality (28). Specific channel blocking therapy, eg, mexiletine or KATP channel openers, may be beneficial in some, and these therapies are undergoing clinical investigation (3,21,30). Although the trend in North America is use of an implantable cardioverter defibrillator (ICD) in patients who have experienced a cardiac arrest or in high risk family members, there are no prospective studies comparing this therapy with combined beta-blocker and atrial pacing therapy (31).

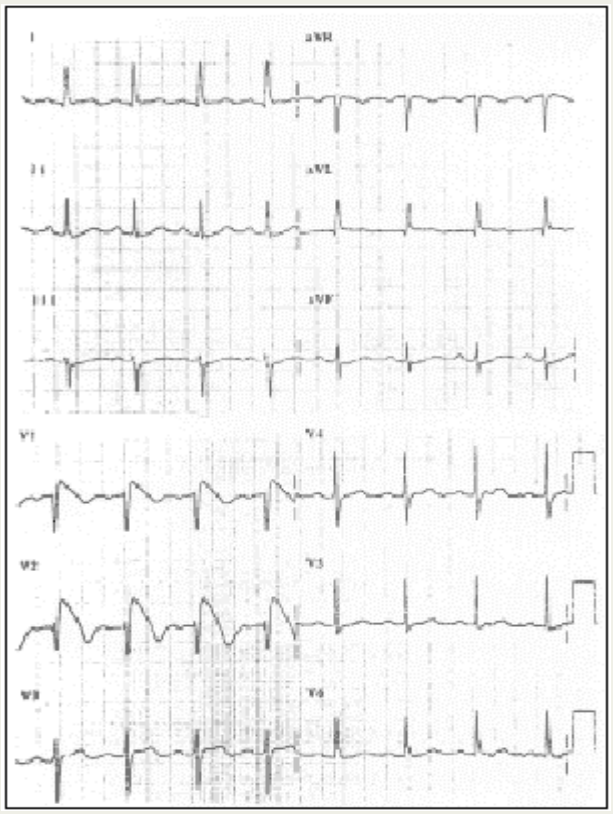

Figure 2) *Twelve-lead electrocardiogram with characteristic changes of Brugada syndrome in leads V_1 to V_3. Reproduced with permission from reference 32*

THE BRUGADA SYNDROME

The Brugada syndrome is characterized by a right ventricular conduction delay abnormality (often associated with PR interval and HV interval prolongation) and ST segment elevation in the right precordial leads in the setting of no structural heart disease. This disorder is associated with a high risk of life-threatening ventricular tachyarrhythmias **(Figure 2)** (4,5,32,33). The ECG abnormalities may be transient, and can be provoked by sodium channel blockers and beta-adrenergic blockers. The prevalence of this disorder varies worldwide but is greatest in males of Asian origin. The Brugada syndrome is a major cause of death in Japan and Southeast Asia, and in those regions it has been characterized as sudden unexplained nocturnal death syndrome (34). The Brugada syndrome is a leading cause of death in young males in Thailand (one in 2500). In Japan, 12 of 22,027 subjects (0.05%) screened had the ECG changes consistent with the Brugada syndrome. A familial occurrence has been observed, and the mode of inheritance is autosomal dominant with variable expression (4,5,33). Mutations of the sodium channel gene *SCN5A* have been described in patients with this disorder.

Risk stratification: The ECG manifestations may be transient. The use of sodium channel blocking agents including procainamide and flecainide or beta-adrenergic blocking agents may be required to unmask the ECGmanifestations in patients when the disorder is suspected. Programmed electrical stimulation induces VTor VF in almost all patients with a history of

syncope or aborted sudden death (4,5,34). Family members should be assessed because of the high incidence of familial occurrence. Screening of family members should include an ECG with pharmacological provocation if required. It is likely that genotyping capabilities may be available for screening family members in the near future.

Therapy: No specific pharmacological therapies, including amiodarone, prevent SCD in patients with the Brugada syndrome (4,5,32,34).

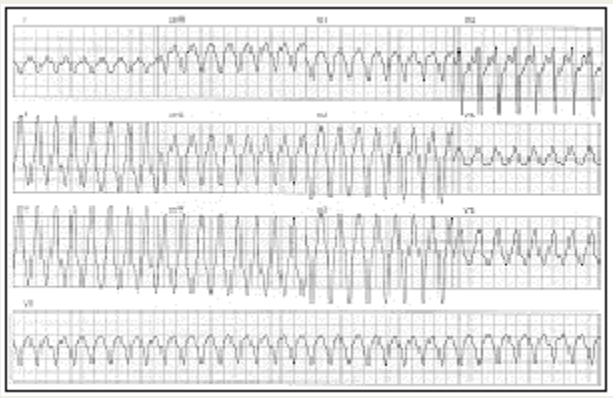

Figure 3) *Twelve-lead electrocardiogram showing sustained ventricular tachycardia originating in the right ventricular outflow tract.*
Courtesy of Dr A Gillis

IDIOPATHIC RVOT VT

RVOT VT is generally a benign condition characterized by a left bundle branch block, inferior axis VT **(Figure 3)**. Most patients present with symptoms of tachycardia, but the risk of SCD is very low - no different from the risk of SCD in a healthy population (6). RVOT VT is usually catecholamine-sensitive and is believed to be secondary to cAMP-mediated triggered activity. The VT may be repetitive and occur at rest, or it may be provoked by exercise.

Investigations: A 12-lead ECG in sinus rhythm and during VT should be obtained. Exercise treadmill testing should be considered when a 12-lead ECG of VT has not been documented. ARVD should be ruled out by the usual screening techniques, which may include echocardiography, radionuclide scintigraphy or magnetic resonance imaging (MRI). EPS is of uncertain value for diagnosis, although rapid atrial or ventricular pacing, or an isoproterenol infusion (1 to 5 µg/min) may provoke the VT and confirm the diagnosis.

Therapy: Beta-blockers are the first line therapy. Calcium channel blockers may be effective in some. Radiofrequency catheter ablation is an effective therapy with low risk and should be considered in patients who are intolerant of drug therapy or for whom drug therapy is not effective.

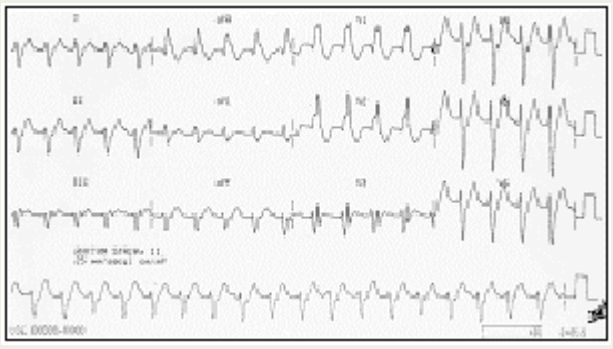

Figure 4) *Twelve-lead electrocardiogram showing sustained ventricular tachycardia originating in the left ventricular septum. Courtesy of Dr A Gillis*

IDIOPATHIC LEFT VT

Idiopathic left VT is characterized by a right bundle branch block tachycardia with left axis deviation **(Figure 4)** (6,7). This VT is thought to arise in the left posterior fascicle. This disorder usually presents in patients between 15 and 40 years of age, and more commonly occurs in males. In the absence of structural heart disease, this is a benign condition. The risk of SCD is very low.

Risk stratification: A12-lead ECG in sinus rhythm and during VTshould be obtained. Structural heart disease should be excluded by the usual screening techniques for assessment of cardiac function.

Therapy: Symptomatic patients usually respond to calcium channel blockers, eg, verapamil 80 to 120 mg tid or sustained release equivalent, or diltiazem 60 to 120 mg tid or the sustained release equivalent. Radiofrequency catheter ablation is effective in eliminating the arrhythmogenic substrate for VT and should be considered for the patient who is not tolerating or is not well controlled on antiarrhythmic drug therapy.

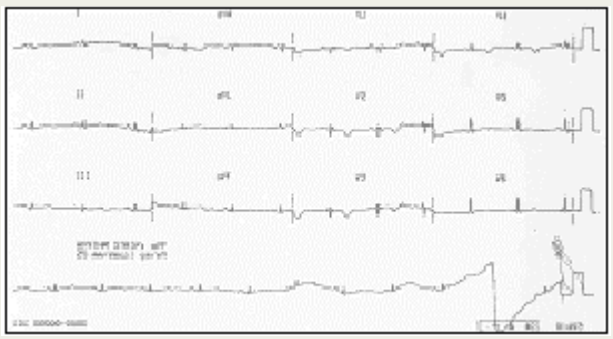

Figure 5) *Twelve-lead electrocardiogram from a patient with arrhythmogenic right ventricular dysplasia. Note the epsilon wave in V_1 and V_2.*
Courtesy of Dr A Gillis

UNSUAL VARIANTS OF SCD IN STRUCTURAL HEART DISEASE

ARVD

ARVD involves progressive fibro-fatty replacement of the RV free wall and is characterized by RV enlargement, right-sided heart failure and recurrent ventricular tachyarrhythmias (35-40). The clinical manifestations of ARVD range from no symptoms to hemodynamically significant VT and SCD. No one clinical feature is diagnostic, which frequently makes premortem diagnosis difficult. A peculiar ECG abnormality has been described in ARVD- the epsilon wave in the right precordial leads, which reflects slow conduction in the RV **(Figure 5)**.

The prevalence of this disorder is estimated to be one in 5000, with a male predominance of 3:1. The disease presents early in life, usually affecting those less than 40 years of age. Many episodes of VT are provoked by exercise, and ARVDis a cause of SCD in young, apparently healthy athletes. The risk of SCD is estimated to be 2.5%/year. On the basis of autopsy series, ARVD appears to account for approximately 5% of SCD under the age of 65 years and for 10% of noncoronary sudden death in this age group (41). ARVD accounts for 17% of a traumatic, sudden unexpected death in the 20-to 40-year age group (42). However, in the pediatric population, ARVDas a cause of sudden unexpected cardiac death is reported rarely (43).

Familial occurrence of ARVD has been reported with incomplete penetrance. Sporadic cases have also been reported. The gene for ARVD has been mapped to 14q23-q24 in one family (44) and to 17q21 in another (45), but specific gene mutations have not yet been characterized.

Risk stratification: Precordial T wave inversions in V1 to V3 and/or the epsilon wave are found in 70% of patients. Radio-nuclide studies are more sensitive than the echocardiogram in

identifying RVenlargement and systolic dysfunction. MRI is showing some promise in the early diagnosis of ARVD in patients with early symptoms or a positive family history, although the specificity and sensitivity of the technique are still under evaluation. Genotyping is not yet possible.

Therapy: EPS may be valuable in diagnosing risk of life-threatening ventricular arrhythmias or to guide selection of antiarrhythmic therapy. Sotalol is very effective in suppressing VT initially. However, the infiltrative process advances, and antiarrhythmic drug efficacy has been reported to decrease over time. Although radiofrequency catheter ablation of VT has been successful in some, VT frequently recurs over time. Surgical therapy is of benefit in selected patients.

TETRALOGY OF FALLOT

Tetralogy of Fallot is the most common cause of cyanotic congenital heart disease worldwide. At the Hospital for Sick Children in Toronto, Ontario, tetralogy of Fallot occurred in 10% of children with congenital heart disease. The prevalence is estimated to be two to three in 10,000 live births.

Most patients will have had either palliative or reparative surgery. Surgical repair is now done with very low mortality.

The incidence of sudden death ranges between 1% and 10% of patients with an estimated annual risk of SCD of two in 1000/year (46). The incidence of sudden death was approximately 2% in the 349 patients with tetralogy of Fallot followed at the Toronto Congenital Cardiac Centre for adults between 1981 and 1996 (47). Although the incidence of sudden death is low, it still accounts for 30% of all deaths in this population. The risk of SCD increases over time.

Risk factors for sudden death in repaired tetralogy of Fallot can be broadly grouped as follows: conduction defects (48-53), ventricular ectopy (50,54-57), operative factors (55,58-60),hemodynamic factors (53,61) and novel indicators (62-65). Postoperative conduction defects may include right bundle branch block (65% to 86%), bifascicular block (usually right

bundle branch block and left axis deviation (9% to 22%) and trifascicular block (4%). Late sudden death has been reported in 2.5% to 4%, 1.8% to 40% and 30% of patients with each of these respective conduction disorders, respectively, depending on the length of follow-up. However, complex ventricular ectopy is frequently associated with conduction system disease and appears to be the more important factor (50). Although complex ventricular ectopy has been reported to be associated with late sudden death following repair of tetralogy of Fallot, other investigators have not reported an association between ventricular arrhythmias and sudden death (56).

The most predictive hemodynamic factor associated with late sudden death following repair of tetralogy of Fallot is residual RVOT obstruction resulting in elevated right ventricular pressure (50,61). Right ventricular dilation related to residual pulmonary insufficiency or other causes may also contribute to morbidity and mortality following tetralogy of Fallot repair but has been difficult to measure by common imaging techniques.

Prolongation of the filtered QRS complex measured on signal-averaged ECG predicts the risk for VT in tetralogy of Fallot with reasonable sensitivity (91% to 100%) and specificity (70% to 75%) (62-64). However, Gatzoulis et al (65) showed that QRS prolongation measured on the standard ECG correlates with x-ray and echocardiographic evidence of right ventricular volume overload, and is a sensitive predictor of life-threatening ventricular arrhythmias (65), a finding confirmed by others (51,52). In adults, the combination of a prolonged QRS duration of 180 ms or more, and QT dispersion greater than 60 ms, QRS dispersion greater than 35 ms or JT dispersion greater than 60 ms is 98% sensitive and 100% specific for predicting the patient with VT. In younger patients, the combination of a QRS duration greater than 170 ms and a JT dispersion greater than 80 ms has specificity of 100%, but a sensitivity of only 21%, for predicting VT (65).

Therapy: Patients presenting with cardiac arrest, sustained VT, syncope, presyncope or significant palpitations, as well as those with complex ventricular arrhythmia noted on non-invasive testing, should be considered for EPS. No specific therapy has been shown to prevent SCD in patients with postoperative tetralogy of Fallot repair.

A number of trials and case reports have described successful arrhythmia suppression with mexiletine, phenytoin, propranalol or amiodarone, and there is general consensus that antiarrhythmic therapy is reasonable in patients with symptomatic arrhythmias. Alternative therapies for sustained VT include radiofrequency ablation if no significant residual hemodynamic lesions are present (66), or mapguided intraoperative cryoablation and repair of residual lesions if they are present (67).

HCM

HCM is a primary and usually familial disorder with heterogeneous expression and a diverse clinical course (68). The prevalence of the disorder is one in 500 (0.2%). HCM is the most common genetically transmitted cardiovascular disease (69). HCM is usually inherited as an autosomal dominant trait. HCM is characterized by a thickened nondilated left ventricle in the absence of conditions that would promote hypertrophy. HCM is the most common cause of SCD in the young, apparently healthy athlete. SCD occurs in 1% to 6% of patients/year (68).

Mutations in genes encoding proteins of the sarcomere have been reported; more than 100 individual diseasecausing mutations have been identified for these genes (69-71). Thus, the precise molecular defect responsible for HCM is usually different in unrelated individuals. Mutations in the beta-myosin heavy chain gene may account for up to 35% of familial HCM. Some of these mutations are associated with a benign clinical course and some with a malignant clinical course. Mutations in the myosin-binding protein C gene may account for up to 20% of familial HCM. This gene defect appears to be associated with a favourable clinical course.

Although HCM is associated with SCD, it has been suggested that the overall risk of SCD has probably been overestimated because of referral bias (72-75). Much of the data in the literature have been published by tertiary centres in North America and Europe, where patients have been referred for specialized care because they have been deemed to be at high risk. However, annual mortality rates and the risk of SCD in unselected populations are reported to be lower (1%/year), with survival closer to that of the general population. The pediatric patient between eight and 18 years of age has an estimated risk of SCD of 2.7%/year (76).

SCD may be the first manifestation of HCM. The risk of SCD is greatest in those with a prior history of cardiac arrest or sustained VT, malignant genotype, family history of SCD, recurrent syncope, recurrent nonsustained VT and massive left ventricular hypertrophy (68,77,78). The mechanism of SCD in HCMis multifactorial. Although VT/VF is the most common cause of SCD, atrial fibrillation with a rapid ventricular response causing ischemia, syncope due to altered baroreceptor control causing hypotension, and ischemia and thromboembolism secondary to atrial fibrillation may also be important causes of SCD. Prospective, controlled trials evaluating the impact of various therapeutic modalities including antiarrhythmic drugs, DDD pacing, myectomy or ICD for prevention of SCD are lacking.

Risk stratification: ECG, echocardiogram and 24 h ambulatory ECG monitoring should be performed to identify patients at risk of SCD. EPS is of uncertain value in risk stratification (79).

Therapy: Patients at high risk of SCD should have optimal medical therapy of HCM. Treatment should be targeted at preventing atrial fibrillation (disopyramide or amiodarone), preventing rapid atrial fibrillation with rate controlling drugs (beta-blockers, verapamil), suppressing nonsustained VT with sotalol or amiodarone, minimizing left ventricular out-flow tract obstruction with myectomy or dual chamber pacing and resecting identified myocardial bridges (80). The ICD may be of benefit in preventing SCD in the asymptomatic patient with a strong family history of SCD (81) and in patients with sustained VT/VF (82). Prospective trials of high risk patients are required to determine the impact of DDD pacing, myectomy, amiodarone or ICD implantation on prevention of SCD in high risk groups.

RECOMMENDATIONS

CONGENITAL LQTS

A. Asymptomatic patients:

1. Patients with a long QT in the absence of apparent causes should be referred for expert cardiological opinion (**Level V, Grade C**).
2. The asymptomatic patient with long QT and a family history of LQTS should be treated with beta-blockers (**Level V, Grade C**).

B. Symptomatic patients:

1. Beta-blockers are the first line of therapy in patients with symptomatic LQTS (**Level V, Grade C**).
2. Beta-blockers in combination with atrial-based pacing are indicated in patients with recurrent syncope (**Level V, Grade C**).
3. ICD implantation is the treatment of choice in patients with recurrent syncope due to VT despite beta-blocker and pacing therapies.
4. An ICD should be considered for the patient with LQTS and a strong family history of SCD (**Level V, Grade C**).

C. Cardiac arrest survivors:

1. Patients surviving resuscitated cardiac arrest should receive an ICD (**Level V, Grade C**).

THE BRUGADA SYNDROME

A. Asymptomatic patients:

1. Asymptomatic persons with ECG features of theBrugada syndrome or asymptomatic persons with a family history of the Brugada syndrome should be referred to an electrophysiologist for an expert opinion in management (**Level V, Grade C**).

B. Symptomatic patients:

1. Patients with the Brugada syndrome presenting with VT/VF should receive an ICD (**Level V, Grade C**).
2. Patients with the Brugada syndrome and a history of syncope in whom VT is induced at EPS should receive an ICD (**Level V, Grade C**).

ARVD

A. Asymptomatic patients:

1. ECG and echocardiographic, radionuclide and/or MRI assessment is indicated to screen family members to identify those with ARVD who may be at risk of SCD (**Level V, Grade C**).
2. Asymptomatic patients with ARVD should be assessed for risk of sudden death by ambulatory ECG monitoring and exercise stress testing, and those who are identified to have nonsustained VT should be referred for expert electrophysiological opinion (**Level V, Grade C**).

B. Symptomatic patients:

1. Implantation of an ICD is the recommended treatment for prevention of SCD in patients with ARVD and documented sustained VT/VF (**Level V, Grade C**).
2. Asymptomatic patients with ARVD and a strong family history of SCD should be considered for an ICD (**Level** V, Grade C).

TETRALOGY OF FALLOT

A. Asymptomatic patients:

1. Asymptomatic patients with tetralogy of Fallot should be assessed by ECG during the yearly clinical examination. Ambulatory ECG should be recorded if the 12-lead ECG shows a QRS duration greater than 160 ms. Patients with significant hemodynamic symptoms or nonsustained VT should be considered for EPS as well as hemodynamic evaluation by echocardiography with or without cardiac catheterization (**Level V, Grade C**).

B. Symptomatic patients:

1. Patients with tetralogy of Fallot and sustained VT should be considered for surgical correction of significant structural abnormalities (ie, pulmonary valve replacement or right ventricular aneurysmectomy, or both) in conjunction with intraoperative electrophysiologically guided cryoablation (**Level V, Grade C**).
2. Radiofrequency catheter ablation of hemodynamically stable VTs, electrophysiologically guided pharmacological therapy, empirical amiodarone or insertion of an ICD may be considered (**Level V, Grade C**).

HCM

A. Asymptomatic patients:

1. Asymptomatic patients with HCM and a strong family history of SCD may be considered for ICD treatment (**Level V, GradeC**).

B. Symptomatic patients:

1. The patient with sustained VT/VF in the setting of HCM and in the absence of a reversible cause should receive an ICD (**Level V, Grade C**).

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Chapter 9: Quality of life issues in the management of patients with ventricular arrhythmias

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The quality of life in patients who are at high risk of sudden cardiac death (SCD) can be affected by a number of factors including the patient's psychological reactions to his or her cardiac condition, the effects of treatment on quality of life and the effects of the disease itself. Studies assessing the quality of life of patients who are at high risk of SCD have typically based their assessment approach on the multi-dimensional model of health proposed by the World Health Organization (WHO). The WHO proposed that health is not simply the absence of disease and infirmity, but also the presence of psychological, social and physical well-being (1). Instruments such as the Sickness Impact Profile (2), the Nottingham Health Profile (3) and Medical Outcomes, Short-Form 36 (SF-36) (4) were developed to measure a multidimensional model of quality of life. Assessment approaches typically involve a generic quality of life instrument such as the instruments just mentioned, as well as a disease-specific measure that aims to assess, in more detail, the domains of quality of life most relevant to patients at high risk of SCD. In reviewing studies of the quality of life effects of patients at high risk of SCD, it is important to keep two limitations in mind. First, rarely has the same generic or disease-specific quality of life instrument been employed in more than one study. Second, because multidimensional instruments provide a profile of functioning across different domains of health (eg, physical, mental and social), it is difficult to derive a global index score that accurately expresses the patient's overall quality of life. Quality of life measures based on the utility measurement approach provide a single value between 0 and 1, indicating the patient's strength of preference for a health-related outcome. Multiattribute utility scales, such as the Health Utility Index (5), the EuroQol

(6) and the Quality of Well-being Scale (7), are examples of multidimensional utility-based instruments. However, re-search to date on patients at high risk of SCD has not employed utility measures, although clearly it is likely that future studies will include this measurement approach. Thus, at this time, the research on the quality of life of patients at high risk of SCD is limited by difficulties in being able to summarize results across different studies that have used different measurement tools and by difficulties in being able to summarize results within studies where effects may vary across different domains of quality of life.

QUALITY OF LIFE EFFECTS OF PATIENTS AT HIGH RISK OF SCD: PREVALENCE OFPSYCHOLOGICAL DISTURBANCE

Point prevalence rates for major depressive disorder, defined by standard psychiatric diagnostic criteria, range from 15% (8) to 18% (9) in postmyocardial infraction (MI) patients. Mild to moderate mood disturbance defined by validated questionnaires or interview assessment range from 28.0% (10) to 31.2% (8). In a population of patients referred for cardiac rehabilitation, the point prevalence rate for elevated psychological distress was 10.8% (11). In arrhythmia populations, the point prevalence rate of elevated depressive symptomatology has been reported to be 9.6% (12), 13.0% (13) and 33% to 35% (14-17). The point prevalence rate for elevated scores on a measure of anxiety was reported to be 12.7% (12) and 31% for any psychiatric disturbance (18). Only two studies (8,14) employed the same measurement tool. The point prevalence rates were very similar, 31.2% (8) and 33.3% (14), suggesting that variation among studies in prevalence rates is likely influenced by differences in the instruments employed to assess mood disturbance.

CLINICAL SIGNIFICANCE OF PSYCHOLOGICAL DISTRESS IN PATIENTS AT HIGH RISK OF SCD

Elevated depressive symptomatology has been associated with increased risk of mortality in several studies (9,13, 14,19-21), including patients being treated by amiodarone (14) or by an implantable cardioverter defibrillator (ICD) (15). Psychological distress (11) and a worsening of depressive symptoms (22) have been associated with recurrent cardiac events. Both the consistency of these findings and the breadth of observations (across different patient

populations, different measures of psychological symptomatology and different countries) provide substantial evidence that negative emotions are markers for adverse cardiac outcomes in patients with known cardiovascular disease.

PSYCHOLOGICAL INTERVENTION

A meta-analysis of psychological interventions for cardiac patients found that the psychosocially treated patients showed greater reductions in psychological distress, systolic blood pressure, heart rate and cholesterol level (23). Patients who did not receive psychosocial treatment showed greater mortality and cardiac recurrence rates during the first two years of follow-up, with log-adjusted odds ratios of 1.70 (95% CI 1.09 to 2.64) for mortality and 1.84 (95% CI 1.12 to 2.99) for recurrent events. Studies published since the meta-analysis have raised questions regarding the effectiveness of psychological interventions. For example, two large psycho-social treatment studies reported no mortality benefit from a psychosocial intervention in postacute MI patients (24,25) and even indicated a possible increase in mortality for women following the psychosocial intervention (25). Both studies had limitations including the use of a nonstandardized intervention delivered by personnel not specifically trained in psychological counselling (25) and lack of data on patient adherence to treatment (24). Another recent study of a comprehensive, multifactor, home-based rehabilitation program for cardiac patients that included a self-help stress management workbook also failed to find specific effects of the intervention on the patients' psychological status (26). In the latter study, no attempt was made to ensure that the patients read the stress management workbook. In contrast to these negative studies, Blumenthal et al (27) found that a structured, 12-week group stress management program was associated with significantly fewer cardiac recurrences over an average of about two years of follow-up and fewer stress-induced episodes of myocardial ischemia compared with a geographical, usual care control group. The stress management group also exhibited greater reductions in psychological distress and hostility. The small sample sizes per group (about 34 patients) and the nonrandomized 'usual care' group are significant limitations in this study. Notwithstanding these limitations, the study suggests that a structured, standardized stress management intervention favourably affects both psychological status and cardiac prognosis.

QUALITY OF LIFE IN PATIENTS MANAGED WITH AN ICD VERSUS MEDICAL MANAGEMENT ALONE

Most studies of the quality of life effects of patients at high risk of SCD who are being treated with ICD therapy or anti-arrhythmic drug therapy are not randomized controlled trials (16-18,28-45). Results of these studies indicate that there are both quality of life costs and benefits associated with ICD therapy.

There have been only two randomized, controlled trials comparing quality of life in patients randomized to ICD therapy versus drug therapy. In the Canadian Implantable Defibrillator Study (CIDS) (46), quality of life at six and 12 months of follow-up was significantly better with ICD therapy than with drug therapy on measures of both psychological and physical function. In the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial (47,48), the results were mixed. In the 34.2% of patients for whom there was complete quality of life data over the follow-up period, quality of life improved to the same extent in the ICD and drug therapy groups. However, in the complete sample of 804 patients who had a quality of life measure for at least *one* follow-up point, the psychosocial component score of the SF-36 improved more in the ICD group than in the drug group (47,48). Taken together, the results of these studies indicate that psychological functioning is better with ICD therapy, and there is some suggestion that physical functioning may also be better.

A factor influencing the quality of life of patients with an ICD is whether they receive shocks from their device. Approximately 50% of patients report pain associated with receiving a shock (45), and 40% to 60% report anxiety related to ICD discharge (16,45). For approximately 30% of patients who have an ICD, anxiety is the single most disturbing aspect of the ICD (45). A consistent finding of studies that have evaluated the relationship between frequency of shocks and psychological outcome is that receiving five or more shocks is associated with significantly poorer psychological outcome (12,15,42,45). In CIDS, the quality of life benefits associated with ICD therapy were lost in patients who received five or more shocks from their device (46).

CONCERNS AND ISSUES

Elevated depressive symptomatology is a marker of higher mortality risk (**Level III, Grade C**). However, it is not known whether treating depression and anxiety in patients who have malignant arrhythmias prevents SCD. Large scale pharmacological and psychological intervention trials are underway to test the effectiveness of intervention for reducing depression and mortality risk in post-MI patients. Given the uncertainty about whether treating anxiety and depression in patients with malignant arrhythmias would lessen the risk of SCD, routine screening for mood disturbance to prevent SCD in this population cannot be recommended at present for the sole purpose of preventing SCD. Compared with sole treatment by antiarrhythmic medication, ICD treatment is associated with better quality of life outcome. However, the quality of life advantage of ICD therapy is lost if the patients receive numerous shocks from their device. Interventions are needed to reduce the likelihood that patients with an ICD will receive numerous shocks from their device, and interventions are needed to help patients cope effectively with ICD shocks to mitigate untoward adverse psychological effects (**Level III, Grade C**).

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

Chapter 10: Current evidence on the cost effectiveness of the implantable cardioverter defibrillator

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The implantable cardioverter defibrillator (ICD), as described in earlier chapters, is the most recent nonpharmacological approach to the treatment of ventricular tachycardia/ventricular fibrillation. As with many nonpharmacological medical technologies, the early evaluative evidence on effectiveness was limited to observational case series, and only recently have randomized trials begun to demonstrate mortality benefits associated with ICD therapy compared with antiarrhythmic drug therapy. But the high cost of ICD therapy - about CDN$22,000 for the hardware alone - has caused anxiety for health care payers. Even if ICD therapy improves survival, the question remains whether this is achieved at an acceptable cost. Put another way, given the numerous health care programs that are competing for scarce health care dollars, do we get the biggest population health 'return' on our investment by expanding provision of ICD therapy or some other medical therapy?

The question of value for money is amenable to systematic enquiry using the various techniques of economic evaluation such as cost effectiveness analysis (1). Cost effectiveness evidence is fast becoming an accepted component of health care technology assessment. For example, manufacturers of all new drugs seeking public reimbursement and formulary listing in the province of Ontario must supply evidence of the drug's cost effectiveness (2). As part of the evidence for evaluating ICD therapy, it is therefore necessary to consider cost effectiveness.

COST EFFECTIVENESS ANALYSIS

Those wanting a more detailed introduction to cost effectiveness analysis should consult standard texts (1,3) and recent guidance papers (4,5). In brief, a cost effectiveness analysis seeks to quantify costs and health outcomes for two or more treatments for a given condition. To focus on an example, consider ICD therapy versus amiodarone. Over a specified time horizon, the analyst would collect data on health care resources used (eg, devices, drugs, hospital days) and use relevant price weights (eg, drug prices, physician fees) to compute mean cost per patient for the treatment and control group. Health outcomes can be quantified in terms of differences in life expectancy (although quality of life is a further consideration of value; see Chapter 9). In most cases, ICD therapy is associated with a higher mean cost per patient than amiodarone, but may also be associated with an increase in life expectancy. By convention, analyses would then present a so-called 'incremental cost effectiveness ratio', this being the ratio of the difference (treatment - control) in cost to the difference in life expectancy. This ratio - expressed as amount in dollars per year of life gained - provides a policy-maker with information about the health return per dollar expended that can be compared with other health care programs that can improve population survival. As such, the analysis provides the best estimate of the health yield per dollar expended, but it is the decision-maker who must decide whether this provides good value, given competing objectives.

EVIDENCE FROM EARLY DECISION ANALYSES

In early attempts to conduct cost effectiveness analysis of ICD therapy - mainly done in the 1980s - the main constraint was the very limited evidence for survival benefits. Kuppermann et al (6) published one of the earliest decision analysis models and estimated that, compared with historicalcontrols from reimbursement data and over a lifetime time horizon, ICD therapy cost effectiveness was US$17,000 per life-year gained. In the United Kingdom, O'Brien et al (7) used case series data in their decision analysis model to compare ICD versus amiodarone therapy over a 20-year time horizon and estimated ICD cost effectiveness to be US$24,564 per life-year gained. These early modelling studies had estimated gains in life expectancy of 1.9

and 1.7 years, respectively, which is a large treatment effect in comparison with trial-based evidence now emerging. In that sense, the more recent modelling study by Owens et al (8) is based on a more conservative treatment effect (derived from ongoing trials) of 0.69 life-years gained over a lifetime horizon and yielding cost effectiveness relative to amiodarone of US$54,203 per life-year gained.

EVIDENCE FROM TRIAL-BASED ANALYSES

Given the numerous threats to the validity of decision analysis models based on observational data, a logical extension to the evidence on the economics of ICD therapy was to conduct cost effectiveness analyses concurrently with randomized controlled trials when they began to recruit subjects in the early 1990s. The inferential basis of such studies is clearly much stronger, permitting the analyst to measure cost, survival and quality of life for individual subjects recruited into the trial. The key economic data from trials are reviewed below and summarized in **Table 1**.

TABLE 1
Trial-based implantable cardioverter defibrillator (ICD) cost effectiveness studies - Summary

	MADIT	AVID	CIDS
Comparison	ICD versus conventional therapy	ICD versus conventional therapy	ICD versus amiodarone
Time horizon (years)	4	3	6
Gain in life-years	0.80	0.24	0.23
Additional cost per patient (US$)	21,580	27,580	35,219
Cost per life-year gained (US$)	27,000	114,914	153,126

AVID Antiarrhythmics Versus Implantable Defibrillators; CIDS Canadian Implantable Defibrillator Study; MADIT Multicenter Automatic Defibrillator Implantation Trial

Multicenter Automatic Defibrillator Implantation Trial (MADIT) (9)

The MADIT cost effectiveness analysis (10) had an analytical time horizon of four years and compared ICD with a mix of conventional antiarrhythmic drug therapies. The mean cost per patient in the drug therapy arm was US$75,980 compared with US$97,560 for ICD patients, for a difference of US$21,580. Life expectancy (within the four-year follow-up) was 2.68 years for conventional therapy and 3.46 years for ICD (a difference of 0.8 years). Hence, the incremental cost effectiveness of ICD therapy is the ratio of these differences ($21,580:0.8) or approximately US$27,000 per year of life gained (with 3% discounting per year).

Antiarrhythmics Versus Implantable Defibrillators (AVID) (11)

A full report of the AVID cost effectiveness analysis has not yet been published but has been reported in abstract form (12). In summary, over a three-year time horizon, the mean cost per patient receiving conventional antiarrhythmic drug therapy was US$48,653 versus US$76,233 for those with an ICD (a difference of $27,580). The gain in life expectancy per patient over the three years was 0.24 years, and hence the cost effectiveness was US$114,917 per life-year gained (with no discounting).

Canadian Implantable Defibrillator Study (CIDS) (13)

The economic analysis from CIDS has been published in an abstract (14). Over a six-year time horizon, data indicate a mean cost per patient on amiodarone of US$27,185 compared with US $62,404 for those with an ICD (a difference of US$35,219). Within the six-year follow-up, life expectancy with amiodarone was 4.35 years and 4.58 years with ICD (a gain of 0.23 life-years). The incremental cost effectiveness of ICD therapy is therefore estimated to be approximately US$150,000 per life-year gained (with 3% discounting per year).

SUMMARY AND COMMENTS

1. ICD cost effectiveness estimates from early decision analysis models are too low because estimates of gains in life expectancy were too high.

2. Despite the careful collection of data on cost effectiveness from randomized trials, there is still a high degree of uncertainty concerning the cost effectiveness of ICD therapy. On the basis of current trial-based evidence, cost effectiveness of ICD therapy varies between uses as primary and uses as secondary prevention.

> *Primary prevention* (eg, MADIT): US$27,000 per life-year gained. This is comparable with many accepted life-extending technologies, and there is good evidence to adopt the technology in these patients.
>
> *Secondary prevention* (eg, AVID, CIDS): range
>
> US$115,000 to 150,000 per life-year gained. This is generally outside accepted benchmarks for funding life-extending technologies.

3. ICD cost effectiveness varies among trials because of a number of factors:

> *Size of treatment effect*: CIDS and AVID demonstrated very similar gains in life expectancy, whereas MADIT showed a larger treatment effect (and hence more favourable cost effectiveness).
>
> *Duration of follow-up:* There is a need to extrapolate cost and effect data beyond trial follow-up using modelling because the cost impact of device and/or generator replacement needs to be captured over the patient's life-time.
>
> *Cost of non-ICD care*: Because of the varying degree of crossover from pharmacological to device aims, and electrophysiological studies to guide drug therapy, comparison among trials is problematic. For example, the relatively high cost difference in CIDS is attributable to a lower cost for amiodarone-treated patients than in studies such as AVID.

4. A limitation of trial-based cost effectiveness evidence for ICD therapy is that no attempt has been made to adjust survival gains for quality of life (eg, quality-adjusted life years [1]). To the

extent that ICD confers additional benefit over drug therapy in terms of improved quality of life, this results in underestimation of ICD cost effectiveness.

5. More research is needed to extrapolate trial-based data to determine how the balance of costs and effects changes through time (eg, device replacements) and as the technology matures (eg, less costly implantation methods and extended battery life).

ACKNOWLEDGEMENTS: Dr O'Brien is supported by a career award in health sciences from the Medical Research Council and Prescription Drug Manufacturers Association of Canada.

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PREVENTION OF SUDDEN DEATH FROM VENTRICULAR ARRHYTHMIA

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