

Ventricular Arrhythmia: Role of the Implantable Cardioverter Defibrillator and Radiofrequency Ablation in Addition to Drugs

AVI FISCHER, M.D.¹, RAJIV VERMA, M.D.¹, JOSEPH A. GOMES, M.D.², AND
DAVENDRA MEHTA, M.D., PH.D.³

Abstract

The control of life-threatening ventricular arrhythmias in the prevention of sudden cardiac death has been a long-standing challenge to clinicians. Large-scale, randomized, controlled trials have contributed immensely to our understanding of the management of life-threatening arrhythmias. There are many causes of these arrhythmias, which occur mostly in the setting of healed myocardial infarction. Available treatments for the management of ventricular arrhythmias include antiarrhythmic drugs, implantable cardioverter defibrillators and catheter ablation. Each therapy provides unique advantages for selected patients with life-threatening arrhythmias. Because the goal of arrhythmia management is not only to provide the single best therapy but to provide the greatest assurance of symptomatic arrhythmia control, the use of combined therapy has become a standard treatment strategy for patients with sustained ventricular arrhythmias. This review will discuss the different modes of treatment available for the treatment of life-threatening ventricular arrhythmias, and their potential risks and benefits. The rationale for using hybrid or combination therapy will be presented. Finally, some of the better-known primary and secondary prevention trials for treatment of ventricular tachycardias will be reviewed.

Key Words: Sudden cardiac death, ventricular tachycardia, antiarrhythmic agents, implantable cardioverter defibrillator, radiofrequency ablation.

Introduction

SUDDEN CARDIAC DEATH is defined as unexpected natural death, from a cardiac cause, occurring less than 1 hour after the onset of symptoms. Sudden cardiac death accounts for 300,000–400,000 deaths annually in the U.S. (1). It is the most common life-threatening manifestation of coronary artery disease and accounts for nearly 50% of the deaths attributable to cardiovascular diseases (2).

The prevention of sudden cardiac death due to life-threatening arrhythmias has been a long-standing challenge to clinicians. Given the high rate of recurrence following such life-threatening manifestations, treatment is mandatory. Large-scale, randomized controlled trials have contributed immensely to our understanding of the nature and management of this condition. There are many causes of life-threatening arrhythmias, which occur in the setting of healed myocardial infarction in a region of ventricular scar (1). Other causes include arrhythmogenic right ventricular dysplasia, cardiac sarcoidosis, nonischemic cardiomyopathies, and ventricular surgery for congenital anomalies. The choice of treatment modalities for ventricular arrhythmias depends on features such as clinical presentation, left ventricular function and associated underlying etiology of the arrhythmia, and co-morbid medical conditions (Table 1).

Available treatments for the management of ventricular tachycardia (VT) include antiarrhythmic drugs, implantable cardioverter defibrillators and surgical or catheter ablation. Each therapy provides

¹Cardiology Fellow, ²Professor of Medicine, Director, Section of Electrophysiology, and ³Associate Professor of Medicine, Director, Clinical Electrophysiology Lab, The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Address correspondence to Davendra Mehta, M.D., Ph.D., Director, Clinical Electrophysiology Lab, The Zena and Michael A. Wiener Cardiovascular Institute, Box 1030, Mount Sinai School of Medicine, New York, NY 10029.

Adapted from a Cardiology Grand Rounds presentation to the Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY on November 27, 2000 and updated as of July 2001.

TABLE 1

Factors to Be Considered in Selection of Therapy for Patients with Sustained Ventricular Tachycardia

1. Type of ventricular tachycardia, documented during the arrhythmic episode
2. Symptoms during the arrhythmic episode
3. Type and severity of underlying heart disease
4. Evidence based on controlled clinical trials
5. Suitability of the patient for the theoretically optimal therapy
6. Available resources

unique advantages for selected patients with life-threatening arrhythmias. The use of antiarrhythmic agents, while noninvasive, may prevent symptomatic arrhythmia recurrences but cannot be considered curative. Implantable cardioverter defibrillators cannot prevent arrhythmia, but they are effective in reducing the risk of sudden cardiac death. The only potential cure for VT is ablative therapy. Since the goal of arrhythmia management is to provide the greatest assurance of symptomatic arrhythmia control, the use of combined therapy has become a standard treatment strategy for patients with sustained ventricular arrhythmias (3).

Antiarrhythmic Therapy

All drugs currently marketed for the treatment of arrhythmias were developed without knowledge of the specific molecular mechanisms by which their therapeutic and possible adverse effects were achieved. Understanding the chemistry of these antiarrhythmic agents and their physiological properties in animals has made it possible to develop new and more effective agents (4). Antiarrhythmic drugs have been grouped according to their common mechanism of action. This approach makes it easier for the clinician to anticipate a patient's response to a given drug. A contemporary view is that all antiarrhythmics exert their desirable effects by interacting with specific molecular targets (4). A common target is the ion channel, the pore-forming protein structure that underlies ionic currents flowing during the action potential. Drug specificity is achieved by targeting a single population of ion channels. Targeting specific cardiac ion channels, however, may result in significant proarrhythmia.

A classification system proposed by Vaughan Williams and widely used among clinical cardiologists subdivides drugs into four broad classes (5). These are: Class I – Na⁺ channel blockers; Class II – β blockers; Class III – K⁺ channel blockers; and Class IV – Ca²⁺ channel blockers (Table 2).

TABLE 2

Antiarrhythmic Drugs

Class	Mechanism	Drug
I	Sodium channel blocker	
	A Moderate phase-0 depression; $\downarrow\downarrow$ retards conduction; \downarrow slows repolarization	procainamide, equinidine, quinidine ¹ , disopyramide, moricizine
	B Less phase-0 depression; \downarrow retards conduction and shortens repolarization	lidocaine, tocainide
C Markedly depresses phase-0; $\downarrow\downarrow\downarrow$ retards conduction; \pm effect on repolarization	encainide, flecainide, propafenone	
II	β -adrenergic blocker	propranolol, others
III	Potassium channel blockers prolongs repolarization	amiodarone ² , bretylium, d-sotalol
IV	Calcium channel blocker	verapamil, diltiazem

¹ Has some Class III effects

² Has some effects of all classes

This classification has been criticized, because many drugs have been found to have more than one effect. For example, quinidine has both class I and III effects, while amiodarone affects all classes. In addition to these actions, these antiarrhythmic drugs may precipitate hemodynamic changes and alter neurohumoral relationships and metabolic pathways. However, a virtue of this classification system is that drugs of a common class frequently exhibit similar toxicities, most notably proarrhythmia, the cause of which may be similar for all drugs in that class (4). Studies evaluating drugs that target predominantly sodium channels (class I agents) indicate that these drugs may have unfavorable proarrhythmic effects and can lead to increased mortality (6, 7). For this reason, Class III agents, which prolong the action potential and refractoriness of cardiac tissues, have emerged as the antiarrhythmic agents of choice for managing life-threatening ventricular arrhythmias (8).

Nonetheless, the outcomes of placebo-controlled clinical trials have now unequivocally confirmed that suppression of arrhythmia, symptomatic or asymptomatic, may not necessarily decrease mortality (6, 7). Consequently, implantable cardioverter defibrillators (ICD) and radiofrequency ablation techniques have been developed to supplement the options offered by drugs alone.

Implantable Cardioverter Defibrillator (ICD) Therapy

One of the most striking therapeutic achievements has been the development of the implantable cardioverter defibrillator, which was first used successfully in 1980 (9). Implantable defibrillators are designed to deliver an electrical shock when ventricular tachyarrhythmias are detected. They can accurately and effectively terminate ventricular tachyarrhythmias in laboratory and clinical settings (9, 10). With regard to ventricular tachyarrhythmias, no other modality of treatment has had as much therapeutic impact as the ICD. Observational studies document low rates of sudden death among patients treated with implanted defibrillators, and a decreased overall mortality has been demonstrated. ICD therapy currently is clearly the most appropriate approach to mortality reduction in patients at risk for sudden death of arrhythmic origin (8).

At present, ICD therapy is the initial treatment of choice for patients resuscitated from documented ventricular fibrillation from a non-reversible cause (e.g., myocardial infarction), patients with poorly tolerated VT, and patients with impaired left ventricular function and unexplained syncope, in whom sustained ventricular arrhythmia is induced at electrophysiologic testing (1). The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for ICD therapy are listed in Table 3 (11).

The use of recently improved leads enables ICD devices to act not only as cardioverter defibrillators, but as pacemakers as well, allowing backup Dual-chamber pacing, Dual-chamber sensing, Dual-chamber inhibiting (DDD) pacing on demand. This feature is useful for patients with intermittent heart block or bradyarrhythmias. Dual-chamber devices are now standard. In addition to terminating tachycardias with shocks, ICDs can terminate arrhythmias through anti-tachycardia pacing (ATP), which is painless. ICDs are multi-programmable and can be customized for each patient and each tachycardia. The ICD can be set to detect slower VTs and allow for ATP prior to the treatment of rhythm with shocks. Even the sequence of shocks can be programmed, with lower energy shocks being delivered prior to higher energy shocks.

Although implantable cardioverter defibrillators are effective in terminating ventricular tachyarrhythmias and preventing sudden cardiac death, patients with defibrillators often receive appropriate shocks triggered by ventricular tachyarrhythmias as well as inappropriate shocks triggered by

TABLE 3

Indications for Implantable Cardioverter Defibrillator Therapy (ACC/AHA Guidelines) (11)

Class I (General agreement that treatment is beneficial, useful and effective)
Cardiac arrest due to VF or VT, not due to a transient or reversible cause
Spontaneous sustained VT
Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at EPS when drug therapy is ineffective, not tolerated or not preferred
Nonsustained VT with CAD, prior MI, LV dysfunction and inducible VF or sustained VT at EPS not suppressible by a class Ia drug
Class II (Conflicting evidence about efficacy/usefulness)
Cardiac arrest presumed to be due to ventricular fibrillation when electrophysiologic studies are precluded by other medical conditions
Severe symptoms attributable to sustained ventricular tachyarrhythmias while awaiting cardiac transplantation
Familial or inherited condition with a high risk for life-threatening ventricular tachyarrhythmias such as long QT syndrome
Nonsustained VT with CAD, prior MI, LV dysfunction and inducible sustained VT or VF at EPS
Recurrent syncope of undetermined etiology in the presence of ventricular dysfunction and inducible arrhythmias at EPS when other causes of syncope have been excluded
Class III (Evidence that treatment is ineffective and in some cases may be harmful)
Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmia
Incessant VT or VF
VF or VT resulting from arrhythmias amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with Wolff-Parkinson-White syndrome, RVOT VT, idiopathic LV VT, or fascicular VT)
VT due to a transient reversible disorder (e.g., MI, drugs, trauma, electrolyte disturbance)
Significant psychiatric illness that may be aggravated by ICD implantation or may preclude systemic follow-up
Terminal illness with life expectancy \leq 6 months
Patients with CAD and LV dysfunction with prolonged QRS duration in the absence of spontaneous or inducible sustained or nonsustained VT who are undergoing coronary bypass surgery
NYHA class IV drug-refractory CHF in patients who are not candidates for cardiac transplantation

CHF = congestive heart failure

VF = ventricular fibrillation

VT = ventricular tachycardia

EPS = electrophysiological study

CAD = coronary artery disease

MI = myocardial infarction

RVOT = right ventricular outflow tract

supraventricular tachyarrhythmias. Moreover, ICDs do not provide absolute protection against death from arrhythmia, since about 2% of episodes of ventricular tachyarrhythmias are refractory to

appropriate defibrillator therapy (12). Administration of antiarrhythmic therapy as an adjunct to ICD may reduce the number of recurrent episodes and the defibrillation threshold, and improve responsiveness to shocks (13).

Recent studies suggest that episodes of ventricular fibrillation, even ones that are successfully terminated by implantable cardioverter defibrillators, may increase the risk of myocardial (14, 15) and cerebral ischemic (16, 17) injury. The avoidance of frequent shocks is crucial for the safety and quality of life of patients with ICDs. An important complication of shocks delivered by implantable defibrillators is that they may evoke serious psychological reactions in as many as one third of these patients (18, 19).

VT Mapping and Ablative Therapy

Studies suggest that ventricular tachyarrhythmias occurring in the setting of structural heart disease are due to a reentrant mechanism (20). The ability to reproducibly initiate and terminate VT with programmed ventricular extrastimuli is considered the *sine qua non* of reentry (21). Sustained monomorphic VTs can be due to reentry involving an area of scar, macro-reentry through the bundle branches, and focal automaticity. Scar-related reentry is the most common cause of VT in patients with heart disease. Reentrant VT typically exists as a “figure eight” with clockwise and counterclockwise rotation of wavefronts that share a central isthmus or diastolic pathway. During tachycardia these pathways are protected by lines of block, the integrity of which is crucial for sustaining the VT. There is evidence that even small changes in the conduction characteristics of these pathways or their morphology can terminate the VT (22). Most VT circuits have a subendocardial location, so that a percutaneous approach can be performed without general anesthesia. However, catheter mapping and ablation of VT remain relatively high-risk procedures, with a 10% overall complication rate (23, 24), including a 1–2% rate of procedural mortality (25). An overall approach to VT ablation is illustrated in Fig. 1. Indications for catheter ablation of ventricular tachyarrhythmias can be seen in Table 4. Mapping can be performed during VT and during sinus rhythm, with identification of regions of scar based on mid-diastolic, low-amplitude and low-voltage electrograms (Fig. 2). Conventional mapping techniques involve pacemapping during sinus rhythm to reproduce an electrogram identical to that of the VT (26) (Fig. 3) and entrainment¹ techniques during VT to confirm the presence of a site located within the di-

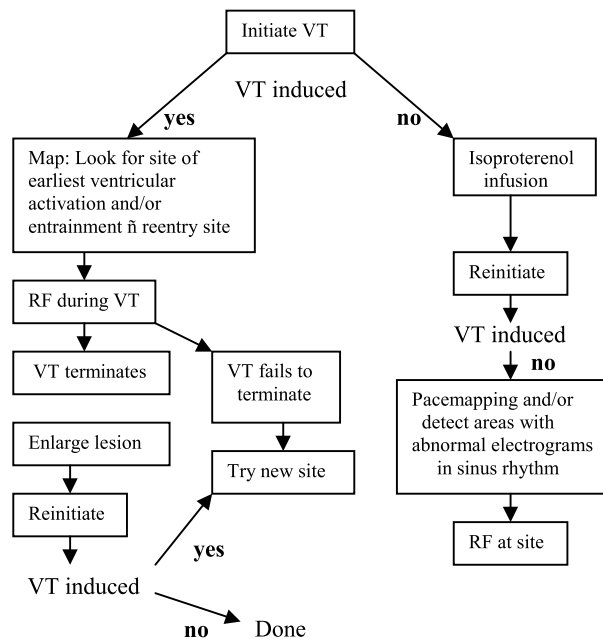


Fig. 1. An algorithm showing how to approach considering VT ablation.

TABLE 4

Indications for Radiofrequency Catheter Ablation in Patients with Ventricular Tachycardia

Catheter Ablation Is the Suggested First-Line Therapy:

- Idiopathic VT: right ventricular outflow tract tachycardia, fascicular tachycardias
- Bundle branch reentry in patients with cardiomyopathy (VT has LBBB-like morphology)

Catheter Ablation Should Be Considered:

- VT in the setting of CAD with multiple ICD shocks
- Slow, incessant VT resistant to multiple medications

No Consistent Data to Suggest Its Efficacy: Ablation Should Not Be Performed

- Arrhythmogenic RV dysplasia
- Dilated Nonischemic Cardiomyopathy

LBBB = left bundle branch block

RV = right ventricle

astolic pathway (22). However, segments that do not participate in the reentrant circuit often may exhibit diastolic activity, leading to low sensitivity and specificity of pacemapping in the presence of infarct scar (26, 27). Concealed entrainment² is demonstrated in only 54–60% of VTs (27, 28)

¹ **Entrainment** is the capture of a reentrant circuit through pacing. The response rate of the circuit, when entrained, is equal to the rate of pacing when pacing at a rate faster than that of the intrinsic tachycardia. The arrhythmia terminates with abrupt cessation of pacing or with pacing at a rate slower than that of the intrinsic tachycardia.

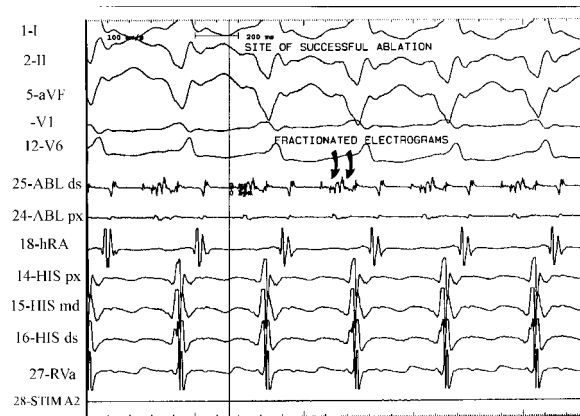


Fig. 2. From top to bottom: limb leads I, II, aVF; precordial leads V1, V6; intracardiac electrograms from distal (ABL ds) and proximal (ABL px) ablation catheter, high Right Atrium (hRA), HIS proximal (HIS px), mid (HIS md) and distal (HIS ds) and Right Ventricle (RVa). Bold arrows show fractionated electrograms in mid-diastole (endocardial recording) at the site of slow conduction. The horizontal bar shown in Lead I represents an interval of 200 milliseconds.

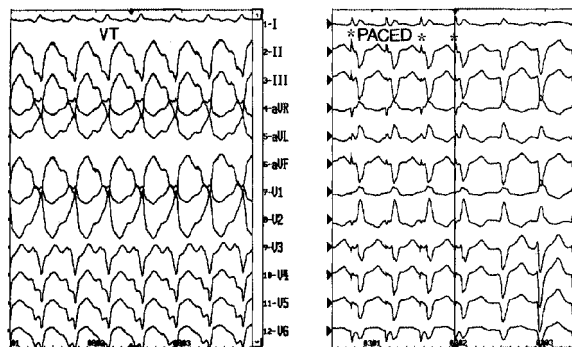


Fig. 3. 12-lead ECG of clinical VT can be seen in the left panel. In the right panel, the first 4 beats are paced (note pacing artifact *), with a QRS morphology identical to the clinical VT (last 3 beats) (no pacing artifact present).

even with the most successful mapping technique for identifying critical regions for ablation. Moreover, when acute ablation is successful, long-term recurrence rates range from 15–50% (23, 24, 29).

The morbidity and mortality of cardiac disease are due, in large measure, to its underlying severity. Patients with scar-related VTs have an average

of three different morphologies of inducible VT at electrophysiologic testing (23, 29). Multiple VT morphologies can be due to multiple reentry circuits that originate from a single region such that ablation of one area may abolish more than one VT. Difficulty in mapping the complex morphology and location of the diastolic pathway is reflected by the frequent failure to eradicate VT in patients with multiple morphologies and the high rates of recurrence of acutely ablated VT. Conventional mapping techniques lack spatial resolution due to the limited number of contact electrodes available, and considerable time is required for mapping at sequential endocardial points.

To overcome these limitations, rapid, high-resolution systems have been developed which map an entire cardiac chamber to identify spatial and temporal relationships critical for maintaining VT (22). Complex ventricular arrhythmias can now be treated even if multiple VT morphologies are present, with high success rates and some of the lowest recurrence rates of targeted VT to date (22, 25). Continued improvements in the computational process of electrogram reconstruction, accuracy of geometry formation, 3-D modeling, and navigation may further improve the results of VT ablation and make the technique more generally available.

Hybrid Therapy

Optimum arrhythmia management has evolved so that the best available management strategies can be combined to reduce or eliminate the risks associated with arrhythmia. Using the combination of catheter ablation and ICDs, or antiarrhythmics and ICDs, may result in greater reduction in the recurrence rate of significant ventricular tachyarrhythmias. This approach has now been accepted as the standard of care (3).

Ablation and ICD

The rationale for combining these modalities stems from several important considerations. Following ablation, the response to programmed stimulation is used to judge its efficacy. However, studies that have assessed the reproducibility of the response to programmed stimulation, or its value in predicting arrhythmia-free survival in patients treated with antiarrhythmic agents, raise considerable doubt about the predictability of the clinical outcome after catheter ablation (30–32). Additionally, the endpoints defining success of catheter ablation for VT in the setting of structural heart disease vary, and the long-term outcomes related to these endpoints have not been determined. The

² **Concealed entrainment** is confirmed by pacing at a rate faster than the intrinsic tachycardia, resulting in an ECG and intracardiac activation identical to the intrinsic tachycardia (see Fig. 3). It occurs as a result of pacing from a site that is orthodromically distal to the area of slow conduction in a reentry circuit, from a site that is distant from the reentry circuit, or from an area of slow conduction in the reentrant circuit.

evolution of ICD and lead technology has resulted in a dramatic reduction in the risk related to implantation of these devices (3). Moreover, studying the efficacy of ablative therapy for VT through the stored diagnostic information in the ICD has great potential for providing important diagnostic information. Indeed, the efficacy of any new antiarrhythmic therapy used for the treatment of ventricular arrhythmias can only be determined in patients with an ICD. Finally, for those patients in whom frequently recurrent VT is not suppressed by antiarrhythmic agents, ablation may serve as an adjuvant therapy to the ICD (3) (Fig. 4).

The disadvantages of combining these modalities include altered pacing thresholds in areas adjacent to endocardial leads and the potential need for additional ICD testing and resetting of antitachycardia pacing features due to changes in VT characteristics as a result of ablative therapy (3).

ICD and Antiarrhythmics

Antiarrhythmic agents remain an important adjuvant to ICD therapy, despite a trend toward less use in patients with ICDs, particularly in those patients presenting with cardiac arrest (33). Antiarrhythmic agents are used to prevent recurrences of arrhythmia and potentially reduce other supraventricular tachycardias that may induce inappropriate shocks from the ICD. Additionally, the use of antiarrhythmics may make the tachycardia amenable to ablative therapy and may reduce the defibrillation threshold. Over the last several years the use of amiodarone and sotalol has increased, while the use of class I agents has decreased. Class III agents,

with the exception of amiodarone, have been shown to decrease the defibrillation threshold (34, 35).

One should be aware of potential adverse reactions when using antiarrhythmics. Class I agents and amiodarone have been associated with an increase in the defibrillation threshold (36). Class I agents also may produce a cycle-length-dependent increase in pacing threshold (37). Slowing the rate of the VT, as occurs with many antiarrhythmic agents, may result in a tachycardia below the rate cut-off for the device. Slowing the sinus rate may result in increased device use via bradycardia pacing.

The well-known proarrhythmic effects of antiarrhythmic drugs may be important. Occasionally, a predictable QT prolongation is noted. However, potentiation of spontaneous arrhythmias, in the absence of surface ECG characteristics such as QT prolongation, may result from alterations in refractoriness due to antiarrhythmic drugs.

Trials

The role of antiarrhythmics and implantable defibrillators for the treatment of ventricular tachyarrhythmias has been studied extensively over the past decade. Some of these trials have had a major impact on the way VT is currently treated. The following is a brief review of some of the primary and secondary prevention trials.

Primary Prevention Trials

CAST: The Cardiac Arrhythmia Suppression Trial (6)

The rationale for CAST was based on the assumption that suppression of asymptomatic ventricular premature depolarizations, a risk factor for sudden death after MI, by chronic antiarrhythmic therapy, would reduce arrhythmic death. Eligible patients had reduced ejection fractions and more than 6 ventricular premature depolarizations/hour. The drugs tested were encainide, flecainide and moricizine. Patients were given "the best drug" based on suppression of ventricular ectopy in an open-label phase. The CAST Data and Safety Monitoring Board recommended that encainide and flecainide be discontinued because of increased mortality from arrhythmia. The study continued with moricizine (CAST II). CAST II was also stopped prematurely due to increased arrhythmic death in the drug treatment population (38).

GESICA: Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina (39)

This study looked at the use of low-dose amiodarone as primary prevention against sudden death in patients with severe congestive heart failure

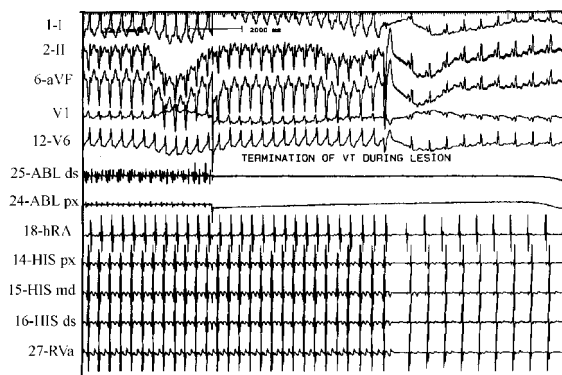


Fig. 4. From top to bottom: limb leads I, II, aVF; precordial leads V1, V6; intracardiac electrograms from distal (ABL ds) and proximal (ABL px) ablation catheter, high Right Atrium (hRA), HIS proximal (HIS px), mid (HIS md) and distal (HIS ds) and Right Ventricle (RVa). Radiofrequency lesions led to termination of VT after the onset of radiofrequency ablation. The horizontal bar shown in Lead I represents an interval of 2000 milliseconds.

(CHF — ejection fraction less than 35%, NYHA classes II, III, and IV). In this population of patients, sudden cardiac death accounts for more than 40% of all deaths. Patients were not being treated with β -blockers and were randomized to receive amiodarone or no therapy. The primary endpoint was total mortality rate, with secondary endpoints of sudden death, progressive heart failure and hospitalization for heart failure. There was a relative-risk reduction in total mortality of 28% in the amiodarone-treated group, which appeared to stem from an early (30-day) reduction in sudden death followed by a later decrease in deaths from progressive heart failure. Interestingly, in this study, amiodarone reduced the total mortality rate without significantly reducing deaths from arrhythmias.

STAT-CHF: Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (40)

Like GESICA, this study examined the effects of amiodarone in patients with CHF (ejection fraction less than 40%). Unlike GESICA, in which only 39% of the patients had coronary artery disease with a prior myocardial infarction, this study enrolled a greater number of patients with ischemic heart disease (72%). The primary endpoint was total mortality rate. The rate of sudden death was not decreased by amiodarone in this study, and there was no significant survival benefit for patients in receiving amiodarone versus placebo. However, in nonischemic heart disease patients (like those in GESICA), a trend favoring amiodarone was noted.

SWORD: Survival with Oral D-Sotalol Study (41)

SWORD attempted to prevent death by using an antiarrhythmic agent in patients at high risk for sudden cardiac death. At the time of this study, the detrimental effects of class I agents in these patients were well known from the CAST trial. Amiodarone, a class III agent, was thought to have a neutral or positive effect in preventing sudden cardiac death. It was hoped that other class III drugs, without the potentially serious adverse effects of amiodarone, would be effective in preventing sudden death. d-sotalol is a pure class III antiarrhythmic agent and lacks the β -blocking effects of d, l-sotalol. This property of d-sotalol may increase its tolerability in patients with left-ventricular dysfunction.

SWORD was a placebo-controlled, randomized study assessing the effects of d-sotalol on the total mortality of patients with a previous myocardial infarction (MI) and reduced left ventricular function. Patients were eligible if they had a previous MI and an ejection fraction less than 40%. QT interval was monitored closely and the study drug was discontinued if the QT interval exceeded prespecified limits.

The primary endpoint was all-cause mortality; the secondary endpoint was cardiac mortality.

The trial was stopped prematurely when it became evident that there were excess deaths in the d-sotalol group. However, there was no excess in serious arrhythmic events or torsades de pointes in the d-sotalol group and few objective data to implicate torsades de pointes or proarrhythmic effects as causes of the increased mortality (42). Interestingly, the adverse effects of the drug were more pronounced in female patients and in patients with an ejection fraction of 30% or greater.

MADIT: Multicenter Automatic Defibrillator Implantation Trial (43)

This was the first trial to study the prophylactic use of implantable cardioverter defibrillators to prevent sudden death from ventricular tachyarrhythmias. The patients were a high-risk group with prior MI, low left ventricular ejection fraction (LVEF) and inducible ventricular arrhythmias. Eligibility criteria included having a myocardial infarction more than 3 weeks prior to enrollment, asymptomatic nonsustained VT and an LVEF less than 35%. There was no placebo arm, but a “conventional therapy” arm was used. The primary endpoint was death from any cause.

After more than 5 years of enrollment, the study was stopped prematurely because superiority of the ICD had been demonstrated. There was no evidence that the use of antiarrhythmic medications or any of the baseline variables of the patients had any influence on the risk of death. In addition, shock discharge occurred in 60% of defibrillator patients within 2 years after implantation.

This study has been criticized for several reasons. After 63 months of enrollment at 32 centers, only 196 patients were enrolled. Additionally, the “conventional therapy” was actually unconventional, with barely half of the patients receiving an angiotensin-converting enzyme (ACE) inhibitor, a β -blocker, or amiodarone.

EMIAT: European Myocardial Infarct Amiodarone Trial (44)

This study examined the use of amiodarone as primary prophylaxis in patients at high risk for death after an acute myocardial infarction. Patients with a documented MI and an ejection fraction less than 40% were randomly assigned to placebo or amiodarone. The primary endpoint was death from any cause, with secondary endpoints of cardiac death, arrhythmic death and arrhythmic death plus resuscitated cardiac arrest. Once again, amiodarone failed to improve survival of patients at high risk of sudden cardiac death.

There was no difference in the all-cause mortality between the treatment groups. However, there was a trend toward reduction in arrhythmic death in the amiodarone group and a significant reduction in the combined endpoint of arrhythmic death and resuscitated cardiac death in the amiodarone group. The reduction in arrhythmic death in the amiodarone group was offset by increases in nonarrhythmic and noncardiac mortality rates. This emphasizes the importance of total mortality rate as an outcome measure in cardiac arrhythmia trials.

CAMIAT: Canadian Myocardial Infarct Amiodarone Trial (45)

The inclusion criteria for this trial were more restrictive than those of EMIAT because of the requirement for spontaneous ventricular ectopy. Patients in this study needed to have at least 10 premature ventricular contractions (PVCs) or at least one run of VT. Unlike EMIAT, the primary endpoint was the composite of resuscitated ventricular fibrillation (VF) or arrhythmic death. Secondary outcomes included arrhythmic death, cardiac death and death from any cause. A high proportion of patients (60%) were taking β -blockers at enrollment, with an even higher proportion at later phases of the trial. By an intention-to-treat analysis, the primary endpoint of resuscitated VF or arrhythmic death was reduced by amiodarone, but the event rate in both groups was low. This study, however, did not use total mortality rate as an endpoint, and the study used a one-sided test of significance which assumes that the use of amiodarone can only be beneficial or neutral if used in this group of patients.

CABG Patch: The Coronary Artery Bypass Graft Patch Trial (46)

This trial tested the hypothesis that prophylactic implantation of a defibrillator at the time of bypass surgery would improve long-term survival of patients at high risk for sudden death. This study included patients with a reduced left-ventricular ejection fraction and an abnormal signal-average-ECG (SAECG), a predictor of increased mortality. Of the patients enrolled, 55% had three-vessel coronary artery disease, 83% had a prior MI, 60% were taking an ACE inhibitor and almost 20% were taking a β -blocker.

Prophylactic implantation of an ICD did not improve survival in this study. An explanation for this may be the potential reduction in ischemia and therefore sudden death, as well as the improvement in LV function in these patients, as a result of revascularization.

MUSTT: Multicenter Unsustained Tachycardia Trial (47)

The ability to guide antiarrhythmic therapy as the result of electrophysiologic (EP) testing in patients at high risk for sudden death was evaluated in this study. Patients included in the study were similar to those in MADIT in that they had coronary artery disease, left-ventricular dysfunction and nonsustained VT. However, more data regarding the inducibility at electrophysiologic testing and responsiveness to antiarrhythmics were obtained in patients enrolled in this study. Patients enrolled had coronary artery disease, and LVEF less than 40%. They underwent electrophysiologic testing with the following endpoints: reproducible induction of sustained VT, reproducible induction of more than 15 complexes of polymorphic VT or ventricular flutter, or noninducibility. Patients who were inducible then were randomized to antiarrhythmic therapy guided by EP testing or no antiarrhythmic therapy. Drugs were assigned randomly, except that amiodarone could only be considered after two failed drug trials. If no drug could be found to prevent inducibility, then a drug that resulted in hemodynamic stability during VT induction could be utilized. ICD therapy could be used after one failed drug trial. The primary endpoint was arrhythmic death or resuscitated cardiac arrest. Secondary endpoints included death from all causes, cardiac death and spontaneous, sustained VT.

In this study, the total mortality in the EP-guided arm was 24% in the ICD-treated patients versus 55% for drug-treated patients and 48% for patients receiving no therapy. The investigators determined that the reduction in total mortality was attributable almost entirely to the use of an ICD in the EP-guided arm. An important lesson from this study is that patients with coronary artery disease, decreased LV function and inducible sustained VT at EP testing, comprise a group of patients at high risk for sudden death and that this risk is reduced substantially by ICD implantation.

Several Trials that Are Still Ongoing

SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial

This trial is enrolling patients with LVEF less than 35%, class II, III, IV, and congestive heart failure for more than 3 months from either ischemic or nonischemic causes. There are no arrhythmia markers included in the eligibility criteria. All patients will be treated with optimized heart failure regimens including afterload reduc-

tion, β -blockers and diuretics. Patients will be randomized for adjunctive therapy with placebo, amiodarone or an ICD. The primary endpoint is death from any cause.

DEFINITE: Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation Trial

This study focuses on patients with a dilated cardiomyopathy of nonischemic causes. Eligibility criteria include a nonischemic cardiomyopathy with a left ventricular ejection fraction of less than 35%, and either nonsustained VT on Holter monitoring or telemetry monitoring or more than 10 PVCs/hour on Holter monitoring. Patients will be assigned to conventional heart-failure treatment with or without an ICD to determine whether defibrillator implantation will improve survival in this group of patients.

DINAMIT: Defibrillators in Acute Myocardial Infarction Trial

Because arrhythmic death is common in high-risk survivors of myocardial infarction, this study was devised to examine the effects of defibrillator implantation in patients with a recent myocardial infarction. Patients have to have suffered a myocardial infarction less than 30 days prior to enrollment, an LVEF less than 35% and abnormal heart-rate variability. In addition to receiving medical therapy with aspirin, ACE inhibitors, β -blockers and lipid-lowering agents (statins), patients will be randomized to therapy with or without an ICD.

BEST + ICD Trial: Beta Blocker Strategy Plus ICD

This European trial being conducted at 50 centers is enrolling 1,500 patients who have had myocardial infarctions, in order to determine if there is any difference in survival following EP-guided therapy and defibrillator therapy in contrast to conventional therapy. Criteria for inclusion in the trial are acute myocardial infarction within 5 to 21 days prior to enrollment, treatment with β -blockers, an LVEF less than 35% and a marker of future arrhythmic events such as decreased heart-rate variability, more than 10 PVC/hour, or prolonged QRS duration on filtered and averaged electrocardiograms (late potentials).

MADIT II: Multicenter Automatic Defibrillator Implantation Trial

To address the concerns from MADIT regarding the arm of "conventional therapy," more attention will be given in this trial to avoiding the use of antiarrhythmics and to optimizing the use of ACE inhibitors and β -blockers. Patient eligibility in-

cludes surviving a myocardial infarction, LVEF less than 30% and more than 10 PVCs or couplets on Holter monitoring. The aim of this study is to assess whether defibrillator therapy will increase overall survival of patients with coronary artery disease, and at great risk for sudden arrhythmic death.

Secondary Prevention Trials

CASCADE: Cardiac Arrest in Seattle: Conventional versus Amiodarone Study (48)

CASCADE evaluated two different approaches to the management of patients who survived out-of-hospital cardiac arrest and who were at high risk for recurrent cardiac arrest. The empiric use of amiodarone without extensive EP testing or Holter monitoring was compared with standard (Class Ia) antiarrhythmic agents (quinidine, procainamide, disopyramide) guided by EP testing or Holter monitoring. The primary endpoint of the study was total cardiac mortality rate, including sudden arrhythmic death, documented resuscitated out-of-hospital VF, and nonarrhythmic cardiac death. In addition, for patients with an ICD, syncope followed by a shock was designated as the equivalent of a cardiac arrest. In this study, ICD therapy was not randomized and no attempt was made to compare outcomes relating ICDs.

The use of amiodarone in this study significantly reduced the primary endpoints of total cardiac mortality, resuscitated cardiac arrest and syncope ICD shock. If the endpoints of sustained VT requiring cardioversion and near-syncope ICD shock were added to the primary endpoints, amiodarone again was associated with a significant reduction. The results of this study indicated that empiric use of amiodarone was more effective in preventing recurrent arrhythmias than conventional antiarrhythmics guided by EP testing. A placebo group was not included in this study, a fact that is clearly important, as learned from the CAST study.

AVID: Antiarrhythmics versus Implantable Defibrillators (49)

With the growing availability of ICDs and the unsatisfactory prevention of death by antiarrhythmics, a study comparing the two modes of therapy was designed. The AVID trial was the first large, randomized, controlled study of the effectiveness of the ICD in the secondary prevention of sudden cardiac death. Patients were eligible for AVID if they had been resuscitated from VF, had sustained VT with syncope, or sustained VT with an LVEF less than 40% and hemodynamic compromise including near-syncope, CHF or angina. Patients were randomized to ICD therapy or antiarrhythmic drugs. Patients receiving

drug therapy were given amiodarone or sotalol guided by EP testing or Holter monitoring.

The trial was stopped prematurely when ICD therapy was shown to result in a significant survival advantage compared to antiarrhythmic drug therapy. Based on the results of this study, it has been concluded that a patient who has survived an episode of VF or unstable VT should receive an ICD as first-line therapy. However, even prior to the completion of this study, multiple single-center studies had shown ICD therapy to be superior to antiarrhythmic therapy for life-threatening ventricular arrhythmias. It was pointed out that the AVID trial was too late and to some extent not necessary, given the already established role of the ICD in the secondary prevention of sudden cardiac death (50).

CIDS: Canadian Implantable Defibrillator Study (51)

CIDS was similar to AVID in its design. It compared amiodarone to ICD therapy in patients at high risk for recurrent ventricular tachyarrhythmias. This study was started virtually simultaneously with AVID, but had a longer enrollment and longer follow-up. Inclusion criteria were documented VF, out-of-hospital cardiac arrest requiring defibrillation, documented sustained VT-causing syncope, or documented VT at a rate of at least 150 bpm causing near-syncope or angina, in patients with LVEF of less than 35%. An additional inclusion criterion not included in AVID was unmonitored syncope with subsequent documentation of either spontaneous VT of at least 10 seconds, or sustained (greater than 30 seconds) monomorphic VT induced at EP testing.

The results of this trial showed an overall trend toward a lower mortality and arrhythmic death associated with use of the ICD. The difference, however, was not statistically significant. Several possibilities exist that may help explain the discrepancy between the results of this study and those of AVID: the lack of the use of sotalol, the greater use of β -blockers in the amiodarone arm, and the fact that 5.5% of patients randomized to receive an ICD never actually had the implantation.

Conclusions

Treatment and prevention of sudden arrhythmic death have been a long-standing challenge to clinicians. An immense amount of information has been obtained from studies of antiarrhythmic agents and implantable cardioverter defibrillators. As we better understand the mechanisms underlying arrhythmias and as technology improves, definitive treatment with ablation will become more widely available. Currently, optimum ventricular tachycardia

management has evolved to combine ICDs with catheter ablative and drug therapy in an attempt to eliminate or reduce arrhythmia risk. Therapy should not be based on the use of a single strategy; rather, it should be based on the use of combined or hybrid therapy that will provide superior control of arrhythmia and relief of symptoms. The presence of underlying heart disease and left ventricular dysfunction remain important variables that will influence the choice of therapy and its effectiveness.

References

1. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation* 1998; 98:2334–2351.
2. Mehta D, Curwin J, Gomes JA, Fuster V. Sudden death in coronary artery disease: Acute ischemia versus myocardial substrate. *Circulation* 1997; 96:3215–3223.
3. Marchlinski FE, Zado ES, Callans DJ, et al. Hybrid therapy for ventricular arrhythmia management. *Cardiol Clin* 2000; 18:391–406.
4. Roden DM. Antiarrhythmic drugs: From mechanisms to clinical practice. *Heart* 2000; 84:339–346.
5. Vaughan Williams EM. A classification of antiarrhythmic actions after a decade of new drugs. *J Clin Pharmacol* 1984; 24:129–147.
6. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; 324:781–788.
7. Siebels J, Cappato R, Ruppel R, et al. ICD versus drugs in cardiac arrest survivors: Preliminary results of the Cardiac Arrest Study Hamburg. *Pacing Clin Electrophysiol* 1993; 16:552–558.
8. Singh BN. Overview of trends in the control of cardiac arrhythmia: Past and future. *Am J Cardiol* 1999; 84:3R–10R.
9. Mirowski M, Reid PR, Mower MM, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980; 303:322–324.
10. Winkle RA, Mead RH, Ruder MA, et al. Long-term outcome with the automatic implantable cardioverter-defibrillator. *J Am Coll Cardiol* 1989; 13:1353–1361.
11. Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). *Circulation* 1998; 97:1325–1335.
12. Pacifico A, Johnson JW, Stanton MS, et al. Comparison of results in two implantable defibrillators. Jewel 7219D Investigators. *Am J Cardiol* 1998; 82:875–880.
13. Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. d,l-Sotalol Implantable Cardioverter-Defibrillator Study Group. *N Engl J Med* 1999; 340:1855–1862.
14. Tokano T, Bach D, Chang J, et al. Effect of ventricular shock strength on cardiac hemodynamics. *J Cardiovasc Electro-physiol* 1998; 9:791–797.
15. Joglar JA, Kessler DJ, Welch PJ, et al. Effects of repeated electrical defibrillations on cardiac troponin I levels. *Am J Cardiol* 1999; 83:270–272, A6.
16. de Vries JW, Bakker PF, Visser GH, et al. Changes in cerebral oxygen uptake and cerebral electrical activity during defibrillation threshold testing. *Anesth Analg* 1998; 87:16–20.

17. Murkin JM, Baird DL, Martzke JS, Yee R. Cognitive dysfunction after ventricular fibrillation during implantable cardioverter/defibrillator procedures is related to duration of the reperfusion interval. *Anesth Analg* 1997; 84:1186–1192.
18. Hegel MT, Griegel LE, Black C, et al. Anxiety and depression in patients receiving implanted cardioverter-defibrillators: A longitudinal investigation. *Int J Psychiatry Med* 1997; 27:57–69.
19. Bourke JP, Turkington D, Thomas G, et al. Florid psychopathology in patients receiving shocks from implanted cardioverter-defibrillators. *Heart* 1997; 78:581–583.
20. Stevenson WG, Khan H, Sager P, et al. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. *Circulation* 1993; 88:1647–1670.
21. Josephson ME, Almendral JM, Buxton AE, Marchlinski FE. Mechanisms of ventricular tachycardia. *Circulation* 1987; 75(4 Pt 2):III41–III47.
22. Chow AW, Schilling RJ, Peters NS, Davies DW. Catheter ablation of ventricular tachycardia related to coronary artery disease: The role of noncontact mapping. *Curr Cardiol Rep* 2000; 2:529–536.
23. Gonska BD, Cao K, Schaumann A, et al. Catheter ablation of ventricular tachycardia in 136 patients with coronary artery disease: Results and long-term follow-up. *J Am Coll Cardiol* 1994; 24:1506–1514.
24. Stevenson WG, Delacretaz E. Strategies for catheter ablation of scar-related ventricular tachycardia. *Curr Cardiol Rep* 2000; 2:537–544.
25. Josephson ME, Waxman HL, Cain ME, et al. Ventricular activation during ventricular endocardial pacing. II. Role of pace-mapping to localize origin of ventricular tachycardia. *Am J Cardiol* 1982; 50:11–22.
26. Miller JM, Marchlinski FE, Buxton AE, Josephson ME. Relationship between the 12-lead electrocardiogram during ventricular tachycardia and endocardial site of origin in patients with coronary artery disease. *Circulation* 1988; 77:759–766.
27. Morady F, Kadish A, Rosenheck S, et al. Concealed entrainment as a guide for catheter ablation of ventricular tachycardia in patients with prior myocardial infarction. *J Am Coll Cardiol* 1991; 17:678–689.
28. Stevenson WG, Friedman PL, Kocovic D, et al. Radiofrequency catheter ablation of ventricular tachycardia after myocardial infarction. *Circulation* 1998; 98:308–314.
29. Rothman SA, Hsia HH, Cossu SF, et al. Radiofrequency catheter ablation of postinfarction ventricular tachycardia: Long-term success and the significance of inducible nonclinical arrhythmias. *Circulation* 1997; 96:3499–3508.
30. Kudenchuk PJ, Kron J, Walance CG, et al. Day-to-day reproducibility of antiarrhythmic drug trials using programmed extrastimulus techniques for ventricular tachyarrhythmias associated with coronary artery disease. *Am J Cardiol* 1990; 66:725–730.
31. Mason JW. A comparison of electrophysiologic testing with Holter monitoring to predict antiarrhythmic-drug efficacy for ventricular tachyarrhythmias. *Electrophysiologic Study versus Electrocardiographic Monitoring Investigators*. *N Engl J Med* 1993; 329:445–451.
32. Wilber DJ, Garan H, Finkelstein D, et al. Out-of-hospital cardiac arrest. Use of electrophysiologic testing in the prediction of long-term outcome. *N Engl J Med* 1988; 318:19–24.
33. Marchlinski FE, Zado ES, Deely MP, et al. Concomitant device and drug therapy: Current trends, potential benefits, and adverse interactions. *Am J Cardiol* 1999; 84:69R–75R.
34. Dorian P, Newman D. Effect of sotalol on ventricular fibrillation and defibrillation in humans. *Am J Cardiol* 1993; 72:72A–79A.
35. Movsowitz C, Marchlinski FE. Interactions between implantable cardioverter-defibrillators and class III agents. [review] *Am J Cardiol* 1998; 82:4II–48I.
36. Huang SK, Tan de Guzman WL, Chenarides JG, et al. Effects of long-term amiodarone therapy on the defibrillation threshold and the rate of shocks of the implantable cardioverter-defibrillator. *Am Heart J* 1991; 122 (3 Pt 1):720–727.
37. Hook BG, Perlman RL, Callans DJ, et al. Acute and chronic cycle length dependent increase in ventricular pacing threshold. *Pacing Clin Electrophysiol* 1992; 15:1437–1444.
38. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. The Cardiac Arrhythmia Suppression Trial II Investigators. *N Engl J Med* 1992; 327:227–233.
39. Doval HC, Nul DR, Grancelli HO, et al. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina (GESICA). *Lancet* 1994; 344:493–498.
40. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995; 333:77–82.
41. Waldo AL, Camm AJ, deRuiter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. *Survival With Oral d-Sotalol*. *Lancet* 1996; 348:7–12.
42. Pratt CM, Camm AJ, Cooper W, et al. Mortality in the survival with oral d-sotalol (SWORD) trial: Why did patients die? *Am J Cardiol* 1998; 81:869–876.
43. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; 335:1933–1940.
44. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. *Lancet* 1997; 349:667–674.
45. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. *Lancet* 1997; 349:675–682.
46. Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. *N Engl J Med* 1997; 337:1569–1575.
47. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; 341:1882–1890.
48. Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (the CASCADE study). *Am J Cardiol* 1991; 67:578–584.
49. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med* 1997; 337:1576–1583.
50. Josephson ME, Nisam S. The AVID trial: Evidence based or randomized control trials — is the AVID study too late? *Antiarrhythmics Versus Implantable Defibrillators*. *Am J Cardiol* 1997; 80:194–197.
51. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000; 101:1297–1302.