Controlling Cardiac Arrhythmias: An Overview With a Historical Perspective

Bramah N. Singh, MD, PhD

During the past decade, several developments in our knowledge of antiarrhythmic drugs have had a major influence on our approach to their use. These developments may be summarized as follows: (1) it has become clear that arrhythmias merit treatment only for the relief of symptoms, with improved quality of life, and for prolongation of survival by reducing arrhythmic deaths; (2) suppression of arrhythmias—symptomatic or asymptomatic—may not necessarily decrease mortality, the net impact on mortality being agent-specific; (3) antiarrhythmic drugs have the propensity to decrease as well as to increase cardiac arrhythmias (producing proarrhythmias); (4) the most important determinant of arrhythmia mortality is the degree and nature of ventricular dysfunction; and (5) only controlled trials have the potential to establish the effect of treatment on mortality in patients with cardiac arrhythmias. To these considerations must be added the advances in nonpharmacologic approaches to controlling cardiac arrhythmias. These include catheter ablation of cardiac arrhythmias, certain surgical techniques that in selected patients offer prospects of cure, and the development of implantable ventricular and atrial cardioverter defibrillators, which allow the evaluation of drugs versus placebo against the background of the defibrillator. This is particularly germane in the case of life-threatening symptomatic ventricular arrhythmias such as sustained ventricular tachycardia and ventricular fibrillation. Antiarrhythmic drugs and implantable devices in the control of arrhythmias cannot be considered in isolation. Their role in mortality reduction needs to be defined alone as well as in combination by controlled clinical trials.

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During the past 10 years, there has been a major revolution in our understanding of (1) how cardiac arrhythmias are generated; (2) the clinical settings in which their presence might be predictive of premature death; and (3) the circumstances in which arrhythmias may be nothing more than troublesome symptoms having no deleterious effect on prognosis. It is now clear that there are clinical settings in which the presence of arrhythmias are associated neither with symptoms nor with an adverse prognosis.[1] It has also been established that there are other settings in which the occurrence of frequent and complex ventricular arrhythmias, especially in the context of serious underlying organic cardiac or electrical disease, is associated with an increased incidence of sudden death resulting in decreased survival.[2,3] Thus, antiarrhythmic therapy and regimens have evolved over many decades, to terminate arrhythmias promptly and effectively, to relieve symptoms by reducing or eliminating episodes of tachyarrhythmias, and/or to prolong survival by decreasing arrhythmia mortality.

This overview focuses on the evolution of pharmacologic approaches. However, the recent development in nonpharmacologic techniques has been impressive and the impact so far-reaching, in some instances, that pharmacologic therapy of cardiac arrhythmias can no longer be considered in isolation. Therefore, wherever relevant, reference will be made to nonpharmacologic methods of arrhythmia control, especially in clinical situations in which nonpharmacologic approaches (e.g., implantable devices) and drug therapy are increasingly being used in combination. It should be emphasized that there is now a need to define clearly the contexts in arrhythmia management in which drug therapies should be front-line, those in which invasive approaches (especially the use of radiofrequency catheter ablation and implantable devices) should be considered first, and those in which a combination of approaches might be chosen to control an individual arrhythmia. Surgery and electrode catheter ablation are discussed elsewhere in this supplement.[4]

EVOLUTION OF DRUG THERAPY OF CARDIAC ARRHYTHMIAS

Since the introduction in 1918 of quinidine as an antiarrhythmic agent, our knowledge of the mechanisms of cardiac arrhythmias has expanded considerably. However, during the decades that followed the introduction of quinidine, some doubt remained as to how the drug produced its observed salutary effects. It was not clear whether the bulk of its actions stemmed from blocking conduction—which it clearly did—or whether its actions are, in part, due to lengthening repolarization, which it also produced. The drug's mechanism became evident when the effects of the drug could be evaluated in isolated cardiac muscle by application of the microelectrode technique to the cardiac membrane.[5]

Based on such analyses in the 1950s and 1960s, it became evident that lidocaine, which gained prominence with the widespread use of coronary care units for the management of arrhythmias in acute myocardial infarction, acted essentially by blocking sodium-channel activity in cardiac muscle, as it did in nerve.[6] Its electrophysiologic properties subsequently led to

From the Division of Cardiology and the Department of Medicine, Veterans Affairs Medical Center of West Los Angeles, and the Department of Medicine, University of California, Los Angeles School of Medicine, Los Angeles, California.

Address for reprints: Bramah N. Singh, MD, PhD, Division of Cardiology 111E, Veterans Affairs Medical Center of West Los Angeles, 11301 Wilshire Boulevard, Los Angeles, California 90073.

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the synthesis and characterization of the orally active congeners of the drug, mexiletine and tocainide. In contrast, disopyramide and procainamide (both, like quinidine, are potent, sodium-channel–mediated conduction blockers in cardiac muscle) were also found to delay repolarization. The question therefore arose as to which of the 2 fundamental actions of these drugs, 1 on conduction and the other on repolarization, were responsible for their antifibrillatory actions. In 1957, Jervell and Lang-Nielsen[7] and Selzer and Wray[8] reported that lengthening of the QT interval, induced either by a congenital abnormality or by such drugs as quinidine, produced what Dessertenne[9] subsequently called torsades de pointes. This arrhythmia was often fatal, which led to the belief that prolongation of repolarization was essentially arrhythmogenic in nature; it was assumed that the beneficial effects of quinidine-like drugs were due to their propensity to delay conduction (with an increase in time-dependent refractoriness).

In the 1960s, several new classes of cardioactive drugs were synthesized specifically to ameliorate ischemia, either by reducing oxygen consumption (β blockers, including sotalol) or by coronary vasodilation (verapamil and amiodarone). All such agents were found to exert potent antiarrhythmic and antifibrillatory actions in clinically relevant experimental models. Very soon after the introduction of β blockers, it was recognized that they exerted antiarrhythmic properties in experimental animals and in patients with heart disease. This was not surprising since it had been known for many years that adrenergic excitation may lead to ventricular fibrillation. The reduction of adrenergic activity to the heart was therefore expected to be antifibrillatory. Similarly, in a systematic search for novel antiarrhythmic mechanisms, Singh and Vaughan Williams[10] found that sotalol, while being a potent β blocker, prolonged the action potential duration in atria and ventricular tissues, as does the long-term administration of amiodarone.[11] The electrophysiologic properties of sotalol and amiodarone differed markedly from those of quinidine, disopyramide, and procainamide but were somewhat similar to those of β blockers, because both agents had significant antiadrenergic effects. (Sotalol is a conventional β blocker whereas amiodarone is a potent noncompetitive β-receptor antagonist.) Sotalol and amiodarone shared the unusual and marked tendency to prolong repolarization with a corresponding lengthening of the effective refractory period.

CLASSIFICATION OF ANTIARRHYTHMIC MECHANISMS: CONVENTIONAL CLASSIFICATION SYSTEM VERSUS THE SICILIAN GAMBIT

In the conventional classification system, antiarrhythmic compounds were grouped on the basis of the electrophysiologic mechanisms believed to cause their salutary effects.[10–16] The classification was based simply on the dominant effects of the drugs: (1) class I agents mediated sodium-channel conduction (with or without an effect on repolarization); (2) class II agents were antagonists of sympathetic excitation (as typified by β blockers); (3) class III agents acted predominantly on refractoriness (with or without some effects on conduction, as exemplified by sotalol and amiodarone); and (4) class IV agents altered calcium-channel–mediated conduction and refractoriness (as typified by verapamil). Despite the inherent limitations of extrapolating data from isolated tissues to the enormously complex situation in the diseased human myocardium, such a classification system has had wide clinical appeal and considerable influence on the synthesis and characterization of newer agents.

The recent drug classification debate has centered on the relevance a classification system based on antiarrhythmic mechanisms might have to the choice of a particular compound for a specific clinical arrhythmia.[17,18] In the prediction of one major end point, there is little doubt that the conventional classification system has had utility in predicting mortality changes related to class actions, as illustrated in Figure 1. The mean data shown are derived from meta-analyses of outcomes in randomized clinical trials in post–myocardial infarction patients.[19] In the case of class I drugs, an adverse effect on mortality is seen across the class without exception. It is clearly a class effect. On the other hand, β blockers as a class, consistently decrease mortality.[18] There are fewer data for class III agents; in Figure 1, the data refer solely to amiodarone, a complex compound with multiple actions. In the case of calcium-channel antagonists (class IV agents), the influence on mortality is either neutral or somewhat deleterious; within the class, it is agent-specific, related undoubtedly to variations in the associated properties of individual compounds, especially their duration of action and possibly the magnitude of heart rate increases they produce. From the standpoint of the clinician, it is evident that the conventional classification of antiarrhythmic mechanisms as originally suggested by Singh and Vaughan Williams[10–16] allows a reasonable, albeit not perfect, prediction of outcomes in mortality. The effect on mortality cannot be ignored even when antiarrhythmic agents are used solely for relief of symptoms.

The Singh and Vaughan Williams classification[10–16] has the merit of simplicity. It identifies the most significant electrophysiologic or pharmacodynamic parameter, subsequently termed the vulnerable parameter in the Sicilian Gambit.[17] This parameter attempts to define the principal determinant of arrhythmia conversion, as well as prevention of the arrhythmia and its deterioration into irreversible cardiac arrest. It is known that the net outcome may not always be determined by the action of an antiarrhythmic agent on a single electrophysiologic parameter. The outcome may also depend critically on the modulating effect on the myocardium of the associated properties of individual compounds. This issue was raised $>$20 years ago[16] and is illustrated cogently by β-blocking actions (in the case of sotalol), by a host of differing actions including noncompetitive adrenergic antagonism (exhibited by amiodarone and its deriva-

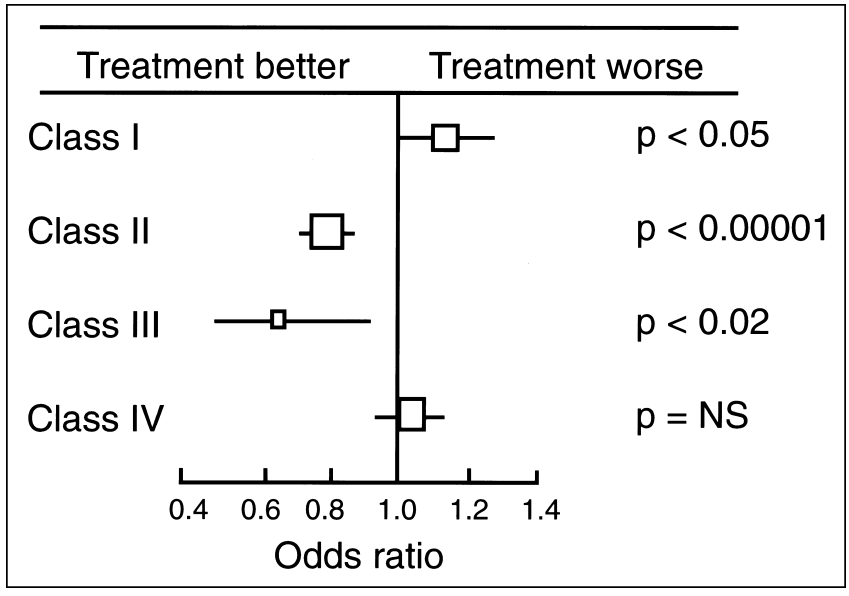

FIGURE 1. Metanalytic data on the effects of various electrophysiologic classes of drugs on the risk of dying among myocardial infarction survivors who received the drug versus survivors who received placebo. Class I drugs increase mortality; β blockers decrease mortality, as do class III agents (sotalol and amiodarone); and calcium antagonists have variable but minor effects. Rectangles represent the number of patients analyzed in each group and vary in size accordingly (data shown with standard deviations). The odds ratio is presented as relative risk. MI = myocardial infarction. (Reprinted with permission from *J Cardiovasc Electrophysiol.*[19])

tives), and by the adrenergic neuron-blocking actions (in the case of bretylium). Another example is the anticholinergic property of disopyramide and quinidine. Of course, not all the associated properties of individual antiarrhythmic agents are beneficial.

An important consequence of the conventional classification of antiarrhythmic drugs has been the synthesis and characterization of antiarrhythmic agents with simpler electrophysiologic profiles. This is exemplified in class I agents by flecainide and encainide and, in class III compounds, by *d*-sotalol, dofetilide, sematilide, E-4031, azimilide, and a host of other agents,[20] many of which have been abandoned and developed no further. These so-called pure or selective agents with a single major electrophysiologic property have served as pharmacologic probes that have allowed the investigator to determine their antiarrhythmic and proarrhythmic correlates, such as incessant ventricular tachycardia (VT) in the case of flecainide and propafenone and torsades de pointes in the case of pure class III agents.

The Sicilian Gambit assumes that a precise understanding of the factors that affect the vulnerable parameter, including changes in receptors, ionic currents, and pumps, allows the clinician to choose the appropriate drug regimen for a particular arrhythmia. For the present, it would appear that with very few exceptions these factors are still the subject of research rather than accepted fact with an established place at the bedside. Except in exceptional instances, the rational targeting of arrhythmic phenomena with drugs having known properties, as defined by the Sicilian Gambit, might be an unrealistic goal, given the present state of knowledge. For example, characterizing the actions of amiodarone in terms of effects on ionic currents, receptors, and pumps, and then correlating the changes with the success or failure of prophylactic control of VT and ventricular fibrillation (VF) have so far yielded conflicting results; with all its complexity of action and its variegated side-effect profile, amiodarone appears to produce the most consistent effect when it is given empirically in the control of VT/VF and in preventing recurrences of atrial fibrillation (AF). On the basis of currently available data, the conventional classification (if fine-tuned and updated in light of increasing data) will remain helpful to clinicians in the choice of agents, at least for the purpose of altering mortality and preventing recurrences of AF. Whereas at present the Sicilian Gambit has little or no direct clinical utility, in the future it might predict mortality changes produced by different classes of antiarrhythmic drugs. Its use in the future may well pave the way for the development of newer and more effective antiarrhythmic compounds. Clearly, the 2 systems of classifying antiarrhythmic mechanisms are not mutually exclusive, and the rational use of antiarrhythmic drugs requires essential elements from both systems.

IS THERE STILL A ROLE FOR CLASS I ANTIARRHYTHMIC DRUGS?

Whereas the data suggesting that sodium-channel blockers increase rather than decrease mortality when used as antiarrhythmic drugs in patients with cardiac disease has been increasing for some time, not until the publication of the results of the Cardiac Arrhyth-

mia Suppression Trials (CAST) was the evidence compelling.[21,22] Do these drugs still have a role in the therapy of cardiac arrhythmias? The data suggest that if they do, the role is a small one, perhaps limited solely to the relief of arrhythmia symptoms and to the maintenance of sinus rhythm in AF patients without demonstrable cardiac disease. There is no decisive evidence from any controlled study to support the premise that this class of drugs has the potential to prolong survival in patients at high risk of sudden death. On the contrary, numerous lines of evidence, including meta-analyses,[19] have yielded evidence that in virtually every subset of patients with significant cardiac disease, this class of compounds increases mortality.[23,24] This applies to patients with cardiac arrest,[25] those surviving myocardial infarctions,[21,22] patients with AF,[26,27] and those in whom premature ventricular contractions occur independently of recent myocardial infarctions.[28] Furthermore, given as electrophysiologically or Holter-guided therapy, these agents are inferior to guided therapy with sotalol,[29,30] to empiric amiodarone,[31] and to implantable cardioverter defibrillators (ICDs) in patients surviving cardiac arrest and those presenting with symptomatic VT/VF.[32]

The realization that class I drugs increase arrhythmia mortality in patients with cardiac disease has had 2 direct consequences: (1) earlier and increasing use of ICDs; and (2) increasing use of drugs with alternative modes of action, especially those that fundamentally prolong the action potential duration and effective refractory period homogeneously while having the potential to block sympathetic stimulation. The increasing use of alternative agents is especially marked in the case of agents that have the added property of attenuating sympathetic excitation in the heart, namely amiodarone and sotalol.[18] Although it is not entirely proved that amiodarone and sotalol, while being powerful sympathetic antagonists, act dominantly by prolonging the action potential duration, the hypothesis has led to the search for and development of pure compounds devoid of other associated properties and having simpler side-effect profiles.[33]

CLASS III ACTION AND THE DILEMMA OF ANTIARRHYTHMIC DRUG THERAPY

Only 3 types of antiarrhythmic agents, β blockers, sotalol, and amiodarone, now appear to offer arrhythmia mortality reduction by preventing ventricular fibrillation in patients with cardiac disease. Sotalol and amiodarone also have a documented propensity for maintaining stable sinus rhythm in patients converted from AF. Both share the property of lengthening repolarization and refractoriness while having antiadrenergic actions in common with β blockers; amiodarone has additional electrophysiologic effects together with exceedingly complex pharmacokinetics and membrane effects.[34] The clinical profiles of sotalol and amiodarone do not, however, reveal which electrophysiologic properties are linked precisely to their clinical antifibrillatory and profibrillatory actions, nor do data from direct, controlled comparisons reveal the agents' relative potencies as antiarrhythmic and antifibrillatory compounds. An understanding of the mechanisms of action and the clinical effects of the so-called pure class III compounds[20,33] is likely to provide insight into the exact significance of lengthening the action potential duration in preventing AF and VF. It is important that both sotalol and amiodarone have potent antisympathetic actions, which may play a crucial role in mediating a significant component of their beneficial actions. The precise importance of antiadrenergic actions may emerge as further data comparing pure class III agents directly with sotalol and amiodarone become available.

SOTALOL AND AMIODARONE: NOT JUST CLASS III AGENTS

Sotalol: Sotalol is a racemic mixture of its dextro- and levo-isomers; the levo-isomer contributes the bulk of the β blocking to the racemate action, whereas both isomers are equipotent in prolonging the action potential duration and the effective refractory period in most cardiac tissues.[35] These 2 properties are, however, unrelated; repolarization is not prolonged by β blockade per se. Thus, the pharmacodynamic properties of the compound stem from its dual actions. Another way to view the overall property and therapeutic utility of sotalol is to consider that its major action is in prolonging repolarization and refractoriness in atrial and ventricular muscle, actions that are modulated favorably by the drug's intrinsic sympathetic blocking actions. Its β-blocking actions slow the sinus rate, and in AF the ventricular response is slowed. On the other hand, the precise efficacy of the drug in the conversion to and maintenance of sinus rhythm in AF patients remains to be defined. It is currently the subject of several major controlled, blind and unblind clinical trials.

In recent years, sotalol has emerged as a major antiarrhythmic agent.[34,35] Because the drug is useful in decreasing mortality directly or indirectly and in controlling arrhythmic symptoms, several areas of clinical utility warrant emphasis: (1) effect on reinfarction and mortality in the survivors of myocardial infarction; (2) conversion of VT/VF; (3) beneficial effect on life-threatening ventricular arrhythmias, especially in patients with symptomatic sustained VT/VF or those surviving cardiac arrest; and (4) its conjoint use with ICDs in reducing the number of shocks and in prolonging survival. Each of these areas will be discussed because they illustrate drug actions that are important in clinical therapeutics.

In a placebo-controlled, double-blind multicenter trial, 1,456 survivors of acute myocardial infarction were randomized to sotalol or placebo.[36] At 12 months, the mortality was 8.8% in the placebo group and 7.3% in the sotalol-treated group. The difference, representing an 18% decrease in mortality, did not reach statistical significance. The class II action of the β blocker might have been expected to confer a greater favorable impact on mortality. It has been argued that several features of the trial design (e.g.,

60:40 randomization in favor of the drug, single daily dose [320 mg] of sotalol, and the possibility that many patients might have been given concomitant diuretics) might have decreased the magnitude of the expected reduction in mortality by slightly increasing the number of deaths, undoubtedly due to the proarrhythmic actions of the drug. This trend was clearly offset during the later stages of the trial, when a trend in favor of mortality reduction developed. The reinfarction rate, however, was decreased significantly, as might be expected of a β blocker (Figure 2). A mortality trial with sotalol in post–myocardial infarction patients is unlikely to be repeated. However, a significant beneficial effect with the drug in this setting is not excluded if the drug is confined to the subsets of patients in whom the likelihood of proarrhythmic reactions is minimized.[37]

The most systematic data on sotalol in VT/VF are from the Electrophysiologic versus Electrocardiographic Monitoring (ESVEM) study.[29] Two discrete observations merit emphasis. First, there were no significant differences between programmed electrical stimulation and Holter monitoring in predicting arrhythmia recurrence, sudden death, cardiac death, or all-cause mortality.[30] Second, sotalol was superior to 6 class I agents individually or collectively on the basis of mean percentage efficacy with respect to total mortality, sudden death, cardiac death, and, especially, VT recurrence.[29] At 1 year, arrhythmia had recurred in 44% of the patients taking class I agents and in 21% of the patients taking sotalol ($p < 0.0007$). Three conclusions can be drawn from these results: (1) the responses are likely drug-specific rather than technique-specific, sotalol being more effective than class I agents because of its unique combination of pharmacodynamic properties[38]; (2) Holter monitoring appeared to have greater clinical applicability for selecting drug therapy for VT/VF; but (3) Holter monitoring and programmed electrical stimulation might have no scientific validity, and sotalol (as with β blockers and amiodarone), may be used empirically.[38] At the very least, sotalol is clearly superior to class I agents in the prophylactic control of VT/VF. The data agree with findings from a blind, controlled study that indicate intravenous sotalol was significantly more effective than intravenous lidocaine in converting sustained monomorphic VT to sinus rhythm (69% vs 18%; $p < 0.01$).[39] On the other hand, it remains unclear whether sotalol is, in fact, superior to β blockers or to amiodarone for controlling VT/VF. There have been no placebo-controlled trials of sotalol for maintaining sinus rhythm after electrical conversion of AF and atrial flutter. However, the potency of the drug appears to be similar to quinidine and propafenone.[40] The efficacy of sotalol and amiodarone in maintaining sinus rhythm in AF is being compared in a double-blind, placebo-controlled Veterans Affairs Cooperative study.

***d*-Sotalol and so-called pure class III action: is antiadrenergic modulation necessary?** As discussed above, class III compounds were synthesized after analyzing the structure–activity relationships of the prototypical class III agents (sotalol, amiodarone, and similar compounds) to circumvent the perceived shortcomings of sotalol (β-blocker side effects and torsades de pointes) and amiodarone (complex side-effect profile). The resulting compounds are simpler molecules that lengthen the action potential duration without other pharmacologic effects. These agents have been targeted against single or multiple repolarizing membrane currents,[20] in particular either or both components of the delayed rectifier potassium current, especially its rapid component (I_{Kr}) E-4031, dofetilide, sematilide, MK 499, azimilide, and the dextroisomer of sotalol (*d*-sotalol) are examples of so-called pure class III agents, all selectively prolonging action potential duration and cardiac refractoriness without affecting myocardial excitability. Ibutilide acts somewhat differently; it prolongs the action potential duration largely by prolonging the duration of the inactivated, inward sodium current. Pure class III agents all elevate VF threshold and reduce ventricular defibrillation threshold. They are weak premature ventricular contraction suppressants but are relatively potent in preventing the VT/VF induced by programmed electrical stimulation. They appear to act by slowing VT, thereby preventing it from deteriorating to VF. In contrast to sodium-channel blockers, potassium-channel blockers as a class do not exhibit negative inotropic actions, but they do produce a variable incidence of torsades de pointes.[41] Thus, in evaluating their use in patients with manifest VT/VF or in those at risk for developing these potentially fatal tachyarrhythmias, this risk has to be balanced against the agents' potential to reduce the incidence of sudden arrhythmic deaths.

Thus, it is pertinent to ask what their clinical role might be in the future. This remains to be defined, but initial clinical results from controlled trials allow some speculations. Pure class III drugs appear to have the greatest utility as antifibrillatory agents, especially in converting AF and atrial flutter to sinus rhythm by acutely prolonging the effective refractory period and the excitation wavelength. This potential has been explored in experimental models.[42] To date, much of the data relate to studies with intravenous ibutilide[43] and dofetilide[44]; experience with azimilide remains to be reported. The major issues regarding the use of pure class III agents in the acute conversion of AF and atrial flutter have been summarized and critically discussed by Roden[45] and Singh.[46] The conversion rates exceed 30% in the case of AF, and 50% in the case of atrial flutter of relatively recent onset; the associated rate of torsades de pointes during the conversion has been as low as 2–3% in the case of AF and as high as 8–12% in atrial flutter; in either case, the condition only rarely required cardioversion. As pointed out elsewhere,[47] the studies with ibutilide and dofetilide are of much clinical importance on several counts. They validate the concept that isolated prolongation of the atrial action potential duration and of refractoriness can restore sinus rhythm in AF and atrial flutter.[47,48] To this extent, clinical data do support the premise that action potential duration lengthening per

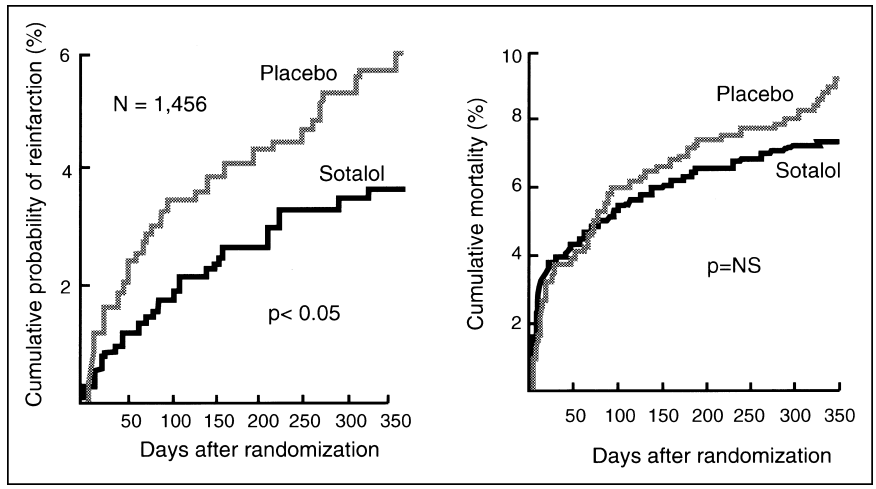

FIGURE 2. Effects of sotalol on reinfarction rate (*left*) and total mortality (*right*) in myocardial infarction survivors randomized to sotalol or placebo. The drug reduced reinfarction rate significantly; total mortality was reduced by 18%, but the reduction was not statistically significant. (Reprinted with permission from *Lancet*.[36])

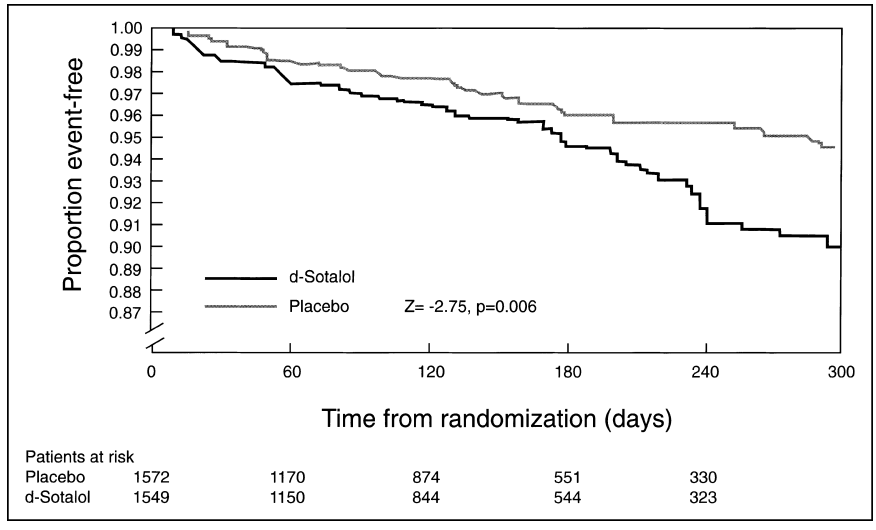

FIGURE 3. Effects of *d*-sotalol on total mortality in the survivors of recent and remote myocardial infarction. The data shown are survival curves of patients in the placebo and *d*-sotalol treatment limbs. *d*-Sotalol significantly reduced survival compared with placebo. (Reprinted with permission from *Lancet*.[49])

se is an antifibrillatory mechanism. Moreover, the data draw attention to the possibility of a systematic approach to the pharmacologic conversion of AF and atrial flutter to sinus rhythm, a method that may play a role in routine conversion in certain subsets of patients with these rhythm disorders.

The role of pure class III agents in the termination of VT/VF and in the prevention of their recurrence is less clear. The significant incidence of torsades de pointes induced in susceptible patients is the Achilles heel of pure class III agents.[37] Several electrophysiologic features of this group favor the development of proarrhythmic reactions that may increase mortality.[42] Thus, evaluating pure class III compounds clinically is a matter of balancing their antifibrillatory and profibrillatory actions. In the case of VT/VF, data from controlled clinical trials are essentially absent.

In this context, 2 mortality trials in high-risk, post–myocardial infarction patients are of much interest. These trials involve dofetilide (results yet to be reported) and the effects of *d*-sotalol, a prototype pure class III agent. Its effects on mortality in post–myocardial infarction patients at risk for high mortality were reported recently in a double-blind, placebo-controlled study, Survival with Oral *d*-Sotalol (SWORD).[49] Post–myocardial infarction patients with a left ventricular ejection fraction of ≤40%, some having history of congestive heart failure, were randomized to placebo or to *d*-sotalol (100 mg twice daily, which was increased to 200 mg twice daily if

tolerated). The trial was stopped prematurely when 3,119 patients had been enrolled (mean follow-up, ≅156 days) because of increased total mortality in the drug-treated patients; 42 (2.7%) died in the placebo group, and 71 (4.6%) died in the *d*-sotalol ($p = 0.005$) group. The Kaplan–Meier survival curves are shown in Figure 3. The increase in mortality induced by *d*-sotalol is of much clinical and theoretical significance. It is the first data from mortality trials in survivors of acute myocardial infarction involving a pure class III compound and raises the possibility that the adverse impact on mortality may be a common feature of pure class III agents, possibly a class action. Little can be said until the outcome of an ongoing trial involving dofetilide, the so-called DIAMOND (Danish Investigation of Arrhythmias and Mortality on Dofetilide) study, becomes available; the electrophysiologic effects of dofetilide are similar but perhaps not identical to those of *d*-sotalol. However, since *d,l*-sotalol did not increase mortality in myocardial infarction survivors (Figure 2), the associated antiadrenergic action appears to be a pharmacologic necessity and should be integral to class III antiarrhythmic agents. It might be inferred that in the absence of associated β-blocking activity, the class III actions (i.e., the effect on the effective refractory period) of pure class III agents (such as *d*-sotalol) might be nullified or even reversed during catecholamine surges during daily activity.

Amiodarone: Like sotalol, amiodarone was not synthesized as an antiarrhythmic compound. Its unique antiarrhythmic action was found serendipitously during an electrophysiologic evaluation of its pharmacologic properties.[11,13] Its molecule was targeted for coronary vasodilation in a systematic search for anti-ischemic agents. The fact that the short-term and long-term effects of the drug are different was recognized early. The first step in delineating its exceedingly complex electropharmacologic properties was finding that when administered at a constant dose over many weeks, the drug produced a stepwise increase in action potential duration with a time-related decrease in heart rate. Important properties of the drug include its propensity to increase the action potential duration in atrial and ventricular tissues after long-term drug administration with lesser effects in the Purkinje fibers[50] and M cells,[51] reduction in QT dispersion,[52] and a lack of reverse-rate dependency on repolarization.[53] The drug is unusual in that it decreases or eliminates the tendency toward early afterdepolarization, despite markedly slowing heart rate and strikingly increasing the QT/QT_c interval.[54] The drug also has a proclivity for noncompetitive antiadrenergic actions, and despite its significant class I actions, the drug does not exhibit proarrhythmic actions typical of the class. Similarly, despite the fact that amiodarone produces marked bradycardia and very prolonged QT intervals on the surface electrocardiogram, this incidence of torsades de pointes induced by the drug is <1%.[37]

From such a background of properties, a wide spectrum of antiarrhythmic effects as well as a complex side-effect profile might be expected. For example, intravenous amiodarone is effective in the control of hemodynamically destabilizing VT/VF (refractory to lidocaine and procainamide) with potency at least as high as that of intravenously administered bretylium.[55,56] On the other hand, the potency of its ability to convert VT/VF to sinus rhythm has not been studied systematically. The drug exerts a powerful suppressant effect on premature ventricular contractions and nonsustained VT and provides control in 60–80% of recurrent VT/VF after continuous oral therapy with conventional drugs has failed.[34] Yet in only a small number of patients does the drug prevent inducibility of VT/VF, as there is little or no systematic relation between the prevention of inducibility of VT/VF and the long-term clinical outcome.[57] The properties of the drug during long-term administration permit predictable control of recurrent paroxysmal supraventricular tachycardia, slowing of the ventricular response in AF and atrial flutter, and maintenance of stability of sinus rhythm in AF and atrial flutter after chemical or electrical conversion.[34] Clearly, the actions of amiodarone extend well beyond its propensity to lengthen the action potential duration. Given its unique, multifaceted pharmacodynamic profile and provided its side-effect profile can be improved upon, amiodarone holds much interest as the prototype for the complex compounds that might be developed for antifibrillatory actions in the atria and ventricles.[34] Thus, sotalol and amiodarone have emerged as the 2 leading antiarrhythmic drugs for the control of life-threatening ventricular tachyarrhythmias, and their therapeutic roles in this setting need to be considered in relation to the increasing indications for the use of ICDs in preventing arrhythmic deaths in patients with serious cardiac disease.

POTENTIAL IMPLICATIONS OF RECENT ARRHYTHMIA MORTALITY TRIALS

Recent arrhythmia mortality trials have a number of common features and objectives. It has become increasingly clear that suppression of arrhythmias may not necessarily lead to a reduction in sudden death. Furthermore, sudden death is often a matter of definition and may not always be due to an arrhythmia. Its reduction may not always correlate with a decrease in total mortality. Sudden death may be a terminal mode of exitus in a patient with advanced cardiac disease, which may be the primary determinant of survival. Thus, the critical end point in primary or secondary arrhythmia trials is increasingly the total mortality. Such an end point is used on the presumption that if an intervention does decrease sudden arrhythmic deaths significantly, the reduction will be reflected in the corresponding decrease in total mortality.

Two major subsets of patients appear to offer the largest scope for arrhythmia mortality reduction during prophylactic therapy: (1) high-risk patients surviving myocardial infarction, and (2) patients with congestive heart failure of any origin. In both subsets, the antifibrillatory tendency increases, as do symptomatic

and asymptomatic ventricular arrhythmias. These changes are related to the magnitude as well as the nature of mechanical and electrical disorders in the ventricular myocardium and to the associated derangement of the autonomic nervous system. These alterations may play a key role in determining the balance between the antifibrillatory and profibrillatory effects of drugs used to prolong survival by preventing ventricular fibrillation, the common mode of death both in patients surviving myocardial infarction and in those presenting with congestive heart failure.

Scope for arrhythmia mortality reduction in post–myocardial infarction survivors: After myocardial infarction, the myocardial substrate is often unstable, and if the patient is not assessed for risk and treated during the first year, mortality after the index event may be inordinately high. The early in-hospital mortality may be reduced by thrombolysis, primary angioplasty, aspirin, and β blockade, whereas late mortality after discharge from the hospital may be influenced favorably by revascularization, aspirin, angiotensin-converting enzyme inhibitors, and, perhaps most consistently, by β blockade.[58] As indicated, the effect of class I agents is deleterious; in the case of calcium-channel antagonists, the effect is either neutral or possibly deleterious.[19] Until recently, only β blockers were thought to derive their protective effect, not only from the prevention of reinfarction but also from a direct antagonism of the arrhythmogenic actions of catecholamines. For example, β blockers have been shown to reduce total mortality in the survivors of myocardial infarction by 18–40% during the first year.[59] It was discovered early that the benefit on mortality was somewhat greater in post–myocardial infarction patients with impaired ventricular function[60]; the magnitude of benefit for all patients appears to be related to the degree of heart-rate reduction, which is least for β antagonists that have significant sympathomimetic actions.[61]

Recent clinical trials suggest that amiodarone, with its antiarrhythmic and antifibrillatory effects, might reduce mortality in myocardial infarction survivors.[62] Amiodarone is appealing in this setting because few antiarrhythmic drugs can be used with impunity in post–myocardial infarction patients with markedly depressed left ventricular ejection fraction. Several post–myocardial infarction trials, albeit relatively small and not blind, revealed that the drug had the potential to increase survival in post–myocardial infarction survivors.[63] This observation is in line with the drug's pharmacologic properties, such as significant antiadrenergic, bradycardic, coronary-dilator, and anti-ischemic actions combined with powerful suppression of ventricular ectopy and runs of ventricular tachycardia. Yet both the European Myocardial Ventricular Amiodarone Trial (EMIAT)[63] and the Canadian Myocardial Infarct Amiodarone Trial (CAMIAT),[64] blind, placebo-controlled studies, showed a significant decrease in arrhythmic deaths (35% for EMIAT, 48.5% for CAMIAT) but without a significant decrease in total mortality (1% for EMIAT and 18% for CAMIAT). The mean data from these two trials are summarized in Figures 4 and 5. How should these data be interpreted and what might their implications be for the post–myocardial infarction patient?

Amiodarone is a powerful antiarrhythmic compound. It has the potential to decrease arrhythmia mortality, but its favorable effect on total mortality may be demonstrable only in a much larger and more selective patient population at high risk for arrhythmic death. Until such trial data are forthcoming—an unlikely event in the foreseeable future—it appears prudent not to advocate the routine, long-term arrhythmic prophylaxis in the post–myocardial infarction patient with continuous amiodarone therapy unless there are other concomitant indications for the drug. The design of future prophylactic trials needs to take into account the continuing effect of early thrombolysis, interventional procedures, aspirin, angiotensin-converting enzyme inhibitors, and β blockade, all of which have led to a striking reduction in mortality in post–myocardial infarction patients.

Controlling arrhythmic deaths in congestive heart failure: The impact on arrhythmia mortality changes effected by various classes of drugs in congestive heart failure has been an area of particularly active investigation in recent years. The Digitalis Investigation Group (DIG) trial clearly showed that cardiac glycosides in heart failure do not increase or decrease total mortality.[65] They can be used to improve ventricular performance, without fear of increasing mortality, in congestive heart failure patients.

The largest number of patients with congestive heart failure have significant numbers of ventricular arrhythmias, and half the deaths in this setting are thought to be due to arrhythmias. For this reason, the findings of the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) are of particular interest.[66] CHF-STAT was the first double-blind, placebo-controlled trial with amiodarone in a subset of patients at high risk for sudden death, as characterized by frequent occurrence of premature ventricular contractions, and ≃80% had nonsustained VT on Holter monitoring. Surprisingly, despite the striking suppression of asymptomatic arrhythmias, including nonsustained VT runs, and despite a 30–40% increase in left ventricular ejection fraction, there was no effect on either total mortality or sudden death. Yet compared with placebo, there did appear to be a strong trend toward a decrease in total mortality in the subset of patients with dilated cardiomyopathy.[66] In contrast, the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) found approximately a 30% decrease in total mortality in a smaller sample size ($n = 516$ in GESICA vs $n = 674$ in CHF-STAT), with lower left ventricular ejection fraction and overall greater severity of congestive heart failure.[67] This raises the question whether the benefit in total mortality might stem from effects other than those directly influencing arrhythmic deaths. It must be emphasized that the difference in total mortality in patients taking amiodarone in GESICA versus CHF-STAT remains essentially unexplained. It happens that >60% of patients in GESICA had conges-

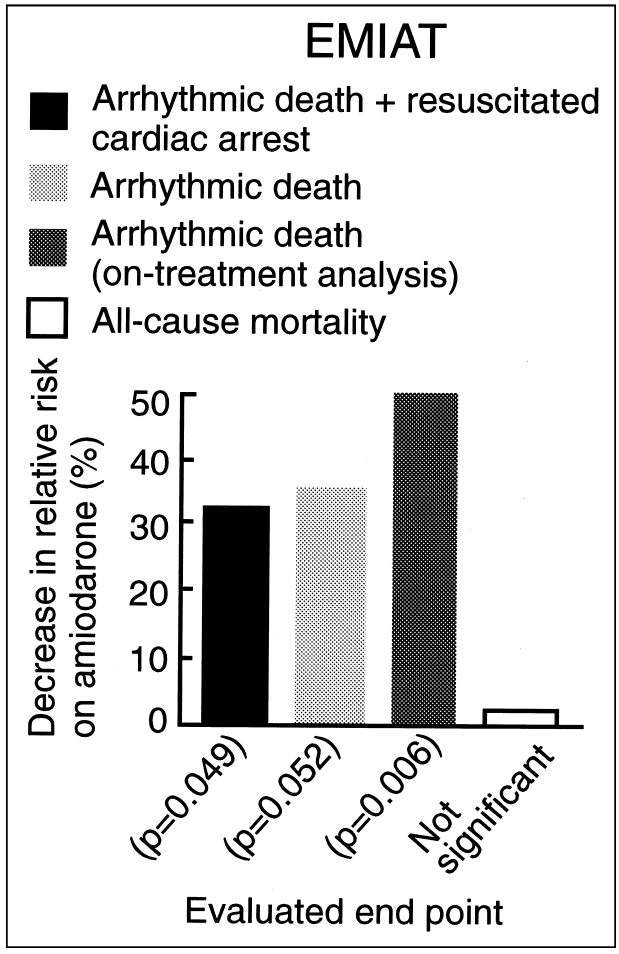

FIGURE 4. Principal outcomes on amiodarone in the European Myocardial Infarction Amiodarone Trial (EMIAT). (Reprinted with permission from *Clin Cardiol.*[78])

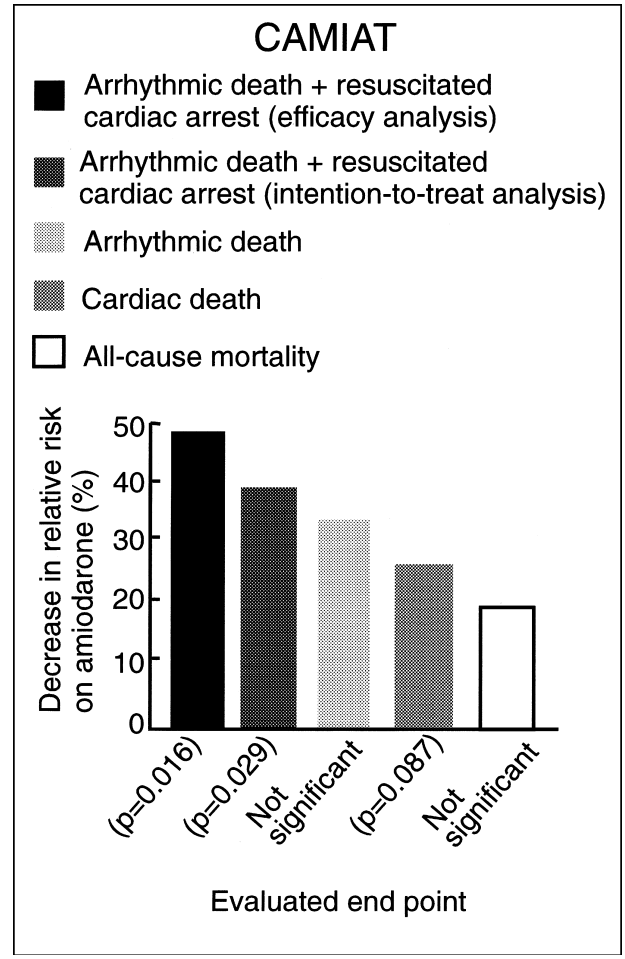

FIGURE 5. Principal outcomes on amiodarone in the Canadian Myocardial Infarction Amiodarone Trial (CAMIAT). (Reprinted with permission from *Clin Cardiol.*[78])

tive heart failure of nonischemic origin. It is possible that mortality for such patients is affected more favorably by pharmacologic agents. Thus, in CHF-STAT,[66] the Prospective Randomized Amlodipine Survival Evaluation Study Group (PRAISE-1),[68] and Cardiac Insufficiency Bisoprolol Study (CIBIS),[69] amiodarone, amlodipine, and bisoprolol, respectively (each having a unique set of actions), appeared to exert a favorable effect on mortality in the setting of congestive heart failure due to nonischemic cardiomyopathy. These agents had no effect on ischemic cardiomyopathy. Whether the difference in response to antifibrillatory drugs in congestive heart failure relative to its origin is a real phenomenon remains unclear.

Against this background, the increasing data from clinical trials of carvedilol in congestive heart failure are of much interest. Packer and others[70–72] have stressed some of the unique properties of this β blocker. In contrast to the actions of metoprolol and bisoprolol, carvedilol decreases myocardial norepinephrine and prevents up-regulation of β receptors—features that may increase its potency as a β antagonist and thus limit increases in exercise capacity that might otherwise occur due to the drug's propensity to increase left ventricular ejection fraction. It is also an antioxidant and an α-adrenergic blocker. Whether these electropharmacologic features play a major role in the drug's clinical utility in congestive heart failure requires further exploration.

REORIENTATION IN DRUGS AND IMPLANTABLE DEVICES FOR ARRHYTHMIA MORTALITY REDUCTION: A CHANGING SCENE

As the ICD has continued to be refined technologically and its versatility increased, it has had a major impact on our understanding of how the ICD should be combined with drugs to reduce arrhythmic deaths in certain subsets of patients with cardiac disease. Whereas appropriate patient subsets may receive a single method of treatment, 2 major subsets of patients may be most suited to the combined approach: (1) patients who develop sustained symptomatic VT followed by cardiac arrest and resuscitation; and (2) high-risk post–myocardial infarction patients and patients with congestive heart failure of whatever etiology.

For both subsets of patients, the perception is that a major opportunity for mortality reduction exists if life-threatening ventricular tachyarrhythmias are

promptly terminated and VT/VF is prevented. The issue is most compelling in patients with markedly decreased ventricular function, especially those with overt or covert cardiac failure, in whom incidence of sudden arrhythmic death is often inordinately high. A detailed background to the use of drugs versus ICDs in patients with manifest VT/VF has been provided elsewhere in this supplement.[73] In this section of the overview, the emerging data from 2 ICD trials (albeit quite preliminary data in 1 case) will be discussed, focusing on the issues that affect current clinical decision-making processes.

The first trial, the Multicenter Autonomic Defibrillator Implantation Trial (MADIT), compared mortality in a group of patients at risk for arrhythmic death treated either by ICD or conventional medical therapy.[74] These patients had previous myocardial infarction, a left ventricular ejection fraction <35%, nonsustained VT, and inducible VT on programmed electrical stimulation that was not suppressible by intravenous procainamide or an equivalent intravenous agent. The patients were randomized to an ICD limb or a so-called conventional drug treatment limb. MADIT was terminated early when the predefined efficacy boundary was crossed prematurely. In <200 randomized patients, a 54% reduction in total mortality (15 ICD patients vs 39 patients receiving drug therapy) over a follow-up period of 27 months was found. MADIT is an important trial, as it used a unique approach to risk stratification in the post–myocardial infarction patient. In the Wilber study,[75] from which MADIT derives its raison d'etre, the absolute numbers of patients in each of its 3 groups (noninducible, inducible and drug-suppressible, and inducible and not drug-suppressible) were relatively small. Indeed, in the most relevant group (the last one), there were only 20 patients.[75] Above all, in MADIT, the number of patients who underwent programmed electrical stimulation to arrive at the 196 patients eventually enrolled over a 5-year period remains uncertain. It would seem that such data would have been valuable for gauging the cost effectiveness as well as the practicality of the approach to arrhythmia mortality reduction in a cohort of patients at high risk for sudden cardiac death.

The MADIT investigators' designation of conventional antiarrhythmic therapy may be under contention. As pointed out elsewhere,[76] at 1-month follow-up, 8% of patients in the drug therapy limb were not taking their antiarrhythmic medications. At the point of last contact, 23% of the patients remaining in the drug treatment limb were not on any antiarrhythmic agents; only 45% were taking amiodarone; and 11% were taking class I antiarrhythmic agents, which have either neutral or deleterious effects on mortality. An additional 14% of patients were taking a β blocker or sotalol. Thus, it would seem that for a large segment of the study period, only 59% of patients in the so-called conventional therapy limb were using potentially effective mortality-reducing therapeutic agents. In contrast, of the 86 ICD patients remaining in the study at the point of last contact, 31 were using β blockers or sotalol, and 7 were using amiodarone. Therefore, 38 of the patients in the ICD limb were taking antiarrhythmic agents capable of influencing mortality favorably, independent of the ICD. Moreover, the use of effective antiarrhythmic medications in the drug limb showed a stepwise decrease as the study progressed, whereas antiarrhythmic medication use increased in the ICD limb. The potential effect on mortality of such a divergence in therapy may need to be examined. For these reasons, the role of the ICD in patients at high risk for sudden death should be studied further. In this regard, the outcomes of the ongoing Multiple Unsustained Ventricular Tachycardia Trial (MUSTT) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT) will be of major importance.

Preliminary results of another ICD trial, the Antiarrhythmic versus Implantable Device Trial (AVID), is also of major importance.[77] AVID was terminated prematurely because of the positive result on mortality during the first year. As a positive ICD trial, AVID is likely to fortify the results of MADIT. It could have profound repercussions in the way cardiologists (at least those in the United States) are likely to treat patients with life-threatening ventricular arrhythmias and patients at high risk for sudden arrhythmic death.

In AVID, 1,016 patients with electrocardiogram-documented VT/VF (with or without cardiac arrests) were randomized to an ICD or to best medical therapy. The drug regimen was empiric amiodarone in most patients and sotalol guided by programmed electrical stimulation in the rest. AVID was terminated prematurely because of the survival figures: mortality was 17.3% in patients given drugs versus 10.9% in patients using the ICD ($p = 0.012$); the adjusted mortality reduction was 33%, the average adjusted survival being 28.5 months for patients receiving drug therapy versus 31.1 months for patients using an ICD, with a net increase in survival of 2.6 months for patients using the device. Forty-two percent of the ICD limb patients were given β blockers. The crossover from the ICD limb to the drug limb was greater than the converse, and the ICD limb patients were hospitalized earlier, 40% at 1 year and 60% at 2 years ($p < 0.017$), during the course of the study. In AVID, the net costs after 3 years were $76,000/patient for the ICD limb and $48,000/patient for the drug (amiodarone) limb, a difference of $27,577. The total cost was estimated to be $127,000/year of additional survival induced by the ICD.

These data from AVID are preliminary, and their precise clinical relevance and applicability are under consideration. However, the use of the ICD has without doubt changed the therapeutic landscape for the prevention and control of sudden arrhythmic death. It has been shown to accomplish what it was intended to do: cardiovert, defibrillate, terminate arrhythmias by antitachycardia pacing, and, if required, provide pacing for a markedly slowed rhythm. There is little doubt the ICD has the potential to prolong survival by reversing transient and potentially reversible disorders of rhythm and conduction that may otherwise prove fatal. Ironically, as a single method of treatment, its

role becomes increasingly limited as the number of shocks needed to prevent death increases. For continuous and incessant aberrations of rhythm or highly repetitive arrhythmias, aggressive pharmacologic therapy is often needed before the ICD can be applied.

For these reasons, interest in the potential of amiodarone, sotalol, and their derivatives to reduce overall mortality in patients with cardiac disease is unlikely to wane. These drugs are unique antiarrhythmic and antifibrillatory compounds, but the precise role of these and other agents in alleviating arrhythmia mortality is likely to evolve alongside the roles of interventional procedures and implantable devices. With the increasing use of ICDs, numerous instances have emerged in which the concomitant use of drugs and devices is the rule rather than the exception. Therefore, as recently emphasized,[76] the debate should move from the relative merits of drugs and devices in isolation to a clear delineation of subsets of patients in whom drugs or devices are the most appropriate single method of treatment and subsets of patients in whom a judicious combination of the 2 methods might reduce arrhythmia mortality most effectively. It is imperative that the roles of antiarrhythmic drugs and ICDs are delineated on the basis of data from carefully controlled clinical trials, with particular attention given to effective trial design and use of the best therapeutic regimens.

1. Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA, Goldberg RJ. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. *N Engl J Med* 1985;312:193–197.

2. Rappaport E, Remedios P. The high risk patient after recovery from myocardial infarction: recognition and management. *J Am Coll Cardiol* 1983;1:391–399.

3. Van Olshausen K, Schafer A, Mehmel HC. Ventricular arrhythmia in dilated cardiomyopathy. *Br Heart J* 1984;51:147–152.

4. Stevensen WG, Ellison KE, Lefroy DC, Friedman PL. Ablation therapy for cardiac arrhythmias. *Am J Cardiol* 1997;80(suppl):56G–66G.

5. Johnson EA, McKinnon MG. The differential effects of quinidine and pyrilamine on the myocardial action potential at various rates of stimulation. *J Pharmacol Exp Therap* 1957;120:460–468.

6. Singh BN. Routine prophylactic lidocaine administration in acute myocardial infarction. An idea whose time is all but gone? *Circulation* 1992;86:764–773.

7. Jervell A, Lang-Nielsen L. Congenital deaf-mutism, functional heart disease with the prolongation of QT interval, and sudden death. *Am Heart J* 1957;54: 59–68.

8. Selzer A, Wray HW. Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. *Circulation* 1964:30; 17–26.

9. Dessertenne F. La tachycardia ventriculaire a deux foyers oppose variables. *Arch Mal Coeur* 1966;59:263–272.

10. Singh BN, Vaughan Williams EM. A third class of anti-arrhythmic action. Effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle, of MJ 1999 and AH 3474. *Br J Pharmacol* 1970;39:675–687.

11. Singh BN, Vaughan Williams EM. The effect of amiodarone, a new antianginal drug, on cardiac muscle. *Br J Pharmacol* 1970;39;657–667.

12. Vaughan Williams EM. Classification of antiarrhythmic drugs. In: Sandoe E, Flenstedt-Jensen E, Olesen KH, eds. *Symposium on Cardiac Arrhythmias*. Sweden: AB Astra, Sodertalje, 1970:440–469.

13. Singh BN. Pharmacological actions of certain cardiac drugs and hormones: focus on antiarrhythmic mechanisms. (Thesis.) Hertford College and the University of Oxford; 1971. Mount Kisco, NY: Futura Publishing, 1991:1–98.

14. Singh BN, Vaughan Williams EM. Effects of altering potassium concentration on the action of lidocaine and diphenylhydantoin on rabbit atrial and ventricular muscle. *Circ Res* 1971;29:286–295.

15. Singh BN, Vaughan Williams EM. A fourth class of anti-dysrhythmic action? Effect of verapamil on ouabain toxicity, on atrial and ventricular intracellular potentials, and on other features of cardiac function. *Cardiovasc Res* 1972;39: 109–119.

16. Singh BN, Hauswirth O. Comparative mechanisms of action of antiarrhythmic drugs. *Am Heart J* 1974;87:367–377.

17. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. The Sicilian Gambit: a new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. *Circulation* 1991;84:1831–1851.

18. Singh BN. The coming of age of the class III antiarrhythmic principle: retrospective and future trends. *Am J Cardiol* 1996:78(suppl 4A):17–27.

19. Yusuf S, Teo KK. Approaches to prevention of sudden death: need for fundamental reevaluation. *J Cardiovasc Electrophysiol* 1991;2:S233–S239.

20. Singh BN. Arrhythmia control by prolonging repolarization: the concept and its potential therapeutic impact. *Eur Heart J* 1993;14:14–23.

21. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321: 1754–1756.

22. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992;327:227–233.

23. Ahmed R, Singh BN. Anti-arrhythmic drugs. *Curr Opin Cardiol* 1993;8:10–21.

24. Singh BN, Ahmed R. Class III antiarrhythmic drugs. *Curr Opin Cardiol* 1994;9:12–22.

25. Hallstrom AP, Cobb LA, Yu BH, Weaver WD, Fahrenbruch CE. An antiarrhythmic drug experience in 941 patients resuscitated from an initial cardiac arrest between 1970 and 1985. *Am J Cardiol* 1991;68:1025–1031.

26. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990;82:1106–1116.

27. Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. *J Am Coll Cardiol* 1992;20:427–532.

28. Morganroth J, Goin JE. Quinidine-related mortality in the short-to-medium-term treatment of ventricular arrhythmias. A meta-analysis. *Circulation* 1991;84: 1977–1983.

29. Mason JW, for the Electrophysiologic Study versus Electrocardiographic Monitoring Investigators. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. *N Engl J Med* 1993;329:452–458.

30. Mason JW, for the Electrophysiologic Study versus Electrocardiographic Monitoring Investigators. A comparison of electrophysiologic testing with Holter monitoring to predict antiarrhythmic-drug efficacy for ventricular tachyarrhythmias. *N Engl J Med* 1993;329:445–451.

31. The CASCADE Investigators. Randomized anti-arrhythmic drug therapy in survivors of cardiac arrest (the CASCADE Study). *Am J Cardiol* 1993;72:280–287.

32. Wever EF, Hauer RN, van Capelle FL, Tijssen JG, Crijns HJ, Algra A, Wiesfeld AC, Bakker PF, Robles de Medina EO. Randomized study of implantable defibrillator as first-choice therapy versus conventional strategy in post-infarct sudden death survivors. *Circulation* 1995;91:2195–2203.

33. Colatsky TJ, Follmer CH, Starmer CF. Channel specificity in antiarrhythmic drug action. Mechanism of potassium channel block and its role in suppressing and aggravating cardiac arrhythmias. *Circulation* 1990;82:2235–2242.

34. Singh BN. Expanding indications for the use of class III agents in patients at high risk for sudden death. *J Cardiovasc Electrophysiol* 1995;6:887–900.

35. Singh BN. Control of cardiac arrhythmias with sotalol, a broad–spectrum anti-arrhythmic with beta-blocking effects and class III activity. *Am J Cardiol* 1990;765:1A–84A.

36. Julian DG, Jackson FS, Prescott RJ, Szekely P. Controlled trial of sotalol for one year after myocardial infarction. *Lancet* 1982;1:1142–1147.

37. Hohnloser S, Klingenheben T, Singh BN. Amiodarone-associated proarrhythmic effects: a review with special reference to torsades de pointes tachycardia. *Ann Intern Med* 1994;121:529–535.

38. Singh BN. Choice and chance in drug therapy of cardiac arrhythmias: technique versus drug-specific responses in evaluation of efficacy. *Am J Cardiol* 1993;72:114–124.

39. Ho DS, Zecchin RP, Richards DA, Uther JB, Ross DL. Double-blind trial of lignocaine versus sotalol for acute termination of spontaneous sustained ventricular tachycardia. *Lancet* 1994;344:18–23.

40. Juul-Möller S, Edvardsson N, Rehnqvist-Ahlberg N. Sotalol versus quinidine for the maintenance of sinus rhythm after direct current conversion of atrial fibrillation. *Circulation* 1990;82:1932–1939.

41. Singh BN, Ahmed R, Sen L. Prolonging cardiac repolarization as an evolving antiarrhythmic principle. In: Escande D, Standen N, eds. *K^+ Channels in Cardiovascular Medicine*. Paris: Springer-Verlag, 1993:247–262.

42. Feld GK, Venkatesh N, Singh BN. Pharmacologic conversion and suppression of experimental canine flutter: differing effects of *d*-sotalol, quinidine and lidocaine and significance of changes in refractoriness and conduction. *Circulation* 1985;74:197–204.

43. Stambler BS, Wood MA, Ellenbogen KA, Perry KT, Wakefield LK, Vander Lugt JT. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. *Circulation* 1996;94:1613–1621.

44. Falk RH, Pollak A, Singh SN, Friederich T, for Dofetilide Investigators. Intravenous dofetilide, a class III antiarrhythmic agent, for the termination of sustained atrial fibrillation or flutter. *J Am Coll Cardiol* 1997;29:385–390.

45. Roden DM. Ibutilide and the treatment of atrial arrhythmias. A new drug—almost unheralded—is now available to US physicians. *Circulation* 1996;94: 1499–1502.

46. Singh BN. Acute conversion of atrial fibrillation and flutter: direct current cardioversion versus intravenously administered pure class III agents. (Editorial.) *J Am Coll Cardiol* 1997;29:391–393.
47. Singh BN, Wellens HJ, Hiraoka M, eds. *Electropharmacological Control of Cardiac Arrhythmias. To Delay Conduction or to Prolong Refractoriness?* Mount Kisco, NY: Futura Publishing, 1994;1–713.
48. Singh BN, Nademanee K. Control of cardiac arrhythmias by selective lengthening of cardiac repolarization: theoretical considerations and clinical observations. *Am Heart J* 1985:109:421–430.
49. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP, SWORD Investigators. Effect of *d*-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996;348:7–12.
50. Papp J Gy, Nemeth M, Krassoi I, Mester L, Hala O, Varro A. Differential electro-physiologic effects of chronically administered amiodarone on canine Purkinje fibers versus ventricular muscle. *J Pharmacol Exp Therap* 1996;1:187–196.
51. Sicouri S, Moro S, Litovsky S, Elizari M, Antzelevitch C. Chronic amiodarone reduces transmural dispersion of repolarization in the canine heart. *J Cardiovasc Electrophysiol* 1997; in press.
52. Cui G, Sen L, Sager P, Uppal P, Singh BN. Effects of amiodarone, sematilide, and sotalol on QT dispersion. *Am J Cardiol* 1994;74:896–900.
53. Sager PT, Uppal P, Follmer C, Antimisiaris M, Pruitt C, Singh BN. Frequency-dependent electrophysiologic effects of amiodarone in humans. *Circulation* 1993;88:1063–1071.
54. Takanaka C, Singh BN. Barium-induced nondriven action potentials as a model of triggered potentials from early afterdepolarizations: significance of slow channel activity and differing effects of quinidine and amiodarone. *J Am Coll Cardiol* 1990;15:213–221.
55. Kowey PR, Levine JH, Herre JM, Pacifico A, Lindsay BD, Plumb VJ, Janosik DL, Kopelman HA, Scheinman MM, for the Intravenous Amiodarone Multicenter Investigators Group. Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia and fibrillation. *Circulation* 1995; 92:3255–3263.
56. Scheinman MM, Levine JH, Cannom DS, Friehling T, Kopelman HA, Chilson DA, Platia EV, Wilber DJ, Kowey PR, for the Intravenous Amiodarone Multicenter Investigators Group. Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. *Circulation* 1995; 92:3264–3272.
57. Nasir N, Swarna U, Bolhene KA, Doyle TK, Pacifico A. Therapy of sustained ventricular arrhythmias with amiodarone: prediction of efficacy with serial electrophysiologic studies. *J Cardiovasc Pharmacol Therapeut* 1996;1:123–132.
58. Hennekins CH, Godfried SL, Albert CM, Gaziano JM, Buring JE. Adjunctive drug therapies during and post acute myocardial infarction. *N Engl J Med* 1996;335:1660–1667.
59. Yusuf S, Peto R, Lewis J, Sleight P. Beta-blockade during myocardial infarction: an overview of randomized trials. *Prog Cardiovasc Dis* 1985;27:335–355.
60. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986;73:503–510.
61. Singh BN. Advantages of beta blockers versus antiarrhythmic agents and calcium antagonists in secondary prevention after myocardial infarction. *Am J Cardiol* 1990;66:9C–20C.
62. Nademanee K, Singh BN, Stevenson WG, Weiss JN. Amiodarone and post-MI patients. *Circulation* 1993;88:764–774.
63. Julian DG, Camm AJ, Frangin G, Janse MJ, Munoz A, Schwartz PJ, Simon P, for the European Myocardial Infarct Amiodarone Trial Investigators. Randomized trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997;349:667–674.
64. Cairns JA, Connolly SJ, Roberts R, Gent M, for the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Randomized trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarizations: CAMIAT. *Lancet* 1997;349:675–682.
65. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525–533.
66. Singh SN, Fletcher RD, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D, for the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmias. *N Engl J Med* 1995;333:77–82.
67. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R, for Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Randomized trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994;344:493–498.
68. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Newberg GW, Frid D, Wertheimer JH, Cropp AB, De Mets DL, for the Prospective Randomized Amlodipine Survival Evaluation Study Group (PRAISE). Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Eng J Med* 1996;335:1107–1114.
69. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1994;90:1765–1773.
70. Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, Kukin ML, Kinhal V, Udelson JE, Klapholz M, Gottlieb SS, Pearle D, Cody RJ, Gregory JJ, Kantrowitz NE, Le Jemtel TH, Young ST, Lukas MA, Shusterman NH, for the Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. *Circulation* 1996;94:2793–2799.
71. Colucci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB, Krueger SK, Hershberger R, Uretsky BF, Bowers JA, Sackner-Bernstein JD, Young ST, Holcslaw TL, Lukas MA, for the US Carvedilol Heart Failure Study Group. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation* 1996;94:2800–2806.
72. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N, for the MOCHA Investigators. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation* 1996;94:2807–2816.
73. Haverkamp W, Eckardt L, Boggrefe M, Breithardt G. Drugs versus devices in controlling ventricular tachycardia, ventricular fibrillation, and recurrent cardiac arrest. *Am J Cardiol* 1997;80(suppl):67G–73G.
74. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M, for the Multicenter Automatic Defibrillator Implantation Trial Investigators (MADIT). Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335:1933–1940.
75. Wilber DJ, Olshansky B, Moran JF, Scanlon PJ. Electrophysiological testing and nonsustained ventricular tachycardia. Use and limitations in patients with coronary artery disease and impaired ventricular function. *Circulation* 1990;82: 350–358.
76. Ogunyankin K, Singh BN. Editorial. Reflections on some recent and contemporary clinical trials in patients with heart failure and those with reduced ventricular function. *J Cardiovasc Pharmacol Therapeut* 1997;2:147–152.
77. Hallstrom A, Zipes DP. Preliminary findings of the Antiarrhythmic Versus Implantable Device Trial (AVID). Presentation at the Annual Scientific Meeting of the North American Society of Pacing and Electrophysiology, New Orleans, May 12, 1996.
78. Singh BN. Amiodarone: the expanding antiarrhythmic role and how to follow a patient on chronic therapy. *Clin Cardiol* 1997;20:608–618.