Amiodarone and Post-MI Patients
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Survivors of acute myocardial infarction (MI) remain at risk of sudden cardiac death after being discharged from the hospital. In these patients, frequent premature ventricular contractions (PVCs) and depressed ventricular function herald sudden cardiac death.1-3 These observations triggered the idea that if PVCs were suppressed by antiarrhythmic agents, then sudden cardiac death could be averted.4,5 That belief led to an explosion in the use of antiarrhythmic drugs 20 years ago, and the pharmaceutical industry mounted a massive development campaign to find more effective antiarrhythmic agents for ventricular arrhythmia suppression, which, it was hoped, would prevent sudden cardiac death. To this end, throughout the 1980s, about two new antiarrhythmic compounds were developed every year.5

As the number of antiarrhythmic drug prescriptions rose dramatically,6 soon came troubling reports that class I antiarrhythmic agents failed to reduce the sudden cardiac death rate. Indeed, many class I compounds had proarrhythmic and negative inotropic effects.7-9 CAST I and II dealt what many considered the fatal blow to the use of class Ic antiarrhythmic drugs in post-MI patients10-11: Encainide and flecainide increased the mortality rate of these patients, whereas moricizine, a class 1a agent, significantly increased the risk of sudden cardiac death during the first 2 weeks of therapy and was not effective over the long term.11 Given the results of CAST and other studies, many physicians were skeptical about whether antiarrhythmic agents played any role in sudden cardiac death prophylaxis. By the 1990s, physicians were in a quandary: How should one treat potentially life-threatening ventricular tachyarrhythmias in MI survivors?

As many antiarrhythmic agents were falling from favor, amiodarone—an antiarrhythmic compound that had been viewed since its approval in 1984 by the Food and Drug Administration as a “last resort” drug—was gaining hard-won acceptance on the basis of several studies showing that the drug effectively controlled life-threatening ventricular tachyarrhythmias.12-19 Data from several trials20-24 suggesting that amiodarone might effectively control and prevent arrhythmias in MI survivors also called for a reevaluation of the “last-resort” status of the drug.

We plan to review the current knowledge of the electrophysiological actions of amiodarone (specifically how the drug works in ischemia-related ventricular arrhythmias), to review the current clinical trials studying the effectiveness of amiodarone in post-MI patients, and to appraise the drug’s value and limitations in these patients.

Antiarrhythmic Actions
The pharmacodynamics and pharmacokinetics of amiodarone are still poorly understood.25,26 The drug was developed in Belgium (Labaz Inc) as an antianginal agent in 196227; only later was it found to possess antiarrhythmic and electrophysiological effects.27-29 Amiodarone relaxes vascular smooth muscle, acts as a coronary and peripheral vasodilator,30 and significantly slows the heart rate and cardiac metabolism.28,29 That is, it increases coronary blood supply but decreases oxygen demand. These effects formed the basis of the pharmacological rationale for the original indication of the compound to treat angina pectoris.

The initial observation28 in dogs that chronic oral amiodarone administration produced progressive bradycardia led to studies of its electrophysiological effects. Singh and Vaughan Williams31 discovered that chronic amiodarone therapy uniformly lengthened the action potential duration (APD) of isolated rabbit atrial and ventricular muscle (Fig 1). This observation suggested that amiodarone belonged to the class 3 antiarrhythmic category: Its defining property—lengthening both the APD of a given tissue and the refractory period—was responsible for the antiarrhythmic effect. However, the drug has other antiarrhythmic properties as well: Amiodarone depresses the fast sodium channel,32 inhibits sympathetic activity,28,29 and blocks the L-type calcium channel.33 The relative contributions of each electrophysiological effect to the overall antiarrhythmic activity and efficacy of amiodarone are still not fully understood.

Effects on the Fast Sodium Channel and Conduction
Amiodarone blocks predominantly the inactivated state (but not the open state) of the sodium channels in a use-dependent manner.32,34 At room temperature, recovery time constants for Na+ current activation are in the order of 1 millisecond at plateau potentials in ventricular myocytes35 and Purkinje cells.34 Pollmer et al34 demonstrated that amiodarone causes tonic block of the sodium channel. Tonic block is composed of both a “true” resting state block and an inactivated channel block. The magnitude of an amiodarone-induced tonic...
block suggests that this action may contribute to the antiarrhythmic efficacy of amiodarone, particularly in depolarized tissues (ie, ischemic myocardium).

Similar to its effect on I_{Na}, amiodarone depresses the V_{max} in a use-dependent manner in different types of cardiac tissues. The effect of amiodarone on V_{max} is characterized by fast onset and offset kinetics. The effect of amiodarone on V_{max} is enhanced at the depolarized potential. Thus, amiodarone blocks the V_{max} and conduction at faster heart rates, at the short premature interval, and more so in diseased (eg, ischemic) than in healthy tissue at a normal heart rate.

**Effects on the Slow Inward Calcium Channels (L-Ca** Channels)**

The effects of amiodarone on I_{Ca} parallel its effects on I_{Na}. The drug blocks I_{Ca} predominantly during the inactivated state and, to a lesser degree, the resting state. Nattel et al reported use-dependent blocking effects of amiodarone on the atrioventricular (AV) nodal conduction time. Amiodarone also decreases phase 4 depolarization in the sinoatrial (SA) node and the amplitude of the APD of the SA node. Nishimura et al demonstrated that amiodarone blocks the calcium channel in guinea pig ventricular myocytes. The drug more effectively blocks depolarized rather than well-polarized cells, which may be pertinent in terms of the antiarrhythmic efficacy of amiodarone.

**Effects on Potassium Channels and Repolarization**

The most profound effect of amiodarone is its lengthening of the APD and refractoriness, especially when the drug is administered over a long period of time. The drug blocks the delay rectifier current (I_{Kr}), causing an increase in the APD; there is evidence suggesting that it may also block the inward rectifier current (I_{K1}). Amiodarone also inhibits the ATP-sensitive potassium channel, which may play a major role in preventing ventricular arrhythmias during ischemia. Unlike other class 3 antiarrhythmic compounds (sotalol, seminalide) and class 1A compounds (quinidine) that show a reverse use-dependent effect on the APD prolongation, amiodarone uniformly lengthens the APD at normal and faster heart rates. The effect of amiodarone on repolarization is evident within the first week of drug treatment and continues to increase in a stepwise fashion over a 6-week period when given at a constant dose. These effects on repolarization have been demonstrated in most cardiac tissues.

**Clinical Electrophysiological Effects**

The clinical electrophysiological effects of amiodarone are generally congruent with those found in the experimental laboratory. Amiodarone-induced prolongation of the APD in cardiac muscle was confirmed in human monophasic action potential recordings. The electrophysiological effects of amiodarone administered intravenously differ strikingly from those that develop when the drug is administered chronically. Chronic oral amiodarone therapy produces a marked increase in the refractory periods of all cardiac tissues, whereas acute intravenous amiodarone therapy has no effects on the refractory periods except on the AV node (Fig 2). The drug when administered chronically has little effect on the QRS duration and His-Purkinje conduction at slower heart rates, but that effect increases significantly at faster heart rates. However, these marked use-dependent effects on conduction were not observed when amiodarone was administered intravenously. The acute effect of intravenous amiodarone on the AV node is similar to the finding of Gloor et al that amiodarone depressed sinus node automaticity and intranodal AV conduction when injected into the SA and AV nodal arteries of anesthetized dogs. These changes were not affected when propranolol or atropine was given but were sensitive to alterations in the level of calcium in the perfusate, suggesting that the primary acute electrophysiological effect of intravenous amiodarone may be due to its ability to block I_{Ca}.

**Latency of the Onset of Antiarrhythmic Action and the Role of Desethylamiodarone, an Amiodarone Metabolite**

There is extensive evidence showing that amiodarone has a delayed onset of antiarrhythmic action and efficacy. Although the mechanism responsible for this delay is unclear, it is clear that this delayed onset of action varies among individuals. The lag could be due...
binding of radioactive-labeled triiodothyronine (T₃). They found that there was only minimal receptor binding to amiodarone. However, all receptor preparations had substantial affinities (Kᵣ) to the DAM analog. They concluded that amiodarone may exert some of its electrophysiological effects by metabolic conversion to DAM, which may then competitively prevent the thyroid hormone from binding to the nuclear receptor sites within the myocardium. The precise link between the effects of amiodarone on the heart and thyroid function remain uncertain.

Whatever the mechanisms governing the delayed onset of action by amiodarone, such a delay and the variability of this delay among individuals makes regulating amiodarone dosing difficult. Indeed, the many disparate views of the efficacy of amiodarone and its toxicity can be attributed at least in part to this delayed onset of action.

### Evidence of Antiarrhythmic Efficacy in Ischemic Ventricular Arrhythmias

MI induces a myriad of metabolic and electrophysiological changes that can cause arrhythmias (Table 1).43,53 During ischemia there is a rapid loss of cellular K⁺, resulting in an extracellular accumulation of K⁺ that partially depolarizes the membrane.50 Other factors such as hypoxia and changes in intracellular calcium may also cause membrane depolarization.57 Tissues that are partially depolarized are potentially arrhythmogenic; ischemia-induced partial depolarization could cause abnormal automaticity or reentry. Since the cellular K⁺ loss during ischemia is largely due to increased K⁺ conductance by the activation of ATP-sensitive K⁺ channels (K₅₋₆), the ability of amiodarone to block K₅₋₆ may help prevent ischemia-induced arrhythmias. The depolarized tissues also allow amiodarone to bind to the inactivated sodium channels more readily. This would have a greater effect on the conduction and excitability of the tissues. Mason et al.53 demonstrated that amiodarone abolished depolarization-automaticity that had been caused by a decreased membrane potential.

Intracellular free [Ca²⁺] increases early during ischemia; the elevated intracellular [Ca²⁺] may activate the depolarizing inward current through nonspecific Ca²⁺-activated channels or electrogenic Na⁺-Ca²⁺ exchange, resulting in afterdepolarization and triggered activity.57 Since amiodarone blocks the inactivated Ca²⁺ channels, it should suppress Ca²⁺-mediated triggered activity caused by delayed afterdepolarization (DAD). Ohta et al.58 found that this was indeed the case: They studied in isolated rabbit ventricle delayed triggered activity
caused by DAD resulting from hypokalemia. They found that chronic amiodarone treatment reduced the amplitude of DAD and the subsequent induction of triggered activity. Amiodarone superfusion depressed the DAD, although much less so than when administered chronically. These observations may explain why amiodarone has a low arrhythmogenic potential despite its ability to markedly increase the QT interval and repolarization.

Elevation of intracellular free [Ca\(^+\)] caused by ischemia may also activate intracellular proteases and phospholipases that degrade phospholipid-producing lysophosphoglycerides. These compounds then accumulate in the sarclemma membrane, causing membrane depolarization and changes in the APD.\(^5\) The products of fatty acid metabolism decrease the resting membrane potential and \(V_{ma}\), especially when the tissues are acidic. Since amiodarone inhibits the phospholipase enzyme,\(^6\) it prevents the breakdown of membrane phospholipids produced by phospholipase. As a phospholipase inhibitor, amiodarone could prevent the accumulation of lysophosphoglycerides and other amphiphiles, thus preventing arrhythmogenesis caused by these products during ischemia.

The data briefly reviewed stress that the electropharmacological and metabolic actions of amiodarone are complex, as are the chain of electrophysiological events occurring during myocardial ischemia. It is tempting to speculate that the multiple pharmacological actions of amiodarone work together to nullify the deleterious electrophysiological consequences of ischemia and prevent arrhythmogenesis after acute coronary occlusion. However, the relative importance of the individual components of the multifaceted actions of amiodarone remains a matter of conjecture.

**Antiadrenergic Effects of Amiodarone**

Charlier and his colleagues\(^{28,29}\) were the first to show in vivo that amiodarone blunted the various cardiovascular effects of catecholamines. When Polster and Broekhuysen\(^6\) studied the inhibitory effects of amiodarone on the heart rate response during incremental doses of isoproterenol infusion and on the norepinephrine-induced contraction of isolated rat aortic strips, they found that amiodarone behaved as a nonspecific sympathetic inhibitor. Using direct ligand binding assays on rat myocardial \(\beta\)-receptors, Nokin et al\(^{69}\) concluded that both propranolol and amiodarone prevented the increases in \(\beta\)-receptor density induced by myocardial ischemia after coronary ligation. Venkatesh et al\(^{69}\) showed that in rabbits that had received chronic amiodarone therapy there was a gradual decrease of \(\beta\)-receptors and a parallel, progressive decrease in the heart rate. Gagnol et al\(^{64}\) showed that in rat heart membrane preparations, amiodarone noncompetitively antagonized the activation of adenylate cyclase by isoproterenol, glucagon, and secretin (but not sodium fluoride). They postulated that amiodarone could either inhibit the coupling of \(\beta\)-receptors with the regulatory unit of the adenylate cyclase complex through different receptors or decrease the number of functional \(\beta\)-receptors on the surface of the myocardium. Either way, the net result is that amiodarone attenuates the positive chronotropic actions of catecholamines, a property that is crucial in warding off arrhythmias precipitated by myocardial ischemia.

The sympathetic-blocking property of amiodarone, similar to that of \(\beta\)-blockers,\(^6\) may improve the mortality rate of post-MI patients. That action may also inhibit ischemia-induced ventricular fibrillation (VF). Lombardi et al\(^{66}\) demonstrated that after 2 minutes of left coronary occlusion, preganglionic sympathetic output increased concomitantly with a fall in the VF threshold. \(\beta\)-Adrenergic blockade prevented the decrease in VF threshold induced by myocardial ischemia. \(\beta\)-Blockade also reduces the incidence of VF during ischemia. \(\beta\)-Adrenergic stimulation during ischemia shortens ventricular refractoriness, increases ventricular excitability, and enhances the temporal dispersion of ventricular repolarization that increases susceptibility to ventricular fibrillation. \(\beta\)-Adrenergic stimulation also provokes afterdepolarization, causing arrhythmias resulting from triggered activity. The antisympathetic property of amiodarone is an important addition to the drug's other antiarrhythmic properties in preventing ischemia-induced VF.

**Antifibrillatory Effects in Experimental Infarct Models**

The data from studies of isolated tissues are consonant with those from studies of hearts and from in vivo experimental models, as follows. Using the Langendorff technique on isolated perfused rat hearts, Lubbe et al\(^{67}\) showed that amiodarone caused a dose-related decrease in heart rate and an increase in the VF threshold before and after coronary ligation. In rats that had been pretreated with amiodarone (range, 2 minutes to 3 weeks), the VF threshold increased in a dose-dependent manner. After coronary ligation was performed on rats that had been pretreated with amiodarone, the incidence of spontaneous arrhythmias decreased, as did the ischemia-induced VF threshold. When the rats that had been pretreated with a sufficiently high dose of amiodarone underwent coronary ligation, the VF threshold exceeded the baseline level in control rats. This study also showed that amiodarone appeared to remain active at the myocardial receptor sites even after it was no longer present in the perfusing myocardium.

When Lubbe et al studied the effects of amiodarone on metabolic changes in rat hearts during ischemia, they found that the antifibrillatory effect of amiodarone was independent of amiodarone-induced heart rate changes. Amiodarone had no effect on the tissue content of adenosine triphosphate or creatine phosphate in either normal or ischemic myocardium. From this they concluded that it was unlikely that the protective effects of amiodarone were due to its ability to attenuate ischemia-induced metabolic damage. Amiodarone prevented the ischemia-induced increase in the tissue cyclic adenosine monophosphate (cAMP) concentration after coronary ligation. The effect of amiodarone on cAMP was dose dependent: After pretreatment for 2 minutes, the cAMP level in ischemic tissue increased only about 18% (compared with a 40% increase in hearts not pretreated with amiodarone). After pretreatment for 1 week, the cAMP level in ischemic myocardium was equivalent to that in the normal myocardium. In line with these findings, the study of Gagnol et al\(^{64}\) in which amiodarone was administered incrementally to rat heart membranes, showed...
that the drug progressively inhibited adenyl cyclase activity stimulated by isoproterenol.

All of these observations suggest that amiodarone, by inhibiting the arrhythmogenic catecholamine response during ischemia, prevents a fall in the VF threshold induced by myocardial ischemia. In the same study, Lubbe’s group also determined the effects of amiodarone on spontaneous ventricular tachyarrhythmias (ventricular extrasystole, ventricular tachycardia, and VF) after coronary artery occlusion and reperfusion experiments. Rats that had been pretreated with amiodarone had a substantial decrease in the incidence of ventricular tachyarrhythmias during ischemia. However, the effects of amiodarone pretreatment on the incidence of ventricular premature extrasystoles, ventricular tachycardia, and VF after reperfusion are even more striking: The incidence of ventricular tachycardia and VF in the control group was 100% when the ischemic myocardium was reperfused. In contrast, a dose-related decrease in the incidence of these arrhythmias occurred after pretreatment with amiodarone. Ventricular tachycardia and VF did not occur after intravenous pretreatment at dosages of 42, 49, and 56 μmol/kg. Riva and Hearse68 confirmed the findings of Lubbe’s group when they studied the antiarrhythmic effects of amiodarone and DAM versus control on ventricular tachyarrhythmias caused by ischemia and reperfusion in anesthetized rats. A 5.0 mg · kg⁻¹ dose of amiodarone and DAM before ischemia reduced the incidence of ventricular tachycardia during the ischemic period from 67% to 20% (P < .02) and 47%, respectively. During reperfusion, mortality was reduced from 53% to 7% and 7% (P < .02), respectively, and reperfusion-induced ventricular fibrillation was reduced from 73% to 20% (P < .01) and 47%, respectively. The antiarrhythmic effects of amiodarone and DAM on reperfusion-induced arrhythmias differ from those of conventional β-blocking agents; β-blockade, although effective on ischemia-induced VF, is ineffective in reperfusion-induced VF.66 This study stressed that DAM, like its parent compound, protects the heart against malignant ventricular arrhythmias as a consequence of myocardial ischemia and reperfusion.

Other studies using different experimental models of ischemic ventricular arrhythmias have confirmed the striking antiarrhythmic efficacy of amiodarone.13,69-71 Rosenbaum et al13 showed that chronic pretreatment with amiodarone prevented VF in dogs after coronary ligation. Chew et al69 studied the antiarrhythmic effects of amiodarone on ischemic ventricular arrhythmias in conscious dogs. Control dogs that had large myocardial infarcts developed early bimodal ventricular arrhythmias peaking at 3 to 5 minutes and at 12 to 125 minutes. (VF occurred equally frequently during each peak.) Chronic amiodarone treatment (30 mg/kg daily) for 3 to 4 weeks markedly suppressed spontaneous ventricular arrhythmias. The incidence of VF was 9% in the treated animals compared with 29% in the control animals. Patterson et al70 conducted a study that used conscious dogs in the attempt to mimic the sudden coronary death that occurs in humans. The investigators randomized their animals on the fourth day after anterior wall myocardial infarction to receive either short-term intravenous amiodarone (10 mg/kg per hour) or long-term oral amiodarone treatment (10 mg/kg per day for 24 days). Both short-term and long-term treatment reduced the incidence of VF provoked by occlusion of the left circumflex artery in the presence of previous anterior MI. The study of short-term intravenous amiodarone revealed an incidence of VF at the rate of 60% and 100% in the amiodarone-treated and control groups, respectively (P < .05); the chronic amiodarone treatment group showed only a 20% incidence of VF compared with 91% in the control group (P < .002).

Their data corroborated other findings that both long-term and short-term amiodarone therapy prevented ischemia-induced VF in animals that had survived MI. Chronic amiodarone treatment appeared to be more effective than acute amiodarone treatment. The difference between the effects of acutely and chronically administered amiodarone could not be accounted for on the basis of differences between the plasma and tissue levels.

Taken together, these data show that chronic amiodarone therapy effectively treats sudden death in the infarcted animal model, one that closely resembles that of MI survivors. Against this experimental background—which provides a cogent argument for the potent antibrillary potential of chronically administered amiodarone—recent clinical trial data will now be discussed to determine the role of amiodarone in post-MI survivors.

Prevention of Sudden Cardiac Death in Post-MI Patients

There is no disagreement that survivors of MI continue to face a significant risk of lethal ventricular arrhythmias and sudden cardiac death even though the incidence of VF declines dramatically 24 hours or more after the episode. Marcus et al71 analyzed the data from 867 post-MI patients enrolled in the Multicenter Post-infarction Program (MPIP); they found that of the 867 patients, 108 patients suffered cardiac death during the 48-month follow-up period. Nearly three times as many of these cardiac deaths were classified as arrhythmic deaths (n=80) rather than myocardial failure (n=28). However, 54 (68%) of the arrhythmic deaths occurred in patients with heart failure, either nondisabling (26 cases, 32.5%) or disabling (28 cases, 35%). Only 26 patients (32.5%) who suffered arrhythmic deaths did not have congestive heart failure. Also, a majority of cardiac deaths (76%) were associated with congestive heart failure. They also found that 60% of the patients had myocardial ischemia preceding the terminal event. Their data also showed that the actuarial survival rate dropped relatively sharply during the first 6 months after the patients were discharged from the coronary care unit and then declined at a constant hazard rate; the first-6-months hazard rate was about three times greater than the corresponding “late” hazard rate. Stevenson et al72 determined the causes of death after MI in 172 victims who had evidence of old MI at autopsy. The majority of these patients died because of the MI (117 [81%] in-hospital deaths and 19 [68%] out-of-hospital deaths). In this study, the mechanism of death after recurrent infarction was due largely to pump failure and arrhythmias. These observations suggest that therapy with antiarrhythmic agents aiming to prevent cardiac and sudden arrhythmic death in post-MI patients must consider not only the effects of the drug
on electrophysiological parameters in the normal heart but also its effects on electrophysiological abnormalities associated with congestive heart failure and recurrent myocardial ischemia. That is, a therapeutic drug regimen should not worsen heart failure or ischemic ventricular arrhythmias. To significantly reduce the mortality rate of ischemia-related deaths, the regimen must decrease either the incidence of recurrent MI or the associated fatal ventricular arrhythmias. An effective regimen should significantly improve the mortality rate within the first 6 months of therapy, which is when the risk of death is highest.

Class 1 agents tend to have a negative inotropic effect, and some have the potential to increase the incidence of VF during ischemia. If a patient who has ventricular dysfunction takes a drug that has negative inotropic effects (eg, class 1 agents), the patient may respond to the drug as far as PVC suppression is concerned only to succumb to lethal heart failure or ischemic VF. This was the case in the CAST II study: Patients who were treated with moricizine had a higher incidence of congestive heart failure than those who were given placebo. Class 1c agents also reduce heart rate variability, a marker for an increase in the sympathetic-parasympathetic ratio. As a result, class 1c agents may decrease the VF threshold. In contrast, amiodarone does not affect heart rate variability and it has a sympathetic-blocking property. All class 1 drugs have inherent proarrhythmic effects; they may suppress nonischemic PVCs but may provoke VF during ischemia or heart failure.

Findings such as these account for why treating postinfarction arrhythmias with antiarrhythmic agents has been virtually abandoned; yet, amiodarone has little or no negative inotropic effects and a very low incidence of proarrhythmic effects compared with other antiarrhythmic drugs. Despite its reputed noncardiac side effects, it may be the safe and effective drug therapy that high-risk post-MI patients need. Recent clinical studies uniformly show that amiodarone effectively reduces the rate of early postinfarction mortality. A review of clinical studies on the role of amiodarone in treating postinfarction arrhythmias follows.

Clinical Studies

Ceremuzynski et al conducted a randomized, double-blind study to evaluate the effect of 1-year treatment with amiodarone (n=305) or placebo (n=308) on mortality, ventricular arrhythmias, and clinical complications in high-risk postinfarction patients who were not eligible to receive β-blockers and who did not necessarily manifest high-density ventricular arrhythmias. In this trial, amiodarone therapy significantly reduced cardiac mortality and ventricular arrhythmias (21 deaths in the amiodarone group [6.9%] versus 33 [10.7%] in the placebo group). Most deaths were cardiac deaths (all 33 deaths were cardiac in the placebo group; 19 of the 21 deaths were cardiac deaths [6.2%] in the amiodarone group). The odds ratio was 0.55 in favor of the amiodarone group (95% confidence interval, 0.32 to 0.99). The difference in cardiac death was statistically significant (P = .048; Fig 3). Most deaths were sudden in both groups—within 1 hour of the onset of symptoms (20 placebo-treated patients and 10 amiodarone-treated patients). However, unlike the findings of the β-blocker trials, in this study amiodarone did not prevent reinfarction: Fourteen and 10 patients developed reinfarction in the amiodarone group and the placebo group, respectively. Other findings are noteworthy. Most deaths occurred in the first 6 months of the trial. The incidence of serious ventricular arrhythmias (Lown grade 4) was also significantly lower in the amiodarone group than in the placebo group (7.5% versus 19.5%). Bearing in mind these data and the efficacy of amiodarone, it is likely that the primary mechanism whereby amiodarone reduces the incidence of sudden cardiac death is its antifibrillatory and antiarrhythmic properties rather than by lowering the incidence of ischemia-related VF episodes that are due to the decrease in the number of ischemic events caused by the drug.

Burkhat et al in the Basel Antiarrhythmic Study of Infarct Size (BASIS) studied 312 survivors of MI who had Lown class 3 or 4B arrhythmias on 24-hour ECG monitoring. Patients were randomized to either individualized antiarrhythmic treatment (n=100), 200 mg/d amiodarone therapy (n=98), or control (n=114). During the 1-year follow-up period, the cumulative mortality rates were 13% in the control group, 10% in the individualized antiarrhythmic treated group, and 5% in the amiodarone group. Amiodarone reduced the total mortality rate by 61% from that in the control group (P < .05) and reduced the incidence of arrhythmic events (P < .01).

These investigators continued to study patients in the BASIS trial in a long-term study to determine if the beneficial effect of amiodarone persisted even though the drug was discontinued 1 year later (mean follow-up, 72 months; range, 55 to 125 months).

Fig 4 shows that the probability of death after 84 months according to actuarial life-table analysis (Kaplan-Meier) was 30% for amiodarone-treated patients and 45% for control patients. For the total follow-up period, the mortality rate was much lower in the amiodarone group than in the control group with respect to all deaths (P = .03) and to cardiac deaths (P = .047). This mortality reduction was due entirely to the first-year amiodarone effect, since there was no difference between the amiodarone and control groups only when considering survival after discontinuation of ami-
odarone. They concluded that the beneficial effect of amiodarone on the survival rate persists for years, while stressing the importance of early postinfarction treatment with amiodarone. Since the rate of sudden death and all cardiac deaths was low during late follow-up (1.2% per year in the amiodarone group and 4.6% per year in the control group), patients may not warrant amiodarone therapy after the first year after infarction.

Pfisterer et al.81 cautioned that the beneficial effects of amiodarone reported in their study were tempered by its lack of efficacy in those patients who had poor left ventricular function (ejection fraction <40%). Even so, this caution itself is tempered by other factors: The number of patients in the amiodarone group was quite small; the data were analyzed as a substudy without a planned randomization scheme to ensure the equality of number and confounding variables in each control and amiodarone group. Regardless, the value of amiodarone in MI survivors who have poor left ventricular function requires further study in larger randomized trials.

In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) Pilot Study, Cairns et al.24 randomized 77 postinfarction patients who had arrhythmias in a double-blind fashion to either 300 to 400 mg/d amiodarone or placebo. One patient (2.1%) in the amiodarone group and four (13.8%) in the placebo group died as a result of arrhythmias; overall mortality rates were 10.4% and 20.7%, respectively. More than one third of the patients in both groups discontinued therapy because of side effects, the most common reasons being elevation of thyroid-stimulating hormone and skin reactions. The authors concluded that moderate loading and maintenance doses of amiodarone effectively suppress ventricular premature depolarizations (VPDs) and does so with acceptable levels of toxicity. There were strong trends favoring amiodarone for the principal outcomes, arrhythmic death and resuscitated VF, as well as for all causes of mortality.

**Trials in Progress**

Cairns et al are continuing the full-scale phase of CAMIAT using the same study population and intervention as those used in the pilot study. A Veterans Administration trial will assess the value of amiodarone in patients with class III and IV congestive heart failure and VPDs. The European Myocardial Infarction Arrhythmia Trial will evaluate the effect of amiodarone in early postinfarction patients who have low ejection fractions (without regard to the frequency of their VPDs). These trials will involve more than 3400 patients and thus increase the available data fourfold.

**Comparing Amiodarone and Other Modalities as Secondary Prevention Treatment in MI Survivors**

Table 2 and Fig 5 summarize the overall effects of amiodarone from the three randomized prospective trials discussed above and from the study of Hockings et al.81 The effects of a combined outcome from these

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**Table 2. Effects of Amiodarone on Mortality Rates in Post-MI Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>Total mortality</th>
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<td>P</td>
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<td>100</td>
<td>1.54 0.63-3.89</td>
<td>.30</td>
</tr>
<tr>
<td>Cairns</td>
<td>48</td>
<td>29</td>
<td>0.45 0.10-1.99</td>
<td>.31</td>
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<td>551</td>
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<td>.07</td>
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<tr>
<td>3 Groups combined</td>
<td>451</td>
<td>451</td>
<td>0.70 0.46-1.05</td>
<td>.07</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; OR, odds ratio; CI, confidence intervals; Ami, amiodarone.
trials suggest that amiodarone effectively reduces the mortality rate of post-MI patients (30% reduction in 1 year, \( P = .07 \)). When comparing these combined data on amiodarone with the overview by Teo et al of 53 randomized trials that treated more than 20,000 patients with various classes of antiarrhythmic agents\(^{82}\) (Fig 6), amiodarone and \( \beta \)-blockers are the only two classes of drugs that improved the survival rate; class 1 agents showed no overall beneficial effect on all causes of mortality and actually increased the mortality rate. The effects of amiodarone on cardiac death and sudden death in MI survivors are even more impressive: Within 1 year of amiodarone treatment, the drug reduced cardiac mortality rate by 46% (\( P = .01 \)) and sudden death rate by 58% (\( P = .005 \)). If these findings are confirmed by the larger trials (including the VA cooperative trial in heart failure patients), amiodarone would be considered the compound that best reduces cardiac mortality in MI survivors during the first year of the follow-up period. But this remains to be seen.

Many other questions about amiodarone still need to be answered. Why does amiodarone succeed where other antiarrhythmic drugs have failed? How does it work? Although proponents of class 3 agents may infer from these data that amiodarone works by prolonging repolarization, the inference that all class 3 agents have the same effect is too simplistic because amiodarone has other antiarrhythmic properties. Similarly, proponents of \( \beta \)-blockers may infer that amiodarone is effective because of its sympathetic-blocking properties. However, \( \beta \)-blockade—while essential—may not be the only factor contributing to the success of amiodarone.

To reiterate, amiodarone is the only antiarrhythmic agent shown thus far to prevent sudden cardiac death during the first year in post-MI patients. Sotalol, a drug that closely resembles amiodarone, has gained recognition recently\(^{83-85}\) and has its own proponents. A comparison of the two drugs, both of which have class 3 antiarrhythmic, antisympathetic, and anti-ischemic properties, would help to illustrate the unique pharmacological status of amiodarone.

Bearing in mind that a study by Julian et al\(^{86}\) did not find that sotalol reduced mortality (although there was a trend suggesting this), the mortality rate in this study was 18% lower in the sotalol than in the placebo group. Sotalol did not prevent sudden death (2.9% in the sotalol group compared with 2.4% in the placebo group), but sotalol did significantly reduce the incidence of MI. This would mean that if the prolongation of the APD and \( \beta \)-blockade were the principal mechanism of action responsible for preventing sudden cardiac death in post-MI patients, then one would expect sotalol to be as effective as amiodarone in this study—or more so.

Sotalol was not shown to be more effective than amiodarone: Therefore, the effectiveness of amiodarone cannot be due solely to its class 3 effect. Having said this, one cannot rule out the possibility that the class 3 action plays a role in the efficacy of amiodarone. The difference may be because sotalol has more proarrhythmic effects than cause fatal arrhythmias.\(^{87}\) This would naturally offset the beneficial effects of sotalol. Unlike sotalol, amiodarone has negligible proarrhythmic effects, perhaps because of its calcium-channel blocking properties, which may prevent early afterdepolarization,\(^{88}\) a mechanism believed to cause torsade de pointes and polymorphic ventricular tachycardia in patients who have abnormal prolongation of the repolarization.

**Amiodarone Toxicity**

Although amiodarone appears to reduce the mortality rate of MI survivors, many physicians are leery of the drug’s reputed toxicity. The toxicity of amiodarone cannot be denied.\(^{89,90}\) The drug affects virtually every organ in the body, especially when it is taken at high doses for a long period of time. However, several facts about amiodarone toxicities deserve emphasis. There is a sharp contrast between the incidence of side effects reported by the European studies\(^{84}\) and the American studies\(^{89,90}\) (which used a higher dose and found a higher incidence of side effects). The findings of Cere- muzynski\(^{107}\) and Cairns\(^{98}\) confirmed the European observation that low-dose amiodarone treatment is associated with few short-term side effects; these observations were also the most systematic assessment of amiodarone because they were the result of a double-blind placebo-controlled study. Cere- muzynski et al found that 55 of the 305 amiodarone-treated patients were withdrawn from the drug because they developed “adverse effects” (as opposed to 19 from the 308 placebo-treated group). However, if one were to exclude inconsequential side effects (eg, first-degree AV block; bundle branch block, etc), the number of serious side effects falls from 55 to approximately 25, which is much closer to the placebo figure. This is an emphatic indication that amiodarone is a very well-tolerated drug in short term.

**Summary**

Amiodarone is a viable drug for preventing sudden cardiac death, particularly during the first year after MI. If larger trials confirm the aforementioned prospective trials of Ceremuzynski et al, Cairns et al, and the BASIS trial, the efficacy of amiodarone would outweigh the risk of its side effects during the first year after MI. Based on the long-term observation from the BASIS trial, the duration of amiodarone therapy need not be more than 1 year—which, as we have learned, is when these
post-MI patients would benefit most from the drug. It is also likely that the effects of amiodarone would complement those of aspirin and angiotensin converting enzyme inhibitors. The SAVE,92 CONSENSUS II,93 and SOLVD trials demonstrated that captopril and enalapril did not reduce the mortality rate during the first year after MI, nor did they reduce the sudden cardiac death rate. Their beneficial effects became evident only during the second year and thereafter.

Unlike other antiarrhythmic agents of various classes, amiodarone possesses antiarrhythmic properties but does not exert deleterious effects on ventricular function. More studies are needed to determine if the benefit of amiodarone could be enhanced by combination therapy92 (eg, angiotensin converting enzyme inhibitors, aspirin, or β-blockers). Whether amiodarone will provide the same protection for patients who have poor left ventricular function or congestive heart failure is not known. The European and VA cooperative studies should help answer this question. If it turns out that amiodarone is beneficial, one must then determine whether higher doses of the drug will offer more protection, and, if so, if that greater protection would be offset by increased toxicity. How much amiodarone should be given to offer the most protection with the least risk? Another intriguing research question is this: If we treat patients with amiodarone for more than 1 year, would the drug continue to improve the mortality rate in subsequent years? Other studies are needed in patients at very high risk of sudden cardiac death (ie, those who have a low ejection fraction and high-density VPDs). A study comparing amiodarone and sotalol in high-risk patients for sudden cardiac death is also needed. These clinical studies should be carried out with basic science research investigating the actions of amiodarone at the molecular and cellular level in order to give us a better understanding of how the drug works.

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References


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