Frequent and repetitive forms of premature ventricular complexes (PVCs) have been recognized as independent markers of increased risk for sudden cardiac death in patients with a previous myocardial infarction. On this basis, the Cardiac Arrhythmic Suppression Trial (CAST) was initiated to test the hypothesis that suppression of these ventricular arrhythmias would reduce the incidence of sudden cardiac death.1

As critically reviewed by Furberg,2 previous studies with antiarrhythmic drugs in post–myocardial infarction patients were seriously flawed in one or more ways, such that they could not conclusively demonstrate whether suppression of ventricular arrhythmias by the antiarrhythmic drugs studied affected survival.

CAST, a placebo-controlled, double-blind, multicenter study, was initiated in June 1987 to evaluate the effect of three antiarrhythmic drugs (encainide, flecainide, and moricizine) in patients who had sustained a myocardial infarction and had asymptomatic or mildly symptomatic ventricular arrhythmias. Approximately 22 months after its initiation, part of the study was prematurely halted, and the remaining part was significantly modified because of excessive mortality in the group of patients randomized to treatment with encainide or flecainide.1 The study is continuing with the third drug, moricizine.

CAST is an important study for several reasons. For the first time, convincing data were provided regarding a mode of antiarrhythmic treatment that existed for some 20 years and was widely applied by practicing physicians. The results of CAST may lead to extensive changes in antiarrhythmic therapy, and they merit careful consideration. Also, results from CAST answered the hypotheses posed for flecainide and encainide in that suppression of frequent PVCs by those two drugs did not favorably influence outcome. On the contrary, despite effective suppression of PVCs, flecainide and encainide significantly worsened the total sudden death mortality compared with placebo overall and across all subgroups analyzed.

Thus, the study answered the main question for these two drugs. However, several questions remain, and many new concerns have been generated, including questions about the scientific and medical implications of the CAST results, therapeutic implications concerning the use of these drugs for management of patients with other arrhythmias, extrapolation of these data to the use of other antiarrhythmic drugs, implications for regulatory authorities, and implications for future studies and new drug development.

To address some of these issues, the Working Group on Cardiac Arrhythmias of the European Society of Cardiology convened a task force committee.

CAST produced surprising results surprisingly early. There was definite evidence of harm after 10 months of mean follow-up. The unexpectedly powerful harmful effect can be analyzed in two components: the relatively low mortality in the placebo group and the unanticipated high mortality in the treatment (encainide or flecainide) group.

Possible Reasons for Unexpectedly Low Mortality of Placebo Group

The low mortality in the placebo, or control, group may relate in part to certain general features of clinical trials. There is a general tendency toward lower-than-expected mortality in placebo or control groups, which is attributed to more careful observation of and attention to patients consequent to their inclusion in a clinical study, even in the absence of an intervention, or the withholding of patients with more advanced diseases from randomized trials. Also, there is an historical trend toward lower mortality rates in coronary artery disease, which is attrib-
uted to new therapeutic modalities and risk factor modification. Nearly two decades have passed since the earliest identification of ventricular arrhythmias as risk factors for sudden cardiac death after myocardial infarction and about 10 years since a large controlled clinical trial such as CAST was first seriously considered. During this time, therapy has changed greatly and has included the introduction of thrombolysis and coronary angioplasty. In the placebo group, 18.7% of the patients had thrombolysis, 18% had angioplasty, and 18.6% had coronary artery bypass surgery with their qualifying myocardial infarction; these interventions may have favorably influenced prognoses.

CAST was designed with a projected mortality rate from sudden cardiac death of 11% over 3 years. Linear extrapolation from the initial report (which will give an exaggerated figure) indicates a 3-year sudden death or cardiac arrest rate of about 4.5% in the placebo group. This rate falls short of the projection and suggests that factors specific to CAST may have been significant. First, it is reported that 19% of the patients were excluded during the drug titration phase because of drug inefficacy or intolerance, proarrhythmia, or death. Second, the number of deaths during the drug titration phase was approximately equivalent to the total number during the blinded follow-up phase in the groups reported. Thus, although all patients who could be treated were entered, a relatively high-risk group was eliminated before randomization. Also, it seems that suppression of ventricular ectopy by therapy, a requirement for randomization in CAST, may define a group with better prognoses. Therefore, the residual group that was randomized was more likely to survive than an unselected group of post–myocardial infarction patients.

There are many studies confirming that ventricular ectopy and reduced ventricular function are predictors of increased risk for lethal ventricular arrhythmias after myocardial infarction. These risk factors must be considered quantitatively. In the case of PVC frequency, more than 85% of the placebo group had more than 10 PVCs/hr. The curve relating frequency and mortality indicates that relatively high risk should have been predicted by this high frequency. Despite the high frequency of PVCs, only 20% of the placebo group had salvos or nonsustained ventricular tachycardia, and one half of these had only one episode. Thus, the study group was characterized by a high prevalence of patients with frequent PVCs but a low prevalence of patients with nonsustained ventricular tachycardia. This feature predicts lesser risk.

The curve relating left ventricular ejection fraction to mortality is hyperbolic, with an upturn in cardiac mortality occurring at ejection fractions less than 40%. In CAST, 50% of the placebo group had an ejection fraction of more than 40%. Thus, one might question whether these particular risk factors were present in the blinded phase of CAST in a sufficient degree to define a high-risk group.

These risk factors generally have been defined in a period relatively soon after myocardial infarction (within weeks). In CAST, these risk factors were assessed up to 2 years after myocardial infarction. It is reported that only 22% of the placebo group was evaluated more than 90 days after myocardial infarction, although more may have been randomized in this later period because of delays during drug titration. The predictive power of these factors defined later is far from certain. It is reported that the mortality in the placebo subgroup recruited late after myocardial infarction is about the same as that recruited early. If so, it would seem that risk factors predict similarly whether assessed early or late after myocardial infarction. It is not clear if this interpretation applies to both ejection fraction and ventricular ectopy.

No data on outcome in the moricizine-treated group and their randomized, placebo-treated controls have been released. The only inference that can be drawn is that the moricizine-treated group has not crossed a boundary of significance for either harm or benefit compared with their controls at the time of publication of the preliminary CAST report. At that time, only 272 patients had been entered into the moricizine-placebo arm (approximately 136 in each) compared with 730 patients who had received encainide or flecainide and their 725 controls. Given the probable selection of patients with lower ejection fraction into the moricizine arm of the study, the sudden death rate for the moricizine randomized placebo group may shed further light on the reasons for the low death rate in the flecainide-encainide placebo group.

**Possible Reasons for Unexpectedly High Mortality in the CAST Encainide-Flecainide Treatment Group**

After randomization and during a follow-up of 10 months, 33 patients in the encainide-flecainide group (4.5%) compared with nine in the placebo group (1.2%) had a nonfatal cardiac arrest or sudden death. The total mortality was 56 of 730 patients (7.7%) treated with encainide or flecainide in contrast to 22 of 725 patients (3.0%) receiving placebo. The inescapable conclusion is that these differences are associated with the use of encainide and flecainide.

The reasons for this outcome are not clear. Antiarrhythmic drugs may cause or aggravate cardiac arrhythmia by multiple mechanisms; this is known as a proarrhythmic effect. The classic type of proarrhythmic response usually occurs early after starting treatment. Of the early proarrhythmic responses, some are characterized by a prolonged QT interval and torsade de pointes. Experimental studies implicate the development of early afterdepolarizations as the most likely arrhythmogenic mechanism for the latter. In other instances, the proarrhythmic effect may be manifest by widening of the QRS complex, sometimes associated with incessant monomorphic
ventricular tachycardia or episodes of nonsustained polymorphic ventricular tachycardia. Animal experiments and clinical studies support reentry caused by drug-induced slowing of conduction and a minimal prolongation of the refractory period as the underlying mechanism.4,5

In the Cardiac Arrhythmia Pilot Study (CAPS), early proarrhythmic effects were rare (3% in the placebo group, 3% in the encainide group, and 1% in the flecainide group). Preliminary analysis of the CAST data indicates a similar incidence in terms of a significant increase of PVCs or new ventricular tachycardia on 24-hour electrocardiographic recordings. Because the deaths reported in CAST were equally distributed throughout the period of drug treatment, mechanisms other than early proarrhythmic effects must have been operative. Proarrhythmic effects not restricted to the early phase of antiarrhythmic treatment may include exacerbation of ischemia-induced conduction delay4,6 and regional differences in myocardial concentration of antiarrhythmic drugs caused by unequal distribution of coronary flow7 leading to heterogeneous electrophysiological effects. Each of these mechanisms could promote reentry. Further, interaction of antiarrhythmic drugs with hemodynamic consequences of heart failure (which could be aggravated by antiarrhythmic drugs9), modulation by the autonomic nervous system,9-11 and other consequences of myocardial ischemia also must be considered. Many of these factors may operate during the whole course of exposure to drug. It is quite possible that a drug suppresses ventricular ectopic activity at one stage and causes arrhythmias at another time when a change in pathophysiological conditions has occurred. Also, because of complex interaction between the drug and the arrhythmia substrate, it is quite conceivable that an antiarrhythmic agent may promote ventricular fibrillation while simultaneously suppressing other forms of arrhythmia. Ventricular fibrillation may be the result of the combination of a suitable substrate for reentry and a trigger that initiates reentry. Ventricular premature beats or an increase in heart rate can serve as a trigger. Suppression of one kind of trigger may leave other triggers unchanged and might be accompanied by changes in arrhythmia substrate. Thus, slowing of conduction produced by encainide or flecainide is more marked at faster heart rates.12,13 Therefore, even when ventricular premature beats are no longer present, an increase in heart rate might enhance the propensity for reentry.

**Implications of CAST**

A strict interpretation of the results of CAST would limit the conclusions of this study to the use of encainide or flecainide in a population of patients defined identically to those randomized in CAST. While such a strict interpretation has the merit of scientific restraint and precision, it forsakes powerful tools of scientific inquiry—generalization and extrapolation. Without generalization and extrapolation, studies must be repeated endlessly with every agent and with every conceivable permutation of patient population, clearly an impossible task. It is, therefore, important to consider which extrapolations from CAST are judicious and appropriate and what areas call for other studies.

To apply the results of CAST to all drugs currently classified as IC would be to ignore the generally acknowledged deficiencies of the classification system. There is overlap of properties among agents of different classes and differences in properties among agents in the same class. At this point, it seems reasonable to extend the conclusions of CAST to the other agents in proportion to the degree that their electrophysiological properties resemble those of encainide and flecainide. There is no definitive information comparable to the data in CAST with respect to agents of other classes except for β-adrenergic-blocking agents, which have been demonstrated unequivocally to reduce mortality after myocardial infarction with only partial suppression of chronic ventricular arrhythmias.

A major question relates to the applicability of the conclusions from CAST to patients with other expressions of coronary disease or with different diseases. It would be treacherous to generalize the substantially enhanced mortality associated with treatment of the CAST population with encainide or flecainide to all types of conditions and to all types of patients; such an approach would eliminate the use of these drugs in higher-risk patients among whom efficacy might exceed proarrhythmic risk and would deny their use in certain relatively benign but troubling conditions in which pronounced efficacy has already been shown. The latter include symptomatic ventricular ectopy and supraventricular arrhythmias, conditions in which the serious proarrhythmic potential of these agents may be much less. It seems reasonable to expect further studies focusing on safety in those conditions and to advise prudence for the present in all conditions in which an acceptable level of safety has not been documented.

**Therapeutic Implications**

It is quite clear that presence of PVCs in a post-myocardial infarction population identifies patients at a greater risk for sudden cardiac death. The role of the PVCs in the initiation of sustained ventricular tachyarrhythmias is less clear—at least three possibilities exist. First, the chronic PVC may be an “innocent bystander,” totally unrelated to the tachyarrhythmia. Second, a PVC of one mechanism may initiate a ventricular tachyarrhythmia of another mechanism. Third, the PVC may be caused by the same mechanism responsible for the sustained arrhythmia and may simply be a single beat expression of that mechanism. Suppression of an innocent bystander will obviously have no effect per se on the sustained arrhythmia. If the PVC plays an initiating role, its suppression might be beneficial. However, if the drug also facilitates the mechanism of the sustained tachyarrhythmia, the net effect may be harm-
ful. When the mechanism of the initiating PVC is the same as that of the sustained arrhythmia, its suppression should equate with eradication of sustained arrhythmia.

The CAST study proved that suppression of PVCs in a post–myocardial infarction population at low risk by flecainide or encainide is harmful. This may be because flecainide and encainide have significant effects on the substrate for sustained arrhythmia, as explained earlier. Therefore, the CAST study has not unequivocally demonstrated that suppression of PVCs may not be beneficial in terms of reducing mortality. In this respect, the outcome of the mori-zine limb of the study may be very enlightening.

Statements made about single PVCs might apply equally to repetitive forms. While salvos of PVCs identify patients at higher risk for sudden death than patients with single premature depolarizations,14 this group was relatively underrepresented in CAST: 10% had one salvo, and another 10% had more than one. The question of whether suppression of salvos reduces mortality is unanswered and may be difficult to answer because of recruitment difficulties.

While no patient with sustained ventricular tachycardia was enrolled in CAST, encainide and flecainide are approved for use in patients with life-threatening tachycardia. Despite such approval, the statements made above may be equally applicable to sustained ventricular tachycardia. That is, a drug may effectively suppress one tachyarrhythmia while promoting another. When the tachycardia is not completely suppressed, the drug may facilitate a more rapid tachycardia or the development of ventricular fibrillation.

Having said that, the net effect of encainide or flecainide in these patients may still be beneficial because untreated patients with sustained ventricular tachycardia have a very high mortality. There are no placebo-controlled data for this high-risk population. CAST again demonstrated the necessity of placebo-controlled studies. If the data of the encainide-flecainide group had been compared with an historical control group, the response to therapy would have appeared to be excellent; for example, in six previous trials with antiarrhythmic drugs, total mortality in the placebo group ranged from 4.1% to 18.4%. Future studies in high-risk patients using placebo controls achieved by implantation of a cardioverter-defibrillator to judge antiarrhythmic efficacy should be undertaken. In the meantime, careful evaluation of efficacy and safety of antiarrhythmic drugs in high-risk patients by, for example, electrophysiologic study, exercise testing to check whether QRS width increases,13 repeated ambulatory electrocardiographic recordings, and determination of drug serum concentrations is essential until further data are available.

At the present time, in the management of patients who have supraventricular tachycardia with flecainide or encainide, it would seem prudent to make a distinction between patients with and without struc-tural heart disease and with and without concomitant ventricular arrhythmias. In patients who present with supraventricular tachycardia but have clinical characteristics similar to the CAST population, the use of flecainide or encainide should be discouraged.

Medical and Medicolegal Implications

The lethal potential of treatment by encainide and flecainide disclosed in CAST has raised both medical and medicolegal issues concerning continued and future therapy of patients who are unlike the CAST population. It is agreed that the CAST results do not impact on therapy for sustained ventricular tachycardia, ventricular fibrillation, and symptomatic nonsustained ventricular tachycardia. Symptomatic arrhythmias, notably supraventricular tachycardias, have been demonstrated to respond well to these agents, and many patients are being treated worldwide. It may be judicious to continue therapy if symptoms are relieved. A relatively long duration of satisfactory therapy may be considered reassuring, but it should be noted that in CAST, the incidence of excess mortality appeared to be the same throughout the period of treatment of almost 1 year. Physicians may choose to advise patients of the results of the CAST study, point out differences between the patient’s condition and those of the CAST population, discuss other options, and arrive at an agreement about continuation of therapy. There is information suggesting that the risk of therapy in patients with supraventricular arrhythmias and minimal ventricular disease may be considerably less than that found in the CAST population. For patients with symptomatic arrhythmias and concomitant features of the CAST population, such as coronary artery disease and healed myocardial infarction, it seems prudent to weigh the possible benefits in terms of quality of life against the probable enhanced risk. Ventricles damaged from other causes may also entail enhanced risk during antiarrhythmic drug therapy, but the information is not yet available. For patients with asymptomatic frequent PVCs in other diseases, such as cardiomyopathy, there are formidable questions regarding the risk-to-benefit ratio for all class I agents that are highlighted and resolved by CAST for only coronary artery disease and encainide and flecainide. For the specific PVC forms of salvos and nonsustained ventricular tachycardia in other diseases, the risk-to-benefit ratio of antiarrhythmic drug therapy remains unresolved. The CAST data do not even resolve the risk/benefit issue for treatment of these arrhythmias after myocardial infarction. Until such questions are resolved for these conditions, the use of these agents solely to suppress ventricular ectopy must be considered neither validated nor invalidated.

Regulatory Implications

It is axiomatic that all therapy requires a consideration of the risk-to-benefit ratio in which the benefit should clearly outweigh the risk. The ideal method by which to establish this is the prospective,
randomized, placebo-controlled trial. In treating asymptomatic patients in an attempt to demonstrate improved survival, that kind of study is the only option. This was the design of CAST. The cost, time, and number of patients involved in such a study are considerable and impractical to apply for all forms of treatment. Therefore, when dealing with patients who have symptomatic arrhythmias, the minimal requirement should be the assessment of the safety of drugs of established efficacy in relieving symptoms. The assessment of safety does not require determination of mortality in a control group on placebo, because 1) it may be unethical or inappropriate not to relieve severe symptoms and 2) because patient and physician may accept a certain risk of mortality in exchange for improved quality of life. For example, surgery for nonfatal conditions is associated with a small but definite risk of perioperative mortality that may exceed that of medical treatment but is accepted if it leads to the relief of symptoms. However, the mortality associated with treatment must be known. This can be achieved by monitoring an appropriately large group receiving the particular therapeutic modality for a sufficient period of time.

Regulatory authorities for drug approval should consider the balance between the necessary safety and efficacy requirements and the desire not to discourage the development of new drugs in an area of medicine where there is still need for therapeutic progress.

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References


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