Interaction of Baseline Characteristics With the Hazard of Encainide, Flecainide, and Moricizine Therapy in Patients With Myocardial Infarction

A Possible Explanation for Increased Mortality in the Cardiac Arrhythmia Suppression Trial (CAST)

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Background: The Cardiac Arrhythmia Suppression Trial (CAST) was designed to test the hypothesis that suppression of ventricular ectopy with antiarrhythmic drugs after a myocardial infarction reduces the incidence of sudden arrhythmic death. Patients in whom ventricular ectopy could be suppressed with encainide, flecainide, or moricizine were randomly assigned to receive either active drug or placebo. The encainide and flecainide arms of the study were discontinued in 1989 (CAST-I) and the moricizine arm in 1991 (CAST-II) because of excess mortality. To explore the mechanisms of these adverse outcomes, we examined the interaction of baseline characteristics with the hazard of therapy with encainide, flecainide, or moricizine compared with their respective placebos.

Methods and Results: CAST-I comprised 755 patients assigned to flecainide or encainide and 743 patients assigned to placebo, whereas in CAST-II, 502 patients received moricizine and 491 patients received placebo. Clinical and laboratory baseline variables of patients receiving active drug and those receiving placebo were similar. In CAST-I patients, there was a significant interaction of active therapy with both all-cause death/cardiac arrest and arrhythmic death/cardiac arrest for non-Q-wave myocardial infarction (total mortality hazard ratios, 1.48 versus 1.49 for Q-wave versus non-Q-wave infarction, \( P = .03 \)). Ventricular premature depolarization (VPD) frequency \( \geq 50 / h \) and heart rate \( \geq 74 \) beats per minute each interacted significantly with total mortality/cardiac arrest only. In the sicker CAST-II patients (ejection fraction \( \leq 40 \% \)), only diuretic use at baseline interacted significantly with moricizine use for both all-cause death/cardiac arrest and arrhythmic death/cardiac arrest (total mortality hazard ratios, 1.9 versus 0.7 for diuretic use versus no use, \( P = .01 \)).

Conclusions: Although active treatment in CAST-I was associated with greater mortality than placebo with respect to almost all baseline variables, the therapeutic hazard was more than expected in patients with non-Q-wave myocardial infarction and (for total mortality) frequent premature VPDs and higher heart rates, suggesting that the adverse effect of encainide or flecainide therapy is greater when ischemic and electrical instability are present. The relative hazard of therapy with moricizine in the sicker CAST-II population was greater in those using diuretics. Thus, although these drugs have the common ability to suppress ventricular ectopy after myocardial infarction, their detrimental effects on survival may be mediated by different mechanisms in different populations, emphasizing the complex, poorly understood hazards associated with antiarrhythmic drug treatment. (Circulation. 1994; 90:2843-2852.)

Key Words: arrhythmia • trials • myocardial infarction

Although numerous studies have shown that there is an increased mortality among patients with asymptomatic ventricular premature depolarizations (VPDs) after myocardial infarction, no study has clearly shown that suppression of such arrhythmias with class I antiarrhythmic drugs can effect any significant reduction in mortality. The Cardiac Arrhythmia Suppression Trial (CAST), a multicenter, randomized, placebo-controlled study, was conducted to test the hypothesis that suppression of asymptomatic or mildly symptomatic VPDs by antiarrhythmic drugs after myocardial infarction decreases the rate of arrhythmic death or nonfatal cardiac arrest. In the Cardiac Arrhythmia Pilot Study (CAPS), which was carried out before CAST, encainide, flecainide, and moricizine were shown to suppress arrhythmias effectively and were well tolerated in the target population. As a result, these drugs were selected for use in CAST. CAST (or “CAST-I”) was terminated earlier than scheduled because of an excess of deaths from arrhythmia and nonfatal cardiac arrest among patients taking flecainide or enca

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be shown.\textsuperscript{4,5} The purpose of this study was to explore the mechanisms of these adverse outcomes by examining the interaction of baseline characteristics with the hazard of encainide and flecainide in those patients enrolled in CAST-I and of moricizine in patients enrolled in CAST-II.

**Methods**

**Rationale and Entry Characteristics of CAST-I**

Based on the results of the Cardiac Arrhythmia Pilot Study\textsuperscript{1} and a review of other available antiarrhythmic agents, encainide, flecainide, and moricizine were chosen for use in CAST. Patients with an average of 6 or more VPDs per hour on baseline ambulatory ECG recording and with a reduced ejection fraction (≤55\%) after myocardial infarction were given randomly assigned antiarrhythmic drugs, titrated in an open-label fashion, to identify those in whom sufficient suppression (≥80\%) of ventricular ectopy could be achieved. If suppression was achieved, patients were randomized to receive the effective drug or a matching placebo and followed for clinical outcome. Details of the study protocol have been published elsewhere.\textsuperscript{2,3}

**Rationale and Entry Characteristics of CAST-II and Overall CAST Results**

In April 1989, the Data and Safety Monitoring Board for CAST-I recommended that the encainide and flecainide arms of the study be discontinued because mortality was higher in patients treated with the drugs compared with those given matching placebo. Because encainide and flecainide were tested first, by protocol, and were highly effective in suppressing VPDs, only 277 patients had been treated with moricizine or its placebo by April 1989.\textsuperscript{5} In addition, a favorable trend in mortality (11 deaths on placebo versus 4 deaths on moricizine) in these patients caused the Data and Safety Monitoring Board to recommend that the study be continued with moricizine (CAST-II).

In CAST-II,\textsuperscript{4,5} the following alterations in the protocol were implemented: (1) the study was continued with moricizine as the only antiarrhythmic drug; (2) the upper limit of eligible left ventricular ejection fraction was lowered from ≤0.55 in CAST-I to ≤0.40; (3) the time from the qualifying myocardial infarction to the qualifying ambulatory ECG recording was shortened to ≤90 days from the myocardial infarction, compared with ≤2 years in CAST-I; (4) the definition of disqualifying ventricular tachycardia was altered to exclude patients with any runs of ≥30 seconds of ventricular tachycardia with a rate ≥120 complexes per minute but to allow enrollment of patients with runs persisting from ≥15 beats up to 30 seconds without symptoms (previously excluded); (5) a higher dose of moricizine (900 mg/d) was permitted if needed to suppress VPDs by ≥80\%; and (6) because controlled data about the initiation of drug treatment were of interest but not studied in CAST-I, CAST-II began with a 2-week, controlled trial of the acute effects of initiation of low-dose moricizine. Steps 2 and 3 were taken because of the low arrhythmic death rate in CAST-I patients with ejection fraction >0.40 and in patients entered more than 90 days after infarction. Patients enrolled during CAST-I and assigned to moricizine or moricizine placebo were analyzed with the CAST-II study results.

Baseline clinical data were recorded, and patients (new patients as well as former CAST-I patients who had been on encainide, flecainide, or placebo and who qualified for CAST-II) were randomized to either low-dose moricizine (200 mg q 8 hours) or control (matching placebo or no drug) for a 2-week period. After 2 weeks, therapy was unblinded, and patients who had been treated with active medication were evaluated by ambulatory ECG recording to determine if VPB complex were adequately suppressed. Patients who had been treated with placebo (or in whom initiation of active therapy was delayed) were begun on active moricizine titration and subsequently evaluated by ambulatory ECG recording.

The primary end point for the 2-week, acute, low-dose comparison was death or cardiac arrest within the 2-week period. The primary end point of CAST-II for the main study and the substudy was arrhythmic death or nonfatal cardiac arrest requiring resuscitation.\textsuperscript{2,4} All events were reviewed by a subcommittee of investigators blinded to study treatment.\textsuperscript{6}

The Data and Safety Monitoring Board recommended early termination of CAST-II for two reasons. First, the available data for the 2-week, low-dose, acute exposure comparison revealed an increased mortality in patients treated with moricizine (15 versus 3 events, P < 0.021, adjusted for sequential monitoring). Second, it appeared very unlikely that the long-term study had any chance of showing improved survival for patients treated with moricizine over those treated with placebo (42 primary events on moricizine versus 32 on placebo, by preliminary classification at the time of the meeting).\textsuperscript{5}

**Statistical Rationale and Analysis**

In this study, we wished to determine the simultaneous effects of more than one factor (ie, factors in addition to drug) on mortality or cardiac arrest outcomes using factorial analysis procedures.\textsuperscript{7} Such factorial analysis procedures allow testing for interaction among factors. An interaction between two factors means that the effect of one factor is not independent of the presence of a particular level of the other factor.\textsuperscript{7} Therefore, interaction between factors in CAST would represent an effect on the outcome variable (mortality/cardiac arrest) in addition to the effects expected for each factor (ie, drug and another baseline factor of interest) considered separately. Specifically, the analyses ask whether the effect on mortality of drug treatment is different in patients with different levels (eg, presence or absence) of other specific baseline factors of interest.

For these analyses, T was chosen to represent the treatment indicator (active versus placebo), or first factor, and G to represent the grouping variable (eg, men versus women, age <60 versus age ≥60 years), the second factor. Survival as a function of G and T was then determined by failure time regression analysis.\textsuperscript{8,9} If the interaction model (survival explained as a function of G, T, and G×T) was improved at least marginally significantly (P ≤ 0.1) over the simple model (survival explained as a function of G and T alone), the qualitative relation of this interaction was investigated by plotting the survival estimates using the product limit method for the four survival curves of patients in categories defined by the two treatments and the two specific subgroups of interest.\textsuperscript{10-12} We chose P ≤ 0.1 (χ ≤ 2.6), because we wished to err on the side of allowing evidence to be considered for any interactions that might seem quantitatively meaningful even though statistically not highly significant. Reported P values have not been corrected for multiple comparisons.

**Results**

The purpose of this study was to explore the interaction of baseline factors with treatment effects. The Table contains the key interaction results, showing all of the groupings based on baseline characteristics that were considered and highlighting those with a potentially significant (P ≤ 0.1) interaction with encainide or flecainide therapy in CAST-I patients and with moricizine therapy in CAST-II patients for total death/cardiac arrest and for arrhythmic death/cardiac arrest events. Because the purpose of the study was not to assess the risk of baseline characteristics per se, the confounding of treatment risk by these factors is not presented (but has been reported elsewhere\textsuperscript{2,3}).
### Subgroup Effects of Encainide/Flecainide and Moricizine Therapy in CAST (table continued)

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Dth/CA indicates death/cardiac arrest; HBP, high blood pressure; MI, myocardial infarction; CHF, congestive heart failure; EF, ejection fraction; HR, heart rate; bpm, beats per minute; VT, ventricular tachycardia; Arrhy sup, arrhythmia suppression; PTCA/CABG, percutaneous transluminal coronary angioplasty/coronary artery bypass graft; VPD, ventricular premature depolarization; NS, not significant, P > .1; and NE, not evaluable.

*History of angina before the index MI.
†Ischemia manifested between the index MI and enrollment in CAST.
### Table continued

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Interaction of Therapy With Baseline Characteristics in CAST-I

A single variable interacted with encaïnide or flecaïnide therapy (CAST-I) in predicting all-cause death or cardiac arrest as well as arrhythmic death or cardiac arrest: the presence of a non-Q-wave myocardial infarction (Table and Fig 1). The hazard ratio of active versus placebo therapy for total death/cardiac arrest events was 7.9 in postinfarction patients with absence of a Q wave (non-Q-wave myocardial infarction) versus 1.8 in those with a Q wave present (Q-wave myocardial infarction) \((P=0.03, \chi^2=4.6)\). For arrhythmic death/cardiac arrest, hazard ratios were 10.7 versus 2.1, respectively \((P=0.08, \chi^2=3.1)\); when the analysis was restricted to those developing new Q waves (versus no Q waves), arrhythmic death/cardiac arrest hazard ratios became 10.6 versus 1.5, respectively \((P=0.03)\).

Three variables interacted with encaïnide or flecaïnide therapy in predicting all-cause death or cardiac arrest.
arrest but not arrhythmic death/cardiac arrest (Table and Fig 1): (1) ≥50 VPDs per hour on baseline monitor recording (hazard ratio, 4.1 in patients with ≥50 VPDs per hour versus 1.4 in those with <50 VPDs per hour, P=0.03), (2) the presence of a heart rate >74 beats per minute (bpm) on baseline ECG (hazard ratio, 3.9 for heart rate ≥74 versus 1.3 for heart rate <74 bpm, P=0.02), and (3) the absence of a history of diabetes (hazard ratio, 3.5 for nondiabetics versus 1.4 for diabetics, P=0.06).

Effective VPD suppression with the first drug administered was associated with an interaction with arrhythmic death/cardiac arrest (hazard ratio, 3.5 for suppression with the first drug versus 0.3 for more than one drug, P=0.02) but not with all-cause death/cardiac arrest (Table and Fig 1).

Interaction of Therapy With Baseline Characteristics in CAST-II

There was one significant interaction and two interaction trends (P>0.1 to <0.2) with moricizine therapy (CAST-II) with respect to both all-cause mortality/cardiac arrest and arrhythmic death/cardiac arrest: (1) diuretic use, (2) a history of congestive heart failure, and (3) presence at baseline of symptoms of myocardial ischemia, defined as a history of discomfort consistent with angina requiring rest or nitroglycerin for relief (Table and Fig 2).

In patients using diuretics, the hazard ratio for death/cardiac arrest was 1.9 compared with 0.7 for those not receiving diuretics (P<0.01, χ²=6.7). Similarly, the hazard ratio for arrhythmic death/cardiac arrest was 2.0 with diuretic use versus 0.5 without diuretic use (P<0.006, χ²=7.6).

Interactions for heart failure history paralleled those for diuretic use but did not achieve significance. In patients with a history of heart failure, the hazard ratio for death/cardiac arrest was 2.0 compared with 1.1 in those without a heart failure history (P=0.15, χ²=2.02) (Table and Fig 2). The hazard ratios for arrhythmic death/cardiac arrest for heart failure history present versus absent were 2.1 versus 1.2, respectively (P=0.19, χ²=1.70).

For patients with a history of ischemia at study entry (postinfarction angina), the hazard ratio for death/cardiac arrest was 2.0 compared with 1.1 for those without ischemia (P=0.17, χ²=1.87). Hazard ratios for arrhythmic death/cardiac arrest were 2.3 versus 1.0 for those with versus without baseline ischemia, respectively (P=0.11, χ²=2.61) (Table and Fig 2).

Gender (hazard ratio, 1.6 for men versus 0.7 for women, P=0.04) and arrhythmia suppression with the first drug administered (hazard ratio, 1.6 versus 0.6 with more than one drug, P=0.04) interacted significantly with moricizine therapy with respect to all-cause death/cardiac arrest but not arrhythmic death/cardiac arrest (Table and Fig 2). Interaction trends were observed for total mortality with QRS duration (P=0.11) and VPD frequency (P=0.07) (Table and Fig 2).

Discussion

Summary of CAST Results

In the Cardiac Arrhythmia Suppression Trial,2-5 treatment with the antiarrhythmic agents encainide or flecainide (CAST-I) was associated with an unexpected increase in risk for total mortality/cardiac arrest (risk ratio, 2.38; 95% CI, 1.59 to 3.57) and arrhythmic death/cardiac arrest (risk ratio, 2.64; 95% CI, 1.60 to 4.36), compared with treatment with placebo, in patients with asymptomatic postinfarction ventricular arrhythmias whose arrhythmias were effectively suppressed (≥80%) during an open-label test phase.2,3 Moricizine treatment (CAST-II) resulted in an increase in mortality/cardiac arrest within the first 2 weeks, during initiation of therapy (17 versus 3 events); thereafter, event rates tended to be higher in the moricizine group (risk ratio, 1.24), but the difference was not significant.4,5 The mechanism(s) of these adverse effects is uncertain. Further analysis of CAST-I showed that an adverse mortality effect was consistently present throughout multiple subgroups.2,3 Thus, therapy appeared to adversely affect the postinfarction population in general rather than only one or a few segments. However, it is still possible that significant differences in the degree of the adverse effect might be found among various subgroups of patients. Identifying subgroups at higher-than-expected risk with therapy might provide clues regarding the mechanism(s) of the adverse interaction between class I antiarrhythmic drug therapy and arrhythmic death/cardiac arrest and could lead to preventive measures.

The overall results of CAST were unexpected, and explanations for the adverse interactions of therapy with postinfarction pathophysiology are speculative. Several possible mechanisms have, nonetheless, been proposed2,3,13: (1) an increased risk of sustained, reentrant ventricular tachycardia, (2) excessive slowing of conduction or abnormal repolarization, (3) heterogeneous electrophysiological effects of drugs in abnormal versus normal myocardium, (4) adverse, proarrhythmic drug interactions with acute ischemia, and (5) exacerbation of cardiac pump dysfunction. Although unappealing, it is even possible, based on the CAST data, that VPD suppression per se causes an adverse effect on mortality or that VPD suppression selects a population that will be at unusually low risk without therapy but prone to one or more adverse reactions with therapy. Identifying predictors of substantially greater (or less) than expected risk, the objective of this study, might provide insight into the actual adverse mechanisms involved.

Summary of This Study: Baseline Interacting Factors

This study identified one factor in the CAST-I population that interacted significantly with encainide/flecainide to increase the hazard ratio of active versus placebo therapy for both arrhythmic death/cardiac arrest and total mortality: non-Q-wave myocardial infarction. Four other possible interactions were: VPD frequency ≥50/h on baseline recording (all-cause mortality), resting heart rate above the mean (all-cause mortality), (absence of) diabetes (all-cause mortality), and effective suppression on first drug (arrhythmic death). Non–Q-wave myocardial infarction, a marker of ischemic jeopardy, was associated with a hazard ratio for arrhythmic death/cardiac arrest of 10.7 compared with 2.1 for Q-wave infarction, a fivefold relative increase, and a hazard ratio for total death/cardiac arrest of 7.9 versus 1.8, a more-than fourfold increase. Non-
Q-wave infarction has also been identified as a specific risk factor based on an analysis limited to baseline ECG parameters alone.14

VPD frequency $\geq$50/h, a marker of increased spontaneous electrical instability, was associated with a threefold relative increase in the hazard ratio for total death or cardiac arrest, as well as a twofold increase (trend) for arrhythmic death. In computer modeling studies, Starmer et al.15 found that both antiarrhythmic and proarrhythmic properties of sodium channel antagonists were dependent on sodium channel availability. The price for increased antiarrhythmic efficacy (VPD suppression) was an increase in proarrhythmic vulnerability to unsuppressed VPDs. Hence, those with a greater frequency of residual VPDs during therapy (to be expected when more baseline VPDs initially are present) may be at increased likelihood of proarrhythmic ventricular tachycardia or ventricular fibrillation,
non-Q-wave
cated
that with
subsequent
more
supply
with drug
sults, putting
myocardial
ventricular
infarction.15-19
recurrent
tion is associated with
conduction
abnormality),
electrolyte
"triggers")
future
treatment
be considered markers
of greater risk
(ie,
intraventricular
delays), the
cause
of greater risk
with
amiodarone
failure,
Heart
Failure,
Therapy, and
interaction
might
in
expected, given
adverse
interaction
between
proarrhythmic effect, with sustained
ventricular tachycardia/fibrillation occurring in 50% of
animals (17 of 34). In contrast, the rate of ventricular
tachycardia/fibrillation was only 14% (5 of 34, P<.05)
when treatment was given after coronary occlusion and
9% (1 of 11, P<.05) when occlusion was given without
aprindine. Aprindine did not cause ventricular tachy-
cardia/fibrillation in the absence of acute ischemia
(none of 16). Pretreated dogs were found to have
ischemic zone myocardial drug concentrations averaging
more than twice that of normal zones. It is tempting
to draw parallels between these data and the CAST
results.

In a sophisticated canine model of sudden cardiac
death, Patterson et al23 imposed fresh myocardial ischemia
caued by electrically induced coronary thrombosis in conscious, ambulatory dogs that had an old
ischemic injury in a distant zone. In this model, class II
(nadolol) and class III therapies (bretylium, sotalol, amiodarone) were effective in reducing the otherwise almost complete (90% to 100%) mortality due to ischemic ventricular fibrillation to between 10% and 50%.23-26 In contrast, flecainide (class IC) (1 mg/kg per hourx4 hours) not only failed to prevent (7 of 8 animals died) but hastened the development of ischemic ven-
tricular fibrillation in the early postinfarction period27: The mean time to ischemic arrhythmic death averaged
203±88 minutes in the flecainide group (n=8) compared with 359±70 minutes in the untreated control
group (n=8). Again, parallels with the CAST results are
suggested.

Acute ischemia has been found to reduce, and
β-blocker therapy or resection of the stellate ganglion
(which supplies sympathetic nerve traffic to the heart) to increase, the cardiac electrical threshold for induction of ventricular fibrillation in open-chest canine models.28-30 In a feline model, acute ischemia plus superimposed sympathetic nervous system stimulation resulted in ma-
lignant ventricular arrhythmia.31 β-Blocker (class II),
amiodarone (class III), and verapamil therapy (class IV) were each found to be effective in arrhythmia prevention, whereas class I antiarrhythmics failed to prevent and occasionally exacerbated these sympathetic-related arrhythmias.31

Heart Failure, Diuretic Therapy, and Other
Risk Factors
Depressed ejection fraction and a history of heart
failure were associated with an increased risk of mor-
tality in CAST, as expected.2,2 Of interest, however, is
that these factors were not associated with a greater-
than-expected increase in the risk of adverse events in
patients on encainide/flecainide therapy, although an
interaction might have been expected, given the adverse
outcomes described among patients with combinations of depressed cardiac function, ventricular arrhythmias,
and antiarrhythmic drug therapy in previous clinical studies.\textsuperscript{32-34} Thus, our data do not support left ventricular dysfunction per se as a critical mechanism of adverse interaction with class IC therapy in the relatively more stable CAST-I postinfarction population; that is, although risk was increased in those with depressed ejection fraction, the increase was not greater than expected. Moricizine, on the other hand, did tend to interact with heart failure, as demonstrated most clearly by the interaction with diuretic therapy in the sicker patient population (ejection fraction \(\leq 0.40\)) recruited in CAST-II. The mechanism of this latter interaction may involve negative inotropic effects and/or therapy-related electrolyte abnormality with its associated increase in electrical instability and requires additional study. Because encainide/flecainide and moricizine were tested in somewhat different patient populations (CAST-I versus CAST-II), distinction of the mechanisms of adverse effect between moricizine compared with encainide/flecainide may not be strictly possible from our database alone.

Of other possible interactions, a high resting heart rate may identify patients with smaller stroke volumes (greater left ventricular dysfunction) and greater sympathetic nervous system activation, possibly explaining the adverse interaction of high resting heart rate with encainide/flecainide for total mortality. Similarly, a QRS complex interval \(\geq 0.1\) second is a well-known marker of greater functional and electrical impairment and may also indicate a substrate more vulnerable to adverse drug interaction (with moricizine). We do not have a good explanation for why patients not responding to the first drug tested (ie, “less” drug responsive) who received “effective” therapy with a subsequently tested drug had a better outcome (hazard ratio <1) for arrhythmic death (encainide/flecainide) or total mortality (moricizine) when given active therapy compared with placebo therapy, a finding contrary to the overall study results. Similarly, we cannot explain the greater relative hazard for total mortality associated with active therapy in nondiabetics (encainide/flecainide) or in men (moricizine). However, it is expected among multiple comparisons that some associations will occur because of chance, and some of these apparent associations may be examples of that.

\textbf{Literature Comparisons With CAST Results}

Comparisons of these results from CAST with other clinical trials are limited due to the small number, limited size, and poor study design of previous arrhythmia suppression trials in postinfarction patients.\textsuperscript{35,36,39} Of interest, however, is that even lidocaine\textsuperscript{40-42} and lidocaine congeners (mexiletine),\textsuperscript{43} when used either early or more chronically after infarction, fail to decrease and may increase mortality risk. Currently, several randomized trials using amiodarone therapy are being performed in the United States, Canada, and Europe that may provide additional insights into the observations made in CAST. Of drugs with antiarrhythmic actions, only the \(\beta\)-blockers clearly have been shown to reduce postinfarction mortality.\textsuperscript{55} Consistent with this, patients in CAST on \(\beta\)-blocker therapy showed improved survival,\textsuperscript{2} although it is recognized that the analysis is retrospective and the comparison unbalanced (ie, patients were not randomly assigned to \(\beta\)-blockade).

It is of note that \(\beta\)-blockers did not interact with the adverse treatment effects of class I agents in CAST-I or CAST-II.

\textbf{Limitations}

Caution must be exerted in interpreting the results of this study. Non-Q-wave myocardial infarction, diuretic therapy, and other factors interacting to increase mortality more than expected, based on the overall CAST results, were determined by retrospective analysis. If accurate adjustment for multiple comparisons could be made, it is likely that few of these associations (ie, perhaps only diuretic use in CAST-II) would remain significant in a formal statistical sense. The results must therefore be considered tentative and hypothesis generating rather than definitive.

However, the results of class IC therapy of CAST-I patients are at least consistent with the hypothesis that latent ischemia and greater electrical instability may be cofactors in the adverse interaction of antiarrhythmic therapy with postinfarction mortality, as observed in animal models of ischemic ventricular fibrillation/sudden death. The results with class I therapy (with moricizine) in CAST-II patients suggest that a greater-than-expected hazard of therapy is present in patients taking diuretics (ie, those with significant left ventricular dysfunction predisposed to electrolyte disturbance) as well as possibly those with baseline ischemia. An adverse benefit/risk ratio has previously been proposed for antiarrhythmic therapy in such patients, based on data apart from CAST-II,\textsuperscript{34,40} and might be due to several mechanisms, including ventricular proarrhythmia induced by electrolyte abnormality, prolonged or disparate repolarization, excessive condition slowing, or negative inotropic effects.

Additional studies, both clinical and experimental, will be needed to test these and other possible mechanisms of adverse interactions between baseline variables and antiarrhythmic therapy.

\textbf{Conclusions and Clinical Implications}

An analysis of baseline variables was studied to assess factors that might contribute excessively to the increased risk of antiarrhythmic therapy in postinfarction patients. Although almost all subgroups of patients showed increased risk with therapy, those with non-Q-wave myocardial infarction showed a greater-than-expected adverse risk (interaction) with all-cause death/cardiac arrest as well as arrhythmic death/cardiac arrest with encainide/flecainide (CAST-I), whereas diuretic use (and possibly ischemia at baseline interacted with moricizine (CAST-II). These observations, taken together with theoretical considerations and the results of experimental studies, suggest the hypothesis that an adverse interaction exists between new ischemic episodes, electrical instability, and chronic antiarrhythmic therapy as an explanation for part of the excessive risk of such therapy (at least with encainide and flecainide), and, in a population with greater left ventricular dysfunction (CAST-II), diuretic use, usually in the setting of heart failure and left ventricular dysfunction with possible electrolyte imbalance.

Because these observations are data derived, additional, prospective studies will be needed. If confirmed, these associations may provide insight into the mecha-
nisms responsible for the adverse results of CAST and may suggest preventive measures. Meanwhile, the detrimental effects of the drugs used in CAST emphasize that adverse drug effects may be unpredictable and mediated by multiple, complex mechanisms and highlight the potential hazards associated with antiarrhythmic drug treatment in patients with recent myocardial infarction.

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Interaction of baseline characteristics with the hazard of encainide, flecainide, and moricizine therapy in patients with myocardial infarction. A possible explanation for increased mortality in the Cardiac Arrhythmia Suppression Trial (CAST).

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