# COOPERATIVE STUDIES

# Events in the Cardiac Arrhythmia Suppression Trial (CAST): Mortality in the Entire Population Enrolled

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To test the hypothesis that suppression of ventricular arrhythmias by antiarrhythmic drugs after myocardial infarction improves survival, the Cardiac Arrhythmia Suppression Trial (CAST) was initiated. Suppression was evaluated before randomization during an open label titration period. Patients whose arrhythmias were suppressed were randomized in the main study and those whose arrhythmias were partially suppressed were randomized in a substudy. Overall survival and survival free of arrhythmic death or cardiac arrest were higher in patients treated with encainide or flecainide than in patients treated with placebo. However, the death rate in patients randomized to placebo therapy was lower than expected. This report describes the survival experience of all patients enrolled in CAST and compares it with mortality in other studies of patients with ventricular arrhythmias after myocardial infarction.

As of April 18, 1989, 2,371 patients had enrolled in CAST and entered prerandomization, open label titration: 1,913 (81%) were randomized to double-blind, placebo-controlled therapy (1,775 patients whose arrhythmias were suppressed and 138 patients whose arrhythmias were partially suppressed during open label titration); and 458 patients (19%) were not randomized because they were still in titration, had died during titration or had withdrawn. Including all patients who enrolled in CAST, the actuarial (Kaplan-Meier) estimate of 1-year mortality was 10.3%.

To estimate the "natural" mortality rate of patients enrolled in CAST, an analysis was done that adjusted for deaths that might be attributable to encainide or flecainide treatment either during prerandomization, open label drug titration or after randomization. Because the censoring procedure excluded patients treated with encainide or flecainide after randomization, the mortality estimate will be less than the unadjusted mortality estimate of 10.3%. A minimal 1-year "natural" mortality rate of 6.3% was estimated by assuming that all deaths during open label titration with encainide or flecainide were due to drug treatment and that after randomization all excess mortality in the group randomized to active treatment was also due to drug effect. A maximal 1-year "natural" mortality rate of 8.4% was estimated by assuming that no deaths during open label titration with encainide or flecainide were due to drug treatment and that after randomization all excess mortality in the group randomized to active treatment was due to drug effect. Thus, the "natural" overall mortality rate in CAST, falling somewhere between 6.3% and 8.4%, is similar to rates observed in other postinfarction natural history studies, suggesting that the low mortality rate in the group randomized to placebo is largely due to the process of selecting only those enrolled patients for the randomized phase of CAST whose ventricular arrhythmias were suppressed in the prerandomization open label titration phase.

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The Cardiac Arrhythmia Suppression Trial (CAST) is an ongoing multicenter, randomized, placebo-controlled study testing the hypothesis that suppression of asymptomatic or mildly symptomatic ventricular arrhythmias after myocardial infarction reduces the incidence of arrhythmic cardiac death [1]. The study is unique among antiarrhythmic drug trials because only patients whose ventricular arrhythmias are suppressed are randomized to receive active drug or placebo and are included in outcome analysis. Although not included in the main CAST study [1], patients with partially suppressed arrhythmias are similarly randomized and followed up in a substudy. Patients whose ventricular arrhythmias increase during open label drug titration or who cannot tolerate drug therapy are not randomized to receive blinded, placebo-controlled drug therapy.

The preliminary CAST report [1] showed that rates of both overall survival and survival free of arrhythmic death or

cardiac arrest in the group treated with placebo were supe-
rior to rates in the group treated with encainide or flecainide.
Over an average 10 month follow-up period, the crude total
mortality in the encainide- and flecainide-treated patients
was 7.7% compared with 3.0% in the placebo control pa-
tients (relative risk 2.5, 95% confidence interval 1.6 to 4.1).
Similarly, deaths from arrhythmia and nonfatal cardiac ar-
rests occurred in 4.5% of the encainide- and flecainide-
treated patients and in 1.2% of the placebo-treated control
patients (relative risk 3.6, 95% confidence interval 1.8 to
7.6). The relatively low death rate in patients randomized to
double-blind therapy was, however, substantially less than
one might have expected (2–14).

The preliminary CAST report provided no information on
25% of the patients who signed consent but were not
randomized in the main study, including 6% who had partial
suppression of their arrhythmias and entered a substudy and
19% who were not randomized to drug therapy. This report
extends the preliminary report by describing the clinical
characteristics and outcome of all patients, both randomized
and nonrandomized, who enrolled in CAST and entered drug
titration before April 18, 1989, the date encainide and
flecainide were dropped from the study, and compares
CAST with other studies of sudden cardiac death and overall
mortality in patients with ventricular premature depolariza-
tions after myocardial infarction. When the mortality expe-
rience of the entire CAST population is examined, CAST
patients do indeed appear similar to those previously re-
ported with ventricular ectopic activity after myocardial
infarction.

## Methods

**Eligibility of patients.** The design of CAST has been
previously described in detail (1). Patients were eligible to be
screened for CAST enrollment between 6 days and 2 years
after documented myocardial infarction. An ambulatory
electrocardiographic (ECG) Holter recording was obtained
with a minimum of 18 h of analyzable data; patients qualified
if they had an average of ≥6 ventricular premature depolar-
izations/h. To enroll potentially high risk patients and main-
tain adequate statistical power, a left ventricular ejection
fraction of ≤0.55 was required for inclusion in the study if
the patient was enrolled within 90 days of myocardial
infarction; the requirement was reduced to ≤0.40 if the
recording was obtained between 90 days and 2 years after
the qualifying infarction. Patients were excluded from the
trial if they had severely symptomatic ventricular arrhyth-
mias (incapacitating symptoms, syncope or presyncope) or
had ≥15 consecutive ventricular premature depolarizations
at a rate of ≥120 beats/min. The protocol was approved by
each participating clinical center's Institutional Review
Board. CAST was monitored independently by an external
Data and Safety Monitoring Board. Written, informed con-
sent was obtained from all patients who participated in the
study.

**Drug titration.** Patients were treated with up to two
doses of three drugs (encainide, flecainide or moricizine) in
unblinded, open label titration. The criteria for suppression
were ≥80% reduction in the frequency of ventricular prema-
ture depolarizations and ≥90% reduction in runs of unsus-
tained ventricular tachycardia, as measured by 24 h ambu-
latory ECG recordings obtained 4 to 10 days after the start of
each drug dose. Doses 1 and 2 for encainide were, respec-
tively, 35 and 50 mg three times a day; for flecainide, 100 and
150 mg twice a day and for moricizine, 200 and 250 mg three
times a day. Unblinded, open label titration was discontin-
ued and the patient was eligible for randomization to blinded
therapy as soon as a drug and dose were found that were well
tolerated and suppressed the ventricular arrhythmia. If only
partial suppression was achieved and the drug was well
tolerated, the patient entered blinded therapy in a substudy.
At the time of randomization, the patient was assigned to
receive either the active drug and dose that suppressed (or
for the substudy, partially suppressed) the ventricular ec-
topic activity or a matching placebo. The nonrandomized
group consisted of individuals who were still in the open
label titration phase; whose arrhythmia increased during this
phase; or who were intolerant of drugs, died before random-
ization or withdrew for any reason.

**Follow-up.** Patients whose arrhythmias were success-
fully suppressed or partially suppressed were scheduled for
postrandomization follow-up visits at 4 month intervals.
Nonrandomized patients were followed up by telephone at 6
month intervals. This report is based on the March 15, 1990
version of the CAST data file. The primary CAST end point
was arrhythmic death or cardiac arrest (1). All primary end
points in randomized patients were reviewed by the Events
Committee, a subcommittee of CAST investigators who did
not know the patients' treatment assignment.

**Statistical analyses.** Contributions to overall mortality
came from deaths 1) during titration, 2) after titration during
randomized therapy, and 3) after titration among the non-
randomized patients. An estimate of mortality after titration
during randomized therapy is accomplished by restricting
the analysis to patients randomized to placebo. No adjust-
ment is needed for contributions to mortality after titration in
the nonrandomized patients because they did not receive the
study drug after titration was completed. However, because
some deaths that occurred during titration (before random-
ization to blinded therapy) may also have been the result of
antiarrhythmic drug use, further adjustment of the mortality
estimate must be made for deaths that occurred in this
phase. An unbiased estimate of natural mortality during
titration is not possible because there was no placebo
control. Thus, by assuming that all deaths occurring during
titration with encainide or flecainide were due to encainide
or flecainide, censoring (that is, assuming that the patient
was simply lost to further follow-up at the time of death)
patients at the time events occurred during titration with or
within 10 days of discontinuing encainide or flecainide
provides a lower boundary on the estimated "natural"

mortality. An upper boundary can be achieved by assuming that all of the deaths during titration were "natural" (that is, not due to encainide or flecainide). Based on the assumption (the aim of randomization) that, except for drug effects, mortality was the same in the patients treated with active drug and in those treated with placebo, the contribution of the placebo-treated patients to the mortality estimate was given a twofold weight because these patients represent both themselves and their randomized counterparts. Event rates were computed by using the Kaplan-Meier method. The weighting procedure provides an unbiased estimate of upper and lower boundaries for overall "natural" mortality. Deaths that occurred during titration with moricizine were not censored because there is no evidence that this drug affects mortality.

Because the moricizine arm of CAST continues, some restrictions on the dissemination of end point data involving moricizine are critical to maintain integrity of the trial, which is ongoing and remains double-blinded. Overall estimates of mortality that include moricizine-treated patients are permitted (as in this report) but individual estimates of mortality for moricizine-treated patients and their placebo-treated counterparts and explicit enumeration of overall events or of events occurring during active therapy are not permitted because the interim moricizine results could be determined by review of all the CAST publications. It is believed that this method of analysis allows for the maximal use of the early CAST data, including placebo information and general overall mortality estimates, while protecting the integrity of the ongoing trial.

## Results

**Demographics.** As of April 18, 1989, 2,371 patients entered open label titration in CAST. The baseline characteristics of all patients who enrolled in CAST and underwent titration are reviewed in Table 1. Suppression of arrhythmias was achieved in 1,775 patients (75%) and partial suppression in 138 (6%); 458 patients (19%) were not randomized. Follow-up of the randomized patients averaged 9.7 months from randomization to blinded therapy with only 4.7% withdrawing from blinded therapy follow-up. Among the nonrandomized patients who survived ≥10 days after completion of titration, follow-up averaged 8.7 months with 8.5% withdrawing from telephone follow-up. The duration of titration averaged 21 days.

**Mortality.** Of the 2,051 patients who entered open label titration and did not enter blinded moricizine therapy (see last paragraph under Methods), 183 patients died or experienced cardiac arrest. Sixty-three of these events occurred during titration; 93 during randomized therapy with encainide, flecainide or corresponding placebo and 27 during follow-up of nonrandomized patients. Of these 183 deaths and cardiac arrests, 168 were classified as cardiac: 122 arrhythmic deaths/cardiac arrests (67 witnessed deaths, 39 unwitnessed deaths and 16 resuscitated cardiac arrests) and

**Table 1.** Baseline Characteristics of 2,371 Patients Randomized to Open Label Titration on or Before April 18, 1989

| | |
|---|---|
| Age (yr) | 61.5 ± 9.9 |
| Male (%) | 80.9 |
| Ejection fraction | 0.37 ± 0.11 |
| VPD/h | 124.9 ± 250.2 |
| Baseline ECG | |
| PR interval (s) | 0.17 ± 0.03 |
| QRS interval (s) | 0.09 ± 0.02 |
| History before index MI (%) | |
| CHF | 15.4 |
| Angina | 46.5 |
| Hypertension | 31.2 |
| Prior MI | 39.0 |
| CABG/PTCA | 17.4 |
| History after index MI (%) | |
| No CHF or NYHA functional class I | 84.6 |
| No angina or Canadian angina class I | 89.9 |
| Thrombolytic therapy | 25.7 |
| PTCA | 18.4 |
| CABG | 17.8 |
| Baseline examination | |
| Sitting HR (beats/min) | 75 ± 13 |
| Systolic BP (mm Hg) | 125 ± 19 |
| Diastolic BP (mm Hg) | 76 ± 10 |
| Concurrent drugs (%) | |
| Beta-adrenergic blocker | 29.1 |
| Calcium channel blocker | 48.7 |
| Digitalis | 24.3 |
| Nitrate | 46.5 |
| Diuretic | 36.7 |

Values are mean values (±SD when appropriate). BP = blood pressure; CABG = coronary artery bypass grafting; CHF = congestive heart failure; ECG = electrocardiogram; HR = heart rate; MI = myocardial infarction; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty; VPD = ventricular premature depolarizations; VT = ventricular tachycardia.

46 nonarrhythmic deaths. There were 12 noncardiac deaths and 3 deaths that could not be classified. Without adjusting for drug effects during or after titration, the 1-year incidence of arrhythmic death/cardiac arrest was 6.6%; that of death due to cardiac but nonarrhythmic causes was 3.0% and that of death due to noncardiac causes or unclassified was 0.9%.

The actuarial 1-year all-cause mortality rate for the 2,371 patients who entered open label titration was 10.3% (Fig. 1). By censoring to adjust for deaths that may have been attributable to encainide or flecainide, the estimated lower boundary on mortality at 1 year was 6.3% (Fig. 2). By not adjusting for deaths occurring during titration (before randomization to blinded therapy) that may or may not have been attributable to encainide or flecainide, the estimated upper boundary on mortality at 1 year was 8.4% (Fig. 2).

## Discussion

**Comparison with previous studies.** The reported all-cause mortality rate after myocardial infarction ranges from 5% at 1 year (11) to 30% at 1.5 years (10). Mortality data derived
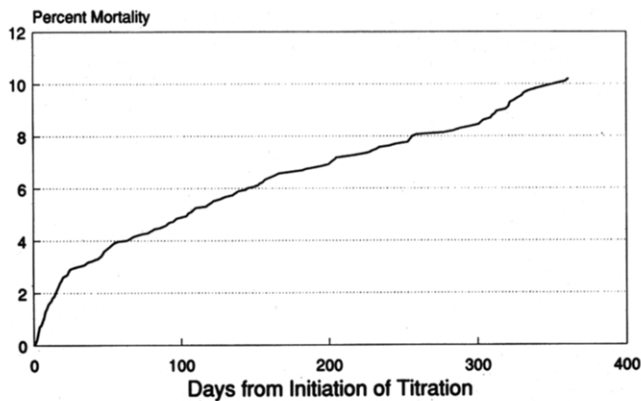
Percent Mortality



**Figure 1.** Overall mortality in CAST (censored at 366 days) for all patients who entered open label titration. Data are not adjusted for drug effects. See text for discussion.

from previous studies are reviewed in Table 2 to provide comparison with the CAST data. The subgroups presented were chosen to highlight postmyocardial infarction patients with a degree of ventricular arrhythmia that was similar to that of patients who participated in CAST. The 1-year 10.3% mortality estimate for patients who signed consent and entered open label titration in the Cardiac Arrhythmia Suppression Trial (CAST) is consistent with results of these earlier investigations. In addition, the frequency of death from all cardiac causes is modified by many factors including, but not limited to, concomitant pharmacologic therapy (including antiarrhythmic drugs), the frequency and complexity of ventricular arrhythmia, the degree of left ventricular dysfunction, underlying coronary anatomy and ischemia (8,9,12). Furthermore, the 1-year estimated 6.6% incidence

**Figure 2.** Estimates of the "natural" mortality uncontaminated by antiarrhythmic drug effects for patients in CAST from time of entry into open label titration (censored at 366 days). The **upper curve** shows the upper boundary of estimated natural mortality, assuming that none of the deaths that occurred during titration were due to encainide or flecainide. The **lower curve** shows the lower boundary of estimated natural mortality, assuming that all of the deaths that occurred during titration with encainide or flecainide were due to encainide or flecainide and censoring patients at the time events occurred during titration with (or within 10 days of discontinuing) these two drugs. See text for discussion.

Percent Mortality
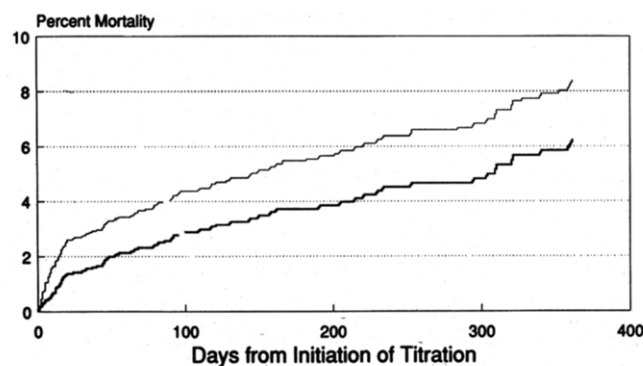


of arrhythmic death/cardiac arrest in the CAST patients reported here is also consistent with the previously reported frequency of sudden cardiac death in patients with ventricular premature depolarizations after myocardial infarction, which ranges from 5% at 1 year (5) to approximately 13% at 1.5 years (10) (Table 2).

**Factors explaining the low mortality in previous CAST report.** Because both overall mortality and arrhythmic death/cardiac arrest rates were seemingly lower in the CAST placebo group than in previous studies, the question has been raised whether the CAST population is representative of postinfarction patients in general (14). However, the death rate for all patients who were recruited to CAST, signed consent and entered prerandomization open label titration is consistent with death rates previously reported. Several factors may explain the apparently low death rate for patients in the initial report (1) of the main CAST results for treatment with encainide and flecainide: 1) to be randomized, patients had to survive the titration phase; 2) prior studies may have overestimated the mortality risk for patients with frequent ventricular ectopic activity because these patients may have been more likely than patients without arrhythmias to have been treated with antiarrhythmic drugs, and these drugs may have been partly responsible for the observed mortality; and 3) patients randomized in CAST were selected because they had suppressible ventricular arrhythmias. Indeed, the results suggest that ventricular arrhythmia suppression by encainide or flecainide may itself be a marker for improved survival.

The relative incidence of arrhythmic death and cardiac arrest compared with that of nonarrhythmic cardiac death in CAST was 2.7:1 (122 arrhythmic deaths/cardiac arrests and 46 nonarrhythmic cardiac deaths). This relative incidence is notably different from the approximate 0.5-1:1 ratio observed by Ruberman et al. (5), by the International Mexiletine and Placebo Antiarrhythmic Coronary Trial (IMPACT) (11) and by Kostis et al. (13) for the Beta-Blocker Heart Attack Trial (BHAT) (Table 2). The reason for the difference is not readily explainable but is probably related to differences in patient selection and in end point definitions. For example, the 15.4% incidence of congestive heart failure in CAST was higher than the 3.5% incidence in IMPACT (11) and 9.8% incidence in BHAT for patients with ≥1 ventricular premature depolarizations (12).

**Limitations of comparing the CAST with other studies.** No other study has required suppression of ventricular arrhythmia as a criterion for entry or randomization to a therapeutic intervention. Surawicz (15) reviewed the reported incidence of sudden cardiac death after myocardial infarction in 21 studies (25 patient groups) in which the study population exceeded 60 patients, average follow-up was ≥12 months and the sudden cardiac death rate was either stated or could be estimated from the data provided. A computed regression line weighted by sample size documents the incidence of sudden death to be only 3.6% at 12 months. Unfortunately, the regression analysis was not restricted to patients with

**Table 2.** Earlier Studies of Outcome in Patients With Ventricular Premature Depolarizations After Myocardial Infarction

| | | | % Patients (follow-up mo) With | | |
| --- | --- | --- | --- | --- | --- |
| Investigation | N | Entry Criteria | Arrhythmic Death/ Cardiac Arrest (sudden death) | Nonarrhythmic Cardiac Death (nonsudden death) | Death |
| Coronary Drug Project (3) | 2,760 | 3 mo post-MI | 8.9 (36)* | — | 21.7 (36)* |
| Ruberman et al. (5) | 1,739 | MI survivors | 4.8 (12)† | 4.6 (12)† | 9.2 (12)† |
| Bigger et al./MPIR (8) | 766 | Prior MI | 12.2 (24)‡ | — | 19.6 (24)‡ |
| Mukharji/MILIS (10) | 533 | 10 days post-MI | 12.8 (18)§ | — | 29.5 (18)§ |
| IMPACT (11) | 630 | Recent MI | 1.3 (9)‖ | 2.6 (9)‖ | 4.8 (9)‖ |
| | 113 | | — | — | 5.4 (9)¶ |
| Kostis et al./BHAT (13) | 3,290 | 3 weeks post-MI | 5.1 (25)** | 4.5 (25)** | 10.9 (25)** |
| | | | 9.0 (25)†† | 8.1 (25)†† | 19.9 (25)†† |
| CAST (1) | 1,455 | 6 days to 2 yr post-MI | | | |
| | 725‡‡ | | 1.2 (10) | — | 3.0 (10) |
| | 730§§ | | 4.5 (10) | — | 7.7 (10) |
| Current study | 2,371 | CAST titrated | 6.6 (12) | 3.0 (12) | 10.3 (12) |

*Limited to 314 patients with ≥1 VPD/12 lead ECG; antiarrhythmic drug use not reported; †limited to 462 patients with "complex" VPDs (R-on-T, runs ≥2, multiform or bigeminal VPDs); antiarrhythmic drug use not reported; ‡limited to 245 patients with ≥3 VPDs/h; §limited to 78 patients with ≥10 VPDs/h; ‖limited to 313 placebo-treated patients; 90% had ≥1 VPD/24 h; ¶these patients had Lown class 2, 4A or 4B VPDs; **limited to 1,640 placebo-treated patients with ≥1 VPDs/h (84%) (1,349 were not receiving an antiarrhythmic drug); ††limited to 1,640 placebo-treated patients with ≥10 VPDs/h (13%) (1,349 were not receiving an antiarrhythmic drug); ‡‡patients treated with placebo; §§patients treated with encainide or flecainide. BHAT = Beta-Blocker Heart Attack Trial; CAST = Cardiac Arrhythmia Suppression Trial; ECG = electrocardiogram; IMPACT = International Mexiletine and Placebo Antiarrhythmic Coronary Trial; MI = myocardial infarction; MILIS = Multicenter Investigation of the Limitation of Infarct Size; MPIR = Multicenter Post-Infarction Research Group; VPD = ventricular premature depolarization.

ventricular arrhythmias and, given the varied entry criteria and follow-up in the pooled investigations, direct comparison with the CAST data base is not possible. However, because the 1-year actuarial mortality for all patients entering CAST open label titration was 10.3%, the CAST population can reasonably be considered a high risk group for death after myocardial infarction.

*Role of beta-blockers.* Beta-adrenergic blocking agents have been shown to decrease the frequency of ventricular arrhythmias after myocardial infarction (7,9,12). In the Beta-Blocker Heart Attack Trial, although 15.4% of patients with ventricular premature depolarizations experienced a decrease in arrhythmia frequency during propranolol therapy (7), Friedman et al. (12) showed that both the patients with and those without ventricular arrhythmias received benefit from beta-blockade. However, in CAST, because only 29.1% of patients who entered open label titration were receiving a beta-blocker and because randomized and non-randomized patients had almost equal beta-blocker usage (30.2% and 24.5%, respectively), it is unlikely that the low event rate in the placebo group was due to the use of these drugs.

*Role of thrombolysis, angioplasty and ischemia.* Because thrombolytic therapy improves survival after myocardial infarction (16,17) and because coronary angioplasty also benefits selected patients (17,18), the question has been raised whether the low mortality in CAST was due to the use of these interventions. Indeed, Théroux et al. (19) showed that fibrinolysis with or without angioplasty reduced the

frequency of ventricular premature depolarizations. However, CAST patients still had significant ventricular ectopic activity (125 ventricular premature depolarizations/h). Furthermore, in CAST the frequencies of thrombolytic therapy and of angioplasty use were modest (25.7% received thrombolytic therapy and 18.4% angioplasty) and also similar in the randomized (26.6% and 19.0%, respectively) and non-randomized (21.8% and 15.9%, respectively) patients. Thus, it is unlikely that the low event rate in the placebo group was due to the use of these interventions. Furthermore, because the treatment for ischemia was the same during and after titration, it is also unlikely that a difference in treatment for ischemia accounted for the low event rate in the placebo group.

**Implications.** The probabilities of survival for patients who enrolled in CAST and entered open label titration and for patients reported on in other studies of mortality after myocardial infarction are similar. The low mortality rate in patients randomized to the main CAST trial may be explained by their selection because they had suppressible ventricular arrhythmias. This relatively good survival rate does not detract from the applicability of CAST findings to other patients with ventricular arrhythmias after myocardial infarction. Specifically, attempts to suppress ventricular premature depolarizations after myocardial infarction by treatment with encainide or flecainide cannot be condoned because mortality was increased despite the ability of these drugs to suppress ventricular arrhythmias. Indeed, the suppression hypothesis itself is called into question because,

despite arrhythmia suppression, patients treated with encainide or flecainide experienced greater mortality than their counterparts treated with placebo. Furthermore, if the treatment of ventricular premature depolarizations in postmyocardial infarction patients is based on the assumption that suppression is beneficial, it makes no sense to continue drugs that are not suppressive. The CAST findings suggest that the ability to suppress ventricular premature depolarizations in postmyocardial infarction patients predicts improved survival independent of antiarrhythmic drug therapy.

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