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# The Cardiac Arrhythmia Suppression Trial: First CAST . . . Then CAST-II

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**The Cardiac Arrhythmia Suppression Trial (CAST) was a study designed to test the hypothesis that suppression of ventricular premature complexes after a myocardial infarction would improve survival. Preliminary results showed that suppression of ventricular premature complexes with encainide and flecainide worsened survival, and the CAST continued as the CAST-II with moricizine compared with its placebo.**

**The protocol for the CAST-II was changed to attempt to enroll patients more likely to experience serious arrhythmias. The enrollment time was narrowed to 4 to 90 days after myocardial infarction; the qualifying ejection fraction was lowered to ≤0.40; a higher dose of moricizine could be used; early titration itself was double-blind with a placebo, and the definition of disqualifying ventricular tachycardia was changed to allow patients with more serious arrhythmias to be entered into the trial.**

**The Cardiac Arrhythmia Suppression Trial-II was subsequently terminated prematurely because 1) patients treated with moricizine had an excessive cardiac mortality rate during the 1st 2 weeks of exposure to the drug, and 2) there appeared to be little chance of showing a long-term survival benefit from treatment with moricizine.**

**This report outlines the rationale behind the Cardiac Arrhythmia Suppression Trial and the reasons for selection of the drugs used in the CAST and CAST-II.**

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The initial results of the Cardiac Arrhythmia Suppression Trial (CAST) (1) led clinicians caring for patients with arrhythmias to question treatment strategies that had been widely accepted, though not validated. The purpose of this report is to summarize how and why the design of the study was changed for the continuation of the trial, called the Cardiac Arrhythmia Suppression Trial-II (CAST-II).

## The Cardiac Arrhythmia Suppression Trial (CAST) Hypothesis and Original Design

Two hypotheses were considered for testing in the Cardiac Arrhythmia Suppression Trial: 1) that drug *treatment* of asymptomatic ventricular premature complexes in patients after a myocardial infarction would improve survival, or 2) that drug *suppression* of asymptomatic ventricular premature complexes would improve survival. These two hypotheses had major implications for study design. With the drug *treatment* hypothesis, patients would simply be randomly assigned to treatment with an antiarrhythmic drug or its placebo; they would be continued on long-term therapy to examine the effect of the drug on survival. The drug *suppression* hypothesis more closely mimicked clinical practice. Analysis of Holter recordings would be required to show that a drug had indeed suppressed ventricular premature complexes adequately before a patient could be randomly assigned to long-term treatment with that agent or its placebo. Ultimately, it was decided to test the drug *suppression* hypothesis in the CAST.

In the original design of the CAST, each patient's ventricular premature complexes were suppressed by an antiarrhythmic drug (selected randomly for the dose titration phase), and the patient was then randomized to treatment with either the active drug that suppressed the ventricular premature complexes or its matching placebo. Thus, the design of the CAST identified "responders" to a drug, who were then randomized either to that drug or to its matching placebo. Patients who had inadequate suppression of ventricular premature complexes or who had proarrhythmic

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responses during the dose titration phase were entered into various substudies and not considered part of the main study.

Because the increased risk for sudden arrhythmic death in the presence of ventricular ectopic activity and depressed left ventricular function may persist long after a myocardial infarction (2), the original entry window included patients 6 days to 2 years after a myocardial infarction, and upper limits for ejection fraction were sought to enroll a high risk population. There was no lower limit on ejection fraction. If the elapsed time since the myocardial infarction was long (90 days to 2 years), the ejection fraction had to be ≤0.40 for the patient to be eligible. For patients with a more recent myocardial infarction (6 to 89 days), the ejection fraction had to be ≤0.55. The rationale for this design was that the highest risk for arrhythmic death is during the first few months after myocardial infarction. After the first few months, the risk decreases and is minimal unless left ventricular function is reduced. Therefore, patients who entered the CAST late after myocardial infarction were required to have a lower ejection fraction to maintain a sufficiently high risk of sudden death that participants in this trial might demonstrate benefit.

Patients with ≥6 ventricular premature complexes/h were entered in the CAST because it appeared that the risk of arrhythmic events begins with 1 ventricular premature complex/h and increases to a plateau at a rate of ≥10 such complexes/h (3).

*The definition of ventricular tachycardia* for the CAST allowed enrollment of patients thought to be at relatively high risk. The length of ventricular tachycardia defined to be disqualifying was ≥15 beats at a rate of ≥120 beats/min. Patients with *bundle branch block* were also included in the CAST.

## Drug Selection for the CAST

The selection of antiarrhythmic drugs for inclusion in the CAST was based on the specific characteristics of the drugs, the proposed patient population and the requirements dictated by the ventricular ectopic activity suppression hypothesis (4). As with all secondary prevention trials, drug selection was based primarily on the relative risk/benefit ratio for each drug. Dependence on a single drug was not considered to be desirable because the intent of the CAST was to test a treatment strategy and not a specific drug.

In late 1986, during the planning phase of the CAST, the Drug Selection and Titration Subcommittee reviewed currently available and investigational antiarrhythmic agents for potential inclusion in the trial. The criteria in Table 1 were assessed for each drug. The Subcommittee also considered: 1) the total number of persons evaluated in clinical studies, 2) the total number of patients who had been evaluated for drug safety and efficacy for >1 year, and 3) the quality of the data base in patients comparable to patients projected for inclusion in the CAST.

Table 1. Criteria for Drug Selection: The Cardiac Arrhythmia Suppression Trial (CAST)

1. High degree of suppression of ventricular premature complexes. Ideally, >80% of patients would have: ≥80% suppression of ventricular premature complexes and ≥90% suppression of ventricular tachycardia at tolerated dosages
2. High degree of tolerance: ≥80% of patients having arrhythmias suppressed and tolerating the drug for >2 years
3. Infrequent dosing
4. Infrequent serious proarrhythmia
5. Infrequent serious noncardiac adverse effects
6. Extensive experience in postmyocardial infarction patients with ventricular ectopic activity
7. Effective in other patient groups
8. Suitable for a multiple dose, multiple drug blinded trial
9. Marketed or soon to be marketed in the United States
10. Minimal negative inotropic effects
11. No drug interactions (specifically, with digitalis and beta-adrenergic blocking agents)
12. Uniform dosing (minimal dose changes required in patients with heart failure, renal failure, liver failure, for example)
13. No additional nonantiarrhythmic actions (for example, intrinsic beta-adrenergic blockade)
14. Efficacious as judged by electrophysiologic study (although electrophysiologic study itself would not be used in the CAST)

### *The "Standard" IA Drugs*

None of the commonly prescribed "standard" antiarrhythmic agents was deemed acceptable for inclusion in the CAST. Inadequate suppression of ventricular premature complexes or unknown degree of suppression of ventricular premature complexes characterized most drugs considered.

**Quinidine.** This drug has a predictably high (approximately 30%) early dropout rate due to gastrointestinal and other toxic effects (5,6) and thus would not achieve the CAST goal of ≥80% suppression of ventricular premature complexes and ≥90% suppression of ventricular tachycardia maintained in at least 80% of patients at 1 year. Additionally, published estimates of proarrhythmia (including torsade de pointes) ranged from 0.5 to 2% (7,8). These data heightened concern about initiating this drug for prophylaxis against sudden death in a large number of outpatients with asymptomatic "potentially lethal" ventricular arrhythmias, even though the proarrhythmic effect of quinidine may be no worse than that of many other drugs. The quinidine-digoxin interaction would also complicate a double-blind trial.

**Procainamide.** This drug was considered of limited use for widespread secondary prevention because of the need for four times daily dosing and the high incidence of drug-induced lupus erythematosus (positive antinuclear antibody in 60% to 70% and lupus symptoms in 20% to 30% of patients at 1 year). In a previous secondary prevention trial by Kosowsky et al. (9), 23% of subjects discontinued therapy within 3 months and 41% terminated use of the drug before completion of the 2-year study. Of additional concern were the reports of procainamide-associated blood dyscrasias, estimated to be as high as 0.5%, which would require weekly blood counts for 12 weeks.

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**Disopyramide.** This drug also had been studied previously in postmyocardial infarction secondary prevention trials (10–12) without evidence of benefit. In 610 patients combined from three studies, the mortality rate was 8.6% with the active drug versus 8.8% with placebo. Other limitations of disopyramide included potential aggravation of congestive heart failure in patients with a low ejection fraction and bothersome anticholinergic side effects in 10% to 40% that often led to withdrawal from therapy.

### *The Class IB Drugs*

**Tocainide and mexiletine.** Neither of the class IB antiarrhythmic agents, tocainide and mexiletine, had demonstrated promise for preventing sudden death in earlier postmyocardial infarction secondary prevention trials (13–16), nor were they very effective in suppressing ventricular premature complexes. Although these trials had not selected subjects for the presence of ventricular premature complexes and had not assessed suppression of ventricular ectopic activity, the dropout rate due to gastrointestinal and central nervous system toxic effects was high, and no favorable survival trends were noted. In fact, a trend toward increased mortality was seen with mexiletine in the largest trial, the International Mexiletine and Placebo Antiarrhythmic Coronary Trial (16), which tested mexiletine versus placebo. This trial observed a 1-year mortality rate of 7.6% with mexiletine versus a 4.8% rate in the placebo group ($p$ = NS). These results were consistent with the many reports (17,18) demonstrating that class IB drugs achieved only moderate suppression of ventricular premature complexes as assessed by Holter monitor and poor suppression of ventricular tachycardia on electrophysiologic study. Furthermore, tocainide, like procainamide, was considered to have an unacceptable safety profile because it rarely induced granulocytopenia.

**Combination of quinidine and mexiletine.** This combination had several merits for consideration for use in the CAST. When used in combination, each agent can be administered in lower doses, decreasing intolerable side effects while enhancing efficacy (19). Reports of success with quinidine plus mexiletine have been encouraging with both Holter-guided therapy and electrophysiologic testing (19,20). Enthusiasm for this drug combination was guarded, however, because of the rather small data base (<400 patients in published reports on this regimen and <100 patients followed up for >1 year) and the undesirable complexity of using two drugs in a CAST population. The proarrhythmic potential of quinidine and its interaction with digoxin also decreased the desirability of this combination.

### *Other Drugs*

**Amiodarone.** The well established toxicity of amiodarone, especially pulmonary fibrosis, diminished enthusiasm for its use in this asymptomatic patient group. Furthermore, its complex pharmacokinetics and its interaction with digoxin and warfarin made it undesirable for use in this blinded trial.

**Propafenone.** This class IC drug with a data base of nearly 1,000 patients (Knoll Pharmaceuticals) appeared to have good suppression of ventricular premature complexes and tolerance. However, the dose-response relation for arrhythmia suppression was not defined, and patients could be either slow or fast metabolizers with different rates of response and side effects (21). Long-term drug efficacy and safety information were somewhat limited, and the potential beta-adrenergic blocking effect (22) would have confounded the ability to test the hypothesis of suppression of ventricular premature complexes. Any reduction in mortality observed could possibly have been due to beta-adrenergic blockade and unrelated to suppression of ventricular premature complexes.

**Other investigational drugs.** These drugs (pirmenol, cibenzoline, indecainide, sotalol, d-sotalol, bepridil, lorcainide, n-acetylprocainamide) were excluded for a variety of reasons, primarily limited patient exposure with an inadequate data base for safety and efficacy in a CAST population, even though some were thought to be promising new agents.

### *Rationale for Encainide, Flecainide and Moricizine in the CAST*

The four drugs tested in the earlier Cardiac Arrhythmia Pilot Study (CAPS) (23) were reassessed for inclusion in the CAST. In the CAPS, imipramine caused only limited suppression of ventricular premature complexes (52%) and had a high rate (26%) of unacceptable side effects, particularly postural hypotension, and thus was eliminated as a candidate for the CAST. Both class IC drugs, encainide and flecainide, had achieved the goal of ≥70% suppression of ventricular premature complexes in the CAPS in 79% and 83% of patients, respectively. The incidence of intolerable side effects for encainide (5%) and flecainide (5%) was comparable to that of placebo (3%). Proarrhythmia did not appear excessive during 1 year of follow-up (encainide 1%, flecainide 3%, placebo 3%). Large data bases (albeit not for patients in the immediate postmyocardial infarction period) were available for both encainide and flecainide. The fourth CAPS drug, moricizine, afforded satisfactory efficacy (66% of patients showed ≥70% suppression of ventricular premature complexes) although the rate of suppression was slightly lower than that of flecainide or encainide. The pharmaceutical manufacturer's data base for moricizine (E.I DuPont deNemours) included 1,190 patients with good drug tolerance and there was a low incidence of proarrhythmia and congestive heart failure.

Deaths and proarrhythmia were infrequent in the CAPS (23). Congestive heart failure requiring hospitalization appeared to occur slightly more frequently in flecainide-treated patients (20% taking flecainide, 6% taking encainide, 10% taking placebo) (24). This finding in the CAPS prompted

CAST investigators to restrict the use of flecainide to patients with an ejection fraction ≥0.30 (24,25). Patients with such an ejection fraction were randomized to either 1) flecainide, then moricizine and then encainide, or 2) encainide, then moricizine and then flecainide. The two class IC antiarrhythmic agents, encainide and flecainide, were always given first because these agents seemed to be better at suppressing ventricular premature complexes. Treatment proceeded from one drug to the next only if ventricular premature complexes were not suppressed by the highest dose of drug or if adverse effects occurred. For patients with an ejection fraction <0.30, the drug sequence was either 1) encainide then moricizine, or 2) moricizine and then encainide. The study was thus designed to identify suppression of ventricular premature complexes at the earliest possible time, both for simplicity of protocol and for ease of patient recruitment and compliance.

Though both class IC drugs, encainide and flecainide, had been marketed for only 1 to 2 years at the initiation of the CAST and moricizine had not received approval of the Food and Drug Administration, these agents appeared to have the most favorable overall profile for application in the CAST protocol.

## Implications of the Open Label Drug Titration Design

Because the study was designed as a suppression trial, an attempt was made to identify rapidly a drug that would suppress ventricular premature complexes for each individual patient. In the CAST, the dose titration phase of the study was not placebo-controlled. The incidence of arrhythmia aggravation during the CAPS dose titration phase (approximately 2 weeks) and, in particular, during the initial 2-day inpatient treatment initiation phase in the CAPS, was very low (1% to 3%) and was similar in all treatment groups, including the placebo group. Furthermore, this arrhythmia aggravation in the CAPS consisted almost exclusively of asymptomatic increases in frequency of ventricular premature complexes. Therefore, in the CAST hospitalization was not required for initiation of treatment. The CAST included higher risk subgroups, such as those with ejection fraction <0.20 or bundle branch block. Investigators recognized that having an open label titration phase at the beginning of the study could result in mortality or side effects during the titration phase that could not be interpreted because no placebo control was included at this time. However, because of the need to identify a successful drug rapidly, this trade-off was accepted.

Only after each patient was identified as a "responder" was the patient randomized to either the successful drug or its placebo. Patients with partial (1% to 79%) suppression of ventricular premature complexes entered a substudy.

## Initial Results of the CAST

**Encainide and flecainide.** Randomization in the CAST began in June 1987. Most patients (75%) achieved satisfactory suppression of ventricular premature complexes, 52% with the first dose of the first drug. In April 1989, encainide and flecainide were removed from the CAST (26). A total of 1,498 patients had been randomized either to encainide or flecainide or to their placebos. At that time, the study determined that both total cardiac mortality and deaths from arrhythmias were increased in the groups treated with encainide or flecainide (1).

**Moricizine.** Only a relatively small number of patients had actually been randomized to moricizine or its placebo (277 as of April 1989) for two reasons: 1) moricizine was the second drug in the sequence for patients with an ejection fraction ≥0.30, but encainide and flecainide were so successful in suppressing ventricular premature complexes that very few patients were exposed to moricizine in this high ejection fraction group; and 2) equal numbers of patients were randomized to encainide or moricizine among those with an ejection fraction <0.30, but fewer patients qualified in this category.

The Data and Safety Monitoring Board and the National Institutes of Health enthusiastically endorsed continuation of the CAST with moricizine, the continuation of the study called the Cardiac Arrhythmia Suppression Trial-II (CAST-II).

## Impact of the Initial CAST Results and Design of CAST-II

The preliminary results of the CAST in patients with myocardial infarction established that either the hypothesis of suppression of ventricular premature complexes was invaliu or that it may be drug specific. It is unknown whether the CAST findings apply only to patients who have recently survived a myocardial infarction. The mechanisms are also unknown—presumably interactions among an antiarrhythmic drug, myocardial scar and some intercurrent factor, such as ischemia or infarct healing.

Because of these results, encainide and flecainide were removed from the CAST. Consideration was given to the addition of another drug or drugs. Because no drug met the original acceptability criteria, and because it would have been logistically difficult to add another drug, the CAST-II continued with moricizine only. After April 1989, several other major changes were made in the protocol for the CAST that continued as the CAST-II (Table 2). Because no sudden arrhythmic deaths occurred in the patients enrolled late after their myocardial infarction, the enrollment time was limited to 4 to 90 days after myocardial infarction. Similarly, the qualifying ejection fraction was lowered to ≤0.40. To attempt to achieve a higher rate of suppression of ventricular premature complexes, a higher dose of moricizine was allowed. Patients formerly treated with encainide or flecain-

**Table 2.** Major Changes in CAST Protocol for Continuation as CAST-II

1. Encainide and flecainide were removed; no new drugs were added
2. Qualifying ejection fraction was reduced to ≤0.40
3. Enrollment time was changed to 4 to 90 days after myocardial infarction
4. A higher dose of moricizine (900 mg/day) was added
5. Titration phase was double-blind with a placebo to detect adverse events/deaths during titration
6. Definition of disqualifying ventricular tachycardia was changed to ≥30 s at a rate of ≥120 beats/min or ventricular tachycardia that was symptomatic

ide (or with encainide placebo or flecainide placebo) could be rerandomized if they met the new entry criteria (except for the criterion of time since myocardial infarction). The titration phase of the CAST-II study was placebo controlled to determine if there was a mortality benefit (or risk) during the 1st 2 weeks of exposure to drug.

**Moricizine.** The results of the CAST-II evaluated the utility of ventricular premature complex suppression with moricizine after myocardial infarction. Initial exposure to moricizine yielded a higher mortality rate than that of initial exposure to placebo. In addition, the long-term phase of the study was unlikely to show any survival benefit from treatment with the drug (CAST Investigators, unpublished observations). Thus, the ventricular premature complex hypothesis was disproved, and we concluded that patients with ventricular premature complexes after myocardial infarction should not be routinely treated with antiarrhythmic agents.

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