CARDIAC ARRHYTHMIA SUPPRESSION TRIAL (CAST)

PROTOCOL

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1. INTRODUCTION

Although overall mortality from cardiovascular disease has been decreasing for over ten years,[1] sudden cardiac death remains a health problem of epidemic proportions in the United States. Over 400,000 persons die suddenly each year in this country.[2] It is generally recognized that the majority of patients who experience sudden death have ventricular fibrillation as the precipitating arrhythmia.[3] While some fatal arrhythmias may start as organized ventricular tachycardia, these arrhythmias commonly degenerate quickly to ventricular fibrillation.[4] Only uncommonly is any form of bradycardia responsible for sudden death.[4] The majority of patients who experience sudden death have significant coronary artery disease, often associated with prior myocardial infarction, angina pectoris, hypertension, and impaired ventricular function.[5] Therefore, if patients could be identified and if adequate therapy were available, reduction in sudden death could be attained.

Certain patient groups have been identified as having a high risk of sudden cardiac death:

a. survivors of recent myocardial infarction;[6-8]
b. resuscitated survivors of ventricular fibrillation not associated with an acute transmural myocardial infarction;[9-11]
c. patients with recurrent ventricular tachycardia.[12-13]

The numbers of patients with recurrent ventricular tachycardia or survivors of ventricular fibrillation not associated with a myocardial infarction are difficult to assess. Nevertheless, the largest of these high risk populations in the United States is the post myocardial infarction group. There are approximately 350,000 patients discharged from the hospital with a myocardial infarction as the primary diagnosis each year in this country. The cumulative risk for cardiac death in the year after myocardial infarction is from 8 to 15%. However, certain characteristics have been identified in the last 15 to 20 years which allow stratification of patients into high risk subsets. Many factors place patients at high risk, although these factors are commonly interrelated: advanced age, male sex, previous myocardial infarction, congestive heart failure, persistent sinus tachycardia, ventricular arrhythmias beyond the acute phase of the infarction, etc. Early studies have suggested that the major factor in determining the risk of death in the year after myocardial infarction is left ventricular function,[14] but it has become apparent that ventricular arrhythmias constitute an independent predictor of death.[6,15,16] Since frequent and complex ventricular arrhythmias are associated with sudden death, one might hypothesize that therapy that suppressed these arrhythmias would improve survival. If this hypothesis is true, either the suppressed arrhythmias are etiologically related to the sudden death, or, alternatively, successful therapy alters both the factor responsible for sudden death and the markers of risk, the ventricular premature depolarizations (VPD's).

Recent placebo-controlled secondary intervention trials in the post myocardial infarction population have shown an improved survival for patients treated with beta blockers.[17-25] A significant reduction in overall cardiac death, and in some a reduction in sudden death, has been demonstrated for many of the beta blockers (timolol, propranolol, practolol, and metoprolol). It still is

uncertain whether the mechanism of this improved survival was reduction of ischemia, prevention of reinfarction, suppression of arrhythmias, or a combination of these or other factors.

In spite of attempts to show that suppression of VPD's after a myocardial infarction might be beneficial, no study to date has been designed or executed properly to achieve this goal. Furberg[26] summarized the studies in post infarction patients and emphasized that methodologic discrepancies in each study could account for the failure to show a benefit from antiarrhythmic therapy: (1) failure to select patients at high risk with arrhythmias post MI; (2) too few patients studied to expect to observe a difference between treated and untreated patients (i.e., the power of the study was too small); (3) the agents chosen were ineffective or given in the wrong dose (e.g., in some studies, dose titration was not performed); (4) only a single drug was tested without the option to proceed to a second drug if the first was ineffective in controlling arrhythmias; or (5) too many patients dropped out of the study due to adverse side effects of the drugs. Thus, studies with phenytoin,[27-28] aprindine,[29] mexiletine[30-31] and tocainide[32-33] all were inadequate to show an improvement from drug therapy. However, with the current ability to identify patients with arrhythmias after myocardial infarction, it should be possible to design a study with antiarrhythmic agents which would be able to show the reduction of post infarction arrhythmic death, if such a beneficial effect of the drugs exist.

Arrhythmias in the post myocardial infarction setting have usually been detected by 24 hour Holter recording. Even short term one hour recording has identified ventricular arrhythmias as an independent risk factor in the post myocardial infarction patient. Ruberman[16] concluded that complex VPD's on a one hour in-office monitor identified the patient at risk for total cardiac and sudden cardiac death. Bigger[34] and Moss[35] likewise found that frequency and complexity of VPD's correlated well with sudden cardiac death after myocardial infarction. The ideal antiarrhythmic drug trial would include only those patients at high risk of arrhythmic death, and patients would be treated with a drug which was easy to administer with few adverse effects. The Cardiac Arrhythmia Pilot Study (CAPS) was begun in 1982 in an attempt to determine whether adequate numbers of patients could be identified and randomized after myocardial infarction to make a large-scale study feasible.[36]

In the United States, as of December 1982, only quinidine,[37-38] procainamide,[39] and disopyramide,[40] had been approved for chronic use to treat ventricular arrhythmias. These drugs, however, had insufficient antiarrhythmic potential, and all were relatively poorly tolerated. New drugs were then being tested which could have efficacy in suppressing arrhythmias with fewer major adverse effects. The toxic - therapeutic ratio of these drugs (e.g., encainide, flecainide, moricizine, imipramine, amiodarone, lorcainide, mexiletine, aprindine, sotalol, and propafenone) potentially could have been better than marketed antiarrhythmic drugs in the United States in 1982. Although all drugs can have proarrhythmic effects and other adverse effects, some of these drugs seemed to have a substantial efficacy in suppressing both VPD's and more complex arrhythmias with few reported adverse effects. With the increased clinical investigational use of these drugs, it was desirable to determine their ability to suppress arrhythmias in this post myocardial infarction population and to assess their safety and tolerance in CAPS, which was planned as the pilot study for a later, large-scale trial with mortality as an end

point. Preliminary calculations suggested that to conduct such an adequate large-scale trial with mortality due to arrhythmia as the endpoint, it would be necessary for an antiarrhythmic treatment to reduce VPD rates by approximately 70% compared to baseline in at least 80% of patients. Because it was not known whether any of the newer antiarrhythmic drugs were capable of this suppression rate without intolerable adverse effects, CAPS was conducted.

CAPS had three main goals: 1) to demonstrate that patients could be identified and recruited who would be willing to comply with the study protocol; 2) to determine whether a treatment regimen was available which would initally provide 70% or greater VPD reduction in at least 80% of the patients and maintain substantial reduction for one year without intolerable adverse effects; and 3) to study the one year course of arrhythmia in placebo-treated patients.

CAPS was a double-blind, randomized trial which evaluated the long-term (one year) antiarrhythmic effects of encainide, flecainide, imipramine, and moricizine, compared with placebo. Ten clinical centers, a coordinating center, a drug distribution center, a Holter reading center and the National Heart, Lung, and Blood Institute (NHLBI) project office participated in this study. Details of the protocol, including rationale for drug selection, are given elsewhere.[36,41-42] In brief, patients were eligible if they had suffered an MI between 6 and 60 days earlier, were less than 75 years of age, had a left ventricular ejection fraction >.20, had no contraindications to any of the medications, provided informed consent, and demonstrated an average of at least 10 VPD's per hour or at least 5 episodes of unsustained ventricular tachycardia (VT) on a 24 hour Holter. The presence of consecutive VPD's (runs) of 10 or more at a rate $\geq$100 per minute was an exclusion criterion because of the concern that patients with such an arrhythmia had a substantial risk of sudden death, could not be treated in a protocol which included a placebo, and would ultimately be given individualized treatment.

After qualifying and giving informed consent, patients were randomly assigned to one of four active drugs or to a placebo. If efficacy, defined as at least 70% reduction of VPD's and more than 90% reduction of runs (3 to 9 consecutive VPD's), was not achieved with dose titration on the first drug, or if there were proarrhythmia, disqualifying VT, conduction abnormalities (including heart block and excessive lengthening of the QRS or QT) or intolerable adverse effects, dose titration with a second agent (which was part of the original randomization assignment) was begun. Placebo patients who demonstrated lack of efficacy were switched to a second placebo. The active drugs and the three dose levels chosen for each are shown below:

	Total Daily Dose		
Drug	Low Dose	Medium Dose	High Dose
Encainide	105mg	150mg	180mg
Flecainide	200mg	300mg	400mg
Imipramine	150mg	225mg	375mg
Moricizine	600mg	750mg	900mg

The study was conducted in 502 post myocardial infarction patients who were followed for one year after randomization.

CAPS determined that it was feasible to enroll and follow sufficient patients and to maintain high levels of patient compliance to the study protocol. CAPS also showed that at least two drugs, encainide and flecainide, reduce ventricular ectopy by $\geq$70% (79% and 83% of patients, respectively) and maintain an average reduction of $\geq$70% in many (75% and 73% of patients, respectively) for at least one year. Of the other active drugs, the initial suppression rates were 52% on imipramine, 66% on moricizine and 37% on placebo.

It would appear that encainide and flecainide were both adequate therapies to achieve the goal of 70% suppression of VPD's in 80% of patients. The initial success rates for encainide and flecainide as first drug were virtually identical, with approximately 80% of patients with greater than 70% average reduction of VPD's on these drugs, compared to 37% with placebo. Long-term tolerance of both drugs met the goals of the study, 78% of patients who were assigned encainide at completion of titration remaining on the drug throughout the year, and 75% of patients assigned flecainide remaining on the drug for the year.

A surprising number of patients (25%) developed new or worsened congestive heart failure (CHF). There may have been some differences between encainide and flecainide in their negative inotropic effects. More patients developed new or worsened congestive heart failure on flecainide than on encainide, a difference which is probably real, even considering the difficulties encountered in this study with the rather subjective definitions of new or worsened congestive heart failure. However, it must be noted that the incidence of new or worsened congestive heart failure on placebo fell between that for flecainide and encainide and that only 26 of 502 patients had to stop the CAPS medication because of new or worsened CHF.

Twelve percent of all patients in CAPS developed disqualifying ventricular tachycardia (defined by the investigators as a run of 10 or more ventricular complexes at a rate of $\geq$ 100 per minute), and which, by protocol, required cessation of the study drug. However, most of the disqualifying runs were unsustained and asymptomatic with length < 15 beats. In addition, of all patients assigned CAPS therapy (active or placebo) at completion of titration, 19% were changed to individualized therapy by the end of the first year. Fifteen percent of the patients assigned at end of titration to encainide and 18% of those assigned to flecainide went on individualized therapy. The impact of these findings on the subsequent large scale study must be considered.

One of the major concerns in CAPS was the potential for adverse reactions and proarrhythmic effects of drugs. Hospitalization was therefore required for initiation or change in drug therapy. CAPS demonstrated that the immediate adverse effects and proarrhythmic effects of these drugs were relatively small and equivalent to placebo, remembering that the study excluded patients with ejection fractions $\leq$ 0.20, included slow titration of doses and excluded patients with $\geq$ 10 beats in a row of ventricular tachycardia on the baseline Holter recording.

The Cardiac Arrhythmia Pilot Study thus suggested that the large scale study, the Cardiac Arrhythmia Suppression Trial (CAST), can be successfully completed. Patients with sufficient ectopy to qualify as moderately high risk can be identified after a myocardial infarction and enrolled in such a study. CAPS showed, however, that many patients must be screened to enable enrollment of sufficient numbers of patients to test the hypothesis that VPD suppression improves survival. With at least two drugs in CAPS (encainide and flecainide), VPD's were successfully suppressed with adequate patient compliance and acceptable adverse effects. Thus, it will be feasible to test whether suppression of VPD's will improve survival in patients who have arrhythmias after a myocardial infarction.

2. OVERVIEW OF STUDY DESIGN

In this section we give a brief simplified description of the CAST design. The details are given in subsequent sections.

A. Objective.

The Cardiac Arrhythmia Suppression Trial (CAST) is designed to determine whether drug therapy results in a reduction in arrhythmic death (as defined below) for patients in whom drug therapy does suppress ventricular arrhythmia. Patients will be randomized during an open label titration phase to a sequence of two or three antiarrhythmic therapies depending upon cardiac ejection fraction. Patients whose arrhythmia is adequately suppressed will then be randomized to the therapy which suppressed the arrhythmia or to a matching placebo. Patients without adequate suppression of arrhythmia will be randomized to the best therapy or to a matching placebo. They will constitute a major substudy, not a subgroup of the main study.

B. Patient Eligibility.

The study participants will be survivors of a myocardial infarction who have 6 or more VPD's/hr on a 24 hour Holter obtained between 6 days and 2 years after the onset of the myocardial infarction. If the screening Holter is obtained between 6 and 90 days after the onset, the patient's ejection fraction must be ≤ 0.55, whereas if the screening Holter is obtained 90 or more days after the onset of myocardial infarction, the ejection fraction must be ≤ 0.40. In the latter case, if the ejection fraction is ≥ 0.30 it must have been obtained within 90 days prior to the qualifying Holter.

Patients with a run of VT of ≥ 15 complexes at a rate ≥ 120 per minute or patients with symptomatic hemodynamically important ventricular tachycardia will be excluded from the study because of the likelihood that the private physician would prefer to treat them with an antiarrhythmic drug.

C. Treatment

During the titration phase, three active drugs will be used (at least initially). These drugs (encainide, flecainide, and moricizine) will be used in a number of sequences which will be assigned randomly. The sequence will contain three drugs for patients with an ejection fraction ≥ 0.30 and two drugs, encainide and moricizine, for patients with an ejection fraction < 0.30. Each drug has two dose levels, and dosing will proceed from the low to the high dose for each drug. Suppression or lack thereof will be documented by a 24 hour Holter. (However, a Holter will not be necessary if limiting adverse effects are present.)

Following the titration phase, patients whose arrhythmia was successfully suppressed will be randomized to the successful therapy or to a matching placebo. Patients whose arrhythmia was not successfully suppressed (though not included in the primary analyses) will be randomized to the best

therapy, that which is most effective among those which are tolerated and which do not increase the VPD rate, or to a matching placebo. During titration, suppression will be defined as ≥ 80% reduction in the VPD rate and ≥ 90% suppression of runs of VT (3-14 VPD's at a rate ≥ 120 per minute).

D. Endpoints

The primary endpoint in the suppression trial will be arrhythmic death as defined below.

Arrhythmic death is defined as (1) death occurring in less than 24 hours from the onset of new symptoms in the absence of severe left ventricular failure or shock which in itself might have been expected to cause death; (2) resuscitated ventricular fibrillation (or, if no rhythm documentation is available, resuscitated cardiac arrest; i.e., resuscitated ventricular tachycardia is not to be counted as an "arrhythmic death"); (3) unwitnessed death without other known noncardiac causes.

In the absence of documentation to the contrary, death occurring in < 24 hours from onset of symptoms will be considered to be a sudden arrhythmic death as long as the only new symptoms were ischemic pain or pressure, syncope, palpitations or dizziness, and as long as the patient died of documented or presumed arrhythmia. Death which occurs as the end result of CHF/shock, even though occurring in < 1 hour from onset of symptoms, will not be considered to be sudden arrhythmic death. In circumstances where the event is witnessed but poorly documented, or for other cardiac conditions, death or cardiac arrest which occurs within 1 hour of onset of symptoms will be considered to be arrhythmic. If any symptoms are separated from onset of death/cardiac arrest by a symptom-free period of 24 hours, then these symptoms will not be considered as part of the death/cardiac arrest event itself.

Secondary endpoints will include:

(1) total cardiac mortality
(2) the combination of sustained ventricular tachycardia and arrhythmic death
(3) total overall mortality (both cardiac and non-cardiac)

Additional objectives of the study will be to evaluate:

(1) the relationship of baseline ejection fraction to the primary and secondary endpoints
(2) the relationship of the time at which drug therapy is initiated to the primary and secondary endpoints
(3) the relationship of other baseline characteristics to the primary and secondary endpoints
(4) suppressable versus unsuppressable patients
(5) the effect of antiarrhythmic therapy on congestive heart failure

Primary analyses will be by intention to treat and will be one-sided, with an alpha value of 0.025. Safety (adverse effects, including potential proarrhythmia) will be monitored by the Data and Safety Monitoring Board.

E. Duration and Estimated Sample Size

Patients will be enrolled for three years, and all patients will be followed to a common termination date, which will be two years beyond enrollment of the last patient. It is expected that 4400 patients will be enrolled into the main study during this period. This number will provide a power of at least 85% to detect a 30% reduction in arrhythmic death. It is expected that 800 to 1200 patients will be enrolled into the substudy of patients with inadequate suppression of VPD's. Because the incidence of arrhythmic death in these patients is unknown, power calculations are problematical. Details of the sample size calculations are included in Appendix 1.

3. ORGANIZATION OF THE CARDIAC ARRHYTHMIA SUPPRESSION TRIAL

A. Introduction

The participating units in this clinical trial include twenty-seven Clinical Centers, a Coordinating Center, a Drug Distribution Center, and the National Heart, Lung, and Blood Institute Project Office.

During the Planning Phase, the organization consisted of a Planning Committee and five Subcommittees. Subsequently, the Planning Committee was transformed into a Steering Committee, and new Subcommittees were appointed. An Executive Committee and a Data and Safety Monitoring Board were also formed.

B. Participating Units

1. Clinical Centers

Twenty-seven Clinical Centers participated in developing the protocol and are each responsible for enrolling and following patients in the main study. Specific duties of each center are:

a. To recruit and randomize patients for CAST, according to the protocol. The 27 centers should each average 163 total randomized eligible patients into the main study within a three-year period.

b. To collect the data for CAST accurately and completely and to transmit the data to the Coordinating Center in a timely fashion.

c. To perform all laboratory and other procedures as specified in the protocol, including storing and sending upon request Holter tapes for quality control reading.

d. To administer the study drugs, according to the protocol, and to maintain good patient adherence to the medication, consistent with optimal medical care.

e. To maintain patient files and to interview and examine the patients periodically, according to the protocol.

f. To cooperate with other centers in assuring that CAST is properly conducted.

g. To assist in making appropriate protocol modifications.

h. To participate in the analysis and reporting of study results.

To accomplish the above, each Clinical Center has a principal investigator, co-investigator(s), project physician(s), and clinic coordinator(s).

The 27 Centers are:

University of Alabama in Birmingham
Baylor College of Medicine
Beth Israel Medical Center
Brown University Affiliated Hospitals
University of Calgary
Case Western Reserve University
Columbia University Affiliated Hospitals
Emory University School of Medicine
George Washington University Medical Center
Gothenburg University
Hahnemann University
Henry Ford Hospital
University of Kentucky
University of Maryland
University of Massachusetts
University of Minnesota
Montreal Heart Institute
Oregon Health Sciences University
University of Ottawa Heart Institute
University of Rochester Medical Center
Rush-Presbyterian-St. Luke's Medical Center
Salt Lake Clinic Research Foundation
St. Louis University Medical Center
SUNY Health Science Center
Vanderbilt University
Medical College of Virginia
Washington Hospital Center

2. Coordinating Center

The Coordinating Center is located at the University of Washington, Seattle. The Coordinating Center has a major role in the design and implementation of the trial. Specific functions of the Coordinating Center are:

a. To work with clinic investigators and the NHLBI Project Office in the development of the study protocol.

b. To play a major role in the development, pretesting, and distribution of forms.

c. To prepare and periodically update the Manual of Operations.

d. To make a random assignment to a treatment group for each enrolled patient.

e. To receive, file and analyze collaboratively study data from all cooperating Centers.

f. To check the completeness, accuracy and timeliness of all data submitted by the Clinical Centers.

g. To prepare periodic reports recording the progress of the study for the Clinical Centers, the Data and Safety Monitoring Board and the NHLBI Project Office. These reports include recruitment, visit adherence, performance of procedures, drug compliance, and completion of forms.

h. To notify Clinical Centers of problems with regard to adherence to the protocol and to keep the Project Office informed of major problems.

i. To analyze periodically the frequency of new events and toxic adverse reactions by treatment group and to report these data to the Data and Safety Monitoring Board.

j. To assist the Clinical Centers in making drug and dose changes based on Holter findings. This will be done in a manner best able to maintain the treatment blind, but not at the expense of patient safety.

k. To assist in the preparation of scientific reports of the study.

l. As necessary, to make visits to Clinical Centers with the Project Office staff.

m. To select Holters for overreading, to send out gold standard tapes, and to analyze the results of quality control reading of Holters.

n. To implement adequate security for any confidential study data.

o. To help train Clinical Center personnel in the carrying out of the study Protocol.

p. To prepare an address directory for CAST.

q. To take, distribute and maintain minutes of all study meetings.

r. At the conclusion of the study, to transmit to the NHLBI Project Office tapes with all study data, along with appropriate documentation.

3. Drug Distribution Center

The Drug Distribution Center is located at the Veterans Administration Cooperative Studies Program Clinical Research Pharmacy Coordinating Center in Albuquerque and is responsible for coordinating the CAST activities. The Center:

a. Acts as a liaison to the pharmaceutical companies that contribute drugs with respect to the supply of capsules and related matters.

b. Packages, labels and ships study drugs to the Clinical Centers.

c. Assures quality control of the drugs.

d. Prepares IND requests for the study drugs.

e. Monitors drug usage and recalls and disposes of unused drugs.

f. Assists the Coordinating Center in recording drug-related problems.

4. National Heart, Lung, and Blood Institute Project Office

The NHLBI Project Office is responsible for providing organizational, scientific, and statistical oversight to CAST, and for participating in the design, conduct, and analysis of the study. Project Office responsibilities are:

a. To collaborate in Protocol design, data analysis, and paper writing activities.

b. To maintain contact with study investigators for the purpose of ensuring collection of high quality data. This may entail site visits. In cases of inadequate performance, the Project Office may consult with the Data and Safety Monitoring Board to consider terminating participation of an individual center.

c. To organize and facilitate the functioning of the Data and Safety Monitoring Board.

d. To implement major Protocol changes (e.g., early cessation of the study or of individual treatment arms); the advice of the Data and Safety Monitoring Board and Steering Committee will (as appropriate) be sought.

e. To review manuscripts written for publication.

f. To be responsible for contractual and financial arrangements between NHLBI and participating centers.

C. Study Administration

1. Data and Safety Monitoring Board

The Data and Safety Monitoring Board acts in a senior advisory capacity to the NHLBI on data matters throughout the duration of the study. In addition, it periodically reviews study results by treatment group and evaluates the treatments for beneficial and adverse effects.

The Board consists of a Chairman and six additional voting members who are appointed by the NHLBI for the duration of the study. The NHLBI Project Officer is an ex-officio, non-voting member. Additional Board members may be appointed by NHLBI. Board meetings will be attended by senior representatives from the Coordinating Center and NHLBI, as well

as by the Chairmen of the Steering Committee. No voting member of the Board may participate in the study as an investigator. The Board will meet twice yearly.

Specific functions of the Data and Safety Monitoring Board are:

a. Initially to review the Protocol and make recommendations to NHLBI.

b. To review subsequent changes in the Protocol and advise the NHLBI.

c. To examine outcome and toxicity data by treatment group, approximately twice yearly.

d. To make recommendations to the NHLBI on any proposed extension or early termination of the study or study arm because of beneficial or adverse effects.

e. To assist the NHLBI in resolving problems referred to it by the CAST Steering Committee.

f. To monitor the performance of Clinical and other Centers.

g. To advise the NHLBI regarding discontinuation of any centers which perform unsatisfactorily.

Members of the Data and Safety Monitoring Board are:

J. David Bristow, M.D., Chairman
David DeMets, Ph.D.
Charles Fisch, M.D.
Alan S. Nies, M.D.
Jeremy Ruskin, M.D.
Harold Strauss, M.D.
Leroy Walters, Ph.D.

2. Planning Committee

During the planning phase of the study, the Planning Committee has responsibility for developing the study Protocol and for initiating the development of the Manual of Operations and study forms.

The Planning Committee consisted of principal and co-investigators from the Clinical Centers, Coordinating Center, Drug Distribution Center, and the Staff of the NHLBI Project Office. Each participating center had one vote on the Planning Committee. J. Thomas Bigger, Jr., M.D., served as chairman of the Planning Committee. The Committee was reconstituted into the Steering Committee once the Protocol had been developed.

Subcommittees of the Planning Committee were:

a. Baseline Data and Eligibility: This subcommittee defined patient eligibility exclusion criteria and proposed stratification factors. It suggested baseline data, screening procedures and logs.

b. Drug Selection and Titration: This subcommittee reviewed the potential treatments and treatment strategies and made recommendations to the planning committee.

c. Endpoints and Followup: This subcommittee developed the instrument for defining arrhythmia-related death and protocols for patient management for events that may occur during followup. These, as well as proposed followup data, were presented to the planning committee.

d. Publications, Presentation and Ancillary Studies: This subcommittee prepared guidelines and procedures for the preparation of publications or presentations and for the inclusion of ancillary studies. They also screened studies proposed during the planning phase and recommended disposition as to appropriateness and funding.

e. Quality Control/Holter: This subcommittee recommended procedures for quality control of Holters, ejection fraction and compliance measures.

3. Steering Committee

Subsequent to the Planning Phase, the Steering Committee provides scientific direction for the study at the operational level. It consists of representatives from the Clinical Centers, Coordinating Center, Drug Distribution Center, and the NHLBI Project Office. Although more than one person from a center may attend meetings, each center has only one vote.

The Chairman and Vice-Chairmen of the Steering Committee are appointed by the NHLBI Project Office for the duration of CAST.

Specific functions of the Steering Committee are:

a. To review the performance of the Clinical and other centers with regard to quality control, patient recruitment, compliance, forms completion, report generation, and special procedures.

b. To advise and assist the Coordinating Center and Drug Distribution Center on operational matters.

c. To review and approve ancillary studies.

d. To implement the study publication data.

e. To make changes in the study Protocol. Major changes must be approved by the Data and Safety Monitoring Board and the NHLBI.

f. To report major problems to the Data and Safety Monitoring Board.

The Steering Committee meets semi-annually. Additional meetings may be called by the Executive Committee if necessary.

4. Subcommittees

To help the Steering Committee accomplish the task of running CAST, several subcommittees will be appointed. Their duties are listed below. (Additional subcommittees may be formed as needed and ad hoc subcommittees will also be used for short term work.) Subcommittees will consist of appropriate and interested investigators and coordinators.

a. The Publication, Presentation and Ancillary Studies Subcommittee:

The Publication, Presentation and Ancillary Studies Subcommittee shall serve as a review body for CAST manuscripts and papers, as well as for slides and scripts for presentation.

In addition, the subcommittee reviews proposed studies of the CAST Clinics to see that they do not interfere with the operation of the CAST Protocol. (Specific information is given in the section on ancillary studies). The subcommittee also reviews ancillary study manuscripts to determine how they relate to CAST and to ensure that they do not threaten the integrity of the study presentations.

b. Quality Control Subcommittee:

This subcommittee will work on quality control efforts associated with the Holters, ejection fraction measures and data quality. The subcommittee will help to solve operational problems relating to Holters and EF measurements as they occur.

c. Events Subcommittee:

The Events Subcommittee will consist of members blinded to the therapeutic assignment. They will review the classification of deaths and selected nonfatal events within CAST. Other intermediate potential endpoints as decided upon by the Steering Committee, Data and Safety Monitoring Board and the Events Subcommittee will be reviewed.

d. Recruitment/Compliance Subcommittee:

The recruitment subcommittee will assist the Coordinating Center in developing recruitment monitoring tools and will develop methods and materials to aid in recruiting.

5. Executive Committee

An Executive Committee, consisting of the Chairman and Vice-Chairmen of the Steering Committee, the Director of the Coordinating Center, and the NHLBI Project Officer, will be established. Functions of this Committee are:

a. In cases where decisions are required between Steering Committee meetings, to make such decisions and report them to the Steering Committee. If the issues are of major importance, a mail or phone vote or a special meeting of the Steering Committee will be held.

b. To recommend to the Steering Committee actions and policies for consideration.

c. To prepare the agenda for the Steering Committee.

d. To serve as ex-officio members of all other committees.

4. PATIENT ELIGIBILITY AND EXCLUSION CRITERIA

A. General Study Population

The general study population is limited to survivors of myocardial infarction, with specific entry eligibility criteria as follows:

1. Myocardial infarction inclusion criteria as detailed in Appendix 2; briefly, ECG with enzyme or symptom evidence, enzymes with symptom evidence, or serial ECG evidence.

   Use of thrombolytic agents and/or percutaneous transluminal angioplasty do not disqualify an eligible patient.

2. MI entry window.

   The entry Holter must be performed 6 or more days and less than 2 years after the MI. Before 6 days, the arrhythmia may be unstable and the prognostic importance is uncertain. Patients qualifying within 90 days of the MI must have left ventricular ejection fraction ≤ 0.55 obtained $\geq$ 24 hours post MI. Patients who qualify $\geq$ 90 days (and hence have survived the highest risk period) must have LVEF ≤ 0.40. (Patients who qualify $\geq$ 90 days with LVEF ≥ 0.30 but ≤ 0.40 must have their LVEF measured $<$ 90 days prior to qualifying).

3. Patient off antiarrhythmic therapy.

   Previous antiarrhythmic therapy does not eliminate a patient. However, a potential participant must qualify while off any antiarrhythmic therapy, other than beta blocking, calcium channel blocking, or digitalis therapy, for a time sufficient for the elimination of the specific drug in question. The half-lives are listed in Appendix 3. In no case should this be earlier than 48 hours after discontinuance of the antiarrhythmic drug.

   Enrollment at the earliest time possible after the MI is strongly encouraged; however, for patients on beta blockers, the qualifying Holter should not be performed until the patient is on a constant dose of beta blocker therapy.

4. Arrhythmia at entry (evaluated locally).

   The qualifying Holter must demonstrate an average of 6 or more VPD's per hour, for a minimum of 18 analyzable hours of a 24 hour Holter. As long as the minimum of 18 analyzable hours is available, all analyzable data must be used in this evaluation. If the original screening Holter fails to meet entry criteria, the patient can have one subsequent Holter assessment within the entry window to meet entry standards. However, failure to qualify on 2 recordings excludes the patient from further consideration for that MI.

5. MI in combination with surgery.

Patients with myocardial infarction after CABG shall not be eligible unless the MI occurs 5 or more days post-operative. Patients with "early" CABG following myocardial infarction shall be eligible for enrollment from 6 days after surgery until 2 years after the infarction. Patients with an MI within 48 hours of non-cardiac surgery are eligible for randomization but must meet specific ECG criteria outlined in Appendix 2.

B. Exclusion Criteria

The presence of any of the following conditions noted during screening excludes the patient from further consideration at that time. For conditions that might be temporary, rescreening at a later time is allowed.

History and Clinical Exclusions

1. * Age > 79 years at the time of qualifying Holter.
2. * Not a CAST MI.
3. * Woman with childbearing potential.
4. Less than 6 days or 2 or more years from the qualifying MI to the time of qualifying Holter.
5. * Known non-atherosclerotic cause of myocardial infarction.
6. * Current New York Heart Association Class IV congestive heart failure.
7. * Current Canadian Cardiovascular Class IV angina.
8. Ejection fraction > 0.55 if patient qualifies for CAST within 90 days of MI, or ejection fraction > 0.40 if patient qualifies for CAST between 90 days and 2 years from date of qualifying MI.
9. * Clinically significant preexisting nonischemic cardiac condition which is symptomatic or requires treatment (e.g., significant valvular disease, idiopathic or alcoholic cardiomyopathy).
10. * Any significant malignancy or other life-threatening disease (other than CHD) that is likely to be fatal within a 2 year period.
11. Persistent systolic blood pressure $\geq$ 180 mmHg and/or diastolic blood pressure $\geq$ 120 mmHg (on treatment).
12. Persistent systolic blood pressure < 80 mmHg (off treatment).
13. Creatinine $\geq$ 2.5 mg %.
14. * Hypokalemia (K^+ < 3.5 mEq/L) at the time of qualifying Holter.
15. * Digitalis toxicity.
16. Presence of automatic implantable cardioverter/defibrillator or antitachycardia pacemaker.
17. Symptomatic (hemodynamically important) unsustained VT or VT $\geq$ 15 consecutive complexes at a rate $\geq$ 120 beats per minute (disqualifying VT) noted $\geq$ 6 days after the onset of the myocardial infarction (noted on ECG or monitor, including when noted on a graded exercise test).
18. VF noted $\geq$ 6 days after the onset of the myocardial infarction (noted on ECG or monitor, including when noted on a graded exercise test).

ECG Criteria

19. QRS $\geq$ 0.18 seconds noted $\geq$ 6 days after the onset of MI.
20. * WPW syndrome.
21. * Congenital long QT syndrome.
22. Prolonged pause of $\geq$ 2.5 seconds noted $\geq$ 6 days after the onset of MI.
23. Mobitz II 2nd degree, advanced or 3rd degree AV block noted $\geq$ 6 days after the onset of MI.
24. Symptomatic sinus node dysfunction.
25. Heart rate < 30 beats per minute for a period lasting at least one minute noted $\geq$ 6 days after the onset of MI.

Drug Therapy

26. Previous serious adverse effect from drug(s) used in CAST.
27. On concurrent antiarrhythmic drug therapy, excluding digitalis, beta blockers, and calcium channel blockers.
28. Any intravenous or oral amiodarone within the last 2 weeks.
29. Any oral amiodarone within the last 6 months.
30. Intravenous amiodarone for $\geq$ 48 hours within last 6 months.

Holter Findings

31. Symptomatic (hemodynamically important) unsustained VT or VT $\geq$ 15 consecutive complexes at a rate $\geq$ 120 beats per minute (disqualifying VT) noted $\geq$ 6 days after the onset of the myocardial infarction (noted on Holter).
32. Insufficient arrhythmia (< 6 VPD's/hr) on both screening Holters.

Miscellaneous

33. Psychologically or physically unfit to participate in the study.
34. Patient is geographically inaccessible.
35. Interpretation of Holter technically difficult.
36. Patient enrolled in a competing interventional trial, e.g., undergoing blinded therapy. Participation in followup after intervention is completed (e.g. thrombolytic trials) may be permissible and will be decided by the Executive Committee on a study by study basis.

C. Recruitment/Screening

Screening Log

Centers will be required to maintain a screening log for all patients identified who are age and CAST MI eligible patients. This log will include minimal information: name, age, sex, date of CAST MI, and principal reason for exclusion when applicable. Data entry will include a log number but not the name.

Holter Registry

A registry will be maintained for all consenting patients who are medically eligible, i.e., are not excluded by any of the *'d exclusions. Patient identifying information, consisting of name, date of birth, social security or other identifying number, and sex will be obtained together with the Holter findings and EF if available (see Appendix 4).

D. Stratification for Randomization

Stratification for randomization will be done on the following variables:

1. Clinical center

2. Left ventricular ejection fraction.
   a) ≥ 0.30
   b) < 0.30

3. Time of qualifying Holter from qualifying MI.
   a) < 90 days
   b) ≥ 90 days

5. DRUGS: ENCAINIDE, FLECAINIDE AND MORICIZINE

A. Rationale for Selection of Drugs for CAST.

Preliminary sample size considerations undertaken for CAST in 1982 indicated that a CAST drug would need to suppress ectopy in approximately 80% of the patients enrolled with minimal adverse effects. At that time, no drugs could be identified with adequate exposure to demonstrate these properties. For that reason the pilot study (CAPS) was undertaken and four drugs, encainide, flecainide, imipramine and moricizine were evaluated against placebo. The pilot demonstrated that two of the drugs, encainide and flecainide, met the above criteria and that a third drug, moricizine, while falling somewhat short in terms of percent of patients suppressed, appeared to provide reasonable suppression as a second line drug and with almost no adverse effects. These three drugs, together with most other antiarrhythmics expected to be available within several years, were evaluated for CAST on several parameters. These included total exposure, exposure to patients similar to those to be entered into CAST, reported suppression levels, reported adverse effects levels, proarrhythmia rates, suitability for CAST in terms of titration, and compliance.

B. Drugs Selected.

Preliminary review reduced the number of drugs considered to the following:

A quinidine/mexilitine combination, pirmenol, propafanone, indecainide, cibenzoline, encainide, flecainide, moricizine, amiodarone and quinidine. Review of available literature was undertaken for each of these drugs and presented to the Drug Selection Subcommittee. A summary of the drugs excluded is given in appendix 5. The drugs selected for initial inclusion in CAST were encainide, flecainide and moricizine.

1. Encainide

In CAPS, encainide achieved 70% suppression of VPD's and 90% suppression of VT in 79% of patients when used as a first drug. Moreover, encainide maintained an average reduction of 70% throughout the year in 75% of patients. Adverse effects reported on encainide were fewer than those reported on placebo.

2. Flecainide

Flecainide was very similar to encainide in the response rates achieved in CAPS. If anything, suppression was slightly better, 83% initially and maintained in 73%. There were however, more episodes of new or worsened CHF and more episodes of disqualifying VT reported for patients on flecainide than for patients on encainide. These differences, while only marginally significant, were in agreement with other reported data. For this reason flecainide was selected for CAST use only for patients with ejection fraction ≥ 0.30.

3. Moricizine

While moricizine's initial suppression rate of 66% in CAPS was less than those achieved by encainide and flecainide, the suppression rates in patients with lower ejection fractions were approximately equivalent for patients on moricizine and encainide. Moreover, although the numbers were small, moricizine appeared to be moderately effective as a second drug in suppressing patients who had failed to be suppressed by flecainide or encainide. These observations, together with a very low recorded profile of adverse effects, made moricizine appear desirable as a second or third drug in the titration process for patients with high ejection fraction and as a first drug for patients with low ejection fraction.

4. Placebo

It was thought to be critical that CAST be placebo controlled. The foremost reason is the fact that no published or unpublished studies known to the investigators have demonstrated a beneficial effect on survival for the use of antiarrhythmic medications in these patients. In particular, the results from CAPS showed no trend for improved survival in patients on the antiarrhythmic medications compared to placebo. It is even possible that drug therapy, while having adverse effects, being costly and inconvenient, may even increase the risk of fatal arrhythmias. Another major reason for a placebo is the fact that the advent of acute therapy (such as thrombolysis and PTCA) may be altering the natural history post myocardial infarction, so that it remains important to characterize the patients who are being treated and their natural course without treatment.

C. Antiarrhythmic Drug Dosing in CAST

Only two doses of each drug will be permitted. These doses will be the low and medium dose levels used in CAPS. In CAPS, most of the patients who were suppressed were suppressed at the low dose, and the high dose was rarely required for suppression.

DRUG DOSING FOR CAST

DRUG	LOW DOSE	MEDIUM DOSE
ENCAINIDE	35mg TID	50mg TID
FLECAINIDE	100mg BID	150mg BID
MORICIZINE	200mg TID	250mg TID

D. Elimination of or Addition to CAST Drugs.

It was the clear intention of the planning committee that CAST should be a trial of the effect of suppression on the primary and secondary endpoints and not a trial of one or even two antiarrhythmic agents. Additional information about other antiarrhythmics could (with Steering Committee, Data and Safety Monitoring Board and NHLBI concurrence) lead to inclusion of another drug into the titration scheme. This inclusion could be in addition to or as a replacement for any of the three drugs initially selected.

6. INTERVENTION

A. Informed Consent

Prior to any intervention required for CAST that is not part of usual care required for the patient, appropriate informed consent will be obtained. The informed consent must have prior Institutional Review Board approval.

B. Enrollment

It is the intention of the study that there should not be interventions which affect arrhythmia, other than the study drugs, between the qualifying Holter and the end of the study. It is required that there be no non-study interventions planned or being considered which might affect arrhythmia between the qualifying Holter and completion of the study drug titration.

Since it is expected that 2 to 5 days, excluding weekends, will elapse between the qualifying Holter and the beginning of study therapy, and since titration will require between about 10 - 60 days (see below), a patient should not be screened unless it seems likely that there will be no inappropriate interventions for at least 30 days.

If a patient's situation meets the conditions listed above, the investigator will obtain an informed consent for the purpose of administering the screening Holter (unless part of standard care) and for inclusion of the patient identifying information into the Holter registry. (The latter may be delayed for patients who qualify for CAST until after they have been approached for participation in CAST).

If the qualifying Holter meets the CAST enrollment criteria as read locally, then informed consent will be obtained for the titration and randomized phases of the study. All qualifying Holter tapes must be kept at the center for the duration of the study.

A radionuclide ventriculographic, angiographic or M-mode or 2D echocardiographic ejection fraction must be obtained prior to randomization at least 24 hours post MI. A separate consent form may be necessary for this procedure. Suggested timing of these tests is given in Table 6.1. Titration must be completed and blinded therapy instituted within 90 days of the qualifying Holter.

Table 6.1 Recommended Timing of Tests

Qualifying Holter	Day 0	Must be (≥Day 6 and < 2 years from MI)
Scanning of Qualifying Holter for Eligibility	Day 1	
Global Ejection Fraction (if not already available)	Day 1 or 2	(≥Day 1 from MI)
Informed Consent and Baseline data collection	Day 1 to 3	(≥Day 6 from MI)
Assignment to titration sequence	Day 2 to 4	(≥Day 6 from MI)
Start of Titration	Day 3 to 64	(≥Day 6 from MI)
Blinded Therapy	Day 8 to 89	(<Day 90 from Day of qualifying Holter)

Assignment to titration sequence will be by telephone call to the Coordinating Center, during which acknowledgment of informed consent, dates of the various tests and test results needed to qualify and stratify will be required.

Between the informed consent for titration and beginning titration, collection of the baseline data must be completed. To assure completion of titration within 90 days of the qualifying Holter it will usually be necessary to start titration within 2 to 3 weeks.

C. Titration Schedule

Titration will be completed within 90 days of the day when the qualifying Holter was obtained. In order to achieve blood level plateaus a minimum of four half-lives must elapse between initiation of a particular drug and dose and evaluation of that drug and dose. There must be a minimum of two days washout between drugs. Based on the experience in CAPS, it is anticipated that 50% of the patients will achieve suppression on the low dose of the first drug.

However, perhaps 10 to 15% of the patients will be evaluated at every dose of each drug. Thus, assiduous attention to titration will be necessary to assure timely completion.

For convenience of scheduling, it is recommended that remonitoring should be scheduled on or after day 4 but no later than day 10. Evaluation should be completed in the next 1 to 2 days. Thus, a complete cycle could require as few as 5 days or as many as 12 days.

D. Drug Sequences

The drug sequences are shown below. All sequences for which a patient is eligible will have equal probability of being assigned. Titration must proceed in the sequence shown.

Titration Sequences

EF $\geq$ 0.30

A low -> A high -> B low -> B high -> C low -> C high
C low -> C high -> B low -> B high -> A low -> A high

where, at least initially, A = encainide, B = moricizine and C = flecainide.

EF < 0.30

D low -> D high -> E low -> E high
E low -> E high -> D low -> D high

where, at least initially, D = encainide and E = moricizine.

E. Criteria for Suppression

Suppression will be defined as $\geq$ 80% reduction in VPD's/hr and $\geq$ 90% reduction in runs/hr as compared to baseline (minimum of 18 analyzable hours) and without the presence of intolerable adverse effects (defined below).

F. Criteria for Selecting Drug and Dose.

A Holter is required at each drug and each dose evaluation unless adverse effects are noted, including an ECG exclusion noted on an arrhythmia monitor. ECG intervals throughout dosing will be measured and documented via a Holter rhythm strip. Submission of Holter data is required to document suppression as defined above or at least minimal suppression on the best drug and dose when 80% suppression is not obtained. When a Holter is obtained that does document suppression, as defined above, titration is to cease at that point, and the drug and dose the patient is suppressed on will be the designated drug and dose for that patient. The Holter tape documenting suppression or best drug and dose (in addition to the qualifying Holter) must be kept at the center until the end of the study.

G. Conditions Requiring Specific Actions during Titration.

1. Conditions requiring permanent cessation of titration. (This patient would not be randomized to blinded therapy and would not be followed as a patient in the main CAST study.)

   a. The appearance of any entry exclusion criteria proven by washout not to be due to drug toxicity with the exceptions explained and described below:

      Certain of the exclusion criteria were included because they were thought to yield a high probability that with the addition of active CAST therapy a safety concern would emerge. However, once a patient has agreed to participate and even entered titration there is no reason to exclude the patient unless the limit for concern is achieved. For this reason criteria 19, 21, and 22 are modified to:

      QRS $\geq$ 0.20 seconds

      QTc $\geq$ 0.6

      Any pause of $\geq$ 3.5 seconds

   b. Resuscitated cardiac arrest when not clearly attributable to the drug.

2. Events requiring interruption of titration

   Events such as open heart surgery, angioplasty, valve replacement, recurrent myocardial infarction, non-cardiac surgery and aneurysmectomy will require interruption of titration.

   If, in the judgment of the investigator, the patient's VPD rates and EF are not significantly altered, the titration may be resumed, where discontinued, at least one week following the event.

   If the investigator judges it prudent to obtain new baseline Holter and LVEF, the patient can restart titration. However, any drug for which an adverse effect not alterable by the event had already been demonstrated will be eliminated during the retitration, as will flecainide if the latest LVEF is < 0.30.

   Digitalis, beta blockers, beta agonists, phenothiazines, tricyclic antidepressants, theophylline derivatives, calcium channel blockers, and anticonvulsants might have some effect upon the incidence of ventricular arrhythmias, but the effect is not likely to be a major one. Every effort should be made to maintain constant therapy during titration but changes in the above drugs will not require special procedures or changes in the titration process.

3. Conditions Shown to Be Due to the Drug Requiring Proceeding to the Next Drug in the Sequence.

a. Arrhythmias producing symptoms. Only serious symptoms such as syncope or presyncope should be considered under this criterion. Palpitations alone would not be regarded as a toxic endpoint.

b. Sustained ventricular arrhythmias, torsades de pointes or a run of $\geq$ 15 consecutive VPD's at a rate of $\geq$ 120/min.

c. Any significant increase in the VPD rate or any significant increase in runs. A significant increase in VPD's includes proarrhythmia, $\geq$ 1500 VPD's/hr, or other significant increase.

For those patients showing $\geq$ 5 runs/day on the baseline Holter, a ten-fold increase will be considered a toxic endpoint. For patients with fewer than 5 runs/day on baseline, 50 or more runs will be considered toxicity.

d. Prolongation of the QTc interval $\geq$ 1.4 times baseline and/or $\geq$ 0.6 sec. The rationale for this criterion is based upon the observation that patients showing marked lengthening of the QTc interval in response to antiarrhythmic agents (usually type I agents) seem to be at increased risk of syncope or sudden death.

e. Development of the following abnormalities in impulse formation or conduction:

-heart rate < 30 for a period lasting a minimum of 1 minute.

-any pause $\geq$ 3.5 seconds.

-second degree Mobitz type II A-V block.

-advanced or third degree A-V block.

-QRS width $\geq$ 2 times baseline or $\geq$ 0.20 sec.

f. Resuscitated cardiac arrest. The patient may proceed to the next CAST drug in the sequence if evidence suggests that the episode is almost certainly due to the drug. However, the investigator can choose to end titration if he does not want to continue through the CAST drug sequence.

g. Development of new or worsened CHF symptoms which are not controlled by therapy for the CHF and which after washout (of sufficient duration for the drug to be eliminated and the physiology to return to normal) are judged by the investigator to be due to the drug.

h. Intolerable adverse symptoms.

i. Investigator concern about safety based on evaluation on dose 1. (Note however, titration does not permit return to a previous drug in the sequence.)

H. Washout Procedure

Washout during titration to verify possible toxic adverse effects or proarrhythmia is to be a minimum of 4 half-lives. Verification is optional; however, return to a previous drug in the sequence is not permitted during titration.

I. Initiation of Blinded Therapy

Patients whose ectopy was successfully suppressed during titration will be randomly assigned to the successful therapy or to matching placebo. Therapy will be instituted immediately in an outpatient setting.

Patients whose ectopy was not successfully suppressed will not be eligible for the main study, but will be randomized to the best CAST therapy or a matching placebo and followed in the same manner as the main study patients. The best CAST therapy will be defined as that which is tolerated and is most effective.

7. RANDOMIZATION

A. Methods

Titration sequencing will be accomplished by telephone communication with the Coordinating Center. At the time of the call, the center calling will be required to provide data needed for stratification, assurance that no exclusionary criteria are present and that the informed consent was signed, and the patient identification number. The center will be provided with a titration sequence. The telephone communication will be made in one of two ways.

1. On working days, between the hours of 7:00 am and 5:00 pm Pacific Time, a call must be placed to a person at the Coordinating Center.

2. At other times, the communication will be by terminal access with the Coordinating Center computer. In this case, the computer will collect the data and assign the therapy sequence. On the first working day following the computer call, the Coordinating Center will review the data.

A second call will be required to complete the randomization process, after the titration sequence has been completed. The blinded therapy assignment that the patient will be followed on for the duration of the study will be given to the center at that time.

B. Titration Sequence

At the time of the initial call the titration sequence will be assigned. The titration sequence list will have been established previously, using blocking factor(s) known only to the Coordinating Center and based on the primary stratification factors of clinical center, ejection fraction and time from MI. These lists will be generated so that each titration sequence will have equal opportunity of exposure. Should drugs be eliminated or added following study start up, the lists will be regenerated to maintain this rationale.

C. Blinded Therapy

Following titration, blinded therapy will be assigned at the completion of a second randomization call to the Coordinating Center.

At the time of this call the Coordinating Center will do the following:

For main study patients:

Require the baseline VPD and run rates and the evaluation VPD and run rates, in order to check the computation showing suppression, as well as the drug and dose of successful therapy. Assign therapy taken from pregenerated lists based on blocking factor(s) known only to the Coordinating Center and based on the stratifying factors of clinical center, ejection fraction and time from MI, as well as on the successful therapy.

For unsuppressed patients:

Require the baseline and evaluation VPD and run rates and the best CAST therapy, that which is most effective among those which are tolerated and which do not increase the VPD rate. Assign active or placebo therapy attempting to achieve balance by clinical center, ejection fraction, time from MI and best CAST therapy.

In both cases the Coordinating Center will then assign temporary medication bottle numbers, a supply of which will be kept at the center, and will immediately provide the Drug Distribution Center with the patient I.D. and therapy so that long term drug supplies can be distributed.

8. DATA COLLECTION

A. Age-CAST MI Eligible Screening Log

The data to be collected on all patients screened and found to be $\leq$ 79 years of age and with a CAST MI are: name, date of contact, age, sex, and principal exclusion if ineligible or the reason for not entering titration when medically eligible and not randomized.

B. Holter Registry

Additional data collected for all patients who are medically eligible (possess none of the *'d exclusion criteria), undergo a Holter and give informed consent will be social security number, date of birth, date of MI, date of Holter, Holter findings (number of VPD's per hour, number of runs of VT per hour, length of the longest run, the maximum VT rate), LVEF (if available), and patient reported risk factors (prior MI, prior CHF, diabetes, smoker).

Patients who are eligible on the basis of Holter findings need not be contacted for the Holter Registry until after they have been approached for participation in the randomized trial.

C. CAST Patients

All eligible patients consenting to titration will have a sequential identification number assigned. These numbers will be assigned at the center from lists of preprinted study labels provided by the Coordinating Center and will include a check digit to eliminate data entry error on the critical identification number. The center will assign an acrostic of 4 letters to this I.D. to assist in communication at the center (perhaps the 1st letter of the first name and the 1st 3 letters of the last name).

Baseline data (see below) and titration data (see below) will be collected on all CAST patients. Followup data will be collected on all CAST patients who are randomized to blinded therapy.

This section describes the data to be collected from the CAST patients.

Entry Measure

1. 24 hour Holter
   Patients will be enrolled into the study on the basis of analysis of a single 24 hour Holter. This Holter will serve both to qualify the patient and for the baseline rates against which to measure drug efficacy during the titration phase. Titration must be completed within 90 days of the qualifying Holter. If a patient fails to

qualify on the first 24 hour Holter, a second Holter may be performed within the entry window. Failure to qualify on two screening Holters excludes the patient from further consideration for the study for that MI. A rhythm strip for interval measurements is to be made for each Holter and retained in the patient files. The qualifying and suppression Holter tapes must be retained indefinitely.

Baseline Measures

1. Measure of LV function
   A baseline measurement of left ventricular ejection fraction will be required prior to randomization. This measurement must be obtained $\geq$ 24 hours after the qualifying MI and within 90 days of the qualifying Holter (the 90 day rule is removed if the EF is < 0.30). The ejection fraction may be determined by:
   a. Radionuclide ventriculography
   b. Left ventricular contrast angiography
   c. Digital subtraction angiography
   d. M-mode or 2D echocardiography

2. Blood Measures
   a. Total cholesterol should be recorded on admission (if available) and obtained at the 4 month visit (optional)

3. 12-lead electrocardiogram
   (obtained $\geq$ 3 days after qualifying MI and within 6 months of titration)

4. Battery of Baseline Forms

Dose Titration Measures

1. 24 hour Holter

   a. A 24 hour Holter should be obtained 4-10 (2-10 days for moricizine) days after the initiation of each drug and dose if the patient is free of intolerable adverse effects, including ECG effects noted on monitor or otherwise.
   b. A measurement of ECG intervals must be obtained for each drug and dose used.

Followup Measures

1. Routine Followup Visits are scheduled every 4 months.

   a. Data to be collected at every visit include:
      1. List of Medications
      2. Adverse Symptoms
      3. CAST Medication use

b. Additional data to be collected at 4 months and then annually include:

1. 12-lead ECG
2. Quality of Life form

2. Events - Certain events (presyncope, syncope, symptomatic unsustained or sustained ($\geq$ 15 beats at $\geq$ 120 bpm) ventricular tachycardia, aborted death, adverse ECG effects including heart block, suspected proarrhythmia, worsened CHF, recurrent MI, angioplasty and cardiac surgery) will require specific data and may require additional followup and testing, e.g., 24 hour Holters and temporary or permanent discontinuation of CAST drug. These are referred to in detail in Section 9.

3. Suppression Holter - One or two Holters to measure continuing suppression and natural change in rates and variation over time will be collected on a subset of patients at a selected followup chosen to maximize the information obtained. These will not be read locally and will be sent to the Coordinating Center.

CAST Testing Schedule

				POLLOWUP																
	ENTRY	BASE-LINE	TITRATION	4 mo	8 mo	1 Yr	4 mo	8 mo	2 Yr	4 mo	8 mo	3 Yr	4 mo	8 mo	4 Yr	4 mo	8 mo	5 Yr
EVALUATION (meds, compliance, adverse effects)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QUALITY OF LIFE		X		X		X			X			X			X			X
ECG		X		X		X			X			X			X			X
RHYTHM STRIP			X*															
HOLTER	X		X**	X***														
EJEC FRAC	X																	

Entry - to qualify for CAST
* Can be taken from Holter
** If adverse effects are not otherwise present
*** At this or some other followup in a subset of patients

9. PROTOCOL FOR SPECIFIC EVENTS DURING FOLLOWUP

Regular followups are scheduled every 4 months. The Coordinating Center will notify the Clinical Centers when followups are due. In addition, the Coordinating Center will monitor incoming data to determine when scheduled followups appear to have been missed. The patient may miss a followup for a number of reasons. For example, the patient may refuse to be followed, the patient may be alive but inaccessible, or the patient may simply be lost to followup. When any of these situations occur, the Clinic must complete the appropriate forms and send notification to the Coordinating Center in writing. It is the Clinical Center's responsibility to make every effort to schedule followups as close to the scheduled appointment time as possible. A window of two weeks is allowed on either side of the scheduled time. However, a delay of much more than one week may cause problems with the patient's drug supply.

If a patient is hospitalized after entry into the study, the Hospitalization form must be completed when the patient is discharged, as well as other relevant and appropriate forms as noted below.

If a patient refuses to continue participation in CAST, the Withdrawal form must be completed.

If the patient is permanently withdrawn from CAST therapy, but continues followup, the Individualized Therapy form must be completed.

The patient and physician will remain blinded throughout the course of the study. The clinic should make every effort to apply uniformity of treatment to all patients as well as to maintain the blinding. The investigators should not try to unblind by measuring serum drug levels or comparing ECG intervals.

The following four criteria are the only acceptable criteria for withdrawal from CAST medication:

1. If the patient insists.
2. If the patient's private physician insists.
3. If the CAST study physicians feel that it is in the best interest of the patient.
4. If required specifically by the protocol.

Most often, cessation of study drug and institution of appropriate therapy can be accomplished without unblinding. If optimal medical treatment requires knowledge of the drug, the Clinical Center should have a physician break the blind who has not been involved in the treatment of the patient as a CAST physician. Every effort should then be made to keep all other individuals from knowing the nature of the study drug.

During followup, temporary or permanent suspension of study medication will be allowed for certain procedures and events. In the absence of contraindications, the drugs will then be restarted. The specifics for each of the events are noted below.

The specific events which would require permanent withdrawal of the study drug for institution of treatment with other antiarrhythmic agents during followup include 1) resuscitated cardiac arrest or ventricular fibrillation, 2) sustained (symptomatic or asymptomatic) ventricular tachycardia ($\geq$ 15 complexes at $\geq$ 120 beats per minute), and 3) symptomatic (hemodynamically important) unsustained ventricular tachycardia.

1. Resuscitated cardiac arrest or ventricular fibrillation.
   The Death or Cardiac Arrest form must first be completed. Only, if it is absolutely necessary, should the drug code be broken, and in no case should it be broken before the form is completed. Such patients may be appropriate for an ancillary study; no additional study followups need be scheduled and no further CAST data should be collected.

2. Disqualifying (symptomatic or asymptomatic) ventricular tachycardia ($\geq$ 15 complexes at $\geq$ 120 beats/min.)
   The VT form must be completed. Only if it is absolutely necessary (i.e., if required by the private physician or CAST physician) should the drug code be broken, and in no case before the form is completed. The patient will proceed to individualized therapy or a substudy as appropriate. Followup will be completed per schedule.

3. Symptomatic (hemodynamically important) unsustained ventricular tachycardia.
   Such symptoms include a) syncope; b) one of the following when probably caused by arrhythmia-related hypoperfusion: presyncope, lightheadedness, dizziness, weakness or diaphoresis; c) one of the following when probably caused by arrhythmia-related hypoperfusion of the heart: shortness of breath or chest pain. Those arrhythmias which only manifest themselves by palpitations are <u>not</u> included. The patient will proceed to individualized therapy or a substudy. If the physician demands, the code may be broken to assist in individualized therapy decisions, but if so the VT form should be completed first. The patient will be followed per protocol.

Temporary discontinuation of the study drug or conversion to the alternate drugs will be allowed (but is not necessarily required for all conditions) for 4) development of heart block (Mobitz II or complete), 5) development of adverse ECG effects as defined for titration, 6) coronary artery bypass graft surgery and/or other cardiac surgery or non-cardiac surgery, 7) congestive heart failure, 8) apparent proarrhythmia, 9) recurrent myocardial infarction, 10) miscellaneous late adverse effects.

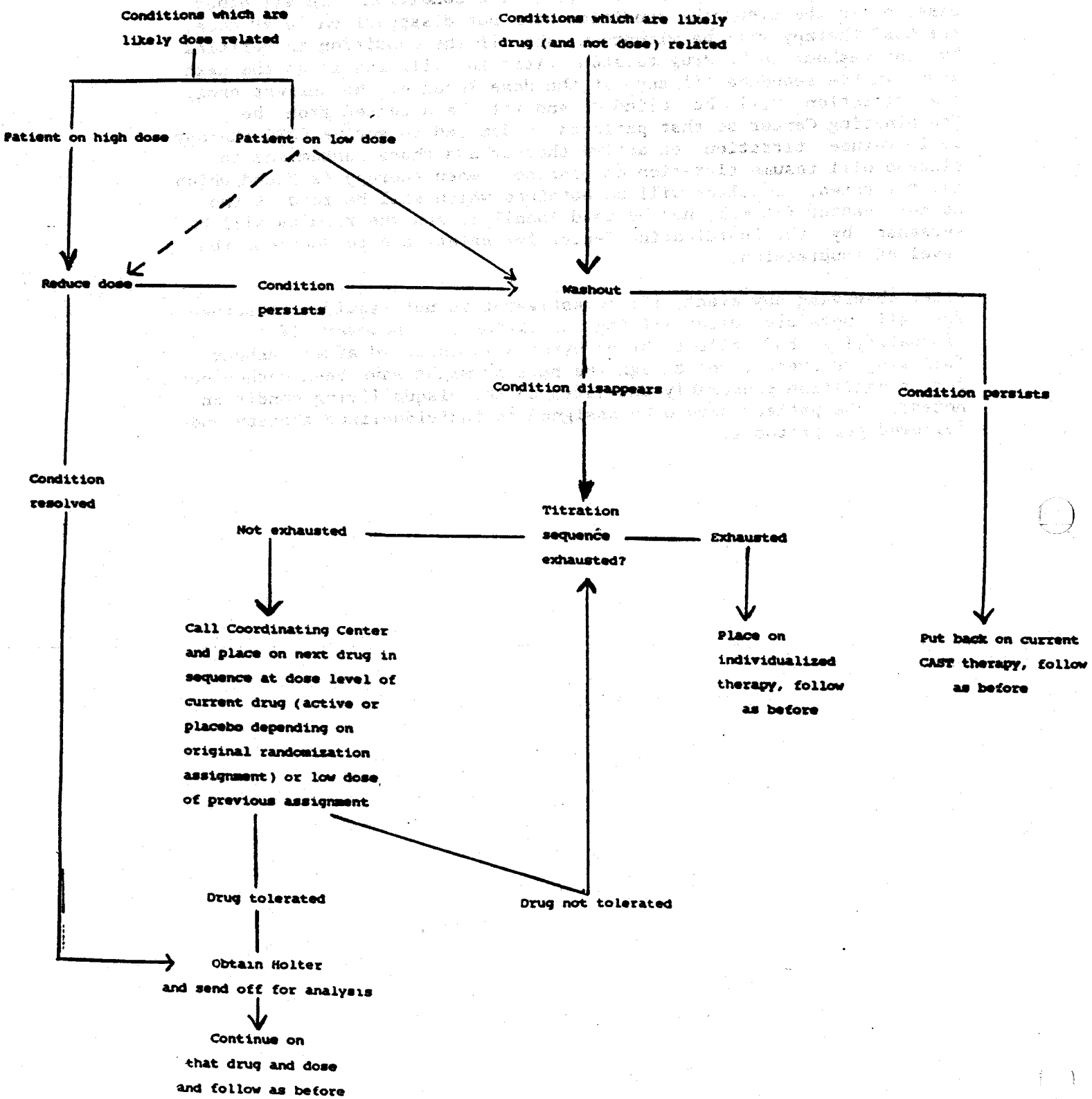
For events or conditions in which only temporary discontinuation is needed (4, 6, 9 below and generally in all conditions where washout does not verify the condition), the patient is to be restarted on discontinued CAST therapy as soon as adequately stabilized.

For conditions which are considered likely to be dose related (4, 5, 10 below), and if the patient is on high dose, the investigator will reduce the dose to attempt to resolve the condition. In all other cases or in the event the condition does not disappear on lower dose, the CAST therapy will be withdrawn, and, if the condition is verified by the washout to be drug related, titration will resume on the next drug in the sequence (if any) at the dose level of the current drug. The titration will be blinded and will be directed from the Coordinating Center so that patients randomized to active CAST therapy will resume titration on active therapy and those randomized to placebo will resume titration on placebo. When therapy is found which is tolerated, a Holter will be obtained which will be read at the Holter center (it will not be read locally), and the results will be screened by the Coordinating Center for safety and to document the level of suppression.

After observing any event, the investigator is not required to screen for all possible disqualifying conditions. However, if a disqualifying ECG effect or arrhythmia is observed after washout following an event (even though the patient might have been washed out for a condition presumably unrelated to the disqualifying condition noted), the patient should be assigned to individualized therapy and followed per protocol.

Figure 1

Retitration Schedule



4. Heart block (Mobitz II advanced or complete).
The drug will be stopped and washed out for a minimum of 4 half-lives of the drug. If block persists and a pacemaker is implanted, CAST drugs should be restarted. Otherwise, the patient will resume titration (see figure 1). If on the high dose, titration will resume by first trying the low dose.

5. Adverse ECG effects.
It is possible that changes on electrocardiogram (besides bradycardia or heart block) could occur which would prompt a reassessment of drug therapy, for example, QT prolongation or QRS prolongation. If the patient develops an intraventricular conduction defect with the QRS duration $\geq$ 2 times baseline or $\geq$ 0.20 seconds, or if the QTc interval is $\geq$ 1.4 times pretreatment or is $\geq$ 0.6, which is verified by washout, alteration in drug or dose will be required. The rationale for these criteria is based upon the observation that patients showing marked lengthening of the QTc interval in response to antiarrhythmic agents seem to be at increased risk of sudden death. Development of the following abnormalities in impulse formation or conduction would also be considered adverse ECG effects, although their detection will be sporadic because of the infrequency of the Holter monitoring and followup: heart rate < 30 for a period lasting at least 1 minute or any pause $\geq$ 3.5 seconds. For all of the above, when verified by washout, the investigator will resume titration if possible (see figure 1). If on the high dose, titration will resume by first trying the low dose.

6. Coronary artery bypass graft surgery and/or other cardiac surgery or non-cardiac surgery.
The CAST therapy will be stopped only for as long as the patient is unable to take medication orally. No other tests are necessary. The patient will be maintained on routine followup as though the surgery never occurred.

7. Congestive heart failure.
Therapy for CHF will be initiated. If CHF is easily controlled, the CAST drug will be continued. If CHF is not easily controlled (i.e., the patient is still symptomatic after therapy for CHF), and if it appears that the drug may be related to heart failure, titration will be resumed if possible (see figure 1). If, however, after withdrawal, the drug does not appear to have caused the CHF, the physician will be encouraged to reestablish the original CAST therapy.

8. Apparent proarrhythmia or excessive VPD's.
In the unlikely event that apparent proarrhythmia is detected during followup, a washout Holter will be obtained. If proarrhythmia is not verified by the washout Holter, the patient will be placed back on the CAST blinded therapy. If proarrhythmia is verified, or in the case of excessive VPD's (see below), alternate CAST therapy will be used (see figure 1), if possible. Titration will resume at the next drug of the sequence at the same dose level as the current drug.

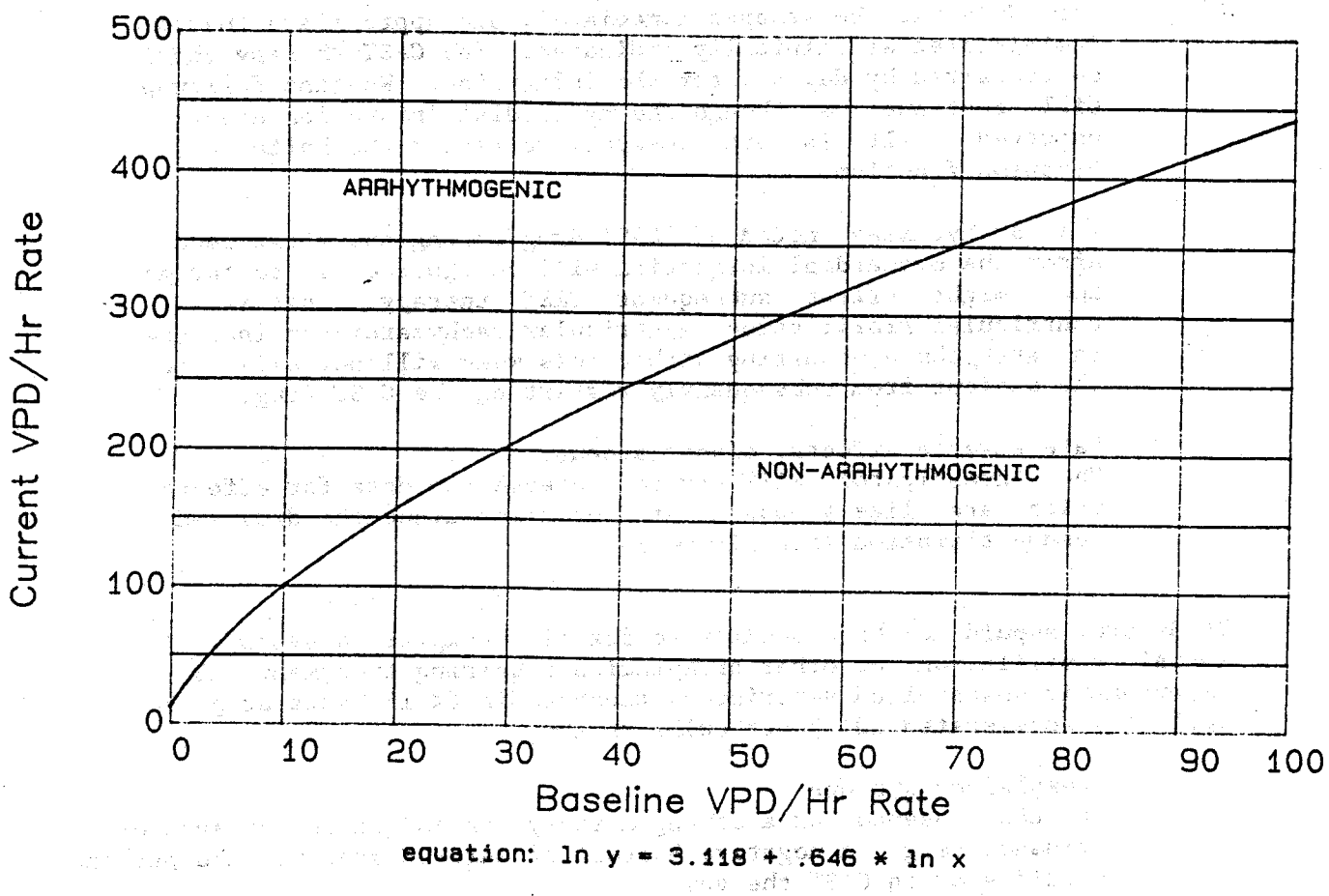
Excessive VPD's is defined as $\geq$ 1500 VPD's/hr independent of pretreatment frequency.

Proarrhythmia is defined as VPD frequency $\geq$ a multiplier depending on pretreatment frequency. This multiplier is a linear function of the log of VPD pretreatment frequency (see figure 2).

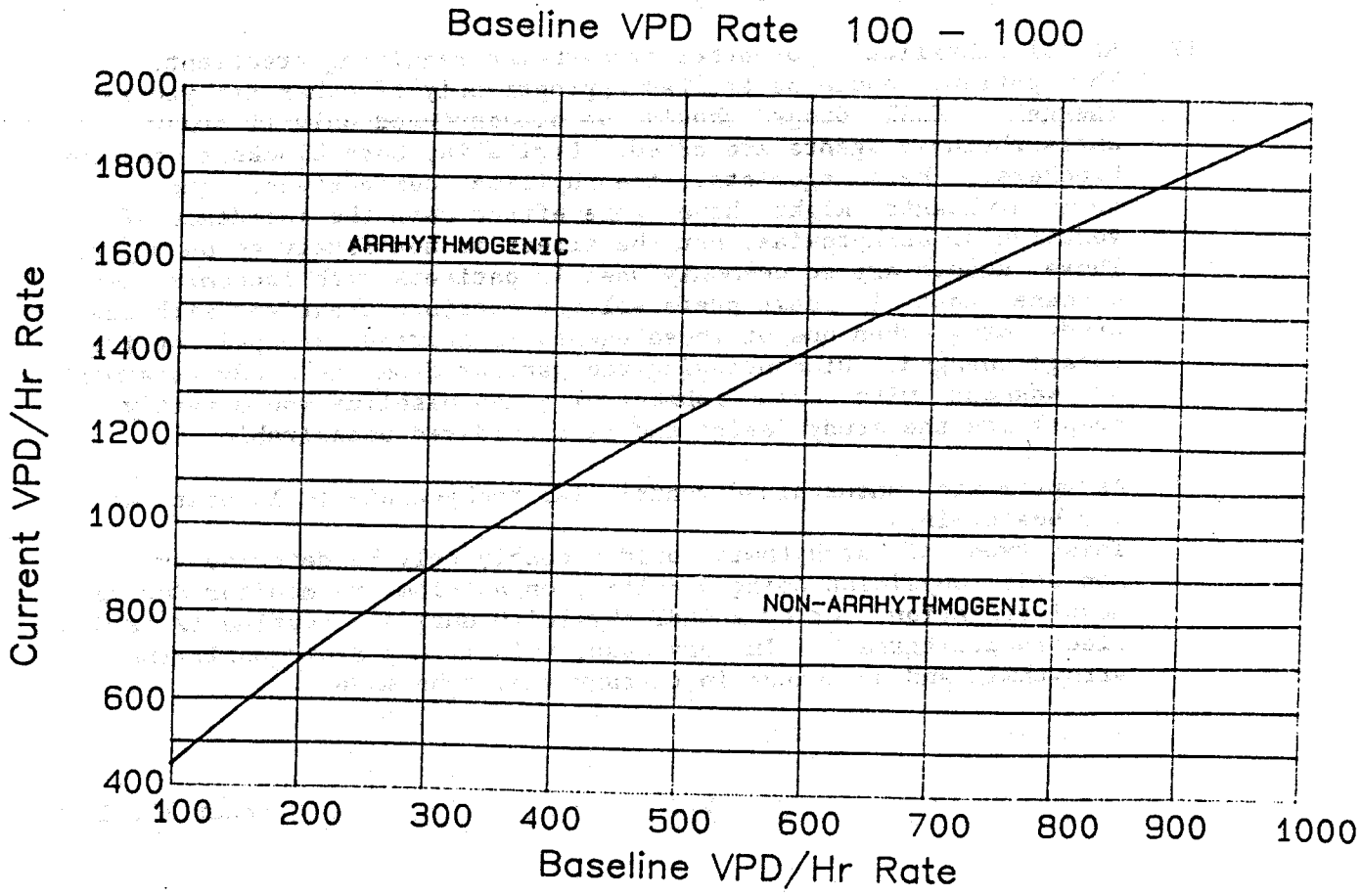
For those patients showing $\geq$ 5 runs/day on the baseline Holter, a ten-fold increase will be considered proarrhythmia. For patients with fewer than 5 runs/day on baseline, 50 or more runs will be considered proarrhythmia.

Figure 2

Arrhythmogenicity Criteria



equation: ln y = 3.118 + .646 * ln x



equation: ln y = 3.118 + .646 * ln x

9. Recurrent myocardial infarction.
The drug will be stopped immediately and appropriate therapy administered as clinically indicated. The CAST therapy should be restarted by day 6 after the infarction. Routine followup will continue as though the myocardial infarction never occurred. It is not necessary to repeat the Holter or ejection fraction.

All arrhythmias noted off CAST drug during the first week after the myocardial infarction will be ignored, in so far as they might affect subsequent CAST therapy. That is, ventricular fibrillation, ventricular tachycardia or increase in arrhythmia occurring within this week will not eliminate the patient from subsequently restarting the CAST drug.

10. Late adverse effects, miscellaneous.
The investigator will try to decrease the dose for effects which are likely dose related or discontinue the drug and resume titration (see figure 1).

Study drug should not be discontinued for 11) unexplained syncope, 12) atrial fibrillation or other arrhythmias requiring treatment, 13) asymptomatic unsustained ventricular tachycardia (< 15 beats at ≥ 120 bpm), 14) accelerated idioventricular rhythm.

11. Unexplained syncope.
In the absence of a strong history for and in the absence of evidence (e.g., a negative Holter) of cardiac syncope, the patient should stay on CAST therapy.

12. Atrial fibrillation or other arrhythmias requiring treatment.
The patient should be treated appropriately if other arrhythmias emerge. CAST drugs should be discontinued only if other antiarrhythmic agents are added. Digitalis, beta blockers, calcium blockers, beta agonists, theophylline derivatives, and anticonvulsants might have some effect upon the incidence of ventricular arrhythmias, but the effect is not likely to be major. These agents are so commonly used in patients with ischemic heart disease that it seems preferable to continue treatment with the study drug when one of these agents is started, stopped, or its dosage changed. Discontinuing the patient from the study treatment or washout with establishment of a new baseline would vastly complicate the study design and is considered undesirable.

13. Asymptomatic unsustained ventricular tachycardia (< 15 beats at ≥ 120 beats/min.).
This type of arrhythmia would probably only be detected by a non-CAST physician doing a Holter, on a telemetry monitor during hospitalization, or by a CAST physician during a routine 12-lead electrocardiagram. In any case, this is not a disqualifying arrhythmia and no change in therapy should be made.

14. Accelerated idioventricular rhythm.
This rhythm will be ignored by CAST. Do not alter the CAST drug therapy or followup protocol.

Study drug should be restarted if at all possible after 15) discontinuation of the CAST drug by the patient or a non-CAST physician.

15. Discontinuation of the CAST drug by the patient or a non-CAST physician.
The investigator will attempt to restart the CAST drug at its previous dose, regardless of the time elapsed since the CAST drug was stopped. Followup will be continued and tests performed as though the CAST drug had never been stopped.

In general, the investigators will attempt to keep patients in CAST with adequate suppression of arrhythmia. For some events, it will not be possible to remain blinded to the therapy or to continue titration. For certain other events, it will be both possible and desirable to change drugs or doses. In such cases where titration is continued, the patient will resume titration with active drug or with placebo depending on the CAST assignment. Therapy will be assigned by the Coordinating Center so the investigator and patient will be blinded. When it appears that adequate resolution of arrhythmias or adverse effects has occurred, the patient will continue on that therapy and a Holter obtained which will not be read locally. The Holter will be used for safety and to document the level of suppression. In no case will the patient be allowed to return to a specific drug once he has proceeded to the next drug in the titration scheme. In addition, a patient advanced to individualized therapy will still be followed per protocol. If a drug code is broken (unblinded), as few individuals as possible will be informed about the unblinded therapy. Likewise, if a drug code is to be broken (unblinded), pertinent event forms must be completed <u>before</u> the code is broken.

At the end of study, the code will be broken. The patient's status may then be reviewed with respect to the history and physical examination, 12-lead electrocardiagram, quality of life, adverse effects, and other medications.

10. COMPLIANCE

A. Introduction

Compliance to the prescribed medication regimen will be measured by means of monitoring pill counts, and compliance to followup schedules will be measured by means of monitoring dataform submission. Compliance will be maintained at acceptable levels by educational efforts which are designed to inform the patient of his responsibilities to the protocol, to discover causes of noncompliance, and to apply remedies to improve unacceptable compliance.

B. Enhancing Compliance through Patient Education

Patients enrolled into CAST will be evaluated by a brief interview. Evaluation will be made of knowledge concerning cardiac disease and effects of treatment, attitudes concerning participation in the clinical trial, expectations for personal benefit from participation, motivation for compliance with treatment regimens and research protocols, and previous experience with medical treatment for chronic disease.

Following initial evaluation, patients will be instructed in procedures required of them for successful participation. Patients will be provided with a handbook summarizing the main features of the trial and the requirements for participation. Further efforts will be made during each repeat visit to the clinical center to reinforce adherence to the drug regimen and required procedures.

C. Remedies for Noncompliance

Remedies for noncompliance will emphasize early detection of poor compliance through prompt entry into the Coordinating Center computer of compliance monitoring data. Minimum standards for compliance will be established with respect to the performance of individual patients, as well as average values across centers. Patients falling below minimum standards of compliance will be identified by means of monitoring pill counts and adherence to followup schedules as recorded in the database, and the Coordinating Center will notify centers of problems. Coordinators should be alerted to possibilities of poor compliance in association with dosage increases, changes in regimen, toxic adverse effects, multiple drug regimens, and frequent clinic appointments (especially in early phases of the study). Behavioral techniques to remedy noncompliance can include using goals and positive reinforcement to establish desired levels of adherence and recruitment of social support for increasing motivation. No patient will be dropped because of poor compliance, and thus continued effort to enhance compliance will be required throughout the duration of the study.

When patients do drop out of the study, intensive efforts, including contact by telephone and in person, will be made to retrieve them. Experience gained from compliance-enhancement strategies of coordinators participating in other clinical trials, as well as those used successfully by CAST coordinators, will be discussed at coordinator meetings.

2. Breaking the code because of concern that the therapy may be jeopardizing patient safety.

If the investigator or the patient's private physician believes that patient safety requires unblinding, the following procedures should be followed:

a. The details of the particular case should be discussed among the Clinical Center staff and the personal physician. In most instances, it will be found that drug discontinuation, followed by usual medical treatment, will provide optimal care. If such care entails the use of an antiarrhythmic agent, such an agent can often be administered without knowing whether the discontinued study drug was active or placebo.

b. If it is thought that medical care can be improved by knowledge of the treatment, that decision can be discussed with Dr. Leon Greene at the Coordinating Center. It may be possible for a physician who does not see study patients to be unblinded, and advice regarding such care could be made by this physician after determining the therapy. This physician should avoid disclosing the study drug identity to other staff or to the patient's personal physician.

c. If the decision is made that the patient's best interest requires that the Clinical Center staff have knowledge of the study drug, either directly or indirectly through advice of the physician mentioned in (b.) above, the patient will be considered to be on individualized therapy from that point on. It will usually be unnecessary for all staff to be unblinded. The staff that are unblinded are urged to preserve the confidentiality of the information.

d. Regardless of the nature and degree of unblinding, the patient should continue to be followed on the usual visit schedule for the duration of the study. If at all possible, since analysis will be by intention to treat, the individualized therapy should be the study drug.

e. Unblinding can be done by:

1. <u>On working days,</u> between the hours of 8:00 am and 5:00 pm Pacific Time, a call should be placed to the Coordinating Center. If a physician other than a CAST investigator will break the blind, it is preferable for the coordinator or CAST investigator to call ahead and alert the Coordinating Center for the expected call if this is possible. The caller should have the patient I.D. number.

The phone number to call is (206) 545-1302.

2. <u>At other times,</u> the Drug Distribution Center's 24-hour answering service can be called. The caller should ask for the pharmacist on call for the Cooperative Studies Program Research Pharmacy, identify the CAST study, and have the patient I.D. number or X-bottle number.

The phone number to call is (505) 265-1711.

3. If necessary, the unblinding envelopes, which will be maintained at each center, may be opened to provide the information. In this case, the opened envelope, with information on the unblinding (reason unblinded, date unblinded) should be sent to the Coordinating Center. (At the end of the study all unblinding envelopes must be accounted for and all opened envelopes must be explained.)

f. Every case of unblinding must be reported to the Coordinating Center.

E. Confidentiality

It must be stressed to all Clinical Center personnel that confidentiality of patient information must be preserved. No unauthorized personnel should have access to patient records or results of interviews or tests. All record storage rooms should be appropriately secured and should contain any necessary locked files or other storage equipment.

No identifiers will be sent to the Drug Distribution Center or NHLBI. Name and social security number will be sent to the Coordinating Center, but these will be kept separate from the main database. The only use of these data will be to conduct future inexpensive and non-invasive long-term mortality followup by National Death Index searches. All communication about patients will utilize numerical and alphabetical codes by which central study files may be linked to individual patients. The Clinical Centers will retain forms which permit such linkage. These Patient Identification Forms contain patient identifiers and the study codes. The forms are securely kept at the Clinical Centers. If, in the future, it is necessary for patient safety reasons to contact individual patients, these locally maintained forms will allow such contact.

12. QUALITY CONTROL

A. Introduction

The quality of any study is based on the quality of the data collected, and a high degree of accuracy and completeness in data collection and recording is essential. Consistency of the data collected must also be a concern, particularly in a multicenter study. Quality control is a concern of all units of the study, with the clinical centers responsible for the careful gathering and recording of the data and the Coordinating Center, with the advice and direction of the Project Office, responsible for monitoring the quality of the data gathered. The Quality Control Subcommittee will develop and review quality control guidelines.

B. Qualifying MI

There will be no program of review of a randomly selected sample of the ECG and enzyme data documenting the qualifying MI.

C. Holter

Quality control of Holter reading will begin during the planning phase of the study. Prior to randomization, all technicians who will scan Holters for the study will be certified. Each technician will read two of the 15 gold standard tapes which were developed in the Cardiac Arrhythmia Pilot Study (CAPS). Certification will require that a technician read the tape within 25% in VPD's/hr. A technician who fails to achieve an accurate reading on the first attempt will be allowed to try again. Although the initial emphasis will be on testing technicians before enrollment begins and before interpretation of study tapes begins, new employees will be certified at a later date in a similar manner, as needed. Only certified technicians will be allowed to read for the study.

During the three years of enrollment, quality reading of Holters will be maintained by two methods, with the gold standard tapes and with overreading of a random sample of tapes from the clinical centers. Every three months the Coordinating Center will send to each technician two copies of the gold standard tapes, to be read in as blinded a fashion as possible.

Additionally, a percentage of all study Holters will be randomly selected (by the Coordinating Center) for overreading. Each center will designate a top technician to overread tapes by all other technicians who are reading study tapes for that center (whether at the same or at another hospital). In order to quality check the top technician, tapes read by the top technician will be selected for overreading at a central facility.

Certification criteria (greater than 25% disagreement on VPD's/hr) will be used to identify discrepant readings. All discrepant tapes will be adjudicated.

All discrepancies will be reported on a regular basis to the clinical center. Periodic reports on the quality of Holter readings of each center technician,

displaying comparative accuracy rates, will be sent to each principal investigator.

D. Left Ventricular Ejection Fraction

Left ventricular ejection fraction will be measured not less than 24 hours after the qualifying MI and prior to enrollment, by one of three methods, radionuclide ventriculography, cine angiography or M-mode or 2-dimensional echocardiography.

Recommendations for a standard protocol for measuring left ventricular ejection fraction for each method will be developed by the Quality Control Subcommittee and included in the Manual of Operations.

E. Study Data

Because quality control of data collection begins with well designed dataforms, the forms will be designed to be easy to read and to use and as unambiguous as possible. A detailed and comprehensive manual of operations will be completed prior to patient enrollment and will be available during the initial training session. The manual will include a detailed description of each form, item by item, as well as information on all aspects of the study protocol.

At an extensive initial training session the details of both the study protocol and study data collection will be presented to clinical personnel. All dataforms will be presented in detail, and techniques of patient management will be discussed. The coordinators will be trained in data entry. Further training sessions will be prepared for later steering committee meetings as needed, particularly, early in the study.

Data entry at the clinical centers will be by means of a programmed forms entry package with range, code and logical checks, required data fietlds and double entry verification. This method will assure that the major percentage of data errors will be caught at the center and can be corrected in a timely fashion.

On a regular basis the database will be surveyed to determine the completeness of data submission for each patient. A report will be sent to each center coordinator, summarizing data forms which are past due and those which appear to be incorrectly or inconsistently coded, along with diagnostic information. Every other month a monitoring report will be distributed to principal investigators and coordinators, assessing center performance, including bar graphs comparing the centers on patient enrollment and on timely and complete baseline and followup data submission.

Periodically accuracy of data entry will be checked. A sample of dataforms will be called from the centers and compared with data entered into the study database. Inconsistencies will be resolved and corrections made where necessary. Reports on the accuracy of data entry will be sent to the centers, and an effort will be made to identify and correct problem areas.

Interform data inconsistencies and data outliers will also be identified, and centers will be notified of questionable data which must be verified or corrected.

13. ANCILLARY STUDIES

A. General Policy

Individual investigators are encouraged to carry out ancillary studies. Such ancillary studies enhance the value of CAST and ensure the continued interest of the investigators. Nevertheless, to protect the integrity of CAST, such ancillary studies must be reviewed and approved by the Publication, Presentation and Ancillary Studies Subcommittee and the Steering Committee before their inception. In general, ancillary studies require outside (non-CAST) funding.

B. Definition of an Ancillary Study

An ancillary study is any research that requires one or both of the following:

1. Supplementary observations, data or procedures to be performed or supplementary specimens to be obtained from all or a subgroup of the CAST population.

2. Additional work performed or information obtained from either the Coordinating Center or the Holter Reading Center. A procedure, observation, or specimen is supplementary if it is not part of Protocol procedures approved by the Steering Committee and detailed in the Manual of Operations. There is no limitation on the physician's right to carry out additional procedures on individual patients for medical indications.

C. Requirements for Approval of an Ancillary Study

Before an ancillary study can be approved, it must be shown that the ancillary study will have scientific merit but will <u>not</u> do any of the following:

1. Interfere with the completion of the main objectives of CAST or complicate interpretation of the CAST results.
2. Result in unblinding of the study drugs.
3. Adversely affect patient cooperation in CAST.
4. Jeopardize the public image of CAST.
5. Create a serious diversion of study resources, either locally or centrally.

D. Preparation of Request for Approval of an Ancillary Study

The request for approval of an ancillary study should initially be submitted on an appropriate two-page form and should contain a brief description of the objectives, methods, significance of the study, and names of definite or possible collaborators. Full details should be given concerning any procedure to be carried out on the study patients, such as interviews or tests. Mention should be made of any substances to be injected or otherwise administered to the patient. Mention should be made of the extent to which the ancillary study will require extra clinic visits by the patients, or will prolong the patient's

usual clinic visits. Information should be given concerning the extent to which the ancillary study will require additional venipuncture, and/or the withdrawal of larger blood specimens beyond those required for the Cardiac Arrhythmia Suppression Trial. If specimens are to be obtained from the patients, mention should be made of all procedures to be carried out on the specimens. Mention should also be made if the ancillary study will require the ~~Holter Reading Center or~~ the Coordinating Center to furnish information to the Clinical Center. If collaboration by the central units is needed, approval of these units must be obtained. If procedures or analyses are likely to lead to treatment group unblinding, arrangements must be made for a data depository. The statistical analyses to be performed should be described. Only after CAST is over may such data be disclosed to the investigators.

E. Procedure for Obtaining Ancillary Study Approval

Investigators will submit their preliminary proposals for an ancillary study to the Chairman of the Publication, Presentation and Ancillary Studies Subcommittee. The Subcommittee will assist investigators with similar interests to communicate with each other and submit a detailed, joint proposal. The Subcommittee will review the detailed ancillary study proposals and, at the appropriate time, make recommendations for approval or disapproval to the Steering Committee. The Steering Committee review will be based on the criteria listed in section C. The Publications, Presentation and Ancillary Studies Subcommittee has the responsibility to track all ancillary studies and to make a report to the Steering Committee as frequently as every 12 months.

F. Funding of Ancillary Studies

If additional funds are not required, the investigator may proceed with the final version of an ancillary study after it has been approved by the Publication Subcommittee and the Steering Commitee. If additional NHLBI funds are needed, the investigator may submit a research grant application to the Division of Research Grants for review in the same manner as any other new research grant application. Such a grant may be submitted to NHLBI after approval of the Subcommittee but before approval of the Steering Committee. It is understood that the investigator will not accept the grant, or activate the ancillary study, until Steering Commitee approval has been received. If non-NHLBI funds are sought, however, permission of both the Subcommittee and the Executive Committee must be obtained before the request is submitted to that institution or company.

G. Ancillary Studies Performed by Individuals Other than Principal Investigators or Co-Investigators

Each investigator will regard the use of his study patients for ancillary studies to be performed by his local colleagues in the same light as any to be performed by himself. That is, to the extent the investigator can control the use of patients for study purposes, he will not permit others to carry out ancillary studies unless prior Steering Committee approval has been obtained.

H. Publication of Ancillary Studies

All reports of ancillary studies to be published or presented must be approved by the Steering Committee. The Committee will determine whether the publication or presentation of the ancillary study adversely reflects on the study as a whole. If it is determined that the publication adversely reflects on the study, all such reports must delete reference to CAST before publication. Guidelines for authorship described in Section 14 pertain to ancillary and to all other CAST or CAST-related papers and presentations.

I. Substudy Papers and Presentations (Reports)

Substudies are not part of the common CAST protocol but are directly related to primary objectives of CAST. They are not performed on all CAST patients because of cost and/or conflict of interest issues. Proposals for such studies utilize data that may or may not be routinely collected in CAST. Proposals should be submitted to the Publications, Presentation and Ancillary Studies Subcommittee for review, and the Subcommittee will then make its recommendation to the Steering Committee. If an appeal of the decision is requested, the proposal or paper will be reviewed again by the Publications Subcommittee and, if necessary, again by the Steering Committee. It may be necessary to obtain Data and Safety Monitoring Board approval if there is any question of main study impact. All substudy papers are reviewed by the Subcommittee, all principal investigators and the Steering Committee prior to submission for publication. The Subcommittee is responsible for monitoring the progress of all substudies.

14. PUBLICATION POLICY

A. Introduction

The Cardiac Arrhythmia Suppression Trial is an important scientific investigation with respect to health care. Because of the great effort that goes into such a study and the large amount of resources used, the study participants have the right and responsibility to communicate their findings to the scientific community and through them to the public at large.

For such publications it is essential that equal opportunity exist for the participating units of CAST to help analyze and present the data. Participation in the writing and analysis of papers shall be open equally to the investigators of all CAST sites, including the Drug Distribution Center, the Coordinating Center and the NHLBI Project Office. All of these units shall have equal status with regard to developing protocols, participating in such studies as approved by the Steering Committee and Publications, Presentation and Ancillary Studies Subcommittee, and collaborating in the development and publication of research papers and abstracts based upon the CAST data. With the approval of the principal investigators, the associate investigators at the various clinics are encouraged to participate in this process.

Because the analyses involve the database and may use a variable amount of the resources at the CAST Coordinating Center, the Coordinating Center will be consulted by the chairman of the writing committee or his designee in the development of any study protocols that require review of data accumulated from the different sites and deposited in the Coordinating Center. The Coordinating Center should also approve all patient and data forms for such studies.

B. Primary (Final and Mainline) and Secondary Studies, Papers

Primary papers are defined as those CAST papers that present baseline data, and key endpoint data by treatment group.
Primary (final, mainstream) papers and presentations (reports) of CAST are to be identified by the CAST Publications, Presentations and Ancillary Studies Subcommittee upon the recommendations of the Steering Committee or of any members of any participating study. For each report thus identified, an ad hoc committee of volunteers, from among the professional staff of all centers, is to be appointed and charged with the responsibility of preparing a report within the stated time limit.

Whether or not specific analyses in papers or abstracts are to be considered primary papers will be decided by the Publications Subcommittee and by the Executive Committee of CAST. Any cases of dispute will be referred to the Steering Committee.

Secondary papers include all other papers reporting results from the common data set of the national collaborative trial. They may present study methodology, baseline data, effects of other factors (age, sex, LV function, history of prior infarction, CHF, etc.) upon outcome.

C. Other Study Papers and Abstracts

It is important to extract optimal scientific information from the CAST database; for this purpose other analyses beyond the primary papers of the study are appropriate. In order to encourage such analyses and to give proper recognition for the work involved, small working subgroups will be formed for such analyses. Some of these secondary papers may have named authorship of the individuals involved, then ending with the phrase "and the ~~CAST~~ Investigators." In order to ensure that all clinics have an equal opportunity to develop and participate in the analyses and papers, proposals for secondary, ancillary, substudy and database studies and papers will be circulated through the office of the Chairman of the Publications Subcommittee to each of the principal investigators for possible participation and later for approval.

All suggestions for papers should be submitted to the Publications Subcommittee who are responsible for approving the study, circulating it to all principal investigators, and then selecting the final chairman and writing committee. It may be necessary to limit the number of writing committees on which an individual serves. In general, all authors of all papers or presenters of CAST study material should be selected from CAST investigators or members of one of the special centers listed above or from the Program Office.

D. Writing Committees and Authorship

The order of authorship of all papers and presentations from CAST should be based upon the quality and quantity of contribution of the individual to formulating the study, performing the study, and writing the paper, rather than priority in submitting the study protocol to the Publications Subcommittee. In general, it is expected that the authors should include the originator(s) of the proposal and that all or most clinics desiring to participate will be able to participate. All ~~CAST~~ papers will contain an appendix containing the principal investigators, co-principal investigators and co-investigators and other individuals deemed appropriate for this appendix from the Clinical Centers, ~~Drug Distribution Center~~, the Coordinating Center, and the Project Office. It is probable that in certain instances CAST may be asked to contribute papers to workshops, symposia, volumes, etc. The individuals to work on such requests may be appointed by the Executive Committee in consultation with the chairman of the Publications Subcommittee. Whenever time permits, a proposal will be circulated to all principal investigators soliciting other possible participants.

Whenever possible, primary papers shall not have named individual authors but shall be published under the byline of "The Cardiac Arrhythmia Suppression Trial (CAST) Investigators". There shall be an appendix containing the principal investigators, co-principal investigators, co-investigators and others as designated from each clinic, ~~the Drug Distribution Center~~, the Coordinating Center, and the Project Office. The writing committee for such a paper shall be listed under that designation in the Appendix to the paper. A member of the Coordinating Center qualified in statistics shall be assigned to each primary paper writing committee.

When it is not possible to use the above authorship procedure, the Publications Subcommittee will determine the order of authorship in consultation with the members of the writing committee. A major criterion for this determination is

the quality and quantity of effort and contribution made by members of the writing committee in the preparation of the paper. At the request of the writing committee chairperson, the names of members of a primary (final or mainstream) paper who have shown little or no interest in participating in the work of the committee or who have failed to contribute to the task of preparing the manuscript may be left off the list of authors. The chairman of the Publications Subcommittee will make the final decision upon receipt of a written request from the chairperson of the respective writing committee in consultation with the Executive Committee. The affected individuals will be informed in writing that they have the right to appeal the decision to the Publications Subcommittee as a whole or, if requested, to the Steering Committee. A credit list shall appear in the appendix as described above.

Whenever possible, secondary papers are also authored by "Cardiac Arrhythmia Suppression Trial (CAST) Investigators," and all individuals and groups are listed at the end of the article, as for primary papers.

E. Review Policy for Manuscripts and Abstracts

All primary and secondary study proposals and papers will be circulated to all principal investigators, who will then meet (as time and finances permit) to review and discuss the papers in detail before the study is initiated or the paper submitted. After a primary, secondary, ancillary, subgroup, or other study protocol is prepared or a manuscript is prepared for publication, it will be submitted to the chairman of the Publications Subcommittee, who will be responsible for assigning a subcommittee for an in-depth review, including a statistical review by the Coordinating Center, when appropriate. Ad hoc consultants may be utilized for this review. The recommendations of the Publications Subcommittee will be forwarded to the Chairman of the Steering Committee, who may either forward the recommendations back to the author or circulate the protocol or manuscript and the Subcommittee recommendations to the Steering Committee. The chairman of the Publications Subcommittee will inform the principal investigators, various study units and the program office when approval is granted. The study may then be initiated or the papers submitted and revised as needed for publication purposes.

Abstracts from CAST analyses must also be approved prior to submission. However, because of deadlines there may occasionally be little time for written feedback from the Publications Subcommittee or the Executive Committee before submission of CAST abstracts for national meetings. In such instances, permission should be obtained by telephone. Abstracts should be submitted for approval at least four weeks before the deadline for submission.

Recommendations as to the timing of presentation of endpoint data and the meetings at which they might be presented will be given by the Publications Subcommittee to the Steering Committee, who will forward their recommendations to the National Heart, Lung, and Blood Institute. However, it is recognized that the Institute has final responsibility for the decision.

If an appeal of a decision is desired, the investigator should notify the chairman of the Publications Subcommittee, who then will appoint a new ad hoc committee. If necessary, an additional appeal can subsequently be made to the Steering Committee.

F. Databank Studies, Papers, Presentations (Reports)

These studies utilize data routinely collected by CAST. In general, such studies include only data analysis and are not funded, although they do use Coordinating Center resources. Like all other studies, they are reviewed by the Publications Subcommittee, which then sends its recommendation to the Steering Committee. The Subcommittee is responsible for monitoring the progress of all databank studies.

G. Studies Using CAST Data

If any research is conducted locally using only, or to a large extent, questions from CAST forms and CAST patients, the individual center may not present the results in a paper. Scientific integrity dictates that a study using the data from all the CAST sites together would have a larger sample size and, in addition, would allow comparison of institutional variability. Such research is considered to be study-wide and is to be reported as such. An individual center is expected not to report data of this type from the individual center alone.

H. Accessibility of Data by External Agencies or Manufacturers

With the special permission of both the Publications Subcommittee and the Steering Committee, limited accessibility to selected portions of primary data from substudy or ancillary studies may be permitted to external agencies or manufacturers who have contributed significantly to the support of such studies. The users of such data must agree in writing not to use the data in direct or indirect advertising, although they may use the data for other purposes. All information provided should be limited to the areas of direct support provided by the agency or manufacturer. Such users shall not be provided any other correlative data regarding the patients until 1995.

15. CLOSEOUT OF THE STUDY

A. Informing the Patients and Primary Care Physicians

In a real way the individuals contributing the most to CAST are the patients who give informed consent to participating in the study. At the end of the study, all appropriate medical and background information will be communicated to the patient and the patient's primary care physician to aid in the patient care. When the study is over, the results and any general recommendations will be presented to the patients and participating physicians so that continuing care for these important participants can be based on the individual patient's response to therapy, the physician's judgment and the most objective information available.

B. Future Drug Therapy of Patients

CAST did not initially consider any drug that was not expected to have FDA approval by the termination date of the study. The same principle will apply to any other drug that might be considered for inclusion in the CAST armament. Thus, patients on active CAST medication should be able to continue that medication after their involvement in CAST is completed, through the resources of their private physicians.

C. Disposition of Sealed Unblinding Envelopes at the End of the Study

All the sealed unblinding envelopes, whether open or still sealed, are to be returned to the Coordinating Center via registered mail at the end of the study. If the envelope has been opened, there should be a written explanation on the envelope as to the reason for the unblinding. (All such unblindings should have been reported as detailed in section 11.D.)

D. Delivery of Material to the National Heart, Lung and Blood Institute

Since CAST is financed by public funds through the National Heart, Lung, and Blood Institute, it is appropriate that the Institute document the study and at the conclusion make information available to the widest possible audience. For this purpose the CAST investigators, especially the Coordinating Center, will supply the Clinical Trials Branch of NHLBI with a study archives of important study documents, computer tapes of the main computer file, and simplified "rectangular" or "flat" files that may be used more easily for analysis. A description of the format and use of the material will also be supplied.

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Appendix 1: Criteria and Assumption for Determining Sample Size

Estimation of Sample Size for CAST

In order to estimate the sample size for CAST, the following assumptions have been made:

1. All participants will be followed for a minimum of three years.

2. The primary endpoint, sudden cardiac mortality, is projected to have a three year incidence of 11% in the placebo group.

3. The use of antiarrhythmic therapy is expected to reduce the incidence of sudden cardiac death by 30%.

4. The Type I or α error was set at a one-tail level of 0.025. The power of the study to detect the hypothesized difference of 0.84.

5. It was assumed that 6% of the placebo group would be assigned antiarrhythmic therapy by their private cardiologists during the study (2% per year).

6. It was also projected that 30% of the patients in the intervention group would stop taking the assigned medication (20% in year one, and 5% in each of the next two years).

These assumptions resulted in the need to randomize 2200 patients to each of the groups - placebo and treatment.

Appendix 2: Acute Myocardial Infarction Criteria

The criteria for an acute myocardial infarction in the CAST protocol have been developed keeping the following objectives in mind:

1) to allow study nurses to efficiently and quickly enter patients into the trial;
2) to allow rapid exclusion of patients not meeting entry criteria;
3) to ensure uniformity in the patient population entered into the study at different centers.

Presenting symptoms and/or cardiac enzymes will identify those patients who warrant further consideration as a study participant. ECG changes will be used to support the diagnosis of myocardial infarction in equivocal situations, as well as to define the location and transmurality of the MI.

Typical symptoms are defined as severe discomfort occurring anywhere in the anterior chest, back, jaw, neck or shoulder, persisting more than 30 minutes unless relieved by morphine or meperidine.

Elevated enzymes are defined as one of the following observed within 72 hours of the onset of symptoms:

1) Total CPK is $\geq$1 1/2 times the upper limit of normal.
2) CK-MB is > 5% of total CPK.
3) LDH is $\geq$1 1/2 times upper limit of normal and LDH_1 is > LDH_2.
4) SGOT (AST) is $\geq$ 3 times upper limit of normal.

The acute infarction should be classified into one of five categories based upon the presenting sypmtoms, available information, and events surrounding the myocardial infarction.

ECG criteria cannot be used to establish MI class in the presence of LBBB.

The classifications are as follows:

CLASS I: Typical symptoms and enzyme criteria
OR
Typical symptoms and ECG with new abnormal Q waves in 2 contiguous leads (includes patients with pacemakers with conducted supraventricular beats)

CLASS II: Atypical symptoms and ECG with new abnormal Q waves in 2 contiguous leads
OR
Atypical symptoms and enzyme criteria and ECG with new abnormal ST-T changes
OR
Atypical symptoms and CK-MB > 5% of total CPK

CLASS III: Asymptomatic and ECG with new abnormal Q waves in 2 contiguous leads and prior ECG without abnormal Q waves in the same 2 contiguous leads obtained within 2 years
OR
Asymptomatic and CK-MB > 5% of total CPK

CLASS IV: MI occurring ≥ 5 days post cardiac surgery
At least two of the following three:
Typical symptoms
ECG with new abnormal Q waves in 2 contiguous leads compared to initial post-operative ECG
CK-MB > 5% of total CPK

(Cardiac surgery includes CABG, valvular surgery, aneurysm resection, or any surgery requiring cardiopulmonary bypass. PTCA is not considered a surgical procedure.)

CLASS V: MI occurring within 48 hours after non-cardiac surgery
ECG with new abnormal Q waves in 2 contiguous leads compared to initial post-operative ECG
OR
CPK ≥ 1.5 times the upper limit of normal and ECG with evolving abnormal ST-T wave changes.
OR
CK-MB > 5% of total CPK only

(Non-cardiac surgery includes vascular surgery, such as abdominal aneurysm resection or carotid surgery, as well as other non-cardiac surgery. PTCA is not considered a surgical procedure.)

Abnormal Q wave is defined as one of the following:

1) Any Q wave ≥0.03 sec in at least two contiguous leads excluding V_1 and aVR (contiguous leads are V_2-V_6; I and aVL; II, III, aVF).
2) Greater than 50% reduction in the R wave in each of at least two contiguous precordial leads as compared to a previous ECG or in the absence of RBBB or RVH the R wave amplitude in V_5 or V_6 less than 25% of that in V_3 or V_4.
3) R/S ratio of 1 or greater in V_1 or V_2 in absence of RBBB.

Abnormal ST elevation is defined as follows:

Any upward-convex ST elevation ≥0.1 mV measured 0.08 seconds after the J point, except for V_1, V_2. In V_1, V_2, the ST segment elevation must be ≥0.2 mV. An early repolarization pattern (upward-concave ST elevation following notched terminal R wave) should not be included here.

Abnormal ST depression is defined as follows:

> Any ST depression ≥ 0.1 mV measured 0.08 seconds after the J point.

Abnormal T wave inversion is defined as follows:

> Any symmetrical T wave inversion ≥ 0.1 mV in any of the leads except for aVR when the R wave amplitude is 0.5 mV or greater.

Specific criteria have been developed for the diagnosis of a myocardial infarction in the presence of RBBB and are listed below.

1) Any Q wave ≥ 0.03 sec in at least two contiguous leads excluding aVR.
2) Any ST elevation ≥ 0.2 mV, measured 0.08 sec after the J point in V_1 or V_2 or any upright T wave ≥ 0.2 mV in V_1 or V_2.

One or more ECG's obtained at the time of the MI will be coded for the following 4 items.

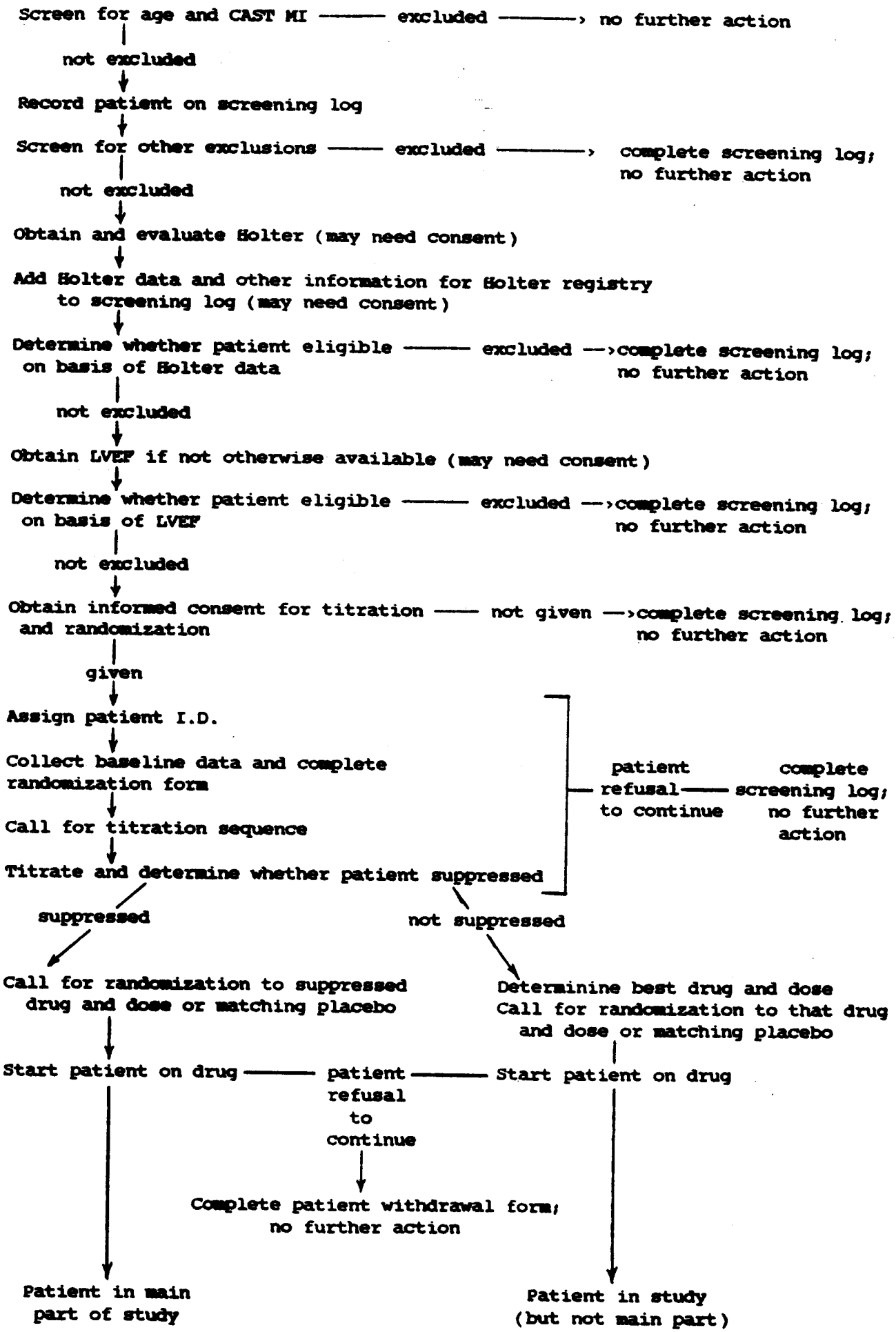
1) Presence or absence of abnormal Q waves
2) Location and age of abnormal Q waves (old versus new)
   - Anterior Q wave in leads V_1-V_4
   - Lateral Q wave in leads I, aVL, V_5, V_6
   - Inferior Q wave in leads II, III, aVF
   - Posterior R wave in leads V_1, V_2
3) Presence or absence of ST-T abnormality
4) Location and age of ST-T abnormality (old versus new)
   - Anterior V_1-V_4
   - Lateral I, aVL, V_5, V_6
   - Inferior II, III, aVF
   - Posterior V_1, V_2

APPENDIX 3

Half-Lives of Some Commonly Used Agents

Drug	Half-Life
Amiodarone	13-103 days
Bretylium	8 hours
Disopyramide	7 hours
Encainide	3-20 hours
Metabolites	6-24 hours
Flecainide	20 hours
Imipramine	4 hours
Metabolites	12 hours
Indecainide	12 hours
Lidocaine	1.5 hours
Lorcainide	8 hours
Mexiletine	7-20 hours
Moricizine	8 hours
Phenytoin	20 hours
Procainamide	3-6 hours
Propafenone	6-30 hours
Quinidine	6-19 hours
Sotalol	24 hours
Tocainide	12-24 hours

Appendix 4A · Patient Screening and Recruitment Chart



SCREENING LOG AND HOLTER REGISTRY INFORMATION/ELIGIBLES LOG

CLINICAL CENTER NUMBER: [ ]

HOSPITAL NUMBER: [ ]

AGE-MI ELIGIBLE:								HOLTER (ARRHYTHMIA) REGISTRY																ELIGIBLE PATIENTS			
								Holter (Arrhythmia) Data							Patient Information			Pt. Reported Hx									
Log#	Last Name & Date of contact M/D/Y	1st Ini	2nd Ini	Age	Sex	<90 dy	Prim Excl	Date M/D/Y	VPD/hr	Runs VT VT/hr	Max VT length	Max VT rate	LVEF	Soc Sec #	Birth Date M/D/Y	MI Date M/D/Y	MI	CHF	Oth Car	Di a b	Di g	C i g	Affix Patient I.D. Label	CAST Drg	CAST Dos	CAST Reas
1001.	___/___/___							1st																			
								2nd																			
1002.	___/___/___							1st																			
								2nd																			
1003.	___/___/___							1st																			
								2nd																			
1004.	___/___/___							1st																			
								2nd																			
1005.	___/___/___							1st																			
								2nd																			
1006.	___/___/___							1st																			
								2nd																			
1007.	___/___/___							1st																			
								2nd																			
1008.	___/___/___							1st																			
								2nd																			

Sex: 1 male, 2 female; <90 dy: <90 days after MI, 1 yes, 2 no; Pt Reported Hx: 1 yes, no for all; Oth Car: Other Cardiac Condition; Diab: Diabetes; Cig: Cigarette Smoker, 1 present, 2 former, 3 never; CAST Drug: 1 encainide, 2 flecainide, 3 moricizine; Reas not Rand: Reason not Randomized, 1 patient refusal, 2 physician refusal, 3 patient death, 4 other.

APPENDIX 4B

Appendix 5: Specific Drugs Considered

Quindine

Quindine was not chosen because it has been extensively studied and it is well known that the incidence of intolerable adverse effects is unacceptably high. Comparative studies have shown that patients tolerate encainide or flecainide much better because of the very high incidence of gastrointestinal adverse effects with quinidine. Carefully performed studies have found that only 60-70% of patients who tolerate the drug have an adequate antiarrhythmic response (greater than 80% VPD reduction). A major disadvantage is the 1-2% incidence of torsades de pointes. Quinidine has the advantage that it does not depress ventricular function when given by the oral route. In summary, it has moderate efficacy (less than encainide or flecainide) but the anticipated withdrawal rate due to intolerable adverse effects would make it an undesirable candidate for CAST.

Mexiletine/Quinidine Combination

This is a highly effective combination which has been found to be better tolerated than either agent alone. However, the overall published experience is limited to only 400 patients. Most of this experience is in patients with highly symptomatic arrhythmias and little experience is available in a population similar to that anticipated in CAST. There is inadequate information to determine the dosages of the two drugs which would be appropriate for use in CAST.

Pirmenol

Pirmenol has been found to have a reasonable degree of antiarrhythmic efficacy but the overall experience with the agent is limited and it is not possible to identify the range of dosages necessary for arrhythmia suppression in the CAST population. It is estimated that only approximately 300 patients have been observed during chronic therapy and the long term safety of the drug is unknown.

Propafenone

Propafenone is a reasonably effective drug which has been found to have efficacy comparable to quinidine and an acceptable adverse effect profile. It has been evaluated in over 1200 patients and can be given every 8 hours. It has mild negative inotropic actions and is probably no worse than flecainide in this respect. A major complicating factor is the fact that it has 1/40 of the potency of propranolol as a beta blocker. Based upon relative plasma concentrations obtained during therapy, many patients will have plasma concentrations greater than 40 times those seen during propranolol therapy. Therefore, an unknown fraction of the population receiving propafenone should develop a significant degree of beta blockade. Since beta blockers have already been found capable of reducing the incidence of sudden death, the inclusion of agents with beta blocking activity would confound the ability to test the hypothesis that arrhythmia suppression reduces sudden death.

Indecainide

Indecainide has been studied for several years but there is still a limited database available to evaluate the efficacy and safety of the product. The pharmaceutical sponsor is attempting to develop a sustained release form of the drug and this preparation is just entering clinical testing. Some studies have indicated a very high proarrhythmia rate but this may be an artifact of its stage of development. This has been experienced with most drugs until the appropriate dosage has been determined. There is very little data on the hemodynamic effects of indecainide and no indication of the safety of the drug when used in patients with reduced ventricular function.

Cibenzoline

The major deficits in the database for cibenzoline are the lack of information regarding the effects of the drug on ventricular function and concerning the dose-response curve and safety in the CAST population.

Amiodarone

Although amiodarone has been used extensively in patients with life-threatening arrhythmias, there is very little data on its dose-response curve in a population similar to that in CAST. It has a very high withdrawal rate due to life-threatening adverse effects which can occur as early as 7 months on a dosage as low as 200 mg. Since the CAST population will have no proven benefit from therapy, it was considered unethical to include a drug which is known to have lethal adverse effects. The pharmacokinetics of the drug make it very difficult to include since patients may not reach therapeutic levels until well after they have passed the period of highest risk of sudden death. Previous studies have observed a half-life of elimination from 13-103 days indicating that it would take from 1 month to 1 year before patients would reach steady state. The use of loading doses would reduce this length of time but might increase the risk of adverse effects even further. Therefore, even though the drug may have a high degree of efficacy and not depress ventricular function, it was felt to have an unacceptable risk/benefit ratio.

CAST

CARDIAC ARRHYTHMIA SUPPRESSION TRIAL

PROTOCOL REVISION

APPROVED 7/27/89 BY THE

DATA AND SAFETY MONITORING BOARD

TABLE OF CONTENTS

INTRODUCTION

The Cardiac Arrhythmia Suppression Trial (CAST) began enrollment in June 1987. The purpose of the trial is to test the hypothesis of whether suppression of VPD's by antiarrhythmic drug therapy in post myocardial infarction patients will reduce the incidence of sudden death subsequent to myocardial infarction. Based on information obtained from the Cardiac Arrhythmia Pilot Study (CAPS), three antiarrhythmic drugs, encainide, flecainide, and moricizine were included in CAST. By April 1989 accumulating data provided convincing evidence that it was highly unlikely that the suppression hypothesis could be established for encainide or flecainide and that there was strong evidence that these drugs were harmful. At the recommendation of the Data and Safety Monitoring Board (DSMB), encainide and flecainide were dropped from the CAST protocol on April 19, 1989.

Analysis of the data revealed a much lower than expected event rate in the placebo treated group, prompting the Steering Committee to recommend a number of changes in inclusion and exclusion criteria. These changes are directed toward excluding very low risk patients and including higher risk patients. Concern about the event rate during titration (CAST does not have a placebo control group during titration) by both the DSMB and the investigators led to a decision to incorporate a control group during titration.

To increase the suppression rate on moricizine, a higher dose (900 mg) was added.

Except for the revisions detailed below, no other changes in the CAST protocol have been approved.

REVISIONS

1. Encainide and Flecainide

Encainide and flecainide were dropped from the study.

This decision was based on the compelling evidence depicted in the following table.

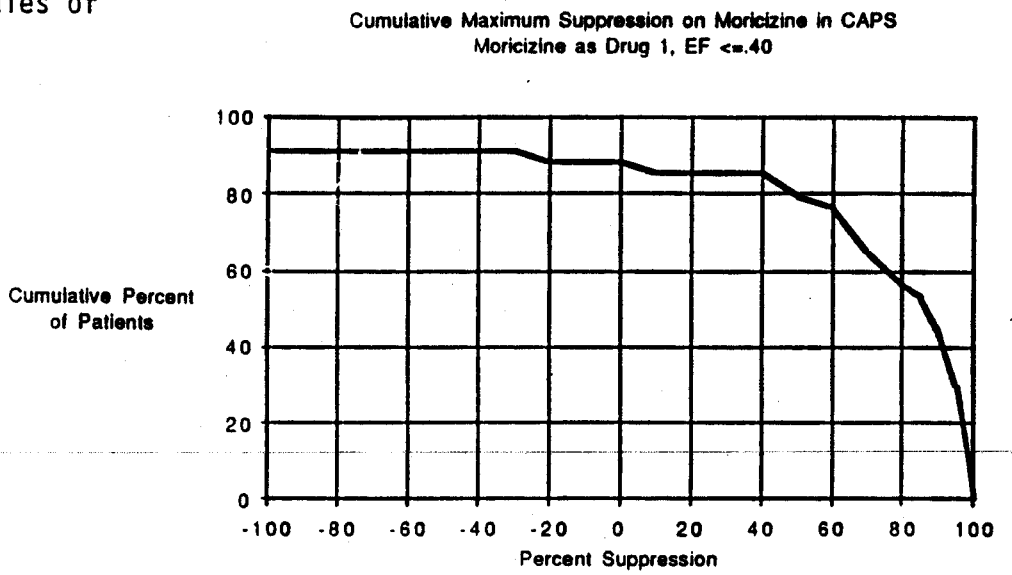
Events in 1455 Patients Randomized to Encainide or Flecainide or Matching Placebo.

	N	Avg. days of Exposure	Arrhythmic Death / Cardiac Arrest	Other Cardiac Death	Noncardiac or Not Yet Classified Death/CA	Total Mortality / Cardiac Arrest
Encainide/Flecainide	730	293	33	14	9	56
Placebo	725	300	9	6	7	22

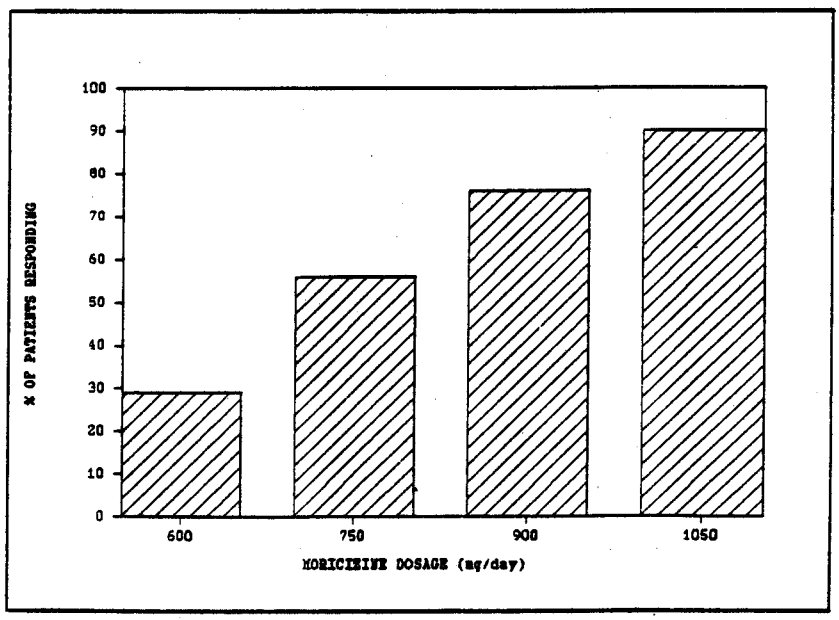
June 23, 1989

2. Moricizine 900 mg dose

Titration on moricizine shall be extended to a third dose of 900 mg daily. Based on response rates observed in CAST with patients with EF < 0.30 (44%), response rates observed in CAPS for patients with EF between ≥ 0.20 and ≤ 0.40, (figure below), and the dose response curve obtained from titration studies of



relatively large numbers of patients shown in the following figure from the manufacturer's database used in the submittal for FDA approval, we estimate that the addition of the 900 mg dose is expected to increase the suppression rate by about 10% from 50-55% to 60-65%.



Titration is to proceed from dose 2 to dose 3 of moricizine if the patient has not achieved suppression on dose 2 and has not experienced any adverse effects precluding continued titration on moricizine. Patients who achieve suppression on moricizine will then be randomized either to the suppressing dose or matching placebo in the main study. Patients who achieve any partial suppression will be randomized to the partially suppressing dose or matching placebo in the morcizine substudy. The other patients will be followed in the withdrawal substudy.

3. Exclusions

a) Patients with ejection fraction > 0.40 are excluded from the trial. The only exceptions to this are patients initially recruited prior to May 20, 1989.

This is based on the observed low event rate (1% by 1 year) in patients in CAST on placebo with ejection fraction > 0.40.

b) Patients without a qualifying Holter within 90 days of their qualifying MI are excluded from further consideration for the study.

This is based on the observed low event rate (0% by 1 year) for arrhythmic death in patients enrolled in CAST > 90 days post MI.

c) Patients who have symptomatic VT or asymptomatic VT at a rate > 120 bpm for $\geq$ 30 secs are excluded from the study. Patients with shorter durations of VT may be excluded, at the investigator's discretion.

This revision will allow inclusion of higher risk patients in the CAST population. It is also aimed at overcoming the simplistic, arbitrary cutoff which decreed that a patient with an asymptomatic run of 14 beats was eligible while a patient with an asymptomatic run of 15 beats was not eligible.

4. Revisions

a) The use of theophylline at baseline is no longer an exclusion for titration on moricizine. However, if during titration on moricizine the dose of theophylline needs to be adjusted, the patient must cease titration on moricizine and will then be followed in the withdrawal substudy.

b) The qualifying Holter may be obtained as early as 4 days after the MI. This change is made to facilitate recruitment because many patients are discharged between 4 and 6 days after MI, and does not effect the 6 day window during which serious arrhythmias (life threatening) are considered transitory and hence not exclusionary.

5. Placebo in titration

When a patient is enrolled in CAST, he will be randomized to blinded therapy, either moricizine dose 1 or a matching placebo, with equal likelihood. The

patient will stay on that blinded therapy for 2 weeks, at which time the therapy assigned will be unblinded to the investigator by the Coordinating Center. The two week period was chosen as a compromise between power for the comparison during the titration period and power for the comparison during the main study. Forms relevant to any events or adverse effects that occur during the 2 weeks must be completed prior to unblinding. Patients who are on and tolerate active moricizine dose 1 will then have a Holter to assess suppression and will continue titration in an open label format as formerly. Patients who are on placebo will be switched to open label titration, beginning with moricizine dose 1, and will proceed through titration as usual.

This revision is prompted by concern about the event rate during the first several weeks of titration in CAST. Adding the placebo control to titration will enable determination of whether there is any excess mortality due to drug.

Dr. Bigger reviewed the 1 week mortality rate in the MDPIT placebo group for a period corresponding to the first week of open label titration in CAST, i.e., approximately days 28 to 34 post MI, and found no difference, 0.8% in MDPIT compared to 0.9% in CAST. This similarity existed in spite of the fact that the CAST population has a lower average ejection fraction and a higher proportion of patients with frequent VPD's than the MDPIT population.

	MDPIT (Placebo)	CAST
Ejection Fraction	0.47	0.39
% > 6 VPD's/hr	25%	100%
Mortality	0.8% (days 28-34 post MI)	0.9% (1st week of titration)

6. Patients enrolled prior to April 19, 1989

a) Patients enrolled prior to April 19, 1989, and randomized to blinded therapy on moricizine or a matching placebo will be retained in the study in the status quo and followed per protocol. All events in these patients from the past, as well as in the future, will be counted toward the endpoints.

b) Patients who had been randomized to encainide or flecainide or matching placebo will be eligible for reentry into the study provided they have no medical exclusion, an ejection fraction ≤ 0.40 (an ejection fraction obtained subsequent to the baseline can be used, but a new ejection fraction study is not required), and an average of at least 6 VPD's/hr on a qualifying Holter obtained after washout from encainide or flecainide. Non-medical exclusions (i.e., the 90 day limit) do not apply to these patients.

c) For patients formerly on CAST-ENC or CAST-FLEC who are eligible for reentry and who are willing to participate, baseline data must be collected as for any new patient, with the exception of the qualifying MI data, and the patient will be followed as a new patient. All such patients will be considered as one stratum in the analysis.

d) Patients who previously tolerated but failed to be suppressed on the low and/or medium doses of moricizine may be tested directly on the middle and/or high dose or may begin over at the low dose at the investigator's discretion.

e) Patients who are not rerandomized will be followed for the duration of CAST. However, the followup will be the same as that used in the followup substudy for patients who are not randomized to blinded therapy, i.e., telephone followup at 6 monthly intervals with detailed acquisition of event data.

7. Duration of Recruitment and Followup

Recruitment will be extended 18 months to January, 1992. Followup will be extended 21 months through March, 1994.

8. Screening

The screening procedures will be the same. However, due to the observed low event rate in the initial phase of CAST emphasis will be placed on maintaining an accurate Holter registry, and in particular, obtaining patient identification necessary for National Death Index followup (Social Security Number, date of birth, name). This will allow us to investigate any low event rate in the placebo group observed in the future.

9. Disqualifying VT

The definition of disqualifying VT is changed to be compatible with the change in exclusion criteria. During both titration and followup disqualifying VT will include arrhythmias producing symptoms (other than palpitations), sustained ventricular arrhythmias, torsades de pointes or a run of $\geq$ 30 seconds at a rate $\geq$ 120 bpm.

10. Blinded Retitration

Only dose reduction will be permitted during blinded retitration.

11. Power

Power considerations are detailed below. These are based primarily on estimates available in CAST. They ignore the problem of dropout and dropin which (in CAST) have so far proven to be small.

The primary endpoint continues to be arrhythmic death or cardiac arrest in patients whose arrhythmias are suppressed by antiarrhythmic drugs. Total mortality is a secondary endpoint. The expected number of patients to be titrated, the expected number of patients to be suppressed or partially suppressed and the primary event rates are presented in the following tables.

Survival Rates To Arrhythmic Death/CA in CAST Placebo Patients

Patients with VPD's Suppressed, enrolled within 90 days of MI and	Event Rate 3 mos	6 mos	9 mos	12 mos
EF < 30	2.0%	5.3%	6.7%	10.1%
30 ≤ EF ≤ 40	0.5%	1.7%	1.7%	3.0%

Expected Enrollment and Rates based on past data and 33 months (4/1/89-12/30/91) of recruitment

Category of Patient	Titration			Blinded Therapy					
				Main Study-Mor Arm Prim Event Rate			Partially Suppressed Substudy[2] Prim Event Rate		
	N	2 week Dth/CA rate	Mor Supp Rate ≥ 80%	N	1 yr	overall	N	1 yr	overall
"Old CAST type pts ≤ 90 days"(43.5 mos fu)[1]									
EF < 30	747	4.6%	55%	411	9.7%	22.4%	168	10%	23.1%
EF ≥ 30 - ≤ 40	859	1.7%	65%	559	2.2%	5.1%	150	5%	11.6%
"higher risk pts because change in VT and age" (avg 43.5 mos fu)									
EF < 30	100	5%	55%	55	11%	25.5%	23	12%	27.8%
EF ≥ 30 - ≤ 40	100	2%	65%	65	2.5%	5.8%	18	6%	13.9%
"old CAST ENC/FLEC pts (avg 54 mos fu) assuming 75% eligible and willing"									
EF < 30	106	1%	80%	85	5%	13.8%	11	6%	16.5%
EF ≥ 30 - ≤ 40	285	.5%	80%	228	1%	2.8%	29	1.5%	4.2%
"old MOR pts (avg 60 mo fu)									
Main Study				272	7.2%	21.6%			
Substudy							43	10%	30%
TOTAL	2197			1675			442		
Average Event Rate		2.7%			12.9%			18.3%	
Power	.72 (a .05 1 sided test and λ = .5)			.73 (a 1 sided 0.025 test and λ = .7)			.28 (a .05 1 sided test and λ = .8)		

1 Assumes recruitment at approximately 1.2 times the rate in the 12 months prior to May 1989.
2 Assumes 50% of the patients not suppressed will be partially suppressed.

a) The main study (Primary analysis -- moricizine suppressed patients). As before, the design of CAST will be a one-sided study testing for benefit with alpha level 0.025.

For an alternative of 30% reduction in arrhythmic death from the expected average of 12.9% over the duration of the study (average of 43.5 months of followup), the power that can be expected from these 1675 patients against a one-sided 0.025 level test is approximately .73.

b) The partially suppressed substudy. Of the patients who are not suppressed by moricizine, half are expected to be partially suppressed. There will be about 442 partially suppressed patients with an average event rate of 18.3% over almost 4 years of followup. The resulting power (for a 20% reduction) and a one-sided 0.05 level test is only .28, but would add to the overall conclusion of CAST. (The test is one-sided because the substudy objective is to support the main study finding.)

c) Placebo in titration. Since the primary concern is an adverse effect of the drug during titration, it is reasonable to consider a one-sided 0.05 level test. There will be about 2197 patients titrated. Assuming that the proportion of patients with ejection fraction < 0.30 and with ejection fraction between 0.30 and 0.40 would be similar to that currently observed in CAST to date (i.e., 43% to 57%) and that the current observed event rates during the first two weeks of titration represent a two-fold increased risk due to the drug, the corresponding power is .72. If the current rates represent a 1.5 fold increase in risk, the power would be .41.