1. Description of the Population

The patient data on this tape includes information on all patients enrolled in CAST. This includes patients enrolled only in CAST-I, patients enrolled only in CAST-II, and patients enrolled in CAST-I and then re-enrolled in CAST-II. The total population is 3549.

Users of this data tape are *strongly* urged to study carefully the CAST Protocol and Manual of Operations before attempting to retrieve data or perform statistical analyses from this data set. The CAST protocol is complex.

Every effort possible has been made to protect the confidentiality of the individual patients. The identification number assigned to each case in this data file has no relationship with the patient (e.g. order of enrollment) or with the clinical center at which the patient was recruited.

CAST I

CAST I began enrolling patients on June 15, 1987. Patients were randomly assigned to begin titration on encainide or flecainide if their ejection fraction was ≥ 0.30 and on encainide or moricizine if their ejection fraction was < 0.30.

CAST I was stopped at the recommendation of its Data and Safety Monitoring Board on April 18, 1989. At that time, all patients on encainide, flecainide or their matching placebo were taken off these drugs. Data on the long term blinded therapy portion of CAST I is, therefore, censored at this date. However, following this date, living patients were followed by telephone every six months until a final follow-up conducted after April 1, 1991 when the Steering Committee voted to discontinue follow-up of this cohort.[1]

Patients not randomized to long-term blinded therapy in CAST I were followed every six months by telephone interview after discontinuing titration. These patients, in general, were also followed through the decision in April 1991 to discontinue follow-up of the encainide/flecainide cohort.

Some patients (n=281) from CAST I were "re-randomized" into CAST II.

Results reported in Echt et al. ("Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo: The Cardiac Arrhythmia Suppression Trial" N Engl J

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[1] During a "transition period" - 4/19/89 to 9/30/89 - some follow-ups were completed using the CAST Follow-up form (CAST 16) rather than the CAST Telephone Follow-up form (CAST 75). Events occurring during this time were recorded on CAST event forms (e.g., Death or Cardiac Arrest CAST 23)

Med 1991:324:781-8.) included the 1,593 patients randomized to long term blinded therapy on encainide, flecainide or their matching placebo. These patients are identified by a known value for the date of randomization to long term blinded therapy (DTRAN12). Exposure to therapy and events are counted from this date through April 18, 1989 or the date of death or resuscitated cardiac arrest.

A small number of patients had new baseline Holters obtained after commencing titration. Suppression on previously tried drugs and doses was recomputed without rechallenging the patient on those drugs and doses. The existing Open Label Titration records (CAST 12) were adjusted based on this information. Thus, the dates of the Open Label Titration records (CAST 12) reflect the dates that the patient was first evaluated on that drug and dose. It is possible, for example, for a patient to have tried dose 1 and dose 2 of encainide and have originally shown a lack of suppression on both doses. A subsequent new baseline Holter could result in changing the results of titration on dose 1 to "successful suppression" and dose 2 to "randomized on an earlier drug or dose." These patients with anomalous titration sequences are identified by the presence of a Holter form (CAST 04) with the "Reason for recording" coded "prospective new baseline." The analysis variable (SUPPRES1) gives the final results regarding whether the patient's arrhythmia was successfully suppressed.

In addition a few patients during CAST I experienced intolerable adverse symptoms during blinded therapy. Rather than discontinue CAST therapy, these patients were "blindedly retitrated" on CAST drugs that they had not tried during open label titration. For example, a patient assigned to encainide (or its placebo) developing intolerable adverse symptoms could have tried moricizine (or its placebo) in a blinded fashion. As long as proarrhythmia or other severe ECG effects did not appear and the patient tolerated the drug, the patient continued on blinded therapy in CAST I on the new drug (or its placebo). See Section 7 of the CAST I Manual of Operations for details. Patients assigned to encainide or flecainide (or their matching placebo) were included in the CAST I analysis, regardless of whether they switched to moricizine (or its placebo) in blinded retitration. Similarly, patients assigned to moricizine or its placebo were included in the CAST II analysis, regardless of whether they switched to encainide or flecainide (or matching placebo). The analysis variables described below properly account for this change of therapy.

CAST II

CAST II was a comparison of moricizine with placebo. It includes all patients entering the trial after April 19, 1989, the 320 patients randomized to moricizine or its placebo prior to that date and the few patients who ended up on moricizine (or its placebo) via blinded retitration.

Blinded therapy was discontinued on August 1, 1991. Thus, only follow-up

information through that date is included on patients who were randomized to long-term blinded therapy on moricizine or its matching placebo.

Patients not randomized to long-term blinded therapy in CAST-II (entered on or after April 19, 1989) were followed by telephone interview for approximately one year after discontinuing titration on moricizine. Thus follow-up information through the one-year interview (which was not usually done at exactly one year) is included.

Two primary comparisons are reported for CAST-II:

1) The results of the first 14 days of exposure to the drug ("acute phase"), primary endpoint is death from any cause or resuscitated cardiac arrest.

2) The results of long-term blinded therapy on moricizine or its matching placebo, primary endpoint arrhythmic death or resuscitated cardiac arrest, secondary endpoint death from any cause or resuscitated cardiac arrest, separate analysis of those with successful suppression and those with partial suppression (see Protocol).

Analysis 1 was performed on all patients randomized to titration (DTRAN21) on or after May 25, 1989 and prior to July 18, 1991 (in order to allow 14 days of exposure prior to the end of the trial) excluding a few patients (n=57) where the clinical center systematically did not follow the protocol (mostly patients entered prior to IRB approval for blinded administration of drug during this acute phase at one site and patients recruited by one particular doctor at a second site. These patients are identified by the variable EXCBTITR = 1.) Therapy assigned was moricizine (600mg/day) or placebo (or no therapy for patients entered prior to IRB approval for blinded administration of drug during this acute phase) and is identified by the variable ACTPLA21. Exposure begins at DTRAN21 and continues for 14 days or until death or cardiac arrest if that occurred during this phase (DTDCA) or the patient was randomized to long-term blinded therapy (DTRAN22).

In analysis of the acute phase, it should be noted that, due to the time required to obtain IRB approval for the revised protocol, some (n=428) patients were randomly assigned to begin open label administration of moricizine (600mg) immediately (n=211), and some were assigned to delay beginning the drug for 14 days (n=217). Analysis of the acute phase, except for mortality and cardiac arrest, excludes these unblindedly treated patients. That is, adverse events other than death were analysed only among patients randomized to a <u>blinded</u> protocol for 14 days.

Analyses 2 were performed on all patients randomized to long-term blinded therapy on moricizine or its placebo. In this data set, these patients are identified by a non-missing value for date of randomization (DTRAN22). Therapy assignment is given by ACTPLA22. Patients are analyzed separately depending on whether their ectopy was successfully suppressed (SUPPRES2 = 1) or partially suppressed (SUPPRES2 =

2). Exposure began at date of randomization (DTRAN22) and continued through August 1, 1991 (end of the trial) or date of death or cardiac arrest (DTCDA).