CASE 13

The Data Monitoring Experience in the Cardiac Arrhythmia Suppression Trial: The Need to Be Prepared Early

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ABSTRACT

The Cardiac Arrhythmia Suppression Trial (CAST) was designed to evaluate the hypothesis that suppression of cardiac ventricular arrhythmias in patients with a recent myocardial infarction would reduce the incidence of sudden death and total mortality, using three drugs known to suppress cardiac arrhythmias. Patients were randomized to receive either active drug or a matching placebo. The trial was terminated after only 15% of the planned-for events had been observed with an unexpected but dramatic increase in sudden death and total mortality in those patients receiving two of the active therapies. Later, the third drug was also discontinued.

INTRODUCTION AND BACKGROUND

Premature contractions/depolarizations of the left ventricle of the heart in a patient population surviving a myocardial infarction are a risk factor for sudden death and cardiac mortality. Increases in these premature contractions/depolarizations are associated with a fourfold higher mortality rate.[1,2] Drugs such an encainide, flecainide, and moricizine were established as being very effective in suppressing these premature ventricular contractions; the first two drugs were approved by regulatory agencies for treatment of serious arrhythmias, but moricizine was not yet approved in the United States. Physicians began to treat patients with ventricular arrhythmias during the 1980s, using encainide and flecainide, as they were more effective and better tolerated than other antiarrhythmic drugs.[3] There was widespread belief that these drugs should reduce mortality because of their antiarrhythmic effect,

despite the fact that previous trials had not shown that use of these drugs reduced the risk of sudden or cardiac death.[4] Thus, despite increasing use of these drugs, the question remained as to whether anti-arrhythmiac treatment was of clinical benefit to the patient surviving a myocardial infarction but experiencing ventricular arrhythmias.

PROTOCOL DESIGN

Following a pilot trial, the Cardiac Arrhythmia Pilot Study (CAPS),[5] which established the arrhythmia-suppressing effect of encainide, flecainide, and moricizine in a population of post-infarct patients, the Cardiac Arrhythmia Suppression Trial (CAST) was designed.[6] The CAPS pilot study had not indicated any major toxicity. CAST, sponsored by the National Heart, Lung, and Blood Institute (NHLBI), was designed as a randomized, placebo-controlled trial to evaluate the effect of these three drugs in reducing the incidence of sudden cardiac death (primary) or death from any cause (secondary).[6] The patient population consisted of men and women with a myocardial infarction who had asymptomatic or minimally symptomatic ventricular arrhythmias with some reduced ventricular function.

The trial started with an open label titration or run-in period, with patients given, in random order, one or more of the three drugs, to identify those who would respond to treatment by having at least an 80% arrhythmia suppression. Patients with this level of arrhythmia suppression were then eligible to be randomized into the main study to either the effective drug or its matching placebo. Patients who had increased arrhythmias or could not tolerate the drugs were not entered.

The primary endpoint in CAST was death due to arrhythmia. Secondary endpoints included total mortality and cardiac death for any cause. Anticipated potential adverse events included an increase in arrhythmias, electrocardiographic changes, and worsening heart failure. The trial was initially designed to randomize 4,400 patients with 90% power to detect a 30% reduction in sudden death, using a one-tailed 0.05 significance level. This design assumed an 11% cumulative rate of sudden death over the three years of planned follow-up. The primary test statistic to compare time to sudden death between active therapy and placebo was the logrank test. CAST had an independent Data and Safety Monitoring Board (DSMB) which was scheduled to meet twice yearly. The rationale for the one-tailed 0.05 test was that it was not the main objective of CAST to demonstrate a harmful effect and that DSMBs were unlikely to allow trials to continue to that level of evidence.[7]

Patient enrollment began in June 1987 and was scheduled to be completed in June 1990. In April 1989, the DSMB recommended that two of the

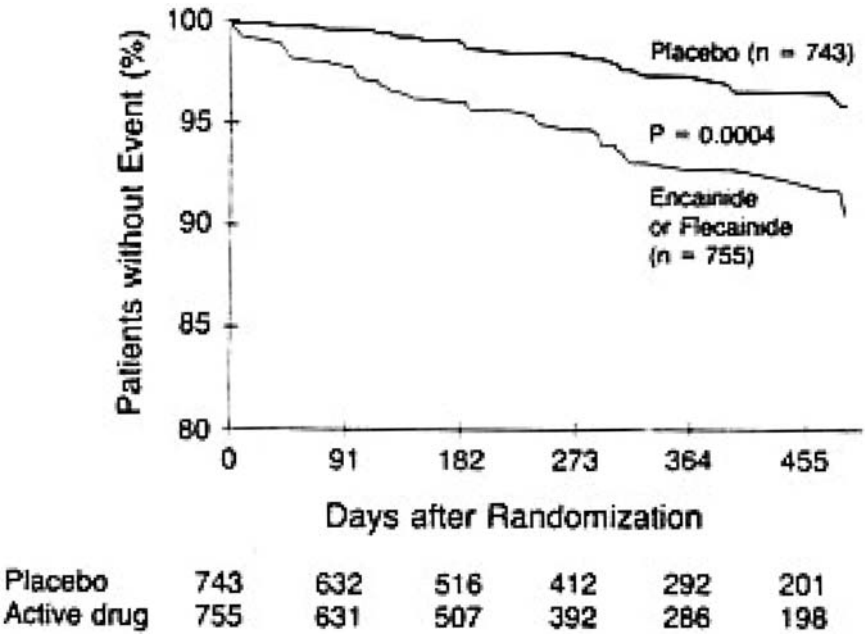

Figure 1 Actuarial Probabilities of Freedom from Death or Cardiac Arrest *Due to Arrhythmia* in 1498 Patients Receiving Encainide or Flecainide or Corresponding Placebo. The number of patients at risk of an event is shown along the bottom of the figure. Reproduced from CAST (1991) with permission of the *N Engl J Med.*

three drugs in CAST, encainide and flecainide, be stopped because of a likely harmful effect from these drugs.[6,8] The final results from these two drugs are shown in Figures 1 and 2, with cause specific mortality shown in Table 1. Later, the DSMB recommended termination of moricizine as well.[9] For the rest of this presentation, we will refer to the first portion of CAST as CAST-I and the subsequent moricizine-alone portion as CAST-II.[9]

DATA MONITORING EXPERIENCE

In March of 1987, the DSMB met for the first time to review the protocol.[10] While the investigators had designed CAST to be a one-tailed 0.05 design, the DSMB voted to recommend a one-tailed 0.025 alpha level to test for treatment benefit, which reduced the power from 90% to approximately 85%. Their rationale was that a trial should require the same level/strength of evidence for benefit, regardless of whether the design was one-tailed or two-tailed. A one-tailed 0.025 requires the same critical value (i.e., 1.96) for

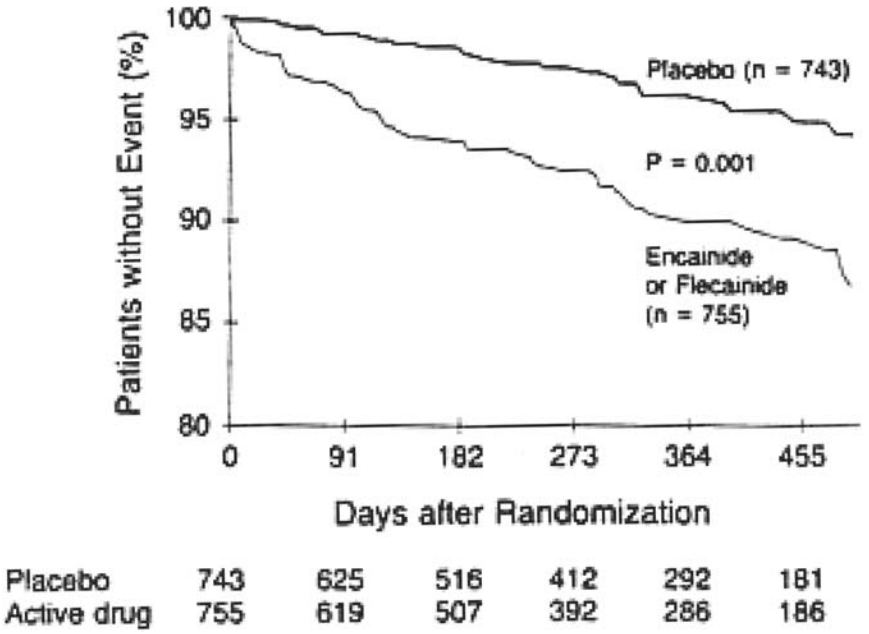

Figure 2 Actuarial Probabilities of Freedom from Death or Cardiac Arrest *Due to Any Cause* in 1498 Patients Receiving Encainide or Flecainide or Corresponding Placebo. The number at risk is shown along the bottom of the figure. Reproduced from CAST (1991) with permission of the *New England Journal of Medicine.*

Table 1 Cause of Death and Cardiac Arrest (with Resuscitation) in the CAST, According to Treatment Group

	Both Groups		
Cause	**Active Drug**	**Placebo**	**Total**
Patients in group	755	743	1498
All deaths and cardiac arrests	63	[†]26	89
Cardiac death or cardiac arrest	60	[‡]21	81
Arrest with resuscitation	7	1	8
Death or arrest due to			
Arrhythmia	43	[§]16	59
Arrest with resuscitation	5	1	6
Death or arrest not due to			
Arrhythmia	17	[¶]5	22
Arrest with resuscitation	2	0	2
Noncardiac death	3	[¥]5	8

[†] P = 0.0001 for comparison with patients receiving active drug.
[‡] P < 0.0001 for comparison with patients receiving active drug.
[§] P = 0.0004 for comparison with patients receiving active drug.
[¶] P = 0.0107 for comparison with patients receiving active drug.
[¥] P = 0.4822 for comparison with patients receiving active drug.
Modified Table 1. N Engl J Med 324:781–788, 1991.

the test statistic as a two tailed 0.05 level design. A conservative group sequential 0.025 boundary was established to monitor for treatment benefit. At the same time, the DSMB recommended a 0.025 lower symmetric advisory boundary for adverse effects as well. In addition, conditional power methods were to be used for assessing the futility of achieving a beneficial effect with an interim observed negative trend. Both the beneficial and harmful sequential boundaries were implemented using the approach of Lan and DeMets,[11,12] using the expected number of cardiac sudden deaths (initially estimated to be 425 and later revised to 300 due to a lower than expected placebo event rate) to calculate the observed information fraction (observed events/expected total events). The sequential boundaries for the logrank test statistic are shown in Figure 3. These lower boundaries were called advisory because the DSMB did not want to be bound to crossing these thresholds for negative or harmful trends.

At the second meeting in January of 1988, before outcome data were available, the DSMB decided to remain partially blinded in their review of interim data, seeing tables by codes with the intent of maintaining objectivity. However, the DSMB also agreed that it could totally unblind its members should they need to in their deliberations.

In September of 1988, the DSMB met to finalize the monitoring plan and to review very preliminary data on 1,147 patients already randomized, which was approximately one-fourth of the target. Data were provided partially

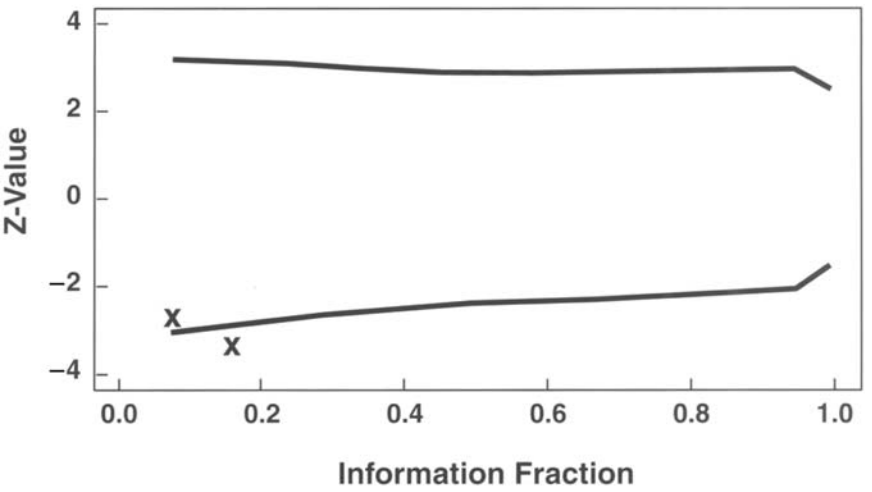

Figure 3 CAST Sequential Boundaries. Reproduced from CAST (1991) with permission of the *N Engl J Med.*

blinded, labeled Drug X and Drug Y. The primary endpoint, sudden death, was 3/576 for Drug X and 19/571 for Drug Y. These 22 events represented approximately 5% of the expected primary events. Since the number of events was very small and the goal of CAST was to evaluate longer/chronic term use of these drugs, the DSMB decided no recommendations were appropriate and remained blinded, with the plan to meet again in six months.

Meanwhile, the CAST Coordinating Center summarized the data monthly for its own internal monitoring and notified the Project Office at the NHLBI in late January of 1989 that the results had become more extreme. On February 13, unblinded updated tables for the primary events were presented to NHLBI. The Chair of the DSMB was notified and a conference call with the board was scheduled for March 2, 1989. The DSMB was informed of the updated analyses and unblinded. The results were substantially trending in a negative or harmful direction. A series of additional analyses were requested including verification of treatment codes and a sweep of the clinical sites for as yet unreported primary events. The DSMB decided to meet at its regularly scheduled meeting on April 16 and 17, 1989, to review all of the available data and the additional analyses.

At the April 1989 DSMB, data presented during the conference call were all confirmed. The advisory boundary for harm, with all three drugs combined, had been crossed. At this time, most of the events were in the encainide and flecainide arms, and their respective placebo controls. Because moricizine was not as effective in suppressing ventricular arrhythmias as were encainide or flecainide, fewer patients were assigned to moricizine or its placebo. Although the initial goal of CAST was to evaluate overall active treatment versus placebo, the DSMB decided to focus on the two treatments that had sufficient numbers of patients and events. In the encainide and flecainide arms, there were 33 sudden cardiac deaths on active treatment and nine on placebo. There were 56 deaths on treatment and 22 on placebo. The DSMB recommended that the encainide and flecainide arms be dropped from the protocol. The DSMB concluded that it was too soon to make judgments about moricizine. Not only were there very few events among those on moricizine or its corresponding placebo, the results were trending slightly in favor of the active drug. That same day, the sponsor of the study—the National Heart, Lung and Blood Institute—was notified. The principal investigators were informed the following day. Because the study was international (clinics in the United States, Canada, and Sweden), the drug regulatory agencies from those countries were also immediately notified. In addition, because of the concerns that many non-study patients were being treated with these drugs, the public was quickly alerted to the findings. A preliminary report was published[6] as rapidly as the data could be assembled.

It should be noted that a subsequent publication[8] reported on the final results, after all outstanding data had been incorporated. At that time, the deaths were 63 in the encainide-flecainide group and 26 in the placebo groups (Table 1).

In retrospect, the observed data (3 vs. 19) on September of 1988 would also have crossed the lower advisory bound for harm. However, if the data sweep had occurred at that time, the updated data (10 versus 22) would not have crossed the lower boundary although still indicating a very negative trend. The interim logrank results are shown on the sequential boundary plot shown in Figure 3.

Following the DSMB recommendation for encainide–flecainide (i.e., CAST-I), the board recommended that CAST be redesigned for the moricizine versus placebo comparison to continue. Moricizine was pharmacologically different from encainide and flecainide, and thus the answer to its effect on sudden death was still unknown. Of the remaining 2,100 patients to be enrolled, half would be randomized to moricizine and the rest to the matching placebo. Patients still on the encainide–flecainide portion could be re-randomized to CAST-II. However, another important design change was made. In CAST-I, the run-in period had patients only on active treatment, so no comparisons with a placebo could be made. The mortality event rate observed during this period appeared to be higher than expected. In the redesign, patients enrolled in the two-week run-in period were randomized to moricizine or placebo. Those who were initially randomized to placebo were subsequently placed on moricizine in order to see if their arrhythmias were suppressed by the drug. If patients had 90% of their arrhythmias suppressed, they were eligible to be randomized to the main study. This redesign allowed the CAST investigators to evaluate the risk of initial exposure to moricizine by having a placebo comparison during the two-week run-in with over 70% power for a two-fold increase in sudden death.[9]

At the April 1991 meeting, the DSMB reviewed interim mortality data, partially blinded as before, for the CAST-II trial. While there were no apparent trends for the moricizine–placebo comparison in the main study, an apparent difference was emerging in the run-in period: 12 versus 3. Given the CAST-I experience, the DSMB decide to unblind and became aware that the 12 sudden deaths were on the moricizine arm, including the last six events.

The advisory lower boundary harm as applied to the run-in period had not been crossed and the confidence intervals around the estimated treatment effect were quite wide. Although at the time that CAST-I ended, moricizine had shown a small, but positive trend, now, with further data, the likelihood of a treatment benefit in the main trial was less than 30%. The DSMB voted to continue CAST-II and meet again in three months.

At the July 1991 meeting, the DSMB recommended that CAST-II be terminated. In the two-week run-in period, there were now 15 sudden deaths on moricizine and still three on placebo, a result that is statistically significant at $p = 0.02$ after adjusting for monitoring. The conditional power for the main study had dropped to less than 10%. Given the total CAST experience, the DSMB felt the results were sufficiently compelling to recommend that moricizine should not be used for these indications. The final data in the run-in period, after all events were accounted for, was 17 to 3.

LESSONS LEARNED

1. The CAST experience has provided both the cardiology and the clinical trial community with many valuable lessons. One fundamental lesson is that conventional wisdom and practice can be wrong. Prior to CAST, the consensus was that suppression of asymptomatic or minimally symptomatic ventricular arrhythmias was beneficial in patients who had survived a myocardial infarction. The fact that the presence of the arrhythmias is correlated with the subsequent risk of sudden or cardiovascular death lead many to view the suppression of arrhythmias as a surrogate for the clinical outcome. CAST proved that suppression of ventricular arrhythmias is not in fact a surrogate for the clinical outcome of sudden or cardiovascular death. Arrhythmia suppression may be important but is clearly not sufficient. This trial is one of many that have demonstrated the challenges and dangers of using invalid surrogate outcomes.[13]

2. A related issue is the one-sided versus the two-sided hypothesis issue that the CAST DSMB raised. Based on conventional wisdom of a treatment's likely effect, it may make sense to consider a one-sided test of the hypothesis of the treatment benefit. However, CAST illustrates that conventional wisdom is not always correct. Many trials may be considered as having two one-sided hypotheses, one for a positive beneficial treatment effect and the other in a negative direction testing for possible harm. The degree of evidence for these two one-sided hypotheses need not be the same. Keeping the level of evidence for treatment benefit to be the same, regardless of whether the hypothesis is posed as one-sided or two-sided hypothesis, seems advisable. For example, the two-sided 0.05 alpha level trial and the one-sided 0.025 alpha level designs both require a test statistic of 1.96 or approximately two standard errors (with no adjustments for interim analysis) to be judged significant and beneficial. The lower boundary for harm could be symmetric as was done for CAST-I or asymmetric as was used in CAST-II. In either case, the lower boundary is more of a guide for the DSMB because clinical judgment is often critical in assessing negative or harmful trends. For example, a DSMB may choose not to wait until a lower sequential boundary

has been crossed depending on other factors observed in the data. For that reason, the CAST DSMB referred to the lower boundary as advisory. Of course, at the time they made those recommendations, they did not anticipate that such boundaries would play a role. It was fortunate that the lower advisory boundary was in place prior to the September 1988 DSMB meeting.

3. Another lesson is that trials must have the DSMB in place prior to the start of the trial. Often DSMBs are convened some months after the trial has started randomizing patients. This may cause two problems. First, the DSMB may have some constructive suggestions regarding the design which are difficult to incorporate once the trial is underway. In CAST, the DSMB made a suggestion as to the significance level that should be required. Furthermore, the negative trends began to emerge at the first DSMB meeting where data were available and got rapidly more negative by the time only 15% of the expected events had been observed. If CAST had waited until 25% or 50% of the expected primary events had been observed, a number of patients would have been unnecessarily harmed. Thus, the DSMB should be appointed and convened prior to the initiation of the trial.

4. In order to support the DSMB, the data management system must be in place and functioning. As CAST demonstrated, having data as early as the first 5% of events and in the months following was critical. While some delay in getting data from the clinics into the database is to be expected, that delay cannot be months. For example, had the CAST DSMB focused on the logrank test statistic at their first analyses, they would have observed that the lower advisory boundary was being approached. Yet, in retrospect, the actual number of events at the point in time would not have been so extreme in the negative direction. The DSMB and CAST would have been in a very awkward situation to have recommended termination due to the extreme test statistic but find that the evidence had weakened with the data clean-up. Fortunately, current informatics technology allows for rapid transmission of key outcome data but unless these are put into place, the DSMB is left vulnerable and consequently current and future patients.

5. Regardless of how detailed the DSMB charter and monitoring plan are, the DSMB will likely have to react to unexpected events and situations. The DSMB has to have contingency plans to react in a timely fashion. For example, the redesign of the run-in period for CAST-II turned out to be extremely important, indicating that simple exposure to these drugs for post infarction patients with ventricular arrhythmias was sufficient to increase the risk of sudden death. The lack of a placebo control in the titration run-in for the pilot and CAST-I made interpretation of initial risk difficult.

6. Finally, the CAST DSMB had to weigh the balance between obtaining convincing and persuasive evidence with ethical responsibility to current and future patients. If the data are not allowed to become convincing, then belief and practice may not change, which would have put even more patients at risk. However, prolonging the trial beyond the point where the data have become persuasive would be placing patients at unnecessary risk. The point at which data become persuasive is largely based on the DSMB's best judgment. Statistical methods such as sequential monitoring boundaries can be very useful for the primary outcome or outcomes but the totality of information must be considered in any DSMB recommendation.[14,15] In CAST, the evidence was accumulating very rapidly so there was not much time for deliberation. This requires that the DSMB and monitoring procedures be put in place at the beginning and that data flow be very current.

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