A case study: CAST

CAST: The Cardiac arrhythmia suppression trial

Background
Arrhythmia after myocardial infarction

Premature contractions/depolarizations of the left ventricle of the heart in patients who have suffered a myocardial infarction are a risk factor for sudden death and cardiac-related mortality.

Drugs such an encainide, flecainide,and moricizine are effective in suppressing these premature ventricular contractions and there was the belief that this would reduce mortality in patients who had previously survived an MI and who were experiencing ventricular arrhythmias.

The CAST trial

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 CAST trial
Statistical design

Endpoints

- The primary endpoint in CAST was death due to arrhythmia.
- Secondary endpoints included total mortality and cardiac death for any cause.

The trial was to randomize 4,400 patients with 90% power to detect a 30% reduction in sudden death, using a one-tailed 0.05 significance level.

The design assumed an 11% cumulative rate of sudden death over the three years of follow-up.

The primary test statistic to compare time to sudden death between active therapy and placebo was the logrank test.

The CAST trial
Drug formulations and stratification

Drug	Dose	Frequency
Placebo		Three times daily
Encainide	35-50 mg	Three times daily
Flecainide	100-150 mg	Three times daily
Moricizine	200-250 mg	Three times daily

Patients were stratified

- Clinical center
- Left ventricular ejection fraction* (≥ 30 versus < 30)
- Time between the qualifying Halter recordings and the MI

*Percent of blood leaving the heart every time it contracts. An ejection fraction of 55% or higher is considered normal.

Statistical considerations
Power and sample size

The study design estimated that there would be $D = 425$ total events necessary for the study to produce 90% power to detect at least a 30% reduction in sudden death compared to placebo at 5% *one-sided* significance level, testing only the superiority of the active arms.

Accrual was to start in June 1987 and be completed by June 1990. In all, 4,400 subjects were to be enrolled in the CAT study.

However, after the DSMB reviewed the protocol, they suggested that the a one-sided significance level should be reduced to 2.5%, the amount of evidence should be the same whether the statistical test were one-sided or two-sided.

Statistical considerations
Sequential boundaries

The sequential boundary selected was as follows:

$$\alpha(t) = \begin{cases} (\alpha/2)t & \text{if } t < 1 \\ \alpha/2 & \text{if } t = 1 \end{cases}$$

A lower symmetric, *non-binding* boundary was also considered. The boundary was non-binding because the DSMB did not want to be bound by the possibility that superiority of placebo were established, particularly early in the study.

Statistical considerations
Sequential boundaries

The top (superiority) and the bottom (non-binding inferiority) boundaries are shown in the following figure:

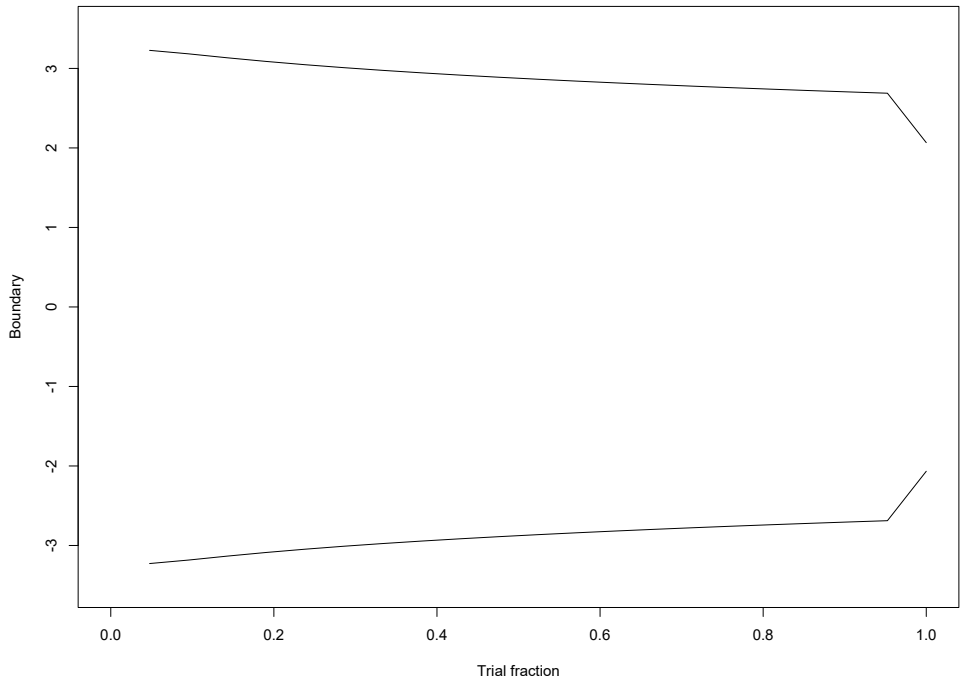

Figure 1: Group sequential boundaries for the CAST study

DSMB reviews
First DSMB review: January, 1988

The first DSMB review occurred in January, 1988.

During that meeting, the Board decided to remain blinded to the study treatment when they met again to review the study data.

DSMB reviews
Second DSMB review: September, 1988

In September 1988, the DSMB met to review preliminary data based on 1,147 patients (or about a quarter of the total).

The DSMB saw data as follows (Pawitan & Halstrom, 1990):

Drug	Events	Total
X	7	576
Y	29	571

Table 1: Results during the first DSMB meeting in September, 1988

The log-rank test value was $z = -2.82$, which would not have crossed the boundary (although this was bad news and the trends were going - unbeknownst to the DSMB - in the wrong direction!) so the DSMB decided to leave the study open.

Sequential boundaries after the September 1988 DSMB review

The situation (I repeat unbenknownst to the DSMB that was blinded to treatment arm during that meeting) was as follows:

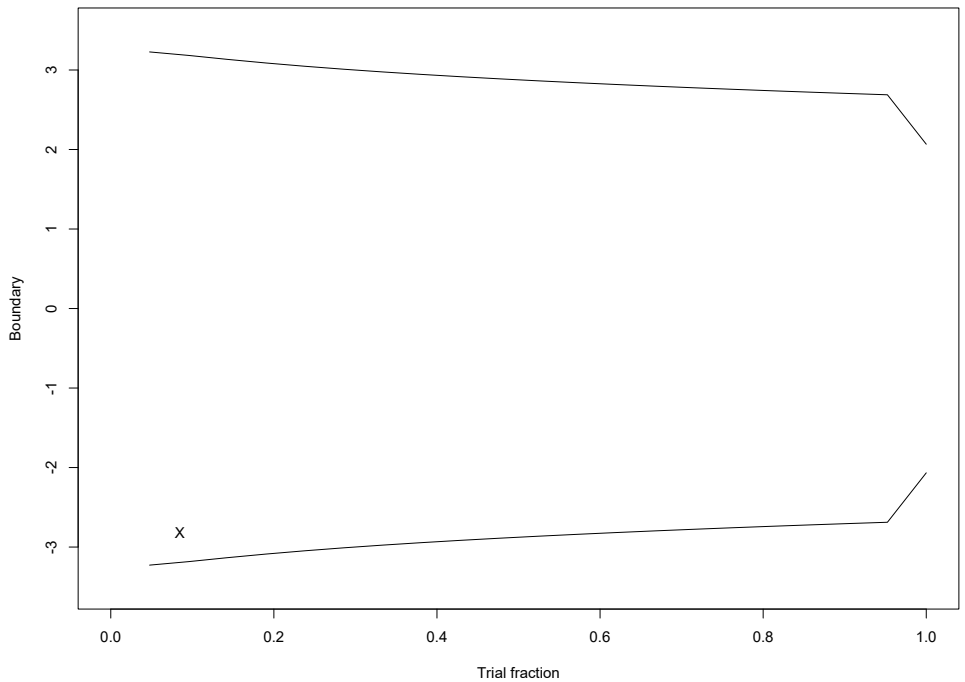

Figure 2: Boundaries for the CAST study: September 1988 review

The trial fraction during this review was $t = 32/425 = 7.5\%$.

DCC internal reviews

Meanwhile, the CAST Data Coordinating Center kept summarizing 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, 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.

The DSMB members were informed of the updated analyses and were unblinded.

DSMB reviews
Third DSMB review: April, 1989

The DSMB saw data from 30 March 1989 (Pawitan & Halstrom, 1990) as follows:

Drug	Events	Total
Placebo	9	725
Active arms	33	730

Table 2: Results during the second DSMB meeting in April, 1989

The log-rank test z-value was $z = -3.22$.

Sequential boundaries after the April 1989 DSMB review

The situation at the April 1989 review was as follows:

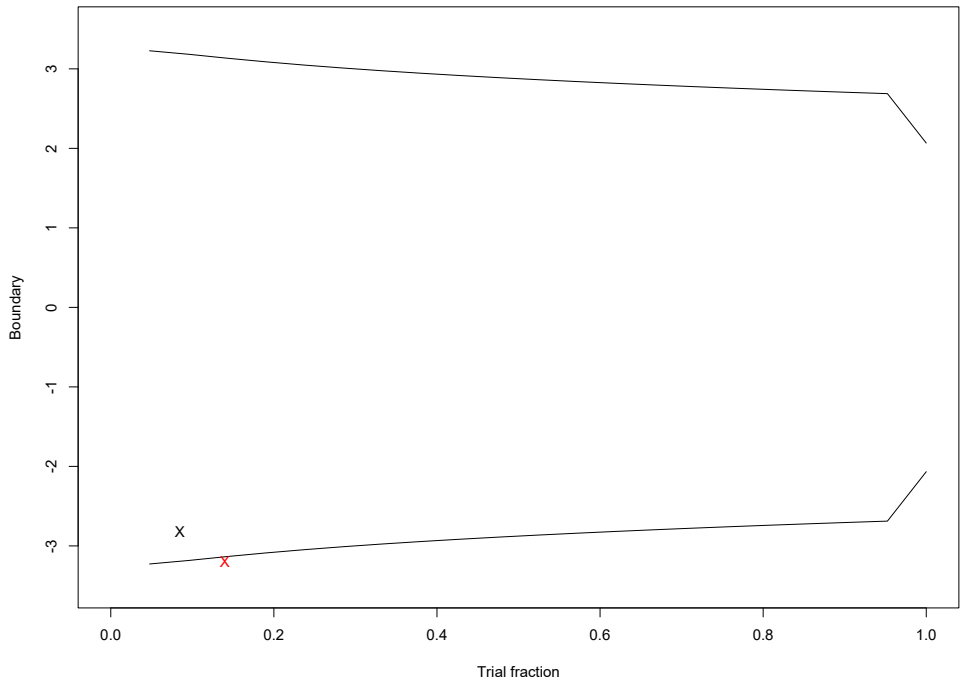

Figure 3: Sequential boundaries for the CAST study: April 1989 review

Note that, during this review, the expected number of events was revised to $D = 300$ instead of $D = 425$ as in the original design. Thus, the trial fraction was now $t = 42/300 = 14\%$.

Survival curves from data available at the April 1989 DSMB review

The Kaplan Meier plots based on data seen at the April 1989 review were as follows (CAST investigators, 1989):

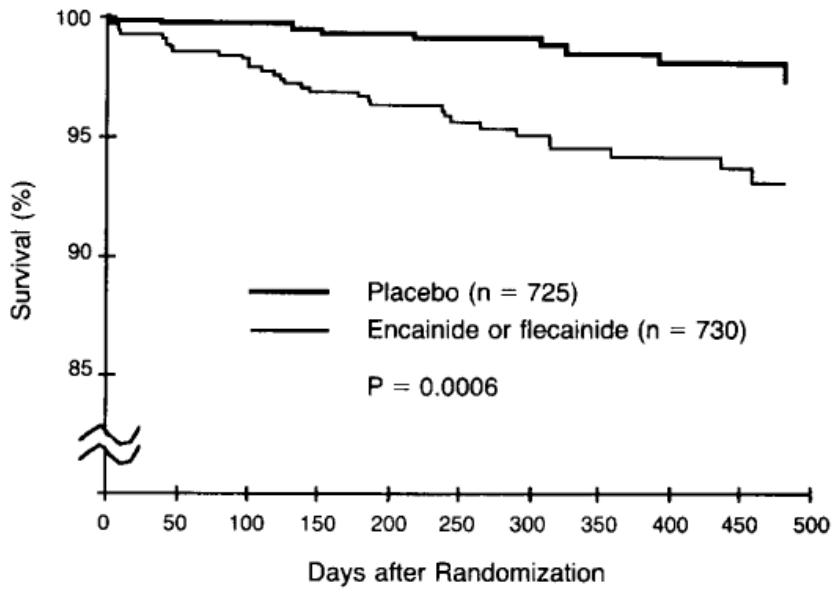

Figure 1. Survival among 1455 Patients Randomly Assigned to Receive Encainide or Flecainide, or Matching Placebo.

The cause of death was arrhythmia or cardiac arrest. The nominal P value was based on a traditional two-sided log-rank test adjusted for multiple groups.

Figure 4: Kaplan Meier plots of active arms vs. placebo

Lessons learned from the CAST study
Design

- You should note how easily the availability of the spending function technology allowed the team to revise the trial fraction once it was decided that the expected number of events would be much lower (300 versus 425) than expected. All that was needed was to simply plot the point on the Z scale on the graph and show that it had crossed the lower boundary.
- As described by Pawitan & Halstrom (1990) and by DeMets & Friedman (2006) there were additional considerations entering in the final decision to stop the study (namely "stochastic curtailment" which showed that there was almost no chance of ever establishing superiority of the active arms), as well as the obvious concerns with the evolving trends of the study, besides crossing the advisory boundary.

Lessons learned from the CAST study
One-sided vs. two-sided bounds

- A technical issue is the one-sided versus the two-sided hypothesis that the CAST DSMB raised. It may make sense to consider a one-sided test of the hypothesis of the treatment benefit. However, CAST illustrates that many trials may be considered as having two one-sided hypotheses, one for a positive beneficial treatment effect and one testing for possible harm.
- While the degree of evidence for these two one-sided hypotheses need not be the same, keeping the level of evidence for treatment benefit the same, regardless of whether the hypothesis is posed as one-sided or two-sided hypothesis,seems advisable. (Both the two-sided 0.05 and the one-sided 0.025 alpha level designs require a test statistic of 1.96 to be judged significant).

Lessons learned from the CAST study
Advisory bounds

- The lower boundary for harm could be symmetric as was done for CAST-I or asymmetric as was used in CAST-II, the follow-up to CAST, which only tested moricizine after the encainide and flecainide were dropped).
- The lower boundary was constructed more as a guide for the DSMB but the Board may choose not to wait until a lower sequential boundary has been crossed to stop the study or not stop the study even after it has been crossed depending on other factors observed in the data. For that reason, the CAST DSMB referred to the lower boundary as advisory. In the case of the CAST study, it was fortunate that the lower advisory boundary was in place prior to the September 1988 DSMB meeting.

Lessons learned from the CAST study
Surrogate markers

- Conventional wisdom can be wrong. The fact that the presence of the arrhythmias is correlated with the risk of sudden death led many to view the suppression of arrhythmias as a surrogate for the clinical outcome.
- CAST proved that this was not in fact a surrogate for the clinical outcome and demonstrated the dangers of using invalid surrogate outcomes.

Lessons learned from the CAST study
The DCC

- Note also that the negative trends began to emerge 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.
- To support the DSMB, the data management system must be in place and functioning. As CAST demonstrated, having data as early as possible is critical to ensure the safety of the patients.

Lessons learned from the CAST study
The DSMB

- The DSMB must be in place prior to the start of the trial, otherwise constructive suggestions the Board might have about the study design will be difficult to incorporate after the start of the trial. In CAST, the DSMB suggested the changes to the significance level for example.
- The DSMB will likely have to react to unexpected events and situations so it must have contingency plans in place in order to react to unexpected events in a timely fashion.
- The CAST DSMB weighed the balance between convincing evidence versus its ethical responsibility to current and future patients. If the data are not convincing, clinical practice may not change, putting more patients at risk, but prolonging the trial past the point where the data have become persuasive would be placing patients at unnecessary risk.

Bibliography

- The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. 1989. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 321:406–412.
- Pawitan Y, Hallstrom A. 1990. Statistical interim monitoring of the Cardiac Arrhythmia uppression Trial. Stat Med 9:1081–1090.
- Data Monitoring in Clinical Trials: A Case Studies Approach. 2006. Edited by David L. DeMets, Curt D. Furberg, Lawrence M. Friedman. Springer.