EDITORIALS

The Events Surrounding the Removal of Encainide and Flecaïnide From the Cardiac Arrhythmia Suppression Trial (CAST) and Why CAST Is Continuing With Moricizine*

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For safety reasons, encainide and flecaïnide were removed from the Cardiac Arrhythmia Suppression Trial (CAST) in April 1989. On April 25, 1989, the news media began reporting the preliminary results of CAST indicating an increase in mortality in the groups treated with encainide and flecaïnide. The next day, physicians in the United States began receiving "Dear Doctor" letters from the manufacturers of encainide and flecaïnide and telephone calls from patients who were taking these drugs. Thus, physicians had the results of CAST thrust on them in a way that many found profoundly distressing. A primary reason for the distress was lack of publication of the CAST results in a medical journal where data could be evaluated and interpreted. Physicians were caught unaware and felt unable to give intelligent comment. The purpose of this editorial is to give an eyewitness account of the events surrounding the removal of encainide and flecaïnide from CAST and to explain why it was necessary to make a public announcement before the publication of the data, why it took from April 25 to August 10, 1989 to publish the results and why CAST is continuing to recruit patients to the moricizine arm of the study.

Removal of encainide and flecaïnide from CAST. On April 16 and 17, 1989, the CAST Data and Safety Monitoring Board (DSMB), the independent body responsible for reviewing the accumulating results on a regular basis to protect the participants, gathered in Seattle for its regular semianual meeting. After review of the safety and outcome information available through March 30, 1989, the DSMB voted on April 17 to recommend discontinuation of encainide and flecaïnide, but to continue the CAST with moricizine and to consider adding other drugs. This recommendation was made because the data indicated that it was very unlikely that benefit could be demonstrated for the active treatments and that it was likely that encainide and flecaïnide were harmful. Later the same day, the National Heart, Lung, and Blood Institute accepted the DSMB recommendation and directed that it be implemented immediately to avoid any additional drug-related deaths. On April 18, a memorandum was sent by overnight mail from the CAST Data Coordinating Center to all CAST Clinical Centers advising them to contact all patients taking encainide or flecaïnide and tell them to discontinue their trial medication. On April 19 the memorandum was received and the process of taking patients off of encainide and flecaïnide therapy began and was quickly completed.

Drug regulatory affairs. Also on April 19, the National Heart, Lung, and Blood Institute notified the Food and Drug Administration and the Health Protection Branch of Canada about the CAST results by telephone and an appointment was made for Dr. Lawrence Friedman (National Heart, Lung, and Blood Institute Project Officer for CAST) to brief Drs. Robert Temple and Raymond Lipicky of the Food and Drug Administration on April 21. Swedish drug regulatory officials were informed through the Göteborg enrolling center. The National Heart, Lung, and Blood Institute notified Bristol Laboratories and Riker/3M by telephone that encainide and flecaïnide were being discontinued from CAST and a confirming letter was sent to these two companies by overnight carrier. The Food and Drug Administration arranged a meeting for 8:00 AM on April 25 with representatives of Bristol Laboratories and Riker/3M to discuss the indications for encainide and flecaïnide and the content of a "Dear Doctor" letter. Bristol Laboratories and Riker/3M requested additional data. To accommodate this request, Dr. Peter Frommer, Deputy Director of the National Heart, Lung, and Blood Institute, scheduled a briefing for the two drug companies from 2:00 to 5:00 PM on Monday April 24, 1989 in his office on the National Institutes of Health campus in Bethesda, Maryland. Drs. Bigger (Chairman of the CAST

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Steering Committee), Friedman, Frommer and Temple met with officials from Bristol Laboratories and Riker/3M to review the findings that prompted the recommendation that encaïnide and flecainide be removed from CAST.

At 8:00 AM on April 25, Food and Drug Administration Commissioner Dr. Frank Young, along with Drs. Temple and Lipicky, met with representatives of Riker/3M and Bristol Laboratories to discuss the "Dear Doctor" letter that would advise physicians about the CAST findings and clarify the companies’ changes in indications for their products as a result of CAST data. Dr. Bigger attended the meeting on behalf of the CAST investigators. The companies proposed to restrict promotional activities to the indication for malignant ventricular arrhythmias and to work with the Food and Drug Administration to relabel the drugs. It was agreed that the CAST findings should be communicated to physicians immediately and accurately. The wording of a "Dear Doctor" letter was discussed and agreed upon by the Food and Drug Administration and the two companies. Separate "Dear Doctor" letters were sent to all American physicians by each company starting on the afternoon of April 25. The letters included an 800 number for physicians to call for further information. Also, the Food and Drug Administration outlined its intention to communicate with physicians through the American Medical Association’s MedNet and by telephone with various organizations (e.g., American College of Physicians, American Association of Family Practice, American College of Cardiology, American Medical Association, American Association of Medical Colleges) later that same day. It was hoped that these organizations could help by communicating with their members. The CAST findings and the ensuing actions by the manufacturers of encainide and flecainide and the Food and Drug Administration would be published in the next Food and Drug Administration Talk Paper.

The press conference. There was concern at the National Heart, Lung, and Blood Institute that the process of discontinuing encainide and flecainide in CAST patients in more than 100 participating hospitals might result in leaks and distortions in the press. The National Heart, Lung, and Blood Institute, the Food and Drug Administration, Bristol Laboratories and Riker/3M agreed that a press conference should be held to help make physicians aware of the CAST findings and to avoid frightening patients with rumors and distortions. The plan was to give the press written background information, present the major CAST findings and answer questions.

At 11:00 AM on April 25 the press conference was held on the National Institutes of Health campus. Drs. Claude Lenfant (Director of the National Heart, Lung, and Blood Institute), Friedman, Bigger and David Bristow (Chairman, CAST DSMB) described the background, conduct and findings of the CAST. Food and Drug Administration Commissioner Young and Dr. Temple stated the joint manufacturer

Food and Drug Administration position that encaïnide (approved 1986) and flecainide (approved 1986) were now only indicated for life-threatening ventricular arrhythmias. Commissioner Young stated that, according to his best information, 586,000 prescriptions were written for these drugs in 1987 and 790,000 in 1988. The Food and Drug Administration repeatedly requested that the press emphasize in all communications that patients should not discontinue encaïnide and flecainide without consulting their physicians. After the statements by representatives of the National Heart, Lung, and Blood Institute and Food and Drug Administration, an extended question and answer period ensued.

Immediately after the National Heart, Lung, and Blood Institute press conference, statements were made to the press by Mr. George Meridith, Vice President and General Manager of Riker/3M, and by Dr. Raymond Egan, President of U.S. Nutritional and Pharmaceutical Group, Bristol-Meyers, Inc. It was stated that between 200,000 and 400,000 patients in the United States were taking encaïnide or flecainide. Three actions were announced by the manufacturers of the two drugs: 1) physicians would be notified of the CAST findings immediately by "Dear Doctor" letters; 2) the companies would work with the Food and Drug Administration over the subsequent weeks to rewrite the labeling for the two drugs; and 3) patients who were taken off these drug regimens by their physicians could be reimbursed for unused supplies.

Publication of CAST preliminary findings. From the moment the findings were known to the CAST investigators on April 17, 1989, publication of the results in a peer-reviewed journal was intensively pursued. The Executive Committee wrote a draft report within 1 week and asked the Coordinating Center to provide additional data for this purpose. To avoid delay in publication, it was decided to base the report on the data summary of March 30, 1989 rather than wait for all information on deaths to be reported and evaluated. Thus, the publication would present the same information reviewed by the CAST DSMB when they made their recommendation to remove encaïnide and flecainide from CAST. Dr. Arnold Relman, Editor of the New England Journal of Medicine, was contacted and told that the CAST investigators intended to submit a manuscript reporting the interim findings. To avoid invoking the Ingelfinger rule (1-3), a letter from Dr. Frommer was faxed to Dr. Relman when the National Heart, Lung, and Blood Institute press conference was scheduled to release the CAST findings to inform him that the purpose of the press conference was to report a matter of urgent importance to the public health and to avoid misinformation from reaching CAST patients, physicians and the public. A draft of a manuscript was circulated at a meeting of the CAST investigators in Washington, D.C. on May 9 to 10, 1989. The manuscript was revised by the investigators and a manuscript was submitted to the New
The conclusion was that moricizine alone open question whether it in mortality. No other ca a safety problem with two drugs. SERK344s Co~~i~~riQ~ wm given BO ents for this action were t hypothesis had been div for encainide an i.e., suppression of ve dial infarction with eith associated with c was c er the the nsive assessment 0 after myocardial infarction. Relman AS. The lngelfinger rule. N Engl4 Med 1981;305:824-6. Relman AS. Reporting the aspirin study: the Journal and the media. 'Id Engi 3. Relman AS. More on the lngelfinger rule. N Engl J Med 1988;318:1125-6. 4. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406-12.

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