BETA-BLOCKER HEART ATTACK TRIAL:

DESIGN, METHODS, AND BASELINE RESULTS

Beta-Blocker Heart Attack Trial Research Group

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INTRODUCTION

Coronary heart disease continues to occupy a position of prominence as a cause of death in the United States. Although a reduction in coronary heart disease mortality has been observed in recent years, the acute and chronic sequelae of coronary atherosclerosis are still responsible for over 600,000 deaths annually in the United States. Sudden cardiac death represents a major factor in these statistics. Furthermore, survivors of a documented myocardial infarction are known to have an increased risk of premature death relative to the general population.

In 1976, an international panel of experts in the field of coronary heart disease was brought together by the National Heart, Lung, and Blood Institute (NHLBI) to consider medical strategies aimed at dealing with coronary heart disease mortality. Particular emphasis was placed on the prevention of sudden cardiac death. A number of different therapeutic regimens were considered; all were directed either toward the treatment and prevention of arrhythmias or toward the use of agents which might limit the amount of myocardial ischemia.[1]

The panel recommended examining the possible effectiveness of the long-term administration of beta-adrenergic blocking agents in survivors of an acute myocardial infarction. Theoretically, an agent which could block the sympathetic nervous activity thought to be involved in precipitating sudden death and which also had non-neurogenic antiarrhythmic properties would be of value to people with coronary heart disease. Already a number of clinical trials primarily conducted in Europe had suggested that beta-adrenergic blocking agents may have a beneficial effect on the mortality rate, particularly sudden death, in patients who experienced acute myocardial infarction.[2-9] However, clear proof of efficacy was lacking.

STUDY DESIGN

1. Objectives

The primary objective of the Beta-Blocker Heart Attack Trial (BHAT) was to determine whether the regular, chronic administration of propranolol to patients who had had at least one documented myocardial infarction would result in a significant reduction in mortality from all causes during the follow-up period.[10] To this end, a projected total of about 4000 eligible volunteer patients were to be recruited to participate in a double-blind clinical trial within 21 days of the onset of hospitalization for the acute event. One-half of the patients were to be randomly assigned to propranolol and one-half to placebo.

The secondary objectives were to determine:

1) whether the regular, chronic administration of propranolol to the study population would reduce:

   a) the incidence of coronary heart disease mortality,

   b) the incidence of sudden cardiac death, defined as death within one hour of onset of symptoms,

   c) the combined incidence of nonfatal myocardial infarction plus coronary heart disease mortality.

2) possible adverse effects of propranolol in chronic use.

3) possible mechanisms of action of propranolol if it were successful in reducing mortality or morbidity.

4) the natural history of coronary heart disease in the placebo group population.

In addition, the following subgroup hypotheses were to be tested:

1) Propranolol is effective in reducing mortality due to sudden cardiac death in patients with prior myocardial infarction who have complex premature ventricular contractions at baseline.

2) Propranolol is effective in reducing mortality in patients with prior anterior acute myocardial infarctions.

2. Design

Due to the required sample size the BHAT was planned as a collaborative clinical trial. In order to meet high methodologic standards, it was decided that a double-blind, placebo-controlled, randomized design was to be employed. The double-blind approach is difficult to imple-

ment in any trial of beta-blockers and it was recognized to be more costly than a single-blind one. However, the double-blind design was selected in preference to a single-blind design because of the potential of:

1) a more unbiased assessment of nonfatal endpoints;

2) a more unbiased assessment of side effects; and

3) more unbiased ancillary intervention including a possibly lower placebo "drop-in" rate (i.e., the rate at which placebo patients are prescribed propranolol).

Thirty-one Clinical Centers were involved in recruiting BHAT patients.* Appendix A lists these and the hospital coronary care units (CCU's) used by each as a source of patients. Other centers also participating in the trial included a Coordinating Center, a Resting ECG Reading Center, an Ambulatory ECG Reading Center, a Central Laboratory, and an NHLBI Project Office. (Study administration will be described below.)

Recruitment took place over 27 months (June 19, 1978 to October 2, 1980). Randomization was stratified by Clinical Center and blocked within each center.

The design features of this trial are described in greater detail elsewhere.[10,11]

3. Study Population

The target population for the BHAT included men and women aged 30 through 69 years admitted to hospital coronary care units (CCU's) or their equivalent and having a confirmed acute myocardial infarction on the current admission. Patients who had contraindications to use of propranolol, conditions where prescription of propranolol by private physicians was judged to be highly likely, or other conditions felt likely to impair long-term participation were not eligible for the BHAT.

After completion of the baseline reference examination the eligible patients were randomized and drug regimen of either placebo or propranolol initiated. Length of follow-up for each patient depended upon the date of entry into the study, since all patients were to be followed to a common termination date. Given over 2 years for recruitment of patients, patient follow-up as originally planned would range from 21 to 48 months, or an average of approximately 3 years.

Specifications of the estimation of sample size for the BHAT are presented in Appendix B.[10] In general, the estimate that a total of

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*One additional Clinical Center was involved initially, but because of lagging recruitment, its participation was terminated. The few patients recruited were transferred to the care of another clinic.

about 4000 patients must be recruited rested on several assumptions: the 3-year mortality rate in the placebo group would be 18 percent; the drug will reduce this rate in the treatment group by 28 percent; the effect of the drug will be immediate; a specified proportion of patients in the propranolol group will stop taking their medication and another specified proportion in the placebo group would be prescribed beta-blockers; patients would be followed for an average of 3 years; total mortality would be the primary endpoint; and a two-tailed significance level (α) of 0.05 and power ($1-\beta$) of 0.90 would be employed. For administrative purposes, the projected sample size was adjusted upwards to 4200 patients. To permit recruitment of patients within a desirable interval of time, the 31 Clinical Centers participated with a projected average enrollment of approximately 135 patients.

At the end of the recruitment period, 3837 patients had been randomized. Although the recruitment goal had not been met, the projected power of the trial was only slightly affected, dropping to 0.89.

4. Patient Recruitment and the Baseline Examination

All patients admitted to the cooperating CCU's were screened for inclusion as BHAT patients. The number of patients screened was approximately 158,000. A log of all these patients was kept during the recruitment phase. The log provided a tool to monitor recruitment at each center, helped to ensure that every CCU admission received consideration for enrollment into the BHAT, and assisted in developing comparisons of yield from each CCU and Clinical Center.

During the first few days after a patient's admission to a CCU, the patient's eligibility for the study was evaluated. Clinical history, electrocardiographic changes, and serum enzymes were used to determine this eligibility. Patients eligible for this study were men and women, aged 30 through 69 years, with one or more documented myocardial infarctions. Patients were recruited while in the hospital for an acute myocardial infarction and enrolled into the study before discharge. It had to appear to the BHAT staff that the study definition of an acute myocardial infarction had been fulfilled. This diagnosis was based either on electrocardiographic records showing evolving Q or QS changes and ST segment and T wave changes, or on elevated serum enzymes and appropriate clinical history together with specified ECG criteria. (The specific requirements for a qualifying myocardial infarction are included in Appendix C.) Electrocardiograms from this MI were initially read at the Clinical Center and later confirmed by the Resting ECG Reading Center.

Approximately 16,400 patients were found to have had a BHAT defined MI, to be age-eligible, and alive five days after admission. In Table 1 are presented CCU log data describing the final disposition of these potentially eligible patients.

Otherwise eligible patients were excluded from enrollment if any of the following types of conditions applied:

1) relative or absolute contraindications to the administration of propranolol;

2) medical conditions for which propranolol is a highly probable treatment drug of choice;

3) presence of any disease other than the patient's CHD associated with a reduced likelihood of survival for the duration of the trial;

4) patient had undergone or was likely to undergo cardiac surgery;

5) the qualifying myocardial infarction resulted from a probable nonatherosclerotic cause;

6) adherence to the study protocol was likely to prove especially difficult.

Appendix D lists specific inclusion and exclusion eligibility criteria.

After the patient had survived at least five days and his clinical status had stabilized, the study with its possible benefits and risks was discussed with him and his physician. A brochure containing such information was made available to the patient. The patient was then asked to sign an informed consent form.

If the patient signed the form and was found to be free of exclusion criteria, a baseline reference examination was carried out. According to protocol, the examination had to occur prior to discharge from the hospital, but not later than 21 days following admission. The primary purpose of the examination was to establish baseline values of study variables.

Included as part of this examination were a clinical history, a physical examination, an electrocardiogram, a PA chest x-ray, urinalysis, hematocrit, white blood cell count, serum cholesterol, serum potassium, SGOT, and serum creatinine. A 24-hour ambulatory ECG (a Holter recording) was also obtained on all patients at baseline and on a random sample of approximately 1,000 patients at 6 weeks.

At this point in the recruitment process, it was known whether or not the patient was eligible for randomization. In Table 1 it is noted that of the approximately 16,400 potentially eligible patients, 23 percent were ultimately randomized.

5. Randomization

Immediately after completion of the baseline reference examination, eligible patients were randomized to either the propranolol or placebo group. Randomization was carried out in a blocked fashion within Clinical Center so that each would have an approximately equal propor-

tion of propranolol and placebo patients. Block size was randomly varied among groups of size 4, 6, and 8. The random assignment to one of the two study groups was made by the Coordinating Center and transmitted to the Clinical Center by telephone (hard copy to follow) after verification that the steps mentioned above had been completed. Each patient was assigned an identification number which had a drug code incorporated in it.

Table 2 describes the pattern of randomization by 3-month periods. At the end of the recruitment period, 3837 patients had been randomized (1916 in the propranolol group and 1921 in the placebo group).

6. Treatment Schedule

Immediately after randomization, patients were given a 20 mg. tablet of assigned BHAT medication. The propranolol and placebo pills were indistinguishable and are referred to collectively as "study medication." If the patient did not exhibit any adverse reactions to the tablet, the dosage was increased to 40 mg. every eight hours. After the patient had been on this schedule for a minimum of six consecutive doses, blood was drawn eight hours after the last dose and sent to the Central Laboratory for a propranolol determination. If the serum drug level was under 20 ng/ml for the propranolol group patients, the dosage was to be increased to a maintenance dose of 80 mg. T.I.D. at the one month follow-up visit ; otherwise, the dosage was increased at this visit to 60 mg. T.I.D. To maintain the blind, a proportional number of placebo group patients were assigned to 60 or 80 mg of study medication. Of the 3837 enrolled patients, 82% were placed on the 60 mg. T.I.D. regimen and 18% on the 80 mg. T.I.D. regimen.

7. Follow-up

The follow-up phase of the trial consisted of a series of visits made to the BHAT Clinic by each patient over a period of from 21 to 48 months. As noted above, patients were recruited into the study at various times over a 27 month period and were followed to a common termination date. Therefore the total duration of follow-up varies among the patients in accordance with their date of entry into the study.

Follow-up visits were scheduled to occur quarterly with the exception of the first two. The first visit took place one month after randomization (at which time the drug dosage was finally increased to its target level). The second visit took place at one and a half months after randomization, i.e., two weeks from the date of the first visit (at which time a second 24-hour Holter monitor was performed on the randomly selected subset of the BHAT population). All subsequent visits occurred at three month intervals from the date of randomization.

The purpose of these follow-up clinic visits was to make regular assessments of the study population in order to evaluate the effects of

propranolol in comparison with baseline data. Specifically, the objectives of the follow-up visits were:

1) to make determinations on endpoint events occurring since the baseline or previous follow-up examination; for example, new cardiac events, congestive heart failure, and stroke (the criteria for these events are described in Appendix E);

2) to update medical history obtained at baseline;

3) to assess the patient's current overall health status;

4) to determine the extent of adverse reactions to BHAT medication;

5) to provide the patient with additional study medication; and

6) to encourage the patient to adhere to his prescribed medication.

The means for making these determinations were by interview, physical examination, ECG, x-ray and laboratory tests on blood and urine specimens. The specific evaluative procedures required at each visit are listed in Appendix F.

The laboratory analyses performed as a result of clinic visits were not primarily intended to detect toxicity or other problems in individual participants or to supplant usual good clinical care of the patient. Rather, they were used to describe the propranolol and placebo groups. If extreme laboratory values were noted, however, the Clinical Center physician was immediately telephoned by the Central Laboratory in addition to receiving the usual written report.

8. Data Analysis

The primary statistical analyses of the mortality and morbidity results of the BHAT were carried out using life table methods. These allow one to observe the pattern of mortality and morbidity by treatment group and can take into account varying lengths of follow-up. Statistical tests of the difference in mortality from any cause, mortality from coronary heart disease, sudden cardiac death, and combined nonfatal myocardial infarction plus coronary heart disease mortality between the two treatment groups were computed throughout the study and at the end of the follow-up period. These data were monitored and submitted to the Policy Data Monitoring Board for review on a regular basis during the study to permit early termination of the study should the data warrant.

Other analyses of interest were done in an attempt to identify subgroups where propranolol might be particularly beneficial or harmful. All subgroup analyses employed baseline characteristics. No patients were withdrawn from the analyses regardless of adherence to study medication or clinic attendance.

9. Quality Control Procedures

A Quality Control Subcommittee was established to monitor the quality (i.e, the completeness, accuracy, and precision) of all study data and to detect and assist in correction of problems in data collection and handling procedures. An Adherence Subcommittee was also established to promote methods for maintaining good adherence to study protocol and medication. Internal and external quality control procedures were implemented as follows:

A. Clinical Centers

The Principal Investigator at each center was responsible for the overall conduct and performance of the Clinical Center. To aid in the efforts of adhering to the protocol and reporting data of high quality, the centers were given feedback on their performance through reports which were regularly generated by the Coordinating Center. These included summary assessments of patient adherence to the drug regimen, missed patient visits, accuracy in the completion of study forms, missing forms and procedures not completed. In addition, the Quality Control and Adherence Subcommittees, after also having received and reviewed these reports, made suggestions for improvements to the Clinical Centers.

B. Resting ECG Reading Center

At the beginning of the trial, performance criteria for the ECG machines used at the Clinical Centers were established. To insure that these machines continued to operate satisfactorily, standardized calibration strips were produced periodically and submitted to the ECG Center for evaluation. Repair or replacement was recommended for machines producing unsatisfactory strips. The ECG's were also monitored for technical quality and suggestions for improvement were given to the centers as needed.

Each ECG was independently coded by two coders at the Reading Center. Discrepancies were adjudicated by the Principal Investigator of the center. In addition an external blind surveillance program for the ECG Center was carried out by resubmitting ECG's using coded identification numbers. Comparing several readings of the same record allowed the repeatability of the coding process to be judged.

C. Ambulatory ECG Reading Center

From the beginning of the study, efforts were made to insure the completeness, consistency and comparability of the Holter data. Each record was reviewed for anomalies and inconsistencies by a quality control officer at the Reading Center itself. Internal as well as external blind resubmission programs were established to assess reproducibility.

D. Central Laboratory

The types of internal quality control used by the Central Laboratory included blind resubmission, pool resubmission and bench controls. Detailed reports for each type of control were presented to the Quality Control Subcommittee for each quarter.

A blind external surveillance program was established for serum propranolol. However, external surveillance of the laboratory was not directly conducted by the BHAT for cholesterol, creatinine and potassium, but was being conducted indirectly by other NHLBI trials. Reports of these data were furnished to the Quality Control Subcommittee.

E. Coordinating Center

The quality control procedures implemented at the Coordinating Center were focused on the accuracy and completeness of the data reported by the Clinical Centers and other participating units and on patient adherence to the procedures stated in the protocol.

Data reported on the study forms received from the Clinical Centers were reviewed for consistency and completeness. Forms with missing or discrepant data were returned to the Clinical Centers for appropriate corrections. Forms were also cross-checked to assure consistency across forms. Detailed reports of the number of errors per form and the number of forms in error were sent to the Clinical Centers each time the computer masterfile was updated.

Also, as noted above, summary performance reports were regularly generated. These were presented to the clinic personnel at semiannual meetings at which specific problems were discussed and remedies suggested.

PARTICIPATING UNITS AND STUDY ADMINISTRATION

The participating units in this collaborative clinical trial included the following: thirty-one individual Clinical Centers, a Coordinating Center, a Resting ECG Reading Center, an Ambulatory ECG Reading Center, a Central Laboratory, an NHLBI Project Office, and a Drug Distribution Center. The units in the study were tied together through a study administration, which maintained operations in the study and ensured effective communication and cooperation among the various study units. During the planning phase, a Planning Committee represented the various investigators. During the course of the trial, the administrative units included a Policy Data Monitoring Board, a Steering Committee, an Executive Committee, various subcommittees and an Assembly of Investigators. These units are described at length elsewhere.[10,11]

In Appendix G are listed all the BHAT investigators and other staff involved in the participating centers. Also listed are the members of the various committees and subcommittees.

1. Participating Units

The functions of the participating units of the Beta-Blocker Heart Attack Trial are described below.

A. Clinical Centers

Thirty-one Clinical Centers were responsible for recruiting the required number of patients, providing patient care, administering the study drugs, and collecting the information required by the study protocol. The Principal Investigator was responsible for the overall conduct and performance of the Clinical Center. The professional and clerical organization of each Clinical Center differed, but each Clinical Center had one person specifically identified as the Clinic Coordinator. This person was responsible for such critical matters as checking coronary care unit logs, maintaining good patient adherence, appointment scheduling, and checking the completeness of forms. He or she also monitored shipment of blood specimens to the Central Laboratory and collection of scheduled and interim event ECG's.

B. Coordinating Center

The Coordinating Center had a major role in the design, implementation, and execution of the study. The staff had the responsibility for collecting, editing, analyzing, and storing all data received from the Clinical Centers, Central Laboratory and the ECG Reading Centers. Some specific functions of the Coordinating Center were to work with the investigators in the development and pretesting of forms and

procedures and in the preparation of the Manual of Procedures, to make a random assignment to a treatment group for each patient, to assume responsibility for review of all data transmitted on study forms, and to check the completeness of records and periodically prepare performance reports to participating Clinical Centers. It was also the responsibility of the Coordinating Center to periodically analyze the frequency of new events and adverse reactions by treatment group and to report these data to the Policy Data Monitoring Board, to prepare interim technical and statistical reports for the periodic meetings of the Assembly of Investigators, to prepare recruitment charts for each Clinical Center, and to assist in the preparation of reports of the study for publications.

C. ECG Reading Centers

The Resting ECG Reading Center read and coded all of the standard 12-lead ECG's collected at baseline and at the follow-up visits. The Center was responsible for developing diagnostic criteria for qualifying and recurrent myocardial infarction and for reading the ECG's associated with these events. The Center also periodically reviewed the performance of the Clinical Center ECG technicians and the quality of Clinical Center ECG machines.

The 24-Hour Ambulatory ECG Reading Center was responsible for reading and coding the 24-hour baseline Holter recording on all patients and the 6-week follow-up recordings on the approximately 1,000 randomly selected patients.

D. Central Laboratory

The Central Laboratory performed selected laboratory tests for all patients enrolled in the study. These included serum determinations of cholesterol and potassium, of propranolol (for drug adherence and dosage adjustment) and of transaminase and creatinine (for potential drug toxicities). The results of all laboratory determinations were forwarded to the Coordinating Center and were also reported routinely to the Clinical Centers (with the exception of serum propranolol determinations). In cases of abnormal results possibly indicating drug toxicity, the Central Laboratory notified the Clinical Center as soon as possible so that appropriate action could be taken.

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

The National Heart, Lung, and Blood Institute was responsible for providing organizational, scientific, and statistical direction to the study through the Clinical Trials Branch, Division of Heart and Vascular Diseases. The Scientific Project Officer was a voting member of the Steering Committee

as well as a nonvoting member of the Policy Data Monitoring Board. Other NHLBI staff also worked with the individual Clinical Centers, Coordinating Center, Central Laboratory, ECG Reading Centers and Drug Distribution Center.

F. Drug Distribution Center

The U.S. Public Health Service Supply Service Center at Perry Point, Maryland, served as a central procurement, storage and distribution point for the study medications. Propranolol for the trial was provided free of charge by Ayerst Laboratories (New York, New York). The company had no other involvement in the trial.

2. Study Administration

A. Planning Committee

During the planning phase of the study, the Planning Committee had the responsibility for developing the final study protocol and for initiating the development of the Manual of Procedures and study forms.

The Planning Committee was composed of Principal Investigators of the Clinical Centers, the Coordinating Center, the Resting ECG Reading Center, the Central Laboratory, and the staff of the NHLBI Project Office. This committee was dissolved upon the establishment of the Steering Committee and Assembly of Investigators.

B. Steering Committee

The Steering Committee provided scientific direction for the study at the operational level. The permanent members of the Steering Committee were the chairman and two other appointed Clinical Center investigators, the Principal Investigators of the Coordinating Center, Central Laboratory, ECG Reading Centers and the NHLBI Project Officer. There were, in addition, six or seven members who were principal or co-principal investigators of the participating Clinical Centers. These representatives were assigned for 1-year terms. In this way, all centers had representation on the Steering Committee by the end of the trial.

Specific functions of the Steering Committee were:

a. To provide overall scientific direction for the study at the operational level.

b. To advise and assist the Coordinating Center, Central Laboratory, ECG Reading Centers and Drug Distribution Center on operational matters.

c. To monitor at six month intervals the performance of the individual Clinical Centers with regard to patient recruitment and adherence to study medication.

d. To monitor the quality of the performance of the Clinical Centers and the central units.

e. To review all proposed ancillary studies.

f. To keep the Assembly of Investigators informed about the progress of the trial.

g. To report major problems to the Policy Data Monitoring Board.

h. To make recommendations concerning changes in the Protocol to the Policy Data Monitoring Board.

Between Steering Committee meetings, an Executive Committee consisting of the Chairman of the Steering Committee, the Principal Investigator of the Coordinating Center, and the NHLBI Project Officer met or had conference calls 3-4 times per month. The function of this committee was to provide on a more current basis direction for the study on the operational and analytical levels. In cases where urgent decisions were required, the Executive Committee was empowered to make such decisions and then report them to the Steering Committee.

In Appendix G is the list of the subcommittees of the Steering Committee.

C. Assembly of Investigators

The Assembly of Investigators met semiannually to review the progress of the study and to vote on major issues.

The Assembly represented all of the operational units participating in the study. The Principal Investigator or one co-investigator from each Clinical Center, and one representative each from the Coordinating Center, the Central Laboratory, the NHLBI Project Office, and the ECG Reading Centers (Resting and Ambulatory) were voting members of the Assembly. Other personnel from the Clinical Centers, Coordinating Center, Central Laboratory, ECG Reading Centers, and NHLBI attended Assembly meetings as nonvoting members.

D. Policy Data Monitoring Board

The Policy Data Monitoring Board acted in a senior advisory capacity to the NHLBI on policy matters throughout the duration of the study. In addition, it reviewed study results by treatment group and evaluated the study treatment for beneficial and adverse effects.

The Board consisted of a chairman, six additional voting members who were appointed by the NHLBI for the duration of the study, and the NHLBI Project Officer as an ex officio, nonvoting member. Board meetings were attended by senior representatives from the Coordinating Center and NHLBI, as well as the chairman of the Steering Committee. No voting member of the Policy Data Monitoring Board participated in the study as an investigator. Regular meetings of the Board were called by the chairman twice a year. He also had the option to call additional meetings.

Specific functions of the Policy Data Monitoring Board were:

a. To review the initial Protocol and make recommendations as to its acceptance to the Director of the NHLBI.

b. To review subsequent changes in the Protocol and make recommendations to the NHLBI.

c. To examine endpoint and toxicity data by treatment group at least once every 6 months.

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

e. To assist the NHLBI in resolving problems referred by the BHAT Steering Committee.

f. To review the performance of the individual Clinical Centers and central units.

g. To make recommendations to the NHLBI on the discontinuation of any centers which perform unsatisfactorily.

BASELINE CHARACTERISTICS

1. Description of Population

Tables 3 through 6 describe the BHAT patient population at baseline. These data were collected before randomization as part of the baseline interview and physical examination.

The mean age at entry for BHAT patients was 54.8 years of age. The percent of the population between 60 and 69 years of age inclusive was 32.6. Males comprised 84.4 percent of the patients. The racial distribution was 88.8 percent white, 8.7 percent black, and 2.5 percent other races (Table 3).

The percent of patients married at baseline was 77.7 percent. The percent with at most a high school education was 62.9 percent. Slightly over 70 percent were employed full time at the time of their BHAT MI (Table 3).

For 86.4 percent of the BHAT patients the MI which qualified the patient for entry into the trial (the BHAT qualifying MI) was their first MI. Only 13.6 percent had had a prior MI (Table 4).

Of the 3837 patients randomized, 26.8 percent had an anteriorly located MI; 32.0 percent had an inferior MI; 9.6 percent had an anterior and inferior MI; 22.8 percent had a nontransmural MI; and 8.9 percent of the patients had an MI that did not fulfill the requirements for a qualifying BHAT MI (Table 4).

At the baseline physical examination, it was the examining physician's opinion that 9.2 percent of the patients had experienced congestive heart failure in the past and 36.1 percent had angina (Table 4).

When a medical history was elicited from the patients at baseline, 40.8 percent responded that they had been told they had hypertension. Of these hypertensives, 58.3 percent had been treated with diuretics. Using the Rose Questionnaire, 11.6 percent were determined to have angina and 2.9 percent to have intermittent claudication. However, according to the opinion of the examining BHAT physician, 36.1 percent of the patients had experienced angina and 4.0 percent intermittent claudication. It was also determined by medical history that 11.5 percent of the patients had diabetes (Table 4).

Myocardial infarction as a cause of death was reported for 25.1 percent of the fathers of BHAT patients (29.3 percent of 86.2 percent). Fourteen percent of the BHAT patients had mothers who had died of an MI. Four percent of the patients had both parents die of an MI. Only 7.7 percent of the patients had both parents still alive (Table 4).

Lifestyle history revealed that of those who worked, 18.6 percent had almost no physical activity associated with the job, while 10 percent

rated the physical activity of their job as heavy. Of the 3837 patients randomized, 18.1 percent rated their leisure time physical activity as being almost non-existent, while 3.5 percent rated it as being heavy (Table 4).

Alcohol was consumed by study participants on an average of two days per week. The percent of the patient population consuming alcohol less than one day a week on the average was 49.2 percent (Table 4).

The lifestyle history further revealed that 57.2 percent of the BHAT population at the time of their qualifying MI were cigarette smokers while 17 percent had never smoked. Smoking histories also indicated that 21.9 percent of the current smokers (i.e., those smoking at the time of their MI) smoked at least two packs of cigarettes per day up until their MI. Current smokers had, on the average, been smoking 33.3 years; 34.1 percent of these smokers reported smoking at least 40 years. Former cigarette smokers reported smoking, on the average, 23.2 years (Table 4).

During hospitalization for their BHAT MI, but prior to randomization, 1.3 percent of the patients experienced cardiogenic shock; 2.6 percent a complete A-V block; 23.1 percent ventricular tachycardia; and 14.6 percent congestive heart failure (Table 4).

Table 5 displays medication usage at baseline. Propranolol was being used by 6.5 percent of the patients before they entered the hospital for their BHAT MI. During hospitalization, but before randomization, 14.6 percent of the entire study population were using propranolol or some other beta-blocker. During this same period, 45.9 percent of the patients were taking some other antiarrhythmics, while 56.6 percent were taking nitroglycerine or a long-lasting coronary vasodilator. Medications used at the time of the baseline physical examination included antiarrhythmics (17.3 percent), anticoagulants (14.5 percent), antihypertensives excluding diuretics (4.5 percent), diuretics (17.0 percent), aspirin prescribed on a continuing basis (5.5 percent), dipyridamole (0.7 percent), sulfinpyrazone (1.2 percent), digitalis (12.7 percent), vasodilators (36.2 percent), and oral hypoglycemics (2.0 percent).

In Table 6 are the baseline physical examination findings. The mean systolic blood pressure for the BHAT patients was 112.0 mm Hg; 45.3 percent of the patients had a SBP of less than 110 mm Hg. (Note that all patients were in the convalescent phase following an acute MI.) The mean diastolic blood pressure was 72.4 mm Hg; 34.9 percent of the patients had a DBP of less than 70 mm Hg. The mean heart rate was 75.9 beats per minute; 25.3 percent of the patients had a heart rate of less than 70 beats per minute. The mean body weight for males was 176.4 lbs. while that for females was 147.6.

At the physical examination, 3.0 percent of the patients were found to have had basilar rales and 1.3 percent had an S_3 gallop (Table 6).

As also indicated in Table 6, the mean serum cholesterol level for the BHAT study population at baseline was 213.2 mg/dl. (Note that serum cholesterol is lower following an acute MI.) The mean serum creatinine level was 1.0 mg/dl; the mean potassium level was 4.5 mEq/l; and the mean SGOT was 20 IU/l. From the baseline resting ECG recording, 63 percent of the patients had a heart rate of 70 beats per minute or greater; 67.4 percent had Q/QS wave abnormalities; 26.2 percent had ST depression; 13.4 percent had ST elevation; 65.3 percent had T wave abnormality; 8.9 percent had a ventricular conduction defect; and 3.6 percent had an A-V conduction defect.

Based upon the number of patients with acceptable x-ray data (N=3245), 35.9 percent had a cardiothoracic ratio of 50 percent or greater.

2. Baseline Differences Between Groups

At baseline, 124 variables (not all of which are presented in this monograph) were measured. Based on chance alone it would have been reasonable to find about six variables in which there was statistical evidence at the 5 percent significance level that the propranolol and placebo groups differed. Four variables showed such a difference: the mean white blood cell count, the percent of patients with a diminished right dorsal pedis pulse, the percent with ST elevation, and the percent with a ventricular conduction defect. The propranolol group had lower values for the first three variables (8042 vs. 8324 WBC/mm^3, 10.2 vs. 12.3 percent of patients with diminished right dorsal pedis pulse, and 12.2 vs. 14.5 percent with ST elevation), while the placebo group had a lower proportion with a ventricular conduction defect (7.5 vs. 10.3 percent). During the evaluation of treatment effect with propranolol, these differences were adjusted for using multivariate techniques such as Cox regression.

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TABLE 1

FINAL DISPOSITION OF POTENTIALLY ELIGIBLE BHAT PATIENTS.
PERCENT DISTRIBUTION OF THE APPROXIMATELY 16,400 CCU PATIENTS
WHO HAD A BHAT DEFINED MI, HAD SURVIVED FIVE DAYS,
AND WERE AGE ELIGIBLE

BHAT CCU LOG DATA

Excluded from study because of contraindication to propranolol (e.g., history of severe congestive heart failure, or history of adverse reaction to beta-blockers)	18%
Excluded because patient was already on a beta-blocker or was likely to be prescribed a beta-blocker (e.g., had significant angina pectoris)	18%
Excluded for technical reasons (e.g., had life-threatening illness other than CHD, lived too far from BHAT clinic, or patient died before randomization)	12%
Excluded because patient had a pacemaker, or had or was going to have cardiac surgery	7%
Excluded because patient did not give consent	15%
Excluded because patient was judged unable to cooperate with study, either physically or psychologically	7%
Patients ultimately randomized	23%

TABLE 2

RANDOMIZATION PATTERN BY QUARTER
AND TREATMENT GROUP
(in percent)

MONTH OF RANDOMIZATION	TREATMENT GROUP PROPRANOLOL (n=1916)	PLACEBO (n=1921)	TOTAL (N=3837)
June 1978	0.9	1.1	1.0
Jul, Aug, Sep 1978	8.9	9.1	9.0
Oct, Nov, Dec 1978	12.4	12.1	12.3
Jan, Feb, Mar 1979	13.2	13.2	13.2
Apr, May, Jun 1979	13.4	13.2	13.3
Jul, Aug, Sep 1979	10.7	11.1	10.9
Oct, Nov, Dec 1979	11.3	10.5	10.9
Jan, Feb Mar 1980	10.3	10.4	10.3
Apr, May, Jun 1980	10.1	10.0	10.0
Jul, Aug, Sep 1980	8.2	8.8	8.6
October 1980	0.6	0.4	0.5
TOTAL	100.0	100.0	100.0

TABLE 3

DISTRIBUTION OF BASELINE SOCIODEMOGRAPHIC CHARACTERISTICS BY TREATMENT GROUP

SOCIODEMOGRAPHIC CHARACTERISTICS	PERCENT OF PATIENTS IN PROPRANOLOL (n=1916)	PLACEBO (n=1921)	TOTAL (N=3837)
Age			
30-39	5.2	4.9	5.1
40-49	21.8	21.1	21.4
50-59	40.9	41.0	40.9
60-69	32.2	33.0	32.6
Mean	54.7	54.9	54.8
Sex			
Male	83.8	85.1	84.4
Female	16.2	14.9	15.6
Race			
White	89.3	88.4	88.8
Black	8.5	8.8	8.7
Other	2.2	2.8	2.5
Marital Status			
Never married	4.9	5.1	5.0
Married	77.7	77.8	77.7
Widowed	6.2	5.5	5.8
Separated	3.8	3.6	3.7
Divorced	7.5	8.0	7.7
Education			
Less than 12 years	34.8	34.3	34.6
High school graduate	28.8	27.9	28.3
Some college or college graduate	30.4	31.3	30.8
Degree beyond college	5.8	6.5	6.2
Work Status			
Employed full time	70.0	70.2	70.1
Employed part time	5.6	5.0	5.3
Retired	17.4	16.5	16.9
Temporarily unemployed	2.3	3.0	2.6
Not employed	4.7	5.4	5.0

TABLE 4

DISTRIBUTION OF BASELINE HISTORY CHARACTERISTICS
BY TREATMENT GROUP

BASELINE HISTORY	PERCENT OF PATIENTS IN PROPRANOLOL (n=1916)	PLACEBO (n=1921)	TOTAL (N=3837)
A. Coronary Heart Disease Indicators			
Number of Prior Myocardial Infarctions			
0	86.1	86.8	86.4
1	11.5	10.7	11.1
2	1.9	1.8	1.9
≧3	0.5	0.8	0.6
Classification of Qualifying MI[1]			
Class I	56.7	55.5	56.1
Class II	32.5	32.2	32.4
Class III	78.5	78.8	78.7
Location of MI[2]			
Anterior Category I	1.4	1.2	1.3
Anterior Category II	22.3	20.6	21.5
Anterior Category III	4.1	3.9	4.0
Anterior and Inferior	9.2	10.0	9.6
Inferior	31.6	32.4	32.0
Nontransmural	22.9	22.6	22.8
Non-BHAT MI	8.6	9.2	8.9
Doctor's Opinion that the Patient has Experienced the Following:			
Angina Pectoris	35.8	36.5	36.1
Congestive Heart Failure	9.0	9.4	9.2
Intermittent Claudication	3.7	4.4	4.0
History of shortness of breath said to be due to heart trouble	5.5	6.3	5.9
a. treated with digitalis	23.6	22.3	22.9
b. treated with diuretics	38.7	33.9	36.1
History of hypertension	41.4	40.1	40.8
a. treated with diuretics	55.7	61.1	58.3
b. treated with other antihypertensives	38.8	40.7	39.7
Angina in past year (by Rose Questionnaire)	11.2	12.0	11.6
Intermittent Claudication (by Rose Questionnaire)	2.9	3.0	2.9

[1]See Definitions in Appendix C. Note: A patient's MI may have more than one classification.
[2]See Definitions in Appendix C.

TABLE 4 (cont.)

DISTRIBUTION OF BASELINE HISTORY CHARACTERISTICS
BY TREATMENT GROUP

BASELINE HISTORY	PERCENT OF PATIENTS IN PROPRANOLOL (n=1916)	PLACEBO (n=1921)	TOTAL (N=3837)
B. Medical History			
Diabetes	11.7	11.3	11.5
Bronchial asthma or emphysema	3.4	3.4	3.4
Cancer	3.3	3.1	3.2
Stroke	2.3	2.7	2.5
Cirrhosis	1.5	2.0	1.7
Valvular heart disease	0.8	0.7	0.7
Parental Death			
Father Dead	86.6	85.8	86.2
a. Death from MI	27.7	30.9	29.3
b. Other Cause of Death	72.3	69.1	70.7
Mother Dead	68.1	66.8	67.5
a. Death from MI	20.5	21.1	20.8
b. Other Cause of Death	79.5	78.9	79.2
Both Parents Dead	62.7	61.2	62.0
a. Death from MI	6.1	7.0	6.5
b. Other Cause of Death	93.9	93.0	93.5
Both Parents Still Alive	7.4	8.0	7.7
C. Lifestyle History			
Physical Activity in Year Prior to MI[1]:			
At work (including housework)			
Percent who work	75.6	75.2	75.4
Heavy	10.7	9.2	10.0
Moderate	30.9	32.4	31.6
Light	39.8	39.7	39.7
Almost none	18.6	18.7	18.6
At home (and other than housework)			
Heavy	3.3	3.6	3.5
Moderate	24.9	25.8	25.3
Light	53.3	52.8	53.1
Almost none	18.4	17.8	18.1
Avg. Number of Days Per Week Alcohol was Consumed in Year Prior to Qualifying Myocardial Infarction			
<1	50.4	47.9	49.2
1-2	20.2	21.7	21.0
3-5	11.0	12.0	11.5
6-7	18.4	18.3	18.3
Mean	2.0	2.0	2.0

[1]See Definitions in Appendix I.

TABLE 4 (cont.)

DISTRIBUTION OF BASELINE HISTORY CHARACTERISTICS
BY TREATMENT GROUP

BASELINE HISTORY	PERCENT OF PATIENTS IN PROPRANOLOL (n=1916)	PLACEBO (n=1921)	TOTAL (N=3837)
Cigarette Smoking History			
Nonsmoker	17.2	16.9	17.0
Former smoker	25.4	26.0	25.7
Current smoker	57.4	56.9	57.2
Number of Cigarettes Smoked by Current Smokers per day			
<10	4.1	4.8	4.
10-19	16.4	18.9	17.
20-29	36.3	36.0	36.
30-39	20.2	19.4	19.
≧40	23.0	20.8	21.
Number of Years Current Cigarette Smokers Smoked Cigarettes			
1-9	1.2	1.5	1.
10-19	6.4	6.2	6.
20-29	23.2	22.8	23.
30-39	35.2	35.6	35.
40-49	26.3	25.4	25.
≧50	7.7	8.6	8.
Mean	33.2	33.4	33.
Number of Years Former Cigarette Smokers Smoked Cigarettes			
1-9	11.5	14.6	13.
10-19	21.6	22.4	22.
20-29	32.9	26.4	29.
30-39	23.6	20.4	22.
40-49	9.2	12.8	11.
≧50	1.2	3.4	2.
Mean	23.0	23.3	23.
Cigar Smoking History in Year Prior to Qualifying Myocardial Infarction	12.9	11.4	12.2
Pipe Smoking History in Year Prior to Qualifying Myocardial Infarction	11.1	10.8	10.9

TABLE 4 (cont.)

DISTRIBUTION OF BASELINE HISTORY CHARACTERISTICS
BY TREATMENT GROUP

BASELINE HISTORY	PERCENT OF PATIENTS IN PROPRANOLOL (n=1916)	PLACEBO (n=1921)	TOTAL (N=3837)
D. Percent in which the following complications occurred during hospitalization for qualifying MI but prior to randomization			
Ventricular tachycardia	23.0	23.2	23.1
Congestive heart failure	14.3	14.9	14.6
Incomplete A-V Block	8.2	8.0	8.1
Persistent hypotension	7.4	6.9	7.2
Atrial fibrillation or flutter	6.8	5.7	6.3
Ventricular fibrillation	5.4	5.2	5.3
Pulmonary edema	2.7	2.7	2.7
Complete A-V Block	2.8	2.3	2.6
Cardiogenic shock	1.5	1.1	1.3

TABLE 5

PERCENT OF PATIENTS USING MEDICATIONS
AT ENTRY BY TREATMENT GROUP

USE OF MEDICATIONS	TREATMENT GROUP PROPRANOLOL (n=1916)	PLACEBO (n=1921)	TOTAL (N=3837)
A. Used just Prior to the Hospitalization for the Qualifying MI:			
Propranolol	6.7	6.2	6.5
Other beta-blockers	0.5	0.6	0.6
B. Used during Hospitalization for the Qualifying MI but Prior to Randomization:			
Propranolol or other beta-blockers	15.0	14.2	14.6
Nitroglycerine or long-acting coronary vasodilators	56.4	56.9	56.6
Nitroprusside	2.1	2.2	2.2
Other antiarrhythmics	45.8	46.0	45.9
C. Other Medications Used at Entry:			
Antiarrhythmics	16.6	17.9	17.3
Anticoagulants	13.9	15.1	14.5
Antihypertensives excluding diuretics	4.3	4.7	4.5
Aspirin prescribed on a continuing basis	5.7	5.3	5.5
Digitalis	12.5	13.0	12.7
Dipyridamole	0.8	0.6	0.7
Diuretics	16.1	18.0	17.0
Insulin	3.5	3.4	3.5
Lipid-lowering agents	0.8	1.0	0.9
Oral hypoglycemics	2.2	1.8	2.0
Sulfinpyrazone	1.0	1.4	1.2
Vasodilators	36.0	36.3	36.2
Other cardiovascular preparations	5.8	6.5	6.2

TABLE 6

DISTRIBUTION OF BASELINE PHYSICAL EXAMINATION FINDINGS
BY TREATMENT GROUP

PHYSICAL EXAMINATION FINDINGS	PERCENT OF PATIENTS IN PROPRANOLOL (n=1916)	PLACEBO (n=1921)	TOTAL (N=3837)
A. a) Systolic Blood Pressure (mm Hg)			
90-99	11.4	14.3	12.8
100-109	33.8	31.2	32.5
110-119	28.9	31.4	30.2
120-129	16.8	15.3	16.0
130-139	7.0	5.7	6.3
140-149	1.7	1.6	1.6
150-159	0.4	0.4	0.4
160-169	0.1	0.1	0.1
170-179	0.0	0.1	0.1
Mean	112.3	111.7	112.0
Standard deviation	11.6	11.6	11.6
b) Diastolic Blood Pressure (mm Hg)			
<60	3.0	3.0	3.0
60-69	31.8	32.0	31.9
70-79	45.9	46.2	46.1
80-89	16.8	16.2	16.5
90-99	2.3	2.4	2.4
100-109	0.2	0.1	0.1
Mean	72.5	72.3	72.4
Standard deviation	7.8	7.9	7.8
c) Heart Rate (beats/min)			
50-59	3.5	3.7	3.6
60-69	21.2	22.2	21.7
70-79	40.0	39.8	39.9
80-89	26.5	26.3	26.4
90-99	7.4	6.8	7.1
100-109	1.1	0.9	1.0
110-119	0.2	0.2	0.2
≧120	0.1	0.1	0.1
Mean	76.2	75.7	75.9
Standard deviation	9.8	9.8	9.8
d) Mean body weight (lbs)			
males	176.8	176.0	176.4
females	148.7	146.5	147.6

TABLE 6 (cont.)

DISTRIBUTION OF BASELINE PHYSICAL EXAMINATION FINDINGS
BY TREATMENT GROUP

PHYSICAL EXAMINATION FINDINGS	PERCENT OF PATIENTS IN PROPRANOLOL (n=1916)	PLACEBO (n=1921)	TOTAL (N=3837)
e) Mean height (inches)			
males	68.6	68.7	68.6
females	62.6	62.6	62.6
B. Rash	2.7	2.8	2.7
Expiratory wheezes	0.7	0.5	0.6
Abnormal neck venous distension present	0.5	0.3	0.4
Basilar rales	3.0	3.0	3.0
S_3 Gallop	1.6	1.0	1.3
Hepatomegaly	0.8	0.7	0.8
Peripheral edema	0.9	0.8	0.9
Hemiplegia			
right side	0.4	0.3	0.4
left side	0.3	0.2	0.2
Gross hemiparesis			
right side	0.3	0.5	0.4
left side	0.4	0.3	0.3
C. Laboratory Findings (means):			
Cholesterol (mg/dl serum)	212.7	213.6	213.2
Creatinine (mg/dl serum)	1.0	1.0	1.0
Potassium (mEq/1 serum)	4.5	4.5	4.5
SGOT (IU/1 serum)	20.3	19.8	20.0
D. Resting ECG Findings[1]:			
Heart rate ≧70	64.3	61.7	63.0
Q/QS waves	67.3	67.4	67.4
ST depression	25.8	26.7	26.2
ST elevation	12.2	14.5	13.4
T wave abnormalities	64.8	65.9	65.3
Ventricular conduction defects	10.3	7.5	8.9
A-V conduction defects	3.5	3.7	3.6
E. Cardiomegaly by Chest X-ray[2]:			
(Cardiothoracic Ratio ≧50%)	37.0	34.7	35.9

[1]These percents are not based on total population figures but rather on the total number of cases for which baseline ECG data are available (1837 patients in the propranolol group and 1831 in the placebo group).

[2]These percents are also based only on the total number of cases for which X-ray data are available (1619 patients in the propranolol group and 1626 in the placebo group).

APPENDIX A

BHAT CLINICAL CENTERS AND ASSOCIATED CORONARY CARE UNITS

Baylor College of Medicine, Houston, Texas

- The Methodist Hospital
- Ben Taub General Hospital
- Veterans Administration Hospital

Boston University School of Medicine, Boston, Massachusetts

- Boston City Hospital
- University Hospital
- Malden Hospital
- Carney Hospital
- Whidden Memorial Hospital
- St. Elizabeth's Hospital
- Melrose Wakefield Hospital

Brown University Affiliated Hospitals, Providence, Rhode Island

- Rhode Island Hospital
- Miriam Hospital
- Memorial Hospital

Emory University, Atlanta, Georgia

- Grady Memorial Hospital (two care units)
- Northside Hospital
- Piedmont Hospital
- Crawford W. Long Hospital
- Georgia Baptist Hospital
- South Fulton Hospital

Evanston Hospital, Evanston, Illinois

- Evanston Hospital
- Glenbrook Hospital
- Illinois Masonic Medical Center

Geisinger Medical Center, Danville, Pennsylvania

- Geisinger Medical Center
- Shamokin State General Hospital
- Lewisburg Evangelical Community Hospital
- Berwick Hospital

Greater Baltimore Medical Center, Baltimore, Maryland

- Greater Baltimore Medical Center
- Loch Raven Veterans Administration Hospital
- Church Hospital Corporation
- Fallston General Hospital and Nursing Center

Henry Ford Hospital, Detroit, Michigan

Henry Ford Hospital
Bon Secours
Wayne County General Hospital

Kaiser Foundation Hospitals, Portland, Oregon

Sunnyside Medical Center
Bess Kaiser Hospital

Lankenau Hospital, Philadelphia, Pennsylvania

Lankenau Hospital
Bryn Mawr Hospital
Mercy Catholic Medical Center, Fitzgerald Mercy Division
Memorial Hospital, Roxborough
Crover-Chester Medical Center

Long Island Jewish-Hillside Center, New Hyde Park, New York

Long Island Jewish Hospital
Queens General Hospital
La Guardia Hospital

Maimonides Medical Center, Brooklyn, New York

Maimonides Medical Center
Downstate Medical Center

Medical University of South Carolina, Charleston, South Carolina

Charleston County Hospital
U.S. Naval Hospital
Veterans Administration Hospital
Medical University Hospital
St. Francis Hospital
Roper Hospital

Medical College of Virginia, Richmond, Virginia

Medical College of Virginia
McGuire Veterans Adminstration Hospital
St. Mary's Hospital
Richmond Memorial Hospital

Miami Heart Institute, Miami, Florida

Miami Heart Institute
Cedars of Lebanon
Jackson Memorial Hospital
Veterans Administration Hospital
South Miami Hospital
Doctor's Hospital
Biscayne Medical Center
Baptist Hospital
St. Francis Hospital

Montreal Heart Institute, Montreal, Quebec, Canada

Montreal Heart Institute

Mt. Sinai Hospital, Minneapolis, Minnesota

Mt. Sinai Hospital
Methodist Hospital
Fairview Hospital
Northwestern Hospital
North Memorial Hospital

Northwestern University Medical School, Chicago, Illinois

St. Joseph's Hospital
Columbus-Cuneo-Cabrini Medical Center
Veterans Administration Hospital
Northwestern Memorial Hospital
Bethesda Hospital

Overlook Hospital, Summit, New Jersey

Overlook Hospital
Morristown Memorial Hospital
St. Barnabas Medical Center
J.F. Kennedy Medical Center
St. Elizabeth Hospital

Pacific Health Research Institute, Honolulu, Hawaii

Castle Memorial Hospital
Kaiser Medical Center
Queen's Medical Center
St. Francis Hospital
Straub Clinic and Hospital
Tripler Army Medical Hospital

Providence Medical Center, Portland, Oregon

Providence Medical Center
Portland Adventist Medical Center
Woodland Park Hospital
Dwyer Hospital
Williamite Falls Hospital

Rush Presbyterian St. Lukes Medical Center, Chicago, Illinois

West Suburban Hospital
Christ Hospital
Community Memorial Hospital of LaGrange
Hinsdale Sanitarium and Hospital
Rush Presbyterian St. Lukes Medical Center
Good Samaritan Hospital

Rutgers Medical School Raritan Valley Hospital, New Brunswick, New Jersey

Raritan Valley Hospital
Middlesex General
St. Peter's Medical Center
Muhlenberg Hospital

Salt Lake Clinic Research Foundation, Salt Lake City, Utah/
Ogden Research Foundation, Ogden, Utah

Cottonwood Hospital (Salt Lake Clinic Research Foundation)
LDS Hospital (Salt Lake Clinic Research Foundation)
Veterans Hospital (Salt Lake Clinic Research Foundation)
McKay-Dee Hospital (Ogden Research Foundation)
St. Benedict's Hospital (Ogden Research Foundation)

State University of New York at Buffalo, Buffalo, New York

Erie County Medical Center
Buffalo General Hospital
Kenmore Mercy Hospital
Veterans Administration Hospital
Deaconess Hospital

University of California at Davis, Davis, California

Kaiser Permanente Medical Center
Veterans Administration Hospital in Martinez

University of California at San Francisco, San Francisco, California

San Francisco General Hospital
Letterman Army Medical Center
Alameda Hospital
Kaiser Hospital, San Francisco

University of Rochester School of Medicine, Rochester, New York

St. Mary's Hospital
Rochester General Hospital (two care units)
University of Rochester School of Medicine

University of Southern California, Los Angeles, California

Los Angeles County U.S.C. Medical Center
White Memorial Hospital

Veterans Administration Hospital, Little Rock, Arkansas

Veterans Administration Hospital

Veterans Administration Hospital, West Roxbury, Massachusetts

Veterans Administration Medical Center-West Roxbury
Veterans Administration Medical Center-Jamaica Plain
Veterans Administration Medical Center-Providence, Rhode Island
Veterans Administration Medical Center-Manchester, New Hampshire
Norwood Hospital
Roger Williams Hospital, Providence, Rhode Island
Roger Williams Medical Unit, Providence, Rhode Island
Mary Hitchcock Memorial Hospital, Hanover, New Hampshire
Keene Clinic, Keene, New Hampshire
Veterans Administration Hospital-White River Junction, Vermont
Springfield Vermont Hospital

APPENDIX B

SAMPLE SIZE FOR BHAT

The sample size for the Beta Blocker Heart Attack Trial (BHAT) is based on several assumptions. These include:

1. Men and women, ages 30-69, with one or more documented MI's who are currently in the hospital for an MI will be recruited over a 2 year period and randomized into one of two groups, propranolol or placebo, before being discharged.

2. The primary endpoint will be total mortality over the follow-up period. All patients will be followed for a minimum of two years and possibly up to four years, or on the average three years, assuming an even recruitment.

3. The 3-year mortality rate in the placebo group based on other studies is estimated to be 18 percent ($P_c = 0.18$). The treatment propranolol is assumed to reduce the total 3-year mortality rate by 28 percent ($P_e = 0.1296$) based on the European beta-blocker studies.

4. The proposed therapeutic effect of propranolol is immediate.

5. The significance level, α, is 0.05 with the hypothesis being two-sided; i.e., H_o: $P_c = P_e$ vs. H_A: $P_c \neq P_e$.

6. The power, the probability of finding a specified difference given that it actually exists, has been set at 0.90.

7. The noncompliance rate in the treatment group, referred to as the "dropout" rate, which is the rate at which those patients who were randomized to propranolol stop their treatment, has been assumed to be 12 percent the first year, 8 percent the second and 6 percent the third for a total of 26 percent total 3 year dropout. The dropout rates are based on other studies including post MI patients.

8. For the control group, the noncompliance rate involves patients randomized to placebo taking propranolol or similar drug and in effect "dropping in" on the treatment regimen. The drop-in rates have been assumed to be 7 percent for each year of the study or a total of 21 percent for the 3 years.

9. Based on a method developed by Halperin et al. (ref. 12), the dropout rate adjusts the nominal $P_e = 0.1296$ upward (back toward the P_c rate) to a realized $P_e^* = 0.1375$. This method takes into account the dropout rate. The method of Halperin has been modified to adjust the control rate $P_c = 0.18$ downward due to "drop-ins" towards the nominal treatment rate to obtain a realized control rate of $P_c^* = 0.1746$.

10. Based on the adjusted rates $P_c^* = 0.1746$, $P_e^* = 0.1375$, $\alpha = 0.05$ and power = 0.90, the total sample size ($2N$) for this study has been estimated to be approximately 4,020. This was adjusted upwards to 4,200 for administrative purposes.

APPENDIX C

QUALIFYING MI CRITERIA

Each patient's qualifying myocardial infarction (QMI) had to be documented. To this end, ECG data were submitted to the Resting ECG Center in Minneapolis and symptom and enzyme data were submitted to the Coordinating Center in Houston. All the data were then collated and each QMI was either confirmed or not and its site noted.

BHAT Definitions for Elevated Serum Enzymes and for Typical MI Symptoms

A. Elevated Serum Enzymes:

An elevation of two or more of the enzymes SGOT, total LDH, total CPK and HBD, of at least twice the upper limits of normal in the local laboratory. (Instead of an elevation of CPK of at least twice the upper limits of normal, an elevation of CPK-MB may be used).

Occurrring within 72 hours of the onset of symptoms of the acute event.

OR

An elevation of SGOT of at least three times the upper limit of normal in the local laboratory.

Occurring within 72 hours of the onset of symptoms of the acute event.

B. Typical Symptoms of Acute Myocardial Infarction:

Severe discomfort occurring anywhere in the anterior chest, back, epigastrium, jaw, neck, shoulder, elbow, forearm or wrist.

This severe discomfort must be present more than 30 minutes unless relieved by morphine or meperidine.

ECG QMI Requirements

All QMI ECG's must be dated prior to the date of randomization. For Class I, all ECG's must be dated at or after onset of acute symptoms. For Class II at least one ECG must be dated no more than 5 days prior to date of admission. For Class III at least one ECG must be dated at or after onset of acute symptoms.

Criteria for the Classification of Qualifying MI

Class I. (The symptom and enzyme changes establish the infarct as acute. Only a single ECG recording is needed for this classification.)

1. Presence of Q or QS findings in any lead.

PLUS

2. ST abnormality (ST elevation 1 mm or more in limb leads or ST elevation 2 mm or more in leads V1-V4) and/or T

wave abnormality (negative or inverted T wave of at least 1 mm or more).

PLUS

3. Absence of LBBB and WPW

PLUS

4. Elevated serum enzymes (see definitions above)

PLUS

5. Typical symptoms of acute myocardial infarction (see definitions above)

Class II. (An evolving pattern of Q or QS (appearance or disappearance) establishes the infarct as acute. Two or more ECG recordings from the acute event within 10 days of each other are needed for this classification, which does not require typical history or enzyme elevation.)

1a. One ECG record showing no Q wave and another record with Q or QS finding.

OR

1b. One ECG record showing a minor Q wave finding and another record showing a major Q or QS finding.

PLUS

2a. One ECG record showing no ST elevation and another record showing elevation (ST elevation 1 mm or more in limb leads or 2 mm or more in precordial leads V1-V4).

OR

2b. One ECG record showing no T wave inversion and another record showing T wave inversion or inverted T wave of at least 1 mm or more.

OR

2c. One ECG record showing no major ST segment depression and another record showing major ST segment depression (ST-J depression of at least 1 mm with ST segment horizontal or downsloping).

PLUS

3. Absence of LBBB or WPW

Class III. (This classification covers nontransmural infarcts and therefore does not require any Q or QS findings. The clinical symptom and enzyme changes establish the infarct as acute. Subgroup a requires only one ECG recording; subgroups b-d require two ECG records.)

1a. ST elevation (ST elevation 1 mm or more in limb leads or 2 mm or more in leads V1-V4) and ST depression (ST depression at least 1 mm with ST segment horizontal or downsloping) in the same record.

OR

1b. Increasing or decreasing ST elevation. One record indicates an ST elevation 1 mm or more in limb leads or 2 mm or more in V1-V4 and another record does not so indicate such an elevation. Least and greatest ST elevations are compared.

OR

1c. Increasing or decreasing ST depression by comparing the least and greatest ST segment abnormalities. One record shows no or minor ST depression (ST-J depression less than 0.5 mm with downsloping ST segment at least 0.5 mm below PR baseline or in ST-J depression of 1 mm or more with upsloping ST segment) and another record showing a major ST segment depression (in ST-J depression at least 0.5 mm with ST segment horizontal or downsloping).

OR

1d. Increasing or decreasing T waves by comparing the least and greatest T wave inversion. One record shows no or minor T wave inversion (T amplitude less than 1 mm inverted but not positive) and another record showing T wave inversion (T amplitude negative or inverted at least 1 mm).

PLUS

2. Absence of LBBB and WPW

PLUS

3. Elevated serum enzymes (see definitions).

PLUS

4. Typical symptoms of acute myocardial infarction (see definitions).

Location of Qualifying MI

The location categories in Table 4 are defined as follows:

Anterior Category I	-	Q waves only present in any of leads I, aVL, and V6.
Anterior Category II	-	Q waves only present in any of leads V1 through V5.
Anterior Category III	-	Q waves only present in any of leads I, aVL, V6, and in any of leads V1 through V5.
Anterior and Inferior	-	Q waves present in any of leads I, aVL, V6, or V1 through V5, and in any of leads II, III, and aVF.
Inferior	-	Q waves only present in any of leads II, III, and aVF.
Nontransmural	-	No Q waves present and is a QMI Class III.
None of the above	-	MI could not be documented as a BHAT qualifying MI (i.e., it is a non-BHAT MI).

APPENDIX D

ELIGIBILITY CRITERIA

Inclusion Criteria

1. Age greater than 29 and less than 70.
2. Documented myocardial infarction occurring five to twenty-one days before randomization.
3. Average heart rate at baseline is greater than 49 beats per minute and no single heart rate reading is less than 45 beats per minute.
4. Average systolic blood pressure at baseline is between 90 and 189 mm Hg, inclusive, and average diastolic is less than 110 mm Hg.

Exclusion Criteria

1. Congestive heart failure within 3 days prior to baseline
2. History of severe congestive heart failure
3. Cardiogenic shock or symptomatic hypotension
4. Pulmonary hypertension with right ventricular failure
5. Mobitz type II, 2:1 A-V block or complete A-V block within 3 days prior to baseline
6. History of frequent or severe intermittent claudication
7. History of bronchial asthma as an adult or chronic obstructive lung disease requiring therapy
8. "Brittle" insulin-dependent diabetes mellitus
9. Patient on MAO-inhibitors, amphetamines and tricyclic antidepressants
10. History of adverse reaction to propranolol or other beta-blocker
11. Women capable of becoming pregnant during the study
12. Wolff-Parkinson-White syndrome
13. Significant angina pectoris since the acute event
14. Other conditions for which the patient is very likely to be placed on propranolol or other beta-blockers before the scheduled termination of the trial
15. Presence of any disease other than the patient's CHD associated with a reduced likelihood of survival for the duration of trial (e.g., cancer, uremia, liver failure)
16. Patient has undergone or is very likely to undergo cardiac surgery
17. Patient has permanent pacemaker
18. Hypertension at baseline uncontrolled by therapy ($\geq$190 mm Hg systolic or $\geq$110 mm Hg diastolic)
19. Qualifying myocardial infarction resulted from surgery, trauma, shock or other nonatherosclerotic cause

20. Patient participating in other heart disease trial

21. Patient has been on propranolol or other beta-blocker within 3 days prior to baseline

22. Patient is unwilling or unable (physically or psychologically) to cooperate with the study

23. Patient lives at such a distance from the clinic that travel for follow-up visits would be unusually difficult

24. Patient doesn't anticipate being a resident of the area for the scheduled duration of the trial

25. Patient unwilling to sign consent form

APPENDIX E

DEFINITION OF NONFATAL EVENTS

1. Myocardial Infarction

In order to qualify as a nonfatal MI, the patient had to survive hospitalization for the event.

The diagnostic criteria for the various classes of nonfatal MI are as follows. (See Appendix C for definitions of elevated serum enzymes and typical MI symptoms.)

a) Definite Class A. There is development of new abnormal Q wave findings (in any lead group) not present on the patient's last ECG. Typical symptoms or elevated serum enzymes are not required.

b) Definite Class B. There are typical clinical symptoms compatible with MI in conjunction with serum enzyme elevation and newly developed nonspecific ECG findings.

1. ST segment elevation and ST segment depression in the same record.

OR

2. Changes in ST segment elevation. One record shows no ST elevation and another record does show an ST elevation; or one has an ST elevation and the other shows a 100% change in ST elevation. For comparison between last prior ECG and acute event ECG, only an increase constitutes a new event. For comparison within a series of acute event ECG's, increase or decrease constitutes a new event.

OR

3. Changes in ST segment depression. One record shows no or minor ST segment depression and another record shows a major ST segment depression; or one has a major ST segment depression and the other shows a 100% change in ST segment depression. For comparison between last prior ECG and acute event ECG, only increase constitutes a new event. For comparison within a series of acute event ECG's, an increase or decrease constitutes a new event.

OR

4. Changes in T wave inversion. One record shows no or minor T wave inversion and another record shows major T wave inversion; or one has a major T wave inversion and the other shows a 100% change in T wave inversion. For comparison between last prior ECG and acute event ECG, only an increase constitutes a new event. For comparison within a series of acute event ECG's, increase or decrease constitutes a new event.

OR

5. New left bundle branch block. Requires complete left bundle branch block of all leads in all new event ECG's and not present in prior ECG.

c) Probable. Serum enzymes are elevated and typical symptoms are present but there are no ECG findings.

d) Possible Class A. No elevated enzymes are recorded, but there is the same development of new nonspecific ECG findings as there is for Definite Class B. Typical symptoms are present.

e) Possible Class B. Serum enzymes are not elevated, but there is development of new nonspecific ECG findings. This development includes a change of minor Q/QS patterns together with T wave and/or ST segment changes within any of the three lead groupings; that is, within the lateral leads (I, aVL, V6), the inferior leads (II, III, aVF), or the anterior leads (V1-V5). Typical symptoms are present.

f) Possible Class C. Typical symptoms are present but enzymes are not elevated and there is no evidence of an MI on ECG's.

All new cardiac events require the submission of a New Cardiac Event Form (see Appendix H for a list of BHAT Study forms). The information on this form, in conjunction with ECG data found on the ECG Center Report Form for Qualifying MI and New Cardiac Events, is processed by the Coordinating Center and the MI is classified by a computer algorithm. All MI's classified as definite or probable have their ECG's re-examined by the Nonfatal Events Subcommittee and these events are possibly re-classified.

2. Congestive Heart Failure

An occurrence of congestive heart failure (CHF) requires the submission of a Congestive Heart Failure Form. Based upon the information found on this form, the diagnostic criteria for a Definite or Probable CHF are as follows:

a) Definite CHF. S_3 Gallop or abnormal venous distension present

AND

Basilar rales are present or there is an increase in pulmonary vascular markings on a chest X-ray

AND

The patient reported fatigue or shortness of breath

b) Probable CHF. Digitalis was newly prescribed for this event

OR

S_3 Gallop was present

OR

The patient reported fatigue or shortness of breath and abnor-

mal venous distension or basilar rales or peripheral edema are present

OR

There is an increase in pulmonary vascular markings on a chest X-ray.

3. Stroke

An occurrence of stroke requires the submission of a Stroke Form.

a) Definite Stroke. An event in which objective neurologic deficits (motor weakness, speech defect, amaurosis or field defect, sensory symptoms) are observed for more than 24 hours and are documented by a physician (i.e., observed by a study physician or recorded in the patient's medical records).

b) Probable Stroke. An event in which objective neurologic deficits (drop attacks or gait disturbance, alteration of consciousness, vertigo or disequalibrium, bilateral blurred vision or diplopia) persist for more than 24 hours and are documented by a physician.

c) Suspect Stroke. An event in which the above criteria for a definite or probable stroke are not met, but which the study physician filling out the stroke form felt existed.

APPENDIX F

BHAT PROCEDURE SCHEDULE

Visit	Holter Monitor*	ECG*	Chest** X-ray	Serum Propranolol Determination*	Hematocrit*** WBC Count Urinalysis	Potassium*	Cholesterol* SGOT Creatinine	Interview/ Physical Examination
Baseline	X	X	X	X+	X	X	X	X
1½ mo.	X++			X		X		X
6 mo.				X				X
12 mo.		X	X	X	X	X	X	X
18 mo.				X				X
24 mo.		X		X	X	X	X	X
30 mo.				X				X
36 mo.		X		X	X	X	X	X
42 mo.				X				X
48 mo.		X		X	X	X	X	X

* Analyzed centrally.

** Chest X-ray analyzed at local Clinical Center. Was not mandatory at baseline.

*** Analyzed at local Clinical Center.

\+ Done 3 to 10 days after baseline.

++ Only in random sample of approximately 1000 patients.

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Joel Morganroth, M.D.
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STEERING SUBCOMMITTEES

A. Adherence Subcommittee: This Subcommittee monitored patient adherence and reviewed methods for maintaining good adherence to study treatment protocol and medication.

Kevin M. McIntyre, M.D., Chairman
Rose Lee Bell, M.P.H.
Lawrence M. Friedman, M.D.
William L. Holmes, Ph.D.
Frank D. McBarron, M.D.
Charlotte Payton-Ross
E. O'Brian Smith, Ph.D. (former)
Pantel S. Vokonas, M.D.
C. Basil Williams, M.D.

B. Bibliography Subcommittee: This Subcommittee created and maintained a current bibliography on propranolol and other beta-blocking agents pertinent to the BHAT.

L. Julian Haywood, M.D., Chairman
Curt Furberg, M.D.
Olga M. Haring, M.D.
Paul Jennings, M.D.
Darwin R. Labarthe, M.D., Ph.D.
J.J. McNamara, M.D.
Phillip J. Ranheim, M.D.
Douglas L. Roberts, M.D.

C. Editorial Review Subcommittee: This Subcommittee reviewed and recommended approval or disapproval of every scientific paper using unpublished BHAT data (including ancillary study data) as well as every paper using published BHAT data that purports to represent official BHAT views or policy. This applied to papers prepared for publication or oral presentation. The Subcommittee also reviewed proposed ancillary studies to ensure that patient safety and BHAT design and scientific integrity were not compromised. In addition, it suggested special studies which might be conducted at one or several centers on an ancillary basis.

James A. Schoenberger, M.D., Chairman
James K. Alexander, M.D.
Nemat O. Borhani, M.D.
Curt Furberg, M.D.
Sidney Golstein, M.D.
Merwyn Greenlick, Ph.D.
C. Morton Hawkins, Sc.D., Executive Secretary
Jeff Raines, Ph.D.
Richard S. Shulman, M.D.

D. Holter Monitoring Advisory Subcommittee: This Subcommittee advised the ECG Centers and the Steering Committee on questions relating to methodology and analysis of Holter recordings.

Edgar Lichstein, M.D., Chairman
Gustave Bermudez, M.D.
Theodore Biddle, M.D.
Robert J. Capone, M.D.
Richard S. Crow, M.D., Executive Secretary
Neil de Soyza, M.D.
Curt Furberg, M.D.
John J. Gregory, M.D.
Ronald B. Harrist, Ph.D.
John B. Kostis, M.D.
Joel Morganroth, M.D.
Eugene Passamani, M.D. (former)
Craig Pratt, M.D.
William Ruberman, M.D.
Barbara C. Tilley, M.S. (former)

E. Mortality Classification Subcommittee: This Subcommittee reviewed in a blind fashion all information concerning cause and circumstance of death of BHAT patients and coded this information for each decedent.

Gary N. Wilner, M.D., Chairman
Daniel Arensberg, M.D
Allen H. Barker, M.D.
Lawrence M. Friedman, M.D.
Charles A. Laubach, Jr., M.D.
Robert W. Peters, M.D.
Jill Robison, M.P.H.
Donald W. Romhilt, M.D.
Diana E. Schreiner, R.N., M.S. (former)

F. Natural History Subcommittee: This Subcommittee suggested appropriate natural history analyses based on placebo group data. It initiated publications and presentations based on these analyses.

Thaddeus E. Prout, M.D., Chairman
William H. Barnwell, II, M.D.
Gerald M. Breneman, M.D.
Robert P. Byington, M.P.H.
Lawrence M. Friedman, M.D., Executive Secretary
Darwin R. Labarthe, M.D., Ph.D.
James H. Mackay, M.D.
Richard R. Miller, M.D., Chairman (former)
Henry F. Mizgala, M.D.
Marvin L. Murphy, M.D.
Ronald Prineas, M.D.
William Ruberman, M.D.
Eve Weinblatt, A.B.

G. Nonfatal Events Subcommittee: This Subcommittee classified, in a blind, standardized fashion, specific nonfatal events. Its primary function was to review and classify information concerning nonfatal myocardial infarctions.

Paul N. Yu, M.D., Chairman
Kul D. Chadda, M.D.
Richard S. Crow, M.D.
J. David Curb, M.D., Executive Secretary
John A. Grover, M.D.
Eugene Passamani, M.D. (former)
Ronald Prineas, M.D.
Norman Reitman, M.D.
G.V.R.K. Sharma, M.D.

H. Quality Control Subcommittee: This Subcommittee monitored the performance of the clinical centers and the central units. Blinded data were not reviewed by this Subcommittee.

Curt Furberg, M.D., Chairman
Rose Lee Bell, M.P.H.
Richard S. Crow, M.D.
Ronald B. Harrist, Ph.D., Executive Secretary
Frank Ibbott, Ph.D.
Robert M. Kohn, M.D.
Hannah Overton
David W. Richardson, M.D.
Barbara C. Tilley, M.S. (former)

APPENDIX H

BHAT FORMS*

CCU LOG

CCU WEEKLY REPORT FORM

QUALIFYING MYOCARDIAL INFARCTION

AMBULATORY ECG FORM

HOLTER MONITORING (H.M.) LOG

DETERMINATION OF ELIGIBILITY

BHAT PATIENT INFORMATION SHEET

BASELINE INTERVIEW AND EXAMINATION

CLINICAL CENTER LABORATORY AND X-RAY RESULTS

HOSPITALIZATION

FOLLOW-UP INTERVIEW AND EXAMINATION

INTERIM VISIT

NEW CARDIAC EVENT

CONGESTIVE HEART FAILURE

STROKE

DEATH NOTIFICATION

CLINICAL CENTER CAUSE OF DEATH

HOLTER MONITOR REPORT (STANDARD HOUR)

HOLTER MONITOR REPORT (24 HOURS)

ECG REPORT (STANDARD HOUR)

ECG CENTER REPORT FORM FOR QUALIFYING MI AND NEW CARDIAC EVENTS

NEW CARDIAC EVENT CLASSIFICATION

MORTALITY COMMITTEE CODING FORM

REPORT OF STUDY DRUG DISCLOSURE

BHAT DRUG REQUISITION FORM

SHIPPING LOG

BHAT SERUM SHIPPING LOG

BHAT DRUG INVENTORY

CLINICAL EVENTS FLOW CHART

ECG LABEL

BASELINE DRUG SECTION

FOLLOW-UP DRUG SECTION

*Copies of forms are available upon request to the BHAT Coordinating Center, 1607 Houston Main Building, 1100 Holcombe Boulevard, Houston, Texas 77030.

APPENDIX I

GUIDELINES USED IN ASCERTAINING PHYSICAL ACTIVITY LEVEL

Heavy Physical Activity: This person does the equivalent of active training in sports such as soccer, handball, ice hockey, or basketball; or engages in very heavy activities such as ditch digging, carrying heavy weights, very heavy farm work, mining, or working as a lumberjack.

Moderate Physical Activity: This person participates in recreational tennis, swimming, or jogging; or works in occupations such as mail carrier, telephone repair, light building and construction; or engages in full housework and home repairs.

Light Physical Activity: This person walks about one mile a day, leisurely rides a bicycle, fishes, bowls, golfs, or engages in light carpentry, light gardening, light industrial work, teaching, or light housework.

Almost None: The sedentary person spends most waking hours in activities such as working at a desk, reading, watching television, or other quiet pursuits.