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A Randomized Trial of Propranolol in Patients With Acute Myocardial Infarction

I. Mortality Results

β-Blocker Heart Attack Trial Research Group

• **The β-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung, and Blood Institute–sponsored, multicenter, randomized, double-blind, and placebo-controlled trial designed to test whether the regular administration of propranolol hydrochloride to men and women who had experienced at least one myocardial infarction would result in a significant reduction in total mortality during a two- to four-year period. During a 27-month interval, 3,837 persons between the ages of 30 and 69 years were randomized to either propranolol (1,916 persons) or placebo (1,921 persons), five to 21 days after the infarction. Depending on serum drug levels, the prescribed maintenance dose of propranolol hydrochloride was either 180 or 240 mg/day. The trial was stopped nine months ahead of schedule. Total mortality during the average 25-month follow-up period was 7.2% in the propranolol group and 9.8% in the placebo group. Arteriosclerotic heart disease (ASHD) mortality was 6.2% in the propranolol group and 8.5% in the placebo group. Sudden cardiac death, a subset of ASHD mortality, was 3.3% among the propranolol patients and 4.6% among the placebo patients. Serious side effects were uncommon. Hypotension, gastrointestinal problems, tiredness, bronchospasm, and cold hands and feet occurred more frequently in the propranolol group. Based on the BHAT results, the use of propranolol in patients with no contraindications to β-blockade who have had a recent myocardial infarction is recommended for at least three years.**

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BY THE mid-1970s, β-blocking agents were used commonly in the treatment of coronary heart disease, primarily for the symptomatic relief of angina pectoris. It had also been demonstrated in experimental animal models that these agents decreased myocardial ischemia and limited infarct size.[1,2] Because of indications that β-blockers would be beneficial, a number of clinical trials had been carried out using these agents in the long-term treatment of survivors of myocardial infarction (MI).[3-10] Several of these studies showed trends favoring the use of β-blockers; however, because of small sample size or other limitations in design and analysis, the results were inconclusive. Based on these studies, the National Heart, Lung, and Blood Institute (NHLBI) decided that a study of sufficient size would be needed to address the question of benefit of β-blockade in patients after myocardial infarction. To this end, the NHLBI initiated the β-Blocker Heart Attack Trial (BHAT) in 1977.

The primary objective of the BHAT was to test in a multicenter randomized, double-blind, placebo-controlled trial, whether the daily administration of propranolol hydrochloride to patients who had had at least one documented MI would result in a significant reduction in mortality from all causes during a two- to four-year follow-up period. Secondary objectives of the trial were to study the effect of chronic administration of propranolol on coronary heart disease (CHD) mortality; sudden cardiac death (death from arteriosclerotic heart disease, occurring within one hour of the onset of symptoms); and

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CHD mortality plus definite nonfatal MI.

Since 1977, the results of other studies of β-blockers in patients after MI have been reported.[11-14] With regard to mortality, one of these, which evaluated alprenolol hydrochloride, showed benefit in a subset of younger patients,[11] and one, which used propranolol, showed no difference.[12] Two recent trials, one of which studied timolol maleate and the other, metoprolol tartrate, demonstrated benefit from β-blockers.[13,14]

The preliminary findings of the BHAT have been released in a special advance report.[15] This article discusses in more detail the final results of the trial with regard to the effect of treatment on mortality.

METHODS

A detailed description of the BHAT design, sample-size calculation, eligibility criteria, response-variable definitions, randomization, and follow-up procedures is published elsewhere[16,17] and will be only summarized here. Participating centers and investigators are listed at the end of this report.

The screening for study participants began on June 19, 1978, and ended on Oct 2, 1980. Men and women from age 30 through 69 years who were hospitalized with an acute MI documented by appropriate symptoms, and ECG and enzymatic changes were candidates for enrollment in the trial. Patients were excluded from the study if they had medical contraindications to propranolol, such as marked bradycardia; a history of severe congestive heart failure or asthma as an adult; a life-threatening illness other than CHD; had or were likely to undergo cardiac surgery; or were already taking or were likely to have β-blockers prescribed to them. Before enrollment, each patient was informed as to the nature of the study and its possible benefits and hazards, and informed consent was obtained. The coordinating center randomly assigned either propranolol or placebo to eligible patients in a double-blind manner, five to 21 days after hospital admission and while the patient was still hospitalized.

Patients were recruited at 31 centers with 134 participating hospitals. During the approximately two-year recruitment phase, a diagnosis of MI using BHAT criteria was made in about 16,400 patients who survived at least five days after admission and who were age eligible. Of these, 77% were not enrolled—18% because of contraindications to propranolol, 18% because they were already receiving or were likely to have propranolol prescribed to them, 26% because of study design considerations (such as living far from the clinic, having a cardiac pacemaker, having had cardiac surgery, or having other life-threatening diseases), and 15% because they or their private physicians did not consent to participate. About 23%, or 3,837 patients of the target population, were randomized (1,916 to propranolol and 1,921 to placebo).

A regimen of assigned study medication was begun (20 mg of propranolol hydrochloride or matching placebo) immediately after randomization. If no adverse reactions were noted, the dose was increased to 40 mg of propranolol hydrochloride or placebo every eight hours. Blood samples were drawn after a minimum of six consecutive doses on the 40-mg schedule, and eight hours after the last dose. For patients in the propranolol group, if the serum propranolol level,[18] as determined by a central laboratory, was below 20 ng/mL, the patient was prescribed 80 mg three times a day (240 mg/day) on his

Table 1.—Baseline Comparison

Variable	Group: Propranolol (n=1,916)	Group: Placebo (n=1,921)	z
Male, %	83.8	85.1	−1.15
White, %	89.3	88.4	0.89
Mean age, yr	54.7	54.9	−0.81
Mean systolic BP, mm Hg	112.3	111.7	1.65
Mean diastolic BP, mm Hg	72.5	72.3	0.95
Mean heart rate, beats per minute	76.2	75.7	1.38
Mean cholesterol, mg/dL	212.7	213.6	−0.65
Mean weight, kg			
Men	80.2	79.8	0.83
Women	67.4	66.5	0.89
Current smoker, %	57.4	56.9	0.26
Medical history, %			
Prior MI*	13.9	13.2	0.64
Hypertension	41.4	40.1	0.82
Angina pectoris	35.8	36.5	−0.48
Congestive heart failure	9.0	9.4	−0.42
Diabetes	11.7	11.3	0.38
Taking propranolol or other β-blocker	7.2	6.8	0.46
In-hospital events occurring before randomization, %			
Atrial fibrillation	6.8	5.7	1.49
Congestive heart failure	14.3	14.9	−0.56
Ventricular tachycardia	23.0	23.2	−0.15
Use of antiarrhythmic drug	45.8	46.0	−0.12
Medications being used at time of randomization, %			
Antiarrhythmic	16.6	17.9	−1.03
Anticoagulant	13.9	15.1	−1.02
Antiplatelet	7.1	6.8	0.40
Diuretic	16.1	18.0	−1.59
Vasodilator	36.0	36.3	−0.21
Digitalis	12.5	13.0	−0.50
Oral hypoglycemic	2.2	1.8	0.93
Location of BHAT MI,* %			
Anterior	27.8	25.7	1.47
Anterior and inferior†	9.2	10.0	. . .
Inferior	31.6	32.4	. . .
Nontransmural	22.9	22.6	. . .
Non-BHAT MI	8.6	9.2	. . .
ECG abnormalities, %			
Q-QS waves	67.3	67.4	−0.04
ST depression	25.8	26.7	−0.58
ST elevation	12.2	14.5	−1.98
T-wave abnormalities	64.8	65.9	−0.66
Ventricular conduction defects	10.3	7.5	2.99
Atrioventricular conduction defects	3.5	3.7	−0.20
Cardiomegaly,‡ %	37.0	34.7	1.34

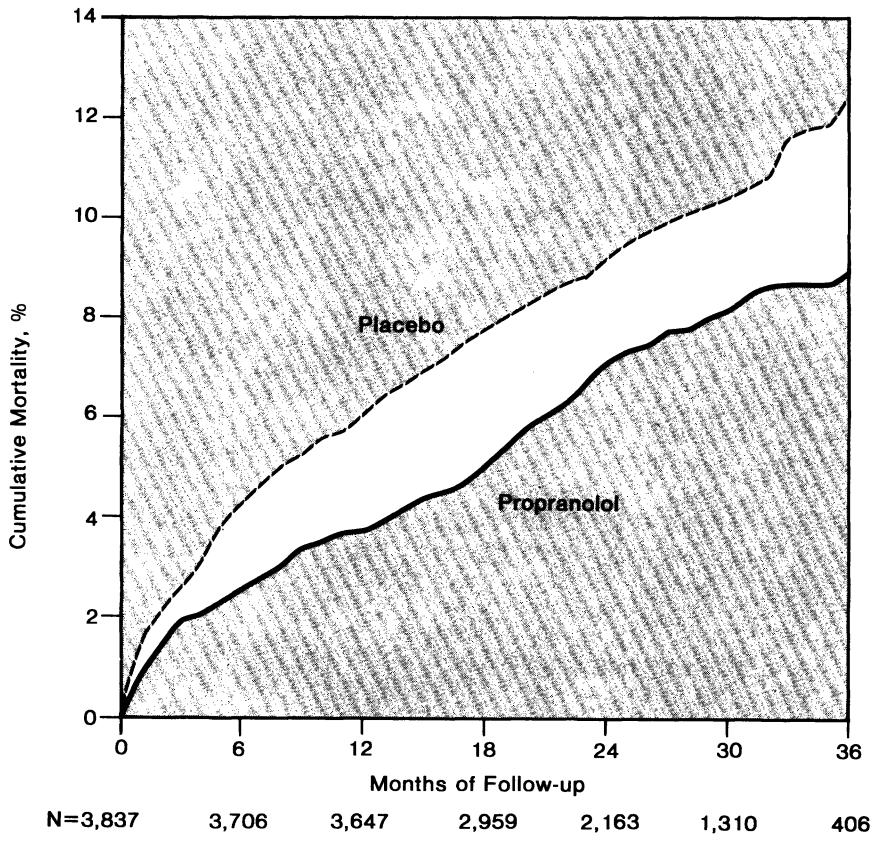
*MI indicates myocardial infarction; BHAT, β-Blocker Heart Attack Trial.

†Evidence of both anterior and inferior MI was present, but it was not determined which was the location of the acute BHAT event.

‡Cardiomegaly is defined as a cardiothoracic ratio of greater than 50% by standard six-foot posteroanterior chest roentgenograms. Data are missing for 15% of BHAT patient population.

Table 2.—Life Tables for Propranolol and Placebo Groups

	Propranolol				Placebo			
Period, mo	No. Alive at Beginning of Intervals	Deaths	Lost to Follow-up	Cumulative Mortality, %	No. Alive at Beginning of Interval	Deaths	Lost to Follow-up	Cumulative Mortality, %
1-3	1,916	37	1	1.93	1,921	50	2	2.60
4-6	1,878	10	0	2.45	1,869	31	0	4.22
7-12	1,868	23	1	3.66	1,838	34	1	5.99
13-18	1,844	24	2	5.03	1,803	30	1	7.69
19-24	1,501	29	0	7.13	1,458	20	1	9.15
25-36	1,087	14	0	9.00	107	22	2	12.52
36+	202	1	0	10.26	204	1	1	13.29
Total	...	138	4	...	...	188	8	...



Life-table cumulative mortality curves for groups receiving propranolol hydrochloride and placebo. N indicates total number of patients followed up through each time point.

return to the clinic at four weeks. If the blood level was at or above 20 ng/mL, the patient was assigned to a schedule of 60-mg tablets of propranolol hydrochloride three times a day (180 mg/day). To maintain the "blind," patients taking placebo were also assigned to either 180- or 240-mg daily dosage schedules. Dosage assignments were made through the coordinating center and remained in effect for the duration of the trial. Of the 3,837 enrolled patients, 82% were assigned the 180-mg/day regimen and 18% were assigned the 240-mg/day regimen.

Patients were asked to report to their clinical center at three-month intervals, with the exception of the first and second visits, which were scheduled for one month and six weeks after entry, respectively. At each visit, adherence to study drug, side effects, health status, the use of non-study medication, and occurrence of morbid events were monitored and additional study medication was dispensed. The clinic physician, on assessment of the patient, could reduce the prescribed dose of medication. Study medication was withdrawn from patients who were prescribed non-study β-blockers, with neither the patients nor the physicians being "unblinded."

All deaths were classified by the mortality classification subcommittee without knowledge of the treatment assignment. Information on cause and circumstances of death was obtained from relatives, witnesses, death certificates, attending physicians, hospital records, and autopsy reports.

Percentages of events in the propranolol and placebo groups, as well as results of life-table analyses, are reported. All enrolled patients, regardless of final eligibility determination or degree of adherence to medication, are included in these analyses and are counted in the study group to which they were assigned originally. Allowances were made in the original sample-size estimate to accommodate the anticipated noncompliance rates.[19,20] Mortality results were analyzed using standard survival analysis methods.[21,22]

Study data were reviewed periodically by a policy and data monitoring board, the members of which were not investigators in the BHAT. Because mortality data were to be analyzed at seven scheduled board meetings during the study, the probability of detecting a significant treatment effect by chance alone was greater than it would have been had the data been analyzed only at the end of the study. A number of statistical methods were proposed to correct for repeated significance testing.[23-26] The policy and data monitoring board was guided primarily by a monitoring technique[26,27] that requires extreme differences between groups early in the trial and smaller differences as the trial proceeds. Thus, the critical z value (observed difference divided by the standard error) at the first meeting of the board, for α=.05 and a two-sided test of significance was 5.46, while at the scheduled end of the trial the critical z value was 2.04. The conventional critical z value for a single test of the data is 1.96.

The board also considered at each review the probability that a statistically significant treatment effect would be identified if the study continued to its scheduled termination.[28,29] This approach to early stopping is also conservative, since the probability of detecting a significant difference is computed under the hypothesis

Table 3.—Cause-Specific Mortality by Treatment Group

Cause of Death	Propranolol No. of Deaths	Propranolol Mortality, %	Placebo No. of Deaths	Placebo Mortality, %	P* (Two-Sided)
Total mortality	138	7.2	188	9.8	<.005
Cardiovascular disease	127	6.6	171	8.9	<.01
Arteriosclerotic heart disease	119	6.2	164	8.5	<.01
Sudden†	64‡	3.3	89	4.6	<.05
Nonsudden	55	2.9	75	3.9	NS
Other cardiovascular disease	8	0.4	7	0.4	NS
Noncardiovascular disease	11	0.6	17	0.9	NS

*Because of the numerous statistical tests performed, the *P* values for cause-specific mortality should be interpreted cautiously.

†Deaths occurring less than one hour from onset of symptoms.

‡One death coded as sudden occurred approximately one week after cardiac surgery.

Table 4.—Mortality by Selected Baseline Variables, by Treatment Group

Variable	Propranolol, No. (%) Mortality	Placebo, No. (%) Mortality	Life-Table Relative Risk
Infarct location			
Anterior	533(7.5)	494(10.9)	0.67
Anterior and inferior	176(11.4)	192(15.1)	0.75
Inferior	605(5.1)	623(8.2)	0.61
Nontransmural	438(8.2)	435(7.8)	1.07
Non-BHAT MI*	164(6.7	177(11.3)	0.58
Risk group			
1	267(13.5)	254(17.3)	0.74
2	527(8.2)	501(11.8)	0.68
3	1,122(5.3)	1,166(7.3)	0.71
Age yr,			
30-39	100(2.0)	95(6.3)	0.31
40-49	417(5.8)	405(6.4)	0.90
50-59	783 (6.6)	788(8.0)	0.82
60-69	616(9.7)	633(14.7)	0.64
Sex			
M	1,605(7.2)	1,635(9.5)	0.75
F	311(7.1)	286(11.5)	0.62
Diastolic BP, mm Hg			
<70	667(5.8)	673(8.3)	0.70
70-76	679(7.8)	696(10.5)	0.72
>76	570(8.1)	552(10.7)	0.74
Heart rate, beats per minute			
<73	683(4.5)	708(7.3)	0.59
73-80	637(8.2)	648(9.9)	0.84
>80	596(9.2)	565(12.7)	0.70

*BHAT indicates β-Blocker Heart Attack Trial; MI, myocardial infarction.

of no difference in mortality between the treatment groups for the remainder of the study.

On Oct 2, 1981, the policy and data monitoring board of the BHAT concluded that the propranolol therapy was effective and recommended that the trial be ended earlier than planned and that the results be reported promptly. Based on this recommendation, official patient follow-up was stopped on Oct 2, 1981, rather than in June 1982 as scheduled.

Because of the issue of multiple significance testing, only the significance level (*P* value) for the primary response variable (total mortality) is unambiguous. For other outcome variables, the indicated significance values should be interpreted cautiously.

RESULTS

Table 1 shows the distribution of selected baseline characteristics. Overall, there was excellent comparability between the two groups. The mean number of days in the hospital before randomization was 13.9 in the propranolol group and 13.7 in the placebo group. The median number of days was nine in each group. A more extensive discussion of the distribution of baseline characteristics in BHAT is available elsewhere.[30]

After an average follow-up period of 25.1 months, 138 patients in the propranolol group (7.2%) and 188 in the placebo group (9.8%) had died. (Since the earlier report of the findings, eight additional patients were found to have died on or before Oct 2, 1981, the official end of the trial—five in the placebo group and three in the propranolol group.) The life-table is shown in Table 2, and the survival curve is presented in Fig 1. At the end of the trial, vital status was unknown for 12 patients (four in the propranolol group and eight in the placebo group). Based on all randomized patients, the life-table *z* value for all-cause mortality is −2.90 (nominal $P<.005$; if repeated testing is taken into account by means of the indicated technique, two-sided $P<.01$). Adjusting for selected baseline variables by means of the Cox model[31] yielded a *z* value of −3.05 (the adjusting variables were treatment group, age, sex, race, smoking status, leisure time activity, prior MI, diabetes mellitus, angina pectoris, history of hypertension, vasodilator use, complications during the qualifying MI [cardiogenic shock, hypotension, congestive heart failure, use of digitalis, pulmonary edema, ventricular fibrillation, atrial fibrillation, atrioventricular block], diminished right dorsalis pedis pulse, heart rate, hematocrit reading, WBC count, serum cholesterol level, ST-segment elevation on ECG, ventricular conduction defect on ECG, diastolic BP, location of MI, intermittent claudication, serum creatinine level, and antiplatelet therapy).

Cause-specific mortality results are presented in Table 3. Cardiovascular mortality was reduced in the propranolol group (6.6% *v* 8.9%, $P<.01$). A subset of this category, arteriosclerotic heart disease (ASHD) mortality, was also reduced (6.2% *v* 8.5%, $P<.01$). Sudden death, a subset of the ASHD category, was less frequent in the propranolol group (5.3% *v* 4.6%, $P<.05$).

Table 4 shows mortality results analyzed by selected baseline variables. A relative risk of less than 1 indicates lower observed mortality in the propranolol group. Most of the subgroups studied exhibit a trend that is consistent with the overall finding of the study. A possible exception was the subset of patients with a nontransmural infarct. Propranolol was as effective in patients with inferior MIs as in those with anterior

MIs (relative risks, 0.61 and 0.67, respectively). To compare findings with those of the timolol trial,[13] risk groups similar to those in that study were also created. Risk group 1 consists of patients who had had at least one MI before the BHAT MI. Risk group 2 consists of patients with a single MI and who experienced at least one of the following complications during hospitalization: cardiogenic shock, persistent hypotension, atrioventricular block, atrial fibrillation, ventricular fibrillation, pulmonary edema, or congestive heart failure. Risk group 3 consists of the remaining patients. The benefits of propranolol were similar in the three groups (relative risks, 0.74, 0.68, and 0.71).

Table 5 shows the percentage of patients from whom study medication was withdrawn at the most recent clinic visit, by reason. The numbers are small because only conditions of sufficient magnitude led to withdrawal of medication. Medication was withdrawn in more patients in the propranolol than placebo group because of hypotension, reduced sexual activity, and gastrointestinal problems. Only slight differences were noted for congestive heart failure, tiredness, and faintness. Regimens were discontinued more frequently in the placebo than propranolol group because of ventricular arrhythmias.

The percentages of patients who complained at any time during the course of the study of symptoms potentially attributable to propranolol are presented in Table 6. Many complaints were as frequent in the placebo group as in the propranolol group. More patients in the propranolol group reported tiredness, bronchospasm, diarrhea, and cold hands or feet. Rapid heartbeat was noted more often among patients in the placebo group.

The frequency of use of non-study drugs during the trial is shown in Table 7. Fewer antiarrhythmic agents were used by patients in the propranolol group, whereas fewer patients in the placebo group used oral hypoglycemic agents. Coronary artery bypass surgery was performed in 9% of the propranolol and 10% of the placebo patients. At the one-year follow-up visit, 46% of the propranolol patients who had been cigarette smokers at

Table 5.—Percent of Patients Having Study Medication Withdrawn for Medical Reasons, at Last Clinic Visit

Reasons	Propranolol	Placebo	P (Two-Sided)
Cardiopulmonary			
Congestive heart failure	4.0	3.5	NS
Hypotension	1.2	0.3	<.005
Pulmonary problems	0.9	0.7	NS
Sinus bradycardia	0.7	0.3	NS
New or extended myocardial infarction	0.4	0.4	NS
Serious ventricular arrhythmia	0.3	1.0	<.025
Heart block	0.1	0.1	NS
Syncope	0.1	0.1	NS
Neuropsychiatric			
Tiredness	1.5	1.0	NS
Disorientation	0.6	0.6	NS
Depression	0.4	0.4	NS
Faintness	0.5	0.2	NS
Nightmares	0.1	0.2	NS
Insomnia	0.2	0.0	NS
Reduced sexual activity	0.2	0.0	<.05
Other			
Gastrointestinal problems	1.0	0.3	<.01
Dermatologic problems	0.3	0.1	NS
Cancer	0.2	0.1	NS

Table 6.—Percent of Patients With Complaints at Any Time During the Trial

Complaint	Propranolol	Placebo	P (Two-Sided)
Cardiopulmonary			
Shortness of breath	66.8	65.5	NS
Bronchospasm	31.3	27.0	<.005
Rapid heartbeat	10.8	15.1	<.001
Cold hands, feet	10.0	7.7	<.025
Neuropsychiatric			
Tiredness	66.8	62.1	<.005
Reduced sexual activity	43.2	42.0	NS
Depression	40.7	39.8	NS
Nightmares	39.7	36.9	NS
Faintness	28.7	26.6	NS
Insomnia	21.1	18.8	NS
Blacking out	9.1	10.3	NS
Hallucinations	5.9	4.5	NS
Other			
Diarrhea	5.5	3.6	<.01

Table 7.—Percent of Patients Taking Non-Study Medications at Any Time During the Trial

Medication	Propranolol	Placebo	P (Two-Sided)
Vasodilator	47.8	47.1	NS
Diuretic	40.8	42.3	NS
Tranquilizer	28.0	30.4	NS
Digitalis	26.9	26.3	NS
Aspirin prescribed on a continuing basis	21.5	21.6	NS
Antiarrhythmic	20.7	25.6	<.001
Potassium	16.3	17.7	NS
Antihypertensive, excluding diuretic	11.8	13.4	NS
Anticoagulant	9.8	8.5	NS
Dipyridamole	6.2	5.5	NS
Insulin	4.8	4.2	NS
Hormonal	4.5	4.4	NS
Oral hypoglycemic	5.5	3.2	<.001
Sulfinpyrazone	4.3	5.0	NS
Lipid-lowering	2.9	2.7	NS

baseline had stopped smoking as compared with 49% of the placebo patients.

At their last completed study visit, study medication was prescribed to 76% of the patients in each group. Sixty percent of all patients were receiving a full-protocol dose (57% in the propranolol group and 63% in the placebo group). In the propranolol group, 24% were not receiving study medication, about one third of whom were known to be receiving nonstudy β-blockers; in the placebo group, 24% also were not receiving study medication, of whom about half were known to be taking β-blockers. Thus, approximately 85% of the propranolol group were taking a β-blocker at the time of their last study visit, as compared with 13% of the placebo group.

At the one-year follow-up visit, mean heart rate was 65 beats per minute in the propranolol group (a drop of 11 beats per minute from baseline) and 73 beats per minute in the placebo group (a drop of three beats per minute from baseline). Mean systolic BP at one year was 127 mm Hg in the propranolol group and 130 mm Hg in the placebo group; mean diastolic BPs were 80 mm Hg and 81 mm Hg in the propranolol and placebo groups, respectively. These results include all patients who were seen at the one-year visit, regardless of compliance to the assigned medication.

COMMENT

The overall results show propranolol to have reduced mortality by 26%. This treatment effect was not explained by any differences between the groups at baseline.

More than 50 subgroups in the BHAT population were examined to investigate the possibility that the difference in mortality between the treatment groups varied from subgroup to subgroup. While small numbers make it difficult to demonstrate statistical significance in various subgroups, trends in favor of propranolol were seen in most subgroups analyzed.

When the effect of propranolol is analyzed according to risk levels similar to those defined in the Norwegian timolol study,[13] comparable results are obtained. That is, regardless of whether the patients had had more than one MI, a single MI with complications (eg, congestive heart failure, hypotension, atrial arrhythmias), or a single uncomplicated MI, propranolol was found to be efficacious.

The results in each age group are consistent with the overall results, in contrast to an alprenolol study.[11] Propranolol also appeared to be beneficial in patients with either inferior or anterior MIs, which differs from the results of a practolol study.[9,10] In 9% of the enrolled patients, the BHAT criteria MI were not confirmed subsequently, although each of these patients had a clinical diagnosis of acute MI. Even these patients benefited from propranolol. Only in patients with a nontransmural infarction was no favorable difference observed, which may well be a chance finding. There is no statistical evidence that propranolol acted differently in any of the subgroups.

More than 90% of the observed deaths were from cardiovascular causes. Most of these were due to atherosclerotic heart disease, and about half were sudden. Both sudden and nonsudden atherosclerotic heart disease mortality was less in the propranolol group.

Study medication was withdrawn from a rather large percentage of patients in both groups for various reasons. At the time of their last clinic visit, "blinded" medications had been replaced by a regimen of a known β-blocker in about 13% of the placebo group and 9% of the propranolol group. Study drugs were withdrawn from about 7% of the patients in each group for reasons related to adherence to the regimen (eg, lost interest, moved away from the clinic). The regimens were discontinued in other patients because of symptoms and signs such as congestive heart failure, hypotension, and tiredness. The small percentages shown in Table 5 are due in part to the fact that only the more serious effects led to complete cessation of administration of study medication. In addition, only patients free of absolute and relative contraindications to propranolol were enrolled in BHAT. Using less stringent definitions, side effects resulting from propranolol use are still infrequent (Table 6). All of the side effects detected in the BHAT have been reported previously and are not unexpected. However, other complaints usually attributed to β-blockers (eg, depression, disorientation, and nightmares) were as common in patients on placebo as on propranolol. The reduced use of antiarrhythmic agents in the propranolol group and the increased use of oral hypoglycemic agents are consistent with known actions of β-blockers.

The impact of the eligibility criteria must be considered in determining in which patients the results can be generalized. Many of the exclusions were for contraindications to propranolol (eg, congestive heart failure, heart block, hypotension). Thus, clearly, the results of the study cannot be extrapolated to this group of patients, about 18% of those otherwise eligible. It seems reasonable to assume that those patients excluded from BHAT because they were already taking or were likely to be placed on a regimen of β-blockers (also 18% of the total) would have a benefit similar to the effect in the 23% who were enrolled. This assumption is supported by the fact that those enrolled patients with angina had the same benefit as patients without angina (relative risks of 0.71 and 0.72, respectively). The majority, but probably not all, of the remaining patients, especially those who declined to participate, whose private physicians refused permission, or who were excluded for reasons of study design, would presumably also respond to β-blockers in a manner similar to those who entered BHAT. Thus, approximately two thirds of the age-eligible patients hospitalized with a documented MI and who survived at least five days might benefit from propranolol therapy.

The results of BHAT are consistent with those of the Norwegian Multicentre Study Group trial of timolol.[13] The percent reductions in mortality at one year (in both studies patients were followed up for a minimum of one year) were approximately 33% in the timolol trial and 39% in BHAT. Like timolol, propranolol is a nonselective β-blocker without intrinsic sympathomimetic activity and has now been shown to reduce total and coronary mortality in patients with a recent myocardial infarction. This is true regardless of patient age or site of infarction. The recent trial of metoprolol,[14] administered shortly af-

ter an MI, also yielded positive results, though results were only reported for a follow-up period of 90 days. The fact that almost all studies of other β-blockers, in various settings and in different populations, have shown positive results (either a trend or statistically significant) supports, in the absence of contraindications the advisability of the use of these agents in post-MI patients.

In BHAT, 82% of the patients were assigned 180 mg/day of medication and 18% were assigned 240 mg/day. The β-blocking effects of these doses are comparable with those in the timolol and metoprolol studies.[32,33] Another clinical trial of propranolol hydrochloride[12] employed a fixed dose of 120 mg/day and showed no benefit for total mortality. That dose may have been inadequate. Thus, although it is not possible to specify the optimal dose of propranolol, one in the range of 180 to 240 mg/day is recommended.

Neither the BHAT nor any other reported trial was designed to answer the question of how long after an MI treatment with β-blockers should continue. It is also not known whether treatment with propranolol is helpful if initiated substantially beyond the immediate postinfarct period. The beneficial effect of propranolol seems most pronounced in the first 12 to 18 months after MI, although the effect was sustained for the duration of the trial (an average of 25 months and a maximum of 39 months). Based on the BHAT results, in conjunction with those of studies reported previously, the investigators recommend the use of propranolol for at least three years in patients with no contraindications to β-blockade who have had a recent MI.

Propranolol hydrochloride and matching placebo were prepared and donated by Ayerst Laboratories, New York.

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