Effect of propranolol in postinfarction patients with mechanical or electrical complications

CURT D. FURBERG, M.D., C. MORTON HAWKINS, Sc.D., AND EDGAR LICHSTEIN, M.D., FOR THE BETA-BLOCKER HEART ATTACK TRIAL STUDY GROUP

ABSTRACT In “post hoc” subgroup analyses, a simple classification system for patients, based on the presence or absence of findings indicative of electrical and/or mechanical complications early during short-term hospitalization, was applied to the data from the Beta-Blocker Heart Attack Trial (BHAT). In the largest subgroup of BHAT patients who had no reported complications, the 25 month mortality was low and the observed benefit of propranolol therapy small. Patients with electrical complications only had intermediate mortality and a pronounced effect of treatment was observed. Those with mechanical complications had the highest mortality and experienced an intermediate relative benefit of β-blocker treatment. They also reported the most adverse effects. Post hoc analyses should always be interpreted cautiously. It is important to determine whether these findings are present in other completed β-blocker trials. On the basis of these analyses alone it is suggested that the present practice of prescribing β-blockers in postinfarction patients should not be altered.


LONG-TERM controlled clinical trials of β-blockers in survivors of myocardial infarction (MI) have convincingly demonstrated benefit with respect to mortality from all causes,1,2 coronary mortality,1,2 and sudden cardiac death.1,2,4 The favorable results have also raised many questions. First, how do the β-blockers exert their positive action? The data from the trials would suggest that the drugs have both an antiarrhythmic and an anti-ischemic effect.5,6 Second, should all patients with MI be treated with β-blockers? Different opinions have been expressed. A view shared by many is that patients at low risk, i.e., those with an uncomplicated hospitalization, have little to gain from treatment.7,8 Third, can β-blockers be used safely in patients with MI who have been in congestive failure?

A simple classification of risk for patients after MI was developed on the basis of a prospective epidemiologic study by Elmfeldt and Wilhelmsen.9 The system has been used for stratified randomization in a few trials performed after patients had an MI.10,11 The patients are classified on the basis of the presence or absence of findings indicative of electrical (rhythm) and/or mechanical (pump) complications early during hospitalization.

A slightly modified system was applied post hoc to the data from the Beta-Blocker Heart Attack Trial (BHAT). Analyses were conducted to address the three aforementioned questions. Because no prior hypotheses were established, the results should be interpreted with due caution.

Methods

BHAT was a randomized, placebo-controlled, clinical trial sponsored by the National Heart, Lung and Blood Institute and was designed to determine the efficacy of long-term treatment with propranolol in patients enrolled 5 to 21 days after a documented MI. A total of 3837 men and women below the age of 70 were recruited at 31 clinical centers in the U.S. and Canada*. 1916 patients were assigned to the propranolol group, and 1921 patients were assigned to the placebo group. After a test dose, the persons assigned to active treatment were given 120 mg of propranolol in three divided doses. In the absence of adverse effects and on the basis of a serum determination of propranolol, a maintenance dose of 60 or 80 mg tid was prescribed at the 1 month visit. Eighty-two percent of participants received the lower dose. The control group was given matching placebo.

BHAT was stopped 9 months before scheduled termination because of favorable results.2 The average follow-up was 25 months. Data were analyzed according to the intention-to-treat principle. Twelve patients (four receiving propranolol and eight receiving placebo) were lost to follow-up. A more complete description of the design, including eligibility criteria, the study population, and overall results, including adverse effects, have been published elsewhere.3,12

*Principal investigators are listed before the references.
All enrolled patients were classified on the basis of findings during the hospital stay but before randomization, which occurred an average of 13.8 days after hospital admission. The following information was obtained retrospectively at the time of randomization, and no attempts were made to standardize collection or to document the occurrence of these complications:

Electrical (rhythm) complication was defined as the reported, clinically determined occurrence of one of the following complications during the hospitalization of patients for the infarct: ventricular fibrillation or tachycardia (3 or more successive ventricular premature beats), complete or incomplete atrioventricular (AV) block (Mobitz Type I or II second-degree AV block), or "new" atrial fibrillation. Mechanical (pump) complication was considered to occur in patients who were reported to have suffered one of the following complications at the time of the infarct but before enrollment: pulmonary edema, cardiogenic shock (oliguria and systolic blood pressure below 90 mm Hg), persistent hypotension (systolic blood pressure below 90 mm Hg for 1 hr or more), basilar rales, or symptoms/signs of congestive heart failure (requiring therapy with digitalis and/or diuretics).

The following definitions were used during the trial: Congestive heart failure — S-3 gallop or increased jugular venous pressure and pulmonary rales or increased pulmonary vascular markings on chest x-ray and dyspnea or fatigue. Hypotension — Systolic blood pressure below 90 mm Hg. Sinus bradycardia — Heart rate below 50 beats/min.

Most of these complications were transitory and were not present within 2 days of randomization of the enrolled patients, since the complications may represent contraindications to β-blocker therapy. Thus, the patients were divided into four groups: (1) neither electrical nor mechanical complication, (2) electrical but no mechanical complication, (3) mechanical but no electrical complication, and (4) both electrical and mechanical complications.

No formal tests of hypothesis are presented because of the problem of assigning proper significance levels for post hoc statistical analyses and for multiple comparisons. Z values are presented in table 1 as a guide for the interpretation of the effect of treatment for a single comparison. Z = 1.96 corresponds to p = .05. The effect of propranolol on mortality (of patients) from all causes was presented in two ways. Benefit is expressed as a relative risk (mortality of propranolol group divided by mortality of placebo group) and as 100 times the difference in the two mortality rates. The latter indicates how many lives were prolonged per 100 patients treated and has been termed "absolute risk reduction."

Results

Approximately 55% of the patients in the BHAT study had no reported electrical or mechanical complication during their hospitalization prior to enrollment. Nearly one-fourth met the definition of having an electrical failure only. A total of 22% suffered a mechanical complication and approximately half of these had an electrical problem as well (table 1).

The mortality from all causes for placebo patients with no complications was 6.6% during the average follow-up period of 25 months. Patients with evidence of mechanical problems were at the highest risk and in the control group had a mortality of around 17%. Those with an electrical complication only had a mortality (10.9%) in between those of the other risk groups (table 1).

In the large subgroup with no complications, the observed benefit of propranolol treatment was only 6%; that is, the relative risk was .94. The most pronounced percentage difference in mortality between the two study groups was observed in the subgroup with electrical problems only. The mortality in the propranolol group was roughly half of that in the placebo group; the relative risk was .48. In the two risk groups with mechanical complications, the relative difference in mortality was 38% and 24%, respectively. Statistical adjustment by logistic regression with the Walker-Duncan method for differences between treatment groups in baseline prognostic factors yielded minor shifts in the relative risks (table 1).

In the subgroup of patients with neither electrical nor mechanical complications, the numerical difference in the mortality for patients receiving propranolol and placebo was −.4/100, indicating that less than half of one life was prolonged per 100 patients treated during 25 months. The highest "absolute risk reduction" was found in the subgroups with either electrical or mechanical problems; between four and six lives were prolonged for every 100 patients treated. Although the relative benefit of propranolol treatment was intermediate in the two risk groups with pump complications, the high mortality for those on placebo in these two groups explain why the numerical differences (mortality for patients on placebo minus mortality for those on propranolol) are high (table 1).

Of the patients receiving placebo who had mechanical problems in BHAT, 25 died instantaneously as compared with 13 of the patients receiving propranolol. In addition there were fewer nonfatal Mls in the actively treated group (15 vs 24) compared with the group receiving placebo.

A more detailed analysis of the individual electrical and mechanical complications is shown in table 2. Patients who had suffered an episode of ventricular tachycardia during hospitalization made up the single largest subgroup. Among these patients, mortality was 44% lower in the propranolol group than in the control group. The lowest relative risk, which suggests patients received special benefit from propranolol therapy, was observed in the small subgroup of patients experiencing ventricular fibrillation before randomization. The highest relative risk, which indicates little benefit from therapy, was seen in the small subgroup of patients who had episodes of pulmonary edema before enrolling in BHAT.
TABLE 1
All cause mortality (%) by risk group and treatment in BHAT

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Propranolol</th>
<th>Placebo</th>
<th>Difference</th>
<th>Relative risk</th>
<th>Adjusted relative risk^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Mortality (P1)</td>
<td>No. of patients</td>
<td>Mortality (P2)</td>
<td>P1-P2</td>
</tr>
<tr>
<td>None</td>
<td>1047</td>
<td>6.2</td>
<td>1079</td>
<td>6.6</td>
<td>-.4</td>
</tr>
<tr>
<td>Electrical only</td>
<td>443</td>
<td>5.2</td>
<td>423</td>
<td>10.9</td>
<td>-5.7</td>
</tr>
<tr>
<td>Mechanical only</td>
<td>201</td>
<td>10.4</td>
<td>202</td>
<td>16.8</td>
<td>-6.4</td>
</tr>
<tr>
<td>Electrical + mechanical</td>
<td>225</td>
<td>12.9</td>
<td>217</td>
<td>17.1</td>
<td>-4.2</td>
</tr>
</tbody>
</table>

^a Adjusted for 13 baseline factors predictive of mortality in BHAT.

The occurrence of symptoms usually attributed to β-blocker therapy was monitored in the trial. When they were severe, the blinded BHAT treatment was stopped either temporarily or permanently. Within the risk groups “none” and “electrical only” there were no major differences in the incidence of congestive heart failure between the propranolol and placebo groups. For example, the incidence of congestive heart failure was similar in both treatment groups, while sinus bradycardia was slightly more common among the patients receiving propranolol (table 3). In the patients with mechanical problems, congestive heart failure was more common. Moreover, in these groups with mechanical problems, propranolol treatment seemed to cause an increased incidence of congestive heart failure. Also, in the risk group with both mechanical and electrical complications, the incidence of sinus bradycardia was increased with propranolol treatment (table 3).

Preliminary data from Holter monitoring performed before the study drug was administered show that complex ventricular premature beats (average of ≥10 VPBs/hr, at least one run of VPBs, or multiform VPBs) occurred in 36.5% of the patients in the “no risk” group and in 44.5% to 49.7% of those in the other three risk groups.

Discussion

When data on mortality is compared across clinical trials it is important to consider the composition of the study population according to the degree of risk. More than half of the patients in BHAT represented a low-risk group with a 25 month mortality of 6.6%. The small relative effect of treatment in this subgroup is in contrast to a greater benefit observed in the three patient subgroups that had an electrical and/or mechanical complication before enrollment. Thus, if these post hoc results hold generally, in a trial of patients at high risk one could expect a greater overall reduction in mortality after β-blocker therapy than that observed in BHAT.

These analyses suggest that patients with MI who

TABLE 2
All cause mortality (%) by reported complication during hospitalization before enrollment and by treatment group in BHAT

<table>
<thead>
<tr>
<th>Complications</th>
<th>Propranolol</th>
<th>Placebo</th>
<th>Difference Propranolol-placebo</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Mortality</td>
<td>No. of patients</td>
<td>Mortality</td>
</tr>
<tr>
<td>Electrical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>104</td>
<td>6.7</td>
<td>99</td>
<td>18.2</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>441</td>
<td>6.8</td>
<td>446</td>
<td>12.1</td>
</tr>
<tr>
<td>Complete AV block</td>
<td>54</td>
<td>9.3</td>
<td>44</td>
<td>15.9</td>
</tr>
<tr>
<td>Incomplete AV block</td>
<td>158</td>
<td>8.9</td>
<td>153</td>
<td>12.4</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>131</td>
<td>11.5</td>
<td>109</td>
<td>14.7</td>
</tr>
<tr>
<td>Mechanical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>52</td>
<td>19.2</td>
<td>51</td>
<td>19.6</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>29</td>
<td>10.3</td>
<td>21</td>
<td>14.3</td>
</tr>
<tr>
<td>Persistent hypotension</td>
<td>142</td>
<td>9.2</td>
<td>133</td>
<td>12.0</td>
</tr>
<tr>
<td>Basilar rales</td>
<td>58</td>
<td>13.8</td>
<td>57</td>
<td>22.8</td>
</tr>
<tr>
<td>Symptoms/signs of CHF</td>
<td>274</td>
<td>13.5</td>
<td>287</td>
<td>17.4</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure
TABLE 3
Incidence of congestive heart failure (CHF) and sinus bradycardia leading to temporary or permanent discontinuation of BHAT treatment by risk group and treatment

<table>
<thead>
<tr>
<th>Risk group</th>
<th>CHF</th>
<th>Sinus bradycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pr-</td>
<td>Placebo</td>
</tr>
<tr>
<td>None</td>
<td>4.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Electrical only</td>
<td>6.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Mechanical only</td>
<td>14.9</td>
<td>8.9</td>
</tr>
<tr>
<td>Electrical + mechanical</td>
<td>16.0</td>
<td>10.6</td>
</tr>
</tbody>
</table>

Risk group: None, Electrical only, Mechanical only, Electrical + mechanical

have an uncomplicated course during hospitalization benefit to a much smaller degree, if at all, from propranolol than do those with complications. Patients with electrical complications seemed to benefit the most from propranolol treatment. This could imply that propranolol exerts its favorable action through an antiarrhythmic effect. This view is supported by recent reports that β-blockers reduce the incidence of ventricular fibrillation and tachycardia in patients with MI.\(^1\)\(^,\)\(^2\) Ongoing analysis of the 24 hr ambulatory electrocardiographic recordings obtained in BHAT might shed more light in this respect.

The benefit of propranolol treatment on mortality from all causes in patients with mechanical problems appears paradoxical because congestive failure was seen more frequently in the propranolol group. However, it is well known that a large proportion of patients with congestive heart failure die suddenly, usually of ventricular fibrillation. The findings of BHAT suggest that propranolol exerts a beneficial antiarrhythmic effect (lower rate of instantaneous death) and an anti-ischemic action (fewer nonfatal MIs) in patients with mechanical complications. It should be noted that the small number of patients who have had an episode of pulmonary edema experienced little benefit from propranolol after having an MI.

In view of the benefit of propranolol in the risk groups with either electrical or mechanical complications, one might have expected the same favorable outcome from treatment in the combined risk group. Two possible reasons may explain the observed smaller benefit in this subgroup. First, the patients experienced more cardiovascular side effects and the cardiodepressant action of the β-blocker may have outweighed some of the favorable effects. Second, the numbers are small and therefore susceptible to chance variation.

The findings presented here may appear contradictory to those previously published from BHAT.\(^3\) When the data were analyzed according to risk levels similar to those in the Norwegian timolol study,\(^1\) benefit was seen regardless of whether the patient had had more than one MI (risk group I), a single MI with complications (risk group II), or a single uncomplicated MI (risk group III).\(^2\) If patients who experienced an episode of ventricular tachycardia are included in risk group III the relative risk is .72, as reported. If, instead, they are included in risk group II, the relative risk for risk group III is .86. This change illustrates one limitation of classification systems.

Previous reports of β-blocker trials have illustrated the potential problems with subgroup analyses. Subsets of patients have been identified in which treatment was claimed to be particularly beneficial or harmful.\(^1\)\(^,\)\(^5\)\(^,\)\(^6\) None of these observations has been confirmed in other β-blocker trials. Post hoc analyses should always be interpreted cautiously.\(^7\) The analyses presented here represent an attempt to address the questions raised by the recent β-blocker trials. It is important to see if these findings are present in other completed trials. On the basis of these analyses alone, present practices for prescribing β-blockers in postinfarction patients should not be altered.

BHAT principal investigators

Clinical Centers: Baylor University, C.M. Pratt; Boston University, P.S. Vokonas; Brown University, R.J. Capone; Emory University, R.C. Schlant; Evanston Hospital, G.N. Wilner; Geisinger Medical Center, PA, C.A. Laubach, Jr.; Greater Baltimore Medical Center, T.E. Prout; Henry Ford Hospital, G.M. Breneman; Kaiser Foundation Hospitals, Portland, J.A. Grover; Lankenau Hospital, W.L. Holmes; Long Island Jewish Med. Ctr., K.D. Chadda; Maimonides Medical Center, E. Lichstein; Medical College of S.C., P.C. Gazes; Medical College of Virginia, D.W. Richardson; Miami Heart Institute, F.L. Canosa; Montreal Heart Institute, P.A. Theroux; Mt. Sinai Hospital, Minneapolis, P.J. Ranheim; Northwestern University, O.M. Haring; Overlook Hospital, NJ, J.J. Gregory; Pacific Health Research Inst., Honolulu, J.J. McNamara; Providence Med. Ctr., Portland, G.L. Maurice; Rush-Presbyterian-St. Lukes, J.A. Schoenberger; Rutgers Medical School, P.T. Kuo; Salt Lake Clinical Research Foundation, A.H. Barker, C.B. Williams; SUNY, Buffalo, R.M. Kohn; U.C., Davis, N.O. Borhani; U.C., San Francisco, M.S. Warnowicz; University of Rochester, R.N. Yu; University of Southern California, L.J. Haywood; V.A. Hospital, Little Rock, M.L. Murphy; V.A. Hospital, West Roxbury, K.M. McIntyre.

Coordinating Center: University of Texas, Houston, C.M. Hawkins, J.D. Curb, R.P. Byington.

ECG Centers: University of Minnesota, R.S. Crow; Anthropometrics Heart Clinic, J. Morganroth.

Central Laboratory: Bio-Science Laboratories, F. Ibbott.


Chairman of Steering Committee: S. Goldstein.

References

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