Secondary Prevention by Raising HDL Cholesterol and Reducing Triglycerides in Patients With Coronary Artery Disease

The Bezafibrate Infarction Prevention (BIP) Study

The BIP Study Group

Background—Coronary heart disease patients with low high-density lipoprotein cholesterol (HDL-C) levels, high triglyceride levels, or both are at an increased risk of cardiovascular events, but the clinical impact of raising HDL-C or decreasing triglycerides remains to be confirmed.

Methods and Results—In a double-blind trial, 3090 patients with a previous myocardial infarction or stable angina, total cholesterol of 180 to 250 mg/dL, HDL-C ≥45 mg/dL, triglycerides ≥300 mg/dL, and low-density lipoprotein cholesterol ≤180 mg/dL were randomized to receive either 400 mg of bezafibrate per day or a placebo; they were followed for a mean of 6.2 years. The primary end point was fatal or nonfatal myocardial infarction or sudden death. Bezafibrate increased HDL-C by 18% and reduced triglycerides by 21%. The frequency of the primary end point was 13.6% on bezafibrate versus 15.0% on placebo (P=0.26). After 6.2 years, the reduction in the cumulative probability of the primary end point was 7.3%, (P=0.24). In a post hoc analysis in the subgroup with high baseline triglycerides (≥200 mg/dL), the reduction in the cumulative probability of the primary end point by bezafibrate was 39.5% (P=0.02). Total and noncardiac mortality rates were similar, and adverse events and cancer were equally distributed.

Conclusions—Bezafibrate was safe and effective in elevating HDL-C levels and lowering triglycerides. An overall trend in a reduction of the incidence of primary end points was observed. The reduction in the primary end point in patients with high baseline triglycerides (≥200 mg/dL) requires further confirmation. (Circulation. 2000;102:21-27.)

Key Words: lipids ■ prevention ■ cardiovascular diseases ■ triglycerides ■ lipoproteins, HDL ■ bezafibrate
without increased triglyceride levels. In a previous publication from the large Bezafibrate Infarction Prevention (BIP) Registry population, we found that 25% of CAD patients had cholesterol levels <200 mg/dL (mean LDL-C, 117 mg/dL); among these patients, more than half had HDL-C levels <35 mg/dL. In addition, 17% of patients with CAD in the BIP Registry had combined low HDL-C (<35 mg/dL) and high triglyceride levels (≥200 mg/dL). 17

The BIP study 18 was designed and initiated in 1990. The primary question of the trial was whether bezafibrate, which raises HDL-C and reduces triglycerides, would reduce CAD mortality and nonfatal myocardial infarction (MI) in patients with established CAD. HDL-C <45 mg/dL, and moderately elevated cholesterol. Recent studies on the mode of action of fibrates indicate that some of these effects are mediated via the peroxisome proliferator-activated receptor pathway, 19 which alters the transcription rate of genes encoding for proteins that control lipoprotein metabolism. The triglyceride-lowering effect is thus linked to an induction of lipoprotein lipase-mediated lipolysis and to lowered apoC-III production, and the HDL-increasing effect is due to an induction in the synthesis of apoAI and apoAII 20–22.

Methods

Study Design and Patients

Between February 1990 and October 1992, 15,524 male and female patients with CAD aged 45 to 74 years were screened for inclusion in the BIP study in 18 of the 25 cardiology departments in Israel. After an initial 2 months on a lipid-lowering diet, 3122 patients who fulfilled the inclusion criteria were randomized to the study between May 1990 and January 1993. A total of 32 of the randomized patients, who were equally distributed between the placebo and bezafibrate treatment groups, never began study medication and were excluded from analysis. Inclusion criteria for men and women comprised the following: age of 45 to 74 years, history of MI ≥6 months but <5 years before enrollment into the study and/or stable angina pectoris confirmed by coronary angiography, and/or radio-nuclear studies or standard exercise tests. In addition, a lipid profile of serum total cholesterol between 180 to 250 mg/dL, LDL-C <180 mg/dL (≤160 mg/dL for patients <50 years), HDL-C ≥45 mg/dL, and triglycerides ≤300 mg/dL was required. The main exclusion criteria were insulin-dependent diabetes mellitus, severe heart failure, unstable angina pectoris, hepatic or renal failure, known sensitivity to bezafibrate, or current use of lipid-modifying drugs. 18

Patients were assigned consecutive randomization numbers within each recruiting center after giving written informed consent. They were allocated to receive either 400 mg of bezafibrate retard or placebo once a day, in addition to dietary advice. Patients were allowed to take prescribed medications for cardiac and other conditions except for lipid-lowering drugs. Lipid profiles, fibrinogen levels, and safety parameters were measured in the Central Laboratory at randomization, at 4 months, and annually thereafter until the end of the study. Additional details of the study design and the patients’ baseline characteristics have been described elsewhere. 18, 23

Routine visits to the clinics were scheduled bimonthly for study medication distribution and compliance assessment by tablet count and every 4 months for clinical evaluation. Compliance was further assessed by annual measurements of alkaline phosphatase. During the 4-month visit, data on any adverse events (as defined in the study protocol), hospitalizations, and study outcomes were obtained. Study medication was withdrawn after the following: (1) a primary end point, (2) an adverse event deemed to be intolerable, (3) an increase in LDL-C to >210 mg/dL (or >190 mg/dL for patients aged <50 years) or triglycerides >500 mg/dL, or (4) safety variables exceeded predefined critical limits. All study participants, regardless of whether they continued to take the trial medication, were followed-up until the last patient had completed 5 years of follow-up.

In July 1994, after the publication of the Scandinavian Simvastatin Survival Study results, 15 the International Review and Advisory Board approved the recommendation of the Steering Committee to add colestipol for patients on study medication if their LDL-C exceeded 180 mg/dL in 2 separate laboratory examinations after reinforcement of dietary advice. Colestipol was given concomitantly with the study medication to 165 patients (57 patients in the bezafibrate and 107 in the placebo group) during the study.

The trial was conducted independently of the sponsor (Boehringer Mannheim GmbH, which is now part of F. Hoffmann-La Roche, Ltd), and it was approved by the Helsinki Committees of each center and the central national Helsinki Committee.

Classification and Review of Study End Points

The primary end point of the study was fatal MI, nonfatal MI, or sudden death (occurring within 24 hours of onset of symptoms). 18

Secondary end points, for patients free of primary end points, included hospitalization for unstable angina, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting. Stroke and death from any cause were also monitored. An independent Critical Event Committee, whose members were blinded to the treatment assignment, reviewed primary end points and all-cause mortality.

An independent International Review and Advisory Board regularly monitored the progress of the study and the incidence of adverse events. Two scheduled interim analyses were performed 4 and 5.5 years after the randomization of the first patient.

Laboratory Methods

Blood samples, which were collected in the 18 participating medical centers using standardized equipment and procedures, were transferred in cooled containers to the Central Laboratory at the Institute of Physiological Hygiene Laboratory at the E. Wolfson Medical Center, Holon. Blood samples were drawn after ≥12 hours of fasting to determine serum levels of cholesterol, HDL-C, triglycerides, and plasma fibrinogen. Laboratory measurements were performed using standard automated procedures with commercially available kits (Roche Diagnostics). HDL-C was measured by precipitation, and LDL was estimated using Friedewald et al’s equation. 24 Fibrinogen was measured by an automated kinetic method. Accuracy and precision of lipid and lipoprotein determinations were under periodic surveillance by the Centers for Disease Control/National Heart, Lung, and Blood Institute’s Lipids Standardization Program; other determinations, including the safety variables, were under surveillance by the Wellcome-Murex Diagnostic Clinical Chemistry Quality Assessment Program.

Statistical Analysis

The study design a priori assumed a cumulative event rate of 16% to 24% in the placebo arm of the study over 6 years and an expected reduction of the event rate of between 20% and 25%. Under these assumptions and using a 1-sided test, as originally planned, a sample size of between 2100 and 3300 would have provided a power of 80% to detect the expected reduction. However, during the course of the study, a decision was made to perform 2-sided rather than 1-sided statistical tests in light of the results of the Helsinki Heart Study II. Furthermore, the cumulative incidence of the primary end point under placebo turned out to be lower than expected. Under these circumstances, the randomization of 3000 patients provides a power between 62% and 85% to detect a 20% to 25% reduction in incidence rate with bezafibrate (α=0.05, 2-sided) when the cumulative incidence of the primary end point is 15%, as was observed in the placebo group.

Data were analyzed using SAS software. 20 All patients who took the study medication at least once (n=3090) were included in the intent-to-treat analysis. Baseline characteristics in the 2 study groups were compared using the χ2 test for dichotomous parameters and the
Changes in laboratory parameters were calculated as the difference between the baseline value (measured before administration of the study medication) and the mean of the values measured in the annual laboratory examinations before the occurrence of a primary end point or during the entire follow-up period for patients free of a primary end point.

The cumulative probability of events was computed using the Kaplan-Meier life-table method. The curves of cumulative probability of event for patients in the placebo and the bezafibrate groups were compared using the log-rank test.

To determine which factors affected primary end points in subgroups of patients by high and low baseline triglyceride and HDL-C levels and by using the cut points recommended by the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (National Cholesterol Education Program), multivariate analyses were performed using Cox’s proportional hazard stepwise regression modeling.

Results

Although 3122 patients were randomized to the study, 32 patients were excluded from analysis because they never started the study medication. Patients in the placebo (n = 1542) and bezafibrate (n = 1548) groups were well balanced in terms of clinical and laboratory baseline characteristics and concomitant medications (Table 1). The number of patients with prior MI (62% in the bezafibrate group and 61% in the placebo group) or angina (38% and 39% in the bezafibrate and placebo groups, respectively) as inclusion criteria was similar in both groups.

The study lasted for a mean of 6.2 years (range, 4.7 to 7.6 years). Vital status at the end of the study was ascertained for all patients except one. A total of 76% of the patients alive at the end of the study were on study medication (74% in the placebo group and 77% in the bezafibrate group). For 511 patients (17%), the study medication was withdrawn for reasons other than the occurrence of a primary end point or death. Of them, 373 patients (237 on placebo and 136 on bezafibrate) received open-label lipid-modifying treatment either before the occurrence of a primary end point or before the end of the study. Reasons for discontinuation of study medication were as follows: lipid levels exceeded predefined limits and necessitated treatment with a lipid-lowering drug.

![Figure 1. Effect of treatment on lipids and fibrinogen. TC indicates total cholesterol. Values are in mg/dL.](image1)

![Figure 2. Changes in lipid values throughout the study period in patients who completed 5 years of follow-up.](image2)
Compliance, according to the tablet count, exceeded 90% in 74% of patients in both groups; it was between 75% and 90% for 17% of patients and 75% for the remaining 9% of patients. These data were confirmed in the bezafibrate group, in which alkaline phosphatase decreased by $10 \text{ U/L}$ in 84% of patients, did not change in 10%, and increased by $10 \text{ U/L}$ in 7% of patients.

**Effect of Treatment on Lipid and Fibrinogen Levels**

Average changes in lipid and fibrinogen levels are shown in Figure 1. The most marked changes were an increase of 18% in HDL-C and a reduction of 21% in triglycerides in the bezafibrate group. In the placebo group, values of total cholesterol and LDL-C remained stable for 3 years; thereafter, they declined (Figure 2).

**Clinical Outcome**

The effect of treatment on the primary end point (nonfatal and fatal MI and sudden death) is shown in Table 2. Among patients treated with bezafibrate, the crude rate of primary end points was 13.6% versus 15.0% in the placebo group (9.4% reduction; $P=0.26$). Figure 3 depicts Kaplan-Meier curves of the primary end point for the bezafibrate and placebo groups throughout the mean study period (6.2 years). The 2 curves started to separate after 2 years, but in the last 2 years of the study, a change in the slope of the placebo group becomes evident. The reduction in the cumulative probability of the primary end point at 6.2 years was 7.3% ($P=0.24$). Beyond 6.2 years, the number of patients at risk and the number of events were small and rather unstable (at 7 years, the reduction in the cumulative probability of the primary end point was 5.3%, but the standard error was 8.8% because only 10 events in the treatment group and 9 events in the placebo group had occurred).

Mortality rates were similar in both groups (Table 2). Among the 161 deaths in the bezafibrate group, 95 were due to cardiac causes, whereas in the placebo group, 88 of 152 deaths were attributed to cardiac causes ($P=0.61$). The distribution of all-cause and cardiac mortality was not different between the 2 study groups. Kaplan-Meier curves for all-cause mortality are shown in Figure 4. The incidence of secondary end points and stroke were comparable between the 2 groups (Table 2).

The study hypothesis was based on the effect of bezafibrate on baseline triglyceride and HDL-C levels. Therefore, we performed a post hoc analysis of the study primary end point by baseline HDL-C and triglyceride levels (Table 3). In patients with triglycerides $<150 \text{ mg/dL}$, no clear benefit of bezafibrate treatment was observed. Among patients with triglycerides $\geq 150 \text{ mg/dL}$, a significant benefit of bezafibrate treatment was noted ($P=0.04$).
Baseline triglycerides $\geq 150$ mg/dL, bezafibrate reduced the crude primary end point rate in direct relationship with the level of baseline triglycerides. Among patients with baseline triglycerides $< 150$ mg/dL (225 patients in the placebo group and 234 in the bezafibrate group), bezafibrate reduced the cumulative probability of a primary end point by 7.9% ($P = 0.43$), whereas among patients with triglycerides $\geq 200$ mg/dL, the reduction in the cumulative probability of an end point was insignificant ($P = 0.02$).

After adjustment for age, sex, prior MI, New York Heart Association class, angina class, and bezafibrate use, the relative risk for primary end points associated with bezafibrate treatment in the subgroup of patients with high baseline triglycerides ($\geq 200$ mg/dL) was 0.57 (95% confidence interval, 0.35 to 0.93). When the interaction between study treatment and different baseline triglyceride levels was further examined by low ($< 35$ mg/dL) and high ($\geq 35$ mg/dL) HDL-C (Table 3), the effect of bezafibrate in patients with baseline triglycerides $\geq 200$ mg/dL was of similar magnitude.

**Safety**

The overall incidence of any adverse event was 69% in both groups, and the frequency of each type of adverse event was similar in both groups. There were 85 cases (5.5%) of newly diagnosed fatal and nonfatal cancers in the bezafibrate group versus 91 cases (5.9%) in the placebo group, with no significant differences between the groups at any site. Seven patients in the placebo group and 5 patients in the bezafibrate group complained of muscular pains during follow-up. Creatine phosphokinase levels exceeding twice the upper normal limit (390 U/L for men and 260 U/L for women) were recorded in 5 patients (4 in the bezafibrate group). For the other safety laboratory parameters, small differences were observed between the study groups; these differences had no clinical significance.

**Discussion**

Although bezafibrate therapy led to a substantial increase in HDL-C and a reduction in triglycerides, the observed reduction in the primary end point was not as expected. In this respect, the time course of the Kaplan-Meier curves of the combined primary end point are intriguing. In the first 5 years of follow-up, the 2 curves diverged; at 5 years, they displayed a cumulative reduction in primary end points of 16.3% ($P = 0.09$) between the bezafibrate and placebo groups. By the end of the study, the overall difference of the cumulative probability of primary end points was markedly reduced (Figure 3), reflecting an unexpected flattening of the placebo curve toward the end of the study. In previous lipid trials with statins and fibrates, a continuous separation of the Kaplan-Meier curves was observed beginning at 12 to 24 months of follow-up and resulting in the desired effect of the active medication on the incidence of end points.

The convergence of the 2 curves of the primary end point could also be due to greater variation of the primary end point incidence rate toward the end of the study, which was caused by the relatively few events occurring in smaller groups of patients at risk in the last months of follow-up. The time course of the Kaplan-Meier curves for the primary end point in subgroups of patients with baseline triglycerides $< 200$ mg/dL and $\geq 200$ mg/dL is shown in Figure 4.

![Figure 4. Kaplan-Meier curves for the primary end point in subgroups of patients with baseline triglycerides $< 200$ mg/dL and $\geq 200$ mg/dL.](http://example.com/fig4)

**TABLE 3. Cumulative Probability of Primary End Points at 6.2 Years of Follow-Up by Baseline Triglycerides and HDL-C Levels**

| & Bezafibrate, n (%) | Placebo, n (%) | Reduction, % | P  |
|---|---|---|---|---|
| Triglycerides |  |  |  |  |
| $< 150$ mg/dL | 938 (12.6) | 901 (13.7) | 7.9 | 0.43 |
| $\geq 150$ mg/dL | 603 (16.3) | 629 (17.1) | 4.6 | 0.48 |
| $\geq 175$ mg/dL | 407 (15.9) | 385 (20.3) | 21.6 | 0.07 |
| $\geq 200$ mg/dL | 234 (12.0) | 225 (19.7) | 39.5 | 0.02 |
| HDL-C $< 35$ mg/dL and triglycerides |  |  |  |  |
| $< 150$ mg/dL | 378 (13.5) | 382 (15.5) | 12.4 | 0.46 |
| $\geq 150$ mg/dL | 420 (18.5) | 436 (19.4) | 4.5 | 0.56 |
| $\geq 175$ mg/dL | 294 (17.2) | 286 (22.2) | 22.6 | 0.09 |
| $\geq 200$ mg/dL | 184 (13.0) | 162 (22.3) | 41.8 | 0.02 |
| HDL-C $\geq 35$ and triglycerides |  |  |  |  |
| $< 150$ mg/dL | 560 (12.0) | 518 (12.2) | 1.6 | 0.77 |
| $\geq 150$ mg/dL | 183 (11.2) | 193 (12.2) | 8.5 | 0.59 |
| $\geq 175$ mg/dL | 113 (12.7) | 99 (15.2) | 16.8 | 0.45 |
| $\geq 200$ mg/dL | 50 (8.2) | 63 (17.8) | 35.9 | 0.33 |

Baseline triglyceride data were missing in 19 patients and baseline HDL-C data were missing in 14 patients.
course of the primary event curve of the placebo group was consistent with the decline in LDL-C levels in this group toward the end of the study (Figure 2). Of note, 373 patients, two-thirds of whom were randomized to placebo, received open-label lipid-modifying drugs before the occurrence of a primary end point or the end of the study. In addition, 164 patients (two thirds of whom were in the placebo group) with high LDL-C levels (>180 mg/dL) were given colestipol as adjunct therapy to the study medication before the occurrence of a primary end point or the end of the study. It is to be expected that adding lipid-modifying therapy to patients in the placebo group would have a greater effect on outcome compared with patients in the bezafibrate group, where one effective therapy was added to or substituted for another.

A beneficial effect of fibric acid derivatives has been reported in the Helsinki Heart Study and in small angiographic secondary prevention trials in patients with isolated low HDL-C28 and in young men after MI.29 Recently, the results of the Veterans Affairs HDL Intervention Trial (VA-HIT), a secondary prevention study with the fibrate gemfibrozil, were published.27 Comparison of mean lipid levels at baseline of patients recruited to VA-HIT and BIP shows that VA-HIT patients had lower HDL (32 mg/dL versus 34.6 mg/dL), lower LDL (111 mg/dL versus 148 mg/dL), and higher triglyceride levels (161 mg/dL versus 149 mg/dL) than BIP participants. After a mean follow-up of 5 years, a 22% reduction in the primary end point (defined as in our study) was observed in the VA-HIT study. By the end of 5 years of follow-up in the BIP study, the cumulative probability of primary end points was reduced by 16.3% with bezafibrate as adjudvant therapy to the study medication before the occurrence of a primary end point or the end of the study. It is to be expected that adding lipid-modifying therapy to patients in the placebo group would have a greater effect on outcome compared with patients in the bezafibrate group, where one effective therapy was added to or substituted for another.

In summary, bezafibrate was found to be safe and was effective in elevating HDL-C and lowering triglycerides. Although the overall effect of bezafibrate on the incidence of primary end points was moderate (P=0.24), the reduction in the primary end point was impressive in the subgroup of patients with high baseline triglycerides (≥200 mg/dL). The latter finding requires confirmation in a controlled, randomized trial designed to test this hypothesis because it was identified in post hoc analysis. Thus, bezafibrate may have a prominent role in the management of dyslipidemia and CAD when targeted to the subgroup of patients with high triglycerides.

Appendix

BIP Study Group: Participating Centers and Committee Membership

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