# 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

Epidemiological evidence has suggested that high-density lipoprotein cholesterol (HDL-C) levels are inversely correlated with coronary artery disease (CAD) and are independently predictive of cardiovascular morbidity and mortality.[1–4] In many prospective studies, triglyceride levels were predictive of CAD in univariate and multivariate analyses controlling for total cholesterol or low-density lipoprotein cholesterol (LDL-C) levels.[5–7] Although in some analyses this association did not persist after adjustment for HDL-C,[8] the predictive value of high triglycerides has been confirmed in a meta-analysis.[9] Nevertheless, direct evidence for the clinical benefit of elevating HDL-C or reducing blood triglyceride levels is scarce because the efficacy of lipid-modifying drugs that lower triglyceride levels and raise HDL-C levels had not been directly assessed in large-scale clinical trials in CAD patients. In the Coronary Drug Project,[10] nicotinic acid, which elevates HDL-C and lowers LDL-C, decreased coronary morbidity; however, HDL-C measurement was not part of the study protocol. An analysis of the joint effects of baseline triglyceride and lipoprotein cholesterol levels, conducted in the framework of the primary prevention Helsinki Heart Study, demonstrated a strong interdependence of LDL-C, HDL-C, and triglycerides as predictors of CAD risk and a beneficial effect of treatment with gemfibrozil.[11]

**See p 2**

The relation of serum total cholesterol and LDL-C with the development and progress of atherosclerosis and CAD has been demonstrated in numerous clinical and epidemiological studies. Moreover, the benefit of LDL-C reduction has now been strongly supported by the significant decrease in cardiovascular events, including cardiovascular mortality, achieved by reducing LDL-C with hepatic hydroxymethylglutaryl coenzyme A reductase inhibitors (statins).[12–16] However, in the Cholesterol and Recurrent Events[14] study, this benefit was not observed in the subgroup of patients with baseline LDL-C concentrations <125 mg/dL. About 40% of patients with CAD have LDL-C levels <130 mg/dL, and most of these patients also have low levels of HDL-C, with or

Received November 3, 1999; revision received January 14, 2000; accepted February 3, 2000.

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A complete list of BIP study participants is given in the Appendix.

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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 radionuclear 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 ($\alpha=0.05$, 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.[25] 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 $\chi^2$ test for dichotomous parameters and the

**TABLE 1. Baseline and Laboratory Characteristics of the 2 Study Groups**

| | Treatment Group | |
|---|---|---|
| | Bezafibrate (n=1548) | Placebo (n=1542) |
| Men | 1412 (91.2) | 1413 (91.6) |
| Age, y | 60.1±6.8 | 60.1±6.7 |
| Systolic blood pressure, mm Hg | 134±18 | 133±18 |
| Diastolic blood pressure, mm Hg | 81.2±9.0 | 80.8±9.0 |
| Weight, kg | 76.5±11.1 | 76.6±11.0 |
| Height, cm | 169.2±7.2 | 169.2±7.4 |
| Body mass index, kg/m$^2$ | 26.7±3.3 | 26.7±3.3 |
| NYHA class ≥2 | 381 (24.9) | 365 (24.1) |
| AP class ≥2 | 404 (26.1) | 389 (25.3) |
| Prior myocardial infarction | 1214 (78.6) | 1194 (77.4) |
| Prior angina | 875 (56.6) | 891 (57.8) |
| Smoking | 176 (11.4) | 188 (12.1) |
| Diabetes | 155 (10.0) | 154 (10.0) |
| History of hypertension | 482 (31.2) | 518 (33.6) |
| Stroke | 14 (0.9) | 21 (1.4) |
| Transient ischemic attack | 7 (0.5) | 16 (1.0) |
| Peripheral vascular disease | 51 (3.3) | 56 (3.6) |
| COPD | 36 (2.3) | 52 (3.4) |
| Treatment at randomization | | |
| β-Blockers | 580 (37.5) | 609 (39.5) |
| Calcium antagonists | 778 (50.3) | 799 (51.8) |
| Anti-platelet aggregation | 1095 (70.7) | 1064 (69.0) |
| ACE inhibitors | 185 (12.0) | 197 (12.8) |
| Nitrates | 793 (51.2) | 781 (50.6) |
| Diuretics | 210 (13.6) | 224 (14.5) |
| Digitalis | 61 (3.9) | 47 (3.0) |
| Oral antidiabetic agents | 78 (5.0) | 78 (5.1) |
| Lipid values, mg/dL | | |
| Total cholesterol | 212±17 | 213±18 |
| HDL cholesterol | 34.6±5.5 | 34.6±5.5 |
| LDL cholesterol | 148±17 | 149±17 |
| Triglyceride | 145±51 | 145±51 |
| Fibrinogen | 349±72 | 351±74 |

Values are mean±SD or n (%). NYHA indicates New York Heart Association; AP, angina pectoris (class according to the Canadian angina classification); COPD, chronic obstructive pulmonary disease; and ACE, angiotensin-converting enzyme.

*t* test for continuous variables. 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),[26] multivariate analyses were performed using Cox's proportional hazard stepwise regression modeling.

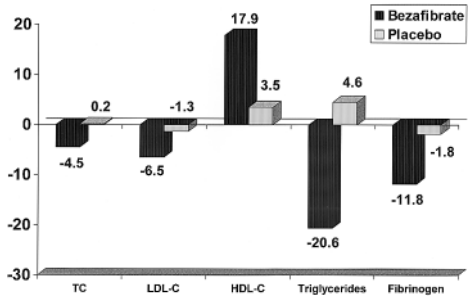


**Figure 1.** Effect of treatment on lipids and fibrinogen. TC indicates total cholesterol. Values are in mg/dL.

## 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

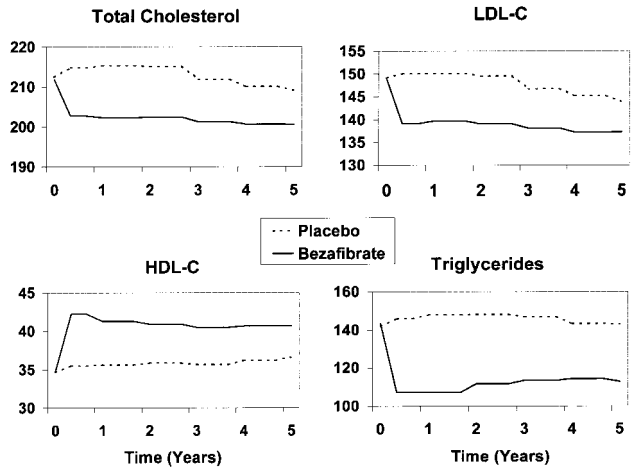


**Figure 2.** Changes in lipid values throughout the study period in patients who completed 5 years of follow-up.

**TABLE 2. Clinical Outcome**

| | Bezafibrate (n=1548) | Placebo (n=1542) | Reduction in Risk, % | *P* |
|---|---|---|---|---|
| Primary end point | 211 (13.6) | 232 (15.0) | −9.4 | 0.26 |
| Non-fatal MI | 150 (9.7) | 172 (11.2) | −12.8 | 0.18 |
| Fatal MI | 18 (1.2) | 17 (1.1) | | 0.87 |
| Sudden death | 43 (2.8) | 43 (2.8) | | 0.98 |
| Secondary end point | 311 (20.1) | 327 (21.2) | −4.9 | 0.44 |
| UAP | 76 (4.9) | 82 (5.3) | | 0.61 |
| CABG | 144 (9.3) | 157 (10.2) | | 0.41 |
| PTCA | 91 (5.9) | 88 (5.7) | | 0.84 |
| All end points combined | 522 (33.7) | 559 (36.3) | −6.6 | 0.14 |
| Mortality | 161 (10.4) | 152 (9.9) | | 0.62 |
| Cardiac | 95 (6.1) | 88 (5.7) | | 0.61 |
| Noncardiac | 66 (4.3) | 64 (4.2) | | 0.87 |
| Stroke | 72 (4.6) | 77 (5.0) | | 0.66 |
| Ischemic stroke | 59 (3.8) | 69 (4.5) | | 0.36 |

Secondary end points were the first event in patients free of the primary end points. UAP indicates unstable angina pectoris; CABG, coronary artery bypass graft; and PTCA, percutaneous transluminal coronary angioplasty. Values are n (%) unless otherwise indicated.

(1.5% and 1.0% in the placebo and bezafibrate groups, respectively), adverse event (5.8% and 6.5%, respectively), patient's request to discontinue study medication (7.0% and 7.2%), and other miscellaneous reasons (2.6% and 1.5%).

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 U/L in 84% of patients, did not change in 10%, and increased by ≥10 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

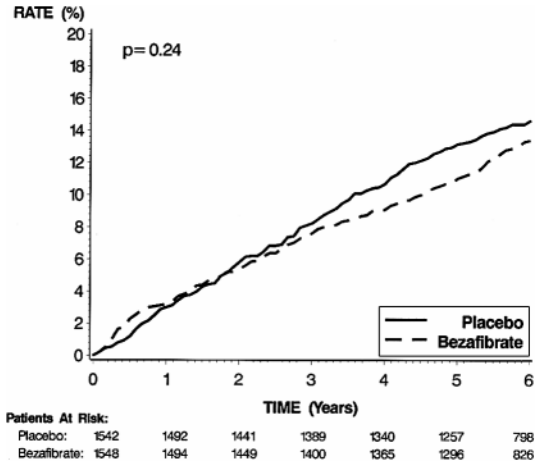


**Figure 3.** Kaplan-Meier curves for the cumulative probability of the primary end point.

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 mg/dL, no clear benefit of bezafibrate treatment was observed. Among patients with

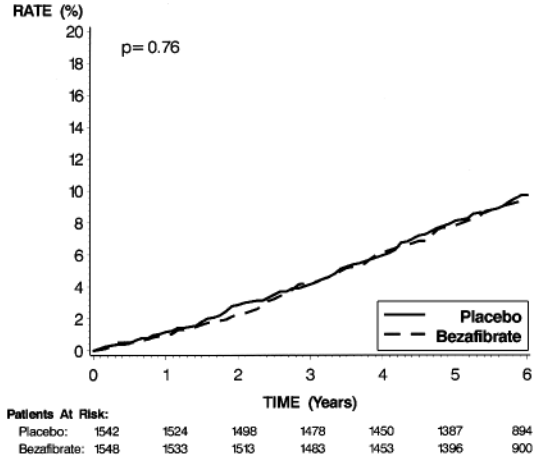


**Figure 4.** Kaplan-Meier curves for the cumulative probability of all-cause mortality.

**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 |
| ≥150 mg/dL | 603 (16.3) | 629 (17.1) | 4.6 | 0.48 |
| ≥175 mg/dL | 407 (15.9) | 385 (20.3) | 21.6 | 0.07 |
| ≥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 |
| ≥150 mg/dL | 420 (18.5) | 436 (19.4) | 4.5 | 0.56 |
| ≥175 mg/dL | 294 (17.2) | 286 (22.2) | 22.6 | 0.09 |
| ≥200 mg/dL | 184 (13.0) | 162 (22.3) | 41.8 | 0.02 |
| HDL-C ≥35 and triglycerides | | | | |
| <150 mg/dL | 560 (12.0) | 518 (12.2) | 1.6 | 0.77 |
| ≥150 mg/dL | 183 (11.2) | 193 (12.2) | 8.5 | 0.59 |
| ≥175 mg/dL | 113 (12.7) | 99 (15.2) | 16.8 | 0.45 |
| ≥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.

baseline triglycerides ≥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 ≥200 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 39.5% ($P=0.02$), whereas among patients with triglycerides <200 mg/dL (1317 patients in the placebo group and 1314 in the bezafibrate group), the reduction in the cumulative probability of an end point was insignificant (Figure 5).

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 (≥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 (≥35 mg/dL) HDL-C (Table 3), the effect of bezafibrate in patients with baseline triglycerides ≥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,[14,15,27] 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

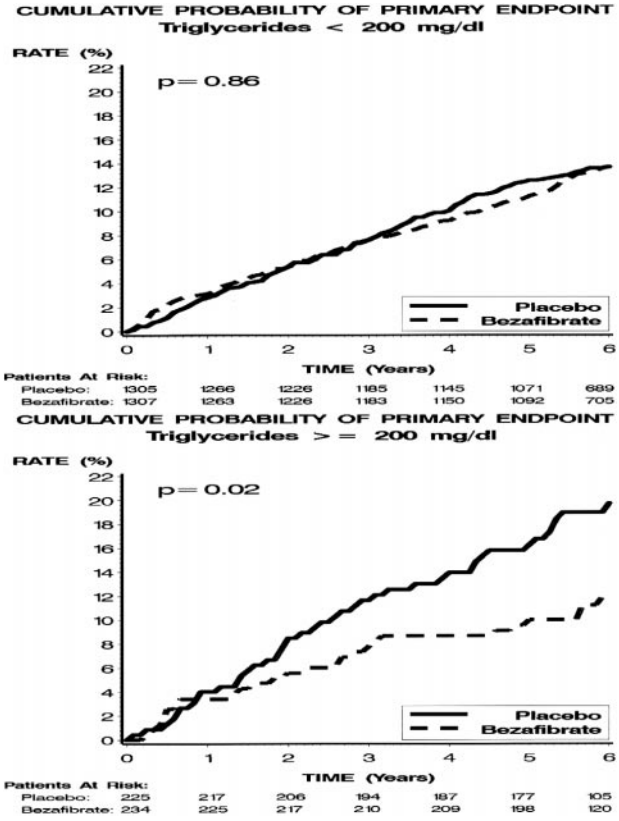


**Figure 5.** Kaplan-Meier curves for the primary end point in subgroups of patients with baseline triglycerides ≥200 mg/dL and <200 mg/dL.

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 adjuvant 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-C[28] 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 ($P=0.09$). It is noteworthy that although the placebo primary end point incidence rate in the VA-HIT study was 22%, this rate was 15% in the BIP study.

The low event rate in the BIP study may be partially explained by different patient characteristics and medical practice in the 2 study cohorts. The VA-HIT population was older and included more diabetic patients. Also, 2% of the placebo group and 1% of the gemfibrozil group were given open-label lipid medication in the VA-HIT study, whereas in the BIP study, 15% and 11% of patients in the placebo and bezafibrate groups, respectively, received such therapy. In addition, differences existed in the lipid responses of the 2 studies. In VA-HIT, HDL-C rose by 8%, in comparison to 18% in BIP, and triglycerides declined by 31%, as compared with 21% in BIP. We cannot rule out the possibility that reducing triglycerides may be more important than elevating HDL-C for secondary prevention in CAD patients with relatively low LDL-C levels and high triglycerides. Our data on patients with triglycerides >200 mg/dL may support this possibility.

The rates of adverse events, cancer, and mortality from any cause during follow-up were equally distributed between the 2 study groups. We can conclude from these data that long-term treatment with bezafibrate is safe.

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

#### *Participating Centers, Responsible Investigators and Physicians*

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## Acknowledgments

Supported by a grant from Boehringer Mannheim GmbH, Mannheim, Germany, which is now part of F. Hoffmann-La Roche Ltd, Basel, Switzerland.

## References

1. Brunner D, Altman S, Loebl K, et al. Alpha-cholesterol percentages in coronary patients with and without increased total serum cholesterol levels and in healthy controls. *J Atheroscler Res*. 1962;2:424–437.
2. Franzen J, Johansson BW, Gustfson A. Reduced high density lipoproteins as a risk factor after acute myocardial infarction. *Acta Med Scand*. 1987;221: 357–362.
3. Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med*. 1990;322:1700–1707.
4. Goldbourt U, Yaari S, Medalie JH. Isolated low HDL cholesterol as a risk factor for coronary heart disease mortality: a 21-year follow-up of 8000 men. *Arterioscler Thromb Vasc Biol*. 1997;17:107–113.
5. Brunner D, Altman S, Lobel K, et al. Serum cholesterol and triglycerides in patients suffering from ischemic disease and in healthy subjects. *Atherosclerosis*. 1977;28:197–204.
6. Austin MA. Plasma triglyceride and coronary heart disease. *Arterioscler Thromb*. 1991;11:2–14.
7. Assmann G, Schulte H, Cullen P. New and classical risk factors: the Munster Heart Study (PROCAM). *Eur J Med Res*. 1997;2:237–242.
8. Austin MA. Plasma triglyceride as a risk factor for coronary heart disease: the epidemiologic evidence and beyond. *Am J Epidemiol*. 1989;129:249–259.
9. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213–219.
10. Berge KG, Canner PL. Coronary drug project: experience with niacin: Coronary Drug Project Research Group. *Eur J Clin Pharmacol*. 1991;40(suppl 1):S49–S51.
11. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation*. 1992;85:37–45.
12. Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333: 1301–1307.
13. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
14. Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001–1009.
15. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
16. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622.
17. The Bezafibrate Infarction Prevention (BIP) study group. Lipids and lipoproteins in symptomatic coronary heart disease: distribution, intercorrelations, and significance for risk classification in 6700 men and 1500 women. *Circulation*. 1992;86:839–848.
18. Goldbourt U, Behar S, Reicher-Reiss H, et al, for the Bezafibrate Infarction Prevention Study Group. Rationale and design of a secondary prevention trial of increasing serum high-density lipoprotein cholesterol and reducing triglycerides in patients with clinical manifest atherosclerotic heart disease (the Bezafibrate Infarction Prevention Trial). *Am J Cardiol*. 1993;71:909–915.
19. Vu-Dac N, Schoonjans K, Laine B, et al. Negative regulation of the human apolipoprotein A-I promoter by fibrates can be attenuated by the interaction of the peroxisome proliferator-activated receptor with its response element. *J Biol Chem*. 1994;269:31012–31018.
20. Auwerx J, Schoonjans K, Fruchart JC, et al. Regulation of triglyceride metabolism by PPARs: fibrates and thiazolidinediones have distinct effects. *Atheroscler Thromb*. 1996;3:81–89.
21. Auwerx J, Schoonjans K, Fruchart JC, et al. Transcriptional control of triglyceride metabolism: fibrates and fatty acids change the expression of the LPL and apoC-III genes by activating the nuclear receptor PPAR. *Atherosclerosis*. 1995;124(suppl):S29–S37.
22. Staels B, Dallongeville J, Auwerx J, et al. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation*. 1998;98:2088–2093.
23. Goldbourt U, Brunner D, Behar S, et al, for the BIP study group. Baseline characteristics of patients participating in the Bezafibrate Infarction Prevention (BIP) study. *Eur Heart J*. 1998;19(suppl H):H42–H47.
24. Friedewald WT, Levy RI, Frederickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
25. SAS Institute Inc. *SAS/STAT User's Guide*. Version 6. 4th ed. Cary, NC: SAS Institute, Inc; 1987.
26. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, National Cholesterol Education Program. Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation*. 1994;89: 1329–1445.
27. Rubins H, Robins SJ, Collins D, et al, for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med*. 1999;341:410–418.
28. Frick MH, Syvanne M, Nieminen MS, et al, for the Lopid Coronary Angiography Trial (LOCAT) study group. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. *Circulation*. 1997;96:2137–2143.
29. Ericsson CG, Hamsten A, Nilsson J, et al. Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male post-infarction patients. *Lancet*. 1996;347:849–853.