

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2004;109:2197-2202; originally published online May 3, 2004;

DOI: 10.1161/01.CIR.0000126824.12785.B6

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

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Peroxisome Proliferator–Activated Receptor Ligand Bezafibrate for Prevention of Type 2 Diabetes Mellitus in Patients With Coronary Artery Disease

Alexander Tenenbaum, MD, PhD; Michael Motro, MD; Enrique Z. Fisman, MD; Ehud Schwammenthal, MD; Yehuda Adler, MD; Ilan Goldenberg, MD; Jonathan Leor, MD; Valentina Boyko, MS; Lori Mandelzweig, MPH; Solomon Behar, MD

Background—Recent studies have shown that type 2 diabetes is preventable by both lifestyle interventions and medications that influence primary glucose metabolism. Whether pharmacological interventions that influence primary lipid metabolism can also delay development of type 2 diabetes is unknown. The goal of this study was to evaluate the effect of the peroxisome proliferator–activated receptor ligand bezafibrate on the progression of impaired fasting glucose phase to type 2 diabetes in patients with coronary artery disease over a 6.2-year follow-up period.

Methods and Results—The study sample comprised 303 nondiabetic patients 42 to 74 years of age with a fasting blood glucose level of 110 to 125 mg/dL (6.1 to 6.9 mmol/L). The patients received either 400 mg bezafibrate retard (156 patients) or placebo (147 patients) once a day. No patients were using statins, and use of ACE inhibitors, which also reduce diabetes incidence, was relatively low. During follow-up, development of new-onset diabetes was recorded in 146 patients: in 80 (54.4%) from the placebo group and 66 (42.3%) from the bezafibrate group ($P=0.04$). The mean time until onset of new diabetes was significantly delayed in patients on bezafibrate compared with patients on placebo: 4.6 ± 2.3 versus 3.8 ± 2.6 years ($P=0.004$). Multivariate analysis identified bezafibrate treatment as an independent predictor of reduced risk of new diabetes development (hazard ratio, 0.70; 95% CI, 0.49 to 0.99). Other significant variables associated with future overt type 2 diabetes in patients with impaired fasting glucose were total cholesterol level (hazard ratio, 1.22; 95% CI 1.0 to 1.51) and body mass index (hazard ratio, 1.10; 95% CI, 1.05 to 1.16).

Conclusions—Bezafibrate reduces the incidence and delays the onset of type 2 diabetes in patients with impaired fasting glucose. Whether the combination of bezafibrate with other recommended drugs for secondary prevention (statins and ACE inhibitors) would be as efficacious as suggested by our results remains to be determined. (*Circulation*. 2004;109:2197-2202.)

Key Words: bezafibrate ■ coronary disease ■ diabetes mellitus ■ glucose ■ prevention

The prevalence of type 2 diabetes continues to expand worldwide.^{1–5} Increased body mass index (BMI), preexisting glucose and insulin abnormalities, physical inactivity, and parental diabetes appear to be acknowledged risk factors for the development of new diabetes.^{6–9}

In 1997, the American Diabetes Association (ADA) adopted new criteria for the detection of diabetes¹⁰ by establishing a single fasting blood glucose of at least 126 mg/dL (7 mmol/L) for the diagnosis of overt diabetes and glucose levels of 110 to 125 mg/dL (6.1 to 6.9 mmol/L) for impaired fasting glucose. People who develop type 2 diabetes usually pass through the phases of excessive adipogenesis, nuclear peroxisome proliferator–activated receptor (PPAR) modulation, insulin resistance, hyperinsulinemia, pancreatic

β -cell stress and damage leading to a progressive decrease in insulin secretion, and impaired glucose postprandial and fasting levels.^{11–17} Fasting glucose is presumed to remain normal as long as insulin hypersecretion can compensate for insulin resistance. The profound metabolic (specifically glucose and fatty acids) abnormalities associated with the impaired fasting glucose phase lead to further disturbance of insulin sensitization and secretion. These mechanisms contribute to the conversion of the impaired fasting glucose phase to overt diabetes.^{11–17}

Bezafibrate is a potent nonselective ligand/activator for PPAR- α ,¹⁸ with triglyceride-lowering and HDL cholesterol-raising effects resulting in decreased systemic availability of fatty acid, diminished fatty acid uptake by muscle, and improved

Received November 14, 2002; de novo received November 5, 2003; revision received February 3, 2004; accepted February 6, 2004.

From the Cardiac Rehabilitation Institute (A.T., M.M., E.Z.F., E.S., Y.A.) and Bezafibrate Infarction Prevention Study Coordinating Center (I.G., J.L., V.B., L.M., S.B.), Neufeld Cardiac Research Institute, Chaim Sheba Medical Center, Tel-Hashomer, affiliated with the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

Correspondence to Alexander Tenenbaum, MD, PhD, Cardiac Rehabilitation Institute, Chaim Sheba Medical Center, Tel-Hashomer, 52621 Israel. E-mail altenen@post.tau.ac.il or altenen@yahoo.com

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000126824.12785.B6

insulin sensitization.^{18–21} In patients with overt diabetes, bezafibrate reduces plasma glucose concentrations.^{19,22}

Recent studies have shown that type 2 diabetes is preventable by lifestyle interventions and by some medications that influence primary glucose metabolism.^{23–26} Whether pharmacological interventions that influence primary lipid metabolism can also delay or prevent development of type 2 diabetes is unknown.

The goal of the present study was to evaluate the effect of bezafibrate on the progression of the impaired fasting glucose phase to type 2 diabetes in patients with healed myocardial infarction and/or stable angina pectoris over a 6.2-year follow-up period.

Methods

Subjects

The major inclusion and exclusion criteria for the Bezafibrate Infarction Prevention (BIP) study and the ethical guidelines have been previously reported.²⁷ In brief, inclusion criteria for men and women included age of 45 to 74 years, history of myocardial infarction between 6 months and 5 years before enrollment in the study, and/or stable angina pectoris confirmed by coronary angiography, radionuclear studies, and/or standard exercise tests. The major exclusion criteria for the BIP study were permanent pacemaker implantation, cerebrovascular disease, chronic hepatic or renal disease, peripheral vascular disease, malignant diseases, estrogen replacement therapy, insulin-dependent diabetes mellitus, and current use of a lipid-modifying drug.

After an initial 2 months of a lipid-lowering diet, the 3122 eligible patients were included in the BIP study between May 1990 and January 1993. There was no difference in the distribution of all-cause and cardiac mortality between the bezafibrate and placebo study groups. However, the reduction in the primary end point was impressive in the subgroup of patients with high baseline triglycerides (≥ 200 mg/dL).²⁸

Among the BIP study patients, there were 311 diagnosed diabetics, 141 patients with a fasting blood glucose level of ≥ 126 mg/dL (7 mmol/L) (undiagnosed diabetics), 2353 patients with a normal fasting blood glucose level of < 110 mg/dL (6.1 mmol/L), and 14 patients with unknown glucose metabolism status. All these patients were excluded from analysis. Thus, the final study sample for this post hoc subgroup analysis comprised 303 nondiabetic patients without any antihyperglycemic treatment and with an impaired fasting blood glucose level of 110 to 125 mg/dL (6.1 to 6.9 mmol/L). In accordance with the ADA classification,¹⁰ we defined the detection of a fasting blood glucose level ≥ 126 mg/dL (7 mmol/L) during the follow-up period as the criterion for new diabetes.

The patients received either 400 mg bezafibrate retard or placebo once a day, in addition to dietary advice. Patients continued to take prescribed medications for cardiac and other conditions except lipid-lowering drugs. Routine visits to the clinics were scheduled bimonthly for study medication distribution and compliance assessment by tablet count, every 4 months for clinical evaluation, and every year for blood analyses. In July 1994, after the publication of the Scandinavian Simvastatin Survival Study (4S) results,²⁹ the International Review and Advisory Board approved the recommendation of the Steering Committee to add colestipol for patients on study medication if their LDL cholesterol was > 180 mg/dL in 2 separate laboratory examinations after reinforcement of dietary advice.

The study was a multicenter prospective trial performed in 18 university-affiliated hospitals. The follow-up period lasted until May 1998 (mean, 6.2 ± 0.8 years; range, 4.7 to 7.6 years).

Laboratory Methods

Detailed data on laboratory methods were given in a previous report.²⁸ Briefly, blood samples, collected in the 18 participating

medical centers using standardized equipment and procedures, were transferred in cooled containers to a central laboratory. Blood samples were drawn after at least 12 hours of fasting for determination of serum levels of cholesterol, HDL cholesterol, and triglycerides. Laboratory measurements were carried out by use of standard automated procedures with commercially available kits (Roche Diagnostics). Fasting blood glucose values were determined by the GOD-PAPP method with a BM/Hitachi 717/911 analyzer.²⁸ For the purposes of this study, serum samples, which had been taken at baseline from each study participant and stored at -70°C , were thawed and assayed for insulin level by routine radioimmunoassay (Insik 5, Sorin Biomedica). The homeostatic indexes of insulin resistance (HOMA IR and QUICKI) were calculated according to the homeostasis model of assessment as follows^{29–32}: Homeostasis Assessment of Insulin Resistance (HOMA IR) = fasting insulin ($\mu\text{U/mL}$) \times fasting glucose (mmol/L) / 22.5, and Quantitative Insulin Sensitivity Check Index (QUICKI) = $1 / [\log \text{fasting insulin } (\mu\text{U/mL}) + \log \text{fasting glucose } (\text{mg}/100 \text{ mL})]$.

Determination of Additional Variables

Criteria for the diagnosis of myocardial infarction, anginal syndrome, hypertension, and congestive heart failure have previously been reported.²⁸ Briefly, the diagnosis of ischemic heart disease was made in patients with documented myocardial infarction or typical angina pectoris in whom there was also a positive exercise test, evidence of myocardial ischemia revealed by radionuclide studies, or at least 60% stenosis of 1 major coronary artery. Functional capacity classes were evaluated according to the New York Heart Association classification. Smoking habits were determined on the basis of self-report during an interview held with a study physician.

Statistical Analysis

Data were analyzed with the SAS software.³³ Continuous variables were presented as mean \pm SD. Comparisons between groups were made by use of χ^2 tests for discrete variables and a *t* test for continuous variables. Kaplan-Meier curves were produced with the LIFETEST procedure.³⁴ The log-rank test was used to compare curves.

Repeated-measures ANOVA was used to evaluate the treatment effect (placebo versus bezafibrate) and changes in mean levels of glucose over time. Multivariate analysis of incidence of new diabetes was performed with the Cox proportional-hazards model (PHREG procedure) to account for different lengths of follow-up and correlation with covariates.³⁴ Variables included in the model were age, gender, total cholesterol, triglycerides, hypertension, previous myocardial infarction, heart failure, peripheral vascular disease, anginal syndrome, chronic obstructive pulmonary disease, smoking status, BMI, and use of ACE inhibitors.

Results

Baseline Data

Our population included 2 groups: a placebo group made up of 147 patients and a bezafibrate group of 156 patients. Patients in the placebo and bezafibrate groups were well balanced in terms of clinical and laboratory baseline characteristics and concomitant medications (Tables 1 and 2). The study groups were similar in regard to age, gender, and prevalence of the most relevant cardiovascular diseases and risk factors (myocardial infarction in the past, hypertension, heart failure, peripheral vascular disease, anginal syndrome, chronic obstructive pulmonary disease). Most patients in both groups were men who had sustained a myocardial infarction in the past. BMI was somewhat higher among patients on placebo. No significant differences between groups were found for all types of cholesterol, apolipoprotein, blood pressure, heart rate, fasting glucose, triglyceride, fibrinogen, and creatinine levels. The fasting insulin level and indexes of

TABLE 1. Baseline Characteristics of the Study Population

Characteristics	Placebo (n=147)	Bezafibrate (n=156)	P
Age, y	60.7±7.0	61.5±5.9	0.3
BMI, kg/m ²	28.1±3.4	27.1±3.1	0.02
Women, n (%)	8 (5)	13 (9)	0.2
Past myocardial infarction, n (%)	126 (81)	114 (78)	0.5
Angina, n (%)	88 (56)	81 (55)	0.8
NYHA class ≥2, n (%)	36 (24.7)	40 (25.8)	0.8
Hypertension, n (%)	61 (39)	58 (40)	0.9
Current or past smokers, n (%)	107 (69)	109 (74)	0.8
Systolic blood pressure, mm Hg	136±17	134±15	0.4
Diastolic blood pressure, mm Hg	82±8	82±8	0.6
Heart rate, bpm	69.7±8.2	70.4±9.0	0.5
Fasting glucose, mg/dL	116±4	116±5	0.5
Total cholesterol, mg/dL	214±18	213±18	0.4
HDL cholesterol, mg/dL	33.7±5.3	34.2±5.6	0.4
LDL cholesterol, mg/dL	150±15	148±17	0.5
Triglycerides, mg/dL	154±54	149±56	0.4
Apolipoprotein A, mg/dL	100±14	101±13	0.7
Apolipoprotein B, mg/dL	103±14	102±13	0.5
Fibrinogen, mg/dL	349±64	352±75	0.7
Creatinine, mg/dL	1.2±0.2	1.2±0.1	0.9

Data are mean±SD when appropriate.

insulin sensitivity (HOMA IR and QUICKI) were determined in 91 patients (30%) randomly selected from the 303 study patients: 45 from the placebo group and 46 from the bezafibrate. No significant differences between were found between the placebo and bezafibrate groups for these parameters: fasting

TABLE 2. Distribution of Cardiovascular Drugs Among Study Patients

Drugs	Placebo (n=147), n (%)	Bezafibrate (n=156), n (%)	P
Baseline			
β-Blockers	74 (50)	70 (45)	0.3
Nitrates	70 (48)	83 (53)	0.3
Calcium antagonists	81 (55)	81 (52)	0.6
Diuretics	22 (15)	28 (18)	0.5
Antiplatelets	101 (69)	110 (71)	0.7
ACE inhibitors	19 (13)	32 (21)	0.5
During follow-up			
β-Blockers	67 (46)	73 (47)	0.8
Nitrates	65 (44)	61 (39)	0.4
Calcium antagonists	68 (46)	69 (44)	0.7
Diuretics	40 (27)	43 (28)	0.9
Antiplatelets	122 (83)	116 (74)	0.07
ACE inhibitors	53 (36)	36 (23)	0
			0.02
Antihyperglycemics	25 (17)	24 (15)	0.0.7

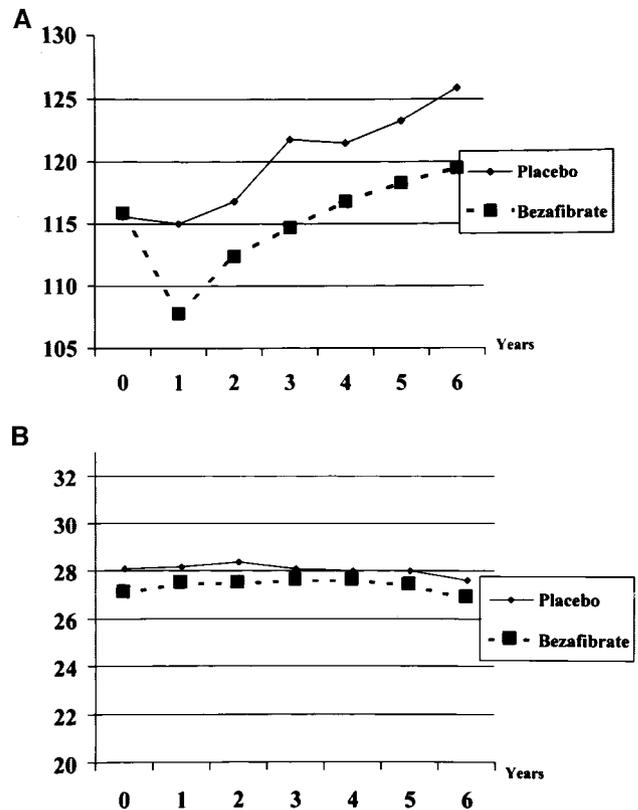


Figure 1. Changes in mean fasting blood glucose (A; mg/dL) and BMI (B; kg/m²) values throughout study period (bezafibrate vs placebo) after annual measurements. Each data point represents mean value for all participants who remained at that time.

insulin level, 15.7±10.3 versus 15.7±8.7 μU/mL, respectively ($P=0.9$); HOMA IR, 4.48±3.01 versus 4.44±2.53 ($P=0.9$); and QUICKI, 0.32±0.02 versus 0.32±0.03 ($P=0.9$).

Cardiovascular Drugs

Data on treatment with cardiovascular drugs among the study groups are presented in Table 2. At baseline, nitrates, calcium antagonists, β-blockers, and antiplatelet drugs (mainly aspirin) were the most commonly used medications. Use of ACE inhibitors at baseline was low. It increased significantly during the follow-up period. In addition, we observed during follow-up a relatively decreased use of calcium antagonists and nitrates, whereas use of antiplatelet drugs and diuretics was augmented. There were no significant differences in the proportion of patients receiving the other cardiovascular drugs.

Changes in Glucose Level and BMI During Follow-Up

No significant differences between groups were found for fasting glucose levels on baseline. In the first year, there was a reduction in the mean level of fasting blood glucose in the bezafibrate group, whereas it was unchanged in the placebo group (Figure 1A). The values rose in parallel in both groups in subsequent years. In total, there was a significant difference in glucose levels over time between bezafibrate and placebo groups ($P=0.02$). There was no significant change in

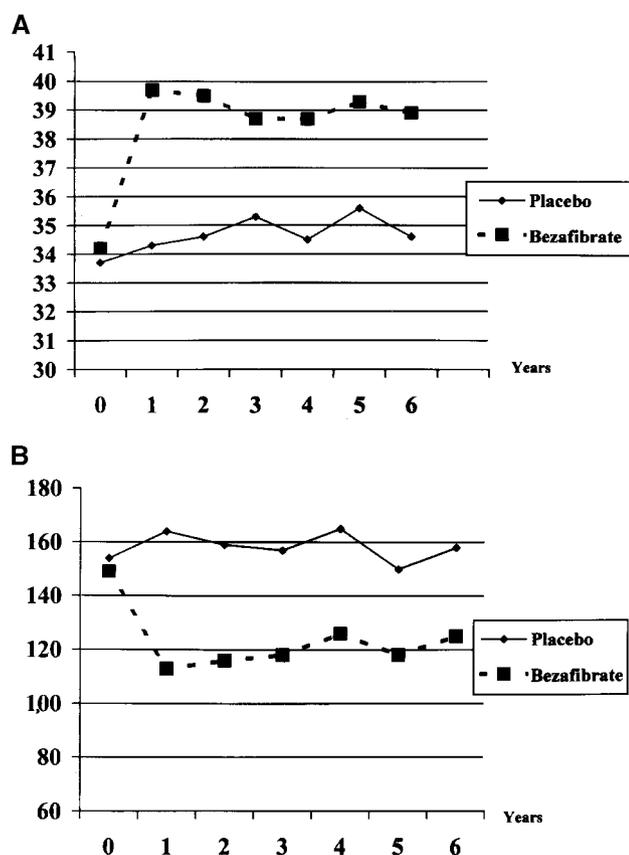


Figure 2. Changes in mean HDL cholesterol (A; mg/dL) and triglyceride (B; mg/dL) values throughout study period (bezafibrate vs placebo) after annual measurements. Each data point represents mean value for all participants who remained at that time.

mean BMI values in either the bezafibrate or placebo group during follow-up (Figure 1B).

Effect of Treatment on Lipid Levels

Average changes in mean HDL cholesterol and triglyceride levels are shown in Figure 2A and 2B. The most marked changes were an increase of 16% ($P=0.0001$) in mean HDL cholesterol (Figure 2A) and a reduction of 24% ($P=0.0001$) in mean triglyceride values (Figure 2B) in the bezafibrate group after the first year of treatment (corresponding to the reduction in mean levels of fasting blood glucose). There were no significant changes in mean HDL cholesterol and triglyceride levels in the placebo group during follow-up.

Development of New Diabetes

Per the definition, there were no patients with diabetes among the study groups at the beginning of follow-up. Patients were followed up from 4.7 to 7.6 years (mean follow-up, 6.2 ± 0.8 years). During this period, development of new diabetes was recorded in 146 patients: in 80 patients (54.4%) in the placebo group compared with 66 patients (42.3%) in the bezafibrate group ($P=0.04$). In addition to a reduction in the incidence of disease, the mean time until onset of new diabetes was significantly delayed in patients on bezafibrate compared with patients on placebo: 4.6 ± 2.3 versus 3.8 ± 2.6 years ($P=0.004$). The mean delay was ≈ 10 months.

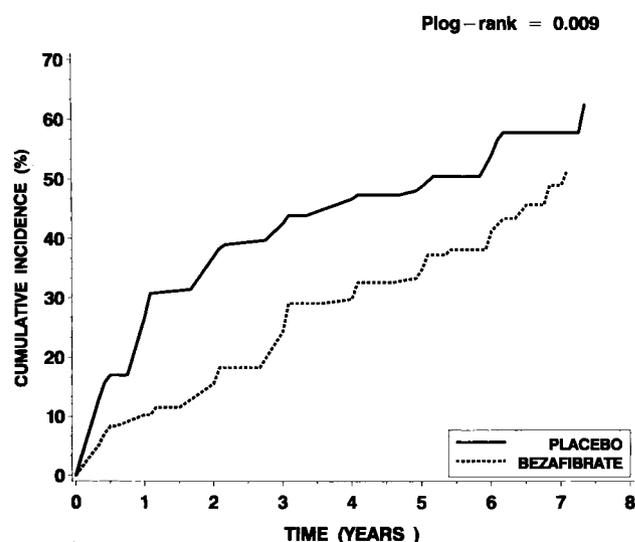


Figure 3. Kaplan-Meier curves of diabetes incidence (in accordance with time of diagnosis after annual fasting blood glucose measurements) for study groups (bezafibrate vs placebo).

All patients in whom diabetes was diagnosed during the study were initially on an antihyperglycemic diet. In addition, 49 of 146 patients (33.6%) with new diabetes thereafter received oral antihyperglycemic drugs. There was no difference in the proportion of patients receiving these drugs between study groups (Table 2).

Kaplan-Meier curves of diabetes incidence (in accordance with the time of diagnosis after annual fasting blood glucose level measurements) for the 2 study groups are presented in Figure 3. The incidence rate of the patients on placebo was significantly worse than in their bezafibrate-treated counterparts (log-rank $P=0.009$). Age-adjusted analysis demonstrated that the rate of diabetes incidence was reduced by 36% among patients on bezafibrate (hazard ratio [HR], 0.64; 95% CI, 0.46 to 0.89).

To assess whether the association between bezafibrate treatment and the reduced rate of new diabetes persisted in diverse categories of metabolic status, diabetes mellitus incidence was determined in patients according to level of BMI, LDL cholesterol, and triglycerides and the presence of ACE inhibitors (Table 3). A lower incidence of diabetes mellitus was found in the patients on bezafibrate regardless of the use of ACE inhibitors and for different levels of BMI, LDL cholesterol, and triglycerides.

Multivariate analysis identified bezafibrate treatment as an independent predictor of reduced risk of new diabetes development (HR, 0.70; 95% CI, 0.49 to 0.99).

Other significant variables associated with future overt type 2 diabetes in patients with impaired fasting glucose were total cholesterol level (20-mg/dL increment) (HR, 1.22; 95% CI, 1.0 to 1.51) and BMI (1-kg/m² increment) (HR, 1.10; 95% CI, 1.05 to 1.16).

Discussion

Our data demonstrate that bezafibrate can reduce the incidence and delay the conversion of impaired fasting glucose

TABLE 3. Diabetes Mellitus Incidence Rate Among Study Patients According to the Level of BMI, LDL Cholesterol, and Triglycerides and the Presence of ACE Inhibitors

	Placebo	Bezafibrate
BMI, kg/m ²		
<27		
Frequency	29	31
Rate, %	48	36
≥27		
Frequency	51	34
Rate, %	59	49
LDL cholesterol, mg/dL		
<160		
Frequency	56	46
Rate, %	52	40
≥160		
Frequency	22	20
Rate, %	58	49
Triglycerides, mg/dL		
<150		
Frequency	35	32
Rate, %	50	37
≥150		
Frequency	43	34
Rate, %	57	49
ACE inhibitors		
Absent		
Frequency	50	35
Rate, %	53	38
Present		
Frequency	30	31
Rate, %	57	48

phase to overt type 2 diabetes in patients with coronary artery disease over a 6.2-year follow-up period.

The Diabetes Prevention Program (DPP) results have shown that individualized, systematic, and intensive lifestyle interventions (including dietary changes, increased physical activity, and weight loss) are the most effective means of preventing type 2 diabetes in general high-risk populations.²³ Unfortunately, they are not easily applied in general practice. Pharmacological interventions by some medications that influence primary glucose metabolism (metformin and acarbose) can also effectively delay progression to type 2 diabetes,^{23,26} but the magnitude of the benefit seems to be somewhat less (58% for DPP lifestyle changes versus 31% for metformin and 25% for acarbose). However, it should be stressed that the DPP was in part related to individualized lifestyle interventions (in contrast to pharmacological studies) and by definition was a randomized but not double-blind trial. Data from our study have shown that a pharmacological intervention (bezafibrate) that influences primary lipid metabolism can also delay the development of type 2 diabetes with a magnitude of benefit similar to that for metformin and acarbose (30%).

Bezafibrate is a potent nonselective pharmacological ligand for PPAR- α , which controls primarily the expression of genes involved in lipid metabolism. However, PPAR- α (in addition to PPAR- γ) also plays a role in glucose homeostasis and in the development of insulin resistance.^{18,35,36} It is important to note that on a whole-body level, lipid and glucose metabolisms interact intimately. In summary, PPAR- α is activated by fibric acids (eg, bezafibrate) and form heterodimers with the 9-cis retinoic acid receptor. These heterodimers bind to peroxisome proliferator response elements, which are located in numerous gene promoters and increase the level of the expression of mRNAs encoded by PPAR- α target genes. Bezafibrate reduces triglyceride plasma levels through increases in the expression of genes involved in fatty acid- β oxidation and a decrease in apolipoprotein C-III gene expression. Fibric acids increase HDL cholesterol partly by increasing apolipoprotein A-I and A-II gene expression. Their triglyceride-lowering and HDL cholesterol-raising effects lead to decreased systemic availability of fatty acid, diminished fatty acid uptake by muscle, improved insulin sensitization, and reduced plasma glucose level.^{18–24}

Moreover, compared with other fibrates, bezafibrate has a unique characteristic profile of action. Clofibrate, fenofibrate, and bezafibrate were developed as hypolipidemic agents through optimization of their lipid-lowering activity in rodents before the discovery of the PPARs. Clofibratic acid and fenofibratic acid, the active metabolites of clofibrate and fenofibrate, are dual activators of PPAR- α and PPAR- γ , with \approx 10-fold selectivity for PPAR- α , whereas bezafibrate activates all 3 PPAR subtypes (α , γ , and δ) at comparable doses.^{37,38} Therefore, bezafibrate operated as a panagonist for all 3 PPAR isoforms with the potential to directly improve insulin sensitization via PPAR- γ activation.

In the BIP study,²⁸ rates of adverse events, hospitalization, and mortality were similar in both study groups. Thus, bezafibrate treatment was safe and effective in diabetes prevention.

Study Limitations

Our study has several important limitations. First, BMI was slightly but significantly lower among patients on bezafibrate, which could have contributed to their lower diabetes incidence. On the other hand, no significant differences at baseline were found between groups in fasting insulin level and indexes of insulin sensitivity (HOMA IR and QUICKI). Second, most of the bezafibrate effects in relation to fasting glucose level and cumulative incidence of diabetes (Figures 1A and 3) were achieved during the first year of treatment, but these favorable effects compared with the placebo group were maintained throughout the whole follow-up period. It is interesting that the same phenomenon was observed for both metformin and lifestyle interventions.²³ Third, our study was initiated in 1990. No patients were using statins, and use of ACE inhibitors, which also reduce diabetes incidence,³⁹ was relatively low. Therefore, whether the combination of the bezafibrate with drugs already recommended for secondary prevention (statins and angiotensin converting enzyme inhibitors) would be as efficacious as suggested by our results remains to be determined.

A partial answer to these unresolved questions is presented in a subgroup analysis (Table 3). To assess whether the association between bezafibrate treatment and the reduced rate of new diabetes persisted in diverse categories of metabolic status, diabetes mellitus incidence was determined in patients according to level of BMI, LDL cholesterol, and triglycerides and the presence of ACE inhibitors. The lower diabetes mellitus incidence was found in patients on bezafibrate regardless of use of ACE inhibitors and for different levels of BMI, LDL cholesterol, and triglycerides. However, the number of participants with new diabetes in the study was too small to make this type of analysis really significant.

Our data suggest that bezafibrate can slow down the progression of impaired fasting glucose to overt type 2 diabetes. Therefore, pharmacological interventions that influence primary lipid metabolism probably can be effective in this context. However, caution should be used in interpreting our finding because it was identified in post hoc subgroup analysis.

Conclusions

Bezafibrate decreased the incidence and delayed the onset of type 2 diabetes in patients with impaired fasting glucose over a 6.2-year follow-up period.

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