Bezafibrate for the Secondary Prevention of Myocardial Infarction in Patients With Metabolic Syndrome

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Background: A consistent relationship between metabolic syndrome (MS) and myocardial infarction (MI) has been demonstrated. We evaluated the effect of bezafibrate retard, a fibric acid derivative, on the incidence of MI in patients with MS enrolled in the Bezafibrate Infarction Prevention (BIP) study.

Methods: Patients who displayed at least 3 of the following 5 risk factors were considered to have MS: (1) a fasting glucose level of 110 mg/dL (6.11 mmol/L); (2) a triglyceride level of 150 mg/dL (1.70 mmol/L); (3) a high-density lipoprotein cholesterol level less than 40 mg/dL (<1.04 mmol/L) in men or less than 50 mg/dL (<1.30 mmol/L) in women; (4) a systolic blood pressure of 130 mm Hg or diastolic blood pressure of 85 mm Hg; and (5) a body mass index of 28.0 kg/m². The study sample for this post hoc subgroup analyses comprised 1470 patients aged 42 to 74 years. The patients received either 400 mg of bezafibrate retard (740 patients) or placebo (730 patients) once a day. The mean follow-up period was 6.2 years for events and 8.1 years for mortality data.

Results: New MI was recorded in 193 patients: 82 (11.1%) of the 740 patients in the bezafibrate group vs 111 (15.2%) of the 730 patients in the placebo group (*P*=.02). Bezafibrate was associated with a reduced risk of any MI and nonfatal MI with hazard ratios (HRs) of 0.71 (95% confidence interval [CI], 0.54-0.95) and 0.67 (95% CI, 0.49-0.91), respectively. The cardiac mortality risk tended to be lower in patients taking bezafibrate (HR, 0.74; 95% CI, 0.54-1.03). In 575 patients with augmented features of MS (4-5 risk factors), the remarkable strengthening of cardiac mortality reduction when taking bezafibrate (HR, 0.44; 95% CI, 0.25-0.80) should be noted.

Conclusion: Bezafibrate reduces the incidence of MI in patients with MS during long-term follow-up.

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METABOLIC SYNDROME (MS), also known as dysmetabolic syndrome X, is a widespread overweight-related clinical condition[1-4] that has an important cluster of atherothrombotic disease risk factors.[2-6] The inclusion of this syndrome in the Adult Treatment Panel III (ATPIII) guidelines[7] and the creation of an *International Classification of Diseases, Ninth Revision*, diagnostic code (277.7) have focused the attention of physicians on this condition.[7-9] People who develop MS usually pass through the phases of excessive adipogenesis, nuclear peroxisome proliferator–activated receptor (PPAR) modulation, and insulin resistance.[10-14] The main components of MS are abdominal obesity, atherogenic dyslipidemia (elevated triglyceride levels, small low-density lipoprotein cholesterol [LDL-C] particles, low levels of high-density lipoprotein cholesterol [HDL-C]), elevated blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states.[7,8,14] Patients with MS have been shown to be at increased risk of myocardial infarction (MI).[15,16]

Because of positive effects on glucose and lipid metabolism, PPAR α-agonists (fibrates) are good potential candidates to reduce the risk of MI in patients with MS.[17-19] Although less clinical intervention studies have been performed with fibrates than with statins, evidence indicates that fibrates may reduce cardiovascular disease, particularly, nonfatal MI.[20-26] Interestingly, reduction of cardiovascular disease with one of the fibric acid derivatives (gemfibrozil) was more pro-

nounced in patients who displayed baseline characteristics similar to MS definitions.[20,21] In the Bezafibrate Infarction Prevention (BIP) study,[25] no difference was apparent in the all-cause and cardiac mortality between the bezafibrate and placebo groups. However, the reduction in the primary end point in 459 patients with high baseline triglycerides levels ($\geq$200 mg/dL [$\geq$2.26 mmol/L]) was significant.[25] Whether pharmacologic intervention by bezafibrate can reduce the risk of MI in patients with MS is unknown. The present post hoc analysis was aimed to evaluate the effect of bezafibrate on the incidence of MI during a long-term follow-up period in coronary patients with MS enrolled in the BIP study.

METHODS

PATIENTS

The major inclusion and exclusion criteria for the BIP study, as well as the ethical guidelines, have been previously reported.[25] In brief, inclusion criteria for men and women comprised the following: age 45 to 74 years, history of MI of no less than 6 months and not more than 5 years before enrollment into the study and/or stable angina pectoris confirmed by coronary angiography, and/or radionuclear studies 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 therapy, type 1 diabetes mellitus, and current use of a lipid-modifying drug. The study was a multicenter prospective trial performed in 18 university-affiliated hospitals. Patients were allocated to receive either 400 mg of bezafibrate retard or placebo once a day in addition to dietary advice. The primary end point of the study was fatal MI, nonfatal MI, or sudden death (occurring within 24 hours of onset of symptoms).

After an initial 2 months of a lipid-lowering diet, 3122 eligible patients were included in the BIP study between May 1990 and January 1993. The follow-up period of the BIP study lasted until May 1998 (mean$\pm$SD, 6.2$\pm$0.8 years; range, 4.7-7.6 years). After the BIP study ended, the patients continued with a community-based treatment and were lost to the BIP study follow-up, except for mortality data (post–BIP study registry). The follow-up period for mortality registration lasted until March 2000 (mean$\pm$SD, 8.1$\pm$0.8 years; range, 4.9-9.7 years).

DEFINITION OF MS

Proposed definitions of MS have differed with respect to components and component cut points. We applied the cut points for MS based on the ATPIII report,[7] with minor modifications as noted. Patients who presented with 3 or more of the following 5 risk factors were defined as having MS[1]: insulin resistance defined as an impaired fasting glucose level of 110 mg/dL (6.11 mmol/L) or current use of oral hypoglycemics[2]; an elevated triglyceride level of 150 mg/dL[3] (1.70 mmol/L); HDL-C level of less than 40 mg/dL (<1.04 mmol/L) in men or less than 50 mg/dL (<1.30 mmol/L) in women[4]; an elevated systolic blood pressure of 130 mm Hg or an elevated diastolic blood pressure of 85 mm Hg[5]; and/or overweight (central obesity). Since the data regarding waist circumference were not available, for purposes of this analysis we used a body mass index (BMI) of 28.0 kg/m² as a criterion for inclusion. The presence of 4 to 5 risk factors for

MS was defined as augmented features of MS. Among the BIP study patients 1470 met the criteria for MS (ie, at least 3 of 5 listed risk factors), and among them 575 patients met the criteria for augmented features of MS (ie, at least 4 of 5 risk factors). All of these patients were included in this post hoc analysis.

LABORATORY METHODS

Detailed data on laboratory methods were given in a previous report.[25] 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-C, and triglycerides. Laboratory measurements were performed using standard automated procedures with commercially available kits (F. Hoffmann-La Roche Ltd, Diagnostics Division, Basel, Switzerland). Fasting blood glucose values were determined by the glucose oxidase–phenol-4-aminophenazone peroxidase method, using a BM/Hitachi 717/911 analyzer (Hitachi Instruments, Inc, San Jose, Calif).[25]

DETERMINATION OF ADDITIONAL VARIABLES

Criteria for the diagnosis of MI, anginal syndrome, hypertension, and congestive heart failure have been previously reported.[25,27] Functional capacity classes were evaluated according to the New York Heart Association classification. Smoking habits were determined on the basis of self-reporting by the patient during an interview held with a study physician.

STATISTICAL ANALYSIS

Data were analyzed using SAS statistical software.[28] Continuous variables were presented as mean$\pm$SD. Comparisons between groups were made using χ^2 tests for discrete variables and the t test for continuous variables. Kaplan-Meier curves were produced using the LIFETEST procedure.[29] The log-rank test was used for comparing the curves.

Repeated-measures analysis of variance was used to evaluate the treatment effect (placebo vs bezafibrate) over time. Hazard ratio (HR) analysis of incidence of the main clinical outcomes was performed using the Cox proportional hazards model (PHREG procedure) to account for different lengths of follow-up and correlation with covariates.[29]

RESULTS

BASELINE DATA

Our population included 2 groups: the bezafibrate group (740 patients) and the placebo group (730 patients). Patients in the placebo and bezafibrate groups were well balanced in terms of clinical and laboratory baseline characteristics (**Table 1**). The study groups were similar in regard to age, sex, and prevalence of the most relevant cardiovascular diseases and risk factors (an MI in the past, hypertension, diabetes, heart failure, anginal syndrome). Most patients in all groups were men who had sustained an MI in the past. No significant differences between the groups were found for all types of cholesterol levels, systolic and diastolic blood pressures, heart rate, BMI, and fasting glucose, triglycerides, and fibrinogen levels. At baseline, nitrates, calcium antagonists, β-blockers, and antiplatelet drugs

Table 1. Baseline Characteristics of the Study Population*

Characteristic	Bezafibrate Retard (n = 740)	Placebo (n = 730)	P Value
Age, y	60.2 ± 6.6	60.0 ± 6.7	.60
Body mass index, kg/m^2	28.2 ± 3.4	28.1 ± 3.5	.50
Weight, kg	80.3 ± 11.8	80.2 ± 11.9	.90
Height, cm	169 ± 7.5	169 ± 7.8	.50
Women	85 (11)	83 (11)	.90
Past myocardial infarction	569 (77)	574 (79)	.40
Angina	435 (59)	437 (60)	.70
NYHA class ≥2	209 (29)	188 (26)	.30
Hypertension	271 (37)	299 (41)	.10
Diabetes	117 (16)	120 (16)	.80
Current or past smokers	516 (70)	519 (71)	.90
Systolic blood pressure, mm Hg	139 ± 16	139 ± 16	.90
Diastolic blood pressure, mm Hg	83 ± 9	83 ± 9	.99
Heart rate, beats/min	70.4 ± 9	70.8 ± 10	.40
Fasting glucose, mg/dL	107 ± 20	107 ± 20	.80
Total cholesterol, mg/dL	213 ± 18	215 ± 18	.10
HDL-C, mg/dL	33.0 ± 5.1	32.9 ± 4.9	.70
LDL-C, mg/dL	146 ± 17	148 ± 17	.10
Non–HDL-C, mg/dL	180 ± 18	182 ± 17	.10
Triglycerides, mg/dL	170 ± 52	172 ± 50	.50
Fibrinogen, mg/dL	356 ± 72	359 ± 76	.40

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NYHA, New York Heart Association.

SI conversion factors: To convert HDL-C, non–HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; glucose to millimoles per liter, multiply by 0.0555.

*Values are presented as either mean ± SD or as number (percentage).

(mainly aspirin) were the most commonly used medications. The use of angiotensin-converting enzyme inhibitors increased significantly during the follow-up period. There were no significant differences between the groups in the proportion of patients who received cardiovascular drugs.

EFFECT OF TREATMENT ON LIPID LEVELS, GLUCOSE LEVELS, AND BMI DURING FOLLOW-UP

Average changes in lipid levels are shown in **Figure 1** (A-D). The most marked changes were an increase from 33.0 to 38.3 mg/dL (0.85-0.99 mmol/L) ($P < .001$) in mean HDL-C levels (A) and a reduction from 170 to 126 mg/dL (1.92-1.42 mmol/L) ($P < .001$) in mean triglyceride values (B) in the bezafibrate group after the first year of treatment. No significant changes occurred in mean HDL-C and triglyceride levels in the placebo group during follow-up. In addition, reductions from 180 to 166 mg/dL (4.66-4.30 mmol/L) ($P < .001$) in mean non–HDL-C (C) and from 146 to 141 mg/dL (3.78-3.65 mmol/L) ($P = .001$) in mean LDL-C values (D) in the bezafibrate group after the first year of treatment were observed.

Fasting glucose levels at baseline did not differ between the 2 groups. In the first year, a reduction occurred from 107 to 105 mg/dL (5.94-5.83 mmol/L) in the mean level of fasting blood glucose in the bezafibrate group in contrast to a rise from 107 to 112 mg/dL (5.94-6.22 mmol/L) in the placebo group (Figure 1E). The values

rose in parallel in both groups in subsequent years. As a whole, a significant difference occurred in glucose levels over time between the bezafibrate and placebo groups ($P = .02$). No significant change occurred in mean BMI in either the bezafibrate or the placebo group during the follow-up (Figure 1F).

CLINICAL OUTCOMES

During the follow-up period, development of a new MI was recorded in 193 patients: 82 (11.1%) of the 740 patients in the bezafibrate group vs 111 (15.2%) of the 730 patients in the placebo group ($P = .02$) (**Table 2**). The rate of fatal MI was unexpectedly low and similar in both study groups, but the rate of nonfatal MI was significantly lower in patients with MS in the bezafibrate group ($P = .009$). The primary end point of the BIP study was fatal or nonfatal MI or sudden death; in general, a significant risk reduction of the primary end point in patients with MS who were taking bezafibrate was observed ($P = .03$).

In addition, in patients *free* of the primary end points, the secondary end points (hospitalization due to unstable angina pectoris, coronary artery bypass graft, and percutaneous transluminal coronary angioplasty) were determined. The rate of hospitalization due to unstable angina pectoris, and coronary artery bypass graft in patients taking bezafibrate tended to be lower than in their counterparts taking placebo, but this trend did not reach statistical significance. The total mortality rate in patients taking bezafibrate also tended to be lower than in their counterparts taking placebo. The decrease in MI incidence in patients taking bezafibrate was reflected in a trend to a 26% reduction of cardiac mortality rate ($P = .056$).

In patients with augmented features of MS (4-5 risk factors for MS, 575 patients), development of a new MI was recorded in 82 patients: 33 (11.4%) of the 740 patients in the bezafibrate group vs 49 (17.1%) of the 730 patients in the placebo group ($P = .05$). The cardiac mortality rate in these patients taking bezafibrate was significantly lower than in their counterparts taking placebo: cardiac death was recorded in 16 patients (5.6%) in the bezafibrate group vs 35 patients (12.2%) in the placebo group (54% risk reduction, $P = .005$).

Kaplan-Meier curves of MI incidence (in accordance with the time of diagnosis) for the 2 study groups are presented in **Figure 2**A. The incidence rate of patients taking placebo was significantly higher than in their bezafibrate-treated counterparts (log-rank $P = .02$). Kaplan-Meier curves of cardiac mortality are presented in Figure 2B. A trend to reduction of cardiac mortality was observed as a relatively late phenomenon during follow-up (log-rank $P = .07$).

The HRs and 95% confidence intervals (CIs) of bezafibrate treatment influence on main outcomes during follow-up were determined in the overall study population (Table 2) and separately in patients with augmented features of MS (**Table 3**). Overall, bezafibrate treatment was associated with reduced risk of any MI and nonfatal MI with HRs of 0.71 (95% CI, 0.54-0.95) and 0.67 (95% CI, 0.49-0.91), respectively. The cardiac mortality risk
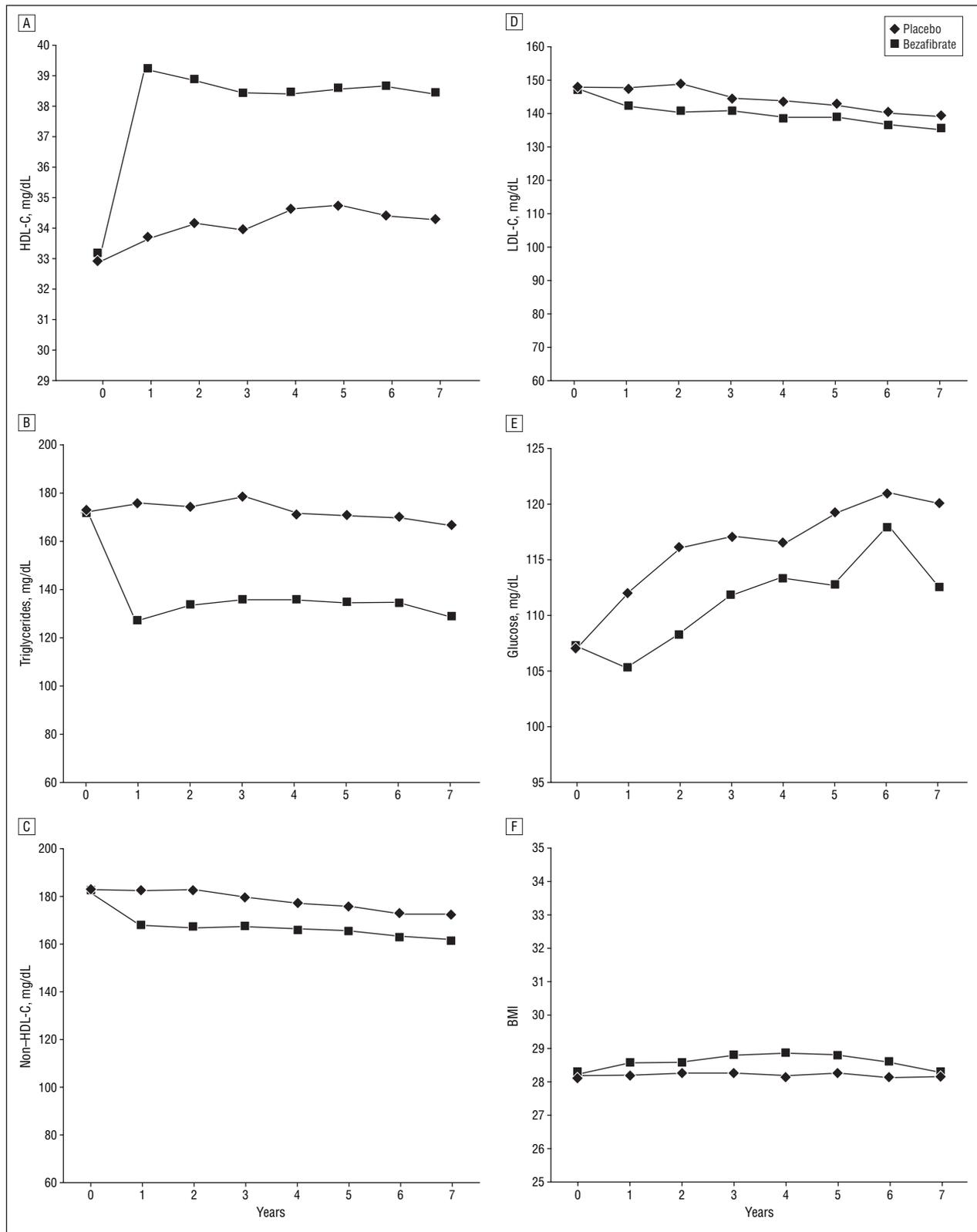
Figure 1. Changes in mean high-density lipoprotein cholesterol (HDL-C) (A), triglyceride (B), non–HDL-C (C), low-density lipoprotein cholesterol (LDL-C) (D), and mean fasting blood glucose (E) levels, and body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) (F) values throughout the study period (bezafibrate retard vs placebo) following annual measurements. Each data point represents the mean value for all participants who remained at that time. To convert HDL-C, non–HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and glucose to millimoles per liter, multiply by 0.0555.

Table 2. Outcomes of the Study Population During Follow-up

Outcomes	No. (%) of Patients		HR (95% CI)	*P* Value
	Bezafibrate Retard (n = 740)	Placebo (n = 730)		
Nonfatal myocardial infarction	70 (9.5)	101 (13.8)	0.67 (0.49-0.91)	.009
Fatal myocardial infarction	14 (1.9)	11 (1.5)	1.26 (0.57-2.77)	.60
Any myocardial infarction	82 (11.1)	111 (15.2)	0.71 (0.54-0.95)	.02
Sudden death	25 (3.4)	26 (3.6)	0.95 (0.55-1.65)	.80
Primary end point*	104 (14.1)	134 (18.4)	0.75 (0.58-0.97)	.03
UAP†	58 (7.8)	73 (10.0)	0.77 (0.54-1.08)	.10
CABG†	115 (15.5)	126 (17.3)	0.90 (0.70-1.16)	.40
PTCA†	72 (9.7)	68 (9.3)	1.04 (0.75-1.46)	.80
Cardiac death	63 (8.5)	84 (11.5)	0.74 (0.54-1.03)	.056
Total No. of deaths	126 (17)	139 (19)	0.90 (0.70-1.14)	.30

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; PTCA, percutaneous transluminal coronary angioplasty; UAP, hospitalizations due to unstable angina pectoris.
*The primary end point of the Bezafibrate Infarction Prevention (BIP) study was fatal or nonfatal myocardial infarction or sudden death.
†Secondary end points of the BIP study were the first event in patients free of the primary end points.
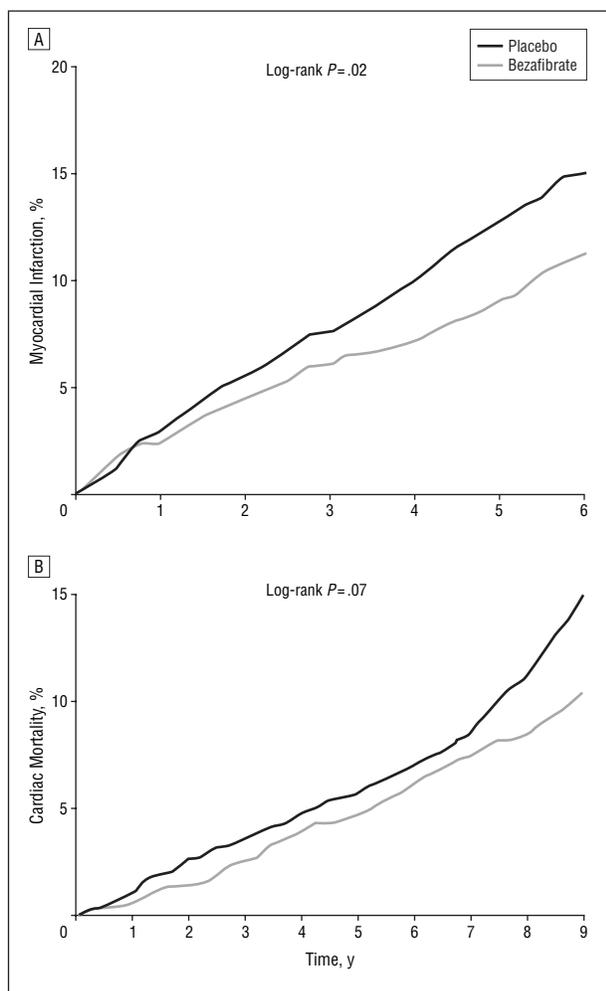
Figure 2. Kaplan-Meier curves of the incidence of myocardial infarction (A) (in accordance with the time of diagnosis; mean follow-up, 6.2 years) and cardiac mortality rate (B) (mean follow-up, 8.1 years) for the study groups (bezafibrate retard vs placebo).

tended to be lower with the bezafibrate regimen (HR, 0.74; 95% CI, 0.54-1.03). This trend persisted in patients with augmented features of MS; of note, a marked reduction in cardiac mortality was observed among these patients taking bezafibrate (HR, 0.44; 95% CI, 0.25-0.80).

COMMENT

Our data demonstrate that bezafibrate can reduce the incidence of MI in patients with MS. The decrease in the incidence of MI among patients taking bezafibrate was reflected in a trend to a late risk reduction of cardiac mortality during a long-term follow-up period. This tendency was strengthened in patients with augmented features (at least 4 risk factors for MS) of MS.

No direct head-to-head comparisons of a statin with a fibrate have been performed in any clinical end point trial. However, compared with statins, fibrates appear to more selectively target the therapeutic goals in obese individuals with features of insulin resistance and MS (ie, with near-goal LDL-C and inappropriate HDL-C and triglyceride levels). In 2 previous small studies,[22,23] bezafibrate decreased the rate of progression of coronary atherosclerosis and decreased the coronary event rate. In another large trial[24] in 1568 men with lower extremity arterial disease with a relatively short follow-up period of up to 3 years, bezafibrate reduced the severity of intermittent claudication and the incidence of nonfatal coronary events, particularly in those older than 65 years at entry. In the BIP study, an overall nonsignificant trend of a 9.4% reduction of the incidence of the primary end point (fatal or nonfatal MI or sudden death) was observed.[25] Recently, reduced incidence of type 2 diabetes mellitus in patients with impaired fasting glucose levels who were taking bezafibrate has been demonstrated.[30] The data from the present study have confirmed the beneficial glucose-lowering properties of bezafibrate in a relatively large population.

The primary prevention trial, the Helsinki Heart Study, showed that treatment with the other fibric acid derivative gemfibrozil led to a significant reduction in major cardiovascular events.[20] In the secondary prevention trial, the Veterans Affairs High-Density Lipoprotein

Table 3. Influence of Bezafibrate Treatment on Main Outcomes During Follow-up in 575 Patients With Augmented Features of Metabolic Syndrome (4-5 Risk Factors for Metabolic Syndrome)

	No. (%) of Patients			
Outcomes	Bezafibrate Retard (n = 288)	Placebo (n = 287)	HR (95% CI)	*P* Value
Nonfatal myocardial infarction	30 (10.4)	44 (15.3)	0.66 (0.41-1.04)	.08
Any myocardial infarction	33 (11.5)	49 (17.1)	0.65 (0.42-1.01)	.05
Cardiac death	16 (5.6)	35 (12.2)	0.44 (0.25-0.80)	.005
Total No. of deaths	46 (16.0)	59 (20.6)	0.76 (0.52-1.12)	.15

Abbreviations: CI, confidence interval; HR, hazard ratio.

Cholesterol Intervention Trial, with 30% being patients with diabetes, gemfibrozil reduced the occurrence of major cardiovascular events by 22%.[21] Similar to the data of the present analysis, reduction of cardiovascular disease with gemfibrozil was more pronounced in patients who displayed augmented features of MS.[31,32] The results of the present study are in accord with previous trials and indicate that fibrates may effectively reduce the incidence of MI in patients with features of MS. The potential clinical benefit of the other fibric acid derivative fenofibrate on the reduction of cardiovascular disease will be specified by the ongoing intervention studies.

Despite increasing use of statins, a significant number of coronary events still occur, and many such events take place in patients with MS. Whereas statins remain the drug of choice for patients who need to achieve the LDL-C level goal, fibrate therapy may represent the alternative intervention for patients with atherogenic dyslipidemia typical of MS and an LDL-C level already close to the goal. In addition, the concomitant use of fibrates seems to be attractive in patients whose LDL-C level is controlled by statin therapy but whose HDL-C and/or triglyceride levels are still inappropriate.[33-36] This strategy will be tested in the ongoing Action to Control Cardiovascular Risk in Diabetes trial.[37]

The triglyceride-lowering and HDL-C–raising effects of fibric acid derivatives lead to decreased systemic availability of fatty acid and diminished fatty acid uptake by muscle, with improvement of insulin sensitization and reduced plasma glucose levels.[37-41] Bezafibrate, compared with other fibrates, has a unique characteristic profile of action since it activates all 3 PPAR subtypes (α, γ, and δ) at comparable doses.[42,43] Therefore, bezafibrate operates as a pan-agonist for all 3 PPAR isoforms.

In the BIP study[25] the rate of adverse events was similar in both study groups. Thus, bezafibrate treatment was safe and effective in the secondary prevention of MI in patients with MS. Our data obtained in a large-scale population of patients with MS suggest that bezafibrate can reduce the incidence of MI and cardiac mortality with a magnitude of benefit comparable to other lipid-lowering medications recommended for secondary prevention (gemfibrozil and statins). However, caution should be used in interpreting our finding, because it was identified in a post hoc analysis. In conclusion, bezafibrate decreased the incidence of MI in patients with MS during a long-term follow-up period. A trend to a risk reduction of cardiac mortality emerged as well.

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