

GEMFIBROZIL FOR THE SECONDARY PREVENTION OF CORONARY HEART DISEASE IN MEN WITH LOW LEVELS OF HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

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ABSTRACT

Background Although it is generally accepted that lowering elevated serum levels of low-density lipoprotein (LDL) cholesterol in patients with coronary heart disease is beneficial, there are few data to guide decisions about therapy for patients whose primary lipid abnormality is a low level of high-density lipoprotein (HDL) cholesterol.

Methods We conducted a double-blind trial comparing gemfibrozil (1200 mg per day) with placebo in 2531 men with coronary heart disease, an HDL cholesterol level of 40 mg per deciliter (1.0 mmol per liter) or less, and an LDL cholesterol level of 140 mg per deciliter (3.6 mmol per liter) or less. The primary study outcome was nonfatal myocardial infarction or death from coronary causes.

Results The median follow-up was 5.1 years. At one year, the mean HDL cholesterol level was 6 percent higher, the mean triglyceride level was 31 percent lower, and the mean total cholesterol level was 4 percent lower in the gemfibrozil group than in the placebo group. LDL cholesterol levels did not differ significantly between the groups. A primary event occurred in 275 of the 1267 patients assigned to placebo (21.7 percent) and in 219 of the 1264 patients assigned to gemfibrozil (17.3 percent). The overall reduction in the risk of an event was 4.4 percentage points, and the reduction in relative risk was 22 percent (95 percent confidence interval, 7 to 35 percent; $P=0.006$). We observed a 24 percent reduction in the combined outcome of death from coronary heart disease, nonfatal myocardial infarction, and stroke ($P<0.001$). There were no significant differences in the rates of coronary revascularization, hospitalization for unstable angina, death from any cause, and cancer.

Conclusions Gemfibrozil therapy resulted in a significant reduction in the risk of major cardiovascular events in patients with coronary disease whose primary lipid abnormality was a low HDL cholesterol level. The findings suggest that the rate of coronary events is reduced by raising HDL cholesterol levels and lowering levels of triglycerides without lowering LDL cholesterol levels. (N Engl J Med 1999;341:410-8.)

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CLINICAL trials have demonstrated that cholesterol-lowering therapy reduces the incidence of major cardiac events in patients with coronary heart disease who have levels of low-density lipoprotein (LDL) cholesterol of 130 mg per deciliter (3.4 mmol per liter) or more.¹⁻³ However, about 40 percent of patients with coronary disease have LDL cholesterol levels below this value, and most of these patients also have low levels of high-density lipoprotein (HDL) cholesterol, with or without increased levels of triglycerides.^{4,5} Overall, low levels of HDL cholesterol without high levels of LDL cholesterol characterize 20 to 30 percent of patients with coronary disease, representing several million people in the United States.^{4,5} Observational studies indicate that low HDL cholesterol levels are strongly and independently associated with a higher risk of coronary heart disease.⁶⁻⁸

The optimal clinical approach is unknown for patients with coronary disease whose primary lipid abnormality is a low HDL cholesterol level, because no large-scale intervention trials with major clinical outcomes have been reported in this population. We report the results of a multicenter trial (the Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial [VA-HIT]), initiated in 1991 to address the hypothesis that therapy aimed at raising HDL cholesterol levels and lowering levels of triglycerides would reduce the incidence of death from coronary heart disease and nonfatal myocardial infarction in men with coronary heart disease who had low levels of both HDL cho-

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lesterol and LDL cholesterol. We chose the fibric acid derivative gemfibrozil for the intervention because we considered it the agent most likely to improve plasma HDL cholesterol and triglyceride values while having the least effect on plasma LDL cholesterol levels.

METHODS

The protocol was approved by the Human Rights Committee of the Cooperative Studies Program Coordinating Center, by each center's institutional review board, and by the Cooperative Studies Program Evaluation Committee. All patients gave written informed consent.

Patients

We have described the study design in detail elsewhere.⁹ Briefly, men were recruited at 20 Veterans Affairs medical centers throughout the United States. Eligibility for the trial required a documented history of coronary heart disease (defined as a history of myocardial infarction, angina corroborated by objective evidence of ischemia, coronary revascularization, or angiographic evidence of stenosis greater than 50 percent of the luminal diameter in one or more major epicardial coronary arteries), an age of less than 74 years, an absence of serious coexisting conditions, an HDL cholesterol level of 40 mg per deciliter (1.0 mmol per liter) or less, an LDL cholesterol level of 140 mg per deciliter (3.6 mmol per liter) or less, and a triglyceride level of 300 mg per deciliter (3.4 mmol per liter) or less. To obtain a population whose lipid values were at or below these levels, we used a multistage lipid-screening method that included two lipid profiles obtained one to two weeks apart while the patients were fasting.^{9,10} The means of two additional fasting profiles were used for the baseline lipid values.

Treatment Regimen and Follow-up

After confirming the patients' eligibility with local personnel by telephone, the Cooperative Studies Program Coordinating Center randomly assigned patients to receive either gemfibrozil (1200 mg per day) or matching placebo, according to a permuted-block design with stratification according to center. Throughout the trial, all patients and local study personnel were blinded to treatment assignment.

From September 1991 through May 1995, patients received slow-release gemfibrozil (Lopid SR, Parke-Davis) at a dose of 1200 mg once daily or a matching placebo. On June 1, 1995, after the manufacturer discontinued production of Lopid SR, patients received regular gemfibrozil (Lopid, Parke-Davis) at a dose of 600 mg twice daily or matching placebo for the remainder of the study. The two formulations have been reported to have equivalent effects on plasma lipid levels,¹¹ and we detected no changes in lipid levels after the substitution.

A study coordinator saw patients one month after randomization and then every three months for the duration of the study. At each follow-up visit, study staff provided counseling regarding adherence to the study regimen and asked about the occurrence of events and side effects since the previous visit, using a standard questionnaire that detailed specific symptoms. In addition, the staff provided instruction in the American Heart Association Step 1 diet and advised each patient to consult with his primary physician about an appropriate exercise regimen. An electrocardiogram was obtained annually, or more frequently if clinically indicated. Every six months for the first half of the study, and then annually, blood for lipid analysis was drawn while patients were fasting and was processed according to a standardized protocol. Plasma total cholesterol, HDL cholesterol, and triglycerides were measured by standardized automated enzymatic methods⁹ at a National Heart, Lung, and Blood Institute—Centers for Disease Control and Prevention regional network reference lipid laboratory. The LDL cholesterol level was calculated by the Friedewald

formula.¹² All patients were asked to attend regular follow-up visits whether or not they were still taking the study medication. All were followed until death, refusal of further visits, or the conclusion of the study.

Outcomes

The primary outcome was the combined incidence of nonfatal myocardial infarction or death from coronary heart disease as determined by the end-points committee, which was blinded to treatment assignment and lipid results. The diagnosis of myocardial infarction was based on an algorithm that incorporated standard electrocardiographic and clinical-history criteria and serial determinations of cardiac enzymes. Clinically silent myocardial infarctions were included, as identified on the basis of the occurrence of new diagnostic Q waves on routine annual electrocardiography. Death from coronary heart disease included sudden death, death due to myocardial infarction, death due to congestive heart failure, and death as a complication of invasive cardiac procedures. All electrocardiograms were read at a central electrocardiographic coding center according to the Minnesota code.¹³ A stroke-adjudication committee composed of three neurologists who were blinded to treatment assignment and lipid levels used predefined criteria to review all suspected instances of stroke, a secondary outcome, on the basis of clinical and radiographic data. Other prespecified secondary outcomes were also assessed. They included death from any cause, transient ischemic attack, revascularization procedures, carotid endarterectomy, and hospitalization for unstable angina or congestive heart failure. With the exception of deaths and strokes, which were adjudicated as described, secondary outcomes were confirmed by the principal investigator at each medical center, using standardized definitions in the protocol.

Statistical Analysis

All analyses followed an intention-to-treat approach. Applying a method of Lakatos¹⁴ to projected event rates in the placebo and gemfibrozil groups, we calculated that, at a type I error rate of 0.05, the study would require 2500 subjects to detect a 20 percent reduction in the primary outcome with 90 percent power. The study had low power to detect a plausible reduction in total mortality (e.g., 20 percent power to detect a 10 percent reduction with a type I error rate of 0.05). Analyses of time-to-event data were performed with the log-rank test.¹⁵ Patients were removed from all time-to-event analyses at the time of death. Relative risks were calculated from Cox models¹⁶ with treatment as the single covariate. Adjustment for base-line variables in the Cox models had a trivial effect on the estimates of the hazard ratios. Since the effect of gemfibrozil did not become apparent for about two years, the reported relative risks should be interpreted as the average reduction in risk over roughly five years. The data monitoring board used conditional power calculations¹⁷ to guide recommendations about study termination. The Veterans Affairs Cooperative Studies Program Coordinating Center in West Haven, Connecticut, maintained exclusive control of all data.

RESULTS

Between September 4, 1991, and December 31, 1993, we enrolled 2531 patients: 1264 were randomly assigned to receive gemfibrozil and 1267 to receive placebo. Final follow-up visits occurred between May 1 and July 31, 1998, as originally planned. The median follow-up was 5.1 years (range, 0 to 6.9). Overall compliance, defined as the number of days on which the patient took the study medication (as determined by pill counts) divided by the number of days he was supposed to take the medication, was 75 percent in both groups. Among patients who attended the last study visit, 71 percent in each treatment

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	PLACEBO (N=1267)	GEMFIBROZIL (N=1264)
Age (yr)	64±7	64±7
Age >60 yr (%)	77	76
Race (%)		
White	90	89
Black	8	8
Other	2	3
Education ≥12 yr (%)	47	47
Current smoker (%)	19	22
Alcohol consumption (%)		
<1 drink/day	94	93
1–3 drinks/day	6	7
>3 drinks/day	<1	<1
Hypertension (%)	57	57
Diabetes (%)	25	24
Prior myocardial infarction (%)	61	61
Time since most recent myocardial infarction (yr)	6±6	6±6
History of congestive heart failure (%)	8	8
CABG or PTCA (%)	58	55
Medication use (%)		
Aspirin	82	81
Nitrates†	46	46
Calcium-channel blockers	52	53
ACE inhibitors	20	22
Beta-blockers	43	43
Any antianginal drug‡	80	82
Body-mass index§	29±5	29±5
Waist-to-hip ratio	0.96±0.05	0.96±0.05
Blood pressure (mm Hg)		
Systolic	132±18	132±19
Diastolic	77±10	77±10
Plasma lipids (mg/dl)¶		
Total cholesterol		
Mean	175±25	175±25
Interquartile range	159–191	160–190
LDL cholesterol		
Mean	112±23	111±22
Interquartile range	97–127	99–125
HDL cholesterol		
Mean	32±5	32±5
Interquartile range	28–35	28–35
Triglycerides		
Mean	160±67	161±68
Interquartile range	111–201	111–201

*Plus–minus values are means ±SD. CABG denotes coronary-artery bypass graft, PTCA percutaneous transluminal coronary angioplasty, and ACE angiotensin-converting enzyme. Hypertension and diabetes were defined by clinical history. A more complete list of base-line characteristics is given in Rubins et al.¹⁸

†Nitrates includes all preparations except as-needed nitroglycerin.

‡Any antianginal drug includes any nitrate (as defined above), calcium-channel blocker, or beta-blocker.

§The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

group were still taking their assigned medication. Only 2 percent of patients in the placebo group and less than 1 percent of those assigned to gemfibrozil had been treated for more than six months with an open-label lipid medication. During the study, 418 patients died; of those who were not known to have died during the study, all but 60 were followed until the conclusion of the study, and vital status was ascertained for all but 3.

Patients randomly assigned to the two treatment groups were similar at base line with respect to demographic and clinical variables (Table 1). The population was characterized by low levels of HDL cholesterol (mean, 32 mg per deciliter [0.8 mmol per liter]), low levels of LDL and total cholesterol (mean, 111 and 175 mg per deciliter [2.9 and 4.5 mmol per liter], respectively), moderate levels of triglycerides (mean, 160 mg per deciliter [1.8 mmol per liter]), advanced age (mean, 64 years), a high prevalence of diabetes (25 percent) and hypertension (57 percent), and abdominal obesity (mean [±SD] waist-to-hip ratio, 0.96±0.05).

Effects on Lipid Levels

One year after randomization, the mean HDL cholesterol level was 6 percent higher in the gemfibrozil group than in the placebo group (34 mg per deciliter [0.9 mmol per liter] vs. 32 mg per deciliter [0.8 mmol per liter], $P<0.001$); the mean total cholesterol level was 4 percent lower (170 mg per deciliter [4.4 mmol per liter] vs. 177 mg per deciliter [4.6 mmol per liter], $P<0.001$); and the mean triglyceride level was 31 percent lower (115 mg per deciliter [1.3 mmol per liter] vs. 166 mg per deciliter [1.9 mmol per liter], $P<0.001$). Significant differences between treatment groups for these three lipids persisted throughout the study (Fig. 1). The mean LDL cholesterol level was 113 mg per deciliter (2.9 mmol per liter) in both groups at one year and never differed significantly between groups.

Outcomes

Overall, 275 patients (21.7 percent) in the placebo group and 219 patients (17.3 percent) in the gemfibrozil group had a primary event (Table 2). Thus, gemfibrozil was associated with a reduction of 22 percent (95 percent confidence interval, 7 to 35 percent) in the rate of death from coronary heart disease or nonfatal myocardial infarction ($P=0.006$). The effect was consistent for both components of the primary outcome, with a 22 percent reduction in death from coronary heart disease (95 percent confidence interval, –2 to 41 percent [the negative number indicates an increase]; $P=0.07$) and a 23 percent reduction in nonfatal myocardial infarction (95 percent confidence interval, 4 to 38 percent; $P=0.02$). The beneficial effect of gemfibrozil did not become apparent until about two years after randomization (Fig. 2).

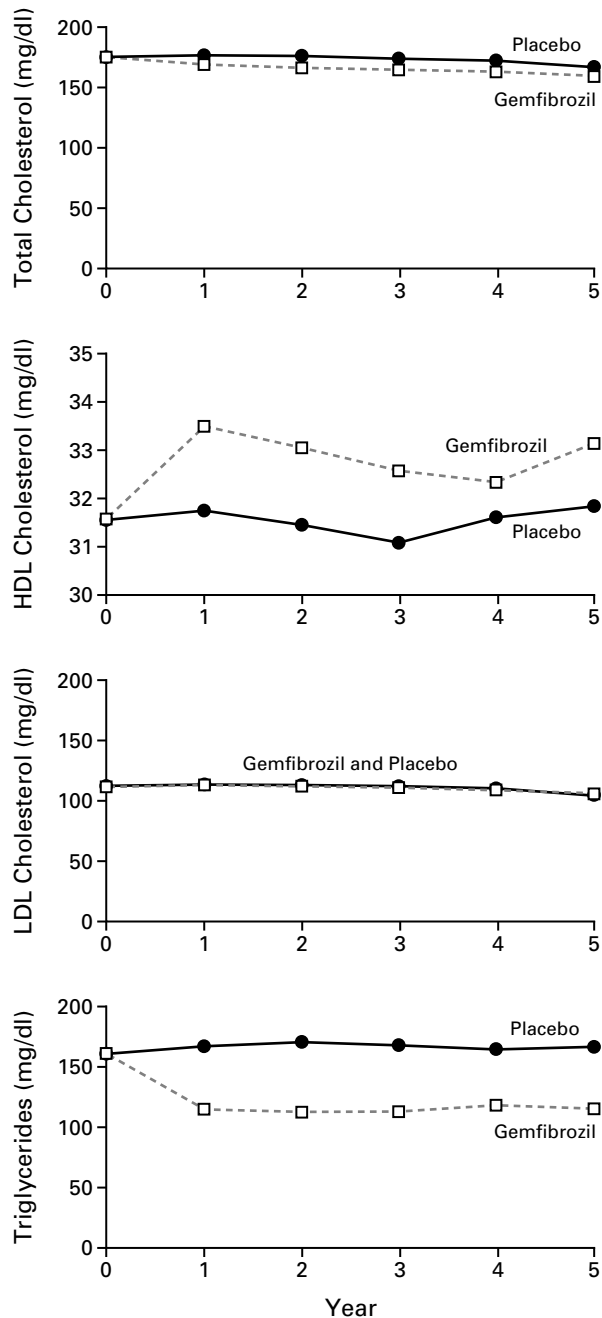


Figure 1. Lipid Concentrations According to Year of Study and Treatment Group.

Values are means and are presented according to the intention to treat. To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129. The y axis for HDL cholesterol levels ranges from 30 to 35 mg per deciliter.

Table 2 also shows the incidence of secondary outcomes according to treatment group. Seventy-six patients taking placebo (6.0 percent) and 58 taking gemfibrozil (4.6 percent) had strokes (relative risk reduction, 25 percent; 95 percent confidence interval, -6 to 47 percent; $P=0.10$). Since several recent secondary-prevention trials reported investigator-designated strokes rather than strokes confirmed by an adjudication committee, we also show such data in Table 2.^{1,2} Gemfibrozil resulted in a relative risk reduction of 24 percent for the combined outcome of death from coronary heart disease, nonfatal myocardial infarction, or confirmed stroke (95 percent confidence interval, 11 to 36 percent; $P<0.001$). Gemfibrozil also resulted in a statistically significant 59 percent reduction in transient ischemic attacks (95 percent confidence interval, 33 to 75 percent; $P<0.001$) and a statistically significant 65 percent reduction in carotid endarterectomy (95 percent confidence interval, 37 to 80 percent; $P<0.001$). The rates of coronary revascularization and hospitalization for unstable angina did not differ significantly between the groups.

Subgroup Analyses

Although the study was not designed to have adequate power for subgroup analyses, we performed exploratory analyses in predefined subgroups, using the expanded outcome of death from coronary heart disease, nonfatal myocardial infarction, or confirmed adjudicated stroke. Gemfibrozil was associated with relative risk reductions ranging from 11 percent to 42 percent in all subgroups except for current smokers (Table 3).

Adverse Events

As shown in Table 4, there were 220 deaths in the placebo group (17.4 percent) and 198 in the gemfibrozil group (15.7 percent). There was no significant difference between the two groups in the rate of death from any specific cause. Cancer was diagnosed during the study in 263 patients, 138 in the placebo group and 125 in the gemfibrozil group.

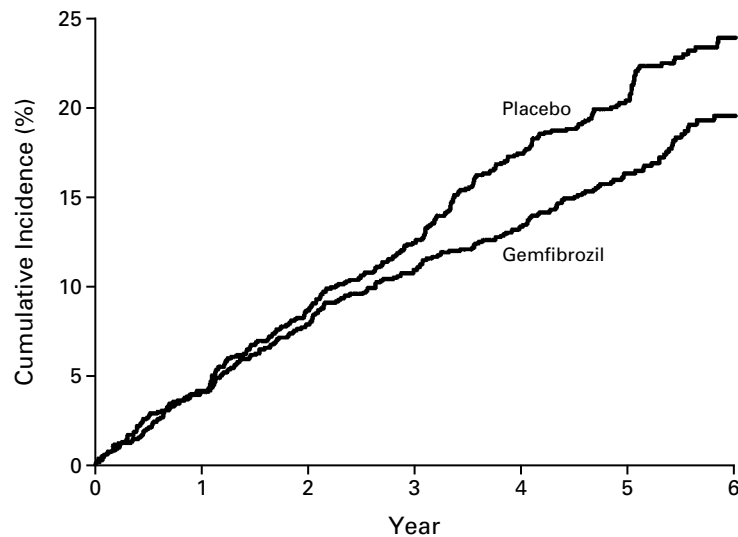
The study medication was generally well tolerated. The only symptom reported more commonly by patients receiving the active treatment was dyspepsia, which occurred in 40 percent of patients taking gemfibrozil and 34 percent of those taking placebo ($P=0.002$). Seven percent of patients in both treatment groups had biliary disease. More patients assigned to gemfibrozil underwent abdominal surgery, but the difference was not statistically significant (5.4 percent vs. 4.3 percent, $P=0.19$). The number of patients with elevations in either creatine kinase or aspartate aminotransferase levels did not differ significantly between the groups. Table 5 shows the reasons for the discontinuation of the study medication.

TABLE 2. MAJOR CARDIOVASCULAR EVENTS ACCORDING TO TREATMENT GROUP.*

EVENT	PLACEBO (N=1267)	GEMFIBROZIL (N=1264)	RISK REDUCTION (95% CI)	P VALUE
	no. (%)	no. (%)	%	
Nonfatal myocardial infarction or death due to CHD	275 (21.7)	219 (17.3)	22 (7 to 35)	0.006
Nonfatal myocardial infarction or death due to CHD (excluding silent myocardial infarction)	241 (19)	195 (15.4)	21 (4 to 34)	0.02
Nonfatal myocardial infarction, death due to CHD, or confirmed stroke†	330 (26)	258 (20.4)	24 (11 to 36)	<0.001
Nonfatal myocardial infarction	184 (14.5)	146 (11.6)	23 (4 to 38)	0.02
Death due to CHD	118 (9.3)	93 (7.4)	22 (-2 to 41)	0.07
Death from any cause	220 (17.4)	198 (15.7)	11 (-8 to 27)	0.23
Investigator-designated stroke	88 (6.9)	64 (5.1)	29 (2 to 48)	0.04
Confirmed stroke	76 (6.0)	58 (4.6)	25 (-6 to 47)	0.10
Transient ischemic attack	53 (4.2)	22 (1.7)	59 (33 to 75)	<0.001
CABG	173 (13.7)	164 (13.0)	6 (-17 to 24)	0.60
PTCA	147 (11.6)	120 (9.5)	21 (-1 to 38)	0.06
CABG or PTCA	287 (22.7)	266 (21.0)	9 (-8 to 23)	0.29
Peripheral vascular surgery	28 (2.2)	19 (1.5)	33 (-20 to 63)	0.18
Carotid endarterectomy	44 (3.5)	16 (1.3)	65 (37 to 80)	<0.001
Hospitalization for unstable angina	453 (35.8)	457 (36.2)	-0.4 (-14 to 12)	0.95
Hospitalization for congestive heart failure	168 (13.3)	134 (10.6)	22 (2 to 38)	0.04

*CI denotes confidence interval, CHD coronary heart disease, CABG coronary-artery bypass graft, and PTCA percutaneous transluminal coronary angioplasty. Relative risk reductions, 95 percent confidence intervals, and P values are derived from Cox models. For risk reductions, negative numbers indicate an increase in risk.

†Confirmed stroke was judged by a blinded adjudication panel of three neurologists.



No. AT RISK	
Placebo	1267 1200 1118 1040 962 666 466
Gemfibrozil	1264 1201 1128 1067 1005 706 498

Figure 2. Kaplan–Meier Estimates of the Incidence of Death from Coronary Heart Disease and Nonfatal Myocardial Infarction in the Gemfibrozil and Placebo Groups.

The relative risk reduction was 22 percent (P=0.006), as derived from a Cox model.

TABLE 3. EFFECT OF GEMFIBROZIL ON DEATH DUE TO CORONARY HEART DISEASE, NONFATAL MYOCARDIAL INFARCTION, AND CONFIRMED STROKE IN PRESPECIFIED SUBGROUPS.*

SUBGROUP†	PLACEBO	GEMFIBROZIL	RISK REDUCTION (95% CI)	P VALUE
	no. with event/total no. (%)		%	
Age				
<66 yr	152/647 (24)	116/618 (19)	22 (1 to 39)	0.04
≥66 yr	178/620 (29)	142/646 (22)	26 (7 to 40)	0.007
Race				
White	293/1139 (26)	228/1128 (20)	24 (10 to 36)	0.002
Nonwhite	37/128 (29)	30/136 (22)	27 (-18 to 55)	0.20
Family history‡				
Yes	77/292 (26)	54/273 (20)	25 (-7 to 47)	0.11
No	252/971 (26)	203/986 (21)	24 (9 to 37)	0.004
Smoking				
Current	57/240 (24)	76/276 (28)	-16 (-63 to 18)	0.41
Former or never	273/1027 (27)	182/988 (18)	34 (20 to 45)	<0.001
Diabetes				
Yes	116/318 (36)	88/309 (28)	24 (-0.1 to 43)	0.05
No	214/949 (23)	170/955 (18)	24 (6 to 30)	0.009
Hypertension				
Yes	191/728 (26)	159/714 (22)	17 (-3 to 33)	0.09
No	139/539 (26)	99/550 (18)	34 (14 to 49)	0.002
Prior myocardial infarction				
Yes	237/774 (31)	182/773 (24)	27 (11 to 40)	0.002
No	93/492 (19)	76/490 (16)	19 (-10 to 40)	0.17
Aspirin use				
Yes	267/1040 (26)	217/1027 (21)	20 (4 to 33)	0.02
No	63/227 (28)	41/237 (17)	42 (14 to 61)	0.007
Beta-blocker use				
Yes	136/549 (25)	118/545 (22)	14 (-4 to 33)	0.24
No	194/718 (27)	140/719 (19)	31 (15 to 45)	<0.001
HDL cholesterol§				
<31.5 mg/dl	169/600 (28)	119/574 (21)	30 (11 to 49)	0.003
≥31.5 mg/dl	136/590 (23)	110/605 (18)	24 (2 to 41)	0.03
Triglycerides¶				
<151 mg/dl	146/595 (25)	111/589 (19)	28 (8 to 44)	0.01
≥151 mg/dl	159/595 (27)	118/590 (20)	27 (7 to 42)	0.01
LDL cholesterol				
<112 mg/dl	139/572 (24)	113/584 (19)	33 (1 to 40)	0.04
≥112 mg/dl	165/616 (27)	116/595 (19)	31 (12 to 45)	0.003
<104 mg/dl	95/404 (24)	85/405 (21)	11 (-20 to 33)	0.46
104-121 mg/dl	99/392 (25)	81/431 (19)	29 (5 to 47)	0.02
>121 mg/dl	119/417 (29)	76/377 (20)	32 (10 to 49)	0.008

*Risk reduction, 95 percent confidence interval (CI), and P value are derived from Cox models. For risk reductions, negative numbers indicate an increase in risk.

†Diabetes and hypertension were defined by clinical history.

‡A family history was defined as having one or more first-degree relatives with either myocardial infarction or sudden death before the age of 55.

§HDL cholesterol levels are shown according to the median value (31.5 mg per deciliter [0.8 mmol per liter]).

¶Triglyceride levels are shown according to the median value (151 mg per deciliter [1.7 mmol per liter]).

||LDL cholesterol levels are shown according to the median value (112 mg per deciliter [2.9 mmol per liter]) and according to the values that divide the subjects into three equal groups (<104, 104 to 121, and >121 mg per deciliter [<2.7 , 2.7 to 3.1 , and >3.1 mmol per liter]).

DISCUSSION

In this trial, among men with coronary heart disease and low HDL cholesterol levels but without high-risk LDL cholesterol levels, gemfibrozil safely reduced the risk of death from coronary heart disease or nonfatal myocardial infarction by 22 percent. Gemfibrozil also resulted in a 24 percent reduction in the combined outcome of death from coronary heart

disease, nonfatal myocardial infarction, or stroke, an effect that was consistent within nearly all of the prespecified subgroups we analyzed. The 29 percent reduction in investigator-designated stroke is similar to the 30 percent reported in trials of statins.^{1,2} Thus, the results of this study suggest that raising HDL cholesterol and lowering triglyceride levels, even without lowering the LDL cholesterol level, reduces ma-

TABLE 4. INCIDENCE OF DEATH FROM VARIOUS CAUSES AND INCIDENCE OF NEWLY DIAGNOSED CANCERS ACCORDING TO TREATMENT GROUP.

CAUSE OF DEATH OR TYPE OF CANCER	PLACEBO	GEMFIBROZIL
	(N=1267)	(N=1264)
	no. (%)	
Cause of death		
Coronary heart disease	118 (9.3)	93 (7.4)
Cancer	51 (4.0)	45 (3.6)
Respiratory disease	12 (0.9)	21 (1.7)
Stroke	9 (0.7)	3 (0.2)
Violence or accident	5 (0.4)	2 (0.2)
Other*	19 (1.5)	31 (2.5)
Unknown	6 (0.5)	3 (0.2)
Total	220 (17.4)	198 (15.7)
Type of cancer†		
Prostate	37 (2.9)	55 (4.4)
Gastrointestinal	25 (2.0)	18 (1.4)
Lung	24 (1.9)	20 (1.6)
Urinary tract	17 (1.3)	11 (0.9)
Hematologic	11 (0.9)	6 (0.5)
Head and neck	8 (0.6)	5 (0.4)
Melanoma‡	9 (0.7)	1 (0.1)
Other	8 (0.6)	15 (1.2)
Total§	138 (10.9)	125 (9.9)

*The other causes of death in the placebo group were sepsis (6 patients), aortic aneurysm (2), endocarditis (2), hepatobiliary disease (2), peripheral vascular disease (2), acquired immunodeficiency syndrome (1), aortic dissection (1), pancreatitis (1), renal failure (1), and amyotrophic lateral sclerosis (1). In the gemfibrozil group they were sepsis (10), aortic aneurysm (3), hepatobiliary disease (3), hypoxic encephalopathy (2), gastrointestinal bleeding (2), renal failure (2), peripheral vascular disease (2), Alzheimer's disease (1), pancreatitis (1), ischemic colitis (1), diabetic ketoacidosis (1), subdural hematoma (1), seizure (1), and intraoperative hemorrhage (1).

†All cancers are included except nonmelanoma skin cancers.

‡P=0.01 by chi-square analysis of the difference between groups. There were no other significant differences.

§The columns do not add up to the total number because some patients had more than one type of cancer.

major coronary events in patients whose primary lipid abnormality is a low HDL cholesterol level.

For the primary outcome, death from coronary heart disease or nonfatal myocardial infarction, the absolute risk reduction was 4.4 percent (21.7 percent for the placebo group minus 17.3 percent for the gemfibrozil group). Thus, in a population similar to the one in this study, 23 patients would need to be treated with gemfibrozil for five years to prevent one nonfatal myocardial infarction or death due to coronary heart disease (the "five-year number needed to treat"). The magnitude of the benefit of gemfibrozil in this population is similar to that of pravastatin in populations with average-to-moderately-high levels

TABLE 5. REASONS FOR DISCONTINUATION OF THE STUDY MEDICATION.*

REASON	PLACEBO	GEMFIBROZIL
	no. (%)	
Request by patient		
Side effect	79 (29)	85 (29)
Other	146 (53)	143 (49)
Decision by physician		
Concern about safety or adverse event	15 (5)	19 (7)
Other	9 (3)	13 (4)
Initiation of other lipid therapy	28 (10)	31 (11)

*Information on reasons for the discontinuation of study medication was available for 277 subjects in the placebo group and 291 in the gemfibrozil group. The percentages given are of these numbers.

of LDL cholesterol. For example, in the Cholesterol and Recurrent Events (CARE) study (average LDL cholesterol level, 139 mg per deciliter [3.6 mmol per liter]) and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study (average LDL cholesterol level, 150 mg per deciliter [3.9 mmol per liter]), the five-year numbers needed to treat to prevent one nonfatal myocardial infarction or death from coronary heart disease were 33 and 28, respectively.^{2,3} The low numbers needed to treat to prevent major cardiovascular events in our study suggest that gemfibrozil, an inexpensive medication, may prove highly cost effective, if not cost saving, for the treatment of patients with coronary heart disease who have this particular lipid profile.^{19,20} Formal cost-effectiveness analysis will be necessary to evaluate this question further.

Several possible mechanisms, including an increase in HDL cholesterol, improvement in triglyceride metabolism, and favorable effects on the size and composition of LDL and on hemostasis, might explain the observed clinical benefit. The 22 percent reduction in major cardiac events (relative to placebo) associated with a 6 percent increase in HDL cholesterol is consistent with an analysis of the results of the Helsinki Heart Study, a primary-prevention trial with gemfibrozil, which suggested that an 8 percent increase in HDL cholesterol would be expected to result in a 23 percent reduction in such events.²¹ HDL is thought to exert an antiatherogenic effect through its role in "reverse cholesterol transport," in which cholesterol from peripheral tissues, including the arterial wall, is transported back to the liver for excretion.²² HDL may also act to prevent atherosclerosis by transporting antioxidants to LDL, thus making LDL less susceptible to oxidation within the endothelium.²³ Furthermore, a low HDL cholesterol

level is often accompanied by a cluster of other abnormalities that predispose the patient to the development of atherosclerotic disease.^{24,25} Often referred to as the metabolic syndrome, these abnormalities, usually seen in the context of abdominal obesity and insulin resistance, include hypertension, diabetes, persistence of highly atherogenic postprandial triglyceride-rich remnant lipoproteins, a preponderance of dense, highly oxidizable LDL particles, and a procoagulant state.^{24,26,27} Gemfibrozil may have favorable effects on these lipid abnormalities; specifically, it decreases the fraction of dense, more oxidizable LDL particles and improves the clearance, and hence the fasting and postprandial levels, of triglyceride-rich lipoproteins, including very-low-density lipoproteins and chylomicrons.²⁸⁻³⁰ These mechanisms may have contributed to the favorable clinical effect of gemfibrozil in the population we studied, which was characterized by a high prevalence of features of the metabolic syndrome.

Gemfibrozil use was not associated with any major adverse events in this trial. The overall incidence of cancer was slightly lower among patients receiving gemfibrozil, and no specific type of cancer was significantly more common in the gemfibrozil group. In fact, melanoma was significantly less common, a finding also reported in a recent trial of lovastatin.³¹ Gemfibrozil was also associated with an 11 percent reduction in overall mortality (95 percent confidence interval, -8 to 27 percent; $P=0.23$). Although this reduction is not statistically significant, as anticipated on the basis of the sample size, it is reassuring that the trend favors gemfibrozil and that deaths due to cancer and violence were less common in the gemfibrozil group. It should be noted, however, that although gemfibrozil proved safe and effective in this population, concern about a possible increase in cancer-related deaths has been aroused by prior studies of fibrates.^{32,33} Ongoing follow-up of the population in this study will provide additional useful information about the long-term safety of gemfibrozil.

Gemfibrozil was generally well tolerated in this population of elderly men with multiple coexisting illnesses. Although significantly more patients who received gemfibrozil reported gastrointestinal upset, compliance with study medication was not significantly affected; by the end of the study, 71 percent of the patients in both treatment groups were still taking their assigned study medications. This rate compares favorably with compliance in most other long-term primary-prevention trials, including those with statins,^{31,34} but is lower than that reported from recent secondary-prevention studies.¹⁻³ Compliance may have been lower in our study than in other secondary-prevention studies because our patients had more coexisting illnesses and were probably taking more concomitant medications.

In conclusion, our study and other recent second-

ary-prevention trials give clinicians the data necessary to provide evidence-based lipid therapy for individual patients with coronary disease according to their predominant lipid abnormality. For patients with moderate or high levels of LDL cholesterol, the Scandinavian Simvastatin Survival Study and the CARE and LIPID studies demonstrate that statins reduce the incidence of major coronary events.¹⁻³ It is uncertain, however, whether statins are beneficial for patients with LDL cholesterol levels of less than 130 mg per deciliter; secondary analyses from recent trials yield conflicting results.³⁵⁻³⁷ For such patients who also have low HDL cholesterol levels, our study demonstrates that gemfibrozil results in a significant reduction in the risk of major cardiovascular events. Moreover, the 22 percent relative reduction in the risk of major coronary events observed with gemfibrozil in this population is similar to the reduction of 23 to 24 percent in risk in the two recent secondary-prevention trials of pravastatin in patients with moderate levels of LDL cholesterol.^{2,3} Thus, for patients with coronary heart disease whose primary lipid abnormality is a low HDL cholesterol level — a finding that often occurs in the context of central obesity, diabetes, and other features of the metabolic syndrome — gemfibrozil is effective for the prevention of myocardial infarction and death from coronary heart disease.

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APPENDIX

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