Insulin Resistance and Cardiovascular Events With Low HDL Cholesterol

The Veterans Affairs HDL Intervention Trial (VA-HIT)

SANDER J. ROBINS, MD[1]
HANNA BLOOMFIELD RUBINS, MD[2]
FRED H. FAAS, MD[3]
ERNST J. SCHAEFER, MD[4]
MARSHALL B. ELAM, MD[5]
JAMES W. ANDERSON, MD[6]
DOROTHEA COLLINS, SCD[7]
ON BEHALF OF THE VA-HIT STUDY GROUP

OBJECTIVE — To assess the effect of insulin resistance and the benefit of the fibrate, gemfibrozil, on the incidence of major cardiovascular events in subjects with low HDL cholesterol and a broad range of triglyceride values who participated in the Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT).

RESEARCH DESIGN AND METHODS — This intention-to-treat analysis, specified as a secondary objective in VA-HIT, determined using Cox proportional hazards models the 5-year combined incidence of nonfatal myocardial infarction, coronary heart disease (CHD) death, or stroke in relation to the presence or absence of insulin resistance (defined by the highest tertile of the homeostasis model assessment of insulin resistance, HOMA-IR) in conjunction with lower and higher levels of HDL cholesterol and triglycerides. The study population consisted of 2,283 men with known coronary heart disease (CHD), treated with either placebo or gemfibrozil, who could be subdivided into groups with diabetes with or without insulin resistance, with no diabetes but insulin resistance, and with neither diabetes nor insulin resistance.

RESULTS — With insulin resistance there was a significantly higher relative risk (RR) of a cardiovascular event both with diabetes (RR of 1.62 with 95% CI of 1.28–2.06) and without diabetes (RR of 1.43 with 95% CI of 1.03–1.98) than without insulin resistance. Throughout both lower and higher ranges of HDL cholesterol and triglycerides, the rate of new cardiovascular events and the reduction of events with gemfibrozil was greater in subjects with insulin resistance than without, despite the finding that an increase in HDL cholesterol and a decrease in triglycerides with gemfibrozil was less with insulin resistance than without insulin resistance.

CONCLUSIONS — Results show that in VA-HIT the occurrence of a new cardiovascular event and the benefit of fibrate therapy was much less dependent on levels of HDL cholesterol or triglycerides than on the presence or absence of insulin resistance.

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The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) was undertaken in men with known coronary heart disease (CHD), a low HDL cholesterol, a low LDL cholesterol, and a broad range of triglyceride values. This multicenter, placebo-controlled study demonstrated that therapy with gemfibrozil significantly reduced the incidence of nonfatal myocardial infarction (MI) and CHD death (1). In VA-HIT there was a high percentage of subjects with diabetes and features of insulin resistance with a high BMI, high waist circumference, and increased fasting concentrations of plasma insulin (2). In this study, the 5-year rate of a new cardiovascular event was highest in subjects with lowest levels of HDL cholesterol, in those with highest levels of triglycerides, and in those with diabetes or with hyperinsulinemia (3,4).

Although a low HDL cholesterol and high triglycerides are frequently found with insulin resistance with or without type 2 diabetes, there is no evidence that the risk of a cardiovascular event associated with this dyslipidemia is modified by the presence of insulin resistance. VA-HIT provided the opportunity to assess the relation of insulin resistance to the cardiovascular risk of a low HDL cholesterol and high triglycerides as well as to the effectiveness of fibrate therapy in conjunction with this dyslipidemia.

RESEARCH DESIGN AND METHODS

— The general design and procedures utilized in the VA-HIT trial have been previously reported (5). End points counted in the present analyses were the first occurrence of nonfatal MI, stroke, or CHD death. All of these events were confirmed during the course of the study by independent end point committees. All present analyses were performed by the principle of intention-to-treat and were specified as secondary objectives in the original VA-HIT study protocol. The incidence of new cardiovascular events were obtained from Kaplan-Meier survival curves for baseline concentrations of HDL cholesterol and triglycerides and the 5-year relative risk (RR) of an event was calculated from Cox proportional hazards models (6) for placebo and treatment groups that were adjusted for the traditional cardiovascular disease risk factors of age, LDL cholesterol, history of hyper-

From the [1]Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; [2]Center for Chronic Disease Outcomes Research, VAMC, Minneapolis, Minnesota; the [3]Department of Medicine, VAMC, Little Rock, Arkansas; [4]Lipid Research Laboratory, Tufts University School of Medicine, Boston, Massachusetts; the [5]Department of Medicine, VAMC, Memphis, Tennessee; the [6]Department of Medicine, VAMC, Lexington, Kentucky; and the [7]Department of Veterans Affairs Cooperative Studies Program Coordinating Center, West Haven, Connecticut.

Address correspondence and reprint requests to Sander Robins, MD, Division of Endocrinology, Nutrition, and Diabetes, Boston University School of Medicine, Evans 204, 88 East Newton St., Boston, MA 02118. E-mail: sjrobins@bu.edu.

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Abbreviations: CHD, coronary heart disease; HOMA-IR, homeostasis model assessment of insulin resistance; MI, myocardial infarction; VA-HIT, Veterans Affairs High Density Lipoprotein Intervention Trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tension, systolic blood pressure, and current smoking. The incidence of events between different groups assigned to placebo was compared by χ^2 analyses.

Fasting levels of plasma insulin and lipids were measured by a central laboratory and fasting plasma glucose by the clinical laboratory at each of 20 individual study sites. Lipids were measured by enzymatic methods that have been previously reported (3). Plasma insulin was determined as total immunoreactive insulin (Coat-A-Count Insulin; Diagnostic Products, Los Angeles, CA). A measure of insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR), was calculated as described by Matthews et al. (7) as fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5.

Diabetes was defined by history or by a fasting plasma glucose value ≥126 mg/dl at baseline. The majority of subjects with a history of diabetes were treated with either insulin (33%) or a sulfonylurea (53%). Other characteristics of the population recruited for VA-HIT have been more fully described in previous publications (1–4).

RESULTS — Insulin resistance was defined by HOMA-IR values at the highest tertile of values for all subjects in the placebo group, except those with diabetes who were treated with insulin. At the highest tertile of HOMA-IR the 5-year rate of cardiovascular events was 32% and was significantly greater than at the mid-tertile range of values, where the event rate was 23% (RR difference 1.4, 95% CI 1.1–1.9, $P = 0.01$), and at the lowest tertile range of HOMA-IR values, where the event rate was 19% (1.8, 1.4–2.5, $P = 0.0001$). There was no significant difference in the rate of cardiovascular events between the first and second tertile of HOMA-IR values ($P = 0.10$). A distribution by deciles showed no difference in the rate of events between the upper three deciles of HOMA- IR values.

Of the 2,531 men recruited for VA-HIT, 2,283 who were not being treated with insulin for diabetes had at baseline fasting measurements of plasma insulin, glucose, and lipids. Of these, 550 had diabetes by history or by a fasting plasma glucose ≥126 mg/dl, and 399 of those with diabetes who were not being treated with insulin had values of HOMA-IR in an increased range of ≥10.20. An additional 363 individuals without diabetes also had increased HOMA-IR.

Table 1—*Characteristics of subgroups with or without diabetes or insulin resistance*

	1: Diabetes with insulin resistance	2: Diabetes without insulin resistance	3: Insulin resistance without diabetes	4: All others
n	399	151	363	1,370
BMI (kg/m^2)	31.5 ± 5.4	27.5 ± 3.9	31.6 ± 4.6	27.7 ± 4.1
Waist (cm)	108 ± 13	100 ± 11	109 ± 11	99 ± 11
Glucose (mg/dl)	160 ± 37	120 ± 25	107 ± 10	97 ± 11
Insulin (μU/ml)*	44 ± 48	26 ± 7	50 ± 16	27 ± 7
HOMA-IR*	16.6 ± 22.2	8.1 ± 1.7	13.0 ± 4.3	6.5 ± 1.8
HDL cholesterol (mg/dl)	30.8 ± 5.2	30.9 ± 5.3	31.2 ± 5.4	32.0 ± 5.2
Triglycerides (mg/dl)*	164 ± 72	138 ± 64	172 ± 67	143 ± 65
LDL cholesterol (mg/dl)	108 ± 22	110 ± 24	110 ± 23	113 ± 22

Data are mean or median* ± SD for subjects not being treated with insulin who had fasting values of lipids, insulin, and glucose measured at baseline. Diabetes was defined by history or by a fasting plasma glucose ≥126 mg/dl. Insulin resistance was defined by the upper tertile level of HOMA-IR, which was associated with a significant increase in cardiovascular events (RESULTS). All values in subgroups 1 or 3 are different from subgroup 4 (at $P < 0.01$), whereas only glucose, HOMA-IR, and HDL cholesterol values in subgroup 2 are different from subgroup 4 (at $P < 0.01$). All values are different between subgroups 1 and 2 ($P < 0.001$) and between subgroups 2 and 3 ($P < 0.001$) except for LDL cholesterol and HDL cholesterol.

Major clinical and laboratory characteristics for subgroups with or without diabetes or insulin resistance are shown in Table 1. In subjects with increased levels of HOMA-IR with or without diabetes, compared with those without increased HOMA-IR, BMI was greater at 31.5 ± 5.1 compared with 27.6 ± 4.0 kg/m^2; waist circumference was higher at 109 ± 12 vs. 99 ± 11 cm; and triglycerides were higher at 170 ± 70 vs. 142 ± 65 mg/dl (all at a *P* value <0.0001). HDL cholesterol and LDL cholesterol were similar in subgroups with either diabetes or insulin resistance and were significantly lower than the subgroup with neither diabetes nor insulin resistance ($P < 0.0001$).

BMI and waist circumference were linearly correlated and waist measurements were strongly correlated with fasting insulin values (Fig. 1). The calculation of HOMA-IR, although dependent on both the concentration of fasting plasma insulin and glucose, was more strongly related to insulin ($r = 0.943$ for all subjects, exclusive of those taking insulin, and $r = 0.969$ for those without a history of diabetes) than to glucose levels ($r = 0.490$ for all subjects and $r = 0.483$ for those without a history of diabetes). Both triglycerides and HDL cholesterol were also linearly related to HOMA-IR levels. However, the range of mean values for both of these lipid measurements from the lowest to highest decile level of HOMA values was relatively small: for HDL cholesterol, values ranged from a mean of 32.4 to 30.5 mg/dl; for triglycerides, from a mean of 133 to 182 mg/dl.

The 5-year cardiovascular event rate for the placebo group (exclusive of those with diabetes who were treated with in-

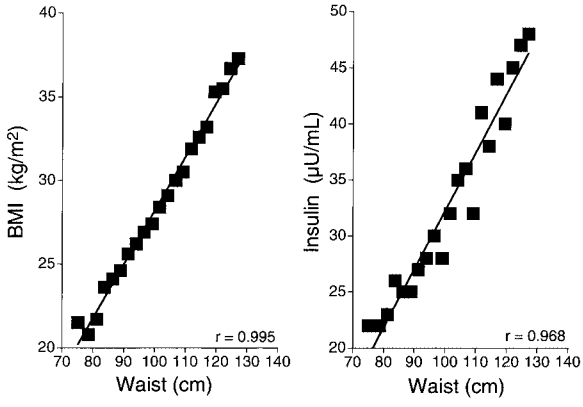

Figure 1—*Relation of mean BMI and median values of fasting plasma insulin to waist circumference measured to the nearest inch at baseline for all subjects* (n = *2,283), excluding those individuals with diabetes who were treated with insulin.*

Table 2—*Cardiovascular events in relation to insulin resistance with lower and higher risk levels of HDL cholesterol and triglycerides*

	No insulin resistance	Insulin resistance	Relative difference in events % (95% CI)	*P*
HDL cholesterol				
<31.5 mg/dl	79/344 (23.0)	75/231 (32.5)	29 (7–46)	0.012
≥31.5 mg/dl	76/404 (18.8)	50/164 (30.5)	38 (16–55)	0.002
P	0.16	0.68		
Triglycerides				
<152 mg/dl	81/418 (19.4)	49/143 (34.3)	43 (24–58)	0.0003
≥152 mg/dl	74/330 (22.4)	76/252 (30.2)	25 (2–43)	0.035
P	0.31	0.40		

Data are *n* with event/total *n* (% events) unless otherwise indicated. Values are shown for the entire placebo group with plasma insulin, glucose, and lipid values measured at baseline ($n = 1,143$). Subjects with diabetes who were being treated with insulin were excluded from analyses. HDL cholesterol and triglycerides were separated into higher and lower cardiovascular risk categories at the median value of HDL cholesterol of 31.5 mg/dl and median value of triglycerides of 152 mg/dl. Insulin resistance was defined by the highest tertile of HOMA-IR values (RESULTS). The relative difference in cardiovascular events between groups with and without insulin resistance and between lower and higher levels of HDL cholesterol and triglycerides was calculated by χ^2.

sulin) was significantly higher for subjects with insulin resistance (mean event rate of 31.7%) than without insulin resistance (mean event rate of 20.7%) (RR of 1.62, 95% CI 1.28–2.06, $P < 0.0001$). With the exclusion of all subjects with diabetes, the cardiovascular event rate was 27.7% with insulin resistance and was still significantly greater than for those without insulin resistance where the event rate was 19.8% (1.43, 1.03–1.98, $P = 0.03$).

Median values of HDL cholesterol (31.5 mg/dl) and triglycerides (152 mg/dl) at baseline were used to separate the entire placebo group into those with lower and higher values of HDL cholesterol and triglycerides, with and without insulin resistance (Table 2). Below the median, HDL cholesterol and triglycerides averaged 27.3 ± 3.0 mg/dl and 108 ± 28 mg/dl, respectively. Above the median, HDL cholesterol and triglycerides were 35.7 ± 3.6 mg/dl and 214 ± 54 mg/dl. With an increased HOMA-IR value, the cardiovascular event rate was significantly greater for all levels of HDL cholesterol and triglycerides than with lower HOMA values. In contrast, the rate of events was not any different comparing lower with higher values of either HDL cholesterol or triglycerides within either the low or high range of HOMA-IR values.

As shown for the entire VA-HIT population in Fig. 2, therapy with gemfibrozil generally resulted in a greater reduction in cardiovascular events for subjects with increased compared with lower HOMA-IR values throughout a tertile range of HDL cholesterol or triglycerides. For those with increased HOMA-IR, gemfibrozil reduced events overall by a significant 28% (95% CI 5–45, $P = 0.02$). In the absence of increased HOMA-IR, gemfibrozil resulted in a smaller 20% reduction in events (95% CI −1 to 37, $P = 0.06$). In the absence of an increased HOMA-IR, cardiovascular events were reduced more at lower levels of HDL cholesterol than at the highest level and more at the highest level of triglycerides than at lower triglycerides. In contrast, with increased HOMA-IR, gemfibrozil reduced events in no apparent pattern but more substantially at both higher levels of HDL cholesterol and lower levels of triglycerides than when HOMA-IR was not increased.

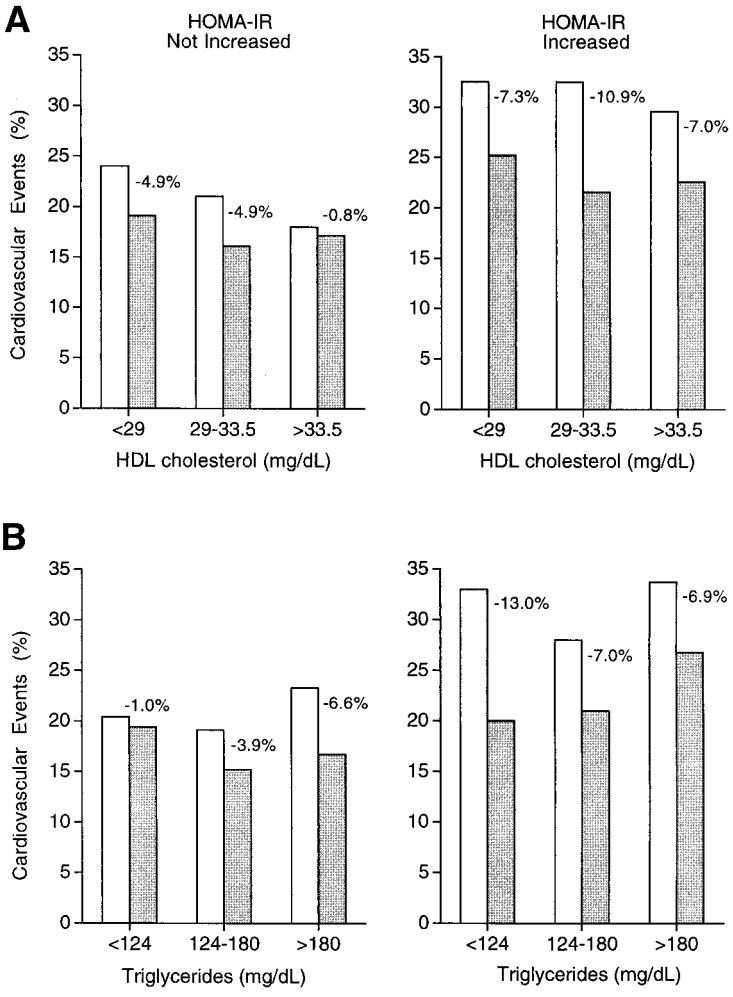

Figure 2—*The 5-year rate of cardiovascular events with placebo or gemfibrozil for tertiles of HDL cholesterol* (A) *and triglycerides* (B) *in subgroups with "not increased" or "increased" levels of HOMA-IR at baseline. Event rates are shown for the placebo group by open bars and for the gemfibrozil group by shaded bars. The absolute reduction in cardiovascular events with gemfibrozil is shown for each tertile division as a percentage change.*

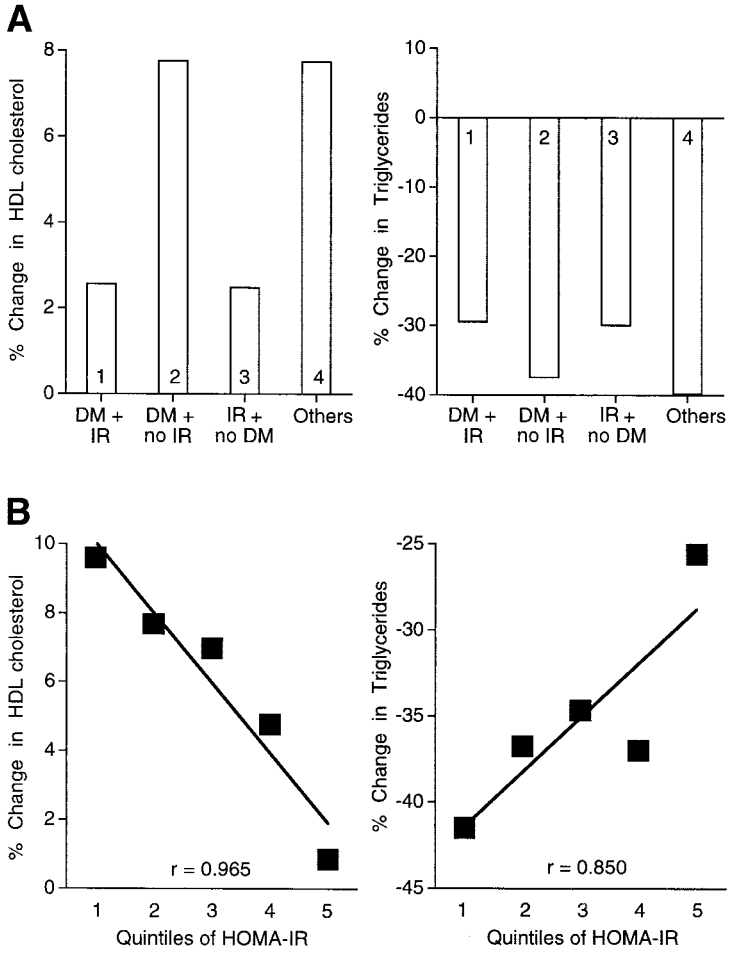

Figure 3—*Percentage change in plasma HDL cholesterol and triglycerides with gemfibrozil. The mean percent changes in HDL cholesterol and triglycerides with gemfibrozil compared with placebo from baseline to the average of on-trial values at 4, 7, 12, and 18 months is shown for the subgroups identified in Table 1* (A) *and is plotted in relation to a quintile range of HOMA-IR values* (B)*. The percent change in HDL cholesterol or triglycerides was not different comparing groups 1 with 3 or 2 with 4* (A)*. However, the change in HDL cholesterol, but not triglycerides, was significantly different comparing either group 1 or 3 with either group 2 or 4* (P = *0.004). DM, diabetes; IR, insulin resistance.*

With gemfibrozil compared with placebo, there was an increase in HDL cholesterol and a decrease in triglycerides in subgroups with diabetes, with insulin resistance, and with neither diabetes nor insulin resistance (Fig. 3). However, the magnitude of change in either HDL cholesterol or triglycerides with gemfibrozil was smaller in subgroups with than without insulin resistance ($P < 0.0001$) (Fig. 3*A*) and was inversely related to quintiles of HOMA-IR (Fig. 3*B*). Changes in LDL cholesterol with gemfibrozil compared with placebo were uniformly small (<2.0%) in all subgroups and are not shown.

CONCLUSIONS — Men who were recruited for VA-HIT with known CHD and a low HDL cholesterol also had a high prevalence of diabetes and hyperinsulinemia (2). We have reported (4) that in VA-HIT the 5-year incidence of major cardiovascular events was highest in subgroups with diabetes or highest levels of plasma insulin, and in these subgroups, therapy with gemfibrozil resulted in a greater reduction in cardiovascular events than in subgroups without diabetes or hyperinsulinemia.

The present analyses show that in VA-HIT the occurrence of new CHD events was much less dependent on the levels of either HDL cholesterol or triglycerides at baseline than on the presence or absence of insulin resistance as measured by the calculation of HOMA-IR (7). In fact, for the entire placebo group, in the absence of insulin resistance the incidence of cardiovascular events was not appreciably different between groups with either lower or higher levels of HDL cholesterol or triglycerides (Table 2). In contrast, within the same range of HDL cholesterol values or triglyceride values, there were highly significant differences in cardiovascular events between groups with and without insulin resistance.

These results would appear to be especially relevant for our understanding of the relationship of triglycerides to cardiovascular risk, which for a long time has been difficult to establish with certainty. We have reported that in VA-HIT there was a 7% increase in CHD events for every 50-mg/dl increase in triglycerides at baseline, which was of marginal significance ($P = 0.045$) (3). In the presence of increased HOMA-IR, however, for the same change in triglycerides, there was a 13% increase in CHD events ($P = 0.02$). Findings similar to ours, recently reported from the Quebec Heart Institute, show that high waist circumference on the basis of increased intra-abdominal fat is strongly related to plasma insulin levels, and that the combination of high triglycerides and high waist circumference will more accurately predict the presence of coronary artery narrowing by angiography than high levels of triglycerides alone (8).

The benefit of gemfibrozil in VA-HIT was much greater with insulin resistance than without insulin resistance at virtually all levels of HDL cholesterol or triglycerides. This response to gemfibrozil therapy clearly conforms to the results of the Helsinki Heart Study, which showed that the largest reduction of CHD with gemfibrozil in men without CHD was in those subjects with highest BMI and other features of insulin resistance (9). At this time, we have no explanation for the selectively greater benefit of gemfibrozil in the presence of insulin resistance. Some, but not all studies, have found that with fibrate therapy a reduction in triglycerides has correlated with a reduction in plasma insulin or other measures of insulin resistance (10–13). However, this correlation has generally been observed with triglyceride values in a relatively high range

(10–12). In VA-HIT, with modestly increased plasma triglycerides, a reduction in triglycerides was not associated with a change in HOMA insulin resistance, measured from baseline to 1 year (data not shown).

Gemfibrozil, like other fibric acid derivatives, is a peroxisome proliferator–activated receptor (PPAR)-α agonist that may decrease cardiovascular events by a broad range of favorable effects on plasma lipids, leading to increases in plasma HDL, decreases in triglycerides, and changes in LDL size and density. However, fibrates also increase the potential for fibrinolysis and promote a variety of anti-inflammatory actions in the arterial wall with inhibition of cytokines that mediate leukocyte adhesion to the endothelium, macrophage infiltration, and endothelium-dependent vascular relaxation (rev. in 14). Given this vast array of potentially favorable effects of fibrates, it may be difficult to implicate which, in particular, have been chiefly instrumental in the reduction by gemifobrozil of MI, stroke, and CHD death, all of which we have found to be strongly linked to insulin resistance in VA-HIT.

In clinical practice, the magnitude of increase in HDL cholesterol or decrease in triglycerides with lipid therapy continues to chiefly influence the choice of therapy as well as to provide an estimation of the success of therapy. The results of the current analyses suggest that, independent of HDL cholesterol or triglyceride values before treatment or as a result of treatment, fibrate therapy may have its optimum benefit in the presence of insulin resistance or hyperinsulinemia, which is associated with an increased rate of major cardiovascular events in both VA-HIT and populations without CHD (15–17).

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