Diabetes, Plasma Insulin, and Cardiovascular Disease

Subgroup Analysis From the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT)

Hanna Bloomfield Rubins, MD, MPH; Sander J. Robins, MD; Dorothea Collins, ScD; David B. Nelson, PhD; Marshall B. Elam, MD, PhD; Ernst J. Schaefer, MD; Fred H. Faas, MD; James W. Anderson, MD; for the VA-HIT Study Group

Background: Diabetes mellitus, impaired fasting glucose level, or insulin resistance are associated with increased risk of cardiovascular disease.

Objectives: To determine the efficacy of gemfibrozil in subjects with varying levels of glucose tolerance or hyperinsulinemia and to examine the association between diabetes status and glucose and insulin levels and risk of cardiovascular outcomes.

Methods: Subgroup analyses from the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial, a randomized controlled trial that enrolled 2531 men with coronary heart disease (CHD), a high-density lipoprotein cholesterol level of 40 mg/dL or less ($\leq 1.04 \text{ mmol/L}$), and a low-density lipoprotein cholesterol level of 140 mg/dL or less ($\leq 3.63 \text{ mmol/L}$). Subjects received either gemfibrozil (1200 mg/d) or matching placebo and were followed up for an average of 5.1 years. In this article, we report the composite end point (CHD death, stroke, or myocardial infarction).

Results: Compared with those with a normal fasting glucose level, risk was increased in subjects with known diabetes (hazard ratio [HR], 1.87; 95% confidence interval [CI], 1.44-2.43; $P = .001$) and those with newly diagnosed diabetes (HR, 1.72; 95% CI, 1.10-2.68; $P = .02$). In persons without diabetes, a fasting plasma insulin level of 39 µU/mL or greater ($\geq 271 \text{ pmol/L}$) was associated with a 31% increased risk of events ($P = .03$). Gemfibrozil was effective in persons with diabetes (risk reduction for composite end point, 32%; $P = .004$). The reduction in CHD death was 41% (HR, 0.59; 95% CI, 0.39-0.91; $P = .02$). Among individuals without diabetes, gemfibrozil was most efficacious for those in the highest fasting plasma insulin level quartile (risk reduction, 35%; $P = .04$).

Conclusion: In men with CHD and a low high-density lipoprotein cholesterol level, gemfibrozil use was associated with a reduction in major cardiovascular events in persons with diabetes and in nondiabetic subjects with a high fasting plasma insulin level.

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glucose and insulin status and the risk of major cardiovascular outcomes and to determine the efficacy of gemfibrozil in subjects with varying levels of glucose tolerance or insulin resistance, using data from the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT). Data from this secondary prevention trial are particularly relevant and unique because this study enrolled a population with a high prevalence of diabetes, an impaired fasting glucose level, and hyperinsulinemia and because of its focus on the classic dyslipidemia of type 2 diabetes (low HDL-C level and elevated triglyceride level in the absence of an elevated low-density lipoprotein cholesterol [LDL-C] level).

METHODS

OVERVIEW OF VA-HIT

The design, rationale, baseline characteristics, and major results of VA-HIT have been previously reported.12 Briefly, men younger than 74 years were eligible for the trial if they had an established diagnosis of coronary heart disease (CHD) and an HDL-C level of 40 mg/dl or less (≤1.04 mmol/L), an LDL-C level of 140 mg/dl or less (≤3.63 mmol/L), and a triglyceride level of 300 mg/dl or less (≤3.39 mmol/L). Subjects were not eligible if they were taking warfarin, had clinical chronic heart failure, or had a left ventricular ejection fraction less than 35% as determined by radionuclide ventriculogram, echocardiogram, or angiogram. In total, 2531 subjects meeting entry criteria were randomized to either gemfibrozil (1200 mg/d) or matching placebo and were then followed up for an average of 5.1 years. In this study, gemfibrozil use associated with a 22% reduction in the primary end point of CHD death and nonfatal myocardial infarction (95% confidence interval [CI], 7%-33%; P = .006) and a 24% reduction in the expanded end point of CHD death, nonfatal myocardial infarction, and confirmed stroke (93% CI, 11%-36%; P < .001). Clinical and demographic information, blood pressure, and anthropometric data were obtained by the study coordinators or investigators from the subject and/or the medical record at the baseline visit.

LABORATORY ANALYSES

Blood was drawn while subjects were fasting and was processed according to a standardized protocol.7 Frozen plasma for insulin and lipid assays was sent to a National Heart Lung and Blood Institute–Centers for Disease Control and Prevention regional network reference lipid laboratory. Total cholesterol, HDL-C, and triglycerides were measured by standardized automated enzymatic methods; LDL-C was calculated from the Friedewald formula.10 Insulin was measured as total immunoreactive insulin (Coat-A-Count Insulin; Diagnostic Products Corp, Los Angeles, Calif) using the same methodology used for Framingham Study insulin measurements.11 All biochemical assays, including the insulin assay, had within-run and between-run coefficients of variation of less than 5%. Fasting plasma insulin values were available for 2491 subjects; FPG values, which were measured at the local clinical laboratories of the 20 participating Veterans Affairs medical centers, were available for 2517 subjects. All baseline lipid measurements represent the average of 2 samples, measured 1 to 2 weeks apart. The follow-up lipid values represent the average of the measurements made at 4, 7, 12, and 18 months following randomization. Insulin and glucose values represent a single measurement at baseline.

DEFINITIONS OF GLUCOSE GROUPS

The 2517 subjects with FPG values were placed in the following mutually exclusive categories:

- **Group 1**: Diagnosed diabetes by clinical history (n = 627 [25%]). This was the diabetes group originally reported in the main results article.
- **Group 2**: Undiagnosed diabetes by an FPG level of 126 mg/dl or greater (≥7.0 mmol/L) at baseline (n = 142 [6%]).
- **Group 3**: Impaired fasting glucose by an FPG level between 110 and 125 mg/dl (6.1-6.9 mmol/L) at baseline (n = 323 [13%]).
- **Group 4**: Normal by an FPG level less than 110 mg/dl (<6.1 mmol/L) at baseline (n = 1425 [57%]).

OUTCOME DETERMINATION

The outcome for these analyses is the combined end point of confirmed major cardiovascular events defined as CHD death, nonfatal myocardial infarction, or stroke. Only the first event was counted for each subject. All investigator-suspected events were adjudicated during the trial by end point committees, who were blinded to treatment assignment and lipid levels and used standardized, predefined algorithms.12

STATISTICAL ANALYSIS

All analyses were by intention to treat. Subgroup analyses by diabetes status and FPI were preplanned, although specific cut points for the latter were not prespecified. Analysis of variance or χ² tests were used to assess the significance of differences in baseline characteristics across glucose groups. Changes in lipid levels from baseline to follow-up were compared across the 4 glucose groups using analysis of variance. Wilcoxon rank sum tests were used for nonnormally distributed variables (body mass index [BMI] and triglyceride and FPI levels). Within the placebo group, Cox proportional hazards survival analyses were used to compare the risk of an event among the different glucose groups, first unadjusted and then adjusting for covariates that either differed between the glucose groups or were associated with the outcome variable at a P value less than .10.

We explored the relationship between insulin and glucose and events in people without diabetes (groups 3 and 4), first with crude incidence rates by quartile of FPI and FPG levels (decile percentiles) and then adjusting for covariates that either differed between the 4 glucose groups or were associated with the outcome variable at a P value less than .10. For all Cox models, the proportional hazards assumption was formally confirmed. Risk reductions associated with gemfibrozil treatment (relative to placebo) were also estimated from Cox proportional hazards models for persons with diabetes (groups 1 and 2) and without diabetes (groups 3 and 4) diabetes and for subject groups stratified by FPI level. For all Cox models, the proportional hazards assumption was formally confirmed.

ROLE OF PHARMACEUTICAL SPONSOR

The study was conducted under the auspices of the Veterans Affairs Cooperative Studies Program Coordinating Center in...
West Haven, Conn, which maintained exclusive control of all data and all analyses. The pharmaceutical company that partially funded this study had no involvement in the data analysis, writing, or review of the manuscript.

INFORMED CONSENT

The protocol of this study 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 subjects gave written informed consent.

RESULTS

BASELINE CHARACTERISTICS

Baseline characteristics of the 4 glucose groups are given in the Table. Within each group, baseline characteristics were well matched between the gemfibrozil and placebo treatment arms. Compared with persons with a normal FPG level, subjects with diagnosed diabetes were older, more likely to be nonwhite and nonsmokers, and less likely to be heavy alcohol drinkers. Among these persons with diabetes, there was a higher prevalence of prior stroke, hypertension, and chronic heart failure and a higher mean BMI and waist circumference. Individuals with diabetes were more often taking angiotensin-converting enzyme inhibitors, digoxin, and calcium channel blockers but less likely to be taking aspirin or β-blockers. Finally, persons with diabetes had significantly lower HDL-C, LDL-C, and total cholesterol levels and a higher triglyceride level than those with a normal FPG level. Many of these differences, though statistically significant, may not be of clinical significance.

CHANGE IN LIPID LEVELS

Compliance with treatment regimen, which ranged between 72% and 76%, did not differ significantly between glucose groups (P = .46). Within all 4 groups, subjects assigned to gemfibrozil therapy experienced significant increases in HDL-C level and significant decreases in triglyceride and total cholesterol levels compared with placebo. However, gemfibrozil induced a lesser increase in HDL-C level and a lesser decrease in triglyceride level in persons with diagnosed diabetes compared with subjects with normal FPG level (HDL-C level,
respectively). The Wald \( \chi^2 \) test was used to compare the event rates between the 2 diabetic and 2 nondiabetic groups.

\[ \begin{array}{c|c|c|c|c}
 & 
\text{Diagnosed Diabetes} & \text{Undiagnosed Diabetes} & \text{Impaired Fasting Glucose Level} & \text{Normal} \\
\text{Total n} & 318 & 73 & 160 & 709 \\
\text{Events (n)} & 116 & 25 & 38 & 149 \\
\end{array} \]

\( +5\% \text{ vs } +8\% \) [\( P = .02 \)]; triglyceride level, \(-20\% \text{ vs } -29\% \) [\( P < .001 \)]. Low-density lipoprotein cholesterol level was not affected by gemfibrozil.

**INCIDENCE OF MAJOR CARDIOVASCULAR EVENTS BY DIABETES STATUS IN THE PLACEBO GROUP**

The effect of diabetes status on event rates in the placebo group is shown in **Figure 1**. Cumulative incidence of major cardiovascular events was higher in the 2 diabetes groups (36.5% and 34.3% for persons with diagnosed and undiagnosed diabetes, respectively) than in the nondiabetic groups (23.8% and 21% for the impaired fasting glucose and normal fasting glucose groups, respectively). The Wald \( \chi^2 \) test indicated that the rates for the 2 diabetes groups differed significantly from the rates for the 2 nondiabetic groups (\( P < .001 \)).

Using the normal FPG subjects as the reference group, we calculated the adjusted HR for major cardiovascular events in the 3 other glucose groups, controlling for age; race; smoking; alcohol use; history of hypertension; stroke; chronic heart failure; myocardial infarction; prior coronary revascularization; BMI; waist circumference; systolic blood pressure; baseline lipid levels; and the use of aspirin, digoxin, angiotensin-converting enzyme inhibitors, and calcium channel and β-blockers. The HR in persons with diagnosed diabetes was 1.87 (95% CI, 1.44 - 2.35; \( P = .001 \)) in persons with undiagnosed diabetes, 1.72 (95% CI, 1.10 - 2.68; \( P = .02 \)); and in subjects with impaired fasting glucose level, 1.15 (95% CI, 0.80 - 1.66, \( P = .46 \)). In other words, even after controlling for confounders, the risk for a major cardiovascular event was increased significantly in persons with diagnosed and undiagnosed diabetes but not in subjects with an impaired fasting glucose level.

**INCIDENCE OF MAJOR CARDIOVASCULAR EVENTS BY FPI AND FPG**

After excluding persons with diabetes (groups 1 and 2), the risk of a major cardiovascular event in the placebo group was significantly higher in the highest quartile of FPI level compared with the 3 lower level quartiles (log-rank test, \( P = .02 \)) (**Figure 2**). There did not appear to be any association between FPG level quartile and event rates.

Cox regression models were used to further assess the association between FPI and FPG levels and risk of events in persons without diabetes (\( n = 1733 \) for FPI; \( n = 1748 \) for FPG). In treatment- and age-adjusted models, an FPI level of 39 µU/mL or greater (\( > 271 \) pmol/L) was associated with a significant 31% increase in risk of events (HR, 1.31; 95% CI, 1.03 - 1.66; \( P = .03 \)), whereas FPG level was not associated with an increased risk (HR per 10 mg/dL [0.6 mmol/L] increase, 1.0; 95% CI 0.99 - 1.01; \( P = .84 \)). Further adjustment of the FPI model for elements of the metabolic syndrome and other cardiac risk factors (HDL-C, FPG, and triglyceride levels; BMI;
smoking; waist girth; and hypertension) did not substantially alter the relative risk estimate.

Efficacy of Gemfibrozil in Persons with Diabetes

The risk reductions (comparing gemfibrozil with placebo) for individuals with diabetes (groups 1 and 2) and for persons without diabetes (groups 3 and 4) are shown in Figure 3. Although gemfibrozil use was associated with a risk reduction for the combined end point in both groups, these data suggest that persons with diabetes, with a 32% risk reduction (HR, 0.68; 95% CI, 0.53-0.88; P = .004), may have benefited more than those without diabetes (18% risk reduction; HR, 0.82; 95% CI, 0.67-1.02; P = .07). Absolute risk reductions were 9.9% in the diabetes group and 3.6% in the nondiabetic group. It should be noted, however, that the interaction term (diabetes × treatment) was nonsignificant (P = .26), indicating that the risk reductions (32% and 18%) did not differ significantly. When we looked at individual end points, both groups had a comparable 21% to 22% reduction in nonfatal myocardial infarction, but persons with diabetes treated with gemfibrozil had much more dramatic reductions in CHD death and stroke than individuals without diabetes. Specifically, persons with diabetes experienced a 41% reduction in CHD death (HR, 0.59; 95% CI, 0.37-0.99; P = .046), whereas individuals without diabetes experienced nonsignificant 3% and 10% reductions for CHD death and stroke, respectively.

Efficacy of Gemfibrozil in Hyperinsulinemic Subjects Without Diabetes

The risk reductions with gemfibrozil therapy were assessed within each quartile of FPI level, as shown in Figure 4. Among these nondiabetic subjects (groups 3 and 4), gemfibrozil appeared to be most efficacious among those with the highest level of FPI. Specifically, subjects with an FPI level of 39 µU/mL or greater (≥271 pmol/L) experienced a significant 35% reduction in major cardiovascular events with therapy (HR, 0.65; 95% CI, 0.43-0.97; P = .04). Decile analysis yielded similar results. Furthermore, the interaction term between treatment and FPI was close to achieving statistical significance (P = .06).

Comment

This is the first large clinical trial to show that a fibrate significantly reduces the risk of major cardiovascular events in diabetic men with established CHD and a low HDL-C level. This finding is especially important in light of the high prevalence of dyslipidemia (low HDL-C level and high triglyceride level) in persons with diabetes and the increasing prevalence of diabetes in this country.4,5 We also report the novel observation that gemfibrozil may be particularly effective in nondiabetic men with high levels of FPI. To our knowledge, no other therapeutic interventions have been reported to reduce major cardiovascular events in nondiabetic subjects with a high FPI level, which is usually assumed to reflect an insulin-resistant state.

Efficacy of Gemfibrozil in Persons with Diabetes

We found that gemfibrozil use resulted in a significant 32% relative and 10% absolute reduction in major cardiovascular events (nonfatal myocardial infarction, CHD death, and stroke) in persons with diabetes. This suggests that only 10 people with diabetes and CHD would need to be treated with gemfibrozil for 5 years to prevent 1 major cardiovascular event. Interestingly, gemfibrozil appeared to be more effective in preventing CHD death and strokes (risk reductions of 40%) than nonfatal myocardial infarctions (risk reduction of 22%).

It is also interesting to note that the clinical efficacy of gemfibrozil was more pronounced in subjects with diabetes than in those without despite the fact that gemfibrozil’s effect on lipids was less pronounced (ie, lesser...
reduction in triglyceride level and lesser increase in HDL-C level in diabetic compared with nondiabetic persons). Other studies have also noted a possible lesser effect of gemfibrozil on HDL-C and triglyceride levels in persons with diabetes compared with those without. Furthermore, fibrates have additional nonlipid effects (eg, on inflammatory and thrombotic processes) that affect the development of atherosclerotic lesions and the occurrence of clinical events, it is not unexpected that medication-related changes in lipid levels only partially explain clinical efficacy. Atherosclerosis and acute coronary events in persons with diabetes may be mediated by other pathophysiological mechanisms that might be particularly responsive to gemfibrozil. There is evidence, for example, that diabetes is associated with a prothrombotic state due to a variety of mechanisms involving fibrinogen, plasminogen activator inhibitor, and platelet function. Fibrates, which are known to favorably affect these parameters, may thus be particularly effective in individuals with diabetes. Furthermore, the atherogenic process in diabetes may be related to abnormalities in lipid metabolism (eg, preponderance of small dense LDL particles and postprandial hypertriglyceridemia) that are favorably affected by gemfibrozil but are not reflected in standard lipid measurements.

Previous large trials of cholesterol-lowering therapy have focused primarily on populations with elevated cholesterol levels, testing agents such as 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors (statins) intended to lower LDL-C level. As a consequence of the emphasis on LDL-C level and other entrance criteria, these trials enrolled relatively small numbers of persons with diabetes, fewer than 10% in all major recent studies with the exception of 1 trial in which individuals with diabetes comprised 14% of the study population. Nevertheless, in several of these trials, statins have been shown to reduce the risk of major cardiac events in persons with diabetes with moderate to high levels of LDL-C (ie, >130 mg/dL [>3.37 mmol/L]). Other trials of fibrates also included relatively small numbers of persons with diabetes. The Helsinki Heart Study, a primary prevention trial, enrolled 135 persons (approximately 3%) with diabetes. The Bezafibrate Infarct Prevention Trial, a secondary prevention study that did not show an overall significant risk reduction, a subgroup of subjects with a high triglyceride level had a significant 40% relative risk reduction with bezafibrate use. Thus, data from several trials indicate that fibrate use may be particularly beneficial in subjects with features of the insulin resistance syndrome. Although gemfibrozil does not appear to directly improve insulin sensitivity, presumably the same putative mechanisms that underlie its enhanced efficacy in diabetes (discussed in the “Efficacy of Gemfibrozil in Persons With Diabetes” section) are also operative in this population. It should be noted, however, that these are all post hoc analyses; prospective trials specifically designed to examine the efficacy of fibrates in nondiabetic subjects with hyperinsulinemia will be required to confirm these observations.

**DIABETIC STATUS AND RISK OF CARDIOVASCULAR EVENTS**

Our finding of a 33% 5-year incidence rate for major cardiovascular events in persons with diabetes confirms previous reports of a very high incidence of cardiovascular morbidity and mortality in this group. In the present study we did not find an association between FPG level and cardiovascular events in subjects without diabetes. Lack of an association is consistent with some but not all previous investigations of the relationship between fasting glucose and cardiovascular event rates in nondiabetic people. A recent meta-analysis of prospective cohort studies concluded that glucose is a significant predictor of cardiovascular events even below the diabetic threshold. However, it appears that this conclusion can be more strongly supported for 2-hour glucose than for fasting glucose level. In this meta-analysis, an FPG level of 110 mg/dL (6.1 mmol/L) was associated with a significant 33% increased risk of cardiovascular events compared with a level of 75 mg/dL (4.2 mmol/L). However, when more rigorous criteria to exclude undiagnosed diabetes were used, this association was no longer statistically significant. Similarly and more recently, the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) Study, a large collaborative European epidemiologic study, did not find a relationship between FPG and cardiovascular mortality, although it did find a significant relationship between 2-hour glucose level and this end point. Thus, de-
HYPERINSULINEMIA AND RISK OF CARDIOVASCULAR EVENTS

Our study is the largest of only a few prospective studies to explore the impact of fasting hyperinsulinemia on cardiovascular events in men with a known history of CHD. The importance of insulin as a cardiac risk factor is controversial. Hyperinsulinemia was first identified as an independent risk factor for cardiovascular disease 20 years ago; subsequent epidemiologic data, however, have not consistently confirmed this early observation. The lack of consistency between studies may reflect different populations (eg, age distribution), use of different measures of insulin resistance (eg, fasting, random nonfasting, and 2-hour postload insulin levels), failure to rigorously exclude individuals with diabetes, and differences in the variables available for multivariate analyses.

Our finding that high FPI level was associated with a significant though potentially modest increase in risk (HR around 1.3) is similar to a recent report from the Kuopio Ischaemic Heart Disease Study. In the present study, this association remained significant in some adjusted analyses but not in others. This observation is consistent with the hypothesis that the “independence” of the association between FPI level and cardiovascular outcomes is highly dependent on what other risk factors are included in the analysis. Nevertheless, while FPI level may or may not be an independent predictor, many authorities, including the authors of the recent NCEP III treatment guidelines, believe that the cluster of risk factors associated with insulin resistance, known as the metabolic syndrome, identifies a group at particularly high risk of cardiovascular disease.

LIMITATIONS

The findings reported herein should be considered in the context of certain limitations. First, these data were derived from a clinical trial that enrolled an elderly male population; the findings may not apply to women and younger people. Second, while we had planned in advance to perform subgroup analyses based on diabetic status and FPI, we did not prespecify the exact cut points that would be used in the analysis. Third, we classified subjects into glucose and insulin categories based on a single measurement, which may have led to misclassification. Nevertheless, in epidemiologic analysis, this misclassification tends to lead to an underestimate rather than an overestimate of risk due to the effect of regression dilution bias. Finally, the analyses of gemfibrozil efficacy for individual end points and for subgroups based on FPI levels are based on relatively small numbers of end points and should therefore be considered as preliminary observations only.

CONCLUSIONS

In conclusion, this subgroup analysis from VA-HIT shows that gemfibrozil use significantly reduces the risk of major cardiovascular events in diabetic men with established CHD and low levels of HDL-C. These data also suggest that gemfibrozil use may reduce cardiac events in nondiabetic men with high levels of FPI. These findings are of particular significance in light of the growing awareness of the high cardiac risk faced by these groups and of the importance of developing new prevention strategies to minimize that risk.

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From the Center for Chronic Disease Outcomes Research, Veterans Affairs Medical Center, Minneapolis, Minn; the Department of Medicine, Boston University School of Medicine, Boston, Mass; the Department of Veterans Affairs Cooperative Studies Program Coordinating Center, West Haven, Conn; the Department of Medicine, Veterans Affairs Medical Center, Memphis, Tenn; the Lipid Research Laboratory, Tufts University School of Medicine, Boston; the Department of Medicine, Veterans Affairs Medical Center, Little Rock, Ark; and the Department of Medicine, Veterans Affairs Medical Center, Lexington, Ky. A complete list of the members of the VA-HIT Study Group was published previously (N Engl J Med. 1999;341:410-418).

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Corresponding author and reprints: Hanna Bloomfield Rubins, MD, MPH, Section of General Internal Medicine (1110), Veterans Affairs Medical Center, 1 Veterans Dr, Minneapolis, MN 55417 (e-mail: bloom013@umn.edu).

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