DYSLIPIDEMIA, PREDIABETES, AND TYPE 2 DIABETES: CLINICAL IMPLICATIONS OF THE VA-HIT SUBANALYSIS

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ABSTRACT

The most serious and common complication in adults with diabetes is cardiovascular disease (CVD), which includes coronary heart disease, peripheral vascular disease, and stroke. Growing clinical evidence suggests that patients who have impaired glucose tolerance and impaired fasting glucose but who do not meet the diagnostic criteria for diabetes are also at increased risk for CVD, even in the absence of established diabetes. Also at risk are individuals with the metabolic syndrome.

This article provides a review of the current clinical evidence supporting correction of the dyslipoproteinemias seen in type 2 diabetes in order to achieve reduced coronary risk. The article also reports on the recent Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) substudy, the first to report on any therapeutic intervention to prevent clinical cardiovascular events in nondiabetic subjects with a high fasting plasma insulin level. Based on these findings, a case is made for aggressive intervention in prediabetic populations, including those with the metabolic syndrome, not only to prevent the progression to type 2 diabetes, but to reduce overall cardiovascular risks (Adv Stud Med. 2003;3(4A):S228-S233)

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The American Diabetes Association estimates that 17 million Americans have diabetes, 6 million of whom are undiagnosed. Based on recent trends seen in this population, this number has been projected to increase to 29 million by 2050. The most common and serious effect of diabetes in adults is cardiovascular disease (CVD). In fact, the leading cause of death in patients with diabetes is CVD. Patients with diabetes have a 2- to 4-fold higher risk of myocardial infarction (MI) and stroke, and are 3 to 4 times more likely to die from coronary heart disease (CHD) than individuals without diabetes. This evidence has prompted the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) to identify diabetes as a CHD risk equivalent, calling for more intense treatment strategies for this population.

Further compounding the considerable public health burden of diabetes are those patients who have above-normal blood glucose levels that do not meet the diagnostic criteria for diabetes. The cause of type 2 diabetes is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. In the latter category, a degree of hyperglycemia and hyperinsulinemia may be present without clinical symptoms for a long period of time before diabetes is detected, while causing pathologic and functional changes in various target tissues. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load. Since this may be inconvenient, criteria have been established for fasting glucose.

The terms impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) refer to a metabolic
stage intermediate between normal glucose homeostasis and diabetes, now referred to as prediabetes. This stage includes individuals who have IGT and individuals with fasting glucose levels $\geq 110$ mg/dL but $<126$ mg/dL. Impaired fasting glucose and IGT are not clinical entities in their own right (except in pregnant women), but rather risk factors for future diabetes. It is estimated that at least 16 million Americans have prediabetes, in addition to the 17 million with diabetes.

Whereas lifestyle and diet interventions are often recommended in such patients to prevent progression to the more serious disease state of diabetes, we now know that IGT and IFG, in and of themselves, pose significant risks to patients’ health. IFG and IGT are associated with increased risks for progressive deterioration in glucose metabolism and for CVD. Yet, clinicians also recognize that patients frequently are unable to sustain lifestyle interventions. Still, others, no matter how rigorous in their efforts to maintain a healthful lifestyle, fail to improve the dyslipidemia typically associated with insulin resistance: high triglyceride levels and low high-density lipoprotein cholesterol (HDL-C). Pharmacologic interventions for such patients become a clinical consideration.

Several subgroup analyses of many of the CHD prevention randomized trials have reported the benefits of lipid-lowering therapy in type 2 diabetes, but few studies have been large enough to also evaluate individuals with insulin resistance. The Scandinavian Simvastatin Survival Study (4S) included a significant number of subjects with diabetes and was large enough to also evaluate individuals with IFG. Patients with diabetes who were treated with statin therapy showed a 42% reduction in risk for major coronary events and those with IFG showed a 38% risk reduction. Among the study’s 4,444 subjects, 678 met criteria for IFG, defined as fasting glucose from $\geq 110$ mg/dL to 125 mg/dL. Compared with the 335 placebo-treated IFG subjects, the 343 simvastatin-treated IFG subjects had significantly reduced total mortality, coronary mortality, major coronary events, and need for revascularizations. A subgroup analysis of the Cholesterol and Recurrent Events (CARE) study of 342 subjects with IFG and a history of MI showed their risks for most coronary events were lower with statin therapy, but the small sample size did not allow for statistically significant findings when compared with subjects treated with placebo. In diabetic subjects with average cholesterol levels, pravastatin treatment reduced the absolute risk of coronary events by 25%.

While limited data is available surrounding statin therapy and CHD in diabetic and prediabetic subjects, until recently the Helsinki Heart Study was the only published analysis of the benefits of primary prevention with fibrate therapy that included patients with diabetes. The 135 patients with non-insulin-dependent diabetes mellitus (NIDDM) who participated in the study showed a trend toward reduced risk for a CHD event. Among the NIDDM patients, 2 taking gemfibrozil (3.4%) and 8 taking placebo (10.5%) had a CHD event during the trial ($P = .19$). The small number of events did not permit an adequate assessment of benefit in NIDDM in this trial.

A separate, post-hoc analysis of this study showed that gemfibrozil was effective primarily in subjects whose body mass index (BMI) was $>26$ kg/m$^2$; among overweight subjects, those with a high triglyceride level and a low HDL level achieved the greatest risk reduction (78%; $P = .002$). A subsequent study, the Diabetes Atherosclerosis Intervention Study (DAIS), was conducted to determine whether correction of the dyslipoproteinemia seen in type 2 diabetes (ie, increased triglycerides and low HDL concentrations) would decrease the rate of angiographic progression of coronary artery disease. The investigation was a double-blind, placebo-controlled study of subjects with controlled type 2 diabetes and mild lipoprotein abnormalities who were given micronised fenofibrate (200 mg/day) or placebo for at least 3 years. Haf of the subjects had no previous clinical coronary disease. The study showed that subjects who received fenofibrate therapy ($n = 207$) experienced a significant change from baseline in total plasma cholesterol, HDL and low-density lipoprotein (LDL), and triglyceride concentrations than subjects in the placebo group ($n = 211$) (Figure). Although the sample and the number of events were too small to allow definitive conclusions about clinical endpoints, the fenofibrate group showed a consistent pattern of reduction in cardiac endpoints. Subjects treated with fenofibrate showed significantly less progression in minimum lumen diameter and percentage diameter stenosis than the placebo group, features indicative of localized coronary artery disease. The investigators concluded that these findings support the value of correcting mild lipid abnormalities that are widely considered to be unimportant in patients with diabetes.
A recently-published substudy of findings from the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) (which enrolled more subjects with diabetes, IFG, and hyperinsulinemia than previous trials) was undertaken because of its focus on the dyslipidemia associated with type 2 diabetes. The objectives of this study were to:

1. Examine the association between glucose and insulin status and the risk of major cardiovascular outcomes, and
2. Determine the efficacy of gemfibrozil in subjects with varying levels of glucose tolerance or insulin resistance.

The VA-HIT is the first large clinical trial to demonstrate that a fibrate significantly reduces the risk of major cardiovascular events in patients with diabetes with established CHD and low HDL-C levels, as well as the first to report on any therapeutic intervention to prevent clinical cardiovascular events in nondiabetic subjects with a high fasting plasma insulin level.

OVERVIEW OF VA-HIT AND SUBSTUDY FINDINGS

The VA-HIT Subanalysis is reprinted in its entirety in this journal. To summarize, the VA-HIT study randomized 2531 subjects to either gemfibrozil (1200 mg/d) or placebo and were evaluated for an average of 5.1 years. Inclusionary criteria were men age <74, an established diagnosis of CHD, an HDL-C level of ≤40 mg/dL, an LDL-C level of ≤140 mg/dL, and a triglyceride level of 300 mg/dL or less. Exclusionary criteria included warfarin use, clinical chronic heart failure, or a left ventricular ejection fraction <35% as determined by radionuclide ventriculogram, echocardiogram, or angiogram.

Fasting plasma glucose (FPG) values were available for 2517 subjects, who were categorized in 1 of the following 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 at baseline (n = 142 [6%]).

Group 3: IFG diagnosed by an FPG level between 110 and 125 mg/dL at baseline (n = 323 [13%]).

Group 4: normal per an FPG level <110 mg/dL at baseline (n = 1425 [57%]).

Study endpoints for this subgroup analysis included confirmed major cardiovascular events: CHD death, nonfatal MI, or stroke. Only the first event was counted for each subject.

Efficacy of Gemfibrozil in Subjects with Diabetes

When compared with placebo, subjects with diabetes (groups 1 and 2) taking gemfibrozil (n = 769) showed a 32% risk reduction for combined endpoints (95% confidence interval [CI], 0.53-0.08; P = .004), as compared with an 18% risk reduction (n = 1748; 95% CI, 0.67-1.02; P = .07) in subjects without diabetes (groups 3 and 4). Despite appearances of a more dramatic risk reduction in subjects with diabetes, the difference in risk reductions between the diabetic and nondiabetic groups did not reach statistical significance as the interaction term (diabetes x treatment) was nonsignificant (P = .26). However, since the coronary event rate was much higher in the diabetic than nondiabetic group, absolute risk reductions were substantially stronger: 9.9% in the diabetes group compared with 3.6% in the nondiabetic group. It would be
expected that this large difference between absolute benefit in diabetic and nondiabetic subjects is statistically significant, although the P value was not reported.

When evaluated in terms of individual as opposed to combined endpoints, both groups had a comparable 21% to 22% reduction in nonfatal MI, but subjects with diabetes treated with gemfibrozil experienced much more dramatic reductions in CHD death and stroke than subjects without diabetes. Subjects with diabetes experienced a 41% reduction in CHD death (95% CI, 0.39-0.91; P = .02) and a 40% reduction in stroke risk (95% CI, 0.37-0.99; P = .046). Subjects who did not have diabetes experienced nonsignificant 3% and 10% reductions for CHD death and stroke, respectively.

**Efficacy of Gemfibrozil in Hyperinsulinemic Subjects without Diabetes**

Among nondiabetic subjects (groups 3 and 4), gemfibrozil appeared to be most effective in those with the highest level of fasting plasma insulin (FPI). Those with an FPI level of ≥39 µU/mL experienced a 35% reduction in major cardiovascular events with gemfibrozil (95% CI, 0.43-0.97; P = .04). The interaction term between treatment and FPI was close to achieving statistical significance (P = .06), suggesting enhanced benefit in patients with progressively higher fasting insulin.

**Discussion of Study Findings**

The VA-HIT study is an important study that identified a population at very high risk for heart disease, despite low LDL levels. The population predominantly was overweight with insulin resistance, high glucose, and low HDL levels. That specific population had not previously been targeted for study or for therapy. The subanalysis identifies a subpopulation of patients with type 2 diabetes, prediabetes, or obesity that is at even higher risk than that identified in the original study. The findings from these 2 studies represent a significant advance in our therapeutic approach to these populations. The subanalysis, in particular, represents a good scientific case for the special effectiveness of fibrate therapy in patients with IGT and IFG, as well as those with the metabolic syndrome.

The ATP III guidelines define the metabolic syndrome as a potential secondary target of therapy following the achievement of LDL goals. Together, the risk factors for the metabolic syndrome, shown in the Table, enhance the risk for CHD. The guidelines base diagnosis of the metabolic syndrome on the presence of ≥3 risk factors. Of particular note is that ATP III has raised the HDL risk cutpoint for women to <50 mg/dL and set the cutpoint for men at <40 mg/dL. This adjustment reflects the disparity between sexes; women tend to have higher HDL levels than men. Management of the metabolic syndrome emphasizes reduction of its underlying causes, obesity and sedentary lifestyles, with intensified efforts to improve diet and exercise habits. A second treatment objective of the metabolic syndrome is to treat associated nonlipid and lipid risk factors. The incidence of type 2 diabetes has been reduced by 58% with weight reduction and increased physical activity. However, lifestyle interventions are ineffective for some patients, particularly those who are noncompliant or unable to sustain efforts over the long term.

Whereas statins have proven to be highly effective in treatment of elevated LDL levels, they are less effec-
tive in treating secondary lipid targets of HDL-C and triglycerides. Too frequently, a patient who has an LDL level that is below the target level for treatment or who has achieved goal with lifestyle changes and/or statin therapy is not treated further. Yet, given the significant coronary risks posed by suboptimal non-LDL lipids, clinicians who fail to treat such patients are putting them at risk for future coronary events. Fibrate therapy has proven to be a safe and effective therapeutic choice for improving low HDL and elevated triglycerides and should be considered, particularly in view of ATP III’s new focus on elevated triglyceride levels. The guidelines set a lower range for acceptable triglyceride levels and emphasize treatment of moderate elevations. Specifically, a triglyceride level of <150 mg/dL is normal, 150 to 199 mg/dL is borderline high, 200 to 499 mg/dL is high, and ≥500 mg/dL is very high. The ATP III guidelines recommend that the primary aim of therapy for patients with elevated triglyceride and low HDL levels is to reach the target LDL-C level. If the LDL-C goal is achieved but the triglyceride level is ≥200 mg/dL, a second goal of non-HDL-C is set, which might be achieved with higher doses of a statin or the addition of nicotinic acid or fibrate. In cases of isolated low HDL, the guidelines suggest that physicians should consider treating with fibrates or nicotinic acid.

Despite the medical evidence supporting the use of fibrates as part of either a combination or monotherapy regimen, anecdotal reports suggest that they are significantly underutilized in clinical practice. Typically, clinicians are uncertain about which patients can benefit from fibrate therapy or whether statin therapy alone is adequate for management of dyslipidemia. The VA-HIT subanalysis identifies clearly the patients who do benefit: those with prediabetes as suggested by IGT, IFG, and the metabolic syndrome.

Whereas type 2 diabetes can be controlled with diet, exercise, and drug therapy, it is a permanent condition for most patients since the full potential of diet and exercise often is not realized. Primary prevention represents the most potent opportunity for addressing the significant risks associated with this growing public health problem. The progression from impaired carbohydrate metabolism to the development of diabetes is not inevitable, but it depends wholly on adept management by an informed clinical community as well as enhanced efforts to educate patients about the overall lipid profile and the risks associated with the metabolic syndrome.

It is equally important for providers to recognize that the overriding goal is not simply to prevent diabetes, but also to reduce cardiovascular risks. The prospective San Antonio Heart Study demonstrates that nondiabetic people who convert to type 2 diabetes have dyslipidemia, high blood pressure, and obesity confirming their high risk. The results also show that atherogenic changes in the prediabetic state are mainly seen in insulin-resistant subjects rather than those with impaired pancreatic insulin secretion. These findings are further supported by the VA-HIT subanalysis, which shows that suboptimal glucose homeostasis and the presence of the metabolic syndrome, in and of themselves, warrant aggressive clinical management.

REFERENCES

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