Treating Diabetic Dyslipidemia with Gemfibrozil for Secondary Prevention of Coronary Heart Disease

Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs High-Density Lipoprotein Intervention Trail (VA-HIT). Arch Intern Med 2002;162:2597–604.

Study Overview

Objective. To determine the efficacy of gemfibrozil on secondary prevention of cardiovascular outcomes in patients with low levels of high-density (HDL) and low-density lipoprotein cholesterol (LDL) with and without diabetes and with varying levels of fasting insulin.

Design. Subgroup analysis of the VA-HIT randomized controlled trial [1].

Setting and participants. 769 men with diabetes, 323 men with impaired fasting glucose, and 1425 men with normal fasting glucose, all of whom had documented coronary heart disease (CHD), were younger than 74 years old, lacked serious comorbidities, had an HDL level of 40 mg/dL or lower, and had an LDL level of 140 mg/dL or lower.

Intervention. Patients were randomized to gemfibrozil (1200 mg/day) or placebo and were followed for an average of 5.1 years.

Main outcome measures. The main outcome was the combination of cardiovascular death, nonfatal myocardial infarction, or stroke. Endpoints were examined in subgroups with various levels of fasting glucose and insulin and patients with and without diabetes.

Main results. Events were reduced 32% (hazard ratio [HR], 0.68 [95% confidence interval {CI}, 0.53–0.88]) in patients with diabetes and 18% (HR, 0.82 [95% CI, 0.67–1.02]) in patients without diabetes. Among patients without diabetes, higher fasting insulin levels were associated with greater risk reduction with gemfibrozil (P = 0.06). Although they benefited more, numerical improvements in HDL and triglycerides were smaller in patients with diabetes than those without.

Conclusion. In patients with CHD, low HDL, and low LDL, gemfibrozil appeared to be especially effective in reducing future cardiovascular events in patients with diabetes or with high fasting insulin levels.

Commentary

Patients with diabetes and CHD are at very high risk for future cardiovascular events and deserve particular attention to secondary prevention. Although adults with diabetes and the "metabolic syndrome" frequently have low HDL and high triglyceride levels, LDL lowering still remains the primary goal of treatment [2]. The best approach to lipid management for this group when LDL is below 130, however, is less clear.

This subgroup analysis extends the earlier findings of the VA-HIT trial in an important way. In the original report, the 24% risk reduction in the group with previously diagnosed diabetes was identical to the risk reduction in the rest of the trial population [1]. In this new report, the VA-HIT investigators grouped together patients with diagnosed and undiagnosed diabetes, resulting in quite different estimates of risk reduction in the diabetic versus nondiabetic groups (32% [95% CI, 12%–47%] versus 18% [95% CI, -2%–33%], respectively). While this study was not large enough to exclude the possibility that this difference was due to chance, it suggests that gemfibrozil is particularly beneficial for adults with diabetes who fit this lipid pattern. In patients without diabetes, the trend towards greater benefit from gemfibrozil with increasing levels of fasting insulin provides additional evidence that this drug is especially helpful in patients with the metabolic syndrome.

These findings are important in light of the fact that statin therapy has not been clearly shown to reduce the risk of future events when the LDL level is below 125 mg/dL [3,4]. It is also notable that the risk reduction in patients with diabetes was seen despite the fact that there was only a modest reduction in serum triglycerides (33 mg/dL), a small rise in HDL (1.6 mg/dL), and no change in LDL in the group with diabetes.

Applications for Clinical Practice

Treatment with the fibric acid derivative gemfibrozil is likely to benefit patients with CHD and diabetes who have low levels of HDL and LDL. These benefits may occur even as traditional lipid measures change only modestly. The role of combination therapy for diabetic dyslipidemia requires further study.

–Review by Stephen D. Persell, MD

References

1. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high–density lipoprotein cholesterol. Veterans Affairs High-Density Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341:410–8.
2. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
3. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001–9.
4. Sacks FM, Moye LA. Davis BR, et al. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events trial. Circulation 1998;97:1446–52.