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Perspective

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# Fibrates in the Treatment of Dyslipidemias — Time for a Reassessment

Allison B. Goldfine, M.D., Sanjay Kaul, M.D., and William R. Hiatt, M.D.

Lowering the concentration of low-density lipoprotein (LDL) cholesterol with statins substantially reduces the rate of cardiovascular events among patients with underlying cardiovascular disease or other risk factors. Yet a substantial risk persists, suggesting that additional lipid-modifying interventions may be needed. High triglyceride levels and low levels of high-density lipoprotein (HDL) cholesterol independently correlate with increased cardiovascular risk, and data from the National Health and Nutrition Examination Survey show that approximately 7% of the U.S. population has combined dyslipidemia of high triglycerides (≥200 mg per deciliter) and low HDL cholesterol (<40 mg per deciliter in men, <50 mg per deciliter in women). However, the clinical benefit of modulating these levels with agents such as niacin, fibrates, or cholesteryl ester transfer protein inhibitors has not been firmly established. Fibrates were introduced more than 35 years ago in Europe, where their regulatory approval was based on favorable changes in the lipid profile, yet there remains considerable controversy regarding their clinical efficacy. Two randomized, placebo-controlled trials of gemfibrozil demonstrated improvements in cardiovascular outcomes,[1,2] but subsequent trials of bezafibrate and fenofibrate showed no significant overall cardiovascular benefit over placebo (see Table 1).[3-5]

The Food and Drug Administration (FDA) first approved fenofibrate (Tricor) in 1993 for severe hypertriglyceridemia. In 1999, fenofibrate was approved for reducing LDL cholesterol, triglyceride, total cholesterol, and apolipoprotein B levels and increasing HDL cholesterol levels in patients with primary hypercholesterolemia or mixed dyslipidemia. Fenofibric acid, the active ingredient of fenofibrate, was approved in 2008 as Trilipix, and similar indications were added for previously approved fenofibrate products. Fenofibric acid is the only fibrate approved for use with a statin for reducing triglyceride levels and raising HDL cholesterol levels in patients with mixed dyslipidemia and coronary heart disease or those who have equivalent risk levels and are receiving optimal statin therapy. This approval was based on three short-term studies examining the agent's effects on lipid variables, but so far there are no data on direct clinical outcomes to support this indication.

The Action to Control Cardiovascular Risk in Diabetes

**Table 1. Cardiovascular Outcomes in Fibrate Trials.***

| Trial | Fibrate | Follow-up | Patient Population | Primary End Point | Absolute Event Rate (%) | | Risk Ratio (95% CI) | P Value |
|---|---|---|---|---|---|---|---|---|
| | | yr | | | Control | Fibrate | | |
| HHS (1982) | Gemfibrozil, 1200 mg | 5.0 | 4081 men with non-HDL cholesterol ≥200 mg/dl (primary prevention) | Fatal or nonfatal MI, or CAD death | 84/2030 (4.1) | 56/2051 (2.7) | 0.66 (0.47–0.92) | <0.02 |
| VA-HIT (1991–1993) | Gemfibrozil, 1200 mg | 5.1 | 2531 men with CAD and HDL cholesterol <40 mg/dl (secondary prevention) | Nonfatal MI or CAD death | 275/1267 (21.7) | 219/1264 (17.3) | 0.78 (0.65–0.95) | 0.006 |
| BIP (1990–1992) | Bezafibrate, 400 mg | 6.2 | 3090 men and women with previous MI or angina (secondary prevention) | Fatal or nonfatal MI or sudden death | 232/1542 (15.1) | 211/1548 (13.6) | 0.91 (0.76–1.08) | 0.26 |
| FIELD (1998–2000) | Fenofibrate, 200 mg | 5.0 | 9795 men and women with type 2 diabetes (primary and secondary prevention) | Nonfatal MI or CAD death | 288/4900 (5.9) | 256/4895 (5.2) | 0.89 (0.75–1.05) | 0.16 |
| ACCORD (2001–2005) | Fenofibric acid, 160 mg | 4.7 | 5518 men and women with type 2 diabetes on statin therapy (primary and secondary prevention) | Nonfatal MI, nonfatal stroke, or death from cardiovascular causes | 310/2765 (11.2) | 291/2753 (10.6) | 0.92 (0.79–1.08) | 0.32 |

* ACCORD denotes Action to Control Cardiovascular Risk in Diabetes trial, BIP Bezafibrate Infarction Prevention study, CAD coronary artery disease, FIELD Fenofibrate Intervention and Event Lowering in Diabetes study, HHS Helsinki Heart Study, MI myocardial infarction, and VA-HIT Veterans Affairs High-Density Lipoprotein Intervention Trial.

(ACCORD) trial was funded by the National Institutes of Health primarily to evaluate the benefit of intensive glycemic control in patients with type 2 diabetes and high risk for cardiovascular disease. The ACCORD-Lipid substudy was designed to determine whether combination therapy with a statin plus fenofibrate would reduce the risk of cardiovascular events as compared with statin monotherapy: it had been observed that at any given LDL cholesterol level, patients with diabetes have excess cardiovascular risk, and it seemed possible that the addition of a fibrate would improve lipid composition and outcomes in this population. After a mean follow-up of 4.7 years, fenofibrate plus simvastatin had not significantly decreased the rate of the primary outcome of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke as compared with simvastatin alone.[5] However, a prespecified subgroup analysis showed a 31% reduction in the rate of the primary outcome among the 17% of patients with baseline triglyceride levels above 204 mg per deciliter and HDL cholesterol levels below 34 mg per deciliter. This finding is consistent with subgroup analyses from previous fibrate-monotherapy trials (see Table 2) and suggests that elevated triglyceride and low HDL cholesterol levels may be required for these agents to be clinically effective. There was a differential response between the sexes, however: among women, the primary outcome rate increased by 38%, whereas it decreased by 18% among men. This effect was not seen in the fenofibrate-monotherapy FIELD trial, and other studies included insufficient numbers of women for such an analysis.

The FDA's Endocrine and Metabolic Drug Advisory Panel (on which we serve) was convened on May 19, 2011, to review the results of the ACCORD-Lipid trial, specifically as they relate to fenofibric acid's current indication for coadministration with a statin. Since the trial was not designed to determine the clinical benefit of treating the subgroup of patients who had residual low HDL cholesterol and high triglyceride levels despite receiving full-dose statins, the data were not adequate to conclusively evaluate the benefits of coadministration specifically in this subpopulation. There are substantial limitations to subgroup analyses, especially given that the overall results showed no statistically significant difference. Although patients were randomly assigned to the primary intervention, subgroups themselves were not randomized and may not have been comparable in terms of baseline characteristics, which might confound the interpretation of results. In addition, the numbers of patients and outcome events in the subgroups were small, resulting in low statistical power, and the results were reported without adjustment for multiple comparisons. Although consistent treatment effects were observed in the subgroups with dyslipidemia in multiple previous trials, there remains uncertainty about the benefits of fibrates in this setting. Accordingly, a properly designed trial is warranted to test the hypothesis that adding fenofibric acid to statin therapy significantly reduces the risk of cardiovascular events among high-risk patients who have reached their LDL cholesterol goal with a statin but have residual mixed dyslipidemia.

The advisory panel unani-

**Table 2. Cardiovascular Outcomes in Dyslipideic Population in Fibrate Trials.***

| Trial | Subgroup | Prevalence of Subgroup | Prespecified Subgroup | Event Rate | | Risk Ratio (95% CI) | Interaction P Value |
|---|---|---|---|---|---|---|---|
| | | | | Control | Fibrate | | |
| HHS | Triglycerides ≥204 mg/dl + HDL cholesterol ≤42 mg/dl | 14% | No | 23/1000 patient-yr | 8/1000 patient-yr | 0.35 (0.16–0.77) | 0.067 |
| | All others | | | 61/1000 patient-yr | 48/1000 patient-yr | 0.79 (0.54–1.14) | |
| BIP | Triglycerides ≥200 mg/dl + HDL cholesterol ≤35 mg/dl | 11% | No | 36/162 (22.3%) | 24/184 (13.0%) | 0.58 (0.37–0.94) | 0.05 |
| | All others | | | 187/1364 (14.2%) | 196/1380 (13.7%) | 0.97 (0.80–1.16) | |
| FIELD | Triglycerides ≥204 mg/dl + HDL cholesterol ≤40/50 mg/dl | 21% | Yes | 173/970 (17.8%) | 141/1044 (13.5%) | 0.73 (0.58–0.91) | 0.053 |
| | All others | | | 510/3930 (13.0%) | 471/3851 (12.2%) | 0.94 (0.83–1.06) | |
| ACCORD | Triglycerides ≥204 mg/dl + HDL cholesterol ≤34 mg/dl | 17% | Yes | 79/456 (17.3%) | 60/485 (12.4%) | 0.69 (0.49–0.97) | 0.057 |
| | All others | | | 231/2309 (10.1%) | 231/2268(10.1%) | 0.99 (0.83–1.19) | |

* ACCORD denotes Action to Control Cardiovascular Risk in Diabetes trial, BIP Bezafibrate Infarction Prevention study, FIELD Fenofibrate Intervention and Event Lowering in Diabetes study, and HHS Helsinki Heart Study. Data for the Veterans Affairs High-Density Lipoprotein Intervention Trial are not shown, since all patients were required to have an HDL cholesterol level of 40 mg per deciliter or lower in order to be enrolled. There was no treatment interaction according to the triglyceride threshold level of 150 mg per deciliter or triglyceride levels divided into thirds.

mously recommended such a trial, while recognizing the challenges involved in both requesting a study to prove the validity of an indication that's already allowed in labeling and enrolling a large number of people from a highly selective cohort. (This cohort, however, is fairly large — about 7% of the U.S. population and 15% of U.S. patients with type 2 diabetes.) The question of the appropriate way to handle the approved indication for fenofibric acid for coadministration with a statin was more controversial; three committee members voted to maintain the indication, six to revise it, and four to withdraw it.

The broader questions are how far the FDA should go to remove ambiguity for physicians who must make individualized decisions for patients and what level of evidence should be required for marketing approval. Should the FDA require a cardiovascular outcome trial before approval, given that improvement in lipid biomarkers, other than lowering of LDL cholesterol levels with statins, has not translated into established clinical benefit? That the use of fenofibrate in the United States more than doubled between 2002 and 2009 despite the absence of clear supporting evidence argues for a trial directly addressing the clinical question and requiring clinical outcome data before approval.

Alternatively, should the FDA continue to allow the labeled indication for the coadministration of fibrates with statins in this subpopulation on the basis of the preponderance of admittedly imperfect evidence and the current regulatory standard of improvement in surrogate lipid biomarkers? This strategy allows for timely availability of potentially beneficial therapeutic options. Under the FDA Amendments Act of 2007, the FDA has increased authority to regulate drugs after initial approval, including requiring postmarketing clinical trials, mandating labeling changes, and restricting distribution and use, so the agency could maintain the current standard but require revision of the label or indication when relevant information becomes available. Postmarketing drug-utilization data that the sponsor provided to the advisory committee suggest that approximately 90% of patients using fenofibrates plus a statin have triglyceride levels of 200 mg per deciliter or above and HDL cholesterol levels below 40 mg per deciliter — so physicians are apparently appropriately targeting patients with the most severe dyslipidemia in whom data suggest there is potential benefit.

On the basis of the FDA review and committee deliberations, we conclude that the benefit of adding a fibrate to statin therapy in reducing the risk of cardiovascular events in patients with type 2 diabetes remains unproven. The possibility of important clinical benefit among patients with diabetes who have elevated triglyceride and low HDL cholesterol levels cannot be ruled out. Until sufficient evidence emerges, physicians who choose to prescribe this combination therapy should selectively target high-risk patients only after optimal control of LDL cholesterol has been achieved with statin therapy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Joslin Diabetes Center and Harvard Medical School — both in Boston (A.B.G.); the University of California, Los Angeles, and the Division of Cardiology, Cedars–Sinai Medical Center — both in Los Angeles (S.K.); and the Division of Cardiology, University of Colorado School of Medicine and CPC Clinical Research — both in Aurora (W.R.H.).

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# Taking the Mystery out of "Mystery Shopper" Studies

Karin Rhodes, M.D.

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When the Department of Health and Human Services (DHHS) announced plans for a "mystery shopper" study of access to primary care — using an essentially deceptive research study design in which researchers would pose as prospective patients calling