

CORRESPONDENCE



Combination Lipid Therapy in Type 2 Diabetes

TO THE EDITOR: In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (ClinicalTrials.gov number, NCT00000620) reported on by Ginsberg et al. (April 29 issue),¹ the use of fenofibrate in patients with type 2 diabetes mellitus who were receiving simvastatin and who were at high risk for cardiovascular disease greatly reduced triglyceride levels but hardly increased levels of high-density lipoprotein (HDL) cholesterol and did not reduce cardiovascular risk. To put these findings into context, it is important to know which lipid variables most strongly predict risk among high-risk patients who receive statins.

We therefore prospectively recorded vascular events among 491 patients with angiographically proven coronary artery disease who were receiving statins. The event rate was 40.5% over 7.2 years. In a Cox regression model including, in addition to lipid variables, age, sex, body-mass index, smoking status, hypertension, and type 2 diabetes, the HDL cholesterol level significantly predicted vascular risk (standardized adjusted hazard ratio, 0.82; 95% confidence interval [CI], 0.68 to 0.99; $P=0.04$), whereas the level of triglycerides did not (hazard ratio, 1.12; 95% CI, 0.97 to 1.30; $P=0.11$). This finding, in particular, held true among patients with type 2 diabetes: the HDL cholesterol level predicted risk (hazard ratio, 0.70; 95% CI, 0.50 to 0.99; $P=0.04$), whereas the level of triglycerides did not (hazard ratio, 1.16; 95% CI, 0.97 to 1.38; $P=0.10$). In light of these data and of the encouraging results from surro-

gate end-point trials,^{2,3} drugs such as niacin that increase the level of HDL cholesterol remain a very promising option to reduce the residual vascular risk after the failure of fenofibrate, which primarily lowers levels of triglycerides.

Christoph H. Saely, M.D.

Vorarlberg Institute for Vascular Investigation and Treatment
Feldkirch, Austria
vivit@lkhf.at

Philipp Rein, M.D.

Private University of the Principality of Liechtenstein
Triesen, Liechtenstein

Heinz Drexel, M.D.

Drexel University College of Medicine
Philadelphia, PA

Dr. Saely reports receiving lecture fees from Pfizer, Merck Sharp & Dohme, and Takeda, consulting fees from Pfizer, AstraZeneca, Merck Sharp & Dohme, and Genzyme, and payment for travel and accommodation expenses from Merck, Pfizer, and Takeda; and Dr. Drexel, receiving lecture and consulting fees from AstraZeneca, Merck, Pfizer, Merck Sharp & Dohme, and Takeda. No other potential conflict of interest relevant to this letter was reported.

1. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563-74. [Erratum, *N Engl J Med* 2010;362:1748.]
2. Brown BG, Zhao X-Q, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583-92.
3. Kastelein JJP, Bots ML. Statin therapy with ezetimibe or niacin in high-risk patients. *N Engl J Med* 2009;361:2180-3.

TO THE EDITOR: The important main result of the ACCORD lipid trial (ACCORD Lipid) was that the use of fenofibrate in patients with diabetes, regardless of their blood lipid concentrations, did not reduce the rate of coronary heart disease events. However, the results of this trial also suggest, although not conclusively, that the drug may prevent coronary heart disease in patients with dyslipidemia (i.e., patients with high levels of triglycerides and low levels of HDL cholesterol); these results were similar to those of previous

THIS WEEK'S LETTERS

- 692 Combination Lipid Therapy in Type 2 Diabetes
- 695 Blood Pressure Control in Type 2 Diabetes
- 698 Bar-Code Technology to Reduce Medication Errors

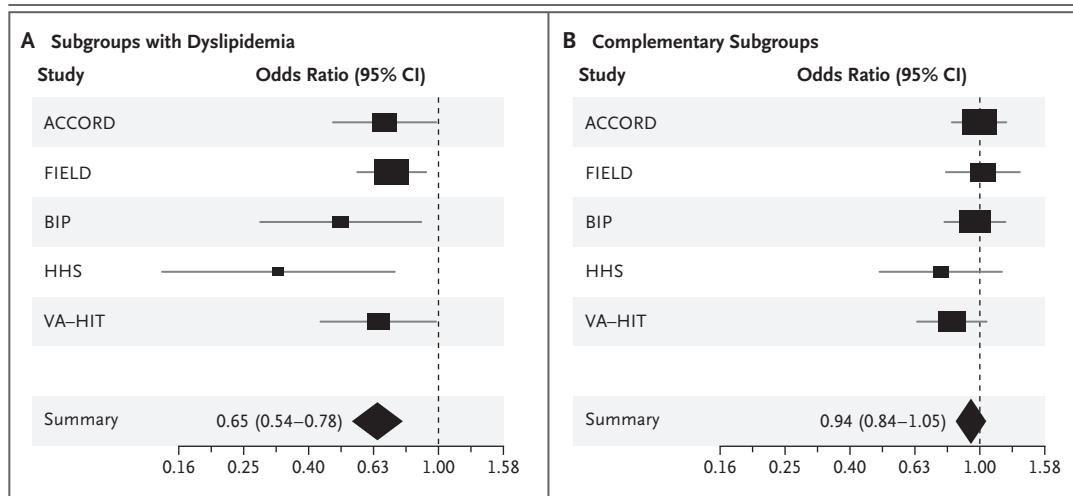


Figure 1. Forest Plot of the Treatment Effect in Subgroups.

Data from a meta-analysis of randomized trials of fibrate drugs are shown; an odds ratio of less than unity indicates a beneficial therapeutic effect. Panel A shows data from subgroups of patients with dyslipidemia (i.e., high levels of triglycerides and low levels of high-density lipoprotein [HDL] cholesterol), and Panel B shows data from the complementary subgroups without this type of dyslipidemia. The subgroup with dyslipidemia defined according to criteria prespecified in the ACCORD Lipid trial (a triglyceride level of ≥ 204 mg per deciliter and an HDL cholesterol level of ≤ 34 mg per deciliter) and the subgroup with levels closest to these lipid criteria in each of the other trials were used. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (Current Controlled Trials number, ISRCTN64783481), the cutoff triglyceride level was greater than or equal to 204 mg per deciliter and the HDL cholesterol level was less than 40 mg per deciliter in men or less than 50 mg per deciliter in women. In the Bezafibrate Infarction Prevention (BIP) study, the triglyceride level was greater than or equal to 200 mg per deciliter and the HDL cholesterol level was less than 35 mg per deciliter. In the Helsinki Heart Study (HHS), the triglyceride level was greater than 204 mg per deciliter and the HDL cholesterol level was less than 42 mg per deciliter. In the Veterans Affairs HDL Intervention Trial (VA-HIT; ClinicalTrials.gov number, NCT00035711), the triglyceride level was greater than 180 mg per deciliter and the HDL cholesterol level was less than 40 mg per deciliter. The outcome defined for the subgroup analysis in each trial was used. The subgroups with dyslipidemia in all five studies included a total of 2428 study participants and 302 events among the patients who received fibrate therapy and 2298 study participants and 408 events among those who received placebo. A random-effects meta-analysis⁵ was used. The area of the rectangles is proportional to the precision of the study-specific estimated effect. The horizontal lines indicate the 95% confidence intervals for study-specific odds ratios. The diamonds represent the summary odds ratios, with the width indicating the 95% confidence interval.

trials of fibrates.¹⁻⁴ Fibrates are approved for the treatment of dyslipidemia, and clinicians need to know whether this current use of fenofibrate reduces the rate of coronary heart disease.

Fibrates that are currently prescribed have been tested in five large, randomized trials involving diverse populations.¹⁻⁴ We calculated the treatment effects in groups that received fibrate therapy as compared with groups that received placebo. The lipid criteria in the subgroup with dyslipidemia in each trial were closest to those prespecified in the ACCORD Lipid study (i.e., a triglyceride level of ≥ 204 mg per deciliter and an HDL cholesterol level of ≤ 34 mg per deciliter). We also calculated the results in the complementary subgroups (patients with a triglyceride level of < 204 mg per deciliter or an HDL cholesterol level of > 34 mg per deciliter). The

odds ratio was reduced by 35% (95% CI, 22 to 46) in the subgroups with dyslipidemia and not significantly by 6% (95% CI, -5 to 16%) in the complementary subgroups (Fig. 1). We conclude that fibrate treatment reduces coronary heart disease events among patients with dyslipidemia.

Frank M. Sacks, M.D.

Harvard School of Public Health
Boston, MA
fsacks@hsph.harvard.edu

Vincent J. Carey, Ph.D.

Harvard Medical School
Boston, MA

Jean-Charles Fruchart, Ph.D.

Foundation Heart and Arteries
Paris, France

Dr. Sacks reports receiving consulting fees from Abbott; and Dr. Fruchart, consulting fees from Solvay. No other potential conflict of interest relevant to this letter was reported.

1. Scott R, O'Brien R, Fulcher G, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care* 2009;32:493-8.
2. The BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation* 2000;102:21-7.
3. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation* 1992;85:37-45.
4. Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* 2001;285:1585-91.
5. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials* 1986;7:177-88.

TO THE EDITOR: The ACCORD Study Group showed that combination therapy with fenofibrate and simvastatin did not reduce the risk of cardiovascular events. The rationale for combination therapy was based on the fibrate's ability to increase HDL cholesterol levels and lower triglyceride levels.

Among the patients enrolled in the ACCORD study, the levels of HDL cholesterol ranged from 30.3 to 45.9 mg per deciliter. Patients with normal HDL cholesterol levels were included in this study because they had hypertriglyceridemia. The recent findings of the Emerging Risk Factors Collaboration revealed that the hazard ratio associated with elevated triglyceride levels, once isolated independently of cholesterol levels, was essentially null.¹ The authors concluded that the triglyceride concentration was not independently related to coronary heart disease, and therefore lipid assessment can be performed without regard to triglyceride levels or the fasting state.

Although fibrate therapy did reduce the rate of coronary heart events among patients in the Veterans Affairs HDL Intervention Trial,² the mean HDL cholesterol concentration in this study group was 31 mg per deciliter, lower than that in the ACCORD trial. The ACCORD study raises questions about treating hypertriglyceridemia in the absence of cholesterol abnormalities.

William J. Perkins, Jr., M.D.

Wake Forest University Baptist Medical Center
Winston-Salem, NC
wperkins@wfubmc.edu

No potential conflict of interest relevant to this letter was reported.

1. Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993-2000.
2. 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 trial (VA-HIT). *Arch Intern Med* 2002;162:2597-604.

THE AUTHORS REPLY: We thank Saely et al. for their thought-provoking comments. A positive association between hypertriglyceridemia and the risk of coronary heart disease events has been established by epidemiologic studies.¹ Although this association is diminished when adjustments for other risk factors, particularly levels of HDL cholesterol, are introduced, the biologic significance of these statistical exercises is uncertain insofar as levels of HDL cholesterol and triglycerides vary in a collinear (inverse) fashion. Saely et al. attribute the failure of fenofibrate to reduce cardiovascular events in the ACCORD Lipid study to modest effects on HDL cholesterol levels. It is more likely that this failure reflects the heterogeneity of the study population in particular, the inclusion of participants with a wide range of triglyceride and HDL cholesterol values. In contrast, a greater increase in HDL cholesterol levels was observed in a fenofibrate-treated subgroup with baseline hypertriglyceridemia and low HDL cholesterol levels, and the use of fenofibrate therapy appeared to be associated with a reduction in cardiovascular events in this subgroup as compared with all other participants ($P=0.06$ for the interaction). As we discussed in our article, this finding is concordant with the findings of enhanced risk reduction in subgroups with hypertriglyceridemia, low HDL cholesterol levels, or both in previous fibrate trials. Although we agree that drugs such as niacin, which are more potent than fibrates in increasing HDL cholesterol levels, hold promise, we do not agree with the conclusion that triglyceride lowering in general and fibrate therapy in particular have no role in reducing cardiovascular risk.

Sacks et al. provide additional analyses in support of our conclusion that fibrates may be effective in reducing cardiovascular events among patients with dyslipidemia. We would add, however, that the term "dyslipidemia" should be used for persons with plasma triglyceride levels greater than 200 mg per deciliter and HDL cholesterol concentrations below 40 mg per deciliter.

Perkins also questions the role of hypertriglyceridemia as a risk predictor. In the analysis cited,

the greatest reduction in the predictive power of triglyceride levels occurred when non-HDL cholesterol levels were introduced into the model.² This finding reflects the fact that triglycerides and non-HDL cholesterol both serve as surrogate markers for atherogenic lipoproteins. In addition to serving as a marker for atherogenic remnant particles, triglycerides may play a causal role in the development of coronary heart disease through remodeling of HDL and low-density lipoprotein.³

The results of the ACCORD Lipid subgroup analysis, together with those of previous fibrate trials, support the hypothesis that fibrate therapy may reduce cardiovascular events among patients with clinically significant dyslipidemia (i.e., hypertriglyceridemia and low HDL cholesterol levels). A definitive clinical trial involving such persons would provide critical information regarding this issue.

Henry N. Ginsberg, M.D.

Columbia University College of Physicians and Surgeons
New York, NY
hng1@columbia.edu

Marshall B. Elam, M.D.

Memphis Veterans Affairs Medical Center
Memphis, TN

Laura C. Lovato, M.S.

Wake Forest University School of Medicine
Winston-Salem, NC

Since publication of their article, the authors report no further potential conflict of interest.

1. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation* 2007;115:450-8.
2. Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993-2000.
3. Sarwar N, Sandhu MS, Ricketts SL, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 2010;375:1634-9.

Blood Pressure Control in Type 2 Diabetes

TO THE EDITOR: The members of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study group (April 29 issue)¹ report that targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the incidence of cardiovascular events in patients with type 2 diabetes. My colleagues and I caution against early conclusions. Nonfatal myocardial infarction and death from cardiovascular causes accounted for more than 85% of the composite outcome. Lowering blood pressure too aggressively can cause harm.^{2,3} A diastolic blood pressure of less than 60 mm Hg was associated with increased mortality in the elderly.³ Among patients with coronary artery disease, the risk of myocardial infarction, but not stroke, was increased when the diastolic blood pressure was less than 70 mm Hg.² A J-shaped relationship between outcome and systolic blood pressure was evident among patients with peripheral-artery disease, with an increased risk when the systolic blood pressure was less than 120 mm Hg.⁴ Many participants in the ACCORD study would fulfill the inclusion criteria of the abovementioned studies. Therefore, we suggest that lowering diastolic blood pressure too aggressively may have obscured the benefits of the intensive treatment protocol. Further analysis of the data from the ACCORD trial might be revealing. We suggest that future trials

of intensive blood-pressure control should include predefined threshold values for diastolic blood pressure in patients with known vascular disease.

Jack F.M. Wetzels, M.D.

Radboud University Nijmegen Medical Center
Nijmegen, the Netherlands
j.wetzels@nier.umcn.nl

No potential conflict of interest relevant to this letter was reported.

1. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362:1575-85.
2. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;144:884-93.
3. Protogerou AD, Safar ME, Iaria P, et al. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. *Hypertension* 2007;50:172-80.
4. Bavry AA, Anderson RD, Gong Y, et al. Outcomes among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the International Verapamil-SR/Trandolapril Study. *Hypertension* 2010;55:48-53.

TO THE EDITOR: The authors of the ACCORD study report that there was no significant between-group difference in the primary outcome among prespecified patient subgroups, but there was at least a suggestion of an interaction with the glucose-lowering intervention (Section 17 in Supplementary Appendix 1, available with the full text of the article at NEJM.org). Among patients