Correspondence

Bone Loss and Inhaled Glucocorticoids

To the Editor: The study by Israel et al. (Sept. 27 issue)[1] of bone thinning in women with asthma did not effectively control for the critical variables of the level of physical activity and the severity of asthma.

Comparisons between patients with mild asthma and those with persistent asthma who are receiving high doses of inhaled glucocorticoids must include a careful evaluation of base-line characteristics.[2] Table 2 of the article shows that the 28 women who did not use inhaled glucocorticoids weighed less than the 42 women who required more than eight puffs of inhaled glucocorticoids per day (mean [±SD], 140±20 vs. 154±40 lb), had nearly twice the level of physical activity (98±54 vs. 55±71 metabolic hours per week), had a lower incidence of past or current use of inhaled glucocorticoids (14±36 percent vs. 62±49 percent), and were less likely to have a history of oral-glucocorticoid use (36±49 percent vs. 79±42 percent). All of these base-line differences appear to be statistically significant. It is as if we compared the bones of a busload of women soccer players with those of a busload of sedentary women.

A relative lack of gravitational exercise can obviously contribute to bone loss, as shown most clearly in astronauts returning from zero gravity. Because the presence of persistent asthma limits one's ability to exercise, the resulting inactivity and other changes in variables reflecting the severity of asthma (e.g., weight, prednisone use, and airway inflammation) invalidate any reliable analysis of the effects of inhaled glucocorticoids on bone loss in groups that were so dissimilar at base line in the absence of a randomized scheme of treatment allocation.

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2. Kaiser DL. Statistical concepts in infection control. In: Wenzel RP, ed. Prevention and control of nosocomial infections. Baltimore: Williams & Wilkins, 1987:591-600.

To the Editor: Israel et al. observed a dose-related decline in bone density at the hip among users of inhaled glucocorticoids. We conducted a large cohort study and found a dose-related increase in the risk of fracture among adult users of inhaled glucocorticoids.[1] However, patients who used bronchodilator drugs had similar degrees of risk. Our conclusion was that this excess risk is more likely to be related to the presence of underlying respiratory disease than to treatment.

Israel et al. found that pulmonary function was similar among the three groups and inferred that there was no confounding related to differences in the severity of asthma. Since treatment was not randomly assigned, the high-dose group most likely had more severe asthma. Despite having similar pulmonary function, more patients in the high-dose group than in the other groups were excluded because they had received more than 30 days of oral or parenteral glucocorticoid therapy. Inhaled glucocorticoids can suppress the symptoms of bronchoconstriction, but they do not cure the disease. Their effects on the natural history of asthma are not clearly understood.[2] Complications may thus occur independently of the level of bronchoconstriction.

The bone loss associated with the use of oral glucocorticoids is principally trabecular, with a greater loss in the lumbar spine and less of a loss in the proximal femur. The spine is associated with the largest increases in the risk of fracture.[3] The pattern of effect on bone density at the spine and hip reported by Israel et al. does not support the hypothesis that inhaled glucocorticoids influence bone in a fashion similar to that of oral glucocorticoids.

We agree that patients using inhaled glucocorticoids have

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an increased risk of fracture. The potential role of asthma in increasing this risk should not be underestimated.

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To the Editor: Israel et al. report that inhaled glucocorticoids lead to a dose-related decline in bone density at the hip in premenopausal women. However, the authors never comment on the control group in the study, which was not exposed to glucocorticoids. The loss of bone mineral density in women older than 25 years of age is well documented, and Israel et al. have given us no means of distinguishing physiologic changes from those resulting from medication.

That there is a normal decline in bone mineral density with age also calls into question the data from the study's bone densitometers. Data from the femoral neck and lumbar spine do not correspond to the expected base-line loss of 0.7 percent per year.[1] Such measuring error calls into question the small changes in density that Israel et al. report as statistically significant. More analysis of the control group and more data are necessary to understand the consequences of this widespread treatment approach.

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The authors reply:

To the Editor: In response to Dr. Kerwin: the "busloads" of women we compared were well matched. There were no statistically significant differences among the groups in weight or the level of physical activity. The apparent difference in the level of physical activity was due to a typographical error in Table 2. The mean level of physical activity in the group of women who did not take inhaled glucocorticoids was 48 metabolic hours per week, not 98. In addition, analyses that also adjusted for weight and level of physical activity did not affect our quantitative conclusions about the dose-related loss in bone density at the hip and trochanter.

Naturally, our groups differed with respect to the use of inhaled glucocorticoids. This was the independent variable used to assemble the groups. We also expected the incidence of a history of oral-glucocorticoid use before the study to differ among the groups. However, the data obtained during the study were not confounded by the use of oral glucocorticoids, which was prospectively monitored; we performed an a priori analysis that was restricted to patients who did not receive oral glucocorticoids during the study. Furthermore, data from van Staa et al.,[1] among others, suggest that the presence of a history of glucocorticoid use before the study was unlikely to affect our outcome, since there is a rapid offset of the effects of oral glucocorticoids on bone density once therapy is stopped.

Since we did not examine any patients without asthma, we cannot confirm the observation of van Staa et al. regarding bronchodilator users and controls. However, when van Staa and colleagues compared users of high-dose inhaled glucocorticoids with those who used bronchodilators alone (an analysis similar to ours), their findings were remarkably similar to ours.[2] They observed an increased rate of hip fracture with the use of high-dose inhaled glucocorticoids. The rate was not a function of the underlying population, since it declined toward base line once the treatment was discontinued. Furthermore, there was an increased rate of hip fracture and not of spinal fracture. Why inhaled glucocorticoids produce a pattern of accelerating bone loss that differs from that reported with oral glucocorticoids is unclear.

Dr. Glazer misunderstands our analysis. Patients who did not use inhaled glucocorticoids were very much part of the analysis (as indicated by the points superimposed on the ordinate in each panel of Figure 2 of our article). In fact, the yearly decline in bone density per puff of inhaled glucocorticoid that we report is the supplementary decline, which would occur in addition to any physiologic change in bone density that would be occurring in the group that was not using inhaled glucocorticoids. We used a very precise technique for measuring bone mass — dual x-ray absorptiometry — and the results were interpreted by one observer. However, as we noted in the article, on the basis of the results of dietary screening, patients received supplemental calcium, vitamin D, or both. This supplementation may have influenced the yearly rate of bone loss in our subjects, including the rate in the group that did not use inhaled glucocorticoids. Nonetheless, we found that inhaled glucocorticoids were associated with a dose-related decrease in bone density that was superimposed on any positive effect that may have resulted from dietary supplementation.

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Urinary Tract Infections and a Multidrug-Resistant *Escherichia coli* Clonal Group

To the Editor: The report by Manges et al. (Oct. 4 issue)[1] regarding the widespread distribution of multidrug-resistant *Escherichia coli* is both important and timely. We have found even higher rates of resistance to trimethoprim–sulfamethoxazole (TMP-SMX) among *E. coli* and other organisms at Elmhurst Hospital in Queens, New York. This hospital serves an incredibly diverse immigrant population that includes large numbers of people from Asia and Latin America. As part of a quality-improvement project, we reviewed more than 900 positive urine cultures that had been obtained since October 1998; approximately 40 percent were resistant to TMP-SMX. The majority of our urine cultures grew *E. coli* with patterns of resistance that were similar to those reported by Manges et al.

Our data also show that about 15 percent of the cultures with minimal resistance to ciprofloxacin were resistant to cephalexin. Ciprofloxacin would seem to be a good choice, but since the World Trade Center tragedy and the anthrax scare, there has been a shortage of ciprofloxacin. Even if the supply of ciprofloxacin were not in question, the cost of treatment with this drug is often prohibitive for indigent, uninsured patients.

Are the authors aware of high levels of resistance in other urban or immigrant populations? What alternatives do they suggest for effective empirical treatment of urinary tract infections at a reasonable cost?

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1. Manges AR, Johnson JR, Foxman B, O'Bryan TT, Fullerton KE, Riley LW. Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. N Engl J Med 2001;345:1007-13.

To the Editor: Manges et al. reported finding a clonal strain of *E. coli* that was responsible for urinary tract infections in women in three states between 1996 and 2000. Is this strain responsible for cases of outpatient urinary tract infections in other geographic areas?[1]

We examined 213 isolates of *E. coli* from urine cultures obtained in 1998 from patients — 85 percent of whom were outpatients and 84 percent of whom were women — to investigate the incidence of antibiotic-resistant strains at Cook County Hospital in Chicago.[2] Our findings were similar to those of Manges et al.; 24 percent of isolates were resistant to TMP-SMX. However, using the same method of pulsed-field gel electrophoresis[3] used by Manges et al., we found that our TMP-SMX–resistant isolates were distinct, unrelated strains. Hence, epidemic spread of a single *E. coli* clone could not explain the high prevalence of resistance to TMP-SMX in urinary isolates in Chicago, although the spread of a common resistance element is conceivable.

Our chart review suggested an alternative hypothesis: 68 percent of the patients had Hispanic surnames. In contrast, only 20 to 30 percent of our outpatient population is Hispanic. Recent travel to or acquisition of TMP-SMX from Mexico or other Latin American countries, where the use of antibiotics is unrestricted, may have contributed to the incidence of TMP-SMX–resistant isolates at our facility. International travel and Hispanic ethnic background were predictors of infection with TMP-SMX–resistant strains in another study of urinary tract infections with *E. coli*.[4] Although Manges et al. do not report their patients' race or ethnic group, their infections and any antecedent antibiotic treatments may have been more likely than those in our patients to have been acquired locally.

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To the Editor: Manges et al. describe an epidemic of antibiotic-resistant *E. coli* urinary tract infections in women, stating that contaminated food may have been the culprit. Much of the antibiotics used in this country are given to food animals.

To date, the concern about infections with antibiotic-resistant food-borne pathogens has focused on salmonella[1,2] and campylobacter.[3] However, food-borne strains of resistant *E. coli* also infect people, either through direct colonization with resistant strains from animals or through the transfer of drug-resistance plasmids from salmonella or *E. coli* in animals to *E. coli* in people.[4] The next logical step in understanding the findings of Manges et al. would be to screen *E. coli* isolates from food animals to determine whether a related strain is present. The finding of a similar strain would be compelling evidence that antibiotic use in animals poses a widespread threat to the nearly 8 million women who have urinary tract infections each year. It would also provide additional scientific data to support actions by the Food and Drug Administration or Congress to phase out the use of medically important antibiotics in livestock and poultry.

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The authors reply:

To the Editor: The prevalence of antibiotic resistance among *E. coli* causing urinary tract infections varies geographically for reasons that are poorly understood.[1] Ethnic background has received little attention to date as a predictor of antibiotic resistance in uropathogenic *E. coli,* so the findings described by Dr. Sandel and colleagues and by Dr. Petrof and colleagues suggest a need for further research. It is probable that some resistant strains are imported into the United States, as indicated by the emergence of TMP-SMX–resistant fecal *E. coli* among tourists who have taken this agent prophylactically while visiting Mexico.[2]

Multidrug-resistant salmonella infections in the United States were found to be associated with Hispanic surnames.[3] In the case of enteric pathogens, such an association could have several possible explanations: resistant organisms may be imported from areas with a high prevalence of resistance, differences in antibiotic use among different populations in the United States may predispose users to acquire multidrug-resistant strains,[3] and cultural or ethnic differences in diet may contribute to an increased risk of exposures to some types of foods contaminated with resistant organisms.[4] In any case, we strongly agree with Drs. Barlam and Moellering that the use of antibiotics as growth promoters in animal feed is a major contributor to the emergence of multidrug-resistant food-borne pathogens and that there is no reason to believe that this situation applies only to traditional enteric organisms, such as salmonella and campylobacter.

Finally, to address the important questions posed by Sandel and colleagues, oral alternatives to TMP-SMX for the treatment of urinary tract infections with TMP-SMX–resistant *E. coli* include ciprofloxacin and other fluoroquinolones, nitrofurantoin, fosfomycin tromethamine, amoxicillin–clavulanate, and extended-spectrum cephalosporins.[1,5] Of these, the fluoroquinolones would probably be the most effective, whereas nitrofurantoin would be the least expensive.[5] However, nitrofurantoin must be given for more than three days, even in cases of cystitis,[5] and is not useful for the treatment of pyelonephritis.

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Polymorphisms of the β_2-Adrenergic Receptor

To the Editor: Dishy et al. (Oct. 4 issue)[1] report that polymorphisms of the β_2-adrenergic receptor influence agonist-promoted desensitization of β_2-adrenergic receptor–mediated vasodilatation. Desensitization can be an important homeostatic event but may also limit the therapeutic effectiveness of agonists (a response called tachyphylaxis). The authors indicate that their findings were unexpected, given results of in vitro studies in which my colleagues and I used polymorphic β_2-adrenergic receptors that were expressed in cells in either recombinant[2] or native[3] form. However, the effect of polymorphisms in vivo is dependent on whether receptors are under static or dynamic regulation. The concept (Fig. 1) is broadly applicable and is important to consider, since the number of polymorphic genes studied in cell-based systems and humans will undoubtedly increase during the next few years.[4] With static regulation, the typically low levels of endogenous agonists (catecholamines) do not appreciably desensitize receptors under normal circumstances in vivo. Thus, the altered regulatory activities, such as desensitization, that result from a polymorphism are observed only after treatment with an exogenous agonist. In contrast, with dynamic regulation, receptors are also constantly regulated by their endogenous agonists, so that highly sensitive polymorphic receptors are "pre-desensitized" before the challenge of an exogenous agonist is presented. Such receptors might not become further desensitized with the persistent presence of an exogenous agonist, thereby revealing an apparently paradoxical phenotype.

The results of Dishy et al. are partially consistent with our in vitro studies if one considers the dynamic model: persons

Single-Nucleotide Polymorphism	In Vitro Phenotype	Effect of Endogenous Agonist	In Vivo Response: Initial	In Vivo Response: After desensitization	Tachyphylaxis
Static model					
Polymorphism A	Moderate down-regulation	None			Moderate
Polymorphism B	Maximal down-regulation	None			Maximal
Dynamic model					
Polymorphism A	Moderate down-regulation	Moderate down-regulation			Moderate
Polymorphism B	Maximal down-regulation	Maximal down-regulation			None

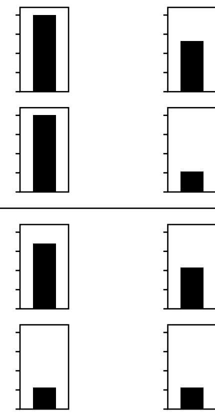

Figure 1. Static and Dynamic Models of the Regulation of Polymorphic Receptors.

Receptors with single-nucleotide polymorphisms and their in vitro and in vivo properties are shown. The in vivo responses before and after a desensitization challenge are shown as bar graphs with arbitrary units. The paradoxical lack of in vivo desensitization in the receptor with polymorphism B, which has enhanced down-regulation in vitro, is apparent in the dynamic model.

with a substitution of glycine for arginine at position 16 (Gly16) do not have desensitization, yet in vitro this receptor has enhanced down-regulation; on the other hand, persons with the wild-type allele, Arg16, have desensitization in vivo, but there is less down-regulation of this receptor in vitro.[2] A similar finding has been reported in patients with asthma: patients who are homozygous for Arg16, but not those who are homozygous for Gly16, have tachyphylaxis to regularly scheduled albuterol.[5] These issues also highlight the necessity of both clinical and basic studies to delineate the physiological consequences and molecular mechanisms of clinically relevant polymorphisms.

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The authors reply:

To the Editor: We are grateful to Dr. Liggett for his comments. In fact, we have previously shown that β_2-adrenergic receptors are indeed dynamically regulated by endogenous catecholamines in vivo,[1,2] and therefore we had considered his suggestion — that persons with the Gly16 variant of the β_2-adrenergic receptor, which has enhanced down-regulation in vitro, did not have further tachyphylaxis in vivo because they were already desensitized in response to endogenous catecholamines. Although we could not definitively exclude the possibility that the Gly16 variants were already desensitized, we thought it unlikely because, as shown in Table 2 of our article, the initial responses to isoproterenol in subjects who were homozygous for Arg16 or Gly16 (but matched for glutamine at position 27 [Gln27]) did not differ, whereas as illustrated in the bottom panel of Dr. Liggett's figure, preexisting desensitization in subjects homozygous for Gly16 should result in a decreased initial response to an agonist. Other factors that may account for differences between studies of adrenergic-receptor regulation performed in vitro and in vivo include different concentrations and duration of agonist exposure and modulation of responses by other genetic or homeostatic mechanisms. We agree that our findings illustrate the critical importance of studying the functional effects of genetic variations in vivo as well as in vitro.

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nist interactions by physiological changes in circulating catecholamines. J Clin Invest 1983;72:164-70.

B-Cell Deficiency and Type 1 Diabetes

To the Editor: Martin and colleagues (Oct. 4 issue)[1] report a case of type 1 diabetes mellitus in a patient with profound B-cell deficiency. It is now clear that B-cell–deficient nonobese diabetic (NOD) mice exhibit profound resistance to spontaneous autoimmune diabetes.[2-4] Indeed, several studies have indicated that the antigen-presenting role of B cells is crucial for the activation of diabetogenic T cells.[3] Recently, detailed characterization of B-cell–deficient NOD mice[5] showed that, despite their resistance to spontaneous autoimmune diabetes, these mice are susceptible to mild insulitis and, on treatment with cyclophosphamide, are susceptible to the development of diabetes.

These findings led us to conclude that in NOD mice, B lymphocytes are required for overcoming a checkpoint in the spontaneous evolution of autoimmune diabetes.[3] Our studies indicate that islet beta cells are targeted in the absence of B lymphocytes and that, given appropriate environmental provocation, B-cell–deficient NOD mice retain the potential for developing autoimmune diabetes. In the absence of a careful epidemiologic analysis of B-cell–deficient patients who harbor a genetic susceptibility to type 1 diabetes mellitus, it is premature to conclude that B cells and autoantibodies are irrelevant to the pathogenesis of this autoimmune disease in humans.

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To the Editor: Martin et al. demonstrate convincingly that autoimmune type 1 diabetes can occur in the absence of humoral immunity. Their report raises the question of whether more common, less severe defects in humoral immunity represent risk factors of type 1 diabetes. There is evidence that clinically apparent common variable immunodeficiency may be more common in children with early-onset disease than in other children.[1] It is possible that common variable immunodeficiency may also occur in older persons with type 1 diabetes.[2,3] The underlying genetic abnormalities in this type of immunodeficiency are probably heterogeneous and less than completely understood.[4-6]

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The authors reply:

To the Editor: In response to our report that neither B cells nor autoantibodies are critically required for the development of type 1 diabetes, Noorchashm and colleagues argue that B cells are required to overcome a checkpoint in the development of diabetes in the NOD-mouse model, and they provide evidence that islet-cell autoimmunity can arise in the absence of B cells. We agree that it is conceivable that B cells and autoantibodies contribute to the development of disease.[1] Nonetheless, the important message of our study is proof of principle, since in our patient type 1 diabetes clearly developed in the absence of B cells. General relevance is suggested by the fact that the patient carried the HLA alleles known to be strongly associated with type 1 diabetes.[2] Interestingly, NOD mice have a similar, critical major-histocompatibility-complex–associated genetic predisposition to autoimmune diabetes.[2] In fact, in NOD mice B cells are not an absolute requirement for the development of diabetes.[3] An important remaining difference between autoimmune diabetes in NOD mice and type 1 diabetes in humans is the presence of autoantibodies against the islet autoantigens glutamic acid decarboxylase and IA-2, which serve as important predictors of type 1 diabetes, in humans, although the diseases in mice and humans share autoantibodies against insulin.[4]

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The Acts of Terrorism

To the Editor: People all over the world were shocked by the disaster of September 11, 2001. I want to emphasize what the editors wrote about medical insurance in the *Journal*'s editorial on the subject (Oct. 11 issue)[1]: "Victims and their families must receive medical and mental health attention regardless of their ability to pay and whether or not they have medical insurance."

I believe that the international community of physicians should fight for justice in medical treatment. It is noteworthy that 40 million Americans have no medical insurance and billions of people in the Third World do not receive basic medical treatment. Physicians may not be able to save the world, but our united voice must be heard loud and clear. Everybody on this planet deserves medical and mental health care, regardless of his or her ability to pay. Justice in medical care might help to prevent hatred and frustration. Justice in medical care will not solve the problem of terrorism, but it might play a part in preventing it.

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1. The Editors. September 11, 2001. N Engl J Med 2001;345:1126.

To the Editor: The editorials on bioterrorism (July 26 issue[1] and Oct. 11 issue) called for an improved national program of preparedness, including a strengthened public-service infrastructure, improvements in diagnosis, better integration of information, and timely reporting of laboratory results. An important omission in these proposals is the role of the nation's 17,000 nursing homes as a necessary addition to the evolving system of response. There are 1,600,000 nursing home beds, of which approximately 200,000 are unoccupied on any given day.[2] The nursing homes have about twice the total number of beds that hospitals have, are located in every community in the United States, employ skilled nursing staffs and medical directors, and are linked with other medical staffs in the community. They also have established mechanisms for rehabilitation, laboratory testing, radiology, and the transportation of patients. Moreover, family and social-service support are part of the work of nursing homes.

With a small amount of additional effort and planning, the nursing homes can enhance the developing response to natural or man-made emergencies. A beneficial byproduct will be a strengthening of the nursing homes in each community and improvement in their performance of their traditional role. Fear of terrorism is understandable, but fear of the nursing home is not an acceptable reason to overlook this opportunity to enhance our response to these threats to the public.

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To the Editor: The same species that eradicated smallpox and has very nearly eradicated poliomyelitis has also committed innumerable acts of violence against itself. Will we ever learn that every war is a civil war?

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The editors reply:

The new threats of massive terrorism have developed amid the anger and resentment that have been building in oppressive, failing countries that do not provide for the basic needs of their people. Dr. Rokach's statement is a reminder that any plan to counter the underlying causes of terrorism should include plans to improve the health of those trapped in severe poverty. The health care resources of the economically developed countries are enormous. Some small fraction of those resources could produce substantial improvements for those living in the poorest countries.

In the aftermath of September 11 and the subsequent acts of biologic terrorism, we know that preparedness is now required for responses to acts that once seemed unimaginable. Those responses should draw on all our health care resources, including nursing homes and their personnel, as Dr. Libow points out. As Dr. Libow also suggests, being forced to create such contingency plans could result in the development of a better perspective on some of the problems in the fragmented health care system of the United States.

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Cerivastatin and Reports of Fatal Rhabdomyolysis

To the Editor: Bayer's voluntary withdrawal of cerivastatin from the U.S. market led to questions regarding the safety of all hydroxymethylglutaryl–coenzyme A reductase inhibitors,

TABLE 1. REPORTED CASES OF FATAL RHABDOMYOLYSIS AND NUMBERS OF PRESCRIPTIONS FOR ALL STATINS DISPENSED IN THE UNITED STATES SINCE THESE PRODUCTS WERE LAUNCHED.

VARIABLE	LOVASTATIN	PRAVASTATIN	SIMVASTATIN	FLUVASTATIN	ATORVASTATIN	CERIVASTATIN	TOTAL
Date approved	8/31/87	10/31/91	12/23/91	12/31/93	12/17/96	6/26/97	—
Fatal cases of rhabdomyolysis*	19	3	14	0	6	31	73
No. of prescriptions dispensed since marketing began†	99,197,000	81,364,000	116,145,000	37,392,000	140,360,000	9,815,000	484,273,000
Reporting rate (per 1 million prescriptions)‡	0.19	0.04	0.12	0	0.04	3.16	0.15

*U.S. cases reported to the FDA before June 26, 2001, that met the following criteria were included: the report included a clinical diagnosis of rhabdomyolysis, a temporal association between rhabdomyolysis and the use of a statin could be identified from the report, and death resulted either directly or indirectly from rhabdomyolysis.

†Data are through May 2001 and are from the National Prescription Audit Plus, excluding the Long Term Care Channel.

‡The reporting rate is the number of fatal cases divided by the number of prescriptions dispensed and is a crude measure of the number of reports received by the FDA relative to the extent of the use of an agent in the U.S. population. Rigorous comparisons between drugs that are based on these data are not recommended, since many factors can affect reporting and an unknown number of cases may not be attributed to the drug or reported to the FDA. Reporting rates are not incidence rates.

or statins. Myopathy and the rarer severe rhabdomyolysis are considered adverse events of therapy with this class of drugs.[1] Concomitant use of drugs that can increase blood levels of statins can increase the risk of myopathy, as can concomitant use of gemfibrozil.[2] We summarize the U.S. reports of fatal rhabdomyolysis associated with all six drugs in this class: lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and cerivastatin.

We reviewed reports in the Adverse Event Reporting System of the Food and Drug Administration (FDA). We also examined the number of prescriptions dispensed in the United States since the marketing of each drug began, according to the National Prescription Audit Plus (IMS HEALTH, Fairfield, Conn.). This is a nationally projected audit of retail pharmacies and mail-order houses.

Our results show that fatal rhabdomyolysis is a rare event among statin users, with reporting rates much lower than 1 death per million prescriptions in the case of most statins (Table 1). The rate of fatal rhabdomyolysis associated with cerivastatin therapy, however, is 16 to 80 times as high as the rates for any other statin. Some of this difference appears to be related to the known, marked interaction (relative to that of other statins) between cerivastatin and gemfibrozil, which in late 1999 led to the listing on the labels of contraindications against the combined use of these agents. The use of this combination was reported in 12 of the 31 deaths. After the exclusion of the 12 cases in which gemfibrozil was used with cerivastatin and the 7 cases in which it was used with lovastatin, the reporting rate of fatal rhabdomyolysis in association with cerivastatin monotherapy is 1.9 per million prescriptions, 10 to 50 times as high as the rates associated with the other statins. Among the 19 deaths associated with cerivastatin in the absence of gemfibrozil therapy, 12 occurred after use of the 0.8-mg dose (which was approved in the United States in July 2000), 6 occurred after use of the 0.4-mg dose, and the dose was not reported in 1 case. This pattern suggests that there is a relation to the dose.

Because of the underreporting of adverse reactions, the use of reporting rates as proxy measures of risk has limitations. Only about 1 percent of all serious events are directly reported by physicians.[3] There is a secular trend of increased reporting to the FDA over the past decade.[4] However, the rate of reports of fatal rhabdomyolysis associated with the use of atorvastatin (approved for use within six months after the approval of cerivastatin) was far less than for cerivastatin. Thus, the increased reporting associated with the use of cerivastatin appears to be more than an artifact related to an increased awareness of statin-associated rhabdomyolysis or to secular trends in reporting.

On the basis of the finding of a markedly increased reporting rate of fatal rhabdomyolysis in association with cerivastatin, Bayer, with the concurrence of the FDA, moved to withdraw cerivastatin from the U.S. market. Clinicians should be aware of this labeled but rare event associated with the use of all statins and should warn patients to watch for symptoms of myopathy, such as muscle pain or weakness, which should prompt an immediate consultation with their physician.

(The views expressed are those of the authors and do not necessarily represent those of, nor imply endorsement by, the FDA or the U.S. government.)

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Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

The ACCORD Study Group*

ABSTRACT

BACKGROUND

We investigated whether combination therapy with a statin plus a fibrate, as compared with statin monotherapy, would reduce the risk of cardiovascular disease in patients with type 2 diabetes mellitus who were at high risk for cardiovascular disease.

METHODS

We randomly assigned 5518 patients with type 2 diabetes who were being treated with open-label simvastatin to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.

RESULTS

The annual rate of the primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (hazard ratio in the fenofibrate group, 0.92; 95% confidence interval [CI], 0.79 to 1.08; P=0.32). There were also no significant differences between the two study groups with respect to any secondary outcome. Annual rates of death were 1.5% in the fenofibrate group and 1.6% in the placebo group (hazard ratio, 0.91; 95% CI, 0.75 to 1.10; P=0.33). Prespecified subgroup analyses suggested heterogeneity in treatment effect according to sex, with a benefit for men and possible harm for women (P=0.01 for interaction), and a possible interaction according to lipid subgroup, with a possible benefit for patients with both a high baseline triglyceride level and a low baseline level of high-density lipoprotein cholesterol (P=0.057 for interaction).

CONCLUSIONS

The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)

The members of the Writing Committee (Henry N. Ginsberg, M.D., Marshall B. Elam, M.D., Laura C. Lovato, M.S., John R. Crouse III, M.D., Lawrence A. Leiter, M.D., Peter Linz, M.D., William T. Friedewald, M.D., John B. Buse, M.D., Ph.D., Hertzel C. Gerstein, M.D., Jeffrey Probstfield, M.D., Richard H. Grimm, M.D., Ph.D., Faramarz Ismail-Beigi, M.D., Ph.D., J. Thomas Bigger, M.D., David C. Goff, Jr., M.D., Ph.D., William C. Cushman, M.D., Denise G. Simons-Morton, M.D., Ph.D., and Robert P. Byington, Ph.D.) assume responsibility for the integrity of the article. Address reprint requests to Dr. Ginsberg at the Department of Medicine, Columbia University College of Physicians and Surgeons, Rm. PH 10-305, New York, NY 10032, or at hng1@columbia.edu.

*The members of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group are listed in Section 20 in Supplementary Appendix 1, available with the full text of this article at NEJM.org. The affiliations of members of the Writing Committee are listed in the Appendix.

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Patients with type 2 diabetes mellitus have an increased incidence of atherosclerotic cardiovascular disease.[1-4] This increase is attributable, in part, to associated risk factors, including hypertension and dyslipidemia. The latter is characterized by elevated plasma triglyceride levels, low levels of high-density lipoprotein (HDL) cholesterol, and small, dense low-density lipoprotein (LDL) particles.[5,6] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was designed to test the effect of intensive treatment of blood glucose and either blood pressure or plasma lipids on cardiovascular outcomes in 10,251 patients with type 2 diabetes who were at high risk for cardiovascular disease. Here we present the findings of the ACCORD lipid trial (ACCORD Lipid).

Although statins are efficacious in patients with type 2 diabetes, rates of cardiovascular events remain elevated in such patients even after statin treatment.[7-9] Fibrate therapy in patients with type 2 diabetes reduced the rate of coronary heart disease events in the Veterans Affairs HDL Intervention Trial (VA-HIT; ClinicalTrials.gov number, NCT00035711)[10] but not in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial (Current Controlled Trials number, ISRCTN64783481).[11] However, a post hoc analysis of data from the FIELD study suggested a benefit for patients with both elevated triglyceride levels and low HDL cholesterol levels.[12] Previous fibrate studies in subjects with diabetes[10,11] or in those without diabetes[13-15] did not address the role of such drugs in patients receiving statin therapy. The hypothesis that we tested in ACCORD Lipid was that in high-risk patients with type 2 diabetes, combination treatment with a fibrate (both to raise HDL cholesterol levels and to lower triglyceride levels) and a statin (to reduce LDL cholesterol levels) would reduce the rate of cardiovascular events, as compared with treatment with a statin alone.

Methods

Study Design

The rationale and designs for the various components of ACCORD have been reported previously.[16-20] The ACCORD study was a randomized trial conducted at 77 clinical sites organized into seven networks in the United States and Canada. (For a full list of participating institutions and investigators, see Section 20 in Supplementary Appendix 1, available with the full text of this article at NEJM.org.) The trial was sponsored by the National Heart, Lung, and Blood Institute (NHLBI), and the protocol was approved by a review panel at the NHLBI, as well as by the institutional review board or ethics committee at each center.

In the ACCORD study, all patients were randomly assigned to receive either intensive glycemic control (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a glycated hemoglobin level of 7.0 to 7.9%). The results of this comparison have been reported previously.[20] A subgroup of patients in the ACCORD study were also enrolled in the ACCORD Lipid trial and underwent randomization, in a 2-by-2 factorial design, to receive simvastatin plus either fenofibrate or placebo. Randomization occurred between January 11, 2001, and October 29, 2005. End-of-study visits were scheduled between March and June 2009. Additional details regarding the trial protocol and amendments are provided in Supplementary Appendix 2, also available with the full text of this article at NEJM.org.

Eligibility

All patients in the ACCORD study had type 2 diabetes and a glycated hemoglobin level of 7.5% or more. If patients had evidence of clinical cardiovascular disease, the age range was limited to 40 to 79 years; if they had evidence of subclinical cardiovascular disease or at least two additional cardiovascular risk factors, the age range was compressed to 55 to 79 years. Patients were specifically eligible to participate in the lipid trial if they also had the following: an LDL cholesterol level of 60 to 180 mg per deciliter (1.55 to 4.65 mmol per liter), an HDL cholesterol level below 55 mg per deciliter (1.42 mmol per liter) for women and blacks or below 50 mg per deciliter (1.29 mmol per liter) for all other groups, and a triglyceride level below 750 mg per deciliter (8.5 mmol per liter) if they were not receiving lipid therapy or below 400 mg per deciliter (4.5 mmol per liter) if they were receiving lipid therapy. All patients provided written informed consent. Additional details regarding eligibility and the protocol for the enrollment of patients are available in Section 3 in Supplementary Appendix 1.

STUDY PROCEDURES

Randomization was performed centrally on the trial's Web site with the use of permuted blocks to maintain concealment of study-group assignments. Open-label simvastatin therapy began at the randomization visit, and the masked administration of either fenofibrate or placebo began 1 month later. The initial dose of simvastatin complied with national lipid guidelines at the time the study began.[21] The dose of simvastatin was modified over time in response to changing guidelines (see Section 6 in Supplementary Appendix 1).[18]

At the start of the trial, the dose of fenofibrate was 160 mg per day. Because of a rise in serum creatinine levels in some patients while receiving this dose of fenofibrate,[22] starting in 2004, the dose of fenofibrate was adjusted according to the estimated glomerular filtration rate (GFR) with the use of the abbreviated Modification of Diet in Renal Disease (MDRD) equation (see Section 7 in Supplementary Appendix 1).[23]

A fasting plasma lipid profile was measured at the ACCORD central laboratory at 4, 8, and 12 months after randomization, annually thereafter, and at the end of the study. Safety profiles, including liver-function tests and measurements of creatine kinase levels, were determined at 1, 4, 8, and 12 months after randomization and annually thereafter. If symptoms or signs suggestive of drug-induced toxic effects developed, tests of liver function (including measurement of alanine aminotransferase), creatine kinase, or both were obtained. If liver-function values were elevated, lipid medications were temporarily discontinued; if creatine kinase values were elevated, lipid medications were permanently discontinued.

PRESPECIFIED OUTCOMES

The prespecified primary outcome was the first occurrence of a major cardiovascular event, including nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Secondary outcomes included the combination of the primary outcome plus revascularization or hospitalization for congestive heart failure (termed the "expanded macrovascular outcome"); a combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina (termed "major coronary disease events"); nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure. Definitions of each prespecified outcome and methods of ascertainment are detailed in Section 8 in Supplementary Appendix 1.

STUDY OVERSIGHT

Fenofibrate and matching placebo were donated by Abbott Laboratories; simvastatin was donated by Merck. The drug manufacturers had no role in the design of the study, in the accrual or analysis of the data, or in the preparation of the manuscript. All authors vouch for the accuracy and completeness of the reported data.

STATISTICAL ANALYSIS

The study was designed to recruit 5800 patients, with a power of 87% to detect a 20% reduction in the rate of the primary outcome for patients in the fenofibrate group, as compared with placebo, assuming a two-sided alpha level of 0.05, a primary outcome rate of 2.4% per year in the placebo group, and an average follow-up of approximately 5.6 years for patients who did not have an event. All statistical analyses were conducted at the coordinating center with the use of S-Plus software, version 8.0 (Insightful) or SAS software, version 9.1 (SAS Institute). Baseline characteristics were compared between study groups with the use of the chi-square test, Fisher's exact test, Wilcoxon rank-sum test, and two-sample t-tests. The incidence of key safety outcomes was compared with the use of Fisher's exact test.

Analyses of primary and secondary outcomes were performed with the use of time-to-event methods, according to the intention-to-treat principle, and occurrences of outcomes were compared with the use of hazard ratios and 95% confidence intervals. Two-sided P values were obtained from likelihood ratio tests from Cox proportional-hazards regression analyses. The Cox models contained a term representing study-group assignment plus terms for the following prespecified variables: assignment to the intensive glycemic intervention, the seven clinical-center networks, and the presence or absence of a previous cardiovascular event. Between-group differences were also examined in prespecified subgroups on 10 baseline characteristics (see Section 9 in Supple-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	All Patients (N=5518)	Fenofibrate (N=2765)	Placebo (N=2753)	P Value
Age — yr	62.3±6.8	62.2±6.7	62.3±6.9	0.69
Female sex — no. (%)	1694 (30.7)	851 (30.8)	843 (30.6)	0.90
Race or ethnic group — no. (%)†				
White	3774 (68.4)	1909 (69.0)	1865 (67.7)	0.30
Black	834 (15.1)	392 (14.2)	442 (16.1)	0.05
Hispanic	407 (7.4)	213 (7.7)	194 (7.0)	0.35
Education — no. (%)				0.19
Less than high school	750 (13.6)	394 (14.2)	356 (12.9)	
High-school graduate or GED	1433 (26.0)	712 (25.8)	721 (26.2)	
Some college	1827 (33.1)	885 (32.0)	942 (34.2)	
College degree or higher	1505 (27.3)	772 (27.9)	733 (26.6)	
Missing data	3 (<0.1)	2 (0.1)	1 (<0.1)	
Previous cardiovascular event — no. (%)	2016 (36.5)	1008 (36.5)	1008 (36.6)	0.90
Previous congestive heart failure — no. (%)	291 (5.3)	151 (5.5)	140 (5.1)	0.54
Cigarette-smoking status — no. (%)				0.42
Current	803 (14.6)	410 (14.8)	393 (14.3)	
Former	2546 (46.2)	1292 (46.7)	1254 (45.6)	
Never	2161 (39.2)	1059 (38.3)	1102 (40.0)	
Missing data	8 (0.1)	4 (0.1)	4 (0.1)	
Weight — kg	94.8±18.7	94.5±18.5	95.2±18.8	0.21
Body-mass index‡	32.3±5.4	32.2±5.4	32.4±5.4	0.32
Blood pressure — mm Hg				
Systolic	133.9±17.8	133.8±17.7	134.0±17.9	0.79
Diastolic	74.0±10.8	73.9±10.7	74.0±10.9	0.58
Medications — no. (%)				
Insulin	1836 (33.3)	919 (33.2)	917 (33.3)	0.95
Metformin	3420 (62.0)	1712 (61.9)	1708 (62.0)	0.92
Any sulfonylurea	2892 (52.4)	1440 (52.1)	1452 (52.7)	0.62
Any thiazolidinedione	973 (17.6)	480 (17.4)	493 (17.9)	0.59
Angiotensin-converting–enzyme inhibitor	2967 (53.8)	1473 (53.3)	1494 (54.3)	0.46
Angiotensin-receptor blocker	838 (15.2)	405 (14.6)	433 (15.7)	0.26
Aspirin	3106 (56.3)	1583 (57.3)	1523 (55.3)	0.15
Beta-blocker	1798 (32.6)	912 (33.0)	886 (32.2)	0.53
Any thiazide diuretic	1473 (26.7)	740 (26.8)	733 (26.6)	0.91
Statin	3299 (59.8)	1641 (59.3)	1658 (60.2)	0.51
Any lipid-lowering agent	3558 (64.5)	1773 (64.1)	1785 (64.8)	0.58
Duration of diabetes — yr				
Median	9	10	9	0.83
Interquartile range	5–15	5–15	5–15	
Glycated hemoglobin — %				
Mean	8.3±1.0	8.3±1.0	8.3±1.0	0.52
Median	8.1	8.1	8.1	
Interquartile range	7.6–8.8	7.6–8.8	7.5–8.8	

Table 1. (Continued.)

Characteristic	All Patients (N=5518)	Fenofibrate (N=2765)	Placebo (N=2753)	P Value
Fasting plasma glucose — mg/dl	175.8±54.9	176.5±54.5	175.1±55.3	0.38
Amputation due to diabetes — no. (%)	110 (2.0)	59 (2.1)	51 (1.9)	0.45
Potassium — mg/dl	4.5±0.4	4.5±0.4	4.5±0.4	0.31
Serum creatinine — mg/dl	0.9±0.2	0.9±0.2	0.9±0.2	0.96
Estimated glomerular filtration rate — no. (%)				
30–49 ml/min/1.73 m^2	141 (2.6)	71 (2.6)	70 (2.5)	0.89
>50 ml/min/1.73 m^2	5347 (97.4)	2668 (97.4)	2679 (97.5)	
Plasma cholesterol — mg/dl				
Total	175.2±37.3	174.7±36.8	175.7±37.9	0.36
Low-density lipoprotein	100.6±30.7	100.0±30.3	101.1±31.0	0.15
High-density lipoprotein	38.1±7.8	38.0±7.8	38.2±7.8	0.25
Plasma triglyceride — mg/dl				
Median	162	164	160	0.15
Interquartile range	113–229	114–232	112–227	

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for glucose to millimoles per liter, multiply by 0.055551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for potassium to millimoles per liter, multiply by 0.2558. To convert the values for creatinine to micromoles per liter, multiply by 88.4. GED denotes general equivalency diploma.
† Race or ethnic group was self-reported, and patients could check multiple categories.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

mentary Appendix 1). Event rates are expressed as the percentage of events per years of follow-up, taking into account the censoring of follow-up data. Kaplan–Meier estimates were used to obtain the proportion of patients who had an event during follow-up.

The primary outcome and total rates of death were monitored by the data and safety monitoring board, using O'Brien–Fleming boundaries determined by the Lan–DeMets approach. For the primary outcome and rates of death, P values have been adjusted to account for the number, timing, and results of interim analyses. Further details regarding the analytic methods are available in Section 11 in Supplementary Appendix 1.

RESULTS

STUDY PATIENTS

A total of 5518 patients were enrolled in the ACCORD Lipid study, with 2765 assigned to receive fenofibrate plus simvastatin and 2753 assigned to receive placebo plus simvastatin. Baseline characteristics were similar between the two groups (Table 1). The mean age was 62 years, and 31% of the patients were female. Thirty-seven percent had a history of a cardiovascular event, and about 60% were taking a statin before enrollment.

The mean duration of follow-up was 4.7 years for the primary outcome and 5.0 years for total rates of death. At the final study visit, 77.3% of the patients in the fenofibrate group and 81.3% of those in the placebo group were taking their assigned medication. At the end of the study, approximately 80% of patients were still taking simvastatin in each group, and an additional 6% were taking an alternative study-approved agent for lowering LDL cholesterol. Additional details related to adherence are in presented in Section 12 in Supplementary Appendix 1. The average daily dose of simvastatin during the follow-up period was 22.3 mg in the fenofibrate group and 22.4 mg in the placebo group.

SAFETY

Elevations of creatine kinase of more than 10 times the upper limit of the normal range at any time during the trial occurred in 10 patients (0.4%) in the fenofibrate group and 9 (0.3%) in the placebo group (for details, see Section 13 in Supplemen-

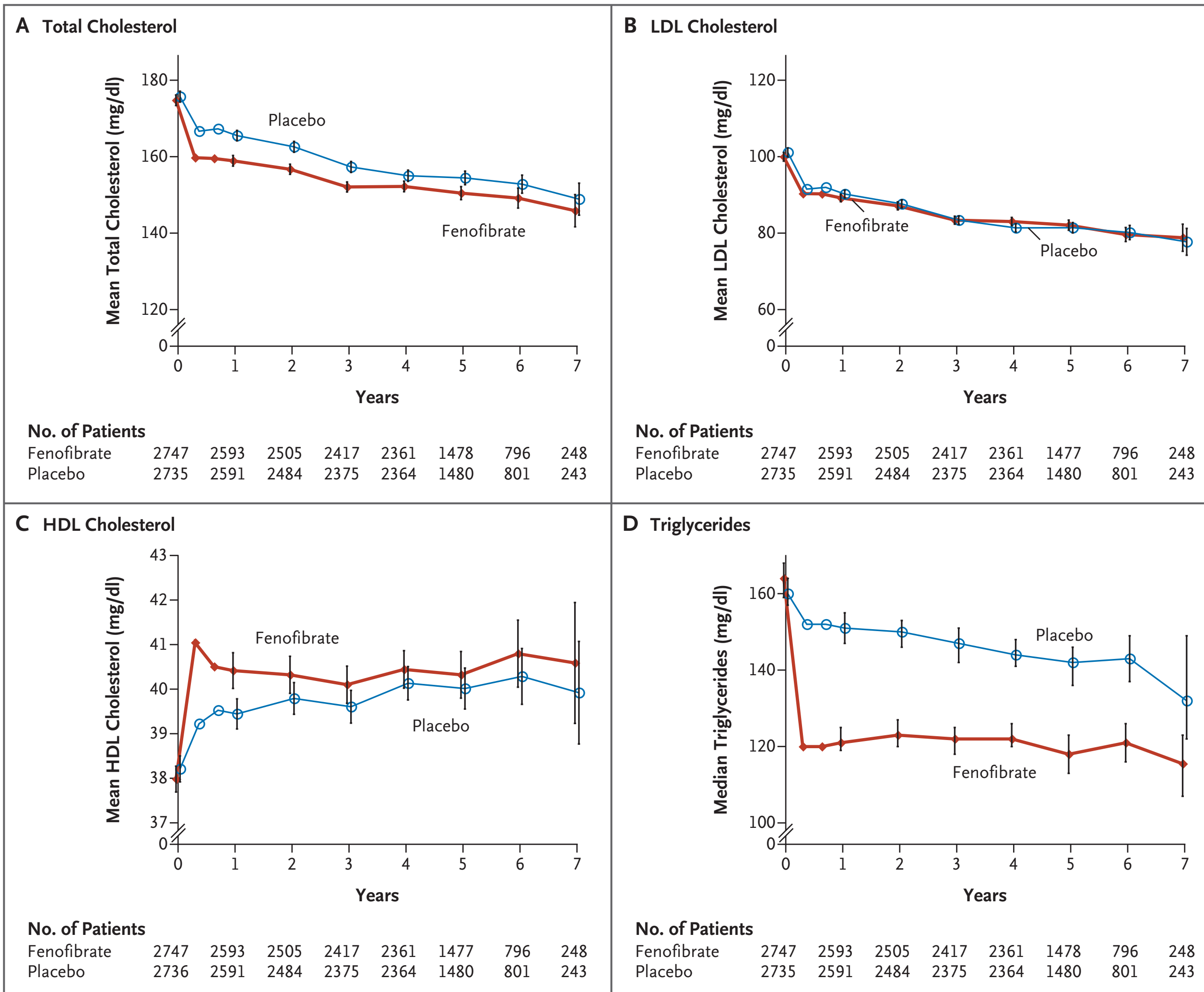

Figure 1. Lipid Values.

Shown are mean plasma levels of total cholesterol (Panel A), low-density lipoprotein (LDL) cholesterol (Panel B), and high-density lipoprotein (HDL) cholesterol (Panel C) and median levels of triglycerides (Panel D) at baseline, 4 months, 8 months, 1 year, and annually thereafter. Nominal P values for differences between the study groups at 4 months and at the end of the study were, respectively: total cholesterol, $P<0.001$ and $P=0.02$; LDL cholesterol, $P=0.11$ and $P=0.16$; HDL cholesterol, $P<0.001$ and $P=0.01$; and triglycerides, $P<0.001$ for both comparisons with the use of nonparametric tests. End-of-study visits were those that occurred in early 2009 and included follow-up at years 4, 5, 6, and 7. The I bars represent 95% confidence intervals. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

tary Appendix 1). An elevation in alanine aminotransferase of more than three times the upper limit of the normal range occurred in 52 patients (1.9%) in the fenofibrate group and 40 (1.5%) in the placebo group.

As noted in other fenofibrate trials,[11,22] mean serum creatinine levels increased from 0.93 to 1.10 mg per deciliter (82 to 97 μmol per liter) in the fenofibrate group within the first year and remained relatively stable thereafter. In the placebo group, mean serum creatinine levels increased from 0.93 to 1.04 mg per deciliter (82 to 92 μmol per liter) during the course of the trial (see Section 15 in Supplementary Appendix 1). The study drug was discontinued by 66 patients (2.4%) in the fenofibrate group and 30 (1.1%) in the placebo group because of a decrease in the estimated GFR. At the last clinic visit, 440 patients (15.9%) in the fenofibrate group and 194 (7.0%) in the placebo group were receiving a reduced dose of either fibrate or placebo because of a decreased estimated GFR. There was no sig-

Table 2. Prespecified Primary and Secondary Outcomes.

Outcome	Fenofibrate (N=2765)		Placebo (N=2753)		Hazard Ratio (95% CI)	P Value
	no. of events	*rate/yr*	*no. of events*	*rate/yr*		
Primary outcome (major fatal or nonfatal cardiovascular event)	291	2.24	310	2.41	0.92 (0.79–1.08)	0.32*
Secondary outcomes						
Primary outcome plus revascularization or hospitalization for congestive heart failure	641	5.35	667	5.64	0.94 (0.85–1.05)	0.30
Major coronary disease event†	332	2.58	353	2.79	0.92 (0.79–1.07)	0.26
Nonfatal myocardial infarction	173	1.32	186	1.44	0.91 (0.74–1.12)	0.39
Stroke						
Any	51	0.38	48	0.36	1.05 (0.71–1.56)	0.80
Nonfatal	47	0.35	40	0.30	1.17 (0.76–1.78)	0.48
Death						
From any cause	203	1.47	221	1.61	0.91 (0.75–1.10)	0.33*
From cardiovascular cause	99	0.72	114	0.83	0.86 (0.66–1.12)	0.26
Fatal or nonfatal congestive heart failure	120	0.90	143	1.09	0.82 (0.65–1.05)	0.10

* P values were adjusted for interim monitoring.
† A major coronary disease event was defined as a fatal coronary event, nonfatal myocardial infarction, or unstable angina.

nificant between-group difference in the incidence of both hemodialysis and end-stage renal disease (75 patients in the fenofibrate group vs. 77 in the placebo group). There was a lower incidence of both microalbuminuria and macroalbuminuria in the fenofibrate group than in the placebo group (see Section 13 in Supplementary Appendix 1).

PLASMA LIPIDS

By the end of the study, the mean LDL cholesterol level fell from 100.0 to 81.1 mg per deciliter (2.59 to 2.10 mmol per liter) in the fenofibrate group and from 101.1 to 80.0 mg per deciliter (2.61 to 2.07 mmol per liter) in the placebo group (Fig. 1, and Section 16 in Supplementary Appendix 1). Mean HDL cholesterol levels increased from 38.0 to 41.2 mg per deciliter (0.98 to 1.07 mmol per liter) in the fenofibrate group and from 38.2 to 40.5 mg per deciliter (0.99 to 1.05 mmol per liter) in the placebo group. Median plasma triglyceride levels decreased from 164 to 122 mg per deciliter (1.85 to 1.38 mmol per liter) in the fenofibrate group and from 160 to 144 mg per deciliter (1.81 to 1.63 mmol per liter) in the placebo group.

CLINICAL OUTCOMES

The annual rate of the primary outcome was 2.2% in the fenofibrate group, as compared with 2.4% in the placebo group (hazard ratio in the fenofibrate group, 0.92; 95% confidence interval [CI], 0.79 to 1.08; P=0.32 after adjustment for monitoring) (Table 2 and Fig. 2). Hazard ratios for the secondary outcomes, including the individual components of the primary outcome, ranged from 0.82 to 1.17 (P≥0.10 for all comparisons) (Table 2). Annual rates of death from all causes were 1.5% in the fenofibrate group and 1.6% in the placebo group (hazard ratio, 0.91; 95% CI, 0.75 to 1.10; P=0.33 for the adjusted comparison). Specific causes of death and enlarged versions of the Figure 2 insets are presented in Sections 17 and 18 in Supplementary Appendix 1.

Study-group effects on the primary outcome across prespecified baseline subgroups are shown in Figure 3. Only sex showed evidence of an interaction according to study group: the primary outcome for men was 11.2% in the fenofibrate group versus 13.3% in the placebo group, whereas the rate for women was 9.1% in the fenofibrate group versus 6.6% in the placebo group (P=0.01 for interaction). There was also a nonsignificant suggestion of heterogeneity when patients who had a triglyceride level in the highest third (≥204 mg per deciliter [≥2.30 mmol per liter]) and an HDL cholesterol level in the lowest third (≤34 mg per deciliter [≤0.88 mmol per liter]) were compared with all the other patients (P=0.057 for interaction). In this subgroup of patients with high

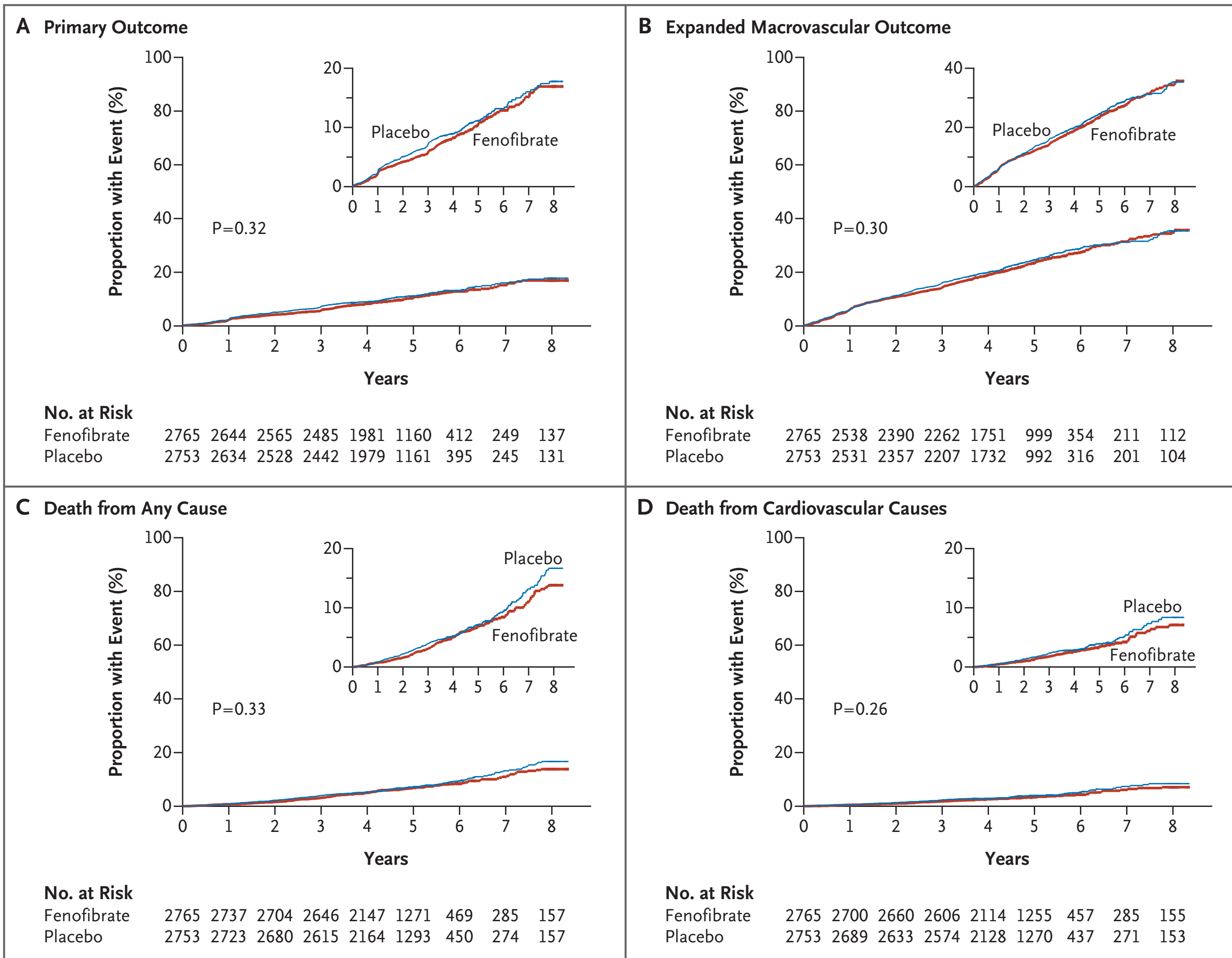

Figure 2. Kaplan–Meier Analyses of the Primary Outcome, Expanded Macrovascular Outcome, and Death.

Shown are the cumulative incidence of the primary outcome (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) (Panel A), the expanded macrovascular outcome (a combination of the primary outcome plus revascularization or hospitalization for congestive heart failure) (Panel B), and death from any cause (Panel C) or from cardiovascular causes (Panel D) during follow-up. The insets show close-up versions of the graphs in each panel.

triglyceride levels and low HDL cholesterol levels, the primary outcome rate was 12.4% in the fenofibrate group, versus 17.3% in the placebo group, whereas such rates were 10.1% in both study groups for all other patients.

DISCUSSION

In this trial, we tested the hypothesis that the use of fenofibrate to increase plasma HDL cholesterol levels and to reduce plasma triglyceride levels in patients with type 2 diabetes who were already receiving simvastatin therapy would result in an additional cardiovascular benefit, as compared with simvastatin therapy alone. However, the rates of the primary outcome did not differ significantly between the fenofibrate group and the placebo group during 4.7 years of treatment and follow-up.

When a study does not support the central hypothesis, it is critical to examine potential reasons for this outcome. One possibility is that the addition of fenofibrate to statin therapy benefited only certain subgroups of patients and that other subgroups that did not benefit diluted the overall effect. Our study was part of a factorial design to simultaneously test the effects of intensive glycemic control[17,20] and combination lipid therapy on cardiovascular outcomes. To allow for efficient

Subgroup	Fenofibrate	Placebo	P Value for Interaction
	% of events (no. in group)		
Overall	10.52 (2765)	11.26 (2753)	
Sex			0.01
Female	9.05 (851)	6.64 (843)	
Male	11.18 (1914)	13.30 (1910)	
Age			0.25
<65 yr	8.11 (1838)	9.50 (1822)	
≥65 yr	15.32 (927)	14.72 (931)	
Race			0.09
Nonwhite	9.70 (856)	8.22 (888)	
White	10.90 (1909)	12.71 (1865)	
Previous cardiovascular disease			0.45
No	7.29 (1757)	7.34 (1745)	
Yes	16.17 (1008)	18.06 (1008)	
Glycemia group			0.36
Standard therapy	10.14 (1391)	11.61 (1370)	
Intensive therapy	10.92 (1374)	10.92 (1383)	
LDL cholesterol			0.12
≤84 mg/dl	9.38 (938)	12.23 (891)	
85–111 mg/dl	9.85 (934)	11.17 (922)	
≥112 mg/dl	12.43 (877)	10.57 (927)	
HDL cholesterol			0.24
≤34 mg/dl	12.24 (964)	15.56 (906)	
35–40 mg/dl	10.12 (860)	9.47 (866)	
≥41 mg/dl	9.08 (925)	8.99 (968)	
Triglycerides			0.64
≤128 mg/dl	9.88 (891)	11.29 (939)	
129–203 mg/dl	10.50 (924)	9.86 (913)	
≥204 mg/dl	11.13 (934)	12.84 (888)	
Triglyceride–HDL cholesterol combination			0.06
Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl	12.37 (485)	17.32 (456)	
All others	10.11 (2264)	10.11 (2284)	
Glycated hemoglobin			0.20
≤8.0%	8.69 (1324)	10.56 (1335)	
≥8.1%	12.20 (1435)	11.94 (1415)	

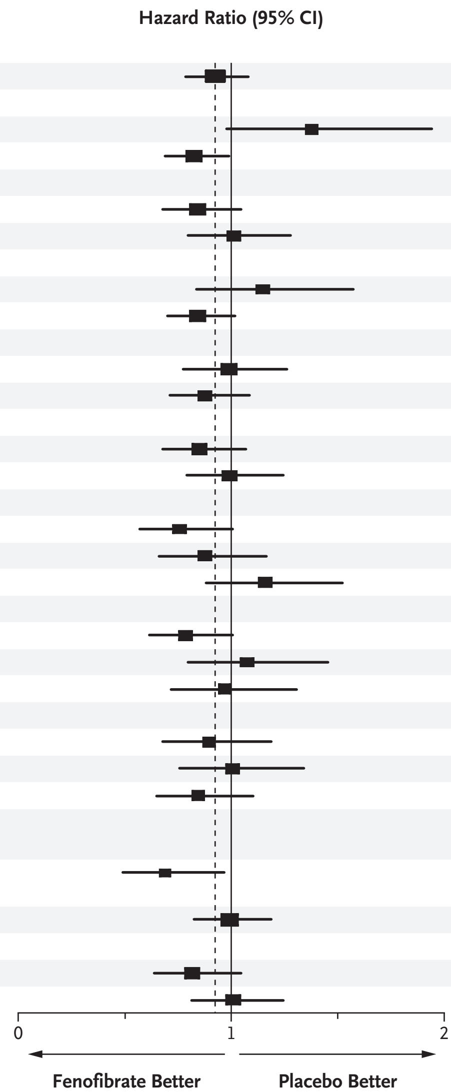

Figure 3. Hazard Ratios for the Primary Outcome in Prespecified Subgroups.
The horizontal bars represent 95% confidence intervals, and the vertical dashed line indicates the overall hazard ratio. The size of each square is proportional to the number of patients. P values are for tests for interaction. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

enrollment of the entire cohort of 10,000 patients while including a group for whom the results of the lipid trial could be widely extrapolated, we used broader inclusion criteria for plasma lipid levels than might have been used if the lipid trial had been an independent study.

A second possibility is that the trial might have had fewer events than anticipated. However, the annual rate of 2.4% in the placebo group was the rate used in the power calculations. Another possibility is poor adherence to the experimental protocol. However, adherence at the end of the study was approximately 80% in both the fenofibrate and placebo groups and 80% for simvastatin. Furthermore, unlike the FIELD study, in which there was a disproportionate drop-in to statin therapy in the placebo group,[11] the prevalence of statin therapy in our study was similar in the fenofibrate and placebo groups. A fourth possibility is that fenofibrate is not as effective as gemfibrozil, which showed benefit in the Helsinki Heart Study (HHS) and VA-HIT,[13,15] studies in which there was no background statin therapy.

In examined subgroups, only sex had a significant interaction with treatment: men seemed to benefit from fenofibrate therapy, whereas there was a trend toward harm among women. This is in contrast to the results of the FIELD study, in which there was no significant interaction effect between treatment and sex on outcome.[11]

There was also a suggestion of heterogeneity according to baseline lipid levels: patients who had both a triglyceride level in the highest third and an HDL cholesterol level in the lowest third (which we termed the subgroup with dyslipidemia) appeared to benefit from fenofibrate, whereas all other patients receiving fenofibrate did not. The mean baseline HDL cholesterol level in the subgroup with dyslipidemia was 29.5 mg per deciliter (0.76 mmol per liter), and the median triglyceride level was 284 mg per deciliter (3.21 mmol per liter), in contrast to the rest of the patients, in whom the mean HDL cholesterol level was 39.9 mg per deciliter (1.03 mmol per liter) and the median triglyceride level was 144 mg per deciliter (1.63 mmol per liter). From baseline to 4 months in the fenofibrate group, the HDL cholesterol level rose 12.9% and the triglyceride level fell 35.0% among patients in the subgroup with dyslipidemia, as compared with a 7.3% rise in the HDL cholesterol level and a 24.1% decrease in the triglyceride level among all other patients receiving fenofibrate. The treatment interaction according to sex for the entire ACCORD Lipid cohort was not observed in the subgroup with dyslipidemia (data not shown).

The results for patients in the subgroup with dyslipidemia are similar to those in post hoc subgroup analyses performed in three of four major fibrate trials, including HHS,[24] the Bezafibrate Infarction Prevention (BIP) trial,[14] and the FIELD trial[12] (see Section 19 in Supplementary Appendix 1 for details). Our subgroup results and those of these previous trials support the view that the addition of fenofibrate to a statin may benefit patients with type 2 diabetes who have substantial dyslipidemia. The use of combination fibrate–statin therapy in such patients is consistent with current guidelines that recommend treatment for patients with hypertriglyceridemia and low HDL cholesterol levels that persist despite statin therapy.[25]

Previous studies[11,22] have raised concern about increases in serum creatinine levels during fenofibrate treatment. Serum creatinine levels increased in the fenofibrate group soon after randomization but thereafter remained constant, as compared with those in the placebo group. In the FIELD study, there was a return of serum creatinine to baseline levels by 8 weeks after the end of the trial.[11] In our study, there was no significant difference in the incidence of end-stage renal disease or need for dialysis between the fenofibrate group and the placebo group. There was a reduction in both microalbuminuria and macroalbuminuria in the fenofibrate group. There has also been longstanding concern regarding an increased risk of myositis or rhabdomyolysis when fibrates are added to statins.[26,27] No evidence for such a risk was noted in our study, a finding that was compatible with evidence that fenofibrate, in contrast to gemfibrozil, does not increase plasma concentrations of statins.[28]

In conclusion, we found that combination therapy with the use of fenofibrate and simvastatin (at a daily dose of 40 mg or less) did not reduce rates of cardiovascular disease, as compared with simvastatin alone. Our findings do not support the use of combination fibrate–statin therapy, rather than statin therapy alone, to reduce cardiovascular risk in the majority of patients with type 2 diabetes who are at high risk for cardiovascular disease.

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

APPENDIX

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