ORIGINAL ARTICLE

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

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ABSTRACT

BACKGROUND

High triglyceride levels are associated with increased cardiovascular risk, but whether reductions in these levels would lower the incidence of cardiovascular events is uncertain. Pemafibrate, a selective peroxisome proliferator–activated receptor α modulator, reduces triglyceride levels and improves other lipid levels.

METHODS

In a multinational, double-blind, randomized, controlled trial, we assigned patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia (triglyceride level, 200 to 499 mg per deciliter), and high-density lipoprotein (HDL) cholesterol levels of 40 mg per deciliter or lower to receive pemafibrate (0.2-mg tablets twice daily) or matching placebo. Eligible patients were receiving guideline-directed lipid-lowering therapy or could not receive statin therapy without adverse effects and had low-density lipoprotein (LDL) cholesterol levels of 100 mg per deciliter or lower. The primary efficacy end point was a composite of nonfatal myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes.

RESULTS

Among 10,497 patients (66.9% with previous cardiovascular disease), the median baseline fasting triglyceride level was 271 mg per deciliter, HDL cholesterol level 33 mg per deciliter, and LDL cholesterol level 78 mg per deciliter. The median follow-up was 3.4 years. As compared with placebo, the effects of pemafibrate on lipid levels at 4 months were –26.2% for triglycerides, –25.8% for very-low-density lipoprotein (VLDL) cholesterol, –25.6% for remnant cholesterol (cholesterol transported in triglyceride-rich lipoproteins after lipolysis and lipoprotein remodeling), –27.6% for apolipoprotein C-III, and 4.8% for apolipoprotein B. A primary endpoint event occurred in 572 patients in the pemafibrate group and in 560 of those in the placebo group (hazard ratio, 1.03; 95% confidence interval, 0.91 to 1.15), with no apparent effect modification in any prespecified subgroup. The overall incidence of serious adverse events did not differ significantly between the groups, but pemafibrate was associated with a higher incidence of adverse renal events and venous thromboembolism and a lower incidence of nonalcoholic fatty liver disease.

CONCLUSIONS

Among patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia, and low HDL and LDL cholesterol levels, the incidence of cardiovascular events was not lower among those who received pemafibrate than among those who received placebo, although pemafibrate lowered triglyceride, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III levels. (Funded by the Kowa Research Institute; PROMINENT ClinicalTrials.gov number, NCT03071692.)

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Although increased triglyceride levels are associated with an elevated cardiovascular risk,[1] whether lowering these levels would also lower the incidence of cardiovascular events remains controversial. One recent trial evaluating high-dose n–3 fatty acid supplementation showed no decrease in the incidence of cardiovascular events despite a 20% decrease in triglyceride levels,[2] whereas in a trial of icosapent ethyl, observed risk reductions did not relate to changes in triglyceride levels.[3] Similarly, a previous trial of niacin[4] and two previous trials of fenofibrate[5,6] showed no significant decrease in cardiovascular risk, although triglyceride levels were lowered by 26%, 29%, and 26%, respectively. Yet, subgroup analyses have strongly suggested that patients with high triglyceride and low high-density lipoprotein (HDL) cholesterol levels might derive substantial clinical benefit from decreased triglyceride levels, particularly if they have concomitant type 2 diabetes.[7,8]

To test this hypothesis directly, we conducted a double-blind, randomized, placebo-controlled trial to evaluate cardiovascular outcomes in patients who received pemafibrate,[9] a potent and selective peroxisome proliferator–activated receptor α (PPARα) modulator. The trial involved patients with type 2 diabetes, triglyceride levels between 200 and 499 mg per deciliter (2.3 and 5.6 mmol per liter), and HDL cholesterol levels of 40 mg per deciliter or less (≤1.0 mmol per liter). Phase 2 studies have shown that, as compared with PPARα agonists such as fenofibrate, pemafibrate had greater triglyceride-lowering and HDL cholesterol–raising actions with fewer off-target effects.[9-14]

METHODS

TRIAL DESIGN AND OVERSIGHT

The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial was a multinational, double-blind, randomized, placebo-controlled, event-driven trial sponsored by Kowa Research Institute, a subsidiary of Kowa, the developer and marketer of pemafibrate. The trial protocol was designed by academic members of the executive committee with input from physicians and operational experts who were employed by the sponsor. A detailed description of the PROMINENT trial design has been published previously.[15] The trial protocol was approved at participating centers by the responsible institutional review board or ethics committee, as applicable, and by regulatory authorities in the 24 countries where the trial was conducted.

Data were gathered by the trial site investigators in collaboration with a contract research organization. All data analyses and end-point adjudication were performed by an academic research organization (the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital) and were independently confirmed by the sponsor and a contract research organization. The first and last authors prepared the first draft of the manuscript, had full access to the trial databases, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

TRIAL POPULATION

Eligibility criteria included the following: a diagnosis of type 2 diabetes, a fasting triglyceride level of 200 to 499 mg per deciliter, and an HDL cholesterol level of 40 mg per deciliter or less. One retest visit for qualifying triglyceride and HDL cholesterol levels was permitted if the first triglyceride level was 175 to 199 mg per deciliter (2.0 to 2.2 mmol per liter) or 500 to 550 mg per deciliter (5.6 to 6.2 mmol per liter) or if the initial HDL cholesterol level was 41 to 45 mg per deciliter (1.1 to 1.2 mmol per liter).

Men who were 50 years of age or older and women who were 55 years of age or older were eligible to participate if they had not had atherosclerotic cardiovascular disease (the primary-prevention cohort) or if they were 18 years of age or older and had established atherosclerotic cardiovascular disease as defined in the protocol (the secondary-prevention cohort). With regard to background lipid-lowering therapy, patients were eligible if they were receiving a stable dose (≥12 weeks) of a qualifying moderate-intensity or high-intensity statin, were untreated or were receiving other lipid-lowering therapy and had a documented LDL cholesterol level of 70 mg per deciliter or less (≤1.8 mmol per liter) within the previous 12 months, or could not receive statin therapy without adverse effects and had a documented LDL cholesterol level of 100 mg per deciliter or less (≤2.6 mmol per liter) within the previous 12 months.

Major exclusion criteria were type 1 diabetes, uncontrolled diabetes, untreated or inadequately treated hypothyroidism or hyperthyroidism, severe heart failure, severe kidney disease, and clinically significant liver disease. Full details regarding inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org. Written informed consent was obtained from all the patients.

TRIAL PROCEDURES

The trial consisted of screening, placebo run-in, and double-blind treatment periods. After informed consent was obtained, the patients entered a 21-day placebo run-in period to assess adherence to oral tablets and the ability to adhere to trial procedures. Patients who met lipid and other eligibility criteria and completed the placebo run-in with high adherence (≥75%, as measured on the basis of tablet count) were randomly assigned in a 1:1 ratio, by means of a computer algorithm, to receive either pemafibrate (0.2-mg tablets twice daily) or matching placebo. Randomization was stratified according sex, history of cardiovascular disease, and statin use. After randomization, telephone visits were alternated with in-person visits, with in-person visits scheduled at 2, 4, 6, 8, and 12 months and every 4 months thereafter.

Previous phase 2 studies of pemafibrate showed slight elevations in LDL particle numbers (with favorable shifts in the distribution of LDL particle size) and small decreases in apolipoprotein B levels,[15] so we took steps to minimize and standardize any changes in concomitant lipid-lowering therapy after randomization. These steps included surveillance of apolipoprotein B levels at 4, 6, and 12 months and annually thereafter (and a recommended algorithm for changes to therapy in patients with persistent or clinically significant increases in apolipoprotein B levels) as well as behavioral and pharmacologic recommendations for instances of severe hypertriglyceridemia (Fig. S1).

END POINTS

At the trial initiation on March 23, 2017, the primary end point was the first occurrence of a major adverse cardiovascular event, defined as a composite of myocardial infarction, ischemic stroke, hospitalization for unstable angina warranting unplanned coronary revascularization, or death from cardiovascular causes. On March 18, 2020, after blinded review of trends in event accrual rates, the primary end point was modified to include any coronary revascularization. No members of the investigative team who were responsible for making this decision had access to unblinded trial data at that time.

Prespecified secondary end points included the following: the original primary end point; a composite of myocardial infarction, ischemic stroke, or death from cardiovascular causes; a composite of the primary end point or hospitalization for heart failure; a composite of the primary end point or death from any cause; individual components of the primary end point; and the end point of new or worsening peripheral artery disease. Additional prespecified end points included in this report were changes in lipid biomarkers, as well as protocol-defined retinopathy and nephropathy (details are provided in the statistical analysis plan, available with the protocol).

STATISTICAL ANALYSIS

This event-driven trial was designed to have 90% power to detect an 18% relative reduction in the risk of an original primary end-point event with pemafibrate as compared with placebo, with accounting for a planned interim analysis and projected loss to follow-up. The initial randomization goal was 10,000 patients, with the additional requirement of at least 300 patients enrolled in Japan and with a targeted composition of at least 20% women and no more than one third from the primary-prevention cohort. The protocol also called for accrual of at least 200 events in women to provide adequate power to exclude the excess hazard associated with fenofibrate observed in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[6]

In March 2020, when the primary end point was expanded to include all coronary revascularizations, the target number of events was increased from 1092 to 1304 in order to detect smaller effect sizes and enhance precision in key prespecified subgroups (patients in the primary-prevention cohort and women). These changes provided the trial with 90% power to detect a relative risk of a primary end-point event that was 16.6% lower in the pemafibrate group than in the placebo group.

Patients were evaluated according to their randomized trial group, irrespective of adherence to

the assigned pemafibrate or placebo. We used analysis of covariance to estimate the effect of treatment on the percentage change in lipid levels from baseline to 4 months, with adjustment for the baseline level of the biomarker as well as randomization strata. For the analysis of the time to a primary end-point event, we used a likelihood-ratio test that was based on a proportional-hazards model stratified according to sex, history of cardiovascular disease, and baseline statin use. A sequential gatekeeping procedure controlled the overall type 1 error at the 5% significance level with the requirement that secondary hypotheses would be tested only if the primary null hypothesis was rejected. The widths of the 95% confidence intervals were not adjusted for multiple comparisons and should not be used to infer definitive treatment effects. The prespecified sensitivity analysis that imputed primary end-point events in patients who withdrew from the trial or were not evaluated at trial end showed a similar treatment effect. This analysis is presented, along with missing biomarker data, in Section S2.

An independent data and safety monitoring board reviewed safety throughout the trial and evaluated futility and efficacy at three prespecified interim time points. On March 18, 2022, on review of the interim data (after 75% of the target number of events had accrued), the data and safety monitoring board unanimously recommended early termination of the trial primarily because prespecified futility boundaries had been crossed.[16] The trial leadership accepted this recommendation and initiated trial close-out, which included a 30-day washout period before the final visit and blood sampling at the end of the trial. Efficacy follow-up ended on April 8, 2022, when the termination of the trial was announced to the trial investigators.

RESULTS

PATIENTS

Trial enrollment began in March 2017, included 876 clinical sites in 24 countries, and was completed in September 2020. The last trial visit occurred in July 2022. A total of 35,085 patients underwent screening, of whom 10,538 (30.0%) underwent randomization and were included in the safety analysis. After randomization, 41 patients were excluded from the intention-to-treat population because of Good Clinical Practice violations (Table S2). Thus, 10,497 patients composed the intention-to-treat population (Fig. S2).

The baseline characteristics of the patients (Table 1 and Table S3) were balanced between the two groups and were generally representative of the population of patients with type 2 diabetes and mixed dyslipidemia (Table S4). The median age was 64 years, 27.5% of the patients were women, and 19.4% identified as Hispanic or Latinx. The primary-prevention cohort made up 33.1% of the trial population. At baseline 10,050 patients (95.7%) were receiving statin therapy and 8410 patients (80.1%) were receiving an angiotensin-converting enzyme inhibitor or an angiotensin II–receptor blocker. The median fasting triglyceride level was 271 mg per deciliter (3.1 mmol per liter), the median HDL cholesterol level was 33 mg per deciliter (0.9 mmol per liter), and the median LDL cholesterol level was 78 mg per deciliter (2.0 mmol per liter) (Table 2). At baseline, 978 patients (9.3%) were receiving a glucagon-like peptide-1 (GLP-1) analogue and 1765 patients (16.8%) were receiving a sodium–glucose cotransporter 2 (SGLT2) inhibitor.

FOLLOW-UP AND ADHERENCE

The median follow-up was 3.4 years (maximum follow-up, 5.0 years). The trial coincided with the coronavirus disease 2019 pandemic, which resulted in temporary interruption of delivery of pemafibrate or placebo to some patients. However, with sponsor support, the majority of the patients were able to continue in the trial by having pemafibrate or placebo shipped directly to their homes and through the use of local rather than central laboratory testing for safety monitoring. Disruptions also occurred in late February through April 2022 because of conflict in Ukraine. Despite these issues, overall trial adherence was high, with a mean adherence of 81.6% at the end of the trial. The incidence of premature discontinuation of pemafibrate or placebo was balanced between the two groups (Fig. S3).

As a result of centralized monitoring of apolipoprotein B levels, the use of ezetimibe at the end of the trial was slightly more common in the pemafibrate group than in the placebo group (Table S5). No major between-group differences were observed with respect to the change in statin intensity or the use of icosapent ethyl, an SGLT2 inhibitor, or a GLP-1 analogue from baseline to the end of the trial.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pemafibrate (N = 5240)	Placebo (N = 5257)
Median age (IQR) — yr	64.0 (58.0–69.0)	64.0 (58.0–70.0)
Female sex — no. (%)	1443 (27.5)	1448 (27.5)
Geographic region — no. (%)		
United States and Canada	1278 (24.4)	1314 (25.0)
Europe	2519 (48.1)	2531 (48.1)
Latin America, South Africa, Japan, Israel, and India	1443 (27.5)	1412 (26.9)
Race — no. (%)†		
White	4477 (85.4)	4542 (86.4)
Black	133 (2.5)	136 (2.6)
Asian	291 (5.6)	251 (4.8)
Other	339 (6.5)	328 (6.2)
Hispanic or Latinx ethnic group — no./total no. (%)†	1014/5201 (19.5)	1007/5220 (19.3)
Median body-mass index (IQR)‡	32.0 (28.7–35.7)	32.0 (28.8–35.6)
Hypertension — no./total no. (%)	4788/5238 (91.4)	4817/5257 (91.6)
Current smoking — no./total no. (%)	854/5188 (16.5)	891/5175 (17.2)
Duration of diabetes ≥10 yr — no./total no. (%)	2430/5238 (46.4)	2403/5257 (45.7)
Primary-prevention cohort — no. (%)§	1732 (33.1)	1739 (33.1)
Secondary-prevention cohort — no. (%)¶	3508 (66.9)	3518 (66.9)
Concomitant medications — no./total no. (%)		
ACE inhibitor or ARB	4194/5240 (80.0)	4216/5257 (80.2)
Any statin	5018/5240 (95.8)	5032/5257 (95.7)
High-intensity statin‖	3621/5214 (69.4)	3610/5230 (69.0)
Glucagon-like peptide-1 analogue	499/5240 (9.5)	479/5257 (9.1)
SGLT2 inhibitor	897/5240 (17.1)	868/5257 (16.5)
Median glycated hemoglobin level (IQR) — %**	7.3 (6.5–8.1)	7.3 (6.5–8.1)

* There were no significant between-group differences in baseline characteristics ($P<0.05$). ACE denotes angiotensin-converting enzyme, ARB angiotensin II–receptor blocker, IQR interquartile range, and SGLT2 sodium–glucose co-transporter 2.
† Race and ethnic group were reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 14 patients in the pemafibrate group and 18 patients in the placebo group.
§ The primary-prevention cohort was composed of men 50 years of age or older and women 55 years of age or older who had not had atherosclerotic cardiovascular disease.
¶ The secondary-prevention cohort was composed of men and women 18 years of age or older who had established atherosclerotic cardiovascular disease.
‖ High-intensity statins were atorvastatin at a dose of at least 40 mg per day or rosuvastatin at a dose of at least 20 mg per day.
** Data were missing for 15 patients in the pemafibrate group and 16 patients in the placebo group.

EFFECTS ON LIPID LEVELS AND OTHER KEY BIOMARKERS

The median percentage change in the fasting triglyceride level from baseline to 4 months was –31.1% in the pemafibrate group and –6.9% in the placebo group, for a relative between-group difference of –26.2%, a difference that persisted over time (Table 2 and Fig. S4). In a subgroup analysis stratified according to statin intensity, these between-group differences were –24.6% in patients who received a high-intensity statin, –28.5% in those who received a moderate-intensity statin, and –34.3% in those who had minimal statin use (because they could not receive

Table 2. Effects of Pemafibrate on Fasting Lipid Levels at 4 Months.*

Variable	Pemafibrate (N = 5240)	Placebo (N = 5257)	Treatment Effect†
	Median Value (IQR)		Mean % Change (95% CI)
Triglyceride-related biomarkers			
Triglyceride level, measured			
Baseline — mg/dl	273 (227 to 342)	269 (226 to 338)	
4 Mo — mg/dl	189 (143 to 253)	254 (193 to 341)	
Median change from baseline — %	−31.1 (−48.9 to −9.6)	−6.9 (−28.4 to 20.2)	−26.2 (−28.4 to −24.10)
VLDL cholesterol level, calculated — mg/dl‡			
Baseline — mg/dl	49 (39 to 63)	49 (39 to 62)	
4 Mo — mg/dl	31 (23 to 42)	43 (32 to 59)	
Median change from baseline — %	−35.0 (−54.1 to −11.5)	−10.5 (−33.3 to 17.4)	−25.8 (−27.8 to −23.9)
Remnant cholesterol level, calculated§			
Baseline — mg/dl	47 (38 to 60)	47 (37 to 59)	
4 Mo — mg/dl	32 (24 to 42)	39 (29 to 52)	
Median change from baseline — %	−31.3 (−49.1 to −8.2)	−15.6 (−36.8 to 10.8)	−18.2 (−20.3 to −16.1)
Remnant cholesterol level, measured			
Baseline — mg/dl	56 (43 to 73)	56 (43 to 72)	
4 Mo — mg/dl	30 (23 to 41)	44 (32 to 61)	
Median change from baseline — %	−43.6 (−57.8 to −24.1)	−20.2 (−38.3 to 3.8)	−25.6 (−27.3 to −24.0)
Apolipoprotein C-III level, measured			
Baseline — mg/dl	15 (13 to 19)	15 (13 to 18)	
4 Mo — mg/dl	11 (9 to 14)	15 (12 to 19)	
Median change from baseline — %	−27.8 (−43.8 to −9.1)	0.0 (−18.8 to 18.8)	−27.6 (−29.1 to −26.1)
Other lipid biomarkers			
Total cholesterol level, measured			
Baseline — mg/dl	161 (139 to 193)	161 (137 to 191)	
4 mo — mg/dl	162 (138 to 190)	158 (134 to 190)	
Median change from baseline — %	−0.5 (−12.2 to 13.2)	−1.2 (−12.1 to 11.0)	0.8 (−0.1 to 1.6)
HDL cholesterol level, measured			
Baseline — mg/dl	33 (29 to 37)	33 (29 to 37)	
4 Mo — mg/dl	36 (30 to 42)	34 (30 to 39)	
Median change from baseline — %	8.3 (−5.3 to 25.0)	3.1 (−7.4 to 15.6)	5.1 (4.2 to 6.1)
LDL cholesterol level, measured			
Baseline — mg/dl	79 (60 to 104)	78 (59 to 102)	
4 Mo — mg/dl	91 (71 to 115)	80 (62 to 105)	
Median change from baseline — %	14.0 (−6.3 to 41.4)	2.9 (−13.5 to 24.6)	12.3 (10.7 to 14.0)
Non-HDL cholesterol level, calculated§			
Baseline — mg/dl	128 (106 to 159)	128 (104 to 157)	
4 Mo — mg/dl	125 (102 to 153)	122 (100 to 154)	
Median change from baseline — %	−2.4 (−18.0 to 15.0)	−2.5 (−16.3 to 13.0)	−0.2 (−1.3 to 1.0)

Table 2. (Continued.)

Variable	Pemafibrate (N = 5240)	Placebo (N = 5257)	Treatment Effect†
	Median Value (IQR)		Mean % Change (95% CI)
Apolipoprotein B level, measured			
Baseline — mg/dl	90 (75 to 108)	89 (74 to 107)	
4 Mo — mg/dl	93 (77 to 111)	87 (73 to 105)	
Median change from baseline — %	3.2 (–12.0 to 19.7)	–1.6 (–13.4 to 11.8)	4.8 (3.8 to 5.8)

* Median levels at baseline and 4 months are shown. All baseline values presented are from the screening visit. Patients could qualify for trial enrollment on the basis of a fasting triglyceride level and high-density lipoprotein (HDL) cholesterol levels from either screening or retest visits. Only one retest was permitted. Information regarding missing data is provided in Section S2 in the Supplementary Appendix. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. CI denotes confidence interval, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.

† The values are derived from analysis-of-covariance models, with the percentage change from baseline to 4 months as the dependent variable, the baseline biomarker level as a covariate, and treatment effect and randomization strata as fixed effects.

‡ The VLDL cholesterol level was calculated by means of preparative ultracentrifugation (the total cholesterol level minus the cholesterol content [gradient density] of <1.006 g per milliliter).

§ The remnant cholesterol level was calculated as the total cholesterol level minus the HDL cholesterol level minus the LDL cholesterol level, and the non-HDL cholesterol level was calculated as the total cholesterol level minus the HDL cholesterol level.

statins without adverse effects or they were receiving a low-intensity statin or no statin).

Pemafibrate, as compared with placebo, also had similar effects on changes from baseline to 4 months and over time on levels of measured very-low-density lipoprotein (VLDL) cholesterol (–25.8%), measured remnant cholesterol (cholesterol transported in triglyceride-rich lipoproteins — such as chylomicrons, very-low-density lipoproteins, and intermediate-density lipoproteins — after lipolysis and lipoprotein remodeling) (–25.6%), and apolipoprotein C-III (–27.6%) (Table 2). An increase in the LDL cholesterol level was observed in the pemafibrate group, with no difference in the total cholesterol or non-HDL cholesterol levels from baseline to 4 months; these findings were consistent with known effects of pemafibrate on cholesterol trafficking between lipoproteins. As a result, a net increase in the between-group difference in apolipoprotein B levels (4.8%) was observed (Table 2).

CLINICAL END POINTS

After randomization, a primary end-point event occurred in 572 patients in the pemafibrate group and 560 patients in the placebo group (hazard ratio, 1.03; 95% confidence interval [CI], 0.91 to 1.15; P=0.67) (Table 3 and Fig. 1). With respect to the key secondary end point of myocardial infarction, ischemic stroke, unstable angina warranting urgent coronary revascularization, or death from cardiovascular causes, the corresponding numbers were 432 patients in the pemafibrate group and 417 patients in the placebo group (hazard ratio, 1.04; 95% CI, 0.91 to 1.19). Effects were neutral for all composite secondary cardiovascular end points and for the individual components of these end points. The hazard ratio for death from cardiovascular causes was 1.00 (95% CI, 0.79 to 1.28), and the hazard ratio for death from any cause was 1.04 (95% CI, 0.91 to 1.20) (Table 3 and Fig. S5). We observed no apparent effect modification in prespecified subgroups (Fig. S6).

ADVERSE EVENTS AND OTHER OUTCOMES OF INTEREST

The incidences of all serious adverse events, infections, and musculoskeletal complications did not differ significantly between the two groups (Table 4). Although there were more total investigator-reported adverse renal events in the pemafibrate group than in the placebo group (in 1463 patients vs. 1347 patients; hazard ratio, 1.12; 95% CI, 1.04 to 1.20; P=0.004), the estimated glomerular filtration rate returned to baseline after pemafibrate or placebo was discontinued (Fig. S7). The number of patients with investigator-reported venous thromboembolism was higher in the pemafibrate group than in the placebo group (in 71 patients vs. 35 patients; hazard ratio, 2.05; 95% CI, 1.35 to 3.17; P<0.001), whereas the

Table 3. Adjudicated Efficacy End Points.

End Point	Pemafibrate (N=5240)		Placebo (N=5257)		Hazard Ratio (95% CI)*	P Value
	No. of Patients with Event	Incidence/ 100 Person-yr	No. of Patients with Event	Incidence/ 100 Person-yr		
Primary composite end point	572	3.60	560	3.51	1.03 (0.91–1.15)	0.67
Components of the primary composite end point						
Nonfatal myocardial infarction	205	1.25	178	1.08	1.16 (0.95–1.42)	—
Nonfatal ischemic stroke	95	0.58	104	0.63	0.92 (0.69–1.21)	—
Coronary revascularization	334	2.08	344	2.13	0.98 (0.84–1.13)	—
Death from cardiovascular causes	133	0.78	133	0.78	1.00 (0.79–1.28)	—
Secondary cardiovascular end points						
Key secondary primary end point†	432	2.68	417	2.57	1.04 (0.91–1.19)	—
Nonfatal myocardial infarction, nonfatal ischemic stroke, or death from cardiovascular causes	381	2.35	376	2.31	1.02 (0.88–1.18)	—
Primary end point or hospitalization for heart failure	650	4.13	635	4.02	1.03 (0.92–1.15)	—
Primary end point or death from any cause	806	5.07	790	4.95	1.02 (0.93–1.13)	—
New or worsening peripheral artery disease	136	0.83	158	0.96	0.87 (0.69–1.09)	—
Death from any cause	414	2.44	399	2.34	1.04 (0.91–1.20)	—

* The widths of the 95% confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. There was no violation of the proportional-hazards assumption (see the Supplementary Appendix).
† The key secondary end point (the original primary end point) was myocardial infarction, ischemic stroke, unstable angina warranting hospitalization for urgent coronary revascularization, or death from cardiovascular causes.

number of patients with any investigator-reported hepatic adverse event was lower in the pemafibrate group than in the placebo group (in 219 patients and 265 patients; hazard ratio, 0.83; 95% CI, 0.69 to 0.99; P=0.04), as was the number of patients with investigator-reported nonalcoholic fatty liver disease (in 155 patients and 200 patients, hazard ratio, 0.78; 95% CI, 0.63 to 0.96; P=0.02) (Table 4).

DISCUSSION

In this double-blind, randomized, placebo-controlled trial involving patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia, a low HDL cholesterol level, and a well-controlled LDL cholesterol level, the incidence of cardiovascular events was not lower among patients who received pemafibrate than among those who received placebo, although levels of triglycerides, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III were 26 to 28% lower in the pemafibrate group. There was no apparent heterogeneity in treatment effects across any prespecified subgroup of patients, including women, patients in the primary- or secondary-prevention cohorts, statin intensity groups, or in patients with baseline triglyceride, LDL cholesterol, non-HDL cholesterol, or apolipoprotein B levels above or below the population median.

These neutral findings with pemafibrate are consistent with those from the contemporary Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial[2] of high-dose n–3 fatty acids, the previous Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial[4] of niacin, and the previous Fenofibrate Interven-

tion and Event Lowering in Diabetes (FIELD)[5] and ACCORD[6] trials of fenofibrate, all of which enrolled populations with high triglyceride levels, evaluated therapies that lower triglyceride levels by 20 to 30%, or both. Our data are also partially consistent with those of the contemporary Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) trial of icosapent ethyl, in which observed risk reductions did not relate to changes in triglyceride levels.[3] With the exception of the FIELD trial, all these trials involved patients who were receiving statins. In the FIELD trial, the disproportionate drop-in to statin therapy in the placebo group may have explained the neutral findings.[5] In this context, our data on a fourth pharmacologic approach add to growing controversy about lowering of triglyceride levels as a method of reducing residual cardiovascular risk among patients who are already receiving intensive statin therapy.

Pemafibrate is a potent and selective synthetic agonist of the PPARα nuclear receptor that lowers plasma triglyceride levels by increasing the activity of lipoprotein lipase (the critical enzyme for hydrolysis of VLDL cholesterol and chylomicron triglycerides) and by reducing hepatic VLDL cholesterol apolipoprotein B levels and triglyceride production,[9-14] although the findings regarding the latter effect of PPARα agonism are less consistent than those regarding increases in the activity of lipoprotein lipase.[17-19] Increased lipolysis of triglycerides in VLDL cholesterol and chylomicrons occurs in the following ways: through drug-induced activation of lipoprotein lipase in the capillary circulation of adipose tissue and muscle; through inhibition of the secretion of apolipoprotein C-III, an inhibitor of lipoprotein lipase; and through increased secretion of apolipoprotein A-V, an activator of lipoprotein lipase. These actions reduce the number of large nascent triglyceride-rich lipoproteins in the plasma pool. Phase 2 trials of pemafibrate involving profiling of lipoprotein particles have shown a decrease in plasma levels of chylomicrons and large and medium VLDL particles, with no change in levels of small VLDL particles; increases in levels of large LDL particles; increases in levels of small and medium HDL particles; and either no change or major reductions in levels of small LDL particles, depending on the method used.[10,11,20]

The data from the PROMINENT trial are consistent with increased efficiency in conversion of

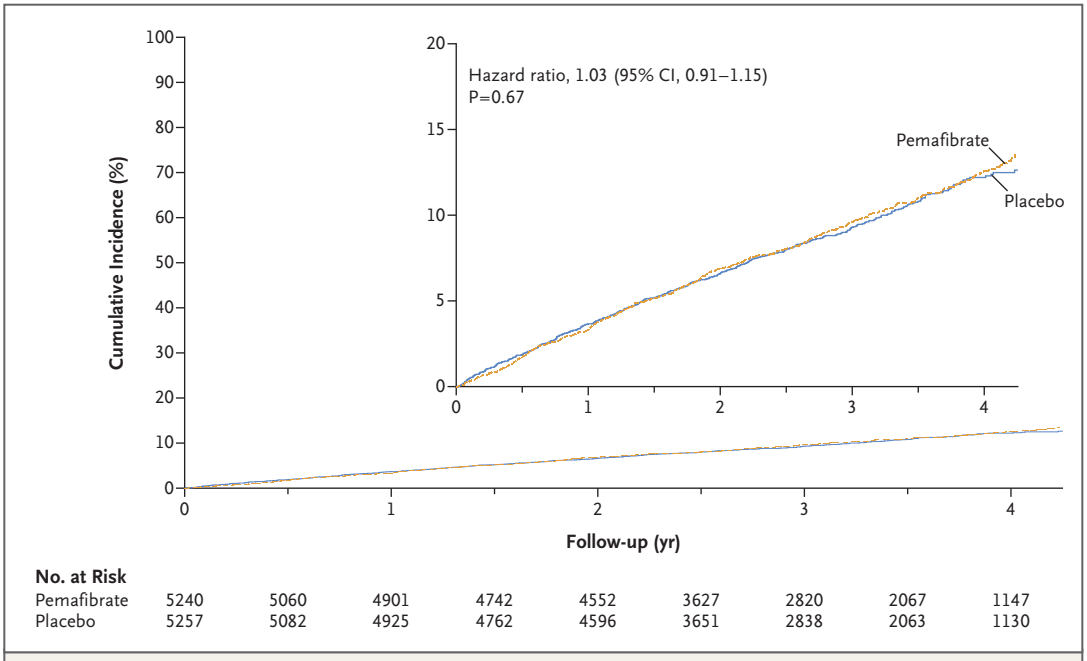

Figure 1. Cumulative Incidence of Cardiovascular Events.

Shown are Kaplan–Meier event curves for the primary trial end point of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. The inset shows the same data on an expanded y axis.

Table 4. Investigator-Reported Safety Outcomes and Other Tertiary Efficacy Outcomes.*

Event	Pemafibrate (N=5240)		Placebo (N=5257)		Hazard Ratio (95% CI)†	P Value
	Event	Incidence Rate	Event	Incidence Rate		
	no. of patients	*per 100 person-yr*	*no. of patients*	*per 100 person-yr*		
Any serious adverse event	1970	14.74	1914	14.18	1.04 (0.98–1.11)	0.23
Any infection-related adverse event	2797	25.86	2877	26.65	0.97 (0.92–1.02)	0.26
Covid-19 infection	646	4.00	621	3.81	1.05 (0.94–1.17)	0.41
Confirmed Covid-19–related death‡	101	0.60	106	0.62	0.96 (0.72–1.27)	0.81
Any musculoskeletal adverse event	1605	12.29	1693	13.06	0.94 (0.88–1.01)	0.08
Myopathy	22	0.13	35	0.21	0.63 (0.35–1.11)	0.12
Rhabdomyolysis	4	0.02	2	0.01	2.01 (0.29–22.26)	0.68
Any renal adverse event	1463	10.67	1347	9.55	1.12 (1.04–1.20)	0.004
Chronic kidney disease	180	1.11	117	0.71	1.56 (1.23–1.99)	<0.001
Acute kidney injury	160	0.97	106	0.64	1.53 (1.19–1.97)	0.001
Proteinuria	110	0.67	101	0.61	1.10 (0.83–1.45)	0.55
Diabetic nephropathy§	848	5.73	779	5.16	1.11 (1.01–1.23)	0.04
Any hepatic adverse event¶	219	1.35	265	1.64	0.83 (0.69–0.99)	0.04
AST >3× ULN	25	0.15	39	0.23	0.64 (0.37–1.09)	0.11
ALT >3× ULN	27	0.16	42	0.25	0.65 (0.38–1.07)	0.10
Nonalcoholic fatty liver disease	155	0.95	200	1.22	0.78 (0.63–0.96)	0.02
Other protocol-defined events of clinical interest§						
Cholelithiasis	125	0.76	119	0.72	1.06 (0.82–1.37)	0.70
Acute pancreatitis	26	0.16	28	0.17	0.94 (0.53–1.65)	0.91
Atrial fibrillation	220	1.35	209	1.27	1.06 (0.88–1.29)	0.55
Venous thromboembolism	71	0.43	35	0.21	2.05 (1.35–3.17)	<0.001
Pulmonary embolism	40	0.24	19	0.11	2.13 (1.20–3.89)	0.008
Deep-vein thrombosis	45	0.27	19	0.11	2.39 (1.37–4.33)	0.001
Diabetic neuropathy	266	1.65	287	1.77	0.93 (0.79–1.10)	0.43
Diabetic retinopathy	140	0.86	161	0.98	0.87 (0.69–1.10)	0.27

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, Covid-19 coronavirus disease 2019, and ULN upper limit of the normal range.
† These Covid-19–related deaths were confirmed by the clinical end-point committee.
‡ Exact 95% confidence intervals are provided for the relative incidence rate between the two groups.
§ These events were defined in the trial protocol and queried at each visit.
¶ These events were determined on the basis of central laboratory assessments.

triglyceride-rich lipoprotein remnants to LDL rather than their removal by the liver.[21] Thus, pemafibrate-mediated reductions in triglyceride-rich lipoprotein remnants were accompanied by increases in plasma LDL cholesterol and apolipoprotein B levels, with no overall change in non-HDL cholesterol and total cholesterol levels. The lack of benefit shown in the trial suggests that beyond the effects on triglyceride-rich lipoprotein remodeling, enhanced clearance of triglyceride-rich lipoprotein remnant particles from the circulation — rather than their conversion to LDL particles — may be needed to abrogate the atherogenic effects of more remnants in patients with hypertriglyceridemia. These issues may be clarified in ongoing trials of agents that use alter-

native pathways to lower levels of triglycerides and remnant particles, including inhibition of apolipoprotein C-III and the angiopoietin-like 3 protein (e.g., ClinicalTrials.gov numbers, NCT05552326, NCT05256654, NCT04998201, NCT04832971, and NCT04720534).

In our trial, pemafibrate was not associated with an increase in the total incidence of serious adverse events. The increases in the numbers of patients with venous thromboembolism and renal adverse events conform with previous observations regarding fenofibrate.[5] The lower numbers of total hepatic adverse events and investigator-reported cases of nonalcoholic fatty liver disease with pemafibrate than with placebo have potential therapeutic interest. These findings are consistent with those in a trial that evaluated liver biomarkers and liver stiffness using standardized hepatic imaging.[22] A second trial of pemafibrate is under way to evaluate histologic markers of liver fibrosis (NCT05327127).

The PROMINENT trial enrolled exclusively patients who had hypertriglyceridemia with diabetes and LDL cholesterol levels that were at or close to guideline-recommended targets, largely because of the concomitant intensive use of statin therapy. Nonetheless, our data cannot rule out the possibility that the observed increases in apolipoprotein B and LDL cholesterol levels in the pemafibrate group negated any benefit of reduction in triglyceride or remnant cholesterol levels. Thus, our data further highlight the complexity of lipid mediators of residual risk among patients with insulin resistance who are receiving statin therapy.[6,23-25]

In this randomized, placebo-controlled trial involving patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia, low levels of HDL cholesterol, and well-controlled levels of LDL cholesterol, pemafibrate did not reduce the risk of cardiovascular events. However, this agent was associated with lower triglyceride, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III levels.

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APPENDIX

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