Research

Association of Fenofibrate Therapy With Long-term Cardiovascular Risk in Statin-Treated Patients With Type 2 Diabetes

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➕ Supplemental content

IMPORTANCE Patients with type 2 diabetes are at high risk of cardiovascular disease (CVD) in part owing to hypertriglyceridemia and low high-density lipoprotein cholesterol. It is unknown whether adding triglyceride-lowering treatment to statin reduces this risk.

OBJECTIVE To determine whether fenofibrate reduces CVD risk in statin-treated patients with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS Posttrial follow-up of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Study between July 2009 and October 2014; 5 years of follow-up were completed for a total of 9.7 years at general community and academic outpatient research clinics in the United States and Canada. Of the original 5518 ACCORD Lipid Trial participants, 4644 surviving participants were selected based on the presence of type 2 diabetes and either prevalent CVD or CVD risk factors and high-density lipoprotein levels less than 50 mg/dL (<55 mg/dL for women and African American individuals).

INTERVENTIONS Passive follow-up of study participants previously treated with fenofibrate or masked placebo.

MAIN OUTCOMES AND MEASURES Occurrence of cardiovascular outcomes including primary composite outcome of fatal and nonfatal myocardial infarction and stroke in all participants and in prespecified subgroups.

RESULTS The 4644 follow-on study participants were broadly representative of the original ACCORD study population and included significant numbers of women (n = 1445; 31%), nonwhite individuals (n = 1094; 21%), and those with preexisting cardiovascular events (n = 1620; 35%). Only 4.3% of study participants continued treatment with fenofibrate following completion of ACCORD. High-density lipoprotein and triglyceride values rapidly equalized among participants originally randomized to fenofibrate or placebo. Over a median total postrandomization follow-up of 9.7 years, the hazard ratio (HR) for the primary study outcome among participants originally randomized to fenofibrate vs placebo (HR, 0.93; 95% CI, 0.83-1.05; *P* = .25) was comparable with that originally observed in ACCORD (HR, 0.92; 95% CI, 0.79-1,08; *P* = .32). Despite these overall neutral results, we continued to find evidence that fenofibrate therapy effectively reduced CVD in study participants with dyslipidemia, defined as triglyceride levels greater than 204 mg/dL and high-density lipoprotein cholesterol levels less than 34 mg/dL (HR, 0.73; 95% CI, 0.56-0.95).

CONCLUSIONS AND RELEVANCE Extended follow-up of ACCORD-lipid trial participants confirms the original neutral effect of fenofibrate in the overall study cohort. The continued observation of heterogeneity of treatment response by baseline lipids suggests that fenofibrate therapy may reduce CVD in patients with diabetes with hypertriglyceridemia and low high-density lipoprotein cholesterol. A definitive trial of fibrate therapy in this patient population is needed to confirm these findings.

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Cardiovascular disease (CVD) risk is increased in patients with type 2 diabetes, particularly in older patients and those with other risk factors for CVD. Compared with their counterparts without diabetes, the relative risk of fatal and nonfatal CVD events can be 2- to 3-fold and 3- to 4-fold higher, respectively, in men and women with diabetes.[1-4] Increased risk of CVD in type 2 diabetes is attributable in part to the high prevalence of associated risk factors including hypertension and diabetic dyslipidemia, the latter characterized by elevated plasma triglyceride levels and low plasma levels of high-density lipoprotein cholesterol (HDL-C).[5,6] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) was a randomized, multicenter, partial double 2 × 2 factorial trial that enrolled 10 251 individuals with type 2 diabetes mellitus who were at high risk of CVD events. The ACCORD study tested the effects of intensive control of blood glucose, blood pressure, and plasma lipids on CVD risk in patients with type 2 diabetes.[7]

The ACCORD-Lipid was conducted in a subset of 5518 ACCORD participants and tested the hypothesis that combination statin-fibrate therapy would more effectively reduce CVD risk compared with statin alone in patients with type 2 diabetes. Although triglycerides and HDL-C are widely recognized as biomarkers of CVD risk,[8] it is uncertain whether pharmacologic therapy directed toward lowering triglyceride levels and raising HDL-C effectively reduces that risk, particularly when added to statin therapy. In ACCORD-Lipid, following a mean 4.7 years of treatment, the rate of occurrence of the composite primary outcome measure of myocardial infarction, stroke, and fatal CVD was not significantly lower in participants randomized to fenofibrate therapy compared with those randomized to placebo.[9] There were also no significant differences between the 2 study groups for any of the prespecified secondary outcomes, including fatal cardiovascular events, nonfatal MI, or nonfatal stroke.[9] In contrast to these findings, prespecified subgroup analyses in ACCORD-Lipid detected significant heterogeneity in treatment effect by baseline lipids suggesting benefit for those with dyslipidemia, predefined as having both high triglycerides and low HDL-C levels at baseline. Heterogeneity in fenofibrate response was also noted by sex, with evidence of benefit for men vs possible harm in women.

The neutral overall CVD outcomes of the glycemia, blood pressure, and lipid treatment arms of ACCORD, along with the findings of heterogeneity of the effect of fenofibrate on cardiovascular outcomes in ACCORD-Lipid,[9-12] supported the need for additional follow-up of participants to detect emergence of long-term "legacy" effects of the interventions and to explore the findings of heterogeneity by baseline dyslipidemia and sex. The ACCORD Follow-On Study (ACCORDION) was designed and conducted for this purpose. In this study, we describe the outcome of extended observational follow-up of ACCORD-Lipid participants in ACCORDION. The extended follow-up findings of the ACCORD blood pressure and glycemia intervention groups have been or will be reported separately.[13]

Key Points

Question Does fenofibrate reduce cardiovascular disease risk in statin-treated patients with type 2 diabetes?

Findings In this posttrial follow-up of the Action to Control Cardiovascular Risk in Diabetes Lipid Study, fenofibrate therapy was associated with reduced cardiovascular disease in study participants with dyslipidemia, defined as triglyceride levels greater than 204 mg/dL and high-density lipoprotein cholesterol levels less than 34 mg/dL.

Meaning Extended follow-up of ACCORD-lipid trial participants confirms the original neutral effect of fenofibrate in the overall study cohort; the continued observation of heterogeneity of treatment response by baseline lipids suggests that fenofibrate therapy may reduce CVD in patients with diabetes with hypertriglyceridemia and low high-density lipoprotein cholesterol.

Methods

ACCORD and ACCORDION Study Design, Eligibility, and Conduct

The rationale, design, and primary results of ACCORD were previously reported.[9-12,14] Briefly, all participants underwent 2 sequential randomizations, the first to intensive vs standard glucose-lowering therapy in the overarching glycemia trial and the second to either intensive vs standard blood pressure or lipid therapy in the ACCORD-Blood Pressure or ACCORD-Lipid trials, respectively, in a partial double 2 × 2 design (**Figure 1**). The primary outcome for all 3 trials was the first occurrence of a nonfatal myocardial infarction (MI), nonfatal stroke, or death from a cardiovascular cause. Participants were recruited from 77 clinical sites across the United States and Canada between January 2001 and October 2005. Follow-up of ACCORD ended in June of 2009.

The ACCORD-Lipid trial, conducted in 5518 participants, was a randomized, placebo-controlled, double-blind treatment arm of ACCORD in which all participants received simvastatin to attain contemporary guideline-based low-density lipoprotein cholesterol (LDL-C) treatment goals[7,15] and were randomly assigned to receive either fenofibrate or matched placebo. In addition to fulfilling the overall ACCORD eligibility criteria, participants were specifically eligible for ACCORD-Lipid if they also met the following: (1) LDL-C levels between 60 mg/dL and 180 mg/dL (to convert to millimoles per liter, multiply by 0.0259), inclusive; (2) HDL-C levels less than 55 mg/dL for women and African American individuals less than 50 mg/dL for all other groups (to convert to millimoles per liter, multiply by 0.0259); and (3) triglyceride levels less than 750 mg/dL if not receiving a lipid medication or less than 400 mg/dL if receiving a lipid medication (to convert to millimoles per liter, multiply by 0.0113). All participants provided written informed consent. Open-labeled simvastatin therapy began at the randomization visit, and the dose was modified over time in response to changing guidelines.[15] The masked fenofibrate/placebo medication was fenofibrate was 160 mg/d in participants with normal renal function and 48 mg/d for

Figure 1. Action to Control Cardiovascular Risk in Diabetes (ACCORD)/
ACCORD Follow-On Study (ACCORDION) CONSORT Diagram
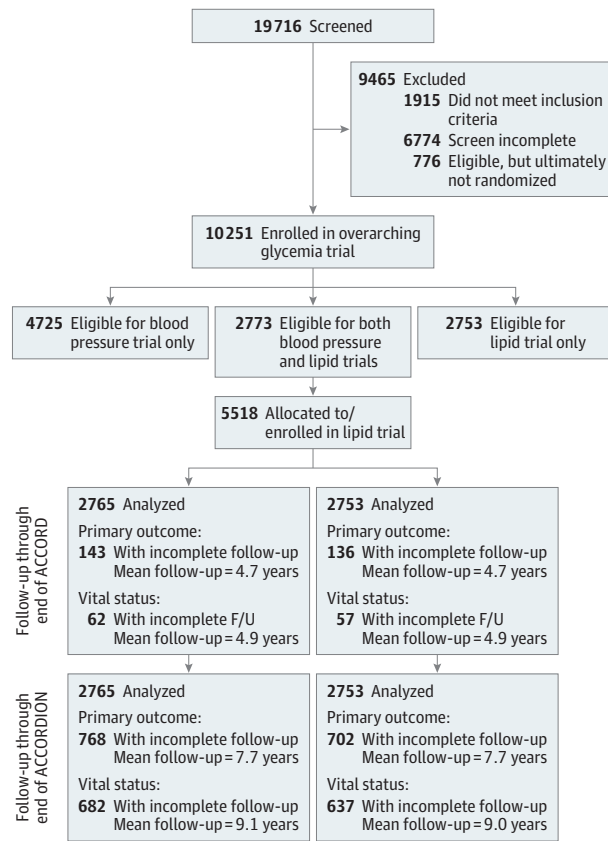
In the ACCORD study, eligible participants underwent 2 sequential randomizations, the first to intensive vs standard glycemia therapy followed by a second randomization to intensive vs standard blood pressure or lipid treatment in a double 2 × 2 factorial design. In the ACCORD lipid trial, participants were randomized to either fenofibrate or placebo on a background of statin therapy. Following completion of ACCORD, a total of 4644 surviving Lipid trial participants agreed to extended passive (nontreatment) follow-up in ACCORDION. Rates of occurrence of cardiovascular end points during the original study and during extended follow-up were assessed in all study participants with censoring for the last date of follow-up.

those with an estimated glomerular filtration rate less than 50 mL/min/1.73 M.[215]

The ACCORD closeout visits were completed by June 2009. Following approval by the coordinating center (Wake Forest University) and participating clinical site institutional review board approvals, consenting participants were invited at these final trial visits to participate in the posttrial, nontreatment, observation-only ACCORDION study. Participant contacts were scheduled approximately every 6 months. These consisted of 2 in-clinic with 4 additional telephone visits annually. Information was collected regarding CVD events, hospitalizations, and medication usage. In-clinic visits also included a physical examination and, at the first and last visits, collection of urine and blood samples for analysis, a standardized electrocardiogram recording, and health-related quality of life data. Follow-up ended on October 31, 2014, or 60 months post-ACCORD, for a total of 5 years of posttrial observation. More

detailed information can be found in the ACCORDION trial protocol (Supplement 2). A complete listing of the ACCORD/ ACCORDION study group is provided in Supplement 1.

Prespecified Outcomes, Subgroups, Event Ascertainment

The prespecified primary outcome for ACCORDION-Lipid was the same as for ACCORD: the first postrandomization occurrence of a major cardiovascular event, specifically nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.[7] Secondary outcomes included an expanded composite macrovascular outcome, a major coronary heart disease event, nonfatal myocardial infarction, nonfatal stroke, total fatal/nonfatal stroke, all-cause mortality, cardiovascular mortality, total fatal/nonfatal congestive heart failure, and CVD-free survival. The consistency of intervention effects was also examined across the same prespecified baseline subgroups examined in ACCORD including sex, age, race/ethnicity, baseline CVD history, hemoglobin A1$_c$, glycemia treatment assignment, tertiles of LDL-C, HDL-C ,and triglyceride, as well as in those with and without dyslipidemia at baseline (defined as the combination of the highest tertile of triglyceride and lowest tertile of HDL-C).

Based on findings of concordance between outcomes reported by investigators and adjudication of outcomes by a centralized endpoint committee in ACCORD (eTable 1 in Supplement 3) The ACCORDION analyses were conducted using outcomes reported by site investigators during both the active (trial) and passive follow-up period, regardless of the original adjudication classification.

Statistical Analysis

Statistical analyses were done by the ACCORDION Coordinating Center using SAS, version 9.4 (SAS Institute), according to a prespecified plan that was finalized before any analyses began. A nominal 2-tailed level of significance of $P < .05$ was used for all analyses without adjustment for multiple testing.

Baseline characteristics of participants enrolled in ACCORD-Lipid and a comparison of those who consented to the posttrial passive follow-up were summarized using means, standard deviations, and percentages. Effects of the original interventions on lipid levels during the active treatment phase and subsequent follow-up were estimated by calculating the mean lipid levels and 95% confidence intervals at follow-up visits by treatment group from the date of randomization through the end of the trial and then beyond through the end of ACCORDION. Follow-up for each participant was defined as the time from randomization until the last date for which the participant's health status was available (Figure 1). All comparisons of intervention groups were performed according to the intention-to-treat principle.[16]

Analyses were conducted using both the original mean 4.7 years of treatment (ACCORD) and with addition of the 5 years of passive posttrial follow-up in ACCORDION, for a mean of 9.7 years of follow-up. The number and annual percentage of participants who had a postrandomization event was determined using Kaplan-Meier estimates. Cox proportional hazards regression analyses were used to estimate the long-term effect of allocation to either fenofibrate or placebo on the primary and

secondary outcomes, using a χ^2 statistic from a likelihood ratio test obtained from proportional hazards models with and without the term for intervention arm. Hazard ratios and 95% confidence intervals were calculated after accounting for variables that were prespecified in the prior ACCORDION analyses. Analyses were conducted on all 5518 ACCORD-Lipid trial participants with censoring of outcomes on the date of the last available information. The consistency of the effect of the study group assignment of the primary outcome and mortality within prespecified subgroups was assessed with the use of statistical tests of interactions between the treatment effect and the subgroup within the Cox models.

Results

Of the original 5518 men and women enrolled in the ACCORD-Lipid Trial,[9] 4644 provided written consent to be followed up during the posttrial period, representing 90% of surviving participants. The baseline characteristics at the time of entry into ACCORD among those consenting to participate in ACCORDION were similar to those of the entire original ACCORD-Lipid cohort including plasma lipoproteins and prevalence of preventive therapies such as statins (**Table 1**). In contrast, the 874 ACCORD participants who did not consent to post-ACCORD follow-up, including those who died during ACCORD, were older, more likely to be nonwhite, and more likely to have had a prior cardiovascular event, a lower prevalence of statin therapy, and a higher LDL-C on entry into ACCORD (Table 1).

The mean duration of follow-up during ACCORD-Lipid was 4.7 years for the primary outcome and 5.0 years for all-cause mortality. With the addition of posttrial follow-up, the overall mean duration of follow-up was 7.7 years for the primary outcome and 9.1 years for all-cause mortality. The maximum length of follow-up for individual participants was more than 12 years. At the final ACCORD study visit, 4754 of the participants (86.0%) remained on a statin and 2137 participants (77.3%) originally assigned to fenofibrate remained on fenofibrate.[9] Following completion of ACCORD, further lipid treatment was guided by primary care clinicians who continued to prescribe statin therapy in 2476 ACCORDION participants (74.1%). In contrast, only 144 ACCORDION participants (4.3%) were continued or started on fibrate therapy following completion of ACCORD.

Plasma Lipids
At the time of entry into ACCORD, fasting plasma lipids at baseline were similar between the participants assigned to fenofibrate and placebo[9] (eFigure 1 in Supplement 3). At entry into ACCORD, 3299 ACCORD-Lipid trial participants (59.8%) were already on statin therapy, and mean LDL was approximately 100 mg/dL (Table 1). During ACCORD, all participants were treated with simvastatin at a dose of 20 mg/d to 40 mg/d.[9] Low-density lipoprotein cholesterol levels progressively decreased to a mean of 80 mg/dL in the placebo group and 81.1 mg/dL in the fenofibrate group over the course of the trial because statin therapy was initiated in all participants and was

intensified in response to accrual of safety information and in response to evolving guidelines[9,15,17] (eFigure 1 in Supplement 3). During the posttrial follow-up period, LDL-C levels declined slightly from a mean of 80.2 mg/dL at the first follow-up visit to an average of 77 mg/dL in both groups. During ACCORD, triglyceride levels were reduced by 22%, from a mean of 187 mg/dL to 145 mg/dL in participants randomized to fenofibrate and declined 8.7%, from a mean of 186.2 mg/dL to 170 mg/dL in those randomized to placebo[9] (eFigure 1 in Supplement 3). During the posttrial period, triglyceride levels continued to decline in the placebo group and increased in the fenofibrate group to a mean of 160.8 mg/dL in both groups, reflecting high rates of discontinuation of fibrate therapy following completion of ACCORD (eFigure 1 in Supplement 3). During ACCORD, HDL-C increased 8.4% in the fenofibrate group (from 38.0 mg/dL to 41.2 mg/dL) and 6.0% in the placebo group (from 38.2 mg/dL to 40.5 mg/dL).[9] During the posttrial period, HDL-C levels declined to a mean level of 40.5 mg/dL in participants originally randomized to fenofibrate to levels comparable with those in participants originally randomized to placebo (eFigure 1 in Supplement 3).

Clinical Outcomes
Rates of occurrence by treatment assignment and hazard ratios for investigator-reported primary and secondary cardiovascular outcome measures during the entire study period, including extended follow-up, are presented in **Table 2**. Following a mean of 9.0 total years of follow-up, 508 primary end point events occurred in the fenofibrate group vs 539 in the placebo group (hazard ratio [HR], 0.93; 95% CI, 0.83-1.05; P = .25) (Table 2). The annual primary outcome rate was 2.38% among participants randomized to fenofibrate vs 2.55% among those randomized to placebo. The HR for the primary end point during extended follow-up in ACCORDION was essentially identical to that observed during the 4.7-year active treatment phase of ACCORD (HR, 0.92; 95% CI, 0.79-1.08; P = .32) (Table 2). Thus, the additional 5 years of follow-up did not change the original neutral findings of the ACCORD study.[9] Similarly, the hazard ratios for the secondary outcomes, including the individual components of the primary outcome, were not statistically different between treatment groups and were comparable with those observed during ACCORD (Table 2). Kaplan-Meier curves describing the almost 10-year accumulation of major cardiovascular events in the 2 groups visually confirm the comparable rates of accrual of outcomes in the 2 treatment groups (**Figure 2**).

In contrast to the overall neutral effect of fenofibrate therapy in the entire ACCORD cohort, heterogeneity in the effect of fenofibrate on the primary cardiovascular outcome continued to be observed during extended follow-up in those with dyslipidemia at study entry. During the combined trial plus posttrial period, the primary outcome in study participants with dyslipidemia who were randomized to fenofibrate was 27% lower than among those with dyslipidemia randomized to placebo but only 1% lower in nondyslipidemic study participants (HR, 0.73; 95% CI, 0.56-0.95 vs HR, 0.99; 95% CI, 0.86-1.13; P = .05 for dyslipidemic vs non-dyslipidemic, respectively) (**Figure 3**). Persistent heterogeneity in fenofibrate

Table 1. Comparison of ACCORD Baseline Characteristics Between Those Who Consented for Post-ACCORD Follow-up
and Those Who Did Not Consent

Baseline Characteristic	All Lipid Trial Participants (n = 5518)	Consented for Post-ACCORD Follow-up (n = 4644)	Did Not Consent for Post-ACCORD Follow-up (n = 874)	Difference (n = 5518)	P Value for Difference
Age, mean (SD), y	62.3 (6.8)	62.0 (6.6)	63.9 (7.5)	−1.9	<.001
Female sex, No./total No. (%)	1694/5518 (30.7)	1445/4644 (31.1)	249/874 (28.5)	2.6	.12
Race/ethnicity,[a] No./total No. (%)					
White	3612/5518 (65.5)	3067/4644 (66.0)	545/874 (62.4)	3.6	
Black	826/5518 (15.0)	655/4644 (14.1)	171/874 (19.6)	−5.5	<.001
Hispanic	407/5518 (7.4)	339/4644 (7.3)	68/874 (7.8)	−0.5	
Education, No./total No. (%)					
Less than high school	750/5515 (13.6)	588/4641 (12.7)	162/874 (18.5)	−5.8	
High school graduate or GED	1433/5515 (26.0)	1184/4641 (25.5)	249/874 (28.5)	−3.0	<.001
Some college	1827/5515 (33.1)	1537/4641 (33.1)	290/874 (33.2)	−0.1	
College degree or higher	1505/5515 (27.3)	1332/4641 (28.7)	173/874 (19.8)	8.9	
Previous cardiovascular event, No./total No. (%)	2016/5518 (36.5)	1620/4644 (34.9)	396/874 (45.3)	−10.4	<.001
Previous congestive heart failure, No./total No. (%)	291/5508 (5.3)	198/4644 (4.3)	93/864 (10.8)	−6.5	<.001
Cigarette-smoking status, No./total No. (%)					
Current	793/5510 (14.4)	640/4638 (13.8)	153/872 (17.5)	−3.7	
Former	2546/5510 (46.2)	2121/4638 (45.7)	425/872 (48.7)	−3.0	<.001
Never	2161/5510 (39.2)	1867/4638 (40.3)	294/872 (33.7)	6.6	
Weight, mean (SD), kg	94.8 (18.7)	94.9 (18.7)	94.7 (18.4)	0.2	.84
Body mass index, mean (SD)[b]	32.3 (5.4)	32.3 (5.4)	32.4 (5.4)	−0.1	.72
Blood pressure, mean (SD), mm Hg					
Systolic	133.9 (17.8)	133.4 (17.5)	136.6 (6.6)	−3.2	<.001
Diastolic	74.0 (10.8)	73.9 (10.7)	74.2 (11.3)	−0.3	.45
Medications, No./total No. (%)					
Insulin	1836/5518 (33.3)	1511/4644 (32.5)	325/874 (37.2)	−4.7	.01
Metformin	3420/5518 (62.0)	2943/4644 (63.4)	477/874 (54.6)	8.8	<.001
Any sulfonylurea	2892/5518 (52.4)	2448/4644 (52.7)	444/874 (50.8)	1.9	.30
Any thiazolidinedione	973/5518 (17.6)	840/4644 (18.1)	133/874 (15.2)	2.9	.04
Angiotensin-converting-enzyme inhibitor	2967/5518 (53.8)	2499/4644 (53.8)	468/874 (53.5)	0.3	.89
Angiotensin-receptor-blocker	838/5518 (15.2)	709/4644 (15.3)	129/874 (14.8)	0.5	.70
Aspirin	3106/5518 (56.3)	2626/4644 (56.5)	480/874 (54.9)	1.6	.37
β-Blocker	1798/5518 (32.6)	1488/4644 (32.0)	310/874 (35.5)	−3.5	.05
Any thiazide diuretic	1473/5518 (26.7)	1251/4644 (26.9)	222/874 (25.4)	1.5	.35
Statin	3299/5518 (59.8)	2819/4644 (60.7)	480/874 (54.9)	5.8	.001
Any lipid-lowering agent	3558/5518 (64.5)	3036/4644 (65.4)	522/874 (59.7)	5.7	.001
Duration of diabetes, mean (SD), y	10.6 (7.5)	10.6 (7.5)	10.9 (7.7)	−0.3	.26
Glycated hemoglobin, %					
Mean (SD)	8.3 (1.0)	8.25 (1.01)	8.43 (1.15)	−0.18	<.001
Median (IQR)	8.1 (7.6 to 8.8)	8.1 (7.5 to 8.8)	8.2 (7.7 to 9.0)	−0.1	.001
Fasting plasma glucose, mean (SD), mg/dL	175.8 (54.9)	176.1 (54.5)	174.2 (57.1)	1.9	.34
Amputation owing to diabetes, No./total No. (%)	110/5518 (2.0)	85/4644 (1.8)	25/874 (2.9)	−1.1	.05
Potassium, mean (SD), mg/dL	4.5 (0.4)	4.47 (0.42)	4.49 (0.46)	−0.02	.41
Serum creatinine, mean (SD), mg/dL	0.9 (0.2)	0.92 (0.22)	0.97 (0.26)	−0.05	<.001
eGFR (mL/min/1.73m^2)					
30-49 mL/min/1.73m^2	141/5488 (2.6)	102/4621 (2.2)	39/867 (4.5)	−2.3	
>50 mL/min/1.73m^2	5347/5488 (97.4)	4519/4621 (97.8)	828/867 (95.5)	2.3	<.001
Total plasma cholesterol, mean (SD), mg/dL	175.2 (37.3)	174.7 (36.9)	177.6 (39.4)	−2.9	.04
Plasma LDL-C, mean (SD), mg/dL	100.6 (30.7)	99.9 (30.3)	103.9 (32.5)	−4.0	.001

(continued)

Table 1. Comparison of ACCORD Baseline Characteristics Between Those Who Consented for Post-ACCORD Follow-up and Those Who Did Not Consent (continued)

Baseline Characteristic	All Lipid Trial Participants (n = 5518)	Consented for Post-ACCORD Follow-up (n = 4644)	Did Not Consent for Post-ACCORD Follow-up (n = 874)	Difference (n = 5518)	P Value for Difference
Plasma HDL-C, mean (SD), mg/dL					
Women	41.4 (7.7)	41.6 (7.8)	40.6 (7.6)	1.0	.07
Men	36.6 (7.3)	36.7 (7.2)	36.3 (7.8)	0.4	.21
Plasma triglycerides, mg/dL					
Mean (SD)	187.6 (112.6)	188.0 (113.4)	185.3 (108.3)	2.7	.53
Median (IQR)	162 (113 to 229)	162 (113 to 230)	162 (112 to 228)	0.0	.69

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACCORDION, ACCORD Follow-On Study; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 76.25; to convert glucose to millimoles per liter, multiply by 0.0555; to convert glycated hemoglobin to proportion of total hemoglobin, multiply by 0.01; to

convert HDL-C to millimoles per liter, multiply by 0.0259; to convert LDL-C to millimoles per liter, multiply by 0.0259; to convert potassium to millimoles per liter, multiply by 1; to convert triglycerides to millimoles per liter, multiply by 0.0113.

[a] Participants could have selected more than 1 racial/ethnic group.

[b] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Prespecified Primary and Secondary Outcomes by Original Treatment Assignment During ACCORDION Extended Follow-up vs During ACCORD Double-Blind Treatment Phase

Outcome	Treatment Effect During ACCORD[a] (Fenofibrate/Placebo)		Hazard Ratios During ACCORDION (Fenofibrate/Placebo)		Treatment Effect During Extended Follow-up ACCORD + ACCORDION (Fenofibrate/Placebo)[b]	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Primary outcome[c]	0.92 (0.79-1.08)	.32	0.93 (0.76-1.34)	.47	0.93 (0.83-1.05)	.25
Secondary outcomes						
Primary outcome plus revascularization or hospitalization for congestive heart failure	0.94 (0.85-1.05)	.30	1.12 (0.95-1.32)	.20	1.00 (0.92-1.10)	.98
Major coronary disease event [d]	0.92 (0.79-1.07)	.26	0.95 (0.77-1.17)	.61	0.91 (0.81-1.03)	.13
Nonfatal myocardial infarction	0.91 (0.74-1.12)	.39	1.05 (0.76-1.44)	.78	0.93 (0.78-1.10)	.37
Nonfatal Stroke	1.17 (0.76-1.78)	.48	0.93 (0.65-1.32)	.67	1.12 (0.87-1.43)	.38
Fatal or nonfatal stroke	1.05 (0.71-1.56)	.80	1.01 (0.71-1.42)	.97	1.12 (0.89-1.42)	.33
All-cause mortality	0.91 (0.75-1.10)	.34	0.96 (0.83-1.11)	.57	0.94 (0.84-1.06)	.32
Cardiovascular mortality	0.86 (0.66-1.12)	.26	0.82 (0.63-1.07)	.14	0.84 (0.69-1.01)	.07
Fatal or nonfatal congestive heart failure	0.82 (0.65-1.05)	.10	0.85 (0.67-1.06)	.15	0.86 (0.71-1.05)	.14
Nonfatal myocardial Infarction, nonfatal stroke or all cause mortality[e]	NR[a]	NR[a]	0.98 (0.84-1.13)	.74	0.97 (0.88-1.07)	.58

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACCORDION, ACCORD Follow-On Study; NR, not reported by Ginsberg et al[9] because it was not an ACCORD Protocol Outcome.

[a] Hazard ratio of events occurring during ACCORD, ACCORDION alone, and combined. Number and event rate during combined follow-up (ACCORD and ACCORDION) in study participants originally randomized to fenofibrate vs placebo.[18]

[b] Rates per 100 person-years during ACCORD (active treatment phase) and

ACCORDION (extended poststudy passive follow-up period).

[c] Primary outcome for original ACCORD study, combined occurrence of nonfatal myocardial infarction, nonfatal stroke, and fatal cardiovascular event.

[d] A major coronary disease event was defined as a fatal coronary event, nonfatal myocardial infarction, or unstable angina.
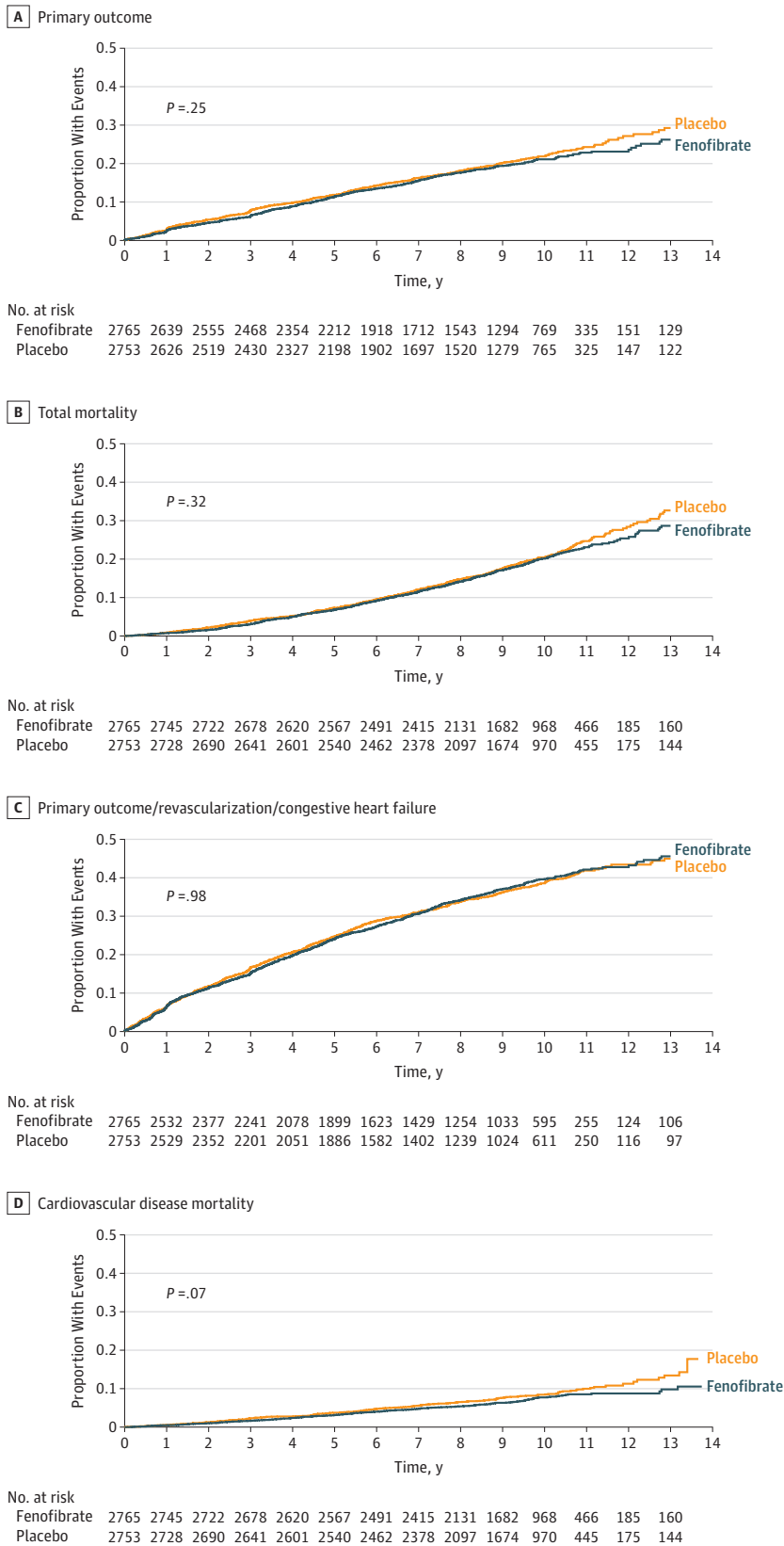
[e] New outcome measure; all other outcomes are an original ACCORD protocol outcome.

response was also observed in men vs women, and the primary outcome in the fenofibrate treatment group was 16% lower for men but 30% higher for women (HR, 0.84; 95% CI, 0.73-0.96 vs HR, 1.30; 95% CI, 1.10-1.68; P = .003 for men vs women, respectively) (Figure 3). These HRs are nearly identical to those observed in the original ACCORD trial (eTable 2 in Supplement 3).[9]
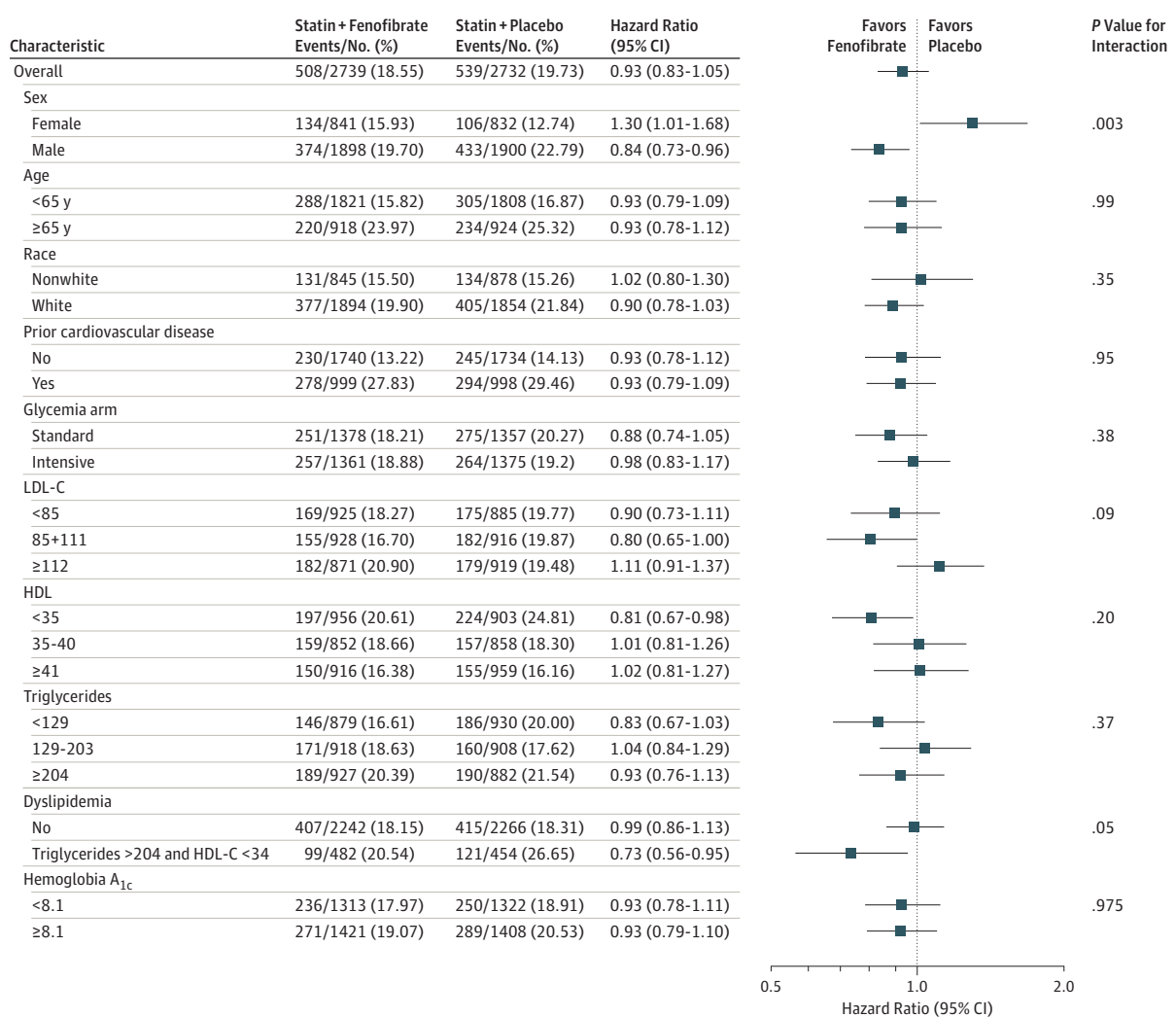
Discussion

Up to 35% of patients with type 2 diabetes are at increased risk of atherosclerotic CVD events related to the presence of diabetic dyslipidemia, defined as hypertriglyceridemia and the associated accumulation of remnant particles, low HDL-C, and

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

A Primary outcome

No. at risk
Fenofibrate   2765 2639 2555 2468 2354 2212 1918 1712 1543 1294 769 335 151 129
Placebo   2753 2626 2519 2430 2327 2198 1902 1697 1520 1279 765 325 147 122

B Total mortality

No. at risk
Fenofibrate   2765 2745 2722 2678 2620 2567 2491 2415 2131 1682 968 466 185 160
Placebo   2753 2728 2690 2641 2601 2540 2462 2378 2097 1674 970 455 175 144

C Primary outcome/revascularization/congestive heart failure

No. at risk
Fenofibrate   2765 2532 2377 2241 2078 1899 1623 1429 1254 1033 595 255 124 106
Placebo   2753 2529 2352 2201 2051 1886 1582 1402 1239 1024 611 250 116   97

D Cardiovascular disease mortality

No. at risk
Fenofibrate   2765 2745 2722 2678 2620 2567 2491 2415 2131 1682 968 466 185 160
Placebo   2753 2728 2690 2641 2601 2540 2462 2378 2097 1674 970 455 175 144

The cumulative incidence of the primary outcome (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) (A), the expanded macrovascular outcome (a combination of the primary outcome plus revascularization or hospitalization for congestive heart failure) (B), and death from any cause (C) or from cardiovascular causes (D) during follow-up.

Figure 3. Hazard Ratios for the Primary Outcome in Prespecified Subgroups

Characteristic	Statin + Fenofibrate Events/No. (%)	Statin + Placebo Events/No. (%)	Hazard Ratio (95% CI)		P Value for Interaction
Overall	508/2739 (18.55)	539/2732 (19.73)	0.93 (0.83-1.05)		
Sex					
Female	134/841 (15.93)	106/832 (12.74)	1.30 (1.01-1.68)		.003
Male	374/1898 (19.70)	433/1900 (22.79)	0.84 (0.73-0.96)		
Age					
<65 y	288/1821 (15.82)	305/1808 (16.87)	0.93 (0.79-1.09)		.99
≥65 y	220/918 (23.97)	234/924 (25.32)	0.93 (0.78-1.12)		
Race					
Nonwhite	131/845 (15.50)	134/878 (15.26)	1.02 (0.80-1.30)		.35
White	377/1894 (19.90)	405/1854 (21.84)	0.90 (0.78-1.03)		
Prior cardiovascular disease					
No	230/1740 (13.22)	245/1734 (14.13)	0.93 (0.78-1.12)		.95
Yes	278/999 (27.83)	294/998 (29.46)	0.93 (0.79-1.09)		
Glycemia arm					
Standard	251/1378 (18.21)	275/1357 (20.27)	0.88 (0.74-1.05)		.38
Intensive	257/1361 (18.88)	264/1375 (19.2)	0.98 (0.83-1.17)		
LDL-C					
<85	169/925 (18.27)	175/885 (19.77)	0.90 (0.73-1.11)		.09
85+111	155/928 (16.70)	182/916 (19.87)	0.80 (0.65-1.00)		
≥112	182/871 (20.90)	179/919 (19.48)	1.11 (0.91-1.37)		
HDL					
<35	197/956 (20.61)	224/903 (24.81)	0.81 (0.67-0.98)		.20
35-40	159/852 (18.66)	157/858 (18.30)	1.01 (0.81-1.26)		
≥41	150/916 (16.38)	155/959 (16.16)	1.02 (0.81-1.27)		
Triglycerides					
<129	146/879 (16.61)	186/930 (20.00)	0.83 (0.67-1.03)		.37
129-203	171/918 (18.63)	160/908 (17.62)	1.04 (0.84-1.29)		
≥204	189/927 (20.39)	190/882 (21.54)	0.93 (0.76-1.13)		
Dyslipidemia					
No	407/2242 (18.15)	415/2266 (18.31)	0.99 (0.86-1.13)		.05
Triglycerides >204 and HDL-C <34	99/482 (20.54)	121/454 (26.65)	0.73 (0.56-0.95)		
Hemoglobia A$_{1c}$					
<8.1	236/1313 (17.97)	250/1322 (18.91)	0.93 (0.78-1.11)		.975
≥8.1	271/1421 (19.07)	289/1408 (20.53)	0.93 (0.79-1.10)		

Favors Fenofibrate — Favors Placebo

0.5 — 1.0 — 2.0
Hazard Ratio (95% CI)

The horizontal bars represent 95% confidence intervals, and the vertical dashed line indicates the overall hazard ratio. *P* values are for tests for interaction. HDL-C indicates high-density lipoprotein and LDL-C indicates low-density lipoprotein cholesterol.

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 0.0112.

small dense LDL.[8,19] However, it is unclear whether pharmacologic therapy directed toward reversing these abnormalities will result in reduced risk of CVD. Although the cardiovascular efficacy of niacin and fibrate (gemfibrozil) monotherapy was clearly established by prestatin-era clinical trials,[20-22] subsequent trials failed to demonstrate efficacy of newer fibrates, specifically fenofibrate and bezafibrate either alone[23,24] or in combination with statin.[9] Furthermore, between 2007 and 2016, a number of trials testing various triglyceride-lowering and HDL-C-raising medical therapies have failed to demonstrate benefit of add-on therapy in statin-treated patients.[25-28] These clinical trial outcomes are reflected in treatment guidelines promulgated by the American Heart Association and the American College of Cardiology that focus on recommendations for statin therapy but do not clearly advocate the use of triglyceride-lowering therapy for CVD prevention.[29]

In the case of fenofibrate, 2 cardiovascular end point trials conducted within the last decade failed to show benefit with administration of fenofibrate in patients with type 2 diabetes either alone in the FIELD study[24] or as add-on therapy to statin in the ACCORD study.[9] Among the possible reasons for the neutral outcome of FIELD was a disproportionately higher drop in statin therapy in the fenofibrate group.[24] In ACCORD, one possible reason for failure to demonstrate benefit of add-on fenofibrate therapy was that the treatment duration of 4.7 years was not sufficient to detect a treatment effect. The goal of ACCORDION was to extend the study with an additional 5.0 years of passive follow-up to detect emergence of a "legacy" effect of fenofibrate treatment, similar to that observed in the niacin arm of the Coronary Drug Project[30] and with glucose lowering in both the United Kingdom Prospective Diabetes Study and the 2008 Veterans Affairs Diabetes Trial.[31,32] A legacy effect did not emerge during extended follow-up in

ACCORDION, thus confirming the original overall ACCORD observations. On the other hand, the lower cardiovascular event rates observed among the subgroup of participants with hypertriglyceridemia and low HDL-C who were randomized to fenofibrate therapy during the active treatment phase of ACCORD continued to be observed during the extended follow-up period. These findings support the hypothesis that individuals with diabetic dyslipidemia may benefit from add-on fenofibrate therapy. This hypothesis is supported by the comparable findings of similar subgroup analyses of several major fibrate trials including the FIELD study,[33] the Helsinki Heart Study (HHS),[34] Bezafibrate Infarction Prevention Trial (BIP),[23] and VA-HDL Intervention Trial (VA-HIT).[35] Insofar as the triglyceride-lowering effect of fibrates is greatest among patients with hypertriglyceridemia,[34] it is not totally unexpected that individuals with hypertriglyceridemia would be most likely to benefit from fibrate therapy. This was clearly evident in the lipid response to fenofibrate in the hypertriglyceridemia/low-HDL-C subset of ACCORD-Lipid participants (eFigure 2 and eFigure 3 in Supplement 3). However, in ACCORD-Lipid, this subset comprised only 17% of all participants (n = 941).[9]

The sex differences in fenofibrate response observed in ACCORD[9] were also observed during extended follow-up in ACCORDION. The observation of sex differences in cardiovascular outcomes with fenofibrate treatment, with men appearing to benefit vs evidence of possible harm in women in ACCORD[9] and now with extended follow-up in ACCORDION, is both unexpected and unexplained, particularly because similar heterogeneity in fenofibrate treatment effect by sex was not observed in the FIELD trial.[24] These differences may be attributed to lower numbers of women participants in ACCORD vs FIELD as well as unexpectedly low event rates among placebo-treated women in ACCORD.[36] Therefore, the sex difference may be a chance finding.

It is important to note in the context of our findings that the safety profile of combination therapy with fenofibrate and statin appears to be acceptable. Specifically, in ACCORD, fenofibrate was used in combination with simvastatin in more than 2500 patients for a mean of 4.7 years without increased incidence of muscle or liver toxicity.[9] This is in distinct contrast to the increased risk of myopathy that occurs with coadministration of the fibrate gemfibrozil and statin owing to a known pharmacokinetic interaction.[37,38] It is also important to note that in ACCORD, fenofibrate treatment slowed progression of diabetic microvascular disease including retinopathy and nephropathy.[9,18] On the other hand, reversible increases in creatinine and paradoxical lowering of HDL-C were also observed with increased frequency in those randomized to fenofibrate in ACCORD-Lipid.[39,40]

Limitations

It is also important to note that these prespecified subgroup analyses can only be considered hypothesis-generating and in some cases are based on a relatively small number of events. Although analyses beyond the original predefined primary outcome measure cannot be considered definitive and therefore not suitable for guideline formulation or product labeling, they inform refinement of our original hypothesis for further testing and provide useful information to clinical practitioners regarding possible treatment for diabetic dyslipidemia.

Conclusions

In conclusion, an additional 5 years of follow-up of surviving ACCORD-Lipid study cohort members extends the original overall neutral outcome of the ACCORD study and provides additional support for possible benefit of fenofibrate therapy in patients with type 2 diabetes in whom triglycerides remain elevated and HDL-C levels remain low despite statin therapy. Our findings support the hypothesis that patients with diabetic dyslipidemia may derive some benefit from add-on triglyceride-lowering therapy. Randomized trials testing the cardiovascular efficacy of fibrate as well as other triglyceride-lowering treatments in this specific patient population are needed.

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