Fenofibrate and Heart Failure Outcomes in Patients With Type 2 Diabetes: Analysis From ACCORD

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OBJECTIVE

Patients with type 2 diabetes (T2D) have a high risk for developing heart failure (HF), which is associated with poor prognosis. Fenofibrate may reduce HF events through multiple mechanisms. We sought to study the effect of fenofibrate (vs. placebo) in HF outcomes among patients with T2D receiving simvastatin enrolled in the Action to Control Cardiovascular Risk in Diabetes lipid trial (ACCORD Lipid).

RESEARCH DESIGN AND METHODS

We used Cox regression analysis with background glucose-lowering strategy as the stratification variable. The median follow-up was 4.7 years.

RESULTS

A total of 5,518 patients were included. Median age was 62 years, and 31% were women. Prior HF history was present in 5% of the patients. The composite outcome of HF hospitalization or cardiovascular death occurred in 190 (6.9%) patients in the fenofibrate group vs. 228 (8.3%) in the placebo group: HR 0.82, 95% CI 0.68–1.00 ($P = 0.048$). The beneficial effect of fenofibrate to reduce HF hospitalizations or cardiovascular death was present among patients receiving standard glucose-lowering strategy, HR 0.64, 95% CI 0.48–0.85, and not among patients receiving intensive glucose-lowering strategy, HR 1.02, 95% CI 0.79–1.33 ($P_{interaction} = 0.017$). A similar pattern was observed for HF hospitalizations alone. The effect of fenofibrate on blood lipids was not influenced by background glucose-lowering therapy in a clinically important manner. Fenofibrate caused more transient worsening estimated glomerular filtration rate (eGFR) events but slowed long-term eGFR decline.

CONCLUSIONS

In patients with T2D treated with simvastatin, fenofibrate reduced the composite of HF hospitalizations or cardiovascular mortality, an effect that was seen predominantly in patients with standard background glucose-lowering therapy.

Type 2 diabetes (T2D) is a global epidemic affecting ∼500 million people worldwide (1). Patients with T2D have a high risk for developing heart failure (HF), which, once occurring, is associated with substantially increased morbidity and mortality (2). Therefore, preventive strategies are needed to decrease the HF risk.

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Statins are one of the most effective drug-class agents for reducing the risk of cardiovascular events in patients with T2D (3,4), including a potential risk reduction in HF hospitalizations (5). The cardiovascular benefits of fibrates when added on top of guideline-directed statin therapy are less well established in patients with T2D. Fenofibrate did not reduce mortality in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, but it reduced total cardiovascular events, mainly due to a reduction in nonfatal myocardial infarctions and revascularizations (6). More patients in the placebo than in the fenofibrate group started statins, which might have led to an underestimation of the potential benefits of fenofibrate in the FIELD study. Investigators of large observational studies found an association between fenofibrate use and lower incidence of mortality and cardiovascular events (7). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial (ACCORD Lipid), the combination of fenofibrate and simvastatin did not reduce the composite of time-to-first of myocardial infarction, stroke, or cardiovascular death compared with simvastatin and placebo (8). However, an 18% reduction in HF events was observed with fenofibrate, albeit not reaching statistical significance ($P = 0.1$). It should be noted that ACCORD had a factorial design with patients randomized to either intensive or standard glucose-lowering strategy in the main study and then to the blood pressure or lipid substudies (9). In the glucose-lowering study, the use of an intensive glucose-lowering strategy could have confounded the effect of fenofibrate, particularly regarding HF events, the risk for which may be increased with more frequent use of certain glucose-lowering medications such as insulin and thiazolidinediones (10–13).

Fenofibrate is a peroxisome proliferator–activated receptor α (PPARα) activator that can display anti-inflammatory effects beyond its lipid-lowering (triglycerides in particular) and uric acid–lowering properties (14,15). It is thus plausible that fenofibrate might have an effect in reducing HF events, and such hypothesis requires further investigation.

In the present analysis, we aim to study the effect of fenofibrate (vs. placebo) in HF events when added on top of simvastatin in patients with T2D enrolled in ACCORD Lipid and whether the fenofibrate effect could have been modified by background glucose-lowering strategy intensity.

RESEARCH DESIGN AND METHODS

ACCORD Lipid Study Design

ACCORD was a multicenter clinical study, sponsored by the National Heart, Lung, and Blood Institute (NHLBI), conducted in 77 clinical centers in the U.S. and Canada. ACCORD enrolled patients with T2D and a glycated hemoglobin level of ≥7.5% and who had evidence of cardiovascular disease or significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current status as a smoker, or obesity).

In the main ACCORD study, a total of 10,251 patients were randomly assigned to receive either intensive antihyperglycemic therapy targeting a glycated hemoglobin level <6.0% or to receive standard therapy targeting a glycated hemoglobin level of 7.0%–7.9%. The results of this comparison have previously been reported (10). A selected subgroup of patients ($n = 5,518$) from ACCORD were also enrolled in ACCORD Lipid and underwent randomization, in a two-by-two factorial design, to receive either simvastatin plus fenofibrate or simvastatin plus placebo so that the comparison is fenofibrate versus placebo. Patients were specifically eligible to participate in the lipid trial if they also had an LDL cholesterol level between 60 and 180 mg/dL, an HDL cholesterol level <55 mg/dL for women and Blacks or <50 mg/dL for all other groups, and a triglyceride level <750 mg/dL if they were not receiving lipid-lowering therapy or <400 mg/dL if receiving lipid-lowering therapy. ACCORD Lipid was conducted between 2001 and 2005, with a median follow-up of 4.7 years, and the primary results have previously been reported (8).

The study protocol was approved by the institutional review board or ethics committee at each center, as well as by a review panel at the NHLBI. All patients provided written informed consent to participate in the study.

Outcomes were independently adjudicated by a central committee whose members were unaware of study group assignments based on predefined criteria. The primary outcome of ACCORD Lipid was first occurrence of a nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. In the current study we used the composite outcome of time-to-first of cardiovascular death or HF hospitalization, HF hospitalization, and cardiovascular death alone as the main outcomes of interest. In ACCORD, HF hospitalization categorization required documented clinical and radiologic evidence for adjudication (8).

Access to the ACCORD database was provided by the NHLBI/BioLINCC (Biologic Specimen and Data Repository Information Coordinating Center) with ethics approval from Centro Hospitalar Universitário São João (process no. 500/2020).

Statistical Considerations

In trials with a two-by-two factorial design, the main analytical issues that may arise relate to investigation of main effects and interaction between interventions in regression models. The results of factorial trials may be confounded if a significant interaction is observed between the randomized interventions (16). In ACCORD Lipid, no significant interaction was observed between the lipid and glycemia interventions for the primary outcome ($P_{interaction} = 0.36$); however, such potential interactions have not been tested for with secondary outcomes, such as HF.

In the current study, the outcomes were analyzed with Cox models, according to the intention-to-treat principle, and the results reported as hazard ratios (HR) and 95% CIs. The Cox models contain a term representing the lipid-lowering treatment assignment (fenofibrate or placebo) plus the glucose-lowering strategy (intensive or standard) as stratification variable. The results are reported for the overall population, and for subgroups of intensive or standard glucose-lowering strategy, along with a lipid-lowering–by–glucose-lowering strategies interaction term. Further subgroup analyses based on sex, atherogenic dyslipidemia, insulin, thiazolidinedione, sulfonylurea therapy, and glycated hemoglobin levels at baseline are also presented. We also performed interaction tests using postrandomization on-treatment use of certain antihyperglycemic drugs in time-updated Cox models.

For studying the effect of fenofibrate (vs. placebo) on blood lipids and

estimated glomerular filtration rate (eGFR) over time, mixed-effects models were used with the variable of interest as outcome; lipid-lowering treatment, baseline blood lipid value or baseline eGFR, study visits, and treatment-by-visit interaction as fixed effects; and patients as random effects, with an unstructured covariance matrix allowing the effects to vary freely between patients; and a random slope at the study visit level. Serious adverse events were reported by the investigators to the ACCORD Coordinating Center and were analyzed by means of logistic regression and stratified according to glucose-lowering strategy (8).

Worsening eGFR adverse events were defined by a drop in eGFR >40% from the baseline value, assessed with the MDRD formula (17).

Associations between blood lipids (log2 transformed) and outcomes were studied with Cox models, with adjustment for the validated Thrombolysis in Myocardial Infarction Risk Score for Heart Failure in Diabetes (TRS-HFDM), which includes prior HF, atrial fibrillation, coronary artery disease, eGFR, and urine albumin-to-creatinine ratio (18).

Mediation analyses were performed with the time-dynamic evolvement of both the potential mediators (eGFR, HDL cholesterol, and triglycerides) and the outcome cardiovascular death or HF hospitalization taken into account (19).

A two-sided P value of <0.05 was considered statistically significant. No correction for multiple testing was performed due to the exploratory nature of this work. All analyses were performed with Stata (StataCorp, College Station, TX).

Data and Resource Availability

The ACCORD database can be fully available from NHLBI/BioLINCC on reasonable request.

RESULTS

Patients' Baseline Characteristics

A total of 5,518 patients were enrolled in ACCORD Lipid, all of whom were receiving simvastatin, with 2,765 randomized to fenofibrate and 2,753 to placebo. Regarding the background glucose-lowering strategy, 1,370 were receiving the standard glucose lowering treatment and placebo, 1,383 were receiving intensive glucose lowering treatment and placebo, 1,391 were receiving standard glucose lowering treatment and fenofibrate, and 1,374 were receiving intensive glucose lowering treatment and fenofibrate (Supplementary Fig. 1 [flowchart]).

The baseline characteristics were well balanced between groups. Median age was 62 years, and ~31% were women. Prior HF history was present for ~5% of the patients, and 10% were using loop diuretics. Most patients were treated with an ACE inhibitor or an angiotensin receptor blocker. Median eGFR was nearly 90 mL/min/1.73 m^2 and glycated hemoglobin 8.1% (Table 1).

HF Outcomes by Subgroups of Glucose-Lowering Strategies

For the composite outcome of HF hospitalization or cardiovascular death, 228 patients (8.3%) experienced an event in the placebo group vs. 190 (6.9%) in the fenofibrate group, corresponding to an HR of 0.82, 95% CI 0.68–1.00 ($P = 0.048$), in favor of fenofibrate. The beneficial effect of fenofibrate to reduce HF hospitalizations or cardiovascular death was only present among patients receiving the standard glucose-lowering strategy treatment, with an HR of 0.64, 95% CI 0.48–0.85, and not among patients receiving the intensive glucose-lowering strategy treatment who did not benefit from fibrate therapy, HR 1.02, 95% CI 0.79–1.33 ($P_{interaction} = 0.017$) (Fig. 1). A similar pattern was observed for HF hospitalizations alone, where only patients receiving the standard glucose-lowering treatment could benefit from fenofibrate: HR 0.60, 95% CI 0.42–0.85, in the standard group and HR 1.05, 95% CI 0.75–1.47, in the intensive group ($P_{interaction} = 0.025$). No between-group differences (interactions) were seen for cardiovascular or all-cause mortality or for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (Table 2).

For the composite outcome of HF hospitalization or cardiovascular death, and in concordance with the findings above described, an intensive glucose-lowering strategy (compared with a standard strategy) was harmful for patients receiving fenofibrate, HR 1.55, 95% CI 1.16–2.07, but not for those receiving placebo, HR 0.96, 95% CI 0.74–1.25 ($P_{interaction} = 0.017$). In agreement with results of the main glucose-lowering treatment report, the intensive glucose-lowering strategy increased the risk of mortality regardless of fibrate therapy, with an HR of 1.3 in both groups ($P_{interaction} = 0.78$) (Supplementary Table 1).

Treatment-by-sex, atherogenic dyslipidemia, insulin, thiazolidinedione, sulfonylurea therapy, and glycated hemoglobin interaction tests (all at baseline) were statistically nonsignificant (Supplementary Fig. 2).

In the 26,324 patient visits with recorded information, insulin and thiazolidinediones were used more frequently in the intensive antihyperglycemic arm than in the standard antihyperglycemic arm: 7,786 (59%) vs. 5,860 (44%) patient visits and 7,078 (54%) vs. 4,342 (33%) patient visits, respectively ($P < 0.001$ for both). No significant differences in the use of insulin and thiazolidinediones were observed between the placebo and fenofibrate groups. Insulin was used in patients in 6,672 (51%) patient visits in the placebo group and 6,786 (51%) patient visits in the fenofibrate group ($P = 0.69$). The time-updated treatment effect of fenofibrate (vs. placebo) on the composite of cardiovascular death or HF hospitalization was HR 0.91, 95% CI 0.65–1.29, without insulin use and HR 0.78, 95% CI 0.62–0.98, with insulin use ($P_{interaction} = 0.42$). Thiazolidinediones were used in patients in 5,639 (43%) patient visits in the placebo group and 5,738 (43%) patient visits in the fenofibrate group ($P = 0.72$). The time-updated treatment effect of fenofibrate (vs. placebo) on the composite of cardiovascular death or HF hospitalization was HR 0.87, 95% CI 0.69–1.10, without thiazolidinedione use and HR 0.73, 95% CI 0.52–1.04, with thiazolidinedione use ($P_{interaction} = 0.42$). The three-way interaction among treatment–insulin use–thiazolidinedione use was nonsignificant ($P_{interaction} = 0.63$).

Effect of Fenofibrate on Blood Lipids by Subgroups of Glucose-Lowering Strategies

Compared with placebo, throughout the follow-up fenofibrate reduced the blood levels of triglycerides by 28.4 mg/dL, an effect that was statistically (but not clinically) different between patients on a standard versus intensive antihyperglycemic strategy: reduction of 31.6 mg/dL on

Table 1—Baseline characteristics of patients by subgroups of glucose-lowering strategies

	Standard glycemia and placebo	Intensive glycemia and placebo	Standard glycemia and fibrate	Intensive glycemia and fibrate
N (total = 5,518)	1,370	1,383	1,391	1,374
Age, years	62.0 (57.8, 67.1)	62.2 (57.7, 67.4)	61.9 (57.7, 67.0)	61.9 (57.7, 67.2)
Women, *n* (%)	431 (31.5)	412 (29.8)	428 (30.8)	423 (30.8)
Race class, *n* (%)				
Black	212 (15.5)	226 (16.3)	188 (13.5)	200 (14.6)
Hispanic	104 (7.6)	90 (6.5)	110 (7.9)	103 (7.5)
Other	164 (12.0)	168 (12.1)	180 (12.9)	161 (11.7)
White	890 (65.0)	899 (65.0)	913 (65.6)	910 (66.2)
CVD history, *n* (%)	497 (36.3)	511 (36.9)	502 (36.1)	506 (36.8)
HF history, *n* (%)	69 (5.0)	71 (5.1)	71 (5.1)	80 (5.8)
Dyslipidemia, *n* (%)	963 (70.3)	959 (69.3)	981 (70.5)	958 (69.7)
Hypertension, *n* (%)	999 (72.9)	985 (71.2)	993 (71.4)	957 (69.7)
Smoking, *n* (%)	207 (15.1)	186 (13.4)	196 (14.1)	214 (15.6)
BMI, kg/m^2	31.9 (28.3, 36.0)	32.1 (28.4, 36.0)	31.7 (28.1, 35.7)	32.0 (28.3, 35.7)
Amputation lower limb, *n* (%)	31 (2.3)	29 (2.1)	28 (2.0)	35 (2.5)
SBP, mmHg	133.0 (123.0, 145.0)	132.0 (122.0, 145.0)	133.0 (121.0, 144.0)	132.0 (121.0, 145.0)
Heart rate, bpm	72.0 (64.0, 81.0)	72.0 (64.0, 80.0)	72.0 (63.0, 80.0)	72.0 (64.0, 80.0)
HbA_{1c}, %	8.1 (7.6, 8.8)	8.1 (7.5, 8.8)	8.1 (7.6, 8.8)	8.1 (7.6, 8.9)
eGFR, mL/min	89.8 (76.3, 104.3)	89.2 (73.9, 105.0)	89.1 (73.9, 104.7)	89.6 (76.3, 103.8)
UACR, mg/g	13.0 (6.0, 42.0)	13.0 (7.0, 41.0)	13.0 (7.0, 42.0)	14.0 (7.0, 51.0)
Total cholesterol, mg/dL	171.0 (149.0, 197.0)	171.0 (149.0, 197.0)	171.0 (149.0, 196.0)	171.0 (147.0, 196.0)
LDL cholesterol, mg/dL	96.0 (79.0, 121.0)	99.0 (79.0, 120.0)	97.0 (78.0, 118.0)	96.0 (78.0, 118.0)
HDL cholesterol, mg/dL	38.0 (33.0, 43.0)	38.0 (33.0, 43.0)	37.0 (32.0, 42.0)	38.0 (33.0, 43.0)
VLDL cholesterol, mg/dL	32.0 (23.0, 45.0)	32.0 (22.0, 46.0)	32.0 (23.0, 47.0)	33.0 (23.0, 46.0)
Triglycerides, mg/dL	161.0 (115.0, 225.0)	161.0 (111.0, 229.0)	162.0 (116.0, 233.0)	163.5 (113.0, 230.0)
Loop diuretics, *n* (%)	139 (10.1)	127 (9.2)	128 (9.2)	128 (9.3)
Thiazide diuretics, *n* (%)	353 (25.8)	380 (27.5)	375 (27.0)	365 (26.6)
MRAs, *n* (%)	35 (2.6)	36 (2.6)	36 (2.6)	43 (3.1)
ACEi/ARBs, *n* (%)	941 (68.7)	950 (68.7)	942 (67.7)	906 (65.9)
CCBs, *n* (%)	262 (19.1)	256 (18.5)	263 (18.9)	262 (19.1)
β-Blockers, *n* (%)	441 (32.2)	445 (32.2)	476 (34.2)	436 (31.7)
Biguanides, *n* (%)	909 (66.4)	911 (65.9)	918 (66.0)	905 (65.9)
Sulfonylureas, *n* (%)	766 (55.9)	773 (55.9)	758 (54.5)	775 (56.4)
Thiazolidinediones, *n* (%)	273 (19.9)	285 (20.6)	265 (19.1)	280 (20.4)
Insulin, *n* (%)	462 (33.7)	455 (32.9)	476 (34.2)	443 (32.2)
Antiplatelet medication, *n* (%)	786 (57.4)	799 (57.8)	815 (58.6)	836 (60.8)

Data are presented as median (percentile 25–75) unless otherwise indicated. ACEi/ARBs, ACE inhibitors/angiotensin receptor blockers; CCBs, calcium channel blockers; CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin; MRAs, mineralocorticoid receptor antagonists; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio. The corresponding results for HbA_{1c} in mmol/mol are 65 (60–73) mmol/L.

standard vs. 25.1 mg/dL on intensive ($P_{interaction} = 0.05$) (Supplementary Table 2). The effect of fenofibrate on total (reduction of 4.9 mg/dL), VLDL (reduction of 5.3 mg/dL), and HDL (increase of 1 mg/dL) cholesterol was less marked and not different between standard and intensive antihyperglycemic strategies ($P_{interaction} > 0.1$ for all). A treatment effect interaction was observed for LDL cholesterol, but the effect magnitude on LDL cholesterol was overall small

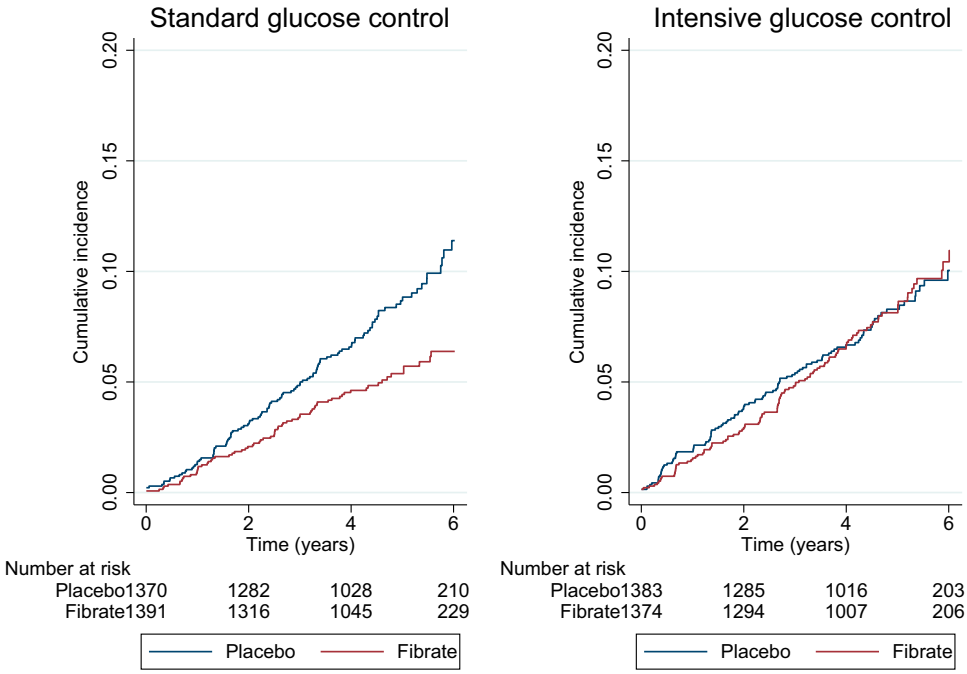

Figure 1—Time to first events of the composite of HF hospitalization or cardiovascular death by subgroups of glucose-lowering strategies. HR 0.64, 95% CI 0.48–0.85, among patients randomized to a standard glucose-lowering strategy and HR 1.02, 95% CI 0.79–1.33, among patients randomized to an intensive glucose-lowering strategy ($P_{interaction}$ = 0.017). Fibrate, fenofibrate.

(−0.7 mg/dL) and of uncertain clinical significance (Supplementary Table 2).

Prognostic Association of Blood Lipids

After adjustment for the TRS-HFDM score, baseline blood lipids were not significantly associated with the outcome of HF hospitalization or cardiovascular death, except HDL cholesterol, where higher concentrations were independently associated with a lower risk of subsequent events: HR 0.62 per doubling HDL concentration, 95% CI 0.45–0.86, $P = 0.004$ (Supplementary Table 3).

Adverse Events by Subgroups of Glucose-Lowering Strategies

Compared with placebo, fenofibrate therapy induced more worsening eGFR events (36.2% vs. 16.1%) irrespective of the glucose lowering strategy ($P_{interaction} = 0.15$). Other hypoglycemic and nonhypoglycemic adverse events did not differ between treatment groups or by glucose-lowering strategy ($P_{interaction} > 0.1$ for all) (Supplementary Table 4).

eGFR Slope Analysis

From baseline to month 4, fenofibrate induced a median eGFR drop of 14.8 mL/min/1.73 m^2 (95% CI 15.5–14.1), and after month 4 fenofibrate slowed the decline in eGFR compared with placebo: annualized eGFR slope in the placebo group −1.7 (−2.1 to −1.3) vs. −0.3 (−0.8 to 0.1) in the fenofibrate group, corresponding to a difference in slopes of 1.4 per year (0.8–1.9) in favor of fenofibrate ($P < 0.001$), without treatment–by–glucose-lowering strategy interaction ($P_{interaction} = 0.37$) (Supplementary Fig. 3).

Mediation Analyses

The effect of fenofibrate to reduce the composite of cardiovascular death or HF hospitalization was not statistically mediated by slope changes in eGFR, HDL cholesterol, or triglyceride, as none of these postrandomization parameters were associated with the composite of HF hospitalization or cardiovascular death: eGFR slope HR 0.98, 95% CI 0.97–1.00, per 5 mL/min/1.73 m^2/year, $P = 0.08$, triglyceride slope HR 1.00, 95% CI 0.99–1.01, per 5 mg/dL/year, $P = 0.77$, HDL cholesterol slope HR 0.98, 95% CI 0.93–1.04, per 5 mg/dL/year, $P = 0.66$. Therefore, requirements for a significant mediation effect were not met.

CONCLUSIONS

Our study shows that fenofibrate reduced the composite of HF hospitalizations or cardiovascular death, an effect that was mainly due to a reduction in HF hospitalizations among patients on a standard glucose-lowering strategy treatment.

While there has been increasing evaluation of sodium–glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists to reduce the risk of cardiovascular events in patients with T2D, the role of fenofibrates and HF risk has largely been unexplored. Furthermore, an intensive glucose-lowering strategy may have confounded the effect of fenofibrate to reduce HF events due to an excess risk of adverse and fatal events with this strategy. The mechanisms by which fenofibrates reduce HF events are not explained by the lowering of triglyceride levels or other lipoproteins, which changes were of similar "clinical" magnitude irrespective of the glucose-lowering strategy. However, fenofibrate induced more transient worsening eGFR events, which likely affected the elimination and circulating concentration of antihyperglycemic drugs, particularly in the intensive treatment arm, which could have led to an excess of adverse events and hospitalizations among patients randomized to both fenofibrate and an intensive glucose-lowering strategy. On the other hand, the effect of fenofibrate in the standard glucose-lowering strategy

Table 2—Outcomes by subgroups of glucose-lowering strategies

Outcome	Events, *n* (%)		Event rate, per 100 person-years		HR (95% CI)	*P*	$P_{interaction}$
	Placebo	Fenofibrate	Placebo	Fenofibrate			
HF hospitalization or cardiovascular death							
Overall population	228/2,753 (8.3)	190/2,765 (6.9)	1.8 (1.6–2.0)	1.5 (1.3–1.7)	0.82 (0.68–1.00)	0.048	
Standard antihyperglycemic strategy	116/1,370 (8.5)	76/1,391 (5.5)	1.8 (1.5–2.2)	1.2 (0.9–1.4)	0.64 (0.48–0.85)		0.017
Intensive antihyperglycemic strategy	112/1,383 (8.1)	114/1,374 (8.3)	1.7 (1.4–2.1)	1.8 (1.5–2.1)	1.02 (0.79–1.33)		
HF hospitalization							
Overall population	149/2,753 (5.4)	121/2,765 (4.4)	1.2 (1.0–1.4)	0.9 (0.8–1.1)	0.80 (0.63–1.02)	0.07	
Standard antihyperglycemic strategy	82/1,370 (6.0)	51/1,391 (3.7)	1.3 (1.0–1.6)	0.8 (0.6–1.0)	0.60 (0.42–0.85)		0.025
Intensive antihyperglycemic strategy	67/1,383 (4.8)	70/1,374 (5.1)	1.0 (0.8–1.3)	1.1 (0.9–1.4)	1.05 (0.75–1.47)		
Cardiovascular death							
Overall population	114/2,753 (4.1)	99/2,765 (3.6)	0.9 (0.7–1.0)	0.7 (0.6–0.9)	0.86 (0.66–1.13)	0.28	
Standard antihyperglycemic strategy	48/1,370 (3.5)	39/1,391 (2.8)	0.7 (0.5–1.0)	0.6 (0.4–0.8)	0.79 (0.52–1.21)		0.62
Intensive antihyperglycemic strategy	66/1,383 (4.8)	60/1,374 (4.4)	1.0 (0.8–1.3)	0.9 (0.7–1.2)	0.91 (0.64–1.29)		
Primary outcome*							
Overall population	310/2,753 (11.3)	291/2,765 (10.5)	2.5 (2.2–2.7)	2.3 (2.0–2.6)	0.93 (0.79–1.09)	0.36	
Standard antihyperglycemic strategy	159/1,370 (11.6)	141/1,391 (10.1)	2.5 (2.2–3.0)	2.2 (1.9–2.6)	0.86 (0.69–1.08)		0.35
Intensive antihyperglycemic strategy	151/1,383 (10.9)	150/1,374 (10.9)	2.4 (2.0–2.8)	2.4 (2.0–2.8)	1.00 (0.80–1.25)		
All-cause mortality							
Overall population	221/2,753 (8.0)	203 (7.3)	1.6 (1.4–1.9)	1.5 (1.3–1.7)	0.91 (0.75–1.10)	0.35	
Standard antihyperglycemic strategy	95/1,370 (6.9)	91/1,391 (6.5)	1.4 (1.2–1.7)	1.3 (1.1–1.6)	0.94 (0.71–1.25)		0.78
Intensive antihyperglycemic strategy	126/1,383 (9.1)	112/1,374 (8.2)	1.9 (1.6–2.2)	1.7 (1.4–2.0)	0.89 (0.69–1.15)		

*The primary outcome was a composite of time-to-first of myocardial infraction, stroke, or cardiovascular death; event rate is represented per 100 person-years.

group is likely an unconfounded effect. Of course, this effect represents a post hoc subgroup analysis; still, the strength of effect and biological plausibility warrant further testing of fibrates to reduce HF events among patients with T2D in adequately powered randomized trials. Still, we tested the hypothesis of whether the more frequent on-treatment use of insulin and thiazolidinediones could have modified the effect of fenofibrate. We did not find evidence supporting this hypothesis; however, because both antihyperglycemic strategies (intensive or standard) involved use of these therapies and these are postrandomization tests, such a hypothesis remains open. In addition, current guidelines recommend treatment goals for T2D that are more similar to those of the standard glucose-lowering arm than those of the intensive glucose-lowering arm of ACCORD (20).

Fenofibrate is a PPARα agonist, a factor that is predominantly expressed in tissues that metabolize fatty acids, such as the liver, kidney, heart, and muscle. The activation of PPARα is essential for fatty acid metabolism, cholesterol homeostasis, differentiation of endothelial progenitor cells, and anti-inflammation (21,22).

In patients with rheumatoid arthritis (a systemic inflammatory condition), treatment with fenofibrate resulted in a significant decrease in C-reactive protein and interleukin-6 concentrations (23). In individuals with metabolic syndrome, treatment with fenofibrate for 8 weeks significantly attenuated the development of endothelial dysfunction, reduced vascular inflammation, and increased adiponectin levels and insulin sensitivity (24). Inflammation and endothelial dysfunction are risk factors for development and progression of HF (25,26); therefore, the anti-inflammatory effect of fibrates may mitigate the risk of HF. Furthermore, the interleukin-6 pathway and other mechanistically related pathways are activated in patients with T2D and HF, further enhancing the biologic plausibility of the HF reduction seen with fenofibrate (27,28).

Perhaps more important than the anti-inflammatory effects of fibrates is that PPARα is a key player in the "nutrient deprivation" cascade and autophagy and also a master controller of cardiac lipid metabolism and cardiac hypertrophy (29). The suppression of PPARα and sirtuin-1 (Sirt1) signaling likely contributes to the diminution of autophagic flux and mitochondrial dysfunction seen in various forms of cardiomyopathy (30). Thus, activation of PPARα (e.g., with fenofibrate) promotes autophagic flux in cardiomyocytes, allowing the maintenance of mitochondrial homeostasis, reducing oxidative stress, and mitigating cardiac injury (31,32). The third player influenced by PPARα/Sirt1 signaling is fibroblast growth factor 21 (FGF21), which is mainly produced by the liver under the control of PPARα. FGF21 is a key player in providing cardiac metabolic flexibility, as it regulates fatty acid oxidation, ketogenesis, and insulin resistance (33). The activation of PPARα increases FGF21, thereby preventing oxidative stress and improving cardiac energy utilization.

Interestingly, another drug class that is thought to act via the PPARα/Sirt1/FGF21 axis is SGLT2i (32). In patients with T2D, SGLT2i consistently led to a 30–40% relative reduction of HF events (34), which is an effect of magnitude similar to that found herein among patients randomized to fenofibrate and a standard glucose-lowering strategy. Further supporting this hypothesis, both fenofibrate and SGLT2i lead to reductions in serum uric acid levels and gout

episodes, effects that are thought to be mediated by a reduction in oxidative stress (15,35).

To further increase the robustness of these results, our findings have been replicated in the Veterans Affairs HDL Intervention Trial (VA-HIT), which included 2,531 men with coronary artery disease and low HDL cholesterol levels, of whom 25% had diabetes, randomized to either the fibrate gemfibrozil or placebo (36). In VA-HIT, gemfibrozil led to a 22% relative reduction in HF hospitalizations ($P = 0.04$). The FIELD trial, which included exclusively patients with T2D, does not include HF hospitalizations reported as an individual end point, but fenofibrate led to a 11% reduction in total cardiovascular disease events ($P = 0.035$) (6).

Despite the increased occurrence of a transient worsening of eGFR with fenofibrate therapy, the long-term kidney effect of fenofibrate was kidney protective, with a slowing of eGFR decline and a reduction in micro- and macroalbuminuria with fenofibrate compared with placebo (8). A decrease of albuminuria progression was also observed in the Diabetes Atherosclerosis Intervention Study (DAIS) (37) and in the FIELD trial (38).

At the start of ACCORD Lipid, the dose of fenofibrate was 160 mg/day in all participants, which is a high dose for individuals with impaired kidney function and may have led to rise in serum creatinine. During the trial, the protocol was revised and fenofibrate dose was then adjusted according to eGFR (8). The rise in serum creatinine with fenofibrate was reversible on discontinuation of the drug (39) and was not associated with concomitant increase in urinary biomarkers representing glomerular or tubular injury, inflammation, or fibrosis (40). This suggests that the rise in creatinine was related to hemodynamic causes. A similar pattern of initial increase of serum creatine has also been observed with SGLT2i, which are associated with long-term renal and cardiovascular protection (41).

Several other potential protective effects of fenofibrate have been identified in patients with T2D. In the ACCORD Eye Study and in the FIELD study, fenofibrate reduced diabetic retinopathy progression (42,43). Importantly, the effect of fenofibrate to reduce major adverse cardiovascular events maybe be more pronounced in patients with certain PPARα variants (rs6008845 T/T homozygotes) (44). In a prespecified analysis of the FIELD trial, fenofibrate reduced the risk of lower-extremity amputations (45), which may be related to a reduction of peripheral neuropathy. Even in the absence of protection from major atherosclerotic cardiovascular events, fenofibrate may have a relevant role in the prevention of several other relevant complications in T2D. A potential protection from HF is of particular relevance given the high residual risk of HF events when the main risk factors are controlled in T2D (46). Further randomized trials are needed to confirm the effect of fibrates on HF events in T2D.

Limitations

Some limitations should be acknowledged in our work. This is a post hoc analysis of a randomized controlled trial, and these tests were not corrected for multiplicity; therefore, there is an increased risk of chance findings, and these results should be regarded as hypothesis generating. However, the strength of the treatment effect seen in patients treated with standard glucose-lowering therapy, the biological plausibility, and external replication in the VA-HIT trial (as above discussed) provide robustness to our analyses. There is a difference of seven HF hospitalization events between the ACCORD Lipid data we had access to and the ACCORD Lipid main report (8); these seven events do not impact the reported estimates.

Conclusion

In patients with T2D treated with simvastatin, fenofibrate reduced the composite of HF hospitalizations or cardiovascular mortality, an effect that was seen predominantly in patients with standard background glucose-lowering therapy. Adequately powered prospective randomized controlled trials are needed to confirm these findings.

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