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**Fenofibrate and heart failure outcomes in patients with type 2 diabetes:
analysis from ACCORD**

Short title: Fenofibrate and heart failure outcomes

Authors:

João Pedro Ferreira, MD, PhD^{1,2}; Francisco Vasques-Nóvoa, MD²; Diana Ferrão, MD²; Francisca Saraiva, PhD²; Inês Falcão-Pires, PhD²; João Sérgio Neves, MD, PhD^{2,3}; Abhinav Sharma, MD, PhD⁴; Patrick Rossignol, MD, PhD¹; Faiez Zannad, MD, PhD¹; Adelino Leite-Moreira, MD, PhD²

Affiliations:

¹ Université de Lorraine, Inserm, Centre d'Investigations Cliniques, - Plurithématique 14-33, and Inserm U1116, CHRU Nancy, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France.

² Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal.

³ Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitário de São João, Porto, Portugal.

⁴ Division of Cardiology, DREAM-CV Lab, McGill University Health Centre, Montreal, Canada.

Contact to:

Dr João Pedro Ferreira

Centre d'Investigation Clinique 1433 module Plurithématique

CHRU Nancy - Hopitaux de Brabois, Institut Lorrain du Coeur et des Vaisseaux

Louis Mathieu

4 rue du Morvan, 54500 Vandoeuvre les Nancy

Tel : +33 (0) 3 83 15 73 15

Fax : +33 (0) 3 83 15 73 24

Mail: j.ferreira@chru-nancy.fr

Abstract

Objectives: 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. To study the effect of fenofibrate (vs. placebo) in HF outcomes among patients with T2D receiving simvastatin enrolled in the ACCORD-Lipid trial.

Research design and Methods: Cox regression analysis with background glucose-lowering strategy as stratification variable. The median follow-up was 4.7 years.

Results: A total of 5518 patients were included. The median age was 62 years and 31% were women. A 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, interaction $P = 0.017$. 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 eGFR events but slowed the long-term eGFR decline.

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.

Key-words: fenofibrate; heart failure; type 2 diabetes; outcomes.

Introduction

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

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 FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial, but it reduced total cardiovascular events, mainly due to a reduction in non-fatal myocardial infarctions and revascularizations.⁶ More patients in placebo than in fenofibrate group started statins, which might have led to an underestimation of the potential benefits of fenofibrate in the FIELD study. Large observational studies found an association between fenofibrate use and lower incidence of mortality and cardiovascular events.⁷ In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid trial, 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, a 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 intensive glucose-lowering strategy could have

confounded the effect of fenofibrate, particularly regarding HF events which risk may be increased with the more frequent use of certain glucose lowering medications such as insulin and thiazolidinediones.¹⁰⁻¹³

Fenofibrate is a peroxisome proliferator-activated receptor alfa (PPAR α) activator which can display anti-inflammatory effects beyond its lipid (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 the ACCORD Lipid trial, and whether the fenofibrate effect could have been modified by background glucose-lowering strategy intensity.

Methods

ACCORD Lipid study design

ACCORD was a multicenter clinical study, sponsored by the National Heart, Lung, and Blood Institute (NHLBI), and conducted in 77 clinical centers in the United States and Canada. ACCORD enrolled patients with T2D and a glycated hemoglobin level of 7.5% or greater 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 10251 patients were randomly assigned to receive either intensive anti-hyperglycemic therapy targeting a glycated hemoglobin level lower than 6.0% or to receive standard therapy targeting a glycated hemoglobin level of 7.0 to 7.9%. The results of this comparison have been reported previously.¹⁰ A selected subgroup of patients (n =5518) from the ACCORD study were also enrolled in the ACCORD Lipid trial and underwent randomization, in a 2-by-2 factorial design, to receive either simvastatin plus fenofibrate or simvastatin plus placebo, so that the comparison is fenofibrate vs. 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 below 55 mg/dL for women and blacks or below 50 mg/dL for all other groups, and a triglyceride level below 750 mg/dL if they were not receiving lipid-lowering therapy or below 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 been previously 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 the first occurrence of a nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. In the present 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 required documented clinical and radiologic evidence for adjudication.⁸

The access to the ACCORD database was provided by the NHLBI/BioLINCC (<https://biolincc.nhlbi.nih.gov/studies/accord/>) with ethical approval from the *Centro Hospitalar Universitário São João* (process number #500/2020).

Statistical considerations

In trials with a 2-by-2 factorial design the main analytical issues that may arise relate to the investigation of main effects and the interaction between the interventions in the 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 (interaction $P = 0.36$); however, secondary outcomes, such as HF, have not been tested for such potential interactions.

In the present study, the outcomes were analyzed by Cox models, according to the intention-to-treat principle, and the results reported as hazard ratios (HR) and 95% confidence intervals (95%CI). 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-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 post-randomization on-treatment use of certain anti-hyperglycemic drugs in time-updated Cox models. To study the effect of fenofibrate (vs. placebo) on blood lipids and 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 greater than 40% from the baseline value, assessed by the MDRD formula.¹⁷

The associations between blood lipids (log₂ transformed) and outcomes were studied using Cox models, adjusting 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, estimated glomerular filtration rate, and urine albumin-to-creatinine ratio.¹⁸

Mediation analyses were performed taking the time-dynamic evolution of both the potential mediators (eGFR, HDL-cholesterol, and triglycerides) and the outcome cardiovascular death or HF hospitalization 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 using Stata® (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

Results

Patients' baseline characteristics

A total of 5518 patients were enrolled in the ACCORD Lipid study all of whom were receiving simvastatin, with 2765 randomized fenofibrate and 2753 to placebo.

Regarding the background glucose-lowering strategy, 1370 were receiving standard glucose-lowering and placebo, 1383 were receiving intensive glucose-lowering and placebo, 1391 were receiving standard glucose-lowering and fenofibrate, and 1374 were receiving intensive glucose-lowering and fenofibrate. **Supplemental Figure 1** (flow-chart).

The baseline characteristics were well balanced between groups. The median age was 62 years, and around 31% were women. A prior HF history was present in about 5% of the patients and 10% were using loop diuretics. Most patients were treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The median estimated glomerular filtration rate was nearly 90 ml/min/1.73m² and the glycated hemoglobin 8.1%. **Table 1**.

Heart failure outcomes by subgroups of glucose-lowering strategies

For the composite outcome of HF hospitalization or cardiovascular death, 228 (8.3%) patients 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 standard glucose-lowering strategy with an HR of 0.64, 95%CI 0.48-0.85 and not among patients receiving intensive glucose-lowering strategy who did not benefit from fibrate therapy

HR 1.02, 95%CI 0.79-1.33, interaction P =0.017. **Figure 1.** A similar pattern was observed for HF hospitalizations alone, where only patients receiving standard glucose-lowering strategy 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, interaction P =0.025. No between group differences (interactions) were seen for cardiovascular or all-cause mortality, nor 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, interaction P =0.017. In agreement with the main glucose-lowering report, the intensive glucose-lowering strategy increased the risk of mortality regardless of fibrate therapy with an HR of 1.3 in both groups, interaction P =0.78.

Supplemental Table 1.

Treatment-by-sex, atherogenic dyslipidemia, insulin, thiazolidinedione, sulfonylurea therapy, and glycated hemoglobin interaction tests (all at baseline) were statistically non-significant. **Supplemental Figure 2.**

In the 26324 patient-visits with recorded information, insulin and thiazolidinediones were used more frequently in the intensive anti-hyperglycemic arm than in the standard anti-hyperglycemic arm: 7786 (59%) vs. 5860 (44%) patient-visits and 7078 (54%) vs. 4342 (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 the fenofibrate groups. Insulin was used in 6672 (51%) patient-visits in

the placebo group and 6786 (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, interaction $P = 0.42$.

Thiazolidinediones were used in 5639 (43%) patient-visits in the placebo group and 5738 (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, interaction $P = 0.42$. The three-way interaction between treatment-insulin- thiazolidinedione use was non-significant, interaction $P = 0.63$.

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 vs. intensive anti-hyperglycemic strategy: -31.6 mg/dL on standard vs. -25.1 mg/dL on intensive, interaction $P = 0.05$.

Supplemental Table 2. The effect of fenofibrate on total (-4.9 mg/dL), VLDL (-5.3 mg/dL), and HDL (+1 mg/dL) cholesterol was less marked and not different between standard and intensive anti-hyperglycemic strategies, interaction $P > 0.1$ for all. A treatment effect interaction was observed for LDL cholesterol, but the effect magnitude on LDL cholesterol was overall small (-0.7 mg/dL) and of uncertain clinical significance. **Supplemental 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. **Supplemental 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, interaction P =0.15. Other hypoglycemic and non-hypoglycemic adverse events did not differ between treatment groups, nor by glucose lowering strategy, interaction P >0.1 for all.

Supplemental Table 4.

eGFR slope analysis

From baseline to month 4 fenofibrate induced an eGFR drop of -14.8 (-15.5 to -14.1) ml/min/1.73m², 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) ml/min/1.73m² vs. -0.3 (-0.8 to +0.1) ml/min/1.73m² in the fenofibrate group, corresponding to a difference in slopes of +1.4 (+0.8 to +1.9) ml/min/1.73m² per year in favor of fenofibrate (P <0.001), without treatment-by-glucose lowering strategy interaction, interaction P =0.37. **Supplemental Figure 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-C, or triglyceride, as none of these post-randomization parameters was 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/1.73m²/year, P =0.08), triglyceride slope (HR 1.00, 95%CI 0.99-1.01 5 mg/dL/year, P =0.77), HDL slope (HR 0.98, 95%CI 0.93-1.04, P =0.66). Therefore, requirements for a significant mediation effect were not met.

Discussion

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.

While there has been increasing evaluation of SGLT2i and GLP-1RA 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 fenofibrate reduce HF events are not explained by the lowering of triglyceride levels nor 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 anti-hyperglycemic drugs, particularly on the intensive 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 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 anti-hyperglycemic strategies (intensive or standard) used these therapies and these are post-randomization tests, such hypothesis remains open. In addition, current guidelines recommend treatment goals for T2D that are more similar to the standard glucose-lowering arm than the intensive glucose-lowering arm of ACCORD.²⁰

Fenofibrate is a PPAR α agonist, a factor that is predominantly expressed in tissues that metabolise fatty acids, such as the liver, kidney, heart, and muscle. The activation of PPAR α 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 eight weeks significantly attenuated the development of endothelial dysfunction, reduced vascular inflammation, increased adiponectin levels and insulin sensitivity.²⁴ Inflammation and endothelial dysfunction are risk factors for the 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 PPAR α 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 PPAR α and sirtuin-1 (Sirt1) signalling likely contributes to the diminution of autophagic flux and mitochondrial dysfunction seen in various forms of cardiomyopathy.³⁰ Thus, activation of PPAR α (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 PPAR α /Sirt1 signalling is fibroblast growth factor 21 (FGF21), which is mainly produced by the liver under the control of PPAR α . FGF21 is a key player in providing cardiac metabolic flexibility, as it regulates fatty acid oxidation, ketogenesis and insulin resistance.³³ The activation of PPAR α increases FGF21, thereby preventing oxidative stress and improving cardiac energy utilization.

Interestingly, another drug class that is thought to act via the PPAR α /Sirt1/FGF21 axis are sodium glucose co-transporter 2 inhibitors (SGLT2i).³² In patients with T2D, SGLT2i consistently led to a 30-40% relative reduction of HF events,³⁴ which is an effect of similar magnitude 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) that included 2531 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, that included exclusively patients with T2D, does not report HF hospitalizations as an individual endpoint, but fenofibrate led to a 11% reduction in total cardiovascular disease events (P =0.035).⁶

Despite the increased occurrence of a transient worsening eGFR with fenofibrate therapy, the long-term kidney effect of fenofibrate was kidney protective, including a slowing of eGFR decline and a reduction in micro- and macroalbuminuria with fenofibrate compared to 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 the 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 estimated glomerular filtration rate.⁸ The rise in serum creatinine with fenofibrate was reversible upon discontinuation of the drug³⁹ 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 SGLT2 inhibitors, that 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 PPAR α 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 on 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 7 HF hospitalization events between the ACCORD Lipid data we had access to, and the ACCORD Lipid main report;⁸ these 7 events do not impact the reported estimates.

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.

Adequately powered prospective randomized controlled trials are needed to confirm these findings.

Declarations

Ethics approval and consent to participate

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. The access to the ACCORD database was provided by the NHLBI/BioLINCC with ethical approval from the *Centro Hospitalar Universitário São João* (process number #500/2020).

Consent for publication

All authors approved the manuscript and consent its publication.

Availability of data and materials

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

Competing interests

Dr Ferreira is a consultant for Boehringer-Ingelheim, and receives research support from AstraZeneca and Novartis. Dr Zannad reports personal fees from Boehringer Ingelheim during the conduct of the study; personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno pharmaceutical, Applied Therapeutics, Merck, Bayer, and Cellprothera outside the submitted work; and other support from CVCT and Cardiorenal, outside the submitted work. Dr Sharma reports receiving support from the Fonds de Recherche Santé Quebec (FRSQ) Junior 1 clinician scholars program, Canada Institute for Health Research (CIHR grant #175095), European Society of Cardiology young investigator grant, Roche Diagnostics, Boeringer-Ingelheim, Novartis, Astrazeneca, and Takeda. All other authors have no potential conflicts of interest to disclose.

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Authors' contributions

JPF performed the statistical analysis and drafted manuscript and its revisions; all other authors provided critical input.

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Dr. João Pedro Ferreira is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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

Characteristic	Standard glycemia and placebo	Intensive glycemia and placebo	Standard glycemia and fibrate	Intensive glycemia and fibrate
N. =5518	1370	1383	1391	1374
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: Black, n. (%)	212 (15.5%)	226 (16.3%)	188 (13.5%)	200 (14.6%)
Hispanic, n. (%)	104 (7.6%)	90 (6.5%)	110 (7.9%)	103 (7.5%)
Other, n. (%)	164 (12.0%)	168 (12.1%)	180 (12.9%)	161 (11.7%)
White, n. (%)	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)
HbA1c, %	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, mg7g	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%)
Beta-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%)
Anti-platelet, n. (%)	786 (57.4%)	799 (57.8%)	815 (58.6%)	836 (60.8%)

Legend: CVD, cardiovascular disease; HF, heart failure; BMI, body mass index; SBP, systolic blood pressure; HbA1c, glycated hemoglobin in %, * the corresponding results for HbA1c in mmol/mol are 65 (60-73) mmol/L; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; MRAs, mineralocorticoid receptor antagonists; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; CCBs, calcium channel blockers.

Table 2. Outcomes by subgroups of glucose-lowering strategies

Outcome	Events Placebo	Events Fenofibrate	Event-Rate Placebo	Event-Rate Fenofibrate	Hazard Ratio (95%CI)	P-value	Interaction P
HF hospitalization or Cardiovascular death							
Overall population	228/2753 (8.3)	190/2765 (6.9)	1.8 (1.6-2.0)	1.5 (1.3-1.7)	0.82 (0.68-1.00)	0.048	
Standard anti-hyperglycemic group	116/1370 (8.5)	76/1391 (5.5)	1.8 (1.5-2.2)	1.2 (0.9-1.4)	0.64 (0.48-0.85)		0.017
Intensive anti-hyperglycemic group	112/1383 (8.1)	114/1374 (8.3)	1.7 (1.4-2.1)	1.8 (1.5-2.1)	1.02 (0.79-1.33)		
HF hospitalization							
Overall population	149/2753 (5.4)	121/2765 (4.4)	1.2 (1.0-1.4)	0.9 (0.8-1.1)	0.80 (0.63-1.02)	0.07	
Standard anti-hyperglycemic group	82/1370 (6.0)	51/1391 (3.7)	1.3 (1.0-1.6)	0.8 (0.6-1.0)	0.60 (0.42-0.85)		0.025
Intensive anti-hyperglycemic group	67/1383 (4.8)	70/1374 (5.1)	1.0 (0.8-1.3)	1.1 (0.9-1.4)	1.05 (0.75-1.47)		
Cardiovascular death							
Overall population	114/2753 (4.1)	99/2765 (3.6)	0.9 (0.7-1.0)	0.7 (0.6-0.9)	0.86 (0.66-1.13)	0.28	
Standard anti-hyperglycemic group	48/1370 (3.5)	39/1391 (2.8)	0.7 (0.5-1.0)	0.6 (0.4-0.8)	0.79 (0.52-1.21)		0.62
Intensive anti-hyperglycemic group	66/1383 (4.8)	60/1374 (4.4)	1.0 (0.8-1.3)	0.9 (0.7-1.2)	0.91 (0.64-1.29)		
Primary outcome*							
Overall population	310/2753 (11.3)	291/2765 (10.5)	2.5 (2.2-2.7)	2.3 (2.0-2.6)	0.93 (0.79-1.09)	0.36	
Standard anti-hyperglycemic group	159/1370 (11.6)	141/1391 (10.1)	2.5 (2.2-3.0)	2.2 (1.9-2.6)	0.86 (0.69-1.08)		0.35
Intensive anti-hyperglycemic group	151/1383 (10.9)	150/1374 (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	221/2753 (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 anti-hyperglycemic group	95/1370 (6.9)	91/1391 (6.5)	1.4 (1.2-1.7)	1.3 (1.1-1.6)	0.94 (0.71-1.25)		0.78
Intensive anti-hyperglycemic group	126/1383 (9.1)	112/1374 (8.2)	1.9 (1.6-2.2)	1.7 (1.4-2.0)	0.89 (0.69-1.15)		

Legend: HF, heart failure; *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.

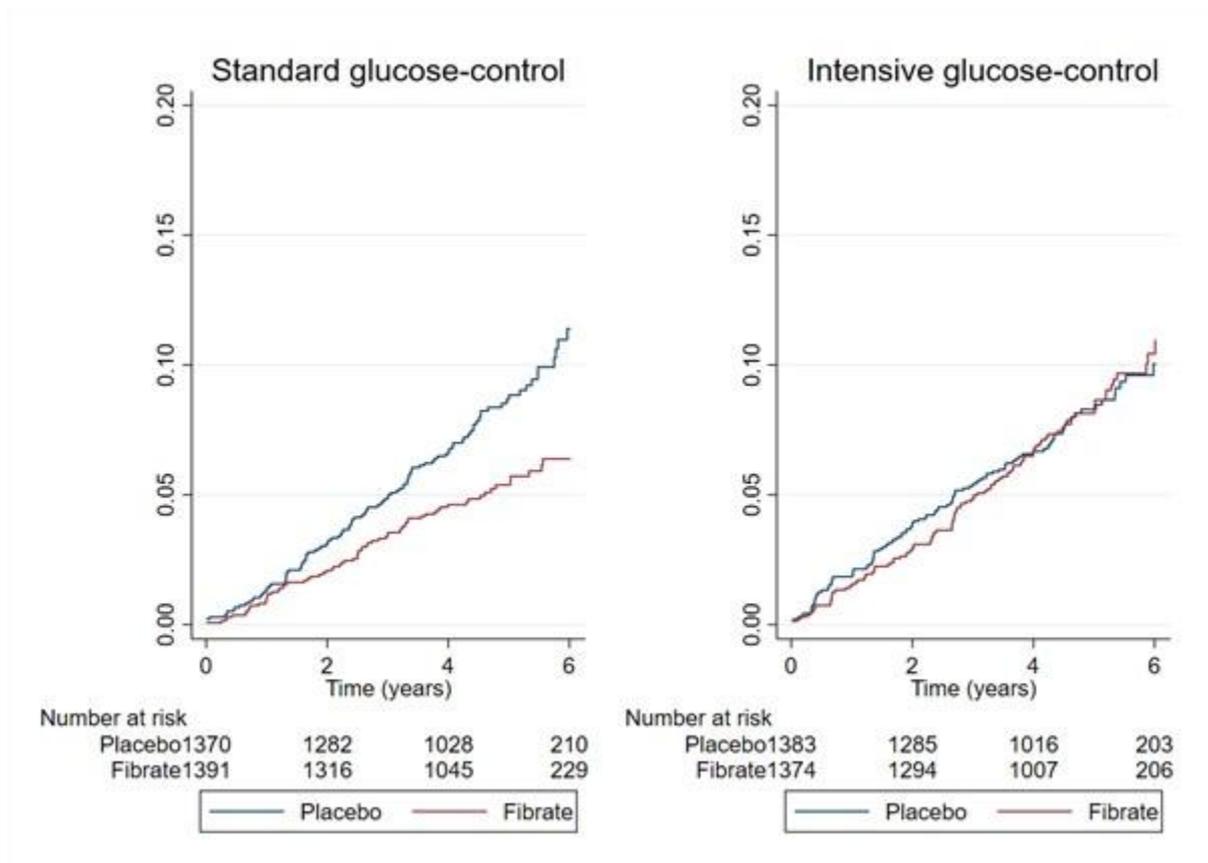


Figure 1. Time-to-first events of the composite of heart failure hospitalization or cardiovascular death by subgroups of glucose-lowering strategies

Legend: Fibrate, fenofibrate; 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, interaction P =0.017.