Cardiol Ther (2025) 14:297–314
https://doi.org/10.1007/s40119-025-00410-y

ORIGINAL RESEARCH

Efficacy and Safety of the Fixed-Dose Combination of Atorvastatin/Fenofibrate Versus Atorvastatin on the Lipid Profile of Patients with Type 2 Diabetes and Dyslipidemia

Francisco G. Padilla-Padilla · Lina N. Ruiz-Bernes · Luis M. Román-Pintos · Juan A. Peraza-Zaldívar · José G. Sander-Padilla · Laura A. Lugo-Sánchez · Kevin F. Rios-Brito · María M. Arguedas-Núñez · Diana Flores-Huanosta · Jorge González-Canudas

Received: January 6, 2025 / Accepted: April 1, 2025 / Published online: May 5, 2025

ABSTRACT

***Introduction*:** In dyslipidemia associated with type 2 diabetes (T2DM), elevated triglycerides (TG), increased low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) levels are commonly found, resulting in a high prevalence of mixed dyslipidemia among patients with T2DM. Therefore, the combination therapy of atorvastatin/fenofibrate may be useful for simplifying pharmacological regimens, enhancing adherence, and requiring fewer doses of each drug to achieve the target, which decreases the number of adverse events.

***Methods*:** We conducted a randomized multicenter, double-blind clinical trial of patients with T2DM and mixed dyslipidemia to evaluate the magnitude of change in lipid profile with a fixed-dose combination (FDC) therapy group of

F. G. Padilla-Padilla · L. N. Ruiz-Bernes
Clinical and Interventional Cardiology, Tarascos, No. Ext. 3469, Int. 507, Monraz, 44670 Guadalajara, Jalisco, Mexico
e-mail: fgpadillap@yahoo.com.mx

L. N. Ruiz-Bernes
e-mail: linaruizbernes@gmail.com

L. M. Román-Pintos
Hospital Hispano, S.A. de C.V., Pedro Moreno No. 934, Centro, Guadalajara, Jalisco, Mexico
e-mail: lmroman@yahoo.com

J. A. Peraza-Zaldívar
Investigación Biomédica Para El Desarrollo de Fármacos S.A. de C.V., Calle Volcán Popocatépetl 3352 Nivel 1 y 2, Colli Urbano, CP. 45070 Zapopan, Jalisco, Mexico
e-mail: p_juan_angel@hotmail.com

J. G. Sander-Padilla · L. A. Lugo-Sánchez · K. F. Rios-Brito · M. M. Arguedas-Núñez · D. Flores-Huanosta · J. González-Canudas (✉)
Laboratorios Silanes, S.A. de C.V., Av. Paseo de Las Palmas No. 340, 3rd Floor, Lomas de Chapultepec, Miguel Hidalgo, 11000 Mexico City, Mexico
e-mail: jogonzalez@silanes.com.mx

J. G. Sander-Padilla
e-mail: jgsander@silanes.com.mx

L. A. Lugo-Sánchez
e-mail: llugo@silanes.com.mx

K. F. Rios-Brito
e-mail: krios@silanes.com.mx

M. M. Arguedas-Núñez
e-mail: marguedas@silanes.com.mx

D. Flores-Huanosta
e-mail: dfloresh@silanes.com.mx

J. González-Canudas
IMSS-Centro Médico Nacional Siglo XXI, Av. Cuauhtémoc 330, Doctores, Cuauhtémoc, Mexico City, México

atorvastatin 20 mg/fenofibrate 160 mg (G_FDC) versus atorvastatin 20 mg monotherapy group (G_M), both oral route, one tablet every 24 h. The magnitude of change in the lipid profile at 2 and 4 months was compared within each group and between groups using the analysis of variance (ANOVA) test. A p value ≤ 0.05 was considered statistically significant.

***Results*:** A total of 76 patients were included (38 per group), with an age of 56.7 ± 10.2 years, and 56.6% were women. The values at 4 months for G_FDC vs. G_M were as follow: TG mg/dL (−144.3 vs. −64.0, $p = 0.004$), TG percentage change (%C) (−47.9 vs. −33.1, $p = 0.007$); LDL-C mg/dL (−50.5 vs. −51.7, $p = 0.784$), LDL-C %C (−42.5 vs. −45.6, $p = 0.899$). The percentage of patients who achieved the targets for triglycerides (TG) was 56.7% compared to 43.8% ($p = 0.309$), while for LDL-C, it was 73.3% compared to 78.1% ($p = 0.660$). Finally, the predictive cardiovascular risk indices (Δ of change) showed a TG/HDL index of −3.9 ± 4.6 vs. −1.5 ± 2.9 ($p = 0.015$) and a Tg/glucose index of −0.7 ± 0.5 vs. −0.3 ± 0.4 ($p = 0.003$).

***Conclusion*:** The FDC therapy of atorvastatin 20 mg/fenofibrate 160 mg achieved a greater percentage reduction in lipid profile than atorvastatin alone. No differences in adverse events were observed between the groups.

***Clinical Trials Registration*:** ClinicalTrials.gov No. NCT04882293, registration date: February 28, 2022.

Keywords: Dyslipidemias; Type 2 diabetes; Fixed-dose combination; Atorvastatin; Triglycerides; Fenofibrate

Key Summary Points

Why carry out this study?

Cardiovascular diseases are considered the main cause of death worldwide; dyslipidemia and type 2 diabetes are the main metabolic factors that influence the incidence of these disorders.

Statins are the cornerstone of therapy for mixed dyslipidemia, effectively lowering low-density lipoprotein cholesterol levels. However, residual risks are associated with elevated triglycerides and low high-density lipoprotein cholesterol concentrations, necessitating additional lipid-lowering therapies such as fibrates for more significant reductions.

This study aimed to evaluate the changes in lipid profile measurements at 2 and 4 months in comparison with baseline values and to assess differences between treatment groups. The treatments compared were fixed-dose combination (FDC) atorvastatin 20 mg and fenofibrate 160 mg versus atorvastatin 20 mg alone.

What was learned from the study?

The study provides evidence supporting the superiority of FDC atorvastatin 20 mg/fenofibrate 160 mg over monotherapy, improving the lipid profile, mainly triglycerides, and using lower doses, which improves tolerability while maintaining a favorable safety profile in patients with T2DM and dyslipidemia, against atorvastatin 20 mg.

INTRODUCTION

Cardiovascular diseases (CVD) are considered the leading cause of death worldwide, with circulatory risk factors such as hypertension (HT), as well as metabolic factors like type 2 diabetes (T2DM) and dyslipidemias [1, 2]. The last one is usually of a secondary cause related to a sedentary lifestyle, excessive intake of saturated fats, obesity, T2DM, and smoking [3, 4].

In Latin America, including Mexico, the prevalence of T2DM is among the highest in the world, and although it is a risk factor for CVD on its own, the presence of comorbidity such as dyslipidemias, which occur in around 35–50% of cases, increases this risk by aggravating atherosclerotic disease [5, 6]. In dyslipidemia associated with T2DM, elevated triglycerides (TG), increased low-density lipoprotein

cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) are commonly found, resulting in a high prevalence of mixed dyslipidemia among patients with T2DM, who are recommended strict management of these alterations; [6] among the markers associated with this risk are the triglyceride-glucose index TG/glucose [7] and TG/HDL-C index [8].

Timely treatment aimed at improving lifestyle, emphasizing weight loss, dietary fat reduction, and physical exercise, is often insufficient and requires accompanying pharmacological treatment [6]. LDL-C and TG levels represent two targets on which therapeutic goals should be defined for the control of dyslipidemia [3]. Among lipid-lowering drugs, statins are the cornerstone; they reduce cholesterol synthesis in the liver through a competitive inhibition mechanism with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) [3] and increase the clearance of LDL and other ApoB-containing lipoproteins, including triglyceride-rich particles [9]. The degree of LDL-C reduction will depend on the dosage, with some variation between statins, aiming for a reduction of over 50% at high doses and between 30 and 50% with moderate doses. Similarly, an increase in HDL-C of 1–10% and a reduction in TG between 10 and 20% is observed [9]. Meanwhile, fibrates are recommended in the initial treatment alongside statins [9–11]. These are agonists of peroxisome proliferator-activated receptors (PPAR-α), promoting the catabolism of triglyceride-rich particles [9]. They also achieve a reduction of ≤ 20% in LDL-C levels and an increase of ≤ 20% in HDL-C [9]. These drugs, statins and fibrates, can be used alone or in combination; but in the presence of hypertriglyceridemia, a common occurrence in patients with T2DM, the use of fibrates is recommended, achieving reductions of 45–50% [9–11].

A review of various studies demonstrated the benefit of combination therapy, achieving a reduction in total cholesterol and TG, with improvement in HDL values but no increase in adverse effects [12].

The combination of atorvastatin/fenofibrate was performed because, among statins, this has been demonstrated as one of the most potent for LDL-C reduction, with an effect on TG, and as being dose-dependent [13, 14]. For its part, fenofibrate has shown minimal risk of increasing statin levels [13] and has demonstrated its safety in combination with a statin without increasing the occurrence of muscle adverse events compared to statin monotherapy [15–17]. The advantage of this combination seems to be due to different mechanisms of action [3, 9–11]. This type of fixed-dose combination (FDC) therapy has proven useful in simplifying pharmacological regimens, enhancing adherence, and requiring fewer doses of each drug to achieve the target, which decreases the number of adverse events as well as the presence of polypharmacy [18–20].

METHODS

A phase III randomized, double-blind, multicenter (four centers in Mexico) clinical trial was conducted. The study was developed following the legal provisions of the General Health Law of the United Mexican States and the Helsinki Declaration of 1964 and its later amendments. The study protocol, informed consent form (ICF), and any other relevant documents according to National Regulation were reviewed and approved by an independent ethics committee (IEC) (Investigación Biomédica para el Desarrollo de Fármacos, S.A. de C.V.), and by Mexican regulatory authorities (Federal Commission for the Protection against Sanitary Risks [COFEPRIS]), with authorization number COFEPRIS: 223300912X1745/2022 and registered in ClinicalTrials.gov No. NCT04882293. It was conducted in accordance with the clinical protocol.

Patients were required to be between 18 and 75 years of age and to have a T2DM diagnosis, with HbA1c ≤ 9.5% and mixed dyslipidemia (LDL-C > 100 mg/dL and TG > 150 mg/dL). Patients meeting the inclusion requirements were invited to participate, the study was explained, and in the case of women with a probability of becoming pregnant, they were advised of the need to use a contraceptive method during the study period. Finally, written informed consent was obtained. During the initial evaluation, patients who had any of the

following were excluded: medical contraindication for the use of any of the drugs; use of oral contraceptives at the time of admission; use of cyclosporine or potent CYP3A4 inhibitors, protease inhibitors, erythromycin, or azoles; acute renal dysfunction or glomerular filtration < 30 mL/min/1.73 m^2; history of chronic liver disease or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 2 times or gamma-glutamyl transferase (GGT) ≥ 3 times the upper normal limit; chronic or acute pancreatitis, except for acute pancreatitis due to severe hypertriglyceridemia; diagnosis of active gallbladder disease; history or presence of myopathies, pregnancy, or lactation; or any other disease with a poor prognosis, such as terminal cancer, renal, cardiac, respiratory, or hepatic failure, or mental illness, or with scheduled surgical or hospital procedures.

Patients selected based on the results of their initial visit received guidance on lifestyle changes and were randomized into one of two groups:

- Treatment A: FDC of atorvastatin 20 mg/fenofibrate 160 mg. Tablet. Manufacturer: Laboratorios Silanes S.A. de C.V. Therapy group (G), fixed-dose combination (FDC), (G_FDC).
- Treatment B: Atorvastatin 20 mg (Lipitor®). Tablet. Manufacturer: Pfizer Pharmaceuticals, LLC. Monotherapy group (G_M).

We used simple randomization via the www.randomization.com platform, balanced by treatment. Sealed randomization envelopes were used for each kit. The sponsor provided the randomized medications, and the study treatments were distributed at each visit by personnel delegated by the principal investigator. In both groups, the treatment was administered orally (PO) once a day over a 4-month follow-up period. Each research subject was provided with a patient diary to record daily medication intake, and they were asked to return their packaging at each visit to verify adherence to the treatment, which consisted of atorvastatin/fenofibrate 91.2% and atorvastatin 95.7% ($p = 0.241$).

Six clinic visits were planned. An initial screening visit to identify inclusion criteria (visit −1, 15 days prior), followed by the initial evaluation (visit 0, at the start), where anthropometric measurements, tobacco consumption history, and laboratory measurements were obtained to verify selection criteria (inclusion and exclusion). Treatment groups were assigned, and during follow-up evaluations at 2 and 4 months (visits 2 and 4), laboratory tests were repeated to measure outcomes. Patients were required to fast for at least 8 h before blood samples were taken. Efficacy measurements were performed, including TG, LDL-C, HDL-C, total cholesterol, and lipoprotein (a) [Lp (a)]. For laboratory safety evaluation, glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, creatine kinase (CPK), creatinine, urea, urinalysis, and the presence of new or increased symptoms of muscle pain were measured. During all visits (visits 1–4), possible adverse events were evaluated, and their frequency, intensity, and causality were analyzed. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

In the efficacy evaluation conducted at 2 and 4 months, TG and LDL-C were measured in mg/dL, along with their delta (Δ) and percentage change, and the percentage of subjects who reached the therapeutic goal, which was for TG (< 150 mg/dL) and for LDL-C (a 30% reduction compared to baseline concentrations). The effects of treatment on other biochemical markers of dyslipidemia, such as total cholesterol and HDL-C, as well as on prognostic indicators (index TG/glucose and TG/HDL-C), were also measured.

The sample size was estimated using a formula for the difference of means, accepting a confidence level of 95% ($\alpha = 0.05$), a statistical power of 90%, considering a difference in triglycerides (primary variable) of 104 mg/dL, and a standard deviation of 129 in favor of the fixed-dose combination therapy. The calculation was 32 patients per treatment group, increased by 20% in case of losses to maintain data stability (38 patients per group). A total of 173 patients were evaluated, with 76 meeting the selection criteria and included in the study.

Statistical Analysis

Baseline characteristics were compared between groups for normally distributed quantitative variables using Student's *t*-test for independent samples, for non-normally distributed quantitative variables using the Mann–Whitney *U* test, and for dichotomous and ordinal variables using the chi-squared test. The comparison of the magnitude of change at 2 and 4 months for all lipid profiles and indexes of cardiovascular risk within each group and between treatment groups was realized through analysis of variance (ANOVA) and the Friedman test depending on data distribution tests for quantitative variables, and with the Cochran, McNemar, and chi-squared test for dichotomous data. A *p*-value of ≤ 0.05 was considered statistically significant.

The authors guarantee the accuracy and integrity of the data and analysis. The analysis was performed by intention to treat, by a person not involved in the study, and the research group prepared the manuscript.

RESULTS

A total of 173 patients were evaluated, of which 76 were included and randomized into the G_FDC (atorvastatin/fenofibrate group; $n=38$) and the G_M (atorvastatin group; $n=38$) at visit 1. During follow-up, six patients were lost to follow-up, four from the G_FDC and two from the G_M. The average age of the population was 56.7 ± 10.2 years, and 56.6% were women. Overweight was observed in 40.8% of the population and obesity in 51.3%. Systolic blood pressure (SBP) was 126.9 ± 17.4 mmHg, and diastolic blood pressure (DBP) was 78.7 ± 11.1 mmHg. Laboratory studies highlighted a glucose level of 110.5 ± 34.8 mg/dL, glycated hemoglobin of 6.4 ± 1.1%, LDL-C of 135.6 ± 24.9 mg/dL, HDL-C of 37.8 ± 7.5 mg/dL in men and 44.1 ± 8.3 mg/dL in women, and TG of 226.5 (180.5, 309.7) mg/dL. Additionally, 32.9% were smokers, with high cardiovascular risk in 9.2% and very high in 1.3%. The use of concomitant medications was recorded, revealing that approximately 40% of patients reported the use of nonsteroidal anti-inflammatory drugs (NSAIDs), with acetylsalicylic acid being the most commonly used. Similarly, 50% of patients were using some antihypertensive medication, predominantly those from the angiotensin II receptor antagonist group. On the other hand, it was observed that 89.5% of patients were being treated with antidiabetic medications, with oral hypoglycemic therapy being the most common. Among those receiving monotherapy (70.6%), metformin was the most commonly employed drug. Regarding dual therapy (13.2%), combinations of biguanides with sulfonylureas were the most reported. Additionally, the prescription of injectable antidiabetics was documented in 16.2% of patients. No differences were observed between the treatment groups. The complete baseline status is shown in Table 1.

For the primary efficacy outcome, changes in the lipid profile were comparable for both treatments (Table 2). Significant changes were observed from the first two months and maintained until four months, particularly in TG concentrations, with a greater reduction in the G_FDC compared with G_M. [Δ change mg/dL (2 months, −133.5 ± 135.7 vs. −66.0 ± 73.0, $p=0.010$), (4 months, −144.3 ± 136.1 vs. −64.0 ± 78.6, $p=0.006$), (Fig. 1)].

Likewise, an analysis of the data obtained for the LDL-C marker was performed, observing that both treatment groups (G_FDC compared to G_M) reported a reduction greater than 50% at 2 months (Δ change mg/dL, 2 months −57.8 ± 5.6 vs. −59.5 ± 4.3, $p=0.813$), and this remained the case until 4 months of intervention (Δ change mg/dL, −50.5 ± 7.5 vs. 51.7 ± 6.1, $p=0.784$).

Within the G_FDC, significant changes in total cholesterol were observed at 2 and 4 months with respect to their baseline visit (216.9 mg/dL vs. 143.0 mg/dL, $p=0.001$ vs. 147.2 mg/dL, $p=0.00$), with an average reduction of more than 30% at the end of the intervention. For the G_M, significant reductions were identified at both 2 and 4 months of follow-up (218.7 mg/dL vs. 148.8 mg/dL, $p=0.001$, vs. 158.3 mg/dL, $p=0.001$). The average reduction at the end of the intervention was lower than that reported with the combination of

Table 1 Baseline sociodemographic, anthropometric, clinical, and biochemical characteristics of the patients enrolled in the study by treatment group

Variable	Total $N = 76$	Atorvastatin 20 mg/fenofibrate 160 mg $n = 38$	Atorvastatin 20 mg $n = 38$	p
Age (years)[a]	56.7 ± 10.2	55.3 ± 9.3	58.0 ± 10.9	0.250
Sex[b]				0.817
Men	33 of 76 (43.4)	16 of 38 (42.1)	17 of 38 (44.7)	
Women	43 of 76 (56.6)	22 of 38 (57.9)	21 of 38 (55.3)	
Anthropometric characteristics				
Weight, Kg[a]	84.1 ± 15.4	85.2 ± 15.2	83.0 ± 15.6	0.534
Height, m[a]	164.1 ± 10.0	164.7 ± 10.3	163.6 ± 9.7	0.630
BMI, Kg/m^{2}[a]	31.2 ± 5.0	31.4 ± 5.2	30.9 ± 5.0	0.692
Normal[b]	6 of 76 (7.9)	3 of 38 (7.9)	3 of 38 (7.9)	0.923
Overweight[b]	31 of 76 (40.8)	16 of 38 (42.1)	15 of 38 (39.5)	
Obesity[b]	39 of 76 (51.3)	19 of 38 (50.0)	20 of 38 (52.6)	
Waist circumference, cm	103.3 ± 12.4	104.1 ± 10.8	102.5 ± 13.9	0.586
Clinical characteristics[a]				
Vital signs				
SBP, mmHg	126.9 ± 17.4	127.8 ± 16.1	126.1 ± 18.8	0.673
DBP, mmHg	78.7 ± 11.1	79.4 ± 11.7	78.0 ± 10.5	0.588
HR, lpm	69.6 ± 8.4	71.2 ± 8.5	68.0 ± 8.1	0.106
RR, rpm	16.8 ± 3.5	16.8 ± 3.6	16.7 ± 3.4	0.897
Temperature, °C	36.4 ± 0.2	36.4 ± 0.2	36.3 ± 0.2	0.173
Biochemical characteristics				
Glucose, mg/dL[a]	110.5 ± 34.8	113.7 ± 39.5	107.3 ± 29.5	0.421
Glycated hemoglobin, %[a]	6.4 ± 1.1	6.5 ± 1.1	6.2 ± 1.1	0.305
Total cholesterol, mg/dL[a]	218.2 ± 32.8	217.7 ± 34.5	218.7 ± 31.5	0.896
HDL cholesterol, mg/dL[a]	41.4 ± 8.5	41.0 ± 10.0	41.7 ± 6.9	0.718
Men	37.8 ± 7.5	36.4 ± 6.7	39.1 ± 8.2	0.317
Women	44.1 ± 8.3	44.3 ± 10.8	43.8 ± 4.8	0.849
LDL cholesterol, mg/dL[a]	135.6 ± 24.9	133.8 ± 27.5	137.5 ± 22.1	0.521
Non-HDL cholesterol[a]	176.8 ± 31.1	176.7 ± 31.9	176.9 ± 30.6	0.969
Triglycerides, mg/dL[c]	226.5 (180.5, 309.7)	224.5 (177.5, 337.2)	227.0 (183.0, 295.7)	0.763
Atherogenic index[a]	5.3 ± 1.1	5.4 ± 1.1	5.3 ± 1.1	0.892

Table 1 continued

Variable	Total $N=76$	Atorvastatin 20 mg/fenofibrate 160 mg $n=38$	Atorvastatin 20 mg $n=38$	p
Lipoprotein (a) [Lp (a)], g/L[c]	16.6 (7.7, 37.7)	15.3 (6.8, 45.9)	18.0 (9.4, 31.4)	0.767
CPK, U/L[c]	84.0 (58.2, 124.5)	84.0 (59.7, 123.5)	84.0 (52.5, 130.5)	0.593
ALT, U/L[c]	22.5 (17.0, 36.5)	22.5 (17.0, 35.7)	22.5 (16.0, 38.0)	0.625
AST, U/L[c]	19.0 (16.0, 26.7)	20.0 (18.0, 26.2)	18.0 (16.0, 27.5)	0.233
Alkaline phosphatase, UI/L[c]	72.5 (57.2, 81.7)	70.5 (55.7, 80.7)	74.5 (54.7, 82.5)	0.647
GGT, U/L[c]	27.0 (19.0, 46.0)	28.0 (19.0, 46.7)	26.0 (19.0, 46.0)	0.947
Smoking[b]				
Yes	25 of 76 (32.9)	13 of 38 (34.2)	12 of 38 (31.6)	0.807
No	51 of 70 (67.1)	25 of 38 (65.8)	26 of 38 (68.4)	
Glomerular filtration rate[a]	105.4 ± 30.3	103.9 ± 32.9	105.7 ± 30.9	0.826
Cardiovascular risk[b]				
Low risk	24 of 76 (31.6)	15 of 38 (39.5)	9 of 38 (23.7)	0.391
Moderate risk	44 of 76 (57.9)	20 of 38 (52.6)	24 of 38 (63.2)	
High risk	7 of 76 (9.2)	3 of 38 (7.9)	4 of 38 (10.5)	
Very high risk	1 of 76 (1.3)	0 of 38 (0)	1 of 38 (2.6)	

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *RR* respiratory rate, *mmHg* millimeters of mercury, *bpm* beats per minute, *rpm* respirations per minute, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyl transferase, *mg/dL* milligrams per deciliter, *IU/l* international units per liter, *IQR* interquartile range (25th and 75th percentiles)

[a]Values are presented as mean ± standard deviation, Student's **t**-test for independent samples

[b]Values are presented as frequency and percentage, chi-squared test

[c]Values are presented as median and IQR (25th and 75th percentiles), Mann–Whitney *U* test

$p < 0.05$ significant

atorvastatin/fenofibrate (25.9%). In addition to the markers described above, non-HDL cholesterol was calculated, with the intention of evaluating the differences reported throughout the follow-up. Within the group with the FDC, statistically significant changes were observed in its evaluation at both 2 and 4 months (175.6 mg/dL vs. 100.8 mg/dL, $p=0.001$ vs. 105.1 mg/dL, $p=0.001$), identifying the highest percentage of reduction at 2 months, with a decrease greater than 46.8%. At the end of the intervention, a higher percentage of reduction was observed compared to G_M (−45.6% vs. −41.3%). Changes in lipid levels were observed in practically all lipid profiles, which was statistically significant ($p \leq 0.001$), except for HDL-C, which showed a minimal increase during follow-up (Table 2).

At the end of follow-up, we analyzed the percentage of patients who achieved the therapeutic goal for TG (<150 mg/dL) and LDL-C (a 30% reduction compared to baseline concentrations). We observed that in the group receiving the combination, this proportion was higher than in the control group for TG (56.7% vs. 43.8%, $p=0.309$). However, for the LDL-C marker

Table 2 Changes in biochemical markers of lipid profile at 2 and 4 months of follow-up by treatment group

Variable	Atorvastatin 20 mg/fenofibrate 160 mg					Atorvastatin 20 mg					p^{+}	p^{++}
	Basal	2 months	*P*	4 months	*p*	Basal	2 months	*p*	4 months	*p*		
Triglycerides, mg/dL[c]	224.5 (177.5, 337.2)	131.5 (99.2, 196.2)	0.001	136.5 (108.0, 209.7)	0.001	227.0 (183.0, 295.7)	171.0 (111.0, 211.0)	0.001	159.5 (116.7, 245.0)	0.001	0.216	0.185
Δ change[a]	–	−135.6 ± 26.2	–	−144.3 ± 24.8	–	–	−66.0 ± 13.2	–	−64.0 ± 14.1	–	0.010	0.004
% change[c]	–	−51.7 (−59.4, −34.9)	–	−47.9 (−61.5, −31.2)	–	–	−30.8 (−43.3, −9.1)	–	−33.1 (−50.6, −6.4)	–	0.004	0.007
Triglycerides, *n* (%)[b] (< 150 mg/dL)[b]	0 of 34 (0)	20 of 34 (58.8)*	0.001	17 of 30* (56.7)	0.004	0 of 36 (0)	15 of 36* (41.7)	0.001	14 of 32* (43.8)	0.001	0.151	0.309
LDL-C, mg/dL[c]	122.2 (113.1, 139.6)	71.9 (57.0, 88.4)	0.001	76.2 (58.7, 92.3)	0.001	134.1 (121.43, 153.9)	71.7 (62.5, 83.9)	0.001	71.6 (61.6, 98.0)	0.001	0.823	0.888
Δ change[a]	–	−57.8 ± 5.6	–	−50.5 ± 7.5	–	–	−59.5 ± 4.3	–	−51.7 ± 6.1	–	0.813	0.784
% change[c]	–	−47.9 (−55.8, −32.1)	–	−42.5 (−58.6, −21.4)	–	–	−45.4 (−56.0, −37.5)	–	−45.6 (−56.4, −33.0)	–	0.842	0.899
LDL-C, *n* (%) (reduction mg/dL ≥ 30%)[b]	0 of 34 (0)	28 of 34* (82.4)	0.005	22 of 30** (73.3)	0.003	0 of 36 (0)	29 of 36* (80.5)	0.083	25 of 32* (78.1)	0.025	0.847	0.660
Total cholesterol, mg/dL[a]	216.9 ± 6.8	143.0 ± 5.1	0.001	147.2 ± 6.8	0.001	218.7 ± 5.8	148.7 ± 6.3	0.001	158.3 ± 9.1	0.001	0.306	0.207
Δ change[a]	–	−76.5 ± 5.8	–	−69.6 ± 7.9	–	–	−69.31 ± 5.4	–	−55.4 ± 7.2	–	0.355	0.197
% change[a]	–	−34.2 ± 2.2	–	−31.2 ± 3.1	–	–	−31.4 ± 2.2	–	−25.9 ± 3.2	–	0.384	0.267
Non-HDL cholesterol, mg/dL[a]	175.6 ± 6.2	100.8 ± 5.1	0.001	105.1 ± 6.7	0.001	177.0 ± 5.7	107.1 ± 6.5	0.001	115.0 ± 8.9	0.001	0.304	0.284
Δ change[a]	–	−77.6 ± 5.7	–	−70.5 ± 7.7	–	–	−68.7 ± 5.8	–	−61.9 ± 7.1	–	0.279	0.209

Table 2 continued

Variable	Atorvastatin 20 mg/fenofibrate 160 mg					Atorvastatin 20 mg				p^{+}	p^{++}
	Basal	2 months	*P*	4 months	*p*	Basal	2 months	*p*	4 months	*p*	
% change[c]	–	−46.8 (−53.3, −36.9)	–	−45.6 (−56.1, −25.3)	–	–	−44.2 (−52.4, −33.3)	–	−41.3 (−54.2, −29.2)	–	0.391	0.583
HDL-C, mg/dL[a]	41.2 ± 1.8	42.2 ± 1.6	0.276	42.1 ± 2.1	0.489	41.7 ± 7.2	41.2 ± 1.5	0.717	43.3 ± 1.4	0.167	0.922	0.675

mg/dL milligrams per deciliter, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *IQR* interquartile range (25th and 75th percentiles)

[a]Values are presented as mean and standard error, and ANOVA test, adjusted by Bonferroni for multiple comparisons for data with normal distribution

[b]Values are presented as frequency and percentage, Cochran and chi-squared test for categorical variables

[c]Values are presented as median and IQR 25, 75, and Friedman test for non-normal variables

*Lipid profile data for four patients in the combination group and two patients in the atorvastatin group were not available at the 2-month visit. Lipid profile data for four additional patients, compared to the previous visit, were missing at the 4-month visit for both treatment groups

(73.3% vs. 78.1%, $p=0.660$), a greater response was observed in the G_M.

In addition to changes in lipid profile markers, triglyceride/glucose and triglyceride/HDL ratios were evaluated as predictors of cardiovascular risk (Table 3). The magnitude of change at 2 and 4 months was analyzed within each treatment group, identifying statistically significant differences ($p=0.001$). At the end of follow-up, statistically significant differences were observed between the treatment groups [–0.7 ± 0.5 vs. –0.3 ± 0.4, $p=0.003$]. The target percentage of < 8.5 points for the TG/glucose index was 9/30 (30%) vs. 5/32 (15.7%), ($p=0.080$). On the other hand, for the TG/HDL index, the magnitude of change (Δ) was greater at both assessment times for the G_FDC than for the G_M (–3.9 ± 4.6 vs. –1.5 ± 2.9, $p=0.015$).

Patients with dyslipidemia and T2DM are at a high risk of CVD, a risk directly linked to the development of atherosclerosis, a chronic inflammatory condition largely driven by lipid profile abnormalities. From a pharmacological perspective, fibrates help reduce residual cardiovascular risk associated with atherogenic dyslipidemia. While statins have been proven effective in significantly lowering LDL-C-associated risk, they fail to adequately mitigate the risk stemming from hypertriglyceridemia and low HDL-C levels. In this context, the present study evaluated a key marker of residual cardiovascular risk, lipoprotein(a) [Lp (a)], a highly proinflammatory lipoprotein associated with premature CVD. At the end of the intervention, the proportion of patients with Lp(a) levels < 30 mg/dL, a threshold considered low risk according to the European Atherosclerosis Society (EAS) and the American College of Cardiology (ACC), was analyzed. This proportion was 63.3% in the FDC group compared to 59.4% in the atorvastatin group.

Of the 76 patients, 15 experienced at least one adverse event (AE). In total, there were 29 AEs, classified as non-serious (20 mild and 9 moderate): 13 in the fixed-dose combination treatment group (G_FDC) and 16 in the atorvastatin group (G_M). The most frequently affected system was the nervous system, with 12 AEs (four in G_FDC and eight in G_M). The most common AE was headache, with four cases in G_M, followed by paresthesia, with three in G_FDC and one in

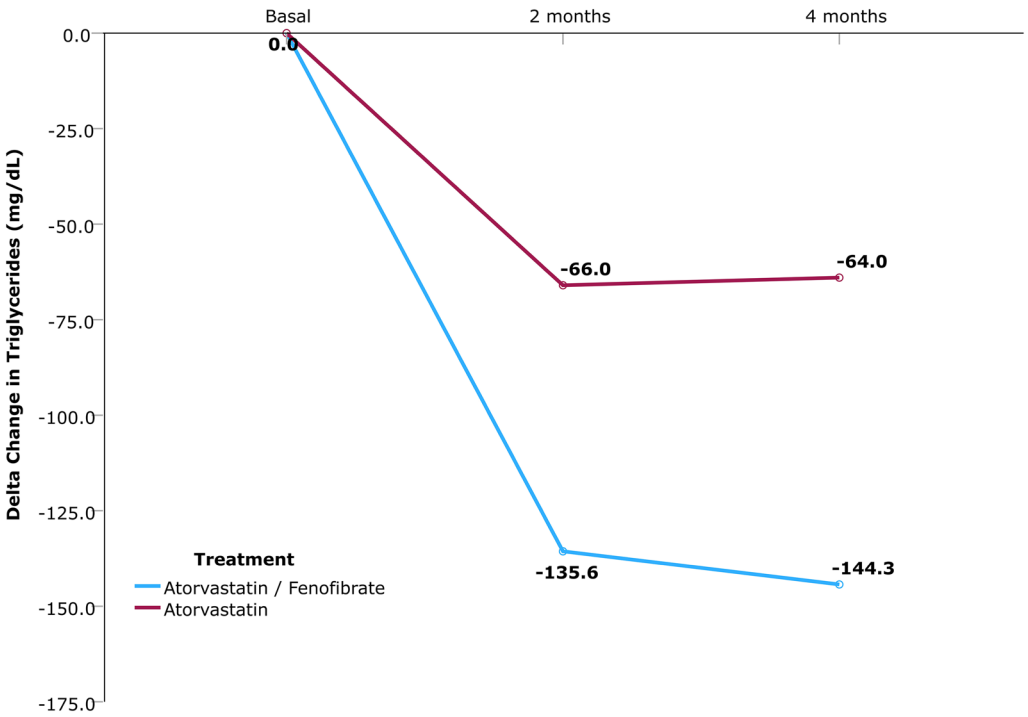

Fig. 1 Delta change in triglycerides at 2 and 4 months compared with baseline by treatment group follow-up (months)

G_M. No significant differences were observed between groups. See Table 4.

As part of the study's safety assessment, we evaluated the primary biochemical markers that have shown alterations associated with the use of statins and fibrates, including ALT, AST, and CPK. At the end of treatment, no clinically or statistically significant increase was observed in ALT [median change, G_FDC 0.5 (–8.2, 12.2) vs. G_M 1.0 (–5.0, 4.0), $p=0.714$], AST [median change, G_FDC 1.0 (–2.2, 11.2) vs. G_M 0.5 (–3.0, 2.7), $p=0.217$] or CPK [median change, G_FDC 3.5 (–11.7, 23.0) vs. G_M 12.5 (–10.7, 12.2), $p=0.447$].

DISCUSSION

The analysis of the results from this confirmatory clinical study on the efficacy and safety of the FDC of atorvastatin/fenofibrate (G_FDC) versus atorvastatin (G_M) provides solid scientific evidence of the advantages of using a combination therapy in T2DM. The reduction in TG (Δ of change) after 4 months for the atorvastatin/fenofibrate group was –144.3 mg/dL, while for the atorvastatin group it was –64.0 mg/dL ($p=0.006$), with a percentage change of –43.1 vs. –22.8 ($p=0.008$), respectively. This outcome was replicated in the predictive cardiovascular risk indices (Δ of change) between the atorvastatin/fenofibrate group of treatment and the atorvastatin group: in the TG/HDL index –3.9 ± 4.6 vs. –1.5 ± 2.9, ($p=0.015$), and in the TG/glucose index –0.7 ± 0.5 vs. –0.3 ± 0.4, ($p=0.003$). The use of the atorvastatin/fenofibrate combination demonstrated a favorable safety profile without any increase in adverse events.

As previously described, T2DM is a metabolic disorder that frequently predisposes individuals to cardiovascular diseases (CVD), with lipid abnormalities being a common condition [6]. According to Hirano's publication on the pathophysiology of dyslipidemia in patients with diabetes, also referred to as "diabetic dyslipidemia," it is associated with an atherogenic lipid profile (hypertriglyceridemia, normal or slightly elevated LDL-C but with an increase in small dense LDL, reduced HDL-C and elevated

Table 3 Predictive indices of cardiovascular risk by treatment group

Variable	Atorvastatin 20 mg/fenofibrate 160 mg					Atorvastatin 20 mg					p^+
	Basal	2 months	*p*	4 months	*p*	Basal	2 months	*p*	4 months	*p*	
Triglycerides/HDL index[a,b]	7.9 ± 5.0	4.1 ± 2.9	0.001	3.9 ± 2.0	0.001	6.3 ± 3.0	5.7 ± 7.1	0.603	4.8 ± 3.4	0.029	0.267
Δ change	–	−3.8 ± 4.9	0.001	−3.9 ± 4.6	0.001	–	−0.5 ± 6.8	0.603	−1.5 ± 2.9	0.029	0.015
< 3 points	2 of 34 (5.6)	13 of 34 (38.2)	0.001	11 of 30* (36.6)	0.004	1 of 36 (2.7)	12 of 36 (33.3)	0.001	11 of 32* (34.3)	0.004	0.463
Triglycerides/glucose index[a,c]	9.6 ± 0.5	9.0 ± 0.7	0.001	8.8 ± 0.6	0.001	9.3 ± 0.4	9.0 ± 0.6	0.003	9.1 ± 0.6	0.002	0.154
Δ change	–	−0.5 ± 0.6	0.001	−0.7 ± 0.5	0.001	–	−0.2 ± 0.4	0.001	−0.3 ± 0.4	0.002	0.003
< 8.5 points	0 of 34 (0)	6 of 34* (17.6)	0.005	9 of 30* (30.0)	0.003	0 of 36 (0)	3 of 36 (8.3)	0.083	5 of 32* (15.7)	0.025	0.080

HDL-C high-density lipoprotein cholesterol

[a]Values are presented as mean and standard deviation, and ANOVA, adjusted by Bonferroni for multiple comparisons

[b]Values are presented as frequency and percentage, McNemar, chi-squared test

[c]Values are presented as frequency and percentage, Cochran, chi-squared test

*Lipid profile data for four patients were not available at the 4-month visit for both the atorvastatin/fenofibrate and atorvastatin groups

$p < 0.05$ significant

Table 4 Adverse events classified by the organ-class system according to the treatment under study

Adverse events by SOC	Total 70 patients	Atorvastatin/fenofibrate *n* = 34 patients	Atorvastatin *n* = 36 patients
Vascular	1	1	
Ecchymosis	1	1	
Gastrointestinal	7	4	3
Dyspepsia	1	1	
Abdominal distension	1	1	
Abdominal pain	1	1	
Upper abdominal pain	1		1
Constipation	1	1	
Nausea	1		1
Vomiting	1		1
Nervous system	12	4	8
Headache	4		4
Dysesthesia	1	1	
Insomnia	1	1	
Dizziness	2	1	1
Myalgia	1		1
Paresthesia	3	1	2
General symptoms	1	1	
Fatigue	1	1	
Musculoskeletal and connective tissue	8	3	5
Muscle contracture	1		1
Back pain	3	1	2
Musculoskeletal chest pain	1		1
Spasms	1	1	
Myalgia	2	1	1
Total adverse events	29	13	16

Chi-squared, $p > 0.05$, in all comparisons

non-HDL cholesterol) that increases the risk of cardiovascular disease [21]. Moreover, this condition is associated with cardiovascular diseases such as stroke, acute myocardial infarction, coronary artery disease, and congestive heart failure, which are the leading causes of death in these patients [22].

In our study, as part of the inclusion criteria for patients, the presence of parameters including total cholesterol, LDL-C, non-HDL cholesterol, and TG above the normal range were included. These were measured at the end of the treatment to evaluate the efficacy of the FDC therapy in comparison with baseline measurements, as reported in several clinical studies. Accordingly, our results showed an overall improvement in the lipid profile of patients treated with the atorvastatin/fenofibrate combination throughout the follow-up, with reductions in parameters such as TG, LDL-C, total cholesterol, and non-HDL cholesterol. All final parameter results were compared with baseline measurements within the group and were found to be both clinically and statistically significant.

The findings in this study align with those reported in the literature. The use of the combination of both drugs has proven effective in improving the lipid profile in patients with T2DM and dyslipidemia. Additionally, the superiority of atorvastatin/fenofibrate FDC compared to monotherapy has been proposed [20, 23–25].

Lella et al. [20] conducted a prospective, open-label clinical trial in patients with T2DM and hyperlipidemia (total cholesterol > 200 mg/dL, TG > 150 mg/dL, LDL-C > 100 mg/dL, and HDL-C < 40 mg/dL). In this study, the atorvastatin 40 mg and fenofibrate 145 mg CDF was compared with atorvastatin 40 mg over 12 weeks in 60 patients, assessing its effects on lipid profiles. After 12 weeks, the reduction in total cholesterol, TG, and very low-density lipoprotein (VLDL) cholesterol was greater in the atorvastatin/fenofibrate group than in the atorvastatin-only group.

In another study conducted by Davidson et al. [25], a multicenter, double-blind, randomized, parallel-group phase IIa clinical trial was conducted in 220 patients with dyslipidemia (non-HDL cholesterol > 130 mg/dL and TG ≥ 150 but ≤ 500 mg/dL). The atorvastatin 40 mg and fenofibrate 100 mg FDC was evaluated against atorvastatin 40 mg or fenofibrate 145 mg for 12 weeks. The primary efficacy endpoints were the mean percentage changes from baseline to week 12 in non-HDL cholesterol, HDL, and TG, concluding that patients treated with the CDF showed improvements in HDL cholesterol and TG levels. As described above, the results are consistent with those obtained in our study, emphasizing that the evidence in the literature supports the value of the FDC atorvastatin/fenofibrate in improving the lipid profile not only of patients with T2DM and mixed dyslipidemia but also of those with isolated lipid abnormalities.

Additionally, it is important to mention that various clinical studies have reported that hypolipidemic therapy plays a key role in reducing mortality in these patients, where statins are the most commonly used drugs to lower LDL-C and cardiovascular risk. However, in diabetic dyslipidemia, residual risk is associated with elevated TG levels and low HDL-C levels, which is why additional hypolipidemic therapies, such as fibrates, are required for more significant cardiovascular risk reduction [26].

Based on the relevance of hypolipidemic therapy and the importance of using additional therapies, this study also evaluated the TG/glucose and TG/HDL indices, showing the advantage of FDC atorvastatin/fenofibrate at 2 and 4 months of follow-up. These reductions in the indices indicate an improvement in insulin resistance and, consequently, a potential decrease in cardiovascular risk [7, 27, 28].

Specifically, in the case of patients with T2DM, several investigations including the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) [24] study and the ACCORD (Action to Control Cardiovascular Risk in Diabetes) [23] study have evaluated the effect of therapy with fibrates, statins, or their combination on various biochemical markers and cardiovascular disease, demonstrating a substantial improvement in the lipid profile. In the long-term follow-up study ACCORDION, where patients from the ACCORD study were followed, a reduction in all-cause mortality was observed in the group treated with fenofibrate + statins [hazard ratio (HR): 0.68; 95% CI: 0.52–0.88], supporting the use of fibrates as complementary therapy to statins in reducing cardiovascular risk in patients with diabetes and dyslipidemia [29, 30].

Recent epidemiological studies have primarily highlighted the positive effects and clinical benefits of statin/fenofibrate therapy in patients with T2DM.

Hong et al. [31] conducted a nationwide propensity-score-matched cohort study investigating the effects of fenofibrate combined with statin therapy on all-cause mortality and atherosclerotic cardiovascular disease (ASCVD) in 110,723 patients with diabetes, triglyceride (TG) levels ≥ 150 mg/dL, and no prior ASCVD diagnosis. Patients using statins plus fenofibrate were matched 1:1 with those using statins alone. Over a mean follow-up of 4.03 years, the fenofibrate/statin group showed significantly lower risk of all-cause mortality (HR 0.71; 95% CI 0.68–0.74) and ASCVD events (HR 0.89; 95% CI 0.85–0.93), including myocardial infarction (HR 0.878; 95% CI 0.827–0.933) and stroke (HR 0.901; 95% CI 0.848–0.957), compared with the control group. These benefits were consistent in patients with TG levels between 150 and 199 mg/dL and particularly in those with elevated LDL-C.

Ku et al. [32] performed a nationwide population-based retrospective observational study to evaluate the preventive effects of fenofibrate on lower extremity amputation (LEA) and peripheral arterial disease (PAD) in patients with T2DM. Using data from the Korean National Health Insurance Service Database (2009–2012), 22,984 statin/fenofibrate users were matched 1:4 with 91,936 statin users. Over a median follow-up of 7.6 years, statin/fenofibrate use was associated with significantly lower risk of LEA and PAD (HR 0.81; 95% CI 0.70–0.94), LEA alone (HR 0.76; 95% CI 0.60–0.96), and PAD alone (HR 0.81; 95% CI 0.68–0.96). No significant differences were observed in safety outcomes, including acute kidney injury and rhabdomyolysis. The benefits remained consistent across age, gender, and lipid profiles.

Concerning the safety profile of the atorvastatin/fenofibrate combination, our study demonstrated no difference against atorvastatin monotherapy; most of the adverse events were mild and moderate, with no severe adverse events reported. This is consistent with the safety data reported in the aforementioned studies [20, 25, 33], confirming that the safety profile of the combination is favorable.

Furthermore, it is important to highlight that the treatment evaluated in this study is supported by previous publications in various guidelines and expert consensus on managing dyslipidemias. The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommend statins as the first-line treatment for lowering cholesterol and advocate for combination therapy with other agents, such as fibrates, particularly due to their triglyceride-lowering effects [11]. Similarly, the European Society of Cardiology (ESC) and the European Atherosclerosis Society's Guidelines for the management of dyslipidaemias: *Lipid Modification to Reduce Cardiovascular Risk* emphasize statin therapy and recommend adding another lipid-modifying agent, such as fibrates, for patients who are intolerant to statins or who fail to therapeutic goals with statin monotherapy, especially when dyslipidemia is characterized by elevated TG levels [9].

In addition to the widely studied efficacy of the combination therapy, the cost–benefit of these drugs in treating dyslipidemia and preventing vascular disease has also been evaluated. According to the AACE guidelines for managing dyslipidemia and preventing cardiovascular risk, [34] non-pharmacological interventions are the most cost-effective options for preventing cardiovascular disease. Unfortunately, in many cases, they fail, and pharmacological intervention is the most recommended option, especially for individuals with moderate to high cardiovascular risk. Among pharmacological interventions, statins have been shown to be cost-effective in preventing primary and secondary cardiovascular events in individuals with moderate to high risk, and fibrate therapy has also been reported as cost-effective as monotherapy and in combination therapy to reduce TG and increase HDL-C [34].

Finally, as discussed earlier, treatment adherence is crucial for achieving therapeutic goals. FDC combinations have the benefit of simplifying drug regimens and the advantages of its combined effects. The preference for these combinations over separate drugs is because FDC therapies with complementary mechanisms of action provide the opportunity to achieve better control with higher patient adherence and a positive safety profile [35]. The two compounds have different mechanisms of action, so the pharmacological effect is additive, which represents a benefit for these patients, where

therapeutic goals are often not reached with monotherapy, requiring combination therapy.

All of this demonstrates that the atorvastatin/fenofibrate combination is safe and effective for managing mixed dyslipidemia. This finding is also consistent with reports from various international guidelines and authors regarding the management of such patients. It is worth mentioning that this combination also has the potential to slow the progression of vascular disease, reduce the risk of complications, and offer cost savings compared to using the individual components separately. Ultimately, it may also help decrease polypharmacy.

Although the present study evaluates the efficacy and safety of atorvastatin/fenofibrate, it has certain limitations. One notable limitation is the lack of analysis of specific biomarkers for assessing cardiovascular risk (ApoB, remnant cholesterol, small, dense LDL particles), which could have provided deeper insights into the clinical benefits of the investigational products. Additionally, the small sample size limits the generalizability of the findings, preventing the results from being fully extrapolated to the broader population. Finally, to assess the long-term clinical benefits, it would be valuable to conduct a follow-up over time of patients undergoing the combination therapy.

CONCLUSIONS

The results of this confirmatory phase IIIb clinical trial on efficacy and safety demonstrate the therapeutic value of an FDC product of atorvastatin/fenofibrate (20/160 mg).

The efficacy variables evaluated were TG, LDL-C, total cholesterol, non-HDL cholesterol, atherogenic index, and TG/glucose index. A clinically significant improvement was observed in the group treated with the FDC of atorvastatin/fenofibrate throughout the follow-ups, which was superior to the group receiving atorvastatin monotherapy. Regarding safety, the treatment was well tolerated and demonstrated a favorable safety profile.

Therefore, it is concluded that the fixed-dose combination of atorvastatin/fenofibrate is safe and effective for the treatment of mixed dyslipidemia (hypertriglyceridemia and hypercholesterolemia) in adult patients with type 2 diabetes mellitus. It is also possible that this treatment is effective and safe in patients with mixed dyslipidemia without T2DM.

ACKNOWLEDGEMENTS

The authors acknowledge all patients who participated in this study, the support of Yulia Romero Antonio for the review process, and Laboratorios Silanes S.A. de C.V. for providing financial support.

Medical Writing, Editorial, and Other Assistance. The Research and Development team at Laboratorios Silanes provided medical writing and other assistance for the draft manuscript preparation and submission under the direction and guidance of the authors and was funded by Laboratorios Silanes S.A. de C.V.

Author Contributions. Jorge González Canudas assisted with manuscript review and final approval. José G. Sander Padilla, Laura A. Lugo Sánchez, and Kevin F. Rios Brito were involved in the conception and design of the study, acquisition, analysis, and interpretation of data, and in drafting and revising the article. María M. Arguedas Núñez and Diana Flores Huanosta made substantial contributions to the clinical execution of the study and data collection. Additionally, Francisco G. Padilla Padilla, Lina N. Ruiz Bernes, Luis M. Román Pintos, and Juan A. Peraza Zaldívar were authors and main investigators involved in the study. All authors take responsibility for the integrity of the work as a whole and have approved this version for publication.

Funding. This research and the journal's Rapid Service Fee were sponsored by Laboratorios Silanes S.A. de C.V., Mexico City.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author (email: jogonzalez@silanes.com.mx) on reasonable request. The data are available at ClinicalTrials.gov/study/NCT04882293?term=NCT04882293&rank=1.

Declarations

Conflict of Interest. Francisco G. Padilla-Padilla, Lina N. Ruiz-Bernes, Luis M. Román-Pintos, Juan A. Peraza-Zaldívar, José G. Sander-Padilla, Laura A. Lugo-Sánchez, Kevin F. Rios-Brito, María M. Arguedas-Núñez, Diana Flores-Huanosta, and Jorge González-Canudas, have nothing to disclose.

Ethical Approval. The study was developed following the legal provisions of the General Health Law of the United Mexican States and the Helsinki Declaration of 1964 and its later amendments. The study protocol, informed consent form (ICF), and any other relevant documents according to National Regulation were reviewed and approved by an independent ethics committee (IEC) (Investigación Biomédica para el Desarrollo de Fármacos, S.A. de C.V.), and by Mexican regulatory authorities (Federal Commission for the Protection against Sanitary Risks [COFEPRIS]), with authorization number COFEPRIS: 223300912X1745/2022 and registered in ClinicalTrials.gov No. NCT04882293.

REFERENCES

1. Du Z, Qin Y. Dyslipidemia and cardiovascular disease: current knowledge, existing challenges, and new opportunities for management strategies. J Clin Med. 2023;12(1):363. https://doi.org/10.3390/jcm12010363.

2. Hernandez-Alcaraz C, Aguilar-Salinas CA, Mendoza-Herrera K, et al. Dyslipidemia prevalence, awareness, treatment and control in Mexico: results of the Ensanut 2012. Salud Publica Mex. 2020;62(2):137–46 (**Prevalencia de dislipidemias, diagnóstico previo, tratamiento y control: resultados de la Ensanut 2012. 10.21149/10520**).

3. Tratamiento de dislipidemias en el adulto. Guía de Práctica Clínica: Evidencias y Recomendaciones. México 2022. (2022).

4. Diagnóstico y Tratamiento Farmacológico de la Diabetes Mellitus Tipo 2 en el Primer Nivel de Atención. pp 1–55 (2018).

5. Gakidou E, Mallinger L, Abbott-Klafter J, et al. Management of diabetes and associated cardiovascular risk factors in seven countries: a comparison of data from national health examination surveys. Bull World Health Organ. 2011;89(3):172–83. https://doi.org/10.2471/BLT.10.080820.

6. Kalra S, Raizada N. Dyslipidemia in diabetes. Indian Heart J. 2024;76(Suppl 1):S80–2. https://doi.org/10.1016/j.ihj.2023.11.002.

7. Zhao M, Xiao M, Tan Q, Lu F. Triglyceride glucose index as a predictor of mortality in middle-aged and elderly patients with type 2 diabetes in the US. Sci Rep. 2023;13(1):16478. https://doi.org/10.1038/s41598-023-43512-0.

8. Che B, Zhong C, Zhang R, et al. Triglyceride-glucose index and triglyceride to high-density lipoprotein cholesterol ratio as potential cardiovascular disease risk factors: an analysis of UK biobank data. Cardiovasc Diabetol. 2023;22(1):34. https://doi.org/10.1186/s12933-023-01762-2.

9. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88. https://doi.org/10.1093/eurheartj/ehz455.

10. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(9):2969–89. https://doi.org/10.1210/jc.2011-3213.

11. Handelsman Y, Jellinger PS, Guerin CK, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease Algorithm—2020 Executive Summary. Endocr Pract. 2020;26(10):1196–224. https://doi.org/10.4158/CS-2020-0490.

12. Zheng S, et al. Systematic review and meta-analysis of statins-fibrates therapy in diabetic dyslipidemia patients. World J Meta-Anal. 2014;2(4):194.

13. R R. Statins: Actions, side effects, and administration. UpToDate. 2024

14. Bakker-Arkema RG, Davidson MH, Goldstein RJ, et al. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. JAMA. 1996;275(2):128–33.

15. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366(9500):1849–61. https://doi.org/10.1016/S0140-6736(05)67667-2.

16. Geng Q, Ren J, Chen H, Lee C, Liang W. Adverse events following statin-fenofibrate therapy versus statin alone: a meta-analysis of randomized controlled trials. Clin Exp Pharmacol Physiol. 2013;40(3):219–26. https://doi.org/10.1111/1440-1681.12053.

17. Guo J, Meng F, Ma N, et al. Meta-analysis of safety of the coadministration of statin with fenofibrate in patients with combined hyperlipidemia. Am J Cardiol. 2012;110(9):1296–301. https://doi.org/10.1016/j.amjcard.2012.06.050.

18. Pappa E, Rizos CV, Filippatos TD, Elisaf MS. Emerging fixed-dose combination treatments for hyperlipidemia. J Cardiovasc Pharmacol Ther. 2019;24(4):315–22. https://doi.org/10.1177/1074248419838506.

19. Ferri N, Ruscica M, Santos RD, Corsini A. Fixed combination for the treatment of dyslipidaemia. Curr Atheroscler Rep. 2023;25(10):691–9. https://doi.org/10.1007/s11883-023-01142-x.

20. Lella M, Indira K. A comparative study of efficacy of atorvastatin alone and its combination with fenofibrate on lipid profile in type 2 diabetes mellitus patients with hyperlipidemia. J Adv Pharm Technol Res. 2013;4(3):166–70. https://doi.org/10.4103/2231-4040.116778.

21. Hirano T. Pathophysiology of diabetic dyslipidemia. J Atheroscler Thromb. 2018;25(9):771–82. https://doi.org/10.5551/jat.RV17023.

22. Al Quran TM, Bataineh ZA, Al-Mistarehi AH, et al. Prevalence and pattern of dyslipidemia and its associated factors among patients with type 2 diabetes mellitus in Jordan: a cross-sectional study. Int J Gen Med. 2022;15:7669–83. https://doi.org/10.2147/IJGM.S377463.

23. Group AS, Buse JB, Bigger JT, et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol. 2007;99(12A):21i–33i. https://doi.org/10.1016/j.amjcard.2007.03.003.

24. Scott R, Best J, Forder P, et al. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: baseline characteristics and short-term effects of fenofibrate [ISRCTN64783481]. Cardiovasc Diabetol. 2005;4:13. https://doi.org/10.1186/1475-2840-4-13.

25. Davidson MH, Rooney MW, Drucker J, et al. Efficacy and tolerability of atorvastatin/fenofibrate fixed-dose combination tablet compared with atorvastatin and fenofibrate monotherapies in patients with dyslipidemia: a 12-week, multicenter, double-blind, randomized, parallel-group study. Clin Ther. 2009;31(12):2824–38. https://doi.org/10.1016/j.clinthera.2009.12.007.

26. Warraich HJ, Rana JS. Dyslipidemia in diabetes mellitus and cardiovascular disease. Cardiovasc Endocrinol. 2017;6(1):27–32. https://doi.org/10.1097/XCE.0000000000000120.

27. Yu Y, Wang J, Ding L, et al. Sex differences in the nonlinear association of triglyceride glucose index with all-cause and cardiovascular mortality in the general population. Diabetol Metab Syndr. 2023;15(1):136. https://doi.org/10.1186/s13098-023-01117-7.

28. Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2019;39(2):e38–81. https://doi.org/10.1161/ATV.0000000000000073.

29. Zhu L, Hayen A, Bell KJL. Legacy effect of fibrate add-on therapy in diabetic patients with dyslipidemia: a secondary analysis of the ACCORDION study. Cardiovasc Diabetol. 2020;19(1):28. https://doi.org/10.1186/s12933-020-01002-x.

30. Banach M, Surma S, Reiner Z, et al. Personalized management of dyslipidemias in patients with diabetes-it is time for a new approach. Cardiovasc Diabetol. 2022;21(1):263. https://doi.org/10.1186/s12933-022-01684-5.

31. Hong S, Kim KS, Han K, Park CY. Fenofibrate's impact on cardiovascular risk in patients with diabetes: a nationwide propensity-score matched cohort study. Cardiovasc Diabetol. 2024;23(1):263. https://doi.org/10.1186/s12933-024-02353-5.

32. Ku EJ, Kim B, Han K, Lee SH, Kwon HS. Fenofibrate to prevent amputation and reduce vascular complications in patients with diabetes: FENO-PREVENT. Cardiovasc Diabetol. 2024;23(1):329. https://doi.org/10.1186/s12933-024-02422-9.

33. Athyros VG, Papageorgiou AA, Athyrou VV, Demitriadis DS, Kontopoulos AG. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. Diabetes Care. 2002;25(7):1198–202. https://doi.org/10.2337/diacare.25.7.1198.

34. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. Endocr Pract. 2017;23(Suppl 2):1–87. https://doi.org/10.4158/EP171764.APPGL.

35. Bangalore S, Gayathri K, Sanobar P, Franz M. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007;120(8):713–9. https://doi.org/10.1016/j.amjmed.2006.08.033.