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# Efficacy and Safety of a Fixed-Dose Combination of Atorvastatin and Fenofibrate versus Atorvastatin and Fenofibrate Monotherapies on Non-HDL Cholesterol in Mexican Adults with Mixed Dyslipidemia: A Randomized Clinical Trial

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## Abstract

# Background.

Atherosclerotic cardiovascular disease is the primary global cause of mortality, driven largely by dyslipidemia. Although statins are the standard of care, significant residual cardiovascular risk persists due to elevated triglycerides and non-high-density lipoprotein cholesterol. The combination of atorvastatin and fenofibrate effectively addresses mixed dyslipidemia without increasing the risk of myopathy; however, its efficacy regarding non-high-density lipoprotein cholesterol as a primary objective remains limited. Furthermore, despite the high prevalence of mixed dyslipidemia in Latin America, Hispanic populations are historically underrepresented in major lipid-lowering clinical trials. The primary objective of this study was to evaluate the efficacy and safety of a fixed-dose atorvastatin-fenofibrate combination in a Mexican population, specifically prioritizing non-high-density lipoprotein cholesterol reduction. **Methods**. This phase III, multicenter, randomized, double-blind trial included Mexican adults with non-high-density lipoprotein cholesterol levels above 130 mg/dL and triglycerides above 150 mg/dL. Participants were randomized to receive a daily fixed-dose combination of atorvastatin 20 mg plus fenofibrate 160 mg, atorvastatin 20 mg monotherapy, or fenofibrate 160 mg monotherapy for twelve weeks. The primary efficacy endpoint was the change from baseline in non-high-density lipoprotein cholesterol. Differences between treatment groups for continuous variables were assessed using ANOVA or Kruskal-Wallis test. Categorical variables were analyzed using the chi-squared test. A p-value of less than 0.05 was considered statistically significant. **Results.** A total of 348 patients were randomized. At week twelve, the fixed-dose combination group demonstrated significantly greater median and percentage reductions in non-high-density lipoprotein cholesterol (-78.0 mg/dL, -47.83%) compared to atorvastatin (-56.5 mg/dL, -33.37%) and fenofibrate (-33.0 mg/dL, -19.71%) ($p < 0.001$ for all comparisons). The combination therapy was also superior in achieving non-high density lipoprotein target of 85 mg/dL and low-density lipoprotein cholesterol target of 70 mg/dL. All treatments were well-tolerated, with no reported cases of myopathy or rhabdomyolysis, and no significant differences in creatine phosphokinase concentration across arms. **Conclusions.** The fixed-dose combination of atorvastatin and fenofibrate is significantly more effective than respective monotherapies for non-high-density lipoprotein cholesterol reduction in Mexican adults with mixed dyslipidemia, while maintaining a comparable safety profile. **Trial registration.** ISRCTN 14937154 (Registration date October 16th 2026).

## BACKGROUND

Atherosclerotic cardiovascular disease is the leading cause of death worldwide.[1] Dyslipidemia is a fundamental factor in the development of atherosclerotic disease.[2] In a dysfunctional endothelium, circulating low- and very-low-density lipoproteins (LDL and vLDL, respectively) infiltrate and accumulate in the subendothelium. After oxidation, an inflammatory response mediated by macrophages leads to the formation of foam cells and the development of atherosclerotic plaque. Over time, the erosion of an unstable atherosclerotic plaque triggers thrombosis, causing major cardiovascular events (MACE) such as myocardial infarction or stroke.[2] In 2019, elevated LDL cholesterol (LDL-C) was responsible for an

estimated 4.4 million deaths and 98.6 million disability-adjusted life years (DALYs) worldwide. The absolute number of deaths attributed to LDL-C increased 46.7% between 1990 and 2019, with the burden shifting toward countries with lower sociodemographic status.[3] A recent systematic review found that Middle East and Latin America have the highest prevalences worldwide.[4] In Mexico, according to the National Health and Nutrition Survey of 2023, the prevalence of hypercholesterolemia was 30.4%, with half of the population affected not receiving any treatment.[5] In the need of early treatment of dyslipidemia and subsequent prevention of MACE, leading scientific societies, such as the American Heart Association (AHA) and the European Society of Cardiology (ESC), developed comprehensive guidelines in which statins are the first-line pharmacological treatment, intensity of medication, and lipid target depending on the individual risk profile.[6, 7] However, although optimal control of LDL-C with statin therapy has proven to reduce MACE, there's a residual risk associated with hypertriglyceridemia and non-high-density cholesterol (non-HDL-C), which has driven the development of non-statin therapy such as fibrates and omega-3 fatty acids. Fibrates in combination with statins can reduce an additional 5–15% of LDL-C and 30–50% of hypertriglyceridemia, also increasing High-density Cholesterol levels (HDL-C)[8] The combination of a statin and a fibrate is therefore a logical therapeutic strategy in patients with mixed dyslipidemia. While initial concerns existed regarding an increased risk of myopathy with older statin-fibrate combinations, newer formulations such as fenofibrate are considered a safer option as it does not significantly inhibit the CYP3A4 metabolic pathway used by most statins, thereby limiting the potential for adverse drug interactions.[9] The use of a fixed-dose combination (FDC) therapy increases tolerance and adherence to treatment. Although the Atorvastatin-Fenofibrate FDC has demonstrated efficacy in reducing LDL-C and triglycerides without increasing the risk of myopathy [10], significant gaps in the evidence remain. Despite the high prevalence of mixed dyslipidemia in Latin America, Hispanic populations are consistently underrepresented in major lipid-lowering clinical trials. Furthermore, the effect of this combination on non-HDL-C, a robust predictor of cardiovascular risk, has not yet been established as a primary endpoint. This study addresses these limitations by evaluating the efficacy and safety of an Atorvastatin/Fenofibrate fixed-dose combination in a Mexican population, prioritizing non-HDL-C as its primary objective.

# METHODS

## Study Design

This is a phase III, multicenter, randomized, double-blinded, three-arm parallel-group clinical trial conducted at four centers in Mexico between October 2016 and January 2019. The study protocol and informed consent forms were approved by the corresponding local research and ethics committees, the protocol was registered in the National Registry of Clinical Trials of Mexico (RNEC) with the following protocol number: EC-1516-2016, and authorized by the Mexican Regulatory authority, COFEPRIS. The trial adheres to CONSORT, and was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines.

## Participants

Eligible participants were men and women aged 18 years or older with a diagnosis of uncontrolled mixed dyslipidemia, defined as a non-HDL-C level > 130 mg/dL with a triglyceride level ≥ 150 mg/dL and ≤ 500 mg/dL. Patients receiving prior lipid-lowering therapy were required to undergo a 2-week washout period. All participants provided written informed consent prior to any study-related procedures being performed.

Key exclusion criteria included hypertriglyceridemia > 500 mg/dL, documented prior diagnosis of familial combined hyperlipidemia or dysbetalipoproteinemia- or a strong suggestive family history-, uncontrolled diabetes (HbA1c > 8.0%), significant renal or hepatic impairment, and known risk factors for myopathy.

## Randomization and Interventions

Following a screening period, eligible participants were randomly assigned in a 1:1:1 ratio to one of three treatment groups for 12 weeks: Group 1 received a fixed-dose combination of atorvastatin 20 mg plus fenofibrate 160 mg once daily; Group 2 received Atorvastatin 20 mg monotherapy once daily; Group 3 received Fenofibrate 160 mg monotherapy once daily. Randomization was performed using balanced blocks of six. To maintain blinding, all study medications were manufactured to have an identical appearance and were packaged in identically labeled containers. The investigational medications were manufactured by Laboratorios Senosiain, in compliance with Good Manufacturing Practices (GMP) and all quality requirements for clinical research.

## Outcomes and Assessments

The primary efficacy endpoint was the change from baseline in non-HDL-C serum concentration after 12 weeks of treatment.

Secondary efficacy endpoints included the change from baseline in other lipid parameters (Total Cholesterol [TC], LDL-C -estimated using the Friedewald formula, HDL-C, VLDL-C, TG), high-sensitivity C-reactive protein (hs-CRP), apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB). The percentage of patients achieving LDL-C goals of ≤ 100 mg/dL and ≤ 70 mg/dL was also assessed.

Safety was evaluated through the monitoring of adverse events (AEs), serious adverse events (SAEs), vital signs, and clinical laboratory tests, including creatine phosphokinase (CPK), liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), and serum creatinine at baseline and at the end of treatment.

# Statistical Analysis

The sample size was calculated to detect a minimum difference of 11.4 mg/dL in non-HDL-C between the combination and monotherapy groups, with 90% power and a two-sided significance level of 0.05. This resulted in a sample of 330 patients (110 per group).

Efficacy and safety analyses were performed on the full analysis set (FAS), which included all randomized patients who completed the 12-week follow-up with evaluable data. Differences between treatment groups for continuous variables were assessed using a one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, as appropriate. A Bonferroni post-hoc test was used for pairwise comparisons. Categorical variables were analyzed using the chi-squared test. A p-value < 0.05 was considered statistically significant. Numerical parametric variables are expressed as Mean ± Standard Deviation, non-parametric variables are expressed as Median (IQR), and categorical variables as % (N).

# RESULTS

A total of 595 patients were screened, and 348 were randomized to a treatment group: 116 to the combination group, 115 to the atorvastatin group, and 117 to the fenofibrate group. The FAS consisted of 241 patients who completed the study: 85 in the combination group, 68 in the atorvastatin group, and 88 in the fenofibrate group. The primary reasons for discontinuation included low adherence and abnormal laboratory values, such as three-times over the superior normality limit of AST, ALT and CPK (Fig. 1).

The baseline clinical characteristics are presented in Table 1. All characteristics were similar across treatment groups. The mean age of the study population was approximately 52 years, and the majority of participants were female (63%). The mean body mass index (BMI) was approximately 30.6 kg/m², and co-morbidities such as diabetes mellitus (45%) and hypertension (63%) were prevalent. Baseline lipid profiles were similar among groups, with a mean non-HDL-C of approximately 174 mg/dL. 18 patients had a baseline triglyceride plasma concentration > 400 mg/dL.

Table 1

**Baseline characteristics by treatment group** Numerical parametric variables are expressed as Mean ± Standard Deviation, non-parametric variables are expressed as Median [IQR], and categorical variables as % (N). Differences between treatment groups for continuous variables were assessed using a one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, Categorical variables were analyzed using the chi-squared test. A $p < 0.05$ is considered statistically significant.

| Variable | Ator + Feno (N = 85) | Atorvastatin (N = 68) | Group 3 Fenofibrate (N = 88) | P-value |
|---|---|---|---|---|
| **Age in years (Mean ± SD)** | 53.5 ± 12.1 | 49.4 ± 10.9 | 53.1 ± 10.8 | 0.291 |
| **Female Sex, % (N)** | 65.9 (56) | 60.3 (48) | 63.6 (56) | 0.880 |
| **Diabetes, % (N)** | 51.8 (44) | 38.2 (26) | 44.3 (39) | 0.242 |
| **Hypertension, % (N)** | 69.4 (59) | 60.3 (41) | 60.2 (53) | 0.370 |
| **Smoking (past or current) % (N)** | 0 (0) | 0 (0) | 0 (0) | NA |
| **Chronic Kidney Disease, % (N)** | 5.9 (5) | 4.4 (3) | 9.1 (8) | 0.478 |
| **BMI in kg/m² (Mean ± SD)** | 30.9 ± 5.0 | 30.9 ± 5.0 | 30.0 ± 5.1 | 0.265 |
| **BMI category %(N)** | | | | 0.775 |
| **Normal (18-24.9 kg/$m^2$ )** | 7.1 (6) | 8.8 (6) | 12.5 (11) | |
| **Overweight (25-29.9 kg/$m^2$ )** | 42.4 (36) | 41.2 (28) | 45.5 (40) | |
| **Obesity I (30-34.9 kg/$m^2$ )** | 29.4 (25) | 33.8 (23) | 30.7 (27) | |
| **Obesity II (35-39.9 kg/$m^2$ )** | 15.3 (13) | 11.8 (8) | 6.8 (6) | |
| **Obesity III (> 40 kg/$m^2$ )** | 5.9 (5) | 4.4 (3) | 4.5 (4) | |
| **Total Cholesterol (mg/dL) (Mean ± SD)** | 217.6 ± 30.5 | 211.9 ± 28.7 | 218.0 ± 34.2 | 0.928 |
| **Non-HDL Cholesterol (mg/dL) (Mean ± SD)** | 175.7 ± 28.4 | 171.0 ± 25.9 | 174.5 ± 31.5 | 0.807 |

| Variable | Ator + Feno (N = 85) | Atorvastatin (N = 68) | Group 3 Fenofibrate (N = 88) | P-value |
|---|---|---|---|---|
| **Triglycerides (mg/dL) (Mean ± SD)** | 250.5 ± 78.4 | 235.0 ± 69.2 | 252.8 ± 84.8 | 0.841 |
| **HDL Cholesterol (mg/dL) (Mean ± SD)** | 42.0 ± 8.8 | 41.6 ± 10.9 | 43.4 ± 9.5 | 0.313 |
| **LDL Cholesterol (mg/dL) (Mean ± SD)** | 124.5 ± 31.7 | 124.2 ± 27.2 | 124.6 ± 33.0 | 0.983 |
| **VLDL Cholesterol (mg/dL) (Mean ± SD)** | 49.1 ± 15.9 | 45.9 ± 13.9 | 49.9 ± 16.8 | 0.723 |
| **Apolipoprotein A1 (mg/dL) (Mean ± SD)** | 139.6 ± 22.5 | 136.6 ± 21.3 | 140.2 ± 22.7 | 0.850 |
| **Apolipoprotein B100 (mg/dL) (Mean ± SD)** | 129.1 ± 24.3 | 128.9 ± 26.6 | 129.1 ± 23.4 | 0.988 |
| **hs-CRP (mg/L) (Median [IQR])** | 4.4 [2.3–6.4] | 4.1 [1.7–6.8] | 3.6 [1.9–7.0] | 0.843 |
| **CPK (U/L) (Median [IQR])** | 87 [62–123] | 101 [68.5–124.2] | 88.5 [63–127] | 0.527 |
| **AST (mg/dL) (Median [IQR])** | 24 [17–39] | 24.5 [18–37] | 21 [16–33] | 0.279 |
| **ALT (mg/dL) (Median [IQR])** | 21 [17–28.5] | 22 [17–26] | 22 [18–27] | 0.996 |
| **Alkaline Phosphatase (U/L) (Mean ± SD)** | 78.0 ± 24.4 | 80.0 ± 25.2 | 85.6 ± 33.0 | 0.074 |
| **Fasting Glucose (mg/dL) (Mean ± SD)** | 128.4 ± 53.5 | 112.7 ± 41.1 | 118.0 ± 45.2 | 0.156 |
| **Serum Creatinine (mg/dL) (Mean ± SD)** | 0.7 ± 0.2 | 0.7 ± 0.2 | 0.8 ± 0.2 | 0.361 |
| **eGFR (CKD-EPI) (mL/min/1.73m²) (Mean ± SD)** | 98.2 ± 24.6 | 102.1 ± 27.0 | 96.7 ± 23.8 | 0.681 |

# Efficacy Outcomes

**Primary Endpoint.** At week 12, FDC therapy demonstrated superior efficacy in lowering non-HDL-C levels compared to both monotherapies. The median reduction from baseline in non-HDL-C was − 78.0 mg/dL for the FDC group, significantly outperforming atorvastatin (-56.5 mg/dL) and fenofibrate (-33.0 mg/dL) ($p < 0.001$ for all comparisons) as monotherapy. This corresponded to a median percentage reduction of -47.83% for the FDC, compared to -33.37% and − 19.71% for the atorvastatin and fenofibrate groups,

respectively (p < 0.001). Notably, atorvastatin monotherapy achieved a significantly greater reduction than fenofibrate (p = 0.02 for absolute median reduction; p < 0.001 for percentage change) (Fig. 2 **and** Table 4).

Table 4
Percentage of change in LDL and Non-HDL Cholesterol

| **Percentage of change** | **Ator+Feno (N = 85)** | **Atorvastatin (N = 68)** | **Fenofibrate (N = 88)** | **Global P-value** | **Inter-group P-values** |
|---|---|---|---|---|---|
| **Non HDL Cholesterol % (IQR 25–75)** | -47.83 (-54.80 – -36.99) | -33.37 (-42.73 – -19.43) | -19.71 (-32.78 – -5.96) | < 0.001 | Group 1 vs 2: < 0.001 Group 1 vs 3: < 0.001 Group 2 vs 3: < 0.001 |
| **LDL Cholesterol % (IQR 25–75)** | -44.60 (-54.47 – -32.10) | -35.50 (-48.96 – -28.34) | -11.55 (-28.68–4.66) | < 0.001 | Group 1 vs 2: < 0.001 Group 1 vs 3: < 0.001 Group 2 vs 3: < 0.001 |

The difference in percentage between groups was analyzed with Kruskal-Wallis. A DSCF post-hoc test was used for pairwise comparisons.

**Secondary Endpoints** FDC therapy yielded the most pronounced median reduction in triglycerides (TG) (-113.0 mg/dL), which was significantly greater than that observed with atorvastatin (-44.5 mg/dL; p < 0.001) and numerically higher, though not statistically different from, fenofibrate monotherapy (-82.0 mg/dL; p = 0.08). Regarding LDL-C, the FDC achieved the largest median absolute (-56.0 mg/dL) and percentage (-44.60%) reductions. While the FDC's impact on LDL-C was significantly superior to fenofibrate (median − 15.50 mg/dL; -11.55%; p < 0.001), it did not differ statistically from atorvastatin in terms of absolute median reduction (-46.8 mg/dL; p = 0.09). However, the percentage of LDL-C reduction

remained significantly greater in the FDC group compared to the atorvastatin group (-44.60% vs. -35.50%; $p < 0.001$) **(**Table 4**).**

The combination therapy was also superior to both monotherapies in reducing TC, ApoB, and hs-CRP (all $p < 0.05$). A significantly greater proportion of patients in the FDC group attained predefined therapeutic targets for both non-HDL-C and LDL-C compared to those receiving monotherapy **(**Tables 2 and 3**).** Regarding non-HDL-C, the FDC group consistently outperformed atorvastatin and fenofibrate across all thresholds: ≤130 mg/dL (33% vs. 18% and 16%, respectively; $p < 0.001$) and ≤ 100 mg/dL (20% vs. 11% and 5%, respectively; $p < 0.001$). For the most stringent non-HDL-C target of ≤ 85 mg/dL, the FDC group demonstrated a superior attainment rate (13.0%) compared to atorvastatin (5.0%) and fenofibrate (2.0%) ($p < 0.001$), whereas no significant difference was observed between the two monotherapy arms. Similarly, LDL-C goal attainment was markedly higher with FDC therapy. For the ≤ 70 mg/dL target, 54.1% of patients in the combination group reached the goal, significantly surpassing atorvastatin (41.8%) and fenofibrate (8.0%) ($p < 0.001$ for all inter-group comparisons). Furthermore, the vast majority of patients in the FDC group (94.1%) achieved the LDL-C goal of ≤ 100 mg/dL, compared to 75.0% in the atorvastatin group and 42.0% in the fenofibrate group ($p < 0.009$ for all comparisons).

Table 2
Percentage of patients achieving LDL cholesterol goals

| **LDL Cholesterol Target** | **Ator + Feno (N = 85)** | **Atorvastatin (N = 68)** | **Fenofibrate (N = 88)** | **Global P-value** | **Inter-group P-values** |
|---|---|---|---|---|---|
| **≤ 100 mg/dL, % (N)** | 94.1% (80) | 75.0% (51) | 42.0% (37) | < 0.001 | Group 1 vs 2: 0.009<br>Group 1 vs 3: < 0.001<br>Group 2 vs 3: < 0.001 |
| **≤ 70 mg/dL % (N)** | 54.1% (46) | 41.8% (29) | 8.0% (7) | < 0.001 | Group 1 vs 2: < 0.001<br>Group 1 vs 3: < 0.001<br>Group 2 vs 3: < 0.001 |

Difference in proportions between groups was analyzed with chi-squared test. A Bonferroni post-hoc test was used for pairwise comparisons.

Table 3

**Percentage of patients achieving Non-HDL cholesterol targets** The difference in proportions between groups was analyzed with chi-squared test. A Bonferroni post-hoc test was used for pairwise comparisons.

| Non-HDL Cholesterol Target | Ator + Feno (N = 85) | Atorvastatin (N = 68) | Fenofibrate (N = 88) | Global P-value | Inter-group P-values |
|---|---|---|---|---|---|
| **≤ 130 mg/dL %(N)** | 33% (79) | 18% (44) | 16% (38) | < 0.001 | Group 1 vs 2: < 0.001 Group 1 vs 3: < 0.001 Group 2 vs 3: < 0.008 |
| **≤ 100 mg/dL % (N)** | 20% (49) | 11% (26) | 5% (11) | < 0.001 | Group 1 vs 2: 0.017 Group 1 vs 3: < 0.001 Group 2 vs 3: < 0.001 |
| **≤ 85 mg/dL %(N)** | 13.0% (32) | 5.0% (11) | 2.0% (6) | < 0.001 | Group 1 vs 2: 0.003 Group 1 vs 3: < 0.001 Group 2 vs 3: < 0.063 |

## Safety and Tolerability

All treatments were favorably tolerated. The overall frequency of non-serious AEs was similar across the groups (Table 5**).** The most common AEs were peptic acid disorders, headache, and urinary tract infections. Two SAEs were reported (one cholecystitis in the combination group, one complete atrioventricular block in the atorvastatin group), neither of which was considered related to the study medication. Importantly, there were no statistically significant differences in median CPK levels among the three groups at the end of the study, and no cases of myopathy or rhabdomyolysis were reported.

Table 5
Frequency of non-serious adverse events by treatment group

| **Adverse Event** | **Ator+Feno (N = 85)** | **Atorvastatin (N = 68)** | **Fenofibrate (N = 88)** | **Total** |
|---|---|---|---|---|
| **Total Events** | 32 | 36 | 30 | 98 |
| Peptic Acid Disorders | 7 | 5 | 5 | 17 |
| Headache | 4 | 8 | 3 | 15 |
| Urinary Tract Infection | 4 | 5 | 6 | 15 |
| Anemia | 4 | 2 | 1 | 7 |
| Dizziness | 1 | 3 | 3 | 7 |
| Abdominal Distension | 1 | 4 | 1 | 6 |
| Myalgia | 2 | 1 | 3 | 6 |
| Gastroenteritis | 1 | 2 | 2 | 5 |
| Respiratory Tract Infection | 2 | 3 | 0 | 5 |
| Nausea | 1 | 1 | 0 | 2 |
| Paresthesia | 0 | 1 | 1 | 2 |
| Back Muscle Spasm | 0 | 0 | 1 | 1 |
| Toothache | 1 | 0 | 0 | 1 |
| Epistaxis | 0 | 1 | 0 | 1 |
| Ecchymosis | 0 | 1 | 0 | 1 |
| Right Ankle Sprain | 0 | 0 | 1 | 1 |
| Gout Exacerbation | 0 | 1 | 0 | 1 |
| Flatulence | 1 | 0 | 0 | 1 |
| Medication Intolerance | 0 | 0 | 1 | 1 |
| Carbohydrate Intolerance | 0 | 1 | 0 | 1 |

# DISCUSSION

The present study demonstrates that a fixed-dose combination (FDC) of atorvastatin and fenofibrate effectively optimizes the lipid profile in Mexican patients with mixed dyslipidemia. The significant reductions observed in non-HDL-C and triglycerides (TG) outperformed both monotherapies without compromising the safety profile or increasing the incidence of adverse events. This comprehensive metabolic improvement is particularly relevant given the high prevalence of atherogenic dyslipidemia in the Hispanic population.

A key finding of this trial is the synergistic impact of FDC therapy on LDL-C and non-HDL-C levels. Interestingly, while the FDC demonstrated a significantly greater percentage reduction in LDL-C compared to atorvastatin monotherapy (-44.60% vs. -35.5%; $p < 0.001$), the absolute median reduction did not reach statistical significance ($p = 0.09$). This discrepancy warrants careful interpretation; the statistical superiority of the percentage change suggests that the FDC provides a more consistent and robust response across varying baseline lipid levels, effectively "normalizing" the therapeutic effect. Furthermore, the FDC's superior performance in reducing non-HDL-C—a parameter that encompasses all atherogenic apolipoprotein B-containing lipoproteins—highlights the synergistic potential of this dual therapy. While atorvastatin remains the cornerstone for LDL-C lowering, the co-administration of fenofibrate addresses the "residual lipid risk" by further attenuating triglyceride-rich lipoproteins and non-HDL-C.

The marked reduction in non-HDL-C observed in our study is of particular clinical importance. Non-HDL-C is now established as a more robust predictor of cardiovascular (CV) risk than LDL-C alone.[11] Evidence suggests that this biomarker is useful in both primary and secondary prevention: In patients without a history of cardiovascular disease (CVD), baseline non-HDL-C levels correlate strongly with future CV risk.[12] Moreover, genetic risk scores for non-HDL-C show a stronger association with coronary artery disease than those for LDL-C [13]. In the context of secondary prevention, non-HDL-C and ApoB concentrations correlate better with myocardial infarction risk than LDL-C in patients already receiving statins. Notably, a prospective study of over 13,000 participants showed that discordant high non-HDL-C (with low LDL-C) was associated with a 1.78-fold increased risk (95% CI 1.35–2.34), whereas discordant high LDL-C did not confer a significant increase in risk.[14] Additionally, meta-analyses have shown that each 1 mmol/L (38.7 mg/dL) reduction in non-HDL-C is associated with an approximately 15% decrease in MACE risk [15]. Our results demonstrate that FDC therapy is a potent strategy for achieving these evidence-based goals by simultaneously targeting multiple risk factors—lowering LDL-C and TG while addressing residual lipid risk—which often remains unaddressed with monotherapy alone.[13] Major international guidelines have established clear non-HDL-C therapeutic targets, ranging from < 130 mg/dL in the AHA/ACC guidelines[16] to more stringent recommendations of < 85 mg/dL by the ESC/EAS[17] or a > 40% reduction as suggested by NICE [18]. The present trial highlights a significant clinical advantage in this context: after 12 weeks, the FDC was superior to atorvastatin monotherapy in achieving stringent targets (< 85 mg/dL for non-HDL-C and < 70 mg/dL for LDL-C). Attaining such

guideline-directed goals often requires high-intensity statin therapy, which may present tolerability challenges or prove insufficient for many patients. [19]

This trial has several strengths, including its double-blind, active-controlled design, which minimizes bias and allows for a direct comparison against both monotherapy components. Furthermore, the use of non-HDL-C as a primary endpoint, supported by a comprehensive panel of secondary markers (ApoB and hs-CRP), provides a broader view of the metabolic effects of the combination treatment. Crucially, this study addresses a significant gap in clinical evidence by focusing on a Mexican population, as Hispanic groups have been historically underrepresented in major lipid trials. [20]

Nonetheless, certain limitations must be acknowledged. First, the two-week washout period for prior lipid-lowering therapy may have influenced the baseline measurements and the subsequent assessment of efficacy. Second, while the 12-week intervention period is sufficient to identify significant changes in the lipid profile, it does not provide data on long-term safety or definitive cardiovascular outcomes. Third, since the primary and secondary endpoints were evaluated using a Full Analysis Set (FAS), which included only those participants who completed the 12-week follow-up with evaluable data, the exclusion of participants who discontinued the trial, may introduce a survivor bias. Consequently, the observed treatment effects should be interpreted with caution, as they primarily reflect the therapeutic response in patients who successfully tolerated and adhered to the 12-week intervention. Future research should involve larger, long-term prospective trials to determine if the superior reduction in non-HDL-C observed here translates into a sustained decrease in major adverse cardiovascular events within this specific population.

# CONCLUSIONS

The combination of atorvastatin and fenofibrate in a fixed-dose formulation effectively reduces non-HDL-C and TG in Mexican patients with mixed dyslipidemia. The favorable changes in the lipid profile are significantly greater than those observed with either monotherapy, while maintaining a comparable safety profile without increasing the incidence of adverse events. These findings support the use of this fixed-dose combination as an effective strategy to reach stringent therapeutic targets.

# Abbreviations

- **AEs:** Adverse events
- **AHA:** American Heart Association
- **ALT:** Alanine aminotransferase
- **ANOVA:** Analysis of variance
- **ApoA1:** Apolipoprotein A1
- **ApoB:** Apolipoprotein **B**
- **AST:** Aspartate aminotransferase

- **BMI:** Body mass index
- **COFEPRIS:** Comisión Federal para la Protección contra Riesgos Sanitarios
- **CPK:** Creatine phosphokinase
- **CVD:** Cardiovascular disease
- **DALYs:** Disability-adjusted life years
- **EAS:** European Atherosclerosis Society
- **ESC:** European Society of Cardiology
- **FAS:** Full analysis set
- **GMP:** Good Manufacturing Practices
- **HDL-C:** High-density lipoprotein cholesterol
- **hs-CRP:** High-sensitivity C-reactive protein
- **IQR:** Interquartile range
- **LDL-C:** Low-density lipoprotein cholesterol
- **MACE:** Major adverse cardiovascular events
- **SAEs:** Serious adverse events
- **TC:** Total cholesterol
- **TG:** Triglycerides
- **VLDL-C:** Very-low-density lipoprotein colesterol

# Declarations

### Ethics approval and consent to participate

The study protocol and informed consent forms were reviewed and approved by the independent Research Ethics Committee of Winsett Rethman S.A. de C.V. (Comité de Ética en Investigación Winsett Rethman S.A. de C.V.; approval reference number: EC-1516-2016) and authorized by the Mexican Federal Commission for the Protection against Sanitary Risks (COFEPRIS). The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent prior to the initiation of any study-related procedures.

### Consent for publication

Not applicable.

### Availability of data and materials

Protocol design, statistical analysis plan, and datasets used are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Author's contributions**

VOR and CVCG conceptualized, designed and acquired the data of this protocol, VAVP and GSMA analized, interpreted and drafted the manuscript. All authors extensively revised and approved the submitted version.

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Not applicable

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# Figures

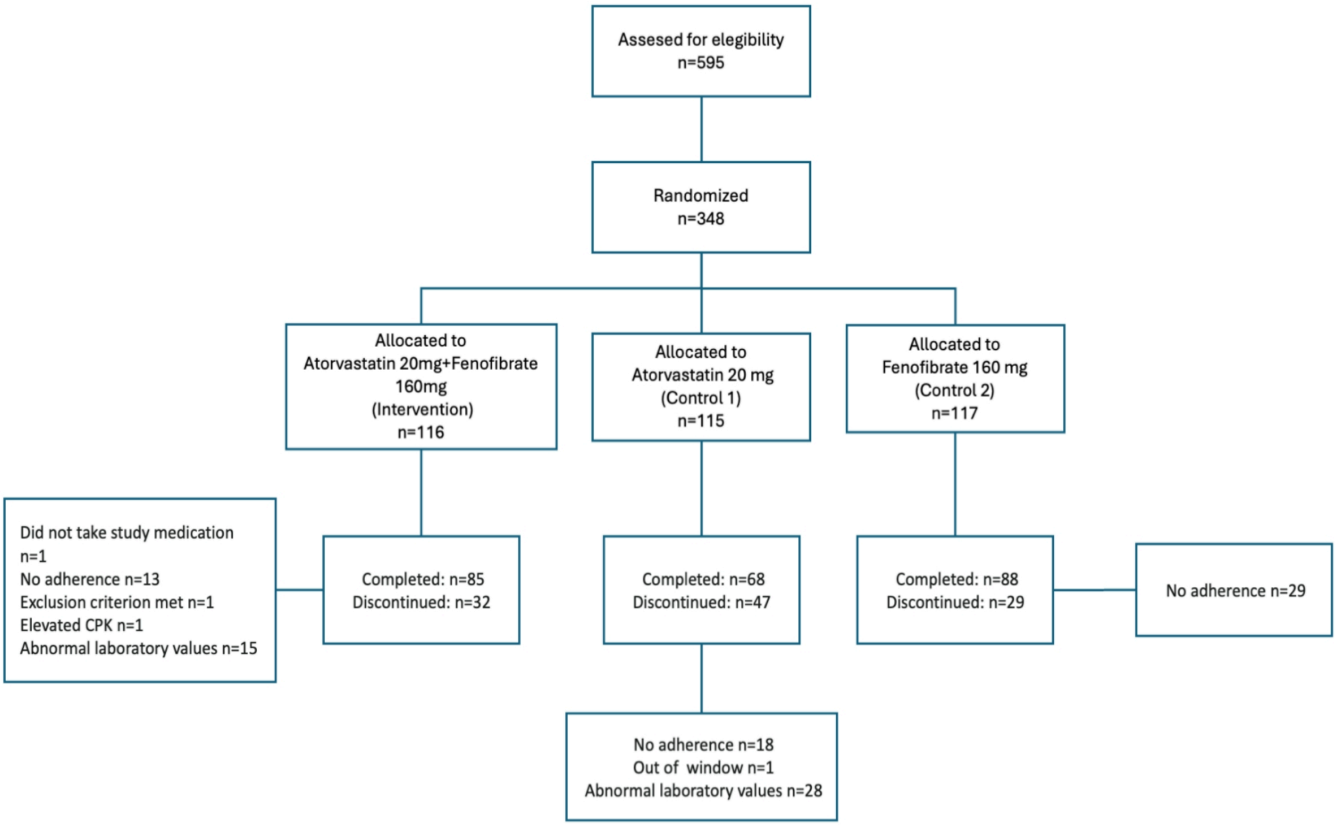


**Figure 1**

**Flowchart of patients**

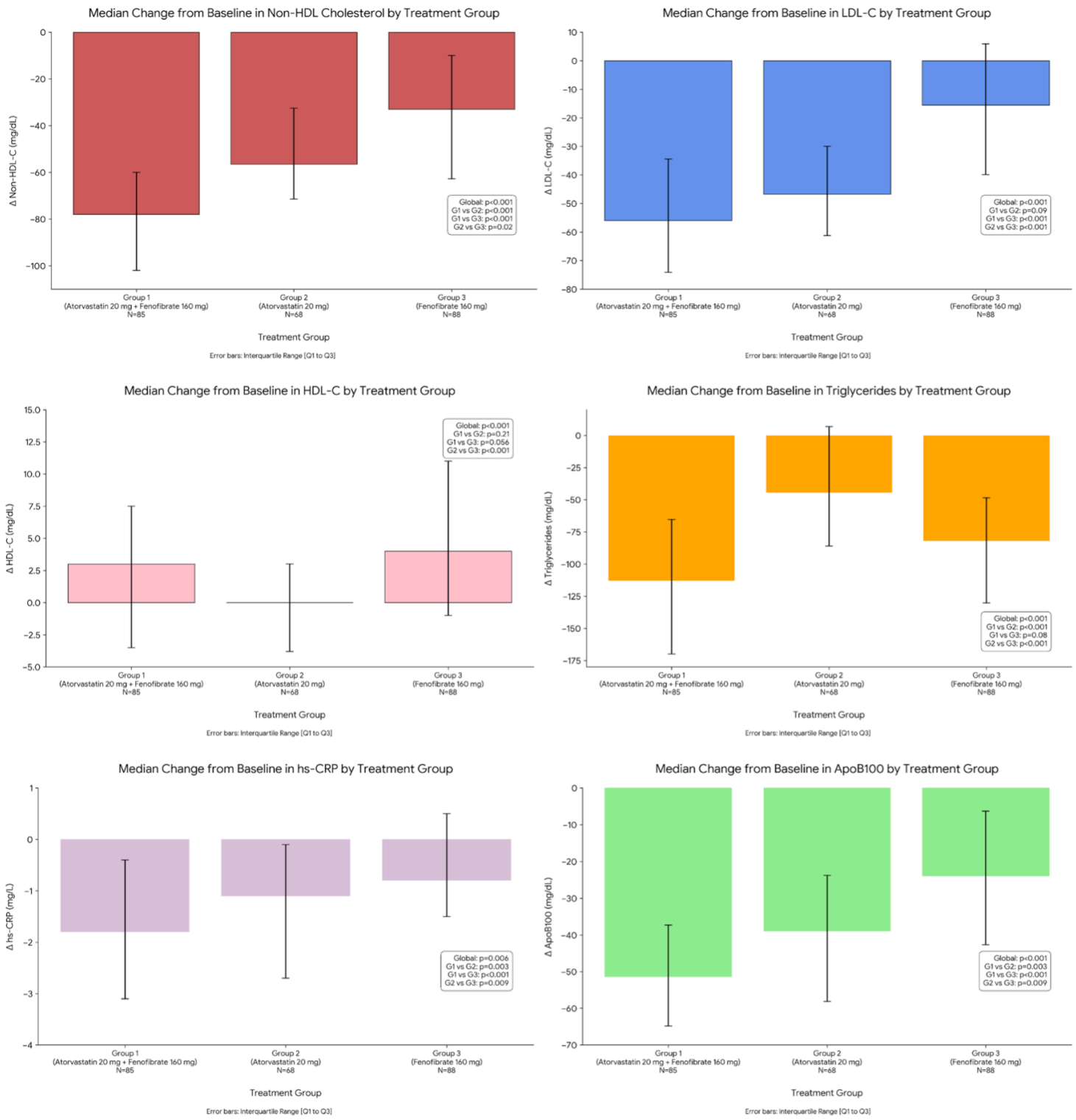


**Figure 2**

**Changes in primary and secondary outcomes**

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