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Real-World Effectiveness of Therapy With Rosuvastatin Combined With Fenofibric Acid in a Sample of Colombian Patients With Mixed Dyslipidemia

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Abstract

Background: Ischemic heart disease is the leading cause of death in the world and is associated with dyslipidemia, high blood pressure, diabetes mellitus, and other factors. **Objective:** To determine the clinical effectiveness on the lipid profile of the rosuvastatin + fenofibric acid combination in Colombian patients with high cardiovascular risk and mixed dyslipidemia. **Methods:** Longitudinal observational study in a random sample of patients with a diagnosis of mixed dyslipidemia and moderate, high, or very high cardiovascular risk who were treated with rosuvastatin + fenofibric acid. Anthropometric, clinical, laboratory, comorbidity, and pharmacological variables were identified. Effectiveness on the lipid profile was determined. **Results:** A total of 386 patients were analyzed. They had a mean age of 60.8 ± 11.4 years, 53.1% were female, and 75.6% had high/very high cardiovascular risk. The initial evaluation showed a mean LDL cholesterol of 138.4 ± 67.1 mg/dL and triglycerides of 679.7 ± 573.6 mg/dL. At the end of follow-up, mean LDL cholesterol was 87.5 ± 41.2 mg/dL (reduced by 43.3%; $P < .001$), and triglycerides were 243.5 ± 170.5 mg/dL (reduced by 64.2%; $P < .001$). Only 35.4% (n = 73) of patients with very high risk reached the goal of metabolic control, compared to 61.6% (n = 53) with high risk and 55.4% (n = 46) with moderate risk. Belonging to the very high-risk group was associated with a lower probability of achieving the control goal (OR: 0.32; 95%CI: 0.192-0.539). **Conclusion:** The combination of rosuvastatin + fenofibric acid is an effective option in patients with mixed dyslipidemia and high cardiovascular risk, providing a therapeutic alternative for those conditions that require it.

Keywords

clinical effectiveness, dyslipidemias, fenofibrate, pharmacoepidemiology, rosuvastatin

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Introduction

Noncommunicable chronic diseases are currently considered an epidemic that affects the majority of the adult population.[1-3] Among them, coronary artery disease and other cardiac conditions are the leading causes of mortality in developed and developing countries and are usually secondary to pathologies such as high blood pressure, obesity, dyslipidemia, and diabetes mellitus, all part of metabolic syndrome or associated with habits such as smoking.[4]

Dyslipidemia, especially hypercholesterolemia, increases cardiovascular risk and is associated with ischemic heart disease, the leading cause of death worldwide. Considering that dyslipidemia is one of the main public health problems, it has become a priority for health systems.[4-9] Although some studies have found that the effectiveness of lipid-lowering therapy is adequate, a significant proportion of patients do not meet the lipid profile goals proposed by clinical practice guidelines. Additionally, the most frequent dyslipidemias are mixed, in which the components of hypertriglyceridemia and low HDL cholesterol (HDL-C) are key reasons for seeking combined therapy with fibrates and statins.[9,10]

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Some meta-analyses have shown a modest impact of fibrates on cardiovascular disease, as well as the safety profile of the combination of rosuvastatin + fenofibric acid, which does not increase the incidence of muscle-related adverse events, rhabdomyolysis, or liver complications, making it a safe therapeutic option for the management of mixed dyslipidemias.[11-13]

The Colombian Health System offers universal coverage to the population through affiliation with 1 of 2 regimes, the contributory regime paid by the employer and the state-subsidized regime. Both regimes provide a benefit plan covering many of the medications used for treating dyslipidemia. Given that there is limited information on combined therapies with statins and fibrates, we sought to determine the effect on the lipid profile and the safety of rosuvastatin combined with fenofibric acid in Colombian patients from the contributory regime with high cardiovascular risk and mixed dyslipidemia between 2016 and 2018.

Methods

This retrospective, longitudinal observational study included patients diagnosed with mixed dyslipidemia and moderate, high, or very high cardiovascular risk who were over 18 years of age, of either sex, and under treatment with the rosuvastatin + fenofibric acid combination covered by 1 healthcare insurer, which includes more than 2 million people affiliated with the contributory regime of the Colombian Health System. The included patients had to have at least 6 months of follow-up with lipid-lowering therapy and at least 3 months of continuous use of the drug between July 1, 2016 and December 31, 2018. From a population of patients identified from the drug database of Audifarma S.A., the main drug-dispensing logistics operator in Colombia, a simple random sampling was performed with a statistical error of 5%, a power of 80%, and a control proportion of 47%, which yielded a probabilistic sample of 383 patients.

A database was built with the variables of interest for the study from the information collected from the clinical records of the patients, which were obtained manually by a doctor trained in pharmacoepidemiological data collection and then validated by the research team, who identified gaps or inconsistencies in the collection of data, which were subsequently incorporated and corrected. The following data were recorded from the clinical history of the patients:

- Sociodemographic variables: age, sex, city of origin.
- Anthropometric measurements: weight, height, body mass index.
- Comorbidities: presence or absence of concomitant diseases: high blood pressure, history of acute myocardial infarction, history of stroke, diabetes mellitus, family history of premature heart disease (first-degree coronary heart disease <55 years in men or <65 years in women), chronic kidney disease.
- Pharmacological: the dose of rosuvastatin + fenofibric acid, as well as the dosage interval and duration of therapy. It was established whether the patient was receiving lipid-lowering therapy before the observation, and that medication was identified.
- Concomitant medications: medications prescribed for other morbidities in the included patients.
- Cardiovascular risk: The cardiovascular risk of each patient was calculated according to the scales of the Framingham Risk Score (2008) (validated for Colombia)[14] and the American Heart Association (AHA-2013),[15] and the frequencies of cases at each risk level were established.
- Safety: Adverse effects reported by the treating physician were identified, as were those reported in the pharmacovigilance program of Audifarma S.A. and those included in the insurer database.
- Effectiveness: values of the lipid profile at the beginning and end of the observation of each patient, as well as intermediate values, if they were available. Total cholesterol, LDL cholesterol (LDL-C), HDL-C, triglycerides, systolic and diastolic blood pressure, and glycemic values were recorded. Based on the results of the scales, the patients were divided into risk groups to establish the effectiveness of the therapy according to the recommendations of the American Society of Clinical Endocrinologists,[16] which defines risk as follows: (1) Very high risk: patients with established coronary, cerebrovascular, peripheral vascular, or carotid disease; recent hospitalization; or a cardiovascular risk $>20\%$ at 10 years, diabetes mellitus, or chronic kidney disease stage 3 or 4 with more than one risk factor. In these patients, the LDL-C goal was <70 mg/dL. (2) High risk: ≥ 2 risk factors and between 10% and 20% cardiovascular risk at 10 years, or diabetes mellitus or chronic kidney disease without other risk factors. In these patients, the LDL-C goal was <100 mg/dL. (3) Moderate risk: $\leq 10\%$ cardiovascular risk at 10 years and ≤ 2 risk factors. In these patients, the LDL-C goal was <100 mg/dL. (4) Low risk: no risk factors. In these patients, the LDL-C target was <130 mg/dL. The expected triglyceride goal in all groups was <150 mg/dL.

Statistical Analysis

The analyses were performed in SPSS version 25.0 for Windows (IBM, USA). Descriptive analyses were performed for categorical and quantitative variables, and normality was tested with the Kolmogorov-Smirnov test. For

Table 1. Sociodemographic, Anthropometric, Cardiovascular, Risk Factors and Pharmacological Characteristics of a Cohort of 386 Patients With Mixed Dyslipidemia Treated With Rosuvastatin + Fenofibric Acid in Colombia.

	Patients	
Characteristics	n = 386	%
Sociodemographic		
Age (mean ± SD, years)	60.8 ± 11.4	
Female (n/%)	205/53.1	
Anthropometric		
Weight (mean ± SD, kg)	74.1 ± 13.0	
BMI (mean ± SD, kg/m^2)	27.9 ± 3.8	
Overweight (BMI: 25-29.9 kg/m^2)	188	48.7
Obesity (BMI: >30 kg/m^2)	115	29.8
Other risk factors		
Hypertension	271	70.2
Current smokers	24	6.2
Ex-smokers	104	26.9
Diabetes mellitus	139	36.0
Family history of coronary disease	53	13.7
Acute myocardial infarction	73	18.9
Stroke	13	3.4
Chronic kidney disease (GFR <60 mL/min)	28	9.8
Personal history of pancreatitis	8	2.1
Lipid-lowering drugs previously used	366	94.8
Atorvastatin	133	34.5
Gemfibrozil	121	31.3
Rosuvastatin	63	16.3
Ciprofibrate	35	9.1
Fenofibrate	32	8.3
Statin + Ezetimibe	21	5.4
Lovastatin	4	1.0
Comedications	339	87.8
Antihypertensives	236	61.1
ACEi/ARB	179	46.4
Beta-blockers	108	28.0
Calcium channel blockers	62	16.1
Aspirin	111	28.8
Oral antidiabetics	105	27.2
Insulins	47	12.2
Proton pump inhibitors	35	9.1
Psychopharmaceuticals	35	9.1

ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; GFR: glomerular filtration rate; SD, standard deviation.

the effectiveness analysis, lipid profile values were compared at the beginning versus at the end of follow-up in each subject using nonparametric tests or by a comparison of means, according to whether the results had a normal distribution. A logistic regression model was built where the dependent variable was the control of LDL-C (according to the patient's risk level) and the covariates were all those associated in the bivariate analysis, in addition to age, sex, and others with biological plausibility that could be useful for model fit. A value of $P < .05$ was established as statistically significant.

Table 2. Estimation of Cardiovascular Risk at the Beginning and End of Follow-up in a Cohort of 386 Patients with Mixed Dyslipidemia Treated With Rosuvastatin + Fenofibric Acid in Colombia.

	Beginning	Final
Characteristics	n = 386	n = 386
Cardiovascular risk		
Framingham CVR (mean ± SD)	14.9 ± 6.5	10.3 ± 6.1
AHA 2013 Score CVR (mean ± SD)	16.5 ± 13.5	12.8 ± 12.4
CVR classification according to Framingham (*n*/%)		
Very high risk	206/53.3	88/22.8
High risk	86/22.3	106/27.5
Moderate risk	83/21.5	111/28.8
Low risk	9/2.3	81/20.9
Not calculable	2/0.5	0

CVR, cardiovascular risk; SD, standard deviation.

Bioethical Considerations

The protocol was endorsed by the Bioethics Committee of the Universidad Tecnológica de Pereira in the category of "research without risk." All information was anonymized, and the principles of confidentiality established by the Declaration of Helsinki were respected.

Results

A total of 386 patients who started therapy with the combination of rosuvastatin + fenofibric acid during the observation period were analyzed. They had an average age of 60.8 ± 11.4 years and 53.1% were women (n = 205). The cases came from 43 different cities in the country. A high frequency of cardiovascular risk comorbidities was found among the cases evaluated, especially overweight or obesity (78.5%, n = 303), high blood pressure, diabetes mellitus, and a history of a previous coronary event. Table 1 shows the main comorbidities and risk factors in the study population. A high proportion of patients with high cardiovascular risk was found according to the Framingham risk score adjusted for Colombia and the American Heart Association (AHA-2013). The classification by risk level showed that 75.6% of patients had a high–very high cardiovascular risk. Table 2 lists the classifications of cardiovascular risk at the beginning and end of follow-up, which shows the proportion of patients who changed their risk level.

Table 3. Blood Pressure, Glycemia, and Lipid Profile at the Beginning, During the Follow-Up, and at the End of the Evaluation in a Cohort of 386 Patients with Mixed Dyslipidemia Treated With Rosuvastatin + Fenofibric Acid in Colombia.

Characteristics	Beginning (n = 386)		During follow-up (n = 261)		Final (n = 386)		*P* value (means)*
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Systolic blood pressure (mmHg)	121.4 ± 13.5	120 (110-130)	118 ± 10.1	120 (110-120)	119.7 ± 11.1	120 (110-125)	.015
Diastolic blood pressure (mmHg)	74.4 ± 8.5	70 (70-80)	73.1 ± 7.3	70 (70-80)	73.4 ± 8.1	70 (70-80)	.071
Glycemia (fasting) (mg/dL)	126.6 ± 53.9	108 (94-137)	115.5 ± 39.8	102 (91-127)	120.7 ± 47.9	103 (91-135)	.058
Lipid profile (mg/dL)							
Total cholesterol	272.5 ± 96.2	258 (208-310)	191.3 ± 77.6	173 (144-218)	175.7 ± 58.2	161 (139-200)	<.001
LDL cholesterol	138.4 ± 67.1	134 (91-176)	90.2 ± 45.7	81.5 (60-109)	87.5 ± 41.2	78.5 (61-108)	<.001
HDL cholesterol	36.9 ± 11.1	35 (30-42)	41.4 ± 12.4	40 (32-48)	41.4 ± 12.2	39 (34-48)	<.001
Triglycerides	679.7 ± 573.6	514 (347-780)	337.2 ± 371.7	232 (163-352)	243.3 ± 170.5	196 (134-286)	<.001

IQR, interquartile range; SD, standard deviation.
*Beginning versus the end of the evaluation.

All patients evaluated began therapy with the combination of rosuvastatin + fenofibric acid (mean dose rosuvastatin: 17.3 mg/day and mean dose fenofibric acid: 135 mg/day) once daily for an average of 10.7 ± 4.8 months (mean of 321 days) of therapy during the study period. Continuous treatment adherence was found in 20.5% (n = 79) of cases, while the remainder had varying months without filling their prescription. A total of 219 (56.6%) patients still took the combination of rosuvastatin + fenofibric acid at the end of the follow-up period. The proportion of patients that did not stop treatment, according to cardiovascular risk groups, were as follows: 57.8% (n = 119) of the patients in the very high risk group, 52.3% (n = 86) in high risk, 56.6% (n = 83) in moderate risk, and 66.7% (n = 6) in low risk.

A total of 9.1% (n = 35) of patients changed doses, and at the end of the observation period, 43.4% (n = 167) had discontinued the medication, changing to rosuvastatin monotherapy (n = 55; 14.2%), no lipid-lowering drug (n = 39; 10.1%), atorvastatin monotherapy (n = 30; 7.8%), gemfibrozil (n = 14; 3.6%), and the rest to different medications and combinations.

The evaluation of the lipid profile at the beginning of the follow-up found a mean LDL-C of 138.4 ± 67.1 mg/dL (range: 20-477 mg/dL) and triglycerides of 679.7 ± 573.6 mg/dL (range: 124-5192 mg/dL). At the end of follow-up, the values were reduced to an average LDL-C of 87.5 ± 41.2 mg/dL (range: 15-313 mg/dL, reduction of 43.3%) and triglycerides of 243.5 ± 170.5 mg/dL (range: 47-1474 mg/dL, reduction of 64.2%). Table 3 shows the results of the lipid profile analysis at the beginning, during, and at the end of the follow-up. At the beginning, all patients were above their LDL-C and triglyceride targets according to cardiovascular risk level, but at the end of the follow-up, 46.9% had reached the LDL-C control for their specific risk level, and 29.8% had reached their triglyceride target.

When evaluating triglycerides in more detail in the subgroup of patients who managed to reach the goal of less than 150 mg/dL by the end of follow-up, we saw that the initial mean for these patients was 527.6 ± 434.0 mg/dL and at the end was 116.3 ± 21.8 mg/dL ($P < .001$).

According to their identified risk score, 35.4% (n = 73) of those with very high cardiovascular risk achieved the goals of metabolic control, while 61.6% (n = 53) of those at high risk achieved it, 55.4% (n = 46) of those at moderate risk, and 77.8% (n = 7) of those at low risk. The mean difference between the initial and final lipid profile values was statistically significant (Table 3).

Multivariate Analysis

The multivariate analysis adjusted for region of the country, age, and sex found that belonging to the very high-cardiovascular-risk group was statistically significantly associated with a lower probability of achieving the control goal (whose LDL-C target was stricter). No variables associated with a greater probability of achieving control were found (see Table 4).

Drug Safety

During the observation period of each patient, only 4 (1.0%) adverse events associated with rosuvastatin + fenofibric acid therapy were reported, all of which were classified as nonserious. Two patients manifested epigastric pain (0.3%), 1 consulted for muscle pain (0.2%), and the last complained of gastroesophageal reflux (0.2%).

Discussion

The combination rosuvastatin + fenofibric acid in this group of Colombian patients treated in a real-life setting

Table 4. Multivariate Analysis of the Variables Associated With Achieving the Lipid Profile Goal in a Cohort of 386 Patients With Mixed Dyslipidemia Treated With Rosuvastatin + Fenofibric Acid in Colombia.

			95% CI	
Variables	*P*	OR	Lower	Upper
Female sex	.613	0.891	0.571	1.391
Age				
18-44 years	.081	Ref	Ref	Ref
45-64 years	.067	0.442	0.184	1.059
≥65 years	.348	0.639	0.250	1.630
Personal history of high blood pressure	.083	1.611	0.940	2.760
Use of β-blockers	.310	0.767	0.459	1.280
Cardiovascular risk classification: very high	<.001	0.321	0.192	0.539
Be treated in Santander	.717	1.111	0.628	1.964

Adjusted for country region, age and sex.
95% CI, 95% confidence interval; OR, odds ratio.

showed significant results in terms of the decreases in LDL-C and triglycerides, without reports of serious adverse events during the follow-up. These data can be useful for physicians, patients with mixed dyslipidemia and high cardiovascular risk, and decision-makers in contexts where an overall impact on both lipid profile and cardiovascular outcomes is sought.[17]

In an earlier study in Colombia, mixed dyslipidemia was the most frequent type of dyslipidemia, with elevated LDL-C and triglycerides, associated with a high cardiovascular risk,[4] a situation similar to that of this study, where more than half of patients had very high cardiovascular risk and another quarter had a high risk, but associated with an average triglyceride value of 679 mg/dL, which increases the probability of complications associated with hypertriglyceridemia, such as acute pancreatitis.[18,19] This type of mixed dyslipidemia creates a complex clinical situation because the doctor must control LDL-C and the high cardiovascular risk with the prescription of statin, but also treat the severe hypertriglyceridemia with a fibrate. This particular combination was previously not possible due to the significant risk of muscle complications such as myopathy, myalgia, or even rhabdomyolysis seen in the statin + gemfibrozil combination, which had to be implemented with extreme caution.[20] However, with the emergence of fenofibric acid, a therapeutic option was available for the global management of this mixed condition by combining this fibrate with a high-intensity statin, and no increase in serious adverse reactions has resulted.[21,22]

During follow-up, the patients who received the combination of rosuvastatin + fenofibric acid had a significant decrease in the average total cholesterol, LDL-C, and triglycerides and an increase in HDL-C, as well as reaching the lipid-control goals in a high proportion of cases, impacting both the long-term risk of cardiovascular disease as well as the residual risk and associated complications.[17] The results in the very high-risk group are worth highlighting, as their goals were stricter, and as found in the multivariate analysis, they had a lower probability of achieving control than patients with lower estimated risk, suggesting the need for stricter and interdisciplinary monitoring.

Roth et al, after 8 weeks of a fixed combination of rosuvastatin + fenofibric acid, also found significant reductions in LDL-C, HDL-C, and triglycerides, without an increase in adverse reactions.[22] Another clinical trial conducted by Jones et al had similar results in patients with type 2 diabetes mellitus and mixed dyslipidemia, without a difference in adverse events between the combination regime and statins in monotherapy.[21] A 1-year follow-up study published in 2012 by Ferdinan et al on the rosuvastatin + fenofibric acid combination at fixed doses found similar results, and the effect was maintained over time and included few reports of adverse reactions.[23] These studies support the use of combined therapy in clinical practice not only in North America but also Colombia,[9] as effectiveness and safety have been confirmed there.

The proportion of days covered was close to 1 year of treatment, and during this time, the included patients achieved significant reductions in LDL-C and total cholesterol and in their estimated cardiovascular risk. Even so, more than half of them continued taking the medications at the end of the observation window. Difficulties regarding adherence to lipid-lowering therapies in the real-world setting have been published in other populations.[24] For example, in a retrospective cohort study conducted in Scotland, the 62.9% of patients with statins discontinued such therapy during follow-up.[25] However, in our study, a third of patients who discontinued the combination at fixed doses of rosuvastatin + fenofibric acid switched to a single lipid-lowering agent such as rosuvastatin, atorvastatin, or gemfibrozil after having reached the expected goals, especially for triglycerides, which shows the importance of continuing treatment

to maintain control of lipid metabolism, which should have a positive impact on long-term cardiovascular risk.[17]

It is evident that this cohort of patients had a significant burden of cardiovascular disease: more than 70% had hypertension, slightly more than a third suffered from diabetes mellitus, approximately 20% had a history of established heart disease, and 10% had chronic kidney disease. These rates emphasize the need to establish a comprehensive and complete treatment of cardiovascular risk.[26] This can be achieved with the correct use of antihypertensive, antidiabetic, or antiplatelet medications, among others, as well as changes in lifestyle, which would include adjusting habits such as sedentariness, smoking, and diets high in saturated fats and sugars to improve metabolic control, added to the effect achieved by lipid-lowering drugs, all of which would be helpful in the studied population due to its high frequency of obesity and overweight.[27,28]

This study has some limitations, such as the fact that it was a follow-up study in a single cohort without a comparison group, as well as that only a population of patients covered by insurance companies of the contributory regime were included. Therefore, the conclusions will be useful only for similar populations. In addition, it is possible that clinical records, the main source of information, did not contain all the information required, particularly on adverse reactions, although the records of the pharmacovigilance program of the company that dispenses the medications were reviewed.

Conclusion

The fixed-dose combination of rosuvastatin + fenofibric acid is an effective and safe option to lower lipid levels in patients with mixed dyslipidemia and high cardiovascular risk. It provides physicians, patients, and decision-makers with a therapeutic option for those conditions that require it. In addition, based on these results, there is a need to study this combination's cost-effectiveness, safety, and effectiveness in the longer term and especially as regards cardiovascular outcomes.

Author Contributions

MEMD participated in the drafting, data collection, data analysis, description of results, discussion, critical revision of the article, and evaluation of the final version of the manuscript. AGM participated in the drafting, data collection, data analysis, description of results, discussion. JEMA participated in the drafting, data analysis, description of results, discussion, critical revision of the article, and evaluation of the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The sponsor did not participate in the process of developing the protocol, collection, analysis, the results or discussion. The authors declare that there are no additional conflicts of interest.

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