

ORIGINAL ARTICLE

Treatment Eligibility and Therapeutic Responses of an Ecuadorian Population at High Cardiovascular Risk Based on the ATP III Guidelines

Isabel Hernández,¹ Andrea Estrella,¹ Jorge Salazar,² Yan Duarte,³ Edmundo Torres,⁴ Camilo López,^{5,6} Santiago Terán,⁷ Alejandra Mendoza,⁷ Enrique Terán^{1,7}

Facultad de Enfermería, Pontificia Universidad Católica del Ecuador,¹ Quito - Ecuador
Servicio de Endocrinología, Hospital de Especialidades Eugenio Espejo,² Quito - Ecuador
Servicio de Cardiología, Hospital Luis Vernaza,³ Guayaquil - Ecuador
Servicio de Medicina Interna, Hospital Carlos Andrade Marín,⁴ Quito - Ecuador
Servicio de Endocrinología, Hospital Teodoro Maldonado Carbo,⁵ Guayaquil - Ecuador
Facultad de Medicina, Universidad de Guayaquil,⁶ Guayaquil - Ecuador
Colegio de Ciencias de la Salud, Universidad San Francisco de Quito,⁷ Quito - Ecuador

Abstract

Background: The Adult Treatment Panel III (ATPIII) guidelines aim to reduce cardiovascular morbidity and mortality. In Ecuador, 20% of people have high LDL cholesterol levels, and 39% have high triglyceride levels.

Objective: To analyze lipid-lowering regimens in Ecuadorian patients and determine the achievement rate of the ATPIII goals for lipid profile.

Methods: Using a retrospective analysis, 385 subjects older than 30 years, who received pharmacological treatment for dyslipidemia for at least three months was randomly selected from institutions at two large cities in Ecuador. Data were collected from patients' medical records and analyzed by chi-square test or paired t-test; p-values less than 0.05 were considered significant.

Results: Baseline total cholesterol values were above 200 mg/dL in 75% of subjects, LDL-c values above 129 mg/dL in 83% of subjects and triglycerides values above 150 mg/dL in 79% of subjects. Most (n = 253, 95.8%) patients at very high cardiovascular risk were taking statins, 50% of them atorvastatin. Considering the ATPIII guidelines' goals, only 24 subjects (19%) at high CV risk achieved an LDL-c < 100 mg/dl, while a significantly lower percentage (p = 0.04) of patients at very high risk reached an LDL-c < 70mg/dl (11%; n = 30).

Conclusion: These data indicate a low rate of compliance with the ATPIII guidelines, independent of the medication used or duration of the treatment. This may be attributed to the prescription of low doses of medication and a therapy targeting isolated lipid fractions rather than a complete lipid profile. (Int J Cardiovasc Sci. 2020; 33(4):371-376)

Keywords: Cardiovascular Diseases/prevention and control; Cholesterol; Triglycerides; Sedentarism; Tabaquism; Lifestyle; Dyslipidemia; Patient Compliance.

Introduction

The development of noncommunicable chronic diseases is associated with smoking, sedentary lifestyle and nutritional factors, and their detrimental effects can be reduced by a healthy lifestyle.^{1,2} In Ecuador, health

care of patients with diabetes mellitus, dyslipidemia, and hypertension accounts for the majority of physician-patient appointments and hospital discharge in the last twenty years.³ Recently, the National Health and Nutrition Survey (Encuesta Nacional de Salud y Nutrición - ENSANUT) presented by the Ecuadorian

Mailing Address: Enrique Teran, MD, PhD

Colegio de Ciencias de la Salud - Universidad San Francisco de Quito - Diego de Robles, s/n. Postal Code: 170157, Quito - Ecuador.
E-mail: eteran@usfq.edu.ec

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Ministry of Public Health showed that dyslipidemia is present in 19.9% of people below 60 years old while hypertriglyceridemia reaches 38.7% nationwide.⁴

For more than a decade, treatment of dyslipidemia by the medical community has been based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines (ATP III and subsequent updates).⁵ This approach relied heavily on the Framingham Heart Risk Score as a predictor of 10-year risk of coronary heart disease (CHD) events, specifically myocardial infarction and CHD-related death. Moreover, ATP III provides therapy guidelines for low-density lipoprotein cholesterol (LDL-c) and non-high-density lipoprotein cholesterol (non-HDL-c) established based on patients' predicted risk and related comorbidities. In general, these guidelines recommend aggressive treatment of LDL-c of patients at higher risk, with specific LDL-c targets for each risk category.⁵

Since the late 1980s, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors ('statins') has been used as the primary treatment of hypercholesterolemia. A pooled analysis of the Cholesterol Treatment Trialists' Collaboration (CTTC) showed that every 1 mmol/L (38.67 mg/dL) reduction in LDL-c with statin therapy was associated with a reduction in any major cardiovascular event by 21% to 28%.⁶

The present study analyzes different lipid-lowering regimens in Ecuadorian patients at high and very high cardiovascular risk, to determine if ATP III guidelines achieve their treatment goals.

Materials and methods

This was a retrospective study approved by the institutional review board of the *Universidad San Francisco de Quito* (2015-044IN). A sample of patients' medical records was calculated (5% precision, 95% confidence interval and 50% variability) and obtained from six hospitals in the two main cities of Ecuador assuming a rate of 2:1 between public and private institutions. In Quito city, the hospitals that participated in the study "Hospital de Especialidades Eugenio Espejo" (public hospital, run by the Ministry of Public Health), "Hospital Carlos Andrade Marín" (public hospital, run by the social security administration), and "Hospital de Los Valles" (private hospital). In Guayaquil, the hospitals included were "Hospital Luis Vernaza" (public hospital, run by the *Junta Beneficencia* – Charity Board), "Hospital

Teodoro Maldonado Carbo" (public hospital, run by the social security administration), and "Clinica Kennedy" (private hospital).

Medical records of subjects that met the following criteria were included in our analysis: (a) subjects that attended an internal medicine, cardiology or endocrinology outpatient clinics, (b) subjects older than 30 years (c) patients with a diagnosis of dyslipidemia evidenced by laboratory tests (d) subjects undergoing pharmacological treatment at one of the mentioned hospitals for at least three months. Subjects that met the above criteria were selected per institution using a random number generator (www.random.org) and data from the medical records were collected using forms specially designed for this study.

According to the ATP III algorithm, subjects are placed in one of three risk categories: (1) established CHD and CHD risk equivalents, (2) multiple (2+) risk factors, and (3) zero to one (0–1) risk factor. CHD risk equivalents include noncoronary forms of clinical atherosclerotic disease, diabetes, and multiple (2+) CHD risk factors with 10-year risk for CHD > 20%. Subjects with CHD or CHD risk equivalents can be categorized as high risk. The goal for LDL-lowering therapy in high-risk patients is an LDL-c level < 100 mg/dL. According to ATP III, for a baseline or on-treatment LDL-c < 100 mg/dL, no further LDL-lowering therapy is recommended. For all high-risk patients with LDL-c levels > 100 mg/dL, LDL-lowering dietary therapy should be initiated.⁵

Other factors that place subjects in the category of very high risk are the presence of established CVD plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglycerides > 200 mg/dL plus non-HDL-C > 130 mg/dL with low HDL-C [< 40 mg/dL]), and (4) patients with acute coronary syndromes.⁵

Statistical analysis

Continuous variables with a normal distribution, assessed by the Shapiro-Wilk test, were described as mean and standard deviation while categorical variables were presented as frequencies. Data were analyzed using the SPSS, using the chi-square test for categorical variables and the paired t-test for the continuous variables. A p-value less than 0.05 was considered as significant.

Results

A total of 385 patients were recruited, with an average age of 59.8 ± 13.2 years; 46% (n = 178) were male and 68% of them were at a very high risk of cardiovascular disease.

Analysis of baseline lipid profile showed total cholesterol levels higher than the desirable (< 200 mg/dL) in 75% of subjects and LDL-c near optimal/above optimal (129 mg/dL) in 83% of subjects. HDL cholesterol was lower than 40 mg/dL in 43% of patients, and triglycerides were above normal (< 150 mg/dL) in 79% of patients. There were no differences in lipid values between subjects at high or very high cardiovascular risk (Table 1).

Very high cardiovascular risk was significantly more frequent in women (57%; p = 0.02). Treatment resulted in a significant reduction of total and LDL cholesterol as well as triglycerides both in high and very high-risk subjects (Table 1).

However, the response rate to treatment ranged from 50% to 75%, with no difference between high and very high-risk subjects (Figure 1). Interestingly, all three parameters (total-c, LDL-c, and triglycerides) were seen to lower in 40% and 47% in high and very high-risk patients, respectively, with no statistical difference between the groups. Finally, improvement in the lipid profile – total-c, LDL-c and triglyceride reductions plus HDL-c increase – was evidenced in only 21% and 28%, respectively, with no statistical difference between the groups.

Regarding the LDL-c goal attainment (NCEP-ATP III therapy guidelines), only 24 (19%) high-risk subjects achieved an LDL-c < 100 mg/dL, while a significantly lower percentage (p = 0.04) of subjects at very high

cardiovascular risk reached an LDL-c < 70mg/dL (11%; n = 30). Additionally, ATP III goals were attained in a larger percentage by men (20.7%) than women (12.6%), although this difference was not statistically significant.

The most common pharmacological treatment was statin-based therapy, i.e. simvastatin at an initial dose of 20 mg in 35% (n = 68) of patients, or atorvastatin at an initial dose of 40mg in 56% (n = 110) of the subjects. Ezetimibe alone or in combination with simvastatin was used in 11 subjects (5.6%). Lastly, fibrates, i.e. gemfibrozil (600 mg) or fenofibrate (160 mg) was the treatment prescribed to only 3% (n = 5) of the patients.

In very-high risk patients, statins were used in 95.8% of the cases (n = 253) and in those, atorvastatin corresponded to 50%, simvastatin 34.8% and rosuvastatin 11% (Table 2).

The 30 patients who reached the ATP III LDL-c goal were prescribed high doses of statins either alone or in combination.

Discussion

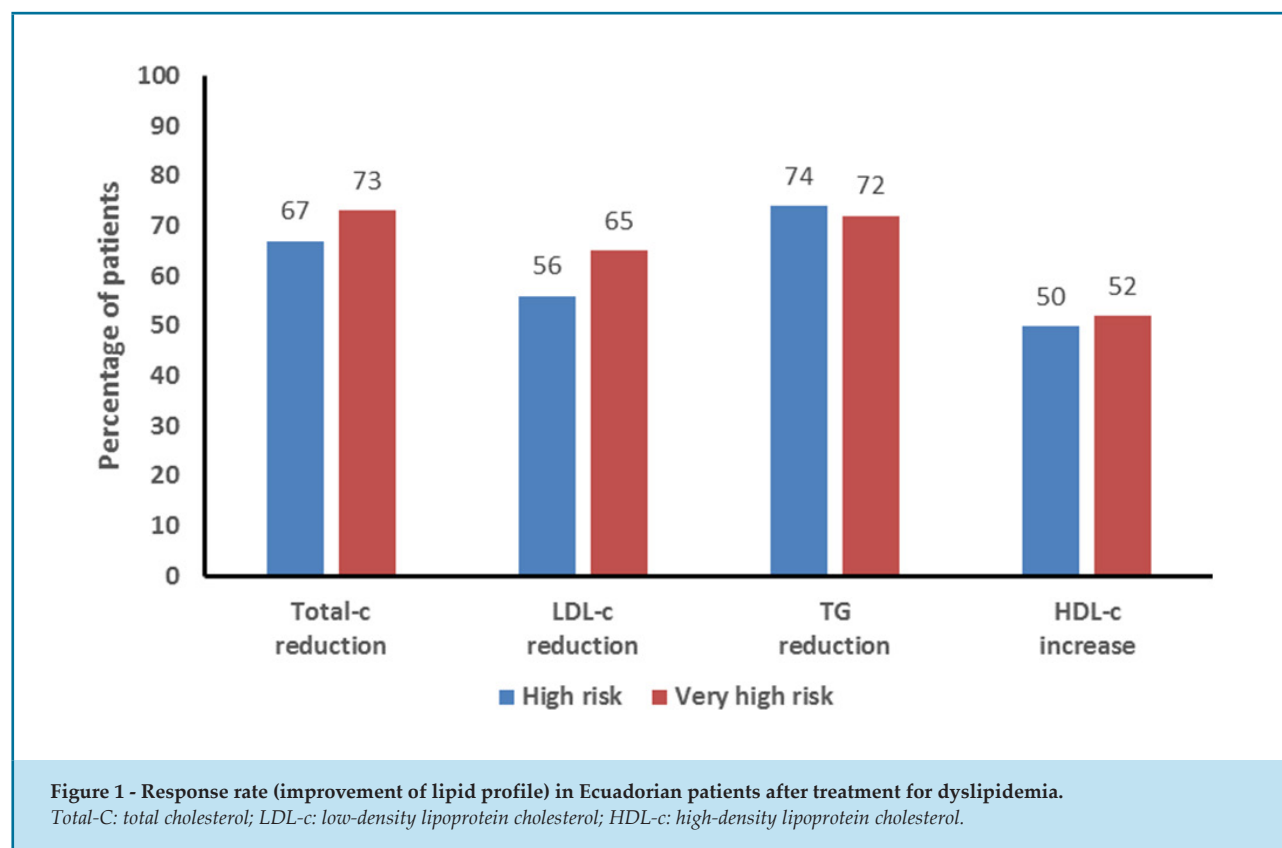
A reduction of lipid values – total-c, LDL cholesterol and/or triglycerides – in patients at high and very high cardiovascular risk was 56% and 53%, respectively. Therefore, we conclude that regardless of the treatment option or its duration, approximately half of the patients did not show an improvement in lipid profile.

It was not surprising that pharmacological treatment for dyslipidemia was mainly based on statins and particularly on atorvastatin. What is surprising is that low doses have been prescribed for high-risk patients, even though it is known that the success rate of such

Table 1 - Lipid values (mg/dL) in Ecuadorian subjects categorized by cardiovascular risk before and after pharmacological treatment for dyslipidemia

	Age	%Female	Total-c	LDL-c	Triglycerides	HDL-c
High risk (n = 125)	54.1 ± 14.3	48.0	235 ± 60	151 ± 62	271 ± 195	49 ± 26
			212 ± 55	135 ± 52	204 ± 156	48 ± 26
			0.018	0.03	0.003	0.76
Very high risk (n = 264)	62.6 ± 11.7	57.2	228 ± 54	140 ± 50	268 ± 285	43 ± 13
			197 ± 51	123 ± 45	208 ± 152	44 ± 13
			< 0.0001	< 0.0001	0.003	0.37

Total-c: total cholesterol; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol.



doses is low.⁷ It is also to be noted that fibrates have been prescribed to high-risk patients, given that recent trials have shown that these medications have failed to achieve a statistically significant reduction in lipid levels and, when combined with statins, have shown an increase in side effects.⁸

Moreover, the use of ezetimibe, particularly in association with statins, was found to be reduced. This may be explained by the fact that ezetimibe is not included in the National Essential Medicines List, which is a mandatory reference in public institutions. In private institutions, however, we could not find a clear explanation other than a misinterpretation of ATP III therapeutic goals by physicians.

In 2013, a new set of recommendations for the management of dyslipidemia were released by the American College of Cardiology (ACC) in collaboration with the American Heart Association (AHA). These guidelines refer to overall atherosclerotic cardiovascular disease and differ significantly from the previous ATP III guidelines by the fact that LDL-c and non-HDL-c goals were completely abolished.⁹ In addition, ATP III and subsequent updates state that

the decrease in the lipid profile solely is not enough to reduce cardiovascular risk.¹⁰

Our analysis shows that the achievement of ATP III treatment goals by patients at high risk was no different between statin therapies, i.e. 22% atorvastatin at 40 mg, 18.2% simvastatin at 40 mg and 18.8% rosuvastatin at 20 mg. Atorvastatin in higher doses allowed an additional 15% while no increase was found with higher doses of simvastatin or rosuvastatin. In patients at very high-risk, the ATP III LDL-C goals were achieved by 18.4% of patients taking atorvastatin at 40 mg, 7.6% of patients taking simvastatin and 3.6% of patients taking rosuvastatin. The use of higher doses did not result in a difference in success rates for LDL-c goal achievement.

We also analyzed our results based on the 2013 ACC/AHA guidelines as reference, and found that although 94% of the patients required a high-intensity statin therapy (atorvastatin at 40/80 mg or rosuvastatin at 20/40 mg), only 35.4% of patients actually received it, and from these, only 10.7% reached the expected goal of 50% reduction LDL-c.⁹

Our results are comparable to those reported in a study conducted in Mexico, which showed that therapeutic

Table 2 - Distribution of pharmacological therapy for dyslipidemia in Ecuadorian patients at very high cardiovascular risk (n = 253)

	10 mg	20 mg	40 mg	80 mg
Atorvastatin (n = 132)	2 (0.8%)	23 (9.1%)	78 (30.8%)	29 (11.5%)
Simvastatin (n = 92)	2 (0.8%)	47 (18.6%)	39 (15.4%)	4 (1.6%)
Rosuvastatin (n = 29)	9 (3.5%)	8 (3.2%)	12 (4.7%)	--
	100 mg	160 mg	300 mg	600 mg
Gemfibrozil (n = 26)	--	--	1 (1.9%)	25 (46.3%)
Fenofibrate (n = 28)	1 (1.9%)	2 (3.7%)	2 (3.7%)	23 (42.6%)
	10 mg			
Ezetimibe (n = 6)	6 (75.0%)			
Ezetimibe 10 mg + simvastatin (n = 2)	2 (25.0%)			

goals were attained by 29% of subjects taking initial dose of statin therapy and and after statin dosage adjustment 42% of the subjects reach the goal at the end of the study. ATPIII therapy goals were better attained in groups at a lower risk.¹¹

As we described in the preliminary analysis of the results, previously published by our group,¹² physicians are probably not evaluating the total lipid profile when selecting and monitoring the therapy. Evidence of this is: a) nearly half of the subjects had a total cholesterol reduction and showed a 60% reduction in triglycerides; b) all three parameters (total-c, LDL-c and triglycerides) were reduced in almost 43% of the subjects; and c) 70% of the study population had mixed hyperlipidemia.

In this sense, although it may be appropriate to adhere to treatment guidelines that recommend addressing LDL-C levels as the first step, it is important to deeper evaluate and treat these patients.¹³

Adherence to treatment is an important factor that affects the success of reaching the proposed target and

is highly dependent on educational and motivational interventions.¹⁴ Previous studies on adherence to statin treatment showed that in longer periods of time (6 months), around 50-60% patients continue on treatment.^{15,16} Treatment adherence was not considered in the present study, but we previously reported that one out of four patients (25%) stated to have forgotten at least one dose of their treatment, regardless of disease and duration of treatment.¹⁷

Although the retrospective design of the study and the lack of a stratified sampling constitute limitations to the analysis of the results, we conclude that there is a very low rate of ATP III therapy goal achievement among patients with dyslipidemia categorized as high and very high cardiovascular risk, independently of the treatment option or its duration. This can be attributed to the prescription of low doses of statins and to potential confounders like the simplistic evaluation of isolated lipid fractions rather than the complete lipid profile.

Author contributions

Conception and design of the research: Hernández I, Estrella A, Salazar J, Duarte Y, Torres E, López C, Terán S, Mendoza A, Terán E. Acquisition of data: Salazar J, Duarte Y, Torres E, López C, Terán S, Mendoza A. Analysis and interpretation of the data: Hernández I, Estrella A, Salazar J, Duarte Y, Torres E, López C, Terán S, Terán E. Statistical analysis: Terán S, Mendoza A, Terán E. Obtaining financing: Estrella A. Writing of the manuscript: Hernández I, Estrella A, Terán E. Critical revision of the manuscript for intellectual content: Hernández I, Estrella A, Salazar J, Duarte Y, Torres E, López C, Terán S, Mendoza A, Terán E.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the USFQ under the protocol number 2015-044IN. All the procedures in this study were in accordance

with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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