### **CASE REPORT**

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## Analysis Of Cardiovascular Risk Stratification And Achievement Of LDL-Cholesterol Therapeutic Goals In A University Endocrinology Outpatient Clinic In Belo Horizonte

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### **HIGHLIGHTS**

### What is already known?

- LDL levels are a key modifiable risk factor for cardiovascular disease.
- The Framingham score guides therapeutic goals for lipid-lowering treatment.
- Most patients fail to achieve their LDL targets with lipid-lowering drugs

### What was shown?

- 78% of the analyzed patients were classified as high cardiovascular risk.
- 69% of the patients did not achieve their therapeutic LDL goals.
- Simvastatin was used in 59% of patients not reaching their treatment goal.

### How can the study aggregate to the literature?

- This study shows why therapeutic inertia in reducing LDL needs to be addressed.
- Patients' adjustment to their therapeutic LDL targets should be encouraged.
- Use of high-potency statins or combined therapy should be stimulated.

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### **ABSTRACT**

Introduction: Dyslipidemia is an important modifiable risk factor for cardiovascular diseases, with statins being the main drug therapy used to reduce LDL levels. However, regarding the use of lipid-lowering drugs, the majority of individuals do not reach the stipulated therapeutic goal and many are associated with other cardiometabolic comorbidities, such as diabetes and overweight/obesity, being followed up through endocrinology outpatient clinic. Objective: Identify the clinical and epidemiological profile of patients using statins at a university outpatient clinic in Belo Horizonte and evaluate the degree of dyslipidemia control based on cardiovascular risk. Method: Retrospective cross--sectional study, approved by the Ethics and Research Committee, based on the analysis of medical records of dyslipidemic patients using statins, followed up at the endocrinology outpatient clinic in 2022. Patients with unlocated and/or incomplete medical records were excluded. Results: 42 individuals were included, 83% were female, median age of 65 years. Regarding cardiovascular risk, 4 (9%) were very high, 33 (78%) high, 4 (9%) intermediate and 1 (4%) was low. The main LDL levels were 86±42 mg/dl. Among the statins used, it was observed that 29 (69%) used simvastatin, 9 (21%) atorvastatin and 4 (10%) rosuvastatin. It was observed that 29 (69%) individuals were outside the therapeutic target according to their cardiovascular risk targets and, of these, 17 (59%) were using Simvastatin. Conclusion: The prescription of statins on an outpatient basis is widespread, however a few patients have LDL levels within the therapeutic target established by cardiovascular risk.

**Keywords:** Heart Disease Risk Factors; Dyslipidemias; Statins; Endocrinology.

### INTRODUCTION

According to the World Health Organisation, around 17.9 million people died from cardiovascular diseases (CVDs) in 2019, representing 32% of all causes of death worldwide, with acute myocardial infarction and stroke being the main etiologies. CVDS have a high morbidity and mortality rate and are a major cost to the National Health Service (SUS), as they are the leading cause of death among Brazilians. It is known that a large proportion of hospitalisations and deaths could be prevented by managing the main risk factors associated with an increase in CVDs, such as systemic arterial hypertension (SAH), diabetes mellitus, obesity, smoking and dyslipidemia, which are guiding principles for the development of primary and secondary prevention strategies. <sup>2,3</sup>

Dyslipidemias are an important modifiable risk factor for CVD, especially with regard to serum levels of low-density lipoprotein (LDLC). LDLC is associated with the formation and progression of atherosclerosis, a chronic multifactorial inflammatory disease that occurs in response to endothelial aggression and dysfunction, favouring the retention of LDLC in the subendothelial space. The deposition of these lipoproteins in the arterial wall, a key process in the initiation of atherogenesis, occurs in proportion to the concentration of these lipoproteins in the plasma and contributes to the occurrence of coronary artery disease. According to the Brazilian Society of Cardiology (SBC), 18.6% of the Brazilian population has elevated LDLC and 32.7% has total cholesterol above the reference values.

Various areas of medicine deal with this problem, but specifically in endocrinology, there is a high prevalence of dyslipidemia (40%) associated with type 2 diabetes mellitus (DM2), since these are more affected by cardiovascular diseases.<sup>5</sup>

In addition, overweight and obesity are comorbidities commonly seen in endocrinology clinics and are an important risk factor for CVD. According to IBGE data, the prevalence of overweight and obese adults was 57.5% in men and 62.6% in women.<sup>2</sup> The high prevalence of these cardiometabolic diseases has led to an increase in the incidence of lipid disorders and consequently the risk of CVDS.<sup>6</sup> This highlights the importance of endocrinologists working together to control these risk factors.

Several studies have attempted to assess the association between the prevalence of risk factors, whether modifiable or non-modifiable, and the pathophysiological mechanisms of CVD, the most famous of which is the Framingham Heart Study, a prospective cohort study published in 2018, which followed 5209 patients for 70 years.7 Based on this, the main aetiological factors associated with CVD were established and the Framingham Score was developed, which is used worldwide to stratify and classify patients' cardiovascular risk into low, intermediate, high and very high risk of developing CVD over the next 10 years.8 Based on this risk stratification, it is possible to define therapeutic targets for lipid-lowering treatment and guidelines for assessing each individual's lipid profile in order to mitigate unfavourable cardiovascular outcomes in the future.

Statins are one of the most scientifically validated therapies for lowering LDLC.<sup>3</sup> However, according to a national analysis conducted in 2020, less than half of patients taking statins achieved the therapeutic targets recommended by the SBC, with results ranging from 35% to 45%, depending on the level of cardiovascular risk.<sup>2</sup> This is partly due to underuse of high-potency statins, low adherence to combination therapies and non-pharmacological treatment.<sup>6</sup>

In this context, national studies are essential to understand the particularities of dyslipidemia management in Brazil. In view of this, the aim of this study was to determine the clinical and epidemiological profile of patients taking statins at a university endocrinology outpatient clinic in Belo Horizonte, and to assess the degree of dyslipidemia control based on the cardiovascular risk of these individuals.

### **METHODS**

### **Study Design**

A retrospective cross-sectional study conducted using data from the medical records of patients using statins and under outpatient follow-up with an endocrinologist at the University Medical Sciences Clinic located in Belo Horizonte, MG, during the year 2022.

The research was reviewed and approved by the local Ethics Committee on September 5, 2023, with opinion CAAE: 70826023.4.0000.5134. This study did not receive any funding from third parties.

### **Participants**

A total of 143 medical records of individuals using statins were analyzed. After applying the exclusion criteria, 42 individuals were included. The inclusion criteria involved patients over 18 years old who had been prescribed statins and whose medical records contained sufficient data to calculate cardiovascular risk. Patients with unallocated or incomplete medical records and individuals who refused to sign the Informed Consent Form were excluded.

#### Instruments

Data were collected through a systematic collection protocol developed by the researchers, consisting of sociodemographic and clinical variables, which were organized and tabulated in Microsoft<sup>®</sup> Office Excel.

### **Procedures**

The medical records of the target population were examined to identify essential clinical information, including demographic data, relevant personal medical history, cardiovascular risk factors, and the most recent lipid profile. Information on continuous medications, primarily lipid-lowering agents and their dosages, was also documented. Subsequently, cardiovascular risk stratification was performed by the researcher based on the data present in the medical records and required by the SBC risk stratification calculator.

### **Statistical Analysis**

Qualitative variables were presented with their respective values of simple frequencies and percentages. Quantitative variables were associated with the median and interquartile range. Data was organized and analyzed using Microsoft® Office Excel.

#### Results

A total of 42 patients with dyslipidemia using statins, followed at the endocrinology outpatient clinic, were included. Among them, 35 (83%) were female, with a mean age of 64±9 years. The individuals had other relevant risk factors associated with dyslipidemia, such as: 39 (93%) had systemic arterial hypertension, 33 (78%) had diabetes, 31 (74%) were overweight or obese, 18 (43%) were smokers, 20 (48%) were sedentary, and 3 (7%) had a history of Coronary Artery Disease (CAD) and had previously undergone some form of myocardial revascularization procedure, either angioplasty or coronary artery bypass surgery.

Regarding the calculated cardiovascular risk, 4 (9%) individuals were classified as very high risk, 33 (78%) as high risk, 4 (9%) as intermediate risk, and 1 (4%) as low risk. The median LDL levels were 86 mg/dl.

Among the statins used, it was observed that 29 (69%) individuals were using simvastatin, 9 (21%) were using atorvastatin, and 4 (10%) were using rosuvastatin. Only one patient was using it in combination with ezetimibe. It was noted that 29 (69%) individuals were not achieving the therapeutic target proposed by the SBC cardiovascular risk calculator, and of these, 17 (59%) were using simvastatin. Additionally, it was observed that the majority of individuals not achieving the therapeutic target were women, accounting for about 62% of the sample. Finally, it was noted that in 93% of the medical records analyzed, there were no changes in the treatment plan regarding medication and dosage.

Table 1 presents all the data mentioned above in a graphical format.

Table 1. Comorbidity Profile and Cardiovascular Risk of the Sample

Statin Used				
Characteristics	Total,	ATORVASTATIN	ROSUVASTATIN,	SINVASTATIN,
Characteristics	N = 421	N = 91	N = 41	N = 291
Female Sex	35 (83%)	6 (67%)	4 (100%)	25 (86%)
Age (years)	65 (59, 69)	68 (61, 69)	59 (56, 60)	65 (60, 70)
Ezetimibe	1 (2.4%)	1 (11%)	0 (0%)	0 (0%)
Systemic Hypertension	39 (93%)	9 (100%)	3 (75%)	27 (93%)
Type 2 Diabetes Mellitus	33 (79%)	6 (67%)	4 (100%)	23 (79%)
Smoking	18 (29%)	3 (43%)	1 (25%)	6 (26%)
Sedentary	20 (48%)	5 (33%)	2 (50%)	13 (59%)
Overweight/Obesity	31 (74%)	7 (78%)	4 (100%)	20 (69%)
Chronic Kidney Disease	7 (17%)	2 (22%)	0 (0%)	5 (17%)
		Cardiovascular Ris	k	
HIGH	33 (79%)	7 (78%)	3 (75%)	23 (79%)
LOW	1 (2.4%)	0 (0%)	0 (0%)	1 (3.4%)
INTERMEDIATE	4 (9.5%)	0 (0%)	0 (0%)	4 (14%)
VERY HIGH	4 (9.5%)	2 (22%)	1 (25%)	1 (3.4%)
LDL Level (mg/dl)	86 (69, 126)	105 (75, 134)	116 (105, 123)	80 (64, 118)
Patient in Therapeutic Target	13 (31%)	1 (11%)	0 (0%)	12 (41%)

1n (%); # Median (interquartile range)

28

### DISCUSSION

In the Brazilian and worldwide context, the CVD represents the principal cause of diseases, the most important behavioral risk factors for the development of cardiovascular diseases are unhealthy diet, lack of physical activity, tobacco use and improper use of alcohol. The effects of the exposure to these behavioral risk factors can be identified in individuals with the increase of blood pressure, glucose and blood lipids, overweight and obesity. 9,10 Such diseases are highly disseminated in the Brazilian population, which increases the susceptibility to CVD.

In this study, we found a frequent prescription of statins for patients in ambulatorial follow up with endocrinologists in a university health service entirely dedicated to the SUS, due to the high prevalence of cardiovascular comorbidities between patients treated at the institution. This practice reflects the recognition, by professionals, of the importance of the cardiovascular risk factor.

The current study revealed that the average of age of participants was 64 years old, with a predominance of female sex, a trend also observed in the study conducted by Schmidt et al., in which women represented the highest proportion of statins use.<sup>11</sup> However, in the findings of Schmidt et al., the average levels of LDL were higher compared to those found in this research, which reinforces the quality of care provided.

Kaze et al. identified that 40% of the diabetics studied also had associated dyslipidemia, which shows the frequent coexistence between these two conditions in the clinical practice.<sup>5</sup> In a similar way, 79% of the individuals evaluated were diagnosed with DM, a condition that represents an important risk factor for CVDS and one of the most observed comorbidities in endocrinology outpatient clinics.<sup>12</sup>

This high rate of dyslipidemia associated with diabetes may suggest both a possible overdiagnosis and a problem with adherence to medical follow-up.

Moreira et al. identified a 10-year increase in the risk of CVD in individuals with obesity, and rapid industrialisation, accompanied by changes in the population's lifestyle and diet, is directly associated with this comorbidity and increased cardiovascular risk. <sup>13</sup> In addition, Malta et al. showed a strong association between overweight, obesity and diabetes mellitus in the Brazilian population due to pathophysiological mechanisms that exacerbate insulin resistance, increase the inflammatory state and circulating free fatty acids, aggravating DM. <sup>14</sup>

Hypertension can also be cited as one of the main risk factors for CVD and affects around one third of the adult population, making it the most common chronic non-communicable disease in the world. Studies show that hypertensive patients have higher levels of atherosclerosis, which leads to a higher risk of CVD. In this study, 93% of the 42 patients analysed had a diagnosis of hypertension.

According to the SBC's cardiovascular risk calculator, 78% of the individuals had a high cardiovascular risk and 4% had a very high risk. In a global comparison, the DA VINCI study, carried out with Europeans in 2020, showed that the majority of patients (67%) were at low to moderate risk, 29% were at high risk and only 4% were at very high risk. In high-risk and very high-risk patients, treatment should include more aggressive modification of risk factors, starting with the use of appropriate medications, combined with lifestyle changes and non-pharmacological treatment. With regard to pharmacological interventions, the use of statins is indicated as a first-line option for primary and secondary prevention.

It is also possible to see a high proportion of patients with very high LDL levels despite the use of statins. This may indicate a problem with adherence. Of the total sample, 69% of patients were taking simvastatin 40mg, which is in line with the study by Schmidt et al. in Ribeirão Preto. The predominant use of simvastatin in Brazilian patients may be due to the fact that the drug is available free of charge from the sus. 11 All the drugs in this class have been shown to reduce cardiovascular events and deaths; however, current guidelines advocate the use of lipid-lowering therapy with a high-intensity statin in the absence of contraindications to reduce morbidity and mortality. 3,18 However, these medications are not widely available on the sus and come at a cost that many patients cannot afford.

According to Ray et al, moderate-intensity statins in monotherapy were the most commonly used regimen for primary prevention, which contrasts with the Brazilian scenario where low-potency statins such as simvastatin are more widely used. Data from the literature shows that LDL reduction varies between statins, with a 6-7% reduction when the dose is doubled, a strategy widely used in the outpatient setting as the minority of patients were on the minimum dose.<sup>3,16</sup>

Despite the use of lipid-lowering agents, 29 individuals were not within the therapeutic LDL target set by the SBC risk calculator, 17 of whom were on simvastatin. This highlights the need for adjustments in the therapy of these patients and possibly the use of higher-potency statins and combinations with ezetimibe and PCSK9 inhibitors (if indicated), and further reinforces the need to use well-established clinical protocols and institutional use to determine the drug effect and doses to be used. The Brazilian EPICO study showed that risk factors for cardiovascular disease are poorly controlled in a large proportion of the Brazilian community and that only 14% of dyslipidemic patients taking statins had LDL values compatible with

the established therapeutic targets. <sup>19</sup> Worldwide, the vast majority of patients also fail to reduce their LDL cholesterol sufficiently to minimise their individual risk of developing CVDS. <sup>6</sup>

The association between treatment goal and history of coronary heart disease was statistically significant, meaning that all people with coronary heart disease had LDL levels within the range recommended by the SBC calculator, reflecting the good adherence and monitoring of these patients. This is in contrast to the study by Gomes et al, which found that only one in three patients with a history of myocardial infarction who were followed up in a tertiary hospital achieved the LDL target. This is partly due to the underuse of effective doses of higher-potency statins as first-line therapy, low use of combination therapy, and poor adherence to lipid-lowering regimens, resulting in insufficient reductions in cumulative cholesterol exposure.

Recent data show that the increase in the life expectancy of the Brazilian population, with the consequent increase in the proportion of elderly people, is associated with an increase in the incidence of CVD and, consequently, with an exponential increase in costs for the sus.<sup>20</sup> In line with this, Malta et al. showed that cardiovascular risk increases with age in both women and men.<sup>17</sup> Failure to achieve the therapeutic target therefore means an overburdening of the public health system, also financially, as CVD hospitalisations are considered to be the most costly of all causes of hospital admissions in Brazil.<sup>20</sup> From this, it is clear that it is important to increase the prevention of cardiovascular diseases in Brazil, with the aim of reducing the financial impact of these pathologies on society and increasing the population's quality of life.

In addition to adjusting statin doses to improve patients' clinical control, new drugs have been scientifically proven to reduce cardiovascular risk. Ezetimibe and PCSK<sup>9</sup> inhibitors can be used in combination with

statins when indicated to improve individual treatment and achieve the appropriate therapeutic goal. According to the Brazilian Dyslipidaemia Guideline, ezetimibe is an isolated therapeutic option for individuals intolerant to statins. The combination of ezetimibe with the treatment is recommended in primary prevention when the LDL target is not achieved despite statin treatment at the maximum tolerated dose.<sup>3,4,19</sup> In the DA VINCI study, ezetimibe was used in combination with moderate- or high-intensity statins in 9% of patients, and only 1% used PCSK9 inhibitors in combination with other therapies.<sup>16</sup> In the study by Gomes et al, only 2 of the 36 patients who were eligible according to the European Society of Cardiology guidelines were using PCSK9.18 In the present study, only 01 individuals were using another lipid-lowering agent, in this case ezetimibe. The other patients were only taking a statin and most were outside the LDL target.

These results highlight the gap between scientific guidelines and clinical practice and, although the values are outside the desired range, they are in line with the results found by previous research. This variability in lipid levels shown by the trials suggests the need to adjust drug doses, use higher-potency statins and drug combinations where appropriate, and highlights the importance of using well-established clinical guidelines.

#### Limitations

This study is part of a broader investigation aimed at comparatively analyzing cardiovascular risk and therapeutic approaches, focusing on the use of statins in specialized outpatient clinics in cardiology, endocrinology, and internal medicine. The comprehensive results will be thoroughly discussed in a separate work, with the goal of conducting a joint analysis of the obtained data. However, this article focuses on the specifics of the endocrinology outpatient clinic, highlighting its particular approach to the treatment of dyslipidemias.

Despite its contributions, the study presents some important limitations. The small sample size may not be representative of the entire population served by endocrinology services, which limits the generalizability of the findings. Additionally, the one-year follow-up period is considered short to fully assess the impact of therapeutic interventions on the control of dyslipidemia and the reduction of cardiovascular events. Another relevant point is that the reasons why many patients did not reach the therapeutic goals for LDL-C were not evaluated, nor were the factors influencing the lack of intensification of lipid-lowering therapy. Furthermore, the study focused solely on LDL-C goals, without analyzing other lipid profile components such as HDL, non-HDL, and triglycerides. These limitations suggest the need for future studies with larger samples that investigate both dyslipidemias and other cardiovascular risk factors, and that assess the achievement of therapeutic goals associated with these factors.

### CONCLUSION

The data from this study indicate that most dyslipidemic patients followed up in the endocrinology outpatient service have high cardiovascular risk and do not reach the therapeutic goal, even with statin treatment. This result reflects the presence of multiple risk factors for the development of cardiovascular diseases and reinforces the importance of maintaining low LDL levels. However, it is important to emphasize that the conclusions were based on a one-year follow-up period, which is considered short for a comprehensive evaluation of the evolution of dyslipidemias and the long-term impact of the interventions performed. Still, the findings highlight the need for more effective measures in terms of primary and secondary prevention, combined with optimized use of lipid-lowering agents, reducing unfavorable outcomes and promoting greater adherence to therapeutic goals proposed by specialized society guidelines. These results serve as a public health alert and emphasize the relevance of longer and more comprehensive investigations into the effectiveness of dyslipidemia treatment.

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