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The use of statins in the treatment of dyslipidemia in Brazil: a population-based study

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Abstract: Dyslipidemia is an important risk factor associated with cardiovascular diseases and statins are the most used lipid-lowering agents in clinical practice. This study aimed to estimate the prevalence of statin use in the Brazilian adult and elderly population, according to socio-demographic characteristics and according to the presence of chronic diseases. This is a cross-sectional study with data from the National Survey on Access, Use, and Promotion of Rational Use of Medicines in Brazil (PNAUM). It is a population-based household survey, based on a probabilistic sample. To compare the proportion of the use of statin in the population aged 20 years old or older, according to socio-demographic characteristics and the number of chronic diseases, we used Pearson's chi-square test with Rao-Scott correction, with a significance level of 5%. The prevalence use of statin was 5.6% (95% CI 5.1; 6.1), being higher among women with 7.2% (95% CI 6.5; 7.8), in the elderly population with 16.7% (95% CI 15.4; 18.1) and the economic classification A/B with 7.3% (95% CI 6.1; 8.6). The North region had the lowest percentage use with 1.7% (95% CI 1.3; 2.2). Those who reported three or more chronic diseases were 38.7% (95% CI 35.9; 41.6) using statin. Regional and economic differences in the use of statins suggest a possible relationship with health service coverage. This study describes the scenario of the use of statins in Brazil, obtaining information on the treatment of dyslipidemia, and creating health policies that promote the diagnosis, access, adherence, and appropriate use of statins. **Keywords**: statins; health surveys; dyslipidemia; medication use, simvastatin.

INTRODUCTION

In 2016, cardiovascular diseases were responsible for about 31.4% of the total deaths in the world. In the same year in Brazil, 27.9% of deaths were caused by cardiovascular diseases, making them the main cause of mortality in the country [1]. Dyslipidemia is the main risk factor associated with atherosclerosis, a health condition that increases the risk of developing cardiovascular disease [2].

Statins are recommended by the Brazilian Dyslipidemia Directive as the most commonly used lipid-lowering agents in clinical practice, as they are relatively safe and accessible. Scientific evidence shows that lower levels of Low-Density Lipoprotein Cholesterol

(LDL-c) obtained with the use of statins, reduce cardiovascular risk [2,3].

Statins act in the inhibition of the enzyme HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase), decreasing the hepatic production of cholesterol. Consequently, there is an increase in the expression of receptors for LDL in hepatocytes, stimulating the decrease of this lipoprotein in the bloodstream, whose intensity in LDL reduction is dose-dependent, and may vary depending on the statin used. This mechanism inhibits the progression of the atherosclerotic plaque, favoring its regression and making important improvements in myocardial perfusion, which impacts on the reduction of mortality and morbidity due to cardiovascular atherosclerotic disease. Also, the use of statins is related to a decrease in triglyceride levels and an increase in the concentration of high-density lipoprotein (HDL) [4,5,6].

In Brazil, the registered and available statins are atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin [7]. Statins have different pharmacokinetic characteristics such as bioavailability, lipophilicity, metabolism, and elimination, and the choice for a particular statin is mainly by the evaluation of cardiovascular risk, therapeutic objectives, the presence of comorbidities and the use of other drugs. In general, the adverse effects of statins depend on the dose used. The most known adverse effects are nausea and abdominal pain, insomnia or drowsiness, myalgia, myopathy, and, more rarely, rhabdomyolysis [4,5].

Results of the National Survey on Access, Use and Promotion of Rational Use of Medicines in Brazil (PNAUM) show a self-reported prevalence of dyslipidemia in Brazil of 10.1% (95% CI 9.4; 10.9) in the adult population (20 years old or older) [8], similar to the National Health Survey (PNS 2013) with 12.5% (95% CI 12.1: 13.0) [9,10].

PNAUM is the first specific national research on drug use and the only one so far. It consists of two independent and complementary investigations: the Population Survey Component used in this study, and the Component Evaluation of Basic Pharmaceutical Care Services [11].

In the Population Survey Component of PNAUM, they conducted 41,433 interviews with people of permanent urban residences, in municipalities in the 26 Brazilian states and the Federal District, to assess access to medicines, their use, aspects of rational use, sources of obtaining and the most prevalent morbidities in which the medicines are used. Based on the post-stratification weights and considering the sample design, this number represents about 171 million Brazilians [11].

This study aimed to estimate the prevalence of statin use in the Brazilian population (adults and the elderly people), according to socio-demographic characteristics and the presence of chronic diseases, analyzing the data from the Population Survey Component of PNAUM.

MATERIALS AND METHODS

Study population and design

The Survey Component of PNAUM is a cross-sectional, population-based study, carried out between September 2013 and February 2014, considering the population who live in the urban area of the Brazilian territory, encompassing the five regions (North, Northeast, Southeast, South, and Midwest).

By producing probabilistic samples and reaching multiple estimates of prevalence or proportions, through home interviews, the sample design included eight demographic domains, two without distinction of gender (age groups from 0 to 4 years old and 5 to 19 years

old), and the others broken down by age and gender (20-39 years old, 40-59 years old, 60 years old and over) for each of the five Brazilian regions, totaling forty sample domains. The National Household Sample Survey (PNAD 2008) defined the sample size, and the acceptable precision criterion was the maximum value of 0.05 for any coefficient of variation in the proportion estimates [12].

Using the cluster sampling method, the sampling units were drawn in three stages. The first stage was the systematic drawing of sixty municipalities by geographic region, with probability proportional to the number of households. In the second stage, two census sectors were drawn for each municipality. In the third stage, households were drawn considering patterns of demographic density for the eight domains. We obtained information on permanent private households from the 2010 National Census Address of the Brazilian Census of the Brazilian Institute of Geography and Statistics (IBGE). Thus, we estimated a minimum number of 960 interviews per domain, carrying out a total of 41,433 interviews [12].

The research instrument for adults was based on the following blocks: interviewee information, chronic diseases, chronic medication records, health services, problems and acute events in the last 15 days treated with medications, contraceptives, pharmacy services, behaviors that they can affect the use of medicines, package inserts and packaging, lifestyle, health insurance, home information and about the reference person. The collection was organized in two databases, one with data on the people interviewed and the second containing data on the drugs used by these individuals. The questionnaires and the databases are in the public domain and can be consulted on the PNAUM website [12,13].

The chronic diseases investigated were hypertension, diabetes, heart disease, hypercholesterolemia, stroke, pulmonary disease, arthritis or rheumatism, depression, and other diseases lasting six months or more. For each reported disease, we searched information related to the diagnosis, medical indication for pharmacological treatment, and registration of the drugs used, presented by the interviewee [11].

In this study, the records of participants aged 20 or over were used, totaling 32,348 individuals interviewed. Investigating the drugs used by these individuals, the main outcome was the report of the use of at least one of the subtypes of statins available in the Brazilian market (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), located in the medicine database, whose data were later added to the personal database.

Variables used and data analysis

According to socio-demographic characteristics, the proportions of statin use was verified using the following variables: gender (female and male), age group (20-39, 40-59, 60 years old or more), economic classification according to the Brazilian Business Association Research (ABEP) categorized in A/B, C, D/E, and geographic region. The use was also verified according to the number of chronic diseases considering the report of at least one chronic disease. We estimated the prevalence of the use of statin and the respective 95% confidence intervals (95% CI). Pearson's Chi-square test (Rao-Scott) compared proportions with a 5% significance level. For the statistical analysis, the post-stratification weights were considered, using the software STATA version 11.0, which already considers the complex sample design of the survey type.

Ethical Approval

The National Research Ethics Commission - CONEP approved PNAUM through registration number 398.131/2013 for national execution. All participants were clarified about the research, read, and signed the informed consent form before the interviews.

RESULTS AND DISCUSSION

The general prevalence of the use of statin Brazil for adults and the elderly population was 5.6% (95% CI 5.1; 6.1). An American study based on data from the National Health and Nutrition Examination Survey found a prevalence use of statin in the adult population of 17.23% (95% CI 15.05; 19.41), higher than the Brazilian population [14]. Considering the data from this same research, it is estimated that statins were used by 12.5 million Americans in the period 1999-2000, 24 million in the period 2003-2004 and approximately 38.7 million people in 2011-2012, showing the increase in the use of statins in this population over the years [14,15]. This can be attributed to the US National Cholesterol Education Program, which focuses on preventing cardiovascular disease.

The lower prevalence of the use of statin in Brazil compared to the American study may be related to the difficulty of access to diagnosis, which is still frequently faced by the Brazilian population [8,14]. The development and alignment of public policies for the prevention of cardiovascular diseases in the country are an important tool to ensure access to the diagnosis of dyslipidemias, their appropriate treatment, and preventive measures.

Secondary stroke prevention in patients with a previous history of this cardiovascular event also includes the use of statins. Another study carried out through the PNAUM database characterized the Brazilian population with a history of stroke and the subsequent management of this patient, indicating that only 24.2% (95% CI 19.9 - 29.1) of the population who reported a history of stroke also reported use of statins [16]. This value should be 100%. These data corroborate our observation of the need to reinforce public policies for the prevention and management of cardiovascular diseases.

Observing that 10.1% of the Brazilian adult and elderly population reported a diagnosis of dyslipidemia, and only 5.6% reported the use of statins, we can say that a portion of Brazilian with dyslipidemias is not using the pharmacological class most indicated in the clinical practice for the treatment of this health condition [8]. However, in some cases, the treatment of dyslipidemia can be performed only with non-pharmacological measures, and the existence of other therapeutic classes can be applied. As it is self-reported research, non-adherence to the proposed treatment can also contribute to the difference between the prevalence of diagnosed and untreated individuals.

Statin use was higher among women than men (7.2% versus 3.8%) and higher in elderly individuals (16.7%); an increase in use was observed depending on the age group (Table 1). A similar increase in the prevalence of statin use was observed for the number of chronic diseases in those who reported at least one disease (p-value <0.001), with five times greater among people with two diseases, and approximately twelve times greater in those with three or more diseases, when compared to those with one chronic disease (Figure 1). The higher prevalence of the use of statin by women, the elderly people, and people with chronic diseases is compatible with the prevalence of dyslipidemia in the country and with the pathophysiology of the disease [3,8,10].

Regarding the economic classification, the prevalence of use was higher in the most

economically favored individuals (A/B) with 7.3%, versus 4.3% among the most vulnerable classes (D/E). When analyzing the geographic regions, South (7.3%) and Southeast (6.5%) presented similar prevalence, as well as between the Midwest (3.9%) and Northeast (4.3%) with the lowest percentage of use identified in the North, with 1.7% (Table 1). The National Health Survey carried out in 2013 pointed out that social inequalities still impact access to the diagnosis and treatment of non-communicable diseases in Brazil [10]. Thus, the regional and economic differences observed in the use of statins may be influenced by the characteristics of organization, coverage, and provision of health services in different regions.

The treatment for dyslipidemia reduces total cholesterol and LDL-c. This decreases the risk of a first cardiovascular event or recurrence of events, such as acute myocardial infarction, angina, heart failure, stroke, or peripheral arterial disease [2]. Although studies show differences in the potency of HMG-CoA reductase inhibitors in their ability to reduce LDL-c, high-intensity therapy (mean reduction ≥50%), moderate-intensity (30-50%), and low-intensity therapy (<30%), all of them are capable of reducing cardiovascular events and deaths [4,5]. Therefore, to use the statin available at the health service and adjust the dose or, eventually, replace the medication to achieve previously established therapeutic goals are recommended [2].

Only pitavastatin was not mentioned by the interviewees among the statins. The most used statin in the Brazilian population was simvastatin with 85.4%, followed by atorvastatin 7.8% and rosuvastatin 6.1% (Figure 2). The statins fluvastatin, lovastatin, and pravastatin were mentioned and classified in the category "other statins". However, the absolute frequency of the use of these statins was not sufficient to obtain point estimates and at intervals with acceptable precision.

The higher prevalence of simvastatin use is mainly due to better evidence of mortality prevention in the treatment of dyslipidemias since it is the first line for the treatment and control of dyslipidemias [2,17] and possibly, because its easy access, available for free in public primary care pharmacies in Brazilian municipalities, according to the National List of Essential Medicines (RENAME) of the Brazilian public health system (Sistema Único de Saúde - SUS) [18,19]. Simvastatin is financed through the Basic Pharmaceutical Assistance Component of SUS offered in Primary Care, or it can be purchased at low cost through the *Programa Farmácia Popular*, which is a Brazilian Government co-payment strategy in partnership with private pharmacies [18-20]. Atorvastatin, fluvastatin, lovastatin, and pravastatin are also available in the SUS, but through the Specialized Pharmaceutical Assistance Component. They are also included in RENAME, both in the 2013 version (in force at the time of data collection) and in RENAME 2020. Rosuvastatin is not included in RENAME, and it is acquired in private pharmacies [18,19].

The limitations of this study were intrinsic to the cross-sectional design and the magnitude of this population survey. The main limitation is the fact that self-reported medication use may be subject to patient underreporting and/or abandoning drug therapy, or not presenting all medications used to interviewers. The scarcity of more Brazilian studies with the scope of PNAUM also hinders to compare with previously published results. Although the data were collected in 2013 and 2014, from the conclusion of PNAUM, there has been no new edition of this research and no other specific national research on the use of medicines.

Table 1. Characterization of the sample and prevalence of the use of statins in the Brazilian population aged 20 years or older, according to socio-demographic characteristics. PNAUM, Brazil, 2014.

Variable	Sample	Prevalence of statins use		*p*-value*
	(%)	%	95%CI	
Gender				
Female	53.7	7.2	6.5; 7.8	<0.001
Male	46.3	3.8	3.3; 4.3	
Age group				
20 to 39	45.3	0.7	0.4; 1.2	<0.001
40 to 59	36.0	5.9	5.3; 6.6	
60 or over	18.7	16.7	15.4; 18.1	
CCEB[a]				
A/B	24.2	7.3	6.1; 8.6	<0.001
C	55.1	5.3	4.8; 5.8	
D/E	20.7	4.3	3.1; 4.7	
Brazilian region				
North	6.7	1.7	1.3; 2.2	<0.001
Northeast	23.4	4.3	3.7; 5.0	
Southeast	47.4	6.5	5.6; 7.5	
South	14.7	7.3	6.5; 8.3	
Midwest	7.8	3.9	3.3; 4.6	
Total		5.6	5.1; 6.1	

[a]Classified according to Brazilian Economic Classification Criterion 2013 of the Brazilian Association of Survey Companies (*Associação Brasileira de Empresas de Pesquisa* – ABEP).

*p-value obtained by Pearson's Chi-Square test (Rao-Scott).

Figure 1. Prevalence of the use of statin among people aged 20 years old and over who reported at least one chronic disease. PNAUM, Brazil, 2014.

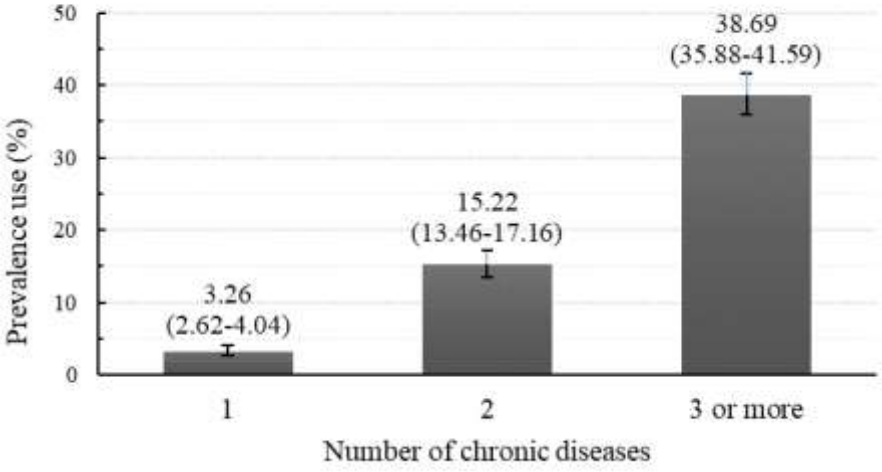
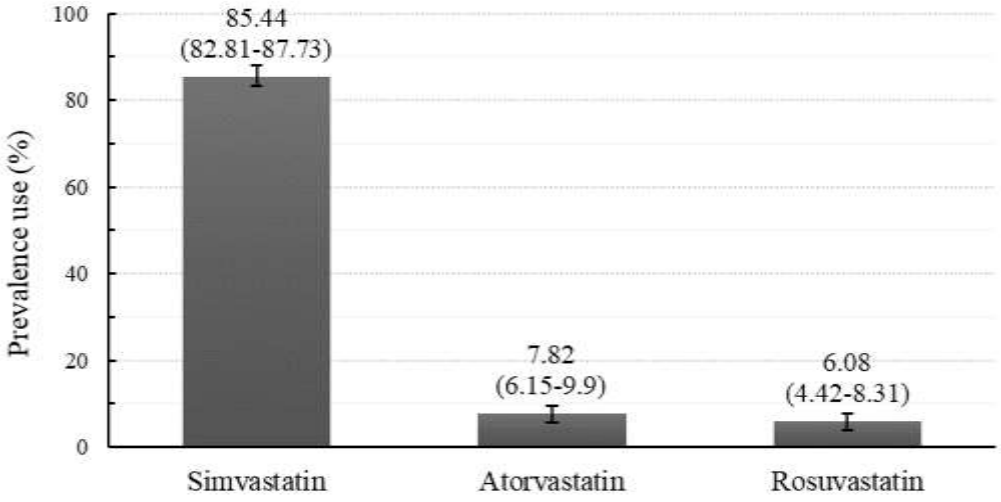


Figure 2. The most used statins in the Brazilian population aged 20 or over. PNAUM, Brazil, 2014.



A survey carried out by the Institute for Applied Research and Economics (IPEA) highlighted a decline in public investment in science and technology over the years. The 2019 Brazilian public budget was below the estimate in the early 2000s [21]. The cycle for the planning and execution of national research, like PNAUM, is long, with high investment and depends on the promotion priorities in the area of research, science, and technologies of the countries. Its periodic application would enable to compare data and show relevant estimates for public policies [22]. The set of specific data obtained by PNAUM is not included in the National Health Survey, which will be carried out periodically in the country.

This is the first population-based study with the magnitude to describe the scenario for the use of statins in the Brazilian population, contributing significantly to obtaining evidence on the treatment of dyslipidemia in the country.

CONCLUSION

We can conclude that the regional and economic differences in the use of statins are relevant and we suggest a possible relationship with the coverage and provision of health services. The results of this study can contribute to the structuring and alignment of health policies that encourage investment in access to diagnosis and promote access, compliance, and the appropriate use of statins, regardless of socio-demographic factors.

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