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Prescription Patterns of Lipid-Lowering Agents in the Community – Analysis of Primary Care Data

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Abstract

Purpose: This study aimed to analyze the prescription patterns of lipid-lowering agents in the community using primary care prescription data.

Methods: Data on drug prescriptions were obtained from the information system to support medical practice in northern Portugal Primary Care Units during 2006 and 2007. ATC/DDD methodology was used and geographical analysis was performed. Standardized prescription ratios were calculated to have age and sex standardized measures of prescription in the different northern Portugal regions.

Results: We analyzed 22 million electronic prescriptions of drugs, and 1.2 million prescriptions of lipid lowering agents, corresponding to 139 million DDD's prescribed. Prescription rates increased with age among men and women, reaching a peak at 70-74 years age group. Statins were clearly the most prescribed lipid-lowering agents, with simvastatin being the group leader. There was a distinctive geographical pattern of prescription, with a trend for coastal regions having lower prescription rates than inner regions. A wide heterogeneity among geographical regions is described regarding prescription rates.

Conclusion: Automated electronic prescription databases are an important tool to support drug utilization studies, although strategies should be developed to increase prescribers' adherence to electronic prescription systems. Lipid-lowering drugs prescription rates increased from coastal to inner regions and a wide variation among different regions was observed. Such a high heterogeneity calls our attention to the need for National standardized policies and recommendations trying to better ensure prescription quality and clinical goals.

Keywords: Lipid-lowering drugs; Statins; Prescription data; Standardized Prescription Ratio (SPR)

Introduction

Cardiovascular diseases (CVD) remain one of the most important public health problems in most industrialized countries, including Portugal, with severe consequences associated with hypercholesterolemia, one of the main risk factors for these diseases. According to the National Institute of Statistics, cardiovascular diseases caused 32.2% of the total deaths in Portugal in 2007 [1]. According to the World Health Organization (WHO) in 2002, hypercholesterolemia was estimated as the cause of 18% of global cerebrovascular disease and 56% of ischemic heart disease and 7.9% of world mortality [2].

Several studies of primary and secondary prevention have demonstrated the importance of reducing LDL cholesterol in reducing morbidity and mortality from coronary and total mortality [3,4]. Currently, lipid-lowering agents are widely used in most European countries and worldwide trying to reduce the risk of coronary events. Nonetheless, there is wide variation in the selection and use of these agents [5-9].

Data on the utilization of lipid-lowering agents are not widely available. More studies on the prescription patterns of these and other drugs, particularly in our country, are needed to better support decision making processes in a wide range of decision settings (from the individual clinical setting to the wider national regulatory or public health settings).

The National Health System (NHS) has been making a strong investment in information technology. In this context, several projects have been developed and implemented, such as the mandatory and universal use of electronic prescriptions for drugs in all healthcare units in the NHS (Hospitals and Primary Health Care facilities). This recent developments allow the implementation of studies on drug utilization, based on prescription data, that were previously very difficult to execute. Most published studies in Europe and Portugal on drugs use are based on sales and consumption data in pharmacies. There are very few studies based on prescription data.

Based on primary care electronic prescription data from Northern Portugal between January 2006 and December 2007, this study aims to analyze the prescription patterns of lipid-lowering agents in northern Portugal; analyze those patterns taking into account the different

therapeutic classes, the active substances and the geographical areas of prescription and analyze the relationship between the prescription of lipid-lowering agents and population characteristics.

Methods

This was a descriptive observational study, [10] based on data from all electronic records of prescriptions in institutions that provide primary health care in the NHS in the north of Portugal, through the information system to support medical practice (Sistema de Apoio ao Médico – SAM), between January 2006 and December 2007.

By 2007, Northern Portugal had 3,745,236 inhabitants, representing 35% of Portuguese Population. Has an administrative structure of 80 municipalities and according to the Nomenclature of Territorial Units for Statistics (NUTS) is divided into 8 NUTS III regions: Grande Porto, Alto-Trás-os-Montes, Minho-Lima, Tâmega, Ave, Douro, Cávado and Entre Douro e Vouga. The distribution of population is not homogenous: population densities are higher on the coast – urban areas. National Health Service (NHS) provides Universal coverage with 108 Primary Health Care Units, representing 31% of Continental Units.

Data collection

The SAM contains the data on drugs prescribed in Primary Health Care Institutions. Data containing variables on drug prescriptions were imported to an Oracle TM and SPSS platform (Table 1).

DDD´s calculation

In order to ensure quality and comparability of data, we used the Anatomical Therapeutic Chemical (ATC) classification index,

DESCRIPTION
Data on drug
ATC code
Drug Description
Brand name
Active Substance
Formulation
Dosage
Package
Drug Price
State partaking
Pharmaceutical company
Quantity
Number of Copies
Total DDDs
Data on patient
Patient sequential number
Sex
Birth Date
Data on prescriber
Episode number
Doctor code number
Recipe code
Consult Data
Data on prescription practice
Primary Health care Institution
Nuts III region
District
County
Town

Table 1: Main variables contained on Oracle TM and SPSS database.

which is the standard method recommended by the WHO for drugs classification [11] in drugs utilization studies. It is revised annually and uses an international unit of measurement for comparative purposes, the recommended defined daily dose (DDD). In the case of drugs with no official DDD, the mean daily dose contained in the Summary of Product Characteristics or the Portuguese official handbook for medicinal products was used [12]

To calculate the number of DDD prescribed, the amount of active substance, for each ATC code, expressed in physical units (typically mg) was previously calculated. Then we divided this amount by the DDD associated with this active substance, expressed in the same unit. Standard DDD was obtained from WHO Collaborating Centre for Drug Statistics Methodology.

To ensure that the use of lipid-lowering agents was expressed regardless of population size in the region, we calculated the number of DDD per 1000 inhabitants per day (DDD/TID), as recommended by the EURO-MED-STAT [13]. The total population for each geographical region and year studied was obtained from the Portuguese National Institute of Statistics (INE) [14].

Data quality

The electronic prescription using the SAM system has been progressively introduced in clinical practice. The data used in this study refers to the experimental electronic prescription period that was running over 2006 and 2007 in the northern region of Portugal.

Due to periods of time where the data were clearly affected by the incomplete adherence of physicians to the electronic prescription system, the first step in the study data analysis was to perform a set of data processing and cleaning procedures to ensure the quality of the analyzed data. We have done a thorough prescription trends graphical analysis for all health centers included in our database, considering monthly prescription quantities in DDDs. Based on this prescription trends graphical analysis we have observed the existence of periods with low quality prescription data that we have excluded from our analysis, because these periods could lead to prescription underestimation. Periods with low quality prescription data where defined as periods were prescription data available were clearly different from the plateau periods (period representative of the usual prescription pattern) for each health center.

Then we estimated the total amount of drugs prescribed for each active substance and each county, having into account existing Health Institutions in each region and the population sex and age distribution. After having the population stratified by sex and age, we calculated annualized DDD, for every age and sex strata, by dividing the total DDD prescribed of each sex and age stratum by the number of months selected as having adequate quality data, and multiplying by 12 months. Annualized DDD are the more appropriate form of analysis of the present data given the existing heterogeneity in time periods of adequate quality data among the included health centers. Nonetheless, it is important to underline that this method is not able to capture or adjust for seasonal variations in prescription patterns that could eventually exist.

Standardized Prescription Ratio (SPR) calculation

Prescription rates vary according to age and sex distribution of populations. We used the method of indirect standardization [15] to calculate an age and sex standardized measure of total amount of drugs prescribed and their associated costs. Using the Anatomical Therapeutic

Chemical (ATC) index we extracted electronic prescriptions for the lipid-lowering agents group. For each sex and age stratum of the Northern Regional Administration of Health (NRAH) population (reference population) we calculated the number of DDD/inhabitant prescribed (reference prescription quantity). For each NUTS III regions, we multiplied the number of males and females in a defined age stratum (categorized by five years) by the appropriate reference prescription quantity, to obtain the number of expected DDDs prescribed, given the average for reference population. The expected amount prescribed for each age/sex stratum was then summed, to obtain the expected total of lipid-lowering agents prescribed for each NUTS III region. The SPR was calculated by dividing the observed number of DDDs prescribed in the NUTS III region by the expected number, and then multiplying by 100. The SPR is a measure of the extent to which the number of DDDs prescribed in a given region is above or below what would be expected given its age and sex population distribution.

Geographical analysis

We performed a detailed analysis by county and NUTS III geographical divisions, to allow an adequate description of patterns and asymmetries among geographical regions regarding lipid lowering agents' prescriptions. As a basis for this analysis, the Northern Health Region only includes the following NUTS III geographical divisions, where data were available: Minho-Lima, Cávado, Ave, Grande Porto, Tâmega, Douro and Alto Trás-os-Montes.

Results

Lipid-lowering drugs prescription

In northern Portugal, between January 2006 and December 2007, there were 22,149,393 drugs prescriptions, corresponding to a total of 26,685,724 drug packages prescribed. Of the total number of prescription drugs, 1,201,658 electronic prescriptions corresponded to lipid-lowering agents, corresponding to a total of 1,331,365 drug packages, thus prescription of lipid-lowering agents represented 4.5% of total prescription drugs.

Of the total prescribed drugs in institutions providing primary health care in the national health system in the north of Portugal, simvastatin appears as the second most prescribed drug with a total of 509,265 electronic prescriptions, corresponding to 2.3% of all prescriptions.

The average age of the population who were prescribed lipid-lowering agents is 63 years with standard deviation of 13.8 years, with 60% of individuals over 65 years of age. In 51% of cases the drugs were prescribed to a female subject.

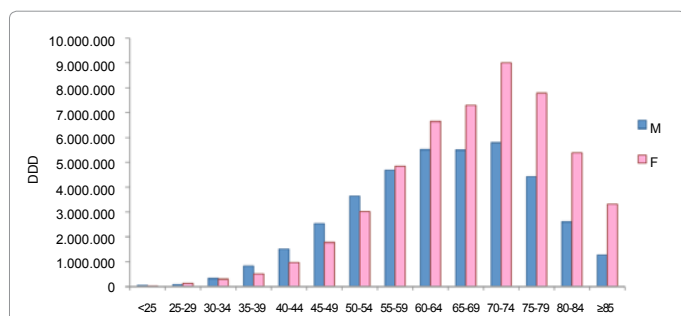Prescription of lipid-lowering agents varied with age (Figure 1). In

both men and women, prescription was lowest among those with less than 20 years of age. Prescription increased with age and was highest among those aged 70-74 years. Subsequently, prescription decreased in the elderly (≥ 75 years). This pattern was similarly observed for men and women, although prescriptions were more common in males until the 50-54 years category and for 55 years or older categories females had higher prescription rates.

An in-depth analysis of lipid-lowering drugs showed very different levels of prescription among the various therapeutic classes. Statins were clearly the most prescribed with 97 DDD/TID. Fibrates were the second most prescribed with 8 DDD/TID. Other drugs, combinations, Bile acid sequestrants and nicotinic acids represented a small proportion with 1.17 / 1.10 / 0.01 and 0.01 DDD/TD, respectively.

Detailed analysis of statins by active substance showed individual variations between the different statins. Simvastatin was the most prescribed statin in northern Portugal with 54 DDD / TID. The second was Pravastatin with 13 DDD/TID. Next, Fluvastatin and Atorvastatin had 10 DDD/TID each. Finally, Rosuvastatin (last statin to enter the market) and Lovastatin had 8 and 2 DDD/TID, respectively.

Geographic analysis of prescription data

Results showed, for the time period analyzed, differences between NUTS III regions analyzed, with Alto-Trás-os-Montes having the highest amount of lipid-lowering agents prescribed and Ave region the lowest prescription rate (Figure 2). Differences in prescription among regions can be also seen in a detailed geographical analysis by county
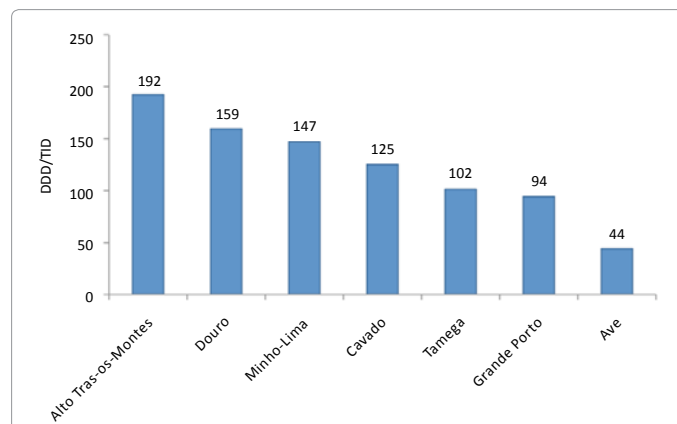

Figure 2: Lipid-lowering agents prescription in DDD/TID by northern Portugal NUTS III regions during 2006-07.
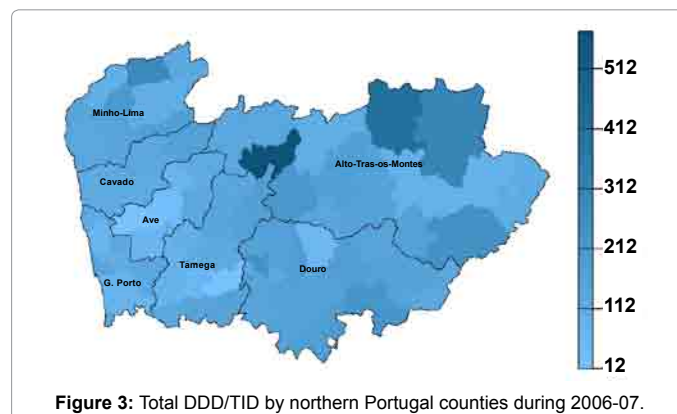

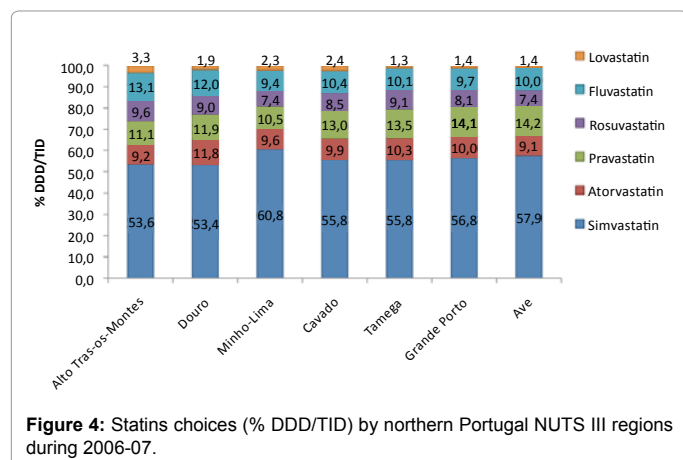**Figure 3:** Total DDD/TID by northern Portugal counties during 2006-07.

Figure 1: Prescriptions in DDD by sex and age in northern Portugal (2006-07).

Figure 4: Statins choices (% DDD/TID) by northern Portugal NUTS III regions during 2006-07.
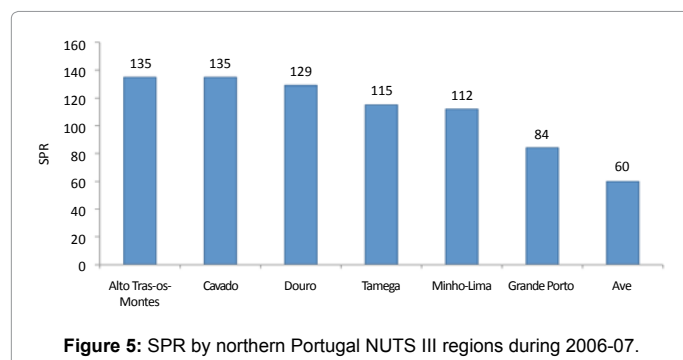

Figure 5: SPR by northern Portugal NUTS III regions during 2006-07.

(Figure 3). The geographical image suggests a pattern where the coastal regions have lower prescription rates than inner regions. However, this is not a clear linear pattern, although it is evident the existence of some important prescription heterogeneity among counties and, consequently, among NUTS III regions.

Although there is wide variation in the amount of statins prescribed, there was not a significant variation in statins choices pattern among the different NUTS III regions (Figure 4).

Data about prescriptions should be interpreted as a function of the age and sex structure of the populations or regions compared. Next, a descriptive analysis regarding sex and age standardized prescription ratios, as previously defined, is presented in order to more adequately describe and better comprehend the prescription patterns among the regions studied. Analyzing the SPRs for total lipid lowering agents prescribed (Figure 5), we could see that prescriptions in Alto Trás-os-Montes were higher than expected given the population structure and in Ave region the observed results were almost half the expected for the sex and age distributions of the populations.

Discussion

The results of this study indicate that lipid-lowering agents are a group with great pharmacological relevance in the global prescription of drugs in the northern region of Portugal, representing 4.5% of total prescription drugs. This is in accordance with data on sales of lipid-lowering agents in Portugal indicating that these are the third group of best-selling drugs [16].

There was an influence of age and sex in prescription patterns, as reported in other studies [17-20]. The number of prescriptions per patient rises with age and is higher in women than in men. This is consistent with published data showing that prescription increases with age and the frequency of prescription in women was 23% higher than in men (RR 1.23, 95% CI 1.11-1.337, p< 0,001) [21]. Less than 55 years old men were prescribed more lipid-lowering drugs than were for women. Based on pharmacoepidemiological data, this finding was also expected [22,23]. Women are prescribed more lipid lowering drugs for age strata higher than 55-59 years, as was also reported by Roe et al [19]. The different course of gender-specific prevalence of hypercholesterolemia by age might be caused by estrogen deficiency in postmenopausal women. It has been extensively described that menopause is highly associated with an unfavorable lipid profile [24-28]. The highest prescription rates were observed in those aged 70-74 years. This was not surprising, since the risk of coronary heart disease is high in this age group. As previously observed by other authors, in the elderly (over 75 years of age), prescription rates were similar to patients aged 50-69 years [29,30].

Within Lipid-Lowering agents, statins were clearly the most prescribed group. The use of fibrates (ATC code CA10AB) was far lower than that of statins and other agents (C10AC/C10AD/C10AX and C10BA) were very rarely used. This tendency is also seen in other European countries [9,31] and suggests a more rational use of lipid-lowering drugs with a higher prescription of first-line drugs for the treatment of dyslipidemia – statins (this is recommended as the most effective and better tolerated therapy for lowering LDL-C) – together with the reduced use of older, less effective drugs [32]. The major prescription of statins follows changes in clinical guidelines for the treatment of dyslipidemia, aimed at lowering cholesterol levels and preventing cardiovascular disease [4,33]. This may also have been prompted by evidence from several clinical studies on statins that demonstrated their efficacy and low rate of adverse effects and the development of new indications, together with aggressive marketing of this class of drugs by the pharmaceutical industry [34]. It may be that growing health concerns among the general population and physicians in particular [35] together with earlier and more effective screening and/or diagnosis, have contributed to the trend of increasing statin prescription, a result of the growing awareness that active treatment of hypercholesterolemia significantly reduces the risk of morbidity and mortality from coronary disease. Governmental policies, particularly the inclusion of statins in the list of drugs reimbursed by the health system and the promotion of generics, may also have contributed to this development.

Within statins pharmacological group, simvastatin was the most prescribed active substance. These findings are consistent with data from sales in Portugal [16]. We can observe this trend in some other European countries, although with variations [9].

There are numerous different drugs on the market, which means that general practioners usually have a choice of several different drugs even when treating the same health problem. Much research has focused on the relation between physician characteristics and drug prescribing. General physician characteristics, such as age, gender or year of graduation, are sometimes found to be associated with specific prescribing patterns but these findings are not consistent [36-38]. Moreover, these characteristics cannot be modified. Others have looked at internal factors related to the prescribing process, such as knowledge, attitudes and personal experience of the prescriber, showing that treatment choices are not always the result of carefully reasoned decision making [39-41]. External factors, such as commercial information sources and the professional network, may influence drug choice and adoption of new drugs. The circumstances in which the practitioner

develops his work in interaction with industry, health authorities, colleagues and patients, may influence his prescription [42,43]. Marketing can be important in drug choice: for example, pravastatin has been used relatively less in most countries, where its marketing is weak, but its use has been high in Ireland, where the local company affiliate is strong [7]. In Portugal, simvastatin marketing has been the strongest, with 98 different laboratories marketing simvastatin.

Portugal has not been the European country with higher statins utilization, being below countries such as Finland, Denmark or Ireland [44]. The differences may result from several factors, such as variations in the prevalence and/or incidence of CVD or in demographic, cultural or socioeconomic characteristics. The lower use in Portugal may reflect lower morbidity [45], as in other Mediterranean countries like Italy and Spain, or it could be due to fewer patients being treated, administration of lower doses, or discontinuation of therapy [46], issues which should be addressed in future studies. The physician's adherence to the computerized prescription system may be also, in our context, a plausible explanation for the lower prescription that we found, although we are convinced that the adjustments and data processing implemented and previously described adequately corrected most of this problem.

Our analysis demonstrates that statin prescription has a wide variation by geographic location within Portugal, with rates increasing as we move from coastal regions to more inner regions of the country. Alto Trás-os-Montes was the NUTS III region with higher prescription rate and Ave had the lowest prescription rate. Although there was important variation of the amount of lipid-lowering drugs prescribed, there was not a significant difference on the pattern of statins choices between regions of northern Portugal.

When we compare prescription data across regions, we should have in consideration that age and sex distribution among regions may be not similar and thus some of the differences found may be explained by population structure. To remove the effects of differences in age and sex distributions we standardized the aggregated data of prescription for the population structure [15]. While the population is mainly older in Alto Trás-os-Montes region, the greater use of statins does not appear to be attributable to the age and sex structure of the population alone, because the prescriptions observed were higher than we expected giving the population structure. Although Ave region has a small prescription per inhabitant and a younger population, it was expected almost twice of the prescription rate giving the age and sex population structure.

This study had some limitations worth noting. First, it should be underlined that although extensive data processing and cleaning and appropriate data analysis procedures were implemented, results presented may be partially related to differential prescription data quality among geographical regions and heterogeneity in physician's adherence to the electronic prescription system. Nevertheless, is important to note that the automated electronic prescription system, along the time span of our study, was already being effectively used by 93% of the studied prescribers, and no major differences among the NUTS III regions existed regarding this percentage. Second, analysis was performed on the available data from 2006 and 2007, which could be outdated given the constant change in drug utilization patterns among populations; however we are planning to update this analysis and perform a comparative trend analysis with more recent data in the near future.

In conclusion, this study demonstrates the utility of clinical automated databases to facilitate the study of prescription drugs in primary care settings. The selection of complete prescription data on the studied region had the advantage of including a representative sample of the entire population allowing complete information about drugs currently prescribed. Lipid-lowering agents are a group with great relevance, due mainly to the large amount of statins prescribed. This study allowed the analysis of prescription patterns taking into account geographical distribution and characteristics of the populations (sex and age). Prescription rates increased from coastal regions to inner regions, and we have shown a wide variation among different regions in the amount prescribed, but a clear stable pattern of statins choices among analyzed regions. The existence of such a high heterogeneity at the regional level calls our attention to the need for National standardized policies and recommendations trying to better ensure prescription quality and clinical goals. Finally, primary care prescription data can provide new opportunities to study different aspects of drug therapy in individual users. For this, the prescriber's role is essential, as an agent that determines the quality of the prescription record. It is also important to develop strategies to increase adherence to electronic prescription systems.

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