Prescription Patterns and Costs of Lipid-lowering Agents in Northern Portugal – Analysis of Primary Care Data

FACULTY OF MEDICINE, UNIVERSITY OF PORTO, PORTUGAL

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MASTER IN HEALTH EVIDENCE AND DECISION MAKING

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Preamble

This research project was carried out during the Master in Health Evidence and Decision Making, at the Faculty of Medicine – University of Porto, under the supervision of Professor Altamiro da Costa Pereira and Dr. Luís Filipe Ribeiro Azevedo.

In my daily work in an Intensive Cardiac Unity I observe the patients' difficulties in dealing with the financial burden of cardiovascular drugs that are generally expensive. My concern about cardiovascular drugs prescription patterns had its basis on several reports analyzing the number of prescriptions and choices of drugs, which show a wide variation in the selection and use of these drugs. The current concern about the rising costs of drugs also stimulated an exploration of data on cardiovascular drugs prescription costs, aiming at describing and explaining current local prescription costs patterns.

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Outline

This thesis consists of eight distinct topics. In the first three topics, the rationale, the objectives and background information about drug use research and dyslipidemia and its pharmacologic treatment are presented.

Topic 4 presents the methods used for drugs prescription and cost patterns analysis. In this topic we describe how the data were collected, presenting considerations on the quality of data. We discuss the methods used to calculate the number of Defined Daily Doses (DDD's) prescribed and their costs, as well as the methods for Standardized Prescription Ratios (SPR's) and Standardized Prescription Costs Ratios (SPCR's) calculation. Methods for geographical data analysis are also described.

In topic 5 results are presented. We show the results of lipid-lowering agents prescription and cost patterns analysis, also presenting a comparative analysis with other European Countries. Results regarding geographical pattern analysis are also presented.

In Topic 6 results are discussed. The discussion is presented taking into account the prevalence of dyslipidemia in the community and the frequency of use of lipid-lowering agents and their costs..

Topics 7 and 8, present the conclusions of this thesis, and recommendations for future work.

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Scientific Results

Original articles submitted for publication to the Journal Pharmacoepidemiology and Drug Safety:

Prescription patterns of lipid-lowering agents in northern Portugal – Analysis of Primary Care Data .

Prescription costs of lipid-lowering agents in northern Portugal – Analysis of Primary Care Data .

Summary

This study aimed to analyze the prescription patterns and costs of lipid-lowering agents in northern Portugal between 2006 and 2007.

Data on drug prescriptions were obtained from the information system to support medical practice in northern Portugal Primary Care Units. ATC/DDD methodology was used and geographical analysis was performed. Standardized prescription ratios and standardized prescription costs ratios were calculated to have age and sex standardized measures of prescription in the different northern Portugal regions. For each active substance it was calculated the cost/DDD and results of prediction models about cost savings related with brand or active substance substitutions are presented.

We analyzed 22 million electronic prescriptions which correspond to 139 million DDD's prescribed and a total spending of € 82 million. The prescription rates and costs increased with age among men and women, reaching a peak in the range of 70-74 years. Statins were clearly the most prescribed lipid-lowering agents, with simvastatin being the group leader. Despite higher total cost (€34 million), simvastatin had the lowest cost/DDD (0.49 €/DDD). There was a distinctive geographical pattern of prescription and prescription costs, with a trend for coastal regions having lower prescription rates and costs than inner regions. If we choose the brand name with the smallest price within the same active substance or simvastatin instead of another statin, we could have a considerable impact on drug costs to the Portuguese Healthcare System with a total annual estimation of national cost savings of 53 or 27 million €, respectively. Although we have to be very cautious interpreting cost savings resulting from brand or active substance substitutions, these results show that there is a large margin for significant cost savings if drug cost is appropriately considered in the prescription decision making process.

Primary Care prescription data can provide new opportunities to study different aspects of drug therapy in individual users. The choice of drugs and brand names is very important and should be made taking into account the specific objectives for each patient but also the best cost-benefit ratio.

1. Rationale

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 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]

Given the public health impact of this issue, several measures have been taken to prevent or treat cardiovascular disease. Several studies of primary and secondary prevention have, for example, demonstrated the importance of reducing LDL cholesterol in reducing morbidity and mortality from coronary and total mortality. [3, 4] As such, professional and scientific societies of many countries have issued a set of standards for the detection and treatment of dyslipidemia. [5, 6]

Currently, lipid-lowering agents are widely used in most European countries to try to reduce the risk of coronary events. Nonetheless, there is wide variation in the selection and use of lipid-lowering agents. [7-11] In the treatment of dyslipidemia there are several pharmacological options currently available, with different active substances, but also with very different marketing and associated costs. Hence arises the need for a culture of medicine based on valid scientific evidence and solid clinical experience.

As such, the central question emerges: is the choice of lipid lowering agents (the active substance and brand name) and the prescribed dose done taking into account the specific clinically relevant objectives for each patient and the need to offer the option with the best cost-benefit ratio?

Data on the extent of use and costs of lipid-lowering agents are not widely available. More studies on the prescription patterns and costs 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.

2. Objectives

Given the concern with (1) the wide variation in the selection and use of lipid-lowering agents, (2) the growth in public health sector spending associated with these agents and (3) the need to promote their rational use while warranting the most effective and efficient prevention of cardiovascular diseases morbidity and mortality, this study aimed to characterize the prescription patterns and costs of lipid-lowering agents in northern Portugal between 2006 and 2007, based on primary care prescription data.

Therefore the specific objectives of this study were:

1) Analyze the prescription patterns and costs of lipid-lowering agents in northern Portugal.

2) Analyze those patterns taking into account the different therapeutic classes, the active substances and the geographical areas of prescription.

3) Analyze the relationship between the prescription and cost of lipid-lowering agents and population characteristics.

4) Evaluate and propose some strategies to promote the rational prescription of lipid-lowering agents.

3. Background

3.1. Studies of drug utilization

Drug exposure and differences in the quality and quantity of drug use, can be studied through drug utilization research.

The World Health Organization (WHO) defined drug utilization as the marketing, distribution, prescription and use of drugs in a society, considering its consequences: medical, social and economic. [12] This definition goes beyond the process or pharmacokinetic aspect of drug utilization to include consideration of the various outcomes or pharmacodynamics of drug use. [13]

Drug utilization studies focus on the factors related to the prescribing, dispensing, administering, and taking of medication, and its associated events, covering the medical and non-medical determinants of drug utilization, the effects of drug utilization, as well as studies of how drug utilization relates to the effects of drug use, beneficial or adverse. [14]

The principal aim of drug utilization research is to *"facilitate the rational use of drugs in populations". [15]* Rational use of drugs is a complex issue with a goal that is difficult to achieve, defined as follows: *"that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community".* [16]

Drug utilization research is important to be able to discuss rational drug use or to suggest measures to improve prescribing habits. Differences and changes in drug utilization patterns and costs between regions or at different times may have medical, social and economic implications both for the individual patient and for society, and should therefore be identified, explained and corrected. [12]

The interest in drug utilization studies has been increasing. This fact is related to the explosion in the marketing of new drugs, the wide variations in the patterns of drug prescribing and consumption, the growing concern about the

cost of drugs, as reflected in the increase in both the sales and the volume of prescription of drugs. [17, 18]

Drug utilization studies may be quantitative or qualitative. The quantitative approach is useful to describe the extent of use at a certain moment and/or at various levels of the health care system (national, regional, local or institutional). Can be used to estimate drug utilization in populations by age, sex, social class, morbidity, and other characteristics, and to identify areas of possible over-or underutilization. These studies are useful to provide denominators to calculate rates of reported adverse drug reactions, to monitor the utilization of drugs from therapeutic categories where particular problems can be anticipated, to monitor the effects of informational and regulatory activities (e.g., adverse events alerts, monitoring urgent safety restrictions). Drug utilization data may be used to produce crude estimates of disease prevalence (e.g., cardiovascular disease), to plan drug importation, production, and distribution, and to estimate drug expenditures. [14] In Europe, Drug utilization studies have been predominantly quantitative: for example, international studies have documented wide variations in the utilization of antidiabetic [17, 19], NSAIDs, [20], antihypertensive drugs, [17] antibiotic drugs [21] and lipid-lowering drugs [22] among European and other countries.

On the other hand, the characterization of drug utilization may be extended linking prescription data to the reasons for the drug prescription – qualitative approach. These studies include the concept of appropriateness, that must be assessed relative to indication for use, daily dose, length of therapy, contra-indications and interactions. Therefore they can document the extent of inappropriate prescribing of drugs and even their associated adverse clinical, ecological, and economic consequences. Moreover, they can also explore the percentage of drugs that adhere to the evidence-based recommendations. In North America, these studies are known as drug utilization review (DUR). [14] Another approach analyzed the number of drugs that accounted for 90% of drug utilization (DU90%) and the percentage of these drugs that adhered to the evidence-based guideline issued by the Drug Committee in the catchment area.

For example, the Swedish Medical Quality Council has recommended the DU90% method for assessing quality in drug prescribing. [23]

A considerable amount of data on drug usage is available as part of databases with administrative, commercial or clinical purposes, and specific investigations may be conducted to collect different types of information, qualitatively and quantitatively, or referring to a particular population.

3.2. Automated databases

The past two decades have seen a growing use of computerized databases containing medical care data, so-called "automated databases", as potential data sources for pharmacoepidemiology studies. These databases can often meet the need for a cost-effective and efficient means of conducting post marketing surveillance studies.

The automated databases used for research are usually generated by request for payments, or claims, for clinical services and therapies or, in contrast, generated by medical records. They may be classified as non-diagnosis-linked or diagnosis-linked. [14] While the latter consider drug utilization linked to its indications and outcomes (e.g. trends in prescribing for heart failure [24]), the former concerns only about describing drug consumption in a population (e.g. statin consumption [7]).

Claims data arise from a person's use of the health care system. When a patient goes to a pharmacy and gets a drug dispensed, the pharmacy bills the insurance company or the health system for the cost of that drug, and has to identify which medication was dispensed. Medical record databases are a more recent development, arising out of the increasing use of computerization in medical care. As medical practices increasingly integrate electronic information systems, this opens up a unique opportunity for pharmacoepidemiology, as larger and larger numbers of patients are available in such systems. [14]

These automated databases have potential for providing a very large sample size. This is especially important in the field of pharmacoepidemiology, where achieving an adequate sample size is uniquely problematic. In addition, these databases are relatively inexpensive to use, especially given the available sample size, as they are by-products of existing administrative or clinical information systems. Studies using these data systems do not need to incur the considerable cost of data collection, other than for those subsets of the populations for whom medical records are abstracted and/or interviews are conducted. These databases can be population-based, they can include outpatient drugs and diseases, and there is no opportunity for recall and interviewer bias, as they do not rely on patient recall or interviewers to obtain their data. [14]

Most of currently available data sources lack information on diagnosis and are mostly used for generating drug statistics and descriptive studies of patterns of drug consumption. Some collect data in the form of drug sales (e.g., The Portuguese National Authority for Medicines and Health Products (INFARMED), the Danish Medicines Agency, the National Agency for Medicines and Social Insurance in Finland, the Norwegian Institute of Public Health, the National Corporation of Pharmacies in Sweden,), pharmaceutical or medical billing data or all prescriptions dispensed (Prescription Pricing Authority in the UK, Spain's Drug Data Bank, Medicaid Management Information System, Portuguese health administrative regions, etc.). [25]

The information on sales available through pharmacy records is the measure most frequently used in drug utilization studies. [7, 26, 27] They provide detailed information on the drugs themselves although data on the consumer is usually very limited: information such as the indication for use or extent to which patients actually consume the drugs will remain largely unknown.

For example, the Odense Pharmacoepidemiologic Database (OPED) and the pharmacoepidemiology prescription database of the County of North Jutland are two similar databases that include about half a million inhabitants in

Denmark. [28] These databases contain all dispensed prescriptions since the early 1990s. The following information is captured for each prescription: a unique person identifier, the date of dispensing, identification of the dispensed product, the pharmacy, and the prescriber. They have been used for a number of population-based pharmacoepidemiologic surveys such as the use of the new antidepressants [29], inappropriate use of inhaled steroids in asthma treatment [30], and low use of long-term hormone replacement therapy. [31]

The Portuguese National Pharmacy Association (ANF) has created since 1994 a centre for pharmacoepidemiology studies and a database containing information on medicine consumption, based on dispensing data information from the Portuguese pharmacies. It has been conducting several drug utilization studies with a number of published work addressing different drug utilization issues such as self-medication [32, 33] and antiasthmatics use [34].

Data from general practioners (GP) records of prescriptions can be more informative about the indication for drugs prescribed, diagnoses and other health-related data, although these records are not always consistently completed. [35] An example of these type of databases is the Integrated Primary Care Information (IPIC) database, established at Erasmus University in the Netherlands, and consisting on computer-based patient records of 150 general practioners. This database has been used to study preventive strategies in patients receiving NSAIDS [36] and trends in primary care prescribing for heart failure [24].

Although these databases provide important data, some methods are needed to ensure the quality of the data and the analysis performed.

3.3. Implementation of the ATC/DDD methodology

The Anatomic Therapeutical Chemical (ATC) classification system is generally used in conjunction with the Defined Daily Dose (DDD) methodology. [15, 37]

An internationally valid classification system of drugs and a measurement system of utilization are necessary to make utilization and costs data comparable between different geographical areas that can use different active ingredients and different packages. These differences could be overcome with the ATC/DDD system. The European Drug Utilization Research Group, recommends the use of the ATC classification system for reporting drug consumption statistics and conducting comparative drug utilization research. [38]

The ATC system is a classification system that divides the drugs into different groups according to the organ or system on which they act and according to their chemical, pharmacological and therapeutic properties. Each ingredient is identified by a specific alpha-numeric code and it is possible to cluster ingredients in groups with similar characteristics according to the different ATC levels. [38]

The DDD methodology was developed in response to the need to convert and standardize readily available volume data from sales statistics or pharmacy inventory data (quantity of packages, tablets, or other dosage forms) into medically meaningful units, to make crude estimates of the number of persons exposed to a particular medicine or class of medicines. [17, 18, 37] The DDD is the assumed average daily maintenance dose for a drug for its main indication in adults. The method has been useful in describing and comparing patterns of drug utilization [17, 18], providing denominator data to estimate reported adverse drug reaction rates [39], performing epidemiologic screening for problems in drug utilization [40], and monitoring the effects of informational and regulatory activities. [41] The DDD methodology is useful for working with readily available gross statistics, allows comparisons between drugs in the same therapeutic class and between different health care settings or geographic areas, and evaluations of trends over time, and is relatively easy and inexpensive to use.

The DDD methodology should be used and interpreted with caution. The DDD is not a recommended or a prescribed dose, but a technical unit of comparison; it is usually the result of literature review and available information on use in various countries. Thus, the DDDs may be high or low relative to actual prescribed doses. Finally, DDDs do not, of course, take into account variations in compliance. [14]

Because the ATC codes and DDDs may change over time with regular revisions, researches must carefully document which version of the classification and DDD assignment is used, so that the resulting drug statistics may be adequately interpreted. [42]

3.4. Drug utilization metrics and their applications

In order to make comparable the information about drugs use, we can employ some indicators like utilization in Defined Daily Doses (DDD) that provides information on the extent of a drug used in a specific geographical area (nation or region). The Utilization in DDDs is also the basis for the calculation of “ratio” indicators, which can provide some information on the appropriateness and quality of drugs utilization. [38]

In the same way, we can obtain information about utilization in DDD / 1000 inhabitants / day (DDD/TID), that gives an estimate of the utilization of drugs in a given area (nation, region etc), which is independent of the dimensions of the population and makes possible comparisons between areas with different population sizes. [38] Sales or prescription data presented in DDDs per 1000 inhabitants per day may provide a rough estimate of the proportion of the study population treated daily with a particular drug or group of drugs. As an example, the figure 10 DDDs per 1000 inhabitants per day indicates that 1% of the population on average might receive a certain drug or group of drugs daily. This estimate is most useful for chronically used drugs**.**

Nevertheless, drugs use can be also expressed in terms of costs (e.g. national currency). Cost figures are suitable for an overall analysis of expenditure on

drugs, but have several limitations. International comparisons based on cost parameters can be misleading and have limited value in the evaluation of drug use. Price differences between alternative preparations and different national cost levels make the evaluation difficult. [15]

If we want to access to the cost paid by a health system to provide specific drugs, we need to calculate the Cost/DDD. This indicator provides information on the actual cost paid for a medicine and allows comparisons between countries (international differences in the expenditure for the same drug). It also allows comparisons between medicines with comparable licensed clinical properties allowing to calculate exact differentials within a country or between countries. [38]

3.5. Population structure adjustment

A strong relation exists between the population structure (for example age and sex) and utilization of drugs. This relationship is important when we compare drugs utilization data between regions, because some of the differences found can be related to some differences in the population structure. For example, all other variables being equal, a country with an older population will use a higher amount of drugs than a country with a younger population. Ideally, aggregated data of utilization and expenditure should be standardized for the population structure to remove the effects of the differences. [38]

The standardized mortality ratio (SMR) is a standard epidemiological tool used to compare mortality within different populations while taking into account their age and sex distribution. The standardized prescription ratio (SPR), is a standardized measure for prescription data, calculated in a similar manner to the SMR, in order to standardize prescription estimates for different population age and sex distributions. Age and sex standardized prescription ratios (SPRs) can be calculated for each geographical region by comparing the observed prescribed amount for a given drug with the respective expected amount, based on the total amount of drug prescribed in the whole sample and for each age

and sex stratum. The resultant SPRs can be expressed as percentages and can be compared with the reference value of 100 for the whole sample (standard population). [43].

3.6. Dyslipidemia and its pharmacologic therapy

Epidemiologic data have documented a continuous, graded relationship between the serum cholesterol concentration and coronary risk.[44] This is true even for younger men (eg, under the age of 40). [45] The causal role of cholesterol in this relationship is suggested by clinical trials which have demonstrated that targeted lowering of cholesterol in patients with hypercholesterolemia reduces CHD morbidity and mortality. A meta-analysis of 38 primary and secondary prevention trials, for example, found that for every 10 percent reduction in serum cholesterol, CHD mortality would be reduced by 15 percent and total mortality risk by 11 percent. [46]

High concentrations of LDL are a particularly important risk factor for atherosclerosis. [47] The Framingham Heart Study, [48] the Multiple Risk Factor Intervention Trial (MRFIT), [49] and the Lipid Research Clinics (LRC) trial [50, 51] found a direct relationship between levels of LDL cholesterol (or total cholesterol) and the rate of new-onset CHD in men and women who were initially free of CHD. The same relation holds for recurrent coronary events in people with established CHD. [52-54] Any LDL cholesterol above 100 mg/dL appears to be atherogenic.

LDL is the major atherogenic lipoprotein and has been identified as the primary target of cholesterol-lowering therapy. This focus on LDL has been strongly validated by recent clinical trials, which show the efficacy of LDL-lowering therapy for reducing risk for CHD.[55]

A low level of high density lipoprotein (HDL) is another important risk factor for atherosclerosis. [56] Low serum HDL is also associated with increased risk of CHD. In contrast, a high serum HDL (above 60 mg/dL) is cardioprotective. [57]

Hypertriglyceridemia is also associated with an increased risk for cardiovascular disease. [58] Hypertriglyceridemia is often associated with reduced levels of HDL-cholesterol. Although the risk ratios for hypertriglyceridemia in both men and women decreased when the HDL cholesterol concentration was included in the analysis, the risk ratios remained significant. An interaction between triglycerides and the total cholesterol/HDL-cholesterol ratio has been demonstrated in several studies. [59-61]. In addition, high levels of triglycerides may directly promote atherothrombosis.

A number of studies have demonstrated the ability of cholesterol lowering medications to reduce the risk of CHD in patients with hypercholesterolemia, even when given for primary prevention. A meta-analysis of primary prevention trials in which statins were administered supported these findings: statin therapy was associated with a 26 percent reduction in overall mortality that was primarily due to a 37 percent reduction in cardiovascular deaths. There was no effect upon non cardiovascular deaths. [62]

The intensity of risk-reduction therapy should be adjusted to a person's absolute risk. Hence, the first step in selection of LDL-lowering therapy is to assess a person's risk status (Table 1).

Table 1. LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents (10-year risk >20%)	<100	≥ 100	≥ 130 (100-129:drug optional)†
2+ Risk factors (10-year risk ≤ 20%)	<130	≥ 130	10-year risk 10%-20%: ≥130 10-year risk < 10%: ≥160
0-1 Risk factor ‡	<160	≥ 160	≥190 (160-189: LDL-lowering drug optional)

*From Detection, Evaluation, and Treatment of High Blood Cholesterol Education Program (NCEP) Expert Panel on Executive Summary of the Third Report of the National Cholesterol in Adults (Adult Treatment Panel III). [55]

† Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol level of 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, eg, nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

‡ Almost all people with 0-1 risk factor have a 10-year risk 10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Risk assessment requires measurement of LDL cholesterol as part of lipoprotein analysis and identification of accompanying risk determinants and secondary causes of dyslipidemia. [55]

A portion of the population whose short-term or long-term risk for CHD is high will require LDL-lowering drugs to reach the designated goal for LDL cholesterol. [55]

Actually, lipid-lowering drugs include statins, fibrates, bile acid sequestrants (anion exchange resins), nicotinic acid, and selective cholesterol absorption inhibitors (e.g. ezetimibe). The currently available drugs that affect lipoprotein metabolism and their major effects are listed in Table 2.

Table 2 Drugs affecting Lipoprotein Metabolism*

Drug Class, Agents, and Daily Dose	Lipid/Lipoprotein effects
HMG-CoA reductase inhibitors (statins)†	LDL ↓18%-55% HDL ↑5%-15% TG ↓7%-30%
Fibric acids¶	LDL ↓5%-20% (may be increased in patients with high TG) HDL ↑10%-20% TG ↓20%-50%
Nicotinic acid ‖	LDL ↑ 5%-25% HDL ↑15%-35% TG ↓ 20%-50%
Bile acid sequestrants‡	LDL ↑15%-30% HDL ↑3%-5% TG No change or increase

*Adapted from Detection, Evaluation, and Treatment of High Blood Cholesterol Education Program (NCEP) Expert Panel on Executive Summary of the Third Report of the National Cholesterol in Adults (Adult Treatment Panel III). [55]

†Lovastatin (20-80 mg), pravastatin (20-40 mg), simvastatin (20-80 mg), fluvastatin (20-80 mg), atorvastatin (10-80 mg), and rosuvastatin (10-40 mg).

¶Gemfibrozil (600 mg twice daily), fenofibrate (200 mg), and clofibrate (1000 mg twice daily).

‖Immediate-release (crystalline) nicotinic acid (1.5-3 g), extended-release nicotinic acid (1-2 g), and sustained-release nicotinic acid (1-2 g).

‡Cholestyramine (4-16 g), colestipol (5-20 g), and colesevelam (2.6-3.8 g).

Lipid-lowering agents' choice should take into account the characteristic of dyslipidemia, as indicated in Table 3. [63]

Table 3: Dyslipidemia type drug choice*

Dyslipidemia Type	First drug choice	Notes
↑ LDL	Statin monotherapy	
↑ LDL resistant to statin monotherapy	Statin + (Ezetimibe or resins) **Or** Statins at high doses	
↑ LDL + ↑ TG	**TG <200** → Statin **TG ≤ 200 <500** Low risk / medium → Statin + Diet + Exercise Very High Risk → Statin + Fibrates or Nicotinic Ac. **TG ≥ 500** → Fibrates (if refractory associate Ac. Nicotinic)	When Hypertriglyceridemia: **Objective 1**: ↓ LDL **Objective 2**: ↓ No HDL Cholesterol → HDL should be 30 mg / dl above value of LDL to achieve **If TG ≥ 500** 1st goal shall be to prevent acute pancreatitis The fibrates are particularly useful in diabetic and in insulin resistance (as observed in Metabolic syndrome)
↓ HDL (<40)	Nicotinic Acid is what has higher ↑ HDL (15-35%) 2nd option: Fibrates	Treatment is reserved for: - People with Coronary Heart Disease or equivalent - Metabolic syndrome

*Adapted from Dyslipidemia (Manual of Good Practice) [63]

Statins are the most efficient and better tolerated drug class for the treatment of dyslipidemia. For this reason they should be considered as the first line drugs in the most cases of dyslipidemia. [64] Currently there are six statins commonly used for this indication, including lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin. All have a similar therapeutic effect (class effect). However, the differences in their chemical structures, pharmacokinetics, and relative efficacy in lipid-lowering led to the question of their therapeutic equivalence. In a meta-analysis [65], results showed that statins can be made therapeutically equivalent in reducing LDL by appropriate adjustment of dose. Atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40/80 mg, and simvastatin 20 mg are equivalent in decreasing LDL-C by 30-40%; and fluvastatin 40 mg, lovastatin 10/20 mg, pravastatin 20/40 mg, and simvastatin 10 mg were similar in reducing LDL-C by 20-30%. Rosuvastatin at 10 mg or higher dose and atorvastatin at 20 mg or higher dose could reduce LDL-C by more than 40% (Table 4) The HDL-elevating and triglyceride-lowering effects were similar among different statins at equivalent doses.

Table 4 Low density lipoprotein (LDL) reduction (%) of different statins in different doses*

LDL reduction (%)	Atorvastatin (mg)	Fluvastatin (mg)	Lovastatin (mg)	Pravastatin (mg)	Rosuvastatin (mg)	Simvastatin (mg)
>40	>20	-	-	-	>5	>40
30-40	10	80	40/80	-	-	20
20-30	-	40	10/20	20/40	-	10
<20	-	20	-	10	-	-

* Data from a systematic review and meta-analysis on the therapeutic equivalence of statins. [65]

Analyzing the weighted mean difference (WMD) with 95% confidence intervals (CI) of the different statins at equivalent doses, meta-analysis [65] indicate that there was not significant heterogeneity for most paired comparisons, except for studies comparing pravastatin 40 mg to simvastatin 10 mg (p=0.07). Most of the differences between statins in lipid-lowering effects at the specified doses were small (Table 5).

Table 5 Weighted mean difference (WMD) with 95% confidence interval (CI) of different statins at equivalent dose*

Statin 1	Statin 2	Studies included (N)	Total Pt. (N)	WMD[a] (statin 1-statin 2) % (95% C.I.)	Heterogeneity test[b]
LDL ↓30–40%					
Atorvastatin 10 mg	Lovastatin 40 mg	1[66]	89	7.00 [2.87,11.13]	None
Atorvastatin 10 mg	Lovastatin 80 mg	1[66]	84	-10.00 [-15.25,-4..75]	None
Atorvastatin 10 mg	Simvastatin 20 mg	11[66-76]	5075	2.17 [1.20,3.14]	0.43
Fluvastatin 80 mg	Lovastatin 80 mg	1[77]	52	- 9.00 [-17.01,-0.99]	None
Fluvastatin 80 mg	Simvastatin 20 mg	1[78]	94	- 4.00 [-10.15,2.15]	None
Lovastatin 40 mg	Simvastatin 20 mg	2[66, 79]	334	- 3.61 [-5.73,-1.48]	0.85
Lovastatin 80 mg	Simvastatin 20 mg	1[66]	60	13.00 [7.36,18.64]	None
LDL ↓ 20–30%					
Fluvastatin 40 mg	Lovastatin 10 mg	1[80]	334	1.00 [-1.70, 3.70]	None
Fluvastatin 40 mg	Lovastatin 20 mg	3[66, 80, 81]	496	- 4.81 [-7.25, -2.36]	0.77
Fluvastatin 40 mg	Pravastatin 20 mg	2[66, 82]	179	-0.38 [-3.89,3.13]	0.82
Fluvastatin 40 mg	Pravastatin 40 mg	2[66, 77]	87	- 9.37 [-14.50, -4.24]	0.45
Fluvastatin 40 mg	Simvastatin 10 mg	2[66, 83]	300	- 4.01 [- 4.77,- 3.26]	0.76
Lovastatin 20 mg	Pravastatin 20 mg	4[66, 77, 84, 85]	393	- 1.10 [- 3.05,0.86]	0.30
Lovastatin 20 mg	Pravastatin 40 mg	1[66]	41	- 5.00 [- 12.28, 2.28]	None
Lovastatin 20 mg	Simvastatin 10 mg	6[66, 79, 85-88]	1773	- 3.50 [- 4.70, -2.31]	0.22
Pravastatin 20 mg	Simvastatin 10 mg	5[66, 73, 85, 89, 90]	945	- 3.87 [- 4.62, -3.12]	0.96
Pravastatin 40 mg	Simvastatin 10 mg	2[66, 73]	421	2.27 [0.31, 4.23]	0.07

[a]WMD (weighted mean difference) is he difference between statin 1 and statin 2 in the specified outcome, weighted by sample size of each study.

[b]Heterogeneity between studies was assessed with the Cochrane Q-test where a P-value of <0.10 suggests possibly non-ignorable heterogeneity.

* Data from a systematic review and meta-analysis on the therapeutic equivalence of statins. [65]

In conclusion, at comparable doses, statins are therapeutically equivalent in reducing LDL-C. So, the choice of statin should be based on the percentage reduction of LDL to be achieved.

Fibrates lower triglycerides and increase HDL quite effectively but they lower total and LDL-cholesterol much less than statins. Since the evidence from clinical trials supporting the wide-spread use of fibrates was not as good as that supporting statins, they were considered useful only for treatment of dyslipidemic patients with low HDL, high triglycerides, and other characteristics of the insulin resistance syndrome and type 2 diabetes. [91]

Nicotinic acid is also an effective lipid-lowering agent, although it may be difficult to use and has some annoying side effects. However, data suggest that it is more effective in increasing HDL-Cholesterol than fibrates. [92]

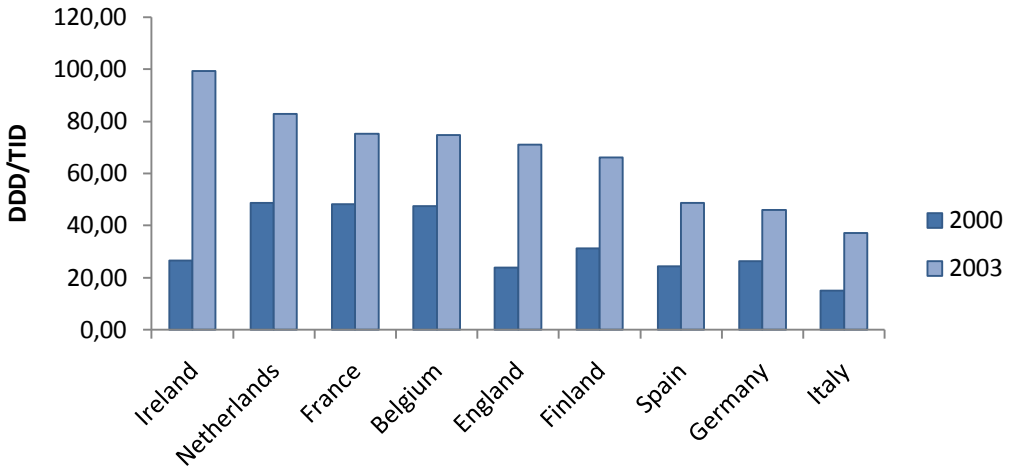
Bile acid sequestrants also decrease total and LDL cholesterol, but tend to increase triglycrides. [93, 94]

In some patients, combination therapy with different lipid-lowering drugs is necessary to achieve the established treatment goals. Sometimes, goals cannot be reached even on maximal lipid-lowering therapy, but they will still benefit from treatment to the extent to which cholesterol has been lowered. [93, 94]

3.7. Prescription and lipid-lowering choices in Europe

According to Walley et al. [11], based on Administrative Data, during the period 200-2003, the use of lipid-lowering agents increased in all European countries studied, mainly due to the increased use of statins (Figure 1), which dominate the market in all countries. The median increase in utilization (DDD/1000/day) was about 35% per year.

Figure 1 Statin utilization in 2000 and 2003 in nine countries*

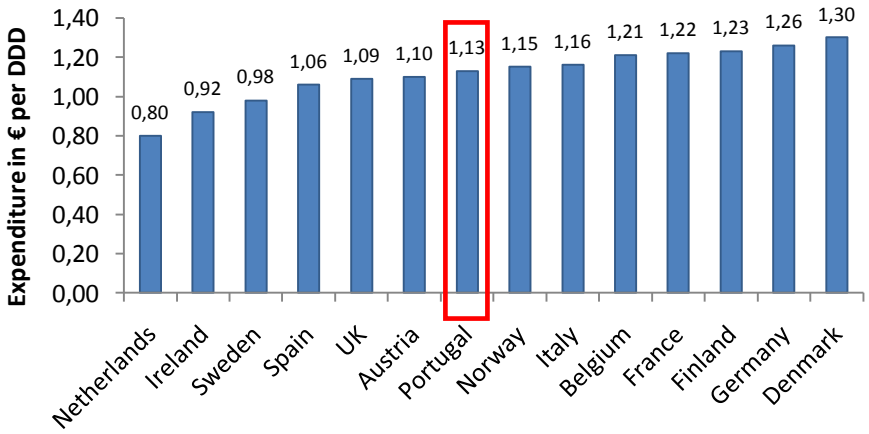


*Adapted from Walley, 2005 [11]

In Portugal, in a study by Teixeira et al. [95], between 1995 and 2004, a high increase of lipid-lowering agents is described (especially since the year 2000), in terms of defined daily doses per 1000 inhabitants per day (DDD/TID) of 10.21 to 67.93 DDD/TID, mainly due to increased use of statins.

Data from the EURO-MED-STAT in 2000 also showed significant variations in the use and prescribing patterns of statins among the different European countries, which are also described in relation with expenditure per DDD's (Figure 2). [96, 97]

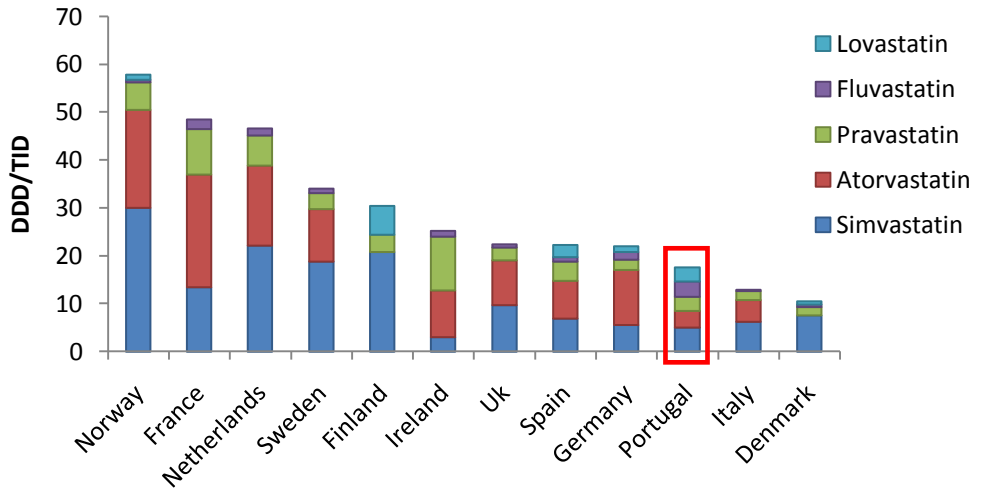
Figure 2 Statin expenditure in €/DDD in 2000*



*Data from EURO-MED-STAT. [96, 97]

The market leader varied in different countries, but the most common were simvastatin and atorvastatin. [11] This is also seen in EURO-MED-STAT data, as described in figure 3.

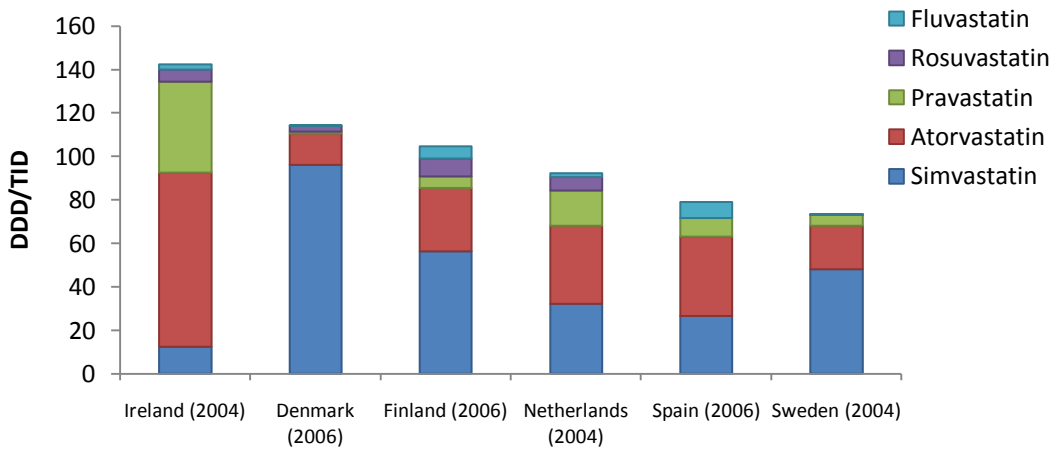
Figure 3 Statins choices in European countries in 2000*



*Data from EURO-MED-STAT. [96, 97]

However, given the high increase in the use of statins, these figures are outdated. For example (Figure 4), data from the EURO-MED-STAT on the use of statins in 2006 in Finland and Denmark and data of 2004 in Sweden, Ireland and Netherlands show values much higher if we compare them with data from 2000. [97, 98] The same is seen in Spain in 2006. [99]

Figure 4 Statins choices in Europe. Data from 2004 and 2006*



*Data from EURO-MED-STAT [97] and lipid-lowering drugs use in Spain [99].

4. Methods

This was a descriptive observational study, [100] 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.

4.1. 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 SPSS platform (Table 6).

Table 6: Main variables contained on SPSS database

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
Data on Cost
Total cost
Total state partaking

4.2. DDD´s and Costs Calculation

In order to ensure quality and comparability of data, we used the Anatomical Therapeutic Chemical (ATC) classification index, which is the standard method recommended by the WHO for drugs classification [101] 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. [102]

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 (Table 7).

Table 7: Standard DDDs from WHO Collaborating Centre for Drug Statistics Methodology

Name	DDD	Unity
Atorvastatin	10	mg
Benflurex	150	mg
Bezafibrate	0,6	g
Ciprofibrate	0,1	g
Colestipol	20	g
Colestyramine	14	g
Etofibrate	0,5	g
Ezetimibe	10	mg
Fenobigrate	0,2	g
Fluvastatin	40	mg
Gemfibrozil	1,2	g
Lovastatin	30	mg
Nicotinic acid	2	g
Omega-3-triglycerides incl. other esters and acids	1	g
Pravastatin	20	mg
Rosuvastatin	10	mg
Simvastatin	15	mg
Simvastatin and ezetimibe	15	mg

Costs were analyzed calculating the cost/DDD for each active substance, based on the market price for each prescription item, as recorded at the time of prescription on the SAM database, in accordance with the national official drug prices database (INFARMED). This indicator allows comparisons between drugs with comparable licensed clinical properties allowing to calculate exact differentials within a country or between countries. [38]

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) and the Cost per 1000 inhabitants per day (€/TID) for each active substance, as recommended by the EURO-MED-STAT. [38] The total population for each geographical region and year studied was obtained from the Portuguese National Institute of Statistics (INE).

Finally, two sets of prediction models were created to evaluate the impact, regarding cost savings, that could be associated with prescribed brand or active substance substitutions. First, for each active substance we calculated the total savings that would result if we substituted the brand name of each prescription for the brand name with the lowest cost/DDD. In this analysis we have neither considered the potency equivalence, regarding efficacy in LDLc reduction, among DDDs of different active substances, nor the existence of doses of active substances that may not be, in certain cases, replaced. Thus, this analysis does not imply that the simulated substitutions are always recommended. It is however a forecasting exercicise that allow us to estimate the impact that the selection of the brand, within the same active substance, may have in reducing costs associated with its utilization.

Second, we analyzed the cost savings that would result if we substituted any other statin prescription for a simvastatin prescription, using as reference the mean cost/DDD of simvastatin. We performed this analysis based on the fact that simvastatin has the lowest cost/DDD among statins and based on the assumption that in most patients with dyslipidemia we could get the necessary and recommended percent reduction of LDL-C with the use of simvastatin. This

active substance may achieve 40 % reduction in LDL-C, as previously indicated [65], and this percent reduction is appropriate for the goals of the majority of patients with dyslipidemia. This forecasting exercise allow us to estimate the impact that prescribed active substance substitution might have on cost savings regarding statins utilization.

These prediction models are for illustrative purposes and are based on the assumption that the proposed substitutions could actually take place in the clinical setting. Of course in many cases that may not be the case, the simulated substitutions may not be the most appropriate clinical decision or they may not even be possible. Although their interpretation must be made with caution, these models allow us to estimate cost savings that, at least in part, may easily be achived in practice, for example through educational initiatives aiming to raise physicians awareness about statins prescription appropriateness and costs based on an adequate individual risk assessment for each patient.

4.3. 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 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 (Concelho), having into account existing Health Centres in each region and the population sex and age distribution. After having the population stratified by sex and age, we calculated annualized DDD and annualized costs, for every age and sex strata, by dividing the total DDD prescribed and total costs of each sex and age stratum by the number of months selected as having adequate quality data, and multiplying by 12 months. Annualized DDD and costs 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.

4.4. SPR´s and SPCR´s Calculation

Prescription rates vary according to age and sex distribution of populations. We used the method of indirect standardization [43] 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.

We used the same method to calculate Standardized Prescription Cost Ratios (SPCRs). The SPCR is the ratio of observed to expected prescription costs for each region expressed as a percentage.

4.5. Geographical analysis

We performed a detailed analysis by county (Concelho) and NUTS III geographical divisions, to allow an adequate description of patterns and asymmetries among geographical regions regarding lipid lowering agents prescription and their associated costs. 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.

5. Results

5.1. Lipid-lowering drugs prescription

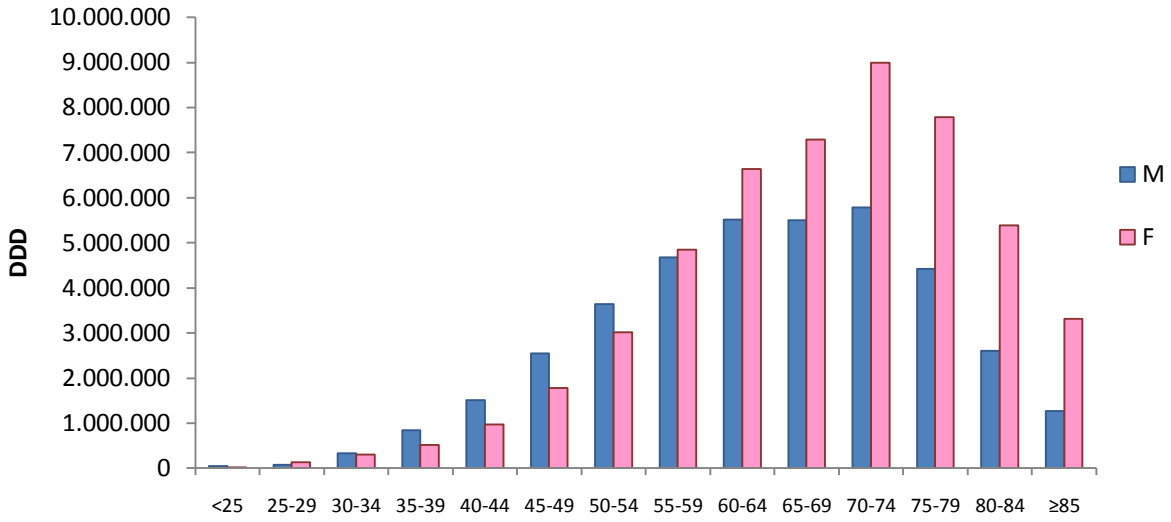
In northern Portugal, between January 2006 and December 2007, 22.149.393 electronic drug recipes were prescribed and recorded in the system, corresponding to a total of 26.685.724 drug packages. Of the total number of prescription drugs, 1.201.658 electronic prescriptions corresponded to lipid-lowering 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.

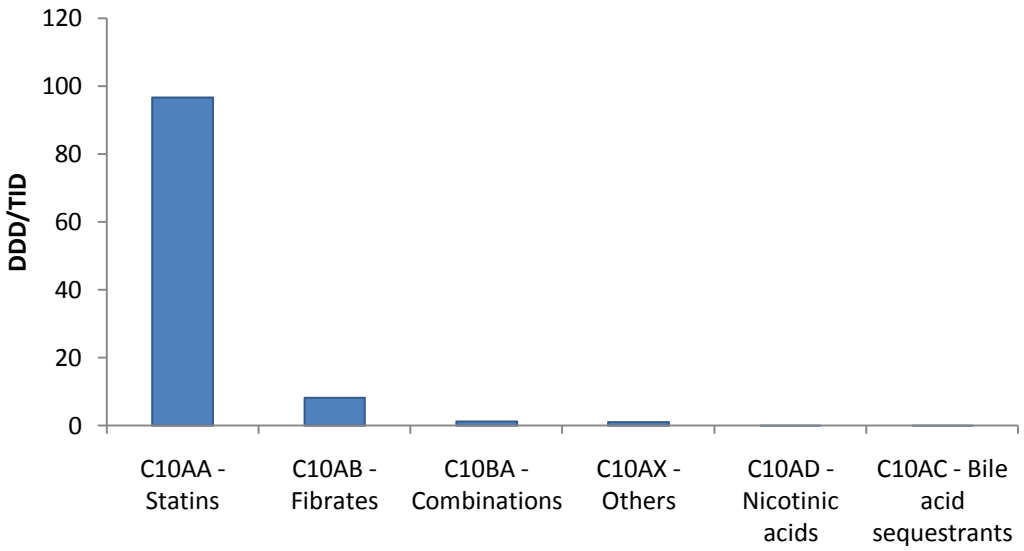
Prescriptions varied between age categories (Figure 5). In both men and women, prescription was lowest among those less than 20 years of age. Prescription increased with age and was highest among those age 70-74 years. Subsequently, prescription decreased in the elderly (≥ 75 years). This pattern was observed in all calendar years and was similar for men and women, although with prescriptions being more common in males until 55 years of age when started to be higher in womens.

Figure 5 Prescriptions in DDD by sex and age in northern Portugal (2006-07)



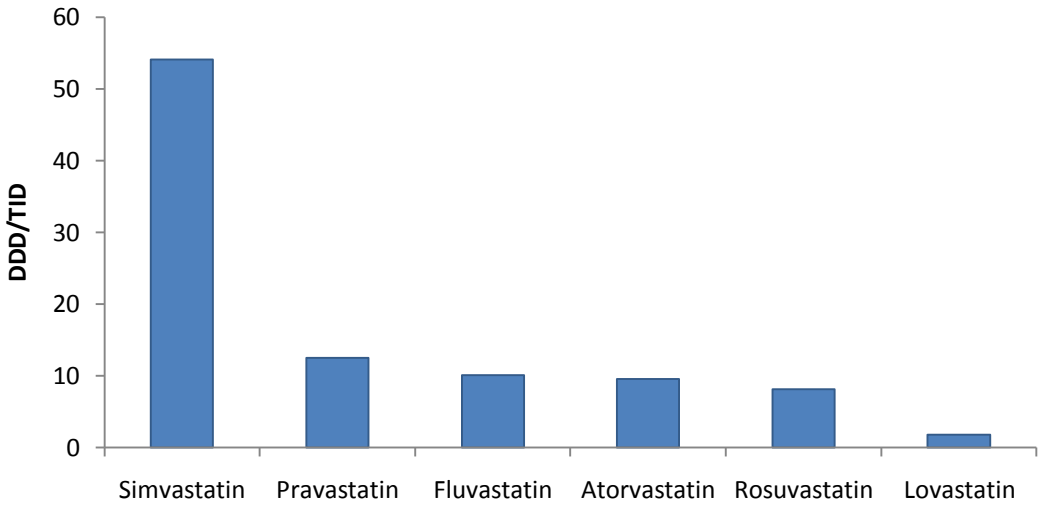
An in-depth analysis of lipid-lowering drugs showed very different levels of prescription among the various therapeutic classes (Figure 6). Statins were clearly the most prescribed with 97 DDD/TID. Fibrates were the second most prescribed with 8 DDD/TID. Other drugs, combinations, Bile acid sequestrants and nicotinic acids were a small proportion with 1.17 / 1.10 / 0.01 and 0.01 DDD/TD, respectively.

Figure 6 Lipid-lowering agents prescriptions in northern Portugal during 2006-07 by therapeutic group, annualized DDD/TID for each group



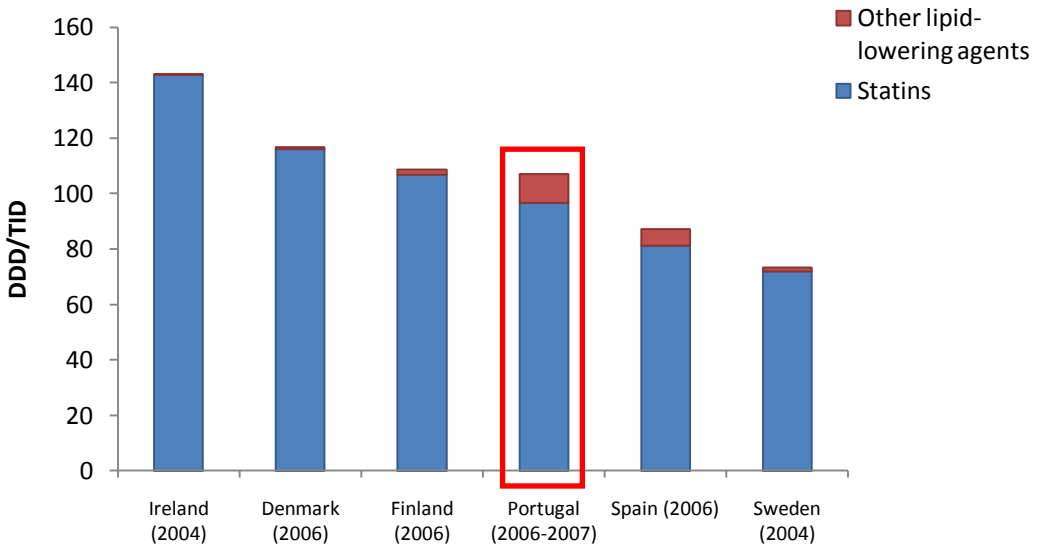
Detailed analysis of statins by active substance (Figure 7) showed individual variations between the different statins. Simvastatin was the most prescribed statin in northern Portugal with 54 DDD / TID. Second place was occupied by Pravastatin with 13 DDD/TID. Next, the most commonly prescribed drug was Fluvastatin and Atorvastatin with 10 DDD/TID. The next one was Rosuvastatin (last statin to come on the market) and Lovastatin with 8 and 2 DDD/TID, respectively.

Figure 7 Statins prescription in northern Portugal during 2006-07 by active substance and year, annualized DDD/TID for each active substance



Comparing the prescription data obtained in our study in 2006-2007 (annualized DDD/TID) with utilization data of 2006 and 2004 in some European countries [97-99] we see that the amount of lipid-lowering agents prescribed in Portugal is lower than Finland, Denmark and Ireland but higher than Spain or Sweden, with 107 DDD/TID (Figure 8).

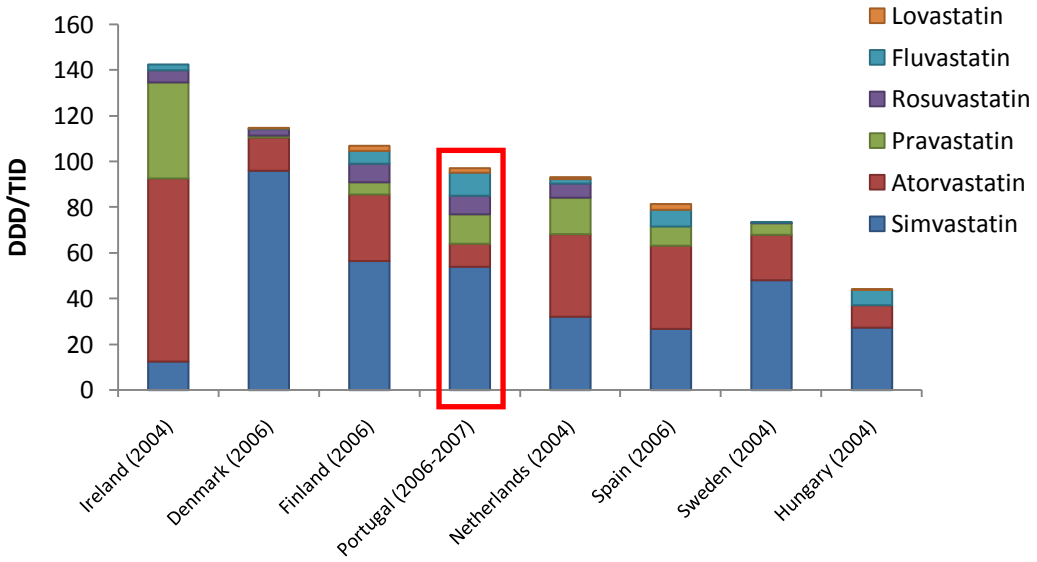
Figure 8 Statins and other lipid-lowering agents utilization: comparison between Portugal (2006-2007) and other European Countries *



*Data from EURO-MED-STAT. [97]

Like in other countries [97-99], in Portugal statins are the most prescribed lipid-lowering agents. However, there are wide variations in statins choice among countries (Figure 9).

Figure 9 Statins utilization by active substance: comparison between Portugal (2006-2007) and other European Countries*

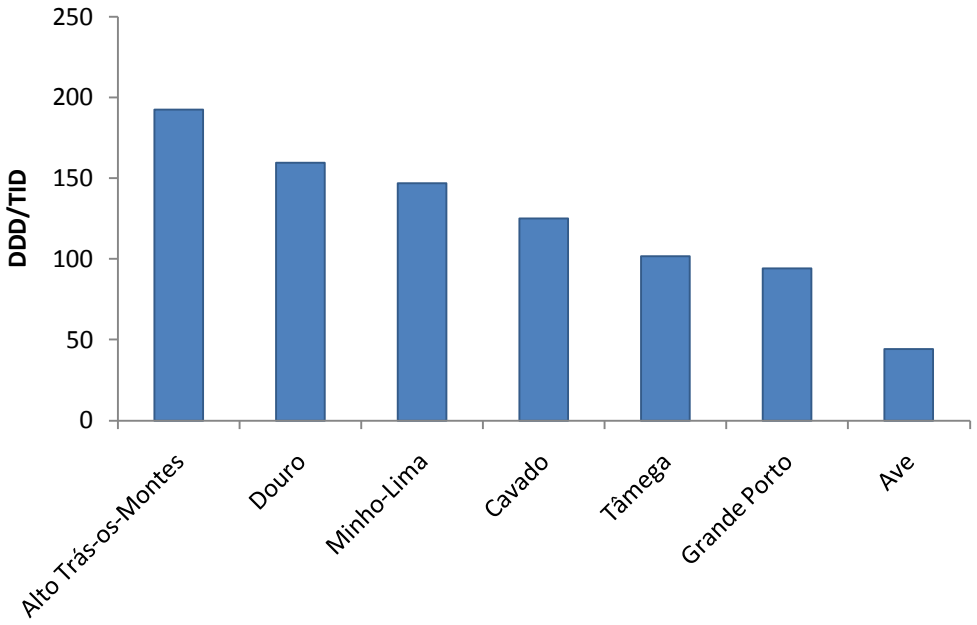


*Data from EURO-MED-STAT. [97] and statins use in Spain [99].

5.2. Geographic analysis of prescription data

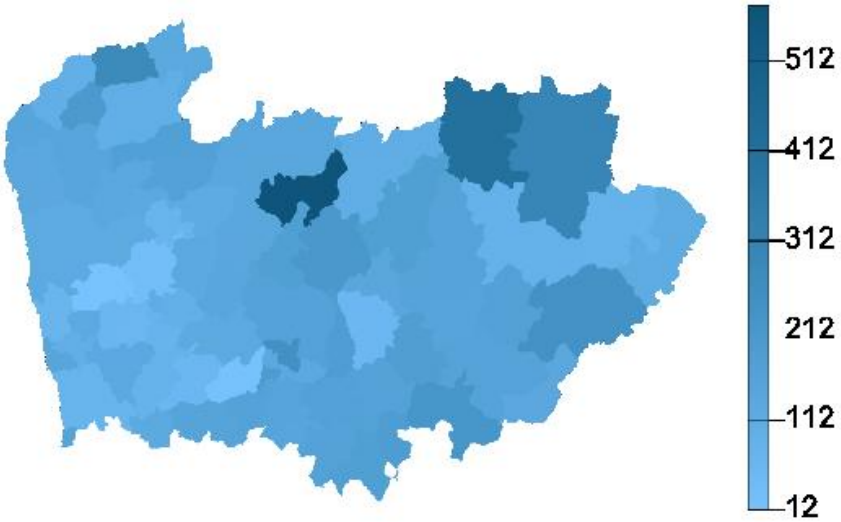
Results showed, for the time period analyzed, that Alto Trás-os-Montes, Douro and Minho-Lima were the Nuts III regions with higher amount of lipid-lowering agents prescription, with 192, 159 and 147 DDD/TID. Cávado, Tâmega and Grande Porto also showed high prescription rates, with 125, 101 and 94 DDD/TID. Ave region showed the lowest prescription rate with 44 DDD/TID (Figure 10).

Figure 10 Lipid-lowering agents prescription in DDD/TID by northern Portugal NUTS III regions during 2006-07



Differences in prescription between regions can be seen in a detailed geographical analysis by county (Figure 11). The geographical image suggests a pattern of prescribing where the coastal regions have lower ratios than inner regions. However, this is not a clear linear pattern.

Figure 11 Total DDD/TID by northern Portugal counties during 2006-07



Although there is wide variation in the amount of statins prescribed, there was not a significant variation in statins choices between the different NUTS III regions (Figure 12 and 13).

Figure 12 Statins choices by northern Portugal NUTS III regions during 2006-07

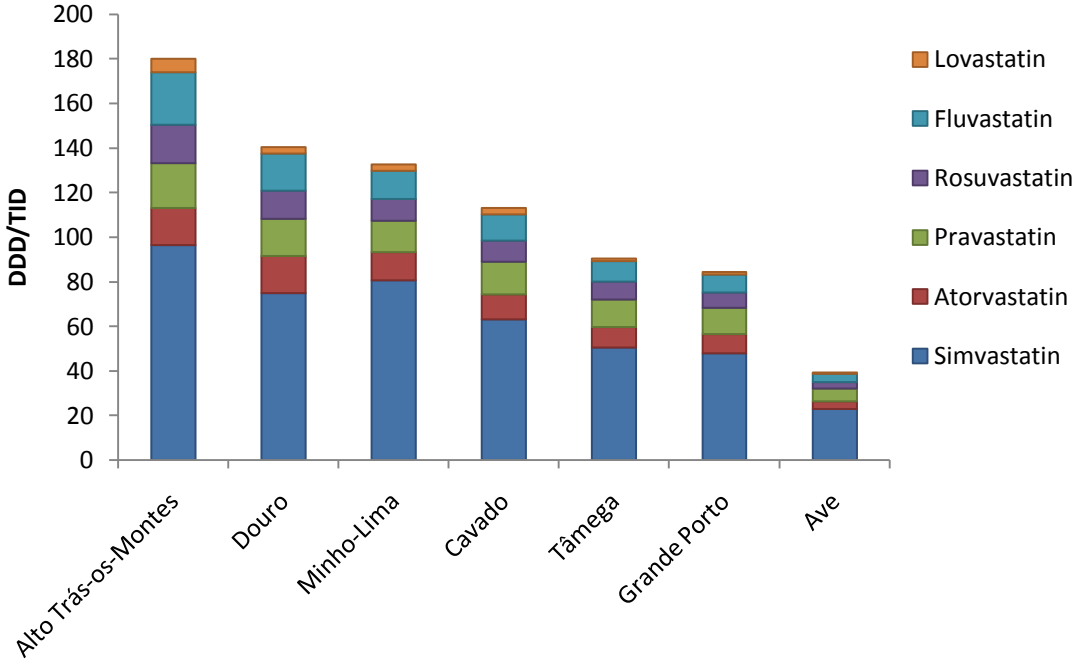
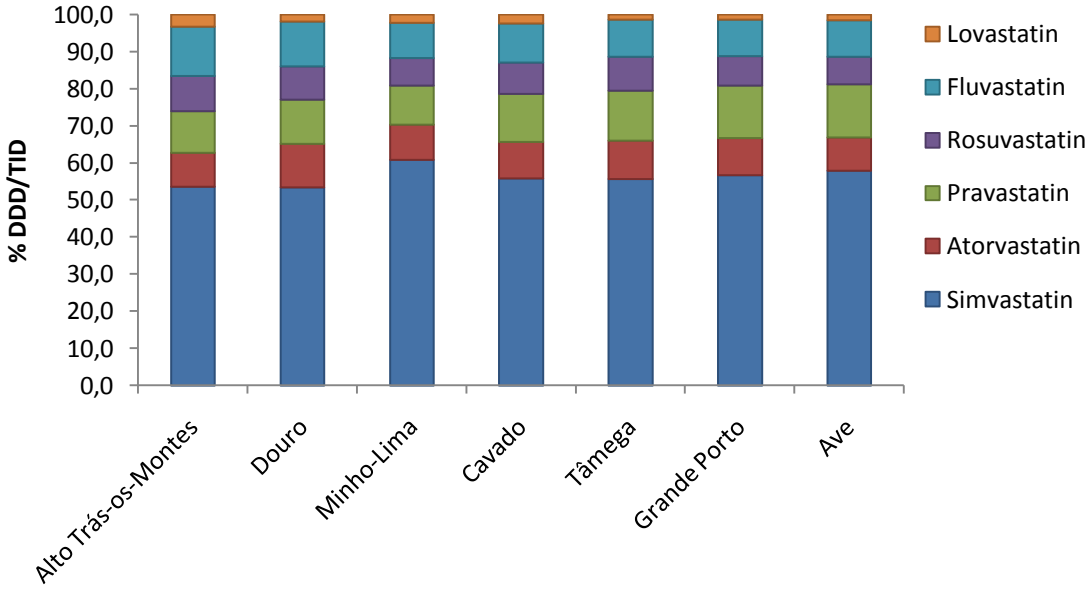
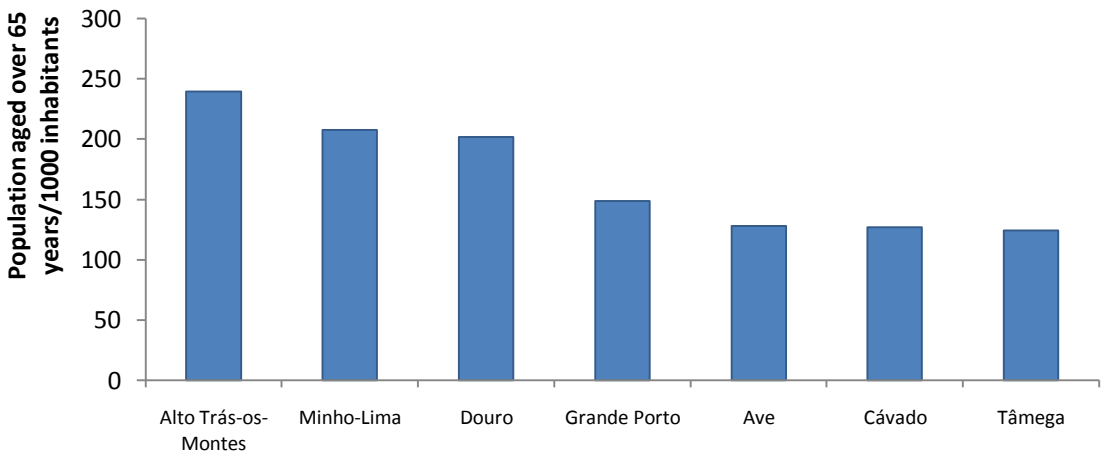


Figure 13 Statins choices (% DDD/TID) by northern Portugal NUTS III regions during 2006-07



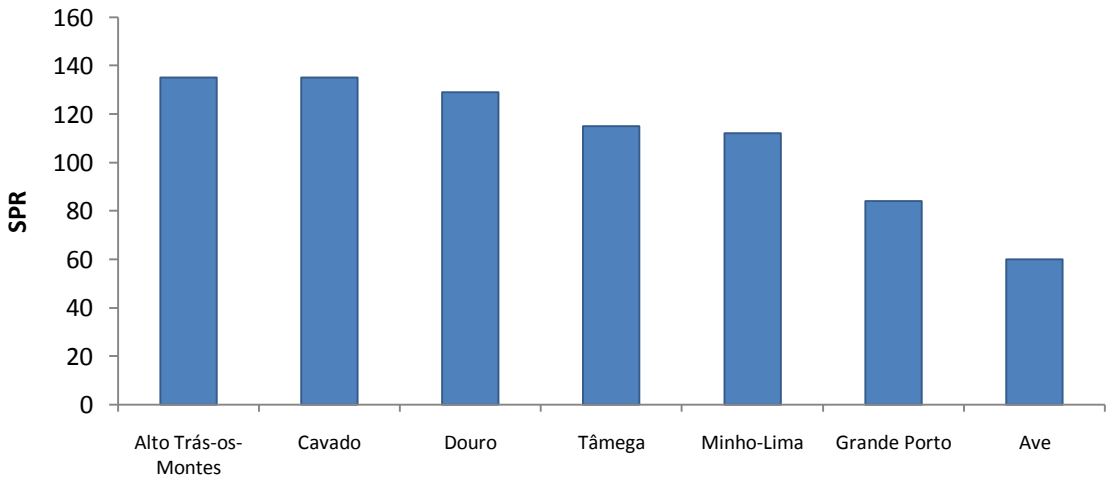
Data about prescriptions are usually interpreted as a function of the age and sex structure of population. Next is presented a descriptive analysis regarding frequency of older age strata in each geographical region and sex and age standardized prescription ratios, as previously defined, in order to describe more adequately and better comprehend the prescription patterns among the regions studied. Considering population aged over 65 years /1000 inhabitants we see that Alto Trás-os-Montes, Minho-Lima and Douro were the regions with higher frequency of older population strata. In Grande Porto, Ave, Cávado and Tâmega regions the population over 65 years is less frequent (Figure 14).

Figure 14 Population aged over 65 years/1000 inhabitants of northern Portugal during 2006-07



Analyzing the SPRs for total lipid lowering agents prescription (Figure 15), we could see that in Alto Trás-os-Montes, Cávado and Douro the results were higher than expected for their age and sex population structure, with SPRs of 135, 135 and 129%, respectively. In Tâmega and Minho-lima there was not a wide difference between the observed and expected amount of lipid lowering agents prescription, with SPRs of 115 and 112 %, respectively. In Grande Porto the results were lower than expected, with an SPR of 84%. In Ave region the observed results were almost half the expected, given its age and sex population distribution, with an SPR of 60%.

Figure 15 SPR by northern Portugal NUTS III regions during 2006-07

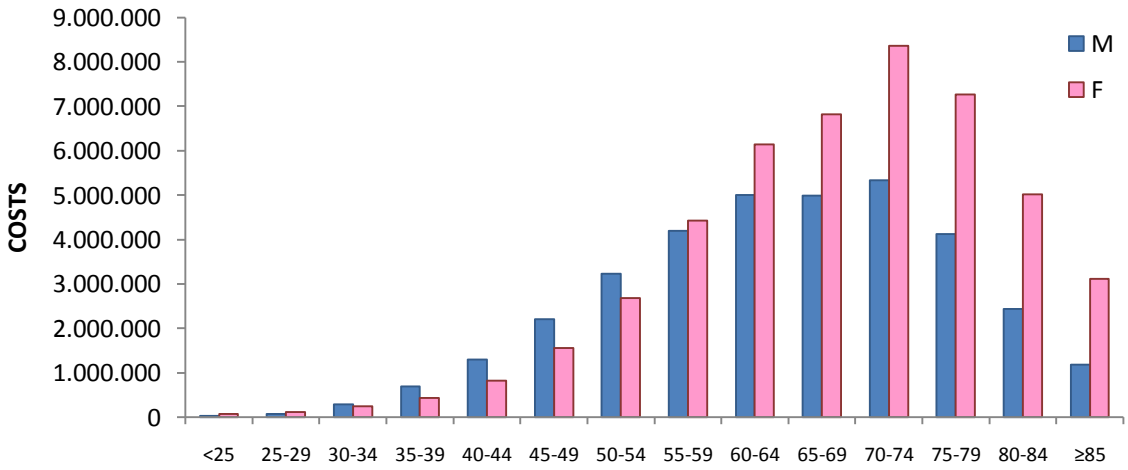


5.3. Prescription Costs

The total annualized costs associated with the prescription of lipid-lowering agents were € 82.128.763 representing a total cost per capita, for the northern region of Portugal, of € 23.2. The total costs for the patients that were prescribed lipid lowering agents (non reimbursed costs) were € 56.284.560 with an average cost for each patient of € 26.

Total annualized prescription costs were higher in men with less than 55 years. In 55-59 age stratum prescription costs started to be higher in women than men (Figure 15). In both men and women prescription costs increased with age and was highest among those age 70-74 years.

Figure 16 Prescription costs by sex and age in northern Portugal (2006-07)



Looking at the total cost per active substance (Table 8), we can see that Simvastatin had the higher total cost, about € 34 million, followed by Pravastatin with of about € 11 million, Atorvastatin with € 10 million, Rosuvastatin with € 9 million and Fluvastatin with € 7 million.

However, analysing the cost/DDD, a more appropriate standardized measure of cost, we can see that Simvastatin had the smallest cost/DDD, with 0.49 €/DDD (Table 7). The second position is occupied by Fluvastatin, with 0.52 €/DDD. The following are Pravastatin, Atorvastatin and Rosuvastatin with 0.66, 0.82 and 0.90 €/DDD, respectively.

Table 8: Total DDDs, total costs and costs/DDD by active substance for statins in northern Portugal during 2006-07

Active substance	*Total DDD*	*Total Cost*	*(€)/DDD*
Simvastatin	70.018.423	34.003.505	0.49
Fluvastatin	13.041.651	6.802.081	0.52
Pravastatin	16.202.256	10.707.182	0.66
Atorvastatin	12.441.684	10.174.250	0.82
Rosuvastatin	10.498.739	9.440.187	0.90
Total	122.202.753	71.127.205	0.58

Next, results of the prediction models to evaluate the impact, regarding cost savings, that could be associated with prescribed brand or active substance substitutions are presented.

Analyzing the total cost savings by active substance if we choose the brand with the lowest cost/DDD, we can see that it could be possible to save 24.142.489 € for Simvastatin, 3.781.957 € for Fluvastatin, 5.599.856 € for Pravastatin and 4.399.127 € for Rosuvastatin (Table 9). Extrapolating the annual cost savings at the national level we see that it could be possible to save 34.062.154 € for Simvastatin, 7.900.725 € for Pravastatin, 6.206.641 € for Rosuvastatin and 5.335.888 € for Fluvastatin.

Table 9: Total DDDs by active substance, total costs, cost/DDD if we choose the brand name with the lowest cost/DDD, total cost savings if we choose the brand name with the lowest cost/DDD and annual estimation of National cost savings if we choose the brand name with lowest cost/DDD*

Active substance	Total DDD	Total Cost	Lower Cost/DDD	Total cost saving (€) if we choose the brand name with the lowest Cost/DDD	Annual estimation of National cost savings (€) if we choose the the brand name with the lowest Cost/DDD
Simvastatin	70.018.423	34.003.505	0,29	24.142.489	34.062.154
Fluvastatin	13.041.651	6.802.081	0,44	3.781.957	5.335.888
Pravastatin	16.202.256	10.707.182	0,48	5.599.856	7.900.725
Atorvastatin	12.441.684	10.174.250	0,82	**	**
Rosuvastatin	10.498.739	9.440.187	0,53	4.399.127	6.206.641
Total	122.202.753	71.127.205	2,56	37.923.429	53.505.407

*Based on northern Portugal data during 2006-07

**There is only one lab that sells Atorvastatin.

We also analyzed the cost savings for each DDD if we choose the simvastatin (considering the average cost/ DDD of Simvastatin = 0.49 €). As can be seen (Table 10), it could be possible to save 5.507.383 € for Fluvastatin, 5.233.262 € for Rosuvastatin, 4.855.687 € for Atorvastatin and 3.498.742 € for Pravastatin. Estimating the annual cost savings at the national level we see that it could be possible to save 7.770.257 € for Fluvastatin, 7.383.505 € for Rosuvastatin, 6.850.792 € for Atorvastatin and 4.936.305 € for Pravastatin.

Table 10 Total costs by active substance, total cost savings if we choose the brand name with the lowest cost/DDD, total cost savings if we choose simvastatin (considering the simvastatin mean cost/DDD=0,93) and annual estimation of National cost savings if we choose the brand name with lowest cost/DDD*

Active Substance	*Total Cost (€)*	*Total cost saving (€) if we choose the brand name with lowest cost/DDD*	*Total cost saving (€) if we choose simvastatin*	*Annual estimation of National cost savings (€) if we choose simvastatin*
Sinvastatin	34.003.505	24.142.489	***	***
Pravastatin	6.802.081	3.781.957	3.498.742	4.936.305
Fluvastatin	10.707.182	5.599.856	5.507.383	7.770.257
Atorvastatin	10.174.250	**	5.233.262	7.383.505
Rosuvastatin	9.440.187	4.399.127	4.855.687	6.850.792
Total	71.127.205	37.923.429	19.095.075	26.940.859

*Based on northern Portugal data during 2006-07

**There is only one lab that sells Atorvastatin

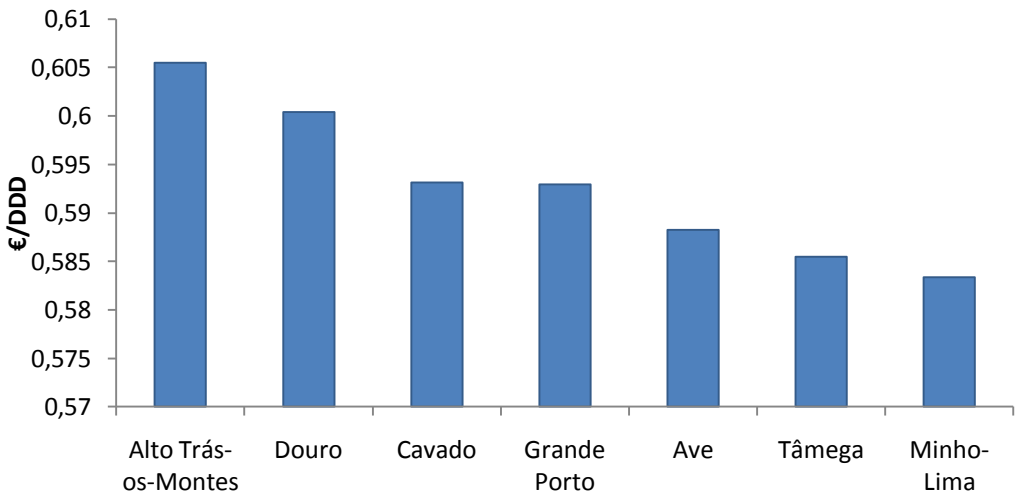
***No possibility of comparison

5.4. Geographical analysis of prescription costs data

A detailed geographical analysis was performed to assess the geographical distribution pattern of lipid lowering agents prescription and associated costs. Results also showed some important variation in cost/DDD of lipid-lowering agents between the different NUTS III regions. Alto Trás-os-Montes was the NUTS III region with higher prescription cost/DDD, with 0.605 €/DDD. Douro, Cávado, Grande Porto, Ave and Tâmega also showed high prescription

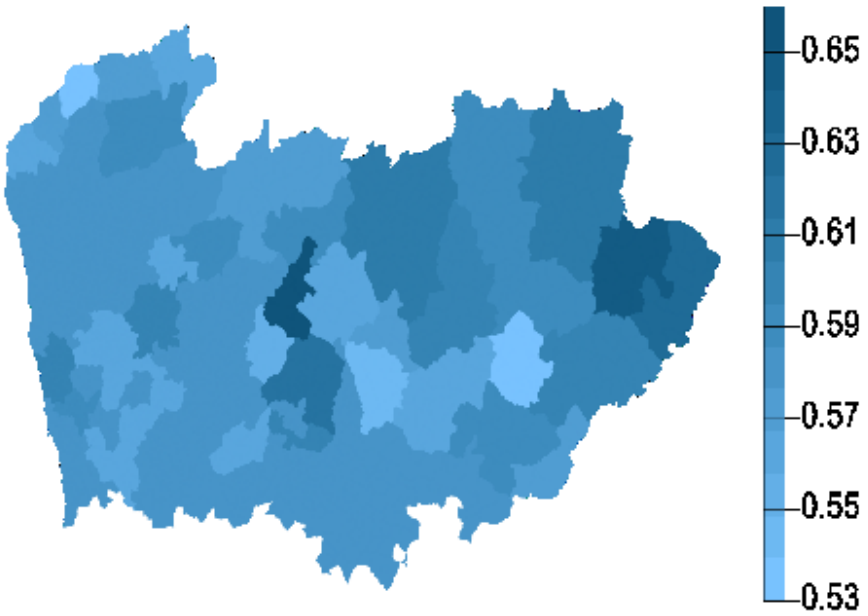
cost/DDD, with 0.600, 0.593, 0.593, 0.588 and 0.585 €/DDD, respectively. Minho-Lima was the region with lower cost/DDD, with 0.583 €/DDD (Figure 17).

Figure 17 Cost/DDD by northern Portugal NUTS III regions during 2006-07



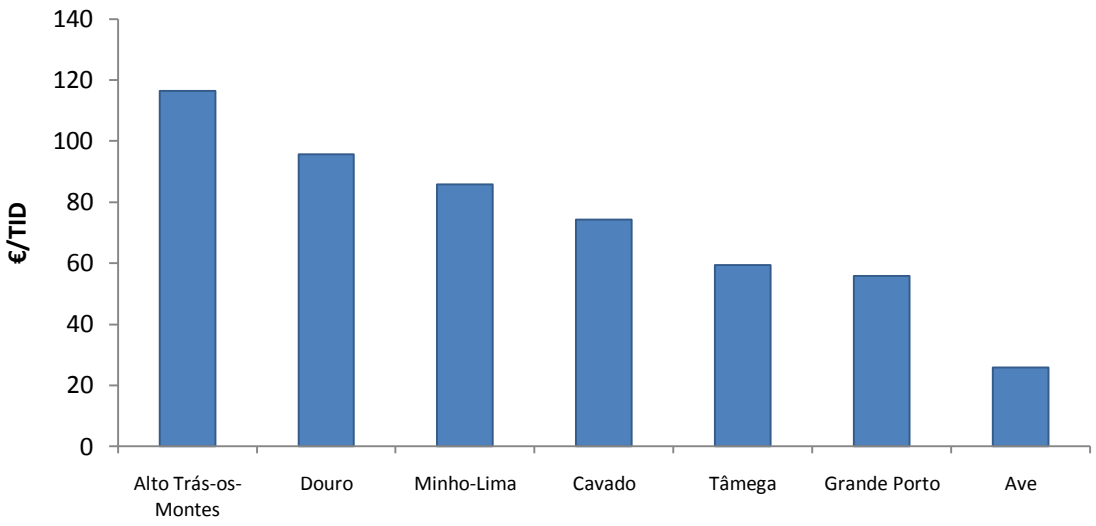
Differences in prescription costs/DDD between regions can be seen in a detailed geographical analysis by county (Figure 18).We can see a prescription trend, with inner regions choosing lipid-lowering agents with higher cost/DDD than coastal regions, despite a wide variation between different regions.

Figure 18 Cost/DDD by northern Portugal counties during 2006-07



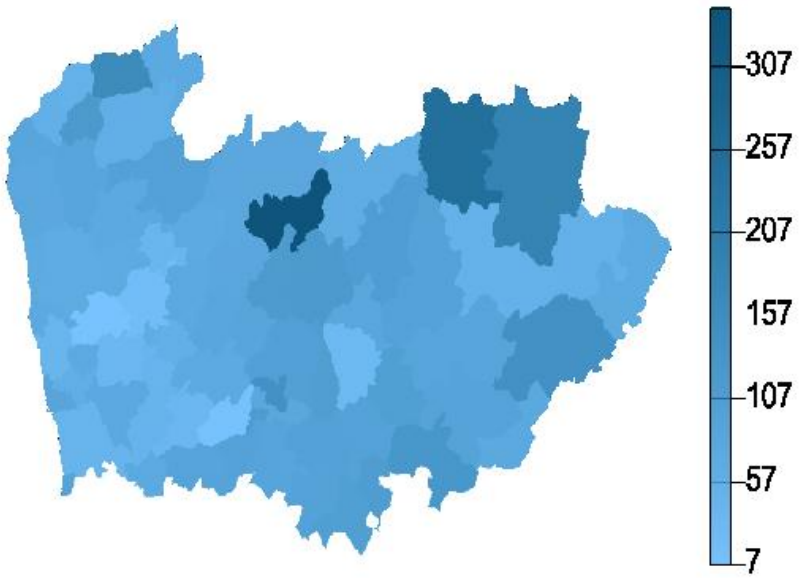
Results showed that Alto Trás-os-Montes, Douro and Minho-Lima were the Nuts III regions with higher prescription costs, with 116, 96 and 86 €/TID (Figure 19). Cávado, Tâmega and Grande Porto also showed high prescription costs, with 74, 59 and 56 €/TID. Ave region showed the lowest prescription cost, with 26 €/TID.

Figure 19 Total €/TID by northern Portugal NUTS III regions during 2006-07



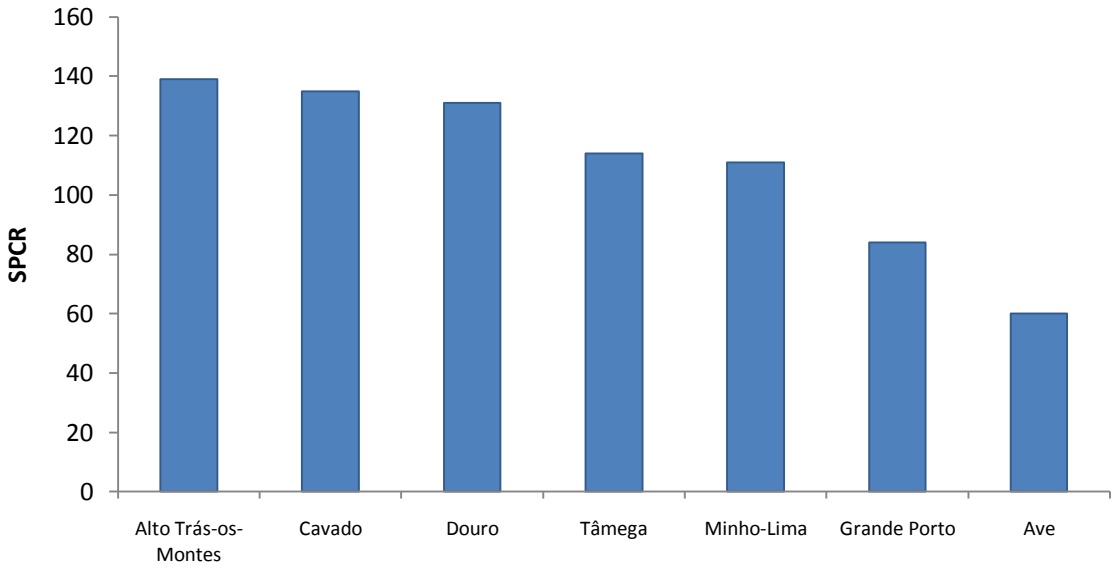
Differences in prescription costs/TID between regions can be seen in a detailed geographical analysis by county (Figure 20).

Figure 20 Total €/TID by northern Portugal counties during 2006-07



These data are usually interpreted as a function of the age and sex structure of population. Analysing the SPCRs (Figure 21), as previously defined, we could see that in Alto Trás-os-Montes, Cávado and Douro the results were higher than expected with SPCRs of 139, 135 and 131 %, respectively. In Tâmega and Minho-lima there was not a wide difference between the observed and expected results, with SPCRs of 114 and 111 %, respectively. In Grande Porto the results were smaller than expected with an SPCR of 84%. In Ave region the observed results were almost half the expected for given its age and sex population distribution, with an SPCR of 60%.

Figure 21 SPCR by northern Portugal NUTS III regions during 2006-07



6. Discussion

6.1. Lipid lowering drugs prescription

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. [103]

There was an influence of age and sex in prescription patterns, as reported in other studies. [104-107] The number of prescriptions and costs per patient rise 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). [108] 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 [109, 110]. Women are prescribed more lipid lowering drugs for age strata higher than 55-59 years, as was also reported by Roe et al. [106] 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. [111, 112]

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 [11, 98] 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. [113] 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, 114] 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. [115] It may be that growing health concerns among the general population and physicians in particular [116] together with earlier and more effective 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. [103] We can observe this trend in some other European countries, although with variations. [11]

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.[117-119] 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.[120-122] 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 and patients, may influence the prescription. [123, 124] 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. [9] In Portugal, simvastatin marketing has been the strongest, with 98 different laboratories marketing simvastatin.

Portugal has not been the European country with higher statins prescription, being below countries such as Finland, Denmark or Ireland [97]. 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 [125], 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 [126], 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.

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 ther 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 between northern 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 standardize the aggregated data of prescription for the population structure. [43] 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. Finally, it should be underlined that although extensive data cleaning and appropriate data analysis procedures were implemented, these results may be partially related to differential prescription data quality among geographical regions.

6.2. Prescription Costs

Taking into account the results of treatment, lipid-lowering drugs had a considerable impact on the costs to the national health system and Portuguese patients. Based on sales data in 2008, the lipid-lowering drugs were the fifth group with higher costs for the National Health Service. [103]

The costs with lipid-lowering drugs were due to higher levels of statins prescription, the most prescribed group. However, there was a wide range of costs within the therapeutic class and thus the promotion of the possibility of substitution for cheaper alternatives and changes in the national drug prices structure could be practical measures to achieve some important cost savings, without reductions of drug therapy effectiveness.

The results of the present study show that within statins group, simvastatin had the higher total cost, which is consistent with sales data where simvastatin was the third active substance with highest expenditure in the National Health Service. [103] However, simvastatin had the lowest cost/DDD. The expenditure per DDD is important because represents a standardized measure of the cost paid by Portuguese health system to provide simvastatin. So, if it is true that simvastatin represented the highest expenditure, it is also important to say that this seems to be, in our context, the active substance with a better cost-benefit ratio.

Although total expenditure with statins increased in value, the cost per DDD did not. Like reported by Teixeira and Shiappa (2007) [95] cost/DDD has been falling since 1995 and this is particularly true for statins, with a 35% reduction between the first half of 1995 and of 2004, due to greater use of cheaper active substances or brands and the use of higher dosage packs, and hence lower cost per DDD. When compared with other European countries in 2000, Portugal (2006-2007 data) had lower prescription cost/DDD.

In an attempt to control rising pharmaceutical expenditures, most EU countries have targeted the supply-side of the market and introduced some form of either direct or indirect price regulation. The evidence of the impact of these schemes is limited and varies, although most stringent regulatory regimes have been more successful. [127]

Portugal began to adopt regulatory measures recently. Since 2000 there were various changes in price regulation of medicines in Portugal. The dimensions of pharmaceutical packages were extensively revised, the use of generics was encouraged, medical prescriptions by international common designation or generic name were introduced, the pharmacist (with doctor's authorization) began to be able to replace prescriptions for generally cheaper generic forms and in 2003 it was implemented the reference pricing for pharmaceutical reimbursement, which groups pharmaceuticals according to their active ingredients and sets a reference price for the group (often the average or lower-priced pharmaceutical in the group). Considering the previous experiences in other countries, the available evidence suggests that a considerable number of products may have a price reduction. [128]

Results show that if we choose the brand name with the smallest price within the same active substance we would have a considerable economic impact on costs to the Portuguese health system and to patients, although this is the result of a global analysis which does not take into account the equivalent potency of DDDs or the existence of doses that may not be replaced. This was particular true for simvastatin where cost savings if we choose the brand name with the

lowest cost/DDD was more significant. Despite the existence of a free competitive market there is still a large cost difference among different drug brands. According to Teixeira and Shiappa [95], simvastatin saw extraordinary growth among generic statins, particularly after the introduction of the reference price system. The increasing use of generic drugs led to the existence of cheaper alternatives with potential cost savings. In 2000 the price of generics was lowered by 20% compared to the original product price, and until 2007 a 35% reduction was achived. [128]

Moreover, if we choose simvastatin (the statin with the lowest cost/DDD) instead of another statin the costs savings may be also significant. The prices of the available statins vary considerably. Therefore, these drugs must be chosen carefully, bearing in mind that it is not necessary to use a statin able to reduce LDL by 50%, more expensive, if the target is only a 30% reduction that can be achieved using a lower cost statin (e.g. simvastatin). Furthermore, the drug associations (most expensive) can be reserved for cases of resistance to statins alone or intolerance with isolated statins in high doses. A very recent meta-analysis of seventy-five studies [65] reporting randomized controlled trials of head-to-head comparisons of statins did not show significant differences among them in lipid-lowering effects when used at their standard dosages. Atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40/80 mg, and simvastatin 20 mg are equivalent in decreasing LDL-C by 30-40%; and fluvastatin 40 mg, lovastatin 10/20 mg, pravastatin 20/40 mg, and simvastatin 10 mg are similar in reducing LDL-C by 20-30%. Rosuvastatin at 10 mg or higher dose and atorvastatin at 20 mg or higher dose could reduce LDL-C by more than 40%. The HDL-elevating and triglyceride-lowering effects are also similar among different statins at equivalent doses.

The results of the prediction models based on substitutions of brand names or active substance prescribed that were presented and discussed in the previous paragraphs are only for illustrative purposes and are based on the assumption that the proposed substitutions could actually take place in the clinical setting.

Of course in many cases that may not be the case, the simulated substitutions may not be the most appropriate clinical decision or they may not even be possible. Although their interpretation must be made with caution, these models allow us to estimate cost savings that, at least in part, may easily be achieved in practice, for example through educational initiatives aiming to raise physicians awareness about statins prescription appropriateness and costs, based on an adequate individual risk assessment for each patient. The choice of the active substance and the brand name is very important and should be made taking into account the specific objectives for each patient, but also the best cost-benefit ratio.

There was an important variation in cost/DDD of lipid-lowering agents among different northern geographical regions. We can see a prescription trend, with inner regions choosing lipid-lowering agents with higher cost/DDD than coastal regions. In Alto Trás-os-Montes are chosen drugs with highest cost/DDD, in contrast to the Minho region where are prescribed drugs with lower cost/DDD. The adequate interpretation of these results has to take into account that a small variation in cost/DDD, a standardized measure, may represent a very significant variation on total costs. For a illustrative purposes, a variation of 0.1 on the costs/DDD may represent a total cost variation of 14 million euros for the northern region of Portugal. Although differences may occur among regions it is hard to explain why they are so high. This variation should be mainly related to differences in criteria for active substance and brand name choice among regions.

To study the extent of drug cost in a defined area we analysed the costs in €/1000inh/day. Alto Trás-os-Montes had the highest costs. Although in Minho-Lima are chosen drugs with lowest cost/DDD, Ave region had the lowest cost per 1000 inhabitants per day. Standardizing the aggregated data of prescription costs for the population age and gender structure we could see that the population structure does not fully explain the higher prescription costs in Alto Trás-os-Montes region. Although Ave region had a small prescription cost per

inhabitant, it was expected almost twice of the prescription costs giving the age and sex population structure.

In conclusion, the wide variation on lipid-lowering drugs prescription costs, described using appropriate standardized measures, is not fully justifiable and demonstrates the need to implement additional educational and policy measures aiming to promote an effective and efficient utilization of this pharmacological group.

6.3. Strengths and limitations

Primary Care prescription data can provide new opportunities to study different aspects of drug therapy in individual users. It is possible to obtain more detailed information allowing the link of the prescribed drugs to the individual patient and often to a reason for prescribing it (indication or diagnosis). Unfortunately, the availability of these prescription databases is limited to few countries. In Portugal, the National Health Service (NHS) has been making a strong investment in information technology services. These prescription data may become in the future part of the “administrative” data. This will allow in the future the availability of prescription data on wider populations and with much higher quality.

The data used in this study was related with the trial period of the universal electronic prescription system (using SAM system) in the primary healthcare sector, that was running over 2006 and 2007 in the northern region of Portugal. This may be a limitation of the study because there were periods in which data quality was very low and clearly influenced by low physicians' adherence to the computerized prescription system. However, to ensure data quality we performed a set of data cleaning procedures. 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 this periods could lead to prescription underestimation. Thus, we are convinced that, although the data quality was not the best, the analysis methods implemented were able to correct for these foreseen limitations.

A detailed investigation of prescription patterns and indications for statins (for example, the proportion of patients treated in primary and in secondary prevention, and their risk levels) would also be interesting in order to assess the cost-effectiveness of their increasing prescription and the appropriateness of investing in them. Our data do not allow us to explore issues related to cardiovascular risks of patients who received the prescriptions.

7. Conclusions and recommendations

This study demonstrates the utility of clinical automated databases to facilitate the study of prescription drugs in primary care settings. The selection of a population-based sample has the advantage of including a representative sample of the entire population allowing information about the drugs currently prescribed. However, the electronic prescription has been gradually introduced in clinical practice, leading to the need of adequate processing and cleaning procedures to ensure the quality of the data, due to periods of time where data were clearly affected by physician's adherence to the electronic prescription.

The results results presented showed that 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 sex and age of the populations of different northern regions covered by the Regional Health Administration. There seems to be an age and sex pattern with an increase of prescriptions with age among men and women reaching a peak in the range of 70-74 years, being higher in women.

Simvastatin was clearly the most prescribed statin in northern Portugal. This is seen in other European Countries, although with some variation in the choice of statin. [11] Nevertheless, the level of use per inhabitant in Portugal is still low comparing with other European countries. [97]

Likewise, this study reveals some geographical prescription pattern, with rates increasing as we move from coastal regions to inner regions, and a wide variation among different regions. Alto Trás-os-Montes was the NUTS III region with higher prescription rate and Ave with the lowest prescription rate. Despite this variation, there was not a significant difference on pattern of statins choices among northern regions.

Treatment with statins has a considerable impact on costs. Although total expenditure with statins increased in value, the cost per DDD did not when compared to sales data in 2000. [97]

Our results also suggest that there is a potential for considerable drug cost savings without, we believe, disadvantaging the efficacy of patients treatment. There was a wide range of prices within the therapeutic class and thus the possibility of substitution for cheaper alternatives.

It can be concluded that the choice of drugs and brand names is very important and should be made taking into account the specific objectives for each patient but also the best cost-benefit ratio. In a global analysis of costs, results showed that within the same active substance we can have a considerable cost reduction if we choose the brand name with the lowest cost/DDD. In another scenario, the substitution for simvastatin, the active substance with lower cost/DDD, that is eventually adequate in many cases, was also demonstrated to be associated with some important potential cost savings.

The existence of differences at the regional level in the prescription costs of lipid-lowering drugs reflects also the need for National policies that ensure the quality of prescription with the best cost-benefit ratio. Results show that the cost paid for the medicines varies widely among different regions of northern Portugal. In Alto Trás-os-Montes are chosen drugs with highest cost/DDD, being also the region with highest costs per 1000 inhabitants per day. Although in Minho-Lima are chosen drugs with lowest cost/DDD, Ave region had the lowest cost per 1000 inhabitants per day.

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 important to develop strategies to increase adherence to the electronic medical prescription systems.

8. Future Work

Future work is required in order to understand more fully the prescription choices and to plan successful interventions to improve the quality of prescription.

A detailed investigation of prescription patterns and indications for statins (for example, the proportion of patients treated in primary and in secondary prevention, and their risk levels) would also be interesting in order to assess the cost-effectiveness of their increasing prescription and the appropriateness of investing in them. Some of these research paths will be developed in the future, although, for now, our data do not allow us to explore issues related to cardiovascular risks of patients who received the prescriptions or other clinical information.

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