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Prescribed Daily Doses (PDDs) of Hypolipidaemic Agents in South Africa with Emphasis on HMG CoA Reductase Inhibitors

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Abstract Dyslipidaemia is a major cardiovascular risk factor in the South African population. The primary aim of the study was to determine the prescribing patterns of hypolipidaemic agents on the South African market with specific emphasis on the Prescribed Daily Doses (PDDs) of HMG CoA reductase inhibitors (statins). A retrospective, cross-sectional pharmacoepidemiological study was conducted on 2011 claims data. All records for hypolipidaemic agents were extracted for analysis. A total of 4 805 patients (56.88% males) were prescribed 38 373 hypolipidaemic agents. The average age of patients was 56.07 (SD=13.32) years. Statins accounted for 93.85% of all prescriptions, followed by fibrates (3.61%). Simvastatin was the most frequently prescribed statin (accounting for 62.59% of all prescriptions), followed by atorvastatin (17.04%) and rosuvastatin (11.68%). The average PDDs were generally lower or in agreement with the Defined Daily Doses (DDDs), except for rosuvastatin. The average PDD of simvastatin was 23.70 mg (DDD=30 mg), pravastatin 25.35 mg (DDD=30 mg), lovastatin 26.31 mg (DDD=45 mg), atorvastatin 20.91 (DDD=20 mg) and fluvastatin 57.29 mg (DDD=60 mg). The average PDD of rosuvastatin was 15.02 mg and the DDD only 10 mg. The fibrates constituted 3.61% of prescribing. Only one cholesterol absorption inhibitor drug was prescribed (ezetimibe). Other hypolipidaemic agents prescribed accounted for only 0.89%. A variety of generic equivalents were available for the statins. Further studies are needed to investigate clinical parameters and diagnoses in relation to the PDDs.

Keywords Prescribed Daily Doses (PDDs), Hypolipidaemic Agents, Statins

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide[1]. Increased levels of low-density lipoprotein cholesterol (LDL-C) are an important modifiable risk factor[1]. The HMG CoA reductase inhibitors (or statins) are the most efficacious lipid-lowering drugs available. Statins lower LDL-C levels and have been reported to reduce the relative risk of coronary events by about 30% in both primary and secondary prevention[2, 3]. Statins are widely and increasingly used in most countries. Studies have, however, shown huge variations in use amongst countries and regions[3, 4].

During the last decade clinical data on the benefits of statins in the prevention of cardiovascular disease have accumulated. High dose statins of all types are, however, associated with adverse effects such as myopathy and very rarely rhabdomyolysis. The risk is much higher in combination with certain medicines and in the elderly[5]. In February 2012, the United States Food and Drug Administration (FDA) had approved important safety label changes for the statins[6]. These changes were made to provide the public with more information for the safe and effective use of statins and are based on the FDA's comprehensive review of the statins.

The dosages in which statins are prescribed are therefore important. The WHO recommends the use of the defined daily dose (DDD) and prescribed daily dose (PDD) methodology in drug utilisation studies. The definition of the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDDs are assigned by the WHO[7]. For instance, the DDD for atorvastain is 20 mg[8]. The prescribed daily dose (PDD) is defined as the average dose prescribed according to a representative sample of prescriptions[7]. The PDD can be determined from studies of prescriptions or medical or pharmacy records. The DDD is a unit of measurement and does not necessarily respond to the recommended or PDD, but the methodology is used internationally and allow for comparisons to be made.

The DDDs for the statins remained unchanged from 1997.

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However, in January 2009, alterations were made to the DDD for five of the six statins in order to better reflect the current daily dosages[9]. Table 1 compares the previous DDD values (prior to January 2009) to the new DDD values (since January 2009) for each statin[8, 9]. The DDDs for atorvastatin and simvastatin have been doubled, whereas for pravastatin, lovastatin and fluvastatin the DDDs have been increased by 50%. There has been no alteration to the DDD for rosuvastatin.

Table 1. Changes to the DDD of the Statins[8, 9]

Active ingredient	Previous* DDD	New** DDD[8]	% Difference
Atorvastatin	10 mg	20 mg	+100%
Simvastatin	15 mg	30 mg	+100%
Pravastatin	20 mg	30 mg	+50%
Rosuvastatin	10 mg	10 mg	—
Lovastatin	30 mg	45 mg	+50%
Fluvastatin	40 mg	60 mg	+50%

* Before January 2009.
** Since January 2009.

A recently published South African study has revealed that despite being on cholesterol-lowering medication, an alarming 48% of patients do not reach their healthy LDL-C levels[10]. This significantly increases their risk for the development or progression of cardiovascular disease and puts them at risk for heart attack or stroke[2]. Dyslipidaemia therefore remains a major cardiovascular risk factor in the South African population. A recently published study by Raal and colleagues[1] in South Africa reported that many patients in South Africa experienced persistent dyslipidaemia despite statin treatment which, according to the authors, supports the concept that there is a need for more intensive statin therapy or the development of novel treatment strategies. Since statins remain among the most effective agents for preventing CVD, studies on their prescribing and the dosages in which they are prescribed are important. The primary aim of the study was therefore to determine the prescribing patterns of hypolipidaemic agents on the South African market with specific emphasis on the Prescribed Daily Doses (PDDs) of HMG CoA reductase inhibitors (statins).

2. Methodology

2.1. Research Design and Setting

A retrospective, cross-sectional drug utilisation study was conducted on the database of a private medical insurance scheme administrator in South Africa. According to the South African Board of Healthcare Funders that represents 72 health insurers in South Africa, only 16% of the South African population is covered by medical insurance[11]. This equates to 3.5 million insured members and their 4.6 million dependents. The remainder of the South African population, that is 39.9 million people, is dependent on the government's medical services for which detailed prescription data are not readily available. Electronically captured claims data for 2011 of a South African medical insurance scheme (medical aid) administrator were analysed in this study. The total database contained 2 298 312 records for medicine, medical devices and procedures and was representative of all provinces in South Africa.

2.2. Data and Statistical Analysis

All records for hypolipidaemic agents were extracted for analysis. The Anatomical Therapeutic Chemical (ATC) Classification System[8], MIMS[12] and the South African Medicines Formulary[13] were used to identify medicines. Each medication record contained information on the age and gender of the patient, with a unique number to identify each patient, the date of the prescription, detailed information on the dispensed drug (name, package size, formulation, strength and quantity) and amount claimed and paid. Microsoft Access® and Excel® were used to analyse the data. Basic descriptive and inferential statistics were calculated. One Euro (€1.00) was equal to R9.81 (South African Rand), one US Dollar ($1.00) was equal to R6.76 and one British Pound (£1.00) was equal to R10.85 at the time of the study (30 June 2011).

2.3. Ethical Approval

Ethical approval to conduct studies on prescription databases has been obtained from the Research Ethics Committee (Human) of the Nelson Mandela Metropolitan University (ethics clearance number: H08-HEA-PHA-005).

2.4. Limitations of the Study

Limitations of the study were that no clinical information or diagnoses were available in the database, and that only data of patients served by the private health care sector in South Africa were included in the study. Patients served by the government or state's health care system (the public health care sector) were therefore not included in the study.

3. Results and Discussion

3.1. Age and Gender Distribution of Patients

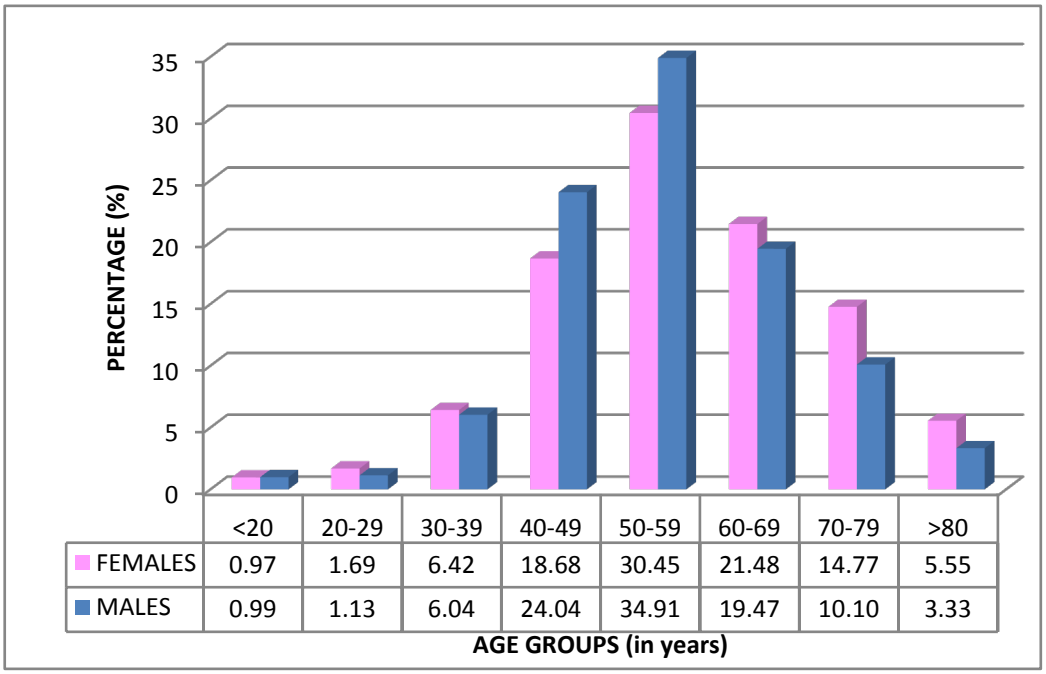
A total of 4 805 patients (56.88% males) were prescribed 38 373 hypolipidaemic agents during 2011. The percentage age and gender distribution of patients is given in Figure 1. The average age of patients was 56.07 (SD=13.32) years. The average age of female patients was 57.32 (SD=13.92) years and of male patients 55.12 (SD=12.77) years. Differences between females and males in the different age groups were observed (χ^2=62.718; d.f.=7; p<0.0001). There were more males in the age groups between 40 and 59 years, and more females in the age groups older than 60 years.

3.2. Prescribing Frequency of Hypolipidaemic Agents

The percentage prescribing frequency of hypolipidaemic products according to age and gender groups is given in Figure 2. Patients were prescribed on average 7.99 (SD=4.85) hypolipidaemic products during the year. Female patients were prescribed on average 7.92 (SD=4.80) products and male patients 8.03 (4.89) products. Prescribing differences between females and males were observed (χ^2=554.86; d.f.=7; p<0.0001). Proportionately more products were prescribed to male patients between 30 and 59 years of age, and after the age of 60 years proportionately more female patients were prescribed hypolipidaemic products.

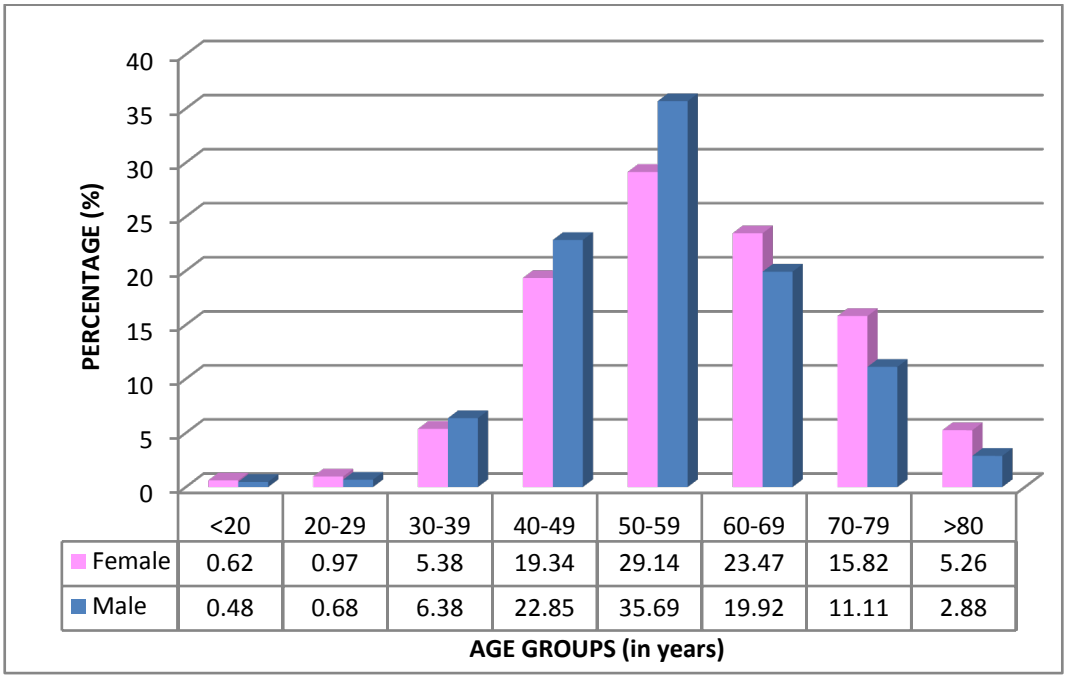
3.3. Prescribing Frequency of Hypolipidaemic Classes

Statins accounted for 93.85% of all prescriptions, followed by fibrates (3.61%) (see Table 2).



* χ^2=62.718; d.f.=7; p<0.0001.

Figure 1. Percentage age and gender distribution of patients (n=4 805)*



* χ^2=554.86; d.f.=7; p<0.0001.

Figure 2. Percentage prescribing frequency of hypolipidaemic agents according to age and gender groups (n=38 373)*

Table 2. Prescribing Frequency of Hypolipidaemic Classes

HYPOLIPIDAEMIC CLASSES	NUMBER OF PRODUCTS		BOTH GENDERS	
	FEMALES (n=16 419)	MALES (n=21 954)	NUMBER	%
7.7.1 Fibrates	3.29	3.85	1 387	3.61
7.7.2 HMG CoA Reductase Inhibitors (statins)	94.23	93.57	36 014	93.85
7.7.3 Cholesterol Absorption Inhibitors	1.41	1.82	630	1.64
7.7.4 Hypolipidaemic Agents (Others)	1.07	0.76	342	0.89
TOTAL	100.00	100.00	38 373	100.00

3.4. Active Ingredients Prescribed

Simvastatin was the most frequently prescribed statin (accounting for 62.59% of all prescriptions), followed by atorvastatin (17.04%) and rosuvastatin (11.68%) (see Table 3). The fibrates constituted 3.61% of prescribing, with most prescriptions for bezafibrate. Only one cholesterol absorption inhibitor drug was prescribed (ezetimibe) accounting for 1.64% of prescriptions. Other hypolipidaemic agents prescribed accounted for only 0.89% and consisted of the combination of ezetimibe and simvastatin, and cholestyramine.

In previous South African studies[14, 15] conducted in 1994/1995 on 2 336 patients, simvastatin was also the single most often prescribed drug, representing 36.8% of prescribing frequency. At that stage, simvastatin and pravastatin were the only statins available on the market and none of them had generic equivalents.

In this study, 15 different generic equivalents of simvastatin were prescribed, five generic equivalents of atorvastatin and three for pravastatin. No generic equivalents were prescribed for fluvastatin, lovastatin and rosuvastatin. A South African study on a medical aid administrator database investigating costs found that patients were stable on initial prescribed drug therapy with a relatively low incidence of switching (less than 25%)[16]. If switching occurred it was mainly to generic simvastatin[16]. A study conducted in the United Kingdom in 2008 to 2009 reported a 14-fold variation in the cost of statins, with United Kingdom prices ranging from £1.72 ($2.72, €2.07) for simvastatin to £29.69 ($46.96, €35.69) for rosuvastatin for 4 weeks' treatment at the recommended dose for secondary prevention[17].

3.5. DDDs and Average PDDs of the Statins

The average PDDs of the statins were generally lower or in agreement with their respective Defined Daily Doses (DDDs), except for rosuvastatin whose average PDD was higher (see Figure 3). The average PDD of simvastatin was 23.70 mg (DDD=30 mg), pravastatin 25.35 mg (DDD=30 mg), lovastatin 26.31 mg (DDD=45 mg), atorvastatin 20.91 (DDD=20 mg) and fluvastatin 57.29 mg (DDD=60 mg). The average PDD of rosuvastatin was 15.02 mg and the DDD only 10 mg. Although the average PDD of rosuvastatin was higher than the DDD, it was still within the acceptable dosage range. The dosage range for rosuvastatin is 10 mg to 40 mg[13].

In the previous South Africa study[14], the average PDD for simvastatin was 12.6 mg and for pravastatin was 12.5 mg, which were significantly lower than the average PDDs in the current study.

In a study[4] comparing statin consumption in Norwegian countries, the estimated PDDs were higher than the DDDs. The average PDDs ranged for simvastatin between 22.5 mg to 25.9 mg, for lovastatin between 28.2 mg to 31.8 mg, and for atorvastatin between 18.0 mg to 21.9 mg[4]. A study investigating the trends in prescribing and utilisation of statin and other lipid lowering drugs across Europe from 1997 to 2003, found that PDDs were greater than DDD values in most cases[3]. A study conducted in the Netherlands[18] to assess the dosing of statins among starters of statins, reported large differences in dosing between statins. The PDD was about 1 DDD per day in patients starting with simvastatin, but patients using pravastatin or atorvastatin received significantly higher doses than users of simvastatin[18].

A study conducted in British Columbia[19] reported that the most commonly prescribed doses of each of the four statins were as follows: rosuvastatin 10 mg (75.8% of all rosuvastatin doses); atorvastatin 10 mg and 20 mg (46.4% and 35.3%, respectively, of all atorvastatin doses); simvastatin 20 mg and 40 mg (42.5% and 31.8%, respectively, of all simvastatin doses); and pravastatin 20 mg and 40 mg (55.0% and 34.1%, respectively, of all pravastatin doses).

Figure 4 shows the variability according to age groups of the average PDDs of atorvastatin, rosuvastatin and simvastatin. Variation existed in the dosages. This can be due to a multitude of factors, such as the severity of the disease state, gender and age. For example, a study conducted on the elderly in the Netherlands, found that the prevalence and incidence of statin use were lower in elderly patients compared with younger patients and that lower **dosages** of **statins** were prescribed[20].

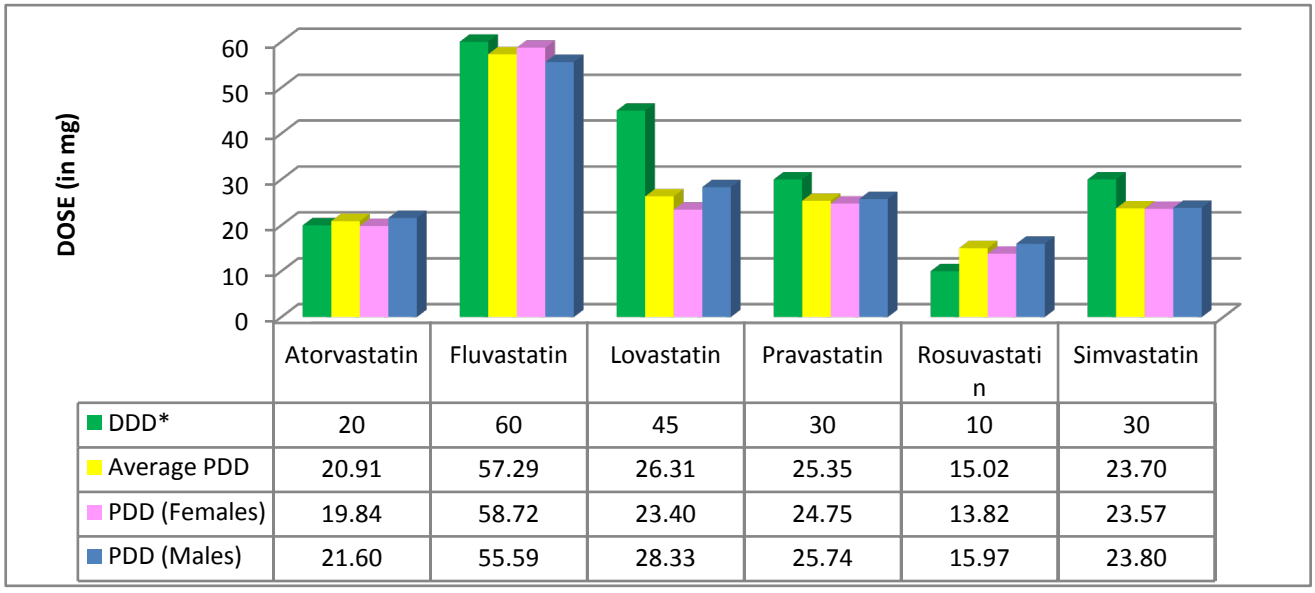
4. Conclusions

The HMG CoA reductase inhibitors were the most often prescribed class of hypolipidaemic agents in this study, accounting for 93.85% of all prescriptions. Simvastatin was the most often prescribed active ingredient, accounting for 62.59% of all hypolipidaemic prescriptions. The average

PDDs were generally lower or in agreement with the established DDDs, except for rosuvastatin. Differences were observed in the pattern of lipid-lowering drug prescriptions for females and males. Male users were on average younger than female users.

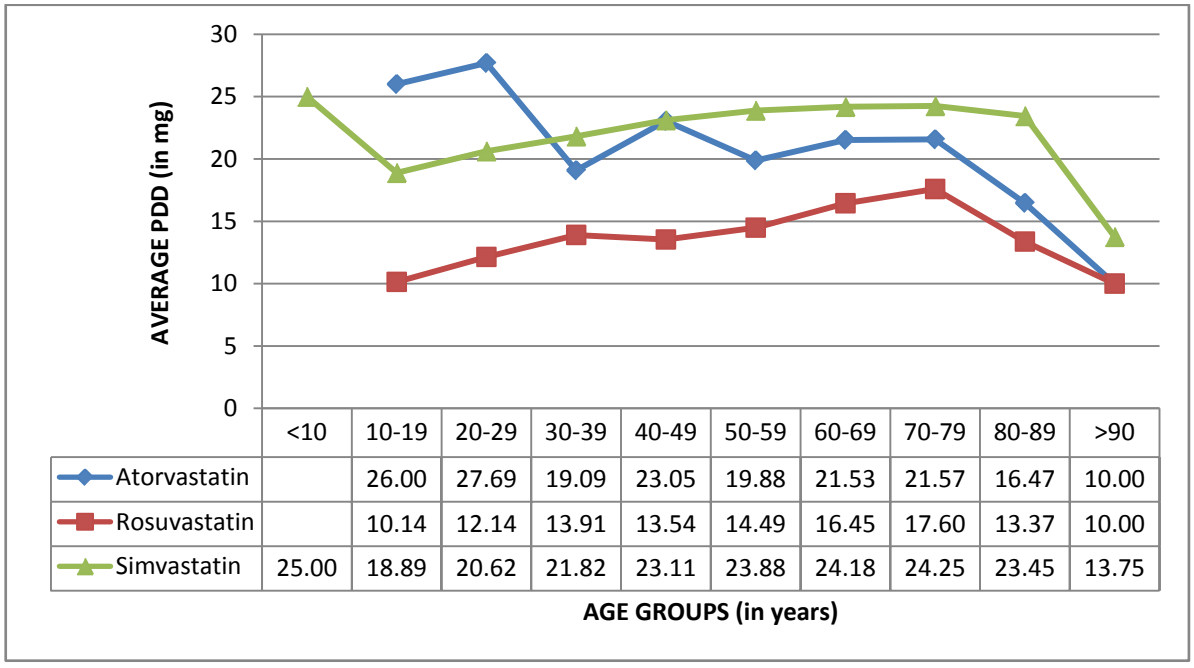
It is important to relate PDDs to the diagnosis on which the dosage is based. This was a limitation of this study since diagnoses and clinical data were not available. Usually when there is a substantial discrepancy between the PDD and the DDD, it is important to investigate this further when evaluating and interpreting drug utilisation figures, particularly in terms of morbidity.

More detailed studies investigating the relationship between patients' cholesterol levels and PDDs are therefore needed to determine the structure of the relationship between the severity of the raised lipid level and the PDD. In addition, there are a variety of generic equivalents available for the statins on the South African market. Further studies can be conducted to investigate the cost implications of generic prescribing.



	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
DDD*	20	60	45	30	10	30
Average PDD	20.91	57.29	26.31	25.35	15.02	23.70
PDD (Females)	19.84	58.72	23.40	24.75	13.82	23.57
PDD (Males)	21.60	55.59	28.33	25.74	15.97	23.80

Figure 3. DDDs and average PDDs of the statins



	<10	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	>90
Atorvastatin		26.00	27.69	19.09	23.05	19.88	21.53	21.57	16.47	10.00
Rosuvastatin		10.14	12.14	13.91	13.54	14.49	16.45	17.60	13.37	10.00
Simvastatin	25.00	18.89	20.62	21.82	23.11	23.88	24.18	24.25	23.45	13.75

Figure 4. Variability according to age groups of the average PDDs of the three most often prescribed statins

Table 3. Prescribing frequency of the different active ingredients

HYPOLIPIDAEMIC CLASS	ACTIVE INGREDIENTS	NUMBER OF PRODUCTS		
		FEMALES	MALES	TOTAL
Fibrates	Bezafibrate	482	779	1 261
	Fenofibrate	59	65	124
	Gemfibrozil	0	2	2
HMG CoA Reductase Inhibitors	Atorvastatin	2 572	3 965	6 537
	Fluvastatin	172	145	317
	Lovastatin	147	212	359
	Pravastatin	120	183	303
	Rosuvastatin	1 973	2 508	4 481
	Simvastatin	10 487	13 530	24 017
Cholesterol Absorption Inhibitors	Ezetimibe	231	399	630
Others	Cholestyramine	83	71	154
	Ezetimibe & Simvastatin	93	95	188
TOTAL		**16 419**	**21 954**	**38 373**

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