

## Lipid-lowering drug use in Italian primary care: effects of reimbursement criteria revision

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### Abstract

**Objective** To assess whether the prescribing pattern of lipid-lowering drugs (LLD) changed after reimbursement criteria revision in a general practice in southern Italy.

**Methods** From the Caserta-1 Local Health Service database, 93 general practitioners (GPs) who had consistently sent data about their patients during the years 2003–2005 were recruited. Prevalence of use and incidence of new treatments were calculated for each year, stratified by three drug cohorts: statins, omega-3 fatty acids, and fibrates. Subanalyses by gender, age, and indication of use were performed.

**Results** Overall, 1-year prevalence of LLD use increased from 2003 to 2004. After reimbursement criteria revision (November 2004), a slight decrease was observed for statins, from 41.1 (95% CI: 39.9–42.2) per 1,000 inhabitants in 2004 to 40.3 (39.2–41.5) in 2005, while omega-3 utilization fell markedly: 14.6 (13.9–15.3) vs. 5.4 (5.0–5.8).

The use of both statins and omega-3 fatty acids was reduced particularly for primary prevention. On the other hand, utilization of statins increased in diabetic patients and as secondary prevention from 2004 to 2005. Concerning individual molecules, 1-year prevalence of use of any statin declined from 2004 to 2005, except for rosuvastatin.

**Conclusions** Revision of reimbursement criteria led to significant changes in the trend in LLD use in general practice in southern Italy: (1) statin utilization was slightly reduced in 2005, although it increased in certain categories, such as diabetic patients, and (2) omega-3 fatty acid use was strongly reduced even though a higher use in post-infarction cases was reported.

**Keywords** Lipid-lowering drug · Statins · Omega-3 fatty acids · Prevalence of use · General practice

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### Introduction

Hypercholesterolemia is a well-known risk factor of cardiovascular (CV) diseases and its successful treatment with lipid-lowering drugs (LLDs) is one of the most important goals in CV disease prevention [1].

Utilization of statins has been progressively increasing worldwide since their marketing in the 1980s, supported by scientific evidence showing both their effectiveness [2, 3] and good safety profile [4] in CV disease prevention.

In addition to statins, fibrates and omega-3 polyunsaturated fatty acids are the main LLDs currently marketed. Omega-3 fatty acids, naturally available in fish, shellfish, soya oil, leafy vegetables, walnuts, and others, have been claimed to have a protective role against coronary ischemic diseases due to lowering of serum triglycerides, platelet aggregation inhibition, endothelial function modulation,

blood pressure regulation, and anti-inflammatory and anti-arrhythmic effects [5].

In Italy omega-3 fatty acids have been marketed since 2001 as prescription drugs totally reimbursed by the National Health System (NHS), while they are considered dietetic integrators in other Western countries. As a result, the consumption of omega-3 fatty acids strongly increased in Italy, moving from 722nd place in terms of national drug expenditure in 2001 to 8th in 2004 [6].

In November 2004, the Italian Drug Agency revised reimbursement criteria of LLDs, as reported in Nota 13 [7], according to updated scientific evidence.

The aim of this study was to assess whether the trend of lipid-lowering drug use changed after reimbursement criteria revision in a general practice in southern Italy. For this reason, this drug utilization study explored the years 2003–2005.

## Methods

### Setting

The investigation was carried out using data that were extracted from the Arianna database in the years 2003–2005. The database was set up by the Local Health Service of the city of Caserta in the year 2000. It currently contains information on almost 300,000 individuals who are living in the catchment area of Caserta and registered on the lists of 225 general practitioners (GPs). This sample of physicians accounts for 74% (225/305) of all the GPs practicing in the same area. In general, participating GPs record data during their daily clinical practice through dedicated software and, monthly, they send complete and anonymous clinical data about their patients to the Arianna database. The information collected includes patient demographics, drug prescriptions (reimbursed by NHS) coded according to the Anatomical Therapeutic Chemical (ATC) classification system, and medical diagnoses coded by the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9 CM) that are linked to any drug prescription.

All the GPs enrolled in the Arianna database had previously received extensive training in data collection techniques. A number of data quality checks are routinely performed, including analysis of several variables such as monthly continuity of data submission, missing patient codes, and number of prescriptions filled daily. Any variation beyond the defined range is investigated and the data are returned to the participating GP in order to receive immediate feedback about data quality and completeness. GPs failing to meet these standard quality criteria are not retained within the analyses, according to basic standards

for the conduct of pharmacoepidemiological studies [8]. So far, the Arianna database has been shown to provide accurate and reliable information on drug utilization [9–11].

### Study population

Overall, 93 GPs that consistently sent reliable data to the Arianna database during the years 2003–2005 were selected for this investigation. Out of the approximately 120,000 individuals registered in their lists, users of LLDs were identified. LLD users were defined as individuals who received at least one lipid-modifying agent (ATC: C10) prescription during the observation years. Patients aged 18 years and over were included in the study, irrespective of whether LLD treatment was initiated by GPs or by specialists. Indeed, in Italy outpatients who receive prescriptions from specialists working in the public or private health-care services get the medicines free of charge only through GP prescriptions. After identification of LLD users, the following information was retrieved using the Arianna database: patient demographics, LLD-related data, including product name, dispensed quantity, indication of use, and concurrent diseases being pharmacologically treated during the years 2003–2005.

Annual utilization of different LLD types was stratified into primary or secondary prevention. A treatment was defined as secondary prevention if the LLD user was affected by coronary heart disease, cerebrovascular disease, peripheral arterial disease, CV procedures, or diabetes prior to the first LLD prescription date.

### Health policy intervention

LLD reimbursement criteria (Nota 13) were revised in November 2004. Briefly, the main changes made by this health-policy intervention are reported below:

1. Omega-3 fatty acids are reimbursed only for treatment of hyperlipidemia in patients with prior myocardial infarction (MI), while they had been totally reimbursed before the revision.
2. Statins are reimbursed in case of hypercholesterolemia that cannot be corrected through diet only, for both primary and secondary CV disease prevention.
3. For primary prevention, statin use is now restricted to high-risk users, based on a national risk profile [12, 13]. For secondary prevention, statin use is reimbursed for patients affected by coronary heart disease, cerebrovascular disease, peripheral arterial disease, CV procedures and, after this health policy intervention, the use of statins was also extended to patients affected by diabetes.

Fibrates, statins, and omega-3 fatty acids are all reimbursable in case of familial hyperlipidemia (FH), as indicated also in the previous reimbursement criteria.

## Study drugs

The following drug cohorts were identified:

1. Statins: simvastatin (C10AA01), pravastatin (C10AA03), fluvastatin (C10AA04), atorvastatin (C10AA05), and rosuvastatin (C10AA07)
2. Omega-3 fatty acids (C10AX06)
3. Fibrates: clofibrate (C10AB01), bezafibrate (C10AB02), gemfibrozil (C10AB04), and fenofibrate (C10AB05)

Patients that were treated only with bile acid sequestrants, nicotinic acid and derivatives, or other lipid-modifying agents were not taken into account in this analysis since these drugs are not reimbursed according to the new health policy intervention.

In addition, lovastatin (C10AA02) and simvastatin-ezetimibe combination (C10BA02) were not considered because they were introduced onto the market at the end of 2005 and no prescriptions were filled by physicians within the observation period.

## One-year prevalence and incidence of use

Annual prevalence of LLD treatment was calculated as the number of LLD users divided by the number of subjects alive and registered in the GPs' lists in any study year. We defined a "new user" as a patient receiving a first LLD prescription within the observation years without any recorded LLD prescription in the previous year. The 1-year cumulative incidence was calculated as the number of new users divided by the number of subjects who did not take lipid-lowering drugs in the previous year.

Both prevalence and incidence per year were expressed as rates per 1,000 inhabitants, together with 95% confidence interval (CI).

## Statistical analysis

Two-tailed chi-squared test for proportions and Student's *t*-test for continuous variables, with a significance level of  $P < 0.05$ , were used for assessing the differences among users of various LLD types. Chi-square for trend was used to evaluate any significant ( $P < 0.05$ ) variation in 1-year prevalence of LLD use during the study years. Statistical analyses were performed using STATA 6.0 (STATA, TX).

## Results

### Prevalence of LLD use

Prevalence of LLD use per 1,000 inhabitants, stratified by drug types and calendar years, is shown in Fig. 1. The most

commonly used LLDs are statins, which account for more than 60% of LLD use. Rate of statin users significantly ( $P < 0.05$ ) increased from 35.3 (34.3–36.4) per 1,000 in 2003 to 41.1 (39.9–41.4) in 2004, while it slightly decreased in the following year (40.3, 39.2–41.4).

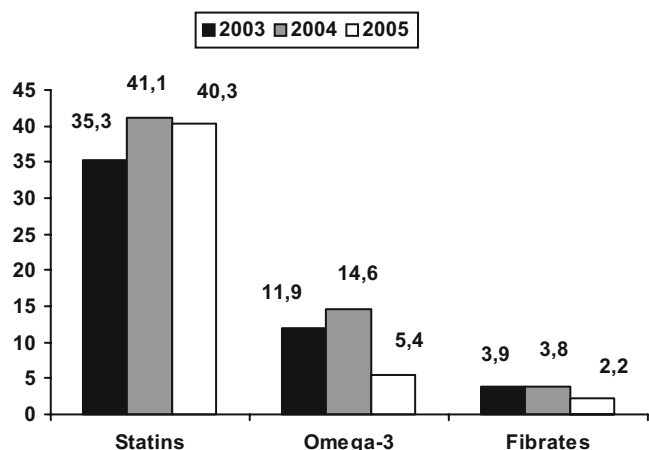
Concerning omega-3 fatty acid use, a significantly decreased use was reported after reimbursement criteria revision: from 14.6 (13.9–15.2) per 1,000 in 2004 to 5.4 (5.0–5.8) in 2005. Fibrate use remained consistently low across the study years, with the lowest rate reported in 2005: 2.2 (2.0–2.5) per 1,000.

No significant differences by gender were reported among statin users. However, after the health policy intervention, the prevalence of statin use decreased from 40.1 (38.6–41.7) per 1,000 in 2004 to 37.1 (35.6–38.5) in 2005 among females, while it rose from 42.0 (40.4–43.7) to 43.8 (42.1–45.5) in males in the same period.

With regard to age, prevalence of statin use per year progressively increased with age during the study period, while it tended to decrease in patients over 75 years, and, in particular, over 85 years: 19.7 (14.8–26.3) per 1,000 in 2005 (data not shown).

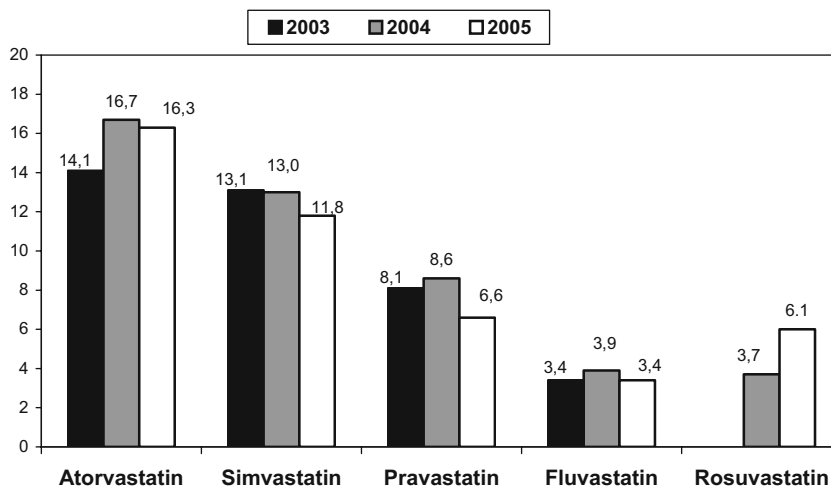
Omega-3 fatty acid users were significantly younger (mean age  $\pm$  SD: 59.8  $\pm$  13.3 years) than statin users (63.8  $\pm$  11.7 years). After the health policy intervention, however, a strong reduction in omega-3 fatty acid use was reported in all age groups (data not shown).

Among statin users, a subanalysis was performed to assess the annual prevalence of use of individual molecules (Fig. 2). Atorvastatin was the most used statin in each study year [in 2005: 16.3 (15.6–17.1) per 1,000], followed by simvastatin and pravastatin. One-year prevalence of use of all statins decreased from 2004 to 2005, except for rosuvastatin, which increased from 3.7 (3.4–4.1) to 6.1 (5.6–6.4).



**Fig. 1** Prevalence of lipid-lowering drug use per 1,000 inhabitants, stratified by drug type and calendar year

**Fig. 2** Prevalence of statin use per 1,000 inhabitants during the years 2003–2005, stratified by molecule



Differences by drug type were highlighted after analyzing the prevalence of use per year, according to indication of use (Fig. 3).

Statin utilization for primary prevention was slightly reduced after reimbursement criteria revision [in 2004: 31.2 (30.2–32.2); in 2005: 27.8 (26.9–28.8)], while a much stronger reduction was reported for omega-3 fatty acid use: from 11.2 (10.6–11.8) in 2004 to 3.8 (3.4–4.1) in 2005.

On the other hand, the rate of statin prescriptions for secondary prevention rose consistently during the study years: from 6.8 (6.3–7.2) per 1,000 in 2003 up to 12.5 (11.9–13.1) in 2005. In particular, the 1-year prevalence of statin use in patients with diabetes progressively increased from 3.1 (2.8–3.5) in 2003 to 6.9 (6.4–7.4) in 2005 (data not shown).

In contrast, omega-3 fatty acid use for secondary prevention decreased from 2004 (3.4; 3.1–3.7) to 2005 (1.6; 1.4–1.9). After the health policy intervention, patients

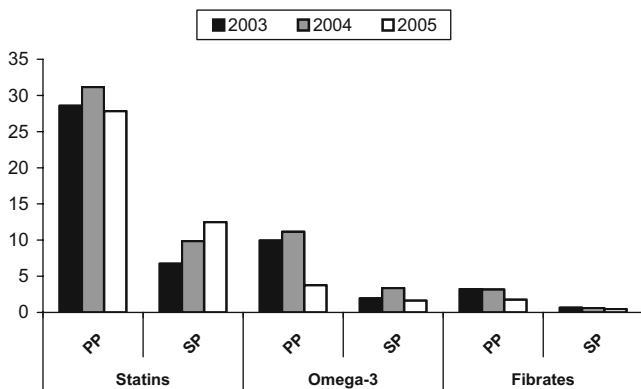
affected by myocardial infarction accounted for the majority of users.

Utilization of fibrates remained very low for both primary and secondary prevention compared to other LLDs during the study years.

One-year incidence of LLD use

A significant decrease in annual incidence of LLD treatment was observed from 2004 to 2005 for all drug classes (Fig. 4). However, a highly significant reduction in 1-year incidence was reported only for omega-3 fatty acid users, falling from 5.4 (4.9–5.8) per 1,000 inhabitants in 2004 to 0.9 (0.7–1.1) in 2005.

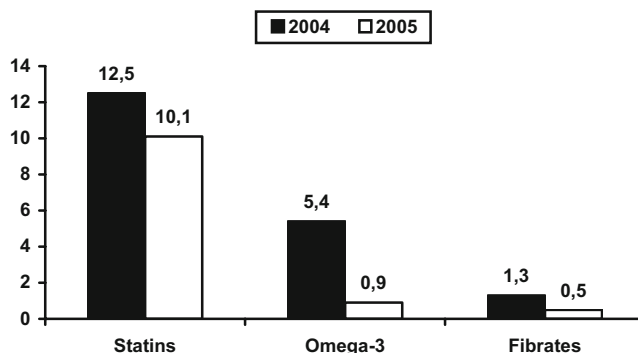
Incident treatments with statins (in 2005: 10.1; 9.5–10.7) remained remarkably higher than other LLDs.



**Fig. 3** Prevalence of LLD use per 1,000 inhabitants during the study years, stratified by drug type and indication of use. PP Primary prevention, SP secondary prevention. Secondary prevention was defined as treatment of patients with well-documented coronaropathy, prior stroke, prior myocardial infarction, peripheral obliterative arteriopathy or diabetes

Discussion

In November 2004, the Italian Drug Agency revised LLD reimbursement criteria (Nota 13) in light of updated



**Fig. 4** One-year incidence (per 1,000 inhabitants) of treatment with LLD for the years 2003–2005, stratified by drug type

scientific evidence [7]. The results of our study highlight that the health policy intervention significantly influenced statin and omega-3 fatty acid use in a general practice in southern Italy.

Concerning statins, a peculiar trend was reported in our analysis: the prevalence of statin use per year increased from 2003 to 2004, while it slightly decreased in 2005 after reimbursement criteria revision. The increase in statin use from 2003 to 2004 is in line with previous investigations that found a constantly growing use of statins in most European countries since their marketing began [14]. In particular, a previous study that explored statin utilization in northern Italy over a 10-year period (1994–2003) reported a 28% average increase per year [15]. On the other hand, the reimbursement criteria revision led to a slight reduction in both 1-year prevalence and incidence of statin use with a different prescribing pattern of these LLDs.

This could be explained by the fact that statin prescriptions are currently reimbursed for primary prevention according to new cardiovascular risk charts [12]. These risk charts lead to a reduction in statin use as primary prevention since the absolute risk in the Italian population is lower than in the U.S. population. Moreover, this reduction mainly relates to women on the basis of scientific evidence supporting that cardiovascular risk factors affect more men than women [16, 17].

The health policy intervention did not determine any significant change in the statin use by age groups, although the time window of the study may have been too short to adequately evaluate it. In all study years, prevalence of use of these LLDs decreased in patients over 75 and, particularly, over 85 years. In line with our results, a British study [18] highlighted that statin use in very old patients is strikingly lower compared to younger patients and, in some cases, the elderly who could benefit from LLD treatment do not receive it. An animated debate is currently underway within the scientific community about the appropriateness of LLD treatment in older patients [19]. Some clinical trials have shown the benefits of statin therapy in cardiovascular prevention also in elderly with hypercholesterolemia [20].

Interestingly, statins were more prescribed for primary than for secondary prevention in all the study years. After reimbursement criteria, however, their use rose in patients for secondary prevention and, in particular, in patients affected by diabetes mellitus. Indeed, patients with hypercholesterolemia can be treated with statins free of charge in case of secondary prevention, including diabetes mellitus, after the health policy intervention.

The revision of reimbursement criteria was based on recent scientific evidence showing a significant reduction in risk of vascular events in diabetic patients who are treated with statins for both primary and secondary prevention [21, 22].

Looking at individual molecules, atorvastatin and simvastatin were the most used statins during the study years, in line with a previous European investigation [14] and the Italian national report [6]. In our investigation, however, the annual prevalence of use of any statin was reduced after reimbursement criteria revision, with the exception of rosuvastatin, which was first marketed in Italy in 2004. The extensive marketing campaign launched by the drug manufacturer to promote this statin could partly explain the unusual increase [23]. This finding confirms the trend of newly marketed drugs to be widely prescribed in general practice immediately after their introduction to the drug market, despite a proven lack of effectiveness and safety data derived from clinical practice [24].

The effect of the reimbursement criteria revision on omega-3 fatty acids was a dramatic reduction, in particular of new treatments, from 2004 to 2005. Our results are in line with an Italian national report that reported a 40% decrease in omega-3 fatty acid use in 2005 compared to the previous year [6]. This finding might be explained by the restriction in reimbursement criteria of omega-3 fatty acids, which are now free of charge only in patients with a history of myocardial infarction. It should be emphasized that omega-3 prescriptions had been totally reimbursed for primary prevention prior to reimbursement criteria revision, although clinical trials [25] that showed omega-3 fatty acid benefits in CV prevention had included only patients with a recent history of myocardial infarction.

Compared to statins and omega-3 fatty acids, use of fibrates was remarkably low during the observation years. Such a finding is in contrast with other European countries where these LLDs account for almost one-fourth of total LLD utilization [14]. We were not able to accurately characterise the users of fibrates in light of the low utilization of these LLDs.

Overall it seems that the health policy intervention led to changes in LLD prescribing patterns that are in line with European recommendations for pharmacological treatment of lipid disorders [26]. On the other hand, a Belgian investigation [27] that analyzed the impact of health policy intervention on statin utilization for secondary prevention highlighted that reimbursement criteria restriction of LLD could also lead to underutilization in patients who would have benefited from LLD therapy.

#### Strengths and limitations of the study

To our knowledge, this is the first drug-utilization study targeted to measure the prevalence of LLD use as both primary and secondary prevention in a general practice in southern Italy. In particular, the availability of prescription data from 2003 to 2005 allowed us to evaluate the effect of reimbursement criteria revision on LLD use in clinical

practice. Moreover, we were also able to evaluate some clinically relevant characteristics of LLD users, such as indication of use.

However, several limitations of our study warrant caution. First of all, we used outpatient prescription data, and we had no information whether LLD prescriptions were actually filled and taken. This limit should be taken into account since around half of the medicines prescribed for people with chronic conditions are not ultimately taken [28]. Nevertheless, our study was aimed at evaluating how the GPs' prescribing behavior was influenced by the health policy intervention. Therefore, this prescription database can be considered suitable for such an investigation. Second, we could not evaluate the number of LLD prescriptions that were not reimbursed by the National Health System. Data from an Italian national report on drug consumption, however, showed a strong decrease in omega-3 fatty acid use after reimbursement criteria revision, thus supporting one of the main findings of our study [29]. Furthermore, we did not take into account familial dyslipidemia as a potential indication of LLD use, even though all LLD treatments are fully reimbursed in such a condition. Indeed, this diagnosis is not accurately codified through ICD-9 codes in general practice, but a previous Italian investigation [30] reported only 13% of statin prescriptions are filled to patients with familial dyslipidemia.

In conclusion, the health policy intervention modified the trend in the lipid-lowering drug use in general practice. Statin utilization was slightly reduced in 2005, although it increased in certain categories of patients (diabetes mellitus and secondary prevention). Conversely, omega-3 fatty acid utilization was markedly reduced in 2005.

In the management of dyslipidemia and cardiovascular prevention, the appropriateness of GP prescribing could be improved through reimbursement criteria revisions based on updated scientific evidence. A definition of these criteria, however, should be developed among regulatory agencies and health professionals.

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