

RESEARCH ARTICLE

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The impact of Regional co-payment and National reimbursement criteria on statins use in Italy: an interrupted time-series analysis

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Abstract

Background: Statins are among the most commonly prescribed drugs worldwide in the prevention of cardiovascular diseases and their effectiveness is largely acknowledged. The consumption of statins increased four-fold during the 2000–2010 decade in Italy and national and regional control policies were developed. Restrictions to reimbursement were fixed at the national level, whereas co-payment was introduced in some, but not all, regions. The aim of the present study is to assess the impact of such policies on the consumption of statins in Italy between 2001–2007 among outpatients.

Methods: The statin use was measured in terms of defined daily doses per 1,000 inhabitants per day (DDD/1000 inh. day) from May 2001 to December 2007. The study was conducted in 17 out of 21 regions, nine of which had implemented a co-payment policy. Time trends in consumption before and after the introduction of co-payment policies and reimbursement criteria were examined using segmented regression analysis of interrupted time-series, adjusting for seasonal components.

Results: The consumption of statins increased by 22.9 DDD/1000 inh. day in May 2001 to 54.7 DDD/1000 inh. day in December 2007. On average, there was a 1.7% increase in statin use each month before the national guideline changed while the increase was about 0.5% afterwards. The revision of the reimbursement criteria was associated with a significant decrease in level (coefficient = -2.80 , 95% CI -3.70 to -1.90 p-value <0.001) and trend (coefficient = -0.33 , 95% CI -0.37 to -0.29 p-value <0.001). The introduction of co-payment was associated with a significant change in trend of consumption so that the overall use of the drug increased by 0.04 (95% CI 0.02 to 0.07, p-value <0.001) DDD/1000 inh. day per month in the post-intervention period, but there was no evidence of a change in level of consumption (p-value = 0.163).

Conclusions: Consumption of statins in Italy increased almost three-fold during the study period. The restriction to reimbursement Interventions was associated with an immediate drop and a decrease in trend of statin use, while the regional copayment was associated with a small increase in trend of statin use.

Keywords: Interrupted time-series, Statin use, Pharmaceutical policy, Italy

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Background

In recent years, many policies have been implemented across the European Union to enhance the appropriate use of drugs and to contain pharmaceutical cost [1,2].

The 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors (statins) were first used in patients with myocardial infarction (MI) and hypercholesterolemia. Several clinical trials, cohort studies and reviews largely acknowledged statins effectiveness: their beneficial effects were evident as lipid-lowering agents in patients with ischemic heart disease (IHD), other atherosclerotic cardiovascular diseases (CVD), diabetes, and even in the treatment of asymptomatic individuals [3-12]. These clinical trials had major implications for cholesterol management that resulted in an increase in the number of patients for whom statins may be considered clinically appropriate [13], such raising the expenditure, at least before the patent expiration of some molecules.

Thus, a wide range of measures to contain the cost of statins was developed in many Countries (e.g. Norway), including lists of preferred generic substitutions and/or medicines for which the patients are reimbursed (Austria and Finland), and co-payment policies (USA, Canada). The effect of these policies was assessed in recent studies with regards to drug expenditure, adherence therapy, or health outcomes [14-19].

Even though Italy has one of the lowest rates of use in Europe [20], the consumption of statins has constantly increased during the last decade, almost quadrupling its level from 14.67 DDD/1000 inhabitants per day (DDD/1000 inh. day) in 2000 to 51.70 DDD/1000 inh. day in 2010 [21,22]. Compared to 2010, in 2011 (the latest available data for a whole year) statin consumption still increased (+7.7%) while the expenditure decreased (-13.1%) Despite this fact, statins rank first in expenditure as a cardiovascular drug subgroup [23].

Most of the costs are charged to the Italian National Health Service (Servizio Sanitario Nazionale, SSN) which provides universal coverage.

In order to contain the cost of drugs, a co-payment policy was first introduced in Italy in 1978, then abolished in January 2001 by the national government, and subsequently it was reintroduced at the local level by some regions, following the decentralization trend [24] of the policy-making government.

The change in Italian Constitutional Chart in 2001, determined a devolution process that transferred legislative, administrative and considerable fiscal powers to regions. According to this, the central government was granted the exclusive power to set "essential levels of care" (Livelli Essenziali di Assistenza, LEAs), a package of benefits that are publicly funded and must be guaranteed to all citizens in all regions. Most essential drugs are included in LEAs. At the same time, regions have

almost full control over the provision of services, regulation, and funding with the mandate to provide LEAs [25]. LEAs hold regions accountable to national standards.

Thus, since 2002, regions have made different choices regarding co-payment policies with subsequent significant cross-regional variation among patient charges for drugs [26]. In regions with a co-payment policy, patients are required to contribute to the cost of pharmaceuticals by a fixed amount per prescription, ranging from 1 to 5 euros, depending on the region [27]. On the other hand, the criteria for the reimbursement of statins were issued and periodically revised at the national level. They contained specific indications, inspired by clinical practice and guidelines, that determined whether the statins could be prescribed and reimbursed for specific diseases and conditions [28]. Their introduction had a dual purpose: cost containment and a more appropriate use of these drugs [29]. In November 2004, according to new scientific evidence, criteria for reimbursement for lipid lowering agents were revised by the new Italian Drug Agency (AIFA). The new criteria (Nota AIFA 13) restricted statin reimbursement to high risk users, based on a national risk profile for primary CVD prevention while they extended reimbursement for patients with diabetes in secondary CVD prevention [30,31].

The aim of this study was to evaluate the impact of the national and regional cost containment measures on statin use in Italy during the period May 2001 – December 2007.

Methods

Data

Data on drug consumption in Italy between May 1, 2001 and December 31, 2007 were collected from the Federfarma database. This database includes all drug use paid by the National Health Service, excluding in-hospital as well as out-of-pocket drug use. Data were provided by the Italian National Institute of Health on an aggregate basis, with regions and time being the unit of analysis. Because no individual data was available, ethical approval of the study was not sought.

The dataset included the number of Defined Daily Doses per 1000 inhabitants per day (DDD/1000 inh. day) for all drugs in the C10AAxx category of the Anatomical Therapeutic Chemical (ATC) system [32]. Data from each Italian region were available on a monthly basis, and they were adjusted by age and sex according to the weights established by the Department of Programming of the Italian Ministry of Health.

The analysis considered 17 out of the 21 Italian regions. They were divided in two groups. The first one included regions which (re)introduced a co-payment: Bolzano, Campania, Liguria, Lombardia, Molise, Piemonte,

Puglia, Sicilia and Veneto. The second one included those regions that did not reintroduce a co-payment: Basilicata, Emilia Romagna, Friuli Venezia Giulia, Marche, Toscana, Trento, Umbria, Valle d'Aosta. We excluded Abruzzo, Calabria, Lazio and Sardegna because these regions modified the co-payment mechanism several times during the study period.

Statistical analysis

A descriptive analysis of the consumption of statins during the study period was first performed. Tables describing the consumption of statins for both regions with and without co-payment policies have been compiled. An average monthly variation index (calculated as: $[(\text{End-period consumption}/\text{Start-period consumption})^{1/n} - 1] * 100$) was provided for both the periods pre- and post-prescribing guideline change. Graphs showing the statins use trends for both regions with and without co-payment policies were plotted. Subsequently, we analysed the series to identify the most appropriate model to describe the data until the time of intervention, and to make a forecast for the post-intervention period in order to assess if there was a significant impact of the policy change on the consumption of statins. We chose the most befitting model (between the ARIMA and the exponential smoothing models) after a residual analysis through the Ljung-Box test [33] and the check of the autocorrelation and partial autocorrelation functions of the residual. The mean absolute error (MAE) and the mean absolute percentage error (MAPE) between the observed and the predicted series were also calculated in order to identify the best forecasting technique for the data as the model that minimized these forecast indices.

The model of choice was the Holt-Winters Additive model, that was the best forecasting technique among the Exponential smoothing models (MAE = 1.516; MAPE = 4.727). This final model was the result of several iterations of the identification, estimation, and checking process, and it met the conventional criteria for the adequacy of the model. The autocorrelation and partial autocorrelation functions of the residuals showed a good fit. The residual plots showed small variations around the zero mean. None of these residuals had its magnitude larger than twice the standard deviation. Residual autocorrelations were not significantly different from zero as a set and had constant variance, thus confirming the adequacy of the model (Ljung-Box statistic = 6.807; p-value = 0.963).

To determine the extent of the impact of policy changes on pharmaceutical utilisation, we used segmented linear regression for the interrupted time-series analysis [34]. This analysis provided estimates of an outcome (DDD/1000 inh. day) before and after defined change points (the introductions of co-payment and the

revision of national prescription guidelines). To eliminate the seasonal component related to the consumption of the drug and assess the "true effect" of the above-mentioned measures, we performed a seasonal decomposition on the series before the estimation of the regression model. Segmented linear regression divides a time-series into pre- and post-intervention segments. In this case, we had two change points at different time periods, so our series was divided into three segments.

The model has two parameters of interest: the level and slope. Therefore the difference between the two segments can be quantified by testing the change in these two parameters. A change in level between the pre- and the post-intervention segments indicates a step-change, and a change in slope indicates a change in trend. The estimated base model is the following:

$$\begin{aligned}
 Y_t = & \beta_0 + \beta_1 * time + \beta_2 * copayment + \beta_3 \\
 & * time after copayment + \beta_4 * reimbursement \\
 & + \beta_5 * time after reimbursement + \sum_{i=1}^{16} \beta_i * D_i + e_t
 \end{aligned}
 \tag{1}$$

Here, Y_t is the mean number of DDD/1000 inh. day in month t ; *time* is a continuous variable indicating time in months at time t from the start of the observation period; *co-payment* is an indicator for time t occurring before (intervention = 0) or after (intervention = 1) its introduction, which occurred at different instants of time for the considered Italian regions; *time after co-payment* is a continuous variable counting the number of months after the intervention at time t , coded 0 before the introduction and 1 (time - time of intervention) after. *Reimbursement* and *time after reimbursement* are two variables built in the same mode of the previous ones but refer to the revision of national reimbursement criteria in November, 2004; e_t is the error term at time t and represents the random variability not explained by the model. In this model, β_0 estimates the baseline level of the outcome (expressed in DDD/1000 inh. day) per month, at time zero; β_1 estimates the pre-intervention slope (i.e. the baseline trend); β_2 estimates the level change immediately after the introduction of co-payment, that is from the end of the preceding segment; β_3 estimates the change in trend relative to the first intervention compared with the pre-existing monthly trend; β_4 and β_5 are respectively the estimate of the level and trend change relative to the revision of AIFA Notes. D represents 17-1 Dummy variables relative to the considered regions. We coded the regional Dummies by the "deviation from means coding" method [35]. This coding expresses effect as the deviation of the "group mean" from the "overall mean".

We tested whether each of these parameters is significantly different from zero from a two-sided *t* test to determine whether a discontinuity at each join point existed.

For statistical analysis we used the software SPSS v.13.0 for Windows environment.

Results

Figure 1 shows the time series of the mean number of statins use (DDD/1000 inh. day) per month, interrupted by the two policy changes: the introduction of co-payment in different dates for each regions, indicated by the arrows in the graph, and the revision of AIFA Notes in November 2004, indicated by the vertical line. The visual inspection of the series suggests that the use of statins increased during the study period for both groups of regions.

As shown in Table 1, the consumption of statins increased by 22.9 DDD/1000 inh. day in May 2001 to 54.7 DDD/1000 inh. day in December 2007. On average, there was a 1.7% increase in statin use each month before the national guideline changed while the increase was about 0.5% afterwards.

As shown in Figure 2, the revision of AIFA Note 13 was associated with a large change in the use of statins because the observed series is outside the 95% confidence interval for the short-term forecast. The short-term forecast beyond the observed series (from May 2001 to November 2004) of statin consumption in all the seventeen regions adequately captured the pattern in the data until the policy change (revision of AIFA Notes) and showed an increasing tendency of drug use with a mean 9.7 DDD/1000 inh. day each month over the observed series during the forecast interval (post intervention period).

This result was confirmed by the estimates of the regression model that explained the effect of policy change. Table 2 contains the parameter estimates from the linear segmented regression model.

The introduction of co-payment was associated with a significant change in slope so that the overall use of the drug increased by 0.04 (95% CI 0.02 to 0.07, *p*-value < 0.001) DDD/1000 inh. day per month in the post-intervention period, but there was no evidence of a change in level (*p*-value = 0.163).

Prescription guidelines showed a large impact on the use of statins. A temporal association between the revision of the AIFA Note in November 2004 and a remarkable reduction in the upward trend of statin use in the same period were observed. This intervention was associated with a significant decrease in level (coefficient = -2.80, 95% CI -3.70 to -1.90 *p*-value <0.001) and slope (coefficient = -0.33, 95% CI -0.37 to -0.29 *p*-value <0.001).

Discussion

This study showed that the change in the national reimbursement criteria influenced the utilization of statins in Italy, determining a statistically significant reduction in the upward trend of prescriptions. On the other hand, the effect of the local co-payment on statin use was negligible. Overall, statin consumption increased from 2001 to 2007, according to previous research showing a similar trend in most European countries [36].

Reimbursement criteria revision that occurred in Italy in 2004 was issued with the aim to improve the appropriateness of drug prescriptions, following updated scientific evidence related to cardiovascular disease risk reduction. Our findings are consistent with Trifirò et al. [37] that reported a significant decrease in the utilization

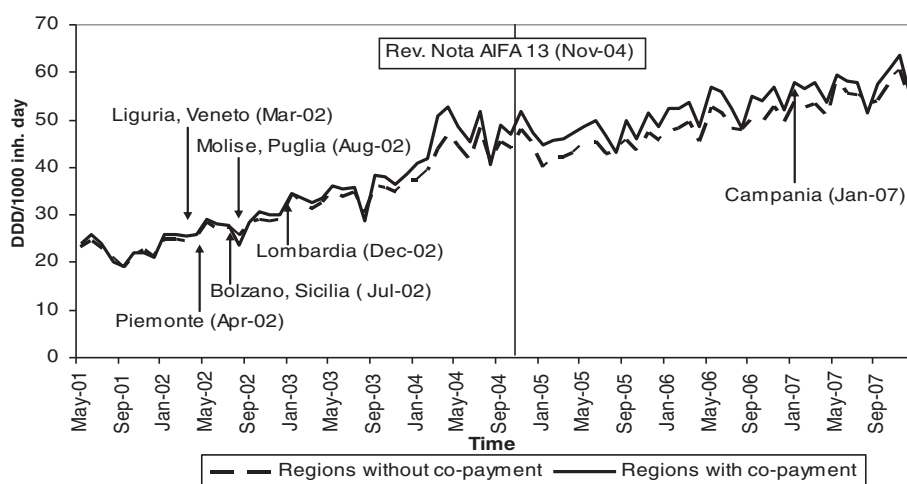


Figure 1 Monthly statins consumption (DDD/1000 inh. day) in the two groups of regions. The arrows show the month and the year in which the indicated regions have applied the co-payment measures.

Table 1 Statins consumption per 1000 inhabitants per month in the considered Italian regions

	Regions	May-01	Nov-04	Dec-07	Δ% (04-01) *	Δ% (07-04) *
Regions with the co-payment	P.A. Bolzano	23.83	40.25	42.99	1.26	0.17
	Campania	26.23	54.00	61.32	1.73	0.33
	Liguria	13.93	47.27	52.91	2.95	0.29
	Lombardia	27.29	48.81	55.83	1.39	0.35
	Molise	17.53	39.79	45.40	1.97	0.34
	Piemonte	23.90	39.62	47.74	1.21	0.48
	Puglia	21.61	47.06	63.55	1.87	0.77
	Sicilia	25.89	55.91	66.84	1.85	0.46
	Veneto	26.61	48.06	59.69	1.42	0.56
Total Regions with co-payment :		22.98	46.75	55.14	1.74	0.42
Regions without co-payment	Basilicata	20.93	50.00	58.43	2.10	0.40
	Emilia-Romagna	27.01	50.10	61.66	1.48	0.53
	Friuli Venezia Giulia	26.57	47.72	57.11	1.40	0.46
	Marche	21.38	45.47	62.00	1.81	0.80
	Toscana	21.60	38.21	49.24	1.37	0.65
	P.A. Trento	24.80	41.27	53.58	1.22	0.67
	Umbria	19.16	39.83	50.50	1.76	0.61
	Valle d'Aosta	21.46	40.73	41.86	1.54	0.07
Total Regions without co-payment:		22.86	44.17	54.30	1.58	0.52
Total:		22.93	45.54	54.74	1.67	0.47

Comparison May, 2001- November, 2004 and November, 2004- December, 2007.
 *Average monthly variation index.

of statin after the Nota 13 change in a general practice in southern Italy. An increased consumption was found only for diabetic patients, which was probably related to the extended criteria of reimbursement for secondary prevention. On the contrary, a study conducted in

Austria by Winkelmayr et al. [15], showed that national change in statin prescribing policies from secondary to primary prevention among diabetic patients did not affect the overall trend of statin use. Northern Europe brings instead some examples of how policies that limit

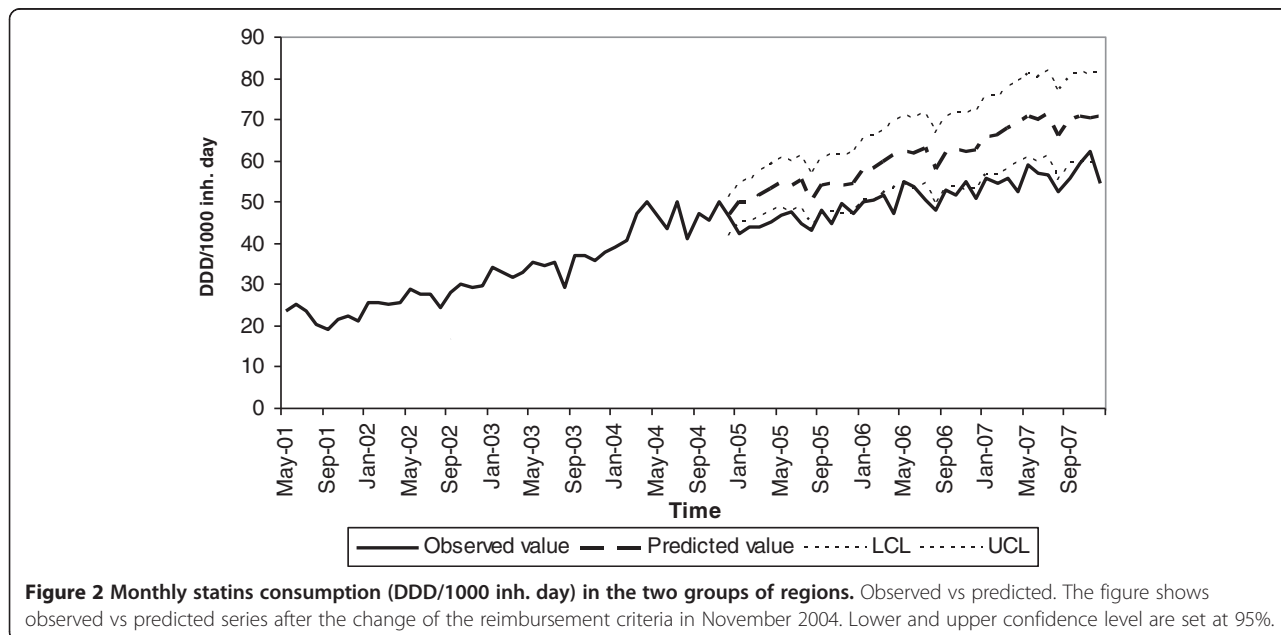


Table 2 Model parameter estimates, standard errors and p-values of statins consumption

Model	Coefficients B	p-value	95% Conf. interval	
			Lower	Upper
(Constant)	18.06	< 0.001	17.43	18.69
time	0.68	< 0.001	0.65	0.71
Co-payment	-0.78	0.163	-1.88	0.32
Time after co-payment	0.04	< 0.001	0.02	0.07
Reimbursement criteria change	-2.80	< 0.001	-3.70	-1.90
Time after reimbursement criteria change	-0.33	< 0.001	-0.37	-0.29

the reimbursement of drugs can be a powerful tool for changing the use of medication. A Norwegian study, conducted in 2007 [14], showed an increase in the consumption of statins and, simultaneously, a decrease of the expenditure after initiating an intervention that forced physicians to prescribe simvastatin or an alternative and to carefully explain the need to use a different statin. Such a policy caused an increase in prescriptions of the less costly statins and an increase in consumption by first-time users while physicians continued to preserve the adherence to the therapy. Similar results came from Finland [16] that reduced costs by instituting policies promoting use of less expensive statins and restricting reimbursement of the more expensive atorvastatin, whose patent expired only in late 2011 [38].

Authors from Harvard and Canada [39] recently applied the interrupted time series study design to assess the impact of the prior authorization (a prescribing-limitation policy that allows the prescription of a non-preferred medication only after the approval from Medicaid) with contrasting results for the two groups regarding the consumption of statins. The policy was associated with a lower use of statins in Michigan, but the effect was negligible in Indiana where there had been little use of non-preferred medications before the policy was implemented.

In our study, the impact of the co-payment on the consumption trend of statins increased statin use in a statistically significant way, but its real effect was very small, as shown in Table 2. Some authors stressed the fact that the main purpose of cost sharing is to introduce incentives so that patients would be able to compare cost to expected outcomes [40]. In Italy, however, the cost shared by the patient is fixed and not proportional as in other countries such as USA or Canada [19]; therefore, this measure becomes irrelevant to a price-oriented behaviour by the consumer. Consequently, it becomes a mere cost-containment tool in the short run [29]. This could conceal some implications for the safety of the population, possibly modifying the adherence to treatment [41-43].

Indeed, Gibson [17] found that as statin cost-sharing levels increase, adherence to statin treatment falls. This could lead to health risks, increasing access to health services and eventually to an increase in expenditure [1,44,45].

Limitations and strengths

Unfortunately, aggregated data do not allow us to collect information about clinical outcomes. For this reason, we cannot assess the appropriateness in the prescription and the adherence to the therapy. As a second limitation, we did not consider the generic market, the marketing strategies such as incentives offered to general practitioners, or the regional policies (e.g., limit on the number of prescriptions for recipe) that may have had an impact on the consumption of statins. A third limitation resides on the observational nature of this study, which does not allow establishing a causal relationship between the intervention and the change in the consumption trend of statins.

However, we would like to highlight the strengths of this study. We could rely on a large dataset covering the entire national territory for a 7-year period. The data are weighted by gender and age, allowing us to overcome differences in the demographic structure among regions. Furthermore, the interrupted time series regression analysis allowed us to obtain more valid estimates of the impact of co-payment and national reimbursement criteria on the utilization of statins compared to a pre-post design [1,34,46].

Conclusions

Consumption of statins in Italy increased almost three-fold during the study period. Interventions at the central level (modification of reimbursement criteria) had an impact in mitigating the growth, showing a temporal association with an immediate drop and a decrease in trend of statin use, while the regional policies (copayment) were associated with a small increase in trend of statin use. In a heavily regulated market, efforts for decentralisation should be aimed at gaining better control over the consumption of statins at the regional level.

Competing interests

The authors declare that there was no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

GD & BF conceived of the study and participated in its design, PN & WR coordinated the study and revised it, AA participated in its design and performed the statistical analysis, LI carried out literature search and drafted the manuscript, CBNAB & GS helped to draft the manuscript and contributed to the interpretation of data, RDC & RR collected data and revised the draft. All authors read and approved the final manuscript.

Acknowledgements

This paper was supported by Faculty Research Fund, Catholic University of the Sacred Heart (Italy), under the title project "Drug utilization and Institutional regulation" (2011).

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Received: 19 July 2013 Accepted: 2 January 2014

Published: 6 January 2014

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doi:10.1186/1472-6963-14-6

Cite this article as: Damiani et al.: The impact of Regional co-payment and National reimbursement criteria on statins use in Italy: an interrupted time-series analysis. *BMC Health Services Research* 2014 **14**:6.

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