

# **Switching among equivalents in chronic cardiovascular therapies: “real world” data from Italy**

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## ABSTRACT

Since August 2012, Italian general practitioners are required to prescribe the generic name of medicines, except for refill of chronic therapy. We evaluated the extent of switching among equivalents in chronic cardiovascular therapies, the influence of the 2012 regulatory intervention and of patient-related or drug-related factors.

Prescription of off-patent antiarrhythmics, oral antidiabetics, and ACE-inhibitors dispensed from August 2011 to August 2013 within the Bologna Local Health Authority (870,000 inhabitants) were collected. The rate of actual switching among equivalents was evaluated monthly. The effect of the regulatory intervention was estimated by interrupted time series analysis. Adjusted odds ratios (aORs) of switching were calculated for: age, gender, number of different equivalents available for each drug, change in dispensing pharmacy between subsequent refills.

The average monthly rates of switches were 9.6%, 16.3%, and 16.3% for antiarrhythmics, antidiabetics, and ACE-inhibitors, respectively. Values significantly increased soon after the regulatory intervention for ACE-inhibitors (+1.81%,  $p=0.00$ ), antiarrhythmics (+1.46%,  $p=0.01$ ) and antidiabetics (+1.09%,  $p=0.01$ ), and no significant decreasing trends were observed in the following 12 months. For all drug classes, odd of switching was higher in case of change in dispensing pharmacy (up to aOR=4.31, 95CI=4.26-4.35 for ACE-inhibitors) and availability of  $\geq 5$  different equivalents (up to aOR=7.82, 95CI=7.39-8.28 for antidiabetics). Switching was lower for age  $\geq 65$  for antidiabetics and ACE-inhibitors (aOR=0.92, 95CI=0.90-0.93; 0.87, 0.86-0.88, respectively).

The Italian regulatory intervention generated an immediate increase, not sustained in time, in switching among equivalents of cardiovascular therapies. Young age, high number of available equivalents and changes in dispensing pharmacy between subsequent refills were associated with switching.

## INTRODUCTION

Pharmaceutical expenditure grew by more than 50% in real terms among OECD (Organisation for Economic Co-operation and Development) countries during the past decade [1], threatening the ability of European healthcare systems to provide comprehensive and equitable healthcare. This scenario is likely to worsen across Europe if not properly addressed, driven by well-known factors, including ageing populations with increases in non-communicable diseases as well as the frequent launch and reimbursement of new premium priced products [2-4]. Many of the new medicines are biological products, often priced at between US\$100,000 - US\$400,000 (Euro74,000 – 296,000) per patient per course or year [4-8]. Initiatives and activities instigated by health authorities across Europe to optimise the use of available resources include developing new models to enhance the appropriate use of new medicines [4] and increasing the prescribing of generic medicines, especially in drug class where all the products are seen as essentially therapeutically similar at appropriate doses [1,9-18]. This can release considerable resources, especially in some European Countries where generic medicines priced as low as 2% to 5% of pre-patent loss prices are available [19-22]. Strategies to enhance the prescribing of generics versus originators include encouraging routine International Non-proprietary Name – INN - prescribing (Lithuania and UK), compulsory generic substitution (Sweden), substitution targets in community pharmacies (France), preference pricing policies (the Netherlands) as well as abolishing co-payments for lower cost generics (Germany and the US) [21,23-30]. Encouraging INN prescribing in the UK by starting from medical school has resulted in generic consumption as high as 97% to 98% for high volume CV drugs including simvastatin, losartan, and lisinopril [25].

The Italian Government introduced a generic substitution policy in 2001, which obliged community pharmacists to inform patients on the cheapest available generic product according to the Italian Medicines Agency equivalent lists. In addition, the Agency introduced a reference pricing system, with patients having to cover the price difference for a more expensive product than the lowest price among the equivalent products available in the regional distribution network (internal reference pricing – IRP [31-34]). IRP system has been now implemented among over 20 EU Member States [31,34,35].

However, despite efforts to promote the prescribing of equivalents in Italy, the generic market is low compared to other European countries. In 2002, generic products accounted for only 1.2% - 2% of the overall Italian market in value terms [32,33] and 17% of the off-patent

market. This low volume was due to issues such as co-marketing strategies, with barriers generated by different companies marketing the same active ingredient, extended patent periods in Italy, and generally higher prices for generics in Italy versus other European countries, making it easier for originator companies to lower their prices to compete.

In August 2012, Italian Government further encouraged the prescribing of generic medicines, with a reform requiring Italian GPs to prescribe the generic name (INN) of medicines with new medicines. The brand name is only allowed in cases of an explicitly defined need for the product or patients with stable chronic disease. Whilst chronic therapies were excluded by the rule, concerns about a possible growth in switch rates among equivalents were expressed by physicians and others. Controversial issues have been reported on interchangeability, both from physicians and patients [36]. It has been argued that substitution with an equivalent product should be carefully considered for medicines with a narrow therapeutic index or highly variability in bioavailability. However, this only applies to a limited number of medicines as seen for instance in the UK with current guidance for INN prescribing [37,38] with, as mentioned, very high INN prescribing rates for the majority of molecules where generics are available [25].

Despite continued efforts, in 2013 generics still only accounted for 30% of total reimbursed doses and approximately a half of off-patent market [39]. Prices of generics also appeared to remain relatively high in Italy, at 40% on the average as compared to pre-patent loss, although with differences among therapeutic classes [34].

The aim of this project is to evaluate the extent of switching among equivalents in different chronic cardiovascular therapies in Italy, whether the regulatory intervention affected this phenomenon and which patient- and drug-related factors can influence the prescribing of generics. Findings will be used to provide further guidance to the authorities in Italy and they will allow comparisons between Countries with different generic prescription rules and habits. Developed methodology could be routinely applied to monitor the impact on future interventions on trend cardiovascular generic dispensation and on switching between equivalents.

## METHODS

This is a cross-sectional study based on information coming from administrative databases.

### *Data source and setting*

Prescription data were extracted from the Drug Reimbursed Database of the Bologna Local Health Authority, covering approximately 870,000 of inhabitants. This database collects all prescriptions dispensed in the Bologna area and reimbursed to all patients by the National Health System.

For this study, we collected and analyzed the prescription of three chronic cardiovascular therapies, identified by the Anatomical Therapeutic Chemical Code dispensed from August 2011 to August 2013. The following classes were considered: ACE-inhibitors (with/without diuretics (ATC code: C09A, C09B)), antiarrhythmics (C01B), and oral hypoglycemic agents (A10B).

### *Identification of switches*

For each prescription, the following data were retrieved: patient characteristics (age and gender) and drug information (ATC code, dispensing pharmacy, dispensation date, number of drug units, and marketing authorisation code). The marketing authorisation code identifies the exact dispensed pharmaceutical product (or medicine) and it allows information to be obtained on active substance, dosage, pharmaceutical formulation, and package strength, e.g. number of tablets into the package.

By using marketing authorisation codes, we grouped pharmaceutical products on the basis of their equivalence in terms of active substance, dosage and formulation. We referred to the equivalent list drawn by the Italian Medicines Agency

[<http://www.agenziafarmaco.gov.it/it/content/liste-di-trasparenza-e-rimborsabilita>] as validation of our grouping procedure.

From the prescriptive history of each subject, we identified the switches among equivalents: a switch was considered when the refill contained an equivalent different from the previous dispensation. Changing in the number of units and changing between originators (named co-marketing products) was not considered as switching.

In order to select only patients susceptible of switching between equivalent products, i.e. potential switchers, new users of a given therapy and patients receiving medicines without

generic equivalents were excluded from analyses. The prevalence of switches was calculated by considering the actual number of switches on the population of potential switchers.

#### *Time trend analyses*

To evaluate the time trend of switching, for each therapeutic class monthly analyses of the total amount of prescriptions and the rate of switches were performed. The effect of the regulatory intervention was estimated by the *interrupted-time-series* methodology. This quasi-experimental design allows evaluation of dynamic changes in medication use following a specific intervention (in our study, it was represented by the regulatory measures taken in August 2012) while controlling for secular changes, that may have occurred in the absence of the intervention [40]. A 6-month period before and after the intervention was selected. Differences between the two segmented periods were estimated for (a) level (value of the series at the beginning of a given interval), representing a potential early modification in the prescription behaviour after the intervention; and (b) trend (slope of a given segment) that indicates a potential continuation of the intervention effect. A difference was considered statistically significant when the  $p$  value of these differences was  $\leq 0.05$ .

#### *Analysis of determinants of switches*

To evaluate the determinants of switching among patient-related (age and gender) and drug-related factors (number of equivalents available on the market for a given drug and change in dispensing pharmacy), a logistic regression model was used, by computing crude and adjusted odds ratios (ORs) with the relevant 95% confidence intervals (CIs).

## RESULTS

Overall, a total of 2,230,575 prescriptions were analysed from the Drug Reimbursed Database. The total amount of generic dispensations at the end of the observed 2-years period was approximately 45% for oral antidiabetics, 38% for ACE inhibitors and 23% for antiarrhythmics (Figure 1).

By looking at the Italian equivalent list, 11 different groups of antidiabetics were identified (i.e., different strengths of sulfonylureas, metformin and repaglinide) containing 2 to 22 different equivalents. As for ACE-inhibitors, we dealt with 31 different groups, with 2 to 25 different equivalents. Among antiarrhythmics, only 4 different equivalent groups were found (amiodarone 200mg, propafenone 150mg, propafenone 300mg and flecainide 100mg) with 4 to 7 different equivalents each one.

From approximately 27,500 total monthly prescriptions of equivalent antidiabetics (including off-patent originators and generics), 86% represented potential switching. As for ACE-inhibitors, we retrieved approximately 57,900 prescriptions of equivalents per month, with an average of 90% potential switching; for antiarrhythmics, out of 3800 monthly prescriptions, 75% were potential switching (see table in supplementary material).

Among patients who received a refill of chronic cardiovascular therapies (potential switching), mean monthly switch rates were 16.3% for antidiabetics, 16.3% for ACE-inhibitors and 9.6% for antiarrhythmics.

Percentages of switches were higher after the approval of the regulatory intervention. The *interrupted-time-series* analysis showed significant changes in level after the intervention for all the considered classes of drugs (level change +1.09;  $p=0.01$  for antidiabetics, +1.46;  $p<0.01$  for antiarrhythmics; +1.81;  $p=0.00$  for ACE-inhibitors). Moreover, we found negligible trend decrease in the months after the intervention (trend change -0.01;  $p=0.92$  for antidiabetics; -0.04;  $p=0.39$  for antiarrhythmics; -0.06;  $p=0.21$  for ACE-inhibitors), compared with baseline (Figure 2).

Table 1 shows the associations between drug-and patient-related factors and the occurrence of switching among equivalents. For all drug classes, switching was significantly lower in females and in those aged  $\geq 65$  years old. Conversely, this occurrence was higher in cases of change in the dispensing pharmacy and increased with increasing number of different equivalents. In particular, when more than 5 equivalents for a given medicine were available on the market, switching increased by about 30% in case of antiarrhythmics, 100% for ACE-inhibitors and up to 8-fold for antidiabetics.

## DISCUSSION

Our findings showed a positive trend towards increased use of generics in all considered cardiovascular drug classes, with a specific market growth after the Italian regulatory intervention on INN name prescription. However, compared with other European countries the use of generics in Italy remains low, especially when considering Germany, Netherlands, Sweden and the UK rates, with their different multiple strategies described earlier [21,23,25,26,31,41].

In our cohort, switches among equivalents during chronic cardiovascular therapies ranged between 10 and 20% per month and were more frequent for antidiabetic medicines and ACE-inhibitors as opposed to antiarrhythmics. The clinical significance of these findings represents a matter of debate, since there is the theoretical risk of important variations in drug bioavailability if switches occur among equivalents with varying AUCs of the drug. As known, the AUCs of an equivalent drug may vary by 20% as compared to the originator: while a simple change from originator to an equivalent will have limited impact on clinical response, sequential switching among equivalents along with time could induce large variations in drug effect that, in case of drugs with low therapeutic index (e.g. antiarrhythmic agents), could have higher influence on benefit-risk profile.

As a matter of fact, different authors showed no difference in outcomes between originators drugs used to treat patients with cardiovascular diseases in their meta-analysis versus generics [42,43]. Concerning a condition usually considered as a reference for the high risk of impaired outcomes in case of pharmacokinetic changes, no differences were also seen between originators and generic medicines used to treat patients with epilepsy [37,38,44]. The Italian League against Epilepsy working group on generic products of antiepileptic drugs (AEDs) concluded that generic AEDs meeting current regulatory criteria for bioequivalence represent a valuable choice in the management of epilepsy particularly in patients initiating monotherapy or adjunctive treatment and in those with persistent seizures. However, concerns remain when patients have achieved seizure remission as well as in case of regular switches between different formulations of the same molecule [45] and this led to recent advice from the UK government [46].

In patients with arrhythmia, prescribers also prefer to avoid substitution between generics from different manufacturers. The risk associated with frequent switches among generics could be higher in the frail elderly population, since kinetic variations can easily impair the risk-benefit profile and precipitate drug-drug interactions. Care is also needed since switches in brand



during refills can cause patient confusion leading potentially to duplication of dosage [47]. Routine INN prescribing help avoids this confusion [48].

Education initiatives for pharmacists and patients are needed to avoid unnecessary switches among equivalent drugs throughout critical chronic therapy, e.g. empowerment of the patient on the importance to remember the medicinal product used, especially in case of antiarrhythmics. On the other hand, substitution could be acceptable if clear information on the equivalence is provided by the pharmacist.

Notably, our data showed a lower frequency of switches in the elderly, with consequent mitigation of clinical risks. The reason(s) for this might be a specific attention by physicians to drug therapies in this population. Another contributing factor could be the habits of the patient to place their prescription at the same pharmacy, where the support of pharmacist in maintaining the same brand might reduce switching. Further research is need though before any definitive statements can be made.

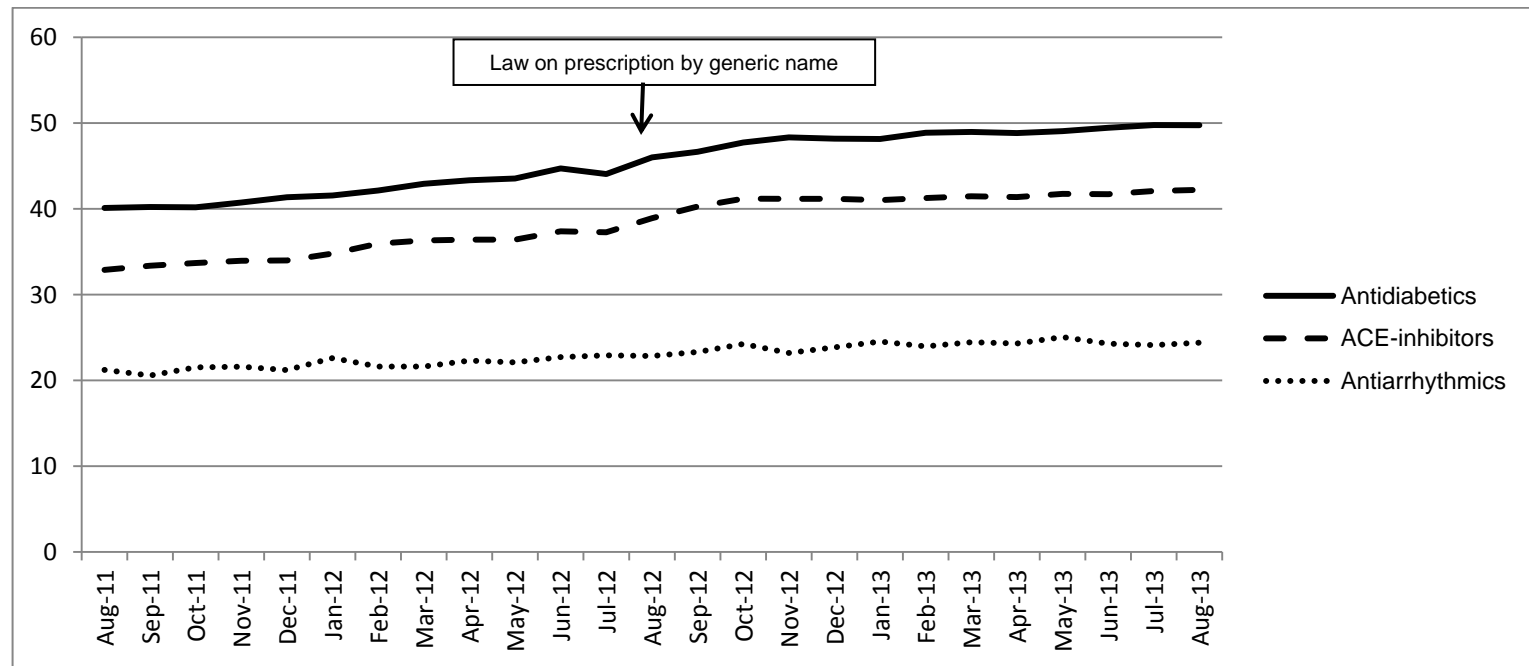
Apart from age, gender and “loyalty” to the same pharmacy, the number of equivalents on the market significantly influenced the switching phenomenon. Although this result can be considered as predictable (at least on the basis of probability), it should represent matter of concern for regulators and generic companies. A limited number of equivalents for each off-patent medicine, e.g., 5 equivalents, could both facilitate the use of generics and limit the clinical risk derived from switching. However, it is difficult to make a definitive statement regarding this given for instance the high level of INN prescribing in the UK, apart from a limited number of cases, without apparent problems for patients [38]. Competition and transparency in pricing has also resulted in low prices for generics in the UK [25,49].

Our study did not include an outcome analysis, and the evaluation of the clinical consequences of switching was beyond the scope of this work. This is because we focused on developing methodology easily applicable by local health authorities in routine activity of monitoring drug utilization patterns, when only prescription data are available. Future studies, based on record linkage analyses including exposure and hospital admission data, will be undertaken to evaluate the possible impact of switching among equivalents on clinical outcomes, although we do not expect to see major differences in outcomes, as showed by already mentioned articles [42-44].

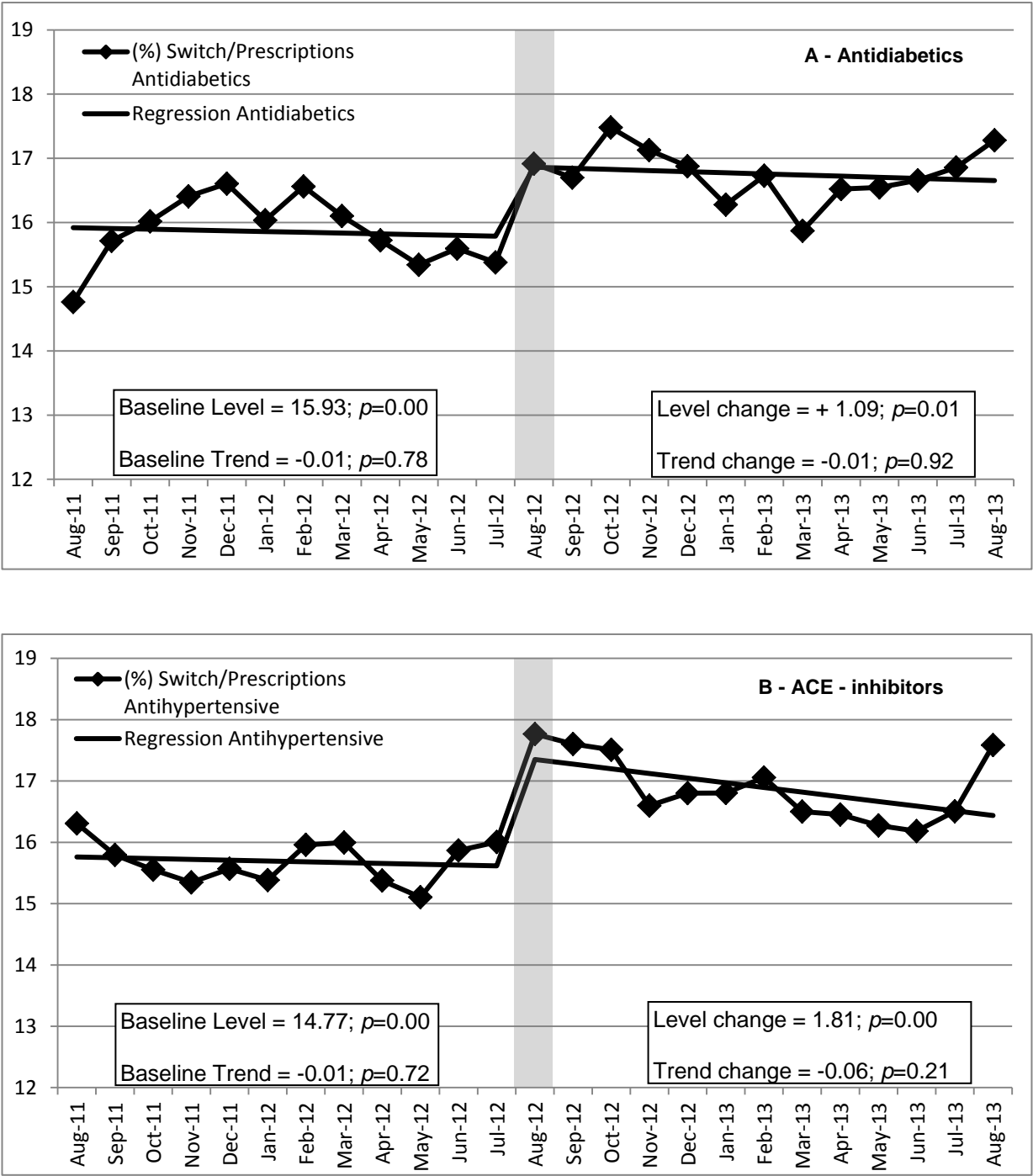
Price difference among equivalents could represent an additional factor influencing the rate of generic prescription and switching phenomenon. In the literature, different points of view are reported: patients could prefer to use generics because of the low cost, and also adherence to the therapy could increase with low-price generics [27,28]. On the other hand, patients (probably influenced by prescribers) could prefer to pay for drugs, since they ascribe high quality to the high cost of originator or other more expensive equivalents. However, there is variable correlation between generic prices and their use among European Countries, with countries with high market share of generics typically having lower prices [31,50]. If doubts on the quality of generic medicines is a possible reason for their low use, strategies must be implemented by health authorities to address this and appear to have worked well in France and Portugal [30], providing guidance to countries where this is a concern.

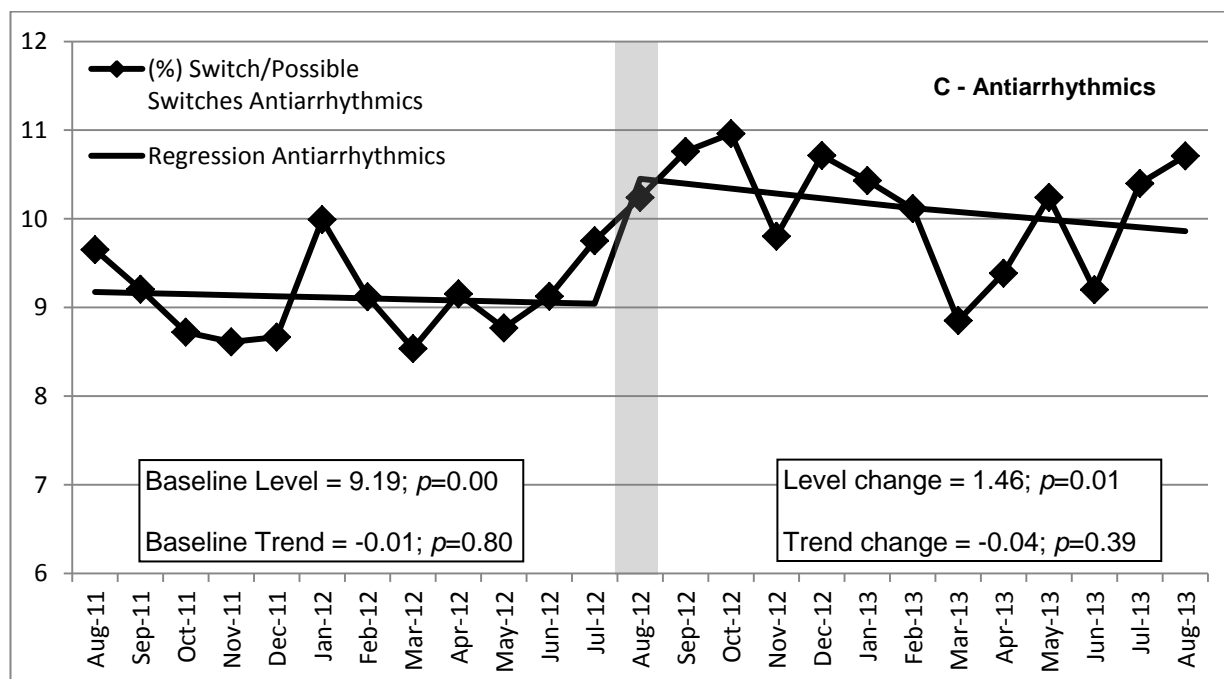
In conclusion, a number of measures can be applied in Italy to further increase equivalent prescribing. Since significant monthly switching between equivalents can generate concerns, not supported by clinical evidence, on the risk of kinetic variations and errors in drug intake, information campaigns should be promoted to encourage generic dispensation and explain behaviors to be observed by patients. The large number of equivalent products of the same originator is a matter of concern for prescribers and pharmacists about possible mistakes by patients: it is not easy to address this in the current regulatory framework of generic medicinal products.

**Figure 1. Percentage of dispensed generics in different cardiovascular drug classes**



**Figure 2 - Interrupted-time-series analysis on the monthly trend in switching across the Italian regulatory intervention on generic prescribing**





**Table 1. Logistic regression analysis on the factors influencing the frequency of switching**

|  | <b>Oral antidiabetic agents<br/>OR and 95% CI</b> |                  | <b>ACE inhibitors<br/>OR and 95% CI</b> |                  | <b>Antiarrhythmics<br/>OR and 95% CI</b> |                  |
|--|---|------------------|---|------------------|--|------------------|
|  | Crude   | Adjusted         | Crude                                   | Adjusted         | Crude                                    | Adjusted         |
| <b><i>Gender</i></b>                                   |   |                  |   |                  |  |                  |
| Male   | 1.00 (reference)                                  | 1.00 (reference) | 1.00 (reference)                        | 1.00 (reference) | 1.00 (reference)                         | 1.00 (reference) |
| Female   | 0.96 (0.95-0.98)                                  | 0.97 (0.95-0.98) | 0.93 (0.92-0.94)                        | 0.95 (0.94-0.96) | 0.93 (0.89-0.98)                         | 0.93 (0.89-0.98) |
| <b><i>Age</i></b>                                      |   |                  |   |                  |  |                  |
| <65  | 1.00 (reference)                                  | 1.00 (reference) | 1.00 (reference)                        | 1.00 (reference) | 1.00 (reference)                         | 1.00 (reference) |
| ≥65  | 0.86 (0.85-0.88)                                  | 0.92 (0.90-0.93) | 0.81 (0.80-0.80)                        | 0.87 (0.86-0.88) | 0.99 (0.93-1.05)                         | 0.96 (0.90-1.03) |
| <b><i>Change in dispensing pharmacy</i></b>            |   |                  |   |                  |  |                  |
| No   | 1.00 (reference)                                  | 1.00 (reference) | 1.00 (reference)                        | 1.00 (reference) | 1.00 (reference)                         | 1.00 (reference) |
| Yes (each change from territory to osp and vice versa) | 3.45 (3.43-3.53)                                  | 3.49 (3.44-3.54) | 4.32 (4.28-4.37)                        | 4.31 (4.26-4.35) | 3.62 (3.44-3.82)                         | 3.64 (3.46-3.84) |
| <b><i>N. of marketed equivalents</i></b>               |   |                  |   |                  |  |                  |
| 0-5 (0)  | 1.00 (reference)                                  | 1.00 (reference) | 1.00 (reference)                        | 1.00 (reference) | 1.00 (reference)                         | 1.00 (reference) |
| 6-10 (1)   | 7.69 (7.27-8.14)                                  | 7.82 (7.39-8.28) | 1.84 (1.78-1.89)                        | 1.98 (1.92-2.04) | 1.27 (1.21-1.34)                         | 1.31 (1.24-1.39) |
| >10 (2)  | 7.79 (7.38-8.24)                                  | 7.92 (7.50-8.38) | 1.91 (1.86-1.96)                        | 1.98 (1.93-2.04) | -  | -                |

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