

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. Prescriptions of off-patent anti-arrhythmics, oral antidiabetics and ACE inhibitors dispensed from August 2011 to August 2013 within the Bologna Local Health Authority (870,000 inhabitants) was 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 the following: age, gender, number of different equivalents available for each drug and change in dispensing pharmacy between subsequent refills. The average monthly rates of switches were 9.6%, 16.3% and 16.3% for anti-arrhythmics, antidiabetics and ACE inhibitors, respectively. Values significantly increased soon after the regulatory intervention for ACE inhibitors (+1.81%, $p < 0.01$), anti-arrhythmics (+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, 95 CI = 4.26–4.35 for ACE inhibitors) and availability of ≥ 5 different equivalents (up to aOR = 7.82, 95 CI = 7.39–8.28 for antidiabetics). Switching was lower for age ≥ 65 for antidiabetics and ACE inhibitors (aOR = 0.92, 95 CI = 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.

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 health care. 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 optimize 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 2–5% of pre-patent loss prices are available [19–22]. Strategies to enhance the prescribing of generics *versus* origi-

nators 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 97–98% 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]). Internal reference pricing system has been now implemented in more than 20 EU Member States [31,34,35].

However, despite efforts to promote the prescribing of equivalents in Italy, the generic market is low compared with 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

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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, the 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. While 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 high 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 the 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 was 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.

Methods

This was a cross-sectional study based on information 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 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 analysed 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)], anti-arrhythmics (C01B) and oral hypoglycaemic 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 authorization code). The marketing authorization 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, for example number of tablets in the package.

Using marketing authorization 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-rimborsabilit%C3%A0>) as validation of our grouping procedure.

From the prescriptive history of each individual, 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.

To select only patients susceptible of switching between equivalent products, that is potential switchers, new users of a given therapy and patients receiving medicines without generic equivalents were excluded from the 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 after 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 12-month period before and after the intervention was selected. Differences between the two segmented periods were estimated for (i) 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 (ii) 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 ≤ 0.05 . To evaluate the extent of autocorrelation [40], we calculated the Durbin Watson statistics, and in case of suggested autocorrelation, we used AutoRegressive Integrated Moving Average (ARIMA) model to adjust results accordingly.

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-year period was approximately 45% for oral antidiabetics, 38% for ACE inhibitors and 23% for anti-arrhythmics (fig. 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 2–22 different equivalents. As for ACE inhibitors, we dealt with 31 different groups, with 2–25 different equivalents. Among anti-arrhythmics, only four different equivalent groups were found

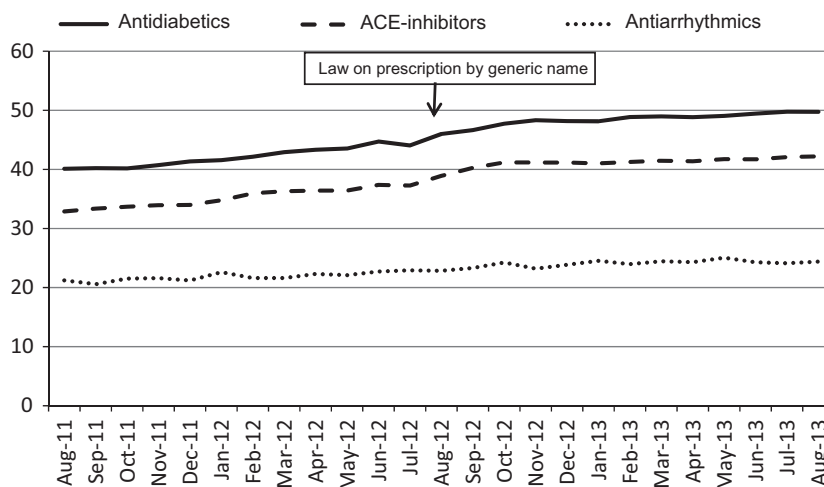


Fig. 1. Percentage of dispensed generics in different cardiovascular drug classes.

(amiodarone 200 mg, propafenone 150 mg, propafenone 300 mg and flecainide 100 mg) with four to seven 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 anti-arrhythmics, 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 anti-arrhythmics.

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 anti-arrhythmics; +1.81; $p < 0.01$ for ACE inhibitors). Moreover, we found a negligible trend decrease in the months after the intervention (trend change -0.01 ; $p = 0.92$ for antidiabetics; -0.04 ; $p = 0.39$ for anti-arrhythmics; -0.06 ; $p = 0.21$ for ACE inhibitors), compared with baseline (fig. 2).

Durbin Watson statistics suggested autocorrelation for antidiabetics and ACE inhibitors (DW = 1.03 and 1.13, respectively); however, the adjustment for autocorrelation by ARIMA did not modify findings obtained by the interrupted-time-series analysis.

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 ≥ 65 years. 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 five equivalents for a given medicine were available on the market, switching

increased by about 30% for anti-arrhythmics, 100% for ACE inhibitors and up to eight-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 rates for Germany, Netherlands, Sweden and the UK, 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 anti-arrhythmics. The clinical significance of these findings represents a matter of debate, as there is the theoretical risk of important variations in drug bioavailability if switches occur among equivalents with varying AUCs of the drug. As it is 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. anti-arrhythmic agents), could have higher influence on benefit-risk profile.

As a matter of fact, various authors demonstrated no difference in outcomes between originator 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 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 anti-epileptic drugs (AEDs) concluded that generic AEDs meeting current regulatory criteria for

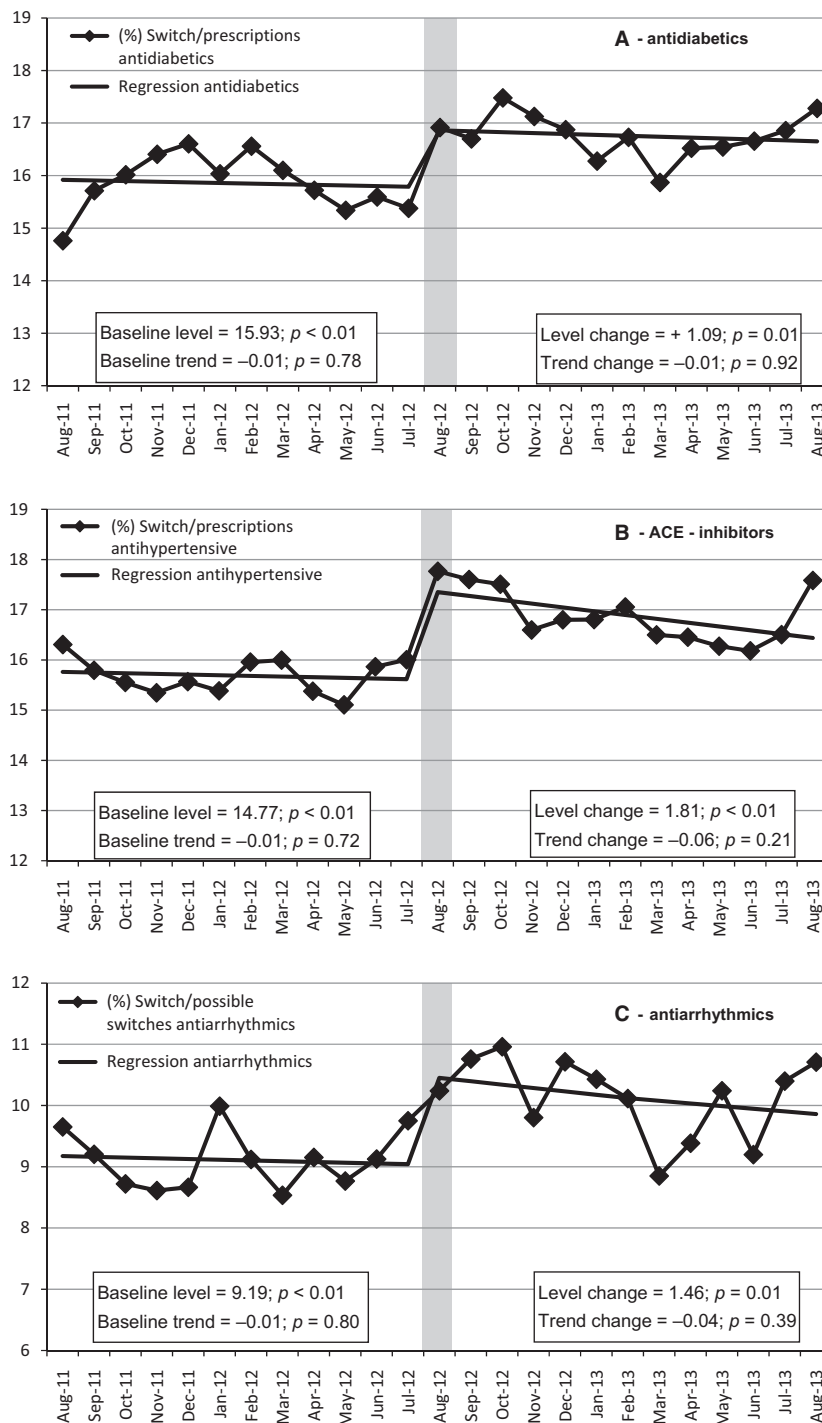


Fig. 2. Interrupted-time-series analysis on the monthly trend in switching across the Italian regulatory intervention on generic prescribing.

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, as kinetic variations can easily impair the risk–benefit profile and precipitate drug–drug interactions. Care is also needed as switches in brand during refills can cause patient confusion leading to potential duplication of dosage [47]. Routine INN prescribing helps to avoid this confusion [48].

Education initiatives for pharmacists and patients are needed to avoid unnecessary switches among equivalent

Table 1.

Logistic regression analysis on the factors influencing the frequency of switching.

| | Oral antidiabetic agents OR and 95% CI | | ACE inhibitors OR and 95% CI | | Anti-arrhythmics OR and 95% CI | |
|--|---|------------------|---------------------------------|------------------|-----------------------------------|------------------|
| | Crude | Adjusted | Crude | Adjusted | Crude | Adjusted |
| Gender | | | | | | |
| 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) |
| Age | | | | | | |
| <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) |
| Change in dispensing pharmacy | | | | | | |
| 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) |
| N. of marketed equivalents | | | | | | |
| 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) | – | – |

drugs throughout critical chronic therapy, for example empowerment of the patient on the importance to remember the medicinal product used, especially in case of anti-arrhythmics. 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 patients to place their prescriptions at the same pharmacy, where the pharmacist support in maintaining the same brand might reduce switching. Further research is needed 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 a matter of concern for regulators and generic companies. A limited number of equivalents for each off-patent medicine, for example five 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 a methodology to be 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 shown 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, as 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. As 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 behaviours 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.

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Author contributions

All authors participated in critical revision of the manuscript for important intellectual content and approved the final version.

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