Ann Ist Super Sanità 2014 | Vol. 50, No. 4: 333-340
DOI: 10.4415/ANN_14_04_07

Generic substitution of antidiabetic drugs in the elderly does not affect adherence

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Abstract

Introduction. The possibility that variation in packaging and pill appearance may reduce adherence is a reason for concern, especially for chronic diseases. The objectives of the study were to quantify the extent of switches between generic antidiabetics and to verify whether switching between different products of the same substance affects adherence.

Materials and methods. All elderly residents of the Umbria Region who received at least 2 prescriptions of antidiabetics in 2010 and 2011 were included in the study. Switching was defined as the dispensing of two different products of the same substance in a series of two prescriptions. Single and multiple switchers were identified according to the number of switches during 2011. Switching relevant to the three off-patent substances with generic use ≥ 5% (metformin, gliclazide and repaglinide) was quantified. The effect of switching on adherence, defined as the proportion of days in 2011 covered by prescriptions (Medication Possession Ratio, MPR), was estimated.

Results. Among the 15 964 patients receiving antidiabetics (14.4% of the elderly population) 9211 were prescribed at least one of the generic substances. Of these patients, 23.3% experienced a single switch and 15.7% were multiple switchers (61.0% never switched). The proportion of multiple switchers increased with the number of prescriptions, reaching 26% among patients with ≥ 11 prescriptions. MPR was 62%, 62% and 72%, respectively among non-switchers, single and multiple switchers.

Conclusions. In elderly patients treated with antidiabetics, the substitution between branded and unbranded products (as well as between generics) of the same substance, did not negatively affect adherence.

Key words
- adherence to medications
- generic substitution
- anti-diabetic drugs

INTRODUCTION

Treatment adherence is a well-known predictor of clinical outcome. Several factors, such as ageing, comorbidities and polypharmacy, may in turn affect adherence and influence the outcome of treatments [1-6].

Diabetes in the elderly population is an ideal setting to study adherence and the characteristics that may modify the continuity of treatment. The disease affects a large proportion of the population (in Italy, more than 5% of the general population and about 20% of the elderly ≥ 75 years old) [7]; several antidiabetics are often required to control the disease [8, 9]; and most of the patients present co-morbidities for which many pharmacological treatments are indicated [6, 10, 11].

Even though the use of generics is an important opportunity to reduce health care expenditure, there is a concern it may affect the attitude of patients in following the prescribed indications. A specific reason for attention was raised on the effect of generic substitution (*i.e.*, switches between brand names and generics, and switches between generics), especially among elderly who receive many different substances for prolonged periods of time. The change in package appearance each time a new prescription is dispensed may create confusion and ultimately reduce patients' adherence [12, 13]. The issue is of great relevance for a chronic condition such as diabetes, since pharmacological treatments include different substances and different packages (of all branded/generic products) of the same substance.

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Few studies estimated the frequency of substitution between generics of the same substance [14-16] and there are controversial findings on the effect of switching between generics on treatment adherence [17-21]. Moreover, no study has been conducted in the diabetes setting.

The objectives of the study were to quantify the extent of switches between generic antidiabetics and to verify whether switching between different products of the same substance affects adherence.

MATERIALS AND METHODS

Study population

The study was conducted in the population of the Umbria Region (907 000 inhabitants in 2011), Italy. All residents are covered by the Italian National Health Service (NHS), which provides comprehensive hospital and outpatient care.

Outpatients receive prescriptions from General Practitioners (GPs) and obtain medicines covered by the NHS from local community pharmacies or in some cases directly from local health units (both types of distribution were considered for the analysis). For each prescription, the following information is available at regional level: patient code (which is anonymized before any subsequent use), date of prescription, drug substance, marketing authorization code (indicating the specific brand or generic products), number of packages. Prescription data were linked through the anonymized code to the regional database of enrollees to retrieve age and gender. No information is available on prescriptions issued during the hospitalization and on medicines use in nursing homes.

The eligible population included the elderly aged ≥ 75 years who were resident in the Region in 2010 and 2011. Patients were considered to be on treatment with antidiabetics if they had filled at least two prescriptions of antidiabetics (identified through the international Anatomical Therapeutic Chemical classification system, ATC code A10) both in 2010 and 2011. Furthermore, to ensure that subjects were still using health care services at the end of 2011, patients were required to have at least a prescription (of any drug) during the last trimester of 2011. Subjects who met the eligibility criteria were included in the study cohort to investigate the utilization patterns of antidiabetics in 2011.

Therapeutic categories and indicators for usage

The following classes of antidiabetics were considered: i) insulins (ATC A10A); ii) biguanides (ATC A10BA); iii) sulphonamides (ATC A10BB); iv) glitazones (ATC A10BG); v) dipeptidyl peptidase-4 (DPP-4) inhibitors (ATC A10BH); vi) alpha-glucosidase inhibitors (ATC A10BF); vii) fixed-dose combinations (ATC A10BD); viii) other blood glucose lowering drugs (ATC A10BX).

All other prescriptions (different from antidiabetics) issued during 2011 were classified according to pre-specified 15 clinical subgroups (*Supplementary Table S1, available online at www.iss.it/anna*) in order to: i) identify co-morbidities associated with diabetes (*e.g.*, users of antihypertensives, antiparkinsons); ii) quantify the extent of polytherapy, defined as the number of different substances at the Vth ATC level (other than antidiabetics) prescribed during 2011.

The list of off-patent drugs, both originator and copies, marketed in Italy is regularly updated by the Italian Medicines Agency [22]. Off-patent medicines were classified as branded and unbranded. Branded products are defined as medicines sold under a proprietary name, whereas unbranded generics are sold under their international non-proprietary name (*i.e.*, the name of the substance).

Drug consumption was evaluated in terms of: prescriptions received; number of packages; total gross expenditure; and defined daily doses (DDDs: the daily maintenance dose for the main indication in adults). Two indicators of drug use were calculated: the prevalence of use (by dividing the number of drug users by the overall resident population); the DDDs per 1000 users per day (the mean number of doses consumed every day by 1000 patients included in the cohort).

Identification of switches

Only generic antidiabetics with a use of generics ≥ 5% (in terms of DDDs for each substance) were considered for the analysis of switches. Only patients filling at least 2 prescriptions of the same substance during 2011 were included. The dispensing date of the first prescription of an off-patent antidiabetic in 2011 was the index date.

Switches were defined as the dispensing of two different products (any of the brand and unbranded packages) of the same substance in a series of two prescriptions in 2011. Three main switching categories were defined:

- no switch: patients who received the same products during the entire follow up;
- single switch: patients who experienced only one switch (from A to B) or who had a total of two switches involving a switch back to the first product (from A to B to A);
- multiple switch: patients with three or more switches, as well as two switches within three different products (from A to B to C).

Adherence to the antidiabetic therapy

Adherence to the generic antidiabetics included in the analysis was determined using the medication possession ratio (MPR) calculated by dividing the theoretical duration of the prescription (we assumed that 1 prescription covered 30 days of therapy) by the number of days between the first and last prescription (plus the days covered by the last prescription).

RESULTS

Descriptive analysis of the selected cohort

In the Umbria Region, 15 964 subjects ≥ 75 years (14.4% of the elderly population) received at least 2 prescriptions of antidiabetics per year in 2010-2011 and were included in the study *(Table 1)*. Antidiabet-

ics represented 21.5% of the per capita pharmaceutical expenditure (200 out of 931 euro) and 20% of the DDDs prescribed in this population.

In addition to antidiabetics, each subject received a median of 10 different substances during 2011, highlighting a high level of polypharmacy, and 25% of the diabetic patients was treated with at least 14 substances *(Table 1)*. Only 1% of the diabetic patients (147 out of 15 964) received no prescriptions in addition to antidiabetics (thus considered as having no comorbidities), whereas more than 80% received prescriptions in at least three different therapeutic categories. Antihypertensives and antiaggregants-anticoagulants were the most frequently prescribed drugs (prevalence of use 90.2% and 69.3% respectively) *(Table 1)*. This level of use, together with the proportion of patients receiving lipid-lowering drugs (42.0%), suggests cardiovascular diseases as the principal comorbidity in this diabetic cohort. Drugs acting on the nervous system (i.e. antidepressants, pain medications and antipsychotics) were frequently prescribed, identifying the group of nervous and psychiatric disorders as the second chronic comorbidity. A further 20.2% of diabetic patients received prescriptions of respiratory drugs.

Gender did not influence the prescription patterns of antidiabetics, whereas the increasing age had a negative association with prevalence of use *(Table 1)* and DDDs/1000 users-die (data not shown). Most of the antidiabetic prescriptions concerned patented medicines (68%), whereas the remaining 32% consisted of branded (20%) and unbranded generics (12%).

Metformin was the most frequently prescribed antidiabetic (prevalence of use 6.8%), followed by insulins (5.1%) and sulphonamides (3.5%) *(Table 2)*. Very few patients were treated with newer oral antidiabetic agents such as a DPP-4 inhibitors or pioglitazone (prevalence of use, 0.1% for each class).

During 2011 each patient received an average of 12 prescriptions of antidiabetics (*i.e.* 1 prescription per month) corresponding to 17 drug packages per year (1.4 packages per month) and around 1.1 doses per day, which is coherent with a treatment model of a chronic diseases *(Table 2)*. These data suggest that elderly diabetic patients were followed up monthly by GPs and that each prescription of antidiabetics typically covered 1 month of treatment. The yearly cost of treatment per user varied among drug classes, from a minimum of 33-42 euro for metformin and sulphonamides to 327-406 euro for DPP-4 inhibitors and insulins *(Table 2)*.

Most of the patients (51.4%) received only one antidiabetic drug and, within monotherapy, 41% were users of metformin. The proportion of patients receiving two antidiabetics during 2011 was 35.7%, and the remaining 12.9% were prescribed more than two antidiabetics.

Among antidiabetics, generics were only available for metformin, gliclazide, glimepiride, and repaglinide *(Table 2)*. The use of unbranded generics was higher for gliclazide and repaglinide (61% and 48% of the DDDs) whereas it represented only 3% of the DDDs of glimepiride. The number of generic products marketed in Italy ranged from 4 for repaglinide to 18 for gliclazide.

Table 1
Characteristics of the antidiabetics users included in the study cohort

Total subjects, N (prevalence, %)	**15 964 (14.4)**
Gender, N (prevalence, %)	
Male	6550 (15.4)
Female	9414 (13.9)
Age class, N (prevalence, %)	
75-79 y	6400 (14.9)
80-84 y	5276 (15.0)
85-89 y	3115 (13.6)
≥ 90 y	1173 (12.2)
Total drug expenditure (euro)	**931**
DDDs/1000 users-die	
Antidiabetics	1078
Any drugs (including antidiabetics)	5588
Median number of substances prescribed in 2011 in addition to antidiabetics (IQR)	**10 (7-14)**
Drug classes most frequently prescribed in 2011 in addition to antidiabetics, % of users*	
Antihypertensives	90.2
Antiaggregants/Anticoagulants	69.3
Antibiotics	60.7
Antacids-Antiulcer drugs	54.4
Lipid lowering drugs	42.0
NSAIDs	37.4
Antidepressants	22.5
Respiratory drugs	20.2
Pain medications (opioids)	18.0
Prostate medication	13.9
Antiglaucoma drugs	11.3
Thyroid medications	8.5
Antipsychotics	5.2
Antiparkinsons	5.2
Osteoporosis medications	4.7

*: for details on the drug classes definitions see Table S1.
DDD: defined daily dose; IQR: interquartile range.

Analysis of switching among generics and its impact on adherence

The analysis was conducted on the 9211 patients receiving at least one of the three substances available as generics: metformin, gliclazide and repaglinide (glimepiride was excluded since 97% of the prescriptions were still relevant to the branded originator).

The majority of diabetic patients (61.0%) did not switch during the year. The proportion of non-switchers was similar for the three substances, ranging from 62.5% with metformin to 57.9% with repaglinide *(Table 3)*. Pa-

Table 2
Use of antidiabetics by drug class in 2011. Substances available as generics are reported in *italics*

	ATC code	Prevalence of use (%)	Prescriptions/ users	Packages/ users	Cost/ users	%DDD Patented	%DDD Branded	%DDD Unbranded
Biguanides								
Metformin	A10BA02	6.8	9	15	33	-	64	36
Insulins	A10A	5.1	8	9	406	100	-	-
Sulphonamides	A10BB	3.5	8	11	42	9	59	32
Gliclazide	A10BB09	1.8	7	9	50	-	39	61
Glimepiride	A10BB12	1.3	8	11	29	-	97	3
Fixed-dose combinations	A10BD	2.5	9	15	86	80	20	-
Other blood glucose lowering drugs	A10BX	1.7	7	8	77	2	51	47
Repaglinide	A10BX02	1.7	7	8	68	-	52	48
Alpha glucosidase inhibitors (*i.e.* acarbose)	A10BF	0.3	8	11	90	100	-	-
Glitazones (*i.e.* pioglitazone)	A10BG	0.1	8	9	225	100	-	-
DPP-4 inhibitors	A10BH	0.1	6	7	327	100	-	-
Total		**14.4**	**12**	**17**	**200**	**68**	**20**	**12**

ATC: anatomical therapeutic chemical classification; DDD: defined daily dose; DPP-4 inhibitors: Dipeptidyl peptidase-4 inhibitors.

Table 3
Characteristics of patients treated with generic antidiabetics by category of switching. For each characteristics the total number of patients may be obtained by adding the number of patients in the three switching categories (no switch; single switch; multiple switch)

	Metformin			Gliclazide			Repaglinide		
	No switch	Single switch	Multiple switch	No switch	Single switch	Multiple switch	No switch	Single switch	Multiple switch
Subjects	4515 (62.5)	1318 (18.2)	1389 (19.2)	1166 (62.3)	459 (24.5)	246 (13.1)	977 (57.9)	458 (27.2)	251 (14.9)
Gender									
Male	1842 (60.5)	591 (19.4)	612 (20.1)	437 (59.8)	195 (26.7)	99 (13.5)	386 (55.6)	195 (28.1)	113 (16.3)
Female	2573 (64.0)	727 (17.4)	777 (18.6)	729 (63.9)	264 (23.2)	147 (12.9)	591 (59.6)	263 (26.5)	138 (13.9)
Age groups									
75-79	2162 (63.5)	606 (17.8)	637 (18.7)	445 (62.7)	171 (24.1)	94 (13.2)	390 (57.8)	178 (26.4)	107 (15.9)
80-84	1480 (62.4)	406 (17.1)	484 (20.4)	380 (60.8)	164 (26.2)	81 (13.0)	338 (57.5)	165 (28.1)	85 (14.5)
85-89	668 (59.9)	238 (21.3)	210 (18.8)	253 (64.7)	81 (20.7)	57 (14.6)	191 (59.7)	82 (25.6)	47 (14.7)
90+	205 (61.9)	68 (20.5)	58 (17.5)	88 (60.7)	43 (29.7)	14 (9.7)	58 (56.3)	33 (32.0)	12 (11.7)
Number of therapeutic categories*									
0	38 (66.7)	7 (12.3)	12 (21.1)	20 (74.1)	5 (18.5)	2 (7.4)	5 (29.4)	8 (47.1)	4 (23.5)
1-2	631 (65.5)	163 (16.9)	169 (17.5)	162 (58.5)	71 (25.6)	44 (15.9)	117 (56.8)	57 (27.7)	32 (15.5)
≥3	3846 (62.0)	1148 (18.5)	1208 (19.5)	984 (62.8)	383 (24.4)	200 (12.8)	855 (58.4)	393 (26.9)	215 (14.7)
Median switches of multiple switchers (IQR)			4 (3-5)			3 (3-4)			3 (3-5)

*: for the definition of therapeutic categories see table S1; IQR: interquartile range.

tients with a single switch ranged from 27.2% for repaglinide to 18.2% for gliclazide. Multiple switches were observed on average in 15.7% of the patients and the median number of switches was comparable for the three selected antidiabetics. The likelihood of switching did not vary by gender, age subgroups and number of therapeutic categories (especially when taking into account that only a few patients were included in some categories).

The probability of switching rises with the increasing number of prescriptions for the same substance *(Figure 1)*. The proportion of non-switchers was on average 78% in the group receiving 2-3 prescriptions and progressively decreased up to an average of 56% in case of 11 or more prescriptions. The opposite trend was observed for multiple switchers with a maximum of 26% among subjects with ≥ 11 prescriptions. The proportion of patients with a single switch (about 20% of the users) was relatively stable with the increasing number of prescriptions.

Switches between generic antidiabetics did not impact negatively on treatment adherence *(Figure 2)*. Similar level of adherence were observed across the three switching categories for the three substances (metformin, gliclazide and repaglinide). Overall, the median MPR was 62%, 62%, and 72% among non-switchers, single and multiple switchers respectively *(Figure 2d)*. Since the number of prescriptions is associated with both the probability of switching and treatment adherence, we also restricted the analysis to patients who received more than 5 prescriptions. The differences between the three switching categories were even smaller, with the median MPR ranging from 75% to 77% *(Supplementary Figure S1, available online at www.iss.it/anna)*.

DISCUSSION

The possibility that variation in packaging and pill appearance may affect adherence is a reason for concern. For instance, Kesselheim and colleagues [17] showed, in a recent article, that changes in pill colors and shapes increased the risk of non-adherence among epileptic patients. If this effect were confirmed, substituting patented originators with generic alternatives, as well as switching between different generics, may carry a risk for patients' outcome, especially in case of chronic diseases.

Our study does not support this concern. In the entire elderly population of patients who received antidiabetics in the Umbria Region, the substitution between branded and unbranded product, as well as between generics, did not negatively affect adherence.

For the three antidiabetics with a generic equivalent included in our analysis, 61.0% of the patients received the same package during the year (non-switchers) and 23.3% experienced only one package substitution (single switch). As expected, the likelihood of any switching increased with the number of prescriptions. Among patients with more than 11 prescriptions (of each substance), 18% did switch once, and 26% experienced multiple switching (if combined 44% of patients did switch at least once during the year). On one hand, the likelihood of switching was not influenced by patients' characteristics such as age, sex and number of therapeutic categories. On the other hand, non-switchers, patients with a single switch and multiple switchers, were equally likely to adhere to the antidiabetic treatment where a generic is available. Adherence data by intensity of switching were consistent for the three substances (metformin, repaglinide and gliclazide), thus suggesting that these findings may apply to other off-patented drugs and generic substitutions.

In the only comparable analysis, Kalisch *et al*. [15] investigated the generic substitution of metformin; the majority of patients were non-switchers, 14% received a single switch and 7% were multiple switchers. Our findings are also comparable with others that focused on different chronic therapies (*e.g.*, calcium channel blockers, selective serotonin reuptake inhibitors, statins) [15, 16]. Around 80% of patients were non-switchers or experienced a single switch, and the proportion of multiple switchers ranged between 19 and 24%.

Our results are also coherent with others in the cardiovascular setting and in postmenopausal women with osteoporosis: adherence was not found to be influenced by generic switches among antihypertensive agents and alendronate, respectively [18-21]. However, in specific settings such as those involving psychiatric and neurological conditions, the effects of generic substitution are still unclear. In particular, two studies by Hartung *et al*. [23] and Duh *et al*. [24] investigated the effect of generic substitution of antiepileptics on a clinical outcome (*i.e.* the rate of hospitalization) and showed opposite findings.

The cohort of patients included in our study can be considered representative of an elderly population with diabetes. The proportion of patient receiving either a single antidiabetic (considered as a proxy of monotherapy) or two substances (considered as a proxy of dual therapy) is consistent with the published literature [11, 25, 26]. Also the proportion of patients treated with metformin as monotherapy is similar to that found in other countries [27-31]. Newer drugs such as DPP-4 inhibitors were prescribed to a minority of patients. Diabetes represents a good example of a chronic condition. On average, each patient included in the study received more than 5 daily doses of any drug (5588 DDDs per 1000 subjects per day) and, in addition to antidiabetics, a median of 10 different substances during the year. The type of comorbidities identified through prescriptions, their estimated frequency, as well as the high rate of polypharmacy fully reflect findings of other reports [25, 32-35].

As for other studies that used prescription databases, a limitation of our analysis is that the calculation of adherence depended on pharmacy records. For instance, prescriptions may overestimate adherence if a drug is collected but not used. Furthermore, we calculated the MPR assuming that 1 prescription covers 1 month of therapy, which may slightly modify the estimates, but is not expected to impact on the comparisons between the three switching categories.

It should be pointed out that the MPR in our study

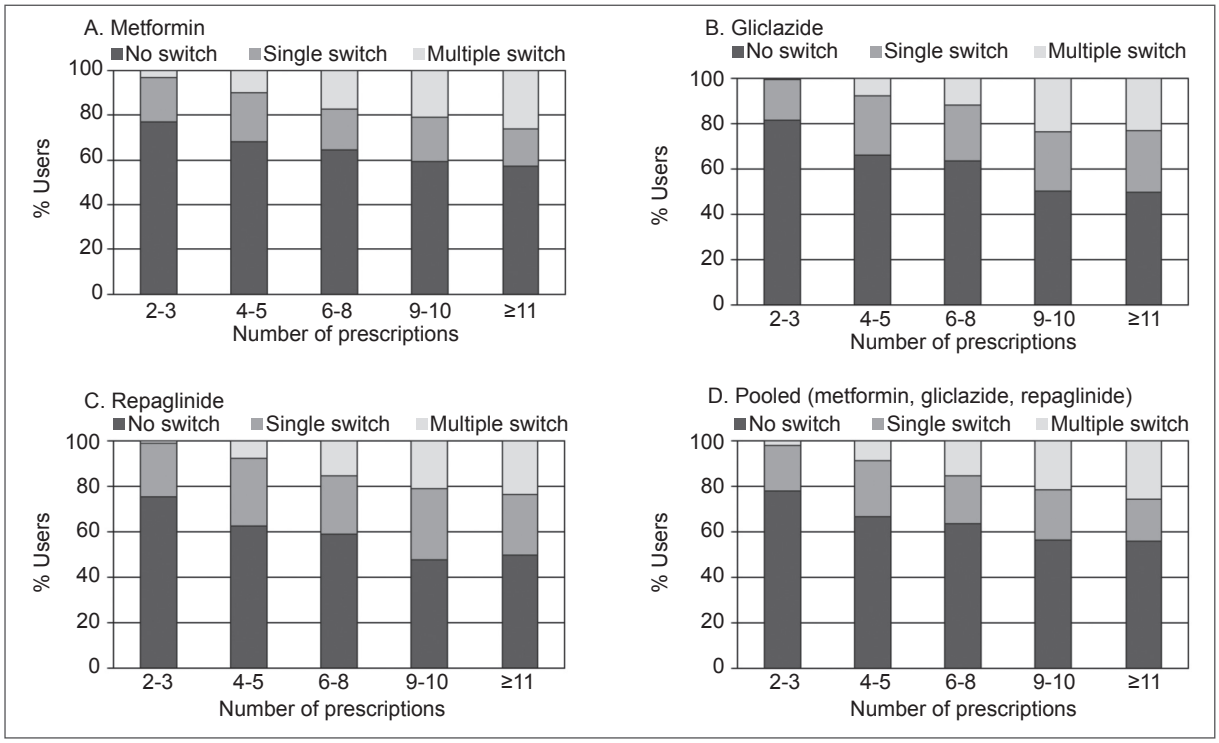

Figure 1
Distribution of switching categories by number of prescriptions.

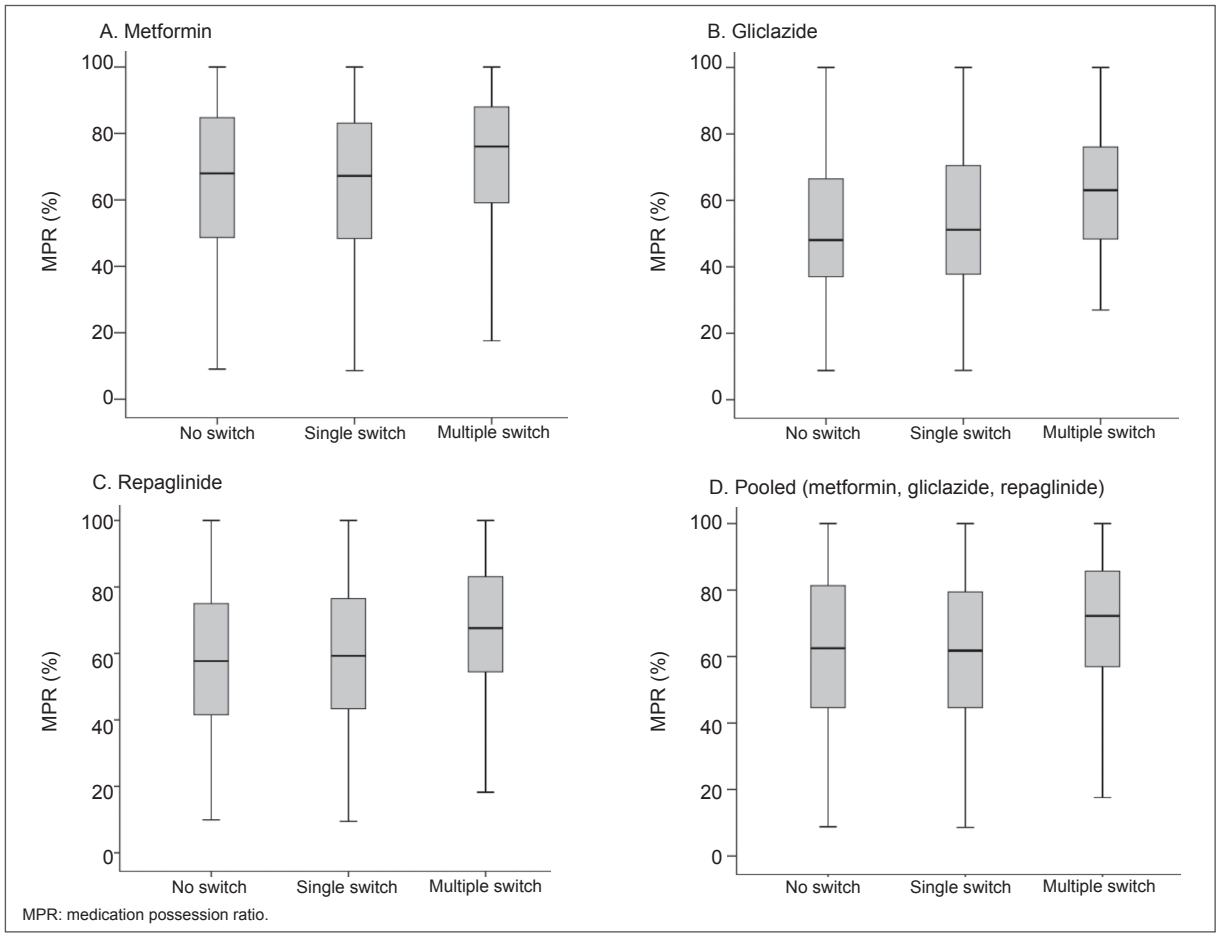

Figure 2
Adherence comparison by switching categories.

was only adopted to perform comparisons between the switching categories of the same substance. As indicated before, a diabetic patient may receive more than 1 antidiabetic (including more than 1 generic substance included in the analysis). The prescription database only covers prescriptions issued to outpatients and does not account for drugs administered in nursing homes and hospitals. This may lead to an underestimation of the adherence, even though no effect is expected on the comparison between switching categories. Moreover, we did not take into account several factors (*e.g.* socio-economic status, life-style) potentially impacting on adherence.

CONCLUSIONS

Our study indicates that generic substitution in the diabetes setting does not influence patients' adherence. This information is particularly useful when considering that even uncertainties of a negative effect on adherence may represent a disincentive in using generic drugs. The fact that our findings are relevant to an elderly population of complex patients with comorbidities supports the view that similar findings may be expected in other chronic treatments.

Acknowledgments

An abstract of this work was submitted to the 13th ISOP annual meeting to be held in Pisa in October 2013, and was accepted as oral communication.

FT, GT, RDC, MM conceived the study design; FT, RDC, MR analyzed the data; FT, GT wrote the manuscript; FT, GT, RDC, MM, MR contributed to the discussion and reviewed the manuscript. All authors approved the final version of the manuscript. GT will act as guarantor for the paper.

The authors wish to thank Stefania Spila Alegiani and Carmen D'Amore of the National Centre for Epidemiology, for their comments and suggestions on the final version of the manuscript.

This study was conducted by investigators employed in public institutions and was supported by research funds from the Umbria Regional Health Authority.

Conflict of interest statement

The authors have no conflict of interest to disclose.

The opinions expressed in this article do not necessarily reflects the view of the authors' institutions.

Received on 14 March 2014.
Accepted on 15 September 2014.

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