

# Generic Substitution of Antihypertensive Drugs: Does It Affect Adherence?

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**BACKGROUND:** Generic substitution is an important opportunity to reduce the costs of pharmaceutical care. However, pharmacists and physicians often find that patients and brand-name manufacturers have doubt about the equivalence of the substituted drug. This may be reflected by decreased adherence to therapy.

**OBJECTIVE:** To assess the association between generic substitution and nonadherence to antihypertensive drugs.

**METHODS:** We conducted a matched cohort study between January 1, 1999, and December 31, 2002. Data were obtained from PHARMO, a record linkage system containing drug-dispensing records from community pharmacies and linked hospital discharge records of approximately 950 000 people in the Netherlands. Residents of 30 medium-sized cities who initiated antihypertensive drug therapy were potential subjects. Refill adherence with antihypertensive drugs after substitution was determined; those with refill adherence below 80% were considered nonadherent.

**RESULTS:** Four hundred sixty-three patients with a substitution in therapy and 565 controls, matched on age, gender, therapy start date, duration of use, and generic product code, were identified. Of the patients who switched from brand-name to generic formulations ("substituted"), 13.6% were nonadherent, and of the non-substituted patients (those who did not switch to generic), 18.7% were nonadherent (OR 0.68; 95% CI 0.48 to 0.96). The association was absent in males. None of the patients discontinued the medication. No differences in hospitalizations for cardiovascular disease in the 6 months after the substitution were observed.

**CONCLUSIONS:** Generic substitution of antihypertensive drugs does not lead to lower adherence or more discontinuation and cardiovascular disease-related hospitalizations compared with brand-name therapy. When a less-expensive antihypertensive generic equivalent becomes available, generic substitution should be considered to achieve economic benefits.

**KEY WORDS:** adherence, antihypertensive drugs, generic substitution.

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Substitution of brand-name drugs with generic equivalents is an important issue with regard to the cost reduction of pharmaceutical care. On June 12, 2003, the Food and Drug Administration (FDA) announced new regulations and review procedures to streamline the process for making safe, effective generic drugs available to

consumers. The changes in the regulations alone will save consumers an estimated \$35 billion over 10 years by making generic alternatives to costly brand-name drugs available more quickly. The improvements in the efficiency of review procedures are expected to save consumers billions more by generally reducing the time for approving new generic drugs.<sup>1</sup> This means that generic substitution could decrease healthcare costs dramatically in the US. About the same situation is true for the Netherlands, where, beginning in May 2003, prices of generic equivalents were defined as 60% of the price of the brand-name drug.

On the therapeutic level, there is little doubt about bioequivalence of generic drugs and brand-name drugs once a generic formulation has been approved.<sup>2-8</sup> The rationale be-

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hind the concept of bioequivalence is that, if 2 pharmaceutical equivalents provide similar plasma concentration–time profiles, there is no reason to expect that the identical dosage forms will exhibit differences in safety and efficacy, regardless of whether other excipients may be used.<sup>5</sup> Although this concept of bioequivalence seems undisputable, it was rejected by the Australian Medical Association until January 2003.<sup>9</sup> Most parties involved in health care seem to be convinced of the cost benefits of the (increased) availability of generic drugs on the macroeconomic level; however, problems may arise on the individual level when a brand-name drug is substituted for a generic equivalent. Patients may resist changing from a brand-name drug, which they know well, to a generic equivalent that may look different.

Brennan and Lee<sup>10</sup> stated, “A generic equivalent normally produces no decrement in quality of treatment, unless the patient will not take it.” Furthermore, physicians may be concerned that patients may become confused, resulting in medication errors, or that their confidence in the therapeutic regimen decreases after generic substitution.<sup>11–17</sup> The latter may result in decreased adherence with the therapeutic regimen, ultimately resulting in less-effective treatment. This implies that, although a certain drug may be bioequivalent, it may not be therapeutically equivalent. The goal of this study was to quantify the degree to which generic substitution influences adherence to treatment with antihypertensive drugs.

## Methods

### DATA SOURCE

We used data from the PHARMO database, a record linkage system containing drug-dispensing records from community pharmacies and linked hospital discharge records of approximately 950 000 subjects in the Netherlands. We selected a cohort of patients who started using antihypertensive drugs between January 1, 1999, and December 31, 2002.

### GENERIC SUBSTITUTION AND ADHERENCE

Within this cohort, a retrospective follow-up design was applied to study the influence of substitution on adherence to treatment. From our cohort of new users, patients who had less than 365 days of follow-up before the start of antihypertensive therapy were excluded. Furthermore, patients who received only one prescription for an antihypertensive were excluded. Subjects were defined as substituted if they had undergone a substitution for the first time of their initially prescribed brand-name antihypertensive drug regimen with a bioequivalent generic drug. Generic equivalency was determined using Generic Product Codes (GPCs), which are assigned to a generic product on the basis of bioequivalence studies that are required for registration.<sup>18</sup> The dispensing date of the first prescription of the generic equivalent was defined as the index date. Matched non-substituted patients continued with the use of brand-name drugs on the index date.

Adherence was determined by calculating the medication possession ratio (MPR) of the prescription following the index date.<sup>19</sup> The MPR was calculated by dividing the theoretical duration of the prescription (number of tablets dispensed divided by prescribed dosage regimen) on the index date divided by the time between the index date and the start date of

the next prescription. A patient with an MPR below 80% was considered nonadherent. In a sensitivity analysis, we studied the influence of different cut-off values of adherence. When a patient discontinued the drug after substitution, he or she was excluded from this analysis because adherence cannot be calculated without an end date of a prescription. However, none of the patients discontinued treatment directly after substitution. Patients with an addition of another antihypertensive agent or with a substitution accompanied by a dose change were not considered in this study.

Substituted patients were matched to non-substituted patients (maximum of 3) on gender, start date of treatment with antihypertensives ( $\pm$  180 days), GPC, duration of unchanged and uninterrupted episode of use, and age (within a 10-y age-band). The relatively large age-band was used to increase the number of matched non-substituted patients. A drug regimen was considered uninterrupted if the gap between the start of a certain prescription X and the consequent one was smaller than 2 times the theoretical duration of prescription X.

### OUTCOME MEASURES

Our primary outcome measure was adherence with the prescription following the index date classified as adherent (MPR  $\geq$ 80) or nonadherent (MPR  $<$ 80). In addition, the analysis was repeated in subgroups defined by gender, type of antihypertensive, age group, and duration of use. Furthermore, the occurrence of cardiovascular hospitalizations, such as ischemic heart disease (ICD-9-CM 410–414), congestive heart failure (ICD-9-CM 428), arrhythmia (ICD-9-CM 426–427), peripheral vascular disease (ICD-9-CM 441, 443.9, 785.4), cerebrovascular disease (ICD-9-CM 430–438), and hypertension (ICD-9-CM 401–405), within 180 days after the index date was compared between substituted and non-substituted patients. The latter was also done to exclude the possibility that the decreased confidence of patients in their medication was not reflected by a later return to the pharmacy, but by not taking the medication as prescribed, resulting in more disease-related hospitalizations, although this follow-up period may be too short to detect cardiovascular consequences of substitution in those relatively low-risk patients.

### POTENTIAL CONFOUNDING FACTORS

Potential confounders were assessed prior to the start date: cardiovascular hospitalization as specified above, use of specific comedication (prescription for an antiasthmatic drug [ATC code R01], lipid-lowering drug [ATC code C10], or antidiabetic drug [ATC code A10]), type of prescriber (cardiologist, internist, general practitioner, or other), and the prescribed daily dose (PDD) being smaller than the defined daily dose (DDD).

### ANALYSIS

Based on an estimated incidence of nonadherence of 15% in the non-substituted patients and a 50% increase in the incidence in the substituted patients to 22.5% (OR 1.5), with  $\alpha = 0.05$  and  $1-\beta = 0.80$ , an estimated 424 patients were needed in the substituted and non-substituted group. Student's *t*-tests and  $\chi^2$  tests were used to analyze differences in basic characteristics between substituted patients and non-substituted patients. To analyze the association between nonadherence (outcome) and substitution (exposure), crude and adjusted odds ratios and 95% confidence intervals were calculated using binary logistic regression (SPSS, version 10.0).

## Results

In the cohort of 39 714 new users of antihypertensive drugs, we identified 463 substituted patients and 595 matched non-substituted patients. Of the original cohort,

7981 patients had a follow-up of less than 365 days before the start of antihypertensive drugs. Of these patients, 6793 received only one prescription. Of the remaining 24 940 patients, only 491 started with a brand-name antihypertensive during a period in which there was a generic equivalent available. Of these 491 patients, 463 (94.3%) were matched to one or more controls. Three hundred thirty-one substituted patients had 1 matched non-substituted patient, 93 substituted patients had 2 matched non-substituted patients, and 26 substituted patients had 3 matched non-substituted patients, meeting the inclusion criteria. Basic characteristics of the subjects are given in Table 1.

#### ADHERENCE AFTER SUBSTITUTION

The percentage of nonadherent patients (MPR <80%) among the substituted cohort was 13.6% versus 18.7% among the non-substituted group (crude OR 0.69; 95% CI 0.49 to 0.96). After adjustment for confounders, substituted patients were still less likely to be nonadherent compared with non-substituted patients (adjusted OR 0.68; 95% CI 0.48 to 0.96). None of the substituted patients (and non-substituted patients) discontinued their antihypertensive regimen directly after substitution (all substituted patients returned for a second generic prescription; Table 2). Adherence was similar among substituted and non-substituted patients before the substitution (91.6% vs 92.1%, respectively;  $p = 0.60$ ). Furthermore, after substitution, adherence was significantly different between both groups (92.4% vs 90.4%, respectively;  $p = 0.037$ ). Small but not significant differences in nonadherence between substituted patients and non-substituted patients were observed for subgroups defined by gender ( $p = 0.40$ ). Substituted females had a higher risk for nonadherence compared with non-substituted females (OR 0.46; 95% CI 0.28 to 0.77); this was not observed in males (OR 0.97; 95% CI 0.60 to 1.58). No differences between substituted and non-substituted patients were observed when defined by type of antihypertensive ( $p = 0.76$ ), age group ( $p = 0.98$ ), and duration of use ( $p = 0.19$ ), although substituted patients with a first episode of use longer than 270 days had a 0.42 times lower risk of nonadherence than matched non-substituted patients.

The association between substitution and nonadherence did not differ significantly for subgroups defined by first prescriber ( $p = 0.70$ ), PDD ( $p = 0.30$ ), nonadherence with previous prescription ( $p = 0.36$ ), comedication ( $p = 0.94$  for antiasthmatic drugs,  $p = 1.00$  for

lipid-lowering drugs,  $p = 1.00$  for antidiabetic drugs), and prior cardiovascular hospitalizations ( $p = 0.49$  for ischemic heart disease,  $p = 0.98$  for congestive heart failure,  $p = 0.71$  for arrhythmias,  $p = 0.29$  for peripheral vascular disease,  $p = 0.99$  for central venous disease). No differences in hospitalizations for cardiovascular disease between substituted (6 admissions) and non-substituted (8 admissions) patients were observed after substitution.

#### ANALYSIS OF SENSITIVITY AND SAMPLING PROCEDURE

In a sensitivity analysis, we analyzed results for different cut-off values of adherence between 50% and 100% (Figure 1) to exclude the possibility that our definition of adherence strongly influenced the outcome of our study. The association between substitution and nonadherence remained essentially the same with ORs, varying from 0.59 (<50%) to 0.83 (<95%) after adjustment. For most cut-off values, the risk of nonadherence for substituted patients was not significantly lower than 1.00.

**Table 1.** Basic Characteristics of the Study Population<sup>a</sup>

Characteristic	Substituted Pts. (n = 463)	Non-substituted Pts. (n = 595)	p Value
Males	228 (49.2)	282 (47.4)	0.55 <sup>b</sup>
Age (y)	60.5 ± 13.99	60.0 ± 14.35	0.59 <sup>b</sup>
≤39	36 (7.8)	49 (8.3)	1.00 <sup>c</sup>
40–59	189 (40.8)	224 (37.6)	1.00 <sup>c</sup>
60–79	208 (44.9)	278 (46.7)	1.00 <sup>c</sup>
≥80	30 (6.5)	44 (7.4)	1.00 <sup>c</sup>
PDD/DDD <1	434 (93.7)	565 (95.0)	0.40 <sup>b</sup>
Duration of use (days)	219.7 ± 195.5	212.1 ± 199.8	0.54 <sup>b</sup>
First prescriber			0.94 <sup>c</sup>
general practitioner	366 (79.0)	461 (77.5)	
internist	61 (13.2)	83 (13.9)	
cardiologist	15 (3.2)	22 (3.7)	
other	21 (4.5)	29 (4.9)	
Prior cardiovascular hospitalizations			
ischemic heart disease	15 (3.2)	10 (1.7)	0.098 <sup>b</sup>
congestive heart failure	1 (0.2)	1 (0.2)	0.86 <sup>b</sup>
cerebrovascular disease	4 (0.9)	1 (0.2)	0.10 <sup>b</sup>
arrhythmia	5 (1.1)	4 (0.9)	0.47 <sup>b</sup>
peripheral vascular disease	1 (0.2)	2 (0.3)	0.72 <sup>b</sup>
Initial antihypertensive drug			0.33 <sup>c</sup>
diuretic	70 (15.1)	117 (19.7)	
β-blocker	253 (54.6)	319 (53.6)	
calcium-channel blocker	27 (5.8)	35 (5.9)	
ACE inhibitor	110 (23.8)	121 (20.3)	
angiotensin II receptor antagonist	0	0	
other	3 (0.6)	3 (0.5)	
Average adherence			
before substitution	91.6 ± 15.2	92.1 ± 14.0	0.60 <sup>b</sup>
after substitution	92.4 ± 14.10	90.4 ± 16.2	0.037 <sup>b</sup>

ACE = angiotensin-converting enzyme; PDD/DDD = prescribed daily dose/defined daily dose.  
<sup>a</sup>Values expressed as number (%) or mean ± SD.  
<sup>b</sup>Student's *t*-test.  
<sup>c</sup> $\chi^2$  Test.

## Discussion

In this study, we demonstrated that generic substitution in patients using antihypertensives does not lead to a decrease in adherence with the prescribed regimen or increased risk for cardiovascular hospitalization within 6 months. In fact, the proportion of adherent patients in the substituted group was higher than in the group that continued unchanged in the non-substituted group (OR 0.68). No differences between non-substituted and substituted males were observed. More females were adherent in the substituted group than in the non-substituted group (OR 0.46). Furthermore, none of the patients discontinued medication directly after the substitution.

## Strengths and Weaknesses

A limitation of our study is that we used pharmacy records for the calculation of adherence, the use of which is accompanied by several forms of bias.<sup>19</sup> The use of pharmacy records leads to an underestimation of nonadherence because prescriptions may be collected but not used. This misclassification is probably non-differentially distributed among substituted and non-substituted. This would lead to a decrease of a potential effect toward the null. However, as our effect is opposite of what we hypothesized, this information bias is not relevant in our situation.

In the Netherlands, pharmacies are allowed to substitute, even when the brand name drug is on the prescription. Physicians can prevent substitution only by writing the brand name of the drug followed by the ® symbol on the prescription. This decision may be triggered by the fact that a physician thinks the generic equivalent is not bioequivalent, substitution would lead to a decrease in adherence, or because the patient asks the physician to do so. In our study, the latter would have led to the inclusion of more nonadherent patients in the non-substituted group, which did not occur (Table 1). Another limitation may be that, in the pharmacy, only patients with good adherence were selected, although a calculation of adherence is not very likely to occur in a busy pharmacy. Dutch pharmacy systems do not report adherence rates when a drug is dispensed. In addition, we corrected for several factors related to adherence, thus minimizing confounding bias based on adherence. However, we found that adherence, as well as the proportion of nonadherent patients, remains the same after substitution within and between both groups. Because our follow-up was complete, no relevant selection bias occurred. Because our follow-up was limited due to the data available, we were able to follow our patients for only 6 months after the substitution. This may be too short to detect actual differences as a result of nonadherence and assess the risk with regard to the safety of generic drugs. One strength

**Table 2.** Association Between Substitution and Nonadherence

Characteristic	Adherent/Nonadherent Pts., n (%) <sup>a</sup>		OR (95% CI) <sup>b</sup>	
	Substituted	Non-substituted	Crude	Adjusted
Overall	63/463 (13.6)	111/595 (18.7)	0.69 (0.49 to 0.96)	0.68 (0.48 to 0.96)
Gender				
male	38/228 (16.7)	47/282 (16.7)	1.00 (0.63 to 1.60)	0.97 (0.60 to 1.58)
female	25/235 (10.6)	64/313 (20.4)	0.46 (0.28 to 0.76)	0.46 (0.28 to 0.77)
Antihypertensive agent				
diuretic	9/70 (12.9)	25/117 (21.4)	0.54 (0.24 to 1.24)	0.41 (0.17 to 1.02)
β-blocker	39/253 (15.4)	60/319 (18.8)	0.79 (0.51 to 1.22)	0.82 (0.52 to 1.30)
calcium-channel blocker	1/27 (3.7)	4/35 (11.4)	0.30 (0.031 to 2.84)	0.44 (0.41 to 4.70)
ACE inhibitor	13/110 (11.8)	22/121 (18.2)	0.60 (0.29 to 1.27)	0.61 (0.29 to 1.29)
angiotensin II receptor antagonist	0/0	0/0		
other	1/3 (33.3)	0/3		
Age (y)				
≤39	5/36 (13.9)	5/49 (10.2)	1.75 (0.42 to 7.34)	1.95 (0.43 to 8.89)
40–59	20/189 (10.6)	45/224 (20.1)	0.49 (0.28 to 0.88)	0.49 (0.27 to 0.90)
60–79	30/208 (14.4)	43/278 (15.5)	0.87 (0.82 to 1.43)	0.85 (0.50 to 1.44)
≥80	8/30 (26.7)	18/44 (40.9)	0.60 (0.24 to 1.50)	0.50 (0.18 to 1.41)
Duration of use (days)				
0–90	20/143 (14.0)	34/207 (16.4)	0.83 (0.46 to 1.51)	0.85 (0.46 to 1.57)
91–180	17/103 (16.5)	26/128 (20.3)	0.78 (0.40 to 1.52)	0.80 (0.40 to 1.61)
181–270	12/79 (15.2)	18/91 (19.8)	0.73 (0.33 to 1.62)	0.62 (0.25 to 1.53)
≥271	14/138 (10.1)	33/169 (19.5)	0.47 (0.24 to 0.91)	0.42 (0.21 to 0.86)

ACE = angiotensin-converting enzyme.  
<sup>a</sup>Number of nonadherent patients/all patients (% nonadherence among all patients).  
<sup>b</sup>Binary logistic regression.  
<sup>c</sup>Adjusted hospitalization for cardiovascular diseases, type of prescriber, and PDDs.

of our study is that we were able to include a sufficiently large number of patients. Furthermore, because of the adherence-enhancing circumstances, it would be very difficult to test the effect of substitution in a randomized clinical trial.

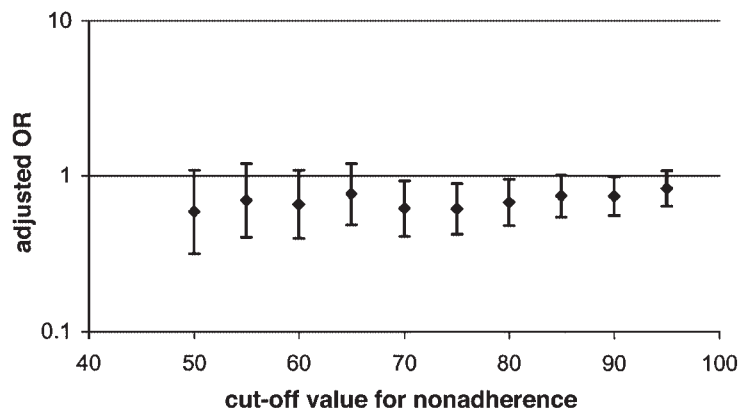
#### EXPLANATION FOR OUR FINDINGS

One possible explanation for the lower number of non-adherent patients among the substituted group may be that they receive extra attention in the pharmacy, since it is common practice in Dutch pharmacies to educate patients about the reasons for generic substitution, possibly increasing awareness about the benefits of adherent drug use. Patient education has been demonstrated to increase the acceptance of generic prescribing.<sup>20</sup> From adherence studies on chronic medication, it is known that adherence decreases rapidly in the first 3–6 months; after this period, the fall is more gradual.<sup>21–24</sup> This would explain the small decrease of adherence, as well as the increased number of nonadherent patients among the non-substituted patients in the comparison between as well as within the cohorts. The fact that the association becomes gradually stronger, and even significant, with an increase in duration of use supports this hypothesis because, at initiation of therapy, most patients are adherent. If an intervention would have any positive effect, it would be hard to detect in this group.

The time needed to instruct a patient should be kept in mind when considering the economic benefits of substitution. The difference we found between substituted and non-substituted females may be explained by general differences in health-related behavior, including reports of adverse effects. Our results demonstrate that adherence-related interventions may have a different impact on males and females.<sup>25,26</sup>

#### GENERALIZABILITY

The design of our study may be applied to evaluations of various other, more complex antihypertensive drug regi-



**Figure 1.** Sensitivity analysis of association between substitution and nonadherence for different cut-off values for nonadherence.

mens. In addition, the influence of generic substitution on adherence to treatment in patients using other types of chronic medications needs to be studied. We expect that our results are generalizable to other asymptomatic chronic diseases. However, in populations such as severe psychiatric disorders (eg, schizophrenia), substitution will probably decrease adherence to treatment. In 2003, the situation with regard to generics changed, and the reimbursement prices of generic equivalents fell by 40%. From this point forward, economic benefits for health insurance providers and patients could be obtained.

Although both brand-name drugs and generic equivalents are still fully covered in the Netherlands, the new situation resulted in active and economic encouragement of pharmacists and physicians to substitute by health insurance companies. In addition, patients were encouraged by health insurance companies to accept this substitution, also from the perspective of cost reductions for public health. Although this constituted a major change, it is not likely that it influenced the generalizability of our results.

#### Conclusions

We found that generic substitution of antihypertensive drugs does not lead to lower adherence or more discontinuation in patients at initiation of therapy. When a generic antihypertensive equivalent becomes available, substitution should be considered to achieve the economic benefits. This type of study should be replicated in patients using other types of chronic medications.

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EXTRACTO

**ANTECEDENTES:** La sustitución de un medicamento de marca por su equivalente genérico representa una gran oportunidad para reducir el coste de los medicamentos. Sin embargo, farmacéuticos y médicos encuentran a menudo que los pacientes y los laboratorios farmacéuticos tienen dudas sobre la equivalencia de los medicamentos genéricos. Esto puede reflejarse en una adhesión reducida al tratamiento.

**OBJETIVO:** Estudiar la asociación que existe entre la sustitución genérica y la falta de adhesión al tratamiento antihipertensivo.

**MÉTODOS:** Se realizó un estudio de cohortes apareadas entre el 1 de enero de 1999 y el 31 de diciembre del 2002. Se utilizó la base de datos Pharm, un archivo de aproximadamente 950 000 personas que permite cruzar los listados de suministro de medicamentos por parte de las farmacias de la comunidad con los informes de alta hospitalaria de los pacientes. Esta población procede de 30 ciudades medianas localizadas en los Países Bajos; los pacientes habían iniciado un tratamiento antihipertensivo. Se estudió la adhesión de estos pacientes a la compra sucesiva de medicamentos genéricos después de haber hecho la sustitución. Los pacientes cuya adhesión al medicamento estuvo por debajo del 80% se consideraron no adherentes al tratamiento.

**RESULTADOS:** Se identificaron 464 pacientes que recibieron un sustituto genérico y 565 controles apareados por edad, sexo, fecha de inicio del uso del medicamento, duración de su uso, y código del producto genérico. De los pacientes que recibieron un sustituto genérico, el 13.6% mantuvieron su adhesión al tratamiento; de los que no recibieron un sustituto genérico, el 18.7% mantuvieron su adhesión al tratamiento (OR 0.68; CI 95% 0.48–0.96). Esta asociación no se observó en los pacientes masculinos. Además, ninguno de los pacientes suspendió su tratamiento. Por último, no se observaron diferencias en la hospitalización por enfermedades cardiovasculares en los primeros 6 meses después de la sustitución por un medicamento genérico.

**CONCLUSIONES:** La sustitución genérica de medicamentos antihipertensivos no conlleva una menor adhesión al tratamiento, tampoco un mayor número de suspensiones de tratamientos u hospitalizaciones relacionadas con enfermedades cardiovasculares, comparado con los pacientes que no recibieron sustituto genérico. Cuando existe un equivalente genérico al más económico del antihipertensivo, se debe considerar su uso para beneficiarse de la reducción del coste de los tratamientos.

Encarnación C Suárez

RÉSUMÉ

**INTRODUCTION:** La substitution générique constitue une opportunité pour réduire les coûts des soins pharmaceutiques. Cependant, les pharmaciens et les médecins sont confrontés au fait que les patients et les compagnies novatrices émettent des doutes quant à la bioéquivalence du médicament substitué. Ceci peut se refléter par une diminution de la fidélité au traitement.

**OBJECTIF:** Évaluer l'association entre la substitution générique et la non-fidélité à un traitement antihypertenseur.

**MÉTHODOLOGIE:** Une étude de cohorte appariée a eu lieu durant la période du 01 janvier 1999 au 31 décembre 2002 utilisant la banque de données Pharm, un système reliant les profils médicamenteux des pharmacies communautaires et les données au départ hospitalier d'environ 950 000 patients. Les citoyens d'une trentaine de municipalités de grosseur moyenne au Pays-Bas ayant débuté une thérapie antihypertensive ont été impliqués. La fidélité au renouvellement après une substitution fut évaluée. Ceux ayant une fidélité inférieure à 80% furent considérés comme non fidèle.

**RÉSULTATS:** Quatre-cent soixante quatre patients ayant eu une substitution et 565 patients du groupe contrôle, appariés pour l'âge, le sexe, la date de début de la thérapie, et de la durée d'utilisation ainsi que le code du produit générique furent comparés. Parmi les patients ayant eu une substitution, 13.6% étaient non fidèles à leur traitement alors que 18.7% étaient non fidèles dans le groupe contrôle (OR 0.68; IC 95% 0.48 à 0.96). Cette association était absente chez les hommes. Aucun patient a discontinué sa thérapie. Aucune différence dans l'hospitalisation pour maladies cardiovasculaires dans les 6 mois après la substitution a été mise à jour.

**CONCLUSIONS:** La substitution générique d'antihypertenseur ne réduit pas la fidélité au traitement, ni ne cause plus d'hospitalisation suite à un arrêt de médication ou d'hospitalisation cardiovasculaire lorsque comparée aux patients dont la thérapie ne fut pas substituée. Lorsqu'un antihypertenseur générique moins coûteux devient disponible, la substitution générique devrait être considérée.

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