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RESEARCH ARTICLE

Initial non-compliance with antihypertensive monotherapy is followed by complete discontinuation of antihypertensive therapy†

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SUMMARY

Purpose Discontinuation with treatment is a major problem in the treatment of hypertension. The objective of our study was to assess the association between non-compliance and discontinuation in patients who started using antihypertensive monotherapy.

Methods A nested case-control study within a cohort of new users of antihypertensive drugs between 1st January 1999 and 31st December 2002 was performed. 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. Cases discontinued their use of antihypertensive monotherapy and were not switched to other antihypertensive treatment, controls stayed on their initially prescribed monotherapy. Conditional logistic regression was used to calculate odds ratios (OR) and their 95% confidence intervals (CI).

Results In a cohort of 39,714 new users of antihypertensive drugs, we identified 9111 cases and 9111 matched controls. The percentage of non-compliant patients (compliance <80%) among cases and controls was 14.0% and 5.8%, respectively [OR 2.86 (95%CI: 2.52–3.24)]. Patients who used less than 90 days had a higher risk on discontinuation [OR 3.10 (95%CI: 2.67–3.59)] than patients who used more than 90 days [OR 2.28 (95%CI: 1.79–2.92)]. The association was generally similar among males and females, among the different types of antihypertensives and among the different age groups.

Conclusion In patients who start antihypertensive monotherapy, non-compliance is often followed by discontinuation of this antihypertensive treatment. The pharmacy medication history is a valuable tool for physicians to identify patients who have a high risk on discontinuation with antihypertensive treatment. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — hypertension; antihypertensives; discontinuation; non-compliance

INTRODUCTION

Discontinuation with antihypertensive treatment is a major problem in the prevention of cardiovascular morbidity and mortality.[1] A large number of antihypertensive drugs are available and effective as demonstrated in randomised clinical trials (RCT).[2] However, adherence to therapy in daily practice differs greatly from adherence observed in those RCTs.[3] This means that patients often fail to benefit from these therapeutic options by not being as compliant as prescribed or by discontinuing with antihypertensive treatment completely.[4–13] Several determinants such as the initial drug choice, side effects, age, gender, co-medication, prescriber and co-morbidity are known to be associated with discontinuation of antihypertensive

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treatment.[4–14] Initial non-compliance, as an indicator of reluctance against the prescribed drug, experienced side effects, carelessness with regard to physicians' instructions or disappointment about the effect on blood pressure, may also be a predictor of discontinuation. The purpose of the present study was to assess the association between non-compliance with the initially prescribed monotherapy and discontinuation with this drug and thus antihypertensive treatment in general by using pharmacy records.

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. This database covers a well-defined geographically diverse, drug-insured population of residents of 30 medium-sized cities in the Netherlands. Clustering of all pharmacies within each city results in drug-dispensing histories that contain more than 95% of all prescriptions dispensed to a particular patient. Records of non-residents of the PHARMO cities are excluded.[15] The data registered in the PHARMO database include age and sex of the patient, name, dispensing date and amount of units dispensed of the drug and prescribed daily dose. Prescribed daily dose (PDD) was expressed as number of defined daily doses (DDD). The DDD is the dosage for the main indication of a drug.[16,17]

Patients

We selected a cohort of patients who used no antihypertensive agents during 1998 and presented their first prescription for a single antihypertensive drug between 1st January 1999 and 31st December 2002 and who collected more than one prescription. These patients were followed until the end of data collection (31st December 2002) or until their disappearance from the database. The latter indicates a move to a city outside the scope of the PHARMO area, death or institutionalisation. All prescription drugs were coded according to the anatomical therapeutic chemical (ATC) classification system.[17] ATC codes C02 (miscellaneous antihypertensives), C03 (diuretics), C07 (beta-blockers), C08 (calcium channel blockers), C09A + B (ACE-inhibitors) and C09C + D (angiotensin II receptor antagonists) were used to categorise antihypertensive drug classes. When information regarding the prescribed dose or type of the initially prescribed antihypertensive drug was not available, the patient was excluded.

Study design

Within a cohort of 39,714 new users of antihypertensive drugs, a nested case control study was performed. Patients were defined as cases (discontinuers) if the time between two prescriptions was at least 180 days or two times the duration of the last prescription, whichever was the smallest, after the theoretical end date of the last prescription. The theoretical end date of the last prescription was calculated by adding the duration of the last prescription to the start date of the last prescription. The duration of a prescription was calculated by dividing the number of tablets by the dose regimen. In a previous study, we assessed the influence of varying the maximum allowed treatment gap on persistence with antihypertensives and found that larger gaps do not include more patients as persistent.[18] The start date of the last prescription was defined as the date of discontinuation. Patients with a change, such as an increase or decrease in daily dose and dose frequency, an addition of another antihypertensive agent, or a switch to another antihypertensive agent were not considered as discontinuers. Controls were randomly selected using risk-set sampling and had not undergone a change of the initially prescribed monotherapy and still used this monotherapy after the date of discontinuation of the case (index-date) to whom they were matched (Figure 1).[19] Cases were matched to controls (1:1) on age (within a 3 years age-band), gender and duration of unchanged use of the antihypertensive monotherapy. Unchanged use was defined as a period of uninterrupted use of an antihypertensive agent with the same initially prescribed dosage regimen.

Definition of compliance and potential confounding factors

Compliance was defined as the number of days for which dosages were dispensed between the start of treatment and date of discontinuation (index date) divided by the number of days between the start of treatment and index date. A patient with a compliance below 80% was considered non-compliant. In a sensitivity analyses we studied the influence of different definitions of compliance on the association between compliance and discontinuation. Potential confounders that were assessed prior to the index -date included: use of specific co-medication, first

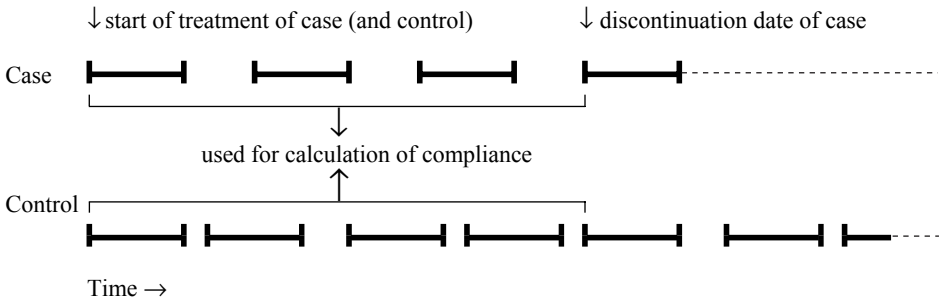

Figure 1. Method of calculation of compliance for cases and their matched controls. For the cases compliance is calculated by dividing all theoretical durations of the prescriptions before the last one, by the time between the start date of treatment and the start date of the last one. For matched controls compliance is calculated by dividing all theoretical durations of the prescriptions before the discontinuation date of the matched case, by the time between the start date of treatment and the discontinuation date of the case

prescriber, being treated with a PDD < DDD, hospitalisation for cardiovascular diseases such as ischaemic heart disease, congestive heart failure, cardiac arrhythmias, peripheral vascular disease and cerebrovascular disease.

Analysis

Student's *t*-tests and chi-square tests were used to analyse differences in basic characteristics between cases and controls. To analyse the association between initial non-compliance and discontinuation, crude and adjusted odds ratios (OR) and their 95% confidence intervals (CI) were calculated using conditional logistic regression (SPSS for Windows, version 10.0).

Results

In the cohort of 39,714 new users of antihypertensive drugs, we identified 9111 cases and 9111 matched controls meeting the inclusion criteria. Basic characteristics of the patients are given in Table 1. There were some small, although significant, differences between cases and controls in the use of co-medication and prior cardiovascular hospitalisations.

We found differences between cases and controls in compliance (Table 2). The average compliance among the cases was slightly, but significantly ($p < 0.001$), lower among cases. The percentage of non-compliant patients (compliance <80%) among the cases was 14.0% versus 5.8% among controls [crude OR 2.86 (95%CI: 2.55–3.20)]. After adjustment for PDD, first prescriber, co-medication, prior cardiovascular hospitalisation and initial type of antihypertensive monotherapy, non-compliant patients still had a 2.86 times higher chance on discontinuation compared to compliant patients [95%CI: 2.52–3.24]. Some small but not significant differences in the association between non-compliance and discontinuation were observed between males and females, between different types of antihypertensives and between different age groups. The association differed for subgroups defined by duration of use ($p = 0.041$). Patients who used shorter than 90 days had a higher risk than patients who used longer than 90 days. The association between compliance and discontinuation did not differ for other subgroups defined by PDD ($p = 0.88$), first prescriber ($p = 0.87$), co-medication ($p = 0.099$ for anti-asthmatic drugs, $p = 0.55$ for lipid lowering drugs and $p = 0.11$ for anti-diabetic drugs) and prior cardiovascular hospitalisations ($p = 0.080$ for IHD, $p = 0.47$ for CHF, $p = 0.71$ for arrhythmias and $p = 1.00$ for PVD, $p = 0.73$ for CVD).

Other factors related to discontinuation

Internists treated more patients who discontinued their medication compared to general practitioners [OR 1.20 (95%CI: 1.03–1.39)], no differences between cardiologists and general practitioners were observed [OR 1.07 (95%CI: 0.95–1.21)]. No differences between patients who were initially prescribed a PDD < DDD and patient who were initially treated with a PDD ≥ DDD were observed [OR 0.99 (95%CI: 0.91–1.08)]. Patients who were hospitalised for cardiovascular disease in the prior to study entrance had a much lower risk on discontinuation, the lowest risk was observed for hospitalisation for arrhythmias [OR 0.021 (95%CI: 0.005–0.085)], the highest risk was observed for congestive hearth failure [OR 0.076 (95%CI: 0.010–0.59)]. The same holds for the use of specific co-medication, the use of anti-diabetic medication [OR 0.068 (95%CI: 0.043–0.11)], lipid lowering medication [OR 0.043 (95%CI: 0.026–

Table 1. Basic characteristics of the study population

	Cases	Controls	*p*-value
Number of patients	9111	9111	
Males	3764 (41.3%)	3764 (41.3%)	1
Age (years)	58.33 (±15.98)	58.48 (±15.63)	0.52
Age group			1
0–19 years	85 (0.9%)	85 (0.9%)	
20–39 years	935 (10.3%)	935 (10.3%)	
40–59 years	3810 (41.8%)	3810 (41.8%)	
60–79 years	3467 (38.1%)	3467 (38.1%)	
≥80 years	814 (8.9%)	814 (8.9%)	
PDD < DDD	3887 (42.7%)	3902 (42.8%)	0.88
Duration of use (days)	90.17 (±153.14)	88.40 (±150.45)	0.43
First prescriber			$p < 0.001$
General practitioner	6870 (75.4%)	6932 (76.1%)	
Internist	1042 (11.4%)	829 (9.1%)	
Cardiologist	496 (5.4%)	519 (5.7%)	
Miscellaneous	703 (7.7%)	831 (9.1%)	
Co-medication			
Anti-asthmatic drugs	723 (7.9%)	30 (0.3%)	$p < 0.001$
Lipid lowering drugs	465 (5.1%)	26 (0.3%)	$p < 0.001$
Anti-diabetic drugs	529 (5.8%)	20 (0.2%)	$p < 0.001$
Prior cardiovascular Hospitalisations			
Ischaemic heart disease	375 (4.1%)	13 (0.1%)	$p < 0.001$
Congestive heart failure	20 (0.2%)	1 (0.0%)	$p < 0.001$
Arrhythmia	93 (1.0%)	3 (0.0%)	$p < 0.001$
Peripheral vascular disease	25 (0.3%)	1 (0.0%)	$p < 0.001$
Cerebrovascular disease	108 (1.2%)	2 (.0%)	$p < 0.001$
Antihypertensive monotherapy			1
Diuretics	2700 (29.6%)	2700 (29.6%)	
Beta-blockers	4252 (46.7%)	4252 (46.7%)	
Calcium channel blockers	739 (8.1%)	739 (8.1%)	
ACE-inhibitors	906 (9.9%)	906 (9.9%)	
Angiotensin II receptor antagonists	435 (4.8%)	435 (4.8%)	
Miscellaneous	79 (0.9%)	79 (0.9%)	
Average compliance	93.54% (±11.48)	96.59% (±9.56)	$p < 0.001$

Values expressed as mean ± SD or number (%).

0.073)] and anti-asthmatic medication [OR 0.044 (95%CI: 0.030–0.065)]. Numbers and percentages are listed in Table 1.

In a sensitivity analysis, we analysed the results for different cut-off values of compliance (Figure 2). Using cut-off values between 60% and 100%, the association between initial non-compliance and discontinuation remained essentially the same with ORs varying from 1.33 (<60%) to 2.19 (<100%) after adjustment. The strongest association was observed around 80%, the cut-off value we used, as is shown in Figure 2. We assessed whether the risk-set sampling was conducted properly to exclude the possibility that the cases and controls were interdependent and found that of the total number of matched controls only 7.1% became cases later on. Of those controls 0.21% were non-compliant after becoming a case indicating that the sampling procedure did not cause a decrease of the difference in number of non-compliant patients between cases and controls.

Discussion

The purpose of our study was to assess the association between non-compliance with the initially prescribed antihypertensive monotherapy and the discontinuation of this drug and thus antihypertensive treatment in general. To our knowledge, the relationship between initial non-compliance and discontinuation has never been studied before.

We have found that patients who are non-compliant with their monotherapy have a 2.86 times higher chance on complete discontinuation with this drug and thus antihypertensive treatment in general compared to compliant patients. In addition, we have found a lower risk on discontinuation among patients

Table 2. Association between non-compliance and discontinuation with treatment for patients who used monotherapy

	Cases*	Controls*	OR crude	OR adjusted†
Non-compliant ($n=9111$)	1277 (14.0%)	532 (5.8%)	2.86 (2.55–3.20)	2.86 (2.52–3.24)
Stratified on gender				
Males ($n=3764$)	485 (12.9%)	218 (5.8%)	2.61 (2.18–3.12)	2.52 (2.05–3.10)
Females ($n=5347$)	792 (14.8%)	314 (5.9%)	3.03 (2.62–3.52)	3.06 (2.61–3.59)
Stratified on type of antihypertensive				
Diuretics ($n=2700$)	494 (18.3%)	208 (7.7%)	2.96 (2.45–3.57)	3.13 (2.54–3.85)
Beta-blockers ($n=4252$)	507 (11.9%)	228 (5.4%)	2.53 (2.13–2.97)	2.54 (2.11–3.06)
Calcium antagonists ($n=739$)	100 (13.5%)	32 (4.3%)	3.96 (2.50–6.25)	3.65 (2.16–6.17)
ACE-inhibitors ($n=906$)	116 (12.8%)	41 (4.5%)	3.27 (2.22–4.83)	3.33 (2.03–5.46)
Angiotensin II receptor antagonists ($n=435$)	45 (10.3%)	14 (3.2%)	4.10 (2.05–8.19)	3.60 (1.71–7.60)
Miscellaneous ($n=79$)	15 (19.0%)	9 (11.4%)	2.00 (0.75–5.33)	1.51 (0.51–4.51)
Stratified on age group				
0–19 years ($n=85$)	19 (22.4%)	12 (14.1%)	1.78 (0.79–4.02)	1.76 (0.74–4.17)
20–39 years ($n=935$)	163 (17.4%)	65 (7.0%)	3.13 (2.25–4.36)	3.30 (2.32–4.69)
40–59 years ($n=3810$)	538 (14.1%)	230 (6.0%)	2.74 (2.31–3.26)	2.70 (2.24–3.26)
60–79 years ($n=3467$)	455 (13.1%)	168 (4.8%)	3.32 (2.71–4.05)	3.46 (2.73–4.38)
$\geq$80 years ($n=814$)	102 (12.5%)	57 (7.0%)	2.00 (1.34–2.86)	1.93 (1.30–2.87)
Stratified on duration of use				
<90 days ($n=7273$)	995 (13.7%)	401 (5.5%)	3.02 (2.65–3.45)	3.10 (2.67–3.59)
$\geq$90 days ($n=1838$)	282 (15.3%)	130 (7.1%)	2.41 (1.92–3.01)	2.28 (1.79–2.92)

*Number of non-compliant patients/all patients (% non-compliance among all patients).
†Adjusted for use of specific co-medication, hospitalisation for cardiovascular diseases, type of prescriber and PDDs.

receiving treatment for a longer period compared to a shorter period. This finding is in line with previous studies.[5,6,8,10,12,23]

In this study we found a relatively low number of non-compliant patients (14.0% among cases and 5.8% among controls). The low number of non-compliant patients may be caused by the fact that we used a database containing computerised pharmacy records potentially overestimating compliance. This overestimation is partly caused by the fact that often patients collect their medication directly after a follow-up visit to the physician independent of their medication at home. Furthermore, in the Netherlands, pharmacies are often electronically linked to general practitioners or the general practitioners send their prescriptions by fax. Therefore the prescription often will be registered the same day as it is requested by a patient and consequently prescribed by a physician, although the patient may collect the prescription later. Although we do not believe that this frequently occurs, the occurrence itself would have lead to an underestimation of the association.

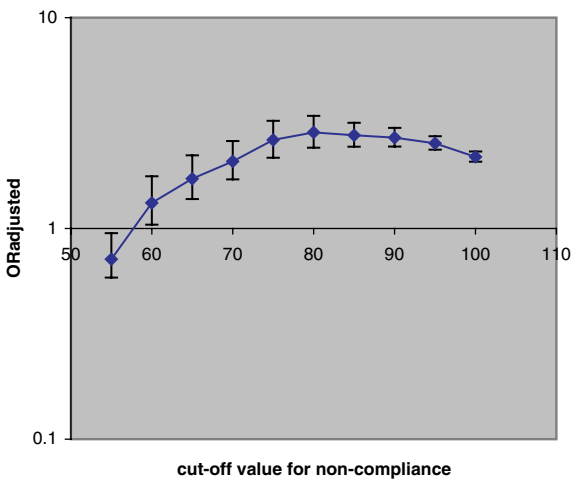

Figure 2. Influence of variation of cut-off value for non-compliance on the association between non-compliance and discontinuation (95% CI)

There are some limitations of this study. The first, and probably the most important one, is the fact that the proportion of patients who discontinue their drug on a prescriber's advice may be relatively high. This would reduce importance of our findings. Another reason may be that the patient is no longer hypertensive. However, we found that the mean duration of the first treatment episode was about 90 days. This is too short to justify such considerations by a physician. The second limitation is that a patient is advised to take his antihypertensive in a lower dose, which is not always registered in the pharmacy database, hereby extending the theoretical duration of a prescription. This would have lead to an overestimation of the actual non-compliance although the

distribution among cases and controls may be non-differential. The latter could be expected in patients with higher PDDs. However, correction for PPD (categorised in PDD < DDD and PDD ≥ DDD) did not have any influence on the magnitude of the association. Furthermore, the number of PDDs ≥ DDD was almost equal in both groups ($p = 0.88$). In this study, we used the relatively rough classification of antihypertensive drugs based on their ATC-code. Although there are differences within a certain antihypertensive drug class with regard to the indication, side effects etc. the association may still be present. This is hypothesis is supported by the absence of effect modification ($p = 0.86$) between different antihypertensive drug classes. A last limitation is the fact that not all patients may have had a diagnosis of hypertension, and that they use antihypertensives for another cardiovascular disease such as angina pectoris or congestive hearth failure. The direction towards which our results would have been influenced by this remains unclear.

The PHARMO-database used in this study is virtually complete with regard to drugs dispensed to patients and computerised pharmacy records have shown to be a reliable source of drug exposure as estimated in a home inventory.[15,24,25] Compliance calculated using pharmacy records can be considered as the maximum possible compliance, the actual compliance being (much) lower. Therefore, the patients we have found to be non-compliant will certainly be non-compliant because they could not have medication available from a previous dispensing. Compliance assessed using pharmacy records was previously found to significantly correlate with compliance as measured with other methods such as pill counts, self-reports and electronic monitoring, although the strength of those correlations were moderate.[26,27]

One of the implications of this study is that in daily medical practice, pharmacy records can be used to identify patients at risk for discontinuation. Therefore, pharmacists should monitor refill compliance as part of their daily routine and actively provide these data to prescribers on a regular basis. The reasons for non-compliance should be detected by physicians during consultations and depending on the reason for dissatisfaction, compliance enhancing strategies[3,28–31] should be directed to these non-compliant patients. The effectiveness of interventions specifically targeted to non-compliant patient determined by pharmacy records has to be determined in future research to study the effectiveness of these interventions with regard to the reduction of cardiovascular morbidity and mortality. Furthermore, the association we have found has to be established for other chronic medication for diseases such as diabetes, asthma, hyperlipidemia, depression, osteoporosis and others in future similar studies.

In conclusion, non-compliance is often followed by discontinuation of the initially prescribed monotherapy and antihypertensive treatment in general. The association is stronger if a patient uses less than 90 days than with larger durations of use. The association is generally similar among females and males, among different age groups and among the different classes of antihypertensives. Using data from pharmacy records may help to identify patients who are not taking their medication as prescribed and thus have a higher risk on discontinuation. This information may be used by pharmacists and physicians to focus on improving continuation and compliance to decrease cardiovascular morbidity and mortality in patients who start using antihypertensive monotherapy.

KEY POINTS

- non-compliance is often followed by discontinuation of antihypertensive treatment
- pharmacy records may help to identify patients who have a higher risk on discontinuation

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