The association between compliance with antihypertensive drugs and modification of antihypertensive drug regimen

Boris L.G. Van Wijk, Olaf H. Klungel, Eibert R. Heerdink and Anthonius de Boer

Background **Non-compliance is an important factor in lack of control of blood pressure. Uncontrolled blood pressure, as well as patients' complaints about the prescribed medication, may lead to modification of the initially prescribed antihypertensive drug regimen. The objective of this study was to assess the association between non-compliance and change in medication regimen.**

Methods **A nested case–control study within a cohort of new users of antihypertensive drugs between 1 January 1999 and 31 December 2002. 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 were subjects whose initial drug regimen was modified. Controls did not undergo such a modification. Conditional logistic regression was used to calculate odds ratios (OR) and their 95% confidence intervals (CI), and to adjust for confounders.**

Results **In a cohort of 39 714 new users of antihypertensive drugs, we identified 11 937 cases and 11 937 matched controls. The percentage of non-compliant patients (compliance < 80%) among cases and controls was 5.1 and 3.6%, respectively [OR 1.39 (95% CI: 1.22–1.58)]. The association is stronger in females [OR 1.64 (95%CI: 1.37–1.94)] than in males [OR 1.14 (95% CI: 0.94–1.40)] and stronger if the duration of episode of use is longer than 6 months.**

Conclusion **Non-compliance is significantly associated with the occurrence of change in antihypertensive medication regimen. Pharmacists and physicians can use pharmacy data, although data tend to overestimate actual compliance, to assess and improve compliance with antihypertensive drugs, before modifying treatment regimens.** ***J Hypertens*** **22:1831–1837 © 2004 Lippincott Williams & Wilkins.**

Journal of Hypertension 2004, **22**:1831–1837

Keywords: hypertension, compliance, pharmacy records

Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences, Utrecht, The Netherlands.

Sponsorship: This study was funded by Dutch Board of Healthcare Insurance Organizations.

Correspondence and requests for reprints to O. H. Klungel, Department of Pharmacoepidemiology and Pharmacotherapy, Faculty of Pharmaceutical Sciences, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands.
Tel: +31 30 253 7324; fax: +31 30 253 9166; e-mail:o.h.klungel @pharm.uu.nl

Received 23 January 2004 **Revised** 19 April 2004
Accepted 3 May 2004

Introduction

Cardiovascular disease (CVD) is the main cause of premature death in industrialized countries. Hypertension is one of the most important risk factors for CVD. During the second half of the twentieth century, the control of hypertension improved considerably, resulting in a decrease in cardiovascular morbidity [1]. However, 70–75% of the patients with hypertension still have poor control of their blood pressure [1]. The full benefit of antihypertensive treatment, as observed in the situation of randomized controlled trials [2–7], can only be obtained if the patient is sufficiently compliant with the prescribed regimen. Non-compliance is an important cause of this lack of control of blood pressure [1,8–10]. If blood pressure is not normalized with an initially prescribed antihypertensive drug regimen, logical next steps involve increasing the dose, substituting the initial drug, or adding another antihypertensive drug. This 'stepped care' approach is recommended in many guidelines [11–14]. Non-compliance may therefore lead to unnecessary adjustments of drug regimens and increased health care costs. Besides dissatisfaction with the achieved blood pressure, patients' dissatisfaction with the prescribed medication (side-effects) may also lead to change in antihypertensive drug regimen, especially dose decrease or switch. In this study, we aimed to assess the association between non-compliance with antihypertensive drugs and the occurrence of an adjustment of the initially prescribed antihypertensive drug regimen.

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 population of residents of 30

0263-6352

medium-sized cities in The Netherlands – a geographically diverse, drug-insured population. 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 one 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].

Patients

We selected a cohort of patients who used no antihypertensive agents during 1998 and presented their first prescription for an antihypertensive drug between 1 January 1999 and 31 December 2002, and who collected more than one prescription. These patients were followed until the end of data collection (31 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 institutionalization. All prescription drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification system [16]. ATC codes C02 (miscellaneous antihypertensives), C03 (diuretics), C07 (beta-blockers), C08 (calcium-channel blockers), C09A+B (angiotensin-converting enzyme (ACE) inhibitors) and C09C+D (angiotensin II receptor antagonists) were used to categorize 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 new users of antihypertensive drugs, a nested case–control study was performed. Patients were defined as cases if they had undergone a change in the initial antihypertensive drug regimen. This change could be an increase or decrease in daily dose and dose frequency, an addition of another antihypertensive agent, or a switch to another antihypertensive agent. Controls were selected using risk-set sampling and had not undergone a change of the initially prescribed regimen until the date of change of the case (index-date) to whom they were matched [17]. Cases were matched to controls (1 : 1) on age (within a 3-year age-band), gender and duration of unchanged episode of use. An unchanged episode of use was defined as a period of continuous use of an antihypertensive agent. Drug use was considered continuous if the time between the theoretical end date of a prescription and the dispensing date of the next prescription was not more than three times the duration of the first prescription.

Definition of compliance and potential confounding factors

Compliance was defined as the number of days for which a drug was dispensed during one episode divided by the number of days between the start date of the first prescription of an antihypertensive agent and the index-date. A patient with compliance below 80% was considered non-compliant. In sensitivity analyses we studied the influence of different definitions of compliance on the association between compliance and change in medication regimen.

Potential confounders that were assessed prior to the index-date included: use of specific co-medication, class of initial antihypertensive drug, and hospitalization 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 compliance and change in medication regimen, crude and adjusted odds ratios (OR) and their 95% confidence intervals (CI) were calculated using conditional logistic regression (SPSS for Windows, version 10.0; SPSS Inc., Chicago, Illinois, USA).

Results

In the cohort of 39 714 new users of antihypertensive drugs we identified 11 937 cases and 11 937 matched controls meeting the inclusion criteria. Basic characteristics of the patients are given in Table 1. Among the cases, 13% had a dose decrease, 32% a dose increase, 27% switched to another antihypertensive drug and 28% had an addition of another antihypertensive drug. Both cases and controls, starting with antihypertensive drug treatment, had an average age of about 60 years. Among both groups, about 46% of the patients were males and the average duration of the first episode of use was about 195 days. There was a small difference in the average number of PDDs at the start of treatment, 0.76 PDDs in cases versus 0.79 PDDs in controls ($P < 0.001$). There was also a small difference between cases and controls in number of patients starting with a PDD below 1, 56.55% among the cases versus 52.45% among controls ($P < 0.001$).

The majority of the initial prescriptions came from the general practitioner. There were some small, although significant, differences between cases and controls in the use of co-medication and prior cardiovascular hospitalizations. Beta-blockers were the most used antihypertensive drug class among starters (46% among the cases versus 44% in controls). We found differences between cases and controls in compliance (Table 2). The average compliance was slightly, but significantly,

Table 1 Basic characteristics of the study population

	Cases	Controls	*P* value
Number	11937	11937	1
Age (years)	59.91 (± 14.57)	59.88 (± 14.45)	0.864
Type of change			
Dose decrease	1550 (13%)	–	–
Dose increase	3862 (32%)	–	–
Switch	3199 (27%)	–	–
Addition	3326 (28%)	–	–
Gender, male (%)	45.9	45.9	1.000
Duration of first episode of use (days)	194.68 (± 236.00)	196.34 (± 235.07)	0.585
DDDeq	0.7591 (± 0.4258)	0.7920 (± 0.4464)	$P < 0.001$
DDDeq < 1	6750 (56.55%)	6260 (52.45%)	$P < 0.001$
First prescriber			
General practitioner	8946 (74.94%)	8595 (72.00%)	$P < 0.001$
Internist	1371 (11.49%)	1522 (12.75%)	$P < 0.001$
Cardiologist	682 (5.71%)	823 (6.89%)	$P < 0.01$
Miscellaneous	997 (8.35%)	938 (7.85%)	0.169
Co-medication			
Anti-asthmatic drugs	1229 (10.29%)	1071 (8.97%)	$P < 0.001$
Lipid-lowering drugs	946 (7.92%)	896 (7.51%)	0.235
Anti-diabetic drugs	1078 (9.03)	846 (7.09)	$P < 0.001$
Prior cardiovascular hospitalizations			
Ischaemic heart disease	560 (4.69%)	483 (4.04%)	$P < 0.05$
Congestive hearth failure	18 (0.15%)	20 (0.17%)	0.871
Arrhythmia	140 (1.17%)	106 (8.88%)	$P < 0.05$
Peripheral vascular disease	28 (0.23%)	27 (0.23)	1.000
Cerebrovascular disease	138 (1.16%)	102 (0.85%)	$P < 0.05$
Initial antihypertensive drug			
Diuretics	200 (19.27%)	2553 (2138%)	$P < 0.001$
Beta-blockers	5545 (46.45%)	5225 (43.77%)	$P < 0.001$
Calcium-channel blockers	1013 (8.48%)	1099 (9.21%)	0.053
ACE inhibitors	2094 (17.54%)	1874 (15.69%)	$P < 0.001$
Angiotensin II receptor antagonists	871 (7.29%)	1081 (9.06%)	$P < 0.001$
Miscellaneous	114 (0.96%)	105 (0.88%)	0.542

ACE, angiotensin-converting enzyme; DDD, defined daily dose. Values expressed as means (± SD) or number (%).

Table 2 Association between non-compliance and adjustment of antihypertensive drug regimen

	Cases[a]	Controls[a]	OR (95%CI)	OR (95%CI)[b]
All subjects	603/11937 (5.05%)	432/11937 (3.62%)	1.42 (1.25–1.61)	1.39 (1.22–1.58)
Male	241/5481 (4.40%)	210/5481 (3.83%)	1.16 (0.96–1.40)	1.14 (0.94–1.40)
Female	362/6456 (5.61%)	222/6456 (3.44%)	1.67 (1.41–1.98)	1.64 (1.37–1.94)
Duration of first episode < 6 months				
Male	141/3652 (3.86%)	150/3652 (4.11%)	0.94 (0.74–1.19)	0.94 (0.74–1.19)
Female	220/4319 (5.09%)	145/4319 (3.35%)	1.55 (1.25–1.92)	1.50 (1.20–1.86)
Duration of first episode ⩾ 6 months				
Male	100/1829 (5.46%)	60/1829 (3.39%)	1.71 (1.23–2.38)	1.71 (1.22–2.40)
Female	142/2137 (6.64)	77/2137 (3.60%)	1.90 (1.43–2.53)	1.88 (1.41–2.52)

[a]Number of non-compliant patients/all patients (% non-compliance among all patients). [b]Adjusted for use of specific co-medication, class of initial antihypertensive drug, hospitalization for cardiovascular diseases, type of prescriber and prescribed daily doses (PDDs). OR, odds ratio; CI, confidence interval.

lower among cases (96.8%) compared to controls (97%). The percentage of non-compliant patients (compliance < 80%) among the cases was 5.1 versus 3.6% among controls [crude OR 1.42 (95%CI: 1.25–1.61)]. After adjustment for PDD, first prescriber, co-medication, prior cardiovascular hospitalization and initial type of antihypertensive drug, non-compliant patients still had a 1.39 times higher chance of receiving a change in their medication compared to compliant patients.

Non-compliant females had a 1.64 times higher risk of receiving a change in their medication compared to compliant females. For males no significant differences in receiving a change between non-compliant patients and compliant patients were observed. However, when we stratified on duration of first episode of use, both males [OR 1.71 (95%CI: 1.22–2.40)] and females [OR 1.88 (95%CI: 1.41–2.52)] who used the medication for longer than 6 months had an increased risk of receiving a change in medication regimen if they were non-compliant.

We defined different types of outcomes for the cases. Therefore, we also analysed the association between compliance and type of change separately (Table 3).

Table 3 Association between non-compliance with antihypertensive drugs and type of adjustment of initial drug regimen

	Cases[a]	Controls[a]	OR (95%CI)	OR (95%CI)[b]
Dose decrease				
Male	39/680 (5.74%)	19/680 (2.79%)	2.05 (1.19–3.6)	2.62 (1.39–4.96)
Female	57/860 (8.83%)	20/860 (2.32%)	3.06 (1.80–5.20)	2.80 (1.60–4.92)
Dose increase				
Male	73/1784 (3.40%)	66/1784 (3.70%)	1.12 (0.79–1.58)	0.98 (0.67–1.42)
Female	119/2078 (5.73%)	62/2078 (2.98%)	2.00 (1.46–2.75)	1.85 (1.30–2.64)
Switch				
Male	66/1480 (4.46%)	66/1480 (4.46%)	1.00 (0.70–1.42)	0.99 (0.70–1.42)
Female	88/1719 (5.12%)	68/1719 (3.96%)	1.31 (0.95–1.81)	1.32 (0.95–1.83)
Addition				
Male	63/1527 (4.13%)	59/1527 (3.86%)	1.07 (0.74–1.54)	1.07 (0.73–1.55)
Female	98/1799 (5.45%)	72/1799 (4.00%)	1.38 (1.01–1.88)	1.41 (1.30–1.94)

[a]Number of non-compliant patients/all patients (% non-compliance among all patients). [b]Adjusted for use of specific comedication, class of initial antihypertensive drug, hospitalization for cardiovascular diseases, type of prescriber and prescribed daily doses (PDDs). OR, odds ratio; CI, confidence interval.

Non-compliant patients had a 2.62 times higher chance of receiving a dose decrease, compared to compliant patients, which was similar for male and female patients. Non-compliant female patients had a 1.85 times higher chance of receiving a dose increase compared to compliant female patients. Among male patients there was no association between non-compliance and dose increase. The association between non-compliance and switching to another antihypertensive drug was only present among females, but not among males. Similarly, non-compliance was only associated with addition of another antihypertensive drug among females, but not among males. We did not observe any material changes in ORs after further stratification on duration of episode of use.

The occurrence of change was higher in patients who were initially treated with beta-blockers [OR 1.35 (95%CI: 1.01–1.79)], calcium-channel blockers [OR 1.14 (95%CI: 1.02–1.27)], ACE inhibitors [OR 1.32 (95%CI: 1.20–1.46)] and miscellaneous antihypertensive drugs [OR 1.37 (95%CI: 1.23–1.53)] compared to patients who were initially treated with diuretics (Table 4). No differences between angiotensin II receptor antagonists [OR 1.12 (95%CI: 0.98–1.26)] and diuretics were observed. For females initially treated with beta-blockers, the incidence of change [OR 1.92 (95%CI: 1.32–2.79)] was different compared to females who were initially treated with diuretics. For males initially treated with calcium-channel blockers, the incidence of change [OR 1.30 (95%CI: 1.10–1.54)] was different compared to males who were initially treated with diuretics. No material differences between males and females were found for the other classes of initially prescribed antihypertensive drugs.

Internists [OR 1.18 (95% CI: 1.06–1.32)] and cardiologists [OR 1.11 (95% CI: 1.01–1.22)] implemented more

Table 4 Influence of type of antihypertensive drug on association between non-compliance and adjustment of initial drug regimen

	Cases[a]	Controls[a]	OR (95%CI)	OR (95%CI)[b]
Diuretics	2300 (19.3%)	2553 (21.4%)	1.00 (ref.)	1.00 (ref.)
Male	822 (15.0%)	801 (14.6%)	1.00 (ref.)	1.00 (ref.)
Female	1478 (22.9%)	1752 (27.1%)	1.00 (ref.)	1.00 (ref.)
Beta-blockers	5545 (46.5%)	5225 (43.8%)	1.36 (1.02–1.80)	1.35 (1.01–1.79)
Male	2596 (47.4%)	2483 (45.3%)	0.75 (0.47–1.19)	0.77 (0.48–1.23)
Female	2949 (45.7%)	2742 (42.5%)	1.99 (1.37–2.87)	1.92 (1.32–2.79)
Calcium-channel blockers	1013 (8.5%)	1099 (9.2%)	1.10 (0.99–1.23)	1.14 (1.02–1.27)
Male	487 (8.9%)	549 (10.0%)	1.27 (1.07–1.50)	1.30 (1.10–1.54)
Female	526 (8.1%)	550 (8.5%)	1.04 (0.90–1.20)	1.08 (0.93–1.24)
ACE inhibitors	2094 (17.5%)	1874 (15.7%)	1.32 (1.20–1.45)	1.32 (1.20–1.46)
Male	1133 (20.7%)	1089 (19.9%)	1.29 (1.12–1.48)	1.30 (1.13–1.50)
Female	961 (14.9%)	785 (12.2%)	1.35 (1.18–1.55)	1.34 (1.17–1.53)
Angiotensin II receptor antagonists	871 (7.3%)	1081 (9.1%)	1.14 (1.01–1.29)	1.12 (0.98–1.26)
Male	412 (7.5%)	508 (9.3%)	1.09 (0.91–1.30)	1.09 (0.91–1.30)
Female	459 (7.1%)	573 (8.9%)	1.19 (1.00–1.42)	1.15 (0.96–1.37)
Miscellaneous	114 (1.0%)	105 (0.9%)	1.39 (1.25–1.55)	1.37 (1.23–1.53)
Male	31 (0.6%)	51 (0.9%)	1.28 (1.10–1.50)	1.28 (1.09–1.49)
Female	83 (1.3%)	54 (0.8%)	1.53 (1.31–1.78)	1.50 (1.29–1.76)

[a]Number of users of classes of initial antihypertensive drug (% initial antihypertensive drug among all patients).
[b]Adjusted for use of specific co-medication, compliance, hospitalization for cardiovascular diseases, type of prescriber and prescribed daily doses (PDDs). ACE, angiotensin-converting enzyme; OR, odds ratio; CI, confidence interval.

changes in the initially prescribed regimen compared to general practitioners.

The association between compliance and change in medication regimen did not differ for subgroups defined by age group ($P = 0.684$), first prescriber ($P = 0.490$), co-medication ($P = 0.308$ for anti-asthmatic drugs, $P = 0.234$ for lipid-lowering drugs, $P = 0.301$ for antidiabetic drugs) and prior cardiovascular hospitalizations ($P = 0.427$ for ischaemic heart disease, $P = 0.869$ for congestive heart failure, $P = 0.428$ for arrhythmias, $P = 0.494$ for peripheral vascular disease, $P = 0.400$ for cerebrovascular disease).

We assessed whether the risk-set sampling was conducted properly to exclude the possibility that the cases and controls were interdependent. We found that, of the total number of matched controls, only 19.9% became cases later on and only 0.11% were non-compliant, indicating that the sampling procedure did not cause the small difference in compliance between cases and controls.

In a sensitivity analysis, we analysed the results for different cut-off values of compliance. Using cut-off values between 60 and 95%, the association between non-compliance and change in medication regimen remained essentially the same, with ORs varying from 1.51 (60%) to 1.25 (95%) after adjustment.

Discussion

We found that a compliance lower than 80% was associated with a 1.39 times increased risk of undergoing a modification in the initially prescribed antihypertensive drug regimen. For female patients this association was independent of the duration of the first episode of use, whereas for males this association was only present when the first episode of use was longer than 6 months. To the best of our knowledge, the association between non-compliance and change in medication regimen has never been studied before.

The PHARMO database used in this study is virtually complete with regard to drugs dispensed to patients [15,18]. Computerized registration of prescription drugs by health maintenance organizations and pharmacies offers a relatively easy, inexpensive and rapid way to collect information on drug use for a large number of patients. Computerized pharmacy records have shown to be a reliable source of drug exposure as estimated in a home inventory [19]. Compliance assessed using pharmacy records was previously found to correlate significantly with compliance as measured using other methods, such as pill counts, self-reports and electronic monitoring, although the strength of these correlations was moderate [20,21].

However, there are also some important limitations to using pharmacy records for assessing compliance. Refill compliance cannot assess the relationship between the duration of action and the timing of doses, which in this case may have had an influence on whether blood pressure could still be controlled or not, and consequently on the occurrence of change in medication regimen. Gaps between prescriptions might not result in therapeutic failure for drugs with long half-lives. On the other hand, refill compliance can be considered as the maximum drug consumption, easily overestimating the actual compliance. Furthermore, sometimes a patient is 'prescribed' not to take a certain drug for a certain period of time and this advice is not always registered in the pharmacy. Another limitation of this study is that we combined the different antihypertensives into six major classes, although the approved indications for these drugs differ greatly within and between classes. When antihypertensive drugs are prescribed for other indications and not for the treatment of hypertension, blood pressure may not be measured on a regular basis in these patients and non-compliance would not necessarily lead to a change in medication regimen. However, side-effects leading to non-compliance may still be a cause of modification of the initially prescribed regimen although the indication is not hypertension.

The association between non-compliance and change in medication regimen found here is probably largely explained by the fact that non-compliance leads to uncontrolled blood pressure and subsequently to changes in medication regimen because of the physicians' dissatisfaction with the achieved result. Furthermore, although blood pressure may be under control, non-compliance can be caused by patients' dissatisfaction with the prescribed antihypertensive regimen, influencing the physician's opinion about his choice, which also may lead to a change.

We also found that the association between non-compliance and change was significantly stronger for females than for males. Females are known to have different health-related behaviour to males, and are known to pay more visits to their physician [22,23]. It is possible that complaints about therapy, resulting in a lower compliance, are more often discussed, and that changes are more frequent as a result of this higher number of visits. We also found that the association was significantly stronger for patients with an episode of use longer than 6 months. This may very well be caused by the fact that the calculation of compliance becomes more valid when the number of prescriptions is larger. Another cause may be that patients at the start of treatment are more motivated to use their medication as prescribed and that motivation decreases over time, so that the relative number of non-compliant

patients in both groups will be relatively low and compliance is not an issue at the start of treatment, and that other issues may play a more important role (side-effects). In persistence studies, the largest decline in persistence for all classes of antihypertensive agents occurred in the first 6 months after initiating treatment [24–29]. This means that the first episodes of use are of relatively short duration. This is consistent with our finding that the average duration of the first episode of use is approximately 6 months (Table 1).

In this study we found a relative low number of non-compliant patients (5.1% among cases and 3.6% among controls). The low number of non-compliant patients may be caused by the fact that we used a database containing computerized pharmacy records, easily 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 prescribed, although the patient may collect the prescription later. Furthermore, in The Netherlands patients are able to order their medication by telephone, after which the general practitioner may prescribe other medication, which the patient did not ask for but which the physician may think the patient needs. For the different types of change, we found the strongest association between non-compliance and dose decrease. This may be explained because patients who are not satisfied with the initial therapy, experiencing side-effects, may discuss this at a follow-up visit with their physician, resulting in a dose decrease. Another explanation may be that the patient was told during a follow-up visit to use the current prescription in a decreased dose, but this was not registered in the pharmacy. The association between non-compliance and dose increase may be explained by our general assumption that low compliance leads to uncontrolled blood pressure and subsequently to an increase of prescribed antihypertensive action, in this case resulting in a dose increase. We only found an association between non-compliance and switching or addition among female patients.

The results of this study indicate that non-compliance is a significant predictor of the occurrence of change of antihypertensive medication regimen. This means that a number of changes in medication regimen may be unnecessary, and implies that physicians should not only focus on the patient's (genetic) resistance to certain antihypertensive drugs, but also on the patient's behaviour towards his medication taking. Pharmacy records could help to identify a number of those non-compliant patients. Therefore pharmacists should monitor refill compliance as part of their daily routine and actively provide these data to prescribers on a regular basis.

In conclusion, non-compliance is significantly associated with the occurrence of change in antihypertensive medication regimen. The association is stronger in females than in males, and stronger if the first episode of use is longer than 6 months. Using data from pharmacy records may help to identify patients who are not taking their medication as prescribed. This information may be used by physicians to focus on improving compliance with antihypertensive drugs, before modifying treatment regimens.

Acknowledgements

We would like to acknowledge the Dutch Board of Healthcare Insurance Organizations for their funding.

References

1 Moser M. World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension – do these differ from the U.S. recommendations? Which guidelines should the practicing physician follow? *J Clin Hypertens* 1999; **1**:48–54.
2 Neaton JD, Grimm RH Jr, Prineas RJ, Stamler J, Grandits GA, Elmer PJ, *et al.* Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. *JAMA* 1993; **270**:713–724.
3 Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, *et al.* Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997; **277**:739–745.
4 MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, *et al.* Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; **335**:765–774.
5 Dahlof B, Hansson L, Lindholm LH, Schersten B, Ekbom T, Wester PO. Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) analyses performed up to 1992. *Clin Exp Hypertens* 1993; **15**:925–939.
6 Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991; **265**:3255–3264.
7 Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994; **50**:272–298.
8 Uemura K, Pisa Z. Trends in cardiovascular disease mortality in industrialized countries since 1950. *World Health Stat Q* 1988; **41**:155–178.
9 Burt VL, Cutler JA, Higgins M, Horan MJ, Labarthe D, Whelton P, *et al.* Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. *Hypertension* 1995; **26**:60–69.
10 Marques-Vidal P, Tuomilehto J. Hypertension awareness, treatment and control in the community: is the 'rule of halves' still valid? *J Hum Hypertens* 1997; **11**:213–220.
11 Polak BC. [CBO guideline 'high blood pressure' (revision)]. *Ned Tijdschr Geneeskd* 2002; **146**:439–440.
12 de Bruijckere PA. [CBO guideline 'high blood pressure' (revision)]. *Ned Tijdschr Geneeskd* 2002; **146**:439.
13 Walma EP, Thomas S, Prins A, Grundmeijer HGLM, Van den Hoogen JPH, Van der Laan JR. NHG-standaard Hypertensie (derde herziening). *Huisarts Wet* 2003; **46**:435–449.
14 Himmelmann A, Kjeldsen SE, Hedner T. Recent hypertension guidelines: JNC-7 and 2003 ESH/ESC. *Blood Press* 2003; **12**:196–197.
15 Herings RMC. *PHARMO: a record linkage system for postmarketing surveillance of prescription drugs in The Netherlands*. Utrecht: Utrecht University; 1993.
16 World Health Organization. *Guidelines for ATC classification and DDD assignment, WHO Collaborating Centre for Drug Statistics Methodology*. Oslo: Nordic Council on Medicines; 1999.

17 Robins JM, Gail MH, Lubin JH. More on 'Biased selection of controls for case-control analyses of cohort studies'. *Biometrics* 1986; **42**:293–299.
18 Strom BL, Carson JL, Morse ML, LeRoy AA. The computerized on-line Medicaid pharmaceutical analysis and surveillance system: a new resource for postmarketing drug surveillance. *Clin Pharmacol Ther* 1985; **38**:359–364.
19 Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol* 1997; **50**: 619–625.
20 Choo PW, Rand CS, Inui TS, Lee ML, Cain E, Cordeiro-Breault M, *et al*. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care* 1999; **37**:846–857.
21 Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997; **50**:105–116.
22 Armitage KJ, Schneiderman LJ, Bass RA. Response of physicians to medical complaints in men and women. *JAMA* 1979; **241**:2186–2187.
23 Kandrack MA, Grant KR, Segall A. Gender differences in health related behaviour: some unanswered questions. *Soc Sci Med* 1991; **32**: 579–590.
24 Conlin PR, Gerth WC, Fox J, Roehm JB, Boccuzzi SJ. Four-year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other antihypertensive drug classes. *Clin Ther* 2001; **23**:1999–2010.
25 Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. *Clin Ther* 1998; **20**:671–681.
26 Jones JK, Gorkin L, Lian JF, Staffa JA, Fletcher AP. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. *BMJ* 1995; **311**:293–295.
27 Degli Esposti E, Sturani A, Di Martino M, Falasca P, Novi MV, Baio G, *et al*. Long-term persistence with antihypertensive drugs in new patients. *J Hum Hypertens* 2002; **16**:439–444.
28 Caro JJ, Speckman JL. Existing treatment strategies: does noncompliance make a difference? *J Hypertens Suppl* 1998; **16**:S31–34.
29 Caro JJ. Stepped care for hypertension: are the assumptions valid? *J Hypertens Suppl* 1997; **15**:S35–39.