ELSEVIER

Journal of Clinical Epidemiology 59 (2006) 11–17

Journal of Clinical Epidemiology

Refill persistence with chronic medication assessed from a pharmacy database was influenced by method of calculation

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

Department of Pharmacoepidemiology & Pharmacotherapy, Faculty of Pharmaceutical Sciences, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands

Accepted 25 May 2005

Abstract

Background and Objectives: In literature, different methods of calculating persistence are used. In this study, the effect of using these different methods on persistence and the association of patients characteristics and persistence are assessed.

Methods: The PHARMO record linkage system was used to calculate persistence with antihypertensive drugs for a cohort of 14,466 new users of antihypertensives. Three different types of methods were used to define the maximum gap allowed between two prescriptions that a patient may have to be defined as a continuous user, one based on a defined number of days (varying from 9–365 days), the second based on the duration of the last prescription (varying from 0.1–4 times the duration), the third based on a combination of both methods, whichever leads to the lowest number of days.

Results: Refill persistence varied between 19.7–86.4% (method 1), between 27.9–90.2% (method 2), and between 19.7–86.4% (method 3). Furthermore, patient characteristics associated with persistence differed between and within the three different methods.

Conclusion: The method used and the variation within a method influenced both persistence and the association between patient characteristics and persistence. Results of persistence studies are highly influenced by the researchers' method of the maximum allowed treatment gap.

Keywords: Persistence; Compliance; Hypertension; Antihypertensives; Pharmacy records; Refill persistence

1. Introduction

Discontinuation with chronic treatment is a major problem for patients, health care providers, and policy makers. Although for many chronic diseases pharmacotherapeutic options are available and effective as demonstrated in randomized clinical trials, patients often do not only take their medication as has been prescribed by their physician (noncompliance), but also fail to use it for a long uninterrupted period of time (nonpersistence) [1,2]. This nonpersistence constitutes a major barrier to controlling chronic diseases leading to an increased morbidity and mortality [2]. Therefore, the persistence rate is an important element in determining the success of any long-term therapy. Computerized registration of prescription drugs by health maintenance organization and pharmacies offers a relatively easy, inexpensive, and rapid way to collect information on drug use for a large number of patients [3–6]. These databases can be used to calculate persistence with chronic therapy. In The Netherlands, pharmacy records are virtually complete with regard to prescription drugs dispensed to patients. In the literature, different approaches are used to define persistence with drug use. A comparison of results of refill persistence studies is therefore complicated due to the variation of the methods [7–15]. The aim of our study was to compare three different methods of calculating a 1-year refill persistence rate and associations between patient characteristics and 1-year persistence. In the first method, a defined number of days, and in the second method a fraction of the theoretic duration of the prescription after which the treatment gap occurs was used to define the maximum allowed treatment gap that a patients may have between two prescriptions to be defined as a continuous user. In the third method, a combination of both methods, whichever leads to the smallest gap, was used. To compare those methods, we used data from new users of antihypertensives, a class of drugs that are intended to be used chronically.

* Corresponding author. Tel.: +31 30 253 7324; fax: +31 30 253 9166.

E-mail address: o.h.klungel@pharm.uu.nl (O.H. Klungel).

0895-4356/06/$ – see front matter
doi: 10.1016/j.jclinepi.2005.05.005

2. Methods and materials

2.1. Data

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 medium-sized cities in The Netherlands, with a geographically diverse, drug-insured population. Clustering of all pharmacies within each city has resulted in drug-dispensing histories that contain more than 95% of all prescriptions dispensed to each individual patient. Records of nonresidents of one of the PHARMO cities are excluded [4]. The data registered in the PHARMO database include age and sex of the patient, name of the drug, dispensing date, the amount of units dispensed of the drug, and prescribed daily dose (PDD). PDD was expressed as the number of defined daily doses (DDD). The DDD is the dosage for the main indication of a drug [16,17].

2.2. Patients

We selected a cohort of patients who used no antihypertensive agents during 1998 and presented their first prescription for an antihypertensive drug (no combination therapy) between January 1, 1999 and December 31, 2002, who collected more than one prescription and had at least 18 months of follow-up available from the start of treatment with antihypertensives until disappearance from the database. Follow-up of patients in this database stopped if they moved to a city outside the scope of the PHARMO area or by death or institutionalization. This means that patients have to be in the database for at least 18 months from the start of antihypertensive drug use, but that they do not have to use antihypertensive drugs at the end of this period. Being in the database thus only means living in the PHARMO area and being eligible to receive medication from the pharmacies and thus to be recorded in the PHARMO database. All prescription drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification system [18]. 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 select users of any of the antihypertensive drug classes. When information regarding the prescribed dose or type of the initially prescribed antihypertensive drug was not available, the patient was excluded. Patients who received only one prescription were excluded. Patients who did not have enough follow-up to be analyzed with one or more of the definitions, resulting in censoring before 365 days, were excluded. This was done to ascertain that the same patients were analyzed with each definition. Patients who discontinued before 365 days, of course, were not excluded. Age, gender, type of insurance (private or public), type of first antihypertensive, type of first prescriber (general practitioner, internist, cardiologist and other), use of specific comedication (antiastmatic drugs, antidiabetic drugs and lipid lowering drugs), and prior hospitalization for cardiovascular diseases such as ischemic heart disease, congestive heart failure, cardiac arrhythmias, peripheral vascular disease, and cerebrovascular disease were studied as predictors of persistence. The goal of the latter is not to show which are the variables of interest and which of them are potential confounders but how their association with persistence differs with the different definitions of persistence described below.

2.3. Definitions

The theoretic duration of a prescription was calculated by dividing the number of units dispensed by the PDD. Thus, the end date of a prescription equals the start date plus the theoretic duration of a prescription.

We compared three different methods of calculating the fraction of patients with an uninterrupted episode of use of antihypertensive drugs of at least 1 year (persistent use, Fig. 1). The first method is based on a defined maximum number of days that the patient is allowed to have between the theoretic end date of a prescription and the start date of the next one to be classified as a continuous user. We varied the maximum number of days between 9 and 360 days. The second method is based on a defined maximum fraction of the theoretic duration of the prescription after which the treatment gap occurs that a patient is allowed to have to be classified as a continuous user. We varied the maximum fraction between 0.1–4 times the theoretic duration of the prescription after which the treatment gap occurs. The third one is based on a combination of the first two methods. The maximum number of days a patient is allowed to have between two prescriptions to be classified as a continuous user is based on both a defined maximum number of days between two prescriptions as well as a defined maximum fraction of the theoretic duration of the prescription after which the treatment gap occurs, whichever is the lowest number of days.

A specific value of 90 days for the maximum allowed treatment gap was chosen, because in The Netherlands health insurance companies only compensate pharmacies for prescriptions with a maximum length of 90 days. A commonly used maximum allowed treatment gap in the literature is 0.1 times the theoretic duration of the prescription after which the treatment gap occurs, which in case of the longest prescription of 90 days is comparable to a gap of 9 days in method 1 [19]. Other commonly used maximum allowed treatment gaps are 30 days (comparable to 0.33 times the theoretic duration), 45 days (comparable to 0.5 times the theoretic duration), 90 days which is comparable to one times the theoretic duration of a prescription and 180 days, which is comparable to two times the theoretic duration of a prescription. [7–15]. Furthermore, we choose to

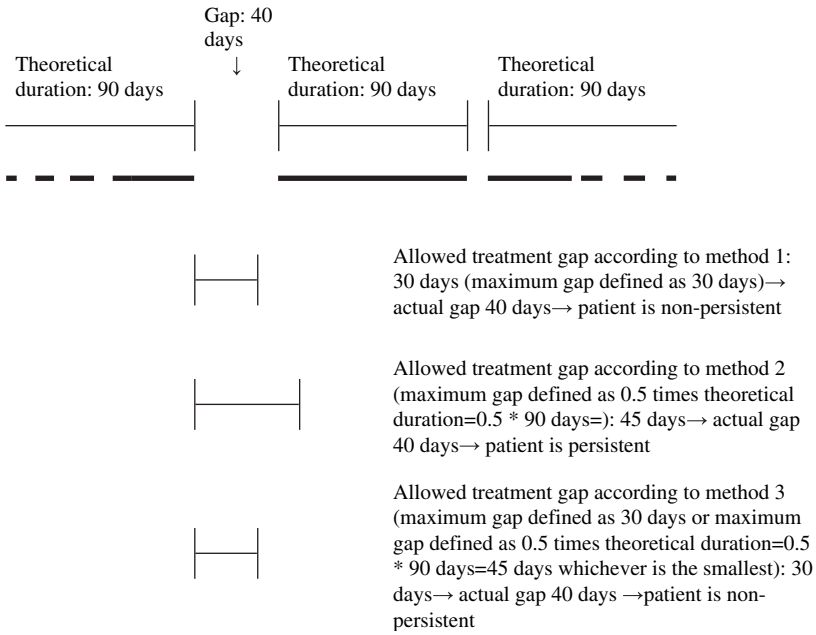

Fig. 1. Gap allowed according to different methods of calculating the fraction of patients who have an uninterrupted episode of use of antihypertensive drugs of at least 1 year.

study the extremes of three and four times the theoretic duration of a prescription (method 2) as well as 270 and 360 days (method 1).

2.4. Statistical analysis

Kaplan-Meier analysis was used to calculate persistence and 95% confidence intervals (95% CI) after 1 year (SPSS 10.0 for windows). Difference in persistence and 95% CI of the differences between methods were calculated according to Altman [20]. Cox proportional hazard analysis with backward elimination with a arbitrary probability of stepwise removal of 0.10 was used to calculate hazard ratios of potential and available predictors of non-persistence and 95% confidence intervals (95% CI).

3. Results

Basic characteristics of the patients are given in Table 1. In the cohort of 39,714 new users of antihypertensive drugs we identified 14,466 patients with at least 18 months of follow-up who started treatment with antihypertensives. The mean age was 60 years. Forty-five percent of the patients were males. The majority of the initial prescriptions came from the general practitioner (75%). Beta blockers were the most common initially prescribed antihypertensive drug class (44%).

In Figs. 2 and 3 the influence of varying the maximum allowed treatment gap between two prescriptions according to method 1 and 3 is displayed (results for method 2 were similar as method 1, and are therefore not displayed). In the first part of Fig. 2, a sharp rise in persistence is clearly visible between a maximum allowed treatment gap of 9–90 days. After this point the slope of the line levels off to a flat line. This means that variation between a maximum allowed treatment gap of 90–360 days does not have any material influence on the percentage of persistent patients. For method 1, the persistence varies from 27.9–90.2%, whereas for method 2 the persistence varies from 19.7–86.4% (not

Table 1
General characteristics of the study population (patients from the PHARMO database who started using antihypertensives in 1998 and had at least an 18-month of follow-up)

No. of patients	14,466
Mean age (years)	60.8 (±14.5)
0–20	82 (0.6%)
20–9	928 (6.4%)
40–9	5,827 (40.3%)
60–9	6,242 (43.1%)
⩾80	1,387 (9.6%)
Males	6,540 (45.2%)
First prescriber	
General Practitioner	10,779 (74.5%)
Internist	1,729 (12.0%)
Cardiologist	879 (6.1%)
Miscellaneous	1,079 (7.5%)
First antihypertensive	
Diuretic	2,256 (15.6%)
Beta-blocker	6,367 (44.0%)
Calcium antagonist	756 (5.2%)
ACE-inhibitor	2,297 (15.9%)
Angiotensin II receptor antagonist	979 (6.8%)
Miscellaneous	131 (0.9%)
Combination	1,680 (11.6%)

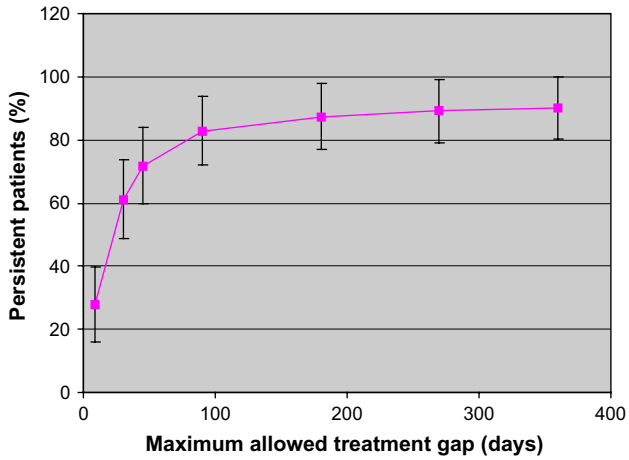

Fig. 2. Influence of variation of allowed treatment gap between two prescriptions in days (method 1) on percentage of persistent patients (95% CI) after 1 year.

displayed). In Fig. 3 the combination of method 1 and 2, method 3, is displayed. It is clearly visible that the variation was large at small fractions of the theoretic duration (0.1–1) of the prescription after which the treatment gap occurs as well as a variation of relatively low maximum allowed number of days between two prescriptions (9–90). This means that varying the maximum allowed treatment gap between two to four times the theoretic duration and 180–360 days, whichever is the lowest, did not have any material influence on 1-year persistence. The absolute persistence for all these combinations differed not more than 10% (data not shown). Absolute persistence varied from 19.7–86.4% for method 3.

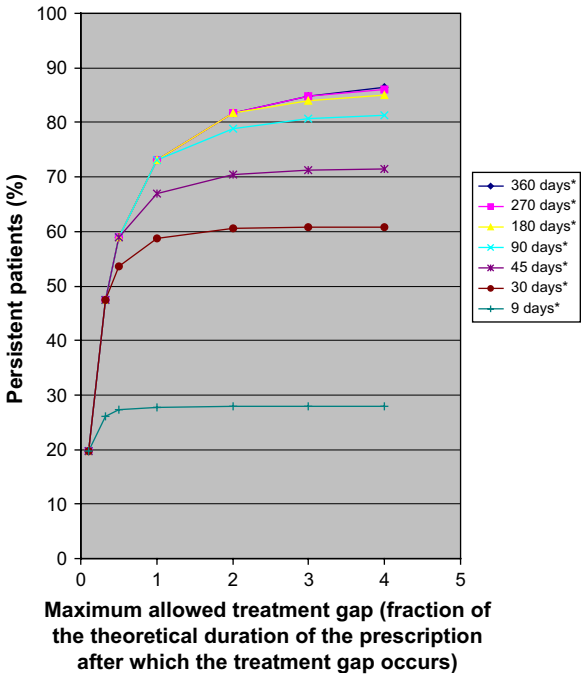

Fig. 3. Influence of variation of combination of maximum allowed number of days between two prescriptions as well as maximum allowed fraction of the theoretic duration of the prescription after which the treatment gap occurs, whichever is the lowest number of days (method 3) on percentage of persistent patients after 1 year.

We also assessed whether the predictors of persistence (age, gender, type of insurance, type of first prescriber, type of first antihypertensive, type of cardiovascular hospitalization prior to the study entrance, and comedication) differed, between and within the three different methods using Cox proportional hazard analysis with backward elimination. [8,21,22] We observed differences in predictors of 1-year persistence in the final models between the definitions. Age, first prescriber, type of first antihypertensive, and hospitalization for ischemic heart disease prior to study entrance were significantly associated with 1-year persistence in all models of all three definitions (data not shown). Gender was a significant predictor in all models except in the models with a maximum allowed treatment gap of 9 days, 0.1 times the duration of the last prescription, and a combination of both, whichever was the lowest number of days (Table 2). However, only for some definitions the type of insurance (public vs. private), type of first prescriber (cardiologist, internist vs. general practitioner), the use of lipid-lowering drugs, the use of antiastmatic drugs, the

Table 2
Influence of variation of maximum allowed treatment gap on the association between 1-year persistence and patients characteristics and the significance of this association

Patients characteristic	No. of definitions included with HR > 1 (percentage of total)	No. of models included with HR < 1 (percentage of total)
Age (lineair)	63 (100%)	0 (0%)
Gender (female vs. male)	60 (95%)	0 (0%)
Type of insurance (public vs. private)	23 (37%)	0 (0%)
Type of first prescriber (cardiologist and internist vs. general practitioner)	63 (100%)	0 (0%)
Type of first antihypertensive vs. diuretic		
Beta-blocker	63 (100%)[a]	0 (0%)[a]
Calcium antagonist	48 (76%)[a]	15 (24%)[a]
ACE-inhibitor	63 (100%)[a]	0 (0%)[a]
Angiotensin II antagonist	63 (100%)[a]	0 (0%)[a]
Miscellaneous	48 (76%)[a]	15 (24%)[a]
Use of lipid-lowering drugs	47 (75%)	2 (3%)
Use of antiastmatic drugs	2 (3%)	1 (2%)
Use of antidiabetic drugs	7 (11%)	0 (0%)
Prior cardiovascular hospitalizations		
Ischemic heart disease	0 (0%)	63 (100%)
Congestive heart failure	6 (10%)	41 (65%)
Cardiac arrhythmias	3 (5%)	3 (5%)
Peripheral vascular disease	5 (8%)	2 (3%)
Cerebrovascular disease	9 (14%)	2 (3%)

Abbreviation: HR, hazard ratio for 1-year persistence.

[a] The separate HRs of the separate types of first antihypertensive were not always significant although the variable ''type of first antihypertensive'' as a whole was significant.

use of antidiabetic drugs, hosptilizations for congestive heart failure, cardiac arrhythmias, peripheral vascular disease, and cerebrovascular disease were associated with 1-year persistence. The direction of these predictors differed for the different definitions used, and no clear trend was visible which definition included which predictor (Table 2). In Fig. 4, we displayed the results of variation of the maximum allowed treatment gap on the adjusted hazard ratios (HRs) for type of antihypertensive for method 1 (results for method 2 were similar and are therefore not displayed). We found that for both method 1 and method 2 the HRs for beta-blockers and calcium antagonists (and miscellaneous antihypertensives) did not differ much within and between the two definitions. However, the HRs for ACE inhibitors varied for method 1 between 1.10 (95% CI:1.03–1.16) and 3.18 (95% CI:3.18–3.93) and for method 2 between 1.11 (95% CI:1.04–1.18) to 2.15 (95% CI:1.87–2.47). For angiotensine II receptor antagonists (AT-II antagonists) the HRs varied for method 1 between 1.11 (95% CI 1.02–1.20) to 2.63 (95% CI 1.99–3.46), and for method 2 between 1.07 (95% CI: 0.99–1.16) and 2.43 (95% CI 1.97–3.00). This means that according to method 1, ACE inhibitors were associated with the highest 1-year persistence compared to diuretics. According to method 2 AT-II receptor antagonists were associated with the highest 1-year persistence compared to diuretics. We also tested whether there was any significant difference when directly comparing ACE inhibitors with AT-II receptor antagonists for both method 1 and 2. We found that, compared to ACE inhibitors, AT-II receptor antagonist were not significantly stronger; associated with 1-year persistence than ACE inhibitors for both methods (data not shown).

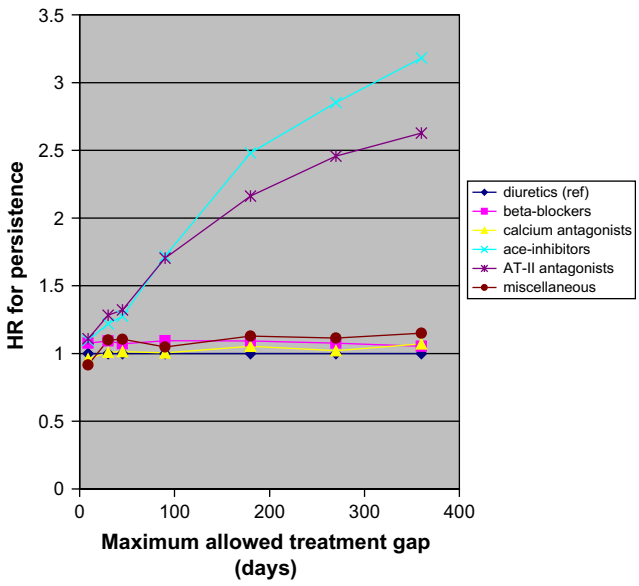

Fig. 4. Influence of variation of maximum allowed treatment gap in days (method 1) on hazard ratios of the different types of antihypertensives compared to diuretics.

4. Discussion

In this study we compared three different methods to calculate 1-year persistence with antihypertensive drugs. The first method and the second method, showed a relatively large influence of the maximum allowed treatment gaps with small number of days (9–90) and small fractions (0.1–1 times) of the theoretic duration on 1-year persistence, namely 28–83% and 20–73%, respectively. At a higher defined number of days (180–360) as well as at larger fractions of the theoretic duration (2 to 4 times) the number of persistent patients did not show any relevant variation, namely 87–90% and 82–86%, respectively (method 1 and method 2). The third method, in which we used a combination of method 1 and 2, revealed the same results. A large variation of the percentage of persistent patients (20–73%) at small fractions (0.1–1 times) of the theoretic duration combined with a small number of days (9–90), and less variation of the percentage of persistent patients (82–86%) at large fractions (2 to 4 times) of the theoretic duration combined with large number of days (180–360). These findings indicate that variation of the allowed treatment gap has a large influence on the 1-year persistence rate, and that the percentage of persistent patients is more stable at larger maximum allowed treatment gaps, although being more stable does not implicate better. Furthermore, we found that the significance of the association between patient characteristics and 1-year persistence as well as that the magnitude (and direction) of the HRs of patient characteristics for 1-year persistence were influenced by both the definition used and the variation within a definition.

A possible mechanism that could explain our findings is that pharmacy records are not precise enough to detect small irregularities in medication taking, or that irregularities in pharmacy records do not reflect irregularities in the actual medication taking. The latter means that although patients may collect their medication irregularly, they intend to persist with treatment.

There are some limitations of this study, and of studies using pharmacy records in general, that may have influenced our findings. The first is that a patient may be nonpersistent with treatment because he was advised to discontinue by his physician because he temporarily did not need pharmacologic treatment or no longer needs pharmacologic treatment. This may be caused by side effects that do not counterbalance the long-term reduction in cardiovascular morbidity and mortality, for example, in the case of mild hypertension. Furthermore, blood pressure may be controlled and medication may be tapered, ultimately resulting in intentional discontinuation. In addition to this, dietary or lifestyle changes may become effective, and antihypertensives are no longer necessary to control blood pressure. Furthermore, a patients may discontinue not on a physicians advice but on his own request but with the agreement of his physician. Although these patients are analyzed as a discontinuer, this discontinuation has no clinical

relevance. A patient may also discontinue (chronic) comedication, which causes hypertension, for example, nonsteroidal anti-inflammatory drugs, and therefore no longer needs antihypertensive treatment. Patients may also use a certain drug for an other indication than hypertension, although it is classified as antihypertensive, and continue with another drug for the same indication that is not classified as an antihypertensive. For example, in the case of benign prostate hypertrophia, patients using an α-blocker may discontinue and start with finasteride, a non-antihypertensive. However, these limitations will not have a material influence on the comparison within and between the three definitions. A third limitation is that we have excluded patients with a follow-up shorter than 365 days, thereby excluding more than 63% of our original cohort of starters. The associations we have found between patient characteristics and persistence need to be confirmed in patients with a shorter available follow-up.

A first strength of our study is that we compared different methods of calculating 1-year persistence in one and the same population and database. Any difference in 1-year persistence or associations between patient characteristics and persistence are therefore completely due to differences in the methods that we compared. Another strength of our study is that these findings may be generalized to persistence studies with other chronic medication, or at least some differences in 1-year persistence with other chronic medication may be expected when using different methods. Researchers who study persistence with medication in, for example, diabetes, depression, osteoporosis, and hyperlipidemia may encounter the same problem.

To our knowledge, this type of methodologic study has never been done before. Steiner et al. [23] evaluated different methods to assess refill compliance instead of refill persistence. Although those two terms refer to different concepts as stated in the introduction section, they are, of course, complementary. Studies using refill compliance are focussing on the (average) exposure to a certain drug during a certain time period, while refill persistence focuses on how long patients continue, with a certain level of compliance, with the use of a certain drug or drug class. A researchers' choice for a certain definition should be related to the reason why he is performing the study. First of all, it seems logical to relate the maximum allowed treatment gap to the duration of the prescription to decrease misclassification based on the length of prescription a patient is receiving. Second, the choice for the length of gap should depend on the aim of the study. If the effectiveness or side effects are compared between drugs or drug classes, the maximum allowed treatment gap should be small, decreasing differential misclassification with regard to exposure. In the latter case, measuring refill compliance instead of refill persistence, is a more appropriate method. However, if the goal of the study is to study continuation with drugs and to compare different drug classes with each other, the maximum allowed treatment gap should be large ($\geqslant$90 days or one times the duration of he last prescription) because small maximum allowed gaps probably indicate a delay. Furthermore, because of differences in compliance leading to different gaps after theoretic end dates of prescriptions, small gaps may result in differential misclassification with regard to the type of antihypertensive. For example, it is likely that patients who use a certain drug class that is accompanied by many side effects (beta-blockers) are less compliant with their treatment than patients who use other drug classes which have relatively mild side effects (AT-II receptor antagonist). This would lead to a different distribution of the gaps after a prescription, and different small maximum allowed treatment gaps lead to different proportions of nonpersistent patients between drug classes and thus to different HRs for nonpersistence for the different drug classes. Therefore, the use of longer maximum allowed treatment gaps may be preferred. On the other hand, it seems unlikely that patients use less than 50% of their prescribed medication on a regular basis, for example, less than once every 2 days 1 tablet in the case of a prescription for once-a-day one tablet. This argument would be in favor of the use of smaller maximum allowed treatment gaps because large treatment gaps may indicate complete discontinuation followed by a next treatment episode. Based on these considerations we would advice the use of one times the theoretic duration (method 2) or one times the theoretic duration combined with 90 days, whichever is the smallest (method 3) in case continuation is studied.

The differences in persistence we have found between patients starting with different types of antihypertensives is in line with other persistence studies in which all of the five classes of antihypertensives drugs were studied [8,14,24,25]. All of these studies demonstrated that the highest proportion of persistent patients was found in patients starting with newer types of antihypertensives, AT-II antagonists and ACE inhibitors, and the lowest proportion of persistent patients was found in patients starting with calcium antagonists, beta blockers and diuretics. All these four studies used maximum allowed treatment gaps of 90 days or 3 months. In our definition in which we used a defined number of days, patients starting with ACE inhibitors demonstrated higher persistence than patients starting with AT-II antagonists. In our definition using fractions of the theoretic duration, we found the same results as in the literature, the highest proportion of persistent patients in patients starting with AT-II antagonist followed by ACE inhibitors. The study of Hasford et al. [12], however, demonstrated no material differences between the different types of antihypertensives. They used a relatively short definition of the maximum allowed treatment gap of 30 days, a definition of which we also demonstrated that it would have led to small differences between the different types of antihypertensives.

As mentioned in the previous section, the approach outlined in this study should be replicated to other chronic medication to estimate the impact of variation on the

allowed treatment gap on persistence with other chronic pharmacologic treatment. Furthermore, validation studies need to be performed to determine which treatment gaps in general reflects discontinuation, by asking patients and physicians, although these studies are always, to some extent, biased. It may be possible to perform a kind of validation study to test which allowed treatment gap best predicts known or suspected consequences of nonpersistence with the highest sensitivity and specificity, such as further increase of the disease severity, blood pressure, cardiovascular, hospitalization, or death, although the clinical relevance of discontinuation differs among the different types of antihypertensive drugs.

In conclusion, different definitions of calculating 1-year persistence lead to different percentages of persistent patients and can also influence the association between patient characteristics and 1-year persistence. The use of one times the theoretic duration (method 2) or one times the theoretic duration or 90 days (method 3) seems to be the most reasonable definition if persistence is studied. Results of studies on persistence with chronic medication must be interpreted with great caution by researchers, policy makers, and physicians while assessing and comparing these studies.

Acknowledgments

The authors acknowledge the Dutch Board of Healthcare Insurance Organizations for funding.

References

[1] Herings R. Chronic pharmacotherapy forever. Utrecht: PHARMO institute; 2002.
[2] Urquhart J. Some economic consequences of noncompliance. Curr Hypertens Rep 2001;3(6):473–80.
[3] Garcia Rodriguez LA, Perez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol 1998;45(5):419–25.
[4] Herings R. PHARMO: a record linkage system for postmarketing surveillance of prescription drugs in the Netherlands. Utrecht: Utrecht University; 1993.
[5] Malcolm E, Downey W, Stand L, McNutt M, West R. Saskatchewan Health's linkable databases and pharmacoepidemiology. Post Marketing Surveill 1993;6:175–264.
[6] Strom BL, Carson JL, Morse ML, LeRoy AA. The computerized online Medicaid pharmaceutical analysis and surveillance system: a new resource for postmarketing drug surveillance. Clin Pharmacol Ther 1985;38:359–64.
[7] Benson S, Vance-Bryan K, Raddatz J. Time to patient discontinuation of antihypertensive drugs in different classes. Am J Health Syst Pharm 2000;57(1):51–4.
[8] Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. Clin Ther 1998;20(4):671–81.
[9] Catalan VS, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. Value Health 2000;3:417–26.
[10] Catalan VS, Couture JA, LeLorier J. Predictors of persistence of use of the novel antidiabetic agent acarbose. Arch Intern Med 2001; 161(8):1106–12.
[11] Dezii CM. A retrospective study of persistence with single-pill combination therapy vs. concurrent two-pill therapy in patients with hypertension. Manage Care 2001;10(2 Suppl):6–10.
[12] Hasford J, Mimran A, Simons WR. A population-based European cohort study of persistence in newly diagnosed hypertensive patients. J Hum Hypertens 2002;16(8):569–75.
[13] 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(7000):293–5.
[14] Marentette MA, Gerth WC, Billings DK, Zarnke KB. Antihypertensive persistence and drug class. Can J Cardiol 2002;18(6):649–56.
[15] Sheehy O, LeLorier J. Patterns of amlodipine and felodipine use in an elderly Quebec population. Can J Cardiol 2000;16(9):1109–17.
[16] Guidelines for ATC Classification and DDD assignment, WHO Collaborating Centre for Drug Statistics Methodology—Nordic Council on Medicines, Oslo. Geneva: World Health Organization; 1999.
[17] 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 (Greenwich) 1999; 1(1):48–54.
[18] WHO. Guidelines for ATC Classification and DDD assignment, WHO Collaborating Centre for Drug Statistics Methodology—Nordic Council on Medicines, Oslo. Geneva: WHO; 1999.
[19] Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50(5): 619–25.
[20] Altman DG. Comparing group: categorical data. In: Altman DG, editor. Practical statistic for medical research. London: Chapman & Hall; 1995. p. 229–76.
[21] Esposti LD, Di Martino M, Saragoni S, Sgreccia A, Capone A, Buda S, et al. Pharmacoeconomics of antihypertensive drug treatment: an analysis of how long patients remain on various antihypertensive therapies. J Clin Hypertens (Greenwich) 2004;6(2):76–84.
[22] Wogen J, Kreilick CA, Livornese RC, Yokoyama K, Frech F. Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. J Manag Care Pharm 2003;9(5):424–9.
[23] Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol 1997;50(1):105–16.
[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 artihypertensive drug classes. Clin Ther 2001;23(12):1999–2010.
[25] 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(6):439–44.