Adherence and persistence with antihypertensive drugs

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Adherence and persistence with antihypertensive drugs

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Voor mijn ouders

Contents

Chapter 1

Introduction and objective

Scope of this thesis

Hypertension is an important risk factor for the development of cardiovascular morbidity and mortality. In 2002, 10.9% of all deaths in the developed countries were attributable to hypertension, making it the second major risk factor of overall death just below tobacco use (12.2%) but over high cholesterol (7.6%), alcohol use (9.2%) and obesity (7.4%)[1]. In addition, about half of all cardiovascular disease (mortality and morbidity combined) is attributable to high blood pressure. Fortunately, it is widely considered as one of the most preventable causes because of the availability of effective antihypertensive drugs. In 2003, $30 billion was spend on antihypertensive drugs in the US, which is about 18% of the costs of all prescription drugs[1]. This is in line with Dutch findings, that in 2004, €916.490 was spent on drugs to treat patients with antihypertensives, which is more than 21% of the total budget of pharmacological treatment in The Netherlands[2]. Using these drugs effectively, every 20 mmHg decrease of systolic blood pressure and 10 mmHg decrease of diastolic blood pressure could potentially lead to a 50% reduction of the risk of cardiovascular disease according to the World Health Organization, although other non-blood pressure related effects of pharmacological treatment may alter these figures[1]. Compared to no treatment, antihypertensives have demonstrated to reduce the risk of major cardiovascular events with 27%, the risk of cardiovascular mortality with 16% and the risk of all cause mortality with 10%[3]. The *number needed to treat* for elderly patients is 190 for major cardiovascular events, 221 for cardiovascular mortality and 244 for all cause mortality[1]. Although high blood pressure has long been identified as an important medical condition, until 1964, the most important strategy for decreasing a patient's blood pressure was a low salt diet[4].

Introduction of pharmacological treatment for hypertension

In his book "The Rise and Fall of Modern Medicine", James le Fanu describes how in 1964, Michael Hammilton and Eileen Thompson, doctors at the Helmsford Hospital in the United Kingdom were the first to demonstrate the protective effect of pharmacological treatment with chlorothiazide on major cardiovascular events in patients with hypertension[5,6]. Before 1964, pharmacological treatment in general was in most cases aimed to treat acute disorders resulting in relatively short duration of treatment. In 1967, the Veterans Affairs Health Cooperation on Antihypertensive Agents Study confirmed their finding[7]. In this study among US military veterans with severe hypertension, twelve out of seventy patients, who

used a placebo, experienced a major cardiovascular event compared to only one out of seventy-three patients who were treated with high doses of chlorothiazide. From that point forward, more than forty different randomized clinical trials have been performed to further develop our insights in the pharmacological treatment of hypertension, although a derivative of that first antihypertensive, hydrochlorothiazide is still widely considered the first choice in the treatment of hypertension, supported by good evidence[3,8]. In the years preceding 1964, various other pharmacological antihypertensive strategies, such as pentaquine, hydralazine, methyldopa, guanetidine and clonidine have been used. Although these compounds all demonstrated the ability to reduce blood pressure, the side-effects were unacceptable for patients, who in the period preceding treatment experienced no symptoms and suddenly were confronted with a dry mouth, dizziness and impotence. These side-effects are especially unappealing considering the chronic nature of the disease. However, as *Le Fanu* stated in his book, with the discovery of the diuretic chlorothiazide and the beta-blocker propranol, hypertension had become a "treatable disease" because "these new drugs interfered so little with a person's life" that hypertensive patients who start with the treatment with antihypertensive drugs "are prepared to take *them* for longer periods"[6]. Are they?

Adherence vs. persistence

The use of antihypertensives for long consecutive periods is important because incorrect use will lead to a less effective treatment in daily practice than observed in RCTs. This thesis focuses on two aspects of "using antihypertensives correctly" namely adherence and persistence. Although these issues are conceptually linked together, and even interchanged in medical literature, they refer to a different problem. Adherence or compliance are both used to define the extent to which a patient "takes his medication as prescribed", or more theoretically, "to which a patient's dosing history corresponds to the prescribed regimen", as defined by Urquhart[9,10]. The term is usually expressed as a percentage or fraction of doses taken as scheduled. In this context, non-adherence or non-compliance refers to problems such as missing doses, intentionally or not, or short periods of so called drug holidays, periods during which patients consciously do not take medication, but restart thereafter. This means that in case of non-adherence, a patient does have the intention to use treatment for longer periods, but not always as prescribed. The long-term consequence is that the full benefit of treatment cannot

be obtained making the patient sub-optimally protected. In addition to the long-term risk associated with non-adherence, Psaty et al. demonstrated that there is also an acute risk associated with non-adherence. Patients who missed doses of beta-blockers had a 4.5 times increased risk of ischemic heart disease[11].

The term persistence, or continuation, is used to characterize patients that continue for a defined period, e.g. one year. In case of non-persistence, patients completely discontinue the use of a certain drug or treatment regimen, in contrast to non-adherence where only some doses are omitted. Therefore, non-persistence constitutes an even greater barrier to attain treatment goals.

Use of prescription databases to elucidate patterns of drug use

With the development of several prescription databases in the 1980s, it became possible to observe large numbers of patients in daily practice. This also provided researchers an easy and inexpensive opportunity to obtain information on patterns of use of various (chronic) medications, including antihypertensives. In 1995, Jones et al. were among the first to evaluate prescription patterns of 37,643 newly diagnosed patients with hypertension who started with the use of antihypertensive drugs[12]. They found that of those patients 41% (diuretics), 49% (beta-blockers), 41% (calcium channel blockers) and 45% (ACE-inhibitors) were still using their first prescribed antihypertensive drug class, the rest of those patients used other classes than the initially prescribed one, or completely discontinued treatment. Those findings were later confirmed in other studies with discontinuation rates varying from 20% to 80%[13-16]. This implies that, contradictory to Le Fanu's statement, more than 40 years after the discovery of chlorothiazide and propranolol, large proportions of patients are not using their antihypertensives for longer periods.

Next to prescription databases, there are several direct and indirect methods to detect problems regarding non-adherence and non-persistence (table 1)[3]. There is no scientific justification to consider one of these as the gold standard, although electronic monitors are often considered as such. All these methods differ with regard to their validity, reliability, sensitivity, and invasiveness. In this thesis, only pharmacy records are used to quantify adherence and persistence.

Table 1: methods of measuring adherence[17]

Methods of measuring adherence	Test advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white coat adherence" can give a false impression of adherence; expensive
Measurement of a biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids, intra-individual variation
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g., pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials, patients can dump medication
Measurement of physiologic markers (e.g., heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

The role of the pharmacist

As is displayed in table 1, pharmacy records provide an objective estimate of adherence. This suggests that in daily practice, community pharmacists, who have

direct access to these data, should be the first to play an active role in monitoring the medication taking of their patients. Most Dutch pharmacist are already active and experienced in using their own data for other purposes than reimbursement and interaction monitoring, e.g. to provide their neighboring general practitioners with information on their prescribing behavior. Next to this, pharmacists are seeking for an active role in the provision of all kinds of services to patients, monitoring and improving adherence could be a potential one. The latter was confirmed by the Dutch Patients and Consumers Federation (NPCF), the Royal Dutch Pharmacist Association (KNMP), the Dutch Association of General Practitioners (NHG) and the Dutch Organization of the Innovative Pharmaceutical Industry (NEFARMA), who together suggested that the pharmacist should be the professional to intervene in non-adherent patients[18].

Outline of the thesis

The aim of this thesis was to assess the prevalence and determinants of non-adherence and non-persistence with antihypertensive drugs and to provide suggestions for intervening to improve it among non-adherent patients with hypertension. This thesis is divided into three main parts. The first part describes methodological issues with regard to the use of pharmacy records to detect several problems concerning adherence and persistence. The second part describes the identification of potential targets for interventions in an observational setting. The last part concerns intervening in patients using chronic treatment. Special emphasis is placed on patients using antihypertensive drugs on the one hand and pharmacists performing the intervention on the other hand. Although some potential reasons for non-adherence will be described in the discussion sections of the presented studies, systematically assessing these reasons is outside the scope of this thesis[19-28]. In addition, only *underuse* of antihypertensive drugs is studied, in contrast to *overuse* because the origin of this problem is totally different.

Drugs labeled as antihypertensives are not only prescribed for the indication of hypertension. In **chapter 2.1**, the indication for which several categories of antihypertensive drugs are prescribed, are shown. In addition, the several forms of bias this introduces to pharmacoepidemiological studies are discussed.

A large number of pharmacoepidemiological studies on persistence to chronic treatment have been performed in several populations. In all studies, different definitions were used to classify patients as non-persistent based on a defined

length of a gap between two prescription refills. In **chapter 2.2**, the results of varying these gaps and the consequences for the proportion of patients classified as persistent, are presented to demonstrate the extent to which results of persistence studies are dependent on this definition in contrast to differences in the population studied or drug classes used.

In **chapter 3.1**, the association between non-adherence and modification of the treatment regimen, such as dose increase, addition of a new antihypertensive drug and switch to another antihypertensive drug, is assessed.

In **chapter 3.2**, the extent to which non-adherence is followed by complete discontinuation is assessed.

In **chapter 4.1**, a cohort of new users of antihypertensive drugs is retrospectively observed over a period of ten years. During this period, adherence and persistence to treatment are assessed using a method suggested in the previous chapter, and several patient related and drug related characteristics associated with non-persistence are identified.

In **chapter 4.2**, a cohort of new users of antihypertensive drugs who discontinue the use thereof are observed over a period of at maximum 6 years. During this period, rate and predictors of a reinitiating treatment were studied.

In **chapter 4.3**, 6-year persistence patterns among new users of antihypertensive drugs between The US (Pennsylvania), Canada (British Columbia) and The Netherlands were compared. In addition, potential predictors of sub optimal persistence were assessed and compared.

Next to effectiveness, other aspects of antihypertensive drug use are important such as persistence to treatment. Therefore, objective methods are needed that facilitate objective comparison between different antihypertensive and classes of antihypertensive drugs. In **chapter 4.4**, two multiple criteria decision making models are presented to determine the first choice antihypertensive drug class for patients with uncomplicated hypertension. These models not only include effectiveness but also costs, clinical experience and persistence to treatment.

In **chapter 5.1**, a literature review is presented examining interventions performed by community pharmacists to increase adherence to treatment with chronic medication. The aim was to identify strategies successful in increasing adherence to treatment that could be extrapolated to increase adherence in non-adherent patients with hypertension. Furthermore, pitfalls in designing interventions aimed to increase adherence to treatment are discussed.

In **chapter 5.2**, the results of a community pharmacist-led intervention strategy aimed to increase adherence to treatment in non-adherent patients with hypertension, is presented. In this study, the medication event monitoring system (MEMS [AARDEX, Ltd]), a pillbox that records every opening thereby providing information on medication intake, was used as an intervention to increase adherence. One of the frequently suggested disadvantages of MEMS when used for the measurement of adherence, is that it increases adherence because patients, aware of the fact that their behavior is studied, open their pillboxes more frequently. In the study presented in this chapter, MEMS is used in combination with discussing non-adherence to lower systolic and diastolic blood pressure.

After a patent has expired, pharmacists and general practitioners often substitute brand name drugs with generic drugs, to reduce costs. In **chapter 5.3**, the consequences for adherence to treatment after switching from the use of brand name antihypertensives to generic equivalents are presented.

Finally, the topic itself, the results, conclusions and recommendations are put in a broader perspective in the **general discussion** section of this thesis. Special emphasis will be placed on the role of the pharmacist in intervening in non-adherent patients.

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Chapter 2

Methodological aspects

Chapter 2.1

Indications for antihypertensive drug use in a prescription database

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Summary

Background: Drugs termed antihypertensives are prescribed and registered for other indications than hypertension alone. In pharmacoepidemiological studies, this could introduce several forms of bias. The objective of this study was to determine the extent to which drugs classified as antihypertensive drugs are prescribed for other diseases than hypertension.

Methods: The NIVEL database was used, containing prescriptions from a sample of general practitioners in The Netherlands. Classes of antihypertensive drugs were analyzed separately, based on ATC-codes: miscellaneous antihypertensives, diuretics, beta-blockers, calcium channel blockers and agents acting on the renin angiotensin system. In addition, these classes were further subdivided based on their specific mechanism of action. All first prescriptions of a patient in the database for an antihypertensive drug were selected. ICPC diagnoses studied were: increased blood pressure, hypertension without organ damage, hypertension with organ damage and hypertension with diabetes mellitus for which the above-defined antihypertensive drugs were prescribed.

Results: Of 24,812 patients who received a first prescription for an antihypertensive drug, 63.0% received a first prescription for hypertension related diagnoses (diuretics: 54.1%, beta-blockers: 59.1%, calcium channel blockers: 60.3%, agents acting on the renin angiotensin system: 82.8% and miscellaneous antihypertensives: 64.6%). Subdividing and restricting these subgroups based on their mechanism of action yields a higher percentage of first prescriptions with hypertension related diagnoses (low-ceiling diuretics: 78.8%, selective beta-blockers: 69.9% and dihydropyridine calcium channel blockers: 76.8%).

Conclusion: If a prescription database lacking diagnoses is used to study antihypertensive drugs in relation to hypertension treatment, the results have to be interpreted with caution because of the potential misclassification that may occur. Subdividing the antihypertensive drug classes and restricting to subgroups decreases this misclassification.

Background

Prescription databases offer a relatively easy and inexpensive way to obtain information on drug utilization, e.g. side-effects, adherence to treatment, persistence and prevalence, in daily practice. A number of databases are available and have been used for a large number of pharmacoepidemiological studies, e.g. MediPlus (German, UK, France), GPRD (UK), Saskatchewan Health (Canada), Medicaid (US), Local health Unit of Ravenna (Italy) Uniformed Services Prescription Database Project (USPDP) and PHARMO (The Netherlands)[1-8]. A limitation of some of these databases is that they lack the indication for which a drug is prescribed[1,3]. In some cases, one drug can be assigned to a single indication with a large degree of certainty e.g. in case of insulin and diabetes mellitus. With antihypertensive drugs, there is more uncertainty because antihypertensive drugs can also be prescribed for e.g. angina pectoris, heart failure, cardiac arrhythmias, but also for other than cardiovascular diseases e.g. migraine prophylaxis or anxiety (beta blockers). This could introduce several forms of bias. In this study we aimed to assess for which diagnoses antihypertensive drugs are prescribed in The Netherlands and whether this differed between the different types of antihypertensive drugs.

Methods

We used a sample from the Second Dutch National Survey of General Practice which was carried out in 2001 by the Netherlands Institute for Health Services Research (NIVEL). This database has been described elsewhere[9]. In short, 195 general practitioners in 104 practices registered all physician-patient contacts during 2001. All prescription drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification system[10]. We studied the following classes of antihypertensive drugs: miscellaneous antihypertensives (ATC-code C02), diuretics (ATC-code C03), beta-blockers (ATC-code C02), calcium channel blockers (ATC-code C08) and agents acting on the renin angiotensin system (ATC-code C09). Furthermore, we subdivided these classes into subgroups based on their mechanism of action. Miscellaneous antihypertensives were subdivided in alpha-blockers and centrally acting antihypertensives. Diuretics were subdivided into low-ceiling diuretics, high ceiling diuretics and potassium sparing agents. Beta-blockers were subdivided into selective beta-blockers, non-selective beta-blockers, alphabeta-blockers and sotalol (which is not registered for hypertension). Calcium channel blockers were subdivided into dihydropyridine calcium channel

blockers, verapamil and diltiazem. Agents acting on the renin angiotensin system were subdivided into ACE-inhibitors and angiotensin II receptor blockers. All first prescriptions of a patient in the database for a defined class were selected. Diagnoses were coded according tot the International Classification of Primary Care[11]. Hypertension related diagnoses studied were: increased blood pressure (K85), hypertension without organ damage (K86), hypertension with organ damage (K87) and diabetes mellitus for which the above-defined antihypertensive drugs were prescribed (T90). Other diagnoses studied were angina pectoris (K74), congestive heart failure (K77) and cardiac arrhythmias (K78). Differences in percentages of prescriptions for hypertension related diagnoses between diuretics and the other four classes, as well as for the low-ceiling diuretics and the other thirteen subgroups based on their mechanism of action, were tested, using the chi-square test.

Results

The results are shown in table 1. A total of 24,812 first prescriptions from an equal number of patients were evaluated. Of these prescriptions, 63% were for hypertension related diagnoses. The fraction of prescription for other cardiovascular and non-cardiovascular diagnoses was generally different among the antihypertensive drug classes, the lowest for diuretics and the highest for agents acting on the renin angiotensin system.

Table 1: Different diagnoses for which antihypertensive drugs are prescribed from 24,812 first prescriptions of 24,812 patients

	Miscellaneous	Diuretics	Beta-blockers	CCBs	AARAS
Number	212	7,360	9,468	2,307	5,465
Hypertension related	137 (64.6%)	3,980 (54.1%)	5,592 (59.1%)	1,391 (60.3%)	4,526 (82.8%)
CHF	0 (0%)	988 (13.4%)	44 (0.5%)	18 (0.8%)	176 (3.2%)
Angina pectoris	2 (0.90%)	75 (1.0%)	556 (5.9%)	223 (9.7%)	72 (1.3%)
Cardiac arrhythmias	0 (0%)	56 (0.8%)	219 (2.3%)	91 (3.9%)	24 (0.4%)
Other cardiovascular	4 (1.90%)	1,351 (18.4%)	1,200 (12.7%)	292 (12.7%)	220 (4.0%)
Other non-cardiovascular	69 (32.6%)	910 (12.4%)	1,857 (19.6%)	292 (12.7%)	447 (8.2%)

CCBs=calcium channel blockers; AARAS=agents acting on the renin angiotensin system; CHF=congestive heart failure

If the five major classes of antihypertensive drugs are divided into subgroups based on their mechanism of action, the percentage of patients with a prescription for a hypertension related diagnosis is generally higher for low-ceiling diuretics, selective beta-blockers, alpha-beta-blockers and dihydropyridine calcium channel blockers (table 2). Of all patients receiving a first prescription for alpha-blockers, 17.3% had a diagnosis of benign prostate hypertrophy. Of all patients receiving a first prescription for a non-selective beta-blocker, 38.1% had an anxiety or tension related diagnosis. In addition, patients receiving a first prescription for diltiazem, 37.8% had a diagnosis of angina pectoris and 23.8% of the patients receiving verapamil had a diagnosis of cardiac arrhythmias. All four classes differed significantly from diuretics with regard to the percentage of hypertension related diagnosis (all four p-values<0.001). All subgroups differed significantly from low-ceiling diuretics (p<0.001) except dihydropyridine calcium channel blockers (p=0.117).

Table 2: different diagnoses for which antihypertensive drugs are prescribed from 24,812 first prescriptions of 24,812 patients; classes are subdivided into subgroups based on their mechanism of action

	Hypertension related	Other cardiovascular	Other non-cardiovascular
Miscellaneous antihypertensives (N=212)	137 (64.6%)	6 (2.8%)	69 (32.6%)
• Alpha-blockers (N=110)	73 (66.4%)	2 (1.8%)	35 (31.8%)
• Central acting (N=102)	64 (62.7%)	4 (3.9%)	34 (33.3%)
Diuretics (N=7,360)	3,980 (54.1%)	2,470 (33.6%)	910 (12.4%)
• Low ceiling (N=3,456)	2,722 (78.8%)	484 (14.0%)	250 (7.2%)
• High ceiling (N=2,264)	328 (14.5%)	1,492 (65.9%)	444 (19.6%)
• Potassium sparing (N=1,640)	930 (56.7%)	494 (30.1%)	216 (13.2%)
Beta-blockers (N=9,494)	5,513 (58.1%)	2,196 (23.1%)	1,785 (18.8%)
• Selective (N=7,494)	5,237 (69.9%)	1,442 (19.2%)	815 (10.9%)
• Non-selective (N=1,366)	208 (15.2%)	200 (14.6%)	958 (70.1%)
• Alpha-beta (N=98)	68 (69.4%)	18 (18.4%)	12 (12.2%)
• Sotalol (N=536)	0 (0%)	536 (100%)	0 (0%)
Calcium channel blockers (N=2,307)	1,391 (60.3%)	624 (27.0%)	292 (12.7%)
• Dihydropyridine (N=1,615)	1240 (76.8%)	209 (12.9%)	166 (10.3%)
• Verapamil (N=345)	88 (25.5%)	192 (55.6%)	65 (18.8%)
• Diltiazem (N=347)	63 (18.2%)	223 (64.3%)	61 (17.6%)
AARAS (N=5,465)	4,526 (82.8%)	492 (9.0%)	447 (8.2%)
• ACE-inhibitors (N=4,251)	3,492 (82.1%)	428 (10.1%)	331 (7.8%)
• ARBs (N=1,214)	1,034 (85.2%)	64 (5.3%)	116 (9.6%)

AARAS=agents acting on the renin angiotensin system; ARBs=angiotensin II receptor blockers

Discussion

In this study we found that the majority (54-83%) of antihypertensive drug prescriptions were prescribed for hypertension related diagnoses, with some differences between antihypertensive drug classes. Furthermore, in a relevant number of cases (8.2% to 32.6%) the diagnosis was not cardiovascular disease related. If the classes are divided into subgroups based on their mechanism of action, it is possible to select a higher percentage of patients with a diagnosis of hypertension. These classes are low-ceiling diuretics, selective beta-blockers, dihydropyridine calcium channel blockers, ACE-inhibitors and angiotensin II receptor blockers.

Our findings provide an estimation of misclassification with regard to indication. This will lead to different forms of bias in different types of pharmacoepidemiological studies. When effectiveness of antihypertensive drugs in terms of cardiovascular hospitalizations is studied, a relevant number of patients

will be incorrectly classified as hypertensive. E.g. among beta blockers, about 6% of the patients are diagnosed with angina pectoris, which is considerably higher than among the other antihypertensive drug classes. These patients will have a higher risk of cardiovascular disease[4].

When effectiveness in reduction of cardiovascular hospitalizations between antihypertensive drugs is compared, this inevitably will increase the number of events among the users of beta-blockers, not because they are less effective but because patients using different antihypertensive drugs are different patients with a higher risk of cardiovascular events. In studies on persistence and adherence to treatment, a relevant number of patients, who do not use antihypertensive drugs for hypertension and not for a chronic disease, will incorrectly be classified as non-adherent or non-persistent. This will lead to an overestimation of the problem of non-persistence or non-adherence. Furthermore, when persistence with alpha-blockers is compared to persistence with other antihypertensive drugs, the other indication for which it is prescribed, benign prostate hypertrophy may be accompanied by a different attitude towards the necessity for good persistence or adherence. The direction to which this misclassification influences associations obtained in these two types of studies remains uncertain.

In the third type of pharmacoepidemiological study, studies on adverse events, misclassification will probably have the least influence on effect estimates. If the disease or disease severity (indication for treatment) is not likely to influence the incidence or severity of adverse events misclassification based on indication will be irrelevant.

Our results need to be confirmed in other countries using databases lacking the diagnosis. In addition, prescriptions (with known indications) from other prescribers have to be analyzed, in our example especially from patients predominantly treated by cardiologists and internists, to obtain data on the whole population of antihypertensive drug users.

In conclusion, 54-83% of the antihypertensive drugs are actually prescribed for hypertension in The Netherlands. If a prescription database lacking diagnoses is used to study antihypertensive drugs in relation to hypertension treatment, the results have to be interpreted with caution because of the potential

misclassification that may occur. Subdividing the antihypertensives classes and restricting to subgroups, based on their specific mechanism of action decreases this misclassification.

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Chapter 2.2

Different definitions of the maximum allowed treatment gaps lead to different rates of refill persistence

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Summary

Background: 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 patient characteristics and persistence were 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 to 365 days), the second based on the duration of the last prescription (varying from 0.1 to 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 from 19.7% to 86.4% (method 1), from 27.9% to 90.2% (method 2) and from 19.7% to 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' definition of the maximum allowed treatment gap.

Background

Non-persistence with chronic treatment is a major problem for patients, healthcare providers and policy makers. Although for many chronic diseases pharmacotherapeutic options are available and effective as demonstrated in randomized controlled trials, patients often do not only take their medication as has been prescribed by their physician (non-adherence) but also fail to use it for a long uninterrupted period of time (non-persistence)[1,2]. This non-persistence 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 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 one-year refill persistence rate and associations between patient characteristics and one-year persistence. In the first method, a defined number of days and in the second method a fraction of the theoretical duration of the prescription after which the treatment gap occurs was used to define the maximum allowed treatment gap that a patient 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. In order to compare those methods, we used data from new users of antihypertensives, a class of drugs that is intended to be used chronically.

Methods

Data

We used data from the PHARMO database; a record linkage system currently containing drug dispensing records from community pharmacies and linked hospital discharge records of approximately 2,000,000 subjects. This database covers a well-defined population of residents of 50 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 non-residents of one of the PHARMO cities are excluded[4]. The data registered in the PHARMO database include age and gender of the patient, name of the drug, dispensing date, amount of units dispensed of the drug and prescribed daily dose. Prescribed daily dose (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].

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 1st 1999 and December 31st 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. 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 blockers) 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 co-medication (antiasthmatic 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.

Definitions

The theoretical duration of a prescription was calculated by dividing the number of units dispensed by the prescribed daily dose. Thus, the end date of a prescription equals the start date plus the theoretical 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 one year (persistent use, figure 1). The first method is based on a defined maximum number of days, which the patient is allowed to have between the theoretical 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 from 9 to 360 days. The second method is based on a defined maximum fraction of the theoretical 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 from 0.1 to 4 times the theoretical 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 theoretical 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 theoretical 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 theoretical duration), 45 days (comparable to 0.5 times the theoretical duration), 90 days which is comparable to 1 times the theoretical duration of a prescription and 180 days, which is comparable to 2 times the theoretical duration of a prescription[7-15]. Furthermore we choose to study the

extremes of 3 and 4 times the theoretical duration of a prescription (method 2) as well as 270 and 360 days (method 1).

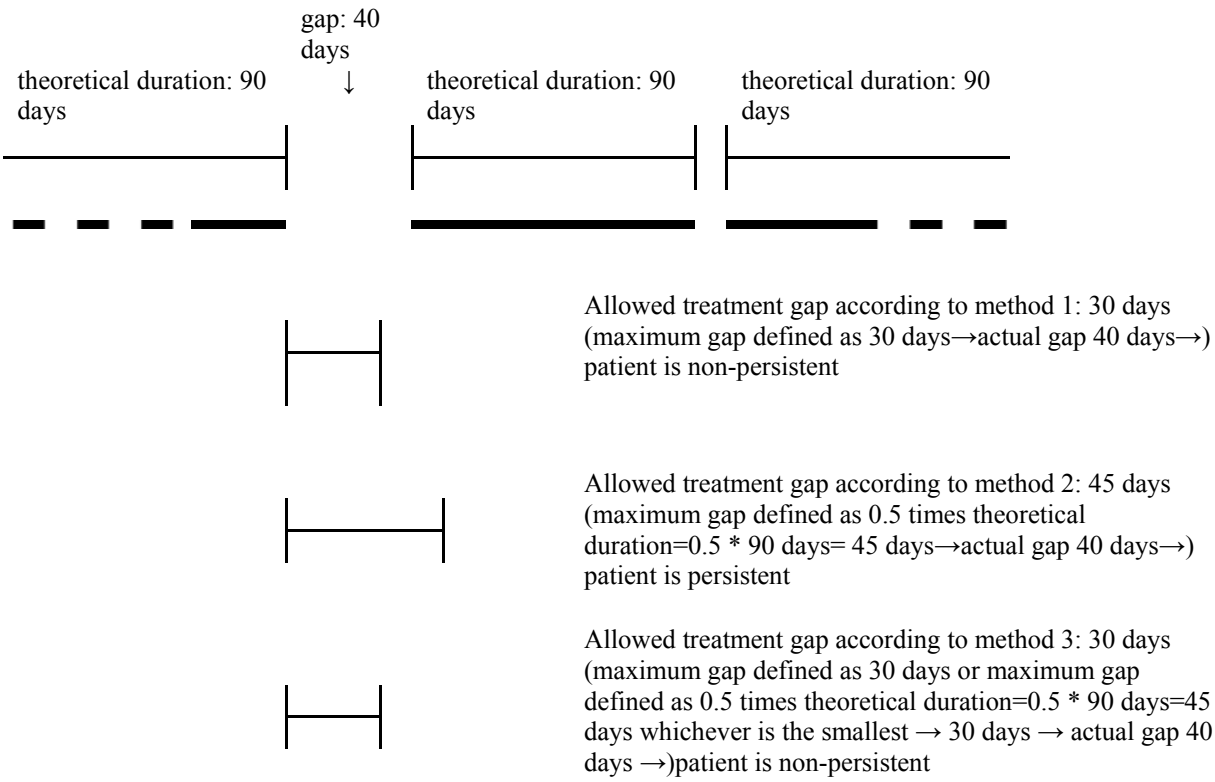

Figure 1: gap allowed according to different methods of calculating the fraction of patients who have an uninterrupted episode of use of antihypertensive drugs of at least one year

Statistical analysis

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

Results

Baseline characteristics of the patients are given in table 1. In a 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%).

Table 1: baseline characteristics of the study population (N=14,466)

Characteristic	Number (%) or Mean (SD)
Age (years)	60.8 (±14.5)
• 0-20	82 (0.6%)
• 20-39	928 (6.4%)
• 40-59	5,827 (40.3%)
• 60-79	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 channel blocker	756 (5.2%)
• ACE-inhibitor	2,297 (15.9%)
• Angiotensin II receptor blocker	979 (6.8%)
• Miscellaneous	131 (0.9%)
• Combination	1,680 (11.6%)

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

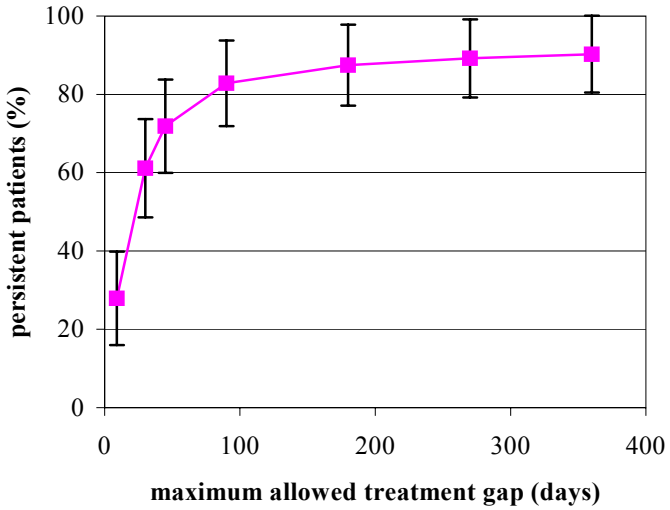

Figure 2: influence of variation of allowed treatment gap between two prescriptions in days (method 1) on percentage of persistent patients (95% CI) after one year

In figure 3, the results for 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 theoretical duration (0.1 to 1) of the prescription after which the treatment gap occurs as well as at a relatively low maximum allowed number of days between two prescriptions (9 to 90). This means that varying the maximum allowed treatment gap from 2 to 4 times the theoretical duration and from 180 to 360 days, whichever is the lowest, did not have any material influence on one-year persistence. The absolute persistence for all these combinations differed not more than 10% (data not shown). Absolute persistence varied from 19.7% to 86.4% for method 3.

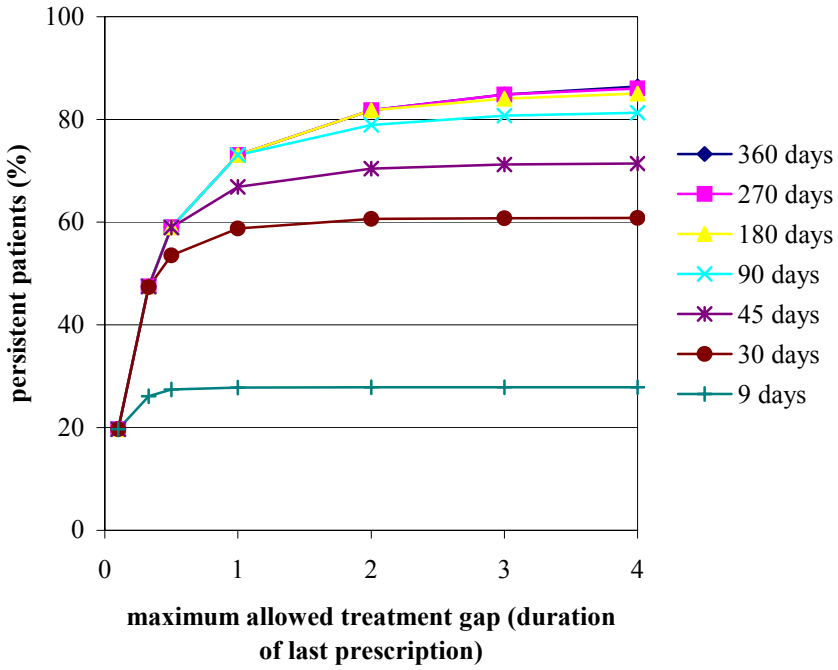

Figure 3: influence of variation of a combination of maximum allowed number of days between two prescriptions (method 1) as well as maximum allowed fraction of the theoretical duration of the prescription after which the treatment gap occurs, whichever is the lowest number of days (method 3) on percentage of persistent patients after one 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 co-medication) 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 one-year persistence in the final models between the three definitions. Age, first prescriber, type of first antihypertensive and hospitalization for ischemic heart disease prior to study entrance were significantly associated with one-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, type of insurance (public vs. private), type of first prescriber (cardiologist and internist vs. GP), the use of lipid lowering drugs, the use of anti-asthmatic drugs, the use of antidiabetic drugs, hospitalizations for congestive heart failure, cardiac arrhythmias, peripheral vascular disease, and cerebrovascular disease were associated with one year persistence. The direction of these predictors differed for the different definitions

used. No clear trend was visible which definition included which predictor (table 2).

Table 2: influence of variation of maximum allowed treatment gap on the association between one-year persistence and patient characteristics and the significance of this association

Patients characteristic	Number of definitions included with HR>1 (percentage of total)	Number of models included with HR<1 (percentage of total)
Age (linear)	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 channel blocker	48 (76%)[a]	15 (24%)[a]
• ACE-inhibitor	63 (100%)[a]	0 (0%)[a]
• Angiotensin II receptor blocker	63 (100%)[a]	0 (0%)[a]
• Miscellaneous	48 (76%)[a]	15 (24%)[a]
Co-medication		
• Use of lipid lowering drugs	47 (75%)	2 (3%)
• Use of anti-asthmatic 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%)

HR=hazard ratio for one-year persistence; a: separate HRs for the separate types of first antihypertensive were not always significant although the variable “type of first antihypertensive” as a whole was significant

In figure 4 we displayed the results of varying the maximum allowed treatment gap on the adjusted 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, 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] and 2.15 [95% CI: 1.87-2.47]. For angiotensin II

receptor blockers (ARBs) 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 one-year persistence compared to diuretics. According to method 2, ARBs were associated with the highest one-year persistence compared to diuretics. We also tested whether there was any significant difference when directly comparing ACE-inhibitors with ARBs for both method 1 and 2. We found that, compared to ACE-inhibitors, ARBs were not significantly more associated with one-year persistence than ACE-inhibitors in both methods (data not shown).

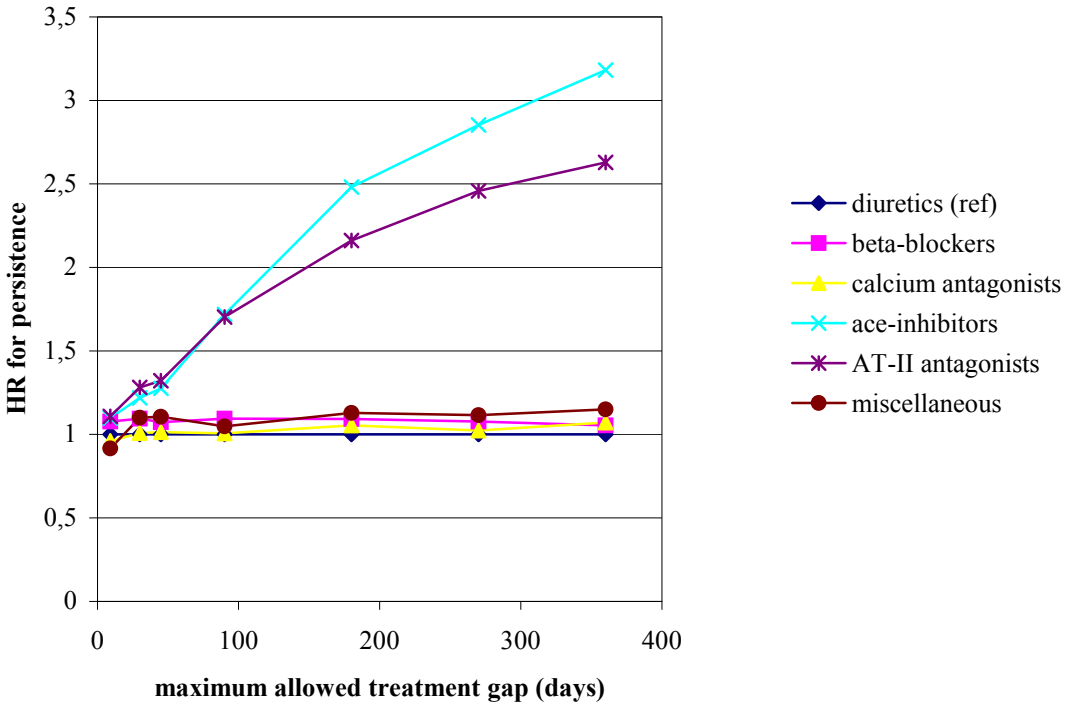

Figure 4: influence of variation of maximum allowed treatment gap in days (method 1) on hazard ratios of the different types of antihypertensives compared to diuretics

Discussion

In this study we compared three different methods to calculate one-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 to 90) and small fractions (0.1 to 1 times) of the theoretical duration on one-year persistence, which varied from 28% to 83% and from 20% to 73% respectively. At higher defined number of days (180 to 360) as

well as at larger fractions of the theoretical duration (2-4 times) the number of persistent patients did not show any relevant variation, namely from 87% to 90% and from 82% to 86% for method 1 and method 2 respectively. 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 to 73%) at small fractions (0.1 to 1 times) of the theoretical duration combined with a small number of days (9 to 90) and less variation of the percentage of persistent patients (82% to 86%) at large fractions (2 to 4 times) of the theoretical duration combined with a large number of days (180 to 360). These findings indicate that variation of the allowed treatment gap has a large influence on one-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 imply better reflecting actual discontinuation. Furthermore we found that the significance of the association between patient characteristics and one year persistence as well as the magnitude (and direction) of the HRs of patient characteristics associated with one-year persistence were influenced by both the definition used and the variation within a definition.

There are some limitations of this study, and of studies using pharmacy records in general that may have influenced our clinical findings. Pharmacy records may not be precise enough to detect small irregularities in medication taking, or irregularities in pharmacy records may 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. In addition, a patient may be non-persistent with treatment because he was advised to discontinue by his physician because he temporarily did not need pharmacological treatment or no longer needs pharmacological treatment. This may be caused by side-effects that do not counterbalance the long-term reduction in cardiovascular morbidity and mortality e.g. in the case of mild hypertension. Furthermore, blood pressure may be controlled and medication may be tapered, ultimately resulting in intentional non-persistence. In addition to this, dietary or lifestyle changes may become effective and antihypertensives are no longer necessary to control blood pressure. Furthermore, a patient may discontinue not on a physician’s advice but on his own request but in agreement with his physician. Although these patients are analyzed as discontinuer, this non-persistence has no clinical relevance. A patient may also discontinue (chronic) co-medication which causes hypertension e.g. NSAIDs and

therefore no longer needs antihypertensive treatment. Patients may also use a certain "antihypertensive" drug for another indication than hypertension and continue with another drug for the same indication, which is not classified as an antihypertensive. E.g. in the case of benign prostate hypertrophy, patients using an alpha-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. Another limitation to the external validity of our clinical observations, 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.

A first strength of our study is that we compared different methods of calculating one-year persistence in one and the same population and database. Any difference in one-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 one-year persistence with other chronic medication may be expected when using different methods. Researchers, who study persistence with medication in e.g. diabetes, depression, osteoporosis and hyperlipidemia may encounter the same problem.

To our knowledge, this type of methodological study has never been done before. Steiner et al. evaluated different methods to assess refill adherence instead of refill persistence[25]. Although those two terms refer to different concepts as stated in the introduction section, they are, of course, complementary. Studies using refill adherence focus on the (average) exposure to a certain drug during a certain period, while refill persistence focuses on how long patients continue, with a certain level of adherence, with the use of a certain drug or drug class. A researchers' choice for a certain definition should be related to the reason why the study is performed. First, it seems logical to relate the maximum allowed treatment gap to the duration of the prescription to decrease misclassification based on the length of a 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 adherence instead of refill persistence is a more appropriate method. However, if the goal of the study is to study persistence with drugs and to compare different drug classes with each other, the maximum allowed treatment gap should be large (≥90 days or 1 times the duration of the last prescription) because small maximum allowed gaps probably indicate suboptimal use. Furthermore, because of differences in adherence leading to different gaps after theoretical end dates of prescriptions, small gaps may result in differential misclassification with regard to the type of antihypertensive. E.g., it is likely that patients who use a certain drug class that is accompanied by many side-effects (beta-blockers) are less adherent to their treatment than patients who use other drug classes that have relatively mild side-effects (ARBs). This would lead to a different distribution of the gaps after a prescription which would lead to different proportions of non-persistent patients between drug classes and thus to different HRs for non-persistence 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 e.g. less than once every 2 days 1 tablet in 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 non-persistence followed by a next treatment episode (although this measured non-persistence may be less clinically relevant). Based on these considerations, we would advice the use of at least 90 days, 1 times the theoretical duration (method 2) or one times the theoretical duration combined with 90 days whichever is the smallest (method 3) in case persistence 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[8,14,26,27]. All of these studies demonstrated that the highest proportion of persistent patients was found in patients starting with newer types of antihypertensives, ARBs 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 three months. In our method in which we used a defined number of days, patients starting with ACE-inhibitors demonstrated higher persistence than patients starting with ARBs. In

our definition using fractions of the theoretical duration, we found the same results as in literature, the highest proportion of persistent patients in patients starting with ARBs followed by ACE-inhibitors. The study of Hasford et al. however, demonstrated no material differences between the different types of antihypertensives[12]. 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 pharmacological treatment. Furthermore, validation studies need to be performed to determine which treatment gaps in general reflects non-persistence, 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 non-persistence with the highest sensitivity and specificity, such as further increase of the disease severity, blood pressure or cardiovascular hospitalization or death although the clinical relevance of acute discontinuation differs among the different types of antihypertensive drugs.

In conclusion, different definitions of calculating one-year persistence lead to different percentages of persistent patients and can also influence the association between patient characteristics and one-year persistence. The use of at least 90 days, 1 times the theoretical duration (method 2) or 1 times the theoretical 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.

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Chapter 3

Adherence with antihypertensives as a predictor of medication events

Chapter 3.1

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

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Summary

Background: Non-adherence 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-adherence and change in medication regimen.

Methods: A nested case-control study within a cohort of new users of antihypertensive drugs between January 1st 1999 and December 31st 2002 was performed. Data from the PHARMO database, a record linkage system currently containing drug dispensing records from community pharmacies and linked hospital discharge records of approximately 2,000,000 subjects, were used. Cases were subjects whose initial drug regimen was modified (dose change, addition, and switch). 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, 11,937 cases and 11,937 matched controls were identified. The percentage of non-adherent patients (adherence<80%) among cases and controls was 5.1% and 3.6%, respectively (OR 1.39 [95% CI: 1.22-1.58]). The association was 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 use was longer than 6 months.

Conclusion: Non-adherence is significantly associated with the occurrence of change in antihypertensive medication regimen. Pharmacists and physicians can use pharmacy data to assess and improve adherence with antihypertensive drugs, before modifying treatment regimens.

Background

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 due to a number of randomized controlled trials, resulting in a decrease in cardiovascular morbidity and mortality[1-8]. However, 70-75% of the patients with hypertension still have poor control of their blood pressure[1]. Non-adherence 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-adherence 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-adherence 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 currently containing drug dispensing records from community pharmacies and linked hospital discharge records of approximately 2,000,000 subjects. This database covers a well-defined, geographically diverse, drug-insured population of residents of 55 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 one of the PHARMO cities were excluded[15]. The data registered in the PHARMO database include age and gender of the patient, name, dispensing date, 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[1,16].

Patients

We selected a cohort of patients who used no antihypertensive agents during 1998 and presented their first prescription for an antihypertensive drug between January 1st 1999 and December 31st 2002 and who collected more than one prescription. These patients were followed until the end of data collection (December 31st 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 (ACE-inhibitors) and C09C+D (angiotensin II receptor blockers) 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 which 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 1 times the duration of the first prescription.

Definition of adherence and potential confounding factors

Adherence 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 till the index date. A patient with adherence below 80% was considered non-adherent. In sensitivity analyses, we studied the influence of different definitions of adherence on the association

between adherence 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, hospitalization for cardiovascular diseases such as ischemic 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 analyze differences in baseline characteristics between cases and controls. To analyze the association between adherence 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).

Results

In a cohort of 39,714 new users of antihypertensive drugs we identified 11,937 cases and 11,937 matched controls meeting the inclusion criteria. Baseline 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 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 vs. 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, 56.6% among the cases vs. 52.5% 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 vs. 44% among controls).

Table 1: baseline characteristics of the study population

	Cases (N=11,937)	Controls (N=11,937)	P-value
Age (years)	59.9 (±14,6)	59.9 (±14,5)	0.864
Type of change			
• Dose decrease	1,550 (13.0%)	-	-
• Dose increase	3,862 (32.3%)	-	-
• Switch	3,199 (26.8%)	-	-
• Addition	3,326 (27.9%)	-	-
Males (%)	5,479 (45.9%)	5,479 (45.9%)	1.000
Duration of first episode (days)	194.7 (±236.0)	196.3 (±235.0)	0.585
DDDeq	0.76 (±0.42)	0.79 (±0.44)	P<0.001
DDDeq<1	6,750 (56.6%)	6,260 (52.5%)	P<0.001
First prescriber			
• General practitioner	8,946 (74.9%)	8,595(72.0%)	P<0.001
• Internist	1.371 (11.5%)	1,522 (12.8%)	P<0.001
• Cardiologist	682 (5.7%)	823 (6.9%)	P<0.01
• Miscellaneous	997 (8.4%)	938 (7.9%)	0.169
Co-medication			
• Anti-asthmatic drugs	1,229 (10.3%)	1,071 (9.0%)	P<0.001
• Lipid Lowering drugs	946 (7.9%)	896 (7.5%)	0.235
• Antidiabetic drugs	1,078 (9.0%)	846 (7.1%)	P<0.001
Prior cardiovascular hospitalizations			
• Ischemic heart disease	560 (4.7%)	483 (4.0%)	P<0.05
• Congestive heart failure	18 (0.2%)	20 (0.27%)	0.871
• Arrhythmia	140 (12%)	106 (8.9%)	P<0.05
• Peripheral vascular disease	28 (0.2%)	27 (0.3%)	1.000
• Cerebrovascular disease	138 (1.2%)	102 (0.9%)	P<0.05
Initial antihypertensive drug			
• Diuretics	2,000 (19.3%)	2,553 (21.4%)	P<0.001
• Beta-blockers	5,545 (46.5%)	5,225 (43.8%)	P<0.001
• Calcium channel blockers	1,013 (8.5%)	1,099 (9.2%)	0.053
• ACE-inhibitors	2,094 (17.5%)	1,874 (15.7%)	P<0.001
• Angiotensin II receptor blockers	871 (7.3%)	1,081 (9.1%)	P<0.001
• Miscellaneous	114 (0.96%)	105 (0.88%)	0.542

We found differences between cases and controls in adherence (table 2). The average adherence among the cases was slightly, but significantly, lower among cases, (96.8%) compared to controls (97.0%). The percentage of non-adherent patients (adherence<80%) among the cases was 5.1% vs. 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-adherent patients still had a 1.39 times higher chance of receiving a change in their medication compared to adherent patients.

Non-adherent females had a 1.64 times higher risk of receiving a change in their medication compared to adherent females. For males no significant differences in receiving a change between non-adherent and adherent 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 longer than 6 months had an increased risk of receiving a change in medication regimen if they were non-adherent.

Table 2: association between non-adherence and adjustment of antihypertensive drug regimen

	Cases[a]	Controls[a]	OR (95% CI)	OR (95% CI)[b]
All subjects	603/11,937 (5.0%)	432/11,937(3.6%)	1.42 (1.25-1.61)	1.39 (1.22-1.58)
• Male	241/5,481 (4.4%)	210/5,481 (3.8%)	1.16 (0.96-1.40)	1.14 (0.94-1.40)
• Female	362/6,456 (5.6%)	222/6,456 (3.4%)	1.67 (1.41-1.98)	1.64 (1.37-1.94)
Duration of first episode < 6 months				
• Male	141/3,652 (3.9%)	150/3,652 (4.1%)	0.94 (0.74-1.19)	0.94 (0.74-1.19)
• Female	220/4,319 (5.1%)	145/4,319 (3.4%)	1.55 (1.25-1.92)	1.50 (1.20-1.86)
Duration of first episode ≥ 6 months				
• Male	100/1,829 (5.5%)	60/1,829 (3.4%)	1.71 (1.23-2.38)	1.71 (1.22-2.40)
• Female	142/2,137 (6.6%)	77/2,137 (3.6%)	1.90 (1.43-2.53)	1.88 (1.41-2.52)

a: number of non-adherent patients/all patients (% non-adherence among all patients), b: adjusted for use of specific co-medication, class of initial antihypertensive drug, hospitalization for cardiovascular diseases, type of prescriber and PDD

We defined different types of outcomes for the cases. Therefore, we also analyzed the association between adherence and type of change separately (Table 3). Non-adherent patients had a 2.62 times higher chance of receiving a dose decrease, compared to adherent patients, which was similar for male and female patients. Non-adherent female patients had a 1.85 times higher chance of receiving a dose increase compared to adherent female patients. Among male patients there was no association between non-adherence and dose increase. The association between non-adherence and switching to another antihypertensive drug was only present among females, but not among males. Similarly, non-adherence was only associated with addition of another antihypertensive drug among females, but not among males. We didn't observe any material changes in ORs after further stratification on duration of episode of use.

Table 3: association between non-adherence 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 (5.7%)	19/680 (2.8%)	2.05 (1.19-3.60)	2.62 (1.39-4.96)
• Female	57/860 (8.8%)	20/860 (2.3%)	3.06 (1.80-5.20)	2.80 (1.60-4.92)
Dose increase				
• Male	73/1,784 (3.4%)	66/1,784 (3.7%)	1.12 (0.79-1.58)	0.98 (0.67-1.42)
• Female	119/2,078 (5.7%)	62/2,078 (3.0%)	2.00 (1.46-2.75)	1.85 (1.30-2.64)
Switch				
• Male	66/1,480 (4.5%)	66/1,480 (4.5%)	1.00 (0.70-1.42)	0.99 (0.70-1.42)
• Female	88/1,719 (5.1%)	68/1,719 (4.0%)	1.31 (0.95-1.81)	1.32 (0.95-1.83)
Addition				
• Male	63/1,527 (4.1%)	59/1,527 (3.9%)	1.07 (0.74-1.54)	1.07 (0.73-1.55)
• Female	98/1,799 (5.5%)	72/1,799 (4.0%)	1.38 (1.01-1.88)	1.41 (1.30-1.94)

a: number of non-adherent patients/all patients (% non-adherence among all patients); b: adjusted for use of specific co-medication, class of initial antihypertensive drug, hospitalization for cardiovascular diseases, type of prescriber and PDD

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 blockers (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.

Table 4: influence of type of antihypertensive drug on association between non-adherence and adjustment of initial drug regimen.

	Cases[a]	Controls[a]	OR (95% CI)	OR (95% CI)[b]
Diuretics	2,300 (19.3%)	2,553 (21.4%)	1.00 (ref)	1.00 (ref)
• Male	822 (15.0%)	801 (14.6%)	1.00 (ref)	1.00 (ref)
• Female	1,478 (22.9%)	1,752 (27.1%)	1.00 (ref)	1.00 (ref)
Beta-blockers	5,545 (46.5%)	5,225 (43.8%)	1.36 (1.02-1.80)	1.35 (1.01-1.79)
• Male	2,596 (47.4%)	2,483 (45.3%)	0.75 (0.47-1.19)	0.77 (0.48-1.23)
• Female	2,949 (45.7%)	2,742 (42.5%)	1.99 (1.37-2.87)	1.92 (1.32-2.79)
Calcium channel blockers	1,013 (8.5%)	1,099 (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	2,094 (17.5%)	1,874 (15.7%)	1.32 (1.20-1.45)	1.32 (1.20-1.46)
• Male	1,133 (20.7%)	1,089 (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)
ARBs	871 (7.3%)	1,081 (9.1%)	1.14 (1.01-1.29)	1.12 (0.98-1.26)
• Male	412 (7.5%)	508 (9.3%)	1.09 (0.91-130)	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)

ARB=angiotensin II receptor blocker; a: number of users of classes of initial antihypertensive drug (percentage initial antihypertensive drug among all patients); b: adjusted for use of specific co-medication, adherence, hospitalization for cardiovascular diseases, type of prescriber and PDDs

Internists (OR 1.18 [95% CI: 1.06-1.32]) and cardiologists (OR 1.11 [95% CI: 1.01-1.22]) implemented more changes in the initially prescribed regimen compared to general practitioners. The association between adherence and change in medication regimen did not differ for subgroups defined by age group (p=0.68), first prescriber (p=0.49), co-medication (p=0.31 for antiasthmatic drugs, p=0.23 for lipid lowering drugs, p=0.30 for antidiabetic drugs) and prior cardiovascular hospitalizations (p=0.43 for IHD, p=0.869 for CHF, p=0.43 for arrhythmias, p=0.49 for PVD, p=0.40 for CVD).

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% was non-adherent indicating that the sampling procedure did not cause the small difference in adherence between cases and controls.

In a sensitivity analysis, we analyzed the results for different cut-off values of adherence. Using cut-off values between 60 and 95%, the association between non-adherence 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 an adherence to treatment 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 our best knowledge, the association between non-adherence and change in medication regimen has never been studied before.

One of the strengths of this study is that 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]. Adherence assessed using pharmacy records was previously found to significantly correlate with adherence measured with other methods such as pill counts, self-reports and electronic monitoring, although the strength of those correlations was moderate[20,21].

However, there are also some important limitations of using pharmacy records for assessing adherence. Refill adherence cannot assess the relationship between the duration of action and the timing of doses, which in this case may have an influence on whether blood pressure can 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 adherence can be considered as the maximum drug consumption, easily overestimating the actual adherence. 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-adherence would not necessarily lead to a change in medication regimen. However side-effects, leading to non-adherence may still be a cause of modification of the initially prescribed regimen regardless whether the indication is hypertension or not.

The association between non-adherence and change in medication regimen we found is probably largely explained by the fact that non-adherence 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-adherence can be caused by patients' dissatisfaction with the prescribed antihypertensive regimen influencing the physicians' opinion about his choice, which also may lead to a change. We also found that the association between non-adherence and change was significantly stronger for females than for males. Females are known to have other health related behavior than males and are known to pay more visits to their physician[22,23]. It is possible that dissatisfaction about therapy, resulting in a lower adherence, is 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 adherence 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. This motivation may decrease over time so that the relative number of non-adherent patients in both groups will be relatively low and adherence is not an issue at the start of treatment. Other issues may play a more important role (side-effects) in this phase. 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 relatively short of 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 relatively low number of non-adherent patients (5.1% among cases and 3.6% among controls). The low number of non-adherent patients

may be caused by the fact that we used a database containing computerized pharmacy records, easily overestimating adherence. This overestimation is partly caused by the fact that patients often 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 will often be registered the same day as it is prescribed, although the patient may collect the medication later. In addition, 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 of which the physician thinks the patient may need it, as well. For the different types of change, we found the strongest association between non-adherence and dose decrease. This may be explained because patients, who are not satisfied with the started therapy because of side-effects, may discuss this with their physician during a follow-up visit, resulting in a dose decrease. Another explanation may be that the patient was already told during a follow-up visit to use the current prescription in a decreased dose but this is of course not yet registered in the pharmacy. The association between non-adherence and dose increase may be explained by our general assumption that low adherence 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-adherence and switching or addition among female patients.

The results of this study indicate that non-adherence 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 to the patient's behavior towards his medication taking. Pharmacy records could help to identify a number of those non-adherent patients. Therefore pharmacists should monitor refill adherence as part of their daily routine and actively provide these data to prescribers on a regular basis.

In conclusion, non-adherence 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 adherence with antihypertensive drugs, before modifying treatment regimens.

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Chapter 3.2

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

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Summary

Background: Discontinuation with treatment is a major problem in the treatment of hypertension. The objective of this study was to assess the association between non-adherence 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 January 1st 1999 and December 31st 2002 was performed. Data from the PHARMO database, a record linkage system currently containing drug dispensing records from community pharmacies and linked hospital discharge records of approximately 2,000,000 subjects, were used. 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, 9,111 cases and 9,111 matched controls were identified. The percentage of non-adherent patients (adherence<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 of 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: Among patients who start antihypertensive monotherapy, non-adherence is often followed by discontinuation of this antihypertensive treatment. The pharmacy medication history is a valuable tool for pharmacists and physicians to identify patients who have a high risk of discontinuation with antihypertensive treatment.

Background

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 randomized controlled trials (RCTs)[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 adherent 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 treatment[4-14]. Initial non-adherence, 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-adherence and discontinuation by using pharmacy records.

Methods

Data source

Data from the PHARMO database, a record linkage system currently containing drug dispensing records from community pharmacies and linked hospital discharge records of approximately 2,000,000 subjects, were used. This database covers a well-defined geographically diverse, drug-insured population of residents of 50 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 were excluded[15]. The data registered in the PHARMO database include age and gender of the patient, name, dispensing date, 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

January 1st 1999 and December 31st 2002 and who collected more than one prescription. These patients were followed until the end of data collection (December 31st 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[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 blockers) 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 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 2 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 substantially 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 which they were matched (figure 1)[19]. Cases were matched to controls (1:1) on age (within a 3 year 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.

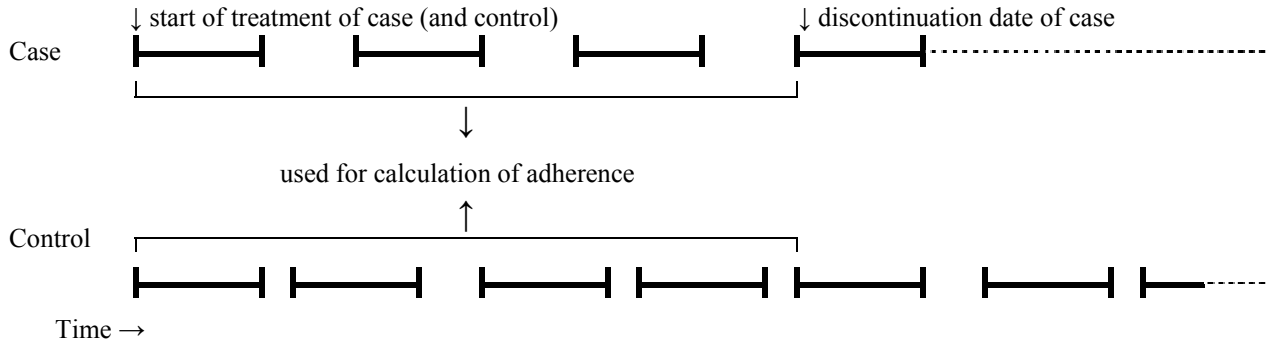

Figure 1: method of calculation of adherence for cases and their matched controls; for the cases adherence was calculated by dividing all theoretical durations of the prescriptions before the last one, by the time between the start date of treatment and the start date of the last prescription; for matched controls adherence was 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.

Definition of adherence and potential confounding factors

Adherence 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 an adherence below 80% was considered non-adherent. In a sensitivity analyses we studied the influence of different definitions of adherence on the association between adherence and discontinuation. Potential confounders that were assessed prior to the index date included: use of specific co-medication, first prescriber, being treated with a PDD<DDD, hospitalization for cardiovascular diseases such as ischemic 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 analyze differences in baseline characteristics between cases and controls. To analyze the association between initial non-adherence 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 9,111 cases and 9,111 matched controls meeting the inclusion criteria. Baseline 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 hospitalizations.

Table 1: baseline characteristics of the study population

	Cases (N=9,111)	Controls (N=9,111)	P-value
Males	3,764 (41.3%)	3,764 (41.3%)	1
Age (years)	58.3 (±16.0)	58.5 (±15.6)	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	3,810 (41.8%)	3,810 (41.8%)	
• 60-79 years	3,467 (38.1%)	3,467 (38.1%)	
• ≥ 80 years	814 (8.9%)	814 (8.9%)	
PDD<DDD	3,887 (42.7%)	3,902 (42.8%)	0.88
Duration of use (days)	90.2 (±153.1)	88.4 (±150.5)	0.43
First prescriber			P<0.001
• General practitioner	6,870 (75.4%)	6,932 (76.1%)	
• Internist	1,042 (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
• Antidiabetic drugs	529 (5.8%)	20 (0.2%)	P<0.001
Prior cardiovascular hospitalizations			
• Ischemic 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 (0.0%)	P<0.001
Antihypertensive monotherapy			1
• Diuretics	2,700 (29.6%)	2,700 (29.6%)	
• Beta-blockers	4,252 (46.7%)	4,252 (46.7%)	
• Calcium channel blockers	739 (8.1%)	739 (8.1%)	
• ACE-inhibitors	906 (9.9%)	906 (9.9%)	
• Angiotensin II receptor blockers	435 (4.8%)	435 (4.8%)	
• Miscellaneous	79 (0.9%)	79 (0.9%)	
• Average adherence	93.5% (±11.5)	96.6% (±9.6)	P<0.001

We found differences between cases and controls in adherence (table 2). The average adherence among the cases was slightly, but significantly (p<0.001), lower among cases. The percentage of non-adherent patients (adherence<80%)

among the cases was 14.0% vs. 5.8% among controls (crude OR 2.86 [95% CI: 2.55-3.20]). After adjustment for PDD, first prescriber, co-medication, prior cardiovascular hospitalization and initial type of antihypertensive monotherapy, non-adherent patients still had a 2.86 times higher chance on discontinuation compared to adherent patients [95% CI: 2.52-3.24].

Table 2: association between non-adherence and discontinuation with treatment for patients who used monotherapy (N=9,111)

	Cases[a]	Controls[a]	OR (95% CI)	OR (95% CI)[b]
Non-adherent	1,277 (14.0%)	532 (5.8%)	2.86 (2.55-3.20)	2.86 (2.52-3.24)
Gender				
• Males (N=3,764)	485 (12.9%)	218 (5.8%)	2.61 (2.18-3.12)	2.52 (2.05-3.10)
• Females (N=5,347)	792 (14.8%)	314 (5.9%)	3.03 (2.62-3.52)	3.06 (2.61-3.59)
Type of antihypertensive				
• Diuretics (N=2,700)	494 (18.3%)	208 (7.7%)	2.96 (2.45-3.57)	3.13 (2.54-3.85)
• Beta-blockers (N=4,252)	507 (11.9%)	228 (5.4%)	2.53 (2.13-2.97)	2.54 (2.11-3.06)
• CCBs (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)
• ARBs (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)
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=3,810)	538 (14.1%)	230 (6.0%)	2.74 (2.31-3.26)	2.70 (2.24-3.26)
• 60-79 years (N=3,467)	455 (13.1%)	168 (4.8%)	3.32 (2.71-4.05)	3.46 (2.73-4.38)
• ≥ 80 years (N=814)	102 (12.5%)	57 (7.0%)	2.00 (1.34-2.86)	1.93 (1.30-2.87)
Duration of use				
• < 90 days (N=7,273)	995 (13.7%)	401 (5.5%)	3.02 (2.65-3.45)	3.10 (2.67-3.59)
• ≥ 90 days (N=1,838)	282 (15.3%)	130 (7.1%)	2.41 (1.92-3.01)	2.28 (1.79-2.92)

CCBs=calcium channel blockers; ARBs= angiotensin II receptor blockers; a: number of non-adherent patients/all patients (% non-adherence among all patients); b: adjusted for use of specific co-medication, hospitalization for cardiovascular diseases, type of prescriber and PDDs

Some small but not significant differences in the association between non-adherence 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 adherence 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 antidiabetic drugs) and prior cardiovascular hospitalizations (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 hospitalized for cardiovascular disease in the year prior to study entrance had a much lower risk of discontinuation, the lowest risk was observed for hospitalization for arrhythmias (OR 0.021 [95% CI: 0.005-0.085]), the highest risk was observed for congestive heart failure (OR 0.076 [95% CI: 0.010-0.59]). The same holds for the use of specific co-medication, the use of antidiabetic medication (OR 0.068 [95% CI: 0.043-0.11]), lipid lowering medication (OR 0.043 [95% CI: 0.026-0.073]) 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 analyzed the results for different cut-off values of adherence (figure 2). Using cut-off values between 60 and 100%, the association between initial non-adherence and discontinuation remained essentially the same with ORs varying from 1.33 (<60%) to 2.19 (<100%) after adjustment. As is shown in figure 2, the strongest association was observed around 80%, the cut-off value we used. 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% of the controls became cases later on. Of those controls 0.21% was non-adherent after becoming a case indicating that the sampling procedure did not cause a decrease of the difference in number of non-adherent patients between cases and controls.

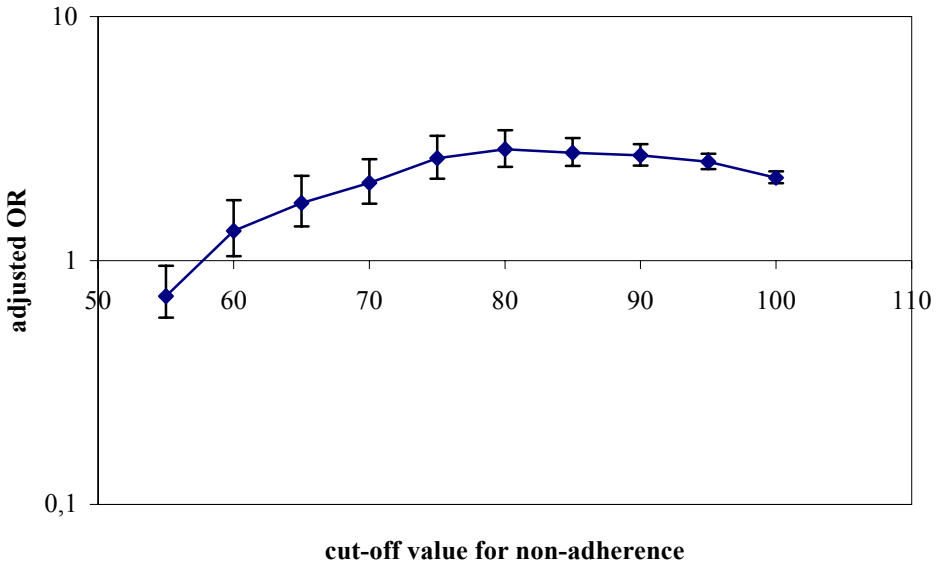

Figure 2: influence of variation of cut-off value for non-adherence on the association between non-adherence and discontinuation (95% CI)

Discussion

The purpose of our study was to assess the association between non-adherence with the initially prescribed antihypertensive monotherapy and discontinuation of this drug and thus antihypertensive treatment in general. To our best knowledge, this relationship has never been studied before. We have found that patients who are non-adherent with their monotherapy have a 2.86 times higher chance on complete discontinuation with this drug and thus antihypertensive treatment in general compared to adherent patients. In addition, we have found a lower risk of discontinuation among patients 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-adherent patients (14.0% among cases and 5.8% among controls). The low number of non-adherent patients may be caused by the fact that we used a database containing computerized pharmacy records, potentially overestimating adherence. 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.

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-adherence 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 (categorized in PDD<DDD and PDD≥DDD) did not have any influence on the magnitude of the association. Furthermore, the number of patients who started with a PDD≥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 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 heart failure. The direction towards which this influenced our results remains unclear.

The PHARMO-database used in this study is virtually complete with regard to drugs dispensed to patients and computerized pharmacy records have shown to be a reliable source of drug exposure as estimated in a home inventory [15,21,22]. Adherence calculated by using pharmacy records could be considered as the maximum possible adherence, the actual adherence being (much) lower. Therefore, the patients we have found to be non-adherent will certainly be non-adherent because they could not have medication available from a previous dispensing. Adherence assessed using pharmacy records was previously found to

significantly correlate with adherence as measured with other methods such as pill counts, self-reports and electronic monitoring, although the strength of those correlations was moderate[23,24].

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 adherence as part of their daily routine and actively provide these data to prescribers on a regular basis. Physicians should detect the reasons for non-adherence during consultations and depending on the reason for dissatisfaction, adherence-enhancing strategies should be directed to these non-adherent patients[3,25-28]. The effectiveness of interventions specifically targeted to non-adherent patients assessed 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-adherence 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 of discontinuation. This information may be used by pharmacists and physicians to focus on improving continuation and adherence to decrease cardiovascular morbidity and mortality in patients who start using antihypertensive monotherapy.

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Chapter 4

Adherence and persistence with antihypertensives in daily practice

Chapter 4.1

Rate and determinants of 10-year persistence with antihypertensive drugs

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Summary

Background: Non-persistence with treatment constitutes a major barrier to reach controlled blood pressure. The objective of this study was to assess the proportion of patients that started with antihypertensive drug treatment and persisted with treatment for at least 10 years.

Methods: A retrospective cohort-study was performed, using the PHARMO record linkage system currently containing drug-dispensing records from community pharmacies and linked hospital discharge records of approximately 2,000,000 subjects. Patients who started using antihypertensive drugs (more than one prescription) in 1992 and did not receive a prescription for any antihypertensive drug in the 365 days preceding the first prescription were included. The main outcome measure was persistence with antihypertensive drugs until 10 years.

Results: Among a total of 2,325 patients, who started using antihypertensive drugs, 39% used continuously during the 10 years of follow-up. About 22% temporarily discontinued and restarted treatment, whereas 39% of the patients discontinued permanently. Older patients were more persistent than younger patients (20-39 years: OR 2.08 [95% CI: 1.52-2.84]; 40-59 years: (reference), ≥60 years: OR 0.69 [95% CI: 0.54-0.89]). More patients who started with diuretics (reference) and beta-blockers (OR 1.15 [95% CI: 0.87-1.52]) discontinued compared to those who started with dihydropyridine calcium channel blockers (OR 0.54 [95% CI: 0.34-0.84]) and ACE-inhibitors (OR 0.38 [95% CI: 0.27-0.55]). Patients who started with combination therapy (OR 0.29 [95% CI: 0.14-0.54]) compared to diuretics or patients who were initially treated by a cardiologist (OR 0.82 [95% CI: 0.61-0.97]) or internist (OR 0.80 [95% CI: 0.62-0.98]) compared to general practitioners, also showed higher persistence.

Conclusion: Long term persistence in daily practice is low and should be considered in the choice of a first line antihypertensive agent.

Background

According to the latest report from the World Health Organization, an estimated 17 million people will die in 2005 of cardiovascular diseases world wide[1,2]. High blood pressure is one of the most preventable causes of these premature deaths. More than 40% of the population in the industrialized countries will suffer from hypertension in 2025[3]. To reduce this cardiovascular morbidity and mortality, a large number of antihypertensive drugs are available and effective, as randomized clinical trials from 1967 onwards have demonstrated[4]. However, these experimental controlled studies lack the ability to demonstrate the problem of discontinuation with treatment in daily practice. A number of population-based studies have demonstrated worrisomely high discontinuation rates varying from 3% to 81%, after one year[5-14]. However, the majority of the patients with a diagnosis of hypertension, need to take antihypertensives for the rest of their lives. Hitherto, the population-based study with the longest follow-up was the study of Conlin et al. reporting four-year discontinuation rates in the US Merck-Medco population[7]. In this study, we report 10-year discontinuation rates of patients starting with the use of antihypertensives in 1992.

Methods

Data source

Data for this study were obtained from the PHARMO medical record linkage system (PHARMO RLS) in The Netherlands. The PHARMO RLS currently includes drug-dispensing records from community pharmacies and hospital discharge records of all 2,000,000 community dwelling inhabitants of 50 medium sized areas in The Netherlands. For all residents, the drug-dispensing records are linked to hospital discharge records of the same patient based on characteristics such as date of birth, gender and code for the general practitioner. The computerized drug-dispensing histories contain data concerning the dispensed drug, type of prescriber, dispensing date, dispensed amount, prescribed dose regimen and the prescription length. 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. Drug names are coded to the Anatomical Therapeutical Chemical (ATC) classification. The hospital records include detailed information concerning the primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All hospital admission and

discharge records were coded according to the ICD-9-CM. 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[15].

Patients

We used data of patients who used no antihypertensive agents during 1991 and presented their first prescription for any drug at least one year prior to the first prescription of an antihypertensive drug to ensure that our patients were starters. In addition, these patients presented their first prescription for a single antihypertensive drug between January 1st and December 31st. These patients were followed until the end of data collection (December 31st 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. Patients were excluded if either before or 30 days after the first prescription for an antihypertensive drug, they had also filled a prescription for short or long acting nitrates, antiarrhythmics, digoxin, anticoagulants, loop diuretics or anti-migraine medication. The rationale behind this was based on the assumption that continuous use of these medications might indicate treatment of a disease other than hypertension (alone) e.g. angina pectoris, heart failure, migraine etc. For the same reason we excluded patients who were hospitalized for cardiac disease (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) prior to the index date. All prescription drugs were coded according to the ATC classification system[16]. We categorized antihypertensives as thiazide diuretics (ATCcode C03A/C03B/C03EA), beta blocking agents (ATCcode C07A/C07B/C07C, except propranolol if the label indicated use for tension or anxiety, and sotalol), dihydropyridine calcium channel blockers (ATCcode C08CA/C08G), ACE-inhibitors (ATCcode C09A/C09B) and alpha-blockers (ATCcode C02CA/C02LE). Patients could not be categorized as starting with angiotensin II receptor blockers (ATCcode C09C/C09D) as this type of antihypertensive was not available in 1992. However for the calculation of adherence to treatment (discussed below) we defined angiotensin II receptor antagonists as a separate class next to ACE-inhibitors. Patients starting with other types of antihypertensives were excluded. Patients who did not present a second prescription in the 365 days following the first prescription were excluded because

continuous use might not be indicated. Patients younger than 20 years were also excluded since these patients are most likely to have secondary hypertension. All patients had complete information on age, gender, prescribed dose or type of initially prescribed antihypertensive drug.

Definition of persistence and adherence

Antihypertensive drug use was evaluated in 365-day intervals following the start date of the first prescription. Patients were considered as user during an interval if two or more prescription were collected. For patients who used only one class of antihypertensives during an interval, adherence was calculated by dividing the sum of the durations of the prescriptions during each interval by the time between the start date of the first prescription and the last prescription for which an end date was available in that interval. For patients who used more than one class of antihypertensives during an interval, adherence was calculated by dividing the sum of the durations of the prescriptions during each interval by the time between the start date of the first prescription and the last prescription for which an end date was available in that interval for each class. In case of two or more simultaneously used classes of antihypertensives, the average was calculated based on length of use, according to Steiner et al.[17]. Patients who collected at least two prescriptions for an antihypertensive drug during each of the 10 intervals were considered as 10 year persistent.

Definition of potential determinants and discontinuation

Co-medication prior to the index date was assessed: lipid lowering drugs (ATCcode C10), antidepressants (ATCcode N06A), antiasthmatic drugs (ATCcode R03), antiglaucoma drugs (ATCcode S01E), antiosteoporotic drugs (ATCcodes A12A, A12CD, A11CC, M05A, G03C), antiparkinsonian drugs (ATCcode N04) and antidiabetic drugs (ATCcode R10). Type of first antihypertensive drug class was assessed, as specified above; patients who started with two or more antihypertensive drug classes or were treated with a combination pill were classified as starters with more than one antihypertensive. In addition, type of prescriber (general practitioner, internist, cardiologist, other) and type of insurance as an indicator of socioeconomic status (private or public) were also considered as potential determinants.

Statistical methods

Binary logistic regression was used to calculate Odds Ratio's (OR) of determinants of discontinuation after 10 years using SPSS 10.0 for Windows. Potential predictors of discontinuation that were significant at the $P<0.10$ level in the univariate analysis were considered in the multivariate analysis.

Results

A total of 8,035 patients presented their first prescription for an antihypertensive between January 1st and December 31st 1992. Of these patients 2,658 patients were excluded since either before or 30 days after the first prescription for an antihypertensive drug, they had also filled a prescription for short or long acting nitrates, antiarrhythmics, digoxin, anticoagulants, loop diuretics or anti-migraine medication. In addition, 30 patients who were hospitalized for cardiac disease prior to the index date were excluded. Patient who started with antihypertensives other than thiazides, specific beta-blockers, dihydropyridine calcium channel blockers, ACE-inhibitors or alpha-blockers (932 patients) were excluded. Two thousand and sixty patients who did not present a second prescription in the 365 days following the first prescription were excluded because continuous use might not be indicated. Forty-five patients were younger than 20 years. A total of 2,325 patients met our inclusion criteria. Baseline characteristics of the cohort are shown in table 1.

Table 1: baseline characteristic of the study population

	Number (%) or mean (SD)
Number	2,325
Age	59.7 (±15.5)
• 20-39 years	431 (18.5%)
• 40-59 years	1,027 (44.2%)
• ≥ 60years	857 (37.3%)
Males	838 (36.0%)
First prescriber	
• General Practitioner	2,094 (90.0%)
• Cardiologist	79 (3.4%)
• Internist	128 (5.5%)
• Miscellaneous	24 (1.0%)
Insurance (Public)	840 (36.1%)
Class of initial antihypertensive	
• Diuretics	540 (23.2%)
• Beta-blockers	1,152 (49.5%)
• Calcium channel blockers	180 (7.7%)
• ACE-inhibitors	342 (14.7%)
• Alfa-blockers	31 (1.3%)
• >1 class of antihypertensive	80 (3.4%)
Co-medication	
• Lipid lowering drugs	42 (1.8%)
• Antidepressants	170 (7.3%)
• Antiasthmatic drugs	174 (7.4%)
• Antiglaucoma drugs	47 (2.0%)
• Antiosteoporotic drugs	174 (7.5%)
• Antiparkinsonian drugs	22 (0.9%)
• Antipsychotic drugs	64 (2.7%)
• Antidiabetic drugs	159 (6.8%)

The majority of patients were between 40 and 59 years of age. About two-third was women. Only one-third of the patients were publicly insured. Half of all patients started with a beta-blocking agent and about a quarter with a diuretic.

Persistence with antihypertensive drug treatment

In figure 1, the percentage of users is shown during the 10-year observation period. Of all patients, about 39% used continuously during the 10 years of follow-up. About 22% temporarily discontinued and restarted treatment. The remaining 39% discontinued and did not restart during the follow-up.

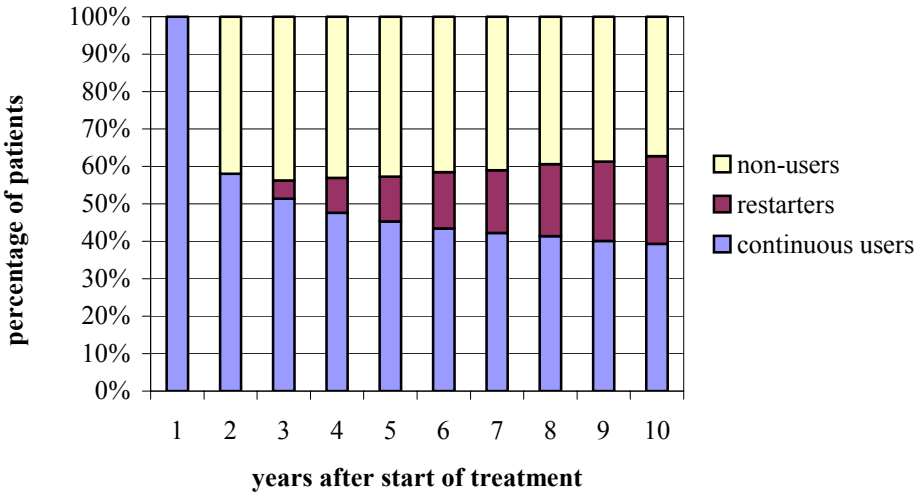

Figure 1: percentage of users in each of the 10 intervals.

In each of the intervals more males than females used continuously (figure 2).

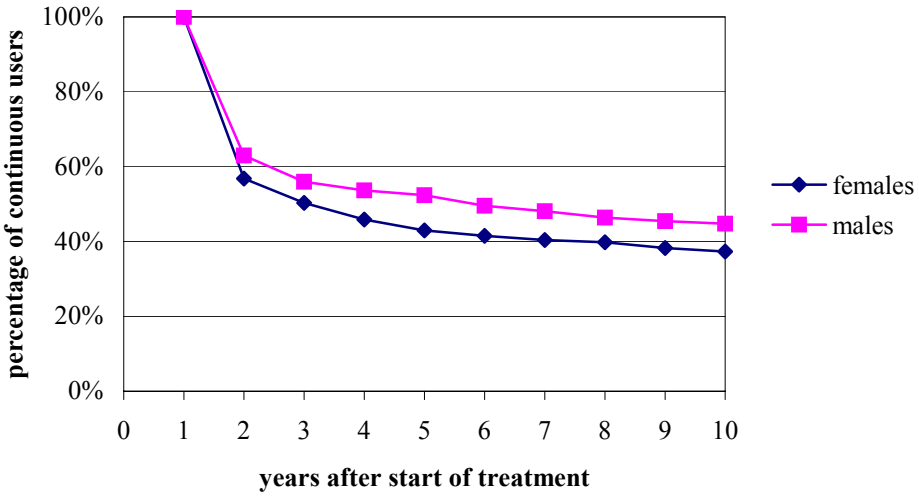

Figure 2: percentage of continuous users in each of the 10 intervals by gender.

More patients who started with conventional antihypertensives (diuretics, beta blockers) discontinued compared to patients who started with ACE-inhibitors or with combination therapy (figure 3).

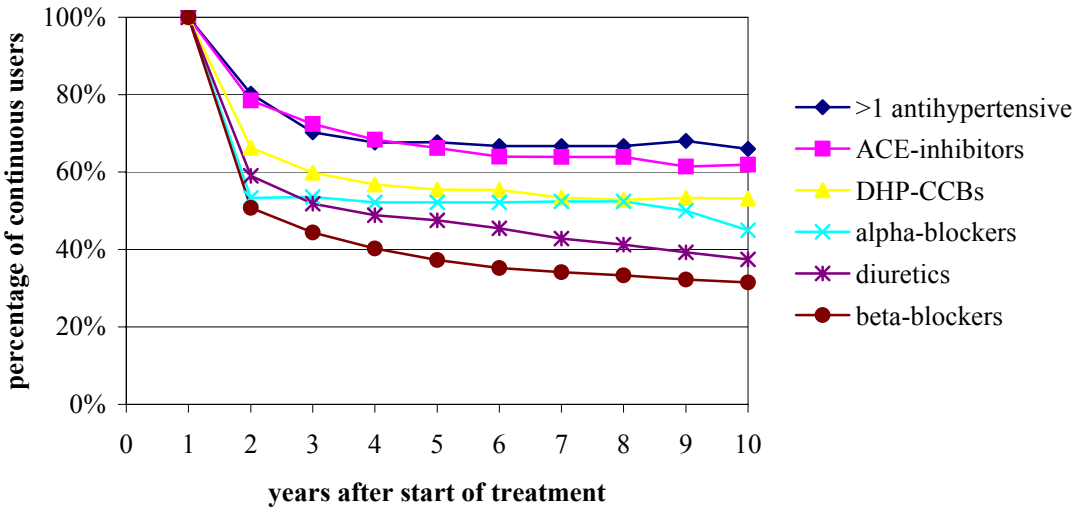

Figure 3: percentage of continuous users in each of the 10 intervals by first antihypertensive

Compared to younger patients, fewer older patients discontinued during our observation period (figure 4).

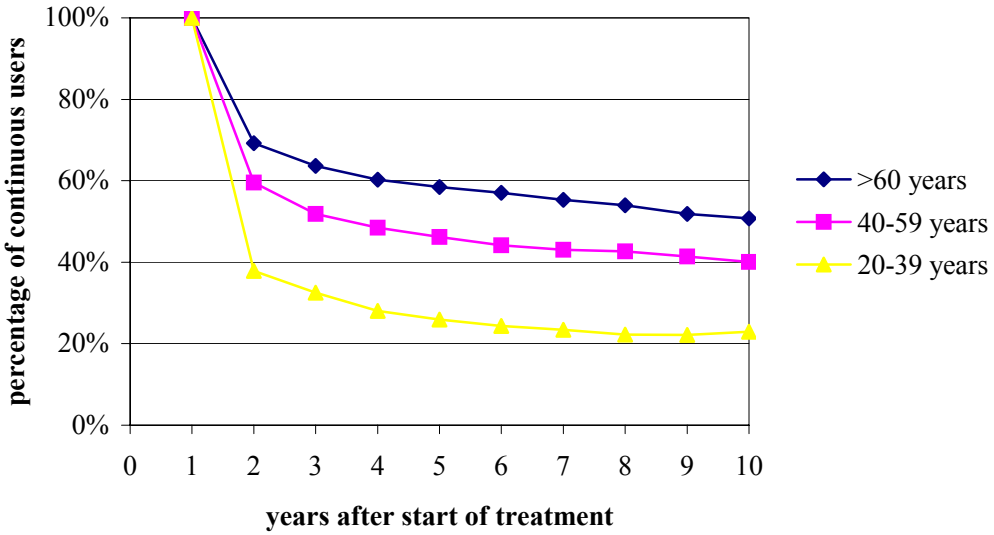

Figure 4: percentage of continuous users in each of the 10 intervals by age group

The estimate for patients who were older than 80 years are less reliable due to a low number of patients in this subgroup. Adherence during each interval differed between continuous users and restarters, continuous users being more adherent (figure 5).

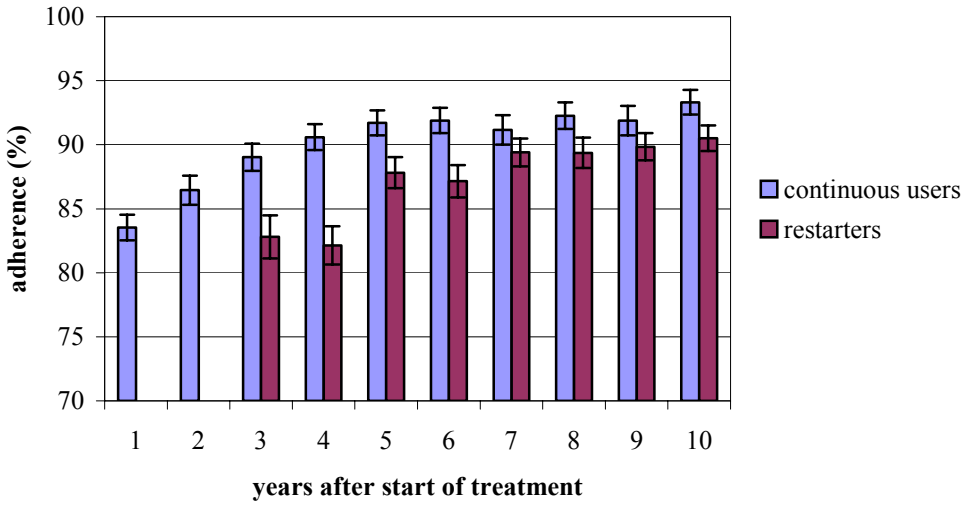

Figure 5: adherence to treatment during each of the 10 intervals among continuous users and restarters.

In table 2 the results of the uni- and multivariate regression analysis are shown. Age, type of first antihypertensive, gender, and type of first prescriber were significant predictors of discontinuation during 10 years. Co-medication prior to the start of antihypertensive treatment and type of insurance were not associated with long-term persistence.

Table 2: Association between potential predictors and discontinuation

	OR (95% CI)	OR (95% CI)[a]
Age group at start		
• ≤ 39 years	2.25 (1.66-3.04)	2.08 (1.52-2.84)
• 40-60 years	Reference	Reference
• ≥ 60 years	0.65 (0.51-0.82)	0.69 (0.54-0.88)
Gender		
• Males	Reference	Reference
• Females	1.36 (1.10-1.69)	1.28 (1.02-1.61)
First prescriber		
• General Practitioner	Reference	Reference
• Cardiologist	0.80 (0.63-0.94)	0.82 (0.61-0.97)
• Internist	0.77 (0.65-0.95)	0.80 (0.62-0.98)
• Miscellaneous	0.95 (0.49-1.99)	1.00 (0.45-2.01)
Initially prescribed antihypertensive		
• Diuretics	Reference	Reference
• Beta-blockers	1.30 (1.03-1.70)	1.15 (0.87-1.52)
• Calcium channel blockers	0.53 (0.34-0.82)	0.54 (0.34-0.84)
• Ace-inhibitors	0.37 (0.26-0.52)	0.38 (0.27-0.55)
• Alfa-blockers	0.75 (0.30-1.82	0.75 (0.30-1.89)
• >1 antihypertensive drug class	0.31 (0.16-0.59)	0.29 (0.15-0.56)
Insurance		
• Private insurance	Reference	Reference
• Public insurance	0.79 (0.64-0.99)	0.86 (0.68-1.08)
Co-medication		
• Lipid lowering drugs	0.86 (0.41-1.79)	NA
• Antidepressants	1.37 (0.91-2.05)	NA
• Antiasthmatic drugs	1.00 (0.66-1.53)	NA
• Antiglaucoma drugs	0.91 (0.41-2.00)	NA
• Antiosteoporotic drugs	1.15 (0.78-1.67)	NA
• Antiparkinsonian drugs	1.44 (0.36-5.67)	NA
• Antipsychotic drugs	1.35 (0.66-2.74)	NA
• Antidiabetic drugs	0.90 (0.35-1.85)	NA

NA=not applicable, a: adjusted for age group, gender, first prescriber, first antihypertensive and type of insurance

Discussion

Despite the evidence that chronic use of antihypertensives reduces the risk of cardiovascular morbidity and mortality, this study demonstrated that only 39% of initially treated patients manage to continue their treatment during 10 years. This clearly demonstrates that in daily practice, the potential benefit, as observed in clinical trials will not be achieved in daily clinical practice. Furthermore, male gender, older age and starting with an ACE-inhibitor were associated with

increased long-term persistence. Also, severity of hypertension, expressed by being initially treated with more than one antihypertensive or being treated by a specialist was associated with increased continuation rates.

The use of pharmacy records is associated with misclassification with regard to the actual use and information bias may very well have occurred. Patients may collect prescriptions but may not use it resulting in misclassification of persistent users and of adherence. Misclassification is probably non-differentially distributed among the subgroups. This kind of misclassification would decrease the associations we observed. The total proportion of patients discontinuing would be larger in case of information bias, the actual problem of non-persistence being even larger. A number of patients may have discontinued on a doctor's advice introducing misclassification bias in our estimates. Although it seems implausible that those patients were no longer hypertensive, doctors may decide that side-effects or other problems associated with the use do not counterbalance the potential benefits with regard to protection against cardiovascular disease. It remains difficult to state whether this has been differentially distributed between subgroups. With regard to the overall proportion of patients discontinuing, it would have caused an overestimation of the proportion of patients discontinuing not on a doctor's advice. The association of determinants would be underestimated, the actual associations being even stronger. In addition, our data do not allow the diagnosis of hypertension to be confirmed. As a previous study demonstrated, in The Netherlands about 80% of the prescriptions for antihypertensives are actually for hypertension. Although we excluded patients based on co-medication indicating other cardiovascular diseases such as nitrates in case of angina pectoris, we cannot be completely certain that this excluded all patients with other diagnoses. Continuation of treatment will be different if hypertension is for instance accompanied by angina pectoris. Furthermore, this difference in persistence due to cardiovascular comorbidity may be non-differentially distributed among subgroups defined by type of first antihypertensive.

We have chosen to classify our patients as users if they collected more than one prescription during each 365-day interval. Theoretically this would allow a patient to collect a prescription for one day on day one of a certain interval and to return on day 365, the adherence of this patients being 1 divided by 365. If this scenario

would have occurred frequently and we included large numbers of patients with low adherence, the average adherence during each interval would be very low. However, we have found that in year one, the year with the lowest adherence, the average adherence among all patients was about 84%, gradually increasing to 93% in year 10. This means that the scenario described above has not frequently occurred. Our method may probably be less applicable to shorter observation periods. Another limitation is that in the determination of discontinuation of patients starting with combination therapy, we did not differentiate between patients starting with two or more separate tablets and patients starting with a combination tablet. Single pill combinations have demonstrated to lead to higher persistence compared to the simultaneous use of two separate tablets[18].

One of the strengths of our study is that we were able to observe the population in daily practice. In clinical trials adherence and persistence are enhanced to obtain the best estimate of effect estimates[19]. In addition, RCTs tend to be short in duration often not exceeding five years and involve highly selected patients. Furthermore, most studies on persistence and adherence with antihypertensives report data after a one-year period, the largest period being four years[5-14]. To our best knowledge, no data have been published on persistence with antihypertensive drugs beyond four years. Finally, we were able to study a relatively large number of patients.

Our results demonstrate that the percentage of patients continuing after one year is about 61%. After 10 years 39% of the total population is still classified as a continuous user. About 22% of the patients restarted using during this period. This suggests that most patients, about 39% decide during the first year to continue or not and that this decision is likely to last for a long time. Other studies found different proportions of patients discontinuing after one year[5-14]. The difference observed with regard to the type of antihypertensive, also observed in other studies, are probably due to side-effects accompanying the use of the various agents[20]. Newer types of antihypertensives may be associated with fewer side-effects compared to thiazides and beta-blockers[21].

Although this study has been conducted in the Netherlands, the results may be applicable to other western countries as well. Most of these countries use guidelines similar to international recommendations and the antihypertensives

available are the same[21-24] The antihypertensives used in 1992 are not very different compared to the antihypertensives used in 2005. In 1992 hydrochlorothiazide, atenolol, metoprolol, nifedipine and enalapril were already available. Currently, angiotensin II receptor blockers are also available. In one trial losartan was more effective than atenolol[25]. Persistence with angiotensin II receptor blockers in short-term studies has been demonstrated to be similar or even superior to ACE-inhibitors[5,7-9,26,27]. Long-term persistence with these agents remains to be assessed.

The clinical implications of our study are important. The results of our study could be used to identify patients with a higher risk of discontinuation. Discontinuation with treatment is a considerable problem. In the assessment of effectiveness of pharmacological treatment, long-term persistence rates should also be considered, next to reduction in morbidity and mortality observed in RCTs. Most adherence and persistence enhancing strategies focusing on patient education are time consuming and often not very effective[28-30]. Therefore, initially treating patients with ACE-inhibitors could be a straightforward approach to increase continuous use. Although effectiveness with regard to reduction of cardiovascular morbidity and mortality seems to be in favor of thiazide diuretic therapy, the higher discontinuation rates may counterbalance the relatively small advantage with regard to effectiveness and costs[4]. Hence, guidelines should also take long-term persistence into account with regard to the choice of the initial agent[21-24].

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Chapter 4.2

Rates and determinants of reinitiating antihypertensive therapy after prolonged stoppage: a population based study

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Submitted

Summary

Background: Population-based studies have demonstrated that a large proportion of patients discontinue treatment after initiation, but many patients then resume therapy. Little is known about patterns of restarting antihypertensive drugs after a prolonged period of discontinuation.

Methods: A retrospective cohort-study was conducted among new users of blood pressure (BP) lowering medication in the PHARMO database in The Netherlands, who had a period of at least 180 days without such medication. A multivariable Cox-proportional hazard analysis was used to explore the baseline variables associated with reinitiating treatment. Case-crossover analysis was used to evaluate determinants of reinitiating treatment.

Results: A total of 35,714 patients were identified as initiating BP-lowering treatment during the period January 1st 1999 to June 30th 2004 were identified. Of the 18,357 (51.4%) patients who discontinued BP-lowering treatment, 19.3% restarted treatment within one year and 60.7% restarted within six years. With every additional year on therapy, patients were more likely to restart (OR: 1.38 [95% CI: 1.34-1.42]). The majority (58.1%) of patients returned to the same drug class they were using at the time of discontinuation. The case crossover analysis revealed that hospitalization for cardiovascular disease (OR: 2.20 [95% CI: 1.84-2.63]) as well as refilling of another cardiovascular medication (OR: 1.25 [95% CI: 1.11-1.40]) were each independently associated with reinitiating treatment. Refilling non-cardiovascular medications was not associated with reinitiating treatment (OR: 1.03 [95% CI: 0.97-1.10)]).

Conclusion: Physicians should be aware that many patients have prolonged periods of discontinuation during the use of BP-lowering medication, and that most of these patients will eventually resume therapy. Ongoing refilling other medications is not associated with reinitiating treatment. This suggests that for some patients, the decision to discontinue may be drug specific rather than a behavioral characteristic applicable to all chronic treatments. Hospitalization for a cardiovascular event may provide an opportunity to reinforce the need to resume antihypertensive therapy.

Background

Hypertension is the most common risk factor for cardiovascular morbidity and mortality[1]. To reduce the burden of hypertension, many different blood pressure (BP) lowering medications are available. These drugs have demonstrated efficacy in lowering blood pressure and reducing the incidence of cardiovascular illness and death[2]. Nevertheless, only 30% of patients with hypertension reach their target blood pressure[3,4]. It is estimated that among the patients not reaching target blood pressure, half of these failures can be attributed to medication non-adherence[5,6]. This is likely related to the asymptomatic nature of high blood pressure, which may be particularly relevant in patients using BP-lowering medication for primary prevention[7]. Several population-based studies[8] have assessed rates of non-adherence, and all report worrisomely high discontinuation rates after the initiation of treatment.

In a previous study over a time period of 10 years, we found that approximately 30% of the patients that discontinued, ultimately reinitiated treatment[9]. Other investigators have found that of patients starting treatment between 1990 and 1993, nearly a third restarted treatment after a 90-day episode of discontinuation[10]. Similar findings were observed in a population initiating treatment between 1997 and 2000[11]. Little is known about the process of restarting BP-lowering treatment. In a study of adherence with osteoporosis medication, we observed that recent hip-fractures, discharge from nursing homes and bone mineral density testing were associated with reinitiating treatment[12]. In the present study, we examined the dynamic process of discontinuing and restarting treatment in a population of patients starting antihypertensive medications.

Methods

Data source

Data for this study were obtained from the PHARMO record linkage system (PHARMO) in The Netherlands. PHARMO currently includes drug-dispensing records from community pharmacies and hospital discharge records of all 2,000,000 community dwelling inhabitants of 50 medium-sized areas in The Netherlands. The computerized drug-dispensing histories contain data concerning the dispensed drug, age and gender, type of insurance, type of prescriber, drug dispensed, dispensing date, dispensed amount, prescribed dose regimen and

prescription length. 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. Drug names are coded according to the Anatomical Therapeutical Chemical (ATC) classification system. The hospital records include detailed information concerning the primary and secondary diagnoses, procedures and dates of hospital admission and discharge. All hospital admission and discharge records were coded according to the ICD-9-CM classification system. Prescribed daily dose (PDD) was expressed as number of defined daily doses (DDD), the dosage for the main indication of a drug according to the WHO[13].

Patients

From a cohort of patients who started using BP-lowering drugs between January 1st 1999 and June 30th 2004, we selected a cohort of patients who started using drugs for hypertension as primary prevention. Patients were required to have presented their first prescription for any drug (for any indication) at least one year prior to the first prescription for a BP-lowering medication. BP-lowering medications were categorized as diuretics (thiazides (e.g. hydrochlorothiazide) and sulphonamides (e.g. chlorthalidone), ATCcode C03A/C03B/C03EA), beta blocking agents (ATCcode C07A except propranolol if the label indicated use for tension or anxiety, and sotalol), dihydropyridine calcium channel blockers (DHP-CCBs, ATCcode C08CA/C08G), ACE-inhibitors (ATCcode C09A) and angiotensin II receptor blockers (ARBs, ATCcode C09C)[13]. Patients, who used more than one BP-lowering drug, either in a combination pill or as two or more separate tablets, were categorized as users of combination therapy, except users of diuretics with potassium sparing diuretics (ATCcode C03EA).

Patients who *started* with miscellaneous BP-lowering medication (ATCcode C02) were excluded. This was done to avoid misclassification because the majority of these patients started with alpha-blockers, which are also indicated for benign prostate hypertrophy. However, patients were allowed to use miscellaneous BP-lowering medications (including alpha-blockers) at discontinuation or at restart, because it is more likely that once another BP-lowering drug has been prescribed, the next prescription (e.g. for an alpha-blocker) is also for cardiovascular disease, potentially in combination with another condition. Patients who also used anti-migraine medication in the 365 days prior to the start of treatment were also excluded because the BP-lowering medication was potentially prescribed as

prophylactic migraine treatment. The rationale behind this was that the use of these drugs for these other indications (BPH and migraine) may be accompanied by different adherence behavior and that the problem of interrupted use is of a different relevance. Patients who were younger than 45 years at the time of discontinuation were excluded.

To increase the likelihood that our patients were using the BP-lowering drugs for hypertension, we also excluded patients who refilled a prescription for nitrates, cardiac glycosides, loop diuretics, anti-arrhythmics or platelet aggregation inhibitors in the 180 days preceding discontinuation. Patients previously hospitalized for cardiovascular disease (defined below) were excluded to increase the likelihood that patients were being treated for primary prevention. This exclusion algorithm has been used in one of our previous studies[9] and in other studies[10,11,14]. Patients were followed until the end of data collection (December 31st 2004) 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. Patients were censored if their follow up in PHARMO was only determined by BP-lowering medication use to circumvent differential misclassification of being at risk for restart.

Definition of discontinuation

Medication episodes were calculated using the dispensing date and theoretical end date of a prescription for a BP-lowering drug. The theoretical end date of a prescription was determined by dividing the number of tablets by the prescribed daily dose. If a prescription was refilled before an existing one theoretically ended, we assumed that the next one was started after the previous one was completed. Patients hospitalized were assumed to have received their drug in hospital.

Patients were defined as discontinuers if the gap between the theoretical end date of a prescription and the next one was at least 180 days (figure 1).

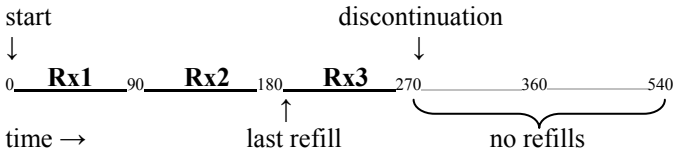


Figure 1: definition of discontinuation

The theoretical end date of the past prescription was then defined as the discontinuation date. For patients using more than one BP-lowering drug, the last theoretical end date was defined as the discontinuation date, regardless of whether a simultaneously used BP-lowering drug was discontinued earlier, to increase specificity. Switching was not considered as discontinuation. In a sensitivity analysis, we assessed the associations between patient characteristics and discontinuation defined as a gap of 90 or 270 days.

Definition of patient characteristics

We first defined patient characteristics at the theoretical end date of the prescription before the 180-day gap and for those who returned to treatment, at restart. We did not include age as a linear variable but categorized age in 10-year age groups because of the possibility of a non-linear association. We also studied the type of prescriber of the BP-lowering drugs at discontinuation (general practitioner, internist, cardiologist, other). Hospitalizations for cardiac disease (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) were identified. Co-medication considered included: lipid lowering drugs (ATCcode C10), antidiabetic drugs (ATCcode R10), nitrates (ATCcode C01DA), loop diuretics (ATCcode C03D), anti-arrhythmics (ATCcode C01B, verapamil, diltiazem, sotalol, digoxine), thrombocyte aggregation inhibitors (ATCcode B01AC, including low dose aspirin which is fully covered in The Netherlands), anti-depressants (ATCcode N06A), anti-parkinsonian drugs (ATCcode N04), anti-psychotics (N05A), anti-glaucoma drugs (ATCcode S01E), anti-osteoporosis drugs (ATCcodes A12A, A12CD, A11CC, M05A, G03C) and anti-asthmatic drugs (ATCcode R03B). Type of insurance (public vs. private) was used as an indicator of socioeconomic status. Although costs of medication and co-payment have been associated with low adherence[15-17], this is not relevant in the present study because in The Netherlands, BP-lowering drugs have no co-payment or dispensing fee that is not covered by the insurance company, although privately insured patients often have a small deductible.

Statistical analysis

First, a cohort study was performed. Kaplan-Meier analysis was used to estimate the distribution of time until a patient restarted blood pressure lowering treatment. We analyzed the association between characteristics at the time of discontinuation and reinitiating treatment using Cox-proportional hazards models. Hospitalizations were assessed during treatment and in the year prior to treatment. Co-medication was assessed during the 180 days preceding the theoretical end date of the prescription before the 180-day gap occurred. Next, we performed a case crossover analysis to identify events during the discontinuation period that were associated with reinitiating BP-lowering treatment. Each patient served as his own control thereby removing the influence of characteristics that are constant over time[18]. We compared the incidence of hospitalizations and refilling other medications in the 30 days prior to restart (hazard period) to the incidence 31-60 days prior to restart (control period). Conditional logistic regression was used to analyze the association between events and restart. We tested the influence of the length of our hazard period by reanalyzing the results with 15, 45 and 60-day hazard periods. All analyses were done using SPSS 12.0 for Windows (SPSS Inc., Chicago).

Results

A total of 35,714 patients started use of BP-lowering drugs between January 1st 1999 and July 1st 2004. Of these patients, 18,357 (51.4%) discontinued use for at least 180 days. Characteristics of these patients at discontinuation are shown in table 1. Patients had an average age of 61 years and were predominantly publicly insured (60.1%) and female (65.0%). General practitioners prescribed the majority of prescriptions (87.6%) at discontinuation. At discontinuation, the majority of the patients was on mono-therapy (93.0%), predominantly diuretics and beta-blockers (68.5%), were prescribed to take their BP-lowering drug once daily (95.4%) and were prescribed on average 0.85 DDD per day. The majority (68.5%) used no co-medications at the time of discontinuation and 73.7% were on treatment 180 days or less before discontinuing.

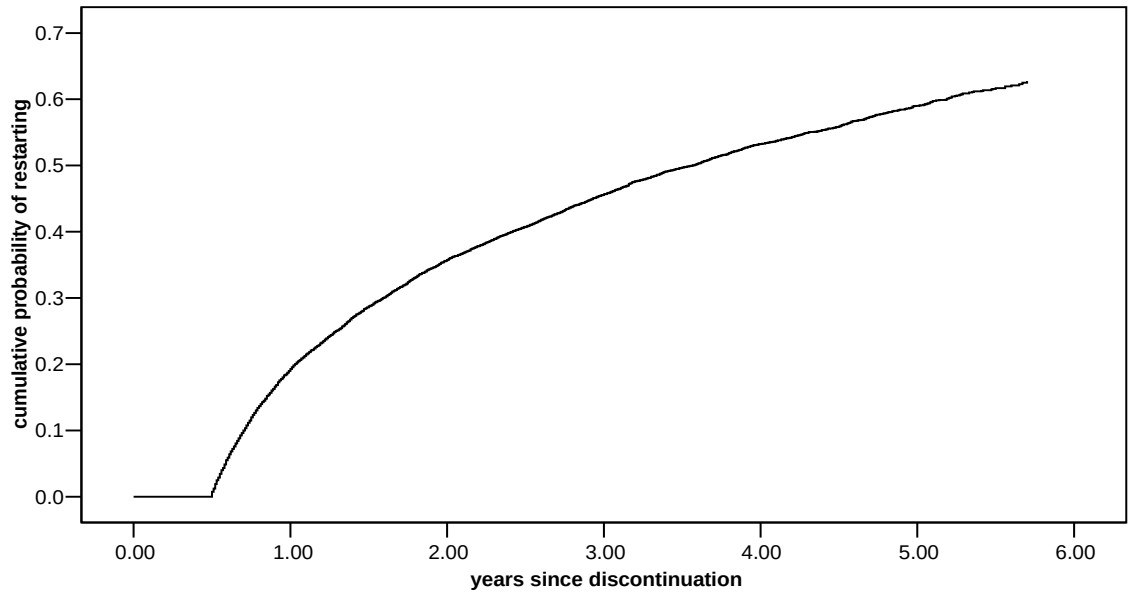
Table 1: patient characteristics at first episode of discontinuation (N=18,357)

	Number (%) or mean (SD)
Sociodemographic characteristics	
Age (years)	60.5 (±11.3)
Age groups	
• 45-54 years	6,987 (38.1%)
• 55-64 years	5,166 (28.1%)
• 65-74 years	3,537 (19.3%)
• 75-84 years	2,168 (11.8%)
• ≥85 years	499 (2.7%)
Gender (females)	11,928 (65.0%)
Insurance (public)	11,027 (60.1%)
Prescriber at discontinuation	
• General Practitioner	16,085 (87.6%)
• Internist	822 (4.5%)
• Cardiologist	500 (2.7%)
• Miscellaneous	950 (5.2%)
Antihypertensive drug at discontinuation	
• Diuretics	5,661 (30.8%)
• Beta-blockers	6,929 (37.7%)
• Dihydropyridine calcium channel blockers	1,319 (7.2%)
• ACE-inhibitors	1,935 (10.5%)
• Angiotensin II receptor blockers	1,221 (6.7%)
• Combination	1,292 (7.0%)
Treatment characteristics at discontinuation	
• Dose frequency (>once daily)	848 (4.6%)
• Prescribed daily dose (DDD)	0.85 (±0.61)
Non-cardiovascular hospitalizations	160 (0.9%)
Number of co-medications at discontinuation	
• 0	12,583 (68.5%)
• 1	4,566 (24.9%)
• ≥2	1,208 (6.6%)
Type of co-medication at discontinuation	
• Lipid lowering drugs	1,237 (6.7%)
• Antidiabetic drugs	1,257 (6.8%)
• Anti-depressants	1,564 (8.5%)
• Anti-parkinsonian drugs	133 (0.7%)
• Anti-psychotics	350 (1.9%)
• Glaucoma drugs	409 (5.7%)
• Anti-osteoporosis drugs	1,195 (6.5%)
• Anti-asthmatic drugs	1,038 (5.7%)

Time on treatment (days)	169.4 (±261.0)
• <181 days	13,532 (73.7%)
• 181-365 days	2,266 (12.3%)
• >365 days	2,559 (13.9%)
Year of discontinuing treatment	
• 1999	2,508 (13.7%)
• 2000	3,380 (18.4%)
• 2001	3,577 (19.5%)
• 2002	3,502 (19.1%)
• 2003	3,498 (19.1%)
• 2004 (until June 30th)	1,892 (10.3%)

Within 1 year after discontinuation, 19.3% of patients returned to treatment. After 2 years 35.7% were on treatment again. At the end of our maximum 6-year follow-up period, 60.7% of the patients were on treatment again. The Kaplan-Meier analysis is shown in figure 2.

Figure 2: Kaplan-Meier estimate of the cumulative probability of restarting treatment



In table 2, patient characteristics that are associated with reinitiating treatment are shown. Middle-aged patients were more likely to reinitiate treatment with increasing age. However, after 65 years of age, the likelihood of reinitiating treatment decreased. Men were more likely to restart treatment after discontinuation (OR 1.14 [95% CI: 1.09-1.20]). Patients who received their BP-

lowering drug at discontinuation from a physician other than a general practitioner were somewhat less likely to restart treatment. Patients who used the newer BP-lowering drugs as well as patients who were on combination therapy were more likely to restart treatment. Those who used antidiabetic drugs (OR 1.24 [95% CI: 1.14-1.35]) were also more likely to restart treatment. Patients using medication for neurological and psychiatric disorders were less likely to restart treatment. The longer a patient was on therapy before discontinuing treatment, the more likely they were to restart. With each additional year on treatment, the probability of restarting treatment increased by 38%.

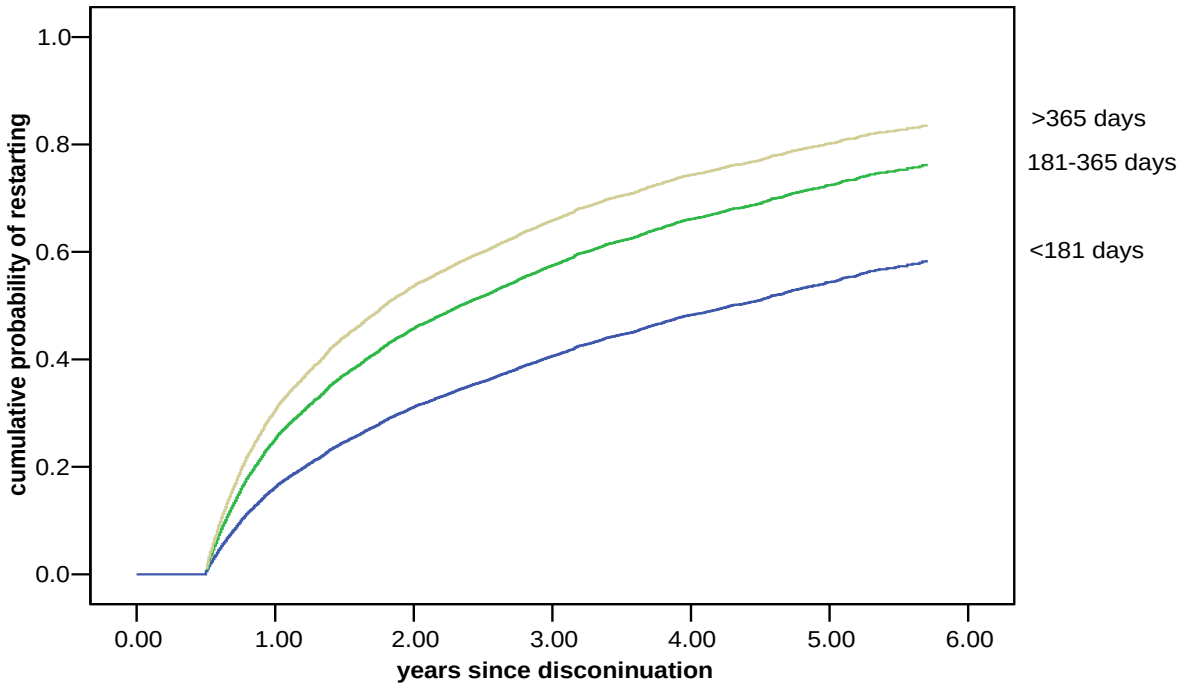
Table 2: Patient characteristics at discontinuation that were associated with reinitiating treatment

	OR (95% CI)	P-value	OR (95% CI)[a]	P-value
Sociodemographic characteristics				
Age groups				
• 45-54 years	1.00 (reference)	<0.001	1.00 (reference)	NA
• 55-64 years	1.12 (1.06-1.19)	<0.001	1.08 (1.02-1.14)	0.010
• 65-74 years	1.29 (1.21-1.37)	<0.001	1.21 (1.14-1.29)	<0.001
• 75-84 years	1.20 (1.12-1.30)	<0.001	1.14 (1.05-1.23)	0.001
• ≥85 years	1.16 (1.00-1.35)	0.045	1.07 (0.92-1.25)	0.356
Gender (males vs. females)	1.20 (1.14-1.25)	<0.001	1.14 (1.09-1.20)	<0.001
Insurance (public)	0.99 (0.94-1.04)	0.635	0.99 (0.95-1.04)	0.783
Prescriber				
• General Practitioner	1.00 (reference)	<0.001	1.00 (reference)	NA
• Internist	0.81 (0.73-0.90)	<0.001	0.94 (0.84-1.04)	0.256
• Cardiologist	0.88 (0.76-1.01)	0.076	0.88 (0.76-1.02)	0.101
• Miscellaneous	0.81 (0.73-0.91)	<0.001	0.85 (0.76-0.95)	0.004
Antihypertensive drug used				
• Diuretics	1.00 (reference)	<0.001	1.00 (reference)	NA
• Bètablokkers	0.82 (0.77-0.87)	<0.001	0.84 (0.79-0.90)	<0.001
• DHP-CCBs	0.96 (0.87-1.05)	0.341	0.96 (0.88-1.06)	0.458
• ACE-inhibitors	1.38 (1.28-1.49)	<0.001	1.20 (1.11-1.30)	<0.001
• Angiotensin II receptor blockers	1.47 (1.34-1.61)	<0.001	1.27 (1.16-1.39)	<0.001
• Combination	1.67 (1.53-1.81)	<0.001	1.57 (1.40-1.75)	<0.001
Treatment characteristics				
• Dose frequency (>once daily)	1.37 (1.24-1.51)	<0.001	1.24 (1.09-1.43)	0.002
• Prescribed daily dose, per DDD	1.08 (1.06-1.09)	<0.001	1.05 (1.03-1.08)	<0.001
• Time on treatment, per year	1.47 (1.43-1.51)	<0.001	1.38 (1.34-1.42)	<0.001
Non-cardiovascular hospitalizations	1.14 (0.89-1.46)	0.298	1.01 (0.79-1.29)	0.95
Co-medication				
• Lipid lowering drugs	1.22 (1.12-1.33)	<0.001	1.05 (0.96-1.15)	0.306
• Antidiabetic drugs	1.57 (1.44-1.70)	<0.001	1.24 (1.14-1.35)	<0.001
• Anti-depressants	0.88 (0.80-0.95)	0.002	0.92 (0.85-1.01)	0.074
• Anti-parkinsonian drugs	0.62 (0.45-0.86)	0.004	0.62 (0.44-0.86)	0.005
• Anti-psychotics	0.76 (0.64-0.92)	0.004	0.81 (0.67-0.98)	0.033
• Glaucoma drugs	1.10 (0.95-1.28)	0.207	1.00 (0.86-1.16)	0.995
• Anti-osteoporosis drugs	0.91 (0.83-1.00)	0.057	1.00 (0.91-1.10)	0.981
• Anti-asthmatic drugs	1.00 (0.90-1.10)	0.938	0.97 (0.88-1.07)	0.534
Year of discontinuing treatment				
• 1999	1.00 (reference)	<0.001	1.00 (reference)	NA
• 2000	1.14 (1.06-1.23)	<0.001	1.10 (1.02-1.19)	0.009
• 2001	1.24 (1.15-1.34)	<0.001	1.13 (1.05-1.22)	0.001
• 2002	1.30 (1.20-1.40)	<0.001	1.13 (1.04-1.22)	0.004
• 2003	1.46 (1.34-1.59)	<0.001	1.17 (1.08-1.29)	<0.001
• 2004	1.60 (1.39-1.84)	<0.001	1.21 (1.05-1.40)	0.009

NA=not applicable; DHP-CCBs=dihydropyridine calcium channel blockers; a: adjusted for all variables in table

Figure 3 presents the Kaplan-Meier analysis stratified by duration of previous antihypertensive drug use. Patients who had a longer previous treatment episode had a higher chance of resuming treatment.

Figure 3: Kaplan-Meier estimate of the cumulative probability of restarting stratified by duration of previous treatment



Only about 46% of patients using DHP-CCBs returned to their old treatment, as were 14.4% of the patients using combination therapy, the latter probably because patients need to be titrated again. Indeed the average PDD at restart was somewhat lower (0.83) than at discontinuation (0.92) for those who restarted. Sixty-seven percent of the patients using beta-blockers at discontinuation resumed beta-blockers. If treatment was modified, the most likely modification was a switch to beta-blockers (26.3%). Only 1.1% switched to miscellaneous BP-lowering drugs, in all cases an alpha-blocker.

Table 3: BP-lowering drugs used at discontinuation and at restart of treatment (N=7,465)

After / Before	Diuretics	Beta-blockers	DHP-CCBs	ACE-Is	ARBs	Combi.	Alpha-bl.[a]	Total
Diuretics	**1,421 (61.6)**	352 (15.3)	67 (2.9)	276 (12.0)	132 (5.7)	46 (2.0)	13 (0.6)	**2,307**
Beta-blockers	281 (11.7)	**1,628 (67.7)**	86 (3.6)	226 (9.4)	135 (5.6)	45 (1.9)	4 (0.2)	**2,405**
DHP-CCBs	60 (11.5)	98 (18.8)	**238 (45.8)**	64 (12.3)	37 (7.1)	17 (3.3)	6 (1.2)	**1,040**
ACE-Is	83 (8.7)	138 (14.4)	43 (4.5)	**553 (57.8)**	111 (11.6)	25 (2.6)	3 (0.3)	**956**
ARBs	44 (7.4)	88 (14.9)	30 (5.1)	65 (11.0)	**328 (55.4)**	34 (5.7)	3 (0.5)	**592**
Combination	103 (15.0)	147 (21.5)	57 (8.3)	101 (14.7)	105 (15.3)	**167 (24.4)**	5 (0.7)	**685**
Total	**1,992 (26.7)**	**2,451 (32.8)**	**521 (7.0)**	**1,285 (17.2)**	**848 (11.4)**	**334 (4.5)**	**34 (0.5)**	**7,465**
Switch to	571 (18.2)	823 (26.3)	283 (9.0)	732 (23.4)	520 (16.7)	167 (5.3)	34 (1.1)	**3,130 (41.9)**
No change	1,421 (61.6)	1,628 (67.7)	238 (45.8)	553 (57.8)	328 (55.4)	167 (24.4)	-	**4,335 (58.1)**

Values are numbers (%); DHP-CCB=dihydropyridine calcium channel blockers; ACE-I=ACE-inhibitors; ARBs=angiotensin II receptor blockers; Combi.=combination therapy; a: patients used no alpha-blockers at discontinuation, hence were not able to restart with alpha-blockers

Table 4 presents the results of the case crossover analysis. The case-cross over analysis demonstrated that patients who were hospitalized for cardiovascular diseases are more likely to restart treatment (OR 2.20 [95% CI: 1.82-2.61]), as were patients refilling cardiovascular co-medication (OR 1.25 [95% CI: 1.11-1.40]). For specific drug classes, only refilling lipid lowering drugs was significantly associated with reinitiating treatment (OR 1.20 [95% CI: 1.00-1.43]). Patients refilling CNS-drugs (OR 1.01 [95% CI: 0.87-1.16]), other chronic co-medication (antidiabetic drugs, glaucoma drugs, osteoporosis drugs, anti-asthmatic drugs) OR 0.98 [95% CI: 0.88-1.09]) or who visited the pharmacy for other refills (OR 1.03 [95% CI: 0.97-1.10]) were not more likely to restart.

Table 4: case crossover analysis of events associated with restarting BP-lowering drug treatment after discontinuation. (N=7,465)

	Control	Hazard	OR (95% CI)	P-value
Cardiovascular hospitalizations	24 (0.3%)	191 (2.6%)	2.20 (1.84-2.63)[b]	<0.001
• Ischemic heart disease	8 (0.1%)	111 (1.5%)	2.35 (1.86-2.87)	<0.001
• Congestive heart failure	1 (0.0%)	19 (0.3%)	2.24 (1.28-3.92)	0.005
• Arrhythmias	8 (0.1%)	28 (0.4%)	1.78 (1.10-2.87)	0.018
• Hypertension	0 (0%)	1 (0.0%)	-	
• Cerebrovascular disease	7 (0.1%)	30 (0.4%)	1.89 (1.21-2.95)	0.005
• Peripheral vascular disease	0 (0%)	2 (0.0%)	-	
Other hospitalizations	8 (0.1%)	15 (0.2%)	1.47 (0.80-2.70)	0.219
			1.46 (0.79-2.69)[b]	0.222
Cardiovascular co-medication	312 (4.2%)	442 (5.9%)	1.25 (1.11-1.40)[b]	0.003
• Lipid lowering drugs	133 (1.8%)	183 (2.5%)	1.20 (1.00-1.43)	0.047
• Nitrates	23 (0.3%)	48 (0.6%)	1.21 (0.85-1.72)	0.289
• Loop diuretics	73 (0.9%)	108 (1.5%)	1.22 (0.96-1.55)	0.108
• Anti-arrhythmics	55 (0.7%)	83 (1.1%)	1.14 (0.86-1.53)	0.359
• Thrombocyte aggregation inhibitors	123 (1.6%)	180 (2.4%)	1.15 (0.95-1.39)	0.151
CNS related co-medication	305 (4.1%)	305 (4.1%)	1.01 (0.87-1.16)[b]	0.918
• Antidepressants	256 (3.4%)	244 (3.3%)	0.96 (0.82-1.13)	0.647
• Anti-parkinsonian drugs	21 (0.3%)	20 (0.3%)	0.96 (0.56-1.63)	0.878
• Anti-psychotics	55 (0.7%)	59 (0.8%)	1.08 (0.78-1.49)	0.642
Other co-medication	549 (7.4%)	551 (3.8%)	0.98 (0.88-1.09)[b]	0.684
• Antidiabetic drugs	259 (3.5%)	267 (3.5%)	0.99 (0.85-1.14)	0.843
• Glaucoma drugs	79 (1.1%)	72 (1.0%)	0.94 (0.71-1.24)	0.655
• Anti-osteoporosis drugs	135 (1.8%)	114 (1.5%)	0.87 (0.70-1.08)	0.205
• Anti-asthmatic drugs	94 (1.3%)	107 (1.4%)	1.06 (0.84-1.33)	0.637
Miscellaneous	2,052 (27.5%)	2,072 (27.8%)	1.03 (0.96-1.09)	0.438
			1.03 (0.97-1.10)[b]	0.340

Values indicate numbers (%); a: adjusted for other variables in the model; b: reduced model with total cardiovascular hospitalizations, other hospitalizations, cardiovascular co-medication, CNS related co-medication, other co-medication and miscellaneous refill

Sensitivity analyses

We tested the robustness of the observed associations between patient characteristics and our definition of discontinuation in models with discontinuation defined as a gap of at least 90 or 270 days instead of 180 days. The strengths of the associations were essentially the same. In the case-crossover analysis, the associations were weaker and the confidence intervals were substantially wider with the 15-day definition as opposed to smaller confidence intervals and stronger associations with the 45 and 60-day intervals, but the overall findings were consistent with those in the main models.

Discussion

We found that of the patients who had a gap in antihypertensive medication use of at least 180 days, about 60% gradually reinitiated BP-lowering treatment over the course of six years. After a steep increase in the proportion of patients returning to treatment, the increase became more moderate after two years. However, the slope of the curve suggests that if observation time had been longer, the proportion of patients reinitiating treatment would probably be higher. Of the patients returning to treatment, 58.1% returned to use the same agent used at discontinuation, whereas the rest switched to other BP-lowering drugs. Time on treatment before discontinuation was a strong (positive) predictor of re-starting therapy, as was the type of BP-lowering drugs used at discontinuation. A recent hospitalization for cardiovascular disease was associated with reinitiating treatment, as was refilling cardiovascular co-medication, although to a lesser extent. Refilling other chronic treatments was not associated with reinitiating treatment.

Several limitations are inherent in this observational setting and the use of pharmacy records. First, although it is likely that refilling indicates restarting[19,20], this cannot be confirmed. The advantage of our method over other methods available for assessing medication use is that it is non-invasive and thus not likely to change medication use itself[21]. Second, some interruptions may be intentional, although we expect that this will only be a small proportion, given the chronic nature of hypertension and the increased risk associated with elevated blood pressure. Third, our data lack a diagnosis for prescribing. It is possible that some patients had a diagnosis other than hypertension. However, in an unpublished review of prescription data from general practitioners, we have found that of prevalent users of BP-lowering drugs, about 80% are prescribed for hypertension. In addition, we excluded patients based on specific co-medication that may be indicative of other cardiovascular diseases, such as loop diuretics (congestive heart failure) or nitrates (angina). Patients with previous cardiovascular hospitalizations were also excluded, to increase the chance that our population included patients prescribed these drugs for primary prevention. The low average PDD, the low number of patients using more than one BP-lowering drug and the fact that the vast majority of the patients received their prescription from the general practitioner suggests that this selection strategy succeeded.

One of the strengths of our study is that we were able to include a large number of patients and that our follow-up was long enough to study reinitiating treatment. Most studies focusing on adherence or persistence have relative short periods of follow-up[8] and are therefore unable to detect reinitiating treatment behavior. Second, since it is unlikely that even normal adherence behavior can be observed in an RCT[22], reinitiating treatment behavior is even harder to quantify in the setting of an RCT. As our data show, discontinuation and consequent reinitiating treatment occur in a large proportion of new users of antihypertensive therapy. Hence, our setting is a useful one in which to study this and to clarify the dynamics of this behavior. Third, we used a gap large enough to detect actual discontinuation. A shorter gap (e.g. 90 days) may be clinically relevant[23] but it may also reflect suboptimal intake, rather than actual discontinuation[24] (higher sensitivity but lower specificity). Gaps of 90 and 270 days did not materially influence our results. The results of our sensitivity analysis for the case-crossover analysis also suggest the robustness of our findings. Fourth, the data obtained are dispensing data rather than reimbursement of prescription data. Fifth, in The Netherlands, free samples are not given to doctors, making the dispensing data set virtually complete.

We found a number of interesting results in this study. First, people do return to treatment after a period of discontinuation. Qualifying patients as discontinuers and assuming that they remain so forever ignores the fact that patients restart. Physicians and pharmacists should realize this during patient-encounters. Although a clear trend was visible that older patients were more likely to reinitiate treatment, the very oldest were not. A recent study assessing predictors of concomitant adherence with lipid lowering and BP-lowering medication found a similar pattern between age and adherence[25]. In addition, we found that patients who received their last prescription from a non-general practitioner were less likely to restart treatment, although this was not statistically significant in the final model. This may be explained by the fact that follow-up of general practitioners is generally more frequent and accessible, probably enhancing restarting[7,26,27]. Our lack of information on physician visits limits further analysis of this problem. The fact that patients who discontinued while using newer BP-lowering drugs, were more likely to restart is in line with the discontinuation differences usually observed between patients starting with the different classes of BP-lowering drugs[8,9]. If discontinuation was caused by perceived side-effects, one would

expect that this would also influence the motivation to restart treatment. The use of newer BP-lowering drugs is probably associated with fewer side-effects than diuretics and especially beta-blockers[28,29], which is in line with the direction of the associations we observe. Another interesting finding was that patients using medication for psychiatric and neurological diseases were less likely to restart. The cognitive impairment associated with diseases that these drugs treat has been associated with lower adherence and continuation rates in other studies and apparently applies to restarting BP-lowering drug use as well[10,30-34].

The case-crossover analysis revealed that cardiovascular hospitalizations appear to precede restarting, probably because it's psychological effect on the patient and because it provides the physician with the possibility of reevaluating and reinitiating treatment. To a lesser extent but potentially for the same reasons, prescribing of cardiovascular co-medication is also associated with reinitiating treatment. As discussed by other investigators, starting, discontinuing and restarting is suggestive of a cyclical behavioral pattern, also observed with other health related behaviors e.g. diet adherence or smoking cessation[35]. Further research conducted over longer periods of time is needed to confirm and quantify this suggestion.

One of the most striking findings of this study was also obtained from the case-crossover analysis. This analysis demonstrated that although patients were filling prescription for other co-medications, they were not more likely to restart BP lowering treatment. On the one hand this suggests that pharmacists and physicians are probably missing easy available opportunities to discuss BP-lowering medication use, because the patients were in the pharmacy to refill other medications, and a proportion of these patients probably visited a physician prior to that. However, computer systems used by pharmacies and general practitioners in The Netherlands did not report discontinuation at the time of the observation period. On the other hand it suggests that although patients are still using medication, and thus demonstrate health-seeking behavior, they specifically decided not to re-fill their BP-lowering prescriptions. This implies that it may be the combination of the asymptomatic disease combined with side-effects of BP lowering drugs that cause the observed continuation and restarting pattern, rather than a general behavioral pattern applicable across a wide variety of treatments.

Further research should extend this work in at least two different directions. First, more than one start-stop-restart cycle needs to be studied to confirm our hypothesis of cyclical patterns. This requires databases with long periods (>10 years) of high quality registration. Second, our case-crossover analysis elucidating that a patient was refilling other medications (health-seeking behavior) but not refilling BP lowering drugs, which is suggestive of BP-lowering medication specific behavior, should be repeated among patients discontinuing other medications used for the treatment of diseases with different levels of symptomatology, and medications with different levels of side-effects. This would further extend our findings on the dynamic process of chronic medication taking and could ultimately lead to strategies to prevent discontinuation and the design of interventions capable of successfully influencing this important process.

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Chapter 4.3

A cross-national study of persistence of antihypertensive medication use in the elderly

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Summary

Background: Little is known about cross-national comparisons of antihypertensive medication treatment persistence, trends in persistence and factors associated with persistence. The objective of this study was to describe and compare patterns of use of antihypertensive drugs in a population of elderly patients in the US (Pennsylvania), Canada (British Columbia) and The Netherlands.

Methods: Design, setting, participants: Retrospective cohort study of Medicare enrollees in a state pharmacy assistance program in Pennsylvania (US), residents from British Columbia (Canada) and residents from The Netherlands registered in the PHARMO-database. Each population included patients 65 years and older who were initiated on blood pressure lowering treatment between January 1st 1998 and December 31st 2003 and who had continuous follow-up for at least 365 days. Main outcome measures were: proportion of patients with at least 180 consecutive days without medication available (non-persistence); predictors of non-persistence were identified using Cox-proportional hazards.

Results: A total of 9,664 Medicare enrollees (US), 25,377 residents from British Columbia and 24,603 residents from The Netherlands were evaluated. During the first year after the initiation of treatment, the proportion of patients with at least 180 days without medication was 23.3% in Pennsylvania, 23.4% in British Columbia and 24.0% in The Netherlands. After six years, this percentage increased to 41.1, 36.3 and 38.2 respectively. Older age, male gender and frequent use of prescription medications in the baseline year was associated with non-persistence in all three populations. Prior occurrence of acute myocardial infarction and hypercholesterolemia was associated with improved persistence.

Conclusion: Despite differences in health care organization and drug coverage, non-persistence patterns are strikingly similar between the three populations, as were factors associated with persistence. This suggests that the problem of non-persistence transcends international boundaries, health system characteristics and prescription drug coverage policies.

Background

Hypertension is the most common risk factor for cardiovascular morbidity and mortality[1] and an important cause of disability adjusted life years[2]. To reduce this burden, the elucidation of effective treatment and in the early identification of patients with hypertension has been stressed[3,4]. Nevertheless, only 30% of patients with hypertension reach their target blood pressure, while the remainder is uncontrolled[5,6]. Among patients who do not reach target blood pressure, half of these failures can be attributed to sub-optimal use or non-use[7,8]. Patients may fail to adhere to prescribed anti-hypertensive therapy for numerous reasons such as the absence of symptoms associated with the condition, medication side-effects, complexity of dosing schedule or medication costs[9].

Efforts to better quantify antihypertensive medication non-persistence are needed, especially when considering the current and future burden of this chronic disease[10]. A better understanding of factors associated with non-adherence may provide targets to intervene and improve medication persistence. Population based studies may offer details about persistence rates and predictors to help identify patients with an increased risk of non-persistence. These studies can be used to assess the breadth of the non-persistence problem, and to explore whether residents of some countries are more adherent to anti-hypertensive medications. It seems plausible that different health care systems, different cultural attitudes about health care and different drug coverage policies could influence medication-taking behavior. While cross-national multi-center randomized trials have been used in the field of hypertension to test effectiveness[11-14], cross-national comparisons of drug utilization are scarce[15]. The aim of this study was to perform a cross-national population-based study on rates and predictors of non-persistence with antihypertensive drugs in the US, Canada and The Netherlands.

Methods

Sources of data

United States

The US population was drawn from the Pharmaceutical Assistance Contract for the Elderly (PACE) program in Pennsylvania. The PACE-program is the largest state prescription benefits program for the elderly in the United States, and offers

generous coverage to low-income elderly residents of the State. Full pharmacy and health care claim information was evaluated for this study, which included demographic characteristics and data for all filled prescriptions (including type of medication, quantity dispensed and days supply). Drug names are coded according to the National Drug Code (NDC) classification system[16]. Claims for services in hospitals and offices are coded according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Diagnostic Related Groupings (DRGs)[17]. Medicare data has been demonstrated to be reliable and complete[18-20]. Based on unique patient identifiers, data of drug use of PACE-enrollees were linked to Medicare data on hospitalizations and outpatient professional services and procedures.

The PACE program has no deductibles and no maximum annual benefit[21]. There is a modest co-payment of $6 for each generic prescription and $9 for each branded prescription. The income ceiling for PACE eligibility is $14,000 if single and $17,200 for a couple. These benefits and eligibility requirements for enrollment result in essentially no out-of-pocket (i.e. out-of-system) medication costs. The maximum amount of days reimbursed without exemptions was 30 days.

Canada

The Canadian population was drawn from administrative files from the British Columbia Pharmacare Program[22-24]. The Ministry of Health collects data on all health care utilization claims of all registered residents of British Columbia. All residents of British Columbia who are 65 years or older are eligible for publicly funded health care, including pharmaceutical benefits. Information on drug use (including type of drug, quantity dispensed, days supplied), was entered and collected by pharmacies through a province wide network called Pharmanet[22,24]. Drug use was linked to health care claims based on unique patient identifiers. This data source has been demonstrated to be a reliable and complete source of health care use[25]. Drug names are coded according to the Drug Information Number/Product Identification Number (DIN/PIN) classification system[24]. Claims for services in hospitals and offices are coded according to ICD-9-CM and the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP)[26].

From January 1st 1997 reference pricing was introduced in British Columbia[27,28]. Reference priced drugs include ACE-inhibitors and calcium channel blockers.

Within each therapeutic class, (e.g. ACE-inhibitors) only one (often the least expensive) agent was fully covered. Patients who filled prescriptions for more expensive agents paid the difference in price out-of-pocket. From January 1st 2002, patients with an annual income of less than CA$16,000 were charged a CA$10 co-payment for each dispensing whereas patients with greater annual income were charged CA$25 co-payment. In May 2003, the co-payment was replaced with a 25% co-insurance plus an income-based deductible policy. Linking deductible cost-sharing levels to income was intended to prevent low-income patients from under-utilizing essential drugs[29]. The maximum amount of days reimbursed without exemptions was 90 or 100 days.

The Netherlands

Data for the Dutch population were obtained from the PHARMO record linkage system (PHARMO-RLS)[30,31]. The PHARMO-RLS currently includes drug-dispensing records from community pharmacies and hospital discharge records of all 2,000,000 community dwelling inhabitants of 50 medium sized areas in The Netherlands. Clustering of all pharmacies within each city results in drug-dispensing histories that contain virtually all prescriptions dispensed to a particular patient. Data include demographic characteristics and data for all filled prescriptions (including type of medication, quantity dispensed and days supply). Drug names are coded according to the Anatomical Therapeutical Chemical (ATC) classification system[32]. The hospital records include detailed information concerning the primary and secondary diagnoses, procedures and dates of hospital admission and discharge, coded according to ICD-9-CM. Outpatient procedures and diagnoses were not available for The Netherlands.

In The Netherlands, all prescription drugs of interest for this study were fully covered by Insurance Companies (funded by monthly premiums and income tax derived government funding) during the study period and no other forms of co-payment or dispensing fees were charged at pharmacies[33]. Most privately insured patients had a small non-income based deductible for all health care costs (approximately €50) throughout the study period. The maximum amount of days reimbursed without exemptions was 90 days.

Patients

For each of the three countries, we selected a new-user cohort of antihypertensive drugs. New use was defined as having no antihypertensive drug fills in the 365 days prior to the first prescription of any antihypertensive drug. The date of the first prescription was defined as the index date. At index date, all patients were 65 or older. For the vast majority of patients enrolled in the PACE-program, this means that they were at least 66 years when eligible for our analysis. Antihypertensive drugs were classified according to their mechanism of action[32]: thiazide diuretics and chlorthalidone, beta-blockers (except sotalol), dihydropyridine calcium channel blockers (DHP-CCB), ACE-inhibitors (ACE-I), angiotensin II receptor blockers (ARB) or miscellaneous antihypertensives (including alpha-blockers and centrally acting antihypertensives, such as methyldopa). Simultaneous use of more than one antihypertensive, in a single pill combination or as two separate tablets, was defined as combination therapy. For the US and Canada, a additional physician visit with a hypertension related diagnosis in the 6 months up to and including the index date was required. In addition, a claim for dispensing of a non-antihypertensive drug in at least three consecutive 6 month-intervals prior to the index date was required to ascertain eligibility and new use. To ascertain ongoing eligibility and to avoid differential misclassification with regard to antihypertensive exposure status, the last dispensing of a non-antihypertensive was defined as the sensor date. Patients were required to have at least one year of follow-up available. Patients who died were censored at 180 days prior to their death date. Nursing home patients were excluded due to concerns that nursing home data are less reliable. To protect the confidentiality of all patients, all personal identifiers were removed prior to analysis.

Definition of persistence

Persistence was assessed by using the information on the dispensing date and prescribed duration of each filled prescription. If a prescription of the same antihypertensive was filled before the previous one expired, the amount left over was added to the dispensing date of the next one. For patients who used two or more antihypertensives simultaneously, the overlapping amount was not included. Patients who had a consecutive 180-day period after the end date of a given prescription during which they filled no prescriptions for any anti-hypertensive medication were identified as non-persistent. This arbitrary threshold was chosen

for two reasons. First, 180 days without medication between the end date of a prescription and the start of the consecutive one would lead to an adherence of at maximum 14% in the US (30/ (30+180), based on a 30-day prescription) and 33% in The Netherlands and Canada (90/ (90+180), based on a 90 day prescription, which seems specific enough to detect actual discontinuation rather than continuous use with suboptimal adherence. In a previous study we found that extending this 180 day gap did not categorize substantially more patients as persistent[34]. Second, 180 days without medication leads to significant blood pressure differences in placebo-controlled RCTs[35,36-38], although there is also an acute risk associated with discontinuation[39]. We performed sensitivity analyses evaluating non-persistence rates and factors associated with non-persistence while varying the treatment gap to 90 and 270 days. For the entire cohort, short term (i.e. 1 year) and long term (6 year) persistence were assessed.

Definition of predictors of persistence

Our selection of sociodemographic, clinical and treatment-related characteristics was based on previous literature[15,40]. The association of these items with persistence during the first year of treatment was studied. In addition to age and gender, which was available for all the three countries, patient ethnicity was identified in the US population. Detailed information on annual income was also available for the US population and was dichotomized at a cut-off value of $10,000. Categories of annual income for residents of British Columbia were estimated based on the amount of income-dependent subsidy and subdivided into three classes: <16,000CA$, 16,000-22,000CA$, >22,000CA$[41]. For residents of The Netherlands, income was categorized based on type of insurance (public vs. private). The income limit for public insurance for those 65 years and older was €20,750 in 2004. Clinical characteristics present in the 12 months preceding the index date were assessed. These included: evidence of stroke, congestive heart failure (CHF), atrial fibrillation, peripheral vascular disease (PVD) and coronary heart disease (CHD). CHD was further categorized into three groups based on previous literature: angina or coronary angiography (group 1), coronary artery bypass graft (CABG), percutaneous transluminal angioplasty (PTCA) or chronic CHD (group 2) or acute MI (group 3). Patients who met the criteria for more than one group were assigned to the most severe one. Furthermore, evidence of hypercholesterolemia, diabetes, COPD, depression, dementia and Parkinson's disease and for the US and Canadian population, the Charlson comorbidity score

was assessed[42]. In addition, treatment-related characteristics in the baseline year included number of prescription medications used, number of physician visits (US and Canada only) and type of antihypertensive treatment. To test for time trends, patients were categorized according to their year of initiating treatment with 1998 as the reference year.

Statistical methods

Cox-regression was used to analyze the association of potential predictors and one-year persistence with antihypertensive treatment. Predictors of suboptimal persistence were considered significant at the $p<0.05$ level. All statistical procedures were performed using SPSS 12.0 for Windows (SPSS Inc. Chicago).

Results

Study population

A total of 9,664 patients from the US, 25,377 patients from Canada and 24,603 patients from The Netherlands met the inclusion criteria of the study. Baseline characteristics of the study population are shown in table 1.

Table 1: Baseline characteristics of the study population

	PA (N=9,664)	BC (25,377)	NL (N=24,603)
Demographics			
Age	77.8 (±6.9)	75.2 (±7.1)	78.2 (±5.8)
• Age 65-74 years	3,270 (33.8%)	12,815 (50.5%)	7,735 (31.4%)
• Age 75-84 years	4,663 (48.3%)	9,538 (37.6%)	13,123 (53.3%)
• Age ≥85 years	1,731 (17.9%)	3,024 (11.9%)	3,735 (15.2%)
Gender			
• Males	1,564 (16.2%)	11,013 (47.1%)[a]	10,345 (42.0%)
Income			
• Low	3,651 (38.8%)	7,180 (28.3%)[a]	13,763 (55.9%)
• Medium	-	2,313 (9.1%)	
• High	6,013 (62.2%)	14,647 (57.7%)	10,840 (44.1%)
Race			
• Whites	9,203 (95.2%)	-	-
• Blacks	340 (3.5%)	-	-
• Other, non-white	121 (1.3%)	-	-
CV history in baseline year			
CHD			
• Angina/angiography	658 (6.8%)	386 (1.5%)	4,221 (17.2%)
• PTCA/CABG/chronic heart disease	905 (9.4%)	665 (2.6%)	-
• Acute MI	467 (4.8%)	718 (2.8%)	2,025 (8.2%)
Stroke	1,798 (18.6%)	1,351 (5.3%)	1,092 (4.4%)
Congestive heart failure	2,450 (25.4%)	2,473 (9.7%)	989 (4.0%)
Atrium fibrillation	968 (10.0%)	390 (1.5%)	1,164 (4.7%)
Peripheral vascular disease	895 (9.3%)	377 (1.5%)	397 (1.6%)
Other comorbid conditions			
• Hypercholesterolemia	2,197 (22.7%)	1,089 (4.3%)	3,285 (13.4%)
• Diabetes	2,966 (30.7%)	3,523 (13.9%)	2,713 (11.0%)
• COPD	2,966 (30.7%)	4,576 (18.0%)	1,085 (7.3%)
• Depression	1,198 (12.4%)	1,551 (6.1%)	1,453 (5.9%)
• Dementia	748 (7.7%)	336 (1.3%)	58 (0.2%)
• Parkinson	246 (2.5%)	201 (0.8%)	195 (0.8%)
• Charlson score	1.94 (±1.9)	0.27 (±0.71)	-
Health services used in baseline year			
Number of hospitalizations	0.50 (±0.9)	0.26 (±0.64)	0.47 (±1.0)
• 0	6,447 (66.7%)	20,602 (81.2%)	18,000 (73.2%)
• 1	2,003 (20.7%)	3,540 (13.9%)	3,855 (15.7%)
• ≥2	1,214 (12.6%)	1,235 (4.9%)	2,748 (11.2%)
Number of prescription medications	6.5 (± 4.2)	5.7 (±3.8)	6.0 (±4.2)
• 0-3	2,607 (27.0%)	8,328 (32.8%)	7,177 (29.2%)
• 4-6	3,124 (32.3%)	8,623 (34.0%)	8,173 (33.2%)
• 7-9	2,013 (20.8%)	4,772 (18.8%)	4,933 (20.1%)
• ≥10	1,920 (19.9%)	3,654 (14.4%)	4,320 (17.6%)

Number of outpatient physician visits	8.7 (± 6.0)	17.4 (±13.6)	-
• 0-5	3,132 (32.4%)	3,149 (12.4%)	-
• 6-10	3,680 (38.1%)	5,732 (22.6%)	-
• 11-15	1,742 (20.8%)	5,089 (20.1%)	-
• ≥16	1,110 (19.9%)	11,407 (45.0%)	-
Year of initiation of treatment			
• 1998	1,854 (19.2%)	4,444 (17.5%)	3,820 (15.5%)
• 1999	1,711 (17.7%)	4,635 (18.3%)	4,420 (18.0%)
• 2000	1,657 (17.1%)	4,713 (18.6%)	4,325 (17.6%)
• 2001	1,532 (15.9%)	4,455 (17.6%)	4,118 (16.7%)
• 2002	1,526 (15.8%)	3,926 (15.5%)	4,099 (16.7%)
• 2003	1,384 (14.3%)	3,204 (12.6%)	3,819 (15.5%)
First antihypertensive			
• Diuretic	1,003 (10.4%)	7,439 (29.3%)	5,726 (23.3%)
• Beta-blockers	2,713 (28.1%)	4,102 (16.2%)	6,201 (25.2%)
• Calcium channel blockers	1,104 (11.4%)	1,700 (6.7%)	1,881 (7.6%)
• ACE-inhibitors	2,921 (30.2%)	10,049 (39.6%)	6,134 (24.9%)
• Angiotensin II receptor Blockers	953 (9.9%)	418 (1.6%)	1,738 (7.1%)
• Miscellaneous	267 (2.8%)	383 (1.5%)	240 (1.0%)
• Combination therapy	703 (7.3%)	1,286 (5.1%)	2,683 (10.9%)

a: Information on gender (4.9%) and income (4.9%) is missing for part of the BC-residents

Although age was similarly distributed in the three populations, other demographic and clinical characteristics were not. In general, patients from Pennsylvania had the highest prevalence of cardiovascular comorbidity, and patients from British Columbia the lowest. Notably, there was greater than a 10-fold difference in prevalence of angina pectoris between The Netherlands (17.2%) and British Columbia (1.5%). The pattern is observed for differences in other non-cardiovascular comorbid conditions. Health services utilization is generally similar between the three countries.

Long-term follow up

In table 2, the percentage of patients who had a period of at least 180 days without medication available during the course of the follow-up is shown. Of interest is the similarity between the proportions of non-persistent patients across all three countries. During the first year, almost 25% of the patients were non-persistent, with less than a one percent difference in absolute non-persistence rates across countries. After six years, the difference between the population with the highest incidence of non-persistence, Pennsylvania, and the population with the lowest incidence, British Columbia is less than five percent. The comparison does not

materially change if 90 or 270-days without medication were used as a definition of non-persistence.

Table 2: percentage of patients who had at least one period of at least 180 days without blood pressure lowering medication available. Percentages in brackets indicate a 270 day and 90 day period of non use respectively

	1 year	2 years	3 years	4 years	5 years	6 years
PA	23.3 (15.1-32.5)	30.1 (23.3-41.0)	34.6 (27.4-46.1)	37.0 (30.0-49.4)	39.3 (32.0-52.8)	41.1 (33.6-55.1)
BC	23.4 (16.4-32.8)	28.6 (23.0-39.8)	31.6 (25.7-43.8)	33.6 (27.6-46.8)	35.0 (28.9-49.0)	36.3 (29.1-50.5)
NL	24.0 (17.0-33.9)	31.6 (27.0-39.8)	34.0 (29.8-43.4)	35.8 (31.3-45.9)	37.1 (32.4-47.7)	38.2 (33.8-49.8)

PA=Pennsylvania; BC=British Columbia; NL=The Netherlands

Predictors of non-persistence in the first year

In table 3, the association between potential predictors and 180 days without medication in the first year after initiation are shown. Older age, male gender and frequent use of prescription medications in the baseline year were associated with non-persistence in the three populations. Prior occurrence of acute myocardial infarction was associated with higher persistence, as was hypercholesterolemia. Angina pectoris was not associated with non-persistence in Pennsylvania (OR 1.02 [95% CI: 0.89-1.18]), associated with higher persistence in The Netherlands (OR 0.85 [95% CI: 0.79-0.91]) and with lower persistence in British Columbia (OR 1.20 [95% CI: 1.01-1.44]). Other demographic and clinical parameters demonstrated different associations between the three countries. In both The Netherlands and British Columbia, a time trend is visible, with patients who were initiated more recently achieving greater medication persistence. A corresponding improvement in persistence rates over time was not seen in the U.S. Similarities was seen between the type of initial antihypertensive selected and persistence in all three countries. In general, patients treated with newer antihypertensives (ACE-inhibitors and ARBs) were less likely to have a 180-day medication gap compared to patients treated with diuretics or beta-blockers (with the exception of patients initiated with beta-blockers in Pennsylvania). Using 90 and 270 days gaps as a definition of non-persistence did not qualitatively change the observed associations.

Table 3: Association between potential predictors and non-persistence

	PA (N=9,664) Adjusted OR[a]	BC (N=25,377) Adjusted OR[a]	NL (N=24,603) Adjusted OR[a]
Demographics			
Age			
• Age 65-74 years	1.00 (reference)	1.00 (reference)	1.00 (reference)
• Age 75-84 years	1.03 (0.95-1.12)	1.05 (1.00-1.10)	1.01 (0.96-1.06)
• Age ≥85 years	1.09 (0.98-1.21)	1.23 (1.15-1.32)	1.05 (1.00-1.15)
Gender			
• Females	1.00 (reference)	1.00 (reference)	1.00 (reference)
• Males	1.21 (1.10-1.33)	1.13 (1.08-1.19)	1.05 (1.01-1.09)
Income			
• Low	1.00 (reference)	1.00 (reference)	1.00 (reference)
• Medium	-	0.86 (0.79-0.93)	
• High	1.06 (0.98-1.14)	0.81 (0.77-0.85)	0.95 (0.90-0.99)
Race			
• Whites	1.00 (reference)	-	-
• Blacks	1.42 (1.19-1.66)	-	-
• Other, non-white	1.29 (0.97-1.73)	-	-
CV history in baseline year			
CHD			
• Angina/angiography	1.02 (0.89-1.18)	1.20 (1.01-1.44)	0.85 (0.79-0.91)
• PTCA/CABG/chronic heart disease	1.04 (0.91-1.17)	0.93 (0.80-1.08)	-
• Acute MI	0.85 (0.70-1.01)	0.64 (0.54-0.76)	0.59 (0.53-0.67)
Stroke	0.93 (0.84-1.03)	0.81 (0.73-0.91)	1.01 (0.90-1.14)
Congestive heart failure	1.10 (1.01-1.20)	0.93 (0.86-1.02)	0.95 (0.83-1.09)
Atrium fibrillation	0.84 (0.74-0.96)	1.40 (1.13-1.74)	0.85 (0.76-0.97)
Peripheral vascular disease	1.01 (0.89-1.14)	1.01 (0.83-1.21)	0.95 (0.79-1.14)
Other comorbid conditions			
• Hypercholesterolemia	0.87 (0.80-0.95)	0.77 (0.68-0.88)	0.77 (0.71-0.83)
• Diabetes	0.99 (0.91-1.08)	0.93 (0.86-1.00)	0.83 (0.76-0.90)
• COPD	1.09 (1.00-1.18)	1.04 (0.98-1.10)	1.04 (0.96-1.13)
• Depression	1.10 (0.99-1.14)	1.14 (1.05-1.25)	1.03 (0.94-1.12)
• Dementia	1.03 (0.90-1.18)	0.92 (0.76-1.12)	1.00 (0.65-1.54)
• Parkinson	1.14 (0.93-1.41)	1.50 (1.21-1.85)	0.95 (0.76-1.18)
• Charlson score	1.00 (0.97-1.02)	1.00 (0.97-1.04)	-
Health services used in baseline year			
Number of hospitalizations			
• 0	1.00 (reference)	1.00 (reference)	1.00 (reference)
• 1	1.03 (0.94-1.14)	0.95 (0.88-1.02)	1.03 (0.96-1.12)
• ≥2	1.14 (1.00-1.29)	0.98 (0.87-1.10)	1.06 (0.95-1.17)
Number of prescription medications			
• 0-3	1.00 (reference)	1.00 (reference)	1.00 (reference)
• 4-6	1.01 (0.92-1.11)	1.01 (0.94-1.06)	1.05 (0.99-1.11)
• 7-9	1.03 (0.93-1.14)	1.06 (0.99-1.14)	1.20 (1.13-1.28)
• ≥10	1.06 (0.94-1.20)	1.25 (1.15-1.36)	1.36 (1.27-1.46)

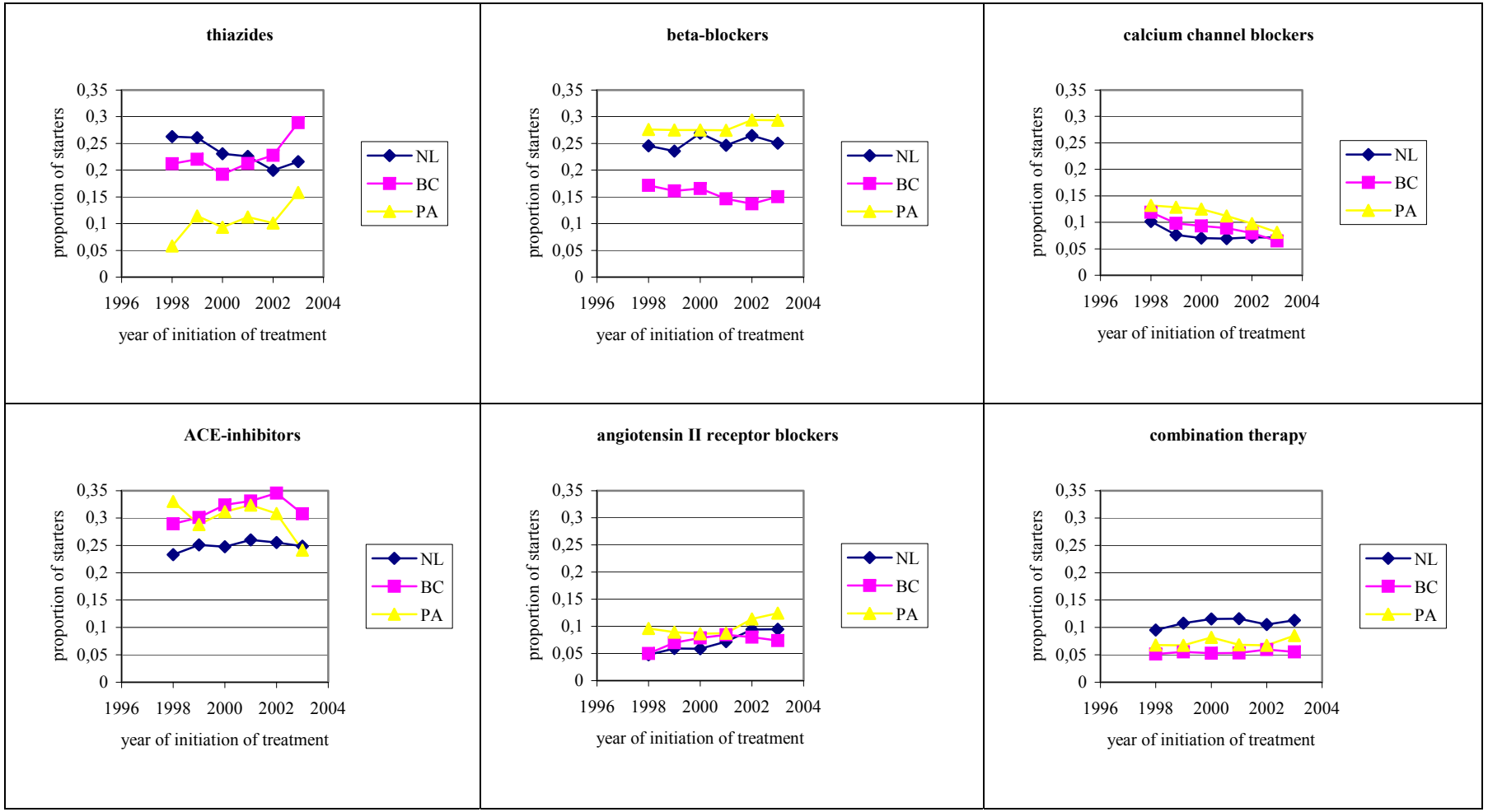
Number of outpatient physician visits			
• 0-5	1.00 (reference)	1.00 (reference)	-
• 6-10	1.07 (0.98-1.17)	0.88 (0.81-0.95)	-
• 11-15	1.15 (1.03-1.28)	0.94 (0.86-1.02)	-
• ≥16	1.36 (1.20-1.55)	0.94 (0.87-1.02)	-
Year of initiation of treatment			
• 1998	1.00 (reference)	1.00 (reference)	1.00 (reference)
• 1999	1.05 (0.94-1.18)	0.84 (0.78-0.90)	0.94 (0.87-1.01)
• 2000	0.96 (0.86-1.09)	0.85 (0.79-0.91)	0.87 (0.81-0.94)
• 2001	1.05 (0.93-1.19)	0.83 (0.77-0.89)	0.86 (0.75-0.87)
• 2002	1.02 (0.90-1.15)	0.77 (0.71-0.82)	0.75 (0.69-0.81)
• 2003	0.96 (0.85-1.09)	0.70 (0.65-0.76)	0.72 (0.66-0.78)
First antihypertensive			
• Diuretic	1.00 (reference)	1.00 (reference)	1.00 (reference)
• Beta-blockers	0.57 (0.51-0.64)	1.05 (0.98-1.12)	0.92 (0.87-0.97)
• Calcium channel blockers	0.54 (0.47-0.62)	0.85 (0.78-0.94)	0.77 (0.71-0.84)
• ACE-inhibitors	0.48 (0.43-0.54)	0.68 (0.64-0.72)	0.62 (0.57-0.67)
• Angiotensin II receptor Blockers	0.50 (0.43-0.58)	0.55 (0.44-0.69)	0.48 (0.44-0.53)
• Miscellaneous	0.80 (0.65-0.98)	2.18 (2.00-2.37)	1.74 (1.49-2.04)

a: adjusted for all the variables in the table

Choice of the initial antihypertensive

The choice of the initial antihypertensive differed remarkably between the three countries. The initiation of treatment with thiazides was relatively low in Pennsylvania, beta-blockers were relatively less frequently prescribed in British Columbia, and ACE-inhibitors were relatively less frequently prescribed in The Netherlands. All the three countries demonstrate an increase in thiazide use after the ALLHAT trial[43]. The use of CCBs and ARBs was generally similar.

Figure 1: patterns of initial drug choice in Pennsylvania, British Columbia and The Netherlands



PA=Pennsylvania; BC=British Columbia; NL=The Netherlands

Discussion

In this study we aimed to assess and compare persistence patterns of new users of antihypertensive drugs in elderly populations from three different countries, the United States, Canada and The Netherlands. We found that despite evidence of effectiveness of antihypertensive treatment[4], almost a quarter of the patients discontinue their medication for at least 180 consecutive days in the first year of treatment. In the subsequent 5 years, another 13-18 percent experience at least one 180-day period without medication. The similarities in the patterns of non-persistence in all three countries were striking, especially when considering the differences with regard to health system organization and delivery, prescription drug coverage and rates of co-morbidities.

To our best knowledge, this is the first study comparing persistence with antihypertensive treatment in more than one country. Although there are many studies available assessing long term utilization patterns with antihypertensives[44-46] comparing persistence rates and its' determinants is difficult because published studies often use different and incomparable methodologies[34]. In this study we used the same definition of persistence for the three populations. In addition, we used the same predictors of persistence and defined them similarly. Our 180-day gap is of clinical relevance and in fact conservative since we assumed that the preceding prescription was completely used.

Nevertheless, these results should be interpreted in light of some limitations. First, treatment could be discontinued at the suggestion of the prescriber for clinically justifiable reasons such as intolerable side-effects or lack of efficacy. However, we classified patients using any type of antihypertensive as continuous users, regardless of whether they switched to another agent (demonstrated to be a common occurrence[44,47]). Second, we could not measure use of antihypertensives obtained from pharmacies outside the state of Pennsylvania. This likely occurs infrequently because prescriptions required a minimal co-payment in Pennsylvania. All prescribing data in British Columbia and in the PHARMO-area in The Netherlands were linked and were captured. We also could not capture the provision of free medication samples which are offered in the U.S. and Canada, but not the Netherlands. In addition, we required ongoing filling of at least one prescription during each of the 180-day intervals following the initiation of treatment. Patients who died were censored 180-days prior to their death date.

Despite similarities in methodology used, there is still a potential for misclassifying patients with regard to the indication in The Netherlands due to differences in origin of the data (dispensing and hospital discharge data in The Netherlands vs. claims data including outpatient procedures in Pennsylvania and British Columbia). Although absolute persistence rates are probably marginally influenced by this, it is still a possible source of misclassification that we were unable to capture and quantify.

The implications of our findings are at least fourfold. First, considering that the proportion of patients with a prolonged period without medication available is large, and although the largest decline is observed shortly after initiation of treatment, the need for adequate follow-up is ongoing. Unfortunately, little effective and feasible strategies to increase adherence for patients with hypertension are currently available[48] which argues for more well performed research in this field. Second, there are striking similarities between the three countries with regard to both absolute persistence rates, after one year and even after six years of follow-up, as well as predictors of suboptimal persistence. Although certain predictors of suboptimal persistence appeared to be population specific in at least the direction of the association with inadequate use, other predictors were consistent across all countries studied, such as age and gender, previous MI and number of prescription medications. Third, the magnitude of the associations of the vast majority of predictors of suboptimal persistence was small. The predictors we studied are similar to information available to clinicians who initiate and treat a patient with hypertension. However, there are probably other characteristics that are unavailable in prescription databases and therefore in our study, such as an interest in one's own health and personal circumstances, that better predict a successful uptake of life long treatment. Although this information is probably more difficult to assess considering the limited time available during consultations and the psychological skills required, knowledge about it could substantially increase the overall success of treatment in an individual patient[9,49]. Fourth, one of the strongest associations in magnitude was the type of antihypertensive treatment initiated. Patients starting with ACE-inhibitors and ARBs persisted better with treatment than patients starting with diuretics. This finding is in contrast to the evidence on efficacy from a thoughtful network meta-analysis[4] and the largest hypertension trial[43] which favor diuretics. In addition, in the ALLHAT trial, there were no material differences in discontinuation rates

between patients initiated with diuretics, calcium channel blockers and ACE-inhibitors. As previously noted by other investigators, the artificial persistence enhancing circumstances of the hypertension trials may not reflect the situation in daily practice[50] which is in line with patterns observed for lipid lowering drugs[51]. Further research is needed to further explore the observed associations between type of antihypertensive and persistence in daily practice.

In the latest report of the World Health Organization on adherence to long term therapy[49], access to affordable drugs is emphasized as one of the most important barriers to treatment adherence. With regard to hypertension, this is increasingly relevant as the prevalence of hypertension is expected to increase world wide with the highest incidence in the developing world where access can be a greater barrier[10]. As a result, antihypertensives have been placed on the WHO essential medicines list[52]. However, as the results of our study demonstrate, even if medication is affordable and available, there is still a substantial proportion of patients that, without proper guidance, will not adhere to therapy and will not optimally benefit from antihypertensive treatment. Further investigations about methods of improving persistence are critical to reducing adverse cardiovascular disease outcomes and improving the public health.

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Chapter 4.4

A comparison of two multiple characteristics decision-making models for the comparison of antihypertensive drugs: Simple Additive Weighting and Technique for Order Preference by Similarity to an Ideal Solution

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Summary

Background: Multiple characteristics decision making (MCDM) models can be used to calculate a score for a number of alternative drugs or drug classes to allow a comparison between them based on a set of characteristics to enhance objective pharmacotherapy. The aim of our study was to compare two MCDM-models, Simple Additive Weighting (SAW) and Technique for Order Preference by Similarity to an Ideal Solution (TOPSIS) to determine the first line antihypertensive drug class.

Methods: Five different classes of antihypertensive drugs: diuretics, beta-blockers, dihydropyridine calcium channel blockers (DHP-CCBs), ACE-inhibitors and angiotensin II receptor blockers (ARBs) were analyzed. Four characteristics were deemed relevant for the determination of the first line antihypertensive: effectiveness, persistence as a measure of tolerability, cost and clinical experience. Weight factors were determined by sending questionnaires to cardiologists, pharmacists, general practitioners (GPs) and internists. Absolute scores were determined from literature (effectiveness and persistence) and health insurance data (costs and clinical experience).

Results: A total of 92 cardiologists (33%), 90 GPs (31%), 87 internists (31%) and 123 pharmacists (43%) completed the questionnaire. Among all professionals, according to both SAW and TOPSIS, ACE-inhibitors were ranked the first-line antihypertensive drug class followed by beta-blockers, DHP-CCBs, ARBs and diuretics respectively.

Conclusion: SAW and TOPSIS-analysis using weight factors assigned by cardiologists, pharmacists, GPs and internists from The Netherlands rank ACE-inhibitors as the first choice among the antihypertensive drug classes for the treatment of uncomplicated hypertension. Both methods are valuable tools in the development of evidence-based pharmacotherapy.

Background

There is an ongoing need for evidence-based medicine in decision making with regard to the choice of pharmacotherapy. Therefore, several characteristics of a certain treatment, next to effectiveness need to be assessed, such as safety, experience with a drug and costs among others. Although several of these characteristics may be considered during prescribing, the result of this consideration may differ between prescribers, based on their own estimation of which drug or drug class is the best option. To solve this problem multiple characteristics decision making (MCDM) models have been developed. MCDM-models can be used to calculate a score for a number of alternative drugs or drug classes to allow a comparison between them based on a set of characteristics, without introducing subjective elements. Currently, two MCDM-models are available, Simple Additive Weighting (SAW) and Technique for Order Preference by Similarity to an Ideal Solution (TOPSIS)[1,2]. SAW-analysis has been used for the analysis of drugs within the System of Objectified Judgment Analysis (SOJA)[3-7]. TOPSIS-analysis has been used previously to compare anti-epileptic drugs and antimigraine drugs[2,8]. Hitherto, these two techniques have never been compared. In this study we aimed to make this comparison. We used antihypertensives as a model for this comparison because of the large between-class differences of several characteristics of these drugs. This analysis will facilitate new insights in whether TOPSIS-analysis provides a different first-line antihypertensive drug class compared to SAW-analysis.

Methods

For comparing SAW and TOPSIS-analysis, we assumed that the within class differences of a certain antihypertensive drug class were smaller than between class differences. To apply the two MCDM-models, absolute scores of the characteristics were assessed using available data from literature. Absolute scores represent a quantification of a certain characteristic into a number, e.g. in the case of the characteristic costs, the absolute score is the actual price of a drug. Subsequently, weight factors, the extent to which a certain characteristic is deemed important for the assessment of antihypertensives, were obtained from health care professionals. Finally, the SAW and TOPSIS combined the absolute scores and the weight factors in a final score.

Assigning absolute scores to the characteristics of antihypertensive drug classes

We only included drug classes that have demonstrated a reduction in morbidity and mortality compared to placebo and for which valid data on all four characteristics were available. Four characteristics were deemed relevant and were available for mutual comparison. These were effectiveness, persistence with treatment, clinical experience and costs. We assumed that side-effects leading to discomfort in use were reflected by lower persistence[9]. However, the other aspects of side-effects were difficult to score and probably more substance than class related, and were therefore not considered in our example, but they should of course be considered in a more detailed analysis. In addition, we also did not consider differences with regard to e.g. interactions, contra-indications and pharmacogenetic differences. We analyzed five different classes of antihypertensives: diuretics, beta-blockers, dihydropyridine calcium channel blockers (DHP-CCBs), ACE-inhibitors and angiotensin II receptor blockers (ARBs)[10]. We determined the absolute scores of the different characteristics for each of the five antihypertensive drugs classes.

Effectiveness

To determine the effectiveness of the different drug classes, we used data from a recent meta-analysis on health outcomes associated with various antihypertensive drug classes[10]. The hazard ratio's (HR) obtained from the meta-analysis were considered as the absolute scores for effectiveness. If a HR of an antihypertensive drug class was absolutely but not significantly different from the reference group, the absolute score assigned to this class was considered similar to the absolute score of the reference group (1.00).

Persistence with treatment

A recent population based study on persistence with antihypertensives, which included all of the five classes studied, was used to estimate differences in persistence for the various drug classes[11]. The HRs obtained from this population-based study were considered as the absolute scores for persistence with treatment. If a HR of an antihypertensive drug class was absolute but not significantly different from the reference group, the absolute score assigned to this class was considered similar to the absolute score of the reference group (1.00).

Clinical experience and costs

Data on clinical experience and costs were obtained from the Dutch Board of Health Insurance Organizations (DBHIO)[12]. The DBHIO collects and analyses data about the use of drugs in the Netherlands from reimbursement claims from pharmacies and patients[12]. The database consisted of claims from about 7.5 million patients, approximately half of the Dutch population. Clinical experience was determined by the sum of the DDDs dispensed in the previous 5 years for a certain drug class. Costs of a certain drug class were determined by the cost of the agent with the lowest price in a certain class recalculated to 2003 costs.

Assigning weight factors for the characteristics of antihypertensive drug classes

To assign weight factors to these four characteristics, a questionnaire was send to 300 cardiologists, 300 pharmacists, 300 internists and 300 general practitioners (GP). The questionnaire is displayed in table 1. We asked participants to indicate the absolute importance of each characteristic, on a visual analogue scale ranging from 0 (very unimportant) to 100 (very important), by drawing a small vertical line on a horizontal 10 cm line. Subsequently, we calculated the average importance for each of the four groups of professionals.

Table 1: questionnaire for cardiologists, pharmacists, GPs and internists

1	In the determination of your choice for an antihypertensive drug, how important do you judge • The effect of an antihypertensive agent on cardiovascular morbidity? • The costs of an antihypertensive agent? • Persistence with treatment? • Clinical experience with an antihypertensive agent?
2	What is your age
3	What is your gender
4	How long do you practice as an GP/cardiologist/internist/pharmacist
5	What would be your first choice antihypertensive drug to prescribe to a male without risk factors for cardiovascular diseases with newly diagnosed hypertension?

Analysis of results

Subsequently, the weight factors and the absolute scores of the different characteristics were combined into a sum score for each of the five classes of antihypertensives by using SAW and TOPSIS-analysis.

Simple Additive Weighting (SAW)

The weight factors assigned to the different characteristics must be normalized so that the sum of all weights is 1. Normalizing is a mathematical procedure where a value, in this study a weight factor, is expressed as the fraction or percentage of the total sum of values, in this study the sum of weight factors assigned by one group of professionals. For each antihypertensive drug class the normalized weights of the four characteristics are multiplied by the absolute scores of the characteristics. The final scores for each antihypertensive drug class were obtained by adding up the total scores for each of the four characteristics. The value of SAW is by definition between 0 (least ideal antihypertensive drug class) and 1 (ideal antihypertensive drug class).

$$SAWi = \sum_{j=1}^{N} a_{ij} w_j \Big/ N, \text{ for } i = 1, 2, 3, ..., M$$

where SAW_i is the SAW score of the i^{th} antihypertensive; M and N are the number of antihypertensives and characteristics respectively; a_{ij} is absolute score for the i^{th} antihypertensive drug of the j^{th} characteristic, and w_j is the normalized weight of the j^{th} characteristic

Technique for Order Preference by Similarity to an Ideal Solution (TOPSIS)

The TOPSIS-method was developed by Hwang and Yoon in 1981 and its basic approach is to find an alternative which is the closest to the ideal solution and the farthest from the least ideal solution in a multidimensional computing space. This multidimensional computing space is specified by characteristics as dimensions. The ideal solution represents a virtual alternative with a set of possibly best synthetic scores in terms of each characteristic, while the least-ideal solution is a virtual alternative with a set of worst scores. Physically, there are two points in the computing space with extreme values as dimensions. First, the weight factors for the different characteristics were normalized so that the sum of all weights is 1, similar to the SAW-method. Second, the absolute scores for each characteristic of an antihypertensive drug class were normalized by dividing this score for an antihypertensive drug class in terms of a characteristic by the square root of the sum of each score for each antihypertensive drug class squared.

$$y_{ij} = \frac{x_{ij}}{\sqrt{\sum_{i=1}^{M} x_{ij}^2}}$$

where y_{ij} is the normalized absolute score, M is the number of antihypertensives; x_{ij} denotes the normalized absolute rating score of the i^{th} antihypertensive in terms of the j^{th} characteristic

These normalized absolute scores are multiplied by the normalized weight factors given by the decision makers, resulting in a weighted normalized decision matrix WY.

$$WY = w_j y_{ij}$$

where w_j denotes the normalized weight factor of the j^{th} characteristic

This results in a maximum score for each characteristic, three intermediate scores and a minimum score:

$$S_j^+ = \max(w_j y_{ij}), S_j^- = \min(w_j y_{ij}), \text{ for } i = 1, 2, 3, ..., M$$

where S_j^+ denotes the maximum score for the j^{th} characteristic and S_j^- denotes the minimum score for the j^{th} characteristic

The combination of all maximum scores for each of the four characteristics is defined as the ideal solution, the combination of minimum scores as the least ideal solution represented as four coordinates. The next step is to calculate the Euclidean distance of each antihypertensive drug class to the ideal solution and the least ideal solution. This is done for each antihypertensive drug class by taking the square root of the sum of the squared difference between an ideal solution of a characteristic minus the true value (normalized absolute score multiplied by weight factor).

$$D_i^+ = \sqrt{\sum_{j=1}^{N} \left(S_j^+ - w_j y_{ij}\right)^2}, \quad for\ i = 1, 2, 3, ..., M$$

$$D_i^- = \sqrt{\sum_{j=1}^{N} \left(w_j y_{ij} - S_j^-\right)^2}, \quad for\ i = 1, 2, 3, ..., M$$

where D_i^+ denotes the Euclidean distance to the maximum score for the i^{th} antihypertensive drug class and D_i^- denotes the Euclidean distance to the minimum score for the i^{th} antihypertensive drug class

This results for each antihypertensive drug class in two Euclidean distances, one Euclidean distance to the ideal solution and one Euclidean distance to the least ideal solution. The closeness to the ideal solution is calculated by dividing the distance to the least ideal solution by the sum of the distance to the least ideal solution and the distance to the ideal solution.

$$C_i = \frac{D_i^-}{D_i^- + D_i^+}$$

where C_i denotes the relative closeness of the i^{th} antihypertensive drug class to the ideal antihypertensive

Finally, this results in five scores, the highest score indicates the most ideal antihypertensive drug class. The value of the closeness is by definition between 0 (least ideal antihypertensive drug class) and 1 (ideal antihypertensive drug class).

Sensitivity analysis

Several sensitivity analyses were performed to test the robustness of our methodology and sensitivity of our absolute scores for effectiveness, persistence, cost and clinical experience. First, we analyzed our results leaving one of the four characteristics out of the analysis. Furthermore, we analyzed our results for both the characteristics effectiveness and persistence for the extremes of the confidence intervals of the risk estimates obtained from the meta-analysis and the persistence study. In addition, we analyzed our results if clinical experience was expressed by the number of DDDs dispensed between 2000-2003, 2001-2003, 2002-2003 and 2003 alone, instead of 1999-2003. Furthermore, we analyzed our results if clinical experience was not expressed by the volume of drug consumption but by the

number of users of a certain drug class between 1999 and 2003. We also analyzed our results if instead of the costs of a DDD of the cheapest antihypertensive in one antihypertensive drug class the average costs of a DDD in an antihypertensive drug class were considered.

Statistical analysis

Student's t-tests were used to compare the weight factors between cardiologists, GPs, pharmacists and internists (SPSS 12.0 for Windows). SAW and TOPSIS analysis do not allow statistical testing for significant differences between the reported scores or between groups of professionals.

Results

Assigning absolute scores to the characteristics of antihypertensive drug classes

Effectiveness

The results of the assignment of absolute scores for each of the four characteristics to each of the five antihypertensive drug classes are displayed in table 2. Diuretics were the most effective antihypertensive drug class followed by ACE-inhibitors and dihydropyridine calcium channel blockers. Beta-blockers were the least effective antihypertensive drug class. ARBs were not significantly different from diuretics and therefore the same score was assigned to this class.

Table 2: absolute and normalized rating of effectiveness, persistence, costs, clinical experience for diuretics, beta-blockers, DHP-CCBs, ACE-inhibitors and ARBs

	Diuretics ARS/NRS	**Beta-blockers ARS/NRS**	**DHP-CCBs ARS/NRS**	**ACE-Is ARS/NRS**	**ARBs ARS/NRS**
Effectiveness[a]	1/0.21	0.89/0.19	0.94/0.20	0.94/0.20	1/0.21
Persistence[b]	0.36/0.11	0.56/0.17	0.62/0.19	0.81/0.24	1/0.30
Costs[c] (€/DDD)	0.16 /0.40	0.42/0.15	0.40/0.16	0.36/0.18	0.57/0.11
Clinical experience[d]	2.45/0.07	11.8/0.31	6.77/0.18	12.5/0.33	4.04/0.11

ARS=absolute rating score; NRS=normalized rating score; a: HR for cardiovascular events[10]; b: HR for persistence[11]; c: Cost per DDD of the cheapest agent in a certain class in The Netherlands in 2003 in euros[12]; normalized absolute scores were calculated by normalizing the reciprocal of the absolute costs; d: number of DDDs/10^9 dispensed by community pharmacies in The Netherlands between January 1999- and December 2003[12]

Persistence with treatment

Patients who started with the use of ARBs demonstrated the highest persistence, followed by ACE-inhibitors, DHP-CCBs and beta-blockers (table 2). Patients who started with diuretics demonstrated the lowest persistence with treatment.

Clinical experience and costs

Clinical experience expressed as the number of DDDs dispensed during the past five years was the highest with ACE-inhibitors and beta-blockers followed by calcium channel-blockers, diuretics were the least frequently used (table 2). Hydrochlorothiazide was the cheapest diuretic (98.7% of all DDDs for diuretics), metoprolol the cheapest beta-blocker (51.4% of all DDDs for beta-blockers), nifedipine the cheapest DHP-CCB (28.0% of all DDDs for DHP-CCBs), enalapril the cheapest ACE-inhibitor (36.5% of all DDDs for ACE-inhibitors) and candesartan the cheapest ARB (13.6% of all DDDs for ARBs). [12]

Assigning weight factors for the characteristics of antihypertensive drug classes

A total of 17 questionnaires that were sent to cardiologists, 10 to GPs, 15 to internist and 13 to pharmacists, were returned unanswered because the addresses were no longer valid. A total of 92 cardiologists (33%), 90 GPs (31%), 87 internist (31%) and 123 pharmacists (43%) completed the questionnaire. In table 3, the results of the questionnaire are displayed. The results of the absolute weight factors of the characteristic are displayed in figure 1.

Table 3: differences between cardiologists, pharmacists, GPs and internists, with regard to the importance of characteristics in the determination of the choice for the first line antihypertensive drug class

	Effectiveness	**Persistence**	**Costs**	**Clinical experience**
CAR vs. PHARM	p=0.278	p=0.123	p<0.001	p<0.005
CAR vs. GP	p=0.719	p=0.789	p<0.001	p=0.468
CAR vs. INT	p=0.483	p=0.485	p=0.470	p=0.827
PHARM vs. GP	p=0.141	p=0.223	p=0.831	p<0.001
PHARM vs. INT	p=0.068	p<0.05	p<0.05	p<0.05
GP vs. INT	p=0.730	p=0.357	p<0.05	p=0.356

CAR=cardiologist; PHARM=pharmacist; GP=general practitioner; INT=internist

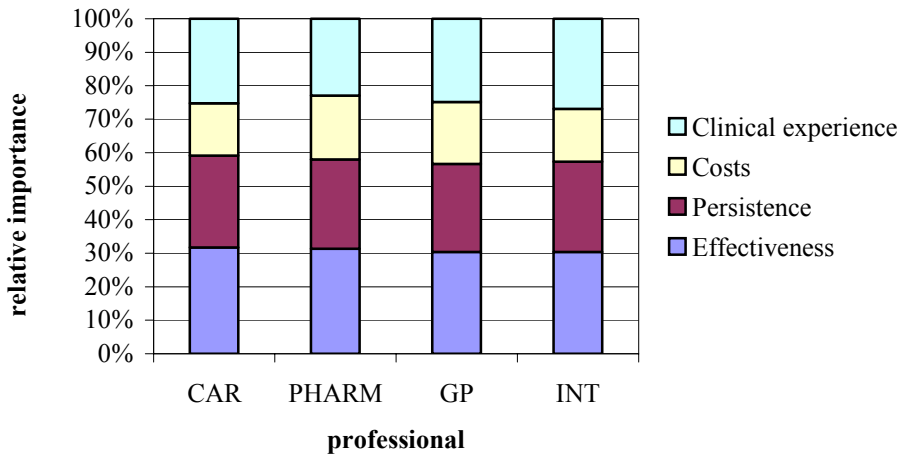

Figure 1: results of questionnaire among GPs, cardiologists, internists, pharmacists on importance of effectiveness, persistence, costs and clinical experience in determining the first line agent in hypertension. CAR=cardiologist; PHARM=pharmacist; GP=general practitioner; INT=internist

GPs and pharmacists rated costs significantly more important than cardiologists and internists. Pharmacists only agreed with internists on effectiveness (p=0.068). Pharmacists rated clinical experience less important than the other three professionals. There were some small significant differences between the four groups of professionals in the scoring of the weight factors. We found no differences within a group of professionals for subgroups defined by age, years of working experience and gender (data not shown).

Analysis of results

Results of SAW- and TOPSIS-analysis

Both SAW and TOPSIS-analysis ranked ACE-inhibitors as the first choice among the antihypertensives followed by beta-blockers and ARB. DHP-CCBs and diuretics were ranked as the last choice according to both methods (table 4 and table 5).

Table 4: SAW scores of cardiologists, pharmacists, GPs and internists

	Cardiologists	Pharmacists	GPs	Internists
Diuretics	11.5%	12.1%	12.6%	11.8%
Beta-blockers	14.8%	14.4%	15.4%	15.0%
DHP-CCBs	12.7%	12.5%	13.2%	12.9%
ACE-Is	16.6%	16.1%	17.2%	16.8%
ARBs	12.8%	12.5%	13.1%	13.1%

DHP-CCBs=dihydropyridine calcium channel blockers; ACE-Is=ACE-inhibitors; ARBs=angiotensin II receptor blockers;

Table 5: TOPSIS-scores of cardiologists, pharmacists, GPs and internists

	Cardiologists	Pharmacists	GPs	Internists
Diuretics	34.4%	40.6%	38.9%	35.4%
Beta-blockers	54.0%	49.5%	51.8%	52.9%
DHP-CCBs	37.3%	35.0%	35.7%	37.0%
ACE-Is	66.9%	61.5%	63.4%	65.9%
ARBs	44.4%	42.5%	41.6%	44.6%

DHP-CCBs=dihydropyridine calcium channel blockers; ACE-Is=ACE-Inhibitors; ARBs=angiotensin II receptor blockers

Sensitivity analysis

Leaving one of the four characteristics out of the analysis, although none of the groups of professionals and none of the individual professionals ranked a characteristic as totally unimportant (weight factor=0), did not lead to a different first line choice. In all cases, ACE-inhibitors remained the first line choice, although the absolute values of the SAW and TOPSIS-analysis were somewhat different. Furthermore, we analyzed our results for both the characteristics effectiveness and persistence for the extremes of the confidence intervals of the risk estimates obtained from the meta-analysis and the persistence study. Again in all cases, ACE-inhibitors remained the first choice. In addition, we analyzed our results if the clinical experience was expressed by the number of DDDs dispensed between shorter periods until 2003 instead of 1999-2003, if clinical experience was not expressed by the volume of drug consumption but by the number of users

of a certain drug class between 1999 and 2003 and if not the cost of a DDD of the cheapest antihypertensive drug in one antihypertensive drug class were considered but the average cost of a DDD in a antihypertensive drug class. In none of these analyses of different absolute scores for clinical experience or costs changed our conclusion that ACE-inhibitors are the first-line choice. In all cases both methods lead to the same conclusion (data of the sensitivity analysis are not shown).

Discussion

In this study we aimed to compare two multiple characteristics decision making models, simple additive weighting and technique for order preference by similarity to an ideal solution. We used antihypertensive drugs and weight factors assigned by cardiologists, pharmacists, GPs and internists as an example to perform this comparison. We found that both methods and all groups of professionals ranked the same drug class, ACE-inhibitors, as the first choice. In addition, professionals working in primary care (pharmacists and GPs), ranked costs more important than cardiologists or internists. This may be explained by the fact that those groups of workers are more often directly confronted with costs, healthcare budgets and dissatisfaction of patients associated with new regulations. Especially pharmacists, and to a relevant degree GPs, are more aware of large groups of patients that need treatment and the payment thereof and may therefore be more focused on costs. Pharmacists ranked clinical experience less important than the other professionals, although differences were small in absolute terms. This may be explained by the fact that pharmacists, at least in The Netherlands, do not prescribe medication, and are therefore less confronted with deciding about the risk associated with starting new treatment, in contrast to GPs, cardiologists and internists, who are aware of the standard proven regimens, and less willing to try new strategies if effective ones exist.

There are some important limitations to this type of study. The first limitation is that we cannot compare our results with a gold standard of what the best antihypertensive drug class actually is, or what the order of preference for the different drug classes should be. In most countries guidelines from large national or international organizations will be used. In the guidelines of the National Institute of Clinical Excellence (UK) on hypertension, the statement on the management of hypertension from the World Health Organization/ International Society of Hypertension and the guideline of the Dutch College of General

Practitioners, effectiveness obtained from clinical trials and meta-analyses (including the meta-analysis of Psaty et al. we used) formed the basis of their decision to rank thiazide diuretics as the first line antihypertensive[10,13,14]. In these guidelines, the other characteristics were also deemed relevant. E.g. persistence is regarded as important, but only in the light of reducing the number of daily dosages and interventions to improve it, but not with regard to the initial drug choice[15]. In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (US), the strategy of determining the first choice is also primarily based on the results of trials and meta-analyses (with reference to the previous version of the meta-analysis we have used)[16,17]. In this guideline, the relation between resistant hypertension and non-adherence is specifically mentioned but no recommendations are made as to whether this should influence decisions about which drug to prescribe. The fact that such important guidelines consider diuretics to be the first-line antihypertensive should lead to large volumes of diuretic prescribing. However, as is demonstrated by our data on clinical experience (only 7% of the patients using antihypertensives used a thiazide diuretic) and from data on persistence we used in this study (24.1% of patients with hypertension receive a diuretic as initial treatment) this is not the case[11,12]. Of course a large number of health care professionals will already take other aspects next to effectiveness into account during their decision what to prescribe. The phenomenon of physicians' non-adherence to guidelines has been described elsewhere[18,19].

Furthermore, it deserves debate whether the visual analogue scale of obtaining weight factors was the most appropriate, although the method has been validated. Another method is the degree of preference-method, where the expert determines to which extent one characteristic is preferred to another one. Another option may be simply dividing e.g. 100 points among the characteristics.

A more content related limitation is that antihypertensives should probably not be analyzed as one group because of the within-group differences with regard to pharmacokinetic and pharmacodynamic characteristics as mentioned in the first paragraph of the methods section. However, data on comparative effectiveness and persistence are scarcely available for individual antihypertensives. Psaty et al. demonstrated that even within the highly variable class of diuretics there are no differences with regard to effectiveness[20]. Hasford et al. demonstrated that one-

year persistence with irbesartan is similar to the rest of the ARBs, 76.8% vs. 74.9%[21]. In a direct comparison between amlodipine and felodipine, patients who received amlodipine, either as a monotherapy or as part of a multiple drug regimen, were only slightly more persistent with their treatment than patients on felodipine. However, it is of course possible that if more data would be available for different antihypertensives within a certain class, the outcome could be different. In our determination of costs of drug classes, we did not consider atenolol, which is cheaper than metoprolol (0.30€/DDD vs. 0.42€/DDD). This was done because atenolol, in a recent publication was rejected as an option in the treatment of hypertension, although this analysis was accompanied by some serious methodological concerns[22]. Therefore, the costs of metoprolol, although slightly different from atenolol (e.g. metabolized by the liver instead of kidney) will probably better represent costs concerning beta-blockers in the near future.

More broadly, for the determination of effectiveness, we used the data of Psaty et al[10]. In this analysis beta-blockers were the least effective treatment among the five groups of antihypertensives. A more recent analysis by Lindholm et al. also suggested that beta-blockers should be rejected for the treatment of hypertension when compared to other antihypertensive drugs[23]. Our analysis ranked beta-blockers as the second choice, which is mainly due to large experience and low costs. Therefore, it deserves debate whether this class of antihypertensives should have been omitted from our analysis, because it may no longer be a possible choice in the treatment of uncomplicated hypertension without comorbidities.

During the past ten years, the DDDs of enalapril (1995), hydrochlorothiazide (1996) and metoprolol (1995) decreased[24]. It is possible that this will also occur in the near future for ARBs. The most likely change in this case would be an increase in DDD, because the blood pressure reduction with the currently available DDDs is often insufficient. E.g. in the VALUE trial more patients reached target blood pressure with 1 DDD amlodipine (DHP-CCB) compared to 1 DDD valsartan and with 2 DDDs amlodipine compared to 2 DDDs valsartan[25]. In the same trial patients in the valsartan group needed more additions of other antihypertensives. The average blood pressure throughout the study was higher in the valsartan group. In the LIFE trial patients starting with 1 DDD of losartan (ARB) were compared paients starting with two-third of a DDD of atenolol (beta-blocker), the

pattern of additions and blood pressure being roughly the same. This makes comparing DDDs of ARBs with other DDD of antihypertensives less valid[26].

Within the group of diuretics, we limited our analysis to the thiazide diuretics leaving out the other types of diuretics such as loop diuretics. The same holds for the calcium channel blockers, from which only the dihydropyridines were analyzed (without verapamil and diltiazem). ACE-inhibitors and ARBs were considered more or less equal. The largest problem may be with the beta-blockers, because only sotalol was excluded and e.g. propranolol, which was used for hypertension in the past and tested in RCTs for that purpose, was not excluded although it is no longer considered as an option for hypertension. Furthermore, the different beta-blockers posses different pharmacodynamic properties with regard to the lipophilicity and the beta-receptor selectivity.

We performed our analysis based on four characteristics, effectiveness, persistence, cost and clinical experience. These characteristics may be subdivided to other more specific ones, although the characteristics should not become complimentary (e.g. if effectiveness is divided in reduction of total morbidity, reduction of total mortality, reduction of cardiovascular morbidity and reduction of cardiovascular mortality). Although regular side-effects may be reflected by lower persistence, less frequently occurring harmful side-effects should also be incorporated in the analysis although the way of quantifying this remains difficult. In addition, different antihypertensives may have other than pharmacokinetic and pharmacodynamic characteristics that determines its score in such analyses, e.g. number of available dosage forms. Although in this study the antihypertensives were used as a model only to compare SAW and TOPSIS-analysis, an analysis, which has the primary aim to indicate the best antihypertensive or antihypertensive drug class, should address these concerns.

An important strength of our study is that we had a sufficient number of respondents making our panel of experts relatively large and our estimates of the relative weight factor relatively precise. However, the response rate was only slightly higher than 30%; therefore our findings may not be representative for the whole community of health care professionals. It seems plausible that physicians regarding only effectiveness as relevant are not willing to cooperate in studies addressing MCDM-models because they consider these models principally

useless. Furthermore, the assessment of the absolute scores of our four characteristics is relatively objective, which is confirmed by the several sensitivity analyses.

Implications

Because our results demonstrate that both methods roughly lead to the same conclusions, and SAW-analysis is easier to understand and to perform, it seems logical to qualify this method as better. However, the advantage of TOPSIS-analysis is that it also takes into account the lack of properties of, in this case antihypertensives, not only the presence, as is the case with SAW-analysis. Furthermore, the outcome of TOPSIS-analysis indicates the extent to which a certain alternative approaches the ideal set of properties, making the outcome more useful in comparing alternatives. In future research, both methods should be applied next to each other; differences in preferences between both methods may be an indicator to carefully reconsider the characteristics used and the method of determining weight factors. More detailed research is needed to determine whether our conclusion with regard to the first line choice among antihypertensive was valid. Furthermore, these studies should be performed in different countries with different health care systems, costs and views about the treatment of hypertension. E.g. in some less developed countries persistence to treatment and experience may be less important compared to costs and effectiveness. In countries that have a traditional view on the patient-doctor relationship, only effectiveness may be considered important. In addition, if a drug is recently added to the WHO essential medicines list accompanied by funding to realize availability in a certain country, professionals will rely more heavily on foreign experience and rank this characteristic as more important[15].

Finally, this analysis is much more difficult for patients at different stages of hypertension, with different comorbidities and more complex regimens. For instance, if a patient is both diagnosed with hypertension and stable angina pectoris, the number of possible options with regard to first line drug class changes immediately[27]. In this scenario, evidence for effectiveness with regard to comorbidities and risk factors are and should be the main determinant of the choice for a specific treatment.

In conclusion, SAW and TOPSIS-analysis using weight factors assigned by cardiologists, pharmacists, GPs and internists in The Netherlands rank ACE-inhibitors as the first choice among the antihypertensive drug classes for the treatment of uncomplicated hypertension. Both methods are valuable tools in the development of objectified pharmacotherapy.

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Chapter 5

Intervening in patients using chronic treatment

Chapter 5.1

Effectiveness of interventions by community pharmacists to improve patient adherence with chronic medication: a systematic review

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Summary

Background: A number of studies that explore the possibilities of community pharmacists with regard to enhancing adherence to treatment have been published. The objective of this study was to systematically review the impact of interventions by community pharmacists on patients' adherence with chronic medication.

Methods: A MEDLINE search (1966–November 30, 2003) and a review of reference sections were done to identify all pertinent English and German language journal articles. Search terms included compliance, adherence, persistence, discontinuation, pharmacist and intervention. From each relevant study, the following data were extracted: study design, country, disease, number of patients, patients' age and gender, type of intervention, duration of follow-up, method of measurement of adherence, adherence rate and data concerning the quality of the included studies.

Results: A total of 162 studies were identified, of which 18 matched our inclusion criteria. Twelve were randomized controlled trials and 6 were non-crossover single-group trials. Eight studies showed significant improvement of adherence at one or more time points. Eight studies did not show any effect, 7 of which were randomized controlled trials. In most studies, adherence rates at baseline were high compared to rates reported in the general population. Counseling, monitoring, and education during weekly or monthly appointments showed some effect. However, these same types of interventions showed no effect in other studies. The overall quality of the included studies was low.

Conclusion: Currently, it is impossible to identify an overall successful adherence-improving strategy performed by pharmacists. More well-designed and well-conducted studies on the effectiveness of interventions by a community pharmacist to improve patient adherence to chronic medication need to be performed.

Background

When patients are not adherent to prescribed medication, the therapeutic goal cannot be attained, resulting in increased morbidity and mortality[1-5]. In the US, reported annual hospitalization costs of medication non-adherence were estimated to be about $13.35 billion in 2000. This represents 1.7% of all healthcare expenditures, which indicates that non-adherence is a medical as well as an economic problem of an enormous magnitude[6].

Pharmacists have the educational background and specific patient-related information to be actively involved in providing pharmacotherapeutic support for patients and prescribers. This support should help make pharmacotherapy as efficient and safe as possible. In many cases, the possibilities of the pharmacist are not used optimally. An example of this is that monitoring patient adherence with the prescribed therapeutic regimen is only part of the routine check that accompanies dispensing in most pharmacies. Instead, monitoring and improving patient adherence should be part of the primary tasks of community pharmacies because, in the chain of healthcare providers, the pharmacist or pharmacy have the best and most logical position to detect problems concerning the chronic use of medication[7]. Therefore, much pharmacy practice research has been done to identify strategies for the pharmacist to intervene in the patient's medication taking. Some strategies appeared to be successful; others did not seem to make any difference. The purpose of this study was to systematically review the research literature on interventions done by community pharmacists to improve patient adherence with chronic medication. The direct relationship between adherence and clinical outcome was, although relevant, outside the scope of this review.

Methods

Search strategy

The MEDLINE database was searched from 1966 to November 30, 2003. Reviews and meta-analyses, as well as reference lists of selected articles, were searched for relevant studies. No conference proceedings were searched; neither were other databases or reference lists of textbooks. The key words used in the search strategy of the MEDLINE database were (noncompliance or non-compliance or compliance or nonadherence or non-adherence or adherence or

discontinuation or persistence or nonpersistence or non-persistence) and (pharmacist or pharmacists) and (intervention or interventions). To minimize the likelihood of articles being overlooked, a second search was performed without the search term (intervention or interventions). This list of titles of the second search was systematically checked for relevant studies and compared to the first search. Different publications on the same group of patients were considered one study. If the abstract clearly indicated that the study did not match our inclusion criteria, the study was excluded. If there was uncertainty about inclusion criteria, a full copy of the article was obtained.

Inclusion and exclusion criteria

Controlled and uncontrolled, prospective and retrospective, and randomized and nonrandomized studies were considered in this review. Patients considered were those prescribed medication for a chronic disease. A disease was considered chronic if it had lasted or was expected to last more than 3 months (e.g., chronic depression, diabetes, hypertension)[8]. Interventions could be directed towards individuals or groups and included all types of actions to improve patient adherence. The primary goal of the intervention did not have to be improving adherence itself, but might also be improvement of clinical outcome. We included only studies in which a community pharmacist in a community pharmacy setting performed these actions. Studies in which pharmacists in other practice settings were involved in an intervention were excluded since their place in the chain of healthcare providers towards the individual patient differs greatly from that of community pharmacists. Studies on interventions that did not involve the pharmacist as the only healthcare professional were excluded.

The primary or secondary outcome measure had to be patient adherence[9]. Adherence could be measured through pill counts, medication diaries, patient self-report, provider report, clinic and pharmacy records, serum and saliva concentrations and biomarkers or other types of measurements. Included studies contained at least one measurement of adherence. Dropouts or withdrawals from clinical trials were not considered measures of adherence. The article had to be published in the English or German language.

The assessment of quality

Titles and abstracts of studies suggested by the electronic search were evaluated and compared to the inclusion criteria if possible. When articles appeared to fulfill the inclusion criteria or in case of doubt, complete copies were obtained. The data reported in the full articles were evaluated. Studies were not rejected because of the absence of a description of the method of recruitment, method of randomization, blinding of the outcome assessor, loss to follow-up, reasons for loss to follow-up and the presence of a power calculation.

Methods of review

Two authors (Van Wijk and Klungel) independently determined study eligibility based on abstracts. They were not blinded with regard to authors or journal. In 15 cases, disagreement between the 2 reviewers occurred, and full copies of the articles were obtained. After assessment of the full copies, both reviewers concluded that all 15 studies should be excluded. Full copies of the remaining studies were obtained and the following data were extracted by Van Wijk: study design, country in which the study was performed, patients' age and gender, number of patients, duration of study, disease or problem that was evaluated, how long patients had to be on therapy, measurement of adherence, whether adherence was the primary or secondary outcome and adherence rate. Furthermore, the following criteria regarding the quality of the studies were extracted: method of recruitment, method of randomization, blinding of the outcome assessor, loss to follow-up, reasons for loss to follow-up and presence of a power calculation.

Results

The search resulted in 162 articles; of these, 144 were excluded. Thirteen review articles and one meta-analysis were excluded. Seventy-three studies in which non-community pharmacists were involved in an intervention were excluded. Among these 73 studies, 69 interventions were performed by a hospital pharmacist, one by a pharmacy officer, one by a research pharmacist and 2 by a pharmacist working in a psychiatric hospital. In 3 studies, a community pharmacist did not perform the intervention, but was involved only in providing dispensing data. Eleven studies on interventions in which the pharmacist was not the only healthcare professional involved in the intervention (nurses and physicians included) were excluded. In 13

studies, no adherence-enhancing intervention was done; these studies were also excluded. In most cases, these studies were of an inventory nature.

Ten studies in which the disease involved was not chronic according to our definition were excluded. Fifteen investigations in which patient adherence was not measured were excluded. In 2 studies, adherence with guidelines was evaluated, but not patient adherence with medication. In one article, drug therapy was not assessed. In another study, the effect of the intervention on adherence was not measured. One article in French was also excluded from this review.

A total of 18 articles are included in this review[10-27], 13 of which were retrieved in the first search[10-13,15,17,18,22-27]. From the search of reference lists, reviews, and meta-analyses, an additional 5 studies were included[14,16,19-21]. Included were 13 randomized controlled trials (RCTs)[10,13,15-18,20-24,26]. The studies were too disparate to perform a meta-analysis. Besides these RCTs, 6 non-crossover single-group trials (NCSGTs) were included[11,12,14,19,25,27]. The results of the search strategy and data extraction are listed in tables 1 and 2[10-27]. Fifteen of these studies were performed in North America[10-12,14-23,25,27]. Fourteen were published in the past 10 years[10,11,13-15,17-19,22-27]. Four interventions focused on treatment of hypertension, 5 on chronic medication in general, 2 on diabetes, 3 on asthma or chronic obstructive pulmonary disease, 2 on hyperlipidemia, one on congestive heart failure and one on coronary heart disease. The number of patients involved varied greatly, ranging from 12 to 397. The type of intervention done by the community pharmacist was, in most cases, education, monitoring and (advanced) counseling and was compared to routine dispensing (usual care). The majority of studies had at least one year of follow-up (5 days to 2 years). In 14 studies, patient adherence was the primary outcome[11,12,14,15,17,19-27]. The measurement of adherence was, in most cases, either self-report or pill counts[10,11,13,14,17,18,20,22,23]. In 8 studies, pharmacy records were used to determine adherence (sometimes next to pill counts or self-report)[16,19-21,23,25-27]. In only one study, the medication event monitoring system (MEMS [AARDEX, Ltd]) was used[24].

Table 1: characteristics of studies on intervention by community pharmacists

Reference	Design	Country	Population	Number Int/Con	Age (years) Int/Con	%Male Int/Con	Follow-up
Ali et al. (2003)[25]	NCSGT	Canada	coronary heart disease	91	NA	NA/NR	6 months
Barnett et al. (2000)[18]	RCT	US	first prescription for chronic medication	30/44	46/46	63/63	5 days
Berringer et al. (1999)[11]	NCSGT	US	type 1 or 2 diabetes	52	62	38/NR	12 months
Bluml et al. (2000)[19]	NCSGT	US	hyperlipidemia	397	57	NA/NA	24 months
Bouvy et al. (2003)[24]	RCT	Netherlands	CHF	48/43	69/70	72/60	6 months
Chabot et al. (2003)[23]	RCT	Canada	hypertension	41/59	<60 22/30 60-69 22/36 ≥70 56/34	32/37	NA
Cordina et al. (2001)[13]	RCT	Malta	asthma	88/66	41/46	42/39	12 months
Dumas et al. (1992)[12]	NCSGT	Canada	chronic medication	241	NA	NA/NR	NA
Grant et al. (2003)[22]	RCT	US	type 2 diabetes	62/58	64/69	45/31	3 months
McDonough et al. (2003)[27]	NCSGT	US	hyperlipidemia	116	55	40/NR	NA
McKenney et al. (1973)[16]	RCT	US	hypertension	24/25	62/58	25/2	12 months
McKenney (1978)[20]	RCT	US	hypertension	70/66	53/56	49/51	4 months
Odedina et al. (2000)[14]	NCSGT	US	asthma	12	54	9/NR	6 months
Park et al. (1996)[15]	RCT	US	hypertension	27/26	57/63	48/50	3 months

Slama et al. (1978)[21]	RCT	US	first prescription for chronic medication	27/26	60/NA	27/NA	1 months
Sturgess et al. (2003)[26]	RCT	Northern Ireland	>3 medications	110/81	73/74	36/36	18 months
Volume et al. (2001)[17]	RCT	Canada	>2 medications	159/204	74/73	36/30	12-13 months
Weinberger et al. (2002)[10]	RCT	US	asthma/COPD	185/129	62/63	3620	12 months

CHF=congestive heart failure; Con=control group; COPD=chronic obstructive pulmonary disease; Int=intervention group; NA=not available; NCSGT=non-crossover single-group trial; NR=not relevant (due to the study design); RCT=randomized controlled trial.

Table 2: results of studies on intervention by community pharmacists

Reference	Intervention	Measurement	Adherence primary outcome	Time points	Adherence[a] Int	Adherence[a] Con	P<0.05
Ali et al. (2003)[25]	education monitoring	pharmacy records	yes	average[b] adherent pts./days per refill			
				before	41/49	NR	yes
				after	56/38	NR	yes
Barnett et al. (2000)[18]	pharmacist incorporated written questions of pts. into counseling	pill counts	no	average adherence after 5 days	87%	86%	no
Berringer et al. (1999)[11]	subjective and objective data related to diabetes gathered with each refill, monthly chart review, recommendations to pts. and physicians	pill counts	yes	average adherence			
				baseline	88%	NR	no
				12 months	90%		
Bluml et al. (2000)[19]	monthly visits for 3 mo, quarterly thereafter: cholesterol measurement, counseling	pharmacy records	yes	average adherence[c] after 24 months	90%	NR	NR
Bouvy et al. (2003)[24]	each month for 6 mo, counseling, monitoring	MEMS	yes	days with medication after[d]	98%	95%	yes
Chabot et al. (2003)[23]	encouragement and rewards for good adherence	self-report (at baseline also pharmacy records)	yes	adherent patients (pharmacy records)			
				baseline	68% (98%)	83% (93%)	no
				after intervention	74%	82%	no
Cordina et al. (2001)[13]	education session, monthly meeting for 12 mo, monitoring, counseling	self-report	no	missing 1 dose			
				1/day	17%	27%	no
				1/week	65%	60%	no
				2-3/week	18%	13%	no
Dumas et al. (1992)[12]	writing a pharmaceutical opinion to pts. or prescribers	NA	yes	positive	76%	NR	yes
				negative	21%		
				neutral	3%		

Grant et al. (2003)[22]	education, referrals	self-report	yes	adherent days in past wk			
				baseline	6.7	6.9	no
				3 months	6.8	7.0	no
McDonough et al. (2003)[27]	identification of drug-related problems, counseling, monitoring	pharmacy records	yes	pts. with increased adherence after	48%	NR	NR
McKenney et al. (1973)[16]	monthly visits for 5 mo, monitoring, counseling, contact with prescribers, education	pharmacy records, pill counts	no	baseline	67%	63%	no
				0-5 months	92%	56%	yes
				5-12 months	70%	60%	no
McKenney (1978)[20]	each refill, monitoring, education	pharmacy records	yes	average adherence after 4 months	80%	74%	yes
Odedina et al. (2000)[14]	monthly meeting for 6 mo, education, counseling, monitoring	self-report	yes	on a scale of 4[e]			
				baseline	1.3	NR	yes
				6 months	0.5		
Park et al. (1996)[15]	monthly visits for 3 mo, BP and HR assessments, counseling on lifestyle modifications and drug therapy	pill counts, pts. not informed	yes	average adherence			
				baseline	87%	88%	no
				1 months	97%	86%	yes
				2 months	97%	87%	yes
				3 months	87%	89%	no
Slama et al. (1978)[21]	counseling at start	pill counts, pharmacy records	yes	1 mo	38%	44%	no
Sturgess et al. (2003)[26]	identification of drug-related problems, implementation of adherence-enhancing strategies	self-report, pharmacy records	yes	baseline	38%/30%	32%/30%	no/no
				6 months	35%/46%	29%/19%	no/yes
				12 months	40%/40%	24%/25%	yes/no
				18 months	47%/40%	15%/41%	yes/no
Volume et al. (2001)[17]	6 telephone calls/mo, education, counseling, monitoring	self-report	yes	average adherence			
				baseline	53%	64%	no
				6-7 months	48%	58%	no
				12-13 months	56%	47%	no

Weinberger et al. (2002)[10]	each refill, education, counseling	self-report	no	adherent[f] /on a scale of 4[e]			
				baseline	65%/1.3	65%/1.2	no
				6 months	73%/1.0	77%/0.8	no
				12 months	78%/0.8	78%/0.8	no

Con=control group; Int=intervention group; MEMS=medication event monitoring system (AARDEX, Ltd); NA=not available; NR=not relevant (due to the study design); a: if not otherwise specified, adherence is expressed as a percentage of the doses taken; b: adherence based on patient's returning for refill within 2 days of the calculated date and having consistent pill counts; c: definition of adherence used in the calculation of the average adherence rate was any patients who missed doses for ≥5 days or who missed a scheduled refill visit by >5 days was considered to be non-adherent at that visit; d: adherence expressed as number of days without medication/total days on therapy; e: adherence ranked on a scale of 0-4, on which 0 = very good adherence and 4 = poor adherence; f: definition of adherent not mentioned.

Eight studies showed a significant improvement in patient adherence; 5 of these were RCTs[12,14-16,20,24-26]. In 3 of these, an effect was shown at some of the time points of measurement, whereas at other time points, no significant effect was shown[15,16,26]. Five of the successful interventions were combinations of education, counseling, and monitoring[14,20,24-26]. In the study performed by McKenney et al., the improvement of patient adherence compared to baseline was significant only during the 5-month intervention period[16]. The difference in average adherence was 36%. In the 7 months after the intervention was performed, adherence rate returned to baseline. Park et al. showed significant differences in adherence during the intervention at one and 2 months of 10% and 9%, respectively[15]. At 3 months, which was the end of the intervention period, there was no significant difference. Sturgess et al. found a difference in adherence 12 and 18 months after the intervention[26]. Three were NCSGTs, and adherence cannot be expressed in a percentage[12,14,25]. In 8 other studies, no significant effect of the intervention was measured, 7 of which were RCTs[10,13,17,18,21-23]. In 2 investigations, there was neither a control group nor a baseline measurement of adherence, which makes it difficult to estimate the impact of the intervention[19-27].

Quality assessment

Table 3 presents the results of the quality assessment. In 7 of the 8 studies that showed any effect, patients were recruited in the pharmacy[12,14-16,20,25,26]. In the other study, the patient was recruited by the cardiologist[24]. In only 2 of the 10 investigations that showed no significant effect, patients were recruited at the pharmacy[11,17]. In 5 of the 10 studies that showed no effect, patients were recruited anonymously. Patients were recruited by nurses and physicians, phone calls, mailed letters, recruitment sessions or referrals[10,13,19,22,23]. In 3 studies, patient recruitment was not specified[12,21,27]. From the RCTs in which randomization took place at the patient level, 3 studies showed an effect[16,20,24]. However, 3 RCTs in which randomization took place at the patient level did not show any effect[10,18,22]. In RCTs in which the randomization took place at a pharmacy level, only one showed an effect[26]. In 2 RCTs, the randomization method was not specified[15,21]. Six of the 8 studies that showed an effect clearly reported selection criteria for study patients[15,16,20,24-26]. Six of the 10 studies that did not show any effect also clearly reported selection criteria[10,11,13,21-23]. Three studies allowed both new and chronic users to be included, none of which showed any effect[17,19,27]. Only 2 of the 8 RCTs in which an independent outcome assessor who was blinded to the

intervention allocation was used showed an effect[24,26]. Three of the 8 RCTs that showed any effect used no independent outcome assessor[15,16,20]. Only 3 investigations showed less than 10% loss to follow-up[11,16,23]. Only 6 of the 12 RCTs reported a power calculation[10,15,17,22,24,26]. Of these, only 3 showed any effect[15,24,26]. None of the NCSGTs reported a power calculation.

Table 3: quality assessment of studies on intervention by community pharmacists

Reference	Recruitment	Randomization described	Selection criteria clearly described	Starters/ chronic users/both	Outcome assessor blinded to intervention allocation	Loss to follow-up (%)	Reasons for loss to follow-up reported	Power calculation reported
Ali et al. (2003)[25]	during pharmacy visit	NR[a]	yes	>3 months	NR[a]	39	yes	no
Barnett et al. (2000)[18]	during pharmacy visit	yes (patient level)	no	NS	yes	0	NS	no
Berringer et al. (1999)[11]	during pharmacy visit based on pharmacy records	NR[a]	yes	>6 months	NR[a]	NR[a]	NR	no
Bluml et al. (2000)[19]	referrals from physicians, pharmacists; self-referral	NR[a]	no	both	NR[a]	45	yes	no
Bouvy et al. (2003)[24]	cardiologists	by investigators on paitent level	yes	chronic	yes	25	yes	yes
Chabot et al. (2003)[23]	phone call by pharmacist	yes (pharmacy level)	yes	>3 months	yes	10[b]	yes	no
Cordina et al. (2001)[13]	recruitment sessions	yes (pharmacy level)	yes	chronic	yes	22	no	no
Dumas et al. (1992)[12]	NRc	NR[a]	no	NS	NR[a]	NR[a]	NR[c]	no

Grant (2003)[22]	called by nurse/physician	on patient level, before patients consented	yes	chronic	yes	15	yes	yes
McDonough et al. (2003)[27]	NRc	NR[a]	no	both	NR[a]	NR	no	no
McKenney (1978)[20]	during pharmacy visit	patient level	yes	chronic	no	4	yes	no
McKenney et al. (1973)[16]	during pharmacy visit	patient level	yes	chronic	no	8	yes	no
Odedina et al. (2000)[14]	advertisement, pharmacist approached pts.	NR[a]	no	chronic	NR[a]	40[b]	NS	no
Park et al. (1996)[15]	pharmacy	NS	yes	chronic	no	15[b]	yes	yes
Slama et al. (1978)[21]	NS	NS	yes	<6 months	yes	NS	NS	no
Sturgess et al. (2003)[26]	during pharmacy visit	pharmacy level	yes	chronic	yes	48	yes	no
Volume et al. (2001)[17]	during pharmacy visit	pharmacy level	no	both	no	20[b]	yes	yes
Weinberger et al. (2002)[10]	letter	patient level	yes	>4 months	yes	20	yes	yes

NR=not relevant (due to the study design); NS=not significant; a: study was a non-crossover single-group trial; b: only loss to follow-up in intervention group; c: patients not asked for agreement of inclusion in the study

Discussion

Relatively little work has been published on adherence-enhancing interventions by community pharmacists that actually measured adherence. The types of interventions that showed an effect were weekly or monthly appointments that consisted of counseling, monitoring, and education. However, the same types of intervention showed no significant improvement of adherence in other studies. Both RCTs and NCSGTs did show an effect. The number of participants in the studies was low, and a power calculation often was not reported. Different methods of measurement of adherence were used. Because of the diversity of the studies included regarding type of intervention and results of the intervention, design, methodological quality, power and method of adherence measurement, it is impossible to assess the overall impact of an adherence-enhancing intervention done by community pharmacists.

Although adherence-enhancing interventions by community pharmacists have not been reviewed systematically before, effect of interventions to improve adherence by other healthcare professionals such as nurses, physicians, and hospital pharmacists has been described[28-31].In general, current methods of improving adherence for chronic health problems are complex and not very effective. The heterogeneity between studies makes it difficult to draw a general conclusion with regard to adherence-enhancing interventions. In one review, hospital pharmacist-led programs of educational and supportive counseling were shown to be effective in improving adherence with antiretroviral therapy[31].

A limitation of our search method is that we only used the MEDLINE database. After searching reference lists of included studies and reviews, we found 3 studies that were not present in MEDLINE[14,20,21]. One of these studies was published in 2000, but this was not an RCT[14]. Furthermore, we excluded articles published in languages other than English or German, which could have provoked publication bias by language. In fact, all included studies were performed in English-speaking countries. Only one investigation was excluded because of the French language. This may also have led to publication bias, because researchers more often publish RCTs in an English-language journal if the results are statistically significant[32]. Publication bias may also be caused by the fact that studies are more likely to be published in general if the results are to some extent positive. Authors have demonstrated to publish the whole article instead of only presenting the abstract at conferences if the results are to some extent positive[33].

There are a number of possible interventions community pharmacists can make due to their position in the chain of healthcare providers, such as educating patients on disease, lifestyle and medication. Examples of such interventions are explaining why a certain drug is prescribed, the dosing regimen and potential adverse effects. Furthermore, community pharmacists could advise use of tools, such as pillboxes and medication calendars, or could send reminders or make telephone calls to encourage patient adherence. Pharmacists could also offer to measure blood pressure and cholesterol and manage blood glucose and asthma. Medication review could help minimize over-prescribing, which may increase a patient's satisfaction with therapy. Monitoring and discussing refill rates with patients could be another method. In only 3 of the 18 presented studies were adherence rates discussed with patients[12,26,27]. Except for the studies of McKenney et al. and Slama et al., the majority of the studies on patient adherence in which a community pharmacist participated were performed in the last 10 years[16,20,21]. This is possibly due to the shift made by pharmacists from their traditional role as medication preparer and dispenser to more patient-oriented activities, termed "pharmaceutical care" by Hepler and Strand[34]. This change is growing at a modest rate and has not yet been fully implemented in daily practice, although there is a clear increase in the number of studies published on the effects of pharmacist–patient communication[29,35]. Although the number of publications on pharmacy services and the number of patient-oriented activities in daily practice is increasing, the outcome is not always promising. Reasons for ineffective delivery of high-level pharmaceutical care services may include the lack of collaboration with other healthcare professionals, the inadequate time and skills of pharmacists for interventions, patients switching between pharmacies, and patients' expectations[36-38]. Furthermore, the appropriateness of the prescribed medication could be assessed, such as whether the drug is appropriate for the indication or the patient, concerning problems such as safety, effectiveness, adverse effects and dose. These problems should be solved before an intervention in a patient's behavior is considered. This was not reported in any of the studies.

Study design

One of the reasons that we found a moderate effect of pharmacy services may involve the design of the studies. It is possible that RCTs are not useful for evaluating (pharmaceutical) services and that observational studies may be better suited for this purpose. One of the major disadvantages of RCTs is the lower external validity compared to observational studies. Another disadvantage is the

presence of the Hawthorne effect, meaning that people aware of the fact that they are being watched closely show higher adherence because of the extra attention they have received in the more natural setting[39]. Furthermore, organizing and performing an RCT requires enormous effort from both researchers and pharmacists compared to observational studies. Nonetheless, RCTs are internally more valid than observational studies, mainly due to randomized allocation of the intervention. In this review, 6 non-RCT studies were included in which patients served as their own controls. This inevitably leads to lower internal validity because patients are not blinded to the intervention. Furthermore, a patient's mental and/or disease status may change over time, which may highly influence behavior towards drug therapy

Selection of patients

An explanation for the high adherence rates at baseline and in the control groups is bias due to the selection of patients. Although most studies clearly described selection criteria allowing a large number of patients to participate, it is possible that only patients with a positive attitude towards healthcare services are willing to participate in a research project. It is feasible that this will result in an increase in adherence levels at baseline. None of the studies clearly commented how many patients were excluded, how many refused to participate, and what the reason for rejection was. It appears from our results that studies recruiting patients personally showed more effect than studies that did not. It may be possible that recruiting patients in a non-personal manner (by advertisements, flyers) leads to inclusion of more people with a relatively positive attitude towards healthcare services, thus increasing adherence at baseline. Recruiting patients in the pharmacy may have a more compelling effect on all patients to participate, leading to a better representation of "real-life" consumers. Furthermore, most studies report a relatively high percentage of loss to follow-up. This may also have led to selection of patients who already adhered to therapy, eliminating non-adherent patients from the analysis.

Another possible explanation for the lack of effect in some studies may be the previously mentioned Hawthorne effect. In 3 studies, at some or all time points when adherence was measured, there were no significant differences[11,15,18]. However, at all of these time points, the adherence rates for both the intervention and control groups were more than 80%. According to a widely used definition of adherence, a rate more than 80% indicates that a patient should be considered

adherent[4]. This means that, in these studies, patients were already adherent at baseline, which makes it very hard to reach a significantly higher rate through intervention. However, 3 RCTs did not show high adherence rates at baseline. In one of them, there was a significant improvement during the intervention at one time point[16]. However, this effect did not last until the end of the study period. In the study performed by Sturgess et al. the effect of the intervention became detectable after 6 months[26]. Adherence rates for hypertension treatment in daily medical practice are reported to be about 50%[41,42]. This means that, in our review, only the adherence rates at baseline and in the control group in the study of McKenney et al. may approximate the levels found in daily practice for hypertension[16]. Park et al. and Chabot et al. showed an adherence rate for antihypertensive treatment at baseline and in the control group of about 68–90%, which is extraordinarily high according to the previously published levels[15-23]. In antidiabetic treatment, recent research showed an average adherence rate of about 30–40% for oral antidiabetic agents[43,44]. The adherence rate at baseline of 88% shown by Berringer et al. for oral antidiabetic drugs also seems to be unrealistic, making it almost impossible that an intervention will significantly increase adherence rates[11]. The same holds for the study of Grant et al., at baseline, patients reported taking their medication as prescribed for 6.7–6.9 days per week[22]. In asthma, average adherence rates of 40–60% are common[45,46]. The adherence rate at baseline of 74% found by Weinberger et al. is also high[10]. Nine studies did not specify how long patients had been on therapy before inclusion in the research[12-15,17,20,24,26,27]. In the other 9 studies, it was specified, varying between zero (new users) and 6 months[10,11,16,18,19,21-23,25].

Measurement of adherence

In the majority of studies, the measurement of adherence was performed by pill counts or self-report. In one study, the validity of self-report, pill counts, and pharmacy records were studied[47]. These methods were compared to the method considered the most reliable in adherence research, the MEMS. Pharmacy records showed the highest correlation with MEMS, and pill counts showed only a moderate correlation. Self-report was useful only in cases of non-adherence. The last 2 methods showed a higher adherence rate than was measured with MEMS. This means that, in the studies reviewed here, the validity of the values of the majority of measurements of adherence is certainly not optimal and overestimation of adherence is likely to occur. However, adherence found in one study was also very high despite the use of MEMS[24]. This could also contribute to

the high adherence levels in the studies that we reviewed. From the results of our review, it is impossible to recommend one of the different types of measurement of adherence.

Sample size and randomization

Most of the studies did not report a power calculation, and only 6 of the 12 RCTs reported a power calculation. Even RCTs done in the last 10 years lacked proper calculation of the required sample size. This calculation is sometimes difficult with regard to the estimation of expected difference and, more importantly, to the estimation of the baseline level of the outcome, the latter largely influencing the required sample size. This may have led to a small study population and thus to the lack of effect of the intervention. In general, as mentioned earlier, implementing such a project in the pharmacy requires time and effort from both patients and pharmacists, which in most cases is not financially compensated. Compared to RCTs with active drugs, the funding for such projects is generally low. Only the RCT conducted by Weinberger et al. reported payment of patients and pharmacists to cooperate, and that study did report a proper power calculation. Furthermore, randomization was often not done on a pharmacy level, but rather on a patient level[10]. Although this could not be concluded from our results, it seems better to randomize on the pharmacy level, the main reason being that the participating pharmacist cannot be blinded to the intervention as in placebo-controlled RCTs. If the intervention is based on extra knowledge about the disease and the pharmacist is trained for this, it may be difficult not to pass this on to patients allocated to the control group, minimizing the differences between the intervention and control groups.

Recommendations

The results of this review highlight a number of problems encountered in adherence research. First, there is proper selection of patients. It appeared that patients should be encountered directly by the pharmacist to join the study; methods that require patients taking the first step for inclusion seem to lead to selection of relatively adherent patients. Furthermore, to study a relatively homogeneous population and target the intervention to the right patient, the intervention has to be directed to chronic users or starters alone, or at least those groups have to be analyzed separately. From persistence studies, it is known that the largest decline in persistence occurs after the start of treatment, with the decline becoming more or less stable after 6 months[48-51]. Therefore, interventions

in this group of patients could lead to clinically relevant improvement of adherence to therapy. On the other hand, adherence-enhancing interventions could be targeted to chronic users, who are known to have low adherence to their therapy. This adherence should be assessed with a reliable method. MEMS, although not ideal, seems to be the most accurate and reliable method compared to self-report, pill count or pharmacy records.

Another problem is the choice for a specific study design accompanied by an accurate sample size calculation. As mentioned earlier, RCTs do not have the best external validity, but the internal validity is the highest among all study designs, and therefore perhaps the most suitable method. Furthermore, to convince other parties (e.g., insurance companies, physicians) of the effect of intervention by community pharmacists, an RCT is the study design that leads to the least debate. In addition, to convince other parties, it is absolutely necessary to judge the effect of an intervention within the framework of a proper cost-benefit or cost-effectiveness analysis. In the majority of our selected studies, no adequate economic evaluation was presented. Few studies documented the cost of the intervention alone, but did not take into account the potential savings as a result from the increased adherence, for example, savings by a lower number of hospital admissions. Because most interventions require additional training of the pharmacist, it seems most appropriate to randomize on a pharmacy level. In addition, the use of a blinded outcome assessor could help increase the objectiveness of the results; in most of our included studies, the latter was not done.

Conclusion

It is not possible to identify one specific successful intervention performed by pharmacists from our review. More well-designed and well-conducted studies on the effectiveness of interventions by a community pharmacist to improve patient adherence with chronic medication need to be performed. Furthermore, it is possible that different types of diseases and patients need different types of approaches. Finally, in case of significant improvement, a proper evaluation should be made to judge the overall economic consequences of the intervention.

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Chapter 5.2

Effectiveness of a community pharmacist-led intervention to increase adherence in patients with hypertension: a randomized controlled study

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Summary

Background: Non-adherence to treatment is an important cause of uncontrolled blood pressure. The objective of this study was to assess the effectiveness of a community pharmacist-led intervention to increase adherence in non-adherent patients with hypertension.

Methods: A randomized controlled clinical trial was conducted on 17 community pharmacies in The Netherlands. Pharmacy records were used to calculate adherence to treatment with antihypertensive drugs (thiazide diuretics, beta-blockers, dihydropyridine calcium channel blockers, ACE-inhibitors and angiotensin II receptor blockers) over the preceding 365 days. Eighty-two patients with hypertension (age>45 years) who were non-adherent with one antihypertensive drug (adherence ratio<0.80) were enrolled in the study and randomly allocated to the usual care (N=36, systolic blood pressure/diastolic blood pressure (SBP/DBP) 149/86 ± 20/13 mmHg) or intervention group (N=46, SBP/DBP 152/86 ± 20/13 mmHg). The intervention consisted of discussing the observed non-adherence. In addition, patients in the intervention group were informed that for the next three months, the antihypertensive they were non-adherent with would be provided in the Medication Event Monitoring System (MEMS, Aardex Ltd) and that their behavior would be monitored. Linear regression analysis adjusted for baseline blood pressure was used to determine the effect of the intervention on blood pressure after three months.

Results: Baseline characteristics were similar in the intervention and usual care group. The intervention was associated with a non-significantly lower systolic blood pressure (–3.2 [95% CI: -11.4-5.1 mmHg], p=0.449) and a non-significantly lower diastolic blood pressure (–2.4 [95% CI: -8.0-3.3 mmHg], p=0.293) after 3 months.

Conclusion: The results of this study are only suggestive of modest effectiveness of discussing non-adherence with patients with hypertension and subsequent monitoring of medication intake with MEMS.

Background

Hypertension is an important risk factor for cardiovascular morbidity and mortality[1]. A large number of clinical trials have demonstrated the benefits of blood pressure control with drugs to reduce cardiovascular morbidity and mortality[2]. Despite the availability of effective antihypertensives, it is estimated that in the developed countries only 25-30% of the patients have their blood pressure controlled adequately[3]. A part of this uncontrolled blood pressure is caused by true treatment resistant hypertension as a result of genetic differences[4]. Adherence to treatment is another important cause of this uncontrolled blood pressure[5]. Burnier et al. demonstrated that non-adherence substantially contributed to uncontrolled blood pressure[6]. A large number of studies addressing interventions to increase adherence with long term therapies, often with limited effectiveness, have been documented[5,7-10]. Most interventions aimed to inform patients about their disease and emphasized the potential risk associated with not taking the treatment. This seems especially necessary for treatment of chronic diseases without symptoms such as hypertension. However, as a meta-analysis by Morrison shows, educational interventions, interventions aimed to increase a patient's knowledge about their disease, are less effective than behavioral intervention strategies, strategies which include a control mechanism which feeds back the patient's changes in behavior[11]. However, the objective measurement of adherence in research settings is complicated because patients often know and have to be informed for ethical reasons that their behavior is monitored. This problem is especially relevant if the Medication Event Monitoring System (MEMS [AARDEX, Ltd]) is used to monitor adherence[12]. The MEMS-monitor is a pill box that records the date and time of opening. The awareness of being monitored may therefore artificially increase the effect of an intervention[13]. As Burnier et al. demonstrated using a before/after design, MEMS can be used to increase adherence in a hospital setting[6]. In this randomized controlled study, we aimed to assess the effect of discussing non-adherence and using the MEMS-monitor to increase adherence in non-adherent patients with hypertension in a community pharmacy setting.

Methods

Selection criteria

Patients who were treated for hypertension or hypertension with co-morbidities (ICD-9) with at least one antihypertensive drug and who were older than 45 years were eligible for inclusion in the study. Patients started treatment at least 365 days before the start of the study. In addition, patients had to be non-adherent with one antihypertensive drug. Antihypertensive drugs included thiazide diuretics (ATCcode C03), beta-blockers (ATCcode C07), dihydropyridine calcium channel blockers (ATCcode C08CA), ACE-inhibitors (ATCcode C09A/C09B) or angiotensin receptor blockers (ARB ATCcode C09C/C09D). Non-adherence was defined as an adherence ratio less than 0.80 over the last 365-days. The cut-off value of 0.80 was used to make our results comparable with other studies, although the clinical significance of this cut-off value remains unclear[14,15]. Adherence was calculated from pharmacy records. Diagnosis was confirmed by patients and their general practitioners. Patients who started the use of antihypertensives less then one year prior to the start of the study were excluded. Patients who were not responsible themselves for their medication intake or received their medication weekly in a dosing cassette were also excluded. Patients with a life-expectancy of less than 6 months were excluded. Patients were recruited between January 2004 and November 2005. General practitioners in the catchments'-area of the participating pharmacies were informed about the study and could object to study-entrance of patients prior to randomization. None of the general practitioners did so.

Intervention program and usual care group

Patients who were non-adherent were informed by their pharmacists about the study and that they may receive their medication in a special medicine container. Upon written consent, the pharmacists randomly allocated patients using a computer generated randomization scheme to one of the two arms: intervention or usual care. Pharmacists and technicians received training about hypertension and the design and the conduct of the study. In the intervention group, pharmacists discussed various topics related to non-adherence such as reasons for non-adherence, potential side-effects, how to integrate medication taking more in their daily routine and consequences of non-adherence. In addition, the antihypertensive drug the patient was non-adherent with was dispensed in a

MEMS-monitor (MEMS-IV ® [Aardex Ltd]), a medicine container with a microchip that records the time and date of opening and this was explicitly explained to the patient. Patients in the usual care group received the antihypertensive they were non-adherent with in the usual package and non-adherence was not discussed. Blood pressure was measured at study entrance and after 3 months in a private consultation room, which was a requirement for participation in the study. Blood pressure was measured 3 consecutive times in sitting position after 5 minutes of rest using the OMRON M5-I, which was validated according to the International Protocol[16]. The average of the last two measurements was used for the analysis. After 3 months, the MEMS-monitor was collected by the pharmacist and data on medication intake were obtained using a MEMS-communicator ® for MEMS-6 and Powerview ® for MEMS-6. The outcome of interest was change in systolic and diastolic blood pressure difference (mmHg) after 3 months *between* the intervention and control group. Secondary outcome were SBP/DBP change *within* the intervention and control group. The Medical Ethical Committee from the University Medical Center Utrecht approved the study.

Sample size

For the primary outcome, we expected the systolic blood pressure to decrease from 161±23 to 143±20 mmHg in the intervention group and to remain unchanged in the usual care group, based on data from the 30 continuously monitored patients from the study of Burnier et al.[6]. With a power of 80%, a type I error (alpha) of 5%, and a drop out rate of 10%, 33 patients were needed in both arms.

Data analysis

Differences in baseline characteristics between the intervention and usual care group were calculated using unpaired t-tests and chi-square tests. The effect of the intervention on blood pressure and changes in blood pressure within one group was calculated using linear regression. Analyses were done using SPSS-software (SPSS for Windows, version 12.0, SPSS Inc, Cary, NC).

Results

A total of 17 pharmacies participated in the study. Of the 82 patients included in the study, 46 were randomly allocated to the intervention group and 36 to the usual care group. A total of 2 patients in the intervention group and 6 patients in

the usual care group dropped out of the study. Of the 2 patients dropping out of the intervention group 1 dropped out because of hospitalization and 1 because switching to receiving her medication in weekly doses. Of the 6 patients dropping out of the usual care group 4 dropped out without giving a reason. One patient moved to another area, and one patient dropped out because of unspecified illness. Patients were predominantly female, with an average age of 64.8 years. Type of antihypertensive used and co-medication were comparable between both groups (table 1), only thiazide diuretic use differed significantly between the intervention and control group (p<0.001).

Table 1: baseline characteristics of non-adherent patients with hypertension

	Usual Care (N=46)	**Intervention (N=36)**	**P-value**
Age	64.1 (±13.5)	65.3 (±12.9)	0.785
Males	19 (41.7)	15 (43.5)	0.837
Baseline AHT-treatment			
• Thiazide diuretics	15 (41.6)	33 (71.7)	P<0.001
• Beta-blockers	15 (41.6)	16 (34.8)	0.322
• DHP-CCBs	9 (25.0)	10 (21.7)	0.581
• ACE-inhibitors	7 (19.4)	5 (32.7)	0.182
• ARBs	8 (22.2)	11 (23.9)	0.857
Co-medication			
• Lipid lowering drugs	6 (16.6)	9 (19.6)	0.736
• Anti-asthmatics drugs	5 (13.9)	7 (15.2)	0.866
• Antidiabetic drugs	2 (5.6)	2 (4.3)	0.801
• TAI	8 (22.2)	7 (15.2)	0.416

Values are numbers (%) or means (SD); DHP-CCBs= dihydropyridine calcium channel blockers; ARBs=angiotensin II receptor blockers; AHT=antihypertensive; TAI: thrombocyte aggregation inhibitors

Effect of the intervention

Blood pressure levels at baseline and after 3 months in the intervention and usual care group with regard to blood pressure are listed in *table 2*. There were some non-significant (p=0.707/0.792) differences in baseline blood pressure between the usual care group and the intervention group (149/86 ± 20/13 mmHg vs. 152/86 ± 20.1/13.4 mmHg). The within group decrease in blood pressure almost reached significance in the intervention group (p=0.065). The linear regression analyses of the effect of the intervention corrected for baseline blood pressure revealed an overall non-significant (p= 0.449) decrease of systolic blood pressure (–3.2 [95%

CI: -11.4-5.1 mmHg]) and a non-significant (p=0.293) decrease of diastolic blood pressure (–2.4 [95% CI: -8.0-3.3 mmHg]).

Table 2: Blood pressure at baseline and after 3 months

	Usual care group	Intervention group	p-value between group
Start of study	149/86 (±20/13)	152/86 (±20/13)	0.707/0.792
3 months	148/87 (±26/14)	147/85 (±21/12)	(0.312/0.693)[a]
p-value within group	0.906/0.622	0.065/0.392	

a: Not relevant because of differences in baseline blood pressure

Discussion

In this study, we assessed the effectiveness of a community pharmacist-led intervention to increase adherence to treatment with antihypertensive drugs by using the MEMS-monitor in combination with confronting patients with their non-adherence. The directions of the blood pressure changes were suggestive of a beneficial effect of the intervention on blood pressure levels. This study can therefore not confirm nor deny the usefulness of implementing this approach in daily practice.

Limitations

There are several limitations about this study. The first and probably most important one is the duration of our observation period. The long term effect needs to be established, especially after MEMS-monitoring is discontinued. Patients are probably not willing to be electronically monitored for longer periods. Second, because we used MEMS as an intervention and the follow-up visit was predefined (making the observation of refill behavior irrelevant), we were not able to determine whether adherence improved in the intervention group (we assumed blood pressure reduction as an indicator of improved adherence). Third, we used pharmacy records which may not correspond with the actual dosing history and patients who are adherent to other antihypertensives may still have a controlled blood pressure. The same holds for patients who are non-adherent with a drug with a long half-life or patients who demonstrate white coat adherence[17]. Fourth, the fact that the pharmacists performed the intervention means that the outcome assessor was not independent and blinded with regard to the intervention and the outcome.

Strengths

An important strength of our intervention was that we included patients that were non-adherent, increasing the chance that the intervention would demonstrate its effect in a relatively small population. We thereby circumvented the inclusion of adherent patients that would dilute the potential effect of the intervention. Our approach may have simulated a situation that may occur in daily practice, a pharmacist detecting non-adherence and intervening on it, and may therefore be relatively easy to implement. The effect may be enhanced if only patients without proper blood pressure control were included, although this may also require a multidisciplinary approach, which is more complicated from a research perspective but may be better reflecting daily practice. As the study of Burnier et al. demonstrated, the effect of improving adherence based on inadequate blood pressure control is larger in terms of blood pressure reduction compared to our non-adherence based intervention. A second important strength was that we used pharmacy records for the detection of non-adherence. Next to the fact that it can be done before a patient visits the pharmacy, it is not very time consuming, needs little further analysis (such as a questionnaire) and does not depend on the care giver patient-relation as to whether a patient is willing to share this information (such as self report). A problem may occur if a patient, especially younger, more mobile ones, presents prescriptions at different pharmacies, although currently a growing number of pharmacies within one region in The Netherlands are linked together. If medication is collected in another pharmacy, the medication history is automatically updated in the primary pharmacy.

Previous research

In the previously mentioned study by Burnier et al.[6], on which we also based our sample size calculation, more or less the same strategy was used, although uncontrolled blood pressure (resistant hypertension) rather than non-adherence was used as a selection criterion. In this single group trial, blood pressure before and after monitoring was compared. They concluded that after using the MEMS-monitor patients were more adherent which was demonstrated by a decrease in SBP/DBP from 161/108 ± 23/14 mmHg to 143/94 ± 22/11 mmHg after 4 months of use compared to pre monitoring levels. Although blood pressure at study entrance was higher, the magnitude of the effect and the setting where the intervention was performed were different (hospital vs. pharmacy and physician vs. pharmacist), the direction of the effect of the intervention was similar to our

study. A lot of other work has been done to elucidate successful intervention strategies in general[7] and specifically with regard to hypertension[18]. Schroeder et al. conducted a systematic review of randomized controlled trials that were focused on the improvement of adherence to blood pressure lowering medication in ambulatory care. They concluded that patient education alone was unsuccessful and that the most successful intervention was the reduction or simplification of the number daily dosages, with an average improvement of adherence from 8% - 19.6% in the 7 out of 9 studies that showed an effect. More complex interventions such as the one presented in this paper, demonstrated mixed effects. In our review on community pharmacist-led interventions, with less stringent inclusion criteria, we found more or less similar results, with regard to the mixed effectiveness[10]. McDonald et al. argued that in complex interventions, with more than one strategy tested against usual care, it is difficult to assess the independent effect of intervention[9]. In contrast to this argument, our intervention consisted of more than one strategy: discussing reasons for detected non-adherence and monitoring adherence with an MEMS-monitor. Therefore one could argue that the 2 strategies should have been tested separately and in combination. This would require 4 different groups of patients. However, in daily practice it is unlikely that the use of the MEMS-monitor will be used separately from the discussion of non-adherence. Furthermore, it seems that the direction of the separate strategies is similar, towards improving adherence, and it seems unlikely that one strategy antagonizes the other.

Recommendations for future studies and daily practice

Our findings suggest that selection of non-adherent patients from pharmacy records, discussing non-adherence and monitoring medication intake, has a modest effect in reducing blood pressure. This implies that pharmacists could provide these services in the near future on a regular basis, separately from the study setting, to further develop the proposed approach. Furthermore, other professionals such as the general practitioner should be involved in this process, although we think that the community pharmacist is well situated to lead this intervention because of his frequent patient encounters and because he has easy access to these data. In a future study or in daily practice, adherence data obtained from the MEMS-monitor may be continuously discussed with the patient. Showing a patient that, as a consequence of taking his medication correctly, his blood pressure decreases, may stimulate adherence in the next interval. Another

possibility may be that a patient, who thinks he takes his medication correctly, can be informed about his actual intake or that insight in ones behavior may help to stimulate. The feasibility of long term use of MEMS, as mentioned earlier, but also of continuously confronting patients with non-adherence needs to be addressed. Next to these more clinical barriers, also practical barriers must be overcome. The pharmacies involved in this study voluntarily participated in the study, received training in hypertension and how to perform the study, and were provided with MEMS-monitors and blood pressure meters by the investigators. In addition, there was no financial incentive to perform the study. Further financial aid together with an investment of time could further help to translate academic work into daily routine. If successful strategies have been identified, they have to be evaluated in the framework of an adequate cost-effectiveness analysis.

In conclusion, the community pharmacist-led intervention of confronting patients with non-adherence combined with electronic monitoring non-significantly reduced blood pressure in patients who received treatment for hypertension. Although our results are not more than suggestive of a possible effect of our approach, they serve as a framework for future studies in this field.

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Chapter 5.3

Generic substitution of antihypertensive drugs: does it affect adherence to therapy?

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Summary

Background: Generic substitution is an important opportunity to reduce the costs of pharmaceutical care. However, pharmacists and physicians often experience that patients have doubt about the equivalence of the substituted drug. This may be reflected by decreased adherence to therapy. The objective of this study was to assess the association between generic substitution and non-adherence to antihypertensive drugs.

Methods: A matched cohort study with data from patients starting the use of antihypertensives between January 1st 1999 and December 31st 2002 was performed. The PHARMO database, a record linkage system currently containing drug-dispensing records from community pharmacies and linked hospital discharge records of approximately 2,000,000 subjects was used. Included patients were residents of 50 medium-sized cities in the Netherlands, who started with the use of antihypertensive drugs. The main outcome measure was refill adherence with antihypertensive drugs after substitution. Patients with a refill adherence below 80% were considered non-adherent.

Results: Four hundred and sixty-three patients with a substitution and 565 controls, matched on age, gender, start date of use, duration of use and generic product code, were identified. Of the substituted patients, 13.6% were non-adherent, and of the non-substituted patients 18.7% were non-adherent (OR 0.68 [95% CI: 0.48-0.96]). The association was absent in males. None of the patients discontinued their 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 to more non-persistence and cardiovascular disease related hospitalizations compared to non-substituted patients. When a less expensive antihypertensive generic equivalent becomes available, generic substitution should be considered to profit from economic benefits.

Background

Substitution of branded drugs with generic equivalents is an important issue with regard to the cost reduction of pharmaceutical care. On June 12, 2003, the US 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, by avoiding time-consuming legal delays. 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[1]. This means that generic substitution could decrease healthcare costs dramatically in the US. About the same situation holds for The Netherlands, were from May 2003 onwards, 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 bio equivalence of generic drugs to brand name drugs once a generic drug has been approved[2-8]. The rationale behind the concept of bio equivalence is that if two pharmaceutical equivalents provide similar plasma concentration-time profiles, there is no reason to expect that the two identical dosage forms will exhibit differences in safety and efficacy regardless of whether other excipients may be used[5]. Although this concept of bio equivalence seems undisputable, this concept was objected by the Australian Medical Association until January 2003[9]. 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 which may look different. Brennan and Lee stated: “A generic equivalent normally produces no decrement in quality of treatment, unless the patient will not take it”[10]. 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[11-17]. The latter may result in a decreased patient adherence with the therapeutic regimen ultimately resulting in less effective treatment. This implies that although a certain drug may be bio-equivalent, it may not be therapeutically equivalent. This study aimed to

quantify the degree to which generic substitution influences adherence to treatment with antihypertensive drugs.

Methods

Data

We used data from the PHARMO database, a record linkage system currently containing drug-dispensing records from community pharmacies and linked hospital discharge records of approximately 2,000,000 subjects in the Netherlands. We selected a cohort of patients who started using antihypertensive drugs between January 1st 1999 and December 31st 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 their start with antihypertensives were excluded. Furthermore, patients who received only one prescription for an antihypertensive were excluded. Patients were defined as substituted if they had undergone a substitution of their initially prescribed brand name antihypertensive drug regimen with a bio equivalent generic drug for the first time. Generic equivalency was determined using Generic Product Codes (GPCs) that are assigned to a generic product on basis of bio equivalence studies, which are required for the registration[18]. 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. [19] 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 a MPR below 80% was considered non-adherent. In a sensitivity analysis, we studied the influence of different cut-off values of adherence. When a patient discontinued after substitution, the patient was excluded from this analysis because adherence cannot be calculated without an end date of a prescription. However, none of the patients discontinued 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 up to 3) on gender, start date of treatment with antihypertensives (±180 days), GPC, duration of unchanged and uninterrupted episode of use and age (within a 10-year 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 two 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≥80) or non-adherent (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 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 to 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 co-medication (prescription for an anti-asthmatic drug (ATC-code R01), lipid lowering drug (ATC-code C10) or antidiabetic drug (ATC-code A10)), type of prescriber (cardiologist, internist, GP or other) and the prescribed daily dose (PDD) being smaller than the defined daily dose (DDD).

Analysis

Based on an estimated incidence of non-adherence of 15% in the non-substituted patients, a 50% increase in the incidence in the substituted patients to 22,5%

(OR=1.5), with α=0.05 and 1-β=0.80, an estimated 424 patients were needed in the substituted and non-substituted group. Student's t-tests and chi-square tests were used to analyze differences in baseline characteristics between substituted patients and non-substituted patients. To analyze the association between non-adherence (outcome) and substitution (exposure), crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) 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, 7,981 patients had a follow up of less than 365 days before the start of antihypertensive drugs. Of these patients, 6,793 received only one prescription. Of the remaining 24,940 patients only 491 started with a brand name antihypertensive during a period where there was a generic equivalent available. Of these 491 patients, 463 patients (94.3%) were matched to one or more controls. Three hundred and 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. Baseline characteristics of the patients are given in table 1.

Table 1: baseline characteristics of the study population

	Substituted patients (N=463)	Non-substituted patients (N=595)	P-value
Males	228 (49.2%)	282 (47.4%)	0.55
Age (years)	60.5 (±14.0)	60.0 (±14.4)	0.59
Age group			1.00
• ≤ 39 year	36 (7.8%)	49 (8.7%)	
• 40-59 year	189 (40.8%)	224 (37.6%)	
• 60-79 year	208 (44.9%)	278 (46.7%)	
• ≥ 80 year	30 (6.5%)	44 (7.4%)	
PDD/DDD<1	434 (93.7%)	565 (95.0%)	0.40
Duration of use (days)	219.7 (±195.5)	212.1 (±199.8)	0.54
First prescriber			0.94
• General practitioner	366 (79.0%)	461 (77.5%)	
• Internist	61 (13.2%)	83 (13.9%)	
• Cardiologist	15 (3.2%)	22 (3.7%)	
• Miscellaneous	21 (4.5%)	29 (4.9%)	
Prior cardiovascular hospitalizations			
• Ischemic heart disease	15 (3.2%)	10 (1.7%)	0.098
• Congestive heart failure	1 (0.2%)	1 (0.2%)	0.86
• Cerebrovascular disease	4 (0.9%)	1 (0.2%)	0.10
• Arrhythmia	5 (1.1%)	4 (0.9%)	0.47
• Peripheral vascular disease	1 (0.2%)	2 (0.3%)	0.72
Initial antihypertensive drug			0.33
• Diuretics	70 (15.1%)	117 (19.7%)	
• Beta-blockers	253 (54.6%)	319 (53.6%)	
• Calcium channel blockers	27 (5.8%)	35 (5.9%)	
• ACE-inhibitors	110 (23.8%)	121 (20.3%)	
• Angiotensin II receptor blockers	0 (0%)	0 (0%)	
• Miscellaneous	3 (0.5%)	3 (0.5%)	
Average adherence of			
• Prescription before substitution	91.6% (±15.2)	92.1% (±14.0)	0.60
• Prescription after substitution	92.4% (±14.1)	90.4% (±16.2)	<0.05

Adherence to treatment after substitution

The percentage of non-adherent patients (MPR<80%) among the substituted patients was 13.6% vs. 18.7% among non-substituted patients (crude OR 0.69 [95% CI: 0.49-0.96]). After adjustment for confounders, substituted patients were still less likely to be non-adherent compared to non-substituted patients (adjusted OR 0.68 [95% CI: 0.48-0.96]). 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% among substituted patients vs. 92.1% among non-substituted patients (p=0.60). Furthermore, *after* substitution adherence was significantly different among both groups, 92.4% among substituted patients and 90.4% among non-substituted patients (p=0.037). Small but not significant differences in non-adherence between substituted patients and non-substituted patients were observed for subgroups defined by gender (p=0.40). Substituted females had a higher risk for non-adherence compared to non-substituted females (OR 0.46 [95% CI: 0.28-0.77]). For males this was not observed (OR 0.97 [95% CI: 0.60-1.58]). No differences between substituted and non-substituted patients were observed between subgroups 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 non-adherence compared to matched non-substituted patients. The association between substitution and non-adherence did not differ significantly for subgroups defined by first prescriber (p=0.70), PDD (p=0.30), non-adherence with previous prescription (p=0.36) co-medication (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 patients (6 admissions) and non-substituted patients (8 admissions) were observed after substitution.

Table 2: association between substitution and non-adherence

	Substituted patients [a]	Non-substituted patients[a]	OR (95% CI)	OR (95% CI)[b]
Overall	63/463 (13.6%)	111/595 (18.7%)	0.69 (0.49-0.96)	0.68 (0.48-0.96)
Gender				
• Males	38/228 (16.7%)	47/282 (16.7%)	1.00 (0.63-1.60)	0.97 (0.60-1.58)
• Females	25/235 (10.6%)	64/313 (20.4%)	0.46 (0.28-0.76)	0.46 (0.28-0.77)
Type of antihypertensive				
• Diuretics	9/70 (12.9%)	25/117 (21.4%)	0.54 (0.24-1.24)	0.41 (0.17-1.02)
• Beta-blockers	39/253 (15.4%)	60/319 (18.8%)	0.79 (0.51-1.22)	0.82 (0.52-1.30)
• CCBs	1/27 (3.7%)	4/35 (11.4%)	0.30 (0.031-2.84)	0.44 (0.041-4.70)
• ACE-inhibitors	13/110 (11.8%)	22/121 (18.2%)	0.60 (0.29-1.27)	0.61 (0.29-1.29)
• Miscellaneous	1/3 (33.3%)	0/3 (0%)	-	-
Age group				
• ≤ 39 year	5/33 (13.8%)	4/48 (10.2%)	1.75 (0.42-7.34)	1.95 (0.43-8.89)
• 40-59 year	20/189 (10.5%)	45/224 (20.1%)	0.49 (0.28-0.88)	0.49 (0.27-0.90)
• 60-79 year	30/208 (14.4%)	43/278 (15.5%)	0.87 (0.82-1.43)	0.85 (0.50-1.44)
• ≥ 80 year	8/30 (26.6%)	18/44 (40.9%)	0.60 (0.24-1.50)	0.50 (0.18-1.41)
Duration of use				
• 0-90 days	20/143 (14.0%)	34/207 (16.4%)	0.83 (0.46-1.51)	0.85 (0.46-1.57)
• 91-180 days	17/103 (16.5%)	26/128 (20.3%)	0.78 (0.40-1.52)	0.80 (0.40-1.61)
• 181-270 days	12/79 (15.2%)	18/91 (19.8%)	0.73 (0.33-1.62)	0.62 (0.25-1.53)
• ≥ 271 days	14/138 (10.1%)	33/169 (19.5%)	0.47 (0.24-0.91)	0.42 (0.21-0.86)

CCBs=calcium channel blockers; ARBs=angiotensin II receptor blockers; a: number of non-adherent patients/all patients (% non-adherence among all patients); b: adjusted, hospitalization for cardiovascular diseases, type of prescriber and PDD

Sensitivity analysis and analysis of sampling procedure

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

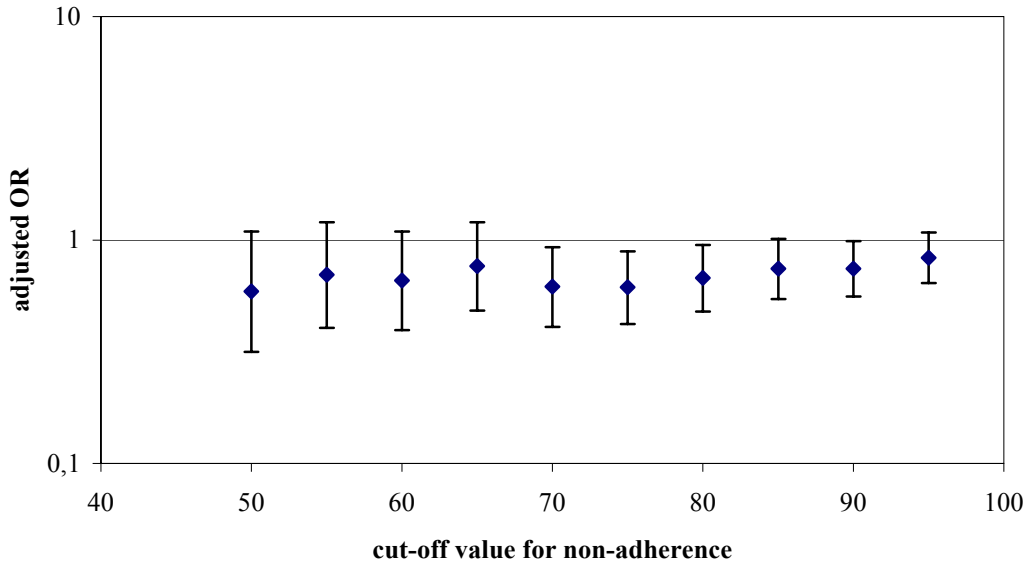

Figure 1: sensitivity analysis of association between substitution and non-adherence for different cut-off values for non-adherence

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 six 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 their 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. The use of pharmacy records leads to an underestimation of non-adherence because prescriptions may be collected but not used[19]. This misclassification is probably non-differentially distributed among substituted and non-substituted. This would lead to a decrease of a potential effect towards 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 only prevent substitution 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 that the generic equivalent is not bio equivalent or that 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 non-adherent 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 minimizing confounding bias based on adherence. However, we found that adherence as well as the proportion of non-adherent 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 only able to follow our patients for at maximum six months after the substitution. This may be to short to detect actual differences as a result of non-adherence and to assess the risk with regard to the safety of generic drugs. One of the strengths of our study is that we were able to include a sufficient large number of patients in our study. Furthermore, because of the adherence enhancing circumstances, it would be very difficult to test the effect of substitution in a randomized controlled 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[20]. From adherence studies on chronic medication it is known that adherence rapidly decreases in the first 3-6 months, after this period, the decrease is more gradual[21-24]. This would explain the small decrease of adherence as well as the increase in number of non-adherent patients among the non-substituted patients in the comparison *between* substituted and non-substituted patients as well as in the comparison *within* substituted and non-

substituted patients. The fact that the association becomes gradually stronger, even significant with an increase in duration of use, supports this hypothesis because at start most patients are still adherent and if an intervention would have any positive effect it would be hard to detect in an adherent population of starters. The difference we have found between substituted and non-substituted females may be explained by general differences in health related behavior by females including complaints about side-effects. Our results demonstrate that adherence related interventions might have a different impact on males and females[25,26].

Generalisability

The design of our study should be applied to various other, more complex antihypertensive drug regimens. 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 generalisable to other asymptomatic chronic diseases. However, e.g. in severe psychiatric disorders such as 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 percent. From this point forward, economic benefits for health insurance boards and patients could be obtained. Although still both brand name drugs and generic equivalents are fully covered, 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 costs reduction for public health. The time needed to instruct a patient should be kept in mind when considering the economic benefits of substitution. Although it constituted a major change, it is not likely that it influences the generalisability of our results.

Conclusion

We have found that generic substitution of antihypertensive drugs does not lead to lower adherence or more non-persistence in patients who started using antihypertensive drugs. When a generic antihypertensive equivalent becomes available, generic substitution should be considered to profit from the economic benefits. This type of study should be replicated in patients using other types of chronic medications.

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Chapter 6

General discussion

Introduction

A paradigm shift in medical practice has taken place in the last 40-50 years. Instead of focusing on *curing* disorders, attention has shifted to *preventing* and *slowing* progression of a disorder. From treatment of a bacterial infection or relieving acute pain, which is directed and measurable at the patient level, the focus of innovation shifted to treatment of large numbers of patients to prevent events that may occur in (small) fractions of the population in the future. Indicators of characteristics of treatment such as *number needed to treat* and more recently, *cost-effectiveness* and *quality adjusted life years* emerged in the field of medical science. This required the afore mentioned change in thinking about the management of disorders, among professionals working in the field as well as among patients diagnosed with such disorders. In daily practice, it appeared that patients with a disease but without symptoms, often failed to adhere to their prescribed medication. Hypertension is such a symptomless disorder. The aim of this thesis was to assess the prevalence and determinants of non-adherence and non-persistence with antihypertensive drugs and to provide suggestions for intervening to improve it among non-adherent patients with hypertension. Special emphasis was placed on the role of the pharmacist. The pharmacist is the health care professional who most frequently encounters patients using chronic medication and who should thus play a role in both detecting and intervening in non-adherent patients. Intervening seems important because control of blood pressure worldwide is still poor. It is estimated that blood pressure is inadequately controlled in approximately two-thirds of people living with hypertension[1]. Although the percentage of patients with hypertension that are actually diagnosed has increased over time, the percentage of patients with controlled blood pressure has not followed the same pattern (table 1)[1].

Table 1: patients with controlled hypertension over time in the US population[1]

	1976-1980	1988-1991	1991-1994	1999-2000
Patients diagnosed with hypertension	51%	73%	68%	70%
Patients treated with antihypertensives	31%	55%	54%	59%
Patients with controlled hypertension	10%	29%	27%	34%

This means that there is room for improvement in the management of hypertension. The aim of the *general discussion* is to place the results of the

studies conducted in a broader perspective and to make recommendations for future research. The discussion section is structured as following: first, the clinical relevance of suboptimal medication intake is described. Second, the existing evidence of the effectiveness of interventions to improve medication intake is discussed. The latter also requires detailing about the psychological background. Finally the potential role of the pharmacist, as mentioned above, is discussed.

Clinical relevance of inadequate medication intake

Although the consequences of uncontrolled hypertension such as myocardial infarction or stroke are very well known among the general population, the vast majority of the patients with hypertension still have inadequately controlled blood pressure, as demonstrated in table 1[2]. Lower adherence with antihypertensive drugs is associated with higher blood pressure, so there is no doubt about the relevance of concerns about sub optimal intake[3]. Sub optimal adherence is partly due to the asymptomatic nature of hypertension; patients experience no symptom relief and more side-effects while taking their medication correctly. This behavior is in line with behavior observed in patients taking other chronic medication, even with chronic treatment where a more direct relation exists between medication intake and symptom relieve. Claxton estimated that the average adherence to antihypertensive drugs is 73% based on electronic monitoring data, which is in line with adherence to other chronic treatment in the developed countries (figure 1)[4].

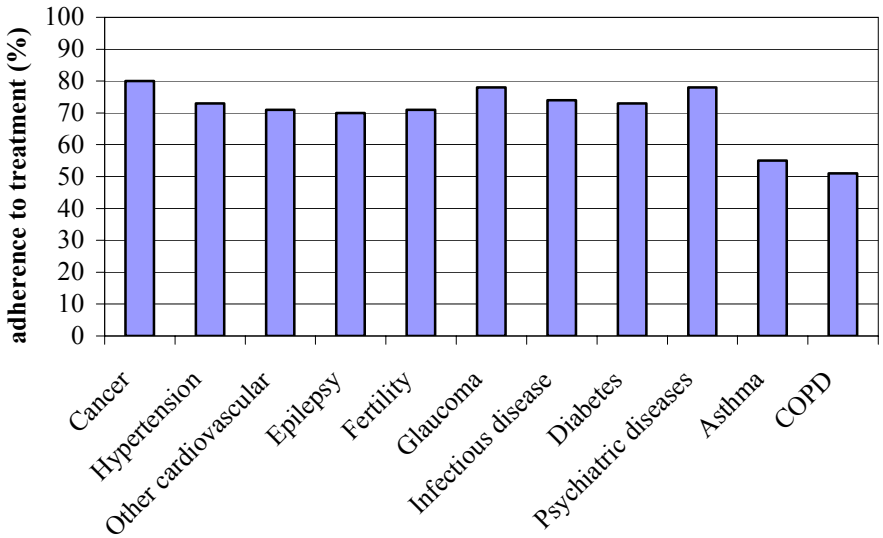

Figure 1: adherence rates by therapeutic area assessed with electronic monitoring[4]

This corroborates findings of DiMatteo, who reported an average adherence of 74,8% among patients using cardiovascular drugs[5]. While trying to assess the clinical relevance of inadequate medication intake, one has to consider several aspects of non-adherence with chronic medication. Without doubt, non-adherence with any form of chronic treatment generally means less protection against worsening of symptoms or protection against the occurrence of complications. Missing one or more doses may also be potentially harmful with regard to interacting drugs or rebound effects, especially in case of beta-blockers[6]. On the other hand, non-adherence with potentially harmful drugs decreases the risk of toxicity and more intake should not be encouraged. In a recent meta-analysis it was demonstrated that higher adherence to potentially harmful drug therapy was associated with increased mortality (OR 2.90 [95% CI: 1.04 to 8.11])[7]. For some drugs with a long half-life or with extended release formulations, missing a dose may be less clinically relevant (forgiving drugs), although non-adherence still reflects unwanted behavior[8,9]. It seems obvious that allowing a patient missing a dose now and then or even allowing longer periods of missing doses (drug holidays), is acceptable if it means that the patient is prepared to continue the use for years. In our study assessing long term persistence with antihypertensive drugs (*chapter 4.1*), we found that adherence to treatment was generally high ranging from around 85% in the first year to about 92% after ten years among the patients who continued the use of antihypertensives chronically[10]. Wannemacher et al. found similar results in US Veterans Affairs Healthcare system[11], although results of other studies are not totally in line with our findings that reported adherence rates varying between 65-75%[12-14]. Our findings indicate that after accepting that a certain drug or regimen is supposed to be taken for long periods, patients seem prepared to do so, occasionally missing doses. The implication of this would be that although not behaving perfectly, the patient is still protected against cardiovascular diseases.

This raises a question often posed when it comes to adherence namely “how much adherence is enough?” There is no mutual agreement among health care professionals about what adequate adherence is. A ratio of 0.80 or 80% is often accepted as cut-off value between adherent and non-adherent in antihypertensive treatment research as well as in other therapeutic areas. The cut-off value of 80% dates back to a suggestion made in the article reporting the results of the Coronary Drug Project Trial, conducted between 1973 and 1983[15-16]. Good adherers to

clofibrate, i.e., patients who took 80 per cent or more of the protocol prescription during the five-year follow-up period, had a substantially lower five-year mortality than did poor adherers to clofibrate (15.0 vs. 24.6 per cent; p=0.00011, interestingly, similar findings were noted in the placebo group, i.e., 15.1% mortality among good adherers and 28.3% among poor adherers; $p=4.7x10^{-16}$)[15-16]. In patients using antiretroviral therapy for the treatment of human immunodeficiency virus or oral contraceptives, a clinical relevant cut off value is much higher[17,18]. In the studies presented in this thesis, we have tried to partially circumvent the problem by several sensitivity analyses varying the cut-off value to estimate the effect on our outcome (these analyses demonstrated that in our studies, the exact cut-off was of minor importance to our conclusions). In case of individual antihypertensive drugs or antihypertensive drug classes, it is impossible to even suggest an overall cut-off value for clinically relevant non-adherence. However, if rebound effects are absent or unlikely to occur, it seems irrelevant to strive for perfection and in this light 0.80 or 80% seems an acceptable limit. In addition, this cut-off value can also be recommended in new studies, because it enables comparison between studies and is the most frequently used cut-off value in pharmacoepidemiology[19].

Next to non-adherence as an outcome, non-adherence can also be a determinant or predictor of medication events. In our study described in *chapter 3.1* we found that patients who are non-adherent have a 1.39 times higher risk of a change in medication regimen. After classifying change of medication regimen in dose decrease, dose increase, switch and addition, we found that the association was the strongest for dose decrease and absent among switchers. The latter means that maybe side-effects leading to non-adherence are discussed leading to a dose decrease in a number of patients, and in other cases, specifically in females, by the lack of effect of medication or lifestyle modifications, to addition or dose increase. The biasing effect of lifestyle modifications, which are often not registered in pharmacoepidemiological studies and may have confounded this study, is discussed in detail in the next paragraph of this *general discussion*. Although the underlying mechanism cannot be elucidated in studies with only pharmacy records, it still would argue for monitoring these patients and to feed back this information to patients and/or prescribers. The latter is certainly true considering the study described in *chapter 3.2*. In this study we assessed the association between non-adherence and discontinuation. We found that non-adherent patients

had a 2.86 times higher chance on complete discontinuation. These findings support the theory of Urquhart et al. that discontinuation of treatment is often preceded by a dwindling adherence to treatment (figure 2)[20].

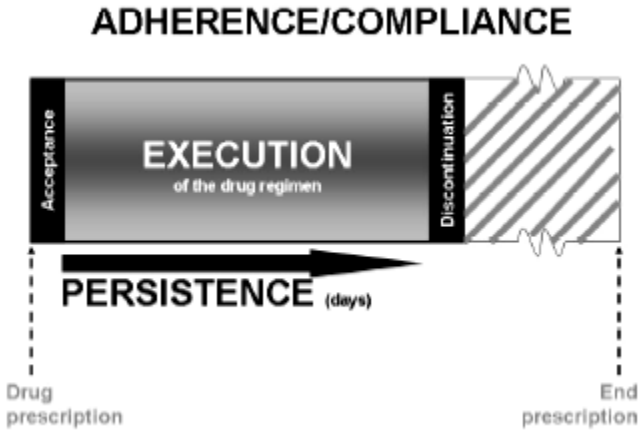

Figure 2: schematic representation of the three phases of ambulatory pharmacotherapy

Urquhart et al. argued that three phases can be identified. Acceptance of the treatment plan, execution of the drug regimen (adherence) and eventually discontinuation (non-persistence) of dosing. The first and third phase are dichotomous, execution is a continuous process. The theory is also supported by the results of the 10-year persistence study presented in *chapter 4.1*. In this study we found that patients, who continued treatment, did so with a generally high adherence. However, the results of the study presented in *chapter 4.1* and *chapter 4.2* also suggest that even the decision to be non-persistent is non-definitive and patients may ultimately decide to reinitiate treatment. The association between adherence and non-persistence argues for actively monitoring adherence and discussing it with patients and prescribers to prevent these non-adherent patients from discontinuation. Of course the effect of these types of interventions needs to be established in future studies.

Next to non-adherence, the problem of non-persistence (complete discontinuation) constitutes an even larger barrier to effective treatment. The extent of non-persistence with antihypertensives is similar to other chronic diseases (figure 3)[21].

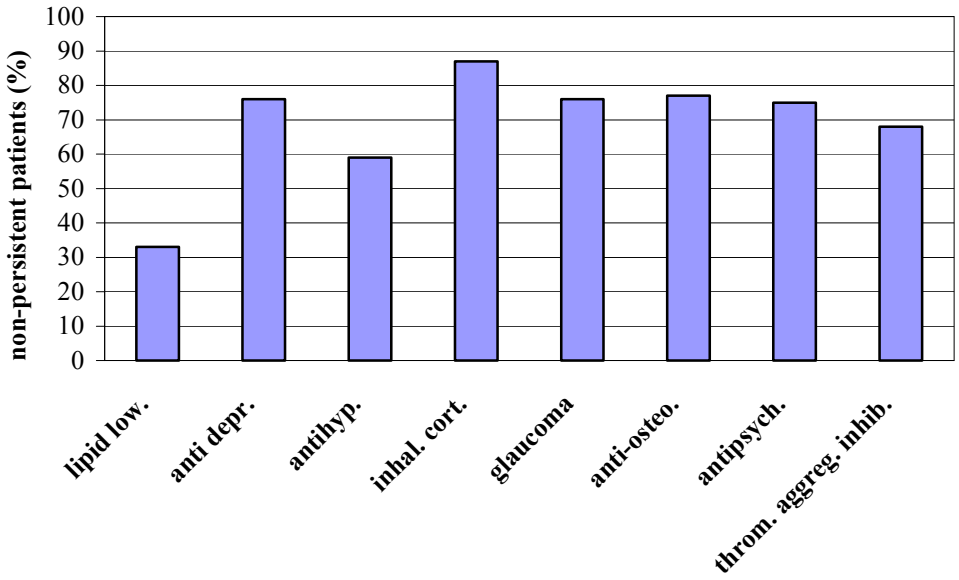

Figure 3: non-persistence rates after one year per therapeutic area assessed with pharmacy records[21]

Because the efficacy of treatment against placebo has long been established for antihypertensives, the question whether complete discontinuation is acceptable deserves less debate[22]. In our 10-year persistence study, we found an overall discontinuation rate of approximately 39% after ten years[9]. Combined with the relatively high adherence rates, our results suggest that not non-adherence but non-persistence is the largest problem and should be subject for intervention and further research.

Of course, direct evidence that non-persistence or non-adherence with antihypertensive treatment increases the number of cardiovascular hospitalizations obtained from RCTs is not available for ethical reasons (although one might argue that placebo controlled trials or the early treatment vs. no treatment trials simulate this situation)[23]. In addition, such evidence from an observational setting has not been obtained yet. The latter is complicated, if not impossible, because of the lack of information on lifestyle in studies using pharmacy data. Patients who are more adherent to treatment may also be more adherent with lifestyle modification (healthy adherer effect). This effect has been documented as early as 1980 in a post hoc analysis of the Coronary Drug Project Trial, as previously mentioned in this g*eneral discussion*[15]. Recently, in a subgroup analysis of the CHARM-trial, adherent patients in the candesartan and placebo group demonstrated a nearly identical risk of death 0.52 [95% CI: 0.41-0.65] in the candesartan group vs. 0.54

[95% CI: 0.43-0.70] in the placebo group) compared to non-adherent patients, which is in line with findings in other trials in patients with a previous myocardial infarction[24-26]. In the previously mentioned recent meta-analysis where both cardiovascular and non-cardiovascular diseases were pooled together, higher adherence was associated with lower mortality (OR 0.56 [95% CI: 0.50 to 0.63])[7]. Rates for active treatment and placebo did not materially differ: good adherence to placebo was associated with lower mortality (OR 0.56 [95% CI: 0.43-0.74]), as was good adherence to beneficial drug therapy (OR 0.55 [95% CI: 0.49-0.62]).

Lifestyle modifications such as salt restriction, increased exercise and weight loss have demonstrated to be effective in reducing blood pressure and non-adherent patients have also demonstrated to adhere less to advice to change lifestyle[27-29]. Therefore, in this thesis, we decided not to perform such an analysis because prescription databases where information on lifestyle was routinely assessed are currently not available. However, as mentioned in the discussion section of *chapter 3.1*, the results of that chapter may also be confounded by the same lack of information. In future observational studies, assessment of life style factors (without selection bias) in a small subset of the population can help to estimate and adjust for the residual confounding resulting from the lack of information in pharmacoepidemiological datasets as was demonstrated by Schneeweiss et al.[30]. For statins, the association between adherence and health outcomes has been assessed in an observational setting, but it is disputable whether the used methodology was sufficient to answer this question[31,34,35]. In the following example, the extent to which in a pharmacoepidemiological study the association between adherence and outcomes can be confounded by the lack of information on smoking is estimated. Wei et al. found that the risk of a *recurrent* myocardial infarction is lower for patients who continue treatment with relatively good adherence (adherence>80%) compared to patients who did not take statins (adherence=0%) adjusted for lipid levels at baseline (which is an absolute prerequisite for this study) and other covariates (table 2)[31].

Table 2: HR for myocardial infarction and all cause mortality at different levels of adherence[31]

Adherence	MI	No MI	Adjusted HR for MI (95% CI)	Adjusted HR for all cause mortality (95% CI)
0%	96.7%	91.7%	1.00 (reference)	1.00 (reference)
≤ 39%	0.8%	1.3%	0.59 (0.22-1.59)	0.94 (0.39-2.27)
40-79%	0.7%	1.7%	0.51 (0.19-1.35)	1.15 (0.44-3.00)
≥ 80%	1.8%	5.3%	0.19 (0.08-0.47)	0.47 (0.22-0.99)
Total	100%	100%	-	-

MI=myocardial infarction

Compared to non-adherent patients, patients with an adherence of more than 80% experience a 5.3 fold risk reduction (1/0.19) on recurrent MI. However, it is known from the large statin trials that statins can reduce the risk of recurrent MI with only 20-26% compared to placebo[32] (which in theory is comparable to non-adherence). In the study of Wei et al. the authors discuss that no information on smoking was available among other potential confounders. However, smoking is a well known risk factor for MI. In the INTERHEART-study, smokers had a 2.95 times higher risk of MI (95% CI: 2.72-3.20)[33]. Wei et al. also demonstrated that statins were far less prescribed to the socioeconomic most deprived patients[31]. A UK health survey, that may be applicable to the Scotland population of Wei et al., revealed that among people with high income 13.3% were smokers, in contrast to 28.8% in the low income group. When this information is used for external adjustment, the observed association between good adherence and outcomes decreases from 0.19 (observed RR) to 0.24 (adjusted RR) which is analogues to a bias reduction of the observed RR of 26.4% in the direction of values observed in RCTs. Although the "external adjustment method" used in this example provides a very crude estimation, it indicates that confounding bias can be substantial, and thus that the results of such pharmacoepidemiological studies are indeed difficult to interpret because of the healthy adherer effect. Future studies addressing the association between sub optimal medication intake or even more complicated, complete discontinuation, should have at least access to information on confounding variables in a subset of a similar population. This information may be obtained from questionnaires send by health insurance companies aimed to evaluate the general health of their beneficiaries. If information in a subset of the study population is available the correction becomes even more reliable. This

would enable propensity score calibration. If outcome information is also available, multiple imputation techniques can even more reliably estimate the true association between non-adherence and outcomes[30]. Thus, although an analysis of the association between adherence and health outcomes is very tempting, researchers should be very careful when designing these studies; otherwise the value of the results is limited.

Next to the lack of information on lifestyle, there are other problems concerning the use of prescription databases for the estimation of non-adherence. Pharmacoepidemiological studies using large databases with pharmacy records often lack a diagnosis or indication for prescribing[36,37]. This is particularly a problem associated with drugs termed antihypertensives, because they may be prescribed for other indications than hypertension. In *chapter 2.1,* we addressed this problem. We found that on average 63% of the patients who received a first prescription for an antihypertensive were actually diagnosed with hypertension. The percentage differed greatly among the several classes of antihypertensives. We also found that subdividing the antihypertensive classes in classes based on their specific mechanism of action such as low-ceiling and high-ceiling diuretics in the group of diuretics could minimize this bias to a certain extent.

Another problem addressed in this thesis is the problem of defining persistence. We already addressed the problem of defining adherence in the current paragraph with regard to the frequently used cut-off value of 80%. The same problem may be encountered with regard to non-persistence. A large number of studies on persistence with antihypertensives have been performed using different definitions[38-45]. When studying persistence, instead of defining a cut-off value, which is the case with adherence, one has to define when a gap between two prescriptions is so large that continuous use can no longer be assumed. The larger the allowed gap the lower the allowed adherence to treatment is. E.g. if a gap of 90 days is allowed, considering that prescriptions in The Netherlands are usually for 90 days, an adherence to treatment of 50% is allowed. In *chapter 2.2,* we have demonstrated that different definitions of persistence lead to different outcomes with regard to persistence. In addition, the size, the strength and the direction of the association between covariates and persistence are largely dependent on the definition. We therefore argued that, first, comparison of persistence studies is difficult and should be done with caution. Second, the absence or presence of an

association is largely dependent on the definition used. The only way to address this problem is by performing sensitivity analyses on the influence of the definition. We have tried to minimize the two pitfalls mentioned above, the absence of an indication and the definition of persistence being arbitrary in *chapter 4.1, chapter 4.2 and chapter 4.3.* In these chapters, we tried to minimize the bias due to the absence of an indication by excluding patients starting with e.g. loop diuretics or verapamil and diltiazem as we suggested in *chapter 2.1.* In addition, in *chapter 4.1* and *chapter 4.2*, patients with concomitant use of short or long acting nitrates, anti-arrhythmics, digoxin, anticoagulants and anti-migraine medication were excluded because this medication might indicate the presence of another disease than hypertension, such as angina pectoris, heart failure and migraine. Furthermore, we excluded patients who were hospitalized for cardiac diseases.

We have tried to circumvent the problem of the definition of persistence being arbitrary, and we have chosen a definition of persistence that did not depend on a gap between two prescriptions in our long term observational study presented in *chapter 4.1*. Instead we defined persistence as collecting at least two prescriptions each 365 days interval after the first prescription. This means that patients at least have to demonstrate the initiative to go to the pharmacy twice a year. This is probably a liberal approach because it would allow patients to collect two one-day prescriptions each year to define them as persistent. However it would lead to a very low adherence to treatment. As the results from our calculation of adherence indicate this did not occur because adherence to treatment among the patients continuing with treatment varied from 83% during the first year to 93% during the tenth year. This definition is probably less useful if shorter time periods are studied and not allowed if Cox-regression analysis is applied because of the limited number of time points. Therefore, in *chapter 4.2* we defined non-persistence as not refilling a prescription at least 180 days after the end date of a previous prescription, which is probably large enough to assume an actual interruption of treatment rather than a sudden decrease to an adherence of approximately 33% in a given interval in case of 90 day-prescriptions. In *chapter 4.3*, it seems even better to define a gap based on a number of days rather than as a proportion of the duration of a prescription, because we compare different countries with different modal prescription lengths. As mentioned in the method section of that chapter 180 days without medication in a given interval would lead

to an adherence of at maximum 14% in the US (30/(30+180), based on a 30-day prescription) and 33% in The Netherlands and Canada (90/(90+180), based on a 90 day prescription. If we would have defined the gap as twice the duration of the last prescription, we would consider a US patient with 60 days without medication non-persistent whereas Dutch and Canadian patient could have 180 days without medication, which is intuitively and probably clinically different. In *chapter 2.2* we demonstrated that extending this gap beyond 180 days, this did not include relevantly more patients as persistent.

Effectiveness of interventions to improve medication taking

Many interventions to increase adherence with antihypertensives have demonstrated no or limited success, as was demonstrated in reviews by Schroeder et al. and Takiya et al.[46,47]. To understand why many efforts have been unsuccessful, the underlying causes of non-adherence and non-persistence should be elucidated.

There are at least five major groups of factors, or *dimensions*, related to a reduced adherence or persistence according to the World Health Organization[48]:

1. Socioeconomic factors
2. Health care setting
3. Disease related factors
4. Treatment related factors
5. Patient related factors

The first dimension is formed by social economic factors, such as low-income, unemployment and level of education. This dimension is particularly important in developing countries. It is reasonable to expect that these countries have other priorities. The second dimension is formed by characteristics with regard to the setting where health care is provided, such as busy practices, lack of knowledge among professionals and the communicative skills of the health care provider. The third group consists of disease related factors, such as disease severity, whether it concerns primary or secondary prevention, but also the presence comorbid conditions. The fourth group consists of treatment related factors, such as side-effects, complex dose regimens and duration of treatment. The fifth, arguably the most important yet difficult dimension consists of patient related factors, such as knowledge, attitude towards health related behavior and expectations[48]. The

above-mentioned subdivision in dimensions emphasizes that adherence is a complex problem because it is very difficult and time consuming to assess the relative importance of each of the five groups in an individual patient.

In our intervention study presented in *chapter 5.2* we experienced that a number of pharmacies eventually failed to cooperate and were unable to include patients. In all cases the reason was that the pharmacy was too busy or lacked a sufficient number of employees to make time available. In this case, the second dimension (the health care setting) seemed to be a problem, especially organizational aspects. The fourth and fifth dimension (treatment and patient related factors) are often regarded as relatively *accessible* to influence by health care professionals. However this does not mean that they are *easy* to influence as is demonstrated by the ineffectiveness of interventions. Hitherto, little success has been obtained in other studies aimed at improving adherence to treatment with medication that is intended to be used chronically[47,49-51]. A study by Friedman et al. evaluated the effect of a telephone linked computer system (TLC) for monitoring and counseling patients with high blood pressure. Small significant differences in the TLC group were observed with regard to diastolic blood pressure, which was lower compared to the intervention group; however systolic blood pressure was not significantly different[52]. Girvin et al. tested in a RCT in a small sample (n=54) enalapril 20 mg once daily vs. enalapril 10 mg twice daily. Although the blood pressure reduction was not significantly different, adherence was significantly better in the once daily group[53]. The latter was in line with the conclusion of the meta-analysis by Schroeder et al. who concluded that simplifying a dose regimen was the most successful intervention[46]. This was confirmed in an observational setting by Dezii et al.[38]. They found that 68.7% of the patients persisted with the combination pill of lisinopril/hydrochlorothiazide and 70.0% with the combination pill of enalapril/hydrochlorothiazide compared to 57.8% and 57.5% of patients using the separate components. Claxton et al. found that with all medications, the less frequent a dose regimen was, the more adherent patients tended to be (table 3)[4]. It is especially important in hypertension because patients often use multiple antihypertensive drugs and drugs for comorbidities.

Table 3: rate of dose taking adherence by frequency of regimen[4]

	Adherence (S.D.)	One times a day	Two times a day	Three times a day
One times a day	79% (±14)	--	--	--
Two times a day	69% (±15)	NS	--	--
Three times a day	65% (±16)	P=0.008	NS	--
Four times a day	51% (±20)	P<0.001	P=0.001	NR

NS=Not Significant, NR=Not Reported

Iskedjian et al. found that adherence with once daily dosages was significantly higher compared to multiple daily dosages (91.4% vs. 83.2%, p<0.001) and to twice daily dosages (92.7% vs. 87.1%, p<0.001). No differences between twice daily dosages and multiple daily dosages were observed (90.8% vs. 86.3%, p=0.069)[52]. It means that until now the most efficient interventions are obtained in the fourth dimension (treatment related factors). Thus, although a lot of work is done addressing the fifth dimension (patient related factors), no advanced patient specific approaches have been elucidated so far.

Influencing the fourth dimension: choosing the optimal treatment

After the discovery of the effectiveness of chlorothiazide and propranolol in 1964, a large number of randomized controlled trials have assessed the effectiveness of a large number of antihypertensives. Currently, there are 13 diuretics, 16 beta-blockers, 13 calcium channel blockers, 11 ACE-inhibitors and 7 ARBs available for the treatment of hypertension in The Netherlands, in varying dosages and different combinations. In addition, 45 RCTs have been performed to demonstrate the effectiveness with regard to cardiovascular morbidity and mortality of these agents against placebo or each other[22,53-55]. In 1997 Monane et al. were the first to clearly demonstrate that the initial drug choice is associated with adherence to treatment in a New Jersey Medicaid population (figure 4)[12].

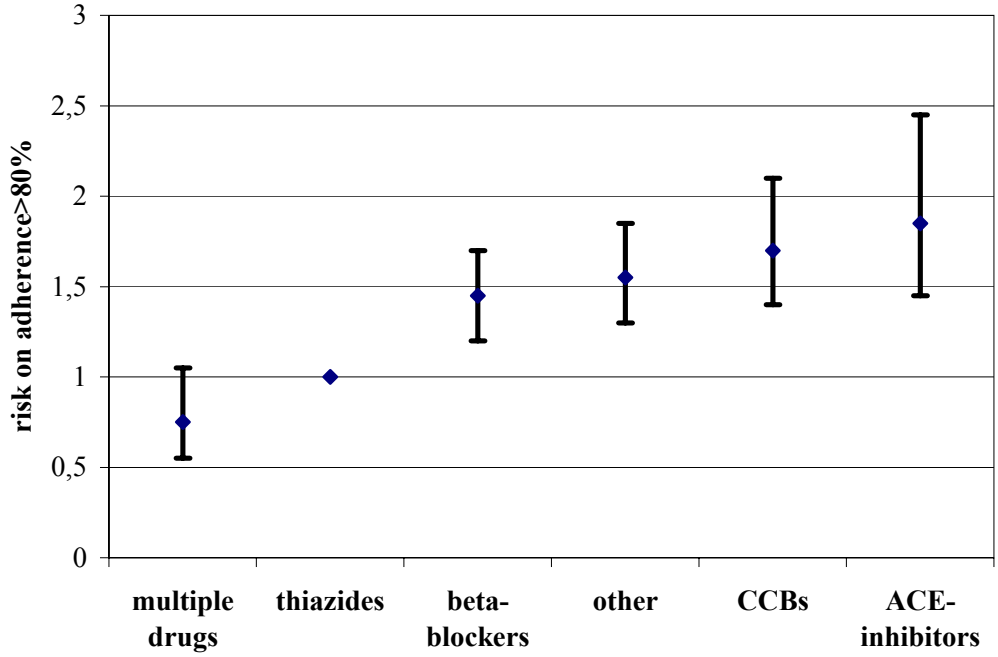

Figure 4: initial drug choice as a factor related to adherence to treatment (≥80% days covered) compared to thiazides[11] CCBs=calcium channel blockers

After this study, Caro et al. demonstrated in the Saskatchewan Health Population that patients with newly diagnosed hypertension who started with ACE-inhibitors and calcium channel blockers were more persistent than patients who started with diuretics, although the difference was not very large, 89% and 86% vs. 80% respectively[58]. In, addition similar studies revealed even larger differences between the newer and older antihypertensives. E.g. the study of Marentette et al. and Chaput et al. demonstrated a more than two-fold difference between angiotensin II receptor blockers and diuretics with regard to persistence in a newly diagnosed hypertensive population[39,59]. In our study presented in *chapter 4.1* and *chapter 4.3*, we found that the initial drug choice is associated with persistence even after 6-10 years. In our study presented in *chapter 4.2*, we demonstrated that the antihypertensive used at discontinuation is associated with the probability to return to treatment. In both studies, patients using newer antihypertensives were more persistent than those who received older ones. Still, The Netherlands, Norway and the US rank diuretics as the first choice in the treatment of hypertension in their guidelines, Finland, Germany, Denmark, the European Hypertension Society and the World Health Organization/ International Society of Hypertension express no clear first choice[60]. Although certain limitations associated with the pharmacoepidemiological studies on adherence and

persistence mentioned above should be taken into account, such as the assumption that the choice for a certain class was made randomly and that not all antihypertensives are prescribed for hypertension (*chapter 2.1*) it implies that the choice for a type of antihypertensive at baseline is an important one with regard to the long term success of treatment. This kind of information cannot be obtained from clinical trials, where compliance is artificially high because of the controlled setting, next to the problem of choice for the method of the measurement of adherence mentioned in the introduction section of this thesis[61]. In the ALLHAT-trial persistence with *primary prescribed antihypertensive drug class* declined from 87.1% the first year to 80.5% in the fifth year among patients assigned to the chlortalidon group, from 87.6% to 80.4% among patients assigned to the amlodipine group and from 82.4% to 72.6% among patients assigned to the lisinopril group[61], which is considerably higher than in the previously mentioned observational studies, including the one presented in *chapter 4.1*. The differences between the class of drugs may be attributable to differences with regard to side-effects. The latter is confirmed by observations by Andrade et al. who found that discontinuation rates for hypercholesterolemic patients using lovastatin (a drug with relatively mild side-effects), observed in RCTs were much more similar compared to the observational setting of a Health Maintenance Organization (HMO)[62]. In contrast, discontinuation rates of patients using fibrates and bile acid sequestrants with more side-effects were much higher in RCTs than in the observational setting. Interestingly, the ALLHAT trial also reported adherence to treatment levels 82-92%, which is generally similar to our results (*chapter 4.1*) and the results of Wannemacher et al.[11] but different from other observational studies[39]. In addition to differences between classes, Breekveldt-Postma et al. found that even two different slow release formulations of nifedipine could lead to differences in persistence[64]. These studies emphasized an important issue namely that the aspects other than effectiveness obtained in RCTs are important for the initial drug choice. Therefore, more objective methods are needed to incorporate these aspects in a comparison between drugs or drug classes. The latter was the basis of our study presented in *chapter 4.4*. In this chapter we have attempted to combine persistence and effectiveness together with costs and experience into a single score to determine the optimal treatment for a patient with uncomplicated hypertension. In this study, various aspects, including persistence with treatment, of the five different classes of antihypertensives were combined into a single score using two different methods and weight factors assigned by cardiologist,

internists, general practitioners and pharmacists. Although there were many methodological concerns, the results suggested that ACE-inhibitors should be considered as the first choice in the treatment of hypertension although this definitely needs more detailed analysis.

Influencing the fifth dimension: the psychology of non-adherence

In *chapter 4.3,* we demonstrated striking similarities in absolute persistence rates as well as patterns of persistence despite large differences related to culture, health care organization, comorbidity and initial drug choice in Pennsylvania, British Columbia and The Netherlands. Appearantly, inadequate medication intake is also a general behavioral characteristic of patients that should be approached not only from a policy perspective but also from a psychological perspective, especially if one considers the generally low explained variance usually observed in population based studies on adherence and persistence. Many psychologists believe that the human race, among other animals, is capable by intuition of avoiding acute risks, such as walking over too narrow mountain roads. Avoiding long-term risks is more difficult, even if sufficient knowledge is available, e.g. smoking or excess eating. The latter can be defined as "errors of commission". Non-adherence or non-persistence can be defined as "errors of omission". However, they refer to a similar kind of problem, namely the problem of our incapability to avoid risks associated with an event that may take place in the future. As mentioned in the *Introduction* section of this thesis, there are two models that are frequently mentioned while discussing the psychological background of suboptimal medication intake (the fifth dimension (patient related factors) identified by the WHO). These are: the Health Believe Model (HBM) and the Stages of Change Model (SCM). The HBM is important because it has had a very large influence on the field of the psychology of reluctance to follow instructions and is an intuitive first reaction when behavioral changes are needed. The SCM is important because it may be readily applicable to the management of patients who are non-adherent to antihypertensive treatment.

Health Belief Model

The HBM has been developed in the US to explain why people do not join (government initiated) intervention programs aimed at prevention or early detection of diseases, especially cardiovascular and diet related diseases. The

essence of the HBM is that the decision to behave healthy is determined by two factors:

1. the potential danger by not adhering to certain rules
2. evaluation of the advised behavior

According to this model patients will take their medication correctly if they think that they are at risk by not taking them correctly and that the advantages counterbalance the disadvantages and their behavior should be evaluated. The HBM also include the concept of a "cue for action" and later the concept of "perceived effectiveness" or believing that someone is capable of changing their behavior increases the chance on success, which is particularly important in lifestyle modifications but may also be of importance for medication taking behavior. As previously mentioned, the HBM is an intuitive first approach. However, it deserves debate whether the approach of explaining the potential danger of being non-adherent is effective if one considers the ineffectiveness of explaining smokers the dangers of smoking.

Stages of Change Model

The Stages of Change Model (SCM) uses the concept of "perceived effectiveness" to influence medication taking behavior and shows at what moment which type of intervention is needed. The SCM identifies six stages (figure 5)[65-67].

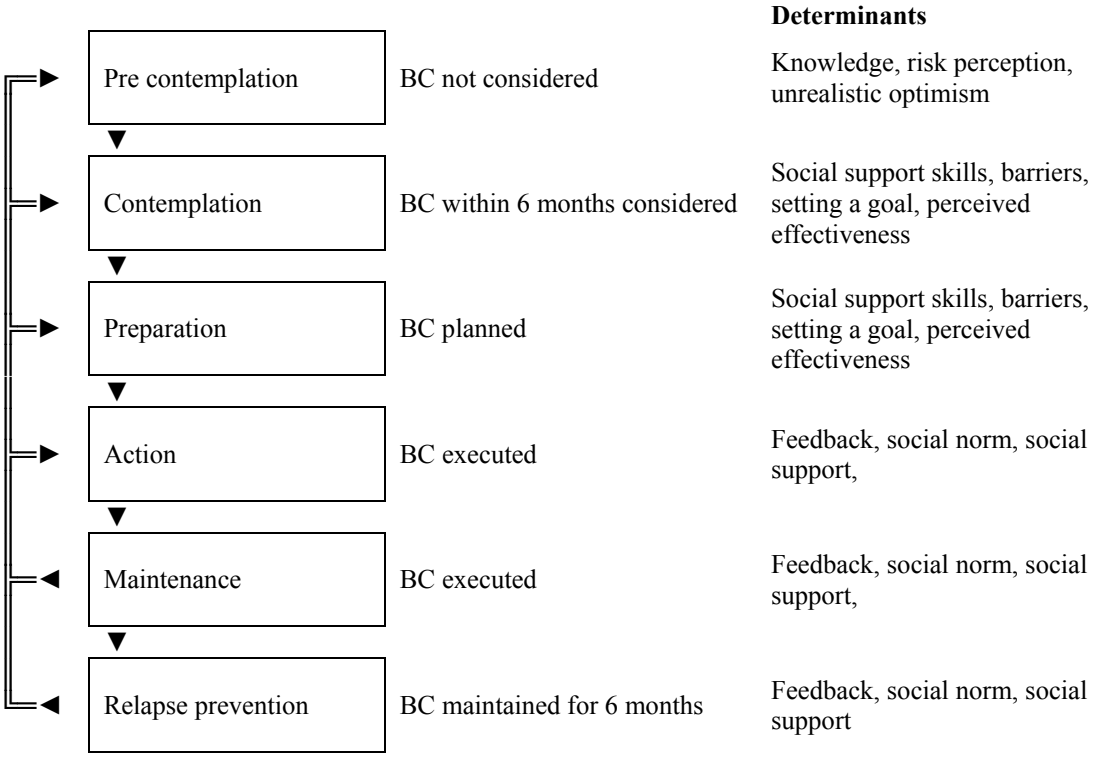

Figure 5: stages of change model, BC=behavioral change (adapted from 65-67)

According to the SCM, a way of obtaining better adherence is to use the feedback mechanisms. First, patients need to have insight in their medication taking, based on objective data. These data stimulate a discussion about reasons for non-adherence and to detect barriers for inadequate use. After the action has been taken feedback is necessary to maintain this behavior. The latter was the basis of the intervention strategy in the RCT described in *chapter 5.2*. In this trial we supported the action phase by reporting objectively measured non-adherence and provided tools for improvement. In, addition we monitored the new behavior, and patients were aware of being monitored, to support the maintenance phase. We did not extend our focus on the relapse prevention phase which would have been better from a psychological perspective as well as from a policy perspective, to estimate the long term feasibility. In addition, we did not identify *a priori*, at which stage the patient was, which possibly could have increased the success of our intervention, although patients would have to be drawn from a smaller

population. However, the latter would require substantial practical experience with the application of the SCM. It would also reduce the external validity of our approach, because most community pharmacists will lack this experience. However it is worth the effort to see whether pharmacists specifically equipped with this knowledge will be able to successfully use it in new studies as well as in daily practice. As it is demonstrated in *chapter 4.2*, a number of patients ultimately reinitiate treatment after a period of non-use. A small proportion can be explained by worsening of the cardiovascular health status. Another part may be explained by the patients own decision to restart using (action phase), preceded by social support, potentially from a physician or pharmacist. In a study by Brookhart et al.[68], it was observed that physician visit preceded restarting in 71% of the patients, although one might argue that a visit to the physician itself may be part of the action phase rather than the preparation phase.

The new role of the pharmacist

The patient oriented intervention we presented in *chapter 5.2* is in line with the changing role of pharmacists in the primary (and secondary) care. The publication by Helper and Strand in 1990 is often regarded and referred to as the beginning of this changing role, nowadays called pharmaceutical care[69]. From this point forward, the pharmacist (at least in developed countries) was aware of the fact that just dispensing medication would not provide him an established position in the future among the other health care professionals. Intervening in sub optimal adherence and persistence was seen as one of the most suitable options. In their 2003 publication called "adherence to long term therapies" the Federation International Pharmaceutique (FIP) made recommendations about the role of the pharmacist with regard to adherence to chronic medication[70]. The FIP stated that "adherence should be recognized as an integral aspect of the whole process of clinical care" and that "all available opportunities should be taken to discuss issues relating to medication with patients"[70].

As mentioned earlier in our review in *chapter 5.1* and our intervention study in *chapter 5.2*, the pharmacist is well equipped to estimate adherence from his own records and has the opportunity to frequently discuss health related behavior because of his position in the chain of health care providers that frequently leads to patient encounters. In *chapter 4.2,* we demonstrated that patients, who discontinued the use of antihypertensive drugs, were refilling other medication.

This gives pharmacists the opportunity to identify these patients and discuss discontinuation with them. It requires knowledge, skills and the adequate setting to apply the knowledge (the second dimension (health care setting) identified by the WHO) and well-identified and applicable strategies obtained from (academic) research.

A lot of research has been done into the role of the pharmacist in enhancing adherence to treatment[51,71-89]. In our review presented in *chapter 5.1*, we analyzed literature on community pharmacist interventions in patients using chronic medication that actually measured adherence to treatment. An overall problem was the quality of the included studies and the high level of adherence at baseline, partly caused by awareness of being monitored (Hawthorne effect)[90]. It complicated the detection of any effect of the intervention in the studies included in our review. In general, the evaluation of pharmacists' services with regard to increasing adherence in RCTs can be questioned. We argue that other *designs*, such as observational studies, may be considered although these designs are limited by internal validity. In addition, observational *methods of measurement* should be considered. As it appeared from our review, using the medication event monitoring system (MEMS [AARDEX, Ltd]) to monitor adherence can lead to artificially increased adherence to treatment[91]. In the randomized controlled study presented in *chapter 5.2*, we aimed to use the biasing effect of MEMS to actually increase adherence in non-adherent patients with hypertension. In addition, we have tried to identify patients who have demonstrated to be non-adherent with antihypertensive drugs, which was based on pharmacy records.

In *chapter 5.3*, we have tested the effect of an intervention in the afore mentioned observational setting in which adherence was measured observationally. In this chapter, one of the many challenges encountered in today's pharmacies concerns generic substitution. On the one hand health insurance companies are becoming more and more demanding to pharmacies to deliver cheaper generic drugs. In addition, pharmacist may financially profit from generic substitution. In contrast, patients may resist changing from a brand name drug that looks familiar to a cheaper generic equivalent. In this chapter, we tested whether generic substitution decreased adherence to treatment. We found that patients who were substituted were not less adherent to treatment after substitution. Although a lot of uncertainties could not be addressed in this study, the results at least give an

indication that adherence is not negatively influenced by substitution and that this design was applicable to evaluate pharmacist services with regard to adherence to treatment.

As mentioned in the *Introduction* section of this thesis, recently the term *concordance* has emerged in the discussion concerning pharmaceutical care and the role of the pharmacist within this process[92-94]. Concordance is in fact combining all five dimensions of adherence identified by the WHO. Implementing concordance-enhancing strategies in daily practice requires the correct setting (private consultation room), knowledge and communicative skills of the health care provider (second dimension). In addition, the health care provider has to take into account the disease status and history of patients (not simply identifying patients with hypertension), the third dimension (disease related factors). Several aspects of treatment should be considered (fourth dimension) and the attitude of the patient towards disease and treatment (fifth dimension). Especially the last dimension may be accompanied by difficulties for healthcare professionals because their attitude towards non-adherence and non-persistence may be different from that of patients. In the end, patients decide what to take or not, based on their own insights on the relative importance of the effectiveness, possible harmful effects and the place of treatment in daily life[95,96].

The recognition of the patient's opinion being the most important, introduced a new insight on the relationship between patients and providers. While adherence and persistence describe the degree to which the patient follows the prescribed regimen, concordance refers to an agreement between patients and healthcare provider about the execution of a treatment, whether this is pharmacological treatment or lifestyle changes, which includes a patient's interests[95]. The consequence of this may be that the initial drug choice may not always be the most effective. In case of antihypertensives, the results of the meta-analysis of Psaty et al. suggest minor, although significant, differences between e.g. ACE-inhibitors and thiazides[24]. ACE-inhibitors may be less bothersome to take compared to thiazides, expressed by higher adherence rates which we confirmed in *chapter 4.1, chapter 4.2* and *chapter 4.3*. After consulting a patient taking thiazide diuretics about side-effects, prescribing an ACE-inhibitor instead of a thiazide diuretic may be an example of concordance[95].

Another example is that during the intervention study presented in *chapter 4.2*, pharmacists discussed reasons for non-adherence with patients and advised them on ways to better incorporate treatment in daily life. The analysis presented in *chapter 4.4,* in which we determined the first line antihypertensive using weight factors obtained from healthcare professionals, should be repeated with weight factors assigned by patients with hypertension. Of course, weight factors may differ between patients, e.g. with regard to different stages of the disease, prior hospitalizations, socio-economic characteristics and interest in health. If pharmacists are willing to play a role in this field, many barriers need to be overcome, such as the willingness of other health care professionals, especially physicians, to collaborate together with pharmacists in the management of chronic diseases. In addition, (political) support from policy makers and the willingness to pay for these services among health insurance companies is needed. This means that parties capable of influencing the second dimension, (health care system related factors) also should make the paradigm shift mentioned in the introduction of the general discussion. Currently, pharmacists are paid for dispensing medication. Recently the state of Minnesota enforced a new law that enabled pharmacist to be compensated for providing advanced pharmaceutical care (medication therapy management)[97]. To establish the required change, pharmacist should (also) be paid for the results of treatment, in this case for the results of stimulating adherence or persistence to treatment of their patients. However, more than any second party or stakeholder, pharmacist themselves are responsible for the development of their own profession. While pharmacist tend to point to doctors and judge them for non-evidence based prescribing, a number of services, including those related to enhancing adherence, are definitely non-evidence based but only of interest from the point of view of a shop keeper, a title most pharmacist who take their profession seriously are horrified and humiliated by. Therefore only those services thoroughly tested are worth paying for. E.g. blindly educating patients about the dose frequency and side-effects of a newly initiated treatment regimen without adequate evidence supporting the effectiveness of this service on *clinical* (surrogate) endpoints (rather than patient satisfaction) is useless. In addition, pharmacy departments of universities have to facilitate research to evaluate these services and the profession should be eager to participate in these studies. A special responsibility that lies with the academics is to carefully design these studies. As Bowen et al. argued and as our review presented in chapter 5.1 confirmed, in the field of adherence not just more but

more *thoughtful* research must be funded and conducted, which may also hold in general for research into pharmacist services.[98]. Consequently, pharmacy departments have to evaluate the results of these studies without professional chauvinism induced prejudice that the pharmacist is the most suitable person to perform the service under evaluation. After equipped with proven strategies and proper knowledge and the realization that pharmacists have to anticipate to the fact that their role as medication dispenser no longer provides them a basis for a future role in health care, even more important, the trust of patients has to be gained. Finally, patients should be convinced that a pharmacist is capable of doing more than just dispensing medication safely and patients should be convinced that pharmacist services are worth paying for not because their health insurance company decides that for them, but because they think it is worth the money. Although the implementation of all this may be very difficult, it is the only way for pharmacists to participate and contribute to the achievement of the paradigm shift mentioned in the introduction of this chapter from cure to prevention and slowing progression of diseases.

Conclusion

The aim of this thesis was to assess the prevalence and determinants of non-adherence and non-persistence with antihypertensive drugs and to provide suggestions for intervening to improve it among non-adherent patients with hypertension. Special emphasis was placed on the role of the pharmacist in both detecting and intervening in non-adherent patients. Throughout the discussion section, we made recommendations for future research on adherence and persistence with antihypertensives and the application of our findings in clinical practice. Three main aspects were highlighted. First, non-adherence seems to be a minor problem compared to non-persistence and future attention should be paid to non-persistence. However, non-adherence can be used to identify patients at risk for modification of their antihypertensive drug regimen and patients at risk for discontinuation. Second, when intervening to increase adherence to treatment, in a research or clinical setting, patients with an increased risk should be identified, rather than randomly intervening in the whole population. Third, insight in the psychological background of patients could help researchers and ultimately health care professionals to further increase the success of interventions aimed to improve medication taking. We argue that in this area, the community pharmacist should be the professional to take the lead.

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Chapter 7

Summary

Summary

The aim of this thesis was to assess the prevalence and determinants of non-adherence and non-persistence with antihypertensive drugs and to provide suggestions for intervening to improve it among non-adherent patients with hypertension. This thesis is divided into three main parts. The first part describes methodological issues with regard to the use of pharmacy records to detect several problems concerning adherence and persistence. The second part describes the identification of potential targets for interventions in an observational setting. The last part concerns intervening in patients using chronic treatment, with special emphasis being placed on antihypertensives. Although some potential reasons will be described in the discussion sections of the presented studies, systematically assessing reasons for non-compliance is outside the scope of this thesis. In addition, only *underuse* of antihypertensive drugs is studied, in contrast to *overuse* because the origin of this problem is totally different.

Drugs termed antihypertensives are also prescribed and registered for other indications than hypertension alone. In pharmacoepidemiological studies, this could introduce several forms of bias. The objective of **chapter 2.1** was to determine the extent to which drugs classified as antihypertensive drugs are prescribed for other diseases than hypertension. The NIVEL database, containing prescriptions from a sample of general practitioners in The Netherlands was used. Classes of antihypertensive drugs were analyzed separately based on ATC-codes: diuretics, beta-blockers, calcium channel blockers, agents acting on the renin angiotensin system and miscellaneous antihypertensives. In addition, these classes were further subdivided, based on their mechanism of action. All first prescriptions of a patient in the database for an antihypertensive drug were selected. ICPC diagnoses studied were: increased blood pressure, hypertension without organ damage, hypertension with organ damage and hypertension with diabetes mellitus for which the above-defined antihypertensive drugs were prescribed. Of 24,812 patients who received a first prescription for an antihypertensive drug, 63.0% received a first prescription for hypertension related diagnoses (diuretics: 54.1%, beta-blockers: 59.1%, calcium channel blockers: 60.3%, agents acting on the renin angiotensin system: 82.8% and miscellaneous antihypertensives: 64.6%). Subdividing these subgroups based on their mechanism of action yields a higher percentage of first prescriptions with hypertension related diagnoses (low-ceiling diuretics: 78.8%, selective beta-blockers: 69.9% and

dihydropyridine calcium channel blockers: 76.8%). In conclusion, if a prescription database lacking diagnoses is used to study antihypertensive drugs in relation to hypertension treatment, the results have to be interpreted with caution because of the potential misclassification that may occur. Subdividing the antihypertensive drug classes into subgroups decreases this misclassification.

Another problem with regard to pharmacoepidemiological studies is addressed in **chapter 2.2**. 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 patient characteristics and persistence were assessed. The PHARMO database, a record linkage system currently containing drug dispensing records from community pharmacies and linked hospital discharge records of approximately 2,000,000 subjects from 50 medium sized cities in The Netherlands, 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) and the third based on a combination of both methods whichever leads to the lowest number of days. 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. 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' definition of the maximum allowed treatment gap.

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 **chapter 3.1** was to assess the association between non-adherence and change in medication regimen. A nested case-control study within a cohort of new users of antihypertensive drugs between January 1st 1999 and December 31st 2002 was performed. Data from the PHARMO database were used. Cases were subjects whose initial drug regimen was modified (dose change, addition and switch). 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. In a cohort of 39,714 new users of antihypertensive drugs, 11,937 cases and 11,937 matched controls were identified. The percentage of non-adherent patients (adherence<80%) among cases and controls was 5.1% and 3.6% respectively (OR 1.39 [95% CI: 1.22-1.58]). The association was 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 use was longer than 6 months. In conclusion, non-adherence is significantly associated with the occurrence of change in antihypertensive medication regimen. Pharmacists and physicians can use pharmacy data to assess and improve adherence with antihypertensive drugs, before modifying treatment regimens.

The objective of **chapter 3.2** was to assess the association between non-adherence and discontinuation in patients who started using antihypertensive monotherapy. A nested case-control study within a cohort of new users of antihypertensive drugs between January 1st 1999 and December 31st 2002 was performed. Data from the PHARMO database were used. Cases discontinued their use of antihypertensive monotherapy (>90 days or 1 times the duration of the last prescription without medication) and were not switched to other antihypertensive treatment, controls stayed on their initially prescribed monotherapy. Conditional logistic regression was used to calculate odds ratios and their 95% confidence intervals. In a cohort of 39,714 new users of antihypertensive drugs, 9,111 cases and 9,111 matched controls were identified. The percentage of non-adherent patients (adherence<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 of 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. In conclusion, among patients who start antihypertensive monotherapy, non-adherence is often followed by discontinuation of this antihypertensive treatment. The pharmacy medication history is a valuable tool for pharmacists and physicians to identify patients who have a high risk of discontinuation with antihypertensive treatment.

Non-persistence with treatment constitutes a major barrier to reach controlled blood pressure. The objective of **chapter 4.1** was to assess the proportion of

patients that started with antihypertensive drug treatment and persisted with treatment for at least 10 years. A retrospective cohort-study using the PHARMO record linkage system was performed. Patients who started using antihypertensive drugs (more than one prescription) in 1992 and did not receive a prescription for any antihypertensive drug in the 365 days preceding the first prescription were included. The main outcome measure was persistence with antihypertensive drugs until 10 years. Among a total of 2,325 patients who started using antihypertensive drugs, 39% used continuously during the 10 years of follow-up. About 22% temporarily discontinued and restarted treatment, whereas 39% of the patients discontinued permanently. Older patients were more persistent than younger patients (20-39 years: OR 2.08 [95% CI: 1.52-2.84]; 40-59 years: (reference), ≥60 years: OR 0.69 [95% CI: 0.54-0.89]). More patients who started with diuretics (reference) and beta-blockers (OR 1.15 [95% CI: 0.87-1.52]) discontinued compared those who started with dihydropyridine calcium channel blockers (OR 0.54 [95% CI: 0.34-0.84]) and ACE-inhibitors (OR 0.38 [95% CI: 0.27-0.55]). Patients who started with combination therapy (OR 0.29 [95% CI: 0.14-0.54]) compared to diuretics or patients who were initially treated by a cardiologist (OR 0.82 [95% CI: 0.61-0.97]) or internist (OR 0.80 [95% CI: 0.62-0.98]) compared to general practitioners, also showed higher persistence. In conclusion, long term persistence in daily practice is low compared to persistence observed in randomized clinical trials and should be considered in the choice of a first line antihypertensive agent.

Population-based studies have demonstrated that a large proportion of patients discontinue treatment after initiation, but many patients then resume therapy. The objective of **chapter 4.2** was to increase our insights about patterns of restarting antihypertensive drugs after a prolonged period of discontinuation. A retrospective cohort-study was conducted among new users of blood pressure (BP) lowering medication in the PHARMO database, who had a period of at least 180 days without such medication. A multivariable Cox-proportional hazard analysis was used to explore the baseline variables associated with reinitiating treatment. Case-crossover analysis was used to evaluate determinants of reinitiating treatment. A total of 35,714 patients were identified as initiating BP-lowering treatment during the period January 1st 1999 to June 30th 2004. Of the 18,357 (51.4%) patients who discontinued BP-lowering treatment, 19.3% restarted treatment within one year and 60.7% restarted within six years. With every additional year on therapy,

patients were more likely to restart (OR: 1.38 [95% CI: 1.34-1.42]). The majority (58.1%) of patients returned to the same drug class they were using at the time of discontinuation. The case crossover analysis revealed that hospitalization for cardiovascular disease (OR: 2.20 [95% CI: 1.84-2.63]) as well as refilling of another cardiovascular medication (OR: 1.25 [95% CI: 1.11-1.40]) were each independently associated with reinitiating treatment. Refilling non-cardiovascular medications was not associated with reinitiating treatment (OR: 1.03 [95% CI: 0.97-1.10)]). Physicians should be aware that many patients have prolonged periods of discontinuation during the use of BP-lowering medication, and that most of these patients will eventually resume therapy. Ongoing refilling other medications is not associated with reinitiating treatment. This suggests that for some patients, the decision to discontinue may be drug specific rather than a behavioral characteristic applicable to all chronic treatments. Hospitalization for a cardiovascular event may provide an opportunity to reinforce the need to resume antihypertensive therapy.

Little is known about cross-national comparisons of antihypertensive medication treatment persistence, trends in persistence and factors associated with persistence. The objective of **chapter 4.3** was to describe and compare patterns of use of antihypertensive drugs in a population of elderly patients in the US (Pennsylvania), Canada (British Columbia) and The Netherlands. A retrospective cohort study of Medicare enrollees in a state pharmacy assistance program in Pennsylvania (US), residents from British Columbia (Canada) and residents from The Netherlands registered in the PHARMO-database was performed. Each population included patients 65 years and older who were initiated on blood pressure lowering treatment between January 1st 1998 and December 31st 2003 and who had continuous follow-up for at least 365 days. Main outcome measures were: proportion of patients with at least 180 consecutive days without medication available (non-persistence); predictors of non-persistence were identified using Cox-proportional hazards. A total of 9,664 Medicare enrollees (US), 25,377 residents from British Columbia and 24,603 residents from The Netherlands were evaluated. During the first year after the initiation of treatment, the proportion of patients with at least 180 days without medication was 23.3% in Pennsylvania, 23.4% in British Columbia and 24.0% in The Netherlands. After six years, this percentage increased to 41.1, 36.3 and 38.2 respectively. Older age, male gender and frequent use of prescription medications in the baseline year was associated

with non-persistence in all three populations. Prior occurrence of acute myocardial infarction and hypercholesterolemia was associated with improved persistence. In conclusion, despite differences in health care organization and drug coverage, non-persistence patterns are strikingly similar between the three populations, as were factors associated with persistence. This suggests that the problem of non-persistence transcends international boundaries, health system characteristics and prescription drug coverage policies.

Multiple characteristics decision making (MCDM) models can be used to calculate a score for a number of alternative drugs or drug classes to allow a comparison between them based on a set of characteristics to enhance objective pharmacotherapy. The aim of **chapter 4.4** was to compare two MCDM-models, Simple Additive Weighting (SAW) and Technique for Order Preference by Similarity to an Ideal Solution (TOPSIS) to determine the first line antihypertensive drug class. Five different classes of antihypertensive drugs were analyzed: diuretics, beta-blockers, dihydropyridine calcium channel blockers (DHP-CCBs), ACE-inhibitors and angiotensin II receptor blockers (ARBs). Four characteristics were deemed relevant for the determination of the first line antihypertensive: effectiveness, persistence as a measure of tolerability, cost and clinical experience. Weight factors were determined by sending questionnaires to cardiologists, pharmacists, GPs and internists. Absolute scores were determined from literature (effectiveness and persistence) and health insurance data (costs and clinical experience). A total of 92 cardiologists (33%), 90 GPs (31%), 87 internists (31%) and 123 pharmacists (43%) completed the questionnaire. Among all professionals, according to both SAW and TOPSIS, ACE-inhibitors were ranked the first-line antihypertensive drug class followed by beta-blockers, DHP-CCBs, ARBs and diuretics respectively. Both methods are valuable tools in the development of evidence-based pharmacotherapy.

A number of studies that explore the possibilities of community pharmacists with regard to enhancing adherence to treatment have been published. The objective of **chapter 5.1** was to systematically review the impact of interventions by community pharmacists on patients' adherence with chronic medication. A MEDLINE search (1966–November 30, 2003) and a review of reference sections were done to identify all pertinent English and German language journal articles. Search terms included compliance, adherence, persistence, discontinuation,

pharmacist and intervention. From each relevant study, the following data were extracted: study design, country, disease, number of patients, patients' age and gender, type of intervention, duration of follow-up, method of measurement of adherence and adherence rate, and data concerning the quality of the included studies. A total of 162 studies were identified, of which 18 matched our inclusion criteria. Twelve were randomized controlled trials and 6 were non-crossover single-group trials. Eight studies showed significant improvement of adherence at one or more time points. Eight studies did not show any effect, 7 of which were randomized controlled trials. In most studies, adherence rates at baseline were high compared to rates reported in the general population. Counseling, monitoring, and education during weekly or monthly appointments showed some effect. However, these same types of interventions showed no effect in other studies. The overall quality of the included studies was low. Currently, it is impossible to identify an overall successful adherence-improving strategy performed by pharmacists. More well-designed and well-conducted studies on the effectiveness of interventions by a community pharmacist to improve patient adherence to chronic medication need to be performed.

Non-adherence to treatment is an important cause of uncontrolled blood pressure. The objective of **chapter 5.2** was to assess the effectiveness of a community pharmacist-led intervention to increase adherence in non-adherent patients with hypertension. A randomized controlled clinical trial was conducted at 17 community pharmacies in The Netherlands. Pharmacy records were used to calculate adherence to treatment with antihypertensive drugs (thiazide diuretics, beta-blockers, dihydropyridine calcium channel blockers, ACE-inhibitors and angiotensin II receptor blockers) over the preceding 365 days. Eighty-two patients with hypertension (age>45 years) who were non-adherent with one antihypertensive drug (adherence ratio <0.80) were enrolled in the study and randomly allocated to the usual care (N=36, systolic blood pressure/diastolic blood pressure (SBP/DBP) 149/86 ± 20/13 mmHg) or intervention group (N=46, SBP/DBP 152/86 ± 20/13 mmHg). The intervention consisted of discussing the observed non-adherence. In addition, patients were informed that for the next three months, the antihypertensive they were non-adherent with would be provided in the Medication Event Monitoring System (MEMS, Aardex Ltd) and that their behavior would be monitored. Linear regression analysis adjusted for baseline blood pressure was used to determine the effect of the intervention on

blood pressure after three months. Baseline characteristics were similar in the intervention and usual care group. The intervention was associated with a non-significantly lower systolic blood pressure (–3.2 [95% CI: -11.4-5.1 mmHg], p=0.449) and a non-significantly lower diastolic blood pressure (–2.4 [95% CI: -8.0-3.3 mmHg], p=0.293) after 3 months. The results of this study are only suggestive of modest effectiveness of discussing non-adherence with patients with hypertension and subsequent monitoring of medication intake with MEMS.

Generic substitution is an important opportunity to reduce the costs of pharmaceutical care. However, pharmacists and physicians often experience that patients have doubt about the equivalence of the substituted drug. This may be reflected by decreased adherence to therapy. The objective of **chapter 5.3** was to assess the association between generic substitution and non-adherence to antihypertensive drugs. A matched cohort study with data from patients starting with the use of antihypertensives between January 1st 1999 and December 31st 2002 was performed. The PHARMO database was used. Included patients were residents of 50 medium-sized cities in the Netherlands, who started with the use of antihypertensive drugs. The main outcome measure was refill adherence with antihypertensive drugs after substitution. Patients with a refill adherence below 80% were considered non-adherent. Four hundred and sixty-three patients with a substitution and 565 controls, matched on age, gender, start date of use, duration of use and generic product code, were identified. Of the substituted patients, 13.6% were non-adherent, and of the non-substituted patients 18.7% were non-adherent (OR 0.68 [95% CI: 0.48-0.96]). The association was absent in males. None of the patients discontinued their medication. No differences in hospitalizations for cardiovascular diseases in the 6 months after the substitution were observed. Generic substitution of antihypertensive drugs does not lead to lower adherence, or to more non-persistence and cardiovascular disease related hospitalizations compared to non-substituted patients. When a less expensive antihypertensive generic equivalent becomes available, generic substitution should be considered to profit from economic benefits.

Finally, the results, conclusions and recommendations are put in a broader perspective in the **general discussion.** The aim of this thesis was to assess the prevalence and determinants of non-adherence and non-persistence and to provide suggestions for intervening to improve it among non-adherent patients with

hypertension. Special emphasis was placed on the role of the pharmacist in both detecting and intervening in non-adherent patients. Throughout the discussion section, recommendations for future research on adherence and persistence with antihypertensives and the application of our findings in clinical practice were made. Three main aspects were highlighted. First, non-adherence seems to be a minor problem compared to non-persistence and future attention should be paid to non-persistence. However, non-adherence can be used to identify patients at risk for modification of their antihypertensive drug regimen and patients at risk for discontinuation. Second, when intervening to increase adherence to treatment, in a research or clinical setting, patients with an increased risk should be identified, rather than randomly intervening in the whole population. Third, insight in the psychological background of patients could help researchers and ultimately health care professionals to further increase the success of interventions aimed to improve medication taking. The authors argue that in this area, the community pharmacist should be the professional to take the lead.

Chapter 8

Samenvatting

Samenvatting

Het doel van dit proefschrift was de prevalentie en determinanten van therapieontrouw te onderzoeken en suggesties te doen om te interveniëren bij therapieontrouwe patiënten met hypertensie. Therapietrouw kan op twee manieren worden uitgedrukt. Ten eerste als het percentage van de tijd in het bezit van medicatie (adherentie), ten tweede als het wel of niet doorgaan met gebruiken (persistentie). Het proefschrift bestaat uit drie onderdelen. Het eerste onderdeel gaat over methodologische aspecten met betrekking tot het gebruik van apotheekaflevergegevens om verschillende aspecten van therapieontrouw te onderzoeken. Het tweede deel gaat over de identificatie van therapieontrouwe patiënten in een observationele setting. Het laatste deel gaat over interveniëren bij patiënten die antihypertensiva gebruiken. Hoewel een aantal mogelijke redenen voor therapieontrouw wordt besproken in de discussiesecties van de gepresenteerde onderzoeken, valt het systematisch vaststellen van redenen voor therapieontrouw buiten het bestek van dit proefschrift. Daarnaast is alleen ondergebruik bestudeerd in tegenstelling tot overgebruik omdat de oorzaken van dit probleem verschillen van die van ondergebruik.

Antihypertensiva zijn geregistreerd en worden ook voorgeschreven voor andere indicaties dan hoge bloeddruk. In farmaco-epidemiologische studies kan dit verschillende soorten vertekening introduceren. Het doel van **hoofdstuk 2.1** was te bepalen in welke mate antihypertensiva voor andere indicaties dan voor hypertensie worden voorgeschreven. Er is gebruik gemaakt van de NIVEL-database, die voorschrijfgegevens van Nederlandse huisartsen bevat. De verschillende klassen antihypertensiva zijn geanalyseerd op basis van ATC-codes: diuretica, bètablokkers, calciumantagonisten, geneesmiddelen die inwerken op het renine-angiotensin systeem en “overige” antihypertensiva. Daarnaast zijn deze klassen verder onderverdeeld op basis van hun werkingsmechanisme. Alle eerste voorschriften in de database zijn geselecteerd. De volgende ICPC-diagnosen zijn bestudeerd: verhoogde bloeddruk, hypertensie zonder orgaanschade, hypertensie met orgaanschade en hypertensie met diabetes mellitus waarvoor de bovengenoemde antihypertensiva zijn voorgeschreven. Van de 24.812 patiënten die een eerste recept kregen voor een antihypertensivum kreeg 63,0% dit voor een aan hoge bloeddruk gerelateerde diagnose: diuretica: 54,1%, bètablokkers: 59,1%, calciumantagonisten: 60,3%, geneesmiddelen die inwerken op het renine-angiotensine systeem: 82,8% en “overige” antihypertensiva: 64,6%. Het verder

onderverdelen van de klassen op basis van hun werkingsmechanisme levert een hoger percentage aan hypertensie gerelateerde diagnoses op: low-ceiling diuretica: 78,8%, selectieve bètablokkers: 69,9% en dihydropyridine calciumantagonisten: 76,8%. Indien een prescriptiedatabase waarin de diagnose ontbreekt, gebruikt wordt om antihypertensiva te bestuderen in relatie tot de behandeling van hypertensie, moeten de resultaten voorzichtig worden geïnterpreteerd vanwege de mogelijke misclassificatie die kan optreden. Het verder onderverdelen van de klassen van antihypertensiva in subgroepen op basis van het werkingsmechanisme vermindert deze misclassificatie.

Een ander probleem met betrekking tot farmaco-epidemiologische studies wordt behandeld in **hoofdstuk 2.2**. In de literatuur worden verschillende methoden gebruikt om persistentie te berekenen. In dit hoofdstuk is de invloed van het gebruik van deze verschillende methoden op persistentie en de invloed op de relatie tussen patiëntkenmerken en persistentie vastgesteld. De PHARMO database is gebruikt om persistentie met antihypertensiva te berekenen voor een cohort van 14.466 nieuwe gebruikers van antihypertensiva. De PHARMO-database bevat apotheekaflevergegevens en ontslaggegevens uit het ziekenhuis van ongeveer 2.000.000 patiënten uit 50 middelgrote steden in Nederland. Drie verschillende soorten methoden zijn gebruikt om het aantal dagen tussen twee voorschriften te bepalen dat een patiënt mag hebben om nog als een continue gebruiker te worden geclassificeerd, één op basis van een gedefinieerd aantal dagen (9-365), één op basis van de gedefinieerde fractie van de theoretische duur van het laatste recept (0,1-4 keer) en één op basis van de combinatie van beide methoden, die leidt tot het kleinste aantal dagen. Persistentie varieerde tussen 19,7%-86,4% (methode een), 27,9%-90,2% (methode twee) and 19,7%-86,5% (methode drie). Daarnaast varieerde de patiëntkenmerken die geassocieerd waren met persistentie tussen en binnen de drie methoden. Geconcludeerd kan worden, dat de gebruikte methode zowel absolute persistentie als de associatie tussen patiëntkenmerken en persistentie beïnvloedt. Resultaten van persistentiestudies worden sterk beïnvloed door de gehanteerde methode om persistentie te berekenen.

Ongecontroleerde bloeddruk en klachten over de voorgeschreven medicatie kunnen leiden tot een verandering van de initieel voorgeschreven behandeling. Het doel van **hoofdstuk 3.1** was vast te stellen of er een associatie bestaat tussen

non-adherentie en verandering van medicatie. Een “genest case-control” onderzoek is uitgevoerd binnen een cohort van nieuwe gebruikers van antihypertensiva, die startten met het gebruik tussen 1 januari 1999 en 31 januari 2002. Gegevens uit de PHARMO-database zijn gebruikt. De “cases” waren patiënten van wie de initiële therapie is veranderd (dosis verandering, additie switch). Controles ondergingen geen verandering. Conditionele logistische regressie is gebruikt om odds ratio’s (OR) en 95% betrouwbaarheidsintervallen (BI) te berekenen en te corrigeren voor confounders. In een cohort van 39.714 nieuwe gebruikers van antihypertensiva, zijn 11.937 cases en 11.937 controles geïdentificeerd. Het percentage non-adherente patiënten (adherentie<80%) onder de cases en de controles was respectievelijk 5,1% en 3,6% (OR 1,39 [95% BI: 1,22-1,58]). De associatie was sterker bij vrouwen (OR 1,64 [95% BI: 1,37-1,94]) dan bij mannen (OR 1,14 [95% BI: 0,94-1,40]) en sterker indien de duur van het gebruik langer was dan 6 maanden. Geconcludeerd kan worden, dat non-adherentie is geassocieerd met het optreden van veranderingen in therapie met antihypertensiva. Apothekers en artsen kunnen apotheekaflevergegevens gebruiken om adherentie te bepalen en te verbeteren voordat bestaande medicatie wordt aangepast.

Het doel van **hoofdstuk 3.2** was vast te stellen of er een associatie bestaat tussen non-adherentie en stoppen met gebruik bij patiënten die gestart zijn met het gebruik van antihypertensiva. Een “genest case-control” onderzoek is uitgevoerd binnen een cohort van nieuwe gebruikers van antihypertensiva, die startten met het gebruik tussen 1 januari 1999 en 31 januari 2002. Gegevens uit de PHARMO-database zijn gebruikt. De “cases” waren patiënten die stopten met het gebruik van hun initiële monotherapie (>90 dagen of 1 maal de duur van het laatste recept zonder medicatie). Controles bleven hun initiële monotherapie gebruiken. Conditionele logistische regressie is gebruikt om odds ratio’s en 95% betrouwbaarheidsintervallen te berekenen. In een cohort van 39.714 nieuwe gebruikers van antihypertensiva, zijn 9.111 cases en 9.111 controles geïdentificeerd. Het percentage non-adherente patiënten (adherentie<80%) onder de cases en de controles was respectievelijk 14,0% en 5,8% (OR 2,86 [95% BI: 2,52-3,24]). Patiënten die korter dan 90 dagen gebruikten hadden een lager risico op stoppen (OR 3,10 [95% BI: 2,67-3,59]) dan patiënten die langer dan 90 dagen gebruikten (OR 2,28 [95% BI: 1,79-2,92]). De associatie was ongeveer hetzelfde voor mannen als voor vrouwen, voor de verschillende klassen antihypertensiva en

voor de verschillende leeftijdsklassen. Geconcludeerd kan worden, dat bij patiënten die startten met het gebruik van monotherapie met antihypertensiva, non-adherentie vaak gevolgd wordt door stoppen met het gebruik van antihypertensiva. Apotheekaflevergegevens zijn een waardevolle bron van informatie voor artsen en apothekers om patiënten te identificeren met een verhoogd risico op stoppen.

Stoppen met het gebruik van antihypertensiva is een groot probleem bij het streven naar een gecontroleerde bloeddruk. Het doel van **hoofdstuk 4.1** was vast te stellen wat het percentage patiënten is dat start met het gebruik van antihypertensiva en daarmee gedurende tien jaar door gaat. Een retrospectief cohortonderzoek uitgevoerd is uitgevoerd waarbij gebruik gemaakt is van de PHARMO-database. Patiënten, die startten met het gebruik van antihypertensiva (meer dan 1 recept) in 1992 en die in de 365 dagen daarvoor geen recept kregen voor een antihypertensivum zijn geselecteerd. De belangrijkste uitkomstmaat was persistentie met het gebruik van antihypertensiva gedurende 10 jaar. Van in totaal 2.325 patiënten, die startten met het gebruik van antihypertensiva gebruikte 39% continu gedurende 10 jaar, 22% stopte tijdelijk, terwijl 39% permanent stopte. Oudere patiënten persisteerden beter dan jongere patiënten (20-39 jaar: OR 2,08 [95% BI: 1,52-2,84]; 40-59 jaar: (referentie), ≥60 jaar: OR 0,69 [95% BI: 0,54-0,89]). Van de patiënten die startten met diuretica (referentie) en bètablokkers (OR 1,15 [95% BI: 0,87-1,52]) bleek een groter percentage te stoppen met het gebruik van antihypertensiva dan van patiënten die startten met calciumantagonisten (OR 0,54 [95% BI: 0,34-0,84]) en ACE-remmers (OR 0,38 [95% BI: 0,14-0,54]). Patiënten die startten met het gebruik van combinatietherapie (OR 0,29 [95% BI: 0,14-0,54]) of patiënten die hun eerste recept voor een antihypertensivum van de cardioloog (OR 0,82 [95% BI: 0,61-0,97]) of internist (OR 0,80 [95% BI: 0,62-0,98] ontvingen, stopten ook minder vaak dan patiënten die hun eerste recept van de huisarts ontvingen. Geconcludeerd kan worden, dat lange termijn persistentie in de dagelijkse praktijk laag is en moet worden meegenomen bij de keuze van een initiële behandeling van hypertensie.

Observationeel onderzoek heeft aangetoond dat een gedeelte van de patiënten die stoppen met het gebruik van antihypertensiva daarna weer begint met het gebruik. Het doel van **hoofdstuk 4.2** was het inzicht te vergroten in herstartpatronen bij patiënten die een periode gestopt te zijn. Een retrospectief cohortonderzoek is

uitgevoerd onder nieuwe gebruikers van antihypertensiva in de PHARMO-database in Nederland, die tenminste 180 dagen stopten met deze geneesmiddelen. Multivariabele Cox-proportional hazards zijn gebruikt om patiëntkenmerken die geassocieerd zijn met herstarten te bepalen. Case-crossover analyse is gebruikt om determinanten van herstarten te bepalen. In totaal zijn 35.714 geïdentificeerd die startten met het gebruik van antihypertensiva tussen 1 januari 1999 en 30 juni 2004. Van de 18.357 (51,4%) patiënten die stopten met het gebruik van antihypertensiva, herstartte 19,3% hun behandeling binnen 1 jaar en 60,7% herstartte binnen 6 jaar. Ieder extra jaar dat antihypertensiva gebruikt werden, vergrootte de kans op herstarten (OR: 1,38 [95% BI: 1,34-1,42]). De meerderheid (58,1%) van de patiënten herstartte met hetzelfde geneesmiddel dat ze gebruikten op het moment van stoppen. De case cross-over analyse toonde aan dat ziekenhuisopnames voor cardiovasculaire ziekten (OR: 2,20 [95% BI: 1,84-2,63]) en het ophalen van cardiovasculaire co-medicatie (OR: 1,25 [95% BI: 1,11-1,40]) onafhankelijk van elkaar geassocieerd waren met het herstarten van de behandeling. Het ophalen van niet-cardiovasculaire geneesmiddelen was niet geassocieerd met herstarten (OR: 1,03 [95% BI: 0,97-1,10)]). Geconcludeerd kan worden, dat artsen en apothekers zich er bewust van moeten zijn dat een groot deel van de patiënten langdurig stopt met de behandeling, maar uiteindelijk de behandeling met antihypertensiva weer zal herstarten. Het ophalen van niet-cardiovasculaire medicatie is niet geassocieerd met herstarten. Dit suggereert dat voor een aantal patiënten de beslissing om te stoppen geneesmiddelspecifiek is, in plaats van een gedragkenmerk van een patiënt dat voor alle chronische behandelingen geldt. Een ziekenhuisopname voor een cardiovasculaire aandoening is een mogelijkheid de behandeling met antihypertensiva opnieuw in te stellen.

Er is weinig onderzoek beschikbaar waarbij persistentie, trends in persistentie en voorspellers van persistentie in verschillende landen vergeleken wordt. Het doel van **hoofdstuk 4.3** was persistentie-patronen van het gebruik van antihypertensiva te beschrijven en te vergelijken in een populatie van oudere patiënten in de VS (Pennsylvania), Canada (British Columbia) en Nederland. Een retrospectieve cohortstudie is uitgevoerd onder via Medicare verzekerde patiënten, inwoners van British Columbia (Canada) en inwoners van Nederland die geregistreerd zijn in de PHARMO-database. Elke populatie omvatte patiënten van 65 jaar en ouder, die startten met het gebruik van bloeddruk verlagende therapie tussen 1 januari 1998

en 31 december 2003 die tenminste 365 dagen follow-up hadden. De belangrijkste uitkomstmaten waren: aantal patiënten met tenminste 180 aaneengesloten dagen zonder medicatie (niet persistent), trends in persistentie en voorspellers van persistentie (berekend met Cox-proportional hazards). In totaal zijn 9.664 via Medicare verzekerde patiënten (US), 25.377 inwoners uit British Columbia en 24.603 inwoners uit Nederland bestudeerd. Tijdens het eerste jaar na de start van de behandeling hadden 23,3% van de patiënten uit Pennsylvania, 23,4% van de inwoners uit British Columbia en 24,0% van de inwoners uit Nederland tenminste 180 dagen zonder medicatie. Na 6 jaar was dit percentage gestegen tot respectievelijk 41,1, 36,3 en 38,2 respectievelijk. Hoge leeftijd, mannelijk geslacht en regelmatig gebruik van geneesmiddelen in het jaar voor de start van de behandeling was geassocieerd met non-persistentie in alle drie de landen. Een eerder doorgemaakt acuut myocardinfarct en hypercholesterolemie waren geassocieerd met hogere persistentie. Ondanks verschillen in de organisatie van de gezondheidszorg en vergoedingsmaatregelen, zijn de persistentiepatronen opvallend gelijk in de drie bestudeerde populaties net zoals factoren die geassocieerd zijn met non-persistentie. Dit suggereert dat het probleem van non-persistentie grensoverschrijdend is, onafhankelijk van eigenschappen van het gezondheidsstelsel en het geneesmiddelvergoedingssysteem.

Multiple criteria beslis (MCB-) modellen kunnen worden gebruikt om een score te berekenen voor een aantal verschillende geneesmiddelen of geneesmiddelgroepen op basis van een aantal criteria ter bevordering van het maken van objectieve farmacotherapeutische keuzen. Het doel van **hoofdstuk 4.4** was twee MCB-modellen, Simple Additive Weighting (SAW) en Technique for Order Preference by Similarity to an Ideal Solution (TOPSIS) te vergelijken om de eerste keuze klasse van antihypertensiva te bepalen. Vijf verschillende klassen zijn geanalyseerd, diuretica, bètablokkers, dihydropyridine calciumantagonisten, ACE-remmers en angiotensin II receptor blokkers. Vier criteria werden van belang geacht voor de bepaling van de eerste keuze klasse van antihypertensiva: effectiviteit, persistentie als maat voor tolerantie, kosten en klinische ervaring. Weegfactoren zijn verkregen door het versturen van vragenlijsten naar cardiologen, apothekers, huisartsen en internisten. Absolute scores zijn bepaald op basis van literatuurgegevens (effectiviteit en persistentie) en met behulp van gegevens van zorgverzekeraars (kosten en klinische ervaring). In totaal vulden 92 cardiologen (33%), 90 huisartsen (31%), 87 internisten (31%) en 123 apothekers

(43%) de vragenlijst in. Onder alle zorgverleners waren ACE-remmers de eerste keuze antihypertensiva, gevolgd door bètablokkers, dihydropyridine calciumantagonisten, angiotensin receptor blokkers en diuretica. Beide methoden zijn waardevol om "evidence based" farmacotherapie te bevorderen.

Er is een groot aantal onderzoeken uitgevoerd om de effectiviteit van interventies door openbaar apothekers om adherentie te verhogen te bestuderen. Het doel van **hoofdstuk 5.1** was een systematisch overzicht te geven van de invloed van interventies door openbaar apothekers op therapietrouw (adherentie en persistentie) met chronische medicatie. Een MEDLINE-search (1966-30 november 2003) en controle van referentielijsten zijn uitgevoerd om alle Engels en Duitstalige onderzoeken te identificeren. De volgende zoektermen zijn gebruikt: "compliance", "adherence", "persistence", "discontinuation", "pharmacist" en "intervention". Uit ieder relevant onderzoek zijn de volgende gegevens geëxtraheerd: onderzoeksopzet, land, aandoening, aantal patiënten, leeftijd van de patiënten, soort interventie, duur van het onderzoek, therapietrouw, methode van het meten van therapietrouw en gegevens over de kwaliteit van de studies. In totaal zijn 162 onderzoeken geïdentificeerd, waarvan er 18 voldeden aan onze selectiecriteria. Twaalf onderzoeken waren gerandomiseerde gecontroleerde trials, 6 waren "non-cross-over single group trials". Acht studies lieten een significante verbetering van de therapietrouw zien op een of meerdere meetpunten. Acht studies lieten geen enkel effect zien, waarvan 7 gerandomiseerde gecontroleerde trials waren. Bij de meeste onderzoeken, was de therapietrouw aan het begin van de studie hoog vergeleken met populatiegegevens. Het adviseren, monitoren en het geven van uitleg gedurende wekelijkse of maandelijkse afspraken lieten enig effect zien. Echter dezelfde interventies lieten geen effect zien in andere studies. In de meeste gevallen was de kwaliteit van de studies laag. Het is niet mogelijk een door een openbaar apotheker uitgevoerde succesvolle therapietrouwverhogende interventie te identificeren. Er moeten meer beter ontworpen en uitgevoerde onderzoeken gedaan worden naar de effectiviteit van interventies door de openbare apotheker om de therapietrouw te verhogen.

Non-adherentie is een belangrijke oorzaak van niet gecontroleerde bloeddruk. Het doel van **hoofdstuk 5.2** was het effect vast te stellen van een door een openbaar apotheker uitgevoerde interventie om adherentie te verbeteren bij non-adherente

patiënten met hoge bloeddruk. Een gerandomiseerd gecontroleerd onderzoek is uitgevoerd in 17 openbare apotheken in Nederland. Apotheekaflevergegevens zijn gebruikt om adherentie met antihypertensiva te berekenen over de voorafgaande 365 dagen. Tweeëntachtig patiënten met hypertensie (leeftijd>45 jaar) die non-adherent waren met één antihypertensivum (adherentie<80%) zijn in de studie geselecteerd en willekeurig verdeeld over de gebruikelijke zorg groep (N=36, systolische bloeddruk/diastolische bloeddruk (SBD/DBD) 149/86 ± 20/13 mmHg) en de interventiegroep (N=46, SBD/DBD 152/86 ± 20/13 mmHg). De interventie bestond uit het bediscussiëren van de gedetecteerde non-aherentie. Bovendien zijn patiënten geïnformeerd dat ze gedurende 3 maanden het antihypertensivum waarmee ze non-adherent waren in een Medication Event Monitoring System (MEMS, Aardex Ltd) zouden krijgen en dat hun geneesmiddelgebruik werd geregistreerd. Lineaire regressie analyse, gecorrigeerd voor bloeddruk op het moment van starten met het onderzoek, is gebruikt om het effect van de interventie na 3 maanden te bepalen. Patiëntkenmerken voorafgaand aan het onderzoek waren gelijk tussen de twee groepen. De interventie was geassocieerd met een niet-significant lagere systolische bloeddruk (–3,2 [95% BI: -11,4-5,1 mmHg], p=0,449) en een niet-significant lagere diastolische bloeddruk (–2,4 [95% BI: -8,0-3,3 mmHg], p=0,293) na 3 maanden. De resultaten van dit onderzoek suggereren een beperkt effect van het bespreken van gedetecteerde non-adherentie en het daaropvolgende registreren van geneesmiddelgebruik met MEMS.

Generieke substitutie is een belangrijke kans om de kosten van farmaceutische zorg te beperken. Echter, apothekers en artsen merken dikwijls dat patiënten twijfelen aan de gelijkwaardigheid van het gesubstitueerde geneesmiddel. Dit zou zich kunnen vertalen in een lagere adherentie. Het doel van **hoofdstuk 5.3** is vast te stellen of er een relatie bestaat tussen generieke substitutie en adherentie met antihypertensiva. Er is een gematcht cohortonderzoek uitgevoerd met patiënten die startten met het gebruik van antihypertensiva tussen 1 januari 1999 en 31 december 2002, die startten met het gebruik van antihypertensiva zijn geselecteerd uit de PHARMO-database. De belangrijkste uitkomstmaat was adherentie met antihypertensiva na substitutie. Patiënten met een adherentie beneden 80% zijn als non-adherent beschouwd. Vierhonderddrieënzestig patiënten met een substitutie en 565 controles, gematcht op leeftijd, geslacht, duur van het gebruik en generieke product code, zijn geïdentificeerd. Van de gesubstitueerde patiënten was 13,6% non-adherent en van de niet- gesubstitueerde was 18,7% non-adherent (OR 0,68

[95% BI: 0,48-0,96]). Bij mannen bleek dit verband niet statistisch significant aanwezig. Geen van de patiënten stopte met het gebruik van hun medicatie. Er zijn geen verschillen in ziekenhuisopnames gevonden in de 6 maanden na de substitutie. Geconcludeerd kan worden, dat generieke substitutie van antihypertensiva niet leidt tot een lagere adherentie of tot meer stoppen en ziekenhuisopnames vergeleken met niet gesubstitueerde patiënten. Indien een minder duur generiek antihypertensivum beschikbaar is, moet generieke substitutie worden overwogen om te profiteren van de economische voordelen.

Ten slotte zijn de bevindingen en aanbevelingen in een breder perspectief geplaatst in de **general discussion**. Het doel van dit proefschrift was vast te stellen wat de prevalentie en determinanten waren van therapieontrouw en suggesties te doen voor het interveniëren bij patiënten met hypertensie. Speciale aandacht is gevestigd op de rol van de apotheker in zowel het detecteren van, als het interveniëren bij therapieontrouwe patiënten. In dit hoofdstuk zijn aanbevelingen gedaan voor vervolgonderzoek naar therapieontrouw met antihypertensiva en voor de toepassing van onze bevindingen in de dagelijkse praktijk. Drie belangrijke aspecten zijn belicht. Ten eerste lijkt non-adherentie een gering probleem vergeleken met het stoppen met gebruik, en moet in de toekomst de aandacht dan ook worden gericht op stoppen. Non-adherentie kan echter wel gebruikt worden om patiënten te identificeren met een verhoogd risico op verandering van hun therapie en op stoppen. Ten tweede, indien er geïntervenieerd wordt op therapieontrouw in een onderzoeks- of in een klinische setting moeten patiënten met een verhoogd risico worden geïdentificeerd in plaats van willekeurig in de hele populatie te interveniëren. Ten derde, inzicht in de psychologische achtergrond van patiënten kan onderzoekers en professionals werkzaam in de gezondheidszorg, helpen het succes van interventies, gericht op het verhogen van de therapietrouw, te vergroten. De auteurs denken dat op dit gebied de openbaar apotheker de professional *zou moeten* zijn om het initiatief hierbij te nemen.

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Publications related to this thesis

BLG van Wijk, OH Klungel, ER Heerdink, A de Boer. Different definitions of the maximum allowed treatment gaps lead to different rates of refill persistence. *Journal of Clinical Epidemiology 2006; 59: 11-17.*

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Curriculum Vitae

Boris van Wijk was born on October 16th 1977 in Nijmegen, The Netherlands. In 1995, he graduated at the *Kandinsky College* in Nijmegen. He started his study Pharmacy in 1995 at the Utrecht University. In 2001 he obtained his Masters degree in pharmacy and in 2002 he became a pharmacist. In the same year he started the work described in this thesis at the department of pharmacoepidemiology and pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences of the Utrecht University. From March until June 2006 he worked at the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Womans' hospital at Harvard Medical School in Boston funded by a travel grant awarded by the Netherlands Organization for Scientific Research (NWO). His work as a PhD-student was combined with a position to obtain his registration as community pharmacist at the Hofstad Apotheek, Apotheek Van Ham and his current employer, Apotheek Oudenbosch.