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

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Abstract

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

Methods—A retrospective cohort study of Medicare enrollees in a state pharmacy assistance programme in Pennsylvania (USA), residents from British Columbia (Canada) and residents from the Netherlands registered in the PHARMO database was conducted. Each population included patients 65 years and older who were initiated on blood pressure-lowering treatment between 1 January 1998 and 31 December 2003 and who had continuous follow-up for at least 365 days. In these populations, the proportion of patients with at least 180 consecutive days without medication available (non-persistence) were identified as were predictors of non-persistence using Cox proportional hazards.

Results—A total of 9664 Medicare enrollees (USA), 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 percentage 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 6 years, these percentages increased to 41.1, 36.3 and 38.2%, respectively. Factors associated with non-persistence were different between the three countries.

Conclusion—Despite differences in factors associated with persistence, non-persistence patterns are strikingly similar in all three populations. This suggests that the problem of non-persistence transcends international boundaries.

Keywords

adherence; antihypertensive drugs; discontinuation; hypertension; persistence

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Introduction

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

Efforts to quantify antihypertensive medication non-persistence are needed, especially when considering the current and future burden of this chronic disease [8]. 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 antihypertensive medications. It seems plausible that different healthcare systems, different cultural attitudes about healthcare and different drug coverage policies could influence medication-taking behavior. Although cross-national multicenter randomized trials have been used in the field of hypertension to test effectiveness, [9–12] cross-national comparisons of drug utilization are scarce [13]. 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 United States, Canada and the Netherlands.

Methods

Sources of data

United States—The US population was drawn from the Pharmaceutical Assistance Contract for the Elderly (PACE) programme in Pennsylvania. The PACE programme is the largest state prescription benefits programme for the elderly in the United States, and offers generous coverage to low-income elderly residents of the state. Full pharmacy and healthcare claims 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 classification system [4]. Claims for services in hospitals and offices are coded according to International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and Diagnostic Related Groupings [14]. Medicare data have been demonstrated to be a reliable source of drug exposure [1,15, 16]. On the basis of unique patient identifiers, data on the drug use of PACE enrollees were linked to Medicare data on hospitalizations and outpatient professional services and procedures.

The PACE programme has no deductibles and no maximum annual benefit [17]. There is a modest co-payment of US$6 for each generic prescription and US$9 for each branded prescription. The income ceiling for PACE eligibility is US$14 000 if single and US$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 [18–20]. The Ministry of Health collects data on all healthcare 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 healthcare, 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 [18,20]. Drug use was linked to healthcare claims based on unique patient identifiers. This data source has been demonstrated to be a reliable and complete source of healthcare use [21]. Drug names are coded according to the Drug Information Number/Product Identification Number classification system [20]. Claims for services in hospitals and offices are coded according to ICD-9-CM and the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures [22].

From 1 January 1997 reference pricing was introduced in British Columbia [23,24]. Reference priced drugs include angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists. 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 1 January 2002, patients with an annual income of less than Can$16 000 were charged a Can$10 co-payment for each dispensing whereas patients with a greater annual income were charged Can$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 underutilizing essential drugs [25]. 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 [26,27]. The PHARMO record linkage system 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 supplied). Drug names are coded according to the Anatomical Therapeutical Chemical classification system [3]. 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. Co-morbidities in the Dutch population were therefore based on proxy medications.

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 [28]. Most privately insured patients had a small non-income-based deductible for all healthcare 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 cohort of users of antihypertensive drugs and who had continuous follow-up for at least 365 days. For the Netherlands 2.0% of the patients were excluded because of limited follow-up, for British Columbia and Pennsylvania, these patients were not present in the initial database. New use was defined as having no antihypertensive drug fills in the 365 days before the first prescription of any antihypertensive drug. The date of the first prescription was defined as the index date. At the index date, all patients were 65 years or older. For the vast majority of patients enrolled in the PACE programme, this means that they were at least 66 years of age when eligible for our analysis. Antihypertensive drugs were classified according to their mechanism of action [3]: thiazide

diuretics and chlorothalidone, selective beta-blockers, dihydropyridine calcium antagonists, ACE inhibitors, angiotensin receptor blockers (ARB) or miscellaneous antihypertensive drugs (including alpha-blockers and centrally acting antihypertensives, such as methyldopa). The simultaneous initiation of more than one antihypertensive drug, in a single pill combination or as two separate tablets, was defined as combination therapy. For the United States and Canada, an additional physician visit with a hypertension-related diagnosis in the 6 months up to and including the index date was required. Although important, information on the type and severity of the blood pressure elevation was not available. In addition, a claim or dispensing for a non-antihypertensive drug in at least three consecutive 6-month intervals before 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 drug was defined as the censor date. Patients were required to have at least one year of follow-up available. Patients who died were censored at 180 days before their date of death. Nursing home patients were excluded because of concerns that nursing home data are less reliable. To protect the confidentiality of all patients, all personal identifiers were removed before analysis.

Definition of persistence

Persistence was assessed by using the information on the dispensing date and prescribed duration (days supplied) of each filled prescription. If a prescription of the same antihypertensive drug was filled before the previous one expired, the amount left over was added to the dispensing date of the next prescription. For patients who used two or more antihypertensive drugs 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 antihypertensive 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 prescription would lead to an adherence of at maximum 14% in the United States [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 a 180-day gap did not categorize substantially more patients as persistent [29]. Second, 180 days without medication leads to significant blood pressure differences in placebo-controlled randomized controlled trials [30–33], although there is also an acute risk associated with discontinuation [34]. 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. one 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 [13,35]. The association of these items with persistence during the first year of treatment was studied. In addition to age and sex, which was available for all 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 US$10 000. Categories of annual income for residents of British Columbia were estimated on the basis of the amount of income-dependent subsidy and subdivided into three classes: less than Can $16 000, Can$16 000–22 000, more than Cam$22 000 [36]. For residents of the Netherlands, income was categorized on the basis of the type of insurance (public versus private). The income limit for public insurance for those aged 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, atrial fibrillation, peripheral vascular

disease 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, percutaneous transluminal angioplasty or chronic CHD (group 2) or acute myocardial infarction (group 3). Patients who met the criteria for more than one group were assigned to the most severe group. Furthermore, evidence of hypercholesterolemia, diabetes, chronic obstructive pulmonary disease, depression, dementia and Parkinson's disease, and for the US and Canadian population, the Charlson co-morbidity score was assessed [37]. In addition, treatment-related characteristics in the baseline year included the number of prescription medications used, number of physician visits (USA 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

Multivariable Cox regression was used to analyse the association of potential predictors and time to first 180-day episode without antihypertensive medication available. 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, Illinois, USA).

Results

Study population

A total of 9664 patients from the United States, 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. Although age was similarly distributed in the three populations, other demographic and clinical characteristics were not. Patients in Pennsylvania were predominantly women. In general, patients from Pennsylvania had the highest prevalence of cardiovascular co-morbidity, and patients from British Columbia the lowest. A similar pattern was observed for differences in other non-cardiovascular co-morbid conditions. Health services utilization was generally different 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 percentage difference in absolute non-persistence rates across countries. After 6 years, the difference between the population with the highest incidence of non-persistence, Pennsylvania, and the population with the lowest incidence, British Columbia, was less than 5%. The comparison does not materially change if 90 or 270 days without medication were used as a definition of non-persistence.

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 sex and frequent use of prescription medications in the baseline year were associated with non-persistence in the three populations. The previous occurrence of acute myocardial infarction was associated with higher persistence as was hypercholesterolemia. Angina pectoris was not associated with non-persistence in Pennsylvania [hazard ratio (HR) 1.02, 95% confidence interval (CI) 0.89–1.18], was associated with higher persistence in the Netherlands (HR 0.85, 95% CI 0.79–0.91) and with lower persistence in British Columbia (HR 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 United States. Similarities were seen between the type of initial antihypertensive drug selected and persistence in all three countries. In general, patients treated with newer antihypertensive drugs (ACE inhibitors and ARB) were less likely to have a 180-day medication gap compared with patients treated with diuretics or beta-blockers (with the exception of patients initiated with beta-blockers in Pennsylvania). Using 90 and 270-day gaps as a definition of non-persistence did not qualitatively change the observed associations.

Choice of the initial antihypertensive drug

The choice of the initial antihypertensive drug differed remarkably between the three countries (Fig. 1). 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 three countries demonstrate an increase in thiazide use after the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [38]. The use of calcium antagonists and ARB was generally similar.

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 the effectiveness of antihypertensive treatment [3], almost a quarter of patients discontinue their medication for at least 180 consecutive days in the first year of treatment. In the subsequent 5 years, another 13–18% experienced at least one 180-day period without medication. The observed similarities in the patterns of non-persistence in all three countries were remarkable.

To the best of our knowledge, this is the first study comparing persistence with antihypertensive treatment in more than one country. Although many studies are available assessing long-term utilization patterns with antihypertensive drugs, [22,39,40] comparing persistence rates and their determinants is difficult because published studies often use different and incomparable methodologies [29]. 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 is conservative because we assumed that the preceding prescription was completely used. Furthermore, the populations were relatively similar with regard to drug coverage and co-payment, two factors that are known to influence adherence [41].

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. We classified patients using any type of antihypertensive drug as continuous users, however, regardless of whether they switched to another agent (demonstrated to be a common occurrence) [22,42]. Because medication is often discontinued intentionally in the period preceding expected death, patients who died were censored 180-days before their date of death. Second, we could not measure the use of antihypertensive drugs obtained from pharmacies outside the state of Pennsylvania. This probably 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 United States and Canada, but not in the Netherlands. In addition, we required the ongoing filling of at least one non-antihypertensive prescription during each of the 180-day intervals after the initiation of treatment. Despite

similarities in the methodologies used, there is still a potential for misclassifying patients with regard to the indication in the Netherlands as a result of differences in origins of the data (dispensing and hospital discharge data in the Netherlands compared with 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 the initiation of treatment, the need for adequate follow-up is ongoing. Unfortunately, few effective and feasible strategies to increase adherence for patients with hypertension are currently available [43], which argues for more well-performed research in this field. Second, there are remarkable similarities between the three countries with regard to both absolute persistence rates, after one year and even after 6 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 sex, previous myocardial infarction and the number of prescription medications. Third, the magnitude of the association of the vast majority of predictors of suboptimal persistence was small. Although the predictors we studied are similar to information available to clinicians who initiate and treat a patient with hypertension, 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, which better predict the successful uptake of lifelong 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. [7,44] Fourth, one of the strongest associations in magnitude was the type of antihypertensive treatment initiated. As reported by us and other authors in similar settings [22,39,40,45], patients starting with ACE inhibitors and ARB persisted better with treatment than patients starting with diuretics. This finding is in contrast to the evidence of efficacy from a thoughtful network meta-analysis [3] and the largest hypertension trial [38], which favor diuretics. In the ALLHAT trial, there were no material differences in discontinuation rates between patients initiated with diuretics, calcium antagonists 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 [46], which is in line with patterns observed for lipid-lowering drugs [47]. Although more frequently reported, further research is needed to explore the observed associations between the type of antihypertensive drug and persistence in daily practice.

In the latest report of the World Health Organization on adherence to long-term therapy [44], 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 worldwide, with the highest incidence in the developing world where access can be a greater barrier [8]. As a result, antihypertensive drugs have been placed on the World Health Organization essential medicines list [48]. As the results of our study demonstrate, however, even if medication is affordable and available, there is still a substantial proportion of patients who, 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 public health.

Abbreviations

ACE-I, ACE-inhibitors
ATC, Anatomical Therapeutical Chemical
ARB, angiotensin receptor blockers
CCP, Canadian Classification of Diagnostic Therapeutic, and Surgical Procedures
CV, Cardiovascular
CI, Confidence Interval
CHF, congestive heart failure
CABG, coronary artery bypass graft
CHD, coronary heart disease
DRGs, Diagnostic Related Groupings
DHP-CCB, dihydropyridine calcium channel blockers
DIN/PIN, Drug Information Number/Product Identification Number
ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification
MI, myocardial infarction
NDC, National Drug Code
OR, Odds Ratio
PTCA, percutaneous transluminal angioplasty
PVD, peripheral vascular disease
PACE, Pharmaceutical Assistance Contract for the Elderly
PHARMO-RLS, PHARMO record linkage system

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B.L.G.vW. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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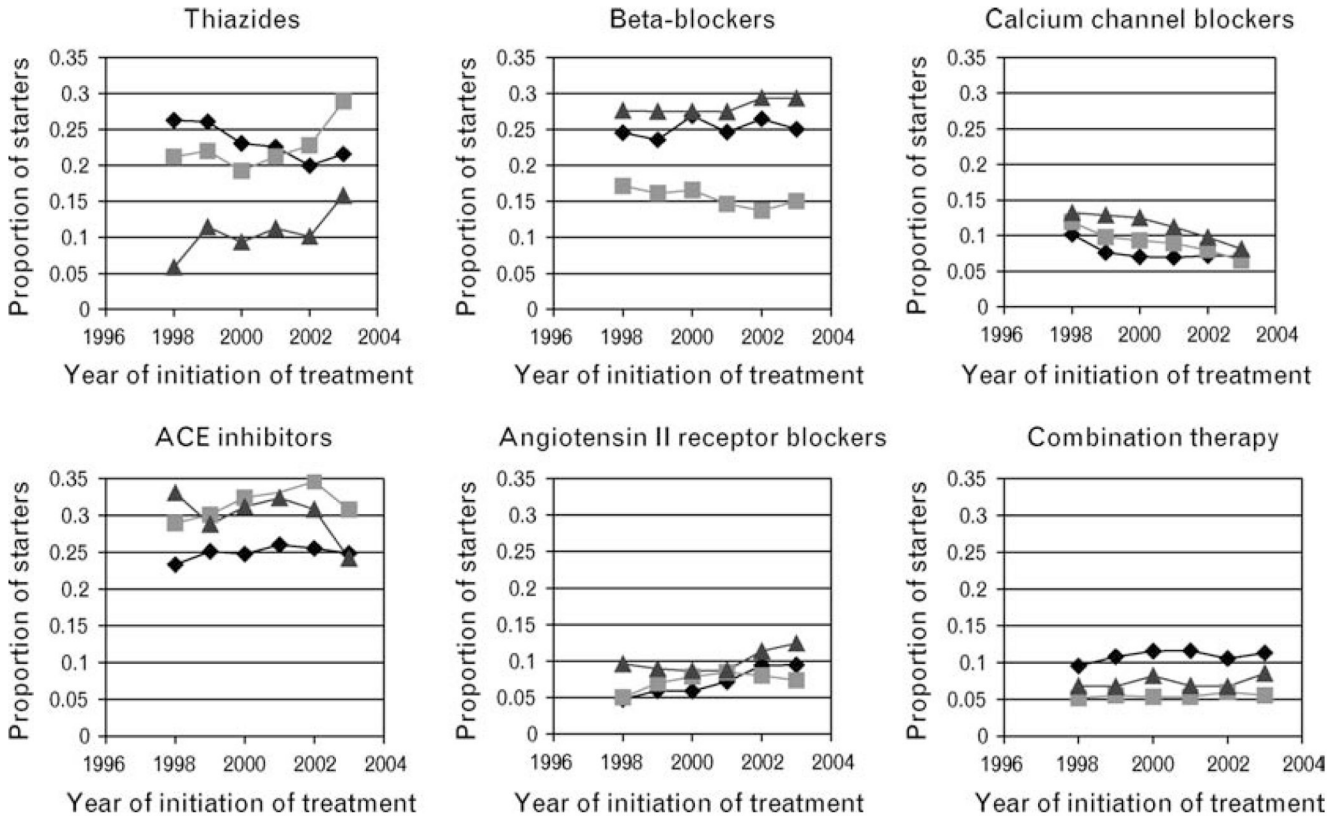

Fig. 1.

Patterns of initial drug choice in Pennsylvania, British Columbia and the Netherlands. ACE, Angiotensin-converting enzyme. The Netherlands; British Columbia; Pennsylvania.

Table 1

Baseline characteristics of the study population

Variable	Pennsylvania (*N*=9664)	British Columbia (*N*=25 377)	The Netherlands (*N*=24 603)
	Number (%) or mean (SD)		
Demographics			
Age (years)	77.8 (±6.9)	75.2 (±7.1)	78.2 (±5.8)
65–74	3270 (33.8)	12 815 (50.5)	7735 (31.4)
75–84	4663 (48.3)	9538 (37.6)	13 123 (53.3)
≥85	1731 (17.9)	3024 (11.9)	3735 (15.2)
Men[a]	1564 (16.2)	11 013 (47.1)	10 345 (42.0)
Income[a]			
Low	3651 (38.8)	7180 (28.3)	13 763 (55.9)
Medium	–	2313 (9.1)	–
High	6013 (62.2)	14 647 (57.7)	10 840 (44.1)
Race			
White	9203 (95.2)	–	–
Black	340 (3.5)	–	–
Other, non-white	121 (1.3)	–	–
Cardiovascular history in baseline year			
CHD			
Angina/angiography	658 (6.8)	386 (1.5)	422 (1.7)
PTCA/CABG/chronic heart disease	905 (9.4)	665 (2.6)	–
Acute myocardial infarction	467 (4.8)	718 (2.8)	2025 (8.2)
Stroke	1798 (18.6)	1351 (5.3)	1092 (4.4)
Congestive heart failure	2450 (25.4)	2473 (9.7)	989 (4.0)
Atrium fibrillation	968 (10.0)	390 (1.5)	1164 (4.7)
Peripheral vascular disease	895 (9.3)	377 (1.5)	397 (1.6)
Other co-morbid conditions			
Hypercholesterolemia	2197 (22.7)	1089 (4.3)	3285 (13.4)
Diabetes	2966 (30.7)	3523 (13.9)	2713 (11.0)
COPD	2966 (30.7)	4576 (18.0)	1085 (7.3)
Depression	1198 (12.4)	1551 (6.1)	1453 (5.9)
Dementia	748 (7.7)	336 (1.3)	58 (0.2)
Parkinson’s disease	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			
No. of hospitalizations	0.50 (±0.9)	0.26 (±0.64)	0.47 (±1.0)
0	6447 (66.7)	20 602 (81.2)	18 000 (73.2)
1	2003 (20.7)	3540 (13.9)	3855 (15.7)
≥2	1214 (12.6)	1235 (4.9)	2748 (11.2)
No. of prescription medications	6.5 (±4.2)	5.7 (±3.8)	6.0 (±4.2)
0–3	2607 (27.0)	8328 (32.8)	7177 (29.2)

Variable	Pennsylvania (*N*=9664)	British Columbia (*N*=25 377)	The Netherlands (*N*=24 603)
	Number (%) or mean (SD)		
4–6	3124 (32.3)	8623 (34.0)	8173 (33.2)
7–9	2013 (20.8)	4772 (18.8)	4933 (20.1)
≥10	1920 (19.9)	3654 (14.4)	4320 (17.6)
No. of physician visits	8.7 (±6.0)	17.4 (±13.6)	–
0–5	3132 (32.4)	3149 (12.4)	–
6–10	3680 (38.1)	5732 (22.6)	–
11–15	1742 (18.0)	5089 (20.1)	–
≥16	1110 (11.5)	11 407 (45.0)	–
Year of initiation of treatment			
1998	1854 (19.2)	4444 (17.5)	3820 (15.5)
1999	1711 (17.7)	4635 (18.3)	4420 (18.0)
2000	1657 (17.1)	4713 (18.6)	4325 (17.6)
2001	1532 (15.9)	4455 (17.6)	4118 (16.7)
2002	1526 (15.8)	3926 (15.5)	4099 (16.7)
2003	1384 (14.3)	3204 (12.6)	3819 (15.5)
First antihypertensive drug			
Diuretic	1003 (10.4)	7439 (29.3)	5726 (23.3)
Beta-blocker	2713 (28.1)	4102 (16.2)	6201 (25.2)
Calcium antagonist	1104 (11.4)	1700 (6.7)	1881 (7.6)
ACE inhibitor	2921 (30.2)	10 049 (39.6)	6134 (24.9)
Angiotensin receptor blocker	953 (9.9)	418 (1.6)	1738 (7.1)
Miscellaneous	267 (2.8)	383 (1.5)	240 (1.0)
Combination therapy	703 (7.3)	1286 (5.1)	2683 (10.9)

ACE, Angiotensin-converting enzyme; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; PTCA, percutaneous transluminal angioplasty.

[a]Information on sex (4.9%) and income (4.9%) is missing for part of the British Columbia residents.

Table 2

Percentage of patients who had at least one period of 180 days without blood pressure-lowering medication available

	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years
Pennsylvania	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)
British Columbia	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)
The Netherlands	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 (33.82–49.8)

Percentages is brackets indicate a 270-day and 90-day period of non-use, respectively.

Table 3

Association between potential predictors and non-persistence

Variable	Pennsylvania (N=9664)		British Columbia (N=25 377)		The Netherlands (N=24 603)	
	Adjusted HR[a]	*P* value	Adjusted HR[a]	*P* value	Adjusted HR[a]	*P* value
Demographics						
Age (years)						
65–74	1.00 (reference)	NA	1.00 (reference)	NA	1.00 (reference)	NA
75–84	1.03 (0.95–1.12)	0.465	1.05 (1.00–1.10)	0.052	1.01 (0.96–1.06)	0.697
≥85	1.09 (0.98–1.21)	0.129	1.23 (1.15–1.32)	<0.001	1.05 (1.00–1.15)	0.037
Sex						
Women	1.00 (reference)	NA	1.00 (reference)	NA	1.00 (reference)	NA
Men	1.21 (1.10–1.33)	<0.001	1.13 (1.08–1.19)	<0.001	1.05 (1.01–1.09)	0.025
Income						
Low	1.00 (reference)	NA	1.00 (reference)	NA	1.00 (reference)	NA
Medium	–		0.86 (0.79–0.93)	<0.001		
High	1.06 (0.98–1.14)	0.130	0.81 (0.77–0.85)	<0.001	0.95 (0.90–0.99)	0.016
Race						
White	1.00 (reference)	NA	–		–	
Black	1.42 (1.19–1.66)	<0.001	–		–	
Other, non-white	1.29 (0.97–1.73)	0.082	–		–	
Cardiovascular history in baseline year CHD						
CHD						
Angina/angiography	1.02 (0.89–1.18)	0.774	1.20 (1.01–1.44)	0.038	0.85 (0.79–0.91)	<0.001
PTCA/CABG/chronic heart disease	1.04 (0.91–1.17)	0.585	0.93 (0.80–1.08)	0.323	–	–
Acute MI	0.85 (0.70–1.01)	0.080	0.64 (0.54–0.76)	<0.001	0.59 (0.53–0.67)	<0.001
Stroke	0.93 (0.84–1.03)	0.142	0.81 (0.73–0.91)	<0.001	1.01 (0.90–1.14)	0.886
Congestive heart failure	1.10 (1.01–1.20)	0.037	0.93 (0.86–1.02)	0.111	0.95 (0.83–1.09)	0.458
Atrium fibrillation	0.84 (0.74–0.96)	0.008	1.40 (1.13–1.74)	0.002	0.85 (0.76–0.97)	0.016
Peripheral vascular disease	1.01 (0.89–1.14)	0.906	1.01 (0.83–1.21)	0.955	0.95 (0.79–1.14)	0.553
Other co-morbid conditions						
Hypercholesterolemia	0.87 (0.80–0.95)	0.003	0.77 (0.68–0.88)	<0.001	0.77 (0.71–0.83)	<0.001
Diabetes	0.99 (0.91–1.08)	0.702	0.93 (0.86–1.00)	0.040	0.83 (0.76–0.90)	<0.001

Variable	Pennsylvania (N=9664)		British Columbia (N=25 377)		The Netherlands (N=24 603)	
	Adjusted HR[a]	*P* value	Adjusted HR[a]	*P* value	Adjusted HR[a]	*P* value
COPD	1.09 (1.00–1.18)	0.049	1.04 (0.98–1.10)	0.256	1.04 (0.96–1.13)	0.293
Depression	1.10 (0.99–1.14)	0.075	1.14 (1.05–1.25)	0.003	1.03 (0.94–1.12)	0.560
Dementia	1.03 (0.90–1.18)	0.657	0.92 (0.76–1.12)	0.416	1.00 (0.65–1.54)	0.987
Parkinson's disease	1.14 (0.93–1.41)	0.210	1.50 (1.21–1.85)	<0.001	0.95 (0.76–1.18)	0.623
Charlson score	1.00 (0.97–1.02)	0.651	1.00 (0.97–1.04)	0.860	–	
Health services used in baseline year						
No. of hospitalizations						
0	1.00 (reference)	NA	1.00 (reference)	NA	1.00 (reference)	NA
1	1.03 (0.94–1.14)	0.532	0.95 (0.88–1.02)	0.148	1.03 (0.96–1.12)	0.383
≥2	1.14 (1.00–1.29)	0.048	0.98 (0.87–1.10)	0.725	1.06 (0.95–1.17)	0.308
No. of prescription medications						
0–3	1.00 (reference)	NA	1.00 (reference)	NA	1.00 (reference)	NA
4–6	1.01 (0.92–1.11)	0.857	1.01 (0.94–1.06)	0.944	1.05 (0.99–1.11)	0.091
7–9	1.03 (0.93–1.14)	0.662	1.06 (0.99–1.14)	0.112	1.20 (1.13–1.28)	<0.001
≥10	1.06 (0.94–1.20)	0.335	1.25 (1.15–1.36)	<0.001	1.36 (1.27–1.46)	<0.001
No. of outpatient physician visits						
0–5	1.00 (reference)	NA	1.00 (reference)	NA	–	
6–10	1.07 (0.98–1.17)	0.154	0.88 (0.81–0.95)	0.002	–	
11–15	1.15 (1.03–1.28)	0.014	0.94 (0.86–1.02)	0.136	–	
≥16	1.36 (1.20–1.55)	<0.001	0.94 (0.87–1.02)	0.148	–	
Year of initiation of treatment						
1998	1.00 (reference)	NA	1.00 (reference)	NA	1.00 (reference)	NA
1999	1.05 (0.94–1.18)	0.376	0.84 (0.78–0.90)	<0.001	0.94 (0.87–1.01)	0.080
2000	0.96 (0.86–1.09)	0.538	0.85 (0.79–0.91)	<0.001	0.87 (0.81–0.94)	<0.001
2001	1.05 (0.93–1.19)	0.400	0.83 (0.77–0.89)	<0.001	0.86 (0.75–0.87)	<0.001
2002	1.02 (0.90–1.15)	0.810	0.77 (0.71–0.82)	<0.001	0.75 (0.69–0.81)	<0.001
2003	0.96 (0.85–1.09)	0.537	0.70 (0.65–0.76)	<0.001	0.72 (0.66–0.78)	<0.001
First antihypertensive drug						
Diuretic	1.00 (reference)	NA	1.00 (reference)	NA	1.00 (reference)	NA

Variable	Pennsylvania (N=9664)		British Columbia (N=25 377)		The Netherlands (N=24 603)	
	Adjusted HR[a]	*P* value	Adjusted HR[a]	*P* value	Adjusted HR[a]	*P* value
Beta-blocker	0.57 (0.51–0.64)	<0.001	1.05 (0.98–1.12)	0.151	0.92 (0.87–0.97)	0.004
Calcium antagonist	0.54 (0.47–0.62)	<0.001	0.85 (0.78–0.94)	0.001	0.77 (0.71–0.84)	<0.001
ACE inhibitor	0.48 (0.43–0.54)	<0.001	0.68 (0.64–0.72)	<0.001	0.62 (0.57–0.67)	<0.001
Angiotensin receptor blocker	0.50 (0.43–0.58)	<0.001	0.55 (0.44–0.69)	<0.001	0.48 (0.44–0.53)	<0.001
Miscellaneous	0.80 (0.65–0.98)	0.032	2.18 (2.00–2.37)	<0.001	1.74 (1.49–2.04)	<0.001
Combination therapy	0.50 (0.42–0.59)	<0.001	0.78 (0.64–0.95)	0.012	0.70 (0.56–0.85)	<0.001

ACE, Angiotensin-converting enzyme; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PTCA, percutaneous transluminal angioplasty.

[a]Each variable was adjusted for the other variables in the table.