Comparison of Persistence Rates with Angiotensin-Converting Enzyme Inhibitors Used in Secondary and Primary Prevention of Cardiovascular Disease

Amédé Gogovor, MSc, Alice Dragomir, MSc, Michelle Savoie, PhD, Sylvie Perreault, PhD
University of Montreal, Montreal, QC, Canada

ABSTRACT

Objectives: On average, 50% of patients are noncompliant with drugs for chronic health problems, despite their proven efficacy. It is therefore essential to have real-world data to devise suitable methods for improving persistence with these therapies. To measure and compare persistence rates with the angiotensin-converting enzyme inhibitors (ACEIs) in primary and secondary prevention and their determinants.

Methods: Two cohorts were reconstructed from the Régie de l’assurance maladie du Québec’s databases. The subjects had to be newly treated with ACEIs between January 1, 1998 and December 31, 2000. The primary prevention cohort consisted of 4596 hypertensive patients and the secondary prevention cohort of 1620 patients. The cumulative persistence rates were determined by the Kaplan–Meier method. The determinants of nonpersistence were evaluated with a Cox regression model.

Results: The 1-year persistence rates for the nonexclusive use of antihypertensive agents by initial prescribed agent: enalapril, fosinopril, lisinopril, quinapril, and ramipril were 66%, 64%, 69%, 65%, and 72% in the secondary prevention cohort, and of 66%, 72%, 71%, 72%, and 75% in the primary prevention cohort. The adjusted 1.5-year nonpersistence rates in primary prevention were higher for quinapril and enalapril than for ramipril. In secondary prevention all of the ACEIs were equivalent in nonpersistence rate. In secondary prevention cohort, having dyslipidemia, respiratory disease ≥4 different classes of drugs/month increase the rate of persistence. Among, the primary prevention cohort, the fact of having diabetes, dyslipidemia, respiratory disease, using ≥4 different classes of drugs/month or prior hospitalization increased significantly the rate of persistence. For both cohorts, the fact of having high number of oral doses/day or elevated health-care resource utilization decreased significantly the rate of persistence.

Conclusion: The 1.5-year persistence rate was low compared with the threshold of 80% generally accepted. The high-risk patients were less likely to discontinue their treatment. These results can be of help in devising methods for improving the effectiveness of these drugs in routine practice.

Keywords: ACEIs, hypertension, noncompliance, persistence, primary prevention, secondary prevention.

Introduction

Patient compliance with treatment has become an important issue that concerns all players in the healthcare system. To avoid confusion, the term compliance here refers to a global term including persistence and adherence, and persistence is defined as the time from initiation to discontinuation of treatment, and adherence refers to how the medication is taken or quality of intake. Studies have shown that about half of patients are noncompliant with drugs for treating chronic conditions [1–5]. This problem was addressed in a recent World Health Organization publication [6]. Noncompliance has considerable clinical and economic repercussions for society and is the key factor in the difference between efficacy and effectiveness [7].

Takiya et al. estimate the consequences of noncompliance with antihypertensive prescribed medications at 125,000 deaths and $100 billion in expenses each year in the United States [8]. In Canada, Coombs et al. [1] assessed the annual cost of noncompliance to be at least $7 billion.

The angiotensin-converting enzyme inhibitors (ACEIs) are recommended as first-line treatment for hypertension [9]. The recommendations for hypertension in the 2006 Canadian guideline include a meta-analysis of 13 randomized clinical trials [10] comparing beta-blockers with other antihypertensive agents, the Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA) trial [11], the Prevention of Events with angiotensine-Converting Enzyme Inhibition (PEACE) trial, The EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) trial [12], the VALsartan In Acute Myocardial Infarction (VALIANT) trial [13], the Morbidity...
and Mortality after Stroke, Eprosartan compared nitrrendipine for Secondary prevention (MOSES) trial [14], the Ramipril Efficacy in Nephropathy 2 (REIN 2) trial [15], the prespecified diabetes subgroup analysis of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) [16], and several studies evaluating fixed dose of drug therapy to improve medication adherence [17]. Clinical outcomes of ACE inhibition include decreases in myocardial infarction (fatal and nonfatal), reinfarction, angina, stroke, end-stage renal disease, and morbidity and mortality associated with heart failure [10–16,18].

Metabolic side effects are not encountered during the long-term therapy with ACEIs. The drugs do not alter plasma concentrations of uric acid or calcium and may actually improve insulin sensitivity in patients with insulin resistance and decrease cholesterol levels and lipoproteins (a) levels in proteinuric renal disease. Serious untoward reactions to ACEIs are rare, and in general ACEIs are well tolerated [19]. At present, the difference between new ACEIs has not been shown to be important in the selection of the agents [19,20].

Noncompliance has been identified as the main reason for poor hypertension control in treated patients [21–25]. To be able to implement more-effective intervention methods, it is essential to better determine the patient profile by approaching the problem from a perspective that focuses more on the risk profile of cardiovascular disease [26–28]. Therapeutic success depends not only on their efficacy and safety, but also on their proper use. Few studies have taken an overall look with this regard to ACEIs [22,23,29].

The objectives are to compare the persistence rates and adherence levels for the ACEIs used in routine practice, to determine if there are any differences within agents among patients treated for primary and secondary prevention of cardiovascular disease, and to determine the role of demographic, clinical and healthcare service utilization-related variables as predictors of persistence rate.

**Methods**

**Data Source**

Régie de l’assurance maladie du Québec (RAMQ) databases were used. The RAMQ administers the public health-insurance program in the province of Quebec, Canada. We used three types of files: the demographic data file, the medical services file, and the pharmaceutical services file. The demographic file includes the age, sex, postal code, and year of death of each person registered with RAMQ. The medical services file lists the medical claims for all inpatients and outpatients according to ICD-9 diagnostic codes [30], the nature of the medical procedure and the date and place (physician’s office, emergency room, hospital) the procedure was performed. The procedures are coded according to the Canadian classification of diagnostic, therapeutic, and surgical procedures [31]. The pharmaceutical file includes people aged 65 years and older, employment assistance recipients (social assistance), and other plan members (individuals not covered by a group or private insurance plan), all of whom account for close to 55% of the Quebec’s population [32].

**Cohort Definition**

A cohort of 17,377 subjects was reconstituted from prescription records. The subjects had to have been covered by Quebec’s prescription drug insurance plan, have been 50 to 64 years of age, and have been newly treated with ACEIs (enalapril, fosinopril, lisinopril, quinapril, and ramipril) between January 1, 1998 and December 31, 2000. That is not having received any prescriptions for these drugs or for drugs in the other classes of antihypertensive (diuretics, β-blockers, ACEIs, calcium-channel blockers [CCBs], angiotensin II receptor blockers or a combined therapy of these agents) during the 12 months preceding the index date.

The index date was the date of the first prescription for these agents.

The ACEIs are appropriate for primary, secondary and tertiary prevention for prevalent and disabling chronic disease such as, hypertension, myocardial infarction, patients at high risk of cardiovascular disease, congestive heart failure, diabetic nephropathy. The study evaluated persistence in two patient cohorts: secondary and primary prevention. The secondary prevention cohort consisted of patients with a diagnosis of coronary artery disease (ICD-9 410–414; vasodilators or medical procedures), stroke (ICD-9 430–438 or nitrrendipine or medical procedures) or peripheral vascular disease (ICD-9 440–440 or pentoxifylline or medical procedures) or who had used antiplatelet agents during the year preceding the index date.

The primary prevention cohort consisted of patients diagnosed with essential hypertension (ICD-9 401) during the year preceding the index date and no diagnoses of coronary artery disease (ICD-9 410–414, vasodilators or medical procedures), stroke (ICD-9 430–438 or nitrrendipine or medical procedures) or peripheral vascular disease (ICD-9 440–440 or pentoxifylline or medical procedures), and patients that had used antiplatelets agents in the year preceding the index date.

Patients with any of the following were also excluded from both cohorts: pulmonary circulation problems (ICD-9 416), heart failure (ICD-9 428 or cardiotonic drugs), a cardiac arrhythmia (ICD-9 426–427; antiarrhythmics drugs: amiodarone, digoxin, quinidine, disopyramide, flecainide, mexiletine, procainamide, propafenone, sotalol; medical procedures), other forms of heart disease (ICD-9 420–424), renal failure (ICD-9 580–589), treated hyperthyroidism...
Doses of medication and utilization of health-care services [34–36]. Age (in years), sex (male or female), social assistance (yes or no), and site of residency (rural or urban) were identified at the index date from data in the beneficiary’s file.

The dichotomous comorbidities variables (yes or no) were defined as follows: diabetes by ICD-9 code 250 or by the use of insulin or hypoglycaemic agents; dyslipidemia, defined by the use of lipid-lowering agents (statins, resin, niacin, fibrates); respiratory disease by the use of at least two prescriptions of inhaled β-agonists or any pharmacologic agents used for respiratory disease during the year preceding the index date and during the follow-up period.

The mean number of different classes of drugs per month (>4 or ≤4) and the mean number of daily doses of medication (continuous) were assessed using the prescription data files in the year preceding the index date and during the follow-up period. The health-care services utilization was measured by computing the number of dispensing pharmacies consulted (>3 or ≤3) and medical visits (continuous) or by identifying the hospitalizations (yes or no) in the year preceding the index date and during the follow-up period.

Persistence is defined as the time from initiation to discontinuation of treatment. Adherence refers to how the medication is taken or quality of intake. The drug database was searched for any ACEIs dispensed to eligible subjects during the study period. To reconstruct the drug regimens, we developed a computer program that used data on the dispensing date, amount dispensed, and duration of treatment. We identified patients who had begun a treatment with a single ACEI and stratified them according to ACEIs agent used: (enalapril, fosinopril, lisinopril, quinapril or ramipril).

The primary outcome of persistence was defined as having any ACEI prescription dispensed at least every 60 days after the end date of a previous prescription for an ACEI. This allowed the assessment of persistence to a therapy with any ACEI agent. A 30-day supply of treatment is the standard. For instance, a subject switching from an ACEI to another ACEI or other antihypertensive classes without interruption is being considered as persistent with nonexclusive use. We also estimated the assessment of persistence with a given ACEI (exclusive use); in this case a subject was considered nonpersistent if he had not renewed his ACEI prescription in the 60-day period after the end of the prescription duration. We examined the effect of this grace period by measuring the impact on the persistence estimate, using 45 days or 120 days for the grace period.

The adherence level was calculated using a Medication Possession Ratio (MPR), a uniform methodology widely used for estimating medication compliance from pharmacy claims data [33]. The MPR indicates the percentage of days for which the patient possessed a supply of medication. MPR was defined as the total of days of antihypertensive agents supply during the follow-up divided by days of follow-up.

**Statistical Analysis**

The subjects’ demographic and clinical characteristics (at the index date) were compared between the different drugs for each cohort using the t-test and chi-squared test. A Kaplan–Meier survival analysis was performed to estimate the cumulative persistence rates in nonexclusive use for the primary and secondary prevention cohorts by initially prescribed ACEI. The difference in persistence was determined with the log-rank test. Cox regression models were used to estimate the rate ratio of nonpersistence to ACEIs agents with nonexclusive use for a maximum of 1.5-year period of follow-up, in both, primary and secondary prevention [37]. All models were adjusted for potential determinants described previously.

All the tests were two-sided, with a 5% level of significance. The analyses were performed with SAS software, v. 9.0 (SAS Institute Inc., Cary, NC).

In Quebec and in the rest of Canada, the 1999 to 2000 periods was marked by a significant increase in the use of antihypertensives, after the introduction of the Canadian Hypertension Education Program [38]. It was also marked by a shift in ACEIs use, with a sharp increase in the use of ramipril after the publication of varied and highly significant clinical results in the HOPE (Heart Outcomes Prevention Evaluation) study [39]. Ramipril was thus used as the reference in the multivariate analysis.

**Ethical Considerations**

The issue of confidentiality did not apply, because the personal identification numbers were scrambled.
during data extraction and transmission. Nevertheless, the Commission d’accès à l’information du Québec’s permission was obtained before database extraction.

**Results**

**Population Characteristics**

In all, 17,377 new ACEI users aged 50 to 64 years were identified in the period from January 1, 1998 to December 31, 2000. After the inclusion and exclusion criteria were applied, 4596 subjects were selected for the primary prevention cohort and 1620 for the secondary prevention cohort (Fig. 1). Compared to patients of the primary prevention cohort, patients in the secondary prevention cohort were more likely to be men and have been hospitalized. They have visited slightly more physicians, and have more comorbidities (Table 1).

Among patients for secondary prevention cohort newly treated with ACEIs, ramipril was used most often for the initial prescription (39%) followed by lisinopril (20%). A total of 12% of patients received an initial prescription of fosinopril, 10% received quinalapril, and 18% enalapril. These estimates were 22%, 23%, 20%, 20%, and 15%, for the primary prevention cohort, respectively (Table 1).

**Persistence Rate**

The persistence to initial prescription of ACEIs decreased in the first 6 months after initiation of treatment with ACEIs in secondary (79%) and primary (77%) prevention cohorts and the rate continued to decline over the next 3 years (58%, 58%, respectively) (Figs 2 and 3). Sensitivity analysis on the definition of persistence was also performed using a grace period of 45 or 120 days; the results revealed similar patterns of progressive discontinuation of ACEIs overtime. At 3 years after the index date, using the definition of persistence based on 45 or 120 days of grace period, persistence rates for the secondary prevention cohort were 52% and 62% (compared to 58%), respectively;

---

![Figure 1](image-url) Diagram showing the composition of the primary and secondary prevention cohorts. ACE, angiotensin-converting enzyme; RAMQ, Régie de l’assurance maladie du Québec.

---

New ACE inhibitor users aged 50 to 64 years from January 1, 1998 to December 31, 2000 (n = 17,377)

Had been registered with the RAMQ (plan members) for at least 12 months (n = 12,034)

Exclusion Criteria (n = 1683)
- Pulmonary circulation problems
- Heart failure
- Cardiac arrhythmia
- Other heart disease
- Renal failure
- Treated hyperthyroidism
- Migraine
- Essential or other tremor
- Anticoagulants

Patients not diagnosed with essential hypertension: no ICD-9 code (n = 4134)

Primary prevention
- Patients diagnosed with essential hypertension (n = 4596)

Secondary prevention
- Patients diagnosed with:
  - Coronary artery disease
  - Stroke
  - A disease of the arteries, arterioles and capillaries or who were using antiplatelet agents (n = 1620)

---

Gogovor et al.
Table 1  Characteristics of patients by ACEIs for primary and secondary prevention in the RAMQ database from 1998 to 2000

<table>
<thead>
<tr>
<th></th>
<th>Secondary prevention (n = 1620)</th>
<th></th>
<th>Primary prevention (n = 4596)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enalapril</td>
<td>Fosinopril</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Number of patients</td>
<td>295</td>
<td>202</td>
<td>332</td>
</tr>
<tr>
<td>Mean age* (±SD)</td>
<td>57.5 ± 4.0</td>
<td>58.2 ± 4.0</td>
<td>57.8 ± 3.9</td>
</tr>
<tr>
<td>Males percentage</td>
<td>66.8</td>
<td>63.9</td>
<td>66.6</td>
</tr>
<tr>
<td>Individuals on social assistance* (%)</td>
<td>38.3</td>
<td>30.2</td>
<td>31.6</td>
</tr>
<tr>
<td>Rural residential setting* (%)</td>
<td>23.4</td>
<td>21.3</td>
<td>34.0</td>
</tr>
<tr>
<td>Mean length of follow-up</td>
<td>217</td>
<td>245</td>
<td>237</td>
</tr>
<tr>
<td>Mean dose used (mg)</td>
<td>7.2</td>
<td>10.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Diabetes† (%)</td>
<td>36.3</td>
<td>49.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Dyslipidemia† (%)</td>
<td>31.2</td>
<td>40.6</td>
<td>41.3</td>
</tr>
<tr>
<td>Respiratory disease† (%)</td>
<td>17.3</td>
<td>11.9</td>
<td>9.0</td>
</tr>
<tr>
<td>Mean number of different classes of drugs/month†</td>
<td>1.2 ± 1.5</td>
<td>1.5 ± 1.6</td>
<td>1.1 ± 1.3</td>
</tr>
<tr>
<td>Mean number of oral doses of drugs/day†</td>
<td>1.9 ± 1.8</td>
<td>1.9 ± 1.4</td>
<td>1.6 ± 1.9</td>
</tr>
<tr>
<td>Number of dispensing pharmacies†</td>
<td>1.3 ± 1.1</td>
<td>1.4 ± 1.0</td>
<td>1.2 ± 1.0</td>
</tr>
<tr>
<td>Mean number of medical visits/month†</td>
<td>0.7 ± 0.6</td>
<td>0.8 ± 0.8</td>
<td>0.5 ± 0.5</td>
</tr>
<tr>
<td>Hospitalization‡ (%)</td>
<td>58.6</td>
<td>43.6</td>
<td>51.5</td>
</tr>
</tbody>
</table>

*At the index date.
†Year preceding the index date.
‡With at least one hospitalization.
ACEIs, angiotensin-converting enzyme inhibitors; RAMQ, Régie de l’assurance maladie du Québec.
and for the primary prevention cohort were 55% and 67% (compared to 58%), respectively.

Persistence after 1-year varied according to the ACEIs (Table 2). Considering an exclusive use of a given ACEI, the persistence rates were 62% with ramipril, and relative lower with enalapril (47%), fosinopril (53%), lisinopril (50%), quinapril (52%) for the secondary prevention cohort; the corresponding figures were at 57% for ramipril, 45% for enalapril, 54% for fosinopril, 47% for lisinopril, 48% for quinapril in the primary prevention cohort. In nonexclusive use, the rate for ramipril, enalapril, fosinopril, lisinopril, quinapril were at 73%, 66%, 66%, 68%, 68% in secondary prevention, respectively; and the corresponding figures for the primary prevention were 75%, 66%, 70%, 71%, 72%.

Adherence Level

For patients with more than 1 year of follow-up (Table 3), the percent of adherence with an exclusive use of initial prescription of ACEIs in the 1-year period

Table 2  One-year persistence rate for the exclusive use of ACEIs and nonexclusive use in the primary and secondary prevention cohorts

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Secondary prevention</th>
<th>Primary prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Exclusive use of the initially prescribed drug</td>
<td>Nonexclusive use†</td>
</tr>
<tr>
<td>ACEIs</td>
<td>1620</td>
<td>45%*</td>
<td>66%*</td>
</tr>
<tr>
<td>Enalapril</td>
<td>295</td>
<td>47%*</td>
<td>66%*</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>202</td>
<td>53%</td>
<td>66%</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>332</td>
<td>50%*</td>
<td>68%</td>
</tr>
<tr>
<td>Quinapril</td>
<td>158</td>
<td>52%</td>
<td>68%</td>
</tr>
<tr>
<td>Ramipril</td>
<td>633</td>
<td>62%</td>
<td>73%</td>
</tr>
</tbody>
</table>

*P-value < 0.05 compared to Ramipril.
†From the same class (ACEIs) or from another class (ARBs, beta-blockers, CCBs, diuretics or combinations).
ACEIs, angiotensin-converting enzyme inhibitors; ARB, angiotensin II-receptor blocker; CCB, calcium-channel blocker.
after the initiation was higher than 67% in the secondary prevention cohort (the highest was 74% for ramipril), and higher than 63% in the primary prevention cohort (the highest was 75% for ramipril). Similar to persistence, higher values were observed for adherence level in nonexclusive use, ranging from 78% to 82% in secondary prevention, and from 77% to 87% in primary prevention.

Predictors of Rate Ratio of Ceasing ACEIs

As shown in Table 4, after accounting for possible confounders relative to patients in the primary prevention cohort, drugs cessation rates were more likely among patients debuting the antihypertensive therapy with quinapril (HR: 1.22; 1.03–1.44) or enalapril (HR: 1.47; 1.28–1.68) comparing to ramipril. Fosinopril and

Table 3  One-year adherence rate for the exclusive use of ACEIs and nonexclusive use in the primary and secondary prevention cohorts (only patients with more than 1 year of follow-up)

<table>
<thead>
<tr>
<th></th>
<th>Secondary prevention</th>
<th>Primary prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Exclusive use</td>
</tr>
<tr>
<td>ACEIs</td>
<td>820</td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>160</td>
<td>67%</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>116</td>
<td>71%</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>195</td>
<td>67%</td>
</tr>
<tr>
<td>Quinapril</td>
<td>101</td>
<td>71%</td>
</tr>
<tr>
<td>Ramipril</td>
<td>248</td>
<td>74%</td>
</tr>
</tbody>
</table>

*P-value < 0.05 compared to Ramipril.
†From the same class (ACEIs) or from another class (ARBs, beta-blockers, CCBs, diuretics or combinations).

ACEIs, angiotensin-converting enzyme inhibitors; ARB, angiotensin II-receptor blocker; CCB, calcium-channel blocker.
Demographic characteristics

The number of total oral doses of drugs/day was associated with a higher cessation rate (HR: 0.36; 0.29–0.45) were also less likely to cease their antihypertensive therapy. But, having a higher number of different classes of drug/month (HR: 0.54; 0.45–0.65), or a higher number of classes of drugs/month (HR: 0.72; 0.69–0.75) were significantly different from ramipril. In secondary prevention cohort, all of the ACEIs were comparable in terms of persistence rate in nonexclusive use.

The adjusted rate ratios of ceasing initiating prescription of ACEIs were nonsignificant for age, meaning that being older did not decrease the rate of cessation among primary and secondary cohorts. Subjects having other cardiovascular risk factors, such as being male (HR: 1.13; 1.01–1.25), have a ceasing rate only slightly increased among primary prevention. The fact of having dyslipidemia decreased the rate of ceasing the antihypertensive agents among primary and secondary prevention cohort; but the fact of having diabetes is only significant among primary prevention cohort (HR: 0.89; 0.73–0.93). The fact of having a respiratory disease (HR: 0.54; 0.45–0.65) and development of cardiovascular disease, exclusion criteria, emigration or loss of insurance plan coverage.

Adjusted rate ratio of nonpersistence of specific ACEI did not achieve a significant difference among secondary prevention; but among primary prevention as compared to ramipril, enalapril, and quinapril present an increasing rate of ceasing therapy by 47% and 22%, respectively. At present, the differences between new ACEIs in terms of efficacy or safety have not been shown to be important in the selection of the agents, but we could argue that a twice-daily administration could be a main reason for the lowest rate

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>1.14 (0.87–1.48)</td>
<td>1.47 (1.28–1.68)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1.03 (0.84–1.51)</td>
<td>1.11 (0.94–1.32)</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>1.04 (0.80–1.36)</td>
<td>1.13 (0.96–1.33)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.02 (0.74–1.42)</td>
<td>1.22 (1.03–1.44)</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Comorbidity factors

The prevalence of hypertension increases with increasing age, and it is important to realize that the burden of hypertension occurs among middle-aged adults, particularly men with poor blood pressure control. Considering that at least 1 to 2 years of treatment are necessary to reduce cardiovascular morbidity and/or mortality, the observed low persistence to treatment is likely to attenuate treatment effectiveness. An understanding of predictors of long-term persistence with ACEIs has implications for the approach to the management of individual patient.

We found that persistence with ACE inhibition, considering nonexclusive use, among secondary prevention cohort had fallen to 79% and 58% at 6 months and 3 years, respectively. In the primary prevention cohort, persistence with ACEIs had fallen to 77% after the first 6 months of treatment, and after 3 years, had declined to 58%. The rates of persistence are low over time. On the other hand, higher values were observed for adherence level in nonexclusive use at 1-year of follow-up, this discrepancy in the estimates of persistence rate and adherence level for each ACEI is explained by the fact that the population used in the estimation of adherence level was a population that need to have at least 1 year of follow-up, excluding those who were censored for the following reason: death, development of cardiovascular disease, exclusion criteria, emigration or loss of insurance plan coverage.

Adjusted rate ratio of nonpersistence of specific ACEI did not achieve a significant difference among secondary prevention; but among primary prevention as compared to ramipril, enalapril, and quinapril present an increasing rate of ceasing therapy by 47% and 22%, respectively. At present, the differences between new ACEIs in terms of efficacy or safety have not been shown to be important in the selection of the agents, but we could argue that a twice-daily administration could be a main reason for the lowest rate

Discussion

We found that persistence with ACE inhibition, considering nonexclusive use, among secondary prevention cohort had fallen to 79% and 58% at 6 months and 3 years, respectively. In the primary prevention cohort, persistence with ACEIs had fallen to 77% after the first 6 months of treatment, and after 3 years, had declined to 58%. The rates of persistence are low over time. On the other hand, higher values were observed for adherence level in nonexclusive use at 1-year of follow-up, this discrepancy in the estimates of persistence rate and adherence level for each ACEI is explained by the fact that the population used in the estimation of adherence level was a population that need to have at least 1 year of follow-up, excluding those who were censored for the following reason: death, development of cardiovascular disease, exclusion criteria, emigration or loss of insurance plan coverage.

Adjusted rate ratio of nonpersistence of specific ACEI did not achieve a significant difference among secondary prevention; but among primary prevention as compared to ramipril, enalapril, and quinapril present an increasing rate of ceasing therapy by 47% and 22%, respectively. At present, the differences between new ACEIs in terms of efficacy or safety have not been shown to be important in the selection of the agents, but we could argue that a twice-daily administration could be a main reason for the lowest rate

Table 4 Rate ratios for nonpersistence with the nonexclusive use of ACEIs initially prescribed 1.5 years of follow-up

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>1.14 (0.87–1.48)</td>
<td>1.47 (1.28–1.68)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1.03 (0.84–1.51)</td>
<td>1.11 (0.94–1.32)</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>1.04 (0.80–1.36)</td>
<td>1.13 (0.96–1.33)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.02 (0.74–1.42)</td>
<td>1.22 (1.03–1.44)</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Comorbidity factors

The prevalence of hypertension increases with increasing age, and it is important to realize that the burden of hypertension occurs among middle-aged adults, particularly men with poor blood pressure control. Considering that at least 1 to 2 years of treatment are necessary to reduce cardiovascular morbidity and/or mortality, the observed low persistence to treatment is likely to attenuate treatment effectiveness. An understanding of predictors of long-term persistence with ACEIs has implications for the approach to the management of individual patient.

We found that persistence with ACE inhibition, considering nonexclusive use, among secondary prevention cohort had fallen to 79% and 58% at 6 months and 3 years, respectively. In the primary prevention cohort, persistence with ACEIs had fallen to 77% after the first 6 months of treatment, and after 3 years, had declined to 58%. The rates of persistence are low over time. On the other hand, higher values were observed for adherence level in nonexclusive use at 1-year of follow-up, this discrepancy in the estimates of persistence rate and adherence level for each ACEI is explained by the fact that the population used in the estimation of adherence level was a population that need to have at least 1 year of follow-up, excluding those who were censored for the following reason: death, development of cardiovascular disease, exclusion criteria, emigration or loss of insurance plan coverage.

Adjusted rate ratio of nonpersistence of specific ACEI did not achieve a significant difference among secondary prevention; but among primary prevention as compared to ramipril, enalapril, and quinapril present an increasing rate of ceasing therapy by 47% and 22%, respectively. At present, the differences between new ACEIs in terms of efficacy or safety have not been shown to be important in the selection of the agents, but we could argue that a twice-daily administration could be a main reason for the lowest rate

Discussion

The prevalence of hypertension increases with increasing age, and it is important to realize that the burden of hypertension occurs among middle-aged adults, particularly men with poor blood pressure control. Considering that at least 1 to 2 years of treatment are necessary to reduce cardiovascular morbidity and/or mortality, the observed low persistence to treatment is likely to attenuate treatment effectiveness. An understanding of predictors of long-term persistence with ACEIs has implications for the approach to the management of individual patient.

We found that persistence with ACE inhibition, considering nonexclusive use, among secondary prevention cohort had fallen to 79% and 58% at 6 months and 3 years, respectively. In the primary prevention cohort, persistence with ACEIs had fallen to 77% after the first 6 months of treatment, and after 3 years, had declined to 58%. The rates of persistence are low over time. On the other hand, higher values were observed for adherence level in nonexclusive use at 1-year of follow-up, this discrepancy in the estimates of persistence rate and adherence level for each ACEI is explained by the fact that the population used in the estimation of adherence level was a population that need to have at least 1 year of follow-up, excluding those who were censored for the following reason: death, development of cardiovascular disease, exclusion criteria, emigration or loss of insurance plan coverage.

Adjusted rate ratio of nonpersistence of specific ACEI did not achieve a significant difference among secondary prevention; but among primary prevention as compared to ramipril, enalapril, and quinapril present an increasing rate of ceasing therapy by 47% and 22%, respectively. At present, the differences between new ACEIs in terms of efficacy or safety have not been shown to be important in the selection of the agents, but we could argue that a twice-daily administration could be a main reason for the lowest rate

Discussion

The prevalence of hypertension increases with increasing age, and it is important to realize that the burden of hypertension occurs among middle-aged adults, particularly men with poor blood pressure control. Considering that at least 1 to 2 years of treatment are necessary to reduce cardiovascular morbidity and/or mortality, the observed low persistence to treatment is likely to attenuate treatment effectiveness. An understanding of predictors of long-term persistence with ACEIs has implications for the approach to the management of individual patient.

We found that persistence with ACE inhibition, considering nonexclusive use, among secondary prevention cohort had fallen to 79% and 58% at 6 months and 3 years, respectively. In the primary prevention cohort, persistence with ACEIs had fallen to 77% after the first 6 months of treatment, and after 3 years, had declined to 58%. The rates of persistence are low over time. On the other hand, higher values were observed for adherence level in nonexclusive use at 1-year of follow-up, this discrepancy in the estimates of persistence rate and adherence level for each ACEI is explained by the fact that the population used in the estimation of adherence level was a population that need to have at least 1 year of follow-up, excluding those who were censored for the following reason: death, development of cardiovascular disease, exclusion criteria, emigration or loss of insurance plan coverage.

Adjusted rate ratio of nonpersistence of specific ACEI did not achieve a significant difference among secondary prevention; but among primary prevention as compared to ramipril, enalapril, and quinapril present an increasing rate of ceasing therapy by 47% and 22%, respectively. At present, the differences between new ACEIs in terms of efficacy or safety have not been shown to be important in the selection of the agents, but we could argue that a twice-daily administration could be a main reason for the lowest rate
of persistence of enalapril, giving that 14% of the patients were receiving a twice-daily administration compared to less than 1% for the other agents. On the other hand, we speculate that the lowest rate of persistence of quinapril in primary prevention may be explained in several ways. Subjects initiating quinapril may have less clinical response or may present diastolic with or without systolic hypertension or isolated systolic hypertension without compelling indications for other medications or having different risk factors or adverse drug effects, since the switching rate for another antihypertensive classes among subjects initiating quinapril agent was at 35% as compared to 26% for ramipril agent; and antihypertensive switching classes were at 5% for beta-blockers, 8% for CCBs, and 8% for combined therapies compared to 4%, 5%, and 2% for subjects initiating ramipril agent, respectively.

Our study identifies patient characteristics that can be used to predict poor persistence. Our results suggest that newly treated middled-aged patients with ACEIs concurrent to secondary prevention, and those with other cardiovascular risk factors such as diabetes, dyslipidemia were the most likely to be persistent to ACEIs. The predictors of suboptimal persistence identified here add information to previous work in which we observed lower persistence in patients who had a social assistance status, a greatest number of pharmacies and greater use of health-care services.

A number of studies have been carried out to estimate persistence with the different therapeutic classes of antihypertensives, with rates that varied substantially. Caro et al. [24] obtained a 1-year persistence rate of 82% for the nonexclusive use of ACEIs, while Marentette et al. [40] noted a 65% persistence rate for the exclusive use of ACEIs as a class. Bloom [41] observed a 1-year persistence rate for the exclusive use of the initially prescribed drug of 64% for angiotensin II-receptor blockers, 58% for ACEIs, 50% for CCBs, 43% for beta-blockers, and 38% for diuretics. Our 1-year results for the exclusive use of ACEIs as a class were similar to Bloom’s results.

Nonpersistence to ACEIs is not an isolated problem because we observed this phenomenon for the treatment of many other chronic diseases. For instance, the persistence at 12 months after an initial statin prescription for the primary and secondary cohorts (53% and 62%) was about the same as the rate we found for antihypertensive agents (65%), but lower than medication for cardiovascular diseases (70%) [42].

A number of steps have been taken for improving patient compliance. These include programs for improvement of the patient/health professional relationship, educational programs, and the streamlining of treatment regimens with single-dose, sustained-release, and combination drugs. Nevertheless, these efforts have been far from sufficient. According to Peterson et al. [43], they have only led to a modest increase in compliance of 4–11%. As Wertheimer et al. wrote, we have not yet found the optimal approach for achieving high compliance levels after 25 years of intensive research on the subject [44]. At this point the critical issue is the education of patients, physicians, and pharmacists concerning the low rate of persistence of antihypertensive therapy. We must reconsider alternative educational strategies to promote optimal drug utilization.

This finding reflects the need for physicians and pharmacists to identify those individuals who may benefit from targeted patient counseling, and more studies of innovative approaches to follow prescriptions for medications are needed, such as continuous electronic monitoring of compliance as a disease management strategy [45]. A realistic new chronic-disease model of disease management, involving implementation of such programs as patient–professional partnerships, multidisciplinary teams, self-management education, clinical information systems, decision support, and clinical indicators, needs to be developed.

Using databases to estimate persistence by refill analysis has its advantages and limitations [46–48]. It makes it possible to follow medication use over a long period of time with good external validity. It also avoid the Hawthorne effect [49], because this is a retrospective approach. The RAMQ database includes data on more than half of Quebec’s population, and requiring a copayment is an argument in favor of actual medication use after purchase. In addition, Tamblyn et al.’s study [50] validated the RAMQ database by showing that it had a good level of data accuracy.

The main limitations are the lack of information on the reasons for discontinuing treatment, on the indication and on the severity of the disease. This can affect the association between the persistence rate and the type of medication [51]. In addition, the evaluation of drug use will be based on dispensation instead of drug administration and may lead to a nondifferential information bias because the drug can be dispensed but not taken. Our results are limited to middle-aged patients (50 to 64 years) and cannot therefore be extrapolated to older patients.

We conclude that persistence with ACEIs was relatively low overtime with the threshold of 80% generally accepted [52]. The patients in the secondary prevention cohort were more persistent than those in the primary prevention cohort. Lastly, the fact of having dyslipidemia or diabetes, the increasing number of concomitant medications has a positive impact on persistence rate. On the other hand, the fact of having higher total oral doses of drugs per day, more medical visit, more dispensing pharmacies has a negative impact on persistence rate. These results can help health professionals better identify patients who are more likely to discontinue their treatment and thus better identify the intervention methods.
This research was carried out as part of Amédé Gogovor’s master’s work-term project, thanks to funding from Sanofi-Aventis. Sylvie Perreault PhD is a research scholar receiving financial support from the Fonds de la recherche en santé du Québec.

Source of financial support: Sanofi-Aventis.

References


45 McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions. JAMA 2002;288:2868–79.