Impact of a Better Adherence to Antihypertensive Agents on Cerebrovascular Disease for Primary Prevention

Fatima-Zohra Kettani, MSc; Alice Dragomir, MSc; Robert Côté, MD, FRCPC; Louise Roy, MD, FRCPC; Anick Bérard, PhD; Lucie Blais, PhD; Lyne Lalonde, PhD; Pierre Moreau, PhD; Sylvie Perreault, PhD

Background and Purpose—The benefits of antihypertensive (AH) drugs on the risks of major cardiovascular outcomes have been demonstrated in clinical trials. However, approximately half of hypertensive patients do not adhere well to their prescribed AH therapy in actual practice. The purpose of this study was to assess the impact of adherence to AH agents on the incidence of cerebrovascular disease (CD) in real-world practice.

Methods—A cohort of 83,267 hypertensive patients was reconstructed from the Régie de l’assurance maladie du Québec databases. Subjects included were between 45 and 85 years old, initially free of cardiovascular disease, and newly treated for hypertension with AH agents between 1999 and 2004. A nested case–control design was conducted to study CD occurrence. Every case was matched for age and duration of follow-up with up to 15 randomly selected control subjects. The adherence to AH drugs was measured by calculating the medication possession ratio. Conditional logistic regression models were performed to assess the association between adherence to AH agents and CD adjusting for various potential confounders.

Results—At cohort entry, the mean patient age was 65 years, 37.3% were male, 8.6% had diabetes, and 19.5% had dyslipidemia. High adherence (≥80%) to AH drugs significantly decreased the risk of CD by 22% (rate ratio, 0.78; 95% CI, 0.70 to 0.87) compared with lower adherence. Male gender, occurrence of cardiovascular disease during follow-up, and dyslipidemia were risk factors for CD.

Conclusion—High adherence to AH therapy is associated with a reduced risk of CD outside the context of clinical trials in primary prevention. (Stroke. 2009;40;213-220.)

Key Words: adherence to treatment • antihypertensive drugs • cerebrovascular disease

Cerebrovascular diseases (CD) are a leading cause of mortality and morbidity worldwide.1,2 Economically, they are a major driver of healthcare costs.1 However, CD are also preventable and primary prevention is particularly important because more than 70% of CD are first events.1 Hypertension represents the strongest modifiable risk factor for CD.1 Clinical trials of primary prevention have shown that antihypertensive (AH) agents, including diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, are associated with a 30% to 40% reduction in the incidence of CD within just a few years.3,4 Yet, the large reductions in risks associated with CD seen in clinical trials may not translate into better prognoses in the “real-world” setting if patients have trouble adhering to their prescribed regimens. It is estimated that approximately half of hypertensive patients do not adhere well to AH therapy.5 Adherence to AH drugs has been associated with improvement of blood pressure, decreased hospitalization rates, and lower medical care costs.6,7 However, there have been no large effectiveness studies assessing the relationship between adherence to AH medication and major cardiovascular outcomes. Our study aimed therefore to evaluate the association between adherence to AH therapy and incident CD among newly treated hypertensive patients for primary prevention.

Methods

Data Sources
This retrospective population-based study used the “Régie de l’Assurance Maladie du Québec” (RAMQ) and Med-Echo databases. The RAMQ, which administers public healthcare insurance programs in the province of Québec, Canada, has 3 types of databases. The beneficiary database lists age, gender, social assistance status, and, when relevant, date of death of all registered persons. The medical services database contains claims for all inpatient and ambulatory services and includes data such as the date, nature and location of medical acts; diagnoses; and procedure codes. Diagnostic codes are classified according to the International Classification of Diseases, 9th revision (ICD-9).8 Surgical procedure codes follow the Canadian classification of diagnostic, therapeutic, and surgical procedures.8 The pharmaceutical database provides data on delivered medication in community pharmacies such as the date of filling,
name of the drug, dose, quantity, dosage form, and duration of therapy. The Med-Echo database gathers information on acute care hospitalizations such as date of admission, length of stay, and primary and secondary diagnoses. All databases contain a unique identifier, the individual’s health insurance number that serves as a link between them.

The RAMQ’s beneficiary and medical services databases and the Med-Echo databases include all residents covered by the Quebec provincial health insurance, ie, the entire population. The RAMQ’s pharmaceutical database covers residents insured under the public drug plan comprising approximately 43% of the population. Those are mainly individuals aged ≥65 years, welfare recipients, and, since January 1997, individuals aged ≤64 years who do not have access to a private insurance program. The loss of persons aged ≥65 years is estimated to have been minimal, because only 2.5% of them have opted to join a private insurance program.

The pharmaceutical database has been evaluated and its validity confirmed.13 As well, validity studies have been done for certain medical services claims of the Quebec administrative databases.12 Other studies have assessed the validity of administrative hospital discharge data.13 For ischemic CD, the sensitivity was 80%, specificity was 96%, and positive predictive value was 91%; for intracerebral hemorrhage, those values were 85%, 94%, and 83%, respectively.13

Cohort Definition
All subjects aged between 45 and 85 years old, who were newly treated with diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or a combination between January 1, 1999, and December 31, 2004, and who were diagnosed with essential hypertension (ICD-9 code: 401) were identified. Patients were considered newly treated if they had not taken any AH agent in the 2 years before the cohort entry date, which was defined as the date of the first prescription. Only patients who had filled at least 3 AH prescriptions in the 6 months after their entry into the cohort were included. In addition, to ensure that the patients need pharmacological treatment, the patients need to have had a medical visit to their physician and to have filled at least one AH prescription for each period of 1.5 years.

Furthermore, the subjects had to have documentation of cardiovascular disease (CVD), based on the absence of a diagnosis (ICD-9) or medical procedure in the last 5 years, and any drug marker in the 2 years before the cohort entry date. Thus, we excluded patients who already had a CD, a coronary artery disease (CAD), a peripheral arterial disease (PAD), chronic heart failure (CHF), or arrhythmia. Patients who received antplatelets (except aspirin) or anticoagulants during the 2 years preceding the cohort entry were also excluded.

Subjects were followed up from the date of issuance of the first prescription of an AH agent until the first-ever CD event or the end of the study period (June 30, 2005). Individuals who lost coverage under the RAMQ drug insurance or had not filled any AH prescription 1.5 years after the last one or died during follow-up were censored. The total death rate was assessed in the cohort.

Nested Case–Control Study
We conducted within our cohort a nested case–control study to evaluate the association between adherence to AH and the risk of CD. A CD was defined as a composite end point of intracerebral hemorrhage (ICD-9 431), other and unspecified intracerebral hemorrhage (432), occlusion and stenosis of precerebral arteries (433), occlusion cerebral arteries (434), acute but ill-defined CD (436), and other and ill-defined CD (437). All CD cases were identified, and up to 15 control subjects were randomly selected from the cohort based on the risk set of each case using density sampling. With this method, control subjects are selected among subjects that were at risk of developing the outcome at the time the case was identified.14 In this way, subjects could serve as control subjects for more than one case occurring at different times, and cases could serve as control subjects before they became cases, which will give an unbiased estimation of the rate ratio.14 Cases were matched to control subjects for age (±1 year) at the cohort entry and duration of follow-up.

Exposure Assessment
Adherence to AH treatment, defined as the extent to which a patient takes AH medication as prescribed, was estimated by calculating the “medication possession ratio.” The medication possession ratio corresponded to the total number of days’ supply of medication dispensed divided by the length of follow-up.15 Cases’ adherence was calculated from the start of follow-up to the time of the CD event (index date). For control subjects, the adherence was calculated from the start of follow-up to the time of selection (index date). The medication possession ratio was dichotomized, setting a threshold of medication possession ratio <80% to identify nonadherent patients, consistently with literature data.16,17

Covariates
Sex and social assistance were identified at the cohort entry date. The occurrence of a CAD, a CHF, a PAD or other CVD was assessed in the year before cohort entry and during follow-up. The number of AH therapies prescribed was assessed in the year before the index date (mono-, bi-, or tritherapy). Diabetes and dyslipidemia were identified in the year before cohort entry and during follow-up by ICD-9 codes or drug markers. Patients with diabetes or dyslipidemia diagnosed in the year preceding the index date were considered newly diagnosed. For the other patients, the use of antidiabetic or hypolipidemic agents in the year before the index date was dichotomized into 2 levels: high adherence (≥80% of the prescribed doses) and low adherence (<80%). Patients who were diagnosed with diabetes or dyslipidemia but never treated were defined as such. The reference categories were subjects with no diabetes and subjects with no dyslipidemia, respectively. Finally, a modified patient’s chronic disease score was evaluated in the year preceding the index date (chronic disease score ≥4 or <4). The chronic disease score is a comorbidity metric that uses drugs dispensed as surrogate markers for chronic illness instead of using clinical diagnoses.18

Statistical Analysis
Descriptive statistics were performed to compare baseline characteristics using χ² analyses and Student t test. A nested case–control design was used and conditional logistic regression models were developed to estimate the crude and adjusted rate ratios (RR) for CD. The nested case–control approach is a useful alternative for cohort analysis when studying time-dependent exposures given that the exposure and covariates information for control subjects reflects values corresponding to the time of selection of their respective case. This approach has been found to yield results that were similar to results of Cox regression on the full cohort with the advantage of superior computational efficiency with the conditional logistic regression.19 To account for the possible effect of time, we stratified the analysis by the time of the case occurrence. Several subgroup analyses were conducted, eg, age groups, type of CD (hemorrhagic: ICD-9: 431 to 432; ischemic: 433 to 436), patients having diabetes or dyslipidemia diagnosis, and those without diabetes and dyslipidemia. All models were adjusted for the covariates that were described previously.

Sensitivity analysis were performed to assess the impact of potential unmeasured confounders on the robustness of our results using the Greenland’s Monte Carlo approach.20,21 We created different scenarios for (1) the relation between the unmeasured confounder and CD; and (2) the estimated proportions of the unmeasured confounder across adherent and nonadherent groups. Then for each scenario, we evaluated how the RR changes after adjusting for the unmeasured confounder.

We performed all statistical analysis using Statistical Analysis System Software for Windows Version 8 (SAS Institute Inc, Cary, NC) with a 95% precision.

Ethical Considerations
The study was approved by the Research and Ethics Committee of the University of Montreal.
Results

Patients’ Characteristics

After applying the inclusion and exclusion criteria (Figure), the cohort consisted of 83,267 patients with a mean age at entry of 65 years, 37.3% of whom were male, 11.6% welfare recipients, 8.6% diabetics, and 19.5% with dyslipidemia (Table 1). As first AH monotherapy treatment, diuretics and angiotensin-converting enzyme inhibitors were similarly the most used (26%). Combined therapy was less likely to be prescribed at the start of therapy (4%). As shown in Table 1, there were no major differences in baseline characteristics across the 5 AH drug classes. Of the 3565 cases of CD identified in our study, 77.3% were ischemic CD, 2.9% were intracerebral hemorrhage, and 19.8% were other and ill-defined CD.

Table 1. Characteristics of Patients Initiating a New Antihypertensive Treatment in the Quebec RAMQ Database in 1999 to 2005

<table>
<thead>
<tr>
<th>Antihypertensive Drug Class*</th>
<th>Entire Cohort</th>
<th>Diuretics</th>
<th>β-blockers</th>
<th>Calcium Channel Blockers</th>
<th>Angiotensin-Converting Enzyme Inhibitors</th>
<th>Angiotensin Receptor Blockers</th>
<th>Combined Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>83,267</td>
<td>21,542</td>
<td>8,601</td>
<td>11,257</td>
<td>21,552</td>
<td>16,644</td>
<td>3671</td>
</tr>
<tr>
<td>Follow-up time, days (SD)</td>
<td>1160 (±614)</td>
<td>1159 (±625)</td>
<td>1256 (±630)</td>
<td>1198 (±615)</td>
<td>1196 (±614)</td>
<td>1088 (±583)</td>
<td>938 (±540)</td>
</tr>
<tr>
<td>Mean age, years (SD)*</td>
<td>65 (±10)</td>
<td>66 (±9.9)</td>
<td>62 (±10)</td>
<td>66 (±10)</td>
<td>64 (±10)</td>
<td>64 (±10)</td>
<td>63 (±10)</td>
</tr>
<tr>
<td>Male sex</td>
<td>37.3%</td>
<td>28.0%</td>
<td>33.9%</td>
<td>40.8%</td>
<td>42.4%</td>
<td>40.8%</td>
<td>42.9%</td>
</tr>
<tr>
<td>Social assistance*</td>
<td>11.6%</td>
<td>10.6%</td>
<td>14.7%</td>
<td>11.4%</td>
<td>12.1%</td>
<td>10.2%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Diabetes†</td>
<td>8.6%</td>
<td>3.2%</td>
<td>3.5%</td>
<td>4.4%</td>
<td>19.2%</td>
<td>7.7%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Dyslipidemia†</td>
<td>19.5%</td>
<td>17.0%</td>
<td>16.8%</td>
<td>16.4%</td>
<td>23.7%</td>
<td>20.7%</td>
<td>18.7%</td>
</tr>
</tbody>
</table>

*At treatment initiation.
†ICD-9 or treatment in the year preceding the cohort entry.
During follow-up, 4.3% of patients had a CD (1.3 per 100 person-years), 13.7% developed a CAD (4.3 per 100 person-years), 4.7% presented a CHF (1.5 per 100 person-years), 3.7% had a PAD (1.2 per 100 person-years), 15.8% had another CVD (4.9 per 100 person-years), and 25.5% took antiplatelets drugs without any CVD (7.9 per 100 person-years). The percent of total death during follow-up was 3.1% (1.0 per 100 person-years).

There were significantly more males, welfare recipients, patients with diabetes or dyslipidemia, and users of antiplatelets drugs among cases than among control subjects. All CVD events that have occurred during follow-up were significantly more prevalent among cases than control subjects (Table 2).

Impact of Adherence Level to Antihypertensive Drugs on Cerebrovascular Disease

The multivariate analysis (Table 3) revealed that adherence of ≥80% to AH drugs was associated with a decreased risk of CD (RR, 0.78; 95% CI, 0.70 to 0.87) compared with lower adherence and this after at least 1 year of exposure.

Risk Factors for Stroke

The adjusted model showed that male sex, social assistance, antiplatelet use, dyslipidemia, and higher chronic disease score increased significantly the risk of CD (Table 3). Developing of a CAD, a CHF, a PAD, or other CVD events during follow-up increased significantly CD risk from 2.0 to 4.6, and those estimates were nearly 1.5 to 2 times higher in the earlier period after the occurrence of CVD.

Subgroup Analyses

Among subjects >65 years, high adherence to AH drugs lessened significantly the risk of CD (RR, 0.77; 95% CI, 0.68 to 0.89) compared with the reference group; the risk reduction was not significant among patients younger than 65 years (OR, 0.81; 95% CI, 0.65 to 1.00). The risk reduction for CD was significant for ischemic CD (RR, 0.80; 95% CI, 0.70 to 0.91) but not for intracerebral hemorrhage (RR, 0.77; 95% CI, 0.32 to 1.85). Finally, among patients with diabetes or dyslipidemia, those with high adherence had a decreased risk of CD (RR, 0.74; 95% CI, 0.58 to 0.93). Similar results were observed with patients without diabetes or dyslipidemia.

Sensitivity Analyses

The reduction in the incidence rate of CD did not vary (RR, 0.78; 95% CI, 0.69 to 0.89) when we excluded patients with ICD-9 code 437 that may reflect a variety of vague conditions.

In the Monte-Carlo analysis (Table 4), only in scenarios with the highest probability (scenarios 5 and 6), with 15% smokers in the high adherence level group as compared with 25% smokers in the low adherence level group and with a risk factor ranging from 3.0 to 4.0, the relationship became nonsignificant without being inverted.

Discussion

Our study reveals that high adherence to AH agents (≥80%) is associated with a 22% decreased risk of CD events among newly treated hypertensive patients in the primary prevention setting compared with lower adherence. This association was only found after 1 year of exposition confirming that AH effectiveness in CD prevention presents a delay before it becomes apparent. The risk reduction associated with medication adherence was consistent across several patient subgroups.

To our knowledge, the association between AH medication adherence and the risk of CD has not been yet evaluated in the context of real practice. Clinical trials for primary prevention demonstrated the benefits of AH drugs on reducing the incidence of CD. Because these medications were shown efficacious compared with placebo in a highly controlled environment, our study was intended to evaluate their effectiveness in real-world practice and, in particular, to assess the impact of medication adherence. Our observed risk reduction was in the same direction of those reported in meta-analysis of clinical trials, which further supports the importance of adherence as a key factor for good clinical outcomes. Diuretics and/or β-blockers have been found to reduce the incidence of CD by 38% (95% CI, 31 to 45). Compared with placebo, angiotensin-converting enzyme inhibitors and calcium channel blockers decreased the risk of CD by 28% (95% CI, 19 to 36) and 38% (95% CI, 18 to 53), respectively. Angiotensin receptor blockers reduced the incidence of CD by 21% (95% CI, 10 to 31) compared with control subjects. Another meta-analysis showed that compared with placebo, an untreated control group, or usual care, any AH active treatment was associated with important reductions in the risk of CD (RR, 0.69; 95% CI, 0.64 to 0.74).

The coefficients associated with CD risk factors such as male sex, social assistance, the presence of CVD, or dyslipidemia agreed with literature data. Previous studies showed that men are at higher risk of CD (RR, 1.50; 95% CI, 1.01 to 2.22) than women and that low socioeconomic groups have higher rates of CD incidence (RR, 1.65; 95% CI, 1.21 to 2.23) than higher groups. Patients with evidence of CAD, CHF, or PAD have an increased risk of first CD as compared with those without such a history (RR, 1.73; 95% CI, 1.68 to 1.78 for men; RR, 1.55; 95% CI, 1.17 to 2.07 for women). Finally, high total cholesterol levels are associated with a 2-fold risk of ischemic CD.

Our design took into account the potential for some methodological problems. To avoid selection bias, we only used incident AH users. Like with any pharmacoepidemiological study, the potential for confounding by indication should be cautiously assessed. First, given that the patients studied were all receiving AH agents, the likelihood of such a bias is minimal. On the other hand, we could not control for all characteristics that may influence the physicians’ choice. Unmeasured comorbidity as well as missing data of hypertension level could lead to residual confounding effects. Although there is no reason to believe that prescribing of different AH agents would be strongly influenced by the hypertension level. The analysis of available baseline characteristics did not reveal preferential prescribing of a particular AH agent to sicker patients. Second, patients with comorbidities may have more motivation to be adherent to prescribed AH agents and may also be more likely to have CVD.
events. Thus, to further minimize the bias, we adjusted for several CVD risk factors such as diabetes, dyslipidemia, and occurrence of CVD (excluding CD) after starting AH therapy.

Third, the RAMQ databases do not provide any information on clinical data and thus does not permit adjustment for clinical severity of hypertension. In the current study, we identified patients on monotherapy, bitherapy, or tritherapy in the year to the index date to adjust for hypertension severity.

Fourth, we could not adjust for blood glucose and cholesterol levels. So for patients who received drugs for their diabetes or dyslipidemia, we assessed their adherence level to these medications and its impact on CD risk. In particular, our
results revealed that high adherence to hypolipidemic drugs decreased the risk for CD by 20%. This confirms recent reports, which have shown that statin therapy reduced major CD by 14.4% in the primary prevention of CVD.26

Fifth, our follow-up period was shorter compared with the large randomized clinical trials. However, our median of follow-up was 3.3 years and a maximum of 6.5 years, which is reasonable length to detect possible differences in outcomes. Sixth, death was also considered as an issue. For instance, most of the deaths occurred relatively soon after a CVD event and, therefore, we captured more likely CD-related deaths.

Seventh, we did not have access to any information regarding patients’ lifestyles such as smoking, physical inactivity, poor diet, or obesity. These factors are well-documented risk factors for CVD.1 They are also more likely to be present among patients who do not adhere to their medication, leading to a potential bias. Indeed, we cannot

Table 3. RR of Cerebrovascular Disease

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th></th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases Occurring in the First Year of Follow-Up and Their Control Subjects</td>
<td>Cases Occurring After 1 Year of Follow-Up and Their Control Subjects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted</td>
<td>Crude</td>
</tr>
<tr>
<td>Antihypertensive agents adherence*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80% (n=9083)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>≥80% (n=47 502)</td>
<td>0.87</td>
<td>0.86 (0.72–1.03)</td>
<td>0.75</td>
</tr>
<tr>
<td>Bitherapy versus monotherapy</td>
<td>1.57</td>
<td>1.35 (1.17–1.57)</td>
<td>1.09</td>
</tr>
<tr>
<td>Tritherapy versus monotherapy</td>
<td>1.82</td>
<td>1.47 (0.92–2.35)</td>
<td>1.35</td>
</tr>
<tr>
<td>Sex, male versus female</td>
<td>1.48</td>
<td>1.39 (1.24–1.56)</td>
<td>1.28</td>
</tr>
<tr>
<td>Social assistance, yes/no</td>
<td>1.19</td>
<td>1.18 (0.92–1.50)</td>
<td>1.66</td>
</tr>
<tr>
<td>Having a coronary artery disease during follow-up, yes/no†</td>
<td>2.88</td>
<td>2.68 (2.47–4.22)</td>
<td>1.37</td>
</tr>
<tr>
<td>Having a chronic heart failure during follow-up, yes/no‡</td>
<td>2.80</td>
<td>3.57 (2.07–6.15)</td>
<td>1.56</td>
</tr>
<tr>
<td>Having a peripheral artery disease during follow-up, yes/no§</td>
<td>9.47</td>
<td>8.40 (7.56–14.93)</td>
<td>3.18</td>
</tr>
<tr>
<td>Having other cardiovascular events during follow-up, yes/no‖</td>
<td>2.79</td>
<td>3.25 (2.50–4.22)</td>
<td>1.62</td>
</tr>
<tr>
<td>Having ≥2 cardiovascular disease during follow-up, yes/no</td>
<td>5.50</td>
<td>7.05 (5.05–9.83)</td>
<td>2.73</td>
</tr>
<tr>
<td>Use of antiplatelets, yes/no¶</td>
<td>1.69</td>
<td>2.06 (1.68–2.53)</td>
<td>1.15</td>
</tr>
<tr>
<td>No diabetes</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Diabetes diagnosed and nontreated**</td>
<td>1.19</td>
<td>1.11 (0.84–1.48)</td>
<td>1.17</td>
</tr>
<tr>
<td>Newly diagnosed with diabetes**</td>
<td>1.13</td>
<td>0.95 (0.68–1.33)</td>
<td>1.52</td>
</tr>
<tr>
<td>Antidiabetic agents adherence &lt;80%**††</td>
<td>1.47</td>
<td>1.31 (0.81–2.11)</td>
<td>1.60</td>
</tr>
<tr>
<td>Antidiabetic agents adherence ≥80%**††</td>
<td>1.24</td>
<td>1.17 (0.87–1.59)</td>
<td>1.35</td>
</tr>
<tr>
<td>No dyslipidemia</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Dyslipidemia diagnosed and nontreated**</td>
<td>0.75</td>
<td>0.76 (0.51–1.12)</td>
<td>0.78</td>
</tr>
<tr>
<td>Newly diagnosed with dyslipidemia**</td>
<td>1.65</td>
<td>1.19 (1.00–1.42)</td>
<td>1.83</td>
</tr>
<tr>
<td>Hypolipidemic agents adherence &lt;80%**††</td>
<td>1.18</td>
<td>1.17 (0.86–1.61)</td>
<td>1.30</td>
</tr>
<tr>
<td>Hypolipidemic agents adherence ≥80%**††</td>
<td>0.66</td>
<td>0.68 (0.53–0.87)</td>
<td>0.89</td>
</tr>
<tr>
<td>Chronic disease score, ≥4 versus &lt;4†††</td>
<td>1.13</td>
<td>1.13 (0.90–1.41)</td>
<td>1.47</td>
</tr>
</tbody>
</table>

*Medication possession ratio (%).
†Diagnosis of CAD (ICD-9 codes: 410 to 414), medical procedure (coronary artery bypass grafting, angiography, or angioplasty), or use of nitrates.
‡Diagnosis of CHF (ICD-9 codes: 398.91, 402.01, 402.11, 402.91, 428.0, 428.1, and 428.9) or a prescription of furosemide alone or with digoxin, ACE inhibitor, spironolactone, or β-blockers.
§Diagnosis of PAD (ICD-9 codes: 440 to 447), medical procedure (noncoronary angioplasty), or use of pentoxifylline.
¶Diagnosis of other CVD: arrhythmia (ICD-9 codes: 427 to 427.9), medical procedure using a pacemaker or use of antiarrhythmics, valvular heart disease, or use of anticoagulants.
††Antiplatelets users: use of dipyridamole, sulfipyrazone, ticlopidine, dipyridamole+aspirin, clopidogrel, aspirin in doses ranging from 80 mg to 650 mg, and that without CVD events.
**ICD-9 or pharmacologic treatment.
†††Medication possession ratio (%) in the year before the index date.
††††In the year before the index date.
exclude that adherence to drug therapy may be a surrogate marker for overall healthy behavior.²² The sensitivity analysis assessed the robustness of our findings regarding potential biases introduced by unmeasured confounders. Highest probability of unmeasured confounders along with a risk of CD ranging from 3.0 to 4.0 will give a nonsignificant RR (without being inverted) and, based on these scenarios, bias of that magnitude is unlikely to be present.

Eighth, there might be some missing or erroneous codes so that subjects with a history of CVD were not identified. However, the probability of such nonmisclassification may be low because we had access to relevant medical and drug information for patients over a period of several years before their entry into the cohort.

Finally, the analysis used prescription refill patterns to assess exposure and therefore does not ascertain whether the dispensed medication was actually taken by the patient. However, some data suggest a good correlation between pharmacy-dispensing records and cumulative drug exposure and gaps in medication-supply.²⁰

In summary, this study of real-world drug use patterns in the Canadian setting showed that adherence to AH medication is associated with a decreased risk of CD in the context of primary prevention of CVD. Adherence to pharmacological therapy is a key factor in determining the success of various therapeutic approaches; thus, greater attention should be paid to this aspect, which may result in improved patient outcome. Educational strategies and interventions involving both health professionals and patients must be increased to enhance adherence to CVD medications if we are to maximize the health benefits in the population as a whole.

Source of Funding
The Canadian Institutes Health Research (CIHR) supported this work.

Disclosures
S.P. is a research scholar who received financial support from the Fonds de la Recherche en Santé du Québec. L.B. and A.B. are research scholars who receive financial support from the CIHR. F.-Z.K. is the recipient of a master scholarship from the Groupe de Recherche en Santé du Québec. L.B. and A.B. are research scholars who receive financial support from the Fonds de la Recherche en Santé du Québec. S.P. is a research scholar who received financial support from the Fonds de la Recherche en Santé du Québec.

References

Table 4. Change in RR of Cerebrovascular Disease After Adjustment for Unmeasured Confounders

<table>
<thead>
<tr>
<th>Scenario</th>
<th>High Adherence Group</th>
<th>Low Adherence Group</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Risk†</td>
<td>Medium Risk†</td>
<td>Estimated RR (95% CI) of CD</td>
</tr>
<tr>
<td>Scenario 1</td>
<td>15% (8%; 7%)</td>
<td>19% (12%; 7%)</td>
<td>1.8 (1.2–2.3)</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>15% (8%; 7%)</td>
<td>19% (12%; 7%)</td>
<td>2.5 (1.6–3.5)</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>15% (8%; 7%)</td>
<td>25% (12%; 13%)</td>
<td>1.8 (1.2–2.3)</td>
</tr>
<tr>
<td>Scenario 4</td>
<td>15% (8%; 7%)</td>
<td>25% (18%; 7%)</td>
<td>3.0 (1.2–4.0)</td>
</tr>
<tr>
<td>Scenario 5</td>
<td>15% (8%; 7%)</td>
<td>25% (18%; 7%)</td>
<td>4.0 (1.2–5.0)</td>
</tr>
</tbody>
</table>

*Risk factor between the confounder and CD.
†High risk; medium risk are defined as smokers (current smokers or former smokers) or obesity (severe or moderate).
‡Proportion at high risk factor and medium risk factor among high adherence and low adherence groups.


Impact of a Better Adherence to Antihypertensive Agents on Cerebrovascular Disease for Primary Prevention
Fatima-Zohra Kettani, Alice Dragomir, Robert Côté, Louise Roy, Anick Bérard, Lucie Blais, Lyne Lalonde, Pierre Moreau and Sylvie Perreault

Stroke. 2009;40:213-220; originally published online November 26, 2008;
doi: 10.1161/STROKEAHA.108.522193

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/1/213

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/