Increases in Antihypertensive Prescriptions and Reductions in Cardiovascular Events in Canada

Norm R.C. Campbell, Rollin Brant, Helen Johansen, Robin L. Walker, Andreas Wielgosz, Jay Onysko, Ru-Nie Gao, Christie Sambell, Stephen Phillips, Finlay A. McAlister; for the Canadian Hypertension Education Program Outcomes Research Task Force

Abstract—The Canadian Hypertension Education Program, an extensive professional education program to improve the management of hypertension, was started in 1999. There were very large increases in diagnosis and treatment of hypertension in the first 4 years after initiation of the program. The purpose of this study was to examine the association between the changes in antihypertensive therapy with changes in hospitalization and death from major hypertension-related cardiovascular diseases in Canada between 1992 and 2003. Using various national databases, Canadian standardized yearly mortality and hospitalization rates per 1000 for stroke, heart failure, and acute myocardial infarction were calculated for individuals aged ≥20 years and regressed against antihypertensive prescription rates. Changes in rates were examined in a time series analysis. There were significant reductions ($P<0.0001$) in the rate of death from stroke, heart failure, and myocardial infarction starting in 1999. There was also a reduction in hospitalization rate from stroke ($P<0.0001$) and heart failure ($P<0.0001$) but not myocardial infarction in 1999. The changes in death ($P<0.001$ for all 3 diseases) and hospitalization ($P<0.0001$ for stroke and heart failure; $P=0.018$ for acute myocardial infarction) were associated with the increases in antihypertensive prescriptions. This study demonstrates that the reduction in cardiovascular death and hospitalization rates is associated with an increase in antihypertensive prescriptions and that it coincides with the introduction of the Canadian Hypertension Education Program. The Canadian Hypertension Education Program educational model for improving health care could be adopted by other countries with well-developed professional and scientific societies. (Hypertension. 2009;53:128-134.)

**Key Words:** hypertension ■ antihypertensive treatment ■ stroke ■ myocardial infarction ■ heart failure ■ epidemiology ■ clinical practice guideline

Increased blood pressure is the leading risk for death in the world. Large randomized, controlled trials and meta-analyses have demonstrated that the treatment of hypertension results in significant reductions in mortality and disability from cardiovascular disease. Hence, the World Health Organization has advised countries to improve the management of hypertension as a mechanism to improve population health. However, despite robust randomized trial evidence confirming the benefits of lowering blood pressure with antihypertensive agents, the expected benefits of antihypertensive treatment in reducing cardiovascular events have not been seen in several observational studies of usual clinical practice. Recently, population changes in antihypertensive therapy were found not to be associated with the expected changes in blood pressure. There are few national programs to use as models for successfully improving hypertension management. In Canada, a program to improve the management of hypertension (the Canadian Hypertension Education Program [CHEP]) was started in 1999. The CHEP was based on annually updated recommendations for the management of hypertension, engagement of many of the hypertension experts and health care organizations in Canada, and a very extensive multipronged implementation program to primary healthcare providers. Substantial increases in the diagnosis and treatment of hypertension have been observed in the first 4 years after initiation of the program. Recently, a population survey in Ontario, Canada, has reported the highest rates in the world for awareness, treatment, and control of hypertension. The purpose of this study was to
examine whether the CHEP or changes in antihypertensive therapy have been associated with changes in the rates of cardiovascular hospitalization and mortality in Canada.

**Methods**

Analyses were conducted on national data from the Canadian Mortality database (Statistics Canada), Canadian Institute for Health Information hospitalization database, Intercontinental Medical Statistics (IMS) CompuScript database, the National Population Health Survey (NPHS), and the Canadian Community Health Survey (CCHS). All of the databases either represent all national data or estimate national data. Specifically, the monthly IMS data were used to examine the association between changes in antihypertensive prescriptions and the quarterly changes in cardiovascular event rates. Although treatment of hypertension is available in the NPHS and CCHS surveys, these are conducted every few years and, therefore, lack statistical power to assess time changes.

**Death and Hospitalization From Stroke, Heart Failure, and Acute Myocardial Infarction**

Age-adjusted mortality rates from stroke, heart failure (HF), and acute myocardial infarction (AMI) among individuals aged ≥20 years were calculated from the Canadian mortality database at Statistics Canada for the years 1992–2003 inclusive. Hospitalization data were obtained from Canadian Institute for Health Information, which collects information on the primary diagnosis and ≤15 secondary diagnoses for all hospitalizations in Canada. Hospital discharges (separations) with stroke, AMI, or HF as the most responsible diagnosis were summed within each month between January 1996 and December 2003. Diagnoses were defined according to the International Classification of Diseases, Ninth Revision (ICD-9),19 and/or the 10th revision of this volume (ICD-10).20 ICD-9 codes 430, 431, 434, and 436 and ICD-10-Canada codes I60, I61, I63, and I64 were used to identify hospitalizations in which stroke was the most responsible diagnosis. ICD-9 code 428 and ICD-10 code I50 were used to identify cases in which HF was the most responsible diagnosis. AMI was defined by ICD-9 code 410 and ICD-10 codes I21 and I22. These codes in the Canadian Institute for Health Information database have been confirmed to accurately identify patients with each of the target conditions.21,22 Hospitalization and mortality rates were standardized to the age (in 5 age groups: 20 to 49, 50 to 59, 60 to 69, 70 to 79, and ≥80 years of age) and sex distribution of the 2000 (July 1) Canadian population aged ≥20 years.

**Antihypertensive Prescriptions**

Information about antihypertensive prescriptions was obtained from IMS Health-Canada.16 The IMS CompuScript database compiles monthly dispensing records from a representative sample of approximately two thirds of all retail pharmacies in Canada. The drug prescription data are adjusted to estimate all prescriptions in Canada by IMS. The CompuScript database does not include information on physician characteristics, patient-level data (eg, age, sex, comorbidities, or concomitant medications dispensed), or indications for use. We examined the number of prescriptions dispensed for all of the antihypertensive agents (thiazide diuretics, β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and angiotensin receptor blockers) between January 1996 and December 2003.16,17 (Electronic databases of earlier years were not available), calculated total 30-day antihypertensive drug prescription rates,17 and adjusted for the changes in the population of Canadians over age 20 years to the year 2000. The IMS CompuScript data were not age standardized, because data on the age of those prescribed the antihypertensive drugs is not collected. Total antihypertensive prescriptions were used, because there is a similar reduction in overall cardiovascular events with all of the major antihypertensive classes used in this analysis.2

**Treatment and Diagnosis of Hypertension**

National estimates of treatment and diagnosis of hypertension in Canada were obtained from the NPHS over 2-year periods (cycle 1: 1994–1995; cycle 2: 1996–1997; cycle 3: 1998–1999) and from the CCHS (cycle 1:1: 2000–2001; cycle 2:1: 2003).23,24 Both surveys are population-based surveys using multistage probability designs with stratification and clustering at various stages. Respondents are representative of Canadian household residents aged ≥12 years, excluding residents of Indian reserves or Crown lands, institutions, some remote areas, and full-time members of the Canadian armed forces. The response rate for all of the surveys was >80%. All of the participants of the NPHS and CCHS who were ≥20 years of age, resided in a province, and were subjected to the chronic disease and drug use survey components were included in our analysis.

Participants were asked whether they had hypertension diagnosed by a healthcare professional and whether they were prescribed antihypertensive medications in the previous month. Those who reported hypertension or treatment for hypertension were considered to be “diagnosed hypertensive individuals.” Those who reported that they were prescribed antihypertensive medications were considered to be “treated hypertensive individuals.” Prevalence rates were age standardized to the year 2000 and weighted to reflect the size of the adult Canadian population.

**Statistical Analysis**

The relationship between standardized yearly rates of mortality and hospitalization per 1000 persons and the numbers of (30-day) prescriptions per 1000 persons was examined. The analysis examined quarterly data from 1996 to 2003 for hospitalization and from 1992 to 2003 for mortality, which was based on availability of data. This analysis was designed to assess the association between the changes in prescriptions and the changes in mortality and hospitalization in Canada. In each case, the standardized mortality or hospitalization rate was regressed against prescription rates for total antihypertensive prescriptions, adjusting for seasonal variation. Residual errors were assumed to follow an autoregressive moving average model. All of the computations were programmed in the R-project implementation of the S language.

**Time Series Analysis**

The times series analysis was conducted to determine whether there was a difference in rates of mortality and hospitalization after 1999 when the CHEP program started. Estimates and CIs for percentage changes in rates were based on times series models for logarithmically transformed data. All of the models included systematic components for periodic calendar variation plus a segmented “switching” linear regression (switching at January 1999, when the CHEP program was initiated). Residual errors were modeled as autoregressive moving average processes. Graphic inspection of residuals revealed no systematic departures from assumptions, except for hospitalizations for AMI. Nonparametric fits of trends were plotted in Figures 2 and 4 using fourth-order splines.

**Results**

The adult Canadian population aged ≥20 years (excluding the territories) increased from 21.6 million in 1996 to 23.7 million in 2003, a 9.7% increase. As reported previously, there were large increases in antihypertensive prescriptions between 1996 and 2003 (Figure 1).6,11 Total annual antihypertensive drug prescriptions increased from 56.6 million to 104.3 million between 1996 and 2003, an 84.4% increase (Table 1). Using the data from the NPHS and the CCHS conducted over this time period, we estimated that, in Canada between 1996 and 2003, there was a 65.1% increase in the number of individuals diagnosed with hypertension (from 2.7 million in 1996 to 4.4 million in 2003) and a 77.0% increase in the number of individuals being treated with antihyperten-
Table 1. Crude Unadjusted Number of Stroke, HF, and AMI Deaths and Hospitalizations, Number of Antihypertensive Prescriptions, and Adults Diagnosed and Treated for Hypertension in Canada 1996, 1999, and 2003

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<td>HF (death)</td>
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Discussion

In developed countries, cardiovascular diseases attributed to hypertension are the leading causes of mortality and hospitalization and major contributors to healthcare costs. In Canada, considerable effort has been made to improve the treatment and control of hypertension. A population survey from Ontario, Canada (where a third of the population of Canada resides), found a very large improvement in the rate of treatment and control of hypertension (from 12% in 1992 to 66% in 2006). Between 1996 and 2003, we witnessed an 84.4% increase in antihypertensive prescriptions in Canada, accompanied by large reductions in mortality rates from stroke, HF, and AMI, on which time series analyses appeared to be related to the upswing in antihypertensive prescribing, particularly after initiation of the CHEP in 1999. Similarly, there were substantial reductions in the rates of hospitalization from stroke and HF. These correlations are plausibly related to the upswing in antihypertensive prescriptions because of the benefit of antihypertensive therapy, as demonstrated in randomized trials.

Large decreases in cardiovascular events initially followed the introduction and widespread use of antihypertensive drugs in the 1970s and 1980s. Previously, Klungel et al. also found similar-to-expected reductions in stroke in a cohort of hypertensive patients from The Netherlands by comparing treated and untreated patients with similar baseline characteristics. The large increase in the treatment of hypertension over a short time period is likely the reason why our study found a strong relationship, whereas other national studies have not. To our knowledge, this is the first study that has been able to statistically associate increased antihypertensive therapy with decreased cardiovascular disease on a national scale and the improvement in outcomes with the start of a national effort to improve hypertension management.

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There are several limitations to the analyses that we conducted. For example, secular changes in the management of cardiovascular events, as well as the prevalence and management of cardiovascular risk factors other than hypertension, could in part explain our findings. However, in Canada there were linear increases in the prevalence of obesity (from 11.9% to 14.9% for body mass index >30) and diabetes mellitus (from 3.2% to 4.6%) between 1996 and 2003, suggesting that, if anything, underlying cardiovascular risk of the Canadian population likely increased modestly over that time frame. Changes in data on leisure-time physical activity and smoking data in Canada favor reduced cardiovascular risk. However, these risks change at a relatively constant rate and, therefore, are likely to contribute to the overall reduction in events from 1996 to 2003 but are unlikely to contribute to the marked change in cardiovascular rates in 1999. Although there has been a large increase in “statin” prescriptions in Canada between 1996 and 2001, the magnitude of its increase has been approximately one-third the magnitude of the increase in antihypertensive therapy, and the changes were linear over time and, therefore, also unlikely to be associated with a large change in cardiovascular event rates in 1999. There are no national data available on aspirin use in Canada; however, we are not aware of Canadian programs to promote aspirin use starting in 1999. In addition, hypertension has consistently been identified as the strongest cardiovascular risk factor, particularly for stroke and HF. In addition, this study relied on administrative databases to extract outcomes, and between 1996 and 2003 there have been changes in the coding of Canadian administrative data from ICD-9-Clinical Modification to ICD-10; however, the ICD-9-Clinical Modification and ICD-10 codes that we used have been shown to accurately identify in these databases the events that we focused on in this study (stroke, HF, and AMI).

The reasons for the lack of decline in hospitalization for AMI in Canada after CHEP are unclear, because treatment of hypertension prevents AMI. The use of more sensitive methods of diagnosing myocardial damage, ie, using troponin levels, may account for some of the increase in hospitalization for myocardial infarction seen in the late 1990s. It is also possible that treatment of hypertension may have resulted in less severe myocardial infarctions, resulting in fewer deaths and more survivors who were subsequently hospitalized. Finally, other risk factors, such as dyslipidemia, are

Figure 2. Mortality rates from stroke (A), HF (B), and AMI (C) in Canada from 1992 to 2003. The dark line is linear modeling for 1992–1998 and 1999–2003, and the dotted line is a nonparametrically modeled line.

Figure 3. Age- and sex-adjusted mortality rates from stroke (s), HF (c), and AMI (a) in relationship to total antihypertensive prescriptions in Canada between 1996 and 2003. Antihypertensive prescriptions were expressed in 30 day prescriptions per person per year.

Figure 4. Annual Rate per 10,000 Total antihypertensive prescriptions (30 day prescriptions per person-year)
more important attributable risks for AMI than hypertension; hence, the lack of association may be because of changes in these confounding risks.40

The United States has had one of the highest rates of awareness treatment and control of hypertension of any nation.45,46 The high rates of treatment and control and improvement in cardiovascular disease rates have been attributed to the National High Blood Pressure Education Program,9 which was initiated in the 1970s. Our finding of clear time-associated reductions in cardiovascular disease that are associated with increased prescriptions of antihypertensive treatment are consistent with observations after the initiation of the National High Blood Pressure Education Program.31 More recently, the United Kingdom has provided specific funding to primary care practices for achieving target blood pressures,10,47 leading to marked increases in the rate of treatment and control of hypertension.10,47

In Canada, the introduction of a national healthcare professional education program lead by healthcare professional and scientific organizations and run by volunteers was associated with large and rapid changes in the diagnosis and treatment of hypertension and with large decreases in cardiovascular death and hospitalization. Although there are many confounders that limit our ability to make a definitive cause-effect conclusion, our data do support the hypothesis that the improved hypertension control seen after initiation of the CHEP contributed to improved cardiovascular outcomes in Canada between 1996 and 2003. Continued increases in antihypertensive prescriptions in Canada up to 2007 suggest that more substantive improvements in the control of hypertension and a reduction in complications have occurred.48 The CHEP educational model for improving health care could be adopted by other countries.

Perspectives

A barrier to developing comprehensive national programs to improve the management of hypertension and other chronic conditions may be the lack of real world evidence that clinical trial data can be translated into health benefits for the population. The CHEP is a comprehensive program designed to improve hypertension management. Our analysis confirms that rapid increases in the treatment of hypertension in the Canadian population were closely associated with a rapid and extensive reduction in cardiovascular events and with the start of the CHEP. The results support calls by the World Health Organization to develop national programs to prevent cardiovascular disease through improved hypertension management.


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<th>Event</th>
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<th>Hospitalization, Mean (95% CI)</th>
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<td>Stroke</td>
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<td>–4.8 (–5.6 to –4.1)</td>
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<td>–3.0 (–3.7 to –2.2)</td>
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<tr>
<td>HF</td>
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<td>–4.8 (–6.2 to –3.5)</td>
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<td>–4.3 (–5.7 to –2.9)</td>
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<tr>
<td>AMI</td>
<td>–3.7 (–4.5 to –2.8)</td>
<td>–5.8 (–6.7 to –4.9)</td>
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<td>–2.1 (–3.0 to –1.3)</td>
<td>–1.5 (–3.3 to 3.5)</td>
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<td>Units are the change in yearly decrease (%)</td>
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Campbell et al Antihypertensive Treatment Reduces Vascular Events 133
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Figure 5. Age- and sex-adjusted hospitalization rates from stroke (s), HF (c), and AMI (a) in relationship to total antihypertensive prescriptions in Canada between 1996 and 2003. Antihypertensive prescriptions were expressed in 30-day prescriptions per person per year.

Acknowledgments
We thank Dr. Hude Quan for assistance in writing the article. We also thank the >100 volunteers of the CHEP program (see www.hypertension.ca for membership) who help develop the hypertension management recommendations, assist in transforming the recommendations to be relevant to their disciplines, and aid in dissemination and detailing the recommendations in their communities, and assist in developing mechanisms for evaluating the impact of the recommendations.

Disclosures
N.R.C.C. has received honoraria for advising and speaking from most major pharmaceutical companies that produce antihypertensive drugs in Canada. The other authors do not have conflicts of interest.

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