

# Trends in cardiovascular drug utilization and drug expenditures in Canada between 1996 and 2001

Cynthia A Jackevicius BScPhm MSc FCSHP<sup>1,2,3</sup>, Karen Tu MD MSc<sup>1,2,3,4</sup>,  
Woganee A Filate MHSc<sup>2</sup>, Susan E Brien PhD<sup>2</sup>, Jack V Tu MD PhD<sup>2,3,5</sup>  
for the Canadian Cardiovascular Outcomes Research Team

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**BACKGROUND:** There is increasing interest in studying trends in drug utilization because drug costs are the fastest growing sector of the health care system.

**OBJECTIVES:** To focus on the trends in the utilization of and expenditures for cardiovascular drugs in Canada by drug class and by province over a six-year period.

**METHODS:** Data from the IMS Health Canada CompuScript Audit database were used for this study from the period of February 1996 to January 2002. Patterns of drug utilization and expenditures in Canada were described for cardiovascular drug classes, individual agents within classes and by provincial analyses.

**RESULTS:** Substantial increases in both the utilization of and the expenditures for cardiovascular medications have occurred in Canada over the last six years. Newer medication classes such as angiotensin converting enzyme inhibitors and statins now comprise the majority of cardiovascular drugs prescribed, along with continued high use of diuretics. Increases in some drug classes, such as angiotensin converting enzyme inhibitors, statins and beta-blockers, appear to be based on trial evidence or guidelines. However, marketing may play a larger role in the increases in use of angiotensin receptor blockers and specific drugs, such as amlodipine besylate and atorvastatin, because their increased utilization cannot be explained by major clinical trial evidence and/or practice guidelines.

**CONCLUSIONS:** Changes in patterns of cardiovascular drug utilization and expenditures in Canada may be associated with clinical trial evidence, clinical practice guidelines, policy changes and/or marketing initiatives.

**Key words:** *Drug utilization; Heart disease; Medication; Practice pattern*

Cardiovascular disease (CVD) remains the leading cause of premature death and disability in Canada in men and women, representing a major societal and population burden (1). Primary and especially secondary prevention of CVD with medications have been emphasized in Canadian practice guidelines to prevent future adverse cardiac events and

## Médicaments à action cardiovasculaire et dépenses en médicaments : tendances au Canada entre 1996 et 2001

**CONTEXTE :** L'étude des tendances quant à l'utilisation des médicaments suscite de plus en plus d'intérêt étant donné que le coût des médicaments est le secteur du système de soins de santé qui connaît la plus forte croissance.

**OBJECTIF :** Étudier les tendances en ce qui concerne l'utilisation des médicaments à action cardiovasculaire au Canada et les dépenses qui y sont liées selon la classe de médicaments, par province, sur une période de six ans.

**MÉTHODE :** Pour ce faire, nous avons eu accès à la base de données d'IMS Health Canada CompuScript Audit pour la période de février 1996 à janvier 2002. Les données sur l'utilisation des médicaments au Canada et les dépenses liées à leur achat étaient divisées par classe de médicaments à action cardiovasculaire, par médicament et par province.

**RÉSULTATS :** Nous avons relevé une augmentation importante et de l'utilisation des médicaments à action cardiovasculaire et des dépenses en la matière au Canada au cours des six dernières années. Les nouvelles classes de médicaments comme les inhibiteurs de l'enzyme de conversion de l'angiotensine (ECA) et les statines constituent maintenant la majorité des médicaments à action cardiovasculaire prescrits, auxquelles s'ajoutent les diurétiques dont l'utilisation reste élevée. Les augmentations dans certaines classes de médicaments, par exemple les inhibiteurs de l'ECA, les statines et les bêta-bloquants, semblent liées à des résultats d'essais cliniques et à des lignes directrices. Toutefois, la commercialisation pourrait jouer un rôle plus important dans l'augmentation de l'utilisation des antagonistes des récepteurs de l'angiotensine et de certains médicaments comme l'amlodipine, le bésylate et l'atorvastatine étant donné que l'accroissement de la demande ne s'explique pas par des résultats d'essais cliniques importants ou des lignes directrices en matière de pratique.

**CONCLUSION :** Les nouvelles tendances en ce qui concerne l'utilisation des médicaments à action cardiovasculaire au Canada et aux dépenses qui y sont liées peuvent être attribuables à des résultats d'essais cliniques, à des lignes directrices en matière de pratique, à des changements de politique ou encore à des initiatives de commercialisation.

mortality. Several clinical trials that have been published in the last six years provide strong evidence to support the routine use of several classes of prescription drugs. Recent evidence from the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial, published in 1998 (2), and the Heart Protection Study, published in 2002 (3), provides additional

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<sup>1</sup>University Health Network, Toronto; <sup>2</sup>Institute for Clinical Evaluative Sciences, Toronto; <sup>3</sup>University of Toronto, Toronto; <sup>4</sup>Department of Family and Community Medicine, University of Toronto, Toronto, Ontario; <sup>5</sup>Division of General Internal Medicine, Sunnybrook and Women's College Health Sciences Centre, Toronto;

Correspondence and reprints: Ms Cynthia Jackevicius, Pharmacy Department, University Health Network – Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, e-mail [cynthia.jackevicius@uhn.on.ca](mailto:cynthia.jackevicius@uhn.on.ca)

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strong support for the use of statins in a wide variety of patients with CVD. Substantial clinical evidence has accumulated now to support the use of beta-blockers in congestive heart failure patients with the publication of the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) (4), the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study (5), the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) (6) and the carvedilol trials (7). The publication of the Heart Outcomes Prevention Evaluation (HOPE) trial (8), which used ramipril for the prevention of cardiac events in high-risk patients, expanded the potential use of angiotensin converting enzyme inhibitors (ACEIs) to a very broad population, in contrast to previous disease-specific evidence in acute myocardial infarction (AMI), diabetic nephropathy, nondiabetic renal disease, hypertension and congestive heart failure (8-10).

Several Canadian and American cardiovascular guidelines have also been published in the last six years, which may impact cardiovascular drug use in Canada. Guidelines for AMI support the chronic use of acetylsalicylic acid, beta-blockers, ACEIs and statins (11,12). Guidelines for congestive heart failure recommend routine use of ACEIs and beta-blockers, and in those with severe heart failure, spironolactone and/or digoxin (13,14). Hypertension guidelines, which traditionally recommended relatively cheaper diuretics and beta-blockers as first-line therapies, have more recently revised their recommendations, based on recent trials, to include more expensive ACEIs and calcium antagonists as possible first-line agents (15,16). There is also an increasing trend for recommending combination therapy if there is only a partial response to monotherapy, compared with previous recommendations of switching to alternative monotherapy if the initial treatment was only partially effective (15). Guidelines for the management of dyslipidemia have specifically recommended the use of statins for many groups of patients at high and very high risk of heart disease, even without elevated lipid levels (17,18).

Another factor that may impact cardiovascular drug use in Canada is the change in the population over time. From 1996 to 2001, the median age of Canadians increased by 2.3 years, from 35.3 years to 37.6 years, reaching an all-time high. This increasing age is due to the decline in the birth rate, the ageing population, and particularly, the ageing of the baby boomer segment of the population. Between 1991 and 2001, the population aged 45 to 64 years increased by 36%, due to the baby boomers entering into this age group. With this large segment of the population ageing, an increase in the use of cardiovascular drugs is likely as this group develops heart disease (19).

The objective of the present study is to focus on the trends in the utilization of and expenditures for cardiovascular drugs in Canada by drug class, province, and in relation to the changes in new clinical trial evidence and guideline information over a six-year period. This information is not disease-specific, but reflects overall rates and illustrates trends in changes over time in utilization of drug classes and individual drugs in the treatment of cardiovascular disease.

## METHODS

### Data sources

Data from the IMS Health Canadian database was used for this study. IMS Health Canada's CompuScript Audit database (IMS Health Canada, Canada) is a source of prescription data obtained by measuring, through an audit, the number and value

of prescriptions dispensed by retail pharmacies throughout Canada.

The target population comprises close to 6800 retail outlets (pharmacies) across Canada. The sampling design used is stratification. The retail outlet population is stratified by province, type of outlet (independent or affiliated with a chain) and size (small or large). Sample stores are selected from over 4400 reporting stores by applying a variety of criteria regarding such characteristics as prescription type and volume, consistency of reporting and payment type. This represents about two-thirds of all retail pharmacies in Canada. Data for the audit are collected monthly by electronic means from the sample comprising approximately 2800 drug stores distributed proportionally within each strata. An additional control is conducted to ensure good representation from the various chains of stores. After passing through various quality control checks, the sample data are projected to the universe in each province and provincial totals are summed to provide a national estimate. Maximum overlap between the waves is maintained to ensure increased reliability of the projected trends from one period to another. The estimator used is the Horvitz-Thompson estimator.

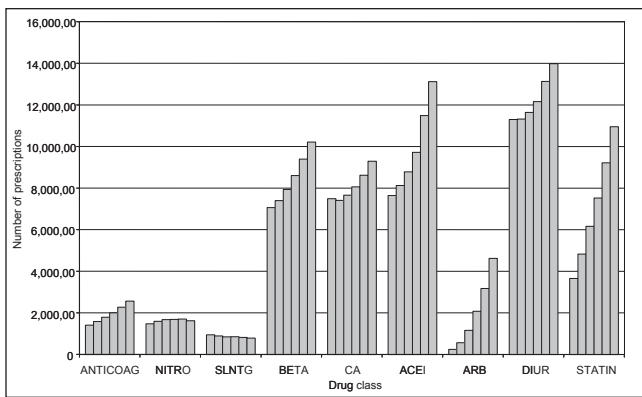
The data collected can be used to ascertain prescription volume by product (or class) and the market share for trending purposes, providing a measure of product utilization. Also available is the cost of the prescription as dispensed (including all mark-ups and the pharmacist's professional fee). IMS Health Canada has drug utilization data for a 72-month period. This study included data from the period of February 1996 to January 2002. IMS Health Canada does not measure population-wide, patient-specific data. However, measuring a large sample of pharmacies and extrapolating the data to the overall population generates estimates of drug utilization in each province.

### Statistical analysis

Descriptive statistics were used to report on the data for cardiovascular drug utilization. The utilization of cardiovascular drug classes described include beta-blockers, calcium antagonists, statins, ACEIs, angiotensin receptor blockers (ARBs), diuretics, nitroglycerin and oral anticoagulants. For each class of drugs, the trends are described by number of prescriptions and total cost of prescription claims (as extrapolated to the total population). The utilization of drugs was summarized nationally and for each province by month and year (1996 to 2001). National monthly utilization data, by province and by agent within each class were used to generate figures illustrating the changes in the trends for each drug class over the six-year study period. Absolute changes in drug utilization and expenditures were assessed, as well as the relative per cent changes in these parameters. For combination products of beta-blockers, ACEIs or ARBs with diuretics, these products were included in the total numbers for the single entity drug product.

## RESULTS

The national pattern of cardiovascular drug utilization is shown in Figure 1 and trends in drug expenditures in Figure 2. Figure 1 shows that utilization of all cardiovascular drug classes is increasing, with the exception of nitroglycerin, for which utilization remains flat. The top three prescribed cardiovascular drugs in Canada are diuretics, ACEIs and statins, with the largest increase in usage seen with statins over the time period of the study. Figures 2 and 3 show increasing expenditures for cardiovascular drugs over time, with substantial increases in the expenditures for statins, ACEIs and ARBs. The remaining drug classes show stable expenditures, including classes of



**Figure 1)** Yearly national number of prescriptions by drug type from 1996 to 2001. Data from IMS Health Canada. Each bar represents the total number of prescriptions of the particular drug type in a year (February 1 to January 31; 1996-2001). ACEI Angiotensin converting enzyme inhibitor; ANTICOAG Anticoagulants; ARB Angiotensin receptor blocker; BETA Beta-blocker; CA Calcium antagonist; DIUR Diuretic; NITRO Nitroglycerin; SLNTG sub-lingual nitroglycerin

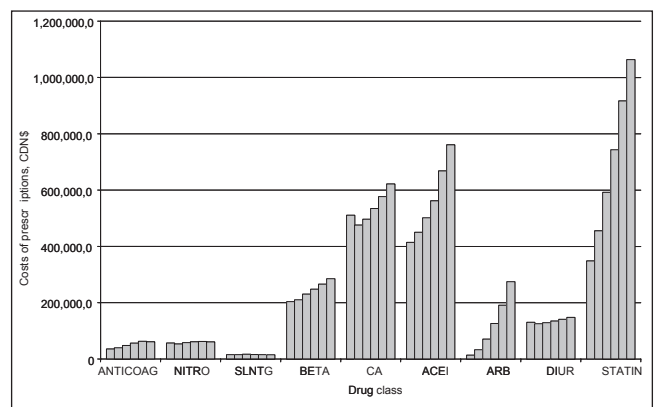
relatively high utilization but relatively low cost medications, such as diuretics and beta-blockers. While the calcium antagonists are the fifth highest drug class by utilization, they are the third highest drug class by cost. The total cardiovascular drug expenditure in Canada has more than doubled over the six-year study period.

Table 1 shows the utilization of drug classes per 100,000 population per year by province. When adjusted by population, utilization of several drug classes is highest in the province of Quebec. Diuretics remain the most commonly used cardiovascular drugs in each individual province, with the exception of Newfoundland and Labrador and Prince Edward Island, where ACEIs slightly surpass the utilization rate of diuretics. In most provinces, ACEIs are the second most commonly used cardiovascular drugs, with beta-blockers as the third most frequently used agent. In a few provinces, this order is reversed. Of note, calcium antagonists are the third most commonly used cardiovascular drug in Quebec, Ontario and Manitoba. A gradient appears to exist for many drugs, with higher utilization in Eastern Canada.

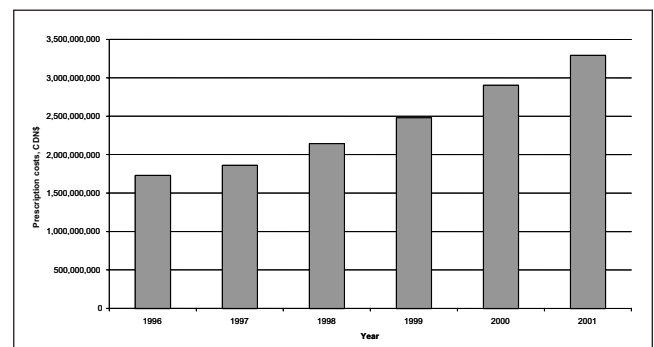
Table 1 also shows the drug utilization ratio for each drug class between the province with the highest number of prescriptions and the province with the lowest number of prescriptions. This ratio is as high as 5.41 for the newer drug class of ARBs, and as low as 2.13 and 2.21 for more established drugs such as anticoagulants and sublingual nitroglycerin (SLNTG), respectively.

Table 2 shows the cardiovascular drug expenditures per 100,000 population per year by province. Similar to utilization, the drug expenditures are higher per population in Quebec than in the other provinces. However, the specific drug classes that comprise the highest costs are different than the most frequently used cardiovascular drugs. ACEIs, statins and calcium antagonists make up the top three cardiovascular drugs by cost for all of the provinces.

Utilization within each cardiovascular drug class was determined to detect trends in utilization of the specific agents. In general, the utilization patterns are consistent with the patterns for expenditures of the drugs. Data on the utilization patterns is presented in the following section.



**Figure 2)** Yearly national drug prescription costs by drug type from 1996 to 2001. Data from IMS Health Canada. Each bar represents the total number of prescriptions of the particular drug type in a year (February 1 to January 31; 1996-2001). ACEI Angiotensin converting enzyme inhibitor; ANTICOAG Anticoagulants; ARB Angiotensin receptor blocker; BETA Beta-blocker; CA Calcium antagonist; DIUR Diuretic; NITRO Nitroglycerin; SLNTG sub-lingual nitroglycerin



**Figure 3)** Total national drug expenditures in Canada by year, from 1996 to 2001. Data from IMS Health Canada

Figure 4 demonstrates the changes in the absolute per cent increase of the individual agents within the ARB class. Losartan remains the most commonly utilized ARB, followed closely by irbesartan. However, it is the newer agents, irbesartan, candesartan cilexetil and valsartan, that have the highest relative increase in utilization rates, while relative utilization increases in losartan potassium have not been as high since December 1998.

ACEI utilization patterns are illustrated in Figure 5, where there were large absolute increases in the rates of utilization of ramipril, as compared with the other agents within the class, with a decline in the utilization of enalapril maleate. The newer agents, such as cilazapril and quinapril, had the largest relative per cent increases in utilization (data not shown), representing growth in the use of these new agents.

Figure 6 shows the changes in statin use over the study period. It was found that the increase in the absolute use of atorvastatin dwarfs the smaller increases in the utilization of simvastatin and pravastatin sodium. Of note, there was a continual increase in the use of cerivastatin from April 1998 until August 2001, when it was abruptly withdrawn from the market due to the increased risk of rhabdomyolysis. There was also a continued decline in the use of the first available statin, lovastatin.

**TABLE 1**  
Average number of cardiovascular drug prescriptions per 100,000 population\* per year by province, from 1996 to 2001

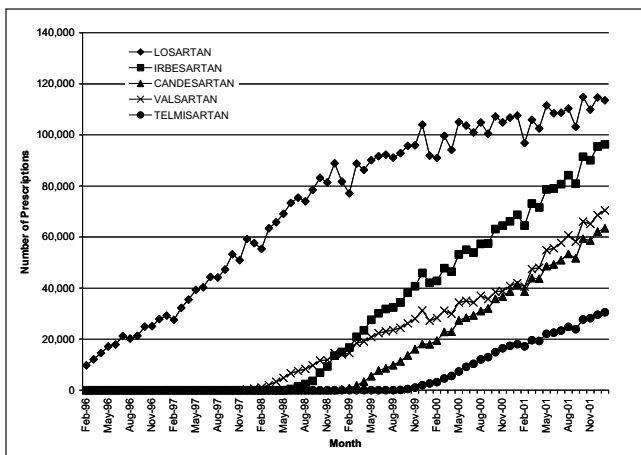
Province	Drug Class								
	Anticoag	NITRO	SLNTG	BETA	CA	ACEI	ARB	DIUR	STATIN
NL/PEI	5398	8655	3051	41,401	29,707	55,751	3186	55,053	19,847
Nova Scotia	5196	9213	3032	39,749	29,578	36,949	6284	47,358	21,298
New Brunswick	5627	8915	2450	33,461	28,946	33,459	2620	42,178	21,112
Quebec	9343	8536	3290	45,126	44,722	44,141	13,139	61,986	42,585
Ontario	4850	3470	2977	20,654	20,739	25,899	3437	29,329	17,402
Manitoba	5484	4899	2768	20,961	21,280	31,360	6466	35,777	16,837
Saskatchewan	9158	5517	2141	28,284	27,363	43,628	8329	64,898	16,995
Alberta	5304	3246	1488	14,259	13,884	21,815	5048	25,860	11,614
British Columbia	4383	3157	1801	14,762	12,691	19,864	2428	23,584	10,883
Ratio highest/lowest†	2.13	2.92	2.21	3.16	3.52	2.81	5.41	2.75	3.91

Data from IMS Health Canada. \*Population data from 2001 Statistics Canada Census (19). †Ratio highest/lowest is the ratio of drug class utilization between the provinces with the highest number of prescriptions and the province with the lowest number of prescriptions. ACEI Angiotensin converting enzyme inhibitor; Anticoag Anticoagulants; ARB Angiotensin receptor blocker; Beta Beta-blocker; CA Calcium antagonist; Diur Diuretic; Nitro Nitroglycerin; NL Newfoundland and Labrador; PEI Prince Edward Island; SLNTG sub-lingual nitroglycerin

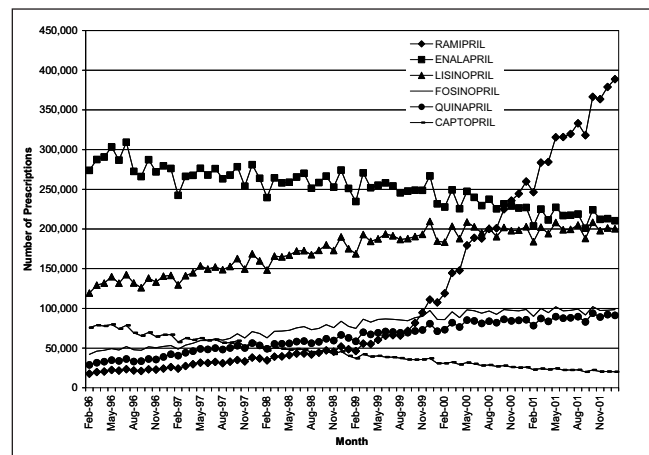
**TABLE 2**  
Average cost of cardiovascular drug prescriptions per 100,000 population\* per year by province, from 1996 to 2001

Province	Drug Class								
	Anticoag (CND\$)	NITRO (CND\$)	SLNTG (CND\$)	BETA (CND\$)	CA (CND\$)	ACEI (CND\$)	ARB (CND\$)	DIUR (CND\$)	STATIN (CND\$)
NL/PEI	159,696	311,954	47,534	1,031,535	1,668,410	2,643,852	182,020	586,177	1,577,853
Nova Scotia	173,548	345,004	59,895	1,279,546	2,119,290	2,226,540	431,599	568,162	2,250,880
New Brunswick	182,242	355,433	52,109	1,045,867	1,965,677	2,009,004	175,788	480,003	2,155,446
Quebec	170,822	253,028	58,985	964,085	2,035,359	1,623,565	564,635	602,273	2,766,204
Ontario	144,378	148,894	55,535	731,362	1,860,122	1,947,976	298,523	366,163	2,370,654
Manitoba	143,991	161,532	34,397	563,985	1,236,566	1,594,448	369,782	354,906	1,509,287
Saskatchewan	231,646	164,383	38,967	605,067	1,375,899	1,841,794	408,783	617,306	1,171,891
Alberta	166,105	127,492	29,965	491,803	1,141,664	1,477,346	403,766	349,208	1,420,730
British Columbia	164,322	146,519	36,172	567,827	1,108,289	1,459,680	216,296	250,958	1,529,174

Data from IMS Health Canada. \*Population data from 2001 Statistics Canada Census (19). ACEI Angiotensin converting enzyme inhibitor; Anticoag Anticoagulants; ARB Angiotensin receptor blocker; Beta Beta-blocker; CA Calcium antagonist; Diur Diuretic; Nitro Nitroglycerin; NL Newfoundland and Labrador; PEI Prince Edward Island; SLNTG sub-lingual nitroglycerin



**Figure 4)** Change in angiotensin receptor blocker prescriptions in Canada, from 1996 to 2001. Data from IMS Health Canada. Note: Data for eprosartin is not shown; it entered the Canadian pharmaceutical market in January 2001



**Figure 5)** Change in angiotensin converting enzyme inhibitor prescriptions in Canada, from 1996 to 2001. Data from IMS Health Canada. Note: Data from benazepril, cilazapril, perindopril and trandolapril are not shown due to low rate of use

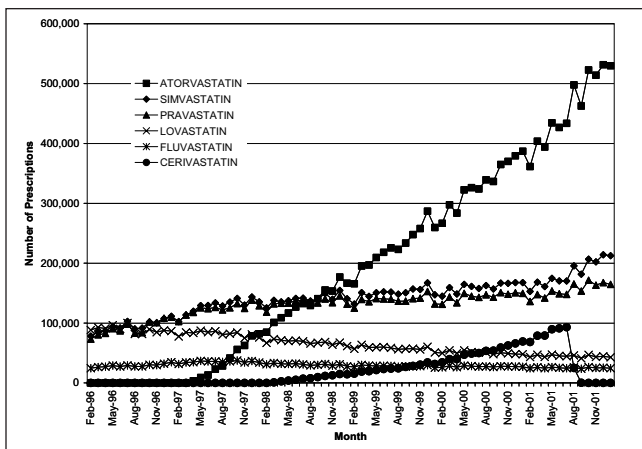


Figure 6) Change in statin prescriptions in Canada, from 1996 to 2001. Data from IMS Health Canada

Figure 7 illustrates the absolute changes in beta-blocker utilization over time, with atenolol and metoprolol tartrate showing, by far, the largest market share and the largest continual increases in utilization rates. The newer beta-blockers, those prescribed mainly for use in heart failure (carvedilol and bisoprolol fumarate), have the largest relative increases in use over time but comprise very little of the overall market share.

Figure 8 illustrates the changes in utilization patterns of calcium antagonists. Amlodipine mesylate utilization was substantially increased during the study period and there were slight decreases in the utilization of nifedipine and diltiazem hydrochloride.

## DISCUSSION

The present study shows that utilization and expenditures of cardiovascular drugs in Canada have steadily increased over the six-year period. The major increases in utilization and expenditures have been with the newer drug classes: the ACEIs and the statins. However, the most frequently used cardiovascular drug class in Canada remains the diuretics. There has been no significant decrease in utilization of any cardiovascular drug class. Therefore, there is an absolute increase in the overall utilization of cardiovascular drugs in Canada. This increase translates into a more than doubling of the total expenditure for cardiovascular drugs in the country from 1996 to 2001 alone. Many of these medications improve outcomes and may temporarily decrease resource utilization in other sectors of the healthcare system, such as hospital admissions. Increases of these particular medications known to have these benefits may be seen as an advance in the healthcare of Canadians. However, this rapid increase in drug utilization, particularly of those drugs not known to improve outcomes, is probably not sustainable for drug plans and solutions need to be found to manage these drug utilization increases.

There are several plausible reasons for the increase in drug utilization over this time period. Many new clinical trials have provided evidence, supported in recent clinical practice guidelines, in support of the use of diuretics, statins, ACEIs, beta-blockers and calcium antagonists in cardiac patients (2-18). In addition, due to the ageing population, there may be

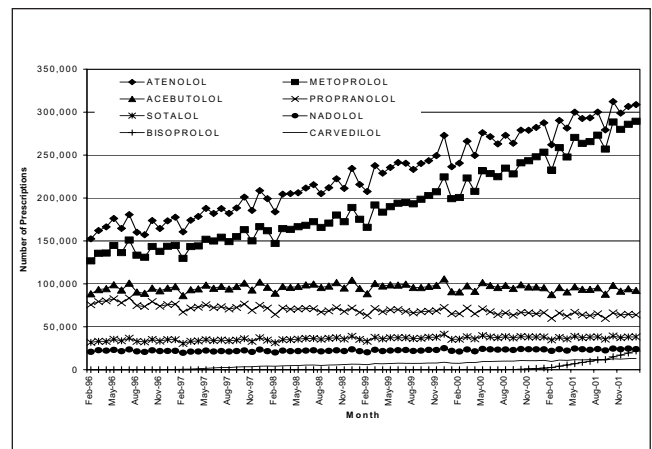


Figure 7) Change in beta blocker prescriptions in Canada, from 1996 to 2001. Data from IMS Health Canada. Note: Data from esmolol is not shown as it is delivered intravenously; data for oxprenolol is not shown as it was removed from the Canadian pharmaceutical market 1999-08-04; data for labetalol, pindolol and timolol are not shown as they have very low use

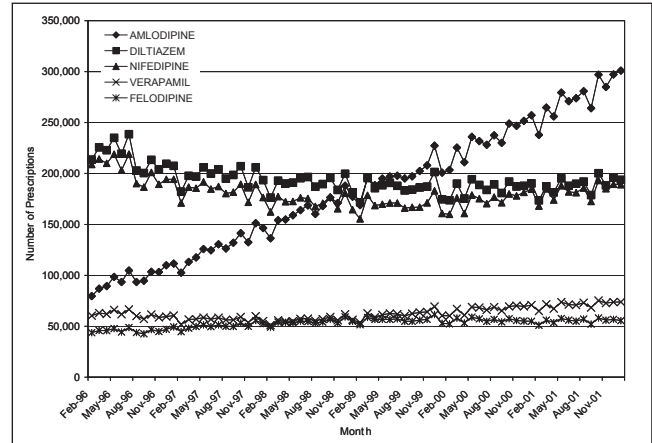


Figure 8) Change in calcium antagonists prescriptions in Canada, from 1996 to 2001. Data from IMS Health Canada. Note: Data from nifedipine is not shown as it has limited use for subarachnoid hemorrhage; data for incardipine is not shown as the drug was removed from the Canadian pharmaceutical market on July 19, 2001

more candidates for cardiovascular drug use as more of the population of Canada may develop, or be at risk for developing, heart disease (hypertension, dyslipidemia and diabetes) (19). Of note, although utilization of calcium antagonists is the fifth highest medication class, its expenditures are the third highest of the classes. Therefore, on a unit basis, calcium antagonists are relatively more expensive than the other new medication classes. Provincially, some similar patterns of both utilization and expenditure for the different drug classes exist; however, there are significant provincial variations in the top three cardiovascular medications used and their subsequent costs.

A large gradient in the magnitude of utilization and costs of cardiovascular drugs across the country was demonstrated. The ratio of the province with the highest use of the particular drug class to the province with the lowest use is as high as five for drugs such as ARBs, a class perhaps where evidence is less certain (Table 1). Ratios of utilization are lowest for classes such as anticoagulants and SLNTGs, drugs for which there is little

controversy about their use. However, there remains a large gradient between provinces in the magnitude of utilization, regardless of whether evidence-based cardiovascular drugs are being examined or not. The east-to-west gradient of drug utilization and costs may relate to the prevalence and burden of cardiac disease across the country. In previous *Canadian Journal of Cardiology* CCORT Atlas Papers, it was shown that hospitalization rates, risk factors and cardiovascular death rates from cardiovascular disease also follow an east-west gradient, being the highest in Newfoundland and Labrador and lowest in British Columbia (20-22). The parallel effect in cardiovascular drug use may very well be appropriate given the varying burden of heart disease across the country.

It is possible that some of the provincial differences reflect variations in drug reimbursement policies. In general, there is little difference between provinces with respect to the patients and medications covered in drug reimbursement policies. However, some differences do exist. One notable exception is with ARBs. Ontario and British Columbia require special procedures for access to ARBs, whereas these agents are included in general benefits in Quebec. These policies are mirrored in the rates of ARB use adjusted per population, with the highest use in Quebec and the lowest use in British Columbia and Ontario. In addition, the Reference Drug Program in British Columbia for ACEIs, calcium antagonists and nitrates (ie, SLNTG and nitroglycerin) may relate to British Columbia having the lowest rates of use of each for these drug classes compared with the other provinces. Since British Columbia has the lowest drug use in all drug categories, these policies only partially explain the differences. Other reasons for these interprovincial variations warrant further investigation.

The absolute use of ARBs is relatively low compared with other classes of agents. However, the sharp incline in the rate of use of ARBs since their introduction in 1996 is quite dramatic. This significant change in the market share of the ARB class is of particular interest because the only major studies to be published during this period were the Losartan Heart Failure Survival Study (ELITE II) (2000) (23) and the Valsartan Heart Failure Trial (Val-HeFT) (2001) (24), which demonstrated that ARBs were not superior in reducing mortality compared with ACEIs for the treatment of heart failure. While more recent evidence has been published about the renal protective effect of some ARBs, this was after the present study period (25). Clinical practice guidelines also did not emphasize the use of ARBs during this period, leaving this class as a second-line agent to ACEIs for heart failure and as a third-line agent for hypertension (13,15). Therefore, the substantial increase in the use of this class of medications demonstrated in the present study was not likely influenced by clinical trial evidence or guidelines, and most probably was secondary to marketing initiatives, and possibly, better tolerability of this class of medications compared with ACEIs for heart failure (23).

It is not surprising that ramipril had the largest increase in the market share in the ACEI class and is the ACEI with the greatest utilization, given the trial evidence in both post-AMI patients (Acute Infarction Ramipril Efficacy [AIRE], 1993) (26) and in general cardiovascular protection (HOPE, 2000) (8). However, there was a sharp increase in ramipril utilization starting from November 1999 when it was presented at the American Heart Association meeting in Atlanta (27). Details of the impact of the HOPE trial on ACEI prescribing in Ontario have been published elsewhere (28).

The present study found that atorvastatin is the statin with the largest market share and the greatest increase in drug utilization rates. Although it is the most potent statin for lowering total cholesterol, low-density lipoproteins and triglycerides, as described in the Comparative Study of HMG-CoA Reductase Inhibitor, Atorvastatin, Versus Equivalent Dose Strengths of Statins (CURVES) (1998) (29), it was not until the Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) trial was published in 2001 (30) that any clinical trial outcome data existed for atorvastatin. Yet, there was a striking increase in utilization apparent from its introduction to the market in April 1997. This increase in use and large market share for atorvastatin is in spite of the fact that simvastatin and pravastatin sodium have demonstrated mortality benefits from large clinical trials, and that pravastatin sodium is relatively less expensive than atorvastatin (2,3,31,32). The impact of the CURVES trial regarding lipid lowering potential, or the marketing efforts for this agent likely influenced its significant impact on utilization and market share within the statin medication class. Previous studies have illustrated the impact of the Scandinavian Simvastatin Survival Study (4S) on the utilization of statins in high-risk patients (33).

While clinical practice guidelines for hypertension and post-AMI continue to promote the use of beta-blockers, the major changes in beta-blocker evidence results from those trials conducted recently (1996 to 2001) in heart failure patients (MERIT, COPERNICUS, CIBIS-II and US carvedilol trials) (4-7). While it was found that the most commonly prescribed agents have remained atenolol and metoprolol tartrate, it is the newest agents, proven beneficial for heart failure, that had the largest relative increases in use. The increases in carvedilol use are apparent from November 1996 onward, and those for bisoprolol, from February 2001, both of which coincide with the publication of supportive clinical trial evidence for their use in heart failure.

Use of the calcium antagonist amlodipine besylate substantially increased over the study period. This is despite a paucity of clinical trial outcome data for this agent within the class or compared with other cardiovascular medication classes. Amlodipine besylate was studied for heart failure in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) 1 (published in 1996) (34) and PRAISE 2 (presented in 2000) (35) studies, and while results of PRAISE 1 appeared promising in a select group with nonischemic cardiomyopathy, the PRAISE 2 trial found no benefit. While long-acting calcium antagonists are now recommended as first-line agents for isolated systolic hypertension and no specific agent is recommended, the clinical trials on which this recommendation is based were not conducted with amlodipine besylate but were based on the Sys-Eur and Sys-China studies with nitrendipine and nifedipine (36,37). So concrete reasons for the substantial increase in the use of amlodipine besylate remain elusive, and the increase may simply be the result of strong marketing initiatives.

It is important to note that many medications, such as ACEIs for congestive heart failure and statins for coronary heart disease, are still underutilized despite the large increase in utilization found in the present study (33). Focusing on using prescribed feedback systems to increase the use of evidence-based medications over those without evidence of benefit must take precedence so that patient outcomes and population health are improved.

## INTERPRETIVE CAUTIONS

IMS Health Canada uses data collected from audits of prescriptions across Canada to describe general trends in drug utilization. These data do not provide us with exact drug utilization by individual patients or by individual providers to determine appropriateness of drug use. In addition, the data used for the analysis is not disease-specific, so it is not possible to extrapolate the appropriateness of utilization of certain medications based on individual disease states. While possible associations between clinical trial publication and the availability of clinical practice guidelines with the utilization patterns of specific medications or classes of medications were raised herein, definitive statements about causality (due to the observational nature of the data) cannot be made. Also, although increased drug utilization was demonstrated, the effects on patient outcomes were not examined. Other studies suggest outcomes are improving and this needs to be balanced against the increasing costs.

## CONCLUSION

The present study found that there were substantial increases in both the utilization of and the expenditures for cardiovascular drugs in Canada from 1996 to 2001. Newer drug classes such as ACEIs and statins now comprise the majority

of cardiovascular drug use, along with continued high use of diuretics. Increases in some drug classes, such as ACEIs, statins and beta-blockers appear to be based on evidence or guidelines (38). However, marketing may play a larger role in the increases in use of ARBs and of specific drugs, such as amlodipine besylate and atorvastatin, because their increased utilization does not appear to be associated with clinical trial evidence and practice guidelines. The causes of interprovincial variations in drug prescribing patterns and the cost effectiveness of the increase in drug expenditures remain to be determined.

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