

SPECIAL ARTICLE

Use of Ezetimibe in the United States and Canada

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ABSTRACT

BACKGROUND

Ezetimibe lowers low-density lipoprotein cholesterol, but current lipid-lowering guidelines in the United States and Canada do not recommend it as a first option for either primary or secondary prevention. We sought to describe the adoption of ezetimibe relative to that of other lipid-lowering agents and compare its use in the two countries.

METHODS

We conducted a population-level, cohort study using data from January 2002 to December 2006, provided by IMS Health, to describe prescribing practices and expenditures for lipid-lowering agents and ezetimibe in the United States and Canada.

RESULTS

From 2002 to 2006, the monthly number of prescriptions for lipid-lowering agents rose from 3719 to 7401 per 100,000 population in Canada and from 3927 to 6827 per 100,000 population in the United States. Of these prescriptions, the proportion for ezetimibe rose from 0.2% in 2003 to 3.4% in 2006 in Canada and from 0.1% in 2002 to 15.2% in 2006 in the United States. Statin use was relatively constant between 2002 and 2006 in Canada, whereas the proportion of statin prescriptions decreased from 86.5 to 80.8% in the United States. In 2006, the ratio of prescriptions for statins to those for ezetimibe was 26:1 in Canada and 5:1 in the United States. In 2006, expenditures for ezetimibe per 100,000 population were higher in the United States than in Canada by a factor of more than 4.

CONCLUSIONS

Distinct patterns of use of ezetimibe emerged in the United States and Canada from 2002 to 2006, a difference that markedly altered the approach to the treatment of hyperlipidemia in the United States. The U.S. pattern increased overall costs, but the effect on clinical outcomes is uncertain.

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THE JANUARY 2008 RELEASE OF RESULTS from the first major study of ezetimibe (the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression [ENHANCE] trial),^{1,2} which compared the effects of simvastatin with those of simvastatin plus ezetimibe on the progression of atherosclerosis, focused attention on the use of ezetimibe to lower cholesterol levels. Statins are the mainstay of lipid-lowering therapy, owing to the abundance of randomized trials supporting their effects in reducing morbidity and mortality, with low rates of intolerance.^{3,4} Unlike statins, ezetimibe (which was introduced as Zetia in the United States in October 2002, as Ezetrol in Canada in May 2003, and in combination with simvastatin [Vytorin] in the United States in July 2004) selectively inhibits the intestinal absorption of cholesterol, primarily lowering low-density lipoprotein (LDL) cholesterol. The drug reportedly has an acceptable side-effect profile.⁵⁻⁷

Given alone, ezetimibe reduces levels of LDL cholesterol by approximately 20%, whereas in combination with statins, it has a synergistic LDL-cholesterol-lowering effect.⁷ All three ezetimibe products are approved as monotherapy for primary hypercholesterolemia and homozygous familial hypercholesterolemia, and Zetia and Ezetrol are also approved for homozygous sitosterolemia and for primary hypercholesterolemia in combination with statins or fenofibrate.⁸⁻¹⁰

The approval of ezetimibe was based on its LDL-lowering effects, since information on its effect on the progression of atherosclerosis and clinical outcomes was not available.⁸⁻¹⁰ Accordingly, current lipid-lowering guidelines in the United States and Canada do not recommend ezetimibe as a first option for primary or secondary prevention.^{11,12} The ENHANCE study by Kastelein et al.² did not provide evidence that ezetimibe, as an adjunct to simvastatin, reduced the progression of atherosclerosis, as compared with simvastatin alone, even though ezetimibe was associated with the expected additional reduction in LDL cholesterol levels.

Despite the absence of data regarding clinical outcomes, ezetimibe was heavily promoted. According to Nielsen Monitor-Plus, more than \$200 million was spent on direct-to-consumer advertising for Vytorin alone in the United States in 2007, and sales recently eclipsed \$5 billion.¹³ In contrast, direct-to-consumer advertising of pre-

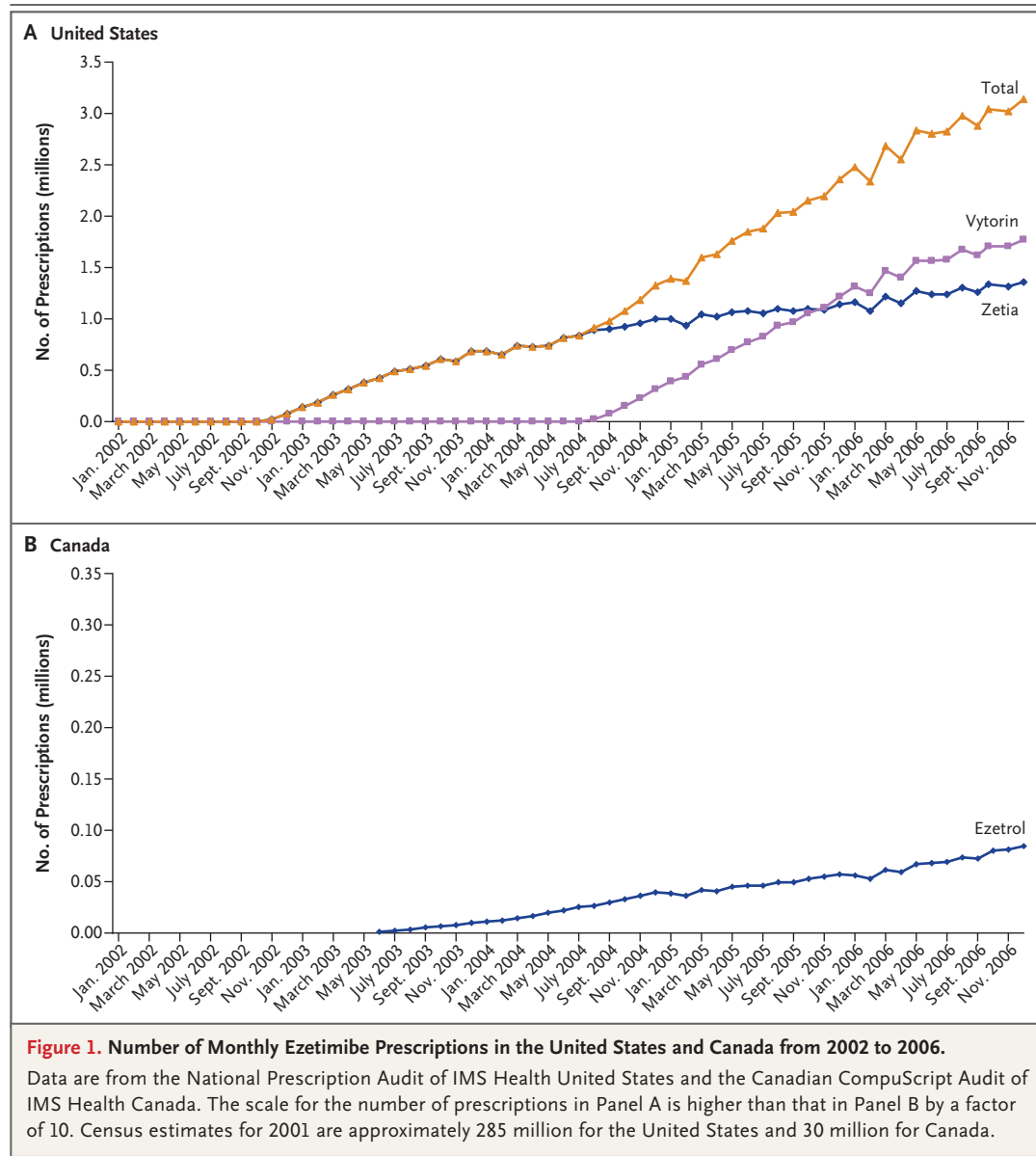
scription drugs is not permitted in Canada. In the context of guideline recommendations, what was the pattern of adoption of ezetimibe in the absence of evidence regarding clinical outcomes? Was the adoption pattern for ezetimibe specific to practice in the United States? Our objectives were to compare prescribing trends and expenditures for ezetimibe and other lipid-lowering agents in the United States and Canada. Canada represents a relevant comparison group, because although there are population similarities, there are critical market differences, particularly in drug promotion and product availability.

METHODS

STUDY DESIGN AND DATA SOURCES

We conducted a population-level, observational cohort study using data collected by IMS Health in the United States and Canada from January 2002 to December 2006 to describe the use of and expenditures for ezetimibe and other lipid-lowering agents. The sources of prescription data were the Canadian CompuScript Audit of IMS Health Canada and the National Prescription Audit of IMS Health United States, both of which measure the number of dispensed prescriptions and their cost to the consumer (product cost, markups, and pharmacist fees). The Canadian CompuScript Audit tracks numbers and costs of prescriptions filled by retail pharmacies in Canada, and the National Prescription Audit covers such data for prescriptions filled by retail, mail-order, and long-term care pharmacies in the United States.¹⁴

We obtained data on numbers and costs of prescriptions but did not have information on the characteristics of patients and prescribers. Data regarding pharmacy outlets were stratified according to region, type (independent, chain, mail order, or long-term care), and size of outlet. Sample stores were selected from the reporting stores by applying criteria such as prescription type and volume, consistency of reporting, and payment type and included approximately two thirds of pharmacies. Data were collected electronically from the sample consisting of drugstores and pharmacy outlets, distributed proportionally within each stratum. After passing through various quality-control checks and stability processes specific to the audits to ensure consistency and accuracy of the estimates, the sample data were projected to the population in each region, and



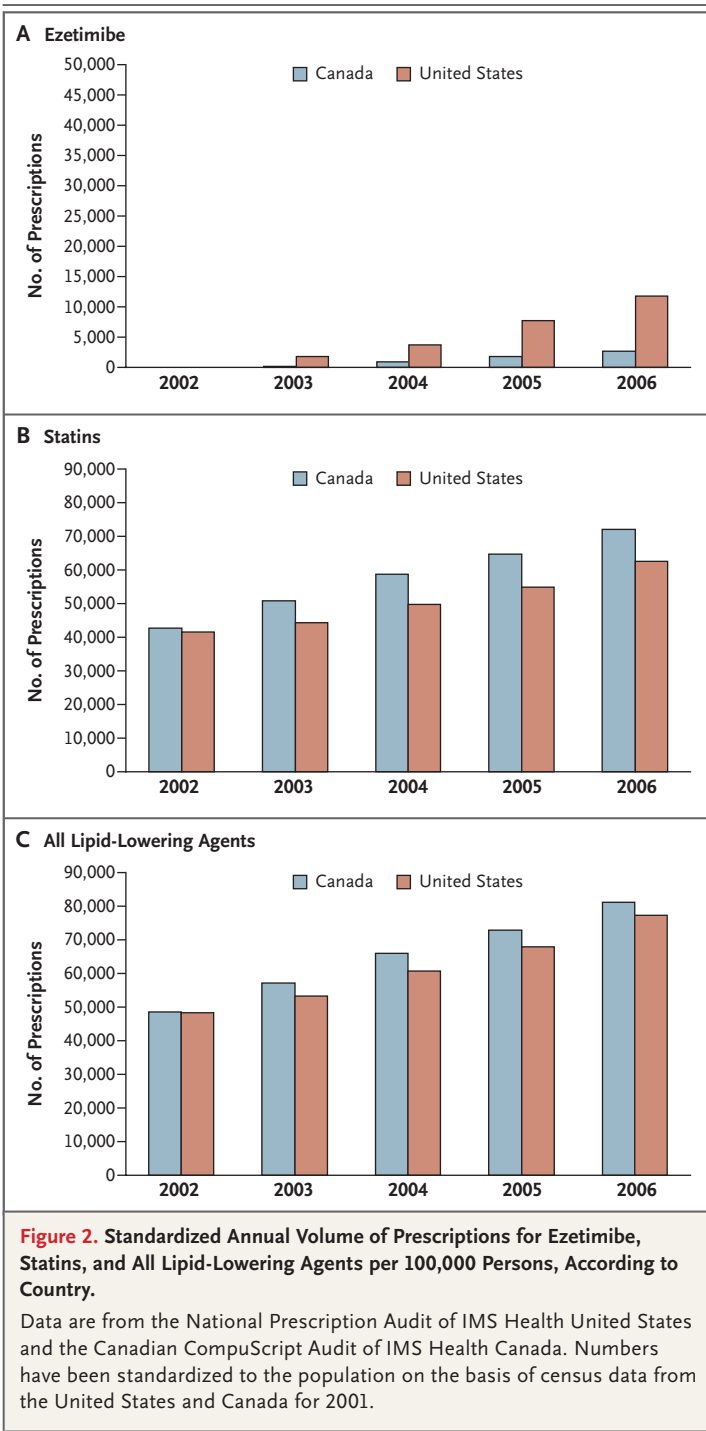
regional totals were summed to provide a national estimate.¹⁴⁻¹⁶ The study was approved by the institutional review board of the Western University of Health Sciences.

STATISTICAL ANALYSIS

The primary variables were the monthly number of prescriptions and expenditures for ezetimibe-containing products in the United States and Canada. Descriptive statistics were used to report on the number of prescriptions and costs of prescription claims for ezetimibe as a single entity and as a combination product. Medication use

and expenditures were also standardized according to the number of prescriptions and costs per 100,000 population in each country with the use of 2001 census statistics for the United States and Canada.^{17,18} All expenditures are expressed in U.S. dollars. Costs in Canadian dollars were converted to costs in U.S. dollars with the use of yearly values for purchasing-power parity from 2002 to 2006, reflecting relative differences in price levels for one time period in the two countries.¹⁹

The rate of change in the number of ezetimibe prescriptions was calculated for each country. The proportions of ezetimibe prescriptions and costs,



as compared with the total for all categories of lipid-lowering agents in each country, were calculated per year to determine the market share for ezetimibe. The ratio of prescriptions for ezetimibe to those for statins was calculated per year to evaluate differences in the relative prescribing

practices according to country. For combination lipid-lowering agents, prescription numbers and costs were calculated for Vytorin as ezetimibe and a statin, for Advicor as a statin and niacin, and for Pravigard and Caduet as statins. Rates of use of ezetimibe were estimated and compared over time by constructing a linear regression model with the use of monthly utilization data and time variables according to country. All analyses were performed with the use of SPSS software, version 11.0.4. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

PRESCRIPTION VOLUME

After Zetia was introduced in the United States in October 2002, its use increased by an average of 27,200 prescriptions per month, reaching 1,360,000 prescriptions per month in December 2006. From July 2004, the monthly use of Vytorin in the United States increased by an average of 61,000 prescriptions, reaching 1,776,000 prescriptions in December 2006. Of all Vytorin prescriptions dispensed in December 2006, 49.4% were composed of 10 mg of ezetimibe and either 10 mg of simvastatin (Vytorin 10/10) or 20 mg of simvastatin (Vytorin 10/20). The rate of ezetimibe use increased after Vytorin became available in the U.S. market ($P < 0.001$) (Fig. 1A). In December 2006, a total of 3,136,000 prescriptions were dispensed for either Zetia or Vytorin in the United States. After Ezetrol was introduced in Canada in May 2003, its use increased by a monthly average of 1954 prescriptions, reaching 84,005 prescriptions in December 2006 (Fig. 1B). The number of prescriptions for ezetimibe increased in both countries during the 5-year period. However, the rate of increase was substantially higher in the United States than in Canada ($P < 0.001$).

The use of all lipid-lowering agents was similar in the two countries between 2002 and 2006. At baseline, 3719 monthly prescriptions for lipid-lowering agents per 100,000 population were dispensed in Canada; the corresponding number was 3927 in the United States. In December 2006, there were 7401 and 6827 monthly prescriptions, respectively. After 2002, the number of population-standardized prescriptions for statins in Canada exceeded that in the United States each year (Fig. 2). At baseline, 3247 monthly statin prescriptions per 100,000 population were dispensed in

Table 1. Annual Volume of Prescriptions for Lipid-Lowering Agents, According to Drug Class.*

Variable	2002		2003		2004		2005		2006	
	Thousands of Prescriptions	Proportion of Total (%)	Thousands of Prescriptions	Proportion of Total (%)	Thousands of Prescriptions	Proportion of Total (%)	Thousands of Prescriptions	Proportion of Total (%)	Thousands of Prescriptions	Proportion of Total (%)
Canada										
Statins	12,796	87.8	15,221	88.7	17,662	89.1	19,413	88.9	21,625	88.7
Fibrates	1,589	10.9	1,709	10.0	1,692	8.5	1,687	7.7	1,703	7.0
Ezetimibe	0	0	37	0.2	283	1.4	558	2.6	824	3.4
Bile acid seques- trants	190	1.3	192	1.1	184	0.9	178	0.8	177	0.7
Niacin	0	0	0	0	0	0	12	0.1	62	0.3
Total	14,575		17,159		19,821		21,848		24,391	
United States†										
Statins	118,801	86.5	126,439	83.3	141,841	81.7	156,813	81.0	178,006	80.8
Fibrates	12,306	9.0	13,774	9.1	15,037	8.7	16,369	8.5	18,106	8.2
Ezetimibe	97	0.1	5,137	3.4	10,665	6.1	22,257	11.5	33,577	15.2
Bile acid seques- trants	2,960	2.2	2,653	1.7	2,394	1.4	2,447	1.3	2,616	1.2
Niacin	3,627	2.6	4,555	3.0	5,612	3.2	6,368	3.3	6,540	3.0
Other‡	13	<0.1	25	<0.1	40	<0.1	150	0.1	1,335	0.6
Total	137,414		151,705		173,605		193,563		220,234	

* Data are from the National Prescription Audit of IMS Health United States and the Canadian CompuScript Audit of IMS Health Canada. Proportions are the percentage of all lipid-lowering agents. Percentages may not total 100 because of rounding.

† U.S. percentages total more than 100 because of sales of combination products.

‡ Included in this category are fish-oil products, inositol, no-flush niacin, probucol, and soy isoflavones.

Canada; the corresponding number was 3423 in the United States. In December 2006, there were 6561 and 5509 monthly prescriptions, respectively.

In Canada, statin use was relatively constant between 2002 and 2006, whereas in the United States, the number of statin prescriptions decreased from 86.5 to 80.8% of all prescriptions for lipid-lowering agents, primarily from 2002 to 2004 (Table 1). In 2006, of the total number of prescriptions for lipid-lowering agents, the proportion for ezetimibe rose from 0.1% in 2002 to 15.2% in the United States and from 0.2% in 2003 to 3.4% in Canada. The ratios of the number of prescriptions for statins to that for ezetimibe were 26:1 in Canada and 5:1 in the United States in 2006, and the number of prescriptions for ezetimibe per 100,000 population was higher in the United States than in Canada by a factor of more than 3 (Fig. 2).

EXPENDITURES

After Zetia was introduced in the United States, the monthly costs associated with its use increased from \$1,281,000 in November 2002 to \$110,182,000 in December 2006. From July 2004 to December 2006, the monthly costs associated with Vytorin use in the United States increased from \$935,000 to \$151,297,000. As of December 2006, the total monthly cost of prescriptions dispensed for either Zetia or Vytorin in the United States was \$261,479,000. After Ezetrol was introduced in Canada, the monthly costs associated with its use increased from \$50,126 in June 2003 to \$6,640,354 in December 2006. Of the total costs for lipid-lowering agents, the proportion for ezetimibe rose from 0.1% in 2002 to 13.8% in 2006 in the United States and from 0.2% in 2003 to 3.9% in 2006 in Canada (Table 2).

In 2006, expenditures for ezetimibe per 100,000 population, adjusted for purchasing-power parity, were higher in the United States than in Canada by a factor of more than 4. Despite similar population-standardized numbers of prescriptions for lipid-lowering agents, expenditures for lipid-lowering agents per 100,000 population were higher in the United States, with costs continuing to diverge through 2006 (Fig. 3). In 2006, the per capita expenditures for ezetimibe were \$9.47 in the United States and \$2.16 in Canada; the corresponding expenditures for statins were \$56.91 in the United States and \$50.31 in Canada.

DISCUSSION

Our study shows that although the use of ezetimibe increased rapidly in the United States and Canada after its introduction on the market, its use increased at a substantially higher rate in the United States than in Canada. The quick uptake was based on the surrogate end point of a reduction in the level of LDL cholesterol in the absence of data from large, randomized trials with clinical outcomes.^{11,12} Moreover, in the United States, prescriptions for ezetimibe partially supplanted those for statins. Since clinicians in the two countries have access to the same evidence, other factors must account for differences in ezetimibe use, such as differences in population characteristics, promotion, and access to medications.^{20,21}

Differences in population characteristics seem unlikely to account for the higher use of ezetimibe in the United States. Prevalence rates of hypercholesterolemia (defined as a total cholesterol level of more than 240 mg per deciliter [6.2 mmol per liter]) are 16 to 17% in both countries, and the age structures of the populations are also similar.^{17,18,22,23} Furthermore, according to our study, a similar proportion of the population in each country is receiving lipid-lowering agents overall, so the issue is not overall use of lipid-lowering agents but rather the differential use of ezetimibe.

Differences in pharmaceutical promotion in the United States and Canada may have contributed to the differential use of ezetimibe. Despite the lack of clinical-outcome data, the LDL-cholesterol-lowering capacity, novel mechanism, and favorable safety profile of ezetimibe have been promoted heavily to clinicians and, in the United States, to the public. Although prescription-drug marketing to health professionals occurs in both countries, direct-to-consumer advertising for prescription drugs is prohibited in Canada. Both types of marketing may influence drug sales.²⁴⁻²⁷ In the United States, in 2007, more than \$200 million was spent on direct-to-consumer advertising for Vytorin alone, which probably had an effect on U.S. sales of ezetimibe.¹³ Also, given the larger potential market in the United States because of a greater population by a factor of 10 and the presence of Vytorin in the U.S. market, promotion to health professionals was probably greater in the United States than in Canada.^{17,18}

Differences between the United States and

Table 2. Annual Expenditures on Prescriptions for Lipid-Lowering Agents, According to Drug Class.*

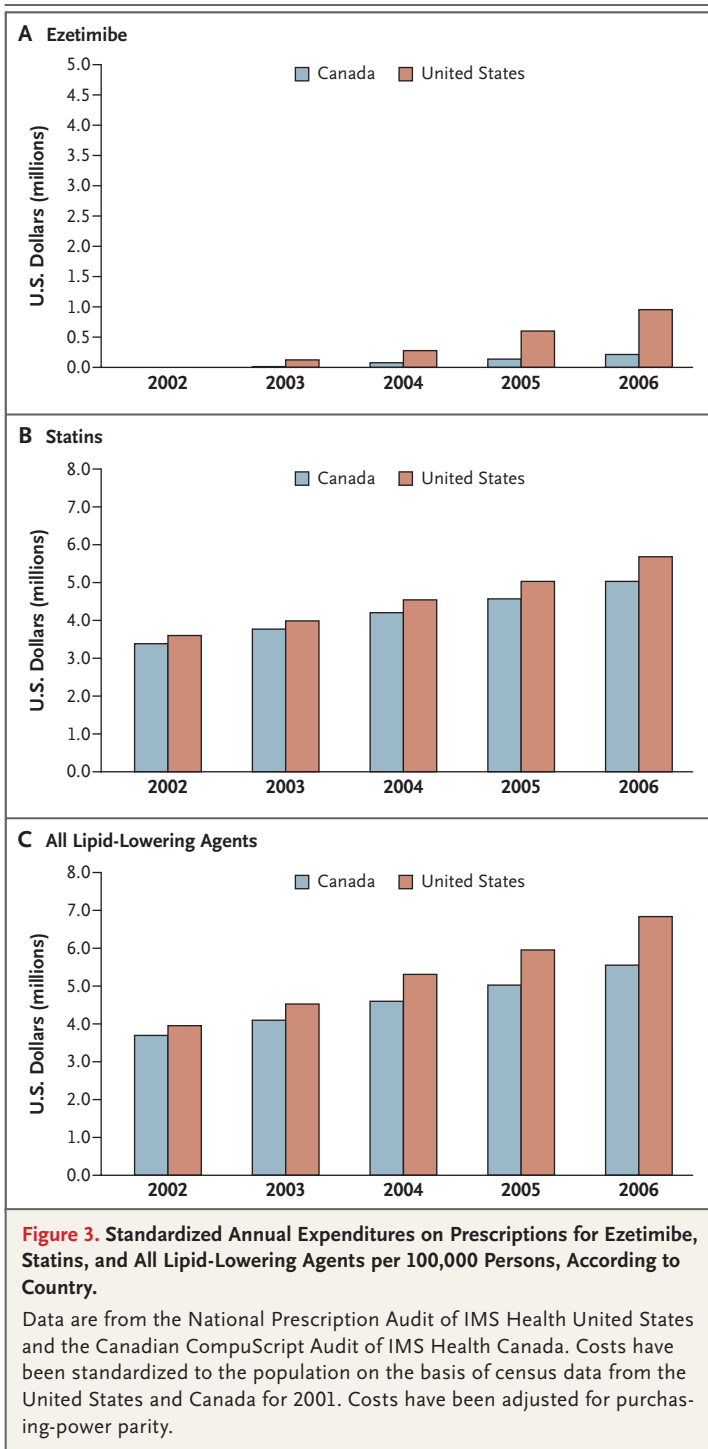
Variable	2002		2003		2004		2005		2006	
	Thousands of Dollars	Proportion of Total (%)	Thousands of Dollars	Proportion of Total (%)	Thousands of Dollars	Proportion of Total (%)	Thousands of Dollars	Proportion of Total (%)	Thousands of Dollars	Proportion of Total (%)
Canada†										
Statins	1,016,790	91.8	1,129,216	92.0	1,262,583	91.6	1,371,294	91.0	1,509,941	90.5
Fibrates	83,396	7.5	87,694	7.1	86,872	6.3	85,456	5.7	81,966	4.9
Ezetimibe	0	0	2,802	0.2	22,107	1.6	42,878	2.8	64,688	3.9
Bile acid seques-trants	7,405	0.7	7,437	0.6	7,024	0.5	6,706	0.4	7,454	0.4
Niacin	0	0	0	0	0	0	719	0	3,716	0.2
Total	1,107,591		1,227,149		1,378,586		1,507,053		1,667,765	
United States‡										
Statins	10,256,899	91.2	11,347,630	88.1	12,940,684	85.6	14,336,890	84.4	16,231,284	83.1
Fibrates	618,505	5.5	797,394	6.2	975,015	6.5	1,107,258	6.5	1,277,245	6.5
Ezetimibe	6,831	0.1	341,788	2.7	771,461	5.1	1,700,203	10.0	2,702,169	13.8
Bile acid seques-trants	220,218	2.0	207,345	1.6	192,778	1.3	200,176	1.2	216,812	1.1
Niacin	159,870	1.4	247,411	1.9	381,997	2.5	507,778	3.0	619,063	3.2
Other§	123	<0.1	197	<0.1	297	<0.1	9,665	0.1	123,315	0.6
Total	11,242,700		12,887,088		15,110,706		16,990,203		19,521,619	

* Data are from the National Prescription Audit of IMS Health United States and the Canadian CompuScript Audit of IMS Health Canada. Proportions are the percentage of all lipid-lowering agents. Percentages may not total 100 because of rounding.

† Canadian expenditures have been converted to U.S. dollars with the use of annual values for purchasing-power parity.

‡ U.S. percentages total more than 100 because of sales of combination products.

§ Included in this category are fish-oil products, inositol, no-flush niacin, probucol, and soy isoflavones.



Canada in access to prescription drugs may also have contributed to differential use of ezetimibe. First, in Canada, the approval time for new medications is longer than that in the United States,²⁸ and the approval of ezetimibe lagged behind that in the United States by 7 months. Second, Vytorin

has been available in the United States since July 2004 but is still not available on the Canadian market.^{5,6} The use of ezetimibe-containing products in the United States increased sharply with the introduction of Vytorin. Some U.S. clinicians may have adopted the combination cholesterol-lowering product to improve adherence to dual therapy, but this option was not available in Canada.²⁹ Third, in Canada, publicly funded provincial drug formularies have been conservative in their coverage of ezetimibe. Two of the three provincial government-funded formularies that serve three provinces (Ontario, Quebec, and British Columbia), in which approximately 75% of Canada's population lives, list ezetimibe with prescribing criteria that limit its use to patients in whom the target level of LDL cholesterol has not been achieved with a statin and patients who cannot tolerate or have a contraindication to statins; a third formulary does not even list ezetimibe as a benefit, although it is currently under review.³⁰⁻³² These formulary criteria appear to be consistent with guideline recommendations that favor medication classes for which data on outcomes are available.^{11,12,33} Public formulary listings often influence medication coverage in private Canadian drug plans.³⁴

Two surges in the use of ezetimibe were observed in the United States, the first from 2002 to 2004, the period when the use of ezetimibe appeared to displace that of statins, and the second after the introduction of Vytorin in 2004. This surge in the number of Vytorin prescriptions translates into large expenditures and may have magnified the difference in ezetimibe use between the two countries. The per capita cost of ezetimibe in the United States is more than four times that in Canada, whereas per capita costs for statins are similar. At daily doses that have a similar effect in reducing LDL cholesterol, the cost of Vytorin 10/20 is more than three times that of 80 mg of simvastatin, which is now available generically in the United States.³⁵

Our study has some limitations. IMS Health uses data collected from audits of prescriptions dispensed to describe general trends in the use of drugs. These data do not provide details with respect to the use of drugs by individual patients or providers that would permit a determination of the appropriateness of use. We did not have access to clinical data, such as medical conditions and cholesterol levels, to determine whether pre-

scribing practices for ezetimibe were clinically appropriate. Although increased ezetimibe use was demonstrated, we could not evaluate the effects on outcomes for patients.

Although distinct patterns of use of specific lipid-lowering agents emerged in the United States and Canada from 2002 to 2006, overall rates of use of lipid-lowering agents were similar. In Canada, reliance on statins predominated, whereas in the United States, statins were initially displaced by ezetimibe, followed by rapid growth in the use of Vytorin, which markedly altered the approach to the treatment of hyperlipidemia and increased drug costs. The effect of this shift in the use of lipid-lowering agents on clinical outcomes is uncertain.

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Drs. Ross and Krumholz report serving as consultants to plaintiffs in litigation against Merck related to rofecoxib. Dr. Krumholz reports being a member of an advisory board for UnitedHealthCare and being under contract to develop performance measures for the Centers for Medicare and Medicaid Services. No other potential conflict of interest relevant to this article was reported.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs, the Canadian Institutes of Health Research, or the Ontario Ministry of Health and Long-Term Care.

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