Impact of Drug Policy on Regional Trends in Ezetimibe Use

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Background—Ezetimibe use has steadily increased in Canada during the past decade even in the absence of evidence demonstrating a beneficial effect on clinical outcomes. Among the 4 most populous provinces in Canada, there is a gradient in the restrictiveness of ezetimibe in public-funded formularies (most to least strict: British Columbia, Alberta, Quebec, and Ontario). The effect of formulary policy on the use of ezetimibe over time is unknown.

Methods and Results—We conducted a population-level cohort study using Intercontinental Marketing Services Health Canada’s data from June 2003 to December 2012 to examine ezetimibe use in these 4 provinces to better understand the association between use and formulary restrictiveness. We found regional variations in the patterns of ezetimibe use. From June 2003 to December 2012, British Columbia (most restrictive) had the lowest monthly increasing rate from $261 to $21926 ($190/100,000 population/mo), whereas Ontario (least restrictive) had the most rapid monthly increase from $223 to $74030 ($647/100,000 population/mo), and Quebec from $130 to $59690 ($522/100,000 population/mo) and Alberta from $356 to $37604 ($327/100,000 population/mo) were intermediate (P<0.001).

Conclusions—Ezetimibe use remains common, increasing during the past decade. Use steadily increased in provinces with the most lenient formularies. In contrast, use was lower, plateauing since 2008 in British Columbia and Alberta, which have more restrictive formularies. The gradient in ezetimibe use was related to variability in restrictiveness of the provincial formularies, illustrating the potential of a policy response gradient that may be used to more effectively manage medication use. (Circ Cardiovasc Qual Outcomes. 2014;7:00-00.)

Key Words: drug utilization ■ ezetimibe ■ health policy

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ezetimibe was approved based on its ability to reduce low-density lipoprotein cholesterol levels.1 Although no completed outcomes trials have shown a clinical benefit of ezetimibe compared with statin therapy,2–4 we previously found that ezetimibe use increased >200-fold in Canada during the past decade, whereas use in the United States declined during the same period.4 Further characterizing the increasing use of ezetimibe is important to identify influential factors that may be contributing to increases in pharmaceutical expenditures in Canada.

Although guidelines are uniform on ezetimibe recommendations across provinces,7,8 they operate under different provincial formulary policies, which may affect prescribing.9 Provincial publicly funded drug plans account for a large proportion of prescription drug spending in Canada10 and exert influence on privately funded formularies.11–13 Among the 4 most populous provinces in Canada, there is a regional gradient in the restrictiveness of ezetimibe in the public-funded formularies (most to least strict: British Columbia, Alberta, Quebec, and Ontario; Table).14–17 Previous studies demonstrate that restrictive drug policies have been associated with reduced drug use and associated expenditures.18–21 However, the degree to which the formulary constraints on a drug product influence its use is uncertain. It is not known whether there is a gradient in ezetimibe use between these provinces, given the variability in the restrictiveness of their formularies.

Therefore, our objectives were to examine regional differences in ezetimibe use trends in these 4 provinces from June 2003 to December 2012 to better understand the association between ezetimibe use and formulary restrictiveness. In addition, because the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression
WHAT IS KNOWN

- Restrictive drug policies are associated with reduced medication use and associated expenditures. The degree to which the formulary constraints on a drug product influence its use is uncertain.

WHAT THE STUDY ADDS

- Our study revealed a regional gradient in ezetimibe use that was related to variability in formulary restrictiveness.
- This policy response gradient may be used to more effectively manage medication use.
- There is an interaction effect between drug policy and clinical evidence for ezetimibe use. That is, response to new clinical evidence was related to the restrictiveness of drug policy.

(ENHANCE) trial,\(^2\) which was published in January 2008 during our study period, showed that the addition of ezetimibe to simvastatin did not reduce the progression of atherosclerosis compared with statins alone, we also sought to compare ezetimibe use before and after this negative evidence to evaluate the influence of the ENHANCE trial on ezetimibe use between provinces. Because statins are standard lipid-lowering therapy and were not restricted by any provinces, we also evaluated ezetimibe use relative to a background of statin use.

Methods

Study Design and Data Source

We conducted a population-level observational cohort study using data from Intercontinental Marketing Services (IMS) Health Canada’s CompuScript Audit database from June 2003 to December 2012 to describe the provincial use of and expenditures for ezetimibe. Ezetimibe was introduced as Ezetrol in Canada since May 2003.\(^2\) No ezetimibe combination product has been marketed in Canada.\(^2\) We compared the expenditures of ezetimibe between the 4 most populated provinces in Canada that comprise 86.0% of the Canadian population and are representative of the range of formulary policies across Canada.\(^2\) In addition, the relative annual use of ezetimibe to statins was also compared between these 4 provinces.

The Canada’s CompuScript Audit of IMS Health Inc is a source of prescription data obtained by measuring, through an audit, the number of dispensed prescriptions and their cost to the consumer (product cost, markups, and pharmacist fees) from Canadian retail pharmacies. IMS stratified pharmacy outlets for data collection according to region, type (independent, chain, mail order, or long-term care), and size of outlet. Samples are drawn from the IMS prescription database panel, which comprises >5000 pharmacies, representing about two thirds of all retail pharmacies in Canada. Criteria such as prescription type and volume, consistency of reporting, and payment type are applied to select the samples. Data are collected electronically each day from the sample pharmacies consisting of drug stores 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 are projected to the universe in each province and summed to generate the provincial total estimate. The data collected can be used to ascertain prescription volume by drug class and the market share for trending purposes, providing a measure of product use. Also available is the cost of the prescription as dispensed (including all product cost, markups, and the pharmacist’s professional fee).\(^2\)–\(^8\) The IMS Health Canada database records aggregate population-wide data rather than patient-specific data.

Primary Variables

The monthly expenditures for ezetimibe in these 4 provinces were the primary outcome of interest. There are different days supplied for prescription refills between provinces: Quebec has 30-day supply, whereas British Columbia, Alberta, and Ontario have 30- to 90-day supply. Quebec ezetimibe use would be overestimated if our outcome was volume of prescriptions. Also, ezetimibe use cannot be indexed by the number of days covered accurately because we do not have exact information on the proportion of prescription refills with 30-, 60-, or 90-day supply in British Columbia, Alberta, and Ontario. The drug cost for ezetimibe is similar across the 4 provinces because ezetimibe is a brand-name medication in Canada. Therefore, we chose to examine the monthly expenditures for ezetimibe, as a proxy for monthly ezetimibe use as a more comparable measure between provinces.

Analysis

Descriptive statistics were used to report the expenditures of prescription claims for ezetimibe. Ezetimibe-associated expenditures were also standardized according to costs per 100 000 population in each province with the use of 2006 Canadian census data used as the standard population to detect any geographic variation.\(^2\) All expenditures are expressed as Canadian dollars. The current exchange rate of the US dollar to Canadian dollar is 1.12 as of 2014. For interprovincial comparisons of drug use, we compared monthly expenditures of ezetimibe between provinces. The differences in trends of ezetimibe-associated expenditures over time between the 4 provinces were tested using linear regression with interaction effect for province and time. We also used an autoregressive integrated moving average (ARIMA) interrupted time series analysis to model the monthly ezetimibe-associated expenditures to assess the use trends before and after the ENHANCE trial within each province, which allows for both intercept and trend changes. Given the availability of a series of ezetimibe data taken over the past decade and the release of the ENHANCE trial in January 2008 the ARIMA model with intervention analysis is well suited to address secular trends of ezetimibe use and evaluate the effect of the intervention, the ENHANCE trial. Three steps were used to construct the ARIMA model using the entire data series for each province—identification, estimation, and a diagnostic test for residuals.\(^3\) Different models were identified and estimated for each province based on their specific data. First, the data series needs to achieve stationarity, which means statistical properties (eg, mean and SD) are all constant over time. The stationarity of the time series was checked using the augmented Dicky–Fuller test.\(^3\) Once stationarity was achieved by differencing, the orders of autoregressive and moving average parameters were determined using autocorrelation and partial autocorrelation function test to identify the ARIMA model. We used the modified sum of square method to estimate the model parameters. The model that gave the minimum Akaike Information Criterion was selected.\(^2\) Last, the Residual Autocorrelation Function was examined to determine whether the residuals were white noise. Then the binary variable I was created to denote the intervention, with pre-ENHANCE coded as 0 and post-ENHANCE coded as 1. The ARIMA model with intervention analysis was used to test for the influence of the ENHANCE trial.

All analyses were performed with SAS 9.3 software. \(P<0.05\) was considered statistically significant. The study was approved by the Institutional Review Board of Western University of Health Sciences.

Results

We first examined whether there was a relationship between formulary restrictiveness and ezetimibe use and found that after ezetimibe was introduced in Canada, the monthly ezetimibe-associated costs increased in significantly different patterns in the 4 provinces during the past decade (\(P<0.0001\)), which was associated with the restrictiveness of their provincial
ezetimibe formulary. From June 2003 to December 2009, British Columbia (most restrictive) had the lowest average increasing rate from $261 to $21,926 ($190/100,000 population/mo), Ontario (least restrictive) had the most rapid average monthly increase from $223 to $74,030 ($647/100,000 population/mo), and Quebec (third most restrictive) from $356 to $37,604 ($327/100,000 population/mo) were intermediate (Figure 1). Alberta had a similar use pattern as British Columbia but a higher rate than British Columbia through the entire study period ($P<0.001$).

We also examined ezetimibe use trends before and after the ENHANCE trial within each province to determine whether there is a relationship between formulary restrictiveness and response to clinical evidence. The increasing rate began declining in British Columbia, Alberta, and Ontario at the time point (January 2008), which coincided with the publication of ENHANCE. In contrast, the cost for ezetimibe seemed to increase steadily in Quebec during the study period. The monthly ezetimibe-associated expenditures, which is a proxy for monthly ezetimibe use, rose from $261 in June 2003 to $18,902 in December 2007 per 100,000 population in British Columbia with an average increase of $345 per 100,000 population per month then reached a relatively steady state with a monthly increase of $50 per 100,000 population post-ENHANCE, a significant decrease of 85.5% in the increasing rate of ezetimibe-associated expenditures ($P<0.0001$). By December 2012, the corresponding cost reached $21,926/100,000 population in British Columbia. At baseline, the population-standardized ezetimibe-associated monthly cost was $356 in June 2003 in Alberta, rising to $27,046 by December 2007, with an average increase of $494/100,000 population/mo. Thereafter, costs increased more slowly at a lower rate of $176 per 100,000 population per month, reaching $37,604 per 100,000 population at the end of the observation period in Alberta, with a significant reduction of 64.4% in increasing rate post-ENHANCE ($P<0.0001$).

In Ontario, the monthly cost for ezetimibe continually increased from $223 in June 2003 to $48,784 in December 2007 per 100,000 population. The average increasing rate in Ontario was $899 per 100,000 population per month pre-ENHANCE and began declining as of January 2008, with the increasing rate of $421 per 100,000 population per month post-ENHANCE. The increasing rate in ezetimibe use was significantly decreased by 53% post-ENHANCE in Ontario ($P<0.0001$). The ezetimibe-associated expenditures was $74,030 in December 2012 per 100,000 population in Ontario. In contrast, the cost for ezetimibe has been consistently rising from $130 to $59,690 in Quebec from June 2003 to December 2012, regardless of the publication of the ENHANCE trial ($P=0.46$). The use of ezetimibe was 2.6-fold higher in Ontario (the highest use) than British Columbia (the lowest use) pre-ENHANCE in December 2007 then increased to 3.4-fold higher in Ontario post-ENHANCE in December 2012.

During the study period, the annual ezetimibe relative to statin use varied among the 4 provinces (Figure 2). The relative use of ezetimibe to statins remained highest in Ontario throughout the study period but reached a steady state since

![Figure 1. Monthly provincial ezetimibe-associated expenditures per 100,000 population in British Columbia, Alberta, Quebec, and Ontario from 2003 to 2012. Y axis, ezetimibe expenditures per 100,000 population in Canadian dollars. Data are from the Canadian CompuScript Audit of Intercontinental Marketing Services (IMS) Health Canada Inc. Numbers were standardized to the population based on Canadian census data for 2006. ENHANCE indicates Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression.](http://circoutcomes.ahajournals.org/Downloaded from)
2008. In contrast, relative ezetimibe to statin use was the lowest in Quebec from 2004 to 2007 but steadily increased during the entire study period. In British Columbia, the ezetimibe use relative to statins initially increased, peaking in 2007, and declining gradually thereafter. Alberta had a similar pattern to British Columbia, while more sharply increasing in the pre-ENHANCE time period, peaking in 2008, and gradually declining thereafter. These patterns were observed in a setting in which the provincial formularies for ezetimibe did not change throughout the study period (Table).

**Discussion**

Our study found that distinct regional patterns of ezetimibe use emerged within the 4 most populated provinces in Canada that seem to be associated with the restrictiveness of the provincial publicly funded drug formularies. The British Columbia formulary has never listed ezetimibe for compensation since its introduction.\(^\text{14}\) This is reflected in the usage patterns we observed, where British Columbia had the lowest monthly increase in ezetimibe-associated expenditures pre-ENHANCE and reached relative steady state post-ENHANCE. In the absence of outcomes evidence,\(^\text{2,5}\) British Columbia did not approve ezetimibe as a benefit resulting in the lowest ezetimibe-associated expenditures with the slowest increase over time. Despite the low ezetimibe use, the prevalence of heart disease did not increase in British Columbia over this time period, in fact it decreased.\(^\text{13}\) Others have found that coverage policies under British Columbia’s PharmaCare are typically marked by evidence-based decision making.\(^\text{13}\)

Alberta, Quebec, and Ontario provide ezetimibe coverage for patients meeting specific criteria, with Alberta having the most criteria for use and Ontario having the fewest criteria for use. The Ontario formulary lists ezetimibe as a limited use product with the only criteria for use being a statin is contraindicated or not tolerated.\(^\text{17}\) Perhaps not surprisingly, Ontario had the most rapid monthly increase in ezetimibe-associated expenditures, although the increasing rate did decline post-ENHANCE. The monthly increase of ezetimibe use in Alberta and Quebec was intermediate in magnitude, with Alberta having a lower increasing rate in ezetimibe use than Quebec over time. Similarly, their prescribing criteria are intermediate in restrictiveness between British Columbia and Ontario. Alberta provides ezetimibe coverage under a special authorization process of specified criteria, with more stringent prescribing criteria that limits its use only to patients who are at high cardiovascular risk (patients need to have ≥1 additional risk factor except for dyslipidemia) and in whom the target level of low-density lipoprotein cholesterol has not been achieved with a statin or who cannot tolerate or have a contraindication to statins.\(^\text{15}\) Ezetimibe is listed as an exceptional medication in Quebec. Quebec reimburses for ezetimibe for patients with dyslipidemia where ≥2 lipid-lowering agents are contraindicated, ineffective, or not tolerated or where the optimized statin treatment failed to achieve the low-density lipoprotein cholesterol goal.\(^\text{16}\)
Our results are consistent with observations in other studies evaluating the association between policy restrictions and medication use.\textsuperscript{18-21,35-37} A restrictive prior authorization policy in the Medicaid program in TN significantly reduced expenditures for nonsteroidal anti-inflammatory drugs with no increase in expenditures in other medical care, whereas a more restrictive policy was found to limit cyclooxygenase-2 inhibitor use and gastrointestinal bleeding outcomes than an unrestricted policy.\textsuperscript{19,35} These results consistently demonstrate that restrictive drug policy limits drug use and associated expenditures. However, the degree to which the formulary constraints on a drug product influence its use has received limited evaluation. Our study further reveals that there is a gradient in ezetimibe use between provinces related to the variability in the restrictiveness of their formularies. These findings illustrate to policy makers the potential of a policy response gradient such that a higher degree of restrictiveness of a formulary policy may more effectively limit medication use.

In addition to the effect of provincial drug policy on ezetimibe use, clinical evidence, such as evidence from the ENHANCE trial, may also influence ezetimibe use. The results from the ENHANCE trial do not support ezetimibe use.\textsuperscript{2} This negative evidence was further supported by subsequent trials.\textsuperscript{3-5} Our study showed that the increasing rate of ezetimibe-associated expenditures began declining in British Columbia, Alberta, and Ontario at the time point, which coincided with the publication of the ENHANCE trial. The negative findings from the ENHANCE trial likely contributed to the blunted increase in ezetimibe use in these 3 provinces, illustrating how clinicians responded to the new evidence. In contrast, the expenditures for ezetimibe seemed to increase steadily in Quebec, with no decline or plateau, as had occurred in the other provinces post-ENHANCE. The different ezetimibe use patterns we observed before and after the ENHANCE trial are further confirmed by our findings of the same regional variation in ezetimibe use relative to a background of statin use.

When new clinical evidence arises, policymakers have a window of opportunity to respond to the evidence in a

\begin{table}
\centering
\caption{Provincial Publicly Funded Ezetimibe Formularies in the 4 Most Populated Canadian Provinces}
\begin{tabular}{|l|p{0.6\textwidth}|}
\hline
Jurisdiction & Ezetimibe Formulary & Formulary Date \\
\hline
British Columbia & Most strict: not approved to be reimbursed by formulary (patients may pay for it out of pocket) & Reviewed on September 27, 2007 \\
\hline
Alberta & Second most strict - special authorization with most criteria for use: 
- For the treatment of hypercholesterolemia in patients who are intolerant to statins or in whom a statin is contraindicated and who are at high cardiovascular risk as defined by possessing one of the following: 
  - For the treatment of hypercholesterolemia when used in combination with a statin in patients failing to achieve target LDL cholesterol (<2.5 mmol/L) with a statin at a maximum tolerable dose or maximum recommended dose as per the respective product monograph and who are at high cardiovascular risk as defined by possessing one of the following: 
    - Premature cardiovascular disease and cerebrovascular disease 
    - Diabetes mellitus 
    - Familial hypercholesterolemia 
    - Three or more of the following risk factors: family history of premature cardiovascular disease, smoking, hypertension, obesity; glucose intolerance, and renal disease & January 1, 2004, to till now \\
\hline
Quebec & Third most strict - exceptional medication with some criteria for use: 
1) Where ezetimibe is not used in association with an HMG-CoA reductase inhibitor (statin): where ≥2 hypolipemiant are contraindicated, ineffective or not tolerated 
2) Where ezetimibe is used in association with an HMG-CoA reductase inhibitor (statin): if the statin treatment, at the optimum dose or at a lower dose in case of intolerance to that dose, did not make it possible to adequately control the cholesterolemia & April 28, 2004, to till now \\
\hline
Ontario & Least strict - limited use product with least criteria for use: 
1) For use in combination with a HMG-CoA reductase inhibitor (statin) in patients with hypercholesterolemia who have not reached target LDL levels, despite the use of maximally tolerated doses 
2) For use as monotherapy in the management of hypercholesterolemia in patients who are intolerant to HMG-CoA reductase inhibitors or where HMG-CoA reductase inhibitors are contraindicated & April 6, 2004, to till now \\
\hline
\end{tabular}
\end{table}

CoA indicates coenzyme A; HMG, 3-hydroxy-3-methylglutaryl; and LDL, low-density lipoprotein.
manner that will stimulate use of optimal therapies, providing an influential role in medication use.\textsuperscript{21,35} We previously found that removal of a prior authorization policy on clopidogrel use in response to clinical evidence was associated with improved access to and prescribing of clopidogrel.\textsuperscript{21} In the current study, in which 3 provinces provided ezetimibe coverage pre-ENHANCE, none responded to the negative evidence from ENHANCE. That is, their provincial formularies for ezetimibe did not change post-ENHANCE, missing a key synergistic opportunity to optimize drug use in a setting in which clinicians were already changing their ezetimibe use patterns. Our results also reveal an interaction effect between drug policy and clinical evidence for ezetimibe use. The province with the most restrictive formulary (British Columbia) had a greater decline in ezetimibe use post-ENHANCE than the province with the most lenient formulary (Ontario), widening the use variability between these provinces from a 2.6-fold difference to a 3.4-fold difference in use. It is possible that ezetimibe use could have declined even further, narrowing the regional differences, if the provinces with the more permissive drug policies had responded in a timely manner to this negative evidence. In light of persistent cost pressures, interest in evidence-based approaches to drug coverage is increasing.\textsuperscript{38} Along with mechanisms to increase the availability and accessibility of critically appraised evidence for clinicians, policy-making frameworks should be developed to facilitate consistent action on such evidence.

It is possible that the regional difference in ezetimibe use may be partially attributed to some other factors. Although the Common Drug Review was established in 2003 in Canada as a model of centralized evidence-based review for new drugs, these recommendations are not mandatory, and this allows for consideration of local factors in regional decision making. For example, the prevalence of heart disease and risk factors differs by region.\textsuperscript{33} Although British Columbia residents tend to be healthier with less heart disease and less smoking,\textsuperscript{31} which may partially explain the lower use of ezetimibe, the prevalence of heart disease was even lower in Alberta than in British Columbia,\textsuperscript{33,31} yet the use of ezetimibe was higher in Alberta. Furthermore, the prevalence of obesity in Quebec and Ontario was stable during our study period, which does not correspond to the continually increasing ezetimibe use over time in these 2 provinces.\textsuperscript{40} Therefore, the regional variability of heart disease and risk factors does not adequately explain the gradient of ezetimibe use observed within these 4 provinces. Local preferences in care among patients and physicians, as well as dissemination, uptake, and adherence to practice guidelines, may also vary regionally.\textsuperscript{41,42} Last, an economic policy to support the local research-based pharmaceutical industry in Quebec may partially explain why Quebec had among the highest ezetimibe use over time.\textsuperscript{43}

Our study has several limitations. First, we cannot assess whether other interprovincial variables such as patient characteristics, physicians’ prescribing behavior, or other province-level characteristics contributed to the difference in ezetimibe use because of lack of data. However, we confirmed that the divergent patterns of ezetimibe use persisted when adjusted for background trends in statin consumption. Because statins are not restricted for use in any province, this provided an estimate of the underlying variability in the use of lipid-lowering agents between provinces without the effect of policy restrictiveness. Nevertheless, we do not have information on the doses of statins used in individual patients because our study evaluates medication use at an ecological, population level. Third, we could not use volume of prescriptions to index actual ezetimibe use for the comparison between provinces. However, the drug cost for ezetimibe is similar across the 4 provinces because ezetimibe is a brand-name medication in Canada. Therefore, the monthly expenditures for ezetimibe were used as a proxy for monthly ezetimibe use as a more comparable measure between provinces. Finally, we do not have regional marketing data for ezetimibe. Therefore, we do not know whether marketing strategies may account for the differences in ezetimibe use between provinces in Canada. However, direct-to-consumer advertising is unavailable in Canada and would not be an influential factor.

Conclusions

Distinct regional patterns of ezetimibe use emerged within the 4 most populated provinces in Canada, which was associated with the restrictiveness of their publicly funded drug formularies. Without the support of clinical outcomes evidence, ezetimibe remains commonly used, particularly in the provinces with the least strict formularies (Quebec and Ontario). In contrast, the use of ezetimibe seems to have plateaued post-ENHANCE in British Columbia and Alberta, which have more restrictive formularies. For pharmaceutical products lacking outcomes evidence, restrictive policies that decrease drug costs may represent an effective healthcare strategy in light of limited healthcare resources. Evidence-based policy-making frameworks should be developed to act on available evidence.

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