Use and Misuse of Ezetimibe: Analysis of Use and Cost in Saskatchewan, a Canadian Jurisdiction With Broad Access

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ABSTRACT

Background: Saskatchewan is the only Canadian province that lists ezetimibe for open formulary access even though it is a second-line agent for lowering cholesterol.

Methods: A retrospective analysis of ezetimibe use in Saskatchewan between 2002 and 2011 was carried out using provincial health administrative databases. Overall use and costs of ezetimibe were described over time. Among new users of ezetimibe, the percentage who received the drug as first-line monotherapy was estimated. First-line monotherapy was defined as no statin dispensations in the 365 days before and the 60 days after the first ezetimibe dispensation. Potential predictors of first-line monotherapy were assessed using generalized linear mixed-effect models.

Results: In 2004, ezetimibe represented 2.5% of cholesterol-lowering dispensations. In 2011, its use increased to 8.8% of cholesterol-lowering dispensations and 13.2% of the total cost of cholesterol-lowering agents.

Ezetimibe is a cholesterol-lowering medication that was released on the Canadian market in 2003. It is recommended as second-line treatment after 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) because of a lack of robust evidence evaluating coronary heart disease (CHD) outcomes,1,6 as well as a relatively high cost compared with first-line therapy. Despite these disadvantages, the percentage of ezetimibe prescriptions in Canada has steadily increased over time.2,8

Provincial health ministries in Canada have taken different approaches to the use of ezetimibe. Four provinces do not list ezetimibe for compensation (British Columbia, Manitoba, New Brunswick, and Newfoundland), whereas 5 provinces provide coverage only for patients meeting specific criteria (Alberta, Ontario, Québec, Nova Scotia, and Prince Edward Island). Distinctively, Saskatchewan is the only Canadian province that provides open formulary access to eligible beneficiaries for all ezetimibe prescriptions. Thus, Saskatchewan residents are eligible to receive coverage for ezetimibe even if it is prescribed as first-line therapy. However, the percentage of ezetimibe used as first-line therapy remains unknown.

Considering ezetimibe’s high cost in comparison with first-line medications and its potentially inferior protection against CHD events, an analysis of its use in Saskatchewan is timely.
Overall, ezetimibe was used as first-line monotherapy in 23% of all new users (4024 of 17,475 patients). Approximately half of all cases of first-line monotherapy were prescribed by 10.4% (112 of 1074) of prescribers in the cohort. Patients who had experienced previous acute coronary syndrome or who had undergone coronary revascularization procedures were significantly less likely to receive first-line monotherapy.

Conclusions: A high proportion of ezetimibe’s use is not in accordance with evidence-based recommendations. Suboptimal prescribing could partially explain current patterns of use; however, other factors such as medication nonadherence may have played an important role. Restricting ezetimibe use in the provincial formulary in addition to improving prescribers’ awareness through academic detailing should be considered.

We aimed to describe the frequency by which ezetimibe has been used as a first-line agent, along with its costs compared with other cholesterol-lowering medications since its introduction in Saskatchewan.

Data Source
This retrospective observational study was conducted using health administrative databases maintained by the Saskatchewan Ministry of Health. Specifically, we integrated information from the person registry file with the hospital services, physician services, and prescription drug databases. The person registry maintains a current record of all active beneficiaries, representing about 99% of the 1 million residents of the province. The hospital and physician services files capture all hospitalizations and virtually all physician services claims for all beneficiaries, whereas the prescription drug file captures claims for approximately 90% of the population. The remaining 10% receive prescription benefits from the federal government (ie, First Nations, Royal Canadian Mounted Police, Canadian Armed Forces, and federal prison inmates). The validity and accuracy of the Saskatchewan prescription drug database has been demonstrated in many studies examining medication use.10-14

Methods
Population use and cost analysis
Using the prescription drug file, we calculated both the annual number of beneficiaries receiving at least 1 dispensation and the annual cost of these dispensations. The following cholesterol-lowering medications were included in this analysis: ezetimibe, statins, fibrates (ie, fibric acid derivatives), resins (ie, bile acid sequestrants), and niacin (vitamin B3) (Supplemental Table S1). Costs included medication price, mark-up, and dispensing fee. Data were described using frequencies and percentages starting in 2002 to provide 2 years of baseline data before the first date of coverage for ezetimibe in January 2004.

Results: En 2004, l’ezétimibe représentait 2,5 % de la délivrance d’hypocholestérolémiant. En 2011, son utilisation a augmenté à 8,8 % de la délivrance des hypocholestérolémiants et à 13,2 % du coût total des agents hypocholestérolémiants. Dans l’ensemble, l’ezétimibe a été utilisé en monothérapie de première intention chez 23 % de tous les utilisateurs (4024/17 475). Approximativement la moitié de tous les cas de monothérapie de première intention ont reçu l’ordonnance de 10,4 % (112/1074) des personnes autorisées à prescrire des médicaments de la cohorte. Les sujets ayant auparavant eu un syndrome coronarien aigu ou subi des interventions de revascularisation coronarienne étaient considérablement moins susceptibles de recevoir la monothérapie de première intention.

Conclusions: Une forte proportion de l’utilisation de l’ezétimibe n’est pas conforme aux recommandations fondées sur les données probantes. Une prescription sous-optimale pourrait partiellement expliquer les modèles actuels d’utilisation. Cependant, d’autres facteurs comme la non-observance de la médication peut avoir joué un rôle important. L’inscription de l’ezétimibe à la liste provinciale des médicaments à accès restreint et l’amélioration de la conscientisation des personnes autorisées à prescrire des médicaments par la formation continue en pharmacothérapie devraient être considérées.

Cohort analysis
A retrospective cohort of new ezetimibe users was identified with the following inclusion criteria: (1) received a new dispensation for ezetimibe between January 1, 2004 and October 31, 2011 and (2) were continuous beneficiaries of the drug plan for at least 365 days before and 60 days after their first ezetimibe dispensation. A new dispensation of ezetimibe was defined as no record of ezetimibe in the preceding 365 days. This first ezetimibe dispensation date in the observation period was set as the index date and start of ezetimibe therapy. For patients who satisfied the inclusion criteria more than once, only the first episode of therapy was considered.

We examined the 365-day period preceding and the 60-day period after the index dispensation to describe ezetimibe’s place in therapy as follows: (1) first-line monotherapy, (2) second-line monotherapy, (3) first-line combination therapy, and (4) second-line combination therapy. First-line therapy was defined as no statin dispensations in the 365 days preceding the index date (ie, first ezetimibe dispensation). Patients receiving at least 1 statin dispensation in the previous year were classified as receiving second-line therapy. In addition, because cholesterol-lowering medications are typically dispensed monthly in Saskatchewan,15 the 60-day period after (and including) the index date was examined to classify individuals as receiving monotherapy or combination therapy. Specifically, patients receiving a statin dispensation during the 60-day follow-up period were categorized as receiving combination (statin-ezetimibe) therapy, whereas those with no statin dispensations were considered to be using monotherapy (ezetimibe only). In sensitivity analyses, stricter definitions of combination therapy were also examined (30 or 90 days vs 60 days). Finally, we examined the subgroup of ezetimibe users who had received a statin dispensation in the previous year to determine the number of unique statin medications filled as well as the final dose achieved (high- or low-dose therapy), based on the dispensation most recent to the index date (Supplemental Table S2).2,5
We categorized ezetimibe’s place in therapy as a dichotomous binary outcome variable (ie, first-line monotherapy/other). We fit a generalized linear mixed-effects model to these data, with the prescribing physician of the first ezetimibe prescription as the random effect, to account for the possibility of clustering of first-line monotherapy prescriptions from some prescribers. Only a random prescriber intercept was included in the model. The extent of clustering from an individual prescriber was examined using the intraclass correlation. The covariates used in the model are provided in Supplemental Appendix S1. We tested for multicollinearity using the variance inflation factor and interpreted values > 10 as having high multicollinearity. We tested whether the variance of the random effect was significantly different from zero using a likelihood ratio test, which asymptotically follows a χ² distribution. We retained only those covariates that had both a P value < 0.05 on the Wald t test and led to an increase in model fit as judged by the Akaike information criterion. SAS, version 9.3 (SAS Institute Inc, Cary, NC) was used to perform the analysis. Ethics approval was received from the University of Saskatchewan Biomedical Research Ethics Board.

Results

Analysis of use and cost

The number of beneficiaries receiving ≥1 dispensation for any class of medication (ie, active provincial beneficiaries) increased by 8% between 2002 and 2011 (from 609,240 to 657,962). Concurrently, the percentage of individuals receiving ≥1 cholesterol-lowering medication among active beneficiaries increased by 117% (from 7.9% to 17.2%). This growth in cholesterol-lowering therapy appeared to be largely driven by an increase in dispensations for statin medications (Fig. 1). As a percentage of all cholesterol-lowering dispensations, ezetimibe use increased from 2.5% in 2004 to 8.8% in 2011 (Fig. 1). In particular, it seems that the use of ezetimibe started to increase in 2006 (Fig. 1). The cost of all cholesterol-lowering medications also increased steadily from 2002 but decreased sharply after 2010 after the emergence of generic atorvastatin on the Saskatchewan formulary. In contrast, the total cost of all ezetimibe dispensations increased from $752,032 to $7,004,180 between 2004 and 2011, and the average cost per dispensation of ezetimibe also increased from $66.30 (standard deviation [SD] = 12.8) to $79.80 (SD = 19.8) during this period. By 2011, ezetimibe accounted for 13.2% of the total cost of all cholesterol-lowering medications, and 14.9% of government spending in this therapeutic class (Fig. 2).

Cohort analysis

A total of 17,870 new ezetimibe users were identified between 2004 and 2011. Of these, 17,475 (98%) met the study inclusion criteria (Fig. 3). The mean age of the cohort was 62.5 years (SD = 11.8), and 46% of patients (n = 7984) were women. More than one quarter (28%; n = 4864) were classified as receiving first-line therapy because they had not received a statin medication in the previous 365 days. Of this number, 83% (n = 4024) were categorized as receiving monotherapy (ie, no statin fills within the following 60 days). In total, first-line monotherapy accounted for almost one quarter (23%) of all new prescriptions for ezetimibe between 2004 and 2011 (Fig. 4). The associated government cost of ezetimibe dispensations originating from this group of first-line monotherapy users was $670,272 in 2011 and $3,188,345 for the entire study period. Also, in patients receiving first-line ezetimibe therapy (ie, no previous statin use), the use of nonstatin cholesterol-lowering medication (fibrate, niacin, or resins) was also infrequent (13.7% [668 of 4864]). Changing the follow-up period to 30 or 90 days made little difference in the estimated percentage of monotherapy (83%) of those receiving first-line ezetimibe (84.1% and 81.7% for 30 and 90 days, respectively).

Among the subgroup of individuals who had a statin prescription in the preceding 365 days (ie, second-line users), the vast majority (89% [n = 11,180]) had never received more than 1 unique agent, and 33% (n = 2694) did not achieve a high-dose statin equivalent based on the most recent statin dispensed before receiving ezetimibe. In total, new ezetimibe use was prescribed by 1074 unique physicians. Of all prescribers identified, 28.4% (305 of 1074) never prescribed ezetimibe as first-line monotherapy. Further, the majority of prescribers initiated ezetimibe as first-line monotherapy in ≤ 10 patients. However, a relatively small
number of prescribers frequently initiated ezetimibe as first-line monotherapy (Fig. 5). In fact, when prescriber information was available, 51.6% (1906 of 3697) of all cases of first-line monotherapy were prescribed by 10.4% of the ezetimibe prescribers. The vast majority of all prescribers of ezetimibe were general practitioners. However, based on the frequency of first-line monotherapy prescriptions, we stratified prescribers into low-frequency (0-1), moderate-frequency (2-9), and...
high-frequency (10-100) groups. The group of prescribers who prescribed ezetimibe with low frequency for first-line mono-therapy had a significantly higher percentage of specialists (12%, 7%, and 6% for low-, moderate-, and high-frequency groups, respectively; \( P = 0.002 \) for the \( \chi^2 \) test) (Fig. 5). Prescriber information was missing for 9% of new ezetimibe prescrip-tions (1497 of 15,978).

In the final multivariable mixed-effects model, there was moderate prescriber variation for first-line monotherapy (intraclass correlation coefficient = 0.13). After adjusting for the effect of prescriber, patients receiving < 4 distinct medications in the previous year had the greatest odds of receiving first-line monotherapy with ezetimibe compared with those using multiple medications (odds ratio [OR], 3.8; 95% confidence interval [CI], 3.21-4.50) (Table 1). Other factors associated with increased odds of patients receiving first-line monotherapy, albeit with smaller ORs, included female sex, no previous government payment for medications, \( \geq 1 \) diuretic dispensation, \( \geq 1 \) diabetes diagnosis in physician billing file, \( \geq 1 \) hypertension diagnosis in physician billing file, advanced age (> 71 years), and high number of outpatient physician visits (Table 1). In contrast, the strongest negative predictor of patients receiving first-line monotherapy was a hospitalization for acute coronary syndrome (OR, 0.60; 95% CI, 0.40-0.90) or revascularization (OR, 0.58; 95% CI, 0.39-0.85) (Table 1).

**Table 1.** Estimated ORs from mixed-effects model for predictors of receipt of first-line monotherapy ezetimibe

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>&gt;71</td>
<td>1.15 (1.01-1.31)</td>
</tr>
<tr>
<td>63-71</td>
<td>1.02 (0.91-1.15)</td>
</tr>
<tr>
<td>55-62</td>
<td>0.94 (0.84-1.06)</td>
</tr>
<tr>
<td>(&lt;55</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.41 (1.30-1.53)</td>
</tr>
<tr>
<td>No prescription costs paid by government health insurance</td>
<td>1.18 (1.07-1.28)</td>
</tr>
<tr>
<td>Number of outpatient physician visits</td>
<td></td>
</tr>
<tr>
<td>&gt;27</td>
<td>1.32 (1.14-1.53)</td>
</tr>
<tr>
<td>17-27</td>
<td>1.22 (1.08-1.38)</td>
</tr>
<tr>
<td>10-16</td>
<td>1.15 (1.03-1.29)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Coronary revascularization procedure</td>
<td>0.58 (0.39-0.85)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0.60 (0.40-0.90)</td>
</tr>
<tr>
<td>Hypertension diagnosis</td>
<td>1.20 (1.09-1.32)</td>
</tr>
<tr>
<td>Diabetes diagnosis</td>
<td>1.11 (1.00-1.24)</td>
</tr>
<tr>
<td>Number of prescription medications</td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>3.80 (3.21-4.50)</td>
</tr>
<tr>
<td>4-6</td>
<td>1.67 (1.45-1.93)</td>
</tr>
<tr>
<td>7-11</td>
<td>1.25 (1.09-1.42)</td>
</tr>
<tr>
<td>( \geq 12 )</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>( \geq 1 ) diuretic dispensation</td>
<td>1.22 (1.10-1.35)</td>
</tr>
<tr>
<td>( \geq 1 ) ( \beta )-blocker dispensation</td>
<td>0.82 (0.74-0.91)</td>
</tr>
<tr>
<td>( \geq 1 ) ACEI/ARB dispensation</td>
<td>0.73 (0.66-0.81)</td>
</tr>
</tbody>
</table>

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CI, confidence interval; OR, odds ratio.

**Discussion**

We conducted a population-based retrospective analysis to describe ezetimibe’s place in therapy among other cholesterol-lowering medications in the province of Saskatchewan between 2002 and 2011. Throughout this period, a striking increase in total statin dispensations was observed, with little evidence that a plateau had been reached by 2011. However, overall costs decreased dramatically after the introduction of generic atorvastatin. Ezetimibe was the only nonstatin lipid-lowering medication to demonstrate significant increases during this time. After ezetimibe was covered by the province in 2004, its use increased to become the second most commonly prescribed cholesterol-lowering medication, accounting for 8.8% of all dispensations and 13.2% of the total cost of medications in this therapeutic category. In particular, it seems that the use of ezetimibe started to increase in 2006. This might correspond with the publication of the 2006 Canadian Cardiovascular Society dyslipidemia treatment guidelines.\(^\text{23}\) However, a substantial percentage of ezetimibe use appears to be inconsistent with its defined role as a second-line agent. Approximately 50% of all new users of ezetimibe since 2004 have received ezetimibe as monotherapy (ie, without a concurrent statin). Moreover, almost one quarter of all new use of ezetimibe was classified as first-line monotherapy. The high percentage of individuals receiving first-line monotherapy cannot be explained with known factors such as intolerance or medication nonadherence. If statin side effects and
nonadherence were primary causes of these findings, it would be expected that first-line monotherapy would be distributed much more equally throughout all prescribers of ezetimibe. In contrast, the vast majority of prescribers have only a few patients using ezetimibe in this way.

Ezetimibe is considered a second-line agent because its impact on CHD outcomes is not fully understood despite its documented effects on lowering LDL cholesterol. In contrast, statins have been clearly associated with improved rates of CHD events in placebo-controlled trials. The results of this analysis suggest that a high percentage of ezetimibe use in Saskatchewan is not consistent with evidence-based recommendations. This constitutes a large population of individuals who may be at considerable risk for ischemic events because of the failure to initiate statin therapy. Although suboptimal prescribing may be considered as the straightforward cause, other patient-related factors may have strongly influenced these findings. As stated earlier, medication nonadherence is a well-known barrier to optimal medication use, and patients may selectively omit their statin prescriptions or refuse to consider statin prescriptions altogether. Additionally, intolerance may explain discontinuing statin medication and starting ezetimibe. However, the majority of ezetimibe prescribers initiated first-line monotherapy in a relatively small number of patients. In fact, almost half of all cases of first-line monotherapy appeared to be initiated by 10% of prescribers identified in the cohort of new ezetimibe users. Also, 89% of new ezetimibe users with a history of statin use filled only 1 type of statin medication in the previous year despite recommendations for rechallenge in cases of statin intolerance. Thus, even if statin intolerance was a frequent reason for ezetimibe use, it would be expected that individuals would be switched to a different statin before starting ezetimibe.

Based on these observations, it would appear that educational interventions such as academic detailing could be an efficient method to address this issue if it were targeted to specific prescribers rather than distributed generally throughout the province. Nevertheless, policies restricting drug reimbursement have been associated with improved guideline adherence with other medication categories, including antibiotics and antipsychotic drugs, and have been used in several Canadian provinces. Restricting the use of ezetimibe decreased overall use in Norway to 1.9% of total statin use in 2009. Regardless of the strategy chosen, optimizing the use of ezetimibe in Saskatchewan could potentially reduce costs without compromising, and potentially improving, patient outcomes.

Disclosures
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References


Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the Canadian Journal of Cardiology at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2013.11.031.