Published in final edited form as:

Am Heart J. 2014 May ; 167(5): 683–689. doi:10.1016/j.ahj.2014.01.014.

Impact of the ENHANCE Trial on the Use of Ezetimibe in the United States and Canada

Lingyun Lu, PharmD, MSc^{1,2}, Harlan M. Krumholz, MD, SM^{3,6}, Jack V. Tu, MD, PhD^{7,8,9}, Joseph S. Ross, MD, MHS^{4,10}, Dennis T. Ko, MD, MSc^{7,8,9}, and Cynthia A. Jackevicius, BScPhm, PharmD, MSc^{1,2,7,8,11}

¹Department of Pharmacy Practice and Administration, College of Pharmacy, Western University of Health Sciences, Pomona, CA

²Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA

³Department of Medicine, Section of Cardiovascular Medicine

⁴Yale University School of Medicine, Center for Outcomes Research and Evaluation, Yale New Haven Hospital, New Haven, CT

⁵Department of Epidemiology and Public Health, Section of Health Policy and Administration, New Haven, CT

⁶Robert Wood Johnson Clinical Scholars Program, New Haven, CT

⁷Institute for Clinical Evaluative Sciences, Toronto, Canada

⁸Department of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto, Toronto, Canada

⁹Division of Cardiology, Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

¹⁰Department of Medicine, Section of General Internal Medicine, New Haven, CT

¹¹University Health Network, Toronto, Canada

Abstract

Background—We previously found the use of ezetimibe increased rapidly with different patterns between the United States (US) and Canada prior to the landmark ENHANCE trial, which was reported in January 2008, and failed to show that the drug slowed the progression of atherosclerosis. What is not known is how practice in the two countries changed after the ENHANCE trial. We examined ezetimibe use trends in the US and Canada before and after the reporting of the ENHANCE trial.

Corresponding and reprint author: Cynthia Jackevicius, BScPhm, PharmD, MSc, BCPS, FCSHP, Western University of Health Sciences, College of Pharmacy, 309 E. Second St., Pomona CA, 91766, Phone: 909-469-5527 Fax: 909-469-5539 cjackevicius@westernu.edu.

Conflict of Interest Disclosure

Dr Krumholz reported being the chair of the cardiac scientific advisory board for UnitedHealthCare and is under contract to develop performance measures for the Centers for Medicare & Medicaid Services. Dr. Ross reported that he is a member of a scientific advisory board for FAIR Health, Inc. None of the other authors reported disclosures.

Methods—We conducted a population-based, retrospective, time-series analysis using the data collected by IMS Health in the US and Compuscript in Canada from January 1, 2002 to December 31, 2009. The main outcome measure was monthly number of prescriptions for ezetimibe-containing products.

Results—The monthly number of ezetimibe prescriptions/100,000 population rose from 6 to 1082 in the US from November 2002 to January 2008, then significantly declined to 572/100,000 population by December 2009 after the release of the ENHANCE trial, a decrease of 47.1% ($P<0.001$). In contrast, in Canada, use continuously rose from 2 to 495/100,000 population from June 2003 to December 2009 ($P=0.2$). US expenditures totaled \$2.24 billion in 2009.

Conclusions—Ezetimibe remains commonly used in both the US and Canada. Ezetimibe use has decreased in the US post-ENHANCE, whereas use has gradually but steadily increased in Canada. The diverging patterns of ezetimibe use in the US and Canada requires further investigation as it reveals that a common evidence base is eliciting very different utilization patterns in neighboring countries.

Introduction

Ezetimibe, an intestinal cholesterol absorption inhibitor, reduces low density lipoprotein cholesterol (LDL-C) levels by approximately 20% when given alone and has synergistic LDL-lowering effects when added to statins.¹ In January 2008, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, an industry sponsored and conducted trial, failed to show that ezetimibe plus simvastatin reduced atherosclerosis progression compared with simvastatin alone, even though LDL-C levels were significantly reduced.² Although clinical outcomes were not evaluated in the ENHANCE trial, the effect of ezetimibe on the surrogate endpoint of carotid intimal media thickness, did not provide support for the drug. Subsequent trials have also failed to show positive clinical benefits when added to or compared with statins, and one trial even suggested the possibility of harm.^{3, 4} No outcomes trial has shown a clinical benefit of ezetimibe compared with statin therapy.²⁻⁴

We previously reported that prior to ENHANCE, different patterns of ezetimibe use emerged in the US and Canada after its introduction on the market, with its use increasing at a substantially higher rate in the US than in Canada. Accordingly, annual adjusted expenditures for ezetimibe per 100,000 population were over 4-fold higher in the US (\$ 947,000) than in Canada (\$ 216,000) in 2006.⁵ The negative results from ENHANCE would be expected to similarly temper ezetimibe use in both the US and Canada given that the similar evidence is available in both countries. However, the remaining uncertainty of ezetimibe makes it difficult to predict how its use has changed over time. Practice guidelines, pharmaceutical marketing (e.g., direct-to-consumer advertising) and drug policy, such as formulary and reimbursement differ between the US and Canada. Therefore, response to the “negative” ezetimibe evidence may also vary. Given that Canada was more conservative on ezetimibe use prior to ENHANCE,⁵ it would be expected that Canada would be more responsive to lower use and expenditures after ENHANCE.

Therefore, our objectives were to compare the utilization of and expenditures for ezetimibe before and after the reporting of the ENHANCE trial in both the US and Canada. Furthermore, since statins have a strong evidence-base and are the most commonly used lipid-lowering agents, we also evaluated statin use between countries to determine how ezetimibe use compares with statin use.

Methods

Study Design and Data Sources

We conducted a retrospective, population-level, time-series analysis using data collected by IMS Health in the US and Canada from January 2002 to December 2009 to describe the use of and expenditures for ezetimibe. Ezetimibe was introduced as Zetia in October 2002 and in combination with simvastatin (Vytorin) in July 2004 in the US. In Canada, it was introduced as Ezetrol in May 2003.^{6,7} We compared the utilization trends of ezetimibe before and after the release of the ENHANCE trial results within each country as well as between the US and Canada. Additionally statin use was compared between the two countries as a reference standard. The trends of ezetimibe and statin use were also compared within each country. The Canadian Compuscript Audit (CCA) of IMS Health Canada Inc. and the National Prescription Audit (NPA) 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) were employed as data sources. The CCA and the NPA data track numbers and costs of prescriptions filled by retail pharmacies (including independent, mail order, mass merchandise and discount houses) in both countries.^{5,8}

We obtained IMS data for the number of dispensed prescriptions and the associated costs without data on patient and prescriber characteristics. IMS selects pharmacy outlets for data collection in a stratified manner according to region, type (independent, chain, mail order, or long-term care), and size of outlet. Samples are selected from the reporting stores by applying criteria such as prescription type and volume, consistency of reporting, and payment type. Data were collected electronically each day from the sample pharmacies comprising drugstores and pharmacy outlets distributed proportionally within each stratum. NPA in the US, and CCA in Canada consist respectively, of approximately 25,000 and 5,657 retail pharmacies which are randomly sampled from the company's database of more than 38,000 and 8,575 stores, accounting for approximately two-thirds of all retail pharmacies in the US and Canada. In both countries, the sample is resized as required based on quality control measures, and major changes typically coincide with a new calendar year. 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 population in each region and regional totals are summed to provide a national estimate (US data are rounded to the nearest 1000 prescriptions).^{5, 8-11}

Study Intervention and Primary Variables

The ENHANCE trial,² the results of which were released in January 2008, represented the intervention event. The monthly number of prescriptions of and expenditures for ezetimibe-containing products in the US and Canada were examined as the primary outcome of

interest. The study's timeframe was divided into 96 monthly intervals from January 2002 to December 2009 (72 months pre-ENHANCE and 23 months post-ENHANCE).

Statistical Analysis

Descriptive statistics were used to report the number of prescriptions and costs of prescription claims for ezetimibe as a single entity and as a combination product. Medication use and costs were also standardized according to number of prescriptions and costs per 100,000 population in each country with the use of 2006 census statistics for the US and Canada.^{12,13} All expenditures are expressed as US dollars. Costs in Canadian dollars were converted to costs in US dollars with the use of yearly values for purchasing-power parity from 2002 to 2009, reflecting relative differences in price levels for one time period in the two countries.¹⁴

We used an autoregressive integrated moving average (ARIMA) interrupted time-series analysis to model the monthly prescription volume to assess the effect of the ENHANCE trial on the primary variable for each country. Given the series of data taken in the past decade and the change of ezetimibe evidence with the report of the ENHANCE trial, the model is particularly well-suited to detect changes of ezetimibe use related to change in clinical evidence. The following procedures were employed. First, we determined the differencing required to produce stationarity of the data and the order of both autoregressive (AR) and moving average (MA) operators to identify the type of the ARIMA model to be estimated. Stationarity means that the statistical parameters (mean and standard deviation) of the series do not change with time. We checked the stationarity of the time series using the augmented Dicky-Fuller test (ADF). The time series were stationarized by differencing. Once stationarity was achieved, the series autocorrelations and partial autocorrelations were examined to determine the number of AR and MA parameters.¹⁵ We conducted an autocorrelation check for the presence of white noise. Secondly, the approximate maximum likelihood estimates of the model parameters were obtained by employing a modified sum of squares method described by McLeod.¹⁶ The model that gives the minimum of the Akaike Information Criterion (AIC) was selected by using goodness-of-fit tests. Lastly, we ran diagnostic checks over the residuals of the models to determine whether they were independent, homoscedastic and normally distributed.¹⁷ To determine whether the residuals were white noise, the Residual Autocorrelation Function (RACF)¹⁸ was examined.

Next, a new variable called "I" was created as a binary variable to denote the intervention (release of the ENHANCE trial result in January 2008). The intervention effect was then added to the model as a dummy variable coded as 1 for the intervention phase (after January 2008) and 0 for the baseline phase (January 2008 and before). The interrupted time series model was used to test for the impact of the intervention (ENHANCE trial). The differences of ezetimibe use between the US and Canada before and after the ENHANCE trial were tested using linear regression with interaction effect of country and time. The difference between the trends of ezetimibe and statin use within each country was assessed using the same methods with interaction effect of medication and time.

All analyses were performed with SAS 9.3 software. P values of < 0.05 were considered statistically significant. The study was approved by the institutional review board of Western

University of Health Sciences. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

Prescription Volume

The monthly number of prescriptions for ezetimibe-containing products rose from 6 to 1082 per 100,000 population in the US from November 2002 to January 2008, then continually declined to 572 per 100,000 population by December 2009 after the release of the ENHANCE trial, a decrease of 47.1%. ($P<0.001$) (Figure 1) Among these, Zetia and Vytorin both showed a similar utilization pattern with the peak of 462 and 620 prescriptions per 100,000 population in January 2008 respectively. By December 2009, prescriptions decreased to 281 for Zetia and to 291 for Vytorin per 100,000 population in the US. In contrast, the monthly number of prescriptions for ezetimibe has been consistently rising from 2 to 495 per 100,000 population in Canada from June 2003 to December 2009, with no change after ENHANCE (P value=0.2), representing a different usage pattern than the US. ($P<0.001$)

During the study period, the use of statins rose steadily in both countries. (Figure 2) Population-adjusted statin use rose more rapidly in Canada than that in the US from 2002 to 2009. ($p<0.001$) At baseline 3261 statin prescriptions per 100,000 population were dispensed in January 2002, increasing to 5470 in January 2008 and 5996 in December 2009 per 100,000 population in the US. The population-adjusted ratio of number of statin prescriptions to ezetimibe prescriptions was 5:1 in January 2008, and then increased to 10:1 in December 2009 in the US. This represents the decrease of ezetimibe-containing product use relative to statin use in the US since January 2008. ($P<0.001$) In contrast, the corresponding number of statin prescriptions dispensed in Canada was 3082 in January 2002, 6576 in January 2008 and 8140 in December 2009 per 100,000 population. The population-adjusted ratio of number of prescriptions for statins to that for ezetimibe was 18:1 in January 2008 and decreased to 16:1 in December 2009 in Canada. This represents the increase of ezetimibe relative to statin use in Canada. ($P<0.001$)

Expenditures

After Zetia was introduced in the US, the monthly costs associated with its use increased from \$1,281,000 in November 2002 to \$125,661,000 in January 2008, then declined to \$88,457,000 in December 2009. From July 2004 to January 2008, the monthly costs associated with Vytorin use in the US increased from \$935,000 to \$174,657,000, then decreased to \$93,023,000 in December 2009. The total monthly cost of prescriptions dispensed for either Zetia or Vytorin in the US was \$300,318,000 as of January 2008 and decreased to \$181,480,000 by December 2009, with a decrease of 39.6% after the ENHANCE trial results were released. After Ezetrol was available in Canada, the monthly costs associated with its use consistently increased from \$62,156 in June 2003 to \$14,967,462 in December 2009, with over a 200-fold increase. Expenditures for ezetimibe-containing products per 100,000 population, adjusted for purchasing-power parity, were

higher in the US than in Canada by a factor of 3.4 in January 2008, and decreased over 50% to 1.5 by December 2009.

Discussion

Our study shows that ezetimibe use increased rapidly in the US but gradually in Canada pre-ENHANCE. And, while use of ezetimibe in the US significantly decreased after the ENHANCE trial² was reported in January 2008, the use of ezetimibe in Canada has been steadily increasing regardless of the release of the ENHANCE trial results. However, even in the US, ezetimibe remains frequently used. The persistent level of use and different patterns among the two countries for a drug without a positive outcomes trial may represent an opportunity for practice improvement.

Ezetimibe was originally approved based on its cholesterol-lowering effect rather than its clinical outcomes benefit,¹⁹⁻²¹ and 10 years after its introduction, still lacks a completed well-designed outcomes trial. The first landmark ezetimibe trial, ENHANCE, showed that the addition of ezetimibe to simvastatin did not reduce the progression of atherosclerosis compared with statins alone.² Clinicians in the US appear to have had some response to this negative evidence, which was then further supported by subsequent trials. During our study period, the SEAS trial was also published in 2008, which found no significant reduction of the composite of aortic-valve-related clinical events and ischemic events in the simvastatin plus ezetimibe group compared with placebo. However, the study did find such therapy reduced the incidence of non-aortic-valve-related ischemic cardiovascular events as one of the secondary outcomes, which is not strong evidence of benefit and warrants further study. This study also raised a concern for cancer with treatment of ezetimibe plus statin, which was ultimately dismissed by many experts.⁴ These negative findings question the net clinical outcomes benefit of ezetimibe and may have contributed to the reduction of its use in the US. However, the use of ezetimibe in Canada continued to grow despite the absence of supportive outcomes evidence.

Why did ezetimibe use patterns differ between the US and Canada after the negative evidence, which was accessible to clinicians in both countries, was reported? Other factors that may have allowed ezetimibe prescribing to flourish in Canada in the setting of emerging negative evidence for this drug include marketing, guidelines, drug policy, and medication access. Marketing via direct-to-consumer advertising remains unavailable in Canada.²² Canadian lipid guideline 2006 and 2009 updates both recommended that ezetimibe can be an add-on therapy to statins in patients who are not able to achieve target LDL-C level on statin monotherapy. Despite the release of the negative ENHANCE trial, the guideline recommendation on ezetimibe did not change.^{23,24} Drug policies based on current evidence may change drug use over time as new evidence emerges for certain medications.

In the US, nearly all state Medicaid programs provided Zetia and Vytorin coverage when these products were first introduced to market. After the release of the ENHANCE trial results in January 2008, there is evidence that state Medicaid programs had limited the use of Zetia or/and Vytorin. For instance, the Mississippi Medicaid program removed Zetia from the preferred drug list, effective 7/1/2008,²⁵ and New York state moved Vytorin from

preferred agents to non-preferred agents since 2008 (effective 4/2008).²⁶ Incentive formulary designs such as preferred drug lists and prior authorization programs, which respond to emerging evidence, have the potential to profoundly influence prescribing and medication use.

In Canada, most, but not all, publicly funded provincial drug formularies were generally conservative in their coverage of ezetimibe from the beginning. However, their formularies did not change throughout the years even though new negative evidence emerged. Among the three largest provinces (Ontario, Quebec, and British Columbia) in which approximately 75% of Canada's population lives, Ontario and Quebec government-funded formularies list ezetimibe with prescribing criteria that limit its use to patients in whom the target level of LDL-C has not been achieved with a statin, and patients who cannot tolerate or have a contraindication to statins. The British Columbia formulary never listed ezetimibe as a benefit to date.²⁷⁻²⁹ Public formulary listings often influence medication coverage in private Canadian drug plans.³⁰ The lack of explicit responsiveness of provincial formularies to the emerging yet uncertain negative ezetimibe evidence of ENHANCE² and SEAS⁴ may have been interpreted by prescribers as permission to continue with current ezetimibe prescribing practices. Without dramatic harms reported for ezetimibe or obvious drug policy changes, many clinicians may have remained hopeful that ezetimibe is beneficial, while awaiting the clinical outcomes results of the IMPROVE-IT trial, which will evaluate whether the addition of ezetimibe to statin therapy improves cardiovascular outcomes (cardiovascular death or major coronary events or non-fatal stroke) compared with simvastatin monotherapy in patients with LDL-C 50-125 mg/dL (50-100 mg/dL if prior statin) after acute coronary syndromes.³¹

Despite the decline in ezetimibe use in the US, this drug remains commonly prescribed in both countries. Prior reports have found that if harmful outcomes are demonstrated in a trial, medication use declines, but may follow varying patterns. Oral hormone replacement therapy (HRT) dramatically declined in the US and Canada following termination and publication of the estrogen-progestin arm of the Women's Health Initiative (WHI) trial.^{32,33} More modest declines in the use of doxazosin and other α -blockers were found after the ALLHAT trial.³⁴ Smaller and more gradual declines were observed for ALLHAT than for HRT, which might be partially due to less intense media coverage for ALLHAT than for WHI.³⁵ Smaller and more variable declines in use have been reported with nesiritide in hospital systems.³⁶ Since the ENHANCE trial did not find evidence of harmful outcomes for ezetimibe, there may be less urgency or alarm amongst clinicians and the media to stimulate as dramatic a change in prescribing as was seen with WHI, resulting in a high level of residual ezetimibe use in both countries. In addition, the WHI trial was initially designed to evaluate clinical outcomes, while the ENAHNCE trial was designed to examine surrogate markers, which may also contribute to the less dramatic change of ezetimibe use post-ENHANCE.

For comparison, we evaluated statin use over the same period. Statin use rose steadily in both countries with higher rates in Canada than in the US. While ezetimibe use relative to statin use decreased by about 50% post-ENHANCE in the US, minimal change was seen in Canada. In this situation of increasing use of the gold standard lipid-lowering agent-statins,

the lack of relative reduction of ezetimibe to statin use in Canada represents a potential problem that warrants further exploration.

Our study has some limitations. First, we cannot determine the appropriateness of the prescriptions. We used IMS health data, which are collected from audits of prescriptions dispensed to describe general trends of drug utilization. These data do not provide exact information with respect to drug use by individual patients or providers. Second, we cannot assess the impact of the prescriptions on outcomes. We did not have access to patient-level data such as medical conditions and lipid levels, to evaluate the impact of ezetimibe prescribing pattern change on patient's clinical outcomes. Finally, we are not certain why the countries diverged in their practice patterns. For example, we do not have marketing data for ezetimibe in both countries. Therefore, we do not know if the marketing strategies may account for the differences of ezetimibe use between the US and Canada. However, direct-to-consumer advertising is still unavailable in Canada.

Conclusion

Ezetimibe use has been significantly decreasing in the US since the results of the ENHANCE trial were released in January 2008. However, ezetimibe remains commonly used in the US and Canada, with annual expenditures of over \$2 billion in 2012 in the US.^{37,38} Despite the absence of positive outcomes evidence after publication of the ENHANCE trial, ezetimibe use and associated expenditures have gradually but steadily increased in Canada over the last decade. The diverging patterns of ezetimibe use in the US and Canada requires further investigation as it reveals that a common evidence base is eliciting very different utilization patterns in neighboring countries.

Acknowledgments

We gratefully acknowledge IMS Health-US and IMS Health Canada Inc. for providing the data required for the analyses from the National Prescription Audit™ and the CompuScript Audit®, respectively. The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the IMS Health Canada Inc. CompuScript® Audit database (2002-2009), and IMS Health National Prescription Audit™ (2002-2009). All Rights Reserved.

Financial Disclosures

This study was funded in part by the College of Pharmacy of Western University of Health Sciences, Pomona, California and in part by a Canadian Institutes of Health Research (CIHR) team grant in cardiovascular outcomes research to the Canadian Cardiovascular Outcomes Research Team. Neither funding source had any role in the design and conduct of the study, collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr. Krumholz is chair of a cardiac scientific advisory board for UnitedHealth and supported by grant U01-HL105270 (Center for Cardiovascular Outcomes Research at Yale University) from the National Heart, Lung, and Blood Institute. Drs. Krumholz and Ross receive support from Medtronic, Inc. to develop methods of clinical trial data sharing, from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting, and from the Food and Drug Administration (FDA) to develop methods for post-market surveillance of medical devices. Dr. Tu is supported by a Canada Research Chair in Health Services Research, and by a Career Investigator award of the Heart and Stroke Foundation of Ontario, Toronto, Ontario. Dr. Ross is currently supported by the National Institute on Aging (K08 AG032886) and by the American Federation of Aging Research through the Paul B. Beeson Career Development Award Program. Dr. Ko is supported by a Clinician Scientist (Phase II) Award from the Heart and Stroke Foundation of Ontario. The Institute for Clinical Evaluative Sciences is supported by an operating grant from the Ontario Ministry of Health and Long-Term Care, Toronto, Ontario.

References

1. Bruckert E, Giral P, Tellier P. Perspectives in cholesterol-lowering therapy: the role of ezetimibe, a new selective inhibitor of intestinal cholesterol absorption. *Circulation*. 2003; 107(25):3124–3128. [PubMed: 12835406]
2. Kastelein JJ, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008; 358(14):1431–1443. [PubMed: 18376000]
3. Villines TC, Stanek EJ, Devine PJ, et al. The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis). *J Am Coll Cardiol*. 2010; 55(24):2721–2726. [PubMed: 20399059]
4. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008; 359(13):1343–1356. [PubMed: 18765433]
5. Jackevicius CA, Tu JV, Ross JS, Ko DT, Krumholz HM. Use of ezetimibe in the United States and Canada. *N Engl J Med*. 2008; 358(17):1819–1828. [PubMed: 18375999]
6. Drugs@FDA: FDA approved drug products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed April 2, 2013
7. Health Canada. Notice of compliance. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/index_e.html. Accessed April 2, 2013
8. Jackevicius CA, Tu JV, Ross JS, Ko DT, Carreon D, Krumholz HM. Use of fibrates in the United States and Canada. *JAMA*. 305(12):1217–1224. [PubMed: 21427374]
9. IMS Health Inc. Information sources: Pharmacies. <http://www.imshealth.com/portal/site/imshealth/menuitem.3e17c48750a3d98f53c753c71ad8c22a/?vgnextoid=abb6e590cb4dc310VgnVCM100000a48d2ca2RCRD#Pharmacies>. Accessed July 18, 2013
10. Tu K, Mamdani MM, Jacka RM, Forde NJ, Rothwell DM, Tu JV. The striking effect of the Heart Outcomes Prevention Evaluation (HOPE) on ramipril prescribing in Ontario. *CMAJ*. 2003; 168(5):553–557. [PubMed: 12615747]
11. Majumdar SR, McAlister FA, Soumerai SB. Synergy between publication and promotion: comparing adoption of new evidence in Canada and the United States. *Am J Med*. 2003; 115(6):467–472. [PubMed: 14567371]
12. Statistics Canada. Census of Canada. 2006. <http://www12.statcan.ca/english/census06/home/Index.cfm..> Accessed April 2, 2013
13. Census Bureau home page. <http://www.census.gov>. Accessed April 2, 2013
14. Vachris MA, Thomas J. International price comparisons based on purchasing power parity. *Month Labor Rev*. 1999; 122(10):3–12.
15. Dickey DA, Fuller WA. Distribution of the estimators for autoregressive time series with a unit root. *J Am Stat Assoc*. 1979; 74:427–431.
16. Mcleod AI, Hipel KW, Lennox WC. Advances in Box-Jenkins modeling 2. Applications. *Water Resources Research*. 1977; 13(3):577–586.
17. Hipel KW, Mcleod AI, Lennox WC. Advances in Box-Jenkins modeling. 1. Model construction. *Water Resources Research*. 1977; 13(3):567–575.
18. Box GEP, Pierce DA. Distribution of autocorrelations in autoregressive integrated moving average time series models. *J Am Stat Assoc*. 1970; 65:1509–1526.
19. Product information: Zetia. Merck/Schering-Plough Pharmaceuticals; North Wales, PA: Sep. 2007 (package insert)
20. Product monograph: Ezetrol. Merck Frosst-Schering Pharmaceuticals; Kirkland, QC, Canada: Oct. 2007 (package insert)
21. Product information: Vytorin. Merck/Schering-Plough Pharmaceuticals; North Wales, PA: Sep. 2007 (package insert)
22. Mintzes B, Mangin D. Direct-to-consumer advertising of prescription medicines: a counter argument. *Future Med Chem*. 2009; 1(9):1555–1560. [PubMed: 21425978]
23. McPherson R, Frohlich J, Fodor G, Genest J. Canadian Cardiovascular Society. Canadian Cardiovascular Society position statement--recommendations for the diagnosis and treatment of

- dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol.* 2006; 22(11):913–927. [PubMed: 16971976]
24. Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. *Can J Cardiol.* 2009; 25(10):567–579. [PubMed: 19812802]
 25. Mississippi Division of Medicaid Preferred Drug List. <http://www.medicaid.ms.gov/Documents/Pharmacy/PDLArchive/PreferredDrugListEffective070108.pdf>. Accessed April 2, 2013
 26. New York State Medicaid Preferred Drug Program-Annual report to the governor and legislature. http://www.health.ny.gov/health_care/medicaid/program/docs/annual_report_preferred_drugs_2008-09.pdf. Accessed April 2, 2013
 27. Ontario Drug Benefit program formulary. <https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet?searchType=luNoteQuery&phrase=exact&keywords=240600049>. Accessed April 2, 2013
 28. Regie de l'assurance maladie Quebec. Registry - list of medications. <http://www.ramq.gouv.qc.ca/en/regie/legal-publications/pages/list-medications.aspx>. Accessed April 2, 2013
 29. British Columbia PharmaCare pro-gram formulary. <http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp>. Accessed April 2, 2013
 30. Marra CA, Lynd LD, Anis AH, Esdaile JM. Approval process and access to prescription drugs in Canada. *Arthritis Rheum.* 2006; 55(1):9–11. [PubMed: 16463404]
 31. Cannon CP, Giugliano RP, Blazing MA, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J.* 2008; 156(5):826–832. [PubMed: 19061694]
 32. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA.* 2004; 291(1):47–53. [PubMed: 14709575]
 33. Austin PC, Mamdani MM, Tu K, Jaakkimainen L. Prescriptions for estrogen replacement therapy in Ontario before and after publication of the Women's Health Initiative Study. *JAMA.* 2003; 289(24):3241–3242. [PubMed: 12824204]
 34. Stafford RS, Furberg CD, Finkelstein SN, Cockburn IM, Alehegn T, Ma J. Impact of clinical trial results on national trends in alpha-blocker prescribing, 1996-2002. *JAMA.* 2004; 291(1):54–62. [PubMed: 14709576]
 35. Naylor CD. The complex world of prescribing behavior. *JAMA.* 2004; 291(1):104–106. [PubMed: 14709583]
 36. Partovian C, Li S, Xu X, et al. Patterns of change in nesiritide use in patients with heart failure: How Hospitals React to New Information. *JACC: Heart Failure.* 2013; 1(4):318–324. [PubMed: 24621935]
 37. Top 100 statistics - Zetia sales data. Drugs.com. <http://www.drugs.com/stats/zetia>. Accessed Oct. 7, 2013
 38. Top 100 statistics - Vytorin sales data. Drugs.com. <http://www.drugs.com/stats/vytorin>. Accessed Oct. 7, 2013

Figure 1. Standardized Monthly Number of Ezetimibe Prescriptions/100,000 Persons in the US and Canada from 2002 to 2009

Legend: Y-axis: No. of Ezetimibe prescriptions/100,000 population

Data are from the National Prescription Audit of IMS Health United States and the Canadian CompuScript Audit of IMS Health Canada Inc.. Numbers were standardized to the population based on census data from both countries for 2006

Figure 2. Standardized Monthly Number of Statin Prescriptions/100,000 Persons in the US and Canada from 2002 to 2009

Legend: Y-axis: No. of Statin prescriptions/100,000 population

Data are from the National Prescription Audit of IMS Health United States and the Canadian CompuScript Audit of IMS Health Canada Inc.. Numbers were standardized to the population based on census data from both countries for 2006