

The Impact of US FDA and Health Canada Warnings Related to the Safety of High-dose Simvastatin

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Abstract

Introduction Between 2010 and 2012, the US Food and Drug Administration and Health Canada issued warnings to healthcare professionals emphasizing the increased risk of muscle problems with high-dose simvastatin.

Objective To measure the impact of the Health Canada safety warning regarding dose-dependent adverse effects of simvastatin on prescribing of low, medium, and high doses of simvastatin.

Methods An interrupted time-series design was used to evaluate the impact of a Health Canada safety warning on 7 November 2012 regarding the safety of high-dose simvastatin. Monthly prescription records were analyzed for beneficiaries of the Nova Scotia Seniors' Pharmacare Program aged 65 years or older who had received > 1 prescription of simvastatin between 1 January 1997 and 31 March 2015. Autoregressive Integrated Moving Average models were used to test changes in the proportion of beneficiaries dispensed a low dose (< 40 mg), medium dose (40 mg to < 80 mg), or high dose (≥ 80 mg) of simvastatin over time.

Results There were 219 monthly periods, of which 29 periods occurred after the Health Canada warning. On average during the pre-warning periods there were 2944 simvastatin users per month, of whom 71% were dispensed a low dose, 26% a medium dose, and 2% a high dose. The proportion of beneficiaries dispensed low-dose simvastatin increased by 0.9% (one-sided *p* value 0.035; 90% CI 0.07–1.65), the proportion dispensed medium-dose simvastatin decreased by 0.7% (one-sided *p* value 0.0496; 90% CI –1.48 to –0), and there was no significant change in the proportion dispensed high-dose simvastatin (–0.15% change, one-sided *p* value 0.205; 90% CI –0.45 to 0.15).
Conclusions The Health Canada Health Care Professional warning had a small effect on increasing the proportion of beneficiaries dispensed low and medium doses of simvastatin but not high doses of simvastatin. Nevertheless, there remain seniors in Nova Scotia receiving high-dose simvastatin for whom the benefit/risk potential may need to be re-evaluated.

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Key Points

The Health Canada warning related to increased risk of muscle problems associated with high-dose simvastatin had a small effect on increasing the proportion of beneficiaries dispensed low and medium doses of simvastatin but not on decreasing the proportion receiving high doses of simvastatin.

Due to the limited effect of “Dear Health Care Professional” letters, other intervention strategies are needed to increase the awareness and the uptake of recommendations related to simvastatin dosage to improve the risk/benefit of prescribing statins.

1 Introduction

Statin medications are useful for prevention and treatment of cardiovascular disease and stroke [1–4]. The evidence on the effectiveness of statins from randomized controlled trials and meta-analyses [4–6] supports the strong recommendations in clinical practice guidelines, which has ultimately led to their widespread use [7]. Prescriptions for statins are increasing in Canada, especially in older adults [8–17].

Although statins are relatively well tolerated, studies have documented the types and prevalence of adverse effects of statins, particularly in high doses. Adverse muscle-related effects are relatively common, occurring in 10–30% of patients [18–20] and may be dose related; however, severe myopathies with clinically relevant elevation in muscle enzymes occur in less than 1% of patients [21]. In addition, other adverse effects have been reported, such as an increased risk of diabetes and acute kidney injury [22–24].

As the published literature and other evidence on the adverse effects of medications are accumulated post-marketing, regulatory authorities have developed mechanisms to communicate these potential adverse effects with prescribers. A common approach is the use of “Dear Health Care Professional” (i.e., “Dear Doctor”) letters, which identify the nature and magnitude of the risk and may be sent by mail, fax, or electronically. The use of these safety communications has been criticized as their impact on changing prescribing has been limited. A systematic review by Piening et al. [25] examined the impact of safety-related regulatory action on clinical practice and concluded that many of the 50 identified articles lacked rigor in study design and statistical analysis. Of these studies, few were from Canada [26–29]. One study evaluated the effect of an alerting system on the prescribing of statins and macrolide antibiotic co-prescriptions, but none were specifically related to simvastatin [30].

Numerous healthcare professional alerts have been issued globally regarding the safety of high-dose simvastatin and an increased risk of myopathy, including rhabdomyolysis. Specifically, the US Food and Drug Administration (FDA) issued a warning to increase the awareness of rhabdomyolysis with high-dose simvastatin on 19 March 2010 [31]. The FDA issued an additional warning on 8 June 2011 that suggested no new patients should be started on 80 mg and should maintain an 80-mg dose only if they had been on this for 12 months in the absence of muscle toxicity [32]. The UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued a warning on 1 May 2010 related to high-dose simvastatin [33]. The European Medicines Agency (EMA) has also issued recommendations regarding dose-related adverse events of simvastatin [34]. Health Canada followed on 7 November 2012 [35], and suggested a recommended daily

dose of simvastatin of ≤ 40 mg. A major impetus for these alerts stems from the findings of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial [36]. The incidence of confirmed myopathy was substantially higher in patients randomized to simvastatin 80 mg (1%) compared to 20 mg ($\sim 0.02\%$) daily [relative risk 26.6, 95% confidence interval (CI) 6.5–109.3] [36].

The impact of the Health Canada warning on statin prescriptions is unknown. Other studies have shown limited impact if direct healthcare professional communications are used alone without other interventions, but the impact varies by drug, level of risk, and other factors [37]. The Nova Scotia Department of Health and Wellness did not have a specific intervention related to statin prescribing in conjunction with the Health Canada warning. This study estimates changes from January 1997 to March 2015 in the proportion of Nova Scotia Seniors’ Pharmacare Program (NSSPP) beneficiaries receiving prescriptions for low-, medium-, and high-dose simvastatin.

2 Methods

2.1 Study Population

The study cohort was derived from NSSPP beneficiaries. Nova Scotia is a Canadian province with a population of about 940,000 residents [38]. Physician services are provided, without charge, for insured services from approximately 1100 family physicians and 1100 medical specialists [39]. The source population comprised of all patients aged 65 years or older registered for Nova Scotia medical services coverage who enrolled and paid the required premiums and co-payments for the NSSPP and received at least one prescription of simvastatin between 1 January 1997 and 31 March 2015. The NSSPP does not provide drug insurance to residents insured by private drug programs or other public sector drug programs such as Veterans Affairs Canada or First Nations and Inuit Health. The NSSPP reimbursed all statins marketed in Canada, including atorvastatin, rosuvastatin, simvastatin, fluvastatin, lovastatin, and pravastatin. Cerivastatin was removed from the market and is not included in the study.

Ethics approval was received from the Dalhousie University Ethics Committee (effective date 8 July 2014; renewal 8 July 2015).

2.2 Study Design

We used an interrupted time-series design, which is the strongest quasi-experimental study design to examine changes following an intervention on a target population

using observational data [40]. Specifically, this design includes the pre-intervention time period as a control and post-intervention periods as treatments. Assuming a trend-stationary model (deterministic trend with stationary error process) with a reasonable number of observations in the pre-intervention period, an adequate model can be identified without requiring a large number of observations in the post-intervention period [41]. This approach has been previously used with Nova Scotia Pharmacare prescription data [42, 43].

We examined the monthly proportion of beneficiaries of dispensed prescriptions for simvastatin high-dose (≥ 80 mg/day), medium-dose (40 mg/day to < 80 mg/day), and low-dose (< 40 mg/day) before and after multiple healthcare professional regulatory warnings. The rationale for categorizing all doses less than 40 mg as low dose and medium dose as 40 mg was to capture changes in dosage from 80 to 40 mg of simvastatin given the Health Canada warning recommended a simvastatin dosage of 5–40 mg. The proportion of beneficiaries was obtained by dividing the monthly beneficiary count by the total NSSPP beneficiaries for a given month. Furthermore, the proportion of beneficiaries per month data was first divided into four time periods: (1) pre-warning or pre-intervention period (January 1997 to February 2010); (2) FDA I period (March 2010 to May 2011); (3) FDA II period (June 2011 to October 2012); and (4) Health Canada period (November 2012–March 2015).

Given Health Canada's warning regarding the potential risks of high-dose simvastatin, our primary aim was to test changes in the proportion of beneficiaries per month receiving simvastatin doses greater than or equal to 80 mg simvastatin before and after the Health Canada regulatory warning on 7 November 2012. However, it is plausible that prescribers in Nova Scotia may be responsive to warnings issued by the FDA and therefore tested for the incremental change in the proportion of high-, medium-, and low-dose simvastatin users after the FDA I and FDA II periods. To our knowledge, there were no other major Nova Scotia provincial-level interventions related specifically to simvastatin dosing during the investigated time period, other than those considered.

2.3 Statistical Analysis

To test changes in the proportion of beneficiaries dispensed low-, medium-, and high-dose simvastatin we employed a time series regression model by applying a two-stage modeling approach. This approach accounts for long-term time effects and other time-related covariate/factor effects as well as serially random fluctuations. Both long-term trend and the seasonal effects can be modelled by either deterministic or random effects as necessary. By

controlling any effects from FDA warnings, any change detected between the FDA I and II and Health Canada periods would thus likely be associated with the Health Canada regulatory warning (intervention) effect.

In the first stage, a linear regression model was fitted with co-variates, stepwise variables corresponding to intervention time periods to examine the FDA warnings and the impact of the Health Canada warning letter. The residuals from this initial model were examined to check the possible autocorrelation for dependence. If the significant autocorrelation was found in the residuals then a suitable Auto-Regressive Integrated Moving Average (ARIMA) model or seasonal ARIMA model was determined for the residual process using the Akaike Information Criterion (AIC). The final model was a regression with an ARIMA error model identified by the residual analysis, which includes checking of autocorrelation function (ACF), partial autocorrelation function (PACF), and normality of residuals [44]. This procedure was followed on one dosage series at a time.

The statistical program used was R 3.1.1 [45].

3 Results

There were a total of 219 time intervals, of which 158 intervals were in the pre-warning period ($\sim 73\%$ of data values), 32 time intervals in the FDA I and II periods (15 time intervals in the FDA I period ($\sim 7\%$ of data values), 17 time intervals in the FDA II period ($\sim 8\%$ of data values)), and 29 time intervals after the Health Canada warning ($\sim 13\%$ of data values). On average in the pre-warning period, there were a total of 2944 simvastatin users per month, of whom approximately 71% were dispensed a low dose, 26% were dispensed a medium dose, and 2% were dispensed a high dose. Table 1 provides descriptive statistics of monthly proportions of three dose categories for the pre-warning, FDA I, FDA II, and Health Canada periods. Briefly, on average across all time periods, over 50% of simvastatin users were dispensed a low dose, between 23 and 39% a medium dose, and less than 5% a high dose.

Figure 1 shows the total NSSPP simvastatin beneficiary count per month over a period of 18 years between 1 January 1997 and 31 March 2015. The interventions are denoted by the vertical colored lines. Clearly Fig. 1 shows the total patient count receiving simvastatin per month was changing over time. With this total count for a given month as the denominator, Fig. 2 shows the three time series proportions of the low, medium, and high dose for a given month with the intervention depicted by vertical lines. These plots show a long-term trend in all three series with some subtle increase in the low-dose series and a slight

Table 1 Descriptive statistics for the percentage of Nova Scotia Seniors' Pharmacare Program (NSSPP) beneficiaries dispensed (a) low dosage (< 40 mg), (b) medium dosage (≥ 40 mg or < 80 mg), and (c) high dosage (≥ 80 mg) simvastatin

Time period	Number of months (N)	Minimum (%)	25th percentile	Median (%)	Mean (%)	Standard deviation	75th percentile	Maximum (%)
(a) Pre-warnings	158	56.5	64.4	71.6	75.3	13.1	88.4	97.0
FDA I	15	55.8	56.4	56.6	56.6	0.4	56.8	57.0
FDA II	17	54.8	55.4	55.7	55.8	0.5	56.2	57.0
HC	29	55.1	57.3	57.6	57.5	0.7	57.9	59.0
(b) Pre-warnings	158	2.9	10.8	26.0	22.8	11.9	33.2	39.0
FDA I	15	38.1	38.7	38.8	38.8	0.4	38.9	39.0
FDA II	17	38.8	39.3	39.6	39.6	0.5	39.8	41.0
HC	29	37.7	38.3	38.7	38.8	0.6	39.1	41.0
(c) Pre-warnings	158	0.0	0.9	2.3	1.9	1.2	2.7	4.0
FDA I	15	4.1	4.5	4.7	4.7	0.2	4.8	5.0
FDA II	17	4.0	4.3	4.7	4.6	0.3	4.8	5.0
HC	29	3.1	3.5	3.7	3.8	0.4	4.1	5.0

FDA US Food and Drug Administration, HC Health Canada, NSSPP Nova Scotia Seniors' Pharmacare Program, SD standard deviation

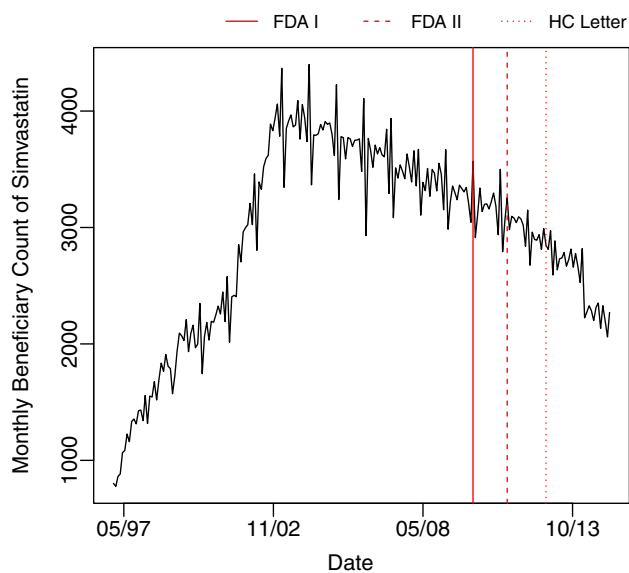


Fig. 1 Monthly beneficiary counts of simvastatin prescription records for eligible Nova Scotia Seniors' Pharmacare Program (NSSPP) beneficiaries, January 1997 to March 2015. FDA US Food and Drug Administration, NSSPP Nova Scotia Seniors' Pharmacare Program

decrease in the medium- and high-dose series after the Health Canada warning, which can be similarly observed in Table 1, the descriptive statistics.

The long-term trend and the serially autocorrelated random fluctuations in the time series of the low-dose beneficiary proportion data were modelled by an ARIMA (5, 1, 0). A regression model with intervention factors of the FDA's and Health Canada's warnings gave reasonable

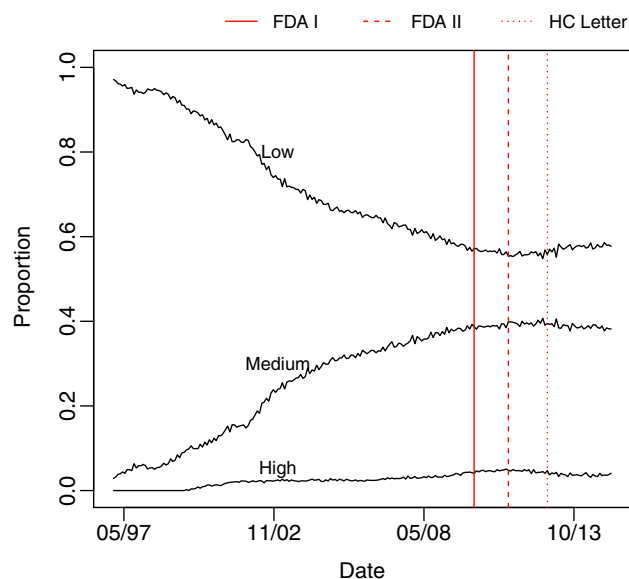


Fig. 2 Monthly proportion of Nova Scotia Seniors' Pharmacare Program (NSSPP) beneficiaries dispensed low (< 40 mg/day), medium (≥ 40 mg/day and < 80 mg/day), and high (≥ 80 mg/day) of simvastatin, January 1997 to March 2015. The red vertical lines indicate timing of safety alert (FDA I: 19 March 2010; FDA II: 8 June 2011; Health Canada: 7 November 2012). FDA US Food and Drug Administration, NSSPP Nova Scotia Seniors' Pharmacare Program

intervention estimates, while incorporating the dependent structure of the ARIMA (5, 1, 0) model. The residual diagnostic analysis confirmed the final model adequacy. Similarly, a regression with a dependent-model ARIMA (13, 1, 0) was applied for the medium-dosage time series. The residual analysis presented no significant anomalies

confirming the model adequacy. For the high-dosage series an ARIMA (4, 1, 0) model was selected to model the long-term and serially time-related autocorrelation in the data since November 1999 because no patient received a high dose before that time. The residual analysis presented some anomalies, which may indicate the evidence of lack of fit. One reason for the model inadequacy might be the complex variations arising during the intervention time period. The model should be interpreted with caution.

The results from the time series regression model described above show that the proportion of beneficiaries receiving low-dose simvastatin increased by 0.9% after the Health Canada warning (one-sided p value 0.035; 90% CI 0.07–1.65) suggesting an overall increase in proportion of beneficiaries dispensed a low dose. On the contrary, the proportion of beneficiaries receiving a medium dose decreased by 0.7% after the Health Canada warning (one-sided p value 0.0496; 90% CI –1.48 to –0). No significant change was observed in the proportion of high-dose users after the Health Canada warning (–0.15% change, one-sided p value 0.205; 90% CI –0.45 to 0.15). By March 2015, less than 5% ($n = 93$) of beneficiaries were receiving 80 mg of simvastatin.

4 Discussion

The “Dear Health Care Professional” letter issued by Health Canada on 7 November 2012 related to high-dose simvastatin was not associated with any significant change in the proportion of NSSPP beneficiaries receiving ≥ 80 mg daily dose of simvastatin. However, there was a small statistically significant increase ($< 1\%$) in the proportion of low-dose statin users and decrease in the proportion of medium-dose statin users. Importantly, our findings raise concerns about the effectiveness of the regulatory warnings to quickly change prescribing.

Our study tested the incremental change in the proportion of simvastatin high-, medium-, and low-dose users of the Health Canada warning following other regulatory warnings. Although the Health Canada warning in November of 2012 emphasized the potential harms of high-dose simvastatin, the potential harms of 80 mg doses had already been communicated by US and European drug regulatory agencies. Therefore, the additional impact of another regulator may be negligible. Furthermore, physicians may be unaware of the regulatory warnings, disagree with the warnings, or disregard the warnings as they may feel their patients have been stable for some time.

Another potential explanation for our findings are that the number of patients dispensed high-dose statins represents a small proportion of users, thereby minimizing the power of our analysis to detect a change in this group. By March 2015 only 93 NSSPP beneficiaries (4% of NSSPP

statin users) were receiving a high simvastatin dose, whereas approximately 38% of NSSPP statin users were receiving a medium dose and approximately 58% of beneficiaries were dispensed a low dose of simvastatin following the Health Canada warning.

Our findings are consistent with previous studies and those included in systematic reviews that note that government drug regulatory agencies’ passive risk communications advisories have a modest effect on changing drug prescribing and monitoring [25]. Studies examining the effect of FDA and EMA warnings found variable effect sizes of regulatory warnings (2–50%) [25, 46–52]. However, the studies note that the effects are variable depending on such factors as the type of physicians targeted, the type of drug, the nature and frequency of risk, patient characteristics, the amount of scientific certainty, supporting documentation from specialist physicians, and the amount of media attention received. Some drug risk communications are associated with a large and fast impact on drug prescribing and monitoring, while others have no impact, more modest impacts, or delayed impacts [46, 48, 49, 52–56]. Many studies had inadequate designs [25, 57, 58] and some studies note that passive dissemination strategies to improve prescribing behaviors have been shown to be modestly successful, with effect sizes in the range of 8% [59, 60].

4.1 Strengths and Limitations

This study had a number of strengths. It used longitudinal data, representing over 80% of Nova Scotia’s older adults, since the majority are enrolled in Pharmacare (Health Data Nova Scotia, personal communication). It involved both urban and rural and academic and non-academic practice settings. We used the Box and Tiao method [44], which has been found to be useful for a limited number of time points.

There are also some limitations to our study. The data set used has only NSSPP beneficiaries and excludes those patients covered by private insurance or other publicly funded drug programs, those paying out-of-pocket, or those receiving prescription drug samples. Prescriptions for residents in nursing homes are included in the data and not reported separately. We are unable to capture prescriptions while patients are in hospital. We examined all prescriptions and did not identify newly started prescriptions separately. Although regulatory health warnings, including the Health Canada warning in November 2012, recommended that no patients initiate simvastatin 80 mg, the warning also pertained to those with ongoing simvastatin 80 mg doses; therefore, we decided to include all NSSPP beneficiaries receiving a statin prescription. Furthermore, given the small number of new users, we did not stratify our sample into incident and prevalent users. We examined the

effect of the Health Canada warnings but physicians may also have been influenced by many sources, including international literature, pharmaceutical industry marketing approaches, media, direct-to-consumer advertising, patient coupons for statins, etc. [52]. We were unable to determine if the physician was unaware of the warning, chose to exceed the dosage in the warning due to a specific benefit/risk assessment, or was aware of the warning but determined that the evidence in the warning was limited [61]. We were unable to determine if prescribers decreased simvastatin dosages for some individuals from a high to a medium dose. Moreover, we did not determine if the small changes in the proportion of statin users using low and medium doses were due to patients switching doses of simvastatin or due to patients switching to alternative statins.

Even though our study examined 29 months of data after the Health Canada warning, physicians had access to published scientific literature related to the association between high-dose simvastatin and myopathy several years before the FDA and Health Canada warnings [62]. We did not determine the risks and benefits of statin therapy for individual patients including co-morbidities, co-prescribing, and the duration of statin therapy, or patient health outcomes. Although beyond the scope of this study, it is important to further study patients who may be receiving sub-optimal simvastatin doses such as those at high risk of a cardiovascular event. We were unable to determine the healthcare system, provider, and patient factors that contributed to the relatively slow uptake of the regulatory warnings. Physicians may have been treating patients to specific target low density lipoprotein concentrations and increasing the dose of simvastatin to reach that target [46].

Further work is needed to assist physicians in determining the potential harms, benefits, and uncertainties of prescribing for individual patients, including approaches to presenting the quality of evidence and the magnitude of the risks [61, 63, 64]. Multicomponent interventions including computerized decision support and personalized audit and feedback may have a greater effect than passively disseminated “Dear Healthcare Professional” letters [65]. However, one study examining the impact of computerized alerts related to medication black-box warnings in ambulatory care had limited effect [66]. Approaches have been taken to increase the effectiveness of the regulatory warnings. A study by Reber et al. [37] examined the characteristics determining the impact of the Direct Health Care Professional Communications in The Netherlands and found that a standard template emphasizing the drug safety issues at hand and the type of serious safety issues were associated with changes in new drug use [37].

5 Conclusion

Statin medications in high doses have the potential to increase the risk of adverse effects. The Health Canada warning in 2012 was associated with a small, statistically significant change in the proportion of beneficiaries dispensed low and medium doses but not high doses of simvastatin. Prior warnings from other regulatory agencies may have diminished the impact of the Health Canada warning. Importantly, there remain older adults in Nova Scotia receiving 80 mg or more of simvastatin for whom the benefit/risk potential may need re-evaluation. Further research on methods to increase the awareness and prescribing changes recommended by regulatory warnings is needed, including incorporation into clinical decision support systems.

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