Use and misuse of ezetimibe: analysis of utilization 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 was carried out between 2002 and 2011 using provincial health administrative databases. Overall utilization and costs of ezetimibe were described over time. Among new users of ezetimibe, the percentage who received the drug as first-line mono-therapy was estimated. First-line mono-therapy was defined as no statin dispensations in the 365 days prior to, and the 60 days following the first ezetimibe dispensation. Potential predictors of first-line mono-therapy 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. Overall, ezetimibe was used as first-line mono-therapy in 23% of all new users (4,024 / 17,475). Approximately half of all cases of first-line mono-therapy were prescribed by 10.4% (112/1,074) of prescribers in the cohort. Subjects with previous acute coronary syndrome or coronary revascularization procedures were significantly less likely to receive first-line mono-therapy.

Conclusions: A high proportion of ezetimibe's use is not in accordance with evidence-based recommendations. Sub-optimal prescribing could partially explain current patterns of use; however, other factors such as medication non-adherence 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.

Background

Ezetimibe (Ezetrol®, MERCK CANADA INC) is a cholesterol-lowering medication released on the Canadian market in 2003. It is recommended as second line after HMG Co-reductase inhibitors (statins) due to a lack of robust evidence evaluating coronary heart disease (CHD) outcomes,[1-6] as well as a relatively high cost compared to first line therapy.[7] Despite these disadvantages, the number of ezetimibe prescriptions in Canada has steadily increased over time.[8,9]

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), while five provinces provide coverage only for patients meeting specific criteria (Alberta, Ontario, Quebec, 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.[10] Thus, Saskatchewan residents are eligible to receive coverage for ezetimibe even if it is prescribed as first-line therapy. However, the percentage of ezetimibe use that is a first-line therapy remains unknown.

Considering ezetimibe's high cost in comparison to first-line medications and its potentially inferior protection against CHD events, an analysis of its use in Saskatchewan is timely. We aimed to describe the frequency by which ezetimibe has been used as a first-line agent along with its costs compared to 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 one 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 (i.e., First Nations, Royal Canadian Mounted Police, Canadian Armed Forces, and federal prison inmates). The validity and accuracy of Saskatchewan prescription drug database has been demonstrated in many studies examining medication utilization.[11-15]

Methods

Population Utilization and Cost Analysis

Using the prescription drug file, we calculated both the annual number of beneficiaries receiving at least one dispensation and the annual cost of these dispensations. The following cholesterol-lowering medications were included in this analysis: ezetimibe, statins, fibrates (i.e., fibric acid derivatives), resins (i.e., 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 in order to provide two years of baseline data prior to the first date of coverage for ezetimibe in January of 2004.

Cohort Analysis

A retrospective cohort of new ezetimibe users was identified with the following inclusion criteria: **a)** received a new dispensation for ezetimibe between January 1st, 2004 and October 31st, 2011; and **b)** were continuous beneficiaries of the drug plan for at least 365 days prior to, and 60

days following 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 subjects 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 following the index dispensation to describe ezetimibe's place in therapy as follows: **a)** first-line mono-therapy; **b)** second-line mono-therapy; **c)** first-line combination therapy; and **d)** second-line combination therapy. First-line therapy was defined as no statin dispensations in the 365 days preceding the index date (i.e., first ezetimibe dispensation). Subjects receiving at least one statin dispensation in the prior year were classified as receiving second-line therapy. In addition, because cholesterol lowering medications are typically dispensed monthly in Saskatchewan,[16] the 60 day period following (and including) the index date was examined to classify individuals as receiving mono-therapy or combination therapy. Specifically, subjects receiving a statin dispensation during the 60-day follow-up period were categorized as receiving combination (statin-ezetimibe) therapy, while subjects with no statin dispensations were considered to be using mono-therapy (ezetimibe only). In sensitivity analyses, stricter definitions of combination therapy were also examined (30 or 90 days versus 60 days). Finally, we examined the subgroup of ezetimibe users who had received a statin dispensation in the prior 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 (i.e., first-line mono-therapy/other). We fit a generalized linear mixed-effects model[17,18] 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 mono-therapy prescriptions from some prescribers. Only a random prescriber intercept was included in the model. The extent of clustering from individual prescriber was examined using the intraclass correlation coefficient (ICC).[19,20] The covariates used in the model are provided in Supplemental Appendix 1. We tested for multicollinearity using the variance inflation factor (VIF) and interpreted values more than 10 as having high multicollinearity.[21] We tested whether the variance of the random effect was significantly different from zero using a likelihood ratio test (LRT), which asymptotically follows a χ^2 distribution.[22] We only retained those covariates that had both a p-value of less than 0.05 on the Wald's t-test and lead to an increase in model fit as judged by the Akaike information criterion (AIC).[23] SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA) was used to perform the analysis. Ethics approval was received from the University of Saskatchewan Biomedical Research Ethics Board.

Results

Analysis of Utilization and Cost

The number of beneficiaries receiving ≥ 1 dispensation for any class of medication (i.e., active provincial beneficiaries) increased by 8% between 2002 and 2011 (i.e., from 609,240 to 657,962). Concurrently, the percentage of individuals receiving ≥ 1 cholesterol-lowering medication among active beneficiaries increased by 117% (i.e., 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 (Figure 1). As a percentage of all cholesterol-lowering dispensations, ezetimibe use increased from 2.5% in 2004 to 8.8% in 2011 (Figure 1). In particular, the use of ezetimibe seems to start increasing in 2006 (Figure 1).

The cost of all cholesterol-lowering medications also increased steadily from 2002 but decreased sharply after 2010 following the emergence of generic atorvastatin onto the Saskatchewan Formulary. In contrast, the total cost of all ezetimibe dispensations increased from $752,032 to $7,004,180 between 2004 and 2011and the average cost per dispensation of ezetimibe also increased from $66.30 (SD=12.8) to $79.80 (SD=19.8) during this period. By 2011, ezetimibe accounted for 13.2% of the total cost of cholesterol-lowering medications and 14.9% of government spending in this therapeutic class (Figure 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 (Figure 3). The mean age of the cohort was 62.5 years (SD=11.8), and 46% of patients (n=7,984) were female.

More than one-quarter (28%; n=4,864) 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=4,024) were categorized as receiving mono-therapy (i.e., no statin fills within the following 60 days). In total, *first-line mono-therapy* accounted for almost one-quarter (23%) of all new prescriptions for ezetimibe between 2004 and 2011 (Figure 4). The associated government cost of ezetimibe dispensations originating from this group of first-line mono-therapy users was $670,272 in 2011 and $3,188,345 for the entire study period. Also, in subjects receiving first-line ezetimibe therapy (i.e., where prior statin use was absent), non-statin cholesterol-lowering medications (fibrates, niacin, or resins) use was also infrequent (13.7%; 668/4,864). Changing the follow-up period to 30 or 90 days made little difference in the estimated percentages (83%)

of mono-therapy 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 (i.e., second-line users), the vast majority (89%; n=11,180) had never received more than one unique agent, and 33% (n=2,694) did not achieve high dose statin equivalent based on the most recent statin dispensed prior to receiving ezetimibe.

In total, new ezetimibe use was prescribed by 1,074 unique physicians. Of all prescribers identified, 28.4% (305/1,074) never prescribed ezetimibe as first-line mono-therapy. Further, the majority of prescribers initiated ezetimibe as first-line mono-therapy in ≤ 10 subjects. However, a relatively small number of prescribers frequently initiated ezetimibe as first-line mono-therapy (Figure 5). In fact, where prescriber information was available, 51.6% (1,906/3,697) of all cases of first-line mono-therapy 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 mono-therapy prescriptions, we stratified prescribers into low (0-1), moderate (2-9), and high (10-100) frequency groups. The group of prescribers who had low frequency of first-line mono-therapy prescriptions had significantly higher percentage of specialists (12%, 7%, and 6% for low, moderate and high frequency groups respectively; p=0.002 for Chi-square test) (Figure 5). Prescriber information was missing for 9% of new ezetimibe prescriptions (1,497/15,978).

In the final multivariable mixed-effects model, there was moderate prescriber variation when receiving first-line mono-therapy (ICC = 0.13). After adjusting for the effect of prescriber, subjects receiving less than 4 distinct medications in the previous year had the greatest odds of receiving first-line mono-therapy with ezetimibe compared to those using multiple medications

(OR 3.8; 95% CI 3.21-4.50) (Table 1). Other factors associated with an increased odds of receiving first-line mono-therapy, albeit with smaller ORs included female gender, no prior government payment for medications, ≥ 1 diuretic dispensation, ≥1 diabetes diagnosis in physician billing file, ≥1 hypertension diagnosis in physician billing file, advanced age (>71 years), and high number of out-patient physician visits (Table 1). In contrast, the strongest negative predictor of receiving first-line mono-therapy was an ACS hospitalization (OR=0.60; 95%CI 0.40-0.90) or revascularization (OR=0.58; 95%CI 0.39-0.85) (Table 1).

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 have decreased dramatically following the introduction of generic atorvastatin. Ezetimibe was the only non-statin 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, the use of ezetimibe seems to start increasing in 2006. This might correspond with the publication of 2006 Canadian Cardiovascular Society (CCS) dyslipidaemia treatment guidelines.[24] However, a substantial percentage of ezetimibe's 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 mono-therapy (i.e., without concurrent statin). Moreover,

almost one-quarter of all new use of ezetimibe was classified as first-line mono-therapy. The high percentage of individuals receiving first-line monotherapy cannot be explained with known factors such as intolerance or medication non-adherence. If statin side effects and non-adherence was a primary cause 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 only have 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.[25-27] In contrast, statins have been clearly associated with improved rates of CHD events in placebo-controlled trials.[28-30] The results of this analysis suggest a high percentage of ezetimibe's use in Saskatchewan is not consistent with evidence-based recommendations. This constitutes a large population of individuals who maybe at considerable risk for ischemic events due to the failure to initiate statin therapy. Although sub-optimal prescribing may be considered as the straightforward cause, other patient-related factors may have strongly influenced these findings. As stated above, medication non-adherence is a well-known barrier to optimal medication use and patients may selectively omit their statin prescriptions,[31] or refuse to consider statin prescriptions altogether. Additionally, intolerance may explain stopping statin medication and starting ezetimibe. However, the majority of ezetimibe prescribers initiated first-line mono-therapy in a relatively small number of subjects. In fact, almost half of all cases of first-line mono-therapy 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 only filled one type statin medication in the previous year despite recommendations for re-challenge in cases of statin intolerance.[32] 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 first prior to 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 anti-psychotics [33-37] and have been employed in several Canadian provinces. Restricting the use of ezetimibe decreased overall usage in Norway to 1.9% of total statin utilization in 2009.[38] Regardless of the strategy chosen, optimizing the use of ezetimibe in Saskatchewan could potentially reduce costs without compromising, and potentially improving, patient outcomes.

Despite the high quality data provided through the Saskatchewan Ministry of Health covering over 90% of the provincial population without regard to age, sex, or employment status, several limitations of this study must be considered. First, prior statin use was defined by the presence of one or more dispensation in the year before starting ezetimibe; however, some patients may have more distant use that was not captured by our washout period. Although a longer period may have identified more individuals as prior users, it would not have changed the fundamental observation that ezetimibe is frequently initiated in individuals with no prior use or a gap of at least one year since they last used a statin. Second, statin medications dispensed in hospitals or provided as samples would not have been captured in our databases resulting in an overestimation of first-line ezetimibe use. However, subjects were required to obtain an ezetimibe dispensation from a retail pharmacy to enter the cohort so it is unlikely that they frequently obtained their statins elsewhere. Third, statin use may have been started later than 60

days following the index ezetimibe dispensation. Regardless, in order to satisfy the primary endpoint, first-line mono-therapy, individuals could not have any statin dispensation for a continuous period of 425 days (i.e., 365 days prior and up to 60 days after starting ezetimibe). Also, in a sensitivity analysis, the follow-up period was extended to 90 days (i.e., 455 days total). Thus, it can be confirmed that the vast majority of individuals were not using statin medications during this time based on the long screening period used. Finally it is impossible to determine the exact reasons for these dispensation patterns using administrative health databases; prescriber preferences as well as patient refusal to obtain statin medications in favour of ezetimibe may contribute to these patterns.

In summary, unrestricted use of ezetimibe in Saskatchewan appears to have resulted in a high proportion of ezetimibe therapy that is not in agreement with current guidelines. Although previous studies described the overall use of ezetimibe in Canada and the USA,[8] we are not aware of previous studies that describe ezetimibe's place in therapy specifically. The situation in Saskatchewan should reinforce the need for drug restriction policies such as prior authorization, especially in this era where new therapies such as antiplatelet and anticoagulant agents are emerging steadily. Health care practitioners must recognize the importance of these policies even if they can cause an administrative burden at the front line. Suboptimal use can be readily observed at the population level even when the majority of prescribers conform to current recommendations.

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Table 1: Estimated odds ratios (ORs) from mixed-effects model for predictors of receipt of first-line mono-therapy ezetimibe[1]

Predictor	OR (95%CI)
Age (years)	
>71	1.15 (1.01-1.31)
63-71	1.02 (0.91-1.15)
55-62	0.94 (0.84-1.06)
<55	1 (reference)
Female gender	1.41 (1.30-1.53)
No prescription costs paid by government health insurance	1.18 (1.07-1.28)
Number of out-patient physician visits	
>27	1.32 (1.14-1.53)
17-27	1.22 (1.08-1.38)
10-16	1.15 (1.03 -1.29)
<10	1 (reference)
Coronary revascularization procedure	0.58 (0.39-0.85)
Acute coronary syndrome	0.60 (0.40-0.90)
Hypertension diagnosis	1.20 (1.09-1.32)
Diabetes diagnosis	1.11 (1.00-1.24)

[1] ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker

Number of prescription medications	
<4	3.80 (3.21-4.50)
4-6	1.67 (1.45-1.93)
7-11	1.25 (1.09-1.42)
≥ 12	1 (reference)
≥1 Diuretic dispensation	1.22 (1.10-1.35)
≥1 Beta blocker dispensation	0.82 (0.74-0.91)
≥1 ACEI/ARB dispensation	0.73 (0.66-0.81)

Figure 1: Frequency of Dispensations for Cholesterol-Lowering Medications in Saskatchewan, 2002 to 2011

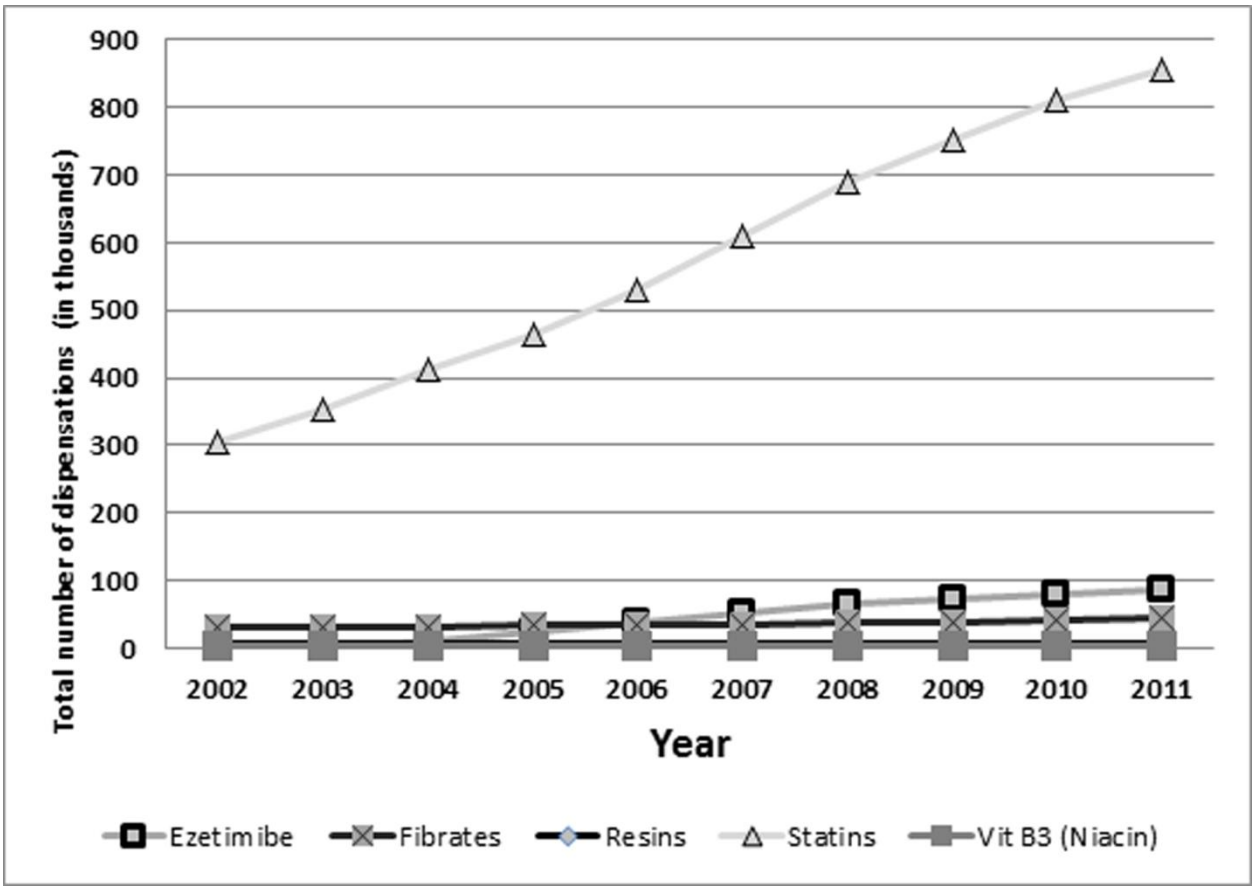


Figure 2: Government Cost of Cholesterol-Lowering Medications in Saskatchewan, 2001 to 2011

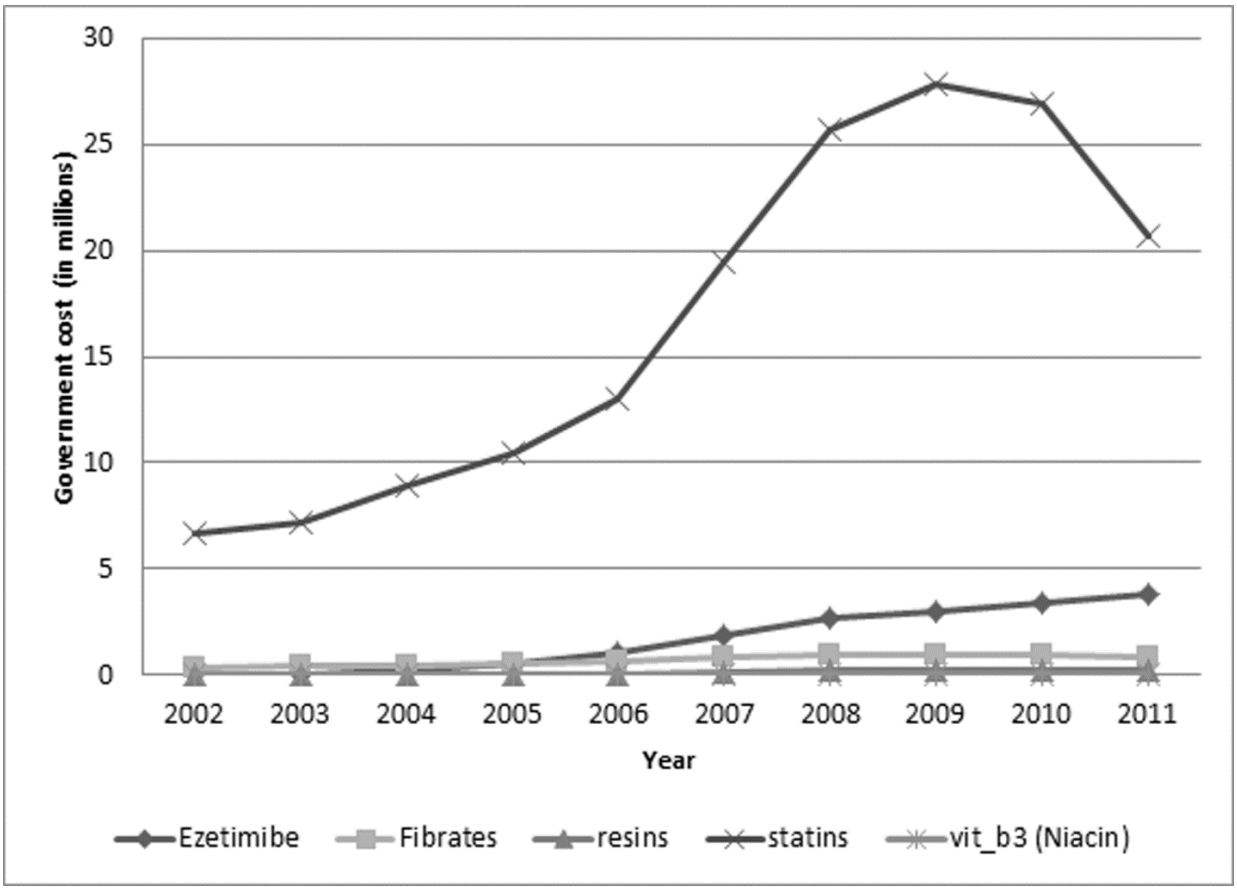


Figure 3: Flow Chart for Inclusion into the Ezetimibe Cohort

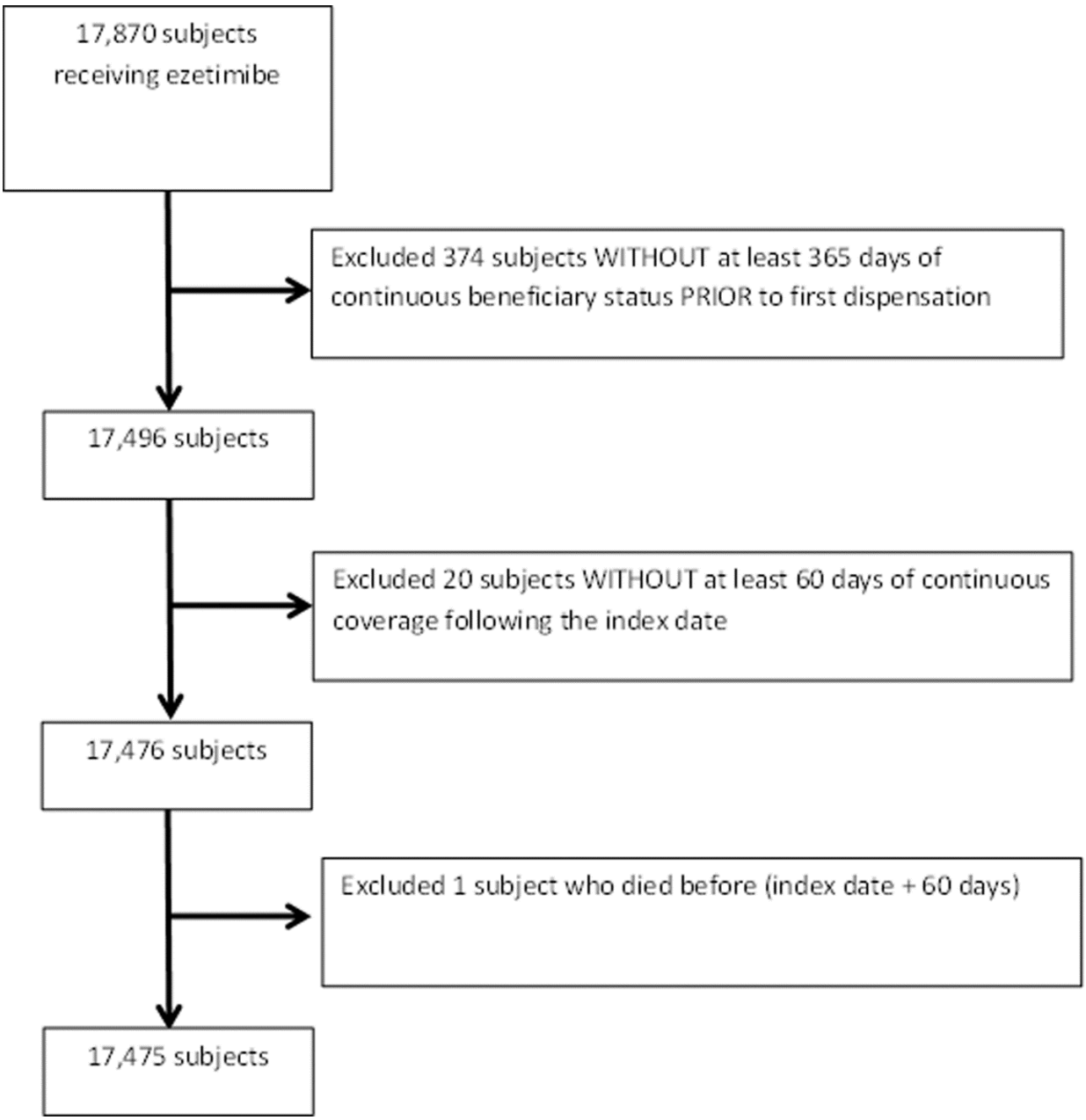
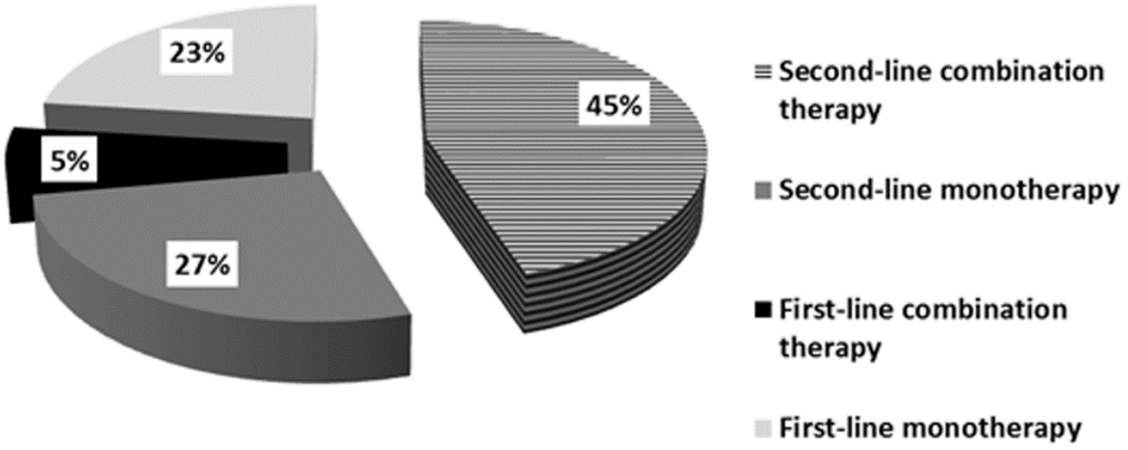


Figure 4: Ezetimibe's Place in Therapy amongst New Users



Second Line Combination Therapy = ≥1 statin dispensation in previous 365 days AND ALSO within 60 days on or following the first ezetimibe dispensation date; **Second-Line Monotherapy** = ≥1 statin dispensation in previous 365 days but NO statin dispensation within 60 days on or following the first ezetimibe dispensation date; **First Line Combination Therapy** = No statin dispensations in previous 365 days BUT ≥1 statin dispensation within 60 days on or following the first ezetimibe dispensation date; **First-Line Monotherapy** = No statin dispensations in previous 365 days AND NO statin dispensation within 60 days on or following the first ezetimibe dispensation date

Figure 5: Frequency of physicians (MD) According to the Number First-Line Mono-Therapy Ezetimibe Prescriptions (Rx)