Utilization patterns of extended-release niacin in Canada: Analysis of an administrative claims database

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BACKGROUND AND OBJECTIVE: To evaluate utilization patterns with extended-release niacin (ERN) compared with those observed with other lipid-modifying drugs (LMDs).

METHODS: A random sample of 17% of patients who had at least one LMD dispensation between January 2004 and February 2007 was obtained from the administrative databases of the Régie de l'assurance maladie du Québec. Primary outcomes included drug adherence, persistence and discontinuation with ERN and other LMDs, and daily maintenance dose attainment (1500 mg and 2000 mg) with ERN at one-year follow-up. Adherence was defined as the sum of days of all dispensations divided by the total number of days of follow-up. Persistence was defined as renewal of prescription before the end of dispensation plus a grace period (50% prescription duration).

RESULTS: Among 26,862 patients, the majority received statins (73.4%), whereas 867 (3.2%) received ERN. The mean age of ERN patients was 62 years and 75% were male. After one year, adherence with ERN was below that of statins (62.0% versus 74.9%), as was persistence (36.1% versus 46.7%), while discontinuation rates were higher (64.0% versus 53.3%). The median time until discontinuation for ERN was shorter than for statins (66 days versus 99 days). After one year, 5.8% of patients were taking 1500 mg or more and 3.2% were on 2000 mg.

CONCLUSIONS: In the present cohort of patients from regular clinical practice in Quebec, ERN use was associated with low prescription rates, inferior adherence and persistence compared with other LMDs, high discontinuation rates, and very low 2000 mg dose attainment.

Key Words: Coronary disease; Flushing; Niacin; Safety; Tolerability; Treatment outcomes

Les profils d'utilisation de la niacine à libération prolongée au Canada : L'analyse d'une base de données administrative de réclamations

HISTORIQUE ET OBJECTIF : Évaluer les profils d'utilisation de la niacine à libération prolongée (NLP) par rapport à ceux d'autres médicaments modificateurs des lipides (MML).

MÉTHODOLOGIE : Les chercheurs ont obtenu un échantillon aléatoire de 17 % de patients qui avaient reçu au moins une délivrance de MML entre janvier 2004 et février 2007 selon les bases de données administratives de la Régie de l'assurance maladie du Québec. Les issues primaires incluaient l'adhésion au médicament, la persistance et l'abandon de la NLP et d'autres MML, ainsi que l'atteinte de la dose d'entretien quotidienne (1 500 mg et 2 000 mg) de NLP au suivi d'un an. L'adhésion était définie comme la somme de tous les jours de délivrance divisée par le nombre total de jours de suivi. La persistance était définie comme le renouvellement de la prescription avant la fin de la délivrance, majorée d'une période de grâce (50 % de la durée de la prescription).

RÉSULTATS : La majorité des 26 862 patients ont reçu des statines (73,4 %), tandis que 867 (3,2 %) ont reçu de la NLP. L'âge moyen des patients qui prenaient de la NLP était de 62 ans, et 75 % étaient des hommes. Au bout d'un an, l'adhésion à la NLP était inférieure à celle des statines (62,0 % par rapport 74,9 %), tout comme la persistance (36,1 % par rapport à 46,7 %), tandis que les taux d'abandon étaient plus élevés (64,0 % par rapport à 53,3 %). Le délai médian avant l'abandon de la NLP était plus court que celui avant l'abandon des statines (66 jours par rapport à 99). Au bout d'un an, 5,8 % des patients prenaient une dose d'au moins 1 500 mg et 3,2 %, de 2 000 mg.

CONCLUSIONS : Dans la présente cohorte de patients d'une pratique clinique régulière au Québec, l'utilisation de la NLP s'associait à de faibles taux de prescription, à une adhésion et à une persistance moins élevées par rapport aux autres MML, à des taux élevés d'abandon et à une atteinte très faible de la dose de 2 000 mg.

On the basis of compelling evidence from clinical trials, consensus guidelines (1,2) continue to identify increased levels of low-density lipoprotein cholesterol (LDL-C) as the primary treatment target and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) as the principal lipid-modifying drugs (LMDs) to reduce the risk of coronary heart disease (CHD). However, considerable residual cardiovascular risk often remains despite extensive LDL-C lowering with statin therapy (3). One theoretical explanation for this residual cardiovascular risk is the presence of other lipid abnormalities such as reduced high-density lipoprotein cholesterol and elevated triglycerides – both of which are strong and independent predictors of CHD (4,5). Furthermore, clinical trials have shown that lipid-modifying therapies such as niacin and fibrates, which target high-density lipoprotein cholesterol and triglycerides in addition to LDL-C, have been associated with a reduction in cardiovascular events (6).

Niacin (nicotinic acid) is a highly effective pharmacotherapy for achieving comprehensive management of multiple lipid abnormalities (6) and, when used alone or in combination with other LMDs, has been shown to have beneficial effects on both long-term cardiovascular events (7-9) and atherosclerotic progression (9-12). However, long-term adherence to niacin therapy has been impaired by tolerability issues, particularly niacin-induced cutaneous vasodilation with flushing (6,13). Flushing is the most common reason for niacin discontinuation in clinical trials, occurring in 70% to 85% of patients who take immediate-release niacin (IRN) (6,14). At usual doses (3000 mg/day or lower), other potential adverse effects include changes in glycemic regulation (which tend to be modest and manageable) and, rarely, hepatotoxicity (15). The need for multiple daily dosing of niacin with food may also contribute to underutilization of IRN (13).

Niaspan (Abbott Laboratories, USA), an extended-release formulation of niacin (ERN), was developed to address tolerability issues

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associated with IRN, in the hope of ameliorating long-term treatment adherence and, with it, patient outcomes (16). Compared with IRN, ERN has an intermediate absorption rate and a more balanced metabolism between pathways associated with hepatotoxicity and flushing, which result in a more favourable tolerability profile (17). Accordingly, clinical trials of IRN and ERN formulations have found that approximately 85% of patients on IRN compared with 66% on ERN experience flushing symptoms (6).

ERN therapy is typically initiated at a daily dose of 500 mg for four weeks (16). Using dose titration to help manage adverse effects such as flushing, the dose is gradually increased by 500 mg/day or less over four weeks to reach a daily 1500 mg or 2000 mg dose for maintenance therapy (16). Despite the efficacy of ERN in achieving comprehensive lipid management and its increased tolerability over other niacin formulations (13,18-20), therapy with ERN is frequently associated with flushing, which often undermines treatment adherence and results in a high rate of discontinuation (13,19,21).

There is a paucity of data on niacin use in clinical practice in Canada, but studies conducted using United States administrative claims data have reported a great degree of suboptimal dose attainment, adherence and persistence associated with ERN use. Studies have reported that approximately one-half of patients on ERN therapy reached the recommended daily maintenance dose of 1000 mg or greater during 6.5 months of follow-up (22), most patients took "drug holidays" (22) and discontinuation rates were greater than 50% at one-year follow-up (23). The results of another study (24) also indicated a poor rate of persistence associated with ERN therapy. Only 10.7% of patients persisted with ERN therapy after nine months and 9.4% did so after one year.

In addition, certain clinical trials have demonstrated that niacin (mainly IRN) treatment is associated with minor increases (approximately 4% to 5%) in fasting glucose and glycosylated hemoglobin (HbA1c) when administered to patients with type 2 diabetes mellitus (T2DM) (14,25,26). However, these data involved treatment using high-dose (greater than 4000 g/day) niacin, which is generally not recommended in clinical practice. Other clinical trials have shown that patients treated with lower daily doses of niacin (1 g to 2.5 g of IRN formulation) showed no significant changes in the use of insulin and antihyperglycemic agents (27), and no clinically relevant changes in HbA1c (IRN or ERN formulation) (27,28). However, there is relatively little information concerning changes in glycemic control and associated changes in resource utilization among T2DM patients treated with ERN in regular clinical practice.

The objective of the present retrospective cohort study was to evaluate utilization patterns for ERN compared with other LMDs in a large Canadian administrative claims database. To this end, the study sought to compare adherence, persistence and discontinuation patterns for ERN therapy with those of other LMDs, evaluate dose attainment associated with ERN therapy, and examine the determinants of ERN treatment discontinuation. As a secondary objective, changes in T2DM severity, as indicated by changes in T2DM medication prescriptions and T2DM-related resource use, were analyzed in patients before and after initiating ERN versus any other LMD.

METHODS

Patients

Patients were selected from the Régie de l'assurance maladie du Québec (RAMQ; www.ramq.gouv.qc.ca) administrative claims database. The database contained information on medical services provided to all Quebec residents as well as records of prescribed medications dispensed to the elderly (65 years of age or older); income security recipients; and, since January 1997, all Quebec residents not covered by a private drug insurance plan. Records of medication services included diagnosis (*International Statistical Classification of Diseases and Related Health Problems, Ninth Revision* codes), date of service provision and sites where services were provided (hospital, emergency department or clinic). Information on dispensation of

prescribed medications included the date of the medication dispensations, drug code, drug dose, quantity of medication dispensed and prescription duration.

To preserve the confidentiality of beneficiaries, the RAMQ database extracted a random sample among all beneficiaries who had received at least one dispensation of a lipid-modifying therapy between January 1, 2004, and February 25, 2007, yielding a total of 116,073 patients. These patients were further screened based on several inclusion and exclusion criteria. Patients were included if they had received at least one dispensation of an LMD (ERN, statins, ezetimibe, fibrates, bile acid sequestrants or other forms of nicotinic acid) between January 1, 2004, and February 25, 2007. Accordingly, the index date was defined as the first date of treatment with an LMD. As an exception, to achieve a sufficient sample of patients on ERN therapy, patients who were initiated on ERN were assigned to the ERN group at the index date regardless of whether patients had received a different LMD before that date. As a result, patients on ERN therapy could have switched from a different LMD or have had ERN added to another LMD at the index date. To achieve sufficient background information, patients were required to have complete coverage from the RAMQ during the year before the index date. Patients who had a prescription for the index drug within one year before the index date were excluded. A total of 26,862 patients met the inclusion and exclusion criteria for the present study.

Outcome measures and definitions

Drug adherence, persistence, discontinuation and dose attainment: The primary outcomes used to compare utilization patterns of ERN and other LMDs included drug adherence, persistence, discontinuation and, in the case of ERN therapy, dose attainment in patients who continued therapy. To measure adherence, the sum of the number of days in which the LMD was dispensed was divided by the total number of days included in the six- and 12-month periods after the index date, respectively.

Persistence was defined as renewal of an index drug prescription before the end of the dispensation plus a 'grace period' (50% of the previous prescription duration). Because prescription durations varied from a low of seven (22.6%) to 120 days, a percentage of the prescription duration (50% grace period) was used as opposed to a fixed duration (eg, two weeks) to balance the opportunity to renew regardless of the prescription duration (29,30). The proportion of patients who persisted with each LMD therapy at one year following the index date was calculated and analyzed using the Kaplan-Meier proportional hazards method, with adjustment for the following covariates: sex, age, comorbidity (chronic disease score [31]; see Addendum), number of hospitalizations, duration of hospitalization, as well as visits to a general practitioner, specialist or emergency room. Additional analyses examined persistence according to index daily dose as well as monotherapy versus add-on therapy with ERN. Sensitivity analyses were conducted using a grace period of 100%.

Treatment discontinuation was analyzed among patients initiated on statin and ERN therapy. Among patients who discontinued therapy before the end of the one-year follow-up, the median time (days) until treatment discontinuation for patients treated with statins and ERN was compared. In addition, comparisons for the time (day) at which 50% of all patients treated with statins and ERN discontinued therapy were performed. A Cox proportional hazards model with adjustment for the above-mentioned covariates was conducted to evaluate determinants of early treatment discontinuation. Analyses of treatment discontinuation accounted for a grace period equivalent to 50% of the previous prescription duration before patients were considered to have discontinued therapy. Sensitivity analyses were conducted using a grace period of 100%.

To analyze dose attainment among patients continuing ERN therapy, the daily drug doses of all dispensations of ERN after the index date were identified for each patient. The average daily dose for patients on ERN therapy was calculated as the formulation dispensed

TABLE 1

Characteristics of all patients initiated on lipid-modifying drugs (LMDs) at the index date

Patients prescribed LMDs	Patients, n		% of total patients		
Index drugs	26,862				
Extended-release niacin (ERN)	867		3		
Statins	19,727		73		
Ezetimibe	347		1		
Fibrates	3431		13		
Bile acid sequestrant	1560		6		
Nicotinic acid (other than ERN)	930		4		
Patient characteristic	ERN (n=867)	Statin (n=19,727)	Ezetimibe (n=347)	Fibrates (n=3431)	Other LMD (n=2490)
Specialty of prescriber, n (%)					
General practitioner	470 (54)	15,917 (81)	258 (74)	2970 (87)	1487 (60)
Internist	88 (10)	755 (4)	21 (6)	123 (4)	116 (5)
Cardiologist	245 (28)	1696 (9)	26 (8)	116 (3)	48 (2)
Endocrinologist	47 (5)	444 (2)	24 (7)	98 (3)	47 (2)
Other	17 (2)	915 (5)	18 (5)	124 (4)	792 (32)
Men, n (%)	648 (75)	9404 (48)	134 (39)	1847 (54)	926 (37)
Age, years, mean $\pm$ SD	62 $\pm$ 11	65 $\pm$ 12	66 $\pm$ 10	59 $\pm$ 14	65 $\pm$ 15
Chronic disease score, mean $\pm$ SD	4.7 $\pm$ 3.3	3.4 $\pm$ 3.2	3.8 $\pm$ 3.2	3.1 $\pm$ 3.1	3.9 $\pm$ 3.5
Resource use/person (year before index date), mean $\pm$ SD					
Number of hospitalizations	0.5 $\pm$ 1.0	0.5 $\pm$ 1.2	0.4 $\pm$ 1.1	0.4 $\pm$ 1.1	0.9 $\pm$ 1.7
Number of days of hospitalization	1.2 $\pm$ 2.9	1.8 $\pm$ 4.7	0.7 $\pm$ 2.0	0.9 $\pm$ 3.3	2.4 $\pm$ 6.2
General practitioner visits	4.3 $\pm$ 3.8	3.9 $\pm$ 3.7	4.1 $\pm$ 4.5	4.1 $\pm$ 3.8	4.9 $\pm$ 4.7
Specialist visits	5.6 $\pm$ 6.1	3.9 $\pm$ 7.7	5.9 $\pm$ 11.9	3.4 $\pm$ 5.7	6.3 $\pm$ 9.5
Emergency room visits	0.8 $\pm$ 1.8	0.9 $\pm$ 1.8	0.8 $\pm$ 2.0	0.8 $\pm$ 1.7	1.6 $\pm$ 2.8

multiplied by the quantity divided by the duration (days) of use (formulation $\times$ [quantity/duration]). Calculations were performed at the index date (initial daily dose), and after three, six, nine and 12 months follow-up. Patients were stated to have 'reached' a specified recommended daily maintenance dose (ie, 1500 mg or 2000 mg for ERN) (16) during the month of the first dispensation of ERN at any point within the one-year follow-up.

T2DM: As a secondary objective, changes in T2DM severity, as indicated by changes in antihyperglycemic agent and T2DM-related resource use, were analyzed in patients before and after initiating ERN and any other LMD. T2DM was considered to be present if there were records of at least two diagnoses of T2DM within two years before the index date. To be included in the analysis, patients diagnosed with T2DM had to receive the same dose of their antihyperglycemic agent(s) in the two last dispensations before the index date and treated continuously with any LMD for one year or more afterward. Patients who received insulin before the second diagnosis were excluded.

Changes in antihyperglycemic agent use for control of T2DM were used as a proxy to evaluate the association between glycemic control (T2DM severity) and exposure to ERN. These methods, based on the Quebec formulary conditions for the reimbursement of thiazolidinediones, have been described previously (32). T2DM was defined as more severe if changes between the antihyperglycemic agent(s) prescribed one month before and one year after initiating LMDs met one or more of the following criteria: switched to a more intensive medication category (mild = metformin, acarbose; moderate = sulfonylureas; severe = thiazolidinediones; and very severe = insulin); added one or more oral antihyperglycemic agent or insulin to existing therapy; and increased the daily dose of existing therapy. T2DM was defined as less severe if the category, number or dose of antihyperglycemic agent(s) was decreased, and stable if these criteria remained unchanged. Additional analyses evaluated T2DM-related resource use, including hospitalizations, and general practitioner, specialist and emergency room visits among T2DM patients one month before and one year after initiation of ERN and any other LMD.

All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, USA). All univariate statistical comparisons were performed using ANOVA or a paired *t* test. Tests were conducted at a two-tailed alpha value of 0.05.

RESULTS

Patient characteristics at index date

A total of 26,862 patients were included in the study (Table 1). At the index date, most patients initiating LMDs received statins (73.4% [n=19,727]) and 3.2% (n=867) received ERN. Of the 867 patients initiated on ERN, the majority of patients were on add-on therapy (76.7%), while 22.5% were on monotherapy. Given the study design, no patient who received a statin or ezetimibe on the index date had received ERN during the year before the index date. The mean duration of follow-up was approximately one-half as long for patients who received ERN on the index date (440 days) compared with statins (784 days) or ezetimibe (752 days).

Adherence and persistence

Rates of adherence to the index drug were lower with ERN compared with those observed with statins or ezetimibe, but were similar to those of fibrates and higher than those with other LMDs. Adherence rates to ERN declined between the first and second six-month periods after LMD initiation (Table 2). At one year following the index date, the rate of adherence to ERN (62.0%) remained below rates with statins (74.9%) and ezetimibe (71.1%) ($P<0.0001$).

Patients on ERN also showed lower rates of persistence to therapy compared with patients on statins or ezetimibe; rates of persistence were the lowest with nicotinic acid (excluding ERN) and bile acid sequestrants (Figure 1). At one-year follow-up, rates of persistence to the index drug, after adjusting for covariates, were 36.1% with ERN, 46.7% with statins and 41.0% with ezetimibe ($P=0.0025$).

The rate of persistence to ERN treatment was substantially higher at lower ERN index doses. In most ERN patients (n=737; 85.0%), treatment was initiated at a daily dose of 500 mg or less, leading to the

TABLE 2

Adherence to extended-release niacin (ERN), statins and other lipid-modifying drugs at six months and one year following the index date

	Rate of adherence*, %, mean (95% CI)					
	ERN (n=867)	Statins (n=19,727)	Ezetimibe (n=347)	Fibrates (n=3431)	Bile acid sequestrant (n=1560)	Nicotinic acid (other than ERN) (n=930)
Six months following index date	71.8 (69.6–74.0)	81.1 (80.7–81.5)	79.7 (76.7–82.6)	74.6 (73.6–75.7)	28.9 (27.5–30.2)	46.3 (44.1–48.5)
One year following index date	62.0 (59.5–64.5)	74.9 (74.4–75.3)	71.1 (67.6–74.5)	64.1 (63.0–65.3)	20.2 (19.0–21.4)	35.0 (32.9–37.2)

*Adherence was defined as the sum of the number of days of all dispensations of the index drug divided by the number of days of the observation period

Figure 1 Persistence (defined as renewal of index drug before the end of the dispensation plus the length of the dispensation [grace period = 50%]) to index drug among patients initiated on extended-release (ER) niacin and all other lipid-modifying drugs, adjusted for covariates (sex, age, chronic disease score, number of hospitalizations, duration of hospitalization, and number of visits to a general practitioner, a specialist and an emergency room). Type of beneficiary was excluded from the multivariate model because the association was not statistically significant

Figure 3 Persistence (defined as renewal of index drug before the end of the dispensation plus the length of the dispensation [grace period = 50%]) to extended-release (ER) niacin monotherapy and add-on treatment, adjusted for covariates (sex, age, chronic disease score, number of hospitalizations, duration of hospitalization, and number of visits to a general practitioner, a specialist and an emergency room). Type of beneficiary was excluded from the multivariate model because the association was not statistically significant

Figure 2 Persistence (defined as renewal of index drug before the end of the dispensation plus the length of the dispensation [grace period = 50%]) to extended-release niacin (ERN) therapy by index daily dose, adjusted for covariates (sex, age, chronic disease score, number of hospitalizations, duration of hospitalization, and number of visits to a general practitioner, a specialist and an emergency room). Type of beneficiary was excluded from the multivariate model because the association was not statistically significant

highest rates of persistence. A minority of patients (n=18) initiated treatment at the highest daily doses (1000 mg to 1500 mg) and did not persist with therapy beyond 60 to 180 days (Figure 2). Patients who received add-on therapy had a higher rate of persistence to ERN therapy than those receiving monotherapy (Figure 3). Results of sensitivity analyses, in which the grace period was increased to 100%, demonstrated similar results.

Discontinuation

At one-year follow-up, discontinuation rates were substantially higher with ERN than with statins; 64.0% of patients on ERN (n=555) discontinued therapy versus 53.3% (n=10,514) on statins. Among these patients, the median time to discontinuation was 99 days for statin users and 66 days for ERN users. Patients who discontinued ERN

add-on therapy (n=408) before one-year follow-up had a longer median time to discontinuation (91 days) than patients who discontinued ERN monotherapy (n=147; 61 days). The median time at which one-half of all patients on statins discontinued therapy was 292 days compared with 156 days among ERN patients. Among patients on ERN add-on therapy compared with those on monotherapy, the median time at which one-half of all patients discontinued therapy was comparatively longer (190 days versus 93 days).

Multivariate analyses to determine the predictors of early treatment discontinuation revealed that men were significantly less likely than women to discontinue ERN treatment (risk ratio 0.73; 95% CI 0.61 to 0.88), as were patients with a higher compared with a lower chronic disease score (risk ratio 0.96; 95% CI 0.93 to 0.98) (Table 3). Interestingly, although patients initiated on higher doses of ERN at the index date exhibited lower rates of persistence than those initiated on lower doses (Figure 2), a higher treatment dose at the index date (1000 mg or greater versus 500 mg) was not a significant predictor of early treatment discontinuation (risk ratio 1.24; 95% CI 0.96 to 1.59) (Table 3). Sensitivity analyses, using a grace period of 100%, yielded similar results.

Dose attainment with ERN

At the index date, the majority of patients were initiated on a 500 mg or lower dose of ERN (85.0%), 11.4% were on 751 mg to 1000 mg, and 3.6% were initiated on all other doses combined (Figure 4). The majority of patients who discontinued ERN (n=555) did so within the first three months of therapy (n=305, 55.0%); most (n=321, 57.8%) did not achieve a daily dose of greater than 500 mg, while only 4.0% reached the highest therapeutic dose of 2000 mg.

Among patients who continued therapy, there was an overall increase in the proportion of patients who were using higher doses of ERN over time (Figure 4). However, at one-year follow-up, a substantial proportion of patients who remained on treatment (n=312) were

TABLE 3
Association between patient characteristics and therapy discontinuation among patients on extended-release niacin (ERN)*, adjusted for baseline characteristics

Characteristic	Risk ratio† (95% CI)
Sex	
Female	1.00 (reference)
Male	0.73 (0.61–0.88)
Age, years	
<65	1.00 (reference)
≥65	1.04 (0.88–1.24)
Chronic disease score	0.96 (0.93–0.98)
Resource use per person in the year before the index date	
Number of hospitalizations (all causes)	1.01 (0.90–1.13)
Number of days of hospitalization	0.99 (0.95–1.03)
General practitioner visits	0.99 (0.98–1.02)
Specialist visits (all specialists)	0.99 (0.98–1.02)
Emergency room visits	1.01 (0.96–1.06)
Diagnosis of myocardial infarction in the year before the index date	
No	1.00 (reference)
Yes	0.91 (0.55–1.52)
Type of physician prescribing the treatment at the index date	
Specialist	1.00 (reference)
General practitioner	1.02 (0.85–1.22)
Daily dose of ERN at the index date	
500 mg	1.00 (reference)
≥1000 mg	1.24 (0.96–1.59)

*Early treatment discontinuation among patients receiving a 500 mg or 1000 mg index dose of ERN; †A risk ratio lower than 1.00 is considered to be protective against early discontinuation

Figure 4) Distribution of average daily dose of extended-release niacin at different intervals following treatment initiation (index date)

taking an average daily dose of 500 mg or less ($n=93$, 29.8%), whereas only 16.0% ($n=50$) and 9.0% ($n=28$) were taking doses of 1001 mg to 1500 mg and greater than 1500 mg, respectively (Figure 4). Therefore, at one-year follow-up, only 5.8% of all patients initiated on ERN therapy ($n=867$) were taking the 1500 mg or 2000 mg dose, and only 3.2% were on the 2000 mg dose for maintenance therapy. Among persistent patients ($n=312$), the mean daily dose of ERN at one-year follow-up was 954 mg (95% CI 907 mg to 1001 mg).

Patients initiated on ERN therapy experienced low rates of attainment of the 1500 mg or 2000 mg daily maintenance doses throughout the one-year follow-up period. At any point within the one-year follow-up, approximately one-half of patients receiving ERN had reached a daily dose of 1000 mg (52.5%, $n=455$), whereas only 9.0% ($n=78$) and 6.8% ($n=59$) reached a daily dose of 1500 mg and 2000 mg, respectively. After attaining a daily maintenance dose of

TABLE 4
Subsequent daily dose of renewed extended-release niacin (ERN) prescriptions among patients who reached the 1500 mg or 2000 mg recommended daily maintenance dose

Daily dose of renewed ERN prescriptions, mg	Renewals, n (%)	
	Patients who reached 1500 mg (n=78)	Patients who reached 2000 mg (n=59)
0 (no renewal)	9 (11.5)	7 (11.9)
500	1 (1.3)	3 (5.1)
1000	1 (1.3)	1 (1.7)
1500	56 (71.8)	0 (0)
2000	9 (11.5)	48 (81.4)
3000	1 (1.3)	0 (0)

TABLE 5
Variations in type 2 diabetes mellitus (T2DM) severity before and after index prescription of extended-release niacin (ERN) versus any other lipid-modifying drug (LMD) among patients with T2DM

	T2DM severity*		
	More severe, n (%)	Stable, n (%)	Less severe, n (%)
ERN at index date (n=80)	37 (46.3)	29 (36.3)	14 (17.5)
LMD at index date (n=1126)	562 (50.0)	384 (34.1)	180 (16.0)
P	0.53	0.70	0.72

*Measured by changes in antihyperglycemic agent(s) prescribed one year after LMD initiation compared with one month before LMD initiation

1500 mg or 2000 mg, the majority of patients received a renewal prescription of ERN (approximately 88%), chiefly at the same daily dose (71.8%, 1500 mg; 81.4%, 2000 mg) (Table 4).

Impact on T2DM

Among patients initiated on ERN, most patients had stable (36.3%) or less severe (17.5%) T2DM, whereas 46.3% of patients experienced more severe T2DM (Table 5). Similar associations with changes in antihyperglycemic agents were observed in patients using any other LMD ($P>0.05$ for all comparisons) (Table 5). Among patients treated with ERN, T2DM-related resource use at one year after compared with one month before the index date was either similar or significantly lower (Table 6). There were no significant differences in the rate of changes in T2DM-related resource utilization among patients initiated on ERN versus any other LMD (all $P\geq 0.20$).

DISCUSSION

According to the present retrospective cohort analysis of the RAMQ administrative claims database, ERN is considerably underutilized in Canada because only 3% of eligible patients received prescriptions for ERN therapy. ERN therapy was associated with high rates of discontinuation because more than 60% of patients discontinued therapy within one year following treatment initiation. Among patients who continued ERN therapy one year after the index date, only approximately one-half of patients reached the 1000 mg dose, while less than 10% reached the 2000 mg daily dose for maintenance therapy. In addition, rates of adherence and persistence with ERN at one-year follow-up were substantially lower than those for statins and ezetimibe, although they were similar to those for fibrates.

One of the most likely explanations for the observed suboptimal dose attainment, adherence and persistence associated with ERN is low patient tolerability, particularly due to flushing severity, which is

TABLE 6

Variations in type 2 diabetes mellitus (T2DM)-related resource use before and after index prescription of extended-release niacin (ERN) versus any other lipid-modifying drug (LMD) among patients with T2DM

	T2DM-related resource use, per person per year, mean $\pm$ SD		P
	1 month before index prescription	1 year after index prescription	
Patients with T2DM on ERN at index date (n=215), n			
Number of hospitalizations	0.2 $\pm$ 0.5	0.1 $\pm$ 0.4	0.063
Days of hospitalization	0.4 $\pm$ 1.5	0.2 $\pm$ 1.0	0.11
General practitioner visits	1.9 $\pm$ 2.3	1.4 $\pm$ 2.4	0.001
Specialist visits	0.9 $\pm$ 1.4	0.8 $\pm$ 1.4	0.17
Emergency room visits	0.1 $\pm$ 0.4	0.02 $\pm$ 0.1	0.007
Patients with T2DM on any other LMD at index date (n=4015), n			
Number of hospitalizations	0.2 $\pm$ 0.7	0.1 $\pm$ 0.4	<0.0001
Days of hospitalization	0.5 $\pm$ 2.1	0.2 $\pm$ 1.3	<0.0001
General practitioner visits	2.1 $\pm$ 2.1	1.7 $\pm$ 2.1	<0.0001
Specialist visit	0.6 $\pm$ 1.2	0.5 $\pm$ 1.2	0.78
Emergency room visits	0.1 $\pm$ 0.3	0.03 $\pm$ 0.2	<0.0001

the most common reason for discontinuation in clinical trials (6). In an analysis of four clinical trials of ERN at doses of 1000 mg to 3000 mg per day, 69% of study participants experienced flushing symptoms, compared with 10% of participants allocated to placebo (33). Likewise, 34% of participants on ERN therapy compared with 10% on placebo discontinued treatment as a result of adverse reactions, citing flushing severity as the most common reason for discontinuing ERN treatment (33).

Another potential contributing factor is physician failure to follow the recommended titration schedule for ERN. According to dosage instructions, ERN therapy should be initiated at a daily dose of 500 mg for four weeks and gradually increased by 500 mg/day or less over four weeks to reach a daily 1500 mg or 2000 mg dose for maintenance therapy (16). The results of the present study indicated that approximately 15% of patients initiated on ERN were prescribed a higher daily dose than the recommended 500 mg initial daily dose. While approximately 40% of patients who initiated therapy at the 500 mg dose were persistent at one-year follow-up, only 30% who initiated therapy at 750 mg to 1000 mg were persistent at one-year follow-up, and all patients prescribed doses of greater than 1000 mg discontinued before the six-month follow-up. Therefore, persistence patterns for ERN therapy could improve significantly if physicians become more compliant to recommended dosage instructions.

Interestingly, patients who received ERN as an add-on therapy to statins had a higher rate of persistence than those on ERN monotherapy. These results are consistent with previous analyses using United States prescription claims data, which found that the rate of persistence to ERN monotherapy (9.4%) after one-year follow-up was markedly lower than that among patients initiated on ERN/statin combination therapy (18.9%; $P<0.05$) (24). A possible explanation for this finding is that patients who receive a statin before ERN therapy are more accustomed to taking their medications, thus enabling them to achieve higher rates of persistence than those who are newly initiated on ERN. To further test this hypothesis, additional analyses should investigate whether combination therapy using other lipid-modifying therapies produces similar results.

When administered to patients with T2DM, previous studies have suggested that treatment with niacin may result in reduced insulin sensitivity and modest (5% or less) increases in indexes of glycemic control (14,25,26). In contrast, results of the present study revealed that more than one-half of T2DM patients on ERN had stable or less severe disease compared with before treatment initiation. Furthermore, ERN was associated with similar patterns in antihyperglycemic agent use in T2DM patients compared with other LMDs, which are not generally associated with changes in glycemic

control. These results are consistent with those of clinical trials, which did not witness any significant changes in the use of insulin and antihyperglycemic agents (27) or HbA1c (27,28) in patients treated with niacin.

Limitations

Although the present study provides valuable insight into utilization patterns of ERN in Canadian regular clinical practice, it has certain potential limitations. As with other pharmacy claims database analyses, the results of the present study relied on prescription patterns, which do not account for patients who have filled a prescription but may not have taken the medication. However, because most patients in Canada are responsible for a co-payment, it is unlikely that patients would repeatedly pay out of pocket and not take a medication. Furthermore, the database only captures prescribed medications. As a result, the use of drugs from other sources, such as over-the-counter supplements (eg, nicotinic acid), were not included. Therefore, the present study may have underestimated total niacin use among these Canadian patients.

For analyses of medical resource use, entry and exit dates for hospitalizations were unavailable in the RAMQ database. Thus, the entry date was assumed to be the date of first medical service in the hospital. A patient was assumed to have been discharged if he or she did not see a hospital-based physician for more than three days. As a consequence, the number of hospital admissions may have been overestimated while the length of stay may have been underestimated among patients hospitalized on a long-term basis and not frequently seen by their physicians. To address such concerns, the algorithm used for the estimation of hospitalizations was previously validated in another study of similar design using the RAMQ database (34).

In addition, since available patient-level data are typically limited in administrative claims databases, it is also not clear whether the results can be extrapolated to patients with distinct clinical characteristics, such as CHD, who may be more adherent and persistent as a result of personal experience with disease symptoms and medical interventions. Finally, although ERN persistence was low in the present Canadian population, the duration of the present study was relatively short and long-term persistence with LMD therapy is known to decrease over time (35). Therefore, further analyses should evaluate ERN utilization patterns among patients with a variety of comorbidities using a longer follow-up period.

CONCLUSIONS

Niacin use in Canada is suboptimal, with low prescription rates, inferior adherence and persistence compared with statins and ezetimibe, high discontinuation rates compared with statins, and very low

2000 mg dose attainment. On the other hand, although previous studies have suggested a negative interaction between the use of ERN and glycemic control, ERN does not appear to be associated with changes in T2DM severity compared with other lipid-modifying therapies. These findings underscore the suboptimal utilization of niacin among patients with dyslipidemia.

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ADDENDUM: Comorbidity was assessed using the chronic disease score (31). Medications for the treatment of specific diseases, excluding those for symptom management (eg, analgesics and antidepressants) and all LMDs, were assigned weighting factors based on the seriousness of the condition. For each patient, the chronic disease score was determined by summing all appropriate weighting factors for each medication across all conditions. The resultant overall scores ranged from 0 (minimum) to 21 (maximum).

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