ORIGINAL ARTICLE

Exploring patient demographic and clinical characteristics associated with lipid-lowering pharmacotherapy use in primary care

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Abstract

Background: Lipid-lowering therapeutics, particularly HMG Co-A reductase inhibitors, can be beneficial in primary and secondary cardiovascular prevention. The Canadian population frequently uses these medications but the manner in which they are used in community-based practice is unknown.

Objectives: To assess the patient characteristics associated with lipid lowering drug use in community-based clinical practice across four geographic regions in Canada. To assess amongst lipid-lowering drugs users the proportion of patients that would meet accepted dyslipidemia management guidelines. To assess the community-based effectiveness of anti-hyperlipidemic drugs.

Methods: Patients filling a prescription for any anti-hyperlipidemia therapy in selected pharmacies in Ontario (ON), Quebec (PQ), British Columbia (BC) and Nova Scotia (NS). All eligible patients were interviewed over the telephone. Physicians who were providing healthcare to the participating patients were requested to provide information from the patient's medical record.

Results: The mean patient age was > 60 yr in all four provinces. There were some differences amongst the four provinces

pertaining to patient characteristics, prescription patterns and therapeutic indicators, but not to outcomes. Anti-hyperlipidemia therapy was associated with a 1.81 mmol/L decrease in LDL-Cholesterol ($P < 0.001$); however only 73% of patients achieved target LDL-Cholesterol concentrations. A lag time of 1.96 yr ($P < 0.0001$) was observed from the diagnosis of dyslipidemia until the drug treatment was initiated. Patients had an average of 2.8 cardiovascular (CV) risk factors and 86% of patients had at two or more CV risk factors. Thirty-nine percent (95% CI, 36% - 42%) of the patients were being treated for secondary prevention. Thirteen percent (11% - 16%) of patients who were being treated for primary prevention had diabetes. Metabolic syndrome was observed in 32% (29% - 35%) of patients.

Conclusion: Almost all patients fulfilled guideline requirements for the use of anti-hyperlipidemic therapy. Although the use of pharmacotherapy was associated with a lowering of LDL cholesterol more aggressive management is required to attain target LDL cholesterol concentrations.

Keywords: statins, lipid-lowering medication, community-based evaluation

Cardiovascular diseases are the leading cause of illness and morbidity in developed countries¹⁻³ and impose a substantial burden on the health care system⁴ resulting in billions of dollars in health care costs. The majority of cardiovascular cases stem from atherosclerosis⁵, and epidemiological studies have identified a number of risk factors for atherosclerosis.⁶

Dyslipidemia, and in particular hypercholesterolemia, is an important risk factor for atherosclerosis.^{6,7} The treatment of hypercholesterolemia includes both non-pharmacological and pharmacological approaches.^{8,9} Non-pharmacological management involves lifestyle enhancements such as diet and exercise, and is the first step of therapy. Drug therapy is initiated if non-pharmacological management does not reach target cholesterol concentrations. However, in high risk patients for cardiovascular events pharmacological treatment should be started concomitant with diet and therapeutic lifestyle changes in order to obtain target concentrations¹⁰. Currently, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) are the principle drugs for the pharmacological approach in treating hypercholesterolemic patients. The primary effect of statins is to reduce LDL-cholesterol. Several large-scale randomized controlled trials and observational studies have demonstrated the efficacy of statins to prevent cardiovascular morbidity and mortality in dyslipidemic patients. However, the cost of the medication is considerable. For example, in the past decade the government of Ontario spent approximately 10% of the annual ambulatory medication budget on statins alone, which amounted to \$148 million CDN.¹¹ This amount is expected to grow in light of the aging population in Canada. Since the cost effectiveness of statin therapy is superior when treatment is used in high risk patients compared to lower risk patients⁸, an important step in assessing the benefit and value of statin therapy in the population would be an evaluation of how these medications are used in community-based practice.

This study was conducted to address the following objectives: (1) To assess the characteristics of patients associated with the use of lipid-lowering pharmacotherapy in community-based clinical prac-

tice, in four geographic regions across Canada; (2) To assess amongst lipid-lowering users the proportion of patients that would meet the 2003 Canadian dyslipidemia management guidelines; (3) To assess the community-based effectiveness of anti-hyperlipidemic drugs; (4) To explore the similarities and dissimilarities amongst Canadian provinces regarding the aforementioned objectives.

Methods

Patients filling a prescription for a lipid-lowering drug between September 2004 and June 2005 in selected pharmacies in Nova Scotia, Quebec, Ontario and British Columbia were eligible to participate in this study. Patients were given an information sheet and a consent form to read by trained pharmacy staff. Patients who agreed to participate signed a consent form giving permission for: (1) the research team to contact them by telephone to ask questions about their lipid lower medication utilization and health; (2) the pharmacist to release the patient's medication profile for the previous 12 months; (3) the family physician to release to the research team medical information related to dyslipidemia therapy and cardiovascular risk, from the patient's medical record. Patients with any of the following criteria were excluded from study: (1) unable to speak either English or French; (2) hearing impaired; (3) cognitively impaired; (4) patients who do not have their own telephone; (5) non-community dwelling (i.e., institutionalized).

Eligible patients were subsequently interviewed over the telephone by trained interviewers using computer assisted interviewing software (CATI). Physicians, identified by the participating patients as their health care provider, were requested to complete a short questionnaire pertaining to information that would be in the patient's medical record. The data obtained from the patient telephone interviews, pharmacist medication dispensing histories and physician medical records included patient characteristics (age, sex, education, height, weight, income, racial background), lipid profile (total cholesterol, LDL-Cholesterol, HDL-Cholesterol, triglycerides), duration and dose of lipid-lowering medication use, adverse

TABLE 1. Population Characteristics

Demographic Data						
	Canada	Nova Scotia (NS)	Quebec (PQ)	Ontario (ON)	British Columbia (BC)	<i>P</i> *
Patients N	1103	265	279	291	268	0.60
(Male)	(54%)	(52%)	(57%)	(58%)	(50%)	
Age Years Mean (SD)	64 (11)	61 (11)	63 (10)	66 (11)	65 (10)	0.0001
[Minimum, Maximum]	[31, 92]	[33, 86]	[39, 87]	[31, 92]	[36, 92]	
BMI Mean (SD)	28.2 (6.1)	28.3 (6.6)	27.8 (6.0)	28.4 (5.8)	28.3 (5.9)	0.55
BMI < 25	28%	25%	31%	30%	27%	0.70
BMI between 25 and 30	42%	43%	43%	38%	43%	
BMI > 30	30%	32%	26%	32%	30%	
Drug Profile						
Statin users (n = 1032)	94%	91%	99.5%	96%	92%	0.001
Fibrate users (n = 92)	8%	7.5%	1.5%	6.5%	6.5%	0.01
Bile acid users (n = 49)	4.5%	2.5%	0.5%	3.5%	1.5%	0.10

* for inter-provincial comparison

events and adherence (including reasons for discontinuation of prior therapy), non-pharmacological interventions (i.e., dietary modifications and exercise), co-morbid conditions (e.g. peripheral vascular disease, diabetes, etc), co-medications, cardiovascular risk factors and quality of life (SF-12). The 2003 Canadian guideline for the management of dyslipidemia was used to assess coronary artery risk categories (low, moderate and high risks) and target lipid concentrations for LDL cholesterol (LDL-C).¹⁰

Descriptive statistics were used to describe patient characteristics and patterns of drug use. Analysis of variance (ANOVA), t-test, chi-square test or non-parametric tests were applied for inferential analysis involving continuous and categorical data, as appropriate. Adjustment for baseline covariates (ANCOVA) was applied where required. All statistical analyses were preformed using SPSS program version 9.0.

Results

A total of 1103 patients participated in the study from four Canadian provinces, and 1100 drug profiles and 938 health records were obtained from pharmacists and physicians, respectively. Slightly more than half of the patients were male and the mean age for all

patients was greater than 60 yr, with a range from 31 to 92 yr. Mean (sd) Body Mass Index (BMI) was 28.2 (6.1) and 30% of patients had a BMI > 30 (Table 1).

Statins were used in 94% of patients, with fibrates and bile acid inhibitors used in 8% and 4.5% of patients, respectively (Table 1). Drug profiles demonstrated that 94% of patients used only one class of anti-dyslipidemic drug during the previous 12-month period (Table 2). There was a mean (s.d.) lag time of 1.96 (3.24) yr between the initial diagnosis of dyslipidemia [8.07 (4.96) yr ago] and the first lipid-lowering drug prescription [6.11 (3.94) yr ago], $P < 0.0001$. The lag time was greater than one year in 34% of patients (Figure 1).

LDL-C hyperlipidemia was observed in 97% of patients prior to initiating treatment as defined in the 2003 Canadian guidelines. The prevalence of various cardiovascular risk factors ranged from 14% for peripheral vascular disease to 55% for a positive family history of premature cardiovascular disease (Table 3). Patients had an average of 2.8 cardiovascular (CV) risk factors. Eighty-six percent of patients had at two or more CV risk factors i.e., dyslipidemia plus at least one additional risk factor, and more than a quarter of all patients had four or more CV risk factors. The high risk patients, which included patients with previous

FIGURE 1. Scatter plot for diagnosis of hyperlipidemia and initiation of drug treatment.

Pearson correlation = 0.76, $P < 0.0001$

cardiovascular events or diabetes, comprised 52% of the patient population; 39% of patients were treated for secondary prevention and 13% of patients being treated for primary prevention had diabetes. The remainder of the patients were distributed between the low risk (14%) and moderate risk (34%) strata (Table 4).

TABLE 2. Number and type of drugs used for dyslipidemia by patients at any time during the previous 12-month period

Number of drugs	Patients, n (%)	Class combination	Number of patients
One Drug	1038 (94%)	Statins only	971
		Fibrates only	52
		Bile acid inhibitor only	15
Two Drugs	60 (5.6%)	Statins + Fibrates	31
		Statins + Bile acid inhibitor	25
		Fibrate + Bile acid inhibitor	4
Three Drugs	5 (0.4%)	Statins + Fibrates + Bile acid inhibitor	5

Anti-hyperlipidemia therapy was associated with a decrease in LDL-C ($P < 0.001$), total cholesterol/HDL-C ratio ($P < 0.001$) and triglycerides ($P < 0.001$). The increase in HDL-C concentration was not statistically significant (Table 5). The reduction in LDL-C was significant for patients in all provinces. Seventy-three percent of patients achieved their target LDL-C concentration. Although achieving the LDL-C

TABLE 3. Patients with cardiovascular risk factors

	Canada	NS	PQ	ON	BC	P^*
Hyperlipidemia (LDL-C)	97%	97%	99%	97%	97%	0.50
Cardiovascular disease	39%	37%	34%	46%	37%	0.02
Diabetics	25%	27%	21%	24%	29%	0.15
Hypertension	50%	47%	44%	50%	60%	0.001
Peripheral vascular diseases	14%	10%	15%	16%	16%	0.15
Cardiovascular family history	55%	56%	52%	57%	56%	0.60
Smoking	15%	14%	15%	19%	10%	0.03

* for inter-provincial comparison

Operational definitions for risk factors -

1. Hyperlipidemia (LDL-C): The 2003 Canadian guideline for the management of dyslipidemia was used to assess coronary artery risk categories (low, moderate and high risks) and target lipid levels for LDL cholesterol (LDL-C)¹⁰
2. Cardiovascular disease: coronary heart disease, myocardial infarction and stroke
3. Diabetics: diabetes treated with pharmacological agents or non pharmacological intervention
4. Hypertension: hypertension treated with pharmacological agents or non pharmacological intervention
5. Peripheral vascular diseases: circulatory problems in legs
6. Cardiovascular family history: family history of coronary heart disease or stroke prior to age 55 years (men) or 65 years (women)
7. Smoking: current and past smoking

TABLE 4 – Frequency of primary or secondary prevention and diabetes

	Canada	NS	PQ	ON	BC	P
Primary prevention	61%	63%	66%	54%	63%	0.02
Secondary prevention	39%	37%	34%	46%	37%	
Primary prevention without diabetes	48%	49%	55%	42%	47%	0.07
Primary prevention in diabetics	13%	14%	11%	12%	16%	
Secondary prevention without diabetes	26%	23%	24%	32%	24%	
Secondary prevention in diabetics	13%	14%	10%	14%	13%	

target was observed in 96% of the low risk patients, this number was considerably lower for high risk patients, only 62% (Table 6).

Approximately one-third of patients met the criteria for metabolic syndrome, varying from 24% in Quebec to 38% in BC. The presence or absence of the metabolic syndrome was not associated with the observed quantity of LDL-C reduction.

As part of non-pharmacological therapy, 73% of patients stated that they had initiated a diet to improve their lipid profile. Reductions in the consumption of dairy products (28%) and fat (27%) constituted the largest proportion of patient reported diet alterations. In addition, some patients reported reducing consumption of red meat (14%), carbohydrates (9%) and eggs/yolk eggs (8%). However, there was no evidence of an effect of patient-reported diet changes upon changes in LDL-C concentration.

Discussion

This cross-sectional, observational study demonstrated that almost all patients (99.6%) fulfilled the 2003 Canadian guideline requirements for the use of anti-hyperlipidemic therapy. This may reflect the

ubiquitous adoption of evidence-based clinical practice amongst physicians with respect to the patients who are receiving hyperlipidemia treatment. The study did not assess whether there were inappropriately untreated patients. The study also indicated that more than half of the patient population receiving lipid-lowering agents were at high risk for cardiovascular disease, i.e., those with previous cardiovascular disease or diabetes.

Although effective drug therapies such as the statins are available for dyslipidemia, non-pharmacological interventions such as diet and exercise are still important initial steps in dyslipidemia management. In this study there was an approximate two-year lag time between the time of diagnosis of dyslipidemia and the initiation of pharmacotherapy. The observed lag period would appear to be appropriate since the data were derived from a patient population with a lengthy history of dyslipidemia (average of 8 yr) and would correspond with the guidelines of that time period. It is only recently that guidelines recommend a shorter time interval for determining whether non-pharmacological interventions are sufficient or not. As a consequence, reduction in lag time should be observed with future community-based clinical practice data⁸.

An analysis of the drug profiles demonstrated that most of the patients (94%) were on single drug therapy during the previous year. Yet more than a quarter of patients (27%) did not achieve their targeted LDL-C concentrations. This may indicate the need for more aggressive dosing or to use combination drug therapy, particularly in high risk patients in order to achieve the LDL-C target. Formulary access for lipid lowering

TABLE 5 - Lipid profile changes

Variables	Prior to Treatment	Post-treatment	Difference	P
LDL-C*	4.36 (1.76)	2.55 (0.85)	-1.81 (1.70)	< 0.0001
HDL-C*	1.25 (0.53)	1.28 (0.38)	0.02 (0.46)	0.10
Total Chol / HDL-C ratio	5.64 (1.69)	3.78 (1.13)	-1.85 (1.45)	< 0.0001
Triglyceride*	2.66 (2.54)	1.78 (1.06)	-0.89 (2.33)	< 0.0001

*mmol/L, mean (SD)

TABLE 6 - LDL-C goal and risk strata

Risk strata / LDL-C goal level*	Patient Distribution	Achieved LDL-C goal	LDL-C concentration*	LDL-C concentration*	LDL-C concentration*
			All patients in strata	Patients who achieved goal	Patients who did not achieve goal
Low risk / 4.5	14%	96%	2.8 (0.8)	2.7 (0.7)	5.2 (0.7)
Moderate risk / 3.5	34%	79%	2.9 (0.8)	2.5 (0.5)	4.1 (0.7)
High risk / 2.5	52%	62%	2.4 (0.8)	1.9 (0.4)	3.1 (0.7)
Weighted average	100%	73%	2.6 (0.8)	2.2 (0.6)	3.4 (0.8)

*mmol/L, mean (SD)

medications did not appear to be a significant factor in achieving target LDL-C concentrations as patients from all four provinces demonstrated comparable effects on LDL-C reduction despite the variation in formulary listings between the provincial drug benefit programs.

Our observed LDL-C results are quite consistent with the results of the CALIPSO study¹². CALIPSO was a cross-sectional study, which recruited patients through primary care and specialist physicians in community practice in Quebec and Ontario. Physicians were randomly selected from a list of the physicians who wrote 75% of the annual statin prescription volume in 2003 in both provinces. Even though the methods for recruiting the patient population and gathering data were different between our study and the CALIPSO study, the results for LDL-C target achievement are comparable. On the other hand, the present study has demonstrated a significantly higher attainment of target LDL-C concentrations compared to studies from European countries¹³⁻¹⁵ and the United States.¹⁶

Several issues may contribute to these differences, including different guidelines used to determine the risk strata for the patients¹⁵, different region-specific clinical practices and different time frames. Perhaps most important was that the proportion of long-term users in the different studies. Patients in the present and the CALIPSO study were on lipid-lowering pharmacotherapy an average of 6.1 and 4.3 years, respectively. This reflects a population of long-term users who are more likely to be adherent (and tolerant) to lipid lowering pharmacotherapy. Whereas it seems that the aforementioned studies from Europe and the

United States were primarily patients who were more recently started on a lipid-lowering drug. It is therefore possible that a larger proportion of potentially non-adherent (and intolerant) patients were included in the latter studies.

Some limitations may constrain the generalizability of the results of this study. As already mentioned, the recruitment strategy that primarily identified patients filling a repeat prescription for a lipid-lowering drug may have induced a bias towards a more adherent (and tolerant) patient population. The selected sample may also not be fully representative since only patients who agreed to participate in the study were assessed and the patients from the four different provinces include in the study may not characterize the patients from the other provinces.

Another limitation is that only the drug dispensing profiles for the previous 12-month period were provided by pharmacies for analysis, even though the patients were commonly on lipid-lowering pharmacotherapy for several years. As a consequence knowledge about medication use prior to the preceding year was dependant upon the available data in the patient's medical record.

In summary, almost all patients in this study that received anti-dyslipidemic drugs were treated in accordance with the 2003 Canadian guidelines. The study also revealed that patients on lipid-lowering drugs in Canadian communities were mostly in the moderate to high risk categories for cardiovascular events. Despite pharmacotherapy lowering LDL-C, approximately one quarter of patients did not attain the targeted LDL-C concentration. Future studies could implement methods such as random cluster

sampling from family practice clinics in order to enhanced the estimate of patients with dyslipidemia who should be treated with pharmacotherapy in the Canadian population. Furthermore, studies should explore the effectiveness of different methods for improving the management of dyslipidemia in the community-based settings such as patient counselling for better adherence, combination drug therapy and drug dose enhancement.

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