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NATURAL LANGUAGE PROCESSING TO ASSESS ATHEROSCLEROTIC CARDIOVASCULAR DISEASE, DIABETES, AND FAMILIAL HYPERCHOLESTEROLEMIA LIPID MANAGEMENT IN CANADA

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ABSTRACT (247/250 words max. per journal guideline)
Background: Elevated low-density lipoprotein cholesterol (LDL-C) leads to atherosclerotic cardiovascular disease (ASCVD). This study assessed treatment patterns & achievement of guideline-recommended LDL-C levels in Canadian patients with ASCVD, diabetes mellitus (DM), or familial hypercholesterolemia (FH).
Methods: Natural language processing (NLP) was utilized to extract demographic, clinical characteristics, and lipid lowering treatment (LLT) information from de-identified electronic health records of patients from cardiology or internal medicine settings in 4 provinces. The study period spanned from 1-January-2016 to 30-November-2020, and included identification, baseline, and 12-month follow-up periods.
Results: A total of 10,992 patients were identified; ASCVD (n=9,415), DM (n=1,132), and FH (n=445). Failure to achieve recommended LDL-C levels was common at baseline (38% ASCVD, 38% DM, and 75% FH) and at follow-up for patients with uncontrolled baseline LDL-C (43% ASCVD, 55% DM, and 52% FH). There was no documented LLT in 33-49% of patients with uncontrolled baseline LDL-C. LDL-C was not documented in 45%, 59%, and 23% of patients with ASVCD, DM, and FH, respectively. LDL-C levels decreased over time in all patients, with the largest decrease in patients receiving PCSK9 monoclonal antibodies, ezetimibe, or high intensity statins.
Conclusions: The present study revealed that over a third of patients with uncontrolled baseline LDL-C lacked documented LLT, almost 50% of patients did not attain recommended LDL-C levels, and that treatment modification in patients with uncontrolled LDL-C could have been more intensive. Our findings were consistent with studies using traditional administrative datasets, suggesting a promising role for NLP in future quality improvement initiatives and research.

Key words: atherosclerotic cardiovascular disease, low-density lipoprotein cholesterol, lipid lowering treatment, natural language processing

GLOSSARY OF TERMS

Term	Definition
Artificial intelligence (AI)	A branch of computer science dealing with the simulation of intelligent behavior in computer systems.
Electronic data capture (EDC)	A computerized system designed for the collection of clinical data in electronic format for use mainly in clinical research.
Natural language processing (NLP)	A field of artificial intelligence that focuses on enabling computers to understand, interpret, and generate human language.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality worldwide[1,2]. In 2021, the number of deaths attributable to cardiovascular diseases was estimated at 19.91 million globally[3]. Despite extensive efforts to improve diagnosis and treatment, ASCVD remains the second leading cause of death and a predominant cause of hospitalization in Canada[2,4–6]. Recently, a study from Ontario showed a CAD $66.6 billion total spending over 12 years for the management of newly diagnosed ASCVD, highlighting the economic burden on the Canadian healthcare system[7].

Elevated low-density lipoprotein cholesterol (LDL-C) is causal to ASCVD, but can be attenuated with lipid lowering therapies (LLTs) that halt atherosclerotic plaque progression[1,8]. It is well known that a 1 mmol/L reduction in LDL-C levels is associated with lowering the annual occurrence of major vascular events (22%), coronary heart disease deaths (20%), and total mortality (10%)[9,10]. The 2016 Canadian Cardiovascular Society (CCS) guidelines recommend that LDL-C levels should consistently be <2.0 mmol/L or that a >50% reduction of LDL-C be achieved in patients receiving LLT, while a lower LDL-C target of <1.8 mmol/L was recommended for patients with a recent acute coronary syndrome[11]. The current CCS guidelines, published in 2021, updated the LDL-C threshold for treatment intensification to 1.8 mmol/L for patients with a history of ASCVD receiving LLT[1].

Despite the well-established benefits of LLT, the CCS guidelines are not implemented consistently in Canadian routine clinical practice, and treatment gaps remain pervasive in patients with ASCVD and those at high risk of experiencing cardiovascular events [i.e., patients with diabetes mellitus (DM) aged ≥40 years or those with familial hypercholesteremia (FH)]. Indeed, in patients with a recent percutaneous coronary intervention (PCI) in Ontario, a concerning proportion (48%) did not have LDL-C measurements within 6 months post-procedure, and of those with LDL-C assessments, 43% had LDL-C levels >70 mg/dl (i.e., >1.8 mmol/L, considered uncontrolled per 2021 CCS guidelines)[12]. Other studies reported LLT underutilization in over half of patients with ASCVD or at high risk of developing ASCVD, and that ≤40% of patients receiving statins achieved LDL-C targets of <2.0 mmol/L[13–16]. Relatedly, the Guideline Oriented Approach to Lipid Lowering (GOAL) Canada program that started in 2015 reported the benefits of using additional LLTs [e.g., ezetimibe and anti-PCSK9 monoclonal antibodies (mAbs)] in patients with ASCVD or FH with uncontrolled LDL-C levels [17]. While a significant increase in the proportion of patients (from 0% at baseline to 50.8% at last study visit, P<0.05) reaching 2016 CCS guideline-recommended LDL-C levels (<2.0 mmol/L) was observed, a large gap clearly remained[17]. Furthermore, both knowledge and action gaps were evident, as 20% of physicians indicated that additional LLT was not necessary for patients with uncontrolled LDL-C, and 15% to 20% indicated that they would add an LLT at the next visit rather than at the visit where LDL-C was found to be above 2.0 mmol/L[17]. Comparable gaps between clinical guidelines and clinical practice for lipid management were also identified in Europe and the United States (US). In the Da Vinci study assessing implementation of European guidelines for LLTs and the impact on LDL-C threshold achievement, 94% of patients with established ASCVD (in whom LDL-C goal attainment could be assessed) were receiving a statin. However, only 45% of patients receiving high-intensity statin monotherapy achieved the 2016 LDL-C goal of <1.8 mmol/L and 22% achieved the 2019 LDL-C goal of <1.4 mmol/L[18]. Failure to achieve guideline-recommended LDL-C levels was partly attributed to lack of physician familiarity with the guidelines[18]. Similarly, a prospective observational registry study from the US (the GOULD study) documented that only 17%

of patients with ASCVD had LLT intensification after 2 years, and only one-third achieved the recommended LDL-C threshold of <70 mg/dl (<1.8 mmol/L)[19].

Recent studies using Canadian provincial administrative databases have described various aspects of ASCVD management[12,15,20]. However, these databases are not always accessible and frequently lack clinical details that may be found in a patient's electronic medical record (EMR). The increased use of EMR platforms provides an opportunity to conduct chart review studies using novel artificial intelligence (AI)-based methods. For example, natural language processing (NLP) techniques are able to 'read' information directly from unstructured data such as clinical notes or narratives[21]. These methods have been used to automatically extract data from unstructured EMRs across therapeutic areas and indications including oncology[22,23], diabetes[24], asthma[25], and cardiology[26]. Reports in the field of healthcare suggest that NLP may extract information more efficiently than with traditional approaches that rely on manual data extraction by research personnel[25], may provide a reliable method for identifying patient populations of interest, and provides a mechanism for extracting relevant data from existing EMRs[23].

The current study uses a novel AI-based NLP method to describe the demographic and clinical characteristics of a contemporary sample of patients at high risk of experiencing cardiovascular events, including those with a history of ASCVD, DM aged ≥40 years, or FH. The objectives of the study were to leverage NLP methodology to automatically extract data from patient EMRs and to describe: 1) baseline patient characteristics and LLT use in patients with ASCVD, DM, and FH; 2) the proportion of patients with ASCVD, DM, and FH whose LDL-C was controlled at baseline; 3) overall baseline LLT use in patients with controlled LDL-C and uncontrolled LDL-C; 4) modifications to LLT over time among patients with uncontrolled baseline LDL-C, and; 5) change in LDL-C levels over time and the proportion of patients achieving LDL-C control at follow-up.

METHODS

Study design

Descriptive, retrospective study of real-world EMR data using automated chart review of Ensho Health's automated electronic data capture platforms (aEDC) system (Apollo).

Data sources

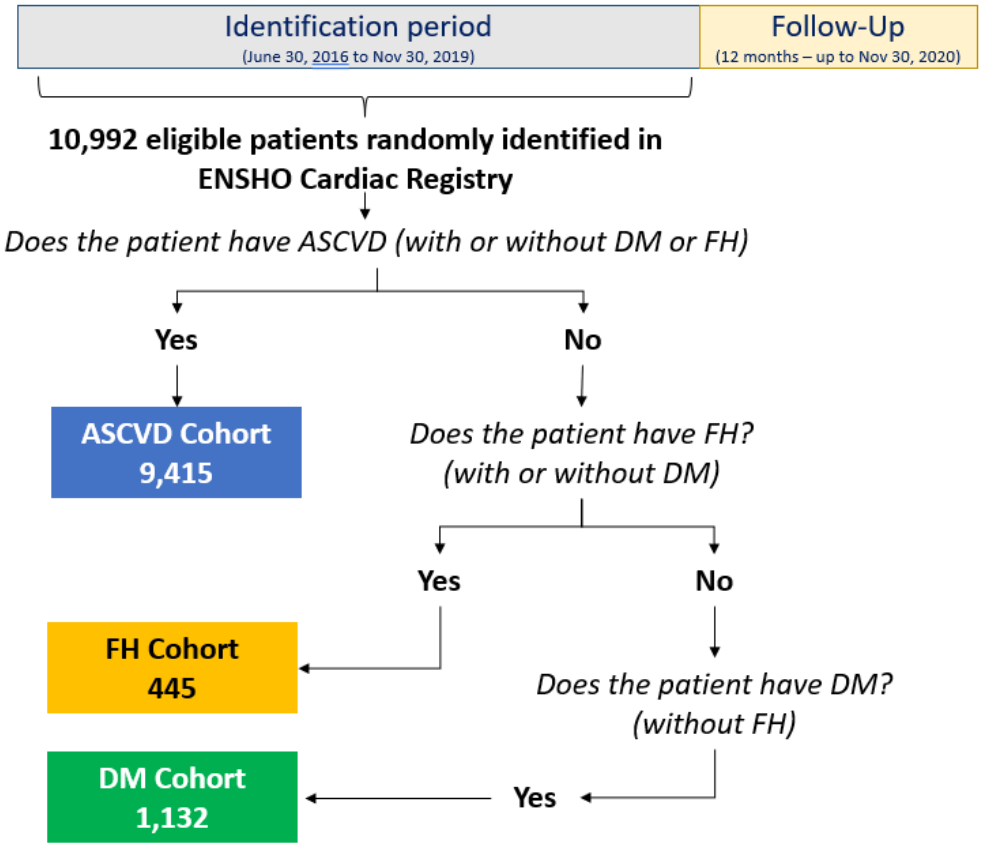
The Ensho Health Platform is a centralized data registry that contains various applications. Approximately 153 cardiologists, internal medicine specialists, and general practitioners in Ontario, Manitoba, Alberta, Saskatchewan, British Columbia, and Nova Scotia subscribe to this platform. It contains complete health records for all patients seen by subscribers since they began recording encounter notes in computerized systems. The registry is updated monthly and includes records produced as far back as 1990. Source data are processed using Apollo, a novel aEDC system that ingests structured and unstructured data from a variety of EMR systems, de-identifies them at the source, and converts them to machine readable text including optical character recognition of images (e.g., TIFFs and PDFs). Data are subsequently queried, and results are interpreted using NLP methods. A portion of extracted clinical features (i.e., demographic and clinical characteristics including ASCVD, DM, and FH) is randomly assigned for manual review by trained clinical abstractors. The accuracy of the Apollo aEDC in its ability to extract challenging data elements, such as left ventricular ejection fraction and heart failure medication history, was previously demonstrated[27].

Patients with ASCVD aged ≥18 years, FH aged ≥18 years, and DM aged ≥40 years (hereafter referred to as ASCVD, FH, and DM, respectively) were identified based on documented diagnoses of ASCVD (as per 2016 Canadian guidelines), DM, or FH detected by NLP and confirmed by trained clinical abstractors. Patients were determined to have ASCVD if their records contained evidence of a diagnosis during the identification period (June 30, 2016, to November 30, 2019) for any of the following: myocardial infarction (STEMI or NSTEMI); coronary artery disease (defined as stenosis of the left anterior descending artery, right coronary artery or vessels of the circumflex branch of the

left coronary artery or obtuse marginal, diagonal, or patent ductus arteriosus branches of ≥50% or described as significant, moderate or extensive); coronary artery revascularization (percutaneous coronary intervention or surgery); peripheral vascular disease, symptoms or prior intervention; stable or unstable angina; stroke; and/or transient ischemic attack with carotid artery stenosis (defined as a stenosis of the carotid artery ≥50%). Patients were determined to have DM or FH if their records contained named diagnoses of either condition. If patient records contained evidence of ASCVD and DM or FH, they were assigned to the ASCVD cohort, and their index date corresponded to the first outpatient encounter on or after first record of ASCVD diagnosis. If a patient had a record of FH and DM, they were assigned to the FH cohort and their index date corresponded to the first outpatient encounter on or after first record of FH. Therefore, patients with ASCVD may also have had records of FH or DM diagnoses, and patients with FH may also have had a diagnosis of DM. Patients with DM could only have a DM diagnosis (i.e., without ASCVD or FH). Only diagnoses from outpatient clinical notes, referral summaries, or hospital discharge summaries were accepted for the inclusion cohort of qualifying diagnoses. Patient cohort selection is summarized in Figure 1.

De-identified records of patients with an outpatient encounter during the identification period and with at least 12 months of relevant follow-up data were considered for inclusion. The index date was the earliest date within the identification period in which a patient qualified for the study according to the presence of a diagnosis of interest. The baseline period comprised the 6 months leading to the index date. The follow-up period included all available time from and up to 24 months post-index. Therefore, the study period spanned January 1, 2016, to November 30, 2020. Among all patients meeting the study's eligibility criteria, 10,992 were selected at random and included in the analysis. All included patients were sourced from 37 cardiologists and three internists from British Columbia, Saskatchewan, Manitoba, and Ontario.

Figure 1: Patient cohort selection process



Ascvd, atherosclerotic cardiovascular disease; dm, diabetes mellitus; fh, familial hypercholesteremia

Study variables

Demographic and clinical characteristics included age, sex, baseline diagnoses, laboratory measurements, and LLT use. Laboratory data included LDL-C, HDL-C, non-HDL-C, total cholesterol, triglycerides, lipoprotein-a [Lp(a)], apolipoprotein-b (ApoB), and hemoglobin A1c (HbA1c). Controlled LDL-C was defined as an LDL-C <2.0 mmol/L for patients with ASCVD and DM, and <2.5 mmol/L for patients with FH as per the 2016 CCS guidelines. Exploratory analyses using the 2021 CCS guidelines were also conducted (threshold of 1.8 mmol/L) for ASCVD patients. Statin treatment intensity was classified as high, medium, or low intensity based on statin dose[28].

The first documented LDL-C value in a patient's EMR within the study period was used to define controlled versus uncontrolled LDL-C at baseline. The last recorded LDL-C value during the study period after the index date was used to determine LDL-C control at follow-up (i.e., terminal LDL-C). Treatment modifications were only assessed in patients with documented LLTs who had uncontrolled baseline LDL-C (≥2.0 mmol/L for ASCVD and DM, and ≥2.5 mmol/L for FH) and ≥1 subsequent uncontrolled LDL-C value (≥2.0 mmol/L for ASCVD and DM, and ≥2.5 mmol/L for FH, or ≤50% reduction in LDL-C levels from baseline on ≥1 occasion). The proportion of patients achieving LDL-C control at follow-up and LDL-C change were only evaluated in patients with uncontrolled LDL-C at baseline and ≥1 subsequent assessment.

Patients were considered to be on LLTs if there was a record of treatment with a statin, anti-PCSK9 mAbs, ezetimibe, fibrates, niacin, bile acid sequestrants, icosapent ethyl, mipomersen, lomitapide, or apheresis. A full list of statins and associated dosages to define treatment intensity is available in Supplementary Table 1.

Statistical analysis

Analyses were descriptive; continuous and categorical variables were summarized using mean and standard deviation (SD), and frequency counts and percentages, respectively.

RESULTS

Baseline demographic and clinical characteristics

A total of 9,415 patients with ASCVD, 1,132 patients with DM, and 445 patients with FH were identified. Most patients were ≥50 years old, with the mean age ranging from 55-69 years. Most patients with ASCVD were male (70%), and approximately half of those with DM and FH were male (56% and 47%, respectively). A summary of patient baseline demographic and clinical characteristics is provided in Table 1.

Table 1. Patient Baseline Demographic and Clinical Characteristics

Characteristics	ASCVD (N = 9415)	DM (N = 1132)	FH (N = 445)
Age at index date			
Years, Mean (±SD)	69.3 (±11.5)	67.9 (±11.3)	55.3 (±12.1)
≤ 49, n (%)	467 (5)	69 (6)	125 (28)
50-59, n (%)	1458 (15)	197 (17)	145 (33)
60-69, n (%)	2694 (29)	351 (31)	127 (29)
≥ 70, n (%)	4796 (51)	515 (45)	48 (11)
Male sex, n (%)	6631 (70.4)	634 (56.0)	207 (46.5)
Baseline Lipid values, Mean (±SD)			
LDL-C (mmol/L)	2.00 (±1.03)	1.91 (±1.00)	3.84 (±1.60)
HDL-C (mmol/L)	1.26 (±0.82)	1.27 (±0.42)	1.42 (±0.69)
Non-HDL-C (mmol/L)	2.72 (±2.47)	2.67 (±1.04)	4.63 (±1.68)
Total cholesterol (mmol/L)	3.98 (±2.50)	4.23 (±6.31)	6.03 (±1.67)
Triglycerides (mmol/L)	1.67 (±7.89)	1.78 (±1.38)	1.96 (±2.08)

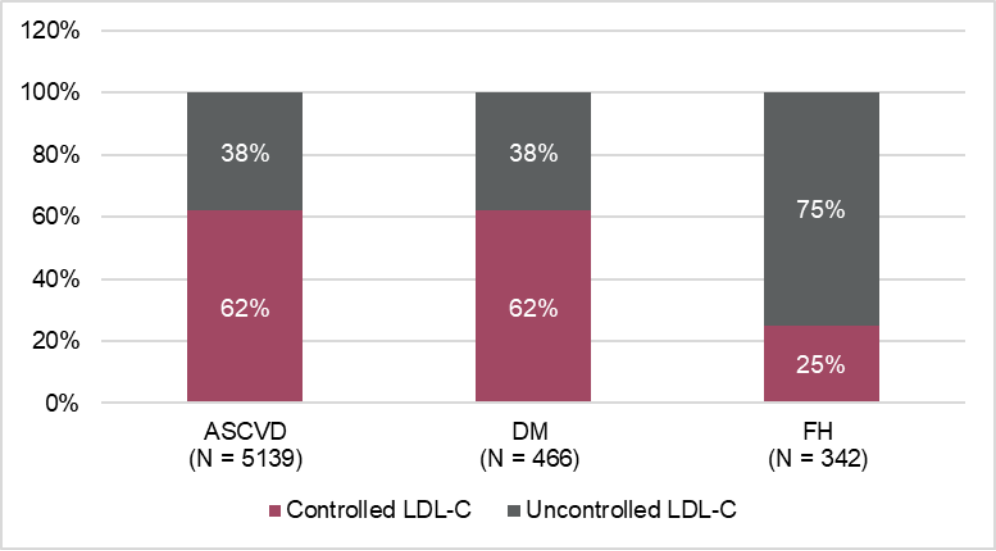
Lipid Lowering Therapies, n (%)			
Statin	3305 (35.1)	253 (22.3)	209 (47.0)
Ezetimibe	555 (5.9)	18 (1.6)	80 (18.0)
Anti-PCSK9 mAbs	26 (0.3)	-	15 (3.4)

Anti-pcsk9 mabs, anti-pcsk9 monoclonal antibodies; ascvd, atherosclerotic cardiovascular disease; dm, diabetes mellitus; fh, familial hypercholesteremia; hdl-c, high-density lipoprotein cholesterol; ldl-c, low-density lipoprotein cholesterol; sd, standard deviation.

The most common comorbidity was hypertension, which was documented in 67.3%, 75.9%, and 36.6% of patients with ASCVD, DM, and FH, respectively (Supplementary Table 2). Diabetes was documented in 29.6% and 8.8% of patients with ASCVD and FH, respectively.
Baseline LDL-C data were available for 55%, 41%, and 77% of patients with ASCVD, DM, and FH, respectively. Mean (±SD) baseline LDL-C levels were 2.00 (±1.03), 1.91 (±1.00), and 3.84 (±1.60) mmol/L for patients with ASCVD, DM, and FH, respectively. Mean HDL-C levels ranged from 1.26-1.42 mmol/L, and mean total cholesterol ranged from 3.98-6.03 mmol/L across groups. Mean (±SD) triglyceride concentrations were 1.67 (±7.89), 1.78 (±1.38), and 1.96 (±2.08) mmol/L for patients with ASCVD, DM, and FH, respectively (Table 1). Baseline Lp(a) and ApoB were documented in 0.5-3.8% of patients with ASCVD and FH (Supplementary Table 2, no values reported for DM).
Statin use was documented in 35%, 22%, and 47% of patients with ASCVD, DM, and FH, respectively; overall, ezetimibe use was reported in 2-18% of patients. Statin intolerance was reported in 8%, 4%, and 21% of patients with ASCVD DM, and FH, respectively. Additional baseline data are provided in Table 1 and Supplementary Table 2.

Proportion of patients achieving CCS guideline-recommended LDL-C levels at baseline and baseline LLT use in patients according to controlled vs uncontrolled LDL-C
At baseline, 62% of patients with ASCVD and DM, and 25% of patients with FH met 2016 CCS guideline thresholds for LDL-C (<2.0 mmol/L for ASCVD and DM, and <2.5 mmol/L for FH) (Figure 2). The updated 2021 CCS guideline threshold LDL-C level of 1.8 mmol/L was reached by 53% of patients with ASCVD.

Figure 2: Proportion of Patients Achieving 2016 CCS Guidelines Target LDL-C Levels at Baseline



Ascvd, atherosclerotic cardiovascular disease; ccs, canadian cardiology society; dm, diabetes mellitus; fh, familial hypercholesteremia; ldl-c, low-density lipoprotein cholesterol.

As per the 2016 ccs guidelines, patients with baseline ldl-c level <2.0 mmol/l (ascvd and dm) or <2.5 mmol/l (fh) were considered as having controlled ldl-c.

Supplementary Figure 1 illustrates baseline LLT use according to controlled versus uncontrolled LDL-C. Statins were documented in >90% of all patients, followed by ezetimibe in 12.8-21.7%, 6.3-6.8%, and 34.8-35.2% of patients with ASCVD, DM, and FH, respectively, and anti-PCSK9 mAbs in 0.6-1.1% and 3.8-12.7% of patients with ASCVD and FH, respectively.
Initial LLT was also assessed only in patients with uncontrolled baseline LDL-C (defined as ≥2.0 mmol/L for ASCVD and DM, ≥2.5 mmol/L for FH). Statin monotherapy was documented in 49%, 43%, and 32% of patients with ASCVD, DM, and FH, respectively; conversely, no LLT was documented in 33%, 49%, and 39% of patients with ASCVD, DM, and FH, respectively (data not shown). Statin and ezetimibe combination therapy was the second most reported LLT regimen among patients with uncontrolled LDL-C (2-17% of patients), followed by ezetimibe monotherapy (2-5% of patients).

LLT modifications over time in patients with uncontrolled baseline LDL-C
Documented treatment modifications in patients with uncontrolled baseline LDL-C are listed in Table 2. The most common modifications were addition of, or switch to statins, representing 49% and 67% of modifications in those patients with ASCVD and DM, respectively. The addition of or switch to ezetimibe was the most common alteration in those with FH and represented 47% of modifications. The time to first documented LLT change was generally longer than time to subsequent changes.

Table 2. Treatment Modifications Over Time in Patients with Uncontrolled Baseline LDL-C

	ASCVD N = 1953	DM N = 175	FH N = 258
Patients with Uncontrolled Baseline LDL-C and ≥1 Treatment modification, n (%)	**805 (41)**	**47 (27)**	**79 (31)**
Documented Baseline Therapy, n (%)[†]			
No documented treatment	203 (25)	13 (28)	28 (35)
Any Statin	509 (63)	28 (60)	33 (42)
Low Intensity Statin	19 (2)	1 (2)	2 (3)
Moderate Intensity Statin	183 (23)	17 (36)	18 (23)
High Intensity Statin	275 (34)	9 (19)	12 (15)
Statin of Unknown Intensity	32 (4)	1 (2)	1 (1)
Ezetimibe	125 (16)	4 (9)	18 (23)
Anti-PCSK9 mAbs	12 (1)	0 (0)	4 (5)
Switch of Statin Dosing Intensity, n (%)[†]			
To Low Intensity	26 (10%)	1 (10%)	10 (32%)
To Moderate Intensity	112 (43%)	5 (50%)	11 (36%)
To High Intensity	122 (47%)	4 (40%)	10 (32%)
Treatment Added/Switched, n (%)[†]			
Statin	347 (49%)	24 (67%)	21 (33%)
Ezetimibe	269 (38%)	8 (22%)	30 (47%)
Anti-PCSK9 mAbs	76 (11%)	0	12 (19%)
Treatment Discontinued, n (%)[†]			

Statin	96 (81%)	2 (100%)	17 (77%)
Ezetimibe	13 (11%)	0	3 (14%)
Anti-PCSK9 mAbs	5 (4%)	0	1 (5%)
Days to Initial Change, Mean (±SD)			
Statin	256 (279)	283 (289)	278 (280)
Ezetimibe	314 (299)	339 (239)	257 (303)
Anti-PCSK9 mAbs	319 (329)	-	186 (147)
Days to Subsequent Change, Mean (±SD)			
Statin	181 (189)	188 (221)	89 (125)
Ezetimibe	195 (208)	160 (-)	141 (245)
Anti-PCSK9 mAbs	246 (226)	-	162 (253)

Anti-pcsk9 mabs, anti-pcsk9 monoclonal antibodies; ascvd, atherosclerotic cardiovascular disease; dm, diabetes mellitus; fh, familial hypercholesteremia; sd, standard deviation.
Only patients treated with ≥ 1 llt during the study period, a documented treatment modification, and an elevated baseline ldl-c value (≥2.0 mmol/l for ascvd and dm, ≥2.5 mmol/l for fh, or ≤50% reduction in ldl-c levels on ≥1 occasion) were included in the analysis. The first observation of elevated ldl-c was determined using the first documented ldl-c value.

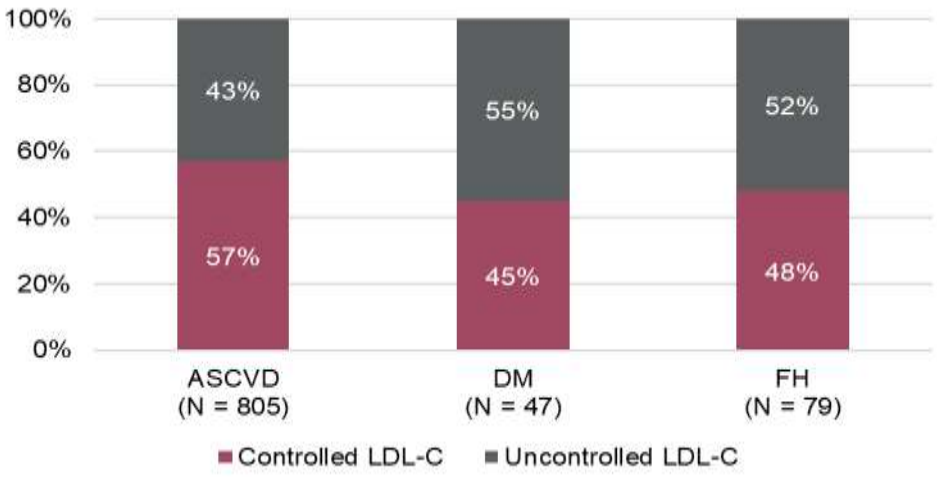
[†]n represents number of observations. Proportion (%) calculated using n for patients with uncontrolled LDL-C at baseline and ≥1 treatment modification as denominator.

Proportion of patients achieving CCS guideline-recommended LDL-C levels by treatment type at follow-up

At follow-up, CCS guideline-recommended LDL-C levels were reached by approximately 50% of patients overall (Figure 3A). Attainment of threshold LDL-C levels did not appear to differ by LLT in patients with ASCVD, while most patients with DM (80%, n=12) achieved threshold LDL-C levels with high intensity statins (Figure 3B). Approximately two-thirds of patients with FH treated with high-intensity statins, ezetimibe, or anti-PCSK9 mAbs met threshold LDL-C levels (Figure 3B).

Figure 3: Proportion of Patients Achieving 2016 CCS Guidelines Target at Follow-up by Treatment Type

A



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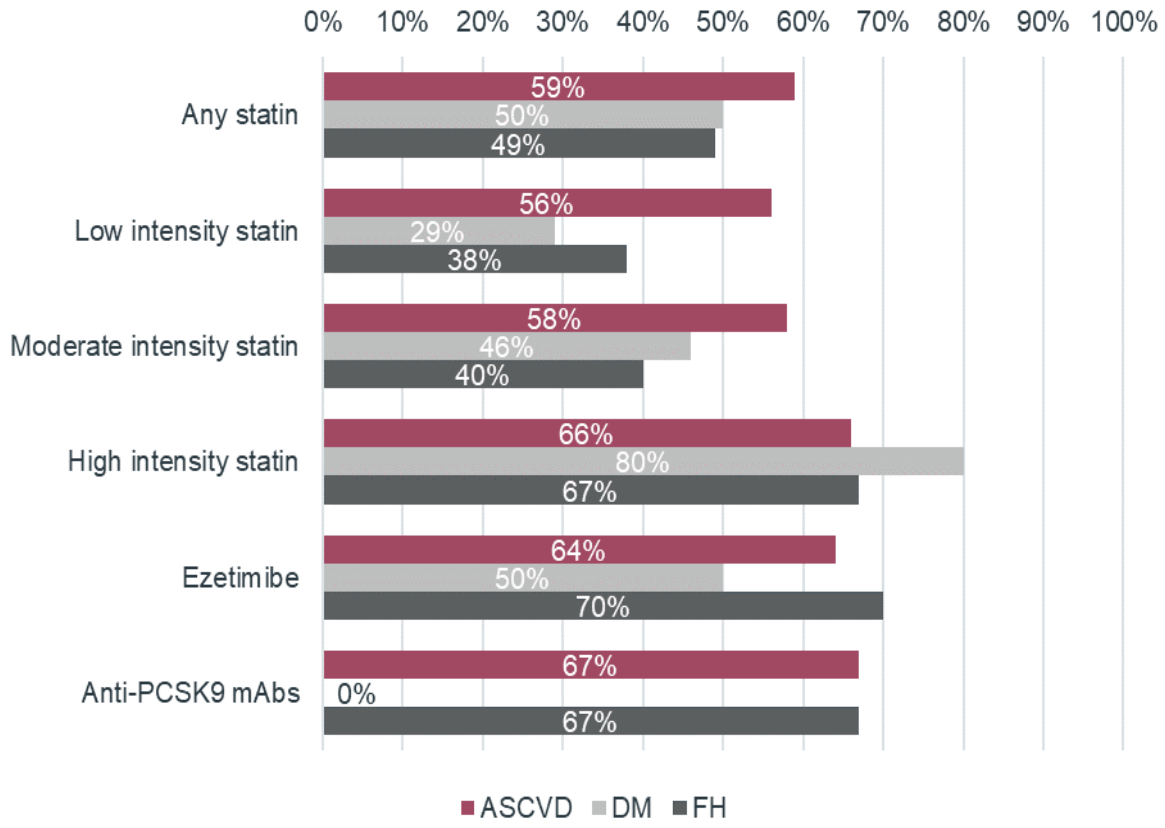


Anti-pcsk9 mabs, anti-pcsk9 monoclonal antibodies; ascvd, atherosclerotic cardiovascular disease; ccs, canadian cardiology society; dm, diabetes mellitus; fh, familial hypercholesteremia; ldl-c, low-density lipoprotein cholesterol.

A. Proportion of patients with ascvd, dm, and fh with uncontrolled ldl-c at baseline achieving 2016 ccs guidelines threshold ldl-c at follow-up.

B. Proportion of patients with ascvd, dm, and fh with uncontrolled ldl-c at baseline achieving 2016 ccs guidelines threshold ldl-c by treatment type at follow-up.

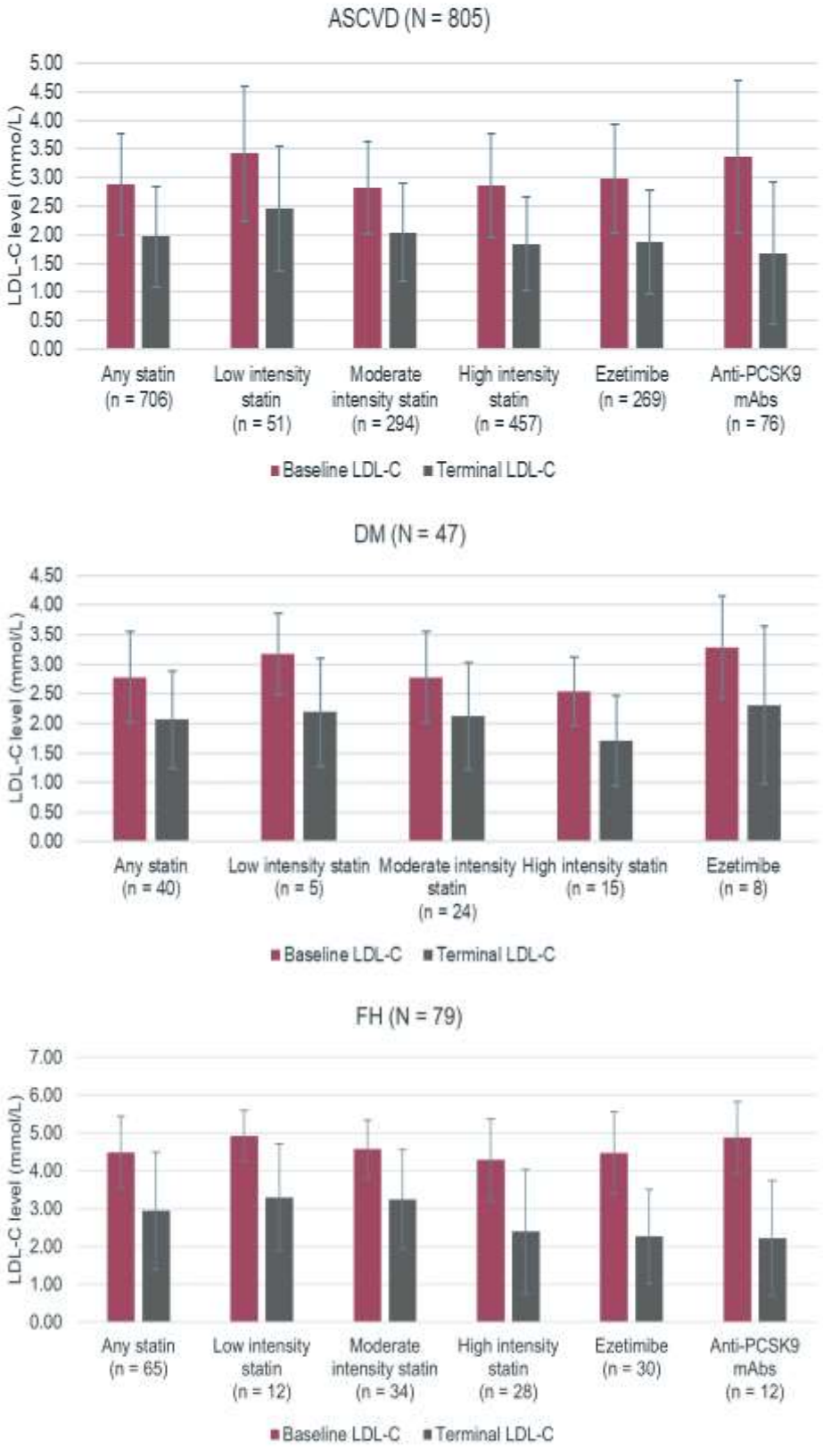
Note: At follow-up, patients may have received more than one treatment type at the same time

Change in LDL-C levels over time by treatment type

LDL-C levels decreased over time for all cohorts, with the greatest decrease in LDL-C noted in patients receiving anti-PCSK9 mAbs, ezetimibe, or high intensity statins alone or in combination with another LLT (Figure 4A). Across all cohorts, patients on ezetimibe or statins experienced decreases in LDL-C levels between 35-45% or 30-40%, respectively (data not shown). A >50% reduction in LDL-C levels was reached in 58%, 33%, and 27% of ASVCD patients treated with anti-PCSK9 mAbs, ezetimibe, and statins, respectively (Figure 4B). In the diabetes cohort, 25% of patients treated with ezetimibe and 20% of those receiving statins achieved a >50% reduction in LDL-C. Most patients with FH treated with ezetimibe (63%) achieved LDL-C threshold levels, followed by anti-PCSK9 mAbs (58%), and statins (38%). Note that all results are for named therapies used alone or in combination with another LLT.

Figure 4: Change in LDL-C Levels Over Time by Treatment Type

A



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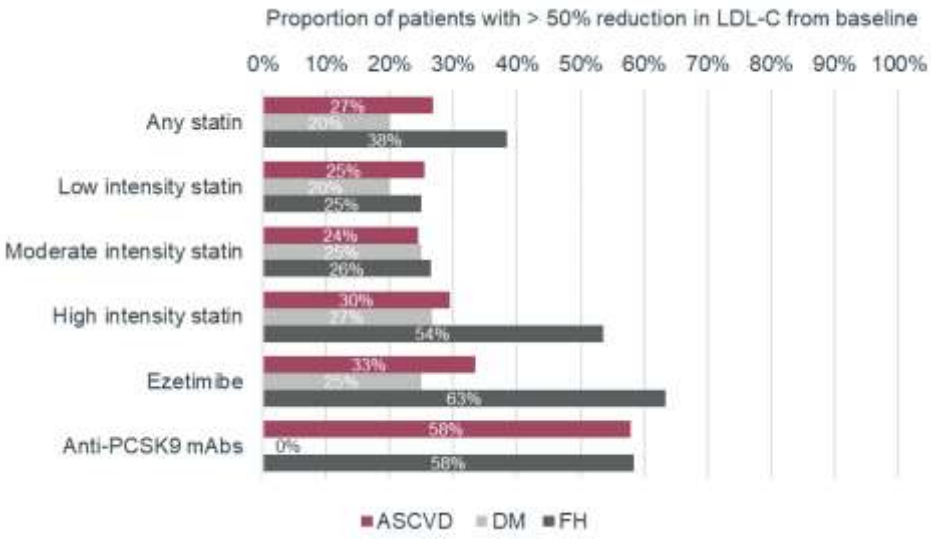

Anti-pcsk9 mabs, anti-pcsk9 monoclonal antibodies; ascvd, atherosclerotic cardiovascular disease; ccs, canadian cardiology society; dm, diabetes mellitus; fh, familial hypercholesteremia; ldl-c, low-density lipoprotein cholesterol.
A. Mean baseline and terminal ldl-c by treatment type in patients with ascvd, dm, and fh with uncontrolled ldl-c at baseline.
B. Proportion of patients with ascvd, dm, and fh with uncontrolled ldl-c at baseline with >50% reduction in ldl-c at follow-up from baseline.

Note: Patients may have received more than one treatment type at the same time.

DISCUSSION

The current study describes the demographic and clinical characteristics of a contemporary sample of adult patients with ASCVD, DM aged ≥40 years, or FH using a novel AI-based NLP method. The application of AI and NLP in healthcare and research is still in early stages; however, recent advances in this rapidly evolving field provide a gateway for new approaches to disease monitoring and management[29,30]. The use of NLP to extract data of interest from similar registries provides an opportunity for clinicians and researchers to quickly access data of interest within an unstructured EMR datasets. This could accelerate access to results from research or clinical quality improvement projects while reducing costs, thereby yielding greater potential to improve patient care. For example, in the context of ASCVD, treatment guideline updates represent an opportunity for clinicians to reassess patients' therapy in a timely manner to determine if action is needed to optimize vascular risk factor control. During the current study period, clinical practice would have presumably been consistent with the 2016 CCS guidelines for dyslipidemia management[11]. Had our study been a quality improvement project designed to assess LDL-C control at or shortly after the release of the 2021 CCS guidelines, the results would have demonstrated areas for improvement that could have served as a trigger to optimize LDL-C control according to new guidelines. Indeed, our results identified the following areas for improvement: 1) 33-49% of patients with uncontrolled baseline LDL-C did not have LLT documented in the EMR at baseline; 2) almost 50% of patients did not attain recommended LDL-C levels at follow-up; and, 3) treatment modifications in patients with uncontrolled LDL-C could have been more intensive.

The 2016 CCS guidelines provided clear recommendations for treatment initiation, intensification, or modification for patients with ASCVD or at risk of developing ASCVD. Nevertheless, 33% to 49% of patients with uncontrolled baseline LDL-C did not have documented baseline LLT. Statins were the most commonly reported baseline LLT, and treatment modifications largely consisted of addition or switches to statins. Baseline statin use was documented in only 22-47% of statin-indicated patients.

These findings align with a population-based Canadian study that documented statin use in 44% of patients in the high CVD risk category[16]. Studies from Manitoba and Alberta also revealed a substantial proportion of patients with ASCVD not receiving statins (71% and approximately 50%, respectively)[14,15,20]. Documented statin use in our patients with FH (47%) is consistent with data from the Canadian FH Registry, in which 51.4% of patients received statins[31].

At baseline, LDL-C was not controlled in 38% of patients with ASCVD or DM, and 75% of patients with FH, while at follow-up, 45-57% of patients with uncontrolled baseline LDL-C achieved recommended LDL-C levels (<2.0 mmol/L for ASCVD and DM, and <2.5 mmol/L for FH). Reasons for patients not achieving LDL-C target levels may vary and include socioeconomic, behavioural, and physiological factors[32]. However, these reasons were not routinely captured in patient medical records and could not be analyzed as part of this study. Our findings are consistent with a previous Canadian report wherein 48.5% of patients with ASCVD had uncontrolled LDL-C levels at diagnosis, decreasing to 36.6% at follow-up[15]. Results from patients with DM align with the DYSlipidemia International Study (DYSIS) in which LDL-C was uncontrolled in 40% of patients with DM[33]. Results from patients with FH are consistent with a study from British Columbia demonstrating that despite increased LLT use in patients with FH, only 35% achieved ≥50% LDL-C level reduction, and only 8.3% achieved LDL-C levels <2.0 mmol/L.

Despite treatment modifications in patients with uncontrolled baseline LDL-C, 43% to 55% of patients did not achieve LDL-C control at follow-up, suggesting that treatment modification could have been more intensive in these patients. Lack of LLT optimization to meet 2016 CCS guideline-recommended LDL-C levels during follow-up may be attributed to knowledge gaps among healthcare providers. Lipid monitoring is recommended after initiating LLT to track adherence and medication efficacy[34]. At baseline, we observed that LDL-C measurements remained undocumented/unreported in 23-45% of patients. Similar findings were reported in Ontario, whereby LDL-C assessments were not conducted in the first six months post-PCI in 48% of patients [12]. A study from Alberta also reported a lack of LDL-C measurement in 22.1% of patients with ASCVD[15]. Lastly, a systematic review revealed that among individuals recommended for screening, 23.6% did not have LDL-C levels measured, further highlighting the gap in LDL-C testing in Canada[13].

As previously noted, guideline updates represent an opportunity to reassess patients' lipids to determine if LLT requires modification. Applying the 2021 CCS guidelines LDL-C threshold (>1.8 mmol/L) increased the proportion of uncontrolled LDL-C in ASCVD patients from 38% to 47%[1]. Similar findings were reported in the European Da Vinci study[18]. Following the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines update in 2019, the proportion of patients categorized as 'very high risk' and 'high risk' achieving new LDL-C threshold levels was approximately 50% lower than those meeting previous thresholds (2016 guidelines: 54%, 2019 guidelines: 33%)[18]. Collectively, these data demonstrate that guideline updates can, and should, serve as a stimulus to revisit patient's LDL-C values and modify treatment if necessary.

Our data documents the real-world benefits of LLT, as evidenced by decreased LDL-C levels at follow-up. High intensity statins were associated with numerically greater LDL-C reduction over time and with a numerically higher proportion of patients achieving >50% reduction in LDL-C. The time to subsequent LLT change was noticeably shorter than the time to initial change across cohorts, possibly reflecting more frequent outpatient visits and closer monitoring once physicians establish a process to optimize LLTs. The reason for, and the identity of, the initiator for LLT change was not routinely documented in patient EMRs. The benefits associated with treatment modifications in patients with uncontrolled LDL-C is well documented[15,17,18,33]. However, restricted access and higher costs of newer treatments (e.g., anti-PCSK9 mAbs) are barriers to treatment modification in patients whose LDL-C levels remain elevated despite a maximized statin dose[35,36].

Thus, despite the causal link between elevated LDL-C and ASCVD, the availability of clinical practice guidelines, and access to laboratory testing, persisting treatment and screening gaps in dyslipidemia remain pervasive[37,38].

Strengths of the present study include access to all EMR data in samples drawn from a variety of cardiology and internal medicine practice settings across 4 Canadian provinces. Additionally, our findings are consistent with previous studies that employed traditional data extraction methods and administrative billing datasets, demonstrating the usefulness of applying AI to EMR database studies. Accordingly, using NLP methodology to analyze patients' medical records is a novel and rapid approach that can easily be leveraged on a large scale to facilitate prompt action to improve LDL-C control and the quality of clinical practice. Data from this study are representative of real-world lipid management in patients with ASCVD, DM aged ≥40 years, and FH, and may be generalizable across Canada. Limitations inherent to the observational nature and data sources should be noted. The lack of pharmacy dispensation data may lead to an under-estimation of the actual rate of LLT use in our population. The potential under-documentation of LDL-C in specialist-based EMRs may be due to communication issues with primary care settings or may reflect a gap in the care process of these patients. Our data sources did not allow for further clarity of this observation. Furthermore, we did not assess whether patients not reaching LDL-C targets were also above ApoB and non-HDL-C target levels. Because those markers are important predictors of cardiovascular event risk and benefit of LLT[39,40], it is possible that some treatment decisions may have been made based on the level of these markers. Finally, our analyses were performed using information only available in the cardiologists' and internists' patient records. It is likely that additional routine data available in patient's primary care physician, hospitalization, and laboratory records (i.e., missing from cardiologists and internists records) may provide additional context to our findings.

CONCLUSION

The current study provided insights regarding real-world lipid management of patients with ASCVD, DM, and FH. Consistent with previous findings, our data highlights the need to optimize lipid management in patients with ASCVD or at high risk of developing ASCVD to narrow the gap between guideline recommendations and clinical practice. The use of AI with NLP methodology to analyze patients' medical records is a novel and rapid approach that could support improved understanding of clinical practice and provide an alternative to traditional chart review approaches in future epidemiological research. Future investigations may assess the value of NLP technology to automatically screen EMR systems and to flag patients not treated per guidelines to ensure they benefit from most recent recommendations.

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Supplementary Material

The following supporting information is included in the Supplementary Materials: Table S1: Definition of Statin Treatment Intensity; Table S2: Additional Patient Baseline Demographic Characteristics; Figure S1: Baseline LLT use according to LDL-C controlled versus uncontrolled.

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