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Clinical Research

Treatment and Low-Density Lipoprotein Cholesterol Management in Patients Diagnosed With Clinical Atherosclerotic Cardiovascular Disease in Alberta

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See editorial by Sparrow et al., pages 813–815 of this issue.

ABSTRACT

Background: Low-density lipoprotein cholesterol (LDL-C) is an important indicator in the development and management of atherosclerotic cardiovascular disease (ASCVD). Herein, we describe the management of LDL-C with lipid-lowering therapy, among patients diagnosed with clinical ASCVD in Alberta, Canada.

Methods: A retrospective study was conducted by linking multiple health system databases to examine clinical characteristics, treatments, and LDL-C assessments. Patients with ASCVD were identified using a specific case definition on the basis of International Classification of Diseases, Ninth Revision, Clinical Modification/International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada codes between 2011 and 2015. LDL-C was assessed at the first measurement (index test) and second measurement (follow-up test) during the study period. LDL-C levels were evaluated on the basis of the 2016 Canadian Cardiovascular Society guideline recommendations for achieving $<$ 2.0 mmol/L or a 50%

RÉSUMÉ

Introduction : Le cholestérol à lipoprotéines de faible densité (cholestérol LDL) est un indicateur important du développement et de la prise en charge de la maladie cardiovasculaire athérosclérotique (MCVAS). Par la présente, nous décrivons la prise en charge du cholestérol LDL à l'aide d'un traitement hypolipémiant chez les patients de l'Alberta, au Canada, qui ont reçu un diagnostic clinique de MCVAS.

Méthodes : Nous avons réalisé une étude rétrospective en procédant au couplage des multiples bases de données du système de santé pour examiner les caractéristiques cliniques, les traitements et les évaluations du cholestérol LDL. Nous avons repéré les patients ayant une MCVAS grâce à une définition particulière de cas selon la Classification internationale des maladies, 9e révision, modification clinique, et la Classification statistique internationale des maladies et des problèmes de santé connexes, 10e révision, adaptation canadienne, entre 2011 et 2015. Nous avons évalué les taux de cholestérol LDL à la première mesure (analyse de référence) et à la deuxième mesure

Dyslipidemia is recognized as a major and modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD).[1,2] ASCVD is defined as any of the following: previous myocardial infarction or angina pectoris (ie, coronary heart disease), coronary revascularization using percutaneous coronary intervention or coronary artery bypass graft surgery, ischemic stroke or transient ischemic attack (ie, cerebrovascular disease), peripheral arterial disease, or other arterial revascularization procedures.[1,2] By definition, patients with any of the aforementioned diagnoses have clinical ASCVD (forthwith referred to as ASCVD). Despite diagnostic and treatment advances, ASCVD remains a leading cause of morbidity and mortality in Canada and worldwide.[3-5] In the Canadian context, this is not surprising, because 37% and 53% of Canadians aged 20 and older are estimated to have poor or intermediate cardiovascular health, respectively.[6] These findings are consistent with a

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reduction. Statin therapies were categorized as low-, moderate-, and high-intensity.

Results: Among the 281,665 individuals identified with ASCVD during the study period, 219,488 (77.9%) had an index LDL-C test, whereas 120,906 (55.1%) and 144,607 (65.9%) were prescribed lipid-lowering therapy before and after their index test, respectively. Most patients who received any lipid-lowering therapy were receiving moderate-/high-intensity statins (n = 133,029; 60.6%). Among the study cohort who had 2 LDL-C tests (n = 91,841; 32.6%), 48.5% of patients who received any lipid-lowering therapy did not achieve LDL-C levels < 2.0 at index date, whereas 36.6% did not achieve LDL-C levels < 2.0 or a 50% reduction at the follow-up test.

Conclusions: The current study revealed that only two-thirds of patients with ASCVD were receiving pharmacotherapy and of those, a significant proportion did not reach recommended LDL-C levels. A remarkable treatment gap was identified for at-risk ASCVD patients. Further implementation strategies are required to address this undermanagement.

(analyse de suivi) durant la période étudiée. Nous avons évalué les taux de cholestérol LDL en nous basant sur les recommandations des lignes directrices de la Société canadienne de cardiologie de 2016 en vue d'obtenir des concentrations < 2,0 mmol/l ou une réduction de 50 %. Nous avons regroupé les traitements par statines en catégories d'intensité, c'est-à-dire faible, modérée et élevée.

Résultats : Parmi les 281 665 individus considérés atteints de la MCVAS durant la période étudiée, 219 488 (77,9 %) avaient une analyse de référence de cholestérol LDL, alors que 120 906 (55,1 %) et 144 607 (65,9 %) se faisaient prescrire respectivement avant et après leur analyse de référence un traitement hypolipémiant. La plupart des patients qui ne recevaient aucun traitement hypolipémiant recevaient des statines d'intensité modérée ou élevée (n = 133 029; 60,6 %). Parmi la cohorte étudiée qui subissait 2 analyses de cholestérol LDL (n = 91 841; 32,6 %), 48,5 % des patients qui ne recevaient aucun traitement hypolipémiant ne parvenaient pas à obtenir des concentrations de cholestérol LDL < 2,0 à la date de référence, alors que 36,6 % ne parvenaient pas à obtenir des concentrations de cholestérol LDL < 2,0 ou une réduction de 50 % à l'analyse de suivi.

Conclusions : La présente étude a révélé que seuls les deux tiers des patients atteints de MCVAS recevaient une pharmacothérapie et, parmi ces derniers, une proportion importante ne parvenait pas à obtenir les concentrations de cholestérol LDL recommandées. Nous avons noté des écarts de traitement considérables entre les patients exposés au risque de MCVAS. D'autres stratégies de mise en œuvre sont requises pour remédier à cette prise en charge inadéquate.

recent systematic review that examined 14 observational studies from Asia, Europe, and the United States, and concluded that real-world patients have a high overall cardiovascular burden.[7] Furthermore, cardiovascular diseases are leading contributors to health care costs in Canada, representing 12% of direct health care costs and 10% of combined direct and indirect costs in Canada in 2010.[8]

A substantial body of evidence has documented the benefits of lowering low-density lipoprotein cholesterol (LDL-C) in patients with ASCVD. In the most recent Canadian Cardiovascular Society clinical practice guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults, statins were indicated for clinical atherosclerosis.[1] The suggested treatment approach is to achieve LDL-C levels that are consistently < 2.0 mmol/L or to achieve a 50% reduction in LDL-C.

Despite the known benefits of statins, a significant treatment gap persists in patients with ASCVD or at high risk of developing ASCVD. In the Canadian context, only 40% of those receiving statins have been reported to achieve dyslipidemia targets.[9] Canadian data sets further show statin use of only 20%-40% in patients with ASCVD or at high risk of developing ASCVD.[9-11] Thus, there remains a need to conduct additional research to better understand contemporary management of these patients.

In the current study we examined current patterns of lipid-lowering therapy for the management of LDL-C among patients identified with ASCVD from the administrative health system data in the province of Alberta, Canada. The objectives of the study were: (1) to characterize the proportion of patients with ASCVD and a statin prescription claim; (2) to describe the intensity level of statins prescribed; and (3) to determine the proportion of statin users who achieved recommended levels of LDL-C.

Methods

Study design

This retrospective observational study was conducted using province-wide, administrative health system data from the province of Alberta, Canada between April 1, 2010 and March 31, 2017.

Data sources

The following data sources were used: (1) Discharge Abstract Database, including inpatient hospital diagnostic information; (2) National Ambulatory Care Reporting System, including facility-based ambulatory care information on services and diagnoses (eg, emergency visits); (3) Practitioner Claims data, containing fee-for-service claims from physicians and other insured health services (eg, specialists); (4) population-based registry data, including demographic and geographic information for individuals who are registered with the Alberta Health Care Insurance Plan; (5) Pharmaceutical Information Network, including medication type, dosage, and days' supply; and (6) Calgary Laboratory Services data (Millennium/Pathnet Calgary Laboratory Services, Sunquest Edmonton Laboratory Services, and Meditech Laboratory Services data) for test results including lipid levels. The study was approved by the Health Research Ethics Board of Alberta Community Health Committee.

Study cohort

A cohort of individuals aged 18 years or older with ASCVD were identified using diagnostic and procedural codes on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)/International Statistical Classification of Diseases and Related

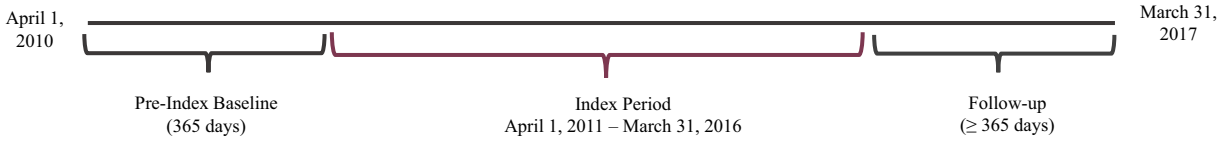

Figure 1. Study and index date time-period.

Health Problems, 10th Revision, Canada (ICD-10-CA); documented in primary, secondary, or other diagnostic fields of the electronic health record in the Discharge Abstract Database, National Ambulatory Care Reporting System, or Practitioner Claims databases.[12,13] The ASCVD ICD-9-CM/ICD-10-CA diagnostic and procedural codes are provided in Supplemental Table S1.

After initial identification of all patients with an ASCVD diagnostic code, the study cohort was limited to individuals with an initial LDL-C test (index date) during the study period. Other requirements for inclusion were: continuous health plan enrollment, defined as 1 year of pre-index data (365 days before the index date) and at least 1 year of post-index (follow-up) data (Fig. 1).

Study variables

Demographic factors included age (< 55, 55 to < 65, ≥ 65 years), sex, and geographic zones according to the centralized health authority (Calgary, Central, Edmonton, North and South). Clinical characteristics included LDL-C test results and medications post-ASCVD diagnosis.

The laboratory test results included LDL-C, high-density lipoprotein and total cholesterol, and triglycerides. If only total and high-density lipoprotein cholesterol and triglycerides were reported, LDL-C levels (mmol/L) were calculated using the Friedewald formula.[14] Patients were excluded if: (1) their lipid results were missing; (2) calculated LDL-C levels were less than 0; or (3) triglycerides were > 4.5 mmol/L, hence

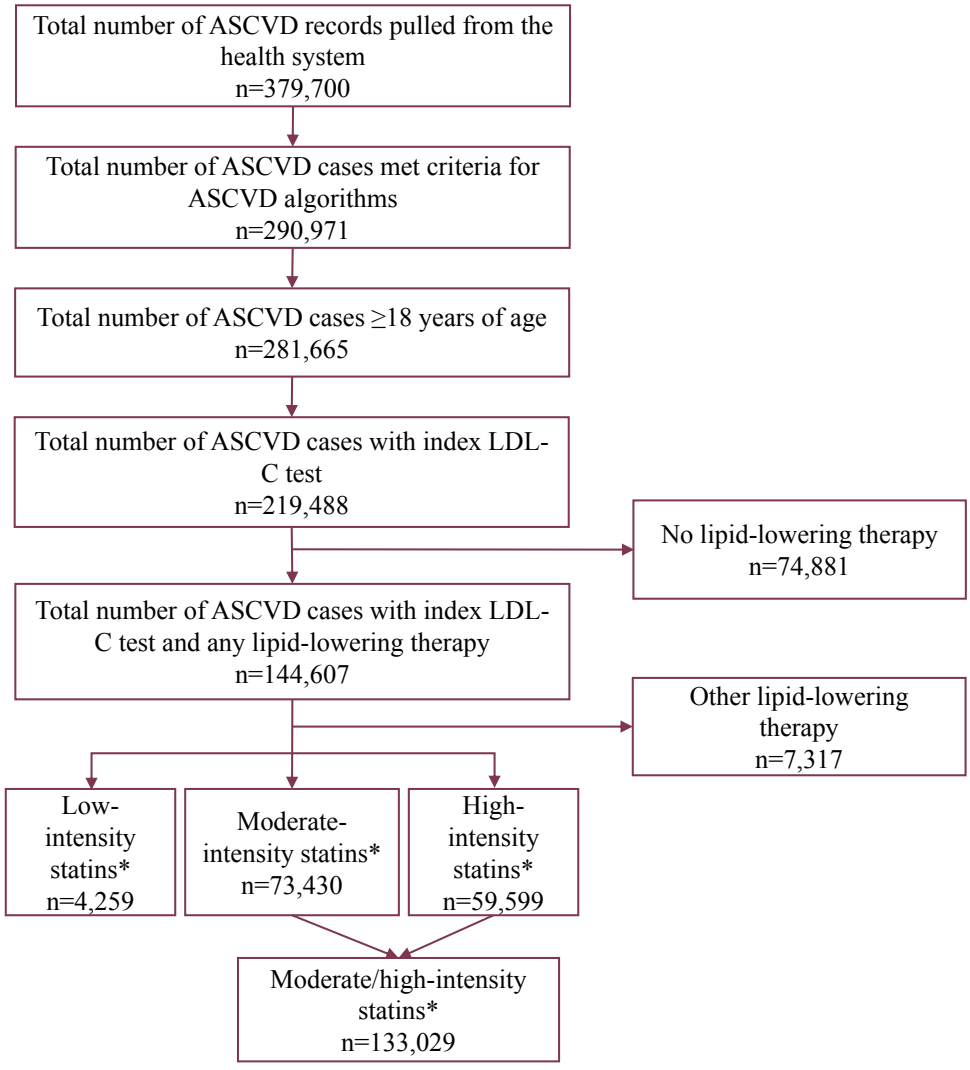

Figure 2. Flow chart of the study cohort. *Patients on statin intensities listed in the 2013 ACC/AHA recommendations; this is a subset of those on any lipid-lowering therapy.

LDL-C levels were not appropriate to calculate using the Friedewald formula. Index LDL-C levels were categorized as < 2.0 and ≥ 2.0 mmol/L. Follow-up LDL-C levels were examined for patients who had a second test at least 2 weeks after the index test, and within 1 year of initiating treatment. For the purposes of the present study, achieved recommended LDL-C levels were defined as an LDL-C < 2.0 mmol/L at the follow-up test or a 50% reduction (relative to the index test) in keeping with current Canadian practice guidelines.[1] As a note, although the most up-to-date Canadian clinical practice guidelines (2016) were used for LDL-C cutoffs, most patients in the current study were managed according to the previous guidelines, which did not significantly differ from the 2016 recommendations.

The main treatment variable was defined as any lipid-lowering therapy prescription claim at least 2 weeks after, and within 1 year of the index LDL-C test date. Statin treatment was classified as low-, moderate-, or high-intensity using the American College of Cardiology/American Heart Association 2013 guidelines for the treatment of dyslipidemia (Supplemental Table S2).[2] Other lipid-lowering therapies were defined as fibrates (bezafibrate, gemfibrozil, fenofibrate), bile acid sequestrants (cholestyramine, colestipol, colesevelam, colextran), nicotinic acid and derivatives, and other lipid-modifying agents (omega-3-triglycerides [other esters and acids], ezetimibe, evolocumab). The first lipid-lowering therapy prescription claim after the index LDL-C test was used for patients with multiple prescriptions. We also examined prescription claims for statins combined with adjunctive ezetimibe and conducted exploratory analyses of incident prescriptions of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor antibody treatments such as alirocumab and evolocumab (note: during the data collection period, there were no prescription claims for alirocumab). See Supplemental Table S3 for details on included medications.

Adherence to treatment was assessed using the proportion of days covered (PDC) within 1 year after the prescription claim date.[15] On the basis of the previous studies, patients were considered adherent with a PDC ≥ 0.8 and nonadherent if the PDC was < 0.80.[16-19]

Finally, the Charlson Comorbidity Index (CCI) was used to classify the burden of comorbidities.[20] CCI scores were derived from data extracted in the 365 days pre-index period and calculated on the basis of a validated claims-based algorithm for ICD-9-CM/ICD-10-CA codes.[20-23]

Statistical methods

Descriptive statistics (ie, frequencies, means, and standard deviations [SDs]) were used to describe demographic and clinical characteristics. Patients with an index and follow-up LDL-C test were analyzed to examine achievement of recommended LDL-C levels. The current study focused on study cohort distributions, because *P* values were not informative in the context of large sample sizes. All analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC).

Results

Of the 379,700 ASCVD records extracted from the health system administrative databases, we identified 281,665 adult patients with ASCVD who met study inclusion criteria between April 1, 2011 and March 31, 2016. Most (77.9%) had an index LDL-C test post-ASCVD diagnosis, and of those, 120,906 (55.1%) received any lipid-lowering therapy before their index test whereas, 144,607 (65.9%) received any lipid-lowering therapy after (between 2 weeks and up to 1 year) their index test (Fig. 2). Nearly all patients received statins, whereas 5.1% received other lipid-lowering therapies. Of the 219,488 patients with an index LDL-C test, most were male (59.9%), ≥ 65 years of age (49.6%), and had a CCI score > 1 (63.8%; Table 1; Supplemental Table S4).

Mean index LDL-C levels were 2.4 ($\pm$ 1.0) mmol/L for the full study cohort (n = 219,488) and those who received any lipid-lowering therapy (n = 144,607). At index, 59.4% of the full study cohort and 47.4% of the subset receiving any lipid-lowering therapy had LDL-C levels ≥ 2.0 mmol/L. Mean length of follow-up for the study cohort was 3.8 $\pm$ 1.5 years.

Table 2 shows the proportions of patients not achieving recommended LDL-C levels in the subset of patients with an index and follow-up test (n = 91,841). These results are presented for patients who received any lipid-lowering therapy and stratified according to different statin intensities. The mean

Table 1. Demographic characteristics among patients with ASCVD

Characteristic	Cases with index LDL-C test, n	Cases receiving any lipid-lowering therapy,* n (%)†
Total	219,488	144,607
Age		
Mean ($\pm$ SD)	64.0 ($\pm$ 13.8)	66.3 ($\pm$ 11.9)
≤ 55	53,796	24,048 (44.7)
55 to < 65	56,907	39,594 (69.6)
≥ 65	108,785	80,965 (74.4)
Sex		
Female	87,986	49,371 (56.1)
Male	131,502	95,236 (72.4)
Geographic Region		
Calgary zone	72,149	49,713 (68.9)
Central zone	25,777	18,193 (70.6)
Edmonton zone	87,586	52,964 (60.5)
North zone	21,713	15,000 (69.1)
South zone	12,259	8737 (71.3)
Diagnoses‡		
Angina	156,365	99,844 (63.9)
Coronary atherosclerosis/ previous myocardial infarction	106,966	91,127 (85.2)
Peripheral arterial disease§	39,365	35,734 (90.8)
Cerebrovascular disease/stroke	35,710	25,207 (70.6)
Transient ischemic attack	11,756	8645 (73.5)
Charlson Comorbidity Index		
0	79,490	43,900 (55.2)
1-2	87,728	61,295 (69.9)
≥ 3	52,270	39,412 (75.4)
Index LDL-C, mmol/L		
Mean ($\pm$ SD)	2.4 ($\pm$ 1.0)	2.4 ($\pm$ 1.0)
< 2.0	89,214	76,043 (85.2)
≥ 2.0	130,274	68,564 (52.6)

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

* Including single statins, combination statins, and other lipid-lowering therapy (ie, fibrates or other lipid-modifying agents).

† Percentages in the far-right column represent proportions of the first column.

‡ Not mutually exclusive.

§ Included patients with percutaneous coronary intervention and coronary bypass graft surgery.

Table 2. Proportions of not achieving LDL-C levels at the follow-up test among patients with ASCVD*

	Not achieving LDL-C levels receiving any lipid-lowering therapy (n = 91,841)†		Not achieving LDL-C levels according to statin intensity					
			Low-intensity (n = 2713)‡		Moderate-intensity (n = 45,491)‡		High-intensity (n = 38,759)‡	
Characteristic	Total n	n (%)	Total n	n (%)	Total n	n (%)	Total n	n (%)
Total	91,841	33,630 (36.6)	2713	1784 (65.8)	45,491	18,257 (40.1)	38,759	10,324 (26.6)
Age								
< 55	15,220	6590 (43.3)	253	195 (77.1)	6701	3404 (50.8)	7386	2368 (32.1)
55 to < 65	25,944	10,335 (39.8)	560	406 (72.5)	11,985	5528 (46.1)	12,124	3513 (29.0)
≥ 65	50,677	16,705 (33.0)	1900	1183 (62.3)	26,805	9325 (34.8)	19,249	4443 (23.1)
Sex								
Female	30,261	12,881 (42.6)	1127	798 (70.8)	17,321	7721 (44.6)	9976	3022 (30.3)
Male	61,580	20,749 (33.7)	1586	986 (62.2)	28,170	10,536 (37.4)	28,783	7302 (25.4)
Charlson Comorbidity Index								
0	28,410	12,465 (43.9)	930	665 (71.5)	16,323	7483 (45.8)	9366	3035 (32.4)
1-2	39,237	14,272 (36.4)	1107	717 (64.8)	18,208	7370 (40.5)	17,943	4842 (27.0)
≥ 3	24,194	6893 (28.5)	676	402 (59.5)	10,960	3404 (31.1)	11,450	2447 (21.4)
Index LDL-C, mmol/L								
< 2.0	47,310	7747 (16.4)	824	235 (28.5)	22,859	4128 (18.1)	22,174	2978 (13.4)
≥ 2.0	44,531	25,883 (58.1)	1889	1549 (82.0)	22,632	14,129 (62.4)	16,585	7346 (44.3)
Received ezetimibe§,‖								
No	84,426	29,557 (35.0)	2579	1705 (66.1)	44,525	17,968 (40.4)	37,322	9884 (26.5)
Yes	2537	808 (31.8)	134	79 (59.0)	966	289 (29.9)	1437	440 (30.6)

ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

* Follow-up LDL-C levels were defined as LDL-C < 2.0 mmol/L or a 50% reduction.

† Including single statins, combination statins, and other lipid-lowering therapy (ie, fibrates or other lipid -modifying agents).

‡ Patients received statin intensities listed in the 2013 ACC/AHA recommendations; this is a subset of those receiving any lipid-lowering therapy.

§ Receiving ezetimibe: statins (single and combinations) and alternative treatments (single and combinations) with ezetimibe.

‖ The sample size with/without ezetimibe was 86,963 (low = 2713; moderate = 45,491; high = 38,759); ezetimibe was adjunctive therapy to other treatment.

time between index and follow-up LDL-C tests was 276.4 ± 217.9 days. Further, mean index and follow-up LDL-C levels were 2.2 ± 1.0 and 1.9 ± 0.8 mmol/L, respectively. Overall, among the 91,841 patients who received any lipid-lowering therapy, 44,531/91,841 (48.5%) had an index LDL-C of ≥ 2 mmol/L. Furthermore, when we examined the follow-up LDL-C, 36.6% did not achieve the recommended LDL-C levels (< 2 mmol/L or a > 50% reduction); see Figure 3 for details. In addition, failure to achieve recommended levels was highest in the low-intensity statin group (65.8%), decreasing to 40.1% and 26.6% in the moderate- and high-intensity groups, respectively, and 33.9% when the moderate- and high-intensity groups were combined. Compared with those who received any lipid-lowering therapy, patients who received combination therapy (statin with ezetimibe) had a slightly lower failure rate of 31.8%.

Most patients (60.2%) who received any lipid-lowering therapy were adherent (PDC ≥ 0.8), with similar rates observed across statin-intensity groups (57.5% to 63.8%; Table 3). Adherence was 76.3% among those who also received ezetimibe (n = 3606; 2.5% of patients who received lipid-lowering therapy).

Last, of the 82 patients who received PCSK9 inhibitors, 41 had pre- and post-treatment LDL-C tests. In these patients, mean LDL-C decreased from 2.5 ± (1.3) mmol/L to 1.3 ± (1.2) mmol/L (mean days between tests, 48.5 ± [45.5] days); see Supplemental Figure S1.

Discussion

In the present study we identified significant under-management of dyslipidemia in the Alberta ASCVD population. This was evident by the observations that: (1) 34% of patients with ASCVD did not receive prescriptions for lipid-lowering drugs; (2) failure to achieve guideline-recommended levels of LDL-C was common among patients who received moderate- or high-intensity statin therapy (33.9%) or any lipid-lowering agents (36.6%); and (3) 40% of patients were not adherent to their treatment regimens. For patients who had an index and follow-up LDL-C test, failure to achieve recommended levels decreased from 48.5% at index to 36.6% at follow-up.

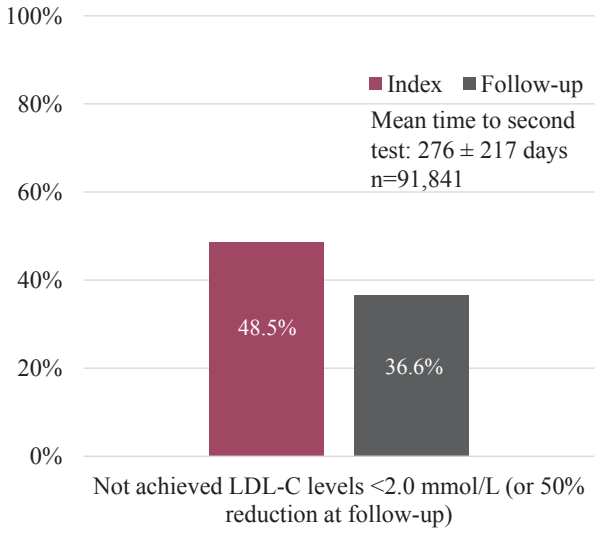

Figure 3. LDL-C levels for patients on any lipid-lowing therapy who had both index and follow-up tests (n = 91,841).

Table 3. Proportions of treatment adherence among patients with ASCVD*

	Adherence to lipid-lowering therapy†		Adherence according to statin-intensity					
			Low-intensity‡		Moderate-intensity‡		High-intensity‡	
Characteristic	Total n	n (%)	Total n	n (%)	Total n	n (%)	Total n	n (%)
Total	144,607	87,048 (60.2)	4259	2524 (59.3)	73,430	42,255 (57.5)	59,599	38,042 (63.8)
Age								
< 55	24,048	11,931 (49.6)	367	152 (41.4)	10,964	4706 (42.9)	11,384	6510 (57.2)
55 to < 65	39,594	23,268 (58.8)	830	444 (53.5)	18,704	10,201 (54.5)	18,166	11,521 (63.4)
≥ 65	80,965	51,849 (64.0)	3062	1928 (63.0)	43,762	27,348 (62.5)	30,049	20,011 (66.6)
Sex								
Female	49,371	28,553 (57.8)	1858	1088 (58.6)	28,753	16,024 (55.7)	15,895	9914 (62.4)
Male	95,236	58,495 (61.4)	2401	1436 (59.8)	44,677	26,231 (58.7)	43,704	28,128 (64.4)
Charlson Comorbidity Index								
0	43,900	25,884 (59.0)	1395	850 (60.9)	25,434	14,331 (56.4)	14,449	9207 (63.7)
1-2	61,295	37,483 (61.2)	1747	1041 (59.6)	29,510	17,165 (58.2)	27,096	17,562 (64.8)
≥ 3	39,412	23,681 (60.1)	1117	633 (56.7)	18,486	10,759 (58.2)	18,054	11,273 (62.4)
Index LDL-C, mmol/L								
< 2.0	76,043	51,293 (67.5)	1360	926 (68.1)	37,481	24,867 (66.4)	37,481	24,037 (68.6)
≥ 2.0	68,564	35,755 (52.2)	2899	1598 (55.1)	35,949	17,388 (48.4)	35,949	14,005 (57.0)
Received ezetimibe§,‖								
No	133,682	80,068 (59.9)	4087	2397 (58.7)	72,060	41,211 (57.2)	57,535	36,460 (63.4)
Yes	3606	2753 (76.3)	172	127 (73.8)	1370	1044 (76.2)	2064	1582 (76.7)

ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PDC, proportion of days covered.

*PDC was calculated on the basis of 1 year of treatment post index LDL-C test. Adherence was defined as PDC ≥ 0.8 and not adherent, PDC < 0.8.

†Including single statins, combination statins, and other lipid-lowering therapy (ie, fibrates or other lipid- modifying agents).

‡Patients received statin intensities listed in the 2013 ACC/AHA recommendations; this is a subset of those receiving any lipid-lowering therapy.

§Receiving ezetimibe: statins (single and combinations) and alternative treatments (single and combinations) with ezetimibe.

‖The sample size with/without ezetimibe was 137,288, because ezetimibe was an adjunctive therapy to other treatment.

Despite the availability of clinical practice guidelines for the management of dyslipidemia for prevention of future vascular events in patients with ASCVD, treatment gaps remain commonly reported in the literature. On the basis of data collected between 2010 and 2015 from the Manitoba Primary Care Research Network repository, Brown et al. reported that most (71%) patients with ASCVD in Manitoba were not receiving a statin, a finding that the authors noted was consistent with similar studies of statin use for secondary prevention in North America and in the European Union.[11] A systematic review of Canadian and American studies in cardiovascular risk factor management noted that in Canadian literature, 59% of patients with dyslipidemia were not treated, and that lipid control was 42% among those treated (defined as LDL-C levels < 2 mmol/L in patients receiving treatment).[10] Similarly, Hennessy et al. observed that 68% of high-risk patients (ie, preexisting high-risk condition or a Framingham Risk Score of at least 20%) in the Canadian Health Measures Survey (data collection years: 2007-2011) were not treated with statins.[9] Despite differences with the aforementioned studies, the more recent data herein on the number of untreated patients (34%) suggests improved management compared with previous reports of untreated patients in other Canadian literature (59%-71%).[9-11] However, unaccounted for in the current study was the patient population without an index LDL-C test (22.1%), which might infer bias toward a reduced percentage of untreated patients. The proportion of patients whose lipids achieved recommended levels were similar, 53% at the index measurement in the present study vs 42% in the systematic review, highlighting a need for further improvement.[10] Patients who achieved recommended LDL-C levels improved slightly with concomitant ezetimibe treatment, but only consisted of 2.5% of our study sample. The reasons for this low rate of adjunctive therapy and modest improvement are unclear but serve to illustrate a subset of patients with unmet treatment needs. In this light, the exploratory LDL-C results (ie, 50% reduction in LDL-C levels) from patients who received PCSK9 inhibitors are encouraging.

Last, the estimates of treatment adherence in this study were consistent with previous research showing similar rates of adherence, ranging from 55% to 66%, to lipid-lowering medications and illustrate the challenge of successfully managing chronic diseases.[24-26] Standardizing care with ASCVD-specific admission orders, implementing risk stratification tools (such as the laboratory-based Framingham Risk Score), and corresponding statin treatment recommendations in laboratory requisitions,[27] electronic medical record review, and a follow-up lipid profile at the time of discharge might reduce the number of untreated or undertreated patients in Alberta.

Because of the nature of the study design, limitations should be taken into consideration for the interpretation of findings. First, data used in this study were collected for hospital administrative purposes and not for research, therefore, administrative data might not always accurately capture patient and clinical characteristics. Second, a study using administrative data cannot confirm that prescribed medications were ingested; only that the prescription was filled at the pharmacy. Further, in the current study we could not determine the specialty of the prescribing physician. In addition, treatment use might be underestimated because patients who received treatment but did not have an index LDL-C test were excluded and data for patients who were diagnosed only through a primary care assessment were not captured. Further, particularly for individuals older than 75 years of age, several other factors might contribute to the lack of prescriptions such as, risk for

intervention not recognized by prescribing physician and/or patients not wanting to take or continue to take prescriptions because of side effects (eg, onset of diabetes, myopathy, and medication interactions).[28] Finally, the additional use of ezetimibe with statin therapy was shown to improve cardiovascular outcomes in the **Imp**roved **R**eduction of **O**utcomes: **V**ytorin **E**fficacy **I**nternational **T**rial (IMPROVE-IT) trial.[29] These results were published toward the end of the study period; thus, ezetimibe prescription dispenses are likely to increase.

Despite these limitations, undermanagement of dyslipidemia in patients with ASCVD in Alberta was present. The failure to achieve recommended LDL-C levels might put patients at a much higher risk for vascular events than previously estimated. Furthermore, in a recent real-world study of patients with high-risk ASCVD, among those who experienced a new vascular event after index, 42% had a subsequent event.[30] This rate of vascular events is substantially higher than estimates derived from randomized controlled trial populations. Because of the evidence from the Cholesterol Treatment Trialists' Collaborators meta-analyses that small decreases in LDL-C levels result in large decreases in the risk of vascular events,[31,32] further therapeutic interventions are warranted for this patient population.

The current study provides a large population-based sample of contemporary real-world Canadian data. Patients with ASCVD were identified from electronic administrative health system data that includes $>$ 4 million residents of Alberta; whereas previous Canadian studies were conducted through surveys with smaller sample sizes.[9-11,33] In addition, the opportunity to link multiple databases including province-wide laboratory data, pharmacy-level prescription claims data, and clinical diagnostic data increased the validity and generalizability of the study. Further association-based studies are warranted to better understand ASCVD in Alberta.

Conclusions

In conclusion, the current study showed an unmet need for improving and optimizing the management of dyslipidemia in patients with ASCVD in Alberta. Additional research is needed to assess the effects of current treatment gaps on morbidity, mortality, and other important outcomes, such as health-related quality of life, functional status, as well as health care societal costs. Finally, determining the reasons for the observed treatment gaps would aid the development of sustainable strategies to improve the management and delivery of care for patients with ASCVD.

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Supplementary Material

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