Real-World Insights Into Evolocumab Use in Patients With Hyperlipidemia: Canadian Analysis From the ZERBINI Study

Milan Gupta, MD, a,b G.B. John Mancini, MD, c Rajvi J. Wani, PhD, d Vineeta Aahooja, MD, e Jean Bergeron, MD, MSc, f,g Priya Manjoo, MD, h,i A. Shekhar Pandey, MD, a,j Maureen Reiner, MS, MA, k Johnny Beltran, MD, MSc, l Thiago Oliveira, MD, d and Erin S. Mackinnon, PhD d

a Department of Medicine, McMaster University, Hamilton, Ontario, Canada; b Canadian Collaborative Research Network, Hamilton, Ontario, Canada; c Centre for Cardiovascular Innovation, Division of Cardiology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; d Amgen Canada Inc., Mississauga, Ontario, Canada; e Heart Health Institute, Scarborough and Ajax, Ontario, Canada; f Department of Medicine, Centre Hospitalier Universitaire de Québec-Laval, Québec, Quebec, Canada; g Department of Laboratory Medicine, Centre Hospitalier Universitaire de Québec-Université Laval, Québec, Quebec, Canada; h Department of Endocrinology, University of British Columbia, Vancouver, British Columbia, Canada; i Cardiometabolic Collaborative Clinic, Vancouver Island Health Authority, Vancouver, British Columbia, Canada; j Cambridge Cardiac Care Centre, Cambridge, Ontario, Canada; k Amgen Inc., Thousand Oaks, California, USA; l Amgen Biotecnologica, Bogota, Colombia

Real-world Impact of Evolocumab Use in Canadian Patients
12-month analysis of the ZERBINI observational study

Patients (N=131) at baseline: Results after 12 months of evolocumab:
- 58% statin use (37% high intensity)
- LDL-C -59%
- 78% of patients achieved an LDL-C <1.8 mmol/L
- 92% persistence
- 0 serious AEs reported

Mean LDL-C (±SD): 3.7 (±1.7) mmol/L

ABSTRACT
Background: The 2021 Canadian Cardiovascular Society guidelines recommend proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor therapy in patients with atherosclerotic cardiovascular disease whose low-density lipoprotein cholesterol (LDL-C) concentration remains ≥ 1.8 mmol/L despite maximally tolerated statin therapy. This 12-month analysis of the ZERBINI observational study shows consistent efficacy and safety of evolocumab initiation.

Patients (N=131) at baseline:
- ASCVD: 39%
- FH & ASCVD: 32%
- FH: 23%
- No FH/ASCVD: 6%

Results after 12 months of evolocumab:
- 78% of patients achieved an LDL-C <1.8 mmol/L
- 92% persistence
- 0 serious AEs reported

Evolocumab initiation, efficacy and safety in Canada are consistent with guideline recommendations and clinical data.

RÉSUMÉ
Introduction : Les lignes directrices de la Société canadienne de cardiologie de 2021 recommandent un traitement par les inhibiteurs de proprotéine convertase subtilisine-kexine de type 9 (PCSK9) aux patients atteints de la maladie cardiovasculaire athérosclérotique chez lesquels les concentrations de cholestérol à lipoprotéines de faible densité restent ≥ 1.8 mmol/L malgré un traitement par les statines maximale tolérée. Cette analyse de 12 mois de l’étude ZERBINI montre une efficacité et une sécurité cohérentes de la initiation à l’évolocumab.

Patients (N=131) à l’baseline :
- ASCVD : 39% 
- FH & ASCVD : 32% 
- FH : 23% 
- Pas de FH/ASCVD : 6% 

Résultats après 12 mois d’évolocumab :
- 78% des patients atteints de LDL-C <1.8 mmol/L
- 92% persistance 
- 0 AEs sévères rapportés

L’évolutomab est initié, efficace et sûr au Canada et est dans les recommandations et les données cliniques de la ligne directrice.

Cardiovascular disease (CVD) is the global leading cause of morbidity and mortality, representing an estimated 32% of all deaths in 2019, largely due to atherosclerotic CVD (ASCVD), including myocardial infarction (MI) and stroke. Despite this clinical burden, many ASCVD events are preventable. Low-density lipoprotein cholesterol...
retrospective and prospective observational study characterizes Canadian patients treated with evolocumab and describes its effectiveness and safety.

Methods: Between August 2017 and July 2019, a total of 131 patients initiated on evolocumab therapy were enrolled at 15 sites in Canada. Data were extracted from medical records every 3 months between 6 months prior to, and for 12 months following evolocumab therapy initiation, until July 6, 2020. Baseline and prospectively collected data are reported as available.

Results: A total of 131 patients were enrolled (59.5% male; mean age [standard deviation (SD)] 64.7 ± 10.6 years), most with a diagnosis of atherosclerotic cardiovascular disease and/or familial hypercholesterolemia (93.4%). Mean (± SD) LDL-C concentration at baseline was 3.7 (± 1.7) mmol/L (n = 119), with 58.0% of patients receiving a statin (36.6% high intensity). Mean (± SD) LDL-C concentration after evolocumab treatment was 1.6 (± 1.0) mmol/L (n = 120), representing a 58.7% decrease from baseline (n = 109). This level remained stable over 12 months. An LDL-C concentration < 1.8 mmol/L was achieved by 77.5% of patients. Persistence was 92%, and no serious treatment-emergent adverse events were reported.

Conclusions: These findings provide real-world evidence of guideline-recommended initiation of evolocumab therapy, as well as confirmation of its effectiveness and safety in a Canadian population. Evolocumab therapy can address a healthcare gap in the management of dyslipidemia, by increasing the proportion of patients achieving LDL-C goals recommended to lower cardiovascular risk.

(LDL-C) is one of the most modifiable cardiovascular risk factors amenable to widely available and well-tolerated pharmacologic therapies. Robust evidence from mechanistic, observational, and intervention studies of lipid-lowering therapies (LLTs) demonstrates a causal relationship between lowering of LDL-C concentration and reduction of ASCVD events.

In Canada, statins are the recommended first-line LLT for cardiovascular risk reduction, yet real-world evidence consistently suggests that patients at high risk of, or with established ASCVD, do not achieve clinically sufficient LDL-C reductions despite treatment. One-third of patients aged ≥ 65 years with ASCVD in Alberta, and one-quarter in Ontario, treated with LLT did not achieve 2016 Canadian guideline-recommended LDL-C goals (< 2.0 mmol/L or > 50% reduction) within 1 year of an ASCVD diagnosis.

Within a similar patient population in Alberta, about 1 in 3 patients did not achieve LDL-C goals despite receiving LLT following an MI. Finally, only 50% of patients in Ontario had their LDL-C concentration measured within 6 months following percutaneous coronary interventions (PCIs). Of those, 43% did not achieve LDL-C goals. These results point to significant care gaps in ASCVD management in Canada and suggest that further intensive efforts are needed to achieve optimal LDL-C concentrations in vulnerable patients.

The updated, 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults recommend intensification of therapy for persons with an LDL-C concentration of ≥ 1.8 mmol/L who are already on maximally tolerated statin therapy in the setting of secondary prevention of ASCVD. Recommended agents include the addition of a cholesterol-absorption inhibitor (ezetimibe), or proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors (the monoclonal antibodies, evolocumab or alirocumab).

Evolocumab was approved in Canada in 2015 and is indicated to prevent cardiovascular events in patients with ASCVD and/or to reduce LDL-C concentration in patients with familial hypercholesterolemia (FH) who are already on a maximally tolerated statin and require additional LDL-C lowering. The large cardiovascular outcome trial, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER), assessed the impact of evolocumab therapy in patients with established ASCVD and demonstrated a 59% reduction in LDL-C, concomitant with a 20% reduction in cardiovascular death, MI, and stroke, with no significant adverse events compared to placebo.
randomized data are reinforced by the international Open-Label Study of Long Term Evaluation Against LDL-C (OSLER-1) trial, which revealed a sustained 56% LDL-C reduction over 5 years of follow-up in a diverse hypercholesterolemic patient population on evolocumab therapy. However, to date, only limited real-world evidence exists on the clinical characteristics of Canadian patients prescribed evolocumab and the ensuing impact on dyslipidemia management, to inform clinical practice and guide treatment decisions.

The Multizonal Observational Study Conducted by Clinical Practitioners on Repatha (Evolocumab) Use in Subjects With Hyperlipidemia (ZERBINI) study is a retrospective and prospective observational chart review study conducted in Canada, Mexico, Columbia, Saudi Arabia, and Kuwait. The purpose of the study was to report data specifically from the Canadian subset of patients. The primary objective was to characterize the clinical characteristics of Canadian patients upon initiation of evolocumab therapy. Secondary and exploratory objectives were to evaluate the effectiveness, safety, and persistence of therapy with evolocumab over time.

Methods

Study design and setting

This was a retrospective and prospective observational study of patients from 15 sites across Canada of those patients who were initiated on evolocumab therapy between August 1, 2017 and July 9, 2019. Data were collected from patient medical records up to 6 months prior to evolocumab therapy initiation and 12 months post-initiation, regardless of continuation or discontinuation of evolocumab therapy, with data collection ending on July 6, 2020 (Supplemental Fig. S1). Chart extraction occurred every 3 months during the 12-month follow-up period. Enrollment in the study was closely monitored as part of study management. The study protocol was reviewed and approved by each site’s institutional review board/institutional ethics committee.

Study participants

Patients were eligible if they met the following criteria: (i) were male or female ≥ 18 years of age; (ii) initiated evolocumab therapy at a physician’s direction between August 1, 2017 and July 9, 2019; (iii) received at least 1 dose of evolocumab; and (iv) had ≤ 6 months of exposure to evolocumab therapy prior to study enrollment. Patients were excluded if they had used a PCSK9 inhibitor within 6 months of exposure to evolocumab therapy initiation.

Variables of interest and outcome measures

Available data were collected from patient medical records using a case report form (CRF). Variables of interest included the following patient demographic and clinical characteristics upon evolocumab initiation: age; sex; race; smoking status; cardiovascular history; FH status, including subtype (heterozygous or homozygous) and method of diagnosis; diabetes status; and LDL-C concentrations, with the last measurement within 6 months prior to evolocumab therapy initiation regarded as the baseline value. Using the CRF, CVD history could be captured as diagnoses of coronary artery disease, peripheral arterial disease, intermittent claudication, stroke, transient ischemic attack, congestive heart failure, atrial fibrillation, hypertension, MI, deep vein thrombosis, and/or pulmonary embolism. The CRF also had a free-text field to specify “other” components of cardiovascular history as judged by the investigator. Additional variables of interest included evolocumab usage (dose, frequency, switching to another PCSK9 inhibitor) and other LLT usage (type, dose, and frequency of therapy) at baseline, and changes to these over the 12-month follow-up period. Statin intensity was defined according to the 2013 American College of Cardiology/American Heart Association guidelines and grouped into low-, moderate-, and high-intensity categories. Other variables of interest included the incidence of LDL-C concentration < 1.8 mmol/L, and change from baseline in LDL-C concentration during the 12-month follow-up period after evolocumab therapy initiation. LDL-C concentrations measured as part of usual care were assessed from patients with available data. The last LDL-C measurement was used for patients with multiple measurements taken within the presented timeframes. The incidences of adverse events and hospitalizations (reason for admission and duration of stay), and the persistence to evolocumab therapy, were also assessed. Data on missed evolocumab doses were captured in the CRF for each month on a quarterly basis, including whether a dose was missed and how many doses were missed per month. Study completion was also captured. Persistence was then assessed as the proportion of patients remaining on evolocumab therapy for the entire follow-up period after initiation without missing doses for more than 56 consecutive days, the allowable gap based on the evolocumab dosing instructions. This assessment was subsequently reported as either persistent or nonpersistent. Those who did not complete the study for reasons deemed unrelated to evolocumab (reimbursement, administrative decision, patient request, lost to follow-up) were not included in the persistence calculations (n = 16). Additionally, those who discontinued study participation due to an adverse event, death, or unknown reasons were captured as nonpersistent.

Data synthesis and analysis

Descriptive statistics were used to summarize study outcomes. Using the available data reported on the CRF, patients with any of the following conditions were classified as having ASCVD, based on the definition included in the current Canadian guidelines: angina; abdominal aortic aneurysm; carotid or coronary artery disease; coronary revascularization procedures including coronary artery bypass grafting; percutaneous transluminal coronary angioplasty; peripheral artery disease; intermittent claudication; MI; stroke; and transient ischemic attack. Patients were then stratified according to a diagnosis of ASCVD only, FH only, concomitant ASCVD and FH, or unknown ASCVD and FH status. Further, in patients with available data, LDL-C measurement characteristics were calculated, including frequency and time to first and last measurement.
Results

Baseline patient demographic and clinical characteristics

The cohort consisted of 131 patients prescribed evolocumab as part of usual care. Baseline demographic and clinical characteristics are provided in Table 1. The majority of patients were male (59.5%) and were enrolled from Ontario (54.2%), British Columbia (26.7%), or Quebec (19.1%). The mean age (± standard deviation [SD]) was 64.7 (± 10.6) years, with a median age (interquartile range [IQR]) of 66.0 (58.0-72.0) years. The mean baseline LDL-C (± SD) concentration was 3.7 (± 1.7) mmol/L, with a median LDL-C concentration (IQR) of 3.5 (2.5-4.6) mmol/L. Twelve patients (9.2%) did not have a baseline LDL-C concentration reported. Of the 131 patients, 38.9% had ASCVD, 32.1% had FH, and 22.9% had FH only. Eight patients (6.1%) had neither an FH nor an ASCVD diagnosis. Among patients with ASCVD, the majority (59.1%) had ≥ 2 conditions, with coronary artery disease (87.1%) and MI (36.6%) being the most common. Finally, 23.7% of patients had diabetes, and other comorbid conditions, as outlined in Table 1. The methods used to diagnose FH are presented in Supplemental Table S1, with most patients (61.1%) diagnosed using the Simon Broome and/or Dutch Lipid Clinic Network methods.

LLT usage at baseline

LLT usage data, including evolocumab dosing at baseline, are presented in Table 2. Of the 131 patients in this cohort, background statin use was reported in 58.0%, with 36.6% on a high-intensity statin. The second most common background LLT was ezetimibe (53.4%) with 40.5% of patients on combined statin and ezetimibe therapy. Intolerance to ≥ 2 statins was reported in 41.2% of patients. Evolocumab was prescribed at a dose of 140 mg every 2 weeks (vs 420 mg every 4 weeks) in 94.7% of patients post-evolocumab therapy initiation, with 71.6% achieving a 50% reduction in LDL-C measurement post-evolocumab therapy initiation.

LDL-C concentrations and measurement characteristics over time

LDL-C concentrations and measurement characteristics over time are presented in Table 3. In patients with available data, the mean (± SD) LDL-C concentration after evolocumab therapy initiation was 1.6 (± 1.0) mmol/L, with a median (IQR) LDL-C concentration of 1.2 (0.8-2.1) mmol/L. The majority of patients (67.9%) had ≥ 2 LDL-C measurements post-evolocumab therapy initiation, with a median (IQR) time to first and last test of 55 (33-106) days and 247 (162-315) days, respectively. For patients with both an LDL-C measurement at baseline and ≥ 1 follow-up measurement post-evolocumab therapy initiation, LDL-C was reduced by 58.7% between baseline and the last LDL-C measurement post-evolocumab therapy initiation (from 3.8 [± 1.6] mmol/L to 1.6 [± 1.1] mmol/L; Fig. 1). LDL-C reductions were similar between patients on evolocumab monotherapy and those on evolocumab therapy plus other LLT (56.5% vs 56.9%). LDL-C was reduced from baseline in 97.2% of patients post-evolocumab therapy initiation, with 71.6% achieving a ≥ 50% reduction (Fig. 2). Five patients were nonresponders or had a

| Table 1. Baseline demographics and clinical characteristics of the full patient cohort |
|--------------------------------------------------|
| Clinical characteristic | N = 131 |
|---|---|
| **Sex** |  |
| Female | 53 (40.5) |
| Male | 78 (59.5) |
| **Age, y** |  |
| Mean ± SD | 64.7 ± 10.6 |
| Median (IQR) | 66.0 (58.0-72.0) |
| **Age group, y** |  |
| < 65 | 57 (43.5) |
| ≥ 65 | 74 (56.5) |
| ≥ 75 | 22 (16.8) |
| **Province** |  |
| Ontario | 71 (54.2) |
| British Columbia | 35 (26.7) |
| Quebec | 25 (19.1) |
| **Race** |  |
| White | 108 (82.4) |
| Asian | 10 (7.6) |
| Black or African American | 5 (3.8) |
| **Smoker status** |  |
| Current | 9 (6.9) |
| Former | 57 (43.5) |
| Never | 65 (49.6) |
| **LDL-C, mmol/L (N = 119)** |  |
| Mean ± SD | 3.7 ± 1.7 |
| Median (IQR) | 3.5 (2.5-4.6) |
| FH only^3 (without ASCVD) | 30 (22.9) |
| ASCVD only (without/unknown FH) | 51 (38.9) |
| FH and ASCVD | 42 (32.1) |
| No FH or ASCVD^3 | 8 (6.1) |
| **Number of ASCVD² conditions** |  |
| 0 | 38 (29.0) |
| 1 | 38 (29.0) |
| 2 | 42 (32.1) |
| ≥ 3 | 13 (9.9) |
| **Type of ASCVD² condition** |  |
| Coronary artery disease | 81 (61.8) |
| Myocardial infarction | 34 (26.0) |
| Coronary revascularization procedures^³ | 5 (3.8) |
| Angina | 2 (1.5) |
| Peripheral artery disease | 19 (14.5) |
| Intermittent claudication | 5 (3.8) |
| Stroke | 9 (6.9) |
| Carotid artery disease | 4 (3.1) |
| Transient ischemic attack | 4 (3.1) |
| Abdominal aortic aneurysm | 1 (0.8) |
| Atrial fibrillation | 8 (6.1) |
| Congestive heart failure | 5 (3.8) |
| Hypertension | 79 (60.3) |
| Diabetes** | 31 (23.7) |

Values are n (%), unless otherwise indicated.

ASCVD, atherosclerotic cardiovascular disease; CRF, case report form; FH, familial hypercholesterolemia; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

* Based on investigator location.

²The last LDL-C concentration measured within 6 months prior to initiation of evolocumab in 119 patients with available data was regarded as the baseline LDL-C concentration. Twelve patients did not have a baseline LDL-C concentration reported.

³All patients were diagnosed with heterozygous FH. Twelve (9.2%) patients had unknown familial hypercholesteremia status.

⁴Data collected do not capture all ASCVD components as defined by the Canadian Cardiovascular Society.

²The definition of ASCVD² outlined on the CRF was not complete. As such, it cannot be confirmed whether these patients had a history of FH or ASCVD.

³Three patients had undergone coronary artery bypass grafting, one patient had undergone a percutaneous transluminal coronary angioplasty, and one patient had a 2- vessel bypass.

**One patient was diagnosed with type 1 diabetes, and 30 patients with type 2 diabetes.
Table 2. Evolocumab dose and lipid-lowering therapy usage at baseline

| Lipid-lowering therapy          | N = 131 n (%) |
|--------------------------------|---------------|
| Statins*                       | 76 (58.0)     |
| Low-intensity†                 | 12 (9.2)      |
| Moderate-intensity†            | 16 (12.2)     |
| High-intensity†                | 48 (36.6)     |
| No statin use                  | 55 (42.0)     |
| Reported statin intolerance    | 81 (61.8)     |
| Number of statins reported intolerant to: |            |
| 1                              | 27 (20.6)     |
| 2                              | 21 (16.0)     |
| 3                              | 23 (17.6)     |
| ≥ 4                            | 10 (7.6)      |
| Ezetimibe                      | 70 (53.4)     |
| Ezetimibe and statin           | 53 (40.5)     |
| Colesevelam                    | 7 (5.3)       |
| Niacin†                        | 3 (2.3)       |
| Evolocumab dose                | 140 mg every 2 wk | 124 (94.7) |
|                                | 420 mg once monthly | 7 (5.3) |
| Evolocumab monotherapy         | 33 (25.2)     |

*Statin intensity was defined based on the 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.†

† Low-intensity statins include atorvastatin (5 mg), lovastatin (20 mg), pravastatin (8.57 mg, 10 mg, and 20 mg), rosuvastatin (0.36 mg, 0.71 mg, 1.07 mg, 1.25 mg, 1.43 mg, and 2.50 mg) and simvastatin (10 mg);

‡ Moderate-intensity statins include atorvastatin (10 mg and 20 mg), pravastatin (40 mg), rosuvastatin (5 mg, 10 mg, and 15 mg) and simvastatin (20 mg and 40 mg).

§ High-intensity statins include atorvastatin (40 mg and 80 mg) and rosuvastatin (20 mg and 40 mg).

One patient was on each of short-acting, intermediate-release, and extended-release niacin.

suboptimal response (≤ 10% decrease in LDL-C) to treatment; they also had discontinued treatment within 3 months and were therefore unlikely to be on evolocumab therapy at the time of their post-treatment LDL-C measurement. Furthermore, 77.5% of patients achieved an LDL-C concentration < 1.8 mmol/L after initiation of evolocumab therapy, including 71.2% of patients with FH, and 85.2% of patients without a diagnosis of FH (Table 3). Among patients who had a baseline and follow-up LDL-C concentration measured during months 1-6 and 7-12 post-evolocumab therapy initiation, the mean reduction in LDL-C from baseline to months 1-6 was 57.9%, and to months 7-12, it was 48.1% (Fig. 3).

LLT usage over time

LLT usage over time is presented in Figure 4 and remained relatively stable over the 12-month study period. Among statin-treated patients at baseline, 7 (9.2%) discontinued statins after initiation of evolocumab therapy, whereas 3 (3.9%) up-titrated and 1 (1.3%) down-titrated the statin dose. Of the 7 patients (10.0%) who discontinued ezetimibe during the study follow-up period, 5 were on a background statin that was not discontinued. Monotherapy with evolocumab was initially noted in 25.2% of patients, and this percentage decreased by approximately 5% as patients received other LLT over the study period.

Table 3. Low-density lipoprotein cholesterol (LDL-C) concentrations and measurement characteristics at baseline and post-evolocumab therapy initiation

| Outcome                                      | Value       |
|----------------------------------------------|-------------|
| Baseline LDL-C concentration, mmol/L         |             |
| L (N = 119)†                                 | 3.7 ± 1.7   |
| Mean ± SD                                    | 3.5 (2.5–4.6) |
| Median (IQR)                                 |             |
| Average number of LDL-C tests post-evolocumab initiation (N = 131) | 2 ± 1       |
| Frequency of LDL-C measurements (N = 131)    |             |
| 0                                            | 11 (8.4)    |
| 1                                            | 31 (23.7)   |
| 2                                            | 48 (36.0)   |
| > 2                                          | 41 (31.3)   |
| Time from evolocumab therapy initiation to LDL-C measurement, d, median (IQR; N = 120) |             |
| First measurement                            | 55 (33–106) |
| Last measurement                             | 247 (162–315) |
| Overall LDL-C concentration post-evolocumab therapy (N = 120)¹ |             |
| Mean ± SD, mmol/L                            | 1.6 ± 1.0   |
| Median (IQR)                                 | 1.20 (0.75–2.14) |
| Incidence of LDL-C < 1.8 mmol/L               | 93 (77.5)   |
| (N = 120)                                    |             |
| In FH patients (N = 66)                      | 47 (71.2)   |
| In non-FH patients (N = 54)                  | 46 (85.2)   |
| Incidence of LDL-C reduction ≥ 50% (N = 109)  | 78 (71.6)   |

*The last LDL-C concentration measured within 6 months prior to initiation of evolocumab therapy in 119 patients with available data was regarded as the baseline LDL-C concentration. Twelve patients did not have a baseline LDL-C concentration reported.

¹Eleven patients did not have an LDL-C measurement post-evolocumab therapy initiation, of which 3 patients had other lipid measures taken (total cholesterol, HDL, non-HDL, and triglyceride; data not reported), and 8 patients had no lipid tests.

**Reasons for discontinuation and persistence of evolocumab therapy**

Self-reported reasons for discontinuation and patient persistence to evolocumab therapy are presented in Table 4. A total of 22 patients (16.8%) discontinued evolocumab therapy over the 12-month study period, with the most common reason being lack of reimbursement (5.3%, n = 7). Evolocumab therapy persistence was 92.2%.

**Adverse events and hospitalizations**

A complete list of adverse events and results regarding hospitalizations are presented in Table 5. The majority of patients (93.1%) did not experience an adverse event, and no injection-site reactions were reported. Of the 9 patients (6.9%) with an adverse event reported, 3 had non-serious reactions leading to discontinuation of evolocumab. Eight patients contributed to 9 reasons for a cardiovascular-related hospitalization, including ischemic cardiomyopathy with moderate-to-severe left ventricular dysfunction, unstable
angina, percutaneous coronary intervention with stent, stent implantation, and abdominal aortic aneurysm. Reasons for non-ASCVD-related cardiovascular hospitalizations included atypical thoracic pain, thoracic pain of undetermined etiology, heart catheterization, and chronic heart failure secondary to atrial fibrillation.

Discussion

This analysis of the ZERBINI study observed real-world baseline clinical characteristics, as well as the effectiveness, safety, and persistence on evolocumab therapy in Canadian patients. Current Canadian guidelines recommend LLT intensification with a PCSK9 inhibitor in patients with ASCVD, and those with FH, whose LDL-C concentration remains above clinical threshold values despite maximally tolerated statin therapy. In this study population with ASCVD, FH, or both, 75% of patients had an LDL-C concentration ≥ 2.5 mmol/L at the time of initiation of evolocumab therapy. The intensification of LLT in this population indicates that clinic practice in Canada was aligned with the recommendations. These characteristics are aligned with the approved Canadian indications for use of evolocumab, in patients with ASCVD and FH. However, only 58% of patients were treated with background statin and/or ezetimibe, which highlights a common care gap in the prevention of cardiovascular disease, particularly as a result of statin intolerance. The reported statin intolerance of 62% in this patient population was not apparent in the larger evolocumab clinical trial, in which background statin use was a requirement. This finding demonstrates a potential difference in real-world use and real-world challenges in achieving appropriate LDL-C reduction. Moreover, the profile of patients initiated on evolocumab therapy herein is consistent with that observed in the larger, real-world HEYMANS study conducted in 10 European countries, wherein 60% of patients reported statin intolerance. Interestingly, however, 75.0% of HEYMANS study patients had an LDL-C concentration ≥ 3.16 mmol/L, yet only 43% were treated with background statin and/or ezetimibe. Thus, the current findings add a Canadian perspective to the growing body of real-world evidence of appropriate patient identification for evolocumab therapy initiation, as well as the contribution of statin intolerance to the existing ASCVD care gap.

The 59% reduction in LDL-C observed over 12 months post-evolocumab therapy initiation in the current study is consistent with the 59% reduction reported in the FOURIER trial cardiovascular outcomes (ASCVD patients) and the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD-2; FH patients) randomized controlled trials. From a real-world perspective, these data are consistent with the those from the HEYMANS European study, in which a 58% reduction in LDL-C was demonstrated within 3 months of evolocumab therapy initiation, and sustained for 18 months of follow-up. The observed LDL-C reduction herein is also consistent with other Canadian real-world data, including a 48% LDL-C reduction in patients with ASCVD in Alberta, a 55% reduction in patients with FH in British Columbia, and a 51% reduction in high-risk patients in Ontario. Hence, this study advances the current understanding of evolocumab use and effectiveness in Canadian clinical practice by providing a more recent cross-country perspective, with more than twice the sample size compared to previous Canadian studies.

Although a slight increase in mean LDL-C concentration was observed between months 1-6 and months 7-12 post-evolocumab therapy initiation in the subset of patients with available data at all timepoints, this finding may be due to a small sample size, changes in background LLT, variability in patient physiology (eg, diet or weight changes), and other aspects related to real-world clinical practice, and it does not
necessarily imply reduced effectiveness of evolocumab. Indeed, mean LDL-C concentration was reduced by 57% in patients on evolocumab monotherapy, and to some extent in almost all patients (97%) regardless of background LLT, with 72% achieving a reduction of > 50% from baseline. This LDL-C response pattern is consistent with that observed in the Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2 (MENDEL-2; hypercholesterolemic patients) randomized controlled trial, in which LDL-C was reduced to some extent in all patients on evolocumab monotherapy, on average by 55%-57%, and 72%-77% of patients achieved an LDL-C reduction of > 50% from baseline. Likewise, in the FOURIER cardiovascular outcomes trial, LDL-C was reduced in 98% of patients on evolocumab therapy, and 80% achieved a reduction of > 50% from baseline. Further, in the current study, 78% of patients still achieved below the new guideline-recommended LDL-C threshold of < 1.8 mmol/L, which is comparable to the 87% reported in the FOURIER cardiovascular outcomes trial in patients strictly with ASCVD. This finding is especially impressive considering the heterogeneity of the patient population of the current study, including patients with ASCVD, and a substantial proportion with an FH diagnosis (55%), among whom 71% achieved an LDL-C concentration < 1.8 mmol/L. Hence, these findings provide real-world evidence of the effectiveness of evolocumab therapy in achieving guideline-recommended LDL-C goals in Canada, to inform decision-making in optimizing dyslipidemia management in clinical practice.

The current findings also highlight an important gap in LDL-C testing in Canadian clinical practice that continues to be identified. Infrequent LDL-C monitoring appears to be pervasive and may partly explain the Canadian real-world data showing that more than 1 in 4 patients with ASCVD do not achieve guideline-recommended LDL-C goals following diagnosis, despite LLT. For instance, in a real-world Alberta study, 28% of patients with a new diagnosis of ASCVD did not have an LDL-C measurement at LLT initiation, and only 33% had both a baseline and follow-up measurement. In another real-world Alberta study, 11% of patients did not have lipid testing in-hospital or within 90 days following acute coronary syndrome, and of those tested, 29% did not have a follow-up test within 12 months. Whether this finding is a reflection of a therapeutic complacency or a "fire and forget" practice pattern is not known. However, as expected, lipid testing was associated with higher rates of not only initiation but also intensification of statin therapy and identification of evolocumab eligibility in 37% of patients. The results of the current study are somewhat reassuring in that 91% of patients had an LDL-C measurement at evolocumab initiation, and 92% had a follow-up measurement over 12 months thereafter. This finding may be explained partly by the requirements for access and prescription renewal. Further, most patients had their first follow-up LDL-C measurement within 33-106 days, compared with an average of 276 days in Alberta. Overall, these data point to potential provincial differences in hyperlipidemia management that warrant further study. Further, these findings highlight the continued need for guidance and implementation of routine LDL-C measurements in high-risk patients, to identify candidates for LLT intensification or modification.

Aligned with current Canadian guidelines, a low LLT discontinuation rate was observed in the current study, with stable statin use and low rates of ezetimibe discontinuation over 12 months. These findings are reassuring in the real-world context considering, anecdotally, that many patients advocate to reduce their number of treatments and associated burden. Although physicians may aim to accommodate patient preferences in other therapeutic scenarios, the clinical benefit of statin therapy and LLT intensification, which are the gold standard of care in ASCVD and FH patients with an LDL-C concentration above clinical threshold values, appears to have been prioritized in the current sample of Canadian practice.

The current findings also add to the growing body of evidence that patients persist with evolocumab therapy. The

---

**Figure 2.** Distribution of percent change from baseline to average low-density lipoprotein cholesterol (LDL-C) post-evolocumab therapy initiation (N = 109). Data represent patients with an LDL-C measurement at baseline (measured within 6 months prior to initiation of evolocumab therapy) and their last LDL-C measurement post-evolocumab therapy initiation.

**Figure 3.** Low-density lipoprotein cholesterol (LDL-C) concentrations over time in patients without missing LDL-C measurements (N = 70). Data represent patients with a baseline LDL-C measurement and subsequent LDL-C measurement within 1-6 months and 7-12 months post-evolocumab therapy initiation. Values are mean ± standard deviation. 1 The last LDL-C measurement within 6 months prior to initiation of evolocumab therapy.

- **Legend:**
  - Baseline: 3.8 ± 1.7
  - Month 1-6: 1.5 ± 1.0
  - Month 7-12: 1.8 ± 1.2
  - LDL-C concentration (mmol/L)
  - 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
  - 3.8 ± 1.7
  - -57.9%
  - 1.5 ± 1.0
  - -48.1%
  - 1.8 ± 1.2
observed 92% persistence rate over 12 months is consistent with that in the 5-year international OSLER-1 open-label extension study, wherein the overall annualized rate of patients remaining on evolocumab was 93%, as well as with the Getting to an Improved Understanding of Low-Density Lipoprotein-Cholesterol and Dyslipidemia Management (GOULD) US real-world study, wherein 92% of patients were still taking a PCSK9 inhibitor at 2 years. Lack of persistence to cardiovascular medications is associated with poor clinical outcomes, including hospitalization and mortality, especially in high-risk patients. International real-world evidence shows a lack of persistence to statin therapy, even among patients who undergo an ASCVD event, which may be attributed to intolerance and fear of known side effects. Hence, the current results re-emphasize the potential for evolocumab therapy to help close the dyslipidemia care gap and improve patient outcomes in Canada.

Underlying persistence to evolocumab therapy may be its favourable safety profile, which was observed in the current study to be consistent with that in the evolocumab clinical trial program and other randomized trials. One exception is that no injection-site reactions were reported in the current real-world study, which is fewer than the approximately 2%-3% consistently reported. In the OSLER-1 open-label extension study, the annualized rate of injection-site reactions decreased from 4% in the first year of evolocumab exposure to 0.2% in year 4 and beyond, perhaps reflecting improved patient counselling and administration skills over time. Further, despite the observed 8 cardiovascular-related hospitalizations in the current study, none were deemed by investigators to be related to use of evolocumab. However, other top reported reasons for evolocumab therapy discontinuation, including reimbursement, patient request, and administrative decision, deserve further consideration to identify barriers to continued LLT intensification in vulnerable patients.

This retrospective and prospective chart review study provides insights into the real-world Canadian patient profile for evolocumab therapy, as well as the effectiveness and safety of evolocumab therapy over 12 months of follow-up. Canadian patients initiated on evolocumab therapy represented various demographics, pathologies, and indications for PCSK9 inhibition. However, important limitations must be addressed. The patient cohort represented a small sample size, with incomplete data collection, owing to the nature of a chart-review study design, which may limit the generalizability of the results. Specifically, the CRF used for data collection lacked sufficient detail to understand the true ethnic, ASCVD, and FH representativeness of the patient population. The CRF did not capture a complete definition of ASCVD as defined by current Canadian guidelines, and patients could not be stratified appropriately into categories of ASCVD event risk, which are important considerations when understanding the effectiveness of evolocumab therapy in vulnerable patient

![Figure 4](image-url)

**Table 4. Evolocumab discontinuation and persistence over study period**

| Outcome                                | n (%)          |
|----------------------------------------|----------------|
| Evolocumab discontinuation (N = 131)    | 22 (16.8)      |
| Reason for evolocumab discontinuation (N = 131) |               |
| Adverse drug reaction                   | 4 (3.0)        |
| Death                                  | 1 (0.8)        |
| Unknown                                | 1 (0.8)        |
| Administrative decision*               | 3 (2.3)        |
| Patient request                        | 4 (3.1)        |
| Reimbursement*                         | 7 (5.3)        |
| Lost to follow-up*                     | 2 (1.5)        |
| Evolocumab persistence (N = 115)*     |                |
| Yes                                    | 106 (92.2)     |
| No                                     | 9 (7.8)        |

* Persistence was assessed as the proportion of patients remaining on evolocumab for the entire follow-up period after initiation without missing doses for more than 56 consecutive days, the allowable gap based on the evolocumab dosing instructions. Additionally, those who discontinued study participation for an adverse event, death, or unknown reasons were captured as nonpersistent. Patients who did not complete the study for reasons deemed unrelated to the evolocumab therapy (reimbursement, administrative decision, patient request, and lost to follow-up) were not included in the persistence calculations (N = 16).
populations. Also, the reason for evolocumab initiation remains unknown for the 6% of patients initiated on evolocumab without a documented diagnosis of ASCVD or FH.

Additionally, this observational study was not sized to detect clinical outcomes, but rather focused on the LDL-C response. However, since the frequency of LDL-C monitoring post-evolocumab initiation was not structured as it was in clinical trials, conclusions about evolocumab efficacy may be limited. Related to this issue, a small amount of data collection occurred during the COVID-19 pandemic, which may have affected access and availability of laboratory testing. Further, persistence was self-reported by patients, which may have affected access and availability of laboratory testing. Finally, the nature of the study does not allow for causal inferences to be made. Future studies should aim to overcome these data collection limitations to advance understanding of the real-world use of evolocumab and the potential to address the LDL-C reduction management care gap in high-risk patients.

### Table 5. Adverse events and hospitalizations over study period

| Outcome | N = 131 |
|---------|---------|
| All treatment-emergent adverse drug reactions | 9 (6.9) |
| Serious* | 0 (0) |
| Nonserious reactions leading to discontinuation of evolocumab | 3 (2.3) |
| Injection-site reactions | 0 (0) |
| Musculoskeletal and connective tissue disorders | 5 (3.8) |
| Myalgia | 2 (1.5) |
| Arthralgia | 1 (0.8) |
| Back pain | 1 (0.8) |
| Muscle discomfort | 1 (0.8) |
| Nervous system disorders† | 2 (1.5) |
| Headache | 2 (1.5) |
| Balance disorder | 1 (0.8) |
| Dizziness | 1 (0.8) |
| Respiratory, thoracic, and mediastinal disorders | 2 (1.5) |
| Sinus congestion | 1 (0.8) |
| Throat irritation | 1 (0.8) |
| Gastrointestinal disorders | 1 (0.8) |
| Nausea | 1 (0.8) |
| Infections and infestations | 1 (0.8) |
| Sinusitis | 1 (0.8) |
| Reason for hospitalization‡ | 8 (6.1) |
| Cardiovascular | 15 (11.5) |
| Non-cardiovascular | 4.5 (1.5–8.5) |
| Noncardiovascular | 8.0 (4.0–36.0) |

Values represent n (%), unless otherwise indicated.

* IQR: interquartile range.

† Criteria for serious adverse event included fatal, immediately life-threatening, required or prolonged hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or other medically important serious event.

‡ The date of adverse reaction was missing for 1 of the 4 patients who discontinued evolocumab following an adverse event, and therefore it is not defined as a treatment-emergent adverse reaction.

§ These adverse events are not mutually exclusive; 2 patients contributed to these 3 conditions.

| Hospitalization (d) | Median (IQR) |
|---------------------|-------------|
| Cardiovascular | 4.5 (1.5–8.5) |
| Non-cardiovascular | 8.0 (4.0–36.0) |

### Conclusions

These findings provide insights into the initiation of evolocumab therapy in routine clinical practice in Canada, which was demonstrated to be in accordance with the approved indication and Canadian guidelines recommending LDL-C intensification at LDL-C levels above clinically significant thresholds in patients with ASCVD/FH. Interestingly, the high rate of reported statin intolerance was unexpected and differs from that found in the context of larger, randomized evolocumab clinical trials wherein all patients were required to be on background statin therapy, pointing to a potential difference in real-world evolocumab use. Nonetheless, this observational chart-review study demonstrated robust LDL-C reductions associated with evolocumab use, alongside a favourable safety profile, similar to clinical trial results. Further, background LLT was relatively consistent following evolocumab therapy initiation, and although reimbursement challenges exist, real-world persistence on evolocumab was 92%. In the context of dyslipidemia care gaps, these results demonstrate appropriate patient identification and evolocumab therapy initiation, strong evolocumab persistence, excellent efficacy, and successful achievement of guideline-endorsed LLT in a real-world Canadian setting.

### Acknowledgements

Glen Sanders, You Wu, and Johnny Wu, of Amgen Inc., assisted with the generation of tables and figures. Editorial assistance was provided by Danyelle Liddle at MEDUCOM Health Inc.

### Funding Sources

This study was funded by Amgen Inc and the preparation of the article was funded by Amgen Canada Inc.

### Disclosures

M.G. has received research grants, speaker honoraria, and/orconsultancies from Amgen, HLS Therapeutics, Novartis, and Sanoﬁ. G.B.J.M. has received research grants and/or consultancies from Amgen, HLS Therapeutics, Novartis, and Sanoﬁ. V.A. has received research grants and/or consultancies from Amgen, Bayer, Boehringer Ingelheim, HLS Therapeutics, Novartis, and Servier. J.B. has received research grants, consultancies, and/or personal fees from Akcea-Ionis, Amgen, HLS Therapeutics, Kowa, Medison Pharma, Novartis, Novo Nordisk, Regeneron Pharmaceuticals, and Sanoﬁ. P.M. has received speaker honoraria from Amgen, HLS Therapeutics, and Novartis. A.S.P. has received speaker honoraria from Amgen, Astra Zeneca, Bayer, HLS Therapeutics, Novartis, Pfizer, and Sanoﬁ Events, and consultancy fees from Amgen, AstraZeneca, HLS Therapeutics, and Novartis. R.W., M.R., J.B., T.O., and E.M. are/ were employees of and own stock in Amgen.

### References

1. World Health Organization. Prevention of cardiovascular disease—guidelines for assessment and management of cardiovascular risk. Available at: https://apps.who.int/iris/bitstream/handle/10665/43685/9789241547178_eng.pdf?sequence = 1&isAllowed = y. Accessed August 26, 2021.
World Health Organization. Cardiovascular diseases. Available at: https://www.who.int/health-topics/cardiovascular-diseases#tab_1. Accessed August 26, 2021.

Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA 2016;316:1289-97.

Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38:2459-72.

Borén J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020;41:2513-30.

Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. Can J Cardiol 2021;37:1129-50.

Fairbairn M. Low-density lipoprotein cholesterol goal attainment and treatment patterns in a cohort of > 143,000 patients with atherosclerotic cardiovascular disease in Canada. In: Oh P, Goeree R, RM R, et al., eds. European Society of Cardiology Congress, Virtual Conference, August 29-September 1, 2020.

Rogora R, Oh P, Goeree P, et al. Patterns of low-density lipoprotein cholesterol management and goal attainment in patients with atherosclerotic cardiovascular disease 65 years and older from Alberta and Ontario. Paper presented at: Canadian Cardiovascular Congress, October 21-24, 2020. Virtual.

Scory T, Chen G, Farris M, et al. Lipid-lowering therapy patterns and low-density lipoprotein-cholesterol management among patients with acute myocardial infarction in Alberta, Canada. J Am Coll Cardiol 2020;75(11):44.

Sud M, Han L, Koh M, et al. Low-density lipoprotein cholesterol and adverse cardiovascular events after percutaneous coronary intervention. J Am Coll Cardiol 2020;76:1440-50.

Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2016;32:1263-82.

Amgen Canada Inc. Repatha (evolocumab) product monograph. Available at: https://www.amgen.ca/~rmedia/ad162719487c459391bd1b1584a25eadashx. Accessed February 18, 2022.

Sabatine MS, Giugliano RP, Kech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.

Koren MJ, Sabatine MS, Giugliano RP, et al. Long-term efficacy and safety of evolocumab in patients with hypercholesterolemia. J Am Coll Cardiol 2019;74:2132-46.

Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(25 suppl 2):S1-45.

Forbes CA, Deshpande S, Sorio-Vilela F, et al. A systematic literature review comparing methods for the measurement of patient persistence and adherence. Curr Med Res Opin 2018;34:1613-25.

Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTH-ERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 2015;385:3351-40.

Ray K, Bruckert E, Van Hout B, et al. Does evolocumab use in Europe match 2019 ESC/EAS lipid guidelines? Results from the HEYMANS study (abstract). Eur Heart J 2020;41(suppl 2):3013.

Chen G, Farris MS, Gowling T, et al. Treatment and low-density lipoprotein-cholesterol management in patients diagnosed with clinical atherosclerotic cardiovascular disease in Alberta. Can J Cardiol 2019;35:884-91.

Razek O, Cermakova L, Armani H, et al. Attainment of recommended lipid targets in patients with familial hypercholesterolemia: real-world experience with PCSK9 inhibitors. Can J Cardiol 2018;34:1004-9.

Pandey AS, Bajaj HS, Garg V, Pandey A, Verma S. The emerging role of proprotein convertase subtilisin/kexin type-9 inhibition in secondary prevention: from clinical trials to real-world experience. Curr Opin Cardiol 2017;32:633-41.

Koren MJ, Lundyquist P, Bolognesi M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2531-40.

Qamar A, Giugliano RP, Keech AC, et al. Interindividual variation in low-density lipoprotein cholesterol level reduction with evolocumab: an analysis of FOURIER trial data. JAMA Cardiol 2019;4:59-65.

Saraz B, Savu A, Kaul P, et al. Lipid testing, lipid modifying therapy and PCSK9 inhibitor eligibility in 22,603 patients with incident acute coronary syndrome. J Am Coll Cardiol 2020;75:172.

Cannon CP, de Lemos JA, Rosenson RS, et al. Use of lipid-lowering therapies over 2 years in GOULD, a registry of patients with atherosclerotic cardiovascular disease in the US. JAMA Cardiol 2021;6:1-9.

Collantino LD, Huang L, Monda KL, et al. Adherence to high-intensity statins following a myocardial infarction hospitalization among Medicare beneficiaries. JAMA Cardiol 2017;2:890-5.

Guglielmi V, Bellia A, Pecchioli S, et al. Effectiveness of adherence to lipid lowering therapy on LDL-cholesterol in patients with very high cardiovascular risk: a real-world evidence study in primary care. Atherosclerosis 2017;263:36-41.

Khunti K, Danese MD, Kitikova L, et al. Association of a combined measure of adherence and treatment intensity with cardiovascular outcomes in patients with atherosclerosis or other cardiovascular risk factors treated with statins and/or ezetimibe. JAMA Newt Open 2018;1:e185554.

Bates TR, Connaughton VM, Watts GF. Non-adherence to statin therapy: a major challenge for preventive cardiology. Expert Opin Pharmacother 2009;10:2973-85.

Wouters H, Van Dijk L, Geers HC, et al. Understanding statin non-adherence: knowing which perceptions and experiences matter to different patients. PLoS One 2016;11:e0146272.

Toth PP, Descamps O, Genest J, et al. Pooled safety analysis of evolocumab in over 6000 patients from double-blind and open-label extension studies. Circulation 2017;135:1819-31.

Supplementary Material

To access the supplementary material accompanying this article, visit CJC Open at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2022.03.003.