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ORIGINAL RESEARCH

Cost-Effectiveness Analysis of Evolocumab in Adult Patients with Atherosclerotic Cardiovascular Disease in Canada

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ABSTRACT

Introduction: To evaluate the cost-effectiveness of evolocumab when added to standard of care lipid-lowering treatment (LLT) for patients with atherosclerotic cardiovascular disease (ASCVD) who cannot adequately control their low-density lipoprotein cholesterol (LDL-C) despite optimized LLT in Canada.

Methods: An incremental cost-utility analysis was conducted using a Markov cohort state transition model adapted to the Canadian setting. Analyses were conducted from a public health and societal perspective using a lifetime time horizon for Canada. Scenario analyses were conducted on the basis of recommendations from the 2021 Canadian Cardiovascular Society (CCS) dyslipidemia guidelines.

Results: In ASCVD patients with prior myocardial infarction (MI) and baseline LDL-C $\geq$ 1.8 mmol/L, adding evolocumab to optimized statin therapy with or without ezetimibe is associated with an incremental cost per quality-adjusted life year (QALY) gained of $66,453 CAD. Furthermore, for every 100 patients treated with evolocumab for lifetime, adding evolocumab to optimized LLT will prevent approximately 52 cardiovascular (CV) events, of which seven would be fatal. The results are generally robust using univariate and simultaneous variation in model input parameters. Scenario analyses for patient populations as per the CCS guidelines suggest that evolocumab added to optimized LLT may be considered cost-effective, given an incremental cost-effectiveness ratio (ICER) threshold of CAD$100,000 per QALY gained. Limitations associated with this analysis should be interpreted in the context of data and modeling assumptions used.

Conclusion: Overall, this analysis supports reimbursement of evolocumab by payers in patients with ASCVD who cannot reach LDL-C thresholds despite optimized LLT to reduce unnecessary fatal and non-fatal CV events.

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Key Summary Points

Why carry out this study?

Atherosclerotic cardiovascular disease (ASCVD) is a major public health problem associated with increasing incidence, hospitalizations, mortality and considerable economic burden in Canada.

As a result of recent clinical studies published, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are now universally recommended across global lipid guidelines as add-ons to lipid-lowering treatment (LLT) with statin (± ezetimibe) when treatment intensification is required.

Evolocumab is one such PCSK9 inhibitor that has demonstrated reduced risk of recurrent cardiovascular (CV) events in patients whose low-density lipoprotein cholesterol (LDL-C) levels are above threshold despite optimized LLT. A robust clinical development program has consistently demonstrated significant reductions in LDL-C in patients on statin therapy, with a favorable safety profile.

This study was conducted to understand the cost-effectiveness of evolocumab when used as an add-on treatment for patients with ASCVD who cannot adequately control their LDL-C despite optimized LLT in Canada.

What was learned from the study?

The base case considered patients with prior myocardial infarction (MI) and baseline LDL-C ≥1.8 mmol/L with evolocumab as add-on treatment to optimized LLT of statins with or without ezetimibe. These patients with ASCVD are at higher risk of additional CV events.

Scenario analyses were also conducted on the basis of additional recommendations included in the 2021 Canadian Cardiovascular Society (CCS) guidelines.

To our knowledge, this is the first Canadian study to assess the cost-effectiveness of evolocumab as an add-on treatment for patients with ASCVD with LDL-C above the recommended threshold levels despite optimized LLT in the context of the updated Canadian Cardiovascular Society dyslipidemia guidelines.

This analysis supports reimbursement of evolocumab by payers in patients with ASCVD who cannot reach LDL-C thresholds despite optimized LLT to reduce unnecessary fatal and non-fatal CV events.

INTRODUCTION

Hypercholesterolemia is a lipid metabolism disorder characterized by unusually high cholesterol, triglycerides, and lipoproteins in blood. Atherosclerotic cardiovascular disease (ASCVD) refers to all clinical conditions of atherosclerotic origin, including acute coronary syndrome (ACS), myocardial infarction (MI), stable or unstable angina, coronary artery disease documented by angiography, coronary or other arterial revascularization (coronary artery bypass graft [CABG] surgery, femoral popliteal bypass graft surgery, etc.), stroke, transient ischemic attack (TIA), documented carotid disease, peripheral artery disease (PAD), and abdominal aortic aneurysm [1]. Numerous interventional, epidemiologic, and genetic studies have established elevated low-density lipoprotein cholesterol (LDL-C) as an important modifiable risk factor for ASCVD [2–7]. Patients with acute coronary syndrome (ACS), i.e., a history of prior myocardial infarction (MI) or unstable angina, and patients with familial hypercholesterolemia with ASCVD or another major risk factor are most likely to experience a

fatal or non-fatal cardiovascular event [8]. The mean LDL-C of 10,000 patients with ASCVD receiving standard of care is estimated to be 3.2 mmol/L, accounting for an additional 113 MIs, 137 ischemic strokes (IS), and 72 deaths over 1 year [9]. Therefore, aggressive and timely LDL-C lowering is extremely important in such a high-risk patient population [5, 10–12].

With increasing incidence, hospitalizations, and mortality, ASCVD is a major public health problem associated with considerable economic burden in Canada [13–16]. In 2017–2018, there were 71,192 hospitalizations associated with acute MI alone, making it the third most common cause of hospitalization in Canada [16]. Heart disease and stroke were the second and third leading cause of death in Canada in 2018 [17]. While most patients with MI or stroke survive, there are serious long-term consequences to non-fatal acute cardiovascular (CV) events [18] including impaired health-related quality of life (HRQoL), decreased mobility and functionality, worsening anxiety, depression, fatigue, and sexual dysfunction [19–24]. Diminishing HRQoL caused by initial MI is also associated with progression of atherosclerosis and deteriorating outcomes [25]. In 2010, the direct and indirect cost resulting from CV diseases in Canada was estimated to be $13.1 billion CAD and $0.64 billion CAD, respectively [26].

As a result of recent clinical studies published, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are now universally recommended across global lipid guidelines as add-ons to lipid-lowering treatment (LLT) with statin (± ezetimibe) when treatment intensification is required. The 2021 Canadian Cardiovascular Society (CCS) Guidelines [1] for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult recommends treatment intensification with PCSK9 inhibitors in patients with ASCVD and LDL-C levels $\geq$ 1.8 mmol/L despite receiving maximally tolerated dose of statins with or without ezetimibe. In addition, specific subsets of patients with ASCVD and additional CV risk factors such as history of MI, recurrent MI, and recent ACS were shown to derive the largest benefit from treatment intensification with PCSK9 inhibitors (Supplementary Table S1). Furthermore, in patients whose LDL-C levels remain above 2.2 mmol/L, PCSK9 inhibitors are recommended as second-line therapy. The rationale for this recommendation is based on the fact that ezetimibe lowers LDL-C by approximately 20% when added to maximally tolerated statin, meaning that patients with LDL-C $>$ 2.2 mmol/L will not reach threshold LDL-C levels with ezetimibe intensification alone.

Evolocumab is one such PCSK9 inhibitor that has demonstrated reduced risk of recurrent CV events in patients whose LDL-C levels are above threshold despite optimized LLT. A robust clinical development program has consistently demonstrated significant reductions in LDL-C in patients on statin therapy, with a favorable safety profile. In 2017, the FOURIER outcomes trial demonstrated a significant reduction in CV outcomes and favorable safety profile of evolocumab in patients with ASCVD [27–29]. Evolocumab was originally approved by Health Canada in September 2015 as an adjunct to diet and maximally tolerated statin in patients with ASCVD who require additional lowering of LDL-C. Following the publication of FOURIER in June 2018, Health Canada approved evolocumab as "an adjunct to diet and standard of care therapy (including moderate- to high-intensity statin therapy alone or in combination with other lipid-lowering therapy), to reduce the risk of MI, stroke, and coronary revascularization in adult patients with atherosclerotic cardiovascular disease" [30].

This study was conducted to understand the cost-effectiveness of evolocumab when used as an add-on treatment for patients with ASCVD who cannot adequately control their LDL-C despite optimized LLT in Canada. The base case considered patients with prior MI and baseline LDL-C $\geq$ 1.8 mmol/L with evolocumab as add-on treatment to optimized LLT of statins with or without ezetimibe. In Quebec, 77% of ACS related hospitalizations were due to MI and 23% due to unstable angina [13], thus MI patients represent the bulk of ACS at clinical presentation. These patients with ASCVD are at higher risk of additional CV events [13]. Scenario

analyses were also conducted on the basis of additional recommendations included in the 2021 Canadian Cardiovascular Society (CCS) guidelines.

METHODS

The cost-utility analysis (CUA) assessed whether evolocumab as an add-on treatment represents a cost-effective use of healthcare resources in Canada for the prevention of CV events in patients with ASCVD who cannot adequately control their LDL-C despite optimized LLT of statins with or without ezetimibe. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Model Structure

A Markov cohort state transition model incorporating the value of preventing multiple events to account for the impact of further events on risk, costs, and utility was used in this economic evaluation. A systematic literature review of modeling-based economic evaluations using CV outcomes (as opposed to intermediate endpoints) was performed to gain insights into modeling methods germane to the development of this CUA [31]. This model was updated for Canada from previously published models for multiple geographies [32–39]. Baseline CV event rates were based on findings from statin-treated patients with ASCVD in a routine clinical setting [40, 35] and efficacy data was taken from FOURIER [27, 35]. The model comprises 11 main health states (Supplementary Fig. S1): "other ASCVD"; MI; IS; post-MI; post-IS; MI2+; IS2+; post-MI2+; post-IS2+; CV death; and non-CV death. The "other ASCVD" health state captures less severe CV events that are not impacted by the treatment effect, such as unstable angina or PAD. The states for MI and IS cover the first year period after the event; post-event health states cover the subsequent years. Additionally, the model includes composite health states that are a combination of either two or three post-event health states that were created to retain memory of previous CVD events.

Target Population

To assess cost-effectiveness of PCSK9 inhibition with evolocumab added to background LLT (i.e., maximally tolerated statins with or without ezetimibe), one base-case and five scenario analyses were considered. The base-case analysis has been submitted to and evaluated by Institut national d'excellence en santé et en services sociaux (INESSS), the health technology assessment agency in Quebec. This evolocumab submission received a positive listing recommendation by INESSS [41]. The populations and subgroups considered in the base-case and scenario analysis are aligned with the populations recommended by the 2021 CSS guidelines [1].

Base-case: Adding evolocumab to patients with prior MI and baseline LDL-C $\geq$ 1.8 mmol/L receiving maximally tolerated statins with or without ezetimibe.

Scenario analyses:

1. Adding evolocumab to patients with recurrent MI (second MI within 2 years) and baseline LDL-C $\geq$ 1.8 mmol/L receiving background LLT of maximally tolerated statins with or without ezetimibe
2. Adding evolocumab to patients with recent ACS (< 1 year) and baseline LDL-C $\geq$ 1.8 mmol/L receiving background LLT of maximally tolerated statins with or without ezetimibe
3. Adding evolocumab to patients with ASCVD and baseline LDL-C > 2.2 mmol/L receiving background LLT of maximally tolerated statins
4. Adding evolocumab to patients with prior MI and baseline LDL-C $\geq$ 1.8 mmol/L receiving maximally tolerated statins with or without ezetimibe (base-case population) assuming retirement age of 70 years
5. Adding evolocumab to patients with prior MI and baseline LDL-C $\geq$ 1.8 mmol/L receiving background LLT of maximally tolerated statins with or without ezetimibe

(base-case population), using medication costs from Ontario Drug Benefit formulary

Note: The model assumes the normal retirement age of 65 years with exception of scenario 4. To assess the impact of indirect costs in the base-case population, scenario 4 assumes the retirement age of 70 years.

Baseline Patient Characteristics

The model uses a baseline CV event rate obtained from statin-treated patients with ASCVD in a routine clinical setting. The baseline CV event rates were derived from observational data from the USA, using a retrospective observational cohort design in patients with ASCVD. The Truven MarketScan database, a large-scale database of claims for the commercially insured and patients with Medicare Supplemental insurance, was used to estimate the rates of non-fatal CV events [40, 35]. The rate of CV death was thus estimated separately by combining NHANES mortality files (2004–2012) [42] and National Vital Statistics Mortality Report 2012 [40, 35]. The CV event rate, defined as non-fatal MI, non-fatal IS, and CV death, in this US practice-based population was 6.40 per 100 patient-years.

The baseline CV event rates are adjusted by age and LDL-C level to ensure they are appropriate for the modeled population of interest. The baseline CV rate is also adjusted for each population depending on the patient's CV history, as described in Supplementary Table S2.

The directly observed or predicted, then adjusted composite CV event rates at baseline are disaggregated to CV event-specific annual rates for MI, IS, and CV death.

Mortality from non-CVD causes is assumed to be the same as that of the general population and is taken from Canadian national life tables by age and gender [43, 44]. Patients are at concurrent risk of both CV events and non-CVD death. Since these risks are provided by distinct and hence unrelated data sources, it is possible that the sum of all risks can be greater than one. To avoid negative transition probabilities, competing risk adjustment [45] was implemented in the model, whereby in each cycle non-CVD death is first taken into account and CV event-specific transition probabilities are then applied, conditional on being alive.

Treatment Efficacy

Reduction in LDL-C

This economic evaluation employs evolocumab's efficacy on LDL-C reduction observed in the FOURIER outcomes trial: At 48 weeks, the least-squares mean percentage reduction in LDL-C levels with evolocumab on top of background LLT, as compared with placebo, was 59% (95% CI 58–60%; $p < 0.001$) [27]. A randomized open-label extension study, OSLER-1 [46, 47], reported similar, sustained reductions in LDL-C for up to 5 years of evolocumab treatment. Thus, the CV event rate reduction, related to the relative LDL-C lowering at week 48, is assumed to remain constant over the modeled time horizon.

Therapy Persistence

Annual completion data from the FOURIER outcomes trial was used to model for discontinuation of evolocumab, using Kaplan–Meier estimates for discontinuation for any reason other than death.

Reduction in CV Event Rates

As summarized by the recent consensus statement of the European Atherosclerosis Society (EAS), LDL-C is not merely a biomarker of increased risk but a causal factor in the pathophysiology of CVD [4]. This causal relationship between lowering LDL-C level by 1 mmol/L and reduction of CV events, as reported by the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analyses, is utilized in this CUA (Table 1) [48]. Pooling all 26 statin trials (a total of 169,138 individuals with a median follow-up of 4.9 years), the rate ratio (RR) for any major vascular event per 1 mmol/L (defined as CHD death, non-fatal MI, stroke, revascularization) of LDL-C reduction was 0.78 (95% CI 0.76–0.80). The model uses endpoint-specific RR reported in Table 1.

Results from the FOURIER outcomes trial with evolocumab showed a statistically

Table 1 Rate ratios of CV events per mmol/L of LDL-C reduction, utility values, and costs for CV events and procedures

Event	Rate ratio per mmol/L LDL-C reduction (95% CI)	Utility values		Direct costs (CAD$)		Indirect costs (CAD$)	
		Year 1 Mean (95% CI)	Subsequent years (post-event) Mean (95% CI)	Year 1	Subsequent years	Year 1	Subsequent years
Non-fatal MI	0.73 (0.70, 0.77)	0.67 (0.62, 0.72)	0.82 (0.80, 0.85)	40,668	14,912	11,079	5238
Non-fatal IS	0.77 (0.70, 0.85)	0.33 (0.26, 0.39)	0.52 (0.47, 0.58)	51,999	21,954	10,101	5238
CV death	0.86 (0.82, 0.90)	–	–	10,409	–	–	–
Other ASCVD	–	–	0.82 (0.80, 0.85)	–	14,343	–	–

ASCVD atherosclerotic cardiovascular disease, *CI* confidence interval, *CV* cardiovascular, *IS* ischemic stroke, *LDL-C* low-density lipoprotein cholesterol, *MI* myocardial infarction [48]

significant 20% relative risk reduction in major CV (CV death, non-fatal MI, non-fatal stroke—3-point MACE) events over a median follow-up of 2.2 years [27]. Pre-specified landmark analyses were conducted for patients alive at the end of first year to estimate the effect of evolocumab on outcomes beyond the first year. As a result of this analyses, it was found that the magnitude of relative risk reduction of major CV events grew over time, from 16% in the first year to 25% beyond the first year. When considering time exposure, evolocumab had very similar effects on the risk of major vascular events per 1 mmol/L of LDL-C reduction as compared to statin-based CTTC meta-analysis.

Given that results from FOURIER (after accounting for LDL-C reduction and study duration) are aligned with the overall evidence base for LDL-C-lowering agents [27], it stands to reason to base the treatment effect in the model on the well-established relationship between absolute LDL-C lowering and reduced CV event rates observed in the meta-analyses conducted by the CTTC.

Application of Treatment Effect in the Model

There are three steps in the model to apply the impact of treatment on incidence of CV events:

(i) Definition of baseline LDL-C level: Mean LDL-C of the patient population being evaluated.

(ii) Calculation of absolute LDL-C reduction: The absolute reduction in LDL-C is computed by multiplying the baseline LDL-C level with the relative LDL-C reduction associated with the use of evolocumab as add-on to statin. The treatment effect on LDL-C is taken from the FOURIER outcomes trial. As non-LLTs were permitted in the trial, the model assumes that the impact of non-lipid-modifying therapies on LDL-C is similar across all treatment arms.

(iii) Application of a relationship between LDL-C reduction and improved CV outcomes.

To construct the rate of CV events after treatment, the rate ratios per 1 mmol/L of LDL-C reduction (taken from the CTTC meta-analyses; see Table 1) are applied to the age- and event-specific transition rates at baseline using the following formula:

$$r_{tx} = r_0 \times RR^{(\Delta LDLc)} \quad (1)$$

where, r_{tx} = rate after treatment, r_0 = rate at baseline, RR = rate ratio per 1 mmol/L of LDL-C reduction, ΔLDLc = absolute LDL-C reduction in mmol/L.

The modified CV event-specific annual rates are then converted into risks (transition probabilities) for patients treated with evolocumab added to background LLT.

Utility Values and Costs

Measuring and Valuation of Health

CVD health state utilities (Table 1) are derived from a utility study based on a general population sample in the UK [19]. Total QALYs are calculated by applying the state-specific utilities to the probabilities of residing in each state over the modeled lifetime time horizon.

Resource Use and Costs

Medical cost estimates (Supplementary Table S3) relevant to the public healthcare and societal perspective were derived from pertinent Canadian data sources. Given that the modeled patient population is older than the normal retirement age of 65 years in the base case and scenarios 1–3 and 5, only medication costs and other direct healthcare costs associated with the modeled CVD health states are considered. Indirect costs, such as productivity losses and informal care costs, are included in scenario 4, wherein retirement age is assumed to be 70 years. All costs are reported in 2021 CAD$. Total costs are calculated by multiplying the state-specific costs by the probabilities of residing in each health state.

Medication Cost Medications costs in scenarios 1–4 are based on the list price of drugs according to the Liste des médicaments du régime général (27 May 2021) provided by the Régie de l'assurance maladie du Québec (RAMQ) [49]. Additionally, a wholesaler markup fee of 6.5% and dispensing fee of CAD$9.00 were assumed when calculating the annual medication costs finally implemented in the economic model. Medication costs in scenario 5 are based on the list price of drugs according to Ontario Drug Benefit Formulary assuming a wholesaler markup fee of 8.0% and dispensing fee of CAD$8.83 (Supplementary Table S4 [50, 51]).

Health State Costs The costs per modeled health state including first-year acute and short-term costs as well as post-event costs for subsequent years are applied in the economic evaluation. Direct costs for the health states for MI, IS, and "other ASCVD" were estimated from ICES claims data in the age group ≥ 60 years, based on publicly funded health services records in Ontario [52]. The cost estimate for CV death was obtained from Table 10 of CADTH's Pharmacoeconomic Review Report on rivaroxaban [53].

This model includes indirect costs beyond the healthcare sector when analyzing scenario 4 with retirement age of 70 years, to reflect the societal perspective in Canada. Indirect costs stem from (i) short-term absenteeism, presenteeism, and caregiver time; (ii) early retirement; (iii) premature mortality.

Economic Analysis

The analysis assumed a lifetime horizon due to the chronic nature of hypercholesterolemia. The quality-adjusted life year (QALY) is the primary measure of health benefit. The incremental cost-effectiveness ratio (ICER) is calculated as the difference in costs divided by the difference in QALYs. No equity issues were considered relevant to this analysis. An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit. Additionally, the model evaluates non-fatal CV event rates for MI

Table 2 Summary of cost-effectiveness results

Population	**Base case: prior MI, LDL-C ≥ 1.8 mmol/L**	
Comparator	**Evolocumab + background LLT**	**Background LLT**
Rates*		
CV events	1.89	2.41
MI	0.62	0.88
IS	0.59	0.78
CV death	0.68	0.75
Non-CV death	0.32	0.25
10-year CV event risk	57%	70%
Number needed to treat*	–	16.47
Survival*	12.72	11.18
Δ cost	285,116	210,804
Medication	70,377	2011
CV events	52,326	70,900
MI	20,798	30,071
IS	25,637	34,201
CV death	5891	6628
Post event	162,414	137,892
Δ cost	–	74,312
Total LY	11.14	9.91
Δ LY	–	1.23
ICER (Δ cost per Δ LY)	–	60,349
Total QALY	8.38	7.26
CV events	0.50	0.71
MI	0.34	0.50
IS	0.16	0.22
Post event	7.87	6.55
Δ QALY	–	1.12
ICER (Δ cost per Δ QALY)	–	66,453

ACS acute coronary syndrome, *ASCVD* atherosclerotic cardiovascular disease, *CV* cardiovascular, *ICER* incremental cost-effectiveness ratio, *IS* ischemic stroke, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy, *LY* life year, *MI* myocardial infarction, *QALY* quality-adjusted life year
*Undiscounted

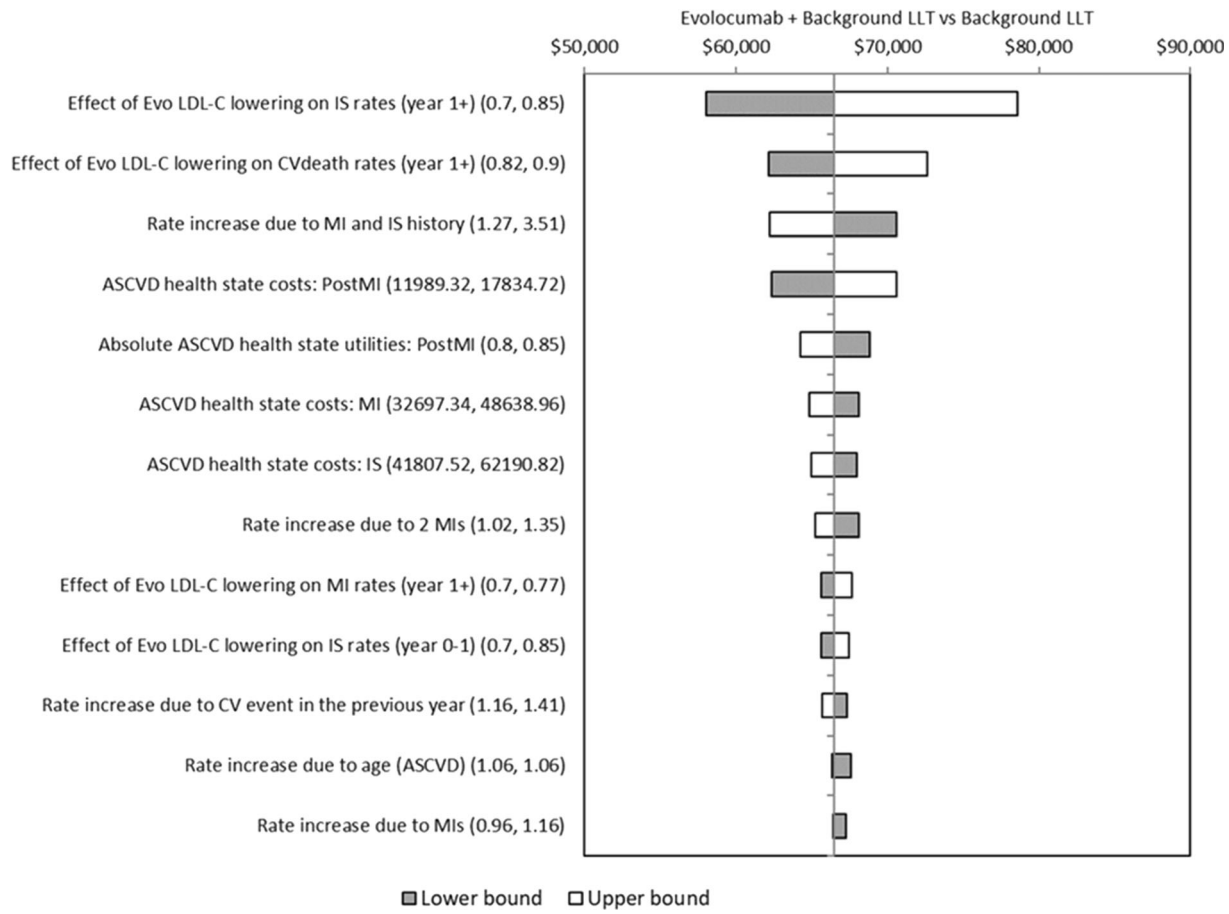

Fig. 1 Tornado diagram (ICER): base case (prior MI, LDL-C $\geq$ 1.8 mmol/L). *ASCVD* atherosclerotic cardiovascular disease, *CV* cardiovascular, *ICER* incremental cost-effectiveness ratio, *IS* ischemic stroke, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy, *MI* myocardial infarction

and IS, RV rates, life years (LY), CV death rates, the 10-year CV event risk, and the number needed to treat (NNT). Costs and outcomes are discounted at an annual rate of 1.5%.

Sensitivity Analyses

Deterministic and probabilistic sensitivity analyses were used to reflect input parameter uncertainty and assess its impact on model results.

Univariate Sensitivity Analysis

One-way sensitivity analyses were performed, in which one parameter was varied at a time relative to its base-case value. They were conducted on the following parameters:

- Reduction in LDL-C
- CV event rate ratios (per 1 mmol/L LDL-C reduction)
- Hazard ratios to adjust baseline CV event rates
- Baseline CV event rates
- CVD health state costs
- CVD health state utilities

Efficacy parameters, hazard ratios to adjust baseline CV event rates, and health state utilities were changed to the lower and upper bound of their 95% confidence intervals (CI). A standard error of 10% of the mean values was

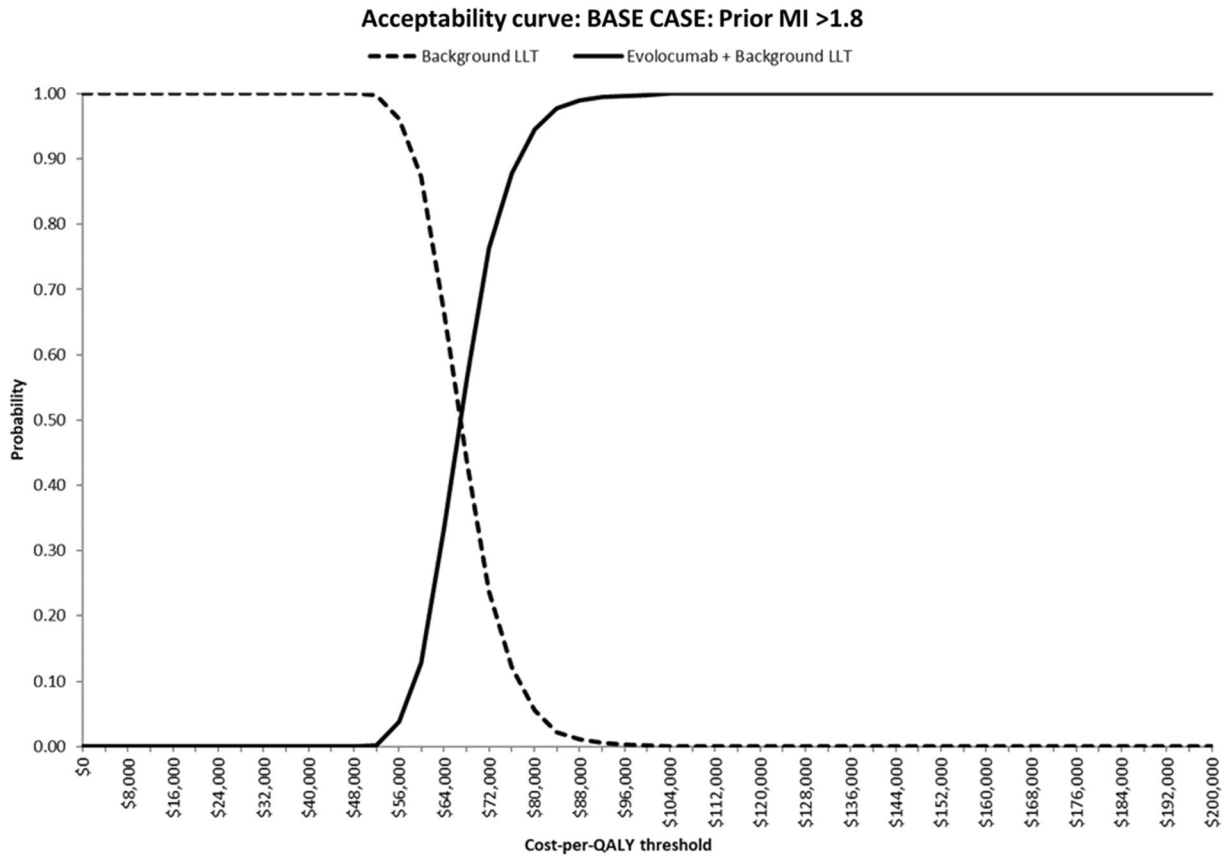

Fig. 2 Cost-effectiveness acceptability curve: base case. *LLT* lipid-lowering therapy, *MI* myocardial infarction, *QALY* quality-adjusted life year

assumed to calculate the 95% CIs for health state costs.

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis was additionally conducted to fully examine the combined effect of parameter uncertainty on the incremental cost per QALY gained. Appropriate probability distributions were assigned to model parameters on the basis of their respective means and standard errors. Values for parameters were then sampled by Monte Carlo simulation with 1000 iterations in each loop. The model allows the flexible use of alternative distributions.

RESULTS

The results from cost-effectiveness analysis of evolocumab when used as an add-on treatment for patients with ASCVD, who are unable to obtain recommended LDL-C thresholds with conventional LLTs, are detailed in this section.

The results are summarized in three key parts:

1. Base-case analysis (Table 2)
2. Sensitivity analysis (Figs. 1, 2, 3)
3. Scenario analyses (Table 3)

Base-Case Results for Patients with prior MI

Adding evolocumab to optimized LLT of maximally tolerated statins with or without

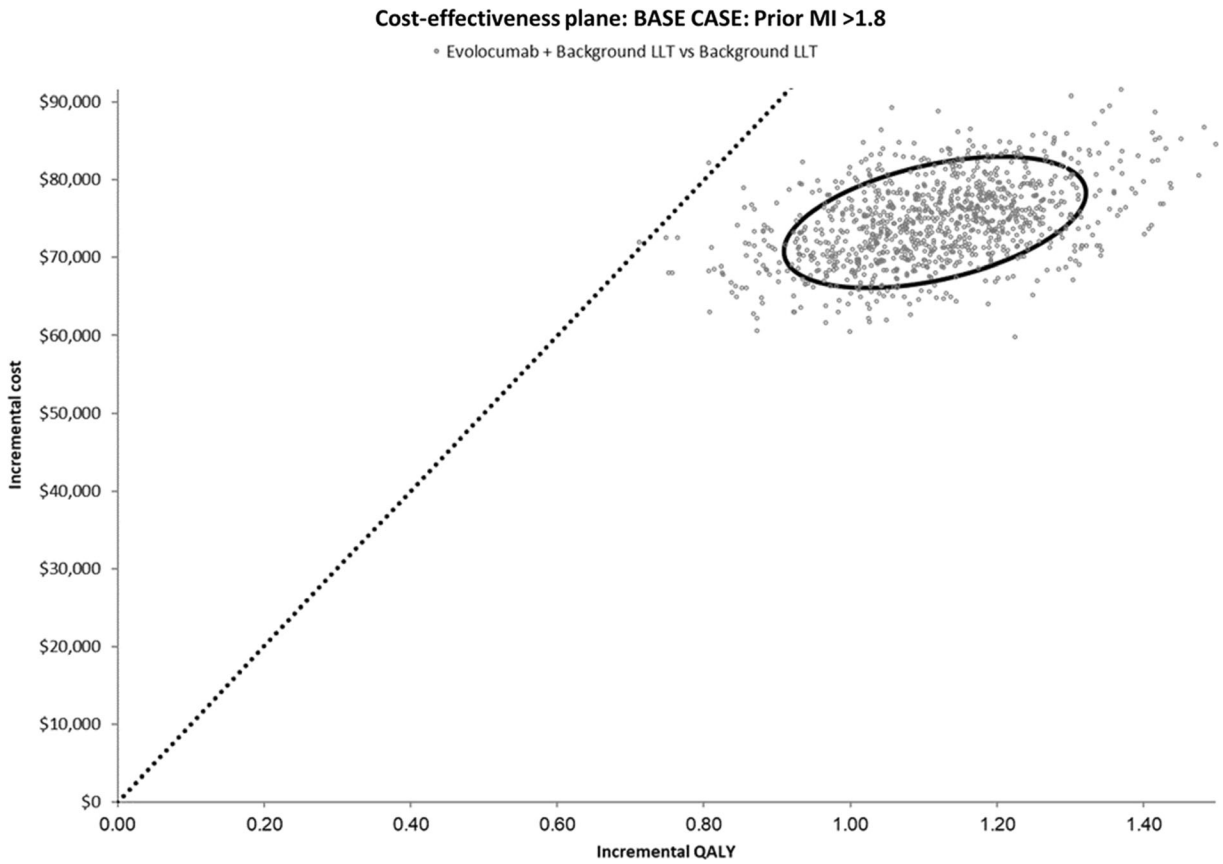

Fig. 3 Cost-effectiveness plane: base case. *LT* lipid-lowering therapy, *MI* myocardial infarction, *QALY* quality-adjusted life year

ezetimibe is associated with an incremental cost per QALY gained of CAD$66,453, in ASCVD patients with prior MI, and baseline LDL-C $\geq$ 1.8 mmol/L (Table 2).

Further, the rate of CV events over a patient's lifetime is decreased by approximately 21% by adding evolocumab to background LLT in patients with prior MI and baseline LDL-C $\geq$ 1.8 mmol/L. The reduction in fatal and non-fatal CV events when evolocumab is added to background LLT would translate into cost savings of approximately CAD$1.86 million for event costs in 100 patients over a lifetime time horizon. Sixteen patients need to be treated to avoid one major CV event (defined as non-fatal MI, non-fatal IS, and CV death) in patients treated with evolocumab added to background LLT compared with background LLT.

Sensitivity Analysis Results

Deterministic Sensitivity Analysis

All parameters that affect the base-case ICER by more than 1% are shown in the tornado diagram (Fig. 1). The ICER is mostly sensitive to the rate ratios per 1 mmol/L of LDL-C reduction for non-fatal IS and CV death events, taken from CTTC meta-analyses. Overall, the one-way sensitivity analysis demonstrated that base-case results were robust to changes in model input parameters.

Probabilistic Analysis

Results of probabilistic analyses are summarized alongside deterministic estimates in the tornado diagram. A cost-effectiveness acceptability curve (CEAC) for the base case illustrates that evolocumab is cost-effective over a range of

Table 3 Scenario analysis results

Scenario	Incremental costs (CAD$)	Incremental QALYs	ICER (CAD$ per QALY)	Change vs base case
Deterministic analysis				
Base-case: Prior MI with baseline LDL-C ≥ 1.8 mmol/L	74,312	1.12	66,453	–
Scenario 1: Recurrent MI with baseline LDL-C ≥ 1.8 mmol/L	72,964	1.12	65,090	− 2.1%
Scenario 2: Recent ACS with baseline LDL-C ≥ 1.8 mmol/L	74,415	1.14	65,525	− 1.4%
Scenario 3: ASCVD with baseline LDL-C > 2.2 mmol/L	78,873	1.08	72,777	+ 9.5%
Scenario 4: Prior MI with baseline LDL-C ≥ 1.8 mmol/L (retirement age 70 years)	71,794	1.12	64,201	− 3.4%
Scenario 5: Prior MI with baseline LDL-C ≥ 1.8 mmol/L (medication cost from ODB formulary)	77,568	1.12	69,364	+ 4.4%
Probabilistic analysis				
Base-case: Prior MI with baseline LDL-C ≥ 1.8 mmol/L	74,127	1.10	67,149	–
Scenario 1: Recurrent MI with baseline LDL-C ≥ 1.8 mmol/L	73,028	1.12	65,421	− 2.6%
Scenario 2: Recent ACS with baseline LDL-C ≥ 1.8 mmol/L	74,400	1.13	65,857	− 1.9%
Scenario 3: ASCVD with baseline LDL-C > 2.2 mmol/L	78,823	1.07	73,347	+ 9.2%
Scenario 4: Prior MI with baseline LDL-C ≥ 1.8 mmol/L (retirement age 70 years)	71,809	1.11	64,700	− 3.6%
Scenario 5: Prior MI with baseline LDL-C ≥ 1.8 mmol/L (medication cost from ODB formulary)	77,465	1.11	69,694	+ 3.8%

ACS acute coronary syndrome, *ASCVD* atherosclerotic cardiovascular disease, *ICER* incremental cost-effectiveness ratio, *LDL-C* low-density lipoprotein cholesterol, *MI* myocardial infarction, *QALY* quality-adjusted life year

cost-per-QALY thresholds (Fig. 2). A cost-effectiveness plane (CEP) was also generated for the base case (Fig. 3). This is presented as a scatter plot of every individual simulation as a combination of incremental costs and incremental QALYs. The dotted line illustrates commonly cited thresholds of CAD$100,000 per QALY. Add-on treatment with evolocumab has 99.9% probability of being cost-effective, at a threshold of CAD$100,000.

Scenario Analyses

The cost-effectiveness of evolocumab was also assessed in alternative population definitions that were highlighted in the 2021 CCS guidelines as they can benefit the most from intensified LLT. In addition to these alternative populations, scenarios 4 and 5 explore the impact of different assumptions in the base-case population: increasing the retirement age to 70 years to assess the impact on indirect costs (scenario 4) and using the drug costs based on ODB-Ontario (as a proxy for Canadian drug costs outside of Quebec) instead of RAMQ-Quebec (scenario 5). Table 3 depicts the deterministic and probabilistic scenario analyses results.

DISCUSSION

To our knowledge, this is the first Canadian study to assess the cost-effectiveness of evolocumab as an add-on treatment for patients with ASCVD with LDL-C above the recommended threshold levels despite optimized LLT in the context of the updated Canadian Cardiovascular Society dyslipidemia guidelines.

When used in patients with prior MI and baseline LDL-C $\geq$ 1.8 mmol/L, adding evolocumab to background LLT of maximally tolerated statins with or without ezetimibe is associated with an ICER of CAD $66,453/QALY.

For every 100 patients treated with evolocumab for a lifetime, adding evolocumab to optimized LLT of maximally tolerated statins with or without ezetimibe will prevent approximately 52 major CV (defined as non-fatal MI, non-fatal IS, and CV death) events, of which seven would be fatal.

Sensitivity analyses suggest that these findings are generally robust to univariate and simultaneous variation in the model input parameters. At an ICER threshold of CAD$100,000/QALY, the use of evolocumab as an add-on treatment has a 99.9% probability of being cost-effective.

Additionally, scenario analyses were conducted to assess the cost-effectiveness of evolocumab in very high risk populations that were highlighted in the 2021 CCS guidelines as priority groups to receive PCSK9 inhibitors. The results suggest that evolocumab added to background LLT may be considered a cost-effective use of resources, given an ICER threshold of CAD$100,000 per QALY gained, supporting its listing as add-on to optimized statin with or without ezetimibe in patients with recurrent MI with baseline LDL-C $\geq$ 1.8 mmol/L, recent ACS, with baseline LDL-C $\geq$ 1.8 mmol/L and as add-on to optimized statin in patients with ASCVD with baseline LDL-C $>$ 2.2 mmol/L to reduce unnecessary fatal and non-fatal CV events. Further, results of the scenario analysis assuming retirement age of 70 years and thereby including indirect costs also suggest that adding evolocumab to background LLT in patients with prior MI and baseline LDL-C $\geq$ 1.8 mmol/L is considered cost-effective. Finally, the results of the scenario analysis considering medications costs based on the list price of drugs according to Ontario Drug Benefit Formulary are aligned with cost-effectiveness base-case analysis considering RAMQ list prices.

The results of this study align with previous cost-effectiveness studies conducted internationally in the USA and in Saudi Arabia, which found that evolocumab is cost-effective in patients with ASCVD based on Markov models. A cost-effectiveness study from a US-specific societal perspective published in 2019 by Fonarow et al. [36] concluded that adding evolocumab to statin therapy with or without ezetimibe was associated with increased costs and improved outcomes in patients with very high risk ASCVD as defined by the 2018 guidelines from the American College of Cardiology and American Heart Association. Base-case ICERs ranged from $7667 to $56,655 USD per QALY gained for a range of subgroups of patients with ASCVD. Similarly, a study conducted in Saudi Arabia published in 2021 by Alghamdi et al. [54] that evaluated cost-effectiveness of evolocumab for the treatment of dyslipidemia concluded that adding evolocumab to a statin with or without ezetimibe was associated with ICERs ranging from $41,757 to $60,708 USD per QALY in patients with clinically evident ASCVD and baseline LDL cholesterol $\geq$ 70 or $\geq$ 100 mg/dL.

The analysis does have some limitations. The predictions of the model were based on extrapolation beyond the duration of the FOURIER trial. Furthermore, any differences in compliance and adherence to evolocumab therapy than those modeled in the analysis based on the FOURIER trial will likely impact cost and clinical effectiveness. There are assumptions made to help simplify the model while ensuring its robustness as a result of a paucity of evidence such as grouping "other ASCVD" as a single health state and its utility value is assumed to be equal to the value attributed to subsequent years of MI. All analyses were conducted considering evolocumab list price in Quebec and Ontario; cost-effectiveness is expected to improve if confidential price discounts are applied as a result of reimbursement agreement and/or third-party negotiations.

There continues to be a high clinical burden of ASCVD and substantial unmet need for secondary prevention of ASCVD in Canada. Specifically, the high clinical burden of ASCVD has been demonstrated by an increasing prevalence rate in Ontario over the past two decades, consequently impacting the economic burden of treatment, which is expected to increase over time [55]. However, current CCS dyslipidemia guidelines have evolved with lower thresholds and new medications, providing opportunity to improve patient outcomes in secondary prevention and reduce this clinical and economic burden in Canada.

CONCLUSION

This economic evaluation assesses whether evolocumab as an add-on treatment for patients with ASCVD with LDL-C above the recommended threshold levels despite optimized LLT represents a cost-effective use of resources in Canada, having received a positive listing recommendation from INESSS. The results of the analysis suggest that the addition of evolocumab to background LLT in patients with ASCVD and LDL-C levels $\geq$ 1.8 mmol/L can be considered cost-effective. Various scenario analyses further demonstrated the robustness of the analyses with ICERs similar to the base-case analysis. Results of this analysis strengthen the demonstrated clinical value with confidence that evolocumab provides economic value in patients with ASCVD and inadequate control over LDL-C despite optimized LLT in populations highlighted in the 2021 CCS guidelines.

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