Proprotein convertase subtilisin–kexin type 9 inhibitors are unlikely to be cost-effective in Canada

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Abstract

Background: The proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, such as evolocumab, have garnered interest due to their ability to lower LDL by up to 60%. The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial has recently shown that non-fatal cardiovascular events can be prevented by the addition of evolocumab to statin therapy. Despite no cardiovascular or overall mortality benefit demonstrated, many believe that with longer treatment such a benefit could be achieved.

Methods: We calibrated the Cardio-metabolic model, a well-validated tool for predicting cardiovascular events and life expectancy, to the reduction in non-fatal events seen in the FOURIER trial. We estimated years of life saved (YOLS) with treatment compared to statins alone. We then estimated the costs of treatment and events prevented arrive at the average cost per YOLS. Finally, we estimated the annual drug costs which would provide a 50% chance of being cost-effective at a willingness to pay of $50,000 and $100,000 respectively.

Results: In secondary prevention treatment would save an average of 0.34 life years (95%CI 0.27-0.41) at a cost of $101,899 (95%CI $97,325-$106,473) yielding a cost per YOLS of $299,482. We estimate that to have a 50% probability of achieving a cost per YOLS below $50,000 and $100,000 would require annual drug costs below $1,200 and $2,300 respectively.

Interpretation: At current pricing, the use of PCSK9 inhibitors for secondary prevention is unlikely to be cost-effective in Canada.

Introduction

Ischemic heart disease is common with an estimated 1 in 12 Canadians older than age 20 affected and more than 150,000 new cases in 2012-2013 (1). There have been tremendous improvements in the care of patients with cardiovascular disease brought about by therapeutic advances in risk factor modification including cholesterol lowering with statins. Over the same period there have also been technical advances in cardiac critical care, including the use of primary percutaneous coronary intervention for myocardial infarction. Consequently, since 2000, the death rate from ischemic heart disease has fallen in Canada by 23% (1).

Despite these advances, there is great interest in other therapies to further decrease attributable morbidity and mortality. Following the success of the statins, several other medications which lower low density lipoprotein (LDL) have been investigated for their ability to impact cardiovascular outcomes. The most recent of these, the proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, such as evolocumab, have garnered interest due to their ability to lower LDL by up to 60% (2). This LDL lowering comes at an estimated cost approaching $7500 Canadian dollars per year. Until recently the impact of these drugs on hard outcomes remained unclear.

With the publication of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial (2) in March 2017, we now have evidence that these agents reduce cardiovascular outcomes in secondary prevention amongst patients who were already taking a statin. In a randomized, double-blind, placebo-controlled trial involving 27,564 patients with pre-existing atherosclerotic cardiovascular heart disease from 1242 sites in 49 countries the addition of evolocumab reduced the risk of the primary endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) from 11.3% to 9.8% after a median duration of 2.2 years. There was no reduction in overall or cardiovascular mortality in this trial although there are many who believe that given a longer follow up period such a benefit might eventually be demonstrated. We

therefore estimated any potential mortality benefit over a patient's lifetime using a previously well-validated disease simulation approach, incorporating the Cardiovascular Disease Life Expectancy Model (3) and to estimate the costs per year of life saved (YOLS) for an average Canadian with established coronary artery disease. We then estimated the price threshold at which these drugs might be considered cost-effective.

Methods

Model Overview

The Cardio-metabolic model was designed to estimate the clinical impact of multiple risk factors for diabetes and cardiovascular disease on life-expectancy. These risk factors include age, gender, blood pressure, total cholesterol, high density lipoprotein cholesterol, and other significant factors as previously described (4). These cardiovascular risk factors in turn increase the risk of dying of coronary disease and cerebrovascular disease. The model includes the Cardiovascular Life Expectancy Model to estimate the risk developing fatal or non-fatal coronary disease, cerebrovascular disease and/or the risk of dying a non-cardiovascular death.

Cardiovascular Life Expectancy Model

This previously published Markov model has been described in detail (3, 5-8). Briefly, the model is based on three logistic regression equations derived from the 15% random sample of the Lipid Research Clinic Cohort (3). The average length of follow-up was 12.2 years. Our equations estimate the annual probability of dying from coronary heart disease, stroke, or other causes. Initially, the model was validated on the fatal outcomes observed in published lipid and hypertension clinical trials (3). Similarly, the cardiovascular outcomes for individuals with diabetes were validated from trial results (8). The life expectancy estimates generated by the model have also been validated against published life tables for Americans and Canadians (5, 6).

Once we validated the model estimates on fatal outcomes observed in clinical trials, we estimated the risk of developing nonfatal cardiovascular disease outcomes as follows. The probabilities of developing coronary insufficiency, a nonfatal myocardial infarction, a transient ischemic attack, or a nonfatal stroke were estimated by the ratios of nonfatal to fatal events predicted by the results of several studies providing primary or secondary cardiovascular disease outcomes. We subsequently also estimated the probability of various vascular procedures using hospitalization and health care utilization data from Canada, and the United States (7).

Calibrating the Model to Estimate the Results of the FOURIER Study

The Cardio-metabolic model was calibrated so that the hazard ratio, treatment vs control, for a combined outcome (cardiovascular death, myocardial infarction, or stroke) over a two-year follow-up period, would be approximate the observed results in the FOURIER trial. We identified lower and upper bounds on our LDL coefficients that produced hazard ratios respectively similar to the upper and lower bound of the confidence intervals for the hazard ratio in the FOURIER trial. We then incorporated uncertainty about the LDL coefficients by eliciting normal distributions with standard deviations equal to one quarter the difference between the upper and lower bounds.

Cardiovascular mortality and total mortality were similar between the treatment and control groups in the FOURIER study despite the positive impact on non-fatal cardiovascular events. We therefore assumed that given the impact of active on non-fatal cardiovascular events by approximately -25 to -20%, fatal events should follow the same trend over time despite the observed short term results.

Estimating Years of Life Saved and The Cost Effectiveness of Lipid Modification

Our modeling approach has been described in detail elsewhere (3). When comparing treatments having a differential effect on risk factors, the benefits associated with one treatment over the other are calculated as the YOLS due to the “first” treatment over the

"second" treatment. This value is computed as YOLS = $LE_{first} - LE_{second}$, where LE indicates life expectancy. In this study, the first treatment was receipt of a PCSK9 inhibitor in addition to a statin and the second was statin treatment alone.

The methods used to assign unit cost to acute events and chronic treatments have also been previously described (7). In this analysis, previously estimated treatment costs were inflated to 2017 costs using the Canadian Health Care Inflation Index published by Statistics Canada. The cost of PCSK9 inhibitors were based on the current Canadian market price of evolocumab or $7,500 annually. Uncertainty about our estimated costs was expressed by eliciting uniform distributions on a range of values (point estimates plus/minus 20%).

We calculated the incremental costs per YOLS of PCSK9 therapy by calculating the difference between lifetime medical costs with and without evolocumab divided by the difference in the forecasted life expectancies. Because the costs and the health outcomes occur at different times, we discounted both by 3% annually.

Simultaneously adjusting for uncertainty in costs and model coefficients involved simulating 1000 sets of values for these coefficients and costs from their respective distributions. For each one simulated set of values we obtained an estimate of years of life saved and lifetime incremental costs. Using these results of YOLS and incremental costs, we constructed confidence intervals around our estimates.

We then generated cost-effectiveness acceptability curves showing the percentage of the 1000 simulated results that would give, for a specified amount, the proportion of simulations resulting in a positive incremental net benefit as a function of the annual drug costs.

Results

The estimated numbers of events prevented with therapy are presented in Table 1 and the estimated costs of cardiovascular or other events are included in the supplemental appendix (Table S1). The estimated cost per year of life saved for male and female patients based on various ages of initiation of evolocumab treatment are presented in Table 2. For a population like that seen in FOURIER, treatment would save, on average, 0.34 life years (95%CI 0.27-0.41) at a cost of $101,899 (95%CI $97,325-$106,473) yielding a cost per YOLS of $299,482. In general, the older the patient the lower the cost per YOLS. This was primarily due to reduced drug costs over the number of treatment years that rather than increased survival benefits at older ages.

Our probabilistic sensitivity analysis (Figure 1) estimated that to have a 50% probability of achieving a cost per YOLS below $50,000 and $100,000 would require annual drug costs below $1,200 and $2,300 respectively. Above $1,800 or $3,000 the probability of cost-effectiveness a ratio equal to$50,000 or $100,000 respectively is zero.

Interpretation

There was no cardiovascular or total mortality benefit seen in the FOURIER trial; nonetheless, the possibility for LDL lowering by PCSK9 inhibitors to reduce mortality over time may exist. However, despite this optimistic assumption these agents are unlikely to be cost-effective at current Canadian prices. More than an 80% discount from current pricing would be required to have a 50% chance of being cost-effective at a willingness to pay of $50,000 per YOLS.

There are several articles on the cost-effectiveness of PCSK9 inhibitors which have both included and not included pharmaceutical industry authors. Our study has the advantage of being the first based on a model calibrated to the observed cardiovascular effect from a large randomized-controlled trial which was specifically designed to look at cardiovascular outcomes in secondary prevention. Hence, the uncertainty surrounding the drugs actual effectiveness is substantially reduced.

Amongst those studies which did not include an industry author, Korman estimated that for the highest benefit secondary prevention group (Norwegian individuals with

diabetes) the estimated cost per quality-adjusted life year (QALY) was 68,400 euros (approximately $100,000 Canadian Dollars) (9). Kazi et. al concluded the drugs were unlikely to be cost-effective for secondary prevention at a threshold of $100,000 US Dollars (approximately $137,000 Canadian dollars) unless the annual price was reduced to $4536 US (approximately $6200 Canadian) (10). Arrieta et al. arrive at the same conclusion with a similar estimate of $4250 US (11). Estimates from the Institute for Clinical and Economic Review suggested an annual price of $3166, $5404, and $7735 US dollars to reach thresholds of $50,000, $100,000 and $150,000 US per QALY respectively (12).

In studies involving an industry author, Gandra estimated that the cost of secondary prevention in the United States would approach US$141,699 per QALY (approximately $190,000 Canadian Dollars) (13) and Toth et. al attempted to identify an upper celling of pricing by comparing current pricing to a willingness to pay of $150,000 US dollars (approximately $200,000 Canadian dollars) per QALY(14). Villa et. al concluded that evolocumab would be cost-effective for secondary prevention in Spain with an incremental cost effectiveness ratio of 45,340 euros per QALY (approximately $67,000 Canadian dollars) (15).

The principal limitation of our study is that the results are based on a model which was developed to evaluate the impact of statins and not specifically developed for PCSK9 inhibitors. The assumption that cardiovascular and all-cause mortality will be lowered by PCSK9 inhibitors remains theoretical. There are several important examples of drugs which lower LDL but have not been shown to reduce mortality (16-18). Thus, our results likely represent a best-case scenario. Our approach is also limited by not including the potential cost of side effects that may only be recognized after a new medication has been used over the longer term. For instance cognitive impairment remains a concern with extremely low LDL levels and a two year trial may be insufficient to address this issue (19). We also assume the drug will maintain efficacy over the duration of treatment; however one such molecule has had development stopped due to immune reactions against the monoclonal antibody (20) and other anti-drug antibodies have been reported (21).

Conclusion

Using a well-validated model for predicting cardiovascular events and mortality we demonstrate that at current pricing the current generation of PCSK9 inhibitors are unlikely to be cost-effective for preventing mortality in secondary prevention patients with high cardiovascular risk. With evolving long term follow up data and adjustments in pricing future analyses will need to re-evaluate whether these medications should become the standard of care for Canadian patients. In the interim, it is likely their use should remain limited to exceptional cases.

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Table 1: Estimated Events Per 1,000 Eligible Patients over Lifetime

Event	Untreated	Treated	Events Prevented
Recurrent Myocardial Infarction	460.8	404.9	56.0
CVD Death	416.7	361.5	55.2
New MI or Recurrent MI	484.2	429.9	54.3
CVD Death, MI (New or Recurrent) or Stroke	752.7	700.7	51.9
Stroke or TIA	354.2	324.9	29.3
Fatal MI	149.2	120.1	29.2
Stroke	293.8	266.3	27.5
Sudden Death	87.5	70.1	17.3
Stroke Death	96.4	83.8	12.5
Transient Ischemic Attack	92.8	85.5	7.3
Newly Diagnosed Diabetes	332.5	327.3	5.2
New Myocardial Infarction	52.1	49.2	2.9
Angina Pectoris	41.5	38.7	2.8
Coronary Insufficiency	9.7	9.1	0.6
CHF Death	84.9	88.5	-3.6
Congestive Heart Failure	107.5	111.2	-3.7
Other Death	579.2	634.6	-55.4

CVD: Cardiovascular disease; MI: Myocardial Infarction; TIA: Transient Ischemic Attack

Table 2: Average Estimated Years of Life Saved and Associated Costs by Gender and Age - Discounted

Sex	Age	Years of Therapy		YOLS	95% CI	Difference in Lifetime Cost	95% CI Lifetime Cost	Cost Per YOLS
		Control	Treated					
Male								
	45	18.6	19.1	0.45	0.37-0.53	144 110	115 628-172 593	318 335
	55	15.6	16.0	0.42	0.34-0.51	120 574	97 031-144 117	284 306
	65	12.1	12.5	0.36	0.29-0.44	93 083	76 276-109 890	257 348
	75	8.6	8.8	0.27	0.23-0.31	65 357	54 354-76 359	243 414
Female								
	45	20.0	20.3	0.29	0.20-0.37	151 539	120 778-182 299	528 009
	55	16.9	17.2	0.29	0.20-0.37	128 236	102 937-153 535	448 221
	65	13.3	13.6	0.26	0.20-0.33	99 871	82 313-117 430	382 796
	75	9.7	9.9	0.17	0.12-0.21	71 607	60 198-83 016	422 710
Overall		**13.3**	**13.6**	**0.34**	**0.27-0.41**	**101 899**	**97 325-106 473**	**299 482**

CI: Confidence Interval; YOLS: Years of Life Saved.
Difference in costs in current Canadian dollars (see Methods).
Overall is weighted for the age and gender distributions seen in the Fourier trial

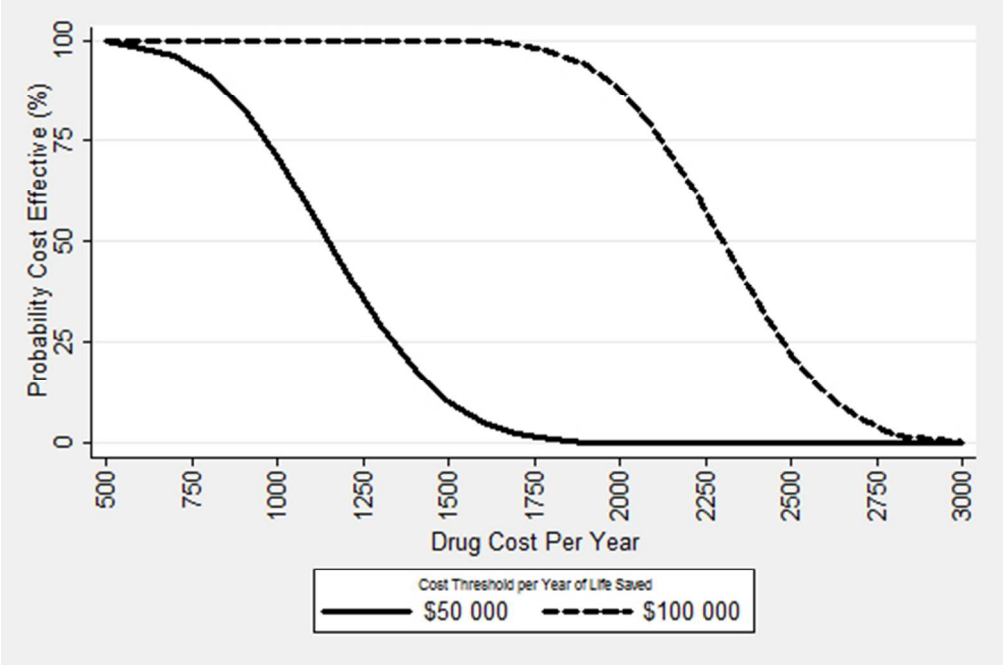

Figure 1: Probability Estimates of Willingness to Pay per Year of Life Saved

Table S1: Estimated Cost of Events Adjusted to 2016 Canadian Dollars

Outcome	Estimated Cost
Sudden Coronary Death	664
Fatal Myocardial Infarction	7 331
Stroke Death	7 169
Angina Pectoris (Uncomplicated)	2 648
Coronary Insufficiency	3 877
Non-Fatal Myocardial Infarction	6 952
Re-Infarction	6 952
Congestive Heart Failure	5 056
Transient Ischaemic Attack	3 133
Stroke	6 745
Angioplasty	8 975
Coronary Artery Bypass Graft Surgery	18 532
Cardiac Catheterisation	4 461
Pacemaker Insertion	15 649
Arrhythmia	3 263
Drug	7500
Post-Hospitalization Costs	
Coronary Heart Disease alone	
First Year	2 938
Subsequent Year	2 719
TIA alone	
First Year	1 436
Subsequent Years	1 396
Stroke Alone	
First Year	6 728
Subsequent Years	10 287
Coronary Heart Disease and TIA	
First Year TIA	2 457
First Year Coronary Heart Disease	2 625
Subsequent Years	2 425
Coronary Heart Disease and Stroke	
First Year Stroke	8 102
First Year Coronary Heart Disease	10 646
Subsequent Years	10 446

TIA: Transient Ischemic Attack

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report,** *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	YES
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	YES
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	YES
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	YES
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	YES – implied.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	YES
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	YES
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	YES
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	YES
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	YES
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	There is only one population

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A.
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Cited + explained.
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	YES, $ Supplement.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Source publications.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Source publications.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	N/A
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	YES
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	YES
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	Figure 1

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Table 2.
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Yes
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Yes.
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Per new journal.

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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