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Title	**Evaluating the cost-effectiveness of Evolocumab in the FOURIER Study: a Canadian analysis**
Authors	Todd C. Lee MD MPH, Mohammed Kaouache PhD, Steven A. Grover
Reviewer 1	Derrick Tam MD
Institution	University of Toronto, Cardiac Surgery, Toronto, Ont.
General comments (author response in bold)	Summary: Lee et al. present a cost-effectiveness analysis of a PCSK-9 inhibitor based on the results of the recently published FOURIER trial and calibration of a previous cardio-metabolic model to forecast long-term outcomes. They found in their base-case analysis that the cost per years of life saved (YOLS) was $299,482, suggesting that this PSK-9 inhibitor would not be cost-effective in the Canadian setting. Impression: The authors here tackle a very important topic in contemporary cardiovascular medicine, that is, the role of novel PSK-9 inhibitors for secondary prevention of CAD. In the setting of the Canadian healthcare system, a serious discussion on cost-effectiveness is warranted prior to widespread adoption of these medications. The senior author (SAG) here has a strong track record in the publication of economic evaluation models in this area. However, there are some limitations that need to be addressed. Introduction 1. This is well written. My only comment is that given contemporary management of CAD and CV disease is quite good, it becomes difficult for these additional novel therapies to improve overall mortality. Perhaps this idea can be strengthened in the introduction. **Thank you. We have added a sentence to address this point.** **"** Given these improvements in care, it has become increasingly challenging for newer therapies to have as large an impact on mortality as seen with previous innovations.**"** Methods 1. Page 6, line 3, “observed in clinical trials”, please provide references for this, as it may confuse readers as to whether you are referring to FOURIER or other clinical trials. **Thank you. This line has been removed to avoid confusion.** 2. Page 6, line 19, “several studies”, please provide references for this. **It was challenging to decide how much detail to include for our model since various versions have been used and published since the late 1990s. In this paper we are using, for the second time, an updated and validated version published in The Lancet Diabetes in 2015. We have sought to balance this, but importantly cite all of the formative work leading to the model so the reader can seek it out if interested.** 3. Page 6, line 26-27, “would be approximate the observed….” This sentence is awkward and unclear. **Sentence has been rewritten to be clearer.** 4. Page 6, line 32-35, please provide a reference for how you’ve addressed uncertainty here and your assumptions for using a normal dist with SD equal to ¼ of the difference between UB and LB. Is this arbitrary? **The distance between the UB and LB of a 95% CI is approximately equal to 4 times the standard error of the estimate**. 5. Page 6, line 43-46, again provide a reference or rationale for this underlying assumption. This is a huge assumption here that fatal events will follow patterns of NF events. Can you provide evidence that this has happened in other lipid trials with longer term followup? **It is indeed an assumption which leads to an improved estimate of cost-effectiveness for the drug. If there is no reduction in mortality, and instead we are only paying for a decrease in small non-fatal cardiac events, it will be nearly impossible for a drug at this price point to be cost effective (in fact, it is estimated at more than 1,000,000/QALY in one of the US papers we cite). We discuss the implications of this in the interpretation. This has been done for all of the cost-effectiveness studies for this drug.** **Early studies of statins did not immediately show a mortality benefit for women; with longer experience this was realized.** 6. Page 6, line 49-50, In this section, please explicitly state the following: model software that was used to create the model, perspective chosen, and time horizon and justification for time-horizon. **The model was developed using the SAS system version 9.3. Patients are followed until they die or the reach the age of 102 in which case we assume they die at the age of 102.**

7. Similar to above, some more details regarding the model should be mentioned – I believe that this is a Markov model, the number of states, transition probabilities assumptions and derivation (if any). Can you provide a figure for the Markov model?

The Markov model consists of three parallel and dependent sub-models for Diabetes, Stroke and Coronary Heart Disease. Within each model a patient can progress from one state to another. The transition probabilities are based on risk equations obtained using the studies such as the Lipid Research Clinics (LRC) , Framingham and the Atherosclerosis Risk in Communities (ARIC) . The three models are dependent. For example, when a patient progresses from No diabetes to Diabetes in the diabetes model, the transition probability from no stroke to stroke will be affected in the stroke model.

We have included a figure for the supplement.

8. Authors present here YOLS, this sounds like life years gained to me, can authors comment if these two terms are interchangeable.

These two terms are frequently used interchangeably. We use years of life saved as that is what we have used in all papers since the 1990s.

9. Page 7, line 17,18. The authors present the market price of evolucumab as $7500, is there a reference or communication reference for this? Does this include mark-ups (i.e. ODB mark up)? Finally, depending on the perspective, authors need to consider physician costs (i.e Ontario schedule of benefits) for the monthly injection (this can be considered in a one-way sensitivity analysis).

This has been cited. We only included drug costs given variation between the provinces in markup and the costs paid by private insurance. We rounded up to $7500 to account for some variances in markup and administration costs.

10. Page 7, 19-21, can authors comment on why a uniform distribution was chosen instead of a gamma distribution which is typically used for costs? Also, why was +/-20% chosen, is this arbitrary or are their specific assumptions for this?

We assumed that the costs could be up to 20% higher or 20% lower because we did not have any information from previous studies about the distribution of these costs.

11. Page 7, 29-30. The authors chose a discount rate of 3%, however, the latest CADTH guidelines recommend 1.5%. Please use 1.5% in the base case and choose a range for one-way sensitivity analyses.

The UK uses a rate of 3.5% and the US 3%. All of the other literature published since FOURIER on PCSK9 cost effectiveness has used 3%. We feel that keeping our main analysis at 3% is more comparable to the remainder of the literature; however, we provide a calculation for 1.5% as well for a sensitivity analysis.

12. Page 7, 33-34, authors should explicitly state that a probabilistic analysis is employed to address uncertainty and address what model is used for this PA.

We are sorry, we are not sure we understand the request.

Results

13. Page 8, 11-14, authors provide the base case results for a population like “FOURIER”, is this point-estimate a weighted average (on gender and age distribution) based on the FOURIER population or a simple average?

Weighted average. Has been clarified.

14. Page 8, 20-27, I do not find the results of the PSA here to be presented in an intuitive manner. While drug price thresholds are provided to estimate 50% CE at certain WTP thresholds, I believe that 50% is a “low bar”, basically, a coin flip. Can authors present a CEAC (WTP vs % of cost-effectiveness) and the ICER plane for their PSA?

We chose 50% because it was a probability intuitively understood by almost any reader – that is, they understand a coin-flip and hence can understand the bar we have set.

15. A set of deterministic one-way SA should be performed for discounting, drug costs and other relevant efficacy or cost inputs.

We performed a sensitivity analysis for discounting rate of 1.5%. In the probabilistic analysis with our cost curves this incorporates the variability of drug costs and built in an uncertainty of +/- 20% around each cost estimate.

Interpretation

16. Overall, the interpretation section is well written and balanced.

	Thank you. 17. Page 8, 38-41, again, 50% chance of being cost-effective is no better than a coin toss, can you provide the threshold drug cost for the point estimate to be 80% chance of being cost-effective as well. **As above, we chose 50% because it was so easy for any reader to understand intuitively. We could have provided 80% but instead provided the graph which a reader could use to infer any probability they wish.** 18. Page 8, 38-41, WTP thresholds of 50-150k have typically been used in Canada, however, these are for $/QALY and not $/LY gained. **Indeed. A ratio per LY gained will always be smaller than a ratio per QALY because the maximum value of a QALY is 1.0, and most QALYs considered are worth less than 1.0. This was confirmed in Kazi's paper to also be true for FOURIER analyses.** 19. Page 9, 43-44, authors describe this as the best case scenario favouring the PCSK-9 inhibitor, authors should add a line that "despite this, evolocumab was shown not to be cost-effective" **Thank you. We added this.** Conclusion 20. This is a well-balanced conclusion. **Thank you** Additional comments 21. Authors should strongly consider applying health utilities to their results to derive $/QALY in their base case scenario. This will allow decision makers to compare the findings from this study to other interventions. Otherwise, there is limited generalizability. **Thank you. As the cost per QALY will necessarily be even higher than the cost per YOLS we believe the current analysis answers the question we sought to pose – "will evolocumab be cost-effective in Canada".** 22. In the interpretation, can the authors briefly discuss other CV secondary preventions that are cost-effective, has this been discussed in statins? **Indeed, Dr. Grover had performed a similar analysis for the statins in 1999. After adjustment for inflation to 2017 dollars this equated to $6522 to $12402 per year of life saved. We have added this to the interpretation along with some context on the differences in availability of generic high-potency statins today. We believe a "mini review" of the other options (fibrates, niacin, ezetimibe, etc.) would be outside the scope of this paper but have also included an estimate from the literature for ezetimibe which is the option included in the Canadian cholesterol guidelines.** 23. Is there any indication that there will be class-effect with other PCSK-9 inhibitors, or should we expect that these results are specific to evolocumab? Otherwise the title should be changed to evolocumab is unlikely to be cost-effective in Canada and results should be interpreted in the context of this specific drug. **One of the drugs was already taken off the market due to inefficacy (neutralizing antibodies); nonetheless we, like industry, believe this will be a class effect. Nonetheless, we have made certain the manuscript is clear that we are analyzing evolocumab only and that we cannot generalize to members of the class for which we currently have insufficient data.**
Reviewer 2	Rajah Rasiah PhD
Institution	University of Malaya, Department of Development Studies, Kuala Lumpur, Malaysia
General comments (author response in bold)	Using a calibrated and validated Cardio-metabolic model and taking account of cardiovascular events and life expectancy, this study attempts to estimate years of life saved (YOLS) with treatment compared to statins alone. The study then estimated the costs of treatment, the average cost per YOLS, and the annual drug costs that would provide a 50% chance of being cost-effective at a willingness to pay of $50,000 and $100,000 respectively. The study looks useful in economic terms, and the results are plausible. However, the authors need to address a number of issues before the paper can be considered noteworthy. 1. There ought to be some qualification of the problems associated with LDL given recent medical evidence suggesting that these claims have been exaggerated. **Indeed, we do address this in our limitations: "There are several important examples of drugs which lower LDL but have not been shown to reduce mortality (citations). Thus, our results likely represent a best-case scenario and, despite this, evolocumab was shown not to be cost-**

	effective." 2. The use of a compound discount rate of 3% requires justification. Is that the rate typically estimated from Canadian historical discount rate data? **This is the standard rate which has been used for most North American analyses up until March 2017 when CADTH recommended 1.5%. It is the rate used in all of the US post-FOURIER studies. We present both rates.** There must also be justification for the willingness to pay thresholds of CD50k and CD100k used. **These are command and standard thresholds involved in such discussions. Industry is trying to advocate for $150,000 per QALY for unsurprising reasons. NICE has suggested that anything more than approximately 30,000 GBP would be unsustainable for their health system to pay for "en masse" despite people accepting WTP of higher for some of these analyses.** 3. The discussion section requires rewriting. It should discuss why this study's data corroborate or differ from other findings. These differences can be accounted for by different treatments, different socio-demographic profile composition of sample observations. Also, the shortcomings of the study should be in the conclusions. **The discussion has been extensively rewritten.** 4. The results of the projections from logistic regressions need to be reported properly - e.g. one will have to see the parameters, coefficients, variables etc. I would have liked to see how the control variables - e.g. socio-demographic - related to the explanatory and dependent variables. Age standardization is also important. **This was standardized to the distribution of patients in FOURIER. Please see our other publications for the details of the model and the supplement.** 5. The conclusions end abruptly. It should provide a proper synthesis, implications for the studies reviewed and for medical practice, and should offer a connect-guide for future research. **We have rewritten the conclusion. Thank you for this comment.** 6. The language requires editing in several places. **We have reread the paper in its entirety and attempted to improve sentence structure and grammar.**
Reviewer 3	Eric Cohen MD
Institution	Sunnybrook Health Science Centre, Division of Cardiology, Toronto, Ont.
General comments (author response in bold)	This is a cost analysis of the potential cost-effectiveness of PCSK9 inhibitors in Canada for patients with established CVD, based on the results of the recent FOURIER trial. The study uses trial outcomes to re-calibrate an existing model that estimates fatal and non-fatal lifetime events. General comments: 1. The high price of PCSK9 inhibitors is well known, and most readers will not find it surprising that they are unlikely to be cost-effective when applied to a broad population with CVD. The authors should be commended for taking a creative approach to deal with the absence of long-term clinical outcome data; however, the fact the results mesh with readers' prior expectations does not exempt the study from potential criticism. The methodology is complex and hard to follow even for someone with modest experience in health economics, let alone a general reader. The use of existing CVD prediction models per se is not overly complicated, but superimposed on these core models are: a) assumptions about the relationship between fatal and non-fatal events; and b) a "re-calibration" of the LDL coefficients in the historical model to produce modelled predictions that match the observed outcomes of the FOURIER trial. This leads to a layering of assumptions that makes it hard to know how valid the findings will be. The basic steps in the analysis appear to be: • observe: FOURIER trial reductions in non-fatal events • re-calibrate LDL coefficients in CV Life Expectancy Model such that the modelled rate for the composite (CV death, MI, stroke) matches the observed in FOURIER • use these re-calibrated coefficients to predict, via the model, and (??) based on the achieved treatment or control LDL values, the lifetime rates of various events under treatment or control, as shown in Table 1 • then calculate associated costs and the resulting ratios **This is correct. Observe FOURIER results. Recalibrate model such that predicted reductions**

in LDL from treatment that were observed lead to predicted reductions in non-fatal events which match that seen in FOURIER. Make assumption that these reductions in non-fatal events would correspond to reductions in fatal events. Use this recalibrated model to provide estimates of years of life saved. Calculate costs and ratios.

2. I have struggled to understand why the following assumption is needed and how it plays out in the analysis (pg 6, lines 39 – 46):
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.

It seems to me the model would have predicted coronary death, stroke death, and other death without the need for this assumption. I may be interpreting this improperly, but I have read it many times over and struggled with it, so this clearly needs better explanation by the authors.

We have clarified in the paragraph. But the crux is as follows: there was no reduction in mortality seen in FOURIER. This could be because PCSK9 inhibitors will lower LDL without effecting mortality in which case they will be even less cost-effective. Or, it could be that we did not have enough follow up time to observe long-term mortality benefits. Hence, we postulated that fatal events would eventually be reduced in a similar proportion to non-fatal events such that we could estimate years of life saved. This is the same hypothesis (that fatal events will eventually decrease) which has been made in each of the major US cost-effectiveness publications in 2017. Kazi (cited in discussion) go further to assume no mortality benefit and demonstrate a cost of nearly 1.7 million per QALY if that proves to be true.

3. A further issue is the uncertainty around non-CV mortality. The original model used separate coefficients to predict coronary, stroke and other death. Based on that model, the re-calibrated LDL coefficients yield an increase in Other Death that exactly offsets the reduction in CV death. The FOURIER trial, having only 2 year follow-up and no reduction in CV death, does not validate or refute this assumption. The fact that the model itself is based on patients recruited and outcomes observed 30 to 40 years ago also raises questions about its continued validity.

That is expected behavior of the model and indeed for life -- everyone eventually dies. If they don't die from CV disease they will die from something else given an infinite timeline.

While the model was originally designed based on 30-40 year old studies, it has continually been updated and validated against published life tables for Americans and Canadians.

4. Finally, I have a concern that very low LDL (ie in the range achieved by PCSK9 inhibition but not achieved by older lipid lowering therapies) was probably rare in the data set that the original model is based on, and when such levels did occur historically, may have been due to other potentially fatal diseases like cancer. Very low LDL achieved by PCSK9 in people free of non-vascular disease could have a very different impact on not only CV but also total mortality. At the very least this remains a substantial and important uncertainty that may impact on the predicted life years saved and thus on cost-effectiveness.

It is an astute observation. Nonetheless, this is not an issue in our model as we do not include any sort of J-point for LDL.

Specific Comments:
5. As noted above, the methodology could be described more fully. For example:
Pg 6, line 53 "Our modeling approach has been described in detail elsewhere (3)." What is described in reference (3) is the model that predicts mortality based on various risk factors, and the potential modification of mortality with risk factor treatment. It does not touch upon the complexities of the current method, specifically the re-calibration of the existing model and the assumptions that may entail. Additional detail on how the coefficients were altered would be helpful, perhaps in the Supplementary Appendix.

6. There are several minor grammatical errors:
a. pg 5, line 32
b. pg 6, line 27
c. pg 6, line 42
d. others not specifically noted

Reread and corrected.