Reviewer’s report

Title: Would treatment decisions about secondary prevention of CVD based on estimated lifetime benefit rather than 10-year risk reduction be cost-effective?

Version: 0 Date: 30 Oct 2019

Reviewer: Michael Power

Reviewer’s report:

This paper addresses an important clinical issue by applying a novel methodology, but I found it hard work to discover what the study was about. My comments are therefore focused on how the cognitive load on the reader could be reduced.

LANGUAGE

There are a few instances where it is obvious that English is not the authors' mother tongue, but I did not find any instance where this would confuse the reader.

Should "REACH-SMART" be "SMART-REACH"?
It is one thing in the paper and the other way around in the references.

Apart from noting that PCSK9-mAbs should be singular when referring to one drug (e.g. Alirocumab), I have not made any copy-editing type of suggestions as this can be done with the next draft.

AIMS

The relevance to patients and clinicians would be clear if benefit to patients were to be identified as an aim. Doing this would have the beneficial side-effect of removing the current ambiguity about the quadrant of the cost-effectiveness plane in which the ICERs lie.

INTRODUCTION

I found this section difficult to understand. In particular I was misled by the focus on primary prevention, and the statement about the aim which does not mention secondary prevention.

I would suggest that this section begin along the following lines (with more detail to be provided by the authors):

The 2016 BMJ paper by Dorresteijn et al (which is cited) summarises a general clinical problem: with chronically progressive diseases the main aim of treatment is often to prolong the disease-free life expectancy, but the potential benefit of treatment is assessed with risk reduction over a fixed period. However, lifetime prediction models that adjust for competing risks provides a more intuitive approach which identifies younger patients who would benefit from treatment they would otherwise be denied and older patients who might not benefit from treatment they would otherwise be offered. Because modelling CVD prevention is complex, we opted to use a simplified model of secondary prevention of CVD with a PCSK9 inhibitor to test the hypothesis that treatment decisions (treatment
with a PCSK9 inhibitor versus no treatment) are both more effective and more cost-effective when based on estimated lifetime benefit than when based on estimated risk reduction over 10 years.

METHODS

Study population
Some readers will want to know what a correlated probability distribution is and why it is needed.

Individual treatment effect estimations
How about: Individualized 10-year risk reduction and life time benefit effects of treatment with a PCSK9 inhibitor versus no treatment were estimated using the SMART-REACH model.

"Scenario analysis" and "Sensitivity analysis"

Replace these two sections with one section for uncertainty analysis
See https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2800325/ section 4.5. Sensitivity Analysis

This section could begin as follows:

Exploration of the effects of uncertainties in the parameters

The dependence of the results on assumptions made for the model's parameters were explored with analyses in which parameters such as drug costs, event probabilities, event costs, treatment effects of PCSK9-mAbs, discount rates, mortality multipliers, and utilities were varied for one-way and multi-way sensitivity analyses. The lower and upper bounds for the sensitivity analyses are shown in Supplemental table 1 for Annual event risks and mortality and in Supplemental table 2 for costs and utilities.

For the multi-way probabilistic sensitivity analysis a Monte Carlo simulation was performed 1000 times with all parameters being varied for each simulated person. For each simulation probabilities, hazard ratios for lowering LDL-c by PCSK9-mAbs, and utilities were randomly chosen from beta distributions. Mortality multipliers and costs were randomly chosen from gamma distributions. Individualized expected effects of PCSK9 inhibition were calculated with the randomly chosen values for the parameters. The probability that risk-based and/or benefit-based treatment for different cut-off values would be cost-effective compared to no treatment with PCSK9-mAbs were displayed graphically for varying thresholds of the willingness to pay (in Euros) per QALY gained.

RESULTS

Readers might want to see the RESULTS section cover: baseline characteristics, benefits, cost-effectiveness, and exploration of uncertainties

Baseline characteristics
This is OK
Benefits (Explicitly identified - should map to the aims and title)

This would refer to Table 2 and note that for each proportion threshold for treating (5%, 10%, and 20%) the groups treated on the basis of lifetime benefit have higher QALYs than those treated on the basis of 10-year risk.

The other measure of benefit (which is one of the drivers for the study) is the identification of younger patients who would benefit from treatment but be excluded on the basis of 10-year risk and older patients who would not benefit from treatment but would be identified on the basis of 10-year risk.

One way of displaying this data would be to have histograms of the numbers for a range of age groups, say 50 or under | 51 - 70 | over 70. The histograms would be displayed in the 4 cells of a 2x2 table. Lifetime benefit would be mapped to the columns, with headings: treated | not treated. 10-year risk would be mapped to the rows with labels: treated | not treated.

Cost-effectiveness (Explicitly identified - should map to the aims and title)

Refer to Table 2 and say that, for each for each proportion threshold for treating (5%, 10%, and 20%) the groups treated on the basis of lifetime benefit have lower ICERs than those treated on the basis of 10-year risk.

There is no need to repeat all the numbers in the text.

Uncertainty analysis

This should replace the sections with headings "Scenario analysis" and "Sensitivity analysis". Delete the sentence "Scenario analyses showed a substantial influence of change in event probabilities, change in annual drug cost, and change in discount."

Then begin with along the lines of "The one-way sensitivity analysis found that therapy becomes less cost-effective if CVD event rates are lower than assumed and more cost-effective if CVD event rates are higher. …

Follow with "The multi-way probability sensitivity analyses found that treatment with PCSK9-therapy is always more expensive than no treatment for all. …

Could you tabulate the results? This would be easier to read and make comparisons.

DISCUSSION

The discussion section should relate to the aims, highlight the clinical importance, discuss the uncertainties due to the model structure (strengths and weaknesses) and warn that the results are from a simplified model so cannot be safely applied to practice, and end with recommendations for future work.

For future work you might want to recommend developing more realistic models for primary and secondary prevention of CVD and for other clinical applications.

The discussion section does not need to repeat data from the results section, and it should avoid terms that are confusing such as "scenario analysis".
CONCLUSIONS
The conclusions should map to the aims, i.e. benefits and cost-effectiveness

TITLE
This should be consistent with the aims and results

How about: Would treatment decisions about secondary prevention of CVD based on CVD-free life expectancy rather than 10-year risk reduction provide clinical benefits and be cost-effective?

Level of interest
Please indicate how interesting you found the manuscript:

An article of importance in its field

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report
including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal