Author’s response to reviews

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

Authors:

Gijs Berkelmans (g.f.n.berkelmans@umcutrecht.nl)

Jacoba Greving (J.P.Greving@umcutrecht.nl)

Yolanda van der Graaf (Y.vanderGraaf@umcutrecht.nl)

Frank Visseren (f.l.j.visseren@umcutrecht.nl)

Jannick Dorresteijn (J.A.N.Dorresteijn-3@umcutrecht.nl)

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Author’s response to reviews:

Dear reviewers and editor,

We would like to thank you for the extensive work and comments that improved the manuscript. Please also find the point-by-point response added in the supplementary files of the manuscript (since tables and figures added will not be displayed in this online respond box)

Reviewer #1: 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 focussed 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.

Response: It is true that the reference state SMART-REACH (from both cohorts of derivation/validation of the model). We changed this in the manuscript.

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.

Response: We thank the reviewer for noticing and changed this in the manuscript

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.
Response: Thank you for this remark. We changed the aim of the paper to “To test the hypothesis that treatment decisions (treatment with a PCSK9-mAbs 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” as suggested by the reviewer in one of the comments below.

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.

Response: We would like to thank the reviewer for this comment. In the manuscript, the introduction has been rewritten based on the reviewers suggestions. This should clarify the aim of the study in a secondary prevention study population.

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

Response: Thank you for this remark. In the revised manuscript we clarified this by adding (page 5, line 7-11): “A correlated probability distributions allows to randomly sample variables for a hypothetical population from a distribution, taking into account the correlation between the different variables. A simplified example: if the variable systolic blood pressure is randomly chosen to be 180 mmHg, a patient is more likely to be older because blood pressure and age are correlated variables (the distribution of which a random age will be drawn, will have a higher mean).”

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.

Response: We changed this sentence to start this section (page 5 line 23) to “Individualized 10-year risk reduction and life time benefit treatment effects of treatment with a PCSK9-mAbs 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.

Response: Thank you for these suggestions. We replaced the sections scenario analyses and sensitivity analyses as proposed by the reviewer.

RESULTS

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

Response: Thank you for these suggestions. We changed the results section and used the mentioned headings by the reviewer as section headings.

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.

Response: We agree with the reviewer and changed this section of the revised manuscript to (page 11, line 18-20): “Compared to standard of care, the QALYs gained were higher for each proportion threshold for treating (5%, 10%, and 20%) the groups with PCSK9-mAbs treated on the basis of the lifetime benefit than those on the basis of 10-year risk (table 2).”

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.

Response: Based on the reviewers comment, we have added a new figure (figure 3) which represents the proposed 2x2 table for different age categories added to the point by point response. It does show that the lifetime benefit approach identifies younger patients with higher benefits compared to the 10-year risk based approach. We added “Also, a higher number of younger patients were identified as treatment candidates on the basis of lifetime benefit than on the basis of 10-year risk (figure ).” to the section benefits in the results of the manuscript.
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.

Response: Agree. We changed this in the manuscript to (page 12, line 1-3): “Treatment decisions (treatment with a PCSK9-mAb versus no treatment) 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 (table 2).”

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. …
Response: We changed the manuscript accordingly to the suggestions of the reviewer

Could you tabulate the results? This would be easier to read and make comparisons.
Response: Good point. We added table 4 with the results to make the comparison of the both strategies easier.

Table 4. Percentage of multi-way probability sensitivity analyses that are cost-effective for a willingness to pay €50,000 per QALY and the lower bound of willingness per QALY in euros for which 50% of the multi-way probability analyses are cost-effective.

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".
Response: In the discussion, we removed the data from the results section, we changed scenario analyses into uncertainty analyses. In the limitations section we discuss the model structure and following we added recommendations for future work: “For future work we would recommend developing more realistic models for primary and secondary prevention of CVD and for other clinical applications that take into account competing risks and enable lifetime estimations of individual risk and benefit of preventive treatment.”

CONCLUSIONS
The conclusions should map to the aims, i.e. benefits and cost-effectiveness
Response: We changed the conclusion to: “Treatment decisions (treatment with a PCSK9-mAb 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.”

**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? Response: We agree with the reviewer and changed the title accordingly.

Reviewer #2: I commend the authors on their work, given paucity of studies focusing on patient-related and economic consequences of alternative risk assessment approaches to inform treatment decisions. Overall, I felt the level of detail provided is sufficient and discussion is well-balanced. However, would like to suggest the authors consider discussing a possible role of the model chosen to estimate 10-year risk-based treatment strategy (the REACH-SMART), in the obtained results, and whether it is likely that using a different model would have led to the different conclusions. Response: We thank the reviewer for this remark and added a paragraph on this topic in the discussion. “Also the use of other 10-year risk models could change the results of this study. However, it seems unlikely that this would lead to a different conclusion. Unlike most other 10-year risk models, the SMART-REACH model takes competing risks into account, preventing overestimation of risk and treatment effect in older patients. Thus, using different 10-year risk models without adjustment for competing risk would probably lead to higher misclassification of older individuals as treatment candidates and, therefore, result in even higher benefit of using a lifetime prediction model.”

Reviewer #3: Please use and add a checklist of appropriate reporting guidelines (e.g. CHEERS). Response: Thank you for this suggestion. We have now added the CHEERS reporting guideline to the submission.

Treatment rates seem low (max. 20%). What percentage of this population is currently receiving treatment in clinical practice? Response: In 2018 a total of ~12.000 patients used PCSK9 inhibition in the Netherlands. The Dutch Heart Foundation estimates a total number of patients with cardiovascular disease of 1,500,000. This would mean that the estimated therapy percentage of treatment is 12.000/1,500,000 *100% = 0.8%. This may seem like a very low estimate, however, due to high costs of treatment, strict reimbursement rules apply and the percentage of patients treated is currently even lower in most other Western countries. Of course, PCSK9 inhibitors were only recently introduced. The percentage of patients treated is likely to grow in the next decade, stressing the need to evaluate tools that help to identify individuals that are most likely to benefit.

You assume good adherence to therapy, whereas 50% reports to stop taking medication after a year. Response: This is the assumption we use since it is unclear what the adherence for PCSK9 inhibition is. However, between the two strategies to identify patients that would benefit from treatment, the adherence rate will probably be similar and therefore, it would make no difference in the difference of effects of treatment between the two decision strategies (10-year risk or lifetime benefit based selection of patients). To clarify this in the manuscript we added to the limitations (page 16, line 2-5): “Also, in this study, the assumption was made that there is a 100% adherence to therapy. In clinical practise this is not true. However, between the two strategies to identify patients that would benefit from treatment,
the adherence rate will probably be similar and therefore, it would not change the difference of effects of treatment between the two decision strategies”

“To estimate individual treatment effects of PCSK9-mAbs on recurrent CVD in this study, a coefficient based on the relative risk reduction of trials or meta-analyses was added to the model.” Please explain how this was done. Which RR was used? Do you mean HR? Was this obtained from trials or from meta-analyses? How was this transformed into a coefficient for the model? Do lines 35-56 p 4 describe how this coefficient was obtained? Perhaps consider moving the end of the previous paragraph ( The number of CVD-free life-years gained…) to a new paragraph at the end of section “individual treatment effect estimations” ).

Response: The individual treatment effects of PCSK9-mAbs were indeed described between lines 35 and 56 on page 4. Good suggestion by the reviewer to move the previous paragraph (the number of CVD-free life-years gained) to the end of the section.

Different abbreviations for MACE are used in text and figures.
Response: Thank you for bringing this to our attention. We changed the MCVE in figure 1 to MACE.

Please explain what is meant by discount rates.
Response: In the revised manuscript we have added the following in a new section about discount rates (page9, line 6): “Often, the costs and benefits considered in a health economic evaluation are not only incurred in the current year, but materialize beyond the present. For the valuation of costs and benefits in the context of an economic evaluation, their timing is relevant because people generally value future costs and effects less than current costs and effects and their value diminishes the more distant in the future they occur. Hence, economic evaluations need to adjust the value of costs and benefits for the time at which they occur, a technique known as discounting. For the Netherlands, a standard discount rate of 4% for costs and 1.5% for health outcomes were applied”

Please define standard of care (p 8).
Response: We changed this sentence to “Compared to treat no one,”

Please check/explain numbers in table 2. (153997681-111727411)/(67057-65897) ≠ 37200

Response: The ICERs were obtained by the multi-way sensitivity analyses (monte-carlo simulations). To make this more clear we have changed the QALYs in table 2 to the QALYs that are the results of our microsimulation instead of the sensitivity analyses.