PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The polypill in the primary prevention of cardiovascular disease: costeffectiveness in the Dutch population
AUTHORS	Paul F. van Gils, Eelco A.B. Over, Heleen H. Hamberg-van Reenen, G. Ardine de Wit, Matthijs van den Berg, Albertine J. Schuit, en Peter M. Engelfriet

VERSION 1 - REVIEW

REVIEWER	Oscar H. Franco Clinical Lecturer University of Cambridge
REVIEW RETURNED	03/10/2011

THE STUDY	The methods should be described in more detail (perhaps with an appendix). Significant omissions include: The polypill: at what price would it become cost effective? Franco OH, Steyerberg EW, de Laet C. J Epidemiol Community Health. 2006 Mar;60(3):213-7)
RESULTS & CONCLUSIONS	Significant omissions include: The polypill: at what price would it become cost effective? Franco OH, Steyerberg EW, de Laet C. J Epidemiol Community Health. 2006 Mar;60(3):213-7)
GENERAL COMMENTS	Overall this is a well presented and relevant manuscript. van Gils et al aimed to model the cost-effectiveness of opportunistic screening and treatment with the polypill (a combination drug) in the Dutch population. The authors found that “all scenarios –evaluated- were cost-effective with an incremental cost-effectiveness ratio between €8,700-12,000 per QALY compared with usual care. Most health gains were achieved with the polypill without aspirin and containing a double dose of statins. With a 10-year risk of 7.5% as threshold, this pill would prevent approximately 3.5% of all cardiovascular events.” The authors conclude: “Opportunistic screening based on global cardiovascular risk assessment followed by polypill prescription to those with increased risk offers a cost-effective strategy.” General Comments: 1. Overall the methods used are not described in detail and their specifics remain unclear. Perhaps providing a detailed appendix could facilitate the understanding of the model. 2. No distinctions in the analyses are made by gender or age of the population. Please discuss. Any differences observed in the cost-effectiveness of the scenarios by gender or other population subgroups?

	3. Some parameters in the calculation of effects remain unclear (beyond what I mentioned in point 1), for example time horizon of effect and benefit and the need (or not) of considering discounting. Please clarify. 4. Adverse effects should always be considered when measuring the effects and cost-effectiveness of an intervention. It's my opinion that these should be included in the main analyses. 5. Please clarify how previous/current exposure to particular items within the polypill and interactions were considered. 6. In the discussion section please discuss further the potential limitations of this study and how your findings compare to previous studies. 7. It is rather surprising that the authors have ignored previous attempts to estimate the cost-effectiveness of the polypill (e.g. The polypill: at what price would it become cost effective? Franco OH, Steyerberg EW, de Laet C. J Epidemiol Community Health. 2006 Mar;60(3):213-7). Please discuss 1) the need of the current analyses and 2) your methods and findings in view of the previous efforts at the discussion (and introduction)

REVIEWER	Elsayed Z Soliman MD, MSc, MS Director, Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston Salem, NC, USA
REVIEW RETURNED	10/10/2011

THE STUDY	Neglecting the cost of side effects in this cost-effectiveness is a major limitation that affects credibility of the conclusions. This cost-effectiveness analysis is based on the Danish healthcare system which is not necessarily similar to other systems in which the polypill could be applied (i.e. generalizabilty issue).
RESULTS & CONCLUSIONS	As known, there are no data yet on the effect of the Polypill on cardiovascular events or hard outcomes (which is acknowledged by the coauthors). Subsequently, any cost-effectiveness analysis would be just a hypothetical discussion that lacks credibility- which is the case in this manuscript. Neglecting the cost of side effects in this cost-effectiveness is another factor that affects credibility of the results.
GENERAL COMMENTS	The manuscript is nicely written and easy to follow. However, because of reasons beyond the coauthors (lack of data on the impact of the polypill on CVD events) the manuscript does not provide any credible information that could inform the policymakers or physicians. Using the available data on intermediate endpoints such as reduction in blood pressure and cholesterol, and trying to indirectly calculate the expected effect on prevention of cardiovascular cannot be an alternative for hard outcomes. Given the ongoing trials that should soon provide data on events, any speculations about the impact of the polypill on events and subsequently its cost-effectiveness seem unnecessary at this stage.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: Oscar H. Franco, Clinical Lecturer, University of Cambridge

The methods should be described in more detail (perhaps with an appendix).

REPLY/comment
As this points is raised again below, we refer to our answer to Comment 1

Overall this is a well presented and relevant manuscript. van Gils et al aimed to model the cost-effectiveness of opportunistic screening and treatment with the polypill (a combination drug) in the Dutch population. The authors found that “all scenarios –evaluated- were cost-effective with an incremental cost-effectiveness ratio between €8,700-12,000 per QALY compared with usual care. Most health gains were achieved with the polypill without aspirin and containing a double dose of statins. With a 10-year risk of 7.5% as threshold, this pill would prevent approximately 3.5% of all cardiovascular events.” The authors conclude: “Opportunistic screening based on global cardiovascular risk assessment followed by polypill prescription to those with increased risk offers a cost-effective strategy.”

General Comments:

1. Overall the methods used are not described in detail and their specifics remain unclear. Perhaps providing a detailed appendix could facilitate the understanding of the model.

REPLY/comment
We appreciate the reviewer’s criticism regarding the lack of detail. Our concern in composing this article was that we had to find a balance between overwhelming the reader with too much detail and maintaining readability. Thus, we decided to move some of the dense and detailed parts of the methods section to the appendix; for a description of the chronic diseases model itself, we referred the reader to a number of articles. Now, at the request of the editor, we have included a full description of the model in the main text, and we have also supplemented this with a few items that were missing in our original text, in particular regarding discounting and the time horizon. However, we still believe that a full description of the CDM, in particular its mathematical structure, would take up too much space and would detract those who are not very familiar with modeling. We invited readers interested in the technical details to consult the references we provided,and/or to contact us for sharing data (see the statement added at the end of the document). We offer full access to both the data used and the computer code.

2. No distinctions in the analyses are made by gender or age of the population. Please discuss. Any differences observed in the cost-effectiveness of the scenarios by gender or other population subgroups?

REPLY/comment
The main reason why we did not make a distinction by gender and age is that we conceived of the intervention as a population intervention in which individuals were eligible on the basis of a risk score that includes age and sex as variables. Thus, it seemed inconsistent to us to subdivide the population into groups a priori according to these variables. Therefore we only tabulated the percentages of eligible persons according to age and sex a posteriori (Table 3). However, we agree that information on cost-effectiveness specified according to age- and sex may be useful. Therefore we have prepared additional tables which are displayed below. However, we have not included them in the text for the

sake of readability. But we have added the following sentences to the results section:
[We also performed analyses with distinctions by gender and age (not tabulated). For all scenarios the costs per QALY were higher for women than for men in all age-categories, but remained far below the threshold of €20,000]

Outcomes Polypill Scenario 2A Polypill Scenario 2B Polypill Scenario 2C Separate medication Scenario 3
Sex\Age 40-49 50-59 60-69 70-75 40-49 50-59 60-69 70-75 40-49 50-59 60-69 70-75 40-49 50-59 60-69 70-75
Cost of intervention (*106 €) Men 13 198 307 100 13 191 297 97 11 196 314 103 7 55 108 45
Women 0 8 160 131 0 8 155 126 0 6 158 134 0 6 50 48
Incremental healthcare costs (*106 €) Men 5 127 484 280 4 103 425 250 4 116 472 288 4 44 161 125
Women 0 18 325 472 0 16 281 419 0 15 334 501 0 13 156 216
Total incremental costs (*106 €) Men 22 372 864 404 17 294 721 347 16 312 786 390 11 99 269 169
Women 0 26 486 603 0 23 436 545 0 22 492 635 0 19 206 264
Life years gained (*103) Men 3.0 48.1 117.5 44.3 2.6 43.5 109.7 41.6 2.7 52.2 130.6 50.0 2.4 21.9 48.5 21.5
Women 0 3.6 46.5 50.5 0 3.3 42.8 47.1 0 3.2 51.9 57.9 0 2.7 24.8 25.4
QALYs gained (*103) Men 3.2 47.5 104.0 35.4 2.8 43.1 97.3 33.5 2.9 52.6 118.1 40.8 2.5 22.6 44.9 17.5
Women 0 2.9 35.0 35.1 0 2.7 32.0 32.6 0 2.6 39.0 40.3 0 2.2 18.7 17.8
ICER (*103 €/LY) Men 7.3 7.7 7.4 9.1 6.4 6.8 6.6 8.3 5.7 6.0 6.0 7.8 4.4 4.5 5.6 7.9
Women NA 7.2 10.4 11.9 NA 7.0 10.2 11.6 NA 6.7 9.5 11.0 NA 7.0 8.3 10.4
ICER (*103 €/QALY) Men 6.9 7.8 8.3 11.4 6.0 6.8 7.4 10.3 5.3 5.9 6.7 9.6 4.2 4.4 6.0 9.6
Women NA 8.9 13.9 17.2 NA 8.7 13.7 16.7 NA 8.4 12.6 15.8 NA 8.7 11.0 14.8

3. Some parameters in the calculation of effects remain unclear (beyond what I mentioned in point 1), for example time horizon of effect and benefit and the need (or not) of considering discounting. Please clarify.

REPLY/comment
Indeed, we should have addressed the issues of discounting and time horizon more explicitly. We have added the following sentences to the Methods and Results sections: [Taken into account time preferences, future costs and effects were discounted according to the Dutch guideline, with a discount rate of 4% for costs and 1.5% for effects. The chosen time horizon was a life-time horizon.]

4. Adverse effects should always be considered when measuring the effects and cost-effectiveness of an intervention. It's my opinion that these should be included in the main analyses.

REPLY/comment
We certainly agree with the reviewer that adverse effects should always be considered. We would like to point out that we did, indeed, consider adverse effects. In the case of statins and antihypertensives, as we explain in the Methods section, these are generally mild and the main influence on cost-effectiveness is the loss of efficacy due to people discontinuing taking the drug. We assumed that this effect was included in the percentages for "drop out" and non adherence during the first years which we used. More serious are the adverse effects of aspirin. In particular, aspirin may cause haemorrhagic stroke. In fact, according to the Cochrane review we used for our effect estimates, the reduction in ischemic stroke due to aspirin use is more or less annulled by an increase in hemorrhagic stroke. The result is that the net effect is zero, or, in other words, that the relative risk for stroke

equals one, which is the value we have used. Hence, indirectly we have taken this into account. We had not, however, taken into account the other major adverse effect of aspirin, namely gastro-intestinal haemorrhages. These occur at a rate of about 8.5 per year per 1000 patients [Berger et al., 2006 JAMA]. Obviously, these increase costs and have a negative impact on quality of life. According to the tariffs in the Netherlands (as determined nationally by NZa [www.nza.nl]) the costs of gastrointestinal bleedings would amount to €3425 per case. Pignone et al.., 2007 estimated the loss of utility to be 0.06. We have now incorporated these costs and effects(disutilities) of the use of aspirin in the analyses.

5. Please clarify how previous/current exposure to particular items within the polypill and interactions were considered.

REPLY/comment
We assumed that the polypill was only prescribed to individuals who not already taking one of the drugs included in the polypill, in other words, to unexposed individuals. We have explained this more explicitly in the Methods section, which now reads [In other words, the polypill was prescribed only to unexposed individuals who did not already use one of the drugs included in the polypill]

6. In the discussion section please discuss further the potential limitations of this study and how your findings compare to previous studies.

REPLY/comment
See below

7. It is rather surprising that the authors have ignored previous attempts to estimate the cost-effectiveness of the polypill (e.g. The polypill: at what price would it become cost effective? Franco OH, Steyerberg EW, de Laet C. J Epidemiol Community Health. 2006 Mar;60(3):213-7). Please discuss 1) the need of the current analyses and 2) your methods and findings in view of the previous efforts at the discussion (and introduction)

REPLY/comment
Thank you for drawing our attention to the study by Franco et al., which we now discuss in the Discussion. In fact, we feel embarrassed that we missed this very relevant study in our literature search.
The major change since that 2006 study is that in the mean time the results of the polycap study have become available. We added the following passage to the text in the Discussion-section:.[Soon, the question of cost-effectiveness was raised. Thus, Franco and colleagues developed a model to estimate the maximum price the polypill could have to be cost effective in the primary prevention of cardiovascular disease. As input, they used the hypothetical effectiveness estimates from Wald and Law's article, and applied them to a population with the characteristics of the Framingham and Framingham offspring study cohort. This population was classified into three classes according to 10 year coronary heart disease risk using a risk score (the Anderson equation). Costs were calculated on the basis of unit costs valid for the healthcare system in the Netherlands. The calculations showed that the pill would be cost-effective (less than €20,000 per life year saved) as long as the yearly costs of the pill would be below approximately €300 in high risk groups and €100 in intermediate risk groups (10% - 20% risk). Indeed, with the yearly costs of the polypill we assumed in our study, which were far below this threshold, we found all scenarios to be cost effective. This was despite the fact that the effectiveness estimates we used were much lower than those of Wald and Law's.]

Reviewer: Elsayed Z Soliman MD, MSc, MS, Director, Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine

Neglecting the cost of side effects in this cost-effectiveness is a major limitation that affects credibility of the conclusions.

REPLY/comment
We certainly agree with the reviewer that adverse effects should always be considered. We would like to point out that we did, indeed, consider adverse effects. In the case of statins and antihypertensives, as we explain in the Methods section, these are generally mild and the main influence on cost-effectiveness is the loss of efficacy due to people discontinuing taking the drug. We assumed that this effect was included in the percentages for "drop out" and non adherence during the first years which we used. More serious are the adverse effects of aspirin. In particular, aspirin may cause haemorrhagic stroke. In fact, according to the Cochrane review we used for our effect estimates, the reduction in ischemic stroke due to aspirin use is more or less annulled by an increase in hemorrhagic stroke. The result is that the net effect is zero, or, in other words, that the relative risk for stroke equals one, which is the value we have used. Hence, indirectly we have taken this into account. We had not, however, taken into account the other major adverse effect of aspirin, namely gastro-intestinal haemorrhages. These occur at a rate of about 8.5 per year per 1000 patients [Berger et al., 2006 JAMA]. Obviously, these increase costs and have a negative impact on quality of life. According to the tariffs in the Netherlands (as determined nationally by NZa [www.nza.nl]) the costs of gastrointestinal bleedings would amount to €3425 per case. Pignone et al.., 2007 estimated the loss of utility to be 0.06. We have now incorporated these costs and effects(disutilities) of the use of aspirin in the analyses.

This cost-effectiveness analysis is based on the Danish healthcare system which is not necessarily similar to other systems in which the polypill could be applied (i.e. generalizabilty issue).

REPLY/comment
We certainly agree with the reviewer that the results of this cost-effectiveness depend on the particular health care system, in this case the Dutch healthcare system (and not the Danish). More than might be the case in hospital care, initiatives in primary prevention are shaped by context and local/national circumstances. That is why we have been careful to clearly specify the assumptions of our study. Unfortunately, results in health economic analyses are less easily generalizable than purely clinical studies.

As known, there are no data yet on the effect of the Polypill on cardiovascular events or hard outcomes (which is acknowledged by the coauthors). Subsequently, any cost-effectiveness analysis would be just a hypothetical discussion that lacks credibility- which is the case in this manuscript. Neglecting the cost of side effects in this cost-effectiveness is another factor that affects credibility of the results.

REPLY/comment
As we emphasized at several places in the text, we certainly agree that hard outcomes are the golden standard that, when available, should obviously decide whether an intervention is to be recommended. However, it will take many years before enough results will be available for the polypill. In the mean time, we have the results of the Polycap study, which is already a major step forward compared to the purely hypothetical paper by Wald and Law. It is exactly in circumstances of incomplete or preliminary data that modeling can be useful and may provide additional insights given the current state of knowledge.

The manuscript is nicely written and easy to follow. However, because of reasons beyond the coauthors (lack of data on the impact of the polypill on CVD events) the manuscript does not provide any credible information that could inform the policymakers or physicians. Using the available data on intermediate endpoints such as reduction in blood pressure and cholesterol, and trying to indirectly calculate the expected effect on prevention of cardiovascular cannot be an alternative for hard outcomes. Given the ongoing trials that should soon provide data on events, any speculations about the impact of the polypill on events and subsequently its cost-effectiveness seem unnecessary at this stage.

REPLY/comment
We appreciate the reviewer's opinion regarding the usefulness (or lack thereof) of modeling studies, but we do not agree on this point. We believe that modeling can be especially informative in circumstances when there is some, but as yet incomplete, information. In this case, we have the results on intermediate end points, but it will take many more years before the effects of hard endpoints will be available.

VERSION 2 – REVIEW

REVIEWER	Oscar H. Franco Clinical Lecturer University of Cambridge
REVIEW RETURNED	17/11/2011

GENERAL COMMENTS	The authors have address all my previous comments