Reviewer's report

Title: A Polypill for primary prevention of cardiovascular disease: A feasibility study of the World Health Organization

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Reviewer: David Wald

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This paper describes a randomised trial of a Polypill (a single tablet designed to lower serum cholesterol, blood pressure and prevent platelet aggregation).

The trial compares the effect of the Polypill with standard treatment on risk factor reduction among individuals selected on the basis of having a 10 year risk of a CVD event of 20% or greater. The trial showed no difference in risk factor levels or estimated 10 year CVD risk between Polypill and standard care groups at the end of follow up.

My comments on the paper are given using the headings suggested with one minor modification.

Major Compulsory Revisions
1. The trial is uninformative on risk factor reduction because the comparison group (standard treatment) also received unspecified cholesterol and blood pressure lowering treatment. The individual treatments and doses used in the standard care arm are not reported and without this there is no basis on which the reader can see what the expected difference in cholesterol and blood pressure would be. The information in Table 2 (giving the proportion of patients in each arm receiving statins or antihypertensive treatment) is both unclear and insufficient. Details of the specific drugs and doses in the standard treatment and Polypill arms of the trial should be given.

Other essential Revisions
2. The authors regard the fact that the standard treatment group received drug treatment as unexpected. Few readers will regard this as unexpected, since individuals were selected according to having a 10 year CVD risk of 20% or greater, in whom drug treatment is recommended and generally offered to reduce cholesterol and blood pressure. Given that there is uncertainty any expected difference in risk factors reductions between the two arms it is questionable whether the primary objective of the study could ever have been achieved. Discussion on this is needed.

3. The Polypill concept, proposed by Wald and Law, is to offer the Polypill to individuals not on the basis of risk factor measurements but to everyone over a given age regardless of risk factor measurements. A comparison of standard treatment in all with a CVD risk of 20% or greater versus Polypill for all 50 years
of age and older (for example) would have been a better design that may have shown a difference in risk factor levels and provided useful information on acceptability. A discussion on this is needed.

4. The choice of a Polypill, which includes aspirin for use in primary prevention needs explanation. Aspirin is not generally used in primary prevention because of concern that the risks of life-threatening bleeding outweigh the benefits in people who have not had an ischaemic vascular event.

5. The adherence to treatment in each arm is not reported. How do the authors know that treatment was taken? Results on this should be given.

6. The side-effects reported in each arm are not reported. These should be given on a symptom by symptom basis indicating which symptoms led to treatment being discontinued.

7. The authors conclude that doctors were "skeptical about not to monitor CVD risk factors (as suggested by Wald and Law)" (page 9). Based on what is reported in this paper, it seems that the authors may have misquoted Wald and Law's recommendation on risk factor measurement. Wald and Law proposed that risk factor measurement should not be used to select individuals for treatment because the risk factor levels add little discrimination to age in predicting who will and will not suffer a future CVD event. This is not the same as "agreeing with Wald and Law on lack of need to monitor CVD risk factors" as stated in table 4, which could relate to the measurement of risk factors after treatment has started to assess an individual's response to treatment. Clarification on what question was asked and, indeed, whether the question was raised in the Wald and Law paper is needed.

8. The table describing the results of the questionnaire is not very informative. More detail is needed on the questions asked, the answers and the scoring system.

9. In the Introduction, the authors state that the TIPS trial suggested that the overall benefit of the Polypill might be less than that predicted by Wald and Law (60% versus 80% risk reduction). The difference between the TIPS trial estimates and the Wald &Law predictions can be explained by the lower dose of simvastatin used in the TIPS trial (20mg rather than 40mg) together with non-adherence to treatment, as correspondence in the Lancet, following publication of the TIPS trial explained (The Lancet, Volume 374, Issue 9692, Page 781, 5 September 2009). This should be stated and referred to.

10. In the Abstract "Patients were recruited according to the pre-specified schedule". This needs to be clarified?

Discretionary Revisions

There is no information on cost and resource use in each arm. One of the potential advantages the Polypill approach is simplicity and a reduced requirement for add-on treatment. Even though this trial design does not adopt the Polypill approach, there may have been differences in the extent to which...
resources were used, clinic visits, clinical staff time, and the costs of treatment. Some comments on cost would be helpful.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I am part of a group developing a Polypill, for which there is a patent granted in the EU and Canada and pending in the USA.