EVIDENCE BASED PUBLIC HEALTH POLICY AND PRACTICE

The polypill: at what price would it become cost effective?

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Introduction: A promising concept in cardiovascular disease prevention (the polypill) was introduced in 2003. Although the polypill may seem as an effective intervention, data on its costs and cost effectiveness remain unknown. The aim of this study was to determine the maximum price of the polypill for it to be a cost effective alternative in the primary prevention of cardiovascular disease.

Methods: Data on the hypothetical effects of the polypill were taken from the literature. Using data from the Framingham heart study and the Framingham offspring study, life tables were built to model the assumed benefits of the polypill. Using a third party payer perspective and a 10 years time horizon, the authors calculated what should be the maximum drug cost of the polypill for it to be cost effective (using a €20 000/year of life saved threshold) in the primary prevention of cardiovascular disease among populations at different levels of absolute risk of coronary heart disease and age.

Results: To be cost effective among populations at levels of 10 year coronary heart disease risk over 20% (high risk), the annual cost of medication for the polypill therapy should be no more than €302 or €410 for men at age 50 and 60 years respectively. For cost effective prevention in populations at levels of coronary heart disease risk between 10% and 20% the costs should be two to three times lower.

Conclusion: Although the polypill could theoretically be a highly effective intervention, the costs of the medication could be its caveat for implementation in the primary prevention of cardiovascular disease.

Cardiovascular disease (CVD) risk management is a combination of interventions oriented to a positive modification of different risk factors.^{1,2} Under the principle that a large preventive effect of CVD would require intervention in everyone at increased risk irrespective of their risk factors levels, modifying several modifiable risk factors together; and reducing these risk factors by as much as possible, in 2003 Wald and Law proposed the polypill concept.³ The polypill is a theoretical combination of six pharmacological compounds that combined and through concomitant modification of four different risk factors for CVD (cholesterol modification with statins, blood pressure lowering with three different antihypertensives, antiplatelet aggregation with aspirin, and reduction of hyperhomocysteinaemia with folic acid) will reduce CVD by more than 80%.³ "No other preventive method would have so great an impact on public health in the Western world" affirmed Wald and Law. However, not being on the market, untested, and with a production yet to be started (to our knowledge), the future cost of the polypill is unknown and its potential cost effectiveness a subject of debate.⁴

Pharmacological prevention of CVD among populations free of the disease should be inexpensive and have considerable effect to ensure a proper balance between costs and effects (cost effectiveness).⁵ As future implementation of polypill would target large sections of the world population, the cost of the medication is a relevant issue if we do not want to exhaust the global health budget in a single effort.

The objective of this study is to estimate the maximum cost of medication and treatment with the polypill for it to be cost effective among adult male populations free of CVD. We considered different levels of 10 year absolute risk of coronary heart disease (CHD) and different ages, to calculate the effects of the polypill in terms of years of life saved (YLS) and CVD events prevented.

METHODS

Data sources

We used data from the Framingham heart study (FHS) and the Framingham offspring study (FOS). The FHS cohort

consisted of 5209 respondents aged 28 to 62 years residing in Framingham, Massachusetts, between 1948 and 1951. Participants have been followed up in periods of two years for a total of more than 48 years of follow up. The FOS cohort is conformed by 5214 participants (the offspring and their spouses of the original FHS) aged 5 to 70 years at baseline and sampled in 1971. Examination of this cohort has taken place at intervals of four to eight years. As the study design and measurement instruments used in the original and offspring cohort are similar, we pooled both datasets. Detailed descriptions of the FHS and the FOS can be found elsewhere.^{6,7} To obtain recent estimates for 10 year CVD and mortality we used follow up from 1968 onward. We used therefore data from participants that attended examinations 11 (calendar years 1968–71), 15 (1977–79), and 20 (1987–1989) of the FHS and examinations 1 (1971–75) and 2 (1979–82) from FOS. Follow up started at the date of the chosen baseline examination. The same participant could therefore be included more than once but for different follow up periods.⁸ Each subject contributed person time from the baseline examination to the date of CHD or stroke diagnosis, death from any cause, lost to follow up, or the following examination, whichever occurred first and dependent on the selected transition (healthy to non-fatal CHD, fatal primary CHD, secondary fatal CHD, stroke and death). In total there were 3742 male participants available for analysis.

Baseline assessment

At baseline participants were classified by level of absolute risk of CHD based on the Anderson formula⁹ and by age group. For the calculation of risk, the Anderson formula includes: age, sex, systolic blood pressure, smoking status, diabetes, the ratio of total cholesterol/HDL cholesterol, and left ventricular hypertrophy (presence on electrocardiogram). The ratio total cholesterol/HDL cholesterol was missing for 812 participants and was imputed based on the other

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; YLS, years of life saved; FHS, Framingham heart study; FOS, Framingham offspring study; CER, cost effective ratio

Table 1 Effects of 10 years' intervention with the polypill in the primary prevention of cardiovascular disease*

Ten years' treatment	Total population†		Moderate risk‡		High risk§	
	Age 50	Age 60	Age 50	Age 60	Age 50	Age 60
Undiscounted YLS	50	215	80	120	152	200
Discounted (by 4%) YLS	34	167	60	100	117	154
Total CHD (fatal and non-fatal) events prevented	76	129	90	85	167	179
Total stroke (fatal and non-fatal) events prevented	11	34	15	33	24	31

YLS, years of life saved; CHD, coronary heart disease. *Effects presented by 1000 participants treated with the polypill. †Includes populations at low, moderate, and high 10 year risk of CHD. ‡Moderate risk refers to a 10 year risk of CHD between 10% and <20%. §High risk refers to a 10 year risk of CHD ≥ 20%.

variables of the formula. Enough data on the variables required for the calculation of risk were available in 3332 participants. Subjects were categorised into three groups based on their level of 10 year absolute risk of CHD: low risk <10% (2396 participants), moderate-risk 10% to <20% (714 participants), and high risk ≥ 20% (222 participants).¹⁰ Participants were categorised in two groups: 45 to 54 and 55 to 65 years of age.

Efficacy of the polypill

The effects of the polypill on CVD prevention were taken from the paper published by Wald and Law.³ To translate the effect of the polypill reduction on CHD and stroke in terms of YLS we created multistate life tables starting at age 50 years and closing at age 100 years, and using a 10 year time horizon. Effects occurred after 10 years were not taken into consideration.

We used the FHS and FOS data to estimate transition rates from healthy to non-fatal CHD, fatal primary CHD, secondary fatal CHD, stroke and death, using Poisson regression with a Gompertz distribution for the total population and for each risk category separately. With these rates, and the assumed reduction attributable to treatment, we estimated the life years saved in the 10 year period of treatment.

Costs

Costs were calculated for the Netherlands and included direct medical costs taken from the literature, the world wide web, and Dutch registries.^{11–13} A visit to the general practitioner (GP) costs €26, a blood sample test €12, a prescription renewal €13, and each pharmacist's fee €7. Based on current Dutch guidelines for statin and antihypertensives treatment, we assumed that treatment with the polypill should include per year two GP visits (€53), two prescription renewals (€26), four pharmacist's fees (€28), and one blood analysis (€13). The minimum (without medication costs) annual cost of treatment with the polypill would hence be: €120. To this basic annual cost, the cost of the medication should be added and the objective of this study is to estimate what the maximum cost of the polypill should be to be cost effective for primary prevention of CVD.

The costs of events were taken from the literature and as we used a third party payer perspective, they were restricted

to direct medical costs. Costs per event were for non-fatal myocardial infarction €6972, for fatal myocardial infarction €1602, for non-fatal stroke €11870, and for fatal stroke prevented €3851.¹⁴

All costs were standardised for calendar year 2003 correcting for inflation (when necessary) and currency (€) adjusting for exchange rates.

Cost effectiveness and expected annual cost of the polypill

All future costs and effects were calculated using a third party payer perspective and discounted using the currently nationally recommended nominal discount rate of 4% per year (for both costs and effects),¹⁵ to take into account time preference. This implies that effects and costs occurring in the future are weighted less than those occurring in the present.¹⁶

The time horizon used for costs and effects was 10 years and the cost effectiveness ratio (CER) was calculated as extra medical costs per YLS.

We calculated the maximum annual cost of the polypill medication to produce CERs under €20 000 ("cheap"), over €40 000 ("expensive"), and negative CERs ("cost saving").^{17–18} We also used €30 000/YLS to define cost effectiveness. We used the effects of the polypill in terms of YLS and the basic cost of treatment, to calculate backwards what should be the annual medication costs. The calculations were repeated for the different levels of absolute risk of CHD ("moderate" and "high") and age groups (45 to 54 and 55 to 65 years). Confidence intervals for the price of medication were estimated by using the confidence intervals of the event reduction effect as published for the polypill.³

All survival analyses were performed using Stata version 8.2 for windows (Stata, College Station, TX, USA, 2003). The multistate life tables were made using Excel spreadsheets.

Sensitivity analysis

We evaluated how cost effective the polypill would be if its price were comparable to the current price of aspirin (€28) or statins (€485) in the Netherlands and the off patent price of statins in Denmark (€157).^{11–13–19}

Additionally, because of the uncertainty of the effects of the polypill, we decided to repeat the analyses considering 50% or 80% of the published effect of the polypill.³

Table 2 Maximum annual cost of the polypill by age group and level of CHD risk*

Cost effectiveness ratio	Age 50			Age 60		
	Total population† cost (95%CI)	Moderate risk‡ cost (95% CI)	High risk§ cost (95%CI)	Total population† cost (95%CI)	Moderate risk‡ cost (95%CI)	High risk§ cost (95%CI)
Cost saving	NQ	NQ	11 (3 to 17)	NQ	NQ	24 (14 to 30)
€20000/YLS	22 (13 to 29)	103 (94 to 110)	302 (288 to 314)	409 (388 to 421)	196 (181 to 207)	410 (389 to 429)
€30000/YLS	64 (52 to 74)	179 (167 to 188)	448 (428 to 462)	616 (594 to 631)	314 (294 to 329)	607 (577 to 629)
€40000/YLS	108 (93 to 117)	256 (241 to 267)	594 (570 to 611)	823 (799 to 844)	433 (407 to 450)	801 (764 to 829)

YLS, year of life saved; CHD, coronary heart disease; NQ, non-quantifiable. *Costs calculated in euros from 2003, represent only medication costs. †Includes populations at low, moderate, and high 10 year risk of CHD. ‡Moderate risk refers to a 10 year risk of CHD between 10% and <20%. §High risk refers to a 10 year risk of CHD ≥ 20%.

Table 3 Sensitivity analysis: expected cost effectiveness of the polypill corresponding to different levels of annual medication cost by age group and level of CHD risk*

Annual cost of medication*	Age 50		Age 60	
	Moderate risk† CER (€/YLS)	High risk‡ CER (€/YLS)	Moderate risk† CER (€/YLS)	High risk‡ CER (€/YLS)
28 (similar to aspirin)	10100	1100	5700	230
157 (similar to off patent statins)	27013	9992	16663	6863
485 (similar to statins)	70004	32495	44470	23714

YLS, year of life saved; CHD, coronary heart disease; CER, cost effectiveness ratio. *Costs calculated in euros from 2003, represent only medication costs. †Moderate risk refers to a 10 year risk of CHD between 10% and <20%. ‡High risk refers to a 10 year risk of CHD ≥ 20%.

Incremental cost effectiveness analysis

The incremental cost effectiveness ratio is the additional cost of a specific strategy divided by its additional benefit. Based on incremental cost effectiveness analysis we calculated how much the polypill might cost for it to become a cost effective (at a cut off point of €20 000/YLS) replacement of aspirin for the primary prevention of CVD. We calculated the costs of aspirin treatment according to the Dutch situation: aspirin treatment includes per year, one GP visit plus the cost of aspirin 100 mg/day (€27.97) for a total of €54.26.^{11–13} The effect of aspirin treatment in terms of risk reduction of CVD was taken from the literature (28% reduction of primary CHD events, 13% reduction of secondary CHD events, and 20% risk reduction of primary or secondary stroke).^{20–21}

RESULTS

Efficacy of the polypill

The authors of the polypill calculated that the polypill given to populations aged 55 to 64 years, would reduce CHD by 88% (95% confidence interval 84% to 91%) and stroke by 80% (95% CI 71% to 87%).³

Ten year effects of the polypill

The polypill represented large gains in terms of YLS that ranged between 50 and 215 per 1000 participants treated with the polypill during 10 years. The highest gains were seen when the polypill was given to the total population from age 60 irrespective of their level of risk (table 1).

In terms of events prevented, giving the polypill to 1000 people would theoretically prevent 76 to 179 CHD events and 11 to 33 strokes.

As expected, higher levels of CHD risk—and/or higher age—were associated with higher gains, except for the CHD events prevented in the populations with moderate risk (table 1).

Acceptable cost of the polypill by level of cost effectiveness

The acceptable cost of the polypill depended on the levels of CHD risk and age of the population (table 2).

Even if the polypill would be offered for free no cost savings would be achieved if the intervention were implemented in populations at moderate levels of risk or if it would be given to the total population irrespective of risk levels (table 2).

We found maximum annual costs of the polypill medication when given to the total population at age 60 (including populations with low, moderate, and high risk) or to a population at age 60 and with high 10 year risk of developing CHD.

To be cost effective at a €20 000/YLS level for the total population irrespective of levels of risk, the polypill should not cost over €22 and €409 per year, for populations at age 50 and 60 years respectively.

For populations at high levels of risk, the annual cost of the medication should be below €24 in the case of men at 60 years of age and €11 for those at age 50, for it to be cost saving. To be cost effective at €20 000/YLS among populations at high levels of risk, the polypill should cost no more than €302 and €410 for age 50 and 60 respectively. For populations with moderate risk the acceptable cost would have to be two to three times lower.

Annual medication costs of the polypill over €600 or €800 would correspond to high cost effectiveness ratios (>€40 000/YLS) in high risks populations aged 50 and 60 respectively (table 2).

Sensitivity analysis

If the polypill would cost as much as aspirin its cost effectiveness would range between €230/YLS and €10 100/YLS. If the polypill would cost as much as the off patent costs of statins in Denmark, the polypill would have cost

Table 4 Sensitivity analysis: maximum annual cost of the polypill by age group and level of CHD risk considering 50% of the published effects of the polypill (44% reduction of CHD and 40% reduction of stroke risk)*

Cost effectiveness ratio	Age 50		Age 60	
	Moderate risk† cost (95% CI)	High risk‡ cost (95% CI)	Moderate risk† cost (95% CI)	High risk‡ cost (95% CI)
Cost saving	NQ	NQ	NQ	NQ
€20000/YLS	2.3	123	47	167
€30000/YLS	45	211	110	274
€40000/YLS	88	299	173	381

YLS, year of life saved; CHD, coronary heart disease; NQ, non-quantifiable. *Costs calculated in euros from 2003, represent only medication costs. †Moderate risk refers to a 10 year risk of CHD between 10% and <20%. ‡High risk refers to a 10 year risk of CHD ≥ 20%.

Table 5 Incremental cost effectiveness analysis: maximum annual cost of the polypill by age group and level of CHD risk to be cost effective (at €20000/YLS) compared with aspirin*

	Age 50		Age 60	
	Moderate risk†	High risk‡	Moderate risk†	High risk‡
Aspirin annual costs§	54	54	54	54
Aspirin effects (YLS) discounted (by 4%)	15	35	19	32
Maximum annual medication costs of the polypill	53	157	148	268

YLS, year of life saved; CHD, coronary heart disease; NQ, non-quantifiable. *Costs calculated in euros from 2003. Effects calculated over a 10 year time horizon and presented in YLS per 1000 participants. Incremental cost effectiveness analysis evaluates the cost effectiveness of the polypill: what should be the maximum annual medication cost of the polypill to be cost effective compared with aspirin therapy using a cut off value of cost effectiveness of €20000/YLS. †Moderate risk refers to a 10 year risk of CHD between 10% and <20%. ‡High risk refers to a 10 year risk of CHD ≥ 20%. §Annual cost of aspirin therapy includes one GP visit (€26.29) plus the cost of aspirin 100 mg/day (€27.97) for a total of €54.26.⁹⁻¹¹

effectiveness ratios above €20 000/YLS only for the population at moderate risk of CHD and age 50. On the other hand if the polypill would cost as much as not off patent statins its cost effectiveness would be over €20 000/YLS in all scenarios (table 3).

When we considered 50% of the published effect of the polypill (44% reduction of CHD and 40% reduction of stroke) we found that even if the polypill would be offered for free, it could not generate cost savings in any of the populations studied. To be cost effective at a cut off level of €20 000/YLS, the annual cost of the polypill medication should not be superior to €123 and €167 for populations at high risk of CHD and at age 50 and 60 respectively (table 4).

If we consider 80% of the published effect of the polypill (70% reduction on CHD and 64% reduction of stroke), the results show once more not potential cost savings at any possible price of the polypill. For populations at age 50 and moderate risk the maximum annual cost of the polypill to be cost effective at a €20 000/YLS cut off level should not be over €64 and double this costs if a €30 000/YLS cut off level of cost effectiveness is taken (data not shown).

Incremental cost effectiveness analysis

We calculated the cost effectiveness of aspirin following the same assumptions as used for the polypill. Aspirin treatment costs €54 per year, leading to €16 949/YLS and €2716/YLS

for a population with 50 years of age and moderate and high risk levels of CHD respectively. For those with 60 years of age the cost effectiveness ratios for aspirin treatment were €12 862/YLS (moderate risk) and €2263/YLS (high risk). To be a cost effective replacement of aspirin in populations free of CVD but with high levels of risk, the annual medication costs of the polypill should not be over €157 (age 50) and €268 (age 60) (table 5).

DISCUSSION

To be cost effective in general populations free of CVD, the annual cost of the medication for polypill therapy should not exceed €300 at age 50 and €400 at age 60. These costs are 10 times the cost of aspirin therapy but three quarters the cost of statin treatment.¹¹⁻¹³ As aspirin and statins are two of the constituents of the polypill, it could be expected that the medication's costs for the polypill could be in this price range or even higher. When compared with aspirin in an incremental cost effectiveness analysis, the maximum costs of the polypill medication should not be over €157 at age 50 and €268 at age 60.

We found that the largest benefits in terms of events prevented and YLS would be obtained if the polypill would be given to everyone from age 60 (irrespective of the levels of risk) or to a population at high risk of CHD and over 60 years of age. Consequently the highest annual costs of the polypill medication were permitted in these two scenarios. This is consistent with the recommendation of the polypill authors to give the polypill to everybody over a certain age irrespective of their levels of risk. However, this would also imply the medicalisation of a large section of the population and the exposure of otherwise healthy subjects to unwanted adverse effects.

Our analyses showed that, even when the effects of the polypill on life expectancy would be large, the treatment costs are critical to make prevention cost effective. The cost

What this paper adds

- To be cost effective in general populations free of cardiovascular disease, the cost of the medication for polypill therapy should not exceed €300 at age 50 and €400 at age 60.
- When compared with aspirin in an incremental cost effectiveness analysis, the maximum costs of the polypill medication should not be over €157 at age 50 and €268 at age 60.
- The largest benefits would be obtained if the polypill would be given to everyone from age 60 or to a population at high risk of coronary heart disease and over 60 years of age. This is consistent with the recommendation of the polypill authors. However, this implies the medicalisation of a large section of the population and the exposure of healthy subjects to adverse effects.

Policy implications

- The polypill seems potentially a highly effective intervention, but potential producers should be aware of the market limitations.
- Although the polypill could theoretically be a highly effective intervention, the costs of the medication could be its caveat for implementing it in the primary prevention of cardiovascular disease.

effectiveness of the polypill will vary according to the levels of CHD risk in the populations as well as the age. If the polypill wants to compete effectively with established interventions in primary prevention like aspirin and smoking cessation with nicotine replacement, it will first have to prove to be much more effective in clinical trials. But, it will also need to be offered in the market at a lower price than the current price of one of its components: statins. The case in secondary prevention of CVD might be different as this implies treating populations with already existing CVD that in consequence are at higher levels of risk. Prevention of events in these populations is known to be more cost effective than treating healthy subjects.

Our cost effectiveness ratios and costs of medication are conservative. We did not include savings in terms of invasive interventions (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) that could be achieved with polypill therapy. The basis of this decision is the continuing change in CVD risk management; the populations we used for our analyses are from the 1970s and 1980s when treatment of CVD included less invasive procedures than currently. Although savings could be underestimated, the effects of the polypill as calculated by the polypill's authors could be overestimated and are at the moment only theoretical. A multiplicative assumption is made on the risk reduction effects of the components of the polypill, and larger levels of risk reduction are assumed compared with previous evidence on the same components.^{22 23}

Because there is no evidence on the benefits of statins (one of the ingredients of the polypill) for periods of time over six years, we selected a 10 year time horizon and did not account for effects (or costs) beyond this period. We considered that modelling the effects and costs of the polypill beyond periods of 10 years would require assumptions on theoretical treatment effects over long unobserved periods, hence introducing further uncertainty to the analyses.

There is no real evidence on the effects of the polypill in terms of clinical trials and this is a requirement before we can seriously think of the polypill as an alternative to prevent CVD. On the other hand, adverse effects could also limit the usability; it is unknown how the components of the polypill will interact when put together in the same presentation and only large randomised controlled trials with long follow up will provide answers to these questions. We presented results for men, as women at the same age have lower levels of CHD risks. The maximum costs of the polypill for women would hence be below those calculated for men. This would further challenge the recommendation of widespread polypill administration and coverage by insurance companies and governments.

The polypill seems potentially a highly effective intervention, but potential producers should be aware of the market limitations. The polypill may be the preventive method with potentially the greatest impact on public health in the Western world,³ but is everything that glitters gold? Even when it is, it should certainly be a lot less expensive than gold to assure a serious impact on the primary prevention of CVD.

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CONTRIBUTORS

All authors participated actively in all and each of the following aspects for this article: conception and design, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published. Oscar H Franco is guarantor for this paper.

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