BMJ open

The polypill in the primary prevention of cardiovascular disease: cost-effectiveness in the Dutch population.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000363
Article Type:	Research
Date Submitted by the Author:	14-Sep-2011
Complete List of Authors:	van Gils, Paul; National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research Over, Eelco; National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research Hamberg, Heleen; National Institute for Public Health and the Environment, Centre for Public Health Forecasting de Wit, G. Ardine; National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research van den Berg, Matthijs; National Institute for Public Health and the Environment, Centre for Public Health Forecasting Engelfriet, Peter; National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research
Primary Subject Heading:	Cardiovascular medicine
Keywords:	Myocardial infarction < CARDIOLOGY, HEALTH ECONOMICS, PUBLIC HEALTH, Stroke < NEUROLOGY

The polypill in the primary prevention of cardiovascular disease: cost-effectiveness in the Dutch population.

Paul F. van Gils [1], Eelco A.B. Over [1], Heleen H. Hamberg-van Reenen [2], G. Ardine de Wit [1], Matthijs van den Berg [2] , Albertine J. Schuit [1] en Peter M. Engelfriet [1]

[1]National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research, Bilthoven, The Netherlands
[2] National Institute for Public Health and the Environment, Centre for Public Health Forecasting, Bilthoven, the Netherlands

Paul van Gils, MSc
Centre for Prevention and Health Services Research
National Institute of Public Health and the Environment
PO Box 1
3723 BA Bilthoven
The Netherlands
Telephone:+31 302748581
Fax: + 31 30 274 4407
Email: paul.van.gils@rivm.nl

Eelco A.B. Over, PhD
Centre for Prevention and Health Services Research
National Institute of Public Health and the Environment
PO Box 1
3723 BA Bilthoven
The Netherlands
Telephone:+31 302742700
Fax: + 31 30 274 4407
Email: eelco.over@rivm.nl

Heleen H. Hamberg, PhD
Centre for Public Health Forecasting
National Institute for Public Health and the Environment
P.O. box 1
3720 BA Bilthoven
The Netherlands
Telephone: +31 30 2742735
Fax: +31 30 2744450
Email: heleen.hamberg@rivm.nl

G.Ardine de Wit, PhD
Centre for Prevention and Health Services Research
National Institute of Public Health and the Environment
PO Box 1
3720 BA Bilthoven
The Netherlands
Telephone: + 31 30 274 3206
Fax: + 31 30 274 4407
Email: ardine.de.wit@rivm.nl

M. van den Berg, PhD
Centre for Public Health Forecasting
National Institute for Public Health and the Environment
P.O. box 1
3720 BA Bilthoven
The Netherlands
Telephone: +31 30 2743349
Fax: +31 30 2744450
Email: matthijs.van.den.berg@rivm.nl

Albertine J. Schuit, PhD
Centre for Prevention and Health Services Research
National Institute of Public Health and the Environment
PO Box 1
3720 BA Bilthoven
The Netherlands
Telephone: + 31 30 274 2945
Fax: + 31 30 274 4407
Email: janinte.schuit@rivm.nl

Peter M. Engelfriet, MD, PhD
Centre for Prevention and Health Services Research
National Institute of Public Health and the Environment
PO Box 1
3720 BA Bilthoven
The Netherlands
Telephone: + 31 30 274 4388
Fax: + 31 30 274 4407
Email: peter.engelfriet@rivm.nl

Correspondence: Paul van Gils
Centre for Prevention and Health Services Research (pb 101)
National Institute of Public Health and the Environment
PO Box 1
3720 BA Bilthoven
The Netherlands

Paul.van.gils@rivm.nl
Phone: + 31 30 2748581
Fax: + 31 30 274 4407

Conflict of interest statement
We declare that no conflict of interest exists for any of the authors.

ABSTRACT

Objective

The aim of the present study was to estimate the cost-effectiveness of the polypill in the primary prevention of cardiovascular disease.

Design

A health economic modeling study.

Setting

Primary health care in the Netherlands.

Intervention

Opportunistic screening followed by prescription of the polypill to eligible individuals. Eligibility was defined as having a minimum10-year risk of cardiovascular death as assessed with the SCORE function of alternatively 5%, 7.5%, or 10%. Different versions of the polypill were considered, depending on composition: 1) the Indian polycap, with three different types of blood pressure lowering drugs, a statin, and aspirin; 2) as 1) but without aspirin; 3) as 2) but with a double statin dose. In addition, a scenario of (targeted) separate antihypertensive and/or statin medication was simulated.

Main outcome measures

Cases of acute myocardial infarction or stroke prevented, QALYs gained, and the costs per QALY gained. All interventions were compared with usual care.

Results

All scenarios 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.

Conclusion

Opportunistic screening based on global cardiovascular risk assessment followed by polypill prescription to those with increased risk offers a cost-effective strategy. Most health gain is achieved by the polypill without aspirin and a double statin dose.

Article summary

Article focus

- Cardiovascular diseases (CVD) continue to be still a major, partly preventable, cause of illness and death.
- A polypill that lowers by targeting several risk factors simultaneously, is in line with the concept that the aim in primary prevention should be to bring down 'global' cardiovascular risk.
- Identifying individuals at increased risk using a risk score followed by offering a drug lowering global risk seems a 'logical' strategy to prevent cardiovascular disease.
- The aim of this study was to estimate the potential cost-effectiveness of polypill prescription after opportunistic screening in the primary prevention of cardiovascular disease.

Key messages

- The results of this study suggest that opportunistic screening and offering a polypill to people with a minimum 10-year risk of cardiovascular mortality of alternatively 5%, 7.5% or 10% is a cost-effective strategy in the primary prevention of cardiovascular diseases.
- A polypill without aspirin but with a double dose of simvastatin leads to most health gains at all risk thresholds considered. At a 10 year risk of cardiovascular death of 7.5% or above, such a strategy would lead to an estimated decrease in the incidence of myocardial infarction and stroke of about 3.5%, at a cost of €9,800 per QALY.
- Opportunistic screening of the population of 40 years or above to select individuals with a mild to moderately increased risk for cardiovascular diseases, followed by polypill prescription would prevent approximately 3.5% of all cardiovascular events.

Strenghts and limitation of this study

- Strong point of the study is that different compositions of the polypil (with and without the addition of aspirin, different doses of statins) have been modeled. Also, realistic estimates for compliance and adherence have been used.
- As only preliminary results of a phase II clinical trial on efficacy of the polypill were available, we had to apply mathematical modeling to estimate cost-effectiveness. This provides insight into the range of health benefits that can be expected. Pending results with regard to established clinical endpoints from large-scale phase III trials, the results of this study should not be taken as a precise estimate of the cost-effectiveness of the polypill.

Introduction

In a by now famous article in the British Medical Journal in 2003, Wald and Law suggested that a 'polypill' could be of great benefit in the prevention of cardiovascular disease [1]. As originally proposed, such a pill would consist of a combination of drugs with proven efficacy and safety in reducing cardiovascular risk, in particular three different types of blood pressure lowering drugs (a beta-blocker, an antidiuretic and an ACE inhibitor), one lipid lowering drug, an antiplatelet agent (aspirin), and folic acid to reduce serum homocysteine. In combination, lower dosages could be used resulting in greater efficacy than single medication with a more favorable safety profile than higher dosages of individual drugs.

Cardiovascular diseases (CVD) are still a major cause of illness and death. For example, estimates show that in the year 2006 more than 80 million people in the United States had one or more forms of CVD [2]. In 2009, CVD was responsible for 29% of all deaths in the Netherlands, taking second place after cancer (32%) as the most important cause of death.[3] Ischemic heart disease and stroke together were responsible for 27% of all hospitalizations.[4] As CVD is the result of a gradual process of atherosclerosis building up over many years, the most rational strategy is stopping, or at least slowing down, the progress of plaque formation. For those whose risk factor levels put them at increased risk, life style measures or medication are available for primary prevention, but identifying who might benefit and what measures are most appropriate is subject of much discussion.[5-8] The recognition that atherosclerotic CVD is the product of multiple interacting risk factors has in the past decades led to new approaches in prevention. In particular, the concepts of global risk, being the aggregate risk of all risk factors together, and total CVD risk assessment have emerged as an important inspiration for developing guidelines on cardiovascular risk management.[9] Examples of methods of global risk assessment are the well known Framingham risk score and the SCORE (Systematic Coronary Risk Evaluation), the latter based on a pooled data set of 12 European cohort studies.[10] A consequence of the global risk approach is that the focus of intervention shifts from treatment of individual risk factors to placing emphasis on reducing total CVD risk, irrespective by what means. Thus, the idea of a polypill, that lowers risk by targeting more than one risk factor simultaneously, seems perfectly tailored to this strategy.[11] In addition, it offers the benefit of a 'one stop shop' when someone could benefit from one type of medication.

Up to the present, no evidence for the effectiveness of such a polypill exists. Yet, randomized clinical trials with several versions of a polypill have been started. The Indian Polycap Study was a phase II randomized double-blind clinical trial designed to test the effects of a version of the polypill on intermediate measures for the development of CVD, in particular blood pressure, cholesterol, heart rate, and urinary dehydrotrombaxane B2.[12] The polypill used in

this RCT differed from the one suggested by Wald and Law by omitting folic acid, as the supposed effects of folic acid on serum homocysteine have not been confirmed.[13] Medication was only given for a period of 12 weeks in the Polycap study.

Even though there is still no evidence regarding the efficacy of a polypill on hard endpoints (acute myocardial infarction, stroke), the extensively validated relation between blood pressure and cholesterol level on the one hand and disease risk on the other, allows a first exploration of the range of costs and benefits that might be expected from the polypill in the prevention of cardiovascular diseases.

The aim of this study was to estimate the potential cost-effectiveness of the polypill in the primary prevention of myocardial infarction and ischemic stroke. In order to explore this issue a scenario of opportunistic screening in primary care was taken as point of departure. Patients were eligible for prescription of the polypill starting from a 5% risk up to 10% risk of cardiovascular death in 10 years, based on their SCORE function.[14]

Methods

We conducted a simulation study using a computer model (RIVM Chronic Disease Model-CDM) developed at our institute.[15, 16] Point of departure for the simulations was a scenario, in which the polypill is offered to eligible patients identified during routine visits to their GP, ('opportunistic screening'). The GP takes the initiative suggesting to patients to determine their 10-year risk for cardiovascular mortality. Those aged 40-75 years of age without known previous cardiovascular disease are eligible for the screening. Starting from risk levels of 5% or higher, people will be offered lifelong preventive medication. Cardiovascular mortality risk is assessed using the SCORE risk function developed and recommended by the European Society of Cardiology, and endorsed in the Netherlands by professional and patient's organizations.[17] The score function is calculated using age, sex, blood pressure, cholesterol, and smoking status as input.

The current Dutch guideline for primary cardiovascular prevention, which was introduced in 2006, recommends the SCORE risk charts to determine treatment recommendations. For this purpose a version of the SCORE was developed adapted to Dutch risk factor and mortality data.[14] It is the algorithm for this version that we used in our analyses.

According to the Dutch guideline, for individuals with a 10-year risk of cardiovascular death of 10% or higher targeted drug therapy is recommended: antihypertensive treatment when SBP $\geq$ 140; statins when LDL cholesterol > 2.5 mmol/L. When risk exceeds 5%, life style counseling should be considered. Aspirin is recommended for secondary prevention only.[18]

Following the rationale that arguments for the polypill are based on the expectancy of a more favorable benefit versus safety profile, we assumed that, in a situation where a polypill would

be available, it would be considered to lower the threshold for prescribing preventive medication. On the other hand, it seems unlikely prescribing the preventive medication to anyone. Especially for risks lower than 5% consensual support is needed. Therefore, in order to assess the effect of different choices for the threshold, we performed analyses for different cut points; 5%, 7.5%, and also 10%, the threshold for drug treatment of the present guideline.

The RIVM Chronic Disease Model

The CDM is a computer simulation model designed to be able to simulate the evolution of several chronic diseases in relation to risk factor levels in the Dutch population. It includes the most common chronic diseases, amongst which COPD, diabetes mellitus type 2, myocardial infarction and stroke, and, besides a number of life style related risk factors, such as smoking, blood pressure and cholesterol. It may be best characterised as a Markov-type, multistate-transition model.[15, 16] The model describes the development over time of demography, risk factor prevalence, disease incidence, and mortality, in 1-year time steps. As input it takes the age- and sex composition of the current Dutch population and the distribution of risk factor levels in the population. It further requires specification of three types of transition probabilities (the probability of going from one state to another in 1 year time): between risk factor levels, between disease states (from no disease to disease, i.e. disease incidence, for each disease in the model), and mortality rates. Disease incidence and mortality depend on risk factor levels and the presence of other diseases via relative risks. Estimates of relative risks were derived from literature, whereas incidence, prevalence, transition rates, and mortality rates in the model apply to the Dutch population. In addition, each disease is associated with average yearly, per patient, costs, and with disability weights. All data are age and sex specific. The model further allows specifying alternative "scenarios", by adjusting the input parameters, and comparing the results obtained with other scenarios with the 'reference scenario (see below)'. Health care costs were based on costs-of-illness studies in the Netherlands [19, 20] and the healthcare outcome measure 'quality-adjusted life year (QALY)' was computed using the Global and Dutch burden of disease studies.[21-24]

Scenarios

Several scenarios were defined based on: 1) different cut-off levels for 10-year risk: 5%, 7.5% and 10%; 2) different compositions of the polypill. These scenarios were compared with the reference scenario of care as usual and with each other. Usual care is represented in our model in the reference scenario by the proportion of individuals currently being treated with statins and/or antihypertensive agents, based on data from the Doetinchem cohort study (details about this study follow later).[25] It is assumed that individuals already being treated with drugs will not switch to the polypill. We further assume that people identified as being at risk by

opportunistic screening would otherwise not receive preventive medication. The different scenarios explored using the CDM model are:

1) The reference scenario represents the expected evolution of the health status and risk factor distribution of the Dutch population as simulated by the model using the basic input parameters that represent the relevant characteristics of the current Dutch population (current practice).

2) The polypill scenarios simulate the situation in which all eligible individuals, not yet treated with statins or antihypertensive agents, and selected by 'opportunistic screening', are offered lifelong medication. Besides the original Indian 'Polycap' composition, we also considered different versions of the polypill without aspirin that would avoid the bleeding risks associated with anti-platelet agents. Thus, the following alternative compositions of polypills were considered:

2A) The 'Indian Polycap', consisting of 20 mg simvastatin, 12,5 mg thiazide, 5 mg ramipril, 50 mg atenolol, 100 mg aspirin.

2B) As 2A) but without aspirin.

2C) As 2B) but with 40 mg simvastatin (double dose statins, i.e. Dutch standard dose when given as monotherapy).

Finally, an alternative scenario was defined (scenario 3: 'separate medication') in which screened individuals eligible for the polypill will not be offered the polypill, but rather medication tailored to the underlying risk factor: a statin in case of hypercholesterolemia, an anti-hypertensive in case of hypertension, both, or none (i.e. the risk score is increased, but blood pressure and hypertension are below the respective cut points).

Basically, the analyses compare the scenarios in which medication is offered in primary care to all eligible individuals in the age group 40-75 years with the scenario in which usual care is continued. The comparison thus is between a hypothetical population with one of the interventions described above and one without, where in all other respects the populations are equal at baseline and represent the current Dutch population. The model is 'run' until all have died and no 'inflow' of younger individuals is taken into account.

Below, we describe how we derived values for the relevant parameters for each scenario.

Estimation of the number of eligible individuals and of the proportion who would be treated

In order to estimate the numbers of individuals who would receive the polypill, the following steps were taken (Fig. 1).

First, the proportion of the population aged 40-75 years without a history of CVD and not yet treated with statins or antihypertensives was estimated. To this end, we applied the SCORE algorithm to the most recent data of the Doetinchem cohort study. The Doetinchem cohort

study is a prospective study of more than 5,000 inhabitants of the city of Doetinchem and surroundings who were included in the years 1987-91. Participants were aged 20-65 years at inclusion, and have been followed for more than 20 years now. So far, 4 rounds of data collection have been completed, roughly at 5-year intervals. We used the data of round 4, collected during the years 2003-2007. Among the data collected all variables necessary to calculate the SCORE are included (age, sex, SBP, LDL cholesterol, smoking status, treatment status of statins and antihypertensive). The Doetinchem cohort has been described elsewhere.[25] The cohort represents the best available source for the Netherlands to determine the current population distribution of risk factors.

Next, we needed to estimate how many people would be reached by opportunistic screening. Data taken from Statistics Netherlands show that approximately 75% of the Dutch population visit their GP al least once every year.[26] We assumed that this figure also applies to our target population. We further assumed that the GP offers a screening consultation to all in the target population (those aged 40-75 years) in the year of the intervention, and that 50% of the invited population consent. Risk assessment consists of one consultation with GP, who explains the procedure, measures blood pressure, and draws blood for a laboratory test of blood cholesterol. The patient is then invited for a second consultation to calculate the SCORE and discuss the consequences.

We finally assumed that of those who are offered the polypill (SCORE ≥ 5%, 7.5%, or 10%), or a separate statin/antihypertensive, 85% will decide to take the pill for at least one year [12], and that compliance rates would stabilize at 50% after 5 years. A flow chart of the process of screening and selecting patients is shown below: for the separate medication scenario (scenario 3) we assumed that adherence (willingness to start with the therapy) to the antihypertensive was 90% and adherence to the statin was 60% [27], which fraction was multiplied by the before-mentioned compliance rate to achieve total compliance (willingness to continue the therapy).

Effects

A crucial parameter in implementing the polypill scenarios is, of course, a measure of its efficacy, in particular the relative risk reduction: the relative risk for acute myocardial infarction or stroke after taking the medication compared to the relative risk before taking it (or in a control (placebo) group). Unfortunately, as mentioned above, so far there are no data on the effects of the polypill on cardiovascular events. Instead, we will have to base our estimate on the effects on "intermediate" measures, i.e. blood pressure and cholesterol. In particular, we use the outcomes of the Indian Polycap Study.[12] As mentioned above, the Indian polypill consist of three blood pressure lowering drugs: hydrochlorthiazide 12.5 mg (a

diuretic), atenolol 50 mg (a β-blocker) and ramipril 5 mg (an angiotensin converting enzyme inhibitor), a lipid lowering drug (simvastatin 20 mg) and an antiplatelet (aspirin 100 mg). The effect of the polypill on blood pressure was a lowering of the diastolic blood pressure with 5.7 mm Hg (95% CI 4.7-6.4) and of the systolic blood pressure with 7.4 mm Hg (95% CI 6.1-8.1). The LDL cholesterol was reduced by 0.80 mmol/L (95% CI 0.62-0.78).[12]

These effects on blood pressure and cholesterol are substantially lower than what Law and Wald predicted. Thus, the RR reductions suggested in their article and in the accompanying meta-analysis of combination treatment with blood pressure lowering drugs [28] could not be relied upon for our purposes. Instead, we took as a basis the reductions in blood pressure and cholesterol observed in the Polycap study and translated these into corresponding RR reductions using meta-analyses providing estimates of these relations. Details of the meta-anlyses we used and the manner we calculated the risk reductions are provided in the appendix. The calculated values we used are shown in Table 1.

Table 1: Relative risks versus no medication (95% CI)

Relative risk	*Statin 20 mg*	*Statin 40 mg*	*BPL in PP*	*BPL separate*	*aspirin*
Total mort.	0.86 (0.76-0.97)	0.71 (0.53-0.92)	0.91 (0.83-1.00)	0.91 (0.83-1.00)	1
CVA	0.81 (0.69-0.95)	0.61 (0.42-0.88)	0.81 (0.70-0.94)	0.81 (0.70-0.94)	1
AMI	0.75 (0.69-0.82)	0.52 (0.42-0.62)	0.84 (0.74-0.94)	0.84 (0.74-0.94)	0.82 (0.75-0.90)

BPL: blood pressure lowering drug; PP: polypill

Costs

Costs were determined from the perspective of the health care payer and according to the national guideline for costing research in health economic analysis.[29] Direct medical costs associated with diseases per patient per year were included in the CDM.[19, 20] Costs due to all medical treatment in life years gained (indirect medical cost) are automatically included in the model.

Costs for screening and drug use

Unit costs, including costs for GP visits, laboratory testing, medication and drug delivery are presented in Table 2.

Costs during the first year consist of two GP visits, one laboratory test, and if indicated the costs of medication and drug delivery.

During the second and subsequent years, the costs consist of one GP visit (control visit), one laboratory test, and the costs of drug delivery.

As currently the polypill is not yet on the market, a price had to be estimated based on its "ingredients". We took as our reference the costs per mg of statins, beta-blockers, ace-inhibitors and aspirin prescribed as generics in the Netherlands, and we assumed that the price

of a pill would be the sum of the prices of its components.[30] Thus, the Polycap pill (scenario 1) would cost € 89.75 per year, including fees for prescription and drug delivery.

Table 2: Intervention costs

Item	unit	costs per unit /quantity in PP	costs per person per year
GP visit *	Standard consultation	€ 29	58 (first year)
			29 (subsequent years)
Blood drawing		Included	
Laboratory		€ 1.70	1.80
Drug costs **			
Simvastatin 20mg dd	1 year	€ 6.69	6.69
Simvastatin 40 mg	1 year	€ 13.39	13.39
Ramipril 2.5 mg	1 year	€ 22.48	22.48
Atenolol 50 mg	1 year	€ 22.48	22.48
Thiazide 12.5 mg	1 year	€ 3.47	3.47
Aspirin 100 mg	1 year	€ 3.70	3.70
Drug delivery costs***	First delivery	€ 5.74	
	Per 3 months	€ 5.74	28.70 (first year)
			22.96 (subsequent years)
Repeat prescription***		Included in basic tariffs	

Costs in the first year consist of 2 GP visits, one laboratory test, 4 times drug delivery, and an additional charge for first drug delivery. Costs in subsequent years: 1 GP visit plus 1 laboratory test plus 4 times drug delivery costs.

* Fees in The Netherlands are determined by the national regulator of Healthcare tariffs: Nederlandse Zorgautoriteit (National Health Authority). In addition to costs per visit, GP's are paid for each patient registered in their practice on a yearly basis. Website http://www.nza.nl. Consulted on June 16, 2011.

** Drug costs are based on the costs as calculated and publicized by the College for Health Insurance, which determines the prices for reimbursement (Pharmaco-therapeutic compass: http//www.cvz.nl/kompas)

*** According to maximum fees set for the year 2011 by National Health Authority (nza, "tariefbeschikking" nr. TB/CU-5000-01, nr. 34 www.nza.nl)

Costs associated with adverse effects

Although the frequency of adverse effects of the use of statins and antihypertensive agents has consistently been reported to be very low, the risks of aspirin cannot a priori be neglected. However, in a first analysis we decided not to take these into account and, instead, consider them in a sensitivity analysis.

Total costs

Total costs were calculated by multiplying unit costs with volumes. Volumes were derived by determining the 'numbers of units per patient' and the numbers of patients at each stage in the process: first screening, then start therapy, first year, and finally all subsequent years of the simulation.

Cost-effectiveness

The main endpoint of this study was the cost-effectiveness ratio expressed as the ratio of the difference in costs and the difference in QALYs when comparing the alternative scenarios with the reference scenario (Cost/QALY)

As the rationale for prescribing the polypill is to prevent cardiovascular disease, we also determined the numbers of myocardial infarctions and strokes prevented in the different scenarios. This was done by calculating the differences in the cumulative incidences between scenarios. Finally, these figures were used to estimate the numbers of patients that would have to be treated (NNT) to prevent one myocardial infarction, respectively stroke.

Probabilistic sensitivity analyses

As several important assumptions had to me made in modeling the cost-effectiveness of the polypill, we explored the range of likely outcomes with a probabilistic multivariate sensitivity analysis. The key variables with known uncertainty were: screening acceptance, adherence to medication, relative risks for developing stroke and myocardial infarction, and the relative risk for all-cause mortality. Screening acceptance was taken to be distributed as a Beta distribution (alpha=5, beta=5) so that the average acceptance was 0.50, with a 95% CI of (0.21-0.79). First year's adherence was taken from a Beta distribution (alpha=42.5, beta=7.5) so that the average first year's adherence was 0.85, with a 95% CI of (0.74-0.93). The relative risks were randomly taken from Beta distributions with characteristics as mentioned in Table 1. We performed 350 simulations in total.

Another key parameter in the model was the price of the polypill. Because the polypill is not commercially available (yet), its price is unknown. As the best estimate, we used the sum of the costs of the separate elements of the polypill. However, if pill prices will be largely determined by production costs, it is likely that the pill will be considerably cheaper than the sum of the costs of its components. On the other hand, if, for instance the added value to the consumer of having to take one pill only will be priced in, it can not be ruled out that the price will be higher. For lack of an informed estimate of price ranges, we explored an array of possible values, in order to compare with the costs of separate medication.

Results

Descriptives

Table 3 shows the proportion of individuals eligible for medication based on a 10-year risk of cardiovascular mortality threshold of 5%, 7.5% or 10%. For example, with a threshold of 7.5%, of all persons between 40 and 75 year more than 31% was eligible for medication. The first half of the table concerns those eligible for the polypill, the second half those eligible for separate medication, based on having a SCORE risk of 7.5% or above together with hypertension and/or hypercholesterolemia ('separate medication scenario', scenario 3).

Effectiveness

Table 4 shows that by using the polypill as described for scenario 3, the total of cases of acute myocardial infarction or stroke prevented was more than for the other medication scenarios, more than 20 and 30 thousand cases, respectively, for a threshold of 7.5% (5% and 10% not shown). It must be noted, though, that the total health gain in the separate medication scenario is only 1/3 to ½ of the total health gain of scenario 3.

Cost-effectiveness

Table 5 shows the incremental cost-effectiveness ratios (ICERs) for all scenarios. The ratio's do not differ very much between the three SCORE cut-off values considered, and are all well within accepted ICER thresholds. The main effect of choosing a different cut point is that the ICERs for the polypill scenarios decrease with lower SCORE thresholds. Opportunistic screening combined with the polypill without aspirin and doubling of the statin doses (scenario 2C) had the most favorable ICER with a SCORE threshold of 5%. For the other thresholds, separate medication has the lowest ICER. It must be noted, though, that the total health gain in the separate medication scenario is only about 1/3 to 1/2 of the total health gain of scenario 2C.

Table 3: Individuals* eligible for the polypill and separate medication (% of total population)

	Polypill									Separate Medication								
	Men			Wom			Tot			Men			Wom			Tot		
Risk threshold	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%
Age																		
40-49	9.1	2.2	0.4	0.0	0.0	0.0	4.0	1.0	0.2	8.7	2.1	0.4	0.0	0.0	0.0	3.8	0.9	0.2
50-59	61.3	38.3	22.7	6.0	1.7	0.5	32.1	19.0	11.0	50.7	32.8	20.1	5.8	1.7	0.5	27.2	16.5	9.8
60-69	98.8	93.4	83.5	72.1	47.5	30.0	85.7	70.9	57.2	74.9	73.3	68.1	61.3	41.2	26.5	68.2	57.6	47.7
70-75	98.9	98.9	98.4	100.0	97.0	87.0	99.4	98.0	92.9	72.7	72.7	72.7	76.3	75.8	71.1	74.5	74.2	71.9
All ages (40-75)	57.4	46.2	37.7	25.0	18.0	13.1	40.3	31.3	24.7	46.2	37.8	31.5	21.9	16.0	11.9	33.4	26.3	21.2

* not yet using statins or antihypertensives

Table 4: number of cases prevented over time by the polypill intervention at a 10-years risk of 7.5%

Scenario (PP intervention)	AMI			Stroke		
Expected*	807 k			1374k		
	Cases prevented			*Cases prevented*		
	Number	*Percentage*	*NNT*	*Number*	*Percentage*	*NNT*
Polypill Scenario 2A	23.8 (8.3-41.6) k	2.89 (1.02-5.06)	31	36.1 (12.3-72.9) k	2.57 (0.86-5.12)	20
Polypill Scenario 2B	22.5 (8.3-38.8) k	2.73 (1.00-4.70)	33	36.2 (12.3-72.9) k	2.57 (0.86-5.14)	20
Polypill Scenario 2C	29.7 (10.5-52.4) k	3.60 (1.30-6.34)	25	47.4 (16.4-95.0) k	3.37 (1.17-6.78)	15
Separate medication (scenario 3)	12.8 (4.9-21.0) k	1.55 (0.60-2.56)	46	19.9 (7.5-37.5) k	1.41 (0.53-2.61)	30

* according to reference scenario
NNT: Number needed to treat

Table 5: Outcomes and ICERs (total costs per LY and QALY gained) compared to current practice. In the current practice scenario the total costs of healthcare were $675*10^9$, total life years $165*10^6$, and total QALYs $128*10^6$.

Outcomes	Polypill Scenario 2A			Polypill Scenario 2B			Polypill Scenario 2C			Separate medication Scenario 3		
Risk threshold	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%
Cost of intervention ($*10^6$ €)	954	907	870	921	876	840	967	914	872	331	319	309
Incremental healthcare costs ($*10^6$ €)	2,210	1,710	1,320	1,940	1,500	1,160	2,240	1,730	1,330	750	720	690
Total incremental costs ($*10^6$ €)	3,160	2,620	2,190	2,860	2,370	2,000	3,210	2,640	2,200	1,080	1,040	999
Life years gained ($*10^3$)	425	314	236	395	291	218	474	349	261	154	147	141
QALYs gained ($*10^3$)	365	266	199	335	244	182	408	296	221	132	126	122
ICER ($*10^3$ €/LY)	7.4	8.4	9.3	7.2	8.2	9.1	6.8	7.6	8.5	7.0	7.0	7.1
ICER ($*10^3$ €/QALY)	8.6	9.8	11.0	8.5	9.7	10.9	7.9	8.9	10.0	8.2	8.2	8.2

Probabilistic sensitivity analysis

Results of the sensitivity analysis are displayed in Table 6 as 95% confidence intervals for the outcomes measures, meaning that 95% of the simulations fell within the indicated ranges. It can be observed that the incremental cost effectiveness ratio's are within a rather small range. In that respect results can be judged to be robust. Nonetheless, there is some overlap between intervals, meaning that the relative order of the different medication compositions could be different.

Table 6: Results of the sensitivity analysis.

Outcomes	Polypill Scenario 2A	Polypill Scenario 2B	Polypill Scenario 2C	Separate medication
Cost of intervention (*10^6 €)	354-1,540	343-1,489	349-1,570	306-341
Incremental healthcare costs (*10^6 €)	580-2,630	560-2,570	640-2,980	290-1,140
Total incremental costs (*10^6 €)	940-4,120	900-4,030	990-4,530	600-1,490
Life years gained (*10^3)	113-517	110-507	130-613	59-241
QALYs gained (*10^3)	94-433	92-427	109-519	50-206
ICER (*10^3 €/LY)	7.5-9.7	7.4-9.6	6.9-8.9	5.9-10.3
ICER (*10^3 €/QALY)	8.9-11.7	8.8-11.6	8.1-10.5	6.9-12.0

Displayed are confidence intervals (95%) of the model outcomes for a 10-years risk threshold of 7.5%.

Figure 2 displays the range of values for costs and effects (QALYs) in the cost-effectiveness plane for 7.5% risk. It shows that most values cluster narrowly along what can be imagined as a line which has as slope the average cost-effectiveness ratio.

Figure 3 shows acceptability curves for the choice of treatment strategy for 7.5% risk. For each cost-effectiveness threshold (the maximum value below which a treatment is accepted as being cost-effective, or the "willingness to pay") it gives the probability that the treatment will be cost-effective. Thus, up to a level of about €9,000/QALY, separate medication is most likely to be cost-effective, but beyond that scenario 2C is most likely the best alternative. Variation of the costs of the most cost-effective polypill (scenario 2C) showed that when the price of the pill would be under 50 € per year (excluding drug delivery costs, and including VAT), scenario 2C would become the most favorable scenario when using a SCORE threshold of 7.5%. In the present calculations we estimated the price of the polypill in scenario 2C to be 65.76 € per year.

Discussion

The results of this study suggest that opportunistic screening and offering a polypill to people with a minimum 10-year risk of cardiovascular mortality of between 5% and 10% is a cost-effective strategy in the primary prevention of cardiovascular diseases. This is the case, whether the threshold chosen is 5%, 7.5% or 10%, but the lower the threshold, the lower the incremental cost-effectiveness ratio. All three differently composed polypills were cost-

effective compared with usual care, as was the single drug option. The polypill without aspirin but with a double dose of simvastatin leads to most health gains with all risk thresholds. At a 10 year risk of cardiovascular death of 7.5% or above, such a strategy would lead to an estimated decrease in the incidence of myocardial infarction and stroke of about 3.5%, at a cost of €9,800 per QALY. This is well below the consensual threshold of €20000 per QALY.[31] Separate medication, targeted at hypertension and/or hypercholesterolemia, is the most cost-effective strategy compared to usual care in the risk classes of 7.5%, respectively 10%, or above. However, total health gains are substantially lower.

Both the strengths and weaknesses of our study revolve around the weak basis of clinical evidence and the use of mathematical modeling. The latter allowed an exploratory investigation based on preliminary results of a phase II clinical trial, thus providing insights into the range of health benefits that can be expected. But with the lack of evidence of efficacy with regard to established clinical endpoints, the results should certainly not be taken as a precise estimate of the cost-effectiveness. We took into account what seemed to be the most important factors determining cost-effectiveness, but neglected, for instance, the costs of side effects.

Since Wald and Law's 2003 article, the appealing idea of a highly effective and safe polypill taken once daily to prevent cardiovascular disease has gained widespread attention and steps towards realization of the concept have been taken. Several prototypes have been developed and large scale clinical trials are currently under way. Yet, the only clinical evidence so far concerns a brief randomized trial of 12 weeks of treatment, the Polycap study. On the basis of this limited evidence it was concluded that the pill seems safe and that the effects on blood pressure and cholesterol are not inferior to the individual substances given separately. However, it must be said that the effects on these intermediate endpoints fall well below the rough estimates made by Law and Wald, who calculated that up to 80% of all cardiovascular events in the population at large could be prevented. There are two main sources for the discrepancy between their estimates and our calculations. Firstly, both the estimated effects on intermediate endpoints and the relative risk reductions (per unit of risk factor level reduction) Law and Wald used seem to have been too optimistic. Secondly, we did not consider the introduction of the polypill in the "universal" manner envisioned in their original article. It seems very unlikely that medicalization of a whole population will ever find wide support. Instead, we imagined a situation in which the polypill would be introduced within the current context of cardiovascular risk management and primary prevention. This approach is in line with current views on focusing on those at increased risk and finding ways of identifying them.[32] Only limited experience exists with this type of primary prevention, which might be best described as opportunistic screening.[38] Hence, we had to make several

assumptions to estimate the number of individuals who would ultimately take the polypill. These include the preparedness of GP's to engage in opportunistic screening, the proportion of eligible individuals who are willing to choose lifelong medication, and their compliance with treatment. Many will probably prefer changing their lifestyles, or will start but not continue. A lack of compliance obviously reduces cost-effectiveness, as investments are made that do not pay out in terms of health gains. On the other hand, the combination of drugs in one pill takes away an obstacle to compliance in patients requiring more than one drug.[33-35, 39] Literature shows that adherence to medication declines with the number of drugs prescribed.[33, 36, 37]

As mentioned above, we neglected the side effects of the drugs. As far as statins are concerned, the most serious complication is rhabdomyolysis, which is very rare, but can be fatal. More frequent are complaints of muscle pain.[40] However, a review and meta-analysis of Weng et al., of 75 trials showed that the incidence of muscle toxicity was low in all trials.[41] The most recent Cochrane meta-analysis did not find significant differences between placebo and treatment groups. The most important consequence would be that the relatively minor side effects would reduce adherence, or lead to discontinuation, an effect that is indirectly included in our model (via reduced compliance). The same applies to the side-effects of the blood pressure lowering components. In particular cough caused by an ACE inhibitor, which is independent of the dose, could lead to discontinuation of the pill.[28] Aspirin can cause gastro-intestinal bleedings and hemorrhagic stroke.[42-44] The latter more or less annul the protective effect on ischemic stroke, such that the net effect is neutral. Taking the occurrence of major bleedings into account would only reinforce our conclusion that a polypill containing aspirin is the least cost-effective option.

To gain more definite insights into the cost-effectiveness of the polypill in the opportunistic screening setting we envisioned, two major "unknowns" need to be clarified. Firstly, the results of large-scale phase III clinical trials will have to show how the effects on intermediate endpoints translate into clinical benefit. In particular, they will need to answer the question whether the "sum is greater than the parts", both with regards to benefits as to safety. Secondly, more needs to be known about the willingness to participate in opportunistic screening initiatives. This applies to eligible persons, but also to general practitioners. Also the practical consequences and logistic difficulties in implementing opportunistic screening will need to be addressed.

Implications

Primary prevention is increasingly seen as a crucial tool in further reducing the burden of cardiovascular disease. In a health care system such as that of the Netherlands, in which the general practitioner occupies a central role, opportunistic screening is a feasible strategy of

which the benefits are currently being actively explored. Thus, in the Netherlands an opportunistic screening by the general practitioners has recently been introduced and reimbursement has been recommended. Obviously, in order to make most out of this opportunity, insights into the relative cost-effectiveness of alternative preventive measures for those at increased risk is essential, as are the implications on effects and costs over a long time. Low doses aspirin are not recommended in the Dutch guideline in the primary prevention of cardiovascular diseases.[18] This is based on the adverse effects like gastrointestinal bleedings and hemorrhagic stroke caused by aspirin [42, 43]. The advantage of using a polypill without aspirin is that these adverse effects due to aspirin could be avoided. Since the introduction of the concept of a polypill by Wald and Law there were different changes in the composition and dosage of the medication put into this pill. One can expect that in the future further changes in the composition and dosage will lead to a better balanced pill. For example, ACE antihypertensive drugs cause often an unpleasant tickling cough. Replacement with a selective type 1 angiotensin II-receptor-(AT_1-) antagonist could solve this problem.

Guidelines on primary prevention cardiovascular suggest first to start with life-style changes like increase the physical activity and diet advices. In our calculation we did not include the costs and the effects of a life-style advisor.

Conclusion

The polypill or variants thereof seem to offer an efficient way to reduce the cardiovascular disease burden. Opportunistic screening of the population of 40 years or above to select individuals with a mild to moderately increased risk for cardiovascular diseases, followed by polypill prescription would prevent approximately 3.5% of all cardiovascular events. The cost-effectiveness of all variants is within the same order of magnitude. Therefore other aspects will determine which composition of pill is to be preferred, such as side effect profile and total health gains. Based on these criteria, our study suggests that the polypill without aspirin and a double statin dose is the most favorable option.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Contributors PFVG: study design, data-analyses, writing; EABO: study design, statistics, data-analyses; HHH: study-design, writing; GADW: study-design, writing; MVDB: writing; AJS: writing; PME: study-design, data-analyses, writing. All authors reviewed the manuscript and critically analysed the work.

References

1. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. Bmj. 2003 Jun 28;326(7404):1419.
2. AHA. Cardiovascular Disease Statistics 2010 [cited 2010 16-12]; Available from: http://www.americanheart.org/presenter.jhtml?identifier=4478
3. CBS. Causes of death 2009, short list. 2010 [cited 2010 0921]; Available from: http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=7052_95&D1=0,7,42&D2=a&D3=0&D4=l&HDR=T&STB=G2,G1,G3&VW=T
4. Vaartjes I, van Dis I, Visseren FLJ, et al. Chapter 1: Cardiovascular disease in the Netherlands (in Dutch). Den Haag, The Netherlands: Dutch Heartfoundation; 2009.
5. Zhao G, Ford ES, Li C, et al. Are United States adults with coronary heart disease meeting physical activity recommendations? Am J Cardiol. 2008 Mar 1;101(5):557-61.
6. Garner JB. Problems of nonadherence in cardiology and proposals to improve outcomes. Am J Cardiol. 2010 May 15;105(10):1495-501.
7. Bates TR, Connaughton VM, Watts GF. Non-adherence to statin therapy: a major challenge for preventive cardiology. Expert Opin Pharmacother. 2009 Dec;10(18):2973-85.
8. Corrao G, Conti V, Merlino L, et al. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. Clin Ther. 2010 Feb;32(2):300-10.
9. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil. 2007 Sep;14 Suppl 2:E1-40.
10. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003 Jun;24(11):987-1003.
11. Lonn E, Bosch J, Teo KK, et al. The polypill in the prevention of cardiovascular diseases: key concepts, current status, challenges, and future directions. Circulation. 2010 Nov 16;122(20):2078-88.
12. Yusuf S, Pais P, Afzal R, et al. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. Lancet. 2009 Apr 18;373(9672):1341-51.
13. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med. 2006 Apr 13;354(15):1567-77.

14. van Dis I, Kromhout D, Geleijnse JM, et al. Evaluation of cardiovascular risk predicted by different SCORE equations: the Netherlands as an example. Eur J Cardiovasc Prev Rehabil. 2010 Apr;17(2):244-9.

15. Hoogenveen RT, van Baal PH, Boshuizen HC. Chronic disease projections in heterogeneous ageing populations: approximating multi-state models of joint distributions by modelling marginal distributions. Math Med Biol. 2010 Mar;27(1):1-19.

16. Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, et al. Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study. Diabetes Care. 2007 Jan;30(1):128-34.

17. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003 Sep;24(17):1601-10.

18. CBO. Dutch Guideline Cardiovascular Risk Management Utrecht, The Netherlands; 2006.

19. Baal PHM, Feenstra TL, Hoogenveen RT, et al. Cost-Efectiveness analysis with the RIVM Chronic Disease Model. Bilthoven, Netherlands: Dutch National Institute for Public Health and the Environment; 2005. Report No.: 260706002.

20. Slobbe LCJ, Kommer GJ, Smit JM, et al. Cost-of-illness in the Netherlands 2003 Bilthoven, Netherlands: National Institute for Public Health and the Environment; 2006. Report No.: RIVM rapport 270751010.

21. Melse JM, Essink-Bot ML, Kramers PG, et al. A national burden of disease calculation: Dutch disability-adjusted life-years. Dutch Burden of Disease Group. Am J Public Health. 2000 Aug;90(8):1241-7.

22. Stouthard MEA, Essink-Bot ML, Bonsel GJ. Disability weights for diseases: A modified protocol and results for a Western European region. European Journal of Public Health. 2000;10(1):24-30.

23. Lopez AD, Murray CC. The global burden of disease, 1990-2020. Nat Med. 1998 Nov;4(11):1241-3.

24. van Baal PH, Hoeymans N, Hoogenveen RT, et al. Disability weights for comorbidity and their influence on health-adjusted life expectancy. Popul Health Metr. 2006;4:1.

25. Verschuren WM, Blokstra A, Picavet HS, et al. Cohort profile: the Doetinchem Cohort Study. Int J Epidemiol. 2008 Dec;37(6):1236-41.

26. CBS. Statistics Netherlands. 2010 [cited 2010 15 December]; Available from: http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=03799&D1=0-1,3-16&D2=0-2&D3=0&D4=a&HDR=G2,T,G3&STB=G1&VW=T

27. Chapman RH, Petrilla AA, Benner JS, et al. Predictors of adherence to concomitant antihypertensive and lipid-lowering medications in older adults: a retrospective, cohort study. Drugs Aging. 2008;25(10):885-92.

28. Law MR, Wald NJ, Morris JK, et al. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. Bmj. 2003 Jun 28;326(7404):1427.

29. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Manual for costing research. Methods and directive prices for economic evaluation in health care (in Dutch) Diemen: Institute for Medical Technology Assessment, Erasmus MC; 2010.

30. CVZ. Medicijnkosten. 2010 [cited 2010 15-12]; Available from: http://www.medicijnkosten.nl/

31. van den Berg M, de Wit GA, Vijgen SM, et al. [Cost-effectiveness of prevention: opportunities for public health policy in the Netherlands]. Ned Tijdschr Geneeskd. 2008 Jun 7;152(23):1329-34.

32. Wald NJ, Simmonds M, Morris JK. Screening for future cardiovascular disease using age alone compared with multiple risk factors and age. PLoS ONE. 2011;6(5):e18742.

33. Saini SD, Schoenfeld P, Kaulback K, et al. Effect of medication dosing frequency on adherence in chronic diseases. Am J Manag Care. 2009 Jun;15(6):e22-33.

34. Pan F, Chernew ME, Fendrick AM. Impact of fixed-dose combination drugs on adherence to prescription medications. J Gen Intern Med. 2008 May;23(5):611-4.

35. Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. Am J Health Syst Pharm. 2007 Jun;64(12):1279-83.

36. WHO. Adherence to long-term therapies: evidence for action. Geneva, Switzerland: World Health Organization; 2003.

37. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001 Aug;23(8):1296-310.

38. van de Kerkhof RM, Godefrooij MB, Wouda PJ, et al. [Cardiometabolic risk factors detected with a preventative screening programme]. Ned Tijdschr Geneeskd. 2010;154:A1860.

39. Erdine S. Compliance with the treatment of hypertension: the potential of combination therapy. J Clin Hypertens (Greenwich). 2010 Jan;12(1):40-6.

40. Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. Circulation. 2002 Aug 20;106(8):1024-8.

41. Weng TC, Yang YH, Lin SJ, et al. A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther. 2010 Apr;35(2):139-51.

42. Sanmuganathan PS, Ghahramani P, Jackson PR, et al. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. Heart. 2001 Mar;85(3):265-71.

43. Hayden M, Pignone M, Phillips C, et al. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002 Jan 15;136(2):161-72.

44. Berger JS, Roncaglioni MC, Avanzini F, et al. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials; 2006 Jan 18. Report No.: 1538-3598 (Electronic).

45. Turnbull F, Neal B, Ninomiya T, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. Bmj. 2008 May 17;336(7653):1121-3.

46. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005 Jun 27;165(12):1410-9.

47. Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2011(1):CD004816.

48. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010 Nov 13;376(9753):1670-81.

49. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005 Oct 8;366(9493):1267-78.

50. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009 May 30;373(9678):1849-60.

Appendix

Effects

As mentioned in the text, we based our estimates of the effects on the outcomes of the Indian Polycap Study.[12] The effect of the polypill on blood pressure was a lowering of the diastolic blood pressure with 5.7 mm Hg (95% CI 4.7-6.4) and of the systolic blood pressure with 7.4 mm Hg (95% CI 6.1-8.1). The LDL cholesterol was reduced by 0.80 mmol/L (95% CI 0.62-0.78).[12]

Blood pressure lowering

For blood pressure, we used a recent meta-analysis of the Blood Pressure Lowering Treatment Trialists' Collaboration.[45] Although the published article only reported results for 'major cardiovascular events' as outcome, supplementary analyses for stroke and coronary heart disease separately were obtained from the authors. For each 5 mm Hg reduction in systolic blood pressure the following risk ratio's were found: for stroke 0.83 (95% CI 0.74, 0.94) for those under 65 years of age, and of 0.91 (95% CI 0.84, 0.99) for those 65 years or older; for coronary heart disease 0.87 (95% CI 0.80, 0.95), and 0.90 (95% CI 0.84, 0.98), respectively; for total mortality, 0.92 (95% CI 0.85, 0.99) , and 0.96 (95% CI 0.91, 1.02), respectively. The relation between blood pressure reduction achieved and risk reduction was found to be log-linear. Moreover, the authors compared various drug classes, and concluded that there were no differences on the effects of lowering blood pressure according to drug class. Also when combinations of drugs are given, the effect on risk has been found to depend only on the reduction in blood pressure achieved.[28]

Assuming the findings of this meta-analysis, we calculated the relative risks corresponding to a 7.4 mm Hg reduction by raising the risk ratio's to the power (7.4/5). This resulted in the following risk ratios: for stroke, 0.76 (95% CI 0.91, 0.64) for those under 65 years of age, and 0.87 (95% CI 0.98, 0.77) for those 65 years or older; for coronary heart disease, 0.82 (95% CI 0.92, 0.72), and 0.86 (95% CI 0.96, 0.77), respectively; for total mortality, 0.88 (95% CI 0.99, 0.79), and 0.94 (95% CI 1.03, 0.87), respectively.

For separate treatment we took treatment with a diuretic or beta-blocker as standard. From a meta-analysis by the Blood Pressure Lowering Treatment Trialists'Collaboration [46], which compared various blood lowering agents both with each other and to placebo, we inferred that on average a diuretic results in a reduction of 7.2 mmHg. As this is almost the same as the reduction achieved by the polypill we used the same relative risk reduction values.

Cholesterol lowering

For statins, we used a recent meta-analysis by the Cochrane Collaboration on statins for the primary prevention of cardiovascular disease.[47] The mean difference in LDL-cholesterol between treatment groups and controls was -0.92 (95% CI -1.10, -.0.74), corresponding to relative risks of 0.72 (95% CI 0.65, 0.79) for coronary events, 0.78 (95% CI 0.65, 0.94) for stroke, and 0.84 (95% CI 0.73, 0.96) for total mortality. As the reduction found in the Polycap study was 0.80, we adjusted the risk ratios reported for the meta-analysis by raising them to the power 0.80/0.92. This is based on the assumption that the risk ratio has a log-linear relation with the reduction in cholesterol level (each mmol/L reduction reduces the risk by the same factor), for which there is much evidence.[48] After this adjustment, we found the following risk ratios: for coronary heart disease events, this was 0.75 (95% CI 0.69, 0.82), for stroke, it was 0.81 (95% CI 0.69, 0.95), and for total mortality, it was 0.86 (95% CI 0.76, 0.97). Again, assuming the log-linearity between level reduction and risk ratios, we calculated for the double dose the following risk ratios: for coronary heart disease events, this was 0.52 (95% CI 0.42, 0.62), for stroke, it was 0.61 (95% CI 0.42, 0.88), and for total mortality, it was 0.71 (95% CI 0.53, 0.92).

In the literature no difference was found in the number of adverse events, or in the number of individuals who developed cancer or myalgia.[41, 47, 49]

Anti-platelet effects

A recent meta-analysis of aspirin in the primary prevention of vascular disease [50] found the following risk ratios for the treatment group versus the control group: any major coronary event 0.82 (0.75-0.90); No significant net effect on stroke (decrease in ischaemic strokes compensated by an increase in haemorrhagic strokes).

Table 1 gives an overview of the risk reductions used due to simvastatin, the blood pressure lowering agents, and aspirin. Relative risks of those using medication versus those without medication as used in the model are expressed separately for the different types of medication. Effects are assumed to be independent. To calculate the aggregate effect of a particular combination relative risks are multiplied.

Table 1: Relative risks versus no medication

Relative risk	*Statin 20 mg*	*Statin 40 mg*	*BPL in PP*	*BPL separate*	*aspirin*
Total mortality	0.86	0.74	0.91	0.91	1
CVA	0.81	0.65	0.81	0.81	1
AMI	0.75	0.56	0.84	0.84	0.82

BPL: blood pressure lowering drug; PP: polypill

Show

Figure 15.5.a: Drummond checklist (Drummond 1996)

Item		Yes	No	Not clear	Not appropriate
Study design					
1.	The research question is stated.	☒	☐	☐	
2.	The economic importance of the research question is stated.	☒	☐	☐	
3.	The viewpoint(s) of the analysis are clearly stated and justified.	☒	☐	☐	
4.	The rationale for choosing alternative programmes or interventions compared is stated.	☒	☐	☐	
5.	The alternatives being compared are clearly described.	☒	☐	☐	
6.	The form of economic evaluation used is stated.	☒	☐	☐	
7.	The choice of form of economic evaluation is justified in relation to the questions addressed.	☒	☐	☐	
Data collection					
8.	The source(s) of effectiveness estimates used are stated.	☒	☐	☐	
9.	Details of the design and results of effectiveness study are given (if based on a single study).	☐	☐	☐	☒
10.	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	☒	☐	☐	☐
11.	The primary outcome measure(s) for the economic evaluation are clearly stated.	☒	☐	☐	
12.	Methods to value benefits are stated.	☐	☐	☐	☒
13.	Details of the subjects from whom valuations were obtained were given.	☐	☐	☐	☒
14.	Productivity changes (if included) are reported separately.	☐	☐	☐	☒
15.	The relevance of productivity changes to the study question is discussed.	☐	☐	☐	☒
16.	Quantities of resource use are reported separately from their unit costs.	☒	☐	☐	
17.	Methods for the estimation of quantities and unit costs are described.	☒	☐	☐	
18.	Currency and price data are recorded.	☒	☐	☐	
19.	Details of currency of price adjustments for inflation or currency conversion are given.	☐	☐	☐	☒
20.	Details of any model used are given.	☒	☐	☐	☐
21.	The choice of model used and the key parameters on which it is based are justified.	☒	☐	☐	☐
Analysis and interpretation of results					
22.	Time horizon of costs and benefits is stated.	☒	☐	☐	☐
23.	The discount rate(s) is stated.	☒	☐	☐	☐
24.	The choice of discount rate(s) is justified.	☒	☐	☐	☐
25.	An explanation is given if costs and benefits are not discounted.	☐	☐	☐	☒
26.	Details of statistical tests and confidence intervals are given for stochastic data.	☒	☐	☐	☐
27.	The approach to sensitivity analysis is given.	☒	☐	☐	☐
28.	The choice of variables for sensitivity analysis is justified.	☒	☐	☐	☐
29.	The ranges over which the variables are varied are justified.	☒	☐	☐	☐
30.	Relevant alternatives are compared.	☒	☐	☐	☐
31.	Incremental analysis is reported.	☒	☐	☐	☐
32.	Major outcomes are presented in a disaggregated as well as aggregated form.	☒	☐	☐	
33.	The answer to the study question is given.	☒	☐	☐	
34.	Conclusions follow from the data reported.	☒	☐	☐	
35.	Conclusions are accompanied by the appropriate caveats.	☒	☐	☐	

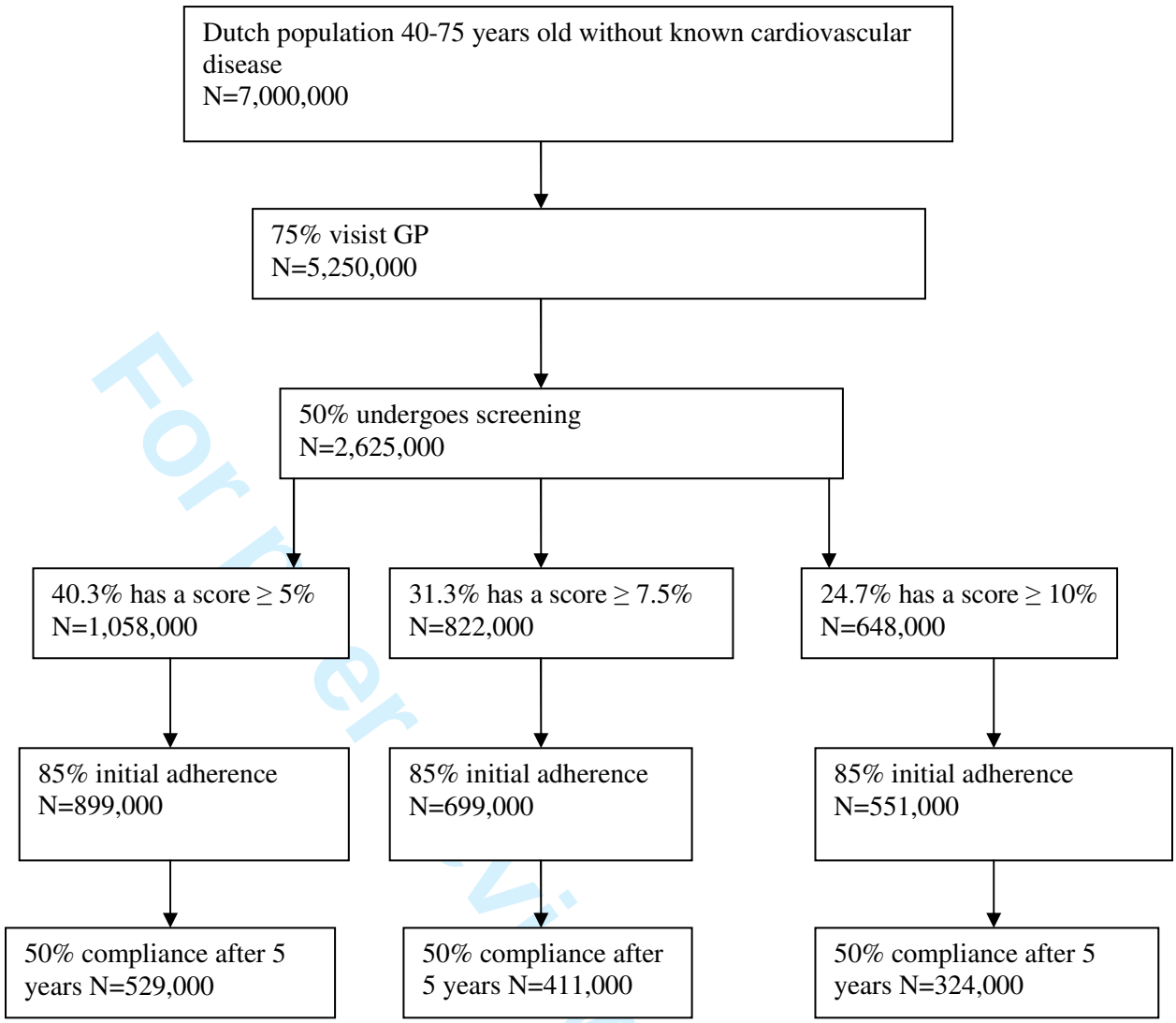


Figure 1. Flow chart of participation

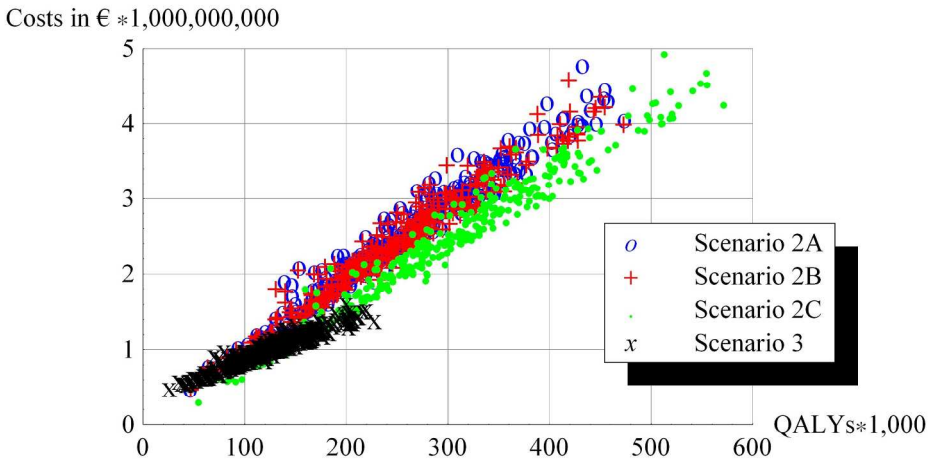


Figure 2. Scatterplot of costs versus QALY's
1058x661mm (72 x 72 DPI)

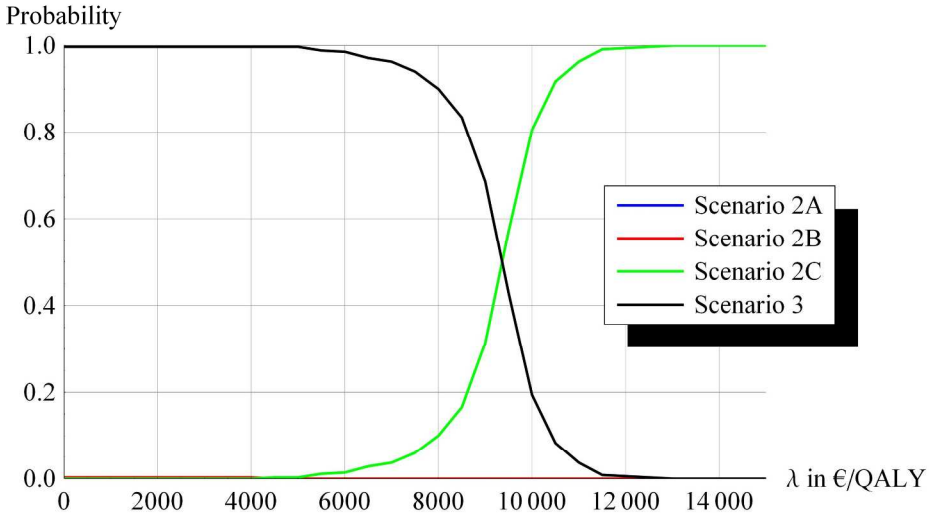


Figure 3. Acceptability curves for the choice of treatment strategy
1058x661mm (72 x 72 DPI)

BMJ open

The polypill in the primary prevention of cardiovascular disease: cost-effectiveness in the Dutch population.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000363.R1
Article Type:	Research
Date Submitted by the Author:	02-Nov-2011
Complete List of Authors:	van Gils, Paul; National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research Over, Eelco; National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research Hamberg, Heleen; National Institute for Public Health and the Environment, Centre for Public Health Forecasting de Wit, G. Ardine; National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research van den Berg, Matthijs; National Institute for Public Health and the Environment, Centre for Public Health Forecasting Engelfriet, Peter; National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Pharmacology & therapeutics, Health economics, Public health
Keywords:	Myocardial infarction < CARDIOLOGY, HEALTH ECONOMICS, PUBLIC HEALTH, Stroke < NEUROLOGY

The polypill in the primary prevention of cardiovascular disease: cost-effectiveness in the Dutch population.

Paul F. van Gils [1], Eelco A.B. Over [1], Heleen H. Hamberg-van Reenen [2], G. Ardine de Wit [1], Matthijs van den Berg [2] , Albertine J. Schuit [1] en Peter M. Engelfriet [1]

[1]National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research, Bilthoven, The Netherlands
[2] National Institute for Public Health and the Environment, Centre for Public Health Forecasting, Bilthoven, the Netherlands

Paul van Gils, MSc
Centre for Prevention and Health Services Research
National Institute of Public Health and the Environment
PO Box 1
3723 BA Bilthoven
The Netherlands
Telephone:+31 302748581
Fax: + 31 30 274 4407
Email: paul.van.gils@rivm.nl

Eelco A.B. Over, PhD
Centre for Prevention and Health Services Research
National Institute of Public Health and the Environment
PO Box 1
3723 BA Bilthoven
The Netherlands
Telephone:+31 302742700
Fax: + 31 30 274 4407
Email: eelco.over@rivm.nl

Heleen H. Hamberg, PhD
Centre for Public Health Forecasting
National Institute for Public Health and the Environment
P.O. box 1
3720 BA Bilthoven
The Netherlands
Telephone: +31 30 2742735
Fax: +31 30 2744450
Email: heleen.hamberg@rivm.nl

G.Ardine de Wit, PhD
Centre for Prevention and Health Services Research
National Institute of Public Health and the Environment
PO Box 1
3720 BA Bilthoven
The Netherlands
Telephone: + 31 30 274 3206
Fax: + 31 30 274 4407
Email: ardine.de.wit@rivm.nl

M. van den Berg, PhD
Centre for Public Health Forecasting
National Institute for Public Health and the Environment
P.O. box 1
3720 BA Bilthoven
The Netherlands
Telephone: +31 30 2743349
Fax: +31 30 2744450
Email: matthijs.van.den.berg@rivm.nl

Albertine J. Schuit, PhD
Centre for Prevention and Health Services Research
National Institute of Public Health and the Environment
PO Box 1
3720 BA Bilthoven
The Netherlands
Telephone: + 31 30 274 2945
Fax: + 31 30 274 4407
Email: janinte.schuit@rivm.nl

Peter M. Engelfriet, MD, PhD
Centre for Prevention and Health Services Research
National Institute of Public Health and the Environment
PO Box 1
3720 BA Bilthoven
The Netherlands
Telephone: + 31 30 274 4388
Fax: + 31 30 274 4407
Email: peter.engelfriet@rivm.nl

Correspondence: Paul van Gils
Centre for Prevention and Health Services Research (pb 101)
National Institute of Public Health and the Environment
PO Box 1
3720 BA Bilthoven
The Netherlands

Paul.van.gils@rivm.nl
Phone: + 31 30 2748581
Fax: + 31 30 274 4407

Conflict of interest statement
We declare that no conflict of interest exists for any of the authors.

ABSTRACT

Objectives

The aim of the present study was to estimate the cost-effectiveness of the polypill in the primary prevention of cardiovascular disease.

Design

A health economic modeling study.

Setting

Primary health care in the Netherlands.

Participants

Simulated individuals from the general Dutch population, aged 45-75 years of age

Interventions

Opportunistic screening followed by prescription of the polypill to eligible individuals. Eligibility was defined as having a minimum10-year risk of cardiovascular death as assessed with the SCORE function of alternatively 5%, 7.5%, or 10%. Different versions of the polypill were considered, depending on composition: 1) the Indian polycap, with three different types of blood pressure lowering drugs, a statin, and aspirin; 2) as 1) but without aspirin; 3) as 2) but with a double statin dose. In addition, a scenario of (targeted) separate antihypertensive and/or statin medication was simulated.

Primary outcome measures

Cases of acute myocardial infarction or stroke prevented, QALYs gained, and the costs per QALY gained. All interventions were compared with usual care.

Results

All scenarios were cost-effective with an incremental cost-effectiveness ratio between €7,900-12,300 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.

Conclusions

Opportunistic screening based on global cardiovascular risk assessment followed by polypill prescription to those with increased risk offers a cost-effective strategy. Most health gain is achieved by the polypill without aspirin and a double statin dose.

Article summary

Article focus

- Cardiovascular diseases (CVD) continue to be still a major, partly preventable, cause of illness and death.
- A polypill that lowers by targeting several risk factors simultaneously is in line with the concept that the aim in primary prevention should be to bring down 'global' cardiovascular risk.
- The aim of this study was to estimate the potential cost-effectiveness of polypill prescription after opportunistic screening.

Key messages

- The results of this study suggest that opportunistic screening and offering a polypill to people with a minimum 10-year risk of cardiovascular mortality of alternatively 5%, 7.5% or 10% is a cost-effective strategy.
- A polypill without aspirin but with a double dose of simvastatin leads to most health gains at all risk thresholds considered. At a 10 year risk of cardiovascular death of 7.5% or above, such a strategy would lead to an estimated decrease in the incidence of myocardial infarction and stroke of about 3.5%, at a cost of €8,900 per QALY.
- Opportunistic screening of the population of 40 years or above to select individuals with a mild to moderately increased risk for cardiovascular diseases, followed by polypill prescription would prevent approximately 3.5% of all cardiovascular events.

Strengths and limitation of this study

- Strong point of the study is that different compositions of the polypill have been modelled. Also, realistic estimates for adherence and compliance have been used.
- As only preliminary results of a phase II clinical trial on efficacy of the polypill were available, we had to apply mathematical modelling to estimate cost-effectiveness. This provides insight into the range of health benefits that can be expected. Pending results with regard to established clinical endpoints from large-scale phase III trials, the results of this study should not be taken as a precise estimate of the cost-effectiveness of the polypill.

Introduction

In a by now famous article in the British Medical Journal in 2003, Wald and Law suggested that a 'polypill' could be of great benefit in the prevention of cardiovascular disease [1]. As originally proposed, such a pill would consist of a combination of drugs with proven efficacy and safety in reducing cardiovascular risk, in particular three different types of blood pressure lowering drugs (a beta-blocker, an antidiuretic and an ACE inhibitor), one lipid lowering drug, an antiplatelet agent (aspirin), and folic acid to reduce serum homocysteine. In combination, lower dosages could be used resulting in greater efficacy than single medication with a more favorable safety profile than higher dosages of individual drugs.

Cardiovascular diseases (CVD) are still a major cause of illness and death. For example, estimates show that in the year 2006 more than 80 million people in the United States had one or more forms of CVD [2]. In 2009, CVD was responsible for 29% of all deaths in the Netherlands, taking second place after cancer (32%) as the most important cause of death.[3] Ischemic heart disease and stroke together were responsible for 27% of all hospitalizations.[4] As CVD is the result of a gradual process of atherosclerosis building up over many years, the most rational strategy is stopping, or at least slowing down, the progress of plaque formation. For those whose risk factor levels put them at increased risk, life style measures or medication are available for primary prevention, but identifying who might benefit and what measures are most appropriate is subject of much discussion.[5-8] The recognition that atherosclerotic CVD is the product of multiple interacting risk factors has in the past decades led to new approaches in prevention. In particular, the concepts of global risk, being the aggregate risk of all risk factors together, and total CVD risk assessment have emerged as an important inspiration for developing guidelines on cardiovascular risk management.[9] Examples of methods of global risk assessment are the well known Framingham risk score and the SCORE (Systematic Coronary Risk Evaluation), the latter based on a pooled data set of 12 European cohort studies.[10] A consequence of the global risk approach is that the focus of intervention shifts from treatment of individual risk factors to placing emphasis on reducing total CVD risk, irrespective by what means. Thus, the idea of a polypill, that lowers risk by targeting more than one risk factor simultaneously, seems perfectly tailored to this strategy.[11] In addition, it offers the benefit of a 'one stop shop' when someone could benefit from one type of medication.

Up to the present, no evidence for the effectiveness of such a polypill exists. Yet, randomized clinical trials with several versions of a polypill have been started. The Indian Polycap Study was a phase II randomized double-blind clinical trial designed to test the effects of a version of the polypill on intermediate measures for the development of CVD, in particular blood pressure, cholesterol, heart rate, and urinary dehydrotrombaxane B2.[12] The polypill used in

this RCT differed from the one suggested by Wald and Law by omitting folic acid, as the supposed effects of folic acid on serum homocysteine have not been confirmed.[13] Medication was only given for a period of 12 weeks in the Polycap study.

Even though there is still no evidence regarding the efficacy of a polypill on hard endpoints (acute myocardial infarction, stroke), the extensively validated relation between blood pressure and cholesterol level on the one hand and disease risk on the other, allows a first exploration of the range of costs and benefits that might be expected from the polypill in the prevention of cardiovascular diseases.

The aim of this study was to estimate the potential cost-effectiveness of the polypill in the primary prevention of myocardial infarction and ischemic stroke. In order to explore this issue a scenario of opportunistic screening in primary care was taken as point of departure. Patients were eligible for prescription of the polypill starting from a 5% risk up to 10% risk of cardiovascular death in 10 years, based on their SCORE function.[14]

Methods

We conducted a simulation study using a computer model (RIVM Chronic Disease Model-CDM) developed at our institute.[15 16] Point of departure for the simulations was a scenario, in which the polypill is offered to eligible patients identified during routine visits to their GP, ('opportunistic screening'). The GP takes the initiative suggesting to patients to determine their 10-year risk for cardiovascular mortality. Those aged 40-75 years of age without known previous cardiovascular disease are eligible for the screening. Starting from risk levels of 5% or higher, people will be offered lifelong preventive medication. Cardiovascular mortality risk is assessed using the SCORE risk function developed and recommended by the European Society of Cardiology, and endorsed in the Netherlands by professional and patient's organizations.[17] The score function is calculated using age, sex, blood pressure, cholesterol, and smoking status as input.

The current Dutch guideline for primary cardiovascular prevention, which was introduced in 2006, recommends the SCORE risk charts to determine treatment recommendations. For this purpose a version of the SCORE was developed adapted to Dutch risk factor and mortality data.[14] It is the algorithm for this version that we used in our analyses.

According to the Dutch guideline, for individuals with a 10-year risk of cardiovascular death of 10% or higher targeted drug therapy is recommended: antihypertensive treatment when SBP $\geq$ 140; statins when LDL cholesterol > 2.5 mmol/L. When risk exceeds 5%, life style counseling should be considered. Aspirin is recommended for secondary prevention only.[18]

Following the rationale that arguments for the polypill are based on the expectancy of a more favorable benefit versus safety profile, we assumed that, in a situation where a polypill would

be available, it would be considered to lower the threshold for prescribing preventive medication. On the other hand, it seems unlikely prescribing the preventive medication to anyone. Especially for risks lower than 5% consensual support is needed. Therefore, in order to assess the effect of different choices for the threshold, we performed analyses for different cut points; 5%, 7.5%, and also 10%, the threshold for drug treatment of the present guideline.

The RIVM Chronic Disease Model

The CDM is a computer simulation model designed to be able to simulate the evolution of several chronic diseases in relation to risk factor levels in the Dutch population. It includes the most common chronic diseases, amongst which COPD, diabetes mellitus type 2, myocardial infarction and stroke, and, besides a number of life style related risk factors, such as smoking, blood pressure and cholesterol. It may be best characterised as a Markov-type, multistate-transition model.[15 16] The model describes the development over time of demography, risk factor prevalence, disease incidence, and mortality, in 1-year time steps. As input it takes the age- and sex composition of the current Dutch population and the distribution of risk factor levels in the population. It further requires specification of three types of transition probabilities (the probability of going from one state to another in 1 year time): between risk factor levels, between disease states (from no disease to disease, i.e. disease incidence, for each disease in the model), and mortality rates. Disease incidence and mortality depend on risk factor levels and the presence of other diseases via relative risks. Estimates of relative risks were derived from literature, whereas incidence, prevalence, transition rates, and mortality rates in the model apply to the Dutch population. In addition, each disease is associated with average yearly, per patient, costs, and with disability weights. All data are age and sex specific. The model further allows specifying alternative "scenarios", by adjusting the input parameters, and comparing the results obtained with other scenarios with the 'reference scenario (see below)'. Health care costs were based on costs-of-illness studies in the Netherlands [19 20] and the healthcare outcome measure 'quality-adjusted life year (QALY)' was computed using the Global and Dutch burden of disease studies.[21-24]

Scenarios

Several scenarios were defined based on: 1) different cut-off levels for 10-year risk: 5%, 7.5% and 10%; 2) different compositions of the polypill. These scenarios were compared with the reference scenario of care as usual and with each other. Usual care is represented in our model in the reference scenario by the proportion of individuals currently being treated with statins and/or antihypertensive agents, based on data from the Doetinchem cohort study (details about this study follow later).[25] It is assumed that individuals already being treated with drugs will not switch to the polypill. We further assume that people identified as being at risk by

opportunistic screening would otherwise not receive preventive medication. In other words, the polypill was prescribed only to unexposed individuals who did not already use one of the drugs included in the polypill. The different scenarios explored using the CDM model are:

1) The reference scenario represents the expected evolution of the health status and risk factor distribution of the Dutch population as simulated by the model using the basic input parameters that represent the relevant characteristics of the current Dutch population (current practice).

2) The polypill scenarios simulate the situation in which all eligible individuals, not yet treated with statins or antihypertensive agents, and selected by 'opportunistic screening', are offered lifelong medication. Besides the original Indian 'Polycap' composition, we also considered different versions of the polypill without aspirin that would avoid the bleeding risks associated with anti-platelet agents. Thus, the following alternative compositions of polypills were considered:

2A) The 'Indian Polycap', consisting of 20 mg simvastatin, 12,5 mg thiazide, 5 mg ramipril, 50 mg atenolol, 100 mg aspirin.

2B) As 2A) but without aspirin.

2C) As 2B) but with 40 mg simvastatin (double dose statins, i.e. Dutch standard dose when given as monotherapy).

Finally, an alternative scenario was defined (scenario 3: 'separate medication') in which screened individuals eligible for the polypill will not be offered the polypill, but rather medication tailored to the underlying risk factor: a statin in case of hypercholesterolemia, an anti-hypertensive in case of hypertension, both, or none (i.e. the risk score is increased, but blood pressure and hypertension are below the respective cut points).

Basically, the analyses compare the scenarios in which medication is offered in primary care to all eligible individuals in the age group 40-75 years with the scenario in which usual care is continued. The comparison thus is between a hypothetical population with one of the interventions described above and one without, where in all other respects the populations are equal at baseline and represent the current Dutch population. The model is 'run' until all have died and no 'inflow' of younger individuals is taken into account.

Below, we describe how we derived values for the relevant parameters for each scenario.

Estimation of the number of eligible individuals and of the proportion who would be treated

In order to estimate the numbers of individuals who would receive the polypill, the following steps were taken (Fig. 1).

First, the proportion of the population aged 40-75 years without a history of CVD and not yet treated with statins or antihypertensives was estimated. To this end, we applied the SCORE

algorithm to the most recent data of the Doetinchem cohort study. The Doetinchem cohort study is a prospective study of more than 5,000 inhabitants of the city of Doetinchem and surroundings who were included in the years 1987-91. Participants were aged 20-65 years at inclusion, and have been followed for more than 20 years now. So far, 4 rounds of data collection have been completed, roughly at 5-year intervals. We used the data of round 4, collected during the years 2003-2007. Among the data collected all variables necessary to calculate the SCORE are included (age, sex, SBP, LDL cholesterol, smoking status, treatment status of statins and antihypertensive). The Doetinchem cohort has been described elsewhere.[25] The cohort represents the best available source for the Netherlands to determine the current population distribution of risk factors.

Next, we needed to estimate how many people would be reached by opportunistic screening. Data taken from Statistics Netherlands show that approximately 75% of the Dutch population visit their GP al least once every year.[26] We assumed that this figure also applies to our target population. We further assumed that the GP offers a screening consultation to all in the target population (those aged 40-75 years) in the year of the intervention, and that 50% of the invited population consent. Risk assessment consists of one consultation with GP, who explains the procedure, measures blood pressure, and draws blood for a laboratory test of blood cholesterol. The patient is then invited for a second consultation to calculate the SCORE and discuss the consequences.

We finally assumed that of those who are offered the polypill (SCORE ≥ 5%, 7.5%, or 10%), or a separate statin/antihypertensive, 85% will decide to take the pill for at least one year [12], and that compliance rates would stabilize at 50% after 5 years. A flow chart of the process of screening and selecting patients is shown below: for the separate medication scenario (scenario 3) we assumed that adherence (willingness to start with the therapy) to the antihypertensive was 90% and adherence to the statin was 60% [27], which fraction was multiplied by the before-mentioned compliance rate to achieve total compliance (willingness to continue the therapy).

Effects

A crucial parameter in implementing the polypill scenarios is the measure of its efficacy, in particular the relative risk reduction: the relative risk for acute myocardial infarction or stroke after taking the medication compared to the relative risk before taking it (or in a control (placebo) group). Unfortunately, as mentioned above, so far there are no data on the effects of the polypill on cardiovascular events. Instead, we will have to base our estimate on the effects on "intermediate" measures, i.e. blood pressure and cholesterol. In particular, we use the outcomes of the Indian Polycap Study.[12] As mentioned above, the Indian polypill consist of

three blood pressure lowering drugs: hydrochlorthiazide 12.5 mg (a diuretic), atenolol 50 mg (a β-blocker) and ramipril 5 mg (an angiotensin converting enzyme inhibitor), a lipid lowering drug (simvastatin 20 mg) and an antiplatelet (aspirin 100 mg). The effect of the polypill on blood pressure was a lowering of the diastolic blood pressure with 5.7 mm Hg (95% CI 4.7-6.4) and of the systolic blood pressure with 7.4 mm Hg (95% CI 6.1-8.1). The LDL cholesterol was reduced by 0.80 mmol/L (95% CI 0.62-0.78).[12]

These effects on blood pressure and cholesterol are substantially lower than what Law and Wald predicted. Thus, the RR reductions suggested in their article and in the accompanying meta-analysis of combination treatment with blood pressure lowering drugs [28] could not be relied upon for our purposes. Instead, we took as a basis the reductions in blood pressure and cholesterol observed in the Polycap study and translated these into corresponding RR reductions using meta-analyses providing estimates of these relations.

Blood pressure lowering

For blood pressure, we used a recent meta-analysis of the Blood Pressure Lowering Treatment Trialists' Collaboration.[29] Although the published article only reported results for 'major cardiovascular events' as outcome, supplementary analyses for stroke and coronary heart disease separately were obtained from the authors. For each 5 mm Hg reduction in systolic blood pressure the following risk ratio's were found: for stroke 0.83 (95% CI 0.74, 0.94) for those under 65 years of age, and of 0.91 (95% CI 0.84, 0.99) for those 65 years or older; for coronary heart disease 0.87 (95% CI 0.80, 0.95), and 0.90 (95% CI 0.84, 0.98), respectively; for total mortality, 0.92 (95% CI 0.85, 0.99) , and 0.96 (95% CI 0.91, 1.02), respectively. The relation between blood pressure reduction achieved and risk reduction was found to be log-linear. Moreover, the authors compared various drug classes, and concluded that there were no differences on the effects of lowering blood pressure according to drug class. Also when combinations of drugs are given, the effect on risk has been found to depend only on the reduction in blood pressure achieved.[28]

Assuming the findings of this meta-analysis, we calculated the relative risks corresponding to a 7.4 mm Hg reduction by raising the risk ratio's to the power (7.4/5). This resulted in the following risk ratios: for stroke, 0.76 (95% CI 0.91, 0.64) for those under 65 years of age, and 0.87 (95% CI 0.98, 0.77) for those 65 years or older; for coronary heart disease, 0.82 (95% CI 0.92, 0.72), and 0.86 (95% CI 0.96, 0.77), respectively; for total mortality, 0.88 (95% CI 0.99, 0.79), and 0.94 (95% CI 1.03, 0.87), respectively.

For separate treatment we took treatment with a diuretic or beta-blocker as standard. From a meta-analysis by the Blood Pressure Lowering Treatment Trialists'Collaboration [30], which compared various blood lowering agents both with each other and to placebo, we inferred that

on average a diuretic results in a reduction of 7.2 mmHg. As this is almost the same as the reduction achieved by the polypill we used the same relative risk reduction values.

Cholesterol lowering

For statins, we used a recent meta-analysis by the Cochrane Collaboration on statins for the primary prevention of cardiovascular disease.[31] The mean difference in LDL-cholesterol between treatment groups and controls was -0.92 (95% CI -1.10, -.0.74), corresponding to relative risks of 0.72 (95% CI 0.65, 0.79) for coronary events, 0.78 (95% CI 0.65, 0.94) for stroke, and 0.84 (95% CI 0.73, 0.96) for total mortality. As the reduction found in the Polycap study was 0.80, we adjusted the risk ratios reported for the meta-analysis by raising them to the power 0.80/0.92. This is based on the assumption that the risk ratio has a log-linear relation with the reduction in cholesterol level (each mmol/L reduction reduces the risk by the same factor), for which there is much evidence.[32] After this adjustment, we found the following risk ratios: for coronary heart disease events, this was 0.75 (95% CI 0.69, 0.82), for stroke, it was 0.81 (95% CI 0.69, 0.95), and for total mortality, it was 0.86 (95% CI 0.76, 0.97). Again, assuming the log-linearity between level reduction and risk ratios, we calculated for the double dose the following risk ratios: for coronary heart disease events, this was 0.52 (95% CI 0.42, 0.62), for stroke, it was 0.61 (95% CI 0.42, 0.88), and for total mortality, it was 0.71 (95% CI 0.53, 0.92).

In the literature no difference was found in the number of adverse events, or in the number of individuals who developed cancer or myalgia.[31 33 34]

Anti-platelet effects

A recent meta-analysis of aspirin in the primary prevention of vascular disease [35] found the following risk ratios for the treatment group versus the control group: any major coronary event 0.82 (0.75-0.90); No significant net effect on stroke (decrease in ischaemic strokes annulled by an increase in haemorrhagic strokes).

Table 1 gives an overview of the risk reductions used due to simvastatin, the blood pressure lowering agents, and aspirin. Relative risks of those using medication versus those without medication as used in the model are expressed separately for the different types of medication. Effects are assumed to be independent. To calculate the aggregate effect of a particular combination relative risks are multiplied.

Table 1: Relative risks versus no medication (95% CI)

Relative risk	*Statin 20 mg*	*Statin 40 mg*	*BPL in PP*	*BPL separate*	*aspirin*
Total mort.	0.86 (0.76-0.97)	0.71 (0.53-0.92)	0.91 (0.83-1.00)	0.91 (0.83-1.00)	1
CVA	0.81 (0.69-0.95)	0.61 (0.42-0.88)	0.81 (0.70-0.94)	0.81 (0.70-0.94)	1
AMI	0.75 (0.69-0.82)	0.52 (0.42-0.62)	0.84 (0.74-0.94)	0.84 (0.74-0.94)	0.82 (0.75-0.90)

BPL: blood pressure lowering drug; PP: polypill

Costs

Costs were determined from the perspective of the health care payer and according to the national guideline for costing research in health economic analysis.[36] Direct medical costs associated with diseases per patient per year were included in the CDM.[19 20] Costs due to all medical treatment in life years gained (indirect medical cost) are automatically included in the model.

Costs for screening and drug use

Unit costs, including costs for GP visits, laboratory testing, medication and drug delivery are presented in Table 2.

Costs during the first year consist of two GP visits, one laboratory test, and if indicated the costs of medication and drug delivery.

During the second and subsequent years, the costs consist of one GP visit (control visit), one laboratory test, and the costs of drug delivery.

As currently the polypill is not yet on the market, a price had to be estimated based on its "ingredients". We took as our reference the costs per mg of statins, beta-blockers, ace-inhibitors and aspirin prescribed as generics in the Netherlands, and we assumed that the price of a pill would be the sum of the prices of its components.[37] Thus, the Polycap pill (scenario 1) would cost € 89.75 per year, including fees for prescription and drug delivery.

Table 2: Intervention costs

Item	unit	costs per unit /quantity in PP	costs per person per year
GP visit *	Standard consultation	€ 29	58 (first year)
			29 (subsequent years)
Blood drawing		Included	
Laboratory		€ 1.70	1.80
Drug costs **			
Simvastatin 20mg dd	1 year	€ 6.69	6.69
Simvastatin 40 mg	1 year	€ 13.39	13.39
Ramipril 2.5 mg	1 year	€ 22.48	22.48
Atenolol 50 mg	1 year	€ 22.48	22.48
Thiazide 12.5 mg	1 year	€ 3.47	3.47
Aspirin 100 mg	1 year	€ 3.70	3.70
Drug delivery costs***	First delivery	€ 5.74	
	Per 3 months	€ 5.74	28.70 (first year)
			22.96 (subsequent years)
Repeat prescription***		Included in basic tariffs	
Gastrointestinal bleeding (adverse event)***		€ 3,425	€3,425

Costs in the first year consist of 2 GP visits, one laboratory test, 4 times drug delivery, and an additional charge for first drug delivery. Costs in subsequent years: 1 GP visit plus 1 laboratory test plus 4 times drug delivery costs.

* Fees in The Netherlands are determined by the national regulator of Healthcare tariffs: Nederlandse Zorgautoriteit (National Health Authority). In addition to costs per visit, GP's are paid for each patient registered in their practice on a yearly basis. Website http://www.nza.nl. Consulted on June 16, 2011.

** Drug costs are based on the costs as calculated and publicized by the College for Health Insurance, which determines the prices for reimbursement (Pharmaco-therapeutic compass: http//www.cvz.nl/kompas)

*** According to maximum fees set for the year 2011 by National Health Authority (nza, "tariefbeschikking" nr. TB/CU-5000-01, nr. 34 www.nza.nl)

Costs and effects associated with adverse events

The frequency of adverse effects of the use of statins and antihypertensive agents has consistently been reported to be very low. We assumed that the costs and effects due to these agents are captured by taking into account nonadherence and stopping taking the pill. The adverse effects of aspirin, however, are known to be more severe. In particular, the risks of major bleedings should be taking into account. The increased risk of hemorrhagic stroke is already incorporated in our estimate of the relative risk for stroke (see above).. The costs and (negative) effects of gastrointestinal bleedings caused by the use of aspirin were added to the model in the following manner. The incidence rate of gastro-intestinal bleedings was

estimated to 8.5 per year per 1000 patients.[38] The loss of utility caused by gastro-intestinal bleedings was estimated to be 0.06.[39] The costs of gastro-intesital bleeding were estimated at €3,425,according to the Dutch Diagnosis Related Group (DRG) tariff (www.nza.nl).

Total costs

Total costs were calculated by multiplying unit costs with volumes. Volumes were derived by determining the 'numbers of units per patient' and the numbers of patients at each stage in the process: first screening, then start therapy, first year, and finally all subsequent years of the simulation.

Cost-effectiveness

The main endpoint of this study was the cost-effectiveness ratio expressed as the ratio of the difference in costs and the difference in QALYs when comparing the alternative scenarios with the reference scenario (Cost/QALY)

As the rationale for prescribing the polypill is to prevent cardiovascular disease, we also determined the numbers of myocardial infarctions and strokes prevented in the different scenarios. This was done by calculating the differences in the cumulative incidences between scenarios. Finally, these figures were used to estimate the numbers of patients that would have to be treated (NNT) to prevent one myocardial infarction, respectively stroke. Taking 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.[36] The chosen time horizon was a life-time horizon.

Probabilistic sensitivity analyses

As several important assumptions had to me made in modeling the cost-effectiveness of the polypill, we explored the range of likely outcomes with a probabilistic multivariate sensitivity analysis. The key variables with known uncertainty were: screening acceptance, adherence to medication, relative risks for developing stroke and myocardial infarction, and the relative risk for all-cause mortality. Screening acceptance was taken to be distributed as a Beta distribution (alpha=5, beta=5) so that the average acceptance was 0.50, with a 95% CI of (0.21-0.79). First year's adherence was taken from a Beta distribution (alpha=42.5, beta=7.5) so that the average first year's adherence was 0.85, with a 95% CI of (0.74-0.93). The relative risks were randomly taken from Beta distributions with characteristics as mentioned in Table 1. We performed 350 simulations in total.

Another key parameter in the model was the price of the polypill. Because the polypill is not commercially available (yet), its price is unknown. As the best estimate, we used the sum of the costs of the separate elements of the polypill. However, if pill prices will be largely

determined by production costs, it is likely that the pill will be considerably cheaper than the sum of the costs of its components. On the other hand, if, for instance the added value to the consumer of having to take one pill only will be priced in, it can not be ruled out that the price will be higher. For lack of an informed estimate of price ranges, we explored an array of possible values, in order to compare with the costs of separate medication. We performed also analyses with different discount rates.

Results

Descriptives

Table 3 shows the proportion of individuals eligible for medication based on a 10-year risk of cardiovascular mortality threshold of 5%, 7.5% or 10%. For example, with a threshold of 7.5%, of all persons between 40 and 75 year more than 31% was eligible for medication. The first half of the table concerns those eligible for the polypill, the second half those eligible for separate medication, based on having a SCORE risk of 7.5% or above together with hypertension and/or hypercholesterolemia ('separate medication scenario', scenario 3).

Effectiveness

Table 4 shows that by using the polypill as described for scenario 3, the total of cases of acute myocardial infarction or stroke prevented was more than for the other medication scenarios, more than 20 and 30 thousand cases, respectively, for a threshold of 7.5% (5% and 10% not shown). It must be noted, though, that the total health gain in the separate medication scenario is only 1/3 to ½ of the total health gain of scenario 3.

Cost-effectiveness

Table 5 shows the incremental cost-effectiveness ratios (ICERs) for all scenarios. The ratio's do not differ very much between the three SCORE cut-off values considered, and are all well within accepted ICER thresholds. The main effect of choosing a different cut point is that the ICERs for the polypill scenarios decrease with lower SCORE thresholds. Opportunistic screening combined with the polypill without aspirin and doubling of the statin doses (scenario 2C) had the most favorable ICER with a SCORE threshold of 5%. For the other thresholds, separate medication has the lowest ICER. It must be noted, though, that the total health gain in the separate medication scenario is only about 1/3 to 1/2 of the total health gain of scenario 2C.We also performed separate analyses by gender and age (Table 6). 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

Table 3: Individuals* eligible for the polypill and separate medication (% of total population)

	Polypill									Separate Medication								
	Men			Wom			Tot			Men			Wom			Tot		
Risk threshold	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%
Age																		
40-49	9.1	2.2	0.4	0.0	0.0	0.0	4.0	1.0	0.2	8.7	2.1	0.4	0.0	0.0	0.0	3.8	0.9	0.2
50-59	61.3	38.3	22.7	6.0	1.7	0.5	32.1	19.0	11.0	50.7	32.8	20.1	5.8	1.7	0.5	27.2	16.5	9.8
60-69	98.8	93.4	83.5	72.1	47.5	30.0	85.7	70.9	57.2	74.9	73.3	68.1	61.3	41.2	26.5	68.2	57.6	47.7
70-75	98.9	98.9	98.4	100.0	97.0	87.0	99.4	98.0	92.9	72.7	72.7	72.7	76.3	75.8	71.1	74.5	74.2	71.9
All ages (40-75)	57.4	46.2	37.7	25.0	18.0	13.1	40.3	31.3	24.7	46.2	37.8	31.5	21.9	16.0	11.9	33.4	26.3	21.2

* not yet using statins or antihypertensives

Table 4: number of cases prevented over time by the polypill intervention at a 10-years risk of 7.5%

Scenario (PP intervention)	AMI			Stroke		
Expected*	807 k			1374k		
	Cases prevented			*Cases prevented*		
	Number	*Percentage*	*NNT*	*Number*	*Percentage*	*NNT*
Polypill Scenario 2A	23.8 (8.3-41.6) k	2.89 (1.02-5.06)	31	36.1 (12.3-72.9) k	2.57 (0.86-5.12)	20
Polypill Scenario 2B	22.5 (8.3-38.8) k	2.73 (1.00-4.70)	33	36.2 (12.3-72.9) k	2.57 (0.86-5.14)	20
Polypill Scenario 2C	29.7 (10.5-52.4) k	3.60 (1.30-6.34)	25	47.4 (16.4-95.0) k	3.37 (1.17-6.78)	15
Separate medication (scenario 3)	12.8 (4.9-21.0) k	1.55 (0.60-2.56)	46	19.9 (7.5-37.5) k	1.41 (0.53-2.61)	30

* according to reference scenario
NNT: Number needed to treat

Table 5: Outcomes and ICERs (total costs per LY and QALY gained) compared to current practice. In the current practice scenario the total costs of healthcare were $675*10^9$, total life years $165*10^6$, and total QALYs $128*10^6$.

Outcomes	Polypill Scenario 2A			Polypill Scenario 2B			Polypill Scenario 2C			Separate medication Scenario 3		
Risk threshold	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%
Cost of intervention ($*10^6$ €)	954	907	870	921	876	840	967	914	872	331	319	309
Incremental healthcare costs ($*10^6$ €)	2,210	1,710	1,320	1,940	1,500	1,160	2,240	1,730	1,330	750	720	690
Total incremental costs ($*10^6$ €)	3,390	2,830	2,400	2,860	2,370	2,000	3,210	2,640	2,200	1,080	1,040	999
Life years gained ($*10^3$)	425	314	236	395	291	218	474	349	261	154	147	141
QALYs gained ($*10^3$)	360	266	195	335	244	182	408	296	221	132	126	122
ICER ($*10^3$ €/LY)	8.0	9.0	10.2	7.2	8.2	9.1	6.8	7.6	8.5	7.0	7.0	7.1
ICER ($*10^3$ €/QALY)	9.4	10.8	12.3	8.5	9.7	10.9	7.9	8.9	10.0	8.2	8.2	8.2
Outcomes	**Polypill Scenario 2A**			**Polypill Scenario 2B**			**Polypill Scenario 2C**			**Separate medication Scenario 3**		
Risk threshold	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%	5%	7.5%	10%
Cost of intervention ($*10^6$ €)	954	907	870	921	876	840	967	914	872	331	319	309
Incremental healthcare costs ($*10^6$ €)	2,210	1,710	1,320	1,940	1,500	1,160	2,240	1,730	1,330	750	720	690
Total incremental costs ($*10^6$ €)	3,390	2,830	2,400	2,860	2,370	2,000	3,210	2,640	2,200	1,080	1,040	999
Life years gained ($*10^3$)	425	314	236	395	291	218	474	349	261	154	147	141
QALYs gained ($*10^3$)	360	266	195	335	244	182	408	296	221	132	126	122
ICER ($*10^3$ €/LY)	8.0	9.0	10.2	7.2	8.2	9.1	6.8	7.6	8.5	7.0	7.0	7.1
ICER ($*10^3$ €/QALY)	9.4	10.8	12.3	8.5	9.7	10.9	7.9	8.9	10.0	8.2	8.2	8.2

Table 6: Outcomes and ICERs compared to current practice. Age and sex specific data for the 7.5% risk numbers in Table 5.

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
ICER ($*10^3$ €/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

Probabilistic sensitivity analysis

Results of the sensitivity analysis are displayed in Table 6 as 95% confidence intervals for the outcomes measures, meaning that 95% of the simulations fell within the indicated ranges. It can be observed that the incremental cost effectiveness ratio's are within a rather small range. In that respect results can be judged to be robust. Nonetheless, there is some overlap between intervals, meaning that the relative order of the different medication compositions could be different. Table 8 shows the results of the analyses of the base case scenario with different discount rates.

Table 7: Results of the probabilistic sensitivity analysis.

Outcomes	Polypill Scenario 2A	Polypill Scenario 2B	Polypill Scenario 2C	Separate medication
Cost of intervention (*10^6 €)	380-1,510	370-1,460	380-1,540	290-360
Incremental healthcare costs (*10^6 €)	580-2,630	560-2,570	640-2,980	290-1,140
Total incremental costs (*10^6 €)	1,070-4,450	940-4,000	1,040-4,490	610-1,460
Life years gained (*10^3)	113-517	110-507	130-613	59-241
QALYs gained (*10^3)	92-424	92-427	109-519	50-206
ICER (*10^3 €/LY)	8.2-10.7	7.4-9.8	6.9-9.0	5.9-10.8
ICER (*10^3 €/QALY)	9.9-13.0	8.8-11.7	8.1-10.7	6.9-12.6
Outcomes	**Polypill Scenario 2A**	**Polypill Scenario 2B**	**Polypill Scenario 2C**	**Separate medication**
Cost of intervention (*10^6 €)	380-1,510	370-1,460	380-1,540	290-360
Incremental healthcare costs (*10^6 €)	580-2,630	560-2,570	640-2,980	290-1,140
Total incremental costs (*10^6 €)	1,070-4,450	940-4,000	1,040-4,490	610-1,460
Life years gained (*10^3)	113-517	110-507	130-613	59-241
QALYs gained (*10^3)	92-424	92-427	109-519	50-206
ICER (*10^3 €/LY)	8.2-10.7	7.4-9.8	6.9-9.0	5.9-10.8
ICER (*10^3 €/QALY)	9.9-13.0	8.8-11.7	8.1-10.7	6.9-12.6

Displayed are confidence intervals (95%) of the model outcomes for a 10-years risk threshold of 7.5%.

Table 8: Sensitivity analyses with different discount rates (7.5% risk)

Discount rates: costs, effects	Polypill Scenario 2A	Polypill Scenario 2B	Polypill Scenario 2C	Separate medication Scenario 3
4%, 1.5%	10,800	9,700	8,900	8,200
0%, 0%	17,300	16,200	15,100	14,200
3%, 3%	16,400	14,900	13,700	12,600
5%, 5%	16,200	14,200	12,900	11,800

Figure 2 displays the range of values for costs and effects (QALYs) in the cost-effectiveness plane for 7.5% risk. It shows that most values cluster narrowly along what can be imagined as a line which has as slope the average cost-effectiveness ratio.

Figure 3 shows acceptability curves for the choice of treatment strategy for 7.5% risk. For each cost-effectiveness threshold (the maximum value below which a treatment is accepted as

being cost-effective, or the "willingness to pay") it gives the probability that the treatment will be cost-effective. Thus, up to a level of about €9,000/QALY, separate medication is most likely to be cost-effective, but beyond that scenario 2C is most likely the best alternative. Variation of the costs of the most cost-effective polypill (scenario 2C) showed that when the price of the pill would be under 50 € per year (excluding drug delivery costs, and including VAT), scenario 2C would become the most favorable scenario when using a SCORE threshold of 7.5%. In the present calculations we estimated the price of the polypill in scenario 2C to be 65.76 € per year.

Discussion

The results of this study suggest that opportunistic screening and offering a polypill to people with a minimum 10-year risk of cardiovascular mortality of between 5% and 10% is a cost-effective strategy in the primary prevention of cardiovascular diseases. This is the case, whether the threshold chosen is 5%, 7.5% or 10%, but the lower the threshold, the lower the incremental cost-effectiveness ratio. All three differently composed polypills were cost-effective compared with usual care, as was the single drug option. The polypill without aspirin but with a double dose of simvastatin leads to most health gains with all risk thresholds. At a 10 year risk of cardiovascular death of 7.5% or above, such a strategy would lead to an estimated decrease in the incidence of myocardial infarction and stroke of about 3.5%, at a cost of €8,900 per QALY. This is well below the consensual threshold of €20,000 per QALY.[40] Separate medication, targeted at hypertension and/or hypercholesterolemia, is the most cost-effective strategy compared to usual care in the risk classes of 7.5%, respectively 10%, or above. However, total health gains are substantially lower.

Both the strengths and weaknesses of our study revolve around the weak basis of clinical evidence and the use of mathematical modeling. The latter allowed an exploratory investigation based on preliminary results of a phase II clinical trial, thus providing insights into the range of health benefits that can be expected. But with the lack of evidence of efficacy with regard to established clinical endpoints, the results should certainly not be taken as a precise estimate of the cost-effectiveness. We took into account what seemed to be the most important factors determining cost-effectiveness, but neglected, for instance, the costs of side effects.

Since Wald and Law's 2003 article, the appealing idea of a highly effective and safe polypill taken once daily to prevent cardiovascular disease has gained widespread attention. 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.[41] 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 year of life saved) as long as the yearly costs of the pill would be below approximately €270 in high risk groups and €160 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.

These lower estimates are due to insights gained since then, as, steps towards realization of the polypill concept have been taken. Several prototypes have been developed and large scale clinical trials are currently under way. Yet, the only clinical evidence so far concerns a brief randomized trial of 12 weeks of treatment, the Polycap study. On the basis of this limited evidence it was concluded that the pill seems safe and that the effects on blood pressure and cholesterol are not inferior to the individual substances given separately. However, it must be said that the effects on these intermediate endpoints fall well below the rough estimates made by Law and Wald, who calculated that up to 80% of all cardiovascular events in the population at large could be prevented. There are two main sources for the discrepancy between their estimates and our calculations. Firstly, both the estimated effects on intermediate endpoints and the relative risk reductions (per unit of risk factor level reduction) Law and Wald used seem to have been too optimistic. Secondly, we did not consider the introduction of the polypill in the "universal" manner envisioned in their original article. It seems very unlikely that medicalization of a whole population will ever find wide support. Instead, we imagined a situation in which the polypill would be introduced within the current context of cardiovascular risk management and primary prevention. This approach is in line with current views on focusing on those at increased risk and finding ways of identifying them.[42] Only limited experience exists with this type of primary prevention, which might be best described as opportunistic screening.[43] Hence, we had to make several assumptions to estimate the number of individuals who would ultimately take the polypill. These include the preparedness of GP's to engage in opportunistic screening, the proportion of eligible individuals who are willing to choose lifelong medication, and their compliance with treatment. Many will probably prefer changing their lifestyles, or will start but not continue. A lack of compliance obviously reduces cost-effectiveness, as investments are made that do not pay out in terms of health gains. On the other hand, the combination of drugs in one pill takes away an obstacle to compliance in patients requiring more than one drug.[44-46, 47]

Literature shows that adherence to medication declines with the number of drugs prescribed.[44 48 49]

Especially in primary prevention, the safty and side effects of a drug are of crucial concern. As far as statins are concerned, the most serious complication is rhabdomyolysis, which is very rare, but can be fatal. More frequent are complaints of muscle pain.[50] However, a review and meta-analysis of Weng et al., of 75 trials showed that the incidence of muscle toxicity was low in all trials.[34] The most recent Cochrane meta-analysis did not find significant differences between placebo and treatment groups. The most important consequence would be that the relatively minor side effects would reduce adherence, or lead to discontinuation, an effect that is indirectly included in our model (via reduced compliance). The same applies to the side-effects of the blood pressure lowering components. In particular cough caused by an ACE inhibitor, which is independent of the dose, could lead to discontinuation of the pill.[28] Aspirin can cause gastro-intestinal bleedings and hemorrhagic stroke.[38 51 52] The latter more or less annul the protective effect on ischemic stroke, such that the net effect is neutral. The increased risk of gastrointestinal bleeding, which we took into account, further contributed to the relatively unfavorable profile of a polypill containing aspirin, which turned out to be the least cost-effective option.

To gain more definite insights into the cost-effectiveness of the polypill in the opportunistic screening setting we envisioned, two major "unknowns" need to be clarified. Firstly, the results of large-scale phase III clinical trials will have to show how the effects on intermediate endpoints translate into clinical benefit. In particular, they will need to answer the question whether the "sum is greater than the parts", both with regards to benefits as to safety. Secondly, more needs to be known about the willingness to participate in opportunistic screening initiatives. This applies to eligible persons, but also to general practitioners. Also the practical consequences and logistic difficulties in implementing opportunistic screening will need to be addressed.

Implications

Primary prevention is increasingly seen as a crucial tool in further reducing the burden of cardiovascular disease. In a health care system such as that of the Netherlands, in which the general practitioner occupies a central role, opportunistic screening is a feasible strategy of which the benefits are currently being actively explored. Thus, in the Netherlands an opportunistic screening by the general practitioners has recently been introduced and reimbursement has been recommended. Obviously, in order to make most out of this opportunity, insights into the relative cost-effectiveness of alternative preventive measures for those at increased risk is essential, as are the implications on effects and costs over a long time. Low doses aspirin are not recommended in the Dutch guideline in the primary

prevention of cardiovascular diseases.[18] This is based on the adverse effects like gastrointestinal bleedings and hemorrhagic stroke caused by aspirin [51 52]. The advantage of using a polypill without aspirin is that these adverse effects due to aspirin could be avoided. Since the introduction of the concept of a polypill by Wald and Law there were different changes in the composition and dosage of the medication put into this pill. One can expect that in the future further changes in the composition and dosage will lead to a better balanced pill. For example, ACE antihypertensive drugs cause often an unpleasant tickling cough. Replacement with a selective type 1 angiotensin II-receptor-(AT_1-) antagonist could solve this problem.

Guidelines on primary prevention cardiovascular suggest first to start with life-style changes like increase the physical activity and diet advices. In our calculation we did not include the costs and the effects of a life-style advisor.

Conclusion

The polypill or variants thereof seem to offer an efficient way to reduce the cardiovascular disease burden. Opportunistic screening of the population of 40 years or above to select individuals with a mild to moderately increased risk for cardiovascular diseases, followed by polypill prescription would prevent approximately 3.5% of all cardiovascular events. The cost-effectiveness of all variants is within the same order of magnitude. Therefore other aspects will determine which composition of pill is to be preferred, such as side effect profile and total health gains. Based on these criteria, our study suggests that the polypill without aspirin and a double statin dose is the most favorable option.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Contributors PFVG: study design, data-analyses, writing; EABO: study design, statistics, data-analyses; HHH: study-design, writing; GADW: study-design, writing; MVDB: writing; AJS: writing; PME: study-design, data-analyses, writing. All authors reviewed the manuscript and critically analyzed the work.

Data sharing statement We invite any reader who is interested in seeing the input data and the software code of our model to contact us. We offer full access to both the data used and the code. The data is available in the Dryad repository with the unique identifier: doi:10.5061/dryad.qg54c627

References

1. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *Bmj* 2003;326(7404):1419.
2. AHA. Cardiovascular Disease Statistics
American Heart Association, 2010.
3. CBS. Causes of death 2009, short list: CBS, 2010.
4. Vaartjes I, van Dis I, Visseren FLJ, et al. Chapter 1: Cardiovascular disease in the Netherlands (in Dutch). *Cardiovascular diseases in the Netherlands, 2009*. Den Haag, The Netherlands: Dutch Heartfoundation, 2009.
5. Zhao G, Ford ES, Li C, Mokdad AH. Are United States adults with coronary heart disease meeting physical activity recommendations? *Am J Cardiol* 2008;101(5):557-61.
6. Garner JB. Problems of nonadherence in cardiology and proposals to improve outcomes. *Am J Cardiol* 2010;105(10):1495-501.
7. Bates TR, Connaughton VM, Watts GF. Non-adherence to statin therapy: a major challenge for preventive cardiology. *Expert Opin Pharmacother* 2009;10(18):2973-85.
8. Corrao G, Conti V, Merlino L, et al. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. *Clin Ther* 2010;32(2):300-10.
9. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2007;14 Suppl 2:E1-40.
10. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24(11):987-1003.
11. Lonn E, Bosch J, Teo KK, et al. The polypill in the prevention of cardiovascular diseases: key concepts, current status, challenges, and future directions. *Circulation* 2010;122(20):2078-88.
12. Yusuf S, Pais P, Afzal R, et al. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. *Lancet* 2009;373(9672):1341-51.
13. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354(15):1567-77.

14. van Dis I, Kromhout D, Geleijnse JM, et al. Evaluation of cardiovascular risk predicted by different SCORE equations: the Netherlands as an example. *Eur J Cardiovasc Prev Rehabil* 2010;17(2):244-9.
15. Hoogenveen RT, van Baal PH, Boshuizen HC. Chronic disease projections in heterogeneous ageing populations: approximating multi-state models of joint distributions by modelling marginal distributions. *Math Med Biol* 2010;27(1):1-19.
16. Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, et al. Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study. *Diabetes Care* 2007;30(1):128-34.
17. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003;24(17):1601-10.
18. CBO. Dutch Guideline Cardiovascular Risk Management In: CBO DIfHI, editor. Utrecht, The Netherlands, 2006.
19. Baal PHM, Feenstra TL, Hoogenveen RT, et al. Cost-Efectiveness analysis with the RIVM Chronic Disease Model. Bilthoven, Netherlands: Dutch National Institute for Public Health and the Environment, 2005.
20. Slobbe LCJ, Kommer GJ, Smit JM, et al. Cost-of-illness in the Netherlands 2003 Bilthoven, Netherlands: National Institute for Public Health and the Environment, 2006.
21. Melse JM, Essink-Bot ML, Kramers PG, et al. A national burden of disease calculation: Dutch disability-adjusted life-years. Dutch Burden of Disease Group. *Am J Public Health* 2000;90(8):1241-7.
22. Stouthard MEA, Essink-Bot ML, Bonsel GJ. Disability weights for diseases: A modified protocol and results for a Western European region. *European Journal of Public Health* 2000;10(1):24-30.
23. Lopez AD, Murray CC. The global burden of disease, 1990-2020. *Nat Med* 1998;4(11):1241-3.
24. van Baal PH, Hoeymans N, Hoogenveen RT, et al. Disability weights for comorbidity and their influence on health-adjusted life expectancy. *Popul Health Metr* 2006;4:1.
25. Verschuren WM, Blokstra A, Picavet HS, et al. Cohort profile: the Doetinchem Cohort Study. *Int J Epidemiol* 2008;37(6):1236-41.
26. CBS. Statistics Netherlands: CBS, 2010.
27. Chapman RH, Petrilla AA, Benner JS, et al. Predictors of adherence to concomitant antihypertensive and lipid-lowering medications in older adults: a retrospective, cohort study. *Drugs Aging* 2008;25(10):885-92.

28. Law MR, Wald NJ, Morris JK, Jet al. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *Bmj* 2003;326(7404):1427.
29. Turnbull F, Neal B, Ninomiya T, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *Bmj* 2008;336(7653):1121-3.
30. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005;165(12):1410-9.
31. Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2011(1):CD004816.
32. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376(9753):1670-81.
33. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366(9493):1267-78.
34. Weng TC, Yang YH, Lin SJ, et al. A systematic review and meta-analysis on the therapeutic equivalence of statins. *J Clin Pharm Ther* 2010;35(2):139-51.
35. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373(9678):1849-60.
36. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Manual for costing research. Methods and directive prices for economic evaluation in health care (in Dutch) Diemen: Institute for Medical Technology Assessment, Erasmus MC, 2010.
37. CVZ. Medicijnkosten. Diemen: CVZ, 2010.
38. Berger JS, Roncaglioni MC, Avanzini F, et al. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *Jama*, 2006:306-13.
39. Pignone M, Earnshaw S, Pletcher MJ, et al. Aspirin for the primary prevention of cardiovascular disease in women: a cost-utility analysis. *Arch Intern Med* 2007;167(3):290-5.
40. van den Berg M, de Wit GA, Vijgen SM, et al. [Cost-effectiveness of prevention: opportunities for public health policy in the Netherlands]. *Ned Tijdschr Geneeskd* 2008;152(23):1329-34.

41. Franco OH, Steyerberg EW, de Laet C. The polypill: at what price would it become cost effective? *J Epidemiol Community Health* 2006;60(3):213-7.
42. Wald NJ, Simmonds M, Morris JK. Screening for future cardiovascular disease using age alone compared with multiple risk factors and age. *PLoS ONE* 2011;6(5):e18742.
43. van de Kerkhof RM, Godefrooij MB, Wouda PJ, et al. [Cardiometabolic risk factors detected with a preventative screening programme]. *Ned Tijdschr Geneeskd* 2010;154:A1860.
44. Saini SD, Schoenfeld P, Kaulback K, et al. Effect of medication dosing frequency on adherence in chronic diseases. *Am J Manag Care* 2009;15(6):e22-33.
45. Pan F, Chernew ME, Fendrick AM. Impact of fixed-dose combination drugs on adherence to prescription medications. *J Gen Intern Med* 2008;23(5):611-4.
46. Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. *Am J Health Syst Pharm* 2007;64(12):1279-83.
47. Erdine S. Compliance with the treatment of hypertension: the potential of combination therapy. *J Clin Hypertens (Greenwich)* 2010;12(1):40-6.
48. WHO. Adherence to long-term therapies: evidence for action. Geneva, Switzerland: World Health Organization, 2003.
49. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;23(8):1296-310.
50. Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. *Circulation* 2002;106(8):1024-8.
51. Sanmuganathan PS, Ghahramani P, Jackson PR, et al. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart* 2001;85(3):265-71.
52. Hayden M, Pignone M, Phillips C, et al. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136(2):161-72.

Appendix

Show

Figure 15.5.a: Drummond checklist (Drummond 1996)

Item		Yes	No	Not clear	Not appropriate
Study design					
1.	The research question is stated.	☒	☐	☐	
2.	The economic importance of the research question is stated.	☒	☐	☐	
3.	The viewpoint(s) of the analysis are clearly stated and justified.	☒	☐	☐	
4.	The rationale for choosing alternative programmes or interventions compared is stated.	☒	☐	☐	
5.	The alternatives being compared are clearly described.	☒	☐	☐	
6.	The form of economic evaluation used is stated.	☒	☐	☐	
7.	The choice of form of economic evaluation is justified in relation to the questions addressed.	☒	☐	☐	
Data collection					
8.	The source(s) of effectiveness estimates used are stated.	☒	☐	☐	
9.	Details of the design and results of effectiveness study are given (if based on a single study).	☐	☐	☐	☒
10.	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	☒	☐	☐	☐
11.	The primary outcome measure(s) for the economic evaluation are clearly stated.	☒	☐	☐	
12.	Methods to value benefits are stated.	☐	☐	☐	☒
13.	Details of the subjects from whom valuations were obtained were given.	☐	☐	☐	☒
14.	Productivity changes (if included) are reported separately.	☐	☐	☐	☒
15.	The relevance of productivity changes to the study question is discussed.	☐	☐	☐	☒
16.	Quantities of resource use are reported separately from their unit costs.	☒	☐	☐	
17.	Methods for the estimation of quantities and unit costs are described.	☒	☐	☐	
18.	Currency and price data are recorded.	☒	☐	☐	
19.	Details of currency of price adjustments for inflation or currency conversion are given.	☐	☐	☐	☒
20.	Details of any model used are given.	☒	☐	☐	☐
21.	The choice of model used and the key parameters on which it is based are justified.	☒	☐	☐	☐
Analysis and interpretation of results					
22.	Time horizon of costs and benefits is stated.	☒	☐	☐	☐
23.	The discount rate(s) is stated.	☒	☐	☐	☐
24.	The choice of discount rate(s) is justified.	☒	☐	☐	☐
25.	An explanation is given if costs and benefits are not discounted.	☐	☐	☐	☒
26.	Details of statistical tests and confidence intervals are given for stochastic data.	☒	☐	☐	☐
27.	The approach to sensitivity analysis is given.	☒	☐	☐	☐
28.	The choice of variables for sensitivity analysis is justified.	☒	☐	☐	☐
29.	The ranges over which the variables are varied are justified.	☒	☐	☐	☐
30.	Relevant alternatives are compared.	☒	☐	☐	☐
31.	Incremental analysis is reported.	☒	☐	☐	☐
32.	Major outcomes are presented in a disaggregated as well as aggregated form.	☒	☐	☐	
33.	The answer to the study question is given.	☒	☐	☐	
34.	Conclusions follow from the data reported.	☒	☐	☐	
35.	Conclusions are accompanied by the appropriate caveats.	☒	☐	☐	

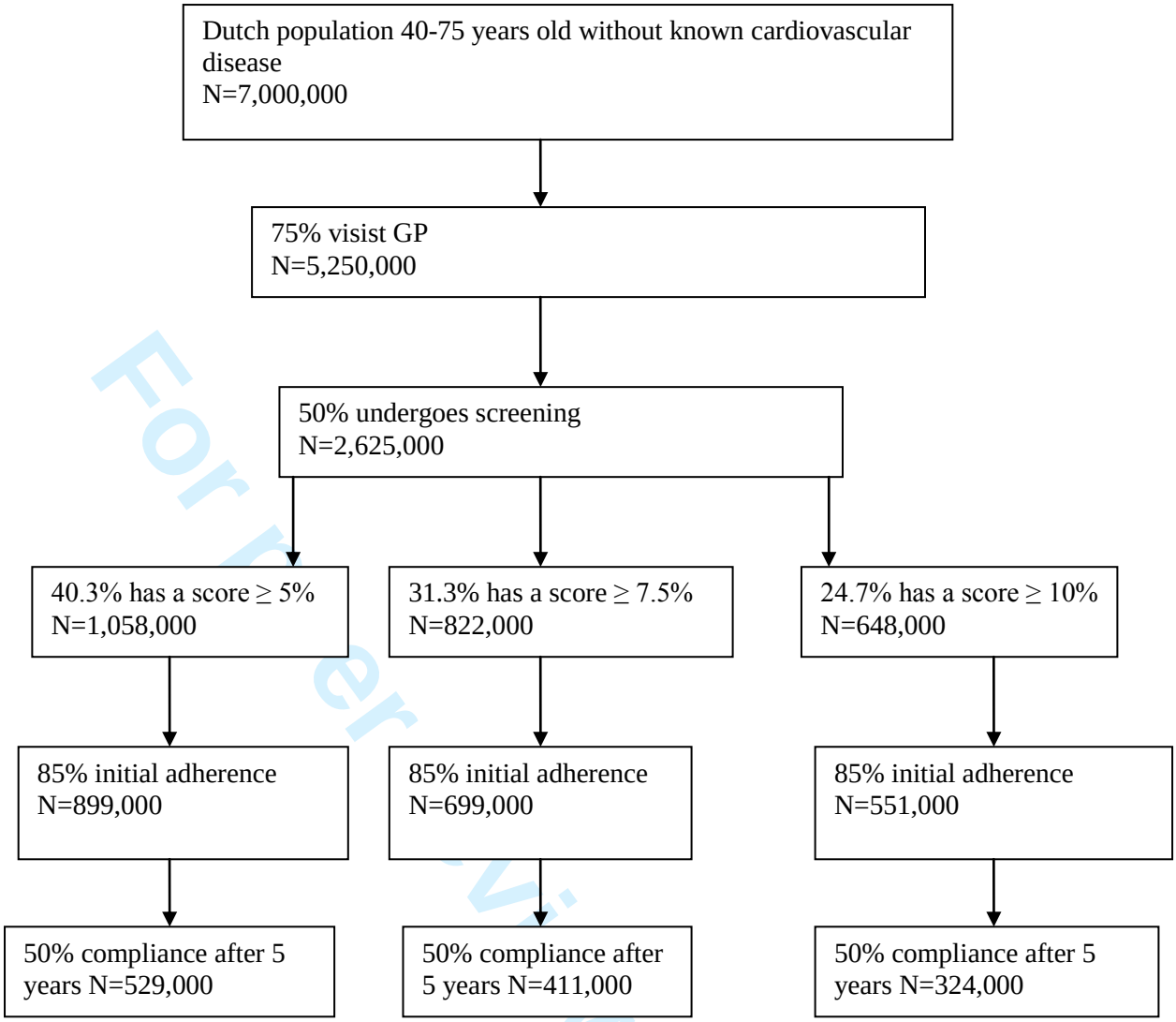
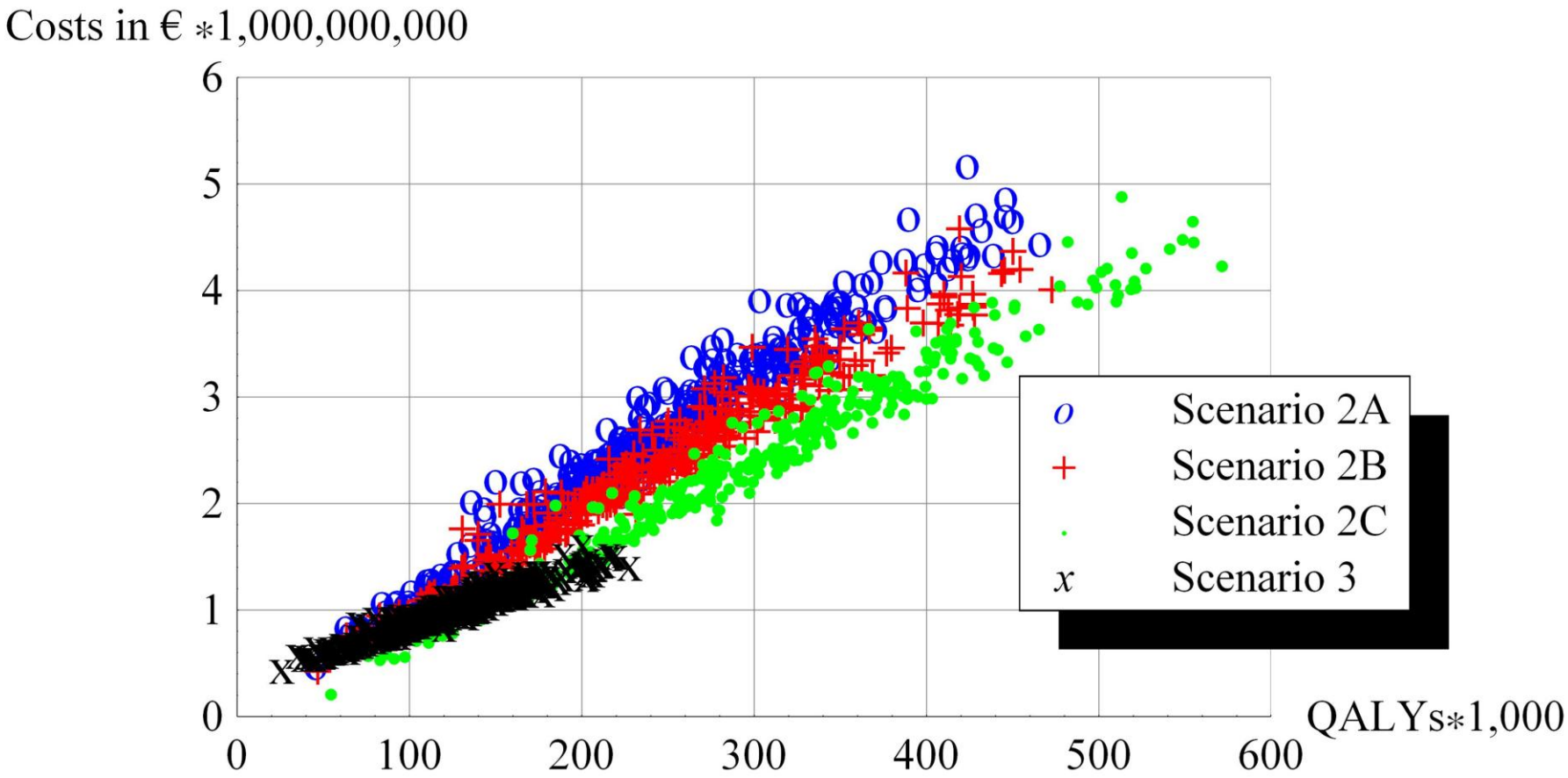
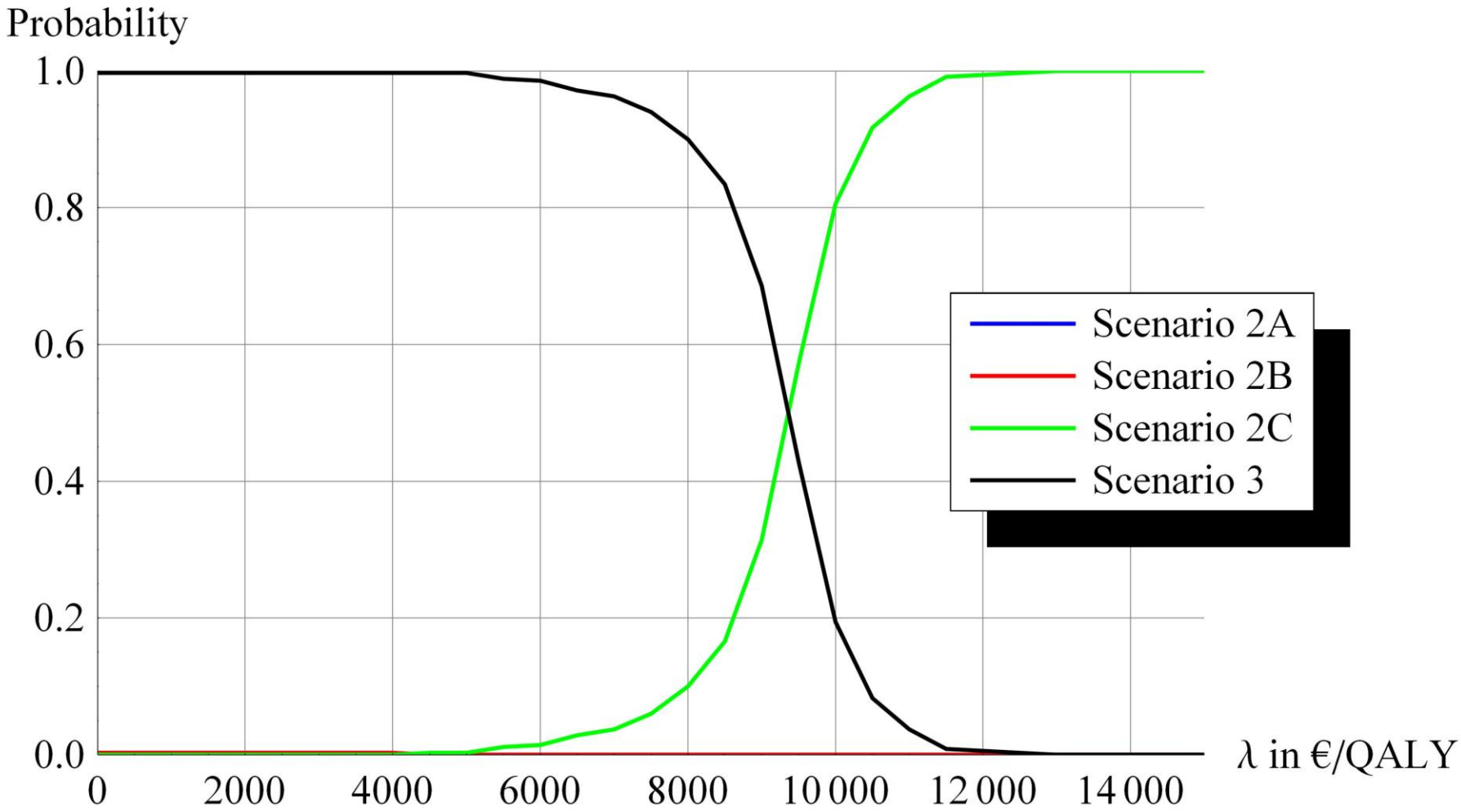


Figure 1. Flow chart of participation


Costs in € ∗1,000,000,000
6
5
4
3
2
1
0
0
100
200
300
400
500
600
QALYs∗1,000
Scenario 2A
Scenario 2B
Scenario 2C
Scenario 3


Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2000
4000
6000
8000
10 000
12 000
14 000
λ in €/QALY
Scenario 2A
Scenario 2B
Scenario 2C
Scenario 3