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Primary prevention of cardiovascular disease: Cost-effectiveness comparison

Oscar H. Franco
University Medical Center Rotterdam and *Unilever Corporate Research*

Arno J. der Kinderen
University Medical Center Rotterdam and *St. Alatus*

Chris De Laet
Belgian Health Care Knowledge Center

Anna Peeters
Monash University Central and *Eastern Clinical School*

Luc Bonneux
Netherlands Interdisciplinary Demographic Institute

Objectives: The aim of this study was to evaluate the cost-effectiveness of four risk-lowering interventions (smoking cessation, antihypertensives, aspirin, and statins) in primary prevention of cardiovascular disease.
Methods: Using data from the Framingham Heart Study and the Framingham Offspring study, we built life tables to model the benefits of the selected interventions. Participants were classified by age and level of risk of coronary heart disease. The effects of risk reduction are obtained as numbers of death averted and life-years saved within a 10-year period. Estimates of risk reduction by the interventions were obtained from meta-analyses and costs from Dutch sources.
Results: The most cost-effective is smoking cessation therapy, representing savings in all situations. Aspirin is the second most cost-effective (€2,263 to €16,949 per year of life saved) followed by antihypertensives. Statins are the least cost-effective (€73,971 to €190,276 per year of life saved).
Conclusions: A cost-effective strategy should offer smoking cessation for smokers and aspirin for moderate and high levels of risk among men 45 years of age and older. Statin therapy is the most expensive option in primary prevention at levels of 10-year coronary heart disease risk below 30 percent and should not constitute the first choice of treatment in these populations.

Keywords: Primary prevention, Cardiovascular disease, Cost-effectiveness analysis

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Cardiovascular disease (CVD) prevention is based on comprehensive risk management of relevant risk factors (14;19). Nowadays four therapies constitute the cornerstone of CVD risk management in populations without previous CVD or diabetes: cholesterol modification, blood pressure (BP) lowering, anti–platelet aggregation therapy, and smoking cessation. Evidence of the benefit of these interventions exists for almost all populations independent of risk factors levels, but proportional to pretreatment levels of absolute risk of coronary heart disease (CHD) (19). Smoking cessation is naturally an exception, being limited to smokers. This means that a large range of populations might benefit from these risk-lowering treatments. However, treating large populations asks for large investments and priority setting is mandatory (6). Currently cutoff levels of pretreatment absolute risk have been used to target healthy persons eligible for risk-lowering treatment (4). However, head to head comparisons of efficiency of various options in cardiovascular disease risk management are scarce: aspirin is cheap, but less effective; statins are more effective but costly (8;22). This study compares the cost-effectiveness of four treatments (aspirin, antihypertensives, statins, and smoking cessation) in the primary prevention of CVD in men at different ages and different levels of risk.

METHODS

Using data from the Framingham Heart Study (FHS) and the Framingham Offspring Study (FOS), we built multistate life tables (MSLTs) to model the cost-effectiveness of the selected interventions in men free of CVD (at baseline). We modeled two synthetic age cohorts over 10 years: from 45 to 55 years and from 55 to 65 years.

Data Sources

The original FHS cohort consisted of 5,209 respondents 28 through 62 years of age residing in Framingham, Massachusetts, between 1948 and 1951. Examination of participants has taken place biannually, and the cohort has been followed up for 46 years in the data made available to us. The FOS cohort consisted of the offspring and their spouses of the original FHS and was sampled in 1971. This cohort consisted of 5,214 participants, 5 through 70 years of age at baseline. Examination of this cohort has taken place at intervals of 4 to 8 years. Because the study design and measurement instruments used in FHS and FOS are similar, we pooled both data sets. Further description of the FHS and the FOS can be found elsewhere (5;15). To obtain recent estimates for 10-year CVD incidence (and mortality), we used follow-up from 1968 onward. We used, therefore, data from participants that attended exams 11 (calendar years 1968–71), 15 (1977–79), and 20 (1987–89) of the FHS and exams 1 (1971–75) and 2 (1979–82) from FOS. Follow-up started at the date of the chosen baseline exam. In total there were 3,742 men for the analysis.

Baseline Assessment

At baseline participants were classified by age group and by level of absolute risk of CHD estimated with the Anderson risk equation (1). This equation includes age, sex, systolic blood pressure (SBP), smoking status, diabetes, the ratio of total cholesterol/high density lipoprotein (HDL) cholesterol, and left ventricular hypertrophy (presence on electrocardiogram [ECG]). The ratio for total cholesterol/HDL cholesterol was missing for 812 participants and was imputed based on the other variables of the formula. Enough data on the variables required for the calculation of risk was available in 3,332 participants. Subjects were categorized into three groups based on their level of 10-year absolute risk of CHD: low risk, <10 percent (2,396 participants); moderate risk, 10 to <20 percent (714 participants); and high risk, ≥ 20 percent (222 participants). There were too few participants with very high risk (≥ 30 percent) to enable the calculation of life tables.

Effectiveness

Benefits of the interventions were calculated as number of deaths prevented, years of life saved (YLS), and disease-free years of life saved within a 10-year time horizon in the two MSLT cohorts. Effects occurring after 10 years were not taken into consideration. Effectiveness and cost-effectiveness were calculated within the same total population. Treatment with aspirin or statins was given to all, antihypertensives were limited to participants with SBP > 140 mm Hg, and smoking cessation therapy to smokers. In the case of statin therapy, a lag time of 6 months was considered before the full risk reduction effect was assumed, as reported by clinical trials on primary prevention populations (27). No lag times were included for the other therapies.

Reduction rates of CVD were taken from recent meta-analyses (9;10;12;17;20;23;28;33). In the case of smoking cessation strategies, we estimated the success rates of cessation therapy after 1 year of follow-up. Relapse rates were set at 0 percent, 20 percent, and 40 percent in sensitivity analysis. The CVD risk modification after smoking cessation was based on a mathematical function derived from a meta-analysis of observational studies comparing quitters and continuing smokers (Table 1) (20).

We used the FHS and FOS data to estimate transition rates for incident nonfatal CHD, fatal primary CHD, secondary fatal CHD, stroke, and death, using Poisson regression with a Gomperz distribution for the total population and for each risk category separately. We calculated two cohorts of 45- and 55-year-old men, followed up for 10 years, with and without risk lowering. Comparisons between populations with and without risk lowering yield YLS, YLS free of CHD, and number of deaths prevented over a 10-year period.

Costs

Direct medical only costs were calculated based on current Dutch guidelines of treatment (2;3;7) In the Netherlands,

Table 1. Risk Reduction Effect[a] of Interventions in the Prevention of Cardiovascular Disease

Treatment	Primary nonfatal CHD[b]	Primary CHD death[b]	Secondary CHD death[c]	Primary stroke[b]	Secondary stroke[c]	Cessation rate[a]	Source
Aspirin	28	13	13	20	20	n.a.	Hayden et al. (9) Weisman and Graham (33)
Antihypertensives	20	26	26	39	28	n.a.	BPLTT Collaboration (23)
Statins	34	29	29	29	29	n.a.	LaRosa et al. (17) Hebert et al. (10)
SC GP advice	Reduction effect taken from a published function for smoking cessation in cardiovascular disease prevention (20)					5	Silagy et al. (28)
SC nicotine substitutes						17	Silagy et al. (28)
SC bupropion						19	Hughes et al. (12)

[a] Reduction effect and cessation rates are expressed in percentages and for 1 year of treatment.
[b] Primary refers to events occurring in populations free of cardiovascular disease.
[c] Secondary refers to events occurring in populations with cardiovascular disease.
CHD, coronary heart disease, including fatal and nonfatal events; SC, smoking cessation; GP, general practitioner; n.a, not applicable.

a visit to the general practitioner (GP) costs €26.29, a telephonic consultation €13.14, a blood sample test €12.19, a prescription renewal €13.14, and each pharmacist's fee €6.68 (2). Aspirin treatment includes per year, one GP visit plus the cost of aspirin 100 mg/day (€27.97) for a total of €54.26. Medication costs of antihypertensives, statins, and nicotine substitutes were calculated using a market share approach based on data from the Rotterdam Study (11) and using a basket including all medications of its kind available for prescription in The Netherlands (further description on the market share approach is in Appendix 1). Yearly treatment with antihypertensives includes two GP visits, two prescription renewals, four pharmacist's fees, one blood analysis, and the medication costs (€122.78), leading to a total annual cost of €240.55. Statin therapy includes two GP visits, two prescription renewals, four pharmacist's fees, one blood analysis, and medication costs (€484.92) for an annual total of €602.69.

Three different strategies were considered for smoking cessation: GP advice, nicotine replacement, and bupropion. General practitioner's advice included only one GP visit and no additional costs, for a one-time cost of €26.29. Because nicotine substitutes can be obtained over the counter without a medical prescription and without prescription renewals, we included only medication costs for 3 months of treatment for a total cost of €117.79 in the first year of nicotine replacement therapy. For smoking cessation using bupropion, the annual costs included one GP visit, one telephonic consultation, two pharmacist's fees, and the medication cost for 3 months of treatment (€135.85) for a total cost of €188.64 in the first year.

The costs of events were taken from the literature and were restricted to direct medical costs (31). Costs per event were for nonfatal myocardial infarction (MI) €6,972, fatal MI €1,602, nonfatal stroke €11,870, and fatal stroke prevented €3,851. All costs were standardized for calendar year 2003 correcting for inflation (when necessary) and currency (€) adjusting for exchange rates.

Cost-Effectiveness

We used a third party payer perspective and discounted future net costs and benefits at a nominal discount rate of 4 percent per year (as recommended in the Netherlands), to take into account time preference (26). This suggests that effects and costs occurring in the future are weighted less that those occurring in the present (13).

We calculated average costs per YLS, costs per YLS free of CHD saved, and costs per deaths prevented for each risk-lowering intervention per categories of risk and age groups. The time horizon used for costs and effects was 10 years. The cost-effectiveness ratio (CER) was the ratio of the medical care costs to the increase in years saved.

Sensitivity analyses test the robustness of our results. As sources of uncertainty, we included different discount rates, different annual relapse rates for the smoking cessation strategies, a lower drug cost for statin therapy (due to the appearance of generic replacements), adverse effects for aspirin treatment, different proportions of smokers, different proportions of populations with suboptimal BP, and giving antihypertensives to all participants with moderate/high level of absolute CHD risk irrespective of BP level. To calculate the impact of adverse effects caused by aspirin treatment, we considered an approximate 1 percent incidence rate of major bleedings among participants receiving aspirin over 10 years of treatment (9). Cost for a major bleeding event ($5,300) were taken from the literature (16). All survival analyses were performed using STATA version 8.2 for windows (Stata Corporation, College Station, TX). MSLTs were made using Excel spreadsheets. Spreadsheets are available upon request.

Table 2. Costs and Effects of 10 Years of Intervention in the Primary Prevention of Cardiovascular Disease[a] for a Population at Moderate Risk[b]

	Costs (€)		YLS/1,000 parts.		HYLS/1,000 parts.		Deaths prevented/ 1,000 parts.[c]	
10 years of treatment	Age 50	Age 60	Age 50	Age 60	Age 50	Age 60	Age 50	Age 60
SC GP advice	−10	−3	2	.9	6	2	1.31	.64
SC nicotine substitutes[d]	−22	−6	7	2.9	21	6	4.55	2.05
SC bupropion[d]	−15	−4	8	3.3	23	6	5.07	2.28
Aspirin	260	243	15	18.9	92	77	6.31	8.97
Antihypertensives[e]	472	418	6	8	19	17	2.47	3.47
Statins	4,620	4534	24	33.8	106	97	9.74	14.01

[a] Costs calculated in Euros from 2003. Net costs/intervention (costs of treatment minus cost of events prevented).
[b] Moderate risk refers to a 10-year risk of coronary heart disease between 10 and <20 percent.
[c] Calculated at the end of 10 years of treatment.
[d] Smoking cessation was given only to smokers: 68 percent of the age 50 group and 21percent of the age 60 group.
[e] Antihypertensives were given only to participants with high blood pressure: 27 percent of the age 50 group and 25 percent of the age 60 group.
YLS, years of life saved; HYLS, "healthy" (free of coronary heart disease) years of life saved; SC, smoking cessation; GP, general practitioner; parts., participants.

Incremental Cost-Effectiveness

The incremental cost-effectiveness ratio (ICER) is the additional cost of a specific strategy divided by its additional benefit. Based on incremental cost-effectiveness analysis, we constructed a league table in which we ranked the interventions based on their ICERs. In some cases, a more expensive intervention was dominated by the less expensive if there was no incremental benefit in terms of YLS (negative value). In other words, the dominant strategy is better in all aspects. The strategy with the largest effectiveness and with an ICER below a threshold value of €20,000 per YLS was considered the most cost-effective.

RESULTS

Statin therapy is the most effective strategy for all risk and age groups, but it also is the most expensive (Tables 2 and 3). Antihypertensive therapy costs are lower compared with statins but higher compared with the other therapies. For all levels of risk and age, aspirin treatment costs less than statins and antihypertensives and had effects (on a population level) superior to antihypertensives but below statins. The three smoking cessation therapies had, on a population level, lower effects than the other three treatments. However, unlike the other treatments, they were always cost saving.

Cost-Effectiveness

The most cost-effective treatment is smoking cessation therapy, representing savings in all situations (Tables 4 and 5; Figure 1). Statin therapy is the least cost-effective treatment (ranging from €73,971 to €19,027 per YLS). Aspirin was the second most cost-effective intervention (ranging from €2,263 to €16,949 per YLS) followed by antihypertensive treatment (ranging from €28,187 to €79,843 per YLS). These rankings were maintained for all age group/risk group categories analyzed.

Table 3. Costs and Effects of 10 Years of Intervention in the Primary Prevention of Cardiovascular Disease[a] for a Population at High Risk[b]

	Costs (€)		YLS/1,000 parts.		HYLS/1,000 parts.		Deaths prevented/ 1,000 parts.[c]	
10 years of treatment	Age 50	Age 60	Age 50	Age 60	Age 50	Age 60	Age 50	Age 60
SC GP advice[d]	−24	−18	4.8	4.2	1.4	1.1	2.89	2.66
SC nicotine substitutes[d]	−67	−50	16.3	14.1	4.9	3.9	9.89	9.22
SC bupropion[d]	−63	−46	18.2	15.8	5.5	4.3	11.13	9.94
Aspirin	96	73	35.2	32.3	18.1	18.2	14.24	11.53
Antihypertensives[e]	1,256	731	34.5	25.9	11.1	7.5	14.59	8.97
Statins	4,263	4,145	49.7	56	20.2	21.6	20.11	19.56

[a] Costs calculated in Euros from 2003. Net costs/intervention (costs of treatment—cost of events prevented).
[b] High risk refers to a 10-year risk of coronary heart disease ≥20 percent.
[c] Calculated at the end of 10 years of treatment.
[d] Smoking cessation was given only to smokers: 91 percent of the age 50 group and 74 percent of the age 60 group.
[e] Antihypertensives were given only to participants with high blood pressure: 82 percent of the age 50 group and 50 percent of the age 60 group.
YLS, years of life saved; HYLS, "healthy" (free of coronary heart disease) years of life saved; SC, smoking cessation; GP, general practitioner; parts., participants.

Table 4. Cost-Effectiveness[a] of Primary Prevention of Cardiovascular Disease in Populations at Moderate Risk[b]

	Cost per YLS		Cost per HYLS		Cost per deaths prevented[c]	
10 years of treatment	Age 50	Age 60	Age 50	Age 60	Age 50	Age 60
SC GP advice[d]	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving
SC nicotine substitutes[d]	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving
SC bupropion[d]	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving
Aspirin	16,949	12,862	2,837	3,147	41,204	27,090
Antihypertensives[e]	79,843	52,217	24,210	23,723	191,093	120,461
Statins	190,276	134,083	43,378	46,749	474,332	323,625

[a] Future effects and costs equally weighted with 4 percent as discount factor, costs calculated in Euros from 2003.
[b] Moderate risk refers to a 10-year risk of coronary heart disease between 10 and <20 percent.
[c] Calculated at the end of 10 years of treatment.
[d] Smoking cessation was given only to smokers: 68percent of the age 50 group and 21percent of the age 60 group.
[e] Antihypertensives were given only to participants with high blood pressure: 27 percent of the age 50 group and 25 percent of the age 60 group.
YLS, years of life saved; HYLS, "healthy" (free of coronary heart disease) years of life saved; SC, smoking cessation; GP, general practitioner.

Labeling CERs under €20,000 per YLS as "cheap," over €40,000 per YLS as "expensive," and in between as "moderate" (18), smoking cessation therapy (the three options) and aspirin therapy were cheap in all situations. Antihypertensive treatment was an expensive option for participants at moderate levels of risk (irrespective of age) and a moderately expensive option for participants at high levels of risk (irrespective of age). Statin therapy was expensive in all situations.

Incremental Cost-Effectiveness and League Table

A cutoff value for the ICER of €20,000 per YLS is chosen. The league table starts with the therapy that represented the lowest costs, which in this case is smoking cessation using nicotine substitutes.

Smoking cessation with nicotine substitutes and bupropion are very cost-effective interventions; in fact they are cost saving (Table 6). Smoking cessation with GP advice is dominated by smoking cessation with bupropion (higher costs, lower effects). Compared with smoking cessation, aspirin is cost-effective for moderate risk populations in the 60 years age group and for high-risk populations irrespective of age. At a population level, antihypertensives are dominated by aspirin treatment. Statins have very high ICERs and appear last in our cost-effectiveness league. However, as they have very high effectiveness, they are never dominated by the other treatments.

Sensitivity Analysis

The order in the CERs presented in Tables 4 and 5 was not sensitive to changing discount factors for either costs or effects (Table 7). Using no discounting for effects and costs resulted in lower CERs, and using higher discount factors resulted in higher CERs. When we used 4 percent to discount future costs and left effects undiscounted, CERs were lower. We choose to present these different combinations of discounting considering the existing controversies and lack of standardization in time preference analysis (30).

The order of our results was not altered when different annual relapse rates (20 percent and 40 percent) were considered for the three smoking cessation strategies, or when costs of adverse events were taken into account for aspirin treatment.

Table 5. Cost-Effectiveness[a] of Primary Prevention of Cardiovascular Disease in Populations at High Risk[b]

	Cost per YLS		Cost per HYLS		Cost per deaths prevented[c]	
10 years of treatment	Age 50	Age 60	Age 50	Age 60	Age 50	Age 60
SC GP advice[d]	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving
SC nicotine substitutes[d]	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving
SC bupropion[d]	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving
Aspirin	2,716	2,263	528	400	6,741	6,331
Antihypertensives[e]	36,399	28,187	11,282	9,699	86,086	81,493
Statins	85,715	73,971	21,097	19,155	229,885	211,912

[a] Future effects and costs equally weighted with 4 percent as discount factor, costs calculated in Euros from 2003.
[b] High risk refers to a 10-year risk of coronary heart disease ≥20 percent.
[c] Calculated at the end of 10 years of treatment.
[d] Smoking cessation was given only to smokers: 91 percent of the age 50 group and 74 percent of the age 60 group.
[e] Antihypertensives were given only to participants with high blood pressure: 82 percent of the age 50 group and 50 percent of the age 60 group.
YLS, years of life saved; HYLS, "healthy" (free of coronary heart disease) years of life saved; SC, smoking cessation; GP, general practitioner.

Table 6. League Table of Primary Prevention of Cardiovascular Disease (Incremental Cost-effectiveness Analysis)

	Moderate risk[a]				High risk[b]			
	Age 50		Age 60		Age 50		Age 60	
10 years of treatment	Costs[c]	ICER[d]	Costs[c]	ICER[d]	Costs[c]	ICER[d]	Costs[c]	ICER[d]
SC nicotine substitutes[e]	−22	Cost saving	−6	Cost saving	−67	Cost saving	−50	Cost saving
SC bupropion[e]	−15	8,033	−4	6,107	−63	2,188	−46	2,355
SC GP advice[e]	−10	Dominated	−3	Dominated	−24	Dominated	−18	Dominated
Aspirin	260	36,207	243	15,799	96	9,336	73	7,213
Antihypertensives[f]	472	Dominated	418	Dominated	1,256	Dominated	731	Dominated
Statins	4,620	488,460	4,534	287,608	4,263	287,496	4,145	171,670

[a] Moderate risk refers to a 10-year risk of coronary heart disease between 10 and <20 percent.
[b] High risk refers to a 10-year risk of coronary heart disease ≥20 percent.
[c] Costs calculated in Euros from 2003. Net costs/intervention (costs of treatment—cost of events prevented).
[d] ICERs are presented in costs per years of life saved.
[e] Smoking cessation was given only to smokers: 68 percent and 91 percent of the age 50 group with moderate and high risk, respectively, and 21 percent and 74 percent of the age 60 group with moderate and high risk, respectively.
[f] Antihypertensives were given only to participants with high blood pressure: 27 percent and 82 percent of the age 50 group with moderate and high risk, respectively, and 25 percent and 50 percent of the age 60 group with moderate and high risk, respectively.
YLS, years of life saved; ICER, incremental cost-effectiveness ratio; SC, smoking cessation; GP, general practitioner.

When a lower medication cost of statin therapy was included, similar to an off-patent cost of simvastatin, the resulting CER of statin therapy was comparable to the CER of antihypertensive treatment. This lower cost of statin therapy represented a reduction of 68 percent in the current cost of statins in The Netherlands and was taken from the current price of generic simvastatin in Denmark (29). However, in an incremental cost-effectiveness analysis, the cheapest statins still cannot compete with smoking cessation or aspirin.

Changing the proportion of smokers and participants with SBP ≥ 140 mm Hg or giving antihypertensives by level of absolute risk irrespective of level of SBP changed the CERs mildly, but not their order nor the order of the league table (not presented).

DISCUSSION

This study confirms that, apart from smoking cessation in smokers, aspirin treatment remains the first pharmacological option in population level primary prevention of CVD. Antihypertensive treatment for moderate hypertension is moderately efficient, but statins will have to be much less

Table 7. Sensitivity Analysis on the Cost-Effectiveness of Primary Prevention of Cardiovascular Disease

	Cost per YLS[a] for a population with 50 years age and High Risk[b]						
Ten-years Treatment	Future Costs Discounted by 4%, Effects Undiscounted	Future Costs and Effects Undiscounted	Future Costs and Effects Discounted by 6%	Statins Drug Costs Reduced by 68%[c] Costs and Effects Discounted 4%	Annual Relapse Rate for SC: 20% Costs and Effects Discounted 4%	Annual Relapse Rate for SC: 40% Costs and Effects Discounted 4%	Considering Adverse Effects of Aspirin[d] Costs and Effects Discounted 4%
SC GP Advice[a]	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
SC Nicotine Substitutes[e]	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
SC Bupropion[e]	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
Aspirin	2087	2461	2856	2716	2716	2716	3655
Antihypertensives[f]	28032	32941	38284	36399	36399	36399	36399
Statins	65806	77441	90240	34889	85715	85715	85715

Abbreviations: YLS, Year of Life Saved; SC, Smoking Cessation; GP, General Practitioner.
[a] Costs calculated in Euros from 2003.
[b] High risk refers to a ten-year risk of coronary heart disease? 20%.
[c] Drug costs reduction of 68% is comparable to the price of Simvastatin in Denmark[29] compared to the price in The Netherlands.
[d] Adverse effects considered were major gastrointestinal bleeding at an incidence rate of 1% in 10 years.
[e] Smoking cessation was given only to smokers: 68% and 91% of the age 50 group with moderate and high risk respectively, and 21% and 74% of the age 60 group with moderate and high risk respectively.
[f] Antihypertensives were given only to participants with high blood pressure: 27% and 82% of the age 50 group with moderate and high risk respectively, and 25% and 50% of the age 60 group with moderate and high risk.

expensive to compete with aspirin in the primary prevention of CVD.

Although smoking cessation therapies represented savings in all situations, the absolute benefits obtained with this treatment were consistently lower compared with the other three alternatives. Also, this therapy can obviously only be offered to a particular population (smokers), which further limits the potential benefits at the population level. For nonsmokers, aspirin remains the most cost-effective option, with large levels of effects and relatively low cost for its benefits. Statins in contrast showed very good results in terms of YLS, YLS free of CHD, and number of deaths prevented, but the cost of treatment is still too high to offer this therapy to everybody who may benefit, even when statins off-patent were considered. Larger reductions in the price of statins are needed before they can be given to populations at levels of 10-year CHD risk below 30 percent. An important limitation of this study is that prevalence of higher risks than 30 percent was too small in the Framingham study populations to be able to estimate life tables, the estimate above which treatment was advocated in most guidelines. Although we cannot judge if use of statins in primary prevention at risks above 30 percent is efficient, below 30 percent it is not. Antihypertensives showed lower costs and better efficiency than statins but also lower effectivity. Another limitation of our study is that we do not present cost-effectiveness estimates for women. We decided to include only men due to the scarcity of evidence for women that did not allow us to find published estimates for all the transition rates required in our analyses.

We did not include savings in terms of CVD interventions (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) secondary to treatment. The reason behind this decision is the constant change in CVD treatment, which makes current populations not comparable with populations from the 1970s and 1980s, in terms of invasive treatments of CHD. Additionally, due to the unavailability of echocardiographic measures, left ventricular hypertrophy was defined in the Framingham populations based on ECG measurements. However, we expect that this would only introduce into our analysis a nondifferential misclassification of the risk levels of the population studied.

We selected a 10-year time horizon and considered no effects (or costs) beyond. The main reason is that cost-effectiveness ratios over longer time horizons are heavily determined by the highest levels of risk at older ages, and require arguable assumptions about health effects of treatment over long periods and at old ages. Additionally, there is no evidence on the benefits of statins for periods of time beyond 6 years. We did not value saved lives after 10 years of treatment, but mentioned this apart as costs per averted death. Nevertheless in terms of cost-effectiveness, our ratios are comparable to the existing CERs in the literature. In the case of statin therapy, our CERs fall within the estimated range for primary prevention of CVD published by Pharoah and Hollingworth (25), using also a life table approach and a 10-year time horizon. If we transform the saved lives into YLS by using the residual population life expectancy at age 55 and 65, the CER are comparable to studies using a lifetime time horizon (data not shown). The main strength of this study is the comparative analysis, using the same methods and showing the same rankings. The ratios of the other therapies fall within the ranges of their correspondent literature (21;22;24).

We decided to use a market share approach and select a single estimate for each strategy because using every potential combination of estimates and specific drugs is beyond the scope of this study. We used only costs based on current Dutch standards, which limits the generalizability of our results.

Except for aspirin, no adverse effects were taken into account in our analysis for the strategies considered, because no evidence of serious complications exists at low or normal dosages. In general, in this study, we have considered compliance of the different therapies selected by using the relative risks results of intention-to-treat randomized controlled trials, which incorporate the trial compliance.

Perhaps in the future, with the advent of a low-cost Polypill (32), the situation may change in the primary prevention of CVD and all the beneficial interventions could be offered to everyone that requires them, without exhausting our budgets. However, in the meantime, we have to deal with our current options and design an effective and realistic strategy.

In conclusion, we found that, for cost-effective pharmacological population prevention of CHD, the first line of intervention should be smoking cessation therapy for smokers and aspirin for all levels of risk. Antihypertensive therapy is efficient over a wide range of risk but not the cheapest option. Statin therapy is an expensive option and should not represent a first-choice in primary prevention; guidelines on primary prevention of CVD should not advise treatment with statins for populations at levels of 10-year CHD risk below 30 percent.

POLICY IMPLICATIONS

For cost-effective pharmacological population prevention of CHD, the first line of intervention should be smoking cessation therapy for smokers and aspirin for all levels of risk. Statin therapy is an expensive option and should not represent a first choice in the primary prevention of cardiovascular disease.

CONTACT INFORMATION

Oscar H. Franco, MD, DSc, PhD (oscar.franco@unilever.com), Scientific Researcher, Department of Public Health,

Erasmus MC, University Medical Center, 50 Dr. Molewaterplein, 3000 CA Rotterdam, Zuid-Holland; Senior Epidemiologist, Unilever Corporate Research, Colworth Park, Sharnbrook, Bedfordshire MK441LQ, UK
Arno J. der Kinderen, MSc (a.d.kinderen@rijnland.nl), Scientific Researcher, Department of Public Health, Erasmus MC, University Medical Center, 50 Dr. Molewaterplein, 3000 CA Rotterdam, Zuid-Holland; Advisor Business Economics, Department of Business Economics, St. Alatus, 1 Simon Smitweg, 2353 GA Leiderdorp, Zuid-Holland
Chris De Laet, MD, PhD (chris.delaet@kenniscentrum.fgov.be), Senior Expert, Belgian Health Care Knowledge Center, Wetstraat 62, 1040 Brussels, Belgium
Anna Peeters, PhD (anna.peeters@med.monash.edu.au), Senior Scientific Researcher, Department of Epidemiology and Preventive Medicine, Monash University Central and Eastern Clinical School, Alfred Hospital, Commercial Road, Melbourne, Victoria 3004, Australia
Luc Bonneux, MD, PhD, (Bonneux@nidi.nl), Senior Researcher, Department of Prognoses and Migration, Netherlands Interdisciplinary Demographic Institute, Lange Houtstraat 19, Den Haag 2511 CV, The Netherlands

REFERENCES

1. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J*. 1991;121:293-298.
2. College, Tarieven, Gezondheidszorg. Available at: www.ctgzorg.nl. Accessed 2004.
3. College voor zorgverzekeringen. *Farmacotherapeutisch Kompas: medisch farmaceuthische voorlichting/uitgave van de Commissie Farmaceuthische hulp van het College voor zorgverzerkeringen*. Amstelveen: College voor zorgverzekeringen; 2003.
4. Committee SMA. Standing Medical Advisory Committee. the use of statins. 1997 (11061 HCD Aug 97 [04]). London: Department of Health.
5. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: The Framingham Study. *Am J Public Health*. 1951;41:279-281.
6. Drummond M, Brandt A, Luce B, Rovira J. Standardizing methodologies for economic evaluation in health care. Practice, problems, and potential. *Int J Technol Assess Health Care*. 1993;9:26-36.
7. Euro-medicines. Available at: www.euromedicines.org. Accessed 2001.
8. Franco OH, Peeters A, Looman CW, Bonneux L. Cost effectiveness of statins in coronary heart disease. *J Epidemiol Community Health*. 2005;59:927-933.
9. Hayden M, Pignone M, Phillips C, Mulrow C. 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;136:161-172.
10. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *JAMA*. 1997;278:313-321.
11. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: The Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7:403-422.
12. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2003;CD000031.
13. Hunink MGM GP, Siegel JE, et al. *Decision making in health and medicine: Interpreting evidence and values*. Cambridge, England: Cambridge University Press; 2001.
14. Jacobson TA. Clinical context: Current concepts of coronary heart disease management. *Am J Med*. 2001;110(Suppl 6A):3S-11S.
15. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol*. 1979;110:281-290.
16. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology*. 2001;120:594-606.
17. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. *JAMA*. 1999;282:2340-2346.
18. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J*. 1992;146:473-481.
19. Law MR, Wald NJ. Risk factor thresholds: Their existence under scrutiny. *BMJ*. 2002;324:1570-1576.
20. Lightwood JM, Glantz SA. Short-term economic and health benefits of smoking cessation: Myocardial infarction and stroke. *Circulation*. 1997;96:1089-1096.
21. Malik IS, Bhatia VK, Kooner JS. Cost effectiveness of ramipril treatment for cardiovascular risk reduction. *Heart*. 2001;85:539-543.
22. Marshall T. Coronary heart disease prevention: Insights from modelling incremental cost effectiveness. *BMJ*. 2003;327:1264.
23. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2000;356:1955-1964.
24. Parrott S, Godfrey C. Economics of smoking cessation. *BMJ*. 2004;328:947-949.
25. Pharoah PD, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: Life table method applied to health authority population. *BMJ*. 1996;312:1443-1448.
26. Report HIC. *Dutch guidelines for pharmacoeconomic research*. Available at: www.ispor.org/PEguidelines/source/PE_guidelines_english_Netherlands.pdf. Accessed 1999.
27. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301-1307.
28. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2002;CD000146.

29. Statistikbank HeD. Available at: www.statistikbanken.dk. Accessed 2004.
30. van Hout BA. Discounting costs and effects: A reconsideration. *Health Econ*. 1998;7:581-594.
31. van Hout BA, Simoons ML. Cost-effectiveness of HMG coenzyme reductase inhibitors; whom to treat? *Eur Heart J*. 2001;22:751-761.
32. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ*. 2003;326:1419.
33. Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. *Arch Intern Med*. 2002;162:2197-2202.