Cardiovascular Disease Prevention

From meta-analyses to life expectancies.

Oscar H. Franco Durán

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Cardiovascular Disease Prevention

From meta-analyses to life expectancies.

Cardiovasculaire ziektepreventie

Van meta-analyses tot levensverwachting

Thesis

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by command of the
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“God makes me play well. That is why I always make the sign of the cross when I walk out onto the field. I feel I would be betraying Him if I didn't."

Diego

Para mis Padres, mis Hermanas y Michelle

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1

General introduction

“It is only with the heart that one can see rightly, what is essential is invisible to the eye” Antoine De Saint-Exupery (1900-44).

Cardiovascular disease

Cardiovascular Disease (CVD) includes dysfunctional conditions of the heart and of the blood vessel system (arteries, veins , and capillaries) that among other functions supply oxygen to all body tissues and organs, including vital life-sustaining areas like the brain and the heart itself. If oxygen doesn't arrive the tissue or organ will die (necrosis). Coronary heart disease and stroke are the principal components of CVD. Coronary heart disease refers to diseases of the blood vessels that supply the oxygen to the heart. Strokes occur as a result of a disruption of the blood supply to the brain caused by either blockage (ischaemic stroke) or the rupture of a blood vessel (haemorrhagic stroke).[1]

Cardiovascular disease now ranks as the world's top cause of death, causing one third of all deaths globally. Approximately 17 million people die each year of CVD worldwide and this number is expected to increase up to 24 million by 2030. The global epidemic of CVD is not only rising, but also shifting from developed to developing countries, partly as a result of increasing life expectancy and lifestyle changes. CVD can no longer be seen as a western society problem or the disease of stressed middle-aged men workers from developed countries. Almost 75% of all CVD deaths occur in developing nations. [2]

Risk factors for cardiovascular disease

More than 300 risk factors have been associated with CVD. Risk factors can be classified as modifiable or non-modifiable. Non-modifiable risk factors include sex, age, race and family history of CVD. Major modifiable risk factors include: physical inactivity, high blood pressure, abnormal blood lipids, tobacco use, obesity, unhealthy diets and diabetes mellitus. Other modifiable risk factors include: low socio-economic status, depression, psychosocial stress, excess homocysteine in blood (hyperhomocysteinemia) and inflammation. Modifiable risk factors can in principle be prevented, treated or controlled.[1]

Physical inactivity:

Worldwide physical inactivity is associated with about 1.9 million deaths, 20% of CVD and 22% of coronary heart disease.[3] Although current recommendations advice only 150 minutes per week of moderate physical activity to prevent CVD,[4] more than 60% of the global population are not sufficiently active. [1]

Hypertension:

High blood pressure (Hypertension) is currently defined as a systolic blood pressure above 140 mmHg and/or a diastolic blood pressure above 90 mm Hg.[5] Hypertension contributes to around half of all cases of CVD. It is a major risk factor for coronary heart disease and the most important risk factor for stroke and one of the most important preventable causes of premature death worldwide. Hypertension is commonly called the "Silent Killer" because frequently its first warning sign is a fatal myocardial infarction or a stroke.[5-7]

Dyslipidemia:

Cholesterol is a very important substance for the organism. It is among other functions used in cell membranes and hormones. However, dyslipidemia (high levels of total cholesterol and/or high levels of LDL cholesterol and/or high levels of triglycerides and/or low levels of HDL cholesterol) leads to clogging of the arteries increasing the risk of CVD. Currently recommended levels of lipids are: < 240mg/dl for total cholesterol, < 160mg/dl LDL cholesterol, < 200mg/dl triglycerides and > 40mg/dl HDL cholesterol.[8-10]

Smoking:

Tobacco is associated with a fifth of CVD worldwide. Smoking increases the risk of CVD through damaging the endothelium of the blood vessels, increasing cholesterol plaques in the arteries, increasing clotting, raising "bad" cholesterol (LDL) and lowering "good cholesterol" (HDL). It also promotes coronary artery spasm. Smoking cessation reduces after two to three years CVD risk to levels similar to those of a person who has never smoked.[11 12]

Obesity:

Obesity is defined as an excessively high amount of body fat or adipose tissue in relation to lean body mass. The prevalence of obesity is increasing globally; this has been dubbed "globesity".[13] Body mass index (BMI) is a measure of weight (kilograms) in relation to height (meters squared). BMI is commonly used to classify obesity. A person with a BMI over 25 is considered overweight and over 30 obese.[14]

In 1995, there were an estimated 200 million obese adults worldwide; by 2000 this number increased to over 300 million. The epidemic of obesity related problems is not restricted to industrialized societies; in developing countries over 115 million people suffer from obesity-related problems.[2 3 13]

Unhealthy diets:

Habitual food intake varies greatly between populations. These differences are related to population prevalence of CVD. Low fruit and vegetable intake is

associated with about one third of coronary heart disease and 11% of stroke worldwide. High saturated fat intake increases the risk of CVD by increasing blood lipids, thrombosis and body weight.[1]

Diabetes mellitus:

Insulin is a hormone produced by the pancreas and used by the organism to regulate glucose (sugar). Diabetes Mellitus is a disease in which the body does not produce or properly use insulin leading to high levels of sugar in blood (hyperglycaemia). Over 190 million people worldwide have diabetes, this number is increasing and by 2030 it is expected to increase to 330 million. Diabetes is a major risk factor for CVD. CVD accounts for 75% of all deaths among people with diabetes of European origin.[1 15]

Cardiovascular disease prevention

Economic transition, urbanization, industrialization and globalisation promote the adoption of western lifestyle and diet. This has increased the population levels of the modifiable risk factors progressively and has made cardiovascular diseases common.[16 17]

Modifiable risk factors can be prevented, treated or controlled; therefore CVD could in principle be prevented. Prevention can be classified as primary, secondary and tertiary prevention. Primary prevention aims at lowering the occurrence rate of the event, i.e. the incidence rate of the disease. Secondary prevention aims at lowering the occurrence of the later and more severe stages of the disease, often by identifying diseases at a curable stage. Tertiary prevention aims at reducing the social consequences of the disease.[18] Intense prevention of CVD at all stages and in all latitudes is every time more relevant and necessary if society wants to control the CVD pandemic. Successful cardiovascular prevention requires a combined global effort implementing health-service interventions at personal and non-personal levels. [19]

Non-personal interventions for preventing CVD

Non-personal or population-wide interventions target not individuals but entire populations. This type of interventions includes among others:

- Salt reduction through voluntary agreements between governments and the food industry for stepwise decrease in salt content of processed foods and labelling.
- Legislation to decrease salt content in processed foods and appropriate labelling.

- Health promotion and education through mass media campaigns focusing on the promotion of healthy lifestyles that include non-smoking, balance diets -low in fat and calories- and promotion of physical activity.
- Legislation on permitted places for smoking activity. Forbidding smoking on bars, public places and mass transportation systems.
- Governmental measures to increase tributary obligations from tobacco companies and taxes revenues from tobacco products.

These interventions have a large potential to prevent CVD and have been shown to be more cost-effective than personal interventions.[19] However, the implementation of this type of interventions is a rather complex task.

Personal interventions for preventing CVD (Cardiovascular risk management)

Personal interventions targeting individuals at increased risk of CVD constitute the basis of CVD risk management. Those at high risk of CVD include people with established CVD as well as those with high levels of risk factors for CVD. The majority of the 32 million individuals who develop cardiovascular disease every year have one or more CVD risk factors and many events would have been prevented if proper action had been taken against these risk factors. [20]

Although evidence is scarce on the effects of modifiable risk factors on total life expectancy and life expectancy with (out) cardiovascular disease, large evidence supports that reducing them by any means lowers the risk of CVD.[17] However, for cardiovascular risk management to achieve its greatest impact, a paradigm shift is required from the treatment of risk factors in isolation to comprehensive CVD risk management.[20] Currently, the treatment of four risk factors for CVD constitute the basis of CVD risk management in populations free of CVD (primary prevention) or diabetes: blood lipids modification, blood pressure lowering, anti-platelet aggregation therapy and smoking cessation. Even though effective treatment is available to treat almost all types of CVD, many patients who could benefit from treatment remain untreated, or inadequately treated. This is mainly due to a combination of high costs and low compliance. The cost-effectiveness balance of cardiovascular risk management is unclear as is the most cost-effective strategy. This is particularly the case for statins, drugs that are highly effective in treating dyslipidemia but also very expensive. [21 22]

In 2003 Wald and Law formally introduced a potential solution to the current inadequacies of cardiovascular risk management: the Polypill concept.[17] The Polypill is a theoretical combination of six drugs that combined and through concomitant modification of four different risk factors for CVD (cholesterol modification with statins, blood pressure lowering with three different

antihypertensives, anti-platelet aggregation with aspirin and reduction of hyperhomocysteinemia with folic acid) will potentially reduce CVD by more than 80%. However the Polypill is not yet available in the market and its efficacy remains unproven. Additionally, potential adverse effects and costs of such intervention have been questioned. Further research is needed to find low cost alternatives to effectively prevent and treat cardiovascular risk in our populations.[23]

This thesis

In this thesis we attempt to provide additional evidence on the effects of different risk factors on total life expectancy and life expectancy with and without CVD. We also evaluate the cost-effectiveness of statins and compare it with other key existing interventions in cardiovascular risk management. Finally we calculate the potential costs and cost-effectiveness of a theoretical intervention (the polypill) and try to find a non-pharmacological alternative.

The main research questions are:

1. What is the effect of risk factors for cardiovascular disease such as physical inactivity and hypertension, in terms of life expectancy and years lived with and without cardiovascular disease?
2. What is the cost-effectiveness of various strategies for cardiovascular risk management and which one is the most cost-effective in the primary prevention of CVD?
3. Could the polypill be a cost-effective intervention in the primary prevention of CVD, and what could be a good alternative to the polypill in populations free of heart disease?

Part A of this thesis, which includes chapters 2 and 3, is based on multi-state life table analyses (MSLT) using data from the Framingham Heart Study (FHS). The FHS is a prospective cohort study consisting of 5209 respondents residing in Framingham, Massachusetts between 1948 and 1951 and followed bi-annually for now over 46 years (and still ongoing). MSLT is a demographic technique that allows calculating life-course measures (e.g. life expectancy) of the effects of interventions or conditions, through combining different transition rates or probabilities between health states (e.g. disability, morbidity, mortality). In chapter 2 we calculate the effects of different levels of physical activity in terms of life expectancy and years lived with and without CVD by sex in adult populations over age 50. We use a

special type of life table analysis: population MSLT. A population MSLT combines information from people at different ages and from different birth cohorts, combining transition rates at different ages from different individuals (collected at the same point in time). In chapter 3 we used a cohort MSLT. This type of MSLT uses data from people at a similar age, here the transition rates at each age come from the same cohort of people as they age. Using a cohort MSLT we determined the impact of high blood pressure levels on total life expectancy and life expectancy with and without CVD (or myocardial infarction or stroke) for both adult men and women at age 50.

In part B (chapters 4, 5 and 6) we systematically review the literature to evaluate the cost-effectiveness of statins and compared the cost-effectiveness of statins with other interventions in the primary prevention of CVD. In chapter 4 we sought to identify sources of heterogeneity of reported cost-effectiveness ratios adjusted for categories of risk of heart disease, age and funding source. We collected all relevant economical analyses evaluating the effect of statins in cardiovascular prevention. In chapter 5 using the studies collected in chapter 4 we aim to identify the various methods used to quantify the benefit (effectiveness) of statin treatment, to illustrate these different methodologies using a life table as standard tool and therefore to indirectly evaluate their reproducibility. In chapter 6 we calculate and compare the cost-effectiveness of four risk-lowering treatments: aspirin, antihypertensives, statins and smoking cessation. We use once more MSLTs and data from the FHS and from the Framingham Offspring Study (FOS). Analyses include males free of CVD at different ages and different levels of risk. We evaluate optimal strategies for CVD risk management.

Part C (chapters 7, 8 and 9) is focused on the polypill concept; here we recur once more to MSLTs and data from the FHS. In chapter 6 we aim to estimate the maximum cost of medication and treatment with the Polypill in order to be cost-effective among adult male populations free of CVD. We considered different levels of 10-year absolute risk of coronary heart disease (CHD) and different ages, to calculate the effects of the Polypill in terms of Years of Life Saved (YLS). In chapter 7 we question the models used by the Polypill investigators in their statistical analyses of the ingredients of the Polypill (statins in particular). In chapter 8 we attempt to define a safer, non-pharmacological, and tastier alternative to the Polypill in the general population: the Polymeal. We also wanted to calculate the potential effects of the Polymeal in terms of total life expectancy and life expectancy with and without cardiovascular disease.

Finally in chapter 10, we give a summary of our findings and answer the three main research questions of this thesis. Limitations on our findings and validity issues of our analyses are discussed as well as practical applications of our results. Lastly, we provide suggestions for future research on cardiovascular risk management.

Before we continue with the next chapter I would like to introduce the reader the main outcome-measures used in this thesis.

The main outcome-measures used in this thesis are:

1. Life Expectancy (LE): LE is the average number of years that for a person of a given age is expected to remain alive.
2. Life Expectancy with and without cardiovascular disease: Is defined as the average number of years that for a person of a given age is expected to remain alive with or free of a determined disease, in our case cardiovascular disease.
3. Average cost-effectiveness ratio (CER): Is the ratio of the total costs of a program or intervention net of savings to the total health effects achieved by the program or intervention, when compared to a null-situation (i.e. no program or intervention).
4. Incremental cost-effectiveness ratio (iCER): Is the ratio of the total costs of a program or intervention net of savings to the total health effects achieved by the program or intervention, when compared to the next best alternative program or intervention.

In chapter 2 and 3 of this thesis we used LE and LE with/out CVD to quantify the long-term effects of hypertension and physical inactivity among adult populations. The justification for using these life-course measures is that first there is ample evidence on the deleterious effect of the mentioned risk factors among adult populations at all ages. Second this type of lifelong outcomes allowed us to calculate the burden of these risk factors on CVD. And third these types of measures allow us to combine data on mortality and morbidity of a specific condition into a single measure.

In chapter 4, 5, 6 and 7 we used CERs and iCERs to be able to compare different interventions for the prevention of cardiovascular disease. We decided to use a single type of CERs (Cost per YLS) in order to assure comparability among strategies and with the literature.

At last in chapter 9 we used once more LE and LE with/out CVD in order to calculate the long-term consequences of adopting a non-pharmacological alternative to the Polypill and to allow a direct comparability of the effects of the Polypill with our proposed intervention.

References

1. Mackay J, Mensah GA. *The Atlas of Heart Disease and Stroke*. Geneve: World Health Organization, 2004.
2. WHO. *The World Health Report: 2003: shaping the future*. Geneve: World Health Organization, 2003.
3. WHO. *The World Health Report 2002: reducing risks, promoting healthy life*. Geneve: World Health Organization, 2002.
4. US Department of Health and Human Services. Physical Activity and Health: A Report of the Surgeon General. Atlanta, Ga: US Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, 1996.
5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289(19):2560-72.
6. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21(6):1011-53.
7. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345(18):1291-7.
8. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285(19):2486-97.
9. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106(25):3143-421.
10. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease and prevention in clinical practice. *Atherosclerosis* 2003;171(1):145-55.
11. Dobson AJ, Alexander HM, Heller RF, Lloyd DM. How soon after quitting smoking does risk of heart attack decline? *J Clin Epidemiol* 1991;44(11):1247-53.
12. McBride PE. The health consequences of smoking. Cardiovascular diseases. *Med Clin North Am* 1992;76(2):333-53.
13. WHO, FAO. Report of the Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases. In: WHO, editor. *Technical Report Series No. 916*. Geneve: World Health Organization, 2002.

14. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res* 1998;6 Suppl 2:51S-209S.
15. IDF. http://www.idf.org/home/index.cfm?node=4: International Diabetes Federation, 2005.
16. Faergeman O. The societal context of coronary artery disease. *European Heart Journal* 2005;7 (supplement A):A5-A11.
17. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326(7404):1419.
18. Detels R, Mcewen J, Beaglehole R, Tanaka H. *Oxford Textbook of Public Health 4th Edition*. Oxford: Oxford University Press, 2002.
19. Murray CJ, Lauer JA, Hutubessy RC, Niessen L, Tomijima N, Rodgers A, et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 2003;361(9359):717-25.
20. WHO. *WHO CVD-risk management package for low - and medium resource settings*. Geneve: World Health Organization, 2002.
21. Standing Medical Advisory Committee, the use of statins. www.doh.gov.uk/cmo/statins2.html, 1997.
22. Raithatha N, Smith RD. Paying for statins. *BMJ* 2004;328(7436):400-2.
23. Franco OH, Bonneux L, de Laet C, Peeters A, Steyerberg EW, Mackenbach JP. The Polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. *BMJ* 2004;329(7480):1447-50.

PART A

Burden on cardiovascular disease of different risk factors.

Effects on life expectancy of physical activity and hypertension.

"Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it" Plato (427-347 BC)

2

Effects of physical activity on total life expectancy and life expectancy with and without cardiovascular disease

Oscar H. Franco, Chris de Laet, Anna Peeters, Jacqueline Jonker, Johan Mackenbach, Wilma Nusselder. Effects of physical activity on total life expectancy and life expectancy with and without cardiovascular disease. *Submitted.*

Abstract

Context:
Physical inactivity is a modifiable risk factor for cardiovascular disease. However, little is known about the effects of physical activity on life expectancy with (out) cardiovascular disease.

Objectives:
To calculate the consequences of different physical activity levels after age 50 in terms of total life expectancy and life expectancy with (out) cardiovascular disease.

Design:
Life table analysis using data from the Framingham Heart Study.

Methods:
We calculated the effects of three levels of physical activity (low, moderate and high) among populations aged over 50 years. We used hazard ratios for three transitions (healthy to death, healthy to disease, disease to death), by levels of physical activity and adjusted for age, sex and other potential confounders.

Results:
Moderate and high physical activity levels led to 1.4 and 3.8 years more in total life expectancy and 1.1 and 3.2 more years lived without cardiovascular disease for men aged 50 compared with those who maintained a low physical activity level. For women the gains were similar.

Conclusions:
Avoiding a sedentary lifestyle during adulthood not only prevents cardiovascular disease independently of other risk factors, but also substantially expands the total life expectancy and the cardiovascular disease-free life expectancy for men and women. This effect is already seen at moderate levels of physical activity, and the gains in cardiovascular disease-free life expectancy are twice as large at higher levels of activity.

Introduction

The beneficial effect of physical activity in the prevention of cardiovascular disease (CVD) is widely known and is supported by a large amount of evidence.[1, 2] From the bus drivers of Morris et al[3, 4] until the more recent Harvard alumni of Paffenbarger et al[5, 6]; different studies have reported a protective effect of physical activity on total mortality, CVD and diabetes in the general population.[7-14] Through lowering the inflammatory response involved in atherogenesis and modifying the traditional risk factors of CVD, increasing physical activity reduces the rates of cardiovascular disease in the general population[6, 15]. Expected effects are seen for at different levels of intensity, from moderate to very high, different durations and for different activity types[11, 16, 17]. However it remains unclear whether physical activity levels have a significant effect on life expectancy (LE) or on time spent with and without cardiovascular disease. This is crucial to assess the contribution of physical activity in cardiovascular risk management.

In this study we calculated the effects of different levels of physical activity in terms of life expectancy and years lived with and without CVD at age fifty.

Methods

Using data from the original Framingham Heart Study (FHS), we built life tables to calculate the relation between different levels of physical activity and total LE and LE with and without CVD at age 50 in the general population.

Data sources

The FHS cohort consisted of 5209 respondents residing in Framingham, Massachusetts, between 1948 and 1951. The study included both men (n = 2336) and women (n = 2873) aged 28 to 62 years. The cohort has been examined biannually for 46 years. Further description of the FHS can be found elsewhere.[18]

Study sample

In order to calculate transition rates by levels of physical activity, we pooled three, non-overlapping follow-up periods of 12 years. Each period started with a measurement of physical activity. In the present investigation, the follow-up periods started at the exams 4, 11 (if present or otherwise 12), and 19 (if present or otherwise 20). Using the pooling of repeated observations (PRO) method[19], follow-up information over three follow-up periods was pooled, yielding a total of 9773 observation-intervals. The same participant may thus be followed during three periods until the event (first onset of CVD or death) occurs or the subject is

censored. However, follow-up time and physical activity status were measured anew for in each interval. We used observation-intervals of no more than 12 years in order to avoid overlapping periods of follow-up. After excluding participants with missing data on physical activity and CVD at exam one, 4220 subjects were available from exam four, 3298 from exam 11/12 and 1663 from exam 19/20 yielding a total of 9181 observation-intervals.

Assessment of physical activity

Participants were asked to estimate how long they spent in a typical day at various levels of activity: sleeping, resting, or engaged in light, moderate and heavy physical activity. The reported levels of activity were weighted based on the estimated oxygen consumption for each activity to reflect metabolic expenditure correspondent to metabolic equivalents (METs). Weights used were: for sleeping 1, for being sedentary 1.1, for light activity 1.5, for moderate activity 2.4 and for heavy activity 5. Finally, a daily physical activity score was calculated by adding the sum of the weighted hours for each level of activity. The minimum possible score is 24 for a participant sleeping 24 hours/day. Further detail on the assessment of physical activity and calculation of the daily physical activity score can be found elsewhere.[12] Based on tertiles of the physical activity score, we grouped the participants into three levels: low (<30), moderate (30-33) and high (>33) physical activity level.

Outcome assessment

The primary outcome of our study is incident or fatal CVD. Cardiovascular disease included coronary heart disease (angina, coronary insufficiency, myocardial infarction and sudden or not sudden death as consequence of coronary disease), congestive heart failure, stroke, transient ischaemic attack and intermittent claudication. A panel of three physicians evaluated all events; agreement of all three was required. More detail on the evaluation of outcomes in the FHS is available elsewhere.[20]

Potential confounders

Potential confounders were measured at each baseline except for education, which was only measured once. All analyses were adjusted or stratified by age and sex. Potential confounders considered were: education (eighth grade or less/ higher than eighth grade), smoking (never, ever or current smoking), marital status (single/married/ widowed/ separated or divorced), comorbidity present at baseline (any of the following diseases: cancer, left ventricular hypertrophy, arthritis, ankle edema or any pulmonary disease), total cholesterol and the start of follow-up (exam 4, 11/12 or 19/20). The exam of start follow-up was included to correct for a

potential cohort and period effect. Intermediate variables considered were hypertension and body mass index (BMI). Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg.[21] For BMI four categories were defined: BMI <18.5 kg/ m², 18.5≤BMI<25 kg/m², 25≤BMI<30 kg/m², BMI ≥ 30 kg/m².[22] For the final analysis, only participants who had information on the selected confounders were included.

Data analysis

To calculate the life expectancy (LE) with and without CVD, we created a population Multi State Life Table (MSLT). The population MSLT, which combined information from people at different ages and from different birth cohorts, included three different states: 'free of CVD', 'history of CVD' and 'death'. The possible transitions were from 'free of CVD' to 'history of CVD', or to 'death' and from 'history of CVD' to 'death'. No back flows were allowed and only the first entry into a state was considered.[23]

To evaluate the differences in risk among persons at age 50 and over for the three levels of activity, we first calculated the overall sex and age-specific transition rates for each transition. Then, hazard ratios by levels of activity were calculated using Poisson regression (Gompertz distribution) and adjusting for sex, age, potential confounders and intermediate variables. Three final models were selected. One basic model adjusted for age and sex. The second model adjusted for confounders that substantially changed the effect of physical activity on CVD or mortality (in addition age and sex). The third model also included intermediate variables (BMI and hypertension).

Finally, the three sets of transition rates were calculated for each physical activity level using the overall transition rates, the adjusted hazard ratios of CVD by activity level; and the prevalence of physical activity level by sex and presence of CVD. Similar calculations have been described previously and the excel worksheets are available upon request.[24]

Separate MSLTs were created for each sex and each level of physical activity, incorporating each of the three transitions. The MSLT was started at age 50 and was closed at age 100. The measures available from the MSLT include overall LE and LE with and without CVD by levels of physical activity and sex.

All statistical analyses were done using STATA version 8.2 for Windows (Stata corporation, college station TX, USA, 2003).

We calculated confidence intervals (CIs) for all LEs and differences in LEs using Monte Carlo simulation (parametric bootstrapping).[25] To calculate the CIs we used @RISK (Anonymous 2000; MathSoft Inc 1999), 10000 runs.

Sensitivity analysis

Finally, since it has been reported that levels and effects of physical activity change with time[26], in a sensitivity analysis we evaluated the effect of length of follow-up on the relation between physical activity and CVD/mortality. All the analyses were repeated for different periods of follow-up: 12, 10, 8 and 6 years.

Results

Baseline characteristics

In general, participants in the low physical activity group tended to be older (mean age 62) compared with the participants of the moderate and high activity groups (mean age 58 and 59, respectively). The level of each of the comorbidities, mean SBP, DBP and total cholesterol was higher among the participants with low physical activity (TABLE 2.1). The low and moderate activity groups tended to have a higher

Table 2.1. Baseline Characteristics by Physical Activity Level*

Characteristics	Level of physical activity (tertiles)		
	Low (n= 2857)	Moderate (n= 3349)	High (n=2975)
Age, mean (SD), y	61.6 (13.1)	57.6 (12.3)	59.1 (11.8)
Women, No. (%)	1790 (63)	2075 (62)	1366 (46)
Pa score, mean (SD)	28.1 (1.15)	31.3 (0.97)	38.1 (5.37)
Marital status, No. (%)			
Single	279 (10)	279 (8)	177 (6)
Married	1944 (68)	2517 (76)	2410 (81)
Widowed	518 (18)	417 (13)	290 (10)
Divorced/Separated	72 (3)	86 (3)	62 (2)
Education, No. (%)			
8^{th} grade or less	709 (26)	855 (26)	743 (26)
Higher than 8^{th} grade	2055 (74)	2416 (74)	2154 (74)
Smoking Status, No. (%)			
Never smoker	1128 (39)	1223 (37)	871 (29)
Former smoker	667 (23)	752 (23)	865 (29)
Current smoker	1062 (38)	1364 (40)	1239 (42)
Any comorbidity†, No. (%)	1326 (47)	1213 (37)	1079 (37)
BMI‡, mean (SD), kg/m^2	26.2 (4.6)	25.9 (4.1)	26.1 (3.9)
SBP, mean (SD), mmHg	140.3 (24.3)	137.2 (22.7)	136.2 (20.9)
DBP, mean (SD), mmHg	88.9 (24.1)	84.7 (18.0)	84.3 (17.7)
Total cholesterol, mean (SD), mg/dl	239.0 (46.8)	234.6 (43.4)	230.6 (41.6)

Abbreviations: Pa, Physical activity; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.
*Subjects included were alive and with no missing data on physical activity
†Any comorbidity: cancer, left ventricular hypertrophy, arthritis, ankle edema or pulmonary disease
‡Body Mass Index, calculated as BMI=weight in kg/height^2 in m^2

proportion of women (63% and 62% respectively) compared to the high physical activity group (46%).

Risk of cardiovascular disease and death

All transition hazard ratios corrected for age and sex, were inversely related to the level of physical activity (TABLE 2.2). Overall there was a dose-response protective relation between physical activity level and incident CVD or death among participants free of CVD and for mortality among participants with CVD.

Selected confounders were: smoking status, presence of comorbidity (cancer, left ventricular hypertrophy, arthritis, ankle edema or any pulmonary disease) and the start of follow-up. Other variables like education, marital status and total cholesterol were also tested, but not included in the final model since they did not alter the relative risks of physical activity substantially. Information on the selected confounders was available for 9003 (98%) observations-intervals.

After adjustment for age, sex and selected confounders the effect of physical activity was significant (two sided p-value < 0.05) for a high level of physical activity with all transitions ("Incident CVD", "No CVD to Death" and "CVD to Death"). For the group with moderate level of activity the protective effect of physical activity was significant for the transition from "No CVD to Death" but not for the other two transitions. The directions and significance but not the magnitude -which was reduced- of these relations remained the same after adjusting for both confounders and intermediate variables (TABLE 2.2).

Table 2.2. Hazard Ratios by Physical Activity Level and Transition *

Transition	No. of Cases	Person-years	Physical Activity Level	HR† (95% CI)	HR‡ (95% CI)	HR§ (95% CI)
Incident CVD	1573	62185	Low	1.00	1.00	1.00
			Moderate	0.92 (0.82-1.04)	0.94 (0.83-1.06)	0.95 (0.84-1.08)
			High	0.74 (0.65-0.84)	0.77 (0.67-0.87)	0.77 (0.68-0.89)
No CVD to Death	629	62185	Low	1.00	1.00	1.00
			Moderate	0.75 (0.62-0.91)	0.78 (0.64-0.94)	0.80 (0.66-0.98)
			High	0.63 (0.54-0.80)	0.68 (0.56-0.84)	0.72 (0.58-0.89)
CVD to Death	1046	15748	Low	1.00	1.00	1.00
			Moderate	0.86 (0.75-0.99)	0.93 (0.81-1.06)	0.95 (0.83-1.09)
			High	0.67 (0.58-0.78)	0.72 (0.62-0.83)	0.75 (0.65-0.87)

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; CVD, Cardiovascular disease.
*Age 50 and over at start of follow-up
† Adjusted for age and sex
‡ Adjusted for age, sex, smoking and any comorbidity: cancer, left ventricular hypertrophy, arthritis, ankle edema or pulmonary disease, and exam of start follow-up.
§ Adjusted for age, sex, smoking, any comorbidity: cancer, left ventricular hypertrophy, arthritis, ankle edema or pulmonary disease, exam of start follow-up, body mass index and hypertension.

Figure 2.1. Effect of Physical Activity at Age 50

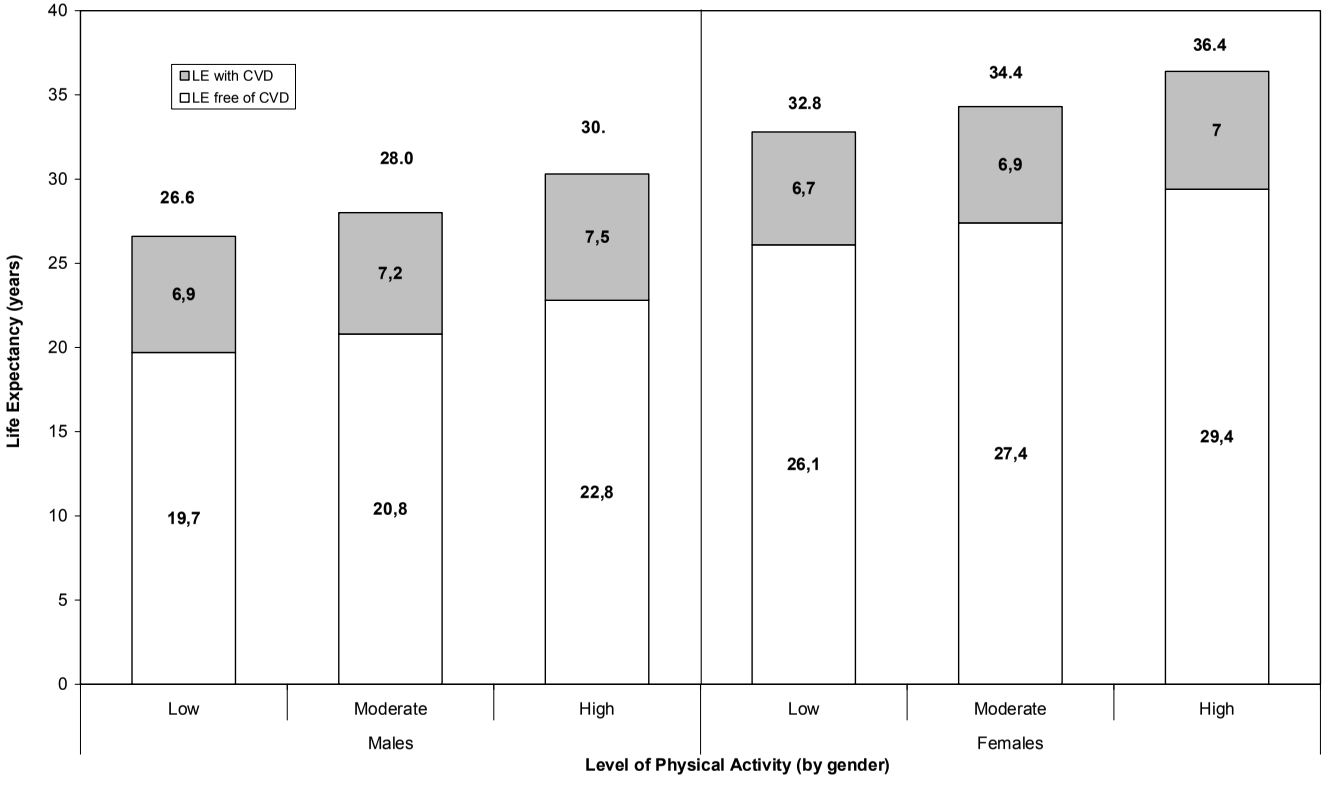

Table 2.3. Life Expectancy in Years at Age 50, Stratified by Sex (95% Confidence Interval)*

Sex	Physical Activity Level	Total LE	Difference† in Total LE	LE free of CVD	Difference† in LE free of CVD	LE with CVD	Difference† in LE with CVD
Men	Low	26.6 (25.8; 27.5)	Ref.	19.7 (18.7; 20.6)	Ref.	6.9 (6.4; 7.6)	Ref.
	Moderate	28.0 (27.0; 29.1)	1.4 (0.4; 2.4)	20.8 (19.6; 21.9)	1.1 (-0.02; 2.1)	7.2 (6.5; 8.0)	0.3 (-0.5; 1.1)
	High	30.4 (29.4; 31.4)	3.8 (2.7; 4.9)	22.8 (21.6; 23.9)	3.2 (1.9; 4.3)	7.5 (6.7; 8.4)	0.6 (-0.3; 1.5)
Women	Low	32.9 (32.1; 33.7)	Ref.	26.1 (25.3; 27.0)	Ref.	6.8 (6.2; 7.3)	Ref.
	Moderate	34.4 (33.4; 35.4)	1.5 (0.4; 2.5)	27.4 (26.4; 28.5)	1.3 (0.1; 2.4)	7.0 (6.3; 7.7)	0.2 (-0.5; 1.0)
	High	36.4 (35.4; 37.5)	3.5 (2.4; 4.6)	29.4 (28.2; 30.6)	3.3 (2.0; 4.5)	7.0 (6.1; 7.9)	0.2 (-0.5; 1.1)

Abbreviations: LE, Life Expectancy; CVD, Cardiovascular Disease; Ref, Reference.
All life expectancies have been calculated with hazard ratios adjusted for age, sex, smoking, any comorbidity: cancer, left ventricular hypertrophy, arthritis, ankle edema or pulmonary disease, and exam of start follow-up.
† Differences are calculated using the Low Physical Activity group as reference: moderate vs. low and high vs. low.

Total life expectancy and life expectancy with and without CVD

Total LE increased proportionally with higher levels of physical activity (FIGURE 2.1). Participants from the moderate and high activity groups live respectively 1.4 and 3.8 more years; and 1.1 and 3.2 more years free of CVD than participants at the low activity group, after adjustment for the selected confounders. This difference was similar for women (TABLE 2.3). This larger total LE for both sexes was composed of these more years lived without CVD but also -although to a lesser degree and not statistically significant- more years lived with CVD (TABLE 2.3).

Sensitivity analysis

The effect of physical activity on CVD and mortality was consistent for all lengths of follow-up, although its magnitude increased as the period of follow-up was reduced; the shorter the period of follow-up the higher the differences in life expectancies between physical activity groups (TABLE 2.4).

Discussion

Life expectancy for sedentary people at age 50 is one and a half years less than for people conducting moderate daily physical activity and over three and a half years

Table 2.4. Life Expectancy in Years at Age 50, Stratified by Sex. Effect of Different Lengths of Follow-up*

Physical Activity Level	10 Years of Follow-up				8 Years of Follow-up				6 Years of Follow-up			
	Total LE	Dif† Total LE	Dif† LE free of CVD	Dif† LE with CVD	Total LE	Dif† Total LE	Dif† LE free of CVD	Dif† LE with CVD	Total LE	Dif† Total LE	Dif† LE free of CVD	Dif† LE with CVD
Men												
Low	27.0	Ref.	Ref.	Ref.	26.7	Ref.	Ref.	Ref.	26.1	Ref.	Ref.	Ref.
Mod	28.6	1.6	1.2	0.5	29.2	2.5	1.7	0.8	28.7	2.6	1.5	1.1
High	31.0	4.1	3.1	1.0	31.3	4.6	3.1	1.5	32.0	5.8	4.0	1.8
Women												
Low	33.4	Ref.	Ref.	Ref.	33.4	Ref.	Ref.	Ref.	33.5	Ref.	Ref.	Ref.
Mod	35.2	1.7	1.4	0.3	36.1	2.6	2.1	0.5	36.4	2.9	2.0	0.9
High	37.2	3.8	3.4	0.3	37.5	4.1	3.4	0.7	39.1	5.6	4.7	0.9

Abbreviations: Mod, Moderate; LE, Life Expectancy; Dif, Difference; CVD, Cardiovascular Disease; Ref, Reference.
All life expectancies have been calculated with hazard ratios adjusted for age, sex, smoking, any comorbidity: cancer, left ventricular hypertrophy, arthritis, ankle edema or pulmonary disease, and exam of start follow-up.
† Differences are calculated using the Low Physical Activity group as reference: moderate vs. low and high vs. low.

less than for people with high physical activity levels. Sedentary people also experience one and tree years more with CVD compared with people at moderate and high levels of activity, respectively. These differences are similar for both sexes.

The larger total LE for participants with higher levels of physical activity was the result of the larger number of years lived without CVD and a slightly larger LE with CVD. The larger number of years lived with CVD among participants at moderate and high physical activity levels compared to the group at low physical activity level, was not statistically significant. In all cases it was below 0.6 years.

The larger CVD-free LE is due to a protective effect of physical activity on the incidence of CVD combined with a protective effect of physical activity on mortality among participants free of CVD. On the other hand, the slightly larger LE with CVD is caused by the effect of physical activity on mortality among participants with CVD -people with CVD at higher levels of physical activity lived longer and therefore experience an increased burden of CVD-. Another reason for the increase in years with CVD is that higher physical activity is associated with increased survival to advanced ages, where the risks of CVD are higher.

The diluting effect of increasing time of follow-up in the preventive role of physical activity on CVD and mortality that we found in this study has been reported before.[26] This reduction or dilution of effect may be explained by misclassification of exposure: subjects tend to change their physical activity behaviours with time. However, it may also be due to less selection and reverse causation (although we corrected for known comorbidity in all analyses), which are the potential biases associated with shorter terms of follow-up. We chose 12 years of follow-up to maximize power and minimize the risks for selection and reverse causation. Importantly, in our study, length of follow-up affected mainly the magnitude of effect. The direction of the relation we found was consistent over the different terms of follow-up.

The hazard ratios we found fall well within the range of the published measures of effect of physical activity on CVD and total mortality. [3-5, 9, 10, 12-17, 26-30] Although similar, the comparison of our results with reported ratios from studies performed in non-FHS populations is limited by the definition and classification of exposure that is unique to the FHS. In the case of primary prevention of CVD the protective effect of physical activity we found is moderately higher that the one found by past investigations of the FHS population. However they used longer periods of follow-up (14 to 16 years), which could explain their lower effects.[12, 27, 30] To our knowledge, this is the first paper to present the effect of physical activity on LE with and without CVD.

A strength of our study is using a well-organized historic cohort that has been followed biannually for decades (we used 36 years), and provides upgraded information on covariates and outcomes.

Some limitations of this study need to be considered. This is a prospective observational study where no intervention was performed; therefore it has the inherent weaknesses of all cohort studies and lacks the strength of causality that a randomised trial could offer. Reverse causation, which means that lower physical activity levels are caused by disease and not the other way around, is an important issue to consider since it could introduce bias in the evaluation of the effect of physical activity. Different approaches exist to reduce the effect of reverse causation but there is no method to eliminate it completely. To correct for reverse causation we adjusted our analyses for co-morbidities at baseline instead of excluding the subjects with disease at the start of follow-up, since our original objective was to evaluate the effect of physical activity in the general population and not on selected healthy populations. Also we ran additional analyses excluding the participants with the lowest levels of physical activity that also have the highest risk of reverse causation, finding no substantial changes in our hazard ratios (data not shown).

Another limitation of our study is the way exposure was assessed in the Framingham study. During the FHS physical activity levels were evaluated by self-report, which may introduce misclassification of exposure. However, this misclassification is likely to be non-differential, which can only attenuate our results, making them less than the true association.

Added value of this study is the combination of assessing the relation between physical activity and onset of cardiovascular disease and mortality in a large prospective study, and the translation of these relations into life expectancy with and without CVD. This study shows that higher levels of physical activity not only prolong total life expectancy but also life expectancy free of CVD at age 50. This effect is already seen at moderate levels of physical activity, and the gains in cardiovascular disease-free life expectancy at higher levels are more than twice as large. Our results underline current recommendations for physical activity, advising even moderate levels of activity in order to enjoy the benefits of a healthier and longer life. The protective effect of physical activity on CVD is also significant in terms of life expectancy free of cardiovascular disease. The role that physical activity plays in cardiovascular risk management should be emphasized to achieve a worldwide implementation of an active pattern of life. Our study suggests that following an active lifestyle is an effective way to achieve healthy aging.

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References

1. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol* 1990;132(4):612-28.
2. US Department of Health and Human Services. Physical Activity and Health: A Report of the Surgeon General. Atlanta, Ga: US Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, 1996.
3. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *Lancet* 1953;265(6796):1111-20; concl.
4. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *Lancet* 1953;265(6795):1053-7; contd.
5. Paffenbarger RS, Jr., Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med* 1986;314(10):605-13.
6. Paffenbarger RS, Jr., Hyde RT, Hsieh CC, Wing AL. Physical activity, other life-style patterns, cardiovascular disease and longevity. *Acta Med Scand Suppl* 1986;711:85-91.
7. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS, Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 1991;325(3):147-52.
8. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH. A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 1992;268(1):63-7.

9. Batty GD. Physical activity and coronary heart disease in older adults. A systematic review of epidemiological studies. *Eur J Public Health* 2002;12(3):171-6.
10. Batty GD, Shipley MJ, Marmot M, Smith GD. Physical activity and cause-specific mortality in men with Type 2 diabetes/impaired glucose tolerance: evidence from the Whitehall study. *Diabet Med* 2002;19(7):580-8.
11. Lee IM, Sesso HD, Paffenbarger RS, Jr. Physical activity and coronary heart disease risk in men: does the duration of exercise episodes predict risk? *Circulation* 2000;102(9):981-6.
12. Kannel WB, Sorlie P. Some health benefits of physical activity. The Framingham Study. *Arch Intern Med* 1979;139(8):857-61.
13. Schnohr P, Scharling H, Jensen JS. Changes in leisure-time physical activity and risk of death: an observational study of 7,000 men and women. *Am J Epidemiol* 2003;158(7):639-44.
14. Crespo CJ, Palmieri MR, Perdomo RP, McGee DL, Smit E, Sempos CT, et al. The relationship of physical activity and body weight with all-cause mortality: results from the Puerto Rico Heart Health Program. *Ann Epidemiol* 2002;12(8):543-52.
15. Rothenbacher D, Hoffmeister A, Brenner H, Koenig W. Physical activity, coronary heart disease, and inflammatory response. *Arch Intern Med* 2003;163(10):1200-5.
16. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA* 2002;288(16):1994-2000.
17. Sesso HD, Paffenbarger RS, Jr., Lee IM. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. *Circulation* 2000;102(9):975-80.
18. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health* 1951;41(3):279-81.
19. Cupples LA, D'Agostino RB, Anderson K, Kannel WB. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. *Stat Med* 1988;7(1-2):205-22.
20. Stokes J, 3rd, Kannel WB, Wolf PA, Cupples LA, D'Agostino RB. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham Study. *Circulation* 1987;75(6 Pt 2):V65-73.

21. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289(19):2560-72.
22. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res* 1998;6 Suppl 2:51S-209S.
23. Peeters A, Mamun AA, Willekens F, Bonneux L. A cardiovascular life history. A life course analysis of the original Framingham Heart Study cohort. *Eur Heart J* 2002;23(6):458-66.
24. Nusselder WJ, Looman CW, Marang-van de Mheen PJ, van de Mheen H, Mackenbach JP. Smoking and the compression of morbidity. *J Epidemiol Community Health* 2000;54(8):566-74.
25. Efron B, Tibshirani R. *An Introduction to the Bootstrap.* London, 1993.
26. Andersen LB. Relative risk of mortality in the physically inactive is underestimated because of real changes in exposure level during follow-up. *Am J Epidemiol* 2004;160(2):189-95.
27. Sherman SE, D'Agostino RB, Cobb JL, Kannel WB. Physical activity and mortality in women in the Framingham Heart Study. *Am Heart J* 1994;128(5):879-84.
28. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med* 2000;343(1):16-22.
29. Wagner A, Simon C, Evans A, Ferrieres J, Montaye M, Ducimetiere P, et al. Physical activity and coronary event incidence in Northern Ireland and France: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). *Circulation* 2002;105(19):2247-52.
30. Sherman SE, D'Agostino RB, Silbershatz H, Kannel WB. Comparison of past versus recent physical activity in the prevention of premature death and coronary artery disease. *Am Heart J* 1999;138(5 Pt 1):900-7.

3

Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women: life course analysis.

Oscar H. Franco, Anna Peeters, Luc Bonneux, Chris de Laet. Blood pressure in adulthood and life expectancy with and without cardiovascular disease in men and women: life course analysis of the Framingham heart study. *Accepted for publication by Hypertension, in press.*

Abstract

Limited information exists about the consequences of hypertension during adulthood on residual life expectancy with cardiovascular disease. We aimed to analyze the life course of people with high blood pressure levels at age 50 in terms of total life expectancy and life expectancy with(out) cardiovascular disease compared to normotensives. We constructed multi-state life tables for cardiovascular disease, myocardial infarction and stroke, using data from 3128 participants of the Framingham Heart Study who had their 50th birthday while enrolled in the study. For the life-table calculations we used hazard ratios for three transitions (healthy to death, healthy to disease, disease to death) by categories of blood pressure level and adjusted by age, sex and confounders. Irrespective of sex, 50-year-olds hypertensives compared to normotensives, had a shorter life expectancy, a shorter life expectancy free of cardiovascular disease, myocardial infarction and stroke, and a longer life expectancy lived with these diseases. Normotensive men (22% of men) survived 7.2 years (95% CI: 5.6-9.0) longer without cardiovascular disease compared to hypertensives and spent 2.1 (0.9-3.4) years of life less with cardiovascular disease. Similar differences were observed in women. Compared with hypertensives, total life expectancy was 5.1 and 4.9 years longer for normotensive men and women respectively. Increased blood pressure in adulthood is associated with large reductions in life expectancy and more years lived with cardiovascular disease. This effect is larger than previously estimated and affects both sexes similarly. Our findings underline the tremendous importance of preventing high blood pressure and its consequences in the population.

Introduction

Elevated blood pressure (BP) is a major modifiable risk factor for cardiovascular disease (CVD) and mortality.[1 2] Suboptimal BP (>115mm Hg Systolic BP) is estimated to be responsible for 62% of cerebrovascular disease and 49% of coronary heart disease (CHD).[3] The relation between BP and CVD risk is continuous and independent of other risk factors.[1 4 5] BP control has been shown to be effective in reducing CVD and mortality, although below expectations from observational evidence.[1 6 7] However, few studies have looked at the impact of BP on life expectancy (LE),[8 9] and none have evaluated its effects on LE with and without CVD. Therefore, whether improving the level of BP in the population will lead to more or less years lived with CVD remained uncertain.

The answer to this question might seem obvious but examples from other risk factors such as smoking or obesity show that results can be counterintuitive. Obesity is associated with a shorter LE and an increase in LE with CVD. Therefore, control of obesity would lead to less cardiovascular morbidity [Pardo Silva M, MD, M.Sc. Obesity in adulthood is associated with a decrease in life expectancy free of cardiovascular disease and an increase in life expectancy with cardiovascular disease. A life table analysis of the Framingham Heart Study, 2003]. Smoking is also associated with shorter LE, but with less years lived with CVD since smokers -on average- die younger due to other causes, not reaching older ages where CVD rates are higher.[10] Therefore, reducing smoking will lead to an increase in total LE but also to more cardiovascular morbidity.

The objective of this study is to determine the impact of increased BP levels at age 50 (independent of blood pressure lowering treatment) on total LE and LE with and without CVD (or myocardial infarction or stroke).
We constructed multi-state life tables using the mortality and CVD experience from 46 years of follow-up of the original Framingham Heart Study (FHS).

Methods

Study base
The FHS is a cohort study involving 5209 respondents aged 28 through 62 years at enrolment, residing in Framingham, Massachusetts between 1948 and 1951. Data on occurrence of CVD and mortality were gathered by standardized biennial examinations, regular surveillance of hospital admissions, death registries and medical records over a follow-up period up to 46 years.[11]

In the present investigation, we followed participants from age 50 years onwards. The participants may have reached this age at any point during the follow-up of FHS. Therefore, start of follow-up in our study did not correspond to FHS enrolment. Eligible participants were those enrolees in FHS who were in the study at age 50, were free of CVD at that age and had BP measured during at least one examination (two measurements) in the 5 years previous to reaching that age (1364 men and 1764 women).

Baseline assessments

BP, weight and total serum cholesterol at age 50 were estimated from the information collected through the biennial examinations. We estimated risk factor status at age 50 from linear regression on age using all data from visits during the 5 years prior to this age. Height and physical activity level were estimated from the closest measurement available, favouring those taken before age 50. Body Mass Index (BMI) was calculated as weight (kg)/ height squared (m^2).[12] Smoking status was self-reported and classified in three categories: never-smoker, ever-smoker and current smoker. We updated the information on smoking history at enrolment with the latest available information on smoking before age 50. Level of education was assessed according to the highest degree achieved at FHS enrolment. Diabetes was defined as either a random blood glucose measurement ≥ 200 mg/dl during a regular examination before age 50 or as treatment with insulin and/or oral hypoglycaemic agent.

Blood pressure level classification

Participants were classified in three groups based on their BP levels and independent of blood pressure lowering treatment, using the JNC-7 criteria: group I: <120 mm Hg systolic BP and <80 mm Hg diastolic BP, also called normal BP; group II: 120-139 mm Hg SBP or 80-89 mm Hg DBP (called high-normal); and group III: ≥140 mm Hg SBP/≥90 mm Hg DBP (called hypertension).[1]

Data analysis

Life expectancies with and without disease are the result of several incidences: the incidence of the disease, the mortality after the disease and mortality without the occurrence of the disease. To calculate LE with and without disease, we constructed multi-state life tables (MSLT) for CVD, myocardial infarction (MI) and stroke. In these MSLTs, we described three different potential states: disease-free, prevalent (history of) disease, and death. The possible transitions from one state to the other were from disease-free to death or to prevalent disease, and from prevalent disease to death. No back flows were permitted and we considered only the first entry into a

state and not subsequent disease events.[13] [14] To construct these MSLTs different steps were followed:

First, we assessed the risk associated with the different levels of BP for each of the three transitions. Hazard ratios for subjects with high BP levels compared with normotensives were calculated for non-CVD death among participants free of CVD, CVD incidence and death among individuals with prevalent CVD. We performed Cox proportional hazards analyses with age as the time scale and stratified by sex. Analyses were performed for each transition using STATA version 8.2 for Windows (Stata corporation, college station TX, USA, 2003). We tested the proportionality of hazards assumption by analysis of the Schoenfeld residuals. Statistical significance was set at the 5% level.[15] [16] In the Cox Analyses we assessed the effect of the potential confounders by adjusting for current smoking status (at age 50), level of education (high school or higher vs. the rest), diabetes and BMI. Information on all these variables was present for 3123 participants (99.8%). Data on cholesterol levels and physical activity were not available for more than 40% of the participants and were therefore not considered. All the analyses were done for CVD, MI and stroke separately. From the several adjustments for potential confounding, only adjustment for BMI substantially changed the hazard ratios associated with BP. Therefore, we additionally performed these analyses stratified by BMI. Based on BMI, subjects were classified in two groups: group 1 with BMI below 25kg/m^2 (normal weight) and group 2 with BMI $\geq$ 25 kg/m^2 (overweight and obesity).[12] For this stratified analysis, 34 subjects with BMI below 18.5 kg/m^2 were excluded. Therefore, the final analyses involved 3089 participants (1341 men and 1748 women).

Second, we used Poisson regression to calculate smoothed age-specific transitions rates for each transition.[14] We assessed graphically the goodness-of-fit of the model to the empirical rates in one-year intervals for the different transitions. We calculated the transition rates for the different BP groups by age directly without assuming proportional hazards.

Finally, after the Cox proportional hazards analyses for assessment of the risk associated with different levels of BP and the Poisson regression models used to calculate smoothed age-specific transitions rates for each transition, we transformed the crude transition rates into probabilities (assuming that within each single 1-year age interval, the hazard is constant) and created MSLTs for the total population stratified by level of BP and sex. We also created MSLTs additionally stratified for BMI. All these MSLTs represented populations that were 50 years of age and free of CVD at baseline. Based on life expectancies of the total FHS sample, the LE at 90

years of age was assumed to be a constant 4.53 years for men and 5.05 years for women in all groups of BP level.[13]

All life table calculations were done in S-plus 2000 (S-Plus 2000 Professional for Windows. Math Soft Inc) and confidence intervals were obtained using a bootstrap procedure with 2000 replicates.[17]

Sensitivity analysis

To test the robustness of our findings and to evaluate the effect of high BP among

Table 3.1. Baseline Characteristics by Blood Pressure Category and Sex*

		BP Category by JNC-VII Criteria‡		
Sex	Characteristics	Group 1	Group 2	Group 3
Men	Number (%)	305 (22)	584 (43)	475 (35)
	SBP, mean (SD), mm Hg	112.6 (5.1)	127.2 (6.4)	149.4 (15.4)
	DBP, mean (SD), mm Hg	75.0 (4.6)	82.5 (5.1)	93.8 (8.8)
	Weight, mean (SD), kg	74.1 (10.7)	78.5 (10.9)	80.7 (11.8)
	Height, mean (SD), kg	1.73 (0.07)	1.73 (0.07)	1.72 (0.07)
	BMI†, mean (SD), kg/m^2	24.8 (3.1)	26.3 (3.2)	27.2 (3.6)
	BMI† ≥ 25, No. (%)	137 (44.9)	385 (65.9)	354 (74.5)
	Diabetes at age 50, No. (%)	6 (2)	7 (1.2)	10 (2.1)
	Smoking Status, No. (%)			
	Never smoker	27 (8.9)	82 (14)	60 (12.6)
	Former smoker	31 (10.1)	85 (14.6)	65 (13.7)
	Current smoker	247 (81)	417 (71.4)	350 (73.7)
	High School Graduated or higher, No. (%)	176 (57.7)	352 (60.3)	284 (59.8)
Women	Number (%)	469 (26)	754 (43)	541 (31)
	SBP, mean (SD), mm Hg	112.3 (5.3)	127.8 (6.7)	155.8 (17.7)
	DBP, mean (SD), mm Hg	73.7 (4.9)	81.2 (5.2)	93.6 (9.7)
	Weight, mean (SD), kg	61.2 (8.8)	64.1 (10.7)	69.1 (13.0)
	Height, mean (SD), kg	1.60 (0.06)	1.59 (0.06)	1.59 (0.06)
	BMI†, mean (SD), kg/m^2	23.9 (3.4)	25.2 (3.9)	27.3 (5.3)
	BMI† ≥ 25, No. (%)	137 (29.2)	343 (45.5)	336 (62.1)
	Diabetes at age 50, No. (%)	3 (0.6)	3 (0.4)	10 (1.8)
	Smoking Status, No. (%)			
	Never smoker	179 (38.2)	363 (48.1)	287 (53.0)
	Former smoker	40 (8.5)	75 (10.0)	51 (9.5)
	Current smoker	250 (53.3)	316 (41.9)	203 (37.5)
	High School Graduated or higher, No. (%)	316 (67.4)	484 (64.2)	320 (59.1)

Abbreviations: BP, Blood Pressure; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; kg, kilograms; m, meters.
*Subjects included were free of cardiovascular disease at baseline and with no missing data BP.
Total No: 3128.
† Body Mass Index, calculated as BMI=weight in kg/height^2 in m^2
‡ JNC-VII indicates the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Group 1 stands for normotensives, group 2 for participants with high-normal BP levels and group 3 for hypertensives.

populations with different age, we repeated the analyses for participants at age 40 and at age 60.

Results

The average follow-up was 27.5 years. Weight and BMI increased with increasing BP. For smoking status, diabetes and education the relation with BP was less clear (Table 3.1).

Blood pressure and risk of disease and mortality

Overall we saw an increase in risk of disease (CVD, MI and stroke) among participants with increased BP levels (groups 2 and 3) (table 3.2), as expected. Significant increases in mortality were observed among hypertensives but not among participants with high-normal BP levels compared to normotensives.

In general HRs changed only slightly after adjusting for age, sex and potential confounders (table 3.2).

There was a clear dose response relation with BP category. The higher the BP levels the higher the risk of incident disease. This increase in risk of incident

Table 3.2. Hazard Ratios by Transition in Men and Women Combined at Age 50, Derived from 46 years of Follow-up

Transition	Outcome	Blood Pressure Category*	HR† (95% CI)	HR‡ (95% CI)
Incident Disease	CVD	High-Normal	**1.43** (1.25-1.64)	**1.41** (1.23-1.62)
	MI	High-Normal	**1.47** (1.18-1.83)	**1.49** (1.19-1.86)
		Hypertension	**2.26** (1.82-2.82)	**2.18** (1.73-2.75)
	Stroke	High-Normal	**1.60** (1.21-2.12)	**1.58** (1.19-2.11)
		Hypertension	**2.79** (2.11-3.69)	**2.68** (2.00-3.58)
Non-disease to Death	CVD	High-Normal	1.01 (0.85-1.20)	1.06 (0.89-1.26)
		Hypertension	**1.26** (1.05-1.53)	**1.34** (1.10-1.64)
	MI	High-Normal	1.12 (0.98-1.28)	**1.17** (1.02-1.34)
		Hypertension	**1.61** (1.40-1.84)	**1.69** (1.46-1.95)
	Stroke	High-Normal	1.10 (0.97-1.25)	1.14 (1.00-1.29)
		Hypertension	**1.50** (1.32-1.71)	**1.54** (1.34-1.77)
Disease to Death	CVD	High-Normal	1.03 (0.97-1.21)	1.05 (0.89-1.24)
		Hypertension	**1.22** (1.04-1.43)	**1.29** (1.10-1.52)
	MI	High-Normal	0.86 (0.66-1.10)	0.86 (0.67-1.11)
		Hypertension	1.02 (0.79-1.31)	1.04 (0.81-1.35)
	Stroke	High-Normal	1.18 (0.84-1.66)	1.16 (0.82-1.63)
		Hypertension	**1.45** (1.04-2.02)	**1.50** (1.07-2.10)

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; CVD, Cardiovascular disease; MI, Myocardial Infarction. Bold HRs are significant at the 0.05 level.
*Normotensive is always the reference category. Classification according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
† Adjusted for age, sex (participants with information on all potential confounders, n= 3089)
‡ Adjusted for age, sex, smoking status, prevalent diabetes and body mass index at age 50 and education level. (n= 3089)

CVD was over 113% for hypertensives compared to normotensives and 41% for participants with high-normal levels compared to normotensives. The effect was similar for MI but stronger for stroke (table 3.2).

The relation of BP with the transition from a disease-free (without incident MI, stroke or any CVD) status to death was less pronounced. The analyses excluding incident MI or stroke after the age of 50 showed a significant increased in risk of mortality among participants with elevated levels of BP compared to normotensives. The risk of mortality among individuals without CVD was significantly increased for hypertensives compared to normotensives. This was not the case for the group with high-normal levels (table 3.2).

The relation of baseline BP with mortality after the onset of disease was only significant for hypertensives in the analyses of mortality subsequent to CVD or stroke after the age of 50. Hypertensives with MI did not have a significant increase in the risk of mortality after disease. In general participants in the group 2 of BP, with CVD, MI or stroke did not have an elevated risk of mortality when compared to normotensives (table 3.2).

The higher relative risks of disease and mortality associated with elevated BP were similar when stratified by sex. (Results not presented)

Blood pressure and life expectancy (total, with and without CVD)

For both men and women, increased levels of BP were associated with strong reductions on total LE and LE without CVD. Participants with elevated BP (groups 2 and 3) lived more years with CVD, MI and stroke than normotensives (table 3.3).

The strong effect of increased BP levels on disease incidence, combined with a weaker effect on non-disease related mortality and on mortality after the onset of disease led to the shorter total LE and LE free of CVD and a longer LE with CVD for groups 2 and 3 compared to group 1 (Table 3.3).

Increased BP levels compared to normotension represented a decrease in LE of 5.1 (95% CI 3.5 to 6.7) years and 1.7 (95% CI 0.1 to 3.2) years for hypertensive and men with high-normal BP respectively. These reductions were in a similar direction for women but at a lower magnitude. Compared to the overall population, having hypertension (group III) at age 50 was associated with a reduction in total LE of 2.6 (95% CI 1.8 to 3.5) and 2.9 years (95% CI 2.2 to 3.7) for men and women respectively.

Hypertensive men at age 50 lived 3.4 (95% CI 2.6 to 4.2) years less without CVD than the overall population and 7.2 (95% CI 5.6 to 9) years less than men with normal BP. Similar differences were observed in women. Hypertension was also associated with more years lived with CVD compared to normotensives: in men 2.1

Table 3.3. Life Expectancy in Years at Age 50 by Category of Blood Pressure and Stratified by Sex

Sex	Blood Pressure Category*	LE free of CVD (95% CI)	LE with CVD (95% CI)	LE with MI (95% CI)	LE with Stroke (95% CI)	Total LE (95% CI)
Men	Overall Population	20.7 (20.0-21.3)	6.6 (6.1-7.1)	2.9 (2.6-3.3)	1.1 (0.9-1.3)	27.3 (26.6-27.9)
	Normal BP	24.5 (23.1-25.8)	5.2 (4.3-6.2)	2.1 (1.5-2.7)	0.9 (0.5-1.4)	29.7 (28.4-30.9)
	High-Normal	21.3 (20.3-22.2)	6.7 (6.0-7.5)	3.1 (2.6-3.7)	0.9 (0.7-1.3)	28.0 (27.1-28.9)
	Hypertension	17.3 (16.3-18.3)	7.4 (6.6-8.2)	3.2 (2.6-3.8)	1.4 (1.1-1.8)	24.6 (23.6-25.6)
	Differences in LE					
	High-Normal vs. Normal	**-3.2** (-4.8- -1.5)	**1.5** (0.4-2.7)	**1.0** (0.2-1.8)	0.1 (-0.5-0.6)	**-1.7** (-3.2- -0.1)
	Hypertension vs. Normal	**-7.2** (-9.0- -5.6)	**2.1** (0.9-3.4)	**1.1** (0.3-2.0)	**0.6** (0.0-1.1)	**-5.1** (-6.7- -3.5)
	Hypertension vs. Overall	**-3.4** (-4.2- -2.6)	**0.8** (0.1-1.5)	0.3 (-0.2-0.8)	**0.4** (0.1-0.6)	**-2.6** (-3.5- -1.8)
Women	Overall Population	26.5 (25.8-27.0)	5.8 (5.4-6.3)	1.4 (1.2-1.6)	1.3 (1.1-1.5)	32.3 (31.7-32.8)
	Normal BP	29.5 (28.3-30.9)	4.7 (3.9-5.8)	0.9 (0.6-1.6)	1.0 (0.6-1.6)	34.3 (33.1-35.5)
	High-Normal	27.6 (26.5-28.4)	5.7 (5.1-6.5)	1.4 (1.1-1.8)	1.4 (1.0-1.8)	33.3 (32.4-34.2)
	Hypertension	22.4 (21.3-23.4)	7.0 (6.2-7.9)	1.8 (1.4-2.2)	1.3 (1.1-1.7)	29.4 (28.4-30.3)
	Differences in LE					
	High-Normal vs. Normal	**-2.0** (-3.7- -0.5)	1.0 (-0.2-2.2)	**0.5** (0.1-1.0)	0.4 (-0.3-1.0)	-1.0 (-2.5- -0.5)
	Hypertension vs. Normal	**-7.2** (-8.7- -5.4)	**2.3** (1.0-3.4)	**0.9** (0.3-1.4)	0.3 (-0.3-0.8)	**-4.9** (-6.4 - -3.4)
	Hypertension vs. Overall	**-4.1** (-5.0- -3.2)	**1.2** (0.5-1.8)	**0.4** (0.3-0.8)	0.1 (-0.2-0.4)	**-2.9** (-3.7- -2.2)

Abbreviations: BP, Blood Pressure; LE, Life Expectancy; CVD, Cardiovascular Disease; MI, Myocardial Infarction; CI, Confidence Interval.
Bold LE differences are significant at the 0.05 level.
*Classification according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

(95% CI 0.9 to 3.4) years and in women 2.3 (95% CI 1.0 to 3.4) years. Smaller increases were seen for participants with high-normal BP compared with normotensives.

In hypertensive men the increase in years lived with CVD was mainly due to the increase in years lived with MI (52%) and stroke (28%). For hypertensive women the increase in years lived with MI (39%) and stroke (13%) explained to a lesser extent the increase in years lived with CVD (figure 3.1).

Blood pressure, BMI and life expectancy (total, with and without CVD)

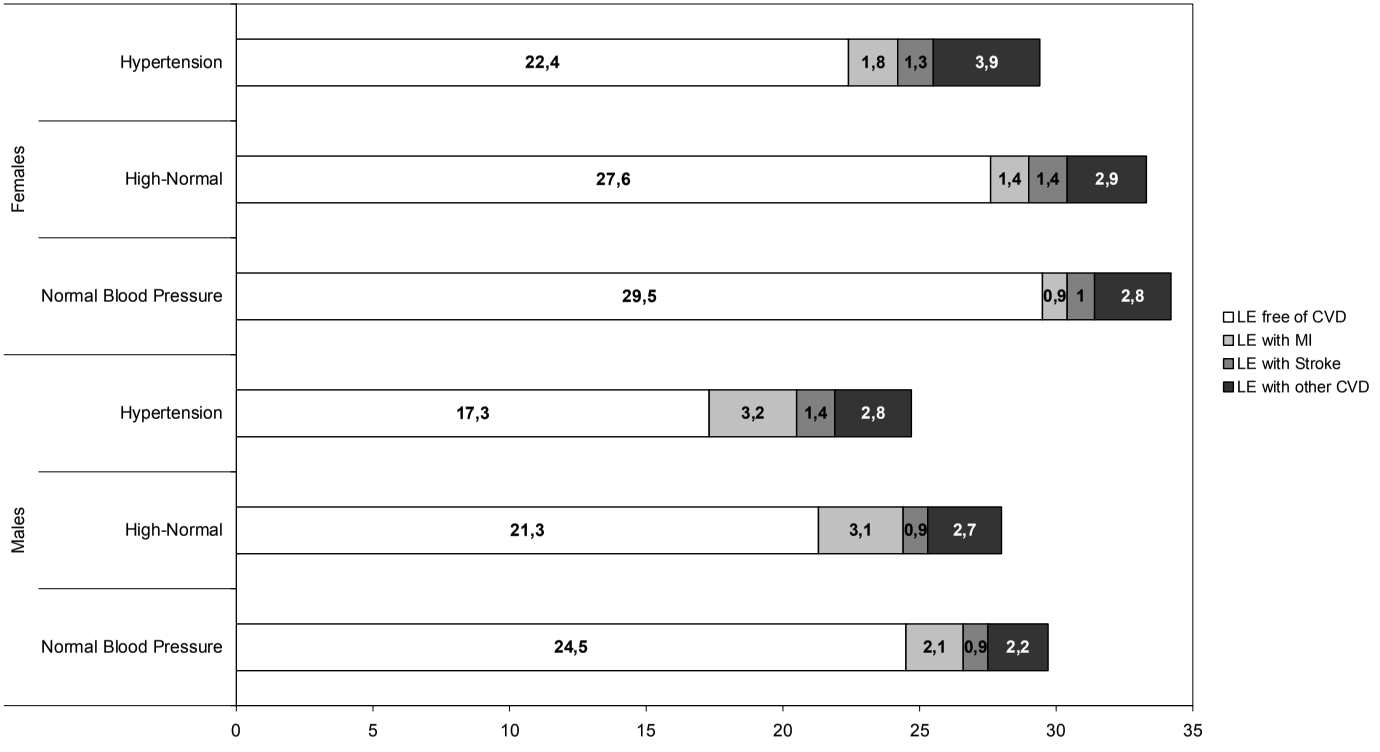
Additional stratification for BMI showed similar differences in life expectancies for the group with BMI<25 compared to the group with BMI≥ 25 in the overall population (Table 3.4).

Table 3.4. Life Expectancy (total, with and without CVD) in Years at Age 50 by Category of Blood Pressure, Stratified by Sex and BMI*

Sex	Blood Pressure Category†	LE free of CVD (95% CI)	LE with CVD (95% CI)	Total LE (95% CI)
Men, BMI <25	Overall	22.2 (21.1-23.2)	5.6 (4.9-6.3)	27.8 (26.6-28.8)
	Normal BP	25.3 (23.5-26.9)	4.4 (3.4-5.6)	29.8 (28.0-31.3)
	High-Normal	21.7 (20.0-23.3)	5.9 (4.7-7.1)	27.7 (25.9-29.2)
	Hypertension	18.5 (16.5-20.7)	6.8 (5.2-8.5)	25.3 (22.8-27.6)
	Differences in LE			
	Hypertension vs. Overall	**-3.6** (-5.6- -1.8)	1.2 (0.1-2.8)	**-2.5** (-4.7- -0.6)
	Hypertension vs. Normal	**-6.8** (-9.4 - -3.9)	**2.3** (0.6-4.5)	**-4.4** (-7.3- -1.6)
Men, BMI ≥25	Overall	19.8 (19.1-20.7)	7.2 (6.6-7.8)	27.0 (26.2-27.7)
	Normal BP	23.8 (21.7-26.1)	6.1 (4.6-7.9)	29.9 (27.9-32.0)
	High-Normal	21.2 (20.1-22.5)	7.1 (6.2-8.1)	28.3 (27.1-29.4)
	Hypertension	16.9 (15.8-18.0)	7.6 (6.8-8.5)	24.5 (23.4-25.7)
	Differences in LE			
	Hypertension vs. Overall	**-3.0** (-4.0- -2.0)	0.5 (-0.2-1.2)	**-2.5** (-3.4 - -1.6)
	Hypertension vs. Normal	**-6.9** (-9.3- -4.3)	1.6 (-0.5-3.3)	**-5.4** (-7.7- -3.2)
Women, BMI <25	Overall	27.8 (26.9-28.7)	5.4 (4.8-6.0)	33.2 (32.4-34.0)
	Normal BP	30.3 (28.7-31.7)	3.7 (2.9-4.7)	34.1 (32.6-35.3)
	High-Normal	28.2 (27.0-29.4)	5.8 (4.9-7.0)	34.0 (32.7-35.2)
	Hypertension	23.1 (21.5-25.0)	7.1 (6.0-8.6)	30.2 (28.6-31.7)
	Differences in LE			
	Hypertension vs. Overall	**-4.7** (-6.2- -3.1)	**1.8** (0.8-3.0)	**-3.0** (-4.5- -1.7)
	Hypertension vs. Normal	**-7.3** (-9.3- -4.9)	**3.4** (1.9-5.0)	**-3.9** (-5.9- -1.7)
Women, BMI ≥25	Overall	24.9 (24.1-25.8)	6.5 (5.8-7.1)	31.4 (30.6-32.2)
	Normal BP	27.6 (25.4-30.1)	7.2 (5.4-9.4)	34.8 (32.6-37.0)
	High-Normal	26.8 (25.5-28.1)	5.8 (4.8-6.9)	32.7 (31.4-33.8)
	Hypertension	21.9 (20.6-23.3)	7.0 (6.0-7.9)	28.9 (27.8-30.2)
	Differences in LE			
	Hypertension vs. Overall	**-3.0** (-4.1- -2.0)	0.5 (-0.3-1.3)	**-2.5** (-3.5- -1.5)
	Hypertension vs. Normal	**-5.7** (-8.3- -3.0)	0.2 (-2.6-1.8)	**-5.9** (-8.3- -3.3)

Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; LE, Life Expectancy; CVD, Cardiovascular Disease; Ref, Reference.
Bold LE differences are significant at the 0.05 level.
*Body Mass Index, calculated as BMI=weight in kg/height^2 in m^2
†Classification according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Figure 3.1. Effect of BP Level at age 50 on Life Expectancy (LE) by Type of CVD and Sex*



Sensitivity analysis

Analyses for participants with hypertension defined at age 40 or at age 60 showed similar differences in life expectancies compared with the group at age 50 (Data not shown).

Discussion

Increased levels of blood pressure at age fifty are associated with large decreases in total LE and LE free of CVD, and increases in the number of years lived with CVD, MI and stroke, for both men and women. The effects of baseline BP level on LE and LE with and without CVD showed a dose response relation.

For hypertensives, the decrease in total LE was between 5.1 (males) and 4.9 (females) years compared to normotensive participants. The reduction in LE free of CVD for hypertensives was 7.2 years for both sexes. In addition to a shorter life expectancy, hypertensives lived over two years more with CVD compared to participants with normal BP. Also for participants with high-normal BP compared to normotensives there was a decrease in LE free of CVD and an increase in LE with CVD but almost half that observed among hypertensives.

The harmful effects of increased BP on LE and CVD observed in our study were independent of BMI. Similar effects were seen among participants above and below a BMI of 25. The same applies to age. Participants at age 40 and 60 with hypertension suffered similar reductions in LE. This suggests that efforts to reduce high BP levels should be increased similarly in lean and obese adult populations and starting as soon as age 40. It is possible that this effect is similar in populations aged below 40 or over 70, however we did not have sufficient data to test this.

We decided not to consider treatment of hypertension in the classification of our population and our analyses since we wanted to evaluate the effect of increased BP levels, which can arise as well in hypertensives under treatment. Besides, BP control in USA during the time most of the FHS participants were around age 50 (the nineteen fifties and sixties) was poor (only 31% of hypertensives were receiving treatment and BP levels were controlled below 140/90 mm Hg in only 10%).[1] Also guidelines and treatment of hypertension have changed substantially with time, as has the coding of hypertension treatment in the FHS. These factors limit the comparability between different time periods.

Our study has several advantages when compared with other studies. Two studies previously compared the relation of BP in adulthood with total mortality and found similar effects but of smaller magnitude.[8 9] Both studies used only a single

reading of BP levels at baseline, which due to random variation in an individual's BP will result in non-differential misclassification of exposure and therefore in a systematic underestimation of the effect of BP on CVD and mortality.[18] We used all BP measurements between age 45 and 50 to predict BP at age 50, each participant had at least two different measures of blood pressure, lowering therefore the probability of dilution of the effect of BP on CVD. This could be the reason why we found larger effects. Furthermore, these studies did not investigate the LE with and without CVD separately and only one of them also reported effects on women and they used shorter follow-up periods. Thus, our study is the first report from a large and continuously followed cohort showing in both sexes the effect of high BP levels on total LE and LE with and without CVD, MI and stroke.

A relevant limitation of our study is that we could not evaluate the effect of high BP levels completely independent of other risk factors of CVD such as cholesterol and physical activity. Although we accounted for some risk factors at baseline by the exclusion of participants with prevalent CVD and the correction for BMI in our analyses; data for physical activity, and serum cholesterol was incomplete, unreliable or unavailable for a large proportion of our population. It is possible that part of the observed differences in LE within the three BP groups could be explained by the differences in blood lipids concentration and physical activity levels. However, the extent of this "lipid" and "physical inactivity" effect cannot be calculated with the available data. Other important risk factors for CVD: sex, age, BMI, smoking and education, were taken into account in our analyses.

Most of the data used in our analyses were collected at least three decades ago. The historical character of the Framingham studies, limits the extrapolation of the findings obtained through analyses of the Framingham studies to today's populations. Great advances in health promotion and in the diagnosis, prevention and treatment of CVD have occurred since the Framingham studies started. However, these results do indicate the potential health impact of hypertension in the absence of appropriate treatment.

The life course perspective used in this study allowed us to show that the harmful effects of hypertension are not limited to decreasing the total LE among those who suffer it but it is also associated with an important reduction in the number of years lived without CVD and an increase in the time spent with this disease.

Perspectives

Our findings indicate that the harmful effects of hypertension are not limited to decreasing the total life expectancy among those who suffer it. Hypertension is also associated with an important reduction in the number of years lived without CVD and an increase in the time spent with this disease. Our results also show that the association between increased BP levels and total LE is higher than previously estimated,[8 9] emphasizing the global need to improve BP control. While similar analyses of treated populations are needed, our results suggest that optimizing the control of BP to keep it at normal levels and avoiding hypertension could potentially lead to a longer LE and, notwithstanding the subsequent ageing of the population, also to a reduction of cardiovascular disease in the general population.

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References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289(19):2560-72.
2. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): a case-control study. http://image.thelancet.com/extras/04art8001web.pdf. In: Lancet, editor, 2004.
3. World Health Organization. World Health Report 2002: Reducing risks, promoting healthy life. Geneva, Switzerland: World Health Organization, 2002. http://www.who.int/whr/2002., 2002.

4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360(9349):1903-13.
5. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345(18):1291-7.
6. Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension* 2001;37(3):869-74.
7. 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(9246):1955-64.
8. Kiiskinen U, Vartiainen E, Puska P, Aromaa A. Long-term cost and life-expectancy consequences of hypertension. *J Hypertens* 1998;16(8):1103-12.
9. Miura K, Daviglus ML, Dyer AR, Liu K, Garside DB, Stamler J, et al. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: the Chicago Heart Association Detection Project in Industry. *Arch Intern Med* 2001;161(12):1501-8.
10. Mamun AA, Peeters A, Barendregt J, Willekens F, Nusselder W, Bonneux L. Smoking decreases the duration of life lived with and without cardiovascular disease: a life course analysis of the Framingham Heart Study. *Eur Heart J* 2004;25(5):409-15.
11. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health* 1951;41(3):279-81.
12. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res* 1998;6 Suppl 2:51S-209S.
13. Peeters A, Mamun AA, Willekens F, Bonneux L. A cardiovascular life history. A life course analysis of the original Framingham Heart Study cohort. *Eur Heart J* 2002;23(6):458-66.

14. Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Ann Intern Med* 2003;138(1):24-32.
15. Grambscha P, Therneau, T. Proportional hazarads tests and diagnostics based on weighted residuals. *Biometrika* 1994;81:515-26.
16. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;69:239-41.
17. Efrom B TR. *Bootstrap Methods for Standard Errors, Confidence Intervals and Other Measures of Statistical Accuracy*, 1986.
18. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335(8692):765-74.

PART B

Current cardiovascular risk management

Cost-effectiveness evaluation.

"Statins should not be considered as a stand-alone wonder-drug in the fight against heart disease. Individuals should be encouraged to reduce their cholesterol and other risk factor levels through lifestyle improvements and actively supported to do so with on-going public health campaigns" Professor Jean-Pierre Bassand, former president of the European Society of Cardiology.

4

Cost-effectiveness of statins in coronary heart disease: systematic review

Oscar H. Franco, Anna Peeters, Caspar W.N. Looman, Luc Bonneux. Cost-effectiveness of statins in coronary heart disease: systematic review. *Accepted for publication by the JECH, in press.*

Abstract

Introduction:
Statin therapy reduces the rate of coronary heart disease, but high costs in combination with a large population eligible for treatment ask for priority setting. Although trials agree on the size of the benefit, economical analyses of statins report contradictory results. We reviewed cost-effectiveness analyses of statins and sought to synthesize cost-effectiveness ratios for categories of risk of coronary heart disease and age.

Methods:
We searched for studies comparing statins to no treatment for the prevention of either cardiovascular or coronary heart disease in men and presenting cost per years of life saved as outcome. Estimates were extracted, standardized for calendar year and currency, and stratified by categories of risk, age and funding source

Results:
24 studies were included (from 50 retrieved), yielding 216 cost-effectiveness ratios. Estimated ratios increase with decreasing risk. After stratification by risk, heterogeneity of ratios is large varying from savings to $59.000 per life year saved in the highest risk category and from $6500 to $490.000 in the lowest category. Our pooled estimates show values of $21571 per life year saved for a ten-year coronary heart disease risk of 20% and $16862 per life year saved for ten-year risk of 30%.

Conclusion:
Statin therapy is cost-effective for high levels of risk, but inconsistencies exist at lower levels. Although the cost-effectiveness of statins depends mainly on absolute risk, important heterogeneity remains after adjusting for absolute risk. Economic analyses need to increase their transparency to reduce their vulnerability to bias and increase their reproducibility.

Introduction

With the advent of statins, the controversy surrounding cardiovascular risk management has shifted from how to treat hypercholesterolemia to the proportion of eligible people that may actually be treated because of financial constraints.[1, 2] Statins reduce the rate of coronary heart disease (CHD) by more than 30%,[1] side effects are unusual and they are well tolerated.[3] However, statins' high costs limit the scope of treatment: society wants the best returns for its investments in health.[4] This asks for priority setting aided by economical analyses, commonly cost-effectiveness analyses (CEA).[5] As relative risk reduction is thought to be constant,[1, 6, 7] benefits are largely determined by absolute risk of CHD. The question is, because of costs, at which level of risk, treatment is cost-effective. Different levels are used worldwide, ranging from 20%[8] to 30%[, 1997 #5] ten-year absolute risk of CHD.

Regardless of comparable health effects and drug costs, CEA of statins have reported contradictory results ranging from very low to very high cost-effectiveness ratios (CERs). The reasons are unknown and subject to speculation about methodological issues and competing interests.

We reviewed CEA of statins and sought to identify sources of heterogeneity of CERs adjusted for categories of risk of CHD, age and funding source.

Methods

We performed a systematic review of the published statin CEA.

Inclusion criteria

We searched for CEA in English, Spanish, Dutch or German on statins for the prevention of either CHD or cardiovascular disease (CVD) in adult male populations (>20 years). Reviews and meta-analyses were excluded. Studies needed to compare cost-effectiveness of statin therapy to no pharmacological treatment and present cost per Years of Life Gained/Saved (YLG, YLS) as outcome. Studies comparing statins with other statins or with other cholesterol lowering drugs were excluded.

Search strategy

We used the databases MEDLINE, the British National Health Service Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effectiveness (DARE) and the Health Technology Assessment database (HTA). We searched for papers published between 1990 and July 2002 and used these terms for searching: Statins OR Hydroxymethylglutaryl-CoA-Reductase Inhibitors AND Cost-effectiveness.

Two independent investigators analysed the abstracts obtained from the databases. All studies that matched our inclusion criteria were retrieved, and their reference lists were checked manually to identify more studies. We contacted experts in the field to find unpublished or ongoing studies.
When the decision of inclusion could not be achieved by reading the abstracts, the papers were retrieved for analysis.

Study selection
Two independent investigators read each one of the articles retrieved and selected the studies to include based on the inclusion criteria. A third investigator was contacted to reach a decision in case of disagreement.

Data extraction
A data extraction form was elaborated based on prior knowledge and literature. Using the form, two independent investigators collected the data from the articles.

Variables included in the form were: publication date, date and country used to calculate costs, annual drug costs, type of model, category of prevention, mean or range of age at the start of treatment, annual level of absolute risk of CHD (fatal and non-fatal events) at the start of treatment, time horizon of active treatment and benefit, method for effect calculation, economical perspective, discount factor, funding source and final outcome (CERs).

Model type could be primary or secondary modelling. Primary modelling studies were conducted parallel to clinical trials. Secondary modelling studies used data from clinical trials or other sources to model the effect of statins. Studies were also divided in two categories of effect calculation: studies that used levels of CHD risk reduction to model the effect, or studies that used intermediate effects (e.g. % cholesterol level reduction) for the modelling procedure. The category of prevention was either primary, for populations free of either CHD or CVD, or secondary, for CHD or CVD patients. Time horizon of active treatment refers to the duration of treatment. Three categories of duration were considered: five years, ten years or >10 years /lifetime. Discount factors are used to weight the value of future benefits and costs; four categories were used: 3%, 5%, 6% or none. Funding source of the studies was classified in two categories: funding provided by the industry and funding provided by others (academic or governmental institutions or none).

For each CER we wanted absolute risk of CHD of the study population before treatment. If not stated in the paper, we estimated risk by the D'Agostino CHD function[10] for primary and secondary prevention respectively, using these variables: levels of total cholesterol (or LDL), HDL cholesterol, smoking, blood pressure, diabetes history and personal history of CHD.

Final outcomes

The CERs were stratified by categories of risk, age groups and funding source, and standardized. To standardize we used only ratios reported as cost per YLG or YLS that were calculated using net costs and with future costs and benefits weighted with the same discount factor. Since the CERs were reported using different currencies and dates, we standardized by calendar year and currency. First, to correct for inflation, we converted all currencies into the same date: 30-12/2001, using the correspondent consumer price index. Afterwards all currencies were converted into US dollars of the date 30-12/2001. Data on consumer price indices and conversions were taken from different sources: Federal Reserve Bank of Indianapolis USA, Bank of Canada and the University of Exeter England.

We considered CERs under $20000/YLS as "cost-effective", over $40000/YLS as "expensive" and in between as "moderate".[11-13]

After standardization, CERs were stratified by categories of risk of CHD, by age groups at the start of treatment and by funding source. The categories of annual risk of CHD at the start of treatment were: <1%, 1-<2%, 2-<3%, 3-4% and >4%. Age groups used were: <45 years, 45-65 years and >65 years.

Outcomes were compared by whether the study was funded by pharmaceutical companies or by others (governmental institutions, academic institutions or none). Once stratified, the CERs were plotted using spreadsheets. For each category of risk the distribution of the outcomes was calculated (median, quartiles and percentiles) and compared.

Statistical analysis

Data were analysed using a linear mixed effect model. The log of the CER was taken as continuous response value, because errors were assumed to become larger with larger CERs. The studies were put at the first level and CERs at the second level. The result of this design is that the power of characteristics of the study is limited to the number of studies and that the power of predictors that differ within the studies is enhanced by the extraction of the variance between studies from the random error. Twelve variables were included in the analysis: absolute risk (continuous), age (<45, 45-65 and >65), treatment duration (<5years, 5-10 years and >10 years (lifetime)), country used as source of costs (USA, Canada and Europe), annual drug costs (continuous), type of model (primary and secondary), effect calculation (direct reduction of risk and indirect risk reduction through lipid lowering), category of prevention (primary and secondary), perspective (societal and third party payer), funding source (pharmaceutical companies and others), year of publication (<1996 and ≥1996) and discount factor (<5%, ≥ 5%). First we performed a univariate

analysis to find overall predictors, and then an analysis of interactions with risk. This last analysis shows the effect modification by variables over changing risk.
Variables were considered significant at a two-sided p-value < 0.05. We used S-PLUS (version 6.0 for windows) for the analyses.

Results

Study identification and selection

We found 308 references using the databases: 235 with Medline and 73 with the NHS EED, DARE and HTA databases. From the 308 references, 186 were rejected because they were not CEA. Of the 122 abstracts selected, 50 studies were retrieved. By checking reference lists we found four new references, but they did not match our inclusion criteria. Finally 24 studies were selected for the analysis.[14-37]
Reasons for exclusion were: seven studies were reviews or meta-analyses,[38-44] seven compared statins with statins or with other lipid lowering medicaments,[45-51] three were cost-utility analyses,[52-54] three compare strategies of cardiovascular risk management,[55-57] three did not use as outcome cost/YLS,[58-60] two were descriptive methodological papers[61, 62] and one study was excluded since it was not possible to determine absolute risk prior to treatment.[63]

Descriptive of the studies

General description of the studies is in table 4.1. All the studies compared statin therapy with no treatment of CHD or CVD risk and were conducted in developed countries.

Mean annual drug cost was US$ 768,7 (ranged from 399 to 1670). Pharmaceutical companies funded thirteen studies. Only one study presented the estimated CERs without any discount factor, the rest used predominantly 5% (15 studies).

Final Outcomes

The outcome selected was cost per YLS standardized by calendar year and currency. From the 24 studies selected we identified 216 CER. The ratios reported ranged over an enormous range: from savings to $489000/YLS (table 4.2).

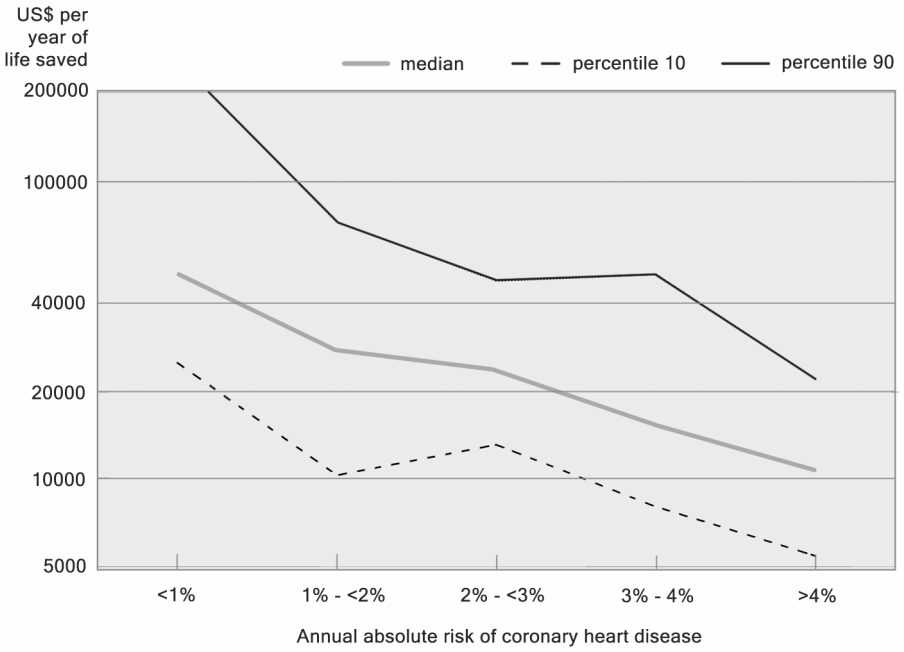
Outcomes were first stratified by categories of risk at the start of treatment since absolute risk is an important determinant of the cost and benefits of statin therapy. We found a strong inverse relation between absolute risk at baseline and the CER (figure 4.1).

Table 4.1. Descriptive of The Studies Included*

Paper	Publication Year	Cost-Country	Age Range (mean)	Modeling†	Prevention Category‡	Treatment Duration	Discount Factor	Funding Source
Ashraf, Am J Cardiol 1996; 78(4): 409-14	1996	United States	60	Both	Secondary	3,10 years	5%	Pharmaceutical Company
Caro, BMJ 1997; 315 (7122): 1577-82	1997	Un. Kingdom	45-64 (55)	Primary	Primary	5 years	6%	Pharmaceutical Company
Ganz, Ann Intern Med 2000; 132 (10): 780-7	2000	United States	75-84	Secondary	Secondary	Lifetime	3%	University
Goldman, JAMA 1991; 265 (9): 1145-51	1991	United States	35-84	Secondary	Both	Lifetime	5%	Government
Goldman, Am J Cardiol 1993; 72 (10): 75D-79D	1993	United States	35-44	Secondary	Primary	Lifetime	5%	Government
Grover, Arch Intern Med 1999; 159 (6): 593-600	1999	Canada	40-70	Secondary	Secondary	Lifetime	3%	University
Grover, Circulation 2000; 102 (7): 722-7	2000	Canada	40-70	Secondary	Both	Lifetime	5%	Pharmaceutical Company
Grover, Diabetes Care 2001; 24 (1): 45-50	2001	Canada	40-70	Secondary	Both	Lifetime	3%	Pharmaceutical Company
Hamilton, JAMA 1995; 273 (13): 1032-8	1995	Canada	30-70	Secondary	Primary	Lifetime	5%	Pharmaceutical Company
Hay, Am J Cardiol 1991; 67 (9): 789-96	1991	United States	35-55	Secondary	Primary	Lifetime	5%	Pharmaceutical Company
Huse, Am J Cardiol 1998; 82 (11): 1357-63	1998	United States	45-65	Secondary	Both	Lifetime	3%	Pharmaceutical Company
Johannesson, N Engl J Med 1997; 336 (5): 332-6	1997	Sweden	35-70	Secondary	Secondary	5 years	5%	Pharmaceutical Company
Jonsson, Eur Heart J 1996; 17(7): 1001-7	1996	Sweden	35-70 (59)	Primary	Secondary	5 years	5%	Pharmaceutical Company
Jonsson, Diabetologia 1999; 42(11): 1293-301	1999	Sweden	35-70 (60)	Primary	Secondary	5 years	3%	University
Martens, Clin Ther 1994; 16 (6):1052-62	1994	Canada	45	Secondary	Primary	Lifetime	5%	Pharmaceutical Company
Muls, Atherosclerosis 1998; 137 Suppl: S111-6	1998	Belgium	60	Both	Secondary	3,10 years	5%	Pharmaceutical Company
Perreault, Arch Intern Med 1998; 158 (4): 375-81	1998	Canada	44-56-57	Secondary	Primary	Lifetime	5%	University
Pharoah, BMJ 1996; 312 (7044): 1443-8	1996	Un. Kingdom	45-64	Secondary	Both	10 years	5%	None
Pickin, Heart 1999; 82 (3): 325-32	1999	Un. Kingdom	55,58	Secondary	Both	5yrs, lifetime	6%	University
Russell, Can J Clin Pharmacol 2001; 8(1): 9-16	2001	Canada	45-65	Secondary	Both	Lifetime	5%	Pharmaceutical Company
Szucs, Herz 1998; 23(5): 319-29	1998	Germany	45-65 (59)	Primary	Secondary	5 years	0%	University
Szucs, Herz 2000; 25(5): 487-94	2000	Germany	45-65 (60)	Primary	Secondary	5 years	3%	University
Riviere, CMAJ 1997; 156(7): 991-7	1997	Canada	35-70 (59)	Secondary	Secondary	5, 10, lifetime	5%	Pharmaceutical Company
Van Hout, Eur Heart J 2001; 22(9): 751-61	2001	Netherlands	25-75	Secondary	Both	5yrs, lifetime	5%	University

* In total 24 studies were included in the final analysis.
† Primary: based on observations from a randomized trial. Secondary: based on expectations from a theoretical model.
‡ Secondary prevention is among patients with clinical coronary heart disease or cardiovascular disease, primary prevention among apparently healthy persons.

Figure 4.1. Cost-effectiveness of statins per categories of absolute risk



Even though there was an external consistency between the studies, the variability among the ratios extracted was high, even after standardization and stratification. In all categories of risk there were cost-effective, moderate and expensive ratios. The distribution of the CERs after stratification by risk is shown in table 4.2.

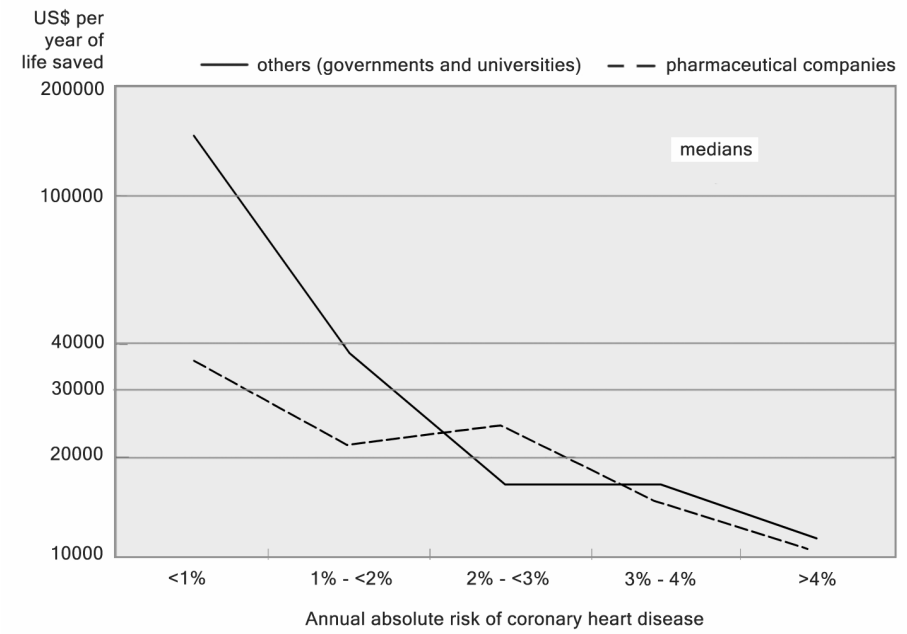
For levels of annual absolute risk over 4% the majority of the CER agreed in showing statins as a cost-effective option, at least 90% of the ratios were not expensive. For the lowest level of risk (<1%) the agreement of the studies was also clear, but in showing statin therapy as an expensive option. For the rest of the levels

Table 4.2. Distribution of CERs by Category of Absolute Risk

	Categories of annual absolute risk (No) *				
Dispersion and Percentile values	<1% (33)	1% - <2% (33)	2% - <3% (13)	3% - 4% (42)	>4% (95)
Percentile 10	24505	10205	12951	7987	5449
Median	48559	26933	23060	15048	10607
Percentile 90	255893	73124	46273	48701	21545

Abbreviation: CERs, cost-effectiveness ratios ($ per year of life saved)
* Number of CERs reported per category of absolute risk

Figure 4.2. Funding source in cost-effectiveness of statins per categories of absolute risk



(1% to 4%) there was no clear agreement. Stratified by risk, the difference between the 10th and 90th percentile of the CERs was still 4 to 7 fold.

A comparison between the age groups was not possible since estimates for younger (<45) and older ages (>65) were few.

Funding source

Estimated CERs from studies funded by others were generally more expensive than estimates from studies funded by pharmaceutical companies. This difference is striking at lower levels of risk (<2%), corresponding to primary prevention (figure 4.2).

Multilevel linear regression

Our aim was evaluate the degree to which explanatory variables account for the observed variability in CERs between the studies. Results of the linear mixed effect model are summarized in table 4.3. In the univariate analysis (second column, table 4.3) only absolute risk and category of prevention are significant. For levels of 2% and 3% annual risk of CHD (equivalent to a 10-year CHD risk of 20% and 30%) the corresponding average CERs were $21571/YLS and $16862/YLS. As annual absolute risk increases by 1% the CER is expected to decrease by 21.8%.

Table 4.3. Multilevel Linear Regression Analyses (Outcome: CERs)

Variables	Univariate Analysis Effect in % (95% CI)	Interaction Effects with Absolute Risk of CHD* Effect in % (95% CI)
Absolute risk of CHD	- 21.8 (-27.6, -15.6) †	--
Age in years		†
<45	Reference	- 53.3 (-62.2, -42.4) †
45-65	23 (-20, 91)	- 26.4 (-32.1, -20.2) †
>65	76 (0, 211)	- 24.3 (-36.6, -9.8) †
Treatment duration		NS
< 5 years	Reference	
5 to 10 years	-22 (-69, 103)	
Lifetime (>10 years)	-42 (-73, 24)	
Cost country		†
United States	Reference	- 27.9 (-35.6, -19.3) †
Canada	165 (-59, 1594)	- 4.4 (-16, 8.8)
Europe	207 (-48, 1764)	- 31 (-40.7, -19.9)†
Effect Modeled		NS
Intermediate effects	Reference	
Risk reduction	69 (-58, 581)	
Type of Modeling ‡		NS
Primary	Reference	
Secondary	-27 (-71, 87)	
Prevention Categories §	†	†
Primary	Reference	- 31.5 (-40.6, -21.1)
Secondary	- 62 (-74, -45)	- 5.6 (-16.8, 7)
Economical Perspective		NS
Societal	Reference	
Third party payer	-53 (-89, 96)	
Funding Source		†
Pharmaceutical companies	Reference	- 13.9 (-22, -5)
Others	-44 (-86, 129)	- 31.3 (-38.8, -23)
Publication Year		†
<1996	Reference	- 40.2 (-49, -29.8)
>= 1996	147 (-55, 1255)	- 16.5 (-23.3, -9.2)
Discount factor		†
>=5%	Reference	- 28.9 (-35.1, -22.2)
<5%	4 (-79, 403)	- 5.6 (-17, 7.3)

Abbreviations: CERs, Cost-effectiveness ratios; CI, confidence interval; NS, not significant effect: CHD, coronary heart disease

* Effects on the cost-effectiveness ratios, per 1% rise in absolute risk of coronary heart disease. The original (univariate) effect of 1% increase in absolute risk (21.8 % decrease in CERs) is compared in each variable category to account for potential interactions.

† P-value: <0.05,

‡ Primary: based on observations from a randomized trial. Secondary: based on expectations from a theoretical model.

§ Secondary prevention is among patients with clinical cardiovascular disease, primary prevention among apparently healthy persons.

Compared to primary prevention, secondary prevention represents a decrease of 62% in the CER: category of prevention is highly correlated with absolute risk.

The fourth column of table 4.3 shows the interaction effects between absolute risk and the other explanatory variables. Here we compared the original (univariate) effect of 1% increase in absolute risk (21.8 % decrease in CERs) in each variable category. For age, cost country, category of prevention, funding source,

year of publication and discount factor the effect of absolute risk in the CER differed significantly between categories. As a result of the multilevel analysis each CER is compared to other CER within the same study, which gives more discriminating power to find interactions.

Lower (more negative) effects imply steeper decreases of cost-effectiveness (CE) by increasing absolute risk. At lower ages (<45 years), high risks at start of treatment seriously improve CE (as expected). In secondary prevention, the gradient of absolute risk is less important, as it is always high. Pharmaceutical companies have interests in expanding treatment thresholds to lower levels of absolute risks (see figure 4.2). Studies published before 1996, generally underestimated the effect of absolute risk since they used individual risk factors, and no comprehensive CHD risk, to calculate levels of risk. High discount rates increase the effect of absolute risk at start of treatment, as they shorten the time frame: increases of absolute risk further in time/age are devalued more by higher discount rates.

Discussion

In randomised trials, meta-analysis pool empirical results, reducing the level of random error and bias. In CEA, systematic reviews may identify agreement and disagreement. As prognosis is such an imported predictor of absolute effects, the model used standardizes for known determinants of health outcomes. Cost-effectiveness of statin treatment is strongly related to absolute risk of CHD. Our pooled estimates show values of $21571/YLS for a 10-year CHD risk of 20 % and $16862/YLS for 10-year risk of 30 %. Most studies agree that statin treatment is cost-effective for high-risk patients (annual absolute risk >4%) but not cost-effective for low risk patients (annual risk <1%). For medium risk patients (annual absolute risk 1 to 4%) the decision of whether treatment is cost-effective depends on the choice of the study. After adjusting for levels of absolute risk, large heterogeneity in the estimated CERs remained. Most of the remaining variability can be explained by interactions between absolute risk and age, cost country, category of prevention, funding source, year of publication and discount factor. We were not able to identify further methodological differences, assumptions or model design that caused the remaining heterogeneity. Variability in the risk reduction with statins underlying each of the studies could not explain the variability in the CERs estimates, as there is general concordance among studies with respect to effect size, and we standardized for absolute risk. The role of costs in the CER was evaluated

standardizing or adjusting for the year costs, year of publication, country of costs, drug costs, economical perspective and currency used.

Diverse levels of survival and prevalences of risk can explain the different effects of absolute risk by age groups. For age group <45, a population at generally low levels of risk, high risks at start of treatment represent low CERs. On the contrary, age group >65 with generally high levels of risk, benefits are limited by a shorter life expectancy and the relative effect of absolute risk on the CERs is lower. However, the effect of age is difficult to disentangle, as it is included in absolute risk. The effect of absolute risk is higher in age groups than the overall risk because of the confounding situation. Age and absolute risk are highly correlated, but risk (corrected for age) is negatively correlated with CER and age (corrected for risk) is positively related with CER.

The different effects of absolute risk by cost-country could be caused by methodological differences, gaps in interventions' prices and the characteristics of the populations studied.

Studies funded by pharmaceutical companies generally showed more cost-effective CERs. We found no clear differences in the methods used, in the populations' characteristics or in the levels of risk. The differences were striking at low levels of risk, representing large eligible populations. It is tempting to suggest competing interests as an explanation, although we could not prove this.

The possibility of studies that could have been missed exists, but the likelihood that these would change our conclusions is low. The outcome for cost-utility studies is years of life gained adjusted by quality weights (QALYs). YLS are solely derived from age specific mortality in treated and untreated cohorts. QALYs add estimates of incidence of disease stages, duration of these stages and value judgements on the utility lost by decreased health in these stages. This leads to so many extra potential sources of heterogeneity, which are often not well described in the articles, that interpretation of that heterogeneity would be extremely difficult. Therefore, we excluded three cost-utility analyses that did not present YLS, the sole outcome of this pooling study.

The primary objective of this study was to evaluate levels of heterogeneity and predictors on CEA of statins; we decided to include only studies reporting results for male populations. Studies of female populations are more rare and more difficult to interpret, as women at the same age run lower heart disease risks. While the absolute CERs will differ by sex, we do not expect the levels of heterogeneity to do so. Of the studies included in this study, 14 separately reported CERs for women. All of them consistently show higher CERs (compared to males).

Not all the studies used absolute risk for their analyses; therefore risk factor combinations were translated into absolute risk of CHD. This approach was not validated and some might have been misclassified. Residual confounding particularly in the first risk group exists (there are great relative differences possible in the group < 1%). However, the variability is seen in all risk groups and misclassification will be limited (people at lower levels of risk factors will be at lower levels of risk).

Other methods exist to standardize CER to a same cost-year, but this will not change our results and conclusions.

In conclusion, this review confirms how the cost-effectiveness of statins treatment in the prevention of CHD is related to the absolute risk of CHD, but demonstrates that within risk strata there still exists large variability in cost-effectiveness estimates. Nearly all studies agree that treatment at high levels of risk is cost-effective and at low levels is expensive. But in practice, it is not difficult to find CERs that fit any decision for the population at large with intermediate annual risk of CHD (1% to 4%). The most likely explanation for these differences is different methodology in the CEA, and the impact of funding source suggests the potential for some estimates to be biased. It was very difficult, even impossible to pinpoint all the divergent model assumptions that caused the variability.

Further standardization of methodology for economic analyses and greater transparency in the presentation of results would aid in the evaluation of potential sources of bias, as well as facilitate the evaluation of reproducibility.

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References

1. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;282:2340-6.
2. Jacobson TA. Clinical context: current concepts of coronary heart disease management. *Am J Med* 2001;110 Suppl 6A:3S-11S.
3. Knopp RH. Drug treatment of lipid disorders. *N Engl J Med* 1999;341:498-511.

4. Creese A. Global trends in health care reform. *World health forum* 1994;15:317-322.
5. 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.
6. 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;333:1301-7.
7. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998;339:1349-57.
8. Expert Panel on Detection E, and Treatment of High Blood Cholesterol in Adults. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) full report. 2002 vol; 2001.
9. Committee SMA. Standing Medical Advisory Committee, the use of statins. 2002 vol; 1997.
10. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001;286:180-7.
11. McKenney JM, Kinosian B. Economic benefits of aggressive lipid lowering: a managed care perspective. *Am J Manag Care* 1998;4:65-74.
12. Laupacis A FD, AS Detsky et al. 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;146:473-81.
13. Tengs TO, Adams ME, Pliskin JS et al. Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal* 1995;15:369-90.
14. Ashraf T, Hay JW, Pitt B et al. Cost-effectiveness of pravastatin in secondary prevention of coronary artery disease. *Am J Cardiol* 1996;78:409-14.
15. Caro J, Klittich W, McGuire A et al. The West of Scotland coronary prevention study: economic benefit analysis of primary prevention with pravastatin. *BMJ* 1997;315:1577-82.
16. Ganz DA, Kuntz KM, Jacobson GA, Avorn J. Cost-effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor therapy in older patients with myocardial infarction. *Ann Intern Med* 2000;132:780-7.

17. Goldman L, Goldman PA, Williams LW, Weinstein MC. Cost-effectiveness considerations in the treatment of heterozygous familial hypercholesterolemia with medications. *Am J Cardiol* 1993;72:75D-79D.
18. Goldman L, Weinstein MC, Goldman PA, Williams LW. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. *JAMA* 1991;265:1145-51.
19. Grover SA, Coupal L, Paquet S, Zowall H. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease: forecasting the incremental benefits of preventing coronary and cerebrovascular events. *Arch Intern Med* 1999;159:593-600.
20. Grover SA, Coupal L, Zowall H, Alexander CM, Weiss TW, Gomes DR. How cost-effective is the treatment of dyslipidemia in patients with diabetes but without cardiovascular disease? *Diabetes Care* 2001;24:45-50.
21. Grover SA, Coupal L, Zowall H, Dorais M. Cost-effectiveness of treating hyperlipidemia in the presence of diabetes : who should be treated? *Circulation* 2000;102:722-7.
22. Hamilton VH, Racicot FE, Zowall H, Coupal L, Grover SA. The cost-effectiveness of HMG-CoA reductase inhibitors to prevent coronary heart disease. Estimating the benefits of increasing HDL-C. *JAMA* 1995;273:1032-8.
23. Hay JW, Wittels EH, Gotto AM, Jr. An economic evaluation of lovastatin for cholesterol lowering and coronary artery disease reduction. *Am J Cardiol* 1991;67:789-96.
24. Huse DM, Russell MW, Miller JD et al. Cost-effectiveness of statins. *Am J Cardiol* 1998;82:1357-63.
25. Johannesson M, Jonsson B, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. Scandinavian Simvastatin Survival Study Group. *N Engl J Med* 1997;336:332-6.
26. Martens LL, Guibert R. Cost-effectiveness analysis of lipid-modifying therapy in Canada: comparison of HMG-CoA reductase inhibitors in the primary prevention of coronary heart disease. *Clin Ther* 1994;16:1052-62; discussion 1036.
27. Muls E, Van Ganse E, Closon MC. Cost-effectiveness of pravastatin in secondary prevention of coronary heart disease: comparison between

Belgium and the United States of a projected risk model. *Atherosclerosis* 1998;137 Suppl:S111-6.

28. Perreault S, Hamilton VH, Lavoie F, Grover S. Treating hyperlipidemia for the primary prevention of coronary disease. Are higher dosages of lovastatin cost-effective? *Arch Intern Med* 1998;158:375-81.
29. 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;312:1443-8.
30. Pickin DM, McCabe CJ, Ramsay LE et al. Cost effectiveness of HMG-CoA reductase inhibitor (statin) treatment related to the risk of coronary heart disease and cost of drug treatment. *Heart* 1999;82:325-32.
31. Russell MW, Huse DM, Miller JD, Kraemer DF, Hartz SC. Cost effectiveness of HMG-CoA reductase inhibition in Canada. *Can J Clin Pharmacol* 2001;8:9-16.
32. Szucs TD, Berger K, Marz W, Schafer JR. [Cost effectiveness of pravastatin in secondary coronary prevention in patients with myocardial infarct or unstable angina in Germany. An analysis on the basis of the LIPID trial]

Kosteneffektivitat von Pravastatin in der koronaren Sekundarpravention bei Patienten mit Myokardinfarkt oder instabiler Angina pectoris in Deutschland. Eine Analyse auf der Grundlage der LIPID-Studie. *Herz* 2000;25:487-94.

33. Szucs TD, Guggenberger G, Berger K, Marz W, Schafer JR. [Pharmacoeconomic evaluation of pravastatin in the secondary prevention of coronary heart disease in patients with average cholesterol levels. An analysis for Germany based on the CARE study]

Pharmakookonomische Bewertung von Pravastatin in der Sekundarpravention der koronaren Herzkrankheit bei Patienten mit durchschnittlichen Cholesterinwerten. Eine Analyse fur Deutschland auf der Grundlage der CARE-Studie. *Herz* 1998;23:319-29.

34. van Hout BA, Simoons ML. Cost-effectiveness of HMG coenzyme reductase inhibitors; whom to treat? *Eur Heart J* 2001;22:751-61.
35. Riviere M, Wang S, Leclerc C, Fitzsimon C, Tretiak R. Cost-effectiveness of simvastatin in the secondary prevention of coronary artery disease in Canada. *Cmaj* 1997;156:991-7.

36. Jonsson B, Johannesson M, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost-effectiveness of cholesterol lowering. Results from the Scandinavian Simvastatin Survival Study (4S). *Eur Heart J* 1996;17:1001-7.

37. Jonsson B, Cook JR, Pedersen TR. The cost-effectiveness of lipid lowering in patients with diabetes: results from the 4S trial. *Diabetologia* 1999;42:1293-301.

38. Troche CJ, Tacke J, Hinzpeter B, Danner M, Lauterbach KW. Cost-effectiveness of primary and secondary prevention in cardiovascular diseases. *Eur Heart J* 1998;19 Suppl C:C59-65.

39. Jacobson TA, Schein JR, Williamson A, Ballantyne CM. Maximizing the cost-effectiveness of lipid-lowering therapy. *Arch Intern Med* 1998;158:1977-89.

40. Thompson D, Oster G. Cost-effectiveness of drug therapy for hypercholesterolaemia: a review of the literature. *Pharmacoeconomics* 1992;2:34-42.

41. Hay JW, Yu WM, Ashraf T. Pharmacoeconomics of lipid-lowering agents for primary and secondary prevention of coronary artery disease. *Pharmacoeconomics* 1999;15:47-74.

42. Wendland G, Klever-Deichert G, Lauterbach K. [Cost effectiveness of lipid lowering therapy]
Kosteneffektivitat der lipidsenkenden Therapie. *Herz* 2001;26:552-60.

43. Shepherd J. Economics of lipid lowering in primary prevention: lessons from the West of Scotland Coronary Prevention Study. *Am J Cardiol* 2001;87:19B-22B.

44. Jacobson TA. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor therapy in the managed care era. *Am J Cardiol* 1996;78:32-41.

45. Smart AJ, Walters L. Pharmaco-economic assessment of the HMG-CoA reductase inhibitors. *S Afr Med J* 1994;84:834-7.

46. Tarraga Lopez PJ, Celada Rodriguez A, Cerdan Oliver M, Solera Albero J, Ocana Lopez JM, de Miguel Clave J. [Cost-effectiveness of atorvastatin against simvastatin as hypolipemic treatment in hypercholesterolemic patients in primary care]
Analisis coste-efectividad de atorvastatina frente a simvastatina como tratamiento hipolipemiante en pacientes hipercolesterolemicos en atencion primaria. *Aten Primaria* 2001;27:18-24.

47. Plans Rubio P, Rovira Forns J. [Cost-effectiveness of pharmacologic treatments for the reduction of blood lipids]
Estudio coste-efectividad de los tratamientos farmacologicos hipolipemiantes. *Med Clin (Barc)* 1995;105:327-33.
48. Elliot W WD. Comparative cost-effectiveness of HMG-CoA reductase inhibitors in secondary prevention of acute myocardial infarction. *Am J Health-Syst Pharm* 1999;56:1726-1732.
49. Cobos A, Jovell AJ, Garcia-Altes A, Garcia-Closas R, Serra-Majem L. Which statin is most efficient for the treatment of hypercholesterolemia? A cost-effectiveness analysis. *Clin Ther* 1999;21:1924-36.
50. Attanasio E, Russo P, Allen SE. Cost-minimization analysis of simvastatin versus atorvastatin for maintenance therapy in patients with coronary or peripheral vascular disease. *Clin Ther* 2001;23:276-83; discussion 274-5.
51. Perreault S VH, F. Lavoie, S. Grover. A head-to-head comparison of the cost effectiveness of HMG-CoA Reductase Inhibitors and Fibrates in Different Types of Primary Hyperlipidemia. *Cardiovasc Drugs Ther* 1996;10:787-794.
52. Chau J, Cheung BM, McGhee SM, Lauder IJ, Lau CP, Kumana CR. Cost-effectiveness analysis of applying the Cholesterol and Recurrent Events (CARE) study protocol in Hong Kong. *Hong Kong Med J* 2001;7:360-8.
53. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. *Am Heart J* 2001;141:727-34.
54. Prosser LA, Stinnett AA, Goldman PA et al. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann Intern Med* 2000;132:769-79.
55. Goldman L. Cost-effectiveness perspectives in coronary heart disease. *Am Heart J* 1990;119:733-9; discussion 739-40.
56. Field K, Thorogood M, Silagy C, Normand C, O'Neill C, Muir J. Strategies for reducing coronary risk factors in primary care: which is most cost effective? *BMJ* 1995;310:1109-12.
57. Assmann G, Schulte H. Primary prevention of coronary heart disease in the Federal Republic of Germany. Analysis of cost-effectiveness. *Drugs* 1990;40 Suppl 1:33-7.
58. Schulman KA, Kinosian B, Jacobson TA et al. Reducing high blood cholesterol level with drugs. Cost-effectiveness of pharmacologic management. *JAMA* 1990;264:3025-33.

59. Perreault S, Levinton C, Le Lorier J. Efficacy and cost of HMG-CoA reductase inhibitors in the treatment of patients with primary hyperlipidemia. *Can J Clin Pharmacol* 2000;7:144-54.

60. Spearman ME, Summers K, Moore V, Jacqmin R, Smith G, Groshen S. Cost-effectiveness of initial therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors to treat hypercholesterolemia in a primary care setting of a managed-care organization. *Clin Ther* 1997;19:582-602; discussion 538-9.

61. Cucherat M, Boissel JP. A mathematical model for the determination of the optimum value of the treatment threshold for a continuous risk factor. *Eur J Epidemiol* 1998;14:23-9.

62. Morris S. A comparison of economic modelling and clinical trials in the economic evaluation of cholesterol-modifying pharmacotherapy. *Health Econ* 1997;6:589-601.

63. Lim SS, Vos T, Peeters A, Liew D, McNeil JJ. Cost-effectiveness of prescribing statins according to pharmaceutical benefits scheme criteria. *Med J Aust* 2001;175:459-64.

5

Effectiveness calculation in economic analysis: the scenario of statins for cardiovascular disease prevention

Oscar H. Franco, Ewout W. Steyerberg, Anna Peeters, Luc Bonneux. Effectiveness calculation in economic analysis: the scenario of statins for cardiovascular disease prevention. *In preparation.*

Abstract

Objectives:
We aimed to evaluate the calculation of estimates of effectiveness in cost-effectiveness analyses of statins for cardiovascular disease prevention.

Methods:
We reviewed cost-effectiveness analyses on statin treatment published between 1995 and 2002. Estimates of life years saved were extracted and compared with estimates calculated using the Dutch male life-table of 1996-2000.

Results:
We considered 19 studies. Of 7 primary modeling analyses, 6 showed all the essential data and assumptions for the presented life savings, in contrast to none of the 12 secondary modeling analyses. The most transparent study estimated 1 year of life saved by 12 years of treatment of coronary heart disease survivors with increased cholesterol. In secondary analyses, the use of lifetime treatment caused the health effects to be dominated by savings at around the mean age of death (75-80 years).

Conclusion:
Reporting of essential data and assumptions was poor for many cost-effectiveness analyses on statins, especially for the secondary modeling analyses. Further standardization in economical analyses is important to guarantee transparency and reproducibility of results.

Introduction

Statins reduce the rate of coronary heart disease (CHD) by more than 30% for the primary or secondary prevention of cardiovascular disease (CVD).[1] Side effects are unusual and are generally well tolerated.[2] Costs of statins are however substantial. Several cost-effectiveness analyses have therefore been performed to refine indications for statin treatment in primary and secondary prevention of CVD. Estimates of effectiveness are essential in such analyses. Years of life saved (YLS) are derived by comparing age-specific mortality of treated and untreated cohorts.[3] Given the mortality risks of the untreated cohort, the YLS by statin treatment are defined by the assumed relative risk reduction. A transparent description of mortality by age in the untreated cohort is therefore important, together with either the relative risk reduction or the mortality by age in the treated cohort.

We reviewed cost-effectiveness analyses (CEAs) of statins with the aim to identify the various methods used to quantify the benefit (effectiveness) of statin treatment. We illustrated the different methodologies with a life table as standard tool.

Methods

Study selection

We searched for cost-effectiveness studies in English, Spanish, Dutch or German on statins for the prevention (primary and/or secondary) of either CHD or CVD in adult populations. Reviews and meta-analyses were excluded. Studies needed to compare costs and effects of statin treatment to no statin treatment and present cost per year of life saved (YLS) as outcome. YLS might be presented with or without discounting. Discounting means that years gained later during the life course are weighted less than years gained nearby. Common discount rates are 3%, 4% or 5%.[4] We excluded studies comparing statins with other statins, or, statins with other cholesterol lowering medicaments.

We used the databases MEDLINE, the British National Health Service Economic Evaluation Database (NHS EED), the Database of Abstracts of Reviews of Effectiveness (DARE) and the Health Technology Assessment database (HTA). We searched for papers published between 1995 and July 2002. Before 1995, no evidence from large randomized clinical trials was available, and the methods of estimating health effects were very diverse.

Two investigators analysed the abstracts obtained from the databases. All studies that matched our inclusion criteria were retrieved, and their reference lists were checked for further identification of studies. When the decision for inclusion could not be reached by reading the abstracts, the papers were retrieved for further analysis. Two investigators read the articles retrieved and selected the studies to include based on the inclusion criteria. A third investigator was contacted in case of disagreement.

Data extraction

We focused on the methods to calculate the effects of mortality reduction due to statin treatment. We searched for data describing mortality in treated and untreated cohorts. Information was extracted on the following variables: time of publication, source of risk for the untreated cohort, survivorship from the end of treatment, source of risk reduction for the treated cohort, treatment period (≤ 10 years or >10 years), time-horizon (trial duration or lifetime), and the outcome (discounted or undiscounted YLS).

We also classified the papers according to the type of modeling: primary or secondary modeling analyses. Primary modeling analyses were defined as being conducted parallel to randomized clinical trials (RCTs). In secondary modeling analyses, mortality in the untreated cohort is either predicted (extrapolated) by risk functions or taken from other sources such as prospective cohorts. Mortality reduction is modeled by changes in risk factor levels (i.e. lowering LDL-cholesterol) or by applying reduction rates on mortality or morbidity from trials.

Treatment period and time horizon

Treatment period can be restricted to the trial period (which in the case of statins it is generally around 5 years), or can be assumed to persist after the trial for limited or unlimited (lifelong) periods. Time horizon is the period of time determined to calculate the effects of treatment and can also be limited to the trial period or extrapolated for additional limited or unlimited (lifetime) periods.

In figure 5.1A the combination of a limited treatment period and a limited time horizon is presented. Treatment period and treatment effects are restricted to the trial period without any additional extrapolation.

The scenario of combining a limited treatment period (restricted to the trial period) with an unlimited (lifetime) time horizon is presented in figure 5.1B. In this case the study extrapolates effects seen during the trial period beyond this time but does not assume additional treatment effect.

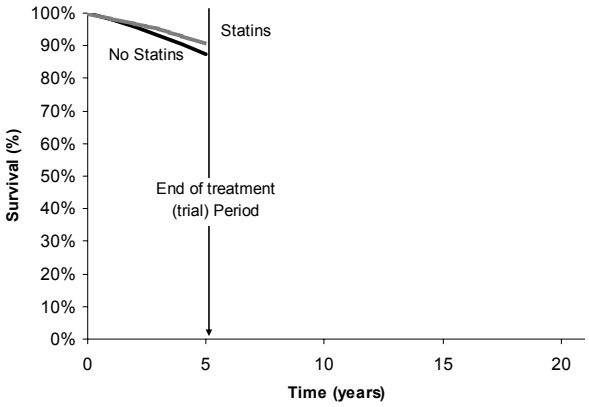

Figure 5.1A. Assumptions in Modeling Treatment and Time Horizons: analysis based on treatment and effects observed during the trial period (treatment effect and time horizon limited to trial period)*

*Trial period in the case of statins is generally around 5 years, treatment effects of statins taken from LaRosa et al[1]

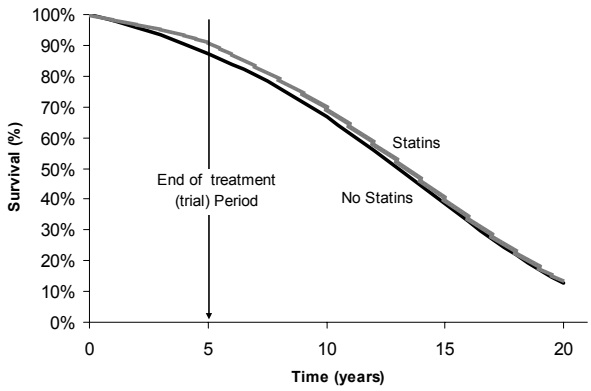

Figure 5.1B. Assumptions in Modeling Treatment and Time Horizons: the study extrapolates effects beyond the trial period but does not assume additional treatment effect (treatment period limited to trial period, time horizon extrapolated beyond trial period for lifetime).*

*Trial period in the case of statins is generally around 5 years, treatment effects of statins taken from LaRosa et al[1]

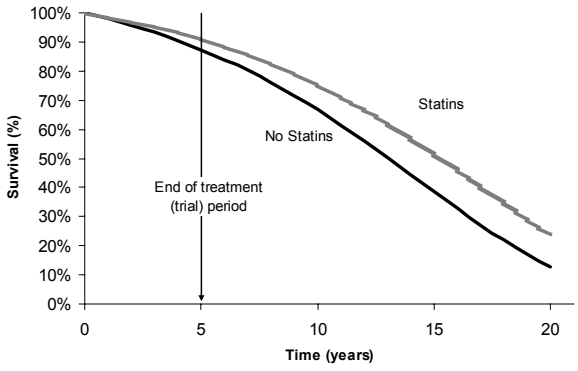

Figure 5.1C. Assumptions in Modeling Treatment and Time Horizons: the study extrapolates beyond the trial period and assumes additional treatment and effect (i.e. same risk reduction as observed during the trial period). Here both treatment period and time horizon are extrapolated beyond the trial period.*

*Trial period in the case of statins is generally around 5 years, treatment effects of statins taken from LaRosa et al[1]

An alternative generally seen in secondary analyses is to extrapolate both treatment period and time horizon beyond the trial period for lifetime: treatment is assumed to continue until extinction of the cohort or till very old ages (Figure 5.1C).

Life-table comparison

To illustrate the different methodologies used in the calculation of effectiveness, we performed analyses with the Dutch male life-table of 1996-2000. The life-table served as a standardizing tool to translate the mortality of treated and untreated persons in years of life saved (YLS). In the Gompertz function of mortality by age, mortality is predicted by a constant α and a relative increase of mortality by age of β. [5] If we assumed β to be constant (and identical to the Dutch male mortality),[6] at any mortality level the residual life expectancy (LE) was determined. The LE is the number of years of life yet to live at age 'x' by a survivor. The YLS over a lifetime (YLS LT) is the LE of the treated minus the untreated cohort.

Effects were calculated using two different scenarios: limited treatment period (5-year) combined with a lifetime time horizon and lifelong treatment period combined with a lifetime time horizon. In addition to undiscounted results, a discount factor of 5% was applied. Finally, we calculated the number of life years needed to treat to save one life-year. All life-tables were built using Excel spreadsheets, which are available upon request.

Results

Description of studies

We included 19 studies, including 7 primary modeling analyses and 12 secondary (table 5.1). Data on mortality during the treatment period were presented by all primary analyses but only by two of the 12 secondary analyses.

Of the primary analyses, 6 presented data on survivorship from the end of treatment, in contrast to 2 of the 12 the secondary analyses. All primary analyses considered treatment periods less than 10 years, while 11 of the 12 secondary analyses modeled the effects of lifelong statin treatment. In primary analyses, the mortality reduction expressed as YLS was generally composed of two components: YLS saved during the trial, and YLS expected to be added by the survivors at the end of the trial, as was illustrated in Fig 1B. For example, the 4S trial, which included survivors of CHD with increased cholesterol levels, showed that the treated cohort saved 0.067 life-years per person during the trial and 0.312 per person after the trial:[7] 3.1% more persons in the treated cohort survived the trial, and were

Table 5.1 Description of the Studies Included.*

		Untreated cohort	Treated cohort				Reported data		
Name and reference	Publi-cation Year	Source of mortality	Source of risk reduction	Treatment duration	Time Horizon	Modeling Scheme (Figure 1)	Mortality in treatment period of untreated cohort	Mortality reduction	YLS
Primary analyses									
Jönsson[8]	1996	4S	4S	<=10 y	Lifetime	B	Yes	Yes	Yes
Johannesson[7]	1997	4S	4S	<=10 y	Lifetime	B	Yes	Yes	Yes
Jönsson[25]	1999	4S	4S	<=10 y	Lifetime	B	Yes	Yes	Yes
Szucs[31]	1998	CARE	CARE	<=10 y	Lifetime	B	Yes	Yes	Yes
Szucs[32]	2000	LIPID	LIPID	<=10 y	Lifetime	B	Yes	Yes	Yes
Ashraf[10]	1996	PLAC	PLAC	<=10 y	10 years	A	Yes	Yes	Yes
Caro[11]	1997	WOSCOPS	WOSCOPS	<=10 y	Lifetime	B	Yes	Yes	Yes
Secondary analyses									
Riviere[12]	1997	4S	4S+survival functions	>10 y	Lifetime	C	No	Yes	No
Ganz[13]	2000	Cohort studies	CARE	>10 y	Lifetime	C	No	Yes	Yes
Huse[16]	1998	risk function (FHS)	risk functions (FHS)	>10 y	Lifetime	C	No	No	No
Perreault[14]	1998	risk function (FHS)	risk functions (FHS)	>10 y	Lifetime	C	No	No	Yes
Russel[15]	2001	risk function (FHS)	risk functions (FHS)	>10 y	Lifetime	C	No	No	No
Hamilton[17]	1995	risk function (LRC)	risk functions (LRC)	>10 y	Lifetime	C	No	No	Yes
Grover[18]	1999	risk function (LRC)	risk functions (LRC)	>10 y	Lifetime	C	No	No	Yes
Grover[19]	2000	risk function (LRC)	risk functions (LRC)	>10 y	Lifetime	C	No	No	Yes
Grover[20]	2001	risk function (LRC)	risk functions (LRC)	>10 y	Lifetime	C	No	No	Yes
Van Hout[21]	2001	trials + survival functions	trials + survival functions	>10 y	Lifetime	C	Yes	Yes	Yes
Pharoah[22]	1996	Vital stats + relative risks	4S/WOSCOPS	<=10 y	10 years	C	Yes	Yes	No
Pickin[23]	1999	Vital stats + relative risks	4S/WOSCOPS	>10 y	Lifetime	C	No	Yes	No

Abbreviations: YLS, Years of life saved; y, years; FHS, Framingham Heart Study; LRC, Lipid Research Clinic Cohort.
*Studies and available information on health benefits. The duration of life of untreated cohorts is specified by mortality during treatment and survivorship after treatment. The years of life saved in the treated cohorts are specified by the mortality reduction, yielding years of life saved. Secondary analyses have rarely sufficient information to judge the validity of the results.

expected to live another 10 years.[7-9] This leads to 0.38 YLS/person by 5.15 years of treatment, or 136 years of treatment to save 10 life-years. In five of seven primary evaluations, all relevant mortality information was presented. A sixth study presented YLS that were discounted by 5%.[10] The seventh study did describe methods but did not present outcomes for LE after the trial.[11]

Of the 12 secondary analyses,[12-23] none clearly described the mortality by age and treatment.

Life-table comparisons

Table 5.2 mimics the West of Scotland Coronary Prevention Study (WOSCOPS). This is a large RCT (n=6595) that studied the effects of statins among a population free of CHD (primary prevention of CHD).[24] Here we evaluate the effects of five years or life-long statin treatment for cohorts of 40, 50, 60, 70 and 80-year olds. The untreated cohorts originate from the Dutch male life-table of 1996-2000. In the treated cohort of WOSCOPS, the all cause mortality was 22% lower than that of the untreated cohort.[24] This relative risk reduction was applied to the untreated cohort for five years or lifelong. Table 5.2 shows that YLS were higher the younger the treatment started. If we assumed that treatment started at age 40, a reduction in all cause mortality by 22% would save 2.38 years. Only 16 years would be needed to treat to save one life-year. Most life-years were however saved around the mean age at death in this population (76 years). Hence, only 0.42 discounted life-years were saved. This is 5.7 times less than the undiscounted values.

If only the savings of treating between age 40 and 45 are considered in combination with a lifetime time-horizon (as illustrated in Fig 5.1B), 71 years of

Table 5.2. Replication of WOSCOPS* trial.

					Treatment period			
	Untreated			Treated	Lifetime		5 years	
Age	5 y risk of death†	LE	LE disc 5%	Risk reduction‡	YLS LT§	YLS LT§ disc 5%	YLS 5y§	YLS 5y§ disc 5%
40	0,9%	36	17	0,2%	2,4	0,4	0,07	0,03
50	2,5%	27	15	0,5%	2,3	0,6	0,12	0,06
60	7,2%	18	12	1,5%	2,0	0,8	0,27	0,15
70	20%	11	8,3	4,0%	1,7	0,9	0,45	0,30
80	46%	6,3	5,2	8,3%	1,2	0,8	0,60	0,46

Abbreviations: LE, Life Expectancy; YLS, Years of Life Saved; y, years; disc, discounted.
*WOSCOPS trial (5 year risk of death 4,17% at age 55, 22% reduction in all cause mortality) extrapolated to younger and older ages. The same risk reduction is translated in 4 life-table measures by two treatment periods: till the end of life (lifetime) and over 5 year (5 year). 5% means that an annual discount rate of 5% is applied to the saved life years in the future cohort. The years of life saved (YLS) apply to the survivors at age x.
† Risk of dying between age x and x+5.
‡ Risk reduction in the treated cohort, the risk is 22% lower (WOSCOPS trial)
§ YLS LT are years of life saved by life time treatment starting at age x, and YLS 5y are years of life saved by 5 year treatment starting at age x

treatment save one life-year. An example of the effect obtained by treating a cohort aged 40-45 over a fixed treatment period of five years and a lifetime time horizon is shown in Figure 5.3.The alternative of calculating this effect over an unlimited (lifelong) treatment period in combination with a lifetime time horizon is presented in Figure 5.2.

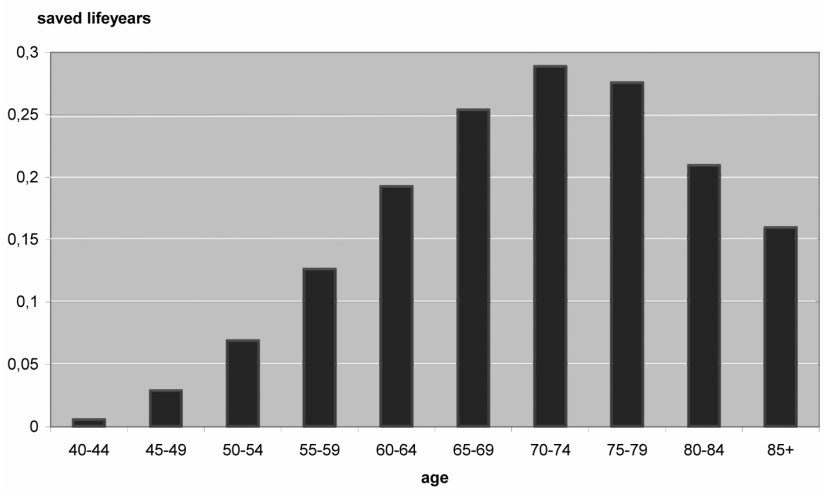

Figure 5.2. Lifelong Treatment Effect with Lifetime Time Horizon Assumption*
*Savings in each 5-year age group by a fixed reduction of mortality risk, of a 40-year-old cohort over the future, assuming lifetime effect and treatment. Note that most savings will fall more than three decades after start of treatment.

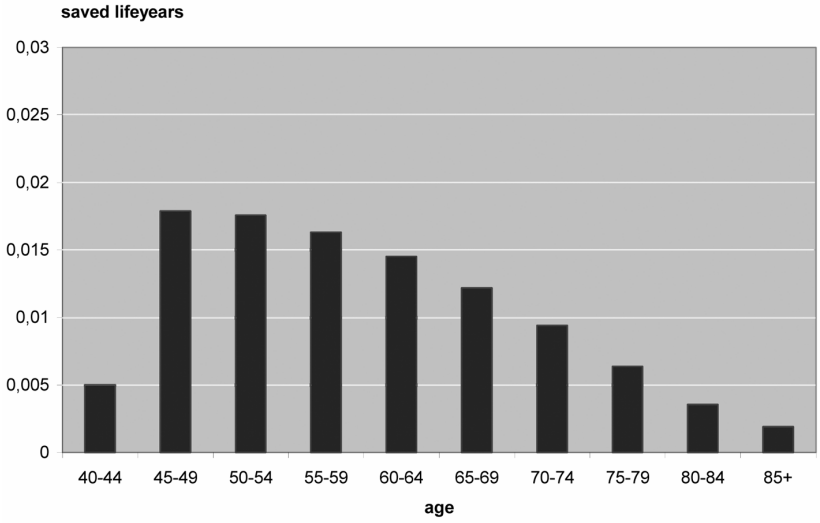

Figure 5.3. 5-years Limited Treatment Effect with Lifetime Time Horizon Assumption*
*Savings in each 5 year age group by a fixed reduction of death risks of a 40year old cohort between age 40 and 44. The life years saved after age 44 are the life years of the additional survivors at age 44 (still subjected to the mortality rates of the untreated).

Life-table comparisons with primary modelling

Most primary modeling analyses considered years of life saved during the trial, and after the trial by the extra survivors who share the LE of the untreated cohort (limited treatment period to the trial period in combination with a lifetime time horizon). This approach is e.g. taken by the 4S evaluators.[7 8 25] The WOSCOPS evaluators did not only take the excess survivors into account, but also the improved prognosis of those treated that survived without CVD. However, the WOSCOPS evaluators failed to clearly report the disease rates and survivorships.[11]

The comparisons with life-table estimations of health benefits of 5-year treatment periods are shown in table 5.3. The estimates of the 4S evaluators (0.35 - 0.38) were close to our life-table estimate (0.41 years), consistent with a slightly lower estimate of the YLS of survivors at the end of the trial compared to our lifetable estimate. The estimate for the LIPID trial was higher than our life-table estimates (0.41 versus 0.34 years), again consistent with a LE at the end of trial that

Table 5.3. Trial Characteristics, and Years of Life Saved by Treatment*.

	Trials				
	4S	LIPID	CARE	WOSCOPS	AFCAPS/ TexCAPS
N	4444	9014	4159	6595	6605
Follow up (mean y)	5.4	6.1	5.0	4.9	5.2
Age (mean, y)	59	62	59	55	58
Men (%)	81	83	86	100	85
History of MI (%)	79	64	100	0	0
TC/HDL ratio	5.67	6.06	5.35	6.17	6.01
Control arm					
5yr risk of death (%)	10.7	11.7	9.4	4.2	2.2
5yr risk of CHD death	7.90	6.84	5.73	1.61	0.44
Lived during trial (years)†	4.77	4.74	4.97	4.90	4.95
Life expectancy (LE, yr)†	15.7	15.1	16.7	22.6	28.1
LE at end of trial (yrs)†	10.93	10.36	11.73	17.70	23.15
Statin arm					
Absolute reduction (all cause mortality, %)	3.10	2.54	0.78	0.91	-0.09
Years saved during trial†	0.067	0.074	0.023	0.024	0.003
Based on all cause mortality					
Total years saved‡	0.41	0.34	0.11	0.18	Harm
NNT 5 yr	32	39	128	110	Harm
YLNT 5 yr	12	14	43	27	Harm
Published estimates	0.38[8] 0.35[25]	0.41[32]	0.22[31]	0.25[11]	

*The savings are calculated by two methods: using absolute reduction in all cause or in coronary heart disease mortality.
†Years lived are based on the life-table of Dutch males 1996-2000 (see text). At a five year risk of death of 10.7% (4S trial), Dutch males had a residual life expectancy of 15.7 years.
‡ Years lived during the trial + the absolute mortality reduction multiplied by the residual life expectancy at the end of the trial.

was 2.7 years higher than that of our life-table (table 5.3). For the CARE trial, YLS were 0.22 versus 0.15 years, again consistent with a lower LE of our life-table. For the WOSCOPS trial, the estimated 0.25 YLS by treatment was higher than our estimate of 0.10 YLS. The WOSCOPS' authors included estimates of an improved prognosis for the survivors without a CVD event, and this could explain the difference. Finally, Ashraf et al.[10] presented all relevant data, but analyzed only 10 CHD deaths and 6 of other causes (using data from the PLAC trial, no presented in table 5.3).

Discussion

Overall we were confronted with a poor transparency in the presentation of essential data among cost-effectiveness analyses of statins. This constituted a major impediment to the interpretation and evaluation of the selected studies.

We found that to calculate the benefits of statin treatment two types of analyses were predominantly used: primary and secondary modeling analyses. Different extrapolations about treatment period and treatment effect were also identified. Primary modeling analyses used mostly a combination of treatment period equal to trial period and a lifetime time horizon to calculate the effect of statins treatment. Secondary modeling analyses used mainly a combination of a lifelong treatment assumption with a lifetime time horizon for the calculation of the effects of treatment. All secondary analyses extrapolated the treatment with statins and its effects to periods of time beyond the available evidence.

Of the 19 evaluated studies, only 6 showed all information on age specific mortality to value the study results transparently. All were primary analyses. A seventh primary analysis, the WOSCOPS study evaluation, was thorough but failed to show how prevented CVD affected survivorship after the trial period. This implied that a large part of the savings remained without a clear explanation. Of the six primary analyses that showed sufficient information, one study described a very small population: confidence limits would show an enormous span.[10] That left five studies for serious evaluation, that described the experience of the 4S, LIPID and CARE trials. Among these, the 4S publications showed most clearly all the essential information. Additionally the results were consistent with our life-table approach. Depending on the data used and the method for estimating survival at the end of the trial, 11 to 13 years of statin use added one year of life.

From the 12 secondary modeling analyses included, none clearly presented the modeled age specific mortality rates of treated and untreated cohorts, leaving the

reader without aggregate outcomes that could be fully interpreted or reproduced. As health benefits are the primary aim of any health intervention, in future publications the modeled age specific rates of control and intervention cohort should be clearly shown. 11 of the 12 secondary analyses used lifelong treatment periods combined with lifetime time-horizons. Modeling treatment over lifelong periods needs assumptions on treatment effects over unobserved long periods and at old ages. The argument that considering lifelong treatment effect is "a more realistic assumption, as treatment is for life"[23] calculates health benefits at a old age (>70 years age) with limited evidence and at a time the studied drugs might be superseded by cheaper substitutes, or a polypill.[26] To model the effect of a drug, it is not necessary to stretch the evidence far beyond observable time periods. As far as evidence is available, statins decrease the risk of CHD regardless of the duration that statins are taken (after allowing for a short lag-time period of six months, maximum two years)[21]. Risk reduction is around 30% (fig 1),[1] regardless if statins have been taken for 2 or five years. There is therefore no need to assume a life-long treatment effect.

Although it is possible that some relevant studies could have not been included in the present analysis, we do not think this could alter our conclusions. We excluded three cost-utility analyses[27-29] that did not present YLS, since our objective was to analyze the calculation methods of effectiveness and not of utilities. The outcome for cost-utility studies is years of life gained adjusted by quality weights (QALYs). YLS are solely derived from age specific mortality in treated and untreated cohorts. QALYs require estimates of incidence of disease stages, duration of these stages and value judgments on the utility lost by decreased health in these stages. This limits their comparability.

In the particular scenario of statins for CVD prevention, competing interests are important.[30] This increases the necessity for robust and transparent methodology.

In general we found that reporting of essential data was poor for many cost-effectiveness analyses on statins. Primary modeling analyses have close links with underlying data from RCTs. Primary analyses reported better and made more reasonable assumptions; hence they should be viewed with more confidence than secondary modeling studies. Better cost-effectiveness analyses should be rooted in the evidence of trials. The value of added survivorship in treated cohorts should be translated into YLS by transparent and interpretable methods (as seen in the primary modeling analyses). Further standardization in economical analyses is therefore important to guarantee transparency and reproducibility of results.

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References

1. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;282(24):2340-6.
2. Knopp RH. Drug treatment of lipid disorders. *N Engl J Med* 1999;341(7):498-511.
3. Bonneux L. How to measure the burden of mortality? *J Epidemiol Community Health* 2002;56:128-31.
4. 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(1):26-36.
5. Gompertz B. On the nature of the function expressive of the law of human mortality. *Phil Trans Royal Soc London* 1825;115:513-83.
6. Kesteloot H, Huang X. On the relationship between human all-cause mortality and age. *Eur J Epidemiol* 2003;in press.
7. Johannesson M, Jonsson B, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. Scandinavian Simvastatin Survival Study Group. *N Engl J Med* 1997;336(5):332-6.
8. Jonsson B, Johannesson M, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost-effectiveness of cholesterol lowering. Results from the Scandinavian Simvastatin Survival Study (4S). *Eur Heart J* 1996;17(7):1001-7.
9. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344(8934):1383-9.
10. Ashraf T, Hay JW, Pitt B, Wittels E, Crouse J, Davidson M, et al. Cost-effectiveness of pravastatin in secondary prevention of coronary artery disease. *Am J Cardiol* 1996;78(4):409-14.
11. Caro J, Klittich W, McGuire A, Ford I, Norrie J, Pettitt D, et al. The West of Scotland coronary prevention study: economic benefit analysis of primary prevention with pravastatin. *BMJ* 1997;315(7122):1577-82.

12. Riviere M, Wang S, Leclerc C, Fitzsimon C, Tretiak R. Cost-effectiveness of simvastatin in the secondary prevention of coronary artery disease in Canada. *Cmaj* 1997;156(7):991-7.
13. Ganz DA, Kuntz KM, Jacobson GA, Avorn J. Cost-effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor therapy in older patients with myocardial infarction. *Ann Intern Med* 2000;132(10):780-7.
14. Perreault S, Hamilton VH, Lavoie F, Grover S. Treating hyperlipidemia for the primary prevention of coronary disease. Are higher dosages of lovastatin cost-effective? *Arch Intern Med* 1998;158(4):375-81.
15. Russell MW, Huse DM, Miller JD, Kraemer DF, Hartz SC. Cost effectiveness of HMG-CoA reductase inhibition in Canada. *Can J Clin Pharmacol* 2001;8(1):9-16.
16. Huse DM, Russell MW, Miller JD, Kraemer DF, D'Agostino RB, Ellison RC, et al. Cost-effectiveness of statins. *Am J Cardiol* 1998;82(11):1357-63.
17. Hamilton VH, Racicot FE, Zowall H, Coupal L, Grover SA. The cost-effectiveness of HMG-CoA reductase inhibitors to prevent coronary heart disease. Estimating the benefits of increasing HDL-C. *JAMA* 1995;273(13):1032-8.
18. Grover SA, Coupal L, Paquet S, Zowall H. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease: forecasting the incremental benefits of preventing coronary and cerebrovascular events. *Arch Intern Med* 1999;159(6):593-600.
19. Grover SA, Coupal L, Zowall H, Dorais M. Cost-effectiveness of treating hyperlipidemia in the presence of diabetes : who should be treated? *Circulation* 2000;102(7):722-7.
20. Grover SA, Coupal L, Zowall H, Alexander CM, Weiss TW, Gomes DR. How cost-effective is the treatment of dyslipidemia in patients with diabetes but without cardiovascular disease? *Diabetes Care* 2001;24(1):45-50.
21. van Hout BA, Simoons ML. Cost-effectiveness of HMG coenzyme reductase inhibitors; whom to treat? *Eur Heart J* 2001;22(9):751-61.
22. 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(7044):1443-8.
23. Pickin DM, McCabe CJ, Ramsay LE, Payne N, Haq IU, Yeo WW, et al. Cost effectiveness of HMG-CoA reductase inhibitor (statin) treatment related to

the risk of coronary heart disease and cost of drug treatment. *Heart* 1999;82(3):325-32.

24. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, 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(20):1301-7.
25. Jonsson B, Cook JR, Pedersen TR. The cost-effectiveness of lipid lowering in patients with diabetes: results from the 4S trial. *Diabetologia* 1999;42(11):1293-301.
26. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326(7404):1419.
27. Chau J, Cheung BM, McGhee SM, Lauder IJ, Lau CP, Kumana CR. Cost-effectiveness analysis of applying the Cholesterol and Recurrent Events (CARE) study protocol in Hong Kong. *Hong Kong Med J* 2001;7(4):360-8.
28. Prosser LA, Stinnett AA, Goldman PA, Williams LW, Hunink MG, Goldman L, et al. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann Intern Med* 2000;132(10):769-79.
29. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. *Am Heart J* 2001;141(5):727-34.
30. Messori A, Santarlasci B, Trippoli S, Vaiani M. "Polypill" to fight cardiovascular disease: cost effectiveness of statins for primary prevention of cardiovascular events is questionable. *BMJ* 2003;327(7418):808-9; discussion 809; author reply 809-10.
31. Szucs TD, Guggenberger G, Berger K, Marz W, Schafer JR. [Pharmacoeconomic evaluation of pravastatin in the secondary prevention of coronary heart disease in patients with average cholesterol levels. An analysis for Germany based on the CARE study]

Pharmakookonomische Bewertung von Pravastatin in der Sekundarpravention der koronaren Herzkrankheit bei Patienten mit durchschnittlichen Cholesterinwerten. Eine Analyse fur Deutschland auf der Grundlage der CARE-Studie. *Herz* 1998;23(5):319-29.

32. Szucs TD, Berger K, Marz W, Schafer JR. [Cost effectiveness of pravastatin in secondary coronary prevention in patients with myocardial infarct or unstable angina in Germany. An analysis on the basis of the LIPID trial]

Kosteneffektivitat von Pravastatin in der koronaren Sekundarpravention bei Patienten mit Myokardinfarkt oder instabiler Angina pectoris in

Deutschland. Eine Analyse auf der Grundlage der LIPID-Studie. *Herz* 2000;25(5):487-94.

6

Primary prevention of cardiovascular disease: cost-effectiveness comparison

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Abstract

Aims:
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 interventions in men. Participants were classified by age and level of absolute risk of coronary heart disease. The effects of risk reduction are obtained as numbers of death averted, life years saved and disease-free life years. 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 (€2263 to €16949 per year of life saved) followed by antihypertensives (€28187 to €79843 per year of life saved). Statins are the least cost-effective (€73971 to €190276 per year of life saved).

Conclusions:
A cost-effective strategy should offer smoking-cessation for smokers and aspirin for all levels of risk among men aged 45 and over. Antihypertensives are efficient over a wide range of risk levels. Statin therapy is the most expensive option in primary prevention at levels of 10-years absolute coronary heart disease risk below 30%.

Introduction

Cardiovascular disease (CVD) prevention is based on comprehensive risk management of relevant risk factors.[1] [2] 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 pre-treatment levels of absolute risk of coronary heart disease (CHD).[1] 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.[3] Currently cut-off levels of pre-treatment absolute risk have been used to target healthy persons eligible for risk-lowering treatment.[, 1997 #12] But head to head comparisons of efficiency of various options in cardiovascular disease risk management are scarce: aspirin is cheap, but less effective, statin is more effective but costly.[5] [6]

This study compares the cost-effectiveness of four risk-lowering 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 original Framingham Heart Study (FHS) and the Framingham Offspring Study (FOS), we built life tables to model the cost-effectiveness of the selected interventions in men free of CVD (at baseline). We modelled two synthetic age cohorts: from 45 to 55 year and from 55 to 65 year.

Data sources

The original FHS cohort consisted of 5209 respondents aged 28 through 62 years residing in Framingham, Massachusetts, between 1948 and 1951. Examination of participants has taken place biannually and the cohort has been followed 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 5214 participants, aged 5 through 70 years at baseline. Examination of this cohort has taken place at intervals of four to eight years. Since the study design and measurement instruments used in FHS and FOS are similar, we pooled both datasets. Further description of the FHS and the FOS can be found elsewhere.[7] [8] 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 (1987-1989) 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. The same participant could therefore be included more than once but for different follow-up periods. In total there were 3742 men for the analysis.

Baseline assessment

At baseline participants were classified by age group and by level of absolute risk of CHD estimated by the Anderson risk equations.[9]

These equations include: age, sex, systolic blood pressure (SBP), smoking status, diabetes, the ratio of total cholesterol/HDL cholesterol and left ventricular hypertrophy (presence on Electrocardiogram). The ratio total cholesterol/HDL cholesterol was missing for 812 participants and was imputed based on the other variables of the formula. Enough data on the variables required for the calculation of risk was available in 3332 participants. Subjects were categorized into 3 groups based on their level of 10-year absolute risk of CHD: Low: <10% (2396 participants), moderate: 10 to <20% (714 participants) and high-risk ≥ 20% (222 participants). There were too few participants with very high risk (≥ 30%) to enable the calculation of lifetables.

Effectiveness

Benefits of the interventions were calculated as number of deaths prevented, life years saved and disease free life years saved within a ten-year time horizon in the two multi-state lifetable (MSLTs) 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 mmHg 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.[10] No lag times were included for the other therapies.

Reduction rates of CVD were taken from recent meta-analyses.[11-18] In the case of smoking cessation strategies we estimated the success rates of cessation therapy after one year of follow-up. Relapse rates were set at 0%, 20% and 40% 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 6.1).[18].

We used the FHS and FOS data to estimate transition rates from healthy to non-fatal CHD, fatal primary CHD, secondary fatal CHD, stroke and death, using

Table 6.1. Risk Reduction Effect of Interventions in the Prevention of Cardiovascular Disease (%)*

Treatment	Primary non-fatal CHD†	Primary CHD Death†	Secondary CHD Death‡	Primary Stroke†	Secondary Stroke‡	Cessation Rate*	Source
Aspirin	28	13	13	20	20	n.a.	
Antihypertensive Treatment	20	26	26	39	28	n.a.	BPLTT Collaboration[14]
Statins	34	29	29	29	29	n.a.	La Rosa et al,[11] Hebert et al[15]
SC GP Advice	Reduction effect taken from a published function for smoking cessation in cardiovascular disease prevention[18]					5	Silagy et al[16]
SC Nicotine Substitutes						17	Silagy et al[16]
SC Bupropion						19	Hughes et al[17]

Abbreviations: CHD, Coronary Heart Disease including fatal and non-fatal events; SC, Smoking Cessation; GP, General Practitioner; n.a, not applicable.
* Reduction effect and cessation rates are expressed in percentage and for one-year treatment.
† Primary refers to events occurring in populations free of cardiovascular disease
‡ Secondary refers to events occurring in populations with cardiovascular disease

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 for ten years, with and without risk lowering. Comparisons between with and without risk lowering yield life years saved (YLS), YLS free of CHD and number of deaths prevented.

Costs

Direct medical only costs were calculated based on current Dutch guidelines of treatment.[19-21] In the Netherlands 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.[20] Aspirin treatment includes per year, one GP visit plus the cost of aspirin 100mg/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[22] and using a basket including all medications of its kind available for prescription in The Netherlands (further description on the market share approach on appendix 6.1). 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. Statins 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. Since nicotine substitutes can be obtained over the counter without a medical prescription and without prescription renewals, we included only medication costs for three months 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 three months 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.[23] Costs per event were for non-fatal myocardial infarction (MI) €6972, fatal MI €1602, non-fatal stroke €11870 and fatal stroke prevented €3851.
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 the recommended in the Netherlands nominal discount rate of 4% per year, in order to take into account time preference.[24] This implies that effects and costs occurring in the future are weighted less that those occurring in the present.[25]

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 SBP level. To calculate the impact of adverse effects caused by aspirin treatment we considered an approximate 1% incidence rate of major bleedings among participants receiving aspirin over 10 years treatment.[12] Cost for a major bleeding event ($5300) was taken from the literature. [26]
All survival analyses were performed using STATA version 8.2 for windows (Stata corporation, college station TX, USA, 2003). MSLTs were made using Excel spreadsheets. Spreadsheets are available at request.

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 €20000 per YLS was considered the most cost-effective.

Results

Net costs (cost of treatment – cost of events prevented) and effects of the different treatments over a 10-year period are presented in table 6.2.

Statin therapy is the most effective strategy for all risk and age groups but also the most expensive. Antihypertensive therapy costs are lower compared to statins but higher compared to the other therapies. For all levels of risk and age, aspirin treatment cost 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

Cost-effectiveness ratios (CERs) in terms of cost per YLS, per YLS free of CHD as well as per death prevented are presented in table 6.3 and figure 6.1. The most cost-effective treatment is smoking cessation therapy, representing savings in all situations. Statin therapy is the least cost-effective treatment (ranging from €73971 to €19027 per YLS). Aspirin was the second most cost-effective intervention (ranging from €2263 to €16949 per YLS) followed by antihypertensive treatment (ranging from €28187 to €79843 per YLS). These rankings were maintained for all age group/ risk group categories analysed.

Labelling CERs under €20000 per YLS as "cheap", over €40000 per YLS as "expensive" and in between as "moderate";[27] 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.

Table 6.2A. Costs and Effects of Ten-Years of Intervention in the Primary Prevention of Cardiovascular Disease* for a Population at Moderate Risk†

	Costs (€)		YLS/ 1000 participants		HYLS/ 1000 participants		Deaths Prevented/ 1000 Participants‡	
Ten-Years Treatment	Age 50	Age 60	Age 50	Age 50	Age 60	Age 60	Age 50	Age 60
SC GP Advice§	-10	-3	2	0.9	6	2	1.31	0.64
SC Nicotine Substitutes§	-22	-6	7	2.9	21	6	4.55	2.05
SC Bupropion§	-15	-4	8	3.3	23	6	5.07	2.28
Aspirin	260	243	15	18.9	92	77	6.31	8.97
Antihypertensives‖	472	418	6	8	19	17	2.47	3.47
Statins	4620	4534	24	33.8	106	97	9.74	14.01

Abbreviations: YLS, Year of Life Saved; HYLS, "Healthy" (free of coronary heart disease) Year of Life Saved; SC, Smoking Cessation; GP, General Practitioner.
* Costs calculated in Euros from 2003, represent net costs per intervention (costs of treatment - cost of events prevented).
† Moderate risk refers to a ten-year risk of coronary heart disease between 10 and <20%
‡ Calculated at the end of ten years treatment.
§Smoking cessation was given only to smokers: 68% of the age 50 group and 21% of the age 60 group.
‖Antihypertensives were given only to participants with high blood pressure: 27% of the age 50 group and 25% of the age 60 group.

Table 6.2B. Costs and Effects of Ten-Years of Intervention in the Primary Prevention of Cardiovascular Disease* for a Population at High Risk†

	Costs (€)		YLS/ 1000 participants		HYLS/ 1000 participants		Deaths Prevented/ 1000 Participants‡	
Ten-Years Treatment	Age 50	Age 60	Age 50	Age 50	Age 60	Age 60	Age 50	Age 60
SC GP Advice§	-24	-18	4.8	4.2	1.4	1.1	2.89	2.66
SC Nicotine Substitutes§	-67	-50	16.3	14.1	4.9	3.9	9.89	9.22
SC Bupropion§	-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‖	1256	731	34.5	25.9	11.1	7.5	14.59	8.97
Statins	4263	4145	49.7	56	20.2	21.6	20.11	19.56

Abbreviations: YLS, Year of Life Saved; HYLS, "Healthy" (free of coronary heart disease) Year of Life Saved; SC, Smoking Cessation; GP, General Practitioner.
* Costs calculated in Euros from 2003, represent net costs per intervention (costs of treatment - cost of events prevented).
† High risk refers to a ten-year risk of coronary heart disease between >=20%
‡ Calculated at the end of ten years treatment.
§Smoking cessation was given only to smokers: 91% of the age 50 group and 74% of the age 60 group.
‖Antihypertensives were given only to participants with high blood pressure: 82% of the age 50 group and 50% of the age 60 group.

Table 6.3A. Cost-Effectiveness* of Primary Prevention of Cardiovascular Disease in Populations at Moderate Risk†

	Cost per YLS		Cost per HYLS		Costs per Deaths Prevented‡	
Ten-Years Treatment	Age 50	Age 60	Age 50	Age 50	Age 60	Age 60
SC GP Advice§	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
SC Nicotine Substitutes§	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
SC Bupropion§	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
Aspirin	16949	12862	2716	2263	41204	27090
Antihypertensives‖	79843	52217	36399	28187	191093	120461
Statins	190276	134083	85715	73971	474332	323625

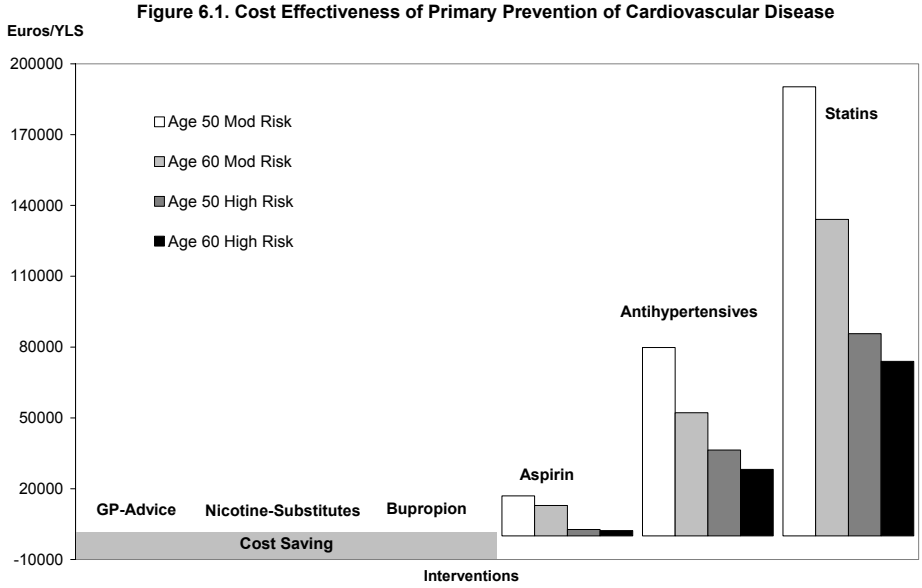
Abbreviations: YLS, Year of Life Saved; HYLS, "Healthy" (free of coronary heart disease) Year of Life Saved; CHD, SC, Smoking Cessation; GP, General Practitioner.
* Future effects and costs equally weighted with 4% as discount factor, costs calculated in Euros from 2003
† Moderate risk refers to a ten-year risk of coronary heart disease between 10 and <20%
‡ Calculated at the end of ten years treatment.
§Smoking cessation was given only to smokers: 68% of the age 50 group and 21% of the age 60 group.
‖Antihypertensives were given only to participants with high blood pressure: 27% of the age 50 group and 25% of the age 60 group.

Table 6.3B. Cost-Effectiveness* of Primary Prevention of Cardiovascular Disease in Populations at High Risk†

	Cost per YLS		Cost per HYLS		Costs per Deaths Prevented‡	
Ten-Years Treatment	Age 50	Age 60	Age 50	Age 50	Age 60	Age 60
SC GP Advice§	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
SC Nicotine Substitutes§	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
SC Bupropion§	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
Aspirin	2716	2263	2837	3147	6741	6331
Antihypertensives‖	36399	28187	24210	23723	86086	81493
Statins	85715	73971	43378	46749	229885	211912

Abbreviations: YLS, Year of Life Saved; HYLS, "Healthy" (free of coronary heart disease) Year of Life Saved; CHD, SC, Smoking Cessation; GP, General Practitioner.
* Future effects and costs equally weighted with 4% as discount factor, costs calculated in Euros from 2003
† Moderate risk refers to a ten-year risk of coronary heart disease between >=20%
‡ Calculated at the end of ten years treatment.
§Smoking cessation was given only to smokers: 91% of the age 50 group and 74% of the age 60 group.
‖Antihypertensives were given only to participants with high blood pressure: 82% of the age 50 group and 50% of the age 60 group.

Figure 6.1. Cost Effectiveness of Primary Prevention of Cardiovascular Disease



Incremental Cost-Effectiveness and League Table

In table 6.4 an incremental cost-effectiveness analysis is presented within a league table ranking the four interventions. A cut-off value for the ICER of €20000 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. Smoking cessation with a GP advice is dominated by smoking cessation with bupropion (higher costs, lower effects). Compared to smoking cessation, aspirin is cost-effective for moderate risk populations in the 60 years age group and for high-risk populations irrespective of age. 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 table 6.3 was not sensitive to changing discount factors for either costs or effects (Table 6.5). Using no discounting for effects and costs resulted in lower CERs and using higher discount factors resulted in higher CERs. When we used 4% to discount future costs and left effects undiscounted

Table 6.4. League Table of Primary Prevention of Cardiovascular Disease (Incremental Cost)

	Moderate Risk*				High Risk†			
	Age 50		Age 60		Age 50		Age 60	
Ten-Years Treatment	Costs‡	ICER§	Costs‡	ICER§	Costs‡	ICER§	Costs‡	ICER§
SC Nicotine Substitutes‖	-22	Cost-saving	-6	Cost-saving	-67	Cost-saving	-50	Cost-saving
SC Bupropion‖	-15	8033	-4	6107	-63	2188	-46	2355
SC GP Advice‖	-10	Dominated	-3	Dominated	-24	Dominated	-18	Dominated
Aspirin	260	36207	243	15799	96	9336	73	7213
Antihypertensives¶	472	Dominated	418	Dominated	1256	Dominated	731	Dominated
Statins	4620	488460	4534	287608	4263	287496	4145	171670

Abbreviations: YLS, Year of Life Saved; ICER, Incremental Cost-Effectiveness Ratio; SC, Smoking Cessation; GP, General Practitioner.
* Moderate risk refers to a ten-year risk of coronary heart disease between 10 and <20%
† High risk refers to a ten-year risk of coronary heart disease ≥ 20%
‡ Costs calculated in Euros from 2003, represent net costs per intervention (costs of treatment - cost of events prevented)
§ ICERs are presented in costs per Years of Life Saved
‖ 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
¶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 respectively

Table 6.5. Sensitivity Analysis on the Cost-Effectiveness of Primary Prevention of Cardiovascular Disease

	Cost per YLS* for a population with 50 years age and High Risk†						
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%‡ 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 § Costs and Effects Discounted 4%
SC GP Advice‖	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
SC Nicotine Substitutes‖	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
SC Bupropion‖	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
Aspirin	2087	2461	2856	2716	2716	2716	3655
Antihypertensives¶	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.
* Costs calculated in Euros from 2003
† High risk refers to a ten-year risk of coronary heart disease ≥ 20%
‡ Drug costs reduction of 68% is comparable to the price of Simvastatin in Denmark[29] compared to the price in The Netherlands
§ Adverse effects considered were major gastrointestinal bleeding at an incidence rate of 1% in 10 years.
‖ 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
¶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 respectively

CERs were lower. We choose to present these different combinations of discounting considering the existing controversies and lack of standardization in time preference analysis.[28] Nor was the order of our results altered when different annual relapse rates (20% and 40%) were considered for the three smoking cessation strategies, nor when costs of adverse events were taken into account for aspirin treatment.

When a lower medication cost of statin therapy was included, similar to an off-patent cost of simvastatin, the resulted CER of statin therapy was comparable to the CER of antihypertensive treatment. This lower cost of statin therapy represented a reduction of 68% 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>= 140mmHg 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 option in primary prevention of CVD. Antihypertensive treatment for moderate hypertension is moderately efficient, but statins will have to be a lot cheaper in order 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 non-smokers, 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. 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%.

An important limitation of this study is that prevalence of higher risks than 30% was too small in the Framingham study populations to be able to estimate lifetables, the estimate above which treatment was advocated in most guidelines. While we cannot judge if use of statins in primary prevention at risks above 30% is

efficient, at 20% 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 management, which makes current populations not comparable with populations from the seventies and eighties, 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 non-differential 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. We did not value saved lives after ten years of treatment, but mentioned these 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 statins therapy, our CERs fall within the estimated range for primary prevention of CVD published by Pharoah et al[30] using also a life table approach and a 10 years time horizon. If we transform the saved lives into saved life years by using the residual population life expectancy at age 55 and 65, the CER are comparable to studies using a lifetime horizon (data not shown). However, absolute CER always will be arguable, witnessing the wide range of published estimates. 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.[6 31 32] We decided to use a market share approach and select a single estimate for each strategy since using every potential combination of estimates and specific drugs is beyond the scope of this paper. We used only costs based on current Dutch standards, which limits the generalizability of our results. Except for aspirin, no adverse effects were taking into account in our analysis for the strategies considered, since no evidence of serious complications exists at low or normal dosages. Perhaps in the future, with the advent of a low-cost Polypill (using only generic components), 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. But, in the meantime we have to deal with our current options and design and effective and realistic primary prevention strategy. In conclusion we found that for a cost-effective 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%.

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Appendix 1. Market Share Approach for Statins, Antihypertensives and Nicotine Substitutes.

Market shares for statins and antihypertensives were derived from data of the Rotterdam study.[22]

For statins four medications were included: simvastatin (daily defined dose (DDD) 15 mg), pravastatin (DDD 20 mg), fluvastatin (DDD 40 mg) and atorvastatin (DDD 10 mg). Market shares were determined on the basis of the relative duration of use = $S_i / \sum_{i=1}^{i=4} S_i$, S_i = duration of use of statin i. The duration of use was determined on the basis of the total duration per pack (DDD) multiplied by the number of packs.

The same procedure was followed for the antihypertensives. Only, the list of antihypertensives was longer and a subdivision within the antihypertensives had to be made. This subdivision consisted of: 1) diuretics, 2) beta-blockers, 3) associate

beta-blockers and diuretics, 4) CA antagonists, 5) ACE inhibitors, 6) antihypertensives combinatory diuretics and ACE inhibitors, 7) angiotensin II antagonists and 8) a residual group of remaining antihypertensives.

Three smoking cessation strategies were evaluated. For smoking cessation with nicotine substitutes no market share information could be retrieved. We assumed that chewing gums and skin patches had equal shares (50%). We only included high (dose per day (DPD) 27,5 mg) and low (DPD 13,75 mg) dose chewing gums of two brands and all assumed a market share of 25%. For skin patches it was assumed that brand 1 (DPD 12,86 mg), brand 2 (DPD 12,86 mg) and brand 3 (DPD 16,8 mg) had equal market shares (33,33%).

Medication	**MS (%)**	**CPY*†**	**MC†**
Simvastatin	66,97	574	384,45
Pravastatin	14,63	313	45,78
Fluvastatin	3,50	245	8,58
Atorvastatin	14,90	309	46,12
Medication costs statins			**484,92**
Diuretics	27,24	39,46	10,75
Beta-blockers	28,76	103,44	29,75
Associate beta-blockers and diuretics	1,43	154,04	2,20
CA antagonists	15,66	187,38	29,34
ACE inhibitors	18,87	164,63	31,07
Combinatory diuretics and ACE inhibitors	2,32	233,87	5,42
Angiotensin II-antagonists	2,46	242,06	5,95
Remaining antihypertensives	3,26	507,54	8,30
Medication costs antihypertensives			**122,78**
Low-dose chewing gum brand 1	25	119,47	29,87
High-dose chewing gums brand 1	25	145,45	36,36
Low-dose chewing gum brand 2	25	67,53	16,88
High-dose chewing gums brand 2	25	88,31	22,08
Medication costs chewing gum			*105,19*
Brand 1 Skin patches	33,33	167,79	55,93
Brand 2 Skin patches	33,33	125,70	41,90
Brand 3 Skin patches	33,33	97,66	32,55
Medication costs skin patches			*130,38*
Chewing gum	50,00	105,19	52,60
Skin patches	50,00	130,38	65,19
Medication costs nicotine substitutes			**117,79**

Abbreviations: MS, market share; CPY, cost per year on the basis of DDD; MC, medication costs.
* Cost per year calculated on the basis of Daily Defined Dose (DDD)
† All costs were calculated in euros from October 2003

References

1. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ* 2002;324:1570-6.
2. Jacobson TA. Clinical context: current concepts of coronary heart disease management. *Am J Med* 2001;110 Suppl 6A:3S-11S.
3. 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.
4. Standing Medical Advisory Committee, the use of statins. 1997. www.doh.gov.uk/cmo/statins2.html
5. Raithatha N, Smith RD. Paying for statins. *BMJ* 2004;328:400-2.
6. Marshall T. Coronary heart disease prevention: insights from modelling incremental cost effectiveness. *BMJ* 2003;327:1264.
7. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health* 1951;41:279-81.
8. 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;110:281-90.
9. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293-8.
10. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, 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;333:1301-7.
11. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;282:2340-6.
12. 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;136:161-72.
13. 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;162:2197-202.
14. 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;356:1955-64.

15. 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;278:313-21.
16. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2002:CD000146.
17. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2003:CD000031.
18. Lightwood JM, Glantz SA. Short-term economic and health benefits of smoking cessation: myocardial infarction and stroke. *Circulation* 1997;96:1089-96.
19. Euro-medicines. www.euromedicines.org, 2001. Last visited november 2004.
20. Gezondheidszorg CT. www.ctgzorg.nl. 2004. Last visited november 2004.
21. *Farmacotherapeutisch Kompas: medisch farmaceuthische voorlichting/uitgave van de Commissie Farmaceuthische hulp van het College voor zorgverzerkeringen.* Amstelveen, 2003.
22. 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;7:403-22.
23. van Hout BA, Simoons ML. Cost-effectiveness of HMG coenzyme reductase inhibitors; whom to treat? *Eur Heart J* 2001;22:751-61.
24. Health Insurance Council Report. Dutch guidelines for pharmacoeconomic research 25-23, 1999.
25. Hunink MGM GP, Siegel JE, et al. *Decision making in health and medicine: interpreting evidence and values.* Cambridge, England: Cambridge University Press, 2001.
26. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001;120:594-606.
27. Laupacis A FD, AS Detsky et al. 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;146:473-81.
28. van Hout BA. Discounting costs and effects: a reconsideration. *Health Econ* 1998;7:581-94.
29. Hvad er Danmarks Statistikbank. www.statistikbanken.dk, 2004.
30. 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;312:1443-8.

31. Malik IS, Bhatia VK, Kooner JS. Cost effectiveness of ramipril treatment for cardiovascular risk reduction. *Heart* 2001;85:539-43.
32. Parrott S, Godfrey C. Economics of smoking cessation. *BMJ* 2004;328:947-9.

PART C

Revolutionary concepts on cardiovascular risk management

The Poly-interventions: the Polypill and the Polymeal

"No other preventive method (than the Polypill) would have so great an impact on public health on the Western world" Professor N. Wald, author of the Polypill publication. Wolfson Institute of Preventive Medicine, The Medical College of St Bartholomew's Hospital, London.

7

The Polypill: at what price would it become cost-effective?

Oscar H. Franco, Ewout W. Steyerberg, Chris de Laet. The Polypill: at what price would it become cost-effective? *Submitted.*

Abstract

Introduction:
A promising concept in cardiovascular risk management: "The Polypill" was introduced in 2003. Although the Polypill may appear as an effective intervention, data on its costs and cost-effectiveness remains unknown. The objective of this paper is to determine the maximum price of the polypill in order to be a cost-effective alternative in the primary prevention of cardiovascular disease.

Methods:
Data on the hypothetical effects of the Polypill was taken from the literature. Using data from the Framingham Heart Study and the Framingham Offspring study, we built life tables to model the assumed benefits of the Polypill. Using a third party payer perspective and a 10-years time horizon, we calculated what should be the medication cost of the Polypill in order to be cost-effective (using a 20000€/Year of Life Saved threshold) in the primary prevention of cardiovascular disease among populations at different levels of absolute risk of coronary heart disease and age.

Results:
To be cost-effective among populations at levels of 10-year coronary heart disease risk over 20% (high risk), the annual cost of medication for the Polypill therapy should be no more than €302 or €410 for age 50 and 60 respectively. . For cost-effective prevention in populations at levels of coronary heart disease risk between 10 and 20% the costs should be 2 to 3 times lower.

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

Introduction

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

Pharmacological prevention of cardiovascular disease among populations free of the disease should be inexpensive and have considerable effect to ensure a proper balance between costs and effects (cost-effectiveness).[4] As future implementation of Polypill would target large sections of the world population, the cost of the medication is a relevant issue if we do not want to exhaust the global health budget in a single effort.

The objective of this study is to estimate the maximum cost of medication and treatment with the Polypill in order to be cost-effective among adult male populations free of cardiovascular disease. We considered different levels of 10-year absolute risk of coronary heart disease (CHD) and different ages, to calculate the effects of the Polypill in terms of Years of Life Saved (YLS).

Methods

Data sources

We used data from the Framingham Heart Study (FHS) and the Framingham Offspring Study (FOS). The FHS cohort consisted of 5209 respondents aged 28 through 62 years residing in Framingham, Massachusetts, between 1948 and 1951. Participants have been followed in periods of two years for a total of more than 48 years of follow-up. The FOS cohort is conformed by 5214 participants (the offspring

and their spouses of the original FHS) aged 5 through 70 years at baseline and sampled in 1971. Examination of this cohort has taken place at intervals of four to eight years. Since the study design and measurement instruments used in the original and offspring cohort are similar, we pooled both datasets. Detailed descriptions of the FHS and the FOS can be found elsewhere.[5 6] To obtain recent estimates for 10 year CVD and mortality we used follow-up from 1968 onward. We used therefore data from participants that attended exams 11 (calendar years 1968-71), 15 (1977-79) and 20 (1987-1989) 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. The same participant could therefore be included more than once but for different follow-up periods.[7] In total there were 3742 male participants for the analysis.

Baseline assessment

At baseline participants were classified by level of absolute risk of CHD based on the Anderson Formula[8] and by age group. For the calculation of risk, the Anderson Formula includes: age, gender, systolic blood pressure, smoking status, diabetes, the ratio of total cholesterol/HDL cholesterol and left ventricular hypertrophy (presence on Electrocardiogram). The ratio total cholesterol/HDL cholesterol was missing for 812 participants and was imputed based on the other variables of the formula. Enough data on the variables required for the calculation of risk was available in 3332 participants. Subjects were categorized into 3 groups based on their level of 10-year absolute risk of CHD: Low-risk <10% (2396 participants), moderate-risk 10 to <20% (714 participants) and high-risk ≥ 20% (222 participants). Participants were categorized in two age groups: 45 to 55 and 55 to 65.

Efficacy of the Polypill

The effects of the Polypill on CVD were taken from the paper published by Wald and Law.[3] To translate the effect of the Polypill reduction on CHD and stroke in terms of Years of Life Gained (YLG) we created Multi State Life Tables (MSLTs) starting at age 50 years and closing at age 100 years, and using a ten-year time horizon. Effects occurred after 10 years were not taken into consideration.

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

Costs

Costs were calculated for the Netherlands and included direct medical costs taken from the literature, the World Wide Web and Dutch registries.[9-11] A visit to the general practitioner (GP) costs €26, a blood sample test €12, a prescription renewal €13 and each pharmacist's fee €7. Based on current Dutch guidelines for statin and antihypertensives treatment, we assumed that treatment with the Polypill should include per year two GP visits (€53) two prescription renewals (€26) four pharmacist's fees (€28) and one blood analysis (€13). The minimum (without medication costs) annual cost of treatment with the Polypill would hence be: €120. To this basic annual cost, the cost of the medication should be added and the objective of this study is to estimate what the maximum cost of the Polypill should be in order to be cost-effective for primary prevention of CVD.

The costs of events were taken from the literature and were restricted to direct medical costs. Costs per event were for non-fatal myocardial infarction (MI) €6972, for fatal MI €1602, for non-fatal stroke €11870 and for fatal stroke prevented €3851.[12]

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

Cost-effectiveness and expected annual cost of the Polypill

All future costs and effects were calculated using a third party payer perspective and discounted using the currently nationally recommended nominal discount rate of 4% per year (for both costs and effects)[13], in order to take into account time preference. This implies that effects and costs occurring in the future are weighted less that those occurring in the present.[14] The time horizon used for costs and effects was 10 years and the cost-effectiveness ratio (CER) was calculated as extra medical costs per year of life saved.

Labelling cost-effectiveness ratios (CERs) under €20000 per YLS as "cheap", over €40000 as "expensive" and "negative" CERs as "cost saving", we estimated what should be the maximum annual cost of the medication (Polypill) in order to produce cheap CERs, expensive CERs and cost savings.[15 16] We used the effects of the Polypill in terms of YLS and the basic cost of treatment, to calculate backwards what should be the annual medication costs. The calculations were repeated for the different levels of absolute risk of CHD ("moderate" and "high") and age groups (45 to 55 and 55 to 65 years). Additionally, we evaluated how cost-effective would the Polypill be if its price were comparable to the current price of aspirin or statins in the Netherlands.[9 11]

Confidence intervals for the price of medication were estimated by using the confidence intervals of the event reduction effect as published by the authors of the Polypill.[3] All survival analyses were performed using STATA version 8.2 for windows (Stata corporation, college station TX, USA, 2003). MSLTs were made using Excel spreadsheets.

Results

Efficacy of the Polypill

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

Ten-year effects of the Polypill

The Polypill represented large gains in terms of Years of Life Saved (YLS) that ranged between 80 and 200 per 1000 participants treated with the Polypill during 10 years (Table 7.1). In terms of events prevented, giving the Polypill to 1000 people would theoretically prevent from 85 to 179 CHD events and 15 to 33 strokes.

As expected, the larger the level of CHD risk –and/or higher age- the higher the gains obtained secondary to the Polypill treatment.

Acceptable Cost of the Polypill by Level of Cost-Effectiveness

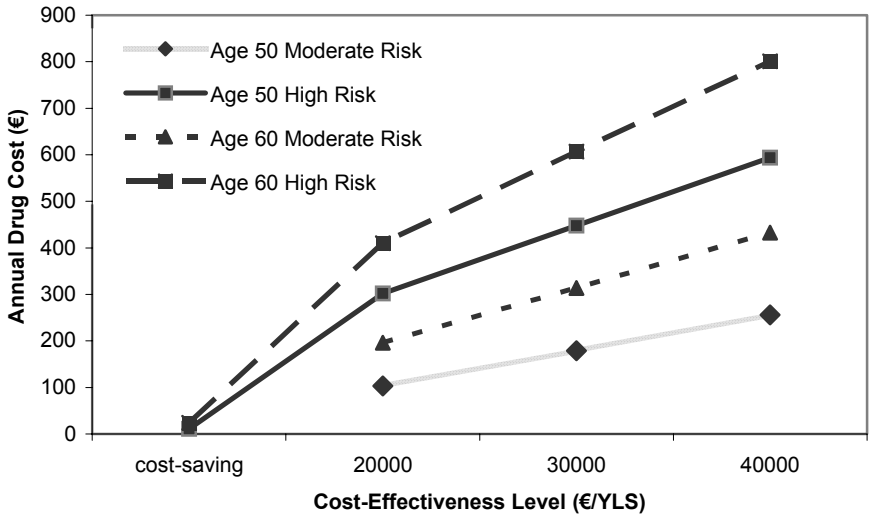
The acceptable cost of the Polypill depended on the levels of CHD risk and age of the population. (Figure 7.1)

Table 7.1 Effects of Ten-Years Intervention with the Polypill in the Primary Prevention of Cardiovascular Disease*

	Moderate Risk†		High Risk‡	
Ten-Years Treatment	Age 50	Age 60	Age 50	Age 60
Undiscounted YLS	80	120	150	200
Discounted (by 4%) YLS	60	100	120	150
Total CHD (fatal and non-fatal) events prevented	90	85	167	179
Total Stroke (fatal and non-fatal) events prevented	15	33	24	31

Abbreviations: YLS, Years of Life Saved; CHD, Coronary Heart Disease.
* Effects presented by 1000 participants treated with the Polypill.
† Moderate risk refers to a ten-year risk of coronary heart disease between 10 and <20%
‡ High risk refers to a ten-year risk of coronary heart disease ≥ 20%

Figure 7.1 Maximum Annual Cost of the Polypill for Different Cost-Effectiveness Levels



Even if the Polypill would be offered for free no cost-savings would be achieved if the intervention were implemented in populations at moderate levels of risk. (Table 7.2) For populations at high levels of risk, the annual cost of the medication should be below €24 in the case of males under 60 years of age and €11 for those under 50, in order to be cost-saving. To be cost-effective at 20000€/YLS among populations at high levels of risk, the Polypill should cost no more than €302 and €410 for age 50 and 60 respectively. For populations at moderate levels of risk

Table 7.2 Maximum Annual Cost of the Polypill by Age Group and Level of CHD Risk*

Cost-Effectiveness Ratio	Age 50		Age 60	
	Moderate Risk† Cost (95% CI)	High Risk‡ Cost (95% CI)	Moderate Risk† Cost (95% CI)	High Risk‡ Cost (95% CI)
Cost-Saving	N.Q	11 (3 to 17)	N.Q	24 (14 to 30)
€20000/YLS	103 (94 to 110)	302 (288 to 314)	196 (181 to 207)	410 (389 to 429)
€30000/YLS	179 (167 to 188)	448 (428 to 462)	314 (294 to 329)	607 (577 to 629)
€40000/YLS	256 (241 to 267)	594 (570 to 611)	433 (407 to 450)	801 (764 to 829)

Abbreviations: YLS, Year of Life Saved; CHD, Coronary Heart Disease; N.Q. Non-quantifiable.
* Costs calculated in Euros from 2003, represent only medication costs.
† Moderate risk refers to a ten-year risk of coronary heart disease between 10 and <20%
‡ High risk refers to a ten-year risk of coronary heart disease ≥ 20%

Table 7.3 Expected Cost-Effectiveness of the Polypill Corresponding to Different Levels of Annual Medication Cost by Age Group and Level of CHD Risk*

	Age 50		Age 60	
Annual Cost of Medication*	Moderate Risk† CER (€/YLS)	High Risk‡ CER (€/YLS)	Moderate Risk† CER (€/YLS)	High Risk‡ CER (€/YLS)
28 (Similar to Aspirin)	10100	1100	5700	230
574 (Similar to Statins)	81600	38600	52000	28200

Abbreviations: YLS, Year of Life Saved; CHD, Coronary Heart Disease; CER: Cost-effectiveness Ratio.
* Costs calculated in Euros from 2003, represent only medication costs.
† Moderate risk refers to a ten-year risk of coronary heart disease between 10 and <20%
‡ High risk refers to a ten-year risk of coronary heart disease ≥ 20%

the acceptable cost would be 2 to 3 times lower. Annual medication costs of the Polypill over €600 or €800 would correspond to high CERs (>40000€/YLS) in high risks populations aged 50 and 60 respectively.

If the Polypill would cost as much as aspirin its cost-effectiveness would range between 235€/YLS and 10100€/YLS (Table 7.3). On the other hand if the Polypill would cost as much as statins its cost-effectiveness would be over 20000€/YLS in all scenarios (Table 7.3).

Discussion

In order to be cost-effective in general populations free of CVD, the cost of the medication for Polypill therapy should not exceed €400 at age 60 and €300 at age 50. These costs are 10 times the cost of aspirin therapy but three quarters the cost of statin treatment.[9-11]

Since aspirin and statins are two of the constituents of the Polypill, it could be expected that the medication's costs for the Polypill could be in this price range or even higher.

Our analyses showed that, even when the effects of the Polypill on life expectancy would be large, the treatment costs are critical to make prevention cost-effective. The cost-effectiveness of the Polypill will vary according to the levels of CVD risk in the populations as well as the age. If the Polypill wants to compete effectively with established interventions in primary prevention like aspirin and smoking cessation with nicotine replacement, it will first have to prove to be much more effective in clinical trials. But, it will also need to be offered in the market at a lower price than the current price of one of its components: statins. The case in secondary prevention of CVD might be different since this implies treating

populations with already existing CVD that in consequence are at higher levels of risk. Prevention of events in these populations is known to be more cost-effective than treating healthy subjects.

Our cost-effectiveness ratios and costs of medication calculated are conservative. Although our cost-effectiveness ratios are calculated using a third party payer perspective, we did not include savings in terms of invasive interventions (Coronary Artery Bypass Grafting or Percutaneous Transluminal Coronary Angioplasty) that could be achieved with Polypill therapy. The basis of this decision is the constant change in CVD management; the populations we used for our analyses are from the seventies and eighties when treatment of cardiovascular disease included less invasive procedures than currently.
Also we selected a 10-year time horizon and considered no effects (or costs) beyond this period. This could also contribute to underestimation of potential savings from taking the Polypill.

Although savings could be underestimated, the effects of the Polypill as calculated by the Polypill's authors could be overestimated and are at the moment only theoretical. A multiplicative assumption is made on the risk reduction effects of the components of the Polypill, and larger levels of risk reduction are assumed compared to previous evidence on the same components.[17] [18] There is no real evidence on the effects of the Polypill in terms of clinical trials and this is a requirement before we can seriously think of the Polypill as an alternative to prevent cardiovascular disease. Furthermore, adverse effects could also limit the usability; it is unknown how the components of the Polypill will interact when put together in the same presentation and only large randomised controlled trials with long follow-up will provide answers to these questions.

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

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References

1. Jacobson TA. Clinical context: current concepts of coronary heart disease management. *Am J Med* 2001;110 Suppl 6A:3S-11S.
2. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ* 2002;324(7353):1570-6.
3. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326(7404):1419.
4. Marshall T. Coronary heart disease prevention: insights from modelling incremental cost effectiveness. *BMJ* 2003;327(7426):1264.
5. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health* 1951;41(3):279-81.
6. 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(3):281-90.
7. Cupples LA, D'Agostino RB, Anderson K, Kannel WB. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. *Stat Med* 1988;7(1-2):205-22.
8. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991;121(1 Pt 2):293-8.
9. Euro-medicines. www.euromedicines.org, Last time visited november 2004.
10. College Tarieven Gezondheidszorg. www.ctgzorg.nl. Last time visited september 2004.
11. *Farmacotherapeutisch Kompas: medisch farmaceuthische voorlichting/uitgave van de Commissie Farmaceuthische hulp van het College voor zorgverzerkeringen.* Amstelveen, 2003.
12. van Hout BA, Simoons ML. Cost-effectiveness of HMG coenzyme reductase inhibitors; whom to treat? *Eur Heart J* 2001;22(9):751-61.

13. Health Insurance Council Report. Dutch guidelines for pharmacoeconomic research 25-23, 1999.
14. Hunink MGM GP, Siegel JE, et al. *Decision making in health and medicine: interpreting evidence and values.* Cambridge, England: Cambridge University Press, 2001.
15. Laupacis A FD, AS Detsky et al. 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(4):473-81.
16. Mark D. *Medical Economics in Cardiovascular Medicine. In: Topol EJ, ed. Textbook of Cardiovascular Medicine.* New York: Lippincott-Raven, 1997.
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(24):2340-6.
18. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326(7404):1423.

8

Mixing up evidence of statins with beliefs in cholesterol

Oscar H. Franco, Luc Bonneux. Mixing up evidence with beliefs in cholesterol. (Letter to the editor, BMJ)
http://BMJ.BMJjournals.com/cgi/eletters/326/7404/1423

Mixing up evidence of statins with beliefs in cholesterol

The article of Law et al[1] heaped up all evidence on the cholesterol lowering properties of statin therapy for cardiovascular risk management. Strangely, the reductions of hard disease events, as observed in major trials and compiled in a meta-analysis,[2] figure only in footnote.

Cohort studies studying correlations of cholesterol with mortality are not randomised clinical trials (RCT) of statins. A cohort involves people, whose cholesterol level is one of many risk factors predicting heart disease, some known, some unknown, to which these people are exposed for life. A RCT observes the unconfounded effects of statins, a drug with manifold and uncertain activities, in randomised populations.

The history of female hormone replacement therapy in the prevention of vascular disease must not be forgotten: a wealth of observational evidence of benefit, but only experimental evidence of harm. Equating short-term effects of complex drugs with poorly understood effects such as statins with lifelong correlations of LDL with CHD mortality shows a naive belief in simplistic linear models. [3]

And why would we wish to calculate the health effects of a belief, if we have hard data? In table 3, Law et al show convincingly, once more, that the observed risk reduction in coronary heart disease is nearly constant and somewhat over 30% for all time periods of three years and more. Reductions in stroke incidence are supported by the same hard evidence[4 5]. There is little evidence that event reduction by statin use differ either by type of drug, duration taken (after 2 years of use) or dose. Only in the 4S trial reductions over 40% have been observed in MI survivors with increased cholesterol and very high risks. Evidence of benefits even higher than this do not exist. Why would we want to exaggerate the great benefits of statins?

Indeed, if this issue of the BMJ is worth keeping, it is as an historical example of the dangers of extrapolation. Extrapolate LDL cholesterol into nothingness, and eradicate 99.9% of coronary heart disease. Extrapolate one century of world records of the 100 m sprint into the far future, and in thousand years we will run 100 meter in less than 1 second.

References

1. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326(7404):1423.
2. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;282(24):2340-6.
3. Libby P, Aikawa M. Mechanisms of plaque stabilization with statins. *Am J Cardiol* 2003;91(4A):4B-8B.
4. Corvol JC, Bouzamondo A, Sirol M, Hulot JS, Sanchez P, Lechat P. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. *Arch Intern Med* 2003;163(6):669-76.
5. 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(4):313-21.

9

The Polymeal: a more natural, safe and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%

Oscar H. Franco, Luc Bonneux, Chris de Laet, Anna Peeters, Ewout W. Steyerberg, Johan P. Mackenbach. The Polymeal: a more natural, safe and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. *BMJ. 2004 Dec 18; 329(7480): 1447-50.*

Abstract

Introduction:
Although the Polypill concept (proposed in 2003) is promising in terms of benefits for cardiovascular risk management, the potential costs and adverse effects are its main pitfalls. The objective of this study was to identify a tastier and safer alternative to the Polypill: the Polymeal.

Methods:
Data on the ingredients of the Polymeal were taken from the literature. The evidence-based recipe included: wine, fish, dark chocolate, fruits, vegetables, garlic and almonds. Using data from the Framingham Heart Study and the Framingham Offspring study, we built life tables to model the benefits of the Polymeal in the general population from age 50, assuming multiplicative correlations.

Results:
Combining the ingredients of the Polymeal would reduce cardiovascular disease events by 76%. For men, taking the Polymeal daily represented an increase in total life expectancy of 6.6 years, an increase in life expectancy free from cardiovascular disease of 9.0 years, and a decrease in life expectancy with cardiovascular disease of 2.4 years. The corresponding differences for women were 4.8, 8.1, and 3.3 years.

Conclusion:
The Polymeal promises to be an effective, non-pharmacological, safe, cheap and tasty alternative to reduce cardiovascular morbidity and increase life expectancy in the general population.

Introduction

Cardiovascular disease continues to be the leading cause of mortality and morbidity in western populations.[1] Although several risk factors for cardiovascular disease have been identified, its prevention is still suboptimal owing to high costs, low compliance and side effects of treatment. In 2003 Wald and Law introduced the concept of the Polypill.[2] The advocates of the Polypill selected six pharmacological components that by modifying different risk factors of cardiovascular disease multiplicatively might reduce the levels of cardiovascular disease in the population by more than 80%.[2] In general, the medical community has welcomed the concept but also questioned the potential adverse effects and costs of such an intervention.[3-5]

Our objective was to define a safer, non-pharmacological, and tastier alternative to the Polypill in the general population: the Polymeal. We also wanted to calculate the potential effects of the Polymeal in terms of total life expectancy and life expectancy with and without cardiovascular disease.

Methods

The recipe

To optimise the Polymeal-ingredients we used an evidence based diet conceptual framework, which follows similar principles to evidence based medicine.[6] The constituting elements of a meal or recipe are selected on the basis of the best available evidence; the evidence available for each ingredient is graded according to the level of evidence. We searched PubMed, informed by expert advice, for non-pharmacological ingredients with evidence levels 1 or 2: randomised controlled trials, meta-analyses of randomised controlled trials and meta-analyses of observational studies.[7] To be included in the Polymeal, the ingredient had to have individually reported effects (not as an element of a diet) on reduction in cardiovascular disease events or modification of risk factors for cardiovascular disease. We checked papers retrieved for further possible ingredients. The following dietary elements met the inclusion criteria to be ingredients of the Polymeal: wine, fish, dark chocolate, fruits and vegetables, almonds and garlic (Allium sativum).

Efficacy of the Polymeal

We obtained information from the literature on the benefits of the interventions (table 1). Daily consumption of 150ml of wine reduces cardiovascular disease by 32% (95% confidence interval 33% to 41%).[8] Fish (114 grams) consumed four times

a week reduces cardiovascular disease by 14% (8% to 19%).[9] For chocolate, fruits and vegetables, almonds and garlic we found data on modification of risk factors for cardiovascular disease. One hundred grams of dark chocolate consumed daily reduces systolic blood pressure by 5.1 mmHg and diastolic blood pressure by 1.8 mmHg, [10] similar reductions on blood pressure correspond to a reduction on cardiovascular disease events of 21% (14% to 27%).[11] A total of 400 grams of fruit and vegetables consumed daily, produced a reduction on blood pressure similar to that observed with chocolate (4.0 mm Hg systolic blood pressure and 1.5 mm Hg diastolic blood pressure), so we decided to assume the same reduction of cardiovascular disease effect as assigned for chocolate (21%).[12] Daily garlic consumption reduced total cholesterol concentrations by 0.44 mmol/L (17.1mg/dl),[13] [14] corresponding to 66% of the reduction (0.66 mmol/L) that was found to be associated with a 38% reduction in cardiovascular disease at age 50.[15] Therefore we considered 66% of the effect previously reported and assumed for garlic a reduction of 25% (21.7% to 27.7%) in cardiovascular disease events. Most of the randomised controlled trials included in the meta-analysis used 600 to 900 mg/day of dried garlic powder preparations, equivalent of 1.8 to 2.7 g/day of fresh garlic.[16] We selected 2.7 g/day of fresh garlic for the Polymeal. Consuming 68 g/day of almonds produced half the reduction in total cholesterol (10mg/dl) observed with garlic,[17] [18] so we assumed a reduction in cardiovascular disease half the one assigned to garlic.

We calculated the combined effect of the ingredients of the evidence-based diet Polymeal by multiplying their correspondent relative risk estimates. This is the same method that was used for the Polypill.[2]

Study population

We applied the effects of the Polymeal to a life-table built using the Framingham study population. The original Framingham heart study cohort consisted of 5209 respondents (2336 men) residing in Framingham, Massachusetts between 1948 and 1951. Participants have been examined biannually, and the cohort has been followed for 46 years.[19]

We used follow up data from participants attending study examinations 4 (1956-8), 11 if present or otherwise 12 (1969-73) and 19 if present or otherwise 20 (1985-9). Follow up started at the date of the chosen baseline examination. Each participant could therefore be included more than once but for different follow-up periods of no more than 12 years in order to avoid overlapping periods. A total of 9181 participants-observation periods of follow up were available for the analysis.

We used 3 endpoints in this study: the composite endpoint of incident non-fatal cardiovascular disease (angina, coronary insufficiency, myocardial infarction,

congestive heart failure, stroke, transient ischaemic attack and intermittent claudication), fatal cardiovascular disease, and other causes of death. In the Framingham heart study a panel of 3 physicians evaluated all events (fatal and non-fatal); agreement of all three was needed.[20]

We selected total cardiovascular disease as outcome (and not coronary heart disease and stroke separated) on the basis of current recommendations in the European guidelines on cardiovascular disease prevention.[21]

Effects of The Polymeal on Life Expectancy and Time with Cardiovascular Disease

To translate the effects of the Polymeal on reduction of cardiovascular disease events (table 1) in terms of differences in life expectancy and life expectancy with and without cardiovascular disease, we created multi-state life tables starting at age 50 years and closing at 100 years of age. We stratified the multi-state life tables by sex and created them separately for the general population with and without the Polymeal. The multi-state life tables included three different states: 'free from cardiovascular disease', 'history of cardiovascular disease' and 'death'. The possible transitions were from 'free from cardiovascular disease' to 'history of cardiovascular disease' or 'death' and from 'history of cardiovascular disease' to 'death'. [22] In the life tables representing the population with the Polymeal, we derived the effects by decreasing the rates for the transitions 'free from cardiovascular disease' to 'history of cardiovascular disease' and 'history of cardiovascular disease' to 'death' by the estimated risk reduction associated with the Polymeal. We used Excel spreadsheets for all analyses.

Results

Effects of the Polymeal

Combining all the ingredients of the Polymeal resulted in cardiovascular disease being reduced by 76% (95% confidence interval 63% to 84%) (Table 9.1). Whether increasing the amount of each ingredient will increase the effect of the Polymeal is uncertain. On the other hand decreasing the quantities could be expected to reduce the effects of the Polymeal. Omitting wine from the Polymeal had the strongest effect on the risk reduction of cardiovascular disease (from 76% to 65%). Excluding any of the other ingredients had a lesser effect: 73% reduction without fish, 70% without chocolate or fruits and vegetables, 68% without garlic and 72.5% without almonds.

Table 9.1 Risk reduction effect of ingredients of Polymeal in prevention of cardiovascular disease

Ingredients	Percentage reduction (95% CI) in risk of CVD	Source
Wine (150 ml/day)	32 (23 to 41)	Di Castelnuovo et al (MA)[8]
Fish (114 g four times/week)	14 (8 to 19)	Whelton et al (MA)[9]
Dark chocolate (100 g/day)	21 (14 to 27)	Taubert et al (RCT)[10]
Fruit and vegetables (400 g/day)	21 (14 to 27)	John et al (RCT)[12]
Garlic (2.7 g/day)	25 (21 to 27)	Ackermann et al (MA)[13]
Almonds (68 g/day)	12.5 (10.5 to 13.5)	Jenkins et al (RCT),[17] Sabate et al (RCT)[18]
Combined effect	76 (63 to 84)	

CVD=cardiovascular disease; MA=meta-analysis; RCT=Randomised controlled trials.

Lifetime effects of the Polymeal

The effect of the Polymeal represented a large increase in total life expectancy and life expectancy free of cardiovascular disease and a decrease in life expectancy with cardiovascular disease for both men and women (Table 9.2). For men, taking the Polymeal will result in increases of 6.6 years in total life expectancy and 9.0 years in life expectancy free of cardiovascular disease. The decrease in life expectancy with cardiovascular disease attributable to the Polymeal was 2.4 years. The reductions were similar for women, although the magnitudes were lower. (Table 9.2).

Adverse effects

No proved serious adverse effects were reported in any of the papers selected. For garlic in addition to body odour, some unproven adverse effects were mentioned: flatulence, oesophageal and abdominal pain, allergic reactions and bleeding.[13] Fish consumed in larger amounts than recommended as part of the Polymeal has been related to elevated blood mercury concentrations, especially with large fish such as shark and swordfish.[9]

Table 9.2 Lifetime effect (years) of Polymeal at age 50, stratified by sex

	Total life expectancy		Life expectancy free from CVD		Life expectancy with CVD	
Intervention	Effect	Difference	Effect	Difference	Effect	Difference
Men						
None (overall)	28.7	Ref	21.0	Ref	7.7	Ref
Polymeal	35.2	6.6	30.0	9.0	5.3	–2.4
Women						
None (overall)	34.2	Ref	26.9	Ref	7.3	Ref
Polymeal	39.0	4.8	35.0	8.1	4.0	–3.3

CVD=cardiovascular disease; Ref=reference.

No association was reported between wine consumption at the level included in the Polymeal and increased risk of breast cancer by the authors of the papers included in our analyses.[8]

Discussion

The Polymeal is an effective, natural, probably safer and tastier alternative to the Polypill to reduce cardiovascular disease and increase life expectancy in the general population. The effect was consistent in both men and women at age 50. Adverse effects reported for garlic include malodorous breath and body odour.[13] As garlic is destined for mass treatment, few people will still notice this after a while. No additional adverse effects should be expected from the other ingredients of the Polymeal (in the quantities recommended here) except in people who are allergic to the components. Another advantage of the Polymeal is that its ingredients can be taken combined as a meal or individually at different times of the day. Taking the Polymeal on a daily basis (fish two to four times per week) should be feasible, considering that the ingredients are generally well tolerated and appreciated among the general population. The development and distribution of specific recipes combining the Polymeal ingredients could enhance the compliance of the population.

Costs and precautions

Although the exact price of the Polymeal is unknown and will be country-specific, it could be expected to be similar to or perhaps higher than that of the Polypill. By checking a local supermarket in Rotterdam, The Netherlands, we estimated a total price for the Polymeal of €21.6 a week (€3.50 for the wine, €6.23 fruits and vegetables, €2.80 for almonds, €4.34 for dark chocolate, €0.14 for garlic and €4.60 for the fish). Although we do not recommend particular brands, spending more - for example, on your favourite bottle of wine or brand of chocolate - might also be rewarded by an improved quality of life.

The Polymeal should not be combined with additional consumption of alcohol, in order to avoid intoxication and conflicts with friends, relatives, and authorities; furthermore additional alcohol consumption could attenuate the effects of the Polymeal and negatively influence other health parameters. We also recommend that driving motor vehicles performing activities that require high levels of attention shortly after the consumption of the Polymeal should be avoided. Moreover considering the disturbing adverse effects of garlic, we do not recommend

taking the Polymeal before a romantic rendezvous, unless the partner also complies with the Polymeal.

Although we believe our search was comprehensive and we looked for additional ingredients to include in the Polymeal, we found no other potential components with a sufficient level of evidence or with clearly reported effects on cardiovascular disease events or on modification of risk factors of cardiovascular disease. It is possible that some other ingredients could be added to the Polymeal (olive oil, echium oil, soy oil, soya beans, tomatoes, oat bran, cereals, nuts, tea, chickpeas, and so on) but this will only improve its effect on cardiovascular disease risk reduction.

Concerns about the validity of the source evidence and the multiplicative model used to calculate effects of the ingredients of the Polymeal might be raised. However, these are shared by the Polypill analyses, as we used a similar approach. None the less, a greater possibility of interaction exists between the dietary factors, as less information is available about underlying mechanisms of action. This might result in an overestimation of the effect of the Polymeal.

Another potential limitation of our study is that no back flows are allowed in the multi-state life tables, and only the first entry into a state considered. This is not always seen in real patterns of morbidity and mortality.

No contraindications to combining the Polymeal with additional interventions seem to exist. After the daily consumption of the Polymeal, for example, half an hour of walking could prevent further cardiovascular disease events. For those people wishing to prevent cardiovascular disease most aggressively, the Polypill can be combined with the Polymeal. The fortification of flour with Polypill ingredients: a statin, two anti-hypertensives instead of three, folic acid and aspirin certainly merit further study. Redundant cardiologists could be retrained as Polymeal chefs and wine advisers.

Conclusions

The preventive strategy outlined here is radical. But the “healthy person” is an outdated concept from the era before scientific prevention. We should recognise that in Western society we all have cardiovascular risk factors, so everyone is at risk, and that diseases they cause are common and often fatal. It may be argued that the Polypill is still more effective, but the Polymeal promises to be an effective, non-pharmacological, safe and tasty alternative for reducing cardiovascular morbidity and increasing life expectancy in the general population.

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References

1. Gluckman TJ, Baranowski B, Ashen MD, Henrikson CA, McAllister M, Braunstein JB, et al. A practical and evidence-based approach to cardiovascular disease risk reduction. *Arch Intern Med* 2004;164:1490-500.

2. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419.

3. Messori A, Santarlasci B, Trippoli S, Vaiani M. "Polypill" to fight cardiovascular disease: cost effectiveness of statins for primary prevention of cardiovascular events is questionable. *BMJ* 2003;327:808-9; discussion 809; author reply 809-10.

4. Midgley AK. "Polypill" to fight cardiovascular disease: old joke has element of truth. *BMJ* 2003;327:808; discussion 809; author reply 809-10.

5. Ramos F. "Polypill" to fight cardiovascular disease: birthday present was much appreciated. *BMJ* 2003;327:808; discussion 809; author reply 809-10.

6. Sacket DL SS, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based medicine: how to practice and teach EBM.* New York: Churchill Livingstone, 2000.

7. Medicine OCfE-b. Levels of evidence and grades of recommendation. Oxford Centre for Evidence-based Medicine. Available at http://www.cebm.net/levels_of_evidence.asp. Accesed August 5, 2004.

8. Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G. Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation* 2002;105:2836-44.

9. Whelton SP, He J, Whelton PK, Muntner P. Meta-analysis of observational studies on fish intake and coronary heart disease. *Am J Cardiol* 2004;93:1119-23.

10. Taubert D, Berkels R, Roesen R, Klaus W. Chocolate and blood pressure in elderly individuals with isolated systolic hypertension. *JAMA* 2003;290:1029-30.
11. 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;356:1955-64.
12. John JH, Ziebland S, Yudkin P, Roe LS, Neil HA. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. *Lancet* 2002;359:1969-74.
13. Ackermann RT, Mulrow CD, Ramirez G, Gardner CD, Morbidoni L, Lawrence VA. Garlic shows promise for improving some cardiovascular risk factors. *Arch Intern Med* 2001;161:813-24.
14. Silagy C, Neil A. Garlic as a lipid lowering agent--a meta-analysis. *J R Coll Physicians Lond* 1994;28:39-45.
15. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;308:367-72.
16. Berthold HK, Sudhop T, von Bergmann K. Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial. *JAMA* 1998;279:1900-2.
17. Jenkins DJ, Kendall CW, Marchie A, Parker TL, Connelly PW, Qian W, et al. Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: a randomized, controlled, crossover trial. *Circulation* 2002;106:1327-32.
18. Sabate J, Haddad E, Tanzman JS, Jambazian P, Rajaram S. Serum lipid response to the graduated enrichment of a Step I diet with almonds: a randomized feeding trial. *Am J Clin Nutr* 2003;77:1379-84.
19. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health* 1951;41:279-81.
20. Stokes J, 3rd, Kannel WB, Wolf PA, Cupples LA, D'Agostino RB. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham Study. *Circulation* 1987;75:V65-73.
21. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, 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;24:1601-10.

22. Peeters A, Mamun AA, Willekens F, Bonneux L. A cardiovascular life history. A life course analysis of the original Framingham Heart Study cohort. *Eur Heart J* 2002;23:458-66.

23. US Department of Health and Human Services. Physical Activity and Health: A Report of the Surgeon General. Atlanta, Ga: US Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, 1996.

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General discussion

"Unless current trends are halted or reversed, over a billion people will die from cardiovascular disease in the first half of the 21st century. The large majority will be in developing countries and much of the life years will be lost in middle age. This would be an enormous tragedy, given that research in the last half of the 20th century showed that cardiovascular disease was largely preventable" Anthony Rodgers, Clinical Trials Research Unit, University of Auckland, New Zealand, 2004.

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide. It is on the rise and has become a true pandemic that respects no borders.[1] The studies presented in this thesis not only confirm the deleterious effects related with certain risk factors for CVD but also illustrate that these effects have been underestimated – in the case of hypertension[2 3] - and the relevance of adequate treatment should be underlined. However our society is limited in resources and costs cannot be forgotten in any CVD risk management program.[4] Our results show that medicaments such as statins although effective, are an expensive option (even off-patent) to prevent CVD in populations at low to moderate risk of CVD and additional alternatives such as lifestyle modification should be considered first. Due to its costs, statins should be reserved for individuals with high risk of heart disease.

Future combinations of medicaments under a single presentation (the Polypill)[5] could solve current insufficiencies of CVD risk management. The Polypill promises to be a good alternative for CVD risk management in the general population, however its possible costs and adverse effects are unknown and could be its caveats. In the studies presented in this thesis the potential cost of this theoretical Polypill are evaluated. We also proposed a non-pharmacological alternative to further reduce global CVD: The Polymeal.[6] On the whole, our results contribute to current epidemiological knowledge, prevention and treatment of CVD, and answer the three principal research questions of this thesis (introduced in Chapter one).

Summary of results to the main research questions

Question 1: What is the effect of risk factors for cardiovascular disease such as physical inactivity and hypertension, in terms of life expectancy and years lived with and without cardiovascular disease?

Physical activity and hypertension are traditional risk factors for CVD. However the evidence of their effect on life expectancy (LE) with and without CVD was inexistent or scarce. Using data from the Framingham Heart Study[7] in combination with multi-state life table analyses, we calculated the effect of these two risk factors for CVD on total LE and LE with/out CVD.

We found that total life expectancy for sedentary people at age 50 is one and a half years less than for people conducting moderate daily physical activity and over three and a half years less than for people with high physical activity levels. Sedentary people also experience one and three years less free of CVD compared with people

at moderate and high levels of activity, respectively. These differences are similar for both sexes.

In the case of hypertension, we found that increased levels of blood pressure (BP) at age 50 are associated with largely decreased total LE and LE free of CVD, and increased number of years lived with CVD, MI and stroke, for men and women similarly. For hypertensives the decrease in total LE was 5 years compared to normotensive participants and irrespective of sex. The reductions in LE free of CVD for hypertensives were 7.2 years in both sexes. Besides living less, hypertensives (≥140 mm Hg SBP/≥90 mm Hg DBP) lived over two years more with CVD compared to normotensives. Also for participants with high-normal BP (120-139 mm Hg SBP or 80-89 mm Hg DBP) compared to normotensives there was a decrease in LE free of CVD and an increase in LE with CVD but almost half that observed among hypertensives.

Question 2: What is the cost-effectiveness of various strategies for cardiovascular risk management and which one is the most cost-effective in the primary prevention of CVD?

This question is addressed in chapters 4, 5 and 6 of this thesis. First, due to the existing controversies about cholesterol-lowering therapy (statins)[8 9] we conducted a systematic review of the existing cost-effectiveness analyses on statins for CVD management. We aimed to pool the published cost-effectiveness ratios by levels of absolute risk of coronary heart disease (CHD) in order to find a single cost-effectiveness ratio per level of risk. Due to the high level of heterogeneity found among the studies selected, the interpretation of pooled estimates was limited and therefore we decided to focus on explaining the reasons behind this heterogeneity. We created a regression model in order to identify potential variables responsible for the existing heterogeneity and also to pool the cost-effectiveness ratios correcting for the level of absolute risk of CVD. Our pooled estimates show values of $21571/YLS for a 10-year CHD risk of 20 % and $16862/YLS for 10-year risk of 30 %. We found that nearly all studies agree that treatment at high levels of risk is cost-effective and at low levels is expensive. But in practice, it is not difficult to find cost-effectiveness ratios that fit any decision for the population at large with intermediate annual risk of CHD (1% to 4%). The most likely explanation for these differences lies in the applied methodology. The impact of funding source suggests the potential for some estimates to be biased. It was very difficult to pinpoint all the divergent model assumptions that caused the variability.

Further standardization of methodology for economic analyses and greater transparency in the presentation of results would aid in the evaluation of potential sources of bias, as well as facilitate reproducibility. Based on our pooled estimates from the selected studies we conclude that statins are a cost-effective alternative for CVD risk management in populations with high absolute risk of CHD. For general populations free of heart disease and at moderate and low levels of risk the answer to this question remains unclear due to the ample heterogeneity found between the selected studies.

Due to the limitations found in the existing literature about statins therapy, we conducted our own cost-effectiveness analysis of statins for CVD risk management in chapter 6. Additionally, we compared statin therapy with other key interventions for the primary prevention of CVD.

Four therapies constitute the basis of CVD risk management in populations without CVD or diabetes: cholesterol modification, blood pressure (BP) lowering, anti-platelet aggregation therapy and smoking cessation.[8 10] A large range of populations might benefit from these risk-lowering treatments.[10] However, treating large populations asks for large investments and priority setting is mandatory.[4] We aimed to calculate and compare the cost-effectiveness of four risk-lowering treatments (aspirin, antihypertensives, statins and smoking cessation) in the primary prevention of CVD in men at different ages and different levels of risk. We found that for a cost-effective prevention of CVD, 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, even with off-patent price, and should not represent the 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%.

Question 3: Could the polypill be a cost-effective intervention in the primary prevention of CVD, and what could be a good alternative to the polypill in populations free of heart disease?

In 2003 Wald and Law introduced the Polypill concept.[5] The Polypill is a theoretical combination of six pharmacological compounds that through concomitant modification of four different risk factors (cholesterol modification with statins, blood pressure lowering with three different antihypertensives, anti-platelet aggregation with aspirin and reduction of hyperhomocysteinemia with folic acid)

might reduce CVD by more than 80%. In general, the medical community has welcomed the concept but also questioned the potential adverse effects and costs of such an intervention.[11-13] Not being on the market, untested, and with a production yet to be started (to our knowledge), the potential future cost of the Polypill is unknown. Using data from the Framingham Heart Study[7] and multi-state life table analysis we calculated what the maximum cost of medication and treatment with the Polypill should be in order to be cost-effective among adult male populations free of CVD. We considered different levels of 10-year absolute risk of coronary heart disease (CHD) and different ages, to calculate the effects of the Polypill in terms of Years of Life Saved (YLS). We found that in order to be cost-effective in general populations free of CVD, the annual cost of the medication for Polypill therapy should not exceed €400 at age 60 and €300 at age 50. These costs are 10 times the cost of aspirin but three quarters the cost of statins.[14] Since aspirin and statins are two of the constituents of the Polypill, it could be expected that the medication costs for the Polypill could be in this price range or even higher. Although the expected maximum costs of the Polypill medication appear relatively accessible, the likely levels of adverse effects (e.g. stroke and gastrointestinal bleeding) are an important potential limitation to the Polypill. Consequently, we aimed to demonstrate that using non-pharmacological ingredients and the same assumptions and methodologies as the Polypill authors; similar risk reductions as the Polypill and with theoretically less adverse effects could be achieved.

Using published literature we designed and proposed the "Polymeal".[6] The Polymeal is a theoretical combination of 6 aliments (wine, fish, chocolate, fruits and vegetables, garlic and almonds) that combined and through simultaneous modification of different risk factors for cardiovascular disease will potentially reduce CVD by 75%. We illustrated that nutritional interventions could have similar effects with probably less adverse effects than the Polypill. However, both the Polypill and the Polymeal are mere theoretical principles that first need to be corroborated before they are considered for societal implementation.

Limitations of the studies

The Framingham studies

The Framingham studies are large ongoing cohort studies that include the Framingham Heart Study (FHS) and the Framingham Offspring Study (FOS).[7 15] The original FHS cohort consisted of 5209 respondents aged 28 through 62 years residing in Framingham, Massachusetts, between 1948 and 1951. Participants have

been examined biannually and the cohort has been followed for over 46 years. The FOS cohort consisted of the offspring and their spouses of the original FHS cohort and was sampled in 1971. The FOS cohort consisted of 5214 participants, aged 5 through 70 years at baseline. Examination of this cohort has taken place at intervals of four to eight years until present time. We used data from the FHS for the analyses in chapters 2, 3, 6, 7 and 9 and in combination with data from the FOS in chapters 6 and 7. In general the FHS and the FOS are large well-organized historic cohort-studies that provide high-quality information on covariates and long-term outcomes. However, these studies also have limitations. Overall, these studies are affected by a moderate level of missing values and by differences in time and population characteristics when compared with current circumstances.[16] The historical character of the Framingham studies limits the extrapolation of the results obtained through analyses of the Framingham data to today's populations. Great advances in health promotion and in the diagnosis, prevention and treatment of CVD have occurred since the Framingham studies started. Additionally the homogeneity of these studies limits the generalizability of the results obtained by analysis of these cohorts. Limitations of these studies specific to the chapters of this thesis, include:

- Chapter 2, analysis of the effect of physical activity on CVD: the definitions and classifications of physical activity are unique to the FHS. This limits the comparability and generalizability of our results with other studies and to other populations. Another limitation is that in the FHS physical activity levels were evaluated by self-report, which may introduce misclassification of exposure.[17-19] However, this misclassification is likely to be non-differential, which can only attenuate our results.
- Chapter 3, analysis of the effect of hypertension on CVD: particular characteristics of the cohort and of the time period when the FHS took place, limit the generalizability and comparability of our results. For instance, blood pressure control in the USA during the time most of the FHS participants were around age 50 (the nineteen fifties and sixties) was poor. Only 31% of hypertensives received treatment. BP levels were controlled below 140/90 mm Hg in only 10%.[20] Also guidelines and treatment of hypertension have changed substantially with time, as well as the coding of hypertension treatment in the FHS. These factors limit the comparability between different time periods.
- Chapters 6 and 7 share the same models and populations used. Therefore, they share also similar limitations: In chapters 6 and 7 we compare current and future therapies for cardiovascular risk management in populations free of CVD. Our analyses were limited due to the low prevalence of participants at higher risks

than 30% 10-year absolute risk of CHD. This did not allow us to make lifetables for these high-risk populations. 30% 10-year absolute risk of CHD is also the estimate above which treatment is advocated in most guidelines.[21] Additionally when we aimed to calculate the costs and cost-effectiveness of cardiovascular risk management we could 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 management, which makes current populations not comparable with populations from the seventies and eighties, in terms of invasive treatments of CHD. This limited our calculation of savings secondary to treatments, which generates higher cost-effectiveness ratios.

- Chapter 9, the Polymeal analysis: there is no data available on the components of the diets taken by the participants of the FHS. This limited our analysis on the potential effect of 6 aliments combined to reduce CVD.

The risk factors in life-table analyses

Chapter 2 and 3 use multi-state life table analyses (MSLT), to evaluate the effect of two risk factors for CVD on total life expectancy and life expectancy with and without CVD. The type of MSLTs included in this thesis had no back-flows allowed: only the first entry into a state was considered. This type of MSLT may well be a good approximation to real patterns of cardiovascular morbidity and mortality because of the low probabilities of back-flows of CVD in the transitions studied. Specific limitations to each analysis are:

- Chapter 2, analysis of the effect of physical activity on CVD: reverse causation, which means that lower physical activity levels are caused by disease and not the other way around, is an important issue to consider. It could introduce bias in the evaluation of the effect of physical activity. Different approaches exist to reduce the effect of reverse causation but there is no method to eliminate it completely. Additional to the already mentioned limitations (correspondent to FHS and the MSLTs) the possibility of remaining reverse causation in this study exists.
- Chapter 3, analysis of the effect of hypertension on CVD: in this chapter we used a cohort MSLT to evaluate the effect of hypertension on CVD among a cohort of participants aged 50 years. Generalizability of results obtained with cohort MSLTs is limited to populations at similar age. Furthermore, we could not evaluate the effect of hypertension completely independent of other risk factors of CVD such as cholesterol and physical activity due to incomplete or unavailable data. Therefore residual confounding might be present in our study

but it might be limited since we took into account another important risk factors for CVD: sex, age, BMI, smoking and education.

The systematic review of statins

In chapters 4 and 5 we performed a systematic review of statins to evaluate the cost-effectiveness of statins in CVD risk management, therefore chapters 4 and 5 share similar limitations

We decided to include only studies reporting results for male populations, since the primary objective of this study was to evaluate levels of heterogeneity and predictors on cost-effectiveness analyses of statins. Studies of female populations are rare and more difficult to interpret, since women at the same age run lower heart disease risks. While the absolute CERs will differ by sex, we do not expect the levels of heterogeneity to do so. Of the studies included in this study, 14 separately reported CERs for women. All of them consistently showed higher CERs compared to males.

Not all the studies used absolute risk for their analyses; therefore risk factor combinations were first translated into absolute risk of CHD.[22] This approach was not validated and some estimates might have been misclassified. Residual confounding particularly in the first risk group exists (there are great relative differences possible in the group < 1%). However, the variability is seen in all risk groups and misclassification will be limited (people at lower levels of risk factors will be at lower levels of risk).

The Polymeal study

The objective of this study was to demonstrate that using non-pharmacological ingredients and the same assumptions and methods as the Polypill authors, could potentially lead to similar risk reduction effects and with theoretically less adverse effects than the Polypill. The results of our analyses were presented in a manuscript published in the traditionally tongue-in-cheek Christmas' edition of the BMJ and was therefore written with a touch of irony.[6] As the Polypill authors,[5] we used appraisal of the evidence in combination with multiplicative models and analyses of life expectancy with and without CVD. To find the ingredients of the polymeal we searched the literature following the principles of Evidence-Based Diet, a variant of Evidence-based Medicine.[23] Published articles with level of evidence 1 or 2 were included. However, the validity level of the source evidence affects the Polymeal study. Although we included only randomised controlled trials or meta-analyses, some of the RCTs included in our study were of a small size. This is particularly the case for chocolate and almonds.[24-26] Evidence-based medicine is explicit about the level of evidence but not about additional matters of quality in the studies (e.g. sample size, correction for confounding) and as we have illustrated in the Polymeal

study, this is an essential issue to secure valid and applicable summaries of evidence. Furthermore assuming multiplicative effects although plausible has not been demonstrated. Further ascertainment of these multiplicative models in randomised controlled trials is required. Another limitation of this study is the limited information available on the potential interaction of the ingredients included in the Polymeal, (less than for the ingredients of the Polypill). It is unclear how these ingredients will act combined in a single meal, over a single day and over a week, therefore our results might be overestimated.

Additionally, we admit to have underestimated the caloric contribution of some of the ingredients of the Polymeal. This is mostly the case for chocolate. Therefore we think it could be better to include on a theoretical Polymeal half the amount of chocolate suggested in our study or in combination with a strong recommendation to cut calories from additional sources. An alternative would be to include small chocolate bars enriched with flavonoids that would also deliver fewer calories or to replace it with other ingredients (e.g. oat bran, green tea)[6]

We believe to have successfully illustrated that nutritional interventions could have large positive effects, and probably less adverse effects than the Polypill. However, the Polymeal is only a theoretical notion and further empirical research including RCTs need to be conducted before a Polymeal can be recommended for implementation in the general population. Noteworthy is also the fact that once sufficient evidence has been accumulated on the benefits of the Polymeal so that it could be implemented, its implementation may be more difficult than that of the Polypill. It is known that promoting a healthy lifestyle is a more difficult task than offering a single pill, especially to individuals at low to moderate levels of risk. Lifestyle changes including dietary changes have been found to be difficult to induce and even more difficult to maintain.[27-29]

Interpretation of the results

Physical inactivity as risk factor for CVD

Physical inactivity is a widely recognized modifiable risk factor for coronary heart disease and stroke.[30 31] Current guidelines of cardiovascular prevention emphasize the importance of promoting the adoption of physical activities in the general population. Through lowering the inflammatory response involved in atherogenesis and modifying the traditional risk factors of CVD (e.g. hypertension, obesity, dyslipidemia) increasing physical activity reduces the rates of cardiovascular disease.[32 33] Taking a life-course approach in our study, we were able to calculate not

only the effect of physical inactivity in terms of CVD event rates and mortality but also its effect in terms of life expectancy with and without CVD.

Compared with the existing literature,[32 34 35] our results confirm that following a sedentary lifestyle is associated with an increased risk of developing cardiovascular disease as well with an increased risk of total mortality in populations free of CVD and of CVD mortality among those with established cardiovascular disease. Additionally our multi-state life table analyses elucidate that being sedentary during adulthood is associated with an important reduction in total life expectancy. Compared with physically active individuals, people with low levels of physical activity tend to live less without the enduring consequences of being affected by heart disease. These results add substantial information to the world's literature on the field, stressing current recommendations about promoting a physically active lifestyle. We show that even moderate levels of physical activity are sufficient to enjoy the benefits of a longer and healthier life, but also that higher levels of physical activity grant even larger benefits and should be adopted whenever possible. This is in correspondence with the counsels included in the guidelines of prevention. Guidelines are supported in recommending even moderate levels of physical activity to prevent CVD.[31] Since still 40% of the world's population follows a sedentary lifestyle,[36] further public health efforts are necessary to achieve a worldwide implementation of an active pattern of life that could represent significant gains in life expectancy and important reductions on CVD in our society.

Hypertension as risk factor for CVD

Hypertension, the feared silent killer, gains every time more relevance in cardiovascular prevention.[20 37] New evidence has shown that hypertension additionally to its wretched consequences on human health is also a pathological condition that is not well recognized, diagnosed or controlled.[20] Global guidelines are not concordant with the "allowed" level of blood pressure, with the classification and nomenclature of hypertension as well as with when and how to treat suboptimal blood pressure levels.[20 37] On the other hand, the agreement of the existing literature on the field is clear: hypertension is one of the most important risk factors for cardiovascular disease. However the evidence runs short on information about the lifetime impact of high levels of blood pressure on total life expectancy and is inexistent about its effects on life expectancy spent with and without cardiovascular disease.[2 3] These measures of total life expectancy and life expectancy with and without CVD aid in the proper estimation of the burden generated by hypertension on health care, and are essential for the formulation of future guidelines and measures to control this noxious pathological process. Using a life-course

perspective, our study showed that high levels of blood pressure besides being an important risk factor for cardiovascular disease and total mortality, it is also associated with important reductions in total life expectancy and life expectancy lived without cardiovascular disease. Furthermore, hypertensives tend to spent longer periods of their lives with cardiovascular disease compared with normotensives. Our results also show that the health effects associated with increased BP levels in total LE is higher than previously estimated,[2, 3] and emphasize the global need to improve BP control.

The hazard ratios we found fall well within the range of the published measures of effect of hypertension on CVD and total mortality. Our study has several advantages when compared with other studies. Two studies previously estimated the impact of hypertension in total life expectancy and compared to our findings, they found similar effects but of a smaller magnitude[2, 3]. Different issues that could explain the differences with our findings affect these studies. For instance, they used only a single reading of BP levels at baseline, which due to random variation in an individual's BP will result in non-differential misclassification of exposure and therefore in a systematic underestimation of the harmful effects of hypertension.[38] In our analyses, we used all BP measurements between age 45 and 50 to predict BP at age 50. Each participant had at least two different measures of blood pressure, lowering therefore the probability of dilution bias in our analyses. This could explain the larger effects (in terms of LE). Only one of these studies also reported effects on women and both of them used shorter follow-up periods than we did.[2 3] Thus, our study is the first report from a large and continuously followed cohort showing in both sexes the effect of high BP levels on total LE and LE with and without CVD. Our results suggest that optimising the control of BP to keep it at normal levels and avoiding hypertension could potentially lead to a longer LE and to a reduction of CVD in the general population. Optimal control of BP as well as prevention of hypertension in the general population should be intensified and should constitute a priority of worldwide public health policies.

Comparison of physical activity and hypertension with other risk factors

Previous life table analyses of the Framingham data about the effect of other risk factors on total LE and LE with and without CVD have not always shown similar results to the ones we obtained for physical inactivity and hypertension. Pardo Silva et al [Pardo Silva M, MD, MSc. Obesity in adulthood is associated with a decrease in LE free of CVD and an increase in LE with CVD. A life table analysis of the Framingham heart study] found an important association of obesity with a shorter total LE and an increase in LE with CVD. These associations are similar to the ones

we found for hypertension and physical inactivity, however of a lesser magnitude compared to hypertension and larger than the effect of physical inactivity. Contrary to hypertension and obesity, we did not find a significant effect of physical inactivity on LE with CVD.

On the other hand, Mamun et al[39] found that smoking was associated with a shorter LE (similar to hypertension, physical inactivity and obesity) but also associated with less years lived with CVD (contrary to obesity and hypertension) since smokers –on average- die younger due to other causes, not reaching older ages where CVD rates are higher. Therefore, reducing smoking will lead to an increase in total LE but more cardiovascular morbidity.

The role of statins in cardiovascular prevention

Statins (Hydroxymethylglutaryl-coenzyme A Reductase Inhibitors) discovered in the seventies by Drs Endo and Kuroda, are relatively new drugs with an incomparable efficacy in reducing blood lipids.[40 41] Through favourably modifying dyslipidemia and additional mechanisms, statins reduce the rate of coronary heart disease (CHD) by more than 30%, with infrequent side effects and high tolerance level.[41 42] However statins are expensive and their costs limit the scope of treatment.[9] With the advent of statins, the controversy surrounding cardiovascular risk management has shifted from how to treat hypercholesterolemia to the proportion of eligible people that may actually be treated because of financial constraints.[8] Worldwide guidelines have used levels of absolute risk of coronary heart disease to select the populations among which statins would be a cost-effective intervention. But there is no agreement on which level of absolute risk to select.[21 43] This is partly due to the contradictory results published by economical analyses on statins. For this reason we aimed to summarize the existing economical evidence on statins for cardiovascular prevention in a systematic review. After a comprehensive appraisal of the literature we found that pooling the different published cost-effectiveness ratios on statins for CVD prevention was a difficult task challenged by ample levels of heterogeneity.

We found that the most likely explanation for the divergences of the reported results is the differences in the methodology used by each economical analysis. Additionally we found that the effect of absolute risk in the cost-effectiveness ratios differed significantly between categories of funding source. These differences between funding sources were particularly striking at low levels of risk, representing large eligible populations. It is tempting to suggest competing interests as an explanation, although we could not prove this. Although we tried to clarify the reasons behind the heterogeneous outcomes reported, it was impossible to determine all the differences in the methodology and assumptions that exists

between studies. It is clear from our studies that transparency in currently published economical analyses of the field is poor, as is uniformity on the approaches used to perform cost-effectiveness analyses.
Reporting of essential data and assumptions was poor for many cost-effectiveness analyses on statins. Further standardization in economical analyses is important to guarantee transparency and reproducibility of results.

Current primary prevention of cardiovascular disease
Primary prevention aims at lowering the occurrence rate of the event, i.e. the incidence rate of the disease.[44] Currently four therapies are the fundaments of cardiovascular risk management in populations without CVD or diabetes: cholesterol lowering with statins, antihypertensives, aspirin and smoking cessation. The populations that could potentially benefit from these therapies are very large as would be the cost if they were fully treated.[10] Limited resources oblige health services and governments to prioritise.[4] We conducted a comparative cost-effective analysis of these four key therapies in order to facilitate the prioritising process. We found that smoking cessation represented savings in all situations. Smoking cessation is the most cost-effective intervention in the primary prevention of CVD and should be adopted before any other therapy. Among non-smokers the most-cost effective treatment is aspirin followed by antihypertensives. Statins were not a cost-effective option among populations at levels of absolute risk of CHD below 30% over 10 years. Analysis of generic statins (68% cheaper than non-generic presentations) showed that they became moderately cost-effective and could play a role in the primary prevention of CVD but only after the adoption of smoking cessation, aspirin and antihypertensive treatment. Statin therapy is an expensive option and should not represent a first-choice in primary prevention of CVD; guidelines on primary prevention of CVD should not advise treatment with statins for populations at levels of 10-year CHD risk below 30%. On the other hand, smoking cessation therapy is a very cost-effective option and health services that do not cover it in their primary prevention plans and budget should reconsider it.

The Polypill: changing the future of cardiovascular prevention?
Under the principle that a large preventive effect of CVD would require intervention in everyone at increased risk irrespective of their risk factors levels, modifying several modifiable risk factors together; and reducing these risk factors by as much as possible, in 2003 Wald and Law introduced the Polypill concept.[5] "No other preventive method would have so great an impact on public health in the Western world" affirmed Wald and Law in their BMJ publication. Certainly the Polypill concept is very promising, however medicalising a large sector of society appears as

a risky and aggressive measure, especially if 15% of the people taking the Polypill could suffer adverse effects.[5] Furthermore the costs of the Polypill are unknown, since large sections of the world population might be treated, the cost of the medication is a relevant issue if we do not want to exhaust the global health budget in a single effort. We conducted a cost-effectiveness analysis to evaluate what should be the maximum cost of the Polypill medication in order to be cost-effective among different populations free of cardiovascular disease. We found that to be cost-effective the Polypill should not cost over €300 per year. Additional considerations are necessary before the Polypill appears in the market and is implemented in the primary prevention of CVD. For instance the large size of the targeted population could make even lower costs unaffordable. Furthermore randomised controlled trials elucidating the effectiveness and adverse effects rates secondary to the Polypill are required before a proper economical analysis of this intervention can be performed. Based on our results we conclude that the Polypill although a potentially highly effective intervention, has at least one important caveat: its cost. Safer and less costly alternatives should be designed for populations without established cardiovascular disease, which constitute the larger size of potentially treated and therefore the larger costs of treatment.

Is the Polymeal a valid alternative to prevent CVD? Messages behind the irony

> "Buried in it (referring to the Polymeal paper) are some things that are sensible, such as fruit and vegetable consumption. This paper helps focus attention on eating a healthy diet, which helps improve cardiovascular health" Professor Wald (author of the Polypill) declares to "New Scientist".

> "The authors of the Polymeal are raising a much more important question. Can nutrition be as affective in preventing CHD as medication? It's a question that needs asking and is most likely one not many scientists are willing to ask" Anonymous contribution posted on the Internet.

Although this paper was written in a tongue-in-cheek tone, important messages are inherent in it.[6] We showed that using the same methods used by the Polypill authors, the combination of non-pharmacological elements could have a similar positive effect as the combination of different pills (the Polypill) and with less adverse effects. Our findings theoretically support other evidence that healthy diets can

effectively contribute to cardiovascular disease prevention. Pharmacological ways are not the only path to follow in the successful prevention of cardiovascular disease. A healthy lifestyle including at least a moderate amount of physical activity in combination with the adoption of a balanced diet low in calories and saturated fats, and no smoking, should be promoted first. It is fundamental to intensify and continue spreading this message among all levels of society. Different strategies exist to promote healthy eating behaviours.[45-47] There are two main categories of nutrition interventions: individual-based and environment-based nutrition interventions.[48 49] Individual-based interventions target individuals or groups of individuals at different settings (e.g. school-based interventions with healthy children, worksite interventions with healthy adults, health care setting interventions with adults at risk of type 2 diabetes).[50] Since individual nutrition behaviour-change strategies are expensive and labour-intensive -relative to the number of persons they affect-,[50] environment-based interventions are generally advocated at a population level.[46] Environment-based nutrition interventions (EBNIs) create an environment supportive of healthy nutrition behaviours. These interventions take place in a variety of community settings and through many channels. Examples of EBNIs include to: develop social networks (e.g. encourage healthier food choices at social functions), influence policies (e.g. require food sanitation training for day care providers), alter physical environments (e.g. remove vending machines from schools), build a community supportive of healthy behaviours (e.g. establish a community garden), and strengthen traditional nutrition programs and services (e.g. author a weekly nutrition column in the newspaper to reinforce healthy nutrition behaviours).[49] An active approach from all people towards the embracing of a healthy lifestyle is indispensable. Finding happiness in a frugal, active lifestyle can spare us a future of pills and hypochondria.

Future research

As we have discussed in this thesis, cardiovascular diseases are largely preventable. However, why are they in the rising and why have they become the number one killer in the world? Something must be missing or needs to be done better; humankind is losing the cardiovascular challenge. Although much is known and has been said about cardiovascular diseases, much more needs still to be found and investigated.

The most important aspect that needs to be improved is current cardiovascular prevention measures and strategies for their implementation. More research is

needed on means to control the global pandemic of cardiovascular disease, particularly in developing countries where partly due to lack of financial support, research on the field is almost inexistent. Theoretical approaches like the Polypill, the Polymeal and the Poly-portfolio[45] (a combination of the Polypill with lifestyle modification oriented for secondary prevention populations) seem promising for the coming years. However they are just hypothetical and need to be tested further before they can be a valid alternative for the prevention and treatment of cardiovascular disease. Particularly more research is needed to evaluate the potential adverse effects of the Polypill. Once in the market the cost of the Polypill medication could importantly limit its widespread implementation. Future economical analysis on the Polypill will determine how cost-effective it could be and its potential role in the primary and/or secondary prevention of CVD. New research on finding alternative cheaper and safer Polypills could facilitate the adoption of the Polypill concept. On the other hand, more evidence is necessary on the effects of the proposed ingredients of the Polymeal. Through new studies' results, also additional ingredients could be incorporated and alternative Polymeals could be designed according to individual needs. Studies evaluating the interaction of heart-healthy aliments such as the ones included in the Polymeal, are fundamental in the process of understanding the mechanisms used by aliments to effectively prevent CVD. Analyses on these interactions are also necessary before multiplicative or additive models are assumed in the calculation of a Polymeal effect on CVD.

From the Polymeal analyses it is clear that more focus is needed in bringing today's society into the common adoption of a healthy lifestyle. More research is needed in order to find optimal ways to facilitate the implementation of a healthy lifestyle by all members of society.

References

1. WHO. *The World Health Report: 2003: shaping the future*. Geneve: World Health Organization, 2003.
2. Kiiskinen U, Vartiainen E, Puska P, Aromaa A. Long-term cost and life-expectancy consequences of hypertension. *J Hypertens* 1998;16(8):1103-12.
3. Miura K, Daviglus ML, Dyer AR, Liu K, Garside DB, Stamler J, et al. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: the Chicago Heart Association Detection Project in Industry. *Arch Intern Med* 2001;161(12):1501-8.

4. 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(1):26-36.
5. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326(7404):1419.
6. Franco OH, Bonneux L, de Laet C, Peeters A, Steyerberg EW, Mackenbach JP. The Polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. *BMJ* 2004;329(7480):1447-50.
7. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health* 1951;41(3):279-81.
8. Jacobson TA. Clinical context: current concepts of coronary heart disease management. *Am J Med* 2001;110 Suppl 6A:3S-11S.
9. Raithatha N, Smith RD. Paying for statins. *BMJ* 2004;328(7436):400-2.
10. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ* 2002;324(7353):1570-6.
11. Messori A, Santarlasci B, Trippoli S, Vaiani M. "Polypill" to fight cardiovascular disease: cost effectiveness of statins for primary prevention of cardiovascular events is questionable. *BMJ* 2003;327:808-9; discussion 809; author reply 809-10.
12. Midgley AK. "Polypill" to fight cardiovascular disease: old joke has element of truth. *BMJ* 2003;327:808; discussion 809; author reply 809-10.
13. Ramos F. "Polypill" to fight cardiovascular disease: birthday present was much appreciated. *BMJ* 2003;327:808; discussion 809; author reply 809-10.
14. Euro-medicines. www.euromedicines.org, 2001.
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(3):281-90.
16. Vasan RS, Sullivan LM, Wilson PW, Sempos CT, Sundstrom J, Kannel WB, et al. Relative importance of borderline and elevated levels of coronary heart disease risk factors. *Ann Intern Med* 2005;142(6):393-402.
17. Kannel WB, Sorlie P. Some health benefits of physical activity. The Framingham Study. *Arch Intern Med* 1979;139(8):857-61.
18. Sherman SE, D'Agostino RB, Cobb JL, Kannel WB. Physical activity and mortality in women in the Framingham Heart Study. *Am Heart J* 1994;128(5):879-84.
19. Sherman SE, D'Agostino RB, Silbershatz H, Kannel WB. Comparison of past versus recent physical activity in the prevention of premature death and coronary artery disease. *Am Heart J* 1999;138(5 Pt 1):900-7.
20. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289(19):2560-72.
21. Standing Medical Advisory Committee, the use of statins. www.doh.gov.uk/cmo/statins2.html, 1997.
22. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001;286(2):180-7.

23. Sacket DL SS, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based medicine: how to practice and teach EBM.* New York: Churchill Livingstone, 2000.
24. Taubert D, Berkels R, Roesen R, Klaus W. Chocolate and blood pressure in elderly individuals with isolated systolic hypertension. *JAMA* 2003;290:1029-30.
25. Sabate J, Haddad E, Tanzman JS, Jambazian P, Rajaram S. Serum lipid response to the graduated enrichment of a Step I diet with almonds: a randomized feeding trial. *Am J Clin Nutr* 2003;77:1379-84.
26. Jenkins DJ, Kendall CW, Marchie A, Parker TL, Connelly PW, Qian W, et al. Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: a randomized, controlled, crossover trial. *Circulation* 2002;106:1327-32.
27. Laitakari J, Vuori I, Oja P. Is long-term maintenance of health-related physical activity possible? An analysis of concepts and evidence. *Health Educ Res* 1996;11(4):463-77.
28. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* 2005;293(1):43-53.
29. Andajani-Sutjahjo S, Ball K, Warren N, Inglis V, Crawford D. Perceived personal, social and environmental barriers to weight maintenance among young women: A community survey. *Int J Behav Nutr Phys Act* 2004;1(1):15.
30. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol* 1990;132(4):612-28.
31. US Department of Health and Human Services. Physical Activity and Health: A Report of the Surgeon General. Atlanta, Ga: US Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, 1996.
32. Paffenbarger RS, Jr., Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med* 1986;314(10):605-13.
33. Rothenbacher D, Hoffmeister A, Brenner H, Koenig W. Physical activity, coronary heart disease, and inflammatory response. *Arch Intern Med* 2003;163(10):1200-5.
34. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *Lancet* 1953;265(6795):1053-7; contd.
35. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH. A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 1992;268(1):63-7.
36. Mackay J, Mensah GA. *The Atlas of Heart Disease and Stroke*. Geneve: World Health Organization, 2004.
37. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21(6):1011-53.
38. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences

in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335(8692):765-74.
39. Mamun AA, Peeters A, Barendregt J, Willekens F, Nusselder W, Bonneux L. Smoking decreases the duration of life lived with and without cardiovascular disease: a life course analysis of the Framingham Heart Study. *Eur Heart J* 2004;25(5):409-15.
40. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326(7404):1423.
41. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;282(24):2340-6.
42. Knopp RH. Drug treatment of lipid disorders. *N Engl J Med* 1999;341(7):498-511.
43. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106(25):3143-421.
44. Detels R, Mcewen J, Beaglehole R, Tanaka H. *Oxford Textbook of Public Health 4th Edition*. Oxford: Oxford University Press, 2002.
45. Seymour JD, Fenley MA, Yaroch AL, Khan LK, Serdula M. Fruit and vegetable environment, policy, and pricing workshop: introduction to the conference proceedings. *Prev Med* 2004;39 Suppl 2:S71-4.
46. Seymour JD, Yaroch AL, Serdula M, Blanck HM, Khan LK. Impact of nutrition environmental interventions on point-of-purchase behavior in adults: a review. *Prev Med* 2004;39 Suppl 2:S108-36.
47. Swinburn BA, Caterson I, Seidell JC, James WP. Diet, nutrition and the prevention of excess weight gain and obesity. *Public Health Nutr* 2004;7(1A):123-46.
48. Contento I, Balch GI, Bronner YL, Lytle LA, Maloney SK, Olson C, et al. Special issue: the effectiveness of nutrition education and implications for nutrition education policy, programs and research: a review of research. *J Nutr Educ* 1995;27:277-422.
49. SNE. www.sne.org, Society for Nutrition Education webpage (Public Health Division). Last visited 06-03/2005, 2004.
50. Ammerman AS, Lindquist CH, Lohr KN, Hersey J. The efficacy of behavioral interventions to modify dietary fat and fruit and vegetable intake: a review of the evidence. *Prev Med* 2002;35(1):25-41.
51. Robinson JG, Maheshwari N. A "poly-portfolio" for secondary prevention: a strategy to reduce subsequent events by up to 97% over five years. *Am J Cardiol* 2005;95(3):373-8.

Summary

"From the point of view of eradicating or markedly reducing prevalence of atherosclerosis, political efforts are required to enhance education and to fashion changes in policies regulating the agriculture, food, and tobacco industries. The alternative is to fully embrace the medicalisation of society, whereby we focus on efforts in biotechnology and industrialized medicine to address the consequences of diseases promoted by industrialization and urbanization" Professor Ole Færgeman, Aarhus University Hospital, Denmark, 2004.

Cardiovascular Disease (CVD) includes dysfunctional conditions of the heart and of the blood vessel system (arteries, veins, and capillaries) that among other functions supply oxygen to all body tissues and organs, including vital life-sustaining areas like the brain and the heart itself. Coronary heart disease and stroke are the principal components of CVD. Cardiovascular disease is the leading cause of mortality and morbidity worldwide. It is on the rise and has become a true pandemic that respect no borders.

This thesis presents studies on different areas of the epidemiology of CVD and its prevention. Three specific research questions were investigated:

1. What is the effect of risk factors for cardiovascular disease such as physical inactivity and hypertension, in terms of life expectancy and years lived with and without cardiovascular disease?
2. What is the cost-effectiveness of various strategies for cardiovascular risk management and which one is the most cost-effective in the primary prevention of CVD?
3. Could the polypill be a cost-effective intervention in the primary prevention of CVD, and what could be a good alternative to the polypill in populations free of heart disease?

In Chapter 2 of this thesis we constructed multi-state life tables using data from the Framingham heart study with the objective to calculate the consequences of different physical activity levels after age 50 in terms of total life expectancy (LE) and LE with (out) CVD. The FHS cohort consisted of 5209 respondents residing in Framingham, Massachusetts, between 1948 and 1951. The study included both men (n = 2336) and women (n = 2873) aged 28 to 62 years. The cohort has been examined biannually for 46 years. We found that moderate and high physical activity levels led respectively to 1.6 and 3.7 years more in total life expectancy and 1.1 and 3.2 more years lived without cardiovascular disease for men aged 50 compared with those who maintained a low physical activity level. For women the gains were similar. Following an active lifestyle during adulthood not only prevents CVD independently of other risk factors, but also substantially expands the total LE and the CVD-free LE for men and women. This effect is already seen at moderate levels of physical activity, and the gains in CVD-free life expectancy are twice as large at higher levels of activity.

The study presented in Chapter 3, analyses the life course of people with high blood pressure (BP) levels at age 50 in terms of total LE and LE with (out)

CVD compared to those with normal levels of BP (normotensives). Using data from 3128 participants who had their 50th birthday while enrolled in the Framingham heart study, we built multi-state life tables. Our analyses showed that irrespective of sex, 50-year-olds with high BP compared to normotensives, had a shorter total LE, a shorter LE free of CVD, myocardial infarction and stroke, and a longer LE lived with these diseases. Normotensive men survived 7.2 years (95% CI: 5.6-9.0) longer without CVD compared to hypertensives and spent 2.1 (0.9-3.4) years of life less with CVD. Similar differences were observed in women. Compared with hypertensives, total LE was 5.1 and 4.9 years longer for normotensive men and women respectively. From our results it can be inferred that high BP levels in adulthood are associated with large reductions in LE and more years lived with CVD. Our findings underline the tremendous importance of preventing high BP and its consequences in the population.

In Chapter 4, we reviewed cost-effectiveness analyses of statins and sought to synthesize cost-effectiveness ratios for categories of risk of coronary heart disease and age. We searched for studies comparing statins to no treatment for the prevention of either CVD or coronary heart disease. Estimates were extracted, standardized for calendar year and currency, and stratified by categories of risk, age and funding source. We included 24 studies, yielding a total of 216 cost-effectiveness ratios (CERs). We found that the CERs increase with decreasing risk. After stratification by risk, heterogeneity of ratios is large varying from savings to $59.000 per life year saved in the highest risk category and from $6500 to $490.000 in the lowest category. Our pooled estimates show values of $21571 per life year saved for a ten-year coronary heart disease risk of 20% and $16862 per life year saved for ten-year risk of 30%. Our findings show that statin therapy is cost-effective for high levels of risk, but inconsistencies exist at lower levels. Although the cost-effectiveness of statins depends mainly on absolute risk, important heterogeneity remains after adjusting for absolute risk. Economic analyses need to increase their transparency to reduce their vulnerability to bias and increase their reproducibility.

Chapter 5 is based on the studies collected during the development of chapter 4. Here, we aimed to evaluate the calculation of estimates of effectiveness in cost-effectiveness analyses of statins for CVD prevention. We reviewed cost-effectiveness analyses on statin treatment published between 1995 and 2002. Estimates of life years saved were extracted and compared with estimates calculated using the Dutch male life-table of 1996-2000. 19 studies were selected: 7 primary analyses and 12 secondary analyses. Of 7 primary modeling analyses, 6 showed all

the essential data and assumptions for the presented life savings, in contrast to none of the 12 secondary modeling analyses. The most transparent study estimated 1 year of life saved by 12 years of treatment of coronary heart disease survivors with increased cholesterol. In secondary analyses, the use of lifetime treatment caused the health effects to be dominated by savings at around the mean age of death (75-80 years). From this analysis we conclude that reporting of essential data and assumptions was poor for many cost-effectiveness analyses on statins, especially for the secondary modeling analyses. Further standardization in economical analyses is important to guarantee transparency and reproducibility of results.

In Chapter 6 we aimed to evaluate the cost-effectiveness of four risk-lowering interventions (smoking-cessation, antihypertensives, aspirin and statins) in primary prevention of CVD. Using data from the Framingham heart study and the Framingham offspring study we built life tables to calculate and compare the cost-effectiveness of the four interventions mentioned. We found that the most cost-effective intervention is smoking-cessation therapy being cost-saving for all sub-groups of participants analysed. Aspirin is the second most cost-effective (€2263 to €16949 per year of life saved) followed by antihypertensives (€28187 to €79843 per year of life saved). Statins are the least cost-effective (€73971 to €190276 per year of life saved). From our results we conclude that a cost-effective strategy should offer smoking-cessation for smokers and aspirin for all levels of risk among men aged 45 and over. Statin therapy is the most expensive option in primary prevention at levels of 10-years absolute coronary heart disease risk below 30%.

In Chapter 7 we evaluated what should be maximum price of the polypill in order to be a cost-effective alternative in the primary prevention of CVD. Data on the effects of the Polypill was taken from the literature. Using data from the Framingham Heart Study and the Framingham Offspring study, we built life tables to model the assumed benefits of the Polypill. We calculated what should be the medication cost of the Polypill in order to be cost-effective (using a 20000€/Year of Life Saved threshold) in the primary prevention of CVD. In order to be cost-effective among populations at levels of 10-year coronary heart disease risk over 20% (high risk), the annual cost of medication for the Polypill therapy should be no more than €302 or €410 for age 50 and 60 respectively. For cost-effective prevention in populations at levels of coronary heart disease risk between 10 and 20% the costs should be 2 to 3 times lower. Although the Polypill could theoretically be a highly effective intervention, the costs of the medication could be its caveat for implementing it in the primary prevention of cardiovascular disease.

Chapter 8 presents a letter to the editor sent to the BMJ. It is a response to the publication of a meta-analysis of statins written by the authors of the Polypill and used in the Polypill analysis. We consider that the models used by the authors in this study overestimate the risk reduction effect of statins (therefore the effects of the Polypill would be overestimated as well).

In Chapter 9, also following the Polypill concept, we aimed to identify a tastier and safer alternative to the Polypill: the Polymeal. We used the literature to select the ingredients of the Polymeal. The evidence-based recipe included: wine, fish, dark chocolate, fruits, vegetables, garlic and almonds. Using data from the Framingham Heart Study, we built life tables to model the benefits of the Polymeal in the general population from age 50, assuming multiplicative correlations. We found that combining the ingredients of the Polymeal would reduce CVD events by 76%. For men, taking the Polymeal daily represented an increase in total LE of 6.6 years, an increase in LE free from CVD of 9.0 years, and a decrease in LE with CVD of 2.4 years. The corresponding differences for women were 4.8, 8.1, and 3.3 years. It may be argued that the Polypill is still more effective, but we have illustrated that nutritional interventions could have similar effects with probably less adverse effects than the Polypill. However, both the Polypill and the Polymeal are mere theoretical principles that first need to be corroborated before they are considered for implementation in the general population.

Finally, in the general discussion in Chapter 10, the general findings and limitations of the studies included in this thesis are discussed. Additionally the overall results are integrated and interpreted. Possibilities and priorities for future research are also presented.

Samenvatting

(Summary in Dutch)

"Voor kwaliteit gecorrigeerde levensjaren worden niet behaald door consumentisme te bestrijden met meer consumentisme: 'a pill for every ill, polypills for many ills'. Kwaliteit is te vinden in wijsheid: vriendschap, solidariteit, een sober en actief leven en – niet te vergeten – het aanvaarden van onze onvermijdelijke eindigheid" Dr. Luc Bonneux

Ons hart en ons bloedvatstelsel (arteriën, venen, capillairen) voorzien al onze organen en weefsels, waaronder de levensbelangrijke hersenen en het hart zelf, van zuurstof. Hart- en vaatziekten (HVZ) zijn een verzameling van aandoeningen waarbij het hart en/ of bloedvatstelsel niet goed functioneert. Deze aandoeningen zijn de belangrijkste oorzaak van sterfte en ziekte in de wereld. Ze komen steeds vaker voor en zijn uitgegroeid tot een pandemie die geen grenzen meer kent. Coronaire hartziekten en beroerte zijn de belangrijkste twee HVZ.

In dit proefschrift worden verschillende onderdelen van de epidemiologie en de preventie van HVZ onderzocht. Drie specifieke onderzoeksvragen stonden centraal:

1. Wat is het effect van risicofactoren voor hart- en vaatziekten zoals lichamelijke activiteit en hypertensie, in termen van levensverwachting en jaren geleefd met en zonder HVZ?
2. Wat is de kosteneffectiviteit van verschillende strategieën van cardiovasculair risico management en welke strategie is het meest kosteneffectief in de primaire preventie van HVZ?
3. Kan de Polypil een kosteneffectieve interventie zijn voor de primaire preventie van HVZ, en wat kan een goed alternatief voor de Polypil zijn in populaties zonder HVZ?

In het eerste deel van het proefschrift komt de eerste onderzoeksvraag aan de orde. De effecten van risicofactoren op levensverwachting, en het aantal jaren geleefd met en zonder HVZ berekenden we door gebruik te maken van gegevens van een grote Amerikaanse studie, de 'Framingham Heart Study' (FHS) en sterftetafel analyses. De FHS is een longitudinale studie onder meer dan 5000 Amerikaanse volwassen (wonend in Framingham, Massachusetts 1948-1959) waarin over de tijd gekeken werd naar risicofactoren voor, aanwezigheid van en sterfte aan HVZ.

Hoofdstuk twee worden de gevolgen van verschillende niveaus van lichamelijke activiteit (na het 50ste levensjaar) in termen van totale levensverwachting (LV) en LV met en zonder HVZ gekwantificeerd. Op basis van gegevens van de FHS construeerden we een "multi-state" sterftetafel. We vonden dat mannen van 50 jaar met een matig of hoog niveau van lichamelijke activiteit, een hogere totale levensverwachting, respectievelijk 1.6 en 3.7 jaar hoger in vergelijking tot mannen met een laag niveau van lichamelijke activiteit. Ook leefden ze respectievelijk 1.1 en 3.2 jaren meer zonder HVZ. Voor vrouwen vonden we vergelijkbare verschillen. Het volgen van een actieve levensstijl gedurende de volwassen levensfase voorkomt dus niet alleen HVZ onafhankelijk van andere

risicofactoren, maar doet ook de totale levensverwachting en de LV zonder HVZ aanzienlijk toenemen. Dit effect wordt al gezien bij matige niveaus van lichamelijke activiteit. De winst in LV zonder HVZ is twee maal zo groot bij een hoog niveau van lichamelijke activiteit.

De studie in Hoofdstuk 3 analyseert de totale levensverwachting en de LV met en zonder HVZ van mensen met een hoge bloeddruk (hypertensieven) op hun 50ste in vergelijking met mensen met een normale bloeddruk (normotensieven). Wederom werden "multi-state" sterftetafels geconstrueerd aan de hand van gegevens uit de FHS, ditmaal gebruik makend van gegevens van 3128 participanten die op hun 50ste verjaardag in de studie zaten. De analyses laten zien dat, onafhankelijk van geslacht, mensen van 50 jaar met een hoge bloeddruk een kortere totale levensverwachting hebben; een kortere LV zonder hartziekte, zonder hartinfarct en zonder 'beroerte'; en een langere LV met deze ziekten. Normotensieve mannen leefden 7.2 jaar langer zonder HVZ (95% betrouwbaarheidsinterval 5.6-9.0) in vergelijking met hypertensieven, en leefden 2.1 (0.9-3.4) jaar van hun leven minder met HVZ. We vonden vergelijkbare verschillen voor vrouwen. In vergelijking met hypertensieven, was de totale levensverwachting voor normotensieve mannen en vrouwen respectievelijk 5.1 en 4.9 jaar langer. Uit deze resultaten kunnen we afleiden dat een hoge bloeddruk in de volwassen levensfase geassocieerd is met grote daling van de levensverwachting en tevens met een groter aantal jaren geleefd mét hart- en vaatziekten. Onze bevindingen onderstrepen het grote belang van preventie van hoge bloeddruk en haar gevolgen in de populatie.

In het tweede deel van het proefschrift wordt gekeken hoe kosteneffectief verschillende preventieve strategieën zijn. In Hoofdstuk 4 bestudeerden we systematisch bestaande kosteneffectiviteits-analyses van statines. We probeerden hun resultaten samen te voegen tot kosteneffectiviteits-ratios (KERs) naar categorieën van risico en leeftijd. We zochten studies die behandeling met statines ter preventie van HVZ ofwel coronaire hartziekten vergeleken met geen behandeling. Schattingen werden gestandaardiseerd voor kalenderjaar en munteenheid, en gestratificeerd naar risico, leeftijd en subsidiegever. We namen 24 studies op, wat een totaal van 216 KERs opleverde. De KERs bleken toe te nemen met een afnemend risico. Na stratificatie naar risico bleven ze zeer verschillend, variërend van kostensparend tot $59.000 per gewonnen levensjaar in de hoogste risico categorie; en van $6500 tot $490.000 in de laagste categorie. Voor een 10-jaar risico op coronaire hartziekten van 20% geeft de samengevoegde informatie een schatting van $21571 per gewonnen levensjaar en $16862 voor een risico van 30%.

Onze bevindingen laten zien dat behandeling met statines kosteneffectief is bij hogere risico's op coronair hartziekten, maar dat er bij de lagere risico's geen overeenstemming is. De kosteneffectiviteit van statines hangt met name af van het absolute risico. Echter, na correctie voor dit absolute risico bleef de verscheidenheid in de risico's groot. Het is van belang dat economische analyses hun transparantie en hun reproduceerbaarheid vergroten en de gevoeligheid voor vertekening ('bias') verminderen.

Hoofdstuk 5 maakt gebruik van dezelfde studies verzameld voor het onderzoek beschreven in hoofdstuk 4. Nu beoordeelden we de gebruikte methoden waarmee de effectiviteit van statines werd geschat. Kosteneffectiviteits-analyses van statines gepubliceerd tussen 1996-2000 werden systematisch bekeken. Schattingen van gewonnen levensjaren werden uit de geselecteerde studies overgenomen en vergeleken met schattingen berekend uit Nederlandse sterftetafel analyses (mannen 1996-2000). Van de 19 geselecteerde studies waren 7 primaire en 12 secundaire analyses. Zes van de 7 primaire analyses rapporteerden alle essentiële gegevens en aannames waarop de berekende gewonnen levensjaren gebaseerd waren, terwijl geen enkele secundaire analyse al deze informatie verschafte. In de secundaire analyses werden door de aanname van levenslange behandeling de gezondheidseffecten gedomineerd door kostenbesparingen rond de gemiddelde leeftijd van overlijden (75-80 jaar). We concluderen we dat het slecht gesteld is met de rapportage van essentiële gegevens en aannames voor veel kosteneffectiviteits-analyses naar statines, en specifiek voor secundaire analyses. Verdere standaardisatie van economische analyses is nodig om transparante en reproduceerbare resultaten te garanderen.

De kosteneffectiviteit van behandeling met statines werd vervolgens vergeleken met andere belangrijke interventies voor primaire preventie van HVZ: verlaging van de bloeddruk, antistollings therapie en stoppen met roken. Een kosteneffectieve preventie van HVZ zou in de eerste plaats ondersteuning bij het stoppen met roken aan rokers moeten geven en aspirine aan personen met een gemiddeld tot hoog risico op HVZ. Antihypertensiva zijn effectief maar niet de goedkoopste optie. Statines zijn duur (zelfs uitgaande van de prijs zonder patent) en zouden niet de eerste keus moeten zijn.

In hoofdstuk 6 trachtten we de kosteneffectiviteit te evalueren van vier interventies ter primaire preventie van HVZ: stoppen met roken; bloeddrukverlagers; aspirine; en statines. Gebruik makend van de Framingham Heart Study en haar opvolger de 'Framingham Offspring Study' (FOS) bouwden we sterftetafels om kosten-effectiviteit van deze vier interventies te berekenen en vergelijken. We

vonden dat stoppen met roken de meest kosteneffectieve interventie is. Deze interventie is kostenbesparend voor alle mensen uit de twee studies. Aspirine komt op de tweede plaats ($2263 tot $16.949 per gewonnen levensjaar) en wordt gevolgd door antihypertensiva ($28.187 tot $79.843 per gewonnen levensjaar). Statines zijn het minst kosteneffectief ($73.971 tot $190.276 per gewonnen levensjaar). Uit de resultaten leidden we af dat een kosteneffectieve strategie stoppen met roken aan moet bieden voor rokers en aspirine voor alle niveaus van risico in mannen van 45 jaar en ouder. Statine therapie is de duurste optie voor primaire preventie (bij niveau's van 10-jaar absoluut risico op coronaire hartziekten onder de 30%).

In het derde deel van het proefschrift evalueerden we de effectiviteit van de Polypil en zochten we naar een goed alternatief voor de Polypil in populaties zonder aanwezige HVZ. In 2003 introduceerden professoren Wald en Law het concept 'Polypil'. De Polypil bevat een combinatie van zes medicijnen en kan in theorie HVZ met meer dan 80% doen afnemen. In hoofdstuk 7 berekenden we hoeveel de Polypil maximaal mag kosten om een kosteneffectief alternatief voor de primaire preventie van HVZ te zijn (gebruik makend van een drempelwaarde van €20.000 per gewonnen levensjaar). Gegevens over de effecten van de Polypil werden uit de literatuur afgeleid. Gebruik makend van de data van de FHS en FOS bouwden we sterfte tafels om de aangenomen effecten van de polypil te modelleren. In populaties zonder HVZ maar met een hoog risico op HVZ mag een kosteneffectieve Polypil jaarlijks niet meer dan 400 euro kosten voor een 60-jarige, en niet meer dan 300 euro voor een 50-jarige. Hoewel de maximale kosten van de Polypil haalbaar lijken, zijn de grote aantallen personen die behandeld zouden kunnen worden en de waarschijnlijke frequentie van bijwerkingen (bijv. beroerte en maag- en darmbloedingen) belangrijke beperkingen van de Polypil.

Hoofdstuk 8 is een brief aan de editor van de 'British Medical Journal'. Het is een reactie op de publicatie van een meta-analyse van statines door de auteurs van het Polypil artikel. We pleiten dat het gebruikte model de risicoreductie veroorzaakt door statines overschat, zodat de effecten van de Polypil worden overschat.

In hoofdstuk 8 zochten we naar een niet-medicamenteus alternatief voor de Polypil. Gebruik makend van dezelfde aannames en methoden als de auteurs van de Polypil ontwierpen we de 'Polymaaltijd'. De ingrediënten van de Polymaaltijd kozen we op basis van de literatuur. Het 'evidence-based recipe' bevat zes ingrediënten: wijn, vis, pure chocolade, fruit, groenten, knoflook en amandelen. Wederom gebruik makend van gegevens uit de FHS en van sterfte-tafels modelleerden we de voordelen van de Polymaaltijd in de algemene populatie van 50

jaar en ouder (onder aanname van een multiplicatief model). We vonden dat de ingrediënten samen HVZ met 76% zou doen dalen (in theorie). Een dagelijkse Polymaaltijd komt overeen met een 6.6 jaar langere totale levensverwachting voor mannen en 4.8 jaar voor vrouwen (9.0 en 8.1 jaar langere LV zonder HVZ en 2.4 en 3.3 jaar kortere LV met HVZ, respectievelijk). Deze analyse illustreert dat voedingsinterventies zoals de Polymaaltijd vergelijkbare resultaten als de Polypil kunnen hebben, met waarschijnlijk minder bijwerkingen. Zowel de Polypil als de Polymaaltijd zijn echter slechts theoretische mogelijkheden voor preventie die zich eerst in onderzoek moeten bewijzen voordat implementatie op grote schaal kan worden overwogen.

Ten slotte worden in de algemene discussie in hoofdstuk 10 de algemene bevindingen en beperkingen van de studies in dit proefschrift besproken. Ook worden de resultaten uit de verschillende studies geïntegreerd en in samenhang geïnterpreteerd. Mogelijkheden en prioriteiten voor toekomstig onderzoek worden gepresenteerd.

Resumen

(Summary in Spanish)

“Come poco y cena menos, que la salud de todo el cuerpo se fragua en la oficina del estomago” Don Quijote de La Mancha, Don Miguel de Cervantes Saavedra(1547-1616)

Enfermedad cardiovascular (CV) incluye condiciones patológicas del corazón y del sistema circulatorio (arterias, venas y capilares) que entre otras funciones llevan oxígeno a todos los tejidos y órganos corporales, incluyendo áreas indispensables para la vida como el cerebro y el corazón. La enfermedad coronaria y los eventos cerebrovasculares (ECV) son los principales componentes de la enfermedad cardiovascular.

La Enfermedad cardiovascular es la causa número uno de mortalidad y morbilidad en el mundo, está en aumento y se ha convertido en una pandemia que no respeta fronteras.

Esta tesis presenta estudios en áreas diferentes de la epidemiología de la enfermedad cardiovascular y su prevención. Tres preguntas de investigación específicas fueron investigadas:

1. Cuál es el efecto de factores de riesgo de enfermedad cardiovascular como sedentarismo e hipertensión, en terminos de expectativa de vida y años vividos con y sin enfermedad cardiovascular?
2. Cuál es el nivel de costo-efectividad de varias estrategias para el manejo de riesgo cardiovascular y cuál es la estrategia más costo-efectiva en la prevención primaria de la enfermedad cardiovascular?
3. Podría ser la Polipíldora una intervención costo-efectiva en la prevención primaria de la enfermedad cardiovascular y cuál podría ser una buena alternativa en lugar de la Polipíldora?

El primer capítulo de esta tesis es la introducción de los conceptos y de las preguntas de investigación tratadas en ella.

En el capítulo dos, construímos “tablas de vida multi-estado” usando información del estudio “Framingham Heart Study”. Estas “tablas de vida” fueron construídas con el objetivo de calcular las consecuencias de diferentes niveles de actividad física a la edad de 50 años, en términos de expectativa total de vida y expectativa de vida con y sin enfermedad cardiovascular. El “Framingham Heart Study” es un estudio longitudinal que incluye 5209 participantes, de 28 a 62 años de edad que vivían en Framingham, Massachusetts, EEUU entre 1948 y 1951. Por medio de nuestros análisis encontramos que niveles moderados y altos de actividad física representan ganancias de 1.6 y 3.7 años en expectativa de vida total y 1.1 y 3.2 más años vividos sin enfermedad cardiovascular en hombres y mujeres comparados con símiles sendentarios. Seguir un estilo de vida activo no solo previene la enfermedad cardiovascular, sino que también expande la expectativa de vida total y la expectativa de vida libre de enfermedad cardiovascular en hombres y mujeres.

En el capítulo tres, analizamos el curso de vida de gente de 50 años de edad con hipertensión arterial (presión elevada de la sangre) y calculamos cuales serían las consecuencias de tener hipertensión a esa edad en términos de expectativa total de vida y expectativa de vida con y sin enfermedad cardiovascular, comparado a tener la tensión arterial normal (normotensión). Usando información de 3128 participantes con 50 años de edad del "Framingham Heart Study", construímos "tablas de vida multi-estado". Nuestros análisis demostraron que personas de ambos sexos a la edad de 50 años con hipertensión arterial tienden a tener una menor expectativa de vida, a vivir menos años libres de enfermedad cardiovascular y a vivir mas años con enfermedades del corazón que personas normotensas de la misma edad. Hombres normotensos sobrevivieron 7.2 años mas sin enfermedades del corazón que hombres hipertensos y vivieron 2.1 años menos con enfermedades del corazón (las diferencias fueron similares para las mujeres). Comparados con los hipertensos, los que tenían tensión arterial normal vivieron en total 5 años más. Podemos inferir de nuestros resultados que tener una tensión arterial alta durante la edad adulta representa disminuciones importantes en la expectativa de vida y mas años vividos con enfermedades del corazón. Nuestros resultados intensifican la importancia de prevenir niveles elevados de tensión arterial en la población general.

En el capítulo cuatro realizamos una revisión sistémica de estudios de costo-efectividad de estatinas (medicamentos utilizados para la reducción del colesterol en la sangre), buscando resumir cocientes de costo-efectividad para diferentes niveles de edad y riesgo de enfermedad cardiovascular. Luego de seleccionar 24 estudios relevantes en el tema, sus 216 cocientes de costo-efectivadad fueron extraídos y estandarizados a la misma moneda y año. Posteriormente, estos cocientes fueron estratificados en categorías de riesgo, edad y tipo de entidad que patrocinaba y pagaba el estudio. Encontramos que los cocientes de costo-efectividad aumentan al reducir el nivel de riesgo de enfermedad cardiovascular en la población estudiada. Luego de estratificar los cocientes de acuerdo a niveles de riesgo, encontramos grandes diferencias entre los estudios. Por ejemplo en la categoría de mayor riesgo de enfermedad cardiovascular variaron desde representar ahorro hasta cocientes de 59000 dólares por año de vida salvado y en la categoría de menor riesgo desde 65000 hasta 490000 dólares. Al sumarizar los cocientes, encontramos valores de $21571 por año de vida salvado en la poblacion con riesgo de enfermedad cardiovascular de 20% en 10 años y de $16862 en la población con riesgo de enfermedad cardiovascular de 30% en 10 años. Nuestros resultados demuestran que la terapia con estatinas es costo-efectiva para poblaciones con alto riesgo de desarrollar enfermedad cardiovascular pero es difícil sacar una conclusión en otras

poblaciones debido a las grandes inconsistencias encontradas. Aunque la costo-efectividad de las estatinas depende principalmente del nivel de riesgo de la población tratada, luego de estratificar de acuerdo al nivel de riesgo grandes diferencias permanecen en los cocientes de costo-efectividad publicados por los diferentes estudios. Los estudios económicos necesitan aumentar su transparencia para asi reducir su vulnerabilidad al sesgo y aumentar su reproducibilidad.

El capítulo 5 esta basado en los estudios recogidos durante el desarrollo del capítulo 4 y esta enfocado en los métodos usados por los diferentes artículos para calcular los años de vida salvados por medio del tratamiento con estatinas. Las estimaciones extraídas de los artículos seleccionados fueron comparadas con estimaciones que calculamos utilizando la tabla de vida de la población masculina en los Países Bajos de 1996 a 2000. De los 19 estudios seleccionados, 7 eran análisis primarios y 12 análisis secundarios. En los análisis secundarios, el uso de horizontes de tiempo para toda la vida, causó que los efectos de las intervención con estatinas fueran dominados por años de vida salvados en la edad promedio de muerte (75-80 años) lo cual es muy distante en el futro y a edades muy avanzadas. Los valores específicos para edad de mortalidad en las cohortes tratadas y no tratadas con estatinas no fueron mostradas en completo por ningun estudio. Seis de los siete análisis primarios mostraron toda la información necesaria para documentar los años de vida salvados, pero discrepancias permanecieron en la forma como las ganancias de vida fueron calculadas al final de los ensayos clínicos. Nuestros resultados demuestran que los estandares existentes para el cálculo de beneficios en salud en los estudios publicados son muy bajos. Mayor estandarisación en los análisis económicos es fundamental para garantizar su transparencia y reproducibilidad.

En el capítulo seis buscamos evaluar el nivel de costo-efectividad de cuatro intervenciones diferentes que son usadas en la prevención primaria de la enfermedad cardiovascular: terapia anti-tabaquismo, anti-hipertensivos, aspirina y estatinas. Usando información de los estudios Framingham, construímos tablas de vida para calcular y comparar el nivel de costo-efectividad de las intervenciones mencionadas. Encontramos que la intervención mas costo-efectiva es la terapia anti-tabaquismo seguida por el tratamiento con aspirina (de €2263 a €16949 por año de vida salvado) y por el tratamiento con anti-hipertensivos (de €28187 a €79843). Las estatinas fueron las menos costo-efectivas (de €73971 a €190276 por año de vida salvado). Basados en nuestros resultados podemos concluir que una estrategia costo-efectiva en la prevención primaria de la enfermedad cardiovascular, deberá ofrecer primero tratamiento anti-tabaquismo a los fumadores y luego aspirina a la población masculina mayor de 45 años. Las estatinas son una opción muy costosa en la

prevención primaria de la enfermedad cardiovascular para poblaciones con niveles de riesgo de enfermedad coronaria inferior al 30% en 10 años.

En el capítulo 7 evaluamos cual debería ser el máximo precio del medicamento polipíldora para poder ser una alternativa costo-efectiva en la prevención primaria de la enfermedad cardiovascular. Información sobre los efectos de la polipíldora fue tomada de la literatura publicada. Nuevamente usamos información de los estudios Framingham para construir tablas de vida que nos permitieran determinar los beneficios secundarios al tratamiento con la polipíldora. Calculamos cual debería ser el máximo costo de la polípildora para poder ser una alternativa costo-efectiva en la prevención de la enfermedad cardiovascular (usando un umbral de costo-efectividad de €20000/año de vida salvado). Los resultados de nuestros análisis muestran que para poder ser costo-efectiva en el tratamiento de poblaciones con un riesgo de enfermedad cardiovascular del 20% en 10 años con una edad de 50 o 60 años, la polípildora no debe costar mas de €302 o mas de €410 por año respectivamente. Para poder ser costo-efectiva en poblaciones con niveles de riesgo entre 10 y 20% en diez años los costos deberían ser 2 o 3 veces menos. Aunque la polipíldora es teoréticamente una intervención altamente efectiva, los costos de la medicacion podrían ser su principal debilidad para poder ser implimentada en la prevención primaria de la enfermedad cardiovascular.

El capítulo 8 es una carta enviada al editor del BMJ en respuesta a la publicación en dicha revista de un meta-análisis sobre el efecto de las estatinas. Este meta-análisis fué publicado por los autores del artículo de la polipíldora y fué fundamental para el cálculo que dichos autores hicieron sobre el teórico beneficio de la polipíldora. En esta carta opinamos que los métodos usados por los autores de la polipíldora sobre-estiman el efecto de reducción de riesgo de las estatinas (uno de los ingredientes de la polipíldora...por lo tanto tambien el efecto de la polipíldora estaría sobrevalorado).

En el capítulo 9, luego de la publicación del artículo sobre la polipíldora, buscamos encontrar una alternativa mas segura y de mejor gusto que la polipíldora: la “polymeal” (la polidieta). Usando la literatura identificamos 6 ingredientes que combinados en una sola comida (polidieta) podrían reducir efectivamente los niveles de la enfemerdad cardiovascular. Los ingredientes seleccionados fueron: almendras, vino, pescado, chocolate oscuro, frutas y vegetales, y ajo. Usando información de los estudios Framingham construímos tablas de vida para poder calcular cuales serían teoréticamente los efectos de dar la polidieta a poblaciones por encima de 50 años de edad. Encontramos que combinando los ingredientes de la polidieta a diario (excepto por pescado que debería ser consumido 4 veces por semana) representaría una

reducción del 76% de la enfermedad cardiovascular y un aumento de la expectativa de vida total de entre 5 y 6 años. También, la polidieta representaría un aumento en el número de años vividos sin enfermedades del corazón (entre 8 y 9 años). Se puede argumentar que la polipíldora es todavía mas efectiva que la polidieta, pero hemos demostrado que intervenciones nutricionales pueden tener efectos positivos similares a los de la polipíldora y con la ventaja de no tener los efectos adversos secundarios a la polipíldora. Sin embargo, es importante considerar que tanto la polidieta como la polipíldora son solo principios teóricos que primero necesitan ser corroborados antes de poder ser implementados en la población general.

Finalmente en el capítulo 10 son comentados los resultados generales y las limitaciones de los estudios presentados en esta tesis. Adicionalmente los resultados generales son integrados e interpretados. Futuras posibilidades de investigación son también presentadas en este capítulo.

Word of thanks

“I challenge anybody in their darkest moment to write what they're grateful for, even stupid little things like green grass or a friendly conversation with somebody on the elevator. You start to realize how rich you are.” Jim Carrey.

After every additional step I take in my life, I realize more that we are nothing and nothing can we achieve without the help, support and guidance given by others. I have many people to thank to. If I forget to mention someone please accept my apologies beforehand. My mind is forgetful but my heart is not.

First I would like to thank God, the promotor and supervisor of my life, my father, brother and friend. More earthly, I thank the Netherlands for adopting me these last four years, for giving me my life-companion and for providing me the scenario for writing this thesis and many wonderful moments of love and laughter.

In the human area my first words of thanks are directed to my promotor, Prof. Dr. Johan P. Mackenbach. Dear Johan, thank you for your unconditional trust and thoughtful guidance. Your comments and ideas were always a motivation for my work. Thank you for giving me the freedom to produce my own ideas, to develop them and to complete them.

Variety is the condition of harmony. Nothing is pleasant that is not spiced with variety. It is generally the case that Ph.D students have one or two (the most) supervisors during their four years of studies. I had the pleasure to have five different supervisors at different points, in the three years that I have spent completing this thesis.

My first supervisor was Luc Bonneux; Luc was also my first key to the doors of the iMGZ department. Dear Luc, thank you for all your help and support. Thank you for guiding my cognitive process in this area of cardiovascular research. In the beginning of my career as scientific researcher, I told Luc that I could not think of anything good enough to write for a research proposal. He advised me to write any stupidity that came to mind. Thanks Luc, your advice stimulated my creativity.

Anna Peeters combines brightness, commitment, hard work and humility so well, it is hard not to be impressed. Thanks Anna, you have been more supportive than you ought to. Your comments and questions were always important, challenging and scientifically accurate.

After the first half of 2003, Luc went back to Belgium and Anna went back to Australia. My third supervisor replaced them: Chris de Laet. Dear Chris, thank you for all your help and for introducing me to Stata and S-plus. Your logic and practicality are admirable, you taught me to develop my ideas further. You always see solutions when others see problems.

Before the end of 2003 I started to explore the fields of physical activity and CVD. Chris went back to Belgium and Wilma Nusselder became my fourth supervisor. At the beginning, Wilma and I seemed more opposite than similar. As I grew to know Wilma I found that we have more in common than I thought… perhaps it's the effect of learning by example. Dear Wilma, your perfectionism and sense of detail are exceptional (among many other qualities that you possess), thank you for all your support, for helping me "setting" the life-tables and for the so many hours spent in endless but highly productive discussions.

In 2004 Ewout Steyerberg became my fifth supervisor. Although he came later, his contribution to the finalization of my thesis has been fundamental. Dear Ewout, thank you for your guidance, sharp questions and thorough comments. Your adaptability is unlimited; I think that is your secret for your "pleiotropism".

Many of the studies included in my thesis, use data from the Framingham studies. I would like to express my gratitude to Dr. Sean Coady and the Framingham investigators: thank you for your collaboration and helpful comments.

I am also grateful to Prof. Dr. Frans Rutten, Dr. Louis Nissen and Dr. Marc Koopmanschap for their valuable comments over the systematic review of statins and to Prof. Dr. Hans Brug for his comments on health promotion.

Remarkably inspirational, Prof. Dr. Albert Hoffman and Prof. Dr. Kenneth Rothman are two key figures in the formation of my epidemiological philosophy. I would like to thank them for their contributions to the science of epidemiology and for being an example to many young researchers around the world.

I would also like to thank my supervisors during my master in Clinical Epidemiology: Dr. Huibert Burger and Dr. Yvonne van der Schouw.

During these three years the department of public health has become my second home. For this I must thank not only my promotor and supervisors but also many wonderful colleagues at iMGZ. In particular I would like to thank the Kindergarden-Cop (Arno), Caspar, Freeman (Lennart), Willem-Jan, Jan B, de Frites, Mauricio, Matejka, the people from automatisering, the secretaries, Mona and Ilse Oonk.

Dear Sandra and Albrecht, thank you for your friendship and your helpful comments for my thesis.

A mi familia: mis padres, hermanas, tíos y amigos muchas gracias por todo lo que me han dado. Su colaboración ha sido indispensable para poder lograr lo que he podido conseguir en el transcurso de mi vida. Muchas gracias por su cariño incondicional y por su ilimitado apoyo. Gracias le doy a Dios por darme la suerte de nacer donde he nacido.

Finally I would like to thank my little giant source of light, love and health promotion: thank you Ty (also for the Samenvatting)!

Curriculum

Vitae

“Live as if you were to die tomorrow. Learn as if you were to live forever”
Mahatma Gandhi

CURRICULUM VITAE

Oscar Franco Durán, was born on January 6, 1975 in Bucaramanga, Colombia. Son of Horacio Franco Sánchez and Benicia Durán de Franco; and brother of Amparo Franco Durán and Maria Victoria Franco Durán. He spent his "Kindergarten" years at "San Patricio" School. His primary education took place at the "La Salle" school. Before he completed his secondary education at the "San Pedro Claver" school in 1991 he spent one year in Surfers Paradise, Australia where he attended "The Southport School".

In 1993 he moved to Bogotá to start his medicine studies. By the end of 1998 he received the title of Doctor in Medicine and Surgery from the "Pontificia Universidad Javeriana". After graduation, he worked as general doctor in the Hospital of Barichara, Colombia until the year 2000. Afterwards he worked as a general doctor in cardiovascular disease prevention, in different health institutions of Bucaramanga, Colombia.

In July 2001 he came to the Netherlands with a scholarship from nuffic (Netherlands organization for international cooperation in higher education), to follow a Masters (MSc) in Clinical Epidemiology at nihes (Netherlands institute for health sciences). He completed his masters' degree by July 2002. In August 2002 with a scholarship from nihes, he started a Doctor in Sciences program (DSc) in Clinical Epidemiology at nihes, which was completed by July 2003. During this year, in August 2002, he started writing the first paper for this thesis.

In July 2003 he started working as scientific researcher at the department of Public Health of the Erasmus MC, University Medical Centre Rotterdam. Since July 2005 he has continued working with the same institution as a postdoc, on the task of contributing to the prevention of cardiovascular diseases. He is married to Michelle Elisabeth Kruijshaar.

Publications

“Democratic societies are unfit for the publication of such thunderous revelations as I am in the habit of making.” Salvador Dalí (1904-1989)

Oscar H. Franco, Luc Bonneux, Chris de Laet, Anna Peeters, Ewout W. Steyerberg, Johan P. Mackenbach. The Polymeal: a more natural, safe and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. *BMJ. 2004 Dec 18; 329(7480): 1447-50.*

Oscar H Franco, Huibert Burger, Corinne E I Lebrun, Petra H M Peeters, Steven W J Lamberts, Diederick E Grobbee, Yvonne T Van Der Schouw. Dietary Intake of Lignans and Cognitive Performance in Postmenopausal Women. *Journal of Nutrition.*135: 1190-1195, 2005.

Oscar H. Franco, Anna Peeters, Luc Bonneux, Chris de Laet. Blood pressure in adulthood and life expectancy with and without cardiovascular disease in men and women: life course analysis of the Framingham heart study. *Accepted for publication by Hypertension, in press.*

Oscar H. Franco, Anna Peeters, Caspar W.N. Looman, Luc Bonneux. Cost-effectiveness of statins in coronary heart disease: systematic review. *Accepted for publication by JECH, in press.*

Oscar H. Franco, Chris de Laet, Anna Peeters, Jacqueline Jonker, Johan Mackenbach, Wilma Nusselder. Effects of physical activity on total life expectancy and life expectancy with and without cardiovascular disease. *Submitted.*

Oscar H. Franco, Arno J der Kinderen, Chris de Laet, Anna Peeters, Luc Bonneux. Primary prevention of cardiovascular disease: cost-effectiveness comparison. *Submitted*.

Oscar H. Franco, Ewout W. Steyerberg, Anna Peeters, Luc Bonneux. Effectiveness calculation in economic analyses: the scenario of statins for cardiovascular disease prevention. *In preparation.*

Oscar H. Franco, Luc Bonneux. Mixing up evidence with beliefs in cholesterol. (Letter to the editor, BMJ).
http://BMJ.BMJjournals.com/cgi/eletters/326/7404/1423

Oscar H. Franco, Ewout W. Steyerberg, Chris de Laet. The Polypill: at what price would it become cost-effective? *Submitted.*

Jacqueline T Jonker, Chris de Laet, Oscar H. Franco, Anna Peeters, Johan P. Mackenbach, Wilma Nusselder. Physical activity and life expectancy with and without diabetes: life table analysis of the Framingham heart study. *Submitted.*

Propositions

(Stellingen)

"Sometimes a scream is better than a thesis." Ralph Waldo Emerson (1803-1882)

Propositions (Stellingen)

Belonging to the thesis: "Cardiovascular disease prevention: from meta-analyses to life expectancies" by Oscar H. Franco Durán.

1. Physical activity not only prolongs total life expectancy but also life expectancy free of cardiovascular disease. (this thesis)
2. Economic analyses need to increase transparency to reduce vulnerability to bias and increase reproducibility. (this thesis)
3. A cost-effective pharmacological strategy to prevent cardiovascular disease should start with smoking-cessation for smokers and aspirin for men aged 45 and over with moderate and high risk. (this thesis)
4. Although the Polypill theoretically is a highly effective intervention, the costs of the medication could be its caveat for implementing it in the primary prevention of cardiovascular disease. (this thesis)
5. Pharmacological ways are not the first option in cardiovascular disease prevention. A healthy lifestyle, including a good diet and exercise, should be promoted first. (this thesis)
6. If Jesus Christ would come back in the 21st century one of His central teachings would probably be the keystone of cardiovascular disease prevention: adoption of a healthy lifestyle.
7. The recommendation for a healthy heart may one day be exercise, eat right and laugh a few times a day. (Michael Miller, MD, F.A.C.C., Centre for Preventive Cardiology at the University of Maryland Medical Centre)
8. Let each of your acts be your last battle on earth. Only under those conditions will your acts have their rightful power. (Don Juan, Lord George Gordon Byron, 1788-1824)
9. Imagination is more important than knowledge. Knowledge is limited whereas imagination embraces the entire world… stimulating progress, giving birth to evolutions. (Albert Einstein 1879-1955)
10. All the knowledge I possess everyone else can acquire, but my heart is all my own. (The Sorrows of Young Werther, Johann Wolfgang von Goethe, 1749-1832)
11. The shortest and most realistic formula of luck (L) results from a simple combination of faith (F) and hard work (HW). [L=F*HW]