Cardiovascular Disease Prevention

Strategies

A Decision-Analytic Approach

Voor Lukas

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Cardiovascular Disease Prevention Strategies

A Decision-Analytic Approach

.

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Chapter 6

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Chapter 7

Rogier L. Nijhuis, MD, Pamela Coxson, Theo Stijnen, PhD, , PhD, Albert Hofman, MD, PhD, M.G. Myriam Hunink, MD, PhD. The performance of the Rotterdam Ischemic heart disease and Stroke Computer simulation model (RISC model) in the US population. Submitted to Medical Decision Making.

Chapter 8

Rogier L. Nijhuis, MD, Theo Stijnen, PhD, Maarten L. Simoons, MD, PhD, Jaap Deckers, MD, PhD, Jacqueline C.M. Witteman, PhD, Albert Hofman, MD, PhD, M.G. Myriam Hunink, MD, PhD. Cost-effectiveness of the "Polypill": a computer simulation study. In preparation.

Chapter 9

Rogier L. Nijhuis, MD, Theo Stijnen, PhD, Kirsten E. Fleischmann, MD, PhD, Albert Hofman, MD, PhD, Jacqueline C.M. Witteman, PhD, M.G. Myriam Hunink, MD, PhD. A decision-analytical approach to select individuals for primary cardiovascular prevention with aspirin. Submitted to NEJM.

Chapter 10

Rogier L. Nijhuis, MD, Theo Stijnen, PhD, J. Polder, Kirsten E. Fleischmann, MD, PhD, Jacqueline C.M. Witteman, PhD, Albert Hofman, MD, PhD, M.G. Myriam Hunink, MD, PhD. Cost-effectiveness analysis of aspirin therapy in the primary prevention of cardiovascular disease: a computer simulation study. In preparation.
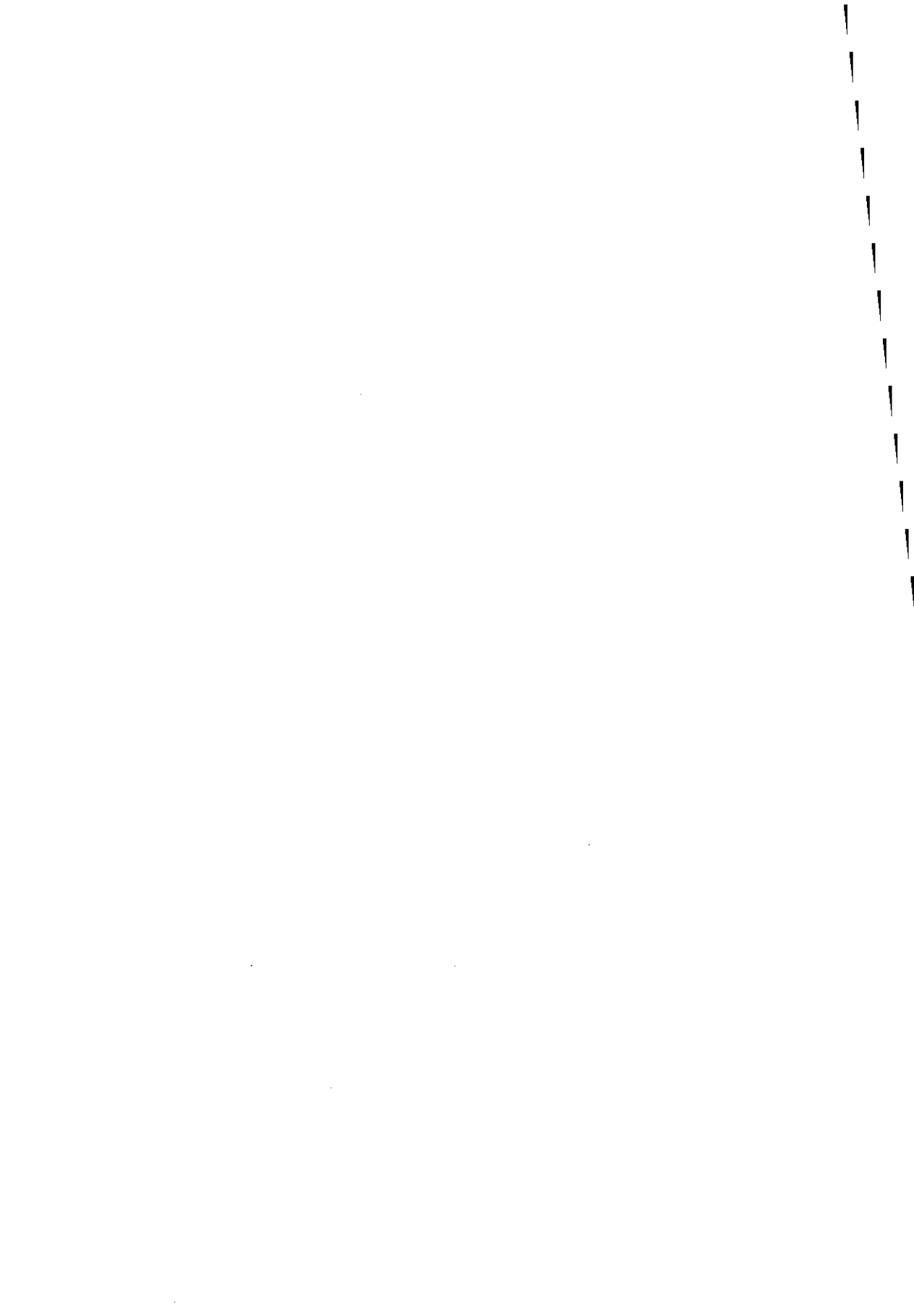
CONTENTS

1

General introduction

Whereas secondary prevention of cardiovascular events through risk factor modification in patients with known coronary and carotid artery disease is recognised as cost-effective, CVD prevention by drug therapy in asymptomatic individuals has shown only modest benefits and to be relatively expensive. These interventions, however, could be cost-effective when targeting individuals at high risk for an event. Based on easily assessable risk factors, high-risk persons for cardiovascular disease can be targeted.

The aim of the studies described in this thesis was to search for the most cost-effective way to prevent cardiovascular disease in the general population. The studies are based on data from the Rotterdam Study, a population-based cohort study composed of 7,983 men and women aged 55 years and over who live in a well-defined suburb of the city of Rotterdam, the Netherlands. Apart from the traditional cardiovascular risk factors, data were collected on the presence and severity of atherosclerosis and the occurrence of cardiovascular events during follow-up.

The study described in chapter 2 investigates the added value of peripheral arterial disease, in the prediction of cardiovascular disease mortality. In chapter 3 we examine whether the ankle-arm index can be used as a continuous risk indicator for cardiovascular disease. In chapters 4 and 5 the development of the Rotterdam coronary heart disease risk function and the Rotterdam cardiovascular disease risk function are described and the added value of the ankle-arm index among other "new" risk indicators are evaluated. In chapter 6 the computer simulation model is introduced, which was developed to predict the future CVD mortality and morbidity in the original Rotterdam Study population. This model will be referred to as the Rotterdam Ischemic heart disease & Stroke Computer simulation model (RISC model) and was externally validated in chapter 7. In chapter 8, the RISC model was used to examine the cost-effectiveness of primary prevention strategies for cardiovascular disease using the "Polypill" (a combination of aspirin, a statin, three blood pressure lowering agents in half dose and folic acid) as described by Wald & Law. In chapter 9 the RISC model was used to develop a prediction rule to estimate the individual's gain in quality-adjusted life years (QALYs) with aspirin therapy (the ΔQALY prediction rule). Finally, in chapter 10, a cost-effectiveness analysis was performed of aspirin therapy in the primary prevention of cardiovascular disease

using the Framingham cardiovascular disease risk function, the Rotterdam cardiovascular disease risk function, the Rotterdam cardiovascular disease risk function with ankle-arm index included, and the ΔQALY prediction rule.

In technical appendices the development and structure of the Rotterdam coronary heart disease risk function, the Rotterdam cardiovascular disease risk function, the ΔQALY prediction rule and the RISC model are described in detail.

In the general discussion in chapter 11, the main findings of this thesis are considered in the context of current clinical practice, relevant methodological aspects are discussed, and suggestions are made for future research in this field.

2

Non-invasively assessed peripheral arterial disease predicts cardiovascular disease mortality

Non-invasively assessed peripheral arterial disease predicts cardiovascular disease mortality

The Rotterdam Study

Abstract

Although individuals with peripheral arterial disease (PAD) are at increased risk of death from cardiovascular disease (CVD), information about CVD mortality associated with asymptomatic PAD in the general population is relatively scarce. Furthermore, its possible role in CVD risk management remains to be clarified. We studied whether PAD, defined as an ankle-arm index <0.90, predicts CVD mortality in the general population and shows additional prognostic value over and above the Framingham CVD risk function within the Rotterdam Study. Baseline data included information on CVD history and risk factors. The Rose questionnaire on intermittent claudication was used to assess whether PAD was symptomatic. Ten-year clinical follow-up data on CVD mortality were obtained. In comparison to those without PAD (4907 subjects), participants with symptomatic PAD (68 subjects) had an almost threefold risk of CVD mortality (hazard ratio 2.70; 95% CI 1.67-4.37). There was also an increased risk albeit less pronounced (hazard ratio 1.89; 95% CI 1.54-2.30) in subjects with asymptomatic PAD (1027 subjects). The ankle-arm index showed a continuous relation with CVD mortality and prognostic interaction with the Framingham CVD risk score (p=0.048). Therefore, measurement of the ankle-arm index may play a role in the prevention of CVD mortality.

INTRODUCTION

Atherosclerosis in the lower limb distal to the aortic bifurcation, generally known as peripheral arterial disease (PAD), usually presents itself as intermittent claudication, i.e. 'cramping', 'fatigue' or 'aching' in the calf of the leg induced by walking and relieved by standing still. Individuals with PAD are at an increased risk of cardiovascular mortality compared to those without PAD.[1-7] Information about CVD mortality associated with asymptomatic PAD in the general population is relatively scarce, even in older individuals who are known to be at high risk of PAD.[9-11]

Studies that analyzed the ankle-arm index (AAI), a non-invasive measure of PAD, suggest that a low AAI is associated with increased mortality[8-10] and may be an independent predictor of future cardiovascular events.[8-15] Several authors discussed the potential role of measuring the AAI in cardiovascular risk management.[12-15] Newman et al. showed that there might be an inverse and graded relation of the AAI with cardiovascular risk factors and subclinical and clinical cardiovascular disease (CVD) among the elderly.[14]

The purpose of this study was to assess whether non-invasively assessed PAD predicts CVD mortality in the general population over age 55 and whether the AAI shows additional predictive value over and above the Framingham risk function[16] in predicting CVD mortality.

METHODS

Population for analysis

This study was part of the Rotterdam Study, a prospective cohort study designed to investigate determinants of the occurrence and progression of chronic diseases in people over age 55. The Rotterdam Study focuses on four areas of research: cardiovascular diseases, neurogeriatric diseases, locomotor diseases, and ophthalmologic diseases. The rationale and design of the study have been described previously.[17] All individuals aged 55 years and over living in a suburb of Rotterdam in the Netherlands (a total of 10,275 subjects) were invited to participate in the study.

Baseline measurements were compiled after an extensive interview at the participant's home and two visits to the research center. The overall response rate was 78% (7,983 subjects; 3,105 men and 4,878 women). Baseline data, collected between 1990 and 1993, included information on history of cardiovascular disease and cardiovascular risk factors, including the AAI.

Intermittent claudication was diagnosed according to the criteria of the WHO Rose-questionnaire,[18] that was included in the home interview. Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. The systolic blood pressure level of the posterior tibial artery at both the left and right leg was measured using a 8 MHz continuous wave Doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK) and a random-zero sphygmomanometer.[19-24] For each leg a single blood pressure reading was taken with the subject in supine position. The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm (AAI) was calculated for each leg. The lowest AAI in either leg was used in the analysis.[23] In agreement with the approach followed by Fowkes et al[25] and by Schroll and Munck,[26] peripheral arterial disease (PAD) was considered present if the AAI was lower than 0.90 on at least one side, a threshold value that prevails in most studies.[2,3,27,28] Hypertension was defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 100 mmHg or over, or current use of antihypertensive drugs for the indication of hypertension.[29] Diabetes mellitus was defined as the current use of antidiabetic drugs or a random or post-load serum glucose level greater than 11.0 mmol/l, after an oral glucose tolerance test.[30] Subjects were categorized in groups of current smokers, former smokers, and those who never smoked. Serum total cholesterol was determined by an automated enzymatic procedure.[31] Serum high-density lipoprotein (HDL) cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium.[32] with a minor modification as described by Grove.[33] Height and weight were measured and the body mass index (kg/m^2) was calculated.

A history of myocardial infarction or stroke was obtained through direct questioning and considered positive when confirmed by a physician. A subject was defined as free of CVD at baseline if no myocardial infarction was diagnosed by a cardiologist or by EKG (verified by cardiologist), no stroke was diagnosed by a

physician, and the subject did not report having undergone coronary revascularisation or carotid endarterectomy.

The follow-up period started at the baseline examination and in the present analysis lasted until December 1999. Information considering the vital status of the participants was obtained from the municipal health service in Rotterdam. Clinical follow-up data on fatal and non-fatal endpoints were obtained from the general practitioners (GPs) working in the research area of the Rotterdam Study through linkage of the GP's automated medical record system to the database of the Rotterdam Study on a regular basis. All possible events, including deaths, reported by the GP were regularly evaluated by research physicians reviewing medical records and discharge reports and letters of medical specialists available at the GP's office of every participant. Information on the cause and circumstances of death were obtained shortly after the reporting of death by the municipal health service or the GP.

All events were classified according to the International Classification of Diseases, 10th version,[34] and coded independently by two research physicians. In case of disagreement, consensus was reached in a separate coding session. A medical expert in the field of cardiovascular disease reviewed and verified all coded events. The judgement of this expert was considered final if no consensus was reached. CVD mortality was defined as death from ischemic heart disease (I20-I25), congestive heart failure (I50), cerebrovascular disease (I60-I69), sudden death (I46 & I49 & R96) and all other I-codes.[34-36]

Data analysis

We used Cox proportional hazards models to examine the risk of CVD mortality in those with an AAI <0.90 with and without symptoms of intermittent claudication, taking all subjects with an AAI ≥0.90 as the reference group. The models included age and sex (Model A), or additionally included other confounders (Model B). We plotted Kaplan-Meier survival curves for CVD mortality, adjusted for age, sex, and medical history of cardiovascular disease. In addition, we used a Cox proportional hazards model to examine the risk of CVD mortality associated with the AAI using different threshold values to define PAD (0.50, 0.70, and 0.90). Finally, we used a Cox proportional hazards model to study the prognostic interaction between the

Framingham CVD risk score and the AAI in predicting CVD mortality within subjects free of CVD at baseline, adjusted for age, sex, and intermittent claudication. Analyses were performed using SPSS software (SPSS for Windows 7.5, SPSS Inc., Chicago, USA).

RESULTS

General characteristics of the participants in whom the AAI was assessed, are given in Table 1. Of the 6,002 participants 18.2% had an AAI <0.90. Among subjects with an AAI <0.90, 6.2% reported symptoms of intermittent claudication whereas among those with an AAI ≥0.90 only 0.6% had a positive Rose questionnaire on intermittent claudication. During the mean follow-up period of 7.0 years (range 0.01 – 11.3 years), 1319 (22.0%) participants died, of which 484 died from CVD (36.7% of the total mortality). CVD mortality was caused by ischemic heart disease (19.5%), congestive heart failure (18.4%), cerebrovascular disease (25.4%), sudden death (27.3%) and other CVD events (9.4%).

In comparison to those with an AAI ≥0.90, participants with both an AAI <0.90 and intermittent claudication had an age- and sex- adjusted nearly threefold risk of CVD mortality (hazard ratio 2.70; 95% CI 1.67-4.37), whereas those with an AAI <0.90 but no intermittent claudication had a relative risk of nearly two (hazard ratio 1.89; 95% CI 1.54-2.30). (Table 2) The risk estimates decreased after further adjusting for multiple confounders, but stayed statistically significant. The risk estimates for only subjects without manifest cardiovascular disease (i.e. prior MI, stroke or coronary revascularization) were slightly lower. Cumulative survival curves (Figure 1) demonstrated a higher CVD mortality in individuals with an AAI <0.90 with intermittent claudication than in individuals with an AAI <0.90 and no intermittent claudication, who in turn had a higher CVD mortality than individuals with an AAI ≥0.90 (reference group).

Whereas symptomatic PAD was clearly associated with increased CVD mortality (hazard ratio 2.70; 95% CI 1.67-4.37), it showed no association with other mortality (hazard ratio 1.27; 95% CI 0.76-2.13). Non-symptomatic PAD, however, showed an association with non-CVD mortality, although less pronounced (hazard

ratio 1.59; 95% CI 1.36-1.87) than with CVD mortality (hazard ratio 1.89; 95% CI 1.54-2.30).

We observed higher relative risks when lower threshold values of AAI were used, namely, from 1.45 (95% CI: 1.10-1.84) for an AAI between 0.90 and 1.10 to 3.04 (95% CI: 2.33-3.99) for an AAI below 0.70. (Table 3)

In Figure 2 we demonstrate the prognostic interaction between the AAI and the Framingham CVD risk score in the prediction of CVD mortality within subjects free of CVD at baseline. The AAI as a continuous measure showed a statistically significant interaction (p=0.048) with the Framingham CVD risk score in predicting CVD mortality. The risk of CVD mortality among subjects with a Framingham CVD risk score in the highest quartile and an AAI lower than 0.70 was almost 10 times higher (hazard ratio 9.71, 95% CI, 4.20-22.44, adjusted for age, sex and intermittent claudication) than among subjects with a Framingham CVD risk score in the lowest quartile and an AAI between 1.10 and 1.50.

DISCUSSION

The findings in our study show that PAD, as assessed by the AAI, is an independent predictor of subsequent CVD mortality. The risk of CVD mortality is significantly higher in those with an AAI <0.90, even in those without intermittent claudication, and also after adjustment for potential confounders. We also found an increasing risk of mortality with lower thresholds for the AAI, strongly suggesting that a lower AAI reflects more advanced generalized atherosclerosis. In our study, the AAI showed a significant interaction with the Framingham CVD risk score in predicting CVD mortality.

Intermittent claudication was present in 6.2% of the subjects with PAD as assessed by the AAI. Thus, the majority of subjects with documented PAD were asymptomatic. Among subjects with an AAI ≥0.9, only 0.6% of the subjects had intermittent claudication on the Rose questionnaire. This may, in part, be explained by the fact that the AAI can be high in subjects with calcified, non-compressible arteries and because of nonvascular causes of leg pain such as spinal stenosis.[22] These

subjects are misclassified which may lead to an underestimation of the risk of CVD associated with a lower AAI. Also medication use such as anticoagulants or aspirin, which may have been prescribed during follow-up, can lead to a similar effect dilution bias and underestimation of the risk estimates. Finally, the use of a single measurement of the AAI to define PAD may have underestimated the actual risk, because taking the mean of consecutive measurements reduces the measurement error in the AAI.

The increased risk of mortality with an AAI <0.90 has also been reported by other authors.[8-15] Newman et al[14] showed almost the same results for the association between PAD and CVD mortality (hazard ratio 2.86, decreased to 2.03 after multivariate adjustment). Although Hooi et al[11] used slightly different cut-off levels, they also showed a gradual increase in risk of cardiovascular mortality with decreasing AAI. Subjects with a AAI <0.70 had a 2.3 times higher risk and subjects with an AAI between 0.70 and 0.95 had a 1.2 higher risk than subjects with an AAI ≥0.95. In contrast, our study showed a statistically significant higher risk for subjects with an AAI between 0.70 and 0.90 compared to subjects with an AAI ≥1.10.

Whereas symptomatic PAD was clearly associated with increased CVD mortality, it showed no association with other mortality. Non-symptomatic PAD showed an association with non-CVD mortality, although less pronounced than with CVD mortality. This counter-intuitive result may be explained by a higher rate of misclassification in asymptomatic PAD than in symptomatic PAD. Another explanation may be that the AAI is a measure of frailty in the elderly and subjects with a low AAI die at a younger age from any disease.

The pathway from risk factors to CVD mortality is probably through the development of subclinical disease (like PAD) and the presence of subclinical CVD may be an important marker of the effect of risk factors on the cardiovascular system. Measurement of the AAI identifies a relatively large amount of asymptomatic individuals with early manifestations of atherosclerosis and inter- and intra observer variability for the measurement of the AAI have shown to be acceptable.[25] This suggests that apart from the assessment of the Framingham CVD risk score, measurement of the AAI may be worthwhile in CVD risk management.

In conclusion, peripheral arterial disease as assessed by measurement of the AAI is an independent predictor of CVD mortality. The risk of CVD increases when

PAD is symptomatic, i.e. when intermittent claudication is present. Both measuring the AAI and assessing presence of intermittent claudication may play a role in the prevention of CVD mortality.

REFERENCES

1. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, Wolfson SK. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Circulation 1993;88:837-45.

2. Fowkes FGR, Housley E, Cawood EHH, Macintyre CCA, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic PAD in the general population. Int J Epidemiol 1991;20:384-92.

3. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. Circulation 1985;71:510-5.

4. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. Atherosclerosis 1991;87:119-28.

5. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381-6.

6. Davey Smith G, Shipley MJ, Rose G. Intermittent claudication, heart disease risk factors, and mortality: the Whitehall Study. Circulation 1990;82:1925-31.

7. Hooi JD, Stoffers HE, Kester AD, Rinkens PE, Kaiser V, van Ree JW, Knottnerus JA. Risk factors and cardiovascular diseases associated with asymptomatic peripheral arterial occlusive disease. The Limburg PAOD Study. Peripheral Arterial Occlusive Disease. Scand J Prim Health Care. 1998;16(3):177-82.

8. Vogt MT, McKenna M, Anderson SJ, Wolfson SK, Kuller LH. The relationship between ankle-arm index and mortality in older men and women. J Am Geriatr Soc 1993;41:523-30.

9. Kornitzer M, Dramaix M, Sobolski J, Degre S, De Backer G. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. Angiology 1995;46:211-9.

10. Vogt MT, Cauley JA, Newman AB, Kuller LH, Hulley SB. Decreased ankle/arm blood pressure index and mortality in elderly women. JAMA 1993;270:465-9.

11. Hooi JD, Stoffers HE, Kester AD, van RJ, Knottnerus JA. Peripheral arterial occlusive disease: prognostic value of signs, symptoms, and the ankle-brachial pressure index. Med Decis Making. 2002;22(2):99-107

12. Newman AB, Sutton-Tyrrell K, Vogt MT, Kuller LH. Morbidity and mortality in hypertensive adults with a low ankle/arm blood pressure index. JAMA 1993;270:487-9.

13. Leng GC, Fowkes FGR, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ 1996;313:1440-4.

14. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, Powe NR, Siscovick D. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol 1999;19:538-45.

15. Jager J, Kostense PJ, Ruhe HG, Heine RJ, Nijpels G, Dekker JM, Bouter LM, Stehouwer CDA. Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects. Five-year follow-up of the Hoorn Study. Arterioscler Thromb Vasc Biol 1999;19:617-24.

16. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J. 1991;121(1 Pt 2):293-8

17. Hofman A, Grobbee DE, Jong PTVM de, Ouweland FA van den. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

18. Rose GA, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. Geneva: World Health Organization, 1982.

19. Stegall HF, Kardon MB, Kemmerer WT. Indirect measurement of arterial blood pressure by Doppler ultrasound sphygmomanometry. J Appl Physiol 1968;25:793-8.

20. Yao ST, Hobbs JT, Irvine WT. Ankle systolic pressure measurements in arterial disease affecting the lower extremities. Br J Surg 1969;56:676-9.

21. Kazamias TM, Gander MP, Franklin DL, Ross J Jr. Blood pressure measurement with Doppler ultrasonic flowmeter. J Appl Physiol 1971;30:585-8.

22. Prineas RJ, Harland WR, Janzon L, Kannel W. Recommendations for use of non invasive methods to detect atherosclerotic peripheral arterial disease in population studies. Circulation 1982;65:1561A-6A.

23. Fowkes FGR. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. Int J Epidemiol 1988;17:248-54.

24. Feigelson HS, Criqui MH, Fronek A, Langer RD, Molgaard CA. Screening for peripheral arterial disease: the sensitivity, specificity, and predictive value of noninvasive tests in a defined population. Am J Epidemiol 1994;140:526-34.

25. Fowkes FGR, Housley E, Macintyre CCA, Prescott RJ, Ruckley CV. Variability of ankle and brachial systolic pressures in the measurement of atherosclerotic peripheral arterial disease. J Epidemiol Community Health 1988;42:128-33.

26. Schroll M, Munck O. Estimation of peripheral arteriosclerotic disease by ankle blood pressure measurements in a population of 60 year old men and women. J Chron Dis 1981;34:261-9.

27. Vogt MT, Cauley JA, Kuller LH, Hulley SB. Prevalence and correlates of lower extremity arterial disease in elderly women. Am J Epidemiol 1993;137:559-68.

28. Newman AB, Sutton-Tyrrell K, Rutan GH, Locher J, Kuller LH. Lower extremity arterial disease in elderly subjects with systolic hypertension. J Clin Epidemiol 1991;44:15-20.

29. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC VI). Arch Intern Med 1997;157:2413-46.

30. World Health Organization. Diabetes Mellitus, report of a WHO Study group. WHO technical report series. No. 727. Geneva: WHO, 1985.

31.   Gent CM van, Voort HA van der, Bruyn AM de, Klein F. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.

32.   Burstein M, Scholnick HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. J Lipid Res 1970;11:583-95.

33.   Grove TH. Effect of reagent pH on determination of high-density lipoprotein cholesterol by precipitation with sodium phosphotungstate-magnesium. Clin Chem 1979;25:560-4.

34.   International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. Geneva: World Health Organization, 1992.

35.   Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. Circulation 1992;85:I2-10.

36.   Cupples LA, Gagnon DR, Kannel WB. Long- and short-term risk of sudden coronary death. Circulation 1992;85:I11-8.

37.   Kuller LH, Shemanski L, Psaty BM, et al. Subclinical disease as an independent risk factor for cardiovascular disease. Circulation. 1995;92(4):720-6

TABLE 1. General characteristics of study population (n=6002).

Characteristic	Mean (SD[*]) or %
Age (years)	68.9 (8.9)
Male gender (%)	40.8
Body mass index (kg/m^2)	26.3 (4.0)
Systolic blood pressure (mmHg)	139 (22)
Diastolic blood pressure (mmHg)	74 (12)
Hypertension[†] (%)	34.9
Serum total cholesterol (mmol/l	6.6 (1.2)
Serum HDL-cholesterol[‡] (mmol/l)	1.3 (0.4)
Smoking (%) Current	22.5
Former	42.4
Diabetes mellitus (%)	10.3
History of myocardial infarction or stroke (%)	15.7
PAD[§] (%)	18.2
Intermittent claudication[‖] (%)	6.2

* SD: standard deviation.

† Defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 100 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.

‡ High density lipoprotein cholesterol.

§ Assessed by measuring the ankle-arm index, with peripheral arterial disease (PAD) present with an ankle-arm index <0.90.

‖ According to the criteria of the WHO Rose-questionnaire. Probability of intermittent claudication among subjects with PAD

TABLE 2. Hazard ratios (95% confidence interval) of CVD mortality in individuals with an ankle-arm index (AAI) <0.90 with and without intermittent claudication (IC) in comparison to individuals with an AAI ≥0.90, adjusted for age and sex (Model A), and for multiple possible confounders (Model B).

| | Baseline category of peripheral arterial disease (PAD) | | | |
| | AAI*<0.90 and IC† | | AAI <0.90 and no IC | |
	Model A‡	Model B§	Model A‡	Model B§
All subjects	2.70	2.18	1.89	1.49
	(1.67-4.37)	(1.34-3.55)	(1.54-2.30)	(1.21-1.85)
In subjects free of	2.05	1.73	1.81	1.49
CVD at baseline	(1.04-4.04)	(0.87-3.43)	(1.40-2.32)	(1.14-1.95)

* Ankle-arm index.

† Intermittent claudication according to the criteria of the WHO Rose-questionnaire.

‡Model A: adjusted for age and sex.

§Model B: adjusted for age, sex, body mass index, hypertension, cholesterol, HDL-cholesterol, smoking, diabetes mellitus and medical history of CVD.

TABLE 3. Hazard ratios (95% confidence interval) of CVD mortality in individuals with PAD defined as an AAI <0.70, as 0.70 ≤ AAI <0.90, and as 0.90 ≤ AAI <1.10, in comparison to individuals with an AAI ≥1.10*, adjusted for age and sex (Model A), and for multiple possible confounders (Model B).

	Baseline category of peripheral arterial disease (PAD)					
	AAI†<0.70 (n = 445)		0.70≤ AAI <0.90 (n = 650)		0.90≤ AAI <1.10 (n = 1899)	
	Model A‡	Model B§	Model A	Model B	Model A	Model B
CVD mortality	3.04 (2.33-3.99)	2.27 (1.70-3.01)	1.85 (1.40-2.44)	1.35 (1.01-1.82)	1.45 (1.10-1.84)	1.24 (0.97-1.58)

*Subjects with an AAI higher then 1.50 were excluded

†AAI: ankle-arm index.

‡Model A: adjusted for age and sex.

§Model B: adjusted for age, sex, body mass index, hypertension, cholesterol, HDL-cholesterol, smoking, diabetes mellitus and medical history of CVD.

Figure 1. Kaplan-Meier survival curves for CVD mortality in individuals with PAD, defined as an ankle-arm index (AAI) <0.90, with or without intermittent claudication (IC), and in individuals with no PAD, i.e. an AAI ≥0.90. The survival curves have been adjusted for age, sex, and medical history of cardiovascular disease.
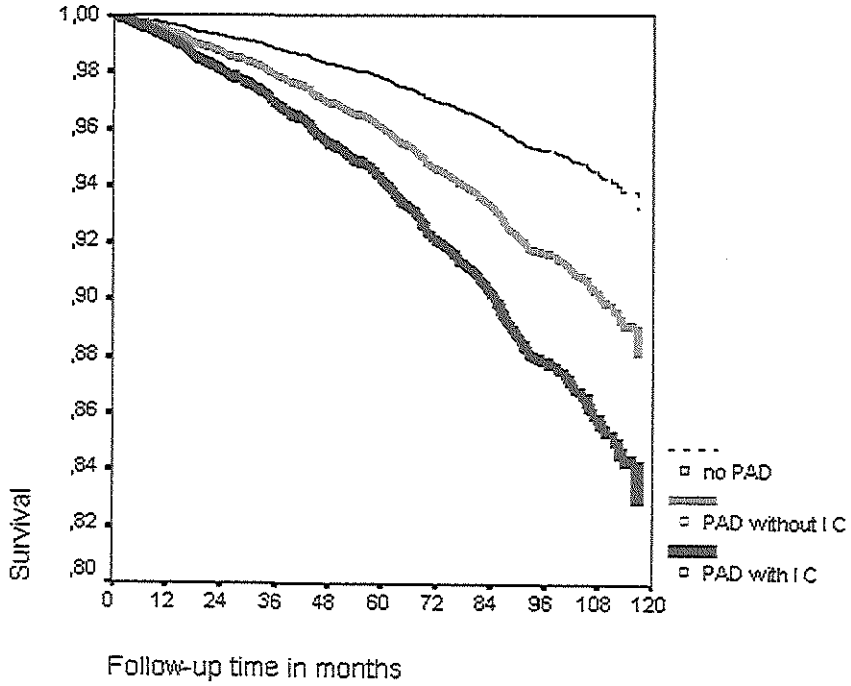
Ankle-arm index is a continuous risk indicator of cardiovascular disease

Abstract

The objective of this study was to examine the shape of the relationship between ankle-arm index (AAI) and cardiovascular disease (CVD), in particular whether there is a threshold above which AAI and CVD are not associated.

We studied the association of the AAI in octiles with baseline Framingham CVD risk, other measures of atherosclerosis (intima media thickness, carotid plaques and aortic calcifications), and incident CVD in the Rotterdam Study, a prospective cohort study in subjects aged 55 years and over. Both association with and additional predictive value to Framingham CVD risk were analyzed. All analyses were adjusted for age and sex.

The AAI showed an inverse graded relation without evidence of a threshold with Framingham CVD risk (from 35.7% in the lowest octile to 22.7% in the highest octile of AAI) and other measures of atherosclerosis. The AAI was gradually associated with incident CVD without evidence of a plateau in the relationship. Subjects with an AAI in the lowest octile had a four times higher risk of CVD compared to subjects with an AAI in the highest octile (hazard ratio 4.23; 95%CI 2.63, 6.81). After adjustment for traditional CVD risk factors and medical history of CVD, the association was less strong, but still evident (OR 2.49; 95%CI 1.52, 4.08). The AAI showed synergy with the Framingham CVD risk score in predicting CVD (p=0.02). We therefore conclude that the AAI can be used as a continuous risk indicator of CVD.

INTRODUCTION

Although the ankle-arm index (AAI) seems a strong and independent predictor of cardiovascular mortality and non-fatal cardiovascular events in the elderly (1, 2), the AAI is seldom used to screen for manifestations of atherosclerotic disease other than lower extremity arterial disease. Most studies (1, 2) used a cut-off of 0.9 below which subjects are marked as being at high risk for cardiovascular disease (CVD). Newman furher devided the subjects in AAI categories up to 1.0 and found increased CVD risk with decreasing AAI among the elderly (3). No studies have examined the association of the AAI with risk of CVD over the whole range of AAI. If the AAI shows predictive value over the whole range of AAI values, the AAI should no longer be dichotomized but should be used as a continuous risk indicator for CVD.

To determine whether the AAI is a continuous risk indicator of CVD, we examined the association of the AAI in octiles with baseline Framingham CVD risk score, other measurements of atherosclerosis, and new CVD events.

METHODS

Study population
The association of the AAI with baseline CVD risk and future CVD events was analyzed in the Rotterdam Study, a population-based prospective cohort study designed to investigate determinants of the occurrence and progression of chronic diseases in the elderly (4). From 1990 to 1993, data on 3105 men and 4878 women aged 55 years and over were collected. Clinical follow-up data on fatal and non-fatal endpoints were obtained from the general practitioners of the participants from 1990 until 1998. The mean duration of follow up was 5.3 years.

Assessment of CVD risk factors
History of CVD and smoking behavior were ascertained by an extensive interview at the participant's home. A person was designated as having a positive medical history for CVD if a myocardial infarction was diagnosed by a cardiologist or by ECG (verified by cardiologist), a stroke was diagnosed by a physician, or if the patient reported having undergone CABG, PTCA or carotid endarterectomy. Subjects were

categorized into smokers (current or quit within last three years) and non-smokers (not smoking in the last three years). At the research center several indices were measured. Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. Diabetes mellitus was defined as the current use of antidiabetic medication and / or a non-fasting serum glucose level greater than 11.0 mmol/L before or after an oral glucose tolerance test. Subjects with missing values on serum glucose but not using antidiabetic medication were initially classified as non-diabetics. Serum total cholesterol was determined by an automated enzymatic procedure. Serum high density lipoprotein (HDL) cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium. In all subjects free of CVD at baseline the Framingham 10-years CVD risk score was calculated (5, 6).

Measures of atherosclerosis

At baseline of the Rotterdam study, the ankle-arm index (AAI) was measured. The AAI left and right was calculated as the ratio of the systolic blood pressure of the posterior tibial artery, as assessed by a 8 MHz continuous wave Doppler probe and a random-zero sphygmomanometer, to the systolic blood pressure at the arm. The lowest AAI of the two legs was used in the analysis (7). Because an AAI higher than 1.50 can be due to arterial calcification and therefore is highly unreliable, AAI's higher than 1.50 were assigned as missing. In the case of an AAI value of zero, the AAI measured by the a. dorsalis pedis was taken instead, because of the possibility of a congenital agenesis of the arteria tibialis posterior. The AAI was categorized into octiles.

The extent of atherosclerotic disease was also assessed using three other measures: the intima media thickness of the common carotid artery (IMT), the plaque score in the carotid artery, and calcifications of the abdominal aorta.

To measure IMT and carotid plaques, ultrasonography of the common carotid artery, carotid bifurcation and internal carotid artery of the left and right carotid arteries was performed with a 7.5-MHz linear-array transducer (ATL Ultra-Mark IV). On a longitudinal, two dimensional ultrasound image of the carotid artery, the anterior (near) and posterior (far) walls of the carotid artery are displayed as two bright white lines separated by a hypogenic space. The distance between the leading edge of the

first bright line of the far wall and the leading edge of the second bright line indicates the IMT. For this study, the IMT measured in millimeters in the common carotid artery was taken into account. The plaque score was derived by counting the number of sites with a plaque, leading to a maximum score of 6. Plaques were defined as focal widenings relative to adjacent segments, with protrusion into the lumen and composed of calcified and/or non-calcified components.

Aortic calcification was diagnosed by radiographic detection of calcified deposits in the abdominal aorta. Lateral abdominal films (T12-S1) were made from a fixed distance while the subject was seated. Aortic calcifications were considered present when linear densities were seen in an area parallel and anterior to the lumbar spine (L1-L4). The value for the extent of calcification (calcAo) was scored according to the length of the involved area (1 cm, 2 to 5 cm, 6 to 10 cm, and >10 cm). In the analyses, we only used present or absent calcification.

Outcome assessment

Information on incident fatal and non-fatal events was obtained from the general practitioners working in the district of the study population. All events were classified according to the International Classification of Diseases, 10th version (8). The outcome-variable of interest includes myocardial infarction (I21) and stroke (I63-I67).

Data analysis

The ankle-arm indices were divided in octiles. The cut-off levels were 0.82, 0.97, 1.04, 1.10, 1.15, 1.21, and 1.28. The Framingham CVD risk score, the IMT and the plaque score in the carotids were compared in octiles of AAI with one-way analysis of variance (adjusted for age and sex). The association between the AAI in octiles and aorta calcifications was determined by age- and sex- adjusted logistic regression analysis. The relation of the AAI octiles to the incident CVD events was determined by Cox proportional hazard analysis, both age- and sex- adjusted and adjusted for all traditional risk factors and medical history of CVD. All analyses were performed using SPSS software (SPSS for Windows 9.0, SPSS Inc., Chicago, USA).

RESULTS

In 6002 of the total of 7983 subjects, the AAI could be measured in at least one leg and CVD risk factors (systolic blood pressure, cholesterol / HDL-ratio, smoking and diabetes) were known. The mean Framingham Heart Study 10-year CVD risk was 27.4%. During follow-up, 216 myocardial infarctions and 210 ischemic strokes occurred (Table 1), comprising a total of 413 CVD events.

Relation to baseline CVD risk

An approximately linear inverse relationship was demonstrated between the AAI (in octiles) and the age and sex-adjusted mean Framingham 10 year-CVD risk score (Figure 1). The 10 year-CVD risk was 34.4% in the lowest octile versus 21.9% in the highest octile of AAI. Also above the AAI value of 1.04 the association was gradual. Adjacent octiles differed all statistically significant, except for octile 5 and 6 (p = 0.140).

Relation to other measures of atherosclerosis

Figure 2 shows the analyses of the relation between AAI and other known measures of atherosclerosis. AAI showed an inverse and graded relationship with intima-media thickness, carotid plaque score and calcification of the aorta. In every octile, the value of carotid plaque score and aorta calcification, respectively, was lower than in the preceding octile and the difference between the values in the seventh compared to the eighth were statistically significant (p = 0.050 and p = 0.043 respectively). For intima-media thickness, a gradual association was less clear with AAI values above 1.09 (the fourth octile).

Relation to future cardiovascular disease

The risk of CVD increases gradually with a decreasing AAI without evidence of a plateau in the relationship (Figure 3). The risk of incident CVD in subjects with an AAI lower than 0.82 was more than four times higher than in subjects with an AAI higher than 1.28 (age-and-sex-adjusted hazard ratio 4.23; 95%CI 2.63, 6.81). After adjustment for the traditional risk factors and medical history of CVD the association was less strong (Table 2.), but still statistically significant (OR 2.49; 95%CI 1.52,

4.08). The association was consistent with the association of AAI with other measures of atherosclerosis.

From Figure 4 we learn that there is an interaction between AAI and the estimated Framingham CVD risk in the prediction of incident CVD. A statistically significant interaction term (p=0.02) was demonstrated between AAI and Framingham CVD risk in predicting CVD. Especially in the highest quartile of Framingham CVD risk, there is clearly a gradual relationship between AAI and incident CVD. The risk of incident CVD was highest among subjects with a Framingham CVD risk in the highest quartile and an AAI in the lowest quartile (hazard ratio 34.9, 95% CI, 11.0-110.9).

DISCUSSION

The AAI showed a gradual and inverse association with the Framingham CVD risk score and other noninvasive measures of atherosclerosis such as intima media thickness, carotid plaques, and aortic calcifications. The AAI also showed a graded relationship with the risk of new CVD events. The difference was especially notable for the lower octiles of AAI, but was also present within the range of AAI values considered as normal. Even above an AAI value of 1.0, different AAIs had different prognostic impact on the risk of CVD.

The presence of subclinical CVD may be an important marker of the effect of risk factors on the cardiovascular system. In our study, the AAI showed additional predictive value to the Framingham CVD risk score in the prediction of new CVD events. The risk of incident CVD was very high among subjects with a Framingham CVD risk in the highest quartile and an AAI in the lowest quartile with a relative risk of 11.0 as the lower bound of the 95% confidence interval.

We are aware that the AAI measurement is affected by intrinsic factors like edema, rheumatoid arthritis, anxiety, diabetes and blood pressure (9-11). In our study we adjusted for diabetes mellitus and systolic blood pressure, but that did not have any effect on the point estimates when studying the association between AAI and incident CVD. The fact that the AAI measurement was performed only once per subjects may also lead to information bias. Fowkes et al, however, showed that the repeatability of the AAI is such that a single measurement is suitable for most

epidemiological studies. (10) Furthermore, they showed a low interobserver variability (10) which may support the generalizability of our results.

Newman et al. already described an inverse dose-response relation of the AAI with CVD risk factors and subclinical and clinical CVD among older adults, but they did not study the association over the whole range of AAI but devided the subjects in AAI categories up to 1.0. (3) Our data suggest that the AAI can be used as a continuous variable, using the whole range off AAI values.

In conclusion, the AAI is a continuous risk indicator of CVD and has a potential role as an additional predictive variable to select high risk subjects for CVD. It's use in clinical practice as a screening tool for CVD needs further research.

REFERENCES

1. Kornitzer M, Dramaix M, Sobolski J, Degre S, De Backer G. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. Angiology. 1995;46:211-9.

2. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ. 1996;313:1440-4.

3. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, Wolfson SK. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation. 1993;88:837-45.

4. Hofman A, Grobbee DE, de Jong PT, et al. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol. 1991;7(4):403-22.

5. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation. 1991;83:356-362.

6. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. Am J Cardiol. 1976;38:46-51.

7. Fowkes FGR. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. Int J Epidemiol 1988;17:248-54.

8. International Statistical Classification of Diseases and Related Health Problem. Geneva, World Health Organization, 1992.

9. Belcaro G, Nicolaides AN. Pressure index in hypotensive or hypertensive patients. J Cardiovasc Surg. 1989;30:614-7.

10. Goss DE, de Trafford J, Roberts VC, Flynn MD, Edmonds ME, Watkins PJ. Raised ankle/brachial pressure index in insulin-treated diabetic patients. Diabet Med 1989;6(7):576-8.

11. Goss DE, Stevens M, Watkins PJ, Baskerville PA. Falsely raised ankle/brachial pressure index: a method to determine tibial artery compressibility. Eur J Vasc Surg 1991;5(1):23-6.

12. Fowkes FG, Housley E, Macintyre CC, Prescott RJ, Ruckley CV. Variability of ankle and brachial systolic pressures in the measurement of atherosclerotic peripheral arterial disease. J Epidemiol Community Health. 1988;42:128-33.

Table 1. Population characteristics.

Determinants	Mean ± sd / proportion
Age at baseline	68.9 years ± 8.9
Male sex	40.8%
Body mass index	26.3 ± 4.0
Hypertension measured / treated *	34.9%
Systolic blood pressure	137.8 mmHg ± 21.9
Diastolic blood pressure	74.1 mmHg ± 11.3
Cholesterol/HDL-ratio	5.22 ± 1.61
Current smoking	22.5%
Diabetes mellitus †	10.3%
Serum glucose level	6.9 ± 3.0
Medical history of cardiovascular disease ‡	15.7%
Lowest measured ankle-arm index	1.06 ± 0.23
Framingham Heart Study 10-year CVD risk	27.4% ± 14.5%
Incident cases of MI during follow up	3.6% (216 cases)
Incident Strokes during follow up	3.5% (210 cases)
Follow up time	1947 days ± 547

* SBP ≥ 160 mmHg and / or DBP ≥ 95 mmHg or using antihypertensive medication

† The current use of antidiabetic medication and / or a non-fasting serum glucose level > 11.0 mmol/L before or after an oral glucose tolerance test.

‡ Myocardial infarction, stroke, CABG, PTCA or carotid surgery in the past

Table 2. The association between ankle-arm index (AAI) and the incidence of cardiovascular disease (CVD) events.

Octiles of AAI	Range of values	Percentage of CVD cases	Hazard ratios* Model 1[†]	Hazard ratios* Model 2[‡]
1	0.00 - 0.81	13.0%	4.23 (2.63, 6.81)	2.49 (1.52, 4.08)
2	0.82 - 0.96	8.7%	3.17 (1.95, 5.16)	2.22 (1.35, 3.65)
3	0.97 - 1.03	7.9%	3.06 (1.87, 5.02)	2.18 (1.31, 3.61)
4	1.04 - 1.09	7.3%	2.83 (1.72, 4.64)	2.07 (1.25, 3.42)
5	1.10 - 1.14	5.0%	1.97 (1.15, 3.36)	1.61 (0.94, 2.76)
6	1.15 - 1.20	4.5%	1.76 (1.04, 2.98)	1.46 (0.86, 2.48)
7	1.21 - 1.27	5.7%	2.13 (1.27, 3.56)	1.90 (1.13, 3.19)
8	1.28 - 1.50	2.9%	1.0	1.0

* Hazard ratios with 95% confidence intervals; the highest octile as reference.

† Model 1: adjusted for age and sex.

‡ Model 2: adjusted for age, sex, body mass index, hypertension, systolic blood pressure, diastolic blood pressure, plasma cholesterol/HDL-ratio, smoking, diabetes mellitus and medical history of cardiovascular disease.

Figure 1. The association between ankle-arm index (AAI) and the Framingham CVD risk score within subjects free of CVD at baseline, adjusted for age and sex.
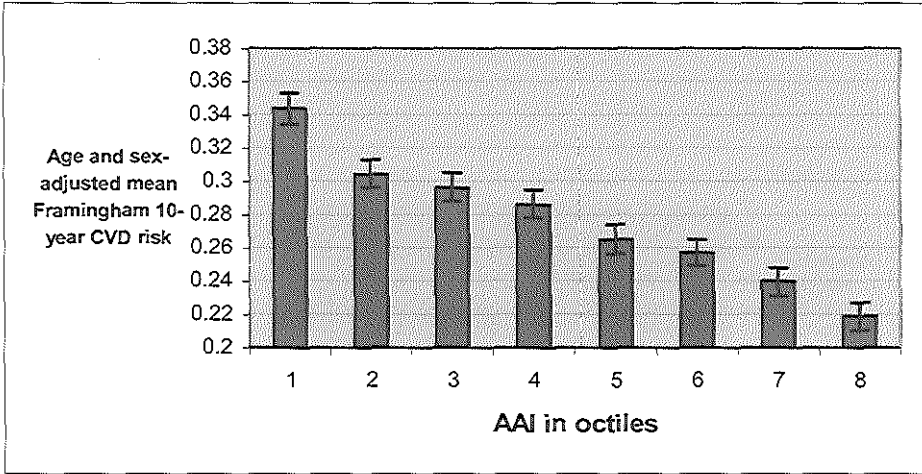
Figure 2. The age-and-sex-adjusted association of ankle-arm index (AAI) with other measures of localized atherosclerosis: a) with Intima Media Thickness (IMT), b) with Carotid Plaque Score (CPS), c) with presence of aorta calcifications (Odds ratios with the highest octile of AAI as the reference group).

a)
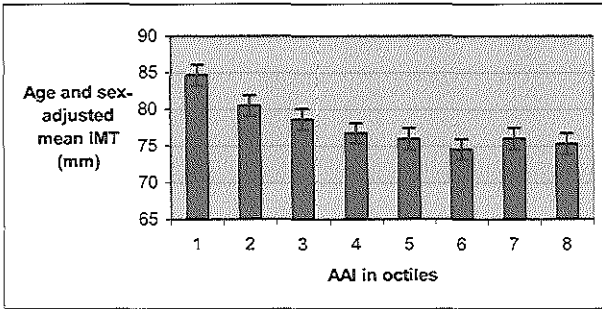
b)
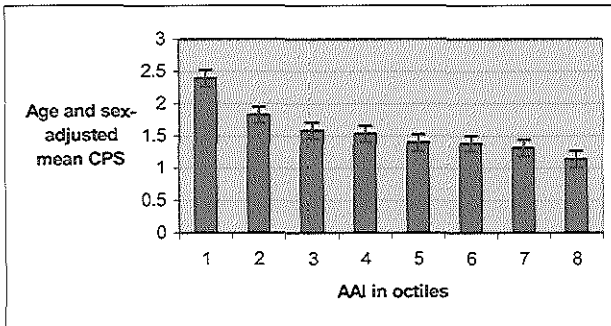
c) Aorta calcifications (Odds ratios)
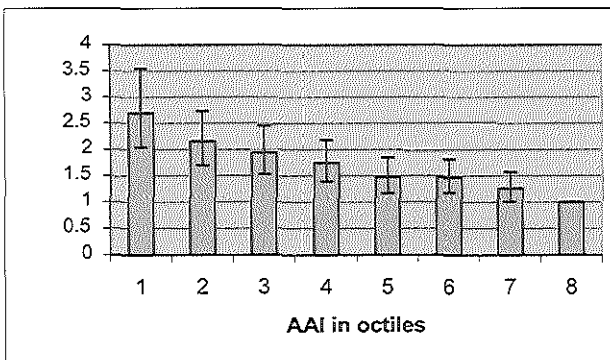
Figure 3. Age and sex adjusted hazard ratios of octiles of ankle-arm index (AAI) for the incidence of cardiovascular disease with the highest octile of AAI as the reference group.
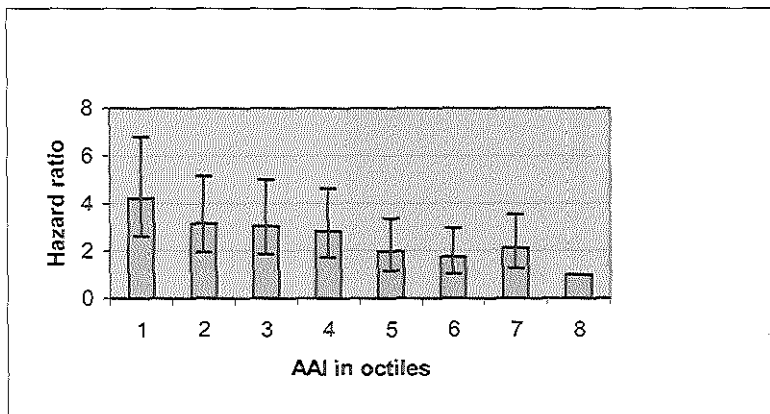
Figure 4. Associations (hazard ratios) of quartiles of Framingham CVD risk (FHS) and ankle-arm index (AAI) with incident CVD within subjects free of cardiovascular disease at baseline.
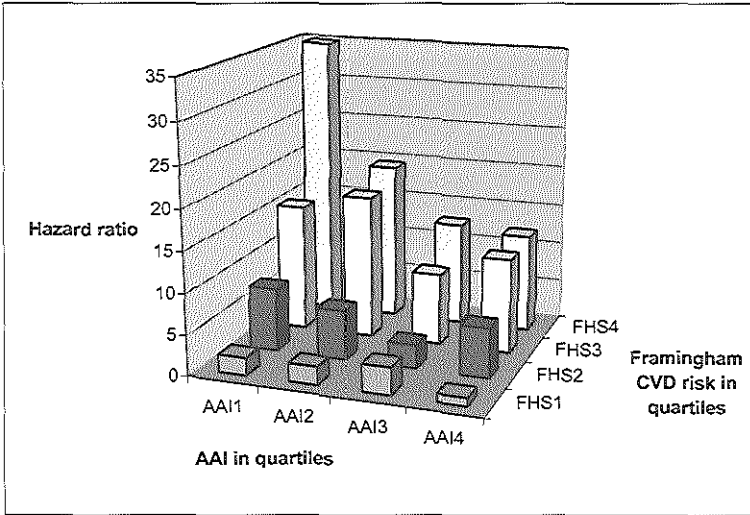
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Coronary heart disease risk prediction in the Rotterdam Study
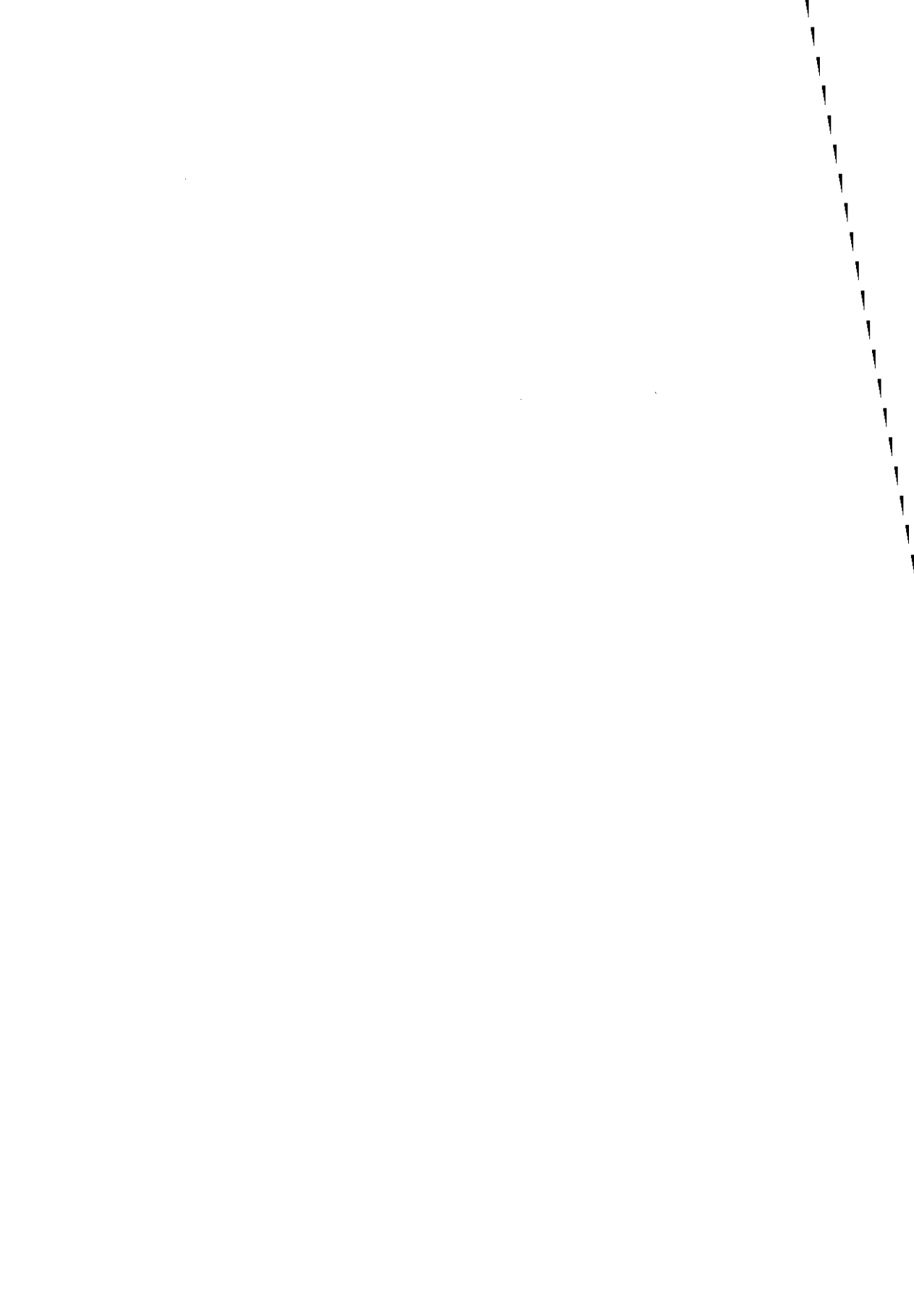
Coronary heart disease risk prediction in the Rotterdam Study

Abstract

Existing coronary heart disease (CHD) risk functions may not be applicable to older adults, in whom mild manifestations of cardiovascular disease (CVD) and subclinical CVD are commonly present. We developed a CHD risk function based on a prospective population cohort (the Rotterdam Study) of 5431 men and women aged 55 to 80 years without evident CVD at baseline using Cox proportional hazard regression analysis. Furthermore, we studied the additional prognostic impact of new risk indicators. Within 7 years of follow-up, 388 cardiac events occurred. Important predictors that were selected for the risk function included medical history, blood pressure measurements, laboratory tests, medication use and mild manifestations of CVD as assessed by questionnaires. The risk function discriminated well between subjects with incident CHD and those without (area under the Receiver Operating Characteristic curve (AUC) = 0.748). The discriminant accuracy was slightly improved (p = 0.039) by including ankle-arm index (AAI) and ECG characteristics (AUC = 0.754). The presented risk function is a promising tool to select subjects for CHD prevention among older adults. Additional measurement of AAI or ECG offers limited additional predictive value.

INTRODUCTION

Coronary Heart Disease (CHD) is the main cause of mortality in industrial countries. Recent trials have shown that reducing serum cholesterol (1), reducing blood pressure (2) and the use of low dose aspirin (3, 4) reduce the incidence of CHD. The absolute benefit of these interventions depends on the pre-treatment level of CHD risk (3, 5). Current guidelines (1, 3, 5, 6) emphasize the importance of selecting subjects based on their absolute risk of CHD.

The Framingham Heart Study (7-9), the Copenhagen City Heart Study (10) and the PROCAM study (11) developed risk functions for assessing risk of developing CHD. These risk functions, however, have several limitations. First, the risk functions are not readily applicable to older populations in which many subjects have mild manifestations of cardiovascular disease (CVD) such as stable angina pectoris, intermittent claudication, and history of transient ischemic attack. These subjects were excluded from the published studies (7-11). It is known, however, that these subjects are generally treated inadequately until they experience a more severe CVD event such as stroke or myocardial infarction (12). Because risk intervention may be especially useful in this group, mild manifestations of CVD may be considered predictors of CHD endpoints (13-16). Second, risk factors can have a different impact within different age groups. Several studies described a change in the relation of blood pressure to CHD with aging (17, 18). These studies showed increasing predictive value of pulse pressure as subjects age. On the other hand, family history of CVD may have less impact in older subjects (19, 20). Third, since the Framingham Heart study had introduced their risk function, new risk indicators are evaluated for additional predictive value. Measures of subclinical CVD like ankle-arm index (AAI) and various ECG characteristics may be useful in population based risk stratification since they can be easily assessed at low cost (21, 22). Especially in the older adults, subclinical CVD is commonly present and may be important to take into account when estimating the risk of CHD (22). Finally, quite often risk functions are not generalizable to populations other than those in which they were developed. Due to overfitting in regression modelling, risk functions could lead to overestimation of high risk and underestimation of low risk subjects. Recently, appropriate statistical methods have become available to correct for overfitting (23-25).

The purpose of this study was to develop a new CHD risk function based on traditional risk factors and mild manifestations of CVD. We also evaluated the additional predictive value of various indicators of subclinical CVD and we corrected for overfitting of the regression models.

METHODS

Study population

Within the Rotterdam Study population, a prospective population cohort of 7983 subjects, we selected 5431 men and women aged 55-80 years without documented myocardial infarction, stroke, coronary revascularization, or carotid intervention at baseline. These subjects were followed for a mean of 7 years (26). All subjects gave written informed consent and the study was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam. The baseline examination was conducted from 1990 to 1993. Participants were interviewed at home by trained research assistants, using a computerized questionnaire. Subsequently, the participants visited the research center for several measurements, including blood pressure at arms and ankles, body mass index, and blood sampling (cholesterol, HDL-cholesterol, and glucose level). Clinical follow-up data were obtained from the general practitioners of the participants from 1990 onwards.

Assessment of risk indicators

Diabetes mellitus was defined as the current use of anti-diabetic medication and/or a non-fasting serum glucose level greater than 11.0 mmol/L before or after an oral glucose tolerance test. Subjects were categorised as current smokers, former smokers and non-smokers. Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. A physician at the research center asked subjects whether they used antihypertensive medication. In these subjects, the blood pressure was measured before they took their medication. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Serum total cholesterol was determined by an automated enzymatic procedure. Serum high-density lipoprotein (HDL)

cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium. The cholesterol/HDL-ratio was calculated.

Height and weight were measured and the body mass index was calculated (kg/m^2). Also the waist-to-hip ratio was measured. A person was defined as having a positive family history of CVD if a first-degree family member was known to have had a myocardial infarction or stroke before the age of 65 years.

The Rose questionnaire (15) was used to detect signs of angina pectoris and/or intermittent claudication. A history of a transient ischemic attack was also assessed during the baseline interview using a structured questionnaire (27). A physician at the research center asked subjects whether they used medication for CVD. Angina pectoris was defined to be present when the questionnaire indicated angina pectoris or when the patient was using medication for angina pectoris. The presence of intermittent claudication and transient ischemic attack was determined analogously.

The ankle-arm index (AAI) was calculated as the ratio of the systolic blood pressure of the posterior tibial artery, as assessed by an 8 MHz continuous wave Doppler probe and a random-zero sphygmomanometer, to the systolic blood pressure at the arm. The lowest AAI, either right or left, was used in the analysis. Because an AAI higher than 1.50 can be due to arterial calcification and therefore is highly unreliable, AAIs higher than 1.50 were assigned as missing. If the systolic pressure over the posterior tibial artery was zero, we assumed this was due to congenital agenesis and the dorsal pedal artery pressure was used instead. Finally, an ECG was made and computer-analyzed by the MEANS program (28) for the presence of left ventricular hypertrophy, atrial fibrillation, and signs indicating silent myocardial infarction.

Missing values were present for plasma glucose level (5.8 percent), plasma cholesterol level (1.2 percent), blood pressure (1.8 percent), body mass index (1.1 percent), waist-to-hip ratio (5.9 percent), the Rose questionnaire (1.0 percent), the AAI (9.3 percent) and ECG (2.9 percent). Because deletion of cases with missing data may cause bias and increases variance, all missing values were predicted from other characteristics using the Expectation Maximization method and were subsequently imputed (25).

Outcome assessment

All events were classified according to the International Classification of Diseases, 10th version. CHD events were defined as myocardial infarction (I21), PTCA

(Z95.5), CABG (Z95.1), death from chronic ischemic heart disease (I20-I25), sudden death (I46, I49, R96), and death due to congestive heart failure (I50). All events were classified independently by two research physicians. If the physicians disagreed, a consensus was reached in a special session. Finally, a CVD expert verified all these events. In cases of unresolved discrepancy, the judgement by the expert was considered definite.

A subject was defined as having a medical history of CVD if a myocardial infarction was diagnosed by a cardiologist or general practitioner, a stroke was diagnosed by a physician, or if the patient reported having undergone CABG, PTCA, or carotid endarterectomy.

Model development

For each risk indicator we performed an age-and sex-adjusted Cox proportional hazard analysis and calculated the Akaike's Information Criterion (AIC) as a measure of increase in model performance for the prediction of CHD (25). The AIC is calculated as the χ^2-change minus two times the degrees of freedom, in which the χ^2 is the difference between two models on the –2log Likelihood scale (25, 30). First we made sets of related risk indicators (Table 1), e.g. for blood pressure we examined systolic blood pressure, diastolic blood pressure, pulse pressure and antihypertensive medication use. For each set of related risk indicators we selected the variable with the highest AIC provided the AIC was positive and examined whether the variable with the next largest AIC was still additionally predictive over and above any variable already included (AIC > 0). We additionally examined whether cholesterol and HDL-cholesterol led to a better model performance when included separately compared to using the cholesterol/HDL-ratio.

Of all selected variables, a backward stepwise analysis with a p-value-to-remove of 0.10 was performed to achieve the pre-final model. This strategy of selection of main effects aimed to include all important risk indicators and therefore used a more liberal criterion than the standard $p < 0.05$ criterion (24, 31). A more conservative approach was followed for non-linear and interaction terms. Quadratic terms of all continuous variables were tested and added to the pre-final model if $p < 0.05$. Subsequently, all interaction terms with age and gender were tested and added to the pre-final model if $p < 0.01$. Also plausible interactions with mild manifestations of CVD were tested

with a p-value-to-enter of 0.05. This final model is referred to as the Rotterdam CHD risk function.

Using the Rotterdam CHD risk function, the AAI was tested for additional prognostic value and added if the model improved significantly ($p < 0.05$). The quadratic term of AAI and interactions of AAI with age, sex, and mild manifestations of CVD were tested in the same way as described above, which yielded 'extended model 1'. The ECG characteristics were tested in a similar fashion, which yielded 'extended model 2'. In 'extended model 3' both AAI and ECG-parameters were tested for additional prognostic value.

Based on the final models, the subject-specific 5-year probability of CHD was calculated as described in the technical appendix.

Model performance

The calibration of the Rotterdam CHD risk function was assessed graphically (32) to study how closely predicted outcomes agree with actual outcomes. The observed 5-year proportion of subjects with CHD was plotted against the average predicted 5-year CHD risk as calculated with the Rotterdam CHD risk function within octiles.

The discriminative ability of the risk function was evaluated by the area under the Receiver Operator Characteristic (ROC)-curve. The ROC curve is a plot of the true-positive rate (sensitivity) against the false-positive rate (1 minus specificity), evaluated for varying thresholds of predicted probability. The area under the ROC curve (AUC) can be interpreted as the probability that the risk function will assign a higher probability of CHD to a randomly chosen subject who gets CHD than to a randomly chosen subject without incident CHD during 5 years.

To determine internal validity, bootstrapping was performed (24, 33). The full selection process was repeated in every bootstrap sample (80 replications). We estimated a shrinkage factor to improve calibration of predictions in future patients, that is, to correct for overfitting of the risk function (24, 25). Bootstrapping also leads to a more reliable estimate of model performance as can be expected in similar populations (33).

The model performance of the Rotterdam CHD risk function was compared to the performance of the Framingham CHD risk function (7) after refitting this risk function to the Rotterdam Study population. Hereto, a new model was run with the

same covariates and interaction terms as in the original Framingham CHD risk function (34).

To study the additional predictive value of subclinical CVD (AAI and ECG characteristics), the model performance of the Rotterdam CHD risk function was compared with the performance of the extended models. All model performances were compared by differences in area under the ROC curve and tested for statistical significance using a paired Z-test.

Analyses were performed using SPSS for Windows 9.0, SPSS Inc., Chicago, USA and S-Plus version 2000, using the Design library (25).

RESULTS

Baseline-data of the study population are described in Table 1. Of the 5431 subjects, 21 percent were younger than 60 years whereas 14 percent were older than 75 years. A substantial proportion of subjects used antihypertensive medication (26 percent), had complaints of angina pectoris (6.7 percent) or had experienced transient ischemic attack (3.8 percent). Only 1.5 percent presented with intermittent claudication, whereas 13.5 percent had peripheral arterial disease (AAI < 0.90). During a mean follow-up period of 7 years, 205 incident myocardial infarctions, 43 PTCAs, 44 CABGs, and 96 primary CHD deaths occurred, comprising a total of 388 CHD events.

Model development

For all the risk indicators taken into consideration, the prognostic impact as measured by the AIC is presented in Table 1. All risk indicators were predictive for incident CHD, except measures of obesity and family history of CVD. The most important predictors were age, gender, diabetes mellitus, systolic blood pressure, antihypertensive medication use, serum cholesterol, HDL-cholesterol and angina pectoris. The use of antihypertensive medication was predictive even over and above systolic blood pressure (AIC=17.4). Serum cholesterol and HDL-cholesterol led to a better model performance when included separately than the cholesterol/HDL-ratio. Cigarette smoking, family history of myocardial infarction, intermittent claudication and transient ischemic attack were also predictive, but only to a moderately extent.

The model building process led to the Rotterdam CHD risk function of which the selected variables and the corresponding hazard ratios are listed in Table 2. The model performance improved significantly (AIC > 0) when taking into account the interaction between systolic blood pressure and antihypertensive medication use, the interaction between smoking and angina pectoris, and the quadratic term of cholesterol.

The AAI, left ventricular hypertrophy and signs of silent myocardial infarction on ECG were statistically significant predictors over and above the Rotterdam CHD risk function. The corresponding hazard ratios, adjusted for the variables used in the Rotterdam CHD risk function, are also listed in Table 2.

Model performance

The predicted probabilities obtained from the Rotterdam CHD risk function showed very good agreement with the observed incidence (Figure 1). The Rotterdam CHD risk function estimated the actual risk more precisely than the refitted Framingham CHD risk function.

The Rotterdam CHD risk function discriminated well between patients with CHD events during follow-up and subjects without, yielding an area under the ROC curve (AUC) of 0.748 (95 percent confidence interval: 0.718, 0.778) (Table 3). The risk function showed adequate internal validity, as indicated by the fact that the variable selection and the value of the risk parameters were stable during the bootstrap procedure. The AUC decreased to 0.732 (95 percent confidence interval: 0.709, 0.751) after bootstrapping (Table 3), suggesting that the discriminatory power will be somewhat lower in other but similar populations than the Rotterdam Study population. The shrinkage factor, derived from the bootstrap procedure was 0.91 for the Rotterdam CHD risk function, and ranged from 0.88 to 0.89 for the extended models. The final risk functions with an example of the calculation of the 5-year CHD risk are presented in the appendix.

The original Framingham CHD risk function was externally validated in our study population, yielding an AUC of 0.693. After refitting the risk function, the AUC increased significantly (p=0.001) to 0.728 (Table 3), indicating that the weight factors of the Framingham CHD risk function were not completely applicable to the Rotterdam Study. The discriminatory power of the Rotterdam CHD risk function was significantly higher than the refitted Framingham CHD risk function (p=0.006 after

bootstrapping). By using the Rotterdam CHD risk function instead of the refitted Framingham CHD risk function, 35.0 percent instead of 30.0 percent of the events could be predicted among subjects within the highest octile of the risk score and 55.2 percent instead of 53.0 percent within the highest quartile (Table 4).

The extended models all showed moderate but statistically significant improvement compared to the Rotterdam CHD risk function, also after bootstrapping (p=0.04). Including the AAI in the risk function increased the proportion of CHD events predicted with 1.2 percent among subjects within the highest octile of CHD risk and with 2.4 percent among subjects within the highest quartile of CHD risk (Table 4). Finally, including ECG characteristics in the model in addition to the AAI did not improve the discriminatory power significantly (p=0.07).

DISCUSSION

We developed a risk function to determine the risk of CHD from the characteristics of 5431 Dutch subjects aged 55 to 80 years without evident CVD at baseline. In addition to traditional risk factors, mild manifestations of CVD had predictive value. The risk function showed good performance as measured by AUC analysis and adequate internal validity as determined by bootstrapping. Adding indicators of subclinical CVD to the risk function improved the model performance slightly. Adding serum C-reactive protein to the risk function did not lead to improvement in model performance (AIC < 0)

In contrast to the Framingham Heart Study (8), in the present study CHD was defined as non-fatal myocardial infarction, need for a coronary intervention, death due to ischemic heart disease, and sudden cardiac death but angina pectoris was not included in our outcome measure. Because mild manifestations of CVD, like angina pectoris, transient ischemic attack and intermittent claudication are present in many older adults, they were used as risk indicators rather than as exclusion criteria or endpoints. The discriminatory power of the Rotterdam CHD risk function was significantly higher compared to the refitted Framingham CHD risk function (p=0.006 after bootstrapping), which at least in part can be ascribed to the additional prognostic value of mild manifestations of CVD.

In contrast to the Framingham Heart Study, no significant quadratic term was found for age. This may be due to the fact that the age range was smaller in our study, which considered subjects aged 55 to 80 years, while the Framingham CHD risk function was fitted on subjects aged 30 to 74 years. Only the quadratic term of the plasma cholesterol level was statistically significant and had a negative sign in our study. This is caused by the fact that with increasing cholesterol level, the association between cholesterol level and incident CHD diminishes. In contrast to the Framingham Heart Study, no significant interaction terms were found with gender. This can be due to the fact that our risk function was derived in an older population in which the gender difference in cardiovascular risk status becomes less pronounced.

The current study showed evidence that systolic blood pressure stronger associated with CHD in subjects not using antihypertensive medication than in medication users. We emphasize the importance of including both antihypertensive medication use and its interaction with systolic blood pressure in the CHD risk function. We also found an interaction, although inversely, between smoking and angina pectoris, which indicates that the predictive value of smoking was stronger in subjects without angina pectoris than in subjects with angina pectoris. This counter-intuitive result is known as the smoker's paradox (35, 36), i.e. non-smokers who present with angina pectoris may have CVD risk factors other than smoking and known CVD risk factors which put them at high risk.

In the middle-aged and elderly, Franklin et al. (18) suggested that pulse pressure might be superior to systolic and diastolic blood pressure in predicting CHD risk. However, in our study systolic blood pressure showed higher predictive power. In agreement with findings from the Framingham study (19), the present study showed additional predictive value of family history of myocardial infarction with an almost similar (24 percent versus 29 percent) increased risk of CHD.

A substantial proportion of subjects had peripheral arterial disease (i.e. AAI < 0.90), left ventricular hypertrophy or signs of myocardial infarction on ECG. Kuller et al already showed that identification of subclinical CVD might provide an important marker of the effect of CVD risk factors on the cardiovascular system among relatively asymptomatic individuals (13). Our results support this finding. The AAI showed additional predictive value, even when intermittent claudication was already in the model. ECG characteristics showed similar additional predictive value to the risk function but no additional predictive value after including AAI. Although the

increase in AUC of the risk function was statistically significant with the addition of AAI or ECG characteristics, the clinical relevance was limited; considering a preventive strategy in which one is willing to treat 12.5 percent of the population with the highest absolute risk of developing CHD, only 1 to 2 percent extra CHD events could be prevented within 5 years.

The Rotterdam CHD risk function showed reasonable discriminative ability (AUC = 0.748, which decreased to 0.732 after bootstrapping). The PROCAM risk function was reported with an apparent area under the ROC curve of 0.82. This higher value may be explained by the fact that the PROCAM risk function was developed in a younger population in which risk factors tend to have more impact. The authors did not present their results after bootstrapping, which could have quite some impact on the expected discriminatory ability of the risk function for other populations.

We believe that the Rotterdam CHD risk function can be applied to all older adults without evident CVD. Before introduction on a wide scale, the model must be tested further to establish whether its predictions are valid in other settings and younger age groups, whether using the prediction rule is cost-effective, and above which threshold of risk, preventive therapy should be advised.

In conclusion, the Rotterdam CHD risk function is a promising tool to select subjects for CVD prevention. This risk function is suitable for a population of older adults in whom mild manifestations of CVD are commonly present and who are often treated for their risk factors. The risk function performed better in older adults than the Framingham CHD risk function.

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. Wright JM, Lee CH, Chambers GK. Systematic review of antihypertensive therapies: does the evidence assist in choosing a first-line drug? Cmaj. 1999;161:25-32.

3. Meade TW, Brennan PJ. Determination of who may derive most benefit from aspirin in primary prevention: subgroup results from a randomised controlled trial. BMJ. 2000;321:13-7.

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

5. Mallion JM, Benkritly A, Hansson L, et al. Effect of intensive antihypertensive treatment and of aspirin in a low dose in the hypertensive. The HOT (Hypertension Optimal Treatment) study. Arch Mal Coeur Vaiss. 1999;92:1073-8.

6. Arends LR, Hoes AW, Lubsen J, et al. Baseline risk as predictor of treatment benefit: three clinical meta-re-analyses. Stat Med. 2000;19: 3497-518.

7. Anderson KM, Odell PM, Wilson PW, et al. Cardiovascular disease risk profiles. Am Heart J. 1991;121:293-8.

8. Anderson KM, Wilson PW, Odell PM, et al. An updated coronary risk profile. A statement for health professionals. Circulation. 1991;83:356-362.

9. Odell PM, Anderson KM, Kannel WB. New models for predicting cardiovascular events. J Clin Epidemiol. 1994;47:583-92.

10. Thomsen TF, Davidsen M, Jorgensen HIT, et al. A new method for CHD prediction and prevention based on regional risk scores and randomized clinical trials; PRECARD and the Copenhagen Risk Score. J Cardiovasc Risk. 2001;8:291-7.

11. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation. 2002; 105:310-5.

12. Psaty BM, Furberg CD, Kuller LH, et al. Traditional risk factors and subclinical disease measures as predictors of first myocardial infarction in older adults: the Cardiovascular Health Study. Arch Intern Med. 1999;159:1339-47.

13. Kuller LH, Shemanski L, Psaty BM, et al. Subclinical disease as an independent risk factor for cardiovascular disease. Circulation. 1995; 92:720-6.

14. Kuller LH. Prevention of cardiovascular disease and the future of cardiovascular disease epidemiology. Int J Epidemiol. 2001;30 (1 Suppl):S66-72.

15. Rose G, McCartney P, Reid DD. Self-administration of a questionnaire on chest pain and intermittent claudication. Br J Prev Soc Med. 1977;31:42-8.

16. Murabito JM, Anderson KM, Kannel WB, et al. Risk of coronary heart disease in subjects with chest discomfort: the Framingham Heart Study. Am J Med.1990; 89: 297-302.

17. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart

disease risk change with aging? The Framingham Heart Study. Circulation. 2001;103:1245-9.

18. Franklin SS, Khan SA, Wong ND, et al. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. Circulation. 1999;100:354-60.

19. Myers RH, Kiely DK, Cupples LA, et al. Parental history is an independent risk factor for coronary artery disease: the Framingham Study. Am Heart J. 1990; 120:963-9.

20. Shea S, Ottman R, Gabrieli C, et al. Family history as an independent risk factor for coronary artery disease. J Am Coll Cardiol. 1984;4:793-801.

21. Shinozaki T, Hasegawa T, Yano E. Ankle-arm index as an indicator of atherosclerosis: its application as a screening method. J Clin Epidemiol. 1998;51:1263-9.

22. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Health Study (CHS) Collaborative Research Group. Circulation. 1993;88:837-45.

23. Van Houwelingen JC, Le Cessie S. Predictive value of statistical models. Stat Med. 1990; 9: 1303-25.

24. Steyerberg EW, Eijkemans MJ, Harrell FE, et al. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med. 2000;19: 1059-79.

25. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15:361-87.

26. Hofman A, Grobbee DE, de Jong PT, et al. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol. 1991;7(4):403-22.

27. Bots ML, van der Wilk EC, Koudstaal PJ, et al. Transient neurological attacks in the general population. Prevalence, risk factors, and clinical relevance. Stroke. 1997;28:768-73.

28. de Bruyne MC, Kors JA, Hoes AW, et al. Diagnostic interpretation of electrocardiograms in population-based research: computer program research physicians, or cardiologists? J Clin Epidemiol. 1997;50:947-52.

29. Azen SP, Van Guilder M, Hill MA. Estimation of parameters and missing values under a regression model with non-normally distributed and non-randomly incomplete data. Stat Med. 1989;8:217-28.

30. Akaike H. Information theory as an extension of the maximum likelihood principle. In: Petrov BN, Csaki F, eds. 2nd International Symposium on Information Theory. Budapest: Akademia Kiado: 1973:267-81.

31. Spiegelhalter DJ. Probabilistic prediction in patient management and clinical trials. Stat Med. 1986;5:421-33.

32. Graf E, Schmoor C, Sauerbrei W, et al. Assessment and comparison of prognostic classification schemes for survival data. Stat Med. 1999;18:2529-45.

33. Steyerberg EW, Harrell FE, Borsboom GJ, et al. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54:774-81.

34. D'Agostino RB, Grundy S, Sullivan LM, et al. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001;286:180-7.

35. Himbert D, Juliard JM, Golmard JL, et al. Revision of the "Smoker's Paradox": smoking is not a

good prognostic factor immediately after myocardial infarction. Arch Mal Coeur Vaiss. 2001;94:262-8.

36. Gourlay SG, Rundle AC, Barron HV. Smoking and mortality following acute myocardial infarction: results from the National Registry of Myocardial Infarction 2. Nicotine Tob Res. 2002;4:101-7.

TABLE 1. Prognostic value of various risk indicators in the Rotterdam Study population

The prognostic value of different risk indicators was measured by the Akaike's Information Criterion (AIC), adjusted for age and sex. The higher the AIC, the higher the prognostic information. An AIC equal to or smaller than zero indicates no additive predictive value over and above age and gender.

Risk indicators *	Mean (SD) / proportion	AIC †
Traditional risk indicators		
Age at interview (years)	67 (7)	46.3
Male sex (%)	40	86.7
Diabetes mellitus (%)	8	13.7
Current cigarette smoking (%)	23	2.6 ‡
Former cigarette smoking (%)	41	-
Systolic blood pressure (mmHg)	138 (22)	23.8
Diastolic blood pressure (mmHg)	74 (11)	6.0
Pulse pressure (mmHg)	64 (17)	19.5
Antihypertensive medication use (%)	26	23.7 §
Serum cholesterol (mmol/l)	6.7 (1.2)	21.2
Serum HDL-cholesterol (mmol/l)	1.4 (0.4)	18.6
Cholesterol/HDL-ratio	5.2 (1.6)	42.1
Cholesterol and HDL-cholesterol		46.0 #
Body mass index (kg/m²)	26 (4)	-2.0
Waist to hip ratio	0.90 (0.09)	-1.3
Family history of cardiovascular disease (%)	24	-0.1
Family history of myocardial infarction (%)	17	2.9
Mild manifestations of CVD		
Angina pectoris (%)	6.7	33.1
Intermittent Claudication (%)	1.5	4.3
Transient ischemic attack (%) **	3.8	1.7
Subclinical CVD		
Peripheral arterial disease †† (%)	13.5	13.7
Ankle-arm index	1.09 (0.19)	34.4
Left ventricular hypertrophy on ECG (%)	4.6	10.1
Signs of myocardial infarction on ECG (%)	5.7	4.9
Atrial fibrillation on ECG (%)	1.7	-1.8
ECG characteristics combined ‡‡		15.3

* A detailed description of all risk indicators can be found in the methods section (Assessment of risk indicators).

† Akaike's Information Criterion

‡ The categories of current smokers and former smokers were compared to the reference group (never smokers)

§ The AIC is measured with adjustment for age, sex and systolic blood pressure was 17.4.

The AIC by adding cholesterol and HDL-cholesterol as two separate variables to the model with age and sex.

** Transient Ischemic Attack(s)

†† Defined as an ankle-arm index lower than 0.90

‡‡ The additional prognostic value was assessed of introducing both left ventricular hypertrophy, signs of myocardial infarction and atrial fibrillation on ECG to the model containing age and sex.

TABLE 2. Multivariable adjusted hazard ratios for the risk of CHD

All variables used in the Rotterdam CHD risk function are listed with corresponding hazard ratios and 95% confidence intervals. Additionally, the hazard ratios of ankle-arm index and the ECG characteristics are listed with the corresponding hazard ratios, adjusted for all variables used in the Rotterdam CHD risk function.

Determinants	Hazard Ratio	95% Confidence Intervals
Rotterdam CHD risk function		
Age (per 10 years)	1.52	1.29, 1.80
Male gender	2.50	1.97, 3.18
Diabetes mellitus	1.54	1.16, 2.06
Smoking *	1.42	1.08, 1.87
Antihypertensive medication use	1.36	1.08, 1.73
SBP† in medication users (per 10 mmHg)	1.05	1.02, 1.08
SBP† in subjects not using medication	1.15	1.12, 1.18
Cholesterol (per mmol/l)	2.28	1.17, 4.42
Cholesterol x Cholesterol	0.96	0.91, 1.00
HDL-cholesterol (per mmol/l)	0.51	0.37, 0.71
Family history of myocardial infarction	1.24	0.96, 1.61
Angina pectoris in non-smokers ‡	3.19	2.00, 5.08
Angina pectoris in smokers ‡	1.57	1.09, 2.27
Intermittent claudication	1.71	0.98, 2.90
Extended models		
Ankle-arm index	0.46§	0.29, 0.74
Left ventricular hypertrophy by ECG	1.63§	1.15, 2.31
Silent myocardial infarction by ECG	1.47§	1.04, 2.06

* Because hazard ratios for past and current smoking were almost identical after introducing angina pectoris in the model, the categories were merged.

† SBP = systolic blood pressure

‡ Reference is non-smoking subjects without angina pectoris

§ The hazard ratio is adjusted for all variables of the Rotterdam CHD risk function

TABLE 3. Model performance

For all risk functions developed, the Area under the Receiver Operating Characteristic Curve (AUC) was calculated as a measure of discriminatory power, with and without bootstrapping. For comparison, the AUC of the Framingham CHD risk function was calculated after refitting the risk function to the Rotterdam Study population.

Risk function	AUC* (apparent†)	AUC After bootstrapping‡
Rotterdam risk function	0.748 [0.718-0.778]	0.732 [0.709-0.751]
Framingham refitted §	0.728 [0.698-0.759]	0.721 [0.691-0.752]
Extended models		
Extended model 1 #	0.754 [0.724-0.784]	0.739 [0.714-0.755]
Extended model 2 **	0.754 [0.725-0.784]	0.739 [0.715-0.755]
Extended model 3 ††	0.759 [0.730-0.789]	0.742 [0.715-0.759]

* AUC = Area under the Receiver Operating Characteristic curve as measure of discriminatory power.

† Mean and 95% confidence interval of AUC calculated in the original dataset

‡ Mean and 95% confidence interval of AUC within 80 different bootstraps

§ A new model was run in the Rotterdam Study population with the same covariates and interaction terms as in the Framingham CHD risk function. (1)

Including ankle-arm index in addition to the risk indicators of the Rotterdam risk function.

** Including ECG characteristics in addition to the risk indicators of the Rotterdam risk function.

†† Including both ankle-arm index and ECG characteristics in addition to the risk indicators of the Rotterdam risk function.

TABLE 4. Clinical discrimination

Percentages reflect the proportion of CHD events predicted among subjects with the highest CHD risk (positive predictive value).

	Highest octile	Highest quartile
Rotterdam risk function	35.0%	55.2%
Framingham refitted*	30.0%	53.0%
Extended model 1†	36.2%	57.6%
Extended model 2‡	35.8%	56.0%
Extended model 3 §	37.0%	58.4%

* A new model was run in the Rotterdam Study population with the same covariates and interaction terms as in the Framingham CHD risk function. (1)

† Including ankle-arm index in addition to the risk indicators of the Rotterdam risk function.

‡ Including ECG characteristics in addition to the risk indicators of the Rotterdam risk function.

§ Including both ankle-arm index and ECG characteristics in addition to the risk indicators of the Rotterdam risk function.

Figure 1.

Calibration plots showing the agreement of the predicted probabilities obtained from the models with the observed incidence of CHD within 5 years of follow-up. The calibration of the Rotterdam CHD risk function is compared to the calibration of the refitted Framingham CHD risk function.
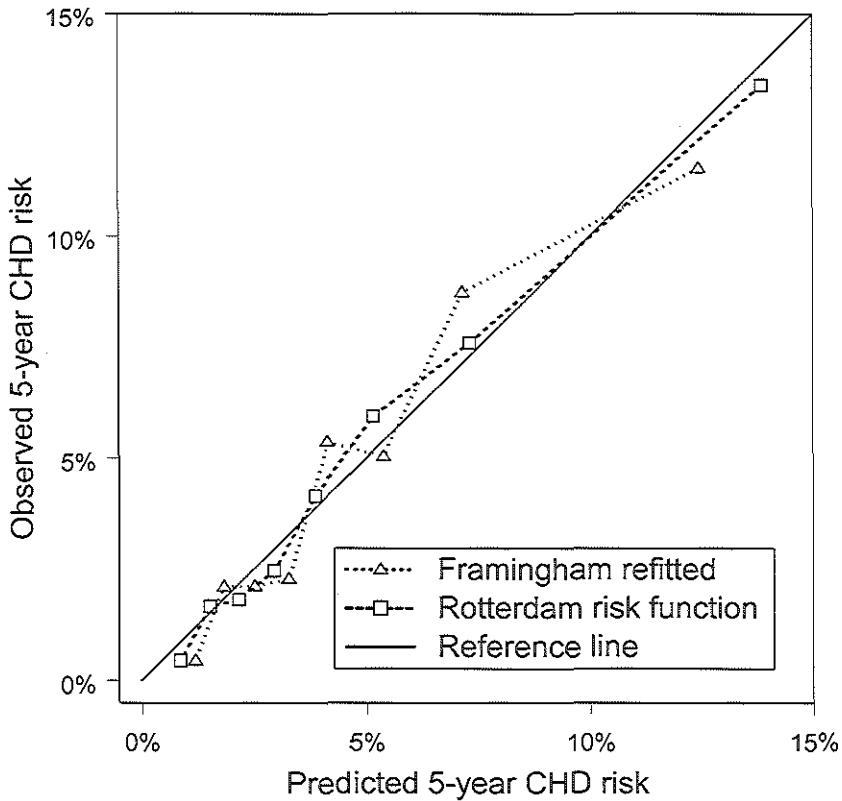
5

Cardiovascular disease risk prediction in the

Rotterdam Study

Prediction of Coronary Heart Disease & Stroke in an older population

Abstract

Context Several risk functions have been developed for risk stratification in the primary prevention of cardiovascular disease (CVD). These risk functions may not be applicable to older adults, in whom mild manifestations of CVD and subclinical CVD are commonly present.

Objective The purpose of this study was to develop a risk function to target older individuals at high risk of CVD.

Design We developed Cox proportional hazard regression models for the joint 5-year risk of coronary heart disease and stroke. A risk function was derived and the additional prognostic impact of new risk indicators was studied with area under the Receiver Operating Characteristic curve analysis.

Setting The Rotterdam Study, a population-based cohort follow-up study.

Participants We included 5431 men and women aged 55-80 years without evident CVD at baseline.

Main Outcome Measure The 5-year risk of cardiovascular disease (CVD).

Results During 7 years of follow-up, 648 CVD events (388 coronary heart disease events and 260 strokes) occurred. Predictors that were selected by multivariable regression analysis included medical history, blood pressure measurements, laboratory tests, medication use and mild manifestations of CVD. The Rotterdam CVD risk function discriminated well between subjects who develop CVD and those who do not (area under the Receiver Operating Characteristic curve (AUC), 0.743; 95% confidence interval 0.719-0.767). The discriminant accuracy of the risk function was slightly improved ($p = 0.002$) by including ankle-arm index and ECG characteristics (AUC, 0.749; 95% confidence interval 0.725-0.773), but not by including serum C-reactive protein ($p > 0.05$).

Conclusion The Rotterdam CVD risk function offers a promising tool to select subjects for CVD prevention among older adults.

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of mortality in industrial countries. Recent trials have shown that lowering serum cholesterol,[1] lowering blood pressure[2] and the use of low dose aspirin[3,4] reduce the risk of cardiovascular events. The absolute benefit of these interventions depends on the pre-treatment level of risk of coronary heart disease and stroke.[3,5] Current guidelines[1,3,5,6] emphasize the importance of selecting subjects based on their absolute risk. Because interventions for coronary heart disease and stroke are largely overlapping, and their treatment will affect both outcomes, it is useful to derive a single risk function to estimate the total risk of CVD instead of the risk of coronary heart disease or the risk of stroke separately.

Several CVD risk functions have been developed for use in primary prevention of CVD.[7-13] These risk functions, however, have several limitations. First, they may not be applicable to older adults in whom mild manifestations of CVD or subclinical CVD are commonly present. Risk intervention may be especially useful in this group, and hence it is worthwhile to consider mild manifestations of CVD as predictors of coronary heart disease and stroke.[14-16] Indicators of subclinical CVD such as ankle-arm index and various ECG characteristics can be easily assessed at relatively low cost and may also be useful for risk stratification in a population of older adults.[17,18]

Second, new risk indicators are evaluated for additional predictive value. In an attempt to improve cardiovascular risk prediction, considerable interest has focused on C-reactive protein (CRP), a marker of inflammation that has been shown in multiple prospective epidemiological studies to predict myocardial infarction, stroke, and cardiovascular mortality.[19-22] None of the presented risk functions[7-13], however, did include CRP or other markers of inflammation in their risk function.

Third, in previous risk functions, stroke and coronary heart disease are combined in the outcome of interest while it is known that risk factors have different impact on stroke than they have on coronary heart disease. For example, plasma cholesterol level appears to be predictive especially of coronary heart disease while systolic blood pressure is more predictive of the risk of stroke.[23] Therefore, it may be better to develop a risk function, which estimates the risk of CVD by calculating the risk for stroke and coronary heart disease separately.

The purpose of the present study was to develop an efficient risk function, especially useful in a population of older adults, based on traditional risk factors and

mild manifestations of cardiovascular disease. We also evaluated the additional predictive value of various indicators of subclinical cardiovascular disease, and of CRP.

METHODS

Study population

Within the Rotterdam Study population, a prospective population cohort of 7983 subjects, we selected 5431 men and women aged 55-80 years without documented myocardial infarction, stroke, coronary revascularization, or carotid intervention at baseline. These subjects were followed for a mean of 7 years.[24] All subjects gave written informed consent and the study was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam.

Assessment of risk indicators

The baseline examination was conducted from 1990 to 1993. Participants were interviewed at home by trained research assistants, using a computerized questionnaire. Subsequently, the participants visited the research center for several measurements, including blood pressure at arms and ankles, body mass index, and blood sampling. The Rose questionnaire[25] was used to detect signs of angina pectoris and/or intermittent claudication. A history of a transient ischemic attack was also assessed using a structured questionnaire.[26] Details about the assessment of these risk indicators are described in earlier publications.[24] Blood samples were drawn at the research center after an overnight fast and were directly put on ice. Serum samples were processed within 30 minutes, after which they were kept frozen at -20 °C. CRP was determined in all subjects who developed CVD and in a random set of controls. CRP was measured using a nephelometric method (Immage®, Beckman Coulter).

Outcome assessment

Subjects were followed from baseline to 2000 and follow-up consisted of three physical examinations and surveillance of hospital admissions, death registries and other available medical sources, ensuring highly accurate follow-up of death and clinical manifestations of CVD. All events were classified according to the

International Classification of Diseases, 10th version. Cardiovascular disease was defined as myocardial infarction (I21-code), PTCA (Z95.5), CABG (Z95.1), stroke (I60-I69), death from ischemic heart disease (I20-I25), sudden death (I46, I49, R96), death due to congestive heart failure (I50) and death from stroke (I60-I69). All events were classified independently by two research physicians. If the physicians disagreed, a consensus was reached in a special session. Finally, a CVD expert verified all these events. In cases of unresolved discrepancy, the judgement by the expert was considered definite.

Model development

Age and sex adjusted Cox proportional hazard models were used to examine the association between various risk indicators and the risk of coronary heart disease and stroke respectively. For blood pressure we examined systolic blood pressure, diastolic blood pressure, pulse pressure and antihypertensive medication use. We selected the blood pressure variable with the highest predictive value and examined whether the blood pressure variable with the next largest predictive value was still additionally predictive over and above the variable already included. We additionally examined whether cholesterol and HDL-cholesterol led to a better predictive value when included separately compared to using the cholesterol/HDL-ratio. All selected risk indicators were combined in one model for coronary heart disease and one for stroke. We tested whether the association between the selected risk indicators and the outcome was linear (quadratic terms) and whether there was synergy between the risk indicators in predicting the outcome (interaction terms).[27,28] In both the model for coronary heart disease and that for stroke, the ankle-arm index was tested for additional predictive value and added if the model improved significantly ($p< 0.05$). The quadratic term of ankle-arm index and interactions of ankle-arm index with age, sex, and mild manifestations of CVD were tested, which yielded 'extended model 1'. The ECG characteristics were tested in a similar fashion, which yielded 'extended model 2'. In 'extended model 3' we tested the additional predictive value of serum C-reactive protein using the same criteria. We tested the additional predictive value of CRP in a case-control design by logistic regression analysis with adjustment for follow-up time.

To determine internal validity, we used a proper biostatistical technique.[27,28] All coefficients were adapted to improve correctness of predictions in future patients. Detailed information about the model development is given in technical appendix A.

Model performance

To study how closely observed outcomes agree with predicted outcomes the observed 5-year risk of subjects with CVD was plotted against the average predicted 5-year CVD risk as calculated with the Rotterdam CVD risk function within octiles.[29]

The discriminant accuracy of the risk function was evaluated by the area under the Receiver Operator Characteristic (ROC)-curve. The area under the ROC curve (AUC) can be interpreted as the probability that the risk function will assign a higher probability of CVD to a randomly chosen subject who develops CVD than to a randomly chosen subject who does not develop CVD during 5 years. The discriminant accuracy of the Rotterdam CVD risk function was compared to that of the Framingham CVD risk function after refitting this risk function to the Rotterdam Study population. Hereto, a new model was run with the same covariates and interaction terms as in the original Framingham CVD risk function.[7]

To study the additional predictive value of subclinical CVD (ankle-arm index and ECG characteristics) and CRP, the discriminant accuracy of the Rotterdam CVD risk function was compared with the discriminant accuracy of the extended models. Differences in discriminant accuracy were compared by differences in area under the ROC curve and tested for statistical significance using a paired Z-test.[30]

Analyses were performed using SPSS (version 9.0, SPSS Inc., Chicago, USA) and S-Plus (version 2000, Insightful Inc., Seattle, WA), using the Design library.[28]

RESULTS

Baseline-data of the study population are described in Table 1. Of the 5431 subjects, 21% were 55 to 60 years old whereas 14% were older than 75 years. A substantial proportion of subjects used antihypertensive medication (26%), had complaints suggestive of angina pectoris (6.7%), or had experienced transient ischemic attack (3.8%). Only 1.5% presented with intermittent claudication, whereas 13.5% had peripheral arterial disease defined as an ankle-arm index <0.90.

During a mean follow-up of 7 years, 611 subjects had a first symptomatic cardiovascular disease event. Among these 611 subjects, 37 had both coronary heart disease and a stroke during follow-up. In total 388 coronary heart disease events and 260 strokes occurred.

Model development

The selected variables within the Rotterdam CVD risk function and the corresponding coefficients are listed in Table 2.

Age was the most predictive variable for stroke while gender was the most predictive variable for coronary heart disease. Serum cholesterol was not predictive of stroke, but was an important predictor of coronary heart disease. Smoking and blood pressure were especially predictive of stroke. Measures of obesity were neither predictive of stroke nor of coronary heart disease.

Antihypertensive medication use significantly added to the prediction of both coronary heart disease and stroke. It also altered the association between systolic blood pressure and incident CVD (negative interaction term). In subjects using antihypertensive medication, systolic blood pressure was less strongly associated with incident CVD than in subjects not using antihypertensive medication.

Cholesterol lowering medication was used in only 1.7% of the subjects at baseline in 1990-1993 of the study and it was not possible to study its additional predictive value. For that reason, we studied the possible predictive value of cholesterol lowering medication use at the time of the third visit at the Rotterdam study center for subsequent CVD. In a total of 1795 subjects without prior CVD, 55 developed CVD during remaining follow-up time. At that time, 10.6% of the subjects used cholesterol-lowering medication, however, medication use did not have predictive value (AIC = -1.625, adjusted for age and gender) and it did not alter the association between cholesterol and the development of CHD.

Both the ankle-arm index and ECG characteristics were statistically significant predictors over and above age and gender. The ankle-arm index was a stronger predictor for coronary heart disease ($\chi 2$= 36.4; p=0.000) than for stroke ($\chi 2$=19.5; p=0.000), while the presence of left ventricular hypertrophy was only predictive of coronary heart disease ($\chi 2$=12.1; p=0.000). Both ankle-arm index and ECG characteristics were still additionally predictive over and above the risk indicators used in the Rotterdam CVD risk function.

Serum CRP was predictive of both coronary heart disease ($\chi2$=6.0; p=0.015) and stroke ($\chi2$=4.7; p=0.031). Serum CRP, however, was not predictive over and above the risk indicators used in the Rotterdam CVD risk function ($\chi2$=0.9; p=0.340 for coronary heart disease and $\chi2$=2.2; p=0.139 for stroke).

The final risk functions to determine the 5-year CVD risk are presented in appendix B. Details about how to calculate the 5-year risk of CVD is described in appendix C.

Model performance

The predicted probabilities obtained from the Rotterdam CVD risk function showed very good agreement with the observed risk. (Figure 1) When using the original Framingham CVD risk function in our population, the risk is overestimated systematically. Refitting of the Framingham CVD risk function in our population improved the agreement between observed and predicted risk. The Rotterdam CVD risk function, which joins the risk of coronary heart disease and stroke, however, showed the best model fit.

The Rotterdam CVD risk function discriminated well between subjects who develop CVD and those who do not develop CVD (area under the Receiver Operating Characteristic curve (AUC), 0.743 (95% confidence interval (CI) 0.719-0.767)). (Table 3)

The discriminant accuracy of the Framingham CVD risk function (AUC 0.713; 95% CI 0.688-0.738) was significantly lower than that of the Rotterdam CVD risk function (p = 0.0001). The discriminant accuracy of the Framingham CVD risk function increased slightly after refitting (AUC 0.724; 95% CI 0.699-0.749) but was still significantly lower than that of the Rotterdam CVD risk function (p = 0.0009). Considering a preventive strategy in which one is willing to treat 12.5% of the population with the highest absolute risk of developing CVD, more than 4% extra cardiovascular disease events could be targeted within 5 years using the Rotterdam CVD risk function instead of the Framingham CVD risk function. (Table 3)

When adding the ankle-arm index, the risk function showed a statistically significant (p = 0.0021) but small improvement in discriminant accuracy (AUC, 0.749 (95% CI 0.725-0.773). Adding ECG characteristics instead of ankle-arm index yielded a similar improvement. Within the highest octile of risk scores, however, including ECG characteristics led to a higher increase in discriminant accuracy than

The Rotterdam CVD risk function is ready to be applied to older adults without evident CVD. Clinical decision analysis would be useful to examine above which threshold of risk (additional) preventive therapy should be advised.

In conclusion, the Rotterdam CVD risk function offers a useful tool to select subjects at high risk for CVD. This risk function is suitable for a population of older adults in whom mild manifestations of CVD are commonly present and who are often already treated for some of their risk factors. Additional measurement of ankle-arm index and ECG offers slightly better discrimination between high and low risk individuals. Serum C-reactive protein did not improve CVD prediction.

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. Wright JM, Lee CH, Chambers GK. Systematic review of antihypertensive therapies: does the evidence assist in choosing a first-line drug? *CMAJ*. 1999;161:25-32.

3. Meade TW, Brennan PJ. Determination of who may derive most benefit from aspirin in primary prevention: subgroup results from a randomised controlled trial. *BMJ*. 2000;321:13-7.

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

5. Mallion JM, Benkritly A, Hansson L, et al. Effect of intensive antihypertensive treatment and of aspirin in a low dose in the hypertensive. The HOT (Hypertension Optimal Treatment) study. *Arch Mal Coeur Vaiss*. 1999;92:1073-8.

6. Arends LR, Hoes AW, Lubsen J, et al. Baseline risk as predictor of treatment benefit: three clinical meta-re- analyses. *Stat Med*. 2000;19:3497-518.

7. Anderson KM, Odell PM, Wilson PW, et al. Cardiovascular disease risk profiles. *Am Heart J*. 1991;121:293-8.

8. Odell PM, Anderson KM, Kannel WB. New models for predicting cardiovascular events. *J Clin Epidemiol*. 1994;47:583-92.

9. Simons LA, Simons J, Friedlander Y, et al. Risk functions for prediction of cardiovascular disease in elderly Australians: the Dubbo Study. *Med J Aust*. 2003;178(3):113-6.

10. Houterman S, Boshuizen HC, Verschuren WM, et al. Predicting cardiovascular risk in the elderly in different European countries. *Eur Heart J*. 2002;23(4):294-300.

11. Pocock SJ, McCormack V, Gueyffier F, et al. A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. *BMJ*. 2001;323(7304):75-81.

12. Menotti A, Lanti M, Puddu PE, et al. The risk functions incorporated in Riscard 2002: a software for the prediction of cardiovascular risk in the general population based on Italian data. *Ital Heart J*. 2002;3(2):114-21.

13. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24(11):987-1003.

14. Psaty BM, Furberg CD, Kuller LH, et al. Traditional risk factors and subclinical disease measures as predictors of first myocardial infarction in older adults: the Cardiovascular Health Study. *Arch Intern Med*. 1999;159:1339-47.

15. Kuller LH, Shemanski L, Psaty BM, et al. Subclinical disease as an independent risk factor for cardiovascular disease. *Circulation*. 1995;92:720-6.

16. Kuller LH. Prevention of cardiovascular disease and the future of cardiovascular disease epidemiology. *Int J Epidemiol*. 2001;30 (1 Suppl):S66-72.

17. Shinozaki T, Hasegawa T, Yano E. Ankle-arm index as an indicator of atherosclerosis: its

application as a screening method. *J Clin Epidemiol.* 1998;51: 1263-9.

18. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Health Study (CHS) Collaborative Research Group. *Circulation.* 1993;88:837-45.

19. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation.* 2003;107(3):363-9.

20. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336(14):973-9.

21. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation.* 1998;98(8):731-3.

22 van der Meer IM, de Maat MP, Kiliaan AJ, van der Kuip DA, Hofman A, Witteman JC. The value of C-reactive protein in cardiovascular risk prediction: the Rotterdam Study. *Arch Intern Med.* 2003;163(11):1323-8.

23. Ellekjaer H, Holmen J, Vatten L. Blood pressure, smoking and body mass in relation to mortality from stroke and coronary heart disease in the elderly. A 10-year follow-up in Norway. *Blood Press.* 2001;10(3):156-63.

24. Hofman A, Grobbee DE, de Jong PT, et al. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol.*1991;7(4):403-22.

25. Rose G, McCartney P, Reid DD. Self-administration of a questionnaire on chest pain and intermittent claudication. *Br J Prev Soc Med.* 1977;31:42-8.

26. Bots ML, van der Wilk EC, Koudstaal PJ, et al. Transient neurological attacks in the general population. Prevalence, risk factors, and clinical relevance. *Stroke.*1997;28:768-73.

27. Steyerberg EW, Eijkemans MJ, Harrell FE, et al. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med. 2000;19: 1059-79.

28. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15:361-87.

29. Graf E, Schmoor C, Sauerbrei W, et al. Assessment and comparison of prognostic classification schemes for survival data. *Stat Med.* 1999;18:2529-45.

30. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* 1988;44(3):837-45.

31. Akaike H. Information theory as an extension of the maximum likelihood principle. In: Petrov BN, Csaki F, eds. 2nd International Symposium on Information Theory. Budapest: Akademia Kiado;1973:267-81.

TABLE 1.   Baseline characteristics.

RISK INDICATORS *	MEAN ± SD / PROPORTION
Age at interview (years)	67 ± 7
Male sex (%)	40
Diabetes mellitus (%)	8
Current cigarette smoking (%)	23
Former cigarette smoking (%)	41
Systolic blood pressure (mmHg)	138 ± 22
Diastolic blood pressure (mmHg)	74 ± 11
Pulse pressure (mmHg)	64 ± 17
Antihypertensive medication use (%)	26
Serum cholesterol (mmol/l)	6.7 ± 1.2
Serum HDL-cholesterol (mmol/l)	1.4 ± 0.4
Body mass index (kg/m^2)	26 ± 4
Waist to hip ratio	0.90 ± 0.09
Family history of cardiovascular disease (%)	24
Family history of myocardial infarction (%)	17
Angina pectoris (%)	6.7
Intermittent Claudication (%)	1.5
Peripheral arterial disease (%) †	13.5
Ankle-arm index	1.09 ± 0.19
Left ventricular hypertrophy on ECG (%)	4.6
Silent myocardial infarction on ECG (%)	5.7
Atrial fibrillation on ECG (%)	1.7
Serum C-reactive protein (mg/l) ‡	2.9 ± 5.4

* A detailed description of all risk indicators can be found in the methods section (Assessment of risk indicators).

† Defined as an ankle-arm index < 0.90

‡ Serum C-reactive protein as measured in a random selection of the controls (n=617)

TABLE 2. The selected risk indicators with the coefficients in the Rotterdam CVD risk function.

	Coronary heart disease	Stroke
Male gender	0.8662	0.2435
Age	0.0372	0.5114
Age x Age	-*	-0.0033
Diabetes mellitus	0.3797	0.5281
Cholesterol (mmol/l)	0.7365	-*
Cholesterol x Cholesterol	-0.0382	-*
HDL-cholesterol (mmol/l)	-0.6163	-*
Family history of MI	0.1771	-*
Systolic blood pressure (mmHg)	0.0139	0.0195
Antihypertensive medication use	1.4958	2.0342
SBP x antihypertensive medication use	-0.0086	-0.0128
Past smoking	0.3069	0.3158
Current smoking	0.3798	0.6076
Angina pectoris	1.0650	-*
Angina pectoris x past smoking	-0.5718	-*
Angina pectoris x current smoking	-0.5757	-*
Intermittent claudication	0.3577	-*
Transient Ischemic Attacks	-*	0.7250

* : Not included in the risk function because of non-significance.

TABLE 3. Discriminant accuracy.

For all risk functions developed, the Area under the Receiver Operating Characteristic Curve (AUC) was calculated as a measure of discriminant accuracy. For comparison, the AUC of the Framingham Cardiovascular Disease risk function was calculated after refitting the risk function to the Rotterdam Study population. The percentages in the last column reflect the proportion of cardiovascular disease events predicted among subjects in the highest octile risk scores.

Risk function	AUC*	% CVD events within highest octile
Rotterdam risk function	**0.743** [0.719-0.767]	31.4%
Framingham †	**0.713** [0.688-0.738]	27.0%
Framingham refitted ‡	**0.724** [0.699-0.749]	27.6%
Extended models		
Model 1 §	**0.749** [0.725-0.773]	32.9%
Model 2 ‖	**0.749** [0.725-0.773]	34.2%
Model 3 ¶	-	

* AUC = Area under the Receiver Operating Characteristic curve as measure of discriminant accuracy.

† The original Framingham Cardiovascular Disease risk function.

‡ A new model was run in the Rotterdam Study population with the same covariates and interaction terms as in the Framingham Cardiovascular Disease risk function.

§ Including ankle-arm index in addition to the risk indicators of the Rotterdam Cardiovascular Disease risk function.

‖ Including ECG characteristics in addition to the risk indicators of the Rotterdam Cardiovascular Disease risk function.

¶ Including serum C-reactive protein in addition to the risk indicators of the Rotterdam Cardiovascular Disease risk function did not lead to improvement in model performance (p > 0.05) and was therefore not tested for improvement in discriminant accuracy.

Figure 1.

Plots showing the agreement of the predicted probabilities with the observed risk of cardiovascular disease within 5 years of follow-up. The model fit of the Rotterdam Cardiovascular Disease risk function is compared to the model fit of the Framingham Cardiovascular Disease risk function.
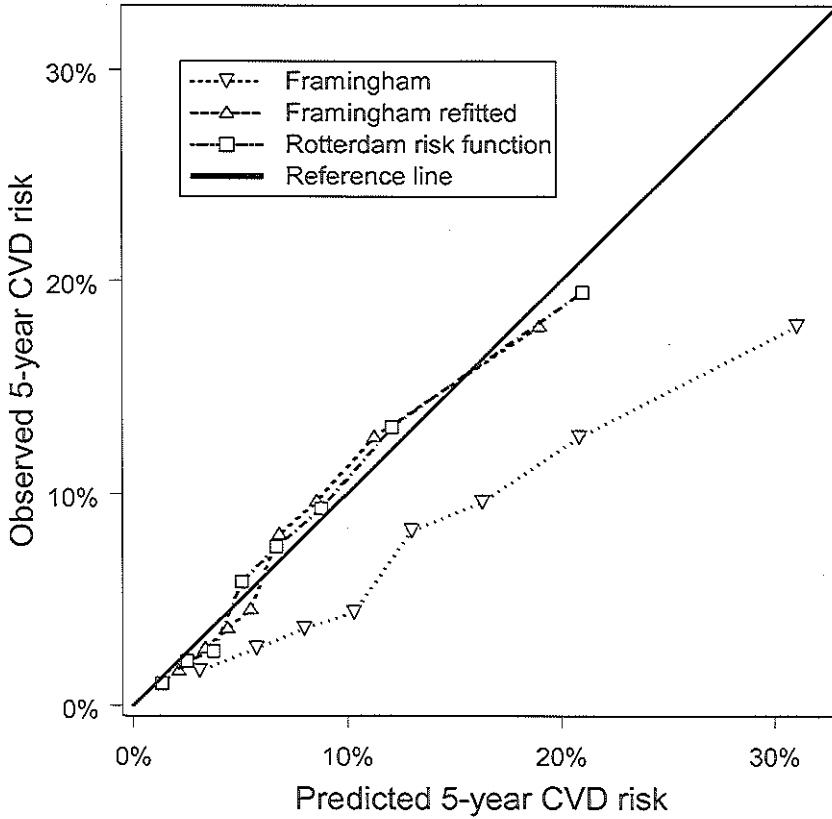
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Validation of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow-up study

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Abstract

Objective. To determine the validity of the Rotterdam Ischemic heart disease & Stroke Computer (RISC) model, a Monte Carlo-Markov model, designed to evaluate the impact of cardiovascular disease (CVD) risk factors and their modification on life expectancy (LE) and cardiovascular disease-free LE (DFLE) in a general population. **Methods.** The model is based on data from the Rotterdam Study, a cohort follow-up study of 6871 subjects aged 55 years and older who visited the research center for risk factor assessment at baseline (1990-1993) and completed a follow-up visit 7 years later (original cohort). The transition probabilities and risk factor trends used in the RISC model were based on data from 3501 subjects (the study cohort). To validate the RISC model, the number of simulated CVD events during 7 years follow-up were compared with the observed number of events in the study cohort and the original cohort, respectively, and simulated (DF)LEs were compared with the (DF)LEs calculated from multi-state life tables.
Results. Both in the study cohort and in the original cohort, the simulated distribution of CVD events was consistent with the observed number of events (CVD deaths: 7.1% vs 6.6% and 7.4% vs 7.6% respectively; non-CVD deaths: 11.2% vs 11.5% and 12.9% vs 13.0% respectively). The distribution of (DF)LEs estimated with the RISC model consistently encompassed the (DF)LEs calculated with multi-state life tables.
Conclusions. The simulated events and (DF)LE estimates from the RISC model are consistent with observed data from a cohort follow-up study.

INTRODUCTION

Over the past 50 years the epidemiology of cardiovascular disease (CVD) has been extensively investigated and described. Large prospective studies have identified and quantified the major modifiable risk factors[1-3] and numerous studies have demonstrated that altering these risk factors causes a reduction in event rates.[4-8]

To evaluate the effect of CVD risk factors on life expectancy (LE) and cardiovascular disease-free LE (DFLE) in a general population, we developed a Monte Carlo-Markov simulation model.[9] The model was based on data from the Rotterdam Study, a cohort follow-up study of adults aged 55 years and older.[10] The model will be referred to as the Rotterdam Ischemic heart disease & Stroke Computer simulation model (RISC model). The Monte Carlo structure enables modeling of uncertainty in transition probabilities and correlations between parameters. Furthermore, the Monte Carlo-Markov model can incorporate individual risk factor profiles and memory of individual life histories.

A common problem with simulation models of this kind is the lack of credibility. Validation of the model is needed to determine whether the model is likely to be useful and improves credibility for decision making in reality. Three levels of validation should be distinguished.[11,12] The first level of validity is apparent validity, or accuracy. This is the validity in the sample used to develop the model. The second level of validity is internal validity, the validity in the population from which the sample originated. The third level of validity is external validity, the validity in other similar populations. To study validity, the simulated events should be compared with observed events. Accurate predictions of the frequency of events are in agreement with the observed outcome frequencies (calibration) and accurate predicted probabilities of an event are higher for those who develop the outcome than for those who do not develop the outcome (discrimination).[11,13,14]

The purpose of this study was to validate the RISC model through comparison of the simulated CVD burden to the observed CVD burden in the Rotterdam cohort follow-up study, that is to examine apparent and internal validity of the model.

METHODS

The RISC model is a Monte Carlo-Markov model, which was developed to predict the future CVD mortality and morbidity in the original Rotterdam Study population, aged 55 and older at study onset, and followed from 1991 to 2000. Through its capability to simulate changes in risk factors in subjects without CVD, the model is very well suited to examine the effects of preventive strategies. Furthermore, the Monte Carlo structure enables the evaluation of variability and uncertainty.[15-16]

The model

The RISC model is a state-transition model (schematically presented in Figure 1) with six states: (1) the CVD death state, (2) the non-CVD death state, (3) the Ischemic Heart Disease (IHD) state, (4) the Stroke state, (5) the IHD and Stroke state and (6) the Well state (being alive without ischemic heart disease or stroke). The model simulates incident CVD events in persons with and without previous CVD. The cycle length is 0.1 years. The model was built in TreeAge (version Data Professional release 10, TreeAge Software, Inc., Williamstown, USA).

To estimate transition probabilities for different risk indicator patterns, we constructed six transition probability functions based on Cox proportional hazard analyses with follow-up time as the time axis. The first probability function models the transition probability from the Well state to the IHD state and from the Stroke state to the IHD & Stroke state. When modeling incident IHD, subjects with incident stroke were censored at the time of their stroke. The second function models the transition probability from the Well state to the Stroke state and from the IHD state to the IHD & Stroke state. When modeling incident stroke, subjects with incident IHD were censored at the time of their IHD event. In both models having experienced IHD or stroke is included as one of the covariates. The third and the fourth functions model the transition probability from the Well state, the IHD state, the Stroke state and the IHD & Stroke state to the CVD death state and the non-CVD death state, respectively. When modeling cardiovascular and non-cardiovascular mortality, subjects with incident IHD or stroke were censored at the time of their event. In the fifth and sixth functions, the cardiovascular mortality rates within 6 months after IHD and stroke respectively (case-fatality) were modeled. The fourth IHD event and the third stroke were assumed always to be fatal.

We performed stepwise-backward Cox proportional hazard analyses to select all important risk indicators for each of the six transition probability functions, as determined by Akaike's Information Criterion (AIC) > 0.[17,18] The AIC can be calculated as the χ^2-change minus two times the degrees of freedom, in which the χ^2 is the likelihood ratio test statistic. Subsequently, quadratic terms of all continuous variables and interaction terms with age, gender and medical history of CVD were tested and added to the transition probability function if AIC was greater than 0.

Individual risk indicator profiles (as sampled from the Rotterdam Study participants) were used to estimate the transition probabilities for each subject. The complete risk indicator profile of each individual was updated every 5 years in the model. Changes in continuous risk indicator levels due to aging were estimated from the Rotterdam Study data using linear regression analysis with age and gender as covariates and modeled as a continuous increase or decrease per 5 years. Changes in dichotomous risk indicators were analyzed using logistic regression analysis with gender and all (updated) continuous risk indicators as covariates and were modeled as "hidden states" using tracker variables. Every 5-year period during follow-up, the presence of each dichotomous risk indicator was updated by drawing from a binomial distribution with a probability parameter given by the logistic model. All events were counted during simulation using tracker variables.

Data sources and study population
The population based risk indicator profiles and transition probability functions were based on data from the Rotterdam study population. The Rotterdam study population consisted of 7983 adults aged 55 and older residing in Ommoord, the Netherlands. Of these respondents, 6871 (86%) visited the research center for risk indicator assessment at baseline (1990-1993) and had a complete follow-up for at least 7 years (original cohort). All subjects signed an informed consent form.[10]

The risk indicators considered were age, sex, smoking status, hypertension, systolic and diastolic blood pressure, diabetes mellitus, plasma glucose level, body mass index, waist to hip ratio, plasma cholesterol and HDL-cholesterol level, plasma creatinine level, family history of CVD, ankle-brachial systolic blood pressure index, manifestations of intermittent claudication, angina pectoris, atrial fibrillation or transient ischemic attacks and prevalent CVD. A person was designated as having prevalent CVD if a myocardial infarction or a stroke was diagnosed by a physician

and/or the patient reported CABG, PTCA, or carotid surgery in the past. Information on all these risk indicators was available in 3501 of the 6871 subjects. The variables mostly missing were plasma creatinine level and ankle-brachial systolic blood pressure index. Plasma creatinine level was missing in 26.2% of the subjects, while ankle-brachial systolic blood pressure index was missing in 10.4% of the subjects. Only 6% of the subjects had 2 or more risk indicators missing. On the basis of the 3501 subjects (study cohort), the transition probability functions and changes in risk indicators with aging were fitted.

All incident events during follow-up were classified according to the International Classification of Diseases, 10th version (ICD-10). The events of interest include IHD (myocardial infarction (I21-code), PTCA and CABG), ischemic stroke (I63, I64), death from cardiovascular disease (mortality due to I10-I15: hypertensive heart disease, I20-I25: ischemic heart disease, I46 & I49: sudden cardiac death, I50: congestive heart failure, I60-I67: cerebrovascular disease, I70-I79: other arterial disease and R96: sudden death), and non-cardiovascular mortality (all other mortality codes).

Uncertainty & Variability

We modeled parameter uncertainty by estimating the distribution of the value of each of the input variables and performing a second-order Monte Carlo simulation.[15] To model the uncertainty in the transition probability functions, 100 bootstrap samples of the study population were drawn. All the transition probability functions were fitted for every bootstrap sample, resulting in 100 sets of linked transition probability functions. For each RISC simulation sample, we drew one set of linked functions randomly from these 100 bootstrap sets. In the second-order Monte Carlo simulation the parameter uncertainty resulted in a confidence interval for the model outcome.[16]

Evaluation of a policy decision for a heterogeneous population requires analysis of the variability within that population. Variability within the population (or heterogeneity) was modeled by simulating every individual subject from the source population separately. Since individual subjects with their entire risk profiles were simulated, correlations between the risk indicators were taken into account. Modeling only the mean values for the risk indicators would result in the wrong outcome since the outcome is a non-linear function of the subject characteristics.[19]

Validity on the population level

To study the validity of the RISC model, we studied how closely the simulated number of incident CVD events and (DF)LE agreed with the observed number of events and (DF)LE. To simulate the mean and distribution around the mean of the outcomes, we drew 100 second-order parameter sets and with each parameter set consecutively simulated all the subjects in the study cohort (100x3501) and original cohort (100x6871), respectively. Apparent validity was examined by comparing the simulated incidence of CVD events within 7 years to the observed incidence of events derived from the 7-year follow-up of the 3501 subjects with complete data (the study cohort). Subsequently, we imputed the 3370 incomplete risk factor profiles using the Expectation Maximization method, used the total of 6871 risk factor profiles as input for the RISC model, and performed the same simulations. Internal validity was studied by comparing the simulated number of CVD events to the observed number of events derived from the 7-year follow-up of the original cohort (6871 subjects).

Furthermore, we performed a life-long simulation to calculate (DF)LE for various subpopulations. Internal validity was further studied by comparing the simulated (DF)LE with the (DF)LE estimates derived from multi-state life tables.[20] We constructed multi-state life tables with the states "free of cardiovascular disease", "cardiovascular disease", and "death", using the 6871 individuals from the Rotterdam Study. The age-specific transition rates for the transitions "free of cardiovascular disease" to "cardiovascular disease", "free of cardiovascular disease" to "death", and "cardiovascular disease" to "death" were estimated from follow-up data until 1999, assuming a Gompertz distribution with age.[21] Estimations were made separately for men and women for ages 55 to 104. For life table construction each age-specific transition rate was converted to a probability, assuming that the hazard is constant within each age interval. The life tables started at age 55, 60, 65, 70, 75 or 80, assuming a prevalence of CVD at the starting age equivalent to that in the original cohort, and they terminated assuming 100% mortality at age 105. Life expectancy was calculated as the total number of years lived per person in the life table. CVD free life expectancy is then the proportion of years lived without CVD. Life expectancies for the total population were calculated as the average of the estimated life expectancies for each of the 6871 Rotterdam Study participants based on their exact age at entry and sex.

Validity on the individual level

To study the validity of the RISC model on the individual level, we performed a 5-year long simulation by sampling the 3501 subjects consecutively and running 100 first-order trials for each subject. The parameters of the transition probability functions were sampled for every trial. The outcome of this simulation consisted of 3501 mean cumulative incidence rates of CVD events, that is, a predicted rate for every individual from the study cohort. We studied validity on the individual level only within the study cohort because this analysis required complete baseline- and follow-up information.

The calibration of the RISC model was assessed graphically to determine how closely the predicted outcomes agreed with the observed outcomes. For each type of event the observed 5-year event rate was plotted against the average simulated 5-year event rate.[22]

We performed Receiver-Operating-Characteristic-Curve (ROC curve) analyses with the observed event as outcome variable ("reference standard") and the predicted probability of an event for each subject as test variable. The ROC curve is a plot of the true-positive rate (sensitivity) against the false-positive rate (1 minus specificity), evaluated for varying thresholds of the predicted probability.[13,22] The area under the ROC curve can be interpreted as the chance that the RISC model will predict a higher number of events (that is, a higher probability of an event) among multiple clones of a randomly chosen subject who actually has an event during follow-up than among multiple clones of a randomly chosen subject who does not have an event.

RESULTS

The study population

Baseline characteristics of both the study cohort (3501 subjects) and the original cohort (6871 subjects) are described in table 1. The original cohort was slightly older, contained more men and had a higher prevalence of CVD at baseline. Cholesterol levels and blood pressure were quite comparable.

Within 7 years of follow-up, 230 IHD events, 168 ischemic strokes, 231 CVD deaths and 403 non-CVD deaths occurred in the population of 3501 subjects. The original cohort of 6871 subjects appeared to be less healthy. Relatively more subjects

died from both CVD and non-CVD causes. More CVD events occurred in the original cohort, especially more ischemic strokes. Within 7 years of follow-up, 489 subjects had an IHD event, 399 subjects had an ischemic stroke, 522 subjects died from CVD, and 893 subjects died from a non-CVD cause in the original cohort.

Validity on the population level

The simulated 7-year cumulative incidences of CVD events with their distributions due to parameter uncertainty are shown in figures 2 en 3. Both in the study cohort of 3501 subjects (Figure 2) and in the original cohort of 6871 subjects (Figure 3), the distribution of CVD events simulated was consistent with the observed number of events (indicated with the reference line).

Based on the results of the multi-state life table, a 55-year old man may expect to live 25.4 years of which 18.6 years free of CVD while a 55-year old woman may expect to live 31.0 years of which 27.2 years free of CVD. The total population had a life expectancy of 16.4 years and a DFLE of 12.3 years. The simulated (DF)LEs for the subgroups were consistent with those calculated with the multi-state life table (Table 2 & 3).

Validity on the individual level

The simulated CVD event rates obtained from the RISC model showed very good agreement with the observed event rates (Figure 4). The RISC model showed good to excellent discriminant accuracy as indicated by the area under the ROC curve, especially in predicting CVD mortality; 57.0% of the CVD deaths during follow-up occurred in subjects in whom the simulated probability of CVD death was within the highest octile (Table 4).

DISCUSSION

In this paper we presented a validation of predicted events simulated with the RISC model in comparison to the observed data during 7 years of follow-up in the Rotterdam Study. Furthermore, we compared simulated (DF)LE with the results of a multi-state life table analysis.

The RISC model showed accurate calibration of the CVD events that actually occurred, both in the study cohort used to construct the model and in the larger population from which the study cohort was derived. This implies that the model is accurate in simulating the mean (DF)LE and the cumulative incidence of events in this population.

The model also showed good discrimination of subjects with a CVD event from those without. In other words, also on the individual level, the model showed accurate results. This is important when modeling individual specific targeting and intervention techniques in the general population.

The major advantages of the current Monte Carlo-Markov model over multi-state life tables, is that individual specific targeting and intervention techniques can be simulated and that the model can incorporate individual risk factor profiles and memory of the individual life histories.[9] Both advantages are due to the use of the first-order Monte Carlo analysis with tracker variables. The tracker variables make it feasible to incorporate multiple risk factors and to let the risk factor levels change with age. Monte Carlo - Markov models are more flexible than multi-state life tables and various prevention strategies can easily be evaluated without changing the model structure. The Monte Carlo structure enables modeling the proper distributions, cross-correlation between parameters and uncertainty in transition probabilities at the same time.[15]

The major disadvantage of Monte Carlo–Markov models variables is the complexity of such models, which has an inherent risk of introducing errors. To avoid errors, we feel it is prudent to validate such complex models against simpler representations of the observed data, such as multi-state life tables. Only if the complex model produces similar (DF)LE as the simpler approach, as was the case for the RISC model, can we trust it. The results, however, will never be identical because the underlying assumptions are different. For example, an underlying assumption of the multi-state life table approach used here was that rates were distributed exponentially with age, whereas in the RISC model age was fitted in each transition probability in whatever the best fit was (using quadratic terms and interaction terms).

As far as we know, the RISC model is the only Monte Carlo-Markov model investigating natural history of CVD and impact of various CVD prevention strategies. The Coronary Heart Disease Policy Model is a Markov model for coronary heart disease only: it does not consider stroke as we have done in the current model.

Furthermore, it uses a cohort rather than a Monte Carlo approach and therefore cannot fully model memory for events. Whereas the Coronary Heart Disease Policy Model studies heterogeneity by dividing the population in subgroups, the RISC model simulates individuals.[23,24]

The main limitation of our study is that, although we have evaluated apparent and internal validity, we still need to evaluate external validity. In particular, because our model is based on data from non-institutionalized individuals 55 years and older who were mostly Caucasian, one can question whether the model will apply to other populations. External validation of the model is needed to demonstrate the generalizability of the model[14] before performing cost-effectiveness analyses of targeting- and intervention strategies in the primary prevention of cardiovascular disease in other populations.

In summary, the RISC model accurately predicts CVD events and (DF)LE estimates compared to observed data from a cohort follow-up study. Following external validation, it can be used to evaluate and compare primary preventive strategies for CVD.

REFERENCES

1. Anonymous. Relationship between baseline risk factors and coronary heart disease and total mortality in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. Prev Med. 1986;15:254-73.

2. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA. 1986;256:2835-8.

3. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA. 1996;275:1571-6.

4. 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.

5. 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.

6. Ebrahim S, Smith GD. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. BMJ. 1997;314:1666-74.

7. MacMahon S, Peto R, Cutler 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;335:765-74.

8. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet. 1990;335:827-38.

9. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making. 1993;13:322-38.

10. 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.

11. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema JD. Validity of prognostic models: when is a model clinically useful? Semin Urol Oncol. 2002;20:96-107.

12. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54:774-81.

13. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15:361-87.

14. Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med. 2000;19:453-73.

15. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. Med Decis Making. 1985;5:157-77.

16. Hunink MGM, Glasziou PP, Siegel JE, et al. Decision making in health and medicine: interpreting evidence and values. Cambridge, England: Cambridge University Press, 2001.

17. Harrell FE, Jr., Lee KL, Matchar DB, Reichert TA. Regression models for prognostic prediction: advantages, problems, and suggested solutions. Cancer Treat Rep. 1985;69:1071-77.

18. Sakamoto Y, Ishiguro, Kitagawa G. Akaike Information Criterion Statistics. 1986: Kluwer Academic Publishers.

19. Kuntz KM, Goldie SJ. Assessing the sensitivity of decision-analytic results to unobserved markers of risk: defining the effects of heterogeneity bias. Med Decis Making. 2002;22:218-27.

20. Bonneux L, Barendregt JJ, Nusselder WJ, der Maas PJ. Preventing fatal diseases increases healthcare costs: cause elimination life table approach. BMJ. 1998;316:26-9.

21. Pollard JH, Valkovics EJ. The Gompertz distribution and its applications. Genus, 1992. 48:15-28.

22. Graf E, Schmoor C, Sauerbrei W, Schumacher M. Assessment and comparison of prognostic classification schemes for survival data. Stat Med. 1999;18:2529-45.

23. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. Am J Public Health. 1987;77:1417-26.

24. Hunink MG, Goldman L, Tosteson AN, et al. The recent decline in mortality from coronary heart disease, 1980-1990. The effect of secular trends in risk factors and treatment. JAMA. 1997;277:535-42.

Table 1. Baseline characteristics (Mean ± SD / proportion)

	Study cohort n = 3501	Original cohort n = 6871
Age at interview (years)	69 ± 8	70 ± 9
Male sex (%)	39.5	40.2
Diabetes mellitus (%)	10.7	11.2
Serum glucose (mmol/l)	6.9 ± 2.6	7.0 ± 2.7
Current cigarette smoking (%)	23.6	22.4
Former cigarette smoking (%)	41.9	41.4
Systolic blood pressure (mmHg)	140 ± 22	140 ± 22
Diastolic blood pressure (mmHg)	74 ± 12	74 ± 12
Pulse pressure (mmHg)	66 ± 18	66 ± 18
Hypertension (%)	36.4	34.8
Serum cholesterol (mmol/l)	6.7 ± 1.2	6.6 ± 1.2
Serum HDL-cholesterol (mmol/l)	1.30 ± 0.36	1.35 ± 0.36
Cholesterol/HDL-ratio	5.3 ± 1.6	5.2 ± 1.6
Serum creatinine (μmol/l)	83 ± 18	83 ± 22
Body mass index (kg/m^2)	26.3 ± 4.2	26.3 ± 3.8
Waist to hip ratio	0.91 ± 0.09	0.91 ± 0.09
Family history of cardiovascular disease (%)	23.0	23.3
Family history of myocardial infarction (%)	16.3	16.4
Angina pectoris (%)	10.4	10.0
Intermittent Claudication (%)	2.1	2.1
TIA(%) **	5.1	7.3
Ankle-arm index	1.05 ± 0.23	1.05 ± 0.23
Medical history of CVD (%)	17.8	25.2
Atrial fibrillation on ECG (%)	2.5	2.9

Table 2. Validation of total life expectancies. Life expectancy (LE) in years with standard error of the mean (SE) in the original cohort of 6871 subjects.

sex, age (years)	MSLT years	RISC years (standard error)
male 55	25.35	25.63 (1.16)
male 60	21.19	21.18 (0.84)
male 65	16.89	17.04 (0.75)
male 70	13.38	13.31 (0.73)
male 75	10.02	9.42 (0.55)
male 80	7.42	6.77 (0.64)
female 55	31.00	30.59 (1.06)
female 60	26.28	25.93 (0.80)
female 65	21.33	21.64 (0.94)
female 70	16.99	17.01 (0.83)
female 75	12.70	13.32 (0.97)
female 80	9.50	8.82 (0.87)
total population	16.53	16.18 (0.60)

MSLT: multi-state life table estimate

RISC: simulation with the Rotterdam Ischemic heart disease & Stroke Computer simulation model

Table 3. Validation of cardiovascular disease-free life expectancies. Cardiovascular disease-free life expectancy (DFLE) in years with standard error of the mean (SE) in the original cohort of 6871 subjects.

sex, age (years)	MSLT years	RISC years (standard error)
male 55	18.63	18.68 (1.12)
male 60	15.30	14.93 (0.86)
male 65	11.17	11.02 (0.69)
male 70	9.10	8.91 (0.55)
male 75	6.27	5.92 (0.45)
male 80	4.84	4.58 (0.48)
female 55	27.16	26.67 (0.96)
female 60	22.39	21.78 (0.74)
female 65	16.63	16.10 (0.73)
female 70	12.74	12.15 (0.61)
female 75	8.23	8.09 (0.59)
female 80	6.29	5.71 (0.54)
total population	12.50	12.26 (0.34)

MSLT: multi-state life table estimate

RISC: simulation with the Rotterdam Ischemic heart disease & Stroke Computer simulation model

Table 4. Discriminant accuracy

For the four outcomes of the RISC model, the Area under the Receiver Operating Characteristic Curve (AUC) with 95% confidence interval was calculated as a measure of discriminant accuracy. The percentages in the last columns reflect the proportion of events that occurred among subjects in the highest octile and the highest quartile of the predicted probability of events.

Event	AUC*	Highest octile	Highest quartile
CVD mortality[†]	0.835 [0.801-0.869]	57.0%	72.2%
non-CVD mortality[‡]	0.786 [0.757-0.815]	49.8%	63.4%
IHD[§]	0.779 [0.742-0.816]	46.0%	64.6%
Stroke	0.704 [0.654-0.753]	34.2%	50%

* AUC = Area under the Receiver Operating Characteristic curve as measure of discriminant accuracy.

† death due to cardiovascular disease

‡ death due to other causes than cardiovascular disease

§ ischemic heart disease

Figure 1. The Rotterdam Ischemic heart disease and Stroke computer simulation (RISC) model shown as an influence diagram.
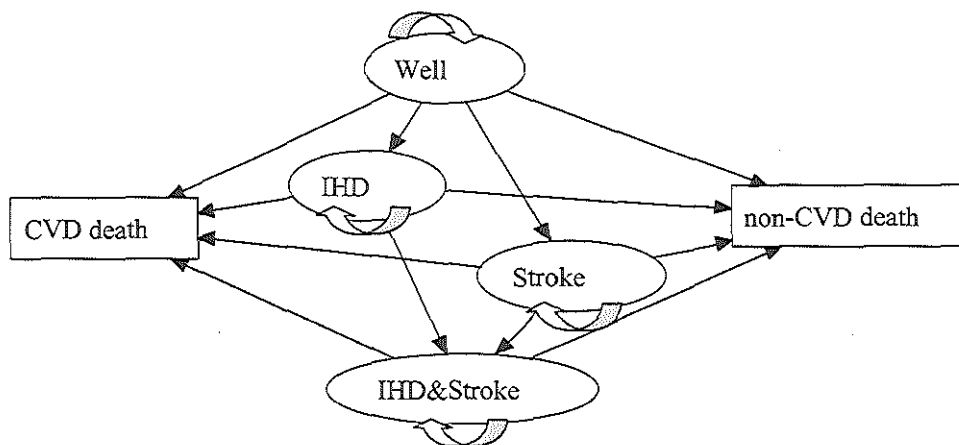
Figure 2. Validation of the distribution of events within 7 years follow-up in the study cohort (apparent validity, population level).

For each event, the distribution of simulated cumulative incidence event rates is shown in a histogram. The observed cumulative incidence of each event is shown as a reference line.
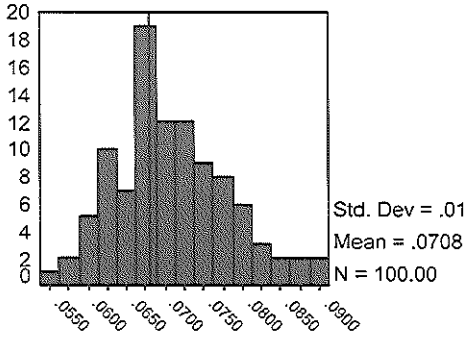
Cardiovascular mortality

Observed: 0.0660
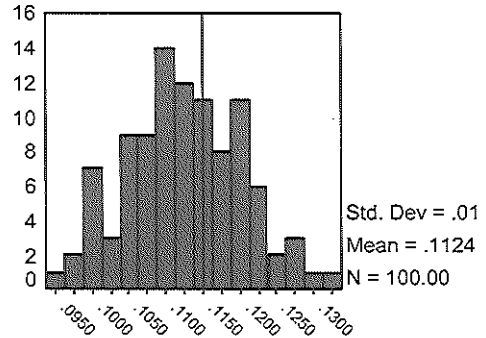
Non-CVD mortality

Observed: 0.1151
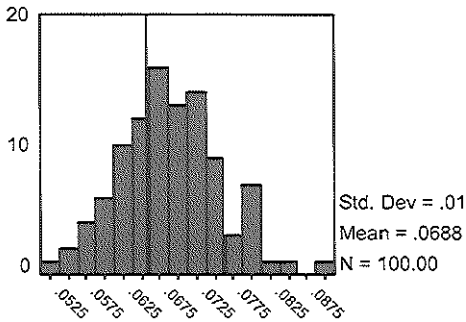
First IHD events during follow-up

Observed: 0.0657
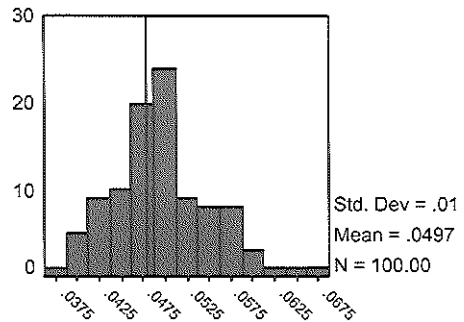
First strokes during follow-up

Observed: 0.0480

Figure 3. Validation of the distribution of CVD events within 7 years follow-up in the original cohort (internal validity, population level).

For each event, the distribution of simulated cumulative incidence event rates is shown in a histogram. The observed cumulative incidence of each event is shown as a reference line.

Cardiovascular mortality

Std. Dev = .01
Mean = .0744
N = 100.00

Observed: 0.0760

Non-CVD mortality

Std. Dev = .01
Mean = .1295
N = 100.00

Observed: 0.1300

First IHD events during follow-up

Std. Dev = .01
Mean = .0708
N = 100.00

Observed: 0.0712

First strokes during follow-up

Std. Dev = .01
Mean = .0539
N = 100.00

Observed: 0.0581
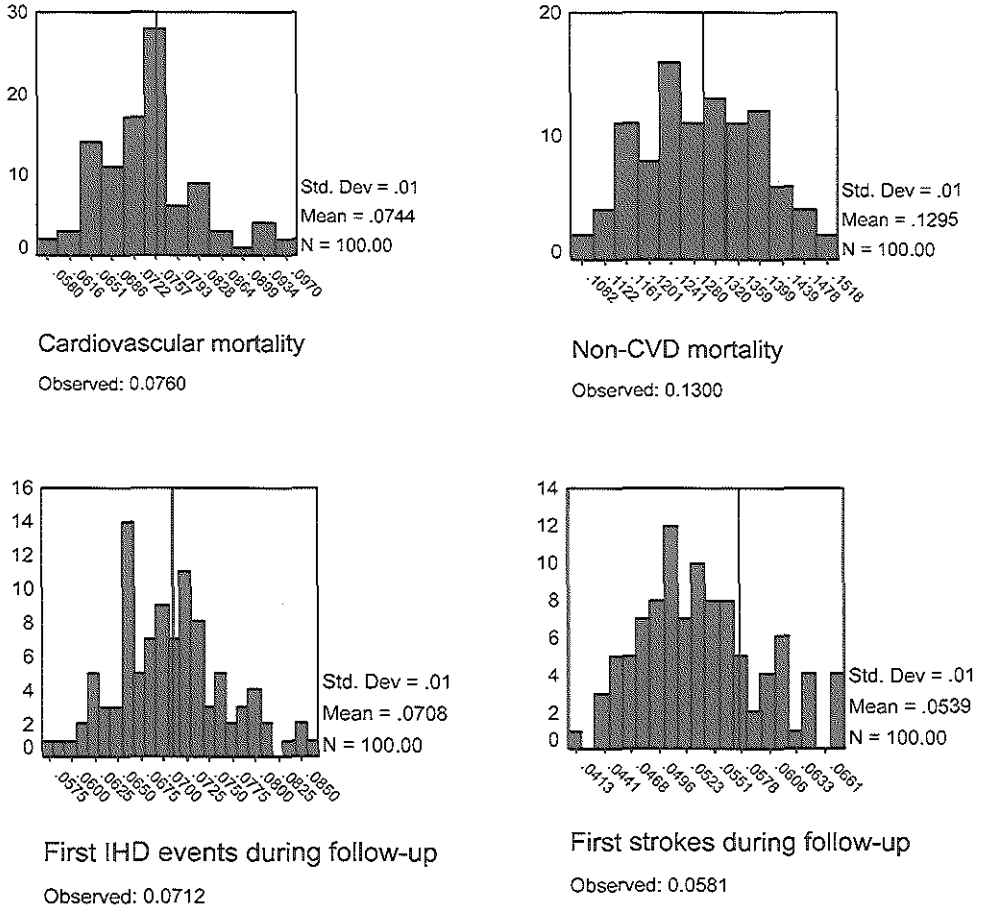
Figure 4.

Calibration plots showing the agreement of the simulated incidences of events with the observed incidences of events within 5 years of follow-up (validity on the individual level).
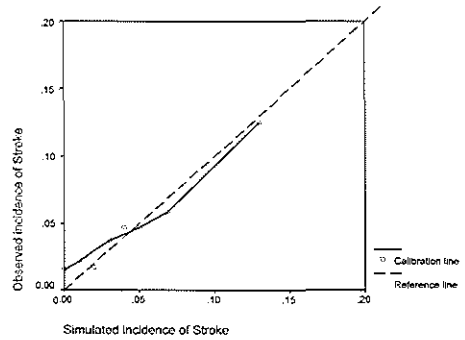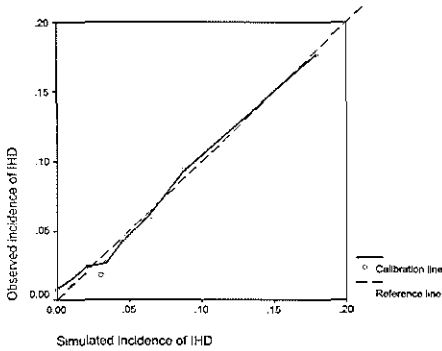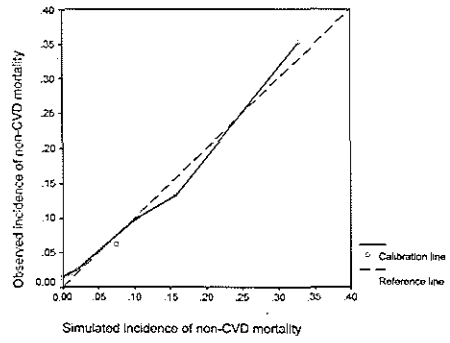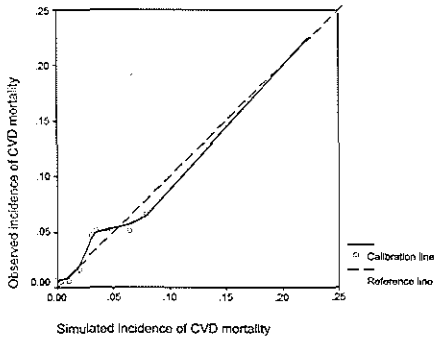
7

The performance of the Rotterdam Ischemic heart disease and Stroke Computer simulation model (RISC model) in the US population

INTRODUCTION

We developed a Monte Carlo-Markov model[1], designed to investigate the impact of cardiovascular disease (CVD) risk factors and their modification on the CVD burden in a general population. The model is based on data from the Rotterdam Study, a cohort follow-up study of 7983 older adults aged 55 years and older.[2] The model will be referred to as the Rotterdam Ischemic heart disease & Stroke Computer simulation model (RISC model).[3]

A common problem with simulation models of this kind is the lack of generalizability and credibility. Although the RISC model showed accurate apparent and internal validity, it's external validity, or generalizability remains to be demonstrated. External validity is the validity of the model in other similar populations. To study validity, the simulated CVD life course should be compared with the observed one. Accurate predictions are in agreement with the observed outcome frequencies and the predicted risk should be higher in patients with the outcome than in patients without the outcome.[4,5]

The Coronary Heart Disease Policy Model is a well known state-transition computer simulation model for the US population.[6] Tsevat and co-authors used this model to forecast potential gains in life expectancy from risk factor modification for the cohort of Americans turning age 35 in 1990.[7,8] Grover and co-authors also developed a life-expectancy model predicting survival benefits from risk factor modification in prevention of CVD.[9]

The purpose of this study was to validate the RISC model in comparison to the actual 10-year CVD life course in the US population and to compare effects of hypothetical prevention strategies with the findings published by Tsevat and Grover.

METHODS

The model

The RISC model is a Monte Carlo state-transition model (schematically presented in Figure 1) with six states: (1) the CVD death state, (2) the non-CVD death state, (3) the Ischemic Heart Disease (IHD) state, (4) the Stroke state, (5) the IHD and Stroke state and (6) the Well state (being alive without ischemic heart disease or stroke). The

model simulates incident CVD events in individuals with and without previous CVD based on risk factor dependent transition probabilities. Individual risk factor profiles were modeled and tracked over time. All incident CVD events were counted using tracker variables during a 10-year simulation period. The cycle length used in the model was 0.1 years.

The model was built in TreeAge (version Data Professional release 10, TreeAge Software, Inc., Williamstown, USA). Detailed information about the model is given in an earlier publication[3] and in a technical appendix available on the World Wide Web[*].

Data sources and simulation of variability

In the Dutch RISC model the risk factor profiles and transition probability functions were based on data from the Rotterdam study population.[2] This population consisted of 7983 respondents from a random sample of adults aged 55 and older that were recruited between 1990 and 1993 and residing in Ommoord, the Netherlands. Of these 7983 respondents, 6871 individuals both visited the research center and signed an informed consent. Individuals were followed from 1990 to 2000 and follow-up consisted of three physical examinations with lifestyle interviews and surveillance of hospital admissions, death registries and other available medical sources, ensuring highly accurate follow-up of death and clinical manifestations of CVD.

In 3501 individuals all important characteristics to predict CVD were known. The RISC model was based on data from these 3501 individuals. The risk factors considered for the transition probability functions were age, sex, smoking status, systolic and diastolic blood pressure, diabetes mellitus, plasma glucose level, body mass index, waist to hip ratio, plasma cholesterol and HDL-cholesterol level, plasma creatinine level, family history of CVD, ankle-brachial systolic blood pressure index, manifestations of intermittent claudication, angina pectoris, atrial fibrillation or transient ischemic attacks and prevalent CVD. Details about the assessment of these risk indicators are described in earlier publications.[2]

Simulation of parameter uncertainty

The Monte Carlo model allowed the evaluation of parameter uncertainty of the transition probability functions.[10] We modeled parameter uncertainty by estimating

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[*] http://www.epib.nl/art/tools.html

the distribution of the value of each of the input variables and performing a second-order Monte Carlo simulation. To model the uncertainty in the transition probability functions, 100 bootstrap samples of the study population were drawn. All the transition probability functions were fitted for every bootstrap sample, resulting in 100 sets of linked transition probability functions. For each RISC simulation sample, we drew one set of linked functions randomly from these 100 bootstrap sets. In the second-order Monte Carlo simulation the parameter uncertainty resulted in a confidence interval for the model outcome.

Validations

For the purpose of external validation we replaced the Rotterdam Study risk factor profiles with the risk factor profiles of the 3rd National Health And Nutrition Examination Survey (NHANES III) from1988 to 1994. The NHANES III contains data from 33,994 individuals aged 2 months and older who participated in the survey. We used the national probability samples of three groups: all individuals aged 35 years and over (11327 samples), all individuals aged 55 years and over (6215 samples), and Caucasian individuals aged 55 years and over (3486 samples). The NHANES III risk factor profiles were sampled with a frequency that corresponds with their sample weights. To simulate the mean and distribution around the mean of the outcomes (standard error), we drew 1000 second-order parameter sets and with each parameter set consecutively simulated 10000 risk factor profiles of the three different population groups.

   To study the external validity of the RISC model, the simulated numbers of CVD events within 100 time-cycles of 0.1 year were compared to the data from the National Center for Health Statistics (NCHS) of the USA between 1991 and 2000. The simulated numbers of cardiovascular and non-cardiovascular deaths were compared with the data from the National Vital Statistics (NVS). The simulated number of myocardial infarctions was compared to the data from the National Hospital Discharge Survey (NHDS) after correcting for double counting, using the Westfall-correction method.[11]

   Tsevat et al.[7,8] calculated the expected gains in life expectancy from eliminating smoking and eliminating coronary heart disease in the US population using the Coronary Heart Disease Policy Model.[6] We simulated the same interventions with the RISC model to study whether the results were comparable in terms of life

expectancies and life expectancies to be gained. First, we selected the NHANES III risk factor profiles of all individuals aged 35 to 36, for men and women separately. Using these risk factor profiles we simulated the life expectancy without adaptation of the risk factor profiles, after setting the smoking variable standard to zero, and after setting the probability of coronary heart disease to zero. We simulated the mean and distribution around the mean (standard deviation) of the life expectancies by sampling from these risk factor profiles 1000 times.

Grover estimated the life years saved from lipid lowering and blood pressure lowering using a life-expectancy model which was developed on the basis of data from the Lipid Research Clinics cohort.[9] In our simulations, we selected risk factor profiles from NHANES III of non-smokers with a systolic blood pressure of 115 to 125 and a diastolic blood pressure of 75 to 85 (low risk group for the lipid-lowering simulations) and we selected smokers with a systolic blood pressure of 155 to 165 and a diastolic blood pressure of 95 to 105 (high risk group for the lipid-lowering simulations). Then we selected the non-smokers with a cholesterol / HDL-cholesterol ratio smaller then 4.5 (low risk group for the hypertension intervention simulations) and smokers with a cholesterol / HDL-cholesterol ratio larger then 6.5 (high risk group for the hypertension intervention simulations). Finally, these four groups were divided in male and female and 4 different age-groups: 35 to 45 years, 45 to 55 years, 55 to 65 years and 65 to 75 years. Grover assumed the impact of lipid-lowering treatment to be a 35% decrease in LDL-cholesterol and an 8% increase in HDL-cholesterol levels from a baseline LDL-cholesterol level of 5.46 mmol/L and an HDL-cholesterol level of 1.1 mmol/L.[9] Because we did not have any data available on LDL-cholesterol levels, we assumed a 30% decrease in total cholesterol and an 8% increase in HDL-cholesterol levels from a baseline cholesterol level of 7 mmol/L and an HDL-cholesterol level of 1.1 mmol/L. Similar to Grover, we assumed reductions of 10 mmHg in systolic blood pressure and 7 mmHg in diastolic blood pressure from a baseline blood pressure of 160 / 100 mmHg. We simulated the mean and distribution around the mean (standard deviation) of the life expectancies by sampling from these risk factor profiles 1000 times.

RESULTS

Baseline-data of both the Rotterdam study cohort and the US populations are presented in Table 1. In 1990 about 80% of the US population was Caucasian. The Caucasian US population >= 55 years was quite comparable with the Rotterdam study cohort, although the prevalence of hypertension and obesity was higher in the US population and serum glucose, serum cholesterol, the presence of CVD, and the proportion current smokers was higher in the Rotterdam study cohort. During a follow-up period of 10 years, 6,605,807 incident myocardial infarctions, 8,011,750 CVD deaths, and 13,198,351 non-CVD deaths occurred in the US population >= 35 years.

The simulated 10-year cumulative incidence rate of myocardial infarction and the 10-year mortality rate were consistent with the observed results from the NHDS and NVS data, although the myocardial infarction rate and CVD mortality rate were consistently underestimated and the non-CVD mortality rate was slightly overestimated (Table 2). In the USA population 35 years and older, which also had more racial differences than the Rotterdam cohort, the predictions from the RISC model were close to the observed results (5.13% versus 5.69% myocardial infarctions, 6.15 versus 6.91% CVD deaths, and 11.59% versus 11.38% non-CVD deaths).

Simulation of the natural history without intervention yielded a mean life expectancy for a 35-year-old man of 40.6 years (Figure 2), while Tsevat[7] calculated a life expectancy of 38.2 years. For 35-year-old women, the RISC model yielded a mean life expectancy of 45.8 years (Figure 2), instead of 44.6 years as calculated by Tsevat.[7] Although the estimated life expectancies were longer with the RISC model (Table 3), we estimated similar population-wide gains in life expectancy through elimination of smoking (0.87 versus 0.8 years in 35-year-old men and 0.63 versus 0.7 years in 35-year-old women) and elimination of coronary heart disease (3.04 versus 3.1 years in 35-year-old men and 2.72 versus 3.3 years in 35-year-old women).

We predicted the years of life saved in low- and high-risk men and women with hyperlipidemia who are free of CVD and on lipid-lowering therapy, which ranged from 0.35 years for men aged 70 years to 4.33 for men aged 40 years (Table 4). The years of life saved by lipid-lowering treatment as estimated with the RISC model were comparable to the results presented by Grover[9], although we found overall lower effects of treatment, especially in men (Table 4). The years of life saved by treatment

of hypertension as estimated with the RISC model were also comparable to the results presented by Grover[9], although we found overall higher effects of treatment, especially in men (Table 5).

DISCUSSION

In this paper we presented a validation of predicted events simulated with the Rotterdam Ischemic heart disease & Stroke Computer simulation (RISC) model in comparison to the observed data during 10 years of follow-up in the US population. Furthermore, we compared simulated life years gained from various CVD risk factor interventions with earlier published findings.

The Monte Carlo-Markov model, which was based on data from the Rotterdam Study, appeared to be an accurate tool to describe the CVD burden in the US population, based on individual risk factor profiles. Also, in the USA population with a wider age range (35 years and older) and more racial differences, the predictions from the RISC model were close to the observed results. So, although the RISC model was based on Caucasian individuals of 55 years and older, the model seems to be generalizable to younger populations with more racial differences. Remaining differences may be due to differences in the assessment of risk factors but also in differences in outcome assessment.

Although life expectancies were consistently overestimated compared to that estimated with the Coronary Heart Disease Policy model, the predicted life-years saved through lowering lipid levels and blood pressure and eliminating smoking and total coronary heart disease were close to the earlier published findings.[7,9] The RISC model may overestimate life expectancies due to the fact that the RISC model is based on data from a relatively healthy Dutch population of individuals who were all able and willing to visit the research center. For future modeling of the US population using the RISC model, the model would need to be recalibrated to the US by increasing the baseline cumulative hazards of the transition probability functions.

Differences in simulation results can also partly be explained by the fact that the Coronary Heart Disease Policy Model and the RISC model differ in their structure. While the Coronary Heart Disease Policy Model is a Markov model for coronary heart disease only[6], we integrated death due to both coronary heart disease and stroke

so that the impact of preventive treatment can be better compared across the two major causes of cardiovascular death. Furthermore, it uses a cohort rather than a Monte Carlo approach and therefore cannot fully model memory for events. Whereas the Coronary Heart Disease Policy Model studies heterogeneity by dividing the population into subgroups, the RISC model simulates individuals by tracking them with dedicated (tracker) variables.

Like Grover[9], we found that high-risk individuals generally benefit more than low-risk individuals and the young more than the elderly, although differences were somewhat smaller in our simulations. This may be due to the fact that we included interaction terms between CVD risk indicators, while Grover did not. Like Grover, we found that men gained more than women, except that in our simulations this was not true for lipid-lowering treatment in older individuals. This reflects the attenuated life expectancy of the elderly, especially in males, therefore reducing the potential benefits of therapy.

Coronary heart disease is the leading cause of death both in the Netherlands and in the United States. It may be surprising, then, to find that the strictest risk factor modifications -eliminating smoking or even eliminating all coronary heart disease- would yield only modest gains in population-wide life expectancy. It is important to realize, however, that the estimated gains in life expectancy are an average across the entire population that is screened and treated, not the expected gain in affected individuals.

We used well-established methods of decision analysis to integrate the available data on the potential benefits of various preventive strategies. Interpretation of our results should, however, consider the assumptions that were made. The risk reductions were assumed to be identical for high and low risk individuals and intervening on one risk factor was assumed not to affect other risk factors. A major problem of the simulation model is that the coefficients of risk are derived from a population-based study. Because of misclassification of both exposure status and to a lesser extent outcome status, the coefficients probably underestimate the true relation between risk factors and disease and therefore may underestimate the benefits of intervention. On the other hand, due to overfitting in regression modelling, risk functions could lead to overestimation in high risk and underestimation in low risk individuals in other populations. Furthermore, our model assumed a benefit from risk factor intervention

in the next cycle (within 0.1 years), whereas in actual fact there may be a delay before the benefit is realized.

In an earlier study[3] we showed good apparent and internal validity. In this study we demonstrated external validity. Although the RISC model is based on data from non-institutionalized individuals 55 years and older who were mostly Caucasian, the model seems to behave well in other populations. Given the demonstrated validity and generalizability of the RISC model, we think it can now be used to perform cost-effectiveness analyses of targeting- and intervention strategies in the primary prevention of cardiovascular disease.

REFERENCES

1. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making. 1993;13:322-38.*

2. 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.*

3. Nijhuis RL ST, Peeters A, Witteman JCM, Hofman A, Hunink MGM. Validation of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow up study. *Med Decis Making. submitted.*

4. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema JD. Validity of prognostic models: when is a model clinically useful? *Semin Urol Oncol. 2002;20:96-107.*

5. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol. 2001;54:774-81.*

6. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. *Am J Public Health. 1987;77:1417-26.*

7. Tsevat J, Weinstein MC, Williams LW, Tosteson AN, Goldman L. Expected gains in life expectancy from various coronary heart disease risk factor modifications. *Circulation. 1991;83:1194-201.*

8. Tsevat J. Impact and cost-effectiveness of smoking interventions. *Am J Med. 1992;93:43-47.*

9. Grover SA, Paquet S, Levinton C, Coupal L, Zowall H. Estimating the benefits of modifying risk factors of cardiovascular disease: a comparison of primary vs secondary prevention. *Arch Intern Med. 1998;158:655-62.*

10. Hunink MGM, Glasziou P.P., Siegel J.E., et al. Decision making in health and medicine: interpreting evidence and values. Cambridge, England; 2001.

11. Petersen LA, Wright S, Normand SL, Daley J. Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. *J Gen Intern Med. 1999;14:555-8.*

Table 1. Descriptive data of the study populations

	US population >=35 years	US population >=55 years	US population >=55 years & Caucasian	Rotterdam study cohort
	N = 115,789,726	N = 50,977,003	N = 42,735,273	N = 3501
Male gender %	46.4	44	44.1	39.5
Medical history of CVD %	7.5	14.4	14.5	17.8
Diabetes Mellitus %	6.3	9.8	8.9	10.7
Hypertension %	27.4	43.4	42.4	36.4
Past smoking %	32.5	39.3	41.3	41.9
Current smoking %	24.6	17.5	16.6	23.6
Transient Ischemic Attack %	5.6	6.2	5.5	5.1
Intermittent Claudication %	1	1.6	1.7	2.1
Angina Pectoris %	4.1	5.2	5.1	5.6
Family history of MI %	16	12	12.8	16.3
RACE: Caucasian %	79.2	83.2	100	100
RACE: Black %	9.9	8.8	n.a.	n.a.
RACE: Mexican/American%	3.8	2.4	n.a.	n.a.
RACE: other %	7.1	5.6	n.a.	n.a.
Age (years)	53.93+/-14.14	67.68+/-8.79	68.04+/-8.84	68.97+/-8.47
Serum glucose (mmol/l)	5.72+/-1.98	6.04+/-2.28	5.98+/-2.14	6.93+/-2.62
Serum cholesterol (mmol/l)	5.54+/-1.1	5.79+/-1.13	5.8+/-1.12	6.67+/-1.24
Serum HDL-cholesterol (mmol/l)	1.31+/-0.41	1.33+/-0.43	1.32+/-0.43	1.33+/-0.36
Systolic blood pressure (mmHg)	127+/-21	137+/-23	136+/-22	140+/-22.35
Diastolic blood pressure (mmHg)	74+/-11	73+/-12	73+/-11	74.13+/-11.74
Pulse pressure (mmHg)	53+/-19	64+/-21	63+/-21	65.86+/-18.04
Body mass index (kg/m^2)	27.17+/-5.68	27.16+/-5.22	27.05+/-5.09	26.34+/-4.17
Waist-hip ratio	0.93+/-0.09	0.9557+/-0.08	0.9551+/-0.08	0.9057+/-0.09
Serum Creatinine (µmol/l)	97+/-28	102+/-35	101+/-30	83+/-18

Table 2. The simulated 10-year cumulative incidence rate (%) of myocardial infarction, cardiovascular deaths and non-cardiovascular deaths compared to the observed numbers in the data from the National Hospital Discharge Survey and the National Vital Statistics.

	35+			55+			55+ Caucasian		
	Observed (%)	Simulated (%)	s.e	Observed (%)	Simulated (%)	s.e.	Observed (%)	Simulated (%)	s.e.
Myocardial infarctions	5.69	5.13	0.009	9.71	8.89	0.007	9.09	8.36	0.007
CVD deaths	6.91	6.15	0.012	14.29	13.24	0.010	13.02	12.42	0.009
Non-CVD deaths	11.38	11.59	0.014	21.26	21.85	0.012	19.76	20.02	0.012
Total deaths	18.29	17.74		35.55	35.09		32.78	32.44	

s.e.: standard error due to uncertainty in the transition probability functions

Table 3. Life expectancy (years) for 35-year-old individuals in the USA with and without intervention. Gains in life expectancy predicted with the RISC model are compared to those predicted by Tsevat.[7]

35-year-old Male

	Mean	SD	Gain by RISC	*Gain by Tsevat*
Natural history	40.59	9.61	-	-
Elimination of smoking	41.46	8.93	0.87	*0.8*
Elimination of CHD	43.63	9.81	3.04	*3.1*

35-year-old Female

	Mean	SD	Gain by RISC	*Gain by Tsevat*
Natural history	45.77	8.62	-	-
Elimination of smoking	46.40	8.50	0.63	*0.7*
Elimination of CHD	48.49	8.91	2.72	*3.3*

CHD: coronary heart disease

SD: standard deviation due to variability and uncertainty in the transition probability functions

Table 4. Predicted life expectancies and years of life saved following lipid level modification in individuals with hyperlipidemia. Gains in life expectancy predicted with the RISC model are compared to those predicted by Grover.[9]

| | Hyperlipidemia* | | | |
-	No treatment	Treatment[†]	Gain by RISC[‡]	*Gain by Grover[§]*
Male, high risk[**]				
40 years	34.3	38.63	4.33	*4.74*
50 years	27.68	30.84	3.16	*3.75*
60 years	17.72	19.44	1.72	*2.40*
70 years	11.59	12.27	0.68	*0.78*
Male, low risk[††]				
40 years	41.9	43.51	1.61	*2.50*
50 years	32.42	33.28	0.86	*2.05*
60 years	25.08	25.75	0.67	*1.40*
70 years	15.13	15.48	0.35	*0.43*
Female, high risk[**]				
40 years	39.79	42.83	3.04	*3.76*
50 years	30.05	32.57	2.52	*3.05*
60 years	22.50	24.46	1.96	*2.15*
70 years	14.66	15.47	0.81	*0.80*
Female, low risk[††]				
40 years	46.22	47.73	1.51	*1.12*
50 years	36.83	38.08	1.25	*1.05*
60 years	26.48	27.71	1.23	*0.85*
70 years	17.97	18.48	0.51	*0.25*

* A baseline cholesterol level of 7 mmol/L and an HDL-cholesterol level of 1.1 mmol/L

† A 30% decrease in total cholesterol and a 8% increase in HDL-cholesterol levels

‡ Gain in life years as estimated by the RISC model

§ Gain as estimated by Grover[9]

** Smokers with a systolic blood pressure of 155 to 65 and a diastolic blood pressure of 95 to 105

†† Non-smokers with a systolic blood pressure of 115 to 125 and a diastolic blood pressure of 75 to 85

Table 5. Predicted life expectancies and years of life saved following treatment of hypertension in individuals with hypertension. Gains in life expectancy predicted with the RISC model are compared to those predicted by Grover.[9]

| | Hypertension[*] | | | |
	No treatment	Treatment[†]	Gain by RISC[‡]	*Gain by Grover[§]*
Male, high risk[**]				
40 years	33.67	35.32	1.65	*1.19*
50 years	26.54	28.14	1.60	*1.05*
60 years	16.73	18.08	1.35	*0.85*
70 years	11.16	12.04	0.88	*0.29*
Male, low risk[††]				
40 years	39.55	40.97	1.42	*0.85*
50 years	30.64	32.02	1.38	*0.75*
60 years	23.82	25.00	1.18	*0.60*
70 years	13.59	14.17	0.58	*0.17*
Female, *high risk[**]*				
40 years	38.03	39.62	1.59	*1.34*
50 years	30.10	31.64	1.54	*1.20*
60 years	21.53	22.74	1.21	*0.90*
70 years	14.13	14.89	0.76	*0.33*
Female, *low risk[††]*				
40 years	43.77	44.43	0.66	*0.59*
50 years	34.23	34.66	0.43	*0.57*
60 years	24.95	25.36	0.41	*0.40*
70 years	16.73	17.08	0.35	*0.13*

* A baseline blood pressure of 160 / 100 mmHg

† Reductions of 10 mmHg in systolic blood pressure and 7 mmHg in diastolic blood pressure

‡ Gain in life years as estimated by the RISC model

§ Gain as estimated by Grover[9]

** Smokers with a cholesterol / HDL-cholesterol ratio larger then 6.5

†† Non-smokers with a cholesterol / HDL-cholesterol ratio smaller then 4.5

Cost-effectiveness of the "Polypill":

a computer simulation study

Abstract

Objectives To evaluate the cost-effectiveness, from a societal perspective, of primary prevention strategies for cardiovascular disease (CVD) using the "Polypill" (a combination of aspirin, a statin, three blood pressure lowering agents in half dose, and folic acid) as described by Wald & Law.

Design Cost-effectiveness analysis using a Monte Carlo-Markov model based on a population-based cohort study. Probabilistic sensitivity analysis and analyses evaluating variability across individuals were performed..

Participants Simulated Rotterdam Study participants aged 55-80 years at baseline, without medical history of CVD at baseline (1990-1993).

Interventions Life-long treatment with the "Polypill" in all 55-80 year old individuals, or only in those identified as being at high risk by the Framingham CVD risk score.

Outcome measures CVD-free life expectancy, 3%-discounted quality-adjusted life years (QALY), and incremental cost-effectiveness ratios.

Results Life-long treatment with the "Polypill" in all 55-80 year old individuals, compared to usual care, increases the population mean CVD-free life expectancy with 3.5 years and would decrease the percentage of total mortality that is due to CVD from 33% to 8%. Life-long treatment in all 55-80 year old individuals was cost-effective compared to usual care (incremental cost-effectiveness ratio €3 176 per QALY) and was cost-effective compared to treating only individuals with a Framingham 5-year CVD risk of more than 5% (incremental cost-effectiveness ratio €18 787 per QALY). Treating all 55 to 60 year-old men was both more effective and cost-saving compared to usual care. Sensitivity analyses showed robustness of the results.

Conclusion: Life-long treatment with the "Polypill" in all 55-80 year old individuals would be a cost-effective strategy to prevent cardiovascular disease in the general population.

INTRODUCTION

Recent trials have shown that lowering serum cholesterol[1], lowering blood pressure[2,3] and the use of low dose aspirin[4] all reduce the risk of cardiovascular disease (CVD). Whereas secondary prevention of cardiovascular events through risk factor modification in patients with known coronary and carotid artery disease is recognised as cost-effective, CVD prevention by drug therapy in asymptomatic individuals has shown only modest benefits and to be relatively expensive.

Wald and Law recently proposed that a single pill containing aspirin, a statin, three blood pressure lowering agents in half dose, and folic acid (the "Polypill") should be provided to all people with vascular disease and those over 55 years old.[5] The decision to implement a new preventive strategy, however, requires that it not only increases length and quality of life, but also that it is economically sound. The cost-effectiveness of the "Polypill" in the general population remains to be determined.[6,7]

Computer simulation models that integrate information on CVD risk factor distributions, epidemiologic, demographic and economic data can provide comprehensive projections that assist future health care planning in the area of cardiovascular disease.[8,9] In a prior study, we developed such a computer simulation model.[10] The model was designed to evaluate the impact of CVD risk factors and their modification on life expectancy, CVD-free life expectancy, quality-adjusted life expectancy, and costs in a general population. The structure and input parameters were based on data from the Rotterdam Study, a cohort follow-up study of adults aged 55 years and older.[11] The model will be referred to as the Rotterdam Ischemic heart disease & Stroke Computer simulation (RISC) model. This model proved to be a valid tool to describe the CVD burden in the Rotterdam Study population based on individual risk factor profiles.[10]

The objective in this study was to examine the cost-effectiveness of primary prevention strategies for CVD with "Polypill" therapy using the RISC model.

METHODS

We performed a computer simulation study based on data from a large cohort follow-up study, the Rotterdam Study, and a cost-effectiveness analysis from the societal

perspective of primary prevention strategies for CVD with "Polypill" therapy in selected Rotterdam Study participants.

Strategies

First of all we considered a primary prevention strategy for CVD in which we would treat all 55-80 year old individuals without evident CVD and with a systolic blood pressure less than 180 mm Hg with the "Polypill", containing three anti-hypertensives at half standard dose, a statin, 80 mg of aspirin, and 0.5 mg of folic acid. This strategy was compared to usual care, that is, the care given to individuals in the Rotterdam Study population between 1990 and 2000. Next, several prevention strategies were analysed based on the Framingham CVD risk function[12] using different thresholds of the risk score above which treatment would be initiated. In the simulation study we examined individuals every 5 years for risk stratification and we assumed that all individuals identified, as being at high risk would be treated with the "Polypill". We assumed that life-long medical therapy would be initiated by a primary care physician, who also annually monitors for adverse events in every individual treated.

Outcomes

The main outcome measures were health benefit expressed in quality-adjusted life years (QALYs), societal costs expressed in Euros, and incremental cost-effectiveness ratios, defined as the additional cost of a specific strategy divided by its additional health benefit. We computed the incremental cost-effectiveness ratio for a strategy in reference to usual care and in reference to the next best prevention strategy based on the Framingham CVD risk function. The strategy with the highest effectiveness and an incremental cost-effectiveness ratio of less than the society's threshold willingness-to-pay[13] was considered the most cost-effective. We considered thresholds of €50000 and €20 000 per QALY.[13] We also expressed the outcomes in net health benefits, defined as the QALYs minus the costs, the costs being transformed to QALY equivalents by dividing them by the threshold willingness-to-pay.[14] We calculated incremental net health benefits to indicate the gain in net health benefit in comparison to the next best strategy. A positive incremental net health benefit indicates a cost-effective strategy in comparison to the next best strategy and the strategy with the highest (incremental) net health benefit was considered the most cost-effective.

Furthermore, we evaluated the gain in cardiovascular disease-free life years and the percentage of total mortality that was due to CVD.

The RISC model

The RISC model is a state-transition model containing 6 states: (1) the CVD death state, (2) the non-CVD death state, (3) the Ischemic Heart Disease (IHD) state, (4) the Ischemic Stroke state, (5) the IHD and Stroke state and (6) the Well state. The model simulated incident CVD events in individuals with and without previous CVD (Figure 1). To provide transition probabilities for different risk factor patterns, we constructed six transition probability functions based on CVD risk indicators with Cox proportional hazard analyses. Details about the RISC model are described in the technical appendix, which is posted on the World Wide Web (http://www.epib.nl/art/tools.html).

Data sources and study population

The population based risk factor profiles and transition probability functions were based on data from the Rotterdam Study population. The Rotterdam Study is a prospective population based study among 7983 men and women aged 55 years and older and living in Ommoord, Rotterdam.[11] Extensive baseline data have been obtained including medical history, classical risk factors, and other risk indicators of cardiovascular disease. The risk indicators considered were age, sex, smoking status, systolic and diastolic blood pressure, diabetes mellitus, plasma glucose level, body mass index, waist to hip ratio, plasma cholesterol and HDL-cholesterol level, plasma creatinine level, family history of CVD, ankle-brachial systolic blood pressure index, manifestations of intermittent claudication, angina pectoris, atrial fibrillation or transient ischemic attacks, and prevalent CVD. A person was designated as having prevalent CVD if a myocardial infarction or a stroke was diagnosed by a physician and/or the patient reported CABG, PTCA, or carotid surgery in the past. Of the 7983 individuals, 4325 individuals were free of evident CVD at baseline, had a systolic blood pressure of no more than 180 mm Hg, and were younger than 80 years at baseline and therefore eligible for "Polypill" therapy.

The efficacy of each of the components of the "Polypill" was based on the data reported in the paper by Wald & Law[5] (Table 1). The adverse events used in the simulations were derived from the studies by Hayden[4] and Bell[15] (Table 2). Health-related quality of life weights for myocardial infarction, angina pectoris, ischemic stroke, transient ischemic attack, peripheral arterial disease, diabetes mellitus, hemorrhagic stroke, gastrointestinal bleeding, and revascularization were derived from the Catalog of Preference Scores of Bell et al.[15] Quality of life for healthy individuals was assumed to depend on age and sex and was based on data from a general population sample assessed in the Beaver Dam study.[16]

Uncertainty & Variability

We accounted for uncertainty of modelled transition probabilities, effects, and costs by estimating the distribution of the value of each of the input variables and performing probabilistic sensitivity analysis with a second-order Monte Carlo simulation.[17] To model the uncertainty in the transition probability functions, we drew 100 bootstrap samples of the study population.[18] All the transition probability functions were fitted for every bootstrap sample, resulting in 100 sets of linked transition probability functions. For each RISC simulation scenario, we drew consecutively one set of linked functions from these 100 bootstrap sets.

The distributions of the effectiveness of interventions (Table 1) were based on the 95% confidence interval as reported.[5] The probabilities of adverse events (Table 2) were modeled with a uniform distribution on a plausible range around the published values. Health-related quality of life weights were modeled as ranging from the lowest to the highest value as described in the Catalog of Preference Scores.[15] Costs of interventions and CVD events

were varied with ± 30% absolute change around the mean value. In the second-order Monte Carlo simulation the parameter uncertainty resulted in different model outcomes for 100 possible scenarios.[19]

If we want to make a policy decision for a heterogeneous population, then variability within the population should be accounted for. Variability within the population (or heterogeneity) was modeled by simulating every individual from the source population separately.[19] Since individuals with their entire risk factor profiles were simulated, correlations between the risk factors were taken into account.

Assumptions

The time cycle used in the analysis was 0.1 years. All CVD events were assumed to occur half way through the time cycle. Changes in continuous risk factor levels were analysed using linear regression analysis with age as covariate and assumed to be constant over time. Categorical risk factor levels were analysed using logistic regression analysis and updated in the model every 5 years. Individuals could only get one ischemic heart disease event and/or one stroke per time cycle. The fourth myocardial infarction and the third stroke were assumed to always be fatal. The number of prior events was assumed not to influence event probabilities or case fatality rates, although individuals experiencing second or subsequent CVD events were distinguished from first CVD events by virtue of the fact that they were in a different Markov-state. The effects of the components of the "Polypill" were assumed to be independent and additive and to be achieved within one year. Adverse events of the "Polypill" (haemorrhagic stroke and gastro-intestinal bleed) were simulated as non-CVD mortality and as utility loss and therefore impacted CVD-free life expectancy only through their effect on total life expectancy.

Cost-effectiveness analysis

The cost analysis included all medical and non-medical costs relevant from the societal perspective associated with both cardiovascular disease and non-cardiovascular disease. Direct medical costs included costs of events, screening costs and prevention costs. We accounted for both the transition (one-time) costs of events and for the incremental (annual) costs following events. Screening costs were the costs of evaluating CVD risk in the individuals (in total €61 per screening event). We considered a 5-yearly visit to the primary care physician for determination of the Framingham risk score in all individuals and an annual risk factor assessment and monitoring for adverse events in the individuals identified as being at high risk. Prevention costs are the costs associated with the prescription of the components of the "Polypill" as determined by the Dutch Health Care Insurance Board. We calculated the costs of the "Polypill" by adding the costs of 80 mg aspirin, 10 mg atorvastatin, 12.5 mg hydrochlorothiazide, 50 mg metoprolol, 5 mg enalapril and 0.5 mg folic acid (in total €727 per person year). We also considered indirect medical costs, that is increased health care costs incurred during gained life years.[20]

Non-medical costs included overhead costs, time costs, travel costs and productivity losses. Productivity losses were estimated with the friction cost method[21]

which enumerates the costs associated with reduced production because sick employees work less or less efficiently and the costs associated with recruitment and training of new employees if an employee is on sick leave due to incident CVD or dies.

To evaluate the cost-effectiveness of primary prevention strategies for CVD with "Polypill" therapy, we consecutively analysed each of the possible 100 scenarios to evaluate the uncertainty of the cost-effectiveness due to the uncertainty of the transition probability functions used in the RISC model. Within each of the 100 scenarios, the life histories of all 4325 individuals were simulated for every prevention strategy.

The model used a lifetime time horizon and a societal perspective. Future costs and quality-adjusted life years were discounted at the currently recommended nominal discount rate of 3% per year[22] to take time-preference into account. This implies that effects and costs occuring in the future are weighed less than those occuring in the present.[19] In the reference case analysis we assumed complete compliance of all individuals. Subgroup analyses were performed in which only 55 to 60 year-old men and 55 to 60 year-old women were considered for "Polypill" therapy.

Apart from the probabilistic sensitivity analysis described above, we performed sensitivity analyses with a discount rate of 5% instead of 3%, a compliance rate of 70% instead of 100%, excluding the costs of medical visits for initiating and monitoring therapy in the treat-all strategy, and excluding the productivity losses.

Furthermore, we recognised that the effect estimates of the "Polypill"[5] were possibly optimistic, and therefore performed two additional sensitivity analyses assuming the relative risk reductions of the "Polypill" components to be 75% and 50%, respectively, of the estimates reported by Wald & Law.

RESULTS

By treating the whole population with the "Polypill", the percentage of total mortality that is due to CVD would decrease from 33% to 8% and the population CVD-free life expectancy would increase with 3.5 years. Furthermore, this strategy would result in an average gain of 0.72 quality-adjusted life years (QALYs) compared to usual care (Table 3). Compared to usual care, treating everyone with the "Polypill" had an

estimated incremental cost-effectiveness ratio of €3 176 per QALY and increased the net health benefits with 0.61 to 0.68 QALY equivalents (considering a threshold willingness-to-pay of €20 000 and €50 000 respectively). Treating everyone was cost-effective compared to usual care in every possible scenario and both more effective and cost-saving in 24% of these possible scenarios for both thresholds of willingness-to-pay.

The most effective prevention strategy based on the Framingham CVD risk function was treating individuals with a Framingham risk higher than 5% (incremental cost-effectiveness ratio of €7 143 per QALY), which would imply treating the 87.5% of individuals who have the highest risk scores (Figure 2). Compared to this strategy, treating all individuals with the "Polypill" remained cost-effective with an incremental cost-effectiveness ratio of €18 787 per QALY and an incremental net health benefit of 0.001 to 0.014 QALY equivalents for a threshold willingness-to-pay of €20 000 and €50 000 respectively (Table 3). Treating all individuals with the "Polypill" was more efective in all possible scenarios but cost-saving in 8% and more expensive in 92% of the possible scenarios. In 6% of the scenarios "Polypill" therapy was too expensive, i.e. more than € 50 000 per QALY (Figure 3). For a threshold willingness-to-pay of € 20 000 per QALY, the treat-all strategy was still cost-effective in 51% of the scenarios (Figure 3).

Selecting individuals for treatment based on a Framingham CVD risk score threshold of 15% or higher was excluded from consideration because of a higher incremental cost-effectiveness ratio than a more effective strategy (Figure 2). Treating individuals with a Framingham CVD risk higher than 12% was cost-effective compared to usual care with an incremental cost-effectiveness ratio of €2 091 per QALY and an incremental net health benefit of 0.127 QALY equivalents (Table 3).

Subgroup analyses

Treating all 55 to 60 year-old men with the "Polypill" would increase their mean life expectancy from 23.66 to 25.39 years, their CVD-free life expectancy from 16.35 to 19.46 years and the discounted quality-adjusted life years from 10.76 to 10.97 years. Furthermore, the societal costs would diminish from €40 880 to €39 245, implying that treating all 50 to 60 year-old men is both more effective and cost-saving compared to usual care. However, the least costly strategy was treating 55 to 60 year-

old men with a Framingham risk score of 7% or higher. Compared to this strategy treating individuals with a Framingham risk higher than 5% was cost-effective with a mean incremental cost-effectiveness ratio of €2 896 per QALY and compared to the latter strategy, treating all individuals was cost-effective with a mean incremental cost-effectiveness ratio of €26 143 per QALY. All other strategies were more costly and less effective than treating individuals with a Framingham risk higher than 7%.

Treating all 55 to 60 year-old women with the "Polypill" would increase their mean life expectancy from 26.96 to 29.17 years, their CVD-free life expectancy from 23.09 to 27.29 years and the discounted quality-adjusted life years from 11.75 to 11.86 years. The least costly strategy in 55 to 60 year-old women was usual care. Compared to usual care, treating 55 to 60 year-old women with a Framingham risk higher than 5% was cost-effective with a mean incremental cost-effectiveness ratio of €23 812 per QALY. Compared to treating those with a risk higher than 5%, treating all individuals was cost-effective with a mean incremental cost-effectiveness ratio of €33 814 per QALY. All other strategies were more costly and less effective than treating individuals with a Framingham risk higher than 5%.

Sensitivity analyses

By changing the discount rate from 3% to 5%, the incremental cost-effectiveness ratio of the treat-all strategy compared to treating individuals with a Framingham risk higher than 5% decreased from €18 787 to €15 473 per QALY. This lower value can be explained by a higher impact of discounting on the difference in costs than on the difference in effectiveness. Assuming a compliance rate of 70% instead of 100%, the incremental cost-effectiveness ratio became €20 269. Excluding the costs of medical visits for initiating and monitoring therapy in the treat-all strategy reduced the total costs per individual with €370, resulting in an incremental cost-effectiveness ratio of €4 770 per QALY compared to prevention based on the Framingham CVD risk function (Table 4). By excluding the productivity losses in the analysis, the incremental cost-effectiveness ratio increased to €19 062, due to the fact that less societal costs are involved when CVD events occur.

Assuming that the efficacy of the "Polypill" components was 75% of the estimates by Wald & Law resulted in an incremental cost-effectiveness ratio of €33 333 (instead of €18 787) per QALY compared to prevention based on the Framingham CVD risk function (Table 4). Treating individuals with a Framingham risk score of

5% was cost-effective compared to treating individuals with a Framingham risk score of 7% (incremental cost-effectiveness ratio €16 455 per QALY).

Assuming that the efficacy of the "Polypill" components was only 50% of that estimated by Wald and Law resulted in an incremental cost-effectiveness €51 600 per QALY compared to prevention based on the Framingham CVD risk function (Table 4). However, excluding the costs of medical visits for initiating and monitoring therapy in the treat-all strategy resulted in an incremental cost-effectiveness ratio of €29 097 per QALY compared to usual care and prevention strategies based on the Framingham risk function became inferior.

DISCUSSION

We examined the cost-effectiveness of primary prevention strategies for CVD with "Polypill" therapy in the Rotterdam Study population. Initiating "Polypill" therapy in all 55-80 year old individuals would increase the population mean CVD-free life expectancy with 3.5 years compared to usual care, would decrease the percentage of total mortality that is due to CVD from 33% to 8%, and would lead to a gain of 0.72 quality-adjusted life years (QALYs). Moreover, this strategy appeared to be highly cost-effective, even in comparison to commonly used prevention strategies based on the Framingham risk function. Sensitivity analyses showed robustness of the results. The incremental cost-effectiveness ratios were insensitive to plausible changes in discount rate and compliance rate. Also, productivity losses had only a limited effect on the cost-effectiveness because of the low proportion of employed individuals in this older population. The "Polypill" therapy in all Rotterdam Study participants remained cost-effective inspite of aspirin intolerance in 5.7% and even if 30% of the total population was assumed to be non-compliant.

By introducing the "Polypill" in the general population, the mean average costs that will be invested life-long per individual was estimated to be approximately €16500. Because of the cost-savings due to prevention of CVD events, average life-long net costs will be only €2295 per individual. For the Netherlands this means that €1625 million would need to be invested annually but there would be an estimated

cost-savings of €1400 million annually, implying a net national annual cost of €225 million to gain 3.5 CVD-free life years and 0.72 discounted QALY's.

Our results suggest that "Polypill" therapy is not only cost-effective but may even be cost-saving in certain subgroups. In particular we found that "Polypill" therapy in all 55 to 60 year-old men was both effective (more than 3 years gain in CVD-free life expectancy) and cost-saving (almost 5% reduction in societal costs) compared to usual care.

The gain in CVD-free life years achieved with "Polypill" therapy was considerably higher than the gain in QALYs. This big difference is due to the fact that the benefit of therapy is mostly at the end of life while the adverse events occur relatively early in life and because the QALYs were discounted with an annual rate of 3%. Furthermore, we took into account that the extra life years gained were at an older age at which individuals have a relatively lower quality of life.[16] Finally, when analysing CVD-free life years, the detrimental effect on quality of life due to adverse events was not taken into account.

Wald & Law showed that 36 out of 100 men without known vascular disease would benefit from taking the "Polypill" from the age of 55 years on. In this 36% they calculated a 12-year gain in life years free of IHD and stroke, resulting in an average gain of (0.36 * 12 =) 4.32 years.[5] Our results showed that initiating "Polypill" therapy in all 55 to 60 year-old men would increase the mean CVD-free life expectancy with 3.11 years. Our lower calculated life expectancy can be explained by the fact that we took both adverse events and competitive mortality into account whereas Wald & Law did not.

Limitations of this study are similar to those of every decision analysis and cost-effectiveness study. Optimising the trade-off between quality-adjusted life expectancy and costs underlie this analysis and in doing so we assumed that society could define a threshold willingness-to-pay for a QALY gained. Even though we assume that the societal willingness-to-pay can be defined, we recognise that the threshold value is difficult to determine, may fluctuate with time, differs across countries, and may differ across types of interventions. The decision to treat all 55-80 year old individuals depends on what society is willing to pay for health care. At a threshold value of €50,000 per QALY, for example, a commonly quoted threshold value, our results suggest that life-long treatment with the "Polypill" in all 55-80 year old individuals is a very cost-effective CVD prevention strategy. Considering the incremental cost-

effectiveness ratios of currently frequently performed primary prevention interventions, a lower threshold willingness-to-pay of for example €20,000 per QALY may be appropriate, in which case cost-effectiveness of "Polypill" therapy in all 55-80 year old individuals is less evident.

We are aware that new CVD risk functions were developed since the introduction of the Framingham risk function. For example, recently the SCORE risk function[23] was introduced in Europe based on follow-up in 200 000 individuals. This function, however, does not consider CVD morbidity, which in our model was a major consideration given the considerable impact on quality of life. Furthermore, the Framingham risk function is well-known and very widely used. Even if we had used the SCORE risk function, the results would probably have been similar.

We used well-established methods of cost-effectiveness analysis to integrate the available data on the potential benefits of the "Polypill" components. Interpretation of our results should, however, consider the assumptions that were made. The proportional risk reductions were assumed identical for the high and low risk strata based on studies that demonstrated that risk reductions are homogeneous across the risk continuum suggesting that the reported results can be extrapolated to groups at intermediate risk.[5] Note, however, that whereas we assumed equivalent proportional risk reductions across the risk continuum, this translates into very different absolute benefits depending on the underlying risk of CVD.

Furthermore, we assumed the effects of the components of the "Polypill" to be independent and additive. If the effects are in fact less than the sum of the parts, then we have overestimated effectiveness and cost-effectiveness would in reality be less favourable. Wald & Law made the same assumption and calculated the combined effect of the components of the "Polypill" by multiplying the relative risks associated with each.[5] However, they did not account for the uncertainty of the relative risks whereas in our simulations the uncertainty of each of the relative risks was accounted for before multiplying the individual effects. Our estimates of the individual effects are based on those presented by Wald & Law. They computed the estimates by combining data from short and long-term clinical trials and longitudinal observational studies and used a number of assumptions such as independency of the relative effect from baseline level of the risk factor. Because the effect estimates are not derived directly from long-term clinical trials in the general population, it could be that they

are too optimistic. Our analyses showed that assuming effectiveness of the "Polypill" to be 75% of the estimates as reported by Wald & Law, "Polypill" therapy in all individuals was still cost-effective, considering a threshold willingness-to-pay of €50 000 per QALY. If society is only willing to pay €20 000 per QALY, treating all individuals would be too expensive, but treating individuals with a Framingham risk score of 5% would still be acceptable. Moreover, assuming that the efficacy of the "Polypill" components was only 50% of that estimated by Wald and Law, we found that treating all individuals would still be cost-effective for a threshold willingness-to-pay just a little over €50 000 per QALY.

We did not include all factors that may increase the cost-effectiveness of the "Polypill". The simulated effectiveness of "Polypill" therapy on total life expectancy may even be higher than estimated. For example, we did not take the non-cardiovascular effects of aspirin into account. Aspirin may also have preventive effects on colorectal cancer.[24] Furthermore, in recent years other beneficial effects of statins have been suggested, such as anti-inflammatory[25], anti-proliferative[26] and immunosuppressive[27] properties. Other than the risk reduction of IHD and stroke, these effects were not modeled. Moreover, the cost-effectiveness of treating all individuals was more favourable when we excluded the costs of medical visits for initiating and monitoring therapy in the treat-all strategy. Reducing, or even eliminating, the costs of medical visits for initiating and monitoring therapy can be expected if prevention with the "Polypill" is implemented through advertisements, educational programs, or other low cost interventions that reach the general population. Although treating individuals with the "Polypill" without medical supervision may seem appropriate to some[5], safety needs to be evaluated. Finally, we calculated the costs of the "Polypill" by summating the costs of generic medications that are not subject to patent protection and have the lowest rate of adverse events. However, when given in combination, the costs of the "Polypill" may still be reduced and the "Polypill" may become even more cost-effective.

We conclude that primary prevention for CVD with "Polypill" therapy is a cost-effective strategy in the general population aged 55 to 80 years old under a wide variety of assumptions and may even be cost-saving in selected subgroups. We advocate a pragmatic clinical trial to study effects and associated costs of the "Polypill" in real life.

REFERENCES

1. 4S. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet 1994;344(8934):1383-9.*

2. Ebrahim S, Smith GD. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. *BMJ 1997;314(7095):1666-74.*

3. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet 1990;335(8693):827-38.*

4. 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.*

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

6. Rodgers A. A cure for cardiovascular disease? Combination treatment has enormous potential, especially in developing countries. *BMJ 2003;326:1407-8.*

7. 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.*

8. Grover SA, Paquet S, Levinton C, Coupal L, Zowall H. Estimating the benefits of modifying risk factors of cardiovascular disease: a comparison of primary vs secondary prevention. *Arch Intern Med 1998;158:655-62.*

9. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. *Am J Public Health 1987;77:1417-26.*

10. Nijhuis RL, Stijnen T, Peeters A, Witteman JCM, Hofman A, Hunink MGM. Validation of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow up study. *Med Decis Making, submitted.*

11. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol 1991;7(4):403-22.*

12. Anderson KM, Odell PM, Wilson PW, et al. Cardiovascular disease risk profiles. *Am Heart J. 1991;121:293-8.*

13. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making 2000;20:332-42.*

14. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making 1998;18:S68-80.*

15. Bell CM, Chapman RH, Stone PW, Sandberg EA, Neumann PJ. An off-the-shelf help list: a comprehensive catalog of preference scores from published cost-utility analyses. *Med Decis Making 2001;21:288-94.*

Table 2. Adverse events of each of the components of the "Polypill".

The estimates of adverse events were drawn independently from uniform distributions ranging from a minimum to a maximum value.

ASPIRIN	Mean	Minimum	Maximum
Prevalence of aspirin intolerance	0.057	0.053	0.060
Annual excess risk of non-fatal haemorrhagic stroke	0.000040	0.000030	0.000050
Annual excess risk of non-fatal gastro-intestinal bleed	0.000616	0.000600	0.000632
Annual excess risk of non-CVD mortality	0.000144	0.000101	0.000187
STATINS			
Disutility* (loss in quality of life)	0.0125	0.020	0.005
ANTIHYPERTENSIVES			
Disutility* (loss in quality of life)	0.0125	0.020	0.005
FOLIC ACID			
No adverse events	n.a.	n.a.	n.a.

Reference: M. Hayden, et al.[4]

Reference: Bell, et al.[15]

(cont.)

n.a. = not applicable

* The health-related quality of life weight for each individual after therapy was calculated by multiplying the pre-treatment health-related quality of life weight with the product of (1-disutility) with statins and (1-disutility) with antihypertensives.

Table 3. Effectiveness, costs, and cost-effectiveness of various prevention strategies. Screening is based on the Framingham risk function and treatment is life-long with the "Polypill".

Strategy	Percentage Treated (%)	Percentage CVD mortality† (se)	CVD-free life years (se)	QALYs‡ (years)	Costs (€)	iCER§ (€/QALY)	iNHB** (WTP 50k)	iNHB** (WTP 20k)
Usual care	0	33.0 (6.7)	18.39 (0.49)	11.579	57 624			
Framingham 19%*	25.0	19.0 (4.9)	19.90 (0.80)	11.761	58 295	ED††	0.169	0.148
Framingham 15%*	37.5	15.0 (4.5)	20.45 (0.90)	11.921	58 472	ED††	0.156	0.151
Framingham 12%*	50.0	12.1 (4.3)	20.90 (0.98)	12.051	58 611	2 091	0.127	0.123
Framingham 9%*	62.5	10.1 (4.2)	21.28 (1.04)	12.153	58 841	2 255	0.097	0.091
Framingham 7%*	75.0	8.8 (4.1)	21.58 (1.07)	12.229	59 135	3 868	0.070	0.061
Framingham 5%*	87.5	8.1 (4.1)	21.78 (1.10)	12.278	59 485	7 143	0.042	0.032
Treat all with "Polypill"	100	7.8 (4.1)	21.89 (1.11)	12.301	59 917	18 787	0.014	0.001

* Prevention strategy in which individuals with a Framingham 5-year CVD risk above the indicated percentage are treated with the "Polypill".

† Percentage of total mortality that is cardiovascular mortality (se = standard error)

‡ QALY = mean discounted quality-adjusted life years

§ iCER = incremental cost-effectiveness ratio (Euros per QALY) in comparison to the next best strategy. A strategy with an iCER < €20 000/QALY is always considered cost-effective.

** iNHB = incremental net health benefit (gain in QALY equivalents, considering a threshold willingness-to-pay (WTP) of €50 000 and €20 000 per QALY respectively) in comparison to the next best strategy (iNHB = ΔQALY – Δcosts / WTP).

†† ED = extended dominated (higher iCER than a more effective strategy)

Table 4. Cost-effectiveness of life-long treatment with the "Polypill" for various effect measures of the "Polypill" components. Incremental cost-effectiveness ratios in comparison to the next best strategy are listed in Euros per QALY.

	Reference-case[*]	75% efficacy[†]	50% efficacy[‡]
Treat FHS[§] > 5%	7,143	16,455	30,368
Treat all	18,787	33,333	51,600
Treat all without monitoring[**]	4,770	11,228	29,097

* Reference-case: In the reference-case analysis we used the effect measures as reported by Wald & Law (88% reduction in IHD risk & 80% reduction in stroke risk).

† In this sensitivity analysis, we assumed the relative risk reductions to be 75% the estimates reported by Wald & Law.

‡ In this sensitivity analysis, we assumed the relative risk reductions to be only half the estimates reported by Wald & Law.

§ Prevention strategy in which individuals with a Framingham 5-year CVD risk higher than 5% are treated with the "Polypill".

** Costs of medical visits for initiating and monitoring therapy were excluded in the treat-all strategy.

Figure 1. Schematic representation of the RISC model.
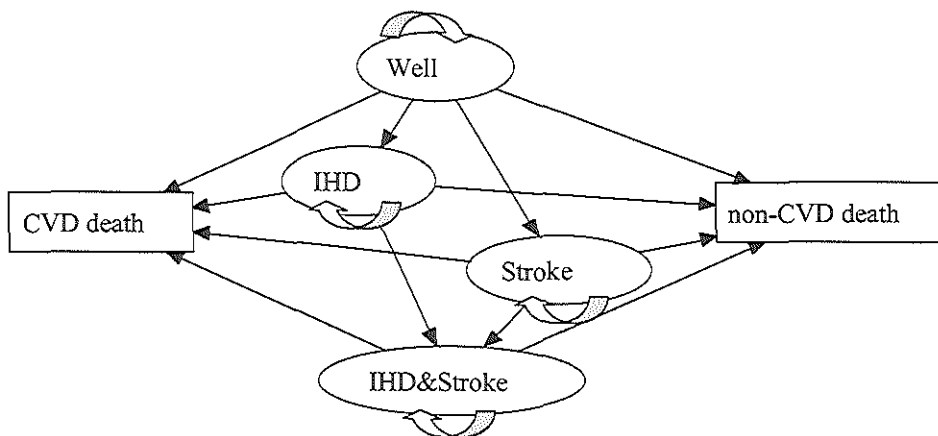
Figure 2. The Cost-Effectiveness graph plots the costs (in 1000 Euros on the y-axis) and quality-adjusted life years (on the x-axis) of each strategy. The presented line connects all options, which are neither eliminated from consideration by absolute dominance nor subject to extended dominance.
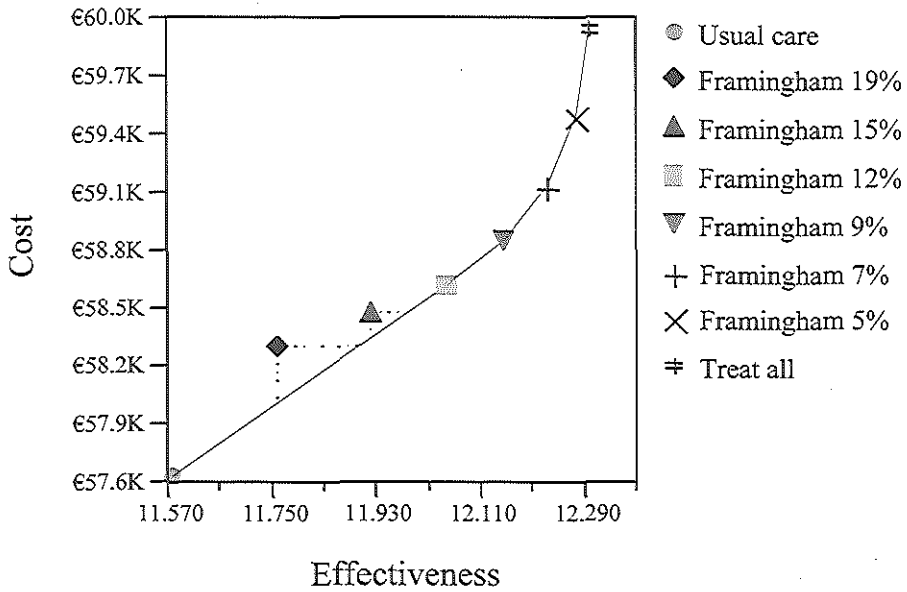
Figure 3. Box plots showing the variability of the incremental Net Health Benefits (NHB) of the treat-all strategy compared to treating individuals with a Framingham 5-year CVD risk higher than 5%, considering a threshold willingness-to-pay (WTP) of respectively €50 000 and €20 000 per quality-adjusted life year. The boxes show the limits of the middle half of the data. The line inside the box represents the median results of all scenarios. The span shown is containing at least 95% of the scenarios. Extreme scenarios (outliers) are also highlighted.[28]
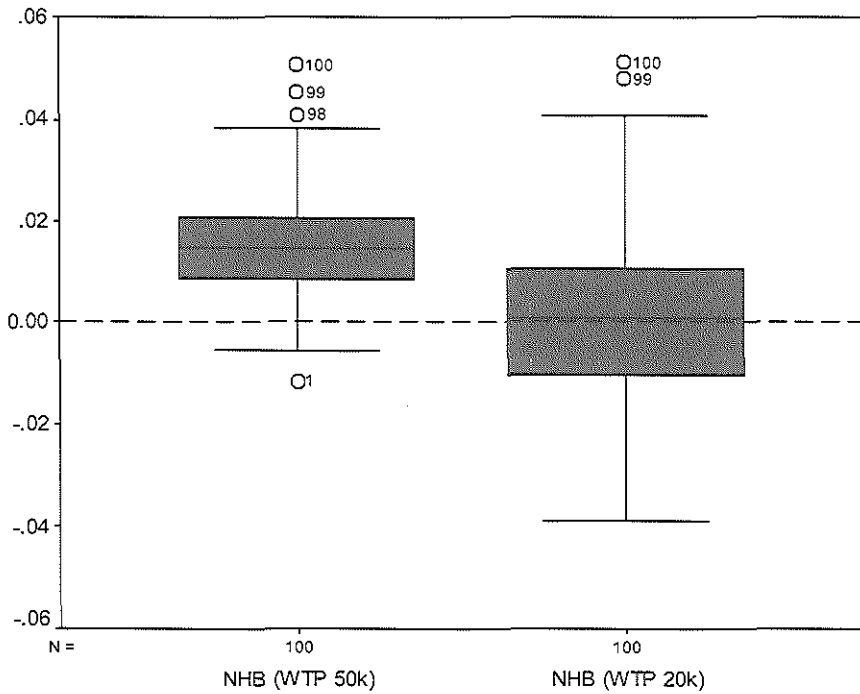
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A decision-analytical approach to select

individuals for primary cardiovascular prevention

with aspirin

A decision-analytical approach to select individuals for primary cardiovascular prevention with aspirin

Abstract

Background. Individuals are generally selected for primary prevention with aspirin therapy based on their risk for cardiovascular disease (CVD). The CVD risk, however, is not a direct measure of the extent to which aspirin therapy lengthens life expectancy and improves quality of life. The purpose of this study was to develop a prediction rule to determine the quality-adjusted life years (QALYs) that can be gained with aspirin therapy based on CVD risk indicators.

Methods. We developed a Monte Carlo-Markov model based on the Rotterdam Study, a cohort follow up study of 7983 individuals aged 55 years and older. Comorbidity, competitive mortality, time-preference, quality of life, and efficacy and adverse events of aspirin were all taken into consideration. A life-long simulation was run on all 55-80 year old Rotterdam Study participants, with a systolic blood pressure lower than 180 mmHg, free of CVD at baseline, and complete information on risk factors (n=3937) to determine the QALYs that would be gained (ΔQALY) with low-dose aspirin therapy. Finally, the association between the individuals' CVD risk factor profiles and the QALYs gained with aspirin therapy was studied using linear regression.

Results. Although the benefit of aspirin therapy generally rose with increasing CVD risk, this relationship was neither monotonic nor straightforward and was largely dependent on age and gender. For example, to gain at least 0.20 QALYs, the threshold Framingham 5-year risk score for treatment with aspirin is 17% in 55-year old women, 19% in 65-year old women, 28% in 75-year old women, 22% in 55-year old men and 29% in 65-year old men. Men aged 75-years or older will never gain more than 0.16 QALYs with aspirin therapy. Furthermore, there was a considerable gain in QALYs in young individuals in spite of fairly low Framingham risk scores.

Conclusion. The ΔQALY prediction rule provides a better method to select individuals for CVD prevention with aspirin therapy than selecting individuals based on their CVD risk.

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of mortality in industrialized countries. Recent trials have shown that the use of low dose aspirin (80 mg) reduces the incidence of CVD.[1,2] The benefit of aspirin therapy is generally considered to depend on the pre-treatment level of CVD risk.[3] Current guidelines emphasize the importance of selecting individuals based on their absolute risk of CVD calculated, for example, with the Framingham risk function.[1,4,5]

While absolute risks are an important indicator of the potential burden of a disease, they give no indication of the impact of that disease on life expectancy and on quality of life. The complex interaction of competing forces of mortality and morbidity makes it difficult to estimate the impact of CVD prevention on an individual's life course. When using the Framingham risk function to determine whether individuals should receive aspirin therapy, their comorbidity and non-cardiovascular mortality is not explicitly taken into account. Aspirin therapy may cause adverse events, such as hemorrhagic stroke and gastro-intestinal bleeding[1], or side effects interfering with the quality of life, which should also be considered. Furthermore, decisions based on absolute risk suggest that it is always more efficient to postpone treatment to a later age because the risk of CVD increases with age. At a higher age, however, the net benefit with aspirin therapy is low because of the fewer remaining years during which a gain can be achieved. Although the decreasing benefit with age is taken into account in some guidelines by increasing the threshold risk with age, most guidelines do not consider factors other than absolute risk when selecting individuals for aspirin therapy.

All in all an absolute risk such as the Framingham risk score is not a direct measure of the benefit of aspirin therapy and therefore difficult to translate to a meaningful treatment decision. A more meaningful approach would be to transform death and incidence probabilities into quality-adjusted life years (QALYs) that can be gained with aspirin therapy. By transforming epidemiological data into a Markov model, the impact of CVD on the life course of a general population can be translated into quality-adjusted life years.[6] The Markov model provides a method for the calculation of lifetime risks, taking into account competing causes of morbidity and mortality, between-patient variability and various sources of uncertainty and can be used to predict the QALYs that can be gained with aspirin therapy.

Purpose of this study was to develop a prediction rule to determine the QALYs that can be gained with aspirin therapy based on known cardiovascular risk indicators.

METHODS

We developed a Monte Carlo-Markov model to predict the future CVD burden in the original Rotterdam Study population, aged 55 and older at study onset, and followed from 1991 to 2000. The model will be referred to as the Rotterdam Ischemic heart disease & Stroke Computer simulation model (RISC model). Through its capability to simulate changes in CVD risk in individuals without CVD, the model was suited to examine the efficacy of CVD preventive strategies in terms of (CVD-free) life expectancy and quality-adjusted life expectancy gained. The model proved to be a valid tool to describe the CVD burden of a general population based on individual risk factor profiles.[7]

The model
The RISC model is a state-transition model containing 6 states: (1) the CVD death state, (2) the non-CVD death state, (3) the Ischemic Heart Disease (IHD) state, (4) the Ischemic Stroke state, (5) the IHD and Stroke state and (6) the Well state. The model simulated incident CVD events in individuals with and without previous CVD (Figure 1). The cycle length was 0.1 years.

To provide transition probabilities for different risk factor patterns, we constructed six transition probability functions based on the levels of independent risk indicators with Cox proportional hazard analyses. Important predictors were selected by multivariable stepwise regression analysis and included variables from the medical history, anthropometric measures, blood pressure measurements, laboratory tests and mild manifestations of CVD as assessed by questionnaires. Detailed information about the RISC model is posted on the World Wide Web.[*]

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[*] http://www.epib.nl/art/tools.html

Data sources

Individual risk factor profiles and transition probability functions were based on data from the Rotterdam study population.[8] The Rotterdam study population consisted of 7983 mostly Caucasian respondents from a random sample of adults aged 55 and older residing in the suburb Ommoord of Rotterdam, the Netherlands, recruited in 1990-1993. Of these respondents, 6871 (86%) visited the research center for risk indicator assessment at baseline, had a complete follow-up for at least 7 years, and signed an informed consent form.

In 3501 of the 6871 individuals all important characteristics to predict CVD were known. On the basis of these 3501 individuals, the transition probability functions and trends of risk indicators with aging were fitted. The risk indicators considered were age, sex, smoking status, systolic and diastolic blood pressure, diabetes mellitus, plasma glucose level, body mass index, waist to hip ratio, plasma cholesterol/HDL ratio, plasma creatinine level, family history of CVD, ankle-arm index, and prevalent CVD. An individual was designated as having prevalent CVD if a myocardial infarction or a stroke was diagnosed by a physician and/or the patient reported CABG, PTCA, or carotid surgery in the past and/or the patient was diagnosed as having angina pectoris, intermittent claudication, or a previous transient ischemic attack by questionnaire.

All incident events during follow-up were classified according to the International Classification of Diseases, 10th version (ICD-10). The events of interest include IHD (myocardial infarction (I21-code), PTCA and CABG), ischemic stroke (I63, I64), death from cardiovascular disease (mortality due to I10-I15: hypertensive heart disease, I20-I25: ischemic heart disease, I46 & I49: sudden cardiac death, I50: congestive heart failure, I60-I67: cerebrovascular disease, I70-I79: other arterial disease and R96: sudden death), and non-cardiovascular mortality (all other mortality codes).

Both efficacy and adverse events of aspirin were derived from the literature. For our simulations we used the risk reductions of aspirin therapy for ischemic heart disease, CVD mortality and ischemic stroke from the meta-analysis of Hayden et al (Table 1).[1] We assumed that aspirin-intolerance was present in about 5.7% of the population.[9] We assumed an absolute annual incremental risk of hemorrhagic stroke of 1 per 10,000, of which 60% were assumed to be fatal and an absolute annual incremental risk of gastro-intestinal hemorrhage of 7 per 10,000, of which 12% were

fatal.[1] These numbers resulted in a 0.00004 risk increase in non-fatal hemorrhagic stroke, a 0.000616 risk increase in gastro-intestinal hemorrhage and a 0.000144 risk increase in mortality per year (Table 1).

We included health-related quality of life by applying quality of life weights to each health state. Health-related quality of life weights used in the simulations were derived from the Catalog of Preference Scores of Bell et al[10] and Fryback et al.[11]

Uncertainty

Parameter values in the RISC model, such as efficacy and adverse events of aspirin and the health-related quality of life weights for the various disease states were derived from various studies with their associated measures of uncertainty. We modeled parameter uncertainty by estimating the distribution of the value of each of the input variables and performing a second-order Monte Carlo simulation.[12] The distributions of the efficacy of aspirin therapy were based on the 95% confidence interval as reported in the literature.[1] The probabilities of adverse events were modeled with a uniform distribution on a plausible range around the published values.[1] Health-related quality of life weights were modeled as ranging from the lowest to the highest value as described in the Catalog of Preference Scores.[10] Uncertainty in the transition probability functions was modeled by drawing 100 bootstrap samples of the study population. All the transition probability functions were fitted for every bootstrap sample, resulting in 100 sets of linked transition probability functions.

A first-order Monte Carlo simulation was performed which simulates individuals one by one (random walks or trials) instead of a whole cohort at the same time. The first-order Monte Carlo analysis accounted for the uncertainty about the actual realized outcome of an individual due to chance (stochastic uncertainty).[12]

Estimating the benefits of aspirin therapy

In 3937 of the 6871 individuals, no CVD was present at baseline, systolic blood pressure was 180 mmHg or lower and all were younger than 80 years old. Baseline charactistics are shown in table 2. As far as we know, none of these individuals were using aspirin. We performed the simulations by sampling all 3937 individuals consecutively and running 500 first-order trials per sample. For each trial we sampled

A computer program to calculate the gain in QALYs and detailed information about the structure of the ΔQALY prediction rule is posted on the World Wide Web.[*]

DISCUSSION

We developed a prediction rule to determine the quality-adjusted life years (QALYs) that can be gained with aspirin therapy based on known cardiovascular risk indicators. With the aid of a computer simulation model we determined the QALYs that would be gained with aspirin therapy in each Rotterdam Study participant initially free of CVD and younger than 80 years. The association between their CVD risk factor profiles and the QALYs that can be gained with aspirin was studied using regression modeling. We designed a user-friendly computer program with which clinicians can identify individuals most likely to benefit from aspirin therapy.[*]

The third U.S. Preventive Services Task Force[4] recommended aspirin therapy for individuals with a Framingham 5-year CVD risk score higher than 7.5% (or a Framingham 5-year coronary heart disease risk score higher than 5%). We showed, however, that there was a considerable gain in QALYs and CVD-free life years in individuals with Framingham risk scores lower than the recommended threshold. At the same time the number of individuals with a high Framingham risk score in whom the harm from aspirin therapy outweighed the benefit was also quite large. Furthermore, we showed that the relation between the Framingham CVD risk and the benefit from aspirin therapy was not straightforward because both depend on age and gender. Because older people have fewer QALYs to gain and through their age have a higher calculated Framingham risk, the threshold risk for treatment should increase with age if QALY gain is to be maximized. Furthermore, comparing men and women who have similar Framingham risk scores, the women have worse risk factor profiles apart from gender and a longer life expectancy because of their gender, which implies that the women have more QALYs to gain. Therefore, to maximize QALY gains, women should be treated at a lower threshold of Framingham risk than men.

The mean gain in life expectancy with aspirin therapy in our study was 80 days (0.22 years). Although this may seem small, it is in fact, fairly large in comparison to

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[*] http://www.epib.nl/art/tools.html

the gain in life expectancy from preventive interventions targeted at populations at average risk.[14] Moreover, the QALYs that can be gained may have been underestimated since we did not take extra-cardiovascular beneficial effects of aspirin into account. Laboratory and epidemiologic data suggest that aspirin has an antineoplastic effect in the large bowel.[15] Furthermore, aspirin may have a role in the prevention and treatment of Alzheimer's disease[16], osteoporosis[17] and arthritis.[18]

We accounted for the most important adverse events of aspirin. We took subsequent mortality and disutility into account in the calculations of the QALYs gained. We did not, however, account for the disutility associated with the need to take medication every day, which is variable among individuals and is probably negligible.

We believe that the selection of individuals for aspirin therapy based on the ΔQALY prediction rule is superior to selection based on an absolute CVD risk function because the former takes into account relevant benefits, risks, adverse events, quality-of-life, and time preference whereas the latter only considers CVD risk. The ΔQALY prediction rule can be applied to adults 55-80 years old without CVD and a systolic blood pressure below 180 mmHg.

Before the prediction rule is introduced on a wide scale, it should be tested further to establish whether its predictions are valid in other settings, whether using the prediction rule is cost-effective, and above which threshold of gain preventive therapy should be advised. The Rotterdam study was a population-based cohort with a high response rate[8]. Individuals that were excluded because of missing baseline information or incomplete follow-up were largely individuals older than 80 years and with cardiovascular disease at baseline (almost 60%). Moreover, we have shown that the RISC model, which is based on a subset of 3501 individuals, is a valid model to simulate the CVD life course in the cohort overall. We therefore believe that the results from our study are generalizable to Caucasian adults 55-80 years old without CVD and a systolic blood pressure below 180 mmHg.

In conclusion, the presented prediction rule is a promising tool to select individuals for CVD prevention with aspirin. Individuals at risk for CVD should be targeted based on the QALYs that can be gained instead of on their absolute CVD risk.

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* http://www.epib.nl/art/tools.html

REFERENCES

1. 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(2):161-72.

2. Hebert PR, Hennekens CH. An overview of the 4 randomized trials of aspirin therapy in the primary prevention of vascular disease. Arch Intern Med 2000;160(20):3123-7.

3. Augustovski FA, Cantor SB, Thach CT, Spann SJ. Aspirin for primary prevention of cardiovascular events. J Gen Intern Med 1998;13(12):824-35.

4. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. Ann Intern Med 2002;136(2):157-60.

5. Lauer MS. Clinical practice. Aspirin for primary prevention of coronary events. N Engl J Med 2002;346(19):1468-74.

6. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13(4):322-38.

7. Nijhuis RL, Stijnen T, Peeters A, Witteman JCM, Hofman A, Hunink MGM. Validation of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow up study. Med Decis Making submitted.

8. 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(4):403-22.

9. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol 1999;28(4):717-22.

10. Bell CM, Chapman RH, Stone PW, Sandberg EA, Neumann PJ. An off-the-shelf help list: a comprehensive catalog of preference scores from published cost-utility analyses. Med Decis Making 2001;21(4):288-94.

11. Fryback DG, Dasbach EJ, Klein R, Klein BE, Dorn N, Peterson K, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Med Decis Making 1993;13(2):89-102.

12. Hunink MGM, Glasziou PP, Siegel JE, et al. Decision making in health and medicine: integrating evidence and values. Cambridge, England: Cambridge University Press, 2001.

13. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. Panel on cost Effectiveness in Health and Medicine. Pharmacoeconomics 1997;11(2):159-68.

14. Wright JC, Weinstein MC. Gains in life expectancy from medical interventions--standardizing data on outcomes. N Engl J Med 1998;339(6):380-6.

15. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348(10):891-9.

16. Thomas T, Nadackal TG, Thomas K. Aspirin and non-steroidal anti-inflammatory drugs inhibit amyloid-beta aggregation. Neuroreport 2001;12(15):3263-7.

17. Bauer DC, Orwoll ES, Fox KM, Vogt TM, Lane NE, Hochberg MC, et al. Aspirin and NSAID use in older women: effect on bone mineral density and fracture risk. Study of Osteoporotic Fractures Research Group. J Bone Miner Res 1996;11(1):29-35.

18. Csuka ME, McCarty DJ. Aspirin and the treatment of rheumatoid arthritis. Rheum Dis Clin North Am 1989;15(3):439-54.

Table 1. Efficacy and risk of adverse events with aspirin therapy

EFFICACY	Hazard ratio* (standard error)
IHD risk reduction	0.72 (0.074)
CVD-mortality risk reduction	0.86 (0.094)
Ischemic Stroke risk reduction	0.98 (0.125)

ADVERSE EVENTS	Probability (minimum - maximum)
Aspirin intolerance (prevalence per 100)	5.3 - 6.0
Non-fatal hemorrhagic stroke (rate per 100 000 per year)	3 - 5
Non-fatal gastro-intestinal bleed (rate per 100 000 per year)	60 - 63
Increased non-CVD mortality (rate per 100 000 year)	10 - 19

Reference: Hayden, Ann Intern Med 2002[1]

* Hazard rate ratios with aspirin therapy compared to no therapy

Table 2. Baseline characteristics

RISK INDICATORS	MEAN ± SD / PROPORTION
Male gender (%)	38
Age at baseline (years)	66 ± 6
Age 55 to 60 years (%)	23.7
Age 60 to 65 years (%)	26.6
Age 65 to 70 years (%)	22.1
Age 70 to 75 years (%)	17.5
Age 75 to 80 years (%)	10.1
Current cigarette smoking (%)	25
Former cigarette smoking (%)	42
Systolic blood pressure (mmHg)	136 ± 20
Pulse pressure (mmHg)	62 ± 16
Hypertension [†] (%)	27
Serum cholesterol / HDL-ratio (mmol/l)	5.1 ± 1.6
Body mass index (kg/m^2)	26 ± 4
Waist-hip ratio	0.90 ± 0.09
Family history of myocardial infarction [‡] (%)	17
Ankle-arm index [§]	1.10 ± 0.18

* The current use of antidiabetic medication and / or a non-fasting serum glucose level > 11.0 mmol/L before or after an oral glucose tolerance test.

(cont.)

† Systolic blood pressure ≥ 160 mmHg and / or diastolic blood pressure ≥ 95 mmHg or using antihypertensive medication for indication of hypertension. Dit is niet meer de huidige definitie van hypertensie, dat is 160/100 for type II of 140/90 for type I

‡ A first-degree family member was known to have had a myocardial infarction before the age of 65 years.

§ The ratio of the systolic blood pressure of the posterior tibial artery, as assessed by an 8 MHz continuous wave Doppler probe and a random-zero sphygmomanometer, to the systolic blood pressure at the arm. The lowest AAI, either right or left, was used in the analysis

Table 3. The percentage of individuals treated with aspirin in which the harm outweighed the benefit (negative), the percentage in which the net benefit was small (0–0.10 QALYs† or 0–0.25 DFLYs‡), and the percentage in which the net benefit was large (>0.10 QALYs† or >0.25 DFLYs‡), within every decile of Framingham risk.

Framingham risk*	Gain in QALYs†			Gain in DFLYs‡		
In deciles	Negative	Small	Large	Negative	Small	Large
	(%)	(%)	(%)	(%)	(%)	(%)
0.01 – 0.04	22.7	47.7	29.6	2.5	40.7	56.7
0.04 – 0.06	23.3	39.0	37.6	2.3	32.3	65.4
0.06 – 0.07	19.9	37.5	42.6	0.9	28.0	71.1
0.07 – 0.09	18.9	34.4	46.7	2.3	27.3	70.4
0.09 – 0.11	18.8	29.9	51.4	1.6	28.9	69.4
0.11 - 0.13	12.5	33.5	54.0	1.8	25.4	72.7
0.13 – 0.15	15.7	30.9	53.3	0.9	26.8	72.3
0.15 – 0.19	10.4	29.5	60.2	0.9	23.1	75.9
0.19 – 0.24	11.3	27.3	61.4	1.2	22.9	76.0
0.24 – 0.53	5.1	30.1	64.8	0.2	26.2	73.6
Mean	15.9	34.0	50.2	1.5	28.2	70.4

* The Framingham 5-year CVD risk score in deciles

† QALYs: quality-adjusted life years

‡ DFLYs: disease-free life years (free of ischemic heart disease and ischemic stroke)

Figure 1. Schematic representation of the RISC model
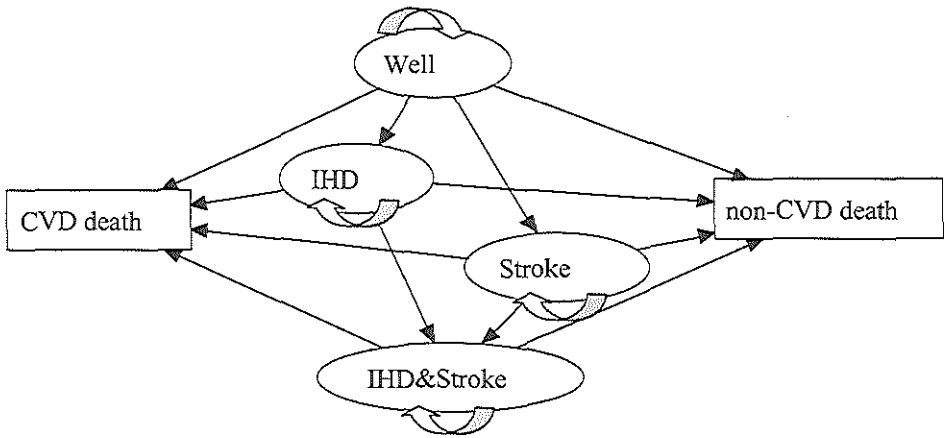
Figure 2. The distribution of effectiveness of aspirin therapy in the Rotterdam Study population, expressed in gain in time-preference and quality-adjusted life years (QALYs). The dashed reference line represents a QALY gain of zero. The mean gain in QALYs was 0.12 with a standard deviation of 0.14.

Increase in QALYs with aspirin therapy
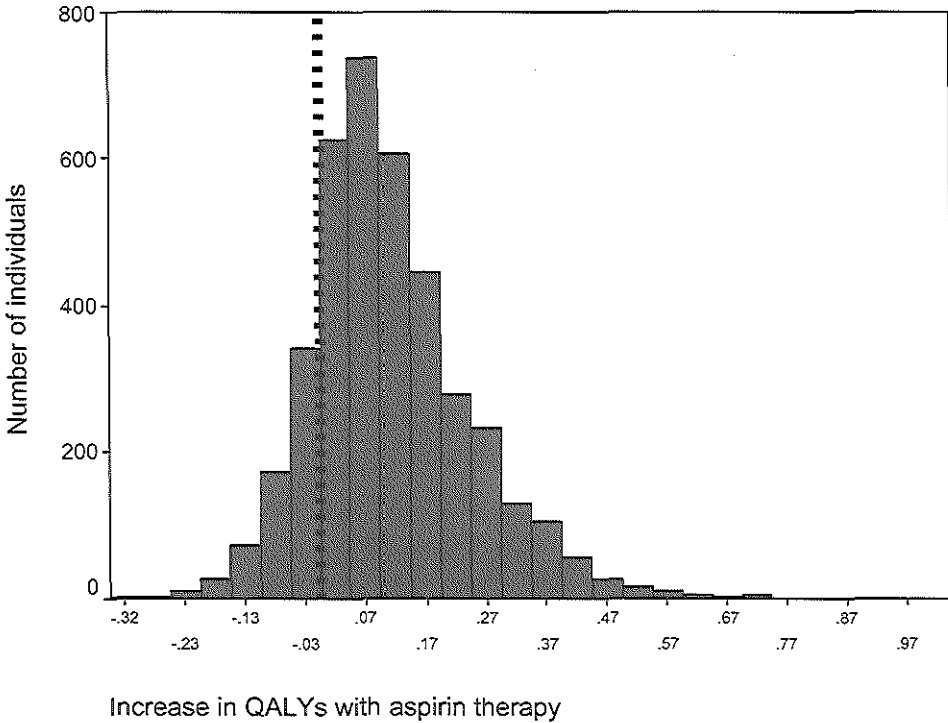
Figure 3. The gain in QALYs with aspirin therapy as a function of the Framingham 5-year CVD risk score, age and gender (regression functions).
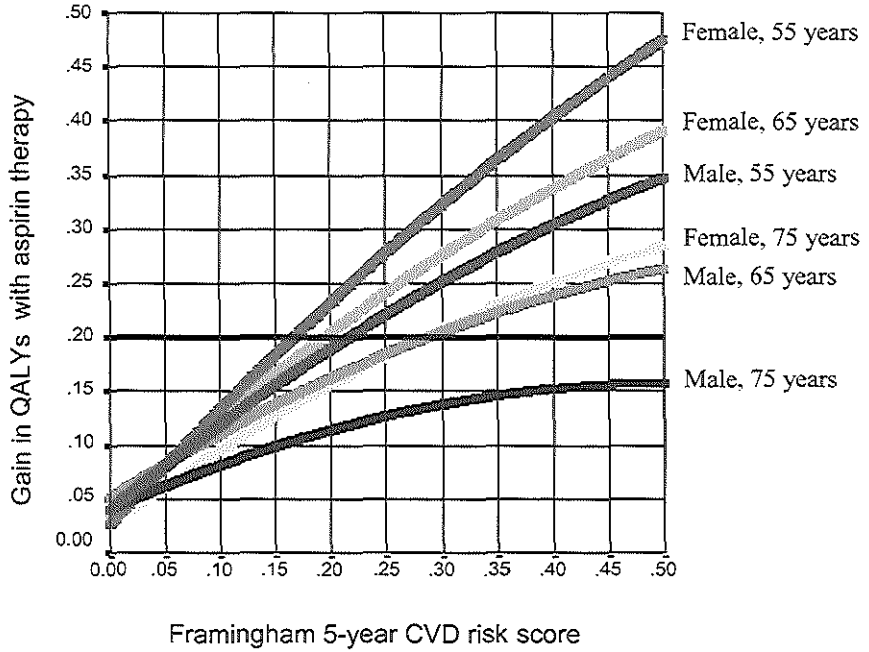
Figure 4. The gain in QALYs with aspirin therapy for various risk indicators.
The net ΔQALY is shown for each particular risk indicator, with all other risk
indicators fixed at their mean. For continuous risk indicators, the 97.5% upper limit is
compared to the 2.5% lower limit.
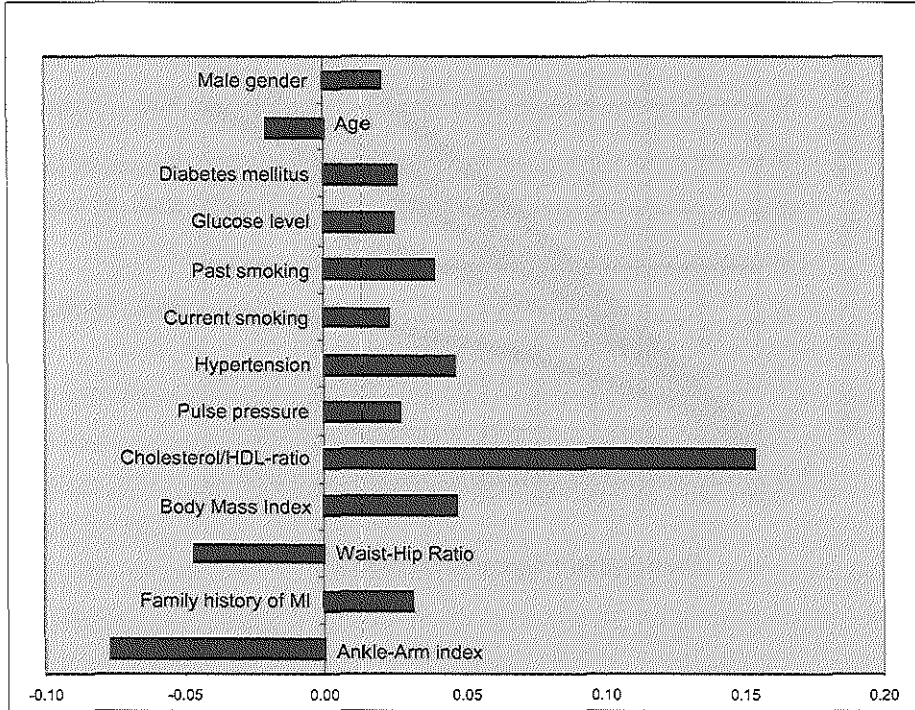
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Cost-effectiveness analysis of aspirin therapy

in the primary prevention of cardiovascular disease:

a computer simulation study

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Abstract

Background. Whereas secondary prevention of cardiovascular events with aspirin therapy in patients with known coronary and carotid artery disease is recognized as cost-effective, the cost-effectiveness of aspirin therapy in asymptomatic individuals remains to be determined.

Objectives. To investigate the cost-effectiveness of aspirin therapy in the primary prevention of cardiovascular disease, using various screening tools.

Design Cost-effectiveness analysis using a Monte Carlo-Markov model based on a population-based cohort study. Probabilistic sensitivity analysis and analyses of variability were performed.

Datasources. The Rotterdam study and published literature data.

Participants. Simulation of 3937 Rotterdam Study participants aged 55-80 years old, without medical history of cardiovascular disease at baseline (1990-1993).

Measurements. Baseline data included information on history of cardiovascular disease and cardiovascular risk factors.

Time horizon. Lifetime

Perspective. Societal

Screening tools. The Framingham cardiovascular disease risk score, the Rotterdam cardiovascular disease risk score, the extended Rotterdam cardiovascular disease risk score which included the ankle-arm index, and the Rotterdam ΔQALY prediction rule, each with various thresholds at deciles of the highest scores.

Interventions. Life-long treatment with aspirin in all individuals with scores above the threshold.

METHODS

We performed a computer simulation study using data from the literature combined with data available from the Rotterdam Study, to estimate the cost-effectiveness of various strategies for primary prevention with aspirin in a general population with subjects aged 55 years and over.

Strategies

The prevention strategies analyzed were based on the Framingham CVD risk function, the Rotterdam CVD risk function, the extended Rotterdam CVD risk function (which included the ankle-arm index), and the Rotterdam ΔQALY prediction rule (which predicts the QALYs that can be gain with aspirin therapy). Different thresholds (at deciles of each score) above which treatment will be initiated were also analyzed. In individuals identified as at risk by a high score, life-long treatment with 80 mg of aspirin daily was initiated by a primary care physician. We considered screening at 5-year intervals[8] by a primary care physician with determination of the CVD risk factor profile in all individuals and an annual risk factor assessment in those identified to be at high risk to monitor for adverse events and to improve compliance.

Outcomes

The main outcome measures were health benefit expressed in quality-adjusted life years (QALYs) and societal costs expressed in Euros. Furthermore, we examined cost-effectiveness, expressed in net health benefits, defined as the discounted QALYs minus the costs, the costs being transformed to QALY equivalents by dividing them by society's willingness-to-pay.[9] Future costs and benefits were discounted at the currently nationally recommended nominal discount rate of 4% per year to take time-preference into account. This implies that effects and costs occurring in the future are weighed less than those occurring in the present.[6] We considered society's thresholds willingness-to-pay of €50 000 and €20 000 per QALY.[10] Incremental net health benefits were calculated to indicate the gain in net health benefit in comparison to the natural history without intervention.[6] A positive incremental net health benefit

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[*] *http://www.epib.nl/art/tools.html*

indicates a cost-effective strategy in comparison to the natural history and the strategy with the highest incremental net health benefit is considered the most cost-effective.

Decision-analytic model

The RISC model is a Monte Carlo-Markov model[6] containing 6 states: (1) the CVD death state, (2) the non-CVD death state, (3) the Ischemic Heart Disease (IHD) state, (4) the Ischemic Stroke state, (5) the IHD and Stroke state and (6) the Well state.

Individuals' risk factor profiles and transition probability functions were based on data from the Rotterdam Study, a prospective population based study among 7983 men and women aged 55 years and older and living in Ommoord, Rotterdam. The model used a lifetime time horizon and a societal perspective. The time cycle used in the analysis was 0.1 years. Detailed information about the RISC model is posted on the World Wide Web.*

Aspirin's efficacy in reducing CVD events and the probability of adverse events were derived from the literature. For our simulations we used the risk reductions of aspirin therapy for ischemic heart disease, CVD mortality and ischemic stroke from the meta-analysis of Hayden et al (Table 1).[11] Relative effects of aspirin were computed irrespective of patient age, blood pressure, diabetes mellitus, cigarette smoking, cholesterol level, and other risk factors.[12] We did not explicitly incorporate compliance into the model, because the primary prevention study groups were analyzed using the intention-to-treat principle.[13,14] Aspirin-intolerance was assumed to be present in about 5.7% of the population.[15] The most important adverse events of aspirin and subsequent mortality and disutility were taken into account in the calculations of the QALYs gained. We did not, however, account for the disutility associated with the need to take medication every day, which is presumably very small and variable among individuals. We assumed an absolute annual incremental risk of hemorrhagic stroke of 1 per 10,000, of which 60% were assumed to be fatal, and an absolute annual incremental risk of gastro-intestinal hemorrhage of 7 per 10,000, of which 12% were fatal.[12] These numbers resulted in a 0.00004 risk increase in non-fatal hemorrhagic stroke, a 0.000616 risk increase in gastro-intestinal hemorrhage and a 0.000144 risk increase in mortality per year (Table 1). The adverse

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* *http://www.epib.nl/art/tools.html*

event risks associated with chronic low-dose aspirin therapy were the same regardless of underlying cardiovascular risk.[14]

We included health-related quality of life by applying quality of life weights to each health state. Health-related quality of life weights used in the simulations were derived from the Catalog of Preference Scores of Bell et al.[16] Quality of life weights for healthy individuals were assumed to depend on age- and sex and were derived from the Beaver Dam Health Outcomes Study.[17]

The simulation model was programmed in decision analytical software (DATA Professional from Treeage).

Cost-effectiveness analysis

The cost analysis included all medical and non-medical costs associated with cardiovascular disease and relevant from the societal perspective. Direct medical costs included costs of cure and care due to events, screening costs and prevention costs. Both the transition (one-time) costs of events and the incremental (annual) costs following events were derived from the National Institute for Public Health and the Environment.[18] Screening costs were the costs of the visits to the primary care physician (in total €61 per screening event and an additional €8.50 if an ankle-arm index was measured). Prevention costs are the costs associated with the prescription of low-dose aspirin (80 mg) as determined by the Dutch Health Care Insurance Board (in total €19 per person annually). Non-related health care costs incurred during gained life years were based on national averages and were age- and sex specific.[19]

Non-medical costs included time costs, travel costs, and productivity losses. Time costs and travel costs were based on data from the Dutch Central Bureau for Statistics. Productivity losses were estimated with age- and sex-specific friction costs.[20] which are the costs associated with reduced production because employees suffer or die from CVD.

The cost-effectiveness analysis was based on simulations of eligible individuals in the Rotterdam Study population. Of the 7983 respondents to the call for Rotterdam Study participants, 6871 (86%) visited the research center for risk indicator assessment at baseline (1990-1993), had a complete follow-up for at least 7 years and signed an informed consent form. Of these, 3937 individuals were free of CVD at baseline, had a systolic blood pressure of no more than 180 mmHg, and were younger than 80 years and were therefore eligible for aspirin therapy. For every individual, the

Framingham CVD risk score, the Rotterdam CVD risk score, the extended Rotterdam CVD risk score, and the Rotterdam ΔQALY prediction score was calculated. The four scores were divided into deciles to make the screening tools comparable and were compared for agreement with the weighted-kappa.[21] To evaluate the cost-effectiveness of primary prevention strategies for CVD with aspirin therapy, we simulated the life histories of all 3937 individuals for every prevention strategy.

Sensitivity analysis

We performed one-way sensitivity analyses to examine the effect of a discount rate of 0% and 7% instead of 4%[22], excluding the productivity losses, and a one-time screening visit in 55-60 year old men and women.

Furthermore, we performed extensive probabilistic sensitivity analyses[23] for various thresholds of the score for the most effective screening tool. We consecutively analyzed 1000 scenarios to account for the uncertainty of modelled transition probabilities, effects, adverse events and costs. To model the uncertainty in the transition probability functions, we drew 100 bootstrap samples of the study population.[24] All the transition probability functions were fitted for every bootstrap sample, resulting in 100 sets of linked transition probability functions. For each RISC simulation scenario, we drew randomly one set of linked functions from these 100 bootstrap sets. The distributions of the effectiveness of aspirin therapy (Table 2) were based on the 95% confidence interval as reported.[11] The probabilities of adverse events (Table 2) were modeled with a uniform distribution on a plausible range around the published values.[11,12] Health-related quality of life weights were modeled as ranging from the lowest to the highest value as described in the Catalog of Preference Scores.[16] Costs of interventions and CVD events were varied with ± 30% absolute change around the mean value. In the second-order Monte Carlo simulation the parameter uncertainty resulted in different model outcomes for 1000 possible scenarios.[22]

RESULTS

The screening tools

Baseline charactistics of all individuals eligible for aspirin therapy are shown in Table 2. For every individual, the Framingham CVD risk score, the Rotterdam CVD risk score, the extended Rotterdam CVD risk score, and the Rotterdam ΔQALY prediction score was calculated. The four scores were divided in deciles. The cut-off levels for each screening tool are shown in Table 3. For example, treatment of 90% of the individuals with the highest scores corresponds with treatment of individuals with a Framingham CVD risk score higher than 0.0374, a Rotterdam CVD risk score higher than 0.0151, an extended Rotterdam CVD risk score higher than 0.0152 and a ΔQALY score higher than 0.0423.

The Framingham CVD risk scores, the Rotterdam CVD risk scores, and the extended Rotterdam CVD risk scores showed very poor agreement with the ΔQALY prediction scores (Table 4), indicating that individuals selected by the first mentioned screening tools are rather different from individuals selected by the ΔQALY prediction rule in deciles of scores. The Rotterdam CVD risk scores also showed poor agreement with the Framingham risk scores. The agreement between the Rotterdam CVD risk scores and the extended Rotterdam CVD risk scores was high, as expected (Table 4).

Cost-effectiveness analysis

The most effective prevention strategy was aspirin therapy in 90% of the individuals ranked as having the highest score on the Rotterdam ΔQALY prediction rule. Compared to natural history, treating the 90% individuals with the highest ΔQALY prediction scores resulted in an average gain of 0.185 QALYs (Table 5). This was associated with a mean gain in total life expectancy of 0.22 years and a mean gain in CVD-free life expectancy of 0.40 years. Furthermore, the net health benefit increased with 0.049 to 0.073 QALY equivalents (considering a threshold willingness-to-pay of €20 000 and €50 000 respectively). Considering a threshold willingness-to-pay of €50 000, this strategy was the most cost-effective strategy (Table 5). However, when a threshold willingness-to-pay of €20 000 was considered, the most cost-effective strategy was aspirin therapy in the 70% of individuals with the highest Rotterdam CVD risk score (incremental net health benefit 0.056 QALY equivalents)

If one is prepared to treat more than 50% of all individuals, the highest gain in QALYs was obtained using the extended Rotterdam CVD risk function or the Rotterdam ΔQALY prediction rule. Thus, screening was the most effective if the ankle-arm index was measured. However, the additional benefit did not outweigh the additional costs of the ankle-arm index measurement (the incremental net health benefits are for the most part higher using the Rotterdam CVD risk function than using the extended Rotterdam CVD risk function).

By introducing primary prevention with aspirin therapy selecting individuals with the Rotterdam ΔQALY prediction rule in the general population, the mean average costs that will be invested life-long per individual was estimated to be approximately €1600. Because of the cost-savings due to prevention of CVD events, average life-long net costs will be only €690 per individual. For the Netherlands this means that €158 million would need to be invested annually but there would be an estimated cost-savings of €90 million annually, implying a net national annual cost of €68 million to gain a total of 0.7 million QALYs nationwide.

Sensitivity analyses

Considering a threshold willingness-to-pay of €50 000, aspirin therapy in the 90% of individuals with the highest Rotterdam ΔQALY score stayed the most cost-effective strategy assuming a 7% discount rate (ΔQALY 0.055 years; incremental net health benefit 0.044 QALY equivalents) and assuming no discounting (ΔQALY 0.185 years; incremental net health benefit 0.157 QALY equivalents)

Considering a threshold willingness-to-pay of €20 000, aspirin therapy in 70% of the individuals based on the Rotterdam risk function stayed the most cost-effective strategy assuming a 7% discount rate (ΔQALY 0.051 years; incremental net health benefit 0.033 QALY equivalents) and assuming no discounting (ΔQALY 0.162 years; incremental net health benefit 0.125 QALY equivalents). Productivity losses had a very limited effect on the cost-effectiveness because of the low proportion of employed individuals in this older population.

DISCUSSION

We examined the cost-effectiveness of primary prevention strategies for CVD with aspirin in the Rotterdam Study population, using four different screening tools. The Framingham cardiovascular disease risk function includes the traditional risk factors such as age, sex, diabetes mellitus, cholesterol/HDL-ratio, smoking and systolic blood pressure.[2] The Rotterdam cardiovascular disease risk function includes the same traditional risk factors but also includes family history of CVD, antihypertensive medication use, and mild manifestations of CVD and was fitted in an older study population. The extended Rotterdam cardiovascular disease risk function includes the ankle-arm index as an extra predictive variable. The Rotterdam ΔQALY prediction rule is based on the same risk indicators but this screening tool does not estimate absolute risk, but estimates quality-adjusted life years gained with aspirin therapy.

In the development of the Rotterdam cardiovascular disease risk functions, cardiovascular disease was defined as myocardial infarction, PTCA, CABG, stroke, death from ischemic heart disease, sudden death, death due to congestive heart failure and death from stroke. The outcome used in the Framingham Heart Study, however, also included mild manifestations of CVD, such as angina pectoris, transient ischemic attacks and peripheral arterial disease. This explains why the Framingham risk scores were over all higher than the Rotterdam CVD risk scores. The four scores showed poor agreement as assessed by weighted-kappa analysis, indicating that individuals selected by the one screening tool are different from individuals selected by the other screening tool in deciles of scores.

The most effective prevention strategy was aspirin therapy given to 90% of the individuals ranked as having the highest gain in QALYs as determined by the Rotterdam ΔQALY prediction rule. Compared to natural history, treating the 90% individuals with the highest ΔQALY prediction scores (ΔQALY score higher than 0.0423) resulted in an average gain of 0.185 QALYs. The Rotterdam CVD risk function with the ankle-arm index was overall the most effective screening tool. However, the Rotterdam CVD risk function without the ankle-arm index was more cost-effective, indicating that the benefit from performing an ankle-arm index measurement does not outweigh the associated costs (€8.50 per measurement). The most cost-effective prevention strategy depended on what society is willing to pay for health care. Considering a threshold willingness-to-pay of €50 000 per QALY,

treating individuals with a ΔQALY score higher than 0.0423 was the most cost-effective strategy. However, when a threshold willingness-to-pay of €20 000 per QALY was considered, treating individuals with a Rotterdam 5-year CVD risk score higher than 0.0307 was the most cost-effective strategy. In this case 70% of all individuals would be treated with aspirin. Even aspirin therapy in all asymptomatic men and women over the age of 55, as suggested by Hirsh[25], appeared to be a cost-effective strategy. Sensitivity analyses showed robustness of the results. The results were rather insensitive to plausible changes in discount rate (0 – 7%) and elimination of productivity losses. The productivity losses were estimated according to the friction costs approach.[4] If these costs had been estimated according to the human capital approach, the estimated net-health benefits would all be higher.

Consensus groups have recommended using the absolute risk of disease over five to ten years when aspirin therapy is considered. The third U.S. Preventive Services Task Force[26] recommended aspirin therapy for individuals with a Framingham 5-year CVD risk score higher than 7.5% (or a Framingham 10-year coronary heart disease risk score higher than 10%), implying treatment in 60 to 70% of the Rotterdam Study participants simulated. We showed, that aspirin therapy was also cost-effective in individuals with lower Framingham risk scores. However, the risk of cerebral hemorrhage associated with aspirin use discourages its widespread use. Modeling the risk of cerebral hemorrhage and determining the individual's risk of this side effect can possibly help to guide decisions for use or non-use in practice in the future.

We used well-established methods of cost-effectiveness analysis to integrate the available data on the potential benefits of aspirin therapy. Interpretation of our results should, however, consider the assumptions that were made. The proportional risk reductions were assumed identical for the high and low risk strata based on studies[26,27] that demonstrated that risk reductions are homogeneous across the risk continuum suggesting that the reported results can be extrapolated to groups at intermediate risk. Note, however, that whereas we assumed equivalent proportional risk reductions across the risk continuum, this translates into very different absolute benefits depending on the underlying risk of CVD. Unlike benefit, which increases linearly with underlying risk, the adverse event rate associated with aspirin therapy was conservatively expected to be constant across the risk continuum.

The gain in life expectancy is an important measure of effectiveness of preventive interventions, but its interpretation requires that it be placed in context. The gain in

life expectancy with aspirin therapy in our study was 80 days (0.22 years) per person, when averaged across the entire target population. Although this may seem small, it is in fact, fairly large in comparison to the gain in life expectancy from preventive interventions targeted at populations at average risk.[28] By comparison, a widely accepted intervention such as mammography screening for women aged 50 to 69 years improves life expectancy by only 12 days.[29]

Furthermore, the QALYs that can be gained may have been underestimated since we did not take extra-cardiovascular beneficial effects of aspirin into account. Laboratory and epidemiologic data suggest that aspirin has an antineoplastic effect in the large bowel.[30] Aspirin may have a role in the prevention and treatment of Alzheimer's disease[31], osteoporosis[32] and arthritis.[33] Moreover, effectiveness of the prevention strategies can be increased by using the structural visits to the primary care physician to promote lifestyle guidelines involving diet, exercise, and abstinence from smoking.[34]

In summary, aspirin therapy in all 55-80 year old individuals appears to be a cost-effective strategy in the primary prevention of CVD. Cost-effectiveness can be maximized by selecting individuals using the Rotterdam ΔQALY score. or the Rotterdam CVD risk functionHowever, the risk of cerebral hemorrhage associated with aspirin use discourages widespread use.Although additional ankle-arm index measurement can improve the effectiveness of screening, it is not cost-effective.

REFERENCES

1. Gaspoz JM, Coxson PG, Goldman PA, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. N Engl J Med. Jun 6 2002;346(23):1800-1806.

2. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J. 1991;121(1 Pt 2):293-298.

3. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation. 2002; 105:310-5.

4. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003.

5. 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. Jul 1991;7(4):403-422.

6. Hunink MGM, Glasziou PP, Siegel JE, et al. Decision making in health and medicine: interpreting evidence and values. Cambridge, England: Cambridge University Press, 2001.

7. Nijhuis RL, Stijnen T, Peeters A, Witteman JCM, Hofman A, Hunink MGM. Validation of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow up study. Med Decis Making, submitted.

8. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation. Jul 16 2002;106(3):388-391

9. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making. Apr-Jun 1998;18(2 Suppl):S68-80.

10. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. Med Decis Making. Jul-Sep 2000;20(3):332-342.

11. 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. Jan 15 2002;136(2):161-172.

12. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ. Jan 1994;308(6921):81-106.

13. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed). Jan 30 1988;296(6618):313-316.

14. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med. Jul 20 1989;321(3):129-135.

15. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol. Aug 1999;28(4):717-722.

16. Bell CM, Chapman RH, Stone PW, Sandberg EA, Neumann PJ. An off-the-shelf help list: a

comprehensive catalog of preference scores from published cost-utility analyses. Med Decis Making. Jul-Aug 2001;21(4):288-294.

17. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Med Decis Making. Apr-Jun 1993;13(2):89-102.

18. Polder JJ TJ, Meerding WJ, Kommer GJ, Stokx LJ. Kosten van ziekten in Nederland - De zorgeuro ontrafeld. Bilthoven, Rotterdam, Houten: Bohn Stafleu Van Loghum; 2002.

19. Polder JJ, Bonneux L, Meerding WJ, van der Maas PJ. Age-specific increases in health care costs. Eur J Public Health. Mar 2002;12(1):57-62.

20. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ. Jun 1995;14(2):171-189.

21. Graham P, Jackson R. The analysis of ordinal agreement data: beyond weighted kappa. J Clin Epidemiol. Sep 1993;46(9):1055-1062.

22. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. Panel on cost Effectiveness in Health and Medicine. Pharmacoeconomics. Feb 1997;11(2):159-168.

23. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. Med Decis Making. Summer 1985;5(2):157-177.

24. Steyerberg EW, Bleeker SE, Moll HA, Grobbee DE, Moons KG. Internal and external validation of predictive models: a simulation study of bias and precision in small samples. J Clin Epidemiol. May 2003;56(5):441-447.

25. Hirsh J, Dalen JE, Fuster V, Harker LB, Salzman EW. Aspirin and other platelet-active drugs. The relationship between dose, effectiveness, and side effects. Chest. Oct 1992;102(4 Suppl):327S-336S.

26. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. Ann Intern Med. Jan 15 2002;136(2):157-160.

27. 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. Oct 28 2002;162(19):2197-2202.

28. Wright JC, Weinstein MC. Gains in life expectancy from medical interventions- standardizing data on outcomes. N Engl J Med. Aug 6 1998;339(6):380-386.

29. Salzmann P, Kerlikowske K, Phillips K. Cost-effectiveness of extending screening mammography guidelines to include women 40 to 49 years of age. Ann Intern Med. Dec 1 1997;127(11):955-965.

30. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med. Mar 6 2003;348(10):891-899.

31. Thomas T, Nadackal TG, Thomas K. Aspirin and non-steroidal anti-inflammatory drugs inhibit amyloid-beta aggregation. Neuroreport. Oct 29 2001;12(15):3263-3267.

32. Bauer DC, Orwoll ES, Fox KM, et al. Aspirin and NSAID use in older women: effect on bone mineral density and fracture risk. Study of Osteoporotic Fractures Research Group. J Bone Miner Res. Jan 1996;11(1):29-35.

33. Csuka ME, McCarty DJ. Aspirin and the treatment of rheumatoid arthritis. Rheum Dis Clin North

Am. Aug 1989;15(3):439-454.

34.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. Jul 6 2000;343(1):16-22.

Table 1. Efficacy and risk of adverse events with aspirin therapy.[5]

EFFICACY	Hazard ratio* (standard error)
IHD risk reduction	0.72 (0.074)
CVD-mortality risk reduction	0.86 (0.094)
Ischemic Stroke risk reduction	0.98 (0.125)

ADVERSE EVENTS	Probability (minimum - maximum)
Aspirin intolerance (prevalence per 1000)	53 - 60
Non-fatal hemorrhagic stroke (annual excess risk per 100 000)	30 - 50
Non-fatal gastro-intestinal bleed (annual excess risk per 100 000)	60 - 63
Increased non-CVD mortality (annual excess risk per 100 000)	10 - 19

Based on: Hayden, Ann Intern Med 2002

* Hazard rate ratios with aspirin therapy compared to no therapy

Table 2. Baseline charactistics of the 3937 Rotterdam Study participants, eligible for aspirin therapy.

RISK INDICATORS	MEAN ± SD / PROPORTION
Male gender (%)	38
Age at baseline (years)	66 ± 6
Age 55 to 60 years (%)	23.7
Age 60 to 65 years (%)	26.6
Age 65 to 70 years (%)	22.1
Age 70 to 75 years (%)	17.5
Age 75 to 80 years (%)	10.1
Diabetes mellitus [*] (%)	7
Current cigarette smoking (%)	25
Former cigarette smoking (%)	42
Systolic blood pressure (mmHg)	136 ± 20
Pulse pressure (mmHg)	62 ± 16
Hypertension [†] (%)	27
Serum cholesterol / HDL-ratio (mmol/l)	5.1 ± 1.6
Body mass index (kg/m^2)	26 ± 4
Waist-hip ratio	0.90 ± 0.09
Family history of myocardial infarction [‡] (%)	17
Ankle-arm index [§]	1.10 ± 0.18

[*] The current use of antidiabetic medication and / or a non-fasting serum glucose level > 11.0 mmol/L before or after an oral glucose tolerance test.

[†] Systolic blood pressure ≥ 160 mmHg and / or diastolic blood pressure ≥ 95 mmHg or using antihypertensive medication

[‡] A first-degree family member was known to have had a myocardial infarction before the age of 65 years.

[§] The ratio of the systolic blood pressure of the posterior tibial artery, as assessed by an 8 MHz continuous wave Doppler probe and a random-zero sphygmomanometer, to the systolic blood pressure at the arm. The lowest AAI, either right or left, was used in the analysis.

Table 3. The threshold levels of deciles of scores for the Framingham 5-year
CVD risk function, the Rotterdam 5-year CVD risk function, the extended
Rotterdam CVD risk function (including the ankle-arm index), and the
Rotterdam ΔQALY prediction rule.

% Targeted	Framingham[*]	Rotterdam[†]	Rotterdam+[‡]	ΔQALY score[§]
90%	0.0374	0.0151	0.0152	0.0423
80%	0.0551	0.0230	0.0229	0.0642
70%	0.0713	0.0308	0.0307	0.0812
60%	0.0878	0.0400	0.0400	0.0963
50%	0.1055	0.0499	0.0495	0.1105
40%	0.1277	0.0610	0.0605	0.1270
30%	0.1527	0.0758	0.0756	0.1459
20%	0.1862	0.0944	0.0929	0.1678
10%	0.2373	0.1270	0.1279	0.2017
0%	0.5305	0.4340	0.4913	0.8839

* The Framingham 5-year CVD risk score.

† The Rotterdam 5-year CVD risk score.

‡ The extended Rotterdam CVD risk score (ankle-arm index included as risk indicator).

§ The Rotterdam ΔQALY prediction rule.

Table 4. Agreement between the prediction rules in selecting individuals for aspirin therapy based on deciles of the scores (weighted kappa's). A low kappa value indicates that individuals selected by the one screening tool are very different from individuals selected by the other screening tool.

	Framingham[*]	Rotterdam[†]	Rotterdam+ [‡]	ΔQALY score[§]
Framingham[*]	1	0.71	0.69	0.38
Rotterdam[†]		1	0.91	0.37
Rotterdam+ [‡]			1	0.39
ΔQALY score[§]				1

* The Framingham 5-year CVD risk score.

† The Rotterdam 5-year CVD risk score.

‡ The extended Rotterdam CVD risk score (ankle-arm index included as risk indicator).

§ The Rotterdam ΔQALY prediction rule.

Table 5. Effectiveness (incremental undiscounted and discounted quality-adjusted life years) and cost-effectiveness (incremental net health benefits (NHBs) considering a willingness-to-pay of €50 000 and €20 000 respectively) of various prevention strategies compared to the natural history without intervention. Screening is based on the Framingham CVD risk function (Framingham), the Rotterdam CVD risk function (Rotterdam), the extended Rotterdam CVD risk function which includes the ankle-arm index (Rotterdam+), and the ΔQALY prediction rule (ΔQALY), and treatment is life-long with low-dose aspirin in the indicated percentage of individuals who have the highest score. For each threshold the screening tool with the largest incremental net health benefit, ie. the most cost-effective tool, has been highlighted.

Incremental Effectiveness (undiscounted QALYs)

% Treated	Framingham	Rotterdam	Rotterdam+	ΔQALY
0	0.000	0.000	0.000	0.000
50	0.135	*0.137*	0.135	0.131
60	0.151	0.153	*0.154*	0.154
70	0.158	0.162	0.165	*0.170*
80	0.166	0.170	0.171	*0.174*
90	0.180	0.177	0.181	*0.185*
100	0.183	0.183	0.183	0.183

Incremental Effectiveness (discounted QALYs[*])

% Treated	Framingham	Rotterdam	Rotterdam+	ΔQALY
0	0.000	0.000	0.000	0.000
50	0.068	*0.071*	0.070	0.062
60	0.076	0.077	*0.078*	0.073
70	0.078	0.081	*0.082*	0.082
80	0.082	0.084	*0.084*	0.083
90	0.087	0.085	0.088	*0.089*
100	0.087	0.087	0.087	0.087

(cont.)

Incremental Net Health benefits[†] (WTP[‡] =

50000)

% Treated	Framingham	Rotterdam	Rotterdam+	ΔQALY
0	0.000	0.000	0.000	0.000
50	0.063	*0.064*	0.062	0.052
60	0.068	0.068	*0.069*	0.061
70	0.068	*0.071*	0.069	0.065
80	0.071	*0.071*	0.070	0.066
90	0.070	0.070	0.070	*0.073*
100	0.070	0.070	0.070	0.070

Incremental Net Health benefits[†] (WTP[‡]= 20000)

% Treated	Framingham	Rotterdam	Rotterdam+	ΔQALY
0	0.000	0.000	0.000	0.000
50	*0.054*	0.053	0.049	0.038
60	0.055	*0.055*	0.055	0.044
70	0.053	*0.056*	0.050	0.040
80	0.052	*0.053*	0.050	0.041
90	0.045	0.046	0.043	*0.049*
100	0.045	0.045	0.045	0.045

* QALYs = mean 4%-discounted quality-adjusted life years

† Incremental Net Health benefit (iNHB) is the gain in QALY equivalents in comparison to the natural history without intervention. A strategy with an iNHB > 0 is considered cost-effective compared to the natural history. The strategy with the highest iNHB is the most cost-effective.

‡ Both a threshold willingness-to-pay (WTP) of €50 000 and of €20 000 were considered.
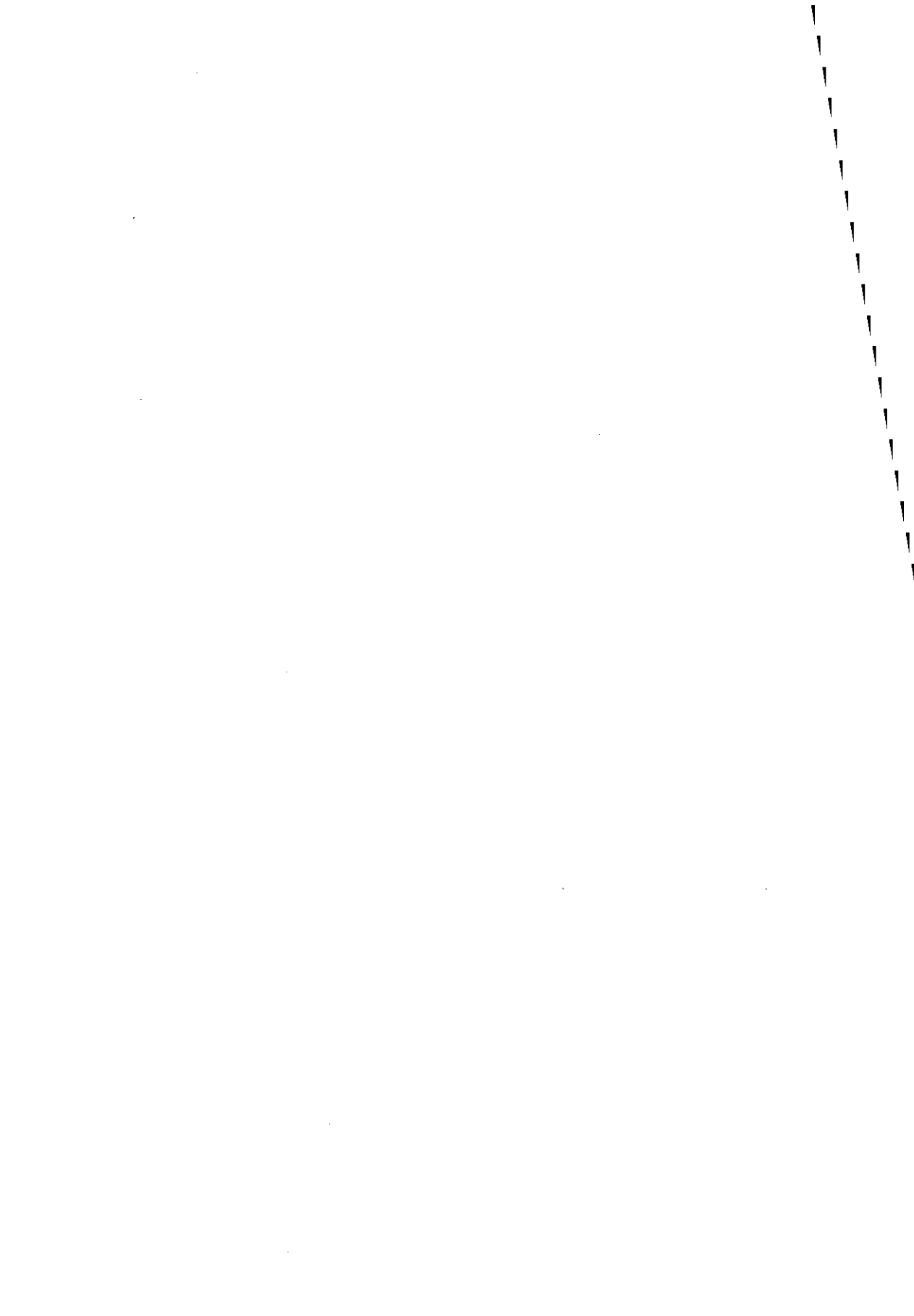
11

Summary

Samenvatting

SUMMARY & GENERAL DISCUSSION

According to estimates from the World Health Organization, 17 million people around the globe die of cardiovascular disease (CVD) each year. In industrialized countries including the Netherlands, CVD mortality has declined over the past 30 years as a result of a combination of public health measures (tobacco policies, health education, nutrition programs, etc.) and improvements in medical care (thrombolysis, PTCA, CABG and drug therapy). However, CVD still remains the leading cause of death, and due to the better prognosis of CVD patients resulting from improved medical care, CVD is often a cause of serious disability, which may last for a considerable number of years.

In Americans, the lifetime risk at age 40 of developing coronary heart disease (CHD) has been estimated to be one in two for men and one in three for women. However, half of all patients with CHD do not have any of the traditional risk factors hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus, marked obesity, or physical inactivity. Non-invasive methods to measure (subclinical) atherosclerosis, such as the ankle-arm index, are valuable tools in epidemiological research and may improve the estimation of cardiovascular risk. In addition, inflammatory mediators, such as C-reactive protein have recently been identified as key players in the etiology of CVD and are expected to contribute importantly to CVD risk prediction in clinical practice.

In search of new risk indicators of cardiovascular disease
"New" factors that are found to prospectively predict CVD independently of the traditional cardiovascular risk factors may be of added value in the clinical assessment of CVD risk. The current debates about whether or not to include ankle-arm index measurement for risk management in primary prevention of CVD are good examples. First of all measurement of such a "new" risk factor has to be simple and achievable in a large part of the general population against relatively low costs.
Second, the measurement must show a high reproducibility and a low interobserver variability. Next, there has to be a relatively high association between the measurement and incident CVD, adjusted for all traditional risk factors and a relatively low association with the known traditional risk factors themselves. It has to

be clear whether the association is graded or whether there is a certain plateau in the relationship. Furthermore, the "new" risk indicator should lead to a considerable gain in discriminant accuracy. The area under the receiver-operating characteristic curve (AUC) provides a good measure of the overall prognostic value of a CVD risk function including the risk indicator of interest, and can be compared to the prognostic value of the risk function without the indicator of interest. The ROC curve is a plot of the true-positive rate (sensitivity) against the false-positive rate (1 minus specificity), evaluated for varying thresholds of predicted probability. The area under the ROC curve can be interpreted as the probability that the risk function will assign a higher probability of CVD to a randomly chosen subject who gets CVD than to a randomly chosen subject without incident CVD during 5 years. Finally, the benefit (the gain in quality-adjusted life years and/or decrease in downstream costs) from measuring the "new" risk indicator within an existing CVD prevention strategy has to outweigh the associated costs. This can be studied with a decision-analytical model, which integrates information from multiple heterogeneous sources.

The role of ankle-arm index measurement in CVD risk stratification
In **chapter 2** we investigated the added value of peripheral arterial disease in the prediction of cardiovascular disease mortality. Peripheral arterial disease as defined by an ankle-arm index lower than 0.90 appeared to be an independent predictor of cardiovascular disease mortality. The risk of cardiovascular disease mortality increases when peripheral arterial disease is symptomatic, i.e. when intermittent claudication is present. Measuring an ankle-arm index is a simple non-invasive technique that can possibly play a role in the prevention of cardiovascular disease.

In **chapter 3** we examined whether the ankle-arm index can be used as a continuous risk indicator for cardiovascular disease. The AAI showed an inverse graded relation without evidence of a threshold with Framingham CVD risk (from 35.7% in the lowest octile to 22.7% in the highest octile of AAI) and other measures of atherosclerosis. The AAI was gradually associated with incident CVD without evidence of a plateau in the relationship. Subjects with an AAI in the lowest octile had a four times higher risk of CVD compared to subjects with an AAI in the highest octile (hazard ratio 4.23; 95%CI 2.63, 6.81). After adjustment for traditional CVD risk factors and medical history of CVD, the association was less strong, but still evident (hazard ratio 2.49; 95%CI 1.52, 4.08). The AAI showed synergy with the

Framingham CVD risk score in predicting CVD (p=0.02). Our results are in agreement with the view that ankle-arm index is a measure of atherosclerosis showing graded associations with incident myocardial infarction and stroke. The AAI should no longer be dichotomized but should be used as a continuous risk indicator for CVD.

Risk functions

The Framingham coronary heart disease risk score performed fairly well in the Rotterdam study population. The original Framingham CHD risk function was externally validated in our study population, yielding an area under the Receiver Operating Characteristic curve (AUC) of 0.693. After refitting the risk function, the AUC increased to 0.728, which was a statistically significant increase.

   In **chapter 4** we derived an efficient risk function to target high-risk people for coronary heart disease based on traditional risk factors and studied the additional prognostic value of indicators of subclinical cardiovascular disease, such as the ankle-arm index, in predicting coronary heart disease. Among 5431 subjects without documented cardiovascular disease at baseline, 388 coronary heart disease events occurred within a mean of 7 years follow-up. The coronary heart disease predictors that were selected by multivariable stepwise regression analysis were age, gender, total serum cholesterol level, the quadratic term of cholesterol, HDL-cholesterol level, systolic blood pressure, antihypertensive medication use, the interaction term between systolic blood pressure and antihypertensive medication use, smoking status, diabetes mellitus, family history of myocardial infarction, angina pectoris, intermittent claudication and the interaction term between angina pectoris and smoking status. The regression model discriminated well between subjects with incident coronary heart disease and those without (area under the Receiver Operating Characteristic curve (AUC), 0.748 (95%CI 0.718-0.778)). The discriminatory power of this risk function was statistically significantly higher compared to the refitted Framingham CHD risk function (p=0.006 after bootstrapping). After adding the ankle-arm index, the risk function showed a small but statistically significant better performance (AUC, 0.754 (95%CI 0.724-0.784). This is largely due to the fact that the ankle-arm index is strongly correlated with the traditional risk indicators themselves. Adding ECG-variables instead of the ankle-arm index yielded a similar performance (AUC, 0.754 (95%CI 0.725-0.784)). More than 55% of the coronary heart disease events occurred in subjects with a coronary heart disease risk score within the highest quartile.

Second, a risk function was developed to estimate the risk of stroke. Among the 5431 subjects, 260 strokes occurred within a mean of 7 years of follow-up. The predictors of stroke that were selected by multivariable stepwise regression analysis were age, the quadratic term of age, gender, systolic blood pressure, antihypertensive medication use, the interaction term between systolic blood pressure and antihypertensive medication use, smoking status, diabetes mellitus, angina pectoris and signs of transient ischemic attacks. Age was far more predictive for stroke and gender was far more predictive for coronary heart disease. Cholesterol was not predictive at all for stroke, but was a very important predictor for the risk of coronary heart disease.

In **chapter 5** the regression model for coronary heart disease and the regression model for stroke were combined by multiplying the 5-year cumulative survival probabilities, which were derived from the Cox Proportional Hazards model with censoring for the other event. We assessed the additional predictive value of ankle-arm index, ECG parameters and C-reactive protein over and above the traditional risk factors in predicting coronary heart disease and stroke. CRP did not add to the predictive value of the Rotterdam cardiovascular disease risk function. The combined regression model discriminated well between subjects with incident cardiovascular disease and those without (area under the Receiver Operating Characteristic curve (AUC), 0.752 (95%CI 0.723-0.781)). In conclusion, the developed cardiovascular disease risk function appeared to be a useful tool to select subjects at high risk for cardiovascular disease in a primary care setting. Risk factors have different impact on the incidence of coronary heart disease and stroke respectively. Additional measurement of either the ankle-arm index or the ECG offers better discrimination between high and low risk individuals.

The development and structure of the Rotterdam coronary heart disease risk function and the Rotterdam cardiovascular disease risk function are described in detail in the technical appendices. A "coronary heart disease risk calculator" and a "stroke risk calculator" were developed which can be used by physicians in general practice and by cardiologists.

The decision-analytical model

Whereas secondary prevention of cardiovascular events through risk factor modification in patients with known coronary and carotid artery disease is recognized

as cost-effective, risk factor interventions in asymptomatic individuals have shown only small benefits and are extremely expensive. These interventions, however, could be cost-effective if individuals at high risk for an event are targeted. High-risk individuals for cardiovascular disease can be targeted based on easily assessable risk factors. The primary purpose of the work presented in this thesis was to evaluate the cost-effectiveness of various cardiovascular preventive strategies in the general population. We developed a Monte-Carlo Markov decision model that simulates outcomes, both costs and effects, under several alternative screening- and intervention strategies on a population level. A Monte-Carlo Markov decision model defines a number of different health states and simulates how individuals may move between the health states under various prevention strategies. The model is able to keep track of the time spent in each health state and the accumulated costs. Our simulation model was based on epidemiological data from the Rotterdam study and literature study concerning costs and effects of various interventions (**chapter 6**). This computer simulation model was developed to predict the future CVD mortality and morbidity in the original Rotterdam Study population and to evaluate the relative cost-effectiveness of various screening strategies with subsequent risk factor modification in identified high-risk subjects with the goal of preventing cardiovascular disease. This model was referred to as the Rotterdam Ischemic heart disease & Stroke Computer simulation model (RISC model). The subject characteristics of the Rotterdam Study and the real follow-up data of this study were used to validate the simulation model in the cohort study (internal validation). The RISC model was validated by comparing the simulated number of cardiovascular disease events with the observed numbers in the Rotterdam Study population during 7 years of follow-up. Furthermore, we compared simulated (disease-free) life expectancies with the result of a multi-state life table. The RISC model appeared to describe the cardiovascular life course of the population accurately. Finally, the RISC model was externally validated using epidemiological data from the U.S.A. (**chapter 7**). The RISC model was able to accurately describe the CVD burden of a general population based on the individual risk factor profiles. The development and structure of the RISC model is described in detail in the technical appendices.

Cost-effectiveness analyses

In **chapter 8**, the RISC model was used to examine the cost-effectiveness of primary prevention strategies for cardiovascular disease using the "Polypill" (a combination of aspirin, a statin, three blood pressure lowering agents in half dose and folic acid) as described by Wald & Law. We concluded that primary prevention for CVD with "Polypill" therapy is a cost-effective strategy in the general population aged 55 to 80 years old under a wide variety of assumptions and may even be cost saving in selected subgroups. We advocate a pragmatic clinical trial to study effects and associated costs of the "Polypill" in real life.

In **chapter 9** the RISC model was used to develop a prediction rule to estimate the individual's gain in quality-adjusted life years (QALYs) with aspirin therapy (the ΔQALY prediction rule). The development and structure of the ΔQALY prediction rule is described in detail in the technical appendices. The presented prediction rule is a promising tool to select individuals for CVD prevention with aspirin. Individuals at risk for CVD should be targeted based on the QALYs that can be gained instead of on their absolute CVD risk.

Finally, in **chapter 10**, a cost-effectiveness analysis was performed of aspirin therapy in the primary prevention of cardiovascular disease using the Framingham cardiovascular disease risk function, the Rotterdam cardiovascular disease risk function, the Rotterdam cardiovascular disease risk function with ankle-arm index included, and the ΔQALY prediction rule. In summary, initiation of aspirin therapy in all 55-80 year old individuals is a cost-effective strategy in the primary prevention of CVD. Overall effectiveness can be increased by treating 90% of the individuals ranked as having the highest Rotterdam ΔQALY scores. Cost-effectiveness can be increased using the Rotterdam CVD risk function or the Rotterdam ΔQALY prediction rule in which case 70% to 90% of the individuals would be considered for aspirin therapy. However, the risk of cerebral hemorrhage associated with aspirin use discourages widespread use. Although additional ankle-arm index measurement can improve the effectiveness of screening for CVD, measurement of the ankle-arm index was not shown to be a cost-effective tool to prevent CVD in the general population. This is partly caused by the fact that the ankle-arm index is also associated with non-cardiovascular disease and therefore can be considered as a measure of frailty. In other words, in individuals with a low ankle-arm index the quality adjusted life years

that can be gained by CVD preventive therapy is limited due to their relatively low life expectancy.

Clinical implications

Current guidelines for prevention of CVD are based on absolute risk of CVD for the individual patient. It is now well known that combined measurement of several CVD risk indicators can not only give the general practitioner insight into the cardiovascular risk factor profile of the patient, but it can also be a basis for more tailored cardiovascular prevention. Measurement of the ankle-arm index has the advantage of being non-invasive, easily obtainable, and rather inexpensive and can be implemented without extra training. Additional measurement of ankle-arm index offers slightly better discrimination between high and low risk individuals in a setting where information on traditional risk indicators is available. However, measurement of the ankle-arm index was not shown to be a cost-effective tool to prevent CVD in the general population, because the cost of measurement of the ankle-arm index in a primary prevention center is, although inexpensive, still too high.

The results of this thesis suggest that screening all 55- to 80-year old individuals periodically is cost-effective. If the general practitioner has a Doppler device available to measure the ankle-arm index the Rotterdam ΔQALY prediction rule can be used. If this tool is not available, the Rotterdam CVD risk function (without the ankle-arm index) should be used. The latter risk function requires only a short patient history, including the Rose questionnaire, a short physical examination, and blood tests to measure plasma cholesterol, HDL-cholesterol and glucose level. In order to calculate the Rotterdam ΔQALY prediction rule, measurement of the systolic blood pressure of the ankles is also necessary to determine the ankle-arm index. Based on the trade-off between risks and benefits and costs, each individual with a Rotterdam CVD risk score higher than 1.5% or a Rotterdam ΔQALY score higher than 0.04 QALYs should be treated with aspirin. This implies that far more individuals older than 55 years in the general population should be treated with aspirin than currently takes place. However, the risk of cerebral hemorrhage associated with aspirin use discourages widespread use in the general population.

On the other hand, if the government is willing to finance the costs associated with the introduction of the so-called "Polypill" and the effects of the "Polypill prove to be as large as stated by Wald & Law, then all 55- to 80 year old individuals can be

treated with the "Polypill" without the need for screening. The small harm of aspirin therapy is largely compensated by the beneficial effects of the lipid-lowering and antihypertensive components of the "Polypill". The savings incurred by not having to screen will eventually compensate for the relatively high introduction costs of the "Polypill". We propose a clinical trial, though, to prove the effects and safety of the Polypill before introducing this drug in the population. Even if the "Polypill" proves to be as effective and safe as stated by Wald & Law, making screening and monitoring superfluous, we would still advocate a periodical visit to the general practitioner, as in the aspirin strategy, to emphasize the importance of lifestyle modification (smoking cessation, diet and exercise) and in order to enhance compliance. In case of the aspirin strategy, education programs are needed in order to educate general practitioners in applying the screening tools. To make sure that every general practitioner will be able to estimate the benefit of preventive treatment in individual cases, the Rotterdam ΔQALY prediction rule and the Rotterdam CVD risk function should be included in national guidelines such as the Diagnostic Compass and the general practitioners' guidelines (NHG-standaarden).

Future research on CVD prevention strategies

The RISC model is, with some adaptation, suitable for studying many more CVD prevention strategies. The recently developed imaging techniques such as spiral or multidetector computed tomography could prove to be a good tool for prediction of CVD. Because these imaging techniques are rather expensive, they have to improve discriminatory ability of CVD risk-stratification substantially to be cost-effective. On the other hand, our results show that initiating "Polypill" therapy in all 55- to 80-year old individuals without use of technologically advanced screening techniques might even be cost-effective when the assumptions about effectiveness and adverse events used are true. Therefore, a pragmatic clinical trial should be performed to study the effects, adverse events and associated costs of "Polypill therapy" in individuals aged 55 to 80 years in real life. Finally, a risk function should be developed to identify those individuals in whom the harms of treatment outweigh the benefits and therefore should not be treated medically.

In summary, it may be cost-effective to select high-risk subjects for cardiovascular disease in a population by means of a risk function based on easy assessable risk-

indicators and subsequently treat those identified to modify their risk and to decrease the burden of cardiovascular disease in the population. Additional measurement of the ankle-arm index in CVD screening strategies increases the ability to discriminate individuals who may benefit from aspirin therapy from individuals who may not. However, the small benefit from performing an ankle-arm index measurement does not outweigh the associated costs. Finally, we would like to state that far more individuals older than 55 years in the general population could be treated with aspirin to prevent cardiovascular disease against relatively low costs. However, the risk of cerebral hemorrhage associated with aspirin use discourages widespread use in the general population.

SAMENVATTING & ALGEMENE DISCUSSIE

Volgens metingen van de Wereld Gezondheids Organisatie (WHO) overlijden wereldwijd jaarlijks 17 miljoen mensen aan hart- en vaatziekten. In geïndustrialiseerde landen waaronder Nederland is het sterftecijfer als gevolg van hart-en vaatziekten de afgelopen 30 jaar kleiner geworden door een combinatie van publieke gezondheidsmaatregelen (tabakbeleid, gezondheidseducatie, voedingsprogramma's etc) en verbeteringen in medische zorg (thrombolyse, PTCA, CABG en medicamenteuze therapie). Hart- en vaatziekten blijven echter de belangrijkste doodsoorzaak en als gevolg van een betere prognose voor hart- en vaatpatiënten, door verbeterde medische zorg, zijn hart- en vaatziekten vaak een oorzaak van ernstige beperkingen die een aanzienlijk aantal jaren kunnen voortduren.

Onder Amerikanen is het "lifetime" risico op 40 jarige leeftijd voor het ontwikkelen van coronair vaatlijden geschat op een op twee voor mannen en een op drie voor vrouwen. Bij de helft van alle patiënten met coronair vaatlijden komen echter geen van de traditionele risicofactoren als hoge bloeddruk, hypercholesteromie, rookgedrag, diabetes mellitus, vetzucht of lichamelijke inactiviteit voor. Non-invasieve methoden om (subklinische) atherosclerose te meten, zoals de enkel-arm index, zijn waardevolle hulpmiddelen binnen epidemiologisch onderzoek en kunnen de schatting van cardiovasculair risico verbeteren.

Daarbij komt dat onlangs gebleken is dat ontstekingsparameters, zoals C-reactief proteïne (CRP) een sleutelrol spelen in de etiologie van hart- en vaatziekten. Er wordt verwacht dat ze een belangrijke bijdrage leveren in de risicovoorspelling van hart - en vaatziekten.

Op zoek naar nieuwe risico indicatoren voor hart- en vaatziekten

"Nieuwe" factoren die zijn gevonden om prospectief en onafhankelijk van de traditionele cardiovasculaire risicofactoren hart- en vaatziekten te voorspellen, zouden toegevoegde waarde kunnen hebben voor het klinisch vaststellen van de kans op hart- en vaatziekten. Actuele discussies over het wel of niet gebruiken van de enkel-arm index ten behoeve van risico management voor primaire preventie van hart- en vaat ziekten zijn goede voorbeelden. Ten eerste moet het meten van zo'n nieuwe risicofactor simpel en bereikbaar zijn voor een groot gedeelte van de populatie en

relatief weinig kosten. Ten tweede moet de meting makkelijk reproduceerbaar zijn en een lage interobserver variabiliteit hebben. Ook moet er een relatief hoge associatie zijn tussen de meting en het optreden van hart-en vaatziekten gecorrigeerd voor alle traditionele risicofactoren en een relatief lage associatie met de bekende traditionele risicofactoren zelf. Het moet duidelijk zijn of de associatie op een continue schaal verloopt of dat er een zeker plateau is in de relatie. Verder zou de "nieuwe"risico indicator moeten leiden tot een aanzienlijke toename in onderscheidend vermogen. De oppervlakte onder de receiver-operating characteristic curve (AUC) geeft een goede maat voor de algehele prognostische waarde van een hart-en vaat ziekten risico functie zonder de betreffende indicator. De receiver-operating characteristic curve is een grafiek die de sensitiviteit uitzet tegen (1 minus de specificiteit), voor verschillende afkappunten van voorspelde kansen. De oppervlakte onder de receiver-operating characteristic curve kan worden geïnterpreteerd als de kans dat de risico functie een hogere kans op hart- en vaatziekten toeschrijft aan een willekeurig gekozen individu die hart-en vaatziekte krijgt dan aan een willekeurig gekozen individu zonder incident vaatlijden gedurende 5 jaar. Tot slot, de winst (de toename in kwaliteitsjaren en/of afname in kosten op langere termijn) van het meten van de "nieuwe" risico indicator binnen een bestaande hart- en vaatziekten preventie strategie, moet de geassocieerde kosten compenseren. Dit kan onderzocht worden met een besliskundig model dat informatie van meerdere heterogene bronnen integreert.

De rol van enkel-arm index meting in risico stratificatie van hart- en vaatziekten
In **hoofdstuk 2** hebben we de toegevoegde waarde van perifeer vaatlijden voor de voorspelling van de cardiovasculaire sterfte onderzocht. Perifeer vaatlijden, gedefinieerd door een enkel-arm index lager dan 0.90, bleek een onafhankelijke voorspeller te zijn voor de sterfte aan hart- en vaatziekten. De kans op cardiovasculaire sterfte neemt toe als perifeer vaatlijden symptomatisch is, met andere woorden, wanneer er sprake is van claudicatio intermittens (kramp in de kuit bij inspanning). Het meten van een enkel-arm index is een eenvoudige non-invasieve techniek die als screeningsmiddel zou kunnen worden opgenomen in cardiovasculair risico management, en kan dus een rol spelen in de preventie van hart-en vaatziekten.

In **hoofdstuk 3** hebben we onderzocht of de enkel-arm index gebruikt kan worden als een continue risico indicator voor hart- en vaatziekten. De enkel-arm index liet een

omgekeerd gradueel verband zien, zonder bewijs voor een bepaald afkappunt, met het Framingham risico voor hart- en vaatziekten (van 35.7% in het laagste octiel tot 22.7% in het hoogste octiel van de enkel-arm index) en andere maten van atherosclerose. De enkel-arm index was gradueel geassocieerd met het optreden van hart-en vaatziekten zonder bewijs voor een plateau in het verband. Personen met een enkel-arm index in het laagste octiel hadden een vier keer zo hoog risico op hart- en vaatziekten als personen met een enkel-arm index in het hoogste octiel (hazard ratio 4.23; 95%CI 2.63, 6.81). Na correctie voor traditionele risicofactoren van hart-en vaatziekten en medische geschiedenis van hart-en vaatziekten, was het verband minder sterk, maar nog steeds duidelijk (hazard ratio 2.49;95%CI 1.52, 4.08). De enkel-arm index toonde synergie met de Framingham risicoscore in het voorspellen van hart- en vaatziekten (p=0.02). Onze resultaten zijn in overeenstemming met het idee dat de enkel-arm index een maat is voor atherosclerose doordat deze een gradueel verband laat zien met het optreden van hartinfarcten en beroertes. De enkel-arm index moet niet langer gedichotomiseerd worden maar moet gebruikt worden als een continue risico indicator voor hart- en vaatziekten.

Risico functies

De Framingham coronary heart disease risico score deed het redelijk goed in de populatie van de "Rotterdam Studie". De originele Framingham coronary heart disease risico functie is extern gevalideerd in onze studie populatie. Dit leverde een oppervlakte op onder de Receiver Operating Characteristic curve (AUC) van 0.693. Na passend maken van de risico functie steeg de AUC toe tot 0.728, een statistisch significante toename.

In **hoofdstuk 4** verkregen we een efficiënte risico functie om mensen te selecteren met een hoog risico op coronair vaatlijden gebaseerd op traditionele risico factoren. Ook bestudeerden we de toegevoegde prognostische waarde van indicatoren van subklinische hart-en vaatziekten, zoals de enkel-arm index, om hart-en vaatziekten te voorspellen. Onder 5431 personen waarbij geen hart- en vaatziekten gedocumenteerd waren op het moment van de aanvang van het onderzoek trad bij 388 coronair vaatlijden op binnen een gemiddelde van 7 jaar vervolg onderzoek. De voorspellers van coronair vaatlijden, die geselecteerd waren door multivariabele stapsgewijze regressie analyse, waren leeftijd geslacht, totaal serum cholesterol niveau, de kwadratische term van cholesterol, HDL-cholesterol, systolische bloeddruk, het

gebruik van bloeddruk verlagende middelen, roken, diabetes mellitus, familie geschiedenis van hartinfarcten, angina pectoris, claudicatio intermittens en de interactie term tussen angina pectoris en roken. Het regressiemodel maakte goed onderscheid tussen individuen die coronair vaatlijden kregen en diegenen die dat niet kregen (oppervlakte onder de Receiver Operating Characteristic curve (AUC), 0.748 (95%CI0.718-0.778)). Het onderscheidend vermogen van deze risico functie was statistisch significant hoger vergeleken met de aangepaste Framingham risico functie (p=0.006 na bootstrapping). Na het toevoegen van de enkel-arm index vertoonde de risicofunctie een klein maar statistisch significant betere prestatie (AUC,0.754 ; 95%CI 0.724-0.784). Het toevoegen van ECG variabelen in plaats van de enkel-arm index leverde een zelfde toename in onderscheidend vermogen (AUC, 0.754 ; 95%CI 0.725-0.784). Meer dan 55% van de coronaire gebeurtenissen vond plaats bij personen met een risico op coronair vaatlijden in het hoogste kwartiel.

Ten tweede is een risicofunctie ontwikkeld om de kans op een beroerte te schatten. Onder de 5431 personen vonden 260 beroertes plaats binnen een gemiddelde van 7 jaar vervolg onderzoek. De voorspellers van beroertes (CVA) die zijn geselecteerd door multivariate stapsgewijze regressieanalyse zijn leeftijd, de kwadratische term van de leeftijd, geslacht, systolische bloeddruk, het gebruik van bloeddruk verlagende middelen, rookgedrag, diabetes mellitus, angina pectoris en tekenen van kortdurende ischemische aanvallen (TIA's). Leeftijd voorspelde CVA veruit het beste en geslacht voorspelde coronair vaatlijden het best. Cholesterol was geenszins voorspellend voor CVA maar was een zeer belangrijke voorspeller voor de kans op coronair vaatlijden.

In **hoofdstuk 5** zijn het regressiemodel voor coronair vaatlijden en het regressiemodel voor CVA gecombineerd door de 5-jaars cumulatieve overlevingskansen. Deze zijn verkregen uit het Cox Proportional Hazards model met censoring voor het andere event. We stelden de toegevoegde voorspellende waarde van de enkelarm index, ECG parameters en C-reactief proteïne vast boven op de traditionele risicofactoren bij het voorspellen van coronair vaatlijden en beroerte. CRP voegde niets toe aan de voorspellende waarde van de Rotterdamse risico functie voor hart- en vaatziekten. Het gecombineerde regressiemodel maakte goed onderscheid tussen personen met optredende hart- en vaatziekten en personen waarbij dit niet het geval was (oppervlakte onder de Receiver Operating Characteristic curve (AUC), 0.752 (95%CI 0.723-0.781)). Concluderend kan gesteld worden dat de ontwikkelde risicofunctie voor hart- en vaatziekten een bruikbaar middel blijkt te zijn in het

selecteren van personen met een hoog risico op hart- en vaatziekten binnen de eerstelijns gezondheidszorg. Risicofactoren hebben een variërende impact op het voorkomen van respectievelijk coronair vaatlijden en beroerte. Het toevoegen van metingen van of de enkel-arm index of het ECG leidt tot beter onderscheid in hoog- en laag risico individuen.

De ontwikkeling en structuur van de Rotterdamse risicofunctie voor coronair vaatlijden en de Rotterdamse risicofunctie voor hart-en vaatziekten worden gedetailleerd beschreven in de technische appendices. Er zijn een risicocalculator voor coronair vaatlijden en een risicocalculator voor CVA ontwikkeld, deze kunnen gebruikt worden door huisartsen en cardiologen.

Het besliskundig model

Terwijl secundaire preventie van cardiovasculaire gebeurtenissen door middel van risicofactor modificatie bij patiënten met bekend vaatlijden erkend wordt als kosteneffectief, laten risicofactor interventies bij asymptomatische individuen slechts geringe voordelen zien en zijn ze extreem duur. Deze interventies kunnen echter wel kosteneffectief zijn als individuen met een hoog risico op hart-en vaatziekten worden opgespoord. Individuen met een hoog risico op cardiovasculaire aandoeningen kunnen opgespoord worden op basis van gemakkelijk vast te stellen risicofactoren. Het primaire doel van het werk dat in deze thesis gepresenteerd wordt, was het evalueren van de kosteneffectiviteit van verscheidene preventiestrategieën van hart-en vaatziekten in de algehele populatie. We ontwikkelden een Monte-Carlo Markov beslismodel dat uitkomsten simuleert, zowel kosten als effecten, voor verscheidene alternatieve screenings- en interventie strategieën op populatieniveau. Een Monte-Carlo Markov beslismodel definieert een aantal verschillende gezondheidstoestanden en simuleert hoe individuen zouden kunnen bewegen tussen de gezondheidstoestanden onder verschillende preventiestrategieën. Het model is in staat om de tijd die in iedere gezondheidstoestand is doorgebracht en de geaccumuleerde kosten bij te houden. Ons simulatiemodel is gebaseerd op epidemiologische data van de Rotterdam Studie en literatuur onderzoek betreffende kosten en effecten van verscheidene interventies (**hoofdstuk 6**). Dit computer simulatiemodel is ontwikkeld om het optreden van hart-en vaatziekten en sterfte in de oorspronkelijke populatie van de Rotterdam Studie te voorspellen en om de relatieve kosteneffectiviteit van verscheidene screeningsstrategieën te evalueren met

daaropvolgend risicofactormodificatie bij geïdentificeerde hoogrisico personen met als doel het voorkomen van hart-en vaatziekten. Dit model werd het Rotterdam Ischemic heart disease & Stroke Computer simulation model (RISC model) genoemd. De (proef)persoonskenmerken van de Rotterdam Studie en de echte follow-up data van dit onderzoek zijn gebuikt voor het valideren van het simulatie model in de cohort studie (interne validering). Het RISC model werd gevalideerd door het gesimuleerde aantal cardiovasculaire gebeurtenissen te vergelijken met de geobserveerde aantallen in de Rotterdam Studie populatie gedurende 7 jaar follow-up.Verder vergeleken we gesimuleerde (ziekte vrije) levensverwachtingen met het resultaat van een multi-state life table. Het RISC model bleek de cardiovasculaire levensloop van de populatie nauwkeurig te beschrijven. Tot slot is het RISC model extern gevalideerd aan de hand van epidemiologische data uit de U.S.A. (**hoofdstuk 7**). Het RISC model was in staat om, gebaseerd op de individuele risico factor profielen, de incidentie van hart-en vaatziekten van een algemene populatie te beschrijven. De ontwikkeling en structuur van het RISC model zijn gedetailleerd beschreven in de technische appendices.

Kosteneffectiviteits analyses

In **hoofdstuk 8** is het RISC model gebruikt om de kosteneffectiviteit te onderzoeken van primaire preventie strategieën voor hart-en vaatziekten, in de vorm van de "Polypill" (een combinatie van aspirine, statine,drie bloeddrukverlagende middelen in halve dosering en foliumzuur) zoals beschreven is door Wald & Law. We concludeerden dat primaire preventie van hart-en vaatziekten met "Polypill" therapie een kosteneffectieve strategie is in de algemene bevolking tussen 55 en 80 jaar, onder een grote verscheidenheid aan assumpties. Het zou zelfs kostenbesparend kunnen zijn in bepaalde subgroepen. We bepleiten een pragmatische klinische trial om effecten en geassocieerde kosten van de "Polypill" in de realiteit te onderzoeken.

In **hoofdstuk 9** werd het RISC model gebruikt om een voorspellingsregel te ontwikkelen om een schatting te kunnen maken van de individuele winst in kwaliteitsjaren (QALYs) met aspirine therapie (de ΔQALY voorspellingsregel). De ontwikkeling en structuur van de ΔQALY voorspellingsregel zijn gedetailleerd beschreven in de technische appendices. De gepresenteerde voorspellingsregel is een veelbelovend hulpmiddel om individuen te selecteren voor preventie van hart-en vaatziekten met aspirine. Individuen met risico op hart-en vaatziekten zouden moeten

worden behandeld op basis van de kwaliteitsjaren die gewonnen kunnen worden in plaats van op hun absolute risico op hart-en vaatziekten.

Tot slot is in **hoofdstuk 10** een kosteneffectiviteit analyse uitgevoerd van aspirine therapie binnen de primaire preventie van hart-en vaatziekten met behulp van de Framingham risicofunctie voor hart-en vaatziekten, de Rotterdamse risicofunctie voor hart-en vaatziekten, de Rotterdamse risicofunctie voor hart-en vaatziekten inclusief de enkel-arm index en de ΔQALY voorspellingsregel. Concluderend kan gesteld worden dat levenslange aspirine therapie bij alle 55-80 jarige individuen een kosteneffectieve strategie is in de primaire preventie van hart-en vaatziekten. Algehele effectiviteit kan vergroot worden door 90% van alle individuen die de hoogste Rotterdam ΔQALY scores hebben, te behandelen. Kosteneffectiviteit kan vergroot worden door de Rotterdamse risico functie voor hart-en vaatziekten of de Rotterdamse ΔQALY predictieregel te gebruiken, in dit geval zou 70% tot 90% van de individuen in aanmerking komen voor aspirine therapie. Hoewel toegevoegde enkel-arm index metingen de effectiviteit van screening op hart-en vaatziekten kan verbeteren is dit geen kosteneffectief middel gebleken voor preventie van hart-en vaatziekten in de algemene bevolking. Dit is gedeeltelijk veroorzaakt door het feit dat de enkel-arm index ook geassocieerd is met niet-cardiovasculaire ziekten en kan daarom beschouwd worden als een maat voor verhoogde sterfte kans Met andere woorden, bij individuen met een lage enkel-arm index zijn de kwaliteitsjaren die gewonnen kunnen worden door preventieve therapie voor hart-en vaatziekten beperkt, als gevolg van hun relatief lage levensverwachting.

Klinische implicaties

Huidige handleidingen voor preventie van hart-en vaatziekten zijn gebaseerd op absolute risico's voor de individuele patiënt. Het is welbekend dat gecombineerde metingen van verschillende risico indicatoren van hart-en vaatziekten niet alleen de huisarts inzicht geven in het cardiovasculaire risicoprofiel van de patiënt, maar het kan ook als basis dienen voor cardiovasculaire preventie op maat. Meting van de enkel-arm index heeft het voordeel non-invasief te zijn, makkelijk verkrijgbaar, vrij goedkoop en kan geïmplementeerd worden zonder extra training. Meting van de enkel-arm index heeft enigszins toegevoegde waarde wanneer de meting gebruikt wordt als een screeningsmiddel in een setting waar informatie betreffende traditionele risicofactoren beschikbaar is. Meting van de enkel-arm index bleek echter geen

kosteneffectief middel te zijn om hart-en vaatziekten in de algemene bevolking te voorkomen, omdat meting van de enkel-arm index in een primair preventief centrum, ondanks de lage kosten, relatief toch te duur bleek te zijn. Als de huisarts echter Doppler apparatuur tot zijn beschikking heeft, zou het waardevol kunnen zijn om de enkel-arm index te gebruiken als screenings middel voor hart- en vaatziekten.

Gebaseerd op de resultaten van dit proefschrift is het mogelijk een kosteneffectieve strategie om alle 55 tot 80 jarigen periodiek te laten screenen door de huisarts. Als de huisarts Doppler apparatuur tot zijn beschikking heeft om een enkel-arm index te meten, kan de Rotterdam ΔQALY voorspellingsregel worden gebruikt om individuen te selecteren voor cardiovasculaire preventie. Als deze geen Doppler apparatuur tot zijn beschikking heeft, kan het best de Rotterdam CVD risico functie worden gebruikt (zonder enkel-arm index). Voor deze risico functie is slechts een korte anamnese, inclusief de "Rose questionnaire", kort lichamelijk onderzoek en bloeddruk meting nodig. Tevens is laboratoriumonderzoek vereist ter bepaling van het cholesterol, HDL cholesterol en glucose gehalte.

Om de Rotterdam ΔQALY voorspellingsscore te bepalen is tevens meting van de systolische bloeddruk aan de enkels nodig om de enkel-arm index vast te stellen. Op basis van een afweging van risico's, effecten en kosten zou ieder individu met een Rotterdam CVD risico score hoger dan 1.5% of een Rotterdam ΔQALY score hoger dan 0.04 kwaliteitsjaren behandeld moeten worden met aspirine. Dit houdt in dat veel meer personen boven de 55 jaar dan nu het geval is, behandeld zouden moeten worden. Er moet echter rekening worden gehouden met het risico dat individuen lopen op een hersenbloeding of ernstige maagbloeding. Als de overheid echter bereid zou zijn om de kosten op zich te nemen voor de introductie van de zogenoemde "Polypill" en de effectiviteit van de "Polypill" zo groot blijkt als verondersteld door Wald & Law, zouden alle personen boven de 55 jaar behandeld moeten worden met de "Polypill" zonder daarbij gebruik te hoeven maken van screening. De kleine kans op bloeding door aspirine weegt niet op tegen de cholesterolverlagende en bloeddrukverlagende effecten van de "Polypill". Het besparen van screeningskosten zal uiteindelijk compenseren voor de relatief hoge introductiekosten. We adviseren wel eerst een klinisch onderzoek om de effecten en veiligheid van de "Polypill" te bestuderen voordat deze therapie daadwerkelijk wordt geïntroduceerd. Hoewel de "Polypill" screening overbodig zou maken, adviseren wij alsnog een periodiek bezoek aan de huisarts om het belang van stoppen met roken, dieet en lichaamsbeweging te

benadrukken en om de therapietrouw te vergroten. In het geval van de aspirine strategie is scholing van huisartsen vereist om gebruik te kunnen maken van de screeningsmethoden. Om er zeker van te zijn dat iedere huisarts de winst van preventieve behandelingen kan voorspellen moeten de Rotterdam ΔQALY voorspellingsregel en de Rotterdam CVD risico functie opgenomen worden in nationale richtlijnen zoals het Diagnostisch Kompas en de NHG-standaarden.

Toekomstig onderzoek naar preventiestrategieën voor hart-en vaatziekten
Het RISC model is na kleine aanpassingen geschikt om veel meer andere preventiestrategieën voor hart-en vaatziekten te onderzoeken. Waarschijnlijk zouden de meer recent ontwikkelde beeldvormende technieken zoals spiraal CT of multidetector CT waardevolle instrumenten zijn om hart-en vaatziekten te voorspellen. Omdat deze beeldvormende technieken relatief duur zijn moeten ze het onderscheidend vermogen van cardiovasculaire risico inventarisatie aanzienlijk verbeteren om kosteneffectief te zijn. Aan de andere kant laten onze resultaten zien dat het levenslang behandelen van alle 55 tot 80 jarige individuen met een combinatie van aspirine, statine, drie bloeddrukverlangende middelen in halve dosering en foliumzuur (de "Polypill") zonder het gebruik van hoogstaande screeningsmethoden kosteneffectief en ook relatief veilig zou kunnen zijn, als de gemaakte assumpties over effectiviteit en neveneffecten juist zijn. Daarom zal een pragmatisch-klinische trial moeten worden verricht om effecten, bijwerkingen en geassocieerde kosten van de "Polypill" therapie te bestuderen bij personen tussen de 55 en 80 jaar. Tenslotte zal een risico functie moeten worden ontwikkeld om die individuen te selecteren bij wie de nadelen van de behandeling groter zijn dan de voordelen en daarom niet medisch behandeld zouden moeten worden.

Concluderend kan gesteld worden dat het kosteneffectief zou kunnen zijn om personen met een hoog risico op hart-en vaatziekten te selecteren door middel van een risicofunctie die gebaseerd is op gemakkelijk vast te stellen risico indicatoren en vervolgens die geselecteerden te behandelen om hun risico te veranderen en om het optreden van hart-en vaatziekten te verminderen. Toevoegen van meting van de enkel-arm index aan screeningsmethoden voor hart-en vaatziekten vergroot de mogelijkheid om individuen die baat zouden kunnen hebben bij aspirine therapie te onderscheiden van individuen die daar geen baat bij zouden hebben. Echter, het kleine

voordeel van het uitvoeren van een enkel-arm index meting weegt niet op tegen de geassocieerde kosten. Ten slotte kan worden verondersteld dat veel meer individuen ouder dan 55 jaar behandeld zouden moeten worden met aspirine om hart-en vaatziekten te voorkomen tegen relatief lage kosten voor de maatschappij. Er moet echter rekening worden gehouden met het risico dat individuen lopen op een hersenbloeding of ernstige maagbloeding.

Technical appendices

APPENDIX 1: THE ROTTERDAM CHD RISK FUNCTION

DERIVATION OF SCORES IN THE RISK FUNCTION

Based on the final models, the subject-specific 5-year probability of CHD was calculated as:

$$1 - (S0_{CHD}(1826)^{\exp(\sum(\beta_i x_i - \beta_i x_m))})$$

where $S0_{CHD}(1826)$ is the baseline cumulative CHD-free survival at the mean of all covariates at 1826 days (5 years) and $\sum(\beta_i x_i - \beta_i x_m)$ is the linear predictor centered at the mean of the covariates.

x_i is the subject specific value of i-th risk indicator and x_m is the mean value of the risk indicator in the study population.

The baseline cumulative survival estimates and the adjusted regression coefficients are listed in the table below. The presented regression coefficients and the constant $\beta_i x_m$ were adjusted for overfitting by multiplying by a shrinkage factor, which was derived from bootstrapping procedures for all three models separately (0.91 for the Rotterdam CHD risk function; 0.89 for extended models 1 and 2).

USING THE RISK FUNCTION IN PRACTICE

Calculating the 5-year Rotterdam CHD risk score requires a short patient history to determine age, smoking behaviour, family history for myocardial infarction, use of antidiabetic medication, use of antihypertensive medication, medication use for cardiovascular disease, and the Rose questionnaire to determine the presence of intermittent claudication or angina pectoris. Next, a short physical examination to assess blood pressure is needed and blood tests have to be performed to measure plasma cholesterol, HDL-cholesterol and glucose level. For calculating the risk score by extended model 1, the physical examination also has to include measurement of the systolic blood pressure of the ankles to determine the ankle-arm index. To calculate the risk score by extended model 2, an ECG is needed to determine left ventricular hypertrophy or signs of myocardial infarction.

For example, we will calculate the 5-year risk of a 55-year-old smoking man, without diabetes mellitus. His systolic blood pressure is 160 mmHg. The blood pressure at the ankle has been measured and is 150 mmHg. There is no history of angina pectoris or intermittent claudication and the man is not using any medication. His brother had a myocardial infarction at the age of 50. The plasma cholesterol level is 6.3 and the HDL-cholesterol is 0.9. Using the Rotterdam CHD risk function, the predicted risk can be calculated as follows:

Linear Predictor = − 7.3950 + 0.8452 * 1 + 0.0387 * 55 + 0.3894 * 0 + 0.7514 * 6.3 - 0.6037 * 0.9 + 0.1952 * 1 + 0.0126 * 160 + 1.4158 * 0 + 0.2831 * 0 + 0.3900* 1 + 1.0490 * 0 + 0.4783 * 0 - 0.0080 * 160 * 0 - 0.0401 * 39.69 − 0.6265 * 0 * 0 - 0.6688 * 0 * 1 = 0.778821

5-year probability of CHD = $1 - ((0.9661)\exp(0.778821))$ = 7.2%

The 5-year risk of CHD as calculated by extended model 1 = 7.7%

Note that the risk calculated by extended model 1 is higher because the AAI is slightly decreased for this otherwise low-risk individual.

	ß-coefficients* Rotterdam risk function	ß-coefficients† Extended model 1	ß-coefficients‡ Extended model 2
S0 at mean of covariates (5 years)	0.9661	0.9662	0.9663
Constant. (mean of linear predictor)	-7.3950	-5.8909	-7.1528
Male gender	0.8452	0.8499	0.8036
Age	0.0387	0.0339	0.0360
Diabetes mellitus	0.3894	0.3469	0.3806
Cholesterol	0.7514	0.7073	0.7721
HDL-cholesterol	-0.6037	-0.5756	-0.5872
Family history of myocardial infarction	0.1952	0.1821	0.1946
Systolic blood pressure (SBP)	0.0126	0.0108	0.0115
Antihypertensive medication use	1.4158	1.3219	1.3679
Past smoking	0.2831	0.2709	0.2712
Current smoking	0.3900	0.3144	0.3585
Angina pectoris	1.0490	1.0038	1.0296
Intermittent claudication	0.4783	0.3112	0.4301
SBP * antihypertensive medication use	-0.0080	-0.0075	-0.0078
Cholesterol * cholesterol	-0.0401	-0.0377	-0.0416
Angina pectoris * past smoking	-0.6265	-0.6011	-0.6428
Angina pectoris * current smoking	-0.6688	-0.6701	-0.6907
Ankle-arm index		-0.6837	
Left ventricular hypertrophy by ECG			0.4347
Silent myocardial infarction by ECG			0.3429

* adjusted with a shrinkage factor of 0.91

† adjusted with a shrinkage factor of 0.89

‡ adjusted with a shrinkage factor of 0.89

APPENDIX 2: THE ROTTERDAM CVD RISK FUNCTION

APPENDIX A. Model development

Age and sex adjusted Cox proportional hazard models were used to examine the association between various risk indicators and the risk of coronary heart disease and stroke separately. The additional predictive value was determined by the Akaike's Information Criterion (AIC). The AIC can be calculated as the χ^2-change minus two times the degrees of freedom, in which the χ^2 is the difference between the model with and the model without the risk indicator of interest on the $-2\log$ Likelihood scale.[28,31]

First, we selected al risk indicators with an AIC > 0 in age and sex adjusted analyses. For blood pressure we examined systolic blood pressure, diastolic blood pressure, pulse pressure and antihypertensive medication use. We selected the blood pressure variable with the highest AIC and examined whether the blood pressure variable with the next largest AIC was still additionally predictive over and above the variable already included (AIC > 0). We additionally examined whether cholesterol and HDL-cholesterol led to a better model performance when included separately compared to using the cholesterol/HDL-ratio. Of all selected variables, a backward stepwise analysis with a p-value-to-remove of 0.10 was performed to achieve the prefinal multivariable model. This strategy of selection of main effects aimed to include all important risk indicators and therefore used a more liberal criterion than the standard $p < 0.05$ criterion.[27] A more conservative approach was followed for non-linear and interaction terms. Quadratic terms of all continuous variables were tested and added to the prefinal model if $p < 0.05$. Subsequently, all interaction terms with age and gender were tested and added to the prefinal model if $p < 0.01$. Also, plausible interactions with mild manifestations of cardiovascular disease were tested with a p-value-to-enter of 0.05.

In both the final multivariable model for coronary heart disease and that for stroke, the ankle-arm index (AAI) was tested for additional predictive value and added if the model improved significantly ($p < 0.05$). The quadratic term of AAI and interactions of AAI with age, sex, and mild manifestations of cardiovascular disease were tested in the same way as described above, which yielded 'extended model 1'. The ECG characteristics were tested in a similar fashion, which yielded 'extended model 2'. In 'extended model 3' we tested the additional predictive value of serum C-reactive protein using the same criteria. Because of missing values in most of the controls, we tested the additional predictive value of CRP in a case-control design by logistic regression analysis with adjustment for follow-up time.

To determine internal validity, bootstrapping was performed.[28] The full selection process was repeated in every bootstrap sample (80 replications). We estimated a shrinkage factor to improve calibration of predictions in future patients, that is, to correct for overfitting of the risk function.[27,28]

Figure Appendix A.

The predictive value of different risk indicators measured by the Akaike's Information Criterion (AIC), adjusted for age and sex. An AIC equal to or smaller than zero indicates no additive predictive value over and above age and gender. The AICs are displayed for coronary heart disease and stroke separately.

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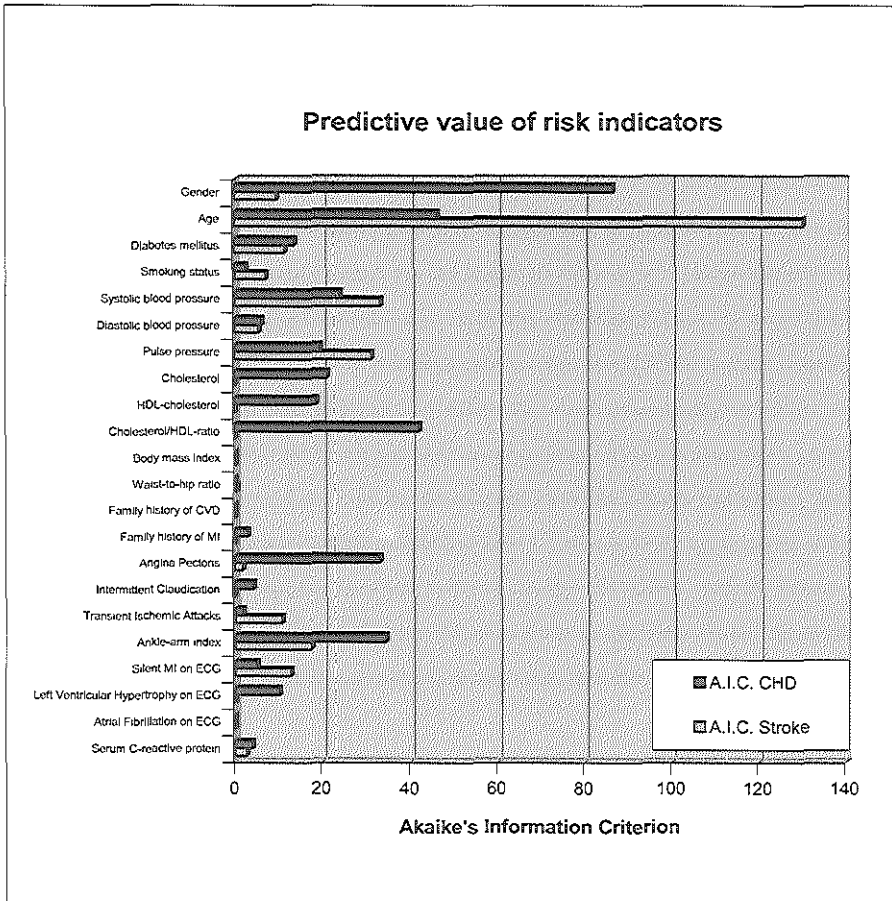
APPENDIX B. The Rotterdam Cardiovascular Disease Risk Function and extended models

	Rotterdam risk function		Extended model 1		Extended model 2	
	CHD	Stroke	CHD	Stroke	CHD	Stroke
S0 at mean of covariates (5 years)	0.9674	0.9794	0.9675	0.9794	0.9676	0.9797
Mean of linear predictor	-7.4503	-23.7629	-5.9258	-23.5318	-7.2371	-24.2173
Male gender	0.8662	0.2435	0.8710	0.2572	0.8250	0.2327
Age	0.0372	0.5114	0.0324	0.5250	0.0347	0.5307
Diabetes mellitus	0.3797	0.5281	0.3367	0.5104	0.3726	0.5259
Plasma cholesterol	0.7365	-	0.6892	-	0.7618	-
HDL-cholesterol	-0.6163	-	-0.5878	-	-0.6021	-
Family history of MI	0.1771	-	0.1636	-	0.1781	-
Systolic blood pressure	0.0139	0.0195	0.0121	0.0182	0.0128	0.0191
Antihypertensive treatment	1.4958	2.0342	1.3985	1.9942	1.4606	1.9405
Past smoking	0.3069	0.3158	0.2933	0.3087	0.2923	0.3037
Current smoking	0.3798	0.6076	0.3013	0.5492	0.3493	0.5596
Angina pectoris	1.0650	-	1.0158		1.0381	
Intermittent claudication	0.3577	-	0.1944		0.3046	
Transient ischemic attacks	-	0.7250	-	0.7050	-	0.7179
Age * Age	-	-0.0030	-	-0.0031	-	-0.0032
Systolic blood pressure * Antihypertensive treatment	-0.0086	-0.0128	-0.0081	-0.0126	-0.0085	-0.0121
Cholesterol * Cholesterol	-0.0382	-	-0.0357	-	-0.0401	-
Past smoking * Angina pectoris	-0.5718	-	-0.5431	-	-0.5886	-
Current smoking * Angina pectoris	-0.5757	-	-0.5722	-	-0.5805	-
Ankle-arm index	#	#	-0.6939	-0.5133	#	#
LVH on ECG	#	#	#	#	0.4568	-
Silent MI on ECG	#	#	#	#	0.3324	0.5992
Shrinkage factor¶	0.9100	0.9110	0.8900	0.9090	0.8900	0.9090

- non-significant

\# not included in risk function

¶ The presented log hazard ratios and the mean of the linear predictor were adjusted for overfitting by multiplying by a shrinkage factor, which was derived from bootstrapping procedures.[27,28]

APPENDIX C. CALCULATING THE 5-YEAR RISK OF CARDIOVASCULAR DISEASE

The regression model for CHD and the regression model for stroke were combined by multiplying the 5-year cumulative survival probabilities that were derived from the Cox proportional hazards model with censoring for the other event. Based on the final multivariable models, the 5-year probability of cardiovascular disease was calculated as:

$$1 - (SO_{CHD}(1826)^{\exp(\sum(\beta_i x_i - \beta_i x_m))} * SO_{Stroke}(1826)^{\exp(\sum(\beta_i x_i - \beta_i x_m))})$$

S0(1826) is the baseline cumulative survival at the mean of all covariates at 1826 days (5 years) for coronary heart disease and stroke respectively.

$\sum(\beta_i x_i - \beta_i x_m)$ is the linear predictor from the Cox proportional hazards model, where x_i is the

subject specific value of the i-th risk indicator, and x_m is the mean value of the risk indicator in the study

population. $\beta_i x_m$ is the mean of the linear predictor.

For example, we will calculate the 5-year risk of a 55-year-old smoking man, without diabetes mellitus. His systolic blood pressure is 160 mmHg. There is no history of angina pectoris or intermittent claudication and the man is not using any medication. His brother had a myocardial infarction at the age of 50. The plasma cholesterol level is 6.3 and the HDL-cholesterol is 0.9. Using the Rotterdam CVD risk function, the predicted risk can be calculated as follows:

Linear Predictor for coronary heart disease= − 7.4503 + 0.8662 * 1 + 0.0372 * 55 + 0.3797 * 0 + 0.7365 * 6.3 - 0.6163 * 0.9 + 0.1771 * 1 + 0.0139 * 160 + 1.4958 * 0 + 0.3069 * 0 + 0.3798* 1 + 1.0650 * 0 + 0.3577 * 0 - 0.0086 * 160 * 0 - 0.0382 * 39.69 − 0.5718 * 0 * 0 - 0.5757 * 0 * 1 = 0.8284

Linear Predictor for stroke= − 23.7629 + 0.2435 * 1 + 0.5114 * 55 + 0.5281 * 0 + 0.0195 * 160 + 2.0342 * 0 + 0.3158 * 0 + 0.6076* 1 + 0.7250 * 0 −0.0030 * 55 * 55 - 0.0128 * 160 * 0 = -0.7398

5-year probability of CVD = 1 − (0.9674 $^{\exp(0.8284)}$ * 0.9794 $^{\exp(-0.7398)}$) = 8.2%

USING THE RISK FUNCTION IN PRACTICE

Calculating the 5-year Rotterdam CVD risk score requires a short patient history to determine age, smoking behaviour, family history for myocardial infarction, use of antidiabetic medication, use of antihypertensive medication, medication use for cardiovascular disease, and the Rose questionnaire to determine the presence of intermittent claudication or angina pectoris. Next, a short physical examination to assess blood pressure is needed and blood tests have to be performed to measure plasma cholesterol, HDL-cholesterol and glucose level. For calculating the risk score by extended model 1, the physical examination also has to include measurement of the systolic blood pressure of the ankles to determine the ankle-arm index. To calculate the risk score by extended model 2, an ECG is needed to determine left ventricular hypertrophy or signs of myocardial infarction.

APPENDIX 3: TECHNICAL APPENDIX OF THE RISC MODEL

CONTENTS

LIST OF ABREVIATIONS

abil	ankle-brachial systolic blood pressure index lowest measured
af	atrial fibrillation
AIC	Akaike's Information Criterion
ap	angina pectoris
aspintol	the probability of aspirin intolerance
aspirin_IHD	ischemic heart disease risk reduction by aspirin therapy
aspirin_stroke	ischemic stroke risk reduction by aspirin therapy
Bcfc	beta coefficients for the risk function of case-fatality of stroke
Bcfi	beta coefficients for the risk function of case-fatality of ischemic heart disease
Bcva	beta coefficients for the risk function of ischemic stroke
Bcvd	beta coefficients for the risk function of cardiovascular mortality
Bihd	beta coefficients for the risk function of ischemic heart disease
Bmot	beta coefficients for the risk function of non-cardiovascular mortality
bCABG	beta coefficients for the risk function of CABG versus MI
bPTCA	beta coefficients for the risk function of CABG versus PTCA
bmi	body-mass index
CABG	coronary artery bypass grafting
chol	cholesterol level
claud	intermittent claudication
creat	serum creatinine
dbp	diastolic blood pressure
dm	diabetes mellitus
ERGO	the Rotterdam Study dataset (n = 3501) in table format
ERGO6871	the Rotterdam Study dataset (n = 6871) in table format
EXP	exponent
famcvd	family history of cardiovascular disease
friction costs	costs associated with production losses for the whole friction period
friction period	the maximum time it takes to replace a sick employee (4 months)
friction time	the actual time that production loss exists
GI bleed	gastro-intestinal bleeding caused by aspirin
gluc	serum glucose level
hdl	HDL-cholesterol level
ht	hypertension
LN	natural logarithm
MI	myocardial infarction
mifam	family history of myocardial infarction
NHANES	the NHANES dataset in table format
p	bootstrap sample of linked transition probability functions
p1	initial probability to be free of medical history for cardiovascular disease
p2	initial probability of ischemic heart disease
p3	initial probability of ischemic stroke
PTCA	percutanous transluminal coronary angioplast

RISC	Rotterdam Ischemic heart disease & Stroke Computer simulation model
sbp	systolic blood pressure
smoke	smoking (current or ever)
smokecur	current smoking
tia	transient ischemic attack
u AP	utility of angina pectoris patient
u CABG	utility of CABG patient
u DM	utility of patient with diabetes mellitus
u Gibleed	utility of patient with gastro-intestinal bleeding
u HemStroke	utility of patient with hemorrhagic stroke
u MI first year	utility of patient with myocardial infarction in the first year
u MI sq	utility of patient with myocardial infarction in the following years
u PAD	utility of patient with intermittent claudication
u PTCA	utility of PTCA patient
u Stroke minor	utility of patient with a minor stroke
uStroke major	utility of patient with a major stroke
u TIA	utility of patient with transient ischemic attack
medhistf	medical history of cardiovascular disease in female
medhistm	medical history of cardiovascular disease in male
whr	waist-to-hip ratio

The RISC model: the Rotterdam Ischemic heart disease & Stroke Computer simulation model is a Monte Carlo-Markov model developed to predict the future CVD mortality and morbidity in the original Rotterdam Study population, aged 55 and older at study onset, and followed from 1991 to 2000. The model was developed in TreeAge (version Data Professional release 10, TreeAge Software, Inc., Williamstown, USA).

Through its capability to simulate changes in risk factors in subjects without CVD, the model is suited to examine the effects of preventive strategies. Furthermore, the Monte Carlo structure allows the evaluation of variability and uncertainty by using random number generation and distribution sampling.

The RISC model is a state-transition model containing 6 states: (1) the CVD death state, (2) the non-CVD death state, (3) the Ischemic Heart Disease (IHD) state, (4) the Stroke state, (5) the IHD and Stroke state and (6) the Well state.
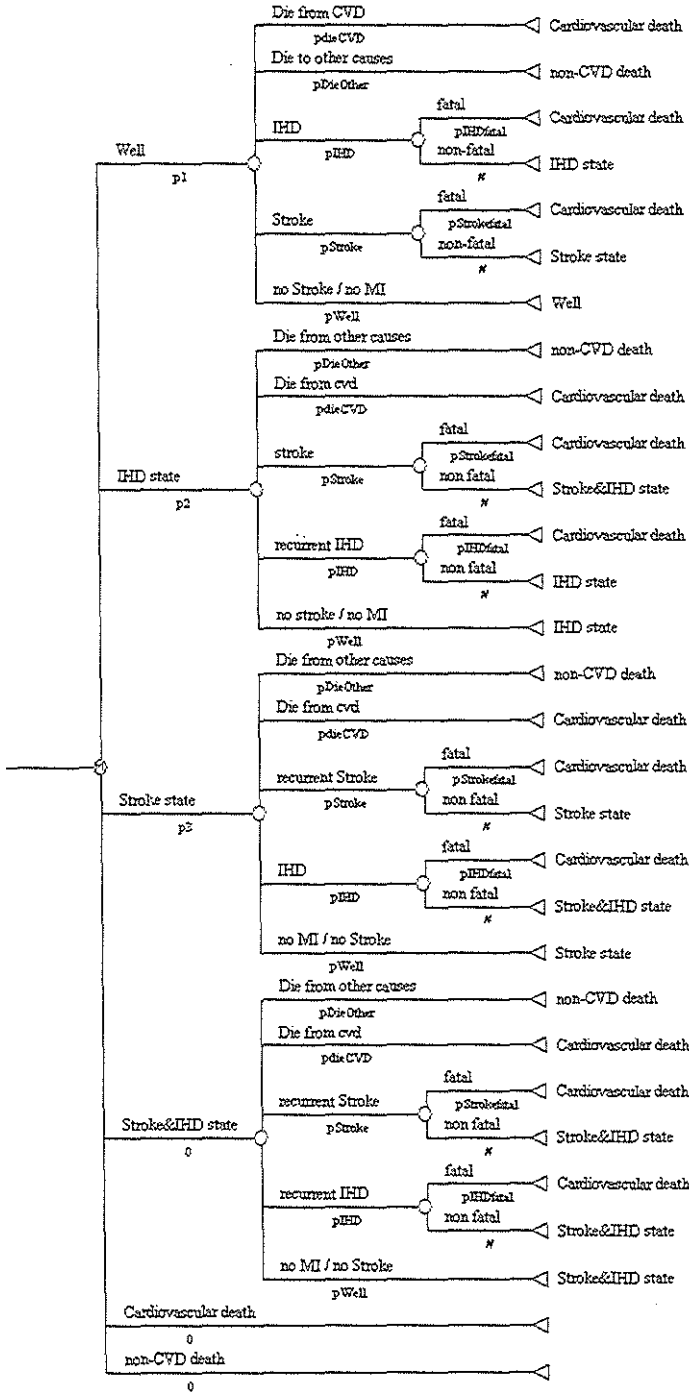
To estimate transition probabilities for different risk indicator patterns, we constructed six transition probability functions based on Cox proportional hazard analyses with follow-up time as the time axis. The first probability function models the transition probability from the Well state to the IHD state and from the Stroke state to the IHD & Stroke state. When modeling incident IHD, subjects with incident stroke were censored at the time of their stroke. The second function models the transition probability from the Well state to the Stroke state and from the IHD state to the IHD & Stroke state. When modeling incident stroke, subjects with incident IHD were censored at the time of their IHD event. In both functions having experienced IHD and/or stroke is included as a covariate. The third and the fourth functions model the transition probability from the Well state, the IHD state, the Stroke state and the IHD & Stroke state to the CVD death state and the non-CVD death state, respectively. When modeling cardiovascular and non-cardiovascular mortality, subjects with incident IHD or stroke were censored at the time of their event. In the fifth and sixth functions, the cardiovascular mortality rates within 6 months after IHD and stroke respectively (case-fatality) were modeled. The fourth IHD event and the third stroke were assumed always to be fatal.

We performed stepwise-backward Cox proportional hazard analyses to select all important risk indicators for each of the six transition probability functions, as determined by Akaike's Information Criterion (AIC) > 0. The AIC can be calculated as the χ^2-change minus two times the degrees of freedom, in which the χ^2 is the likelihood ratio test statistic. Subsequently, quadratic terms of all continuous variables and interaction terms with age, gender and medical history of CVD were tested and added to the transition probability function if AIC was greater than 0.

Individual risk factor profiles (as sampled from the Rotterdam Study participants) were used to estimate the transition probabilities for each subject. The complete risk factor profile of each individual was updated every 5 years in the model. Changes in continuous risk factor levels due to aging were estimated from the Rotterdam Study data using linear regression analysis with age and gender as covariates and modeled as a continuous increase or decrease per 5 years. Changes in dichotomous risk factors were analyzed using logistic regression analysis with gender and all continuous risk factors as covariates and were modeled as "hidden states" using tracker variables. Every 5-year period during follow-up, the presence of each dichotomous risk factor was updated by drawing from a binomial distribution conditional on the previous risk factor profile.

To model the lifelong event history of a cohort, follow-up time was divided in 5-year intervals. For the first 5 years the baseline risk factor profiles and the follow-up time dependent baseline cumulative survival from the Cox model were used in the RISC model. For the following 5 year-periods the same baseline cumulative survival was used but the complete risk factor profile was updated every time.

Schematic representation of the RISC model

Die from CVD
pdieCVD
Cardiovascular death

Die to other causes
pDieOther
non-CVD death

IHD
pIHD
fatal
pIHDfatal
Cardiovascular death
non-fatal
N
IHD state

Well
p1

Stroke
pStroke
fatal
pStrokefatal
Cardiovascular death
non-fatal
N
Stroke state

no Stroke / no MI
pWell
Well

Die from other causes
pDieOther
non-CVD death

Die from cvd
pdieCVD
Cardiovascular death

stroke
pStroke
fatal
pStrokefatal
Cardiovascular death
non fatal
N
Stroke&IHD state

IHD state
p2

recurrent IHD
pIHD
fatal
pIHDfatal
Cardiovascular death
non fatal
N
IHD state

no stroke / no MI
pWell
IHD state

Die from other causes
pDieOther
non-CVD death

Die from cvd
pdieCVD
Cardiovascular death

recurrent Stroke
pStroke
fatal
pStrokefatal
Cardiovascular death
non fatal
N
Stroke state

Stroke state
p3

IHD
pIHD
fatal
pIHDfatal
Cardiovascular death
non fatal
N
Stroke&IHD state

no MI / no Stroke
pWell
Stroke state

Die from other causes
pDieOther
non-CVD death

Die from cvd
pdieCVD
Cardiovascular death

recurrent Stroke
pStroke
fatal
pStrokefatal
Cardiovascular death
non fatal
N
Stroke&IHD state

Stroke&IHD state
0

recurrent IHD
pIHD
fatal
pIHDfatal
Cardiovascular death
non fatal
N
Stroke&IHD state

no MI / no Stroke
pWell
Stroke&IHD state

Cardiovascular death
0

non-CVD death
0

Variables RISC model

Risk factor profiles were available from individuals who participated in the Rotterdam Study, in Dutch also known by the acronym ERGO. Continuous variables were drawn from the subjects' risk factor profiles (x) and updated with a constant (c), derived from linear regression analysis, adjusted for age and gender, for example:

age	ERGO[x;3]	*(is baseline age for subject x)*
	(age is in the third column of the table "ERGO")	
ageMKV	age+(t_stagecount5)*5	*(is 5-yearly updated age)*
sbp	ERGO[x;19]	*(is baseline systolic blood pressure for subject x)*
	(systolic blood pressure is in the 19th column of the table "ERGO")	
sbpMKV	(sbp+t_stagecount5*5*c_sbp)	*(is 5-yearly updated systolic blood pressure)*

Dichotomous variables were drawn from the subjects' risk factor profiles (x) and updated using a binomial distribution with a probability parameter, derived from logistic regression analysis adjusted for age, gender and all updated continuous risk factors. For example, for atrial fibrillation:

af	ERGO[x;2]
	(atrial fibrillation is in the second column of the table "ERGO")
afMKV	If(t_stagecount5>0;(If(DistSamp(30)=1;1;af));af)
	DistSamp(30) is a binomial distribution with the probability t_Afrisk
	(see "hidden states", page 240)

All other variables used in the RISC model are described in "Distributions", page 259.

Model parameters

discRATE	= discount rate (default = 0.04)
dt	= cycle length (default = 0.1 years)
p	_sample *(Every sample, another bootstrap sample of linked transition probability functions is drawn)*
x	_trial *(Every trial, another subjects' risk factor profile is drawn)*
p1	= 1-ERGO[x;17] *is initial probability of being in the Well state*
	(medical history of CVD is in the 17th column of the table "ERGO")
p2	= (1-p1) * 0.5
p3	= p2

To model the lifelong event history of a cohort, follow-up time was divided into 5-year intervals. For the first 5 years the baseline risk factor profiles (as sampled from the Rotterdam Study participants) and the follow-up time dependent baseline cumulative survival from the Cox model were used in the RISC model. During subsequent follow-up the same baseline cumulative survival was used but the complete risk factor profile was updated every 5 year-period. The clock for the baseline cumulative hazard was reset at zero at the start of each 5-year period.

{T} t_stagecount5

If((_stage)<=5/dt;0;If((_stage)<=10/dt;1;If((_stage)<=15/dt;2;If((_stage)<=20/dt;3;If((_stage)<=25/dt;4;If((_stage)<=30/dt;5;If((_stage)<=35/dt;6;If((_stage)<=40/dt;7;If((_stage)<=45/dt;8;If((_stage)<=50/dt;9;If((_stage)<=55/dt;10;If((_stage)<=60/dt;11;If((_stage)<=65/dt;12;If((_stage)<=70/dt;13;If((_stage)<=75/dt;14;If((_stage)<=80/dt;15;If((_stage)<=85/dt;16;If((_stage)<=90/dt;17;If((_stage)<=95/dt;18;If((_stage)<=100/dt;19;If((_stage)<=105/dt;20;21)))))))))))))))))))))

Risk functions

We analyzed screening strategies based on the Framingham CVD risk function, the Rotterdam CVD risk function, the extended Rotterdam CVD risk function, and the Rotterdam ΔQALY prediction rule, using different thresholds-above which treatment will be initiated- for each screening tool.

The Framingham CVD risk function

FHSCVD   1-(Exp(-(Exp(ref_base))))

ref_base   (Ln(5)-logitCVD_base)/(Exp(0.6536-(0.2402*logitCVD_base)))

logitCVD_base   18.8144-1.2146*fem-1.8443*Ln(age)+0.3668*Ln(age)*fem-1.4032*Ln(sbp)-
0.3899*smokecur-0.539*Ln(chol/hdl)-0.3036*dm-0.1697*dm*fem-0.3362*lvh

The Rotterdam CVD risk function

ERGO_CVDrisk 1-((0.9674^(Exp(0.9519*male+0.0409*age+0.4172*dm+0.8093*chol-
0.6772*hdl+0.1946*mifam+0.0153*sbp+1.6437*ht+0.3373*smoke+0.0801*smokecur+1.1703*ap+0.3931*claud-
0.0095*sbp*ht-0.0420*chol*chol-0.6283*ap*smoke-0.0043*ap*smokecur-8.18713645)))
*(0.9794^(Exp(0.2673*male+0.5614*age+0.5797*dm+0.0214*sbp+2.2329*ht+0.3466*smoke+0.3204*smokecur-
0.0140*sbp*ht+0.7958*tia-0.0033*age*age-26.08444535))))

The extended Rotterdam CVD risk function

ERGOCVDabiRisk   1-((0.9675^(Exp(0.9786*male+0.0364*age+0.3783*dm+0.7744*chol-
0.6604*hdl+0.1838*mifam+0.0136*sbp+1.5714*ht+0.3295*smoke+0.009*smokecur+1.1413*ap+0.2184*claud-
0.0091*sbp*ht-0.0401*chol*chol-0.6102*ap*smoke-0.0327*ap*smokecur-0.7797*abil-6.65822303)))
*(0.9794^(Exp(0.2829*male+0.5776*age+0.5615*dm+0.02*sbp+2.1938*ht+0.3396*smoke+0.2646*smokecur-
0.0139*sbp*ht+0.7756*tia-0.0034*age*age-0.5647*abil-25.8875747))))

Transition probabilities

The subjects-specific 0.1-year hazards were calculated as follows:

r (rate) = <u>one-cycle increment in baseline cumulative hazard</u> * *Exp(Log Hazard Equation)*

rdieCVD   <u>(h0cvdmort[((((_stage)-t_stagecount5*(5/dt))+1)*365.25*dt);p]-
h0cvdmort[((((_stage)-t_stagecount5*(5/dt)))*365.25*dt);p])</u>

(Exp(Bcvd[p;1]*ageMKV+Bcvd[p;2]*male+Bcvd[p;3]*dmMKV+Bcvd[p;4]*hdlMKV*medhist+Bcvd[p;5]*ht+Bcvd[p;6]*ht*ageMKV+Bcvd[p;7]*smoke+Bcvd[p;8]*medhist+Bcvd[p;9]*abilMKV+Bcvd[p;10]*abilMKV*abilMKV+Bcvd[p;11]*afMKV+Bcvd[p;12]*afMKV*male+Bcvd[p;13]*ageMKV*afMKV*afMKV+Bcvd[p;14]*male*medhist+Bcvd[p;15]*medhist*cholMKV*cholMKV-Bcvd[p;16]))

rDieOther   <u>(h0mortoth[((((_stage)-t_stagecount5*(5/dt))+1)*365.25*dt);p]-h0mortoth[((((_stage)-
t_stagecount5*(5/dt)))*365.25*dt);p])</u>

(Exp(Bmot[p;1]*male+Bmot[p;2]*ageMKV+Bmot[p;3]*dmgluc+Bmot[p;4]*cholMKVoth+Bmot[p;5]*smokecurMKV+Bmot[p;6]*smokecurMKV*ageMKV+Bmot[p;7]*bmiMKV+Bmot[p;8]*bmiMKV*ageMKV+Bmot[p;9]*whrMKV+Bmot[p;10]*whrMKV*ageMKV+Bmot[p;11]*whrMKV*medhist+Bmot[p;12]*famcvd+Bmot[p;13]*famcvd*ageMKV+Bmot[p;14]*abilMKV+Bmot[p;15]*abilMKV*ageMKV+Bmot[p;16]*medhist-Bmot[p;17]))

rIHD   <u>(h0ihd[((((_stage)-t_stagecount5*(5/dt))+1)*365.25*dt);p]-h0ihd[((((_stage)-
t_stagecount5*(5/dt)))*365.25*dt);p])</u>

(Exp(Bihd[p;1]*male+Bihd[p;2]*ageMKV+Bihd[p;3]*ageMKV*ageMKV+Bihd[p;4]*dmMKV*glucMKV+Bihd[p;5]*cholMKV+Bihd[p;6]*hdlMKV+Bihd[p;7]*ppMKV+Bihd[p;8]*ppMKV*male+Bihd[p;9]*apMKV+Bihd[p;10]*abilMKV+Bihd[p;11]*abilMKV*abilMKV+Bihd[p;12]*smokecurMKV+Bihd[p;13]*mifam+Bihd[p;14]*medhist+Bihd[p;15]*creatMKV-Bihd[p;16]))

rIHDfatal

<u>Bcfi[p;1]</u>*(Exp(Bcfi[p;2]*(age_at_IHD)+Bcfi[p;3]*dmMKV*glucMKV+Bcfi[p;4]*ht+Bcfi[p;5]*ht*(age_at_IHD)+Bcfi[p;6]*creatMKV-Bcfi[p;7]))*

<u>**rStroke** (h0stroke[((((_stage)-t_stagecount5*(5/dt))+1)*365.25*dt);p]-
h0stroke[((((_stage)-t_stagecount5*(5/dt)))*365.25*dt);p])</u>

(Exp(Bcva[p;1]*male+Bcva[p;2]*ageMKV+Bcva[p;3]*ht+Bcva[p;4]*ht*ageMKV+Bcva[p;5]*sbpMKV+Bcva[p;6]*smokecurMKV+Bcva[p;7]*mifam+Bcva[p;8]*tiaMKV+Bcva[p;9]*medhist+Bcva[p;10]*medhist*male+Bcva[p;11]*afMKV+Bcva[p;12]*abilMKV-Bcva[p;13])))

rStrokefatal   <u>Bcfc[p;1]</u>*
(Exp(Bcfc[p;2]*(age_at_stroke)+Bcfc[p;3]*smoke+Bcfc[p;4]*famcvd+Bcfc[p;5]*abilMKV+Bcfc[p;6]*cholMKVoth+Bcfc[p;7]*creatMKV+Bcfc[p;8]*hdlMKVoth+Bcfc[p;9]*abilMKV*abilMKV+Bcfc[p;10]*(age_at_stroke)*hdlMKVoth-Bcfc[p;11]))*

Then the hazards after aspirin therapy were calculated as:

hdieCVD   rdieCVD*Eff_asp_dieCVD [*(page 246)*] * t_T_Asp2 [*(page 247)*]

hDieOther   rDieOther+($DistSamp(64)$) [*(page 259)*] * dt * t_T_Asp2 [*(page 247)*]

hIHD   rIHD*Eff_asp_IHD [*(page 248)*] * t_T_Asp2 [*(page 247)*]

hIHDfatal   rIHDfatal

hStroke rStroke*Eff_asp_Stroke [*(page 248)*] * rStroke*t_T_Asp2 [*(page 247)*]

hStrokefatal   rStrokefatal

htot   hdieCVD + hDieOther + hIHD + hStroke

Subjects were targeted for treatment with aspirin based on age, absolute risk and systolic blood pressure (sbp) by using tracker-variables:

{T} t_T_Asp1   (If(age<=80&base_risk>cutoff&sbp<=180;1;0))*ST_asp[S]

{T} t_T_Asp2   If(t_T_Asp1=1;1;(If(ageMKV<=80&fup_risk>cutoff&
                 sbpMKV<=180;1;0)))*ST_asp[S]*(1-aspintol)

"base_risk" is the risk score as calculated by one of the four risk functions

"fup_risk" is the 5-yearly updated risk score

"cutoff" is the level of the risk score above which subjects should be treated

"ST_asp[S]" are preventive strategies in which aspirin is involved

S	Aspirin	Smoking cessation	Hypertensive medication	Cholesterol lowering drugs	Anti-diabetic medication
0	0	0	0	0	0
1	1	0	0	0	0
2	0	1	0	0	0
3	0	0	1	0	0
4	0	0	0	1	0
5	0	0	0	0	1
6	1	1	0	0	0
7	1	1	1	0	0
8	1	1	1	1	0
9	1	1	1	1	1

"aspintol" is the probability of aspirin intolerance as drawn from a binomial distribution (see "Distributions", page 259)

Effectiveness of interventions

Eff_asp_dieCVD	DistSamp(55)[¶]	= hazard ratio of aspirin for CVD mortality
Eff_asp_IHD	DistSamp(54)[¶]	= hazard ratio of aspirin for ischemic heart disease
Eff_asp_Stroke	DistSamp(56)[¶]	= hazard ratio of aspirin for ischemic stroke

(¶ See page 259 for distributions)

Adverse effects

{T} t_GIbleeding	DistSamp(36)[¶] * t_T_Asp2	= risk of gastro-intestinal bleeding
{T} t_HemorStroke	DistSamp(35)[¶] * t_T_Asp2	= risk of hemorrhagic stroke

(¶ See page 259 for distributions)

The transition probabilities are then calculated as follows:

pdieCVD = (hDieCVD/htot)*(1-Exp(-htot))

pDieOther = (hDieOther/htot)*(1-Exp(-htot))

pIHD = (hIHD/htot)*(1-Exp(-htot))

pIHDfatal = If(IHDcount<4;(1-Exp(-hIHDfatal));1)

pStroke = (hStroke/htot)*(1-Exp(-htot))

pStrokefatal = If(Strokecount<3;(1-Exp(-hStrokefatal));1)

pWell = Exp(-htot)

Within the IHD state, the proportions of CABG, PTCA and MI are calculated with the following polynomial regression functions: (t_CABG + t_MI + t_PTCA = 1)

{T} t_CABG

(Exp(bCABG[p;1]+bCABG[p;2]*male+bCABG[p;3]*(age+((_stage)*dt))+bCABG[p;4]*dmgluc+bCABG[p;5]*cholMKV+bCABG[p;6]*smokecurMKV+bCABG[p;7]*mifam+bCABG[p;8]*abilMKV+bCABG[p;9]*medhist+bCABG[p;10]*apMKV))/(1+(Exp(bPTCA[p;1]+bPTCA[p;2]*male+bPTCA[p;3]*(age+((_stage)*dt))+bPTCA[p;4]*dmgluc+bPTCA[p;5]*cholMKV+bPTCA[p;6]*smokecurMKV+bPTCA[p;7]*mifam+bPTCA[p;8]*abilMKV+bPTCA[p;9]*medhist+bPTCA[p;10]*apMKV))+(Exp(bCABG[p;1]+bCABG[p;2]*male+bCABG[p;3]*(age+((_stage)*dt))+bCABG[p;4]*dmgluc+bCABG[p;5]*cholMKV+bCABG[p;6]*smokecurMKV+bCABG[p;7]*mifam+bCABG[p;8]*abilMKV+bCABG[p;9]*medhist+bCABG[p;10]*apMKV)))

{T} t_MI

1/(1+(Exp(bPTCA[p;1]+bPTCA[p;2]*male+bPTCA[p;3]*(age+((_stage)*dt))+bPTCA[p;4]*dmgluc+bPTCA[p;5]*cholMKV+bPTCA[p;6]*smokecurMKV+bPTCA[p;7]*mifam+bPTCA[p;8]*abilMKV+bPTCA[p;9]*medhist+bPTCA[p;10]*apMKV))+(Exp(bCABG[p;1]+bCABG[p;2]*male+bCABG[p;3]*(age+((_stage)*dt))+bCABG[p;4]*dmgluc+bCABG[p;5]*cholMKV+bCABG[p;6]*smokecurMKV+bCABG[p;7]*mifam+bCABG[p;8]*abilMKV+bCABG[p;9]*medhist+bCABG[p;10]*apMKV)))

{T} t_PTCA

(Exp(bPTCA[p;1]+bPTCA[p;2]*male+bPTCA[p;3]*(age+((_stage)*dt))+bPTCA[p;4]*dmgluc+bPTCA[p;5]*cholMKV+bPTCA[p;6]*smokecurMKV+bPTCA[p;7]*mifam+bPTCA[p;8]*abilMKV+bPTCA[p;9]*medhi

st+bPTCA[p:10]*apMKV)/(1+(Exp(bPTCA[p:1]+bPTCA[p:2]*male+bPTCA[p:3]*(age+((_stage)*dt))+bPTC
A[p:4]*dmgluc+bPTCA[p:5]*cholMKV+bPTCA[p:6]*smokecurMKV+bPTCA[p:7]*mifam+bPTCA[p:8]*abilM
KV+bPTCA[p:9]*medhist+bPTCA[p:10]*apMKV))+(Exp(bCABG[p:1]+bCABG[p:2]*male+bCABG[p:3]*(age
+((_stage)*dt))+bCABG[p:4]*dmgluc+bCABG[p:5]*cholMKV+bCABG[p:6]*smokecurMKV+bCABG[p:7]*mif
am+bCABG[p:8]*abilMKV+bCABG[p:9]*medhist+bCABG[p:10]*apMKV)))

Hidden states

Within every state, subjects may suffer mild manifestations of cardiovascular disease which were modeled with tracker variables:

Probability	= Exp(linear predictor) /(1 + Exp(linear predictor))	
{T} t_AFrisk	regAF/(1+regAF)	risk of atrial fibrillation
{T} t_APrisk	regAP/(1+regAP)	risk of angina pectoris
{T} t_Claudrisk	regClaud/(1+regClaud)	risk of intermittent claudication
{T} t_DMrisk	regDM/(1+regDM)	risk of diabetes mellitus
{T} t_TIArisk	regTIA/(1+regTIA)	risk of transient ischemic attacks

{T} regAF   Exp(0.0101*ageMKV+0.0134*creatMKV-
0.0217*sbpMKVoth+0.0481*dbpMKV-8.6498*abilMKV-
0.3642*cholMKVoth+0.0994*abilMKV*ageMKV-2.3696)

{T} regAP   (Exp(0.39688*ageMKV-0.02256*dbpMKV-
0.21987*bmiMKV-0.74143*abilMKV-
0.00334*ageMKV*ageMKV+0.00364*ageMKV*bmiMKV+0.
42940*cholhdlr-0.02311*cholhdlr*cholhdlr-13.45753))

{T} regClaud   Exp(2.90669*male+0.38410*smokecurMKV
+0.016680*sbpMKV-0.02880*dbpMKV+0.521*abilMKV-
2.66828*abilMKV*abilMKV-
0.03303*male*dbpMKV+0.15763*cholhdlr-3.46832)

{T} regDM   Exp(0.099377*ageMKV+0.27387*smokecurMKV
+0.03079*creatMKV-0.00008561*creatMKV*creatMKV
+0.05498*sbpMKV-0.02851*dbpMKV+0.02111*bmiMKV-
- 0.70624*abilMKV+0.12664*cholhdlr-0.0004878*ageMKV*sbpMKV-12.52915)

{T} regTIA   Exp(0.03451*ageMKV+0.00815*sbpMKV-
0.01433*dbpMKV+0.11234*cholhdlr-6.06146)

Costs of events [1]

(from the National Institute for Public Health and the Environment, Johan Polder)

costs_CABG	DistSamp(45)*32390	= costs of procedure
cost_CABGppy	DistSamp(46)*((1-nursingCABG)*1000 +nursingCABG*Cost_nursingpy) = costs per patient per year after the procedure	
costs_PTCA	DistSamp(45)*11685	= costs of procedure
cost_PTCAppy	DistSamp(46)*(500*(1-nursingPTCA) +nursingPTCA*Cost_nursingpy) = costs per patient per year after the procedure	
cost_eventMI	DistSamp(48)*7260	= costs of event
cost_MIppy	DistSamp(46)*(1000*(1-nursingMI)+nursingMI*Cost_nursingpy) = costs of MI patient per year after the event	
cost_eventStroke	DistSamp(49)*7735	= costs of event
cost_Stroke	DistSamp(50)*(If(t_ayearsStroke<=1;39610;20970)) = costs of Stroke patient per year after the event	
cost_IHDStroke	DistSamp(46)*1000+cost_Stroke = costs of patient with MI and stroke per year after the event	
Cost_nursingpy	40000	= costs of nursing home per year
nursingCABG	DistSamp(52)	= proportion of patients in Nursing homes
nursingMI	DistSamp(59)	
nursingPTCA	DistSamp(63)	
cost_casefatality	DistSamp(47)*370 = costs of case-fatality	
cost_DieCVD	DistSamp(47)*2167	= costs of CVD mortality
cost_nonCVD	DistSamp(51)*(If(male=1;costDieOtherm[ageMKV]; CostDieOtherf[ageMKV])) = costs of non-CVD mortality including costs in preceding year	

Costs of interventions

(from the Dutch Health Care Insurance Board)

cost_Asp	18.89	= costs of aspirin prescription per person per year
cost_enalapril	199.06	= costs of enalapril per person per year
cost_Lipd	317.56	= costs of atorvastatin per person per year
cost_metoprolol	151.16	= costs of metoprolol per person per year
cost_smok	180.00	= costs of smoking cessation program per person per year
cost_Tolbutamin	33.65	= costs of tolbutamin per person per year

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[1] All costs are in euros 2002

Screening costs

(from the "Preventief Medisch Centrum", Rotterdam, dr. Dalmulder)

cS_abil	DistSamp(57)*8.50	
	= costs of measurement of ankle-brachial systolic blood pressure index	
cS_chol	DistSamp(57)*3.68 = costs of cholesterol measurement	
cS_ecg	DistSamp(57)*4;25 = costs of public electrocardiogram	
cS_gluc	DistSamp(57)*1.27 = costs of glucose measurement	
cS_GP	22.00 = costs of general practitioner appointment	
cS_overhead	DistSamp(58)*26 = overhead costs per patient per year	
cS_time	DistSamp(53)*5 = time costs for patient	
cS_travel	DistSamp(53)*2.80 = travel costs for patient	

Friction costs[1]

Fcosts4   Fcosts4[ageMKV;male+1]

= costs associated with production losses for the friction period of 4 months

Age	Female	Male
55	1815	9348
57	1815	9348
62	545	3903
65	0	0

fcostsCABG	Fcosts4* DistSamp(60)*0.50	friction time = 2 months
fcostsDie	Fcosts4* DistSamp(60)*0.25	friction time = 1 month
fcostsMI	Fcosts4* DistSamp(60)*0.6	
fcostsPTCA	Fcosts4* DistSamp(60)*0.3	
fcostsStroke	Fcosts4* DistSamp(60)*1.0	friction time = friction period = 4 months

cost_Screen   = cS_GP + cS_overhead + cS_travel + cS_time + (Fcosts4/2880) + cS_chol + cS_gluc + cS_abil + cS_ecg)

PrevCosts   = (t_T_Asp2*cost_Asp)+(t_T_chol2*cost_Lipd)+(t_T_dm2 *cost_Tolbutamin)+(t_T_ht2*(If(dmMKV=1;cost_enalapril;cost_meto prolol))+(t_T_smoke2*cost_smok)

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[1] Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ 1995;14:171-89.

Transition costs   = onetime costs

CVD MORTALITY
UtilDiscount(cost_DieCVD+fcostsDie;discRATE*dt;_stage)

NON-CVD MORTALITY
UtilDiscount(cost_nonCVD+fcostsDie;discRATE*dt;_stage)

IHD
UtilDiscount((t_MI*(Cost_eventMI+fcostsMI)+t_PTCA*(costs_PTCA+fcostsPTCA)+t_CABG*(Costs_CABG+f
costsCABG));discRATE*dt;_stage)

STROKE
UtilDiscount(cost_eventStroke+fcostsStroke;discRATE*dt;_stage)

FATAL EVENT
UtilDiscount(cost_casefatality+fcostsDie;discRATE*dt;_stage)

Utilities   (ref. Bell, Chapman, Neumann)

uWell   Min(uAlive;uOther)

uAlive   If(male=1;utility_men[ageMKV];utility_women[ageMKV])[1]:

utility_men[ageMKV]		utility_women[ageMKV])	
0	1	0	1
45	0.94	45	0.90
55	0.87	55	0.87
65	0.84	65	0.83
75	0.84	75	0.79
85	0.82	85	0.80

uOther   {1.0-(1- u_HemorStroke)*t_HemorStroke)*(1.0-(1- u_GIbleeding)
                *t_Gibleeding} *{Min(uAP;uDM;uPAD; uTIA)}

uAP	If(apMKV=1;DistSamp(41);1)	utility for angina pectoris
uDM	If(dmMKV=1;DistSamp(42);1)	utility for diabetes mellitus
uPAD	If(claudMKV=1;DistSamp(43);1)	utility for intermittent claudication
uTIA	If(tiaMKV=1;DistSamp(44);1)	utility for transient ischemic attacks

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[1] Fryback DG, Dasbach EJ, Klein R, Klein BE, Dorn N, Peterson K, et al. The Beaver Dam Health
Outcomes Study: initial catalog of health-state quality factors. Med Decis Making 1993;13(2):89-102.

| u_GIbleeding | DistSamp(61) | utility for gastro-intestinal bleed |
| u_HemorStroke | DistSamp(62) | utility for hemorrhagic stroke |

uMI	(If((ageMKV-age_at_IHD)<1.0;DistSamp(27);DistSamp(39)))*uWell
uCABG	DistSamp(37)*uWell
uPTCA	DistSamp(38)*uWell
uStroke	(If(majorstroke=1;DistSamp(28);DistSamp(40)))*uWell
uIHDStroke	DistSamp(39)*uStroke

INCREMENTAL REWARDS

= yearly, accumulating effects / costs

WELL STATE

INCREMENTAL EFFECT
UtilDiscount(uWell*dt;discRATE*dt;_stage)

INCREMENTAL COSTS
UtilDiscount((cost_Screen*t_treat+PrevCosts+cost_nonCVD+(Cost_nursingpy*t_HemorStroke))*dt;discRATE*dt;_stage)

| *cost_Screen* | = cS_GP + cS_overhead + cS_travel + cS_time + (Fcosts4/2880) + cS_chol + cS_gluc + cS_abil + cS_ecg) |
| *PrevCosts* | = (t_T_Asp2*cost_Asp)+(t_T_chol2*cost_Lipd)+(t_T_dm2 *cost_Tolbutamin)+(t_T_ht2*(If(dmMKV=1;cost_enalapril;cost_meto prolol))+(t_T_smoke2*cost_smok) |

IHD STATE

INCREMENTAL EFFECT
UtilDiscount((t_MI*uMI+t_CABG*uCABG+t_PTCA*uPTCA)*dt;discRATE*dt;_stage)

INCREMENTAL COSTS
UtilDiscount((t_MI*cost_MIppy+t_PTCA*cost_PTCAppy+t_CABG*cost_CABGppy+cost_nonCVD)*dt;discRATE*dt;_stage)

STROKE STATE

INCREMENTAL EFFECT
UtilDiscount(uStroke*dt;discRATE*dt;_stage)

INCREMENTAL COSTS
UtilDiscount((cost_Stroke+cost_nonCVD)*dt;discRATE*dt;_stage)

IHD&STROKE STATE

INCREMENTAL EFFECT
UtilDiscount(uIHDStroke*dt;discRATE*dt;_stage)

INCREMENTAL COSTS
UtilDiscount((cost_IHDStroke+cost_nonCVD)*dt;discRATE*dt;_stage)

UNCERTAINTY & VARIABILITY

Variability within the population (or heterogeneity) was modeled by simulating every individual subject (x) from the source population separately. Since individual subjects with their entire risk factor profiles were simulated, correlations between the risk factors were taken into account.

Parameter values in the RISC model, such as the transition probability functions, effects and adverse effects of aspirin use, utilities and costs for the various disease states are estimated and therefore uncertain. The utilization of Monte Carlo simulation gives us the opportunity to study uncertainty by using random number generation and distribution sampling. In the second-order Monte Carlo simulation the parameter uncertainty results in a population mean with standard error.

To model the uncertainty in the transition probability functions, 100 bootstrap samples of the study population were drawn. All the transition probability functions were fitted for every bootstrap sample, resulting in 100 sets of linked transition probability functions (p).

Costs of both interventions and CVD events were varied by ± 30% absolute change around the mean value (see page 260). Utilities were modeled as ranging from the lowest to the highest value as described in the Catalog of Preference Scores (see page 260).

For the effects of interventions these distributions were varied by the 95% confidence interval as published in the article of Law and Wald. (Table 1) Adverse effects were modeled with an arbitrary range around the values published. (Table 2)

Table 1. **Effectiveness of each of the components of the Polypill.**

Hazard ratios indicate the relative risk reductions.

ASPIRIN	Hazard Ratio	Distribution	μ	σ
Ischemic Heart Disease	0.68	lognormal	-0.3879	0.067
Stroke	0.84	lognormal	-0.1759	0.055

STATINS		Distribution	μ	σ
Ischemic Heart Disease	0.39	lognormal	-0.9514	0.14
Stroke	0.83	lognormal	-0.1876	0.05

ANTIHYPERTENSIVES		Distribution	μ	σ
Ischemic Heart Disease	0.54	lognormal	-0.6183	0.065
Stroke	0.37	lognormal	-0.9998	0.105

FOLIC ACID		Distribution	μ	σ
Ischemic Heart Disease	0.84	lognormal	-0.1748	0.031
Stroke	0.76	lognormal	-0.2763	0.061

ref. MR Law et al., BMJ 2003

Table 2. **Adverse effects of each of the components of the "Polypill".**

ASPIRIN	Mean	Minimum	Maximum
(yearly rates)			
Aspirin intolerance	0.057	0.053	0.060
Hemorrhagic stroke (non-fatal)	0.00004	0.00003	0.00005
Gastro-intestinal bleed (non-fatal)	0.000616	0.000600	0.000632
Increased non-CVD mortality	0.000144	0.0001008	0.0001872

STATINS			
Utility* (quality of life)	0.9875	0.980	0.995

ANTIHYPERTENSIVES			
Utility* (quality of life)	0.9875	0.980	0.995

EFFECTS FOLIC ACID			
No adverse effects		-	-

ref. M. Hayden et al., Annals of Internal Medicine, 2002
ref. Campbell, MDM 2000

DISTRIBUTIONS

DistSamp	DATASETS	DISTRIBUTION	RANGE			SAMPLING
1	*ERGO*	*uniform*	*1*		*3501*	*per patient*
2	*NHANES*	*triangular*	*1*		*11327*	*per patient*
3	*Bootstraps*	*uniform*	*1*		*100*	*per group of patients*
4	*ERGO6871*	*uniform*	*1*		*6871*	*per patient*
	VARIABLES					
5	abi	normal	age and sex dependent			per patient
6	whr	normal	"			per patient
7	gluc	normal	"			per patient
8	chol	normal	"			per patient
9	famcvd	binomial	"			per patient
10	smoke	binomial	"			per patient
11	smokecur	binomial	"			per patient
12	dbp	normal	"			per patient
13	tia	binomial	"			per patient
14	dm	binomial	"			per patient
15	af	binomial	"			per patient
16	ht	binomial	"			per patient
17	sbp	normal	"			per patient
18	mifam	binomial	"			per patient
19	ap	binomial	"			per patient
20	bmi	normal	"			per patient
21	medhistm	binomial	"			per patient
22	creat	normal	"			per patient
23	hdl	normal	"			per patient
24	medhistf	binomial	"			per patient
25	claud	normal	"			per patient
29	% major stroke	binomial	0.5		1	per patient
30	*af*	*binomial*	*regression functions*			*per patient, per Markov stage*
31	*dm*	*binomial*	*regression functions*			*per patient, per Markov stage*
32	*ap*	*binomial*	*regression functions*			*per patient, per Markov stage*
33	*tia*	*binomial*	*regression functions*			*per patient, per Markov stage*
34	*claud*	*binomial*	*regression functions*			*per patient, per Markov stage*
54	effect aspirin IHD	lognormal	-0.3338086		0.103	per group of patients
55	effect aspirin CVD-mortality	lognormal	-0.1452026		0.109	per group of patients
56	effect aspirin Stroke	lognormal	-0.00213783		0.125	per group of patients
26	aspintol	binomial	0.054		0.06	per patient
35	hemorrhagic stroke	binomial	0.00003		0.00005	per patient
36	GI bleed	binomial	0.0006		0.000632	per patient
64	increased non-CVD mortality	uniform	0.0001008		0.0001872	per group of patients
52	% nursing CABG	binomial	0.006		0.01	per patient
59	% nursing MI	binomial	0.05		0.15	per patient
63	% nursing PTCA	binomial	0.02		0.04	per patient

	UTILITIES				
27	uMI first year	uniform	0.7	0.9	per group of patients
28	uStroke major	uniform	0.2	0.4	per group of patients
37	u CABG	uniform	0.917	0.973	per group of patients
38	u PTCA	uniform	0.981	0.995	per group of patients
39	u MI sq years	uniform	0.9	0.98	per group of patients
40	u Stroke minor	uniform	0.75	0.8	per group of patients
41	u AP	uniform	0.7	0.8	per group of patients
42	u DM	uniform	0.83	0.9	per group of patients
43	u PAD	uniform	0.6	0.85	per group of patients
44	u TIA	uniform	0.77	0.8	per group of patients
61	u GIbleed	uniform	0.8	0.95	per group of patients
62	u HemStroke	uniform	0.2	0.4	per group of patients
	COSTS		*cprop = 0.3*		
45	coronary interventions	uniform	0.7	1.3	per group of patients
46	policlinical	uniform	0.7	1.3	per group of patients
47	death	uniform	0.7	1.3	per group of patients
48	MI event	uniform	0.7	1.3	per group of patients
49	Stroke event	uniform	0.7	1.3	per group of patients
50	stroke patient	uniform	0.7	1.3	per group of patients
51	non-CVD costs	uniform	0.7	1.3	per group of patients
53	time-and travel costs	uniform	0.7	1.3	per group of patients
57	target tools	uniform	0.7	1.3	per group of patients
58	overhead costs	uniform	0.7	1.3	per group of patients
60	friction time	uniform	0.7	1.3	per group of patients

APPENDIX 4: THE ROTTERDAM ΔQALY PREDICTION RULE

a prediction rule to determine the quality-adjusted life years (QALYs) that can be gained with aspirin therapy based on CVD risk indicators

ΔQALY =

male*0.02335995987859

+ age*0.00690295313237

- age*age*age*0.0000005909702440229

+ diabetes*0.02534184097909

+ glucose*0.01945786010316

- pulse pressure*0.0018584323831

- current smoking*0.01625017652518

+ smoking*0.08872856504431

- body mass index*0.004103481337158

- waist-hip ratio*0.1293188157561

+ family history of MI*0.01407501539683

+ ankle-arm index*0.0289142121011

+ cholesterol-HDL ratio*0.01359453323971

+ hypertension*0.1277460441602

- male*age*0.0002363527911965

- male*pulse pressure*0.0005863340006238

+ male*family history of MI*0.04411584470863

+ male*cholesterol-HDL ratio*0.008011455253458

- age*glucose*0.0002568471322575

- age*smoking*0.0007506500729954

+ age*ankle-arm index*0.003337178223863

- age*cholesterol-HDL ratio*0.00002313363518533

- age*hypertension*0.001250024372499

+ pulse pressure*pulse pressure*0.00001860926553077

+ body mass index*body mass index*0.0001409298800608

- ankle-arm index*ankle-arm index*0.1600049945916

+ cholesterol-HDL ratio*cholesterol-HDL ratio*0.0009075223234744

- 0.2245322189384.

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Rogier.

About the author

Rogier Laurens Nijhuis was born on March 22nd 1973 in Oldenzaal, the Netherlands. In June 1991, he graduated from the Bernardinus college in Heerlen (Gymnasium B). He started his medical studies at the Katholieke Universiteit Nijmegen. After he finished his medical study in 1998, he started working as a cardiology resident in the Medisch Spectrum Twente in Enschede. In 2000 he started the work described in this thesis at the department of Epidemiology & Biostatistics of the Erasmus MC, University Medical Center, in Rotterdam (head: Prof.dr. A. Hofman). During his research he was trained as a clinical epidemiologist at the Netherlands Institute for Health Sciences and in 2002 he received his Master of Science in Clinical Epidemiology. In 2002 he was appointed as a visiting fellow at Department of Medicine, University of California, San Francisco, USA, where he worked from September until December 2002. Januari 2004 he started his training as a cardiologist at the Thoraxcenter (head: Prof.dr. ML Simoons), which includes a two years residency at the department of internal medicine of the Sint Franciscus Gasthuis in Rotterdam. He is married to Karen Fenna Meeske and has a son, Lukas Jesse.