Evaluating Strategies for the Primary Prevention of Cardiovascular Disease

Bob Johannes Hendrikus van Kempen

501599-L-bw-van Kempen

Evaluating Strategies for the Primary Prevention of Cardiovascular Disease

Dissertation, Erasmus University, Rotterdam, the Netherlands

ISBN	978-94-028-0019-7
Author	Bob Johannes Hendrikus van Kempen
Layout	A.W. Everaers (concept lay-out), Legatron Electronic Publishing (production lay-out)
Cover design	A.W. Everaers
Print	Ipskamp Drukkers, Enschede

Financial support for the printing of this thesis was provided by:
The Departments of Radiology and Epidemiology of the Erasmus Medical Center, the Erasmus University Rotterdam

'Ik heb niets te verbergen' – Giuseppe Verdi aan Antonio Barezzi, 1852

Omslag: foto Bernd Uhlig. Still from 'La Traviata', productie van Andrea Breth voor Operahuis La Monnaie, Brussel 2012.

Evaluating Strategies for the Primary Prevention of Cardiovascular Disease

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
Dinsdag 26 januari 2016 om 15:30 uur.

door

Bob Johannes Hendrikus van Kempen
geboren te Vlijmen

Erasmus University Rotterdam

501599-L-bw-van Kempen

Promotiecommissie:

Promotoren:	Prof.dr. M.G.M. Hunink
Overige leden:	Prof.dr. K.E. Fleischmann Prof.dr. E.W. Steyerberg Prof.dr. J.W. Deckers

Contents

Chapter 1

Introduction

In a nutshell:

Prevention of cardiovascular disease (CVD) comprises one of the biggest healthcare challenges in modern Western society [1]. Tremendous efforts have been made to discover new risk markers beyond the well-known traditional Framingham risk factors in order to identify individuals at high risk of a future occurrence of a CVD event [2]. Perhaps even greater efforts have been made to evaluate drug treatment therapies to prevent CVD events in such individuals [3-6]. Both at the population level (i.e. is a preventive intervention beneficial to a group of individuals, against acceptable costs for society?), and at the individual level (for which specific individual can we expect a preventive intervention to be beneficial?), decision modelling can provide significant insights into these complex decision problems, when trial-based evidence is either lacking, takes too much time or is infeasible.

To elaborate on that:

Approximately one out of every three deaths is attributable to cardiovascular disease which makes it the number 1 cause of death throughout the world [1]. WHO statistics revealed that CVD killed 17.5 million people in 2012 -of these, 7.4 million died of ischaemic heart disease, the remaining 6.7 million died of stroke [7]. A number of -commonly well known, modifiable physiological and behavioural risk factors -such as high blood pressure, increased levels of cholesterol and smoking, have been identified and it has been established that they play a causal role in the aetiology of the disease [8]. Targeting individuals by using these risk factors and preferentially modifying them in individuals with unfavourable levels of these factors, can reduce the future risk of CVD within these individuals, even if they do not have overt symptoms of the disease yet or have ever experienced a CVD event before.

In general, prevention can be achieved by either shifting the distribution of a modifiable risk factor for a population as a whole or targeting and treating the individuals with the highest levels of the risk factor -as described by Geoffrey Rose [9]. As efficacious and efficient some population based strategies sometimes may seem -exemplified by the projected reduction in deaths attributable to CVD by reducing the daily intake of salt [10], their effectiveness sometimes fades in the face of implementation in reality [11]. Correspondingly, most guidelines on prevention of CVD in Western societies incorporate some form of an individualized risk-based approach [12-16]. As an elaborate example, initiation of statins is currently recommended if the future risk of CVD surpasses the (rather arbitrarily picked) threshold of 7.5% within 10 years. Below that level, initiation of statins is only recommended if the level of low density lipoprotein cholesterol (LDL) is exceedingly high. In the case of statins, most side effects are considered fairly mild, and serious side effects rare [17]. Considering aspirin, however, there is a clear trade-off. On the one hand it reduces the risk of future heart disease and ischemic stroke, while at the same time it increases the risk of a -possibly fatal, episode of major bleeding [18]. In this case, a precise and correct estimate of the net benefit of the preventive intervention in an individual-weighing both the potential gain in life expectancy due to a lower risk of heart disease and ischemic stroke, and the potential decrease in life expectancy due to

higher risk of major bleeding, is of utmost importance. The main determinant of this net benefit is the risk of the CVD event one tries to prevent. For years, the Framingham risk factors -calendar age, smoking status, total cholesterol level, systolic blood pressure, use of anti-hypertensive medication and diabetes mellitus status, have been used to estimate the risk of a future CVD event [2, 19-21] and are incorporated in risk scores used in guidelines as mentioned before. These risk factors are well established, used worldwide and are relatively easy and inexpensive to obtain.

During the last decades, 'novel' or 'non-traditional' markers of future cardiovascular risk have become available, and allow for detection of subclinical atherosclerotic disease or provide measures of general systemic inflammation. These novel risk markers have been shown to improve the prediction of future CVD risk beyond the traditional Framingham risk factor based scores [3]. It has even been shown that -dependent on the distribution of the novel risk marker and the concordant distribution in traditional risk factors within a certain population, the estimated future risk of CVD within individuals changes based on the additional information in the novel risk marker, to the extent that a number of these individuals will now surpass a risk-based threshold used in prevention guidelines as mentioned before, compared to the 'old' or 'current' situation in which only the traditional risk factors were used. Improved classification of an individual's future CVD risk suggests that -by using the novel marker, we would be better able to estimate an individual's net benefit of initiating preventive treatment, and by doing so more adequately inform a patient about whether or not to initiate therapy based on his or her unique characteristics. But the improvement in (correct) classification due to a novel risk marker in itself is not sufficient to prove that we actually *should* use it [22]. Some of the novel risk markers are costly or bear harms in itself, i.e. due to an associated radiation induced increased risk of future cancer as a result of the technical modality used to obtain the result of a novel risk marker. The challenge at hand is to evaluate the impact of using novel risk markers, from the perspective of a decision maker. The latter can be the government of a country, which has to decide if it should implement a novel risk marker as a screening instrument in order to prevent CVD in its population. It's not enough to project the number of CVD events avoided, as by lowering the risk for a single cause of death, another 'competing' cause of death is given the opportunity to take its place [23]. Some events will cause a chronic state with reduction in quality of life, some events will induce lifelong substantial increases in medical expenditures. All of these aspects have to be evaluated simultaneously in order to correctly inform a decision maker.

The one facing the decision can also be an individual sitting in front of a practitioner's desk, who may not be interested in novel risk markers, but wants to know what he or she is expected to gain from the (currently, traditional risk factor based) recommended initiation and continuation of taking medication such as statins daily for the rest of his or her life. If a patient brings his own preferences and characteristics into the equation, it may not be sufficient to inform the individual patient's decision on averaged, population-level results.

Ideally, clinical trials would inform us about the optimal decision in both cases. But -in an attempt to address the value of novel risk markers at the population-level decision, trials typically cover a relatively short period of follow up and include a limited number of trial arms, due to feasibility issues. For the decision at the individual level, the number of possible combinations of an individual patient's characteristics and preferences will be limitless, and therefore impossible to evaluate in a trial setting. By synthesizing all available information on all relevant parameters -including distributions of traditional and novel risk markers and their correlations within a population, treatment effects of cardio-protective medication, risks of competing events, and by extrapolating short term results, decision modelling can overcome the boundaries of trial-based studies.

In this thesis, strategies for the primary prevention of cardiovascular disease, based on risk assessment and early detection of subclinical cardiovascular disease, were evaluated by such decision models.

In order to adequately synthesize evidence and evaluate interventions based on cardiovascular risk assessment, we studied 1) the (individualized) underlying truth in decision models, based on long-term CVD risk predictions and their improvement using novel risk markers; 2) the validity of and critical assumptions underlying decision models and their relation to the outcome of such models and finally; 3) the comparative effectiveness and cost-effectiveness of guiding preventive (medical) treatment based on risk-stratification using both established risk scores and novel risk markers.

More specifically, in **chapter 2**, the comparative effectiveness and cost-effectiveness of computed tomography screening for coronary artery calcium -one of the promising novel risk markers for CVD, was studied using a population level decision model based on Rotterdam Study data [24]. **Chapter 3** addressed the validity of a previously developed individual level simulation model to investigate the effects of modifying cardiovascular disease risk factors on the burden of CVD: the Rotterdam Ischemic heart disease and Stroke (RISC) model [25]. In **chapter 4**, we evaluated the influence of using different methods of modelling statin treatment effectiveness on the outcomes of a decision model. In **chapter 5**, we used the RISC model to predict personalized lifetime benefits of statin therapy in asymptomatic individuals. In **Chapter 6** we analysed the performance of long-term Framingham cardiovascular disease predictions [21] in the Rotterdam Study, taking into account competing risks and the additional disentangling of CVD into coronary heart disease and stroke separately. Using similar methodology, **Chapter 7** studied the separate prediction of intracerebral hemorrhage and ischemic stroke – again taking into account competing risks.

Focussing on the United States general population using data from the National Health and Nutrition Examination Survey (NHANES) -a cross-sectional study designed to be a representative sample of the U.S. general population, **Chapter 8** dealt with the evaluation of the added predictive value of four novel risk markers of CVD beyond the Framingham based risk scores, using a new micro-simulation model. In **Chapter 9** this

model was extended to compare the cost-effectiveness of these four novel risk markers for screening asymptomatic individuals in the U.S. population. **Chapter 10** evaluated the trade-off between future CVD risk and the disutility of lifelong daily medication in the comparative effectiveness and cost-effectiveness of initiating statin therapy for the primary prevention of CVD events. Finally, in **Chapter 10** the main findings of this thesis were summarized. We additionally discussed the methodological issues that have been raised in these research projects and provided future perspectives for further research.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart Disease and Stroke Statistics--2013 Update: A Report From the American Heart Association. Circulation. 2013;127(1):e6-e245.
2. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-47.
3. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012;308(8):788-95.
4. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581-90.
5. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;1:CD004816.
6. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. Bmj. 2009;338:b1665.
7. WHO. 2014.
8. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224-60.
9. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985;14(1):32-8.
10. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med. 2010;362(7):590-9.
11. Marrero NM, He FJ, Whincup P, Macgregor GA. Salt intake of children and adolescents in South London: consumption levels and dietary sources. Hypertension. 2014;63(5):1026-32.
12. Force USPST. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;150(6):396-404.
13. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr., Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110(2):227-39.
14. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, 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. 2002;106(3):388-91.
15. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013.
16. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Sr., Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013.
17. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. 2006;97(8A):52C-60C.
18. Berger JS, Lala A, Krantz MJ, Baker GS, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. Am Heart J. 2011;162(1):115-24 e2.
19. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P, Group CHDRP. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001;286(2):180-7.

20. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.

21. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation. 2009;119(24):3078-84.

22. Cook NR, Ridker PM. Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. Ann Intern Med. 2009;150(11):795-802.

23. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26(11):2389-430.

24. Hofman A, Darwish Murad S, van Duijn CM, Franco OH, Goedegebure A, Ikram MA, et al. The Rotterdam Study: 2014 objectives and design update. Eur J Epidemiol. 2013;28(11):889-926.

25. Nijhuis RL, Stijnen T, Peeters A, Witteman JC, Hofman A, Hunink MG. Apparent and internal validity of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow-up study. Med Decis Making. 2006;26(2):134-44.

Chapter 2

Comparative Effectiveness and Cost-Effectiveness of Computed Tomography Screening for Coronary Artery Calcium in Asymptomatic Individuals

Bob J. H. van Kempen
Sandra Spronk
Michael T. Koller
Suzette E. Elias-Smale
Kirsten E. Fleischmann
M. Arfan Ikram
Gabriel P. Krestin
Albert Hofman
Jacqueline C. M. Witteman
M. G. Myriam Hunink

(J Am Coll Cardiol 2011;58:1690–701)

ABSTRACT

Objectives: The aim of this study was to assess the (cost-) effectiveness of screening asymptomatic individuals at intermediate risk of coronary heart disease (CHD) for coronary artery calcium with computed tomography (CT).

Background: Coronary artery calcium on CT improves prediction of CHD.

Methods: A Markov model was developed on the basis of the Rotterdam Study. Four strategies were evaluated: 1) current practice; 2) current prevention guidelines for cardiovascular disease; 3) CT screening for coronary calcium; and 4) statin therapy for all individuals. Asymptomatic individuals at intermediate risk of CHD were simulated over their remaining lifetime. Quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios were calculated.

Results: In men, CT screening was more effective and more costly than the other 3 strategies (CT vs. current practice: 0.13 QALY [95% confidence interval (CI): 0.01 to 0.26], $4,676 [95%CI: $3,126 to $6,339]; CT vs. statin therapy: 0.04 QALY [95%CI : 0.02 to 0.13], $1,951 [95%CI : $1,170 to $2,754]; and CT vs. current guidelines: 0.02 QALY [95%CI: 0.04 to 0.09], $44 [95%CI: $441to$486]).The incremental cost-effectiveness ratio of CT calcium screening was $48,800/QALY gained. In women, CT screening was more effective and more costly than current practice (0.13 QALY [95%CI: 0.02 to 0.28], $4,663 [95%CI: $3,120 to $6,277]) and statin therapy (0.03 QALY [95%CI: 0.03 to 0.12], $2,273 [95%CI: $1,475 to $3,109]). However, implementing current guidelines was more effective compared with CT screening (0.02 QALY [95%CI: 0.03 to 0.07]), only a little more expensive ($297 [95%CI: $8 to $633]), and had a lower cost per additional QALY ($33,072/QALY vs. $35,869/QALY). Sensitivity analysis demonstrated robustness of results in women but considerable uncertainty in men.

Conclusions: Screening for coronary artery calcium with CT in individuals at intermediate risk of CHD is probably cost-effective in men but is unlikely to be cost-effective in women.

INTRODUCTION

In asymptomatic individuals, primary prevention of coronary heart disease (CHD) is often based on the predicted 10-year risk of a CHD event. The Framingham risk factors are widely adopted for this purpose [1-2]. Guidelines on cardiovascular disease (CVD) prevention recommend advice on a healthy lifestyle (e.g. smoking cessation, regular physical activity)) for individuals with a low CHD risk (<10%, 10-year risk) supplemented by statins, anti-hypertensives, and sometimes aspirin for individuals at high CHD risk (>20%, 10-year risk) [3-5]. In individuals at intermediate risk (10-20%, 10-year risk) the decision to treat with drugs is generally only recommended when either serum cholesterol or blood pressure levels are above a defined threshold. In this group, performing a non-invasive test may be able to identify those who could benefit from more aggressive treatment. Coronary artery calcium on computed tomography (CT), quantified by the CT coronary calcium score, is such a test [6-7].

Recent studies have demonstrated that the CT calcium score is a strong predictor of CHD risk, independent of the Framingham risk factors [7-16]. In fact, more than half of the individuals originally classified at intermediate risk, based on the Framingham risk factors, are reclassified to the high (>20%) or low (<10%) risk category when the calcium score is taken into account [7,17]. Accordingly, these individuals should be treated more aggressively (high risk) or less aggressively (low risk). The reclassification to another risk category suggests that using CT may be beneficial but reclassification by itself is insufficient evidence to justify implementation [18-19]. Studies, ideally clinical trials, demonstrating comparative effectiveness and cost-effectiveness are necessary.

In the absence of clinical trials showing the benefit of CT screening, an extensive evaluation of CT coronary calcium scoring using observational data is warranted [20]. The objective of this study was to assess the comparative effectiveness and cost-effectiveness of screening an asymptomatic elderly population at intermediate risk for CHD for coronary calcium with CT.

METHODS

We developed a Markov decision model using TreeAge for Health Care (TreeAge Pro 2009 – TreeAge Software Williamstown MA) to analyze relevant strategies in asymptomatic elderly individuals at intermediate risk for CHD. The model structure, model parameters, and data sources are briefly described here. Details of the modeling assumptions and parameter estimation are given in a technical appendix.

Model structure

The following four strategies were considered (Figure 1):

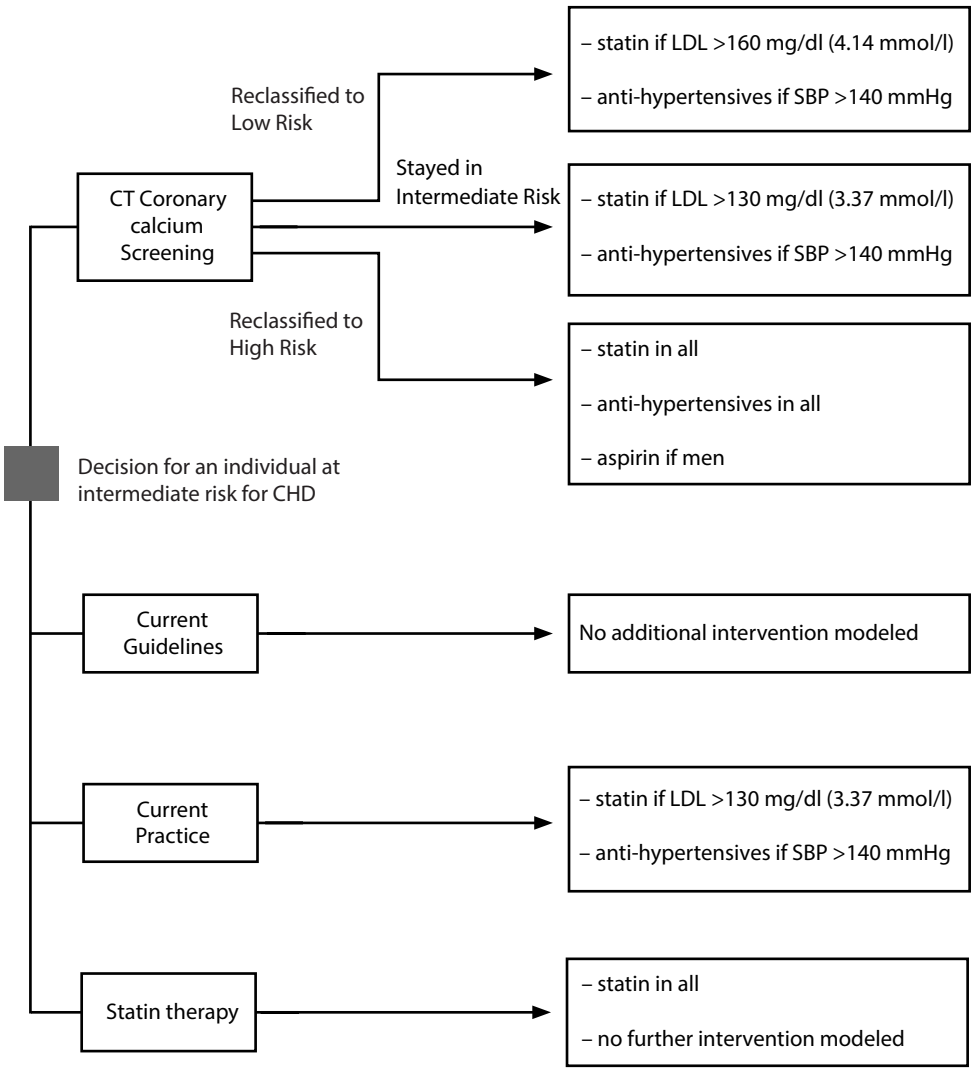


Figure 1. Schematic representation of the four alternative strategies for an individual at intermediate risk for CHD

(1) 'Current practice'. This strategy reflects the incidence of CHD and non-CHD events of individuals at intermediate risk without any additional preventive intervention, as observed in the Rotterdam Study and is used as the reference strategy. Some individuals were treated at baseline with statins, anti hypertensive medication or aspirin by their general practitioners, which is considered to be reflected in the observed incidence of CHD and stroke,
(2) 'Current guidelines'. This strategy, based on fully implementing the most recent guidelines on primary prevention of CHD for individuals at intermediate risk for CHD, implies giving lifestyle advice to all, statin therapy when baseline low density lipoprotein (LDL) cholesterol exceeds 130 mg/dL (3.37 mmol/l) [4], and anti-hypertensive medication when baseline systolic blood pressure exceeds 140 mmHg [5]. In a sensitivity analysis, we lowered the LDL threshold to 100 mg/dL (2.59 mmol/L)
(3) 'CT calcium screening'. In this strategy a CT scan was performed to determine the coronary calcium score and the 10-year CHD risk was recalculated based on the Framingham risk factors and the calcium score combined. Consequently, a number of individuals will be reclassified to the high risk or low risk category. Individuals reclassified to the low risk category received life style advice and pharmacological treatment if systolic blood pressure was above 140 mm Hg (21) and/or plasma LDL levels were >160 mg/dL (4.14 mmol/l) [4]. Individuals who remained in the intermediate risk category were treated as recommended for individuals at intermediate risk, similar to strategy 2. Individuals reclassified to the high risk group received lifestyle advice, statin therapy, and anti-hypertensive medication, irrespective of their baseline cholesterol and blood pressure levels. In addition, men received low dose aspirin (80-100 mg daily). For both the current guidelines and CT calcium screening strategy, we assumed that individuals who used any of the three drugs at baseline, would continue to use them.
(4) 'Statin therapy'. For this strategy we assumed that everyone not currently on a statin would receive a moderate dose statin and was otherwise managed according to 'current practice'. Although initiating statins in all individuals is not always considered feasible in all situations, it puts the CT calcium screening strategy into a broader perspective, between the least aggressive strategy ('current practice') and fairly aggressive strategy ('statin therapy'), providing a range of possibilities for an individual at intermediate risk of CHD [20]. Conceptually, an even more aggressive strategy would be to treat everyone not only with statins, but also with anti-hypertensives and aspirin (in men). In a sensitivity analysis we substituted the statin therapy strategy with this 'aggressive medical treatment' strategy.

For each of the four strategies, the model kept track of quality of life, costs and time spent in one of the following health states: (a) well; (b) post CHD event; (c) post-major bleeding; (d) post stroke event; (e) post stroke event & CHD event; (f) post stroke & major bleeding ; (g) post CHD event & major bleeding; (h) post CHD event & stroke event & major bleeding (i) CHD or stroke death; and (j) non-CHD or non-stroke death. Each simulated individual started out in the 'well' state. Age- and gender-specific probabilities

of non-CHD death, fatal- and non-fatal MI, fatal- and non-fatal major bleeding due to aspirin use, fatal and non-fatal stroke and lethal cancer due to radiation, determined the transition to the other states during each annual cycle. The time horizon was the remaining lifetime of the simulated individuals.

A CHD event was defined as any of the following outcomes: non-fatal myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, and CHD mortality. In sensitivity analysis we repeated the analysis using 'hard' CHD events as outcome, consisting of non-fatal myocardial infarction and CHD mortality. Stroke was defined as ischemic, hermorrhagic or undefined stroke on cerebral CT. Major bleeding due to aspirin therapy (defined as extra cranial hemorrhage leading to substantial disability) was modelled as a secondary event.

Following a CHD event, stroke event or a major bleeding episode, individuals moved to the 'post-CHD-event', 'post stroke event' or 'post-major bleeding' state, respectively, or the combined states if two or all three events occurred. Following a major bleeding episode, we assumed that aspirin therapy would be discontinued. In the case of a non-fatal CHD or stroke individuals would be allocated medical treatment for secondary CVD prevention. Non-CHD deaths included fatal cancer due to radiation associated with CT scanning.

Data sources

Effectiveness of treatment, cost data, and transition probabilities were retrieved from the literature and from primary data collection and summarized in table 1 with their data sources [17, 22-34].

Rotterdam Study and event rates

From 1997 onwards, 2028 participants in the Rotterdam Study underwent CT to determine their coronary calcium score and were subsequently followed for 9.2 years (median) [12, 17, 35]. Primary care physicians were blinded for the findings on CT. Inter- and intra-observer agreement on calcium scoring has been found to be excellent [36]. Two regression models were developed to predict the 10-year risk of CHD based on the Framingham risk factors (prediction model 1) and based on Framingham plus the coronary calcium score (prediction model 2) [17]. The Framingham risk factors included were: age, systolic blood pressure, anti-hypertensive medication, total and HDL-cholesterol, diabetes and current smoking [4]. More than 50% of the individuals classified as Framingham intermediate-risk were reclassified to either high- or low-risk when CT coronary calcium was added as risk factor and the C-statistic increased significantly from 0.72 to 0.76 [17]. The net improvement in reclassification was found to be 0.14 ($P<0.01$).

After excluding individuals who had a history of CHD or stroke prior to the CT coronary calcium scan, we used the baseline Rotterdam Study data and the two prediction models to: (1) determine the baseline characteristics of the target population, (2) determine the proportion of Framingham intermediate-risk individuals reclassified to low- and

high-risk when the coronary calcium score was added. Of all individuals reclassified to the low, intermediate or high risk category, we observed how many of them actually suffered from a CHD or stroke event using survival analysis stratified by sex (Table 1).

Probabilities of having a non-CHD event were calculated on the basis of age-and sex-specific mortality rates from national life tables of the general population [37]. Life-expectancy was adjusted for quality-of-life using mean health-related quality-of-life weights based on literature data (Table 1) [32].

Effectiveness of treatment

The benefit of statin and anti-hypertensive treatment on CHD and stroke incidence was obtained from meta-analyses, and considered equal for men and women [24, 30]. Based on a recent update, there is evidence that elderly men benefit from aspirin therapy in primary prevention of CHD. For elderly women there remains considerable controversy [3]. Therefore, aspirin treatment for primary prevention was, when applicable, only modeled in men [38].

Treatment adherence is an important determinant of treatment benefit [39]). While we used intention-to-treat-based relative risk reductions based on clinical trials, which take into account adherence, the adherence rate in a population-based intervention is less than that achieved in the controlled setting of a trial. Based on expert opinion, we assumed adherence to treatment in our population to be 70% of the adherence in the original trials for the reference case analysis and explored a range of 20 – 100% in a sensitivity analysis.

For secondary prevention and primary prevention in high risk individuals, statins, anti-hypertensive medication, and, in men, aspirin therapy are combined. Wald et al [40] estimated the effect of combining medication for CHD prevention but their approach does not account for possible synergy or dyssynergy between the drugs [41]. Instead, we estimated the effect of combining drugs by multiplying the individual relative risks and multiplying the product by a synergy factor, which we varied in sensitivity analyses between 0.9 and 1.10, 0.9 implying synergy, 1.0 implying independent effects, and 1.10 implying dyssynergy (see Technical Appendix for details). The range in the synergy factor was chosen such that a combination of drugs was at least as effective as a single component of the combination of the same drugs.

Since we considered a population at intermediate risk, we accounted for the fraction of individuals that used (a combination of) statins, aspirin, or anti-hypertensive medication at baseline. An individual using statins at baseline, but with LDL cholesterol levels >160, >130 and >90 mg/dL for the low, intermediate and high risk category respectively, was assumed to switch to a higher dose or more potent statin. The same was assumed for an individual using anti-hypertensives at baseline and systolic blood pressure levels >140, >140, and >120 mm Hg for the three risk categories respectively.

Table 1. Data included in the Markov model on CHD primary prevention strategies for asymptomatic elderly men and women identified as being at intermediate risk for a CHD event (10-year risk 10-20%). Risk group classification, associated risk prediction, and prevalence of medication use at baseline are based on a prospective observational cohort study (the Rotterdam Coronary Calcification Study).

Parameters	Base-case value men†	Base-case value women†	Distribution	Data source‡	Ref
Probabilities and Characteristics of Reclassification groups					
	Total: 329	Total: 247			
Individuals Reclassified to Low risk group					
N (%)	101 (31% (26%, 35%))	95 (38% (33%, 45%))	Beta	Cohort study	(17)
Observed 10-year CHD Risk	0.05 (0.02, 0.12)	0.08 (0.04, 0.16)	Beta	Cohort study	(17)
Observed 10-year stroke Risk	0.05 (0.02, 0.12)	0.12 (0.04, 0.16)	Beta	Cohort study	(17)
Individuals not Reclassified#					
N(%)	148 (45% (40%, 50%))	98 (40% (34%, 46%)	Beta	Cohort study	(17)
Observed 10-year CHD Risk	0.10 (0.06, 0.17)	0.15 (0.09, 0.25)	Beta	Cohort study	(17)
Observed 10-year stroke Risk	0.06 (0.03, 0.12)	0.12 (0.04, 0.12)	Beta	Cohort study	(17)
Individuals Reclassified to High risk group					
N(%)	80 (24% (20%, 29%))	54 (22% (17%, 27%)	Beta	Cohort study	(17)
Observed 10-year CHD Risk	0.30 (0.21, 0.43)	0.23 (0.13, 0.38)	Beta	Cohort study	(17)
Observed 10-year stroke Risk	0.16 (0.09, 0.28)	0.14 (0.05, 0.24)	Beta	Cohort study	(17)
First-year CHD-related mortality following a CHD-event*	0.18 (0.13, 0.22)		Beta	Cohort study	(22)
RR of recurrent CHD-event*	1.5 (1.13, 1.9)		Triangular	Cohort study	(26)
First-year stroke-related mortality following a stroke event*	0.20 (0.15, 0.26)		Beta	Cohort study	(28)
RR of recurrent stroke-event*	2 (1.5, 2.5)		Triangular	Cohort study	(28)

Table 1. *Continued*

Parameters	Base-case value men[†]	Base-case value women[†]	Distribution	Data source[‡]	Ref
Lifetime risk of developing cancer due to radiation associated with CT coronary calcium scanning	0.00008 (0.00005, 0.00012)	0.00020 (0.00014, 0.00028)	Uniform	Simulation study	(29)
One year case-fatality given cancer due to radiation risk	0.65 (0.61, 0.73)	0.70 (0.63, 0.78)	Triangular	Simulation study	(27)
Treatment effectiveness of statins					
RR on incident CHD, statins vs placebo	0.70 (0.61, 0.81)		Log normal	Meta-analysis	(24)
RR on incident stroke, statins vs placebo	0.81 (0.71, 0.93)		Log normal	Meta-analysis	(24)
Cost of statins, yearly	$ 570			Pharmacy reference	(33)
RR of hepatitis, statins vs placebo	3.51	6.5	Log normal	Meta-analysis	(42)
RR of myopathy, statins vs placebo	1.53	1.53	Log normal	Meta-analysis	(42)
Expected cost of hepatitis episode	$120			Cohort study	(43)
Expected cost of myopathy episode	$250			Cohort study	(43)
Expected disutility of hepatitis episode	0.05 QALY			Cohort study	(43)
Expected disutility of myopathy episode	0.025 QALY			Cohort study	(43)
Treatment effectiveness of antihypertensives					
RR of incident CHD, anti-hypertensives vs placebo	0.85 (0.81, 0.89)		Log normal	Meta-analysis	(30)
RR of incident stroke, anti-hypertensives vs placebo	0.64 (0.56, 0.73)		Log normal	Meta-analysis	(30)
Cost of anti-hypertensives, yearly	$ 670			Pharmacy reference	(33)
Treatment effectiveness of aspirin					
RR of incident CHD, aspirin vs placebo	0.82 (0.75, 0.90)		Log normal	Meta-analysis	(38)
RR of incident stroke, aspirin vs placebo	0.95 (0.85, 1.06)		Log normal	Meta-analysis	(38)
Annual rate major extracranial bleeding	0.0010 (0.00096, 0.0012)		Log normal	Meta-analysis	(38)
RR of major extracranial bleeding	1.54 (1.30, 1.82)		Log normal	Meta-analysis	(38)

Table 1. *Continued*

Parameters	Base-case value men†	Base-case value women†	Distribution	Data source‡	Ref
One year case-fatality due to major extra cranialbleeding*	0.03 (0.02, 0.04)		Log normal	Estimate	(28)
Cost of aspirin, yearly	$ 20		Triangular	Pharmacy reference	(33)
Synergy Factor	1 (0.9, 1.1)	1 (0.9, 1.1)	Uniform		See text
Utilities					
Asymptomatic elderly	0.86 (0.85, 0.86)	0.83 (0.83, 0.84)	Normal	Survey	(32)
Post- CHD event	0.76 (0.74, 0.77)	0.67 (0.65, 0.69)	Normal	Survey	(32)
Post-major-bleeding	0.72 (0.70, 0.74)	0.67 (0.65, 0.69)	Normal	Survey	(32)
Post-stroke event	0.69 (0.67, 0.71)	0.61 (0.59, 0.63)	Normal	Survey	(32)
Disutility due to CHDevent	-0.10 (-0.13, -0.08)	-0.16 (-0.20, -0.12)	Triangular	Survey	(32)
Disutility due to major bleeding	-0.14 (-0.10, -0.17)	-0.16 (-0.20, -0.12)	Triangular	Survey	(32)
Disutility due to stroke event	-0.19 (-0.24, -0.16)	-0.22 (-0.26, -0.19)	Triangular	Survey	(32)
Costs, dollars¶					
Performing a CT coronary calcium score*	$ 105 (85, 125)		Triangular	Official tariff	See text
First year costs of CHD-event*	$ 21233 (17196, 25207)		Gamma	Cost-study	(45)
First year costs of stroke-event	$ 24000		Gamma	Cost-study	(56)
First year costs of major extracranial bleeding*	$ 13400 (10500, 23450)		Gamma	Cost-study	(31,34)
Annual follow-up post-CHD or stroke event *	$ 1330 (1006, 1601)		Gamma	Cost-study	(46,56)
Adherence, reference case analysis	70% (40%, 100%)		Uniform	Expert opinion	See text

Notes: Major bleeding = hemorrhagic stroke, gastrointestinal bleeding
CHD = coronary heart disease, CT SCREENING = computer tomography calcium score
* Risk of events, probabilities, utilities and cost estimates described for men are identical for women.
† Data in parenthesis are 95% CIs for the beta- and lognormal distributions and ranges for the triangular- and uniform distributions
‡ Risk group classification, associated risk prediction, and prevalence of medication use at baseline are based on a prospective observational cohort study (the Rotterdam Coronary Calcification Study).
# Individuals stayed in intermediate risk group
¶ Costs are 2010 U.S. dollars.

We assumed that all individuals in the Rotterdam Coronary Calcium Study received lifestyle advice consistent with current primary care practice and that therefore the observed CHD and stroke event rates reflected this intervention.

Adverse Effects

Hemorrhagic stroke due to aspirin therapy was accounted for in the odds ratio's of net treatment benefit for stroke from the meta-analysis. Extra cranial major bleeding due to aspirin therapy was modeled explicitly as a secondary event using probabilities based on a recent meta-analysis [23]. Myopathy and hepatitis were modeled based on a meta analysis of the adverse effects of statins [42]. Based on a recent modeling study by Pletcher et al [43], we calculated the expected costs and disutilities of a myopathy and hepatitis episode, including costs for associated complications such as hospital admission, workup and mortality, weighted by the probability of complications.

Costs

Costs incorporated in the model included health-care costs and non-health-care costs and were assessed from the societal perspective for the U.S. (Table 1). All costs were converted to the year 2010 using the consumer price indices.

Health-care costs included costs of diagnostic procedures, costs for personnel, materials, equipment, costs for medication, costs for health care resource use in subsequent years after an event, and overhead. The costs for a non-contrast cardiac CT were based on healthcare reimbursement rates in 2009. Medication costs were based on pricing information from the 2009 Red Book [33], which were comparable with current prices for statins, anti-hypertensives, and aspirin. Based on baseline LDL cholesterol, we assumed that 30% of our population would need a potent and more expensive statin such as Rosuvastatin or Atorvastatin, and the remaining 70% could do with a generic statin such as Simvastatin. For antihypertensive medication we assumed that everyone would need at least a thiazide, combined with either an angiotensin II receptor blocker, ACE inhibitor or calcium channel blocker in 60% of individuals [44]. Medication costs were only accounted for in adherent individuals. In a sensitivity analysis we used generic prices for statins and anti-hypertensives, estimated to be $ 160 yearly for generic statins and $300 for antihypertensives [33]. For both strategy 2 and 3, we accounted for the costs of obtaining the Framingham risk factors by a general practitioner, including laboratory costs. Event-related costs included the costs of hospitalization, diagnostic workup, interventions, and rehabilitation during the first year after an event and was assumed to reflect the average cost following a non-fatal myocardial infarction, coronary artery bypass graft or percutaneous coronary intervention [31, 34, 45-46]. Non-health care costs included travel costs and patient time costs.

Analysis

All authors agreed on the model structure and data input prior to performing the analyses to ensure an objective and unbiased analysis.

Important baseline characteristics such as lipid levels, blood pressure and medication use, were determined for the cohort of individuals at intermediate risk, stratified by sex. The number of individuals using a statin, anti hypertensive or aspirin under each strategy was determined. Quality-adjusted life years (QALYs), life time costs, incremental cost-effectiveness ratios (i.e., additional costs divided by QALYs gained), and net health benefit (QALYs minus (costs / willingness-to-pay)) were calculated for all strategies. To take into account time preference, future costs and effectiveness were discounted at the currently recommended U.S. discount rate of 3% for both costs and effectiveness [47-48]. To take into account second order uncertainty, 100,000 independent samples were drawn from each of the input parameter distributions, generating outcome distributions for QALYs and costs for each strategy. Calculations were done for men and women separately.

Strategies were first ordered according to increasing cost. A strategy was considered dominated if another strategy was both more effective and less costly. A strategy was considered extended dominated if another strategy achieved more effectiveness at a lower incremental cost-effectiveness ratio. After eliminating dominated and extended dominated strategies, the incremental cost-effectiveness ratios were calculated as the difference in mean lifetime costs divided by the difference in mean QALYs for each strategy compared to the next best non-dominated strategy. We considered 50,000 U.S. dollar per QALY gained as a commonly accepted threshold for the societal willingness-to-pay threshold for primary prevention [49-51] and varied it between 15,000 and 100,000 dollar in sensitivity analyses. For the reference case analysis we analyzed the model with input parameters as given in Table 1.

Extensive one-way, two-way, multi-way, and probabilistic sensitivity analyses were performed using plausible ranges of the parameter values. In particular, we explored model sensitivity to drug costs, aspirin therapy in women, and the relative risk of an event with aspirin therapy. As some clinicians would be reluctant to withhold therapy from an individual who starts out with a predicted risk of 11% (putting him originally at intermediate risk), and after inclusion of coronary calcium a revised risk of 9% (putting him at low risk), we explored the effect of an alternative assumption in which treating individuals reclassified to the 5%-10% risk category as individuals with intermediate risk (10-20%), and checked whether the optimal decision would change. Reclassification probabilities for this assumption are presented in Table 4 in the technical appendix.

As the 2004 guidelines on the initiation of statin therapy include an optional cutoff value of 100 mg/dl for individuals at intermediate risk, we did an additional analysis using this cutoff value in the 'current guidelines' strategy and the 'CT calcium screening' strategy for the individuals who remained in the intermediate risk group.

Probabilistic sensitivity analysis was performed using the outcome distributions of 100,000 Monte Carlo simulations [52]. We calculated the probability that CT screening was cost-effective compared to current practice, current guidelines and statin therapy strategies for varying willingness-to-pay thresholds, which yielded acceptability curves.

RESULTS

Reference case analysis

Review of the baseline characteristics of the cohort at intermediate risk demonstrated that women were older than men and had less favorable risk factor levels apart from smoking and calcium scores (Table 2). In men, implementing current guidelines for all individuals at intermediate risk, led to a steep increase in the number of statin and anti hypertensive users (from 12% to 75% and 23% to 64%) compared to current practice (Table 5 in the technical appendix). In women, a similar pattern was observed (from 15% to 87% and 52% to 84%) (Table 6 in the technical appendix). Implementing the CT screening strategy results in slightly fewer statin users compared with implementing current guidelines in both men (69% vs 75%) and women (41% vs 87%). In men, statin users with either current practice or CT screening had a higher expected 10 year risk of CHD compared to non-users (Table 7 in the technical appendix). This difference disappeared between users and non-users with current guidelines. In women, this was only the case for CT screening (Table 8 in the technical appendix).

In men (Table 3a), CT calcium screening was more effective and more costly compared to current practice (QALY-gain: 0.13 [95%CI 0.01;0.26], cost-increase: $4,676 [95%CI 3,126 ; 6,339]), more effective and more costly than statin therapy (QALY-gain: 0.04 [-0.02;0.13], cost-increase: $1951 [1170 ; 2754]) and more effective but slightly more costly than current guidelines (QALY-gain: 0.02 [-0.04;0.09], cost-increase: $44 [-441 ; 486]). The cost effective plane in figure 2a shows that in men, current guidelines is extended dominated by CT screening, as the latter leads to a higher expected quality adjusted life expectancy against a lower incremental cost effectiveness ratio. The incremental cost effectiveness ratio of statin therapy is $30,278 per QALY and for CT calcium screening it is $48,800 per QALY gained (Table 3a).

In women (Table 3b), CT screening was more effective and more costly than current practice (QALY-gain: 0.13 [0.02;0.28]; cost-increase $4,663 [3,120 ; 6,277]), more effective and more costly than statin therapy (QALY-loss: 0.03 [-0.03 ; 0.12], cost-savings: $2273 [1475 ; 3109]) and less expensive but also less effective compared to current guidelines (QALY-loss: 0.02 [-0.03 ; 0.07], cost-savings: $297 [-8 ; 633]). The cost effective plane in Figure 2b shows that in women, CT screening is extended dominated by current guidelines, as the latter leads to a higher expected quality adjusted life expectancy against a lower incremental cost effectiveness ratio, and therefore, CT screening is not considered cost-effective in women.

Sensitivity analysis

In men, at a willingness-to-pay threshold of $50,000 per QALY, a slight dyssynergy between drugs would change the optimal decision from CT screening to statin therapy (Table 4a). This shift would also occur if treatment adherence dropped below 58%, the effect of aspirin therapy on CHD was less protective, the cost of a CT rose above $200 or the risk of radiation induced cancer increased more than ten-fold. In women, the

optimal strategy changed from 'current guidelines' to statin therapy in case of a slight dyssynergy between drugs, and strong protective effects of aspirin on the incidence of CHD and/or stroke (Table 4b). Using generic drug prices made the CT screening more cost-effective in men with an ICER of $24,675 / QALY whereas in women current guidelines became more cost effective with an ICER of $21,140 / QALY. Substituting the statin therapy strategy with the aggressive medical treatment strategy did not change the optimal decision in men. In women the optimal decision switched from current guidelines to aggressive medical treatment.

Table 2. Baseline characteristics of study population with initial risk of CHD between 10-20%

Variable	Men (n=329)	Women (n=247)
Age, years	70 (66 – 73)	74 (71 – 78)
Body mass index, kg/m^2	26.5 (24.8 – 28.7)	28 (25 – 31)
Systolic blood pressure, mmHg	144 (131 – 155)	149 (135 – 161)
Diastolic blood pressure, mmHg	78 (70 – 85)	76 (69 – 82)
Total cholesterol, mg/dl	222 (201 - 240)	240 (217 – 232)
(mmol/l)	5.7 (5.2 – 6.2)	6.2 (5.6 – 6.8)
HDL cholesterol, mg/dl	46 (33 – 63)	50 (39 - 54)
(mmol/l)	1.2 (1.1 – 1.4)	1.3 (1.1 – 1.4)
LDL cholesterol, md/dl	146 (124 – 165)	158 (135 – 178)
(mmol/l)	3.75 (2.42 – 5.1)	4.1 (2.63 – 5.62)
Cholesterol lowering medication (%)	52 (11.9%)	44 (17.1%)
Anti Hypertensive medication(%)	87 (22.5%)	117 (45.5%)
Anti thrombotic agents (%)	97 (20.4%)	43 (16.7%)
Smokers (%)		
Never	29 (9%)	124 (50%)
Current	70 (21%)	33 (13%)
Former	230 (70%)	90 (36%)
Diabetes Mellitus	19 (5.8%)	42 (17.0%)
Calcium score (%)		
0	11 (3%)	16 (7%)
1-100	122 (37%)	104 (42%)
101-400	79 (24%)	65 (26%)
401-1000	64 (20%)	37 (15%)
>1000	53 (16%)	25 (10%)

Categorical variables are presented as absolute number (percentage). Continuous values are expressed as mean (inter quartile range).

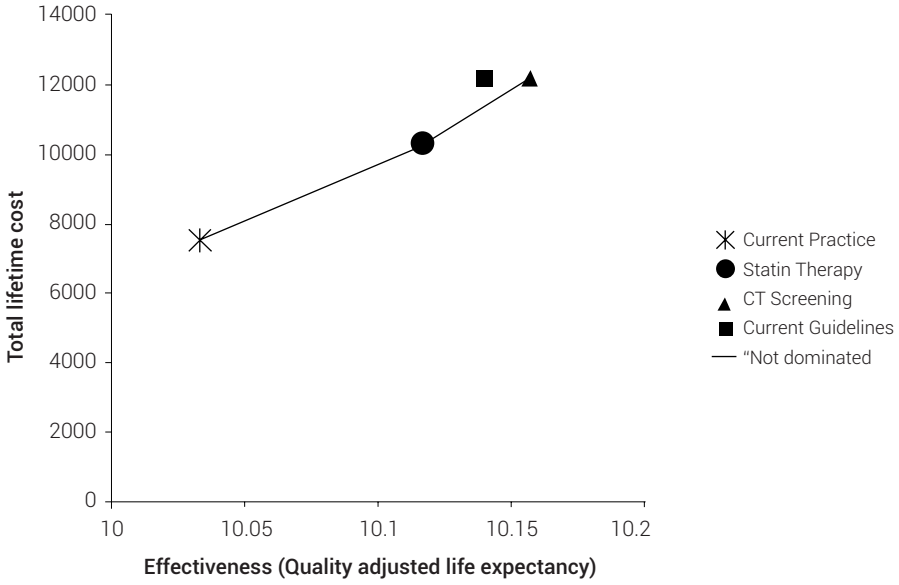


Figure 2a. Cost effectiveness plane for the base case analysis in men.

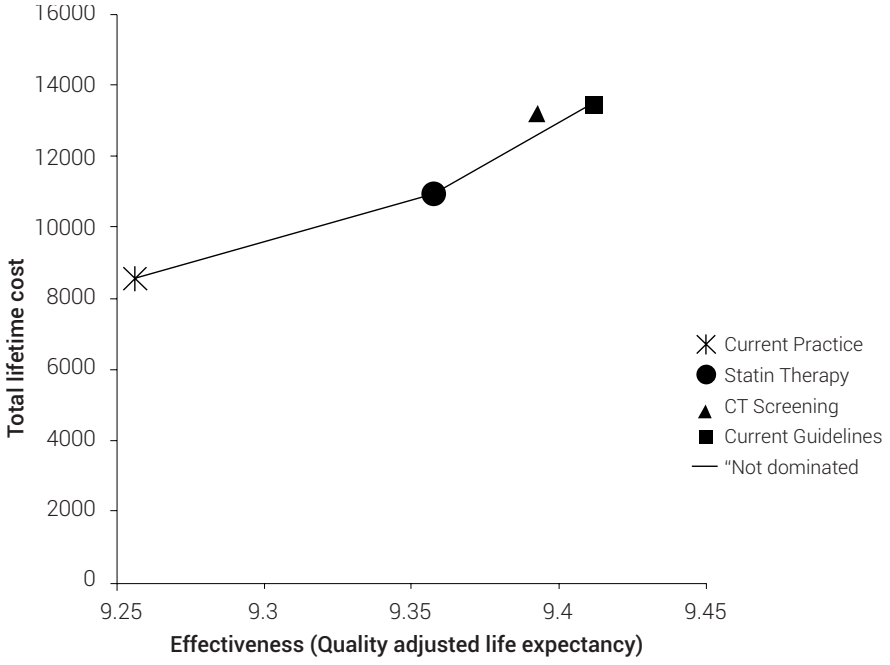


Figure 2b. Cost effectiveness plane for the base case analysis in women.

Probabilistic sensitivity analysis demonstrated that in men CT screening was cost-effective compared to current practice in the majority of simulations if the willingness to pay threshold was above $50,000 (Figure 3a). In women, even at higher willingness to pay thresholds, CT calcium screening would be cost effective in less than 20% of the simulations (Figure 3b).

DISCUSSION

In this study we evaluated the comparative effectiveness and cost-effectiveness of CT coronary calcium screening within the framework of current CVD prevention guidelines. In men, the incremental cost effectiveness ratio for CT screening was just below the willingness-to-pay threshold of $50,000 per QALY and small changes in assumptions changed CT screening from being cost-effective to not cost-effective. Some of the assumptions could be considered plausible, such as a slight dyssynergy between drugs, or a treatment adherence lower than 60%, whereas others were more extreme (for example, a more than 10-fold increase in radiation risk). The uncertainty in optimal decision was further illustrated by the acceptability curves, which showed that in a minor but substantial proportion of the simulations, CT screening was not cost-effective. However, using generic drug prices the ICER for CT screening dropped and the result was more robust in sensitivity analysis.

In women CT screening was not found to be cost-effective, even after using a wide range of varying assumptions, which included assumptions more favourable to the CT calcium screening strategy by treating individuals in the higher end of 'low risk' (5-10% risk) more aggressively, and using more treat-prone LDL thresholds. The difference in the optimal decision between men and women can be explained by the fact that compared to men, more women were reclassified to the low risk group leading to less aggressive treatment. Furthermore, within the low risk group, the observed risk of CHD is higher in women than in men, so the foregone benefit with less aggressive treatment is higher in women. The benefit of CT screening is obtained in the high-risk group, where individuals are treated more aggressively compared to current guidelines for treatment of intermediate-risk individuals. Since fewer women were reclassified to high-risk, the potential benefit of CT screening is lower than in men. The balance is further shifted due to the fact that aspirin is prescribed in men at high risk, but not in women due to controversy regarding its efficacy in primary prevention of CHD.

The ATP-IV guidelines, which will be published soon, are expected to recommend more aggressive statin treatment than the current statin treatment guidelines. Our statin therapy strategy can be considered quite aggressive and is likely to be similar to the antcipated ATP-IV recommendation, ensuring future applicability of our results. Of note, when we compared CT screening with an even more aggressive treatment strategy, as we did in the sensitivity analysis with the 'medical treatment' strategy, CT screening remained cost effective in men. This implies that CT screening does not simply put more individuals on treatment, but allocates treatment to individuals who are expected to benefit most.

Table 3a. Cost, clinical effectiveness, and cost-effectiveness of strategies for asymptomatic men (mean age 70) who have an intermediate risk (10-20%, 10-year risk) of CHD. (Strategies ordered by increasing cost).

	Total Lifetime Costs*†	Quality-Adjusted Life Expectancy* (years)	Incremental Costs per Quality-Adjusted Life Year ($/QALY)* compared with current practice'	Incremental Costs per Quality-Adjusted Life Year ($/QALY)* compared with next best strategy'
Current Practice	7551	10.03	reference	reference
Statin therapy	10276	10.12	30278	30278
Current Guidelines	12184	10.14	42118	dominated''
CT Screening	12228	10.16	35977	48800

QALY = Quality-Adjusted- Life Year; CHD= coronary heart disease; WTP = Willingness-To-Pay;
* Future costs and life years were discounted at 3% per year
† 2010 U.S. dollars
' Because not all strategies are considered feasible in all situations, we have presented ICERs compared with both 'current practice' and compared with the next best strategy
'' Dominated by 'extended dominance' - implies that there is another strategy,(CT screening) which yields higher effectiveness at a lower incremental cost-effectiveness ratio.

Table 3b. Cost, clinical effectiveness, and cost-effectiveness of strategies for asymptomatic women (mean age 74) who have an intermediate risk (10-20%, 10-year risk) of CHD. (Strategies ordered by increasing cost).

	Total Lifetime Costs*†	Quality-Adjusted Life Expectancy* (years)	Incremental Costs per Quality-Adjusted Life Year ($/QALY)* compared with current practice'	Incremental Costs per Quality-Adjusted Life Year ($/QALY)* compared with next best strategy'
Current Practice	8553	9.26	reference	reference
Statin therapy	10944	9.36	23910	23910
CT Screening	13216	9.39	35869	dominated''
Current Guidelines	13514	9.41	33073	51400

QALY = Quality-Adjusted- Life Year; CHD= coronary heart disease; WTP = Willingness-To-Pay;
* Future costs and life years were discounted at 3% per year
† 2010 U.S. dollars
' Because not all strategies are considered feasible in all situations, we have presented ICERs compared with both 'current practice' and compared with the next best strategy
'' Dominated by 'extended dominance' - implies that there is another strategy (current guidelines) which yields higher effectiveness at a lower incremental cost-effectiveness ratio.

Table 4a. Optimal strategy in one-way sensitivity analysis, using a willingness to pay of 50,000 $ per QALY in men.

Variable of Interest	Range assessed in deterministic sensitivity analysis	Optimal decision (base case: CT screening)
Synergy Factor	0.9 – 1.1	Statin therapy if synergy factor >1.02
Treatment adherence	0.2 – 1.0	Statin therapy if adherence <0.58
Relative Risk of aspirin treatment on CHD	0.2 – 1.0	Statin therapy if RR >0.84
Relative Risk of aspirin treatment on stroke	0.2 – 1.0	CT screening
Cost of CT coronary calcium scan	$ 20 – $ 600	Statin therapy if cost of CT >$ 200
Annual incidence of radiation induced cancer	1/100,000 – 1/100	Statin therapy if radiation risk increases >10 fold
Outcome	'Hard CHD'	CT screening
Discount rates	4% for costs, 1.5% for QALY's	CT screening
LDL threshold for statin initiation	100 mg/dl	CT screening
Treatment of invididuals reclassified to 5-10%	similar to 'intermediate risk'	CT screening
Yearly drug prices of statins and anti hypertensives	generic drug prices	CT screening
Aggressive medical treatment instead of statin therapy	n/a	CT screening

n/a not applicable

Table 4b. Optimal strategy in one-way sensitivity analysis, using a willingness to pay of 50,000 $ per QALY in women.

Variable of Interest	Range assessed in deterministic sensitivity analysis	Optimal decision (base case: current guidelines)
Synergy Factor	0.9 – 1.1	Statin therapy if synergy factor >1.02
Treatment adherence	0.2 – 1.0	Current guidelines
Relative Risk of aspirin treatment on CHD	0.2 – 1.0	Statin therapy if RR >0.73
Relative Risk of aspirin treatment on stroke	0.2 – 1.0	Statin therapy if RR >0.62
Cost of CT coronary calcium scan	$ 20 – $ 600	Current guidelines
Annual incidence of radiation induced cancer	1/100,000 – 1/100	Current guidelines
Outcome	'Hard CHD'	Current guidelines
Discount rates	4% for costs, 1.5% for QALY's	Current guidelines
LDL threshold for statin initiation	100 mg/dl	Current guidelines
Treatment of invididuals reclassified to 5-10%	similar to 'intermediate risk'	Current guidelines
Yearly drug prices of statins and anti hypertensives	generic drug prices	Current guidelines
Aggressive medical treatment instead of statin therapy	n/a	Medical treatment

n/a not applicable

A number of cost-effectiveness papers on CT coronary calcium scoring have previously been published but differed from our study in the strategies, target population considered or they dichotomized the calcium score rather than including the score in a risk prediction. These studies found that cost effectiveness of CT screening was highly sensitive to the population screened and downstream costs [53-55]. The relatively high incremental cost effectiveness ratio we found for CT screening in men is comparable with results of other cost-effectiveness studies on interventions for primary prevention of CHD such as the study by Pletcher et al [43]. Generalizability of our findings is further supported by comparable reclassification data on coronary calcium found by Polonsky et al in the Multi-ethnic study of atherosclerosis [7].

Our results should be interpreted in the light of the limitations. First, we focused on individuals at intermediate risk, which implied individuals were on average older than 69 years of age. Screening for coronary calcium could potentially have value in other subgroups but we explicitly chose to investigate CT screening in the intermediate risk group as advocated by recent guidelines and current consensus. Second, the time horizon in our analysis was the remaining lifetime. Therefore, we had to extrapolate the incidence of CHD beyond the available 10-year data, but few simulated individuals lived beyond 15 years. Finally, although we stratified by sex, further stratification by different combinations of baseline risk factors was not possible due to a limited sample size.

As with all models of screening and diagnostic tests, the differences between the four strategies in terms of quality adjusted life expectancy were small. Even though in women, the results seem robustly unfavourable for the CT calcium screening strategy, the residual uncertainty reflected in the acceptability curves indicates that further research might be beneficial. In men the results indicated that CT screening was cost-effective in the majority of simulations. Nevertheless, in a substantial proportion of simulations in men, current guidelines or statin therapy was optimal compared to CT screening, indicating that further research is necessary.

In conclusion, screening for coronary artery calcium with CT is probably cost-effective in men at intermediate risk of CHD. For women at intermediate risk for CHD, CT screening does not appear to be cost effective.

TECHNICAL APPENDIX

Model

Figure 1a to 1d show the cycle tree of the Markov model, with all states and possible transitions between them. Within a cycle, the incidence of one type of event did not exclude the possibility of another type.

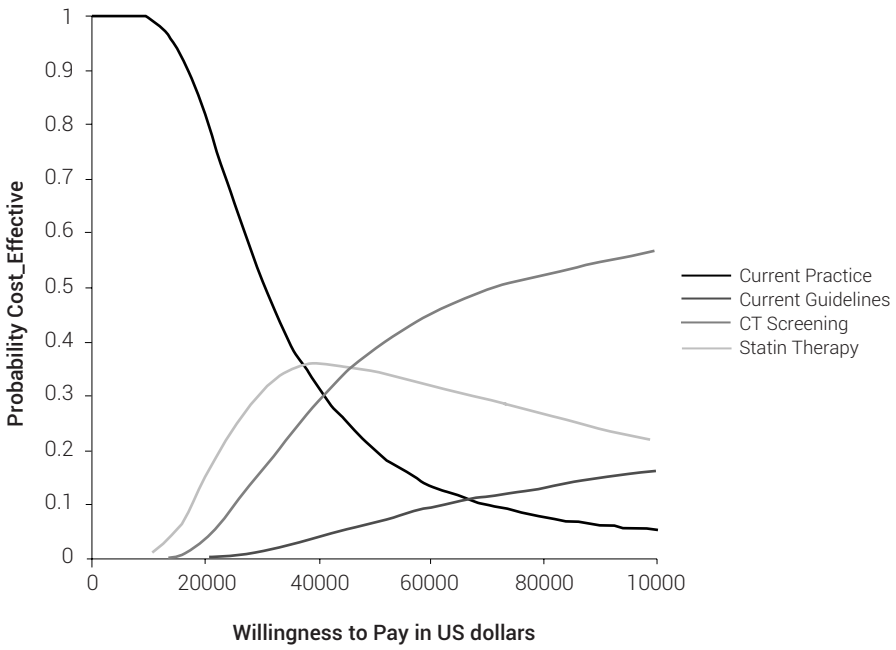


Figure 3a. Acceptability curve in men. For varying willingness-to-pay thresholds, the proportions of simulations that demonstrated cost-effectiveness for each strategy are indicated.

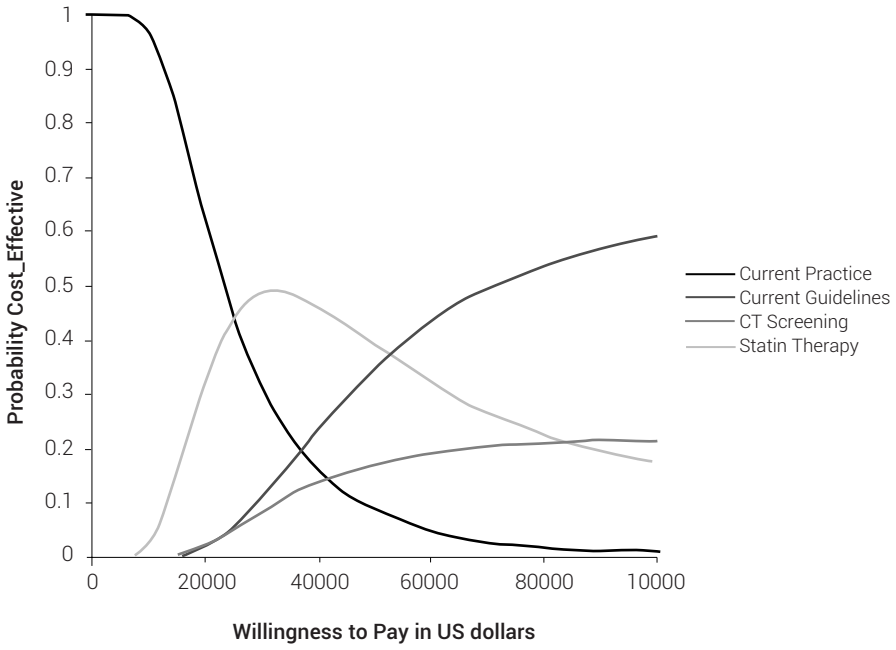


Figure 3b. Acceptability curve in women. For varying willingness-to-pay thresholds, the proportions of simulations that demonstrated cost-effectiveness for each strategy are indicated.

CHD incidence

The probability of incident CHD was determined by first converting observed 10 year probabilities p to average rates r per time unit t (equation (1)).

$$r = \frac{-\ln(1-p)}{t} \tag{1}$$

Zhich was assumed to be constant over time and extrapolated beyond 10 years. This assumption was validated by observing the fairly constant rate over a 10-year follow-up period (Figures 2 and 3). Subsequently, the calculated rate was converted to an annual probability, by:

$$p = 1 - e^{-r} \tag{2}$$

Adjusting for efficacy of Treatment

Drug treatment efficacies, in terms of Relative Risks (RR) were obtained from meta analyses and considered the relative risk in incidence of CHD (any of the following outcomes: non-fatal myocardial infarction, CABG, PCI, and CHD mortality) or stroke (ischemic, hemorrhagic or unspecified) compared to placebo. The relative risk of a certain treatment or intervention was assumed to be constant over time.

Derived annual probabilities of CHD and stroke respectively, were multiplied by the RR of the appropriate strategy.

$$P_{after\_treatment} = P_{unadjusted} \bullet R_{strategy} \tag{3}$$

Adjusting the treatment efficacies for treatment adherence, baseline prevalence and treatment goals.

The model incorporates 3 basic drug treatments: statins, anti-hypertensives and aspirin, each with their own specific treatment goals. In order to estimate the combined effect, we made the following assumptions:

(1) An individual already on statins at baseline who had not reached the treatment goal, i.e. >160 (4.92), >130 (3.37) and >90 (2.50) mg/dL (mmol/l) for the low, intermediate and high risk category respectively, was assumed to switch to a higher dose or more potent statin, and assigned half of the reduction in risk based on a full dose given to a non-user.The same holds for an individual using anti-hypertensives at baseline and SBP >140, >140, >130 mm Hg respectively.

(2) When a combination of drugs was assigned, the net effect of the drugs together on risk reduction was assumed to be the product of the individual RR's, times a factor for potential (dys)synergy, *SF*, where .90 < SF <1.10. This range was chosen to make sure that a combination of 2 or 3 drugs was at least as effective as the effect of a single drug. For the base case analysis we used a synergy factor of 1. When 2 drugs were jointly taken, the joint effect was corrected with SF. When 3 drugs were jointly taken, the joint effect was corrected with SF^2.

The RR of each strategy was corrected for adherence and baseline prevalence of statin, anti-hypertensives and aspirin use. To simplify, the adherence for aspirin, anti-hypertensives and statin or any combination of them was considered to be equal.

For the individuals reclassified to the low risk group in the CT screening strategy, the RR's for both CHD and stroke (RR_1) were determined by:

$$RR_1 = C\left(\begin{array}{l} f_{LDL^{+,N}\cap BP^{+,N}}\cdot RR_{antiH}\cdot RR_{statin}\cdot SF + f_{LDL^{+,N}\cap BP^{+,U}}\cdot\frac{1}{2}\cdot\left(1+RR_{antiH}\right)\cdot RR_{statin}\cdot SF + f_{LDL^{+,N}\cap BP^{-}}\cdot RR_{statin} + \\ f_{LDL^{+,U}\cap BP^{-}}\cdot\frac{1}{2}\cdot\left(1+RR_{statin}\right) + f_{LDL^{-}\cap BP^{+,N}}\cdot RR_{antiH} + f_{LDL^{-}\cap BP^{+,U}}\cdot\frac{1}{2}\cdot\left(1+RR_{antiH}\right) + \\ f_{LDL^{+,U}\cap BP^{+,N}}\cdot RR_{antiH}\cdot\frac{1}{2}\cdot\left(1+RR_{statin}\right)\cdot SF + f_{LDL^{+,U}\cap BP^{+,U}}\cdot\frac{1}{2}\cdot\left(1+RR_{antiH}\right)\cdot\frac{1}{2}\cdot\left(1+RR_{statin}\right)\cdot SF \end{array}\right) + 1-(1-f_{LDL^{-}\cap BP^{-}})\cdot C \quad (4)$$

Where *C* equals the percentage of therapy adherent individuals and *f* equals a fraction sub-indexed by:

LDL^{+} indicates LDL >160 mg/dL (4.92 mmol/l); LDL^{-} indicates LDL ≤160 mg/dL (4.92 mmol/l),

LDL^{U} indicates statin use at baseline ; LDL^{N} indicates no use at baseline,

BP^{+} indicates SBP >140 mm Hg ; BP^{-} indicates SBP <140 mm Hg,

BP^{U} indicates anti-hypertensives use at baseline ; BP^{U} indicates no use at baseline,

RR_{Statin} equals the relative risk of CHD (stroke) for someone taking statins versus placebo,

RR_{antiH} equals the relative risk of CHD (stroke) for someone taking anti-hypertensives vs placebo,

SF equals the synergy factor discussed earlier.

The baseline fractions of *f* for strategy I are given in Table 1.

For the current guidelines strategy, consisting of both statins and anti-hypertensives when indicated, and the individuals reclassified to the intermediate risk group in the CT screening strategy, the RR's for both CHD and stroke (RR_2) were determined by

$$RR_2 = C\left(\begin{array}{l} f_{LDL^{+,N}\cap BP^{+,N}}\cdot RR_{antiH}\cdot RR_{statin}\cdot SF + f_{LDL^{+,N}\cap BP^{+,U}}\cdot\frac{1}{2}\cdot\left(1+RR_{antiH}\right)\cdot RR_{statin}\cdot SF + f_{LDL^{+,N}\cap BP^{-}}\cdot RR_{statin} + \\ f_{LDL^{+,U}\cap BP^{-}}\cdot\frac{1}{2}\cdot\left(1+RR_{statin}\right) + f_{LDL^{-}\cap BP^{+,N}}\cdot RR_{antiH} + f_{LDL^{-}\cap BP^{+,U}}\cdot\frac{1}{2}\cdot\left(1+RR_{antiH}\right) + \\ f_{LDL^{+,U}\cap BP^{+,N}}\cdot RR_{antiH}\cdot\frac{1}{2}\cdot\left(1+RR_{statin}\right)\cdot SF + f_{LDL^{+,U}\cap BP^{+,U}}\cdot\frac{1}{2}\cdot\left(1+RR_{antiH}\right)\cdot\frac{1}{2}\cdot\left(1+RR_{statin}\right)\cdot SF \end{array}\right) + 1-(1-f_{LDL^{-}\cap BP^{-}})\cdot C \tag{4}$$

Where *C* equals the percentage of therapy adherent individuals and *f* equals a fraction sub-indexed by:

LDL^{+} indicates LDL >130 mg/dL (3.37 mmol/l); LDL^{-} indicates LDL ≤130 mg/dL (3.37 mmol/l),

LDL^{U} indicates statin use at baseline ; LDL^{N} indicates no use at baseline,

BP^{+} indicates SBP >140 mm Hg ; BP^{-} indicates SBP <140 mm Hg,

BP^{U} indicates anti-hypertensives use at baseline ; BP^{U} indicates no use at baseline,

RR_{Statin} equals the relative risk of CHD (stroke) for someone taking statins versus placebo,

RR_{antiH} equals the relative risk of CHD (stroke) for someone taking anti-hypertensives vs placebo,

SF equals the synergy factor discussed earlier.

The baseline fractions of *f* for strategy II are given in Table 2.

For the individuals reclassified to the high risk group in the CT screening strategy, the RR's were determined by:

$$RR_3 = C \cdot \begin{pmatrix} f_{LDL^N \cap BP^N \cap A^N} \cdot RR_{antiH} \cdot RR_{statin} \cdot RR_{asp} \cdot SF^2 + f_{LDL^N \cap BP^N \cap A^U} \cdot RR_{antiH} \cdot RR_{statin} \cdot SF + \\ f_{LDL^N \cap BP^{+,U} \cap A^N} \cdot RR_{statin} \cdot \frac{1}{2} \cdot (1 + RR_{antiH}) \cdot RR_{asp} \cdot SF^2 + f_{LDL^N \cap BP^{+,U} \cap A^U} \cdot RR_{statin} \cdot \frac{1}{2} \cdot (1 + RR_{antiH}) \cdot SF \\ + f_{LDL^N \cap BP^{-,U} \cap A^N} \cdot RR_{statin} \cdot RR_{asp} \cdot SF + f_{LDL^N \cap BP^{-,U} \cap A^U} \cdot RR_{statin} + \\ f_{LDL^{+,U} \cap BP^N \cap A^N} \cdot \frac{1}{2} \cdot (1 + RR_{statin}) \cdot RR_{antiH} \cdot RR_{asp} \cdot SF^2 + f_{LDL^{+,U} \cap BP^N \cap A^U} \cdot \frac{1}{2} \cdot (1 + RR_{statin}) \cdot RR_{antiH} \cdot SF \\ f_{LDL^{+,U} \cap BP^{+,U} \cap A^N} \cdot \frac{1}{2} \cdot (1 + RR_{statin}) \cdot \frac{1}{2} \cdot (1 + RR_{antiH}) \cdot RR_{asp} \cdot SF^2 \end{pmatrix} +$$

$$C \cdot \begin{pmatrix} f_{LDL^{+,U} \cap BP^{+,U} \cap A^U} \cdot \frac{1}{2} \cdot (1 + RR_{statin}) \cdot \frac{1}{2} \cdot (1 + RR_{antiH}) \cdot SF + f_{LDL^{+,U} \cap BP^{-,U} \cap A^N} \cdot \frac{1}{2} \cdot (1 + RR_{statin}) \cdot RR_{asp} \cdot SF + \\ f_{LDL^{+,U} \cap BP^{-,U} \cap A^U} \cdot \frac{1}{2} \cdot (1 + RR_{statin}) + f_{LDL^{-,U} \cap BP^N \cap A^N} \cdot RR_{antiH} \cdot RR_{asp} \cdot SF + f_{LDL^{-,U} \cap BP^N \cap A^U} \cdot RR_{antiH} + \\ f_{LDL^{-,U} \cap BP^{+,U} \cap A^N} \cdot \frac{1}{2} \cdot (1 + RR_{antiH}) \cdot RR_{asp} \cdot SF + f_{LDL^{-,U} \cap BP^{+,U} \cap A^U} \cdot \frac{1}{2} \cdot (1 + RR_{antiH}) + f_{LDL^{-,U} \cap BP^{-,U} \cap A^N} \cdot RR_{asp} \end{pmatrix} +$$

$$1 - (f_{LDL^{-,U} \cap BP^{-,U} \cap A^U}) \cdot C \qquad (5)$$

All sub-indexes are similar to the ones used in (4), except for

RR_{asp} which is the relative risk of incident CHD for someone taking aspirin vs placebo,

A^U indicates aspirin use at baseline ; A^N indicates no use,

LDL^+ indicates LDL >90 mg/dL (2.5 mmol/l); LDL^- indicates LDL ≤90 mg/dL (2.5 mmol/l),

BP^+ indicates SBP >130 mm Hg ; BP^- indicates SBP <130 mm Hg

Note that aspirin is only prescribed in males. Fractions of *f* for strategy III are given in Table 3.

Secondary prevention

In high-risk individuals, the risk of a recurrent CHD event was assumed to be 1.5-fold higher than their risk of a primary CHD event [22]. In low- and intermediate-risk individuals, the risk of a recurrent CHD event was assumed to be similar to the risk of a primary CHD event in high-risk individuals. Treatment for secondary prevention of CHD and stroke was assumed to be similar to the medical treatment of high-risk individuals/ secondary prevention of CVD.

Major bleeding rate

We modeled the excess rate of major bleeding due to the use of aspirin in males. From the most recent meta analysis, the bleeding rate in the placebo group was converted to a yearly probability $P_{MajorBleeding}$. The annual probability of excess major bleeding $P_{ExcessMajorBleeding}$ was calculated by:

$$P_{ExcessMajorBleeding} = (R - 1) \bullet P_{MajorBleeding} \tag{6}$$

where *RR* equals the relative risk of major bleeding for males taking aspirin compared to placebo.

Death due to radiation

A recent simulation study estimated the lifetime attributable risk (LAR) of cancer from a single CT Coronary Calcium scan. We divided the LAR by the expected remaining lifetime of our cohort, and used this as approximation for the annual cancer risk due to radiation. Making this simplifying assumption led to slight overestimation of the radiation risk but since the risk is extremely low, it's influence will be negligible.

.

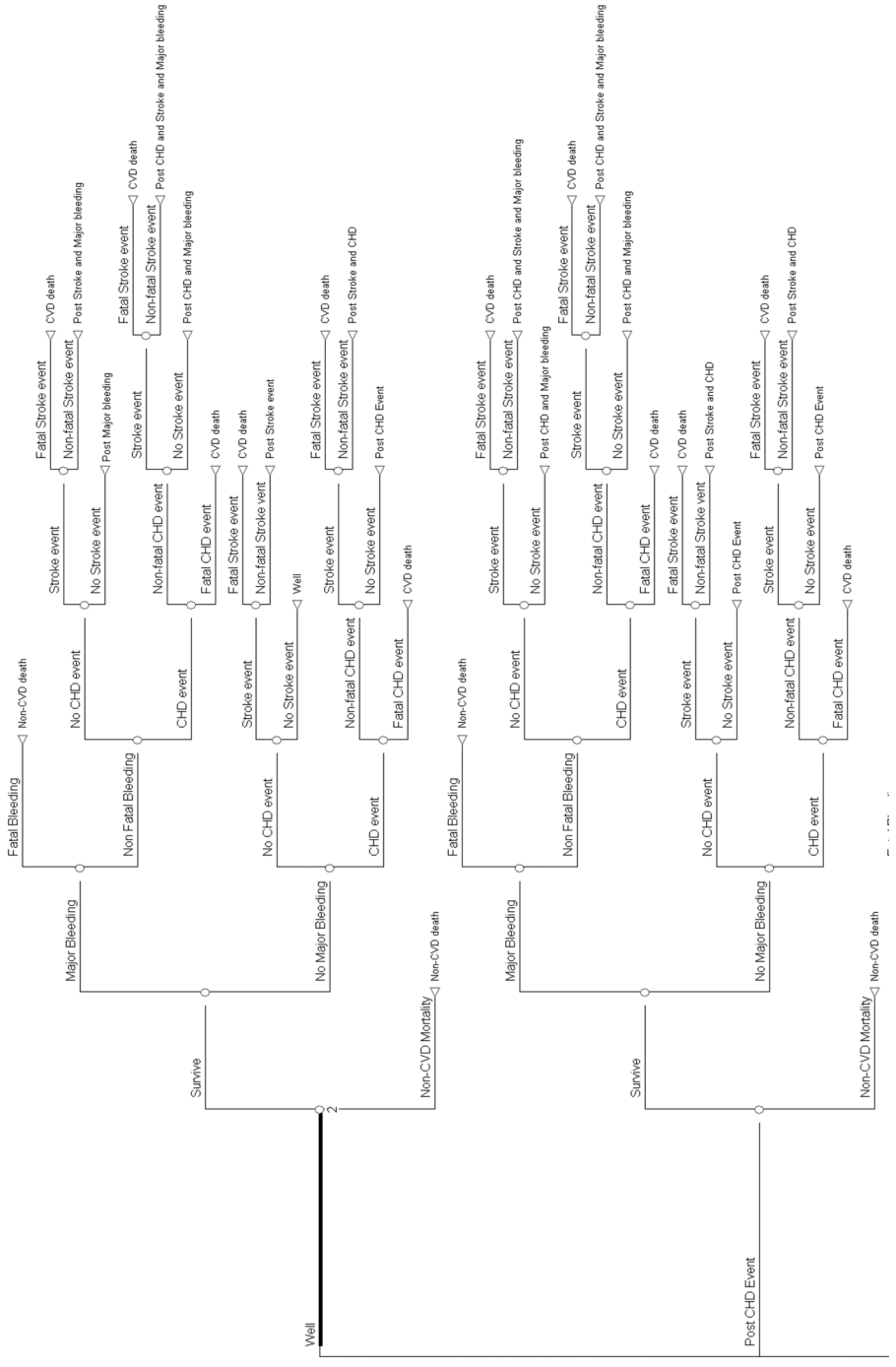


Figure 1a. Schematic presentation of the Markov simulation model. The cycle tree of each health state is presented.

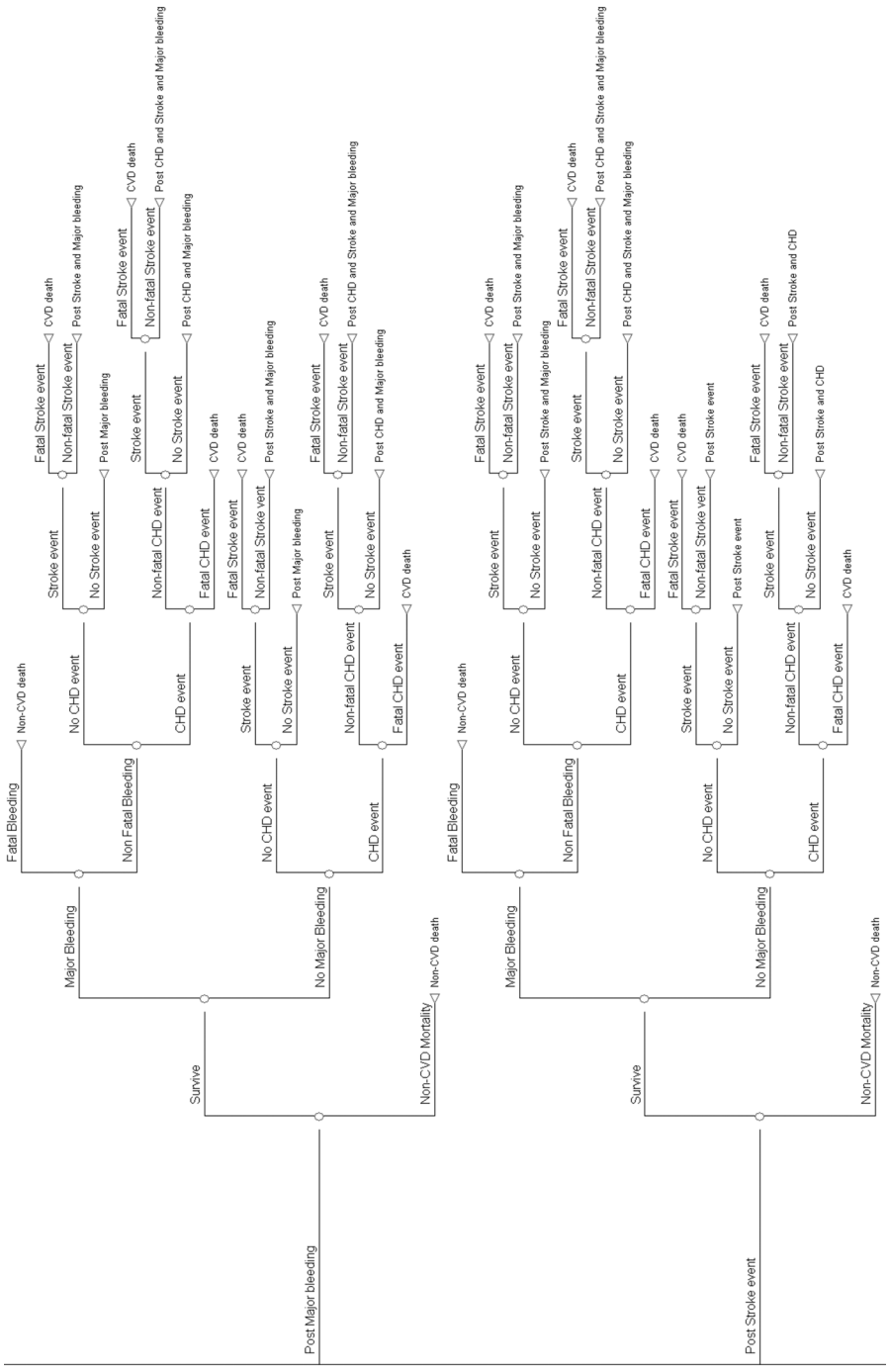


Figure 1b. Second part of Markov model. The cycle tree of each health state is presented.

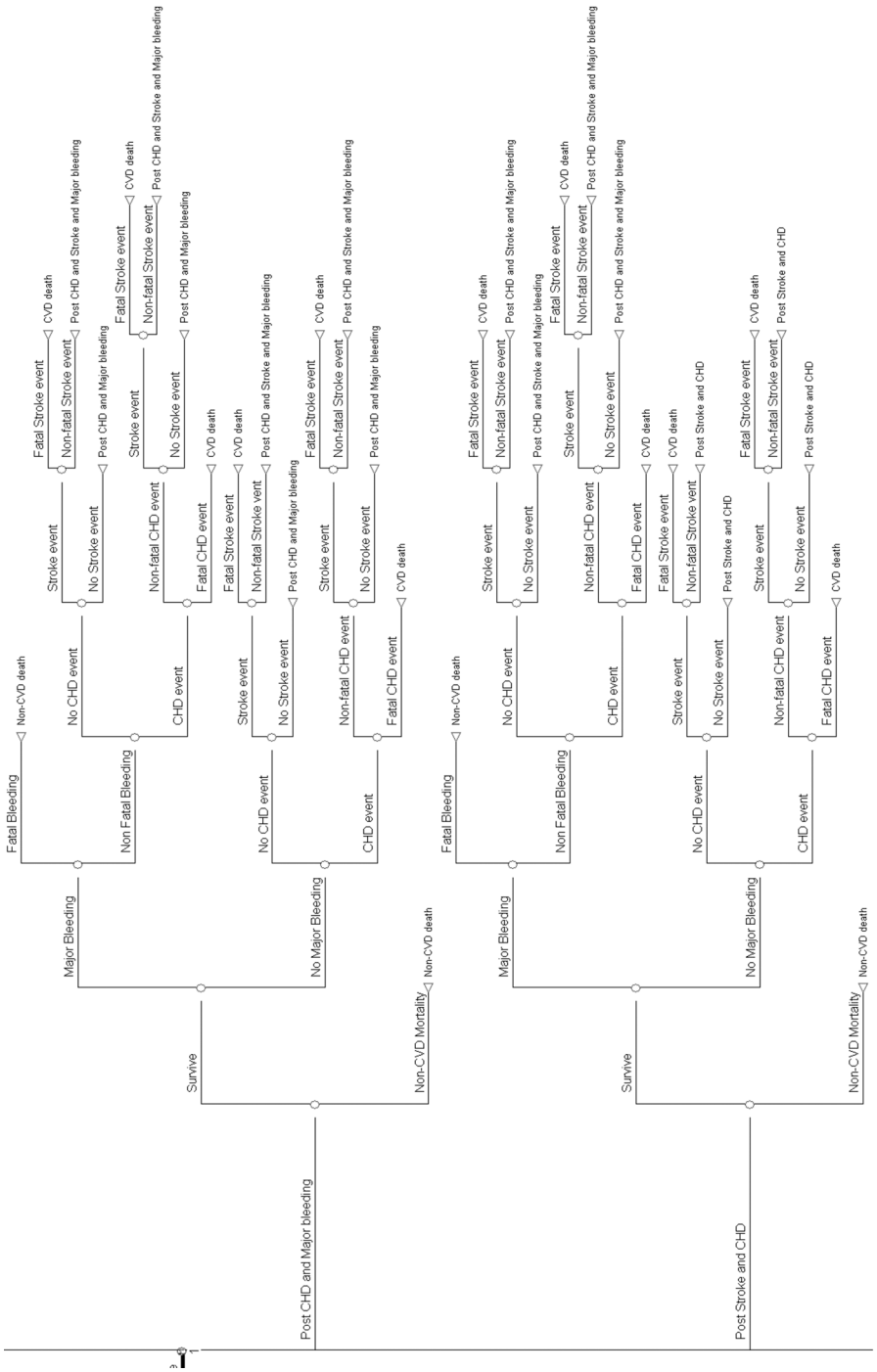


Figure 1c. Third part of Markov model. The cycle tree of each health state is presented.

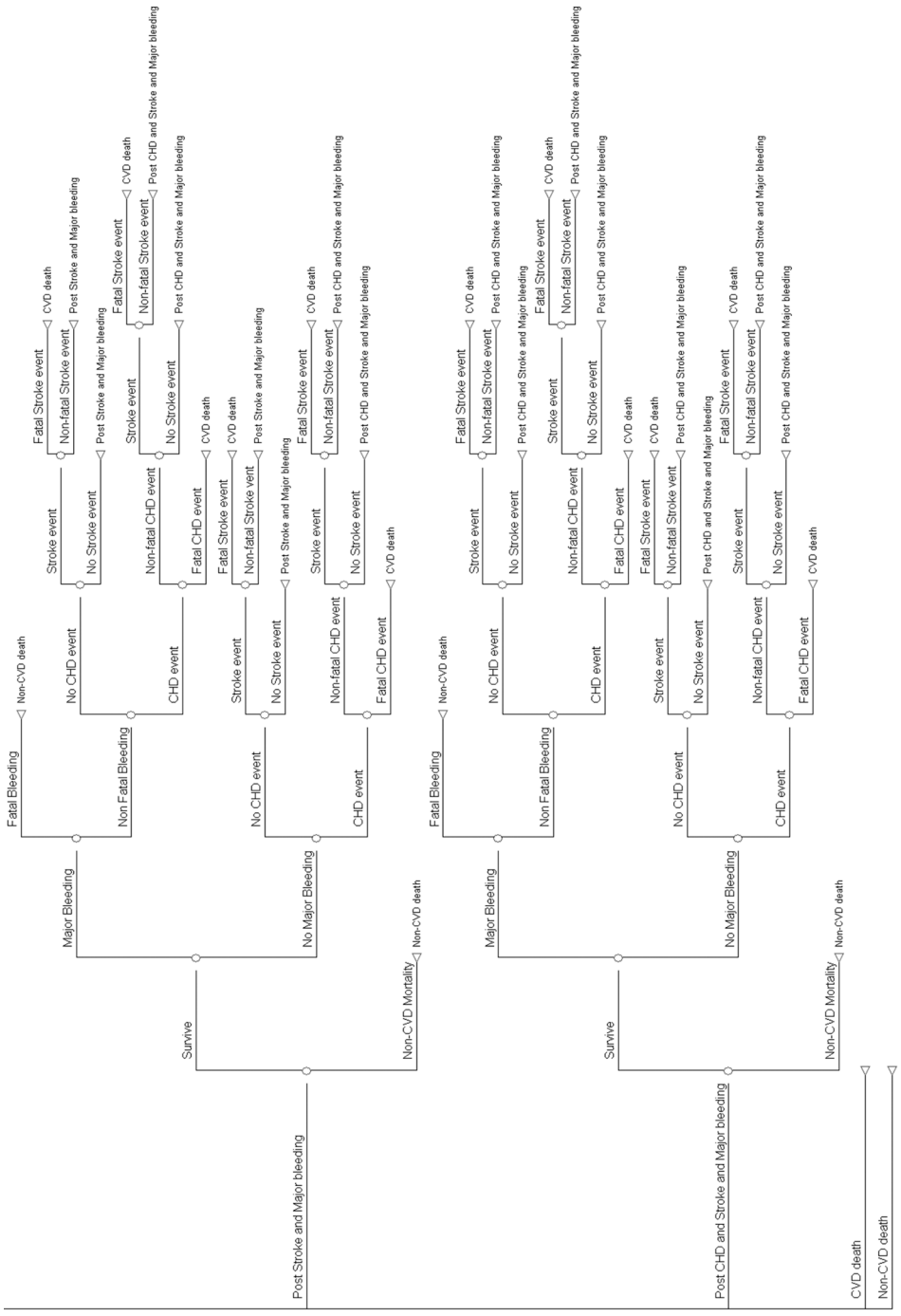


Figure 1d. Fourth part of the schematic presentation of the Markov simulation model.

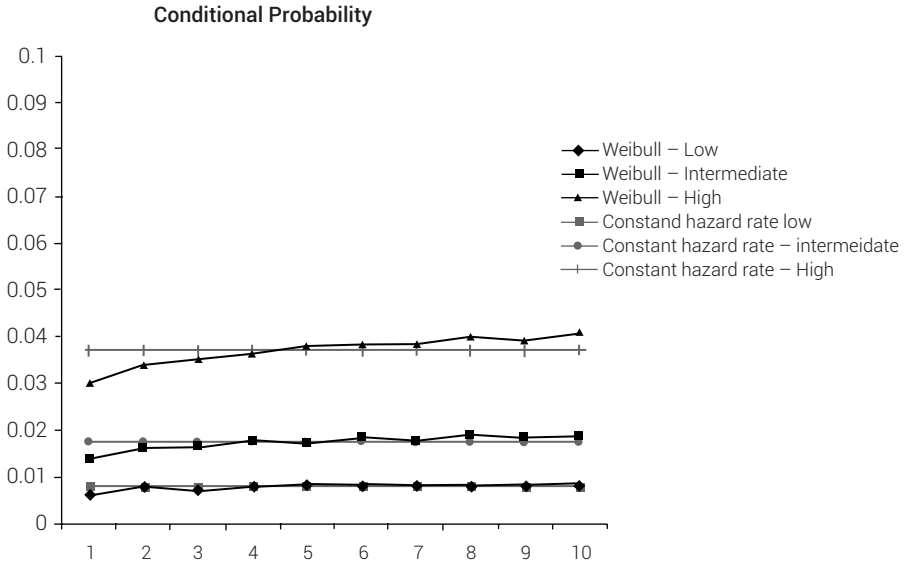


Figure 2. Probability of CHD in year ***t*** for ***men***, conditional on survival up until beginning of year ***t***. For each risk category (low, intermediate and high), both the probability calculated assuming a constant hazard rate and the Weibull distribution are drawn.

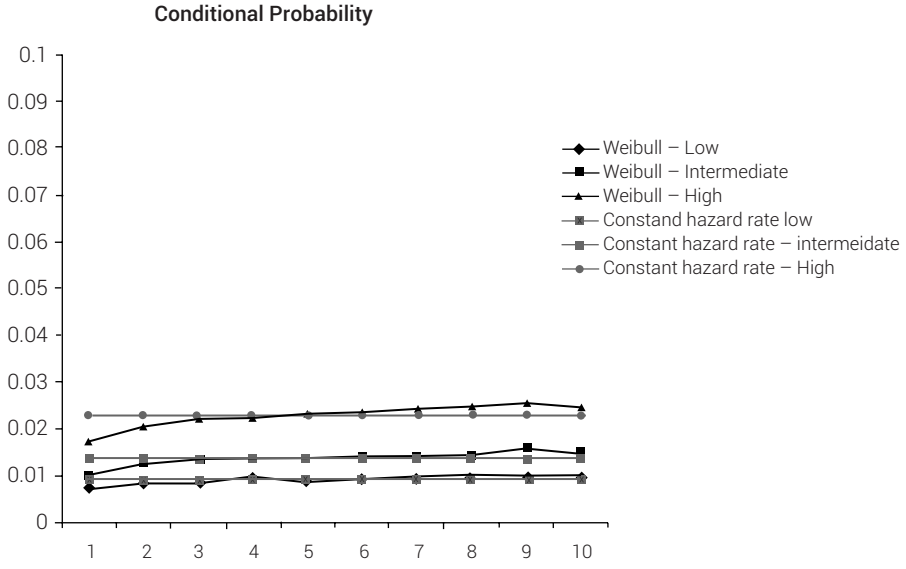


Figure 3. Probability of CHD in year ***t*** for ***women***, conditional on survival up until beginning of year ***t***. For each risk category (low, intermediate and high), both the probability calculated assuming a constant hazard rate and the Weibull distribution are drawn.

Table 1. Fractions of different combinations of statin use, anti-hypertensives use, LDL-level and SBP level at baseline, stratified by sex, used in the CT screening strategy for individuals reclassified to the low risk category.

Fraction	Men	Women
LDL >160 mg/dl SBP >140 mmHG No Statin No anti-hypertensives	0.11	0.13
LDL >160 mg/dl SBP >140 mmHG No Statin anti-hypertensives use	0.02	0.10
LDL >160 mg/dl SBP <140 mmHG No Statin _*	0.10	0.17
LDL >160 mg/dl SBP >140 mmHG Statin use No anti-hypertensives	0.00	0.01
LDL >160 mg/dl SBP >140 mmHG Statin use anti-hypertensives use	0.00	0.01
LDL >160 mg/dl SBP <140 mmHG Statin use _*	0.00	0.01
LDL <160 mg/dl SBP > 140 mmHG _* No anti-hypertensives	0.29	0.19
LDL <160 mg/dl SBP > 140 mmHG _* anti-hypertensives use	0.10	0.22
LDL < 160 mg/dl SBP <140 mmHG _* _*	0.39	0.17

*Irrespective of statin and anti-hypertensives use respectively

Table 2. Fractions of different combinations of statin use, anti-hypertensive use, aspirin use, LDL-level and SBP level at baseline, stratified by sex, used in the 'current guidelines' strategy, and for the individuals reclassified to the intermediate risk category in the CT screening strategy.

Fraction	Men	Women
LDL >130 mg/dl SBP >140 mmHG No Statin No anti-hypertensives	0.24	0.23
LDL >130 mg/dl SBP >140 mmHG No Statin anti-hypertensives use	0.09	0.22
LDL >130 mg/dl SBP <140 mmHG No Statin _*	0.30	0.26
LDL >130 mg/dl SBP >140 mmHG Statin use No anti-hypertensives	0.04	0.02
LDL > 130 mg/dl SBP > 140 mmHG Statin use anti-hypertensives use	0.02	0.02
LDL >130 mg/dl SBP <140 mmHG Statin use _*	0.01	0.04
LDL <130 mg/dl SBP > 140 mmHG _* No anti-hypertensives	0.13	0.07
LDL <130 mg/dl SBP > 140 mmHG _* anti-hypertensives use	0.06	0.08
LDL <130 mg/dl SBP <140 mmHG _* _*	0.12	0.04

*Irrespective of statin and anti-hypertensives use respectively

Table 3. Fractions of different combinations of statin use, anti-hypertensive use, aspirin use, LDL-level and SBP level at baseline, stratified by sex, used in the CT coronary calcium screening strategy for individuals reclassified to the High risk category.

Fraction	Men	Women
–*	0.50	0.33
–*		
No Statin		
No anti-hypertensives		
No Aspirin		
–*	0.14	0.07
–*		
No Statin		
No anti-hypertensives		
Aspirin use		
–*	0.04	0.19
SBP >130 mmHG		
No Statin		
Anti-hypertensives use		
No Aspirin		
–*	0.04	0.04
SBP >130 mmHG		
No Statin		
Anti-hypertensives use		
Aspirin use		
–*	0.05	0.19
SBP <130 mmHG		
No Statin		
Anti–hypertensives use		
No Aspirin		
–*	0.01	0.04
SBP <130 mmHG		
No Statin		
Anti-hypertensives use		
Aspirin use		
LDL >90 mg/dl	0.09	0.02
–*		
Statin use		
No Anti-hypertensives		
No Aspirin		

Table 3. *Continued*

Fraction	Men	Women
LDL >90 mg/dl	0.04	0.02
_*		
Statin use		
No Anti-hypertensives		
Aspirin use		
LDL >90 mg/dl	0.06	0.04
SBP >130 mmHg		
Statin use		
Anti-hypertensives use		
No Aspirin		
LDL >90 mg/dl	0.01	0.04
SBP >130 mmHg		
Statin use		
Anti-hypertensives use		
Aspirin use		
LDL >90 mg/dl	0.03	0.00
SBP <130 mmHg		
Statin use		
Anti-hypertensives use		
No Aspirin		
LDL >90 mg/dl	0.00	0.04
SBP <130 mmHg		
Statin use		
Anti-hypertensives use		
Aspirin use		
LDL <90 mg/dl	0.00	0.02
_*		
Statin use		
No Anti-hypertensives		
No Aspirin		
LDL <90 mg/dl	0.00	0.00
_*		
Statin use		
No Anti-hypertensives		
Aspirin use		

Table 3. *Continued*

Fraction	Men	Women
LDL < 90 mg/dl	0.00	0.00
SBP > 130 mmHg		
Statin use		
No Anti-hypertensives		
No Aspirin		
LDL <90 mg/dl	0.00	0.00
SBP >130 mmHg		
Statin use		
No Anti-hypertensives		
Aspirin use		
LDL <90 mg/dl	0.00	0.00
SBP <130 mmHg		
Statin use		
Anti-hypertensives use		
No Aspirin		
LDL <90 mg/dl	0.00	0.00
SBP <130 mmHg		
Statin use		
Anti-hypertensives use		
Aspirin use		

*Irrespective of statin and anti–hypertensives use respectively

Table 4. Reclassification for <5%,5-20% and >20% for the low, intermediate and high risk category.

Parameters	Base-case value men†	Base-case value women†
Probabilities and Characteristics of Reclassification groups		
	Total: 329	Total: 247
Individuals Reclassified to alternative low risk group (<5%)		
N (%)	37 (12%)	40 (16%)
Observed 10-year CHD Risk	0.03	0.03 (0.04, 0.16)
Observed 10-year stroke Risk	0.09	0.06 (0.04, 0.16)
Individuals reclasified to alternative intermediate risk (5-20%) group‡		
N(%)	212 (64%)	153 (62%)
Observed 10-year CHD Risk	0.09	0.14
Observed 10-year stroke Risk	0.05	0.14
Individuals Reclassified to alternative high risk group (>20%)		
N(%)	80 (24%)	54 (22%)
Observed 10-year CHD Risk	0.30	0.23
Observed 10-year stroke Risk	0.16	0.14

Table 5. Total number (baseline users plus new indicated users) of individuals on a certain drug (statins, anti hypertensives or aspirin), per strategy in men.

Men		Statins	Anti-hypertensives	Aspirin
Current practice				
	Number on drug (%)	39 (11.9%)	74 (22.5%)	67 (20.4%)
Current guidelines				
	Number on drug (%)	247 (75.1%)	209 (63.5%)	67 (20.4%)
	Number (%) with increased dosage/ more potent drug	20 (6.1%)	53 (16.1%)	
CT screening				
	Number on drug (%)	228 (69.3%)	234 (71.1%)	128 (38.9%)
	Number (%) with increased dosage/ more potent drug	29 (8.8%)	57 (17.3%)	
Statin therapy				
	# on drug (%)	329 (100%)	74 (22.5%)	67 (20.4%)

Table 6. Total number (baseline users plus newly users) of individuals on a certain drug (statins, anti hypertensives or aspirin), per strategy in women.

Women		Statins	Anti-hypertensives	Aspirin
Current practice				
	Number on drug (%)	37 (15.0%)	129 (52.2%)	44 (17.8%)
Current guidelines				
	Number on drug (%)	215 (87.0%)	209 (84.6%)	44 (17.8%)
	Number (%) with increased dosage/ more potent drug	21 (8.5%)	81 (32.8%)	
CT screening				
	Number on drug (%)	183 (74.1%)	218 (88.3%)	44 (17.8%)
	Number (%) with increased dosage/ more potent drug	22 (8.9%)	88 (35.6%)	
Statin therapy				
	Number on drug (%)	247 (100.0%)	129 (52.2%)	44 (17.8%)

Table 7. 10 year predicted risk, and a number of baseline risk factors of statin vs no statin users and anti hypertensive vs no anti hypertensive users for the current practice, current guidelines and CT calcium screening strategy in men.

		Statin user	No statin user	Anti-hypertensive user	No anti-hypertensive user
Current practice					
	Predicted 10 year risk of CHD	0.21	0.14	0.16	0.15
	Age	69	69	67	70
	Systolic blood pressure (mmHg)	154	142	149	142
	Total cholesterol (mg/dL)	210	222	222	222
	HDL cholesterol (mg/dl)	48	48	52	47
	Diabetes	8%	6%	5%	6%
	Current smoking	23%	21%	14%	24%
	ln(Calcium score)	6.08	4.75	5.18	4.83
Current guidelines					
	Predicted 10 year risk of CHD	0.14	0.14	0.16	0.13
	Age	69	71	69	70
	Systolic blood pressure (mmHg)	144	144	154	127
	Total cholesterol (mg/dL)	235	186	222	222
	HDL cholesterol (mg/dl)	48	48	50	46
	Diabetes	5%	9%	8%	3%
	Current smoking	21%	23%	18%	28%
	ln(Calcium score)	4.87	5.01	5	4.74

Table 7. *(Continued)*

		Statin user	No statin user	Anti-hypertensive user	No anti-hypertensive user
CT screening					
	Predicted 10 year risk of CHD	0.18	0.08	0.17	0.11
	Age	69	70	69	70
	Systolic blood pressure (mmHg)	145	142	151	127
	Total cholesterol (mg/dL)	233	201	222	222
	HDL cholesterol (mg/dl)	48	48	49	46
	Diabetes	6%	6%	7%	3%
	Current smoking	21%	22%	18%	29%
	ln(Calcium score)	5.59	3.354	5.22	4.1

Table 8. 10 year predicted risk, and a number of baseline risk factors of statin vs no statin users and anti hypertensive vs no anti hypertensive users for the current practice, current guidelines and CT calcium screening strategy in women.

		Statin user	No statin user	Anti-hypertensive user	No anti-hypertensive user
Current practice					
	Predicted 10 year risk of CHD	0.14	0.14	0.14	0.14
	Age	73	75	73	76
	Systolic blood pressure (mmHg)	148	149	147	150
	Total cholesterol (mg/dL)	226	245	238	247
	HDL cholesterol (mg/dl)	48	50	51	48
	Diabetes	19%	17%	19%	14%
	Current smoking	14%	13%	7%	20%
	ln(Calcium score)	4.58	4.29	4.4	4.27
Current guidelines					
	Predicted 10 year risk of CHD	0.14	0.12	0.14	0.14
	Age	74	76	74	75
	Systolic blood pressure (mmHg)	147	157	152	130
	Total cholesterol (mg/dL)	250	199	238	257
	HDL cholesterol (mg/dl)	50	50	50	47
	Diabetes	15%	28%	19%	8%
	Current smoking	15%	3%	11%	26%
	ln(Calcium score)	4.37	4.08	4.33	4.38

Table 8. *(Continued)*

		Statin user	No statin user	Anti-hypertensive user	No anti-hypertensive user
CT screening					
	Predicted 10 year risk of CHD	0.16	0.07	0.14	0.11
	Age	73	75	74	70
	Systolic blood pressure (mmHg)	147	154	151	127
	Total cholesterol (mg/dL)	254	215	238	222
	HDL cholesterol (mg/dl)	49	51	50	47
	Diabetes	15%	22%	18%	2%
	Current smoking	15%	8%	12%	29%
	ln(Calcium score)	4.92	2.66	4.44	5.15

Chapter 3

Validation of a model to investigate the effects of modifying cardiovascular disease (CVD) risk factors on the burden of CVD: the Rotterdam Ischemic Heart Disease and Stroke Computer Simulation (RISC) model

Bob J. H. van Kempen
Bart S. Ferket
Albert Hofman
Ewout Steyerberg
Ersen B. Colkesen
S. Matthijs Boekholdt
Nicholas J. Wareham
Kay-Tee Khaw
M. G. Myriam Hunink

BMC Medicine 2012 Dec 6;10(1):158

ABSTRACT

Background: We developed a Monte Carlo Markov model designed to investigate the effects of modifying cardiovascular disease (CVD) risk factors on the burden of CVD. Internal, predictive, and external validity of the model have not yet been established.

Methods: The Rotterdam Ischemic Heart Disease and Stroke Computer Simulation (RISC) model was developed using data covering 5 years of follow-up from the Rotterdam Study. To prove 1) internal and 2) predictive validity, the incidences of coronary heart disease (CHD), stroke, CVD death, and non-CVD death simulated by the model over a 13-year period were compared with those recorded for 3,478 participants in the Rotterdam Study with at least 13 years of follow-up. 3) External validity was verified using 10 years of follow-up data from the European Prospective Investigation of Cancer (EPIC)-Norfolk study of 25,492 participants, for whom CVD and non-CVD mortality was compared.

Results: At year 5, the observed incidences (with simulated incidences in brackets) of CHD, stroke, and CVD and non-CVD mortality for the 3,478 Rotterdam Study participants were 5.30% (4.68%), 3.60% (3.23%), 4.70% (4.80%), and 7.50% (7.96%), respectively. At year 13, these percentages were 10.60% (10.91%), 9.90% (9.13%), 14.20% (15.12%), and 24.30% (23.42%). After recalibrating the model for the EPIC-Norfolk population, the 10-year observed (simulated) incidences of CVD and non-CVD mortality were 3.70% (4.95%) and 6.50% (6.29%). All observed incidences fell well within the 95% credibility intervals of the simulated incidences.

Conclusions: We have confirmed the internal, predictive, and external validity of the RISC model. These findings provide a basis for analyzing the effects of modifying cardiovascular disease risk factors on the burden of CVD with the RISC model.

INTRODUCTION

Decision models are being increasingly used to guide decisions on medical interventions in healthcare [1-3]. Both for healthcare policy-makers who have to make decisions for specific populations and weigh both benefits and costs, and for a general practitioner facing a medical decision for a particular patient, decision models can provide valuable information to aid the decision at hand. Empirical and trial-based studies on (cost-) effectiveness of medical interventions often evaluate a limited number of strategies, and typically cover a limited period of follow-up. Decision modeling can overcome these limitations by synthesizing the available information and extrapolating short-term study results, providing policy-makers with information on expected long-term outcomes and accompanying uncertainties [4]. However, because decision models are based on a necessarily simplified representation of the underlying disease and the intervention being studied, the validity of the model is not automatically guaranteed. Earlier research has shown that importance of model validation before the results of a simulation study can be used for medical decisions [5-8].

Three types of validity have been described. With internal validation, the output of the model is compared with the data that was used to build the model [9, 10]. Although model output and data are inherently dependent on each other with this type of validation, internal validity is a necessary condition, and provides an indication of how well the model output represents the data. Whereas the follow-up period in observational studies and clinical trials is necessarily limited, medical decisions often require long-term outcomes. A common approach is to extrapolate the results of a simulation model beyond the period on which it was originally based. The validity of a model with regard to its accuracy to simulate results beyond the original timeframe is called 'predictive' or 'prospective' validity [11, 12], and constitutes the second form of validity. In evaluating predictive validity, the model output is compared with data from the new follow-up period, which has become available after the model was developed. The extent to which the results of a model can be applied to other populations different from the original one is the third form of validity, external validity [9, 10]. Because potential differences between populations affect many of the parameters used in a model, external validity is a more rigorous test of model validity than the other two validity measurements.

The objective of this study was to assess the internal, predictive, and external validity of the Rotterdam Ischemic Heart Disease and Stroke Computer Simulation (RISC) model [13]. The RISC model was designed to investigate the effects of modifying cardiovascular disease (CVD) risk factors on the CVD burden in a general population. The model is based on data from the Rotterdam Study, a cohort follow-up study of 7,983 adults aged 55 years and older. Validation of the RISC model is required before the results produced by the model can be used for decision-making.

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 coronary heart disease (CHD) state, 4) the stroke state, 5) the CHD and stroke state, and 6) the well state (being alive without CHD or stroke). The model simulates incident CVD events in individuals with and without previous CVD based on risk-actor-dependent transition probabilities, using Cox regression equations.

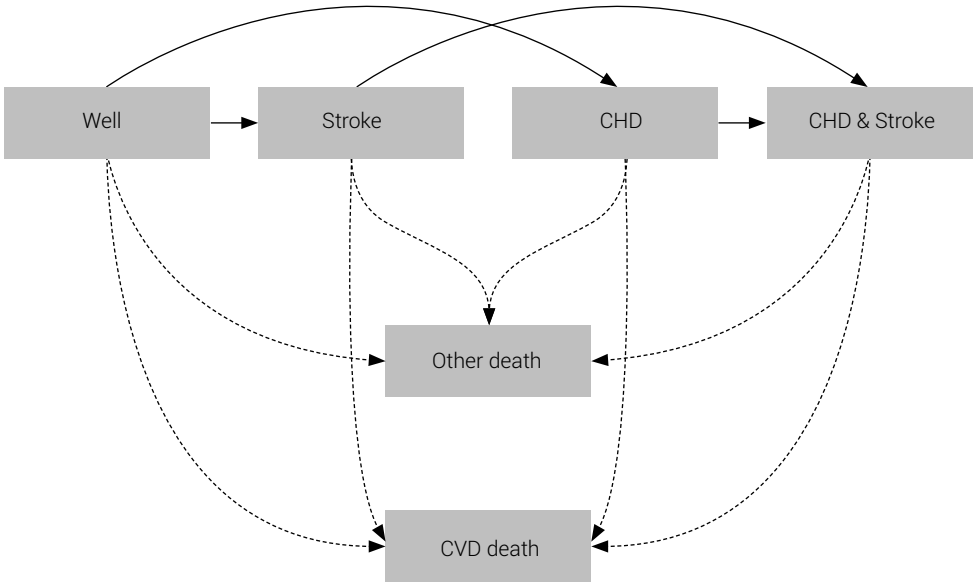


Figure 1. Schematic presentation of the Rotterdam Ischemic Heart Disease and Stroke Computer Simulation (RISC) model.
CHD = coronary heart disease, CVD = cardiovascular disease. Arrows indicate transitions between the health states

Individual risk-factor profiles are modeled and tracked over time. Incident CVD events are counted using tracker variables during the period of simulation. CHD is defined as: acute myocardial infarction (*International Classification of Diseases*, 10th edition (ICD-10) code I21), percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG). Stroke is limited to non-hemorrhagic and unspecified strokes (ICD-10 codes I63, I64). Cardiovascular death is defined as mortality due to hypertensive diseases (ICD-10 codes I10 to 15), ischemic heart disease (ICD-10 codes I20 to I25), sudden cardiac death (ICD-10 codes I46, I49), congestive heart failure (ICD-10 code I50), cerebrovascular disease (ICD-10 codes 160 to 167), other arterial disease (ICD-10 codes

I70 to I79), or sudden death (ICD-10 code R96). Non-cardiovascular death is defined as mortality due to all other causes (all other ICD-10 codes). The model was built using TreeAge software (version Data Professional release 2009; TreeAge Software, Inc., Williamstown, USA). Detailed information about the model has been given in an earlier publication [13] (see also Additional file 1).

Ethics approval

In the RISC model, the risk-factor profiles and transition probability functions were based on data from the Rotterdam Study population. The Rotterdam Study was originally approved by the institutional review board of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports [14].

Data sources

This population consisted of 7,983 respondents from a random sample of adults aged 55 years and older, who were recruited between 1990 and 1993 and were residing in Ommoord, the Netherlands. Of these 7,983 respondents, 6,871 both visited the research center and signed an informed consent document. These individuals were followed up from 1990 to 2000; the follow-up consisted of three physical examinations with interviews, and the surveillance of hospital admissions, death registries, and other available medical sources ensured accurate follow-up of death and clinical manifestations of CVD.

In 3,501 of the participants, all important characteristics for prediction of CVD were known, and the RISC model is based on 5-year follow-up data from these 3,501 individuals. The risk factors considered for the transition probability functions were age, sex, smoking status, systolic and diastolic blood pressure, body mass index, waist-to-hip ratio, ankle-brachial index; levels of plasma glucose, plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, and plasma creatinine; family history of CVD, presence of hypertension (blood pressure over 160/90 or use of anti-hypertensive medication) or diabetes mellitus; manifestations of intermittent claudication, angina pectoris, atrial fibrillation or transient ischemic attacks; and prevalent CVD. Details about the assessment of these risk indicators have been described in earlier publications [15]. The Cox regression equations that described the state-transition probabilities were centered around the mean of the risk factors of these 3,501 participants. This enabled the analysis of populations other than the original one, by substituting the centered cumulative baseline hazard and the average values of the risk factors by the values from the other population(s).

Simulation of parameter uncertainty

The RISC model allows for the evaluation of parameter uncertainty [16]. The majority of the parameter uncertainty in the model stems from the β-coefficients underlying the transition probability functions, and these β-coefficients are potentially dependent on each other. To model the uncertainty of the coefficients, 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, which allowed for the dependency between them. The transition probabilities were based on Cox regression equations, and parameter uncertainty around the baseline hazards of the CVD events, CVD death, and non-CVD death was also included.

Simulation of heterogeneity

The RISC model was designed to simulate individuals who each had a unique risk-factor profile for CVD [17]. Model outcomes are expected to be different for individuals with high-risk profiles (older age, male, high blood pressure, high lipid levels, diabetes mellitus) than for those with more favorable profiles. To allow for differences in outcomes resulting from individual differences in risk-factor profiles (that is, heterogeneity), we used the RISC model to simulate different individuals one at a time.

Simulation of the history for each individual

The risk factors used in the RISC model reveal trends over time. As an example, total cholesterol levels were found decline with age in the Rotterdam Study. To take these trends in risk factors over time into account, each risk-factor profile for a particular individual was updated every 5 years during their simulated life in the model, based on the trends seen during the first 5 years in the Rotterdam Study. Therefore, the development of the risk factors needed to be tracked over time.

Events occurring during an individual's simulated life could influence the occurrence of other events. As an example, a CHD event increases the risk of dying in subsequent years. All cardiovascular events in the RISC model were therefore tracked and linked to the transition probabilities. The inclusion of variables used to track CVD events and changes in risk factors over time for each individual required the simulation of each individual multiple times to account for stochastic uncertainty [17].

Internal and predictive validation

From our cohort of 3,501 individuals from the Rotterdam Study on which the RISC model was based, we selected 3,478 who had at least 13 years of follow-up as of 1 January 2007. The remaining subjects were lost to follow-up because they had moved out of the area or had discontinued their participation. We calculated the cumulative incidences for total mortality, CVD mortality, non-CVD mortality, CHD, and stroke as defined previously for the 13-year period of follow-up (beginning of year 1 until end of year 13). We then compared this with the simulated cumulative incidences of the same events during the 1st year until the end of the 13th year by the RISC model. We furthermore stratified the analyses for the internal and predictive validity for CVD mortality by tertiles of age for the 3,501 participants, and for men and women separately. We choose CVD mortality because it is one of the most important clinical outcomes, and there would be enough events for it in each stratum to obtain stable results.

External validation

For the external validation, we used data from the EPIC-Norfolk study [18], which is a prospective population study of 25,663 men and women aged 45 to 79 years old residing in Norfolk, UK. This study had been approved by the Norwich District Health Authority ethics committee, and all participants gave signed informed consent [18]. Participants were originally recruited from age and gender registers of general practices in Norfolk as part of the 10-country collaborative EPIC study designed to investigate dietary and other determinants of cancer. Additionally, characteristics including anthropometry, blood pressure, and lipid levels were obtained for the assessment of determinants of other diseases. For the baseline survey from 1993 to 1997, participants completed a detailed health and lifestyle questionnaire and attended a clinic visit. All participants were followed up and mortality, linked to the UK Office of National Statistics, was recorded. Participants admitted to hospital were identified by their unique National Health Service number by data linkage with the East Norfolk Health Authority (ENCORE) database, which identifies all hospital contacts throughout England and Wales for Norfolk residents.

The EPIC data did not contain all variables used in the RISC model. In particular, the following information was not readily available: ankle-brachial index, serum glucose levels, and a history at baseline of angina pectoris, atrial fibrillation, intermittent claudication, or transient ischemic attack. Consequently, we imputed the missing data in the EPIC dataset based on the multiple variables that were available [19]. All major risk factors such as age, sex, cholesterol levels, and blood pressure were available and did not need to be imputed.

We used EPIC-Norfolk mortality data from 1993 until 31 March 2008. From the 25,663 participants, we selected 25,492 who had a follow-up of at least 10 years. For the external validation, we calculated the cumulative incidence of CVD and non-CVD mortality in the EPIC dataset. We compared this with the simulated cumulative incidences of the same events after year 1 until year 10 by the RISC model, using the 25,492 EPIC profiles as input.

We did not calculate or simulate CHD and stroke events in the external validation, because the EPIC study did not document CABG and PCI events and furthermore, non-fatal events were only recorded if the patient was hospitalized. In the Rotterdam Study, both CABG and PCI were counted as CHD events, and all CHD and stroke events were recorded whether or not the patient was hospitalized, making the definition of CHD and stroke inherently different between the two cohorts [20, 21].

Statistical analysis

Important baseline characteristics for the baseline 3,478 Rotterdam Study participants and 25,492 EPIC participants were calculated and tabulated to evaluate their differences.

To take into account parameter uncertainty, the heterogeneity of the participants, and the stochastic uncertainty, we performed a three-level simulation [16, 17]. We calculated the mean and distribution around the mean of the cumulative incidences by drawing from 100 second-order sets of linked β-coefficients from the state-transition probabilities and values for the baseline hazards of the events (outer simulation loop for parameter uncertainty). For each set of linked β-coefficients and baseline hazards, we consecutively simulated 2,000 randomly drawn risk-factor profiles from the 3,478 Rotterdam profiles for the internal and predictive validation. and 2,000 from the 25,492 EPIC profiles for the external validation (middle simulation loop for heterogeneity). For each profile, 200 random walks were simulated, needed for the tracking of the individual cardiovascular histories (microsimulation, inner simulation loop for stochastic uncertainty). This implies 100 × 2,000 × 200 runs per analysis. We did not model any particular intervention or treatment in this study; only the observed history (current practice) was simulated for purposes of validation. For the stratified analyses we aggregated on the individual level (n = 3,501× 200 × 100 runs per analysis).

For the internal and predictive validation, we determined the average simulated cumulative incidences of CVD death, non-CVD death, CHD, and stroke for the 13-year period. For the external validation, we determined the average simulated cumulative incidences of CVD death and non-CVD death for year 1 until year 13. Because the Rotterdam Study and EPIC-Norfolk population are potentially different with respect to the distribution of risk factors and incidence of CVD, we subsequently recalibrated the RISC model by substituting the centered cumulative baseline hazards and mean values of the risk factors from the original model based on the Rotterdam data with the corresponding ones from the EPIC-Norfolk cohort (22). We then ran again 2,000 randomly drawn participants from the 25,492 EPIC participants.

For all cumulative incidences, we calculated the 2.5% and 97.5% percentiles of the variation around the average incidences (credibility intervals) from the RISC simulations, to quantify the influence of parameter uncertainty. We compared the observed with the simulated incidences for all events.

RESULTS

Compared with the Rotterdam Study, the the EPIC-Norfolk study participants were 10 years younger on average, and there were more men in the EPIC-Norfolk study (Table 1). On average, EPIC participants had lower total cholesterol levels and higher HDL levels (Table 1). The number of Rotterdam Study participants with a history of CVD at baseline exceeded that of the EPIC participants.

Table 1. Baseline characteristics of the risk factors used in the Rotterdam Ischemic Heart Disease and Stroke Computer Simulation (RISC) model for the 3,478 Rotterdam study participants and 25,492 European Prospective Investigation of Cancer (EPIC)-Norfolk study participants.[a]

Variable	RISC (n = 3,478)	EPIC (n = 25,492)
Age	69.0 (62 to 75)	59.2 (51 to 67)
Male subjects, %	39%	45%
Smoker		
Never	34.5%	46.0%
Former	41.9%	42.3%
Current	23.6%	11.7%
BMI	26.3 (23.8 to 28.5)	26.3 (23.7 to 28.4)
WHR	0.91 (0.84 to 0.97)	0.86 (0.78 to 0.93)
Systolic BP	140.0 (124 to 155)	135.5 (122.5 to 146.5)
Diastolic BP	74.1 (66 to 82)	82.5 (74.5 to 89.5)
Hypertension	36.4%	29.9%
Total cholesterol	6.67 (5.8 to 7.4)	6.19 (5.4 to 6.9)
HDL cholesterol	1.34 (1.1 to 1.5)	1.41 (1.1 to 1.6)
Glucose[b]	6.93 (5.5 to 7.5)	6.67 (5.5 to 7.3)
Creatinine	82.5 (72 to 91)	86.7 (76 to 97)
Diabetes mellitus	10.7%	12.2%
Angina pectoris[b]	10.4%	9.2%
Atrial fibrillation[b]	2.5%	2.9%
Intermittent claudication [b]	2.1%	1.5%
TIA[b]	5.1%	4.8%
CVD	17.8%	4.3%
Family history of MI	16.3%	18.4%
Family history of CVD	23.0%	23.3%

Abbreviations: BMI = body mass index, BP = blood pressure, CVD = cardiovascular disease, MI = myocardial infarction, TIA = transient ischemic attack, WHR = waist-to-hip ratio.

[a]Average values and inter-quartile ranges (brackets) are given for continuous variables, while categorical variables are given as percentages.

[b]Indicates imputed risk factors for the EPIC-Norfolk dataset.

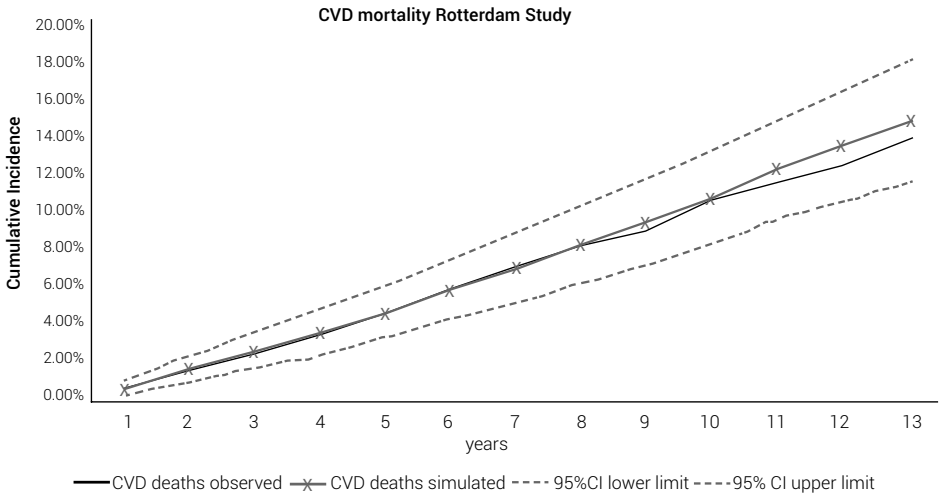


Figure 2. Cardiovascular disease (CVD) mortality during 13 years of follow-up. The first 5 years refer to the internal validation, the remaining years to the predictive validation. Simulated versus observed values for the Rotterdam Study data

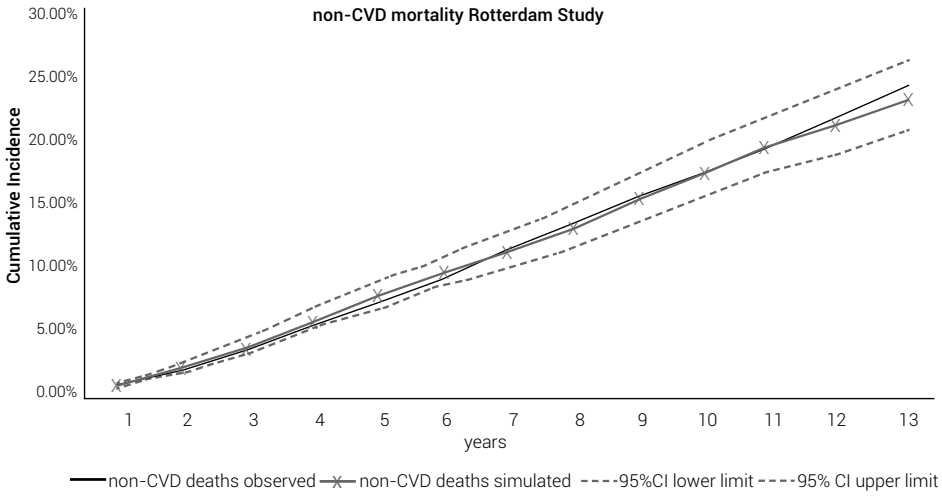


Figure 3. Non-cardiovascular disease (CVD) mortality during 13 years of follow-up. The first 5 years refer to the internal validation, the remaining years to the predictive validation. Simulated versus observed values for the Rotterdam Study data

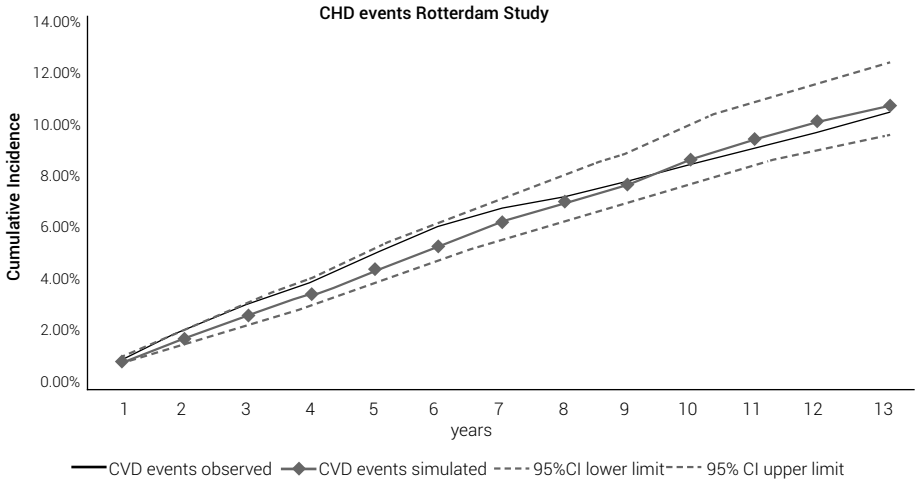


Figure 4. Coronary heart disease (CHD) events during 13 years of follow-up. The first 5 years refer to the internal validation, the remaining years to the predictive validation. Simulated versus observed values for the Rotterdam Study data

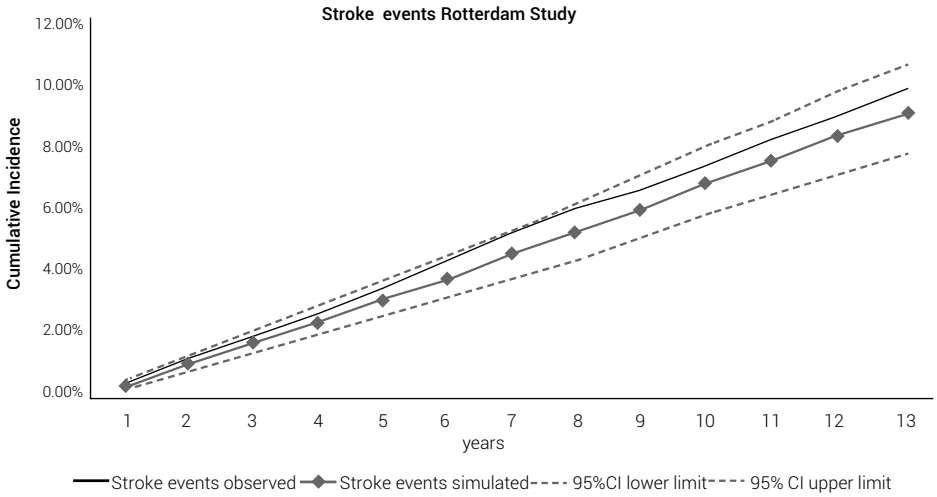


Figure 5. Stroke events during 13 years of follow-up. The first 5 years refer to the internal validation, the remaining years to the predictive validation. Simulated versus observed values for the Rotterdam Study data

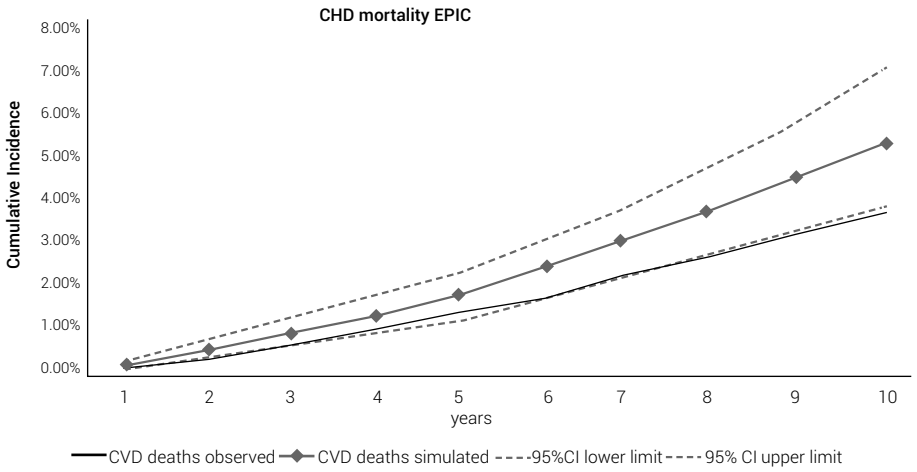


Figure 6. Cardiovascular disease (CVD) mortality during 10 years of follow-up. Simulated versus observed values for the European Prospective Investigation of Cancer (EPIC)-Norfolk data

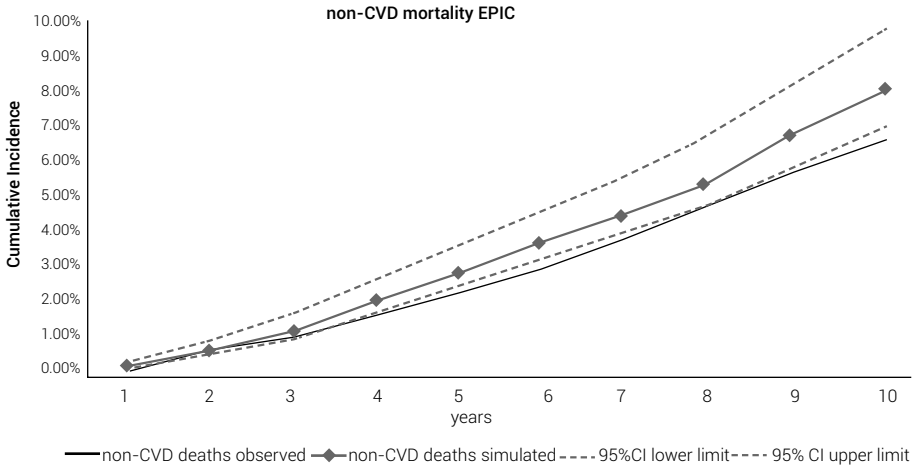


Figure 7. Non-cardiovascular disease (CVD) mortality during 10 years of follow-up. Simulated versus observed values for the European Prospective Investigation of Cancer (EPIC)-Norfolk data

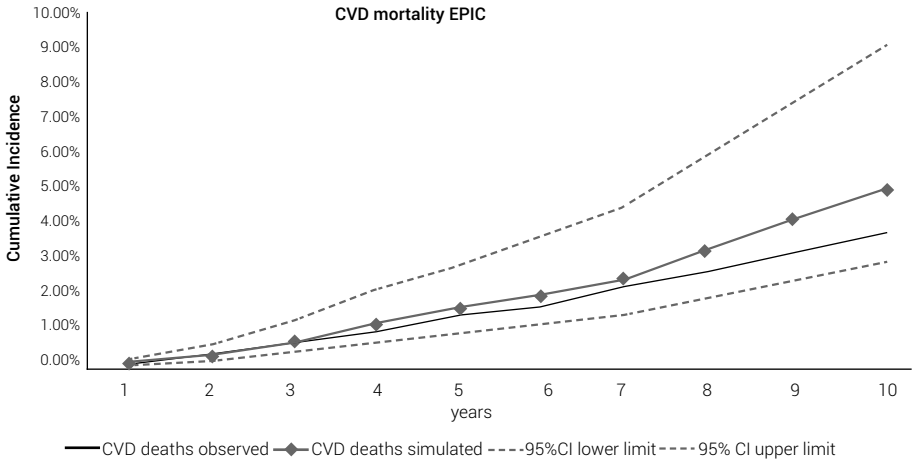


Figure 8. Cardiovascular disease (CVD) mortality during 10 years of follow-up in the recalibrated model. Simulated versus observed values for the European Prospective Investigation of Cancer (EPIC)-Norfolk data

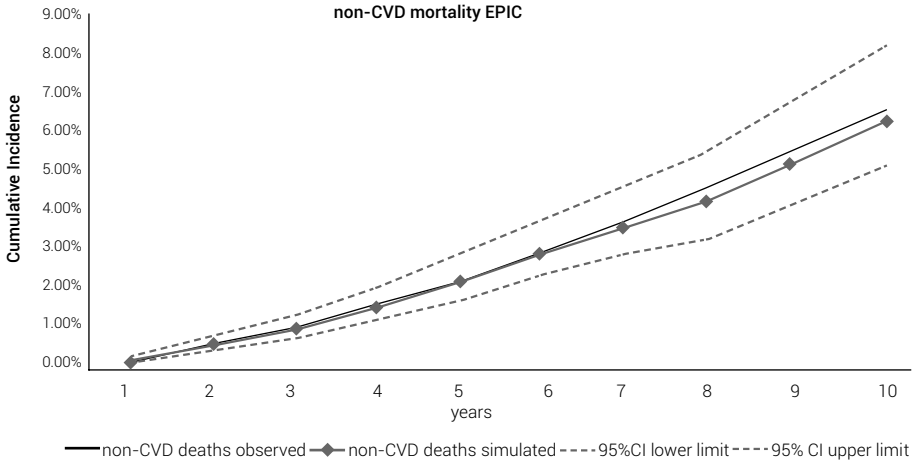


Figure 9. Non-cardiovascular disease (CVD) mortality during 10 years of follow-up in the recalibrated model. Simulated versus observed values for the European Prospective Investigation of Cancer (EPIC)-Norfolk data

Internal and predictive validation

During the 13 years of follow-up, 367 CHD events, 343 stroke events, 494 CVD deaths, and 846 non-CVD deaths occurred in the 3,478 Rotterdam Study participants, The cumulative incidences of CVD and non-CVD mortality during the13 years of follow-up for the Rotterdam Study participants were compared with the incidences generated by the RISC model (Figure 2, Figure 3). The observed values, both during the first 5 years (internal validation) and for the extrapolated period (predictive validation), were consistent with the simulated ones. The cumulative incidences of CHD and stroke events during the 13-year follow-up were compared with the incidences generated by the RISC model (Figure 4, Figure 5). The observed values were again consistent with the simulated events. For the cumulative incidences of CVD mortality, stratified by tertiles of age, for men and women respectively, the observed values were also consistent with the simulated values (see Additional file 1, Figure S2, Figure S3).

External validation and recalibration

During the 10-year follow-up of the 25,492 EPIC-Norfolk participants, 943 CVD deaths and 1,661 non-CVD deaths occurred. The cumulative incidence of CVD and non-CVD mortality during the 10-year follow-up of the 25,492 EPIC participants were compared with the incidences generated by the RISC model, using the EPIC-Norfolk profiles as input (Figure 6, Figure 7). The observed values were within the 95% credibility intervals of the simulated values, but the RISC model overestimated the incidences for all years, for both CVD and non-CVD mortality. We then estimated the cumulative incidences of CVD and non-CVD mortality, after substituting the centered cumulative baseline hazards and average values of the risk factors with those based on the EPIC data, which recalibrated the model (Figure 8, Figure 9). After this recalibration, the observed CVD and non-CVD mortality incidences matched the simulated incidences from the RISC model.

DISCUSSION

In this study, we evaluated the internal, predictive, and external validity of the RISC model. The simulated cumulative incidence of CVD and non-CVD deaths, CHD events, and strokes adequately represented the data during the original follow-up period of 5 years on which the RISC model was based. Extrapolation of the simulated results beyond this period proved to be valid for 13 years of follow-up, the maximum length that we analyzed in this paper. Although the results of the RISC model overestimated the CVD and non-CVD mortality compared with the observed 10-year incidences in the EPIC-Norfolk population, recalibrating the model with the cumulative baseline hazards and mean values of the risk factors substantially improved performance.

Other decision models used to evaluate preventive and treatment strategies for CVD have been well established. A recent review by Unal et al identified forty-two such models, of which six major ones have been described in detail [23]. Although some of the

forty-two models reported assessment of validity, most did not. Of the six major models, three have not been validated [24-26], two models had information on internal validity reported [27, 28], and an external validation had been performed fo two models [29, 30].

In the present study, the predictive validity of the RISC model was tested against follow-up data for more than twice the length of the period on which the model was originally based. The fact that the observed and simulated incidences matched closely even when extrapolated beyond the original data makes it plausible to expect projections beyond 13 years to be valid as well. The trends in risk factors over time and their effects on the incidence of events, which are jointly modeled in the RISC model, seem to provide a valid basis to extrapolate results, without the need to recalibrate the model for the Rotterdam Study population. We furthermore showed the robustness of the internal and predictive validity by providing results for the stratified analyses by tertiles of age and sex. As for the external validation, the EPIC-Norfolk population was on average younger and healthier than the Rotterdam Study population. It was to be expected that an unadjusted model, using the baseline hazards and mean of the risk factors from the Rotterdam Study, would overestimate the observed incidences in the EPIC-Norfolk study. In the recalibrated model, we updated only the baseline cumulative hazards of the events and the mean values of the risk factors, a method very commonly used when applying models to other populations than that for which the model was originally developed in [22, 31]. This result suggests that the relative strengths of the associations of the risk factors with the incidence of the events in the RISC model are the same for both the EPIC-Norfolk population and Rotterdam Study. The resulting external validity of the RISC model after this adjustment strongly supports this assumption.

Our analysis does have some limitations. The RISC model was designed to investigate the effects of modifying cardiovascular risk factors on the burden of CVD in the middle-aged and older general population. We validated the model in the EPIC-Norfolk data, which included people aged from 45 years upwards. Although most current guidelines on the primary prevention of CVD mostly start at the age of 45 years and older, some do (or in the future potentially will), suggest that CVD prevention should begin at an earlier age Whether the RISC model also performs well in a younger population remains to be determined. The RISC model is intended to be used for projections during the remaining lifetime of an individual. The model proved to be valid for projections during 13 years of follow-up, and for most older people this is sufficiently long to cover their remaining lifespan. For younger people, this is less likely, and model extrapolation beyond this period therefore has to be made, which currently has not been validated. Because the Rotterdam Study is ongoing, and longer follow-up data are being collected, we will be able to test whether this additional extrapolation is valid as well.

A number of risk factors used for the RISC model were not documented in the EPIC-Norfolk study. To make the EPIC-Norfolk dataset suitable for the RISC model, we imputed missing data based on the correlations between the missing risk factors and the documented variables. These correlations stemmed from the Rotterdam Study data,

thereby introducing dependency between the (imputed) EPIC-Norfolk data and the RISC model. However, the major traditional risk factors such as age, sex, cholesterol level, and blood pressure were available in EPIC. The prevalence of a number of missing risk factors such as atrial fibrillation and intermittent claudication were low in the Rotterdam Study data on which the RISC model was developed, and the incremental value beyond the traditional risk factors of the other variables, such as the ankle-brachial index, has been found to be limited [32]. It is therefore less likely that the imputation influenced the external validity in favor of concordance. Although the EPIC-Norfolk dataset contains information on (hospitalized) patients with MI, the RISC model simulates CHD as a combined endpoint, including CABG and PCI. This is consistent with most clinical trials using similar combined endpoints. The design of the RISC model therefore did not allow for direct comparison of simulated MIs as a sole endpoint. Although acute MI is the major component of CHD, both CABG and PCI interventions are inherently different from acute MIs, and we therefore did not externally validate CHD events in the EPIC dataset.

At the time of this paper, we did not have datasets other than EPIC-Norfolk at our disposal to perform additional external validation. The fact that the RISC model, after updating the model with the baseline hazards and mean values for the risk factors from EPIC, proved to be valid for the EPIC-Norfolk cohort, does not automatically imply that it will be valid in other populations as well. The EPIC-Norfolk cohort was younger on average, and included more men than the RISC cohort. However, the fact that the cohort was different with regard to these important risk factors, and yet RISC still provided valid results, does make a strong case that the model will be valid for other cohorts as well. We do intend to validate the model with other data as they become available. Both the Rotterdam Study and the EPIC-Norfolk study were population-based studies and included individuals regardless of pre-existing risk-factor profiles or disease status. Although risk-factor distributions of the study participants might in principle be different from the populations they intend to represent, it is very likely that the RISC model is valid for most western European populations in general after adjusting for baseline hazards. A simpler model with a reduced set of parameters, excluding the less common ones such as atrial fibrillation and ankle-brachial index, would possibly allow for a more rapid validation process in other populations. In an ongoing effort to optimize our model, we also intend to make efforts to simplify our current model.

We modeled and validated the cardiovascular histories of the participants of the Rotterdam Study and EPIC-Norfolk cohort as they were observed; that is, without any interventions. Although the results with regard to this validity seem promising, the RISC model will be used to evaluate interventions for the primary prevention of CVD. In that case, the validity of the model to evaluate an intervention depends not only on the observed CVD history, but also on the extent to which other structural assumptions are made, such as modeling the treatment effect of an intervention [33]. A more extensive framework of model validation proposed by Kopec et al [34] also includes between-model comparisons, and comparisons of evidence from examining the consequences

of model-based decisions. Between-model comparisons are specifically useful when analyzing certain interventions compared with the natural history of the disease, as we did in the current analysis. Being a simplifying abstraction of reality, a model will be valid with regard to some (but not necessarily all) mechanisms or relationships seen in real life. Assumptions made to assure that particular mechanisms are characterized can cause the model to be less valid with regard to other possible mechanisms. This makes the modeling of complex interrelationships more of an art than an exact science. For each particular decision problem, it is important to determine the assumptions to which each approach is sensitive, determine the appropriateness of these assumptions, and judge the relevance of the model sensitivity to them in the context of the decision problem and the forthcoming decisions that will result from it.

CONCLUSIONS

This study shows that the RISC model accurately predicts mortality and CVD events during the period of 5 years on which it is based (internal validity) and during an extended follow-up period up for 13 years (predictive validity). In addition, after recalibration, it accurately predicts mortality in the EPIC-Norfolk cohort as well (external validity). These findings provide a basis to generalize results from the RISC model.

REFERENCES

1. Hayward RA, Krumholz HM, Zulman DM, Timbie JW, Vijan S: Optimizing statin treatment for primary prevention of coronary artery disease. Ann Intern Med 2010, 152:69-77.
2. Pletcher MJ, Lazar L, Bibbins-Domingo K, Moran A, Rodondi N, Coxson P, Lightwood J, Williams L, Goldman L: Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern Med 2009, 150:243-254.
3. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, Goldman L: Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med 2010, 362:590-599.
4. Hunink M GP, Siegel J, et al.: Decision making in health and medicine. Integrating evidence and values. Cambridge: Cambridge University Press; 2001.
5. van Kempen BJH, Ferket BS, Spronk S, Hofman A, Steyerberg E, Hunink M: Do different methods of modeling statin treatment effectiveness influence the optimal decision? Med Decis Making 2012.
6. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, Woolacoot N, Glanville J: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004, 8:iii-iv, ix-xi, 1-158.
7. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, Luce BR, Studies ITFoGRP--M: Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--modeling studies. Value Health 2003, 6:9-17.
8. Goldhaber-Fiebert JD, Stout NK, Goldie SJ: Empirically evaluating decision-analytic models. Value Health 2010, 13:667-674.
9. Eddy DM, Schlessinger L: Validation of the archimedes diabetes model. Diabetes Care 2003, 26:3102-3110.
10. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, Lammert M, Spinas GA: Validation of the CORE Diabetes Model against epidemiological and clinical studies. Curr Med Res Opin 2004, 20 Suppl 1:S27-40.
11. Kim LG, Thompson SG: Uncertainty and validation of health economic decision models. Health Econ 2010, 19:43-55.
12. Welsing PM, Severens JL, Hartman M, van Gestel AM, van Riel PL, Laan RF: The initial validation of a Markov model for the economic evaluation of (new) treatments for rheumatoid arthritis. Pharmacoeconomics 2006, 24:1011-1020.
13. Nijhuis RL, Stijnen T, Peeters A, Witteman JC, Hofman A, Hunink MG: Apparent and internal validity of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow-up study. Med Decis Making 2006, 26:134-144.
14. Hofman A, van Duijn CM, Franco OH, Ikram MA, Janssen HL, Klaver CC, Kuipers EJ, Nijsten TE, Stricker BH, Tiemeier H, et al: The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 2011, 26:657-686.
15. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA: Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991, 7:403-422.
16. Groot Koerkamp B, Weinstein MC, Stijnen T, Heijenbrok-Kal MH, Hunink MG: Uncertainty and patient heterogeneity in medical decision models. Med Decis Making 2010, 30:194-205.
17. Groot Koerkamp B, Stijnen T, Weinstein MC, Hunink MG: The combined analysis of uncertainty and patient heterogeneity in medical decision models. Med Decis Making 2011, 31:650-661.
18. Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, Wareham N: EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. Br J Cancer 1999, 80 Suppl 1:95-103.
19. Little R, An H: Robust likelihood-based analysis of multivariate data with missing values. Statistica Sinica 2004, 14:949-968.
20. Sinha S, Myint PK, Luben RN, Khaw KT: Accuracy of death certification and hospital record linkage for identification of incident stroke. BMC Med Res Methodol 2008, 8:74.

21. Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM: Incidence, risk, and case fatality of first ever stroke in the elderly population. The Rotterdam Study. J Neurol Neurosurg Psychiatry 2003, 74:317-321.

22. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P, Group CHDRP: Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001, 286:180-187.

23. Unal B, Capewell S, Critchley JA: Coronary heart disease policy models: a systematic review. BMC Public Health 2006, 6:213.

24. Gunning-Schepers L: The health benefits of prevention: a simulation approach. Health Policy 1989, 12:1-255.

25. Hamilton VH, Racicot FE, Zowall H, Coupal L, Grover SA: The cost-effectiveness of HMG-CoA reductase inhibitors to prevent coronary heart disease. Estimating the benefits of increasing HDL-C. JAMA 1995, 273:1032-1038.

26. Murray CJ, Lopez AD: Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997, 349:1498-1504.

27. 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, 77:1417-1426.

28. Grover SA, Abrahamowicz M, Joseph L, Brewer C, Coupal L, Suissa S: The benefits of treating hyperlipidemia to prevent coronary heart disease. Estimating changes in life expectancy and morbidity. JAMA 1992, 267:816-822.

29. Naidoo B, Thorogood M, McPherson K, Gunning-Schepers LJ: Modelling the effects of increased physical activity on coronary heart disease in England and Wales. J Epidemiol Community Health 1997, 51:144-150.

30. Capewell S, Morrison CE, McMurray JJ: Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. Heart 1999, 81:380-386.

31. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS: Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation 2009, 119:3078-3084.

32. Ankle Brachial Index C, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, et al: Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008, 300:197-208.

33. van Kempen BJ, Ferket BS, Hofman A, Spronk S, Steyerberg E, Hunink MG: Do different methods of modeling statin treatment effectiveness influence the optimal decision? Med Decis Making 2012, 32:507-516.

34. Kopec JA, Fines P, Manuel DG, Buckeridge DL, Flanagan WM, Oderkirk J, Abrahamowicz M, Harper S, Sharif B, Okhmatovskaia A, et al: Validation of population-based disease simulation models: a review of concepts and methods. BMC Public Health 2010, 10:710.

TECHNICAL APPENDIX

In this Appendix, we provide additional information on the RISC model and analyses.

RISC Model

The RISC model is a Monte Carlo state-transition model (schematically presented in Figure S1) with six states: 1) the CVD death state, 2) the non-CVD death state, 3) the Coronary Heart Disease (CHD) state, 4) the Stroke state, 5) the CHD and Stroke state and 6) the Well state (being alive without coronary heart disease or stroke). The model simulates incident CVD events in individuals based on risk factor dependent transition probabilities, using Cox regression equations. Individual risk factor profiles were modeled and tracked over time. The model was built in TreeAge (version 2009, TreeAge Software, Inc., Williamstown, USA).

Probabilities for the transitions between the six health states were based on six multivariable Cox regression equations. The development of these equations was described in a previous article on the RISC model [(1)]. The first equation estimated the cumulative hazard from the Well state to the CHD state and from the Stroke state to the CHD & Stroke state. The second equation estimated the cumulative hazard from the Well state to the Stroke state and from the CHD state to the CHD & Stroke state. In developing these models, censoring was performed for an incident stroke and CHD respectively. In both equations, previous CHD and/or stroke were included as a covariable. The third and fourth equations estimated the 6-months cardiovascular mortality rate (case-fatality) after a CHD and stroke event respectively. Six-month case-fatalities were used as proxies for the immediate fatality rates of these events. The probability of dying from a fourth CHD event and third stroke event were assumed to be 100%. The fifth and sixth Cox regression equations estimated the cumulative hazards of the remaining CVD mortality, which is caused by other causes than CHD or stroke (see Table S1 for equations). For extrapolation to a lifelong follow-up, follow-up time was divided into 5-year intervals and a cycle length of one year was chosen. The first 5 years, baseline values of covariables were used together with the one-year cumulative hazards from the Cox models for each cycle. For the remaining follow-up, the same baseline one-year cumulative hazards were used, but values of the covariables were updated every 5 years by using multiple linear regression for continuous variables and logistic regression for dichotomized variables. From the outcomes of the logistic regression equations regarding dichotomized variables, binomial distributions were created. Every 5 year period during follow-up, presence (1 or 0) of the dichotomized variables was derived from these distributions. Cumulative hazards of fatal and non-fatal events were separately weighted for their total cumulative hazards to ascertain that all probabilities for respectively cardiovascular and non-cardiovascular mortality vs. survival and stroke and CHD events vs. disease-free survival summed to one. For each transition, cumulative hazards were converted to probabilities by exponentiation. Occurrences of events and duration in each health state were stored using Monte Carlo tracker variables to allow for the calculation of incidences of the different events. These tracker variables are variables used to count the occurrences of a state transition representing an event in TreeAge.

Table S1. Model Input Parameters

Cox Proportional Hazards Equations	**Equations***
CHD:	Hazard function = baseline cumulative hazard x EXP(β1*male + β2*age + β3*age*age + β4*diabetes*glucose + β5*TC + β6*HDL +β7*PP + β8*PP*male + β9*angina + β10*ABI + β11*ABI*ABI + β12*smoking + β13*famhistMI + β14*CVD + β15*creat-β16)
Stroke:	Hazard function = baseline cumulative hazard x EXP(β1*male + β2*age + β3*hypertension + β4*hypertension*age + β5*SBP + β6*smoking + β7*famhistMI + β8*TIA + β9*CVD + β10*CVD*male + β11*AF + β12*ABI-β13)
6-months CHD event mortality:	Hazard function = baseline cumulative hazard x EXP(β1*age + β2*diabetes*glucose + β3*hypertension + β4*hypertension*age + β5*creat-β6)
6-months Stroke event mortality:	Hazard function = baseline cumulative hazard x EXP(β1*age + β2*smoking + β3*famhistCVD + β4*ABI + β5*TC + β6*creat + β7*HDL + β8*ABI*ABI + β9*age*HDL-β10)
CVD mortality:	Hazard function = baseline cumulative hazard x EXP(β1*age + β2*male + β3*diabetes + β4*HDL + β5*hypertension + β6*hypertension*age + β7*smoking + β8*CVD+β9*ABI + β10*ABI*ABI + β11*AF + β12*AF*male + β13*age*AF + β14*male*CVD + β15*CVD*TC*TC-β16)
Non-CVD mortality:	Hazard function = baseline cumulative hazard x EXP(β1*male + β2*age + β3*diabetes*glucose + β4*TC + β5*smoking + β6*smoking*age + β7*BMI + β8*BMI*age + β9*WHR + β10*WHR*age + β11*WHR*CVD + β12*famhistCVD + β13*famhistCVD*age + β14*ABI + β15*ABI*age + β16*CVD-β17)

*Beta coefficients were drawn from a table comprising estimated beta coefficients from Cox regression equations developed in 100 bootstrapped datasets.
Abreviations: ABI = ankle-brachial index, AF = atrium fibrillation, BMI = body mass index, CHD = coronary heart disease, C.I.'s = confidence intervals, creat = creatinine, CVD = cardiovascular disease, HDL = famhistMI, family history of myocardial infarction, high-density lipoprotein, famhistCVD = family history of cardiovascular disease; PP = pulse pressure, SBP = systolic blood pressure, TC = total cholesterol, TIA = transient ischaemic attack, WHR = waist-to-hip ratio

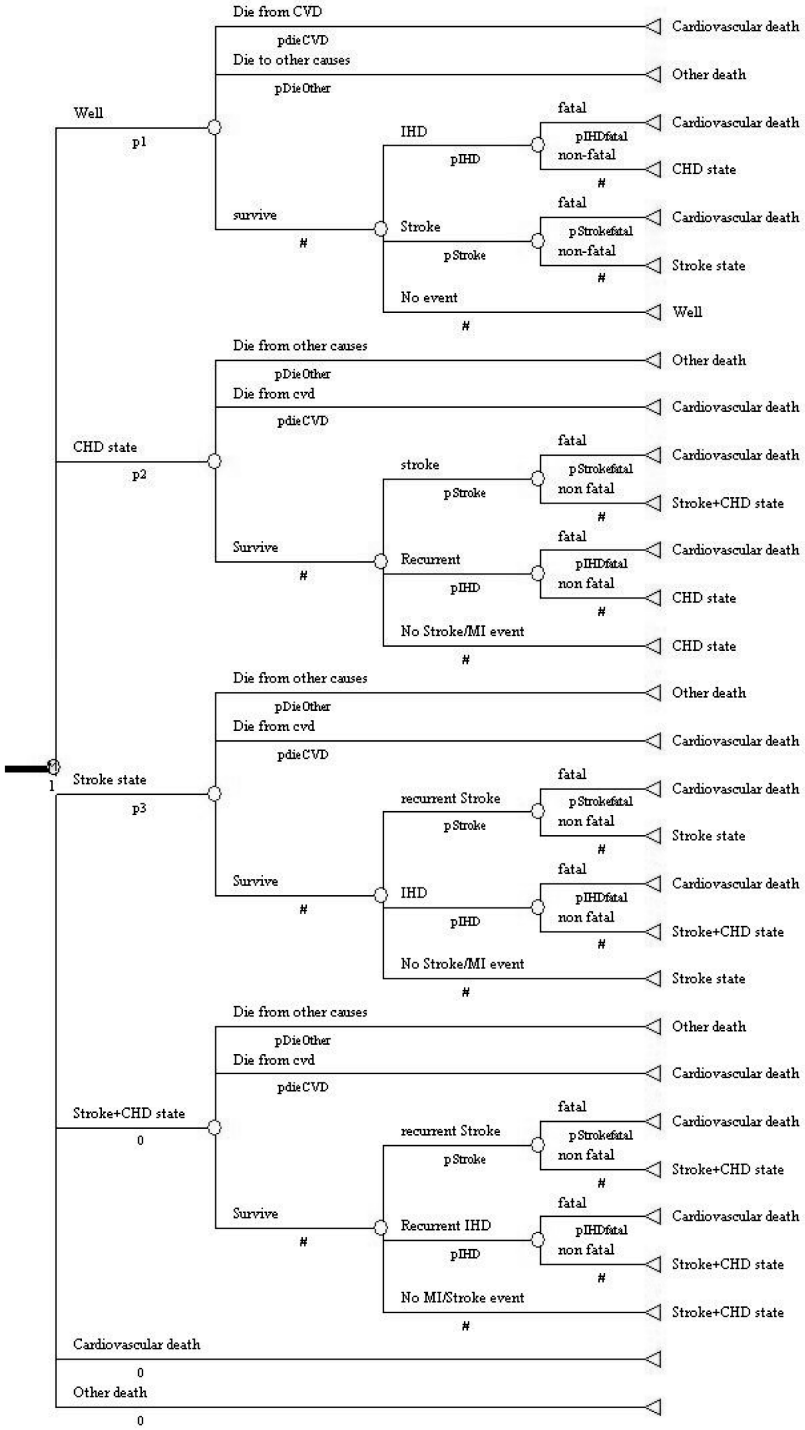


Figure S1. Schematic presentation of RISC model.

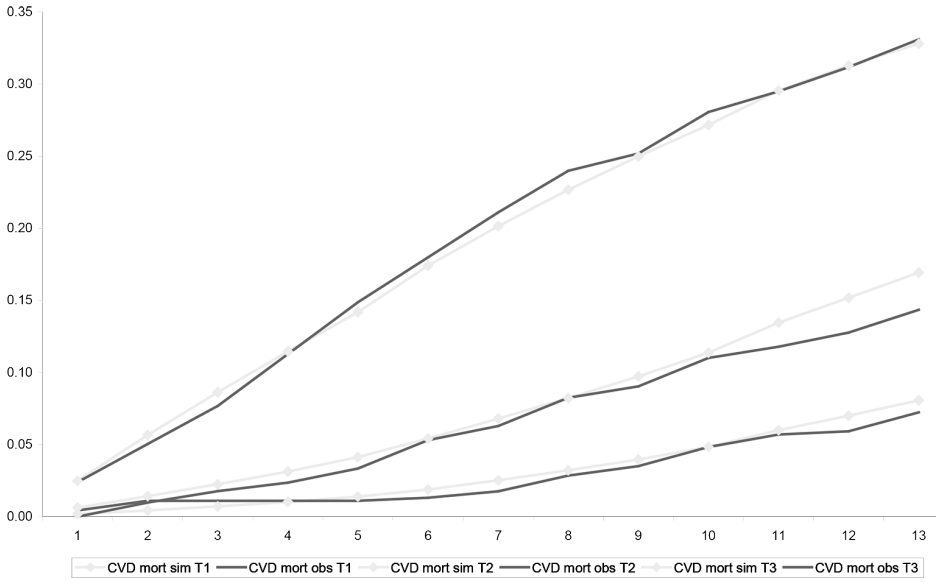


Figure S2. CVD mortality during 13 years of follow-up. Simulated vs observerd values per tertile of age in men for the Rotterdam Study data

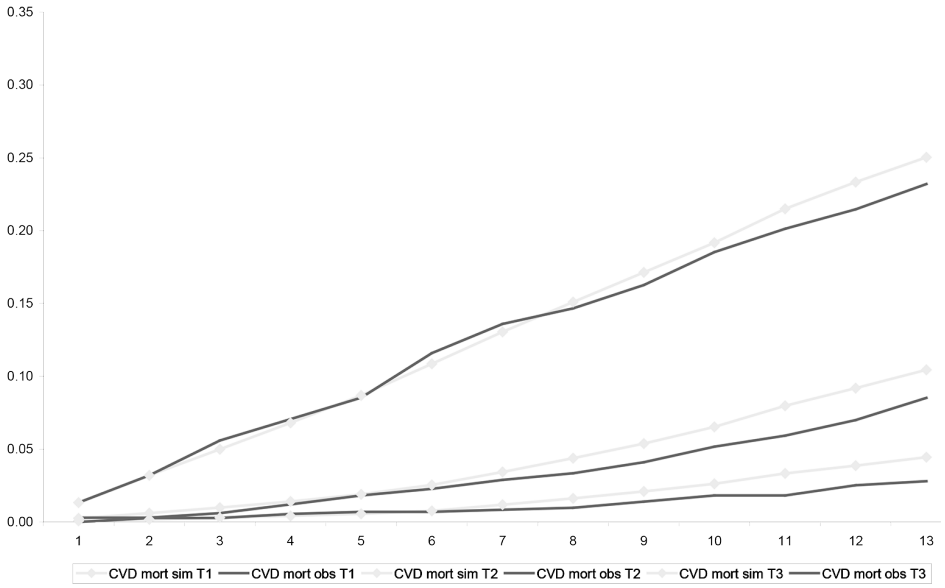


Figure S3. CVD mortality during 13 years of follow-up. Simulated vs observerd values per tertile of age in women for the Rotterdam Study data

REFERENCES

1. Nijhuis RL, Stijnen T, Peeters A, Witteman JC, Hofman A, Hunink MG. Apparent and internal validity of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow-up study. Med Decis Making 2006;26:134-44.

2. Pletcher MJ, Lazar L, Bibbins-Domingo K, et al. Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern Med 2009;150:243-54.

Chapter 4

Do different methods of modeling statin treatment effectiveness influence the optimal decision?

Bob J. H. van Kempen
Bart S. Ferket
Albert Hofman
Sandra Spronk
Ewout W. Steyerberg
M. G. Myriam Hunink

Medical Decision Making 2012 May-Jun;32(3):507-16

ABSTRACT

Purpose: Modeling studies which evaluate statin treatment for the prevention of cardiovascular disease (CVD) use different methods to model the effect of statins. The aim of this study was to evaluate the impact of using different modeling methods on the optimal decision found in such studies.

Method: We used a previously developed and validated Monte Carlo-Markov model based on the Rotterdam Study (RISC model). The RISC model simulates coronary heart disease (CHD), stroke, cardiovascular death and death due to other causes. Transition probabilities were based on 5-year risks predicted by Cox regression equations, including (amongst others) total and HDL cholesterol as covariates.

In a cost-effectiveness analysis of implementing the ATP-III guidelines we evaluated the impact of using three different modeling methods of statin effectiveness: *(I) Through lipid level modification:* statins lower total cholesterol and increase HDL, which through the covariates in the Cox regression equations leads to a lower incidence of CHD and stroke events; *(II) Fixed risk reduction of CVD events:* statins decrease the odds of CHD and stroke with an associated odds ratio which is assumed to be the same for each individual; *(III) Risk reduction of CVD events proportional to individual change in LDL Cholesterol:* the relative risk reduction with statin therapy on the incidence of CHD and stroke was assumed to be proportional to the absolute reduction in LDL-cholesterol levels, for each individual. The probability that the ATP-III strategy was cost-effective, compared to usual care as observed in the Rotterdam study, was calculated for each of the three modeling methods for varying willingness-to-pay thresholds.

Result: Incremental cost-effectiveness ratios for the ATP-III strategy compared with the reference strategy were 56,642 euro/QALY, 21,369 euro/QALY and 22,131 euro/QALY for modeling method I, II and III respectively. At a willingness-to-pay of 50,000 euro/QALY, the probability that the ATP-III strategy was cost effective was about 40% for modelling method I, and more than 90% for both method II and III. Differences in results between the modeling methods were sensitive to both the time horizon modeled and age distribution of the target population.

Conclusion: Modeling the effect of statins on CVD through the modification of lipid levels produced different results and associated uncertainty than modeling it directly through a risk reduction of events. This was partly attributable to the modeled effect of cholesterol on the incidence of stroke.

INTRODUCTION

As the burden of cardiovascular disease (CVD) is still increasing globally, the primary prevention of CVD is more important than ever. Most Western populations are ageing, and given limited health care resources, research in CVD prevention should evaluate not only effectiveness but also cost-effectiveness. Randomized clinical trials in this area are scarce and a number of recent papers have used simulation models to analyze the cost-effectiveness of preventive interventions for CVD [1-11]. Frequently, the intervention in these studies consisted of statin treatment for asymptomatic individuals, often based on the third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (ATP-III) [12].

As in all modeling studies, assumptions have to be made for the relationship between the disease of interest and the intervention proposed [1-2, 5-6, 8, 10, 13]. The assumptions made differed between the reviewed simulation models. Some authors modeled the effect of statin therapy through the modification of lipid levels [2, 8, 14-18], others used observed risk reductions from trials [9, 19-21], or used a combination of lipid level changes and observed risk reductions [1]. A natural question arises when optimizing effectiveness and cost-effectiveness of statin therapy: does making different structural model assumptions about the treatment effect of a statin change the decision about statin initiation? If so, a decision maker, faced with the results from a modeling study, should interpret the conclusion in light of these assumptions.

As the ATP-III guidelines are frequently studied with decision models, it provides a suitable decision analytic example to illustrate the use of different modeling methods of statin effectiveness [12]. The purpose of this study was to evaluate the impact of using different methods of modeling statin treatment effectiveness on the lifetime effectiveness and cost-effectiveness of implementing the ATP-III guidelines.

METHODS

To evaluate the impact of using different methods of modeling treatment effectiveness of a statin, we used the previously developed Rotterdam Ischemic Heart Disease & Stroke Computer Simulation Model (RISC model). The model will be briefly outlined, after which three different modeling methods of statin effectiveness will be described, applied to the RISC model. Finally the decision problem used to evaluate the different modeling methods will be outlined.

The model

The RISC model is a Monte Carlo state-transition model (schematically presented in Figure 6 of the technical appendix) with six states: (1) the CVD death state, (2) the non-CVD death state, (3) the coronary heart disease (CHD) state, (4) the Stroke state, (5) the CHD and Stroke state and (6) the Well state (being alive without coronary heart disease

or stroke). The model simulates incident CVD events in individuals based on risk factor dependent transition probabilities, using Cox regression equations. Individual risk factor profiles were modeled and tracked over time. The model was built in TreeAge (version 2009, TreeAge Software, Inc., Williamstown, USA). Detailed information about the model is given in an earlier publication [22] and technical appendix.

The Rotterdam Study

In the RISC model the risk factor profiles and transition probability functions were based on data from the Rotterdam study population [23]. 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 accurate follow-up of death and clinical manifestations of CVD.

In 3501 individuals all important characteristics to predict CVD were completely 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 [23]. We define a CVD event as any of the following events: a fatal or non-fatal myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), fatal or non fatal ischemic or unspecified stroke, or death due to heart disease, cerebrovascular disease or other arterial disease.

Modeling statin effectiveness

In this study, three methods of modeling statin effectiveness applied to the RISC model were evaluated:

(I) *Through lipid level modification:* clinical trials have shown that statins increase HDL-cholesterol, and decrease both total cholesterol, triglycerides and LDL-cholesterol (24). In the RISC model, both total cholesterol and HDL-cholesterol are included in the Cox regression equations describing the hazards of a (fatal or non-fatal) CHD event (myocardial infarction, percutaneous transluminal angioplasty, or coronary artery bypass graft intervention), the 6-month case-fatality rate after a stroke event, and other cardiovascular mortality (CVD related mortality, not due to a fatal CHD or stroke event within 6 months). Table 1 provides an overview of the hazard rate ratios for both total and HDL cholesterol underlying the transition probabilities for these 3 events. In accordance with earlier research [25], the total incidence of

stroke is unchanged by total and HDL-cholesterol – only the fraction of fatal events is reduced. This method of modeling statin effectivenss assumes that the statin-induced reduction in total cholesterol and increase in HDL cholesterol, causes a decrease in the hazard rates for cardiovascular related events via the Cox regression equations, and lowers the annual probabilities of having such events in the model, compared with not taking statins. Based on the most recent meta-analysis by Brugts et al [24], we assumed an average 15.7% reduction in total cholesterol from baseline when using statins and a 3.1% increase in HDL.

Table 1. Hazard rate ratios in transition probabilities relating to Total cholesterol and HDL cholesterol.

Transition probability	**Hazard rate ratio per 1 mmol/L increase in Total cholesterol [95% confidence interval]****	**Hazard rate ratio per 1 mmol/L increase in HDL cholesterol [95% confidence interval]******
CHD event¶	1.22 [1.13 1.36]	0.30 [0.18 0.44]
Stroke event§	n/a	n/a
6 month fatality rate after a CHD event	n/a	n/a
6 month stroke case fatality rate	0.78 [0.62 0.93]	Age 60 – 0.14† Age 65 – 0.26† Age 70 – 0.46† Age 75 – 0.86† Age 80 – 1.56†
Other CVD mortality±	1.01 [0.99 1.03]	n/a

* Anual transition probabilities
** Hazard rate ratio > 1 indicates that a 1 mmol/L increase in Total or HDL cholesterol increases the specific probability
¶ A CHD event is defined as fata or non-fatal myocardial infarction, CABG or PCI
§ A stroke event is defined as a fatal or non-fatal ischemic or unspecified stroke event
± Other CVD mortality is defined as mortality due to heart disease, cerebrovascular disease or other arterial disease, not due to a fatal CHD or stroke event within 6 months
† HDL cholesterol included as variable on its own and as interaction term with age. An increase in HDL cholesterol lowers this hazard up until age 76, and increases the hazard for individuals aged 77 and over
n/a: not applicable, i.e. total cholesterol or HDL-cholesterol was not included in the regression equation underlying the specific state transition probability

(II) *Fixed risk reduction of CVD events:* based on the same meta-analysis, clinical trials have shown an average reduction in the incidence of a first fatal or non-fatal myocardial infarction (OR 0.7 95%CI [0.61 0.81]) and first fatal or non-fatal stroke event (OR 0.81 95%CI [0.71 0.93]) [24]. Directly applying these odds ratio's to the annual odds of a first fatal or non-fatal myocardial infarction and fatal or non-fatal stroke, lowers the incidence of having such events in the model, compared with not taking statins. We assumed that the case-fatality rate following a CHD or stroke event remained unchanged.

(III) *Risk reduction of CVD events proportional to individual change in LDL cholesterol:* the third modeling method assumes that the statin induced reduction in LDL cholesterol is an indicator of the risk reduction that can be expected from statin therapy. Given an individual's baseline LDL cholesterol, the expected absolute reduction in LDL cholesterol in mmol/L was calculated, based on the same meta-analysis as used in methods 1 and 2 which demonstrated an average relative reduction in LDL of 23.7% [24]. Based on another source, the risk reduction in the incidence of first fatal or non-fatal myocardial infarction was estimated to be 0.23 per mmol/L LDL reduction, and 0.17 for first fatal or non-fatal stroke [26]. Multiplying each individual's baseline LDL level (mmol/L) with the relative reduction in LDL and with the risk reduction per mmol/L LDL reduction, we obtained each individual's estimated risk reduction under statin therapy. Applying these individual risk reductions to the annual probabilities of a first non-fatal myocardial infarction and first fatal or non-fatal stroke, lowers the incidence of having such an event in the model, compared with not taking statins. This method differs from method I, because it does not affect the beta-coefficients in the state-transition probabilities but affects the probabilities of incident myocardial infarction and stroke similarly as method II. It does differ from method II, as the risk reduction is not fixed for each individual, but depends on the individual's baseline LDL level.

Decision Problem

To illustrate the impact of using the three different methods, the cost-effectiveness of applying the ATP-III guidelines [12] to the Rotterdam study population, compared to current practice without implementing the ATP-III guidelines (reference strategy). For simplicity we assumed that the individuals in the Rotterdam study did not use statins at baseline. For the ATP-III guidelines strategy, we assumed that an individual would be assigned a statin if one of the following were true:

(1) The predicted 10-year risk for a hard CHD event, based on the Framingham risk score [27] would be lower than 10%, and baseline LDL cholesterol would exceed 160 mg/dL
(2) The predicted 10-year Risk based on the Framingham risk score would be between 10 and 20%, and baseline LDL cholesterol would exceed 130 mg/dL
(3) The predicted 10-year Risk based on the Framingham risk score would be 20% or higher, and baseline LDL cholesterol would exceed 100 mg/dL
(4) An individual had experienced a previous CVD event at baseline
(5) An individual had been diagnosed with diabetes at baseline

We did not explicitly model the exact dosage and type of statin given to an individual, but assumed that the statin type and dose would match those covered in the meta-analyses [24, 26] used. We used tracker variables to model myopathy and hepatitis, two of the most important side effects of statins, and used hazard rate ratios to model the increased risk of these events due to statin use based on a meta-analysis of side effects [28]. We modeled the associated decrease in quality of life and costs of both events [2]. For the

purpose of this study, adherence to statin treatment was assumed to be equivalent to that obtained in the studies included in the meta-analysis.

Table 2 provides an overview of the most important parameter values with regard to probabilities, costs and utilities. Parameter distributions were determined directly from its source, or additional assumptions were made.

Table 2. Important model parameters and assumptions.

Model assumptions			
Parameter	**Base case – 95%CI**	**Distribution**	**Reference**
Statin cost per year	300 euro"		(33)
% decrease total cholesterol with statin	15.7 [15.0 16.6]	beta	(34)
% decrease LDL cholesterol with statin	23.7 [22.7 25.6]	beta	(35)
% increase HDL cholesterol with statin	3.1 [2.7 3.5]	Beta	(24)
Odds ratio non fatal and fatal myocardial infarction with statin	0.70 [0.61 0.81]	lognormal	(24)
Odds ratio non fatal and fatal stroke with statin	0.81 [0.71 0.93]	lognormal	(24)
Relative risk reduction per mmol/L decrease in LDL cholesterol on non fatal and fatal myocardial infarction with statin	0.77 [0.74 0.8]	lognormal	(24)
Relative risk reduction per mmol/L decrease in LDL cholesterol on non fatal and fatal stroke with statin	0.83 [0.78 0.88]	lognormal	(24)
5 year risk of myopathy episode with statin	0.002	binomial	(26)
Hazard rate ratio of a myopathy episode during one year with statin use	6.15 [5.19 7.3] (men) ; 2.97 [2.36 3.74] (women)	gamma	(26)
Cost of myopathy*	238 euro	-	(28)
QALY loss myopathy*	0.18	-	(28)
5 year risk of hepatitis episode with statin	0.014	binomial	(2,28)
Hazard rate ratio of a hepatitis episode during one year with statin use	1.53 [1.41 1.66]	gamma	(2,28)
Cost of hepatitis*	116.5 euro	-	(28)
QALY loss hepatitis*	0.0429	-	(28)

* Number given is a one time decrease in quality adjusted life years and a one time cost penalty for one episode of myopathy or hepatitis. Details of these numbers are provided in the technical appendix
" Assumed use of generic statins

Analysis

For each of the 3501 individuals, the 10-year Framingham risk score, based on the original paper from 1998, was calculated [27]. Important baseline variables were calculated, stratified by three risk categories: low (10 year Framingham risk <10%), intermediate (10-20%) and high (>20%). Individuals with a history of CVD or diabetes at baseline were considered to be at high risk. Quality-adjusted life years (QALYs), life time costs, incremental cost-effectiveness ratios (i.e., additional costs divided by QALYs gained) were calculated for the ATP-III strategy and reference strategy, for all three modeling methods separately. To take time preference into account, future costs and effectiveness were discounted at the currently recommended U.S. discount rate of 3% for both costs and effectiveness [29]. Strategies were first ordered according to increasing cost. A strategy was considered dominated if another strategy was both more effective and less costly. A strategy was considered extended dominated if another strategy achieved more effectiveness at a lower incremental cost-effectiveness ratio. After eliminating dominated and extended dominated strategies, the incremental cost-effectiveness ratios were calculated as the difference in mean lifetime costs divided by the difference in mean QALYs for each strategy compared to the next best non-dominated strategy.

A three-level simulation was performed. The first loop consisted of 1000 parameter drawings, including the joint distributions of the beta coefficients from the Cox proportional hazards equations, representing parameter (second order) uncertainty. The second loop consisted of a fixed subset of 200 randomly drawn individuals from the 3501 individuals, each with their own risk profile, representing heterogeneity. Average values of the baseline characteristics for these 200 individuals were not significantly different from those of the 3501 individuals. The third and final loop consisted of 100 random walks (stochastic uncertainty) which was necessary because multiple tracker variables were used in the model [30]. For each of the three modeling methods, we calculated the probability that the ATP-III strategy was cost-effective, for a range of willingness-to-pay thresholds, generating acceptability curves.

In order to get more insight into possible differences between the modeling methods with regard to the ICERs, we determined intermediate outcomes such as the age of death, the percentage of all deaths due to CVD and non-CVD causes, and the percentage of individuals with incident CHD, stroke and total incident CVD.

Sensitivity analysis

As the first method directly affects both the hazards of CVD events and other CVD mortality, and includes an interaction with age and HDL cholesterol in one of the transition probabilties, the potential differences in outcomes between the three methods are anticipated to be sentitive to the time horizon modeled, as well as the age range of the population simulated. In a sensitivity analysis, we checked whether the results would be different when using a follow up of 5, 10, 15 and 20 years. In another sensitivity analysis, we stratified the analysis by age groups. We ran the (lifetime) simulation with individuals who belonged to the first, second, third and fourth age

quartile, respectively. We calculated the ICER of implementing ATP-III vs the reference strategy, and the probability that the ATP-III stratey was cost-effective, for each of the modeling methods in each subgroup and a willingness-to-pay of 50,000 euro.

RESULTS

Base case analysis

Important baseline characteristics of the 3501 individuals from the Rotterdam Study, stratified by the Framingham risk score categories can be found in Table 3. As expected, on average risk factor profiles were less favourable for individuals in higher risk categories. The incremental cost-effectiveness ratio's of the ATP-III strategy compared with the reference strategy for the three different modeling methods were 56,642 euro/QALY, 21,369 euro/QALY and 22,131 euro/QALY, respectively (Table 4). Acceptability curves (Figure 1) show that for a willingness-to -pay between 30,000 and 60,000 euro/QALY, the ATP-III guidelines strategy had a less than 50% probability of being cost-effective using modeling method I, but more than 85% probability of being cost-effective using modeling method II or III.

Table 3. Baseline characteristics of the 3501 individuals of the Rotterdam Study. Mean values and standard devations between brackets.

Variable	Low Risk N= 1400	Intermediate Risk N = 1058	High Risk* N = 1043
Age, Years	66 (7.90)	71 (8.15)	72 (9.78)
Men (%)	3%	55%	66%
Glucose level (mmol/L)	6.11 (1.31)	6.57 (1.35)	7.86 (2.81)
BMI	25.9 (4.74)	27.9 (3.92)	26.8 (2.77)
Total Cholesterol (mg/dL)	257.6 (42.4)	252.0 (49.4)	262.4 (44.3)
HDL Cholesterol (mg/dL)	57.7 (14.8)	54.6 (17.9)	45.7 (15.6)
LDL Cholesterol (mg/dL)	169.3 (36.5)	167.7 (43.7)	181.6 (36.5)
Waist to hip ratio	0.85 (0.07)	0.98 (0.09)	0.94 (0.08)
Systolic Blood Pressure (mm Hg)	129 (17)	140 (17)	149 (18.6)
Diagnosed with Hypertension (%)	10%	39%	55%
Diagnosed with Diabetes Mellitus (%)	-	-	28%

*Includes individuals with a history of CVD or Diabetes at baseline.

Table 4. Average costs, QALYs and incremental cost-effectiveness ratio's (ICER) for the reference strategy and the ATP-III strategy calculated with each modeling method. The ICER comparing ATP-III with the reference strategy is presented for each modeling method.

	Cost (Euro) [95%CI]	QALY [95%CI]	ICER (Euro/QALY)
Reference Strategy[¶]	10,230 [9,623 10,942]	9.35 [8.97 9.75]	
I. Through Lipid Level Modification	12,942 [12,321 13,599]	9.40 [9.02 9.80]	56,642
II. Fixed Risk Reduction	12,702 [12,046 13,396]	9.47 [9.09 9.87]	21,369
III. Risk Reduction proportional to LDL	12,736 [12,135 13,739]	9.47 [9.09 9.87]	22,131

[¶] Reference strategy consists of the current practice in the Rotterdam Study without implementing the ATP-III guidelines

Intermediate outcomes

The age at death increased with the ATP-III strategy compared to the reference strategy and was the highest for method II and III (Table 5). Of all deaths, the percentage from CVD decreased with ATP-III and as a consequence, the non-CVD causes of death increased slightly, which was the most prominent with methods II and III. Incident CHD and CVD decreased with ATP-III, but the decrease was larger with modeling method II and III compared to method I. The incidence of stroke decreased with method II and III, but increased slightly with method I.

Sensitivity analysis

The four selected groups based on age-quartiles were on average 59, 65, 71 and 81 years of age. Figure 2 shows that the incremental cost-effectivess of the ATP-III guidelines declined when older populations were simulated compared with younger ones, for method II and III, but increased for method I. Figure 3 shows that an increase in follow-up duration decreased the ICER of the ATP-III strategy in general, but the decline was larger with method I compared to II and III.

The probability that the ATP-III strategy is cost-effective declines when older populations are simulated with method I, while it increases slightly with method II and III (Figure 4). Longer follow-up was associated with a higher probability that the ATP-III strategy is cost effective for all three methods (Figure 5).

Table 5. Intermediate outcomes for the base case analysis for each of the three modeling methods.

	Age at death	% that died from CVD cause	% that died from other cause	% with incident CHD	% with incident Stroke	% with incident CVD
Reference Strategy	86.6	38.1	61.9	13.6	19.4	20.7
ATP-III: I. Through Lipid Level Modification	86.7	37.7	62.3	11.2	19.6	19.4
ATP-III: II. Fixed Risk Reduction	86.8	36.9	63.1	10.4	17.1	18.3
ATP-III: III. Risk Reduction proportional to LDL	86.8	36.9	63.1	10.7	17	18.1

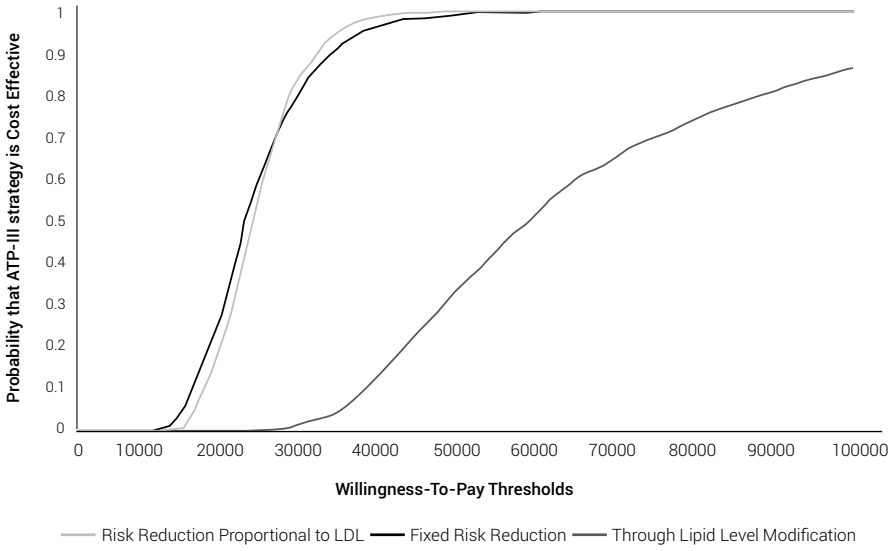


Figure 1. Acceptability curves showing the probability that the ATP-III strategy is cost effective for each of the three modeling methods, for a range of willingness-to-pay values.

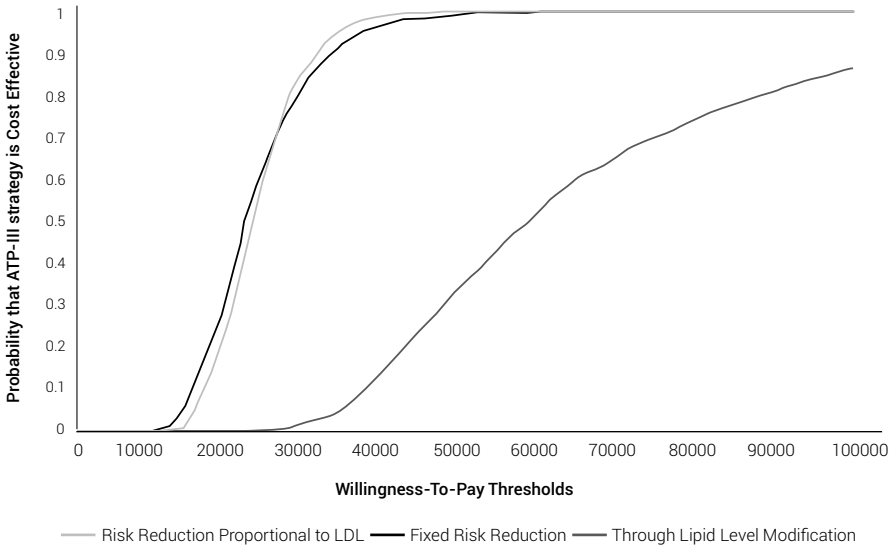


Figure 2. Incremental Cost-Effectiveness Ratio's for the four age-quartiles, for modeling method I, II and III.

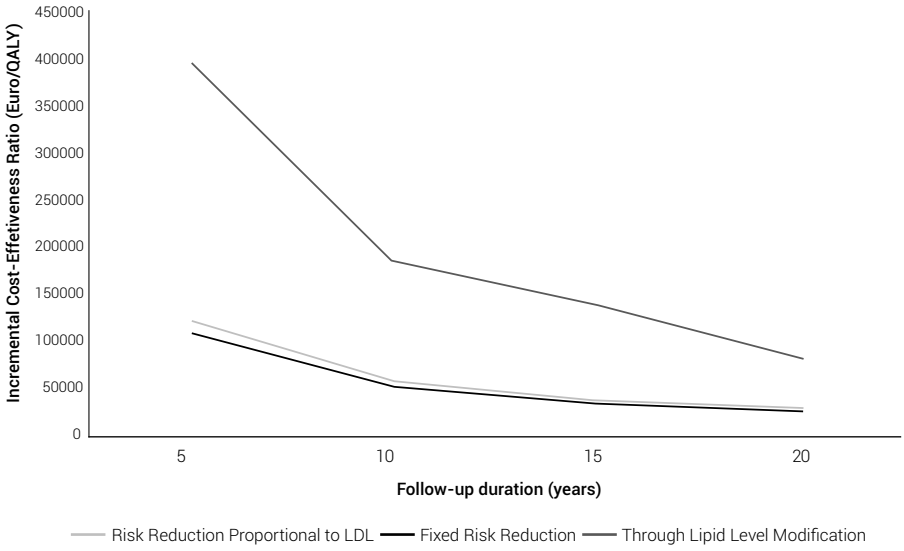


Figure 3. Incremental Cost-Effectiveness Ratio's for the four different follow-up durations, for modeling method I, II and III.

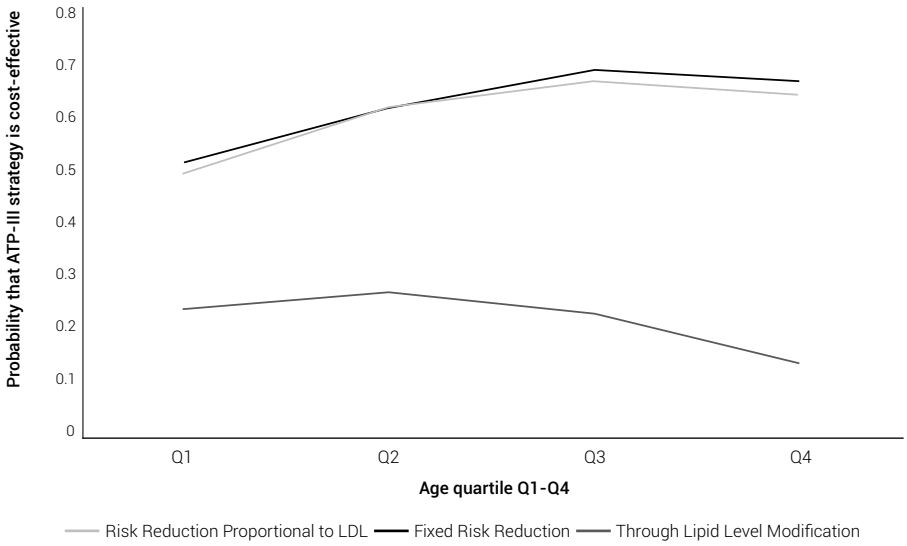


Figure 4. Probabilities that the ATP-III strategy is cost-effective given a willingness-to-pay of 50,000 Euro / QALY, for the four age-quartiles, for each of the three modeling methods.

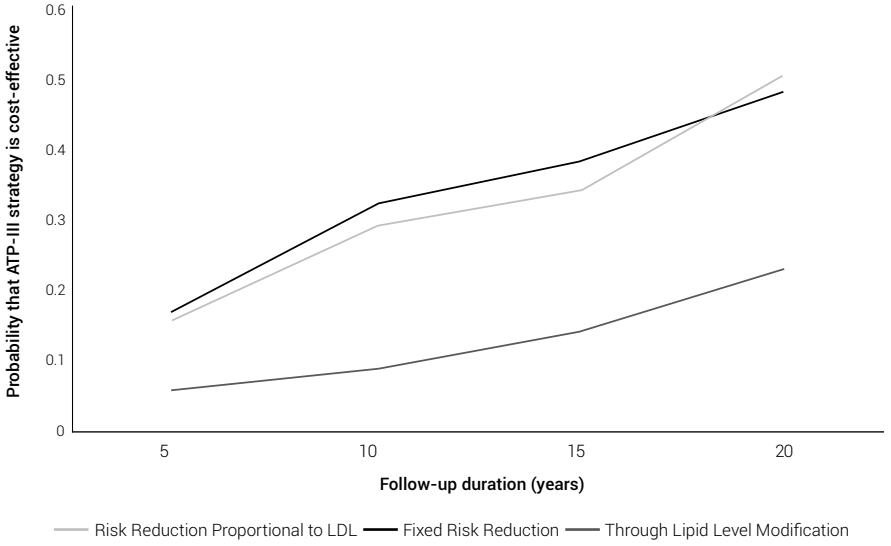


Figure 5. Probabilities that the ATP-III strategy is cost-effective given a willingness-to-pay of 50,000 Euro / QALY, for the four different follow-up durations, for each of the three modeling methods.

DISCUSSION

In this study, we evaluated the consequences of using different modeling methods of statin treatment effectiveness on the cost-effectiveness of implementing the ATP-III guidelines for the primary prevention of cardiovascular disease. We found that different modeling assumptions about the effect of statin therapy affected the results such that the optimal decision would change. For willingness-to-pay thresholds of 30,000 – 60,000 euro/QALY, modeling methods II and III would lead to the conclusion that the ATP-III guidelines are cost-effective, whereas using method I would lead to the conclusion that the ATP-III guidelines are not cost-effective.

These results were not obvious a priori as the three methods influence different events compared to another. Modeling method I leads to a lower probability of CHD, the 6-month case-fatality rate after a stroke (a conditional probability) and other cardiovascular mortality. Methods II and III lower the incidence of CHD and stroke as well, but do not affect the latter two probabilities. An indirect effect was present on the incidence of stroke with model I: since the hazard rate ratio of incident stroke is unchanged with statins with method I and as a result of competing risks in the model, an increase in the incidence of stroke was observed compared with this method compared to the reference strategy. As strokes are an important determinant of cardiovascular disease, these differences between the modeling methods partly explain the QALY and cost disadvantage for method I compared to II and III.

Two important sensitivity analyses showed how age and the decision time-frame influenced our findings. For individuals aged 77 and over, a statin-induced increase in HDL cholesterol would lead to an increase in the hazard of stroke mortality due to the interaction with age (Table 1). This can partly explain the steep increase in the ICER of the ATP-III with this method, observed in Figure 2. The steeper decline in ICER of the ATP-III with method I when follow-up is extended from 5 to 10 years can be explained by the fact that a substantial part of the effect of statin treatment with this method is obtained through the reduction in other CVD mortality. The probability of CVD mortality is higher after a non-fatal CVD event and non-fatal CVD events accumulate with a longer follow-up.

Are these findings generalizable to other models than the RISC model and would a similar difference between method I vs II/III have been found? Several investigators have modeled the treatment effect of a statin similar to method I [2, 8, 14-18]. These models are, just like the RISC model, based on risk factor dependent transition probabilities with total and HDL-cholesterol as lipid-based risk factors [15-18]. The treatment effect of statins was, similar to method I, modeled through these risk factors and accompanying regression coefficients. While the magnitude of the beta coefficients of total and HDL-cholesterol may differ from those in the RISC model, it is highly likely that similar associations between cholesterol risk factors and CHD and stroke events would have been found. More specifically, other data supports the lack of an association between

total cholesterol, HDL cholesterol and incident stroke [25], but did find a trend for HDL cholesterol on fatal stroke. Thus, any simulation model based on risk factor dependent transition probabilities based on observational data, that would incorporate stroke events, would likely be subject to the same phenomenon as observed with modeling method I in the RISC model. It would be interesting to see if models using a method similar to method I would report worse cost-effectiveness ratios of statin interventions than models using a method similar to method II or III. However, the papers we looked into were too heterogeneous with regard to the exact statin-based intervention to make a meaningful comparison.

With regard to the possible mechanisms underlying the treatment effect of statins, other authors have suggested that statins have a cardioprotective effect beyond the improved lipid levels [31-32]. This would suggest a preference for methods II and III, which directly model the relation between statin therapy and outcomes and capture the (potential) effects on events beyond lipid lowering. However, the validity of a model only partly depends on the structural modeling of the treatment effect. Being a simplifying abstraction of reality, a model will be valid with regard to some (but not necessarily all) mechanisms or relationships as observed in real life. Assumptions made to assure that particular mechanisms are characterized can cause the model to be less valid with regard to other possible mechanisms. For example, if the decision problem requires that the modeled reduction in incident CHD and stroke corresponds to the same reduction as observed in trials, the resulting reduction in fatal total CVD events produced by this model is unlikely to match the observed reduction in fatal total CVD events in the same trials if no further adjustments or assumptions are introduced. This makes the modeling of complex interrelationships more of an art than an exact science. For each particular decision problem it is important to determine which assumptions each approach is sensitive to, determine the appropriateness of these assumptions, and judge the relevance of the model sensitivity to them in the context of the decision problem studied. Rather than determining the validity of the three methods against some arbitrary chosen ''gold standard'', we demonstrated how the different methods currently used in practice can affect the results and alter the conclusions of a decision analysis.

Our study bears some limitations. The state transition probabilities in the RISC model did not include LDL cholesterol as a covariate. Similarly, the original Framingham risk score and the European SCORE function, do not include LDL cholesterol as well. Instead, they include HDL and total cholesterol, as does the RISC model. Although we demonstrate large differences in results, our study does not provide information on which modeling method is optimal. The complex interplay between various aspects of Markov decision models, including competing risks and extrapolation to lifetime events, make it practically impossible to say beforehand which method would be preferable in terms of model validity. The only proper way to find out is to perform a thorough validation analysis, both internal and external, before a simulation model is used to evaluate a decision problem.

In our analysis, we evaluated the ATP-III treatment scenario. Although our results could be different for other statin treatment scenario's – such as pure risk-based treatment interventions, it is likely that such scenarios are subject to the same effects of modeling treatment effectiveness. Though we explicitly looked into the effect of statins, other interventions targeting risk factors or intermediate outcomes in primary prevention of cardiovascular disease such as smoking cessation, weight loss and blood pressure are likely to be subject to the same phenomenon. Smoking status, systolic and diastolic blood pressure, and weight-related risk factors such as BMI or waist-to-hip ratio are included as covariates in the RISC model. An intervention on these risk factors can be assumed to work through the modification of these covariates, similar to method I, or directly on event incidence rates as in method II and III. With this in mind, our results further stress the importance of thorough consideration of the assumptions underlying a simulation model and performing extensive model validation.

In conclusion, this study points out that the choice of modeling method of the effectiveness of statin treatment in simulation studies can influence the optimal decision and the uncertainty associated with it.

REFERENCES

1. Hayward RA, Krumholz HM, Zulman DM, Timbie JW, Vijan S. Optimizing statin treatment for primary prevention of coronary artery disease. Ann Intern Med 2010;152:69-77.
2. Pletcher MJ, Lazar L, Bibbins-Domingo K, et al. Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern Med 2009;150:243-54.
3. Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med 2010;362:590-9.
4. 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.
5. Jacobs-van der Bruggen MA, Engelfriet PM, Hoogenveen RT, et al. Lipid-lowering treatment for all could substantially reduce the burden of macrovascular complications of diabetes patients in the Netherlands. Eur J Cardiovasc Prev Rehabil 2008;15:521-5.
6. Kongnakorn T, Ward A, Roberts CS, O'Brien JA, Proskorovsky I, Caro JJ. Economic evaluation of atorvastatin for prevention of recurrent stroke based on the SPARCL trial. Value Health 2009;12:880-7.
7. Kottke TE, Faith DA, Jordan CO, Pronk NP, Thomas RJ, Capewell S. The comparative effectiveness of heart disease prevention and treatment strategies. Am J Prev Med 2009;36:82-88.
8. Martikainen JA, Soini E, Paulsson T. Cost-effectiveness of single agent, uptitration and switching statin treatment strategies for lipid lowering in Sweden. Curr Med Res Opin 2010;26:389-96.
9. Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Ann Intern Med 2006;144:326-36.
10. Roze S, Liens D, Palmer A, Berger W, Tucker D, Renaudin C. A health economic model to determine the long-term costs and clinical outcomes of raising low HDL-cholesterol in the prevention of coronary heart disease. Curr Med Res Opin 2006;22:2549-56.
11. Smith-Spangler CM, Juusola JL, Enns EA, Owens DK, Garber AM. Population strategies to decrease sodium intake and the burden of cardiovascular disease: a cost-effectiveness analysis. Ann Intern Med 2010;152:481-7, W170-3.
12. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227-39.
13. 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.
14. Huse DM, Russell MW, Miller JD, et al. Cost-effectiveness of statins. Am J Cardiol 1998;82:1357-63.
15. Goldman L, Weinstein MC, Goldman PA, Williams LW. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. JAMA 1991;265:1145-51.
16. Hamilton VH, Racicot FE, Zowall H, Coupal L, Grover SA. The cost-effectiveness of HMG-CoA reductase inhibitors to prevent coronary heart disease. Estimating the benefits of increasing HDL-C. JAMA 1995;273:1032-8.
17. Martens LL, Rutten FF, Erkelens DW, Ascoop CA. Clinical benefits and cost-effectiveness of lowering serum cholesterol levels: the case of simvastatin and cholestyramine in The Netherlands. Am J Cardiol 1990;65:27F-32F.
18. Murray CJ, Lauer JA, Hutubessy RC, et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. Lancet 2003;361:717-25.
19. Greving J, Visseren F, de Wit G, Algra A. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. BMJ 2011;342:d1672.

20. Capewell S, Morrison CE, McMurray JJ. Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. Heart 1999;81:380-6.

21. Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. Lancet 2006;368:679-86.

22. Nijhuis RL, Stijnen T, Peeters A, Witteman JC, Hofman A, Hunink MG. Apparent and internal validity of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow-up study. Med Decis Making 2006;26:134-44.

23. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam Study: 2010 objectives and design update. Eur J Epidemiol 2009;24:553-72.

24. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ 2009;338:b2376.

25. Bots ML, Elwood PC, Nikitin Y, et al. Total and HDL cholesterol and risk of stroke. EUROSTROKE: a collaborative study among research centres in Europe. J Epidemiol Community Health 2002;56 Suppl 1:i19-24.

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

27. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.

28. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006;97:52C-60C.

29. Gravelle H, Brouwer W, Niessen L, Postma M, Rutten F. Discounting in economic evaluations: stepping forward towards optimal decision rules. Health Econ 2007;16:307-17.

30. Groot Koerkamp B, Weinstein MC, Stijnen T, Heijenbrok-Kal MH, Hunink MG. Uncertainty and patient heterogeneity in medical decision models. Med Decis Making 2010;30:194-205.

31. Yeung AC, Tsao P. Statin therapy: beyond cholesterol lowering and antiinflammatory effects. Circulation 2002;105:2937-8.

32. Almuti K, Rimawi R, Spevack D, Ostfeld RJ. Effects of statins beyond lipid lowering: potential for clinical benefits. Int J Cardiol 2006;109:7-15.

33. Rice Nea. Red Book 2009: Pharmacy's Fundamental Reference (Red Book Drug Topics). 113 ed: Thomson Reuters, 2009.

34. Kauf TL, Velazquez EJ, Crosslin DR, et al. The cost of acute myocardial infarction in the new millennium: evidence from a multinational registry. Am Heart J 2006;151:206-12.

35. Buskens E, Nederkoorn PJ, Buijs-Van Der Woude T, et al. Imaging of carotid arteries in symptomatic patients: cost-effectiveness of diagnostic strategies. Radiology 2004;233:101-12.

TECHNICAL APPENDIX

In this Appendix, we provide additional information on the RISC model and analyses.

RISC Model

The RISC model is a Monte Carlo state-transition model (schematically presented in Figure 6) with six states: (1) the CVD death state, (2) the non-CVD death state, (3) the Coronary Heart Disease (CHD) state, (4) the Stroke state, (5) the CHD and Stroke state and (6) the Well state (being alive without coronary heart disease or stroke). The model simulates incident CVD events in individuals based on risk factor dependent transition probabilities, using Cox regression equations. Individual risk factor profiles were modeled and tracked over time. The model was built in TreeAge (version 2009, TreeAge Software, Inc., Williamstown, USA).

Probabilities for the transitions between the six health states were based on six multivariable Cox regression equations. The development of these equations was described in a previous article on the RISC model [(1)]. The first equation estimated the cumulative hazard from the Well state to the CHD state and from the Stroke state to the CHD & Stroke state. The second equation estimated the cumulative hazard from the Well state to the Stroke state and from the CHD state to the CHD & Stroke state. In developing these models, censoring was performed for an incident stroke and CHD respectively. In both equations, previous CHD and/or stroke were included as a covariable. The third and fourth equations estimated the 6-months cardiovascular mortality rate (case-fatality) after a CHD and stroke event respectively. Six-month case-fatalities were used as proxies for the immediate fatality rates of these events. The probability of dying from a fourth CHD event and third stroke event were assumed to be 100%. The fifth and sixth Cox regression equations estimated the cumulative hazards of the remaining CVD mortality, which is caused by other causes than CHD or stroke (see Table 6 for equations). For extrapolation to a lifelong follow-up, follow-up time was divided into 5-year intervals and a cycle length of one year was chosen. The first 5 years, baseline values of covariables were used together with the one-year cumulative hazards from the Cox models for each cycle. For the remaining follow-up, the same baseline one-year cumulative hazards were used, but values of the covariables were updated every 5 years by using multiple linear regression for continuous variables and logistic regression for dichotomized variables. From the outcomes of the logistic regression equations regarding dichotomized variables, binomial distributions were created. Every 5 year period during follow-up, presence (1 or 0) of the dichotomized variables was derived from these distributions. Cumulative hazards of fatal and non-fatal events were separately weighted for their total cumulative hazards to ascertain that all probabilities for respectively cardiovascular and non-cardiovascular mortality vs. survival and stroke and CHD events vs. disease-free survival summed to one. For each transition, cumulative hazards were converted to probabilities by exponentiation. Occurrences of events and duration in each health state were stored using Monte Carlo tracker variables to allow for the calculation of incidences of the different events. These tracker variables are

variables used to count the occurrences of a state transition representing an event in TreeAge.

Myopathy and Hepatitis

An individual could experience an episode of myopathy each cycle, tracked by t_myopathy. If an episode of myopathy occurred, we assumed a 1.6% probability of hospital admittance, for an average stay of 7.5 days, and a reduction of 0.5 in quality of life. In case of hospital admittance, a 10% mortality rate was assumed and an average remaining life expectancy of 15 years for individuals who would have survived [(2)]. After admittance, a 30 day recovery period with a reduction of 0.2 in quality of life was modelled. In case of hospitalisation we assumed a one time cost of $13,000. Standard lab follow up was expected to cost $30. An individual could experience an episode of hepatitis each cycle, tracked by t_hepatitis. If an episode of hepatitis occurred, we assumed a 0.45 % probability of hospital admittance, for an average stay of 7.1 days, and a reduction of 0.5 in quality of life [(2)]. After admittance, a 30 day recovery period with a reduction of 0.2 in quality of life was modelled. In case of hospitalisation we assumed a one time cost of $17,000. Standard lab follow up was expected to cost 40$. Based on the probabilities of hospital admittance, we calculated the expected costs in case of myopathy and hepatitis to be 180 euro and 90 euro respectively (costs were converted to 2010 euro's).

Table 6. Model Input Parameters

Cox Proportional Hazards Equations	**Equations***
CHD:	Hazard function = baseline cumulative hazard x EXP(β1*male + β2*age + β3*age*age + β4*diabetes*glucose + β5*TC + β6*HDL + β7*PP + β8*PP*male + β9*angina + β10*ABI + β11*ABI*ABI + β12*smoking + β13*famhistMI + β14*CVD + β15*creat-β16)
Stroke:	Hazard function = baseline cumulative hazard x EXP(β1*male + β2*age + β3*hypertension + β4*hypertension*age + β5*SBP + β6*smoking + β7*famhistMI + β8*TIA + β9*CVD + β10*CVD*male + β11*AF + β12*ABI-β13)
6-months CHD event mortality:	Hazard function = baseline cumulative hazard x EXP(β1*age + β2*diabetes*glucose + β3*hypertension + β4*hypertension*age + β5*creat-β6)
6-months Stroke event mortality:	Hazard function = baseline cumulative hazard x EXP(β1*age + β2*smoking + β3*famhistCVD + β4*ABI + β5*TC + β6*creat + β7*HDL + β8*ABI*ABI + β9*age*HDL-β10)
CVD mortality:	Hazard function = baseline cumulative hazard x EXP(β1*age + β2*male + β3*diabetes + β4*HDL + β5*hypertension + β6*hypertension*age + β7*smoking + β8*CVD + β9*ABI + β10*ABI*ABI + β11*AF + β12*AF*male + β13*age*AF + β14*male*CVD + β15*CVD*TC*TC-β16)
Non-CVD mortality:	Hazard function = baseline cumulative hazard x EXP(β1*male + β2*age + β3*diabetes*glucose + β4*TC + β5*smoking + β6*smoking*age + β7*BMI + β8*BMI*age + β9*WHR + β10*WHR*age + β11*WHR*CVD + β12*famhistCVD + β13*famhistCVD*age + β14*ABI + β15*ABI*age + β16*CVD-β17)

*Beta coefficients were drawn from a table comprising estimated beta coefficients from Cox regression equations developed in 100 bootstrapped datasets.

Abreviations: ABI = ankle-brachial index, AF = atrium fibrillation, BMI = body mass index, CHD = coronary heart disease, C.I.'s = confidence intervals, creat = creatinine, CVD = cardiovascular disease, HDL = famhistMI, family history of myocardial infarction, high-density lipoprotein, famhistCVD = family history of cardiovascular disease, PP = pulse pressure, SBP = systolic blood pressure, TC = total cholesterol, TIA = transient ischaemic attack, WHR = waist-to-hip ratio

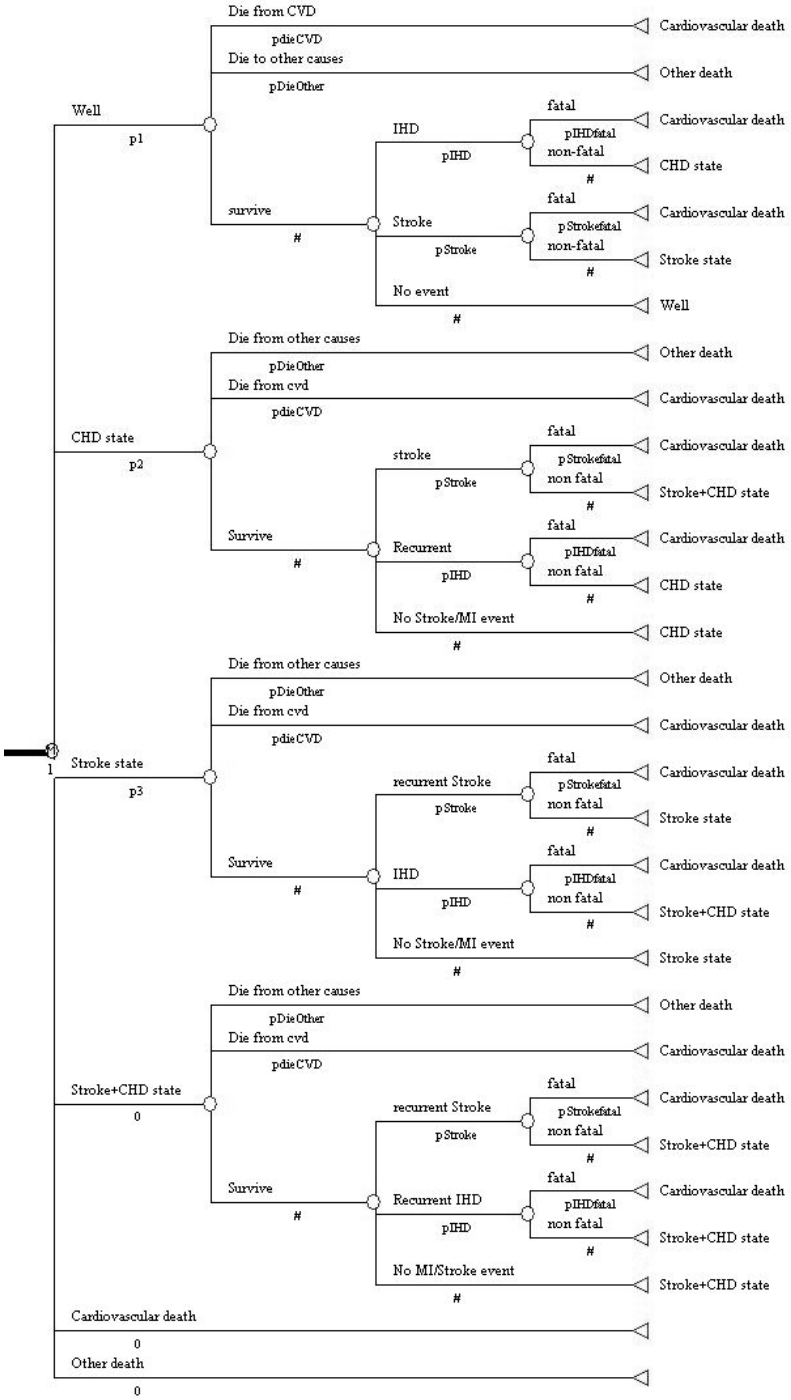


Figure 6. Schematic presentation of RISC model.

REFERENCES

1. Nijhuis RL, Stijnen T, Peeters A, Witteman JC, Hofman A, Hunink MG. Apparent and internal validity of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow-up study. Med Decis Making 2006;26:134-44.

2. Pletcher MJ, Lazar L, Bibbins-Domingo K, et al. Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern Med 2009;150:243-54.

Chapter 5

Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study

Bart S. Ferket
Bob J. H. van Kempen
Jan Heeringa
Sandra Spronk
Kirsten E. Fleischmann
Rogier L. Nijhuis
Albert Hofman
Ewout W. Steyerberg
M. G. Myriam Hunink

PLoS Medicine. 2012 Dec;9(12):e1001361

ABSTRACT

Background: Physicians need to inform asymptomatic individuals about personalized outcomes of statin therapy for primary prevention of cardiovascular disease (CVD). However, current prediction models focus on short-term outcomes and ignore the competing risk of death due to other causes. We aimed to predict the potential lifetime benefits with statin therapy taking into account competing risks.

Methods and Findings: A microsimulation model based on 5-year follow-up data from the Rotterdam Study, a populationbased cohort of individuals aged 55 years and older, was used to estimate lifetime outcomes with and without statin therapy. The model was validated in-sample using 10-year follow-up data. We used baseline variables and model output to construct: 1) a web-based calculator for gains in total and CVD-free life expectancy and 2) colour charts for comparing these gains to the SCORE (Systematic COronary Risk Evaluation) charts. In 2,428 subjects (mean age 67.7, 35.5% men), statin therapy increased total life expectancy by 0.3 years (SD 0.2) and CVD-free life expectancy by 0.7 years (SD 0.4). Age, sex, smoking, blood pressure, hypertension, lipids, diabetes, glucose, body mass index, waist-to-hip ratio, and creatinine were included in the calculator. Gains in total and CVD-free life expectancy increased with blood pressure, unfavourable lipid levels and body mass index after multivariable adjustment. Gains decreased considerably with advancing age, while SCORE 10-year CVD mortality risk increased with age. Twenty-five percent of subjects with a low SCORE risk achieved equal or larger gains in CVD-free life expectancy than the median gain in subjects with a high SCORE risk.

Conclusions: We developed tools to predict personalized increases in total and CVD-free life expectancy with statin therapy. The predicted gains we found are small. If the underlying model is validated in an independent cohort, the tools may be useful in discussing with patients their individual outcomes with statin therapy.

Abbreviations: CHD = coronary heart disease, CVD = cardiovascular disease, ESC = European Society of Cardiology, OECD = Organisation for Economic Co-operation and Development; RISC = Rotterdam Ischemic Heart Disease & Stroke Computer Simulation, SCORE = Systematic COronary Risk Evaluation

INTRODUCTION

Current guidelines recommend that asymptomatic individuals at high cardiovascular disease (CVD) risk should be identified for statin therapy. For this purpose, risk assessment is performed using prediction models estimating short-term, i.e. 5 to 10-year CVD risk [1, 2]. The higher the predicted CVD risk, the stronger is the recommendation to initiate statin therapy. This reasoning is based on solid evidence demonstrating a CVD risk reducing effect [3, 4] with an expected larger absolute benefit as CVD risk increases [5]. For shared decision making, physicians need to communicate to the patient personalized information about the outcomes of statin therapy [6]. Whether the magnitude of the expected benefit would outweigh the disadvantages of statin therapy (e.g. side effects, the disutility of taking a pill every day), can be discussed with the individual in order to reach agreement on initiation of the drug therapy.

Using the currently available short-term CVD prediction models for estimating treatment benefits has limitations. First, statin therapy is generally continued over the remainder of the course of a lifetime, and information for decision-making should reflect the expected long-term benefit [7]. Second, shortterm risk reductions are generally small and difficult to interpret by lay people [8]. Third, competing risk of death due to other causes than CVD is generally not taken into account. Especially in frail individuals, who are also at high risk of dying due to other causes, ignoring the competing risk of non-CVD death leads to overestimation of CVD risk and thus overestimation of the treatment benefit [9]. Decision models have the ability of extrapolating short-term follow-up data to a lifetime horizon while taking into account competing risks of death. Results can be expressed on a time scale, as gains or losses in (CVD-free) life expectancy. Life expectancy measures have the advantage that the aggregated treatment benefits over the full life span can be represented by a single value. This could provide information complementary to the conventional communication of risk reduction, which is limited to the use of fixed time points [10]. Presenting data in various different ways can be helpful to assess the certainty about therapy choices and could improve the quality of decision-making [11].

Our aim was to predict personalized lifetime benefits with statin therapy for prevention of CVD in asymptomatic individuals without a history of CVD.

METHODS

The decision model

We used a previously developed microsimulation state-transition model, the Rotterdam Ischemic Heart Disease & Stroke Computer Simulation Model (RISC model), which was built in TreeAge (version Data Professional release 10, TreeAge Software, Inc., Williamstown, USA) [12]. The RISC model was developed using 7-year follow-up data from 3,501 participants of the Rotterdam Study, a population-based cohort study of individuals aged 55 years and older followed from 1990 and onwards. Only participants were used with complete data on the baseline risk factors in the development of the RISC model [13]. Instead of using the 7-year hazard rates, more stable 5-year hazard rates were used for extrapolation to a lifetime horizon in order to evaluate the

lifetime effects of CVD preventive strategies. In the model, life courses of subjects are simulated using six health states: well, post non-fatal coronary heart Disease (CHD), post non-fatal stroke, post non-fatal CHD and nonfatal stroke, cardiovascular death, and non-cardiovascular death (see Figure 1). CHD was defined as: acute myocardial infarction (International Classification of Diseases, 10th version (ICD-10) code I21), PTCA and CABG. Stroke was limited to non-hemorrhagic and unspecified strokes (ICD-10 codes I63, I64) in order to be able to model the adverse bleeding risk of preventive interventions such as aspirin therapy separately. Cardiovascular death was defined as mortality due to hypertensive diseases (ICD-10 codes I10-15), ischemic heart disease (ICD-10 codes I20-I25), sudden cardiac death (ICD-10 codes I46, I49), congestive heart failure (ICD-10 code I50), cerebrovascular disease (ICD-10 codes 160 – 167), other arterial disease (ICD-10 codes I70-I79), or sudden death (ICD-10 code R96). Noncardiovascular death was defined as mortality due to all other causes (all other ICD-10 codes). Within 5 years of follow-up, 176 CHD events, 127 stroke events, 165 CVD deaths, and 264 non-CVD deaths occurred in the development population of 3,501 subjects. Transitions between health states were individualized using multivariable Cox regression models, while adjusting for competing risk. Consequently, the "one-cycle cumulative incidence" for each event was calculated by the ratio of the cumulative hazard of the event of interest censored for all other events to the cumulative hazard of any event, multiplied by the probability of any event. If constant hazards are assumed within each cycle, the overall cumulative incidences will be estimated correctly [14]. The Cox regression models were fitted in 100 bootstrapped datasets to take into account the parameter uncertainty of hazard ratios. Each simulated individual entered the model starting in the Well state, with his or her baseline risk profile. Secular trends in risk factor levels were modeled across the age span using crosssectional analyses of baseline data. The individual's risk profile at baseline and (if alive) the updated risk profile at the beginning of each simulated subsequent fifth year was used as input for the Cox regression equations. In addition, the Cox regression equations included age-risk factor interactions. Two life course scenarios were modeled: "with statin therapy" vs "without statin therapy". A cycle length of 1 year without discounting to provide an "actual" life expectancy was applied (for more information about the RISC model, see Text S1).

Model validity

The RISC model was constructed with extrapolation of 5-year predictions based on 7-year follow-up data of 3,501 subjects. However, at the moment of this analysis, we had access to data with a mean follow-up duration of 11.8 years including 367 CHD events, 343 stroke events, 494 CVD deaths and 846 non-CVD deaths. Therefore, we were able to evaluate the validity of extrapolation to the longer term by comparing simulated and observed cumulative incidences at 5 and 10 years follow-up. We modelled the life courses of the 3,501 Rotterdam Study participants. To assess parameter uncertainty, we calculated 95% confidence intervals (95%CIs) by consecutively sampling beta coefficient estimates from the Cox regression analyses performed in the 100 bootstrapped datasets. Observed cumulative incidences and 95% CIs were calculated with taking into account the competing death risks and loss-to-follow-up by using the R cuminc function available from the mstate package. To assess model discrimination, we calculated the Harrell's C-statistic [15] for 10-year CHD events, stroke events, CVD mortality and non-CVD mortality. We adjusted the C-statistic for competing risk by setting the censoring time to "infinity" (i.e. the maximum follow-up time of 10-years +1) for those who died of causes other than the event of

interest [9]. In addition, we compared the 10-year CVD mortality risk from the RISC model with the European Society of Cardiology (ESC) SCORE (Systematic COronary Risk Evaluation) charts. Because uncertainty exists about which SCORE charts to use for Dutch individuals [16], we compared 10-year CVD mortality risk to the three available versions: high-risk region, low-risk region and Dutch recalibrated SCORE charts. SCORE 10-year CVD mortality risks were calculated using the equations provided by Conroy et al [17] and Van Dis et al [16]. For calculation of the RISC model's 10-year CVD mortality risk, we included death by CVD other than stroke and CHD. The RISC model's average 10-year CVD mortality risk estimations and the predictions by each SCORE equation were plotted by tenths of predicted 10-year CVD mortality by the RISC model. This was only done for a subset of 1,047 asymptomatic subjects younger than 65 years, meeting the population criteria for which the SCORE equations are applicable [17]. The 95% CIs of estimates by the RISC model were calculated by sampling from the 100 beta coefficient bootstrap replicates as previously described; 95%CIs of SCORE predictions were estimated using non-parametric bootstrapping of the data in each tenth.

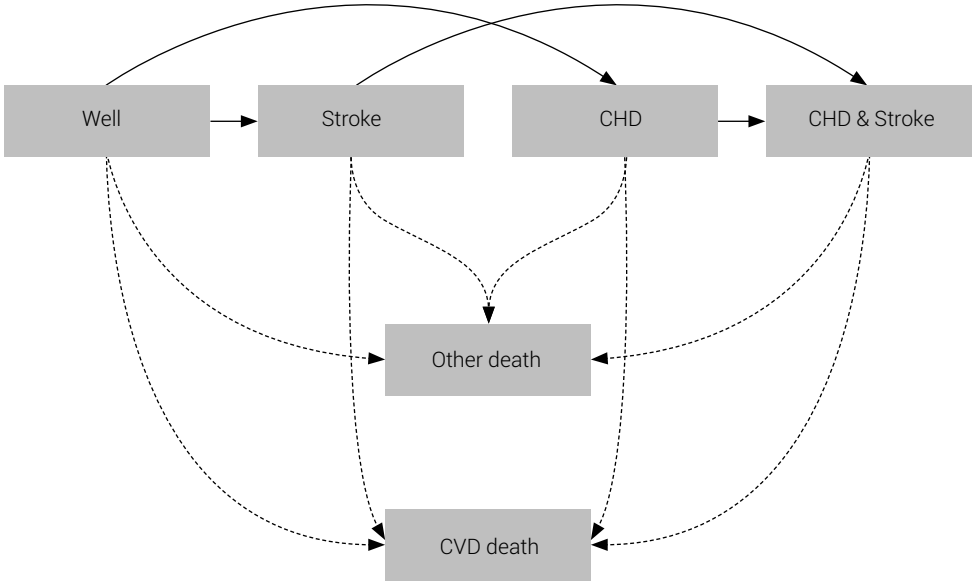


Figure 1. Schematic representation of the RISC model.

Statin therapy efficacy

The effect of statin therapy was modeled on the occurrence of first CHD and stroke events in 2,428 subjects who did not use statin therapy at baseline and were free of CVD (defined as: myocardial infarction, transient ischaemic attack, stroke diagnosed by a physician and/or a self-reported history of CABG, PTCA, or carotid surgery); angina pectoris; intermittent claudication; and atrial fibrillation. We conservatively assumed that there was no statin effect on direct transitions from the Well state to the Cardiovascular Death state, but that this was solely effectuated through its

effect on CHD and stroke events. We did not model additional therapy effects after occurrence of CVD and did not consider the negligible fatal adverse effects of statin therapy [18]. The odds ratios (ORs) for first CHD and stroke events were derived from a recent meta-analysis (see Table S1) [3]. This meta-analysis provides effect estimates for statins with doses that are generally recommended for primary prevention. We assumed that adherence to statin therapy was adequately captured in the statin effect, as observed in trials with an intention-to-treat analysis. Because benefits are known to be significant within the first year of treatment [19], we assumed that the full extent of the statin effect was achieved within one year. In addition, we kept odds ratios (ORs) constant over all ages and risk factor levels [3, 20].

Personalized Prediction of Lifetime Benefits

We ran the RISC model for the 2,428 subjects under the scenarios with and without statin therapy. To take into account parameter uncertainty of the Cox-regression beta coefficients underlying the state transition probabilities, 100 linked sets of coefficients were derived using bootstrapping. ORs with statin therapy for first CHD and stroke events were randomly sampled using log-normal distributions based on the reported 95% confidence limits. To limit the stochastic error in event occurrences, we used 200 random walks per parameter set. Thus, the RISC model output consisted of the average lifetime outcomes from 20,000 runs per subject (100 parameter sets x 200 random walks) under the two scenarios ("with statin therapy" vs "without statin therapy"). The uncertainty in the predictions was addressed by running the RISC model while aggregating at the parameter level. To show this parameter uncertainty, we presented average outcomes with 95%CIs. Heterogeneity was addressed by running the RISC model while aggregating at the individual level (Rotterdam Study subjects); the standard deviations presented represent the variation in outcomes across individuals.

Because it is infeasible to run the complicated RISC model for use in clinical practice, we developed easily programmable equations that predict the RISC model's output using the baseline risk profile of the individual. We used the data generated by the RISC model while aggregating at the individual level as described above. Depending on the outcome chosen, linear and generalized linear models with repeated measure statements were used for constructing these equations. Our primary outcomes were total life expectancy and CHD/stroke-free life expectancy. In addition, we predicted the lifetime risk of developing a first CHD or stroke event (either fatal or non-fatal), lifetime CHD/stroke mortality risk, and lifetime total CVD mortality risk. We selected the following candidate predictors: age; sex; current smoking; systolic and diastolic blood pressure; hypertension (defined as either reporting use of antihypertensive medication and/or a systolic blood pressure ≥160 mmHg or a diastolic blood pressure ≥95 mmHg at baseline); total cholesterol; high-density lipoprotein (HDL) cholesterol; diabetes mellitus (defined as either reporting use of antidiabetic medication and/or a random or postload serum glucose level ≥11.0 mmol/L at baseline); serum glucose; body mass index; waist-to-hip ratio; and serum creatinine. We chose these variables, because they are reliably and easy to obtain during an office-based health check. Interactions with statin therapy, age and sex were tested. Continuous variables were entered as linear and quadratic terms. Final models were selected based on the Akaike's Information Criterion (AIC), which calculates the log-likelihood penalized for the number of parameters used. All analyses

were performed using R version 2.12.2 (R Foundation for Statistical Computing, www.R-project.org). For details on statistical analyses see the Text S1.

The predictions by the RISC model have not been independently validated and are thus not ready for clinical use. However, to facilitate validation, we developed a web-based calculator using the Cleveland Clinic risk calculator constructor (http://rcc.simpal.com/) provided by the Cleveland Clinic Foundation (Cleveland, OH, USA), a non-profit corporation. The calculator is available at http://www.erasmusmc.nl/clinical-epidemiology/patientcare/. As the calculator is constructed using software hosted by the Cleveland Clinic Foundation, users are asked to agree to the software license of this organization upon first use. To illustrate the output of the web-based calculator, we contrasted the expected lifetime benefits (expressed in total life expectancy and CHD/stroke-free life expectancy) with statin therapy to 10-year total CVD mortality risks for four different risk profiles.

In order to compare gains in total and CHD/stroke-free life expectancy with office-based assessment of 10-year total CVD mortality risk as recommended in the ESC 2007 guidelines, we constructed colour charts similar to SCORE risk charts. To show the distribution of the simulated gains in total and CHD/stroke-free life expectancy according to SCORE risk estimations we drew scatter plots for the asymptomatic population younger than 65 years.

Ethics Statement and Data Access

The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare, and Sports. The approval has been renewed every 5 years. The steering committee of the Rotterdam Study does not allow free sharing of data. Currently, Rotterdam Study data are only shared within collaborative research projects. Therefore, the data needed for constructing the web-based calculator unfortunately cannot be made available for altering to different scenarios.

RESULTS

Model Validity

At year 5, the observed (95% CI) vs simulated (95% CI) incidences of CHD, stroke, CVD and non-CVD mortality were 5.0 (4.3 – 5.8)% vs 4.7 (4.2 – 5.4)%, 3.6 (3.0 – 4.3)% vs 3.2 (2.7 – 3.8)%, 4.7 (4.0 – 5.4)% vs 4.8 (3.6 – 6.1)%, and 7.6 (6.7 – 8.5)% vs 8.1% (7.1 – 9.2)%, respectively. At year 10, these percentages were 8.5 (7.6-9.5)% vs 8.9 (7.9 – 10.0)%, 7.6 (6.7 – 8.5)% vs 6.9 (5.9 – 8.1)%, 10.9 (9.9 – 12.0)% vs 10.9 (8.6 – 13.6)% and 17.7 (16.5 – 19.0)% vs 17.9 (16.1 – 20.0)%. The C-statistic (95% CI) for CHD was 0.73 (0.70 – 0.76), for stroke 0.67 (0.64 – 0.70), for CVD mortality 0.80 (0.78 – 0.82) and for non-CVD mortality 0.74 (0.72 – 0.76).

In the 1,047 subjects younger than 65 years, the low-risk region SCORE equation provided 10-year total CVD mortality estimations that were most similar to the RISC model output (see Figure S1). The other two SCORE equations overestimated 10-year total CVD mortality risk as compared to the RISC model, particularly in the upper two deciles of SCORE risk estimations (see Figures S2 and S3).

Population Results

The baseline characteristics of the study population are summarized in Table 1. In the 2,428 subjects (mean age 67.7, SD 8.1, 35.5% men), the average total life expectancy without statin therapy was 18.3 years (SD 6.5). The average remaining life expectancy for females (males) at the age of 60 years was 25.5 (20.4) years, at 65 it was 21.4 (16.7) years and at 80 it was 10.5 (7.0) years. These figures were less favourable in the original Rotterdam Study cohort including symptomatic individuals (N = 3501): 25.3 (19.8) years, 21.1 (16.1) years and 10.2 (6.6) years respectively. Average CHD/strokefree life expectancy in the asymptomatic study population was 16.0 years (SD 5.8). For females (males) this was 21.8 (16.4) years at the age of 60, 18.4 (13.5) years at 65 and 9.6 (5.6) years at the age of 80.

Statin therapy resulted in an average gain in life expectancy of 0.3 (95%CI 0.2 – 0.3) years, and ranged from 0.0 to 2.0 years. The gain in CHD/stroke-free life expectancy with statin therapy was 0.7 (95%CI 0.5 – 1.0) years and ranged from 0.1 to 2.8 years. The absolute risk reduction in CVD incidence by statin therapy was larger than the decrease of CVD mortality: 6.6 (95% CI 4.5 – 8.5)% vs. 3.0 (95%CI 2.0 – 3.9)%. The competing other CVD and non-CVD lifetime mortality risks increased with 0.9 (95%CI 0.3 – 1.7)% and 2.1 (95%CI 1.3 – 3.0)%, respectively. The effects of statin therapy on the various outcomes are summarized in Table 2. Both the heterogeneity (SDs and ranges) and the parameter uncertainty (95%CIs) of gains with statin therapy are shown.

Personalized Prediction of Lifetime Benefits

For the use of the web-based calculator (http://www.erasmusmc.nl/clinical-epidemiology/patientcare/), information on 13 predictors is required: age, sex, smoking, sytolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), hypertension, total cholesterol (mmol/L), HDL cholesterol (mmol/L), diabetes mellitus, serum glucose (mmol/L), body mass index (kg/m^2), waist-to-hip ratio, and serum creatinine (µmol/L). Ranges for possible values of continuous predictors were based on the 2.5th and 97.5th centiles of these variables in the 2,428 subjects (see Table 1). Higher systolic blood pressure, higher total cholesterol, lower HDL cholesterol, and larger body mass index considerably increased gains in total and CHD/stroke-free life expectancy with statin therapy, adjusted for the other co-variables. Increasing age however most importantly decreased these gains. Diabetes mellitus also slightly decreased these gains. Effects of the other predictors on changes in total and CHD/stroke-free life expectancy were generally small. Table 3 presents the 10-year total CVD mortality risks and lifetime outcomes with and without statin therapy for selected risk profiles. Subjects with a low 10-year CVD risk can achieve a similar or larger gain in (CHD/stroke-free) life years with statin therapy as

subjects with a high 10-year risk. For example, a 55-year-old non-smoking female at a 10-year risk of 2% could achieve a similar gain in (CHD/stroke-free) life expectancy with statin therapy as a 65-year-old smoking male at a 10-year risk of 15% (see risk profiles 1 and 2 from Table 3). A 55-year old non-smoking male with hypercholesterolemia and hypertension at a 3% 10-year risk can achieve a larger gain in (CHD/strokefree) life years with statin therapy than a 75-year old smoking male with hypertension and diabetes at a 21% 10-year risk (see profiles 3 and 4 from Table 3).

Table 1. Characteristics of 2,428 subjects aged 55 years and older, free of cardiovascular disease and symptoms at baseline.

Characteristics	**RISC model study population**
Age (years)	67.7 (8.1)
2.5^{th} – 97.5^{th} range	55 – 85
Male sex – no. (%)	863 (35.5)
Current cigarette smoking – no. (%)	582 (24.0)
Blood pressure (mm Hg)	
Systolic	139.2 (22.4)
2.5^{th} – 97.5^{th} range	100 – 186
Diastolic	74.7 (11.6)
2.5^{th} – 97.5^{th} range	53 – 98
Hypertension – no. (%)	768 (31.6)
Serum cholesterol (mmol/L)	6.7 (1.3)
2.5^{th} – 97.5^{th} range	4.5 – 9.2
Serum HDL-cholesterol (mmol/L)	1.4 (0.4)
2.5^{th} – 97.5^{th} range	0.8 – 2.2
Diabetes mellitus – no. (%)	215 (8.9)
Serum glucose (mmol/L)	6.8 (2.5)
2.5^{th} – 97.5^{th} range	4.3 – 13.6
Body mass index (kg/m^2)	26.2 (4.3)
2.5^{th} – 97.5^{th} range	20.1 – 34.3
Waist-to-hip ratio	0.90 (0.09)
2.5^{th} – 97.5^{th} range	0.73 – 1.08
Serum creatinine (µmol/L)	80.6 (15.8)
2.5^{th} – 97.5^{th} range	58 – 110

Hypertension is defined as either reporting use of antihypertensive medication or having a systolic blood pressure ≥160 mmHg or a diastolic blood pressure ≥95 mmHg. Diabetes mellitus is defined as either reporting use of antidiabetic medication or having a serum glucose level ≥11.0 mmol/L. HDL = high-density lipoprotein. Data are number of individuals (%) or mean (SD).

Table 2. Predicted outcomes and changes with statin therapy for the study population (N = 2,428) aged 55 years and older, free of cardiovascular disease and symptoms at baseline.

Outcome	Baseline value (SD)	Mean absolute change (SD)	Minimum; maximum absolute change	95%CI absolute change
Total life expectancy (years)	18.3 (6.5)	+0.3 (0.2)	0.0; +2.0	+0.2; +0.3
CHD/stroke-free life expectany (years)	16.0 (5.8)	+0.7 (0.4)	+0.1; +2.8	+0.5; +1.0
CHD/stroke incidence (%)	33.2 (10.6)	-6.6 (1.7)	-11.0; -2.8	-8.5; -4.5
CHD/stroke mortality (%)	12.8 (5.3)	-3.0 (1.2)	-11.5; -0.9	-3.9; -2.0
Other CVD mortality (%)	26.0 (8.7)	+0.9 (0.7)	-0.8; +6.8	+0.3; +1.7
Non-CVD mortality (%)	61.3 (10.9)	+2.1 (0.9)	+0.1; +7.7	+1.3; +3.0

Presented are the means, standard deviations (SDs) and ranges to reflect the heterogeneity in the predicted outcomes, and 95% confidence intervals (95%CIs) to reflect the parameter uncertainty.

Table 3. Changes (Δ) in total life expectancy and CHD/stroke-free life expectancy with statin therapy, compared with predicted 10-year total CVD mortality risk for different risk factor profiles.

Risk Profile	Total life expectancy in years		CHD/stroke-free life expectancy in years		10-year total CVD mortality
	No statin	Δ*	No statin	Δ**	
55 yr old, non-smoking ♀, blood pressure 140/80 mm Hg, hypertension +, total cholesterol 6.0 mmol/L, HDL cholesterol 1.5 mmol/L, diabetes-, glucose 6.0 mmol/L, BMI 25.0, WHR 0.80, creatinine 80 µmol/L	28.9	+ 0.3	24.9	+ 1.0	2%
65 yr old, smoking ♂, blood pressure 130/70 mm Hg, hypertension +, total cholesterol 7.0 mmol/L, HDL cholesterol 1.0 mmol/L, diabetes +, glucose 6.0 mmol/L, BMI 30.0, WHR 1.06, creatinine 90 µmol/L	13.1	+ 0.4	9.7	+ 1.0	15%
55 yr old, non-smoking ♂, blood pressure 140/75 mm Hg, hypertension +, total cholesterol 7.0 mmol/L, HDL 1.3 mmol/L, diabetes -, glucose 6.5 mmol/L, BMI 27.0, WHR 1.00, creatinine 80 µmol/L	23.9	+ 0.4	18.7	+ 1.2	3%
75 yr old, smoking ♂, blood pressure 120/80 mm Hg, hypertension +, total cholesterol 4.5 mmol/L, HDL 1.0 mmol/L, diabetes +, glucose 6.0 mmol/L, BMI 21.0, WHR 1.00, creatinine 90 µmol/L	6.5	+ 0.1	6.1	+ 0.1	21%

Hypertension is defined as either reporting use of antihypertensive medication or having a systolic blood pressure ≥160 mmHg or a diastolic blood pressure ≥95 mmHg; diabetes is defined as either reporting use of antidiabetic medication or having a serum glucose level ≥11.0 mmol/L.

BMI = body mass index, CHD = coronary heart disease, CVD = cardiovascular disease, HDL = high-density lipoprotein, WHR = waist-to-hip ratio.

Conventional conversion factors: To convert HDL and total cholesterol to miligrams per deciliter, divide by 0.0259; creatinine to miligrams per deciliter divide by 88.4; glucose to miligrams per deciliter, divide by 0.0555.

*The gain in total life expectancy in years can be computed by: 0.2632 – 0.0077 x age in years + 0.0138 x (if male sex) – 0.0115 x (if current cigarette smoking) + 0.0023 x systolic blood pressure in mm Hg – 0.0018 x diastolic blood pressure in mm Hg + 0.0479 x (if hypertension) + 0.0548 x total cholesterol in mmol/L – 0.1448 x HDL cholesterol in mmol/L - 0.0218 x (if diabetes mellitus) + 0.0086 x serum glucose in mmol/L + 0.0099 x body mass index in kg/m2 – 0.3989 x waist-to-hip ratio + 0.0025 x serum creatinine in µmol/L.

**The gain in CHD/stroke-life expectancy in years can be computed by: 1.8854 – 0.0330 x age in years + 0.0470 x (if male sex) + 0.0049 x systolic blood pressure in mm Hg – 0.0040 x diastolic blood pressure in mm Hg + 0.1157 x total cholesterol in mmol/L – 0.3605 x HDL-cholesterol in mmol/L – 0.0899 x (if diabetes mellitus) + 0.0049 x serum glucose in mmol/L + 0.0175 x body mass index in kg/m^2 – 0.2915 x waist-to-hip ratio + 0.0023 x serum creatinine in µmol/L.

Predictions for lifetime CHD/stroke incidence, CHD/stroke mortality, and total CVD mortality for these risk profiles, are shown in the Appendix 2 Table 2.

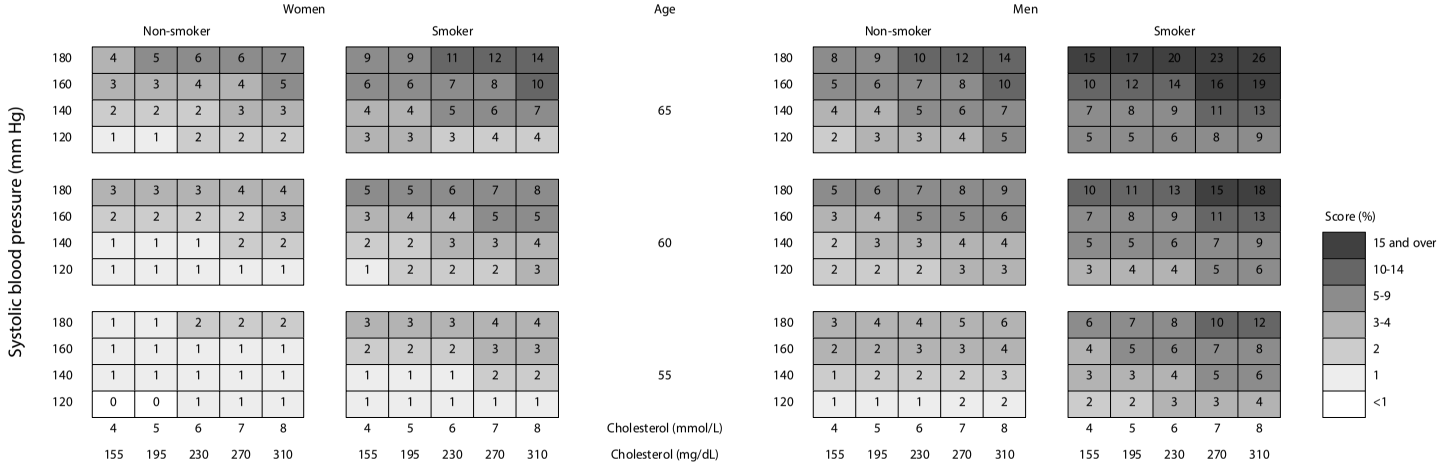


Figure 1. Schematic representation of the RISC model.

CHD = coronary heart disease, CVD = cardiovascular disease.

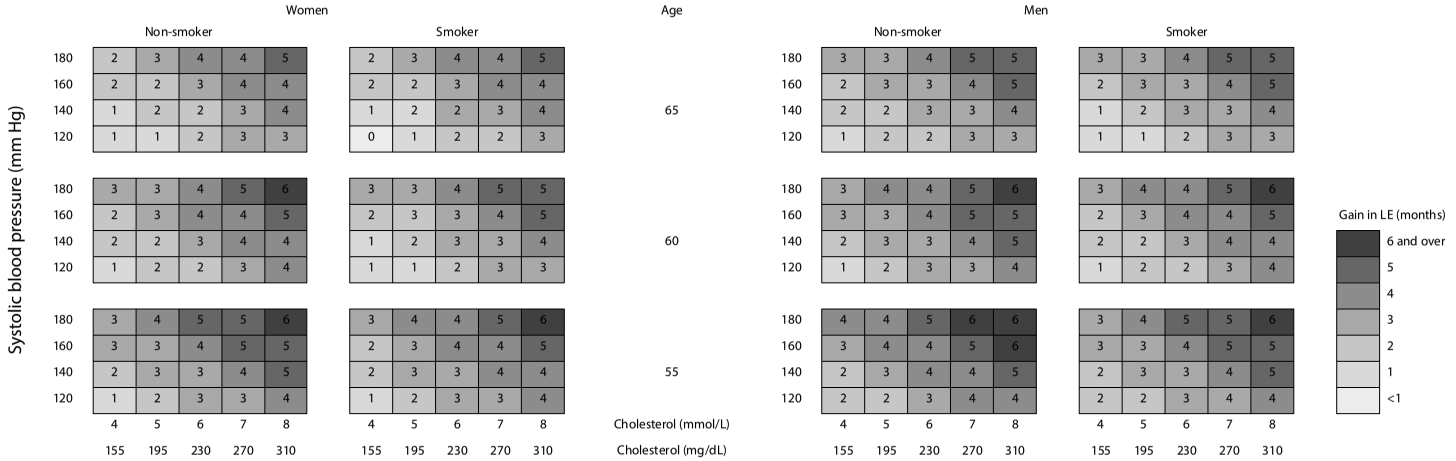


Figure 2. Ten year total cardiovascular disease (CVD) mortality risk (%) predicted by SCORE- European Low-Risk Charts.

Adapted with permission by the European Society of Cardiology. Copyright © 2007, the Oxford University Press. Note that these charts demonstrate that the 10-year total CVD mortality risk is highest for elderly smoking individuals with otherwise high risk factor levels suggesting that these individuals would benefit most from statin therapy.
SCORE = Systematic COronary Risk Evaluation.

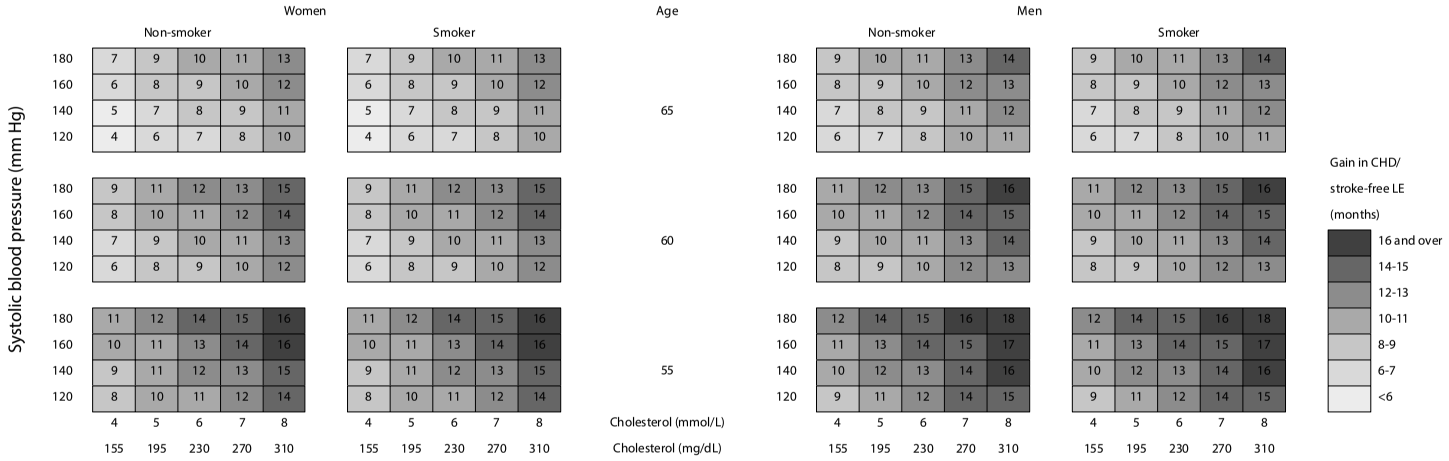


Figure 3. The gain in life expectancy (LE) in months with statin therapy calculated with the RISC model.

Note that these charts demonstrate that life expectancy gained with statin therapy is highest for young non-smoking individuals with otherwise high risk factor levels.

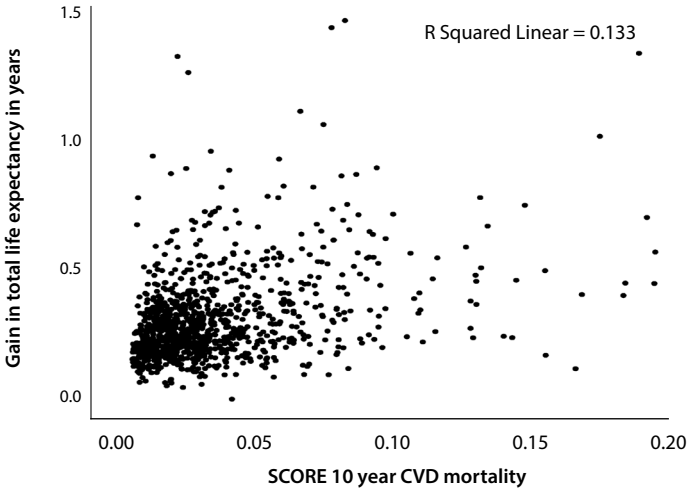


Figure 4. The gain in CHD/stroke-free life expectancy (LE) in months with statin therapy calculated with the RISC model.

Note that these charts demonstrate that CHD/stroke-free life expectancy gained with statin therapy is highest for young individuals with otherwise high risk factor levels.

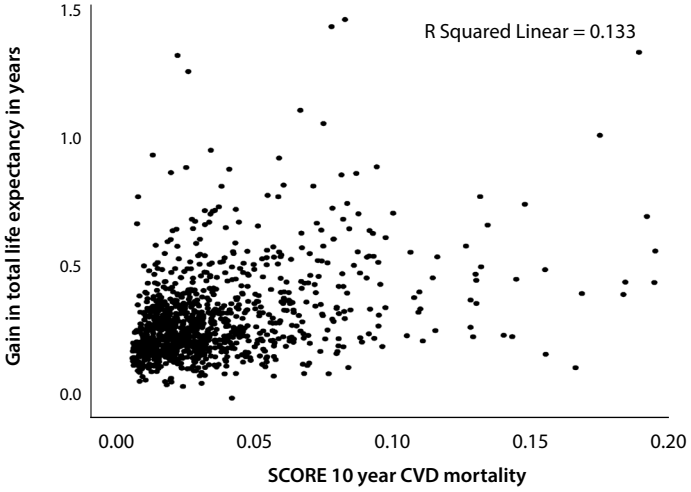


Figure 5. Distribution of gains in total life expectancy according to SCORE 10-year total cardiovascular disease (CVD) mortality risk (%).

Note that many individuals with a low SCORE 10-year CVD mortality achieved similar and higher gains as those with high SCORE 10-year CVD mortality. Ten year CVD mortality risks were calculated using the SCORE- European Low-Risk equation in 1047 subjects younger than 65 years without cardiovascular disease and/or symptoms at baseline.
SCORE = Systematic COronary Risk Evaluation.

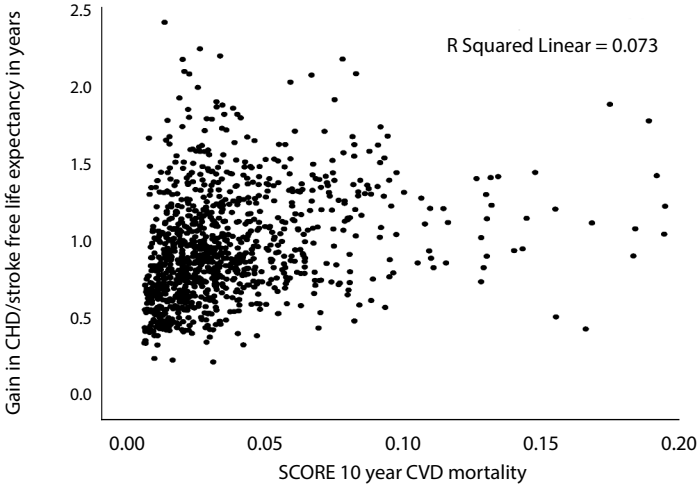


Figure 6. Distribution of gains in CHD/stroke-free life expectancy according to SCORE 10-year total cardiovascular disease (CVD) mortality risk (%).

Note that many individuals with a low SCORE 10-year CVD mortality achieved similar and higher gains as those with high SCORE 10-year CVD mortality. Ten year CVD mortality risks were calculated using the SCORE- European Low-Risk equation in 1047 subjects younger than 65 years without cardiovascular disease and/or symptoms at baseline.
SCORE = Systematic COronary Risk Evaluation.

We compared the low-risk region SCORE charts with the predicted gain in life expectancy by statin therapy (Figure 2). These charts demonstrate that the 10-year total CVD mortality risk is highest for elderly smoking individuals with otherwise high risk factor levels, suggesting that these individuals would benefit most from statin therapy. Figures 3 and 4 however, demonstrate that the lifetime benefits with statin therapy are highest for young non-smoking individuals with otherwise high systolic blood pressure and cholesterol levels. For example, a 55-year-old non-smoking female at a 10-year CVD mortality risk of 1% could achieve a similar gain in total life expectancy with statin therapy as a 65-year-old smoking male at a risk of 26%. Figures 5 and 6 plot SCORE risk estimations vs. gains in total and CHD/stroke-free life expectancy. These plots demonstrate that many individuals with low SCORE values achieved similar or larger gains than those with high SCORE values. In Figure 5, 19% and in Figure 6, 25% of the subjects with a SCORE below 0.05 had benefits greater than or equal to the gains observed in 50% of the population with a SCORE of 0.05 or more.

DISCUSSION

In this modeling study, we found that in 2,428 asymptomatic subjects, statin therapy resulted in robust, small gains in total life expectancy and somewhat larger gains in CHD/stroke-free life expectancy. The expected benefit of statin therapy was determined by a number of baseline variables. From these variables, we constructed a web-based calculator and colour charts. Once the underlying model has been independently validated, these tools can be used for communication of the expected lifetime benefits with statin therapy in persons aged 55 years and older. Inconsistencies occurred between the predicted benefits and what can be expected from the currently recommended 10-year CVD risk assessment. These inconsistencies were predominantly caused by age, which acts on lifetime benefits in the opposite direction to its effect on 10-year CVD risk. Individuals at low 10-year CVD risk may achieve a similar or even larger gain in total and CHD/stroke-free life expectancy as those at high 10-year risk.

For CVD prevention in asymptomatic individuals, most decision tools are used for predicting the individual's risk over a time period ranging from 5 to 10 years without calculating potential treatment benefits [1]. If treatment benefits are presented, they are usually calculated as absolute risk reductions without taking into account competing risks [21, 22, 23, 24, 25]. Two decision tools for making choices on statin therapy were based on Markov models predicting lifetime outcomes with and without statin therapy [26, 27]. The underlying decision models used data from multiple sources for estimating CVD events and age- and sex-specific life tables for competing death probabilities, which are not necessarily compatible [28]. In contrast, we used event probability estimations from one data source. Furthermore, we modeled the occurrence of stroke events separately from CHD events. Statin therapy has a different effect on strokes [3] and ignoring this effect would lead to incomplete estimation and communication of treatment benefits.

Despite these strengths, our results must be interpreted in the light of some limitations. First, the RISC model was used to extrapolate 5-year predictions to a lifetime horizon, which may be very sensitive to the method chosen [29]. The RISC model extends cumulative incidence functions by updating age and risk factor levels using 5-year time intervals. Secular trends in risk factor levels were modeled across the age span using cross-sectional data and thus potential chronological and cohort effects were not taken into account. We evaluated the validity of these extrapolations with subsequently available Rotterdam Study data not used in developing the RISC model and found that the deviations were generally limited. Developing predictions on longer follow-up data, e.g. 30 years, would allow for a more comprehensive evaluation of long-term validity [30]. However, this approach is also questioned given the chronological changes in CVD event rates and associated risk factors [31, 32], which are less likely to affect validity if more recent and thus shorter follow-up data is used [33]. We did not evaluate the model's performance on predicting outcomes at the individual level (discrimination) and group level (calibration) using external data. This would be necessary to investigate to what extent the personalized predictions are transportable to other settings and geographical

sites, but is beyond the scope of this study. Second, the relative risk reducing effect of statin therapy was kept constant over age and various risk factor levels. Although, a number of observational studies [34] found that the protective effect of cholesterol lowering on CVD events decreases in individuals aged 70 to 89, this was not confirmed by experimental research [20, 21]. Meta-analyses of statin trials demonstrate that effects on cardiovascular events are fairly independent of various risk factor levels [3, 35]. These trials however predominantly included subjects with elevated risk factor levels. In the Rotterdam Study, individuals with normal risk factor levels were also included and it is therefore not known whether the relative risk reduction will be different for these individuals. Thus, we can not exclude a small overestimation of the statin therapy effect in those with normal risk levels. Third, although we did account for baseline statin use, we did not take into account initiation of statin therapy during followup.Omitting this information would lead to an underestimation of the effect of statin therapy. However, in the 90s, mass screening for dyslipidemia was not advocated and statins were only prescribed to patients with a history of CVD or with persistent severe dyslipidemia after dietary intervention [36]. Follow-up examinations of the Rotterdam Study population in 1997 revealed that the statin use was quite limited [37]. Thus, the underestimation of the statin effect by treatment drop-ins will be small. Fourth, the RISC model's outcomes did not perfectly match with all the outcomes as evaluated within statin trials. Therefore, we were not able to model a statin effect on total stroke events and solely modeled an effect on first ischemic and unspecified stroke. However, these stroke subtypes contribute to 92% of all first stroke events in the Rotterdam Study [38]. In addition, we did not model a direct statin effect on CVD mortality by causes other than MI and stroke. Although a reduction in a major component of CVD mortality, sudden cardiac death, is observed in symptomatic patients treated with statins, the effect for subjects without manifest CVD seems negligible [39]. Nevertheless, we cannot exclude a small underestimation of benefits due to these choices. Finally, the RISC model's output on cardiovascular mortality was most compatible with a population resembling inhabitants of a low CVD risk region. This finding confirms results from another cohort study [16], suggesting that cardiovascular mortality in Dutch individuals is most similar to predictions by the low-risk region SCORE equation. In addition, the generalizability of our results also depends on the competing mortality rate due to other diseases. Our estimations of remaining life expectancy for females and males at the age of 60, 65 and 80 years, however reasonably match with those of low CVD risk countries projected by the Organisation for Economic Co-operation and Development [40]. Thus, the web-based calculator and colour charts should be used with caution in individuals from higher CVD risk regions.

The competing mortality risks from other CVD and non-CVD death causes, which were not affected by statin therapy, sometimes resulted in counterintuitive lifetime outcomes. For example, age is the most important factor for increasing both the yearly probabilities for occurrence of CHD and stroke events, and the fatality of these events. Thus, age is expected to increase the health benefit by statin therapy. However, in the Rotterdam Study age is even stronger associated with an increase in yearly mortality by other death causes [9]. Subsequently, changes with statin therapy in lifetime outcomes

were smaller with increasing age, because prevented CHD and stroke events were also increasingly substituted by fatal other events. Although the average gain in total life expectancy with statin therapy may seem small, it is larger than calculated for some other preventive interventions targeted at the general population [29]. One should recognize that gains were much larger in particular subjects, and were averaged out by subjects who never experienced CVD. It should also be acknowledged that with the benefits of statin therapy, the costs, side effects and disutility of daily pill use are likely to be acceptable across various age groups and risk levels, especially in a "low statin cost era" [41, 42]. In addition, we observed that gains in CHD/stroke-free life expectancy were generally larger than those in total life expectancy. Two phenomena can explain this observation. First, a large proportion of the CHD and stroke events were not fatal. Gains in CHD/stroke-free life expectancy are mainly driven by statin effects on non-fatal CHD and stroke event rates, while gains in total life expectancy are driven by effects on CHD and stroke death rates. Second, individuals in whom fatal CHD and stroke events are avoided are also likely to be at elevated risk for death by other causes. Our finding of a smaller effect of statin therapy on life expectancy is in agreement with the results from statin trials, in which generally only modest effects are demonstrated for crude total mortality risks, while effects on crude CHD and stroke incidence risks are more pronounced [3].

Currently, statin therapy choices are based on short-term CVD risk assessment without statin therapy and an expected risk reduction with statin therapy over the same time period. We converted survival benefits with statin therapy into total life expectancy and CHD/stroke-free life expectancy. We believe that the prediction of statin therapy effects on (disease-free) life expectancy can be complementary to the 10-year CVD risk assessment in two ways. First, instead of regarding a fixed time point i.e. 10 years, the benefit of statin therapy considering the entire survival curve can be communicated by primary care physicians. Second, the benefit of statin therapy is calculated taking into account competing mortality risks. The potential value of personalizing the gain in total and CHD/stroke-free life expectancy with statin therapy is best illustrated by Figures 5 and 6. A substantial number of individuals with 10-year total CVD mortality risk lower than 5%, for whom statin therapy is generally not recommended according to current ESC guidelines, may benefit to the same extent as individuals with a high risk. A similar pattern will apply to predictions based on other CVD risk models, such as risk scores based on the Framingham Study [43, 44], because these use the same risk factors with effects pointing in equal directions.

While making decisions on statin therapy, the benefit in life expectancy that diminishes with advancing age may be considered by physicians, especially in the elderly. If independently validated, physicians may use the web-based calculator and colour charts to frame survival outcomes in different ways and to discuss them with the patient in light of the expected duration of statin use. The longer the life expectancy, and therefore the expected duration of statin use, the higher the costs and possibility of adverse effects. Besides the costs averted by CVD prevention, these important outcomes would

influence the decision, but were not taken into account in our analysis. In addition, it should be acknowledged that the calculated differences in the personalized lifetime outcomes may vary across different clinical settings and are subject to the parameter uncertainty in the underlying decision model. These caveats would need to be discussed with patients when they are informed on the benefits of statin therapy.

In conclusion, we demonstrated that life expectancy benefits with statin therapy can be predicted using an individual's risk factor profile. The predicted gains in life expectancy we found are generally small. If the underlying model is validated in an independent cohort, the developed tools may be useful in discussing with patients their individual outcomes with statin therapy. Ideally, communication of personalized outcomes will ultimately result in better clinical outcomes. Improved understanding of potential gains, will however not necessarily go hand-in-hand with an improvement of clinical outcomes, because patients could make more conservative choices about statin therapy when more information on benefits is provided (45). In addition to an external validation of our predictions, personalized estimates for costs and side effects of statin therapy should be included in future research. Finally, the impact of communicating life expectancy benefits on satisfaction, behavioural and clinical outcome measures should be studied.

REFERENCES

1. Matheny M, McPheeters ML, Glasser A, Mercaldo N, Weaver RB, et al. . (2011) Systematic review of cardiovascular disease risk assessment tools. Report no. 11-05155-EF-1. Rockville (Maryland): US Agency for Healthcare Research and Quality.
2. Ferket BS, Colkesen EB, Visser JJ, Spronk S, Kraaijenhagen RA, et al. (2010) Systematic review of guidelines on cardiovascular risk assessment: which recommendations should clinicians follow for a cardiovascular health check? Arch Intern Med 170: 27–40.
3. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, et al. (2009) The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ 338: b2376.
4. Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, et al. (2011) Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 1: CD004816.
5. Jackson R, Lawes CM, Bennett DA, Milne RJ, Rodgers A (2005) Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet 365: 434–441.
6. Col N (2011) Shared decision making. In: Fischhoff B, Brewer NT, Downs JS, editors. Communicating risks and benefits: an evidence-based user's guide. Silver Spring (Maryland): US Food and Drug Administration.
7. Heart Protection Study Collaborative Group (2011) Bulbulia R, Bowman L, Wallendszus K, Parish S, et al. (2011) Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial. Lancet 378: 2013–2020.
8. Halvorsen PA, Kristiansen IS (2005) Decisions on drug therapies by numbers needed to treat: a randomized trial. Arch Intern Med 165: 1140–1146.
9. Wolbers M, Koller MT, Witteman JC, Steyerberg EW (2009) Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology 20: 555–561.
10. Halvorsen PA, Wisloff TF, Stovring H, Aasland O, Kristiansen IS (2011) Therapeutic decisions by number needed to treat and survival gains: a cross-sectional survey of lipid-lowering drug recommendations. Br J Gen Pract 61: e477–e483.
11. McNeil BJ, Pauker SG, Sox HC Jr, Tversky A (1982) On the elicitation of preferences for alternative therapies. N Engl J Med 306: 1259–1262.
12. Nijhuis RL, Stijnen T, Peeters A, Witteman JC, Hofman A, et al. (2006) Apparent and internal validity of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow-up study. Med Decis Making 26: 134–144.
13. Hofman A, van Duijn CM, Franco OH, Ikram MA, Janssen HL, et al. (2011) The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 26: 657–686.
14. Koller MT, Raatz H, Steyerberg EW, Wolbers M (2011) Competing risks and the clinical community: irrelevance or ignorance? Stat Med 31: 1089–1097.
15. Harrell FE Jr, Lee KL, Mark DB (1996) Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15: 361–387.
16. van Dis I, Kromhout D, Geleijnse JM, Boer JM, Verschuren WM (2010) Evaluation of cardiovascular risk predicted by different SCORE equations: the Netherlands as an example. Eur J Cardiovasc Prev Rehabil 17: 244–249.
17. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, et al. (2003) Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 24: 987–1003.
18. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, et al. (2004) Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 292: 2585–2590.
19. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, et al. (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366: 1267–1278.

20. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM (2010) Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med 152: 488–496, W174.

21. Dorresteijn JA, Visseren FL, Ridker PM, Wassink AM, Paynter NP, et al. (2011) Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ 343: d5888.

22. ClinRisk (2012) QIntervention [calculator]. Available: http://qintervention.org/index.php Accessed 20 February 2012.

23. Jackson R (2000) Updated New Zealand cardiovascular disease risk-benefit prediction guide. BMJ320: 709–710.

24. HealthDecision (2011) HealthDecision [calculator]. Available:https://www.healthdecision.org/index/tool# Accessed 20 February 2012.

25. The University of Edinburgh (2010) Cardiovascular risk calculator [calculator]. Available:http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp Accessed 20 February 2012.

26. Grover SA, Lowensteyn I, Joseph L, Kaouache M, Marchand S, et al. (2007) Patient knowledge of coronary risk profile improves the effectiveness of dyslipidemia therapy: the CHECK-UP study: a randomized controlled trial. Arch Intern Med 167: 2296–2303.

27. Weatherley ND, Jackson PR (2011) The new Sheffield risk and benefit tables for the elderly. QJM104: 3–12.

28. Grover SA, Abrahamowicz M, Joseph L, Brewer C, Coupal L, et al. (1992) The benefits of treating hyperlipidemia to prevent coronary heart disease. Estimating changes in life expectancy and morbidity. JAMA 267: 816–822.

29. Wright JC, Weinstein MC (1998) Gains in life expectancy from medical interventions—standardizing data on outcomes. N Engl J Med 339: 380–386.

30. Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS (2009) Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. Circulation 119: 3078–3084.

31. Hunink MG, Goldman L, Tosteson AN, Mittleman MA, Goldman PA, et al. (1997) The recent decline in mortality from coronary heart disease, 1980–1990. The effect of secular trends in risk factors and treatment. JAMA 277: 535–542.

32. Unal B, Critchley JA, Capewell S (2005) Modelling the decline in coronary heart disease deaths in England and Wales, 1981–2000: comparing contributions from primary prevention and secondary prevention. BMJ 331: 614.

33. Hippisley-Cox J, Coupland C, Robson J, Brindle P (2010) Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ 341: c6624.

34. Prospective Studies Collaboration (2007) Lewington S, Whitlock G, Clarke R, Sherliker P, et al. (2007) Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 370: 1829–1839.

35. Cholesterol Treatment Trialists' (CTT) Collaborators (2012) Mihaylova B, Emberson J, Blackwell L, Keech A, et al. (2012) The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 380: 581–590doi:10.1016/S0140-6736(12)60367-5.

36. Erkelens DW (1991) [Revision of consensus cholesterol.]. Ned Tijdschr Geneeskd 135: 2337–2340.

37. Elias-Smale SE, Proenca RV, Koller MT, Kavousi M, van Rooij FJ, et al. (2010) Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J Am Coll Cardiol 56: 1407–1414.

38. Wieberdink RG, Ikram MK, Koudstaal PJ, Hofman A, Vingerling JR, et al. (2010) Retinal vascular calibers and the risk of intracerebral hemorrhage and cerebral infarction: the Rotterdam Study. Stroke41: 2757–2761.

39. Levantesi G, Scarano M, Marfisi R, Borrelli G, Rutjes AW, et al. (2007) Meta-analysis of effect of statin treatment on risk of sudden death. Am J Cardiol 100: 1644–1650.

40. Organisation for Economic Co-operation and Development (2011) OECD.StatExtracts: health status [database]. Available: http://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT Accessed 20 February 2012.

41. Pletcher MJ, Lazar L, Bibbins-Domingo K, Moran A, Rodondi N, et al. (2009) Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern Med 150: 243–254.

42. Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L (2011) Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation 124: 146–153.

43. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, et al. (1998) Prediction of coronary heart disease using risk factor categories. Circulation 97: 1837–1847.

44. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, et al. (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 117: 743–753.

45. O'Connor AM, Bennett CL, Stacey D, Barry M, Col NF, et al. (2009) Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 8: CD001431.

Chapter 6

Performance of Framingham cardiovascular disease (CVD) predictions in the Rotterdam Study taking into account competing risks and disentangling CVD into coronary heart disease (CHD) and stroke

Bob J. H. van Kempen
Bart S. Ferket
Maryam Kavousi
Maarten Leening
Ewout W. Steyerberg
M. Arfan Ikram
Jacqueline Witteman
Albert Hofman
Oscar H. Franco
M. G. Myriam Hunink

Int J Cardiol. Feb 15 2014;171(3):413-418

ABSTRACT

Background: To evaluate the performance of Framingham predictions of cardiovascular disease (CVD) risk corrected for the competing risk of non-CVD death, in an independent European cohort of older individuals and subsequently extend the predictions by disentangling CVD into coronary heart disease (CHD) and stroke separately.

Methods: We used the Rotterdam Study data, a prospective cohort study of individuals aged 55 years and older (N = 6,004), to validate the Framingham predictions of CVD, defined as first occurrence of myocardial infarction, coronary death or stroke during 15 years of follow-up, corrected for the competing risk of non-CVD death. We subsequently estimated the risks of CHD and stroke separately, and used the sum as a predictor for the total CVD-risk. Calibration plots and c-statistics were used to evaluate the performance of the models.

Results: Performance of the Framingham predictions was good in the low- to intermediate risk (≤30%, 15-yr CVD-risk) (17.5% observed vs 16.6% expected) but poorer in the higher risk (>30%) categories (36.3% observed vs 44.1% expected). The c-statistic increased from 0.66 to 0.69 after refitting. Separately estimating CHD and stroke revealed considerable heterogeneity with regard to the contribution of CHD and stroke to total CVD-risk.

Conclusions: Framingham CVD-risk predictions perform well in the low- to intermediate risk categories in the Rotterdam Study. Disentangling CVD into CHD and stroke separately provides additional information about the individual contribution of CHD and stroke to total individual CVD-risk.

INTRODUCTION

The use of risk scores as tools to predict cardiovascular disease (CVD) has been widely advocated in primary prevention [1-5]. Guidelines on the prevention of CVD incorporate risk scores in order to make treatment recommendations [6, 7]. However, older individuals are at high risk of death due to other causes than CVD. Currently recommended Framingham risk scores tend to overestimate CVD risk in an older population, as non-CVD mortality competes with CVD events [8], and the competing risk is not taken into account in these models.

Although traditional Framingham risk scores have been successfully externally validated in some other populations, recalibration was often necessary to obtain valid estimates [9]. The 30-year CVD risk function developed by Pencina et al [3], based on the Framingham Offspring cohort was developed to address the need for both long-term CVD prediction and taking into account the competing risk of non-CVD death. The function estimates total CVD as the combination of coronary heart disease (CHD) and stroke. In contrast with more traditional risk scores, this Framingham risk function has not been externally validated.

Both CHD and stroke contribute to the risk of total CVD, but can be regarded as different clinical events, for which different risk factors have been identified [5, 10]. As the prevention of both events sometimes are associated with different recommendations [11], disentangling the risk of total CVD into both components could provide clinicians with useful additional information for treatment management.

Therefore, using 15-year follow-up data from the participants of the Rotterdam Study Cohort -a population based cohort study of elderly individuals [12], we aimed to 1) evaluate the performance of Framingham predictions of cardiovascular disease (CVD) risk corrected for the competing risk of non-CVD death, in an independent European cohort and 2) update the predictions by disentangling CVD into coronary heart disease (CHD) and stroke separately.

METHODS

Study Population

Of the 7,983 respondents originally included in the Rotterdam Study, 6,871 individuals both visited the research center and signed an informed consent. Of those, 6,004 individuals had no history of CHD and stroke. Individuals have been followed in an ongoing effort from 1990 onwards and consisted of regular examinations with interviews and direct digital linkage to medical files from the general practitioners working in the research area, death registries and other available medical sources, ensuring accurate follow-up of fatal and non-fatal CVD events and cause-specific mortality [12]. The medical records of nursing home were also evaluated. At baseline, participants were interviewed

at home by trained research assistants using a computerized questionnaire. Baseline data included information on the current health status, history of cardiovascular disease, current medication use, and cardiovascular risk factors. Subsequently, the participants were invited to the research center in order to obtain measurements on cardiovascular risk factors, including body mass index, blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, and non-fasting glucose level. All subjects gave written informed consent, and the study was approved by the medical ethics committee of Erasmus MC.

Assessment of risk factors

Details of the assessment of CVD risk factors and medical history in the Rotterdam Study are described into more detail elsewhere [13]. In short, participants were categorized with regard to current smoking status (nonsmoker defined as never smoked or abstinence for at least 2 years). Systolic blood pressure was calculated as the mean of two measurements [14]. Serum total and HDL cholesterol levels were determined by an automated enzymatic procedure. Diabetes mellitus was defined as current use of anti-diabetic medication and/or a random or post-load serum glucose ≥200 mg/dL (11.1 mmol/L).

Clinical end points

Events were classified using ICD-10 codes. We focused on 'hard' CVD as the outcome of interest, defined as the composite of hard CHD (consisting of myocardial infarction and coronary death and stroke, both fatal and non-fatal -in correspondence with the outcome used in the Framingham CVD risk function. In order to adjust for the competing risk of non-CVD death -as was done in the Framingham model, we defined non-CVD mortality as any death due to causes other than from CVD events. All events were independently adjudicated by two research physicians. Consensus was met in a separate session and if necessary medical specialists were consulted. We used follow-up information available until January 1, 2007 leading to a maximum follow-up duration of 17 years for an individual.

Statistical analysis

Complete risk profiles were available in 5,436 of the 6,004 individuals used in the analysis. We imputed missing values of systolic blood pressure, total and HDL cholesterol, diabetes status, antihypertensive medication use and current smoking status of the Rotterdam Study participants with imputation models that included all risk factors – age, sex, systolic blood pressure, use of anti-hypertensives, smoking, diabetes, total and HDL cholesterol, and the log cumulative hazard for hard CVD [15]. All continuous variables were log-transformed by taking the natural logarithm in correspondence with the Framingham model, and truncated at their 1st and 99th percentile. Fifteen-year risks of hard CVD and competing non-CVD death for the 6,004 Rotterdam Study Participants were calculated using the baseline survival at 15 years of both events as reported by Pencina [3], and the linear predictors of CVD and non-CVD death calculated using the published hazard rate ratios (model 1).

A standard Cox model may provide biased estimates of absolute long-term risk because it treats those who die of a non-CVD cause as eligible for the development of a CVD event. We therefore used the model proposed by Andersen et al [16, 17], as incorporated by Pencina in the Framingham model. This model calculates the cumulative incidence of CVD per individual, by summation of the cause-specific hazard multiplied by the survival of the CVD event and the competing non-CVD death event at each failure time.

We compared the average predicted 15-year risk of CVD, with the average observed outcome in the Rotterdam Study participants [18]. We then recalibrated the Framingham CVD model by updating the 15-year baseline survival of CVD -and non-CVD death as well, with the survival as observed in the Rotterdam Study (model 2). To check whether the overall effect of the risk factors based on the Framingham data is valid for the Rotterdam Population, we recalibrated model 2, by allowing for a different effect for the slope of the linear predictors of CVD and non-CVD death (model 3). Subsequently, we refitted the Framingham CVD model for CVD and non-CVD death, and compared the coefficients of the risk factors found by fitting the model in the Rotterdam Population data, with the original ones published by Pencina (model 4). Finally, we refined the original model by estimating the hazards of hard CHD and stroke separately. This was done as the weights assigned to different risk factors and the shape of the lifetime hazard function may be different for CHD and stroke [2]. Accounting for this difference could potentially further improve CVD risk classification. We therefore fitted three cause-specific Cox-models, one for hard CHD, one for stroke and on for the competing event defined as death from any cause other than MI, coronary disease or stroke (model 5). We subsequently calculated the cumulative incidences for hard CHD and stroke, and added the cumulative incidences of hard CHD and stroke to obtain the estimate for (total) CVD.

Discrimination for each model was assessed by the concordance index (c-statistic) adjusted for the competing risks by setting the failure time of an individual who experienced the competing event to infinity. In practice, this was done by adding 1 to the maximum follow up time i.e. 15 years [8]. Subsequently, calibration of CVD was assessed by calibration plots, comparing predicted risks of CVD with observed incidences, per decile of predicted CVD risk, for each of the five models. We used deciles of predicted CVD risk to make the categories consistent across the plots. The observed incidences were adjusted for competing risks, using the R 'CumInc' function, which is included in the R 'mstate' library [17].

An Excel risk score calculator was constructed to provide clinicians with a tool to estimate the cumulative incidences of CHD, stroke and CVD conditional on an individuals' risk profile. All analyses were performed using SPSS version 19 (SPSS for Windows) and R version 2.14 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics of the 6,004 Rotterdam Study participants used in this analysis are presented in Table 1. During 15 years of follow up, 539 (first) hard CHD, 630 (first) stroke and 1,719 competing non-CVD deaths occurred in these individuals.

Table 1. Baseline characteristics for the 6,004 Rotterdam Study Participants included in the analysis.

Risk Factor	
Men, n (%)	2251 (37.5)
Systolic BP mmHg, median (IQR)	138 (123 – 153)
missing data, n (%)	52 (1.0%)
Antihypertensive drugs, n (%)	654 (10.9 %)
missing data, n (%)	4 (0.0%)
Current smoking, n (%)	1,345 (22.4 %)
missing data, n (%)	162 (2.7%)
Total cholesterol mg/dL, median (IRQ)	255.8 (224.8 – 286.8)
missing data, n (%)	77 (1.3%)
HDL-cholesterol mg/dL, median (IRQ)	50.4 (42.6 – 62.0)
missing data, n (%)	103 (1.7%)
Diabetes mellitus, n (%)	618 (10.3 %)
missing data, n (%)	406 (6.7%)

IQR: interquartile range

Calibration

Calibration of the Framingham CVD model was found to be good in the low- to intermediate risk (<=30%, 15-yr risk) categories (17.5% observed vs 16.6% expected) but relatively poor in the higher risk (>30%, 15-yr risk) categories (36.3% observed vs 44.1% expected) (Figure 1). Updating the baseline hazards and slope of the linear predictors of CVD and non-CVD death improved calibration in the higher risk categories slightly (36.2% observed, vs 42.3% expected) but overestimation remained. After refitting the CVD risk function in the Rotterdam data, calibration improved substantially (low to intermediate categories: 16.6% observed vs 16.6% expected ; higher risk categories: 39.3% observed vs 38.9% expected). Separately estimating CHD and stroke improved calibration even somewhat further (low to intermediate categories: 16.7% observed vs 16.6% expected ; higher risk categories: 38.8% observed vs 38.8% expected) (Figure 2). Calibration of the competing non-CVD death event, evaluated by plotting the observed risk of non-CVD death vs predicted per decile of CVD risk, revealed that the risk of non-CVD is underestimated for the original Framingham CVD function for all categories of

individuals, and increased with CVD risk. After refitting, calibration of non-CVD mortality improved as well (Figure 3).

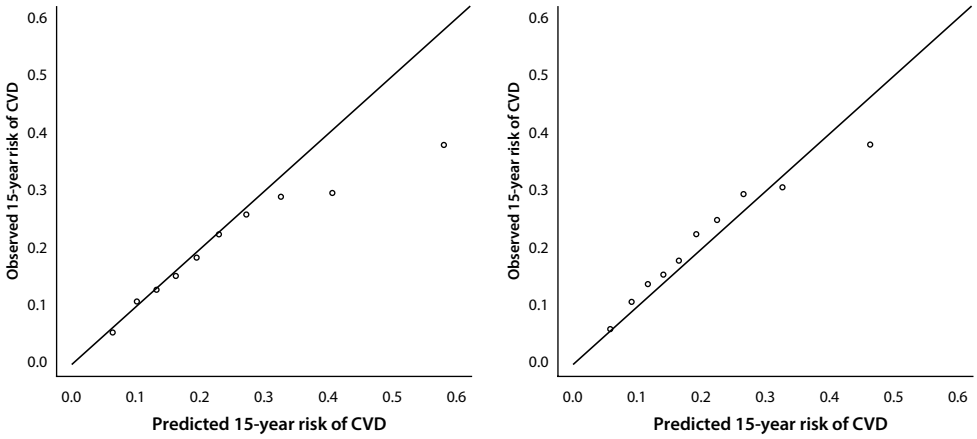


Figure 1. Calibration plot, showing predicted and observed 15-year risk of CVD for each decile of predicted 15-year CVD risk -based on the original Framingham CVD function [3] (model 1, left) and the recalibrated score by adjusting baseline hazards of CVD and non-CVD death (model 2, right)

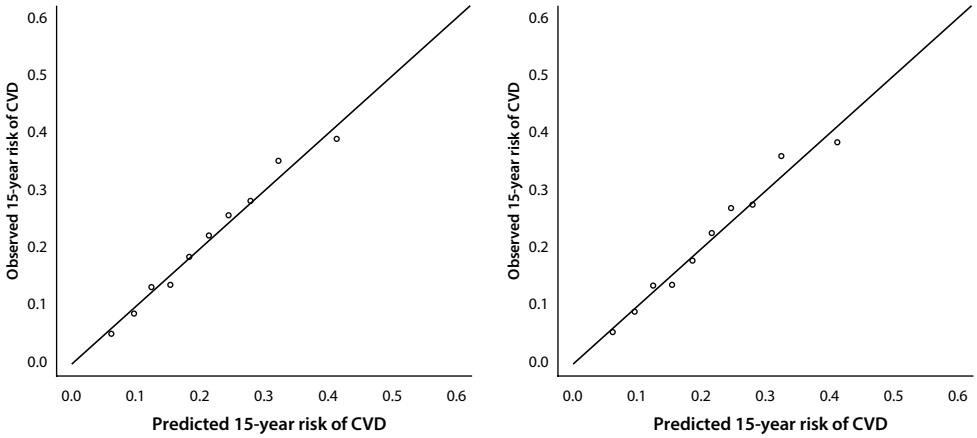


Figure 2. Calibration plot, showing predicted and observed 15-year risk of CVD for each decile of predicted 15-year CVD risk -based on the refitted function (model 4, left) and refitting the CVD and non-CVD death function, by separately analyzing CHD and stroke (model 5, right)

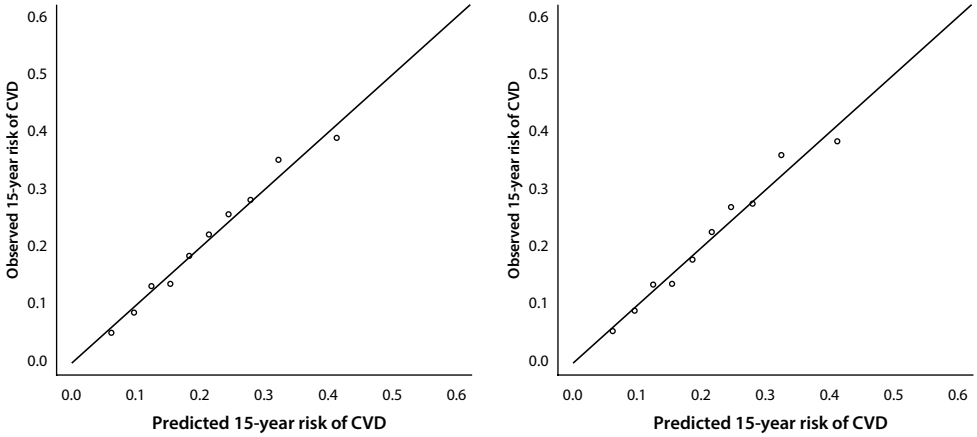


Figure 3. Calibration plot, showing predicted and observed 15-year risk of *competing non-CVD death* for each decile of predicted 15-year *CVD risk* -based on the original Framingham CVD function [3] (model 1, left) and after refitting the CVD and non-CVD death function in the Rotterdam Study data (model 4, right)

Discrimination

C-statistics for the Framingham CVD risk function applied to the Rotterdam Study population for the prediction of 15-year CVD risk was 0.66 and 0.68 after refitting the Framingham CVD risk function in the Rotterdam Study population. Estimating the hazard of CVD separately for CHD and stroke and using the sum as an estimate for total CVD, did not further increase the c-statistic for 15-year CVD risk rounded at two decimal points.

Beta coefficients

Refitting the Framingham CVD risk function in the Rotterdam data led to differences in beta coefficients compared to the original ones published by Pencina (Table 2a). For CVD, the log of age was found to have a stronger effect on CVD whereas sex, the log of systolic blood pressure, log of total and HDL cholesterol, current smoking status and diabetes were significantly less strong. For the competing risk of non-CVD death, the log of age was also found to have a significantly stronger effect, whereas the log of systolic blood pressure, current smoking and diabetes mellitus had a less strong effect (Table 2b). Separately estimating the hazards CHD and stroke, resulted in different beta coefficients for both events compared to estimating the hazard of CVD as a combined endpoint (Table 2c).

Table 2. Coefficients for the Framingham CVD risk function, for 15-year CVD and non-CVD competing death in the Rotterdam Study data, evaluating a refitted function for CVD as combined endpoint (**A**, model 4), competing non-CVD death (**B**, model 4), and for CHD and stroke separately (**C**, model 5). Original: coefficients reported by Pencina [3].

A

CVD	**Refitted**		**Original**	
	coefficient	**p-value in refitted model**	**coefficient**	**p-value refitted vs original**
Male sex	0.44	<0.0001	0.55	0.08
Natural logarithm of age	5.28	<0.0001	2.28	<0.001
Natural logarithm of systolic blood pressure	1.68	<0.0001	2.00	0.11
Natural logarithm of serum Total cholesterol	0.24	0.46	1.48	<0.001
Natural logarithm of serum HDL cholesterol	-0.49	<0.0001	-0.88	0.002
Current smoking	0.33	<0.0001	0.70	<0.001
Use of antihypertensives	0.23	0.004	0.39	0.05
Diabetes mellitus	0.46	<0.0001	0.91	<0.001

B

Non-CVD death	**Refitted**		**Original**	
	coefficient	**p-value**	**coefficient**	**p-value refitted vs original**
Male sex	0.37	<0.001	0.48	0.07
Natural logarithm of age	8.49	<0.001	3.531	<0.001
Natural logarithm of systolic blood pressure	0.28	0.11	1.43	<0.001
Natural logarithm of serum Total cholesterol	-0.92	<0.001	0.01	<0.001
Natural logarithm of serum HDL cholesterol	-0.12	0.24	0.09	0.042
Current smoking	0.58	<0.001	0.97	<0.001
Use of antihypertensives	0.05	0.56	0.12	0.34
Diabetes mellitus	0.19	0.01	0.45	<0.001

C

	CHD		**Stroke**	
	coefficient	**p-value**	**coefficient**	**p-value**
Male sex	0.64	<0.0001	0.12	0.2
Natural logarithm of age	5.89	<0.0001	6.09	<0.0001
Natural logarithm of systolic blood pressure	1.0006	<0.0001	2.06	<0.0001
Natural logarithm of serum Total cholesterol	0.97	<0.0001	-0.76	0.001
Natural logarithm of serum HDL cholesterol	-0.91	<0.0001	-0.07	0.65
Current smoking	0.27	0.0028	0.35	<0.0001
Use of antihypertensives	0.39	<0.0001	0.22	0.06
Diabetes mellitus	0.51	<0.0001	0.39	<0.0001

15-year risk of CHD, stroke and CVD

To illustrate the effect of different individual risk profiles on CVD risk and on the mixture of CHD and stroke, the cumulative incidences of CHD, stroke and CVD were plotted for a 15-year period for 4 individuals (Figure 4 A-D). For individual A and B, stroke was the major component of CVD. The opposite was true for individuals C and D.

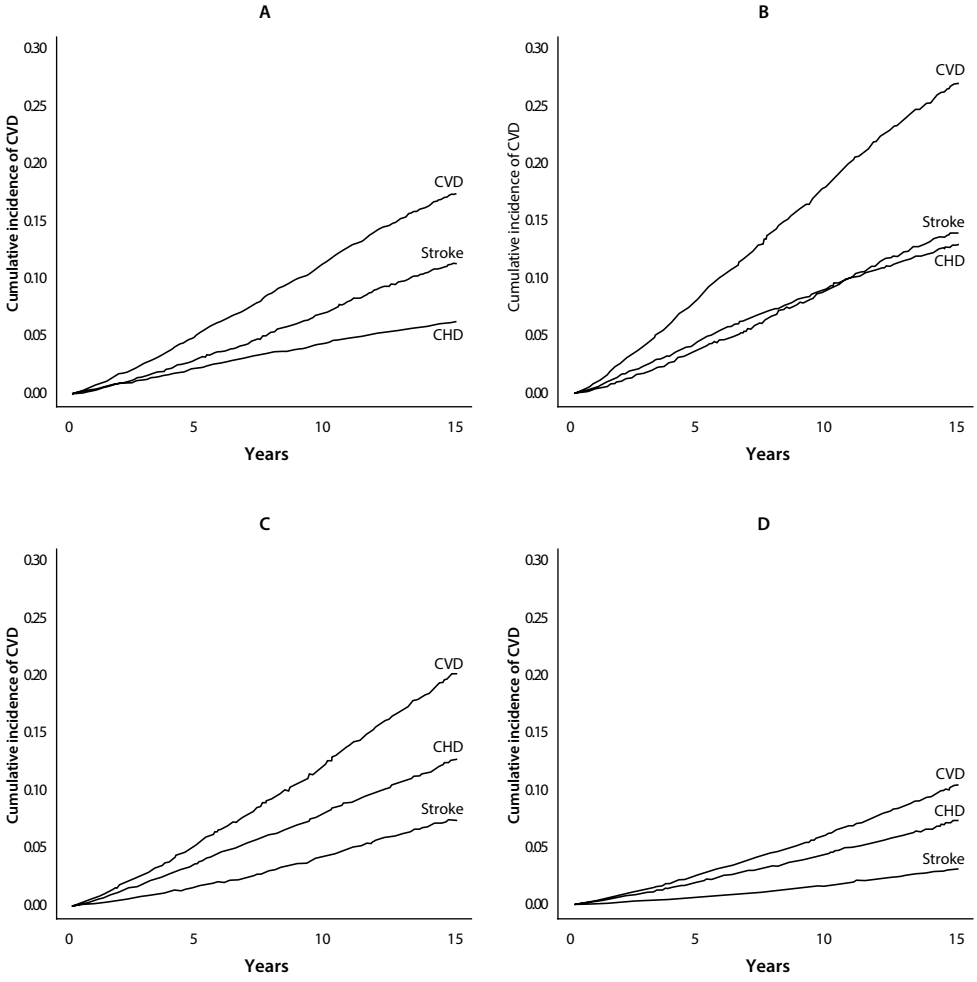


Figure 4. Individual predictions for 4 individuals. (**A**) 70-year old woman, smoker, systolic blood pressure of 103, total (HDL) cholesterol 4.1 mmol/L 1.5, treated for Hypertension (**B**) 70 year old man, systolic blood pressure of 132, Total (HDL) cholesterol 5.0 mmol/L 1.80, Diabetic (**C**) 56-year old man, Systolic blood pressure of 124, Total (HDL) cholesterol 6.4 mmol/L 0.9, and (**D**) 65-year old woman, Systolic blood pressure of 129, Total (HDL) cholesterol 6.7 mmol/L 0.9, Treated for Hypertension

DISCUSSION

Our analyses show that the Framingham CVD risk predictions perform reasonably well in predicting in the relatively older Rotterdam population for individuals at low to intermediate risk. For the higher risk categories, recalibration by refitting the function in the Rotterdam Study population was required to obtain valid estimates. Disentangling CVD into CHD and stroke separately revealed considerable heterogeneity with regard to the contribution of CHD and stroke to the total risk of CVD.

To our knowledge, this is the first attempt to validate this Framingham CVD risk function corrected for competing death in another population. Previous studies on the validity of Framingham risk functions in the Rotterdam Study focused on 10-year CHD and stroke separately [14, 19] and found predictive performance to be reasonable in the lower risk categories for both events -but recalibration was necessary for the apparent overestimation in the higher risk categories. In the current analysis we extended the previous work by incorporating a longer period of follow-up and made adjustments for competing risks. In accordance with the earlier findings for 10-year CHD and stroke, we found that recalibration was especially important in the higher CVD risk categories.

Our study bears some limitations. First, the weights of the risk factors in the original Framingham CVD risk function were estimated over a 30-year period, whereas we validated the risk function for a 15-year period. If the hazard ratios of the risk factors included in the Framingham function would change over time, this could contribute to part of the miscalibration we observed of the original function. For the original Framingham function, Pencina did not find evidence for the hazard rate ratios to be time-dependent, which makes different hazard rate ratios for different time-horizons less likely [3]. From a clinical point of view, a 15-year risk is probably of greater interest in older individuals due to the shorter life expectancy and the potential effect of co-morbidities and competing causes of death. Second, when separately analyzing CHD and stroke, we used the same set of risk factors. A further improvement in predictive performance could be expected if we would allow for a different set of risk factors for both events and competing event respectively. Third, we did not evaluate the inclusion of novel risk factors, which might further contribute to improvement in risk classification.

As the Framingham population was younger on average than the Rotterdam Study participants, we expected the baseline hazard of CVD to be higher in the Rotterdam Data. However, we observed that the Framingham function overestimated CVD risk, especially in the higher risk strata. Part of this overestimation could be explained by the fact that the Framingham function at the same time underestimated the risk of the competing non-CVD death which is of particular importance in older individuals. Underestimation of the competing event results in a higher predicted risk of the CVD event [8]. After adjusting the baseline hazards for both the CVD event and the competing risk of non-CVD death, the overestimation of CVD risk diminished.

The hazard rate ratios of the risk factors were sometimes different in magnitudes and significance of the effects from the ones reported by Pencina et al [3]. Our observation that total cholesterol (in the presence of other factors) did not appear a significant predictor for CVD in the Rotterdam data was supported by earlier analyses from Bos et al in the Rotterdam Study [20, 21]. They found that serum cholesterol has a protective effect on stroke, whereas HDL-cholesterol has no significant effect. This is similar to what we found when we analyzed the hazard of stroke separately from CHD. This could explain the non-significant effect for serum total cholesterol on total CVD in our analysis, as the coefficient for total CVD is a weighted average of the coefficients for stroke and CHD separately. The difference in coefficients for age can be partly explained by the log-transformation (log), together with the older age of the Rotterdam Study cohort compared to Framingham. The increase from log 70 years to log 71 years -a one unit increase on the age scale, is smaller than the log increase from 40 to 41. This implies that the coefficient for age in the Rotterdam data should compensate for these smaller increments in the log-transformed risk factor.

We demonstrated that estimating the hazards for CHD and stroke separately allows for the simultaneous prediction of the risks of these events and found that the weights assigned to the risk factors included in the Framingham risk function are different for both. By separately estimating the hazards of these events, discrimination increased only very little, whereas calibration improved substantially compared to predicting CVD as a combined endpoint. The major contributor to CVD, being either CHD or stroke, differed between individual risk profiles, as illustrated by the four examples. This can have important clinical implications for the allocation of preventive interventions. For example, aspirin is currently recommended in men with a high risk of CHD, while in women the recommendation is only made for those with a high risk of stroke [11].

As we treated CHD, stroke and non-CVD as competing events, our risk function provides information on the separate events and also allows for adding the separate risks of CHD and stroke to obtain an estimate of total CVD risk. This provides clinicians with additional information beyond a risk function which estimates CVD as a single endpoint or separate models for CHD and stroke which do not account for competing risks. Secondly, treatment benefits of preventive interventions such as cholesterol-lowering drugs can be more precisely estimated by applying the different risk reductions for CHD and stroke separately instead of applying the overall reduction on CVD. Further improvement in the prediction of CVD could be obtained by subcategorizing CHD and stroke in fatal and non-fatal events, ischemic and non-ischemic events in the case of stroke, and myocardial infarction and heart failure in the case of CHD.

In conclusion, Framingham CVD-risk predictions perform well in the low- to intermediate risk categories in the Rotterdam Study. Recalibration is necessary as the Framingham function overestimates CVD risk in the higher risk strata of the Rotterdam Study population. Disentangling CVD into CHD and stroke separately provides additional information about the individual contribution of CHD and stroke to total individual CVD-risk and provides clinicians with additional information about the relative contribution of CHD and stroke.

REFERENCES

1. 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.
2. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987-1003.
3. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation. 2009;119:3078-84.
4. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA. 2007;297:611-9.
5. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-47.
6. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143-421.
7. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, 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. 2002;106:388-91.
8. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology. 2009;20:555-61.
9. Matheny M, McPheeters ML, Glasser A, Mercaldo N, Weaver RB, Jerome RN, et al. Systematic Review of Cardiovascular Disease Risk Assessment Tools [internet. In: Assessments RMAfHRaQUEST, editor. 2011/08/06 ed2011.
10. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke. 1991;22:312-8.
11. Force USPST. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;150:396-404.
12. Hofman A, van Duijn CM, Franco OH, Ikram MA, Janssen HL, Klaver CC, et al. The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol. 2011;26:657-86.
13. Leening MJ, Kavousi M, Heeringa J, van Rooij FJ, Verkroost-van Heemst J, Deckers JW, et al. Methods of data collection and definitions of cardiac outcomes in the Rotterdam Study. Eur J Epidemiol. 2012;27:173-85.
14. Koller MT, Steyerberg EW, Wolbers M, Stijnen T, Bucher HC, Hunink MG, et al. Validity of the Framingham point scores in the elderly: results from the Rotterdam study. Am Heart J. 2007;154:87-93.
15. Little R, An H. Robust likelihood-based analysis of multivariate data with missing values. Statistica Sinica. 2004;14:949-68.
16. Rosthoj S, Andersen PK, Abildstrom SZ. SAS macros for estimation of the cumulative incidence functions based on a Cox regression model for competing risks survival data. Comput Methods Programs Biomed. 2004;74:69-75.
17. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26:2389-430.
18. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation and Updating. New York: Spri--nger; 2008.
19. Voko Z, Hollander M, Koudstaal PJ, Hofman A, Breteler MM. How do American stroke risk functions perform in a Western European population? Neuroepidemiology. 2004;23:247-53.
20. Bos M. Causes and Risk of Stroke: the Rotterdam Study: Chapter 4.1, page 125 [Dissertation. Rotterdam: Erasmus Medical Center; 2008.
21. Wieberdink RG, Poels MM, Vernooij MW, Koudstaal PJ, Hofman A, van der Lugt A, et al. Serum lipid levels and the risk of intracerebral hemorrhage: the Rotterdam Study. Arterioscler Thromb Vasc Biol. 2011;31:2982-9.

Chapter 7

Separate prediction of intracerebral hemorrhage and ischemic stroke: results from the Atherosclerosis Risk in Communities Study, Rotterdam Study, and Cardiovascular Health Study

Bart S. Ferket
Bob J. H. van Kempen
Renske G. Wieberdink
Ewout W. Steyerberg
Peter J. Koudstaal
Albert Hofman
Eyal Shahar
Rebecca Gottesman
Jorge R. Kizer
Richard A. Kronmal
Bruce Psaty
Will Longstreth
Thomas Mosley
Aaron R. Folsom
M. G. Myriam Hunink
M. Arfan Ikram

Neurology. May 20 2014;82(20):1804-1812

ABSTRACT

Importance: Distinguishing intracerebral hemorrhage (ICH) and ischemic stroke (IS) risks may improve clinical decision-making.

Objective: To develop and validate 10-year cumulative incidence functions of ICH and IS.

Design, Setting, and Participants: We used data on 27,493 participants from three population-based cohort studies: the Atherosclerosis Risk in Communities (ARIC) Study, median age 54, 45% male, median follow-up 20.7 years; the Rotterdam Study, median age 68, 38% male, median follow-up 14.3 years; and the Cardiovascular Health Study (CHS), median age 71, 41% male, median follow-up 12.8 years. Among these participants 325 ICH events, 2,559 IS events, and 9,909 non-stroke deaths occurred. We developed 10-year cumulative incidence functions for ICH and IS using stratified Cox regression and competing risks analysis. Basic models including only established, non-laboratory risk factors were extended with diastolic blood pressure, the total cholesterol/HDL-cholesterol ratio, body-mass index, waist-to-hip ratio, and glomerular filtration rate. The cumulative incidence functions' performances were assessed in each cohort separately by the Harrell's C-statistic, cross-validation, and calibration plots.

Main Outcome and Measures: Intracerebral hemorrhage and ischemic stroke events during 10-year follow-up.

Results: The total cholesterol/HDL-cholesterol ratio was associated inversely with ICH, but positively with IS (p for difference across stroke subtypes <0.001). For the basic ICH model, C-statistics (95% CI) of 0.805 (0.739 – 0.871), 0.625 (0.555 – 0.695) and 0.676 (0.603 – 0.750) in the ARIC, Rotterdam, and CHS cohort increased to 0.811 (0.743 – 0.879), 0.626 (0.556 – 0.696) and 0.696 (0.624 – 0.767) by model extension. For IS, C-statistics of 0.789 (0.768 – 0.811), 0.696 (0.677 – 0.716) and 0.658 (0.637 – 0.679) increased to 0.798 (0.777 – 0.819), 0.697 (0.677 – 0.717) and 0.663 (0.642 – 0.684) by model extension. Improvements in C-statistics were in general reproduced by cross-validation. Models were well calibrated in all cohorts. Correlations between 10-year ICH and IS risk were moderate in each cohort (r = 0.57, 0.59, 0.37, respectively).

Conclusions and Relevance: We developed and cross-validated cumulative incidence functions for separate prediction of absolute10-year ICH and IS risk. These functions can be useful to further specify an individual's stroke risk.

INTRODUCTION

Stroke is the second leading cause of death and one of the major causes of disability in most Western countries [1]. The incidence of stroke steadily increases from middle-age onwards. Although most strokes are ischemic strokes (IS), approximately 10% are intracerebral hemorrhages (ICH) which has a higher case-fatality than IS: 41% vs 14% [2].

Multiple risk factors that influence stroke risk are well established and can be used to estimate an individual's stroke incidence over a 10-year time period [3-6]. These established 10-year stroke risk models generally apply to IS only or to any stroke. Distinguishing the cumulative incidences of stroke subtypes, i.e. ICH vs. IS, could be valuable for various reasons. First, risk factors may vary for the different stroke subtypes or may have different or even opposing effects [7]. Consequently, the likely effects of modifying these risk factors may vary per stroke subtype. Second, although prevention with aspirin therapy has a net preventive effect on stroke, it decreases the occurrence of IS, whereas it increases the risk of ICH [8]. Therefore, decision-making for aspirin therapy can be improved on the individual level by predicting ICH and IS risk separately. Third, the consequences (e.g. the case-fatality) of both subtypes differ and a more refined risk communication to the individual and the public can be facilitated.

Also, currently used stroke risk scores were developed using standard Cox regression modeling. Standard survival analysis will generally overestimate the cumulative incidence, because it fails to treat those who die of non-stroke causes as ineligible for development of stroke events. Methods to adjust for competing risks are now increasingly being used for cardiovascular risk prediction [9].

In this study, we aimed to develop and validate separate prediction models for estimation of the 10-year cumulative incidences of ICH and IS. We therefore performed a combined analysis of individual data from three population-based cohort studies: Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), and the Rotterdam Study.

METHODS

Study design and population

We constructed a dataset with data from: 1) the ARIC Study; 2) the CHS; and 3) the Rotterdam Study. The ARIC study cohort [10] comprises 15,792 individuals aged 45 to 64 years old at baseline, who were recruited from 4 different regions in the U.S. from 1987 to 1989. In the CHS [11], individuals over the age of 65 living in 4 U.S. communities were recruited from the Health Care Financing Administration (HCFA or Medicare) eligibility lists in two phases. First, 5,201 participants were recruited from 1989 to 1990. In a second wave, 687 African-Americans were recruited from 1992 to 1993 leading to a cohort of 5,888 participants. The Rotterdam Study [12] consists of 7,983 inhabitants

of Ommoord, a district in the city of Rotterdam, the Netherlands, aged 55 years and older. Baseline examinations were conducted from 1990 to 1993. For details on baseline measurements of the three studies see Appendix 3. All studies received approval from medical ethical committees.

The subjects eligible for the current analysis were those without prior stroke (N = 15,297 in the ARIC cohort, N = 5,639 in CHS, N = 7,546 in the Rotterdam Study), did not use anticoagulation (N = 15,222 ARIC study, N = 5,572 CHS, N = 7,177 Rotterdam Study), and did not have atrial fibrillation (N = 15,217 ARIC cohort, N = 5,446 CHS, N = 6,910 Rotterdam Study) at baseline. The latter two exclusion criterions were used because specific guidelines and prediction models already exist for these patients [13]. In addition, we excluded participants who were not African-American or white/European, leaving N = 27,493 subjects (N = 15,170 ARIC study, N = 5,413 CHS, N = 6,910 Rotterdam Study) for the analysis. Based on results from the Framingham Study [3, 14] and previous work conducted in the ARIC, CHS and Rotterdam cohorts [4, 5, 15, 16], we considered age, gender, African-American ethnicity, current smoking, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and history of coronary heart disease as established predictors in a basic non-laboratory model for each stroke type. Subsequently, we evaluated whether predictions could be improved by extending the models with the following risk factors: diastolic blood pressure; total cholesterol; high-density lipoprotein cholesterol; body mass index; waist-to-hip ratio; and estimated glomerular filtration rate (eGFR).

Outcome definitions

Details of outcome ascertainment are described elsewhere [17-19] and in Appendix 3 Table 1. In brief, ARIC outcomes were ascertained through yearly telephone interviews, follow-up examinations, community hospital surveillance, and reported deaths. CHS outcomes were ascertained through 6 monthly telephone interviews, surveillance of HCFA Medicare Utilization files and reported deaths. In the Rotterdam Study, participants were continuously monitored for events through automated linkage of the study database with files from general practitioners and the municipality. The medical records of nursing homes were also evaluated. We excluded ascertained subarachnoid and traumatic hemorrhages. Furthermore, we assumed that most unspecified stroke events would be ischemic of nature. Therefore, we estimated the cumulative incidence of IS using a combined endpoint of classified ischemic and unspecified stroke events as a proxy for the true IS incidence in order to avoid underestimation. Any stroke was defined as the sum of ICH and IS. The censoring date was December 31st 2009 for the ARIC study, January 1st 2009 for the Rotterdam Study, and June 30th, 2008 for the CHS dataset.

Table 1. Baseline characteristics

	ARIC (N = 15,170)	Rotterdam (N = 6,910)	CHS (N = 5,413)
Age, years – median (IQR)	54 (49, 59)	68 (62, 76)	71 (68, 76)
Male gender, n (%)	6,828 (45)	2,633 (38)	2,240 (41)
African American ethnicity, n (%)	4,072 (27)	0	838 (15)
Systolic BP, mmHg – median (IQR)	119 (108, 131)	137 (123, 153)	134 (121,149)
	14 (0)	728 (11)	9 (0)
Diastolic BP, mmHg – median (IQR)	70 (66, 80)	73 (66, 81)	70 (63, 78)
missing data, n (%)	16 (0)	729 (11)	16 (0)
Antihypertensive medication use, n (%)	3,787 (25)	2,085 (30)	2,487 (46)
missing data, n (%)	85 (1)	6 (0)	7 (0)
Current smoking, n (%)	3,981 (26)	1,520 (23)	654 (12)
missing data, n (%)	15 (0)	205 (3)	6 (0)
Diabetes mellitus, n (%)	1,780 (12)	637 (11)	843 (16)
missing data, n (%)	141 (1)	975 (14)	55 (1)
Prior coronary heart disease, no%	1,707 (12)	949 (16)	1,071 (20)
missing data, n (%)	330 (2)	1074 (15)	47 (1)
Total cholesterol, mmol/l – median (IQR)	5.5 (4.8, 6.2)	6.6 (5.8, 7.4)	5.5 (4.8, 6.1)
missing data, n (%)	239 (2)	700 (10)	46 (1)
HDL-C, mmol/l – median (IQR)	1.3 (1.0, 1.6)	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)
missing data, n (%)	237 (2)	726 (11)	54 (1)
BMI, kg/m^2 – median (IQR)	26.9 (24.0, 30.4)	26.0 (23.8, 28.4)	26.1 (23.5, 29.2)
missing data, n (%)	25 (0)	772 (11)	17 (0)
Waist-to-hip ratio – median (IQR)	0.94 (0.88, 0.98)	0.90 (0.84, 0.97)	0.94 (0.87, 0.98)
missing data, n (%)	28 (0)	1081 (16)	34 (1)
eGFR, ml/min/ 1.73 m2 – median (IQR)	89.0 (79.7, 102.3)	77.3 (67.3, 87.7)	76.7 (64.2, 89.9)
missing data, n (%)	146 (1)	2254 (33)	59 (1)
Statin therapy use, n (%)	85 (1)	141 (2)	121 (2)
missing data, n (%)	115 (1)	6 (0)	7 (0)

Abbreviations: ARIC = Atherosclerosis Risk in Communities Study; BMI = body-mass index; BP = blood pressure; CHS = Cardiovascular Health Study; GFR = glomerular filtration rate; HDL = high-density lipoprotein; IQR = interquartile range

Statistical analysis

Two separate prediction models for the 10-year cumulative incidence of ICH and IS were developed using competing cause-specific hazards methodology (see Appendix 3 for more details). In addition, we developed an 'any stroke' model, which can be subdivided into an ICH and IS component. Cause-specific Cox regression models stratified by study cohort were developed with time since study entry as time scale. All continuous predictors

were truncated at their 1st and 99th percentile to limit the influence of extreme values [20]. In the basic models, effect modification by gender was evaluated for age, systolic blood pressure, diabetes mellitus and history of coronary heart disease. An interaction term for systolic blood pressure and antihypertensive medication use was included [3, 14]. In the extended models, we evaluated replacement of total and HDL cholesterol variables by the total cholesterol/HDL ratio and systolic by diastolic blood pressure [21]. We verified the assumption of linearity for continuous predictors included in the extended models using restricted cubic spline functions with four knots adjusted for study and all other predictors. Non-linearity was solved by square or log transformations. Finally, we tested heterogeneity of effects across studies by study-predictor interaction terms.

Discriminative ability was assessed by Harrell's concordance statistic (C-statistic) adjusted for competing risks by setting the follow-up time to the maximum follow-up time if competing death occurred [22]. Model calibration was assessed by calibration plots and Chi square statistics, comparing predicted with observed cumulative incidences using the R 'CumInc' function of the R 'mstate' library. Equally sized groups per study were made according to age tertiles for ICH and quintiles for IS. Cross-validation of the predictions was performed in each study dataset separately. For this purpose, models were fit in two cohorts and evaluated in the other. Reclassification by extending the basic models was assessed by the continuous net reclassification improvement [23]. Ninety-five % CIs were estimated by bootstrapping datasets with recalculation of the observed cumulative incidences within each bootstrap sample. Scatter plots showing the relationship between the ICH and IS components within any stroke risk were made for each dataset using extended models.

Missing covariables were imputed for each study separately using single imputation with the R 'aregImpute' function of the R 'Hmisc' library. Imputation models included all potential predictors and the log cumulative hazard for each outcome. Hypothesis tests were two-sided and decisions on selection of predictor main effects were made upon an improvement of the Akaike Information Criterion (AIC). Interactions and non-linear effects were included using a P value <0·05. The effect of excluding predictors with highly significant heterogeneous hazard ratios (P <0·01 for ICH, P<0·001 for IS and competing death) on cross-validated model performance was evaluated in a sensitivity analysis. We used R version 2.14.2 for all statistical analyses.

RESULTS

Study population

The baseline characteristics of the included ARIC (median age 54, 45% male), Rotterdam Study (median age 68, 38% male), and CHS (median age 71, 41% male) participants are given in Table 1. Systolic blood pressure levels were lower in the ARIC study than in the Rotterdam and CHS cohorts. Rotterdam Study participants had an average total cholesterol level that was higher than observed in the two U.S. cohorts. The CHS

included more subjects treated by antihypertensive drugs and subjects with a history of coronary heart disease, but fewer current smokers. In total, 325 participants experienced an ICH, 2,559 experienced an IS event, and 9,909 died from a competing death cause. The 10-year cumulative incidence for ICH was approximately one-ninth of the 10-year cumulative incidence of IS in all studies (Table 2).

Table 2. Incident event data

	ARIC (N = 15,217)	Rotterdam (N = 6,910)	CHS (N = 5,446)
Overall incident events, n			
Intracerebral hemorrhage	103	99	123
Ischemic stroke	920	820	819
Competing non-stroke death	3,727	3,035	3,147
10-year incident events, n (cumulative incidence, %)			
Intracerebral hemorrhage	42 (0.3)	57 (0.8)	62 (1.1)
Ischemic stroke	360 (2.4)	523 (7.6)	530 (9.8)
Competing non-stroke death	1,179 (7.8)	1,814 (26.3)	1,433 (26.5)
Median follow-up duration, years (IRQ)	20.7 (17.5, 21.7)	14.3 (7.2, 16.2)	12.8 (7.4, 18.3)
Person-years of follow-up	279,741.9	81,997.6	66,325.4

Abbreviations: ARIC = Atherosclerosis Risk in Communities Study, CHS = Cardiovascular Health Study
* Sum of hemorrhagic and IS events may exceed the total of any stroke events, since a hemorrhagic event may be preceded by an ischemic event and vice versa.

Hazard ratios

Gender, diabetes, prior coronary heart disease, waist-to-hip ratio and eGFR were not found to be statistically significant and were excluded from ICH models, whereas these were included in IS models. Table 3 shows the multivariable-adjusted HRs and 95% CIs for incident ICH and IS events. Both for ICH and IS, replacement of total and HDL cholesterol by total cholesterol/HDL-C ratio and the simultaneous inclusion of systolic and diastolic blood pressure (despite correlations of 0.69, 0.59, and 0.51 in ARIC, Rotterdam, and CHS cohorts) improved AIC. The extended ICH model is reported without BMI, although BMI had a statistically significant inverse relation with the ICH hazard: 0.97 (95%CI 0.94 – 0.99) per unit increase. However, the BMI association varied significantly across the three studies and exclusion improved the cross-validated model performance as compared to the basic model.

Although for both stroke subtypes, risk increased if diastolic blood pressure was high, low and mid-range values were less positively associated with ICH than with IS. Mid-range total cholesterol/HDL-C ratio values as compared to low and high values were inversely associated with ICH, whereas total cholesterol/HDL-C ratio were monotonically positively associated with IS risk. The association of the total cholesterol/HDL-C ratio statistically differed across stroke subtypes ($P < 0.001$). The HRs for ICH additionally censored for IS and vice versa are given in eTables 8 and 9 in the Supplement; these did not largely differ from those shown in Table 3.

Table 3. Included predictors and hazard ratios with 95% CIs

Predictor	Basic ICH	Extended ICH	Basic IS	Extended IS
Age per 10 y increase	1.85 (1.55 – 2.21)	1.95 (1.63 – 2.35)	-	-
in men	–	–	1.89 (1.75 – 2.05)	1.87 (1.72 – 2.04)
in women	–	–	2.13 (1.99 – 2.28)	2.09 (1.94 – 2.25)
Male gender	–	–	2.62 (1.55 – 4.42)	2.21 (1.31 – 3.74)
African American	1.78 (1.33 – 2.39)	1.54 (1.14 – 2.09)	1.34 (1.20 – 1.50)	1.35 (1.20 – 1.51)
Current smoking	1.53 (1.17 – 2.00)	1.51 (1.15 – 1.98)	1.63 (1.49 – 1.80)	1.62 (1.47 – 1.78)
Diabetes	-	-	1.77 (1.60 – 1.95)	1.67 (1.52 – 1.85)
Antihypertensive medication use	5.53 (1.26 – 24.32)	5.59 (1.32 – 23.67)	3.83 (2.33 – 6.30)	3.31 (2.02 – 5.45)
Systolic BP per 10 mm Hg increase				
if medication use	1.10 (1.01 – 1.20)	1.04 (0.95 – 1.15)	1.11 (1.08 – 1.14)	1.09 (1.06 – 1.13)
if no medication use	1.26 (1.19 – 1.34)	1.19 (1.11 – 1.29)	1.20 (1.17 – 1.23)	1.17 (1.14 – 1.21)
Prior coronary heart disease	–	–		
in men	–	–	1.64 (1.42 – 1.89)	1.60 (1.39 – 1.85)
in women	–	–	1.22 (1.07 – 1.40)	1.19 (1.04 – 1.37)
Diastolic BP per 10 mm Hg increase	–	0.25 (0.11 – 0.55)	–	0.71 (0.52 – 0.98)
Diastolic BP per 10 mm Hg increase squared	–	1.10 (1.05 – 1.16)	–	1.03 (1.00 – 1.05)
Total cholesterol/HDL ratio	–	0.55 (0.39 – 0.78)	–	1.05 (1.03 – 1.08)
Total cholesterol/HDL ratio squared		1.05 (1.01 – 1.08)	–	-
GFR per 10 ml/min/ 1.73 m^2 increase	–	–	–	0.77 (0.70 – 0.86)
GFR squared	–	–	–	1.01 (1.01 – 1.02)
Waist-to-hip ratio per 0.1 increase	–	–	–	1.11 (1.05 – 1.18)

Abbreviations: BP = blood pressure, GFR = glomerular filtration rate, HDL = high-density lipoprotein, ICH = intracerebral hemorrhage, IS = ischemic stroke

Table 4. Prognostic performance

	Basic ICH model	Extended ICH model	Basic IS model	Extended IS model
Model development in ARIC, Rotterdam and CHS				
Evaluated in ARIC				
C statistic (95%CI)	0.805 (0.739, 0.871)	0.811 (0.743, 0.879)	0.789 (0.768, 0.811)	0.798 (0.777, 0.819)
total NRI (95%CI)	–	0.28 (-0.06, 0.62)	–	0.29 (0.18, 0.39)
event NRI (95%CI)	–	0.10 (-0.17, 0.47)	–	0.28 (0.17, 0.38)
non-event NRI (95%CI)	–	0.18 (0.17, 0.20)	–	0.01 (0.00, 0.03)
Chi-Square calibration	6.15	7.06	10.24	12.55
Evaluated in Rotterdam				
C statistic (95%CI)	0.625 (0.555, 0.695)	0.626 (0.556, 0.696)	0.696 (0.677, 0.716)	0.697 (0.677, 0.717)
total NRI (95%CI)	–	0.19 (-0.03, 0.45)	–	0.15 (0.06, 0.23)
event NRI (95%CI)	–	-0.16 (-0.37, 0.18)	–	0.11 (0.02, 0.21)
non-event NRI (95%CI)	–	0.35 (0.31, 0.37)	–	0.03 (0.01, 0.07)
Chi-Square calibration	5.86	6.90	10.20	10.03
Evaluated in CHS				
C statistic (95%CI)	0.676 (0.603, 0.750)	0.696 (0.624, 0.767)	0.658 (0.637, 0.679)	0.663 (0.642, 0.684)
total NRI (95%CI)	–	0.04 (-0.26, 0.31)	–	0.05 (-0.026, 0.13)
event NRI (95%CI)	–	0.03 (-0.23, 0.30)	–	-0.20 (-0.31, -0.12)
non-event NRI (95%CI)	–	0.00 (-0.02, 0.03)	–	0.25 (0.23, 0.28)
Chi-Square calibration	3.62	2.46	9.92	14.46
Cross-validation				
C statistic (95%CI) in ARIC	0.729 (0.652, 0.806)	0.734 (0.653, 0.814)	0.760 (0.737, 0.783)	0.768 (0.745, 0.790)
C statistic (95%CI) in Rotterdam	0.622 (0.552, 0.693)	0.626 (0.556, 0.696)	0.694 (0.674, 0.713)	0.692 (0.672, 0.712)
C statistic (95%CI) in CHS	0.667 (0.595, 0.740)	0.684 (0.614, 0.753)	0.651 (0.630, 0.672)	0.654 (0.633, 0.676)

Abbreviations: ARIC = Atherosclerosis Risk in Communities Study, CHS = Cardiovascular Health Study, ICH = intracerebral hemorrhage; IS, ischemic stroke, NRI = net reclassification improvement

Event NRI is calculated as the difference in the probability being reclassified upwards and the probability being reclassified downwards conditional on experiencing the event within 10 years: P(up | event) – P(down | event)

Non-event NRI is calculated as the difference in the probability being reclassified downwards and the probability being reclassified upwards conditional on not experiencing the event within 10 years: P(down | event) – P(up | event)

Total NRI is calculated as the sum of event NRI and non-event NRI.

Model performance

Extending the basic models generally led to small improvements in the C-statistic, ranging from 0.001 to 0.020 for ICH, and 0.001 to 0.009 for IS. The continuous total NRIs were positive, with more pronounced changes in the ARIC cohort. Improvements in C-statistics were reproduced by cross-validation except for IS predictions in Rotterdam Study data (Table 4). Model calibration in each cohort was good and did not differ to a

relevant extent between basic and extended models both for ICH and IS prediction; also see the Chi square statistics in Table 4. C-statistics (95% CI) for any stroke predictions were similar to IS predictions, and did not improve with model extension: 0.788 (0.767 – 0.809), 0.690 (0.671 – 0.709), 0.659 (0.638 – 0.679). Results on calibration by the any stroke prediction models were similar to those on IS prediction. Predicted ICH risk tended to increase with IS risk for each study, but the correlation between both predicted risks was moderate in ARIC, Rotterdam, and CHS cohorts (r = 0.57, 0.59, 0.37, Figure 1).

DISCUSSION

In this study, we developed and cross-validated cumulative incidence functions for estimating 10-year risks of ICH and IS using three population-based cohorts consisting of middle-aged and elderly individuals. In addition to estimating the incidences of the two stroke subtypes separately, any stroke incidence was estimated by taking into account the mutually competing risk of both stroke subtypes and death by other causes. Extending basic non-laboratory ICH and IS models with more risk factors only led to limited improvement of discriminative ability, with more pronounced improvement in the ARIC cohort. By using our prediction models, individuals can be identified with low 10-year IS risk, but high ICH risk, and vice versa.

Studies on hemorrhagic stroke prediction are scarce. By performing a systematic literature search (see eAppendix), we found only two studies, both conducted in Chinese populations. In one study [25], a prediction model for hemorrhagic stroke was developed and validated in a cohort of 4,400 steelworkers free of stroke at baseline with an average age of 45 years. The number of hemorrhagic strokes was low: 33 events in the development set and 15 in the validation set. Multivariable-adjusted HRs of age (1.89 per 10 years) and systolic blood pressure (1.22 per 10 mmHg) were similar to ours. For diastolic blood pressure (1.49 per 10 mmHg) and total cholesterol (1.00 per mmol/L), non-linearity was not explored, and therefore these associations are not comparable with ours. In addition, the model was not validated in the general population or in older adults. In the other study [26], major bleeding risk scoring schemes designed for atrial fibrillation patients treated with anticoagulation were validated in 3,602 individuals without atrial fibrillation at baseline, who experienced 54 ICH events during approximately 18 years of follow-up. C-statistics of the various risk scores ranged from 0.59 to 0.72. Individuals with previous stroke were however not excluded and ICH event ascertainment was registry-based. Other prognostic studies focused on either assessment of any stroke risk [3, 4, 14, 16, 27-33] or IS risk [5, 6, 20, 34, 35] usually within a time horizon of 5 to 10 years.

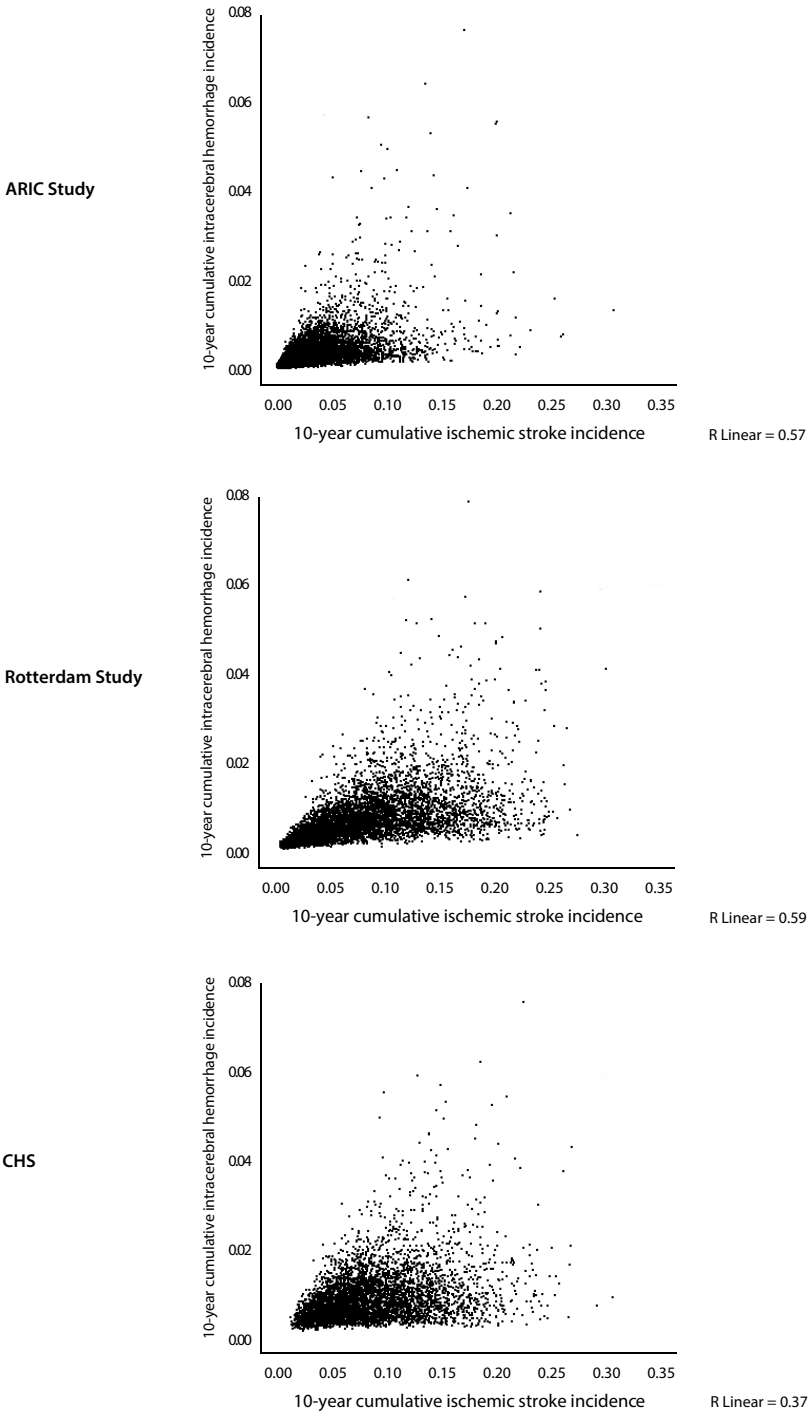


Figure 1. Contribution of intracerebral hemorrhage and ischemic stroke to 10-year any stroke incidence

In contrast to these previous studies, we developed models for the separate 10-year risk assessment of ICH and IS while taking into account competing risks. By combining data from three large population-based cohorts, we were able to acquire a sufficient number of ICH events for multivariable prediction modeling. Furthermore, we also included elderly individuals with an age above 75, which increases the generalizability of our prediction models. Especially in those at older age, competing risks become relevant, mainly because the competing death rate rapidly increases. We demonstrated that also in the older age categories predictions were well calibrated. A final strength of our study is that the measurement of risk factors was reasonably similar across the three studies.

Despite these strengths, our results must be interpreted in the light of some limitations. First, we did not consider novel risk markers such as biomarkers, genetic risk factors, and imaging tests that are also known to be associated with stroke risk. For example, studies have demonstrated an independent association of C-reactive protein with IS but not ICH risk [36], and carotid intima-media thickness measurement (cIMT), and apolipoprotein E genotype with both ICH and IS risk [37-39]. However, cIMT and apolipoprotein E genotype are generally difficult to assess during an office-based risk assessment, which would limit the translation to clinical practice, and C-reactive protein was not available as baseline variable in the ARIC study. A second study limitation is that neuroimaging was not performed in all participants with stroke symptoms. The Rotterdam Study in particular included participants living in nursing homes, who could not be referred to a neurologist or admitted to a hospital. As a consequence, a proportion of strokes were not further specified. We included these as IS events, which could have led to some small bias in prediction, a small overestimation of the average IS risk and underestimation of ICH risk. Third, the baseline age ranges of the ARIC, Rotterdam and CHS cohorts did not entirely overlap. As a consequence the age association was not fully determined by the three datasets combined. Therefore, our predictions should additionally be validated in other independent populations with varying age ranges.

Specifying whether a first stroke is either ICH or IS, is potentially clinically valuable. Specifically, a more refined estimate of the expected benefits and harms can be made about preventive interventions with different effects on ICH and IS risk. For example, according to U.S. Preventive Services Task Force guidelines, middle-aged and elderly women are encouraged to use aspirin when the potential benefit of reduction in ischemic strokes outweighs the bleeding risks [40]. Our cumulative incidence functions may be used to refine communication of the expected benefit (by number of IS events avoided) and harm (by number of induced ICH events in addition to gastrointestinal bleedings) to support shared decision making. However, differences in consequences of ICH and IS events, e.g. the varying case-fatality rates, should be considered as well. In addition, to estimate expected absolute risk differences and numbers needed to treat, stratified analyses of randomized clinical trials that disentangle the effects of various preventive interventions on stroke subtype and competing death rates are required.

CONCLUSIONS

We developed and cross-validated cumulative incidence functions for separate prediction of absolute10-year ICH and IS risk. These functions can be useful to further specify an individual's stroke risk.

REFERENCES

1. Organisation for Economic Co-operation and Development (2011) OECD.-StatExtracts: health status [database]. Available: http://stats.oecd.org/index.aspx?DataSetCode = HEALTH_STAT. Accessed 14 May 2013.
2. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8:355-69.
3. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22:312-8.
4. Lumley T, Kronmal RA, Cushman M, Manolio TA, Goldstein S. A stroke prediction score in the elderly: validation and Web-based application. J Clin Epidemiol 2002;55:129-36.
5. Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2004;160:259-69.
6. Assmann G, Schulte H, Cullen P, Seedorf U. Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Munster (PROCAM) study. Eur J Clin Invest 2007;37:925-32.
7. Leppala JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP. Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. Stroke 1999;30:2535-40.
8. Antithrombotic Trialists C, Baigent C, Blackwell L et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.
9. Koller MT, Raatz H, Steyerberg EW, Wolbers M. Competing risks and the clinical community: irrelevance or ignorance? Stat Med 2012;31:1089-97.
10. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129:687-702.
11. Hofman A, van Duijn CM, Franco OH et al. The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 2011;26:657-86.
12. Fried LP, Borhani NO, Enright P et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1:263-76.
13. Goldstein LB, Bushnell CD, Adams RJ et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:517-84.
14. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. Stroke 1994;25:40-3.
15. Sturgeon JD, Folsom AR, Longstreth WT, Jr., Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke 2007;38:2718-25.
16. Voko Z, Hollander M, Koudstaal PJ, Hofman A, Breteler MM. How do American stroke risk functions perform in a Western European population? Neuroepidemiology 2004;23:247-53.
17. Rosamond WD, Folsom AR, Chambless LE et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke 1999;30:736-43.
18. Ives DG, Fitzpatrick AL, Bild DE et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol 1995;5:278-85.
19. Wieberdink RG, Ikram MA, Hofman A, Koudstaal PJ, Breteler MM. Trends in stroke incidence rates and stroke risk factors in Rotterdam, the Netherlands from 1990 to 2008. Eur J Epidemiol 2012;27:287-95.
20. Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. Bmj 2013;346:f2573.
21. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation and Updating. New York: Springer; 2008.

22. Franklin SS, Lopez VA, Wong ND et al. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. Circulation 2009;119:243-50.

23. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology 2009;20:555-61.

24. Pencina MJ, D'Agostino RB, Sr., Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11-21.

25. Zhang XF, Attia J, D'Este C, Yu XH, Wu XG. A risk score predicted coronary heart disease and stroke in a Chinese cohort. J Clin Epidemiol 2005;58:951-8.

26. Lip GY, Lin HJ, Hsu HC et al. Comparative assessment of the HAS-BLED score with other published bleeding risk scoring schemes, for intracranial haemorrhage risk in a non-atrial fibrillation population: The Chin-Shan Community Cohort Study. Int J Cardiol 2013.

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

28. Bineau S, Dufouil C, Helmer C et al. Framingham stroke risk function in a large population-based cohort of elderly people: the 3C study. Stroke 2009;40:1564-70.

29. Borglykke A, Andreasen AH, Kuulasmaa K et al. Stroke risk estimation across nine European countries in the MORGAM project. Heart 2010;96:1997-2004.

30. Jee SH, Park JW, Lee SY et al. Stroke risk prediction model: a risk profile from the Korean study. Atherosclerosis 2008;197:318-25.

31. Moons KG, Bots ML, Salonen JT et al. Prediction of stroke in the general population in Europe (EUROSTROKE): Is there a role for fibrinogen and electrocardiography? J Epidemiol Community Health 2002;56 Suppl 1:i30-6.

32. Truelsen T, Lindenstrom E, Boysen G. Comparison of probability of stroke between the Copenhagen City Heart Study and the Framingham Study. Stroke 1994;25:802-7.

33. Chien KL, Su TC, Hsu HC et al. Constructing the prediction model for the risk of stroke in a Chinese population: report from a cohort study in Taiwan. Stroke 2010;41:1858-64.

34. Simons LA, McCallum J, Friedlander Y, Simons J. Risk factors for ischemic stroke: Dubbo Study of the elderly. Stroke 1998;29:1341-6.

35. Qiao Q, Gao W, Laatikainen T, Vartiainen E. Layperson-oriented vs. clinical-based models for prediction of incidence of ischemic stroke: National FINRISK Study. Int J Stroke 2012;7:662-8.

36. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132-40.

37. Ohira T, Shahar E, Iso H et al. Carotid artery wall thickness and risk of stroke subtypes: the atherosclerosis risk in communities study. Stroke 2011;42:397-403.

38. Folsom AR, Yatsuya H, Psaty BM, Shahar E, Longstreth WT, Jr. Carotid intima-media thickness, electrocardiographic left ventricular hypertrophy, and incidence of intracerebral hemorrhage. Stroke 2011;42:3075-9.

39. Sudlow C, Martinez Gonzalez NA, Kim J, Clark C. Does apolipoprotein E genotype influence the risk of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage? Systematic review and meta-analyses of 31 studies among 5961 cases and 17,965 controls. Stroke 2006;37:364-70.

40. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;150:396-404.

APPENDIX

Baseline measurements and predictor definitions

In the three studies, participants were asked to fast for 12 hours before undergoing a clinical examination. Height, weight, waist circumference, and hip circumference were measured at the study center. Current smoking status was assessed by home-interview in the Rotterdam Study and telephone interview in ARIC and CHS. In the Rotterdam Study, previous coronary heart disease history was defined as self-reported prior myocardial infarction, PTCA or CABG verified by medical records. In ARIC and CHS, history of coronary heart disease was based on questions about physician-diagnosed myocardial infarction, coronary bypass, and coronary angioplasty, or based on ECG evidence of myocardial infarction. In the Rotterdam Study, atrial fibrilliation was defined by ECG at baseline and information from general practitioners. In ARIC and CHS, atrial fibrilliation was determined by ECG. In all 3 studies, systolic and diastolic blood pressure was calculated as the average of two consecutive measurements, with in ARIC and CHS the average of the 2nd and 3rd of three measurements. In ARIC and CHS, current use of antihypertensive medication use was self-reported, in the Rotterdam Study it was additionally based on information from the general practitioner. All 3 studies enzymatically measured 12-hour fasting total and high density lipoprotein (HDL) cholesterol. In all studies, diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dL (≥7 mmol/L) or non-fasting plasma glucose ≥200 mg/dL (≥11.1 mmol/L) or self-reported use of diabetes medications or diagnosed diabetes. Serum creatinine was assessed by Jaffé methods and standardized to Modification of Diet in Renal Disease (MDRD) values. Because serum creatinine assessment methods were not calibrated to be traceable to isotope dilution mass spectrometry (IMDS), we used the original abbreviated MDRD equation for glomerular filtration rate eGFR: $186.3*(\text{serum creatinine})^{-1.154}*(\text{age})^{-0.203}*(0.742$ if female)*(1.212 if African American) see abstract: Levey et al, J Am Soc Nephrol 11:A0828, 2000.

Outcome definitions and ascertainment

In ARIC, stroke was defined as a rapid onset neurological deficit lasting >24 hours or until death, without an apparent cause such as trauma, tumor, infection or anticoagulation therapy. In CHS and the Rotterdam Study the same definition was used, but anticoagulation therapy used at the time of the event did not preclude events as being classified as a stroke. However, we did not exclude these events, because a previous study showed that exclusion did not alter results. If ascertained, subarachnoid hemorrhage was excluded as an outcome. We adopted the classification of stroke subtypes as made by each study (see Table 1). If a stroke did not match any of these criteria, it was classified as an unspecified stroke event. We assumed that most unspecified stroke events would be ischemic of nature.

In the ARIC study, stroke criteria were implemented as a computer algorithm and reviewed by a physician blinded to the automated results. A second physician resolved disagreements between the computer and initial physician. In the CHS, potential

stroke events were referred to a Cerebrovascular Adjudication Committee, consisting of a neurologist from each site, a neuroradiologist, and a neurologist or internist representing the coordinating center. In the Rotterdam Study, an experienced stroke neurologist (P.J.K.) verified all diagnoses.

Analyses

We calculated cumulative incidence functions for each individual using the predictor effects derived from the Cox regression analyses and cause-specific baseline hazard functions estimated in the pooled dataset. For each stroke subtype, the cumulative incidence was obtained by summation of the individualized cause-specific hazard multiplied by the individualized survival of the stroke subtype and the competing event (i.e. death by other causes) at each failure time using the following equation:

$$I_{stroke}(10) = \sum_{t_i<10} h_{stroke}(t_i)S(t_{i-1})$$

We therefore estimated predictor effects of cardiovascular risk factors on time to first 1) fatal or non-fatal intracerebral hemorrhage, and 2) ischemic stroke, by using Cox regression with censoring for end-of-study, loss-to-follow-up or death by other causes for each subtype. Hazard ratios were estimated using the complete available follow-up. The end-of-study censoring date was December 31st 2009 for the ARIC study, June 30th, 2008 for the CHS and January 1st 2009 for the Rotterdam Study dataset. While modeling ischemic stroke, subjects were allowed to experience intracerebral hemorrhage(s) earlier on and vice versa. Therefore, the cumulative incidences of the stroke subtypes derived from this analysis will exceed the cumulative incidence of any stroke if added. Time to death by other causes was modeled with censoring for the stroke subtype of interest and including the same predictors as used in each final stroke subtype model.

For prediction of any stroke (either intracerebral hemorrhage or ischemic stroke), we modeled the cumulative incidences of intracerebral hemorrhage and ischemic stroke events in absence of having one of the other stroke events. Cumulative incidences of both stroke subtypes derived from this analysis can be added to obtain the cumulative incidence of any stroke. Subjects who experienced ischemic stroke were in addition censored for estimating the intracerebral hemorrhage hazard and vice versa. The competing events for intracerebral hemorrhage were defined as ischemic stroke and death by other causes than intracerebral hemorrhage; and for ischemic stroke as intracerebral hemorrhage and death by other causes than ischemic stroke. For the competing death Cox models, we included all candidate predictors considered for the basic stroke models. For the extended competing death models, additional predictors were selected if also included in the extended stroke model. Predictor effects for the any stroke model were selected from those included in the intracerebral hemorrhage, ischemic and non-ischemic stroke mortality cause-specific models.

Systematic review

We searched MEDLINE by PubMed for studies on stroke prediction to May 14, 2013 with search terms for "stroke", "prediction", "risk scores", "validation", and "cohort studies". We limited our search to articles in the English language. We identified 1469 citations and scanned titles and abstracts on relevancy. We included eligible articles for review of full text if the study purpose was to develop or validate prediction models for individualizing the absolute risk of non-fatal and/or fatal stroke events in asymptomatic subjects who were not selected on risk factor status.

Full Pubmed search syntax

stroke* [tiab] AND (prediction [tiab] OR risk scor* [tiab] OR risk function* [tiab] OR validation[tiab] OR validate[tiab]) AND (communit* [Text Word] OR cohort studies[MeSH Terms] OR cohort*[Text Word] OR population-based [Text Word]) AND English[lang]

Results May 14, 2013:
1469 titles

Inclusion after reading titles/abstracts:
22 studies[1-22]

Inclusion for data extraction:
18 studies[1-15, 20-22]

4 studies[16-19] were excluded, because no prediction model for calculation of individual risks was presented.

Table e-1. Outcome definitions per study

Study	Intracerebral hemorrhage	Ischemic stroke
Rotterdam	1) Intraparenchymal hemorrhage by CT/ MRI; or 2) if the person lost consciousness permanently or died within 24 hours of onset	Neurological deficit 1) with no evidence of other diagnoses by CT or MRI scan carried out within 4 weeks after the event; or 2) limited to 1 limb or completely recovered within 72 hours; or 3) with atrial fibrillation in the absence of anticoagulant therapy
ARIC	1) Intraparenchymal increased density by CT/MRI; 2) bloody spinal fluid by LP and evidence from cerebral angiograpy with focal deficit or decreased level of consciousness or coma > 24 hours; or 3) surgical or autopsy evidence of hemorrhage	Neurological deficit with 1) no CT/MRI or LP blood; or 2) CT/MRI showing infarct or decreased density; or 3) surgical or autopsy evidence of ischemic infarction
CHS	1) Intraparenchymal increased density by CT/MRI; 2) bloody spinal fluid by LP with focal deficit; or 3) death from stroke within 24 hours of onset and no LP, CT, MRI or autopsy; or 4) surgical or autopsy evidence of hemorrhage	Neurological brain deficit with 1) no CT/MRI or LP blood; or 2) CT/MRI with mottled cerebral pattern or showing decreased density in a compatible location; or 3) surgical or autopsy evidence of ischemic infarction

Table e-2. Test results heterogeneity in predictor effects intracerebral hemorrhage

Predictor	P value cohort interaction in the basic model	P value cohort interaction in the extended model
Age per 10 y increase	0.96	0.86
Male sex	–	–
African American	0.01	0.03
Current smoking	0.75	0.81
Diabetes	–	–
Antihypertensive medication use	0.03	0.02
Systolic BP per 10 mm Hg increase		
if medication use	0.04	0.04
if no medication use	0.08	0.05
Prior coronary heart disease	–	–
Diastolic BP per 10 mm Hg increase	–	0.29
Diastolic BP per 10 mm Hg increase squared	–	–
Total cholesterol/HDL cholesterol ratio	–	0.15
Total cholesterol/HDL cholesterol ratio squared	–	–
BMI per 5 units increase	–	<0.01

Abbreviations: BP = blood pressure, BMI = body-mass index, HDL = high-density lipoprotein

Table e-3. Test results heterogeneity in predictor effects ischemic stroke

Predictor	P value cohort interaction in the basic model	P value cohort interaction in the extended model
Age per 10 y increase		
in men	0.39	0.39
in women	0.62	0.54
Male sex	0.46	0.43
African American	<0.001	<0.001
Current smoking	0.001	<0.001
Diabetes	<0.001	<0.001
Antihypertensive medication use	0.08	0.09
Systolic blood pressure per 10 mm Hg increase		
if medication use	0.03	0.04
if no medication use	0.22	0.22
Prior coronary heart disease		
in men	0.01	0.01
in women	0.24	0.27
Diastolic BP per 10 mm Hg increase	–	0.05
Diastolic BP per 10 mm Hg increase squared	–	–
Total cholesterol/HDL cholesterol ratio	–	<0.001
GFR per 10 ml/min/ 1.73 m^2 increase	–	0.22
GFR per 10 ml/min/ 1.73 m^2 increase squared	–	–
Waist-to-hip ratio per 0.1 increase	–	0.02

Abbreviations: BP = blood pressure, GFR = glomerular filtration rate, HDL = high-density lipoprotein

Table e-4. Test results heterogeneity in predictor effects competing death censored for any stroke

Predictor	P value cohort interaction in the basic model	P value cohort interaction in the extended model
Age per 10 y increase		
in men	0.80	0.64
in women	0.44	0.08
Male sex	0.90	0.49
African American	<0.001	<0.001
Current smoking	<0.001	<0.001
Diabetes	<0.001	<0.001
Antihypertensive medication use	0.01	0.01
Systolic BP per 10 mm Hg increase		
if medication use	0.002	0.002
if no medication use	0.08	0.07
Prior coronary heart disease		
in men	<0.001	<0.001
in women	0.004	0.02
Diastolic BP per 10 y increase	–	0.003
Diastolic BP per 10 y increase squared	–	–
Total cholesterol: HDL ratio	–	<0.001
Total cholesterol: HDL ratio squared	–	–
GFR per 10 ml/min/ 1.73 m^2 increase	–	0.004
GFR per 10 ml/min/ 1.73 m^2 increase squared	–	–
Waist-to-hip ratio per 0.1 increase	–	<0.001

Abbreviations: BP = blood pressure, BMI = body-mass index, GFR = glomerular filtration rate, HDL = high-density lipoprotein

Table e-5. Sensitivity analysis intracerebral hemorrhage models with and without strongly heterogeneous predictor effects

	Basic model including all predictors	**Basic model excluding heterogeneous predictors**	**Extended model including all predictors**	**Extended model excluding heterogeneous predictors**
Development in CHS and Rotterdam, validation with ARIC				
C statistic (95%CI)	0.729 (0.652, 0.806)	0.731 (0.654, 0.808)	0.702 (0.611, 0.792)	0.734 (0.653, 0.814)
Chi-Square calibration	6.46	6.47	6.59	6.82
Development in ARIC and CHS, validation with Rotterdam				
C statistic (95%CI)	0.622 (0.552, 0.693)	0.622 (0.552, 0.693)	0.632 (0.564, 0.700)	0.625 (0.556, 0.694)
Chi-Square calibration	6.30	6.30	6.87	7.18
Development in ARIC and Rotterdam, validation with CHS				
C statistic (95%CI)	0.667 (0.595, 0.740)	0.664 (0.593, 0.735)	0.687 (0.615, 0.758)	0.684 (0.614, 0.753)
Chi-Square calibration	6.61	5.81	4.78	4.75

Abbreviations: ARIC = Atherosclerosis Risk in Communities Study, CHS = Cardiovascular Health Study

Table e-6. Sensitivity analysis ischemic stroke models with and without predictors with strongly heterogeneous hazard ratios

	Basic model including all predictors	**Basic model excluding heterogeneous predictors**	**Extended model including all predictors**	**Extended model excluding heterogeneous predictors**
Development in CHS and Rotterdam, validation with ARIC				
C statistic (95%CI)	0.760 (0.737, 0.783)	0.750 (0.726, 0.773)	0.768 (0.745, 0.790)	0.750 (0.727, 0.772)
Chi-Square calibration	5.78	5.89	6.43	8.27
Development in ARIC and CHS, validation with Rotterdam				
C statistic (95%CI)	0.694 (0.674, 0.713)	0.687 (0.667, 0.707)	0.692 (0.672, 0.712)	0.684 (0.664, 0.704)
Chi-Square calibration	13.86	16.54	12.47	12.11
Development in ARIC and Rotterdam, validation with CHS				
C statistic (95%CI)	0.651 (0.630, 0.672)	0.651 (0.629, 0.673)	0.654 (0.633, 0.676)	0.661 (0.639, 0.682)
Chi-Square calibration	15.24	13.88	23.26	10.38

Abbreviations: ARIC = Atherosclerosis Risk in Communities Study, CHS = Cardiovascular Health Study

Table e-7. Predictors and hazard ratios with 95%CIs for competing death censored for any stroke

Predictor	Basic model HR (95%CI)	Extended model HR (95%CI)
Age per 10 y increase		
in men	2.93 (2.82 – 3.05)	2.79 (2.67 – 2.91)
in women	3.09 (2.98 – 3.20)	2.97 (2.85 – 3.08)
Male sex	2.19 (1.68 – 2.85)	2.23 (1.71 – 2.91)
African American	1.17 (1.11 – 1.24)	1.13 (1.06 – 1.20)
Current smoking	2.13 (2.04 – 2.23)	2.09 (2.00 – 2.19)
Diabetes	1.64 (1.55 – 1.73)	1.56 (1.48 – 1.64)
Antihypertensive medication use	1.97 (1.52 – 2.55)	1.85 (1.43 – 2.39)
Systolic blood pressure per 10 mm Hg increase		
if medication use	1.04 (1.02 – 1.05)	1.04 (1.02 – 1.06)
if no medication use	1.08 (1.06 – 1.09)	1.08 (1.06 – 1.09)
Prior coronary heart disease		
in men	1.68 (1.57 – 1.80)	1.65 (1.54 – 1.76)
in women	1.47 (1.37 – 1.58)	1.44 (1.35 – 1.55)
Diastolic BP per 10 y increase	–	0.55 (0.47 – 0.65)
Diastolic BP per 10 y increase squared		1.04 (1.03 – 1.05)
Total cholesterol/HDL ratio	–	0.81 (0.76 – 0.87)
Total cholesterol/HDL ratio squared		1.02 (1.01 – 1.03)
GFR per 10 ml/min/ 1.73 m^2 increase	–	0.68 (0.64 – 0.72)
GFR per 10 ml/min/ 1.73 m^2 increase squared	–	1.02 (1.02 – 1.02)
Waist-to-hip ratio per 0.1 increase	–	1.13 (1.10 – 1.16)

Abbreviations: BP = blood pressure, GFR = glomerular filtration rate, HDL = high-density lipoprotein

Table e-8. Predictors and hazard ratios with 95%CIs for intracerebral hemorrhage censored for ischemic stroke and competing death

Predictor	Basic model HR (95%CI)	Extended model HR (95%CI)
Age per 10 y increase	1.99 (1.65 – 2.40)	2.08 (1.72 – 2.52)
Male sex		
African American	1.83 (1.35 – 2.49)	1.58 (1.14 – 2.17)
Current smoking	1.50 (1.13 – 2.00)	1.49 (1.12 – 1.99)
Diabetes		
Antihypertensive medication use	5.76 (1.20 – 27.74)	5.84 (1.27 – 26.79)
Systolic BP per 10 mm Hg increase		
if medication use	1.08 (0.98 – 1.19)	1.03 (0.93 – 1.13)
if no medication use	1.24 (1.16 – 1.33)	1.18 (1.08 – 1.27)
Prior coronary heart disease		
Diastolic blood pressure per 10 y increase	–	0.21 (0.09 – 0.48)
Diastolic blood pressure per 10 y increase squared	–	1.12 (1.06 – 1.18)
Total cholesterol/HDL ratio	–	0.58 (0.40 – 0.85)
Total cholesterol/HDL ratio squared	–	1.04 (1.00 – 1.08)

Abbreviations: BP = blood pressure, CHS = Cardiovascular Health Study, HDL = high-density lipoprotein

Table e-9. Predictors and hazard ratios with 95%CIs for ischemic stroke censored for intracerebral hemorrhage and competing death

Predictor	Basic model HR (95%CI)	Extended model HR (95%CI)
Age per 10 y increase		
in men	1.89 (1.75 – 2.05)	1.88 (1.73 – 2.05)
in women	2.13 (1.99 – 2.28)	2.09 (1.95 – 2.25)
Male sex	2.62 (1.55 – 4.42)	2.21 (1.30 – 3.75)
African American	1.33 (1.19 – 1.48)	1.34 (1.19 – 1.50)
Current smoking	1.64 (1.49 – 1.80)	1.63 (1.48 – 1.79)
Diabetes	1.78 (1.61 – 1.96)	1.68 (1.52 – 1.86)
Antihypertensive medication use	3.80 (2.30 – 6.26)	3.29 (2.00 – 5.42)
Systolic BP per 10 mm Hg increase		
if medication use	1.11 (1.08 – 1.14)	1.09 (1.06 – 1.13)
if no medication use	1.20 (1.17 – 1.23)	1.17 (1.14 – 1.21)
Prior coronary heart disease		
In men	1.64 (1.42 – 1.89)	1.60 (1.39 – 1.85)
In women	1.22 (1.06 – 1.40)	1.19 (1.04 – 1.36)
Diastolic blood pressure per 10 y increase	–	0.72 (0.52 – 0.99)
Diastolic blood pressure per 10 y increase squared	–	1.03 (1.00 – 1.05)
Total cholesterol: HDL ratio	–	1.05 (1.03 – 1.08)
GFR per 10 ml/min/ 1.73 m^2 increase	–	0.78 (0.70 – 0.87)
GFR per 10 ml/min/ 1.73 m^2 increase squared	–	1.01 (1.01 – 1.02)
Waist-to-hip ratio per 0.1 increase	–	1.11 (1.05 – 1.18)

Abbreviations: BP = blood pressure, BMI = body-mass index, GFR = glomerular filtration rate, HDL = high-density lipoprotein

Table e-10. Performance of standard survival models vs. cumulative incidence functions

	Basic ICH model	Extended ICH model	Basic IS model	Extended IS model
Model development in ARIC, Rotterdam and CHS, validation with ARIC				
C statistic (95%CI) – standard	0.803 (0.738, 0.869)	0.809 (0.741, 0.877)	0.789 (0.767, 0.811)	0.798 (0.776, 0.819)
Chi-Square calibration – standard	7.51	7.54	15.91	19.54
C statistic (95%CI) – CIF	0.805 (0.739, 0.871)	0.811 (0.743, 0.879)	0.789 (0.768, 0.811)	0.798 (0.777, 0.819)
Chi-Square calibration – CIF	6.15	6.33	10.24	12.55
Model development in ARIC, Rotterdam and CHS, validation with Rotterdam				
C statistic (95%CI) – standard	0.611 (0.543, 0.679)	0.618 (0.550, 0.685)	0.697 (0.677, 0.716)	0.697(0.677, 0.717)
Chi-Square calibration – standard	16.48	14.35	65.59	69.36
C statistic (95%CI) – CIF	0.625 (0.555, 0.695)	0.626 (0.556, 0.696)	0.696 (0.677, 0.716)	0.697 (0.677, 0.717)
Chi-Square calibration – CIF	5.86	6.90	10.20	10.03
Model development in ARIC, Rotterdam and CHS, validation with CHS				
C statistic (95%CI) – standard	0.658 (0.587, 0.730)	0.676 (0.606, 0.746)	0.656 (0.635, 0.677)	0.659 (0.638, 0.680)
Chi-Square calibration – standard	1.50	1.61	18.82	16.53
C statistic (95%CI) – CIF	0.676 (0.603, 0.750)	0.696 (0.624, 0.767)	0.658 (0.637, 0.679)	0.663 (0.642, 0.684)
Chi-Square calibration – CIF	3.62	2.46	9.92	14.46

Abbreviations: ARIC = Atherosclerosis Risk in Communities Study, CIF, = cumulative incidence function, CHS = Cardiovascular Health Study, ICH = intracerebral hemorrhage, IS = ischemic stroke

Table e-11. Performance of any stroke prediction for the ARIC, CHS and Rotterdam studies

	Basic model	**Extended model**
Model development in pooled ARIC, CHS and Rotterdam dataset		
Validation with ARIC		
C statistic (95%CI)	0.788 (0.767, 0.809)	0.785 (0.765, 0.806)
total NRI (95%CI)	–	0.05 (0.02, 0.09)
event NRI (95%CI)	–	0.03 (0.00, 0.05)
non-event NRI (95%CI)	–	0.02 (0.00, 0.03)
Chi-Square calibration	9.69	11.17
Validation with Rotterdam		
C statistic (95%CI)	0.690 (0.671, 0.709)	0.690 (0.671, 0.710)
total NRI (95%CI)	–	0.17 (0.10, 0.26)
event NRI (95%CI)	–	0.06 (-0.02, 0.15)
non-event NRI (95%CI)	–	0.11 (0.09, 0.14)
Chi-Square calibration	10.08	10.24
Validation with CHS		
C statistic (95%CI)	0.659 (0.638, 0.679)	0.658 (0.638, 0.679)
total NRI (95%CI)	–	-0.06 (-0.14, 0.05)
event NRI (95%CI)	–	-0.29 (-0.37, -0.21)
non-event NRI (95%CI)	–	0.23 (0.20, 0.25)
Chi-Square calibration	15.92	15.68

Abbreviations: ARIC = Atherosclerosis Risk in Communities Study, CHS = Cardiovascular Health Study, NRI = net reclassification improvement

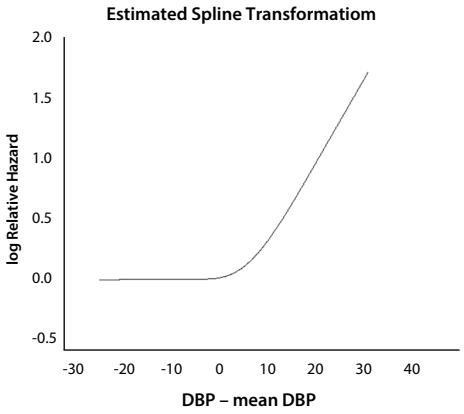


Figure e-1. Multivariable adjusted relation of diastolic blood pressure with the log hazard of intracerebral hemorrhage

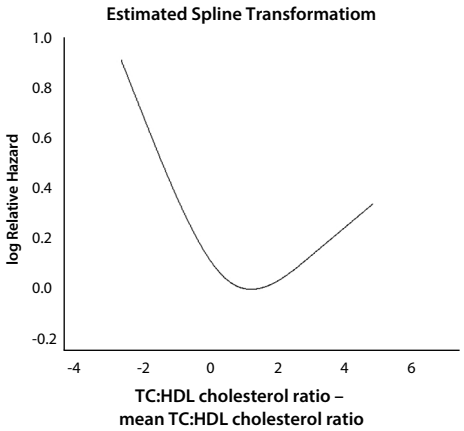


Figure e-2. Multivariable adjusted relation of total cholesterol:HDL cholesterol ratio with the log hazard of intracerebral hemorrhage

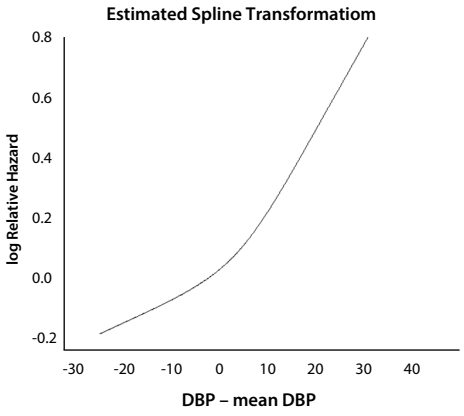


Figure e-3. Multivariable adjusted relation of diastolic blood pressure with the log hazard of ischemic stroke

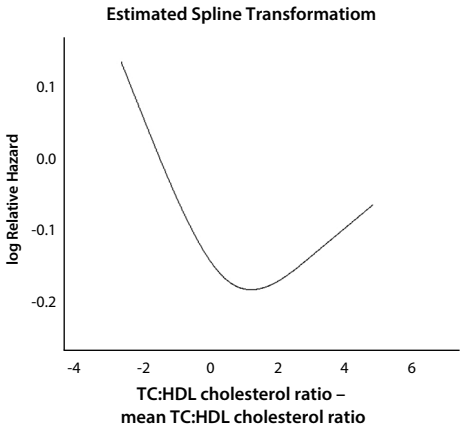


Figure e-4. Multivariable adjusted relation of total: HDL cholesterol ratio with the log hazard of ischemic stroke

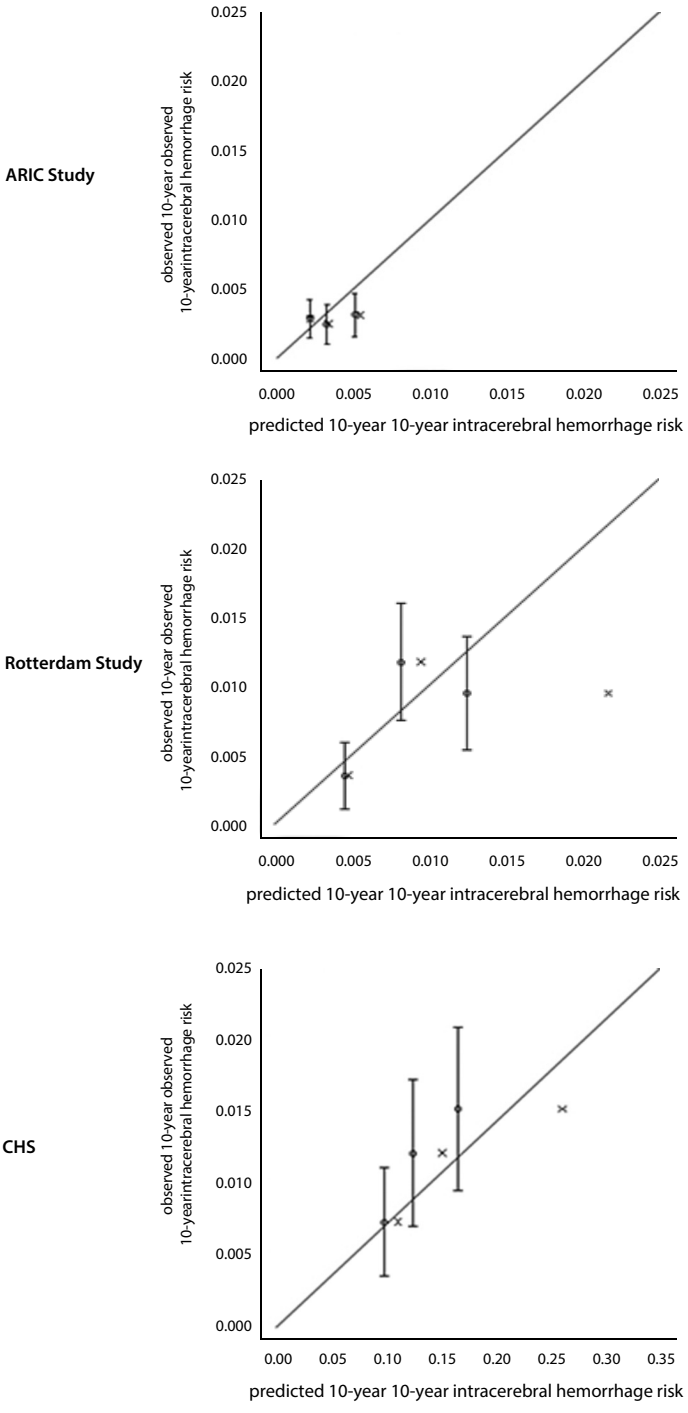


Figure e-5. Calibration plots of cumulative incidence functions for intracerebral hemorrhage in the three cohorts – Basic model

Predicted vs observed 10-year cumulative incidence (95%CI) of intracerebral hemorrhage within age tertiles. Predictions based on cumulative incidence functions are indicated by circles, predictions based on standard survival models are indicated by crosses. Because 95%CIs are equal, these are only depicted for cumulative incidence functions.

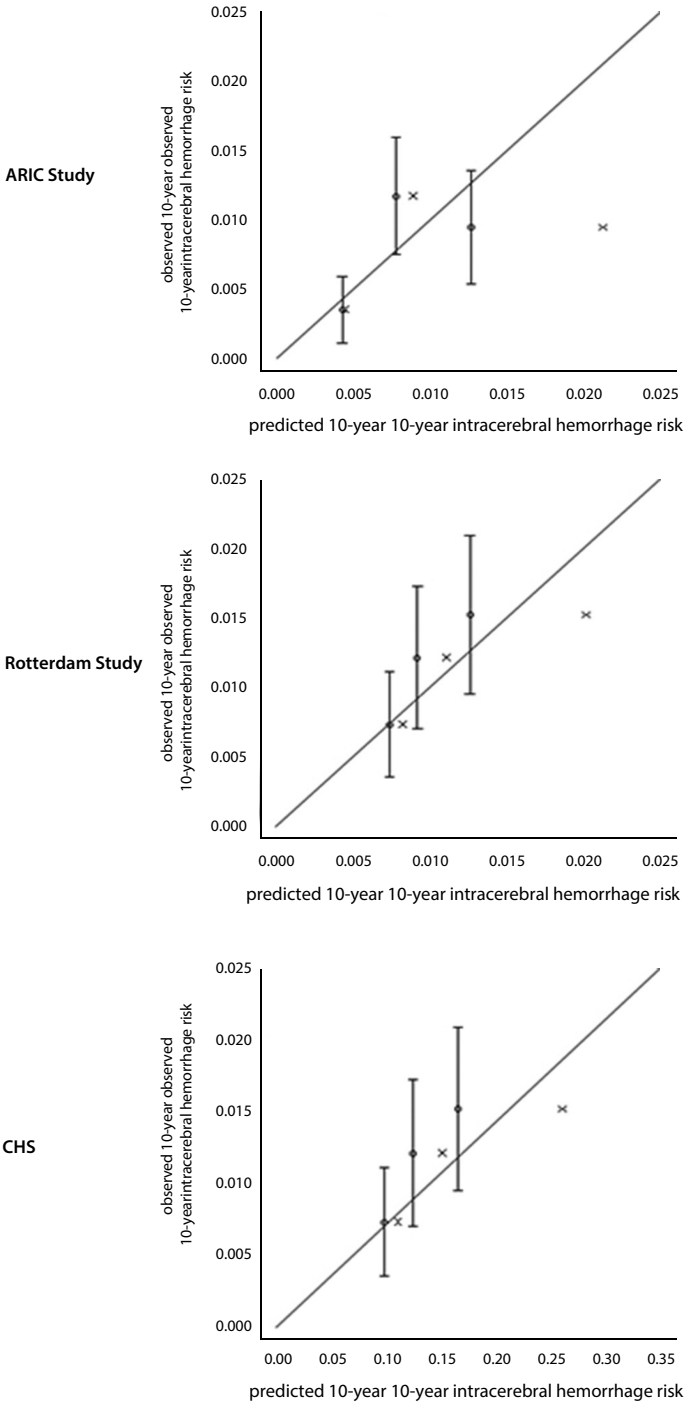


Figure e-6. Calibration plots of cumulative incidence functions for intracerebral hemorrhage in the three cohorts – Extended model

Predicted vs. observed 10-year cumulative incidence (95%CI) of intracerebral hemorrhage within age tertiles. Predictions based on cumulative incidence functions are indicated by circles, predictions based on standard survival models are indicated by crosses. Because 95% CIs are equal, these are only depicted for cumulative incidence functions.

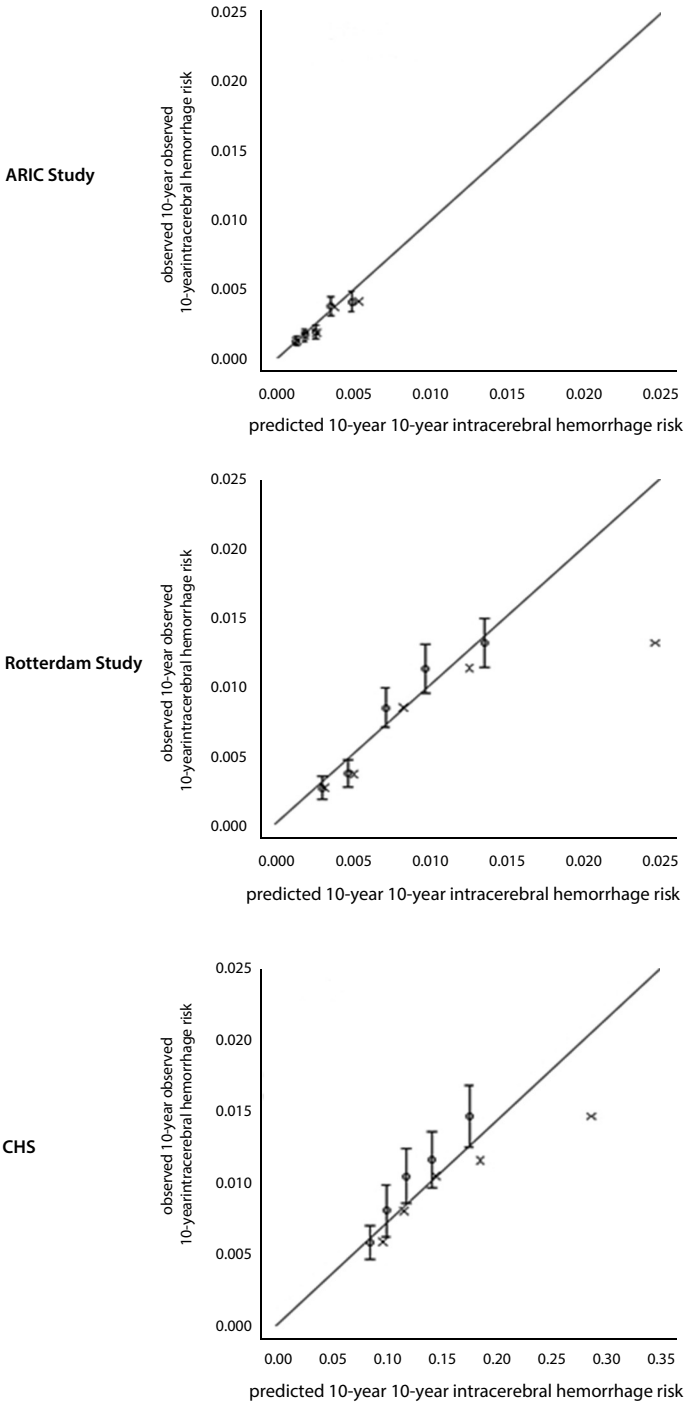


Figure e-7. Calibration plots of cumulative incidence functions for ischemic stroke in the three cohorts – Basic model

Predicted vs observed 10-year cumulative incidence (95%CI) of ischemic stroke within age quintiles. Predictions based on cumulative incidence functions are indicated by circles, predictions based on standard survival models are indicated by crosses. Because 95% CIs are equal, these are only depicted for cumulative incidence functions.

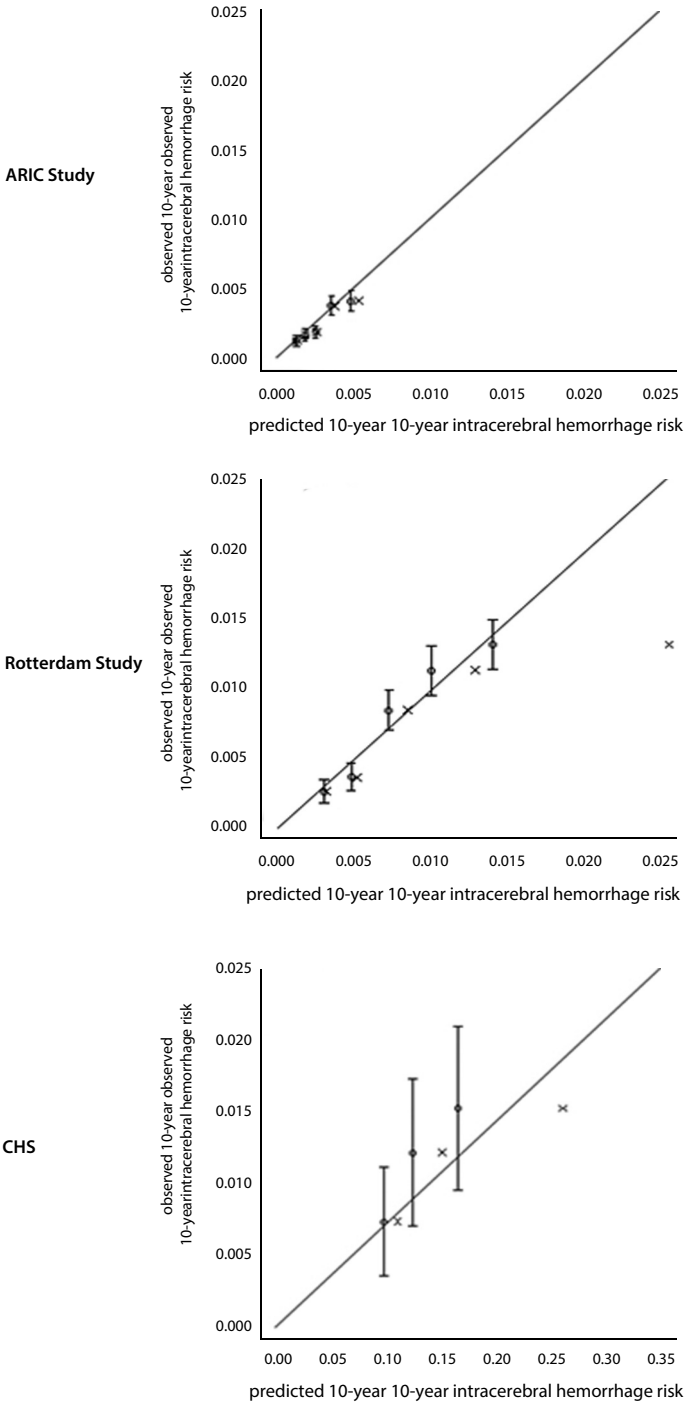


Figure e-8. Calibration plots of cumulative incidence functions for ischemic stroke in the three cohorts – Extended model

Predicted vs observed 10-year cumulative incidence (95%CI) of ischemic stroke within age quintiles. Predictions based on cumulative incidence functions are indicated by circles, predictions based on standard survival models are indicated by crosses. Because 95% CIs are equal, these are only depicted for cumulative incidence functions.

E-REFERENCES

e1. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. AmHeart J 1991;121:293-298.

e2. Assmann G, Schulte H, Cullen P, Seedorf U. Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Munster (PROCAM) study. Eur J Clin Invest 2007;37:925-932.

e3. Bineau S, Dufouil C, Helmer C, et al. Framingham stroke risk function in a large population-based cohort of elderly people: the 3C study. Stroke 2009;40:1564-1570.

e4. Borglykke A, Andreasen AH, Kuulasmaa K, et al. Stroke risk estimation across nine European countries in the MORGAM project. Heart 2010;96:1997-2004.

e5. Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2004;160:259-269.

e6. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22:312-318.

e7. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. Stroke 1994;25:40-43.

e8. Jee SH, Park JW, Lee SY, et al. Stroke risk prediction model: a risk profile from the Korean study. Atherosclerosis 2008;197:318-325.

e9. Lumley T, Kronmal RA, Cushman M, Manolio TA, Goldstein S. A stroke prediction score in the elderly: validation and Web-based application. J Clin Epidemiol 2002;55:129-136.

e10. Moons KG, Bots ML, Salonen JT, et al. Prediction of stroke in the general population in Europe (EUROSTROKE): Is there a role for fibrinogen and electrocardiography? J Epidemiol Community Health 2002;56 Suppl 1:i30-36.

e11. Simons LA, McCallum J, Friedlander Y, Simons J. Risk factors for ischemic stroke: Dubbo Study of the elderly. Stroke 1998;29:1341-1346.

e12. Truelsen T, Lindenstrom E, Boysen G. Comparison of probability of stroke between the Copenhagen City Heart Study and the Framingham Study. Stroke 1994;25:802-807.

e13. Voko Z, Hollander M, Koudstaal PJ, Hofman A, Breteler MM. How do American stroke risk functions perform in a Western European population? Neuroepidemiology 2004;23:247-253.

e14. Zhang XF, Attia J, D'Este C, Yu XH, Wu XG. A risk score predicted coronary heart disease and stroke in a Chinese cohort. J Clin Epidemiol 2005;58:951-958.

e15. Chien KL, Su TC, Hsu HC, et al. Constructing the prediction model for the risk of stroke in a Chinese population: report from a cohort study in Taiwan. Stroke 2010;41:1858-1864.

e16. Asayama K, Ohkubo T, Kikuya M, et al. Use of 2003 European Society of Hypertension-European Society of Cardiology guidelines for predicting stroke using self-measured blood pressure at home: the Ohasama study. Eur Heart J 2005;26:2026-2031.

e17. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. Lancet Neurol 2007;6:1106-1114.

e18. Wu Y, Zhang L, Yuan X, Wu Y, Yi D. Quantifying links between stroke and risk factors: a study on individual health risk appraisal of stroke in a community of Chongqing. Neurol Sci 2011;32:211-219.

e19. Molshatzki N, Goldbourt U, Tanne D. Perceived hardships at midlife: Prediction of long-term stroke mortality. Int J Cardiol 2013.

e20. Lip GY, Lin HJ, Hsu HC, et al. Comparative assessment of the HAS-BLED score with other published bleeding risk scoring schemes, for intracranial haemorrhage risk in a non-atrial fibrillation population: The Chin-Shan Community Cohort Study. Int J Cardiol 2013.

e21. Qiao Q, Gao W, Laatikainen T, Vartiainen E. Layperson-oriented vs. clinical-based models for prediction of incidence of ischemic stroke: National FINRISK Study. Int J Stroke 2012;7:662-668.

e22. Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. Bmj 2013;346:f2573.

Chapter 8

Predictive value of updating Framingham risk scores with novel risk markers in the U.S. general population

Bart S. Ferket*
Bob J. H. van Kempen*
M. G. Myriam Hunink
Isha Agarwal
Maryam Kavousi
Oscar H. Franco
Ewout W. Steyerberg
Wendy Max
Kirsten E. Fleischmann

* Shared first authorship

PLos One. 2014;9(2):e88312

ABSTRACT

Background: According to population-based cohort studies CT coronary calcium score (CTCS), carotid intima-media thickness (cIMT), high-sensitivity C-reactive protein (CRP), and ankle-brachial index (ABI) are promising novel risk markers for improving cardiovascular risk assessment. Their impact in the U.S. general population is however uncertain. Our aim was to estimate the predictive value of four novel cardiovascular risk markers for the U.S. general population.

Methods and findings: Risk profiles, CRP and ABI data of 3,736 asymptomatic subjects aged 40 or older from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 exam were used along with predicted CTCS and cIMT values. For each subject, we calculated 10-year cardiovascular risks with and without each risk marker. Event rates adjusted for competing risks were obtained by microsimulation. We assessed the impact of updated 10-year risk scores by reclassification and C-statistics. In the study population (mean age 56 ± 11 years, 48% male), 70% (80%) were at low (<10%), 19% (14%) at intermediate (≥10 – <20%), and 11% (6%) at high (≥20%) 10-year CVD (CHD) risk. Net reclassification improvement was highest after updating 10-year CVD risk with CTCS: 0.10 (95%CI 0.02 – 0.19). The C-statistic for 10-year CVD risk increased from 0.82 by 0.02 (95%CI 0.01 – 0.03) with CTCS. Reclassification occurred most often in those at intermediate risk: with CTCS, 36% (38%) moved to low and 22% (30%) to high CVD (CHD) risk. Improvements with other novel risk markers were limited.

Conclusions: Only CTCS appeared to have significant incremental predictive value in the U.S. general population, especially in those at intermediate risk. In future research, cost-effectiveness analyses should be considered for evaluating novel cardiovascular risk assessment strategies.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death in the U.S. population [1]. Current guidelines recommend aggressive risk modifying treatment regimens in apparently healthy individuals deemed to be at high cardiovascular risk [2]. These individuals can be identified using risk scores based on traditional risk factors as defined by the Framingham Heart Study [3, 4]. However, the accuracy of Framingham risk scores (FRS) for predicting CVD outcomes can be improved by adding novel risk markers, including imaging techniques and biomarkers.

Recently, the U.S. Preventive Services Task Force and the American College of Cardiology Foundation/American Heart Association Task Force published recommendations on which novel risk markers to use for cardiovascular risk assessment [5, 6]. Four novel risk markers that are expected to have added predictive value beyond the FRS are: the CT coronary artery calcium score (CTCS), high-sensitivity C-reactive protein (CRP), the ankle-brachial index (ABI) and measurement of carotid intima-media thickness (cIMT). Most importantly, studies should have demonstrated that risk assessment including these novel markers should correctly reclassify individuals into clinically relevant risk categories. These risk categories are defined by 10-year risk: e.g. <10% (low risk), 10 – 19% (intermediate risk) and ≥20% (high risk).

Due to heterogeneous results [7-9] and selection of study populations it remains difficult to generalize from published cohort studies that adding these novel markers to the FRS would indeed lead to improved classification in the U.S. population as a whole [10]. In order to synthesize the existing evidence quantitatively, computer simulation modeling with data input from meta-analyses combined with study data representative of the entire population overcomes a number of these limitations [11].

In this study, we aimed to update traditional 10-year FRSs by the published independent associations of CTCS, cIMT, CRP, and ABI with cardiovascular events. Our final purpose was to assess to what extent the predictive value of traditional risk assessment would be improved by these four novel markers in asymptomatic participants of the National Health and Nutrition Examination Survey (NHANES), a cross-sectional study designed to be a representative sample of the U.S. general population.

METHODS

Systematic Review of the Novel Risk Markers' Predictive Effects

We adopted two recent individual-level meta-analyses for the association of a one unit SD (1.11) log mg/L increase of CRP, and the association of a 0.1 mm increase in mean cIMT with coronary heart disease (CHD) and stroke event rates [12, 13]. Both were adjusted for traditional risk factors. For CTCS and ABI, we updated the 2009 systematic review by the USPSTF [14] through April 19, 2013 (for detailed search syntaxes and study inclusion

criteria see the Text S1). Two reviewers independently included potentially eligible articles based on title and abstract. Only studies that recruited subjects from the general population, and which excluded or adjusted for prior CHD and stroke were included. Articles were included if both reviewers agreed that the study design was a cohort, nested case-control, or case-cohort study. Also, systematic reviews that included these study types were considered. Relative risk estimates had to be calculated for CHD and/or stroke, with CHD defined as myocardial infarction or coronary death. We excluded studies that analyzed the novel risk marker with adjustment for less than 5 of the 8 Framingham risk factors: age, sex, smoking, systolic blood pressure, antihypertensive drug therapy, total cholesterol, high density (HDL) cholesterol and diabetes mellitus. One reviewer extracted the reported relative risks and 95% CI limits of an increase in 1 unit log (CTCS + 1) for CTCS, and of an ABI ≤0.90 vs >0.90. If relative risks were reported using other units, these were converted in order to match the aforementioned units (see the Text S1 for details). Data extraction was checked by a second reviewer. We used the R 'meta.summaries' function of the 'rmeta' package to compute summary estimates and 95% CIs by random-effects modeling. Heterogeneity was assessed statistically with the Woolf's test where values <0.05 indicate significant heterogeneity.

Study Population

We selected data on 3,736 individuals aged 40 or older without a history of myocardial infarction or stroke at baseline from the 2003 – 2004 NHANES exam, taking into account the sampling weights. We used the following datasets: NHANES 2003 – 2004 Demographics Data, NHANES 2003 – 2004 Examination Data, NHANES 2003 – 2004 Laboratory Data, and NHANES 2003 – 2004 Questionnaire Data, see http://wwwn.cdc.gov/nchs/nhanes/search/nhanes03_04.aspx. We included the following variables: age at the exam visit, sex, current smoking, systolic blood pressure, total cholesterol, HDL cholesterol, fasting plasma glucose level, anti-diabetic treatment, antihypertensive treatment, ankle-brachial index, and high-sensitivity C-reactive protein. Because values for CTCS and cIMT were not measured in the NHANES study, we merged the NHANES dataset with a subset of the Rotterdam Study Cohort. The Rotterdam Study is a population-based cohort study of individuals aged 55 years and older living in Rotterdam, the Netherlands [15]. Baseline examinations were performed between 1990 and 1993 (Rotterdam Study-I). Traditional FRS risk factors, CTCS, cIMT, hs-CRP, ABI, and information on cardioprotective drugs were simultaneously measured during the third examination round (1997 to 1999) in a subset (N = 1,915) of the Rotterdam Study-I cohort. Details on how these novel risk markers and the other variables were measured are published elsewhere [16, 17]. We imputed the missing CTCS and cIMT values of NHANES subjects within the merged dataset. For the imputation, we used a flexible additive imputation model including all other variables. After the imputation, only NHANES individuals were selected for the analysis (see Table 1 for baseline characteristics, andText S1 for details on the dataset preparation).

Table 1. Baseline characteristics of 3,736 NHANES and 1,915 Rotterdam Study individuals

Variable	NHANES Median [IQR]	RS Median [IQR]
Age	53 [46 – 63]	70 [66 – 75]
Sex (%male)	48%	45%
Current Smoking	23%	16%
Systolic blood pressure (mm Hg)	125 [115 – 139]	140.0 [124 – 155]
HRX	27%	28%
Total cholesterol (mg/dl)	209 [183 – 235]	225 [203 – 250]
HDL cholesterol (mg/dl)	51 [42 – 63]	51 [43 – 62]
Glucose (mg/dl)	97 [90 – 106]	99 [94 – 110]
Anti diabetic medication	8%	6.2%
CTCS*		
0	37%	10%
1-100	36%	41%
101-400	14%	23%
400-1000	8%	15%
≥1000	5%	11%
Natural logarithm of (CTCS+1)	2.6 [0 – 4.8]	4.81 [2.6 – 6.3]
cIMT (mm)*	0.78 [0.69 – 0.93]	0.86 [0.76 – 0.95]
CRP (mg/L)	2.1 [0.9 – 4.6]	2.4 [1.2 – 4.4]
ABI ≤0.9	5.0%	15.6%

Abbreviations: CTCS = CT coronary artery calcium score, HDL = high-density lipoprotein, HRX = antihypertensive drug treatment, NHANES = National Health and Nutrition Examination Survey; RS, Rotterdam Study.
SI conversion factors: To convert CRP to nanomoles per liter, multiply by 9.524; HDL and total cholesterol to millimoles per liter, multiply by 0.0259.
*Imputed by multivariable algorithms

Updating Framingham Risk Scores

For both the 10-year cardiovascular risk assessment and simulation of event rates, we used the 30-year FRS as basis for our models [18]. It uses the 8 aforementioned traditional risk factors to calculate 30-year cumulative incidences for both CVD and non-CVD deaths, while taking into account competing risks. CVD is defined as myocardial infarction, coronary death and stroke, non-CVD death is defined as mortality due to all causes other than CVD. In order to calculate CHD and stroke risks separately, we applied a sex-specific ratio of the reported CHD to stroke events to the baseline CVD survival function. For men, the CHD: stroke event ratio was 348/104 and for women it was 133/86. We assumed that the reported regression coefficients of the traditional risk factors were similar for CHD and stroke. To resemble currently recommended risk assessment, we calculated 10-year CVD and CHD risks without adjustment for competing risk. We used the baseline CHD and CVD survival probability at year 10 and subsequently updated

the traditional FRS with one novel risk marker at a time. We recalibrated the baseline survival probability by assuming no change in the average survival probability. For both 10-year CVD and CHD, the different models (FRS only, FRS + CTCS, FRS + IMT, FRS + CRP, and FRS + ABI) were used to classify the 3,673 NHANES subjects into to the following risk categories: <10%, ≥10-<20%, ≥20%. In addition, we also classified into <6%, ≥6-<20%, ≥20%: categories [19].

Cardiovascular outcomes

To simulate cardiovascular event rates, we constructed a state-transition model using TreeAge software (2009 version, TreeAge Software, Inc., Williamstown, MA, USA), consisting of three health states: 'Well', 'Post-CVD' and 'Dead' (see Table S1 for input parameters). A one-year cycle length was used. One-year transition-probabilities were based on the 30-year FRS updated with all four novel risk markers together, assuming independency of predictive effects. We recalibrated the baseline survival function through 30 years of follow-up, while ascertaining that the average 30-year cumulative incidences for CVD and non-CVD death calculated by the state-transition model were equal to the average risks calculated by the original 30-year FRS for the NHANES study sample (see the eMethods for details).

Predictive Value of the Four Updated Risk Scores

Reclassification tables were created by cross-tabulating NHANES individuals using the three risk categories of the traditional and each updated FRS. Occurrences of events within these individuals were modeled through a state-transition model using Monte Carlo microsimulation. We calculated risks in subjects reclassified upwards and downwards for both cases and non-cases and calculated the net reclassification improvement (NRI) applicable to survival and competing risk data [20]. For the intermediate risk category, we calculated a bias-corrected NRI [21]. In addition, long-term 30-year risks were reported in the reclassification tables to evaluate whether those who are reclassified have a long-term risk that is in agreement with the reclassification. To further assess the models' discriminative performance, we calculated the Harrell's C-statistic [22] using simulated 10-year time-to-event data. To take into account the uncertainty of the hazard ratios of the novel risk markers, 95% CIs were calculated by randomly sampling from lognormal distributions defined by the summary estimates and standard errors taken from the meta-analyses.

Ethics Statement

For the 2003 – 2004 NHANES, Institutional Review Board (IRB) approval and documented consent was obtained from all participants (Protocol #98-12). The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare, and Sports. The approval has been renewed every 5 years.

RESULTS

Systematic Review of the Novel Risk Markers' Predictive Effects

From the USPSTF report [14], eight studies on CTCS and ten studies on ABI were included in our review. For ABI, we did not use the reported estimates on CHD and stroke, because these were based on a comparison between an ABI ≤0.9 and 1.11 – 1.40 instead of ≤0.9 vs >0.9 [23]. Combined with the citations found through our additional search, in total 1,107 citations were included in our systematic review. Seventeen articles were used for the data extraction; for reasons of exclusions see Figure 1. In 11 of the articles the effect of the novel risk marker was adjusted for seven or more Framingham risk factors (for the study details see Table S2).

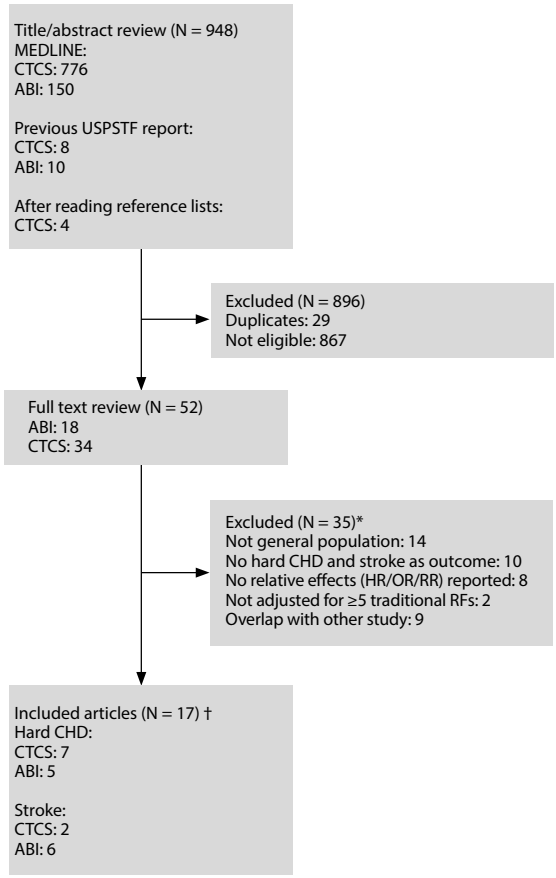


Figure 1. Literature search and selection

Numbers of articles of each step of the review process are indicated.

*Group total exceed the reported number for the excluded articles because several reasons for exclusion were allowed. †Group total exceed the number for the included articles, because one article may include estimates for both CHD and stroke.

Abbreviations: ABI, ankle-brachial index; CHD, coronary heart disease; CTCS, computed tomography calcium scoring; HR, hazard ratio; OR = odds ratio, RR = risk ratio, USPSTF = United States Preventive Services Task Force

For the association between CTCS and CHD, we performed a meta-analysis on a total of 30,945 individuals and 548 events. Only two studies were found on the association of CTCS with stroke, comprising 7,118 subjects and 117 stroke events. For the ABI meta-analyses, 21,122 subjects with 1,206 CHD events and 36,941 subjects with 987 stroke events were used. One study on the association between ABI and CHD also counted angina as a CHD event [24]. As the authors explicitly stated that the analysis limited to hard CHD events (i.e., excluding angina) showed similar results, we included this study in the analysis. Summary estimates from the meta-analyses are given in Table 2. We found no statistical evidence for heterogeneity between studies. The forest plots are included in the Figures S1-S4.

Table 2. Hazard Ratios and confidence intervals from the meta-analyses

Novel risk marker	HR [95%CI] for CHD	HR [95%CI] for Stroke	Source
Log(CTCS+1)	1.35 [1.28 – 1.43]	0.97 [0.84 – 1.12]	This manuscript
0.1 mm IMT	1.08 [1.05 – 1.10]	1.12 [1.10 – 1.15]	Den Ruijter et al [13]
Log(CRP) / SD* (mg/L)	1.22 [1.17 – 1.27]	1.16 [1.10 – 1.27]	Emerging Risk Factors Collaboration [12]
ABI ≤0.9	1.47 [1.18 – 1.84]	1.26 [1.05 – 1.50]	This manuscript

* Pooled SD = 1.11 mg/L

Predictive Value of the Four Updated Risk Scores

Most NHANES subjects were at low (<10%) 10-year CVD and CHD risk: respectively 2,641 (71%) and 2,999 (80%). The number of NHANES subjects with intermediate (≥10-<20%) risk was limited: 697 (19%) for CVD and 525 (14%) for CHD as the outcome. These numbers approximately doubled with using the alternative threshold values ≥6-<20% to 1385 (37%) for CVD and 1075 (29%) for CHD.

Amongst the updated models, the FRS + CTCS had the highest NRI (Table 4). For the FRS updated with the other novel risk markers, the reclassification was limited and the NRI was close to zero for both CVD and CHD as end point (see Table 4 and Tables S4 and S5). Net reclassification improvement results were similar when using the <6, ≥6-<20%, ≥20% risk categorization. The number of high risk (≥20%) individuals reclassified to lower risk was limited -even for CTCS. Those who were reclassified upwards had a much higher 30-year CVD and CHD risk than the risk for those remaining in their risk category or who were reclassified downwards (Table 3 and Table S4a).

Subjects who were traditionally classified as intermediate (≥10-<20%) 10-year CVD risk, were most frequently reclassified by CTCS. In this intermediate risk category, 0.39 (95%CI 0.23 – 0.55) of those with a CVD event within 10 years were reclassified upwards, whereas only 0.17 (95%CI 0.09 – 0.27) were reclassified downwards. For the subjects who did not experience an event, 0.37 (95%CI 0.35 – 0.39) were reclassified downwards

and 0.18 (95%CI 0.11 – 0.25) upwards. The resulting bias-corrected NRI from updating FRS by CTCS in the intermediate risk category was 0.15 (95%CI 0.05 – 0.27). Defining ≥6-<20% as the intermediate risk category, the bias-corrected NRI was 0.13 (95%CI 0.06 – 0.21). The C-statistic of the FRS increased most by adding CTCS (Table 4 and Table S5). It increased from 0.82 (95%CI 0.79 – 0.85) to 0.84 (95%CI 0.81 – 0.86) for predicting CVD and from 0.84 (95%CI 0.82 – 0.86) to 0.87 (95%CI 0.84 – 0.89) for predicting CHD.

Table 3. Ten-year cardiovascular disease (CVD) risk reclassification by CTCS

	FRS + CTCS			Overall
FRS	**<10%**	**≥10-<20%**	**≥20%**	
<10%				
N	2520.53	116.06	4.41	2641
% Events [95% CI]				
10 yr CVD	2.5 [1.9 – 3.2]	11.2 [6.1 – 16.6]	19.7 [0 – 85.8]	2.9 [2.3 – 3.5]
30 yr CVD	14.8 [13.0 – 16.2]	49.2 [39.8 – 57.3]	68.6 [0 – 100]	16.4 [15.0 – 18.0]
≥10- <20%				
N	240.28	309.36	147.36	697
% Events [95% CI]				
10 yr CVD	6.7 [3.5 – 9.6]	12.9 [9.0 – 16.4]	24.8 [17.7 – 31.4]	13.3 [10.8 – 16.0]
30 yr CVD	32.5 [27.0 – 38.9]	50.5 [45.5 – 55.9]	69.3 [60.9 – 77.6]	48.3 [43.6 – 51.9]
≥20%				
N	6.62	80.72	310.66	398
% Events [95%CI]				
10 yr CVD	9.7 [0 – 42.9]	13.9 [7.8 – 21.3]	40.3 [33.0 – 47.9]	34.4 [28.8 – 40.6]
30 yr CVD	33.7 [0 – 75.0]	48.4 [39.9 – 58.2]	74.1 [68.3 – 78.9]	68.2 [63.2 – 72]
Overall				
N	2767.43	506.14	462.43	3736
% Events [95% CI]				
10 yr CVD	2.8 [2.3 – 3.5]	12.7 [9.6 – 15.4]	35.2 [30.0 – 40.0]	8.2 [7.3 – 40.0]
30 yr CVD	16.4 [14.8 – 17.8]	49.8 [45.0 – 54.3]	72.5 [67.6 – 76.7]	27.9 [26.3 – 76.7]

Classification on the basis of 10-year CVD risk assessment using <10%, ≥10-<20%, and ≥20% as risk thresholds.
Abbreviations: CTCS = CT coronary artery calcium score.

Table 4. Predictive value of novel risk markers for 10-year cardiovascular disease

	FRS+CTCS	FRS+cIMT	FRS+CRP	FRS+ABI
Δ C-statistic vs. FRS [95%CI]	0.02 [0.01 – 0.03]	0.00 [0.00 – 0.01]	0.00 [0.00 – 0.01]	0.00 [0.00 – 0.00]
NRI with <10%, ≥10-<20%, and ≥20%				
NRI | event [95%CI]	0.07 [-0.02 – 0.17]	0.00 [-0.02 – 0.03]	0.01 [-0.02 – 0.05]	-0.01 [-0.04 – 0.02]
NRI | no event [95%CI]	0.02 [0.00 – 0.05]	0.01 [0.01 – 0.01]	0.00 [0.00 – 0.01]	0.01 [0.01 – 0.01]
NRI total [95%CI]	0.10 [0.02 – 0.19]	0.01 [-0.01 – 0.04]	0.01 [-0.02 – 0.05]	0.00 [-0.03 – 0.03]
NRI with <6%, ≥6 -<20%, and ≥20%				
NRI | event [95%CI]	0.06 [-0.03 – 0.15]	-0.01 [-0.03 – 0.02]	0.00 [-0.03 – 0.04]	-0.01 [-0.03 – 0.01]
NRI | no event [95%CI]	0.07 [0.05 – 0.09]	0.03 [0.03 – 0.03]	0.02 [0.01 – 0.02]	0.01 [0.01 – 0.01]
NRI total [95%CI]	0.13 [0.05 – 0.22]	0.02 [-0.01 – 0.05]	0.02 [-0.01 – 0.06]	0.00 [-0.02 – 0.02]

Abbreviations: ABI = ankle-brachial index, cIMT = carotid intima-media thickness, CRP = high-sensitivity C-reactive protein, C-statistic = Harrell's concordance index, CTCS = CT coronary artery calcium score, FRS = Framingham risk score, NRI = net reclassification improvement.

DISCUSSION

In this study, we modeled the predictive value of adding four novel cardiovascular risk markers to traditional Framingham risk scores (FRSs) in individuals representative of the U.S. general population. Whereas previous studies have focused on the predictive value of risk markers in specific longitudinal cohorts, we aimed to study the potential value of using risk markers in the US population as a whole. We used the two most commonly used endpoints 10-year CVD and CHD risk, together with two recommended risk categorization methods: <10%, 10-19%, ≥20% and <6%, 6 – 19%, ≥20% for low, intermediate, and high risk respectively. Among the four updated risk scores, the FRS updated with CTCS showed the most impact on reclassification for both CVD and CHD as endpoint, regardless of the risk thresholds used. Most reclassification occurred in those traditionally at intermediate risk; in other risk categories reclassification was less evident. FRS updated by cIMT, CRP and ABI had limited value with regard to appropriate reclassification and improvement of the C-statistic.

Previous cohort studies have demonstrated the added predictive value of CT coronary artery calcium score (CTCS), carotid intima-media thickness (cIMT), high-sensitivity C-reactive protein (CRP), and the ankle-brachial index (ABI) beyond FRS. The latter three risk markers were recently evaluated in large individual-level meta-analyses combining data from several cohort studies [12, 13, 23, 25]. Although the meta-analyses showed that these markers are associated with CVD independently from Framingham risk factors, the impact on improving risk prediction and classification was generally limited. The meta-analysis evaluating cIMT for 10-year CVD prediction showed similar C-statistics for the FRS: 0.757, and FRS with addition of common cIMT: 0.759. Only a small NRI: 0.008 was observed in the total population, which increased to 0.036 in individuals at intermediate risk [13]. This meta-analysis did not include recently published Framingham Study data that showed similar results: a small change in the C-statistic: 0.748 to 0.751 and 0.0 NRI. The meta-analysis on CRP showed a change in the C-statistic of 0.0039, and the NRI was 0.0152 for CVD prediction. The Framingham Offspring data included within the analysis showed that the C-statistic of 0.7779 increased by 0.0040. In the other included cohort studies, changes in the C-statistic varied from -0.0027 to 0.0157 [25]. In the meta-analysis on ABI, CHD risks were calculated after cross-tabulating a FRS for predicting 10-yr CHD risk categories by four different ABI categories. Meaningful reclassification by ABI was limited to women only: 7% of women at low risk and 10% of the women at intermediate risk were reclassified as high risk based on an ABI ≤0.90 [23]. Changes in the C-statistic and NRI with ABI ≤0.90 have not been established. A recent study in the Atherosclerosis Risk in Communities Study (ARIC Study) showed only modest improvement in the C-statistic: 0.756 to 0.758 and a NRI of 0.008 [26]. For CTCS, individual-level meta-analyses have not yet been conducted, although a systematic review of cohort studies shows that the impact on the C-statistic and NRI is generally larger: changes in the C-statistic varied from 0.04 to 0.13 and NRIs varied from 0.14 to 0.25 [9]. The four risk markers were evaluated in a direct comparison by only two cohort studies: the Multi-Ethnic Study of Atherosclerosis (MESA) and the Rotterdam Study [17, 27]. Both studies concluded that

among the four markers, CTCS has the most added value in those at intermediate risk. In MESA, addition of CTCS, cIMT, CRP or ABI to a FRS plus race/ethnicity led to NRIs of 0.659, 0.102, 0.079, and 0.036 respectively. In the Rotterdam Study, these were 0.393, 0.046, 0.092, and 0.073. These NRIs were, however, not bias-corrected [21].

Generalizing results on reclassification from cohort studies to the general population is not straightforward. The impact of a novel risk marker on improving risk classification is determined by the strength of the association with the outcome, but also depends on the joined distribution of the marker and traditional risk factors in the population [10]. Because the distribution of risk factors in cohort studies is not comparable to the general population, we reproduced cardiovascular risk predictions by Framingham risk factors and novel risk markers within a recent NHANES sample while hypothesizing that these are generalizable. Although we were able to apply the summarized independent associations of novel risk markers with CVD to the NHANES sample, our study bears some important limitations. First, the NHANES did not include measurements of CTCS and cIMT. We therefore had to impute these measurements. We used correlations between Framingham risk factors and the other two novel risk markers as observed in the Rotterdam Study for the imputation process. Thus, the CTCS and cIMT values were distributed in the NHANES subjects conditionally on the assumption that the correlations in the Rotterdam Study are applicable to the NHANES population. Second, the NHANES data do not include CVD event rates and we therefore had to assume that the FRS [18] would be valid for the NHANES population in predicting event rates. However, it has been shown that Framingham-based predictions perform fairly well in most U.S. subpopulations [28]. Third, for the simulation of CVD event rates, we assumed that the associations of the four novel risk markers with CVD were independent of each other. Few studies published the change in hazard ratios of these novel risk markers after subsequently adding them to the FRS. Generally, the amount of confounding is limited [29]. Fourth, because our purpose was to evaluate the additional value of novel risk markers in the light of competing risk by non-CVD death, we chose a FRS that took into account the competing risk of non-CVD death for our simulation model. This FRS however uses total CVD as outcome and does not allow associations of traditional risk factors to be different for CHD and stroke events [3]. We therefore hypothesized that these effects would be similar. Although this seems to be a reasonable assumption for the most important cardiovascular risk factors -age and sex, this may be less true for other risk factors such as lipid levels [30]. However, CHD comprises the major part of total CVD. This implies that the associations of the traditional risk factors with CVD are closer to that of CHD than of stroke, and the results for reclassification of CHD will be relatively unaffected by this assumption. Finally, putting CHD and stroke and under the same term might be problematic when the goal is to individualize predictions while considering the difference in pathophysiology. For example, cIMT might well improve predictions of future stroke but not CHD. A separate assessment of stroke risk is generally however not advocated by most guideline groups, and we therefore did not evaluate a potential improvement of stroke prediction [31].

Instead of a priori focusing on individuals at intermediate risk [14, 27], we also included low and high-risk individuals. In theory, reclassifying high-risk individuals without events downwards could be beneficial as well. However, we demonstrated that CTCS has the largest value in refining decision-making in the intermediate risk category. Reclassification of subjects originally at low or high risk was much more limited. The size of the U.S. general population considered to be at intermediate risk largely depends on the chosen outcome and risk thresholds. Thus, the potential impact of additional testing with novel risk markers to decrease the total number of events will vary with this definition. Its impact will also depend on the indirect association of the novel risk marker with competing non-CVD death, e.g. through a strong correlation with age. There is, however, no indication that those reclassified to high risk suffer from a larger risk of competing death as demonstrated by a concordant increase in long-term, 30-year risk. Ultimately, costs and effects of recommended preventive treatment on quality-adjusted life expectancy should be considered for evaluating the impact of novel cardiovascular risk assessment strategies [32].

In conclusion, among four promising novel risk markers, only CTCS is expected to have significant incremental predictive value in the U.S. general population, and especially in those at intermediate risk. Future research should be performed to evaluate the clinical impact and cost-effectiveness of various novel cardiovascular risk assessment strategies.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, et al. (2012) Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 125: e2-e220.
2. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr., Clark LT, et al. (2004) Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 110: 227-239.
3. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, et al. (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 117: 743-753.
4. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, et al. (1998) Prediction of coronary heart disease using risk factor categories. Circulation 97: 1837-1847.
5. U.S. Preventive Services Task Force (2009) Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 151: 474-482.
6. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, et al. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 56: e50-e103.
7. Shah T, Casas JP, Cooper JA, Tzoulaki I, Sofat R, et al. (2009) Critical appraisal of CRP measurement for the prediction of coronary heart disease events: new data and systematic review of 31 prospective cohorts. Int J Epidemiol 38: 217-231.
8. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR (2008) C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation 118: 2243-2251, 2244p following 2251.
9. Peters SA, den Ruijter HM, Bots ML, Moons KG (2012) Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart 98: 177-184.
10. Wald NJ, Hackshaw AK, Frost CD (1999) When can a risk factor be used as a worthwhile screening test? Bmj 319: 1562-1565.
11. Hunink MGM, Glasziou PP, Siegel JE, Weeks J, Pliskin J, et al. (2001) Decision making in health and medicine: Integrating evidence and values. Cambridge: Cambridge University Press.
12. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, et al. (2010) C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 375: 132-140.
13. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, et al. (2012) Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. Jama 308: 796-803.
14. Helfand M, Buckley DI, Freeman M, Fu R, Rogers K, et al. (2009) Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med 151: 496-507.
15. Hofman A, van Duijn CM, Franco OH, Ikram MA, Janssen HL, et al. (2011) The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 26: 657-686.
16. Elias-Smale SE, Proenca RV, Koller MT, Kavousi M, van Rooij FJ, et al. (2010) Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J Am Coll Cardiol 56: 1407-1414.
17. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, et al. (2012) Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med 156: 438-444.
18. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS (2009) Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation 119: 3078-3084.

19. Greenland P, Smith SC, Jr., Grundy SM (2001) Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. Circulation 104: 1863-1867.

20. Pencina MJ, D'Agostino RB, Sr., Steyerberg EW (2011) Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 30: 11-21.

21. Paynter NP, Cook NR (2012) A Bias-Corrected Net Reclassification Improvement for Clinical Subgroups. Med Decis Making.

22. Pencina MJ, D'Agostino RB, Sr., Song L (2012) Quantifying discrimination of Framingham risk functions with different survival C statistics. Stat Med 31: 1543-1553.

23. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, et al. (2008) Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. Jama 300: 197-208.

24. Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, et al. (2010) The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 56: 1506-1512.

25. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, et al. (2012) C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med 367: 1310-1320.

26. Murphy TP, Dhangana R, Pencina MJ, D'Agostino RB, Sr. (2012) Ankle-brachial index and cardiovascular risk prediction: an analysis of 11,594 individuals with 10-year follow-up. Atherosclerosis 220: 160-167.

27. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, et al. (2012) Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. Jama 308: 788-795.

28. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P, Group CHDRP (2001) Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. Jama 286: 180-187.

29. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, et al. (2008) Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 168: 1333-1339.

30. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB (1991) Probability of stroke: a risk profile from the Framingham Study. Stroke 22: 312-318.

31. Ferket BS, Colkesen EB, Visser JJ, Spronk S, Kraaijenhagen RA, et al. (2010) Systematic review of guidelines on cardiovascular risk assessment: Which recommendations should clinicians follow for a cardiovascular health check? Arch Intern Med 170: 27-40.

32. van Kempen BJ, Spronk S, Koller MT, Elias-Smale SE, Fleischmann KE, et al. (2011) Comparative effectiveness and cost-effectiveness of computed tomography screening for coronary artery calcium in asymptomatic individuals. J Am Coll Cardiol 58: 1690-1701.

TEXT S1

Meta-analyses

To standardize the reported units and categories into the desired units for CTCS: natural logarithm of (CTCS + 1) and the categorization of ABI: ≤0.9 vs >0.9, we assumed a log-linear relation between the hazard of coronary heart disease (CHD) and stroke with the natural logarithm of (CTCS + 1) and continuous ABI up to a value of 1.4. If categories were reported, we performed linear regression on the log hazard ratios with the reported median values of each category as co-variables to derive relative risks on a continuous scale. If medians were not reported for each category we estimated them using the group mean and standard deviation assuming a normal distribution. Medians on the untransformed CTCS scale were taken assuming that the natural logarithm of the median would approximate the median of the natural logarithm of (CTCS + 1). Two studies [1, 2] reported the HR of $\log_2$(CTCS+1) instead of the natural logarithm, these were converted to the natural logarithm scale using a factor 1.4427.

Imputation of CTCS and cIMT Values

The Rotterdam Study is a population-based cohort study of individuals aged 55 years and older living in Rotterdam, the Netherlands [3]. Demographics, traditional risk factors, CTCS, cIMT, hs-CRP, ABI, and information on cardioprotective drugs were measured during re-examination visits in a subset (N = 1,915) of this cohort (for baseline characteristics see Table 1 in manuscript). Details on how these novel risk markers and the other variables were measured are published elsewhere [4, 5].

First we imputed missing values of the traditional risk factors in the NHANES individuals (N = 16,602), taking into account the according sample weights published by NHANES. Then we merged the imputed NHANES set with 1,915 individuals of the Rotterdam Study, including the novel risk markers. This extended set was bootstrapped with covariates age, sex, traditional risk factors, CVD history, cardioprotective drug information, and novel risk markers as input for the imputation algorithm. For imputation we have used the R 'aregImpute' function from the 'Hmisc' package. After the imputation procedure, we excluded NHANES subjects with prior CVD, NHANES subjects younger than 40 years of age and the Rotterdam study participants, leaving a study population of 3,736.

Recalibration of Updated Framingham Risk Scores (FRS)

We developed a state-transition model with three health states: Alive and CVD-free (Well), Post-CVD, and Dead (see Figure S5). One-year transition probabilities of Well → CVD and Well → Dead were based on the 30-year FRS, which calculates the cumulative incidence of CVD and competing non-CVD death. 30-year cumulative CVD incidence I_{CVD} is calculated by summing the product of CVD hazard h_{CVD} at failure time t_i and the survival of competing events $S(t_i\text{-}1)$ for all failure times up to 30 year follow-up:

$$I_{CVD}(30) = \sum_{t_i<30} h_{CVD}(t_i)S(t_{i-1})$$

We divided the baseline CVD-survival function into 2 survival functions: 1) coronary heart disease (CHD) and 2) stroke using the reported number of coronary heart disease and stroke events for men and women. The linear predictor of the 30-year FRS was extended with adjusted HRs of 4 novel risk markers based on systematic reviews of literature. Individual risk profiles including data on traditional and 4 novel risk factors were taken from 3,736 asymptomatic subjects of the National Health and Nutrition Examination Survey (NHANES) 2003 – 2004 examination round. To mimic survival selection of NHANES subjects at each time interval, we simulated cloned copies of NHANES subjects using Monte Carlo microsimulation within the state-transition model.

We followed a 4-step iterative calibration process:

(1) The microsimulation model was run for cycle t, starting at the first year t = 1, using the extended linear predictor values of NHANES subjects (uncalibrated simulated outcomes for cycle t)
(2) The baseline CVD survival function was then recalibrated by a fixed term assuming that the average of the simulated outcomes during cycle t would equal the average calculated cumulative incidence based on the original FRS prediction (without the novel risk factors included) for cycle t.
(3) The microsimulation model was then updated using the recalibrated CVD function for the next cycle t +1.
(4) NHANES individuals who remained alive and CVD-free after the cycle t were selected for the recalibration step for the next period (transition from t = t to t = t+1).

For validation, we compared the cumulative CVD incidences of the microsimulation state-transition model at each year t with the cumulative CVD incidence calculated by the original FRS (Figure S6).

Systematic Review Search Strategy

Inclusion criteria:

Population:	General (non-hospital) adult population free of hard coronary heart disease/ cardiovascular disease at baseline, not selected based by cardiovascular risk factors (e.g. renal disease, diabetes mellitus)
Intervention:	Novel risk factor/biomarker + traditional "Framingham" risk factors: age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, smoking status, and diabetes mellitus
Comparison:	Odds/risk/rate/hazard with and without biomarker adjusted for traditional "Framingham" risk factors
Outcomes:	1) Hard coronary heart disease events: non-fatal myocardial infarction and fatal coronary heart disease
2) Non-fatal/fatal stroke	
Published:	1 September 2008 (ABI) / 1 July 2008 (CAC) – 19 April 2013
Study type:	Cohort study or nested case-control study or case-cohort study or systematic review or meta-analysis of these study types
Language:	English

Pubmed Search Syntaxes

Coronary Artery Calcium

(1) cohort studies [MeSH Terms] OR cohort*[Text Word] OR controlled clinical trial [Publication Type]
(2) case-control studies [MeSH Terms] OR (case*[Text Word]) AND control*[Text Word])
(3) systematic [sb]
(4) #1 OR #2 OR # 3
(5) cardiovascular diseases [MeSH Terms]
(6) coronary disease [MeSH Terms]
(7) cardiovascular disease* [Title/Abstract]
(8) coronary artery disease* [Title/Abstract]
(9) coronary heart disease*[Title/Abstract]
(10) #5 OR #6 OR #7 OR #8 OR #9
(11) risk assessment [MeSH Terms]
(12) risk factors [MeSH Terms]

(13) prognosis [MeSH Terms]
(14) risk factor* [Title/Abstract]
(15) predict* [Title/Abstract]
(16) Framingham [Title/Abstract] OR traditional [Title/Abstract] OR established [Title/Abstract] OR independent [Title/Abstract] OR conventional [Title/Abstract]
(17) (#11 OR #12 OR #13 OR # 14 OR #15) AND #16
(18) tomography, X-ray computed [MeSH Terms]
(19) electron beam computed tomograph* [Text Word]
(20) electron beam* [Text Word]
(21) ebct [Text Word]
(22) calcium scor* [Text Word]
(23) coronary calcium [Text Word]
(24) coronary artery calcium [Text Word]
(25) cacs [Text Word]
(26) #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
(27) #4 AND #10 AND #17 AND #26
(28) #27 AND English[lang] AND ("2008/07/01"[PDAT] : "2015/01/01"[PDAT])

Ankle Brachial Index

(1) cohort studies [MeSH Terms] OR cohort*[Text Word] OR controlled clinical trial [Publication Type]
(2) case-control studies [MeSH Terms] OR (case*[Text Word]) AND control*[Text Word])
(3) systematic [sb]
(4) #1 OR #2 OR # 3
(5) cardiovascular diseases [MeSH Terms]
(6) coronary disease [MeSH Terms]
(7) cardiovascular disease* [Title/Abstract]
(8) coronary artery disease* [Title/Abstract]
(9) coronary heart disease*[Title/Abstract]
(10) #5 OR #6 OR #7 OR #8 OR #9
(11) risk assessment [MeSH Terms]
(12) risk factors [MeSH Terms]
(13) prognosis [MeSH Terms]
(14) risk factor* [Title/Abstract]
(15) predict* [Title/Abstract]
(16) Framingham [Title/Abstract] OR traditional [Title/Abstract] OR established [Title/Abstract] OR independent [Title/Abstract] OR conventional [Title/Abstract]
(17) (#11 OR #12 OR #13 OR # 14 OR #15) AND #16
(18) blood pressure [MeSH Terms] AND (ankle [Text Word] OR ankle [MeSH Terms])
(19) ankle brachial blood pressure [Text Word]
(20) ankle brachial pressure [Text Word]
(21) ankle brachial index [Text Word]
(22) abi [Text Word]
(23) 23 #18 OR #19 OR #20 OR #21 OR #22
(24) 24 #4 AND #10 AND #17 AND #23
(25) 25 #24 AND English[lang] AND ("2008/09/01"[PDAT] : "2015/01/01"[PDAT])

REFERENCES

1. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, et al. (2008) Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 358: 1336-1345.
2. Mohlenkamp S, Lehmann N, Moebus S, Schmermund A, Dragano N, et al. (2011) Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. J Am Coll Cardiol 57: 1455-1464.
3. Hofman A, van Duijn CM, Franco OH, Ikram MA, Janssen HL, et al. (2011) The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 26: 657-686.
4. Elias-Smale SE, Proenca RV, Koller MT, Kavousi M, van Rooij FJ, et al. (2010) Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J Am Coll Cardiol 56: 1407-1414.
5. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, et al. (2012) Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med 156: 438-444.
6. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS (2009) Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation 119: 3078-3084.
7. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC (2004) Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. Jama 291: 210-215.
8. Kondos GT, Hoff JA, Sevrukov A, Daviglus ML, Garside DB, et al. (2003) Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation 107: 2571-2576.
9. LaMonte MJ, FitzGerald SJ, Church TS, Barlow CE, Radford NB, et al. (2005) Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol 162: 421-429.
10. Wong ND, Gransar H, Shaw L, Polk D, Moon JH, et al. (2009) Thoracic aortic calcium versus coronary artery calcium for the prediction of coronary heart disease and cardiovascular disease events. JACC Cardiovasc Imaging 2: 319-326.
11. Elias-Smale SE, Wieberdink RG, Odink AE, Hofman A, Hunink MG, et al. (2011) Burden of atherosclerosis improves the prediction of coronary heart disease but not cerebrovascular events: the Rotterdam Study. Eur Heart J 32: 2050-2058.
12. Jain A, McClelland RL, Polak JF, Shea S, Burke GL, et al. (2011) Cardiovascular imaging for assessing cardiovascular risk in asymptomatic men versus women: the multi-ethnic study of atherosclerosis (MESA). Circ Cardiovasc Imaging 4: 8-15.
13. Abbott RD, Petrovitch H, Rodriguez BL, Yano K, Schatz IJ, et al. (2000) Ankle/brachial blood pressure in men >70 years of age and the risk of coronary heart disease. Am J Cardiol 86: 280-284.
14. Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, et al. (2010) The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 56: 1506-1512.
15. Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, et al. (2004) Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. Circulation 110: 3075-3080.
16. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, et al. (1999) Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. Arterioscler Thromb Vasc Biol 19: 538-545.
17. Abbott RD, Rodriguez BL, Petrovitch H, Yano K, Schatz IJ, et al. (2001) Ankle-brachial blood pressure in elderly men and the risk of stroke: the Honolulu Heart Program. J Clin Epidemiol 54: 973-978.
18. Hollander M, Hak AE, Koudstaal PJ, Bots ML, Grobbee DE, et al. (2003) Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. Stroke 34: 2367-2372.
19. Tsai AW, Folsom AR, Rosamond WD, Jones DW (2001) Ankle-brachial index and 7-year ischemic stroke incidence: the ARIC study. Stroke 32: 1721-1724.

Table S1. Model Input Parameters

Parameter	Estimate	Source
One-year probability of having a first CHD event	Depending on cumulative CVD hazard function, and updated FRS	Pencina et al [6] Pooled estimates for hazard ratios of the four novel risk markers from the systematic review
One-year probability of having a first stroke event	Depending on cumulative CVD hazard function, CHD: stroke event ratio 104/348 for men and 86/133 for women, and updated FRS	Pencina et al [6] Pooled estimates for hazard ratios of the four novel risk markers from the systematic review
One-year probability of dying from non-cardiovascular mortality	Depending on cumulative hazard function for non-CVD death and original hazard ratios from the Framingham study	Pencina et al [6]

Table S2. General characteristics of included studies

a. CTCS – CHD studies										
First author, year	**Country**	**Study population**	**N subjects**	**Mean age (years)**	**% Men**	**Follow-up duration**	**Predictor definition**	**N traditional risk factors used in multivariable analysis**	**Outcome**	**N events**
Detrano, 2008 [1]	U.S.	MESA cohort	6,722	62.2	47	Median 3.9 years	Log_2(CTCS+1)	8	Non-fatal MI and CHD death	89
Elias-Smale, 2010 [4]	The Netherlands	Rotterdam Study	2,028	69.6	43	Median 9.8 years	Ln(CTCS+1)	8	Non-fatal MI and CHD death	135
Greenland, 2004 [7]	U.S.	South Bay Heart Watch	1,029	65.7	90	Mean 6.3 years	Per 1-SD increase in CTCS (399)	7 (summarized in ATPIII FRS)	Non-fatal MI and CHD death	84
Kondos, 2003 [8]	U.S.	Self-referred	4,151	51	100	Mean 3.1 years	CTCS per quartile	5	Non-fatal MI and CHD death	52
LaMonte, 2005 [9]	U.S.	Preventive health exam and self-referred	10,746 total 6,835 men 3,911 women	53.8 total 53.5 men 54.2 women	64	Mean 3.5 years	no detectable CTCS and sex-specific CTCS thirds	5	Non-fatal MI and CHD death	81 total

a. CTCS – CHD studies *(Continued)*

First author, year	Country	Study population	N subjects	Mean age (years)	% Men	Follow-up duration	Predictor definition	N traditional risk factors used in multivariable analysis	Outcome	N events
Mohlenkamp, 2011 [2]	Germany	Heinz Nixdorf Recall (HNR) study	3,966	59.3	47	Median 5.0 years	Log_2(CTCS+1)	6 (included in FRS)	Non-fatal MI and CHD death	91
Wong, 2009 [10]	U.S.	Self-referred or referred by physician, enrolees of EISNER study	2,303	56	62	Mean 4.4 years	Ln(CTCS+1)	7 (summarized in ATPIII FRS), if diabetic score of 20% or FRS if higher	Non-fatal MI and CHD death	16

b. CTCS – Stroke studies

First author, year	Country	Study population	N subjects	Mean age (years)	% Men	Follow-up duration	Predictor definition	N traditional risk factors used in multivariable analysis	Outcome	N events
Elias-Smale, 2011 [11]	The Netherlands	Rotterdam Study	2,153	69.2	45	Median 3.5 years	CTCS per tertile	8	TIA and fatal or non-fatal ischemic stroke	52
Jain, 2011 [12]	U.S.	MESA	4,965	61.5	48	Median 5.8 years	Per 1-SD increase of Ln(CAC+1)	8	Fatal or non-fatal stroke	65

c. ABI – CHD studies

First author, year	Country	Study population	N subjects	Mean age (years)	% Men	Follow-up duration	Predictor definition	N traditional risk factors used in multivariable analysis	Outcome	N events
Abbott, 2000 [13]	Hawaii	Honolulu Heart Program	2,767	77.8*	100	6 years follow-up	ABI <0.8 and ABI 0.8≤ ABI <1.0 vs ABI ≥1.0	6	Non-fatal MI and CHD death	186
Criqui, 2010 [14]	U.S.	Multi-Ethnic Study of Atherosclerosis	6,647	62.0*	47	Median 4.8 years Mean 5.3 years Max 6.5 years	ABI <1.0 vs 1.0≤ ABI <1.4	8	Non-fatal MI, CHD death, resuscitated cardiac arrest, and angina**	226
Kavousi, 2012 [5]	The Netherlands	Rotterdam Study	5,933	69.1	41	Median 6.8 years	ABI ≤0.9 vs 0.9 < ABI ≤1.4	8	Non-fatal MI and CHD death	347
Lee, 2004 [15]	Scotland	Edinburgh Artery Study	1,507	Not reported (55-74)	Not reported	Not reported (more than 12 years)	ABI ≤0.9 vs 0.9 < ABI ≤1.5	7	Non-fatal and fatal MI	259
Newman, 1999 [16]	U.S.	Cardiovascular Health Study	4,268	Not reported (≥65 years)	Not reported	Mean 5.1 years, 22 months black cohort Max 6 years, 2 years black cohort	ABI <0.9 vs. 0.9 ≤ ABI <1.5	6	Non-fatal and fatal MI	188

d. ABI – Stroke studies

First author, year	Country	Study population	N subjects	Mean age (years)	% Men	Follow-up duration	Predictor definition	N traditional risk factors used in multivariable analysis	Outcome	N events
Abbott, 2001 [17]	Hawaii	Honolulu Heart Program	2,767	77.8*	100	6 years follow-up	ABI <0.9 vs 0.9 ≤ ABI ≤1.5	6	Fatal or non-fatal stroke	91
Criqui, 2010 [14]	U.S.	Multi-Ethnic Study of Atherosclerosis	6,647	62.0*	47	Median 4.8 years Mean 5.3 years Max 6.5 years	ABI <1.0 vs 1.0 ≤ ABI <1.4	8	Fatal or non-fatal stroke	89
Hollander, 2003 [18]	The Netherlands	Rotterdam Study	6,913	69.5	39.7	Mean 6.1 years	ABI ≤1.5 per tertile	7	Fatal or non-fatal stroke	378
Lee, 2004 [15]	Scotland	Edinburgh Artery Study	1,507	Not reported (55-74)	Not reported	Not reported (more than 12 years)	ABI ≤0.9 vs 0.9 < ABI ≤1.5	7	Fatal or non-fatal stroke	143
Newman, 1999 [16]	U.S.	Cardiovascular Health Study	4,268	Not reported (≥65 years)	Not reported	Mean 5.1 years, 22 months black cohort Max 6 years, 2 years black cohort	ABI <0.9 vs 0.9 ≤ ABI <1.5	6	Fatal or non-fatal stroke	110
Tsai, 2001 [19]	U.S.	Atherosclerosis Risk In Communities Study	14,839	Not reported (≥45 years)	45	Median 7.2 years	ABI <0.9 vs ABI ≥0.9	7	Fatal or non-fatal ischemic stroke	206

Table S3. Ten-year cardiovascular disease (CVD) risk reclassification by cIMT, CRP, and ABI

a. cIMT				
	FRS + cIMT			**Overall**
FRS	**<10%**	**≥10-<20%**	**≥20%**	
<10%				
N	2604.21	36.79	0	2641
% Events [95%CI]				
10 yr CVD	2.8 [2.2 – 3.4]	11.5 [2.4 – 21.4]	NA	2.9 [2.3 – 3.5]
30 yr CVD	16 [14.5 – 17.6]	46.4 [30.1 – 59.5]	NA	16.4 [15.0 – 18.0]
≥10-<20%				
N	65.09	599.27	32.64	697
% Events [95%CI]				
10 yr CVD	7.5 [1.7 – 12.9]	13.5 [11.1 – 16.2]	21.9 [10.3 – 37.7]	13.3 [10.8 – 16]
30 yr CVD	37.3 [28.2 – 50.1]	48.8 [44.0 – 53.8]	61.1 [44.6 – 77.2]	48.3 [43.6 – 51.9]
≥20%				
N	0	30.77	367.23	398
% Events [95%CI]				
10 yr CVD	NA	17 [4.8 – 31.1]	35.9 [30 – 42.6]	34.4 [28.8 – 40.6]
30 yr CVD	NA	53.3 [38.1 – 69.0]	69.5 [64.2 – 73.4]	68.2 [63.2 – 72]
Overall				
N	2669.3	666.83	399.87	3736
% Events [95%CI]				
10 yr CVD	2.9 [2.4 – 3.5]	13.5 [11.2 – 16.4]	34.8 [29.1 – 41.4]	8.2 [7.3 – 41.4]
30 yr CVD	16.5 [15.0 – 18.1]	48.8 [44.5 – 52.9]	68.8 [63.7 – 73.0]	27.9 [26.3 – 73.0]

b. CRP

	FRS + CRP			Overall
FRS	**<10%**	**≥10-<20%**	**≥20%**	
<10%				
N	2556.88	84.12	0	2641
% Events [95%CI]				
10 yr CVD	2.7 [2.0 – 3.3]	9.6 [4.5 – 14.9]	NaN [NA – NA]	2.9 [2.3 – 3.5]
30 yr CVD	15.5 [14.0 – 17.1]	42.9 [33.0 – 51.6]	NaN [NA – NA]	16.4 [15.0 – 18.0]
≥10-<20%				
N	101.76	546.83	48.41	697
% Events [95%CI]				
10 yr CVD	8.2 [3.3 – 13.1]	13.4 [10.6 – 16.4]	23.6 [10.9 – 34.6]	13.3 [10.8 – 16.0]
30 yr CVD	36.7 [27.9 – 44.3]	48.7 [44.4 – 52.8]	68.6 [56.7 – 80.3]	48.3 [43.6 – 51.9]
≥20%				
N	0	44.6	353.4	398
% Events [95%CI]				
10 yr CVD	NaN [NA – NA]	18.8 [8.9 – 33.0]	36.4 [30.7 – 42.2]	34.4 [28.8 – 40.6]
30 yr CVD	NaN [NA – NA]	53.8 [43.2 – 65.2]	70 [64.6 – 73.9]	68.2 [63.2 – 72.0]
Overall				
N	2658.64	675.55	401.81	3736
% Events [95%CI]				
10 yr CVD	2.9 [2.3 – 3.4]	13.2 [10.7 – 16.0]	34.9 [29.1 – 40.6]	8.2 [7.3 – 40.6]
30 yr CVD	16.3 [14.7 – 17.9]	48.3 [43.8 – 52.1]	69.8 [64.5 – 74.0]	27.9 [26.3 – 74.0]

c. ABI

	FRS + ABI			Overall
FRS	**<10%**	**≥10-<20%**	**≥20%**	
<10%				
N	2616.7	24.3	0	2641
% Events [95%CI]				
10 yr CVD	2.8 [2.2 – 3.4]	10.6 [0 – 23.1]	NA	2.9 [2.3 – 3.5]
30 yr CVD	16.1 [14.7 – 17.7]	47.6 [28.7 – 68.0]	NA	16.4 [15.0 – 18.0]
≥10-<20%				
N	42.46	638.3	16.24	697
% Events [95%CI]				
10 yr CVD	8.8 [1.1 – 16.5]	13.3 [10.6 – 16.2]	23 [0 – 46.6]	13.3 [10.8 – 16.0]
30 yr CVD	39.5 [25.3 – 53.5]	48.4 [43.6 – 52.2]	63.9 [41.4 – 85.7]	48.3 [43.6 – 51.9]
≥20%				
N	0	30.44	367.56	398
% Events [95%CI]				
10 yr CVD	NA	20.3 [6.6 – 33.9]	35.6 [29.8 – 41.7]	34.4 [28.8 – 40.6]
30 yr CVD	NA	57.1 [42.6 – 73.0]	69.1 [64.3 – 72.9]	68.2 [63.2 – 72.0]
Overall				
N	2659.16	693.04	383.8	3736
% Events [95%CI]				
10 yr CVD	2.9 [2.4 – 3.5]	13.6 [11.2 – 16.9]	35.1 [29.3 – 41.4]	8.2 [7.3 – 41.4]
30 yr CVD	16.5 [15.0 – 18.1]	48.8 [44.2 – 52.8]	68.9 [64.0 – 73.2]	27.9 [26.3 – 73.2]

Classification on the basis of 10 yr CVD risk - i.e. combined endpoint of CHD and Stroke – assessment using <10%, ≥10-<20%, and ≥20% as risk thresholds

Abbreviations: ABI = ankle-brachial index, cIMT = carotid intima-media thickness, CRP = high-sensitivity C-reactive protein, CVD = cardiovascular disease, FRS = Framingham risk score.

Table S4. Ten-year coronary heart disease (CHD) risk reclassification tables

a. CTCS

	FRS + CTCS			Overall
FRS	**<10%**	**≥10-<20%**	**≥20%**	
<10%				
N	2828	158	13	2999
% Events [95%CI]				
10 yr CHD	2 [1.4 – 2.3]	12.8 [7.6 – 18.2]	28.1 [0 – 58.7]	2.6 [2.1 – 3.3]
30 yr CHD	11.5 [10.5 – 12.4]	47.7 [38.8 – 55.6]	70.2 [33.3 – 100]	13.7 [12.3 – 15.0]
≥10-<20%				
N	191	180	154	525
% Events [95%CI]				
10 yr CHD	5.6 [2.4 – 8.9]	13.8 [8.8 – 19.3]	27.7 [21 – 36.1]	15.0 [11.5 – 19.1]
30 yr CHD	24.2 [18.8 – 29.8]	47.1 [40.6 – 53.6]	64.5 [55.4 – 70.8]	43.9 [39.7 – 47.8]
≥20%				
N	16	37	159	212
% Events [95%CI]				
10 yr CHD	7.7 [0 – 23.7]	12.4 [2.6 – 24.0]	42.4 [34.4 – 50.9]	34.5 [27.4 – 41.3]
30 yr CHD	25.2 [6.2 – 50.0]	36.9 [23.2 – 52.6]	66.3 [56.9 – 74.2]	58 [51.9 – 64.2]
Overall				
N	3035	376	325	3736
% Events [95%CI]				
10 yr CHD	2.2 [1.6 – 2.7]	13.2 [9.4 – 16.7]	34.9 [29.0 – 40.7]	6.2 [5.2 – 40.7]
30 yr CHD	12.4 [11.3 – 13.3]	46.4 [41.1 – 50.8]	65.5 [58.4 – 71.4]	20.4 [19.1 – 71.4]

b. cIMT

	FRS + cIMT			Overall
FRS	**<10%**	**≥10-<20%**	**≥20%**	
<10%				
N	2968	30	0	2999
% Events [95%CI]				
10 yr CHD	2.5 [2.0 – 3.2]	13.8 [4.9 – 24.1]	NA	2.6 [2.1 – 3.3]
30 yr CHD	13.4 [12 – 14.7]	38.8 [22.8 – 52.3]	NA	13.7 [12.3 – 15]
≥10-<20%				
N	55	444	25	525
% Events [95%CI]				
10 yr CHD	9.3 [3.6 – 15.2]	14.9 [11.5 – 19.4]	28.1 [13.9 – 48.3]	15.0 [11.5 – 19.1]
30 yr CHD	33.7 [20.9 – 44.7]	44.4 [40.1 – 48.5]	56.9 [39.3 – 72.6]	43.9 [39.7 – 47.8]
≥20%				
N	0	11	201	212
% Events [95%CI]				
10 yr CHD	NA	19.4 [0 – 45.5]	35.3 [28.1 – 42.9]	34.5 [27.4 – 41.3]
30 yr CHD	NA	51.7 [27.3 – 81.8]	58.4 [52.2 – 64.5]	58 [51.9 – 64.2]
Overall				
N	3024	485	227	3736
% Events [95%CI]				
10 yr CHD	2.7 [2.1 – 3.3]	14.9 [11.5 – 19.4]	34.5 [27.2 – 41.3]	6.2 [5.2 – 41.3]
30 yr CHD	13.8 [12.4 – 15.1]	44.2 [40.0 – 48.4]	58.2 [51.8 – 64.3]	20.4 [19.1 – 64.3]

c. CRP

	FRS + CRP			Overall
FRS	**<10%**	**≥10-<20%**	**≥20%**	
<10%				
N	2938	61	0	2999
% Events [95%CI]				
10 yr CHD	2.5 [2.0 – 3.1]	11.8 [4.5 – 19.3]	NA	2.6 [2.1 – 3.3]
30 yr CHD	13.1 [11.8 – 14.5]	39.5 [30.4 – 50.4]	NA	13.7 [12.3 – 15.0]
≥10-<20%				
N	77	428	20	525
% Events [95%CI]				
10 yr CHD	8.4 [2.6 – 15.6]	15.2 [11.1 – 19.2]	36.1 [16.2 – 57.3]	15.0 [11.5 – 19.1]
30 yr CHD	31.6 [23.1 – 40.9]	45.1 [40.5 – 49.3]	64.6 [44.3 – 81.2]	43.9 [39.7 – 47.8]
≥20%				
N	0	25	187	212
% Events [95%CI]				
10 yr CHD	NA	23.4 [8.0 – 42.9]	36.0 [27.9 – 42.5]	34.5 [27.4 – 41.3]
30 yr CHD	NA	53.9 [36.0 – 70.1]	58.6 [52 – 65.1]	58.0 [51.9 – 64.2]
Overall				
N	3015	514	207	3736
% Events [95%CI]				
10 yr CHD	2.6 [2.0 – 3.3]	15.2 [11.3 – 18.9]	35.9 [28.5 – 42.0]	6.2 [5.2 – 42.0]
30 yr CHD	13.6 [12.3 –15.0]	44.9 [40.8 – 49.0]	59.2 [52.5 – 65.6]	20.4 [19.1 – 65.6]

d. ABI

	FRS + ABI			Overall
FRS	**<10%**	**≥10-<20%**	**≥20%**	
<10%				
N	2984	15	0	2999
% Events [95%CI]				
10 yr CHD	2.6 [2.0 – 3.2]	14.4 [0 – 37.2]	NA	2.6 [2.1 – 3.3]
30 yr CHD	13.5 [12.3 – 14.9]	43.1 [18.1 – 68.6]	NA	13.7 [12.3 – 15.0]
≥10-<20%				
N	46	452	27	525
% Events [95%CI]				
10 yr CHD	8.4 [2.0 – 16.7]	14.7 [11.4 – 18.7]	29.7 [10.0 – 48.3]	15.0 [11.5 – 19.1]
30 yr CHD	31.5 [18.4 – 45.2]	44.3 [39.7 – 48.6]	56.4 [37.9 – 70.8]	43.9 [39.7 – 47.8]
≥20%				
N	0	17	195	212
% Events [95%CI]				
10 yr CHD	NA	19.8 [5.4 – 38.2]	35.8 [28.7 – 42.8]	34.5 [27.4 – 41.3]
30 yr CHD	NA	55.7 [33.3 – 77.8]	58.3 [52.3 – 64.2]	58.0 [51.9 – 64.2]
Overall				
N	3030	484	222	3736
% Events [95%CI]				
10 yr CHD	2.7 [2.1 – 3.4]	14.9 [11.5 – 18.7]	35.1 [28.1 – 41.9]	6.2 [5.2 – 41.9]
30 yr CHD	13.8 [12.5 – 15.2]	44.7 [39.9 – 49.0]	58.1 [51.6 – 63.7]	20.4 [19.1 – 63.7]

Classification on the basis of risk assessment using <10%, ≥10-<20%, and ≥20% as risk thresholds
Abbreviations: ABI = ankle-brachial index, cIMT = carotid intima-media thickness, CRP = high-sensitivity C-reactive protein, CTCS = CT coronary artery calcium score, CHD = coronary heart disease, FRS = Framingham risk score.

Table S5. Predictive value of novel risk markers for 10 yr coronary heart disease

	FRS + CTCS	FRS + cIMT	FRS + CRP	FRS + ABI
Δ C-statistic vs. FRS [95%CI]	0.03 [0.02 – 0.04]	0.00 [0.00 – 0.01]	0.00 [0.00 – 0.01]	0.00 [0.00 – 0.00]
NRI with <10%, ≥10-<20%, and ≥20%				
NRI | event [95%CI]	0.21 [0.08 – 0.32]	0.02 [–0.01 – 0.05]	0.01 [–0.03 – 0.05]	0.01 [–0.02 – 0.05]
NRI | no event [95%CI]	–0.01 [–0.03 – 0.015]	0.00 [0.00 – 0.01]	0.01 [0.00 – 0.01]	0.01 [0.00 – 0.01]
NRI total [95%CI]	0.21 [0.09 – 0.30]	0.02 [–0.01 – 0.05]	0.02 [–0.02 – 0.06]	0.02 [–0.01 – 0.05]
NRI with <6%, ≥6 -<20%, and ≥20%				
NRI | event [95%CI]	0.16 [0.04 – 0.27]	0.02 [0.01 – 0.05]	0.01 [–0.03 – 0.04]	0.01 [–0.02 – 0.05]
NRI | no event [95%CI]	0.05 [0.02 – 0.07]	0.01 [0.01 – 0.01]	0.01 [0.00 – 0.01]	0.01 [0.01 – 0.01]
NRI total [95%CI]	0.21 [0.11 – 0.30]	0.03 [0.00 – 0.06]	0.01 [–0.02 – 0.05]	0.02 [–0.01 – 0.06]

ABI = ankle-brachial index, cIMT = carotid intima-media thickness, CRP= C-reactive protein, C-statistic = Harrell's concordance index, CTCS = CT coronary artery calcium score, FRS = Framingham risk score, NRI = net reclassification improvement.

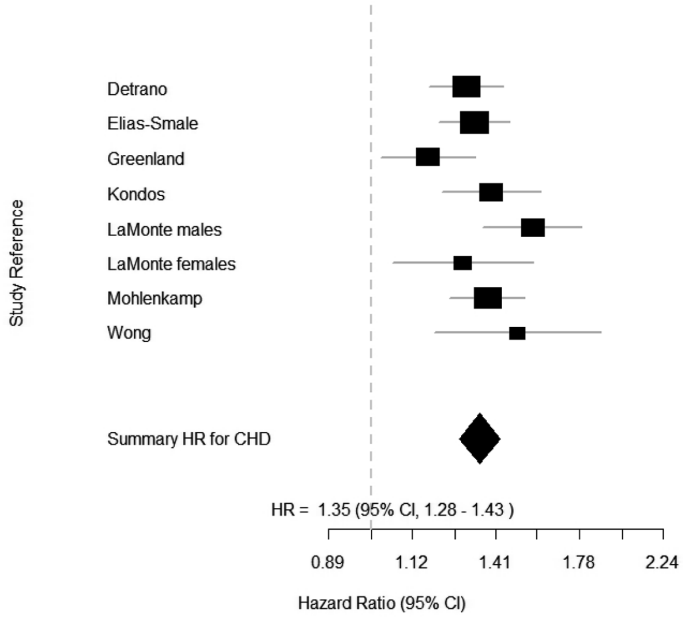


Figure S1. Forrest plot of hazard ratios of one unit increase in the natural logarithm of (CTCS+1) for CHD
Estimated heterogeneity variance: 0.0023 P = 0.146

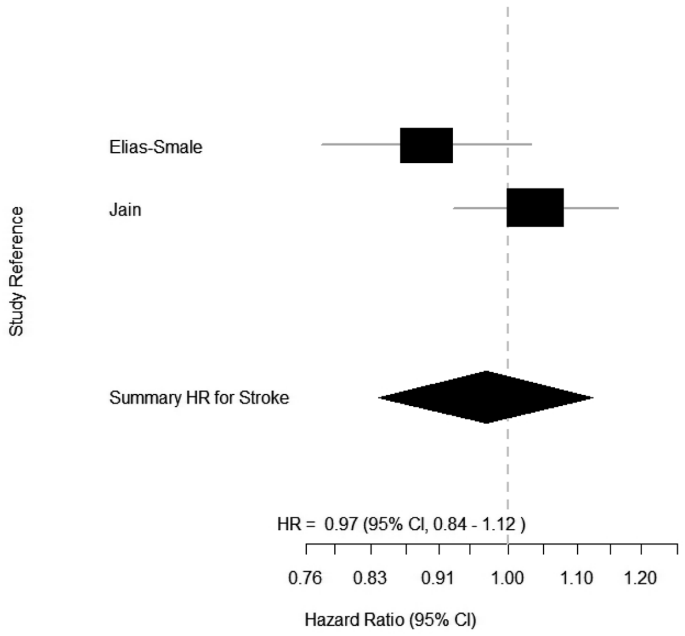


Figure S2. Forrest plot of hazard ratios of one unit increase in the natural logarithm of (CTCS+1) for stroke
Estimated heterogeneity variance: 0.0069 P = 0.107

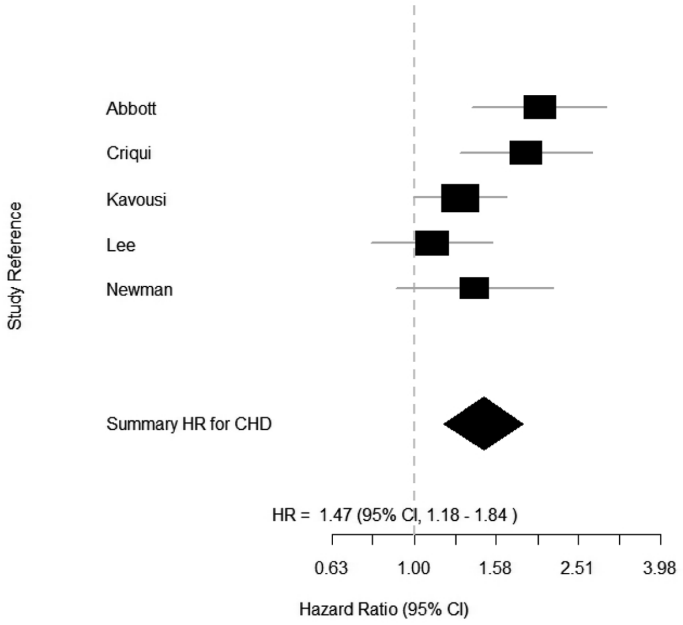


Figure S3. Forrest plot of hazard ratios of an ABI ≤0.9 vs 0.9 for CHD
Estimated heterogeneity variance: 0.032 P = 0.09

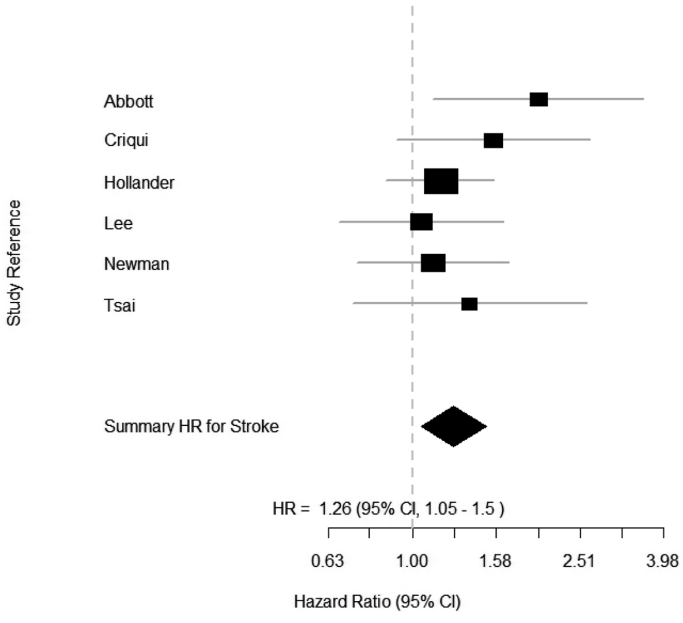


Figure S4. Forrest plot of hazard ratios of an ABI ≤0.9 vs >0.9 for stroke
Estimated heterogeneity variance: 0 P = 0.503

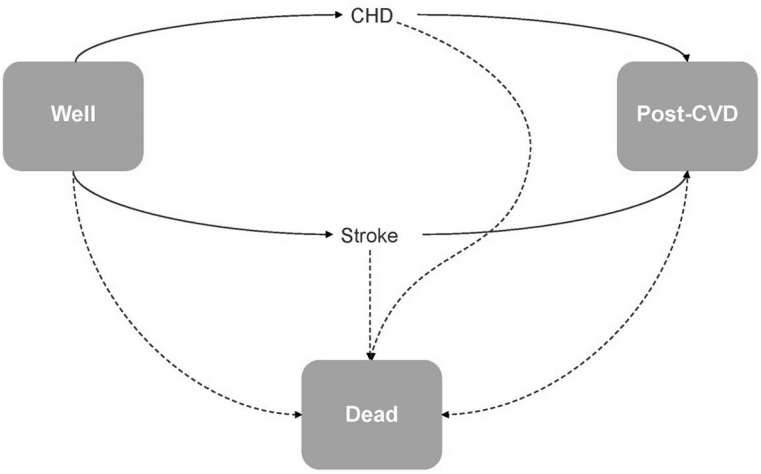


Figure S5. Schematic representation of the microsimulation state-transition model

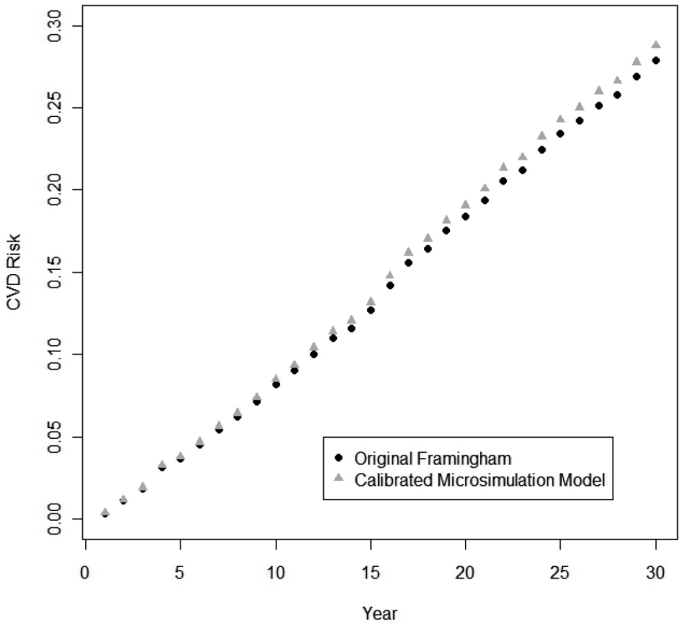


Figure S6. Comparison Original Framingham CVD estimations vs. Model's predictions over a 30-yr time horizon

Chapter 9

Comparing the cost-effectiveness of four novel risk markers for screening asymptomatic individuals to prevent cardiovascular disease (CVD) in the US population

Bob J. H. van Kempen*

Bart S. Ferket*

Ewout W. Steyerberg

Wendy Max

M. G. Myriam Hunink#

Kirsten E. Fleischmann#

* Shared first authors

Shared senior authors

Int J Cardiol. Oct 21 2015;203:422-431

ABSTRACT

Background: High sensitivity CRP (hsCRP), coronary artery calcification on CT (CT calcium), carotid artery intima media thickness on ultrasound (cIMT) and ankle-brachial index (ABI) improve prediction of cardiovascular disease (CVD) risk, but it's unclear what's the benefit of screening with these novel risk markers in the US population.

Methods and Results: A microsimulation model evaluating lifelong cost-effectiveness for individuals aged 40 – 85 at intermediate risk of CVD, using 2003 – 2004 NHANES-III (N = 3,736), Framingham Heart Study, US Vital Statistics, meta-analyses of independent predictive effects of the four novel risk markers and treatment effects was constructed. Using both *an intention-to-treat* (assumes adherence <100% and incorporates disutility from taking daily medications) and an *as-treated* (100% adherence and no disutility) analysis, quality adjusted life years (QALYs), lifetime costs (2014 US $), incremental cost-effectiveness ratio (ICER in $/QALY gained) of screening with hsCRP, CT coronary calcium, cIMT and ABI was established, compared with current practice, full adherence to current guidelines, and ubiquitous statin therapy. In the *intention-to-treat analysis* in men, screening with CT calcium was cost effective ($32,900/QALY) compared with current practice. In women, screening with hsCRP was cost effective ($32,467/QALY). In the *as-treated analysis* for both men and women, statin therapy was both more effective and less costly than all other strategies.

Conclusions: When a substantial disutility from taking daily medication is assumed, screening men with CT coronary calcium is likely to be cost-effective whereas screening with hsCRP has value in women. The individual perceived disutility for taking daily medication should play a key role in the decision.

INTRODUCTION

Cardiovascular disease (CVD) remains one of the main causes of death in Western societies -including the United States [1]. Guidelines on CVD prevention recommend lifestyle changes in low risk individuals (<7.5% 10-year risk of CVD including nonfatal MI, stroke or cardiac death) but advise supplemental drug therapy with statins for individuals at higher CVD risk (>7.5%) as well as anti-hypertensives as needed and sometimes aspirin [2-6]. Risk stratification in current guidelines is largely based on traditional Framingham risk factors [7-9]. These risk predictions can be improved by using novel risk markers such as coronary artery calcification on CT (CT calcium), high sensitivity CRP (hsCRP), carotid artery intima media thickness on ultrasound (cIMT) and the ankle-brachial index (ABI). All four markers have been identified by the U.S. Preventive Services Task Force and the American College of Cardiology Foundation/American Heart Association as potentially valuable for screening individuals for CVD [10, 6]. A recent meta-analysis has demonstrated that all four markers are independent predictors of CVD risk, and improve prediction beyond traditional Framingham risk factors [11].

A substantial proportion of individuals from the U.S. population, classified as intermediate risk based on the Framingham risk factors -traditionally defined as a 10-year risk of coronary heart disease (CHD) of between 5 – 20% [12], are reclassified to the high risk category when the novel risk markers are taken into account [13] and may benefit from more aggressive treatment based on their reclassified risk. Reclassification to other risk categories suggests that the novel risk markers may be beneficial but reclassification by itself is insufficient evidence to justify implementation [14, 15]. Studies, ideally clinical trials, demonstrating comparative effectiveness and cost-effectiveness are necessary. However, trial-based studies of (cost-) effectiveness often evaluate a limited number of strategies, typically cover a relatively short period of follow-up, and require large sample sizes. Decision modeling can overcome these limitations by synthesizing the best-available evidence and extrapolating short-term study results, providing clinicians and policy-makers with information on expected long-term outcomes and accompanying uncertainties [16]. Cost-effectiveness studies have been performed for a number of novel risk markers individually [17-19], but none have evaluated these markers in a comparative analysis.

In the absence of clinical trials assessing the benefit of screening individuals with novel risk markers, an evaluation using observational data is warranted [20]. The objective of this study was to assess the comparative effectiveness and cost-effectiveness of screening asymptomatic individuals aged 40 and over from the U.S. population at intermediate risk of CVD, with either CT coronary calcium, hsCRP, ABI and cIMT.

METHODS

We developed a state-transition model using TreeAge for Health Care (TreeAge Pro 2009 – TreeAge Software Williamstown MA) to analyze 7 strategies for an asymptomatic U.S. individual at intermediate risk for CVD. We considered an individual with a 10-year risk of CVD (combined endpoint of non-fatal MI, stroke and cardiac death) of 5% – 7.5% to be at intermediate risk for our base case analysis, and used both a risk of 2.5% – 7.5%, and a risk of 5% – 10% in sensitivity analyses. The model structure, model parameters, and data sources are briefly described here. Details of the modeling assumptions and parameter estimation are given in a supplementary online file.

Model structure

The following strategies were considered (Figure 1):

(1) 'Current practice' (reference strategy) reflects no additional interventions and accounts for the proportion of individuals treated at baseline with statins, anti-hypertensive medication or aspirin by their general practitioners, which is reflected in the incidence rates of CVD as modeled in this strategy

(2) 'Current guidelines' reflects full implementation of the 2013 ACC/AHA guidelines on the treatment of blood cholesterol and JNC-8 guidelines on high blood pressure [21] for primary prevention of CVD. This implies giving lifestyle advice to all, statin therapy when baseline low density lipoprotein (LDL) cholesterol exceeds 190 mg/dL (4.91 mmol/l) or an individual aged 40 to 75 is diagnosed with diabetes [5, 6], and anti-hypertensive medication when baseline systolic blood pressure exceeds 140 mmHg in an individual aged 40 – 60, and 150 mm Hg in an individual aged >60 years [21]. In a sensitivity analysis we used 140 mmHg as threshold for individuals aged 60 years or over –in concordance with the JNC-7 guidelines [22].

(3-6) 'Screening' with each of the four novel risk markers respectively. In these four strategies, either a CT scan was performed to determine the coronary artery calcium score [**3**], a serum hsCRP level was measured [**4**], the intima-media thickness was established by ultrasound (cIMT), [**5**] or the ankle-brachial index (ABI) was determined [**6**]. The 10-year CVD risk was recalculated on the basis of the Framingham risk factors, combined with each of the risk markers separately. In each of the screening strategies, a number of individuals were reclassified to a 10-yr CVD risk of 7.5% or higher (or 10% or higher in the sensitivity analysis). These individuals received therapeutic lifestyle advice, statin therapy -irrespective of their baseline cholesterol levels, and anti-hypertensive medication if systolic blood pressure was over 130 mmHg. In addition, men received low dose aspirin (80 – 100 mg daily) in accordance with the USPTSF guideline (2). Currently, aspirin is not recommended in women. Individuals who remained at a risk of 7.5% or lower (10% or lower in the sensitivity analysis) were treated as in strategy 2. For the 'current guidelines' and 'screening' strategies, we assumed that individuals who used any of the three drugs at baseline, would continue to use them.

(7) 'Statin therapy': Everyone not currently on statin therapy would receive a moderate dose statin and would be otherwise treated as individuals in strategy 2. This strategy puts the four 'screening' strategies into a broader perspective, between the least aggressive strategy ('current practice') and a fairly aggressive strategy ('statin therapy'), providing a range of possibilities for an individual at intermediate risk of CVD [20].

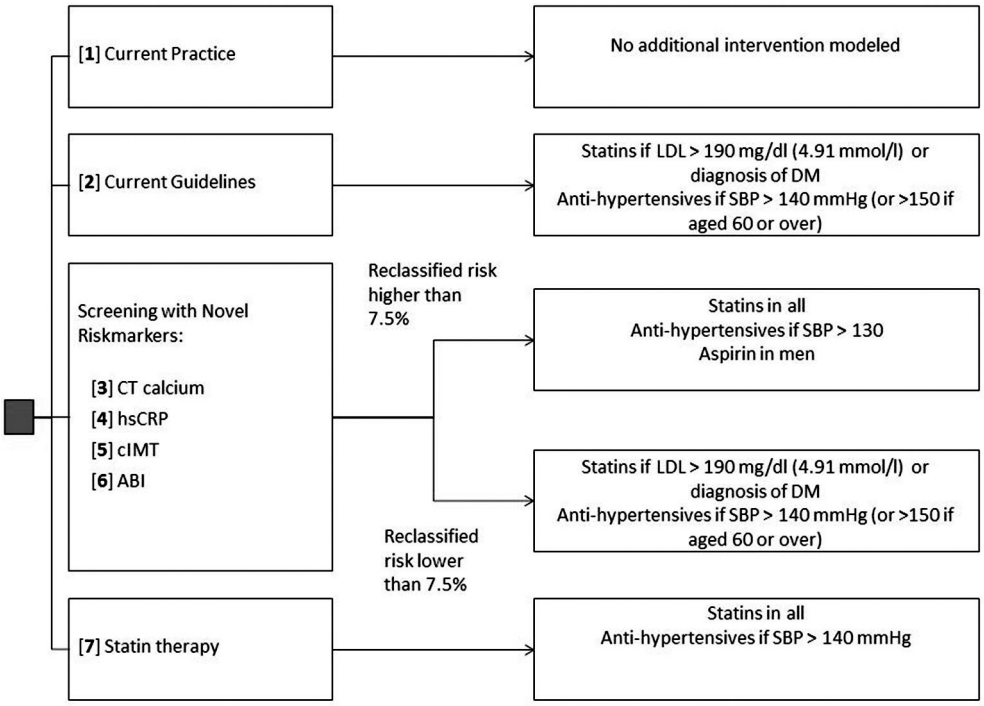


Figure 1. Schematic representation of the 7 strategies modeled for individuals at intermediate risk for CVD: Current practice, Current Guidelines, Screening with CT calcium, hsCRP, cIMT and ABI, and Statin Therapy.
LDL = low-density lipoprotein; SBP = systolic blood pressure.

Study Population and risk stratification

We analyzed 3,736 individuals aged 40 to 85 without a history of CHD or stroke at baseline from the 2003 – 2004 NHANES exam, taking into account the sampling weights for the U.S. population. The NHANES dataset was merged with a subset of the Rotterdam Study cohort (N =1,915) [23] in which all novel markers were measured to allow for estimation of CT coronary calcium and cIMT values as previously described [13]. Only NHANES individuals were used for subsequent analyses.

The Framingham CVD model was used to model 30-year cumulative incidence of CVD (myocardial infarction, coronary death and stroke), while taking into account the competing risk of non-CVD death [8]. To resemble currently recommended risk assessment, we also calculated 10-year CVD risks without adjustment for the competing risk of non-CVD death. Of the 3,736 NHANES individuals aged 40 – 85, we selected a total of 618 individuals who had a calculated 10-year risk of CVD of 5% – 7.5% for the base case analysis.

Risk reclassification and treatment initiation for screening with each of the 4 novel risk markers.

We updated the Framingham based 10-year CVD risk score with each of the four risk markers [11] to yield 4 new risk stratification scores. For these updated scores, we recalibrated the baseline survival probability by assuming no change in the average survival probability compared to the old score. For each individual, we calculated updated 10-year CVD risks; one for each novel risk marker. In a number of cases, this new recalculated risk would surpass the 7.5% risk threshold (10% in sensitivity analysis), leading to medical therapy.

Simulation model

For each of the 7 strategies, the simulation model tracked quality of life, costs, and time spent in one of the following three health states: 1) well; 2) post CVD event; 3) death (Figure 2). Each simulated individual started out in the "well" state. Individualized probabilities of a CHD event, stroke event, non-CVD death, case fatality rates of CHD and stroke events, extracranial major bleeding due to aspirin use, and lethal cancer due to radiation determined the transition to the other states during each annual cycle. The time horizon was the remaining lifetime of the simulated individuals. After a CVD event, individuals moved to the post-CVD-event state. After an extracranial major bleeding episode, we assumed that aspirin therapy would be discontinued. In the case of a nonfatal CVD event, individuals would be allocated medical treatment for secondary CVD prevention.

Event rates

A one-year cycle length was used. One-year transition-probabilities of CVD events and the probabilities for non-CVD events were both based on the 30-year Framingham CVD model (which adjusts for competing risk) updated and recalibrated with all four novel risk markers together, assuming independence of predictive effects of each individual novel risk marker. In order to calculate the incidences of CHD and stroke separately, we applied a sex-specific ratio for CHD to stroke events to the baseline CVD incidence function. Case-fatality rates of CHD and stroke events were based on one-year mortality rates of myocardial infarction and stroke events as observed in cohort studies [24]. A hazard ratio of prior CVD for all-cause mortality was derived from the literature and used to adjust the post-CVD all-cause mortality [25]. Extracranial bleeding rates and corresponding hazard rate ratios for aspirin use were taken from a recent meta-analysis on aspirin in the primary prevention of CVD [26]. The additional risk of radiation induced fatal cancer due to CT scanning was added to the non-CVD event probability [27, 28].

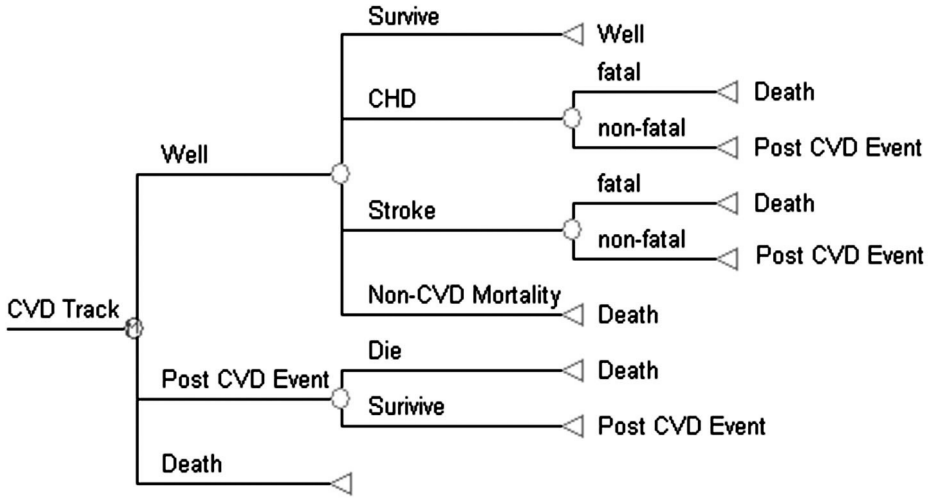


Figure 2: Markov model, with the 'Well', 'Post CVD event' and 'Death' state, and possible transitions between them.

Statin TherapyABIcIMThsCRPCT CalciumCurrent GuidelinesCurrent Practice$18.0K$18.2K$18.4K$18.6K$18.8K$19.0K$19.2K$19.4K 16.19016.13016.07016.010CostEffectivenessMen - 5%-7.5% - As-treated

Model Calibration

The model was calibrated on mortality data from the US National Vital Statistics, such that the annual simulated total mortality for the 3,736 NHANES individuals would match the age and sex adjusted observed mortality for year 1 to 30 (eFigure 2).

Effectiveness of treatment

The benefits of statin and antihypertensive treatment on CHD and stroke incidence were obtained from meta-analyses and considered equal for men and women [29-31]. The relative risks for CHD and stroke were obtained from a meta-analysis of aspirin in primary prevention [26]. Treatment adherence is an important determinant of treatment benefit [32]. Although we used intention-to-treat-based relative risk reductions from clinical trials which take into account adherence, we assumed adherence in a population-based setting to be 70% of that in the original trials [33].

Costs

Costs incorporated in the model included health-care costs and non-health-care costs and were assessed from the societal perspective for the U.S. (Table 2) adjusted to the year 2014 using consumer price indices. Health-care costs included costs of diagnostic procedures, personnel, materials, equipment, medications, costs for health care resource use in subsequent years after an event, and overhead. Costs for a non-

contrast cardiac CT were based on healthcare reimbursement rates in 2014. Medication costs were based on 2014 retail prices from online pharmacy price lists across the US, assuming moderately potent generic statin use in individuals reclassified to >7.5% without diabetes, and potent statin use in diabetics [5], (rosuvastatin in the base case and atorvastatin (40 – 80mg) in a sensitivity analysis). Antihypertensive medication was a diuretic, combined with either an angiotensin II receptor blocker, ACE inhibitor or calcium channel blocker in 60% of individuals [21, 34]. Medication costs were only accounted for in adherent individuals. For all strategies except 'Current practice', we included the costs of obtaining risk markers. Event-related costs included the costs of hospitalization, diagnostic workup, interventions, and rehabilitation during the first year after an event [35-41].

Analysis

Important baseline characteristics, such as lipid levels, blood pressure, and statin, aspirin, or antihypertensive medication use, were determined for the U.S. individuals at an initial risk of 5 – 7.5% (N = 618), 5 – 10% (N = 980) and 2.5 – 7.5% (N = 1,502) and accounted for in the simulation model. For each of these three groups, the number of individuals who initiated statins, anti-hypertensives and aspirin in each strategy were determined. Quality-adjusted life years (QALYs), lifetime costs, incremental cost-effectiveness ratios (ICER) (i.e., additional costs divided by QALYs gained), were calculated. Future costs and effectiveness were discounted to take into account time preference, at the currently recommended U.S. discount rate of 3% for both costs and effectiveness [42]. We considered $50,000/QALY gained as a commonly accepted threshold for the societal willingness-to-pay threshold for primary prevention [43, 44]. We analyzed the results in two distinct ways. First, as an *intention-to-treat* analysis, in which we assumed the base case treatment adherence of 70% and a disutility of 6 months for taking daily medication for the remainder of an individual's lifetime [45, 46]. Second, we analyzed the results assuming each individual would actually take the medication, without incorporating a disutility for taking daily medication, similar to the *as-treated* analysis of an RCT and assuming that substantial disutility would lead to non-adherence.

To model second-order parameter uncertainty, 1,000 independent samples were drawn from each of the input parameter distributions, generating outcome distributions for QALYs and costs for each strategy (outer loop simulation). In addition, 10,000 individuals were randomly drawn with replacement from the U.S. population at intermediate risk and were individually run through the model (inner loop simulation), modeling both heterogeneity and stochastic uncertainty. The results were aggregated at the parameter level and 95% credibility intervals (95%CI) were calculated to reflect parameter uncertainty. Furthermore, we calculated the probability that each of the strategies (1 to 7) was cost-effective for varying willingness-to-pay thresholds. All analyses were done separately for men and women, and separately for the 3 definitions of intermediate risk (5% – 7.5%, 2.5% – 7.5%, and 5% – 10%). In sensitivity analyses, we checked whether the following alternative assumptions would affect the results: 1. using all generic medication –assuming similar effectiveness and generic statin prices, 2. use of systolic

blood pressure threshold of 140 mmHg in individuals older than 60 years -as used in the JNC-7 guidelines on hypertension, 3. assuming that the joint effect of 2 (or 3) types of medication would be lower or greater than the multiplication of their individual effects

RESULTS

Baseline characteristics, Treatment initiation

Review of the baseline characteristics (Table 1) of the US population at intermediate risk of CVD shows that women were older than men, and apart from smoking, HDL, and calcium score, had less favorable risk factor profiles. Compared with current practice, the number of men who would initiate anti-hypertensive medication and statins in a screening strategy was largest for the CT calcium strategy, closely followed by the hs-CRP strategy (Table 3). This pattern was seen for all three definitions of the intermediate risk category. In women, the hs-CRP strategy resulted in the largest number of individuals initiating anti-hypertensive medication and statins, closely followed by the CT-calcium strategy.

Intention-to-treat analysis

Using the base-case definition of intermediate risk of 5%-7.5%, statin therapy was the least effective (Figure 3). HsCRP, ABI, cIMT and current guidelines were all less effective and more costly than current practice and CT-calcium (Figure 3). CT calcium was the most effective at a cost of $32,900/QALY gained compared with current practice (eTable 3). In women, CT calcium, ABI and cIMT were not considered cost-effective (Figure 4). Compared to current practice, hs-CRP was more effective at a cost of $32,467/QALY gained (eTable 4).

In men at 2.5% – 7.5% risk, CT calcium was the most effective at a cost of $22,300/QALY (Figure 5). In women at 2.5%-7.5% risk, hsCRP was the most effective but at a substantially higher cost of $185,091/QALY gained (Figure 6). In men at 5% – 10% risk, CT calcium was again the most effective at a cost of $32,700/QALY (Figure 7). In women at 5 – 10% risk, hsCRP was again the most effective at a cost of $15,050/QALY (Figure 8).

As-treated analysis

In men, statin therapy dominated all other strategies irrespective of the definition of risk (Figure 3, Figures 5 and 7, eTable 3). In women, statin therapy was the most effective with a cost of $6,059/QALY gained compared with current practice with a range of $4,270-$10,556/QALY for varying risk definitions (Figure 4, Figures 6 and 8, eTable 4).

Table 1. Baseline characteristics of US population at intermediate risk, defined as a 10 year CVD risk of between 5% – 7.5% (base case), 2.5% – 7.5% and 5%-10%. Values are median values and inter quartile range, or mean percentages.

Intermediate risk category definition	**5%–7.5%**		**2.5% – 7.5%**		**5%– 10%**	
Sex	Men	Women	Men	Women	Men	Women
N	334	284	774	728	517	463
Framingham Risk Factors:						
Age	49 [46–54]	60 [54–66]	48 [44–52]	55 [49–62]	50 [46–55]	63 [55–69]
Current Smoking	30%	20%	20%	24%	33%	20%
Systolic blood pressure (mm Hg)	123 [117–133]	131 [122–145]	122 [115 – 130]	127 [118–139]	125 [117–134]	132 [123–146]
Anti hypertensives	14%	39%	12%	24%	15%	48%
Total cholesterol (mg/dl)	204 [184–233]	224 [197–248]	203 [186 – 229]	215 [193–241]	207 [184–236]	221 [195–245]
HDL cholesterol (mg/dl)	45 [38–54]	56 [49–69]	47 [39 – 56]	56 [47–71]	44 [37–51]	57 [47–67]
Glucose (mg/dl)	99 [93–107]	96 [91–105]	97 [91 – 103]	95 [88–102]	98 [93–107]	97 [91–105]
Anti diabetic medication	1%	5%	1%	4%	2%	6%
Novel Biomarkers:						
CT coronary calcium score:						
0	13%	21%	23%	38.5%	11.8%	19.7%
1-100	57%	56%	53%	43.8%	60.5%	52.3%
101-400	21%	12%	16%	10.4%	18.4%	16.0%
400-1000	6.6%	7.4%	6.3%	5.9%	7.2%	8.2%
≥1000	1.8%	3.2%	1.2%	1.4%	2.1%	3.9%
Natural logarithm of (CTCS+1)	2.73 [0.94–4.93]	2.33 [0.57–4.39]	2.25 [0.57 – 4.52]	1.12 [0.0–3.62]	2.86 [1.11–8.23]	2.83 [0.71–4.97]
cIMT (mm)*	6.87 [6.34–8.09]	7.50 [6.8–8.42]	7.13 [6.8–7.9]	7.31 [6.81–8.13]	7.39 [6.9–8.23]	7.67 [6.91–8.62]
CRP (mg/L)	1.44 [0.63–2.69]	2.41 [1.27–5.62]	1.31 [0.73 – 2.52]	2.69 [1.27 – 2.69]	1.53 [0.82–2.69]	2.53 [1.35–5.40]
ABI ≤0.9	0%	7%	1%	5%	2%	9%

Table 2. Data included in the Markov model on CVD primary prevention strategies for asymptomatic U.S. individuals identified as being at intermediate risk for a CVD event.

Parameters	Base-case value men†	Base-case value women†	Distribution	Data source‡	Reference
Novel Risk Markers					
CT coronary calcium					
Adjusted HRR per log (calcium score+1) unit increase					
HR [95%CI] for CHD	1.35 [1.28 – 1.43]		log-normal	Meta analysis	(11)
HR [95%CI] for Stroke	0.97 [0.84 – 1.12]		log-normal	Meta analysis	(11)
Cost of a CAC scan, $	110 [90 – 130]		gamma	Official tarif	See text
High sensitivity CRP					
Adjusted HRR per Log(CRP) / SD* (mg/L) unit increase					
HR [95%CI] for CHD	1.22 [1.17 – 1.27]		log-normal	Meta analysis	(55)
HR [95%CI] for Stroke	1.16 [1.10 – 1.27]		log-normal	Meta analysis	(55)
Cost of hs-CRP measurement, $	20 [15 – 30]		gamma	cost-effectivenss analysis	(48)
Carotid intima media thickness					
Adjusted HRR per 0.1 mm IMT unit increase					
HR [95%CI] for CHD	1.08 [1.05 – 1.10]		Log-normal	Meta analysis	(11)
HR [95%CI] for Stroke	1.12 [1.10 – 1.15]		Log-normal	Meta analysis	(11)
Cost of cIMT measurement	325 [244 – 404]		Gamma	cost-effectivenss analysis	(56)
Ankle brachial index					
Adjusted HRR: ABI ≤ 0.9 vs > 0.9					
HR [95%CI] for CHD	1.47 [1.18 – 1.84]		Log-normal	Meta analysis	(11)
HR [95%CI] for Stroke	1.26 [1.05 – 1.50]		Log-normal	Meta analysis	(11)
Cost of ABI measurement, $	50 [40, 70]		Gamma	cost-effectivenss analysis	(57)
Lifetime risk of developing cancer due to radiation associated with CT coronary calcium scanning	0.00008 (0.00005, 0.00012)	0.00020 (0.00014, 0.00028)	Uniform	Simulation study	(28)
One year case-fatality given cancer due to radiation risk	0.65 (0.61, 0.73)	0.70 (0.63, 0.78)	Gamma	Simulation study	(27)

Table 2. *(Continued)*

Parameters	Base-case value men†	Base-case value women†	Distribution	Data source‡	Reference
Treatment effectiveness of statins					
RR on incident CHD, statins vs placebo	0.76 (0.73, 0.79)		Log-normal	Meta-analysis	(29)
RR on incident stroke, statins vs placebo	0.78 (0.62, 0.89)		Log-normal	Meta-analysis	(29)
Cost of moderate intensity statin, yearly	$ 73 ($40, $160)		Triangular	Retail prices	See text
Cost of potent statin, yearly	$ 840 ($630, $1,050)		Triangular	Retail prices	See text
RR of hepatitis, statins vs placebo	3.51	6.5	Log-normal	Meta-analysis	(58)
RR of myopathy, statins vs placebo	1.53	1.53	Log-normal	Meta-analysis	(58)
Expected cost of hepatitis episode	$120			Cohort study	(52)
Expected cost of myopathy episode	$250			Cohort study	(52)
Expected disutility of hepatitis episode	0.05 QALY			Cohort study	(52)
Expected disutility of myopathy episode	0.025 QALY			Cohort study	(52)
Treatment effectiveness of antihypertensives					
RR of incident CHD, anti-hypertensives vs placebo	0.85 (0.81, 0.89)		Log-normal	Meta-analysis	(31, 59)
RR of incident stroke, anti-hypertensives vs placebo	0.64 (0.56, 0.73)		Log-normal	Meta-analysis	(31, 59)
Cost of anti-hypertensives, yearly	$ 500 ($400, $625)			Pharmacy reference	(60)
Treatment effectiveness of aspirin					
RR of incident CHD, aspirin vs placebo	0.86 (0.74, 1.00)		Log-normal	Meta-analysis	(26)
RR of incident stroke, aspirin vs placebo	0.94 (0.84, 1.06)		Log-normal	Meta-analysis	(26)
Annual rate major extracranial bleeding	0.0013 (0.0099, 0.0017)		Log-normal	Meta-analysis	(26)
RR of major extracranial bleeding	1.62 (1.31, 2.00)		Log-normal	Meta-analysis	(26)
One year case-fatality due to major extra cranialbleeding*	0.03 (0.02, 0.04)		Log-normal	Cohort Study	(61)
Synergy Factor	1 +/- 10%		-		See online supplement

Table 2. *(Continued)*

Parameters	Base-case value men†	Base-case value women†	Distribution	Data source‡	Reference
Utilities					
Asymptomatic elderly	0.86 (0.85, 0.86)	0.83 (0.83, 0.84)	Normal	Survey	(62)
Post- CHD event	0.76 (0.74, 0.77)	0.67 (0.65, 0.69)	Normal	Survey	(62)
Post-major-bleeding	0.72 (0.70, 0.74)	0.67 (0.65, 0.69)	Normal	Survey	(62)
Post-stroke event	0.69 (0.67, 0.71)	0.61 (0.59, 0.63)	Normal	Survey	(62)
Disutility due to CHDevent	-0.10 (-0.13, -0.08)	-0.16 (-0.20, -0.12)	Triangular	Survey	(62)
Disutility due to major bleeding	-0.14 (-0.10, -0.17)	-0.16 (-0.20, -0.12)	Triangular	Survey	(62)
Disutility due to stroke event	-0.19 (-0.24, -0.16)	-0.22 (-0.26, -0.19)	Triangular	Survey	(62)
Disutility due to taking medication daily[a]	6		Triangular	Survey	(45)
Costs, dollars[¶]					
Costs of obtaining Framingham Risk factors including blood panel and phycician visit*	$ 80 (60, 100)		Triangular	Official tariff	(63, 64)
First year costs of CHD-event*	$ 34376 (27500, 41251)		Gamma	Cost-study	(36, 40)
First year costs of stroke-event	$ 22871 (18297, 27445)		Gamma	Cost-study	(35, 41)
First year costs of major extracranial bleeding	$ 13400 (10500, 23450)		Gamma	Cost-study	(37, 38)
Annual follow-up post-CHD	$4400 ($2200, $6600)		Gamma	Cost-study	(35, 39)
Annual follow-up post-Stroke	$3963 ($1980, $5995)		Gamma	Cost-study	(35, 39)

Table 2. *(Continued)*

Parameters	Base-case value men†	Base-case value women†	Distribution	Data source‡	Reference
Adherence, reference case analysis	70%		-	Cohort study	(33)
Proportion of CVD events being stroke	0.23 (0.16, 0.28)	0.39 (0.26, 0.47)	Beta	Cohort study	(8)
Hazard Ratio for mortality after CVD event	1.90 (1.60 to 2.40)		Log-normal	Cohort study	(25)

Notes: Major bleeding = hemorrhagic stroke, gastrointestinal bleeding

* Risk of events, probabilities, utilities and cost estimates described for men are identical for women

† Data in parenthesis are 95% CIs for the beta- and lognormal distributions and ranges for the triangular- and uniform distributions

¶ Costs are 2013 U.S. dollars

[a] The number of months traded away was divided by the average life expectancy (522 -in months) of the survey's population

Table 3. Percentages of initiation of anti-hypertensive treatment, statins and aspirin for each strategy, separately for men and women, for 3 definitions of intermediate risk.

Treatment allocation 5% – 7.5%						
	Guidelines	**CT calcium**	**hsCRP**	**cIMT**	**ABI**	**Statin therapy**
Initiate antihypertensives						
men	7%	10%	8%	8%	7%	7%
women	14%	15%	16%	14%	14%	14%
Initiate Statins						
men	7%	16%	15%	9%	7%	83%
women	11%	15%	23%	13%	13%	76%
Initiate Aspirin						
men	-	11%	9%	3%	0%	0%

Table 3. (*Continued*)'

Treatment allocation 2.5% – 7.5%						
	Guidelines	**CT calcium**	**hsCRP**	**cIMT**	**ABI**	**Statin therapy**
Initiate antihypertensives						
men	4%	6%	5%	5%	4%	4%
women	14%	15%	15%	15%	14%	14%
Initiate Statins						
men	5%	9%	8%	6%	5%	85%
women	6%	8%	11%	7%	7%	80%
Initiate Aspirin						
men	-	5%	4%	1%	0%	0%
Treatment allocation 5% – 10%						
	Guidelines	**CT calcium**	**hsCRP**	**cIMT**	**ABI**	**Statin therapy**
Initiate antihypertensives			11%	11%	10%	10%
men	10%	11%	14%	14%	14%	14%
women	14%	14%				
Initiate Statins			13%	10%	9%	84%
men	8%	13%	19%	14%	11%	77%
women	10%	18%				
Initiate Aspirin			5%	2%	0%	0%
men	-	6%				

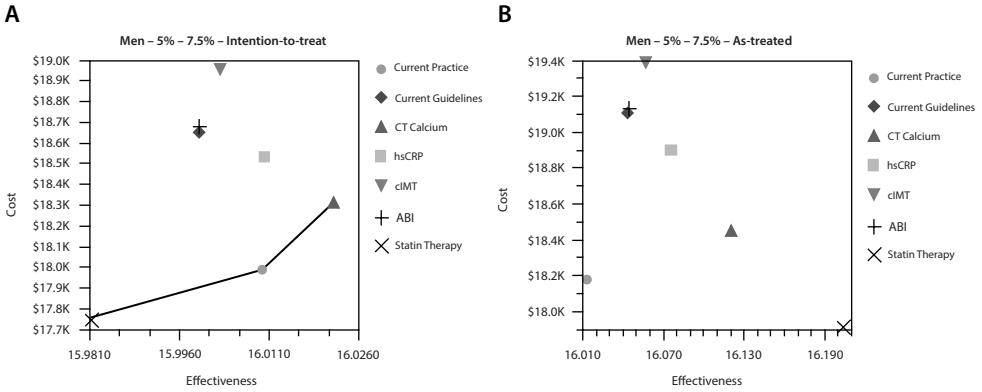


Figure 3. Cost (US dollars over the remaining lifetime) versus effectiveness (quality adjusted life years (QALYs)) of strategies 1 to 7 in **men** at intermediate risk of CVD (**5% – 7.5%**) ***a*** *intention-to-treat* and ***b*** *as-treated analyses*. Strategies closer to the bottom-right corner are more preferable (more effective and less costly). The solid line indicates strategies on the efficiency frontier: the choice depends on the societal willingness-to-pay for a QALY. The slope of the line represents the incremental cost-effectiveness ratio. Scale of the x-axis (effectiveness) and y-axis (cost) chosen to optimize visual comparison of strategies.

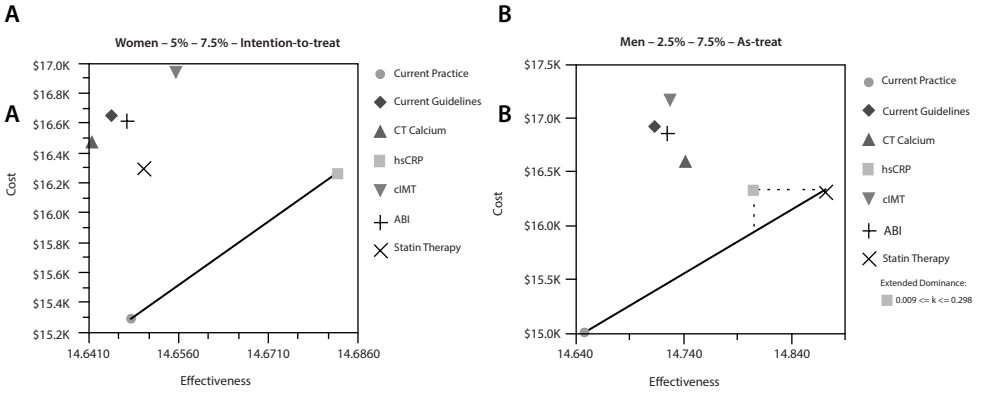


Figure 4. Cost (US dollars over the remaining lifetime) versus effectiveness (quality adjusted life years (QALYs)) of strategies 1 to 7 in **women** at intermediate risk of CVD (**5%-7.5%**) ***a*** *intention-to-treat* and ***b*** *as-treated analyses*. Strategies closer to the bottom-right corner are more preferable (more effective and less costly). The solid line indicates strategies on the efficiency frontier: the choice depends on the societal willingness-to-pay for a QALY. The slope of the line represents the incremental cost-effectiveness ratio. Scale of the x-axis (effectiveness) and y-axis (cost) chosen to optimize visual comparison of strategies.

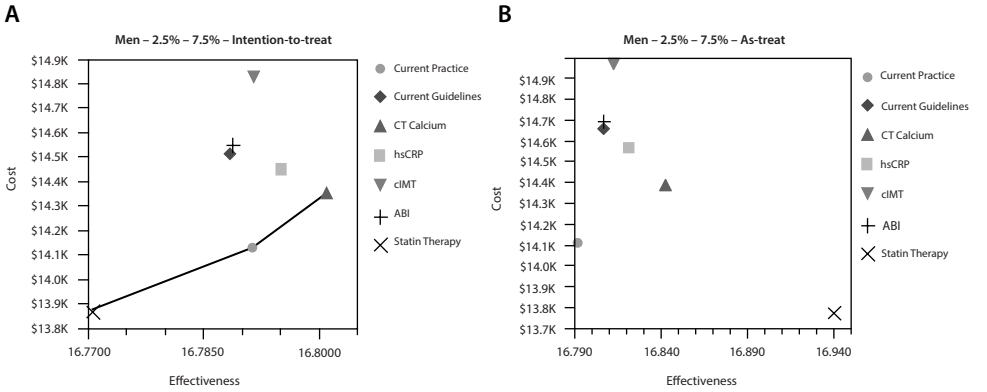


Figure 5. Cost (US dollars over the remaining lifetime) versus effectiveness (quality adjusted life years (QALYs)) of strategies 1 to 7 in **men** at intermediate risk of CVD (**2.5% – 7.5%**) ***a*** *intention-to-treat* and ***b*** *as-treated analyses*. Strategies closer to the bottom-right corner are more preferable (more effective and less costly). The solid line indicates strategies on the efficiency frontier: the choice depends on the societal willingness-to-pay for a QALY. The slope of the line represents the incremental cost-effectiveness ratio. Scale of the x-axis (effectiveness) and y-axis (cost) chosen to optimize visual comparison of strategies.

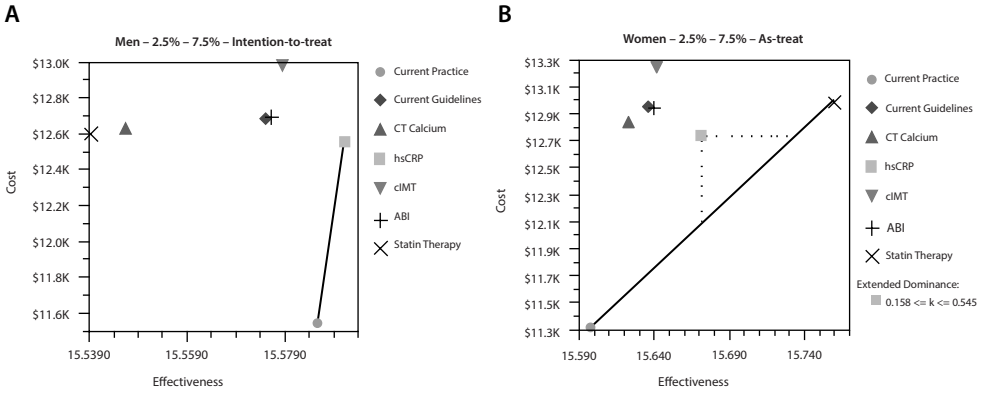


Figure 6. Cost (US dollars over the remaining lifetime) versus effectiveness (quality adjusted life years (QALYs)) of strategies 1 to 7 in **women** at intermediate risk of CVD (**2.5% – 7.5%**) ***a*** *intention-to-treat* and ***b*** *as-treated analyses*. Strategies closer to the bottom-right corner are more preferable (more effective and less costly). The solid line indicates strategies on the efficiency frontier: the choice depends on the societal willingness-to-pay for a QALY. The slope of the line represents the incremental cost-effectiveness ratio. Scale of the x-axis (effectiveness) and y-axis (cost) chosen to optimize visual comparison of strategies.

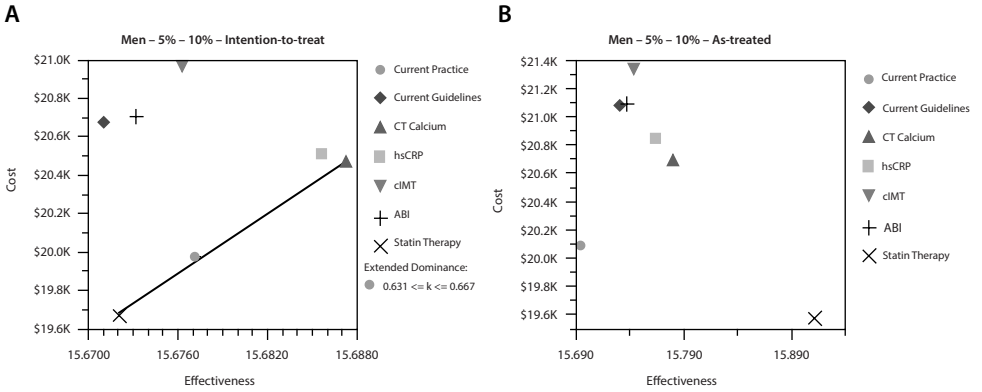


Figure 7. Cost (US dollars over the remaining lifetime) versus effectiveness (quality adjusted life years (QALYs)) of strategies 1 to 7 in **men** at intermediate risk of CVD (**5% – 10%**) ***a*** *intention-to-treat* and ***b*** *as-treated analyses*. Strategies closer to the bottom-right corner are more preferable (more effective and less costly). The solid line indicates strategies on the efficiency frontier: the choice depends on the societal willingness-to-pay for a QALY. The slope of the line represents the incremental cost-effectiveness ratio. Scale of the x-axis (effectiveness) and y-axis (cost) chosen to optimize visual comparison of strategies.

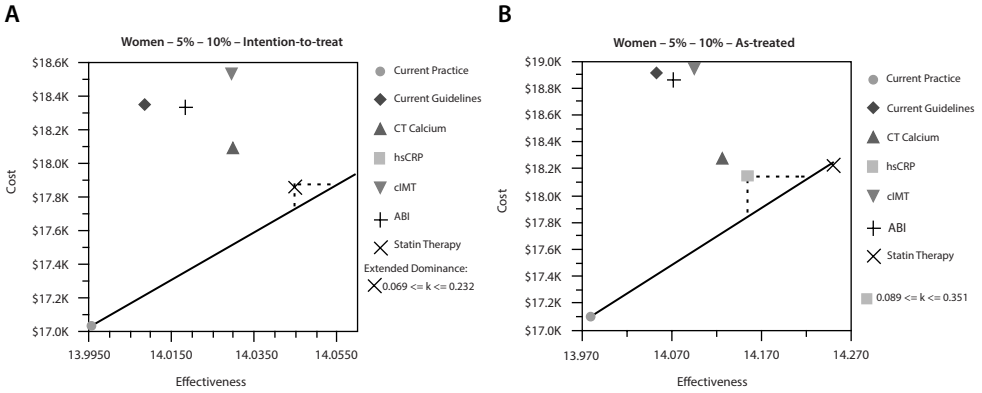


Figure 8. Cost (US dollars over the remaining lifetime) versus effectiveness (quality adjusted life years (QALYs)) of strategies 1 to 7 in **women** at intermediate risk of CVD (**5% – 10%**) ***a*** *intention-to-treat* and ***b*** *as-treated analyses*. Strategies closer to the bottom-right corner are more preferable (more effective and less costly). The solid line indicates strategies on the efficiency frontier: the choice depends on the societal willingness-to-pay for a QALY. The slope of the line represents the incremental cost-effectiveness ratio. Scale of the x-axis (effectiveness) and y-axis (cost) chosen to optimize visual comparison of strategies.

Sensitivity analysis

The use of all generic medication, 140 mmHg threshold for initiating anti-hypertensive treatment in individuals over 60, or assuming synergy between multiple drugs, did not change the optimal strategy in men (CT calcium) or women (hsCRP) at a 5% – 7.5% risk in the intention-to-treat analysis (eTable 5). Assuming dyssynergy between the drugs resulted in less favorable results of screening ($162,486/QALY for CT calcium in men, $59,800/QALY for hsCRP in women).

Probabilistic sensitivity analysis

In men, the probability that CT calcium was cost-effective was marginally higher than the probability that current practice was cost-effective (35% vs 30%) (eFigure 3). In women, the probability that hsCRP was cost-effective was higher than the probability that current practice was cost-effective (45% vs 25%) (eFigure 4).

DISCUSSION

We analyzed the comparative effectiveness and cost-effectiveness of screening United States individuals at intermediate risk with either CT calcium, hsCRP, ABI and cIMT, compared to current practice and guidelines or initiating statin therapy without screening. Whereas prior modeling studies evaluated a single novel biomarker [17,47-49], this study compared multiple novel biomarkers. Furthermore, published studies considered initiation of a single drug (most often a statin) based on the information derived from the novel biomarker, whereas in this study we modeled the effect of all relevant cardioprotective medications for the primary prevention of CVD. Finally, previous studies compared screening vs. no screening as comparator, whereas this study evaluated three realistic comparison strategies.

In the intention-to-treat analysis, screening men with CT calcium was effective with acceptable ICER's. All other novel biomarkers were more costly and less effective. This is explained in part by the observation that CT calcium results in the highest percentage of men being allocated any of the three cardioprotective drugs compared with screening with the other biomarkers. This, in turn, stems from both the strength of the association between the novel biomarker with CVD risk [12] and the distribution of the biomarker within the U.S. population at intermediate risk [13]. Only in the statin therapy strategy were more men allocated statins, but at the cost of a substantial disutility from taking daily medication [45]. Sensitivity analyses of the intention-to-treat scenario revealed the robustness of the favorability of CT calcium in men -only in the unlikely event of dyssynergy between cardioprotective drugs did the ICER exceed $100,000. However, analysis of parameter uncertainty suggests that the favorability of CT calcium appears to be a "close call" compared with current practice. Thus, policymakers should interpret the results for CT calcium with caution and future research in this area is justified.

In women, the intention-to-treat analysis revealed that screening with hsCRP was the optimal strategy, and was, associated with the highest percentage of women being allocated to cardioprotective drugs. Moreover, CT calcium is less favorable in women due to a higher risk of cancer due to radiation associated with a cardiac CT [27, 28]. Results in women proved to be robust in sensitivity analyses as well, and analysis of parameter uncertainty revealed that favorability of hsCRP is fairly substantial, with current practice less of a competitor.

Disutility from daily medication plays a key role in the decision. Ubiquitously initiating statins results in a lower quality adjusted life expectancy in individuals without a clear indication for statins, whereas this penalty seems to be outweighed in individuals with an increased risk of CVD based on testing. In the as-treated analysis, which assumed no medication disutility initiating statins (without further screening) dominated all other strategies in men and was the most effective strategy in women with acceptable ICERs.

A number of cost-effectiveness studies on CT calcium, hsCRP and ABI individually have previously been published [17, 47-49]. For CT calcium, previous results are consistent with ours for the more favorable statin assumptions scenario (as-treated analysis) [19, 49] and generic availability of statins [17]. For hsCRP, results were consistent when the potential harm of statin use was taken into account, corresponding to our intention-to-treat analysis (48. Initiation of anti-platelet medication based on ABI was found to be more effective than current practice {Vaidya, 2014 #586) which corresponds to our as-treated results, in which ABI was slightly more effective than current practice as well –but dominated by statin therapy in both men and women.

The results need to be interpreted in light of limitations related to the required modeling assumptions and imperfect available evidence. First, the ACC/AHA guidelines on risk assessment uses the Pooled Cohort Equations for calculating CVD risk, but has been criticized for overestimating actual risk [50]. We used a Framingham Study based model by Pencina which was based on the same risk factors as the Pooled Cohort Equations and has been shown to perform fairly well in most U.S. subpopulations [51]. Moreover, because our purpose was to evaluate the cost-effectiveness of the novel risk markers in light of competing risk by non-CVD death, we chose the Pencina model that took this competing risk into account. Second, the NHANES dataset did not include measurements of CT calcium and cIMT. We used correlations between Framingham risk factors and the other two novel risk markers as observed in the Rotterdam Study to add these values to the NHANES dataset -conditional on the assumption that the correlations in the Rotterdam Study are applicable to the NHANES population. As in other cost-effectiveness analyses, the differences in strategies with regard to the quality adjusted life expectancy were small [17, 52, 53]. This finding is inherent to primary prevention and reflects the fact that many individuals need to be subjected to the preventive intervention in order to avoid events in a few. Fourth, we assumed that treatment adherence is independent of an individual's disutility for taking daily medication. To account for this, we used the median (lower) instead of the mean value as reported by Fontana, using the fixed

value of 6 months instead of the full disutility distribution which included extremely high values of up to 10 years [45]. Fifth, we focused on individuals at intermediate risk of CVD. As the recent ACC/AHA guidelines on risk assessment do not explicitly define an intermediate risk group, we used three different definitions, and our results indicated substantial agreement regardless of the definition chosen. One could argue that the novel biomarkers could have value in other subgroups as well, but generally, the largest impact is expected in an intermediate risk group [13].

Overall, this study sheds light on the comparative (cost-)effectiveness of four novel screening biomarkers for primary prevention of CVD [12]. For U.S. individuals at intermediate risk, screening men with CT coronary calcium is likely to be cost-effective compared with the full range of relevant alternatives, but subject to parameter uncertainty, whereas screening with hsCRP has value in women. The perceived disutility of taking daily medication plays a key role in the optimal decision for an individual patient. Patients with a low tolerance for medication will benefit more from screening than individuals with high tolerance. Furthermore, recent studies have suggested that [54] the results of screening with CT calcium may influence treatment initiation and continuation downstream. The interplay between an individual's disutility for taking daily medication, the result of screening with a novel biomarker and treatment adherence should be the subject of future research in order to elucidate the optimal decision for a patient.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart Disease and Stroke Statistics--2013 Update: A Report From the American Heart Association. Circulation. 2013;127(1):e6-e245.
2. Force USPST**.** Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;150(6):396-404.
3. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr., Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110(2):227-39.
4. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, 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. 2002;106(3):388-91.
5. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013.
6. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Sr., Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013.
7. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.
8. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS**.** Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation. 2009;119(24):3078-84.
9. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB**.** Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-47.
10. Force USPST**.** Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151(7):474-82.
11. Ferket BS, van Kempen BJH, Hunink MGM, Agarwal I, Kavousi M, Franco O, et al. Predictive Value of Updating Framingham Risk Scores with Novel Risk Markers in the U.S. General Population 2013.
12. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012;308(8):788-95.
13. Ferket BS, van Kempen BJ, Hunink MG, Agarwal I, Kavousi M, Franco OH, et al. Predictive value of updating Framingham risk scores with novel risk markers in the U.S. general population. PLoS One. 2014;9(2):e88312.
14. Cook NR, Ridker PM**.** Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. Ann Intern Med. 2009;150(11):795-802.
15. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS**.** Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008;27(2):157-72; discussion 207-12.
16. Hunink M GP, Siegel J, et al. ***Decision making in health and medicine. Integrating evidence and values.*** Cambridge: Cambridge University Press; 2001.
17. van Kempen BJ, Spronk S, Koller MT, Elias-Smale SE, Fleischmann KE, Ikram MA, et al. Comparative effectiveness and cost-effectiveness of computed tomography screening for coronary artery calcium in asymptomatic individuals. J Am Coll Cardiol. 2011;58(16):1690-701.
18. Galper BZ, Moran A, Coxson PG, Pletcher MJ, Heidenreich P, Lazar LD, et al. Using stress testing to guide primary prevention of coronary heart disease among intermediate-risk patients: a cost-effectiveness analysis. Circulation. 2012;125(2):260-70.

19. Pletcher MJ, Pignone M, Earnshaw S, McDade C, Phillips KA, Auer R, et al. Using the coronary artery calcium score to guide statin therapy: a cost-effectiveness analysis. Circ Cardiovasc Qual Outcomes. 2014;7(2):276-84.

20. Pletcher MJ, Pignone M**.** Evaluating the clinical utility of a biomarker: a review of methods for estimating health impact. Circulation. 2011;123(10):1116-24.

21. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.

22. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289(19):2560-72.

23. Hofman A, Darwish Murad S, van Duijn CM, Franco OH, Goedegebure A, Ikram MA, et al. The Rotterdam Study: 2014 objectives and design update. Eur J Epidemiol. 2013;28(11):889-926.

24. Adabag AS, Therneau TM, Gersh BJ, Weston SA, Roger VL**.** Sudden death after myocardial infarction. JAMA. 2008;300(17):2022-9.

25. Hooi JD, Kester AD, Stoffers HE, Rinkens PE, Knottnerus JA, van Ree JW**.** Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. J Clin Epidemiol. 2004;57(3):294-300.

26. Berger JS, Lala A, Krantz MJ, Baker GS, Hiatt WR**.** Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. Am Heart J. 2011;162(1):115-24 e2.

27. Einstein AJ, Henzlova MJ, Rajagopalan S**.** Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. Jama. 2007;298(3):317-23.

28. Kim KP, Einstein AJ, Berrington de Gonzalez A**.** Coronary artery calcification screening: estimated radiation dose and cancer risk. Arch Intern Med. 2009;169(13):1188-94.

29. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581-90.

30. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;1:CD004816.

31. Law MR, Morris JK, Wald NJ**.** Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. Bmj. 2009;338:b1665.

32. Ho PM, Bryson CL, Rumsfeld JS**.** Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009;119(23):3028-35.

33. Gagne JJ, Choudhry NK, Kesselheim AS, Polinski JM, Hutchins D, Matlin OS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. Ann Intern Med. 2014;161(6):400-7.

34. Gu Q, Burt VL, Dillon CF, Yoon S**.** Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health And Nutrition Examination Survey, 2001 to 2010. Circulation. 2012;126(17):2105-14.

35. Earnshaw SR, Scheiman J, Fendrick AM, McDade C, Pignone M**.** Cost-utility of aspirin and proton pump inhibitors for primary prevention. Arch Intern Med. 2011;171(3):218-25.

36. Kauf TL, Velazquez EJ, Crosslin DR, Weaver WD, Diaz R, Granger CB, et al. The cost of acute myocardial infarction in the new millennium: evidence from a multinational registry. Am Heart J. 2006;151(1):206-12.

37. Lightowlers S, McGuire A**.** Cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. Stroke. 1998;29(9):1827-32.

38. Saini SD, Schoenfeld P, Fendrick AM, Scheiman J**.** Cost-effectiveness of proton pump inhibitor cotherapy in patients taking long-term, low-dose aspirin for secondary cardiovascular prevention. Arch Intern Med. 2008;168(15):1684-90; discussion 91.

39. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. Am Heart J. 2001;141(5):727-34.

40. Menzin J, Wygant G, Hauch O, Jackel J, Friedman M. One-year costs of ischemic heart disease among patients with acute coronary syndromes: findings from a multi-employer claims database. Curr Med Res Opin. 2008;24(2):461-8.

41. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18-e209.

42. Gravelle H, Brouwer W, Niessen L, Postma M, Rutten F. Discounting in economic evaluations: stepping forward towards optimal decision rules. Health Econ. 2007;16(3):307-17.

43. Corso PS, Hammitt JK, Graham JD, Dicker RC, Goldie SJ. Assessing preferences for prevention versus treatment using willingness to pay. Med Decis Making. 2002;22(5 Suppl):S92-101.

44. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014;371(9):796-7.

45. Fontana M, Asaria P, Moraldo M, Finegold J, Hassanally K, Manisty CH, et al. Patient-accessible tool for shared decision making in cardiovascular primary prevention: balancing longevity benefits against medication disutility. Circulation. 2014;129(24):2539-46.

46. Hutchins R, Viera AJ, Sheridan SL, Pignone MP. Quantifying the utility of taking pills for cardiovascular prevention. Circ Cardiovasc Qual Outcomes. 2015;8(2):155-63.

47. Vaidya A, Joore MA, Ten Cate-Hoek AJ, Ten Cate H, Severens JL. Screen or not to screen for peripheral arterial disease: guidance from a decision model. BMC Public Health. 2014;14:89.

48. Lee KK, Cipriano LE, Owens DK, Go AS, Hlatky MA. Cost-effectiveness of using high-sensitivity C-reactive protein to identify intermediate- and low-cardiovascular-risk individuals for statin therapy. Circulation. 2010;122(15):1478-87.

49. Sniderman AD, Thanassoulis G, Lawler PR, Williams K, Furberg CD. Comparison of coronary calcium screening versus broad statin therapy for patients at intermediate cardiovascular risk. Am J Cardiol. 2012;110(4):530-3.

50. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. Lancet. 2013;382(9907):1762-5.

51. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P, Group CHDRP. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001;286(2):180-7.

52. Pletcher MJ, Lazar L, Bibbins-Domingo K, Moran A, Rodondi N, Coxson P, et al. Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern Med. 2009;150(4):243-54.

53. Ferket BS, van Kempen BJ, Heeringa J, Spronk S, Fleischmann KE, Nijhuis RL, et al. Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study. PLoS Med. 2012;9(12):e1001361.

54. Nasir K, McClelland RL, Blumenthal RS, Goff DC, Jr., Hoffmann U, Psaty BM, et al. Coronary artery calcium in relation to initiation and continuation of cardiovascular preventive medications: The Multi-Ethnic Study of Atherosclerosis (MESA). Circ Cardiovasc Qual Outcomes. 2010;3(3):228-35.

55. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375(9709):132-40.

56. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. 2012;308(8):796-803.

57. Marshall N. A Cost Effectiveness Analysis of Using the Ankle-Brachial Index to Screen for Peripheral Artery Disease. UCLA Electronic Thesis and Dissertations. - on July 19th, 20142012;https://escholarship.org/uc/item/9g83j2zb#page-1.

58. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. 2006;97(8A):52C-60C.

59. Blood Pressure Lowering Treatment Trialists C, Sundstrom J, Arima H, Woodward M, Jackson R, Karmali K, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014;384(9943):591-8.

60. ***Red Book 2010: Pharmacy's Fundamental Reference***: PDR Network, LLC; 2010.

61. Greving JP, Buskens E, Koffijberg H, Algra A**.** Cost-effectiveness of aspirin treatment in the primary prevention of cardiovascular disease events in subgroups based on age, gender, and varying cardiovascular risk. Circulation. 2008;117(22):2875-83.

62. Nyman JA, Barleen NA, Dowd BE, Russell DW, Coons SJ, Sullivan PW**.** Quality-of-life weights for the US population: self-reported health status and priority health conditions, by demographic characteristics. Med Care. 2007;45(7):618-28.

63. Centers for Medicare & Medicaid Services. Physician Fee Schedule. - on July 19th, 2014

64. Centers for Medicare & Medicaid Services. Clinical Laboratory Fee Schedule. 2013. - on July 19th, 2014

ONLINE SUPPLEMENT

Study Population

We analyzed 3,736 individuals aged 40 to 85 without a history of CHD or stroke at baseline from the 2003 – 2004 NHANES exam, taking into account the sampling weights for the U.S. population. We included the following variables: age at the exam visit, sex, current smoking, systolic blood pressure, total cholesterol, HDL cholesterol, fasting plasma glucose level, anti-diabetic treatment, antihypertensive treatment, ankle-brachial index, and high-sensitivity C-reactive protein. Because values for CT coronary calcium and cIMT were not measured in the NHANES study, we merged the NHANES dataset with a subset of the Rotterdam Study cohort (N = 1,915) [(1)] in which all novel markers were measured and estimated these values using a multivariable imputation model for each of the individuals in the NHANES data as previously described [(2)]. Only NHANES individuals were used for subsequent analyses.

Imputation of CTCS and cIMT Values

The Rotterdam Study is a population-based cohort study of individuals aged 55 years and older living in Rotterdam, the Netherlands. Demographics, traditional risk factors, CTCS, cIMT, hs-CRP, ABI, and information on cardioprotective drugs were measured during re-examination visits in a subset (N = 1,915) of this cohort. Information on baseline risk factors of this cohort can be found in eTable 1. Details on how these novel risk markers and the other variables were measured are published elsewhere [(1, 3, 4)].

First we imputed missing values of the traditional risk factors in the NHANES individuals (N = 16,602), taking into account the according sample weights published by NHANES. Then we merged the imputed NHANES set with 1,915 individuals of the Rotterdam Study, including the novel risk markers. This extended set was bootstrapped with covariates age, sex, traditional risk factors, CVD history, cardioprotective drug information, and novel risk markers as input for the imputation algorithm. For the imputation, we used a flexible additive imputation model including all other variables using the R 'areglmpute' function from the 'Hmisc' package. After the imputation procedure, we excluded NHANES subjects with prior CVD, NHANES subjects younger than 40 years of age and the Rotterdam study participants, leaving a study population of 3,736.

Risk stratification

We used the 30-year Framingham CVD model published by Pencina et al as the basis for calculating an individual's CVD risk [(5)]. It uses the 8 traditional risk factors to calculate the 30-year cumulative incidence of CVD (defined as myocardial infarction, coronary death and stroke), while taking into account the competing risk of non-CVD death (mortality due to all causes other than CVD). To resemble currently recommended risk assessment, we also calculated 10-year CVD risks without adjustment for the competing risk of non-CVD death. Of the 3,736 NHANES individuals aged 40 – 85, we selected a total of 618 individuals who had a calculated 10-year risk of CVD of 5% – 7.5% for the base case analysis. Baseline characteristics of these 618 individuals can be found in

Table 1. In sensitivity analyses we redefined intermediate risk as 2.5 – 7.5% and 5% – 10% respectively.

eTable 1. Baseline characteristics of 1,915 Rotterdam Study individuals

Variable	Median [IQR]
Age	70 [66 – 75]
Sex (%male)	45%
Current Smoking	16%
Systolic blood pressure (mm Hg)	140.0 [124 – 155]
HRX	28%
Total cholesterol (mg/dl)	225 [203 – 250]
HDL cholesterol (mg/dl)	51 [43 – 62]
Glucose (mg/dl)	99 [94 – 110]
Anti diabetic medication	6.2%
CTCS	
0	10%
1-100	41%
101-400	23%
400-1000	15%
≥1000	11%
Natural logarithm of (CTCS+1)	4.81 [2.6 – 6.3]
ABI ≤ 0.9	15.6%
CRP (mg/L)	2.4 [1.2 – 4.4]
cIMT (mm)	0.86 [0.76 – 0.95]

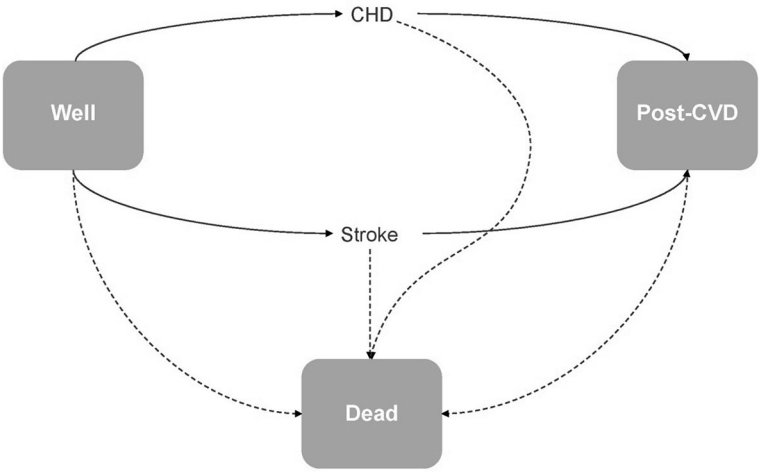
Risk reclassification by screening with each of the 4 novel risk markers

For each individual, we used 10-year risk of CVD for risk stratification, and updated this Framingham based score for each of the four risk markers. We extended the linear predictor based on the 8 traditional risk factors, to which we added each novel risk factor as a new variable, together with the corresponding Framingham score adjusted beta-coefficient from the meta-analysis [6]. This yielded 4 updated risk stratification scores (one for each four novel risk markers), each of which represents scores that could be used in the future. For each of these updated scores, we recalibrated the baseline survival probability by assuming no change in the average survival probability compared to the old score. For each individual, we calculated four updated 10-year risks of CVD, one for each new risk marker.

Recalibration of Updated Framingham Risk Scores (FRS)

We developed a state-transition model with three health states: Alive and CVD-free (Well), Post-CVD, and Dead (see eFigure 1). One-year transition probabilities of Well → CVD and Well → Dead were based on the 30-year FRS, which calculates the cumulative incidence of CVD and competing non-CVD death. 30-year cumulative CVD incidence I_{CVD} is calculated by summing the product of CVD hazard h_{CVD} at failure time t_i and the survival of competing events $S(t_i\text{-}1)$ for all failure times up to 30 year follow-up:

$$I_{CVD}(30) = \sum_{t_i<30} h_{CVD}(t_i)S(t_{i-1})$$



eFigure 1. Schematic representation of the microsimulation state-transition model.

We divided the baseline CVD-survival function into 2 survival functions: 1) coronary heart disease (CHD) and 2) stroke using the reported number of coronary heart disease and stroke events for men and women. The linear predictor of the 30-year FRS was extended with adjusted HRs of 4 novel risk markers based on systematic reviews of literature. Individual risk profiles including data on traditional and 4 novel risk factors were taken from 3,736 asymptomatic subjects of the National Health and Nutrition Examination Survey (NHANES) 2003-2004 examination round. To mimic survival selection of NHANES subjects at each time interval, we simulated cloned copies of NHANES subjects using Monte Carlo microsimulation within the state-transition model.

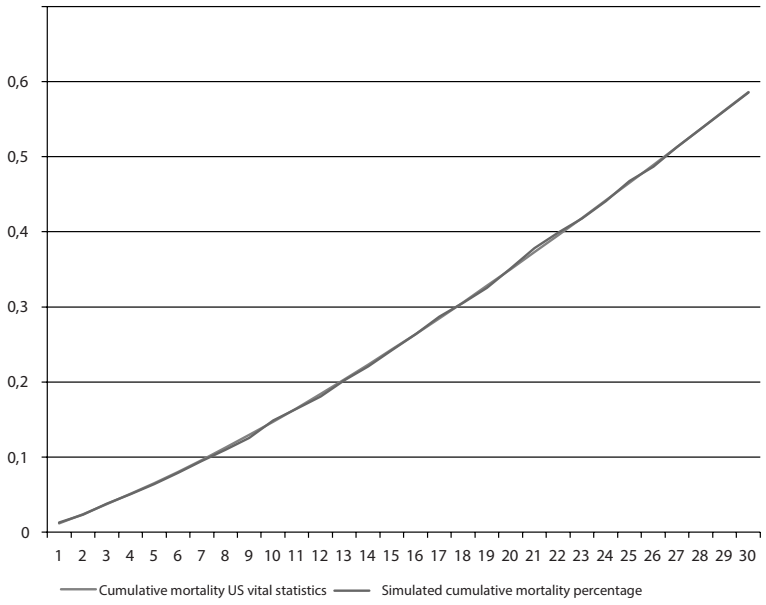
We followed a 4-step iterative calibration process:

(1) The microsimulation model was run for cycle t, starting at the first year t = 1, using the extended linear predictor values of NHANES subjects (uncalibrated simulated outcomes for cycle t).

(2) The baseline CVD and non-CVD survival function was then recalibrated by a fixed term assuming that the average mortality (both due to CVD and non-CVD causes) simulated by the model at cycle t, would be equal to the average mortality calculated based of the NHANES subjects at time t, based on US life tables from 2003 and up, adjusted for sex and age of the NHANES subjects population.
(3) The microsimulation model was then updated using the recalibrated CVD function and non-CVD mortality function for the next cycle t +1.
(4) NHANES individuals who remained alive and CVD-free after the cycle t were selected for the recalibration step for the next period (transition from t = t to t = t+1).

From the 'Well' state, one-year cumulative hazards for CHD, stroke, and non-CVD mortality were divided by the sum of these cause-specific hazards and subsequently multiplied with 1-exp(-cumulative total hazard) to take into account the competing risks. This provides unbiased estimates of cumulative incidences assuming constant hazards increasing with age but that are constant per over a one year time interval.

For internal validation, we compared the cumulative mortality incidence of the NHANES population based on the microsimulation state-transition model at each year t, with the cumulative mortality incidence of this population based on US vital statistics (eFigure 2).



eFigure 2. Simulated cumulative mortality percentage (red line) and US Vital Sstatistics based mortality (blue line) for year 1 – 30.

Adjusting for efficacy of Treatment

Drug treatment efficacies, in terms of Relative Risks (RR) were obtained from meta analyses and considered the relative risk in incidence of CHD or stroke compared to placebo. The relative risk of a certain treatment or intervention was assumed to be constant over time. Derived annual probabilities of CHD and stroke respectively, were multiplied by the RR of the appropriate strategy.

$$P_{after\_treatment} = p_{unadjusted} \cdot R_{strategy}$$

Adjusting the treatment efficacies for treatment adherence, baseline prevalence and treatment goals

The model incorporates 3 basic drug treatments: statins, anti-hypertensives and aspirin (in men). In order to estimate the combined effect, we made the following assumptions:

(1) An individual already on statins at baseline who had not reached the treatment goal, i.e. an LDL level >190 (4.92) was assumed to switch to a higher dose or more potent statin, and assigned half of the reduction in risk based on a full dose given to a non-user. The same holds for an individual using anti-hypertensives at baseline and a systolic blood pressure higher than 140 mmhg (or 150 if aged 60 or older).
(2) When a combination of drugs was assigned, the net effect of the drugs together on risk reduction was assumed to be the product of the individual RR's, times a factor for potential (dys)synergy, SF, where .90 < SF < 1.10. This range was chosen to make sure that a combination of 2 or 3 drugs was at least as effective as the effect of a single drug. For the base case definition of intermediate risk (5% – 7.5%), we calculated whether the comparative cost-effectiveness would change if using either 0.9 or 1.1.

Statins, anti-hypertensives and aspirin drug prices

We performed an online search on websites of U.S. pharmacies to estimate current retail prices of commonly prescribed statins, anti-hypertensive medication and aspirin. We restricted our search to drug retailers with nationwide presence. We assumed that if an individual would be prescribed a statin, this would normally be a moderately potent statin, we assumed that patients would be prescribed the generic moderate-intensity statin Simvastatin. In case an individual would be prescribed a potent statin -in case of both diabetes and a 10 year CVD risk over 7.5%, we assumed that Crestor would be the statin of choice.

eTable 2. Model Input Parameters

Parameter	Estimate	Source
One-year probability of having a first CHD event	Depending on cumulative CVD hazard function, and updated FRS	Pencina et al [5] Pooled estimates for hazard ratios of the four novel risk markers from the systematic review
One-year probability of having a first stroke event	Depending on cumulative CVD hazard function, CHD: stroke event ratio 104/348 for men and 86/133 for women, and updated FRS	Pencina et al [5] Pooled estimates for hazard ratios of the four novel risk markers from the systematic review
One-year probability of dying from non-cardiovascular mortality	Depending on cumulative hazard function for non-CVD death and original hazard ratios from the Framingham study	Pencina et al [5]

eTable 3. Costs, QALYS and ICERs for all strategies in **men**, for all three definitions of intermediate risk, intention-to-treat and as-treated, Dominated strategies (both more costly and less effective) were omitted. Italicized ICER indicates an extended dominated strategy. ICER of the most effective strategy was calculated excluding extended dominated strategies. Strategies ordered by increasing cost.

Men							
5% – 7.5%	**ITT**			**AT**			
	QALY	**Cost**	**ICER**		**QALY**	**Cost**	**ICER**
Statin therapy	15.98 (15.54 – 16.38)	$17,760 ($13,897 -$21,678)		Statin therapy	16.01 (15.56 – 16.42)	$18,175 ($14,420 – $22,615)	-
Current practice	16.01 (15.57 – 16.41)	$17,985 ($14,055 – $22,367)	$7,500				
CT calcium	16.02 (15.58 – 16.42)	$18,314 ($14,873 – $22,263)	$32,900				
2.5% – 7.5%	**ITT**			**AT**			
	QALY	**Cost**	**ICER**		**QALY**	**Cost**	**ICER**
Statin therapy	16.77 (16.52 – 17.00)	$13,880 ($11,127 – $16,431)		Statin therapy	16.94 (16.68 – 17.17)	$13,784 ($11,600 – $16,816)	-
Current practice	16.79 (16.50 – 17.02)	$14,129 ($11,184 – $17,256)	$12,450				
CT calcium	16.80 (16.53 – 17.04)	$14,352 ($11,498 – $17,496)	$22,300				
5% – 10%	**ITT**			**AT**			
	QALY	**Cost**	**ICER**		**QALY**	**Cost**	**ICER**
Statin therapy	15.67 (15.37 – 16.00)	$19,683 ($16,292 – $24,183)		Statin therapy	15.91 (15.56 – 16.25)	$19,600 ($16,147 – $23,371)	-
Current practice	15.68 (15.38 – 16.01)	$19,973 ($16,155 – $24,392)	***$57,417***				
CT calcium	15.69 (15.42 – 16.02)	$20,469 ($16,829 – $24,690)	$32,701				

ITT = intention-to-treat, AT = as-treated, ICER = incremental cost effectiveness ratio). Values are average discounted quality adjusted life years (QALY) (95%CI) and average discounted costs (95%CI)

eTable 4. Costs, QALYS and ICERs for all strategies in **women**, for all three definitions of intermediate risk, intention-to-treat and as-treated, Dominated strategies (both more costly and less effective) were omitted. Italicized ICER indicates an extended dominated strategy. ICER of the most effective strategy was calculated excluding extended dominated strategies. Strategies ordered by increasing cost.

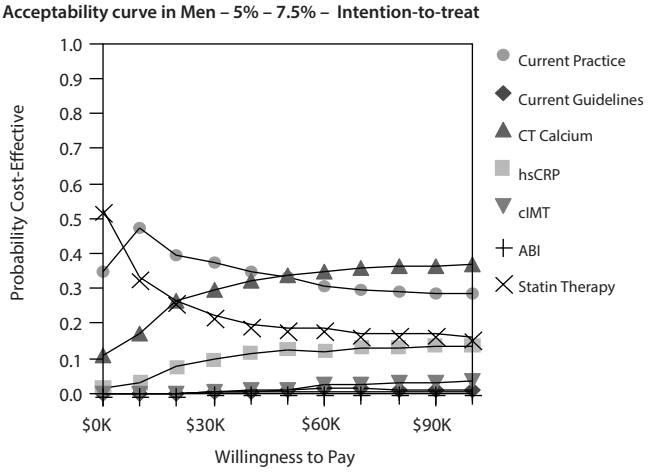
Women							
5% – 7.5%	**ITT**				**AT**		
	QALY	**Cost**	**ICER**		**QALY**	**Cost**	**ICER**
Current practice	14.65 (14.19 – 15.03)	$15,290 ($12,014 – $19,621)		Current practice	14.65 (14.21 – 15.09)	$15,009 ($12,079 – $19,046)	
hsCRP	14.68 (14.28 – 15.07)	$16,264 ($12,954 – $20,383)	$32,467	hsCRP	14.80 (14.39 – 15.23)	$16,330 ($13,769 – $19,583)	***$8,807***
				Statin therapy	14.87 (14.49 – 15.28)	$16,342 ($13,485 – $19,865)	$6,059
2.5-7.5	**ITT**				**AT**		
	QALY	**Cost**	**ICER**		**QALY**	**Cost**	**ICER**
Current practice	15.58 (15.35 – 15.86)	$11,540 ($9,149 – $14,890)		Current practice	15.60 (15.35 – 15.82)	$11,313 ($8,777 – $13,600)	
hsCRP	15.59 (15.36 – 15.87)	$12,556 ($10,137 – $15,568)	$185,091	hsCRP	15.67 (15.33 – 15.88)	$12,735 ($10,538 – $14,943)	***$20,314***
				Statin therapy	15.76 (15.51 – 15.99)	$13,002 ($10,395 – $15,178)	$10,556
5%– 10%	**ITT**				**AT**		
	QALY	**Cost**	**ICER**		**QALY**	**Cost**	**ICER**
Current practice	14.00 (13.65 – 14.34)	$17,029 ($13,173 – $20,926)		Current practice	13.98 (13.64 – 14.33)	$17,096 ($14,301 – $21,255)	
Statin therapy	14.04 (13.69 – 14.38)	$17,870 ($14,249 -$21,336)	***$21,025***	hsCRP	14.15 (13.78 – 14.52)	$18,146 ($15,527 – $22,151)	***$6,176***
hsCRP	14.06 (13.71 – 14.36)	$17,932 ($14,433 – $21,618)	$15,050	Statin therapy	14.25 (13.89 – 14.63)	$18,249 ($15,641 – $22,424)	$4,270

ITT = intention-to-treat, AT = as-treated, ICER = incremental cost effectiveness ratio). Values are average discounted quality adjusted life years (QALY) (95%CI) and average discounted costs (95%CI)

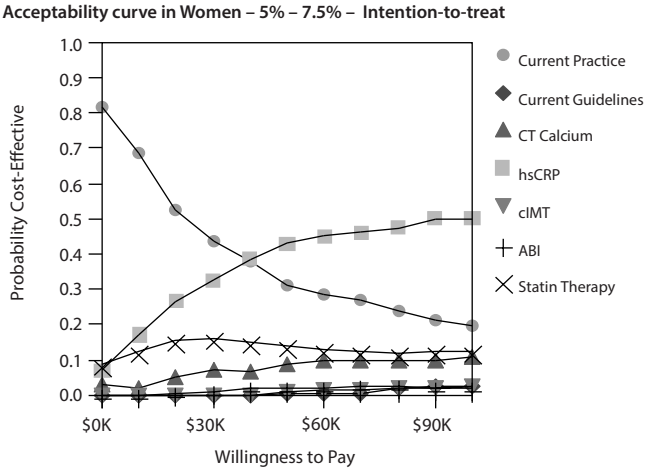
eTable 5. Costs, QALYS and ICERs for all strategies in **men** and **women** at intermediate risk of 5% – 7.5% for the sensitivity analyses. Dominated strategies (both more costly and less effective) were omitted. Italicized ICER indicates an extended dominated strategy. ICER of the most effective strategy was calculated excluding extended dominated strategies. Strategies ordered by increasing cost.

Men	*Generic statin prices*			**Women**	*Generic statin prices*		
5% – 7.5%	**ITT**			**5% – 7.5%**	**ITT**		
	QALY	**Cost**	**ICER**		**QALY**	**Cost**	**ICER**
Statin therapy	16.02	$17,715		Current practice	14.61	$15,140	
Current practice	16.04	$18,171	*$22,800*	Statin therapy	14.63	$15,731	*$29,550*
CT calcium	16.06	$18,222	$12,675	hsCRP	14.66	$15,833	$13,860
Men	*SBP <140*			**Women**	*SBP <140*		
5% – 7.5%	**ITT**			**5% – 7.5%**	**ITT**		
	QALY	**Cost**	**ICER**		**QALY**	**Cost**	**ICER**
Statin therapy	16.01	$17,845		Current practice	14.66	$15,155	
Current practice	16.03	$18,022	$8,850	Statin therapy	14.67	$16,535	*$138,000*
CT calcium	16.04	$18,326	$30,400	hsCRP	14.71	$16,541	$27,720
Men	*SF 0.9*			**Women**	*SF 0.9*		
5% – 7.5%	**ITT**			**5% – 7.5%**	**ITT**		
	QALY	**Cost**	**ICER**		**QALY**	**Cost**	**ICER**
Statin therapy	16.04	$17,942		Current practice	14.65	$15,204	
Current practice	16.05	$18,219	*$27,700*	Statin therapy	14.67	$16,099	*$44,750*
CT calcium	16.08	$18,273	$1,800	hsCRP	14.69	$16,142	$23,450
Men	*SF 1.1*			**Women**	*SF 1.1*		
5% – 7.5%	**ITT**			**5% – 7.5%**	**ITT**		
	QALY	**Cost**	**ICER**		**QALY**	**Cost**	**ICER**
Statin therapy	15.98	$17,721		Current practice	14.68	$15,042	
Current practice	16.01	$17,890	$5,633	hsCRP	14.7	$16,238	$59,800
CT calcium	16.01	$18,343	$162,486				

ITT = intention-to-treat, AT = as-treated, ICER = incremental cost effectiveness ratio). Values are average discounted quality adjusted life years (QALY) (95%CI) and average discounted costs (95%CI)



eFigure 3. Acceptability curve in **men** at intermediate risk of between 5% – 7.5%. Each line corresponds to a strategy and depicts the percentage of all simulations in which a strategy was cost-effective giving all parameter uncertainty in the model, for varying thresholds of willingness to pay values.



eFigure 4. Acceptability curve in **women** at intermediate risk of between 5% – 7.5%. Each line corresponds to a strategy and depicts the percentage of all simulations in which a strategy was cost effective giving all parameter uncertainty in the model, for varying thresholds of willingness to pay values.

REFERENCE

e1. Hofman A, Darwish Murad S, van Duijn CM, Franco OH, Goedegebure A, et al. (2013) The Rotterdam Study: 2014 objectives and design update. Eur J Epidemiol 28: 889-926.

e2. Ferket BS, van Kempen BJ, Hunink MG, Agarwal I, Kavousi M, et al. (2014) Predictive value of updating Framingham risk scores with novel risk markers in the U.S. general population. PLoS One 9: e88312.

e3. Elias-Smale SE, Proenca RV, Koller MT, Kavousi M, van Rooij FJ, et al. (2010) Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J Am Coll Cardiol 56: 1407-1414.

e4. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, et al. (2012) Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med 156: 438-444.

e5. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS (2009) Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation 119: 3078-3084.

e6. Ferket BS, van Kempen BJH, Hunink MGM, Agarwal I, Kavousi M, et al. (2013) Predictive Value of Updating Framingham Risk Scores with Novel Risk Markers in the U.S. General Population

Chapter 10

Comparative effectiveness and Cost-Effectiveness of Statin Therapy for Primary Prevention of Cardiovascular Events: A trade-off between future risk and the disutility of lifelong daily medication

Vinícius Bicalho
Bob van Kempen
Bart S. Ferket
Srishti Gupta
Mohammed Khanji
Steffen E. Petersen
Kirsten E. Fleischmann
Myriam Hunink

Submitted

ABSTRACT

Objective: To assess the comparative effectiveness and cost-effectiveness of statin therapy for the primary prevention of cardiovascular disease in low- and intermediate risk individuals.

Design: Micro-simulation state-transition model to analyze the costs and effectiveness from the societal perspective for the United States. Synthesis of best-available evidence on risks, benefits, patient preferences, and costs. External validation and modeling of parameter uncertainty. Intention-to-treat analysis accounted for non-adherence and disutility of daily medication. As-treated analysis assumed individuals were adherent and disutility of daily medication was zero. Threshold analysis of lowest risk and highest disutility of daily medication at which statin therapy was cost-effective.

Participants: Population-based sample from the National Health and Nutrition Examination Survey, without diabetes mellitus or a prior cardiovascular disease event, not on statin therapy and with a 10-year cardiovascular disease risk (based on the Pooled Cohort Equations) of <2.5% to 20%.

Interventions: Initiating generic moderate-intensity statin therapy for primary prevention vs withholding statin therapy until the development of disease or disease-equivalents or >20% risk.

Main outcomes: Quality-adjusted life years, lifetime costs, incremental cost-effectiveness ratios, probability of cost-effectiveness at a societal willingness-to-pay of $50,000/quality-adjusted life year.

Results: The model produced similar age- and sex-specific life expectancies compared to U.S. life tables, demonstrating external validity. In the intention-to-treat analysis, prescribing statin therapy resulted in fewer quality adjusted life years and higher costs than withholding statin therapy. The as-treated analysis demonstrated that statin therapy was cost-effective for 40 – 44 year-old women at ≥10% risk, 45 – 65 year-old women at ≥7.5% risk, 40 – 59 year-old men at ≥5% risk, and for all women 65 and older and men 60 and older. For individuals at a 5-10% risk, statin therapy is cost-effective only if disutility is less than 25 (1 – 50) days.

Conclusion: Statin therapy for primary prevention of cardiovascular disease in individuals at low- or intermediate risk is effective and cost-effective but only if the individual's disutility of taking daily medication is justified by the gain in effectiveness.

INTRODUCTION

At least half of major cardiovascular disease (CVD) events occur in people without prior CVD, even though many are at low absolute risk [1, 2]. This underscores the value of primary prevention in reducing the CVD burden to society. Statin therapy can substantially reduce CVD events, which makes it a candidate for primary prevention [3, 4]. The 2013 American Heart Association (AHA) and American College of Cardiologists (ACC) guidelines recommend statin therapy for primary prevention if an individual's 10-year risk of a CVD event is 7.5% or higher [4, 5]. The 7.5% threshold is supported by randomized clinical trials (RCTs), which have shown that individuals at low-risk of CVD benefit from preventive statin therapy [6]. Findings from a meta-analysis indicate that a lower threshold may even be appropriate [3].

Although primary prevention with statin therapy can reduce CVD events, such an approach may be associated with non-adherence, adverse events, disutility associated with daily medication, and an impact on healthcare costs [7, 8]. Evidence on the comparative (cost-)effectiveness, especially in the light of reduced medication costs with generic statins, is lacking [9, 10]. This lack of information may restrain the primary care physician from implementing primary prevention with statins in lower risk patients [11].Furthermore, using the 7.5% risk threshold would imply prescribing statin therapy to nearly one half of the 40 – 75 year-old United States population [12]. Critics see such widespread use of statins as over-medicalization.

The aim of this study was to assess the comparative effectiveness and cost-effectiveness of statin therapy for the primary prevention of CVD in asymptomatic U.S. individuals. The purpose was to determine the lowest CVD risk threshold and highest disutility associated with daily medication for which statin therapy is cost-effective. Two questions were addressed: first, whether to prescribe statin therapy, which is the equivalent of an intention-to-treat analysis, and second, whether statin therapy is (cost-) effective if actually taken, which is the equivalent of an as-treated analysis.

METHODS

We developed a micro-simulation state-transition model (eFigure 1) with 1-year cycle length using TreeAge for Health Care (TreeAge Pro 2013 – TreeAge Software Williamstown MA) to analyze the costs and effects of prescribing statin therapy to U.S individuals at 10-year CVD risk lower than 20%. With this model we studied the comparative (cost-)effectiveness of statin therapy in men and women for varying age and CVD risk. The model synthesized the best-available evidence on risks, benefits, patient preferences, and costs and was developed according to published recommendations for such analyses [13, 14]. (A detailed description of the modeling assumptions and input parameters is available in the online-only data supplement.)

The study population consisted of National Health and Nutrition Examination Survey (NHANES) individuals aged 40 to 79 years old (Figure 1), without a history of CVD or diabetes at baseline, with data on CVD risk factors. We extracted individual characteristics and risk factors to represent the heterogeneity of the population (eTable 1).

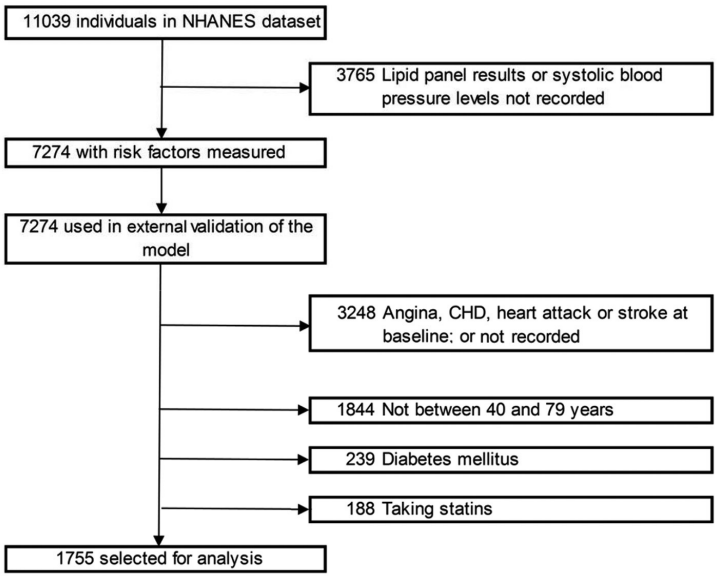


Figure 1. Flowchart showing the selection of the study population based on NHANES 2001-2002 data collection.

Model Structure

Individuals were categorized by age, sex and baseline CVD risk and for each group two strategies were compared:

(1) 'No statin therapy' (reference strategy): withhold statin therapy for primary prevention until the development of CVD or CVD-equivalents or 10-year CVD risk of 20% or higher, consistent with current practice and the Adult Treatment Panel III (ATPIII) guidelines [8].
(2) 'Statin therapy': prescribe generic moderate-intensity statins [4] for primary prevention.

Efficacy of treatment was modelled by reducing the incidence of coronary heart disease (CHD) and stroke events in the statin strategy according to evidence from systematic

reviews and meta-analyses of RCTs [3, 6]. Lifestyle recommendations were assumed to be given to all individuals in both strategies. Individuals who developed a CVD event, diabetes mellitus, other CVD equivalent, or surpassed the threshold risk of 20% during follow-up were prescribed statin therapy. We assumed that statin benefits and costs would cease immediately in the case of therapy withdrawal due to non-adherence or serious side effects (myopathy, asymptomatic elevation of liver enzymes).

For each cycle, the modeled individuals could stay in one of the following mutually exclusive health states: 1) well; 2) post-CHD event; 3) post-stroke event; 4) withdrawal from statins; 5) diabetes; 6) diabetes and post-CVD; and 7) dead (eFigure 1). Every person started the simulation in the "well" state. The transition to the other states could occur once each annual cycle and was determined by age- and sex-specific probabilities. The model simulated the remaining lifetime of the individuals and kept track of costs, quality of life and time spent in each health state.

CVD Event Rates

CVD events were defined as nonfatal myocardial infarction (MI) or CHD death, or fatal or nonfatal stroke to match the endpoint used in the AHA/ACC Pooled Cohort Equations, which were used to estimate the individualized baseline 10-year risk of CVD events [5]. We modeled the annual increase in CVD risk and estimated age-, sex-, and ethnicity-specific annual incidence rates [15]. Using sex-specific proportions, we estimated the annual incidence of CHD vs stroke events and fatal vs nonfatal events (Table 1).

Mortality Rates

We obtained data on mortality from the National Center for Health Statistics [16, 17]. To model competing mortality risks, we derived life tables that provided sex-specific probabilities of dying from all causes eliminating ischemic heart diseases, CVD and diabetes mellitus. The probabilities of dying from an MI or stroke were age-dependent and based on 30-day case-fatality rates [18]. In the years following a nonfatal MI or nonfatal stroke, the all-cause mortality rates were modified with a hazard rate ratio for manifest CVD (Table 1) [19].

Diabetes Natural History

The probability of developing diabetes was estimated based on data from the National Health Interview Survey (NHIS) and reflects the incidence of diagnosed diabetes in the year 2000 (Table 1) [20]. Starting at the time of diagnosis, patients with diabetes experienced increased rates of CHD events, stroke events, and non-CVD mortality [21, 22]. After a nonfatal CVD event, all-cause mortality was increased (Table 1) [23].

Table 1. Model parameters.

Parameter	Base-case value men[a]	Base-case value women[a]	Distribution	Data Source	Ref
Statin Therapy					
Relative Risk for incident CHD events, statin vs placebo[b]	0.73 (0.67 to 0.80)		Lognormal	Meta-analysis	6
Relative Risk for incident stroke events, statin vs placebo[b]	0.78 (0.62 to 0.89)		Lognormal	Meta-analysis	6
Risk of myopathy, per 100,000 person-years[b c]	97			Meta-analysis	29
Risk of high liver enzymes episode, per 100,000 person-years[b c]	110			Meta-analysis	29
Odds Ratio for diabetes mellitus, statin vs placebo[b]	1.18 (1.01 to 1.39)		Lognormal	Meta-analysis	6
Primary adherence to statin therapy[b d g]	60% (50% to 70%)		Triangular	Cohort study	33
Disutility of taking a pill every day, in months traded away[b e]	6 (1 to 36)		Triangular	Survey	7
Natural History Events					
Incident CVD	see text				
Non-CVD mortality	US life tables				17
Proportion of incident CVD events being stroke events	0.23 (0.16 to 0.28)	0.39 (0.26 to 0.47)	Beta	Cohort study	41
30-day fatality rate of MI events[b]				Cohort study	18
<65 years	0.025	-			
65 to 74 years	0.11	-			
75 to 84 years	0.22	-			
>84 years	0.28	-			
30-day fatality rate of Stroke events[b]				Cohort study	18
<65 years	0.13	-			
65 to 74 years	0.11	-			
75 to 84 years	0.16	-			
>84 years	0.32	-			

Table 1. *(Continued)*

Parameter	Base-case value men[a]	Base-case value women[a]	Distribution	Data Source	Ref
Hazard Ratio for mortality after CVD event[b]	1.90 (1.60 to 2.40)	-	Lognormal	Cohort study	19
Risk of developing diabetes mellitus, per 1,000 per year				NHIS	20
45 to 64 years	10.30 (8.65 to 12.25)	9.90 (8.40 to 11.50)	Beta		
65 to 79 years	14.50 (11.10 to 18.25)	9.40 (7.60 to 11.50)	Beta		
Diabetes-specific Events					
Hazard Ratio for non-CVD mortality, diabetic vs nondiabetic	1.35 (0.99 to 1.84)	1.81 (1.17 to 2.78)	Lognormal	Cohort study	21
Hazard Ratio for CHD incidence, diabetic vs nondiabetic	1.89 (1.73 to 2.06)	2.59 (2.29 to 2.93)	Lognormal	Meta-analysis	22
Hazard Ratio for stroke incidence, diabetic vs nondiabetic	2.16 (1.84 to 2.52)	2.83 (2.35 to 3.40)	Lognormal	Meta-analysis	22
Hazard Ratio for mortality among those with CVD, diabetic vs nondiabetic	1.66 (1.35 to 2.04)	2.16 (1.68 to 2.78)	Lognormal	Cohort study	23
Costs, $[f]					
Cost of moderate-intensity statins, per pill[b]	$0.20	($0.11 to $0.44)	Triangular	Retail Prices	eTable 4
Cost of additional physician visit, yearly[b g]	$62.03 ($39.55 to $88.55)	-	Gamma	Fee Schedule	42
Cost of additional lipid panel, yearly[b g]	$17.90 ($11.70 to $25.80)	-	Gamma	Fee Schedule	43
Cost of myopathy episode					
Cost of creatine kinase blood test[b g]	$17.50 ($11.25 to $25.15)	-	Gamma	Fee Schedule	43
Creatine kinase tests per episode[b g]	3 (1 to 5)	-	Discrete	Expert opinion	
Cost of high liver enzymes episode					
Cost of hepatic function panel[b g]	$10.84 ($7.05 to $15.50)	-	Gamma	Fee Schedule	43
Hepatic function panels per episode[b g]	3 (1 to 5)	-	Discrete	Expert opinion	
Annual cost of diabetes mellitus[b g]	$7,206 ($3,603 to $10,809)	-	Gamma	Cost study	28
CHD events				Cost study	25
Initial hospitalization costs[b]	$27,340 [$37,454]	-	Gamma		
Total first-year costs of CHD event[b]	$32,112 [$40,662]	-	Gamma		

Table 1. *(Continued)*

Parameter	Base-case value men[a]	Base-case value women[a]	Distribution	Data Source	Ref
Stroke events				Cost study	44
Initial hospitalization costs[b]	$18,648 [$32,845]	-	Gamma		
First-year follow-up costs[b]	$29,863 [$64,474]	-	Gamma		
Cost of following years after CHD event[b g]	$4400 ($2200 to $6600)	-	Gamma	Cost study	27
Cost of following years after stroke event[b g]	$3963 ($1980 to $5995)	-	Gamma	Cost study	27
Utilities					
Healthy population				Survey	45
45 to 54 years	0.941	0.901			
55 to 64 years	0.874	0.871			
65 to 74 years	0.841	0.833			
75 to 84 years	0.838	0.792			
>84 years	0.817	0.800			
Diabetes	0.782 (0.768 to 0.796)	0.734 (0.723 to 0.746)	Beta	Survey	46
After myocardial infarction	0.754 (0.736 to 0.773)	0.675 (0.652 to 0.698)	Beta	Survey	46
After stroke	0.722 (0.702 to 0.743)	0.670 (0.649 to 0.690)	Beta	Survey	46
Disutility due to MI event	-0.10 (-0.13 to -0.08)	-0.16 (-0.20 to -0.12)	Triangular	Survey	46
Disutility due to stroke event	-0.19 (-0.24 to -0.16)	-0.22 (-0.26 to -0.19)	Triangular	Survey	46
Disutility due to myopathy episode[b]	-0.20 (-0.32 to -0.10)	-	Triangular	Survey	31

CVD stands for atherosclerotic cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction; NHIS, National Health Interview Survey; and US, United States of America. [a] Data in parenthesis are 95% confidence intervals for the beta, gamma and (log)normal distributions and ranges for the triangular, uniform and discrete distributions. Data in brackets are standard deviations for gamma distributions. [b] Risk of events, probabilities, utilities and cost estimates described for men are identical for women. [c] Myopathy was defined as muscle pain, tenderness, or weakness sufficient to consult a physician or to stop taking prescribed tablets. High liver enzymes episode was defined as ALT levels ≥ 3× upper limit of normal (or ≥ 120 U/L) in two consecutive measures. [d] Primary adherence to statins was modeled reducing the benefits and harms of treatment proportionally to the adherence rates. [e] Disutility was implemented in the model dividing the number of months traded away by 522, which is the average life expectancy, in months, of the survey's population (mean age of the respondents was 38 years-old). In patients taking statins, the calculated value was discounted and deducted from each annual cycle`s rewards. [f] All costs are 2013 U.S. dollars. [g] 95% confidence interval or range based on clinical judgment.

Costs

We estimated costs for the model from the U.S. societal perspective (Table 1). All costs were inflated to 2013 U.S. dollars using consumer price indices. Future costs and effectiveness were discounted at a rate of 3% [24]. Retail prices of generic moderate-intensity statins [4] were retrieved from online price lists of pharmacies with nationwide presence in the U.S. (eTable4). We assumed that monitoring of therapy cost one additional physician visit and lipid panel per year and adverse events induced additional physician visits and laboratory costs.

Costs for MI and stroke events included hospitalization-, procedural-, outpatient-, and pharmacy costs [25, 26, 27]. The costs for diabetes were estimated from the average annual cost per case of type 2 diabetes mellitus, which included physician office and emergency visits, ambulance services, hospital outpatient and home health visits, hospital inpatient care, nursing/residential facility care, hospice care, podiatry visits, insulin, oral agents, and diabetic supplies [28].

Statin Therapy

We modeled the effects of moderate-intensity statin therapy using relative risk reductions for CVD events reported in a systematic review and meta-analysis of RCTs comparing statins with usual care or placebo (Table 1) [6]. The increased risk of developing diabetes mellitus, myopathy, and asymptomatic elevation of liver enzymes were also derived from systematic reviews of RCTs (Table 1) [6, 29, 30]. Quality of life penalties of a myopathy episode were based on those for mild osteoarthritis of the hip that does not impair function [15, 31]. We assumed there is no quality of life loss due to the asymptomatic elevation of liver enzymes.

In the intention-to-treat analysis, we accounted for a disutility of daily medication of 6 months (nocebo effect or loss in quality of life associated with taking medication), ranging from 1 to 36 months [7]. In addition, we assumed that 60% (50% to 70%) of patients would be adherent to therapy [32, 33]. With the exception of diabetes, all side-effects were assumed to cause withdrawal from statin therapy. In the as-treated analysis, we modeled 100% adherence and no disutility from daily medication, which assumes that patients experiencing significant disutility from daily medication would be non-adherent and therefore not the target population of the as-treated analysis.

Analysis

To minimize bias, all authors approved the model structure, the data inputs and the validation results, prior to performing the comparative effectiveness and cost-effectiveness analyses. Internal validity of the model was tested by comparing CVD incidence produced by the model to the ACC/AHA Pooled Cohort Equations incidence rates. In addition, competing mortality rates produced by the model were compared to those from life tables. For external validation, we compared calculated age- and sex-specific life expectancies to published U.S. life expectancies [16].

For all analyses, we first selected a subset of the NHANES population based on age, sex, and CVD risk. Only subgroups with documented individuals in NHANES were analyzed. We modeled patient heterogeneity by micro-simulating every individual in the NHANES subgroup. In addition, one thousand samples were taken from the input distributions (Table 1) to model parameter uncertainty. For each set of individuals, we calculated mean quality-adjusted life years (QALYs) and mean lifetime costs and their 95% credibility intervals (95%CI). We calculated incremental cost-effectiveness ratios (ICERs) dividing the mean increase in costs by the additional QALYs gained. A societal threshold willingness-to-pay of $50,000/QALY was considered [34]. Given the parameter uncertainty reflected in the input distributions, we calculated the probability that the statin therapy strategy was cost-effective for each set of individuals [14]. Finally, we determined thresholds for change in utility associated with daily medication as function of CVD risk.

RESULTS

Model Validity

Internal validity of the model was demonstrated by consistent CVD incidence rates and competing mortality rates (eFigures 2-5). More importantly, the model produced similar age- and sex-specific life expectancies compared to U.S. life tables demonstrating external validity (Figure 2).

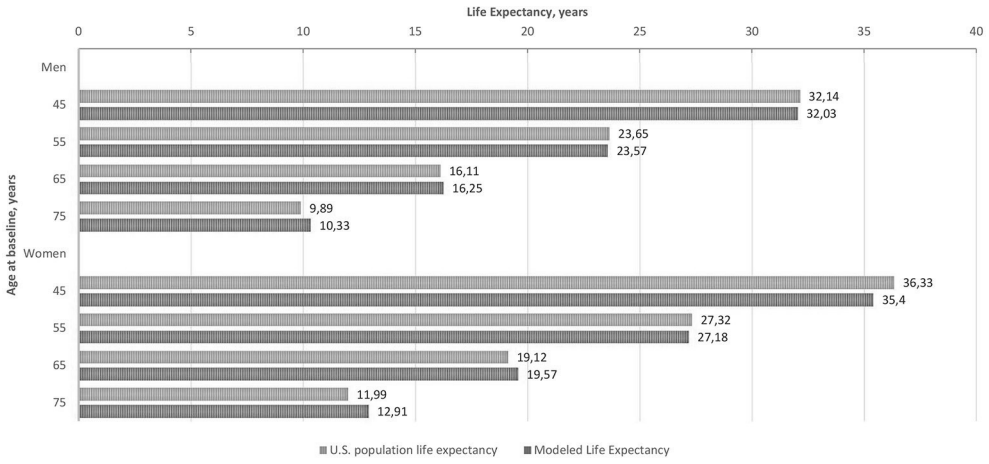


Figure 2. External validation: life expectancy from published U.S. life tables compared to life expectancy as calculated by the model, for men and women aged 45, 55, 65, and 75 years old.

Intention-to-treat analysis

Prescribing statin therapy resulted in lower average quality adjusted life expectancy (QALE) in all subgroups analyzed (Table 2). The reduction of QALE was more pronounced in younger ages and lower risk categories. For all subgroups except one, average lifetime costs were higher for statin therapy which was more pronounced in younger ages and lower risk groups (exception was females 70 – 74 years, risk 15% – 19.9%). The probability of statin therapy being cost-effective ranged from 0.2% (females 40 – 44 years, risk <2.5%) to 47.6% (females 70 – 74 years, risk 15%-19.9%).

As-treated analysis

Statin therapy was cost-effective compared to withholding statins (Table 2) for all women 65 years and older, regardless of their 10-year CVD risk. For 45 – 65 year-old women, statin therapy was cost-effective for those with a risk of 7.5% or higher. In 40 – 44 year-old females, statins were only cost-effective above a 10% risk threshold. In men of all ages with a risk of at least 5% statin therapy was the optimal decision (Table 2), which included the entire male population of 60 years and older. Statins were less effective than no statins for males younger than 55 years old with a predicted 10-year risk lower than 2.5%.

Threshold analysis

The lower the 10-year CVD risk, the lower the disutility associated with daily medication needs to be in order to warrant statin therapy (Figure 3). For individuals at a CVD risk of 15 – 20%, statin therapy is cost-effective if disutility is less than 100 (70 – 300) days. For individuals at a CVD risk of 10 – 15%, disutility needs to be less than 70 (25 – 125) days. For individuals at a CVD risk of 5 – 10%, statin therapy is cost-effective only if disutility is less than 25 (1 – 50) days. For lower risk, statin therapy would need to have a placebo effect (a gain in utility from daily medication) in order to make therapy cost-effective.

DISCUSSION

In this study we analyzed the comparative effectiveness and cost-effectiveness from the societal perspective of prescribing statin therapy to United States individuals at low- and intermediate risk, synthesizing the best-available evidence on risks, benefits, patient preferences, and costs. The intention-to-treat analysis, which addressed the policy-making decision, demonstrated a decrease in QALE for prescribing statins to individuals for primary prevention of CVD, across the full range of risk thresholds analyzed, including the current recommendation of 7.5% or higher [4, 5]. This decrease can be attributed to a modest gain in average life expectancy with statin therapy and a substantial decrease in QALE due to the disutility associated with taking daily medication [7]. In contrast, the as-treated analysis, which addressed the decision for an individual adherent patient with no disutility from daily medication, demonstrated that statin therapy was cost-effective for 40 – 44 year-old women at ≥10% risk, 45 – 65 year-old women at ≥7.5% risk, 40 – 59 year-old men at ≥5% risk, and for all women 65 and older and men 60 and older.

Table 2. Cost-effectiveness of initiating statin therapy in asymptomatic individuals for primary prevention of CVD compared with withholding treatment until a CVD event, CVD equivalent, or 10-year CVD risk of 20% or higher, by sex, age, and risk group. The intention-to-treat analysis addresses whether to prescribe statin therapy taking into account disutility from daily medication and non-adherence. The as-treated analysis addresses whether statin therapy is (cost-) effective if the individual is adherent and has no measurable disutility from daily medication. Only subgroups with documented individuals in NHANES were analyzed.

		Intention-to-treat			As-treated		
Age Group	**Risk Group[a]**	**Incremental QALYs, Mean (95%CI)**	**Incremental Costs, Mean (95%CI), $**	**ICER, $/ QALY[b]**	**Incremental QALYs, Mean (95%CI)**	**Incremental Costs, Mean (95%CI), $**	**ICER, $/ QALY[b]**
Women							
40 – 44							
	<2.5%	-0.33 (-0.67, -0.07)	3147 (1256, 5878)	NA	-0.11 (-0.31, 0.06)	5331 (1996, 9740)	NA
	2.5% to 4.9%	-0.27 (-0.65, 0.06)	2350 (-1044, 6407)	NA	-0.03 (-0.38, 0.27)	4061 (-676, 9947)	NA
	5% to 7.4%	-0.26 (-0.84, 0.44)	2171 (-5561, 11357)	NA	-0.01 (-0.78, 0.79)	4024 (-6281, 16166)	NA
	7.5% to 9.9%	-0.21 (-0.88, 0.44)	1825 (-5805, 10677)	NA	0.04 (-0.75, 0.83)	2995 (-6415, 14425)	71098
	10% to 14.9%	-0.19 (-1.16, 0.97)	1631 (-10288, 16086)	NA	0.08 (-1.13, 1.32)	2509 (-12634, 19626)	30834
45 – 49							
	<2.5%	-0.29 (-0.6, -0.06)	2719 (875, 5260)	NA	-0.08 (-0.26, 0.08)	4483 (1288, 8605)	NA
	2.5% to 4.9%	-0.24 (-0.56, 0.05)	2054 (-740, 5765)	NA	-0.02 (-0.35, 0.27)	3471 (-661, 9044)	NA
	5% to 7.4%	-0.21 (-0.59, 0.16)	1784 (-2266, 7061)	NA	0 (-0.45, 0.41)	3009 (-2442, 9680)	1729372
	7.5% to 9.9%	-0.16 (-0.58, 0.24)	1339 (-3458, 6951)	NA	0.06 (-0.41, 0.53)	2347 (-3824, 9923)	39321
	10% to 14.9%	-0.09 (-0.61, 0.52)	801 (-6379, 8118)	NA	0.04 (-0.57, 0.72)	1113 (-6742, 10346)	30792
50 – 54							
	<2.5%	-0.26 (-0.54, -0.04)	2234 (631, 4271)	NA	-0.05 (-0.23, 0.09)	3755 (1243, 7348)	NA
	2.5% to 4.9%	-0.20 (-0.47, 0.02)	1749 (-507, 4451)	NA	-0.01 (-0.23, 0.17)	3009 (-39, 7070)	NA
	5% to 7.4%	-0.18 (-0.50, 0.11)	1481 (-1431, 4768)	NA	0 (-0.31, 0.29)	2479 (-1634, 7544)	583384
	7.5% to 9.9%	-0.16 (-0.59, 0.28)	1337 (-3935, 7253)	NA	0.05 (-0.44, 0.56)	2178 (-4895, 8690)	40969
	10% to 14.9%	-0.11 (-0.66, 0.60)	767 (-7194, 8172)	NA	0.07 (-0.59, 0.80)	1566 (-8247, 11393)	23315

Table 2. *(Continued)*

Age Group	Risk Group[a]	Intention-to-treat			As-treated		
		Incremental QALYs, Mean (95%CI)	Incremental Costs, Mean (95%CI), $	ICER, $/QALY[b]	Incremental QALYs, Mean (95%CI)	Incremental Costs, Mean (95%CI), $	ICER, $/QALY[b]
Women							
55 – 59							
	<2.5%	-0.21 (-0.50, 0.02)	1763 (-248, 4291)	NA	-0.02 (-0.24, 0.18)	3079 (471, 6517)	NA
	2.5% to 4.9%	-0.18 (-0.43, 0.02)	1480 (-264, 3678)	NA	0 (-0.19, 0.17)	2447 (-93, 5631)	NA
	5% to 7.4%	-0.15 (-0.41, 0.10)	1257 (-1422, 4127)	NA	0.02 (-0.25, 0.29)	2052 (-1717, 5626)	106730
	7.5% to 9.9%	-0.14 (-0.93, 0.74)	1170 (-7474, 11528)	NA	0.04 (-0.98, 1.09)	1833 (-10094, 15148)	44129
	10% to 14.9%	-0.09 (-0.49, 0.33)	629 (-4382, 5820)	NA	0.06 (-0.43, 0.64)	1046 (-5731, 7619)	18582
60 – 64							
	<2.5%	-0.19 (-0.65, 0.25)	1521 (-3592, 7344)	NA	0.01 (-0.56, 0.57)	2587 (-3137, 9314)	180385
	2.5% to 4.9%	-0.15 (-0.36, 0.02)	1201 (-382, 2752)	NA	0.02 (-0.15, 0.18)	1965 (-332, 4302)	93800
	5% to 7.4%	-0.14 (-0.33, 0.02)	1070 (-310, 2460)	NA	0.03 (-0.10, 0.15)	1736 (-644, 3994)	56912
	7.5% to 9.9%	-0.10 (-0.31, 0.10)	761 (-1329, 3001)	NA	0.05 (-0.17, 0.26)	1070 (-2204, 3997)	23636
	10% to 14.9%	-0.06 (-0.24, 0.11)	474 (-1438, 2221)	NA	0.06 (-0.13, 0.25)	776 (-2108, 3103)	13419
	15% to 19.9%	-0.02 (-0.31, 0.43)	177 (-4404, 5300)	NA	0.02 (-0.41, 0.53)	356 (-5372, 6719)	20324
65 – 69							
	2.5% to 4.9%	-0.11 (-0.54, 0.34)	803 (-3605, 4936)	NA	0.04 (-0.49, 0.57)	1611 (-3854, 7548)	39381
	5% to 7.4%	-0.09 (-0.28, 0.11)	692 (-1383, 2597)	NA	0.06 (-0.15, 0.26)	1085 (-2017, 3709)	19086
	7.5% to 9.9%	-0.06 (-0.26, 0.13)	416 (-1990, 2307)	NA	0.08 (-0.11, 0.29)	645 (-2623, 3172)	7651
	10% to 14.9%	-0.03 (-0.16, 0.10)	190 (-1564, 1441)	NA	0.07 (-0.07, 0.24)	290 (-1828, 1911)	4017
	15% to 19.9%	-0.02 (-0.15, 0.15)	101 (-1858, 1633)	NA	0.03 (-0.12, 0.24)	203 (-2105, 2335)	6173

Table 2. *(Continued)*

Age Group	Risk Group[a]	Intention-to-treat			As-treated		
		Incremental QALYs, Mean (95%CI)	Incremental Costs, Mean (95%CI), $	ICER, $/ QALY[b]	Incremental QALYs, Mean (95%CI)	Incremental Costs, Mean (95%CI), $	ICER, $/ QALY[b]
Women							
70 – 74							
	7.5% to 9.9%	-0.06 (-0.31, 0.20)	463 (-2134, 2842)	NA	0.07 (-0.17, 0.37)	734 (-2935, 3729)	9875
	10% to 14.9%	-0.02 (-0.15, 0.11)	142 (-1695, 1479)	NA	0.07 (-0.08, 0.25)	179 (-2483, 1934)	2507
	15% to 19.9%	-0.01 (-0.08, 0.10)	-37 (-1292, 895)	NA	0.05 (-0.06, 0.18)	-65 (-1807, 1121)	NA
75 – 79							
	10% to 14.9%	-0.04 (-0.49, 0.56)	78 (-6000, 4312)	NA	0.20 (-0.39, 1.02)	233 (-7845, 5710)	1191
	15% to 19.9%	-0.04 (-0.33, 0.27)	37 (-3675, 1850)	NA	0.04 (-0.11, 0.24)	-97 (-2287, 1392)	NA
Men							
40 – 44							
	<2.5%	-0.26 (-0.57, -0.03)	2740 (702, 5923)	NA	-0.03 (-0.21, 0.12)	4548 (1348, 9348)	NA
	2.5% to 4.9%	-0.22 (-0.51, 0.02)	2262 (-51, 5366)	NA	0.03 (-0.18, 0.20)	3643 (-272, 8176)	104170
	5% to 7.4%	-0.17 (-0.44, 0.09)	1608 (-1556, 5166)	NA	0.07 (-0.17, 0.29)	2765 (-1493, 7607)	37873
	7.5% to 9.9%	-0.13 (-0.51, 0.29)	1173 (-4203, 6986)	NA	0.08 (-0.36, 0.56)	1809 (-4738, 9375)	22239
	10% to 14.9%	-0.08 (-0.36, 0.25)	666 (-3512, 4930)	NA	0.10 (-0.26, 0.50)	1137 (-5147, 7077)	11750
45 – 49							
	<2.5%	-0.25 (-0.57, 0)	2452 (85, 5408)	NA	-0.01 (-0.22, 0.19)	3964 (466, 8322)	NA
	2.5% to 4.9%	-0.2 (-0.47, 0.02)	2078 (-36, 4760)	NA	0.02 (-0.15, 0.18)	3417 (135, 7428)	149943
	5% to 7.4%	-0.16 (-0.42, 0.07)	1545 (-1110, 4451)	NA	0.06 (-0.15, 0.26)	2556 (-1192, 6781)	42186
	7.5% to 9.9%	-0.13 (-0.37, 0.08)	1147 (-1397, 3886)	NA	0.09 (-0.13, 0.32)	1888 (-2242, 5726)	20147
	10% to 14.9%	-0.07 (-0.33, 0.18)	634 (-2572, 4190)	NA	0.09 (-0.17, 0.36)	886 (-3913, 5073)	9582
	15% to 19.9%	-0.01 (-0.29, 0.49)	39 (-5519, 5283)	NA	0.04 (-0.39, 0.63)	124 (-7143, 7445)	2938

Table 2. *(Continued)*

Age Group	Risk Group[a]	Intention-to-treat			As-treated		
		Incremental QALYs, Mean (95%CI)	Incremental Costs, Mean (95%CI), $	ICER, $/QALY[b]	Incremental QALYs, Mean (95%CI)	Incremental Costs, Mean (95%CI), $	ICER, $/QALY[b]
Men							
50 – 54							
	<2.5%	-0.23 (-0.58, 0.11)	2273 (-1255, 6847)	NA	-0.01 (-0.40, 0.39)	3553 (-1659, 9857)	NA
	2.5% to 4.9%	-0.18 (-0.44, 0.02)	1850 (-83, 4159)	NA	0.02 (-0.15, 0.19)	3040 (-43, 6593)	126650
	5% to 7.4%	-0.15 (-0.40, 0.05)	1476 (-655, 4026)	NA	0.05 (-0.13, 0.22)	2439 (-460, 5657)	46361
	7.5% to 9.9%	-0.12 (-0.35, 0.10)	1088 (-1432, 3756)	NA	0.07 (-0.16, 0.28)	1787 (-1964, 5392)	25598
	10% to 14.9%	-0.07 (-0.29, 0.17)	627 (-2048, 3462)	NA	0.10 (-0.13, 0.37)	1065 (-3037, 4976)	11066
	15% to 19.9%	-0.03 (-0.13, 0.07)	219 (-1160, 1449)	NA	0.07 (-0.28, 0.44)	341 (-4983, 5362)	5175
55 – 59							
	2.5% to 4.9%	-0.17 (-0.48, 0.14)	1675 (-1675, 5861)	NA	0.02 (-0.32, 0.36)	2515 (-2287, 7849)	129192
	5% to 7.4%	-0.14 (-0.38, 0.07)	1315 (-1008, 4075)	NA	0.05 (-0.16, 0.24)	2075 (-1239, 5623)	40555
	7.5% to 9.9%	-0.11 (-0.33, 0.11)	1013 (-1630, 3791)	NA	0.07 (-0.16, 0.30)	1580 (-2191, 4923)	22527
	10% to 14.9%	-0.07 (-0.25, 0.10)	590 (-1444, 2504)	NA	0.08 (-0.09, 0.25)	967 (-2065, 3776)	12485
	15% to 19.9%	-0.03 (-0.24, 0.18)	224 (-2274, 2564)	NA	0.06 (-0.17, 0.33)	298 (-3301, 3449)	4789
60 – 64							
	5% to 7.4%	-0.12 (-0.49, 0.30)	1038 (-3645, 5894)	NA	0.04 (-0.42, 0.56)	1811 (-4654, 9108)	42045
	7.5% to 9.9%	-0.10 (-0.35, 0.14)	931 (-1733, 3385)	NA	0.06 (-0.20, 0.29)	1551 (-1907, 4915)	26652
	10% to 14.9%	-0.06 (-0.21, 0.09)	646 (-1152, 2457)	NA	0.05 (-0.11, 0.21)	1090 (-1388, 3373)	20748
	15% to 19.9%	-0.02 (-0.12, 0.09)	172 (-1185, 1411)	NA	0.04 (-0.07, 0.17)	280 (-1619, 2012)	6867

Table 2. *(Continued)*

Age Group	Risk Group[a]	Intention-to-treat			As-treated		
		Incremental QALYs, Mean (95%CI)	Incremental Costs, Mean (95%CI), $	ICER, $/ QALY[b]	Incremental QALYs, Mean (95%CI)	Incremental Costs, Mean (95%CI), $	ICER, $/ QALY[b]
Men							
65 – 69							
	10% to 14.9%	-0.05 (-0.22, 0.12)	532 (-1493, 2484)	NA	0.07 (-0.10, 0.24)	928 (-2081, 3199)	13173
	15% to 19.9%	-0.01 (-0.11, 0.09)	200 (-1108, 1632)	NA	0.03 (-0.08, 0.16)	302 (-1652, 2062)	10163
70 – 74							
	10% to 14.9%	-0.05 (-0.31, 0.23)	406 (-2585, 3098)	NA	0.11 (-0.17, 0.45)	607 (-3372, 4126)	5532
	15% to 19.9%	-0.01 (-0.10, 0.13)	40 (-1367, 1128)	NA	0.04 (-0.10, 0.19)	93 (-1650, 1602)	2502
75 – 79							
	10% to 14.9%	-0.07 (-0.44, 0.38)	321 (-4350, 3735)	NA	0.12 (-0.27, 0.61)	601 (-4624, 4149)	5050
	15% to 19.9%	-0.01 (-0.28, 0.41)	75 (-4009, 3268)	NA	0.08 (-0.28, 0.55)	305 (-4308, 4457)	4031

Statin therapy is not effective.
Statin therapy is effective but not cost – effective at a WTP of $50,000/QALY.
Statin therapy is cost – effective.
CI stands for credibility interval; ICER, incremental cost – effectiveness ratio; QALY, quality – adjusted life years; NA, not applicable; and WTP, willingness – to – pay.
[a] Patients were classified in risk groups according to the baseline Pooled Cohort Equations 10 – y risk of atherosclerotic cardiovascular events.
[b] ICER is not calculated when the treatment strategy is less effective or less costly than the reference strategy.

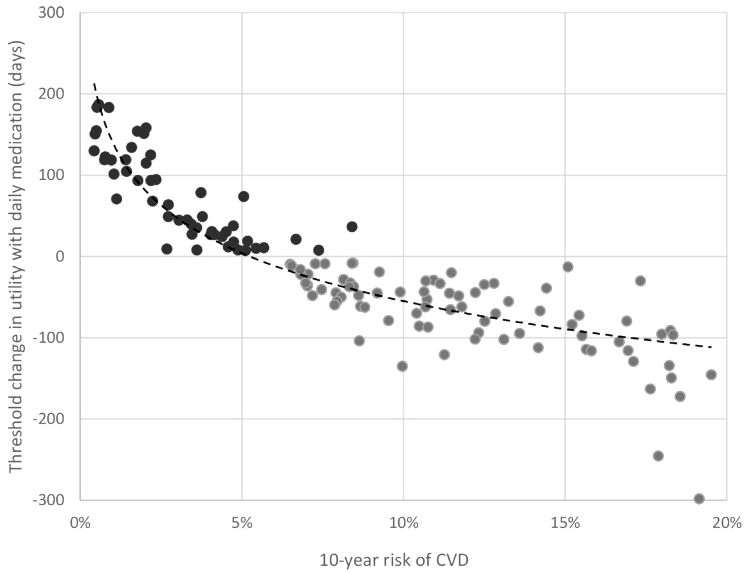


Figure 3. Threshold analysis of change in utility associated with daily medication (expressed in days) vs 10-year risk of CVD. The absolute values of negative thresholds (blue dots) indicate the maximum nocebo effect (maximum disutility / loss in utility) that would make statin therapy cost-effective. Positive threshold values (red dots) indicate the minimum placebo effect (minimum gain in utility) that would make statin therapy cost-effective. Note that placebo effects are unlikely in the context of primary prevention.

Furthermore, we demonstrated that the decision to advise an asymptomatic individual to take statins depends highly on his or her individual preferences with regard to taking daily medication.

The modest gain in QALYs that we found with statin therapy for primary prevention was comparable with that found in previous comparative effectiveness and cost-effectiveness analyses [8, 15, 35, 36]. Previous analyses modelled the ATP III guidelines [8], focused on primary prevention of CHD only rather than CVD [35] analyzed statin therapy in patients with chronic kidney disease [15], analyzed effectiveness only [36], or used high drug prices based on patented statins [37]. In contrast, our analysis modelled the recently published and highly debated ACC/AHA guideline using the Pooled Cohort Equations for CVD risk [4,5], modelled both MI and stroke, analyzed both costs and effectiveness, and used generic statin prices. Irrespective of the differences in the models, they all showed modest gains in QALYs, a finding inherent to primary prevention which reflects the fact that many individuals need to be subjected to the preventive intervention in order to avoid events in a few individuals.

From a policy-makers perspective, prescribing statin therapy in low- and intermediate risk individuals does more harm than good and costs money. For the individual, the decision depends on the trade-off between future risk versus the disutility from daily medication. Disutility from medical therapy is in part due to symptomatic side-effects and in part due to the act of having to take pills every day. Symptomatic side effects due to statin therapy are infrequent and only a small minority of symptoms attributed to statin therapy are genuinely side effects of statins [6, 29, 30]. In particular, muscle weakness and muscle aches are frequently attributed to statin therapy but occur just as frequently with placebos and may therefore be considered a nocebo effect [30]. We modelled genuine side effects of statins by assuming that patients would stop taking their medication and found that the average loss in QALY's is very small. The disutility associated with taking daily medication, however, can be substantial when considering that all individuals may experience some disutility, which includes nocebo effects, and is lifelong [7]. The disutility of daily medication was a decisive factor in determining whether statin therapy was effective and cost-effective. In individuals with very low risk, a placebo effect would even be required in order to make statin therapy cost-effective, which is unlikely in the context of primary prevention. Disutility of daily medication reflects an individual's preference: patients may experience the act of taking a pill every day as disconcerting. It is a small act that is required lifelong on a daily basis in order to reduce a future risk of an event that is uncertain to happen. This small act can influence experienced quality of life through psychological mechanisms that are poorly understood. Most important, our results underscore the importance of taking individual patient preferences into account by means of shared decision making prior to advising patients to start statin therapy [4,7].

Limitations

Our results need to be interpreted in the light of the limitations caused by the required modeling assumptions and imperfect available evidence. First, the ACC/AHA Pooled Cohort Equations that we used to model CVD incidence have been criticized for overestimating the risk of CVD [38]. Nevertheless, we found that calculated life expectancies matched closely with those published, demonstrating external validity. Second, we assumed that treatment adherence is independent of an individual's disutility of taking daily medication. In reality individuals who remain adherent are probably less affected by taking daily pills. To account for this we chose to use the reported median value (rather than the mean) and omitted extremely high disutility values since patients with extremely high disutilities are not the target population. Third, the disutility values were taken from a UK population sample: US individuals may be more willing to take medication for primary prevention.

Fourth, we assumed that all simulated patients who effectively took statins would benefit equally in relative terms from the treatment, justified by studies suggesting this is a reasonable assumption [3]. Fifth, we modeled the effects of type 2 diabetes mellitus (DM2) by increasing the rates of cardiovascular events and non-cardiovascular mortality, independent of modifiable risk factors [22]. We assumed that the diabetes-

effect is nonreversible and constant over time whereas in reality the risk starts low and increases over time [39]. Nevertheless, given the low frequency of statin-induced diabetes, this is unlikely to have a major effect on our results. Sixth, we modeled myopathy episodes in people taking statins because muscle pain was cited as primary reason for discontinuation by 60% of former statin users [30, 40]. Even if myopathy is not caused by statin therapy, its occurrence still lowers adherence rates of treatment, especially in the primary prevention setting, and thus we considered it prudent to model this effect.

Clinical implications

The widely publicized concerns about over-medicalization and the associated costs of statin therapy motivated us to perform this analysis. Our results imply that the current recommendation for statin therapy in individuals at 7.5% risk or higher is cost-effective in women 45 and older and men 40 and older but only if the disutility of daily medication is negligible and patients adhere to therapy. In fact, the results suggest that the threshold in men can even be reduced to 5% if the patient has zero disutility from medical therapy. Taking the disutility of daily medication into account can, however, potentially change the optimal decision for many patients. Our findings demonstrate that the trade-off between future CVD risk and the individual disutility of daily medication is decisive in the choice whether to advise a patient to initiate statin therapy or not. Shared decision making with elicitation of patient preferences is indispensable in this context.

REFERENCES

1. World Health Organization. The global burden of disease : 2004 update. Geneva, Switzerland: World Health Organization; 2008.
2. Kerr AJ, Broad J, Wells S, Riddell T, Jackson R. Should the first priority in cardiovascular risk management be those with prior cardiovascular disease? Heart. Feb 2009;95(2):125-129.
3. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. Aug 11 2012;380(9841):581-590.
4. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. Nov 7 2013.
5. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. Nov 12 2013.
6. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;1:CD004816.
7. Fontana M, Asaria P, Moraldo M, et al. Patient-Accessible Tool for Shared Decision Making in Cardiovascular Primary Prevention: Balancing Longevity Benefits Against Medication Disutility. Circulation. April 17, 2014 2014.
8. Pletcher MJ, Lazar L, Bibbins-Domingo K, et al. Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Annals of internal medicine. Feb 17 2009;150(4):243-254.
9. Krumholz HM. The new cholesterol and blood pressure guidelines: perspective on the path forward. JAMA. Apr 9 2014;311(14):1403-1405.
10. Ioannidis JP. Guidelines for cardiovascular risk assessment and cholesterol treatment--reply. JAMA. Jun 4 2014;311(21):2235-2236.
11. Schulte JM, Rothaus CS, Adler JN. Starting Statins — Polling Results. New England Journal of Medicine. 2014;371(4):e6.
12. Pencina MJ, Navar-Boggan AM, D'Agostino RB, et al. Application of New Cholesterol Guidelines to a Population-Based Sample. New England Journal of Medicine. 2014;0(0):null.
13. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. Oxford University Press, USA; 1996.
14. Hunink MG, Weinstein MC, et.al. Decision making in health and medicine: integrating evidence and values. 2nd ed. Cambridge, UK: Cambridge University Press; 2014.
15. Erickson KF, Japa S, Owens DK, Chertow GM, Garber AM, Goldhaber-Fiebert JD. Cost-effectiveness of statins for primary cardiovascular prevention in chronic kidney disease. Journal of the American College of Cardiology. Mar 26 2013;61(12):1250-1258.
16. Arias E, Curtin LR, Wei R, Anderson RN. United States decennial life tables for 1999–2001, United States life tables. National Vital Statistics Reports. Vol 57 no 1. Hyattsville, MD: National Center for Health Statistics. 2008.
17. Arias E, Heron M, Tejada-Vera B. United States life tables eliminating certain causes of death, 1999–2001. National vital statistics reports; vol 61 no 9. Vol 61. Hyattsville, MD: National Center for Health Statistics; 2013.
18. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). The Lancet. 2005;366(9499):1773-1783.
19. Hooi JD, Kester AD, Stoffers HE, Rinkens PE, Knottnerus JA, van Ree JW. Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. J Clin Epidemiol. Mar 2004;57(3):294-300.

20. Centers for Disease Control and Prevention (CDC). Crude Incidence of Diagnosed Diabetes per 1,000 Population Aged 18–79 Years, by Sex and Age, United States, 1997–2011. http://www.cdc.gov/diabetes/statistics/incidence/fig5.htm. Accessed May 14, 2014.

21. Preis SR, Hwang S-J, Coady S, et al. Trends in All-Cause and Cardiovascular Disease Mortality Among Women and Men With and Without Diabetes Mellitus in the Framingham Heart Study, 1950 to 2005. Circulation. April 7, 2009 2009;119(13):1728-1735.

22. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. Jun 26 2010;375(9733):2215-2222.

23. Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W. Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. Archives of Internal Medicine. 2007;167(11):1145-1151.

24. Gravelle H, Brouwer W, Niessen L, Postma M, Rutten F. Discounting in economic evaluations: stepping forward towards optimal decision rules. Health Econ. Mar 2007;16(3):307-317.

25. Menzin J, Wygant G, Hauch O, Jackel J, Friedman M. One-year costs of ischemic heart disease among patients with acute coronary syndromes: findings from a multi-employer claims database. Curr Med Res Opin. Feb 2008;24(2):461-468.

26. Engel-Nitz NM, Sander SD, Harley C, Rey GG, Shah H. Costs and outcomes of noncardioembolic ischemic stroke in a managed care population. Vasc Health Risk Manag. 2010;6:905-913.

27. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. American Heart Journal. 2001;141(5):727-734.

28. Dall TM, Zhang Y, Chen YJ, Quick WW, Yang WG, Fogli J. The Economic Burden Of Diabetes. Health Affairs. February 1, 2010 2010;29(2):297-303.

29. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. Apr 17 2006;97(8A):52C-60C.

30. Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. European journal of preventive cardiology. 2014;21(4):464-474.

31. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. Medical Care. Jun 2000;38(6):583-637.

32. Gagne JJ, Choudhry NK, Kesselheim AS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. Annals of internal medicine. Sep 16 2014;161(6):400-407.

33. Tamblyn R, Eguale T, Huang A, Winslade N, Doran P. The Incidence and Determinants of Primary Nonadherence With Prescribed Medication in Primary CareA Cohort StudyPrimary Nonadherence With Prescribed Medication in Primary Care. Annals of internal medicine. 2014;160(7):441-450.

34. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. The New England journal of medicine. Aug 28 2014;371(9):796-797.

35. Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation. Jul 12 2011;124(2):146-153.

36. Ferket BS, van Kempen BJ, Heeringa J, et al. Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study. PLoS medicine. 2012;9(12):e1001361.

37. Mitchell AP, Simpson RJ. Statin cost effectiveness in primary prevention: a systematic review of the recent cost-effectiveness literature in the United States. BMC research notes. 2012;5:373.

38. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. Lancet. Nov 30 2013;382(9907):1762-1765.

39. Sattar N. Revisiting the links between glycaemia, diabetes and cardiovascular disease. Diabetologia. Apr 2013;56(4):686-695.

40. Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. Predictors of statin adherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education. Journal of clinical lipidology. Sep-Oct 2013;7(5):472-483.

41. Pencina MJ, D'Agostino RB, Larson MG, Massaro JM, Vasan RS. Predicting the 30-Year Risk of Cardiovascular Disease: The Framingham Heart Study. Circulation. June 23, 2009 2009;119(24):3078-3084.

42. Centers for Medicare & Medicaid Services. Physician Fee Schedule. 2013; http://www.cms.gov/apps/physician-fee-schedule/overview.aspx. Accessed May 13, 2014.

43. Centers for Medicare & Medicaid Services. Clinical Laboratory Fee Schedule. 2013; http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/index.html. Accessed May 13, 2014.

44. Earnshaw SR, Scheiman J, Fendrick AM, McDade C, Pignone M. Cost-utility of aspirin and proton pump inhibitors for primary prevention. Arch Intern Med. Feb 14 2011;171(3):218-225.

45. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Medical decision making : an international journal of the Society for Medical Decision Making. Apr-Jun 1993;13(2):89-102.

46. Nyman JA, Barleen NA, Dowd BE, Russell DW, Coons SJ, Sullivan PW. Quality-of-life weights for the US population: self-reported health status and priority health conditions, by demographic characteristics. Med Care. Jul 2007;45(7):618-628.

SUPPLEMENT

Study Population

We selected our study population based on individuals from the National Health and Nutrition Examination Survey (NHANES) using the 2001-2002 data collection. To address our research questions we selected patients in the age range of 40 to 79 years, without a diagnosis of diabetes mellitus, without known cardiovascular disease and who were not taking statins at the time of the interview (see Figure 1 of the main paper). There were a total of 1755 eligible patients, which formed our study population. The baseline characteristics of the selected sample are described in eTable 1.

Cardiovascular Event Rates

We estimated the cardiovascular events incidence using the AHA/ACC Pooled Cohort Equations. These sex- and ethnic-specific equations were applied to all individuals in the NHANES sample. The Pooled Cohort Equations developed for Whites were applied to NHANES individuals classified as Mexican American, Multi-Racial or Other Hispanic, following the recommendation of the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [(1)].

We estimated an annual increase on modifiable risk factors based on least-squares linear regressions performed with the 2001 – 2002 NHANES data. We assumed all patients experienced a yearly increase of 0.78 mg/dL in the total cholesterol levels, 0.36 mg/dL in the HDL-cholesterol levels and of 0.55 mmHg in the systolic blood pressure levels. For all patients, we estimated the 10-year risk of an atherosclerotic cardiovascular disease (CVD) event using the Pooled Cohort Equations. The equations were used to estimate the risk at baseline and at each following year until all patients turned 79 years old.

To transform the calculated 10-year risks into annual rates, we used a solver function. As the model runs on 1-year cycles, we used a solver function to estimate the individual's age-specific annual incidence rates of CVD events allowing them to increase by year. This resulted in smoothed annual incidence rates of CVD for each individual that increased with advancing age. The rates were expressed as [(2)]:

$$Rate\ of\ ASCVD_{Age} = \alpha \times e^{\beta \times (Age)}$$

For each patient, the solver function calculated the best-fitting Alpha and Beta to minimize the difference between the Pooled Cohort 10-year probability and the 10-year probability resultant from the rate equation. In this way, each patient entered the model with a fixed Alpha and Beta that determined the annual increasing incidence rates of CVD events until age 89. After this age, we used a constant rate extrapolating from age 89. The results from the solver function were compared to the 10-year risk from the Pooled Cohort Equations for selected patients (see eFigure 2, eFigure 3, eFigure 4 and eFigure 5). For this comparison, we assumed that individuals would have their CVD risk assessed every 10 years (or when they turn 79 years). We also assumed that the

incidence rates from the Pooled Cohort Equations would be constant in the intervals between risk assessments.

Competing Mortality Rates

To model competing mortality, we derived the probability of dying of causes not related to ischemic heart diseases, cerebrovascular diseases and diabetes mellitus from published life tables [3,4]. To select the excluding deaths we used the codes I20 to I25, I60 to I69 and E10 to E14, according to the 10th revision of the International Classification of Diseases. We had data on the number of deaths in 5-year age intervals, which provided us 5-year probabilities of death (see eTable 2 and eTable 3). To create a smoother increase of the mortality rates over the years we applied the same solver function used to estimate the increase of cardiovascular risk. We defined the mortality rates as:

$$Competing\ Mortality\ Rate_{Age} = \alpha \times e^{\beta \times (Age)}$$

Subsequently, we programmed the solver function to estimate the Alpha and Beta values that provided the minimal difference between the 5-year probability of death from the life table and the 5-year probability of death from the newly calculated mortality rates. The constant rates from the 5-year probabilities and the estimated annual rates from the solver function are plotted in eFigure 6 and eFigure 7.

Validation

We compared the life expectancies resultant from the model to published life expectancies of the U.S. population [4]. For this comparison, we used the same NHANES individuals as in the analysis. In order to make the sample comparable to the target values, which were from the whole U.S. population, this comparison was performed without exclusion of diabetic patients and patients with previous cardiovascular disease. We retrieved the prevalence of diabetes mellitus in the year 2000 from the Centers for Disease Control and Prevention (CDC) and this value represented the percentage of individuals that started the model in the diabetes state [5]. A probabilistic sensitivity analysis was run with 10000 samples (outer loop) for each group of patients with the same age at baseline (inner loop). The life expectancies resultant from the analysis are shown in the main paper (Figure 3).

Costs

We estimated costs for the model from the societal perspective for the U.S (see manuscript Table 1). All costs were inflated to 2013 U.S. dollars using consumer price indices. To include time preference in the model, we discounted future costs and effectiveness at a rate of 3% [6].

The costs of an MI event were averaged from the index-hospitalization costs of patients with acute coronary syndrome. For surviving patients, costs for the first year after an MI included inpatient, outpatient and pharmacy costs [7]. Stroke event costs were based on hospitalization costs for a first ischemic stroke in a managed care population. Costs

for the first year were allocated to nonfatal stroke events and represented medical and pharmacy costs [8]. The costs for the subsequent years after a nonfatal MI and after a nonfatal stroke were estimated from actual resource utilization of patients in a six-year clinical trial [9]. We assumed that the costs would accrue for the remaining lifetime of the patients.

The costs after a diabetes diagnosis were estimated from the average annual cost per case of type 2 diabetes mellitus, which included physician office and emergency visits, ambulance services, hospital outpatient and home health visits, hospital inpatient care, nursing/residential facility care, hospice care, podiatry visits, insulin, oral agents, and diabetic supplies [10].

Statin Drug Prices

We performed an online search on websites of U.S. pharmacies to estimate current retail prices of commonly prescribed statins (see eTable 4). We restricted our search to drug retailers with nationwide presence. Most of the retailers offered free delivery to any address in the United States. In these cases, we assumed that the costs related to filling a prescription would be solely the costs of the medication itself. Some grocers charge an annual subscription fee for their discount program. This cost was taken into account in the price per pill, which was calculated using the prices corresponding to a 3-month supply.

For the model, we assumed that patients would be prescribed a generic moderate-intensity statin. The prices for this drug class ranged from $0.11 to $0.45 per pill in our results from the web search. The 2014 prices were deflated to represent 2013 U.S. dollars. We created a distribution for Probabilistic Sensitivity Analysis (PSA) to take into account the differences in prices found.

Sensitivity Analysis for Disutility of Taking Daily Medication

To study the impact of varying disutility related to taking a pill daily, we ran a sensitivity analysis for selected individuals of the NHANES sample. We selected 145 low- and intermediate risk individuals with different risk factors and, for each of them, determined from which value of disutility statin therapy would start to be cost-effective at a willingness-to-pay of $50,000/QALY. Other model parameters were the same as used in the intention-to-treat analysis (Table 1 of the main paper). For 58 individuals, statin therapy was not cost-effective irrespective of the value of disutility. For the remaining 87, disutility thresholds ranging from 0 to 297 days of life traded away would change the optimal decision. Figure 3 of the main paper shows the relationship between the disutility threshold and the baseline CVD risk of the individuals.

eTable 1. Baseline characteristics of the study population.

Characteristic	Value (N = 1755)
Male sex, no. (%)	877 (49.97%)
Ethnicity	
NonHispanic White, no. (%)	977 (55.67%)
NonHispanic Black, no. (%)	331 (18.86%)
Other	447 (25.47%)
Mean age (SD), yr	55.12 (11.08)
Mean total cholesterol (SD), mg/dL	211.93 (39.91)
Mean HDL-cholesterol (SD), mg/dL	53.56 (16.27)
Mean systolic blood pressure (SD), mmHg	128.28 (19.42)
Hypertension treatment, no. (%)	387 (22.05%)
Current smoking, no. (%)	419 (23.87%)
10-year CVD Risk, no. (%)[a]	
< 2.5%	534 (30.43%)
2.5% to 4.9%	311 (17.72%)
5% to 7.4%	207 (11.79%)
7.5% to 9.9%	143 (8.15%)
10% to 14.9%	207 (11.79%)
15% to 19.9%	120 (6.84%)
>20%	233 (13.28%)

HDL stands for high density lipoprotein; CVD = atherosclerotic cardiovascular disease.
[a] 10-year CVD risk was estimated using the AHA/ACC Pooled Cohort Equations.

eTable 2. Number of deaths from specific causes and probability of dying from all causes except CHD, Stroke and Diabetes for the U.S male population.

Age (years)	Number surviving to age x	All deaths	Ischemic heart diseases (I20-I25)	Cerebrovascular diseases (I60-I69)	Diabetes mellitus (E10-E14)	Ischemic heart diseases, cerebrovascular diseases and diabetes deaths	All deaths not related to CHD, stroke or diabetes	Probability of death
		Number dying of 10,000,000 born alive						
0–1	10000000	76144	76	328	8	413	75731	0.007573119
1–5	9923856	14322	21	109	13	143	14179	0.001428757
5–10	9909534	8717	27	79	17	123	8594	0.000867278
10–15	9900817	11800	35	93	64	191	11609	0.001172489
15–20	9889017	46408	129	175	132	435	45973	0.004648920
20–25	9842609	67895	358	328	297	983	66912	0.006798233
25–30	9774714	63269	930	527	540	1997	61272	0.006268403
30–35	9711445	72924	2670	936	1107	4713	68211	0.007023823
35–40	9638521	99657	7239	1853	1789	10881	88776	0.009210572
40–45	9538864	144868	17532	3635	3129	24297	120571	0.012640021
45–50	9393996	212154	35154	6343	5573	47071	165083	0.017573289
50–55	9181842	292142	61585	9504	9188	80277	211865	0.023074339
55–60	8889700	434589	100898	15258	14931	131086	303503	0.034140960
60–65	8455111	630985	148744	24658	22288	195690	435295	0.051483095
65–70	7824126	875069	205336	37330	30467	273133	601936	0.076933279
70–75	6949057	1180225	280318	61779	38448	380545	799680	0.115077485
75–80	5768832	1491907	365791	95359	45141	506292	985615	0.170851820
80–85	4276925	1624228	412495	123212	43544	579252	1044976	0.244328905
85–90	2652697	1405429	370269	118047	31215	519532	885897	0.333961015
90–95	1247268	861765	236265	74480	15327	326072	535693	0.429493480
95–100	385503	321033	90309	26288	4282	120878	200155	0.519204566
100+	64470	64470	18800	4545	616	23961	40508	0.628333598

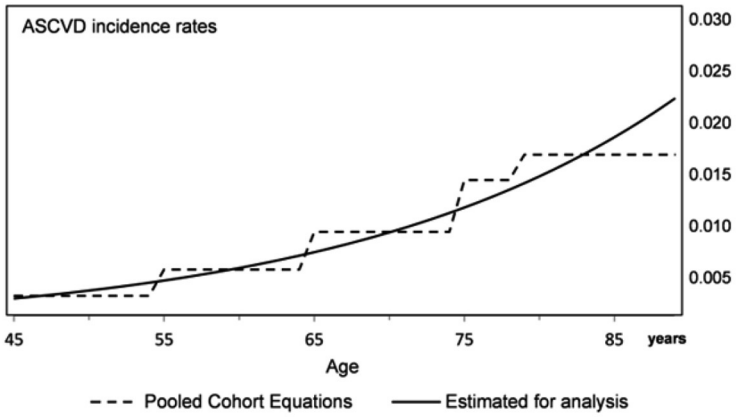
eTable 3. Number of deaths from specific causes and probability of dying from all causes except CHD, Stroke and Diabetes for the U.S female population.

Age (years)	Number surviving to age x	All deaths	Ischemic heart diseases (I20-I25)	Cerebrovascular diseases (I60-I69)	Diabetes mellitus (E10-E14)	Ischemic heart diseases, cerebrovascular diseases and diabetes deaths	All deaths not related to CHD, stroke or diabetes	Probability of death
		Number dying of 10,000,000 born alive						
0-1	10000000	62492	61.30073166	226.4626923	5.108192444	292.8716164	62199.12838	0.006219913
1-5	9937508	11457	18.9882431	139.8166656	20.71362686	179.5185356	11277.48146	0.00113484
5-10	9926051	7064	13.20661163	64.37953186	21.45989609	99.04603958	6964.95396	0.000701684
10-15	9918987	7871	18.17753601	120.6276855	52.8780098	191.6832314	7679.316769	0.000774204
15-20	9911116	19595	58.85299301	154.6928101	107.612648	321.1584511	19273.84155	0.001944669
20-25	9891521	23283	168.663208	321.3343506	257.4231262	747.4206848	22535.57932	0.002278272
25-30	9868238	26421	340.789093	500.0314331	486.3330383	1327.153564	25093.84644	0.00254289
30-35	9841817	36587	949.5269775	917.4640503	768.5580444	2635.549072	33951.45093	0.003449714
35-40	9805230	55947	2426.106201	1887.685913	1256.556274	5570.348389	50376.65161	0.005137733
40-45	9749283	84495	5209.748047	3538.92749	2113.332031	10862.00757	73632.99243	0.007552657
45-50	9664788	122273	9845.302734	5590.108887	3739.870117	19175.28174	103097.7183	0.010667354
50-55	9542515	181631	19667.68945	7944.460938	6872.379883	34484.53027	147146.4697	0.015420093
55-60	9360884	284220	37006.34375	12459.02441	12015.43945	61480.80762	222739.1924	0.023794675
60-65	9076664	433397	65908.17188	19771.10156	19441.14844	105120.4219	328276.5781	0.036167096
65-70	8643267	621378	104628.5156	32400.98828	28106.69336	165136.1973	456241.8027	0.052785805
70-75	8021889	890833	164260.75	57050.60547	37978.32422	259289.6797	631543.3203	0.078727507
75-80	7131056	1285545	266534.5	105528.4922	49034.34766	421097.3398	864447.6602	0.121222952
80-85	5845511	1662498	384543.75	165701.4688	53223.69531	603468.9141	1059029.086	0.181169634
85-90	4183013	1789367	456272.9063	198688.2031	45230.54688	700191.6563	1089175.344	0.260380578
90-95	2393646	1437672	396820.2188	162903.125	27631.22266	587354.5664	850317.4336	0.355239427
95-100	955974	737689.2969	215807.0625	77883.625	11243.0293	304933.7168	432755.5801	0.452685512
100+	218284.7031	218284.7031	68798.02344	19243.19922	2316.927979	90358.15063	127926.5525	0.586053675

eTable 4. Retail prices of different statins availabe on nationwide pharmacy chains.

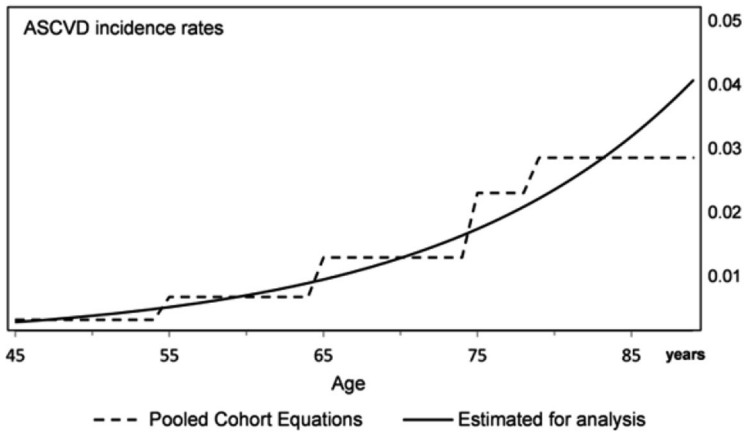
Statin	Pharmacy	Annual Subscription	Price per 1-month supply*		Price per 3-month supply*		Date	Free delivery	Total Price per pill
			Total	Per Pill	Total	Per Pill			
High-intensity statins									
Atorvastatin 80 mg	drugs.com	$0.00	$25.25	$0.84	$67.25	$0.75	29-05-14	No	$0.75 + delivery
	Walmart	$0.00	$30.00	$1.00	$0.00	$0.00	04-06-14	Yes	$1.00
	Costco	$0.00	$20.33	$0.68	$49.20	$0.49	04-06-14	Yes	$0.49
Rosuvastatin 20 mg	Costco	$0.00	$196.59	$6.55	$645.41	$6.45	04-06-14	Yes	$6.45
Moderate-intensity statins									
Atorvastatin 10 mg	drugs.com	$0.00	$16.25	$0.54	$40.25	$0.45	29-05-14	No	$0.45 + delivery
	Costco	$0.00	$14.68	$0.49	$33.25	$0.33	04-06-14	Yes	$0.33
Rosuvastatin 10 mg	Costco	$0.00	$194.45	$6.48	$635.70	$6.36	04-06-14	Yes	$6.36
Simvastatin 20 mg	Kmart	$10.00	$5.00	$0.17	$10.00	$0.11	04-06-14	Yes	$0.14
	Walgreens	$20.00	$10.00	$0.33	$20.00	$0.22	04-06-14	Yes	$0.28
	Costco	$0.00	$5.90	$0.20	$10.83	$0.11	04-06-14	Yes	$0.11
	Rite Aid	$0.00	$9.99	$0.33	$15.99	$0.18	17-06-14	No	$0.18 + delivery
Simvastatin 40 mg	Kmart	$10.00	$5.00	$0.17	$10.00	$0.11	04-06-14	Yes	$0.14
	Walgreens	$20.00	$15.00	$0.50	$30.00	$0.33	04-06-14	Yes	$0.39
	Costco	$0.00	$5.90	$0.20	$10.83	$0.11	04-06-14	Yes	$0.11
	Rite Aid	$0.00	$9.99	$0.33	$15.99	$0.18	17-06-14	No	$0.18 + delivery
Pravastatin 40 mg	Costco	$0.00	$175.59	$5.85	$572.83	$5.73	04-06-14	Yes	$5.73
	Rite Aid	$0.00	$9.99	$0.33	$15.99	$0.18	17-06-14	No	$0.18 + delivery
Lovastatin 40 mg	Kmart	$10.00	$5.00	$0.17	$10.00	$0.11	04-06-14	Yes	$0.14
	Walgreens	$20.00	$5.00	$0.17	$10.00	$0.11	04-06-14	Yes	$0.17
	Costco	$0.00	$8.52	$0.28	$16.50	$0.17	04-06-14	Yes	$0.17
	Rite Aid	$0.00	$9.99	$0.33	$15.99	$0.18	17-06-14	No	$0.18 + delivery

All prices are 2014 prices. *Total price represent price for 90 tablets in drugs.com, Walmart, Kmart, Walgreens and Rite Aid. Total price represent price for 100 tablets in Costco.



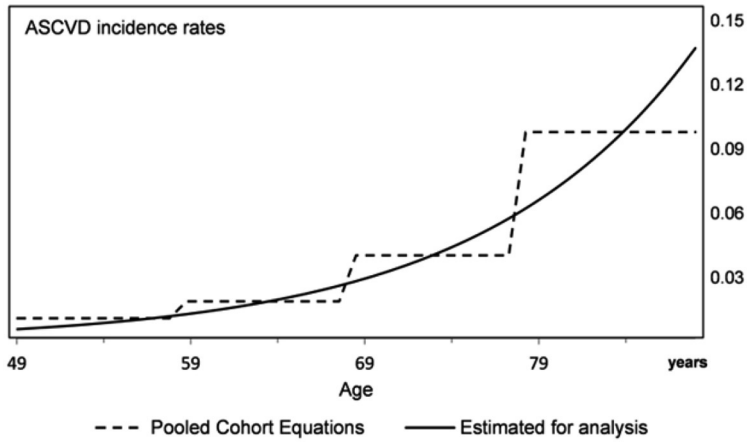
eFigure 2. Annual incidence rates of CVD events for a 45-year-old male with 3.2% 10-year risk at baseline.

Incidence rates estimated for a patient with the following risk factors at baseline: ethinicity = nonHispanic Black; total cholesterol = 183 mg/dL; HDL-cholesterol = 61 mg/dL; systolic blood pressure = 117 mmHg; smoking = no; diabetes = no; antihypertensives = yes.

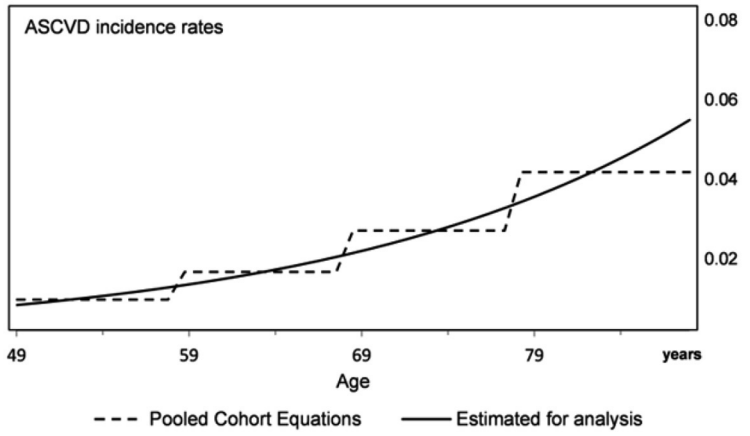


eFigure 3. Annual incidence rates of CVD events for a 45-year-old female with 3.2% 10-year risk at baseline.

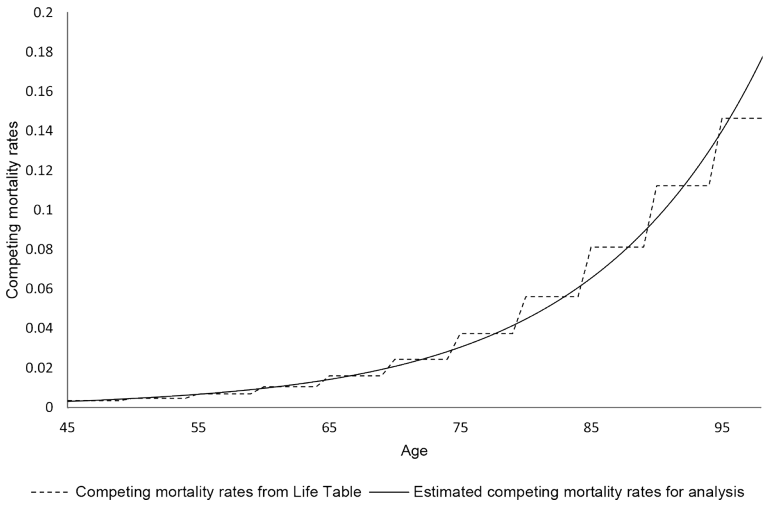
Incidence rates estimated for a patient with the following risk factors at baseline: ethinicity = nonHispanic Black; total cholesterol = 171 mg/dL; HDL-cholesterol = 53 mg/dL; systolic blood pressure = 139 mmHg; smoking = no; diabetes = no; antihypertensives = yes.



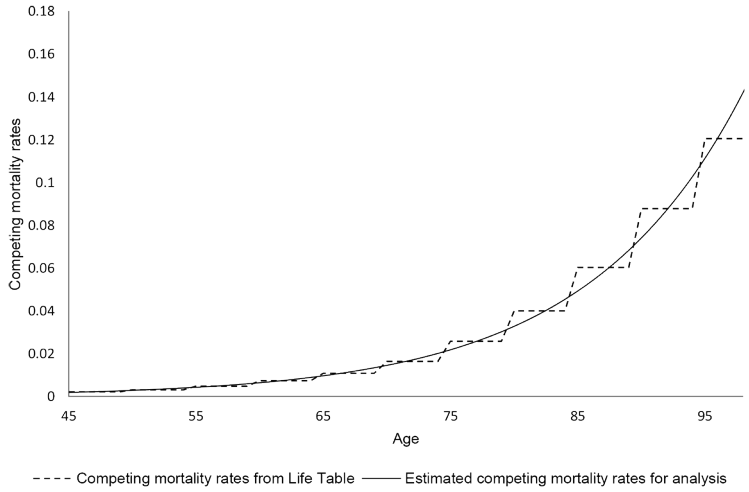
eFigure 4. Annual incidence rates of CVD events for a 49-year-old female with 10% 10-year risk at baseline.
Incidence rates estimated for a patient with the following risk factors at baseline: ethinicity = nonHispanic White; total cholesterol = 232 mg/dL; HDL-cholesterol = 48 mg/dL; systolic blood pressure = 162 mmHg; smoking = yes; diabetes = no; antihypertensives = yes.



eFigure 5. Annual incidence rates of CVD events for a 49-year-old male with 9% 10-year risk at baseline.
Incidence rates estimated for a patient with the following risk factors at baseline: ethinicity = nonHispanic White; total cholesterol = 240 mg/dL; HDL-cholesterol = 44 mg/dL; systolic blood pressure = 118 mmHg; smoking = yes; diabetes = no; antihypertensives = no.



eFigure 6. Comparison between competing mortality rates from abridged life table and estimated competing mortality rates from solver function for men.



eFigure 7. Comparison between competing mortality rates from abridged life table and estimated competing mortality rates from solver function for women.

REFERENCES

e1. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. Nov 12 2013.

e2. Erickson KF, Japa S, Owens DK, Chertow GM, Garber AM, Goldhaber-Fiebert JD. Cost-effectiveness of statins for primary cardiovascular prevention in chronic kidney disease. Journal of the American College of Cardiology. Mar 26 2013;61(12):1250-1258.

e3. Arias E, Heron M, Tejada-Vera B. United States life tables eliminating certain causes of death, 1999–2001. National vital statistics reports; vol 61 no 9. Vol 61. Hyattsville, MD: National Center for Health Statistics; 2013.

e4. Arias E, Curtin LR, Wei R, Anderson RN. United States decennial life tables for 1999–2001, United States life tables. National Vital Statistics Reports. Vol 57 no 1. Hyattsville, MD: National Center for Health Statistics. 2008.

e5. Centers for Disease Control and Prevention (CDC). Percentage of Civilian, Noninstitutionalized Population with Diagnosed Diabetes, by Age, United States, 1980–2011. http://www.cdc.gov/diabetes/statistics/prev/national/menuage.htm. Accessed June 14, 2014.

e6. Gravelle H, Brouwer W, Niessen L, Postma M, Rutten F. Discounting in economic evaluations: stepping forward towards optimal decision rules. Health Econ. Mar 2007;16(3):307-317.

e7. Menzin J, Wygant G, Hauch O, Jackel J, Friedman M. One-year costs of ischemic heart disease among patients with acute coronary syndromes: findings from a multi-employer claims database. Curr Med Res Opin. Feb 2008;24(2):461-468.

e8. Engel-Nitz NM, Sander SD, Harley C, Rey GG, Shah H. Costs and outcomes of noncardioembolic ischemic stroke in a managed care population. Vasc Health Risk Manag. 2010;6:905-913.

e9. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. American Heart Journal. 2001;141(5):727-734.

e10. Dall TM, Zhang Y, Chen YJ, Quick WW, Yang WG, Fogli J. The Economic Burden Of Diabetes. Health Affairs. February 1, 2010 2010;29(2):297-303.

Chapter 11

Summary and Discussion

In this thesis we aimed at contributing to the evidence on the optimal strategy for the primary prevention of cardiovascular disease in modern Western populations using a risk based approach. More specifically, we constructed models by abstracting and deducing data from the cumulative work of others. If one would characterize this thesis in an overly simplistic approach, one could argue that we have merely aggregated and synthesized data that has already been produced through the extensive efforts of others. In fact, that is exactly what we did. Nevertheless, data synthesis is a far more daunting task than it may seem. Besides summarizing the main findings in this thesis, this chapter will be used to elaborate on the complexity of data synthesis and how this process has an important place in assessing the optimal strategy for the primary prevention of cardiovascular disease. The limitations and challenges of this approach will also be discussed.

In order to adequately synthesize evidence and evaluate interventions based on cardiovascular risk assessment, we have studied 1) the (individualized) underlying truth in decision models, based on long-term CVD risk predictions and their improvement using novel risk markers; 2) the validity of and critical assumptions underlying decision models and their relation to the outcome of such models; and finally 3) the comparative effectiveness and cost-effectiveness of guiding preventive (medical) treatment based on risk-stratification using both established risk scores and novel risk markers.

We embarked on our journey by looking into the value of screening asymptomatic individuals at intermediate risk for coronary heart disease by using the coronary calcium score determined with computed tomography. Using observational data from the Rotterdam study, which included the CT-coronary calcium score from 1997 onwards -with a follow-up of a median of 7 years, we calculated -at the population level, which percentage of individuals were reclassified to a higher or lower risk category when CT calcium was taken into account, compared to the classification using only the traditional Framingham risk factors (**chapter 2)**. We explicitly chose not to use the original Framingham risk score itself -with the accompanying baseline hazards and association strengths found in the Framingham population, as this could have caused the reclassification in risk to be due both to recalibration of the original score within the Rotterdam Study and the addition of the calcium score. The recalibrated traditional risk score included all the original Framingham risk factors, but allowed for different accompanying coefficients, so the effect sizes of the individual risk factors and their correlations were slightly different than in the Framingham risk score [(1)], thereby isolating the effect of adding CT calcium to the model. If an individual was reclassified to the high risk category, (>20%, 10 year risk of coronary heart disease), an individual was treated with a statin, anti-hypertensive medication and -in men, also aspirin. Compared to current practice, current guidelines and the statin therapy alternative (in which individuals were assigned a moderately potent statin regardless of their initial LDL levels –considered to be the most 'aggressive' strategy), screening with CT calcium in men yielded the highest quality adjusted life expectancy, against a lower incremental cost-effectiveness ratio (compared to current practice) than the current

guidelines strategy did. Part of this result could be explained by the fact that individuals targeted and allocated preventive medication in the CT calcium screening strategy, had higher predicted risks of CHD compared to the individuals allocated medical treatment in the statin therapy and current practice alternative. Arguably, this was inherent to the underlying model, but apparently, this mechanism outweighed the higher costs of the strategy, and harm of the screening itself. In a sensitivity analysis, CT calcium screening was outranked by the statin therapy strategy when the cost of CT increased more than 2-fold, or the incidence of radiation induced cancer increased more than 10-fold. In women CT screening was not found to be cost-effective, even after using a wide range of varying assumptions, which included assumptions more favourable to the CT calcium screening strategy by treating individuals in the higher end of 'low risk' (5 – 10% risk) more aggressively, and using more treat-prone LDL thresholds. The difference in the optimal decision between men and women can -at least in part, be explained by the fact that compared to men, more women were reclassified to the low risk group leading to less aggressive treatment. Furthermore, within the low risk group, the observed risk of CHD is higher in women than in men, so the foregone benefit with less aggressive treatment is higher in women. The benefit of CT screening is obtained in the high-risk group, where individuals are treated more aggressively compared to current guidelines for treatment of intermediate-risk individuals. Since fewer women were reclassified to high-risk, the potential benefit of CT screening is lower than in men. Having said all that, the average age in the analysis was 70 for men, and 74 for women (as the requirement was for them to be at 'intermediate risk for CHD'; for which calendar age is the most important driver), and residual life expectancy not too much over 10 years. One could make a valid argument that primary prevention should take place earlier in life, since at the age of 70 atherosclerotic plaque has had ample time to accumulate. Moreover, in spite of the availability of a number of novel risk markers, this particular analysis does not evaluate these. In chapters 8 and 9 we did analyze these markers and we return to these later on in the discussion.

As stated before, we have built on the cumulative work of others, and not all of our efforts were put into assessing the value of 'novelties', but in the evaluation of current recommendations in the prevention of cardiovascular disease as well. More specifically, European guidelines on the prevention of CVD have provided clinicians with their world famous risk charts [2] in order to individualize decisions on the initiation of statins. The rationale behind these charts is that the higher an individuals' expected risk of CVD, the bigger the expected benefit of preventing it (CVD). However, the (traditional) risk factors used to estimate CVD risk are also related to 'competing' events. For example, an individual's calendar age will affect both the estimated risk of future CVD events, but also the risk of developing cancer. By not taking into account competing risks, and by possibly ignoring the (indirect) effect of an intervention targeted at lowering the risk of CVD on the competing event risk, the net effect of an intervention could be incorrectly estimated [3]. In order to evaluate these charts at an individual patient level, **Chapter 3** looked into the validity of a previously constructed model: the Rotterdam Ischemic heart disease and Stroke Computer simulation (RISC) model. Aside from the traditional risk

factors, the model included body mass index, waist-to-hip ratio, ankle-brachial index, plasma creatinine; family history of CVD, manifestations of intermittent claudication, angina pectoris, atrial fibrillation or transient ischemic attacks; and prevalent CVD. As decision models often extrapolate from existing data, we first showed that, by using observational data for the period of 5 years -on which the RISC model was originally based, the model was able to correctly estimate CVD mortality, non-CVD mortality, CHD events and Stroke events up until 13 years (the maximum length of observational data available at that time which was used to validate the model). Extrapolation beyond 5 years was grounded in both the modelling of trends in risk factors over time and their effects on the incidence of events, which are jointly modelled in the RISC model. Their interplay seemed to have caused a valid basis to extrapolate results, without the need to recalibrate the model for the Rotterdam Study population. Extrapolation was also valid when we stratified for sex and tertiles of age. As for the external validity, the RISC model appeared to be valid for other populations than the Rotterdam Study participants as well, after only adjusting for the baseline cumulative hazards of the events and the mean values of the risk factors -a method very commonly used when applying models to other populations than that for which the model was originally developed in [4, 5]. The model was able to correctly simulate CVD and non-CVD mortality for the EPIC Norfolk population for up until 10 years (again; the maximum length of observational data available to us at that moment). However, extrapolating short term to lifetime risks -one of the goals we frequently try to achieve when addressing decision problems covering the residual life time of an individual, has been shown to be fairly difficult. For participants of the QRISK study in England and Wales, of the (arbitrarily chosen) top 10% classified at high risk with either the lifetime risk model or the 10 year risk model, only 14.5% were high risk on both measures [6]. Moreover, patients with the high lifetime risk were more likely to be younger, male, and much more likely to have a positive family history of coronary heart disease than those with a high 10 year risk. This implies –at the very least, that extrapolating (far) beyond 10 years by using data from a limited time horizon is not without a serious risk of a simulation model producing data that would be (far) from reality, in the sense that it would 1) not calibrate well for the long run on average, but more importantly: 2) would select individuals for preventive treatment based on risk factors that matter for the shorter time horizon, but no so much for the long run (i.e. for the QRISK population we should select the younger, male individuals with a positive family history). As an alternative, one could 'wait' until the long-term data has become available [5], but at the cost that recent trends in event rates [7] will be inadequately captured; aside from the fact that we have to face a decision now, and often do not have time to wait for 30 years. Furthermore, in chapter 3 we 'only' validated the 'naturally occurring' cardiovascular histories of the participants of the Rotterdam Study (and EPIC-Norfolk cohort) as they were observed; that is: without any interventions. Although the results with regard to this validity seemed promising, our aim was to use the RISC model to evaluate the initiation of statin therapy for the primary prevention of CVD –more specifically to evaluate the Score risk charts. The validity of our modelling efforts to evaluate these charts (or any intervention more in general) depend not only on the validity of the simulated CVD history, but also on the extent to which

other structural assumptions are made, such as modeling the treatment effect of an intervention [8].

Besides having covered the validity of the prognostic part of the simulation model in chapter 3, **chapter 4** focussed on the impact of using different structural assumptions about the treatment effect (which is incorporated in every screening strategy evaluated in this thesis, which stems from the main concept of targeting high risk individuals and treating them), using statin therapy as an example. Three commonly used assumptions were analysed: 1) statins lower LDL cholesterol, and being an independent risk factor of CVD, the effect of statin therapy was assumed to be equal to the projected decrease in predicted CVD risk through the associated hazard rate ratio of LDL on CHD -obtained from non-experimental study designs; 2) a fixed reduction in CVD risk based on observed risk reductions on CHD and stroke from (meta analyses of) clinical trials and 3) a reduction of CVD risk (again obtained from clinical trials) proportional to the expected decrease in LDL-cholesterol levels. All three methods have been identified in existing decision models of CVD. We found that for the decision to initiate statins according to the ATP-III guidelines, these three different modelling assumptions would lead to different conclusions about the cost-effectiveness of initiating statin therapy. A priori, there is no 'superior' way of modelling the treatment effect. For our statin therapy/ ATP-III guidelines example, if it would have been required that the modeled reduction in incident CHD and stroke events corresponded to the same reduction as observed in trials (a requirement which could have been validated if we would have simulated individual-level trial data [9]), the resulting reduction in fatal total CVD events produced by the RISC model would have unlikely matched the observed reduction in fatal total CVD events in the same trials if no further adjustments or assumptions would have been introduced. In other words, imposing some kind of constraint to force some relationship or construct to hold within a decision model, induces additional assumptions and/or constructs that can conflict with 'reality' as well. It also enables a designer of a decision model to 'prove' his or her model is valid in some ways -but never in all possible ways. How 'exact' the process of model building and validating may seem, the modeling of complex interrelationships is more of an art than an exact science. For each particular decision problem it is important to determine which assumptions drive the results, determine the appropriateness of these assumptions, and judge the relevance of the model sensitivity to them in the context of the decision problem studied.

In **chapter 5** we evaluated the predicted individual gains from initiating statin therapy in asymptomatic individuals free of CVD at baseline (without incorporating any form of screening), by taking into account the competing risk of non-CVD deaths and use of a lifetime time horizon. We found that in 2,428 individuals free of CVD from the total of 3,501 Rotterdam Study participants on which the RISC model was originally based, statin therapy resulted in robust, small gains in total life expectancy (0.3 years, with a range of between 0 and 2 full years) and somewhat larger gains in CHD/stroke-free life expectancy. Using baseline levels of risk factors in these individuals, we found that a higher systolic blood pressure, higher total cholesterol, lower HDL cholesterol, and

larger body mass index considerably increased the expected individual gains in total and CHD/stroke-free life expectancy with statin therapy. However, increasing age most importantly *de*creased these gains, as did diabetes mellitus to a lesser extent. With advancing age, the risk of death due to other causes than CVD increases rapidly. By preventing a (potentially fatal) CVD event at an older age, the prevented CVD event is almost immediately exchanged for a non-CVD related death, resulting in a smaller net benefit in terms of all cause survival than a CVD event prevented in a younger individual -for which the risk of death due to other causes is much lower. As a consequence, the expected individual gains of statin therapy for an individual is expected to be higher in younger individuals, whereas the current European guidelines on initiating statin therapy is purely CVD risk based- of which calendar age is the most important determinant; which implies recommending it in older individuals instead –for which we have just argued that the expected individual gains are lower. A number of important assumptions had to be made for the modelling of the effect of life-long statin therapy. First -as mentioned before, although the RISC model adequately reproduced 13 year incidences of CHD, Stroke, CVD and non-CVD mortality, the extrapolation beyond 13 years remains to be established. Second, the relative risk reducing effect of statin therapy was kept constant over age and various risk factor levels. Although, a number of observational studies found that the protective effect of cholesterol lowering on CVD events decreases in individuals aged 70 to 89, this was not confirmed by experimental research [10, 11]. Moreover, as we will come to discuss later on, we did not impose any penalty or disutility for taking daily medication [12, 13]. If younger individuals were to be allocated statins for longer periods of time, one could easily imagine that such a disutility would accumulate to substantial levels, decreasing the net benefit of the intervention.

In **chapter 6** we studied the validity of the long term Framingham CVD risk (combined endpoint of myocardial infarction, coronary death and stroke) predictions which take into account the competing risk of non-CVD death. As it has become clear, taking into account competing risks is a critical asset of CVD predictions if they are to be used in long term decision models. We found that the Framingham CVD risk predictions perform reasonably well in predicting 15 year risk of CVD in the -on average older, Rotterdam population for individuals at low to intermediate risk. This finding is comparable to previous studies on the validity of Framingham risk functions in the Rotterdam Study using 10-year CHD and stroke as separate outcomes. Recalibration was necessary for the apparent overestimation in the higher risk categories. Part of this overestimation could be explained by the fact that the Framingham function at the same time underestimated the risk of the competing non-CVD death which is of particular importance in the older Rotterdam study participants. The most recent guidelines on prevention of CVD classify individuals based on their risk of CVD as a combined endpoint -in contrast to some older guidelines which merely focused on coronary heart disease. However, we demonstrated that estimating the hazards for CHD and stroke separately allows for the simultaneous prediction of the risks of these events and found that the weights assigned to the risk factors included in the Framingham risk function are different for both events. Discrimination increased only very little, but calibration improved substantially

compared to predicting CVD as a combined endpoint. The hazard rate ratios of the risk factors were sometimes different in magnitude and significance of the effects from the ones from Framingham. Our observation that total cholesterol (in the presence of other factors) did not appear a significant predictor for CVD in the Rotterdam data was supported by earlier analyses in the Rotterdam Study. Whereas serum cholesterol was found to have a protective effect on stroke, HDL-cholesterol had no significant effect -similar to what we found when we analysed the hazard of stroke separately from CHD. Moreover, the major contributor to an individuals' predicted risk of CVD, (being either CHD or stroke), differed between individual risk profiles, as illustrated with a number of specific examples in chapter 6. This can have important clinical implications for the allocation of preventive interventions. For example, aspirin is currently recommended in men with a high risk of CHD, while in women the recommendation is only made for those with a high risk of stroke [11]. Both reasons (more precise estimation of the total CVD risk when estimating CHD and stroke separately and potential different clinical implications) illustrate the potential refinement in CVD risk assessment by separate prediction of the constituents of the CVD event as a combined endpoint. Similarly, in **chapter 7** we developed risk functions for the separate prediction of ischemic and haemorrhagic stroke, and found that a number of risk factors currently adopted in risk scores for stroke as a combined endpoint of ischemic and haemorrhagic stroke, had different effect sizes when analyzing subtypes of stroke separately. Again, the subtype of a stroke event is clinically relevant for treatment decisions –analogous to the case of CVD as a combined endpoint.

In **chapter 8** we modeled the predictive value of adding four novel cardiovascular risk markers to traditional Framingham risk scores: CT coronary calcium, high sensitivity CRP, carotid intima media thickness on ultrasound and the ankle-brachial index. We explicitly studied the predictive value of these novel risk markers in individuals representative of the U.S. general population by using the NHANES 2003 – 2004 exam data -where previous studies focused on the predictive value of (single) novel risk markers in the specific observational cohort in which they were measured to design the basic setup of evaluating screening strategies by using these novel risk markers later on -as the final goal of implementing screening strategies will most likely be their employments in a general population rather than a strictly defined study cohort population. Among the four novel risk markers, the Framingham risk score updated with CTCS showed the most impact on reclassification for both CVD and CHD as endpoint, regardless of the risk thresholds used. However, generalizing results on reclassification from specific cohort studies to a general population is not without difficulties. The impact of a novel risk marker on improving risk classification is determined by the strength of the association with the outcome (for which most cohort studies showed consensus in strengths of the association), but also depends on the joined distribution of the novel risk marker and traditional risk factors within the population one aims to study. The exact distribution of the novel risk markers in the U.S. population is unknown and had to be estimated by assuming 1) the correlation between the traditional risk factors and hsCRP and the ankle-brachial index as observed within the NHANES 2003 – 2004 data also holds for

the U.S. general population and 2) – since NHANES did not have data on CTCS and cIMT, the correlation between the traditional risk factors and CTCS and cIMT as observed in the Rotterdam Study data, would hold for the U.S. general population. Second, having constructed the estimated risk profiles of the U.S. population including the 4 novel risk markers, we had to come up with event rates to make inferences about the improvement of risk classification –since our dataset did not include outcome data on events. We therefore constructed a simulation model in which the yearly probabilities of CHD, stroke and non-CVD death were based on the 30-year Framingham CVD risk prediction model, updated with all four novel risk-markers -under the assumption that the actual average risk of the U.S. population as a whole would not change due to the addition of the novel risk markers, and used the (not updated) Framingham CVD risk predictions as a proxy for the actual average risk (as it has been shown that Framingham-based predictions perform fairly well in most U.S. subpopulations) [4]. Our conclusion that CTCS improves CVD risk classification (in contrast to hsCRP, ABI and cIMT) was congruent with MESA and Rotterdam study data.

As mentioned before, improvement in (correct) CVD risk classification is not sufficient for a novel risk marker to be used as a screening tool. In order to analyse the comparative effectiveness and cost-effectiveness of screening United States individuals at intermediate risk, with either CT calcium, hsCRP, ABI and cIMT, we extended the model from chapter 8 in **chapter 9** by adding treatment effects of statins, anti-hypertensive medication, cost and QALYs of relevant health states, side effects of treatment, compliance and a disutility for taking daily medication. The risk thresholds in the screening strategies were derived from the latest AHA guidelines -using 7.5% as cutoff for 10 year risk of CVD [14]. Compared to current practice (the reference strategy) and fully adopting current guidelines -and compared to initiating statins instead of screening, we found that screening men from the U.S. population with CT calcium was cost-effective with an ICER ranging from $22,300 to $49,600. All other novel biomarkers were more costly and less effective. This result is in part explained by the observation that CT calcium results in the highest percentage of men being allocated any of the three cardioprotective drugs compared with the other biomarkers. Only in the case of the statin therapy strategy were more men allocated statins, but at the cost of a substantial disutility from taking daily medication. Ubiquitously initiating statins results in a lower quality adjusted life expectancy in individuals without the need of statins, whereas this penalty seems to be outweighed in individuals with an increased risk of CVD based on CT calcium testing. In women, screening with hsCRP was found to be the optimal strategy with an associated ICER ranging from $15,050 to $185,091. Unlike our results in men, the percentage of women being allocated cardio-protective drugs was highest in the hsCRP strategy. Moreover, CT calcium is less favorable in women due to a higher risk of cancer due to radiation associated with a cardiac CT [15]. Both can explain the inferiority of CT calcium in women compared to men. For both men and women, the disutility of taking daily medication played a pivotal role in the optimal decision. When assuming 100% treatment adherence and no disutility, blindly initiating statins was superior compared to screening with any of the novel biomarkers. As such,

patients with a low tolerance to medication seem to benefit more from screening than individuals with high tolerance.

A similar pattern was observed in **chapter 10** in which we analyzed the comparative effectiveness and cost-effectiveness of prescribing statin therapy to United States individuals at low and intermediate risk (without screening with novel risk markers). This analysis revealed a decrease in quality adjusted life expectancy for prescribing statins to individuals for primary prevention of CVD, across the full range of risk thresholds analysed -including the current recommendation of 7.5% or higher. This decrease was fully attributable to a modest gain in average life expectancy with statin therapy but a substantial decrease in QALE due to the disutility associated with taking daily medication. From a policy-makers perspective, prescribing statin therapy in low-and intermediate risk individuals does more harm than good and costs money (assuming a policy maker is unable to ethically, legally and objectively differentiate individuals based on their disutility-preferences). For the individual, the decision depends on the trade-off between future risk versus the disutility from daily medication –a phenomenon illustrated in chapter 9 as well.

Policy implications and Future Directions

After all these elaborative efforts in modelling primary prevention strategies, we remain with the question what the clinical and policy implications are of the results and what research would be worthwhile pursuing in the future? Can we make policy based on our findings or do we need to perform clinical trials? Should we pursue large scale multinational multicentre clinical trials using standard frequentist statistical inference methods with rejection of the null hypothesis with a 95% level of confidence evaluating the CT coronary calcium score in men? More likely than not, statistical power will be a major limitation to overcome. In fact, a number of clinical trials using a screening modality (functional testing and coronary CT -but not the coronary calcium score as we have studied) have been performed in diabetic individuals -considered to be at high risk already according to the latest guidelines [14], and were unable to find statistically significant differences on hard endpoints [16, 17]. Recently, a trial including more than 50,000 individuals from the general population followed up for 10 years was unable to detect a significant difference using similar endpoints, although the screening procedure and intervention were slightly different from ours (lifestyle counselling). Looking at the parameter uncertainty represented in our results -which are in fact Bayesian derived credibility intervals (CI's), one can deduce from e-tables 3 and 4 in chapter 9 that the CI's of our primary outcome measures tend to overlap quite dramatically. We already elaborated on feasibility issues of clinical trials in the setting of our decision problems in the introduction of this thesis. So are we right back where we started from?

At the very least, our research has (re-)established the potential role of CT coronary calcium screening, without actually 'experimenting' with a single patient in real life. Although this result is concordant with the current opinions of mastodons in the field [18, 19], we came to our conclusions by estimating the effects of screening on long

term, hard endpoints (and effects on cost/resource usage as well). Both investigators referenced, conclude in their latest expert opinions that demonstrating the value of CT coronary calcium screening in a trial setting is unlikely to ever happen given the complexity and expense of such an endeavour.

Rather than trying to replicate what we learned from our decision models in real life with an infeasible clinical trial, we could arguably learn more if we use the direction in which our results point us and then add something new to it.

Recent studies have suggested that the results of screening with a novel biomarker – CT calcium in this case – influence treatment initiation and continuation downstream [20], and -more importantly, seem to improve compliance to statin therapy [21]. Although the latter observation was made in a non-controlled setting and another study could not confirm this finding[22] , there is accumulating evidence that visualizing an individual's risk of CVD by use of coronary CT may motivate individuals to co-operate in the preventive efforts being made for their own wellbeing [23]. Extrapolating from these findings one could expect that visualisation of subclinical disease may change someone's perception of taking medication from being a disutility to being an investment in his or herself.

In conclusion, we have developed an extensive framework to evaluate screening-based interventions for the primary prevention of cardiovascular disease. Our approach goes beyond establishing improvement of predictive performance of a novel risk marker to include benefit in terms of long term survival, quality of life, and cost-savings. Furthermore, our results suggest that future research in the field of novel biomarkers through trial-based studies should incorporate the interplay between an individual's perceived disutility for taking daily medication, the communicated results of CT coronary calcium, the resulting treatment adherence and the extent of potentially resulting behavioural changes.

REFERENCES

1. Koller MT, Steyerberg EW, Wolbers M, Stijnen T, Bucher HC, Hunink MG, et al. Validity of the Framingham point scores in the elderly: results from the Rotterdam study. Am Heart J. 2007;154(1):87-93.
2. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33(13):1635-701.
3. Andersen PK, Geskus RB, de Witte T, Putter H**.** Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol. 2012;41(3):861-70.
4. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P, Group CHDRP**.** Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001;286(2):180-7.
5. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM, Vasan RS**.** Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation. 2009;119(24):3078-84.
6. Hippisley-Cox J, Coupland C, Robson J, Brindle P**.** Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ. 2010;341:c6624.
7. Ben-Shlomo Y, Kuh D**.** A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31(2):285-93.
8. Kopec JA, Fines P, Manuel DG, Buckeridge DL, Flanagan WM, Oderkirk J, et al. Validation of population-based disease simulation models: a review of concepts and methods. BMC Public Health. 2010;10:710.
9. Kim LG, Thompson SG**.** Uncertainty and validation of health economic decision models. Health Econ. 2010;19(1):43-55.
10. Dorresteijn JA, Visseren FL, Ridker PM, Wassink AM, Paynter NP, Steyerberg EW, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. Bmj. 2011;343:d5888.
11. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM**.** Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med. 2010;152(8):488-96, W174.
12. Fontana M, Asaria P, Moraldo M, Finegold J, Hassanally K, Manisty CH, et al. Patient-accessible tool for shared decision making in cardiovascular primary prevention: balancing longevity benefits against medication disutility. Circulation. 2014;129(24):2539-46.
13. Hutchins R, Viera AJ, Sheridan SL, Pignone MP**.** Quantifying the utility of taking pills for cardiovascular prevention. Circ Cardiovasc Qual Outcomes. 2015;8(2):155-63.
14. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013.
15. Kim KP, Einstein AJ, Berrington de Gonzalez A**.** Coronary artery calcification screening: estimated radiation dose and cancer risk. Arch Intern Med. 2009;169(13):1188-94.
16. Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, Knight S, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. JAMA. 2014;312(21):2234-43.
17. Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, Taillefer R, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA. 2009;301(15):1547-55.
18. Greenland P**.** More evidence for coronary calcium as a measure of cardiovascular risk: has anything changed? JAMA. 2014;311(3):247-8.
19. Mamudu HM, Paul TK, Veeranki SP, Budoff M**.** The effects of coronary artery calcium screening on behavioral modification, risk perception, and medication adherence among asymptomatic adults: a systematic review. Atherosclerosis. 2014;236(2):338-50.

20. Nasir K, McClelland RL, Blumenthal RS, Goff DC, Jr., Hoffmann U, Psaty BM, et al. Coronary artery calcium in relation to initiation and continuation of cardiovascular preventive medications: The Multi-Ethnic Study of Atherosclerosis (MESA). Circ Cardiovasc Qual Outcomes. 2010;3(3):228-35.

21. Kalia NK, Miller LG, Nasir K, Blumenthal RS, Agrawal N, Budoff MJ**.** Visualizing coronary calcium is associated with improvements in adherence to statin therapy. Atherosclerosis. 2006;185(2):394-9.

22. O'Malley PG, Feuerstein IM, Taylor AJ**.** Impact of electron beam tomography, with or without case management, on motivation, behavioral change, and cardiovascular risk profile: a randomized controlled trial. JAMA. 2003;289(17):2215-23.

23. Orakzai RH, Nasir K, Orakzai SH, Kalia N, Gopal A, Musunuru K, et al. Effect of patient visualization of coronary calcium by electron beam computed tomography on changes in beneficial lifestyle behaviors. Am J Cardiol. 2008;101(7):999-1002.

About the author

Bob Johannes Hendrikus was born on April 27th in Vlijmen, The Netherlands. He started his academic career at the faculty of Business and Economics at Tilburg University where he studied both Economics and Econometrics & Operations Research. In his final year of Econometrics he wrote a thesis on Longitudinal Models in Epidemiology. Having worked for a while as an econometrician for Liberty Global Inc., he decided to start his medical studies at the university of Rotterdam in 2006. In 2011 he graduated from the Netherlands Institute for Health Sciences (NIHES) Master of Science program in Clinical Epidemiology and received the NIHES Master of Science Award 2011 for the best Master's thesis written in his year during the graduation ceremony in 'de Doelen' in Rotterdam. He obtained his M.D. license in the summer of 2014.

PhD Portfolio

Research skills

2009 – 2011	Master of Science in Clinical Epidemiology Netherlands Institute for Health Sciences, Rotterdam, the Netherlands

In-depth courses

October 2010	SMDM short course Introduction to Discrete-Event Simulation for Healthcare, Society for Medical Decision Making Annual Meeting Toronto, Canada

Invited lectures and seminars

October 2011	Interview by Anthony DeMaria on the 'Cost-effectiveness of CT Calcium Screening' https://www.youtube.com/watch?v=Ln5tbk5xh6Q
May 2011	"Modeling cardiovascular disease prevention: from cohort research to personalized medicine", seminar at the Helmholtz Zentrum München, Institute of Epidemiology, Munich, Germany
Janurary 2010	University of Oslo, Norway Department of Health Management and Health Economics. Visiting scholar teaching one week course on Medical Decision Making

International conferences

October 2012	Poster presentation: "Modeling the Added Predictive Value of a Novel Cardiovascular Risk Marker with a Simple State Transition Model". Society for Medical Decision Making 34th Annual Meeting, Phoenix, AZ, USA
	Poster presentation: "Iterative calibration of state-transition microsimulation models used for evaluating the impact of updating traditional cardiovascular risk prediction with novel risk markers" Society for Medical Decision Making 34th Annual Meeting, Phoenix, AZ, USA
November 2011	Poster presentation: "Coronary Artery Calcium Screening Cost-effective In Men, Not In Women". Scientific Sessions of the American Heart Association, Orlando, Miami
October 2010	Oral presentation: "Do different methods of modeling statin effectiveness influence the optimal decision?" Society for Medical Decision Making 32nd Annual Meeting, Toronto, Canada
	Poster presentation: "Personalized Prevention of Coronary Artery Disease"
	Society for Medical Decision Making 32nd Annual Meeting, Toronto, Canada

Teaching activities

February 2010 - 2013	Advanced Topics in Decision-making in Medicine Clinical Epidemiology Winter Program course Netherlands Institute of Health Sciences, Rotterdam, the Netherlands
August 2011 - 2014	RDS 288 Methods for Decision Making in Medicine Clinical Effectiveness Summer Program course Harvard School of Public Health, Boston, MA, USA
2007, 2009 - 2013	Evidence-based medicine classes for first and third year medical students Erasmus University, Medical school, Rotterdam, the Netherlands

List of Publications

(1) Verhelst J, de Goede B, **van Kempen BJ**, et al. Emergency repair of inguinal hernia in the premature infant is associated with high direct medical costs. *Hernia.* Dec 14 2015.

(2) **van Kempen BJ**, Ferket BS, Steyerberg EW, Max W, Myriam Hunink MG, Fleischmann KE. Comparing the cost-effectiveness of four novel risk markers for screening asymptomatic individuals to prevent cardiovascular disease (CVD) in the US population. *Int J Cardiol*. Oct 21 2015;203:422-431.

(3) Kenchadze G, Pipia I, Demetrashvili Z, et al. Incisional Hernia: Plastic Aspects, Component Separation, Technical Details & Pediatrics. *Hernia*. Apr 2015;19(Suppl 1):S187-S194.

(4) de Goede B, Verhelst J, **van Kempen BJ**, et al. Very low birth weight is an independent risk factor for emergency surgery in premature infants with inguinal hernia. *J Am Coll Surg*. Mar 2015;220(3):347-352.

(5) de Goede B, Timmermans L, **van Kempen BJ**, et al. Risk factors for inguinal hernia in middle-aged and elderly men: results from the Rotterdam Study. *Surgery*. Mar 2015;157(3):540-546.

(6) **van Kempen BJ***, **Ferket BS**, Kavousi M, et al. Performance of Framingham cardiovascular disease (CVD) predictions in the Rotterdam Study taking into account competing risks and disentangling CVD into coronary heart disease (CHD) and stroke. *Int J Cardiol*. Feb 15 2014;171(3):413-418.

(7) Ferket BS, **van Kempen BJ**, Wieberdink RG, et al. Separate prediction of intracerebral hemorrhage and ischemic stroke. *Neurology*. May 20 2014;82(20):1804-1812.

(8) **Ferket BS**, **van Kempen BJ***, Hunink MG, et al. Predictive value of updating Framingham risk scores with novel risk markers in the U.S. general population. *PLos One*. 2014;9(2):e88312.

(9) de Goede B, Eker HH, Klitsie PJ, et al. Incisional hernia after liver transplantation: risk factors and health-related quality of life. *Clin Transplant*. Jul 2014;28(7):829-836.

(10) Bicalho V, van Kempen BJ, Ferket BS, et al. Comparative effectiveness and Cost-Effectiveness of Statin Therapy for Primary Prevention of Cardiovascular Events: a trade-off between future risk and the disutility of lifelong daily medication *submitted*. 2014.

(11) Timmermans L, de Goede B, Eker HH, **van Kempen BJ**, Jeekel J, Lange JF. Meta-analysis of primary mesh augmentation as prophylactic measure to prevent incisional hernia. *Dig Surg*. 2013;30(4-6):401-409.

(12) de Goede B, **van Kempen BJ**, Polak WG, et al. Umbilical hernia management during liver transplantation. *Hernia*. Aug 2013;17(4):515-519.

(13) de Goede B, Klitsie PJ, **van Kempen BJ**, et al. Meta-analysis of glue versus sutured mesh fixation for Lichtenstein inguinal hernia repair. *Br J Surg*. May 2013;100(6):735-742.

(14) de Goede B, Klitsie PJ, Hagen SM, et al. Meta-analysis of laparoscopic versus open cholecystectomy for patients with liver cirrhosis and symptomatic cholecystolithiasis. *Br J Surg.* Jan 2013;100(2):209-216.
(15) **van Kempen BJ**, Ferket BS, Hofman A, et al. Validation of a model to investigate the effects of modifying cardiovascular disease (CVD) risk factors on the burden of CVD: the rotterdam ischemic heart disease and stroke computer simulation (RISC) model. *BMC Med.* 2012;10:158.
(16) **van Kempen BJ**, Ferket BS, Hofman A, Spronk S, Steyerberg E, Hunink MG. Do different methods of modeling statin treatment effectiveness influence the optimal decision? *Med Decis Making.* May-Jun 2012;32(3):507-516.
(17) Ferket BS, **van Kempen BJ**, Heeringa J, et al. Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study. *PLoS Med.* 2012;9(12):e1001361.
(18) **van Kempen BJ**, Spronk S, Koller MT, et al. Comparative effectiveness and cost-effectiveness of computed tomography screening for coronary artery calcium in asymptomatic individuals. *J Am Coll Cardiol.* Oct 11 2011;58(16):1690-1701.
(19) Spronk S, **van Kempen BJ**, Boll AP, Jorgensen JJ, Hunink MG, Kristiansen IS. Cost-effectiveness of screening for abdominal aortic aneurysm in the Netherlands and Norway. *Br J Surg*. Nov 2011;98(11):1546-1555.
(20) Collaboration IT. Operation compared with watchful waiting in elderly male inguinal hernia patients: a review and data analysis. *J Am Coll Surg.* Feb 2011;212(2):251-259 e251-254.
(21) Ferket BS, **van Kempen BJ**, Janssens AC. Assessing predictive performance beyond the Framingham risk score. *JAMA.* Apr 14 2010;303(14):1368; author reply 1369.

Acknowledgements (Dankwoord)

Dit proefschrift (en de auteur ervan) zou er niet zijn geweest zonder de inspanningen en bijdragen van een groot aantal mensen die mij op meerdere niveaus dierbaar zijn. Wat ik hieronder ga schrijven kwalificeert in de regel als het vaakst dan wel enige daadwerkelijk (nauwkeurig) gelezen deel van een proefschrift. Het zal ongetwijfeld afbreuk doen aan de waarde van de rol die zij die ik expliciet zal benoemen gespeeld hebben, maar uiteraard ga ik desalniettemin een poging wagen. En ja, dat gaat persoonlijk worden, dus wees gewaarschuwd ;)

Allereerst mijn promotor en supervisor, prof.dr. M.G. Myriam Hunink. Beste Myriam, wat heb jij veel geduld met mij gehad. Toen wij elkaar in 2007 ontmoetten was er meteen een klik op meerdere fronten. Jij bent degene die in een vroeg stadium in mij geloofde, dat bleef doen, en me in een pril stadium de kans gaf om zonder restricties te beginnen aan een traject wat uitmondde in deze promotie. Je gaf me je boek en een aantal ideeën, maar bovenal de ruimte om zelf een heleboel dingen te leren. Onze gesprekken vingen meestal aan met de stand van zaken van mijn wetenschappelijke bezigheden, om het binnen enkele minuten vaak te hebben over muziek, psychologie (Influence!) en een breed scala aan andere dingen die het leven boeiend en bijzonder maken. Dank ook voor het mij –met zachte hand maar doordachte wijze, over obstakels heen te helpen die al dan niet door mijzelf waren opgeworpen. De ontspannende wandeling in een zonnig park voorafgaand aan ons gezamenlijke interview met de hoofdredacteur van JACC zal me altijd bijblijven.

Leden van de kleine commissie, prof.dr. E.W. Steyerberg, beste Ewout, ik heb altijd een buitengewone bewondering gehad voor de snelheid waarmee jij in staat bent een besliskundig probleem terug te brengen tot de geabstraheerde kern, en wanneer normale stervelingen zoals ik nog 'in awe' zijn van het gemak waarmee zo'n model zich ontspruit aan jouw brein, je reeds geanticipeerd hebt op de met het voorgestelde model gepaard gaande validiteits kwesties verderop in het proces. Ook al duurde een ontmoeting nooit per se lang gezien de talrijke parallelle processen waarmee je tegelijkertijd bezig was, de informatiedichtheid was meer dan genoeg om vol nieuwe ideeën richting de 21e verdieping terug te lopen. Beste prof.dr.J.W. Deckers, hartelijk dank voor het plaatsnemen binnen de kleine commissie als klinisch expert aangaande de primaire preventie van cardiovasculaire ziekten, en meer in het bijzonder voor het buitengewoon gastvrije ontvangst op de afdeling cardiologie van het Erasmus MC. Dear Kirsten, thank you for the opportunity to share your wisdom with me and keeping me in check when needed. Moreover, thank you for giving me the trust to participate in the NIH project together with Bart.

Beste leden van de grote commissie, prof.dr. H.J. de Koning, prof.dr. M. Sturkenboom, prof.dr. O.H. Franco: veel dank voor het plaats hebben in mijn commissie.
Beste Paranimfen, Barry de Goede en Marieke A.'Podiumplaatsje' Langhout.
Beste Barry, wat is er in 5 jaar veel gebeurd. Eind 2010 raakte de totstandkoming van onze vriendschap in een stroomversnelling in Boston, waar we dagelijks bijna 2 uur in de Boston Sports Club te vinden waren, op dezelfde dag ons haar verloren, midden in de nacht op een sportveld rondjes aan t rennen waren. Terug in Nederland werkten we het merendeel van de nachten die een week gemiddeld telt aan uitermate belangrijke extra-curriculaire activiteiten in een Jack&Jones V-neck, waarin met een frequentie van 2 maal per 15 minuten 2 vingers de lucht in gingen. Onderwijl evolueerde jouw ontwikkeling in (onder andere) stijl, mode en vormgeving, waar je me (gelukkig) eea van hebt mee gegeven. In een vroeg stadium heb ik de illusie opgegeven ooit jouw niveau daarin te benaderen. Op de een of andere manier maakt jouw simpele nabijheid dat ook mijn persoonlijkheid ongemerkt wordt geuppergraded. Als een soort onaantastbare twee-eenheid bewogen we ons voort op de betere feestjes van 010. Zo lang ik je ken ben ik jaloers op je drive en doorzettingsvermogen (naast je conditie, symmetrie, morfologie, social skills, het gegeven dat je een briljant chirurg gaat zijn en het feit dat ik een van de uitverkorenen ben die je vertrouwt, naast nog 100 andere dingen). Het feit dat jij in staat bent ver bovengemiddeld succesvol te zijn in zaken waar je niet van nature dol op bent –maar die je desalniettemin gewoon doet, is echt bewonderingswaardig. Ik heb vaak het idee dat je jezelf niet eens realiseert hoe bijzonder dat wel niet is omdat je ook nog eens een niveau van perfectionisme nastreeft op gebieden die je intrinsiek niet eens echt aan het hart gaan. Ik ken je kracht dan ook wanneer je die onfeilbare drive en skills samenbrengt met iets wat je echt wil, en weet dat je elk bestaand niveau van iets wat jij echt wil zal overstijgen, of beter gezegd opnieuw zal definiëren. Daarnaast ben je zo inherent geworden aan mijn geschiedenis de afgelopen jaren dat ik je als familie beschouw. Maar bovenal ben ik enorm trots dat jij aan m'n zijde staat vandaag.

Beste Marieke, er zijn een aantal mensen die ik ben tegen gekomen in mijn leven die ik echt heel slim vind. Er zijn ook maar een beperkt aantal mensen in staat mij vrijwel altijd te laten lachen om hun grapjes. Dat ik je voortdurend pest met je spraak komt slechts voort uit n vrij primitieve neiging tot overcompensatie als ik geconfronteerd wordt met de manifestatie van je IQ en/of woordenspel. Dank dat je dat al die tijd getolereerd hebt. Dank ook dat we op een soms absurdistische wijze een soort van Reviaans gevoel van leegte kunnen delen. Als er tijdens de verdediging een vraag wordt gesteld die ik niet echt begrijp, kan ik me troosten met de gedachte dat er iemand dicht in de buurt is die dat wel doet.

Beste Bart, dank dat je me hebt meegenomen in jouw verbazingwekkend snelle ontwikkeling binnen de wetenschap van modelleren en predictie van cardiovasculaire ziekten. Zonder jou was dit proefschrift er niet geweest. Dank ook dat je je niet teveel stoorde aan dat ik veel te snel was afgeleid en te veelvuldig koffie wilde drinken, dank dat je een voorbeeld voor me bent en blijft, en dank ook dat ondanks een buitengewoon bijzondere persoonlijkheid waarvan veel mensen slechts een glimp te zien krijgen, ik

je ook persoonlijk een beetje heb mogen leren kennen. Ik heb een waanzinnig leuke tijd met jou en je familie in Toronto gehad. Meer dan vereerd ben ik nog steeds dat ik paranimf op jouw promotie mocht zijn.

Beste Jan-Willem, er zijn niet veel mensen die me kennen zoals jij. Je hebt je wel eens laten ontvallen dat het soms lastig was om vrienden met me te zijn omdat het leek alsof ik in veel dingen 'beter' zou zijn, maar als ik zo vrij mag zijn geloof ik heilig dat jouw invloed in mijn leven groter is geweest dan andersom. Nog steeds heb ik enorm respect voor de innerlijke kracht die je hebt waarmee je ooit besloot te kiezen voor wat jij echt wilde, de uitdaging die je durfde aan te gaan en de ontwikkeling die je daarna in korte tijd hebt doorgemaakt. Op zo'n niveau keuzes durven maken is iets waarvan ik hoop dat ik dat ook ooit een beetje kan. Alsof dat nog niet genoeg was komt daar bij dat je in staat bent volledig jezelf te blijven en dat soort keuzes kan maken, zonder dat je voorbij gaat aan anderen in dat proces. En dat kan je dan ook nog eens op een manier zonder ook maar enige vorm van trots en waardigheid te verliezen. Ik benijd je daarom. Ook al zien we elkaar weinig zal ik je altijd blind vertrouwen. Ik koester de herinnering aan het moment dat Salijn pas geboren was en je haar in mijn armen toevertrouwde om bij Roos te gaan kijken.

Beste Bardia, beste matti: toen wij elkaar voor het eerst ontmoetten dachten we ongeveer hetzelfde van elkaar, en diezelfde conclusie kunnen we jaren later nog steeds trekken, zij het met een totaal ander substraat. Ik ben bevoorrecht dat ik jou in die mate heb mogen leren kennen dat ik een van de mensen ben die jij vertrouwt. Ik heb oneindig vaak moeten denken dat het onmenselijk is hoe veel jij aankan op persoonlijk, emotioneel en professioneel vlak tegelijkertijd (en er dan nog steeds zo goed uitzien) dat ik tenminste in halfgoden ben gaan geloven. Ik bewonder de manier waarop je met een gevoel voor stijl en een groter goed –waarmee ik me slechts ten dele kan identificeren op het niveau waarop jij dat doet, vaker dan niet een veel lastigere keuze maakt dan een louter pragmatisch iemand zou doen. Je adagio 'stijl voor alles' omvat een door jou nagestreefde levenswijze die eigenlijk ook alleen maar voor iemand van jouw kaliber in zijn volledigheid kan worden begrepen en gepoogd na te leven. Dat blijft voor mij een voortdurende inspiratie.

Beste Joost, onze geschiedenis dateert uit een tijd dat er alleen nog maar potentie leek te bestaan met een nog niet concreet geduid optimisme, waarin ik altijd tegen jouw zelfverzekerdheid, openheid, wil en intelligentie heb opgekeken. Ik heb altijd gevoeld dat jij vaak al een paar stappen verder was in de manier waarop jij mensen, relaties en de wereld zag, maar je wachtte altijd geduldig op me. Door jou heb ik in een gradueel proces onbevooroordeeld leren luisteren, de waarde van autonomie leren kennen en een besef van een onbeschrijfelijk aantal zaken van belang gekregen, die ik zonder jou niet had gehad of pas veel later wellicht had begrepen. Dat je tegelijkertijd een van m'n beste vrienden bent geworden en gebleven is iets waar ik buitengewoon dankbaar voor ben.

John en Thea, Pappa en Mamma, zoals in de eerste alinea van dit dankwoord valt af te leiden wil ik jullie allereerst bedanken voor het verschaffen van alle ingrediënten die me hebben gemaakt tot wat ik nu ben, alle liefde, alle ondersteuning, alle ruimte, alle hulp. Pap, zelfs nu ik geacht word volwassen te zijn en tal van studies heb afgerond, is er één iemand in mijn leven die altijd raad weet wanneer ik op wat voor manier dan ook in paniek ben (ook al is dat zelden), en dat ben jij. Al bel ik midden in de nacht, slechts een door jou in alle rust uitgesproken 'ja?', wanneer mama de telefoon aan jou geeft is voldoende om mij meteen het gevoel te geven dat alles goedkomt. Een nieuw bed, auto of set winterbanden is vaak al tot in de puntjes georkestreerd zonder dat ik de behoefte ooit hardop heb uitgesproken; je weet vaak al voor ik het zelf weet wat ik nodig heb. Daarnaast lees je mij als geen anders- zonder iets te zeggen weet jij eigenlijk in een oogopslag wat er bij me speelt. Vaak verdenk ik je er ook van dat je van te voren al weet hoe zaken gaan lopen, maar je hebt me nooit een strobreed in de weg gelegd tot dezelfde conclusie te komen door het me zelf te laten ervaren. Mama, voor mij ben jij een onuitputtelijke bron van zorgzaamheid. En hoewel onuitputtelijke bronnen misschien normaal zouden overstromen, weet jij die zorgzaamheid vorm te geven zonder dat iemand het ooit als een overvloed beleeft. Je hebt een formidabel talent jezelf weg te cijferen, en nooit in een strijd te belanden slechts om het uitoefenen van macht. Toch -wanneer jou iets aan het hart gaat, zal wat jij wil ook gebeuren, en daarmee schuilt in jou een bewonderingswaardig grote kracht, die misschien niet door eenieder wordt opgemerkt, maar altijd aanwezig is. Ik zie elke dag uit naar de ochtend en welterusten appjes die altijd een glimlach bij me ontlokken, omdat ze me telkens herinneren dat je er altijd voor me bent. Ik zal nooit vergeten hoe het voelde toen je me voor de deur van de Schaepmanlaan uitzwaaide, toen ik voor het eerst met een grote weekendtas vol kleren naar m'n kamer in Tilburg afreisde.

Babs, m'n grote zusje, ik herinner me nog meer dan goed dat ik bij pa en ma thuis zat te wachten tot je belde vanuit het ziekenhuis. Ik beeldde me in dat het krijgen van een nichtje – het eerste kindje van m'n zus, me heus niet zoveel zou doen. Laconiek liep ik door de schuifdeuren van het Groot Ziekengasthuis, nog wat slaapdronken gezien het vroege uur. Ik heb nog nooit ergens zo ver naast gezeten. Toen ik Benthe zag, toen ik jou en Aaron met haar zag, toen ik d'r geluidjes hoorde, werd ik geraakt door een gevoel van kwetsbaarheid. Het voelde alsof ze ook (een beetje) bij mij hoorde. Ik weet vrij zeker dat –hoewel ik daar (zoals het hoort) zelf nooit direct getuige van ben geweest, je tegen anderen met veel trots over me spreekt. Ik hoop dan ook dat het je niet zal verbazen als ik zeg dat ik over jou aan anderen ook met heel veel trots vertel. Hoe jij in staat bent mensen met een volstrekt uniek en verschillend ontwikkelingsniveau, individuele en extreme gevoeligheden, handicaps, persoonlijkheden, temperamenten en culturen te doorgronden, te weten wat ze voelen en wat ze bedoelen als ze zich op een voor een normaal iemand totaal onverklaarbare manier uiten en gedragen, vind ik fenomenaal. Het duizelt me helemaal als ik bedenk dat je ook nog in staat bent de groepsdynamiek en interacties tussen zulke individuen te managen. Wat me daarom weer niet verbaast is dat je samen met Aaron twee zulke heerlijke boefjes hebt gekregen, die met een gezonde overdosis aan temperament en persoonlijkheid samen de wereld aan het

ontdekken zijn, en waarvoor ik dankbaar ben dat ik daar als oom deelgenoot van mag zijn. Aaron, toen ik je voor het eerst ontmoette wist ik (en de rest van de familie) dat het goed zat. M'n zusje heeft (gezien haar eigen temperament –dat ik al sinds m'n geboorte ken ;)), een evenzo sterke persoonlijkheid als tegenwicht nodig, en het moge duidelijk zijn dat ze die in jou gevonden heeft. Ik zou je tekort doen om je slechts als partner/vader van aan te duiden, dus wil tenminste hebben opgemerkt dat ik een ongekend respect heb voor de manier waarop je je werk, gezinsleven en leidende rol als oudste zoon van je familie in Cromvoirt weet te combineren. Daarnaast ben je waanzinnig sociaal en gevat, en weet je overal -van een lokale kroeg tot de meest pretentieuze hipster lounge van Rotterdam, een feestje te bouwen.

Lieve Sanne, hoewel onze ontmoeting vrij exact te duiden is (een kerk!), evenals het tijdstip en de omstandigheden, weet ik eigenlijk niet goed waar te beginnen. Beiden met torenhoge muren ter bescherming van onze meest kwetsbare gevoelens, beiden met een sterk gevoel van trots en eigenwaarde, en elk een vrij extensieve geschiedenis in (bijna) totaal verschillende werelden, begon een reis van uitersten. Extreem dichtbij en soms extreem veraf, als twee sterk gepolariseerde magneten waarvan de richting van het veld soms ineens om kon slaan. In dat proces heb ik dingen met je gedeeld, beleefd en ervaren die ik onmogelijk ooit nog met iemand anders op die manier zal kunnen. Terugkijkend daarop zijn het niet eens (de intensiteit van) die ervaringen op zich die me bijstaan; wel dat ik ze heb mogen beleven met jou. Hoewel de richting van onze velden soms maakte dat er momenten zijn geweest waarop we niet bij elkaar waren, is er altijd een onzichtbaar lijntje geweest dat ons onlosmakelijk met elkaar verbond. En dat lijntje zal voor altijd blijven bestaan.

Leden en oud leden van de ART groep, Farzin, als twee 'laatste der Mohikanen' troffen we elkaar vaak op latere uren op de 25e. Er zijn onnoemelijk veel zaken waarmee jij je tegelijkertijd bezig kan houden en succesvol in weet te zijn. Daarnaast ken jij op tal van terreinen wegen waarvan ik –wanneer je ze niet met me had gedeeld, het bestaan nooit had weten te vermoeden. Nathalie, jij hebt me als eerste ooit meegenomen naar de Frankborrel, waarmee er een wereld voor me openging. Een vrij omvangrijke wereld mag ik wel zeggen ;)

Alle andere leden, collega's, jaargenoten, teveel om met naam en toenaam op te noemen: hartelijk dank!