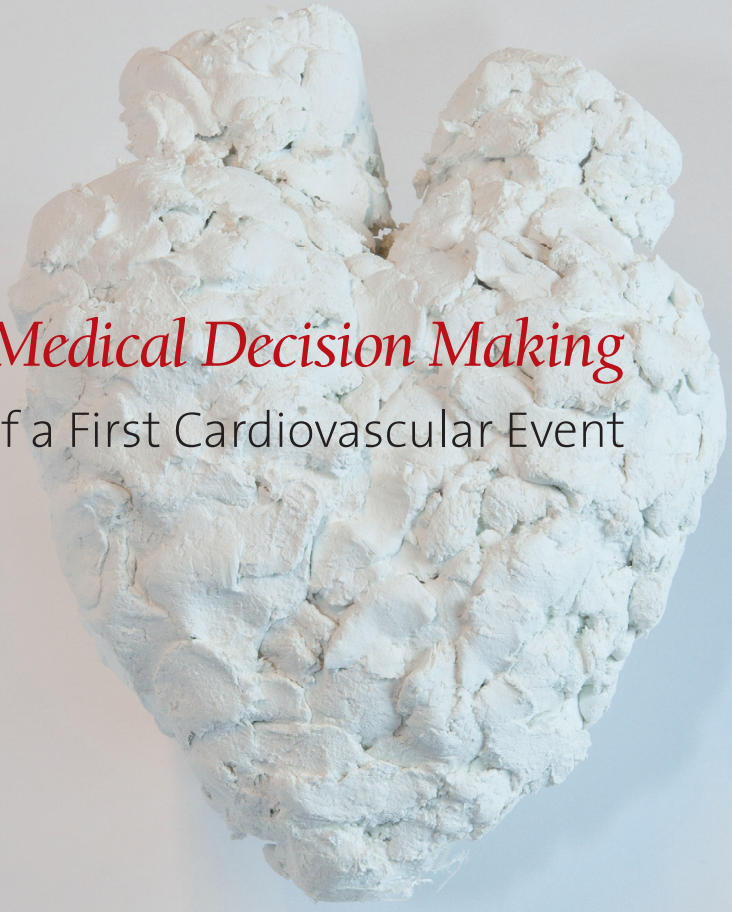

Personalized Medical Decision Making

for Prevention of a First Cardiovascular Event

Bart Ferket

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Personalized Medical Decision Making for Prevention of a First Cardiovascular Event
Dissertation, Erasmus University, Rotterdam, the Netherlands

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Personalized Medical Decision Making
for Prevention of a First Cardiovascular Event

Geïndividualiseerde medische besluitvorming ter
preventie van een primair cardiovasculair incident

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
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Prof. dr. H.G. Schmidt

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	Dr. S.E. Petersen
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CONTENTS

Chapter 1

General introduction and outline

BACKGROUND

Epidemiology and etiology

Atherosclerotic cardiovascular disease (CVD) remains the leading cause of mortality worldwide, accounting for approximately 30% of total mortality (1). In the Netherlands, the total number of coronary attacks a year is estimated to be 82,100: 6.13 per 1,000 men and 3.91 per 1,000 women (2). Approximately 35,600 experience a stroke each year: 2.12 per 1,000 men vs. 2.23 per 1,000 women (3). The majority of CVD events comprises first events. According to American Heart Association statistics, of all coronary attacks approximately 60% is a primary event, whereas 75% of all strokes are first strokes (4).

CVD is a multi-factorial disease par excellence, with a number of modifiable physiological risk factors such as high blood pressure, high total cholesterol, high blood glucose, and high body-mass index. Also modifiable behavioral factors play a causal role and include increased alcohol use, (second-hand) tobacco smoking, unhealthy diet and physical inactivity. The risk of disease can potentially be diminished through the modification of these risk factors in individuals without a history of CVD (5).

Preventive strategies

Two different approaches for primary prevention exist: 1) the population strategy including one-size-fits-all type of interventions aimed at large groups of individuals selected on demographics only (6,7); and 2) the individualized or personalized strategy, which comprises interventions tailored to single individuals taking into account multiple risk factors and preferences. Examples of the population strategy are: smoking bans in public spaces, salt reduction in processed food, and the poly-pill concept, i.e. recommending the use of a pill that consists of different cardio-protective medications to all adults aged 55 years and older (8).

The theoretical benefit of a perfect personalized approach should, however, always be equal or larger than the benefit of a population-based approach. For example, let us consider the choice between starting preventive aspirin treatment or no aspirin treatment for a group of elderly men. If the effect of aspirin on CVD is expected to be beneficial in the majority of men, but harmful in some, then making the optimal decision per individual will result in a better average outcome than either to treat all or to withhold aspirin.

Personalized primary CVD prevention is however limited by the need of gathering sufficient information about the individual's expected outcomes. One should be able to individualize risk estimates, preventive treatment effects, and preferences. This requires medical screening and profound discussions between well-informed primary care physicians and clients. In order to have a large scale impact on CVD burden, the personalized approach should be offered to a large group of individuals, which may result in unwarranted harms by the screening tests and may require enormous healthcare resources.

Current practice

The Framingham Study is regarded as the landmark study that moved the CVD research field from investigating causal associations between factors such age, gender, smoking, diabetes mellitus, blood pressure, lipid levels and CVD towards prediction modeling of future CVD events

with these factors (9). Within the first cohort, 5,209 men and women between the ages of 30 and 62 were recruited in 1948 from a small town Framingham, Massachusetts. Later on, new cohorts were enrolled to reflect a more diverse and up to date population. The risk scores derived within these Framingham Study cohorts can be used to calculate an individual's CVD risk (9-13). These Framingham risk scores have been an inspiration for the development of similar risk scores in other regions of the world, such as the European Systematic COronary Risk Evaluation (SCORE) charts (14), the German Prospective Cardiovascular Münster (PROCAM) risk scores (15), and the United Kingdom's QRISK risk scores (16,17). Within the last two decades, these traditional risk scores are increasingly recommended for the allocation of effective preventive interventions such as statin therapy, blood pressure lowering therapy and lifestyle counseling.

Challenges

With the increasing number of novel cardiovascular biomarkers, including imaging tests, becoming available, traditional risk scores can potentially be improved. In addition, the results of randomized clinical trials show that the indication for preventive interventions should probably be broadened to lower risk individuals and individuals with elevated novel risk marker levels (18,19). Furthermore, because health care has become less paternalistic, and patients are more and more involved in the medical decision-making process, there is a need for a more informative representation of health outcomes. The communication of competing CVD outcomes and other outcomes for different clinical scenarios is necessary to inform both the physician and the client such that they can "equally" participate in the decision-making. The extent of this shared decision-making process will vary per situation, but with regard to primary prevention it might be especially important, because the freedom of choice to initiate an intervention seems larger than when disease is already present.

AIMS AND OUTLINE OF THIS THESIS

The main objective of this thesis was to develop and evaluate new tools to improve personalized primary prevention of CVD. In *Part 1*, we aimed to evaluate the currently recommended practice regarding personalized prevention of first CVD events. In *Part 2*, we aimed to improve the currently recommended practice by decision and prediction modeling.

Part 1

In *Chapter 2*, we describe the recommendations of guideline groups with respect to cardiovascular health checks for the general population.

Cohort studies have demonstrated that the performance of traditional risk scores can be improved by adding cardiovascular imaging. In *Chapter 3* we have systematically reviewed and critically appraised guidelines that contained recommendations about these imaging tests.

Abdominal aortic aneurysms (AAAs) are usually not included as an outcome in most traditional risk scores. Ruptured AAAs account for 0.5% of the total mortality in Western countries. However, given its long screen-detectable preclinical phase and the availability of an accurate and safe screening test in the form of ultrasound, a window of opportunity for mass screening

seems to be present. In *Chapter 4*, we have reviewed guidelines on AAA screening and discussed how these could be further personalized.
Subjects with peripheral artery disease are at high risk for CVD regardless of the presence of symptoms such as intermittent claudication. Therefore screening for asymptomatic PAD may be useful. In *Chapter 5*, we have critically appraised PAD screening guidelines.

Part 2

Multi-state computer simulation models can be used to take into account multiple outcomes and the competing risks of these outcomes. An elegant solution to keep track of events for different individual risk profiles and preferences is the use of microsimulation. In *Chapter 6*, we have evaluated the validity of the predictions made by such a model: the Rotterdam Ischemic heart disease and Stroke Computer simulation (RISC) model. In many cardiovascular prevention modeling studies, preventive treatment effects are modeled through modification of risk factor levels. For example, statin therapy can be modeled to beneficially modify cholesterol levels in individuals adhering to the therapy. When cholesterol levels are modeled to affect CVD risk, the CVD event rates will automatically drop in these individuals. This approach can be criticized, because it does not necessarily have to be concordant with treatment effects as obtained from experimental research. In *Chapter 7*, we describe the implications of using different methods for modeling the effect of statin therapy for primary prevention of CVD on decision-making. Once statin therapy has been prescribed for primary preventive use, it is generally continued over the remainder of the course of the lifetime. Therefore, information for shared decision-making should also reflect a lifetime horizon. In *Chapter 8*, we used the RISC model to predict lifetime benefits of statin therapy to the individual's risk profile at baseline, and developed decision tools that can support the shared-decision making. Distinguishing intracerebral hemorrhage from ischemic stroke may be important for risk communication and decision-making on interventions that act differently on both outcomes. In *Chapter 9*, we developed prediction models for a 10-year risk assessment of intracerebral hemorrhage and ischemic stroke, while taking into account competing risks. In *Chapter 10*, we validated a long-term Framingham CVD risk function that takes into account competing non-CVD death risk (13) using Rotterdam Study data. This function was originally designed to predict a combined endpoint of coronary heart disease and stroke. However, because it is known that risk factors and preventive interventions may act differently on these CVD subtypes, we also developed separate prediction models. In *Chapter 11*, we selected four of the most promising novel risk markers, including two imaging markers, and evaluated whether they would have added predictive value beyond Framingham risk scores in the U.S. general population by using microsimulation. For individuals without a history of CVD, but with stable chest pain, more invasive testing is justified, because generally the risk of future CVD is much higher than if no symptoms are present. In *Chapter 12*, we compared the costs and effectiveness of a novel coronary computer tomography (CT) based test strategy vs. the traditional diagnostic strategy using a Markov model.

Finally, *Chapter 13* summarizes the main findings of this thesis. We additionally discuss the methodological issues that have been raised in these research projects and provide future perspectives for clinical practice and further research.

REFERENCES

1. Lozano R, Naghavi M, Foreman K et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-128.
2. Poos MJ, Dis van I, Engelfriet PM, Deckers JW. Hoe vaak komen coronaire hartziekten voor en hoeveel mensen sterven eraan? In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven: RIVM, 2011.
3. Gommer AM, Poos MJ. Beroerte: prevalentie, incidentie en sterfte naar leeftijd en geslacht. In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven: RIVM, 2011.
4. Roger VL, Go AS, Lloyd-Jones DM et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125:e2-e220.
5. Lim SS, Vos T, Flaxman AD 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;380:2224-60.
6. Rose G. Sick individuals and sick populations. Int J Epidemiol 1985;14:32-8.
7. Wald NJ, Simmonds M, Morris JK. Screening for future cardiovascular disease using age alone compared with multiple risk factors and age. PLoS One 2011;6:e18742.
8. Wald NJ, Wald DS. The polypill concept. Heart 2010;96:1-4.
9. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. AmHeart J 1991;121:293-298.
10. 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.
11. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22:312-8.
12. D'Agostino RB, Sr., Vasan RS, Pencina MJ et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-53.
13. 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.
14. Conroy RM, Pyorala K, Fitzgerald AP et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987-1003.
15. 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.
16. Hippisley-Cox J, Coupland C, Vinogradova Y et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. Bmj 2008;336:1475-82.
17. 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.
18. Cholesterol Treatment Trialists' Ctt C. 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.
19. Ridker PM, Danielson E, Fonseca FA et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-207.

Part 1

Systematic reviews

Chapter 2

Systematic review of guidelines on cardiovascular risk assessment: Which recommendations should clinicians follow for a cardiovascular health check?

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ABSTRACT

Objective

To appraise guidelines on cardiovascular risk assessment to guide selection of screening interventions for a health check.

Data sources

Guidelines in the English language published between January 1, 2003, and May 2, 2009, were retrieved using MEDLINE and CINAHL. This was supplemented by searching the National Guideline Clearinghouse, National Library for Health, Canadian Medical Association Infobase, and G-I-N International Guideline Library.

Study selection

We included guidelines developed on behalf of professional organizations from Western countries, containing recommendations on cardiovascular risk assessment for the apparently healthy population. Titles and abstracts were assessed by 2 independent reviewers. Of 1984 titles identified, 27 guidelines met our criteria.

Data extraction

Rigor of guideline development was assessed by 2 independent reviewers. One reviewer extracted information on conflicts of interest and recommendations.

Results

Sixteen of 27 guidelines reported conflicts of interest and 17 showed considerable rigor. These included recommendations on assessment of total cardiovascular risk (7 guidelines), dyslipidemia (2), hypertension (2), and dysglycemia (7). Recommendations on total cardiovascular risk and dyslipidemia included prediction models integrating multiple risk factors, whereas remaining recommendations were focused on single risk factors. No consensus was found on recommended target populations, treatment thresholds, and screening tests.

Conclusions

Differences among the guidelines imply important variation in allocation of preventive interventions. To make informed decisions, physicians should use only the recommendations from rigorously developed guidelines.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality in Western society, accounting for approximately one-third of total mortality (1). Much of the burden of CVD can potentially be relieved by primary prevention, that is, reducing CVD incidence in the apparently healthy population. Detecting and treating those at highest CVD risk is regarded as an essential complement to a population-based approach (2). The primary care physician plays a pivotal role in providing prevention on the individual level and is thus essential for the success rate of this strategy. However, most physicians find implementing even rudimentary preventive services difficult, and the management of increased CVD risk remains suboptimal (3).

Although historically controversial (4,5), cardiovascular health checks have now been widely accepted as a means to efficiently detect high-risk individuals in primary care practice. As a result of the Diabetes, Heart Disease and Stroke pilot studies, UK citizens aged 40 to 74 years will be offered a cardiovascular health check every 5 years. This includes a questionnaire on risk factors and measurement of weight, hip to waist ratio, blood pressure, and total cholesterol level. People at high risk for developing diabetes undergo measurement of glucose levels (6). In the United States, cardiovascular health checks are already common practice as part of the periodic health examination (7). In the absence of a blueprint for the content of cardiovascular health checks, decisions on selection of appropriate individual screening interventions should be guided by the best available medical evidence. For translating research into clinical practice, clinical practice guidelines are commonly assumed to be the remedy. Clinical practice guidelines are defined by the Institute of Medicine as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (8). However, guidelines on the same topic can conflict with each other, and concern exists about the quality and independence of guidelines. Therefore, clinicians should be able to identify guidelines that are developed systematically and provide transparent estimates of the benefits and harms of interventions (9,10). Various notable organizations have developed guidelines containing recommendations for cardiovascular screening to prevent a first CVD event. Although guideline compendiums exist (11), it is not feasible for the busy physician to identify and critically appraise all possible relevant guidelines.

We therefore conducted a systematic review of guidelines containing recommendations for cardiovascular risk assessment in apparently healthy adults, that is, adults free of established CVD who are not already receiving treatment for high-risk conditions such as diabetes, hypertension, and hypercholesterolemia. We appraised guidelines using a validated instrument and assessed potential conflicts of interest. Finally, we examined recommendations from rigorously developed guidelines in detail to guide primary care physicians in deciding which screening interventions to use within a cardiovascular health check.

METHODS

Data sources and guideline selection

To identify appropriate guidelines, a literature search was performed by using MEDLINE and

CINAHL between January 1, 2003, and May 2, 2009. We supplemented this by searching the following 4 guideline-specific databases: the National Guideline Clearinghouse (United States), National Library for Health on Guidelines Finder(United Kingdom), Canadian Medical Association Infobase (Canada), and G-I-N International Guideline Library (http://www.g-i-n.net). We restricted our search to national guidelines from the United States, Canada, the United Kingdom, Australia, and New Zealand and to international guidelines written in English.

The MEDLINE search syntax served as a basis for all search strategies. The syntax consisted of the following 3 elements intersected by the Boolean term "AND": 1) subject headings and free text terms for interventions regarding the health check content (ie; risk assessment, screening, early detection, early diagnosis, early intervention, periodic evaluation, periodic examination, periodic check-up, prevention, and risk management); 2) subject headings and free text terms for conditions that could define high risk for CVD and CVD outcomes that should be prevented (ie, arteriosclerosis, atherosclerosis, hypertension, hyperlipidemia, diabetes, cardiovascular disease, coronary heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, and aortic aneurysm); and 3) publication types and title words that cover clinical practice guidelines (ie, practice guideline, guideline, guidance, standards, statement, position paper, position stand, recommendation, and consensus). A search on a number of Websites of guideline development organizations was performed for additional relevant guidelines. Details on the search syntax are provided in *Appendix 1*. Retrieved references were considered guidelines if they met the Institute of Medicine definition. We only considered guidelines recommending cardiovascular risk assessment specifically aimed to prevent a first CVD event. We excluded guidelines if they 1) did not contain recommendations involving the apparently healthy adult population, 2) were entirely focused on early detection of CVD, 3) were not produced on behalf of a professional organization, or 4) were not applicable to Western countries. In addition, only guidelines produced or updated from 2003 onward were eligible for inclusion to be more certain about the currency of guidelines (12).

Review of titles and abstracts was assessed independently by two of us (B.S.F. and E.B.C.). For an article to be excluded, both reviewers had to agree that the article was ineligible. For abstracts, discrepancies between the reviewers were discussed and resolved by consensus. The final selection for full data extraction was made by the first reviewer (B.S.F.) because of the broad array of potentially eligible guidelines.

Guideline quality assessment

We used the 7-item Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument (13) to determine the quality of development for each included guideline. This domain considers the reporting of 1) methods to search for evidence; 2) criteria for selecting the evidence; 3) methods for formulating the recommendations; 4) health benefits, adverse effects, and risks; 5) supporting evidence; 6) procedures for external expert review; and 7) the update process. Each item is rated on a 4-point Likert scale. In conformity with the instructions (14), two of us (B.S.F. and J.J.V.) independently rated the 7 items. Websites of guideline developers were examined by both reviewers for background information on the development processes followed. Average rigor scores were obtained by expressing the sum of individual item scores as a percentage of the maximum possible

score. Reproducibility of the 2 reviewers' average rigor scores was good, with an intraclass correlation coefficient of 0.78. We ranked included guidelines according to their average scores. Moreover, editorial independence from the funding body and external funding and disclosure of relationships with industry by individual guideline group members were assessed by one reviewer (B.S.F.).

Recommendation extraction

One reviewer (B.S.F.) extracted all relevant recommendations from each included guideline. General lifestyle advice was not considered. Subsequently, a recommendation matrix grouped by screen-detectable conditions was constructed. Each matrix was divided into 1) a methods section, 2) target group and delivery of screening, 3) recommended screening tests, and 4) thresholds for follow-up. Strength of recommendation was classified as "for," "consider," "not for not against," "insufficient evidence," and "against." If possible, cardiovascular risk factors were classified into major, underlying, and emerging risk factors according to the World Heart and Stroke Forum 2004 scientific statement (42). In this report, we present only the recommendations of guidelines wwith an average rigor score of 50% or higher (indicating considerable rigor).

RESULTS

The search retrieved 1984 titles, of which 323 were identified as potentially eligible. Many were excluded on the basis of the abstract (n=209) and on review of the full report (n=87). Finally, 27 guidelines relevant to cardiovascular risk assessment were included (Figure 1). Table 1 summarizes the selected guidelines, together with the rigor score and conflict of interest results, categorized by the following screen-detectable conditions: total cardiovascular risk, dyslipidemia, hypertension, and dysglycemia (diabetes mellitus, impaired glucose tolerance, and/or impaired fasting glucose). Eleven guidelines did not report that they were developed independently from funding organizations or have a statement about conflicts of interest of group members. The development of 2 guidelines (from the New Zealand Guidelines Group [NZGG] and the National Health and Medical Research Council [NHMRC]) was funded by external governmental sources. Guidelines from the Canadian Diabetes Association (CDA) and the International Diabetes Federation (IDF1 and IDF2) were financially supported by industry partners. Although sponsors did not take part in the development of these guidelines, commercial organizations were allowed to comment on draft versions of the IDF1. Only 2 guidelines (from the American Heart Association [AHA1] and the CDA) reported that recusal of group members with conflicts of interest was accomplished when relevant areas were under discussion.

Seventeen of the 27 guidelines had an average rigor score equal to or greater than 50%. Recommendations for total cardiovascular risk assessment extracted from these guidelines are demonstrated in Table 2, excluding the recommendation of the AHA2 guidelines that did not explicitly describe treatment thresholds. Advice concerning screening primarily for single risk factors (dyslipidemia, hypertension, and dysglycemia) are tabulated in Tables 3, 4, and 5.

Areas of agreement

Recommendations of 16 of 17 guidelines supported risk assessment. In general, there was consensus on how screening tests should be administered to the target population. A selective screening approach based on prior knowledge of patient characteristics (record-based screening) or during non-preventive patient visits (case finding or opportunistic screening) was advocated in 10 of 17 guidelines. A mass screening approach was suggested as an alternative by only 1 guideline (from the National Heart, Lung, and Blood Institute [NHLBI]). Many guidelines recommended integrating age, sex, smoking, blood pressure, and lipid levels into total cardiovascular risk assessment by using prediction models (Tables 2 and 3). In only 2 hypertension guidelines (from the US Preventive Services Task Force [USPSTF2] and the AHA2 guidelines) were treatment decisions merely guided by elevated blood pressure levels (Table 4). The recommended prediction models were all based on the concept that CVD is best predicted by multiple risk factors and that these risk factors interact. If a risk score was not recommended as a primary screening test, it was frequently used to guide treatment in a second stage for individuals with elevated single risk factors (USPST1 and NHLBI guidelines).

Thresholds for initiation of treatment were based on short-term (5- or 10-year) risk for CVD, with exceptions often made for those with extreme levels of single risk factors. In general, the same thresholds across guidelines were used for the initiation of treatment with aspirin, statins, and antihypertensives. The guideline from the European Society of Cardiology for total cardiovascular risk assessment (ESC1) used a higher threshold for the use of aspirin because of the risk for major gastrointestinal tract bleeding. The ESC1 guideline may represent a common, cautious European viewpoint. However, we did not observe a more conservative attitude with respect to preventive treatments among the European guidelines compared with the others.

Guidelines that specifically covered dysglycemia screening were mainly focused on selecting individuals for interventions to lower glucose levels and did not report or were short on initiation of statin and aspirin therapy (Table 5). Guidance for these treatments was based on single risk factors, and none of the recommendations contained models predicting CVD. Fasting glucose level was usually the test of first choice, except for 1 guideline (ESC3) in which an antecedent risk score for developing type 2 diabetes mellitus was recommended. Although guidelines did not make firm statements about screening intervals, frequently reported periods of screening for individuals at low risk were 5 years for total cardiovascular risk and dyslipidemia screening, 2 years for hypertension screening, and 3 years for dysglycemia screening. Only 2 guidelines based these intervals on modelling studies (NZGG and USPSTF3).

Areas of disagreement

We found no consensus on target populations for screening among the recommendations (Tables 2, 3, 4, and 5). Target groups varied from middle-aged and younger adults with and without risk factors to unspecified patients asking for screening themselves. From these recommendations, health checks that included assessment of lipid levels, blood pressure, and dysglycemia could be designed that would start at 20 years of age (using the NLHBI, USPSTF2, and ESC3 guidelines) or that would start at middle age (eg, using the guidelines from the Scottish Intercollegiate Guidelines Network [SIGN] and the NHMRC guidelines).

Guidelines on total cardiovascular risk, dyslipidemia, and hypertension screening (Tables 2, 3,

and 4) disagreed on tests to be performed in addition to those primarily recommended. The most frequently recommended risk modifiers not included in formal risk assessment were a family history of premature CVD, obesity, and socioeconomic deprivation. In the total cardiovascular risk recommendations, only 1 prediction model (the ASSIGN score) was used that incorporated some of these risk factors, namely, family history and socioeconomic status in addition to the major risk factors. Other total cardiovascular risk guidelines provided instructions for simple multiplication of the predicted risk by the relative risk of the additional risk factor (guidelines from the National Institute for Health and Clinical Excellence [NICE] and Canadian Cardiovascular Society [CCS]) or only made general statements about the relative contribution to the total cardiovascular risk estimation (SIGN, AHA1, NZGG, and ESC1 and guidelines from the World Health Organization [WHO]).

Recommendations for dysglycemia screening (Table 5) varied in strength. For example, for a 60-year-old patient without risk factors, screening could both be not supported and recommended at the same time, depending on which guideline the physician follows. Discrepancies in decision making could also occur with regard to the initiation of treatment guided by total cardiovascular risk (Table 2). Apart from differences in thresholds indicating high risk, recommended risk models varied over the use of datasets, predictors, and endpoints, including fatal and non-fatal CVD outcomes. For example, the NICE, SIGN, CCS, and NHLBI guidelines all used a threshold of 20% to define high risk. The NICE guidelines recommended the 1991 Framingham model using coronary artery disease and stroke events as a composite endpoint, whereas the CCS and NHLBI guidelines used Framingham models for predicting coronary artery disease alone (ie, without stroke). The SIGN guideline endorsed the ASSIGN score, which includes coronary artery disease, heart failure, aortic aneurysm, peripheral arterial disease, and stroke. Because of this lack of consistency, making comparisons of recommended indications for aspirin, statin, and antihypertensive therapy and intensive lifestyle changes is not straightforward.

COMMENT

We identified 27 guidelines involving cardiovascular risk assessment that could be performed within a cardiovascular health check. A great variation in rigor of development and transparency about conflicts of interest was found among the guidelines. Guidelines on screening for total cardiovascular risk and dyslipidemia embraced, to a different extent, decision making based on multiple risk factors. This approach contrasted with the recommendations for hypertension and dysglycemia screening, which focused on single risk factors. Most of the guidelines supported a selective screening strategy. We found differences between guidelines with respect to the selection of target groups, screening tests in addition to those for major CVD risk factors, and treatment thresholds. Different statements about strength were given to recommendations that considered comparable patient populations with respect to dysglycemia screening. No firm recommendations could be made for screening intervals in people at low risk for developing a first cardiovascular event.

Previously published reviews of CVD prevention guidelines were not systematically performed

or did not use a validated instrument to assess the quality of identified guidelines (43,44). We used a sensitive search strategy to identify guidelines and the AGREE instrument to select guidelines of considerable quality. This article can therefore be of additional value to already available guideline compendiums and libraries such as the US National Guideline Clearinghouse and the UK National Library for Health because these libraries depend on submissions by guideline organizations. Although a guideline synthesis tool can be found on the National Guideline Clearinghouse Web site (45), this tool is only available for a sample of US guidelines.

Despite a number of strengths, there are several limitations that could have biased our findings. First, the AGREE instrument considers the whole guideline and is not intended for individual recommendations. However, a global appraisal will probably reflect the quality of the individual recommendations to some extent. Second, AGREE evaluates a guideline's construction process and not the quality of its content. It is beyond the scope of this review to appraise the quality of the evidence underpinning the recommendations. However, an analysis of underlying evidence should be considered when evaluating guidelines. One would expect that the quality of the development methods correlates with the quality of the content, but it may be possible to create a solid guideline with a poor process. Third, only 2 reviewers rated the AGREE rigor items, and a more precise estimate would be obtained if we could have used more resources. Finally, our search strategy's sensitivity could be improved. We did not use a search engine for an Internet search, and therefore we might have missed some eligible guidelines.

The finding that many guidelines recommended multivariable risk assessment conforms with historical developments. The rationale of its use is explained by studies showing that arbitrary elevations of single risk factors are of little clinical relevance when they are interpreted separately from other risk factors (46). The performance of multivariable risk assessment mainly depends on the selection of appropriate risk predictors. Prediction models using the traditional major risk factors may be updated through inclusion of emerging risk factors (47). However, the additional prognostic value is often questionable (48,49). Few of the reviewed guidelines used a prediction model incorporating 1 or more of the emerging risk factors. The value of general statements about their contribution to risk seems ambiguous if consistency of health care is intended.

Implementation of cardiovascular risk assessment into practice has been shown to be difficult (50). It is questionable whether the generally recommended opportunistic screening strategy could overcome this problem. Arguments in favour of opportunistic screening originate from disappointing results of population based periodic health examinations and nurse-led cardiovascular health checks (5,51,52). Although health information technology may in part solve difficulties (53), the sheer volume of preventive care tasks per patient visit would put an overwhelming pressure on the workload of primary care physicians (54). Periodically inviting individuals for a preventive visit using already recorded determinants could be a valuable alternative. The workload and cost-effectiveness of this strategy will depend on risk factor distributions in the selected target populations and applied thresholds that indicate elevated risk. Given the controversy about target populations, treatment thresholds, and screening intervals, we advocate a decision-analytic approach to resolve these issues (55).

Although guidelines on total cardiovascular risk, dyslipidemia, and hypertension all agreed on added value with screening, those on screening for dysglycemia sometimes disagreed. The case for dysglycemia screening has been uncertain in the absence of randomized trials but becomes stronger with the rising prevalence of overweight (56). Because CVD is by far the leading cause of mortality in persons with diabetes mellitus, preventing CVD seems more crucial than reducing microvascular complications. Although intensive lowering of glucose levels in longstanding diabetes has not been shown to reduce CVD, in patients with newly diagnosed diabetes it may be beneficial (57,58). The efficacy of statins has been shown in a meta-analysis of 14 randomized controlled trials (59). The use of aspirin therapy in diabetes, however, is still controversial (60,61). Included guidelines were predominantly focused on selection of individuals for therapy to lower glucose levels but were not unanimous with regard to statins. Some guidelines advised that all patients with diabetes should receive a statin, whereas most allocated statins only to those with raised cholesterol levels in addition to diabetes. However, sustained benefits of statins are seen even in diabetic patients with low cholesterol levels (59), and thus it is argued that the decision for statin therapy in diabetes should also be based on total cardiovascular risk irrespective of initial cholesterol levels (62). Recommended risk models do not incorporate dysglycemia as a covariate or perform poorly in estimating CVD risk in diabetes (62,63). Prediction models specifically developed for people with dysglycemia (64,65) exist but have to be validated. Integration of dysglycemia screening within a cardiovascular health check thus remains complex.

Some guidelines provided recommendations to select high-risk individuals for aspirin use. Recommended treatment thresholds for aspirin were predominantly the same as those for statins and fixed according to sex and age. These recommendations contrast with the recent conclusions of the USPSTF (66), which established its guidance on an assessment of the net benefit of aspirin, determined by the potential preventable number of CVD events and the potential harm due to gastrointestinal tract hemorrhages. The USPSTF's thresholds for aspirin use depend on age and sex because the risk for serious bleeding increases with age and among men. The approach for aspirin use as demonstrated in the USPSTF guideline could lead to more individualized decision making. However, this approach can be made more sophisticated through expression of the benefit and harm in utility measures and might then also be applicable to the provision of other preventive treatments.

CONCLUSIONS

We identified guidelines providing recommendations for various screening interventions that can be performed within cardiovascular health checks. By using different recommendations, there are several ways to integrate multiple screening interventions into a single program. Although methods for guideline adaptation are available (10), our purpose was not to create one international set of recommendations. Nevertheless, physicians can easily adopt the presented recommendations applicable to their own health context. However, they should be wary of the differences, which can have important consequences for selection of individuals for preventive interventions (67). In addition, physicians should be able to balance the utility

and disutility of potential lifelong preventive treatment. Complete and unbiased information on benefits and harms is thus desirable. Transparency about how judgments have been made within guidelines allows physicians to make informed decisions on adopting recommendations (68). Disclosure of conflicts of interest allows the industry influence on guideline development and the professional integrity of guideline group members to be assessed (69). The AGREE rigor scores of many guidelines demonstrated poor quality, and several guidelines lacked statements about conflicts of interest. We therefore encourage physicians to use the tabulated guidelines with higher AGREE rigor scores and unambiguous declarations about conflict of interest from this review for organizing their cardiovascular health checks.

TABLE 1. CHARACTERISTICS OF 27 GUIDELINES AND 32 RECOMMENDATIONS

Medical Condition	Organization responsible for guideline development	Year	Country that guideline applies to	AGREE Rigour Score, %	Conflicts of Interest
Total Cardiovascular Risk					
NICE (15)	National Institute for Health and Clinical Excellence	2008	United Kingdom	98%	EI, SCI
SIGN (16)	Scottish Intercollegiate Guidelines Network	2007	United Kingdom	83%	-
AHA1 (17)	American Heart Association	2007	United States of America	76%	SCI[ab]
AHA2 (18)	American Heart Association and American Stroke Association	2006	United States of America	71%	SCI[a]
NZGG (19)	New Zealand Guidelines Group	2003	New Zealand	67%	EI, FPO, SCI[a]
WHO (20)	World Health Organization	2007	International	60%	-
ESC1 (21)	European Society of Cardiology	2007	Europe	55%	-
CCS (22)	Canadian Cardiovascular Society	2006	Canada	50%	EI, SCI[a]
NHF1 (23)	National Heart Foundation of Australia, and Cardiac Society of Australia and New Zealand	2005	Australia	43%	SCI[a]
JBS (24)	Joint British Societies	2005	United Kingdom	19%	-
ACS (25)	American Cancer Society, American Diabetes Association, and American Heart Association	2004	United States of America	14%	-
ESC2 (26)	European Society of Cardiology	2007	Europe	14%	SCI[a]
Dyslipidemia					
USPSTF1 (27)	U.S. Preventive Services Task Force	2008	United States of America	95%	EI
NHLBI (28)	National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services	2002 (updated 2004)	United States of America	50%	-
NHF2 (29)	National Heart Foundation of Australia, and Cardiac Society of Australia and New Zealand	2001 (still valid 2009)	Australia	45%	-
ACS (25)	American Cancer Society, American Diabetes Association, and American Heart Association	2004	United States of America	14%	-
Hypertension					
USPSTF2 (30)	U.S. Preventive Services Task Force	2007	United States of America	81%	EI, SCI
AHA2 (18)	American Heart Association and American Stroke Association	2006	United States of America	71%	SCI[a]
BHS (31)	British Hypertension Society	2004	United Kingdom	24%	-
ACS (25)	American Cancer Society, American Diabetes Association, and American Heart Association	2004	United States of America	14%	-
Dysglycemia					
USPSTF3 (32)	U.S. Preventive Services Task Force	2008	United States of America	95%	EI, SCI
NHMRC (33)	National Health and Medical Research Council	2001 (updated 2005)	Australia	79%	FPO
ESC3 (34)	European Society of Cardiology and European Association for the Study of Diabetes	2007	Europe	74%	-
CDA (35)	Canadian Diabetes Association	2008	Canada	74%	EI, FIP, SCI[ab]
CTF (36)	Canadian Task Force on Preventive Health Care	2005	Canada	69%	SCI[a]
AACE (37)	American Association of Clinical Endocrinologists	2007	United States of America	50%	SCI[a]
CCS (22)	Canadian Cardiovascular Society	2006	Canada	50%	EI, SCI[a]
IDF1 (38)	International Diabetes Federation	2005	International	48%	FIP, SCI[a]
IDF2 (39)	International Diabetes Federation	2007	International	24%	EI, FIP, SCI[a]
ADA (40)	American Diabetes Association	2009	United States of America	17%	SCI[a]
ACS (25)	American Cancer Society, American Diabetes Association, and American Heart Association	2004	United States of America	14%	-
DUK (41)	Diabetes UK	2006	United Kingdom	10%	-

Abbreviations: AGREE, Appraisal of Guidelines Research and Evaluation; EI, editorial independence declared; FIP, funding by industrial partner reported; FPO, funding by external public organization reported; SCI, statement about conflicts of interest of group members present. [a] Relationship with industry is reported by any group member. [b]A group member is reported recused when a relevant area is under discussion.

TABLE 2. RECOMMENDATIONS FOR SCREENING FOR TOTAL CVD RISK IN 7 GUIDELINES

	NICE	SIGN	AHA1	NZGG	WHO	ESC1	CCS Step 1	CCS Step 2
AGREE Rigour score	98%	83%	76%	67%	60%	55%	50%	
Method to evaluate evidence	Systematic review; review of published systematic reviews	Systematic review; review of published systematic reviews	Systematic review; review of published systematic reviews	Systematic review; review of published systematic reviews	Systematic review; review of published systematic reviews	Systematic review; review of published systematic reviews	Systematic review; review of published systematic reviews	
Method to formulate recommendations	Consensus development conference	Formal consensus	Formal consensus and voting	Formal consensus	Formal consensus	Formal consensus	Formal consensus	
Consideration of costs	CEA; cost-impact analysis; systematic review of CEA studies	Systematic review of CEA studies	Not reported	CEA; cost-impact analysis	Systematic review of CEA studies	Not reported	Not reported	
Target group	Age ≥ 40 y, prioritise those ≥ 20% risk using Framingham and pre-existing record of risk factors; self presenting	Age ≥ 40 y; any if first-degree relative with premature CVD or familial dyslipidaemia	Women age ≥ 20 y	Men age ≥ 45 y; women age ≥ 55 y; men age ≥ 35 y and ≥ 1 RF[a]; women age ≥ 45 y and ≥ 1 RF[a]	Age ≥ 18 y	Age ≥ 18 y and ≥ 1 RF[b]; middle aged and smoking; self presenting	Men age ≥ 40 y; women postmenopausal and / or age ≥ 50 y; age ≥ 18 y and ≥ 1 RF[c]	10-y CHD risk 10% - 19%
Strategy	Record-based screening; opportunistic screening / case-finding	Opportunistic screening / case-finding	Not reported	Not specified, population screening is not warranted	Not reported	Opportunistic screening / case-finding	Opportunistic screening / case-finding	Opportunistic screening / case-finding
Strength of recommendation	For	For	For	For	For	For	For	Consider
Screening tests								
Major risk factors								
Prediction model	Framingham, CHD/Stroke events 10 y	ASSIGN, general CVD events 10 y	Framingham, CHD/ Stroke events 10 y	Framingham, general CVD events 5 y	WHO/ISH CVD risk prediction charts, CHD/ Stroke events 10 y	SCORE, general CVD mortality 10 y	Framingham, CHD events 10 y	
Age	√[1]	√[1]	√[1]	√[1]	√[1]	√[1]	√[1]	
Sex	√[1]	√[1]	√[1]	√[1]	√[1]	√[1]	√[1]	
Blood pressure	√[1]	√[1]	√[1]	√[1]	√[1]	√[1]	√[1]	
TC	√[1]	√[1]	√[1]		√[1]	√[1]	√[1]	
LDL-C		√[2]	√[2]	√[2]		√[2]		
HDL-C	√[1]	√[1]	√[1]		√[2]	√[1]	√[1]	
TC:HDL-C ratio	√[1]			√[1]	√[2]	√[1]	√[1]	
Smoking	√[1]	√[1]	√[1]	√[1]	√[1]	√[1]	√[1]	
Glucose for DM		√[1]	√[2]	√[1]		√[2]		
Overweight /obesity	√[2]	√[2]	√[2]	√[2]	√[2]	√[2]		
Physical inactivity					√[2]	√[2]		
Atherogenetic diet					√[2]	√[2]		
Socioeconomic factors	√[2]	√[1]	√[2]		√[2]			
Family history premature CVD	√[2]	√[1]	√[2]		√[2]	√[2]	√[2]	
Genetic /racial factors	√[2]				√[2]			
Triglycerides			√[2]	√[2]	√[2]	√[2]	√[2]	
Renal function		√[2]			√[2]	√[2]		
Heart rate				√[2]	√[2]	√[2]		
Apolipoproteins /lipoproteins					√[2]			√[2]
Glucose for insulin resistance					√[2]			
Prothrombotic markers					√[2]	√[2]		
C-reactive protein						√[2]		√[2]
Subclinical atherosclerosis	√[1] (LVH in history)				√[2] (PE)	√[2] (PE)		√[2] (ABI, carotid US, resting ECG, exercise treadmill test)

TABLE 2. RECOMMENDATIONS FOR SCREENING FOR TOTAL CVD RISK IN 7 GUIDELINES (CONTINUED)

	NICE	SIGN	AHA1	NZGG	WHO	ESC1	CCS Step 1	CCS Step 2
Thresholds								
Further screening	No	No	No	No	No	No	10-y CHD risk 10% - 19%	No
Aspirin	Not reported	10-y CVD risk ≥ 20% and controlled BP < 150/90; DM2 and age ≥ 50 y or high CVD risk	10-yr CHD/Stroke risk ≥ 20%; DM	5-y CVD risk ≥ 15%	10-y CHD/Stroke risk ≥ 30%	10-y CVD mortality ≥ 10% and controlled BP <140/90	Not reported	Not reported
Statins	10-y CHD/Stroke risk ≥ 20%; age ≥ 74 y and smoking or hypertension	10-y CVD risk ≥ 20%; 10-y CVD risk 10 - 19% and TC > 310 mg/dL; DM2 or DM1	10-y CHD/Stroke risk ≥ 20%; DM; LDL-C ≥ 160 mg/dL and 10-y CHD/Stroke risk < 10% and multiple risk factors; LDL-C ≥ 130 mg/dL and 10-y CHD/Stroke risk 10 - 20% and multiple risk factors; LDL-C ≥ 190 mg/dL	5-y CVD risk ≥ 15%; TC ≥ 310 mg/dL; TC:HDL-C ratio ≥ 8	10-y CHD/Stroke risk ≥ 30%; 10-y CHD/Stroke risk 20 - 29% and age ≥ 40 y with persistently TC > 195 mg/dL or LDL-C > 115 mg/dL, despite a lipid-lowering diet	10-y CVD mortality ≥ 5% (in elderly ≥ 10%) and TC ≥ 195 mg/dL or LDL-C ≥ 115 mg/dL; (DM2 or DM1) with microalbuminuria and TC ≥ 195 mg/dL or LDL-C ≥ 115 mg/dL; severe hyperlipidaemia	10-yr CHD risk ≥ 20%; 10-y CHD risk 10% - 19% and LDL-C ≥ 135 mg/dL or TC/HDL-C ratio ≥ 5.0; 10-y CHD risk< 10% and LDL-C ≥ 195 mg/dL or TC:HDL-C ratio ≥ 6.0	Lipoprotein(a) ≥ 0.3 g/L if TC:HDL-C ratio ≥ 5.0 or other major risk factors indicates a need for earlier and more intensive LDL-C lowering; hsCRP ≥ 3.0 mg/L indicates high risk; subclinical atherosclerosis
Antihypertensives	Not reported	10-y CVD risk ≥ 20% and BP ≥ 140/90; 10-y CVD risk 10 - 19% and BP ≥ 160/100; (DM 2 or DM1) and BP ≥ 140/90 or ≥ 130/80 if complications	10-y CHD/Stroke risk ≥ 20% and BP ≥ 140/90; DM and BP ≥ 130/90	5-y CVD risk ≥ 20%; BP ≥ 170/100	10-y CHD/Stroke risk ≥ 30% and BP ≥ 130/80; 10-yr CHD/Stroke risk 20 - 30% and BP ≥ 140/90 despite intensive lifestyle counseling	10-y CVD mortality ≥ 5% (in elderly ≥ 10%) and BP ≥ 140/90; (DM2 or DM1) with microalbuminuria and BP ≥ 140/90; severe hypertension	Not reported	Not reported
Intensive lifestyle counseling	10-y CHD/Stroke risk ≥ 20%	10-y CVD risk ≥ 20%; 10-y CVD risk 10 - 19% and BP ≥ 160/100 or TC > 310 mg/dL	10-y CVD risk ≥ 20%; DM; LDL ≥ 160 mg/dL and 10-y CHD/Stroke risk < 10% and multiple risk factors; LDL ≥ 130 mg/dL and 10-y CHD/Stroke risk 10 - 20% and multiple risk factors; LDL ≥ 190 mg/dL	5-y CVD risk ≥ 15%	10-y CHD/Stroke risk ≥ 20%	10-y CVD mortality ≥ 5% (in elderly ≥ 10%); (DM2 or DM1) with microalbuminuria; severe hyperlipidaemia or hypertension	Not reported	Not reported
High-risk monitoring	Monitoring is unnecessary, clinical judgment and patient preference should guide the review of drug therapy and whether to review the lipid profile	Monitor risk profile every six to twelve months if 10-y CVD risk ≥ 20%	Not reported	Further risk assessment at least annually, monitor risk profile every 3 to 6 months if 5-y CVD risk ≥ 15%	Monitor risk profile every 3-6 months if 10-y CHD/Stroke risk ≥ 20%; monitor risk profile every 6-12 months if 10-y CHD/Stroke risk 10-20%	Monitor risk profile if 10-y CVD mortality ≥ 5%	More frequent testing if abnormal values or if treatment is initiated	More frequent testing if abnormal values or if treatment is initiated
Screening intervals	Further risk assessment on an ongoing basis	Further risk assessment every one to five years, depending on clinical circumstances if 10-y CVD risk 10 - 19%; further risk assessment in five years if 10-y CVD risk < 10%	Not reported	Further risk assessment in 5 years if 5-y CVD risk 10 - 15%; further risk assessment in 5 to 10 years if 5-y CVD risk < 10%	Further risk assessment every two to five years depending on clinical circumstances and resource availability if 10-y CHD/Stroke risk < 10% and BP ≥ 140/90	Further risk assessment at regular (5 year) intervals if 10-y CVD mortality < 5%	Not reported	Not reported

Abbreviations: ABI, ankle-brachial index; BP, blood pressure; CEA, cost-effectiveness analysis; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; ECG, electrocardiography; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RF, risk factor; TC, total cholesterol; [a]Family history of premature CVD, family history of diabetes, smoking, overweight/obesity, high-risk ethnicity; [b]Family history of premature CVD or major risk factor such as hyperlipidemia; [c]Family history of premature CVD, smoking, overweight/obesity, high-risk ethnicity; V[1]: Formal screening test (included in prediction model); V[2]: Additional screening test; SI conversion factors: To convert HDL-C, LDL-C and TC from mg/dL to mmol/L multiply by 0.0259; lipoprotein(a) from g/L to µmol/L multiply by 3.57; hsCRP from mg/L to nmol/L multiply by 9.524.

TABLE 3. RECOMMENDATIONS FOR SCREENING FOR DYSLIPIDEMIA IN 2 GUIDELINES

	USPSTF1	USPSTF1	NHLBI Step 1	NHLBI Step 2
AGREE Rigour score	95%		50%	
Method to evaluate evidence	Systematic review; review of published systematic reviews		Review of published systematic reviews; literature identified by panel members and by a MEDLINE search	
Method to formulate recommendations	Formal consensus and voting; balance sheets		Formal consensus	
Consideration of costs	Not reported		Review of CEA studies	
Target group	Men age ≥ 35 y; women age ≥ 45 y and ≥1 RF[a]; men aged 20 - 35 y and ≥1 RF[a]; women age 20 - 45 y and ≥1 RF[a]	Men age 20 - 35 y; women age ≥ 20 y	Age ≥ 20 y	Multiple risk factors ≥ 2
Strategy	Opportunistic screening / case-finding	Opportunistic screening / case-finding	Opportunistic screening / case-finding; public screening programs	Opportunistic screening / case-finding; public screening programs
Strength of recommendation	Recommendation for (strongly for men age ≥ 35 y, women ≥ 45 y and ≥1 RF[a])	Recommendation not for not against	Recommendation for	Recommendation for
Screening tests				
Major risk factors				
Prediction model				Framingham, CHD events 10 y
Age			√[2]	√[1]
Sex				√[1]
Blood pressure			√[2]	√[1]
TC	√[1]	√[1]	√[1]	√[1]
LDL-C	√[1]	√[1]	√[1]	
HDL-C	√[1]	√[1]	√[1]	√[1]
TC:HDL-C ratio				
Smoking			√[2]	√[1]
Family history premature CVD			√[2]	
Triglycerides			√[1]	
Thresholds				
Further screening	Total risk assessment with age, gender, diabetes, elevated blood pressure, family history (in younger adults), and smoking if abnormal values	Total risk assessment with age, gender, diabetes, elevated blood pressure, family history (in younger adults), and smoking if abnormal values	Total risk assessment if multiple risk factors ≥ 2: HDL cholesterol < 40 mg/dL; age men ≥ 45 y or women ≥ 55 y; family history of premature CHD; smoking; blood pressure ≥ 140/90 mmHg	No
Statins	Choice of treatment should consider overall risk, costs of treatment, and patient preferences	Choice of treatment should consider overall risk, costs of treatment, and patient preferences	Consider if 0-1 risk factor and LDL-C ≥ 190 mg/dL; optional after 3 months lifestyle change if 0-1 risk factor and LDL-C 160 - 189 mg/dL	Initiate if 10-y CHD risk ≥ 20% and LDL-C ≥ 130 mg/dL; consider if 10-y CHD risk ≥ 20% and LDL-C 100 - 129 mg/dL; optional after 3 months lifestyle change if 10-y CHD risk 10 - 20% and LDL-C ≥ 130 mg/dL
Intensive lifestyle counseling	Not specified	Not specified	0-1 risk factor and LDL-C ≥ 160 mg/dL	10-y CHD risk ≥ 20%; LDL-C ≥ 130 mg/dL
High-risk monitoring	Not specified	Not specified	Monitor risk profile 3 months if 0-1 risk factor and LDL-C ≥ 160 mg/dL	Monitor risk profile 3 months if LDL-C ≥ 130 mg/dL
Screening intervals	Rescreen every 5 years, shorter intervals for people who have lipid levels close to those warranting therapy, and longer intervals for those not at increased risk who have had repeatedly normal lipid levels	Rescreen every 5 years, shorter intervals for people who have lipid levels close to those warranting therapy, and longer intervals for those not at increased risk who have had repeatedly normal lipid levels	Rescreen in 1 year if 0-1 risk factor and LDL-C 130-159 mg/dL; rescreen in 5 years if 0-1 risk factor and LDL-C < 130 mg/dL	Rescreen < 1 year if 10 - y CHD risk ≥ 20% and LDL-C < 100 mg/dL; rescreen in 1 year if LDL-C < 130 mg/dL

Abbreviations: CEA, cost-effectiveness analyis; CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RF, risk factor; TC, total cholesterol; [a]Family history of premature CVD, family history of diabetes, smoking, overweight/obesity; √[1]: Formal screening test; √[2]: Additional screening test; SI conversion factors: To convert HDL-C, LDL-C and TC from mg/dL to mmol/L multiply by 0.0259.

TABLE 4. RECOMMENDATIONS FOR SCREENING FOR HYPERTENSION IN 2 GUIDELINES

	USPSTF[2]	AHA[2]
AGREE Rigour score	81%	71%
Method to evaluate evidence	Systematic review; review of published systematic reviews	Review of published systematic reviews; literature identified by panel members
Method to formulate recommendations	Formal consensus and voting	Formal consensus
Consideration of costs	Not reported	Not reported
Target group	Age ≥ 18 y	Age ≥ 18 y
Strategy	Opportunistic screening / case-finding	Opportunistic screening / case-finding
Strength of recommendation	Recommendation For	Recommendation For
Screening tests		
Major risk factors		
Age	√[3]	
Sex	√[2]	
Blood pressure	√[1]	√[1]
Smoking	√[2]	
Overweight/obesity	√[2]	
Physical inactivity	√[2]	
Thresholds		
Antihypertensives	BP ≥ 140/90	BP ≥ 140/90
Intensive lifestyle counseling	BP ≥ 140/90	Not reported
High-risk monitoring	Not reported	Not reported
Screening intervals	Rescreen every year if SBP 120-139 mm Hg and/or DBP 80-99 mm Hg; rescreen every 2 years if BP < 120/80 mm Hg, but optimal interval for screening is not known	Rescreen regularly, at least every 2 years in most adults and more frequently in minority populations and the elderly if BP <140/90

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; √[1]: Formal screening test; √[2]: Additional screening test

TABLE 5. RECOMMENDATIONS FOR SCREENING FOR DYSGLYCEMIA IN 7 GUIDELINES

	USPSTF[3]	NHMRC	NHMRC	ESC[3]	CDA	CTF	AACE	CCS
AGREE Rigour score	95%	79%		74%	74%	62%	69%	50%
Method to evaluate evidence	Meta-analysis for drug and lifestyle effects; systematic review; review of published systematic reviews	Systematic review; review of published systematic reviews		Systematic review; review of published systematic reviews	Systematic review	Systematic review; review of published systematic reviews	Systematic review	Systematic review; review of published systematic reviews
Method to formulate recommendations	Formal consensus and voting; balance sheets;	Formal consensus		Formal consensus	Formal consensus	Formal consensus	Formal consensus	Formal consensus
Consideration of costs	Review of CEA studies	Not reported		Review of CEA studies	Not reported	Not reported	Not reported	Not reported
Target group	Age ≥ 18 yrs	Age ≥ 45 yrs and BMI ≥ 30; age ≥ 35 yrs and high-risk ethnicity	Age ≥ 55 yrs; age ≥ 45 yrs and first degree relative with DM2; women and previous gestational diabetes	Age ≥ 18 yrs	Age ≥ 40 yrs; age < 40 yrs and ≥ 1 RF[b]	Age ≥ 18 yrs and ≥ 1 RF[a]; if overall risk of CVD would be raised to more than 10% with DM	Age ≥ 30 yrs and ≥ 1 RF[c]	Age ≥ 40 yrs; age < 40 yrs and ≥ 1 RF[d]
Strategy	Opportunistic screening / case-finding	Opportunistic screening / case-finding	Opportunistic screening / case-finding	Not reported	Not reported	Opportunistic screening / case-finding	Not reported	Opportunistic screening / case-finding
Strength of recommendation	Insufficient evidence to make a recommendation	Recommendation For	Insufficient evidence to make a recommendation	Recommendation For	Recommendation For	Recommendation Consider	Recommendation For	Recommendation For
Screening tests								
Prediction model				Non-invasive risk score, e.g. FINDRISC, DM2 10 yrs				
Fasting plasma glucose	√[1]	√[1]	√[1]		√[1]	√[1]	√[1]	√[1]
Random plasma glucose		√[1]	√[1]					
OGTT	√[1]			√[1]		√[1]	√[1]	
HbA1c	√[1]							
Age				√[1]				
Sex								
BMI				√[1]				
Waist circumference				√[1]				
Physical activity				√[1]				
Diet				√[1]				
Family history of DM				√[1]				

TABLE 5. RECOMMENDATIONS FOR SCREENING FOR DYSGLYCEMIA IN 7 GUIDELINES (CONTINUED)

	USPSTF[3]	NHMRC	NHMRC	ESC[3]	CDA	CTF	AACE	CCS
Thresholds								
Confirmatory testing	No	FPG if FPG ≥ 126 mg/dL or RPG ≥ 200 mg/dL; OGTT if FPG 100 - 125 mg/dL or RPG 100 - 199 mg/dL	FPG if FPG ≥ 126 mg/dL or RPG ≥ 200 mg/dL; OGTT if FPG 100 - 125 mg/dL or RPG 100 - 199 mg/dL	OGTT if high score values on the non-invasive risk score	FPG if FPG ≥ 126 mg/dL; OGTT if FPG 100 - 109 mg/dL and ≥ 1 RF[b] or FPG 110 - 125 mg/dL	Repeat tests, 2 occasions warranted for diagnosis	Repeat tests if FPG ≥ 126 mg/dL or 2h PG ≥ 200 mg/dL	HbA1c if FPG ≥ 109 mg/dL
Aspirin	Not reported	DM: confirmatory FPG ≥ 126 mg/dL or 2h PG > 200 mg/dL	DM: confirmatory FPG ≥ 126 mg/dL or 2h PG > 200 mg/dL	Not reported	DM: confirmatory FPG ≥ 126 mg/dL or 2h PG > 200 mg/dL and increased CVD risk[e]	Not reported	DM: confirmatory FPG ≥ 126 mg/dL or 2h PG ≥ 200 mg/dL	Not reported
Statins	Attention to lipid levels if DM	Base on lipid levels exceeding target levels if DM	Base on lipid levels exceeding target levels if DM	Consider If: DM and age 18 - 39 yrs and other risk factors; DM and TC > 135 mg/dL	DM and increased CVD risk[e]	Not reported	DM and LDL-C ≥100 mg/dL or HDL-C ≤ 40 mg/dL in men and ≤ 50 mg/dL in women or TG ≥150 mg/dL	Initiate if established DM, not required if younger age and no RF[cj]
Glucose lowering drugs	DM	DM; IFG: confirmatory FPG 110 - 125 mg/dL and 2h PG < 140 mg/dL	DM; IFG: confirmatory FPG 110 - 125 mg/dL and 2h PG < 140 mg/dL	DM; IGT	DM; IFG: confirmatory FPG 110 - 125 mg/dL and 2h PG < 140 mg/dL; IGT: confirmatory FPG < 140 mg/dL and 2hPG 140 - 200 mg/dL	DM: confirmatory FPG ≥ 126 mg/dL or 2h PG > 200 mg/dL; IFG: confirmatory FPG 110 - 125 mg/dL and 2h PG < 140 mg/dL; IGT: confirmatory FPG < 140 mg/dL and 2hPG 140 - 199 mg/dL	DM	Not specified
Intensive lifestyle counseling	Attention to lifestyle if DM	DM; IFG	DM; IFG	DM; IGT; high score values on the non-invasive risk score	DM; IFG; IGT	DM; IFG; IGT	Confirmatory FPG ≥100 mg/dL or 2h PG ≥140 mg/dL	Not specified
High-risk monitoring	Not reported	Retest in 1 year if IFG	Retest in 1 year if IFG	Not reported	Retest more frequently than every 3 years	Not reported	Not reported	Not reported
Screening intervals	ADA recommends every 3 years, optimal interval for screening is not known	Rescreen every 3 years	Rescreen every 3 years	Not reported	Rescreen every 3 yrs	Optimal interval for screening is not known	Rescreen anually	Not reported

Abbreviations: BMI, body mass index; CEA, cost-effectiveness analyis; CVD, cardiovascular disease; DM, diabetes mellitus; FINDRISC, Finnish type 2 diabetes risk score; FPG, fasting plasma glucose; HbA1c, hemoglobin type A1c; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; RF, risk factor; RPG, random plasma glucose; TC, total cholesterol; TG, triglycerides; 2h PG, 2-hour postload plasma glucose; [a]Smoking, increased age; [b]Family history of diabetes, overweight/obesity, high-risk ethnicity; [c]Family history of diabetes, overweight/obesity, high-risk ethnicity, sedentary lifestyle; [d]Family history of diabetes, overweight/obesity; [e]Men aged ≥ 45 y, women aged ≥ 50 y, multiple cardiovascular risk factors, extreme level of a single cardiovascular risk factor, duration of diabetes > 15 y with age > 30 y; √[1]: Formal screening test; √[2]: Additional screening test; SI conversion factors: To convert glucose from mg/dL to mmol/L multiply by 0.0555; HDL-C, LDL-C and TC from mg/dL to mmol/L multiply by 0.0259; triglycerides from mg/dL to mmol/L multiply by 0.0113.

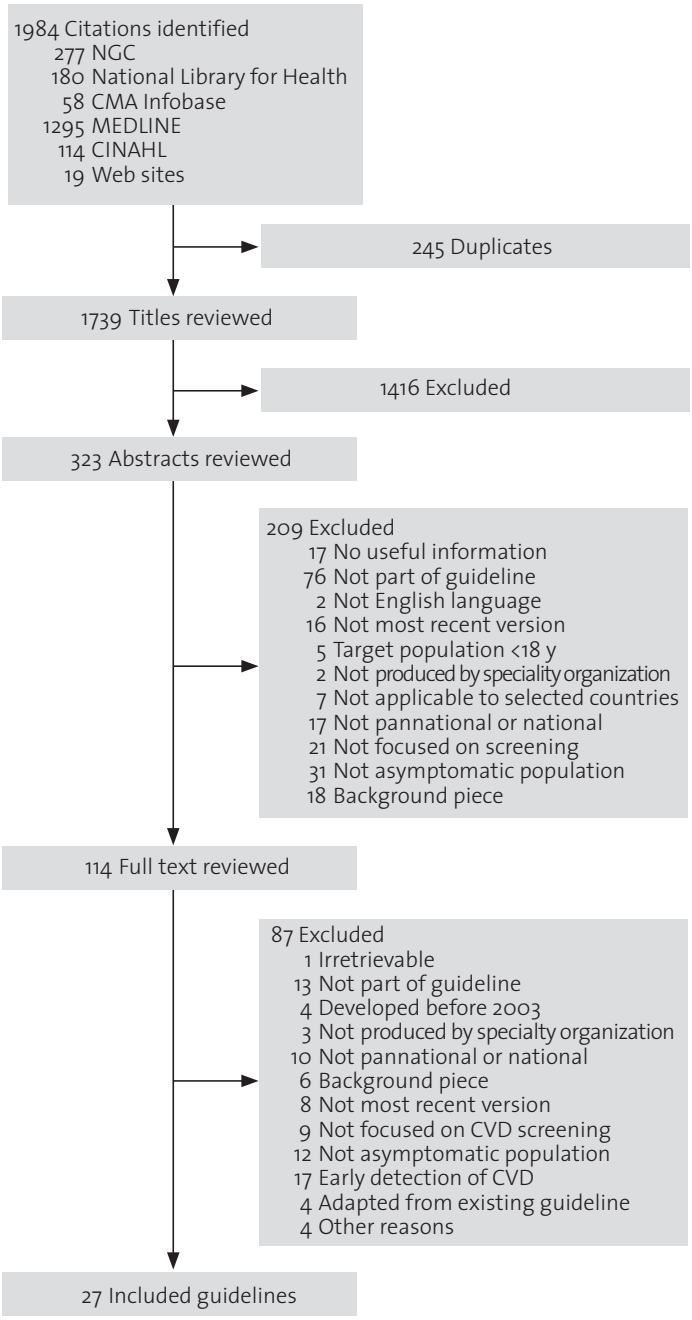

Figure 1. Summary of guideline search and review process.
Numbers of guidelines at each step of the process are indicated. Group totals may exceed the reported numbers for the excluded articles at abstract and full text level because several reasons for exclusion were allowed. CMA indicates Canadian Medical Association; CVD, cardiovascular disease; and NGC, National Guideline Clearinghouse.

REFERENCES

1. World Health Organization. The Global Burden of Disease: 2004 Update. Geneva, Switzerland: World Health Organization; 2008.
2. Jackson R, Lynch J, Harper S. Preventing coronary heart disease. BMJ. 2006;332(7542):617-618.
3. van Wyk JT, van Wijk MA, Sturkenboom MC, Moorman PW, van der Lei J. Identification of the four conventional cardiovascular disease risk factors by Dutch general practitioners. Chest. 2005; 128(4):2521-2527.
4. Mant D. Prevention. Lancet. 1994;344(8933):1343-1346.
5. Wonderling D, Langham S, Buxton M, Normand C, McDermott C. What can be concluded from the Oxcheck and British family heart studies: commentary on cost effectiveness analyses. BMJ. 1996;312(7041):1274-1278.
6. NHS Health Check: helping you prevent heart disease, stroke, diabetes and kidney disease. NHS Improvement Programme Web site. 2009. http://www.improvement.nhs.uk/vascularchecks/. Accessed May 4, 2009.
7. Prochazka AV, Lundahl K, Pearson W, Oboler SK, Anderson RJ. Support of evidence-based guidelines for the annual physical examination: a survey of primary care providers. Arch Intern Med. 2005;165(12):1347-1352.23.
8. Field M, Lohr K. Clinical Practice Guidelines: Directions for a New Program. Washington, DC: National Academy Press; 1990.
9. Grilli R, Magrini N, Penna A, Mura G, Liberati A. Practice guidelines developed by specialty societies: the need for a critical appraisal. Lancet. 2000;355(9198):103-106.
10. Graham ID, Harrison MB. Evaluation and adaptation of clinical practice guidelines. Evid Based Nurs. 2005;8(3):68-72.
11. Weingarten S. Using practice guideline compendiums to provide better preventive care. Ann Intern Med. 1999;130(5):454-458.
12. Shekelle PG, Ortiz E, Rhodes S, et al. Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? JAMA. 2001;286(12): 1461-1467.
13. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care. 2003;12(1):18-23.
14. AGREE Collaboration Web site. 2004. http://www.agreecollaboration.org/instrument/. Accessed May 4, 2009.
15. National Institute for Health and Clinical Excellence. NICE clinical guideline 67 lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease.2008. http://www.nice.org.uk/nicemedia/pdf/CG67NICEguideline.pdf. Accessed May 4, 2009.
16. Scottish Intercollegiate Guidelines Network (SIGN).Risk estimation and the prevention of cardiovascular disease: a national clinical guideline. February 2007. http://www.sign.ac.uk/pdf/sign97.pdf. Accessed May 4, 2009.
17. Mosca L, Banka CL, Benjamin EJ, et al; Expert Panel/Writing Group; American Heart Association; American Academy of Family Physicians; American College of Obstetricians and Gynecologists; American College of Cardiology Foundation; Society of Thoracic Surgeons; American Medical Women's Association; Centers for Disease Control and Prevention; Office of Research on Women's Health; Association of Black Cardiologists; American College of Physicians; World Heart Federation; National Heart, Lung, and Blood Institute; American College of Nurse Practitioners. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. Circulation. 2007;115(11):1481-1501.
18. Goldstein LB, Adams R, Alberts MJ, et al; American Heart Association; American Stroke Association Stroke Council. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group [published correction appears in Circulation.2006;114(22):e617]. Circulation. 2006; 113(24):e873-e923. doi:10.1161/01.STR.0000223048.70103.F1.
19. New Zealand Guidelines Group (NZGG). Assessment and management of cardiovascular risk. July 6, 2003. http://www.nzgg.org.nz/guidelines/dsp_guideline_popup.cfm?guidelineID=35&guideline_popup_mode=newsDisplay&NewsID=21. Accessed May 4, 2009.
20. World Health Organization. Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk. 2007. http://www.who.int/cardiovascular_diseases/guidelines/PocketGL.ENGLISH.AFR-D-E.rev1.pdf. Accessed May 4, 2009.
21. Graham I, Atar D, Borch-Johnsen K, et al; European Society of Cardiology (ESC); European Association for Cardiovascular Prevention and Rehabilitation (EACPR); Council on Cardiovascular Nursing; European Association for Study of Diabetes (EASD); International Diabetes Federation Europe (IDF-Europe); European Stroke Initiative (EUSI); Society of Behavioural Medicine (ISBM); European Society of Hypertension (ESH); WONCA Europe (European Society of General Practice/Family Medicine); European Heart Network (EHN); European Atherosclerosis Society (EAS). European guidelines on cardiovascular disease prevention in clinical practice: full text: Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil. 2007;14(suppl 2):S1-S113.
22. McPherson R, Frohlich J, Fodor G, Genest J; Canadian Cardiovascular Society. Canadian Cardiovascular Society position statement: recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. Can J Cardiol. 2006;22(11):913-927.
23. Tonkin A, Barter P, Best J, et al; National Heart Foundation of Australia; Cardiac Society of Australia and New Zealand. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: position statement on lipid management–2005. Heart Lung Circ. 2005;14(4):275-291.

24. British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart. 2005;91(suppl 5):v1-v52.
25. Eyre H, Kahn R, Robertson RM, et al; American Cancer Society; American Diabetes Association; American Heart Association. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. Circulation. 2004;109(25):3244-3255.
26. Collins P, Rosano G, Casey C, et al. Management of cardiovascular risk in the peri-menopausal woman: a consensus statement of European cardiologists and gynaecologists. Eur Heart J. 2007; 28(16):2028-2040.
27. US Preventive Services Task Force. Screening for lipid disorders in adults: US Preventive Services Task Force recommendation statement. June 2008. http://www.ahrq.gov/CLINIC/uspstf/uspschol.htm. Accessed May 4, 2009.
28. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106(25):3143-3421.
29. National Heart Foundation of Australia; Cardiac Society of Australia and New Zealand. Lipid management guidelines—2001: National Heart Foundation of Australia, the Cardiac Society of Australia and New Zealand. Med J Aust. 2001;175(suppl): S57-S85.
30. US Preventive Services Task Force. Screening for high blood pressure: US Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2007;147(11):783-786.
31. Williams B, Poulter NR, Brown MJ, et al; British Hypertension Society. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004—BHS IV. J Hum Hypertens. 2004;18(3):139-185.
32. US Preventive Services Task Force. Screening for type 2 diabetes mellitus in adults: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;148(11):846-854.
33. National Health and Medical Research Council. National evidence based guidelines for the management of type 2 diabetes mellitus. 2005. http://www.nhmrc.gov.au/publications/synopses/di16to19syn.htm. Accessed May 4, 2009.
34 Ryde´n L, Standl E, Bartnik M, et al; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD).Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary: the Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007;28(1):88-136.
35. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes. 2008;32(suppl 1):S1-S201.
36. Feig DS, Palda VA, Lipscombe L; Canadian Task Force on Preventive Health Care. Screening for type 2 diabetes mellitus to prevent vascular complications: updated recommendations from the Canadian Task Force on Preventive Health Care. CMAJ. 2005;172(2):177-180.
37. Rodbard HW, Blonde L, Braithwaite SS, et al; AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus [published correction appears in Endocr Pract.2008;14(6):802-803]. Endocr Pract. 2007;13(suppl 1):1-68.
38. IDF Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. Brussels, Belgium: International Diabetes Federation; 2005.
39. Alberti KG, Zimmet P, Shaw J. International Diabetes Federation: a consensus on type 2 diabetes prevention. Diabet Med. 2007;24(5):451-463.
40. American Diabetes Association. Standards of medical care in diabetes: 2009. Diabetes Care. 2009;32(suppl 1):S13-S61.
41. Diabetes UK. Position statement: early identification of people with type 2 diabetes. 2006. http://www.diabetes.org.uk. Accessed May 4, 2009.
42. Smith SC Jr, Jackson R, Pearson TA, et al. Principles for national and regional guidelines on cardiovascular disease prevention: a scientific statement from the World Heart and Stroke Forum. Circulation. 2004;109(25):3112-3121.
43. Ballantyne C, Arroll B, Shepherd J. Lipids and CVD management: towards a global consensus. Eur Heart J. 2005;26(21):2224-2231.
44. McAlister FA, van Diepen S, Padwal RS, Johnson JA, Majumdar SR. How evidence-based are the recommendations in evidence-based guidelines? PLoS Med. 2007;4(8):e250.
45. National Guideline Clearinghouse Web site. 2009. http://www.guideline.gov/. Accessed May 4, 2009.
46. Jackson R, Lawes CM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet. 2005;365(9457):434-441.
47. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes.N Engl J Med. 2008;358(20):2107-2116.
48. Shah T, Casas JP, Cooper JA, et al. 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. 2009;38(1):217-231.
49. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med. 2006; 355(25):2631-2639.
50. Beswick A, Brindle P. Risk scoring in the assessment of cardiovascular risk. Curr Opin Lipidol. 2006;17(4):375-386.
51. South-East London Screening Study Group. A controlled trial of multiphasic screening in middle-age: results of the South-East London Screening Study, 1977. Int J Epidemiol. 2001;30(5):935-940.
52. Han PK. Historical changes in the objectives of the periodic health examination. Ann Intern Med. 1997;127(10):910-917.

53. Wells S, Furness S, Rafter N, et al. Integrated electronic decision support increases cardiovascular disease risk assessment four fold in routine primary care practice. Eur J Cardiovasc Prev Rehabil. 2008;15(2):173-178.
54. Yarnall KS, Pollak KI, Ostbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? Am J Public Health. 2003;93 (4):635-641.
55. Manuel DG, Kwong K, Tanuseputro P, et al. Effectiveness and efficiency of different guidelines on statin treatment for preventing deaths from coronary heart disease: modelling study. BMJ. 2006;332(7555):1419.
56. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U; EUROASPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet. 2009;373(9667):929-940.
57. Skyler JS, Bergenstal R, Bonow RO, et al; American Diabetes Association; American College of Cardiology Foundation; American Heart Association.Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. J Am Coll Cardiol.2009;53(3):298-304.
58. Kahn SE. Glucose control in type 2 diabetes: still worthwhile and worth pursuing. JAMA. 2009;301(15):1590-1592.
59. Kearney PM, Blackwell L, Collins R, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371(9607):117-125.
60. Belch J, MacCuish A, Campbell I, et al; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) Trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008; 337:a1840. doi:10.1136/bmj.a1840.
61. Ogawa H, Nakayama M, Morimoto T, et al; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2008;300(18):2134-2141.
62. Guzder RN, Gatling W, Mullee MA, Mehta RL, Byrne CD. Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed type 2 diabetes: results from a United Kingdom study. Diabet Med. 2005;22(5):554-562.
63. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. Diabetes Care. 2007;30(5):1292-1293.
64. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Nilsson PM, Gudbjornsdottir S; Swedish National Diabetes Register. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes Care. 2008;31(10):2038-2043.
65. Simmons RK, Sharp S, Boekholdt SM, et al. Evaluation of the Framingham risk score in the European Prospective Investigation of Cancer-Norfolk cohort: does adding glycated hemoglobin improve the prediction of coronary heart disease events? Arch Intern Med. 2008;168(11):1209-1216.
66. US Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;150(6):396-404.
67. Unwin N, Thomson R, O'Byrne AM, Laker M, Armstrong H. Implications of applying widely accepted cholesterol screening and management guidelines to a British adult population: cross sectional study of cardiovascular disease and risk factors. BMJ. 1998;317(7166):1125-1130.
68. Oxman AD, Glasziou P, Williams JW Jr. What should clinicians do when faced with conflicting recommendations? BMJ. 2008;337:a2530.
69. IOM (Institute of Medicine). Conflict of Interest in Medical Research, Education, and Practice. Washington, DC: National Academies Press; 2009.

Chapter 3

Systematic review of guidelines on imaging of asymptomatic coronary artery disease

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ABSTRACT

Objectives

The purpose of this study was to critically appraise guidelines on imaging of asymptomatic coronary artery disease (CAD).

Background

Various imaging tests exist to detect CAD in asymptomatic persons. Because randomized controlled trials are lacking, guidelines that address the use of CAD imaging tests may disagree.

Methods

Guidelines in English published between January 1, 2003, and February 26, 2010, were retrieved using MEDLINE, Cumulative Index to Nursing and Allied Health Literature, the National Guideline Clearinghouse, the National Library for Health, the Canadian Medication Association Infobase, and the Guidelines International Network International Guideline Library. Guidelines developed by national and international medical societies from Western countries, containing recommendations on imaging of asymptomatic CAD were included. Rigor of development was scored by 2 independent reviewers using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument. One reviewer performed full extraction of recommendations, which was checked by a second reviewer.

Results

Of 2,415 titles identified, 14 guidelines met our inclusion criteria. Eleven of 14 guidelines reported relationship with industry. The AGREE scores varied across guidelines from 21% to 93%. Two guidelines considered cost effectiveness. Eight guidelines recommended against or found insufficient evidence for testing of asymptomatic CAD. The other 6 guidelines recommended imaging patients at intermediate or high CAD risk based on the Framingham risk score, and 5 considered computed tomography calcium scoring useful for this purpose.

Conclusions

Guidelines on risk assessment by imaging of asymptomatic CAD contain conflicting recommendations. More research, including randomized controlled trials, evaluating the impact of imaging on clinical outcomes and costs is needed.

INTRODUCTION

As many as 50% of myocardial infarctions occur in persons without a known history of symptomatic coronary artery disease (CAD) (1). To diminish disease burden, primary prevention on the individual level is currently rendered by targeting high-risk subjects, who are identified by office-based risk assessment using multiple traditional cardiovascular risk predictors: age, sex, smoking, lipid levels, and blood pressure. Screening using these traditional predictors, however, misses a considerable proportion of persons who will suffer from coronary events (2). Because symptomatic CAD has a pre-clinical detectable phase (i.e., coronary atherosclerosis), early detection of CAD in apparently healthy persons may be an important substitute for or supplement to risk assessment based on the traditional risk factors.

Because technical developments have created various imaging techniques to assess a patient's coronary condition, clinicians are faced with multiple options to choose from. Before a doctor decides to test for asymptomatic disease, the intervention should meet a set of specific screening criteria ([3], [4] and [5]). Hence, clinicians and decision makers usually rely on clinical practice guidelines in which recommendations are made on the basis of these criteria. As opposed to cancer screening, few large randomized controlled trials (RCTs) studying the effect of early detection of CAD on event rates within an asymptomatic population have been performed. In absence of RCTs demonstrating a net health benefit of imaging, the weighing of harms and benefits is more likely to result in different judgments, and therefore, conflicting recommendations. Therefore, a critical appraisal of guidelines and review of the agreements and the differences among recommendations can serve as a guide for deciding which imaging tests to use in clinical practice.

For this purpose, we systematically reviewed guidelines containing recommendations on imaging of asymptomatic CAD within the general population.

METHODS

Data sources and searches

To identify appropriate guidelines, the literature search used for a previous article on cardiovascular risk assessment (6) was updated and covered a period from January 1, 2003, to February 26, 2010. Briefly, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and 4 guideline databases - the National Guideline Clearinghouse (United States), the National Library for Health (United Kingdom) on Guideline Finder, Canadian Medical Association Infobase (Canada), and the Guidelines International Network (G-I-N) International Guideline Library - were searched. Searches were limited to guidelines from the United States, Canada, United Kingdom, Australia, and New Zealand, and international guidelines in the English language. A search on websites of guideline development organizations was performed for additional guidelines. Details on the search syntax are provided in *Appendix 1*.

Study selection

Articles were considered if they met the Institute of Medicine definition for clinical practice

guidelines. The Institute of Medicine defines clinical practice guidelines as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." If doubt existed whether a report met this definition or not, we verified eligibility by checking the inclusion of similar reports in the National Guideline Clearinghouse. This database also uses the Institute of Medicine definition. For this reason, we also considered American Heart Association (AHA) expert consensus documents and scientific statements, and American College of Cardiology Foundation (ACCF) appropriateness criteria reports. We included guidelines if they: 1) contained recommendations on imaging of asymptomatic CAD specifically aimed to prevent a first coronary event; 2) involved apparently healthy persons, that is adults without, for example, diabetes mellitus; and 3) were produced on behalf of a national or international medical specialty society. For completeness, we also included guidelines on electrocardiography and exercise tolerance tests, because these tests are traditionally used in the diagnosis of CAD.

The SRS 4.0 (Mobius Analytics, Ottowa, Ontario, Canada), a web-based software package developed for systematic review data management, was used. Review of titles and abstracts was performed independently by 2 reviewers (B.S.F. and E.B.C.). For a paper to be excluded, both reviewers had to agree that the article was ineligible. For abstracts, disagreements between the reviewers were discussed and resolved by consensus. The final selection based on the full text was performed by the first author.

Data extraction and quality assessment

One reviewer (B.S.F.) extracted all relevant recommendations from each included guideline. A second reviewer (T.S.S.G.) checked the results obtained for accuracy and completeness. Discrepancies were resolved by consensus. Each guideline could provide 1 or more relevant recommendations. Data extracted on a guideline level included the reported methodology for evidence synthesis, and formulating of recommendations. On the recommendation level, we extracted data on consideration of cost effectiveness, the target population, the strategy for delivery of the test, coronary atherosclerosis tests, intervention, and follow-up. In addition, the strength of the recommendation was classified as "for," "consider," "not for, not against," "insufficient evidence," or "against." We assessed the quality of development for each included guideline using the 7-item Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument (7). This domain considers the reporting of: 1) methods to search for evidence; 2) criteria for selecting the evidence; 3) methods for formulating the recommendations; 4) consideration of health benefits, side effects, and risks; 5) supporting evidence; 6) procedures for external peer review; and 7) the update process. Each item was independently rated on a 4-point Likert scale by 2 reviewers (B.S.F. and T.S.S.G.). Websites of guideline developers were examined by both reviewers for additional information on the development processes. For each reviewer, AGREE scores were calculated as a percentage using the sum of the 7 items and the maximum possible score. If the total AGREE scores of the 2 reviewers differed >20%, a third independent reviewer (J.J.V.) also assessed the guideline. Final rigor scores were calculated by averaging the AGREE scores from all reviewers. Three guidelines ([8], [9] and [10]) were rated by 3 reviewers. We ranked included guidelines according to their score. Editorial independence from funding body, external funding, proportion of guideline

panel member-industry relationships, and disclosure of identities and relationships with industry of peer reviewers were assessed by 1 reviewer (B.S.F.) and checked by a second reviewer (T.S.S.G.). Discrepancies were resolved by consensus.

Data synthesis and analysis

A table for comparison of the recommendations from the selected guidelines was constructed. The table was divided into 1) methodology of guideline development; 2) consideration of cost effectiveness regarding the recommendation; 3) target group and delivery of early detection; 4) tests considered; and 5) thresholds for intervention and follow-up. Agreement between reviewers on AGREE scores was assessed using the intraclass correlation coefficient. Given the limited number of guidelines, only explorative quantitative analyses were possible. We examined the correlation between the proportion of guideline panel members who reported relationships with industry and the AGREE score with guidelines as units of analysis. Furthermore, we examined whether the proportion of panel members with industry relationships and the AGREE score were associated with a positive recommendation ("consider" or "for") by logistic regression. Two guidelines that had no explicit statement on conflicts of interest of panel members were excluded from the analyses. An alpha level of 0.05 was used to indicate statistical significance. All analyses were performed using SPSS, version 15.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Selected guidelines

Fourteen guidelines ([8-22]) relevant to testing of asymptomatic CAD were eligible for full data extraction (Figure 1). Table 1 summarizes the selected guidelines, together with AGREE score and conflict of interest results. Most guidelines (10 of 14) were developed in the United States. The AGREE scores varied from 21% to 93%, with a median AGREE score of 57%. Reproducibility of the 2 reviewers' average AGREE scores was good, with an intraclass correlation coefficient of 0.76. Examples of low scoring guidelines are the ACCF appropriateness criteria reports (ACCF2-4) ([20], [21] and [22]). These guidelines provided excellent information on the methods followed for achieving consensus and formulating recommendations, but did not contain detailed information on the search strategy used to identify the evidence. Although "a standardized literature review" was performed for these reports, key words used in the search strategy, and inclusion and exclusion criteria for selecting articles were not reported. In addition, these guidelines did not explicitly discuss benefits and harms of recommendations and methodology for guideline updating.

Twelve of the 14 guidelines contained disclosure of relationships with industry, and in 11, at least 1 panel member declared having a relevant financial relationship. In this limited set of 12 guidelines, no relationship between the AGREE score and the proportion of panel members with an industry relationship was observed (Pearson's correlation $r = -0.205$; $p = 0.523$).

General findings among the recommendations

The 14 included guidelines contained 26 recommendations on testing of asymptomatic CAD

(Table 2). The following tests were considered: computed tomography (CT) calcium scoring, CT angiography, magnetic resonance (MR) angiography, single-photon emission computed tomography (SPECT), positron emission tomography (PET), stress echography, resting electrocardiography, and exercise tolerance testing. The majority of guidelines, except for the Canadian Cardiovascular Society (CCS) 2 guideline (19), were based on a comprehensive review including study quality assessment. Apart from the Canadian Association of Radiologists (CAR) (18) and CCS2 (19) guidelines, a grading system for assigning the level of evidence was used. Evaluation of cost effectiveness of recommended tests was explicitly done in only 2 guidelines, the U.S. Preventive Services Task Force (USPSTF) 1 (11) and ACCF1 (15) guidelines, by reviewing decision modeling studies on exercise tolerance testing ([23], [24] and [25]) and CT calcium scoring ([26] and [27]), respectively. However, both guideline groups were unable to find a sufficient number of high-quality cost-effectiveness analyses on which to base their recommendations. In other guidelines (ACCF2 [20] and ACCF4 [22]), group members were requested to consider costs in their decision making as well, but this was not based on a review of cost-effectiveness studies or decision analyses.

Eight of the 14 guidelines recommended against or concluded that there is insufficient evidence for testing of asymptomatic CAD. In the remaining 6 guidelines (ACCF1 [15], AHA2 [8], National Cholesterol Education Program [NCEP] [[16] and [17]], CAR [18], CCS2 [19], and ACCF2 [20]), testing was only advocated for patients with an a priori elevated risk level based on absolute CAD risk or multiple risk factors. Generally, risk was determined by Framingham risk equations for estimation of a 10-year risk for coronary events (fatal and nonfatal) using the categories <10%, 10% to 20%, and >20% for, respectively, low, intermediate, and high risk. However, 2 guidelines (CAR [18] and CCS2 [19]) did not specify any criteria for low, intermediate, and high risk. None advocated a universal screening approach or screening based on an age criterion alone. Whether a guideline contained a recommendation that supports testing or not did not statistically significantly depend on AGREE score or proportion of panel members with industry relationships. Adjusted odds ratios per 10% increase were 0.73 (95% confidence interval: 0.41 to 1.33) and 0.68 (95% confidence interval: 0.35 to 1.32), respectively.

The indications for further testing and primary preventive measures were not described in much detail. Overall, in guidelines that recommended for consideration of testing of asymptomatic CAD within an intermediate-risk population (ACCF1 [15], AHA2 [8], NCEP [[16] and [17]], CAR [18], and CCS2 [19]), all (previous intermediate risk) subjects were marked as high risk after a positive test. None of these guidelines contained recommendations in which traditional prediction models were updated by including test results as covariate. In addition, none of the guidelines reported whether the tests should be performed once or periodically in case of a negative test result.

CT calcium scoring

Most guidelines (10 of 14) considered the CT calcium score as a test for improvement of total coronary risk assessment based on traditional risk factors. Among these 10 guidelines (USPSTF1 [11], USPSTF2 [12], New Zealand Guidelines Group [NZGG] [13], ACCF1 [15], CCS1 [10], AHA2 [8], NCEP [[16] and [17]], CAR [18], CCS2 [19], and ACCF4 [22]), 4 guidelines (ACCF1 [15], AHA2 [8], NCEP [[16] and [17]], and CCS2 [19]) concluded that there was sufficient evidence for consideration of

its use, and 1 guideline (CAR) (18) recommended for its use. These guidelines recommended CT calcium scoring solely in an intermediate CAD risk population. In contrast, the USPSTF2 (12), NZGG (13), and ACCF4 (22) guidelines concluded that there is insufficient evidence for the intermediate-risk population. For low CAD risk persons and persons already known to be at high CAD risk, guidelines were unanimous in not advocating CT calcium scoring.

Electrocardiography and exercise tolerance testing

The USPSTF1 guideline (11) recommended against performing electrocardiography testing in a low-risk population and found insufficient evidence for subjects at elevated risk. No other guidelines provided recommendations for this test. Exercise tolerance testing was considered in 4 guidelines (USPSTF1 [11], NCEP [[16] and [17]], CCS1 [10], and AHA3 [9]): 1 (NCEP [[16] and [17]]) recommended considering testing, and 3 (CCS1 [10], USPSTF1 [11], and AHA3 [9]) were inconclusive.

Myocardial perfusion imaging

Single-photon emission computed tomography was considered in 3 guidelines (AHA2 [8], NCEP [[16] and [17]], and ACCF2 [20]), of which 2 (AHA2 [8] and NCEP [[16] and [17]]) also considered PET. The AHA2 guideline (8) recommended against any use of myocardial perfusion imaging in asymptomatic subjects, whereas the NCEP ([16] and [17]) and ACCF2 (20) guidelines recommended its use for different target populations: either for intermediate-risk subjects (NCEP [[16] and [17]]) or solely for those at high risk (ACCF2 [20]).

CT angiography and MR angiography

The AHA1 (14), CAR (18), CCS2 (19), and ACCF4 (22) guidelines considered these tests for the asymptomatic population. None of these guidelines advocated their use. For subjects at high risk, insufficient evidence was found by the ACCF4 guideline (22).

Stress echocardiography

Only 1 guideline (ACCF3 [21]) provided recommendations for stress echocardiography. For adults at high risk, insufficient evidence was found for its use; for the remaining asymptomatic population, stress echocardiography is not justified according to the ACCF3 guidelines (21).

DISCUSSION

In summary, we identified 14 guidelines on testing of asymptomatic CAD. In the development of most guidelines, relationships with the industry were present. A considerable number of guidelines achieved a low AGREE score. Various inconsistencies were observed among the guidelines regarding interpretation of the value of early detection of CAD. Many guideline groups recommended against testing of asymptomatic CAD or concluded that there is insufficient evidence. The guidelines that contained recommendations to consider testing of asymptomatic CAD only reported benefit for those at elevated risk, that is, those who were either at intermediate or high absolute risk for having a CAD event. The majority of these guidelines supported consideration of CT calcium scoring in case of intermediate CAD risk.

Some possible limitations of this review deserve attention. First, only guidelines developed by national or international medical specialty organizations were reviewed. Hence, guidelines developed by local organizations, private organizations, and individual experts were not considered. An example of an often-cited guideline, therefore, not included is the Society for Heart Attack Prevention and Eradication (SHAPE) guideline (28). The SHAPE guideline recommends periodic measurement of coronary calcium or carotid intima-media thickness in all asymptomatic men ages 45 to 75 years and women ages 55 to 75 years except those defined at very low risk. Such a universal screening approach is, however, not advocated by any of the guidelines included in this systematic review. Second, we used the AGREE instrument, which provides an overall score of the construction process of guidelines, not components. Although we expect that the quality of development across the whole guideline influences the quality of individual recommendations, in theory, a solid recommendation could be created within a poorly developed guideline and vice versa. Third, the AGREE instrument only considers the reported information related to the development of the guideline. The actual quality of the guideline development can, therefore, not be fully captured. For example, guideline groups that performed a full search for evidence and that did not report detailed information on the search strategy followed, received a low AGREE score for this item. In reality, the search followed may be adequate for identifying solid evidence. Fourth, it was difficult to quantify the true degree of influence by industry relationships, also because guidelines did not report payment amounts. Fifth, the ability to detect statistically significant relationships in the quantitative analyses, such as an association between industry relationships and the likelihood of a positive recommendation, was limited owing to the small set of included guidelines.

The disagreements on the value of early detection of CAD across the guidelines could partly be explained by the paucity of experimental research. A search on ClinicalTrials.gov (29) up to March 22, 2010, using search terms "coronary artery disease" and "prevention" or "screening," provided 97 interventional studies. We found 5 RCTs on the effect of early detection of CAD versus current practice of risk assessment using traditional risk factors. Only 1 RCT (ClinicalTrials.gov identifier: NCT00927693) was conducted in an apparently healthy population, with CT calcium scoring as the intervention. The study's results on hard endpoints are, however, not yet published (30). One RCT (ClinicalTrials.gov identifier: NCT00769275) was performed in a population with diabetes and revealed no effect of screening by myocardial perfusion scans on cardiac event rates, although event rates in the screened and not-screened groups were low, and no standardized preventive treatment strategy was used (31). Other RCTs (ClinicalTrials.gov identifiers: NCT00431977, NCT00488033, and NCT00547872), on CT angiography and exercise tolerance testing, were also conducted in diabetic patients, and are still ongoing.

Patients with subclinical atherosclerosis identified by accurate imaging tests can be expected to benefit from preventive treatment because they are at elevated risk for an event. Ideally, decision making as to whether imaging individual patients is beneficial should be based on RCTs comparing preventive measures guided by imaging versus not imaging and evaluating CAD event rates as outcome. Such RCTs are, however, expensive and time-consuming and not always feasible. In the absence of these RCTs, one would want to combine data from trials evaluating the effect of preventive measures with data from cohort studies reporting the association between imaging test results and CAD event rates. Qualitatively weighing

and combining the relevant harms and benefits, as was done in the development of the reviewed guidelines, is difficult and may lead to different judgments about net health gains. Disagreements across guidelines can occur for other reasons, including different judgments about which research is relevant; risk of biases in selected research; the applicability of the research findings to the key questions; the relative importance of the anticipated costs; and also poor guideline development processes and conflicts of interests (32). We explored whether the latter 2 influenced the variation in recommendations, but found no evidence for this in the limited set of guidelines reviewed. Quantitatively, as opposed to qualitatively, weighing harms and benefits can be done using decision models that integrate the best-available evidence from multiple sources. Beneficial effects, adverse effects, and incurred costs of preventive treatment and follow-up can be summarized in an incremental cost-effectiveness ratio. In a few of the included guidelines, decision modeling studies were discussed; however, their quality was considered too low for policy making.

The recommended methods of refining CAD risk stratification using imaging test results can be improved by updating existing prediction models (33). None of the guidelines contained recommendations for the use of prediction models combining traditional risk factors and test results to calculate a new risk estimate. Instead, the Framingham-based intermediate risk (10% to 20% 10-year CAD risk) is reclassified to high risk (a 10-year CAD risk >20%), if the test result is positive, rather than updating the risk estimate. This approach has limitations. First, it requires consensus on these risk categories, which is not the case. Second, validity of the reclassified risk might become an issue. A positive test result may not elevate the predicted absolute CAD risk to the level of high risk if the subject was at the lower end of the intermediate risk distribution, for example, if the 10-year CAD risk was between 10% and 15% (34). Reported risk ratios of asymptomatic CAD adjusted for traditional risk factors, which might reclassify individuals, are usually derived from a comparison with a reference group without or with low indication for asymptomatic CAD ([34], [35], [36] and [37]). However, converting a risk ratio to absolute risk also depends on the distribution of the risk marker within the general population, which consists of subjects with and without this risk marker (38). Finally, a communication of a refined numerical risk theoretically offers a benefit in informing patients. Thus, we believe that future research should also focus on the value of updating traditional prediction models.

CONCLUSIONS

Guidelines on risk assessment by imaging of asymptomatic CAD contain conflicting recommendations. More research, including RCTs, evaluating the impact of imaging on clinical outcomes and costs is needed.

TABLE 1. CHARACTERISTICS OF 14 GUIDELINES ON IMAGING OF ASYMPTOMATIC CORONARY ARTERY DISEASE

Guideline, Year (Reference)	Organization(s) Responsible for Guideline Development	Country Applied	AGREE Rigor Score, %	Conflicts of Interest	Proportion of panel members with reported industry relationships
USPSTF1, 2004 (11)	U.S. Preventive Services Task Force	United States of America	93	EI, DIRp	-
USPSTF2, 2009 (12)	U.S. Preventive Services Task Force	United States of America	90	EI, SCI	0/23
NZGG, 2003 (13)	New Zealand Guidelines Group	New Zealand	79	EI, FPO, SCI*, DIRp	9/35
AHA1, 2008 (14)	American Heart Association	United States of America	76	SCI*, DIR, SCIR	8/11
ACCF1, 2007 (15)	American College of Cardiology Foundation, American Heart Association	United States of America	74	SCI*,DIR, SCIR*	4/14
CCS1, 2009 (10)	Canadian Cardiovascular Society	Canada	59	SCI*	20/23
AHA2, 2006 (8)	American Heart Association	United States of America	57	SCI*, DIR,SCIR*	1/4
AHA3, 2005 (9)	American Heart Association	United States of America	57	SCI*, DIR, SCIR*	6/12
NCEP, 2002, 2004 update (16,17)	National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association	United States of America	52	SCI*, DIR	6/28
CAR, 2009 (18)	Canadian Association of Radiologists	Canada	36	-	-
CCS2, 2009 (19)	Canadian Cardiovascular Society	Canada	31	SCI*	1/13
ACCF2, 2009 (20)	American College of Cardiology Foundation et al.	United States of America	24	SCI*, DIR^{p}, SCIR*	13/29
ACCF3, 2008 (21)	American College of Cardiology Foundation et al.	United States of America	21	SCI*, DIR^{p}, SCIR*	15/23
ACCF4, 2006 (22)	American College of Cardiology Foundation et al.	United States of America	21	SCI*, DIR^{p}, SCIR*	11/25

*Relationship with industry reported by at least 1 person.
ACCF American College of Cardiology Foundation; AHA American Heart Association; CAR Canadian Association of Radiologists; CCS Canadian Cardiovascular Society; DIR disclosure of the identities of peer reviewers;
DIR^{p} disclosure of the identities of peer reviewers for some parts of the guidelines; EI editorial independence from funding organization declared;
FPO funding by external public organization reported; NCEP National Cholesterol Education Program; NZGG New Zealand Guidelines Group;
SCI statement about conflicts of interest of panel members present; SCIR statement about conflicts of interest of external peer reviewers present.

TABLE 2. RECOMMENDATIONS (N=26) IN GUIDELINES (N=14) ON IMAGING OF ASYMPTOMATIC CORONARY ARTERY DISEASE

	USPSTF1	USPSTF1	USPSTF2	NZGG	AHA1
AGREE rigor score, %	93%	93%	90%	79%	76%
Method to evaluate evidence	Systematic review* covering 1966 - June 2002	Systematic review* covering 1966 - June 2002	Systematic review* covering 1966 - July 2008; meta-analysis	Systematic review* covering 1989 - August 10, 2002; review of published systematic reviews, meta-analyses or guidelines	Standardized review† with MEDLINE search covering 1990 - 2006
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	Yes, a review of cost-effectiveness studies is performed	Yes, a review of cost-effectiveness studies is performed	No, because of limitations in the evidence of effectiveness, little information is available on cost-effectiveness	NR	NR
Target group	Adults at low CAD risk: <5-10% 10-year risk of CAD events	Adults at increased CAD risk: >15-20% 10-year risk of CAD events	Adults in the intermediate CAD risk category with 10-year CAD risk 10% - 20% (FRS)	Adults regardless of risk	Adults regardless of risk
Strategy	Opportunistic screening / case-finding	Opportunistic screening / case-finding	Opportunistic screening / case-finding	NR	NR
Strength of recommendation	Against	Insufficient evidence to make a recommendation	Insufficient evidence to make a recommendation	Insufficient evidence to make a recommendation	Against
Tests considered	CTCS; r-ECG; ETT	CTCS; r-ECG; ETT	CTCS	CTCS	CTA; MRA
Intervention(s) considered	More intensive risk factor modification or follow-up testing / ICA if: presence of calcium, r-ECG abnormalities, ST-segment depression ≥ 1 mm; CABG / PCI if severe CAS	More intensive risk factor modification or follow-up testing / ICA if: presence of calcium, r-ECG abnormalities, ST-segment depression ≥ 1 mm; CABG / PCI if: severe CAS	Agressive risk reduction if reclassified 10-year CAD risk > 20% using CAC score categories: none, 1-100, 101-300, and >300, no established norms for the general population	Statins, aspirin, and intensive lifestyle therapy if 5-year CVD risk ≥ 15%, cut-off values for CAC score not specified	NR
Screening intervals	NR	NR	NR	Traditional risk assessment: annually if 5-year CVD risk ≥15%, in 5 years if 5-year CVD risk 5 - 15%, in 10 years if 5-year CVD risk < 5%; NR for CTCS	NR
	ACCF1	**ACCF1**	**CCS1**	**AHA2**	**AHA2**
AGREE rigor score, %	74%	74%	59%	57%	57%
Method to evaluate evidence	Standardized review† with MEDLINE search covering 1998 – early 2005; review of published systematic reviews, meta-analyses or guidelines	Standardized review† with MEDLINE search covering 1998 – early 2005; review of published systematic reviews, meta-analyses or guidelines	Systematic review* covering January 1, 2006 - February 1, 2009; review of published systematic reviews, meta-analyses or guidelines	Standardized review†	Standardized review†
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	Yes, a review of cost-effectiveness studies is performed	Yes, a review of cost-effectiveness studies is performed	NR	NR	NR
Target group	Adults at high CAD risk: 10-year risk of CAD events ≥ 20% or other high-risk diagnosis; adults at low CAD risk: 10-year risk of CAD events < 10%	Adults at intermediate CAD risk: 10-year risk of CAD events 10 - 20%	Men at least 40 years of age, women at least 50 years of age or postmenopausal, adults at any age and ≥ 1 cardiovascular risk factor (family history of premature CAD, smoking, obesity)	Clinically selected intermediate CAD risk patients (eg, those with a 10-year CAD risk 10 - 20% FRS)	Adults regardless of risk
Strategy	NR	NR	NR	NR	NR
Strength of recommendation	Against	Consider	Insufficient evidence to make a recommendation	Consider	Against
Tests considered	CTCS	CTCS	CTCS; ETT	CTCS	h-SPECT-CT/h-PET-CT
Intervention(s) considered	Pharmacologic treatment according to NCEP guidelines if 10-year CAD risk ≥ 20% based on high CAC score (≥ 400)	Pharmacologic treatment according to NCEP guidelines if 10-year CAD risk ≥ 20% based on high CAC score (≥ 400)	Statins and lifestyle intervention if subclinical atherosclerosis	More agressive target values for lipid-lowering therapies if high CAC score based on absolute plaque burden	NR
Screening intervals	NR	NR	NR		Serial imaging is not indicated at this time

TABLE 2. RECOMMENDATIONS (N=26) IN GUIDELINES (N=14) ON IMAGING OF ASYMPTOMATIC CORONARY ARTERY DISEASE (CONTINUED)

	AHA3	NCEP	CAR	CAR	CAR
AGREE rigor score, %	56%	52,0%	36%	36%	36%
Method to evaluate evidence	Standardized review†; review of published guideline	Standardized review† of literature identified by the panel members and by a MEDLINE search; review of published systematic reviews, meta-analyses or guidelines;	Systematic review* covering 1966 - October 2008; review of published systematic reviews, meta-analyses or guidelines	Systematic review* covering 1966 - October 2008; review of published systematic reviews, meta-analyses or guidelines	Systematic review* covering 1966 - October 2008; review of published systematic reviews, meta-analyses or guidelines
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	NR	NR for this recommendation	NR	NR	NR
Target group	Adults regardless of risk	2002: multiple risk factors and 10-year CAD risk ≤ 20%, 0-1 risk factor and LDL-C 160-189 mg/dL after lifestyle changes; 2004 update: 10-year CAD risk 10 - 20% and LDL-C 100-129 mg/dL (FRS)	Adults at intermediate CAD risk	Adults at low CAD risk or high CAD risk	Adults regardless of risk
Strategy	NR	Opportunistic screening / case-finding	NR	NR	NR
Strength of recommendation	Insufficient evidence to make a recommendation	Consider	For	Against	Against
Screening tests considered	ETT	2002: CTCS; ETT; SPECT/PET; 2004 update: CTCS	CTCS	CTCS	CTA
Intervention(s) considered	NR	2002: Statins and lifestyle intervention if subclinical atherosclerosis; 2004 update: consider statins if CAC score ≥ 75th percentile for a person's age and sex to achieve LDL-C < 100 mg/dL	Calcium scoring using a traditional scoring system may influence the decision to intensify risk factor modification	Calcium scoring using a traditional scoring system may influence the decision to intensify risk factor modification	If CAS ≥ 50%, intervention(s) not further specified
Screening intervals	NR	Traditional risk assessment in 3 months - 1 year depending on LDL-C level, NR for recommended tests	NR	NR	NR
	CCS2	**CCS2**	**ACCF2**	**ACCF2**	**ACCF2**
AGREE rigor score, %	31%	31%	24%	24%	24%
Method to evaluate evidence	Review‡	Review‡	Standardized review†	Standardized review†	Standardized review†
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus: Delphi method	Expert consensus: Delphi method	Expert consensus: Delphi method
Consideration of costs	NR	NR	Cost were considered implicitly in the appropriateness determination	Cost were considered implicitly in the appropriateness determination	Cost were considered implicitly in the appropriateness determination
Target group	Adults at intermediate CAD risk	Adults regardless of risk	Adults at low CAD risk or at intermediate CAD risk with an interpretable ECG (FRS)	Adults at intermediate CAD risk with an uninterpretable ECG (FRS)	Adults at high CAD risk (FRS)
Strategy	NR	NR	NR	NR	NR
Strength of recommendation	Consider	Against	Against	Insufficient evidence to make a recommendation	Consider
Screening tests considered	CTCS	CTA	SPECT	SPECT	SPECT
Intervention(s) considered	NR	Optimal medical therapy; PCI; CABG if test results consistent with high-risk CAD	NR	NR	NR
Screening intervals	NR	NR	NR	NR	NR

TABLE 2. RECOMMENDATIONS (N=26) IN GUIDELINES (N=14) ON IMAGING OF ASYMPTOMATIC CORONARY ARTERY DISEASE (CONTINUED)

	ACCF3	ACCF3	ACCF4	ACCF4	ACCF4	ACCF4
AGREE rigor score, %	21%	21%	21%	21%	21%	21%
Method to evaluate evidence	Standardized review†	Standardized review†	Standardized review†	Standardized review†	Standardized review†	Standardized review†
Method to formulate recommendations	Expert consensus: Delphi method	Expert consensus: Delphi method	Expert consensus: Delphi method	Expert consensus: Delphi method	Expert consensus: Delphi method	Expert consensus: Delphi method
Consideration of costs	NR	NR	Cost were considered implicitly in the appropriateness determination	Cost were considered implicitly in the appropriateness determination	Cost were considered implicitly in the appropriateness determination	Cost were considered implicitly in the appropriateness determination
Target group	Adults at low CAD risk or intermediate CAD risk (FRS)	Adults at high CAD risk (FRS)	Adults at low CAD risk or intermediate CAD risk (FRS)	Adults at high CAD risk (FRS)	Adults at low CAD risk (FRS)	Adults at intermediate CAD risk or high CAD risk (FRS)
Strategy	NR	NR	NR	NR	NR	NR
Strength of recommendation	Against	Insufficient evidence to make a recommendation	Against	Insufficient evidence to make a recommendation	Against	Insufficient evidence to make a recommendation
Screening tests considered	SE	SE	CTA	CTA	CTCS	CTCS
Intervention(s) considered	NR	NR	NR	NR	NR	NR
Screening intervals	NR	NR	NR	NR	NR	NR

*Comprehensive literature review, which includes a search strategy that covers multiple databases and other sources, study selection criteria, and quality assessment of the evidence. †Comprehensive literature review, which includes quality assessment of the evidence; ‡Comprehensive literature review without systematic methods; CABG=coronary artery bypass graft; CAD=coronary artery disease; CAS=coronary artery stenosis; CT=computed tomography; CTA=computed tomography angiography; CTCS=computed tomography calcium score; CVD=cardiovascular disease; ETT=exercise tolerance test; FRS=Framingham Risk Score; h-SPECT=hybrid single-photon emission computed tomography; h-PET=hybrid positron emission tomography; ICA=invasive coronary angiography; LDL-C=low-density lipoprotein cholesterol; MRA=magnetic resonance angiography; NR=not reported; PCI=percutaneous coronary intervention; PET=positron emission tomography; r-ECG=resting electrocardiography; SE=stress echocardiography; SPECT=single-photon emission computed tomography.

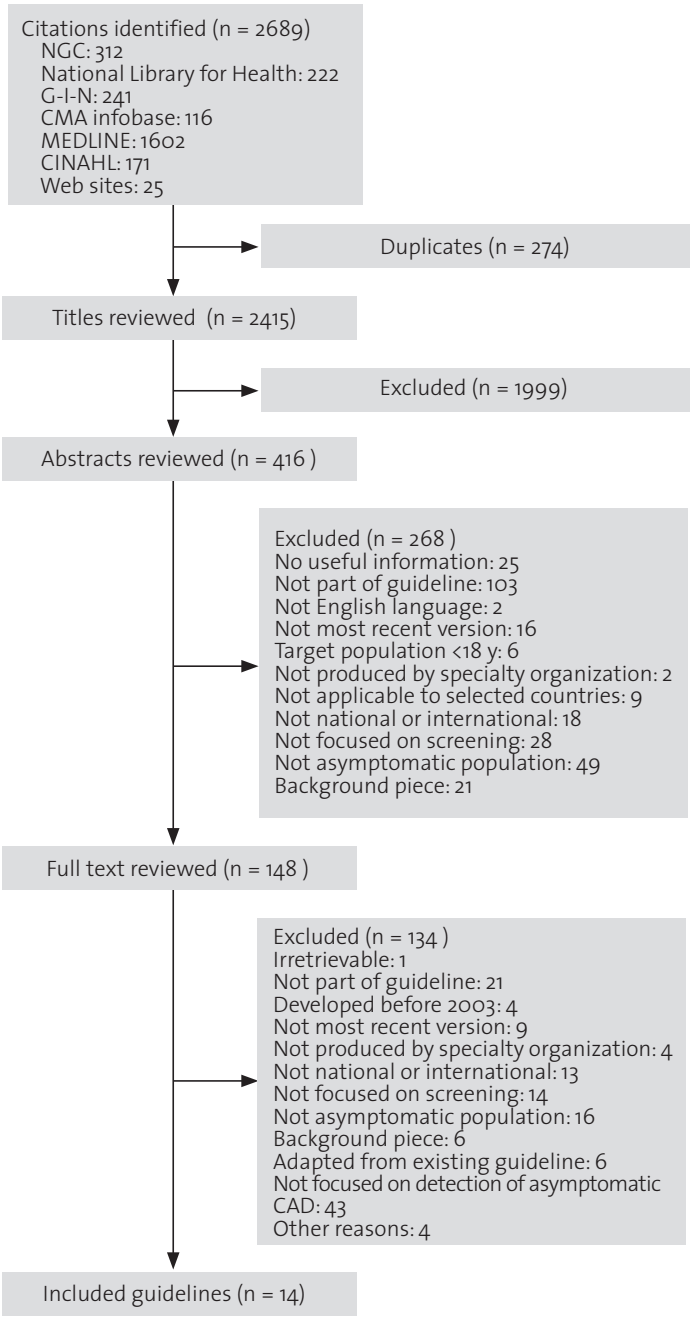

Figure 1. Literature search and selection

Numbers of guidelines for each step of the process are indicated. Group totals may exceed the reported numbers for the excluded articles at abstract and full text level because several reasons for exclusion were allowed. CAD = coronary artery disease; CINAHL = Cumulative Index to Nursing and Allied Health Literature; CMA = Canadian Medical Association; G-I-N = Guidelines International Network; NGC = National Guideline Clearinghouse.

REFERENCES

1. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women. Circulation 1996;93:1981–92.
2. Law M, Wald N, Morris J. Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy. HealthTechnol Assess 2003;7:1–94.
3. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21–35.
4. UK National Screening Committee. Programme appraisal criteria. 2009. Available at: http://www.screening.nhs.uk/criteria/. Accessed March 22, 2010.
5. Wilson J, Jungner G. Principles and practice of screening for disease. Public Health Paper. Geneva: World Health Organization, 1968.
6. Ferket BS, Colkesen EB, Visser JJ, et al. Systematic review of guidelines on cardiovascular risk assessment: which recommendations should clinicians follow for a cardiovascular health check? Arch Intern Med 2010;170:27– 40.
7. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12:18 –23.
8. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation 2006;114: 1761–91.
9. Lauer M, Froelicher ES, Williams M, Kligfield P. Exercise testing in asymptomatic adults: a statement for professionals from the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Circulation 2005; 112:771– 6.
10. Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult- 2009 recommendations. Can J Cardiol 2009;25:567–79.
11. U.S. Preventive Services Task Force. Screening for coronary heart disease: recommendation statement. Ann Intern Med 2004;140: 569 –72.
12. U.S. Preventive Services Task Force. Using nontraditional risk factors in coronary heart disease risk assessment: recommendation statement. Ann Intern Med 2009;151:474–82.
13. New Zealand Guidelines Group (NZGG). Assessment and management of cardiovascular risk. July 6, 2003. Available at: http://www.nzgg.org.nz/guidelines/dsp_guideline_popup.cfm?guidelineID35&guideline_popup_modenewsDisplay&NewsID21. Accessed March 22, 2010.
14. Bluemke DA, Achenbach S, Budoff M, et al. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography. A scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention, and the Councils on Clinical Cardiology and Cardiovascular Disease in the Young. Circulation 2008;118:586–606.
15. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). J Am Coll Cardiol 2007;49:378–403.
16. 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.
17. 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.
18. Dennie CJ, Leipsic J, Brydie A. Canadian Association of Radiologists: consensus guidelines and standards for cardiac CT. Can Assoc Radiol J 2009;60:19 –34.
19. Chow BJ, Larose E, Bilodeau S, et al. The "what, when, where, who and how?" of cardiac computed tomography in 2009: guidelines for the clinician. Can J Cardiol 2009;25:135–9.
20. Hendel RC, Berman DS, Di Carli MF, et al. ACCF/ASNC/ACR/ AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. J Am Coll Cardiol 2009;53:2201–29.
21. Douglas PS, Khandheria B, Stainback RF, et al. ACCF/ASE/ACEP/ AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, American Society of Echocardiography, American College of Emergency Physicians, American Heart Association, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 2008;51:1127–47.
22. Hendel RC, Patel MR, Kramer CM, Poon M. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac

computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation/ American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. J Am Coll Cardiol 2006;48:1475–97.
23. Sox HC Jr., Littenberg B, Garber AM. The role of exercise testing in screening for coronary artery disease. Ann Intern Med 1989;110: 456 – 69.
24. Pilote L, Pashkow F, Thomas JD, et al. Clinical yield and cost of exercise treadmill testing to screen for coronary artery disease in asymptomatic adults. Am J Cardiol 1998;81:219 –24.
25. Stason WB, Fineberg HV. Implications of alternative strategies to diagnose coronary artery disease. Circulation 1982;66:III80–6.
26. O'Malley PG, Greenberg BA, Taylor AJ. Cost-effectiveness of using electron beam computed tomography to identify patients at risk for clinical coronary artery disease. Am Heart J 2004;148:106 –13.
27. Shaw LJ, Raggi P, Berman DS, Callister TQ. Cost-effectiveness of screening for cardiovascular disease with measures of coronary calcium. Prog Cardiovasc Dis 2003;46:171– 84.
28. Naghavi M, Falk E, Hecht HS, et al. From vulnerable plaque to vulnerable patient—Part III: executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. Am J Cardiol 2006;98:2H–15H.
29. U.S. National Institutes of Health clinicaltrials.gov web site. 2010. Available at: http://clinicaltrials.gov/. Accessed March 22, 2010.
30. Shaw LJ, Min JK, Budoff M, et al. Induced cardiovascular procedural costs and resource consumption patterns after coronary artery calcium screening: results from the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study. J Am Coll Cardiol 2009;54:1258–67.
31. Young LH, Wackers FJ, Chyun DA, 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;301:1547–55.
32. Oxman AD, Glasziou P, Williams JW Jr. What should clinicians do when faced with conflicting recommendations? BMJ 2008;337:a2530.
33. Steyerberg EW. Updating for a new setting. Clinical prediction models. A Practical Approach to Development, Validation, and Updating. New York, NY: Springer, 2009:361–90:
34. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210 –5.
35. Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. Circulation 2005;112:572–7.
36. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.
37. Balady GJ, Larson MG, Vasan RS, Leip EP, O'Donnell CJ, Levy D. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. Circulation 2004;110:1920 –5. Dupont WD, Plummer WD Jr. Understanding the relationship between relative and absolute risk. Cancer 1996;77:2193–9.

Chapter 4

Systematic review of guidelines on abdominal aortic aneurysm screening

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ABSTRACT

Objectives

Usually, physicians base their practice on guidelines, but recommendations on the same topic may vary across guidelines. Given the uncertainties regarding abdominal aortic aneurysm (AAA) screening, physicians should be able to identify systematically and transparently developed recommendations. We performed a systematic review of AAA screening guidelines to assist physicians in their choice of recommendations.

Methods

Guidelines in English published between January 1, 2003 and February 26, 2010 were retrieved using MEDLINE, CINAHL, the National Guideline Clearinghouse, the National Library for Health, the Canadian Medication Association Infobase, and the G-I-N International Guideline Library. Guidelines developed by national and international medical societies from Western countries, containing recommendations on AAA screening were included. Three reviewers independently assessed rigor of guideline development using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument. Two independent reviewers performed extraction of recommendations.

Results

Of 2415 titles identified, seven guidelines were included in this review. Three guidelines were less rigorously developed based on AGREE scores below 40%. All seven guidelines contained a recommendation for one-time screening of elderly men by ultrasonography to select AAAs ≥ 5.5 cm for elective surgical repair. Four guidelines, of which three were less rigorously developed, contained disparate recommendations on screening of women and middle-aged men at elevated risk. There was no agreement on the management of smaller AAAs.

Conclusions

Consensus exists across guidelines on one-time screening of elderly men to detect and treat AAAs ≥ 5.5 cm. For other target groups and management of small AAAs, prediction models and cost-effectiveness analyses are needed to provide guidance.

INTRODUCTION

Abdominal aortic aneurysm (AAA) contributes significantly to disease burden in developed countries, accounting for approximately 0.5% of total mortality in the United States (1). Because rupture of AAA is preceded by a preclinical detectable phase and because accurate tests and effective treatment are available, screening is likely to be beneficial. A recent Cochrane systematic review including four screening trials, showed a significant decrease in AAA-related mortality in asymptomatic men aged 65 to 79 years who underwent ultrasound screening (2). A beneficial effect on total mortality was not demonstrated and uncertainties remain regarding other target groups, the optimal screening strategy, policy towards small AAAs, cost-effectiveness, and psychological effects of screening.

In the United Kingdom, the National Health Service Abdominal Aortic Aneurysm Screening Program is being introduced gradually with a full coverage across England expected by March 2013. In this program, men aged 65 are invited for a one-time ultrasound examination. In the United States, an abdominal ultrasound study for AAA detection is offered as part of the one-time "Welcome to Medicare" preventive health examination. Medicare covers AAA screening for all men who turned 65 years of age and smoked at least 100 cigarettes and individuals with a family history of AAA (3). In many Western countries, however, systematic, nation-wide screening programs are not implemented and decisions on screening are made on the individual level by primary care physicians. For example, in the Netherlands, systematic screening programs are only allowed in a research setting (4). Instead, opportunistic screening of siblings of patients with an AAA is recommended.

The purpose of guidelines is to close the gap between the best available evidence and what physicians do in their practice. The usual method of disseminating and implementing guidelines is rather passive, by publication in medical journals or mailing to targeted professionals. This method does not seem to achieve the guidelines' aim: changing physicians' behaviour (5). Variations in recommendations across guidelines on the same topic, may cause physicians to lose confidence in the construction process and validity of guidelines and lead to a further derivation from this aim. In addition, relationships with the industry can potentially influence choices made within guideline development, making the validity of recommendations even more questionable (6). Given the potential uncertainties regarding AAA screening, physicians require recommendations that have been developed systematically and transparently (7). Our purpose was to assist physicians in their choice of recommendations on AAA screening by a systematic review and critical appraisal of current guidelines.

METHODS

Data sources and searches

The literature search, used for a previous article on cardiovascular risk assessment (8), was updated to identify guidelines of interest. Briefly, MEDLINE, CINAHL, and four guideline specific databases: the National Guideline Clearinghouse (US), the National Library for Health (UK) on Guideline Finder, Canadian Medical Association Infobase (Canada), and the G-I-N International

Guideline Library on (http://www.g-i-n.net) were searched. Guidelines published from January 1st 2003 to February 26th 2010, and in the English language were considered. Additional guidelines were sought by searching websites of guideline development organizations. Details on the search syntax are provided in *Appendix 1*.

Study selection

We considered guidelines on AAA screening. A guideline was only considered if it met the Institute of Medicine (IOM) definition for clinical practice guidelines. In order to meet this definition a guideline has to contain "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances". In order to meet inclusion criteria, guidelines had to: (1) be developed on behalf of a national or international medical specialty society (2) contain recommendations for an asymptomatic population with no previous diagnosis of AAA; (3) originate from or apply to Western countries (e.g. the US, Canada, Australia, New Zealand or the UK). Titles and abstracts were reviewed independently by two reviewers (B.S.F. and E.B.C.). Articles were only excluded if both reviewers agreed on the decision. Discrepancies were resolved by consensus. The first author made the final selection of articles based on full text.

Data extraction and quality assessment

Relevant recommendations from the included guidelines were independently extracted by two reviewers (B.S.F. and N.G). Discrepancies were resolved by consensus. Each guideline provided one or more relevant recommendations. Data extracted included the reported methodology for evidence synthesis, formulating of recommendations, consideration of cost-effectiveness, the target population, the strategy for delivery of the test, recommended tests, and test thresholds for intervention and follow-up. In addition, the recommendation was classified as "for", "consider", "not for not against", "insufficient evidence" or "against".

The quality of development of each included guideline was determined using the "Rigor of Development" domain of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument, a 7 item score (9). This score looks at: (1) methods to search for evidence; (2) criteria for selecting the evidence; (3) methods for formulating the recommendations; (4) consideration of health benefits, side effects, and risks; (5) supporting evidence; (6) procedures for external peer review; and (7) the update process. Each item is rated on a 4-point Likert scale. Three reviewers (B.S.F., N.G., and J.J.V.) independently scored each guideline. Additional information on development was also examined by these three reviewers by perusing websites of guideline developers. For each reviewer, AGREE scores were calculated as a percentage using the sum of the 7 items and the maximum possible score. Final rigor scores were calculated by averaging the AGREE scores from all reviewers. Reproducibility of the three reviewers' average rigor scores was measured with an intraclass correlation coefficient. We ranked included guidelines according to their average score. Editorial independence from funding body, external funding, and disclosure of relationships with industry by individual guideline group members were assessed (B.S.F.) and checked (N.G.). Discrepancies were resolved by consensus. SRS® 4.0 (Mobius Analytics, Ottowa, Ontario, Canada), a web-based software package developed for systematic review data management was used to remove duplicates, store citations and track results at title, abstract, quality assessment and data extraction levels.

Data synthesis and analysis

We constructed a table to compare the recommendations from the included guidelines. The table was divided into the following sections: (1) methodology of guideline development; (2) consideration of cost-effectiveness regarding the recommendation; (3) target group and delivery of AAA screening; (4) tests considered; and (5) thresholds for intervention and follow-up.

RESULTS

Selection and assessment of guidelines

We screened 2415 guidelines for eligibility at title level, of which 416 were included for review at abstract level (Figure 1). Of these, 7 guidelines relevant to AAA screening were eligible for full data extraction. Table 1 summarizes the selected guidelines, together with rigor scores and conflict of interest results. Most guidelines (6 of 7) were developed in North America. AGREE scores varied from 17% to 79% with 3 guidelines (CCS, SVS1, and SVS2) having an AGREE score below the median, 40%. Reproducibility of the AGREE scores by the three reviewers was good, with an intraclass correlation coefficient of 0.86. In 2 of the 7 guidelines (ACC, SVS2) at least one panel member declared having a relevant financial relationship with the industry. None of these guidelines reported exclusion of group members from voting or discussions. Only one guideline (USPSTF) contained a statement of being developed independently from the funding organization. One guideline (NSC) neither reported that it was developed independently from funding organization(s), nor did it report a statement about conflicts of interest of group members.

The 7 included guidelines contained 11 recommendations on AAA screening (Table 2). Two (USPSTF and ACC) of the 7 guidelines were developed on the basis of a systematic review of the medical literature. The remaining 5 guidelines were developed using a non-systematic selection of previously developed systematic reviews or primary research. Evaluation of cost effectiveness of screening strategies was done in 6 of 7 guidelines, by reviewing existing decision modeling studies.

Areas of agreement and disagreement among recommendations

All guidelines contained at least one recommendation that supported AAA screening in elderly men Although guideline groups (6 of 7) generally agreed on the age at which screening should be started in elderly men (that is 65 years of age), they disagreed on whether a smoking history should be present or not. In recommendations from two (USPSTF and ACC) of the 7 guidelines, ever smoking (current or past smoking) was required. In the other 5 guidelines screening was recommended for elderly men regardless of smoking habits.

Three guidelines (USPSTF, ACC, and NSC) only contained recommendations for AAA screening in elderly men or recommended explicitly against screening women. These three guidelines had the highest AGREE scores. Guidelines with lower AGREE scores also contained recommendations for other target groups. Four guideline groups (CSVS, CCS, SVS1, and SVS2) recommended screening in women if risk factors for development of AAA are present. Although in two of these guidelines (CSVS and CCS) multiple risk factors were required, in two guidelines

(SVS1 and SVS2) the presence of one risk factor was considered sufficient reason to screen. Three guidelines (CCS, SVS1, and SVS2) recommended screening of middle-aged men (that is 50 or 55 years) if a family history of AAA is present. Although not all guideline groups reported an age criterion when screening should no longer be offered, in most guidelines (4 of 7) 75 years of age was considered as the upper age limit. Abdominal ultrasonography was unanimously advocated as the primary screening test and only one guideline group (ACC) recommended physical examination as a useful screening tool in addition to ultrasonography. All guideline groups recommended elective surgical repair at an abdominal aortic diameter of 5.5 cm in elderly men. Some guideline groups advocated using a lower threshold (i.e., 5.0 cm) for women (CCS and SVS2) or young healthy patients (SVS2) as an indication for surgical repair.
Except for the USPSTF guideline, all guidelines contained recommendations for surveillance of those with aneurysms smaller than 5.5 cm in diameter. These recommendations, however, varied across the guidelines with respect to the intensity of follow-up and aorta diameter cut-off values for the monitoring intervals. The two Canadian guideline groups (CSVS and CCS) were unique in recommending periodic re-screening for individuals with abdominal aortic diameters below 3 cm; the remaining guideline groups recommended one-time screening.

DISCUSSION

In summary, we identified 7 guidelines on AAA screening. A majority of guidelines lacked a systematic method for the evaluation of the evidence or achieved a low AGREE score for rigor of development. Most guidelines contained recommendations that were in favor of one-time AAA screening for men 65 years and older using ultrasonography. Four guidelines, of which three had low AGREE scores, also contained disparate recommendations on screening women and middle-aged men at elevated risk, whereas guidelines with higher AGREE scores did not. Although an abdominal aortic diameter of 5.5 cm was unanimously used as criterion for elective surgical repair in elderly men, no consensus existed on management of smaller AAAs.
A previously published review already summarized and discussed a selection of 3 guidelines on AAA screening, but the review was neither systematic nor were the selected guidelines appraised on quality (10). We used a sensitive search strategy to identify guidelines and we assessed the included guidelines by a validated tool, the AGREE instrument. Our article can also have additive value to guideline summaries provided by the National Guideline Clearinghouse, as this database has only summarized some of the guidelines that we reviewed, and does not appraise guidelines on quality of development (11). We tried to create awareness of differences across guidelines from Western countries, which generally have a comparable population health status and access to medical resources (12). The differences, which we identified, can have major implications for clinical practice. Because most guidelines were produced by North American organizations, this report is most valuable to guide physicians from this region in choosing which recommendations to follow. Physicians may decide on the basis of AGREE scores and their specific clinical context which recommendations to adopt or to avert.
Despite these strengths, we have to face certain limitations of our review. First, we neither evaluated the source nor the quality of the underlying evidence that supported the

recommendations, but instead assessed the guidelines' construction processes. For example, disparate evidence cited by guideline developers could provide possible causes for variation in recommendations. Transparent development methods and complete information on how judgments were made increase the reliability of recommendations and allow physicians to make more informed decisions on adopting them. Which recommendations would result in better outcomes can be determined in comparative effectiveness research (13), but this was beyond the scope of our review. Second, the AGREE instrument only considers the details of reporting information related to the development of the guideline. The true quality of the guideline can, therefore, not be fully captured. For example, a guideline group which performs a systematic search for evidence and which does not report detailed information on the search strategy followed, will receive a low AGREE score for this item. In reality, the search followed may be adequate for identifying solid evidence. Although we did search the organization's web site for additional background information, we did not contact guideline developers for additional information that was lacking in the guideline document or on the website. Third, the AGREE instrument provides a quality score on a linear scale. This means that each item is weighed equally. We believe that all items of the AGREE Rigor of Development domain are relevant, supporting equal weighting across items. The contribution of each individual item to the total quality of a guideline is however difficult to assess. Fourth, it was difficult to quantify the true degree of influence by industry relationships. We had to rely on the disclosures that were believed to be relevant for decision-making by group members themselves. We also could not assess the size of entanglements with industry, because guidelines did not report the payment amounts received.

Although all guidelines agreed upon screening elderly men, some guidelines advocated a more selective screening regime based on smoking history. Selective screening instead of whole population screening could result in too many missed AAAs (14). Nevertheless, a modeling study showed that selective screening of men aged 65 to 75 years who have ever smoked, as recommended by the USPSTF and ACC, did not severely affect the detection rate (15). Using ever-smoking as pre-selection tool, however, potentially has the disadvantage that ever-smoking not only acts on prevalence of AAA, but also on co-morbidities (16). The expected gain in life years by AAA screening could then be nullified by the raised competing risk due to other death causes. This was not taken into account for calculation of the effectiveness of screening in the previously mentioned modeling study (15). Other guideline groups recommended screening also in populations other than men aged 65 to 75 years if risk factors are present, e.g. men aged 50 to 65 years, men older than 75 years, and women. For these populations, no clear evidence exists from experimental research for such a recommendation (2). The reasoning is that the risk of having an AAA is markedly increased if risk factors are present. The odds ratio, however, generally needs to be high before a risk factor can be used for risk classification (17). The odds ratios of single risk factors other than smoking are low for clinically relevant large AAAs (14,18). Therefore, combining risk factors may be warranted to avoid unnessary ultrasonographies and overdiagnosis of small AAAs for which the optimal treatment strategy is unclear (19, 20). On the other hand, when screening is recommended both at a younger age if risk factors are present and at an older age regardless of risk factors, such in ACC, CCS, SVS1, and SVS2 guidelines, then a bias similar to lead time bias could occur. Only the AAAs, which are

vulnerable to rupture in the short term contribute to benefit of screening at an earlier age. Slowly growing AAAs would most likely be identified at the older screening age. The additional benefit of screening in middle-aged men and women at elevated risk can be explored by comparing the different screening strategies in a decision analysis.

The variation in recommendations for policy towards small asymptomatic AAAs is relevant, because with screening approximately 90% of the detected AAAs will be smaller than 5.5 cm in diameter (18, 21). Two guideline groups (CCS and SVS2) suggested using smaller diameters for women and healthy young patients as threshold for elective surgical repair. Two meta-analyses did not show an improvement of overall survival in the immediate surgical repair group as compared to those allocated to surveillance (19,20). There was insufficient power to identify subgroups, that might benefit from immediate repair. A recent published trial not included in the two meta-anayses also did not demonstrate a benefit on overall mortality after immediate endovascular repair, although this trial was stopped earlier because the event rate of the primary outcome measure of rupture or aneurysm related death was too low to achieve sufficient statistical power (22). According to the Cochrane review (20), an individual patient-level data meta-analysis is underway to conduct subgroup analyses, which are expected to elucidate risks and benefits of each treatment option for aneurysm size subgroups, and age subgroups (for example ≤ 69 years, and > 69 years). Multivariable prediction models of rupture and operative risk could also be used to identify those expected to benefit from immediate surgical repair. Multiple predictors determine rupture (23, 24) and operative risk (25) and therefore variation in treatment effect is difficult to be captured by single patient characteristics. The use of prediction models for rupture risk and operative risks has the advantage that predictors that influence both, for example female sex (26) can be taken into account. A combination of a high predicted rupture risk and a low predicted operative risk is then likely to result in a survival benefit from immediate surgical repair. In the absence of experimental evidence for a survival benefit, the trade-off between immediate surgical repair and surveillance can be based on costs and quality of life by using decision modeling and cost-effectiveness analyses. Also the optimal screening and monitoring intervals can then be evaluated.

Although methods are available for integrating various recommendations into a single guideline, our purpose was not to create a new "universal" AAA screening guideline. However, a summarizing screening algorithm comprising the recommendations which the guidelines had in common and our suggestions for future research is depicted in Figure 2. The actual implementation of these recommendations in primary care is critical in optimizing patient outcomes. Methods to measure and improve the delivery and adherence of AAA screening interventions are for example performance measures and decision support systems, but these are still topics for further research (27, 28).

CONCLUSION

Consensus exists across guidelines on one-time screening of elderly men to detect and treat AAAs ≥ 5.5 cm. For strategies towards other target groups, and management of small AAAs, prediction models and cost-effectiveness analyses are needed to provide guidance.

TABLE 1. CHARACTERISTICS OF 7 GUIDELINES ON AAA SCREENING

Guideline, Year (Reference)	Organization(s) Responsible for Guideline Development	Country that guideline applies to	AGREE Rigor Score, %	Conflicts of Interest
USPSTF, 2005 (29)	U.S. Preventive Services Task Force	United States of America	79%	EI
ACC, 2005 (30)	American College of Cardiology, and American Heart Association	United States of America	63%	SCI[a]
NSC, 2007 (31)	National Screening Committee	United Kingdom	41%	-
CSVS, 2007 (32)	Canadian Society for Vascular Surgery	Canada	40%	SCI
CCS, 2005 (33)	Canadian Cardiovascular Society	Canada	38%	-
SVS2, 2009 (34)	Society for Vascular Surgery	United States of America	25%	SCI[a]
SVS1, 2004 (35)	Society for Vascular Surgery, American Association of Vascular Surgery, and Society for Vascular Medicine and Biology	United States of America	17%	SCI

AAA, Abdominal aortic aneurysm; AGREE, Appraisal of Guidelines Research and Evaluation; EI, editorial independence declared; SCI, statement about conflicts of interest of group members present.
[a]Relationship with industry reported by any group member.

TABLE 2. RECOMMENDATIONS (N=12) IN GUIDELINES (N=7) ON SCREENING FOR ABDOMINAL AORTIC ANEURYSM

	USPSTF	USPSTF	USPSTF	ACC	NSC
AGREE rigor score, %	79%	79%	79%	63%	41%
Method to evaluate evidence	Meta-analysis; systematic review	Meta-analysis; systematic review	Meta-analysis; systematic review	Systematic review	Review of published systematic reviews, meta-analyses or guidelines; review
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	Systematic review of cost-effectiveness studies	Systematic review of cost-effectiveness studies	Systematic review of cost-effectiveness studies	Review of cost-effectiveness studies	Review of cost-effectiveness studies
Target group	Men aged 65 - 75 y who have ever smoked[c]	Men aged 65 - 75 y who have never smoked	Women	Men aged ≥ 60 y who are siblings or offspring of patients with AAAs; men aged 65 - 75 y who ever smoked[c]	Men aged 65 y
Strategy	Opportunistic screening / case-finding	Opportunistic screening / case-finding	Opportunistic screening / case-finding	Not reported	Population-based / mass screening
Recommendation	For	Not for not against	Against	For	For
Primary screening tests	Abdominal ultrasonography	Abdominal ultrasonography	Abdominal ultrasonography	Abdominal ultrasonography; physical examination	Abdominal ultrasonography
Intervention(s)	Endovascular repair or open surgical repair if AAA ≥ 5.5 cm	Endovascular repair or open surgical repair if AAA ≥ 5.5 cm	Endovascular repair or open surgical repair if AAA ≥ 5.5 cm	Surgical repair if infrarenal or juxtarenal AAAs ≥ 5.5 cm (repair is probably indicated in patients with suprarenal or type IV thoracoabdominal aortic aneurysms 5.5 - 6.0 cm); no intervention if infrarenal or juxtarenal AAAs 4.0 - 5.4 cm, but repair can be beneficial in patients with infrarenal or juxtarenal AAAs 5.0 - 5.4 cm	Referral to a vascular surgeon if AAA ≥ 5.5 cm
Surveillance	Not reported	Not reported	Not reported	Monitoring by ultrasound or computed tomographic scans every 6 to 12 months to detect expansion if infrarenal or juxtarenal AAAs 4.0 - 5.4 cm; monitoring by ultrasound examination every 2 to 3 years is reasonable if AAAs smaller than 4.0 cm in diameter	A follow-up will be arranged in 3 months if AAA 4.5 - 5.4 cm; a follow-up will be arranged in one year if AAA measures 3.0 - 4.4 cm
Screening Intervals	One-time screening	One-time screening	One-time screening	One-time screening if not in above categories	One-time screening if not in above categories

TABLE 2. RECOMMENDATIONS (N=12) IN GUIDELINES (N=7) ON SCREENING FOR ABDOMINAL AORTIC ANEURYSM (CONTINUED)

	CSVS	CSVS	CSVS	CSVS
AGREE rigor score, %	40%	40%	40%	40%
Method to evaluate evidence	Review of published systematic reviews, meta-analyses or guidelines; review	Review of published systematic reviews, meta-analyses or guidelines; review	Review of published systematic reviews, meta-analyses or guidelines; review	Review of published systematic reviews, meta-analyses or guidelines; review
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	Review of cost-effectiveness studies and published systematic review of cost effectiveness studies; cost effectiveness analysis using projection of real cost data	Review of cost-effectiveness studies and published systematic review of cost effectiveness studies; cost effectiveness analysis using projection of real cost data	Review of cost-effectiveness studies and published systematic review of cost effectiveness studies; cost effectiveness analysis using projection of real cost data	Review of cost-effectiveness studies and published systematic review of cost effectiveness studies; cost effectiveness analysis using projection of real cost data
Target group	Men aged 65 - 75 y who are candidates for surgery and are willing to participate	Women aged > 65 y and multiple RFs[a]	Women aged > 65 y, adult populaton aged < 65 y	Deducted from text: Men aged > 75 y and multiple RFs[a]
Strategy	Population-based / mass screening	Individualized investigation	Population-based / mass screening	Individualized investigation
Recommendation	For	Consider	Against	Consider
Primary screening tests	Abdominal ultrasonography	Abdominal ultrasonography	Abdominal ultrasonography	Abdominal ultrasonography
Intervention(s)	Deducted from text: surgical repair at ≥ 5.5 cm	Deducted from text: surgical repair at ≥ 5.5 cm	Deducted from text: surgical repair at ≥ 5.5 cm	Deducted from text: surgical repair at ≥ 5.5 cm
Surveillance	Policy not clearly described in guideline if AAA 4.4 - 5.4 cm; an annual abdominal ultrasound is an acceptable practice if AAA 3.0 - 4.4 cm. The true effective interval of re-screening is unknown for this group and it is likely that every 2 years is also acceptable for the smaller aneurysms	Policy not clearly described in guideline if AAA 4.4 - 5.4 cm; an annual abdominal ultrasound is an acceptable practice if AAA 3.0 - 4.4 cm. The true effective interval of re-screening is unknown for this group and it is likely that every 2 years is also acceptable for the smaller aneurysms	Policy not clearly described in guideline if AAA 4.4 - 5.4 cm; an annual abdominal ultrasound is an acceptable practice if AAA 3.0 - 4.4 cm. The true effective interval of re-screening is unknown for this group and it is likely that every 2 years is also acceptable for the smaller aneurysms	Policy not clearly described in guideline if AAA 4.4 - 5.4 cm; an annual abdominal ultrasound is an acceptable practice if AAA 3.0 - 4.4 cm. The true effective interval of re-screening is unknown for this group and it is likely that every 2 years is also acceptable for the smaller aneurysms
Screening Intervals	No follow-up ultrasound is necessary before 3 to 5 years if aortic diameter < 3.0 cm	No follow-up ultrasound is necessary before 3 to 5 years if aortic diameter < 3.0 cm	No follow-up ultrasound is necessary before 3 to 5 years if aortic diameter < 3.0 cm	No follow-up ultrasound is necessary before 3 to 5 years if aortic diameter < 3.0 cm

	CCS	SVS2	SVS1
AGREE rigor score, %	38%	25%	17%
Method to evaluate evidence	Review	Review	Review
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	Review of cost-effectiveness studies	Review of cost-effectiveness studies, but not for AAA screening	Review of cost-effectiveness studies
Target group	Men aged 65-74 y; women aged 65 y with cardiovascular disease and positive family history of AAA; men aged ≥ 50 y and positive family history of AAA	Men aged ≥ 65 y; men aged ≥ 55 y and family history of AAA; women aged ≥ 65 y and family history of AAA or who have smoked	Men aged 60 - 85 y; women aged 60 - 85 y and cardiovascular risk factors (not specified); men and women aged > 50 y and family history of AAA
Strategy	Population-based / mass screening	Population-based / mass screening	Population-based / mass screening
Recommendation	For	For	For
Primary screening tests	Abdominal ultrasonography	Abdominal ultrasonography	Abdominal ultrasonography
Intervention(s)	Referral to vascular surgeon if AAA ≥ 4.5 cm; surgical repair if men AAA > 5.5 cm and if women AAA > 5.0 cm; consider surgical repair if > 1 cm growth in 1 year	Surgical repair if fusiform AAA ≥ 5.5 cm, saccular AAA[b], young healthy patients, and especially women, with AAA 5.0 - 5.4 cm[b]; statins[b], smoking cessation, ACE inhibitors/angiotensin receptor blockers[b] if surveillance (AAA 3.5 - 5.4 cm: not clearly described)	Referral to a vascular specialist if AAA > 4.5 cm; surgical repair if > 5,5 cm: policy not clearly described
Surveillance	Repeat ultrasound every 6 months if AAA ≥ 4.5 cm; repeat ultrasound in 1 year if AAA 4.0 - 4.5 cm; repeat ultrasound in 2 year if AAA 3.5 - 3.9 cm; repeat ultrasound in 3 years if AAA 3.1 - 3.4 cm	Repeat ultrasound every 6 months if AAA 4.5 - 5.4 cm; repeat ultrasound in 1 year if AAA 3.5 - 4.4 cm; repeat ultrasound in 3 years if AAA 3.0 - 3.4 cm; repeat ultrasound in 5 years if AAA 2.6 - 2.9 cm	Repeat ultrasound every 6 months if AAA 4.0 - 4.5 cm; annual ultrasound examination if AAA 3.0 - 4.0 cm
Screening Intervals	Repeat ultrasound follow-up in 3-5 years if aortic diameter < 3.0 cm	One time screening if aortic diameter < 2.6 cm and 65 years of age or older; not reported if aortic diameter < 2.6 cm and age 55 - 65 years of age	One time screening if aortic diameter < 3.0 cm

AAA, Abdominal aortic aneurysm; ACC, American College of Cardiology; AGREE, Appraisal of Guidelines Research and Evaluation; CCS, Canadian Cardiovascular Society; CSVS, Canadian Society for Vascular Surgery; NSC, National Screening Committee; RFs, risk factors; SVS, Society for Vascular Surgery; USPSTF, United States Preventive Services Task Force; [a]Past or current smokers; [b]Family history of AAA, smoking history, cerebrovascular disease, age 70 years old; [c]Level of recommendation is weak, or benefit is uncertain.

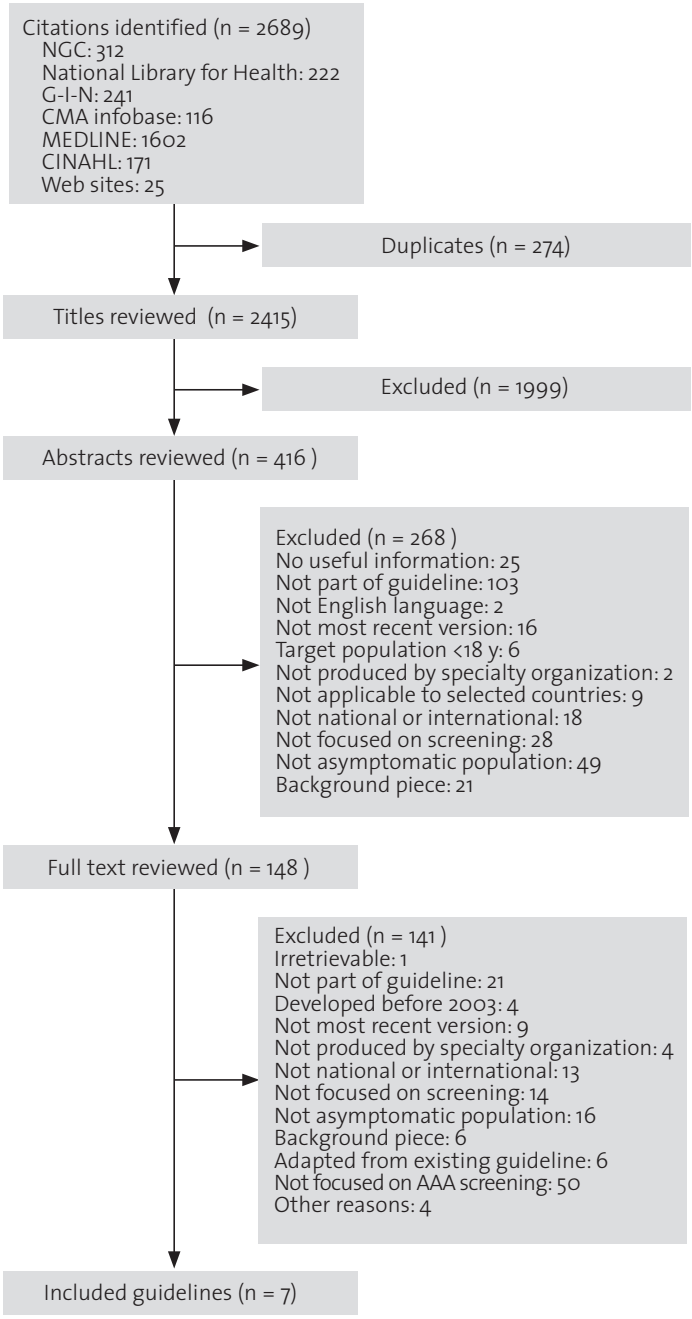

Figure 1. Literature search and selection. Numbers of guidelines of each step of the process are indicated. Group totals may exceed the reported numbers for the excluded articles at abstract and full text level because several reasons for exclusion were allowed. AAA, Abdominal aortic aneurysm; CMA, Canadian Medical Association; NGC, National Guideline Clearinghouse.

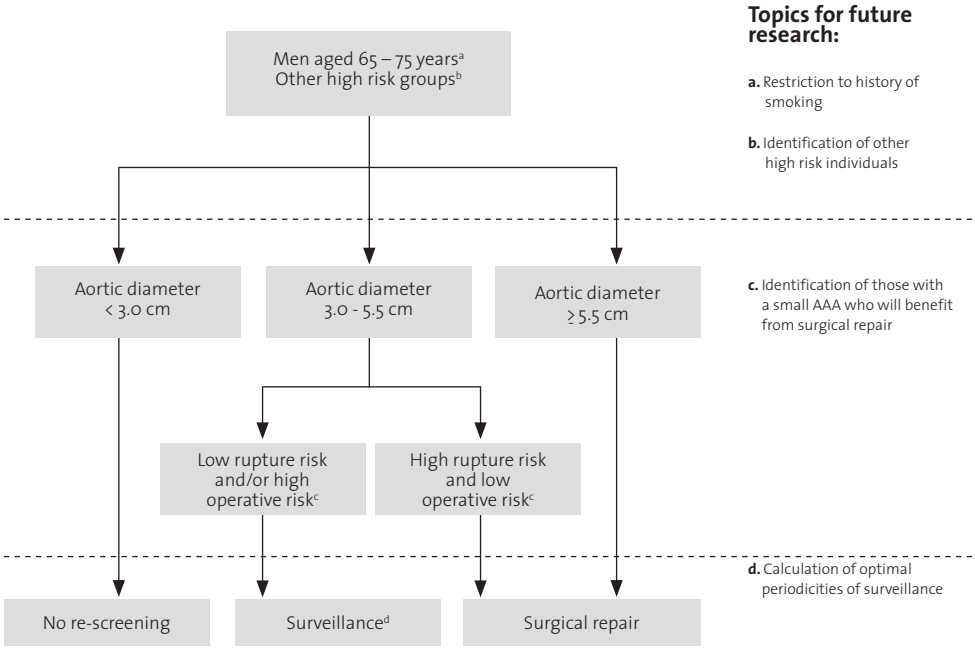

Figure 2. Summarizing screening algorithm and suggestions for future research. [a] Restricting this target group by adding a history of smoking requires the reduced life expectancy caused by smoking to be taken into consideration in decision analysis. [b] Multivariable modeling to predict abdominal aortic aneurysm (AAA) risk can be used to identify groups at high risk within men 50 to 65 years, men 75 years, and women 60 years. Variables to consider are age, gender, family history of AAA, history of smoking, history of cardiovascular disease, other cardiovascular risk factors (14,18). The expected benefit of screening these groups can be calculated by decision analysis. [c] Prediction models considering variables such as age, gender, aortic diameter size, smoking status, blood pressure, history of cardiovascular disease, pulmonary and renal impairment can estimate these risks (23-25). [d] The optimal intervals for periodic ultrasound scan surveillance can be calculated with cost-effectiveness analysis.

REFERENCES

1. Heron MP HD, Murphy SL, Xu JQ, Kochanek KD, Tejada-Vera B. Deaths: Final data for 2006. National vital statistics reports; vol 57 no 14. Hyattsville, MD: National Center for Health Statistics; 2009.
2. Cosford PA, Leng GC. Screening for abdominal aortic aneurysm. Cochrane Database Syst Rev 2007;18(2): CD002945.
3. Medicare Web site. Abdominal Aortic Aneurysm (AAA) Screening. 2010 http://www.medicare.gov/ [Accessed April 19, 2010].
4. Koelemay MJ, Henebiens M, Vahl AC. [Guideline 'Diagnosis and treatment of abdominal aortic aneurysm']. Ned Tijdschr Geneeskd 2009;153: A572.
5. Feder G, Eccles M, Grol R, Griffiths C, Grimshaw J. Clinical guidelines: using clinical guidelines. BMJ 1999;318(7185): 728-730.
6. Sniderman AD, Furberg CD. Why guideline-making requires reform. Jama 2009;301(4): 429-431.
7. Oxman AD, Glasziou P, Williams JW, Jr. What should clinicians do when faced with conflicting recommendations? Bmj 2008;337(337): a2530.
8. Ferket BS, Colkesen EB, Visser JJ, Spronk S, Kraaijenhagen RA, Steyerberg EW, et al. Systematic review of guidelines on cardiovascular risk assessment: Which recommendations should clinicians follow for a cardiovascular health check? Arch Intern Med 2010;170(1): 27-40.
9. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12(1): 18-23.
10. Pande RL, Beckman JA. Abdominal aortic aneurysm: populations at risk and how to screen. J Vasc Interv Radiol 2008;19(6 Suppl): S2-8.
11. National Guideline Clearinghouse Web site. 2010. http://www.guideline.gov. [Accessed April 19, 2010].
12. World Health Organization. World health statistics 2010. Geneva: World Health Organization; 2010.
13. Manuel DG, Kwong K, Tanuseputro P, Lim J, Mustard CA, Anderson GM, et al. Effectiveness and efficiency of different guidelines on statin treatment for preventing deaths from coronary heart disease: modelling study. BMJ 2006;332(7555): 1419.
14. Spencer CA, Jamrozik K, Norman PE, Lawrence-Brown MM. The potential for a selective screening strategy for abdominal aortic aneurysm. J Med Screen 2000;7(4): 209-211.
15. Fleming C, Whitlock EP, Beil TL, Lederle FA. Screening for abdominal aortic aneurysm: a best-evidence systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2005;142(3): 203-211.
16. Lederle FA, Nelson DB, Joseph AM. Smokers' relative risk for aortic aneurysm compared with other smoking-related diseases: a systematic review. J Vasc Surg 2003;38(2): 329-334.
17. Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? Bmj 1999;319(7224): 1562-1565.
18. Lederle FA, Johnson GR, Wilson SE, Chute EP, Littooy FN, Bandyk D, et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group. Ann Intern Med 1997;126(6): 441-449.
19. Lederle FA, Kane RL, MacDonald R, Wilt TJ. Systematic review: repair of unruptured abdominal aortic aneurysm. Ann Intern Med 2007;146(10): 735-741.
20. Ballard DJ, Filardo G, Fowkes G, Powell JT. Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev 2008;8(4): CD001835.
21. Ashton HA, Buxton MJ, Day NE, Kim LG, Marteau TM, Scott RA, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet 2002;360(9345): 1531-1539.
22. Ouriel K, Clair DG, Kent KC, Zarins CK. Endovascular repair compared with surveillance for patients with small abdominal aortic aneurysms. J Vasc Surg;2010: 19.
23. Brown PM, Zelt DT, Sobolev B. The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. J Vasc Surg 2003;37(2): 280-284.
24. Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. Ann Surg 1999;230(3): 289-296; discussion 296-287.
25. Steyerberg EW, Kievit J, de Mol Van Otterloo JC, van Bockel JH, Eijkemans MJ, Habbema JD. Perioperative mortality of elective abdominal aortic aneurysm surgery. A clinical prediction rule based on literature and individual patient data. Arch Intern Med 1995;155(18): 1998-2004.
26. Grootenboer N, van Sambeek MR, Arends LR, Hendriks JM, Hunink MG, Bosch JL. Systematic review and meta-analysis of sex differences in outcome after intervention for abdominal aortic aneurysm. Br J Surg 2010;97(8): 1169-1179.
27. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. Jama 2007;297(1): 61-70.
28. Wells S, Furness S, Rafter N, Horn E, Whittaker R, Stewart A, et al. Integrated electronic decision support increases cardiovascular disease risk assessment four fold in routine primary care practice. EurJ Cardiovasc Prev Rehabil 2008;15(2): 173-178.
29. U.S. Preventive Services Task Force. Screening for abdominal aortic aneurysm: recommendation statement. Ann Intern Med 2005;142(3): 198-202.
30. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular

Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006;113(11): e463-654.

31. Abdominal aortic aneurysm screening. UK National Screening Committee Website. 2007. [Accessed April 19, 2010].
32. Mastracci TM, Cina CS. Screening for abdominal aortic aneurysm in Canada: review and position statement of the Canadian Society for Vascular Surgery. J Vasc Surg 2007;45(6): 1268-1276.
33. Abramson BL, Huckell V, Anand S, Forbes T, Gupta A, Harris K, et al. Canadian Cardiovascular Society Consensus Conference: peripheral arterial disease - executive summary. Can J Cardiol 2005;21(12): 997-1006.
34. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg 2009;50(4 Suppl): S2-49.
35. Kent KC, Zwolak RM, Jaff MR, Hollenbeck ST, Thompson RW, Schermerhorn ML, et al. Screening for abdominal aortic aneurysm: a consensus statement. J Vasc Surg 2004;39(1): 267-269.

Chapter 5

Systematic review of guidelines on peripheral artery disease screening

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ABSTRACT

Background

Peripheral artery disease (PAD) screening may be performed to prevent progression of PAD or future cardiovascular disease in general. Recommendations for PAD screening have to be derived indirectly because no randomized trials comparing screening versus no screening have been performed. We performed a systematic review of guidelines to evaluate the value of PAD screening in asymptomatic adults.

Methods

Guidelines in English published between January 1, 2003 and January 20, 2011 were retrieved using MEDLINE, CINAHL, the National Guideline Clearinghouse, the National Library for Health, the Canadian Medication Association Infobase, and the G-I-N International Guideline Library. Guidelines developed by national and international medical societies from Western countries, containing recommendations on PAD screening, were included. Two reviewers independently assessed rigor of guideline development using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument. One reviewer performed full extraction of recommendations, which was validated by a second reviewer.

Results

Of 2779 titles identified, 8 guidelines were included. AGREE scores varied from 33% to 81%. Five guidelines advocated PAD screening, others found insufficient evidence for PAD screening or were against it. Measurement of the ankle-brachial index (ABI) was generally recommended for middle-aged populations with elevated cardiovascular risk levels. Those identified as having PAD are reclassified as high risk, warranting intensive preventive interventions to reduce their risk of a cardiovascular event. The underlying evidence mainly consisted of studies performed in patients with established PAD. A meta-analysis that evaluated ABI testing in the context of traditional cardiovascular risk assessment was interpreted differently.

Conclusions

Recommendations on PAD screening vary across current guidelines, making the value of PAD screening uncertain. The variation seems to reflect lack of studies that show added value of detection of early PAD beyond expectant management and traditional risk assessment.

INTRODUCTION

Peripheral artery disease (PAD) is a common manifestation of generalized atherosclerosis in the middle-aged and elderly. The prevalence in the general population aged ≥ 40 years is approximately 4%, but it strongly increases with age up to 15% (1). In both asymptomatic and established PAD, the risk of cardiovascular mortality is elevated, and this relation is independent of traditional cardiovascular risk factors, such as age, sex, blood pressure, smoking, cholesterol, and diabetes (2, 3). Early detection of PAD can theoretically lead to health benefits through two pathways. First, identifying and treating early diagnosis of PAD could avoid progression of PAD itself, averting development of claudication, impaired walking and amputation. Second, identifying PAD could improve risk management of future cardiovascular disease (CVD), i.e. coronary artery disease and stroke. The latter would result from a more accurate selection of high-risk individuals for intensive preventive interventions by reclassifying individuals based on the absence or presence of PAD (4).

To date, no randomized controlled trials (RCTs) of PAD screening vs. no screening have been performed. In the absence of clear evidence from screening RCTs showing a beneficial effect on the progression of PAD or occurrence of CVD events, decisions on PAD screening can be based on a combination of 1) non-experimental research on accuracy of the screening test and 2) treatment RCTs performed in patients with PAD, preferably identified through screening (5). Guideline developers systematically summarize and appraise such studies and provide recommendations for clinical decision-making based on the best-available evidence. Instead of performing an extensive review of studies on the potential benefit and harm of PAD screening, decision-making can also be based on a review of guidelines relevant to this topic. However, guidelines may suffer from non-systematic development methods and conflicts of interest (6, 7), and these issues should thus be taken into account.

The aim of this study was to evaluate the value of PAD screening in asymptomatic adults, by performing a systematic review and critical appraisal of current guidelines.

METHODS

Data sources and searches

The literature search, used for a previous article on cardiovascular risk assessment (8), was updated to identify guidelines of interest. Briefly, MEDLINE, CINAHL, and four guideline specific databases: the National Guideline Clearinghouse (US), the National Library for Health (UK) on Guideline Finder, Canadian Medical Association Infobase (Canada), and the G-I-N International Guideline Library on (http://www.g.i-n.net) were searched. Guidelines published from January 1st 2003 to January 20th 2011, and in the English language were considered. Additional guidelines were sought by searching websites of guideline development organizations. Details on the search syntax are provided in *Appendix 1*.

Guideline selection

This review is part of a larger project that comprised systematic reviewing of guidelines on cardiovascular disease prevention. The project was guided by a written protocol based on a manual

for guideline adaptation (9). For this report, we only considered guidelines containing recommendations on PAD screening. Articles were included for further review if they met the Institute of Medicine (IOM) definition for clinical practice guidelines (10). To meet this definition, articles were required to contain "systematically developed statements to assist physicians and patient decisions about appropriate health care for specific clinical circumstances". The following inclusion criteria were used: (1) guideline development was performed on behalf of a national or international medical specialty society (2) recommendations were applicable to an asymptomatic population with no previous diagnosis of PAD; (3) recommendations were applicable to at least one of the following countries: the US, Canada, Australia, New Zealand or the UK.
Two reviewers (B.S.F. and B.E.C.) independently scanned titles and abstracts for eligibility. Exclusions were accomplished if both reviewers agreed on the decision. Discrepancies were resolved by consensus. Final selection based on the full text was performed by the first author.

Data extraction and quality assessment

Two authors (B.S.F., and S.S.) rated each included guideline for quality of development using the 7-item "Rigor of Development" domain of the first version of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument (11). This domain considers the reporting of: 1) methods to search for evidence; 2) criteria for selecting the evidence; 3) methods for formulating the recommendations; 4) consideration of health benefits, side effects, and risks; 5) supporting evidence; 6) procedures for external peer review; and 7) the update process. We also checked websites of guideline developers for additional information on development methods followed. Each item was independently scored on a 4-point Likert scale by the two authors conform instructions of the AGREE instrument manual (12). If the two authors rated items with a difference of more than 2 points, a consensus meeting was performed. Overall AGREE rigor scores were calculated by averaging the AGREE scores of the two reviewers. Reproducibility of the two reviewers' average rigor scores was measured with an intraclass correlation coefficient.
SRS® 4.0 (Mobius Analytics, Ottowa, Ontario, Canada), a web-based software package developed for systematic review data management was used to remove duplicates, store citations and track results at title, abstract, quality assessment and data extraction levels.
Recommendations on PAD screening from the included guidelines were extracted by one reviewer (B.S.F.) and validated for completeness and accuracy by another (S.S.). Discrepancies were resolved by consensus. We extracted information on: 1) methodology of guideline development; 2) consideration of cost-effectiveness regarding the recommendation; 3) target group and delivery of PAD screening; 4) tests considered; 5) strength of the recommendation; 6) the objective (prevention of general cardiovascular disease and/or complications by PAD itself); and 7) interventions (aspirin, statin, blood pressure lowering, glucose lowering, and lifestyle therapy) and 8) follow-up. The strength of the recommendation was classified as "for", "consider", "neither for nor against", "insufficient evidence" or "against". In addition, we extracted data about possible conflicts of interest. This comprised statements about editorial independence from funders, presence of external funding, and relationships with industry.

Data synthesis and analysis

We ranked included guidelines according to their average AGREE Rigor scores. Subsequently,

we constructed a recommendation matrix for comparison of the recommendations from the selected guidelines. The table was divided into 1) methodology of guideline development; 2) consideration of cost effectiveness regarding the recommendation; 3) target group and delivery of screening; 4) strength of the recommendation; 5) tests considered and method of assessment; and 6) thresholds for further testing, intervention and follow-up. For each recommendation, the evidence base was summarized descriptively as reported in the guideline document.

RESULTS

Selected guidelines

We screened 2779 guidelines for eligibility at title level, of which 148 were included for review at full-text level (Figure 1). Eight guidelines relevant to PAD screening were eligible for full data extraction (13-21). Table 1 summarizes the selected guidelines in descending order of AGREE rigor scores. Seven guidelines were developed in North America, whereas one (Inter-Society Consensus for the Management of Peripheral Arterial Disease [TASC]) (20) was developed by an international collaboration (Europe, North America, Australia, South Africa, and Japan). AGREE rigor scores varied from 33% to 81%, with 3 guidelines (Canadian Cardiovascular Society [CCS2] (19), TASC (20) and CCS1 (21) having an AGREE rigor score below the median, 63%. For 2 guidelines (American College of Cardiology [ACC2] (15) and National Cholesterol Education Program [NCEP] (17,18)), large differences between authors' scores of one item were resolved by a consensus meeting. Reproducibility of the AGREE scores by the 2 reviewers was good, with an intraclass correlation coefficient of 0.89.

In 4 of the 8 guidelines (ACC1 (16) ACC2 (15), NCEP (17, 18), and CCS2 (19)), at least one panel member declared having a relevant financial relationship with industry. The TASC guideline (20) was developed with funding from 2 biopharmaceutical companies, both being producers of cardiovascular preventive agents. Group members of the ACC1 (16), ACC2 (15), NCEP (17, 18), and CCS2 (19) guidelines also had relationships with biopharmaceutical companies producing cardiovascular preventive medication. One of these guidelines (ACC2 (15)) reported exclusions of panel members from voting on topics other than PAD screening for which potential conflicts of interest existed. Three guidelines (U.S. Preventive Services Task Force [USPSTF1] (14), USPSTF2 (13), and TASC (20)) contained a statement about being developed independently from the funding organization. One guideline (CCS1 (21)) neither reported that it was developed independently from funding organization(s) nor included a statement about conflicts of interest of group members.

In 3 (USPSTF1 (14), USPSTF2 (13), and CCS2 (19)) of the 8 guidelines, full search strategies and methods for inclusion and exclusion of articles were reported. Evaluation of cost-effectiveness of preventive strategies was done in 3 guidelines (ACC1 (16), NCEP (17,18), and TASC (20)) by reviewing existing decision-modeling studies for, respectively, treatment of PAD, LDL-cholesterol lowering therapy, and risk factor management, but not specifically for PAD screening.

Guidelines' recommendations

The 8 included guidelines contained 9 recommendations on PAD screening (Table 2). Most advocated PAD screening (ACC1 (16), ACC2 (15), NCEP (17,18), TASC (20) and CCS1 (21)); the USPSTF1

guideline (14) contained a recommendation against PAD screening, whereas the others (USPSTF2 (13) and CCS2 (19)) concluded that insufficient evidence existed. AGREE scores did not differ extremely between guidelines advocating PAD screening and guidelines that did not: 54% versus 68% on average. The ankle-brachial index (ABI) was unanimously considered as the primary screening tool. The method of calculating the ABI was not reported in much detail in the USPSTF1 (14), NCEP (17,18), and CCS2 (19) guidelines. Target groups generally comprised middle-aged subjects with one or more cardiovascular risk factors, and the elderly.

Evidence base for PAD screening to prevent progression of PAD

USPSTF1 (14), TASC (20) and CCS1 (21) guidelines considered PAD screening from the perspective of preventing PAD progression (including claudication, amputation, and impaired ambulation). In the TASC (20) and CCS1 (21) guidelines, recommendations for smoking cessation were based on non-experimental research showing protective effects from non-smoking on PAD (22-25) and evidence that effective interventions exist to modify smoking behaviour (26-28). The CCS1 (21) guideline's recommendations on exercise were based on trials of walking programs showing improvements on the maximum walking distance in symptomatic PAD patients (29,30). The USPSTF1 guideline (14) identified a randomized trial on a combination of these interventions specifically conducted in patients with screen-detected PAD, which showed beneficial effects only on the maximum walking distance, not on smoking cessation rates (31) The USPSTF (13, 14) however, concluded that the evidence base to justify PAD screening is too thin because these interventions also are recommended regardless of PAD presence. The USPSTF (13, 14) also found insufficient evidence for a clear benefit of early treatment as advantageous over waiting until PAD is detected clinically. This was based on a cross-sectional study that showed an association between statin use and lower-extremity function, which was independent of presence of established PAD (32).

Evidence base for PAD screening to prevent future CVD events

USPSTF2 (13), ACC2 (15), ACC1 (16), NCEP (17,18), CCS2 (19), TASC (20), and CCS1 (21) guidelines also mainly considered PAD screening as a strategy to prevent cardiovascular disease events other than PAD. The ACC1 (16), NCEP (17,18), TASC (20) and CCS1 (21) guidelines based their conclusions that there is sufficient evidence for use of ABI testing to prevent CVD on: 1) several cohort studies demonstrating that the presence of PAD carries an increased risk for future CVD equal to that of established CHD4 and 2) randomized trials showing that aggressive risk factor modification (angiotensin-converting enzyme inhibitors, antiplatelet, and statin therapy) is effective in preventing CVD in PAD patients (33-36). The USPSTF2 (13) and ACC2 (15) guidelines specifically considered ABI testing as a method to reclassify individuals at intermediate risk (10%-20%) for coronary artery disease events based on traditional Framingham risk factors to either low (< 10%) or high risk (≥ 20%). Intensive risk modification is generally recommended only for the high-risk category, while many events also occur in the intermediate-risk category. The USPSTF2 guideline (13) found insufficient evidence to recommend ABI testing for individuals at intermediate risk, because it is uncertain whether reclassification would occur in men. The linked evidence consisted of a meta-analysis incorporating combined data on 48,294 individuals from 16 studies. In this report, a table demonstrates 10-year coronary event rates in men and

women by Framingham risk score categories and ABI results. Results support reclassification of women with an intermediate 10-year coronary event risk (10%-19%) to high risk (≥ 20%) if the ABI ≤ 0.90. Reclassification to low risk did not occur in women. In men at intermediate risk, reclassification to low risk occurred if the ABI > 1.40, but no reclassification to high risk occurred. Using the same data (4), the ACC2 guideline (15) concluded that the ABI is a reasonable method to improve traditional risk classification in both men and women. The CCS2 (19) guideline stated that ABI testing may detect high-risk individuals missed by traditional risk factors, but reported that there is no evidence from clinical trials that ABI testing also would improve outcomes. None of the guidelines contained recommendations in which both ABI results and traditional cardiovascular risk factors were incorporated in a multivariable risk model.

DISCUSSION

In summary, we identified 8 guidelines on PAD screening. The majority of these guidelines lacked a systematic method for evaluation of the evidence or achieved a low AGREE score for rigor of development. Five of the 8 guidelines recommended PAD screening, others found insufficient evidence for PAD screening or were against it. Guidelines that advocated PAD screening generally recommended measurement of the ABI, sometimes in combination with a screening questionnaire or physical examination. Target groups were middle-aged populations with elevated cardiovascular risk levels, and the elderly. Intensive CVD risk modifying therapy was recommended for all individuals diagnosed with PAD.

As far as we know, this is the first review of multiple guidelines on PAD screening. We used a thorough search strategy to identify all relevant guidelines. One of the limitations of our study might be that we mainly found North American guidelines. Hence, our results may be not that generalizable to readers from other than North America. However, many guidelines from other Western countries exist on cardiovascular risk assessment and prevention in asymptomatic individuals and therefore, this review is relevant to these countries as well. Another limitation could be that we used the AGREE instrument for rating the quality of development of included recommendations. Originally, the AGREE instrument was meant to be used for complete guideline documents. As we only considered recommendations on PAD screening that were derived from guidelines comprising various recommendations, AGREE score results may not always correspond to the PAD screening recommendations. Still, one can expect that a certain correlation exists between the complete guideline and its single recommendations. A third limitation may be that we did not appraise the evidence that was considered by the guideline groups for developing their recommendations.

We observed conflicting recommendations, which did not seem to depend on the variation in rigor of development. A reason could be that the perspective from which judgments about the value of screening was made varied across guidelines. However, only one guideline (USPSTF1 (14)) was solely focused on prevention of progression of PAD; all other guidelines also considered prevention of CVD in general. The USPSTF1 guideline has been criticized by focusing on progression of PAD only (37). Some of the discrepancies seem to originate from uncertainty

about the value of the ABI in the context of CVD risk assessment using traditional risk factors. Whether individuals formerly not at high CVD risk can be treated as high-risk individuals after an abnormal ABI result, as argued by guideline groups advocating PAD screening, was put in doubt by other guidelines. This doubt was mainly based on a meta-analysis performed by the ABI collaboration, which did not show any reclassification of men from intermediate to high cardiovascular risk (4). It remains questionable, however, whether a recommendation for screening women at intermediate risk is still justified. Guidelines that did recommend PAD screening advocated interventions after detection of PAD, which generally consisted of 3 components: lifestyle intervention, statin therapy, and antiplatelet therapy. Cited RCTs demonstrate a similar effect of these interventions in reducing CVD events in patients with established PAD and in high-CVD-risk patients without PAD (35, 38-40). However, PAD patients included in these RCTs were presumably diagnosed by various diagnostic pathways. Thus, answering the question of whether these interventions also would be effective in an exclusively screen-detected PAD population is difficult. Recently, an antiplatelet therapy RCT was performed in such a population and a statistically significant effect on CVD events could not be demonstrated. Probably, the event rates were too low to achieve sufficient power (41). Due to its recent publication date, this RCT was not considered in the guideline reports.

Another reason for the observed disagreements could be that some recommendations were biased toward a more aggressive screening policy as a result of the financial relationships between guideline developers and the pharmaceutical industry. These are relevant because recommendations for aggressive screening would lead to increased allocation to cardiovascular preventive medication. Because of the lack of clear-cut evidence as described above, weighing of harms and benefits may be more sensitive to subjectivity and conflicts of interest (42). Nevertheless, we can only speculate about the influence of industry on the decisionmaking.

As many guidelines did not report complete information on potential conflicts of interest, a way to deal with this problem is to rely on the guidelines that have undergone a transparent and rigorous development process, reflected by high AGREE rigor scores.

CONCLUSIONS

Recommendations on PAD screening vary across current guidelines, making the value of PAD screening uncertain. The variation seems to reflect lack of studies that show added value of detection of early PAD beyond expectant management and traditional risk assessment.

TABLE 1. CHARACTERISTICS OF 8 GUIDELINES ON PERIPHERAL ARTERY DISEASE SCREENING

ID Code	Organization responsible for guideline development	Country that guideline applies to	AGREE rigor score[a], %	Conflicts of Interest
USPSTF2, 2009 (13)	U.S. Preventive Services Task Force	United States of America	81%	EI, SCI
USPSTF1, 2005 (14)	U.S. Preventive Services Task Force	United States of America	81%	EI
ACC2, 2010 (15)	American College of Cardiology Foundation, and American Heart Association	United States of America	71%	DIR, SCI[b],SCIR[b]
ACC1, 2005 (16)	American College of Cardiology, and American Heart Association	United States of America	67%	DIR, SCI[b],SCIR[b]
NCEP, 2002 (17), 2004 update (18)	National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association	United States of America	60%	SCI[b], DIR
CCS2, 2009 (19)	Canadian Cardiovascular Society	Canada	43%	SCI[b]
TASC, 2007 (20)	Trans-Atlantic Inter-Society Consensus	International	38%	EI, FIP
CCS1, 2005 (21)	Canadian Cardiovascular Society	Canada	33%	-

AGREE = Appraisal of Guidelines Research and Evaluation; DIR = disclosure of the identities of peer reviewers; EI = editorial independence from funding organization declared; FIP = funding by industrial partner reported; SCI = statement about conflicts of interest of panel members present; SCIR = statement about conflicts of interest of external peer reviewers present. [a]Rigor scores are calculated as the average of (– item scores - 7)/(28 - 7) provided by the two authors. Item scores were scored as: 4 = strongly agree; 3 = agree; 2 = disagree; 1 = strongly disagree. For further information: http://www.agreecollaboration.org and the article about the development of the AGREE instrument (11). [b]Relationship with industry reported by at least one person.

TABLE 2. RECOMMENDATIONS (N=9) IN GUIDELINES (N=8) ON SCREENING FOR PERIPHERAL ARTERY DISEASE

	USPSTF2	USPSTF1	ACC2	ACC1
AGREE rigor of development	81%	81%	71%	67%
Method to evaluate evidence	Systematic reviewa covering 1966 - September 2008	Systematic reviewa covering 1994 - June 2005	Standardized reviewb with MEDLINE search covering March 2008 – April 2010; review of published systematic reviews, meta-analyses or guidelines	Standardized reviewb
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	Because of limitations in the evidence of effectiveness, little information is available on cost-effectiveness	Not reported	Generally there was no evidence found on cost-effectiveness. Where exceptions were identified, cost-related information was included, but not for PAD screening.	Review of cost-effectiveness studies, but not for PAD screening.
Objective	Prevention of CAD	Prevention of progression of PAD	Prevention of CVD	Prevention of CVD
	National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association	United States of America	60%	SCI[b], DIR
Target group	Adults in the intermediate CAD risk category with 10-year CAD risk 10% - 20% (FRS)	Adult population	Adults aged ≥ 20 y in the intermediate CAD risk category with 10-year CAD risk 10% - 20% (FRS)	Adult population aged < 50 y and diabetes and ≥ 1 RF; adult population aged 50 to 69 y and ≥ 1 RFd; adult population aged ≥ 70 y
Strategy	Opportunistic screening / case-finding	Opportunistic screening / case-finding	Not reported	Not reported
Strength of recommendation	Insufficient evidence to make a recommendation	Against	Consider	For
Screening tests	ABI	Quest, ABI	ABI	Quest, ABI
Method of calculation ABI	The ratio of the systolic blood pressure at each ankle to the systolic blood pressure in the right arm. The lower of 2 measurements is used. No further details reported.	The ratio of systolic pressures in the lower and upper extremities. No further details reported.	The highest lower-extremity blood pressure (measured in left and right posterior tibial, and dorsalis pedis arteries) is divided by the highest of the upper-extremity blood pressures (measured in left and right brachial arteries)	For each leg: ratio of higher of the ankle systolic pressure of the posterior tibial and dorsalis pedis arteries to higher brachial systolic blood pressure of either arm.
Further testing	Not necessary	Angiography if ABI less than 0.9	Not necessary	Pulse volume recording , toe-brachial index if ABI greater than 1.30 (abnormal); ABI after exercise test if ABI 0.91 to 1.30 (borderline & normal)
Intervention(s)	If reclassified 10-year CAD risk > 20% (no accepted ABI categories for reclassification): therapeutic lifestyle changes, and, when appropriate, initiating drug treatment to reduce LDL-C	If screening-detected PAD: statins, lifestyle intervention (exercise; smoking cessation)	An abnormally low or abnormally high ABI is associated with increased cardiovascular risk in both men and women. If reclassified 10-year CAD risk ≥ 20%: intensive risk factor modification	If ABI ≤ 0.90 or abnormal confirmatory test results: aspirin/ASA, lifestyle intervention (smoking cessation), LDL-C < 100 mg/dL or < 70 mg/dL if very high risk, blood pressure management according to JNC-7 guidelines, ACE inhibition may be considered, HbA1c < 7%
Screening intervals	Not reported	Not reported	More research is warranted for repeat risk assessment	Not reported

TABLE 2. RECOMMENDATIONS (N=9) IN GUIDELINES (N=8) ON SCREENING FOR PERIPHERAL ARTERY DISEASE (CONTINUED)

	NCEP	CCS2	TASC	CCS1	CCS1
AGREE rigor of development	60%	43%	38%	33%	33%
Method to evaluate evidence	Standardized review[b] of literature identified by the panel members and by a MEDLINE search; review of published systematic reviews, meta-analyses or guidelines	Systematic review[a] covering January 1, 2006 - February 1, 2009; review of published systematic reviews, meta-analyses or guidelines	Review[c]	Review[c]	Review[c]
Method to formulate recommendations	Expert consensus	Expert consensus	Expert consensus	Expert consensus	Expert consensus
Consideration of costs	Review of cost-effectiveness studies, but not for PAD screening.	Not reported	Review of cost-effectiveness studies, but not for PAD screening.	Not reported	Not reported
Objective	Prevention of CAD	Prevention of CVD	Prevention of CVD	Prevention of CVD	Prevention of CVD
			Prevention of progression of PAD	Prevention of progression of PAD	Prevention of progression of PAD
Target group	Multiple RF[s] and 10-year CAD risk ≤ 20%; to guide a decision about LDL-C-lowering drugs after lifestyle changes if 0-1 RF and LDL-C 160-189 mg/dL; the test is most likely to be positive in persons aged > 50 y and other RF[s]	Men aged ≥ 40 y, women aged ≥ 50 y or postmenopausal, adults at any age and ≥ 1 RF[f]	Adult population aged 50-69 y and ≥ 1 RF[e]; adult population aged ≥ 70 y; Framingham risk score 10% - 20%	Men aged > 40 y; women aged > 50 y or postmenopausal; adult population and a recognized cardiovascular RF	Men aged > 40 y and ≥ 1 RF[g] ; women aged > 50 y or postmenopausal and ≥ 1 RF[g]
Strategy	Opportunistic screening / case-finding	Not reported	Not reported	Not reported	Not reported
Strength of recommendation	Consider	Insufficient evidence to make a recommendation	For	For	For
Screening tests	ABI	ABI	ABI	Quest, PE	ABI
Method of calculation ABI	By measuring the systolic blood pressure in brachial, posterior tibial, and dorsalis pedis arteries. No further details reported. An ABI of <0.9, found in either leg, is diagnostic of PAD	The ratio of systolic blood pressure in the dorsalis pedis or posterior tibial artery to the systolic blood pressure in the brachial artery. No further details were reported.	For each leg: ratio of higher of the ankle systolic pressure of the posterior tibial and dorsalis pedis arteries to higher brachial systolic blood pressure of either arm. The index leg is often defined as the leg with the lower ABI.	For each leg: the ratio of the highest tibial pressure over the higher of the two brachial pressures.	For each leg: the ratio of the highest tibial pressure over the higher of the two brachial pressures.
Further testing	Not necessary	Not necessary	Toe brachial index or velocity wave form, pulse volume recording, duplex imaging if ABI > 1.40	ABI, segmental limb pressures, treadmill study if abnormal primary screening results	Duplex scanning, CTA, MRA if ABI less than 0.9 or over 1.3
Intervention(s)	If ABI of less than 0.9:	If ABI of less than 0.9:	If ABI ≤ 0.90 or abnormal confirmatory test results:	If ABI ≤ 0.90 or abnormal confirmatory test results:	If ABI ≤ 0.90 or abnormal confirmatory test results:
	LDL-C < 100 mg/dL or < 70 mg/dL if very high risk , lifestyle intervention (exercise, diet, weight reduction)	statins, lifestyle intervention	aspirin/ASA can be considered; lifestyle intervention (weight reduction, smoking cessation), LDL-C < 100 mg/dL, blood pressure < 140/90 mmHg and < 130/80 mmHg if diabetic or renal disease, HbA1c < 7.0% or as close to 6.0% as possible	statins, lifelong antiplatelet therapy with aspirin (75 to 325 mg/d) or clopidogrel (75 mg/d), lifestyle intervention (smoking cessation, exercise)	statins, lifelong antiplatelet therapy with aspirin (75 to 325 mg/d) or clopidogrel (75 mg/d), lifestyle intervention (smoking cessation, exercise)
Screening intervals	Traditional risk assessment in 3 months - 1 year depending on LDL-C level, not reported for recommended tests	Not reported	Not reported	Not reported	Not reported

Abbreviations: ABI, ankle-brachial index; ACE, angiotensin-converting enzyme, ASA, acetylsalicylacid; CAD, coronary artery disease; CVD, cardiovascular disease; JNC-7, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C, low density lipoprotein cholesterol; PE, physical examination; RF, risk factor; Quest, questionnaire.
[a]Comprehensive literature review, which includes a search strategy that covers multiple databases and other sources, study selection criteria, and quality assessment of the evidence.
[b]Comprehensive literature review, which includes quality assessment of the evidence.
[c]Comprehensive literature review without systematic methods.
[d]Smoking, dyslipidemia, hypertension, or hyperhomocysteinemia
[e]Smoking, diabetes, hypertension, or elevated cholesterol levels.
[f]Family history of premature CAD, smoking, obesity.
[g]Family history of peripheral artery disease, coronary artery disease or stroke, cigarette smoking, diabetes, dyslipidemia, systolic and diastolic hypertension.

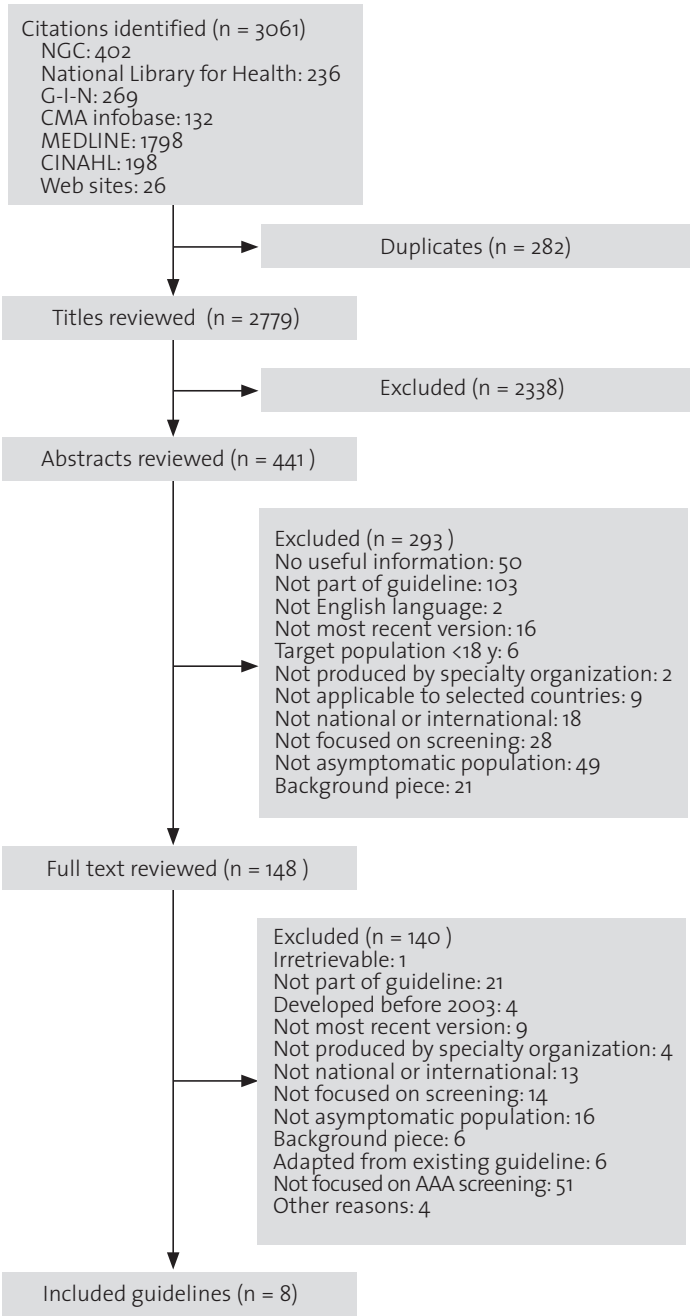

Figure 1. Summary of guideline search and review process (number of guidelines).
The number of reasons for exclusion may exceed the number of citations excluded, because several reasons for exclusion at the abstract and full-text level were allowed.

REFERENCES

1. 1. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation. 2004;110(6):738-743.
2. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med. 2001;344(21):1608-1621.
3. Heald CL, Fowkes FG, Murray GD, Price JF. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. Atherosclerosis. 2006;189(1):61-69.
4. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300(2):197-208.
5. Sawaya GF, Guirguis-Blake J, LeFevre M, et al. Update on the methods of the U.S. Preventive Services Task Force: estimating certainty and magnitude of net benefit. Ann Intern Med. 2007;147(12):871-875.
6. Mendelson TB, Meltzer M, Campbell EG, et al. Conflicts of interest in cardiovascular clinical practice guidelines. Arch Intern Med. 2011; 171(6):577-584.
7. Lo B. Serving two masters—conflicts of interest in academic medicine. N Engl J Med. 2010;362(8):669-671.
8. Ferket BS, Colkesen EB, Visser JJ, et al. Systematic review of guidelines on cardiovascular risk assessment: which recommendations should clinicians follow for a cardiovascular health check? Arch Intern Med. 2010;170(1):27-40.
9. Graham ID, Harrison MB. Evaluation and adaptation of clinical practice guidelines. Evid Based Nurs. 2005;8(3):68-72.
10. Field MJ, Lohr KN. Clinical Practice Guidelines: Directions for a New Program. Washington, DC: National Academy Press; 1990.
11. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care. 2003;12(1):18-23.
12. Appraisal of Guidelines Research and Evaluations (AGREE). AGREE Web site. Available at: http://www.agreecollaboration.org. Accessed January 20, 2011.
13. U.S. Preventive Services Task Force. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151(7):474-482.
14. U.S. Preventive Services Task Force. Screening for Peripheral Arterial Disease: Recommendation Statement. Rockville, MD: U.S. Preventive Services Task Force; 2005.
15. Greenland P, Alpert JS, Beller GA, 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. 2010;56(25):e50-e103.
16. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/ Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113(11):e463-e654.
17. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults III. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-3421.
18. 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(2):227-239.
19. Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol. 2009;25(10):567-579.
20. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33(Suppl 1):S1-S75.
21. Abramson BL, Huckell V, Anand S, et al. Canadian Cardiovascular Society Consensus Conference: peripheral arterial disease – executive summary. Can J Cardiol. 2005;21(12):997-1006.
22. Fowkes FG, Housley E, Riemersma RA, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol. 1992;135(4):331-340.
23. Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. Acta Med Scand. 1987; 221(3):253-260.
24. Faulkner KW, House AK, Castleden WM. The effect of cessation of smoking on the accumulative survival rates of patients with symptomatic peripheral vascular disease. Med J Aust. 1983;1(5):217-219.

25. Ingolfsson IO, Sigurdsson G, Sigvaldason H, et al. A marked decline in the prevalence and incidence of intermittent claudication in Icelandic men 1968-1986: a strong relationship to smoking and serum cholesterol—the Reykjavik Study. J Clin Epidemiol. 1994;47(11):1237-1243.
26. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142(4):233-239.
27. Tonstad S, Farsang C, Klaene G, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomized study. Eur Heart J. 2003;24(10):946-955.
28. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med. 1999;340(9):685-691.
29. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. JAMA. 1995;274(12):975-980.
30. Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication. Cochrane Database Syst Rev. 2000;2(2):CD000990.
31. Fowler B, Jamrozik K, Norman P, et al. Improving maximum walking distance in early peripheral arterial disease: randomised controlled trial. Aust J Physiother. 2002;48(4):269-275.
32. McDermott MM, Guralnik JM, Greenland P, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. Circulation. 2003;107(5):757-761.
33. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342(3):145-153.
34. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22.
35. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-1278.
36. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71-86.
37. Beckman JA, Jaff MR, Creager MA. The United States preventive services task force recommendation statement on screening for peripheral arterial disease: more harm than benefit? Circulation. 2006;114(8):861-866.
38. Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterollowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371(9607):117-125.
39. Berger JS, Roncaglioni MC, Avanzini F, et al. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA. 2006;295(3):306-313.
40. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007;45(4):645-54; discussion 53-4.
41. Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010;303(9):841-848.
42. Nissen SE. Can we trust cardiovascular practice guidelines?: comment on "conflicts of interest in cardiovascular clinical practice guidelines". Arch Intern Med. 2011;171(6):584-585.

Part 2

Modeling studies

Chapter 6

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

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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 factor-dependent transition probabilities, using Cox regression equations.

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 *Appendix 2*).

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.

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 ß-coefficients underlying the transition probability functions, and these ß-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 ß-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 ß-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 x 2,000 x 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 x 100 x 200 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.

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 the 13 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.

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 for 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.

TABLE 1. BASELINE CHARACTERISTICS OF THE RISK FACTORS USED IN THE RISC MODEL

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

BMI, body mass index; MI, myocardial infarction; TIA, transient ischemic attack; WHR, waist-to-hip ratio. * indicates imputed risk factors for the EPIC-Norfolk dataset.

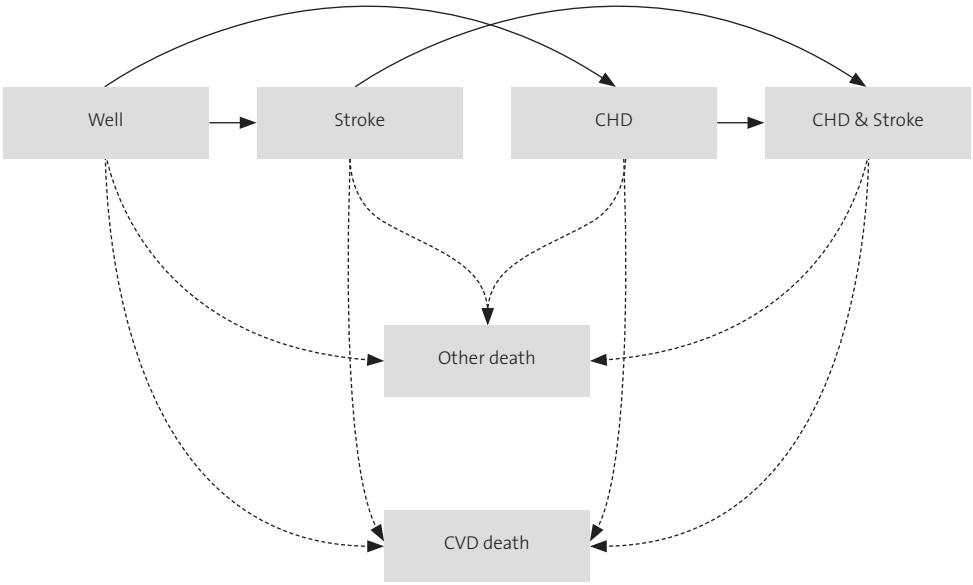

Figure 1. Schematic presentation of the RISC model. CHD: coronary heart disease ; CVD: cardiovascular disease. Arrows indicate transitions between the health states

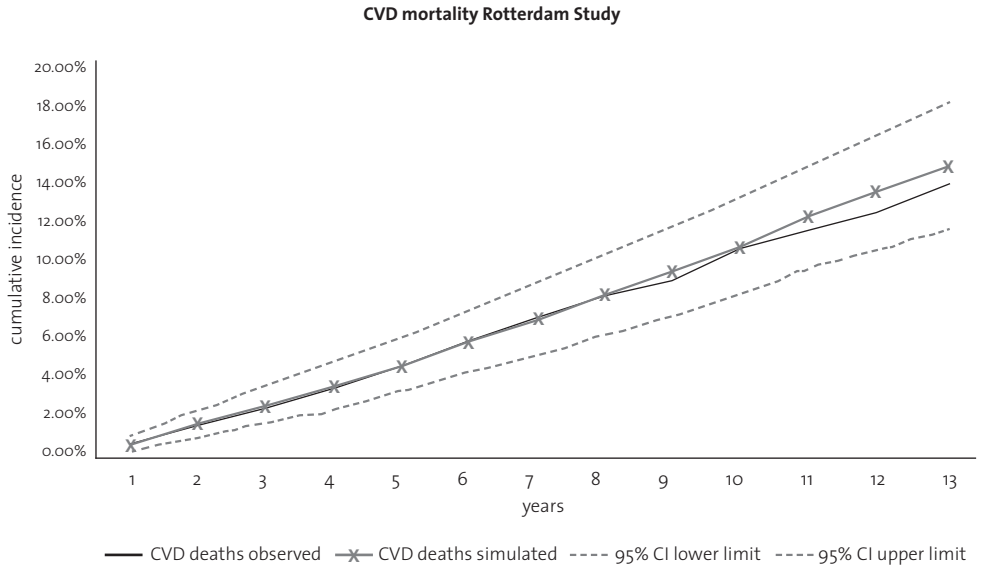

Figure 2. CVD mortality during 13 years of follow up. The first 5 years refer to the internal validation, the remaining years to the predictive validation. Simulated vs observed values for the Rotterdam Study data

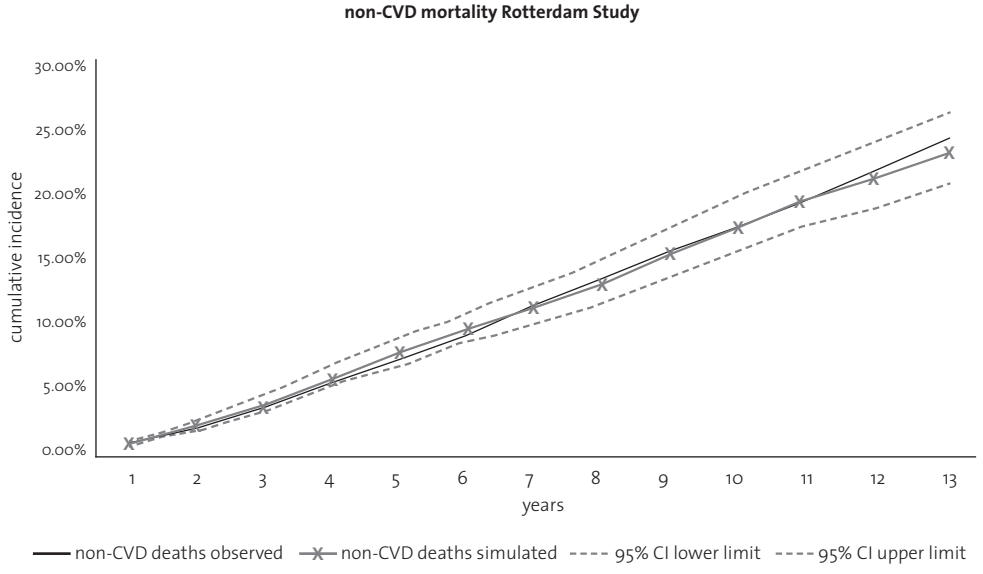

Figure 3. Non-CVD mortality during 13 years of follow up. The first 5 years refer to the internal validation, the remaining years to the predictive validation.Simulated vs observed values for the Rotterdam Study data

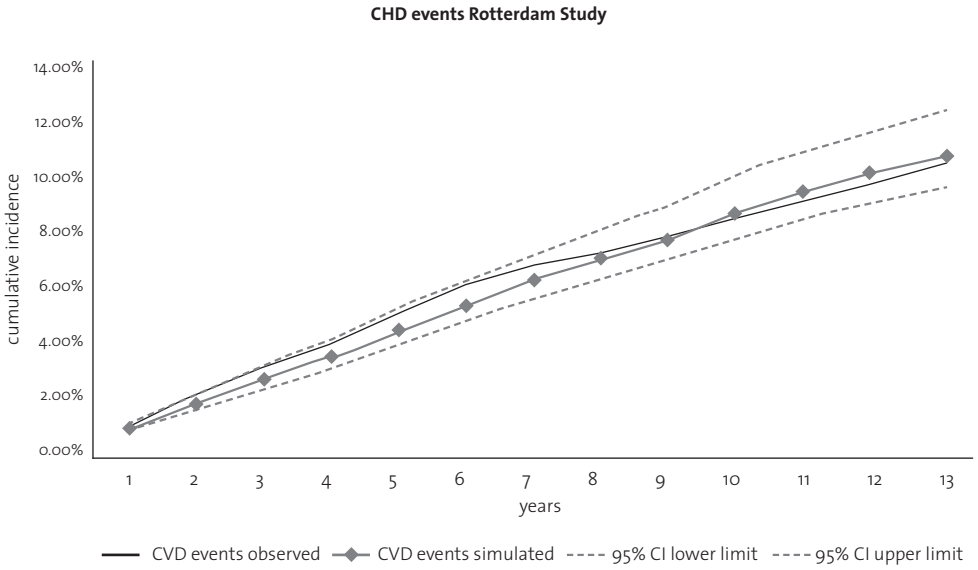

Figure 4. CHD events during 13 years of follow up. The first 5 years refer to the internal validation, the remaining years to the predictive validation. Simulated vs observed values for the Rotterdam Study data

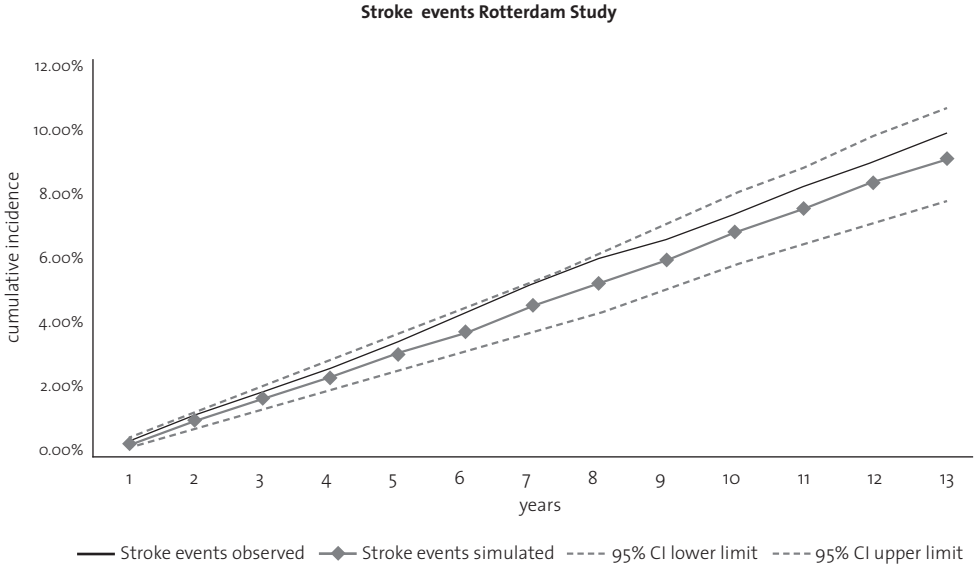

Figure 5. Stroke events during 13 years of follow up. The first 5 years refer to the internal validation, the remaining years to the predictive validation. Simulated vs observed values for the Rotterdam Study data

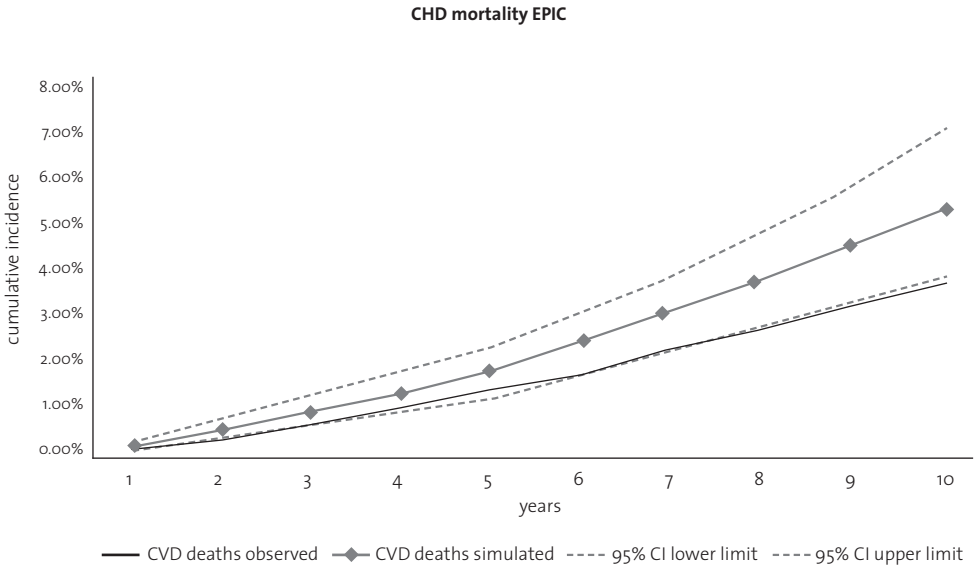

Figure 6. CVD mortality during 10 years of follow up. Simulated vs observed values for the EPIC data

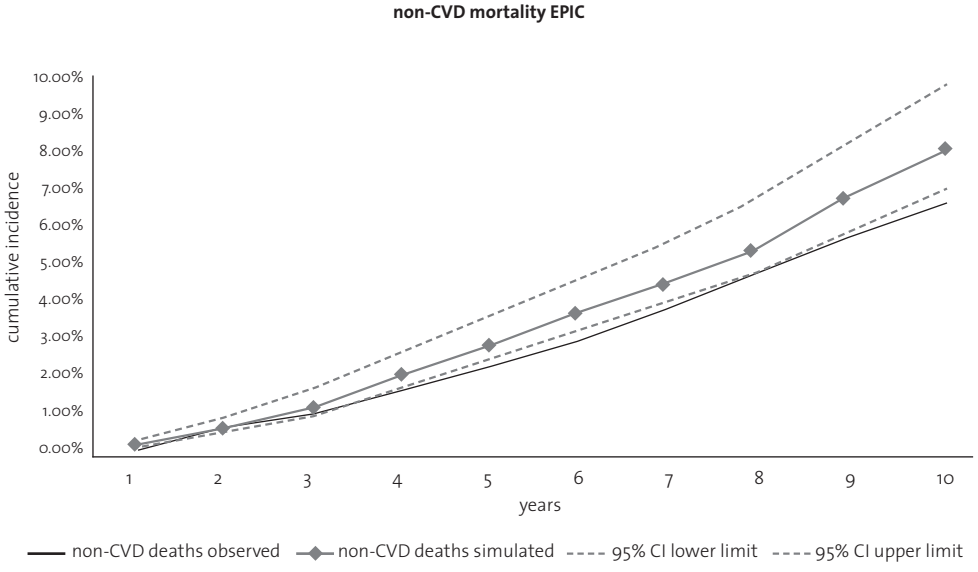

Figure 7. Non-CVD mortality during 10 years of follow up. Simulated vs observed values for the EPIC data

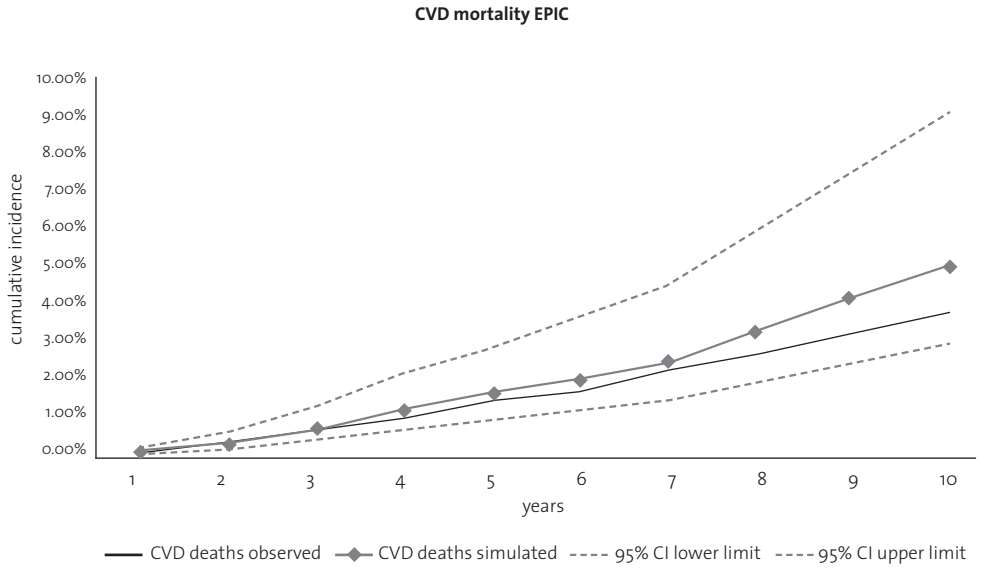

Figure 8. CVD mortality during 10 years of follow up in recalibrated model. Simulated vs observed values for the EPIC data

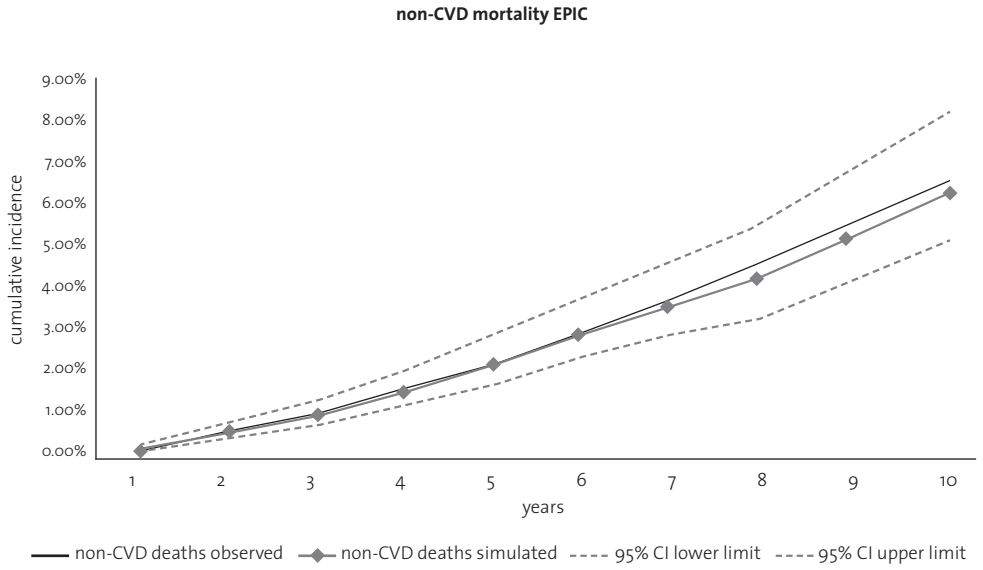

Figure 9. Non-CVD mortality during 10 years of follow up in recalibrated model. Simulated vs observed values for the EPIC data

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.

Chapter 7

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

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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. Different modeling methods of statin treatment effectiveness in simulation studies influence the results and the associated uncertainty in decision- and cost-effectiveness analyses of strategies for primary prevention of CVD.s whereas methods II and III. 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 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 *Appendix 2*.

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 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.

(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:

a) 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
b) 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
c) 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
d) An individual had experienced a previous CVD event at baseline
e) 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.

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. Qualityadjusted 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 costeffective using modeling method I, but more than 85% probability of being cost-effective using modeling method II or III.

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).

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.

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

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.
** Assumed use of generic statins

TABLE 3. BASELINE CHARACTERISTICS OF THE 3501 INDIVIDUALS OF THE ROTTERDAM STUDY. MEAN VALUES AND STANDARD DEVATIONS BETWEEN BRACKETS

Variable	Low RiskN=1400	Intermediate RiskN=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.

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

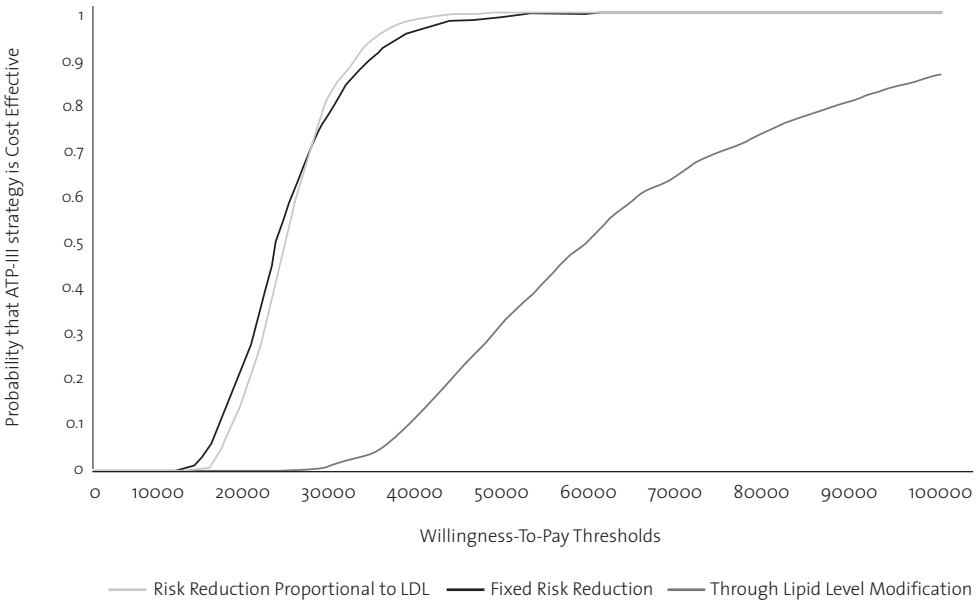

Figure 1. Acceptability curves showing the probability that the ATP-III strategy is cost effective for each of the three modeling methods, for a range of willingness-to-pay values.

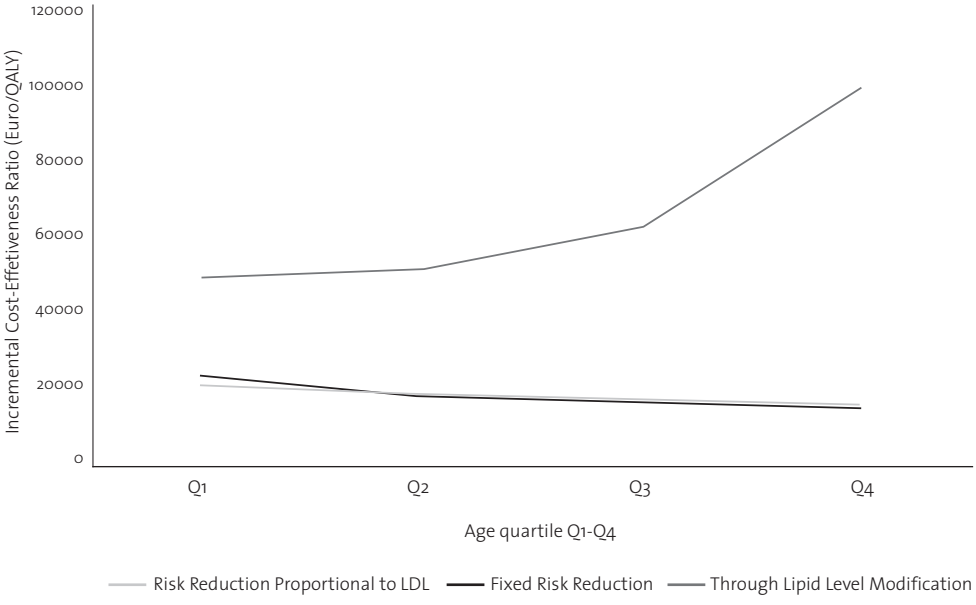

Figure 2. Incremental Cost-Effectiveness Ratio's for the four age-quartiles, for modeling method I, II and III.

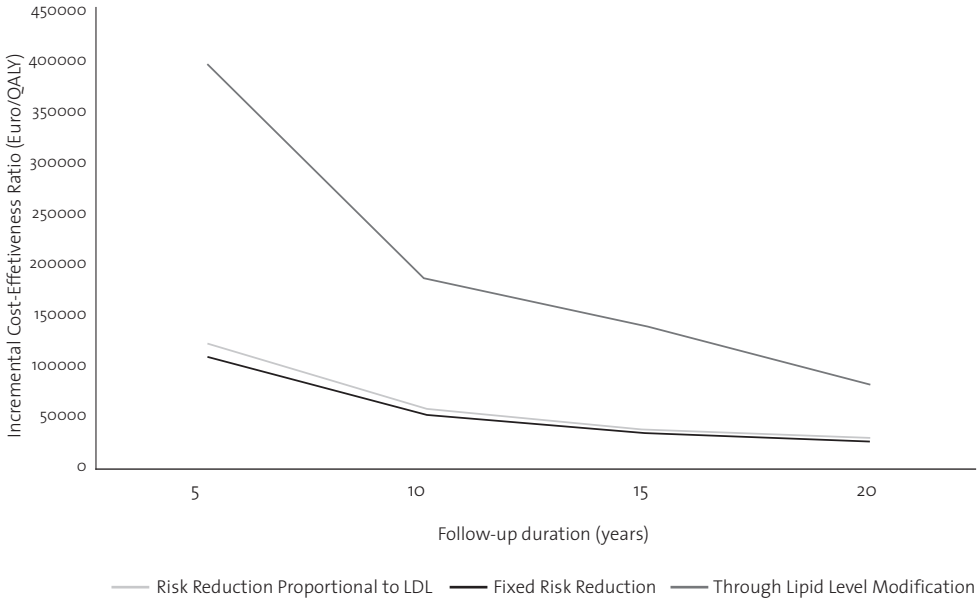

Figure 3. Incremental Cost-Effectiveness Ratio's for the four different follow-up durations, for modeling method I, II and III.

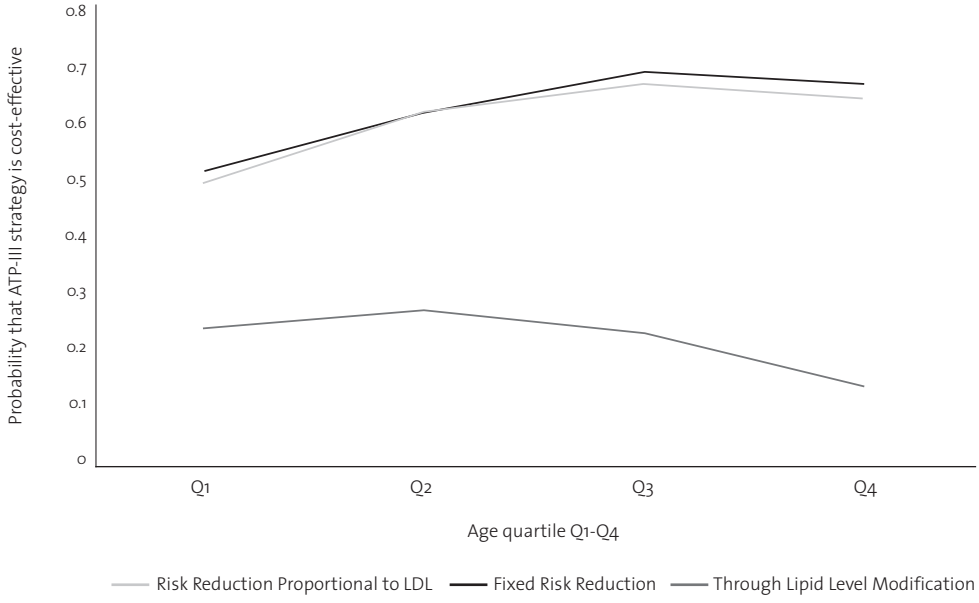

Figure 4. Probabilities that the ATP-III strategy is cost-effective given a willingness-to-pay of 50,000 Euro/QALY, for the four age-quartiles, for each of the three modeling methods.

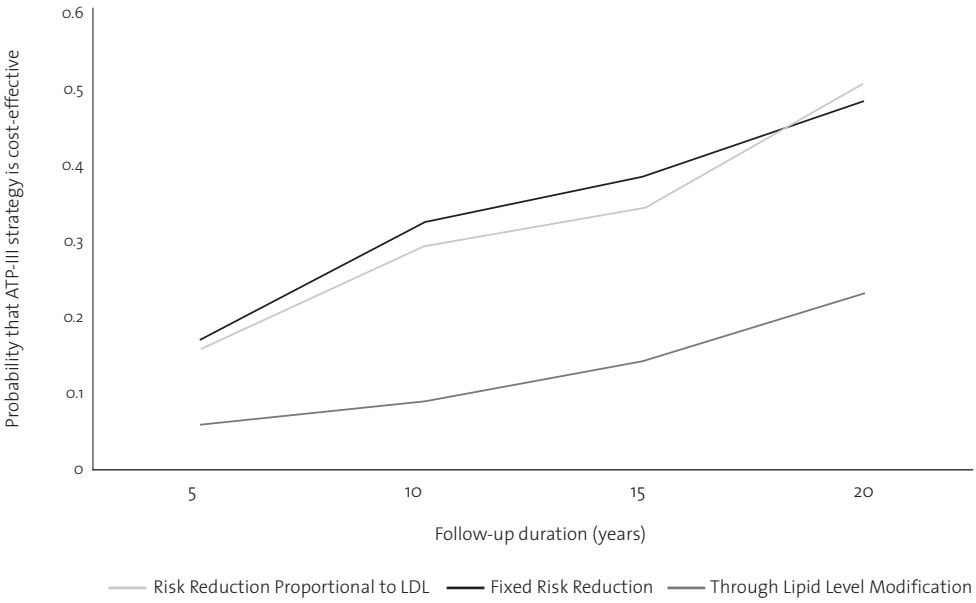

Figure 5. Probabilities that the ATP-III strategy is cost-effective given a willingness-to-pay of 50,000 Euro/QALY, for the four different follow-up durations, for each of the three modeling methods.

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;36:82–8.
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, for 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.
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 cardiovasculardisease 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., et al. The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol, 2011. 26(8): p. 657–86.
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. Physicians Desk Reference. Red Book 2009: Pharmacy's Fundamental Reference (Red Book Drug Topics). 113th ed. New York: Thomson Reuters; 2009.

Chapter 8

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

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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 population-based 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.

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, short-term 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). Non-cardiovascular 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 *Appendix 2*).

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.

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 1, *Appendix 2*) (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 *Appendix 2*.

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. 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.

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).

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.

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)
2.5th - 97.5th 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)
2.5th - 97.5th range	100 - 186
Diastolic	74.7 (11.6)
2.5th - 97.5th range	53 - 98
Hypertension – no. (%)	768 (31.6)
Serum cholesterol (mmol/L)	6.7 (1.3)
2.5th - 97.5th range	4.5 - 9.2
Serum HDL-cholesterol (mmol/L)	1.4 (0.4)
2.5th - 97.5th range	0.8 - 2.2
Diabetes mellitus – no. (%)	215 (8.9)
Serum glucose (mmol/L)	6.8 (2.5)
2.5th - 97.5th range	4.3 - 13.6
Body mass index (kg/m^2)	26.2 (4.3)
2.5th - 97.5th range	20.1 - 34.3
Waist-to-hip ratio	0.90 (0.09)
2.5th - 97.5th range	0.73 - 1.08
Serum creatinine (µmol/L)	80.6 (15.8)
2.5th - 97.5th 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 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 female, 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 male, 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 male, 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 male, 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/m^2 – 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.

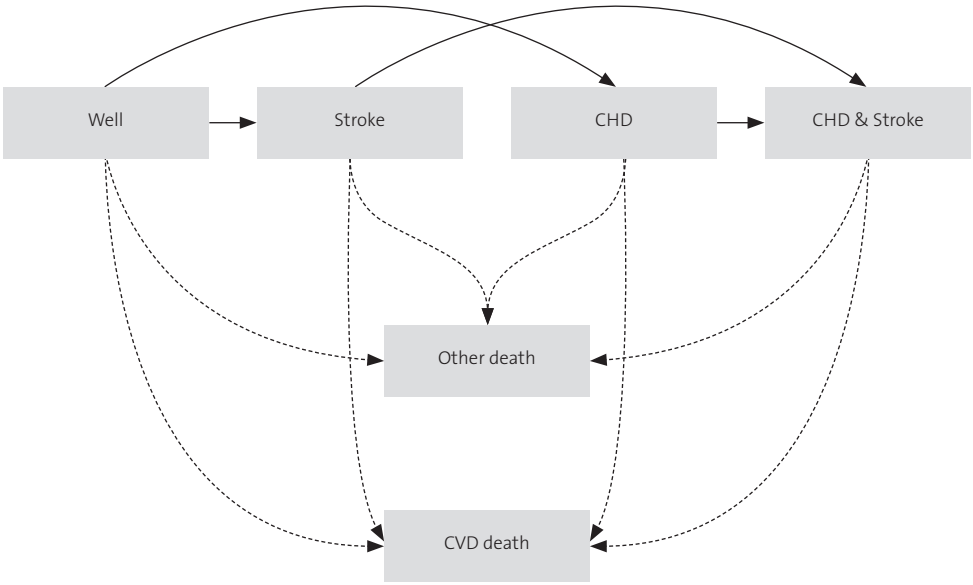


Figure 1. Schematic representation of the RISC model.
CHD = coronary heart disease. CVD = cardiovascular disease.

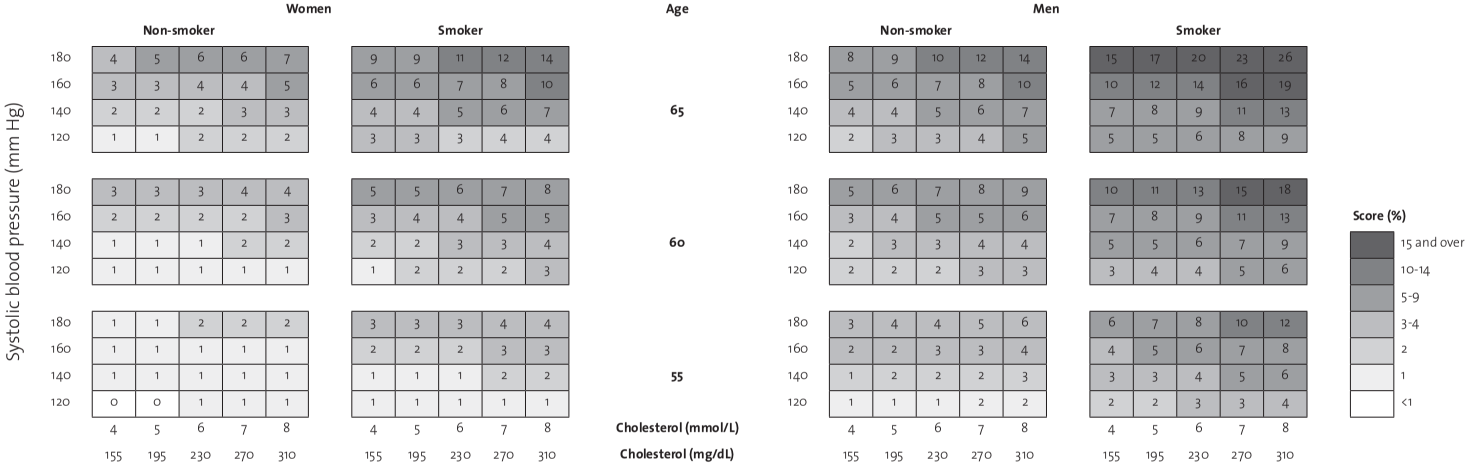


Figure 2. Ten year total cardiovascular disease (CVD) mortality risk (%) predicted by SCORE- European Low-Risk Charts.
Adapted with permission by the European Society of Cardiology. Copyright © 2007, the Oxford University Press. Note that these charts demonstrate that the 10-year total CVD mortality 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.

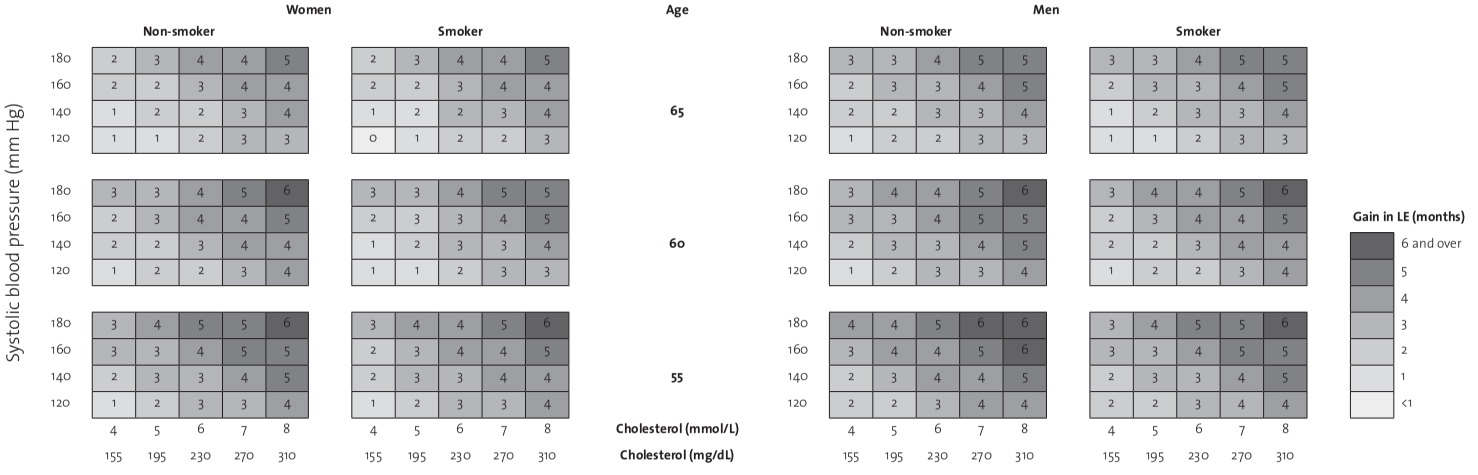


Figure 3. The gain in life expectancy (LE) in months with statin therapy calculated with the RISC model.
Note that these charts demonstrate that life expectancy gained with statin therapy is highest for young non-smoking individuals with otherwise high risk factor levels.

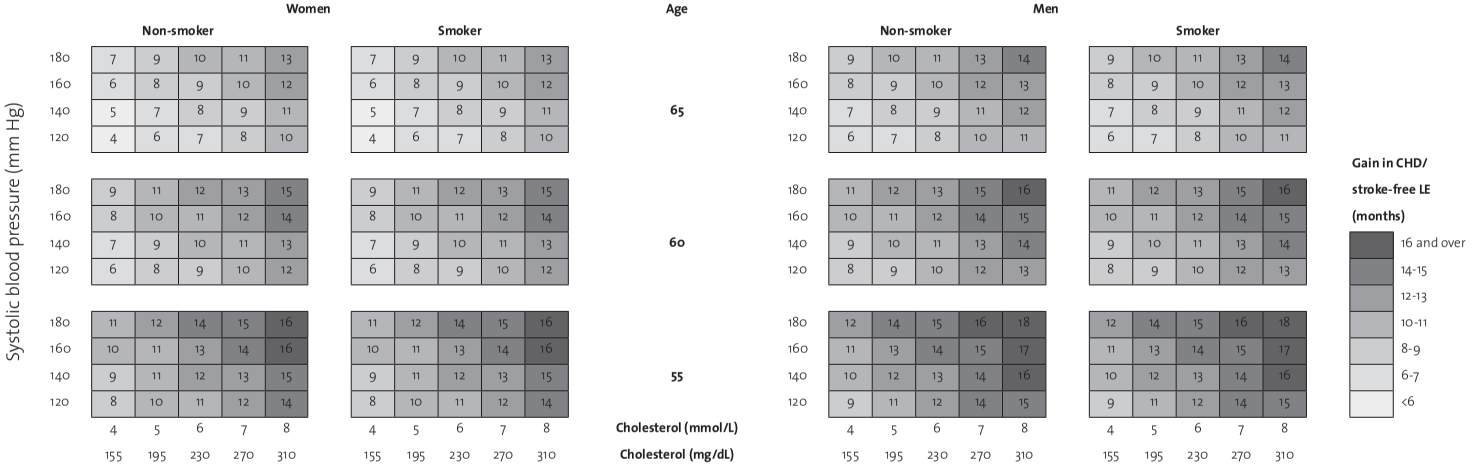
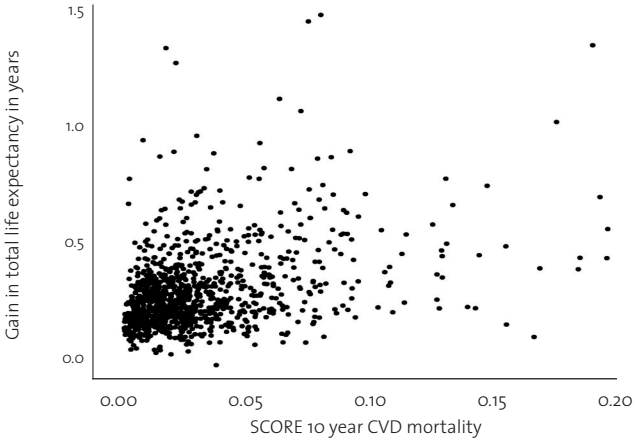


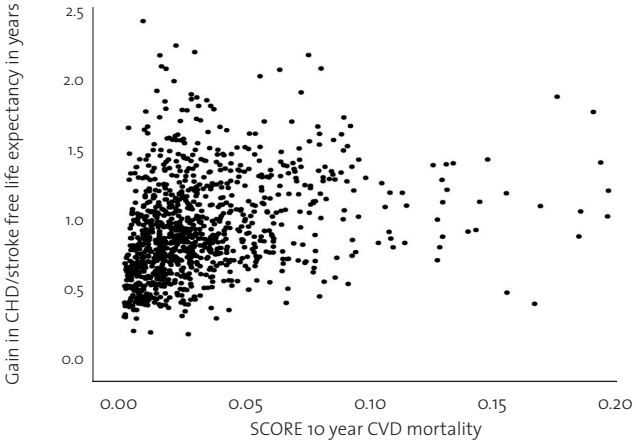
Figure 4. The gain in CHD/stroke-free life expectancy (LE) in months with statin therapy calculated with the RISC model.
Note that these charts demonstrate that CHD/stroke-free life expectancy gained with statin therapy is highest for young individuals with otherwise high risk factor levels.

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.

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 9

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

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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.

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).

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 ($p < 0.001$).

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 *Appendix 3*), 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.

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.

ACKNOWLEDGEMENTS

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TABLE 1. BASELINE CHARACTERISTICS

	ARIC	**Rotterdam**	**CHS**
	(n=15,170)	(n=6,910)	(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)
missing data, n (%)	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	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 values, 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 values, n (%)	28 (0)	1081 (16)	34 (1)
eGFR, ml/min/ 1.73 m^2 – median (IQR)	89.0 (79.7, 102.3)	77.3 (67.3, 87.7)	76.7 (64.2, 89.9)
missing values, n (%)	146 (1)	2254 (33)	59 (1)
Statin therapy use, n (%)	85 (1)	141 (2)	121 (2)
missing values, 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

TABLE 2. INCIDENT EVENT DATA

	ARIC	**Rotterdam**	**CHS**
	(n=15,217)	(n=6,910)	(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

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

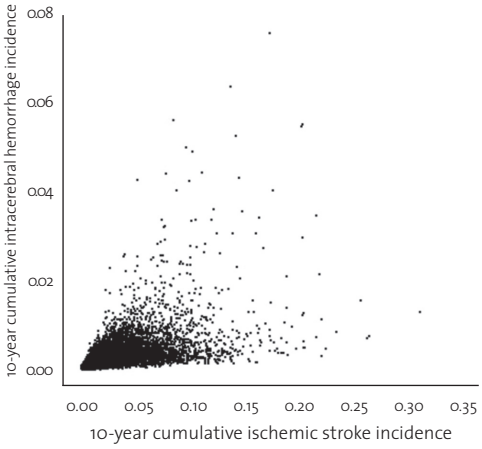
TABLE 4. PROGNOSTIC PERFORMANCE

	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.

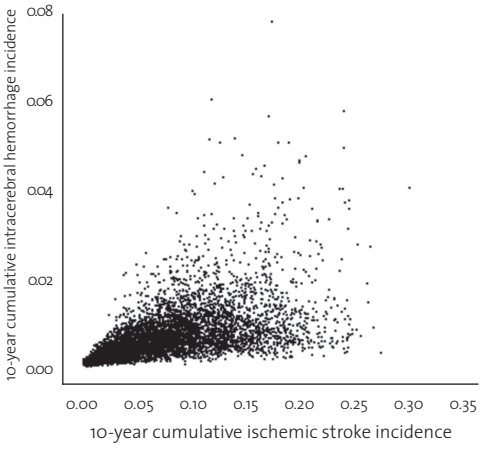
Figure 1. Contribution of intracerebral hemorrhage and ischemic stroke to 10-year any stroke incidence.

ARIC Study



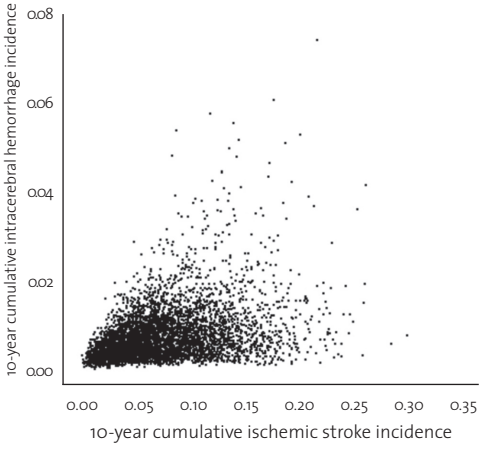
R Linear = 0.57

Rotterdam Study



R Linear = 0.59

CHS



R Linear = 0.37

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.

Chapter 10

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

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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.

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).

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).

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.

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.

TABLE 1. BASELINE CHARACTERISTICS FOR THE 6,004 ROTTERDAM STUDY PARTICIPANTS INCLUDED IN THE ANALYSIS.

Risk Factor	
Age, years – median (IRQ)	68 (62 – 75)
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%)

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

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

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)

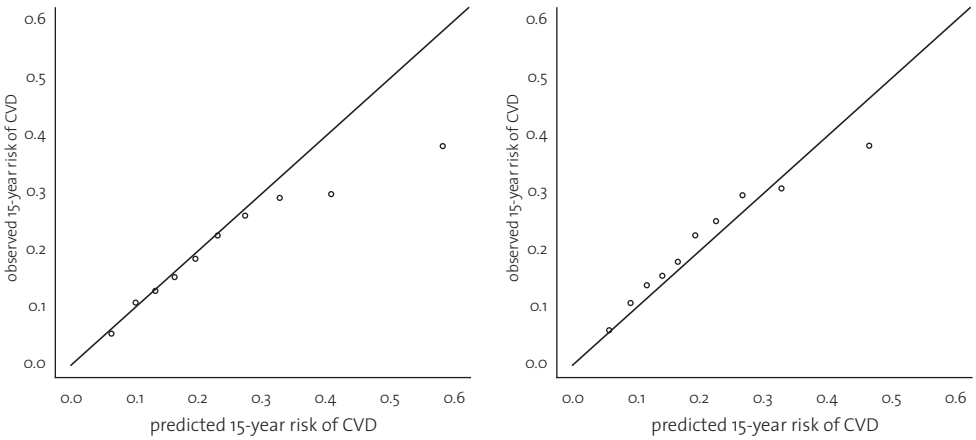


Figure 2. Calibration plot, showing predicted and observed 15-year risk of CVD for each decile of predicted 15-year CVD risk -based on the refitted function (model 4, left) and refitting the CVD and non-CVD death function, by separately analyzing CHD and stroke (model 5, right)

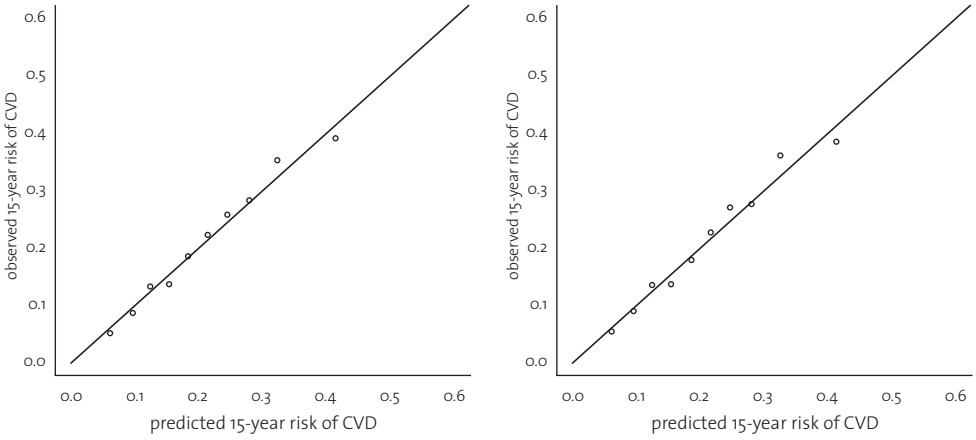


Figure 3. Calibration plot, showing predicted and observed 15-year risk of competing non-CVD death for each decile of predicted 15-year CVD risk -based on the original Framingham CVD function (3) (model 1, left) and after refitting the CVD and non-CVD death function in the Rotterdam Study data (model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

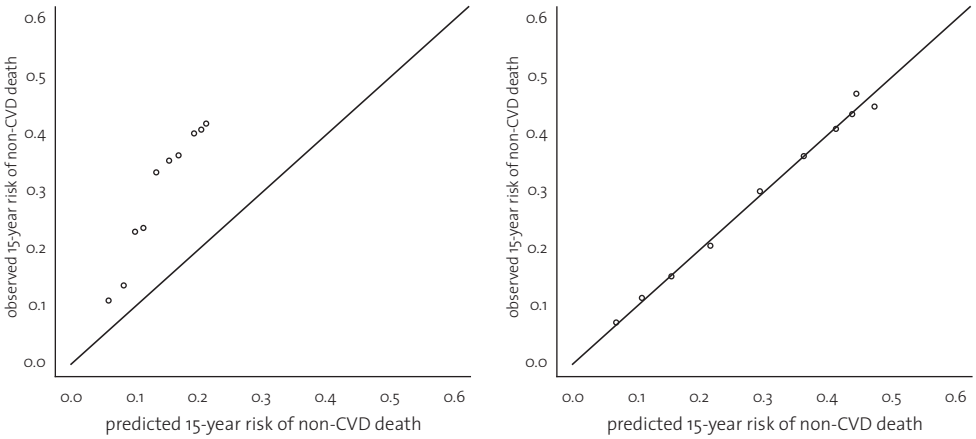
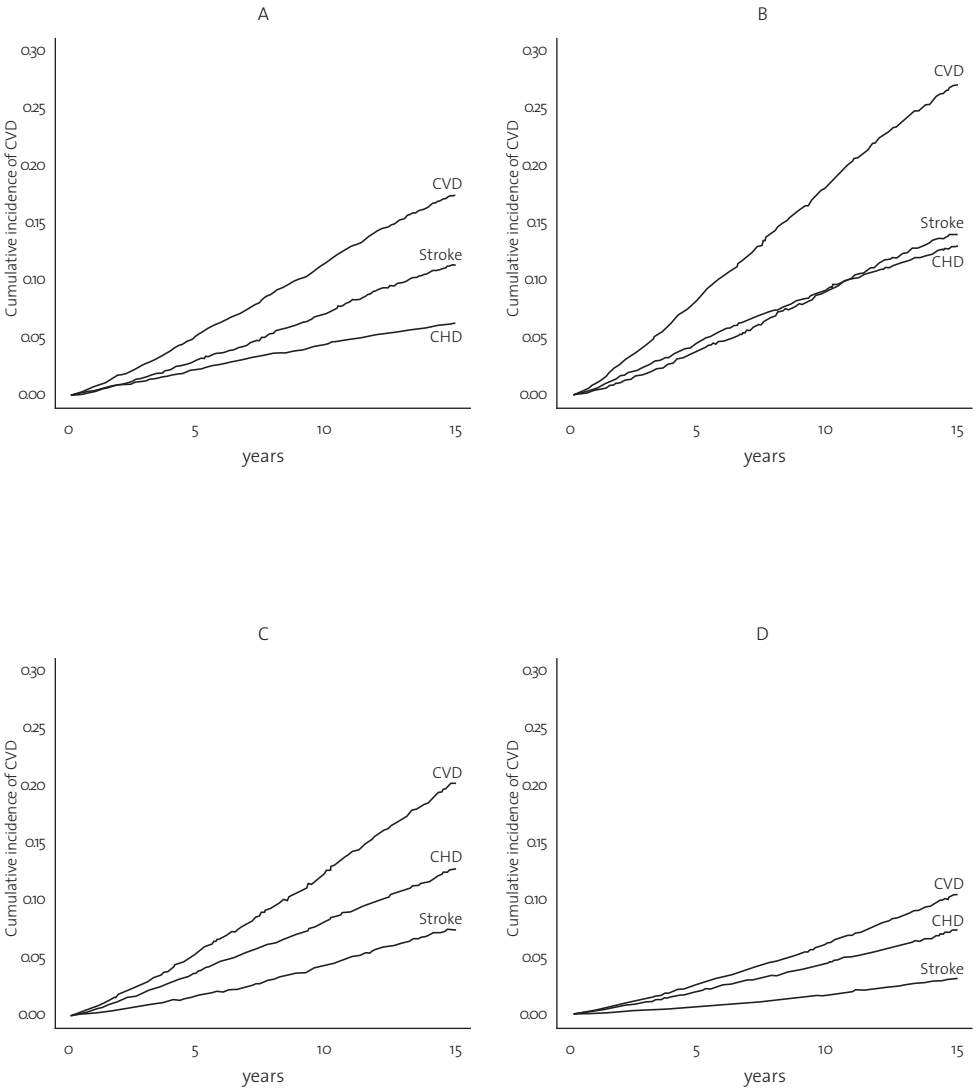


Figure 4. Individual predictions for 4 individuals. (A) 70-year old woman, smoker, systolic blood pressure of 103, total (HDL) cholesterol 4.1 mmol/L 1.5, treated for Hypertension (B) 70 year old man, systolic blood pressure of 132, Total (HDL) cholesterol 5.0 mmol/L 1.80, Diabetic (C) 56-year old man, 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.



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: Springer; 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 11

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

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ABSTRACT

Objectives

To estimate the predictive value of four novel cardiovascular risk markers, for the U.S. general population.

Background

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 unknown.

Methods

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 imputed 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.

Results

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.

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 selecting those at high risk 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. 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 (10).

In this study, we aimed to combine meta-analyses of published predictive effects of CTCS, cIMT, CRP, and ABI, with traditional 10-year FRS. Our 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 (11,12). For CTCS and ABI, we updated the 2009 systematic review by the USPSTF (13) through September 5, 2012 (for detailed search syntaxes and study inclusion criteria see the eMethods). 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 *Appendix 4* 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 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 (14) in which all novel markers were measured and imputed these values. 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). For details on the dataset preparation see *Appendix 4*.

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 (15). 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 predictor effects 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 (16).

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'. 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 *Appendix 4* 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 (17). For the intermediate risk category, we calculated a bias-corrected NRI (18). 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 (19) 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.

RESULTS

Systematic review of the novel risk markers' predictive effects

From the USPSTF report (13), 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 (20). Combined with the citations found through our additional search, in total 947 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 in *Appendix 4*). 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 predictive effect of CTCS on 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 (21). 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.

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 for CVD). 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 for CVD).

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). 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.

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 (hsCRP), 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 (11,12,20,22). 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 (12). 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 (22). 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 (20). 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 (23). 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 (24,25). 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 (18).

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. 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 predictive effects of novel risk markers 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 (15) 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 (26). Third, for the simulation of CVD event rates, we assumed that the predictive effects of the four novel risk markers 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 (27). 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 does not allow predictive effects 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.(28) However, CHD comprises the major part of total CVD. This implies that the predictive effects of the traditional risk factors on CVD are closer to that of CHD than of stroke, and the results for reclassification of CHD will be relatively unaffected by this assumption.

Instead of a priori focusing on individuals at intermediate risk (13,24), 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 (29).

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.

TABLE 1. BASELINE CHARACTERISTICS OF 3,736 NHANES INDIVIDUALS

Variable	**Median [IQR]**
Age	53 [46 – 63]
Sex (% male)	48%
Current Smoking	23%
Systolic blood pressure (mm Hg)	125 [115 – 139]
HRX	27%
Total cholesterol (mg/dl)	209 [183 – 235]
HDL cholesterol (mg/dl)	51 [42 – 63]
Glucose (mg/dl)	97 [90 – 106]
Anti diabetic medication	8%
CTCS*	
0	37%
1-100	36%
101-400	14%
400-1000	8%
≥1000	5%
Natural logarithm of (CTCS+1)	2.6 [0 – 4.8]
cIMT (mm)*	0.78 [0.69 – 0.93]
CRP (mg/L)	2.1 [0.9 – 4.6]
ABI ≤ 0.9	5.0%

Abbreviations: CTCS, CT coronary artery calcium score; HDL, high-density lipoprotein; HRX, anti/hypertensive drug treatment.
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

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. (12)
Log(CRP) / SD* (mg/L)	1.22 [1.17 - 1.27]	1.16 [1.10 - 1.27]	Emerging Risk Factors Collaboration (11)
ABI ≤ 0.9	1.47 [1.18 - 1.84]	1.26 [1.05 - 1.50]	This manuscript

* Pooled SD = 1.11 mg/L

TABLE 3. TEN-YEAR CARDIOVASCULAR DISEASE (CVD) RISK RECLASSIFICATION BY CTCS

	FRS + CTCS			Overall
FRS	**<10%**	**≥10-<20%**	**≥20%**	
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.

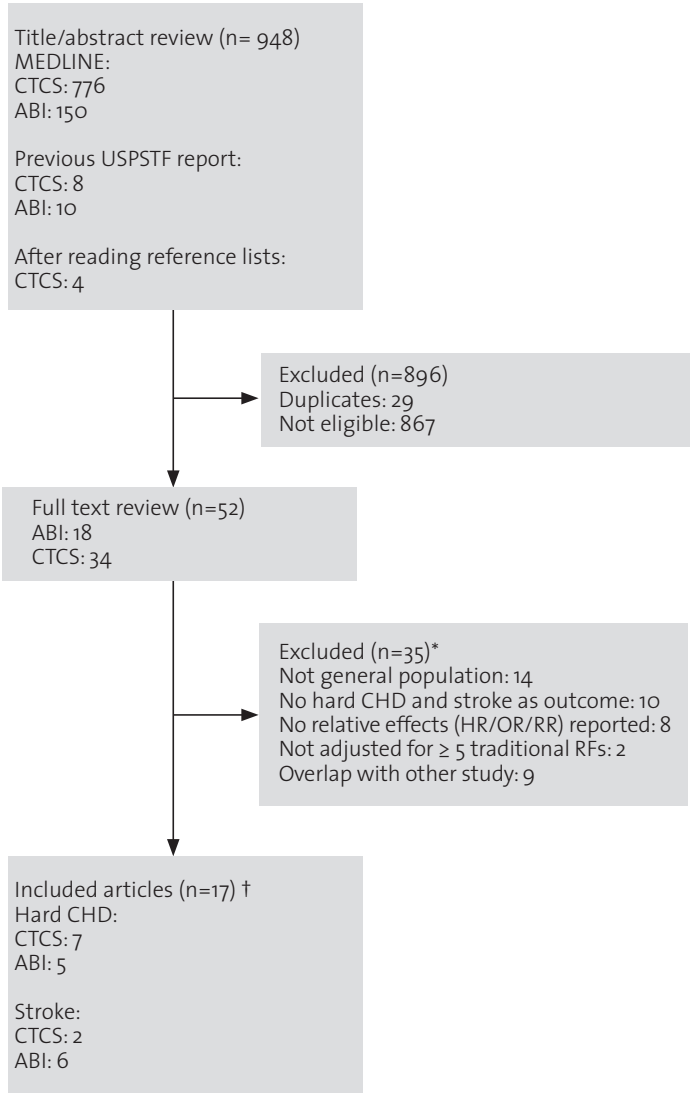

Figure 1. Literature search and selection.
Numbers of articles of each step of the review process are indicated.
*Group total exceed the reported number for the excluded articles because several reasons for exclusion were allowed.
†Group total exceed the number for the included articles, because one 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

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125:e2-e220.
2. 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.
3. D'Agostino RB, Sr., Vasan RS, Pencina MJ et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-53.
4. 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.
5. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;151:474-82.
6. Greenland P, Alpert JS, Beller GA et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary. Circulation 2010;122:2748-64.
7. Shah T, Casas JP, Cooper JA et al. 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 2009;38:217-231.
8. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation 2008;118:2243-51, 4p following 2251.
9. Peters SA, den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart 2012;98:177-84.
10. Hunink MGM, Glasziou PP, Siegel JE et al. Decision making in health and medicine: Integrating evidence and values. Cambridge: Cambridge University Press, 2001.
11. Emerging Risk Factors Collaboration, 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.
12. Den Ruijter HM, Peters SA, Anderson TJ et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. Jama 2012;308:796-803.
13. Helfand M, Buckley DI, Freeman M et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:496-507.
14. Hofman A, van Duijn CM, Franco OH et al. The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 2011;26:657-86.
15. 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.
16. Greenland P, Smith SC, Jr., Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. Circulation 2001;104:1863-7.
17. 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.
18. Paynter NP, Cook NR. A Bias-Corrected Net Reclassification Improvement for Clinical Subgroups. Med Decis Making 2012.
19. Pencina MJ, D'Agostino RB, Sr., Song L. Quantifying discrimination of Framingham risk functions with different survival C statistics. Stat Med 2012;31:1543-53.
20. Fowkes FG, Murray GD, Butcher I et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300:197-208.
21. Criqui MH, McClelland RL, McDermott MM et al. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2010;56:1506-12.
22. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med 2012;367:1310-20.
23. Murphy TP, Dhangana R, Pencina MJ, D'Agostino RB, Sr. Ankle-brachial index and cardiovascular risk prediction: an analysis of 11,594 individuals with 10-year follow-up. Atherosclerosis 2012;220:160-7.
24. Yeboah J, McClelland RL, Polonsky TS et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. Jama 2012;308:788-95.
25. Kavousi M, Elias-Smale S, Rutten JH et al. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med 2012;156:438-44.
26. 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;286:180-7.
27. Folsom AR, Kronmal RA, Detrano RC et al. 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 2008;168:1333-9.
28. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22:312-8.
29. 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 2011;58:1690-701.

Chapter 12

Coronary computed tomography versus exercise testing in patients with stable chest pain: comparative effectiveness and costs

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ABSTRACT

Background

To determine the comparative effectiveness and costs of a CT-strategy and a stress electrocardiography-based strategy (standard-of-care; SOC-strategy) for diagnosing coronary artery disease (CAD).

Methods

A decision analysis was performed based on a well-documented prospective cohort of 471 outpatients with stable chest pain with follow-up combined with best-available evidence from the literature. Outcomes were correct classification of patients as CAD–(no obstructive CAD), CAD+(obstructive CAD without revascularization) and indication for Revascularization(using a combination reference standard), diagnostic costs, lifetime health care costs, and quality-adjusted life years (QALY). Parameter uncertainty was analyzed using probabilistic sensitivity analysis.

Results

For men (and women), diagnostic cost savings were €245 (€252) for the CT-strategy as compared to the SOC-strategy. The CT-strategy classified 82% (88%) of simulated men (women) in the appropriate disease category, whereas 83% (85%) were correctly classified by the SOC-strategy. The long-term cost-effectiveness analysis showed that the SOC-strategy was dominated by the CT-strategy, which was less expensive (-€229 in men,-€444 in women) and more effective (+0.002 QALY in men,+0.005 in women). The CT-strategy was cost-saving (-€231) but also less effective compared to SOC (-0.003 QALY) in men with a pre-test probability of ≥70%. The CT-strategy was cost-effective in 100% of simulations, except for men with a pre-test probability ≥70% in which case it was 59%.

Conclusions

The results suggest that a CT-based strategy is less expensive and equally effective compared to SOC in all women and in men with a pre-test probability <70%.

INTRODUCTION

The current guideline still recommends stress electrocardiography(X-ECG) as first line diagnostic test for patients with stable chest pain (1). However, the diagnostic accuracy of X-ECG is limited (2).
Coronary CT angiography (CCTA) is an alternative modality for diagnosing coronary artery disease (CAD). Its diagnostic accuracy compared to catheter-based coronary angiography (CAG) in highly selected patients has been studied extensively (3-7), demonstrating that CCTA is reliable in ruling out CAD (sensitivity 95-100%). Furthermore, previously published decision analyses indicate that CCTA as triage test in patients referred for CAG is cost-effective in patients with a low-intermediate probability of disease (8-10).
Recently, results from a Dutch outpatient chest pain clinic were published (11-12). Patients with stable chest pain were evaluated by X-ECG, CT calcium scoring, and CCTA. Results suggested that CT calcium scoring, selectively followed by CCTA could replace X-ECG as first line diagnostic test. However, long-term effectiveness and costs of CCTA compared to standard-of-care (SOC) in outpatients presenting with chest pain remain unclear.
Ideally, a large randomized controlled trial (RCT) comparing a CT-based strategy to SOC should be performed to evaluate comparative effectiveness and costs. Exploration of diagnostic strategies and preliminary estimates of outcomes can help design such a trial and can justify the investment of research resources. Furthermore, trial results will only be available after several years and in the meantime diagnostic testing decisions have to be made. A decision-analytic approach summarizing the evidence can be helpful in such situations.
Aim of this study was to determine the comparative effectiveness and costs of a hypothetical CT-strategy compared with SOC using a decision-analytic approach combining data from a well-documented prospective patient cohort with the best-available evidence from the literature.

MATERIALS AND METHODS

Patient population

The model was based on a prospective clinical cohort (11) of 471 patients who presented with stable chest pain and no history of CAD. All patients were scheduled for X-ECG and CCTA (Table 1). During a mean follow-up (complete in 90%) of 2.6 years, 44 major adverse cardiovascular events (MACE: cardiac death, myocardial infarction, unstable angina requiring hospitalization, and revascularization) occurred in 30 patients (13). The study complied with the Declaration of Helsinki and the ethical committee at our institution approved the study. Informed consent was obtained from all patients.

Decision model

We developed a decision model (in DATA Pro 2009 Suite, TreeAge Software Inc, Williamstown, MA, USA) to evaluate the comparative effectiveness and costs of a hypothetical CT-based strategy compared to an X-ECG-based strategy (reflecting standard-of-care; SOC-strategy). Short-term diagnostic outcomes were modeled with a decision tree (Figure 1, 2). Long-term

prognosis (lifetime) was modeled using a Markov-Model. Model parameters were based on the clinical cohort with follow-up combined with best-available evidence from the literature.
Model probabilities for diagnostic test results were based on the clinical cohort and conditional on the "underlying truth", sex, and the pre-test probability. To model the "underlying truth", a disease category was assigned to all patients in the cohort: No obstructive CAD(CAD–), Obstructive CAD(CAD+) or Revascularization(Revasc) (Figure 3), which represents the true disease status at baseline. This was based on CAG(if performed), the treatment initiated and CCTA otherwise and included 6-month follow-up information. For example, if a patient was initially treated with medication only, but electively revascularized within 6 months, the patient was labeled as Revascularization. The modified reference standard was used in all analyses.
The diagnostic model classifies patients in one of the disease categories. Classification is correct if the classified category matches the underlying truth, and incorrect when the classified category does not match the underlying truth. Underlined categories refer to the underlying 'true' disease category, whereas italic categories refer to the disease category as classified by the diagnostic work-up. Individuals classified as CAD– by the diagnostic strategy, who are CAD+ or Revascularization according to their underlying truth are "under-classified". Patients classified as CAD+ who are Revascularization according to the underlying truth are "under-classified". Individuals classified as CAD+, who are CAD– according to the underlying truth, are "over-classified". The next paragraph explains how patients are classified by the diagnostic work-up.

Short-term decision tree

The SOC-strategy consists of initial evaluation with X-ECG according to the guideline (1) (Figure 1). Non-diagnostic X-ECGs are common (~25% (33))– which warrants further testing with pharmacological stress myocardial perfusion imaging (MPI) using single photon emission CT (SPECT). Patients unable to exercise are evaluated by MPI. We assume that a CAG classifies patients in the correct category.
The CT-strategy starts with a coronary artery calcification (CAC) scan in every patient and a CCTA in patients with a CAC>0 and <400 (Figure 2). Patients with CAC=0 and a pre-test probability <70% do not undergo CCTA, because obstructive CAD is unlikely to be present (34). This cutoff was chosen to capture the high-risk patients with typical presentation (14), which is consistent with clinical practice at our institution. Thus, a patient with zero calcium and a pre-test probability ≥70% will undergo CCTA (Figure 2). Based on evidence that revascularization does not always improve survival beyond optimal medical treatment in patients with moderate disease (35), the CT-strategy consists of medical treatment for patients with moderate disease on CCTA and referral to CAG only if the CCTA shows severe CAD (left main-, three vessel-, or proximal left anterior descending artery disease).

Long-term Markov model

We used a Cox proportional hazards model to estimate the sex-specific rates of MACE for CAD–, CAD+, and Revascularization patients in the clinical cohort. Prognosis after the diagnostic work-up in the model depended on the correct vs. incorrect classification. Correctly classified individuals in the model were assigned the adjusted event rate as observed in the cohort.

Under-classified (and under-treated) individuals experienced a higher event rate because of the forgone benefit of treatment (hazard rate ratio (HRR) based on the combined effectiveness of statins (29) and aspirin (27)). Over-classification only occurs when a CAD- patient is classified as CAD+ and we assumed that medical treatment does not alter the event rate in these patients.
To mimic clinical follow-up of patients with chest pain, we assumed that every under-classified patient will be diagnosed with the correct disease category within the first year. We assumed that those patients remain symptomatic prior to the correct diagnosis because they are under-treated for a short period. As in clinical practice, patients with persistent angina are re-evaluated by the cardiologist. This implies that our model assumes that the benefit in terms of better outcomes of a diagnostic strategy can only be obtained in the first year after the initial assessment. In contrast, individuals who are over-classified are assumed not to reclassify to the CAD– category, but to remain in CAD+. The negative implications of overestimating the severity of disease in a CAD– patient consists of extra costs for medication and a (slightly) lower quality-of-life. We modeled the risk of dying from non-cardiac causes based on age- and sex-specific mortality rates from the Dutch Central Bureau for Statistics (25).

Costs

Costs were based on a previous cost analysis (8) and expert opinion (Table 1), expressed in 2009 euros. We used the health care perspective according to recommendations for cost-effectiveness analyses (36), and a willingness-to-pay threshold (WTP) of €80,000/QALY (37). Medication costs were obtained via a registry provided by the Dutch Health Care Insurance board (16). Medication use was based on self-reported cardiovascular disease-related medication at the time of the last patient contact during follow-up and assumed to be constant over time.

Quality-of-life

Age and sex-specific utilities of the general population (30) were used to model the quality of life for CAD– patients. For CAD+ and Revascularization patients, the mean reduction in quality-of-life as compared to the general population was assumed to be 5% and 10%, respectively. Furthermore, under-classification (and under-treatment) was assumed to result in symptoms of angina due to the forgone benefit of anti-ischemic therapy. Based on reported relative reductions in utility due to anginal symptoms, the reduction in quality-of-life was estimated to be 10% (30) and 15% (32) if under classification occurred by 1 or 2 categories, respectively. The quality-of-life of CAD– patients who are classified as having CAD+ was adjusted to reflect the disutility of taking medication.

Data analysis

All variables were entered in the model as distributions. Outcomes were calculated as the mean results from probabilistic sensitivity analysis, drawing random values from the parameter distributions(10000 samples).
Short-term outcomes included diagnostic costs, radiation exposure, and correct classification. Long-term outcomes included health care costs and quality-adjusted life years (QALYs). Both future costs and effectiveness were discounted at 3.5% (36).

Sensitivity analysis

The probability that a strategy was cost-effective was determined by the proportion of simulations in the probabilistic sensitivity analysis that demonstrated cost-effectiveness for that strategy (38). Value of information analysis was performed to determine the value of future research (39).

For the patients in the clinical cohort who did not undergo CAG, disease severity may have been overestimated by CCTA, which in turn could have caused a bias in favor of CCTA (since these data were used to determine the probability of correct classification, which would turn out high for the CT-strategy). To explore this limitation, we re-analyzed the model assuming that 40% of CAD+ men and women (randomly selected) who did not undergo CAG would actually be CAD– patients. Furthermore, we re-analyzed the model assuming that a proportion of patients with abnormal X-ECG would not be referred for CAG.

RESULTS

Short-term analysis

Analysis of the short-term model revealed that the average diagnostic costs for the SOC-strategy were €739 (95CI:547-978) and €526 (95CI:€395-684) for men and women, respectively. The CT-strategy cost €494 (95CI:€375-641) and €274 (95CI:€205-356) for men and women, respectively (Table 2,3). The SOC-strategy classified 83% (95%CI:80-87%) of men correctly, whereas the CT-strategy classified 82% (95%CI:77-85%) correctly. The SOC-strategy classified 85% (95%CI:82 -88%) of women correctly, whereas the CT-strategy classified 88% (95%CI:85-92%) correctly. The SOC-strategy classified 85% (95%CI:82 -88%) of women correctly, whereas the CT-strategy classified 88% (95%CI:85-92%) correctly.

Subgroup analysis

For men with a pre-test probability of <70% and ≥70%, diagnostic cost-savings for the CT-strategy as compared to SOC were -€211 and -€312, respectively. In men with a pre-test probability ≥70%, the percentage correctly classified by CT was 11% lower compared to SOC (Table 2).

When re-analyzing women with a pre-test probability of <70% and ≥70%, diagnostic cost-savings for the CT-strategy as compared to SOC were -€234 and -€317, respectively (Table 3).

Long-term analysis

Analysis of the long-term model demonstrated a small gain in average quality-adjusted life years (QALYs)(+0.002,+0.004) and a decrease in health care costs (-€229,-€444) for the CT-strategy as compared with SOC, for men and women respectively (Table 4,5). Therefore, the CT-strategy is superior to the SOC-strategy (more effective and less expensive, SOC is dominated).

Subgroup analysis

For men with a pre-test probability of <70%, the difference in health care costs and effectiveness for the CT-strategy compared with SOC was -€227 and +0.004 QALY, respectively. For men with

a pre-test probability of ≥70%, this difference was -€231 and -0.003 QALY, respectively (Table 4, Figure 4).

For women with a pre-test probability of <70%, the difference in health care costs and effectiveness for the CT-strategy compared with SOC was -€444 and +0.004 QALY, respectively. For women with a pre-test probability of ≥70%, this difference was -€782 and +0.006 QALY, respectively (Table 5, Figure 5).

Sensitivity analysis

In probabilistic sensitivity analysis the probability that the CT-strategy was cost-effective was 100% in all subgroups, except for men with a pre-test probability ≥70% in which case it was 59% Value of information analysis suggested no value for future research, except for men with a pre-test probability ≥70%.

The short-term diagnostic costs were insensitive to changes in underlying disease status based on CT (not shown). In men, the long-term cost-savings were reduced from -€229 (reference case) to -€135, and there was no longer a difference in QALYs. For men with a pre-test probability <70%, long-term cost-savings were reduced from -€227 to -€95, and for men with a pre-test probability ≥70% from -€231 to -€217. In women, the long-term cost-savings were reduced from -€444 (base case) to -€296 and the net gain in QALYs was reduced from +0.004 (reference case) to +0.003.

Short-term diagnostic costs for SOC were lowered when a proportion of patients with abnormal X-ECG would not undergo CAG, which reduced cost savings for CT. However, long-term costs were increased for SOC (due to over treatment in patients with false-positive X-ECG and follow-up testing), which was in favor of CT.

DISCUSSION

Summary

We explored a hypothetical CT-strategy for its potential effectiveness and costs compared to SOC based on current guidelines for patients with stable chest pain. Short-term results suggest that the CT-strategy is less expensive compared to SOC. This is explained by the fact that fewer patients undergo subsequent MPI or CAG, which are costly. Simultaneously, our results suggest that CT is more effective in correctly classifying patients, except for men with a pre-test probability ≥70%. Men with a pre-test probability ≥70% are more often correctly classified using SOC, because patients in the SOC-strategy are more often referred for CAG immediately after an abnormal test (which results in correct classification).

Long-term analyses demonstrated that the CT-strategy was slightly more effective and less costly compared to the SOC-strategy. Results were altered when the (potential) degree of disease severity overestimation by CCTA was taken into account. Because cost savings were robust, the CT-strategy remained favorable even when the CT-strategy resulted in fewer QALYs, for example in men with a pre-test probability ≥70%. Results for CT were more favorable in women, which is explained by the lower prevalence of disease in women and the higher prevalence of zero calcium.

As expected, the gain in QALYs for the CT-strategy is small, since patients with persistent complaints will return to their physician until symptoms are treated adequately. The model assumes that within one year, all patients who are under–treated become appropriately treated. A benefit was gained from avoiding lifelong medication (over-treatment) in a substantial proportion of cases but this mainly affects costs. Nevertheless, even if the gain in QALYs is very small or close to zero, the CT-strategy remains optimal because it is less costly. Furthermore, several expected additional benefits of the CT-strategy were not incorporated in the model, such as a reduced total time to final diagnosis and a reduction in additional downstream health care costs through a more expedient work-up. In addition, since the negative predictive value of CCTA is higher compared to X-ECG, physicians can be more confident in reassuring a patient after a negative CCTA.

Previous publications

Previous reports based on patient-level data from the US indicated that CCTA compared with SPECT reduces 1-year CAD-related health care expenditures (based on administrative databases and Medicare reimbursements) by 26% in a low risk population (41-42). No differences in clinical outcomes were observed. These reports analyzed 1-year outcomes of patients who underwent CCTA and who were matched to a cohort that underwent SPECT, whereas the current study analyzed the long-term outcomes of a pre-specified diagnostic protocol for patients presenting with chest pain. Furthermore, the current analysis is based on a cohort of patients who underwent both CCTA and X-ECG. In spite of these differences, the main conclusion is the same, namely that CT is cost-saving and equally effective as compared to SOC. However, other reports suggest that using CCTA increases costs as compared with MPI (43-44). Lastly, a recent cost-effectiveness analysis which compared several CCTA-based strategies with myocardial perfusion SPECT and direct CAG found that the CCTA-based strategies were optimal up to a prevalence of CAD of 80% (45).

Limitations

Firstly, not all patients in the cohort underwent CAG. CCTA may have caused an overestimation of disease in these patients. To overcome this limitation, we included 6-months follow-up data in our reference standard in determining the disease category. Furthermore, we performed a sensitivity analysis to explore the magnitude of possible bias due to overestimation of disease by CCTA.

Secondly, we only observed the prognosis of patients who underwent both CCTA and X-ECG. Treatment decisions were based on the findings of both CCTA and X-ECG. We assumed that correctly classified patients would have a similar prognosis to that observed within follow-up of the clinical cohort. For patients incorrectly classified, however, prognosis was not observed. Therefore, several assumptions regarding unnecessary treatment and benefit of treatment forgone were made to estimate the prognosis of incorrectly classified patients.

Thirdly, model parameters were based on the patient cohort where possible, whereas best-available evidence from the literature was used otherwise. For example, we modeled the effect of SPECT using sensitivity and specificity as reported in a meta-analysis (3).

Fourthly, CCTA involves the possibility of incidental findings, which can occur in up to 28% of

CCTAs (46-47). As of today, it is unclear whether it is useful or cost-effective to follow up on incidental findings. Moreover, the associated ethical and legal issues are difficult (if not impossible) to incorporate in a decision model. Also, although we estimated the radiation exposure, we did not model the harmful effects. Since the difference in radiation exposure between the two strategies was small, this is unlikely to have an effect on the optimal decision.

Generalizability

Our analysis was based on a real-world Dutch population and Dutch cost estimates, which limits the generalizability. Nevertheless, in probabilistic sensitivity analysis we explored the effect of the uncertainty around our parameter inputs and found that our results were robust for all women and for men with a prior probability <70%. Furthermore, we compared only two strategies that reflect current practice at our institution. Other hospitals may have a different standard-of-care, which could alter the conclusion about the comparative effectiveness and costs.

Future research

Our analysis suggests that the CT-strategy is superior to SOC. However, the data in the model was based on a non-randomized observational study in which patients were prospectively recruited to undergo both tests. We did not directly observe the prognosis of patients who underwent X-ECG or CCTA only but instead estimated their prognosis with a decision model. A RCT would give valuable insight regarding outcomes and costs for both diagnostic strategies separately. In lieu of such a trial, this study provides preliminary estimates of the outcomes for a CT-strategy as compared with SOC. Our results can be used to make decisions regarding CT for patients presenting with stable chest pain, as long as RCTs with long-term follow-up are on-going. Furthermore, our results suggest that future research would mainly be beneficial for the decision regarding men with a pre-test probability ≥70%.

Conclusion

Analysis of our model suggests that a diagnostic strategy using initial evaluation with CT is less expensive and equally effective as compared to SOC, which was most pronounced for men with atypical symptoms and all women irrespective of their presenting symptoms. Although the results were robust, randomized controlled trials with long-term follow-up are needed to confirm our results.

TABLE 1.BASELINE CHARACTERISTICS, DIAGNOSTIC TEST RESULTS*, COST ESTIMATES AND RADIATION EXPOSURE*

Baseline characteristics	**Value**
Age(years), mean(SD)	56 (10)
Female: male	227:224 (0.48:0.52)
Risk profile	
Nicotine use	138 (0.29)
Hypertension	233 (0.49)
Diabetes	68 (0.14)
Dyslipidaemia	28 (0.59)
Family history of cardiovascular disease	214 (0.45)
Chest pain (40)	
Typical	146 (0.31)
Atypical	251 (0.53)
Non-anginal chest pain	74 (0.16)
Catheter-based coronary angiography	98 (0.21)
≥50% stenosis, any vessel	57/98 (0.58)
≥70% stenosis, any vessel	29/98 (0.30)
Percutaneous coronary intervention	46 (0.10)
Coronary bypass graft surgery	13 (0.03)
X-ECG Not performed	48/471 (0.10)
Normal	190/423 (0.45)
Non diagnostic	140/423 (0.33)
Abnormal	93/423 (0.22)
CCS Not performed	8/471 (0.02)
Mean CCS (median)	206 (15)
Range	0-4817
Interquartile range	0-145
CCTA Not performed	16/471 (0.03)
Non-diagnostic	3/471 (0.01)
No obstructive CAD	311/471 (0.66)
Obstructive CAD (≥50%)	141/471 (0.34)
Severe CAD (3VD, LM, prox. LAD)	48/141
CAG performed	121/471 (0.26)
≥50% stenosis, any vessel	71/121 (0.59)
≥70% stenosis, any vessel	34/121 (0.28)
Percutaneous coronary intervention	53/471 (0.11)
Coronary artery bypass graft surgery	18/471 (0.04)

TABLE 1.BASELINE CHARACTERISTICS, DIAGNOSTIC TEST RESULTS*, COST ESTIMATES AND RADIATION EXPOSURE (CONTINUED)*

	Cost estimates (euros)	Radiation exposure (mSv)
Exercise tolerance test (Expert opinion)	106	-
Coronary calcium score (8)	64	0.8
CT coronary angiography (8)	206	4.7
Single photon emission CT (Expert opinion)	545	12
Catheter-based coronary angiography (8)	1394	7.0
Percutaneous coronary intervention (24)	5000	15
Coronary bypass graft surgery (24)	14000	-

Results are shown as numbers (proportion of total) unless stated otherwise. X-ECG = exercise electrocardiography, CCTA = coronary computed tomography angiography, CAG = catheter-based coronary angiography
*Modified with permission from (11).

TABLE 2. SHORT-TERM RESULTS (MEN).

	SOC-strategy			CT-strategy			Difference(CT vs. SOC)	
Disease category*	**CAD–**	**CAD+**	**Revasc.**	**CAD–**	**CAD+**	**Revasc.**	**Mean**	**95%CI†**
CAD–	0.55	0.05	-	0.56	0.04	-	+0.01 ‡	-0.01,+0.03
CAD+	0.07	0.10	-	0.04	0.14	-	+0.03 ‡	+0.01,+0.06
Revascularization	0.04	0.01	0.18	0.04	0.06	0.12	-0.06 ‡	-0.09,-0.03
		Mean	95%CI†		Mean	95%CI†	Mean	95%CI†
Diagnostic costs(euros)		739	547,978		494	375,641	-245	-560,-117
Pre-test<70%		509	372,681		298	223,390	-211	-357,-87
Pre-test≥70%		1206	873,1617		894	654,1197	-312	-516,-146
% Correctly classified§		0.83	0.80,0.87		0.82	0.78,0.85	-0.01	-0.06,+0.02
Pre-test<70%		0.82	0.77,0.87		0.85	0.80,0.89	+0.03	-0.02,+0.07
Pre-test≥70%		0.85	0.79,0.89		0.74	0.66,0.82	-0.11	-0.19,-0.03
Radiation exposure‖(mSv)		6.2	4.5,8.3		5.7	4.4,7.1		
Pre-test<70%		4.1	2.9,5.6		4.1	3.1,5.3		
Pre-test≥70%		10.4	7.5,13.9		8.9	6.9,11.2		

SOC = standard-of-care, CT = computed tomography, Revasc. = revascularization, CI = confidence interval
*See Figure 4
†Based on a probabilistic sensitivity analysis (10000 samples)
‡Difference applies to correct classified cell(grey shaded)
§Correct classification by the diagnostic strategy
‖Radiation exposure related to diagnostic imaging

TABLE 3. SHORT-TERM RESULTS (WOMEN).

	SOC-strategy			CT-strategy			Difference(CT vs. SOC)	
Disease category*	**CAD–**	**CAD+**	**Revasc.**	**CAD–**	**CAD+**	**Revasc.**	**Mean**	**95%CI†**
CAD–	0.77	0.07	-	0.80	0.04	-	+0.03‡	+0.01,+0.05
CAD+	0.05	0.03	-	0.02	0.05	-	+0.02‡	+0.01,+0.04
Revascularization	0.03	0.00	0.05	0.02	0.04	0.03	-0.02‡	-0.04,-0.01
		Mean	95%CI†		Mean	95%CI†	Mean	95%CI†
Diagnostic costs(euros)		526	395,684		274	205,356	-252	-398,-127
Pre-test<70%		447	329,596		213	157,280	-234	-368,-113
Pre-test≥70%		796	581,1057		480	340,652	-317	-542,-123
% Correctly classified§		0.85	0.82,0.88		0.88	0.85,0.92	+0.03	-0.00,+0.06
Pre-test<70%		0.87	0.83,0.90		0.89	0.85,0.93	+0.02	-0.01,+0.06
Pre-test≥70%		0.81	0.75,0.85		0.86	0.78,0.92	+0.05	-0.03,+0.12
Radiation exposure‖(mSv)		5.1	3.6,7.0		4.1	3.1,5.3		
Pre-test<70%		3.9	2.7,5.4		3.3	2.4-4.3		
Pre-test≥70%		9.3	6.4-12.8		6.7	5.1-8.6		

SOC = standard-of-care, CT = computed tomography, Revasc. = revascularization, CI = confidence interval
*See Figure 4
†Based on a probabilistic sensitivity analysis (10000 samples)
‡Difference applies to correct classified cell(grey shaded)
§Correct classification by the diagnostic strategy
‖Radiation exposure related to diagnostic imaging

TABLE 4. LONG-TERM RESULTS (MEN)

	SOC-strategy		CT-strategy		Difference (CT vs. SOC)	
	Mean	**95%CI***	**Mean**	**95%CI***	**Mean**	**95%CI***
Health care costs (euros)	12969	10170,17764	12740	9957,17486	-229	-554,-84
Pre-test<70%	9691	7670,12588	9464	7457,12368	-227	-399,-56
Pre-test≥70%	19740	14439,30323	19509	14242,29952	-231	-448,-41
Effectiveness(QALYs)	11.671	11.079,12.158	11.672	11.078,12.160	+0.002	-0.002,+0.004
Pre-test<70%	11.980	11.505,12.403	11.984	11.510,12.406	+0.004	0.001,+0.007
Pre-test≥70%	11.025	9.935,11.703	11.022	9.926,11.703	-0.003	-0.011,+0.002
Radiation(mSv)	9.5	7.1,12.3	8.4	6.6,10.4		
Pre-test<70%	6.5	4.7,8.8	5.5	4.2,7.0		
Pre-test≥70%	15.6	11.8,20.1	14.2	11.1,17.9		
ICER(mean)	Dominated		Superior			
Pre-test<70%	Dominated		Superior			
Pre-test≥70%	30406		-			
Probability						
cost-effective (%)†	1		99			
Pre-test<70%	0		100			
Pre-test≥70%	41		59			

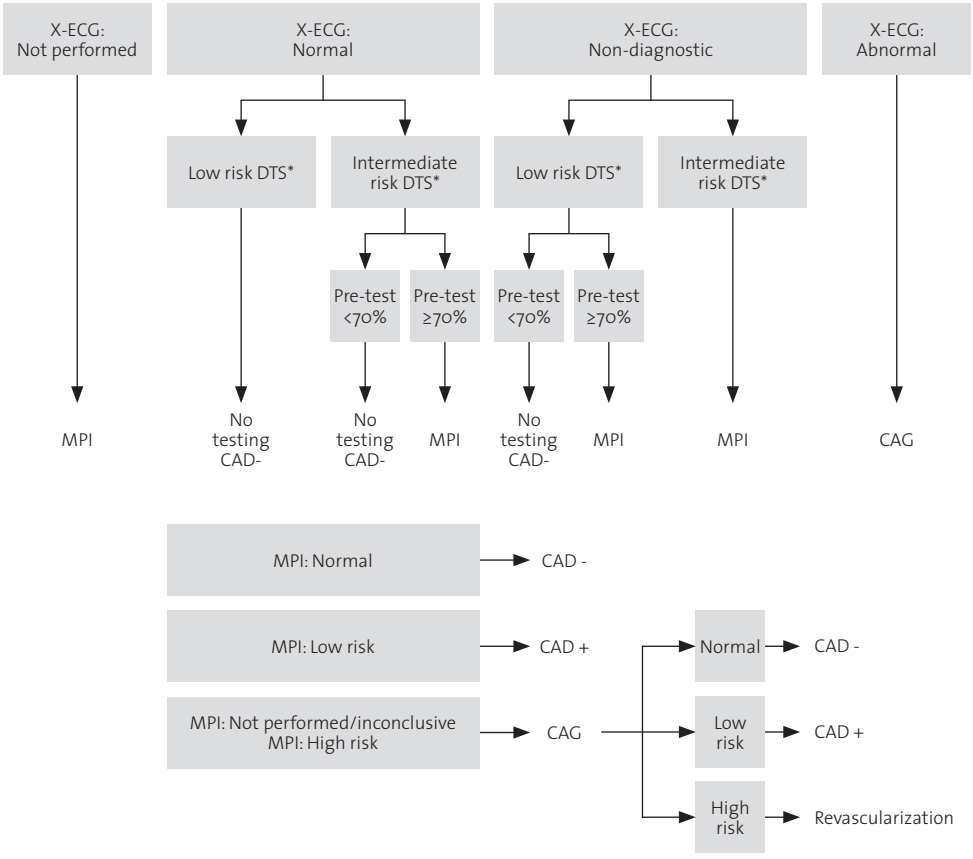
SOC = standard-of-care, CT = computed tomography, CI = confidence interval, ICER = incremental cost-effectiveness ratio
*Based on a probabilistic sensitivity analysis (10 000 samples)
†Proportion of simulations that showed the CT-strategy to be cost-effective, using a willingness-to-pay threshold of €80.000/QALY

TABLE 5. LONG-TERM RESULTS (WOMEN)

	SOC-strategy		CT-strategy		Difference (CT vs. SOC)	
	Mean	**95%CI***	**Mean**	**95%CI***	**Mean**	**95%CI***
Health care costs (euros)	8513	6977,10574	8068	6520,10134	-444	-696,-219
Pre-test<70%	7808	6303,9792	7464	5964,9457	-344	-582,-119
Pre-test≥70%	10896	8292,14736	10112	7474,13986	-782	-1319,-327
Effectiveness(QALYs)	12.684	12.269,13.097	12.689	12.273,13.101	+0.004	+0.002,+0.007
Pre-test<70%	12.727	12.306,13.139	12.731	12.310,13.144	+0.004	+0.002,+0.006
Pre-test≥70%	12.537	12.018,12.998	12.543	12.023,13.004	+0.006	+0.000,+0.012
Radiation(mSv)	6.8	4.9,9.1	5.2	4.0,6.7		
Pre-test<70%	5.6	3.9,7.8	4.3	3.2,5.6		
Pre-test≥70%	11.0	7.7,15.0	8.4	6.2,10.9		
ICER(mean)	Dominated		Superior			
Probability						
cost-effective (%)†	0		100			

SOC = standard-of-care, CT = computed tomography, CI = confidence interval, ICER = incremental cost-effectiveness ratio
*Based on a probabilistic sensitivity analysis (10000 samples)
†Proportion of simulations that showed CT-strategy to be cost-effective, using a willingness-to-pay threshold of €80.000/QALY

Figure 1. Further testing algorithm after X-ECG.



*Low risk DTS = DTS ≥5, intermediate risk DTS = DTS -10 to 5, high risk DTS = DTS ≤-11. DTS: Duke Treadmill Score.

Figure 2. Further testing algorithm after CAC.

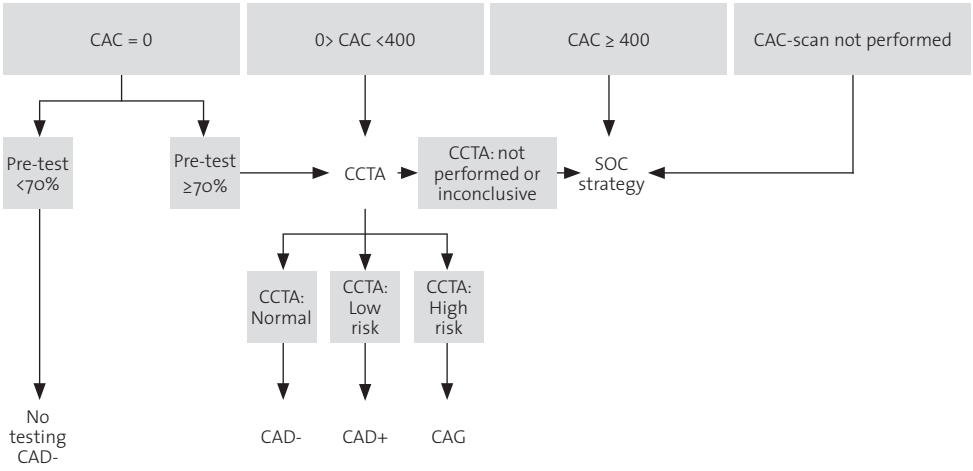
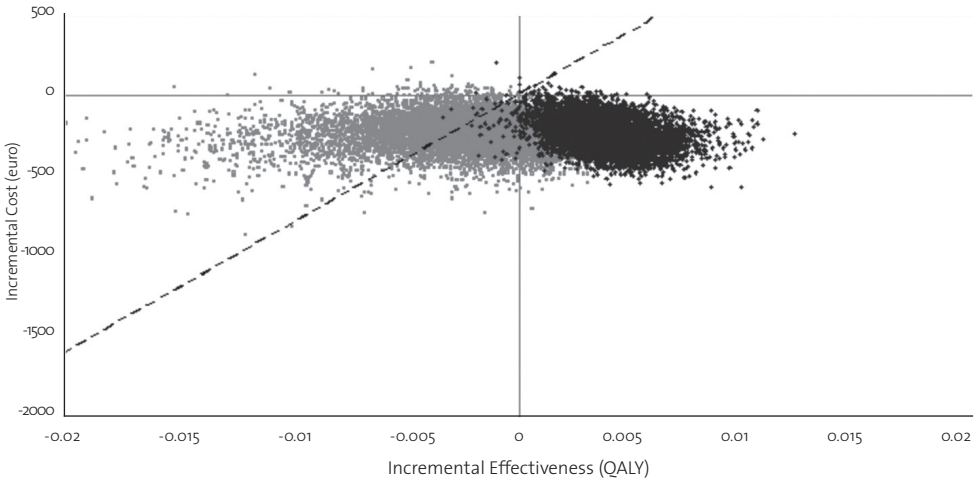


Figure 3. Definition of the disease category, as determined for each patient in the clinical cohort.

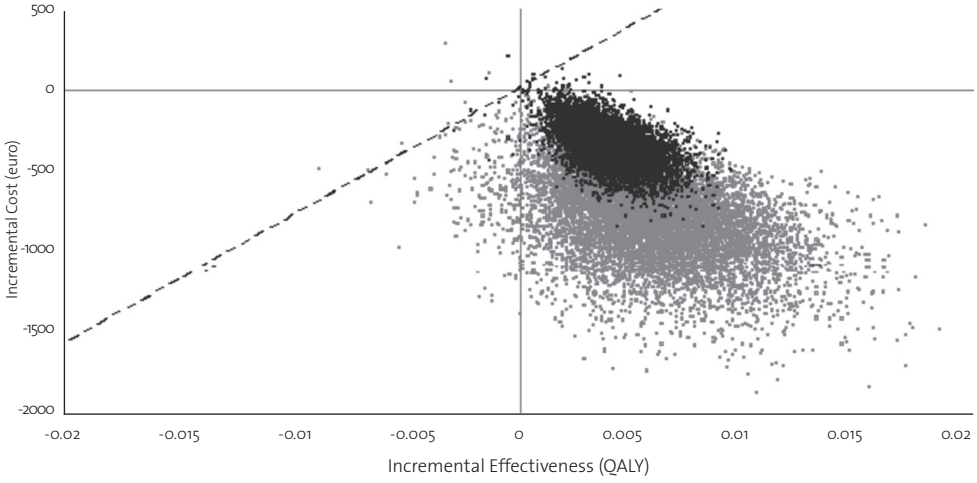
CAD- (no obstructive CAD)	No obstructive CAD on CCTA or CAG within the first 6 months.
CAD+ (obstructive CAD)	Obstructive CAD (≥50% diameter stenosis) determined in 78% by CCTA and 22% by CAG, without revascularization within the first 6 months. Patients are assumed to managed with medical therapy only.
Revascularization	Obstructive CAS treated with revascularization, either as initial treatment strategy, or performed within the first 6 months.

Figure 4. Incremental costs and effectiveness of the CT-strategy as compared with SOC, results from a probabilistic sensitivity analysis (10 000 samples) in men.



Blue squares indicate results for men with a pre-test probability <70% and pink squares indicate men with a pre-test probability ≥70%. The dotted line represents the willingness-to-pay threshold of €80.000/QALY.

Figure 5. Incremental costs and effectiveness of the CT-strategy as compared with standard-of-care, results from a probabilistic sensitivity analysis (10 000 samples) in women.



Blue squares indicate results for women with a pre-test probability <70%, pink squares indicate women with a pre-test probability ≥70%. The dotted line represents the willingness-to-pay threshold of €80.000/QALY.

REFERENCES

1. Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary - the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006; 27:1341-1381.
2. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999; 83:660-666.
3. Vanhoenacker PK, Heijenbrok-Kal MH, Van Heste R, et al. Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. Radiology 2007; 244:419-428.
4. Sun Z, Lin C, Davidson R, Dong C, Liao Y. Diagnostic value of 64-slice CT angiography in coronary artery disease: a systematic review. Eur J Radiol 2008; 67:78-84.
5. Schuetz GM, Zacharopoulou NM, Schlattmann P, Dewey M. Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. Ann Intern Med 2010; 152:167-177.
6. von Ballmoos MW, Haring B, Juillerat P, Alkadhi H. Meta-analysis: Diagnostic Performance of Low-Radiation-Dose Coronary Computed Tomography Angiography. Ann Intern Med 2011; 154:413-420.
7. Kristensen TS, Engstrom T, Kelbaek H, von der Recke P, Nielsen MB, Kofoed KF. Correlation between coronary computed tomographic angiography and fractional flow reserve. Int J Cardiol 2010; 144:200-205.
8. Genders TS, Meijboom WB, Meijs MF, et al. CT coronary angiography in patients suspected of having coronary artery disease: decision making from various perspectives in the face of uncertainty. Radiology 2009; 253:734-744.
9. Halpern EJ, Savage MP, Fischman DL, Levin DC. Cost-effectiveness of coronary CT angiography in evaluation of patients without symptoms who have positive stress test results. AJR Am J Roentgenol 2010; 194:1257-1262.
10. Pontone G, Andreini D, Bartorelli AL, et al. Comparison between low-dose multidetector computed coronary angiography and myocardial perfusion imaging test in patients with intermediate pre-test likelihood of coronary artery disease. Int J Cardiol 2011; 147:454-457.
11. Nieman K, Galema T, Weustink A, et al. Computed tomography versus exercise electrocardiography in patients with stable chest complaints: real-world experiences from a fast-track chest pain clinic. Heart 2009; 95:1669-1675.
12. Nieman K, Galema TW, Neefjes LA, et al. Comparison of the value of coronary calcium detection to computed tomographic angiography and exercise testing in patients with chest pain. Am J Cardiol 2009; 104:1499-1504.
13. Dedic A, Genders TS, Ferket BS, et al. Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing. Radiology 2011; 261:428-436.
14. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979; 300:1350-1358.
15. Oostenbrink J, Bouwmans C, Koopmanschap MA, Rutten FFH. Dutch Manual for Cost-Analyses [in Dutch]. Amstelveen, The Netherlands: Dutch Health Care Insurance Board, 2004.
16. GIP databank. Dutch Health Care Insurance Board. http://www.gipdatabank.nl/. Accessed January 13, 2012
17. Gibbons L, Blair SN, Kohl HW, Cooper K. The safety of maximal exercise testing. Circulation 1989; 80:846-852.
18. Johnson GG, Decker WW, Lobl JK, et al. Risk stratification of patients in an emergency department chest pain unit: prognostic value of exercise treadmill testing using the Duke score. Int J Emerg Med 2008; 1:91-95.
19. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990; 175:621-628.
20. Noto TJ, Jr., Johnson LW, Krone R, et al. Cardiac catheterization 1990: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). Cathet Cardiovasc Diagn 1991; 24:75-83.
21. Mettler FA, Jr., Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology 2008; 248:254-263.
22. Heijenbrok-Kal MH, Fleischmann KE, Hunink MG. Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. Am Heart J 2007; 154:415-423.
23. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007; 147:703-716.
24. NZA. Dutch National Authority of Health Care. http://ctg.bit-ic.nl/Nzatarieven/top.do. Accessed January 2011
25. Dutch Central Bureau of Statistics. http://statline.cbs.nl. Accessed 10 January 2011
26. Deckers JW, Goedhart DM, Boersma E, et al. Treatment benefit by perindopril in patients with stable coronary artery disease at different levels of risk. Eur Heart J 2006; 27:796-801.
27. Berger JS, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis. Am J Med 2008; 121:43-49.
28. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006; 368:581-588.
29. 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; 366:1267-1278.
30. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Med Decis Making 1993; 13:89-102.
31. 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; 150:243-254.
32. Hlatky MA, Boothroyd DB, Melsop KA, et al. Medical costs and quality of life 10 to 12 years after randomization to angioplasty or bypass surgery for multivessel coronary artery disease. Circulation 2004; 110:1960-1966.
33. Morise AP, Bobbio M, Detrano R, Duval RD. Incremental evaluation of exercise capacity as an independent predictor of coronary artery disease presence and extent. Am Heart J 1994; 127:32-38.
34. Esteves FP, Khan A, Correia LC, et al. Absent coronary artery calcium excludes inducible myocardial ischemia on computed tomography/positron emission tomography. Int J Cardiol 2011; 147:424-427.
35. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007; 356:1503-1516.
36. National Institute for Clinical Excellence (NICE). Guide to the methods of technology appraisal. Oxford, England: Radcliff Medical Press, 2004.
37. RIVM. Dutch National Institue for Public Health and the Environment. http://www.rivm.nl/vtv/object_document/o31711n17964.html. Accessed March 2008
38. 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.
39. Groot Koerkamp B, Nikken JJ, Oei EH, Stijnen T, Ginai AZ, Hunink MG. Value of information analysis used to determine the necessity of additional research: MR imaging in acute knee trauma as an example. Radiology 2008; 246:420-425.
40. Diamond GA. A clinically relevant classification of chest discomfort. J Am Coll Cardiol 1983; 1:574-575.
41. Min JK, Kang N, Shaw LJ, et al. Costs and clinical outcomes after coronary multidetector CT angiography in patients without known coronary artery disease: comparison to myocardial perfusion SPECT. Radiology 2008; 249:62-70.
42. Min JK, Shaw LJ, Berman DS, Gilmore A, Kang N. Costs and clinical outcomes in individuals without known coronary artery disease undergoing coronary computed tomographic angiography from an analysis of Medicare category III transaction codes. Am J Cardiol 2008; 102:672-678.
43. Nicol ED, Stirrup J, Leatham E, et al. Clinical management and short-term cost - 64-slice MDCT vs. myocardial perfusion scintigraphy. Int J Cardiol 2010; 144:248-250.
44. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. JAMA 2011; 306:2128-2136.
45. Min JK, Gilmore A, Budoff MJ, Berman DS, O'Day K. Cost-effectiveness of coronary CT angiography versus myocardial perfusion SPECT for evaluation of patients with chest pain and no known coronary artery disease. Radiology 2010; 254:801-808.
46. Koonce J, Schoepf JU, Nguyen SA, Northam MC, Ravenel JG. Extra-cardiac findings at cardiac CT: experience with 1,764 patients. Eur Radiol 2009; 19:570-576.
47. Bendix K, Jensen JM, Poulsen S, Mygind N, Norgaard BL. Coronary dual source multi detector computed tomography in patients suspected of coronary artery disease: Prevalence of incidental extra-cardiac findings. Eur J Radiol 2010.

Chapter 13

Summary and discussion

The overall objective of this thesis was to develop and evaluate tools that may improve personalized primary prevention of CVD. In *Part 1* of this thesis, we assessed the current recommended practice with regard to personalized primary prevention of CVD by performing systematic reviews of recently published clinical practice guidelines. Recommendations from these guidelines are used by physicians in order to select high-risk individuals for preventive interventions.

In *Part 2* of the thesis, we aimed to develop and evaluate methods that may improve the current recommended practice. We performed decision-analytic and prediction modeling studies that took into account competing risks between multiple relevant outcomes and we evaluated the heterogeneity in these outcomes. In addition, we used systematic reviews combined with meta-analyses to evaluate novel cardiovascular risk markers that may have added clinical value beyond the traditional CVD risk scores.

In this chapter, the main findings of our studies are summarized and subsequently put into context of current knowledge. Also some important methodological issues of our studies are discussed. Finally, possible benefits and disadvantages of personalized primary prevention of CVD for clinical practice are outlined, uncertainties about these issues are discussed and suggestions are made for further research.

MAIN FINDINGS

Primary care physicians play a pivotal role in the delivery of preventive interventions that are aimed at decreasing CVD incidence in the general population. They can select individuals for a simple office-based risk assessment or cardiovascular health check and, using the results from this health check, either decide about preventive interventions or opt for more advanced testing with novel cardiovascular biomarkers and cardiovascular imaging. In some cases, individuals may be directly selected for advanced testing without a preceding health check. These decisions usually will depend on the individual's estimated "pre-test risk" and discriminative performance of the test.

To guide decisions about what individuals to select for which cardiovascular screening methods and when to initiate preventive treatment, primary care physicians use clinical practice guidelines. Guidelines are designed to increase the level of evidence-based practice, and also serve as an educational source for both physicians and their clients. Clinical practice guidelines are defined by the Institute of Medicine as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (1). However, multiple guidelines on the same topic can be identified, and concerns exist about the quality and transparency of recommendations made (2,3).

In *Part 1* of this thesis, we aimed to select and present recommendations of current guidelines on primary CVD prevention, ranked according to the quality of their development process. We therefore critically appraised guidelines using the 7-item Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument (4). In addition, we assessed the level of potential conflicts of interest.

In *Chapter 2*, we systematically reviewed 27 guidelines involving office-based cardiovascular

risk assessment of individuals without a history of CVD and presented the recommendations from 17 guidelines with higher AGREE rigor scores in more detail. The majority of the reviewed guidelines embraced the use of multiple risk factors with prediction of absolute CVD risk within a period of 10 years to make decisions about preventive interventions. We found, however, a large variation across these guidelines with regard to rigor of development and transparency about conflicts of interest. We furthermore found differences between guidelines with respect to the selection of target groups, and use of novel risk markers in addition to traditional risk factors, outcomes used for prediction and treatment thresholds. No firm recommendations could be made for follow-up or periodicity of screening of people at low CVD risk.

With office-based cardiovascular health checks, high-risk individuals are identified for whom the benefits of aggressive modification of cardiovascular risk factors are considered to outweigh treatment costs and adverse effects. The benefits of intensive lifestyle counseling, aspirin, blood pressure and cholesterol lowering drugs on decreasing coronary heart disease and stroke event rates have been demonstrated by large randomized controlled trials (RCTs) (5-8). In low risk individuals, the benefit from aggressive risk factor modification is expected to be low (9); therefore only lifestyle advice is given, since this is generally safe and inexpensive. For individuals with an intermediate risk, gathering more information about the actual underlying risk might be worthwhile, with imaging of the coronary arteries as one of the most important options (10,11).

We assessed 14 guidelines about coronary artery imaging (*Chapter 3*). Eight guidelines recommended against testing of asymptomatic coronary artery disease or concluded that there is insufficient evidence for imaging, whereas six concluded that imaging can be valuable for those at intermediate and/or high risk. The CT calcium score was considered to be the most useful imaging marker. The nature of the recommendation did not seem to depend on relationships with the industry and AGREE rigor score.

Besides the two major CVD subtypes, coronary heart disease and stroke, two other CVD outcomes could be prevented by screening strategies: rupture of abdominal aortic aneurysms (AAAs) and peripheral artery disease (PAD). However, clear-cut evidence on prevention of AAA rupture by screening is restricted to elderly men (12), whereas the case for PAD screening is much more controversial in general (13). We found conflicting recommendations concerning AAA screening in other populations than elderly men and concerning PAD screening in general (*Chapters 4 and 5*). According to the reviewed PAD prevention guidelines, screening for PAD using the ankle-brachial index may only be useful to improve CVD risk assessment for prevention of coronary and stroke events in individuals at intermediate CVD risk.

To improve personalized decision making on one of the most important preventive measures, cholesterol lowering with statin therapy, we used a microsimulation model: the Rotterdam Ischemic heart disease and Stroke Computer simulation (RISC) model (14). This decision-model was based on 5-year follow-up data of the Rotterdam Study, a population-based cohort study conducted in Ommoord, a district of Rotterdam, the Netherlands (15).

First, we demonstrated that the 5-year predictions extrapolated by the RISC model to a longer period of 13 years were comparable to observed outcomes in the Rotterdam Study. After updating the baseline survival functions, we showed that the RISC model's forecast of 10-year

CVD and non-CVD mortality was also generalizable to a population-based cohort study from the United Kingdom, the EPIC-Norfolk study (16) (*Chapter 6*).

Second, we evaluated in *Chapter 7* how different modeling methods of statin therapy would influence the results of a cost-effectiveness analysis on U.S. guidelines for cholesterol screening (17) in Rotterdam Study participants. Modeling the treatment effect according to relative risk estimates as observed in statin trials led to the conclusion that U.S. guidelines are cost-effective, whereas if the effect was modeled through the associations of cholesterol levels with CVD event rates as observed in the Rotterdam Study, the conclusion would be that these guidelines are not cost-effective.

Finally, we used the RISC model to calculate the lifetime benefits of statin therapy in asymptomatic Rotterdam Study subjects (*Chapter 8*). The model estimated that statin therapy increases average life expectancy by 0.3 years and CVD-free life expectancy by 0.7 years, both explained by drops in CVD incidence and CVD mortality. These gains increased with blood pressure, unfavorable cholesterol levels, and body mass index but decreased with age. The gains were not concordant with 10-year CVD risk predicted by the currently recommended European risk score (18). A web-based calculator was developed for prediction of lifetime outcomes with and without statin therapy to support personalized decision-making see http://www.erasmusmc.nl/clinical-epidemiology/patientcare/.

Our review showed that current guidelines recommend the use of risk scores that are developed using standard survival modeling. However, these will frequently overestimate risk when the aim is to estimate the cumulative CVD incidence, especially in the elderly (19).

In *Chapter 9*, we developed and cross-validated prediction models for estimating 10-year intracerebral hemorrhage and ischemic stroke risks while taking into account competing risks. We used three population-based cohorts consisting of middle-aged and elderly individuals: the Atherosclerosis Risk in Communities (ARIC) Study (20), the Cardiovascular Health Study (CHS) (21), and the Rotterdam Study (15). In addition, we evaluated whether simple non-laboratory risk models could be improved by extension with more risk factors. Model extension only led to limited improvement.

Subsequently, we validated a Framingham-based risk function for long-term CVD risk (22) using the Rotterdam Study cohort in *Chapter 10*. Predictions were only well-calibrated in Rotterdam Study subjects at low risk. We subsequently refitted the Framingham risk function, but now subdivided CVD risk into coronary heart disease and stroke risk using cause-specific hazards modeling, with additionally taking into account the mutual competing risks of these two CVD outcomes. We observed considerable heterogeneity with regard to the contribution of CHD and stroke risk to the total risk of CVD within Rotterdam Study participants.

Many reviewed guidelines advocated the use of novel cardiovascular risk markers for those assessed to be at intermediate 10-year CVD risk. We selected four promising novel risk markers: CT calcium score (CTCS), carotid intima-media thickness measurement (cIMT), serum C-reactive protein (CRP), and the ankle-brachial index (ABI) and estimated their independent associations with CVD using meta-analyses. We subsequently modeled the added predictive value of each novel risk marker beyond traditional Framingham risk scores using cross-sectional data on individual risk profiles representative of the U.S. general population. Event rates were modeled with Monte Carlo microsimulation. Among the four novel risk markers, CTCS improved the

predictive performance of Framingham risk scores, whereas the other three novel markers did not (*Chapter 11*).

In individuals with chest pain and presence of coronary artery disease, the risk for myocardial infarction and other CVD events is regarded to be extremely high (23). Effective treatment by coronary revascularization(24) or high-dose cardio-protective agents(23,25,26) is recommended according to the extent of affected coronary arteries. The ability to detect and correctly categorize coronary artery disease will determine the health outcome and number of (unnecessary) medical procedures and costs. Within a decision-modeling study, an innovative coronary CT angiography strategy was compared to the Dutch standard-of-care, which comprises of triage based on exercise testing (*Chapter 12*). The cost-effectiveness analysis showed that the standard-of-care strategy was outperformed by the CT angiography strategy, which was particularly less expensive.

INTERPRETATION AND METHODOLOGICAL CONSIDERATIONS

Current recommendations

Given the various cardiovascular guidelines that contained conflicting recommendations on the same topic, as shown in *Part 1* of this thesis, guidance is needed about which of the recommendations should be used (3). First, we have to understand why these guidelines varied. One important explanation is that for many issues concerning CVD prevention, the evidence remains to be incomplete (27). This implies that inferences and extrapolations using the available data are made by the guideline committees to fill gaps in the evidence. These inferences are generally based on the judgments of experts. Experts however vary per guideline committee and therefore the judgments, opinions, and inferences also vary (2). For example, in contrast to cancer screening (28-30), little is known about the effectiveness of cardiovascular screening itself (31). Recommendations for aggressive risk factor modification by intensive lifestyle counseling, aspirin and blood pressure and cholesterol lowering drug agents are based on RCTs performed in already selected populations (5-8). In other words, the randomization in these trials has been performed after the cardiovascular screening. Guideline committees thus have to judge whether treatment effects from these trials are generalizable to individuals selected by the recommended cardiovascular screening method. With the expanding number of novel cardiovascular screening tests including imaging tests (32), inference-making becomes complicated. Consequently other, possibly inappropriate, target populations are sometimes selected, interactions between the treatment and the novel screening test could be present (33), and the additional harms and costs of the testing should be considered (34).

Grading the recommendations of guidelines without making judgments about the evidence itself has limitations. In *Chapters 2-5*, we appraised guidelines according to the transparency and rigor of their development processes and we assessed the amount of reported relationships with the industry by guideline group members. We assumed that the recommendations within well-developed and transparent guidelines would be less biased and more informative (3). Theoretically it may, however, be possible that suboptimal recommendations have been produced within a sound guideline development process, and that (cost-)effective recommendations are

found within poorly developed guidelines. Ideally large RCTs are performed to compare the clinical impact of various recommendations, but conducting these trials is generally not feasible. As an alternative, decision-modeling studies can be performed. For example, Manuel et al. modeled six national and international cholesterol guidelines for prevention of coronary mortality in a Canadian population (35). They concluded that the New Zealand, British, and Australian guidelines outperformed European, U.S., and Canadian guidelines according to efficiency (number needed to treat) and total number of coronary deaths avoided over 5 years.

Limitations of the current recommendations

The majority of the reviewed guidelines, apart from the AAA screening guidelines, used an individualized, risk-based approach for making treatment decisions, which implies that the individuals' absolute CVD risks are estimated using multiple risk factors. However, it has been suggested that the current recommended cardiovascular risk scores can be improved.

First, they were based on standard survival analytic methods to calculate the risk of the CVD event. The pitfall of standard survival analytic methods, such as Kaplan-Meier estimates, is that the survival estimate applies to a situation in which the competing death by other causes is removed (due to right censoring). This is a controversial topic within prediction modeling (36). It might be argued that by removing competing death, the estimates become more generalizable. However, it will result in an overestimation of risk if the aim is to estimate the cumulative CVD incidence and the competing death rate is high, for example in the elderly (19). Therefore, many researchers now would opt for an analysis that takes into account the competing death risk. With techniques such as Fine and Gray regression and modeling the cumulative incidence function by cause-specific Cox regression (37), the resulting risk estimates would be lower, more closely reflecting reality, and resemble the cumulative incidence.

A second limitation of the current decision tools is the use of combined end points, ignoring a possible variation in outcomes. In some cases, it can then be difficult to evaluate and communicate the effect of preventive interventions. For example, it is known that statin therapy has a different effect with respect to coronary heart disease and stroke (38). For aspirin, the effect on coronary heart disease and ischemic stroke is beneficial, whereas the risk for intracerebral and gastrointestinal bleeding increases with its use (6). Decision-making and risk communication can be further personalized if relevant outcomes are analyzed separately (39).

Third, some argue that instead of the commonly used 10-year time horizon, risks should be calculated over a long-term or lifetime period (40,41). Predicting 10-year risks, young adults with elevated risk factor levels are deemed to be at low risk, while taken over a long period, a high risk would be predicted (42). Therefore, these young individuals would be falsely reassured regarding their lifestyle behavior. Also, some preventive interventions are generally prescribed for lifelong use. Long-term predictions are then required to completely estimate the potential costs and savings with these interventions (43).

Decision and prediction modeling to improve personalized and shared decision making

In *Part 2*, we developed and evaluated tools in order to deal with the above mentioned limitations. We first validated the extrapolations made by the RISC model using extended Rotterdam Study follow-up data and demonstrated that the RISC model was able to correctly

extrapolate recent 5-year follow-up data to a longer time period (*Chapter 6*). However, a controversy exists on how to predict outcomes over a longer time period (41). An alternative method to the method we used would be to use long-term follow-up data that fully comprise the long-term horizon needed for the prediction (22). The latter approach has the disadvantage that recent decreases in CVD event rates (44,45) cannot be (fully) captured, which could affect the external validity of predictions.

It has been demonstrated that the associations of lipid levels with CVD outcomes obtained from a cohort study can be used to model the effectiveness of modifying these lipid levels. Resulting drops in CVD event rates corresponded well with those observed in statin trials (46). Due to heterogeneity in the size of associations across cohorts (47), we however found a much smaller benefit with lipid modification for Rotterdam Study participants in *Chapter 7*, than the benefits resulting from direct modeling of statin trial effects. Our study indicated that outcomes expected from RCTs cannot always be predicted on the basis of actual changes in risk factor levels. The validity of the chosen modeling method of the treatment effect can be explored by simulating individual-level trial data (48).

In *Chapter 8*, we demonstrated the influence of personalizing risks with adjustment for competing risks and the use of a lifetime horizon on survival gains by statin therapy. Three important assumptions were made for the modeling of statin therapy. First, we assumed that the relative effect of statin therapy in preventing coronary and stroke events as observed in RCTs would be generalizable to the Rotterdam Study population. Second, we assumed the relative effect would stay constant with increasing follow-up time and age. Third, we assumed that the relative effect would not depend on risk factor levels. These assumptions were partly supported by subgroup analyses of the statin trials (38,49-51).

The most important determinant for the extent of survival gains with statin therapy was age. With increasing age, gains in CVD-free survival and life expectancy decreased. This was explained by the strong effect of increasing age on death due to other causes than coronary heart disease and stroke. In our model, with increasing age, prevented coronary and stroke events were increasingly substituted by death due to other causes. This phenomenon is overlooked when traditional risk scores that consider a 10-year horizon are used, as demonstrated by Figures 5 and 6 in *Chapter 8*. One should however realize that with age, the duration of statin therapy will also decrease. The disadvantage of therapy duration was not explicitly taken into account in our analysis, since we did not consider the costs, side effects and disutility of taking pills. However, cost-effectiveness analyses show that with increasing age, the incremental cost-effectiveness ratio of statin therapy vs. no statin therapy also becomes less favorable (43).

In *Chapters 9 and 10*, we aimed to predict various CVD outcomes that are relevant for clinical decision-making and risk communication. To adjust for the mutual competing risks of CVD outcomes and mortality by other causes, we modeled the cumulative incidence function using cause-specific Cox regression (37). The advantage of this method is that the estimated hazard ratios are comparable or equal to those obtained by standard Cox survival analysis. The disadvantage is that it is difficult to present the complete equation needed to calculate cause-specific cumulative incidences. In addition to the linear predictor equation, the survival or hazard function at each failure time is needed for each cause. Therefore, we also developed risk

calculators, which can be made available online. As an alternative, one can opt to directly model cause-specific cumulative incidences by Fine and Gray regression on the subdistribution hazard (37). The advantage of the Fine and Gray technique is that equations can be written out. However, subdistribution hazard ratios are generally different from those obtained from standard Cox regression. Although subdistribution hazard ratios provide a direct interpretation of changes in the cumulative incidence, they can generally not be used for making causal inferences.

We hypothesized that prediction models used to predict a combined CVD endpoint would not be necessarily useful in estimating the risk of single CVD outcomes. For ischemic stroke and intracerebral hemorrhage, male gender, a history of coronary heart disease, diastolic blood pressure, glomerular filtration rate, waist-to-hip ratio and cholesterol levels had different effects. These differences led to moderate associations between intracerebral hemorrhage and ischemic stroke risk within ARIC, CHS, and Rotterdam Study participants (r for correlation =0.57, 0.37, 0.59).

For coronary heart disease and stroke, we found substantially different associations for male gender, systolic blood pressure, and cholesterol levels. Similar differences were observed in the Framingham Heart Study: female gender was less inversely associated with stroke than coronary events, systolic blood pressure was more positively associated with stroke, whereas cholesterol levels were only associated with coronary events. The correlation between coronary and stroke predictions was moderate: r for correlation = 0.64 (52). These findings confirm our hypothesis that a separate prediction of multiple CVD outcomes instead of a combined CVD endpoint could refine risk assessment. Consequently, the expected benefits and harms of preventive interventions with different effects on these outcomes can be further personalized in order to support shared decision making (53).

Novel cardiovascular biomarkers and cardiovascular imaging

Our final purpose was to evaluate whether decision-making based on traditional prognostic and diagnostic models can be improved using novel cardiovascular biomarkers and cardiovascular imaging tests (*Chapters 11 and 12*). According to most guidelines, these novel risk markers are useful in reclassifying individuals found to be at intermediate CVD risk. Several methods have been suggested to evaluate the added value of a new predictor or diagnostic test as compared to traditional ones (54). Advocated methods are: 1) assessing improvement in the receiver operating characteristic (ROC) curve or the survival C-statistic for time to event data and 2) assessing improvement in risk classification with risk thresholds based on guidelines. If improvements of these measures are demonstrated, then the next step would be 3) to show improvement of clinical outcomes and monetary costs by implementing the updated model in clinical practice (34,55).

These concepts are in essence the same for individuals from the general population and patients with stable chest pain suspected for coronary artery disease. For the general population, correct classification of future cardiovascular disease risk is desired, with guideline-based 10-year CVD risk categories of < 10%, ≥10-<20%, and ≥20%. For patients with stable chest pain, the aim is to exclude disease or to correctly classify the severity of the disease if present. Improved classification has impact on outcomes, because this will determine whether the

correct treatment is given. If misclassified, individuals will be either under or overtreated, which affects the effectiveness and efficiency of the chosen intervention.
To determine whether CTCS, cIMT, CRP, and ABI could improve risk classification of the U.S. general population (*Chapter 11*), observed event rates are needed. For example, U.S. citizens traditionally assessed to be at intermediate risk (≥10-<20%) who experience events, should be reclassified to high risk (≥ 20%), whereas those who stay event-free to low risk (< 10%). Unfortunately, our study dataset did not include outcome data. We therefore used a decision model with transitions based on the most parsimonious risk equations possible to model underlying event rates. These equations were defined by a traditional risk score (22) that was updated with all four novel markers. To yearly assign individual disease status over a total follow-up duration of 30 years, Monte Carlo microsimulations were performed. Risk classification by four nested risk scores, each updated with one of the four novel markers could then be compared to traditional risk scores (not updated). Our conclusion that in contrast to cIMT, CRP, and ABI, solely CTCS is expected to improve risk classification for the U.S. general population was in agreement with the observations in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Rotterdam Study. Both studies also concluded that among these four novel markers, CTCS has the most added value for correctly reclassifying those at intermediate risk (56,57).
For our study on patients with stable chest pain (*Chapter 12*), we also did not have sufficient information about the underlying true outcome status. To model the underlying disease status, disease categories were assigned based on combined data from coronary angiography if performed, clinical follow-up and coronary CT angiography otherwise. Similar as described above, "nested diagnostic models", i.e. the standard-of-care and coronary CT angiography diagnostic strategy were then compared with the reference standard regarding classification. Predicting the underlying event rate using a parsimonious model as compared to using observed data will however increase the precision of predictions to some extent (58), whereas model specification can become an issue.

CONCLUSIONS AND FUTURE DIRECTIONS

Part 1 of this thesis shows that the current recommended personalized practice to prevent first CVD events consists of risk-based decision-making using fixed risk thresholds for initiation of preventive interventions. Our modeling studies in *Part 2* subsequently demonstrate how personalized decision-making can be refined by taking into account treatment effects, competing risks and by including cardiovascular imaging.
It was however beyond the scope of this thesis to evaluate our findings within experimental research. Also, some other aspects that have not been addressed in this thesis would open opportunities for further improvement. Finally, there are some ethical issues that should be addressed in order to concretize possible implementation into clinical practice. In this section, these topics are briefly outlined and recommendations are made for further research.
An important focus for personalized CVD prevention is the individualization of expected absolute treatment effects (treatment benefits minus harms). These are determined by outcome

rates and the treatment's relative effectiveness on these rates. Some argue that such tailored absolute treatment benefits should be used for preventive treatment allocation rather than a dichotomous cut-point above which treatment is recommended (59,60). In *Chapter 8*, we developed decision tools, which can be used to predict survival gains with lifetime use of statin therapy based on an individual's risk profile. Indeed, we demonstrated that absolute statin benefits were only weakly associated with any chosen guidelines' 10-year risk threshold. However, a comparative (cost) effectiveness analysis of statin allocation based on predicted lifetime survival gains versus strategies based on 10-year risk thresholds would ideally be performed with a RCT or with another decision-modeling study using an external independent dataset.

For statin therapy, it is presumed that other risk factors do not or minimally affect its relative effectiveness on decreasing CVD event rates (38,51). However, for other preventive treatments, such as aspirin, this is probably not true (61). Subgroup and multivariable regression analyses of RCTs may be helpful to personalize other relative treatment effects (33,51,62), which then can be used in decision-modeling. For further personalization of treatment responsiveness, genetic testing may play a role (63). For example, a genome-wide association study (GWAS) identified a single-nucleotide polymorphism (SNP) located within SLCO1B1, a gene that regulates the metabolism of statins in the liver, which was associated with an increased risk of statin-induced myopathy (64). The predictive performance of screening with SNPs remains, however, questionable (65-67).

To support shared decision making on statin therapy, we chose to primarily present gains as absolute changes in total life expectancy and CVD-free life expectancy instead of using e.g. absolute risk reductions and lifetime numbers needed to treat (68). It is however known that the presentation or framing of health outcomes will influence the decisions made by physicians and patients (68-71). To evaluate the consequences of these framing effects, different perspectives can be chosen. From a utilitarian point of view, improved decisions should maximize utility by reducing disease and mortality (72). On the other hand, the quality of cognitive processes can be used as criterion (73). For the latter, improved decisions, defined as those that for example result in increased satisfaction, less distress or remorse after a decision, do not necessarily result in better health outcomes on the long term. For primary prevention of CVD, it can be debated whether health policy makers and physicians should override the decision-making of apparently healthy individuals by more paternalistic care entirely aimed at improving health outcomes (72).

A possible pitfall of paternalistic medical decisions is that health conditions are generally valued using the average values (e.g. weights for quality of life) observed in the general population or patient groups, whereas these values may vary according to preferences of individuals. Then, also from a utilitarian point of view, suboptimal decisions will be made (74). It is therefore advocated that patient-centered decision aids also help to clarify how patients value the various possible outcomes themselves (73). How these outcomes should be personalized and framed could be a topic for future research.

To conclude, this thesis presents various examples of methods that can be used to further personalize medical decision-making on the prevention of first CVD events. Further research is needed to improve and evaluate prediction modeling of outcomes with and without preventive treatment and to identify how these outcomes should be communicated to physicians and their clients.

REFERENCES

1. Field MJ, Lohr KN. Clinical practice guidelines: directions for a new program. Washington, DC: National Academy Press, 1990.
2. Sniderman AD, Furberg CD. Why guideline-making requires reform. Jama 2009;301:429-31.
3. Oxman AD, Glasziou P, Williams JW, Jr. What should clinicians do when faced with conflicting recommendations? Bmj 2008;337:a2530.
4. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12:18-23.
5. Lin JS, O'Connor E, Whitlock EP, Beil TL. Behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2010;153:736-50.
6. 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.
7. 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.
8. 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.
9. Jackson R, Lawes CM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet 2005;365:434-441.
10. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;151:474-82.
11. Peters SA, den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart 2012;98:177-84.
12. Ashton HA, Buxton MJ, Day NE et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet 2002;360:1531-9.
13. Beckman JA, Jaff MR, Creager MA. The United States preventive services task force recommendation statement on screening for peripheral arterial disease: more harm than benefit? Circulation 2006;114:861-6.
14. 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.
15. Hofman A, van Duijn CM, Franco OH et al. The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 2011;26:657-86.
16. Day N, Oakes S, Luben R et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. Br J Cancer 1999;80 Suppl 1:95-103.
17. 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.
18. Graham I, Atar D, Borch-Johnsen K et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). EurJ Cardiovasc Prev Rehabil 2007;14 Suppl 2:S1-113.
19. 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.
20. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129:687-702.
21. Fried LP, Borhani NO, Enright P et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1:263-76.
22. 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.
23. Deckers JW, Goedhart DM, Boersma E et al. Treatment benefit by perindopril in patients with stable coronary artery disease at different levels of risk. Eur Heart J 2006;27:796-801.
24. Bravata DM, Gienger AL, McDonald KM et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007;147:703-16.
25. Berger JS, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis. Am J Med 2008;121:43-9.
26. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006;368:581-8.
27. McAlister FA, van DS, Padwal RS, Johnson JA, Majumdar SR. How evidence-based are the recommendations in evidence-based guidelines? PLoS Med 2007;4:e250.
28. Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database Syst Rev 2006:CD001877.
29. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev 2007:CD001216.
30. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev 2013;1:CD004720.

31. Beswick AD, Brindle P, Fahey T, Ebrahim S. 2008.
32. Helfand M, Buckley DI, Freeman M et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:496-507.
33. Hingorani AD, Windt DA, Riley RD et al. Prognosis research strategy (PROGRESS) 4: stratified medicine research. BMJ 2013;346:e5793.
34. Pletcher MJ, Pignone M. Evaluating the clinical utility of a biomarker: a review of methods for estimating health impact. Circulation 2011;123:1116-24.
35. Manuel DG, Kwong K, Tanuseputro P et al. Effectiveness and efficiency of different guidelines on statin treatment for preventing deaths from coronary heart disease: modelling study. BMJ 2006;332:1419.
36. Koller MT, Raatz H, Steyerberg EW, Wolbers M. Competing risks and the clinical community: irrelevance or ignorance? Stat Med 2011.
37. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26:2389-430.
38. Cholesterol Treatment Trialists' Ctt C. 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.
39. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;150:396-404.
40. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. Lancet 1999;353:89-92.
41. 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.
42. Lloyd-Jones DM, Leip EP, Larson MG et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113:791-8.
43. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. Bmj 2006;333:1145.
44. Hunink MG, Goldman L, Tosteson AN et al. The recent decline in mortality from coronary heart disease, 1980-1990. The effect of secular trends in risk factors and treatment. JAMA 1997;277:535-42.
45. Unal B, Critchley JA, Capewell S. Modelling the decline in coronary heart disease deaths in England and Wales, 1981-2000: comparing contributions from primary prevention and secondary prevention. BMJ 2005;331:614.
46. 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.
47. 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.
48. Kim LG, Thompson SG. Uncertainty and validation of health economic decision models. Health Econ 2010;19:43-55.
49. 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.
50. 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;152:488-96, W174.
51. Dorresteijn JA, Visseren FL, Ridker PM et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. Bmj 2011;343:d5888.
52. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. AmHeart J 1991;121:293-298.
53. Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. N Engl J Med 2012;366:780-1.
54. Steyerberg EW, Vickers AJ, Cook NR et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21:128-38.
55. Steyerberg EW, Moons KG, van der Windt DA et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. PLoS Med 2013;10:e1001381.
56. Yeboah J, McClelland RL, Polonsky TS et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. Jama 2012;308:788-95.
57. Kavousi M, Elias-Smale S, Rutten JH et al. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med 2012;156:438-44.
58. Rapsomaniki E, White IR, Wood AM, Thompson SG, Emerging Risk Factors C. A framework for quantifying net benefits of alternative prognostic models. Stat Med 2012;31:114-30.
59. Timbie JW, Hayward RA, Vijan S. Variation in the net benefit of aggressive cardiovascular risk factor control across the US population of patients with diabetes mellitus. Arch Intern Med 1037;170:1037-44.
60. 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.
61. Dorresteijn JA, Visseren FL, Ridker PM et al. Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects. Eur Heart J 2011;32:2962-9.
62. Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. Jama 2007;298:1209-12.

63. O'Donnell CJ, Nabel EG. Genomics of cardiovascular disease. N Engl J Med 2011;365:2098-109.
64. Group SC, Link E, Parish S et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med 2008;359:789-99.
65. Janssens AC, Gwinn M, Bradley LA, Oostra BA, van Duijn CM, Khoury MJ. A critical appraisal of the scientific basis of commercial genomic profiles used to assess health risks and personalize health interventions. Am J Hum Genet 2008;82:593-9.
66. Palomaki GE, Melillo S, Neveux L et al. Use of genomic profiling to assess risk for cardiovascular disease and identify individualized prevention strategies--a targeted evidence-based review. Genet Med 2010;12:772-84.
67. Pepe MS, Gu JW, Morris DE. The potential of genes and other markers to inform about risk. Cancer Epidemiol Biomarkers Prev 2010;19:655-65.
68. Halvorsen PA, Wisloff TF, Stovring H, Aasland O, Kristiansen IS. Therapeutic decisions by number needed to treat and survival gains: a cross-sectional survey of lipid-lowering drug recommendations. Br J Gen Pract 2011;61:e477-83.
69. McNeil BJ, Pauker SG, Sox HC, Jr., Tversky A. On the elicitation of preferences for alternative therapies. N Engl J Med 1982;306:1259-62.
70. Tversky A, Kahneman D. The framing of decisions and the psychology of choice. Science 1981;211:453-8.
71. Brock DW, Wartman SA. When competent patients make irrational choices. N Engl J Med 1990;322:1595-9.
72. Buchanan DR. Autonomy, paternalism, and justice: ethical priorities in public health. Am J Public Health 2008;98:15-21.
73. Stacey D, Bennett CL, Barry MJ et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2011:CD001431.
74. Basu A, Meltzer D. Value of information on preference heterogeneity and individualized care. Med Decis Making 2007;27:112-27.

SAMENVATTING

De algemene doelstelling van deze thesis was om hulpmiddelen te ontwikkelen en te evalueren die geïndividualiseerde preventie van hart- en vaatziekten zouden kunnen verbeteren. In *Deel 1* van deze thesis, hebben we de huidige klinische adviezen met betrekking tot geïndividualiseerde preventie van hart- en vaatziekten uiteengezet. Dit hebben we gedaan door middel van een systematisch literatuuronderzoek van recent gepubliceerde klinische praktijkrichtlijnen. Aanbevelingen uit deze richtlijnen worden door artsen gebruikt om hoog- risico individuen te selecteren voor preventieve interventies.
In *Deel 2* van de thesis, beoogden wij hulpmiddelen die deze aanbevelingen zouden kunnen verbeteren te ontwikkelen en te evalueren. We voerden besliskundige en voorspellende modelleerstudies uit, rekening houdend met belangrijke, met elkaar concurrerende aandoeningen en we evalueerden de variatie in deze uitkomsten in de studiepopulaties. Tevens, gebruikten we systematisch literatuuronderzoek gecombineerd met meta-analyses om nieuwe cardiovasculaire risicomarkers te evalueren, die mogelijk toegevoegde klinische waarde hebben ten opzichte van de traditionele hart- en vaatzieken risicofuncties.
In dit hoofdstuk, worden de belangrijkste bevindingen van onze studies samengevat en vervolgens in de context van de huidige kennis geplaatst.

BELANGRIJKSTE BEVINDINGEN

Eerstelijnsartsen spelen een centrale rol in het aanbieden van preventieve zorg die gericht is op verlaging van de incidentie van hart- en vaatziekten in de algemene populatie. Zij kunnen bijvoorbeeld individuen voor een simpele gezondheidscheck uitnodigen en op basis van de resultaten hiervan vervolgens beslissen om preventieve interventie of meer geavanceerde diagnostiek met cardiovasculaire biomarkers of beeldvorming voor te schrijven. In sommige gevallen kunnen individuen direct door hen worden uitgenodigd voor geavanceerde diagnostiek. Deze beslissingen worden in het algemeen gemaakt op basis van de a priori kans op ziekte en de eigenschappen van de cardiovasculaire screeningstesten die gebruikt worden.
Voor het maken van deze soms moeilijke beslissingen, gebruiken artsen in de eerstelijn zogenaamde klinische praktijkrichtlijnen en standaarden. Richtlijnen worden door het Amerikaanse Institute of Medicine gedefinieerd als "systematisch ontwikkelde aanbevelingen die de zorgverlener en patiënt assisteren in het maken van de juiste medische keuzes in specifieke klinische situaties". Er kunnen echter verschillende richtlijnen over dezelfde casuïstiek worden gevonden en er bestaan zorgen over de kwaliteit en transparantie van de aanbevelingen die worden gemaakt.
In *Deel 1* van de thesis, beoogden wij de aanbevelingen van verschillende richtlijnen voor cardiovasculaire preventie te selecteren en te rangschikken naar kwaliteit van de gevolgde procedures van ontwikkeling. Voor de kwaliteitsbeoordeling gebruikten wij een gevalideerd meetinstrument bestaande uit 7 items: het zogenaamde "Rigor of Development" domein van het "Appraisal of Guidelines Research and Evaluation" (AGREE) instrument. Bovendien beoordeelden we ook de mate van mogelijke belangenverstrengeling met de medische en farmaceutische industrie.

In *Hoofdstuk 2* hebben we 27 richtlijnen met betrekking tot cardiovasculaire gezondheidschecks van gezonde individuen zonder een voorgeschiedenis van hart- en vaatziekten systematisch beoordeeld. We presenteerden de richtlijnen van 17 richtlijnen met hogere AGREE rigor scores in detail. De meerderheid van deze richtlijnen omarmde het gebruik van meerdere risicofactoren en voorspelling van een 10-jaars absoluut risico op hart- en vaatziekten voor beslissingen omtrent preventieve interventie. We vonden echter grote verschillen tussen deze richtlijnen wat betreft de degelijkheid van de ontwikkeling van aanbevelingen en mate van mogelijke belangenverstrengeling. Verder vonden we verschillen met betrekking tot selectie van doelgroepen voor cardiovasculaire screening, gebruik van nieuwe risicomarkers aanvullend op traditionele risicofactoren, uitkomsten voor het voorspellen van de risico's, alsmede te hanteren afkapwaarden voor hoog risico. Er konden geen duidelijke aanbevelingen gemaakt worden over het vervolgen van mensen met een normaal cardiovasculair risico en de eventuele periodiciteit van de gezondheidschecks.

Met dergelijke cardiovasculaire gezondheidschecks worden hoog- risico individuen opgespoord voor wie de voordelen van intensieve modificatie van cardiovasculaire risicofactoren zouden opwegen tegen de kosten en bijwerkingen van behandeling. De voordelen van intensieve leefstijlprogramma's, aspirine, bloeddruk- en cholesterolverlagende medicijnen ten aanzien van verlaging van hartinfarcten en beroertes zijn inmiddels aangetoond in grote gerandomiseerde klinische studies. In mensen met een laag risico, verwacht men weinig absoluut voordeel, daarom wordt aan hen meestal slechts algemene leefstijladviezen gegeven, omdat deze over het algemeen goedkoop en veilig zijn. Voor individuen met een intermediair risico, zou het verkrijgen van meer informatie over het daadwerkelijk onderliggende risico waardevol kunnen zijn. Een van de belangrijkste opties hiervoor is beeldvorming van de coronaire arteriën.

We hebben 14 richtlijnen over coronaire beeldvorming beoordeeld in *Hoofdstuk 3*. Acht richtlijnen raadden het gebruik van coronaire beeldvorming bij mensen zonder symptomen af of concludeerden dat er onvoldoende bewijs voor enig voordeel bestaat. Daarentegen concludeerden zes richtlijnen dat beeldvorming waardevol kan zijn in individuen met een intermediair en/of hoog risico. In deze laatste richtlijnen werd de CT calcium score als meest waardevolle test beschouwd. Het soort aanbeveling leek niet af te hangen van gerapporteerde relaties met de industrie, noch van de AGREE rigor score.

Naast de twee belangrijkste hart- en vaatziekten, coronair vaatlijden en beroerte, zijn er nog twee belangrijke hart- en vaatziekten die mogelijk voorkomen kunnen worden door screening: ruptuur van aneurysma's van de abdominale aorta (AAAs) en perifeer arterieel vaatlijden (PAV). Duidelijk bewijs voor een voordeel van screening op AAAs beperkt zich tot oudere mannen, terwijl voor screening op PAV er een grotere controverse bestaat.

We vonden tegenstrijdige aanbevelingen over screening op AAA in populaties anders dan oudere mannen en over screening op PAV in het algemeen (*Hoofdstuk 4 en 5*). Volgens de richtlijnen ter preventie van PAV, is screening op PAV met de enkel-arm index alleen zinvol om toekomstig coronair vaatlijden en beroerte te voorkomen in individuen met een intermediair cardiovasculair risico.

Om geïndividualiseerde besluitvorming omtrent een van de belangrijkste preventieve maatregelen, cholesterolverlaging middels statinetherapie, te verbeteren, gebruikten wij een

computer- microsimulatiemodel: het Rotterdam Ischemic heart disease and Stroke Computer simulation (RISC) model. Dit besliskundig model is gebaseerd op data van de Rotterdam studie met een follow-up duur van 5 jaar. De Rotterdam studie is een bevolkingsonderzoek uitgevoerd in Ommoord, een wijk in Rotterdam.

We hebben eerst aangetoond dat extrapolatie van uitkomsten door het RISC model, van 5-jaar naar een langere periode van 13 jaar, overeenkomen met de daadwerkelijk geobserveerde uitkomsten in de Rotterdam studie. Na het aanpassen van de uitgangswaarden voor de overlevingsfuncties die zijn opgenomen in het RISC model, konden we ook aantonen dat de voorspellingen voor 10-jaars sterfte aan hart -en vaatziekten en andere oorzaken ook generaliseerbaar zijn naar een bevolkingsonderzoek dat werd georganiseerd in het Verenigd Koninkrijk: de EPIC-Norfolk studie (*Hoofdstuk 6*).

Vervolgens, hebben we in *Hoofdstuk 7*, verschillende methoden voor het modelleren van statinetherapie in de Rotterdam studiepopulatie geëvalueerd met de uitslag van een kosteneffectiviteitanalyse van een van de Amerikaanse cholesterolscreeningsrichtlijnen als criterium. Het modelleren van therapie-effecten middels de relatieve effectiviteit zoals geobserveerd in gerandomiseerd onderzoek leidde tot de conclusie dat deze Amerikaanse richtlijnen kosteneffectief zijn. Als het effect echter gemodelleerd werd via de associaties van cholesterolwaarden met hart- en vaatziekten zoals geobserveerd in de Rotterdam studie, was de conclusie dat deze niet kosteneffectief zouden zijn.

Tenslotte gebruikten wij het RISC model om de levenslange voordelen van statinetherapie te voorspellen voor deelnemers aan de Rotterdam studie zonder een voorgeschiedenis van hart- en vaatziekten (*Hoofdstuk 8*). Het model schatte dat levenslang statinegebruik de gemiddelde levensverwachting met 0.3 jaar en de hart- en vaatziektevrije levensverwachting met 0.7 jaar zou doen toenemen. Deze toenames werden verklaard door een afname van de incidentie van en sterfte aan hart- en vaatziekten. Overlevingsvoordelen door statinegebruik namen verder toe met bloeddruk, ongunstige cholesterolwaarden, BMI, maar verminderden met stijgende leeftijd. De voordelen kwamen niet overeen met de 10-jaarsrisico's op sterfte aan hart- en vaatziekten zoals voorspeld door de in Europa aanbevolen risicotabellen. Een internet rekenhulp werd ontwikkeld voor voorspelling van uitkomsten bij levenslang statinegebruik ter ondersteuning van geïndividualiseerde besluitvorming, zie http://www.erasmusmc.nl/clinical-epidemiology/patientcare/.

Ons literatuuronderzoek liet zien dat huidige richtlijnen risicofuncties die ontwikkeld zijn met standaard overlevingsmodellen aanbevelen. Deze zullen echter vaak het risico overschatten als men het doel heeft om de cumulatieve incidentie van hart- en vaatziekten te voorspellen, vooral bij ouderen.

In *Hoofdstuk 9*, ontwikkelden we en kruis- valideerden wij predictiemodellen die 10-jaarsrisico's op een hersenbloeding en ischemische beroerte schatten, rekening houdend met de onderling concurrerende risico's. We maakten gebruik van drie bevolkingsonderzoeken met deelnemers van middelbare en oudere leeftijd: de Atherosclerosis Risk in Communities (ARIC) studie, de Cardiovascular Health Study (CHS), and de Rotterdam studie. Bovendien evalueerden we of simpele risicofuncties zonder laboratoriumtesten konden worden verbeterd door uitbreiding met meer risicofactoren. Dit leidde tot slechts geringe verbetering.

Vervolgens valideerden wij in *Hoofdstuk 10* een op de Framingham studie gebaseerde

risicofunctie voor het schatten langetermijnrisico's op hart- en vaatziekten in de Rotterdam studiepopulatie. Voorspellingen waren alleen goed gekalibreerd voor de laag- risico individuen. Vervolgens werd de Framingham risicofunctie opnieuw geschat in de Rotterdam studiedata, maar nu met een onderverdeling naar risico op coronair vaatlijden en beroerte rekeninghoudend met de onderling concurrerende risico's. We vonden een substantiële variatie in de verhouding van de risico's op coronair vaatlijden en beroerte in de Rotterdam studiepopulatie.

In onze richtlijnoverzichten werden veel aanbevelingen gevonden voor het gebruik van nieuwe cardiovasculaire risicomarkers om individuen met een intermediair cardiovasculair risico aanvullend te screenen. We selecteerden vier veelbelovende nieuwe risicomarkers: de CT calcium score (CTCS), intima-media diktemeting van de carotis arterie (cIMT), serum C- reactive protein (CRP), en de enkel-arm index (EAI). We schatten hun onafhankelijke associaties met hart- en vaatziekten door middel van meta-analyses. Vervolgens bestudeerden wij of de nauwkeurigheid van risicovoorspellingen door traditionele Framingham risicofuncties zou verbeteren met deze nieuwe markers. Hiertoe gebruikten wij cross-sectionele data over risicoprofielen die representatief waren voor de Amerikaanse algemene bevolking. Uitkomsten werden gesimuleerd met Monte Carlo microsimulaties. Van de vier nieuwe markers verbeterde alleen CTCS de nauwkeurigheid van de voorspellingen door Framingham risicofuncties (*Hoofdstuk 11*).

Bij patiënten met pijn op de borst en vernauwde coronair arteriën wordt het risico op een hartinfarct en andere hart- en vaatziekten als extreem hoog beoordeeld. Beslissingen over effectieve ingrepen zoals dotterbehandeling, bypassoperatie en risicoverlagende medicatie met een hoge dosering, worden gemaakt op basis van de mate van het coronair arteriële vaatlijden. De nauwkeurigheid waarmee deze mate kan worden geschat, zal uiteindelijk de overleving, maar ook het aantal (onnodige) medische ingrepen en kosten bepalen. Door middel van een besliskundige modelleerstudie werd een innovatieve diagnostische strategie gebaseerd op CT- angiografie vergeleken met de huidige Nederlandse standaarddiagnostiek die gebaseerd is op inspanningsonderzoek (*Hoofdstuk 12*). De kosteneffectiviteitanalyse liet zien dat de op CT- angiografie gebaseerde strategie goedkoper dan en even effectief als de standaarddiagnostiek was.

Chapter 14

Appendices

APPENDIX 1

Websites searched:

- American Academy of Family Physicians (AAFP), USA (http://www.aafp.org/online/en/home.html)
- American Association of Clinical Endocrinologists, USA (http://www.aace.com/pub/guidelines/)
- American College of Cardiology, USA (http://www.acc.org/)
- American College of Physicians, USA (http://www.acponline.org/)
- American College for Preventive Medicine, USA (http://www.acpm.org/)
- American Diabetes Association (ADA), (http://www.diabetes.org/home.jsp)
- American Geriatrics Society, AGS (USA) (http://www.americangeriatrics.org/)
- American Heart Association (AHA), USA (http://www.americanheart.org/)
- American Medical Association (AMA), USA (http://www.ama-assn.org/)
- American Stroke Association, USA (http://www.strokeassociation.org/)
- Australian Diabetes Society (ADS), AUS (http://www.racp.edu.au/ads/research_case.htm)
- Australian Medical Association (AMA), AUS (http://www.ama.com.au/web.nsf/)
- British Cardiac Society (BCS), UK (http://www.bcs.com/pages/default.asp)
- British Hypertension Society (BHS), UK (http://www.bhsoc.org/default.stm)
- Canadian Hypertension Society (CHS), CAN (http://www.hypertension.ca/)
- Canadian Task Force on Preventive Health Care (CTFPHC), CAN (http://www.ctfphc.org/)
- Cardiac Society of Australia and New Zealand (CSANZ), AUS (http://www.csanz.edu.au/)
- Centers for Disease Control and Prevention (CDC),USA (http://www.cdc.gov/)
- Department of Health (DOH), UK (http://www.dh.gov.uk/en/index.htm)
- European Society of Cardiology (http://www.escardio.org/)
- European Society of Hypertension (http://www.eshonline.org/)
- International Diabetes Federation (IDF) (http://www.idf.org/)
- International Society of Hypertension (http://www.ish-world.com/)
- National Health and Medical Research Council (NHMRC), AUS (http://www.nhmrc.gov.au/index.htm)
- National Heart Foundation, AUS (http://www.heartfoundation.org.au/index.htm)
- National Heart Lung and Blood Institute, USA (http://www.nhlbi.nih.gov/guidelines/index.htm)
- National Institute for Health and Clinical Excellence (NICE), UK (http://www.nice.org.uk/)
- New Zealand Guidelines Group, NZ (http://www.nzgg.org.nz/index.cfm?)
- Royal College of General Practitioners (RCGP), UK (http://www.rcgp.org.uk/default.aspx)
- Scottish Intercollegiate Guidelines Network (SIGN), UK (http://www.sign.ac.uk/)
- U.S. Preventive Services Task Force (USPSTF), USA (http://www.ahrq.gov/clinic/uspstfix.htm)
- World Heart Federation, (http://www.world-heart-federation.org/)
- World Health Organisation (WHO), (http://www.who.int/en/)
- World Hypertension League, (http://www.worldhypertensionleague.org/Pages/Home.aspx)

National Guideline Clearinghouse:

Disease/Condition:
cardiovasc* OR coronary OR heart OR cerebrovasc* OR arteri* OR peripher* OR vascular OR stroke* OR cva* OR aneurysm OR atherosclerosis OR arteriosclerosis OR hypertension OR hyperlipid* OR dyslipid* OR cholesterol OR diabetes OR (metabolic syndrome)
Guideline Categories:
Prevention, Risk Assessment, Screening
Age Range:
Adult (19 to 44 years), Aged (65 to 79 years), Aged, 80 and over, Middle Age (45 to 64 years)
Publication Date(s):
2011, 2010, 2009, 2008, 2007, 2006, 2005, 2004, 2003
Sort Order:
by publication date

National Library for Health:

Search:
((cardiovasc* OR coronary OR heart OR cerebrovasc* OR arteri* OR peripher* OR vascular OR stroke* OR cva* OR aneurysm OR atherosclerosis OR arteriosclerosis OR hypertension OR hyperlipid* OR dyslipid* OR cholesterol OR diabetes OR metabolic syndrome) AND (prevent* OR risk OR screen* OR early OR periodic exam* OR periodic evaluat* OR periodic check*))
Sort by: Publication date

Canadian Medical Association Infobase:

1. vascular OR coronary OR myocardial
2. arterial OR peripheral OR aneurysm
3. heart OR stroke OR cva
4. arteriosclerosis OR atherosclerosis
5. hypertension OR lipid OR cholesterol
6. diabetes OR metabolic syndrome

Target Population: Adult, Elderly, General
Domain: Diagnosis, Preventive
Language: English
Published: From: 2003/01/01 To: 2011/01/10
Display: 50 results
Sort By: Date

G-I-N International Guideline Library (g-i-n.net):

Disease/Condition:
Cardiovascular Disorders (MeSH C14), Diabetes Mellitus (MeSH C19.246), Glucose Metabolism Disorders (MeSH C18.452.394), Hyperlipidemia (MeSH C18.452.494)
Date of Publication: (range)
From: 1 January 2003 To: 10 January 2011

Languages:
English
Publication Scope:
Screening, Prevention
Publication Status:
Published
Publication Type:
Guideline
Country(s) that the publication applies to:
Australia, Canada, International, New Zealand, United Kingdom, United States

MEDLINE (Ovid):

1 cardiovascular diseases/
2 exp coronary disease/
3 exp cerebrovascular disorders/
4 exp aortic aneurysm/
5 peripheral vascular diseases/
6 heart failure/
7 exp arteriosclerosis/
8 (cardiovascular adj3 disease$).tw.
9 (coronary adj3 disease$).tw.
10 heart disease$.tw.
11 (stroke$ or cerebrovasc$ or cva$).tw.
12 (aort$ adj5 aneurysm).tw.
13 (abdominal adj5 aneurysm).tw.
14 (thoracoabdominal adj5 aneurysm).tw.
15 (arteri$ adj3 (occlusi$ or stenosis)).tw.
16 (peripher$ adj5 (occlusi$ or arteri$ or vascular)).tw.
17 heart failure.tw.
18 atherosclerosis.tw.
19 arteriosclerosis.tw.
20 hypertension/
21 exp hyperlipidemias/
22 exp diabetes mellitus/
23 hypertension.tw.
24 hyperlipid?emia.tw.
25 dyslipid?emia.tw.
26 cholesterol.tw.
27 diabetes.tw.
28 metabolic syndrome.tw.
29 or/1-28
30 exp cardiovascular diseases/pc

31 exp primary prevention/
32 preventive medicine/
33 exp risk assessment/
34 exp mass screening/
35 early diagnosis/
36 prevent$.tw.
37 (risk adj3 (reduc$ or manage$ or managing or intervent$ or assess$)).tw.
38 early adj3 interven$.tw.
39 early adj3 detect$.tw.
40 early adj3 diagnos$.tw.
41 periodic adj3 (exam$ or evaluat$ or check$).tw.
42 screen$.tw.
43 or/ 30-42
44 guideline.pt.
45 practice guideline.pt.
46 guideline$.ti.
47 guidance$.ti.
48 (position paper or position stand).ti.
49 statement$.ti.
50 recommendation$.ti.
51 consensus development conference.pt.
52 consensus.ti.
53 practice parameter$.ti.
54 standards.ti.
55 or/ 44-54
56 29 and 43 and 55
57 animals/
58 human/
59 57 not (57 and 58)
60 comment.pt.
61 letter.pt.
62 editorial.pt.
63 or/59-62
64 56 not 63
65 limit 64 to (english language and yr="2003 - 2011")

CINAHL (EBSCOhost):

((MH "Cardiovascular Diseases") OR (MH "Aortic Aneurysm+") OR (MH "Myocardial Ischemia+") OR (MH "Arteriosclerosis+") OR (MH "Cerebrovascular Disorders+") OR (MH "Peripheral Vascular Diseases") OR (MH "Heart Failure, Congestive+") OR (TX (cardiovascular N3 disease*)) OR (TX (coronary N3 disease*)) OR (TX heart disease*) OR (TX (stroke* or cerebrovasc* or cva*)) OR (TX (aort* N5 aneurysm)) OR (TX (abdominal N5 aneurysm)) OR (TX (thoracoabdominal N5 aneurysm)) OR (TX (arteri* N3 occlusi*)) OR (TX (arteri* N3 stenosis)) OR (TX (peripher* N5 occlusi*))

OR (TX (peripher* N5 arteri*)) OR (TX (peripher* N5 vascular)) OR (TX heart failure) OR (TX atherosclerosis) OR (TX arteriosclerosis) OR (MH "Hypertension") OR (MH "Hyperlipidemia") OR (MH "Diabetes Mellitus") OR (TX hypertension) OR (TX hyperlipid?emia) OR (TX dyslipid?emia) OR (TX cholesterol) OR (TX diabetes) OR (TX metabolic syndrome))
AND
((MH "Cardiovascular Diseases/PC") OR (MH "Preventive Health Care") OR (MH "Health Screening") OR (MH "Risk Assessment") OR (MH "Cardiovascular Risk Factors") OR (MH "Early Intervention") OR (TX prevent*) OR (TX (risk N3 reduc*)) OR (TX (risk N3 manage*)) OR (TX (risk N3 managing)) OR (TX (risk N3 intervent*)) OR (TX (risk N3 assess*)) OR (TX early N3 interven*) OR (TX early N3 detect*) OR (TX early N3 diagnos*) OR (TX screen*) OR (TX (periodic N3 exam*)) OR (TX (periodic N3 evaluat*)) OR (TX (periodic N3 check*)))
AND
((PT Practice Guidelines) OR (TI guideline*) OR (TI guidance*) OR (TI (position paper or position stand)) OR (TI statement*) OR (TI recommendation*) OR (TI consensus) OR (TI practice parameter*) OR (TI standards))
NOT
((PT commentary) OR (PT letter) OR (PT editorial))
Limit results to English language and publication year 2003 – 2011

APPENDIX 2

Description of the Rotterdam Study

The Rotterdam Study is a population-based cohort study of subjects aged 55 years or older living in the well-defined Ommoord district in the city of Rotterdam, the Netherlands. The study targets cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric and respiratory diseases in the elderly. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports (1).

The cohort used for this study had baseline examinations between July 1989 and September 1993. These examinations comprised extensive clinical examinations at the research center and an interview at home including questions on current health status, history of cardiovascular diseases, medication use and cardiovascular risk factors. Smoking behaviour was categorized into current, former or never smoking. Former smoking was defined as abstinence of at least two years of smoking. Participants were asked to fast for 12 hours before the clinical examinations. For systolic and diastolic blood pressure, the average of two consecutive measurements was used. Blood pressure was measured with a random-zero sphygmomanometer at the right brachial artery in sitting position after a 5 minutes rest. Hypertension was defined as either reported use of antihypertensive medication, or having a systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg. Serum total cholesterol was determined by an automated enzymatic procedure using the Roche CHOD-PAP reagent agent and serum high density lipoprotein (HDL)-cholesterol was measured with the Roche HDL cholesterol assay using PEG-modified enzymes and dextran sulphate. Diabetes mellitus was defined as either reported use of antidiabetic medication or a serum glucose level ≥ 11.0 mmol/L. Twelve-lead resting electrocardiograms were computer-analyzed by the MEANS program (2). Angina pectoris was assessed using the Rose questionnaire (3). The ankle-brachial index was calculated as the ratio of the systolic blood pressure of the posterior tibial artery, measured by an 8 MHz continuous wave Doppler probe and a random-zero sphygmomanometer, to the systolic blood pressure at the arm. The lowest ABI in either side was used and the left and right sided readings combined for analysis.

Outcome data were continuously collected from general practitioners and hospital discharge reports. All events were classified independently by two research physicians. If disagreements occurred, a consensus was reached by a meeting. Finally, all events were verified by a cardiologist or neurologist affiliated with the study. In cases of unresolved discrepancy, the judgment by the expert was considered definite.

RISC model

The RISC model consists of six health states: Well, Coronary Heart Disease (CHD), Stroke, CHD & Stroke, Cardiovascular Death and Non-cardiovascular Death (see Figure 1). 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 (4). 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 co-variable. The third and fourth equations estimated the 6-months case-fatality after a CHD and stroke event respectively. Six-month cardiovascular mortality as defined above was used as outcome for the case-fatality rates of these events. The probability of dying from a fourth CHD event and third stroke event was assumed to be 100%. The fifth and sixth Cox regression equations estimated the cumulative hazards of the remaining CVD mortality (other than CHD or stroke within 6 months) and non-CVD mortality (see Table 1 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 used. The first 5 years, baseline values of co-variables 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 co-variables were updated every 5 years by using multiple linear regression for the continuous variables systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-cholesterol, plasma glucose, ankle-brachial index, body mass index, waist-to-hip ratio, and serum creatinine, and logistic regression for the dichotomized variables atrial fibrillation, angina pectoris, and diabetes. Age and sex were used as independent variables in these regression equations to take into account the secular changes in risk factor levels due to aging for males and females separately. From the outcomes of the logistic regression equations regarding dichotomized variables, binomial distributions were created. Every 5 year period presence (1 or 0) of the dichotomized variables was derived from these distributions. The updating of the co-variables each 5-year period required the use of tracker variables. One-year cumulative hazards of CHD, stroke, other CVD mortality, and non-CVD mortality were weighted for their total cumulative hazards to take into account the competing risks for occurrence of a first event within each cycle. For each transition, the weighted one-year cumulative hazard was converted to a one-year cumulative incidence by exponentiation. If constant cause-specific hazards are assumed for the events, the cumulative incidence for each event will be estimated correctly (5). This is a reasonable assumption given the cycle length of one year. The effect of statin therapy on the transitions from the Well state to the CHD state or the Stroke state was modelled by multiplying the odds ratio of statin therapy after converting probabilities to the odds scale. Occurrences of events and duration in each health state were monitored using Monte Carlo tracker variables.

Modeling 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 (6). 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 (6). 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 euros).

Statistical analyses personalized lifetime benefits with statin therapy

For the two main outcomes, life expectancy and CHD/stroke free life expectancy, extended linear models with main effects of all variables, quadratic terms of all continuous variables, and interaction terms with statin therapy, age and sex were constructed. An unstructured covariance matrix was selected for both outcomes. Parameters were removed on the basis of improvement in the Akaike's Information Criterion (AIC), using the R function stepAIC, which calculates the log-likelihood penalized for the number of parameters and subjects used. The best candidate model is the one with the minimum AIC value. Final models were fitted with the restricted maximum likelihood method. A web-based calculator was constructed in using the equations derived from the models. For modelling CVD event and mortality risks, generalized linear models were fitted with the number of tracked events and non-events per 20,000 runs as dependent variable using a logit link function and binomial distribution type. To ensure face validity, all predictors selected for the main outcome measures were used as independent variables in the generalized linear models predicting CVD event and mortality risks.

TABLE 1. RISC MODEL INPUT PARAMETERS

Outcomes	**Cox-regression equations***
CHD	Hazard function = baseline cumulative hazard x EXP(b1*male+b2*age+b3*age*age+b4*diabetes*glucose+b5*TC+b6*HDL+b7*PP+b8*PP*male+b9*angina pectoris+b10*ABI+b11*ABI*ABI+b12*smoking+b13*famhistMI+ b14*CVD+b15*creat-mean linear predictor)
Stroke	Hazard function = baseline cumulative hazard x EXP(b1*male+b2*age+b3*hypertension+b4*hypertension*age+b5*SBP+b6*smoking+b7*famhistMI+b8*TIA+b9*CVD+b10*CVD*male+b11*AF+b12*ABI-mean linear predictor)
6-months CHD event mortality	Hazard function = baseline cumulative hazard x EXP(b1*age+b2*diabetes*glucose+b3*hypertension+b4*hypertension*age+b5*creat-mean linear predictor)
6-months Stroke event mortality	Hazard function = baseline cumulative hazard x EXP(b1*age+b2*smoking+b3*famhistCVD+b4*ABI+b5*TC+b6*creat+b7*HDL+b8*ABI*ABI+b9*age*HDL-mean linear predictor)
other CVD mortality	Hazard function = baseline cumulative hazard x EXP(b1*age+b2*male+b3*diabetes+b4*HDL*CVD+b5*hypertension+b6*hypertension*age+b7*smoking+b8*CVD+b9*ABI+b10*ABI*ABI+b11*AF+b12*AF*male+b13*age*AF+b14*male*CVD+b15*CVD*TC*TC-mean linear predictor)
Non-CVD mortality	Hazard function = baseline cumulative hazard x EXP(b1*male+b2*age+b3*glucose+b4*TC+b5*smoking+b6*smoking*age+b7*BMI+b8*BMI*age+b9*WHR+b10*WHR*age+b11*WHR*CVD+b12*famhistCVD+b13* famhistCVD*age+b14*ABI+b15*ABI*age+b16*CVD-mean linear predictor)
Statin Therapy Effects	**Odds Ratio (95% Confidence interval)**
CHD risk reduction	0.70 (0.61 – 0.81)
Stroke risk reduction	0.81 (0.71 – 0.93)

*Beta coefficients were drawn from a table comprising estimated beta coefficients from Cox regression equations developed in 100 bootstrapped datasets.
ABI = ankle-brachial index. AF = atrial fibrillation. BMI = body mass index. CHD = coronary heart disease. Creat = creatinine. CVD = cardiovascular disease. FamhistMI = family history of myocardial infarction. FamhistCVD = family history of cardiovascular disease. HDL = high-density lipoprotein. PP = pulse pressure. SBP = systolic blood pressure. TC = total cholesterol. TIA = transient ischaemic attack. WHR = waist-to-hip ratio.

TABLE 2. RISC MODEL PREDICTIONS FOR LIFETIME CHD/STROKE INCIDENCE, CHD/STROKE MORTALITY, AND TOTAL CVD MORTALITY FOR FOUR RISK PROFILES

Risk Profile	**Lifetime CHD/stroke incidence**		**Lifetime CHD/ stroke mortality**		**Lifetime total CVD mortality**	
	Statin -	Statin +	Statin -	Statin +	Statin -	Statin +
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	42%	34%	17%	13%	43%	42%
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	52%	43%	19%	13%	52%	49%
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	55%	46%	18%	13%	48%	45%
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	25%	19%	10%	7%	31%	29%

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.

REFERENCES

1. 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.
2. van Bemmel JH, Kors JA, van Herpen G (1990) Methodology of the modular ECG analysis system MEANS. Methods Inf Med 29: 346-353.
3. Kuller LH, Shemanski L, Psaty BM, Borhani NO, Gardin J, et al. (1995) Subclinical disease as an independent risk factor for cardiovascular disease. Circulation 92: 720-726.
4. 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.
5. Koller MT, Raatz H, Steyerberg EW, Wolbers M (2011) Competing risks and the clinical community: irrelevance or ignorance? Stat Med.
6. 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.

APPENDIX 3

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*(serum creatinine) -1.154*(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:

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

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 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

REFERENCES

1. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am.Heart J. 1991;121:293-298.
2. 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.
3. 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.
4. Borglykke A, Andreasen AH, Kuulasmaa K et al. Stroke risk estimation across nine European countries in the MORGAM project. Heart 2010;96:1997-2004.
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. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22:312-8.
7. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. Stroke 1994;25:40-3.
8. Jee SH, Park JW, Lee SY et al. Stroke risk prediction model: a risk profile from the Korean study. Atherosclerosis 2008;197:318-25.
9. 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.
10. 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.
11. Simons LA, McCallum J, Friedlander Y, Simons J. Risk factors for ischemic stroke: Dubbo Study of the elderly. Stroke 1998;29:1341-6.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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;26:2026-31.
17. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. Lancet Neurol 2007;6:1106-14.
18. 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;32:211-9.
19. Molshatzki N, Goldbourt U, Tanne D. Perceived hardships at midlife: Prediction of long-term stroke mortality. Int J Cardiol 2013.
20. 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.
21. 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.
22. 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.

APPENDIX 4

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 log2 (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. 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. 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 ICVD is calculated by summing the product of CVD hazard hCVD at failure time ti and the survival of competing events S(ti-1) for all failure times up to 30 year follow-up:

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

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.

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
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) – now
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 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 #18 OR #19 OR #20 OR #21 OR #22
24 #4 AND #10 AND #17 AND #23
25 #24 AND English[lang] AND ("2008/09/01"[PDAT] : "2015/01/01"[PDAT])

TABLE. GENERAL CHARACTERISTICS OF INCLUDED 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	Log2(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
Mohlenkamp, 2011 (2)	Germany	Heinz Nixdorf Recall (HNR) study	3,966	59.3	47	Median 5.0 years	Log2(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

Table a. CTCS – CHD studies

TABLE. GENERAL CHARACTERISTICS OF INCLUDED 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

Table b. CTCS – Stroke studies

TABLE. GENERAL CHARACTERISTICS OF INCLUDED 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

c. ABI – CHD studies

TABLE. GENERAL CHARACTERISTICS OF INCLUDED 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

d. ABI – Stroke studies

REFERENCES

1. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. Mar 27 2008;358(13):1336-1345.
2. Mohlenkamp S, Lehmann N, Moebus S, et al. Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. J Am Coll Cardiol. Mar 29 2011;57(13):1455-1464.
3. Hofman A, van Duijn CM, Franco OH, et al. The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol. Aug 2011;26(8):657-686.
4. Elias-Smale SE, Proenca RV, Koller MT, et al. Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J Am Coll Cardiol. Oct 19 2010;56(17):1407-1414.
5. Kavousi M, Elias-Smale S, Rutten JH, et al. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med. Mar 20 2012;156(6):438-444.
6. 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. Jun 23 2009;119(24):3078-3084.
7. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. Jama. Jan 14 2004;291(2):210-215.
8. Kondos GT, Hoff JA, Sevrukov A, et al. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation. May 27 2003;107(20):2571-2576.
9. LaMonte MJ, FitzGerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol. Sep 1 2005;162(5):421-429.
10. Wong ND, Gransar H, Shaw L, et al. Thoracic aortic calcium versus coronary artery calcium for the prediction of coronary heart disease and cardiovascular disease events. JACC Cardiovasc Imaging. Mar 2009;2(3):319-326.
11. Elias-Smale SE, Wieberdink RG, Odink AE, et al. Burden of atherosclerosis improves the prediction of coronary heart disease but not cerebrovascular events: the Rotterdam Study. Eur Heart J. Aug 2011;32(16):2050-2058.
12. Jain A, McClelland RL, Polak JF, et al. Cardiovascular imaging for assessing cardiovascular risk in asymptomatic men versus women: the multi-ethnic study of atherosclerosis (MESA). Circ Cardiovasc Imaging. Jan 2011;4(1):8-15.
13. Abbott RD, Petrovitch H, Rodriguez BL, et al. Ankle/brachial blood pressure in men >70 years of age and the risk of coronary heart disease. Am J Cardiol. Aug 1 2000;86(3):280-284.
14. Criqui MH, McClelland RL, McDermott MM, et al. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. Oct 26 2010;56(18):1506-1512.
15. Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, Fowkes FG. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. Circulation. Nov 9 2004;110(19):3075-3080.
16. Newman AB, Shemanski L, Manolio TA, et al. 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. Mar 1999;19(3):538-545.
17. Abbott RD, Rodriguez BL, Petrovitch H, et al. Ankle-brachial blood pressure in elderly men and the risk of stroke: the Honolulu Heart Program. J Clin Epidemiol. Oct 2001;54(10):973-978.
18. Hollander M, Hak AE, Koudstaal PJ, et al. Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. Stroke. Oct 2003;34(10):2367-2372.
19. Tsai AW, Folsom AR, Rosamond WD, Jones DW. Ankle-brachial index and 7-year ischemic stroke incidence: the ARIC study. Stroke. Aug 2001;32(8):1721-1724.

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Co-authors: Arfan Ikram, Renske Wieberdink, Prof.dr. A. Hofman, Roderik Kraaijenhagen, Matthijs Boekholdt, Wendy Max, Koen Nieman, Admir Dedic, collaborating EPIC-Norfolk Study, ARIC Study and CHS researchers and CHS researchers, and all other co-authors. Thank you for the wonderful collaborations, without your help this would not have been possible.

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LIST OF PUBLICATIONS

Publications and manuscripts based on the chapters in this thesis

Systematic review of guidelines on cardiovascular risk assessment: Which recommendations should clinicians follow for a cardiovascular health check? **Ferket BS**, Colkesen EB, Visser JJ, Spronk S, Kraaijenhagen RA, Steyerberg EW, Hunink MG. Arch Intern Med 2010 Jan 11; 170(1): 27-40.

Systematic review of guidelines on imaging of asymptomatic coronary artery disease. **Ferket BS**, Genders TS, Colkesen EB, Visser JJ, Spronk S, Steyerberg EW, Hunink MG. J Am Coll Cardiol. 2011 Apr 12;57(15):1591-600.

Systematic review of guidelines on abdominal aortic aneurysm screening. **Ferket BS**, Grootenboer N, Colkesen EB, Visser JJ, van Sambeek MR, Spronk S, Steyerberg EW, Hunink MG. J Vasc Surg 2012;55:1296-1305.

Systematic Review of Guidelines on Peripheral Artery Disease Screening. **Ferket BS**, Spronk S, Colkesen EB, Hunink MG. Am J Med 2012 Feb;125(2):198-208.e3.

Do different methods of modeling statin treatment effectiveness influence the optimal decision? Van Kempen BJ, **Ferket BS**, Hofman A, Spronk S, Steyerberg EW, Hunink MG. Med Decis Making 2012 May;32(3):507-16.

Coronary computed tomography angiography in patients with stable chest pain: comparative costs and effectiveness of a fast-track chest pain clinic. Genders TS, **Ferket BS**, Dedic A, Galema TW, Mollet NR, de Feyter PJ, Fleischmann KE, Nieman K, Hunink MG. Int J Cardiol 2012 Apr 18.

Validation of the Rotterdam Ischemic heart disease and Stroke Computer simulation model (RISC model). Van Kempen BJ, **Ferket BS**, Hofman A, Steyerberg EW, Colkesen EB, Boekholdt SM, Wareham NJ, Khaw KT, Hunink MG. BMC Med. 2012 Dec 6;10(1):158.

Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study. **Ferket BS**, van Kempen BJ, Heeringa J, Spronk S, Fleischmann KE, Nijhuis RL, Hofman A, Steyerberg EW, Hunink MG. PLoS Med. 2012 Dec;9(12):e1001361. doi: 10.1371/journal.pmed.1001361.

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. Van Kempen BJ, **Ferket BS**, Kavousi M, Leening M, Steyerberg EW, Ikram MA, Witteman J, Hofman A, Franco OH, Hunink MG. Submitted.

Predictive value of updating Framingham risk scores with novel risk markers in the U.S. general population. **Ferket BS**, Van Kempen BJ, Hunink MG, Agarwal I, Kavousi M, Franco OH, Steyerberg EW, Max W, Fleischmann KE. Submitted.

Separate prediction of intracerebral hemorrhage and ischemic stroke: results from the Atherosclerosis Risk in Communities Study, Rotterdam Study, and Cardiovascular Health Study. **Ferket BS**, Van Kempen BJ, Wieberdink RG, Steyerberg EW, Koudstaal PJ, Hofman A, Shahar E, Gottesman RF, Rosamond W, Kizer JR, Kronmal RA, Psaty BM, Longstreth Jr WT, Mosley T, Folsom AR, Hunink MG, Ikram MA. Submitted.

Other publications

Assessing predictive performance beyond the Framingham risk score. **Ferket BS**, van Kempen BJ, Janssens AC. JAMA. 2010 Apr 14;303(14):1368. [Letter-to-the-editor]

Effects on cardiovascular disease risk of a web-based health risk assessment with tailored health advice: a follow-up study. Colkesen EB, **Ferket BS**, Tijssen JG, Kraaijenhagen RA, van Kalken CK, Peters RJ. Vasc Health Risk Manag. 2011;7:67-74.

Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing. Dedic A, Genders TS,**Ferket BS**, Galema TW, Mollet NR, Moelker A, Hunink MG, de Feyter PJ, Nieman K. Radiology. 2011 Nov;261(2):428-36.

A comparative analysis of three widely used lipid management guidelines in the EPIC-Norfolk cohort. Colkesen EB, Jørstad HT, Peters RJ, Boekholdt SM, Tijssen JG, **Ferket BS**, Wareham NJ, Khaw KT. Eur J Prev Cardiol. 2013 Feb;20(1):98-106. doi: 10.1177/2047487311435456.

Restriction of the referral of patients with stable angina for CT coronary angiography by clinical evaluation and calcium score: impact on clinical decision making. Dharampal AS, Rossi A, Dedic A, Cademartiri F, Papadopoulou SL, Weustink AC, **Ferket BS**, Boersma E, Meijboom WB, Galema TW, Nieman K, de Feyter PJ, Krestin GP. Eur Radiol. 2013 Jun 19.

PHD PORTFOLIO

PhD TRAINING

Research skills

2007 – 2009 Master of Science in Clinical Epidemiology
Netherlands Institute for Health Sciences, Rotterdam, the Netherlands

In-depth courses

October 2012 SMDM short course Advanced Designing of Evidence-Based Patient Decision Aids, Society for Medical Decision Making Annual Meeting, Phoenix, AZ, USA

October 2012 SMDM short course Introduction to Designing Evidence-Based Patient Decision Aids, Society for Medical Decision Making Annual Meeting, Phoenix, AZ, USA

October 2010 SMDM short course Introduction to Discrete-Event Simulation for Healthcare, Society for Medical Decision Making Annual Meeting Toronto, Canada

October 2009 SMDM short course Prediction Models in Medicine: Development, Evaluation and Implementation, Society for Medical Decision Making Annual Meeting, Hollywood, CA, USA

September 2010 NVTAG workshop Perspective and Uncertainty in HTA, Nederlandse Vereniging voor Technology Assessment in de Gezondheidszorg Symposium, Utrecht, the Netherlands

Invited lectures and seminars

August 2011 "Modeling cardiovascular disease prevention: towards (even) more personalized medicine", seminar at the Center for Health Decision Science, Harvard School of Public Health, Boston, MA, USA

May 2011 "Modeling cardiovascular disease prevention: from cohort research to personalized medicine", seminar at the Helmholtz Zentrum München, Institute of Epidemiology, Munich, Germany

International conferences

October 2012 Poster presentation: "Modeling the Added Predictive Value of a Novel

Cardiovascular Risk Marker with a Simple State Transition Model" 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

October 2010 Poster presentation: "Personalized Prevention of Coronary Artery Disease"
Society for Medical Decision Making 32nd Annual Meeting, Toronto, Canada

October 2009 Poster presentation: "Systematic review of guidelines on cardiovascular risk assessment"
Society for Medical Decision Making 31st Annual Meeting, Hollywood, CA, USA

TEACHING ACTIVITIES

Teaching assistant

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 - 2013	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

ABOUT THE AUTHOR

Bart Stephan Ferket was born on July 12, 1979 in Purmerend, the Netherlands. He studied medicine at the Academic Medical Center of the University of Amsterdam (UvA), Amsterdam, the Netherlands and obtained his medical degree in 2005. Subsequently he worked as a research physician at the NDDO Institute of Prevention and Early Diagnostics (NIPED). In 2007, he started with the Netherlands Institute for Health Sciences (NIHES) Master of Science program in Clinical Epidemiology. In 2009, he obtained his Master of Science degree and began his Ph.D. program at the department of Epidemiology (chair: Prof.dr. A. Hofman), and the department of Radiology (chair: prof.dr. G.P. Krestin), Erasmus Medical Center, Rotterdam, the Netherlands. Bart will continue his career as postdoctoral associate of epidemiology in the division of biostatistics and epidemiology, department of public health of Weill Cornell Medical College in New York, NY, United States.