Identifying Persons at Increased Risk of Cardiovascular Disease

Methodological Considerations and Practical Applications in the General Population

Maarten J.G. Leening

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Cover: Rembrandt H. van Rijn – The Storm on the Sea of Galilee.
Oil on canvas, dated 1633.

This painting is part of the collection of the Isabella Stewart Gardner Museum, Boston, MA, U.S. Along with 12 other works of art, the painting was stolen from the museum on March 18, 1990. With a total worth of $500 million, this is considered to be the largest unresolved property theft in human history. In 1924, Isabella Stewart Gartner stipulated in her will, that the museum should remain unchanged according to her aesthetic vision and intent. Therefore, for the past 26 years, empty frames hang in the Dutch Room gallery as placeholders for the missing works.

The work on the cover of this thesis is symbolic for the link between Rotterdam and Boston, the places where the work compiled in this thesis was written. The painting was crafted by Dutch hands and hung for years in the Bostonian museum that is situated across the street from the Harvard T.H. Chan School of Public Health.

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in the General Population

Herkenning van personen met verhoogd risico op hart- en vaatziekten

Methodologische overwegingen en praktische toepassingen
in de algemene bevolking

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Erasmus Universiteit Rotterdam
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Financial support by the Department of Research Policy of the Erasmus MC; and the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged. Additional support from Capri Cardiac Rehabilitation is gratefully acknowledged.

Ethics Approval

The Rotterdam Study has been approved by the medical ethics committee according to the 'Wet Bevolkingsonderzoek: ERGO' ('Population Screening Act: Rotterdam Study') executed by the Ministry of Health, Welfare, and Sport of the Netherlands.[1]

Participants of the Rotterdam Study (RS) provided written informed consent to participate in the study at enrollment and at each repeat examination, and to obtain clinical information from their treating physicians, separately. The latter includes permission to obtain information from the general practitioner, medical specialists, and pharmacists.

The Cardiovascular Health Study (CHS) has been approved by the Institutional Review Boards of all 4 participating study sites. All CHS participants provided written informed consent to participate and for follow-up data collection.

In loving memory of J.L. Leening

Table of Contents

This thesis is based on articles published in various scientific journals. Differences may exist in exact wording and abbreviations between the text in this thesis and the text of the published version of the articles due to editorial changes and linguistic differences. Permission to reproduce the individual chapters in this thesis was obtained from the publishers of the various scientific journals.

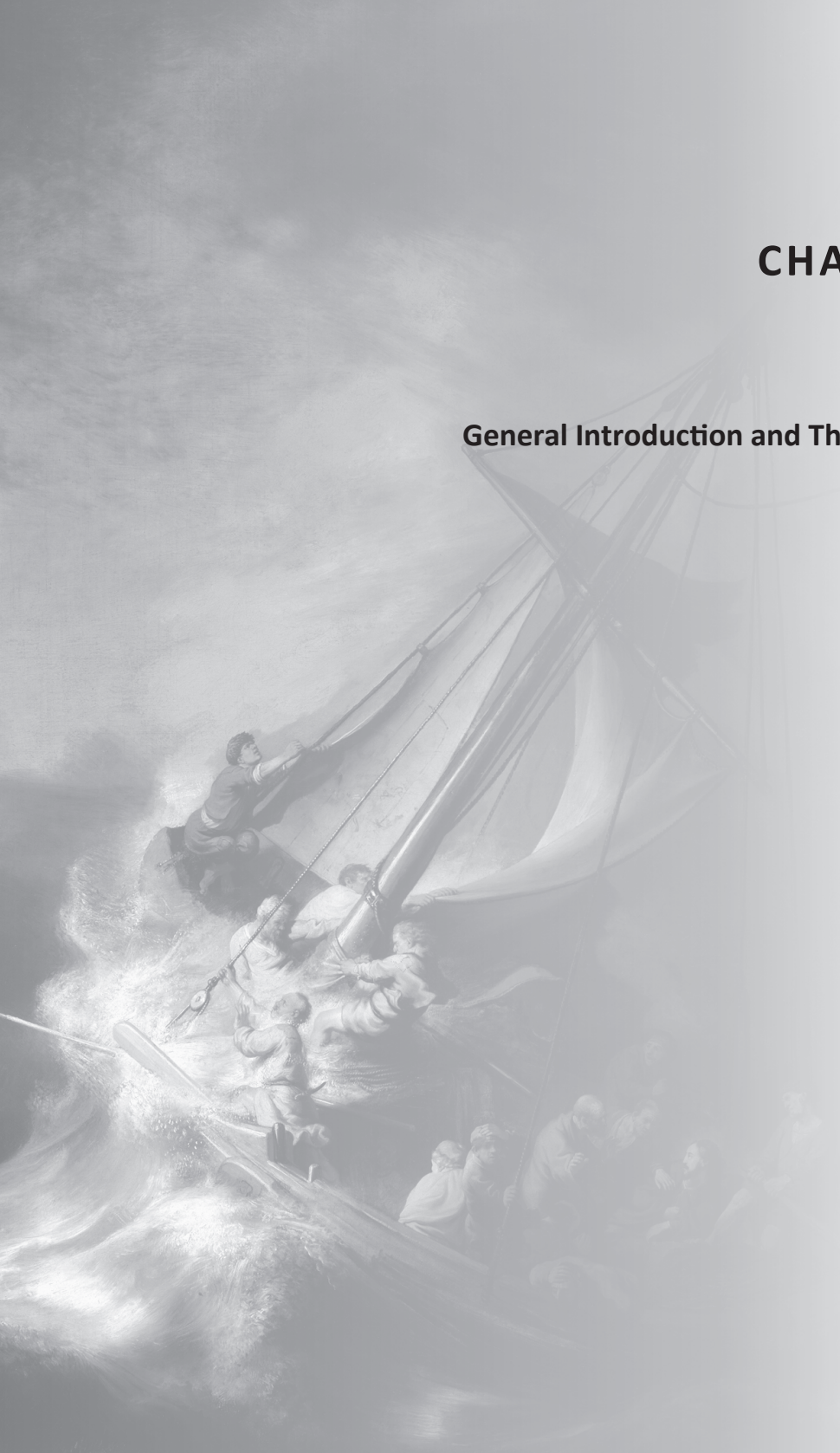
List of Abbreviations

ABI	ankle-brachial index
ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
ASCVD	atherosclerotic cardiovascular disease
ATC	Anatomical Therapeutic Chemical
ATP III	Adult Treatment Panel III
AUC	area under the receiver operating characteristic curve
BI	*betrouwbaarheidsinterval*
BMI	body mass index
CABG	coronary artery bypass grafting
CAC	coronary artery calcification *(coronaire calcium)*
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
cIMT	carotid intima-media thickness *(intima-mediadikte van de A. carotis)*
CORE	coronary risk in the elderly
CRP	C-reactive protein *(C-reactieve proteïne)*
CT	computed tomography
CVD	cardiovascular disease
ECG	electrocardiogram
ECG-LVH	left ventricular hypertrophy on electrocardiography
ERGO	*Erasmus Rotterdam Gezondheid Onderzoek*
ESC	European Society of Cardiology
FPS	Framingham point score
GP	general practitioner
HDL	high-density lipoprotein
HR	hazard ratio *(hazardratio)*
ICD	implantable cardioverter-defibrillator
ICD-10	International Classification of Diseases, tenth revision
ICPC	International Classification of Primary Care
IDI	integrated discrimination improvement
LDL	low-density lipoprotein
MEANS	Modular ECG Analysis System
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
NA	not applicable
NCEP	National Cholesterol Education Program
NICE	National Institute for Health Care and Excellence
NRI	net reclassification improvement
NHANES III	Third National Health and Nutrition Examination Survey
NT-proBNP	N-terminal pro-brain natriuretic peptide *(N-terminaal pro-breinnatriuretisch peptide)*
OR	odds ratio

PCI	percutaneous coronary intervention
PWV	pulse wave velocity *(aortale polsgolfsnelheid)*
RS	Rotterdam Study
SCD	sudden cardiac disease
SCORE	Systematic Coronary Risk Evaluation
SD	standard deviation
vWF	*von Willebrand-factor*
WHO	World Health Organization

Clinicians who see patients for primary prevention of cardiovascular disease (CVD) are fortunate to have multivariable models that can predict, with reasonable reliability, the absolute risk for future CVD events. The absolute risk for future development of disease can be predicted for very few diseases, much less with the precision afforded by current CVD risk prediction models. These 'risk scores' are a major advance over clinical risk prediction using relative risk estimates, and CVD prevention is one of the few areas in clinical practice to incorporate the use of absolute risk prediction into clinical practice guidelines.

- Donald M. Lloyd-Jones and Lu Tian
Predicting cardiovascular risk. So what do we do now?
Arch Intern Med 2006;166(13):1342-4



CHAPTER 1

General Introduction and Thesis Outline

Despite expanding primary prevention efforts, the majority of individuals in Western societies will develop cardiovascular disease (CVD) during their lifetime.[2] CVD is an age-related disease and comes in many forms, ranging from exertional angina and intermittent claudication to disabling stroke, myocardial infarction or sudden cardiac death. Since a substantial proportion of first CVD events has fatal or incapacitating consequences primary prevention is of key importance. Primary prevention encompasses all efforts to anticipate the development of atherosclerosis and forestall its progression to clinical manifestations. A focus on prevention does not imply that all CVD can be eliminated but instead embraces Fries's model of 'compression of morbidity'.[3] In this model disease-free life span is extended through the prevention of complications and the symptom burden is compressed into a limited period preceding death.[4] Thus, primary prevention is ideally suited to address chronic conditions, such as CVD, that take decades to develop and then manifest as life-threatening and ultimately fatal events. Well-established modifiable risk factors, which contribute to build up of atherosclerosis, include smoking, diabetes, obesity, high blood pressure and serum low-density lipoprotein (LDL) cholesterol. As such, prevention of CVD can be executed according to two parallel strategies. First, through population measures to disincentivize smoking and to adhere to a healthy lifestyle by means of diet and exercise. And second, by treating individuals to attain optimal glucose, blood pressure, and cholesterol levels using pharmacological agents.

Clinical practice guidelines for primary prevention of CVD at individual level are centered on a traditional high-risk approach. Based on an individual's age and risk factor profile, CVD risk calculators provide clinicians with an estimate of the individual's probability for developing CVD in the following 10 years.[5-7] The role of cardiovascular risk assessment in clinical practice is twofold. First, it serves as a starting point for risk communication between physicians and patients. Secondly, it is used as the primary mode to select candidates at high risk of CVD for lipid-lowering treatment (see Appendix Figures 1.1, 1.2, and 1.3 for current guideline recommendations).[8-10]

Outline of this thesis

Part I – Methodological considerations in cardiovascular epidemiologic research

Traditionally, most data on occurrence and risk factors for cardiovascular diseases have been derived from prospective population-based cohort studies. These studies are designed to follow large groups of healthy individuals over a longer period of time. Potential risk factors and subclinical measures of cardiovascular disease are measured using standardized methods, at times when the participants have not yet experienced any cardiovascular events. Already over 50 years ago, the pioneers from the Framingham Heart Study leveraged this design to provide insight into the growing burden of cardiovascular disease in the general population and enabled the identification of causal factors, such as cholesterol and blood pressure.[11] The Framingham Heart Study, established in 1948, is a cohort study comprised of healthy volunteers from the general population of the town of Framingham, MA, U.S. The study design of enrolling healthy, rather than diseased, individuals in order to study risk factors, potential high-risk indicators, and frequency of occurrence of disease, was adopted by many other researchers and made the field of epidemiology come to full fruition by the end of the 20th century.

Most of the work in this thesis is based on data from the Rotterdam Study, a Dutch prospective population-based cohort study with similar design and objectives as the Framingham Heart Study (Figure 1.1). In *Chapter 2* of this thesis the methods for the follow-up of incident cardiac events is detailed, since any comparison to data from other studies (such as in *Chapters 4* and *15*) requires clear definitions of disease outcomes.

The Framingham Heart Study aimed to be "not atypical" of the general American suburban population.[12] Shortly after the initiation of this seminal study, however, the investigators noted that the participants who volunteered were more healthy than those who declined to participate and hence raised the question to what extend findings were generalizable to the general population.[12] This phenomenon was referred to as the 'healthy volunteer effect'. In *Chapter 3* of this thesis the impact of the healthy volunteer effect on cardiovascular risk estimates in the Rotterdam Study is presented.

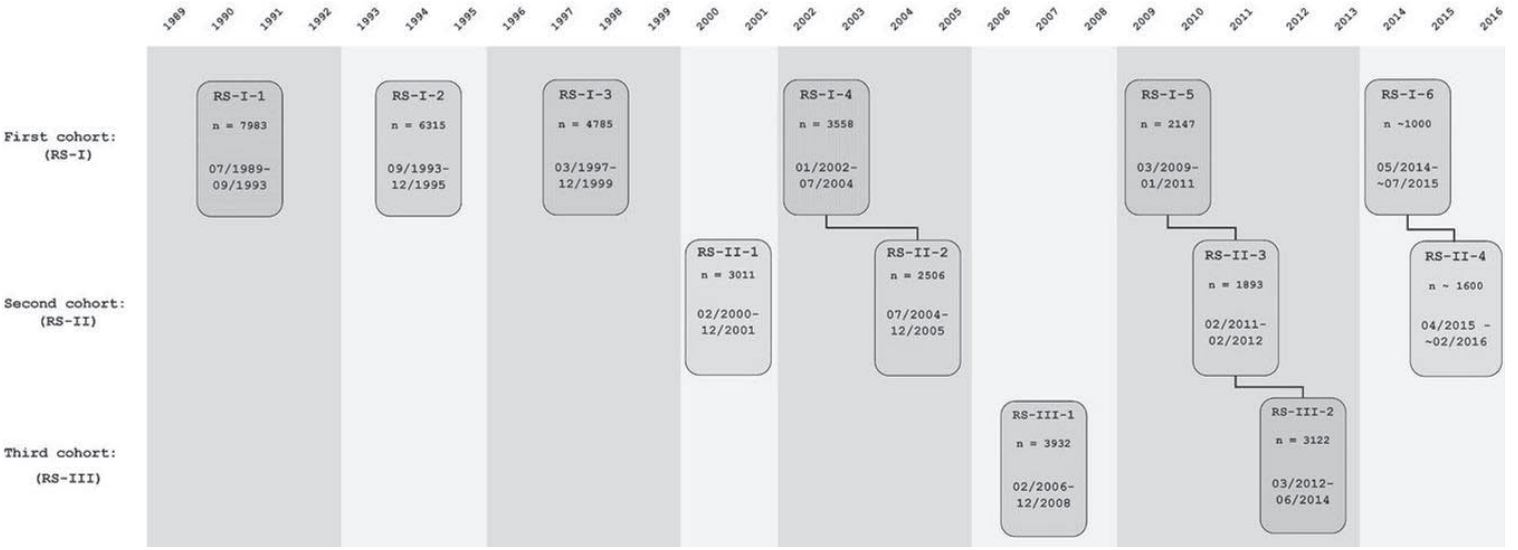
Over the last 6 decades population science has evolved from small case-control studies to prospective population-based cohort studies, and more recently to "mega cohorts" where data from multiple cohort studies are pooled.[13, 14] Different study designs have different strengths and weaknesses, which are clearly brought to light when results on similar research questions – answered using these different study designs – are directly compared. In *Chapter 4* reasons for widely varying estimates on lifetime risk of CVD and risk of death from cardiovascular causes obtained in the Rotterdam Study and the British QResearch administrative database are discussed.

Part II – Methodological considerations in quantifying improvements in risk stratification

The first ever risk estimation tools in the field of CVD originate from the original publications of the Framingham Heart Study [11] and comprised of graphs and cross-tabulations of systolic blood pressure and total cholesterol levels with subsequent 6-year risk of coronary heart disease (CHD). Ever since, risk stratification tools have become more and more sophisticated, nowadays being released with online calculators (e.g. https://www.framinghamheartstudy.org/risk-functions/index.php) and companion applications for mobile devices (e.g. https://itunes.apple.com/us/app/ascvd-risk-estimator/id808875968). Nowadays, the majority of risk stratification tools in clinical practice rely on traditional CVD risk factors, including age, sex, blood pressure, cholesterol levels, smoking, and diabetes mellitus. These CVD risk prediction models provide reasonable precision for a group, but uncertainty about any individual patient's true risk as estimated by these models remains.[15] Therefore, in order to improve CVD risk estimations, a plethora of newer risk factors and high-risk indicators have been proposed (including in *Chapters 13* through *15* of this thesis).

A key challenge of this field of research is how to quantify the improvements in risk estimation obtained by adding a new marker. Well-known model parameters of discrimination (i.e. the ability to distinguish individuals who will go on to have an event from those who will not) and calibration (i.e. the agreement between predicted and observed risk in groups of individuals) are of limited clinical relevance when risk thresholds are in place to guide clinical decision making as is the case in the field of primary prevention of CVD.[8-10]

Figure 1.1 – Diagram of the design of the Rotterdam Study



RS-I-1 refers to the baseline examination of the original cohort (pilot phase from July 1989 to December 1989; recruitment from January 1990 to September 1993). RS-I-2, RS-I-3, RS-I-4, RS-I-5, and RS-I-6 refer to re-examinations of the original cohort. RS-II-1 refers to the baseline examination of persons in the study district that became 55 years since the start of the study or those of 55 years or over that migrated into the study district. RS-II-2, RS-II-3, and RS-II-4 refer to re-examinations of the extension cohort. RS-III-1 refers to the baseline examination of persons aged 45 years and over living in the study district that had not been examined already (i.e. mainly comprising those aged 45 to 60 years). RS-III-2 refers to the first re-examination of this third cohort. Examination RS-I-4 and RS-II-2 were conducted as one project and feature an identical research program. Similarly, examinations RS-I-5, RS-II-3, and RS-III-2 share the same program. Examinations RS-I-6 and RS-II-4 also feature identical in program. RS = Rotterdam Study.

Part II of this thesis focusses on a relatively novel statistical method to quantify improvements in risk stratification in the presence of one or more clinically meaningful risk thresholds. This method, net reclassification improvement (NRI), summarizes changes in risk classification when comparing 2 methods to categorize individuals in different risk strata.[16, 17] Generally, NRI is used to compare a more parsimonious prediction model to a model that includes a new maker under study.

Chapter 5 of this thesis is an overview of practical applications of NRI in research published in top-medical journals which highlights a number of challenges and limitations of NRI. These may be clear to the statisticians who use NRI in daily practice but are less clear to clinicians writing, reviewing or reading articles that make use of this method. Hence, we aimed to construct an educational part on NRI specifically for clinicians with examples from the literature and clear clinical applications.

Specific challenges and pitfalls in the use of NRI are discussed in the subsequent chapters. *Chapter 6* delineates how NRI incorporates an implicit weighing factor for the frequency of occurrence of the studied outcome. *Chapter 7* contains a discussion on the clinical and statistical importance of the placement of risk thresholds. *Chapter 8* provides an example of how the selection of the outcome under the study, in this instance CHD versus a broader CVD outcome, can influence the estimates and subsequent interpretation of NRI for a newer risk marker. Finally, *Chapter 9* of this thesis highlights the role of model calibration on the interpretation of NRI.

Part III – Quantifying the burden of cardiovascular disease

CVD has been ever present in the 4000 year history of human kind.[18] In fact cardiac symptoms were common enough to be mentioned in ancient writings, dating as far back as 1550 BCE: "If thou examinst a man for illness in his cardia, and he has pains in his arms, in his breast and on one side of his cardia … it is death threatening him".[19] Yet, the burden of CVD on society has varied greatly over time with a sharp rise in incidence and mortality in the first half of the 20th century and a marked decline afterwards, following major advancements in treatment and prevention of CVD.[20] In order to identify further opportunities for CVD prevention and allocation of adequate resources to do so, it is important to have insight into the actual contemporary burden of CVD.[21]

Chapter 10 is an up-to-date compilation of quantitative data on incidence, prevalence, mortality, and interventions related to heart disease in the Netherlands, including temporal trends.

Most data on the occurrence of CVD are expressed as 10-year cumulative incidences or age-specific incidence rates. However, preventive strategies generally aim to reduce long-term risk of CVD and pharmacological treatment to reduce blood pressure and LDL cholesterol is prescribed for indefinite periods of time. Therefore, it is of interest to both patients and clinicians to quantify risk over longer periods of time or even over a lifetime. Attempts to estimates such parameters have traditionally been hampered by the amount of follow-up in studies, as well as computational challenges on how to adjust for informative censoring due to competing non-cardiovascular causes of death in older individuals. In *Chapter 11* of this thesis

the lifetime risk of CVD and the distribution of its first manifestations are presented for men and women from the Rotterdam Study. This novel approach allows for unique opportunities to study the relative contribution of various types of CVD (i.e. CHD, cerebrovascular disease, and heart failure) among the sexes, which may have bearing on prioritizing specific preventive efforts in men and women.

Part IV – Improving cardiovascular risk stratification

Optimal prevention of CVD starts with identifying those who are most likely to benefit from it. In *Chapter 12* of this thesis we present the implications for recommendations on cholesterol-lowering therapy from current European [8] and American [9] prevention guidelines on a contemporary population sample, free of CVD, from the Rotterdam Study.

Over the past 30 years many new risk indicators for CVD have been proposed, including markers of blood coagulation, inflammation, and renal function, as well as parameters related to the extent of subclinical atherosclerosis. Most research has focused on the contribution of single markers, but seldom research aimed to compare the contribution of multiple putative markers that might improve CVD risk estimation in a primary prevention setting. In *Chapter 13* a total of 12 newer risk markers for CHD risk prediction are evaluated within the framework of the Rotterdam Study. These blood biomarkers represent a variety of processes contributing to atherosclerosis and atherothrombosis, or come from non-invasive measurements that quantify the extent of accrued subclinical vascular damage. Both improvements in traditional model performance parameters and NRI were used to compare the markers.

Commonly used CVD risk prediction models focus on hard atherosclerotic end points such as CHD mortality, myocardial infarction, and stroke. When evaluating the cost-effectiveness of newer candidate CVD risk markers for clinical practice, it is important to consider other costly CVD outcomes, such as heart failure, that could be prevented with the measurement of these candidate markers. Since heart failure is predominantly attributed to coronary atherosclerosis in older individuals,[22] it is of importance to evaluate whether markers of subclinical atherosclerosis can improve heart failure risk prediction. One of the most promising risk indicators to improve CVD risk prediction is the coronary artery calcification (CAC) score, obtained from non-contrast computed tomography (CT). *Chapter 14* contains data on the ability of the CAC score to predict future heart failure in individuals free of overt CHD from the Rotterdam Study. Again, both improvements in traditional model performance parameters and NRI are presented.

Life expectancy has been increasing at a steady pace for nearly 2 centuries.[23] Not only do we live longer, but we also live healthier lives with frailty, sickness, and disability increasingly confined to the final stages of life.[3] As a consequence, cardiology patients nowadays are typically older individuals with specific needs associated with advancing age.[24] These demographic changes have implications for CVD prevention, as traditionally cardiovascular risk calculators have been developed for individuals of middle age. However, the aging of the population creates a group of healthy elderly individuals, who have been promoted as candidates for primary prevention of CVD.[25, 26] CVD prediction models for elderly persons should take into account, that with growing age and frailty, clinical CVD may be precluded by death from competing non-cardiovascular causes.

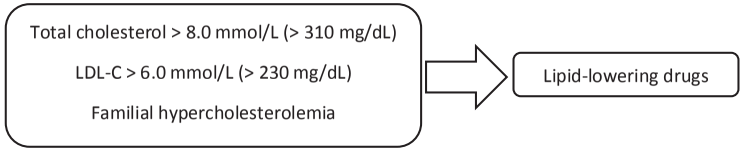
Chapter 15 describes the development and transatlantic validation of the coronary risk in the elderly (CORE) model, a CHD prediction model tailored to older populations. The CORE model is based on data from participants aged 65 years and older from the Rotterdam Study and the Cardiovascular Health Study. Competing risks regression methodology was used throughout in order to account for risks of non-coronary causes of death. The risk estimates from the CORE model were compared to those from the Adult Treatment Panel III (ATP III) model underlying the previous iteration of the American cholesterol treatment guidelines.[27] Moreover, since the predictive ability of traditional cardiovascular risk factors declines with advancing age,[28-30] we aimed to evaluate the added value of easily available newer CVD risk markers in this elderly population. In line with the other chapters of this part of the thesis, both traditional model parameters and NRI are presented.

Part V – General discussion and summary

In *Chapter 16* general methodological considerations on the research described in this thesis are discussed, as well as future perspectives and challenges for risk-based strategies in primary prevention of CVD. In particular, two items are discussed in debt. First, the opportunities for a transition from traditional 10-year risk estimates to lifetime risk perspectives. And second, the dominant role of age in cardiovascular risk calculators and alternative treatment allocation strategies.

Appendix

Appendix Figure 1.1 – Summary of the treatment recommendations for primary prevention of cardiovascular disease, based on the European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice (version 2012) [8]



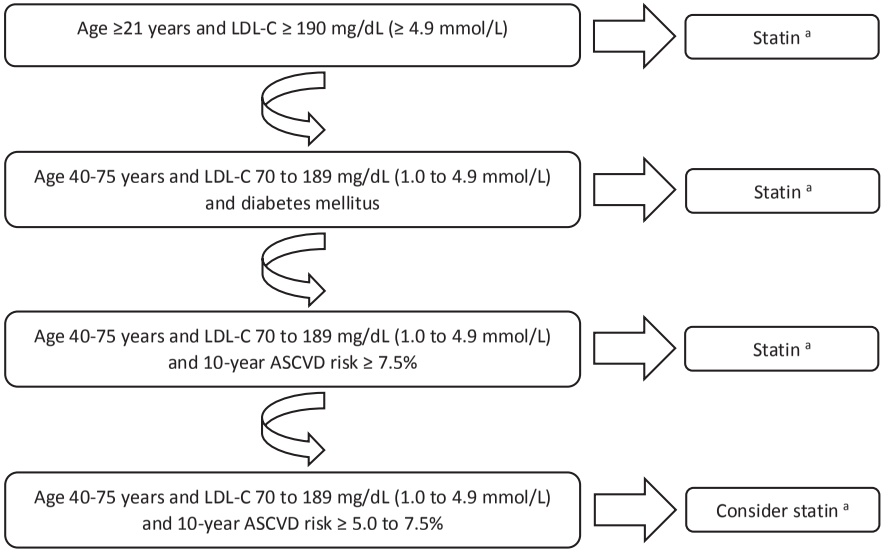
Men age ≥ 40 years and women age ≥ 50 years or postmenopausal					
	LDL-C level				
Cardiovascular risk (10-year SCORE)	< 1.8 mmol/L (< 70 mg/dL)	1.8 to < 2.5 mmol/L (70 to < 100 mg/dL)	2.5 to < 4.0 mmol/L (100 to < 155 mg/dL)	4.0 to < 4.9 mmol/L (155 to < 190 mg/dL)	≥ 4.9 mmol/L (≥ 190 mg/dL)
< 1%	No intervention	No intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drugs if uncontrolled
1 to < 5%	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drugs if uncontrolled	Lifestyle intervention, consider drugs if uncontrolled	Lifestyle intervention, consider drugs if uncontrolled
5 to < 10%, or high risk [a]	Lifestyle intervention, consider drugs	Lifestyle intervention, consider drugs	Lifestyle intervention and immediate drugs	Lifestyle intervention and immediate drugs	Lifestyle intervention and immediate drugs
≥ 10%, or very high risk [b]	Lifestyle intervention, consider drugs	Lifestyle intervention and immediate drugs	Lifestyle intervention and immediate drugs	Lifestyle intervention and immediate drugs	Lifestyle intervention and immediate drugs

LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic COronary Risk Estimation.

[a] High risk features: diabetes mellitus with optimal risk factors and no target organ damage; chronic kidney disease stage 3 (estimated glomerular filtration rate 30-59 mL/min/1.73 m^2); markedly elevated single risk factor (e.g. severe hypertension).

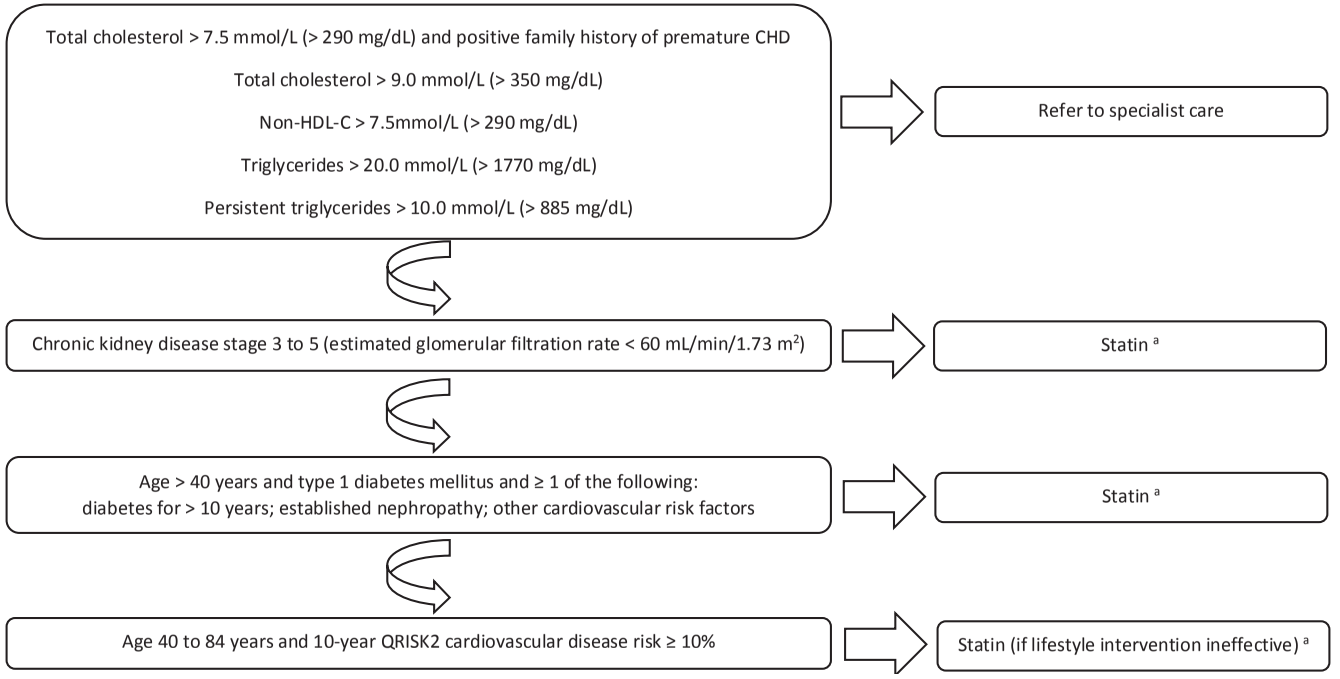
[b] Very high risk features: diabetes mellitus with one or more risk factor and/or target organ damage (e.g. microalbuminuria); chronic kidney disease stages 4 and 5 (estimated glomerular filtration rate < 30 mL/min/1.73 m^2).

Appendix Figure 1.2 – Summary of the treatment recommendations for primary prevention of cardiovascular disease, based on the 2013 American College of Cardiology/American Heart Association guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults [9]



ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.
[a] For detailed recommendations on dosing of statins for the various indications refer to the guideline document.[9]

Appendix Figure 1.3 – Summary of the treatment recommendations for primary prevention of cardiovascular disease, based on the NICE guidance on lipid modification and cardiovascular risk assessment for prevention of cardiovascular disease [10]

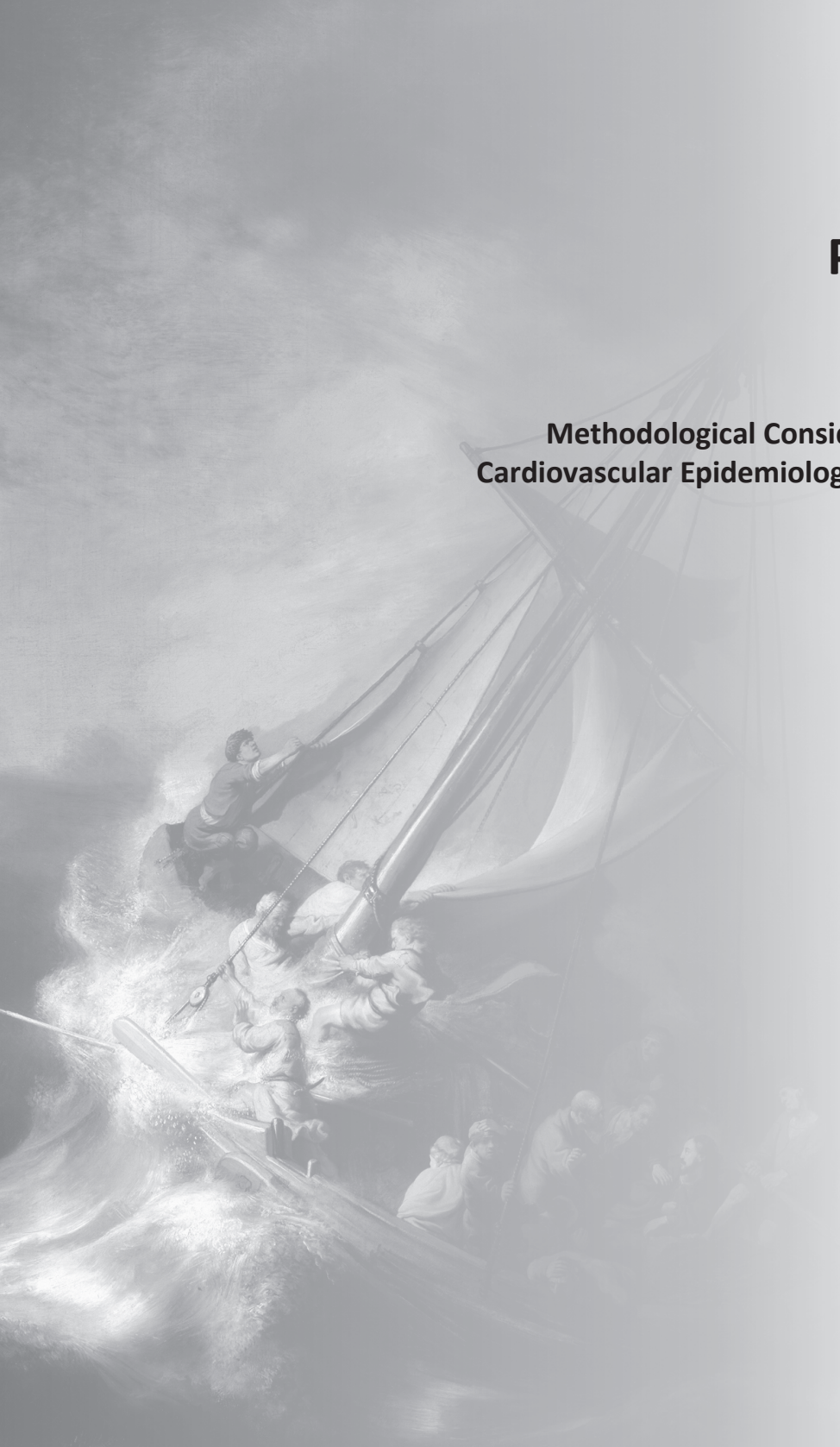


CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol.

[a] For detailed recommendations on dosing of statins for the various indications refer to the guideline document.[10]

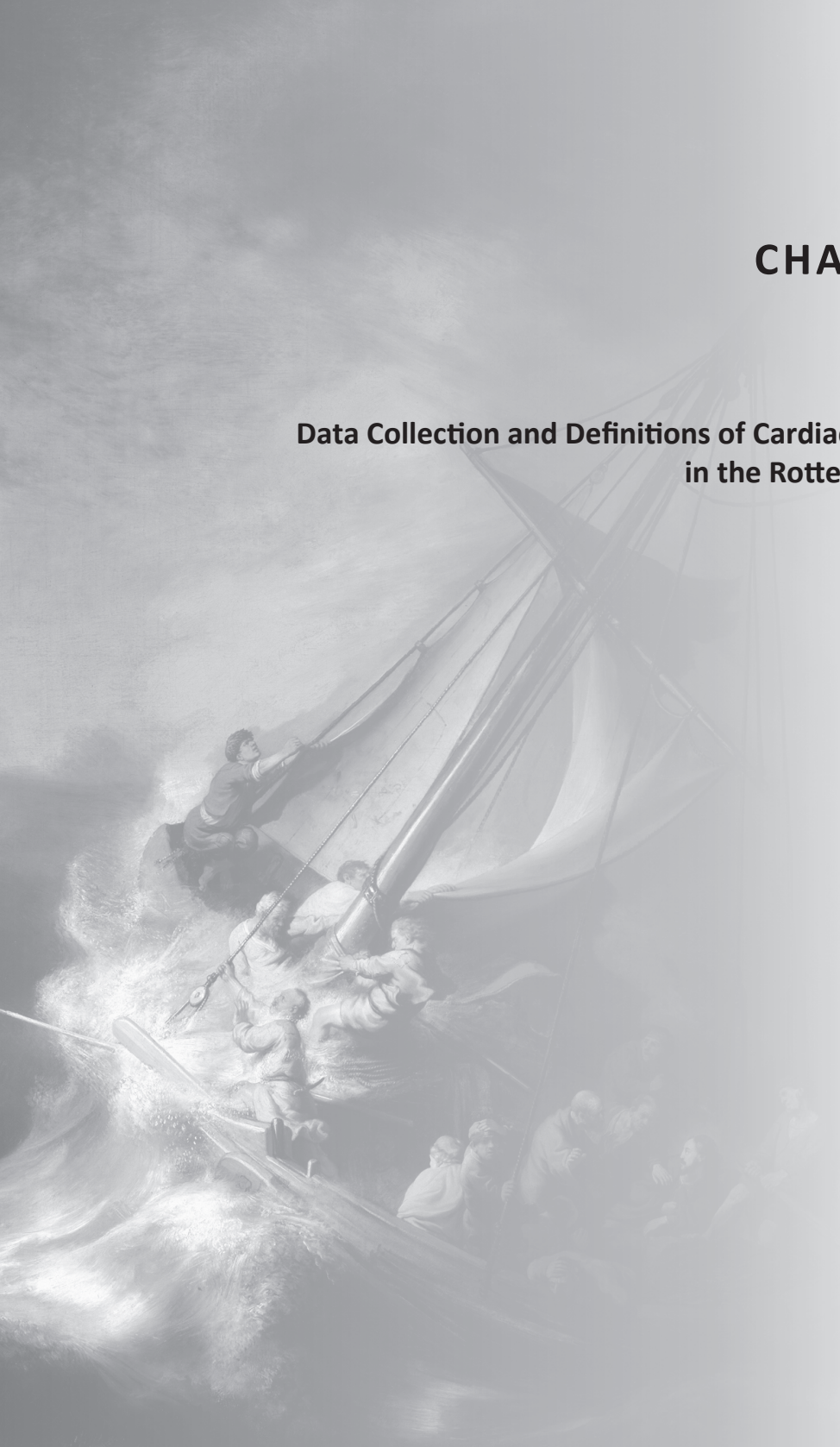
There is sometimes a tendency to regard an experiment as providing the higher form of evidence. This seems completely unrealistic. Certainly the classic experiment is a powerful tool for investigation, but it can be neither designed nor interpreted except by reference to observed unmanipulated reality. The community study provides this kind of reference for the investigation of chronic diseases in human populations.

- Tavia Gordon (1917 – 2004)
Some methodological problems in the long-term study of cardiovascular disease: observations on the Framingham Study.
J Chron Dis 1959;10(3):186-206



PART I

Methodological Considerations in Cardiovascular Epidemiologic Research



CHAPTER 2

Data Collection and Definitions of Cardiac Outcomes in the Rotterdam Study

The prevalence of cardiovascular diseases is rising. Therefore, adequate risk prediction and identification of its determinants is increasingly important. The Rotterdam Study is a prospective population-based cohort study ongoing since 1990 in the city of Rotterdam, the Netherlands. One of the main targets of the Rotterdam Study is to identify the determinants and prognosis of cardiovascular diseases. Case finding in epidemiologic studies is strongly depending on various sources of follow-up and clear outcome definitions. The sources used for collection of data in the Rotterdam Study are diverse and the definitions of outcomes in the Rotterdam Study have changed due to the introduction of novel diagnostics and therapeutic interventions. This chapter gives the methods for data collection and the up-to-date definitions of the cardiac outcomes based on international guidelines, including the recently adopted cardiovascular disease mortality definitions. In all, detailed description of cardiac outcome definitions enhances the possibility to make comparisons with other studies in the field of cardiovascular research and may increase the strength of collaborations.

Despite major advances in prevention and treatment, the prevalence of cardiovascular diseases (CVD) is rising.[21, 31] Nowadays, the majority of healthy adults will be confronted with some form of CVD during their lifetime and still heart disease is the leading cause of death in the western world, claiming approximately 1 out of every 5 lives.[31] Therefore, the continued search for determinants and predictors of occurrence and prognosis of CVD is of paramount importance.

The Rotterdam Study is a prospective population-based cohort study ongoing since 1990 in a suburb of the city of Rotterdam, the Netherlands. The original cohort comprised of 7983 inhabitants, aged 55 years or older and living in the well-defined Ommoord city district. The participants undergo repeated extensive examinations every 3-4 years at the Rotterdam Study research center, located in the middle of the study area. They are followed for a variety of diseases that are frequent in the general population. At initiation, the study focused on cardiovascular, neurological, ophthalmological, and endocrine diseases. The rationale and design of the Rotterdam Study have been described extensively 2 decades ago.[32] However, over the years the original cohort has been extended twice, the scope has been broadened, and the characteristics of repeated examinations have changed. As of December 2008, 14,926 individuals aged 45 years or over comprise the Rotterdam Study cohort (Figure 1.1). Therefore, its objectives and design have been updated regularly.[33-38] Parallel to extensions in the design of the Rotterdam Study, medical technology has advanced and clinical presentation of heart disease is evolving.

Within the Rotterdam Study, multiple cardiac outcomes are considered, namely recognized and unrecognized myocardial infarction (MI), myocardial revascularization, coronary heart disease (CHD) mortality, heart failure, atrial fibrillation (AF), and sudden cardiac death (SCD). The sources used for collecting the data are diverse and up until now their corresponding methods and the definitions of various cardiac outcomes in the Rotterdam Study have not been reported combined together in an overview. Furthermore, implementation of novel diagnostics and therapeutic interventions in everyday cardiac care has urged us to change definitions since our earliest reports on prevalence and incidence of MI and CHD.[39-41] Above all, in today's era of large transatlantic collaborations in epidemiologic research comparability of outcome definitions has gained importance.[14, 42] In this chapter the methods of data collection and up-to-date definitions of the cardiac outcomes in the Rotterdam Study will be presented.

Methods of data collection

Dutch health care system

In order to understand the methods of data collection used in the Rotterdam Study a brief introduction into the Dutch health care system is essential. Primary care, provided by general practitioners (GPs), plays a central role in the health care in the Netherlands. In the Netherlands there are almost 11,000 practicing GPs, who each have had 3 years of specialist training in family medicine. All Dutch inhabitants can register at a single general practice of choice. The GPs act as the gatekeepers to hospital care and must give their approval before patients can get referred to a medical specialist. In doing so, the vast majority of problems presented in primary care are handled by the GPs themselves.[43]

For decades, emergency and after-hours care is handled by primary care cooperatives. In order to provide adequate after-hours care, full electronic exchange of patient data is of great importance. Therefore, virtually all GPs in the Netherlands use computer-based GP information systems based on requirements set by the professional organizations of Dutch general practice (Dutch GP Society [NHG] and Nationwide Association of GPs [LVH]). These computer systems have been designed specifically for use in primary care and consist of a set of specific modules (e.g. medical, electronic communication, prescription, financial).Using the digital systems, all encounters in primary practice are coded using the International Classification of Primary Care (ICPC).[44, 45] As discussed above, Dutch GPs have a coordinating role in the overall health care utilization process of their patients enlisted. They refer their patients to medical specialists and are reported back on every hospital admission and results from outpatient contacts with medical specialists, preferably using electronic communication.[46] Further details on the structure of the health care system in the Netherlands and the use of electronic medical records have been described in detail.[43, 47-50]

With regards to concerns of general accessibility to medical care in the Netherlands, insurance status is not allowed to be considered in referral of patients. Cardiac hospital care, including invasive procedures, is covered by the basic health care insurance plan in the Netherlands, which is obligatory by law.[47, 48]

Assessment of cardiovascular disease status at baseline

Upon entrance in the Rotterdam Study cohort, baseline CVD status of each participant is ascertained in the following way. During a baseline home interview, trained non-medical interviewers administer a standardized questionnaire to obtain information on medical history (e.g. MI, myocardial revascularization) and health status (e.g. chest discomfort, breathlessness), and labels of current medication are copied (both prescription and over-the-counter usage). Medication use is coded according to the Anatomical Therapeutic Chemical (ATC) classification index.[51] Questions on indication of cardiovascular medication and breathlessness were lacking at the start of the Rotterdam Study, but have subsequently been added. Consequently, these questions were asked in most (70%) of the participants at baseline of the original Rotterdam Study cohort (RS-I-1; Figure 1.1). After the interview, the participants are invited to visit the research center where they undergo a physical examination in some detail by one of the

study physicians and various tests are performed (e.g. resting electrocardiogram [ECG], echocardiography). In addition to these examinations, information on prevalent disease status is obtained by accessing data from the Nationwide Medical Registry (Dutch Hospital Data [LMR], Utrecht, the Netherlands). This is a national registration on all primary and secondary hospital discharge diagnoses of Dutch inhabitants, with linkage on the basis of zip code, date of birth, sex, and GP. Records from this registry are linked to the study database. For potential events identified in this registry, copies of hospital discharge letters and ECGs are requested. Most importantly, clinical information on prevalent CVD status is obtained from the GPs for each participant: the entire medical records of the GPs are hand screened at the GPs' office by trained research assistants. Using the aforementioned sources (interview, examination at the research center, Nationwide Medical Registry, and full screening of GPs' records), disease status at baseline is available for all participants of the Rotterdam Study. An overview of the sources used for ascertaining disease status at baseline is presented in Table 2.1.

Clinical follow-up

Follow-up starts after the baseline home interview of each individual participant. Data on clinical cardiovascular outcomes are collected continuously through an automated follow-up system. The follow-up system involves automated digital linkage of the study database to digital files from GPs in the study area. On a weekly basis, all ICPC codes of diagnoses of interest made by the GPs and medical specialists in study participants are entered to the Rotterdam Study database. Moreover, the entire medical record of each participant living in the research area is checked by hand on a regular basis at the GPs' office by trained research assistants for diagnoses of interest. This is the primary source of information on CVD events, since all letters of medical specialists, discharge reports in case of hospitalization, and ECGs are copied by the research assistants. Subsequently, all the collected information is compared to the ICPC codes entered to the study database for each individual participant. This is done in order to make sure no clinical information on potential events is missed out. Additional information is obtained from the hospitals in case the automated follow-up system or medical records contain insufficient information. Medical records of the participants under the care of nursing home physicians or GPs working outside the study area are checked annually for potential events. Furthermore, before every repeat examination the participants are interviewed on the occurrence of cardiac events since their last visit to the research center.

With respect to the vital status of all participants, information is obtained on a weekly basis from the central registry of the municipality in Rotterdam and through the digital linkage with GPs working in the study area. For participants living outside the research area, the GPs are the primary source of information, complemented by the municipality records in the place of residence. After notification, cause and circumstances of death are established by requesting information from the medical records of the GPs or nursing home physicians.

As of January 1991 onwards all drug prescriptions dispensed to participants by 7 fully automated pharmacies in the study area are routinely stored in the database. At baseline, nearly all (99.7%) participants were registered at 1 of these pharmacies. This data consists of information on the date of delivery, the total amount of drug units per prescription, the prescribed daily number of units, product name of the drugs, and the ATC code.[51, 52]

Table 2.1 provides an overview of the sources used for obtaining information on the occurrence of cardiac outcomes during follow-up.

Table 2.1 – Sources of data in the Rotterdam Study

Source	Data obtained on disease status at study baseline	Data obtained on occurrence of outcomes during follow-up
Regular checks of medical records at the GPs' office	Full medical history	Intercurrent medical history
	Hospital discharge letters	Intercurrent hospital discharge letters
	Reports on outpatient contacts with medical specialists	Intercurrent reports on outpatient contacts with medical specialists
	Previous ECGs	Intercurrent ECGs
		Cause and circumstances of death
Continuous linkage of the study database with GPs' digital files		ICPC codes of all diagnoses made
		Date of death
Home interviews	Medical history	Intercurrent medical history
	Current health status	Current health status
	Current medication use	Current medication use
Research center visits	Resting ECG	Resting ECG
	Physical examination	
Pharmacy prescription records	Current medication use	Continous monitoring of all presciptions filled
Nationwide Medical Registry (LMR)	History of hospital discharge diagnoses for any outcome of interest	Intercurrent hospitalization with AF or atrial flutter
Municipality records		Date and place of death
Hospitals	Hospital discharge letters	Hospital discharge letters
	Previous ECGs	Intercurrent ECGs

GP = general practitioner; ECG = electrocardiogram; ICPC = International Classification of Primary Care; AF = atrial fibrillation.

Electrocardiography

At baseline and at each follow-up visit to the research center, every participant has a 10 s 12-lead resting ECG (on average 8-10 beats) recorded using an ACTA Gnosis IV ECG recorder (Esaote Biomedica, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. All ECGs are processed by the standardized Modular ECG Analysis System (MEANS) to obtain ECG

measurements and interpretation. The ECGs are analyzed off-line using MEANS. The MEANS program has been evaluated extensively and determines common onsets and offsets for all 12 leads together on 1 representative averaged beat, with the use of template matching techniques.[53-57]

Event adjudication

For each outcome 2 cardiovascular research physicians independently classify information on occurrence, certainty, and date of onset of all data collected on potential events according to the corresponding definitions below. Cases on which the research physicians disagree are discussed in order to reach consensus in a separate session. Afterwards, a panel of medical specialists in CVD reviews potential events for each diagnosis separately. This panel consists of a cardiologist, 2 geriatricians, and a GP experienced in cardiac disease. The medical specialist's judgment is considered decisive. The research physicians and the medical specialists base their decisions on the same data. This procedure is similar for both prevalent and incident outcomes.

Definitions of cardiac outcomes

Within the Rotterdam Study 8 highly prevalent cardiac outcomes are considered subdivided into 3 categories, namely CHD, heart failure, and cardiac arrhythmias (Table 2.2).

Table 2.2 – Cardiac outcomes in the Rotterdam Study

Categories	Underlying outcomes
Coronary heart disease	MI
	Unrecognized MI
	Myocardial revascularization
	CHD mortality
	Overall CHD
Heart failure	Heart failure
Cardiac arrhythmia	Atrial fibrillation and atrial flutter
	Sudden cardiac death

MI = myocardial infarction; CHD = coronary heart disease.

Coronary heart disease

Myocardial infarction

The triad of chest pain, ECG abnormalities, and rise of cardiac enzymes has been a generally accepted definition of acute MI for many years. However, during the past decades development of more sensitive and specific blood markers (e.g. creatinin kinase MB, troponins) and enhanced imaging techniques allow for detection of smaller MIs. Widespread introduction of troponin testing in the Netherlands happened around the turn of the century and took several years to be fully implemented in the hospitals in the research area.[58] This has had implications for adjudication of MIs in the Rotterdam Study. Accordingly, clinical practice, as well as epidemiologic research required a more precise definition of MI.[59]

Methods on follow-up and event adjudication of prevalent and incident MI for the Rotterdam Study have been described previously in brief.[60] The diagnosis of MI is classified as definite, probable, possible or unlikely. Definite MI is defined as pathology findings of an acute MI within 28 days of death, or a rise/fall in cardiac biomarkers and/or objective indicative ECG changes, and preferably the presence of symptoms or signs (e.g. cardiac pain, cardiogenic shock). Also, for definite MI, the diagnosis has to have been made by a medical specialist, preferably a cardiologist or an internist. If the MI was diagnosed by a GP or a nursing home physician it is classified as probable. MI is classified as possible when 1 of the criteria for probable or definite MI cannot be met. MI is considered unlikely if symptoms or signs are present, but objective evidence showing myocardial necrosis is lacking. Accordingly, diagnoses of unstable angina, acute coronary syndromes, and invasive procedure related ischemia are also considered as MI events whenever they are accompanied by a significant rise in cardiac biomarkers. Thereby, the current definition of MI in the Rotterdam Study includes the clinical type 1, 2, 4a, 4b, and type 5 MI as defined in the endorsed universal definition of MI.[59] In accordance with the international epidemiologic CHD case definitions, only definite and probable cases are included in the Rotterdam Study definition, unless otherwise noted.[61] For participants of the original Rotterdam Study cohort, the presence of MI at baseline (RS-I-1; Figure 1.1) is based on verification of either self-reported MI or ECG abnormalities indicative of prior MI. In subsequent cohorts, the medical records of all participants are screened for prevalent MI, regardless of their self-reported history or ECG abnormalities. The presence of MI during follow-up is based on clinical information from the medical records. The date of incident MI is defined as the day of the first occurrence of symptoms suggestive of MI.

Unrecognized myocardial infarction

Unrecognized MI, although prevalent, is not always considered as an outcome in epidemiologic studies on CHD, since determining an exact date of occurrence of the MI is impossible by definition.[60] Therefore, unrecognized MI is not included as an outcome in studies on the occurrence of CHD in the Rotterdam Study, unless otherwise noted. However, separate studies within the framework of the Rotterdam Study have been conducted on the prognosis of this type of presentation of CHD.[62-64]

Methods on definition of prevalent and incident unrecognized MI within the Rotterdam Study have been summarized previously.[60, 64] This definition is in accordance with the criteria for 'prior MI' (type 3) defined by the international Task Force for the Redefinition of MI, as follows in detail.[59] At baseline of the Rotterdam Study all participants were asked whether they had ever experienced a heart attack and who established the diagnosis. Afterwards, an ECG was obtained and analyzed using MEANS as described above. To determine MI, MEANS uses a comprehensive set of criteria that partly derive from The Minnesota Code.[65, 66] Pathological Q-waves are central in the diagnosis of MI using MEANS, next to auxiliary criteria, such as QR-ratio and R-wave progression. A cardiologist with expertise in electrocardiography, whose judgment was considered final, reviewed all cases that were classified by MEANS as possible, probable, or definite MI. At baseline of the Rotterdam Study, unrecognized MI was considered to be present in all participants with confirmed ECG characteristics matching a MI, but without documented history or self-reported MI. An incident unrecognized MI is considered to have occurred if there is confirmed electrocardiographic evidence of MI on follow-up examinations at the research center, given the absence of an incident clinically recognized MI at baseline or during follow-up. The unrecognized MI is considered to have occurred in the middle of the time interval between the examination at which the unrecognized MI is detected and the examination before that.

Myocardial revascularization

Invasive myocardial revascularization is an established treatment for acute MI, relief of unstable angina, and medically intractable stable angina. Furthermore, patients with symptomatic or asymptomatic severe coronary artery disease benefit from myocardial revascularization by improving survival.[67] Especially during the past decade, a great number of novel and hybrid cardiac interventions, and other transcatheter interventions have been introduced.[67, 68]

Within the Rotterdam Study data is collected on incident coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCIs) for atherosclerotic CHD, separately. For PCI, previously termed percutaneous transluminal coronary angioplasty, the following interventions are considered: coronary stenting, coronary balloon angioplasty, coronary recanalization, intracoronary thrombosuction, and (although very rare) intracoronary laser and brachytherapy. CABG and PCI are also adjudicated for combined cardiopulmonary surgery and other combined or hybrid cardiac procedures.[67, 68] Any attempt of revascularization is adjudicated, regardless of success, given the indication is still present at the time of the attempt. For participants of the original Rotterdam Study cohort (RS-I-1; Figure 1.1), the presence of myocardial revascularization at baseline is based on self-reported CABG or PCI, verified by clinical data from the medical records. In subsequent cohorts, the medical records of all participants are screened for prevalent myocardial revascularization procedures, regardless of their self-reported history. The presence of CABG and PCI during follow-up is based on clinical information from the medical records. The date of incident myocardial revascularization is obtained from the hospital discharge letters.

As mentioned before, myocardial revascularization procedures are available to everyone in the Netherlands, regardless of insurance status. Myocardial revascularization is fully covered by the basic health care insurance in the Netherlands, which is obligatory by law.[47, 48]

Coronary heart disease mortality

Fatal CHD is often an unheralded presentation of presymptomatic coronary artery disease and is mainly attributed to sudden death, ischemic heart failure, and sequelae of a MI.[69] Originally, the CHD mortality definitions in the Rotterdam Study have been based on the International Classification of Diseases, tenth revision (ICD-10) codings.[70, 71] Recently, a classification used in other large cohort studies with specific focus on CVD has been adopted in order to improve the quality of the outcome data and enhance comparability with other epidemiologic studies. This system is a marginally adapted classification applied by both the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study.[72-75] From 2003 onward, this classification

Table 2.3 – Cardiovascular mortality classification and definitions for underlying cause of death

Mortality categories (hierarchical)		Underlying cause of death
1. Coronary heart disease	Definite fatal MI	No known non-atherosclerotic cause, and definite MI within 28 days of death
	Definite fatal CHD	No known non-atherosclerotic cause, and at least one of the following: cardiac pain within 72 h of death or a history of ischemic heart disease in the absence of significant valvular heart disease or non-ischemic cardiomyopathy
	Possible fatal CHD	No known non-atherosclerotic cause, and mode of death consistent with CHD in the absence of significant valvular heart disease or non-ischemic cardiomyopathy
2. Cerebrovascular disease		Non-traumatic intracerebral hemorrhage or infarction
3. Other atherosclerotic disease		Atherosclerotic disease other than CHD or cerebrovascular disease (including ruptured abdominal aortic aneurysm, peripheral vascular disease, and visceral vascular disease)
4. Other cardiovascular disease		CVD other than 1-3 (including valvular heart disease, non-ischemic cardiomyopathy, endocarditis, hypertensive renal disease, pulmonary embolism, ruptured thoracic aortic aneurysm, and complications from cardiovascular interventions other than 1-3)
5. Noncardiovascular disease		All other causes of death other than 1-4 (including natural, due to trauma, suicide, and death of unknown or uncertain cause)

MI = myocardial infarction; CHD = coronary heart disease; CVD = cardiovascular disease.

has served as a basis for the endorsed international case definition for out-of-hospital CHD mortality in epidemiologic studies.[61]

As a first step, all deaths (both cardiovascular and non-cardiovascular) in the Rotterdam Study are adjudicated based on ICD-10 codes. Subsequently, all available clinical information for each potential new fatal CHD and CVD case is reviewed by the research physicians in order to ascertain the underlying cause of death and adjudicate a CHD or CVD mortality category. The underlying definitions for the CHD and CVD mortality categories are presented in Table 2.3. CVD mortality is subdivided into the following hierarchical categories: CHD (definite fatal MI, definite fatal CHD, and possible fatal CHD), non-traumatic cerebrovascular disease, other atherosclerotic disease, and other CVD. Within the Rotterdam Study, none of the deaths are classified as due to heart failure. The classification system used in the Rotterdam Study focuses on the underlying etiology, rather than the mode of death: i.e. participants dying with decompensated heart failure are mostly classified as deaths being from CHD or valvular heart disease. In rare cases where no possible underlying etiology of heart failure can be established from the medical records, these deaths are classified as being from other CVD. The date of death is established from the medical records or municipality records.

Coronary heart disease

The many forms of presentation of CHD make up for many possibilities of combining these into an overall disease outcome. The definition of combined CHD outcomes may depend on the research question at hand.

Within the Rotterdam Study 2 different combined outcomes have been used as described previously.[70] First, 'total CHD' is defined as a combined outcome of myocardial revascularization (as a proxy for significant coronary artery disease), MI (fatal and nonfatal), and fatal CHD. Second, 'hard CHD' is defined as MI (fatal and nonfatal) and fatal CHD. Heart failure morbidity and unrecognized MI are not part of the combined CHD definitions, unless otherwise noted.

Heart failure

The presentation and etiology of heart failure is heterogeneous.[76] Strict case definition and diagnostic criteria for follow-up studies are therefore of utmost importance.

Methods on event adjudication of prevalent and incident heart failure for the Rotterdam Study have been described previously.[77, 78] The diagnosis of heart failure is classified as definite, probable, possible or unlikely. Definite heart failure is defined as a combination of the presence of typical symptoms or signs of heart failure, such as breathlessness at rest or during exertion, ankle edema, and pulmonary crepitations, confirmed by objective evidence of cardiac dysfunction (chest X-ray, echocardiography). This definition is in accordance with the criteria of the European Society of Cardiology (ESC).[76] Also, for definite heart failure, the diagnosis has to have been made by a medical specialist, preferably a cardiologist or an internist. Heart failure is classified as probable when at least 2 typical symptoms suggestive of heart failure are present, and at least 1 of the following: history of CVD (e.g. MI, valvular heart disease,

hypertension), positive response to initiated treatment for heart failure, or objective evidence of cardiac dysfunction, while symptoms cannot be attributed to another underlying disease, such as chronic obstructive pulmonary disease. Heart failure is classified as possible when 1 of the criteria for probable heart failure cannot be met. For both probable and possible heart failure, a diagnosis of a GP or a nursing home physician suffices. Heart failure is considered unlikely if symptoms or signs are present, but when objective evidence fails to show cardiac dysfunction, and if symptoms or signs can be attributed to another underlying disease. In accordance with the ESC guidelines, only definite and probable cases are used in the Rotterdam Study definition.[76] Inclusion of probable heart failure depends on the research question at hand and is detailed in the methods of the corresponding analyses. A participant is not considered as having heart failure, if heart failure occurs directly postoperative after cardiac surgery. For participants of the original Rotterdam Study cohort, the presence of heart failure at baseline (RS-I-1; Figure 1.1) is based on clinical information from the medical records for all participants and by using a validated score, similar to the definition of heart failure by the ESC.[76, 77, 79] In subsequent cohorts, the medical records of all participants are screened for prevalent heart failure. The presence of heart failure during follow-up is based on clinical information from the medical records. The date of incident heart failure is defined as the date of the first occurrence of symptoms suggestive of heart failure, obtained from the medical records, or the day of receipt of a first prescription for a loop diuretic or an ACE inhibitor, whichever comes first.

Cardiac arrhythmia

Atrial fibrillation and atrial flutter

AF and atrial flutter are the most common sustained cardiac arrhythmia and are well-known risk factors for stroke and mortality.[80] Within the Rotterdam Study both AF and atrial flutter are a single outcome and referred to as AF, given the likewise natural course.[81]

Methods on follow-up and event adjudication of prevalent and incident AF for the Rotterdam Study have been described previously.[80] In accordance with the ESC guidelines, an ECG that verifies the diagnosis for all potential cases of AF is required.[82] A participant is not considered as having AF, if AF occurs during the process of dying and is not the cause of death, or if transient AF occurs during a MI or directly postoperative after cardiopulmonary surgery. The presence of AF at baseline is based on clinical information from the medical records for all participants of the Rotterdam Study. Additionally, at baseline a resting ECG is obtained using the aforementioned methods and analyses software (MEANS). Notably, MEANS is characterized by a high sensitivity (96.6%) and a high specificity (99.5%) in coding arrhythmias.[56] To verify the diagnosis of AF, all ECGs with a diagnosis of AF or atrial flutter or any other rhythm disorder are recoded independently by 2 research physicians who are blinded to the MEANS diagnosis. The judgment of a cardiologist is asked and taken as decisive in case of persistent disagreement. The presence of AF during follow-up is based on ECG evidence from the medical records. Furthermore, cases of newly diagnosed AF are obtained during the follow-up examinations at the research center and by accessing the hospital discharge diagnoses data from the Nationwide Medical Registry. The date of incident AF is defined as the date of the first occurrence of symptoms suggestive of AF with subsequent ECG verification, obtained from the medical records. When diagnosed at the research center and no other information on a diagnosis of AF is available from either

the GPs' files and/or the Nationwide Medical Registry, the date of onset of AF is defined as the midpoint of the time interval between examination at which AF is detected and the previous examination at the research center.

Sudden cardiac death

The term SCD is commonly used for a mode of cardiac death. The clinical presentation of sudden cardiac death is frequently used as a surrogate implying that a specific mechanism is involved. The underlying etiology can be diverse, but most often results from tachyarrhythmia or mechanical complications of MI.[83] SCD is an outcome of special interest in studies on genetics, certain ECG parameters, and pharmacological adverse effects on the heart.[84-86]

During the past century there has been some debate on the definition of this clinical presentation of heart disease, however Myerburg's definition has been accepted and endorsed widely: "A natural death due to cardiac causes, heralded by abrupt loss of consciousness, within 1 h after the onset of acute symptoms or an unwitnessed, unexpected death of someone seen in a stable medical condition less than 24 h previously with no evidence of a non-cardiac cause."[83, 87]

Within the Rotterdam Study the methods of adjudicating SCD are based on the definition supported by the ESC and have been described previously.[83, 85] All available information from GPs and a copy of the medical records are used to assess if the death can be classified as a SCD using the aforementioned definition proposed by Myerburg.[83, 87] First, potential cases are subdivided on the basis whether the death is witnessed. If death is witnessed and occurs within 1 h after the start of symptoms (if present) it is assumed to be a SCD, without additional review of the medical records for a medical history of CVD. In case of an unwitnessed death, evidence of underlying cardiac or non-cardiac causes is searched for. Inclusion of unwitnessed SCD in the Rotterdam Study definition depends on the research question at hand. The date of death is established from the medical records or municipality records.

Discussion

Comparability

The necessity of research on the etiology and prognosis of heart disease has been obvious for many decades. This has resulted in countless epidemiologic studies with a focus on CHD or CVD at large. However, multiple, and sometimes inconsistent, definitions of cardiac outcomes are in use. For instance, the inclusion of stable or unstable angina pectoris, myocardial revascularization procedures, and specific subtypes of CHD mortality varies greatly in overall CHD outcome definitions. This may influence the conclusions drawn and impede the overall comparability of studies on CHD.

A substantial proportion of the CHD mortality occurs out-of-hospital.[69] Classification of out-of-hospital death is often based on limited information, due to its sudden onset or unwitnessed occurrence. Therefore, a clear coding system is of key importance. Various classifications by the World Health Organization (WHO), using data from death certificates, or self-developed

CHD mortality definitions are used in epidemiologic and clinical research. Within the Rotterdam Study, ICD-10 has been the classification of choice during the past decade for fatal and nonfatal events.[70, 71] However, the ICD-10 causes confusion when coding mortality. ICD-10 contains codes for both underlying disease (cause of death), as well as mechanisms and circumstances of dying (mode of death). For instance, cardiac arrest (code I46), heart failure (code I50), sudden death (code R96), and unattended death (code R98) could very well be attributed to CHD as to other conditions, depending on one's individual medical history. More recently, in order to avoid confusion and enhance comparability in our multiple large transatlantic collaborations with other epidemiologic studies, a classification used by other large cardiovascular cohort studies has been adopted by the Rotterdam Study.[14, 42, 88] As mentioned before, this classification has been proposed as the international standard for epidemiologic research.[61] As a consequence, harmonization of the outcome definitions used in our large epidemiologic collaborations will strengthen the consistency of future results. Furthermore, the categorization of the events as such helps to avoid inaccuracy in the immediate cause of death reporting, complicated by the presence of comorbid conditions, particularly in the elderly.[73] Therewith, this classification allows for more accurate adjudication of the cause of death by underlying etiology and result in less misclassification.

Variability

Insight into outcome definitions does not only facilitate comparability between studies, it may also explain variability between or even within studies. Reported incidences of CVD vary over different geographic areas and may reflect differences in presence of risk factors, active treatment, and differences in CVD susceptibility among populations. However, the differences may also be a result of differences in coding systems used or differences in clinical practice of adjudication of events.[89] In a recent report on the WHO Burden of Disease Program the incidence of fatal ischemic heart disease varied greatly. For instance, incidence of fatal ischemic heart disease was reported to be 54 per 100,000 in the Netherlands, and 98 per 100,000 in the U.S., accounting for 11.3% and 17.9% of the total mortality, respectively. Besides transatlantic differences, great dissimilarities among neighboring nations in Western Europe were observed. Incidences of fatal ischemic heart disease varied from 38 per 100,000 in France to 90 per 100,000 in both Germany and the United Kingdom.[90] Despite the fact that all countries applied the same WHO coding system for adjudication of the causes of death, such differences in incidences are unlikely to be fully explained just by variation in presence and management of cardiovascular risk factors. The precise cause of this variability remains uncertain.

Variability in incidences is also known to occur within the same study. It is well known that calendar time is a cause of variability in observed incidences of heart disease in a single study population due to changes in prevalence or treatment of risk factors, or introduction of novel sensitive diagnostics over time (e.g. creatinin kinase MB, troponins).[91] Furthermore, researchers may decide on including outcomes of various certainties (e.g. definite, probable). Depending on the research question at hand, more or less sensitive criteria may be applied in different analyses. Next, one should also be aware that a study population is of higher average health status at baseline of a study or shortly after an active repeat research center visit.[92] After all, those who attend in a visit to a research center are necessarily healthy enough to undergo the examinations.

Quality control

In the Netherlands, many studies on incidence and prognosis of heart disease rely on data provided by the Nationwide Medical Registry. This registry includes all discharge diagnoses for every hospital admission in the Netherlands and has shown a good sensitivity and good positive predictive value for acute CHD diagnoses, but less for chronic conditions such as heart failure.[93] Within the Rotterdam Study, a validation study for evaluating the clinical follow-up event registration of incident MI was performed. This was done by obtaining data on hospital discharge diagnoses in Rotterdam Study participants from the Nationwide Medical Registry. A total of 100 discharge diagnoses of MI were obtained from the registry. In 59 instances MI was the primary discharge diagnosis, and in 41 instances MI was mentioned as a secondary discharge diagnosis. These 100 hospitalized MIs were compared to incident events observed through our clinical follow-up system and this showed that none of the primary diagnoses were missed and only 2 of the secondary discharge diagnoses were not detected, resulting in a 98% case finding of hospitalized MIs in our study population.

Strengths and limitations

Within the Rotterdam Study we have over 2 decades of experience in data collection. It is known that use of various sources for data collection is needed to achieve complete follow-up in large epidemiologic studies.[94] Within the Rotterdam Study, multiple sources for potential events are consulted, namely the linkage of the medical records and pharmacy data to the study database, regular screening of medical records at the GPs' office, follow-up interviews and examination at the research center, and consultation of the central registry of the local municipality (Table 2.1). The Rotterdam Study thereby has a virtually complete follow-up with respect to vital status: using the sources described above, exactly 22 years after start of the study, less than 1.8% of the participants have been lost to follow-up. This is predominantly due to emigration.

At initiation of the Rotterdam Study most GPs in the research area were already using standardized digital patient records, resulting in over 85% of the enrolled participants having their medical record digitally linked to the study database.[50] Still, 22 years after initiation of the study, the great majority (79%) of all participants alive are enlisted with a GP with linkage to the automated follow-up system. This results in high quality documentation. Furthermore, the GPs in the research area have a low threshold to refer patients for community based laboratory testing and (exercise) ECGs. However, this does not fully apply to the participants living in nursing homes. Predominantly, the oldest of old and diseased participants are less likely to undergo diagnostic tests (e.g. ECG, echocardiography, cardiac biomarker testing), or to get referred to a medical specialist in comparison to elderly in other European countries.[95] This is usually due to lack of diagnostic accuracy of physical examination and reduced mobility of the nursing home residents.[96] Moreover, clinical benefit is uncertain and care for other comorbid conditions (such as Parkinson's disease or advanced dementia) is considered to take priority over performing diagnostic procedures outside the nursing home.[97, 98] In all, this may result in missing non-hospitalized nonfatal events in nursing home residents.

Although nowadays the typical cardiac patient is of old age, elderly persons are still highly underrepresented in cardiovascular research.[99, 100] The Rotterdam Study has no upper age limit

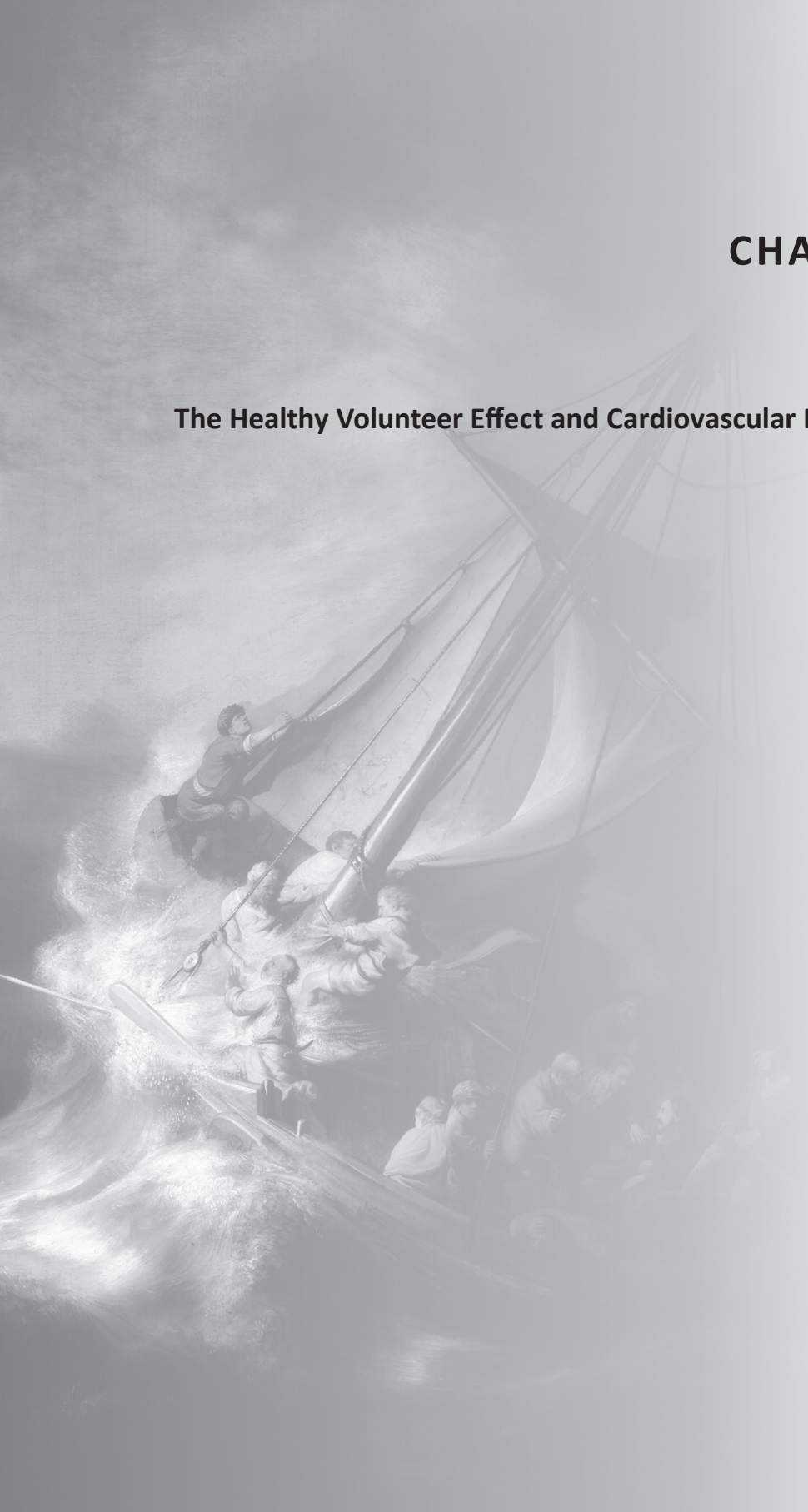
and can thereby study the determinants and outcomes of heart disease in older participants. This implies challenges in adjudication of diagnosis of especially chronic diseases (e.g. heart failure), which are associated with a wide range of comorbid conditions.[101, 102] Symptoms of other common disease in older individuals, such as chronic obstructive pulmonary disease and chronic venous insufficiency, can be easily misattributed to the failing heart. Strict case definitions are therefore insurmountable in order to prevent misadjudication, however this may result in missing some cases where limited information is available.

Conclusions

The need for studying occurrence and prognosis of heart disease is obvious. Case finding in epidemiologic studies is strongly depending on the availability of various sources of clinical follow-up and clear outcome definitions. The presentation of the up-to-date definitions of cardiac outcomes in epidemiologic studies will result in enhanced possibilities to compare results with other studies in the field of cardiovascular research and may increase the strength of future collaborations.

CHAPTER 3

The Healthy Volunteer Effect and Cardiovascular Disease Risk



Most cardiovascular risk prediction functions are developed using data from cohort studies. Invariably, a proportion of invitees will not participate in such studies because relatively good health status is required for a person to agree to undergo the examinations. This implies that persons enrolled in a study requiring active participation are healthier than those who declined to participate. It is thus unclear whether the cardiovascular risk distributions among study participants adequately reflect the risk distribution of the source population. We aimed to quantify the consequences of this 'healthy volunteer effect'.

Methods

Study design, setting, and population

The Rotterdam Study is a prospective population-based cohort study ongoing since 1990. The original cohort comprised of 7983 inhabitants living in a well-defined suburb in the city of Rotterdam, the Netherlands (RS-I). Using municipality data, all 10,215 inhabitants aged 55 years or over of the Ommoord district were invited to participate (overall participation rate 78%; age 55 to 59 participation rate 83%; age 90 years and older participation rate 71%).[103] No upper age limit was set and no exclusion criteria were defined. Over the past 2 decades, the participants have been invited to undergo repeated home interviews and examinations at the Rotterdam Study research center, located in the middle of the Ommoord district. The rationale and design of the Rotterdam Study have been described in detail elsewhere.[32-37]

We used response data from the third examination of the cohort (RS-I-3; Figure 1.1), conducted between 1997 and 1999 (mean 6.3 years after enrollment). This round included both a home interview and a subsequent extensive clinical examination at the research center. For the present analysis we excluded permanent nursing home residents (n = 105), persons who moved out of the Rotterdam area (n = 34), those without follow-up regarding vital status (n = 17), persons who did not provide or withdrew informed consent for follow-up data collection (n = 35), and those not invited for undefined reasons (n = 29). This left a total of 5423 persons available for analyses.

We classified these persons on the basis of their response as participating in both the home interview and extensive clinical examination at the research center, participating in the home interview only, or nonparticipating. Formal invitations for the third examination were sent by mail and participants were subsequently contacted by trained interviewers through telephone during the following week. During the call, an appointment for home interviewing was made if the invitee agreed to participate or reasons for declining the invitation were asked. At the end of the home interview, appointments for the clinical examination at the research center were made. Repeated attempts were undertaken if invitees could not be reached. Ultimately, in rare instances where the invitees could not at all be reached by the interviewers a letter was sent with a request to contact the study center to make an appointment.

Assessment of coronary risk

The nature of nonparticipation in population research makes it inherently difficult to investigate.

Therefore, we examined nonparticipation during a follow-up visit rather than at study enrollment. This ensured that we had data on cardiovascular risk factors for all persons, including the nonparticipants of the third examination. For each person, we estimated the predicted absolute 10-year coronary heart disease risk at enrollment (RS-1-I; 1990 to 1993; Figure 1.1) based on traditional cardiovascular risk factors under the Adult Treatment Panel III guidelines.[27] Coronary risk was expressed in percentage-points (range between 1 and 30%) of the Framingham point score as originally published and in the recommended clinical risk categories (< 10% low-risk, 10 to 20% intermediate-risk, and > 20% high-risk).[27] The cardiovascular risk factors were measured in a standardized fashion at study enrollment as described in detail previously.[104]

Assessment of outcome

In order to minimize the possibility of asymmetrical follow-up data collection between those who participated and those who did not participate in the third examination, we focused on all-cause mortality as the outcome of interest. With respect to the vital status of all persons enrolled in the Rotterdam Study, information is obtained on a weekly basis from the central registry of the municipality of the city of Rotterdam, through direct digital linkage of the study database with the electronic medical records of the general practitioners working in the study area, and through active follow-up as described in more detail elsewhere.[105] Follow-up data collection was done irrespective of participation during follow-up examinations.

Statistical analysis

All analyses were performed for 2 different comparisons. First, nonparticipation in the home interview was compared to participation in the home interview (reference category). Second, nonparticipation in the center visit was compared to participation in the center visit (reference category).

We studied the association between predicted coronary risk and participation during the third examination by logistic regression models adjusted for age at the date of invitation, sex, and level of education. P for trend was obtained by entering coronary risk categories into the logistic models as a continuous variable. Since it is the difference in coronary risk distributions between the study participants and the entire underlying population that is of interest,[106] we compared distributions of predicted coronary risks between all invitees and subgroups of participants using χ^2 test for categorical data.

Hazard ratios (HRs) adjusted for age at start of follow-up, sex, and level of education (in 7 categories) were computed using Cox proportional hazards models.[107] In order to assess changes of the hazards over time since the start of follow-up the proportional hazards assumption was tested, by entering interaction-terms of log-transformed follow-up time with participation status, and violated ($P < 0.001$). Therefore, the HRs over the 10-year follow-up are to be interpreted as a weighted average over this period.[108] Start of follow-up was defined as follows: participants in the center visit were followed from the date of examination at the research center onwards; participants in the interview only were followed from the date of home interview onwards; and the nonparticipants were followed from the date of declining the

invitation onwards.

Missings in cardiovascular risk factors (0.2 to 5.7%) were handled by single imputation using an expectation-maximization algorithm.[109] With the exception of the baseline characteristics (Table 3.1), results are reported for imputed data. All estimates of relative risk are presented with 95% confidence intervals (CIs). Exact 95% CIs using a Poisson distribution were calculated for the absolute mortality rates. Data were analyzed using the IBM SPSS Statistics version 20.0.0.1 (IBM Corp., Somers, NY, U.S.) and R version 2.15.1.[110]

Results

Of 5423 eligible invitees (mean age 73.5 years; 39% men), 87% participated, of whom 76% visited the research center (Table 3.1). Nonparticipants had lost interest (50%), had physical complaints (34%), or considered themselves too old to participate (12%; mean age 86.9 years). Persons who were elderly, women, less educated, and with higher levels of specific cardiovascular risk factors were less likely to participate (Table 3.1).

Nonparticipation was strongly associated with mortality (HR 1.71; 95% CI 1.56-1.88]). This was most pronounced shortly after invitation (0-3 months, HR 4.85; 95% CI 2.43-9.71), with a diminishing healthy volunteer effect during follow-up (P for trend < 0.001) (Table 3.2).

Every percentage-point increase in coronary risk yielded an approximately 3% lower probability of participating (Table 3.3). Those categorized as high-risk were least likely to participate (odds ratio 0.56; 95% CI 0.45-0.71) (Table 3.3). There was a slightly lower proportion of high-risk persons among the examined participants compared with all invitees (23% versus 24%) (Table 3.4).

Discussion

More than 5 decades ago, investigators from the Framingham Heart Study observed higher mortality rates in those who refused to participate.[12] They speculated that mortality in participants and nonparticipants might converge later during follow-up. We indeed noticed declining differences in mortality rates at long-term follow-up. The large difference shortly after invitation is presumably attributable to clinical or subclinical disease that makes invitees less likely to volunteer.[92] Residual differences at long-term follow-up could reflect a health-care-aversive attitude or a lower awareness of health in general.[106] However, long-term benefits of participation in population-based research cannot be ruled out because most studies (including the Rotterdam Study) disclose results from measurements (e.g. blood pressure and cholesterol levels) and incidental findings (e.g. aneurysms and indolent cancers) to the participants.[106, 111]

Methodological considerations

Follow-up examinations of many cohort studies extend over decades to accrue repeated measurements on changes in risk factors or to introduce state-of-the-art diagnostics as the

Table 3.1 – Characteristics of the study population

	All invitees	Home interview			Center visit		
		Participants	Non-participants		Participants	Non-participants	
	n = 5423	n = 4692	n = 731	P value [a]	n = 4126	n = 1297	P value [a]
Demographics:							
Age at invitation for the third examination, y	73.5 (7.8)	72.9 (7.5)	77.2 (8.5)	< 0.001	72.3 (7.1)	77.4 (8.4)	< 0.001
Men	2141 (39.5)	1897 (40.4)	244 (33.4)	0.040	1728 (41.9)	413 (31.8)	< 0.001
Education:				< 0.001			< 0.001
Primary	1826 (34.2)	1492 (32.3)	334 (46.5)		1234 (30.4)	592 (46.5)	
Lower/intermediate general and lower vocational	1514 (28.4)	1319 (28.6)	195 (27.2)		1182 (29.1)	332 (26.1)	
Higher general and intermediate vocational	1495 (28.0)	1352 (29.3)	143 (19.9)		1230 (30.3)	265 (20.8)	
Higher vocational and university	499 (9.4)	453 (9.8)	46 (6.4)		416 (10.2)	83 (6.5)	
NCEP ATP III risk factors: [b]							
Age, y	67.2 (7.7)	66.6 (7.4)	70.8 (8.4)	< 0.001	66.0 (7.1)	71.0 (8.3)	< 0.001
Systolic blood pressure, mmHg	138 (21)	137 (21)	144 (23)	< 0.001	136 (21)	143 (22)	< 0.001
Use of blood pressure-lowering medication	1177 (21.7)	979 (20.9)	198 (27.1)	0.020	836 (20.3)	341 (26.3)	0.021
Current smoking	1197 (22.1)	1019 (22.1)	178 (24.8)	< 0.001	883 (21.7)	314 (24.7)	< 0.001
Total cholesterol, mmol/L	6.7 (1.2)	6.7 (1.2)	6.7 (1.3)	0.22	6.7 (1.2)	6.7 (1.2)	0.29
HDL cholesterol, mmol/L	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	0.46	1.4 (0.4)	1.4 (0.4)	0.76

Values are counts (percentages) or means (standard deviations); unimputed data.
HDL = high-density lipoprotein.
[a] Adjusted for age and sex.
[b] Measured at the first examination (enrollment).

Table 3.2 – Risk of mortality associated with nonparticipation in the third examination, by time since invitation

Follow-up time	Deaths	Participants	Non-participants	HR (95% CI) [b]
		Mortality rate (95% CI) [a]	Mortality rate (95% CI) [a]	
Home interview:				
0-10 years	2175	45.3 (43.3-47.6)	88.7 (80.5-97.4)	1.44 (1.29-1.60) [c]
0-3 months	41	21.4 (13.8-31.5)	88.3 (50.4-143.3)	2.79 (1.45-5.36) [d]
3-6 months	40	24.1 (16.0-34.8)	67.9 (35.1-118.5)	2.16 (1.07-4.35) [d]
6-12 months	108	31.7 (24.9-39.9)	101.8 (70.9-141.6)	2.18 (1.44-3.32) [d]
1-2 years	214	36.6 (31.2-42.6)	77.9 (57.8-102.7)	1.44 (1.04-1.99) [d]
2-5 years	645	40.5 (37.0-44.2)	86.1 (72.5-101.6)	1.53 (1.27-1.85) [d]
5-10 years	1127	56.4 (52.9-60.1)	94.1 (80.8-108.9)	1.23 (1.05-1.45) [d]
Center visit:				
0-10 years	2175	39.5 (37.5-41.7)	94.4 (87.9-101.2)	1.71 (1.56-1.88) [c]
0-3 months	41	12.6 (6.7-21.6)	87.2 (57.9-12.6)	4.85 (2.43-9.71) [d]
3-6 months	40	14.6 (8.2-24.1)	79.8 (51.7-117.8)	4.57 (2.32-8.97) [d]
6-12 months	108	23.6 (17.4-31.2)	98.7 (75.3-127.1)	2.83 (1.89-4.26) [d]
1-2 years	214	29.8 (24.7-35.7)	83.5 (67.6-102.1)	1.82 (1.37-2.43) [d]
2-5 years	645	34.3 (30.9-37.9)	90.4 (79.8-102.1)	1.81 (1.53-2.14) [d]
5-10 years	1127	51.4 (47.9-55.1)	103.1 (92.3-114.9)	1.44 (1.26-1.64) [d]

[a] Per 1000 person-years.
[b] Adjusted for age at start of follow-up, sex, and level of education; participants are the reference category.
[c] Proportional hazards assumption violated (P < 0.001); interpret HR as weighted average over 10-year follow-up time.
[d] HR is interpreted to be conditional on the survival until the start of the time interval.[108]

study progresses. These follow-up examinations often serve as new baselines for analysis. The healthy volunteer effect may be different during follow-up compared to study enrollment. All persons enrolled have demonstrated a positive attitude towards population-based research and subsequent drop-outs might be more likely for reasons of health or disease, rather than lack of interest. Conversely, highly committed persons might be less likely to decline an invitation, even if they face problems with their health.

We would have preferred to have measurements on cardiovascular risk factors at the time of invitation. Using measurements obtained at enrollment (mean 6.3 years prior to the invitation for the third examination) will most likely result in an underestimation of the association

Table 3.3 – Participation during follow-up, by levels of predicted coronary heart disease risk

NCEP ATP III FPS	Participation in home interview OR (95% CI) [a]	Participation in center visit OR (95% CI) [a]
Per percentage-point increase	0.974 (0.961-0.987)	0.970 (0.959-0.980)
Risk categories:		
Low (< 10%)	1.00 (reference)	1.00 (reference)
Intermediate (10-20%)	0.72 (0.58-0.90)	0.68 (0.57-0.82)
High (> 20%)	0.59 (0.45-0.77)	0.56 (0.45-0.71)
P for trend	< 0.001	< 0.001

Predicted 10-year coronary heart disease risks were derived from the FPS and categorization of risk was based on the NCEP ATP III guidelines.[27]
FPS = Framingham point score.
[a] Adjusted for age at invitation for the third examination, sex, and level of education.

between predicted coronary risk and nonparticipation. Alternatively, we could have used data from the local general practice registries where no active participation is required. However, the data stored in such databases were collected for clinical purposes rather than research purposes and therefore incompleteness and lack of standardization of measurements would be bring forward other important limitations.

We explicitly chose to study the effects associated with nonparticipation on all-cause mortality, rather than cardiovascular end points. This decision was driven by the exploration of the available data on cause-specific mortality showing that a cause of death could not be adjudicated in 59 (3.4%) persons who died after the home interview and 32 (7.4%) persons who died after declining the home interview (P < 0.001). Follow-up on vital status on the other hand was virtually complete (n = 17 lost to follow-up at 10 years, predominantly due to emigration; 99.7% complete for participants versus 99.6% for nonparticipants, P = 0.61). Patterns and point estimates were, however, almost identical for all-cause and cardiovascular mortality (data not shown).

Last, the participation rates, as observed in our elderly study population (mean age at invitation 73.5 years) (Table 3.1), may mitigate the underestimation of the mortality rates and the distributions of predicted cardiovascular risk in the underlying population. In order to attain such participation figures, we visit invitees for extensive home interviews and have built a dedicated research center in the Ommoord district prior to the start of the Rotterdam Study. As a consequence, our results may not be generalizable to studies with much lower participation rates.[112, 113]

Implications

Our focus on distributions of absolute cardiovascular risk is new information. This is important in light of the recent shift in cardiovascular epidemiologic research toward evaluating new risk markers on the basis of their clinical utility in risk prediction (i.e. whether the predicted risks with addition of a new marker change sufficiently to alter recommended therapy) rather than the marker's association with cardiovascular disease expressed as an odds ratio or HR.[114] In contrast to the study of associations, the risk distribution in the study population affects the magnitude of measures of risk reclassification, such as net reclassification improvement.[115] Given that most people have a low predicted cardiovascular risk (Table 3.4), underrepresentation of persons at higher cardiovascular risk will usually mean that smaller proportions of persons are reclassified, resulting in lower estimates of net reclassification improvement;[115] therefore, the contribution of emerging risk markers could be underestimated. We observed a small underrepresentation of persons at high cardiovascular risk (1.2% less at high risk) (Table 3.4); thus, results from analyses on absolute cardiovascular risk are not likely to be severely affected. However, future simulation studies could quantify the degree of bias on measures of risk reclassification.

Table 3.4 – Distributions of predicted 10-year coronary heart disease risk, by degrees of participation during follow-up

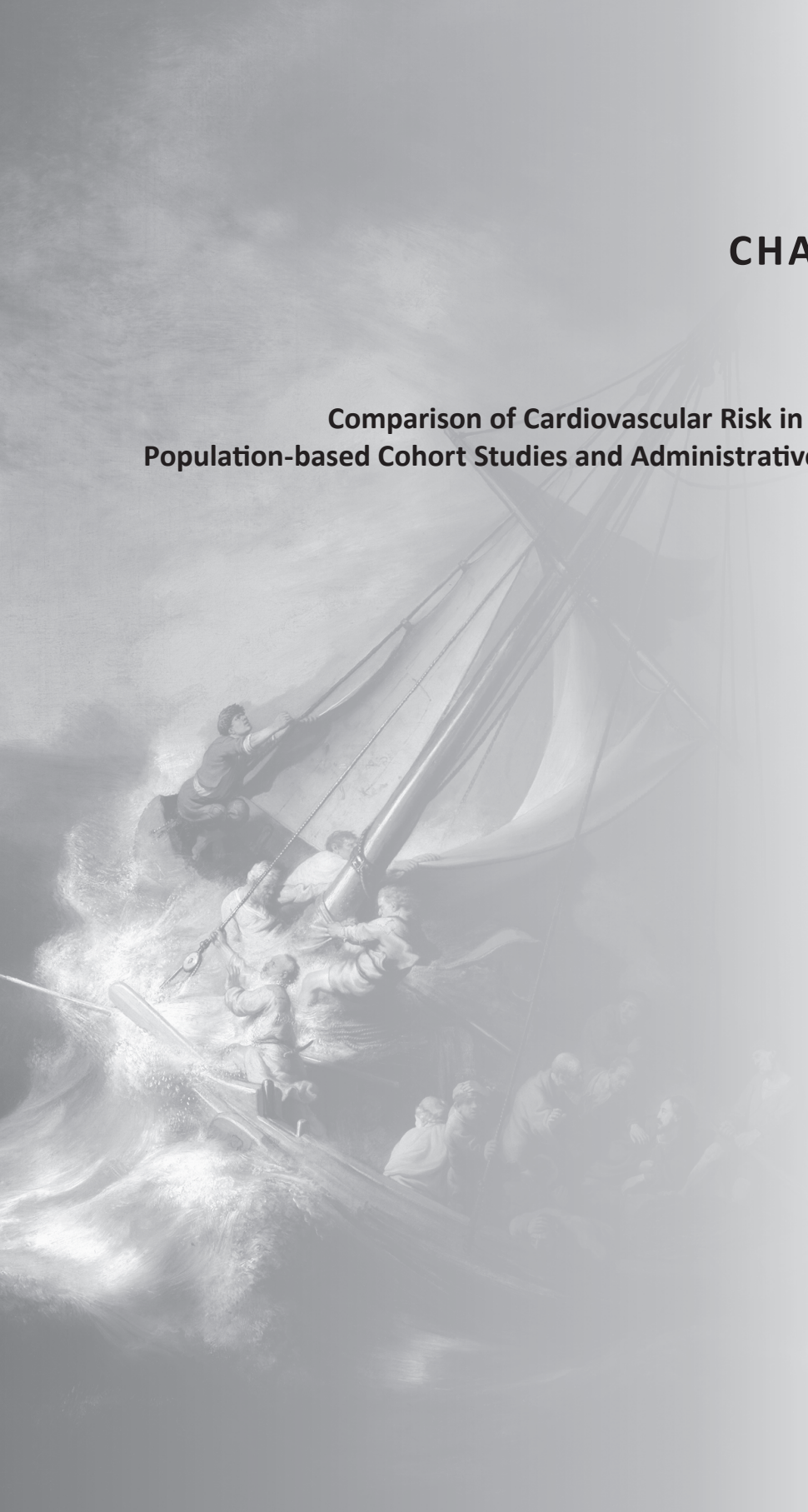
NCEP ATP III risk categories	All invitees	Participants in home interview	Participants in center visit
	n = 5423	n = 4692	n = 4126
Low (< 10%)	2318 (42.7)	2070 (44.1)	1867 (45.2)
Intermediate (10-20%)	1783 (32.9)	1514 (32.3)	1302 (31.6)
High (> 20%)	1322 (24.4)	1108 (23.6)	957 (23.2)
P value [a]	Reference	< 0.001	< 0.001

Values are counts (percentages). Predicted 10-year coronary heart disease risks were derived from the Framingham point score and categorization of risk was based on the NCEP ATP III guidelines.[27]

[a] P value for comparison in distributions of risk over clinical risk categories between all invitees (reference) and participants in home interview or visit to the research center.

CHAPTER 4

Comparison of Cardiovascular Risk in Prospective Population-based Cohort Studies and Administrative Databases



Hippisley-Cox and colleagues noticed a nearly 2-fold higher lifetime risk of cardiovascular disease (CVD) in the Rotterdam Study [116] as compared to results from the QResearch database.[117] In this chapter we discuss how these differences might be explained.

Part of the discrepancies in results may arise from the difference in CVD definitions used in the 2 studies. Other differences in study design should also be highlighted. Population-based cohort studies are generally smaller than administrative databases and will inevitably lack information on invitees unwilling or unable to participate. However, cohort studies collect baseline information on risk factors (e.g. smoking and cholesterol levels) in a standardized way for every participant, whereas availability of information in administrative databases depends on healthcare-seeking behavior of patients and not all important risk factors are assessed and registered in every patient. Moreover, due to the use of multiple data sources,[105] follow-up in prospective cohort studies is more detailed and may include more outcomes as compared to studies solely relying on administrative data.

The Rotterdam Study is a prospective population-based cohort study of an unselected sample of the population of the city of Rotterdam, the Netherlands (Figure 1.1).[32-37] Population-based cohort studies, including in the Rotterdam Study,[118] have repeatedly been shown to represent a lower risk population than the underlying eligible source population due to selective non-participation of individuals with a poorer health status. This results in somewhat lower event rates rather than an overestimation of cardiovascular risk and thus does not explain the difference observed by Hippisley-Cox and colleagues. Besides, the Netherlands is considered a low risk country by the European Society of Cardiology.[8] Recent work from the Rotterdam Study has shown that established cardiovascular risk calculators, including the SCORE calculator for low risk countries,[5] overestimate risk in the Rotterdam Study.[104, 119] This indicates that the Rotterdam Study population is not a particular high-risk population. Finally, lifetime risks of CVD in the Rotterdam Study are comparable to those found in a recent meta-analysis on 5 prospective population-based cohort studies from the U.S.[120]

What then may explain the observed difference in results? For one, the comparison of crude incidence rates over the studies are hampered by differences in age distribution. Mean (SD) age was 67.6 (8.9) in the Rotterdam Study [116] and 48.1 (14.3) in QResearch.[117] A comparison of prevalence of diabetes mellitus is similarly flawed, since glucose levels were measured in all Rotterdam Study participants at baseline, whereas these were missing for many individuals in QResearch.

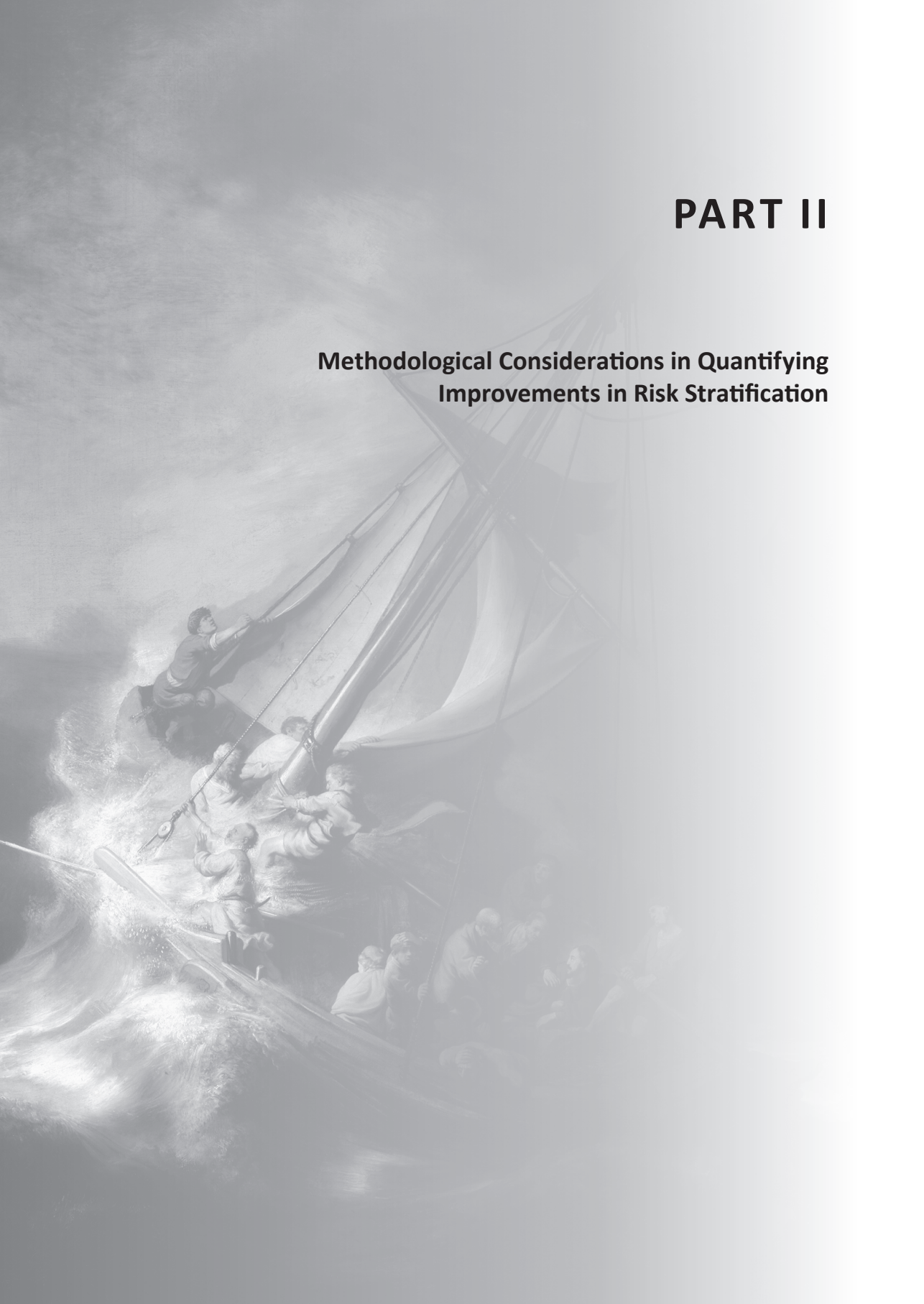
Lifetime risk of death from cardiovascular causes is a uniform way to compare cardiovascular risk between populations. A greater burden of CVD will be reflected by a greater proportion of deaths attributable to CVD. We calculated lifetime risk of death due to CVD using the data described in *Chapter 11*.[116] When applying a broad definition that also included non-atherosclerotic end points and sudden deaths,[105] remaining lifetime risk of death due to CVD was 34.3% (95% CI 32.6-35.8%) at age 55; using a stricter definition based on International Classification of Diseases, tenth revision (ICD-10; codes I00-I99), we estimated this to be 28.7% (95% CI 27.2-30.2%). These results are in line with nationwide data from Statistics Netherlands (CBS) on the second decade of our study period (2003-2010; 31% for ages 18 and over),[121, 122] as well as the data presented in the 2012 statistics report from the British Heart Foundation (33% for ages 55 and over).[123]

In this context it is remarkable that the lifetime risks at age 55 in QResearch (37% in men and 28% in women for fatal and non-fatal CVD combined) are similar to or lower than the 33% probability of dying from CVD according the British Heart Foundation.[123] This makes one wonder whether the striking difference in results might be due to an underestimation of lifetime risks in QResearch rather than an overestimation in the Rotterdam Study.

Mortality from CVD is declining in Western societies. Yet the prospect that 2 out of 3 healthy adults at age 55 will face some form of CVD during their lifespan should reinforce efforts to motivate people to adopt a healthy lifestyle and underscores the importance of primordial and primary prevention.

Epidemiologic methods are useless. They can only give you answers.

- Jay S. Kaufman and Miguel A. Hernán
Epidemiologic methods are useless. They can only give you answers.
Epidemiology 2012;23(6):785-6



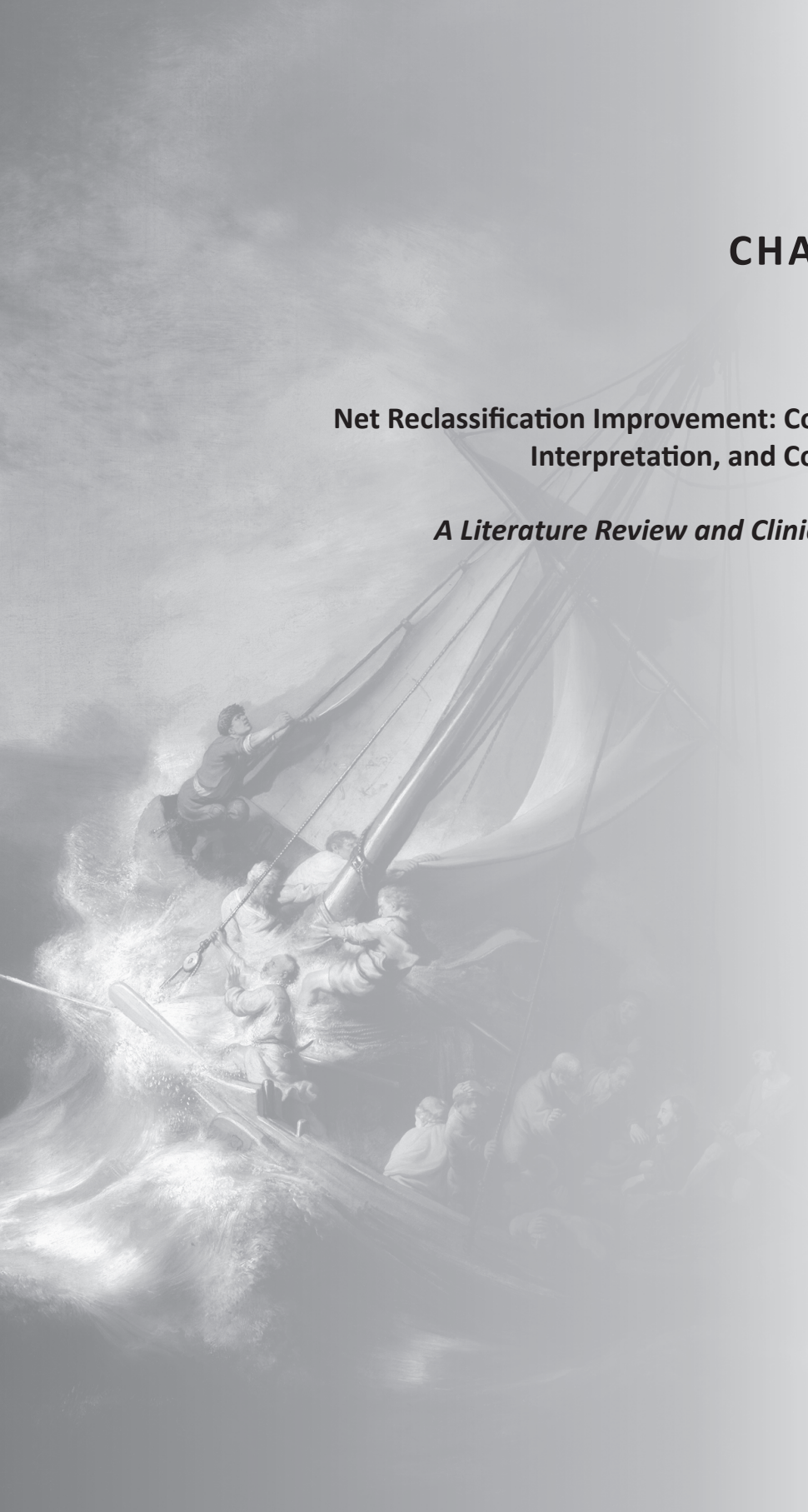
PART II

Methodological Considerations in Quantifying Improvements in Risk Stratification

CHAPTER 5

Net Reclassification Improvement: Computation, Interpretation, and Controversies

A Literature Review and Clinician's Guide



The net reclassification improvement (NRI) is an increasingly popular measure for evaluating improvements in risk predictions. This chapter details a review of 67 publications in high-impact general clinical journals that considered the NRI. Incomplete reporting of NRI methods, incorrect calculation, and common misinterpretations were found. To aid improved applications of the NRI, the chapter elaborates on several aspects of the computation and interpretation in various settings. Limitations and controversies are discussed, including the effect of miscalibration of prediction models, the use of the continuous NRI and 'clinical NRI', and the relation with decision analytic measures. A systematic approach toward presenting NRI analysis is proposed: detail and motivate the methods used for computation of the NRI, use clinically meaningful risk cut-offs for the category-based NRI, report both NRI components, address issues of calibration, and do not interpret the overall NRI as a percentage of the study population reclassified. Promising NRI findings need to be followed with decision analytic or formal cost-effectiveness evaluations.

Since the introduction of the term risk factor more than 50 years ago,[11] many such factors have been identified. Risk factors have been incorporated into statistical models to predict occurrence of disease, to more adequately diagnose patients, and to predict outcomes after disease has been diagnosed. A substantial number of clinical guidelines have incorporated risk prediction models to aid clinicians in everyday decision making in various fields of medicine, including cardiology, oncology, and respiratory medicine.[8, 27, 124-128]

Many markers, such as biomarkers, genetic factors, and imaging results, have been proposed to improve these prediction models. In the past 3 decades, the most commonly used measure to quantify these improvements has been the change in the c-statistic, also known as the area under the receiver operating characteristic curve (AUC). Studies have emphasized the limitations of the AUC, including the difficulty in interpreting the usually small changes in this statistic and the relation of the magnitude of improvement to the performance of the baseline model.[17, 129-131] A more relevant criterion may be to assess whether the addition of the marker to an existing model will influence clinical practice,[114] which is the case if the newly predicted risk crosses a clinically meaningful threshold for an individual. This has led to the introduction of the concept of risk reclassification,[132] which involves cross-tabulating categories of predicted risk for 2 models—usually one with the new marker under study and the other without it—to see how persons are classified differently when these models are used. The subsequent changes in risk classification can be quantified by the net reclassification improvement (NRI).[16] Risk reclassification analysis with the NRI has become popular: more than 1000 publications have cited the 2008 article that introduced the NRI.[16] However, reporting of the methods used is of heterogeneous quality,[133] and misconceptions are common in interpreting the NRI.[134]

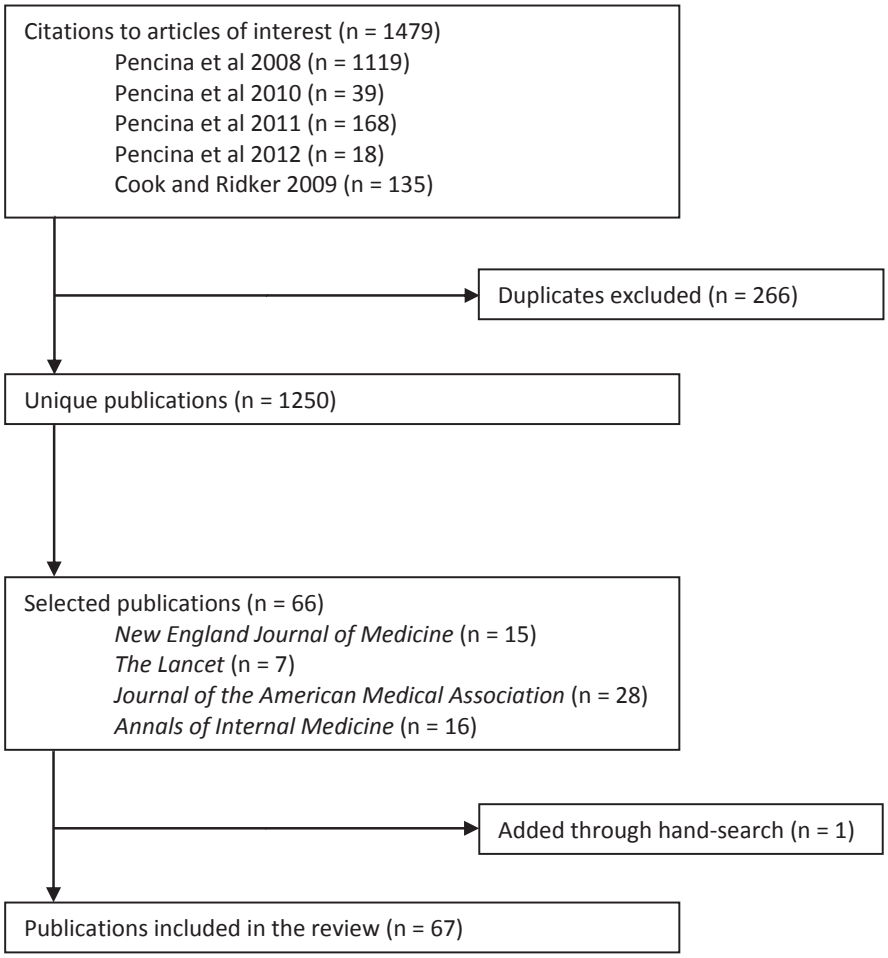
In this chapter, we aim to provide a systematic assessment of the reporting practices in analyses involving the NRI and address some controversies relating to its use and interpretation. We also make recommendations on how to report and interpret the NRI.[135]

Overview of current reporting

Literature search and data extraction

We systematically collected studies that computed the NRI or discussed results from NRI analysis. We used the Thomson Reuters Web of Knowledge (version 5.9) to identify all publications that cited 1 of 4 methodological articles by Pencina and colleagues [16, 136-138] or a methodological review on reclassification measures by Cook and Ridker.[139] The search was last updated on 23 April 2013 and yielded 1250 unique citations (Figure 5.1). We selected all 67 citations in the 4 general clinical journals with the highest impact factors (*New England Journal of Medicine*, *The Lancet*, *Journal of the American Medical Association*, and *Annals of Internal Medicine*) for data extraction (Appendix Tables 5.1 and 5.2).[104, 139-204] Our rationale was that these articles may be expected to have broad impact and be used as examples for others.

Figure 5.1 – Summary of literature search and selection of articles



The search was last updated on 23 April 2013.

Two evaluators independently extracted data from the publications. Cases on which the evaluators disagreed were discussed with a third evaluator to reach consensus. All publications were searched for NRI calculations or results. If these were found, we checked which version of the NRI was used: the category-based NRI [16] or the continuous (category-free) NRI [137] (Table 5.1). Next, we reviewed all articles to determine whether risk categories corresponding to diagnostic or treatment thresholds from clinical guidelines were used to evaluate the category-based NRI or whether other categorization was justified. We determined which NRI components were reported: solely the overall NRI, or the event NRI and the nonevent NRI (Table 5.1). Moreover, we categorized studies that reported estimates of the overall NRI on the basis of whether they reported it as a unitless statistic or a percentage.

Table 5.1 – Formulas and interpretation of the net reclassification improvement

NRI type	Formula and interpretation
Category-based: [a]	
Event NRI	= Pr(up|event) – Pr(down|event) = (number of events classified up – number of events classified down) / number of events The net percentage of persons with the event of interest correctly classified upwards The category-based event NRI can be interpreted as a percentage with a range of -100% to +100% [b]
Nonevent NRI	= Pr(down|nonevent) – Pr(up|nonevent) = (number of nonevents classified down – number of nonevents classified up) / number of nonevents The net percentage of persons without the event of interest correctly classified downwards The category-based nonevent NRI can be interpreted as a percentage with a range of -100% to +100% [b]
Overall NRI	= [Pr(up|event) – Pr(down|event)] + [Pr(down|nonevent) – Pr(up|nonevent)] = event NRI + nonevent NRI The sum of the net percentages of correctly reclassified persons with and without the event of interest Thereby, the category-based overall NRI is a statistic that is implicitly weighted for the event-rate and cannot be interpreted as a percentage The theoretical range of the category-based overall NRI is -2 to +2

Table 5.1 (*continued*)

NRI type	Formula and interpretation
Continuous: [c]	
Event NRI	= Pr(higher|event) – Pr(lower|event) = (number of events with increased predicted risk – number of events with decreased predicted risk) / number of events The net percentage of persons with the event of interest correctly assigned a higher predicted risk The continuous event NRI can be interpreted as a percentage with a range of -100% to +100% [b]
Nonevent NRI	= Pr(lower|nonevent) – Pr(higher|nonevent) = (number of nonevents with decreased predicted risk – number of nonevents with increased predicted risk) / number of nonevents The net percentage of persons without the event of interest correctly assigned a lower predicted risk The continuous nonevent NRI can be interpreted as a percentage with a range of -100% to +100% [b]
Overall NRI	= [Pr(higher|event) – Pr(lower|event)] + [Pr(lower|nonevent) – Pr(higher|nonevent)] = event NRI + nonevent NRI The sum of the net percentages of persons with and without the event of interest correctly assigned a different predicted risk Thereby, the continuous overall NRI is a statistic that is implicitly weighted for the event-rate and cannot be interpreted as a percentage The theoretical range of the continuous overall NRI is -2 to +2

NRI = net reclassification improvement; Pr = probability.
[a] Assumes that clinically meaningful categories of predicted risk can be defined.
[b] Negative percentages are interpreted as a worsening in risk classification (i.e. the number of incorrectly reclassified events [or nonevents] exceeds the number of correctly reclassified events [or nonevents]).
[c] Does not consider any categorization.

Results

The predominant reason for citing any of the methodological articles was the computation of NRI estimates (n = 39) (Table 5.2). In 2 (5%) articles, only the continuous NRI was computed. In 5 articles, the NRI was used to compare 2 different models instead of the nested addition of 1 or more new risk markers to a simpler model.

Of the 37 articles that computed category-based NRI results, 34 (92%) detailed the cut-offs for the risk categories chosen. The number of risk categories defined in the computation of the NRI

Table 5.2 – Results from the literature review on reporting of the net reclassification improvement

Reporting of NRI feature	Studies, n (%)
Reason for citing methodological article on NRI:	
Claimed to have calculated NRI	39 (58.2) [a]
Discussed NRI results from previous analysis	4 (6.0) [a]
Suggested alternative methods for quantifying predictive abilities	16 (23.9) [a]
Computed other (non-NRI) measures elaborated on in this article	8 (11.9) [a]
Risk categorization:	
Only continuous (category-free) NRI computed	2 (5.1) [b]
Categorization for computing NRI detailed	34 (91.9) [c]
Categorization for computing NRI justified in text	10 (27.0) [c]
Reference given for NRI categorization	14 (37.8) [c]
Categorization for computing NRI corresponded to diagnostic or therapeutic implications in clinical guidelines	4 (10.8) [c]
Time horizon and follow-up:	
Predicted horizon detailed	30 (78.9) [d]
Observed follow-up detailed (mean, median, or maximum)	37 (97.4) [d]
Predicted time horizon longer than observed follow-up	7 (23.3) [e]
Components:[f]	
Overall NRI	36 (92.3) [b]
Event NRI and nonevent NRI in text or tables	11 (28.2) [b]
Reclassification table for main findings	25 (67.6) [c]
Unit:[f]	
Reported as a percentage	24 (66.7) [g]
Interpreted as a percentage or proportion	8 (22.2) [g]

NRI = net reclassification improvement.
[a] Of all 67 publications included in the literature review.
[b] Of 39 studies that calculated the NRI.
[c] Of 37 studies that calculated the category-based NRI.
[d] Of 38 prospective studies that calculated the NRI.
[e] Of 30 prospective studies that calculated the NRI and detailed the predicted horizon and follow-up.
[f] Table 5.1 provides more details.
[g] Of 36 studies that reported the overall NRI.

varied between 2 and 6, with 3 being the most common number (Appendix Table 5.1). These risk categories were justified in the text, by references, or both ways in 15 (41%) instances and fully matched clinically meaningful categories with clear implications from guidelines in 4 (11%) instances (Table 5.2). For outcomes other than atherosclerotic cardiovascular disease (CVD), the rationale for the risk categorization could not be traced in 10 of 12 instances. Another 8 studies on the prediction of various manifestations of CVD used cut-offs for the NRI that are the subject of ongoing debate [145, 176, 186, 205, 206]—for example, a 10-year risk cut-off of 6% (rather than 10%) for low risk for coronary heart disease. Fourteen publications applied cut-offs for coronary risk stratification to broader definitions of CVD (Appendix Table 5.1).

Among 38 prospective studies that calculated the NRI, 30 (79%) clearly reported the time horizon at which the risk predictions were evaluated. In 7 of 30 (23%) instances where both predicted horizon and observed follow-up were detailed, we could infer that the authors studied a predicted horizon beyond the observed follow-up time (Table 5.2). We identified another 7 studies that used events occurring beyond the predicted horizon in the reclassification analysis.

Nearly all studies reported the overall NRI. Only 11 (28%) articles presented its components—the event NRI and the nonevent NRI—in the results section. However, 25 (68%) presented reclassification tables stratified for events and nonevents (Table 5.2), which allowed for computation of both NRI components by a knowledgeable reader. By combining the components presented in the text and the reclassification tables, we identified 29 (74%) studies with information on the event NRI and nonevent NRI presented for at least 1 reclassification analysis. Of note, 1 study claimed to have calculated the NRI, but no such results could be traced. Another study presented P values but no point estimates of the NRI.

Of the 36 studies presenting estimates of the overall NRI, 24 (67%) expressed it as a percentage (Table 5.2). Eight (22%) articles in our review interpreted the overall NRI as a percentage or proportion of the entire study population that was correctly reclassified or used similar wording, such as interpreting an overall NRI of 0.29 as "29% of patients were correctly reclassified".[134, 156]

NRI computation, components, and interpretation

Predicted time horizons and follow-up

When prospective data are involved, such as cardiovascular events occurring during follow-up, the time horizon used to calculate the predicted risks should be clear. Because virtually every prospective study has some loss to follow-up, it is important to adequately handle observations with incomplete follow-up in the analysis. In our review, we found that studies published shortly after the introduction of the NRI often did not report how incomplete follow-up was handled. Some studies classified censored observations as nonevents ('naive extrapolation') or excluded persons with incomplete follow-up. Better methods have been proposed to limit loss of useful information, including Kaplan-Meier estimates of the expected number of events and nonevents ('prospective NRI')[137, 194] and inverse-probability weighting.[207] Similarly, not every study has sufficient follow-up available for the predicted time horizons used in clinical guidelines (for example, 10-year risk for coronary heart disease [205]). In the articles we reviewed, authors made various attempts to overcome this problem, such as using Weibull extrapolation,[165, 170] adjusting

the predicted risk cut-offs by the ratio of actual to desired follow-up,[141] or extrapolating the observed rates on the Kaplan-Meier survival estimates to the predicted time horizon for presentation purposes.[139]

Risk categories

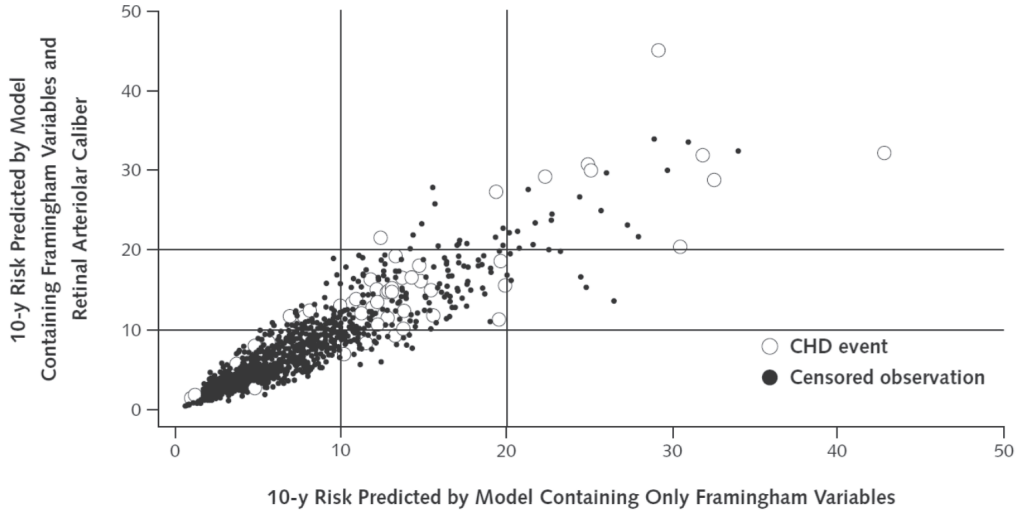
The NRI was introduced with the example of the added value of high-density lipoprotein cholesterol level to coronary risk prediction in the Framingham Heart Study.[16] Current clinical guidelines on primary prevention of CVD recommend clear cut-offs for initiation of statin treatment.[8, 27, 205, 206] These recommendations are supported by cost-effectiveness analyses. The NRI captures the change in a person's predicted risk that crosses one of such cut-offs and thus translates into a clinically meaningful change in treatment recommendations.

Our review of the literature confirms the findings of Tzoulaki and colleagues: selected risk cut-offs are generally poorly motivated and rarely correspond to therapeutic implications. Both shortcomings have been shown to yield significantly higher NRI estimates.[133, 197] In some cases, the existing clinical cut-offs may result in limited reclassification. For example, in a study of a population at very low risk for CVD, only a small number of participants would be considered to be at high risk; therefore, few will cross the recommended risk thresholds after the addition of a new marker.[208] Using the existing cut-offs illustrates the limited utility of a new marker in real-life application to such a low-risk population. Choosing a priori clinically meaningful cut-offs has been frequently emphasized.[16, 133, 136, 137, 176, 179, 197, 208-214] In addition, the estimates of the NRI and its components increase with the number of categories.[211, 215] Limiting analysis to clinically meaningful categories will forestall authors from presenting results from the cut-offs with the highest magnitude of NRI in their data. Moreover, consistent use of cut-offs enhances comparability of results on the same markers between studies provided that the same outcome definition and time horizons are used.

Although many risk prediction algorithms are described in the medical literature, a limited number of clinical guidelines outside the field of cardiology explicitly recommend risk thresholds for use in clinical practice. In the fields where meaningful cut-offs are lacking or evolving, various options have been suggested to overcome this problem. Each has its own caveats. First, in some cases, classification thresholds exist for related outcomes. For example, a 20% 10-year risk for 'hard coronary heart disease' corresponds to a 25% 10-year risk for 'total coronary heart disease'.[216] In these situations, a conversion factor based on the ratio of event rates—in this example, a ratio of 1.25—can be used to translate cut-offs from one application to another. Such conversion assumes that the associated clinical implications are similar for the different outcome definitions, which may not always be true. For example, the protective effect of statins on the occurrence of cardiovascular manifestations other than coronary heart disease, such as heart failure, may be less.[217] Similarly, conversion factors can be used to define risk cut-offs for different predicted time horizons (for example, 30-year versus 10-year risks [218]). In the absence of published conversion factors, the data under study can be examined to define the relative occurrence of the outcomes. Second, some researchers have suggested defining risk categories based on the event rate. A cut-off equal to the event rate would be used for binary classification, and cut-offs equal to half the event rate, the event rate, and twice the event rate would be used when more than 2 categories are desired.[215, 219] Such cut-offs, however, have no direct clinical

interpretation. The appropriateness of risk cut-offs should be related to the anticipated use of the prediction model. As an example, myocardial infarction risk thresholds for a model used to select patients with chest pain for early discharge from an emergency department will be much lower than those for a model used to identify patients with chest pain who will benefit from early invasive coronary angiography. Third, the continuous NRI was introduced as an alternative in the absence of any categorization (Table 5.1).[137] However, it does not quantify the clinical impact of risk reclassification (see limitations and controversies section). The relation between cut-offs and the risk distribution in the data can be elegantly visualized in reclassification graphs with superimposed cut-offs (Figure 5.2 [220]).

Figure 5.2 – Example of a reclassification graph with superimposed cut points of predicted risk



The graph shows 10-year risk for incident CHD in women from the Atherosclerosis Risk in Communities (ARIC) Study predicted by a model containing only the Framingham risk score variables (horizontal axis) against risk predicted by a model containing Framingham risk score variables and retinal arteriolar caliber (vertical axis). Lines at predicted risks of 10% and 20% are superimposed to show reclassification over clinically relevant cut points [27, 205] and thereby create a visual representation of a reclassification table (e.g. Tables 13.3 and 13.4 [165, 221]). Of note, most women in this study have a low (< 10%) predicted risk for CHD, both with the Framingham variables and with the model that includes retinal arteriolar caliber. The graph also shows that a limited number of women are reclassified over the cut points (i.e. only a small proportion of dots lies in the off-diagonal cells of the graph). CHD = coronary heart disease. Reproduced from McGeechan and colleagues [220] with permission of the *American Journal of Cardiolo*gy.

Case-control studies

Because of cost and feasibility, the predictive value of new biomarkers is often studied in subsets of persons with events and nonevents from larger prospective studies, especially when the event rates are low. The NRI can be used in both cohort studies and (nested) case-control studies.[137] In the latter, the researcher determines the ratio of events (cases) to nonevents (controls) by selective oversampling of cases, which implies artificial weighting by the investigators.[160] This should not lead to different estimates in magnitude of the NRI compared with results derived from a full cohort provided that the cases and controls are randomly selected.[137, 222] However, difficulties arise when selected controls are not representative of the entire underlying subset

they were drawn from, as in the case when matching on certain risk factors (even as simple as age and sex) is done.[222-224] This can be overcome by weighting for the inverse of the sampling probability for cases and controls.[217, 222]

Components and interpretation

Although the article that introduced the NRI recommended reporting the components of the overall NRI,[16] we noticed in our review that a limited number of studies did so. The components are easier to interpret than the combined number: when only 1 cut-off is being evaluated, the event NRI equals the improvement in sensitivity and the nonevent NRI equals the improvement in specificity.[16] The NRI components then express the net percentages of persons with or without events correctly reclassified (Table 5.1). Negative percentages for the components are interpreted as a net worsening in risk classification. The overall NRI is the sum of these 2 underlying components; as a result, an identical point estimate of this statistic may have different interpretations depending on its components.[178, 209] Large positive values of the event NRI indicate that the investigated marker aids in the detection of persons with the outcome of interest. This enables clinicians to initiate targeted treatment and thereby prevent events. On the other hand, an overall NRI driven by the nonevent NRI indicates the marker's property of correctly decreasing risk estimates for nonevents and is thus useful for reducing overtreatment. However, such markers will have limited contribution to decreasing the burden of disease. This illustrates the difficulty of interpreting the overall NRI without knowledge of its components.[225] Although it is tempting to do so, the overall NRI cannot be interpreted as the "net percentage of persons correctly reclassified" [165] in a straightforward manner because of the implicit weighting by the event rate: the overall NRI is the sum of 2 fractions with different denominators (the number of events and nonevents).[134] Such misinterpretations may have contributed to the popularity of the overall NRI, which therefore should not be presented as a percentage but as a unitless statistic.[134] Moreover, the components of the overall NRI may be reasonably well interpretable, whereas their sum is less so because of the implicit weighting related to the event rate (the costs of misclassification are assumed to be proportional to the odds of nonevents) (Table 5.1).[226]

As with most summary statistics, the NRI should not be interpreted on its own but in the context of complementary statistical measures. If a marker is not associated with the outcome or does not yield an increase in the AUC, a positive NRI should not be expected.[210] In rare instances where this does occur, random chance or differences in calibration between the models are the most likely causes. Also, presenting reclassification tables (in tabular or graphical form) will aid in the broader interpretation of summarized reclassification statistics (e.g. Figure 5.2 [220] and Tables 13.3 and 13.4 [165, 221]).

Limitations and controversies

Miscalibration

Unlike such rank-based statistics as the AUC, the NRI is affected by miscalibration of a model (that is, the average predicted risk is not close to the event rate).[226-228] Systematic miscalibration

does not occur when the performance of models is assessed on the same data set that was used to develop them but is often present when prediction models are validated in other populations. A well-recognized example of this phenomenon is the application of the Framingham cardiovascular risk models to European populations.[104, 229, 230] When performing a head-to-head comparison between a Framingham function (using the published coefficients and baseline hazard) and a new risk function developed from the data under study, one might find an NRI that favors the new model and no difference in the AUCs.[231, 232] This discrepancy can be avoided by deriving both the reference model and the model including the marker under investigation from the same data set that is used to compute the NRIs or by recalibrating both models in case of independent validation.[233]

The traditional Hosmer-Lemeshow goodness-of-fit test is strongly dependent on the sample size of the study.[234] Therefore, calibration might better be assessed graphically in a plot with predicted risks on the horizontal axis and observed event rates on the vertical axis (e.g. Figure 15.2 [104]). For perfectly calibrated models, the plot forms a diagonal line where the observed event rates equal the predicted risks. Such graphs can show systematic underestimation or overestimation as well as issues of overfitting (which can be quantified using the calibration slope [235]).

Classification or reclassification?

Some researchers have argued that before addressing the issue of reclassification, one should first focus on risk classification and examine the margins of a reclassification table.[160] Accordingly, examining reclassification is useful only to the extent to which it quantifies change in the size of these margins. This might be of particular relevance in head-to-head comparisons of non-nested models with substantial reclassification (that is, if the 2 models have low correlation). In this case, knowing how many persons are classified in the clinically relevant subgroups is of greater interest than the exact reclassification within the inner cells of the table (e.g. Table 15.2 [104]).[209, 212] Therefore, when choosing between competing models for clinical practice, the main question is which one leads to better classification (which relates to both discrimination and calibration of the models). On the other hand, when the focus is primarily on the potential of a new marker, the improvements in discrimination and subsequent risk reclassification that it can induce are of primary interest.

Continuous NRI

The continuous NRI was originally proposed to overcome the problem of selecting categories in applications where they do not naturally exist.[137] It does not require any risk categorization and considers all changes in predicted risk for all events and nonevents. This has several consequences. First, most changes in predicted risk do not translate into changes in clinical management; for example, a middle-aged woman whose 10-year predicted coronary risk doubles from 1% to 2% will probably not be treated differently.[208, 236] Therefore, the interpretation of the continuous NRI is different from that of the category-based NRI (Table 5.1).[130] Second, when the addition of a normally distributed marker is considered, the continuous NRI is less affected by the performance of the baseline model and can therefore be seen as a rescaling of the

measures of association (for example, an odds ratio of 1.65 per standard deviation corresponds to a continuous NRI of 0.395).[130, 138] Consequently, the continuous NRI is often positive for relatively weak markers.[130] Moreover, it is strongly affected by miscalibration, especially in the setting of external validation.[228]

As such, the continuous NRI is less suitable for head-to-head comparisons of competing models unless these models have been developed from the same data or are correctly calibrated. The most appealing application of the continuous NRI comes in quantifying the effect of an added predictor in settings where the distributions of other risk factors may not be representative of the population.[237] For example, when the same marker for coronary risk prediction is evaluated in 2 populations, one with wide and the other with narrow age ranges, the conclusions about its usefulness might be different if based on the increment in AUC.[131] The continuous NRI, however, would give a consistent message and is therefore marker-descriptive rather than model-descriptive. Furthermore, its magnitude should be assessed on its own scale [130] and should not be compared with that of the category-based version.

Clinical NRI

Reclassification measures, including the NRI, can be used to evaluate markers in specific subgroups of the study population defined by the reference model. Specifically, the added value of new risk markers may be of greater importance in persons with a risk categorization that has more uncertainty about the clinical implications (for example, persons at intermediate risk for coronary heart disease [150, 165, 178, 188, 189, 202]). This 'clinical NRI',[238] however, has been found to be biased because it does not take into account incorrect reclassification from other risk categories into the intermediate-risk category.[178] Adding randomly generated non-informative markers to existing prediction models leads to positive clinical NRIs more frequently than expected on the basis of chance.[215, 239] A method for correcting this systematic overestimation has been published.[239]

Decision analytic measures

The overall NRI implicitly weights for the event rate, p, with $1 / p$ and $1 / (1 - p)$ serving as costs for false-negative results (events classified downward) and false-positive results (nonevents classified upward), respectively.[226, 240] However, a different weighting of false-positive and false-negative results is often more clinically appropriate.[214] This can readily be incorporated in a weighted version of the NRI if the event NRI and nonevent NRI are presented separately or when a reclassification table is provided.[137, 241] In its broadest form, the weighted NRI can be interpreted as the average savings (for example, in dollars or quality-adjusted life-years) per person resulting from using the new model instead of the old one.[137]

The weighted NRI is a decision analytic measure and is mathematically a transformation of changes in net benefit and relative utility.[241] These measures use the harm-benefit ratio to define an optimum decision threshold for binary classification as high risk versus low risk.[242] The harm-benefit ratio also defines the weights of true-positive and false-positive classifications to calculate a single summary measure.[241-243] However, the use of such decision analytic measures

is limited by the fact that weights for harms and benefits are not firmly established in most fields of medicine,[243] although a range of decision thresholds can be considered in a sensitivity analysis with visualization in a 'decision curve'.[244]

The non-weighted category-based NRI analysis is regarded as an early-stage analysis in the evaluation of new markers or prediction models. For assessment of the potential clinical utility of promising markers, decision analytic approaches are needed in the next step, after the NRI analyses but before a full formal cost-effectiveness analysis that incorporates changes in costs and clinical outcomes in more detail.[114]

Recommendations

In our literature review, we encountered several common flaws in the presentation and interpretation of the NRI and insufficient documentation of the computational methods. On the basis of our observations, we make the following recommendations for clinical research (Table 5.3).[135]

Clearly defining which type of NRI is used is essential because their applicability and relevance vary substantially. The most appropriate NRI type and cut points depend on several factors, as discussed in this review. We recommend separate reporting of the NRI for events and nonevents in all circumstances. Also, the sum of the NRI components should not be interpreted as a percentage. If authors choose to present the category-based NRI, they should discuss the implied costs of misclassification by the event rate. The cut-offs selected for the NRI analyses should preferably match risk thresholds that have clear clinical implications or can be motivated on clinical grounds. In general, the category-based NRI is directly applicable in settings where meaningful risk categories exist and models are well calibrated. If either of these conditions is not satisfied, one must carefully determine what information the NRI offers and whether it can be interpreted meaningfully. Using cut- offs that have no direct clinical meaning impedes the interpretation of the category-based NRI. Several methods have been proposed to define cut points in situations where meaningful thresholds do not exist, but each has its own caveats. Presenting graphical displays similar to a decision curve [244] for a range of cut-offs could be considered as an alternative. The continuous NRI can be recommended in only a few settings, including those where the primary focus is on the strength of the marker rather than model performance. Authors must be careful not to overinterpret the magnitude of the continuous NRI, which is usually much larger than that of the category-based NRI, and must ascertain that the models are well calibrated. Finally, for mathematical reasons, we recommend against calculating P values for any of the forms of the NRI when the contribution of a new marker is being evaluated.[245, 246] Instead, after a marker has been shown to be statistically significantly associated with the outcome, only CIs for the NRI should be presented.

Our recommendations are meant to improve completeness, transparency, and clinical relevance of research involving risk reclassification. However, because the scientific debate on the NRI and related performance measures is ongoing, our recommendations may be subject to advances or additions in the future.

Table 5.3 – Recommendations for reporting the net reclassification improvement

Article section	Recommendation
Methods:	
Type of NRI	Specify the type of NRI computed (category-based and/or continuous NRI).
Follow-up	Specify the horizon of risk prediction if the NRI was computed for prognostic evaluations (e.g. 10-year risk). Describe how censored observations (e.g. persons lost to follow-up before the specified horizon) were handled. Use the event status at the predicted time horizon and ignore events occurring beyond the predicted time horizon (e.g. when predicting 10-year risk of CHD consider participants with a myocardial infarction occurring after 10-year of follow-up as nonevents).
Cut-offs	For category-based NRI ideally the categorization should ideally have clear consequences in clinical practice. Where possible, give references to formal clinical guidelines used to define the risk categories for the computation of the NRI. If alternative cut-offs were used, clearly motivate them.
Results:	
Components	Report the NRI for events and nonevents separately. Reclassification tables stratified for persons with and without the event of interest are informative beyond the NRI (e.g. Tables 13.3 and 13.4).
Unit	The event and nonevent NRI can be presented as percentages. However, the overall NRI has no unit and should therefore not be presented as a percentage (see Table 5.1).
Calibration	Provide information on the calibration of the models being compared.
Discussion:	
Interpretation	The components of the overall NRI can be interpreted as a net percentage of the number of persons with or without events. However, the overall NRI should not be interpreted as a net percentage of the study population correctly reclassified.
Comparisons	Do not draw strong comparative conclusions based on direct comparisons of NRIs obtained in different populations or using different outcomes or cut-offs.

CHD = coronary heart disease; NRI = net reclassification improvement.

Appendix Tables

Appendix Table 5.1 – List and main characteristics of the 67 articles included in the literature review

Study	Article type	Marker / comparison	Outcome of interest / topic	Cut-offs used for NRI
Adabag et al, 2008	Original article		Sudden death after MI	NA
Auer et al, 2012	Original article	ECG abnormalities	CHD	7.5% and 15% at 7.5 years
Breteler et al, 2011	Editorial		Dementia	NA
Buckley et al, 2009	Meta-analysis	CRP level	CHD	NA
Chou et al, 2011	Review	Resting or exercise ECG	CVD	NA
Cook et al, 2009	Methods	CRP level	CVD	5%, 10%, and 20% at 10 years [a]
Cook et al, 2009	Letter	CRP level	CVD	NA
Cornelis et al, 2009	Original article	Genetic risk score	Type 2 DM	NA
de Boer et al, 2012	Original article	25-hydroxyvitamin D level	Composite of hip fracture, MI, cancer, and death	50 nmol/L vs. season-specific at 10 years
de Lemos et al, 2010	Original article	Troponin T level	Cardiac structure; and death	NA
deFilippi et al, 2010	Original article	Troponin T level	Heart failure; and CVD death	10% and 20% at 10 years
den Ruijter et al, 2012	Original article	cIMT	MI; and stroke	5%, 10%, and 20% at 10 years
Devereaux et al, 2012	Original article	Troponin T level	Death after non-cardiac surgery	1%, 5%, and 10% at 30 days

Study	Article type	Marker / comparison	Outcome of interest / topic	Cut-offs used for NRI
Di Angelantonio et al, 2012	Original article	Cholesterol; apolipoprotein; and Lp(a) levels	CVD	10% and 20% at 10 years
Eddy et al, 2011	Original article	Hypertension guidelines	MI; and Stroke	Not specified
Farooq et al, 2013	Original article	Coronary revascularization strategies	Death	NA
Fonarow et al, 2012	Original article	NIH Stroke Scale	Stroke fatality	Not specified at 30 days
Gulati et al, 2013	Original article	Myocardial fibrosis	Death; and major arrhythmia	5%, 10%, and 20% at 5 years (death); 15% at 5 years (major arrhythmia)
Helfand et al, 2009	Review	CAC score; leukocyte count; periodontal disease; ABI; cIMT; CRP; Lp(a); homocysteine; and fasting glucose levels	CHD	NA
Hingorani et al, 2009	Commentary		CVD	NA
Hlatky et al, 2012	Editorial		CHD	NA
Janes et al, 2008	Methods		Risk stratification tables	NA
Janssens et al, 2011	Methods		GRIPS statement	NA
Kaptoge et al, 2010	Original article	CRP level	CHD; stroke; and death	NA

Study	Article type	Marker / comparison	Outcome of interest / topic	Cut-offs used for NRI
Kaptoge et al, 2012	Original article	CRP; and fibrinogen levels	CVD	10% and 20% at 10 years
Kathiresan et al, 2008	Original article	Genetic risk score	CVD	10% and 20% at 10 years
Kavousi et al, 2012	Original article	CKD; leukocyte count; CAC score; cIMT; PAD; PWV; vWF antigen; NT-proBnP; fibrinogen; CRP; homocysteine; and uric acide levels	CHD	10% and 20% at 10 years [a]
Keller et al, 2011	Original article	Serial changes in troponin I level	MI	NA
Kengne et al, 2012	Letter	CRP level; and CAC score	CVD	NA
Khera et al, 2011	Original article	Cholesterol efflux capacity	Obstructive CAD	NA
Kim et al, 2008	Original article	Hyponatremia	Death in ESLD	NA
Kivimäki et al, 2011	Original article	Working hours	CHD	5% and 10% at 10 year
Koller et al, 2012	Original article	BMI; CRP level; cIMT; ABI; and ECG-LVH	CHD	10% and 20% at 10 years
Lubitz et al, 2010	Original article	Family history of atrial fibrillation	Atrial fibrillation	5% and 10% at 8 years
Lyssenko et al, 2008	Original article	Genetic polymorphisms	Type 2 DM	10% and 20% at an unspecified horizon

Study	Article type	Marker / comparison	Outcome of interest / topic	Cut-offs used for NRI
Manolio et al, 2010	Review		Genetic risk prediction	NA
Martinez et al, 2012	Original article	U.K. and U.S. guidelines	Advanced colorectal dysplasia	Number, type, and size of adenomas at 1 year
Matsushita et al, 2012	Original article	CKD-EPI and MDRD equations	Death; and ESRD	eGFR of 90, 60, 45, 30, and 15 mL/min per 1.73 m^2 at an unspecified horizon
McEvoy et al, 2010	Letter	CAC score	CHD	NA
Meigs et al, 2008	Original article	Genetic risk score	Type 2 DM	2% and 8% at 8 to 10 years
Melander et al, 2009	Original article	CRP; cystatin C; Lp-PLA2; MR-proADM, MR-proANP; and NT-proBNP levels	CHD; and CVD	6%, 10%, and 20% at 10 years
Melander et al, 2009	Letter reply	CRP level	CVD	NA
Omland et al, 2009	Original article	Troponin T level	CVD death; heart failure; and MI	NA
Palomaki et al, 2010	Meta-analysis	Chromosome 9p21 polymorphisms	CHD	5%, 10%, and 20% at 10 years [a]
Paynter et al, 2009 [c]	Original article	Chromosome 9p21.3 polymorphisms	CVD	5%, 10%, and 20% at 10 years [a]
Paynter et al, 2010	Original article	Genetic risk score	CVD	5%, 10%, and 20% at 10 years
Peralta et al, 2011	Original article	Urine albumin-creatine ratio; creatinine; and cystatin C levels	Death; and ESRD	Continuous NRI at an unspecified horizon

Study	Article type	Marker / comparison	Outcome of interest / topic	Cut-offs used for NRI
Pischon et al, 2008	Original article	BMI; and abdominal adiposity	Death	2.5%, 5%, and 7.5% at 5 years
Pletcher et al, 2010	Letter		CVD	NA
Polak et al, 2011	Original article	cIMT	CVD	6% and 20% at 10 years [a]
Polonsky et al, 2010	Original article	CAC score	CHD	3% and 10% at 5 years
Ripatti et al, 2010	Original article	Genetic risk score	CHD	5%, 10%, and 20% at 10 years
Rosenberg et al, 2010	Original article	Gene expression test	Presence of obstructive CAD	20% and 50%
Schelbert et al, 2012	Original article	Unrecognized MI	Death	Continuous NRI at an unspecified horizon
Schnabel et al, 2009	Original article	Echocardiographic measurements	Atrial fibrillation	5% and 15% at 10 years
Selvin et al, 2010	Original article	Glycated hemoglobin level	Type 2 DM; CHD; and death	5%, 10%, and 20% at 10 years
Steyerberg et al, 2010	Letter	CRP level	CVD	5%, 10%, and 20% at 10 years [a]
Tammemägi et al, 2013	Original article	Smoking intensity; and history of cancer	Lung cancer	1% and 2% at 6 years
Tangri et al, 2011	Original article	Calcium phosphate; bicarbonate; and albumin levels	CKD	Not specified
Tzoulaki et al, 2009	Review	86 predictors	CHD	NA

Study	Article type	Marker / comparison	Outcome of interest / topic	Cut-offs used for NRI
Wacholder et al, 2010	Original article	Genetic polymorphisms	Breast cancer	NA
Wilson et al, 2009	Editorial		CHD	NA
Wormser et al, 2011	Original article	BMI; and abdominal adiposity	CHD; and stroke	5%, 10%, and 20% at 10 years
Wormser et al, 2011	Letter reply	BMI; and abdominal adiposity	CHD	NA
Yeboah et al, 2012	Original article	cIMT; CAC score; brachial FMD; ABI; CRP levels; and family history of CHD	CHD; and CVD	5% and 20% at 10 years [a]
Zethelius et al, 2008	Original article	Troponin I; NT-proBNP; cystatin C; and CRP levels	CVD death	6% and 20% at an unspecified horizon
Zoungas et al, 2010	Original article	Severe hypoglycemia	CVD	NA

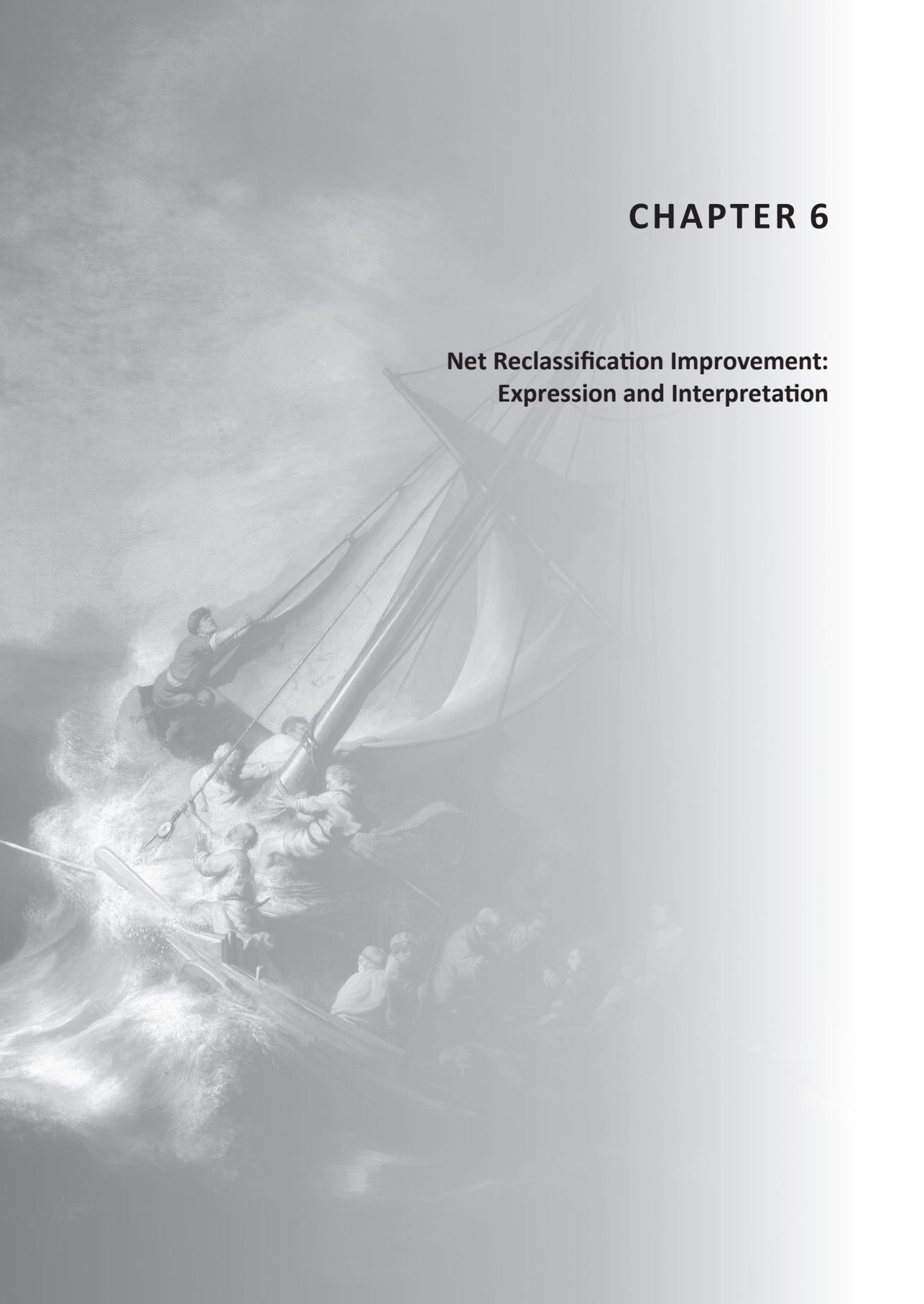
ABI = ankle-brachial index; BMI = body mass index; CAC = coronary artery calcium; CAD = coronary artery disease; CHD = coronary heart disease; cIMT = carotid intima-media thickness; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRP = C-reactive protein; CVD = cardiovascular disease; DM = diabetes mellitus; ECG = electrocardiography; ECG-LVH = electrocardiographic left ventricular hypertrophy; eGFR = estimated glomerular filtration rate; ESLD = end-stage liver disease; ESRD = end-stage renal disease; FMD = flow-mediated dilation; GRIPS = Genetic Risk Prediction Studies; Lp(a) = lipoprotein (a); Lp-PLA_2 = lipoprotein-associated phospholipase A_2; MDRD = Modification of Diet in Renal Disease; MI = myocardial infarction; MR-proADM = midregional proadrenomedullin; MR-proANP = midregional proatrial natriuretic peptide; NA = not applicable (NRI was not calculated); NIH = National Institutes of Health; NRI = net reclassification improvement; NT-proBNP = N-terminal fragment of prohormone B-type natriuretic peptide; PAD = peripheral arterial disease; PWV = pulse wave velocity; vWF = von Willebrand factor.

[a] Observations from a follow-up period shorter than the predicted time horizon were used.

[b] Identified through hand-search with erroneous citation linkage to a methodological article on NRI.

Appendix Table 5.2 – Summary characteristics of the 67 articles included in the literature review

Characteristic	Studies, n (%)
Journal:	
New England Journal of Medicine	15 (22.4)
Lancet	7 (10.4)
Journal of the American Medical Association	28 (41.8)
Annals of Internal Medicine	17 (25.4)
Year of print publication:	
2008	8 (11.9)
2009	13 (19.4)
2010	16 (23.9)
2011	12 (17.9)
2012	15 (22.4)
2013	3 (4.5)
Cited methodologic article:	
Pencina et al, 2008	56 (83.6)
Pencina et al, 2010	3 (4.5)
Pencina et al, 2011	9 (13.4)
Pencina et al, 2012	0 (0)
Cook and Ridker, 2009	11 (16.4)
Country of address for correspondence:	
Australia	1 (1.5)
Canada	2 (3.0)
Finland	1 (1.5)
Germany	2 (3.0)
Greece	1 (1.5)
The Netherlands	6 (9.0)
Norway	1 (1.5)
South Africa	1 (1.5)
Sweden	4 (6.0)
Switzerland	1 (1.5)
U.K.	8 (11.9)
U.S.	39 (58.2)



CHAPTER 6

Net Reclassification Improvement: Expression and Interpretation

Gulati and colleagues examined whether information about the presence of myocardial fibrosis aided in the prediction of mortality and major arrhythmia in 472 patients with non-ischemic dilated cardiomyopathy.[156] The predictive ability of fibrosis over left ventricular ejection fraction was quantified using the net reclassification improvement (NRI).[16]

The NRI is the sum of net percentages of patients with and without the outcome of interest reclassified correctly. The patients are assigned to more appropriate risk categories that ideally correspond with diagnostic or treatment thresholds from clinical guidelines. The NRI has a range of -2 to 2.We believe that the authors misinterpreted the NRI results and consequently overestimated the contribution of myocardial fibrosis in risk reclassification for mortality and arrhythmias.

The authors erroneously simplified the interpretation of the NRI of 0.29 for the arrhythmic composite outcome by stating “Overall, 29% of patients were correctly reclassified after adding midwall fibrosis status to the risk model (NRI 0.29; 95% CI 0.11-0.48, P = 0.002)”. Presumably this misinterpretation comes from the implicit weighting of patients with and without the outcome by the event rate in the summation of 2 percentages with different denominators (i.e. the number of patients with and without events).[16, 137, 240]

The NRI is computed by adding up the improvement for patients with major arrhythmia ([23 – 11] / 65) and improvements in patients without arrhythmia ([89 – 46] / 407), which indeed equals 0.29. However, for the entire study population, a total of 23.7% ([23 + 89] / 472) of the patients were correctly reclassified, offset by the 12.1% ([11 + 46] / 472) of patients who were incorrectly reclassified. As a result, only 11.7% of all patients were net correctly reclassified after adding midwall fibrosis status, rather than the stated 29%. Similarly, for predicting mortality in these patients (Table 6.1 [156]), the NRI of 0.26 corresponds to a net of 15.5% of the study population with improved categorization rather than the suggested “26% of patients”.

The NRI aims to reflect changes in clinical decision making as opposed to more traditional measures of model performance.[208] The example above, however, shows that the NRI is difficult to interpret and how it is tempting to express the NRI as the percentage of the study population correctly reclassified. We would like to raise awareness that the overall NRI should neither be expressed nor interpreted as a percentage.

Table 6.1 – Risk reclassification with the addition of midwall fibrosis status to a risk model based on left ventricular ejection fraction

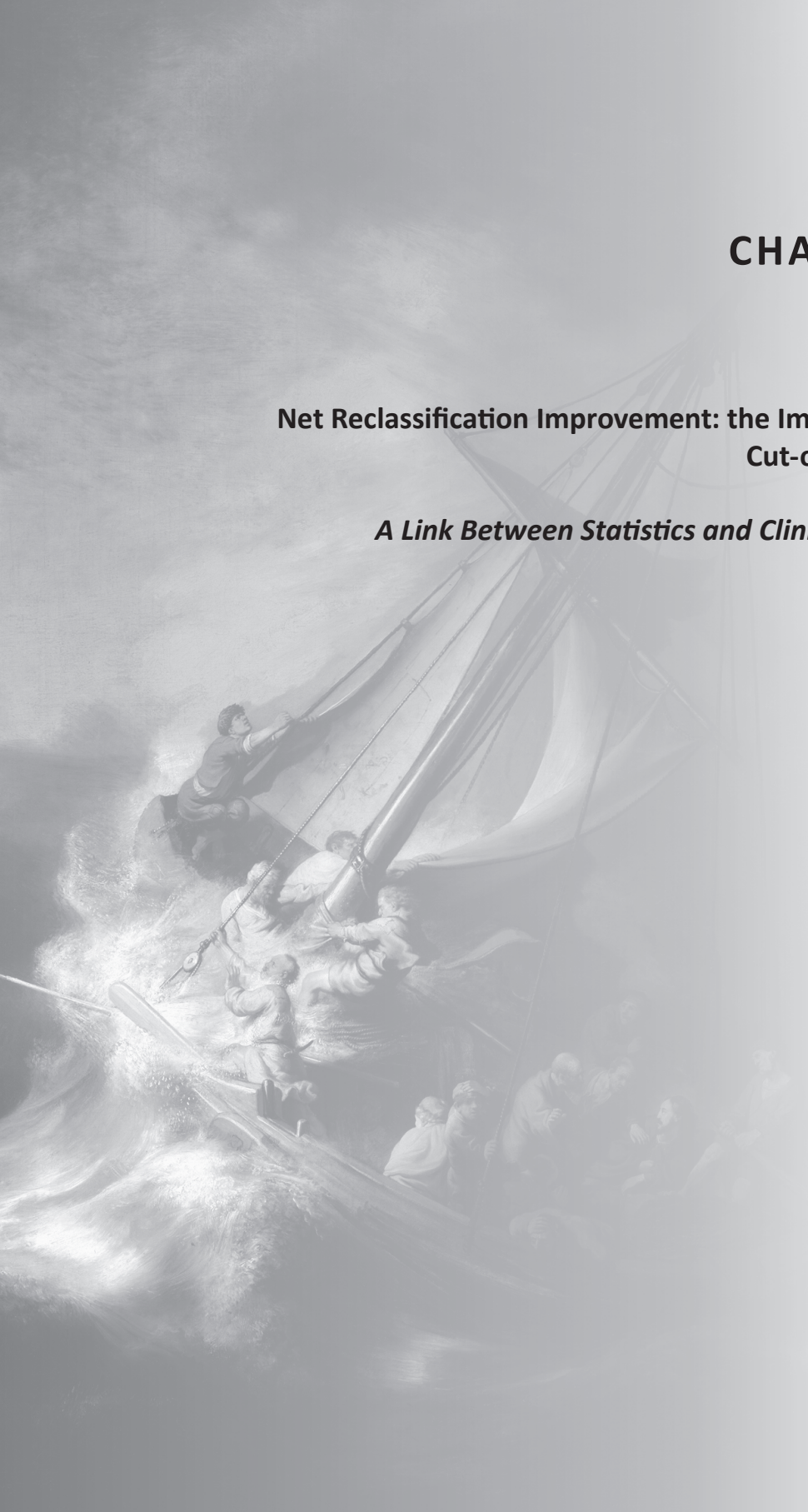
Risk based on LVEF	Risk based on LVEF and midwall fibrosis	
	0-15%	> 15%
Patients with arrhythmia (n = 65):		
0-15%	12	23
> 15%	11	19
Patients without arrhythmia (n = 407):		
0-15%	218	46
> 15%	89	54

Values represent the number of patients with non-ischemic dilated cardiomyopathy in each risk category according to the risk model based on LVEF alone and the risk model based on LVEF and midwall fibrosis status (presence or absence) for patients who had an arrhythmic event or did not have an arrhythmic event. LVEF = left ventricular ejection fraction. Adapted from Gulati and colleagues.[156]

CHAPTER 7

Net Reclassification Improvement: the Importance of Cut-off Selection

A Link Between Statistics and Clinical Practice



A little over a decade ago, European [247] and U.S. guidelines [27] on cardiovascular disease (CVD) prevention first recommended the use of various global risk assessment models. These guidelines directly aid clinicians in making decisions on consultation of a healthy lifestyle and initiation of drug treatment. The recommendations to use risk scoring algorithms invigorated researchers to improve on these existing functions and thereby heralded the current upswing in risk prediction research. Ever since a plethora of additional risk factors have been proposed, ranging from simple questions on familial predisposition and laboratory measures, to state-of-the-art vascular imaging. In order to provide guidance the American Heart Association issued a comprehensive statement on the stepwise evaluation of the value of novel markers.[114] The expert panel suggested that a new marker should be prospectively associated with the outcome, it should add predictive information over established risk factors, the addition of the marker should have the potential to modify an individual's risk sufficiently to change treatment recommendations, and finally whether this improves clinical outcomes in a cost-effective manner.

For many years, the main criterion used in evaluating and comparing prediction models was the c-statistic, or the area under the receiver operating characteristic curve (AUC) for binary data.[248, 249] This measure, however, is quite insensitive to the addition of strong markers.[129, 130] Its typically small changes in value can be difficult to interpret, especially in the presence of other strong predictors.[17] Various new statistical methods have been introduced to gauge the effect of the addition of a biomarker on clinical decision making. One such method is risk reclassification,[17] which has gained immediate widespread use and has resulted in a paradigm shift, at least in preventive cardiology, from reporting measures of association to changes in clinical management. The most commonly used measure for this is the net reclassification improvement (NRI).[16] The NRI summarizes the net changes of allocation in clinical meaningful risk categories for events and nonevents when extending an existing prediction model with a novel marker. It can be computed by summing up the proportions of correctly upward classified events (correctly qualifying for treatment) and downward classified nonevents (correctly abstaining from treatment), subtracted by the proportions of incorrectly downward classified events (incorrectly abstaining from treatment) and upward classified nonevents (unnecessarily qualifying for treatment). The relative simplicity of the NRI has undoubtedly contributed to its popularity.

The NRI, however, has several properties that may impede its clinical interpretation. Recently, Mühlenbruch and colleagues clearly illustrate the dependency of the NRI on the number of risk categories chosen and the cut points of these categories.[211] They use empirical data from the EPIC-Potsdam study which was previously used to develop the German Diabetes Risk Score, a model designed to predict the absolute 5-year risk of developing type 2 diabetes. The authors show that increasing the number of risk categories results in an increase of the NRI. Moreover, the placement of the cut points of absolute risk categories has a substantial influence on the magnitude of the NRI. The most extreme values of the 2-category NRI occur at thresholds at the edge of the data. Few individuals, for example, have predicted diabetes risk > 9%, resulting in a limited number of participants getting reclassified when higher cut-offs are chosen. Others have similarly shown that the value of the NRI changes as threshold cut points change.[210, 236, 250] Mealiffe and colleagues, however, found that while the NRI tends to be larger when the cut points are widely spaced and smaller when the cut points are close together, it was otherwise only weakly dependent on the precise placement of the cut points.[250]

In fields other than CVD, established meaningful risk categories with direct consequences for clinical practice may be sparse. Therefore the results from the present study by Mühlenbruch and colleagues are important in that they clearly underline the recommendations to compute the NRI only in the setting of a priori meaningful risk categories that have a clear consequence for patient care.[16] As the authors acknowledge, care should be taken to identify categories that have clinical relevance, which would ideally correspond to treatment thresholds or clinical risk strata.

A suggested alternative in the absence of firmly established cut-offs is to consider the continuous version of the NRI.[137] In settings of population prevention, however, typically the majority of the population is at low risk, and the purpose of the model is to screen and identify a smaller subset that needs clinical attention. For example, in the U.S. Women's Health Study cohort over 85% of women had a very low estimated 10-year cardiovascular risk of less than 5% using the Framingham risk score variables.[139] These women are of limited clinical concern and would not generally be followed closely. Small changes in the estimated risk for these women, even a doubling from 1 to 2%, would not have clinical impact. Continuous measures, particularly the rank-based AUC and continuous NRI, are based on the observed distribution in the entire study population, and the lower 85% would have a large impact. While these have advantages with respect to avoiding the need to prespecify categories, they may not be as relevant clinically since they give weight to regions that may not be clinically important. The continuous NRI has also been found to exhibit unusual behavior in particular situations.[236, 251] Unlike the AUC, it does not depend on the performance of the baseline model and is thus not a measure of model improvement.[130] This limits the interpretation of the continuous NRI as a model specific performance improvement indicator, but it may help evaluate the discriminatory potential of a new predictor.[130]

In analyzing the diabetes data from Potsdam, the German Diabetes Risk Score offered less incremental benefit in model fit over a simpler model containing age, anthropometrics, and hypertension status. This was reflected by the substantially lower values of the NRI and minimal increase in AUC.[211] Another way of demonstrating this is by computing the reclassification calibration statistic,[139] a derivative of the Hosmer-Lemeshow goodness of fit test [252] that compares the observed and expected number of events in each cell of the reclassification table rather than deciles of predicted risk, thus focusing on calibration rather than discrimination. While this test is also affected by the threshold cut-offs chosen, these have less impact than in the calculation of the NRI.[215, 236] Since sufficient numbers of participants in each cell are a prerequisite to get reasonable estimates of the observed rates, in most circumstances 3 or 4 risk strata are appropriate, with a focus on the area of the risk distribution that is of most clinical relevance.

Besides calibration, model validation must also be considered. Because these models are nested and fit in the same data, the fit can only improve when assessed in the derivation data set. This is true for the difference in AUC, all versions of the NRI, as well as the reclassification calibration statistic. The comparison of the AUC for such models has been shown to be biased by several authors with overly conservative P values.[215, 245, 253, 254] While the other measures have been shown to have an appropriate probability of false positive findings,[215] the estimates of fit will still be optimistic. It is only in other populations or adjustment through resampling that proper estimates can be derived.[233]

In addition, in many fields, including cardiovascular risk prediction, treatment implications are clear for those considered at high risk or low risk of the outcome, but less so for those considered at intermediate risk. Often additional testing is ordered to guide decision making and to gain insight at what side of the risk spectrum an individual resides. Such cascaded testing can be more cost-effective and potentially have the greatest impact on clinical practice. Researchers have recently shown interest in examining reclassification properties for additional tests within subgroups of the population defined by the reference model.[202] The 'clinical NRI' based on those at intermediate risk only has been suggested as a relevant criterion.[238] This, however, has been found to be inflated even under the null hypothesis,[215] and a solution has been offered to correct the bias.[215, 239]

Thus, as pointed out by Mühlenbruch and colleagues, care must be taken when computing and interpreting the NRI in all its forms. The number of categories, the placement of cut points, and the distribution of risk in the population of interest all need to be taken into account. As a result, the various ways of quantifying risk reclassification all have advantages and caveats. While the continuous NRI is attractive, it is not a panacea since it is based on ranks rather than changes in magnitude of predicted absolute risk. The categorical NRI, moreover, can be very useful when evaluating improvement in assignment to clinically relevant risk strata. Risk stratification already exists in a variety of settings,[255] and is often incorporated into clinical guidelines.[27, 125-127, 247] While care must be taken in its interpretation, reclassification analysis, including the NRI, can be a useful step toward evaluating utility of risk prediction models for use in clinical practice.

CHAPTER 8

Net Reclassification Improvement: Outcome Selection

Yeboah and colleagues compared the ability of several risk markers to improve prediction of coronary heart disease (CHD) and cardiovascular disease (CVD) among individuals at intermediate risk in the Multi-Ethnic Study of Atherosclerosis (MESA).[202] They reported that coronary artery calcification (CAC) provided superior reclassification compared with other novel risk markers and recommended CAC as a tool for refining cardiovascular risk prediction in individuals at intermediate risk. While the added predictive ability of CAC in CHD risk prediction was substantial and confirmed previous findings,[165] supporting CAC as a candidate for CVD screening based on the results is less grounded.

While it is straightforward to define an intermediate-risk group for CHD, this is not the case for CVD because accepted thresholds are lacking. Yeboah and colleagues [202] included persons at intermediate risk for CHD and therefore the results might not necessarily apply to persons at intermediate risk for CVD.[256]

While CAC has been shown to accurately predict CHD in different populations, CAC has not been proven to be a useful predictor for stroke.[257] In the study by Yeboah and colleagues,[202] addition of CAC to the Framingham risk score provided overall net reclassification improvement of 0.659 for CHD and 0.466 for CVD risk categorization. The net percentage correctly reclassified in the group without events hardly changed after adding a non-CAC-related outcome such as stroke (40.4% for CHD and 36.0% for CVD) (Table 8.1 [202]). However, the net percentage correctly reclassified for those with events, which reflects the ability to identify persons who will benefit from intensive treatment, dropped from 25.5% for CHD and 10.6% for CVD (Table 8.1 [202]).

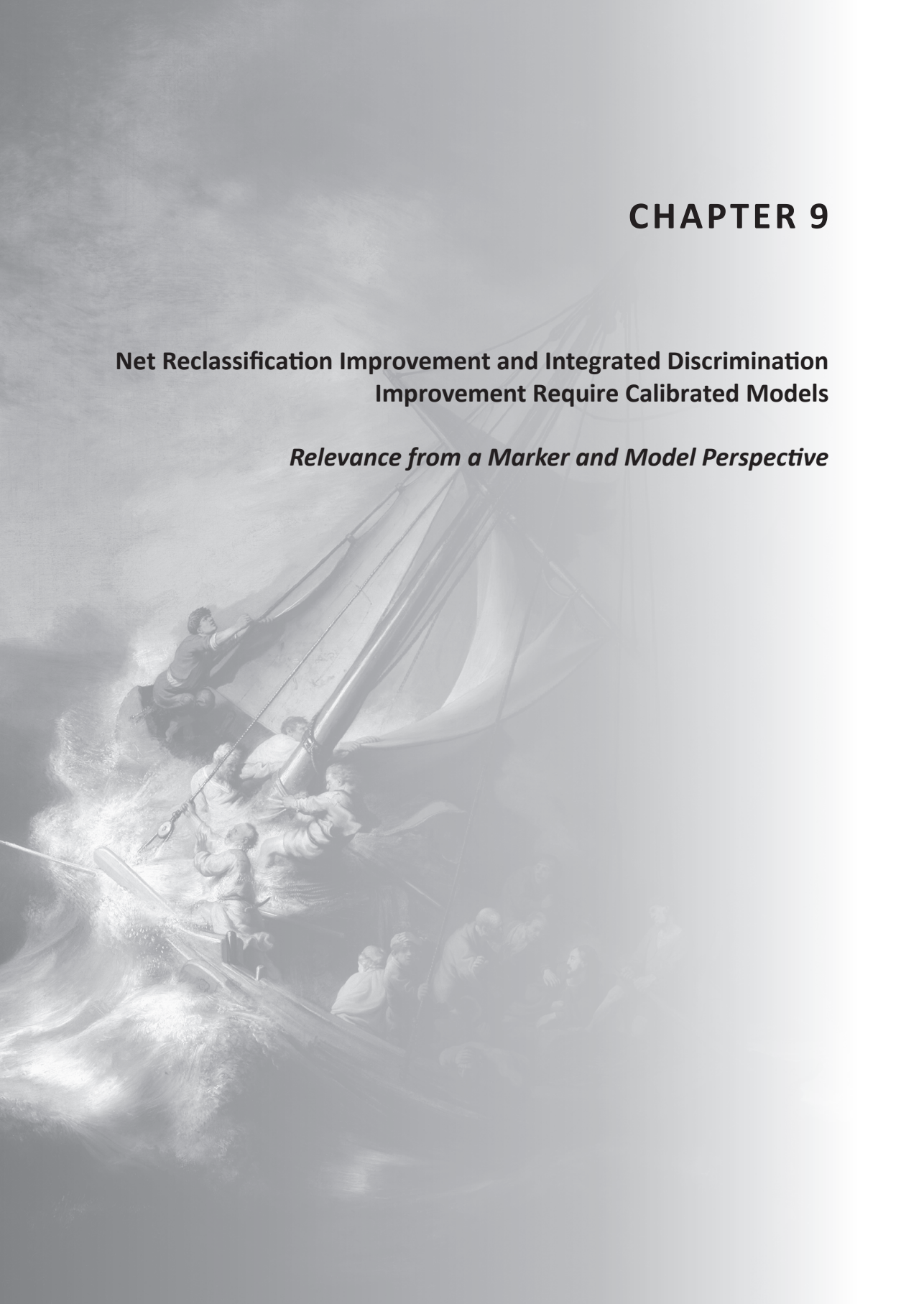
The net 25.5% correctly reclassified persons with CHD events in the current study [202] and 24.0% previously reported [165] imply that adding CAC to risk prediction models moves a substantial proportion of persons initially at intermediate risk to the high-risk group, in which they qualify for more intensive preventive treatment. This supports the incorporation of CAC in CHD risk assessment. However, whether the net 10.6% correctly reclassified persons with CVD events provided by CAC is sufficiently large to warrant recommending CAC as a screening tool for CVD is doubtful.

The general trend in developing new guidelines on CVD prevention is moving toward focusing on broader CVD risk rather than on CHD risk only.[258] However, before considering new markers for CVD risk prediction, all components of this broad outcome should be considered and limitations for stroke risk prediction should be recognized.

Table 8.1 – Net reclassification improvement for incident coronary heart disease and cardiovascular disease with the addition of coronary artery calcification to the Framingham risk score in MESA participants at intermediate-risk of coronary heart disease

Outcome	Risk category based on FRS predictors and CAC				
	Low (< 5%)	Intermediate (5-20%)	High (> 20%)	Net correctly reclassified	Overall NRI
CHD					0.659
Persons with event (n = 94)	12	46	36	25.5%	
Persons without event (n = 1236)	589	557	90	40.4%	
CVD					0.466
Persons with event (n = 123)	16	78	29	10.6%	
Persons without event (n = 1207)	493	655	59	36.0%	

Values represent the number of MESA participants at intermediate CHD risk by the FRS alone reclassified in risk categories according to the model based on FRS plus CAC for participants who had a CHD (or CVD) event or did not have a CHD (or CVD) event. CAC = coronary artery calcification; CHD = coronary heart disease; CVD = coronary heart disease; FRS = Framingham risk score; MESA = Multi-Ethnic Study of Atherosclerosis; NRI = net reclassification improvement. Adapted from Yeboah and colleagues.[202]



CHAPTER 9

Net Reclassification Improvement and Integrated Discrimination Improvement Require Calibrated Models

Relevance from a Marker and Model Perspective

For the last 3 decades, clinical prediction models have mainly been evaluated on the basis of their ability to discriminate between persons who develop the event of interest and persons who do not, as quantified by the c-statistic or area under the receiver operator characteristic curve (AUC).[248, 249] The AUC considers sensitivity and specificity of the model over all possible cut points of predicted risk. However, prediction models are often used to classify patients into risk categories that correspond to diagnostic or therapeutic decisions. This provoked the idea of comparing models according to their ability to adequately assign clinical risk categories based on absolute risk estimates.[16, 17, 132, 137] Analyses of risk reclassification have hit the ground running: uptake of measures such as net reclassification improvement (NRI) has been enormous,[115] and guidance documents on evaluations of markers and prediction models embraced it as a step prior to full-blown cost-effectiveness analysis.[114] More recently, several researchers reviewed the current applications of reclassification analysis and expressed concerns about inappropriate use.[115, 133, 134, 210, 251, 259-261]

In the introductory article on NRI and integrated discrimination improvement (IDI), Pencina and colleagues point out that "IDI (and by extension NRI as well) depends on model calibration" because "the discrimination slope suffers from the drawback of being dependent on model calibration, the same might also affect the IDI" and "When evaluating the performance of a model after addition of a new marker, it is essential to check for improvement (or at least no adverse effect if other measures improve) in calibration".[16, 226] Recently, Hilden and Gerds warned "not (to) rely on IDI and NRI" and that these measures "offer guidance that cannot be trusted" when evaluating the added value of markers to prediction models.[228] They employ theoretical examples and sophisticated mathematical developments to conclude that "If IDI and NRI are used to measure gain in prediction performance, then poorly calibrated models may appear advantageous, and in a simulation study, even the model that actually generates the data (and hence is the best possible model) can be improved on without adding measured information".[228] This puts IDI and continuous NRI in the category of metrics that are "nonproper", in contrast with AUC or Brier score.

One can easily reach the same conclusion as Hilden and Gerds without simulations and mathematical developments. For example, when simply doubling predicted risks for all individuals in a study, usually a substantial proportion will be reclassified to other risk categories, and differences in predicted risks will be inflated. The question regarding the relevance of these findings is not convincingly answered in the article by Hilden and Gerds: should we indeed no longer trust the conclusions from the over 1000 scientific publications presenting NRI or IDI results?

Theoretical example

The example by Hilden and Gerds [228] illustrates the consequences of miscalibration on NRI and IDI: a population is broken down into 3 groups sized 50%, 30%, and 20%. The observed event rates are 30%, 60%, and 80% in each respective group. Hilden and Gerds compare 2 models: the first model correctly assigns a risk of 30%, 60% and 80% to each respective group, while the second model assigns a risk of 0% to all persons in the first group and a risk of 100% to all persons in the second and third group. Continuous NRI and IDI are positive when comparing the second model to the first model (0.76 and 0.22, respectively), suggesting that the second model

is better, whereas using the 'proper' metrics of AUC and Brier score one observes decreased model performance (AUC goes down from 0.71 to 0.69, and Brier score goes up from 0.21 to 0.31).

We consider a third model to show that even 'proper' measures do not have to agree: the model assigns a constant predicted risk to everyone, equal to the event rate in the entire population (49%) or randomly assigns risks from the interval 48% to 50%. When comparing the third model with the second model, we obtain negative continuous NRI and IDI of substantial magnitude (-0.76 and -0.38, respectively), suggesting that the third model, which has no discriminatory capacity, is much worse than the second. Inference based on AUC concurs (0.69 for the second versus 0.50 for the third model). Yet, Brier scores suggest that the third model is better (0.31 for the second versus 0.25 for the third model).

This paradox can be explained. Brier score is a combined measure of discrimination and calibration, whereas AUC, continuous NRI, and IDI are measures intended to evaluate discrimination only. Furthermore, AUC is not affected by calibration whereas NRI and IDI are. Our extension of Hilden and Gerds' example shows how it can be challenging (and confusing) to try to summarize both discrimination and calibration with a single metric.

Marker versus model perspective

We consider 2 perspectives on the evaluation of prediction models: one with the primary focus on quantifying the contributions of an added marker ('marker perspective', focus on the intrinsic predictive value of the marker), and another more general perspective on comparing the predictions of various candidate models to support clinical decision making ('model perspective').

Marker perspective

By far, the most common way of evaluating improvements in predictions by a new marker is by fitting 2 nested models on the same data set—one model without the marker and one with the marker under study—and subsequently compare the predictions from these models.[17] In such situations, both models are expected to fit the data well without miscalibration, where calibration is defined in the weak sense: if the event rate is p among persons whose calculated risks are equal to p, then the model risk p(covariables) is considered well calibrated.[262] Markers are typically added to models which contain a limited number of well-known predictors.[133] Therefore, with adequate sample sizes, miscalibration due to overfitting is unlikely, and NRI or IDI hence do not suffer from the suggested bias and spurious inference in this context.[138, 233] Although Hilden and Gerds question "What can happen in real applications?",[228] they do not bring up any examples from the literature, because the setting of validating unaltered nested models in an external population is not how markers are assessed in medical research. It is common practice to refit both models in studies that attempt to verify the value of a marker, hence focusing on replication of the previous marker assessment.

Miscalibration would be a relevant concern when the 2 nested models are applied unaltered to an external validation population as studied by Hilden and Gerds.[228] Pepe and Janes suggest that calibration should be assessed first, and any lack of calibration needs to be corrected before one can decide whether a marker holds sufficient promise.[262] This can be done by recalibrating the model, for example by adjusting the intercept and calibration slope to the external population.[233] We note that such recalibration does not guarantee calibration in a stronger sense, i.e. by each covariable pattern.[263] Evaluating biomarker's value using miscalibrated models can lead spurious practical recommendations. Imagine a study on whether a new expensive blood biomarker should be added to the Framingham risk score. The Framingham and Framingham-plus-biomarker models are applied to a population in Europe, where the Framingham risk score is known to overestimate absolute risks of cardiovascular disease (CVD).[104, 229, 230] Without recalibration, we could end up with a recommendation to measure the biomarker in the entire population because it might improve apparent model performance by improving calibration. Such a conclusion is merely of theoretical interest, because a more sensible strategy would be to use available resources to recalibrate the Framingham risk score or develop and validate a new prediction model.

Model perspective

When comparing several distinct candidate models, it may be relevant to assess which of them provides the best risk classification (and concomitant decision-making) for a specific population or patient group (e.g. [104, 217, 232]). Direct head-to-head comparison of a new model versus an existing model or comparison of 2 existing models with coefficients and intercepts applied as published (i.e. without refitting or recalibrating) mimics the application of risk models in everyday clinical practice. Systematic underestimation or overestimation of established risk functions is a fact of life and a well-recognized phenomenon in CVD prediction models (e.g. [104, 217, 229, 230, 232, 264]).

In this context, a careful assessment of both calibration and discrimination of the models is necessary. This can, for example, be accomplished by using AUC for discrimination and the slope-and-intercept approach for calibration (or graphically by calibration plots)[235, 243], or by decomposing a summary measure such as the Brier score.[265] In situations where clinically meaningful risk categories exist, the components of the category-based NRI can be used to quantify differences in risk classification due to both discrimination and calibration. It should be noted that, in these situations, NRI needs to be interpreted in the context of the complementary measures of calibration and discrimination.[115] Decision analytic summary measures, such as the change in net benefit,[244] relative utility,[266] or weighted NRI,[137] may however be most appropriate for head-to-head comparisons of prediction models used for classification purposes. Findings on substantive miscalibration of established risk functions may inspire efforts to recalibrate or adapt these models.[217, 229, 230]

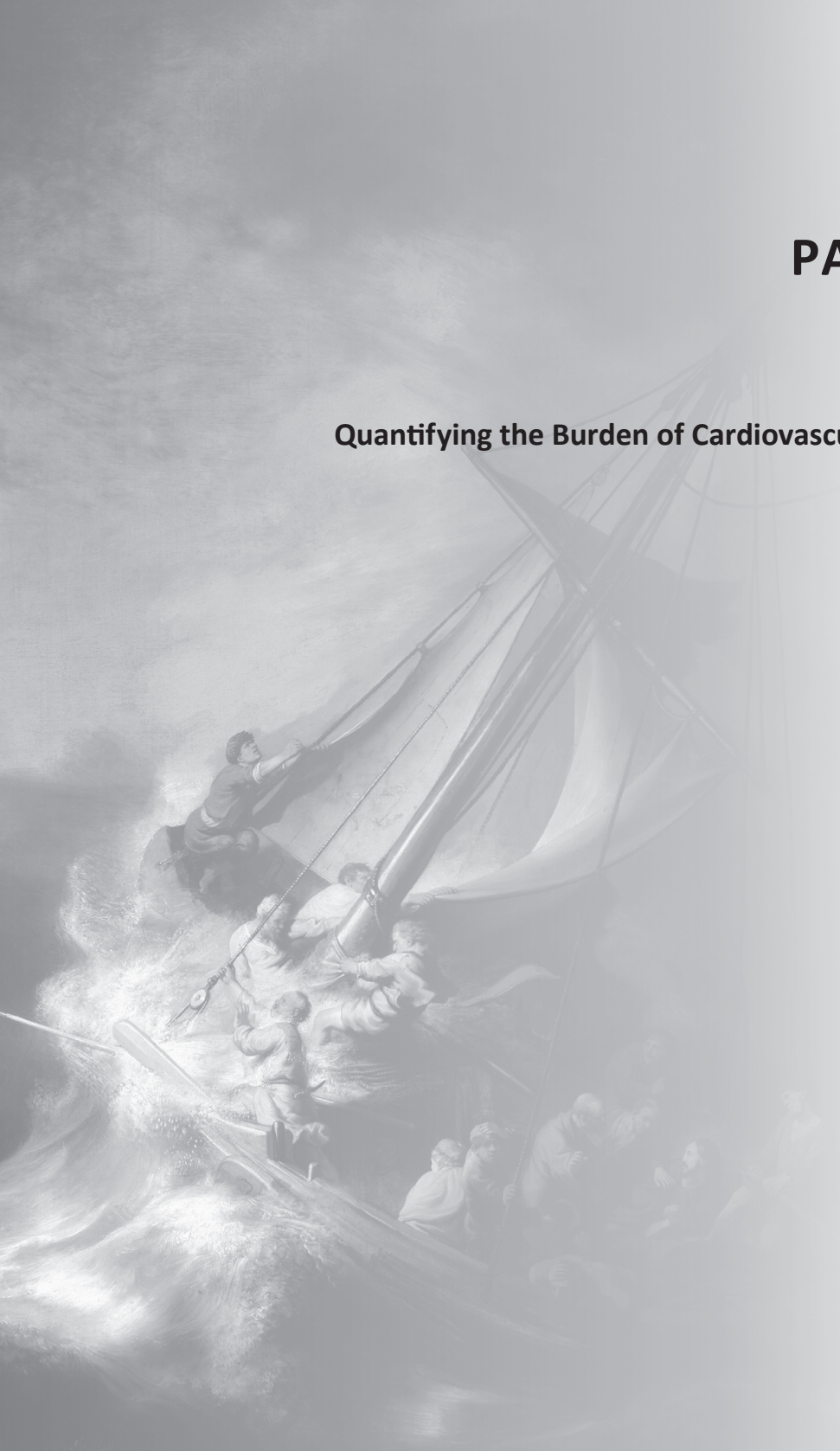
We note that IDI [16] and continuous NRI [137] were not proposed for the 'model perspective'. However, differences in discrimination between candidate models can be quantified by continuous NRI or IDI but only after ascertaining adequate calibration.

Conclusions

Appropriate application and interpretation of the NRI and IDI are imperative to avoid spurious claims of improved prediction and erroneous clinical inference.[115, 133] Like most other summary statistics, NRI and IDI should not to be interpreted on their own, but combined with metrics such as the change in AUC, calibration measures, and decision analytic measures in order to assess increments in clinical usefulness.[114, 115, 133, 210, 259] Depending on the perspective, model calibration is a necessary condition for the evaluation of the intrinsic value of an added marker or can be an inherent part of head-to-head comparisons of candidate models. We do not see this property as limiting the applicability of NRI and IDI, especially not when examining the potential of a new marker using nested models that are fitted on the same study population.

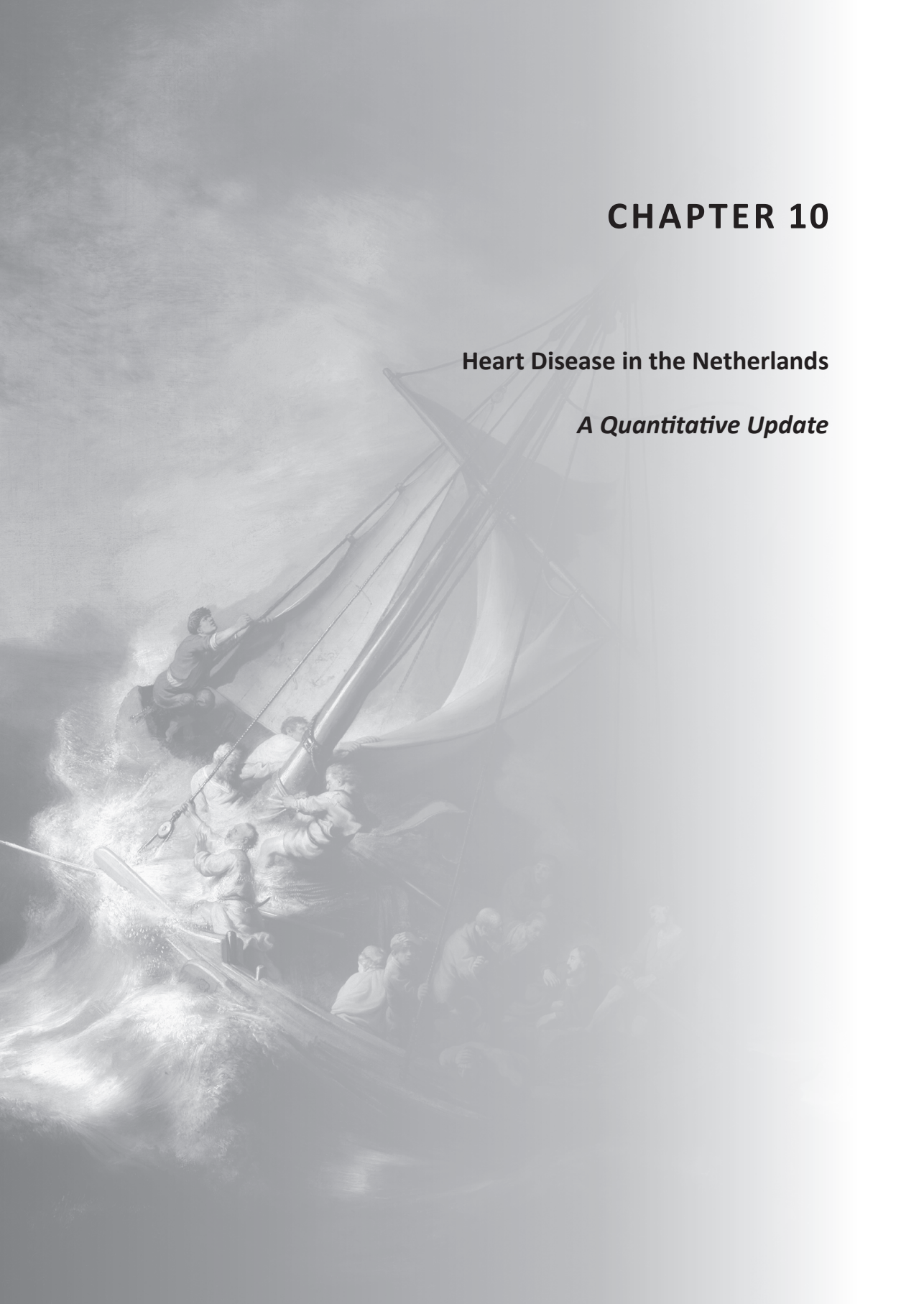
Heart attacks were recognized as a public health problem only in this century. They are likely to lose this notoriety early in the next.

- Michael S. Brown and Joseph L. Goldstein
Heart attacks: Gone with the century?
Science 1996;272(5262):629



PART III

Quantifying the Burden of Cardiovascular Disease



CHAPTER 10

Heart Disease in the Netherlands

A Quantitative Update

In this chapter we discuss cardiovascular mortality, incidence and prevalence of heart disease, and cardiac interventions and surgery in the Netherlands. We combined most recently available data from various Dutch cardiovascular registries, Dutch Hospital Data (LMR), Statistics Netherlands (CBS), and population-based cohort studies, to provide a broad quantitative update. The absolute number of people dying from cardiovascular diseases is declining and cardiovascular conditions are no longer the leading cause of death in the Netherlands. However, a substantial burden of morbidity persists with 400,000 hospitalizations for cardiovascular disease involving over 80,000 cardiac interventions annually. In the Netherlands alone, an estimated 730,000 persons are currently diagnosed with coronary heart disease, 120,000 with heart failure, and 260,000 with atrial fibrillation. These numbers emphasize the continuous need for dedicated research on prevention, diagnosis, and treatment of heart disease in the Netherlands.

This chapter provides an update on the current number of persons with cardiovascular and cardiac disease manifestations in the Netherlands. Although the mortality from cardiovascular disease (CVD) in our country has declined, its disease burden remains high. Therefore, recent data on the number of patients with specific clinical cardiac disease entities, those having undergone surgical or percutaneous procedures, as well as estimates of the number of hospitalizations for cardiac reasons, are also given.

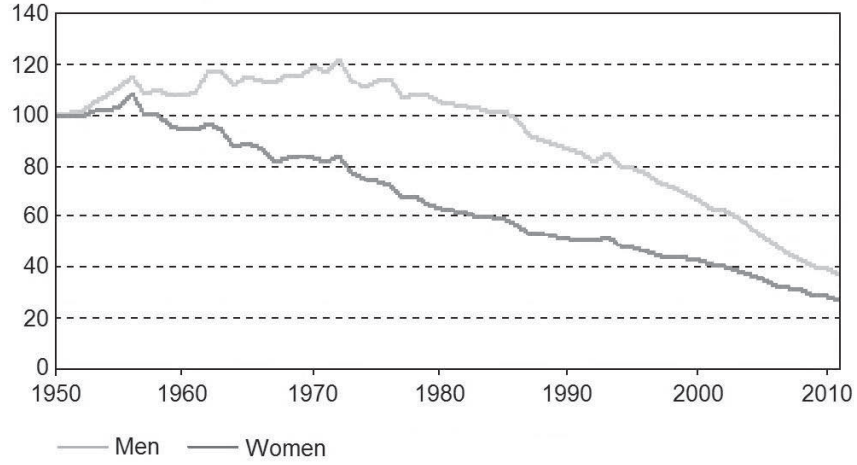
Data have been derived from various sources. Because it was not possible to obtain information from the year 2012 in every instance, exact present-day numbers of procedures or hospitalizations may be slightly dissimilar from those provided herein. Still, we hope that our numbers will provide some insight into the actual burden of heart disease in the Netherlands and its management.

Cardiovascular mortality

Since its peak in the late 1950s (in women) and the early 1970s (in men), cardiovascular mortality in the Netherlands has gradually declined. This reduction has occurred despite the larger number of elderly persons as well as the more advanced age of contemporary Dutch citizens. After correction for these changes (standardization), the drop in cardiovascular mortality that has taken place, a reduction of about 70%, is considerable.[122, 267] Cardiovascular mortality from 1950 to 2012 is delineated in Figure 10.1. After 1980, the cardiovascular mortality rates in women and men tend to converge.[267] Currently, CVD accounts for 27% of all deaths. This percentage was 33% 10 years ago, 37% in 1992 and between 45 and 50% in earlier decades. In the year 2012, 39,048 persons (20,733 women and 18,315 men) died from a primary cardiovascular cause (Table 10.1).[122] The number of persons dying from CVD amounted to 46,942 in 2003, and thus a drop in absolute numbers of deaths from CVD has taken place concomitantly with the relative decrease in fatal CVD. Cardiovascular mortality as a fraction of total mortality in the last 10 years is presented in Table 10.1. The specific causes of cardiovascular mortality in the year 2012 are presented in Table 10.2.[122]

Inspection of the data makes it clear that most cardiovascular deaths result from atherosclerotic disease affecting the coronary, cerebral, and other arterial vessels. Women die more often from

Figure 10.1 – Standardized cardiovascular mortality per 100,000 inhabitants in the Netherlands from 1950 through 2011



Adapted from the National Public Health Compass (National Institute for Public Health and the Environment [RIVM]).[267]

more 'mature' atherosclerotic manifestations such as stroke and heart failure than men: the latter die in larger numbers from myocardial infarction (MI). However, one should appreciate that the primary cause of death is often difficult to ascertain and, in particular in persons over 80 years of age, may not be accurate.[73, 89] For instance, the number of 766 individuals supposedly dying from infectious CVD could well be false, since neither the incidence of

Table 10.1 – Total and cardiovascular mortality in the Netherlands from 2003 through 2012

Year	Cardiovascular mortality n (%)	Non-cardiovascular mortality n (%)	Total n
2003	46,942 (33)	94,994 (67)	141,936
2004	44,638 (33)	91,915 (67)	136,553
2005	43,350 (32)	93,052 (68)	136,402
2006	41,720 (31)	93,652 (69)	135,372
2007	40,849 (31)	92,173 (69)	133,022
2008	40,129 (30)	95,007 (70)	135,136
2009	38,897 (29)	95,338 (71)	134,235
2010	39,009 (29)	97,049 (71)	136,058
2011	38,132 (28)	97,609 (72)	135,741
2012	38,371 (27)	102,442 (73)	140,813

Source: Statistics Netherlands (CBS). Adapted from Vaartjes and colleagues.[122] Reproduced with permission of the Dutch Heart Foundation.

Table 10.2 – Cardiovascular causes of death in the Netherlands in 2012

Cause of death	Men n (%)	Women n (%)	Total n (%)
Ischemic heart disease	5691 (31)	4029 (19)	9720 (25)
Myocardial infarction	3514	2681	6195
Cerebrovascular disease	3302 (18)	5222 (25)	8524 (22)
Congenital heart disease	64 (< 1)	46 (< 1)	110 (< 1)
Rheumatic and valvular heart disease	698 (4)	1023 (5)	1721 (4)
Infectious heart disease	331 (2)	435 (2)	766 (2)
Other heart diseases	5778 (32)	7543 (36)	13,321 (34)
Heart failure	2625	4136	6761
Atrial fibrillation	538	939	1477
Arterial vascular disease	1067 (6)	714 (3)	1781 (5)
Atherosclerosis and/or hypertension	1023 (6)	1227 (6)	2250 (6)
Other vascular disease	361 (2)	494 (2)	855 (2)
Total	18,315 (100)	20,733 (100)	39,048 (100)

Source: Statistics Netherlands (CBS). Adapted from Vaartjes and colleagues.[122] Reproduced with permission of the Dutch Heart Foundation.

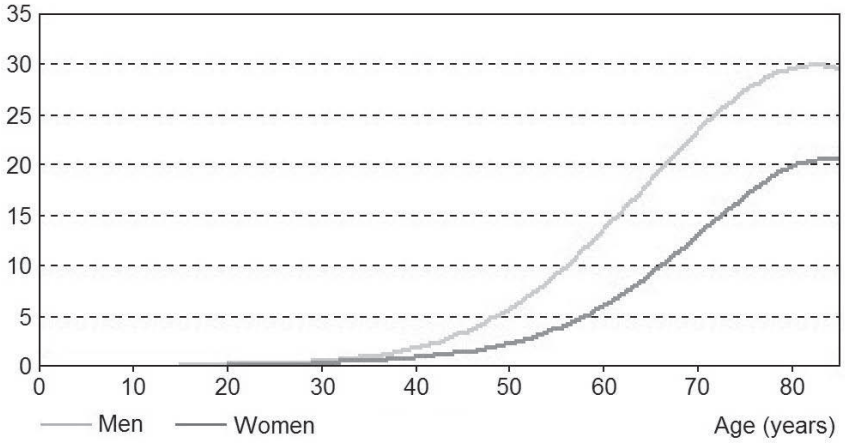
bacterial endocarditis (estimated to be approximately 300 cases per year in the Netherlands) nor its clinical course (estimated case fatality less than 20%) are able to account for the numbers reported.[268] Although the incidence of infective endocarditis has been stable in other parts of Europe over the past decades,[269] it must be noted that contemporary data from the Netherlands are lacking.

On their own, atrial fibrillation (AF) and hypertension represent unlikely primary causes of death, yet thousands of deaths are attributed to these morbid conditions. Also, the mortality statistics combine causes and modes of death. For instance, heart failure is not a disease entity in itself, but merely a symptom of underlying cardiac conditions. Presumably many more persons die from the consequences of heart failure,[270] but these deaths are attributed to for instance coronary, valvular, or congenital heart disease. This is likewise also the case for sudden cardiac death, which now only constitutes a minor part of the cause of death statistics ('Other heart diseases' in Table 10.2), whereas Dutch population-based studies have demonstrated that approximately 10% of all deaths in adults fulfill the criteria for sudden cardiac death.[85, 271]

Coronary heart disease

On the basis of estimates from registries in the general population from 2007, 648,300 Dutch citizens had coronary heart disease (CHD) (estimated prevalence in women 3%, and 5% in men). Combined with the incidence of CHD in the same year (82,100 persons), the total number of women and men with CHD was estimated to be 730,400. Of these, an estimated 298,100 had angina.[267] Although men and women are struck by cerebrovascular disease at about the same age (data not shown), women develop CHD disease approximately 10 years later than their male counterparts (Figure 10.2).

Figure 10.2 – Coronary heart disease incidence per 1000 inhabitants in the Netherlands in 2007



Source: general practice registry. Adapted from the National Institute for Public Health and the Environment (RIVM).[267]

Myocardial infarction

In 2012, 3514men and 2681 women died from an MI (Tables 10.2 and 10.3).[122] Their absolute numbers in the years between 1980 and 2012 are presented in Table 10.3. MI-associated mortality declined significantly by more than 70% over time in both men and women. Age-standardized mortality declined even further. The number of hospitalizations for MI in 2012 was 20,025 in men and 9653 in women. Between 1980 and 2012, the age-standardized MI admission rate (year of standardization: 2012) declined by 42% in men and by 23% in women. However, the absolute number of hospitalizations for MI has not changed much.[122]

Significant discordance in mortality statistics based on self-reports of hospitals (performance indicators) and data from clinical registries is noted. Hospital mortality from MI is between 5 and 10% according to data from Statistics Netherlands (CBS), with age being the main determinant of adverse outcomes. The incidence of first MI has been declining by about 3 to 4% per year in the last decade, both in men and women. Total incidence declined by 38% in men and by 32% in women between 1998 and 2007.[272, 273]

Table 10.3 – Absolute number of fatal myocardial infarctions in the Netherlands from 1980 through 2012

Year	Men		Women	
	n (%)	Per 100,000 inhabitants	n (%)	Per 100,000 inhabitants
1980	12,634	180	7718	108
1985	12,486	174	8082	110
1990	10,002	135	7300	97
1995	8888	116	6800	87
2000	7291	93	5668	70
2005	5361	66	4141	50
2010	3840	47	2983	36
2012	3514	42	2681	32

Data are not standardized. Source: Statistics Netherlands (CBS). Adapted from Vaartjes and colleagues.[122] Reproduced with permission of the Dutch Heart Foundation.

Surgical procedures

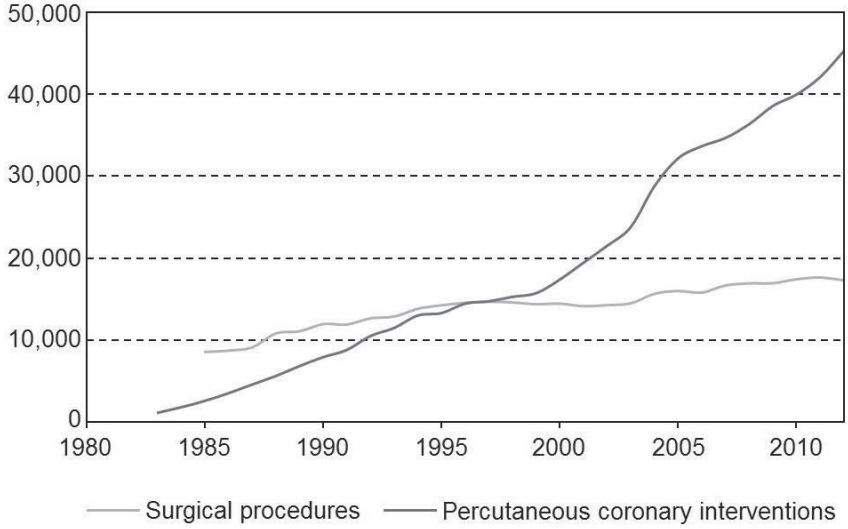
The total number of surgical procedures, including pediatric surgery, has gradually increased over the years to 17,293 operations in 2012, performed in 16 surgical centers (Figure 10.3).[122] Seven percent of these interventions are 'urgent' (i.e. take place before the start of the next working day after the decision to operate has been taken).[274]

About two-thirds of the 16,262 operations in adults in 2012 involved coronary artery bypass grafting (CABG), while half of all surgical procedures are represented by isolated CABG (source: Supervisory Committee for Cardiac Interventions in the Netherlands [BHN]). In these procedures, the use of only arterial grafts has increased from 15% in 1995 to nearly 26% in 2011.[274] The 30-day mortality of isolated CABG in 2010 was 1.2%.[122]

In 2012, a total of 3020 operations were related to diseases of the aortic valve, and in 41% of these procedures coronary bypass grafts were implanted (source: Supervisory Committee for Cardiac Interventions in the Netherlands [BHN]). The type of prostheses implanted has gradually changed from mainly mechanical prostheses in the 1990s to the use of bioprostheses in nearly 80% of the operations nowadays. In addition to CABG and aortic valve surgery, mitral valve surgery is the most common indication for cardiac surgery with approximately 1750 operations annually. Concomitant CABG is performed in 36% of these operations.[122] The proportion of mitral valve repairs has increased to over 75%. Active endocarditis is reported in less than 200 surgical procedures per year.[274] Overall the 30-day mortality associated with valvular surgery in 2010 was 3.6%.[122]

Mainly as a result of varying availability of donor hearts, the number of yearly heart transplants

Figure 10.3 – Absolute number of surgical procedures and percutaneous coronary interventions in the Netherlands from 1983 through 2012



Source: Supervisory Committee for Cardiac Interventions in the Netherlands (BHN). Adapted from Vaartjes and colleagues.[122] Reproduced with permission of the Dutch Heart Foundation.

has varied considerably over the years. On average, about 40 to 50 transplants are performed each year in 3 academic medical centers.[275]

Other procedures include aortic surgery (approximately 1000 operations per year), transcatheter aortic valve implantation, and less frequently performed procedures such as surgical left ventricle reconstruction, ventricular septal rupture repair, rhythm surgery (as a concomitant or as a stand-alone procedure), surgery for correction of congenital heart disease, or management of cardiac trauma.[276, 277]

Percutaneous coronary interventions

While the number of surgical procedures has only risen gradually in the last decade, this has not been the case with the percutaneous interventions (PCIs). Their number has risen much more quickly in recent years. For instance, in 2012, 45,305 PCIs were performed in 30 centers, and this number represents more than a doubling of these procedures in a time frame of only 10 years (Figure 10.3).[122, 278] The most frequent indications for PCI were stable angina (42%), acute MI (33%) and unstable angina (22%). Over 90% of the procedures involved stent placement.[275]

ICD and pacemaker implants

There has been a substantial increase in the number of implantable cardioverter-defibrillator (ICD) implants in the last 10 years. Symptomatic patients with advanced heart failure (e.g. left ventricular ejection fraction < 30%) are the main recipients. Currently, their number is in

the order of about 5000 new implants per year (Table 10.4). Registration of indications is not complete, but most (approximately 80%) implants are prophylactic, i.e. implanted in patients at high risk for sudden cardiac death. The other patients receive an ICD after successful resuscitation. In addition to the new ICD implants, their replacement currently adds over 1000 procedures to the numbers presented in Table 10.4.[275] ICDs now have the ability to perform biventricular pacing in patients with heart failure and conduction abnormalities in order to emulate physiological cardiac function (i.e. cardiac resynchronization therapy). Biventricular systems are becoming more popular and now account for almost 40% of all procedures. The average age of the patients is 66 years and 23% of them are women. Relatively few (6%) ICDs are implanted beyond the age of 80 years.

Based on the Dutch ICD and Pacemaker Registry (DIPR), an additional 10,389 pacemakers (excluding cardiac resynchronization therapy) were implanted in 92 contributing hospitals in 2011. A fourth of the pacemaker implantations were replacements of another device.

Table 10.4 – Absolute number of new implantable cardioverter-defibrillator implants based on 29 centers in the Netherlands from 2003 through 2012

Year	Non-CRT	CRT	Total
	n (%)	n (%)	n
2003	800 (82)	180 (18)	980
2004	1237 (79)	327 (21)	1564
2005	1724 (72)	665 (28)	2389
2006	2005 (67)	967 (33)	2972
2007	2590 (72)	1030 (28)	3620
2008	2644 (69)	1175 (31)	3819
2009	2890 (68)	1385 (32)	4275
2010	2986 (62)	1804 (38)	4790
2011	3192 (61)	2007 (39)	5199
2012	3051 (63)	1830 (37)	4881

CRT = cardiac resynchronization therapy. Source: Netherlands Heart Rhythm Association (NHRA). Adapted from Vaartjes and colleagues.[275] Reproduced with permission of the Dutch Heart Foundation.

Heart failure

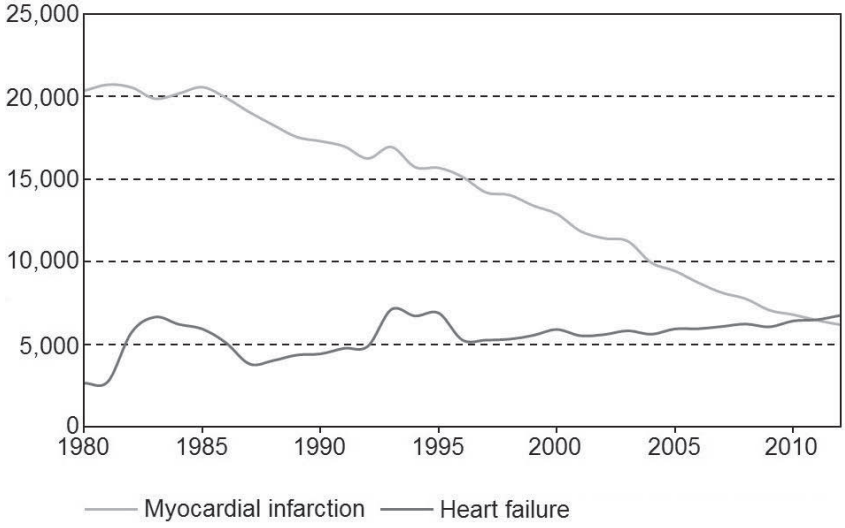
As with most other CVD, the presence of heart failure casts a shadow over the last phase of life in a considerable number of Dutch individuals. Between 20 and 30% of the general population will develop some form of heart failure, usually when they are over 70 years of age.[78] Incidence rates in the Netherlands increase steeply from about 1 per 1000 person-years below 60 years of age to almost 50 per 1000 person-years in those aged 90 years and over.

Due to the ageing of the population, an increase in the number of patients with heart failure in the Netherlands was already predicted in the 1990s.[279] Contemporary data have confirmed that forecast, and an estimated 120,000 individuals with heart failure, about 1% of the adult Dutch population, were reportedly present in 2008. The continuing ageing of the population is expected to raise their numbers to an approximate 200,000 in the coming decade.[270]

The majority of heart failure is diagnosed in chronic stages, but episodes of acute cardiac decompensation can lead to hospitalization. In 2011, 29,916 hospital admissions were registered in the Netherlands with heart failure as the primary discharge diagnosis (source: Dutch Hospital Data [LMR]).[273] The numbers are equally distributed over both sexes. This number includes readmissions which are known to be frequent in patients with heart failure. Recent Dutch data on the ratio of first admissions to readmissions is lacking, but studies from U.S. registries consistently report 30-day readmission rates up to 25%.[280] Between 1980 and 1990, the number of hospitalizations for heart failure increased by about 50%. Thereafter, a decrease was observed but, as of 2002, the number of hospitalized patients increased again, although the total number of days spent in hospital has more or less stabilized.[270]

The prognosis of patients with heart failure has been described as being more 'malignant' than that of many common cancers.[281] Five-year survival after the initial diagnosis ranges from approximately 25 to 35% in population-based studies.[78] The in-hospital mortality associated with decompensated heart failure is poor, even for first occurrences, and has been reported to be in the order of 15% in the Netherlands.[78] This is worse than the currently observed in-hospital mortality associated with acute MI.

Figure 10.4 – Absolute number of deaths attributed to myocardial infarction or heart failure as the primary cause of death in the Netherlands from 1980 through 2012



Source: Statistics Netherlands (CBS). Adapted from Vaartjes and colleagues.[122] Reproduced with permission of the Dutch Heart Foundation.

The absolute number of Dutch citizens dying either from MI or heart failure has been depicted in Figure 10.4, and clearly shows the direction of the change in both causes of death. Since 2012, the number of deaths from heart failure (n = 6761) has surpassed the mortality from MI (n = 6195) (Table 10.2 and Figure 10.4).[122]

Atrial fibrillation

AF is the most common sustained cardiac arrhythmia. The condition carries serious health consequences, including increased risk for stroke and heart failure. AF is found to be present in about a quarter of patients presenting with an ischemic stroke. The presence of many other cardiometabolic disorders, such as coronary and valvular heart disease, cardiomyopathies, hypertension, and diabetes, predispose to the development of AF.

Estimates from a Dutch population-based cohort study indicate that the lifetime risk of AF is in the order of 20 to 25%. As with heart failure, its occurrence strongly increases with age: the incidence rate of AF below 60 years of age is less than 1 per 1000 person-years, but rises to almost 20 per 1000 person-years in persons over 85 years of age.[80] These estimates may underestimate the true incidence since the presence of AF, either permanent or paroxysmal, may go undetected clinically.

On the basis of the best available data, an estimated 260,000 Dutch individuals are currently affected by AF.[282] These were responsible for 42,188 hospital admissions in 2011 with AF as the primary discharge diagnosis (source: Dutch Hospital Data [LMR]).[273] Between 1994 and 2006, no major changes in its prevalence were observed but, given current demographic developments, an increase in the number of persons with AF in the coming years is projected.[282]

Hospitalizations for cardiovascular disease

During the last years, the number of hospitalizations associated with CVD has stabilized at around 400,000 (2400 per 100,000 inhabitants). Almost 115,000 (29%) of these comprise 1 day admissions related to diagnostic or therapeutic procedures, or observations of cardiovascular symptoms. In the remaining cases, the mean duration of hospital stay is about 6 days (source: Statistics Netherlands [CBS]). Admission rates for rhythm disturbances are on the rise.[273]

Discussion

With plausible estimates of 730,000 patients with CHD, of 120,000 persons with heart failure, and of 260,000 men and women with AF, the total count of Dutch individuals with some manifestation of heart disease could be as high as 1 million. In addition, a substantial number of women and men have other forms of atherosclerotic disease, either of the cerebral and/or the peripheral arterial system. However, since atherosclerosis is usually not limited to one organ system and many cardiac and vascular diseases co-exist, the simple summation of the various disease manifestations will likely overestimate the number of individuals with cardiovascular and/or heart disease. In view of the high CVD prevalence, it is striking that actual mortality

from CVD has declined so much. Currently, 27% of all deaths result from CVD, and cancer has overtaken CVD as the main cause of death in the Netherlands in both women and men (source: Statistics Netherlands [CBS]). Cardiovascular mortality in the Netherlands is low in international comparisons. The current Dutch age-standardized mortality from CVD is 147 per 100,000, and only Spain and France have lower cardiovascular mortality rates (143 and 126 per 100,000, respectively). In all other European countries, including for instance Switzerland and Greece, cardiovascular mortality is higher.[283]

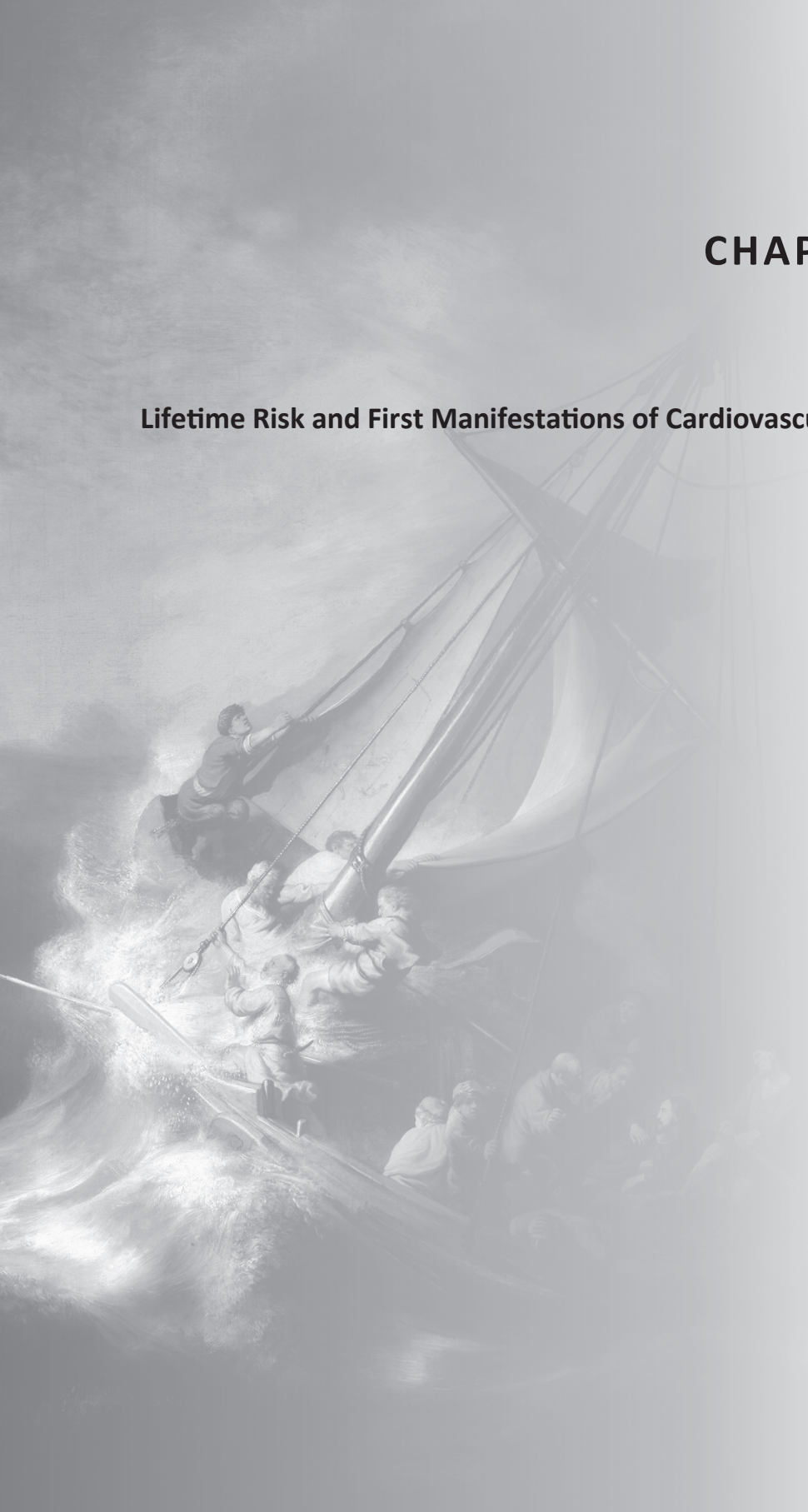
The number of cardiac procedures in the Netherlands, in particular that of PCI and CABG, is below the Organisation for Economic Cooperation and Development (OECD) average. As in most other European countries, the rate of PCI versus CABG is in the order of 2.5. Both the numbers of percutaneous and surgical cardiac procedures in the Netherlands are 50% lower than in our affluent neighboring countries, Belgium and Germany.[283] Patients with an acute MI are the main PCI target population with about 13,000 procedures in 30,000 patients hospitalized for MI. The 15,000 PCIs performed for stable angina constitute a relatively large proportion of PCI procedures, although the large number of patients with angina in the population must be taken into account.

Throughout our review we have cited various sources from which we obtained data on CVD in the Netherlands. However, data from different sources can be conflicting due to differential participation of hospitals in registries or due to the outcome definitions used. As an example, cardiovascular mortality is defined differently in the statistical updates from the Dutch Heart Foundation [272] compared to Statistics Netherlands (CBS). This results in minor discrepancies in the annual number of deaths attributable to CVD, in this case related to the inclusion or exclusion of congenital and perinatal heart disease and vascular autoimmune disorders (e.g. Tables 10.1 and 10.2).

Future projections are always fraught with uncertainty, but demographic trends undeniably suggest an increase in the number of patients with heart disease and other forms of CVD in the not too distant future. Still, these trends are not dissimilar to the circumstances observed in the last decades, during which time cardiovascular mortality decreased so markedly. Most likely, these developments will continue, and high morbidity (and high prevalence) but relatively low mortality from CVD remains the most plausible scenario for the foreseeable future.

CHAPTER 11

Lifetime Risk and First Manifestations of Cardiovascular Disease



Objective

To evaluate differences in first manifestations of cardiovascular disease (CVD) between men and women in a competing risks framework.

Design

Prospective population-based cohort study among persons living in the community in Rotterdam, the Netherlands.

Participants

8419 participants (60.9% women) aged 55 years or older and free from CVD at baseline.

Main outcomes

First diagnosis of coronary heart disease (CHD; myocardial infarction, revascularization, and coronary death), cerebrovascular disease (stroke, transient ischemic attack, and carotid revascularization), heart failure, or other cardiovascular death; or death from non-cardiovascular causes. Data were used to calculate lifetime risks of CVD and its first-incident manifestations adjusted for competing non-cardiovascular death.

Results

During follow-up of up to 20.1 years, 2888 participants developed CVD (826 CHD, 1198 cerebrovascular disease, 762 heart failure, and 102 other cardiovascular death). At age 55, overall lifetime risks of CVD were 67.1% (95% CI 64.7-69.5%) for men and 66.4% (95% CI 64.2-68.7%) for women. Lifetime risks of first-incident manifestations of CVD in men were 27.2% (95% CI 24.1-30.3%) for CHD, 22.8% (95% CI 20.4-25.1%) for cerebrovascular disease, 14.9% (95% CI 13.3-16.6%) for heart failure, and 2.3% (95% CI 1.6-2.9%) for other deaths from CVD. For women the figures were 16.9% (95% CI 13.5-20.4%), 29.8% (95% CI 27.7-31.9%), 17.5% (95% CI 15.9-19.2%), and 2.1% (95% CI 1.6-2.7%), respectively. Differences in the number of events that developed over the lifespan in women compared with men (per 1000) were 7 fewer for any CVD, 102 fewer for CHD, 70 more for cerebrovascular disease, 26 more for heart failure, and 1 fewer for other cardiovascular death; all outcomes manifested at a higher age in women. Patterns were similar when analyses were restricted to hard atherosclerotic CVD outcomes, but absolute risk differences between men and women were attenuated for both CHD and stroke.

Conclusions

At age 55, though men and women have similar lifetime risks of CVD, there are considerable differences in the first manifestation. Men are more likely to develop CHD as a first event, while women are more likely to have cerebrovascular disease or heart failure as their first event than men, although these manifestations appear most often at older ages.

For both men and women, cardiovascular disease (CVD) remains among the leading causes of death and disability in Western societies.[284, 285] Considerable sex differences exist, however, in the occurrence of the various manifestations of CVD. Men have a higher risk of CHD than women, especially at younger ages.[286] Women, on the other hand, have a similar or greater propensity for developing stroke [287] and heart failure.[78, 288] Because strategies for prevention of stroke and heart failure might differ from strategies for prevention of coronary heart disease (CHD), knowledge about the first manifestation of CVD is important for primary prevention purposes. Population-based data on sex differences in CVD are scarce for the various first manifestations of CVD.

Women have a higher life expectancy than men and consequently have more time to develop CVD. Cardiovascular risk factors, such as smoking, not only increase the susceptibility for CVD but are also associated with an increased risk of dying from non-cardiovascular causes before the development of CVD.[289, 290] Therefore, in comparisons of first manifestations of CVD, competing risks among the different manifestations and death from non-cardiovascular causes cannot be neglected. To date no studies have compared multiple first manifestations of CVD between men and women in a competing risks framework.

We used long term follow-up data from the prospective population-based Rotterdam Study to calculate the lifetime risks of CVD and the first-incident manifestations of CVD in middle-aged and elderly men and women.

Methods

Study design, setting, and population

This study was performed within the Rotterdam Study, a prospective population-based cohort designed to study the occurrence and determinants of age related diseases in the general population. Details regarding the objectives and design have been reported previously.[32-37] Briefly, for the initial cohort (RS-I-1; Figure 1.1) all inhabitants aged 55 years or older from a well-defined suburb in the city of Rotterdam, Netherlands, received an invitation to participate, and 7983 (78.1%) were enrolled. Levels of participation at baseline did not differ for men and women but were lower with increasing age.[103] Between 1990 and 1993, baseline data were collected during standardized home interviews and 2 visits to the research center. Starting in 2000, the Rotterdam Study was extended with a second cohort (RS-II-1; Figure 1.1) of inhabitants who reached the age of 55 and persons who migrated into the research area since the start of RS-I-1. A total of 3011 (67.3%) were enrolled, and baseline data were collected between 2000 and 2001. Besides the minimum age, there were no other criteria for eligibility for participation in either of the cohorts.

For the present analysis, we excluded all participants with a history of CVD (CHD, cerebrovascular disease, or heart failure) at baseline (n = 1421), those who did not visit the research center at baseline for assessment of cardiovascular risk factors (n = 1034), those who did not provide, or withdrew, informed consent for collection of follow-up data (n = 76), and those without any available follow-up data (n = 44). This left a total of 8419 persons eligible for the present analysis.

Data collection during follow-up

Follow-up started at the date of assessment of cardiovascular risk factors at the research center. Methods for the follow-up and data collection in the Rotterdam Study have been described in detail elsewhere.[105, 291] Briefly, data on clinical outcomes are collected continuously through an automated follow-up system involving digital linkage of the study database to medical records maintained by general practitioners working in the research area. Moreover, well-trained research assistants affiliated with the study regularly check the medical records of each participant by hand for diagnoses of interest. Notes, outpatient clinic reports, hospital discharge letters, electrocardiograms, and imaging results are collected from general practitioner records and hospital records. Subsequently, research physicians independently adjudicate all data on potential events. Afterwards, medical specialists whose judgments are considered decisive review the potential cases. Information on vital status is additionally obtained from the central registry of the municipality of the city of Rotterdam.

Assessment of cardiovascular disease outcomes

All participants were followed up for the occurrence of incident CHD, cerebrovascular disease, heart failure, other cardiovascular death, and non-cardiovascular death. Definitions and procedures on the adjudication of cardiovascular outcomes have been described in detail previously.[78, 105, 291, 292] Briefly, CHD was defined as fatal or non-fatal myocardial infarction (MI), surgical or percutaneous coronary revascularization procedure (as a proxy for unstable or incapacitating angina), or death from CHD.[105] Cerebrovascular disease was defined as stroke,[291] transient ischemic attack,[292] or carotid revascularization procedure. In accordance with the guidelines of the European Society of Cardiology heart failure was defined as the combination of typical symptoms and signs, confirmed by objective evidence of cardiac dysfunction or a positive response to initiated treatment.[78, 105] Other deaths from CVD included all cardiovascular mortality other than fatal CHD or fatal stroke, such as deaths from aortic aneurysms, peripheral vascular disease, valvular heart disease, and pulmonary embolisms.[105]

Hard CHD was defined as fatal and non-fatal MI or definite coronary mortality. Hard cerebrovascular disease was defined as non-hemorrhagic stroke. Other atherosclerotic cardiovascular deaths mainly encompassed deaths from abdominal aortic aneurysms and peripheral vascular disease. These definitions of hard atherosclerotic CVD correspond with the endpoints used in clinical trials and guidelines for primary prevention of atherosclerotic CVD.

Assessment of cardiovascular risk factors

Standardized assessment of anthropometrics, cardiovascular risk factors, and medication use at baseline has been described in detail for both RS-I-1 [104] and RS-II-1.[165] In RS-I-1, diabetes mellitus was defined as a random or post-load serum glucose concentration ≥ 11.1 mmol/L, or the use of blood glucose-lowering medication. In RS-II-1, diabetes mellitus was defined as a fasting serum glucose concentration ≥ 7.0 mmol/L, a non-fasting serum glucose concentration ≥ 11.1 mmol/L (only if fasting serum was unavailable), or the use of blood glucose-lowering medication. A family history of premature MI was defined as having a parent, sibling, or child

who experienced a MI before the age of 65. Use of blood pressure-lowering medication was defined as the use of antiadrenergics, diuretics, β blockers, calcium channel blockers, or renin-angiotensin system modifying agents.

Statistical analysis

We used linear regression models or Mann-Whitney U tests for continuous data and χ^2 tests for categorical data to compare baseline characteristics between men and women.

We calculated remaining lifetime risks for first-incident CVD and its components (CHD, cerebrovascular disease, heart failure, and other cardiovascular death) for men and women at age 55, 65, 75, and 85. When older individuals are followed for longer time periods, death from non-cardiovascular causes precludes the occurrence of CVD in many. Similarly, when first manifestations of CVD are studied, the occurrence of one manifestation precludes consideration of any subsequent CVD event. The preclusion of disease-specific outcomes of interest by death or other outcomes are referred to as competing risks.[293, 294] Standard application of survival analysis, such as Cox regression and Kaplan-Meier estimates, do not take competing risks into account as those who develop competing events are censored. Consequently, absolute risks are overestimated.[293, 294] We therefore used a method that takes into account the occurrence of competing events to compute lifetime cumulative incidences in left truncated data with age as time scale.[295] This enabled us to compute lifetime risks with only 20.1 years of follow-up. Lifetime risk estimates reflect the cumulative incidences to the age of last observation: in the present analysis the maximum age was 106.4 years for men and 107.0 years for women. In the setting of competing risks analysis, the sum of the lifetime risks of CVD and competing non-cardiovascular death equals 1; the sum of the lifetime risks of the different first manifestations of CVD equals the lifetime risk of CVD.[293, 294] We computed the excess number of events occurring over the lifespan in women compared with men (per 1000) by subtracting the lifetime risk in men from the lifetime risk in women for each of the manifestations of CVD and multiplying it by 1000.

To evaluate the effect of adjustment for cardiovascular risk factors on sex differences, we quantified the association of sex with the subdistribution hazard of CVD (or the specific first manifestations) and non-cardiovascular death using the method proposed by Fine and Gray.[296] Results are presented for models that were unadjusted (model 1); adjusted for age (as a linear covariable) and level of education (model 2); and additionally adjusted for systolic and diastolic blood pressure, concentrations of total and high-density lipoprotein cholesterol, diabetes mellitus, smoking status, family history of premature MI, body mass index (BMI), C-reactive protein concentration, use of blood pressure-lowering medication, and use of statins (model 3).

Next, we used the data augmentation proposed by Lunn and McNeil to enable direct comparisons between the effect estimates of sex on specific first manifestations of CVD by traditional Cox regression.[297] This allows inference on the difference in cause-specific hazard ratios (HRs) of sex on particular manifestations of CVD in the presence of competing manifestations and non-cardiovascular death.[294] We present P values from the fully adjusted models (model 3).

To exclude the influence of differences in the inclusion of 'softer' events in CHD and cerebrovascular disease, we then limited the analysis to first-incident hard atherosclerotic cardiovascular events.

As a secondary analysis, we also repeated the main analysis with CVD categorized as fatal or non-fatal. A first manifestation of CVD was considered fatal if death occurred within 28 days of the event and death was attributed to CVD.

As participants of RS-II-1 were enrolled 6 to 8 years after the baseline examination of the participants of RS-I-1, we allowed for strata of cohorts in the regression analyses and repeated all the analysis in each cohort separately. A total of 476 (5.7%) individuals had missing values for 1 or more traditional cardiovascular risk factors (range 0-2.5% per risk factor) and other covariables were missing in up to 3.5% of the participants. These missing values were handled separately for each cohort by a single imputation with an expectation-maximization algorithm.[109] We used the level of significance of $P < 0.05$. All measures of association are presented with 95% confidence intervals (CIs). Data were handled and analyzed with the IBM SPSS Statistics version 21.0.0.1 (IBM Corp., Somers, NY, U.S.), R version 3.0.0 and its libraries cmprsk, etm, and mstate.[110]

Results

Baseline characteristics

On average women were older than men and had lower levels of attained education (Table 11.1). Cholesterol concentrations and BMI were generally higher in women, whereas men had higher diastolic blood pressure and were more often smokers. Several baseline characteristics differed between both cohorts, including an overall increase in the level of highest attained education, higher blood pressure, lower concentrations of total cholesterol, more frequent use of statins, and higher BMI in RS-II. Also, although still significant, sex differences in smoking status were less pronounced in RS-II.

Lifetime risk of cardiovascular disease

During a total of 81,276 person-years (median 13.5 years for persons censored alive) of follow-up, 2888 participants developed a CVD event, which corresponds to an incidence rate of 35.5 (95% CI 34.2-36.9) per 1000 person-years for any first manifestation of CVD. Of these 2888 events, 826 were CHD, 1198 were of cerebrovascular origin, 762 were heart failure, and 102 were other cardiovascular deaths. Of the first CVD events, 608 (21.1%) were fatal. Another 1532 individuals died from non-cardiovascular causes, and 20 participants were lost to follow-up over the course of the study (mainly from emigration). In the analysis restricted to hard atherosclerotic outcomes, we included 1700 cardiovascular events, of which 766 were hard CHD, 869 non-hemorrhagic stroke, and 65 other atherosclerotic cardiovascular deaths. Details regarding the amount of follow-up and the number of specific events observed in men and women of each cohort are shown in Table 11.2 and the online supplement of the original publication.[116]

Table 11.1 – Characteristics of study populations

	Rotterdam Study I (1990-1993)			Rotterdam Study II (2000-2001)		
	Men	Women		Men	Women	
	n = 2287	n = 3758	P value	n = 1006	n = 1368	P value
Age, y	67.9 (8.3)	69.7 (9.4)	< 0.001	63.7 (7.1)	64.6 (8.0)	0.003
Education:			< 0.001			< 0.001
Primary	353 (15.7)	1024 (28.3)		62 (6.3)	129 (9.7)	
Lower/intermediate general and lower vocational	755 (33.5)	1702 (47.0)		260 (26.2)	789 (59.2)	
Higher general and intermediate vocational	805 (35.8)	738 (20.4)		395 (39.8)	283 (21.2)	
Higher vocational and university	338 (15.0)	159 (4.4)		275 (27.7)	131 (9.8)	
Systolic blood pressure, mmHg	139 (22)	140 (22)	0.24	144 (21)	142 (22)	0.077
Diastolic blood pressure, mmHg	75 (12)	73 (11)	< 0.001	81 (11)	78 (10)	< 0.001
Use of blood pressure-lowering medication	474 (20.7)	1149 (30.6)	< 0.001	221 (22.0)	357 (26.5)	0.013
Total cholesterol, mmol/L	6.3 (1.2)	6.8 (1.2)	< 0.001	5.6 (1.0)	6.0 (0.9)	< 0.001
HDL cholesterol, mmol/L	1.2 (0.3)	1.4 (0.4)	< 0.001	1.2 (0.3)	1.5 (0.4)	< 0.001
Use of statins	24 (1.1)	57 (1.5)	0.13	82 (8.2)	134 (9.9)	0.14
Diabetes mellitus	214 (9.4)	374 (10.0)	0.42	119 (11.8)	124 (9.1)	0.029
Smoking:			< 0.001			< 0.001
Current	696 (31.0)	674 (18.5)		267 (26.7)	275 (20.5)	
Former	1361 (60.5)	1022 (28.1)		567 (56.8)	519 (38.6)	
Never	191 (8.5)	1945 (53.4)		165 (16.5)	549 (40.9)	
Family history of premature MI	326 (14.8)	630 (17.5)	0.006	156 (15.8)	219 (16.3)	0.75
Body mass index, kg/m^2	25.6 (3.0)	26.7 (4.0)	< 0.001	26.9 (3.4)	27.5 (4.5)	< 0.001
C-reactive protein, mg/L [a]	1.78 (0.83-3.81)	1.79 (0.89-3.30)	0.23	0.90 (0.30-2.20)	1.00 (0.40-2.50)	0.104

Values are counts (percentages) or means (standard deviations); unimputed data. HDL = high-density lipoprotein; MI = myocardial infarction.
[a] Median (interquartile range) because of its skewed distribution.

Table 11.2 – First-incident cardiovascular events during follow-up

First-incident event		Rotterdam Study I		Rotterdam Study II	
	Total n = 8419	Men n = 2287	Women n = 3758	Men n = 1006	Women n = 1368
Cardiovascular disease	2888 (34.3)	1053 (46.0)	1491 (39.7)	164 (16.3)	180 (13.2)
CHD	826 (9.8)	361 (15.8)	338 (9.0)	81 (8.1)	46 (3.4)
Myocardial infarction	417 (5.0)	188 (8.2)	157 (4.2)	44 (4.4)	28 (2.0)
Coronary revascularization	164 (1.9)	81 (3.5)	46 (1.2)	25 (2.5)	12 (0.9)
CABG	80 (1.0)	44 (1.9)	17 (0.5)	13 (1.3)	6 (0.4)
PCI	84 (1.0)	37 (1.6)	29 (0.8)	12 (1.2)	6 (0.4)
Other fatal CHD	245 (2.9)	92 (4.0)	135 (3.6)	12 (1.2)	6 (0.4)
Cerebrovascular disease	1198 (14.2)	382 (16.7)	674 (17.9)	44 (4.4)	98 (7.2)
Stroke	725 (8.6)	231 (10.1)	416 (11.1)	23 (2.3)	55 (4.0)
Ischemic	396 (4.7)	133 (5.8)	213 (5.7)	17 (1.7)	33 (2.4)
Hemorrhagic	72 (0.9)	25 (1.1)	35 (0.9)	2 (0.2)	10 (0.7)
Unspecified	257 (3.1)	73 (3.2)	168 (4.5)	4 (0.4)	12 (0.9)
Transient ischemic attack	470 (5.6)	151 (6.6)	256 (6.8)	20 (2.0)	43 (3.1)
Carotid revascularization	3 (0.0)	0 (0)	2 (0.1)	1 (0.1)	0 (0)
Heart failure	762 (9.1)	267 (11.7)	430 (11.4)	37 (3.7)	28 (2.0)
Other cardiovascular death	102 (1.2)	43 (1.9)	49 (1.3)	2 (0.2)	8 (0.6)
Non-cardiovascular death	1532 (18.2)	573 (25.1)	791 (21.0)	93 (9.2)	75 (5.5)
No event (censored alive)	3999 (47.5)	661 (28.9)	1476 (39.3)	749 (74.5)	1113 (81.4)
Follow-up time:					
Total person-time, pys	81,276	22,769	42,234	6709	9564
Median, y	8.6 (5.9-14.9)	10.5 (4.8-15.3)	13.2 (6.2-16.0)	7.2 (5.9-8.3)	7.4 (6.3-8.4)
Median, y [a]	13.5 (7.7-16.2)	16.0 (15.1-16.7)	16.2(15.2-17.1)	7.7 (6.8-8.4)	7.7 (6.7-8.4)

Values are counts (percentages) or medians (interquartile range). CABG = coronary artery bypass grafting; CHD = coronary heart disease; PCI = percutaneous coronary intervention. [a] Follow-up for participants censored alive.

Table 11.3 – Remaining lifetime risks of first-incident manifestation of cardiovascular disease by age

	Lifetime risk			
	Men	Women	P value	Excess events[a]
Risk at 55 years of age:	n = 3293	n = 5126		
Cardiovascular disease	67.1% (64.7-69.5)	66.4% (64.2-68.7)	0.34	-7
Coronary heart disease [b]	27.2% (24.1-30.3)	16.9% (13.5-20.4)	< 0.001	-102
Cerebrovascular disease [c]	22.8% (20.4-25.1)	29.8% (27.7-31.9)	< 0.001	70
Heart failure	14.9% (13.3-16.6)	17.5% (15.9-19.2)	0.014	26
Other cardiovascular death [d]	2.3% (1.6-2.9)	2.1% (1.6-2.7)	0.39	-1
Risk at 65 years of age:	n = 3001	n = 4832		
Cardiovascular disease	63.4% (61.1-65.7)	65.6% (63.7-67.5)	0.077	22
Coronary heart disease [b]	21.6% (19.6-23.6)	14.7% (13.3-16.2)	< 0.001	-69
Cerebrovascular disease [c]	22.7% (20.7-24.7)	30.3% (28.4-32.1)	< 0.001	76
Heart failure	16.8% (15.0-18.5)	18.2% (16.7-19.7)	0.113	14
Other cardiovascular death [d]	2.4% (1.6-3.1)	2.4% (1.8-3.0)	0.49	0
Risk at 75 years of age:	n = 1648	n = 3180		
Cardiovascular disease	58.7% (55.8-61.6)	63.4% (61.2-65.6)	0.006	48
Coronary heart disease [b]	15.4% (13.2-17.5)	12.5% (11.0-14.0)	0.014	-29
Cerebrovascular disease [c]	21.9% (19.4-24.3)	28.9% (26.8-31.0)	< 0.001	70
Heart failure	18.3% (16.0-20.6)	19.4% (17.6-21.2)	0.24	11
Other cardiovascular death [d]	3.1% (2.1-4.2)	2.7% (2.0-3.5)	0.26	-4
Risk at 85 years of age:	n = 438	n = 1296		
Cardiovascular disease	52.0% (46.6-57.3)	57.1% (53.9-60.3)	0.054	51
Coronary heart disease [b]	11.0% (7.6-14.3)	11.6% (9.6-13.7)	0.38	6
Cerebrovascular disease [c]	19.3% (15.1-23.5)	24.8% (22.0-27.6)	0.017	55
Heart failure	17.3% (13.2-21.3)	17.9% (15.5-20.4)	0.40	6
Other cardiovascular death [d]	4.4% (2.2-6.6)	2.8% (1.7-3.9)	0.095	-16

Values are remaining lifetime risks (95% confidence intervals) of first-incident cardiovascular event adjusted for competing non-cardiovascular death.

[a] Excess number of events per 1000 women was computed as the absolute difference in remaining lifetime risk between men and women multiplied by 1000.

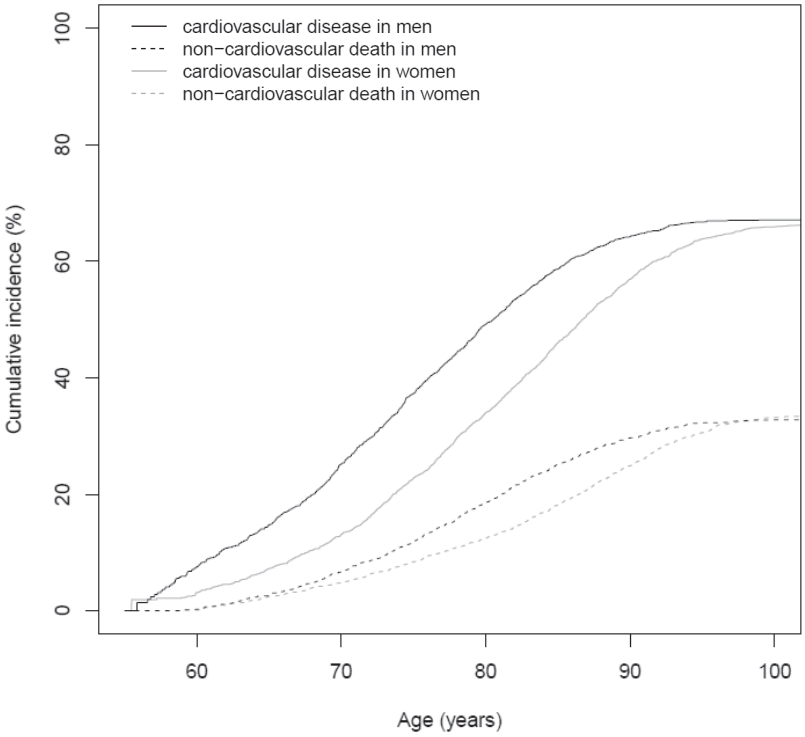
[b] Coronary heart disease was defined as myocardial infarction, coronary revascularization, or death from coronary heart disease.

[c] Cerebrovascular disease was defined as stroke, transient ischemic attack, or carotid revascularization.

[d] Other cardiovascular death was defined as all cardiovascular mortality other than fatal coronary heart disease or stroke.

The overall lifetime risk of CVD was similar for men and women at the age of 55 (Table 11.3, Figure 11.1), with 67.1% (95% CI 64.7-69.5%) for men and 66.4% (95% CI 64.2-68.7%) for women. Remaining lifetime risks of CVD decreased with advancing age as the incidence of competing non-cardiovascular death increased. The decrease was larger for men than for women: for those aged 85 without CVD the remaining lifetime risk of CVD was 52.0% (95% CI 46.6-57.3%) in men and 57.1% (95% CI 53.9-60.3%) in women. The cumulative incidence of CVD in men increased steadily with age, whereas in women up to the age of 70 the cumulative incidence remained low and increased steeply thereafter (Figure 11.1).

Figure 11.1 – Cumulative incidence of cardiovascular disease and competing non-cardiovascular death for men and women aged 55

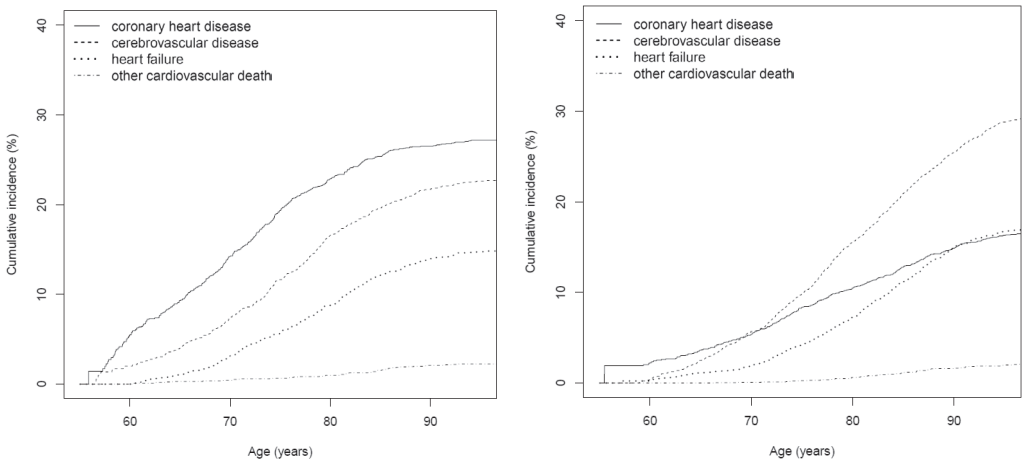


First manifestation of cardiovascular disease

Although the overall lifetime risks of developing any CVD were similar for men and women, the first manifestations were different (Table 11.3, Figure 11.2). At age 55, lifetime risks of the first manifestations of CVD in men were 27.2% for CHD, 22.8% for cerebrovascular disease, and 14.9% for heart failure versus 16.9%, 29.8%, and 17.5%, respectively, for women. For every 1000 women, this would translate into 102 fewer first manifestations with CHD developing over the lifespan, but 70 more with cerebrovascular disease and 26 more with heart failure when compared with men. With increasing age, excess risk remained about the same for cerebrovascular disease but decreased for CHD and heart failure. Cerebrovascular disease and

heart failure became the most common initial manifestations for men free from CVD at age 75 or higher. In women, cerebrovascular disease was the most common first manifestation in the remaining lifespan at every age. The cumulative incidences for the various CVD manifestations are shown in Figure 11.2. In men, the cumulative incidence of CHD is higher than that of cerebrovascular disease and heart failure at all ages with the cumulative incidences of the latter 2 catching up until age 70 and all curves running about parallel thereafter. In women, the curves were steeper for cerebrovascular disease and heart failure than for CHD, especially at higher ages, indicating that most cases of cerebrovascular disease and heart failure occurred in the later part of the lifespan. Women were on overage older than men when CVD manifested, which was the case for each of the separate CVD outcomes (Table 11.4). In both men and women, those with CHD as the first manifestation were the youngest, followed by those in whom CVD manifested with cerebrovascular disease and heart failure; those who died from other cardiovascular causes were the oldest.

Figure 11.2 – Cumulative incidence of first cardiovascular disease manifestations adjusted for competing non-cardiovascular death for men (left) and women (right) aged 55



Coronary heart disease was defined as myocardial infarction, coronary revascularization, or death from coronary heart disease. Cerebrovascular disease was defined as stroke, transient ischemic attack, or carotid revascularization. Other cardiovascular death included all cardiovascular mortality other than fatal coronary heart disease or stroke.

In line with the pattern of later onset of CVD in women shown in Figure 11.1, hazards (i.e. instantaneous risks) were lower for women than men with respect to any first cardiovascular event or death from non-cardiovascular causes (Table 11.5). The adjusted cause-specific HR of sex for development of CVD was not significantly different from the HR for competing non-cardiovascular death (Lunn and McNeil P = 0.33 for model 3), which corroborates with the comparable lifetime risk of CVD. There was a large sex difference in the unadjusted hazards for the development of CHD as a first manifestation of CVD. Also, despite the overall lower hazards of CVD, women had a somewhat higher hazard than men for developing cerebrovascular disease but not for heart failure. The age adjusted HRs (model 2) were generally similar to the ones additionally adjusted for traditional and newer cardiovascular risk factors (model 3). Even after adjustment for these risk factors, cause-specific HRs for the sex differences remained significantly lower for CHD than cerebrovascular disease (Lunn and McNeil P < 0.001 for model

Table 11.4 – Age of first-incident cardiovascular event or non-cardiovascular death

First-incident event	Men n = 3293	Women n = 5126	P-value [a]
Cardiovascular disease	75.8 (8.3)	80.2 (8.9)	< 0.001
Coronary heart disease [b]	73.1 (8.1)	78.7 (9.5)	< 0.001
Cerebrovascular disease [c]	76.4 (8.0)	79.8 (8.8)	0.009
Heart failure	78.1 (7.8)	81.7 (8.2)	0.006
Other CVD death [d]	80.0 (8.4)	84.0 (7.4)	0.17
Non-cardiovascular death	78.8 (8.4)	82.7 (9.5)	< 0.001

Values are mean (standard deviation) age in years of occurrence of first-incident cardiovascular event or competing non-cardiovascular death during follow-up among men and women.
[a] Adjusted for age at start of follow-up and cohort.
[b] Coronary heart disease was defined as myocardial infarction, coronary revascularization, or death due to coronary heart disease.
[c] Cerebrovascular disease was defined as stroke, transient ischemic attack, or carotid revascularization.
[d] Other cardiovascular death included all cardiovascular mortality other than fatal coronary heart disease or stroke.

3) or heart failure (Lunn and McNeil P = 0.010 for model 3). Competing risk regression, with Fine and Gray models, yielded smaller HRs than traditional Cox models for all associations except for cerebrovascular disease (Table 11.5). Estimates were similar in both cohorts. These are presented in the online supplement of the original publication.[116]

Hard atherosclerotic cardiovascular disease

Lifetime risks for hard atherosclerotic CVD were substantially lower than with the broad definition of CVD (Table 11.6 and the online supplement of the original publication).[116] For those aged 55, the lifetime risk of atherosclerotic CVD was 43.2% (95% CI 40.7-45.6%) for men and 38.1% (95% CI 36.2-40.1%) for women. For men and women free from atherosclerotic CVD at age 85, remaining lifetime risks were about 31%. Again sex differences were apparent in the first manifestation of atherosclerotic CVD (Table 11.6, Figure 11.3). At age 55, lifetime risks of first manifestations of atherosclerotic CVD were 23.5% for hard CHD and 17.8% for non-hemorrhagic stroke in men versus 14.4% and 22.5%, respectively, in women. For every 1000 women, this translates into 91 fewer first manifestations of CHD over the lifetime and 48 more first manifestations of stroke compared with men. In men CHD was the most common first manifestation in the remaining lifespan except for those aged 85 years and older, whereas in women stroke was the predominant presentation during the remaining lifespan at all ages, especially in older individuals. Identical patterns of the first occurrence of atherosclerotic CVD outcomes by rising age were observed as were seen for the broad CVD outcome, although the cumulative incidence of cerebrovascular disease crossed that of CHD in women at a somewhat higher age (Table 11.6, Figure 11.3).

Table 11.5 – Hazard ratios for cardiovascular disease and non-cardiovascular death for women compared to men

	Traditional Cox model HR (95% CI)	Competing risks model [a] HR (95% CI)
Model 1 (unadjusted):		
Cardiovascular disease	0.75 (0.70-0.81)	0.81 (0.76-0.88)
Coronary heart disease [b]	0.48 (0.42-0.55)	0.52 (0.46-0.60)
Cerebrovascular disease [c]	0.99 (0.88-1.12)	1.15 (1.02-1.29)
Heart failure	0.83 (0.72-0.96)	0.95 (0.82-1.09)
Other cardiovascular death [d]	0.67 (0.45-1.00)	0.79 (0.53-1.17)
Non-cardiovascular death	0.68 (0.61-0.75)	0.78 (0.71-0.86)
Model 2:[e]		
Cardiovascular disease	0.62 (0.57-0.67)	0.73 (0.67-0.79)
Coronary heart disease [b]	0.42 (0.37-0.49)	0.50 (0.43-0.58)
Cerebrovascular disease [c]	0.83 (0.73-0.93)	1.06 (0.94-1.20)
Heart failure	0.62 (0.53-0.72)	0.79 (0.68-0.93)
Other cardiovascular death [d]	0.53 (0.35-0.80)	0.72 (0.48-1.09)
Non-cardiovascular death	0.51 (0.46-0.57)	0.67 (0.60-0.74)
Model 3:[f]		
Cardiovascular disease	0.68 (0.62-0.75)	0.76 (0.69-0.83)
Coronary heart disease [b]	0.45 (0.37-0.53)	0.51 (0.43-0.60)
Cerebrovascular disease [c]	0.96 (0.83-1.11)	1.16 (1.00-1.33)
Heart failure	0.62 (0.52-0.75)	0.73 (0.61-0.88)
Other cardiovascular death [d]	0.73 (0.44-1.19)	0.96 (0.61-1.50)
Non-cardiovascular death	0.63 (0.55-0.71)	0.76 (0.66-0.87)

Values are hazard ratios (95% confidence intervals) for the risk of a first-incident cardiovascular event or competing non-cardiovascular death; men served as the reference category; all regression analyses used follow-up time as time scale and were stratified on cohort (see the online supplement of the original publication for results per cohort).[116]

[a] Fine and Gray method for subdistribution regression with competing risks.[296]

[b] Coronary heart disease was defined as myocardial infarction, coronary revascularization, or death due to coronary heart disease.

[c] Cerebrovascular disease was defined as stroke, transient ischemic attack, or carotid revascularization.

[d] Other cardiovascular death was defined as all cardiovascular mortality other than fatal coronary heart disease or stroke.

[e] Adjusted for age (as a linear covariable) and level of education.

[f] Adjusted for age (as a linear covariable), level of education, systolic and diastolic blood pressure, concentrations of total and high-density lipoprotein cholesterol, diabetes mellitus, smoking status, family history of premature myocardial infarction, body mass index, concentration of C-reactive protein, use of blood pressure-lowering medication, and use of statins.

Table 11.6 – Remaining lifetime risks of first-incident manifestation of hard atherosclerotic cardiovascular disease by age

	Lifetime risk			
	Men	Women	P value	Excess events [a]
Risk at 55 years of age:	n = 3293	n = 5126		
Hard cardiovascular disease	43.2% (40.7-45.6)	38.1% (36.2-40.1)	< 0.001	-51
Hard coronary heart disease [b]	23.5% (21.4-25.6)	14.4% (13.0-15.8)	< 0.001	-91
Non-hemorrhagic stroke	17.8% (15.8-19.7)	22.5% (20.8-24.2)	< 0.001	48
Other atherosclerotic cardiovascular death [c]	1.9% (1.3-2.6)	1.2% (0.8-1.6)	0.037	-7
Risk at 65 years of age:	n = 3159	n = 5003		
Hard cardiovascular disease	40.3% (38.0-42.7)	37.8% (35.8-39.7)	0.050	-26
Hard coronary heart disease [b]	20.8% (18.8-22.7)	13.7% (12.3-15.1)	< 0.001	-70
Non-hemorrhagic stroke	17.7% (15.8-19.5)	22.8% (21.0-24.5)	< 0.001	51
Other atherosclerotic cardiovascular death [c]	1.9% (1.3-2.6)	1.3% (0.8-1.7)	0.057	-6
Risk at 75 years of age:	n = 1934	n = 3560		
Hard cardiovascular disease	35.5% (32.7-38.3)	36.2% (34.1-38.4)	0.34	7
Hard coronary heart disease [b]	16.8% (14.6-18.9)	11.9% (10.5-13.4)	< 0.001	-48
Non-hemorrhagic stroke	16.7% (14.5-18.8)	22.9% (21.0-24.8)	< 0.001	62
Other atherosclerotic cardiovascular death [c]	2.1% (1.3-2.9)	1.4% (0.9-1.9)	0.093	-6
Risk at 85 years of age:	n = 594	n = 1619		
Hard cardiovascular disease	31.4% (26.9-35.8)	31.6% (28.9-34.4)	0.46	3
Hard coronary heart disease [b]	14.1% (10.8-17.4)	10.3% (8.5-12.1)	0.023	-38
Non-hemorrhagic stroke	15.9% (12.4-19.4)	20.2% (17.8-22.5)	0.026	42
Other atherosclerotic cardiovascular death [c]	1.3% (0.3-2.4)	1.2% (0.5-1.8)	0.41	-1

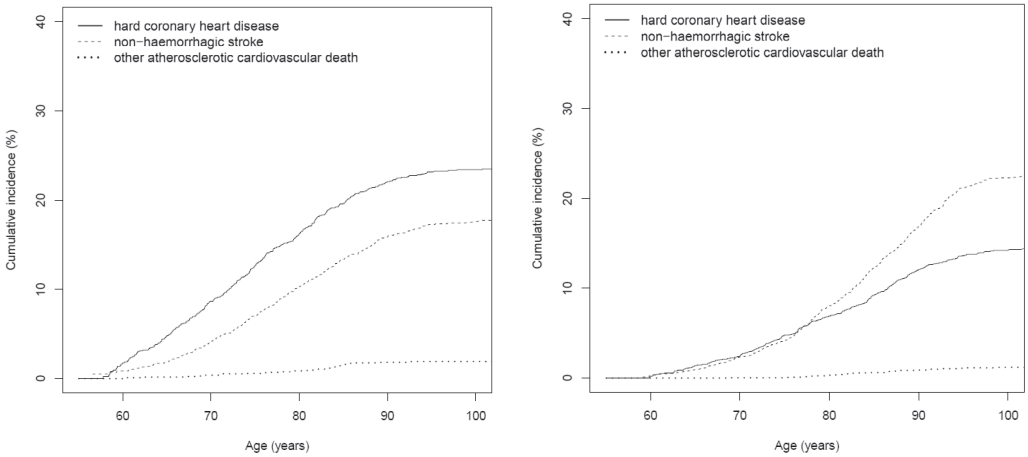
Values are remaining lifetime risks (95% confidence intervals) of first-incident hard atherosclerotic cardiovascular event adjusted for competing non-atherosclerotic death.

[a] Excess number of events per 1000 women was computed as the absolute difference in remaining lifetime risk between men and women multiplied by 1000.

[b] Hard coronary heart disease was defined as myocardial infarction or death from coronary heart disease.

[c] Other atherosclerotic cardiovascular death was defined as all atherosclerotic cardiovascular mortality other than fatal coronary heart disease or non-hemorrhagic stroke.

Figure 11.3 – Cumulative incidence of first hard atherosclerotic cardiovascular disease manifestations adjusted for competing non-atherosclerotic death for men (left) and women (right) aged 55



Hard coronary heart disease was defined as myocardial infarction or death from coronary heart disease. Other atherosclerotic cardiovascular death included all atherosclerotic cardiovascular mortality other than fatal coronary heart disease or non-hemorrhagic stroke.

Case fatality

In both men and women, fatality of the first manifestation of CVD increased with age, with women being slightly more likely to have their CVD presenting with a fatal event (18.0% of first events in men aged 55 years or older versus 20.9% in women, P = 0.047), but this was predominantly because of more fatal events in women at old age. Data are presented in the online supplement of the original publication.[116] Fatal first manifestations of CVD other than CHD, cerebrovascular disease, or heart failure were rare in all age and sex groups (Tables 11.3 and 11.6).

Discussion

Within a contemporary prospective population-based cohort of the general population, we used competing risks analysis to appropriately quantify lifetime risk of CVD and its first manifestations in both sexes. At age 55, the risk of developing any CVD over the lifespan was similar for men and women. We found large sex differences in the initial manifestation of CVD. Men are more likely to develop CHD as a first event, while women are more likely to develop cerebrovascular disease or heart failure as a first event, although these manifestations appear most often at older age.

According to data from various American cohort studies, about 60% of middle-aged men and little over half of the middle-aged women develop CVD during their remaining lifespan.[120] We report higher estimates of lifetime cardiovascular risk. These differences can be explained by

our inclusion of 'softer' cardiovascular manifestations, such as transient ischemic attack and arterial revascularization procedures. Such manifestations generally have less impact on the lives of the patients, but do significantly contribute to the overall burden of consumption of healthcare and its associated costs.

An important point to consider is that within the Rotterdam Study one of the soft coronary events, non-invasively managed angina, was not adjudicated. Angina can constitute 34% of first diagnoses of CHD in men and 42% in women, though the contribution of new onset isolated angina to the incidence of CHD is small after age 70.[286] Angina is difficult to adjudicate, but based on these estimates of angina, we covered about half of the angina events with the inclusion of coronary revascularizations. These represent the more definite and severe cases of unstable or incapacitating exertional angina. The lack of non-invasively managed angina could have reduced absolute risk difference for CHD between men and women. We therefore also conducted an analysis restricted to hard cardiovascular outcomes. In this analysis, overall lifetime risk of CVD was somewhat lower in women than in men (38.1% versus 43.2% at age 55) and excess risk attenuated for both CHD and cerebrovascular disease compared with the broad CVD endpoint. The pattern of sex differences, however, remained the same: CVD presented more often with CHD in men and more often with cerebrovascular disease in women.

The results of our regression analysis of the sex differences for the various cardiovascular manifestations were not materially affected by adjustment for cardiovascular risk factors (Table 11.5). This indicates that variation in risk factors between men and women does not explain the observed differences in risk. The pattern of sex differences was less pronounced for first manifestations of cerebrovascular disease based on the HRs compared with lifetime risks, while the sex difference in hazards for heart failure even reversed in the adjusted models. This might be explained by the fact that HRs have a more limited interpretation for the lifetime perspective [108] and even more so after adjustment for age as higher life expectancy in women is one of the driving forces behind a high lifetime risks.

Implications

The recently released British and American guidelines on primary prevention of CVD recognize the importance of assessment of lifetime risk.[6, 298] Most middle-aged women, even those with a moderate to high burden of risk factors, are at (often falsely reassuring) low short term risk of developing CVD and thereby might still not qualify for intensive preventive measures based on their global 10-year cardiovascular risk.[217, 299, 300] Our results indicate that many women have a lifetime risk of CVD that is similar to that of men. Clinicians should therefore be aware that the risk of CVD rises more steeply in women at older age than in men and that a low 10-year risk might come with a high lifetime risk. On the other hand, CVD manifests at higher ages in women than in men. Onset of CVD at older age might not have the same impact as onset at younger age, which is not accounted for by the use of lifetime risks.

The global cardiovascular risk scoring algorithms that are currently recommended in the prevention guidelines no longer include only CHD as the outcome of interest.[5, 6, 8, 9, 298] The British and American guidelines now recommend consideration of the risk of stroke besides CHD to identify individuals at high risk of CVD.[6, 9, 298] Compared with the older guidelines based

on coronary risk, substantially more women will be considered at high risk under these new guidelines and thereby qualify for more intensive risk factor control.[119] Our results on lifetime risk of hard atherosclerotic CVD (hard CHD and stroke) support this as the estimates were only somewhat lower in women than in men (Table 11.6). Despite that most attention on current prevention guidelines has focused on the indications for lipid lowering treatment, adequate control of the main modifiable causes of stroke – hypertension and smoking [301] – should remain top priorities for clinicians and policy makers to reduce the population burden of cerebrovascular disease.

We noticed that heart failure constitutes about a quarter to a third of the first manifestation of CVD in both men and women. This is a substantial proportion, especially given that by definition none of the cases of heart failure in our study were preceded by overt CHD, which is considered to be the most important cause of heart failure in older persons.[22] The high risks and similarity in men and women is in agreement with the results from 3 American population-based cohorts.[302] In the light of primary prevention of CVD this finding once more emphasizes the need to also focus on risk factors other than hyperlipidemia, as lipid lowering treatment has so far not been proved beneficial to reduce the risk of non-ischemic heart failure. Lifestyle modification and blood pressure control are the main targets for prevention of heart failure, especially in women, in whom blood pressure is known to play a more prominent role in the development of heart failure than in men.[303]

Up to age 75, first manifestations of CVD were rarely fatal in our study, and case fatality of the first manifestation of CVD increased with age. The European guidelines for prevention of CVD recommend the use of the SCORE algorithm, which can be used to estimate the 10-year risk of fatal CVD.[5, 8] A consequence of the use of fatal events only is that treatment allocation, based on absolute risk thresholds from the SCORE algorithm, disproportionately increases the likelihood for older individuals to be considered as candidates for preventive treatment. Unfortunately, the expected absolute benefit from prevention wanes with advancing age because of the increased risk of competing non-cardiovascular death.[304, 305]

Limitations

Our study has some limitations that need to be considered. Various different manifestations of CVD were adjudicated according to standardized definitions. We did not have adjudicated events available on incident angina that was managed with non-invasive treatment, non-fatal peripheral vascular disease, and non-fatal abdominal aortic aneurysms. Within a subset of the RS-I cohort, surgery for abdominal aortic aneurysms has been adjudicated, which represented only 1.3% of the first manifestations of CVD. Second, as our results were obtained from a population aged 55 years and over our results cannot be directly generalized to younger individuals who might have an even higher lifetime risk of CVD. Third, the Rotterdam Study cohorts are predominantly of European descent (97.8% white). This is relevant because lifetime risk of CVD and its manifestations vary by race.[306] Fourth, as the incidence of CVD has decreased substantially over the past decades, estimates of lifetime risk are subject to birth cohort effects. We used data from a broad age range (age 55.0-106.2 at baseline) with long follow-up (over 20 years) to ensure that individuals from various birth cohorts contribute to different age-specific cumulative incidences and thereby reduce these effects.[289] Also, the long follow-up will

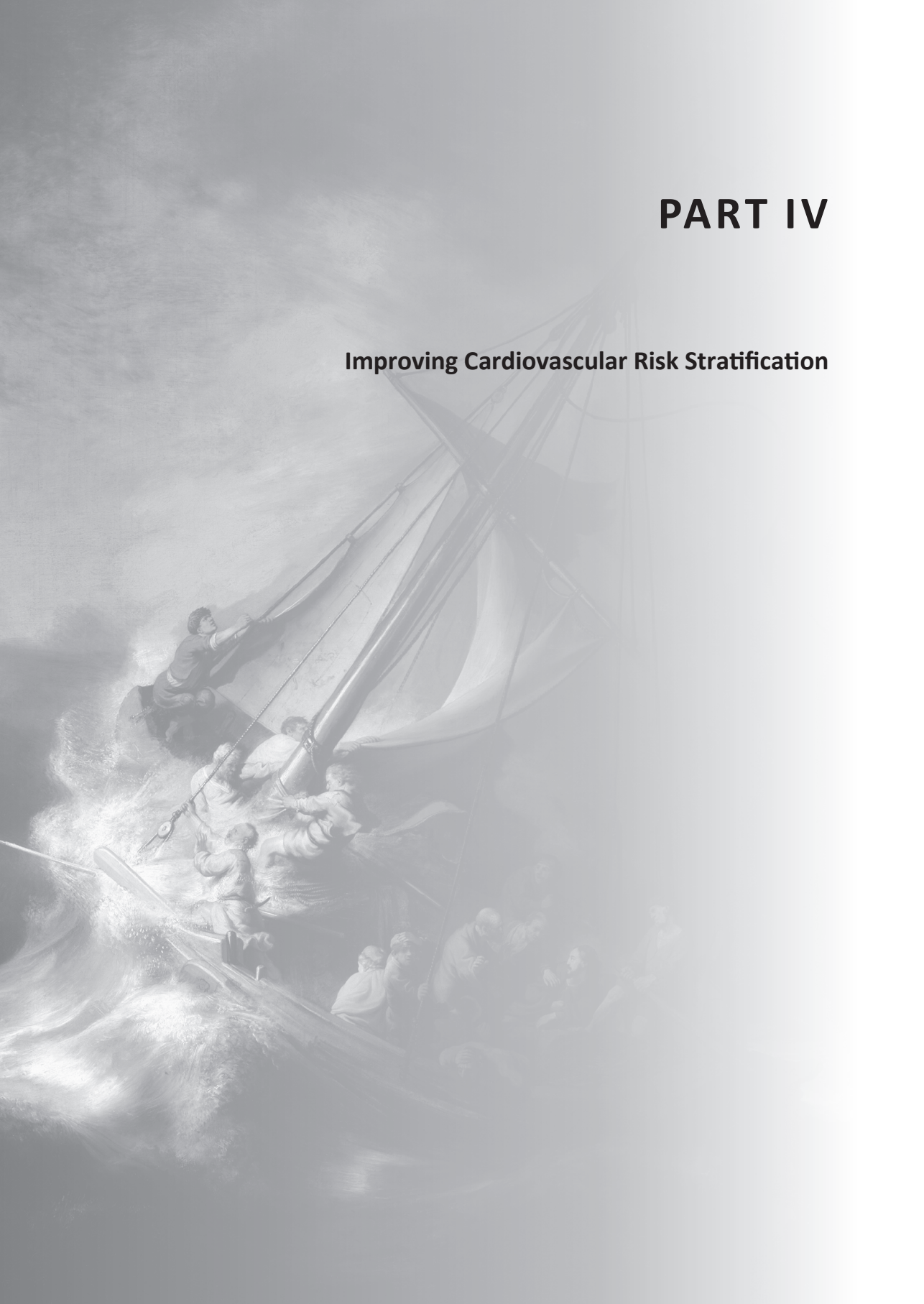
mitigate the 'healthy volunteer effect' that is known to cause an underestimation of the actual incidence of most diseases shortly after baseline in population-based studies that require active participation.[118] Participation rates at enrolment were similar for men and women in all age groups,[103] therefore this is unlikely to explain the sex differences we observed. Nonetheless, the lifetime risks of CVD in our study could be somewhat underestimated. Fifthly, we did not take into account changes in treatment and risk factors during follow-up in the multivariable regression models. Finally, in younger women MI more often presents without the hallmark symptom of chest pain.[307] This compromises optimal recognition of CHD in women and might thereby explain part of the observed sex differences in first manifestation of CVD in our study.

Conclusions

Men and women of middle age have similar overall lifetime risks of CVD, with 2 out of 3 facing some form of CVD during their life. These numbers underline that primary prevention of CVD is of paramount importance in both men and women. There are, however, considerable differences in the first manifestation of CVD, with men being more likely to develop CHD as a first event, while women are more likely to have cerebrovascular disease or heart failure as their first event, although these manifestations appear most often at older age. Our results underscore the importance of adequate control of risk factors for stroke and heart failure in primary prevention of CVD.

As with any risk classification system, perfect prediction will not be achieved, but an overall improvement in the targeting of prescription drugs to those with the most appropriate levels of risk should help maximize benefits while minimizing cost and toxicity.

- Paul M. Ridker and Nancy R. Cook
Algorithms for assessing cardiovascular risk in women
JAMA 2007;298(2):177-8

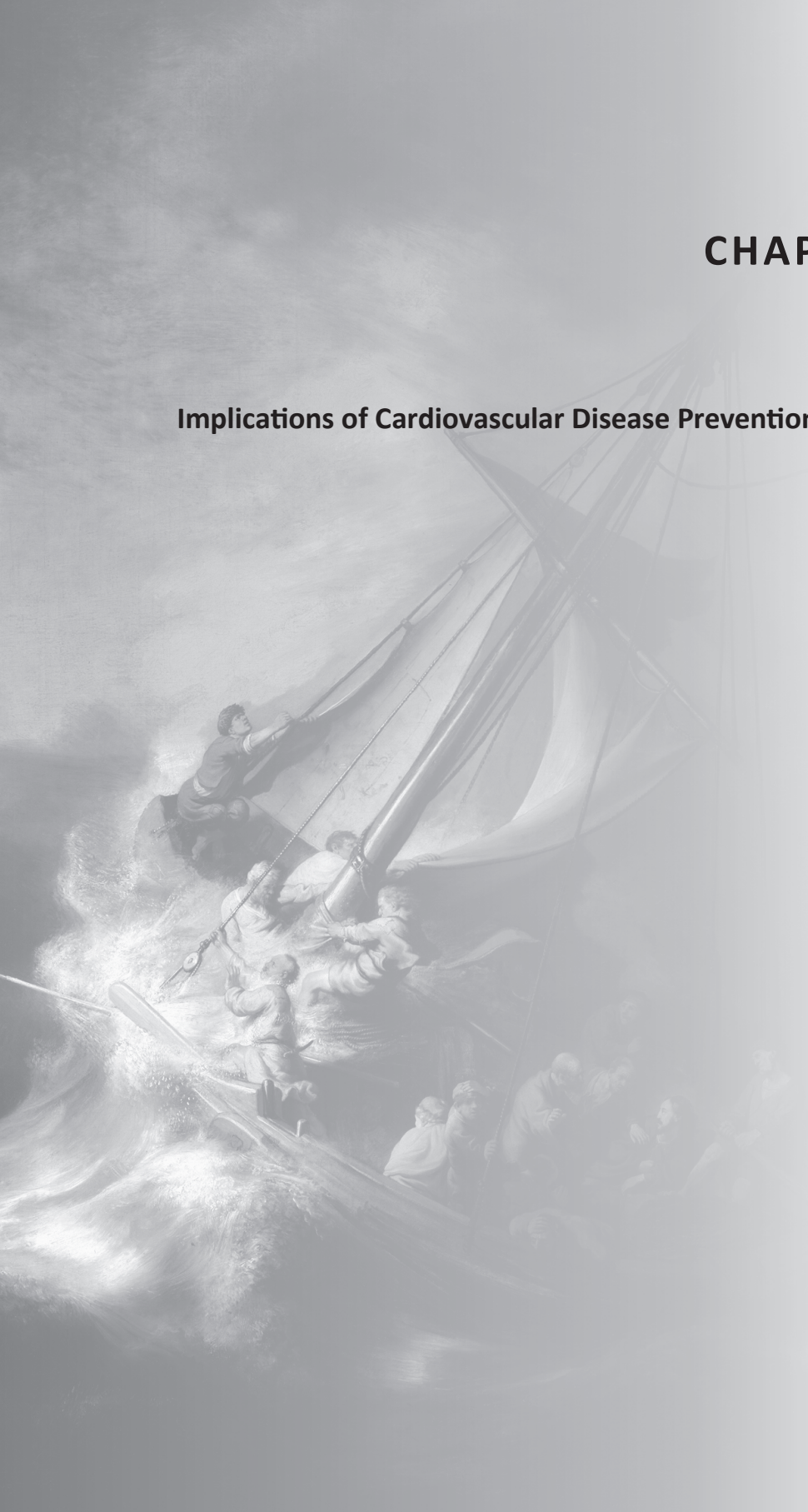


PART IV

Improving Cardiovascular Risk Stratification

CHAPTER 12

Implications of Cardiovascular Disease Prevention Guidelines



Importance

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines introduced a prediction model and lowered the threshold for treatment with statins to a 7.5% 10-year hard atherosclerotic cardiovascular disease (ASCVD) risk. Implications of the new guideline's threshold and model have not been addressed in non-U.S. populations or compared with previous guidelines.

Objective

To determine population-wide implications of the ACC/AHA, the Adult Treatment Panel III (ATP III), and the European Society of Cardiology (ESC) guidelines using a cohort of Dutch individuals aged 55 years or older.

Design

We included 4854 Rotterdam Study participants examined between 1997 and 2001. We calculated 10-year risks for hard ASCVD events (including fatal and nonfatal coronary heart disease [CHD] and stroke) (ACC/AHA), hard CHD events (fatal and nonfatal myocardial infarction, CHD mortality) (ATP III), and atherosclerotic CVD mortality (ESC).

Main outcomes

Per guideline, we calculated proportions of individuals for whom statins would be recommended and determined calibration and discrimination of risk models.

Results

The mean age was 65.5 (SD 5.2) years. Statins would be recommended for 96.4% (95% CI 95.4-97.1%; n = 1825) of men and 65.8% (95% CI 63.8-67.7%; n = 1523) of women by the ACC/AHA, 52.0% (95% CI 49.8-54.3%; n = 985) of men and 35.5% (95% CI 33.5-37.5%; n = 821) of women by the ATP III, and 66.1% (95% CI 64.0-68.3%; n = 1253) of men and 39.1% (95% CI 37.1-41.2%; n = 906) of women by ESC guidelines. With the ACC/AHA model, average predicted risk versus observed cumulative incidence of hard ASCVD events was 21.5% (95% CI 20.9-22.1%) versus 12.7% (95% CI 11.1-14.5%) for men (192 events) and 11.6% (95% CI 11.2-12.0%) versus 7.9% (95% CI 6.7-9.2%) for women (151 events). Similar overestimation occurred with the ATP III model (98 events in men and 62 events in women) and ESC model (50 events in men and 37 events in women). The c-statistic was 0.67 (95% CI 0.63-0.71) in men and 0.68 (95% CI 0.64-0.73) in women for hard ASCVD (ACC/AHA), 0.67 (95% CI 0.62-0.72) in men and 0.69 (95% CI 0.63-0.75) in women for hard CHD (ATP III), and 0.76 (95% CI 0.70-0.82) in men and 0.77 (95% CI 0.71-0.83) in women for CVD mortality (ESC).

Conclusions

In this European population aged 55 years or older, proportions of individuals eligible for statins differed substantially among the guidelines. The ACC/AHA guideline would recommend statins for nearly all men and two-thirds of women, proportions exceeding those

with the ATP III or ESC guidelines. All 3 risk models provided poor calibration and moderate to good discrimination. Improving risk predictions and setting appropriate population-wide thresholds are necessary to facilitate better clinical decision making.

Prevention of cardiovascular disease (CVD), the leading cause of death worldwide,[284, 285] remains feasible yet suboptimal.[308] The common approach in CVD primary prevention is to identify individuals at high enough risk for cardiovascular events to justify targeting them for more intensive lifestyle interventions, pharmacological interventions, or both.

The CVD prevention guidelines developed by the National Cholesterol Education Program expert panel,[27] succeeded by the American College of Cardiology/American Heart Association (ACC/AHA) task force,[9] and the European Society of Cardiology (ESC)[309] are the major guidelines influencing clinical practice. While the Adult Treatment Panel III (ATP III) guidelines were based on the 10-year risk of coronary heart disease (CHD) only,[27] the ACC/AHA guidelines broaden to comprise risk of all hard atherosclerotic CVD (ASCVD), including CHD and stroke,[9] using the Pooled Cohort equations.[6] An additional substantial change in the U.S. guideline is a lower risk threshold for statin treatment in asymptomatic individuals from 20% CHD risk in the ATP III guidelines [27] to 7.5% ASCVD risk in the new guidelines.[9] The potential implications of the ACC/AHA guidelines in largely widening the populations endorsed for treatment and the accuracy of the ACC/AHA risk calculator have received much attention.[264, 310-313]

To be clinically useful, risk prediction models should provide good discrimination. Because decisions for statin treatment are based on an individual's absolute risk, calibration of the risk prediction models as well as the risk threshold for treatment are important. Varying approaches to CVD risk estimation and application of different criteria for therapeutic recommendations would translate into substantial differences in proportions of individuals qualifying for treatment at a population level. We therefore aimed to determine implications of the ACC/AHA, the ATP III, and the ESC guidelines in a prospective cohort of Dutch individuals aged 55 years or older. Our first aim was to determine what proportion of the population would be treated based on each guideline. We then sought to examine discrimination and calibration of the 3 risk prediction models underlying these guidelines.

Methods

Study design, setting, and population

Analyses were performed within the framework of the Rotterdam Study, a prospective population-based cohort study among persons aged 55 years or older in the Ommoord district of Rotterdam, the Netherlands. The rationale and design of the Rotterdam Study have been described elsewhere.[32-37] The baseline examination took place between 1990 and 1993 (RS-I-1). In 2000, the cohort was extended to include inhabitants who reached the age of 55 years between 1990 and 2000 and persons aged 55 years or older who migrated into the research area (RS-II-1; Figure 1.1).

The present study used data from the third examination of the original cohort (RS-I-3; examined

between 1997 and 1999) and the first examination of the extended cohort (RS-II-1; recruited between 2000 and 2001; Figure 1.1). Among the participants aged 75 years or younger, there were 2209 men and 2645 women with measurements required for the analyses. Among these individuals, 315 men and 330 women were receiving statin treatment at baseline and therefore were excluded from the population for whom the eligibility for treatment based on each guideline was assessed. For further analyses on examining the performance of each risk scoring model, exclusions were made using the criteria from each guideline.

Main outcome and follow-up

The main outcome measures were incident hard ASCVD, hard CHD, and atherosclerotic CVD mortality. ASCVD composed of fatal and nonfatal myocardial infarction (MI), CHD mortality, and stroke. Hard CHD was composed of fatal or nonfatal MI, or CHD mortality.[105] Strokes were adjudicated based on rapidly developing typical clinical signs of focal (or global) neurological deficits lasting 24 h or longer or leading to death.[291] Atherosclerotic CVD mortality was defined as death due to CHD, cerebrovascular disease, or other atherosclerotic disease (including abdominal aortic aneurysms, peripheral vascular disease, and visceral vascular disease).[105] Prevalent CVD was defined as a history of MI, coronary or other arterial revascularization procedure, stroke, focal transient ischemic attack, or heart failure.

Events were adjudicated until January 1, 2012. Only first-incident events were included in the analyses. The information on study outcomes was gathered from general practitioners and from letters and discharge reports from medical specialists. Events were adjudicated by study physicians and medical specialists as described previously.[105, 291] Total number of events for each outcome and number of individuals who were lost to follow-up are presented in the online supplement of the original publication.[119] As is the overall Clark's C of completeness of follow-up, which was calculated for each particular outcome.[314]

Cardiovascular risk factors and medication use

Information on medication use and smoking behavior was collected by trained interviewers during a computerized home interview. Anthropometric measures were obtained during the visit at the research center. Blood pressure was measured at the right brachial artery with a random-zero sphygmomanometer with the participant in sitting position, and the mean of 2 consecutive measurements was used. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medication. Serum glucose and serum total and high-density lipoprotein (HDL) cholesterol levels were measured with standard laboratory techniques. Diabetes mellitus was defined as a fasting blood glucose level of ≥ 7.0 mmol/L, or nonfasting blood glucose levels of ≥ 11.1 mmol/L (only if fasting serum was unavailable), or use of blood glucose-lowering medication. Serum creatinine levels were measured by using an enzymatic assay (Roche Diagnostics, Basel, Switzerland), which was calibrated by isotope dilution mass spectrometry. We recalibrated our creatinine measures. For this purpose, mean creatinine values from the Rotterdam Study, by sex-specific age groups (< 60, 60 to 69, and ≥ 70 years), were aligned with the corresponding corrected means from the Third National Health and Nutrition Examination Survey (NHANES III) participants, as

described previously.[315] The NHANES III creatinine measures were calibrated to the Cleveland Clinic Laboratory (Cleveland, OH, U.S.).[316] The glomerular filtration rate was estimated by the abbreviated Modification of Diet in Renal Disease equation [317, 318] as recommended by the National Kidney Foundation.[319] Chronic kidney disease was defined as estimated glomerular filtration rate of less than 60 mL/min per 1.73 m^2. Family history of MI was defined as a self-reported history of MI occurring before the age of 65 in first degree family members.

Data on dispensing of statins during follow-up were obtained from all 7 fully computerized, pharmacies in the Ommoord district. We used the WHO Anatomical Therapeutic Chemical codes C10AA and C10B for statins.[51]

Statistical analysis

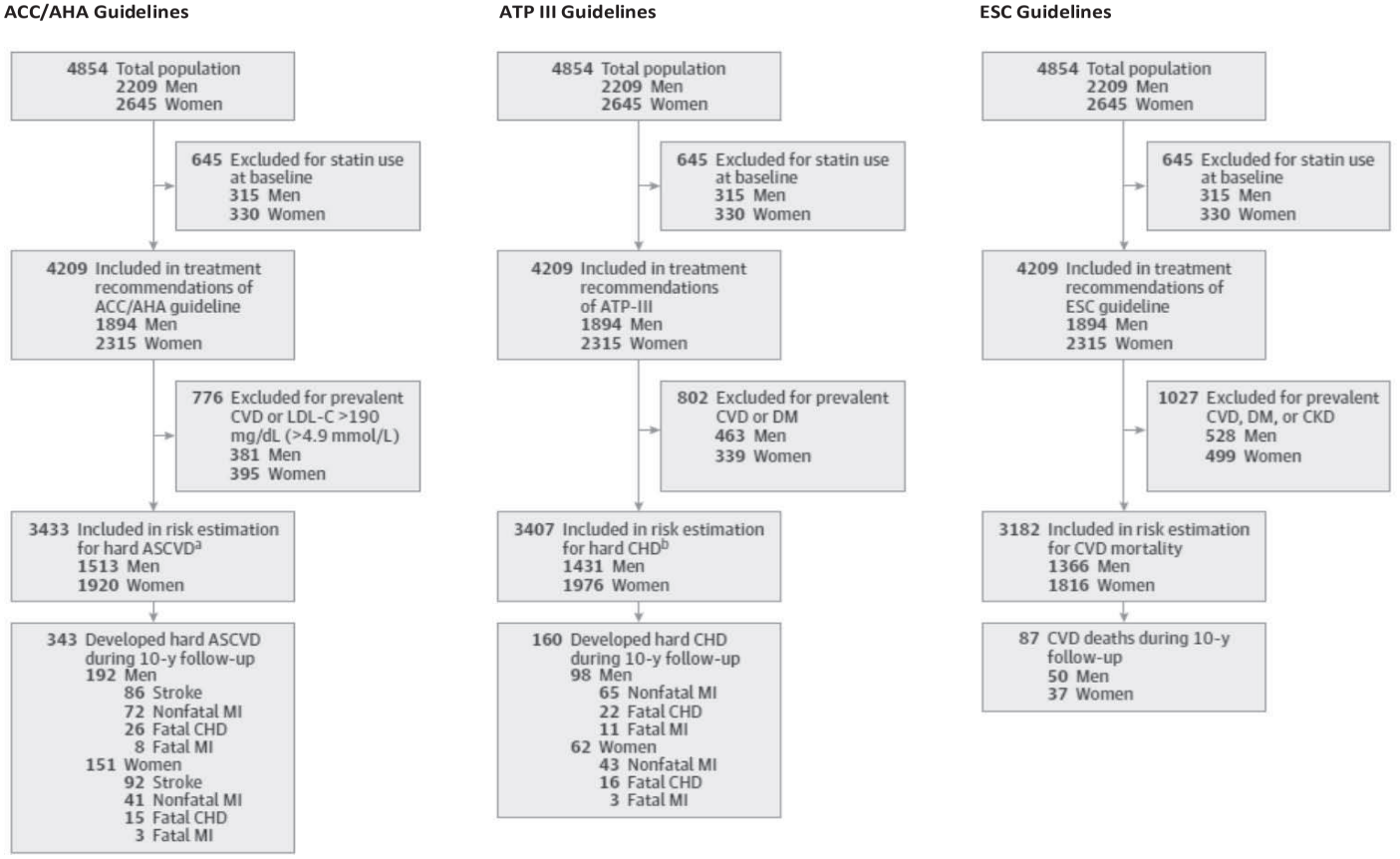
We calculated the 10-year risk of hard ASCVD events for each individual based on age, systolic blood pressure, treatment of hypertension, total and HDL cholesterol levels, current smoking, and history of diabetes mellitus, using the sex-specific parameters from the ACC/AHA Pooled Cohort equations.[6] We used the recommended 5% and 7.5% risk thresholds for categorization of the 2 respective categories of discussion on initiation of 'treatment considered' and discussion on initiation of 'treatment recommended'.[9] To comply with the ACC/AHA guideline,[9] the risk estimation for hard ASCVD was calculated among individuals who were not receiving lipid-lowering medication, were free of CVD at baseline, and had low-density lipoprotein (LDL) cholesterol levels < 190 mg/dL (4.9 mmol/L).

Using the continuous ATP III risk prediction model based on age, systolic blood pressure, treatment of hypertension, total and HDL cholesterol levels, and current smoking (Online calculator: http://www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/hard-10-year-risk.php). We also calculated the 10-year risk of hard CHD for the individuals who were not receiving lipid-lowering medication and were free of CVD and diabetes mellitus, to comply with the ATP III guideline.[27] The risk thresholds used for categorization were 10% and 20%, corresponding to the cut-off points for defining the intermediate- and high-risk categories by the ATP III guideline.[27]

The 10-year risk of CVD mortality for each participant was based on age, systolic blood pressure, total cholesterol levels, and current smoking using the sex-specific intercepts and regression coefficients from the Systematic Coronary Risk Evaluation (SCORE) equation for low-risk European countries.[5] We used the recommended 1%, 5%, and 10% risk thresholds, corresponding to the cut-off points for defining the moderate-risk, high-risk, and very-high-risk groups, respectively, based on the ESC guideline.[8, 309] To comply with the ESC guideline, the SCORE risk estimation was performed among the individuals who were not receiving lipid-lowering medication at baseline and were free of CVD, diabetes mellitus, and chronic kidney disease.[309] Figure 12.1 describes the inclusion and exclusion criteria for different risk prediction models.

Based on each guideline, we formed 3 categories of treatment: 'treatment recommended', 'treatment considered', and 'no treatment'. The criteria used to form these 3 treatment categories by each guideline are described in Tables 12.3 to 12.5.

Figure 12.1 – Inclusion and exclusion criteria for assessment of different guideline recommendations and risk prediction models



ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; ATP III = Adult Treatment Panel III; CHD = coronary heart disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; ESC = European Society of Cardiology; LDL-C = low-density lipoprotein cholesterol.

[a] Hard ASCVD includes fatal CHD, nonfatal MI, and stroke.

[b] Hard CHD includes fatal CHD and nonfatal MI.

We assessed the discrimination and calibration of each risk prediction model in our population. Discrimination refers to probability of the model to assign a higher risk to individuals who develop the outcome of interest compared with those who remain free of disease. The discriminative performance of each risk-scoring model was assessed using the c-statistic.[28] Calibration is the agreement between the predicted probabilities of disease, based on the risk prediction model, and the actual incidence of events in the population. To assess the calibration of each risk prediction model, the average predicted 10-year risks for each risk function were compared with the average 10-year observed risks (i.e. cumulative incidence of the event). Calibration plots were generated to assess the agreement between the predicted and observed risks over the entire range.

Results

Baseline characteristics of the participants are presented in Table 12.1. The mean age of the participants was 65.5 (SD 5.2) years and 54.5% were women.

Table 12.1 – Characteristics of the study population

	Men n = 2209	**Women** n = 2645
Age, y	65.5 (5.3)	65.4 (5.2)
Systolic blood pressure, mmHg	143 (21)	140 (21)
Diastolic blood pressure, mmHg	79 (11)	76 (11)
Use of blood pressure-lowering medication	486 (21.2)	643 (24.3)
Body mass index, kg/m^2	26.7 (3.3)	27.3 (4.5)
Total cholesterol, mmol/L	5.6 (1.0)	6.0 (0.9)
HDL cholesterol, mmol/L	1.2 (0.3)	1.5 (0.4)
LDL cholesterol, mmol/L	3.6 (0.9)	3.8 (0.9)
Use of lipid-lowering medication [a]	315 (14.3)	330 (12.5)
Current smoking	437 (19.8)	522 (19.7)
Diabetes mellitus	315 (14.3)	282 (10.7)
Chronic kidney disease	139 (6.3)	226 (8.5)
History of CVD	414 (18.7)	186 (7.0)

Values are counts (percentages) or means (standard deviations). CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
[a] Statins constituted 96% of all lipid-lowering medications.

Based on the ACC/AHA guideline,[9] the 'treatment recommended' group included 96.4% (95% CI 95.4-97.1%; n = 1825) of men and 65.8% (95% CI 63.8-67.7%; n = 1523) of women while the 'treatment considered' group included 3.3% (95% CI 2.6-4.2%; n = 63) of men and 14.2% (95%

Table 12.2 – Treatment recommendations based on different guidelines

Treatment categories	Guidelines		
	ACC/AHA	ATP III	ESC
Men (n = 1894):			
Treatment recommended	96.4 (95.4-97.1)	52.0 (49.8-54.3)	66.1 (64.0-68.3)
Treatment considered	3.3 (2.6-4.2)	14.2 (12.6-15.8)	31.6 (29.5-33.7)
No treatment	0.3 (0.1-0.7)	33.8 (31.7-35.9)	2.3 (1.6-2.9)
Women (n = 2315):			
Treatment recommended	65.8 (63.8-67.7)	35.5 (33.5-37.5)	39.1 (37.1-41.2)
Treatment considered	14.2 (12.8-15.7)	14.1 (12.7-15.6)	51.4 (49.3-53.4)
No treatment	20.0 (18.3-21.6)	50.4 (48.4-52.5)	9.5 (8.3-10.8)

Values are percentages (95% CI) of the population in different categories of treatment recommendations.[9, 27, 309] Individuals receiving statin treatment at baseline (n = 315 men and n = 330 women) were excluded. ACC/AHA = American College of Cardiology/American Heart Association; ATP III = Adult Treatment Panel III; ESC = European Society of Cardiology.

Table 12.3 – Treatment recommendations based on the ACC/AHA guidelines

Treatment categories	Men	Women
	n = 1894	n = 2315
Treatment recommended:		
Clinical CVD [a]	256 (13.5)	141 (6.1)
LDL-C > 190 mg/dL (4.9 mmol/L)	125 (6.6)	254 (11.0)
Diabetes mellitus	206 (10.9)	217 (9.4)
10-year ASCVD risk > 7.5%	1238 (65.4)	911 (39.3)
Treatment considered:		
10-year ASCVD risk 5-7.5%	63 (3.3)	330 (14.2)
No treatment:		
10-year ASCVD risk < 5%	6 (0.3)	462 (20.0)

Values are counts (percentages) in each recommended treatment category.[9] 10-year risk for hard ASCVD was based on the Pooled Cohorts Equations.[6] Individuals receiving statin treatment at baseline (n = 315 men and n = 330 women) were excluded. ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

[a] Clinical CVD includes a history of myocardial infarction, arterial revascularization, stroke, focal transient ischemic attack, and heart failure.

CI 12.8-15.7%; n = 330) of women. Only 0.3% of men (95% CI 0.1-0.7%; n = 6) and 20.0% (95% CI 18.3-21.6%; n = 462) of women were categorized in the 'no treatment' group (Tables 12.2 and 12.3).

Using the ATP III guideline,[27] 52.0% (95% CI 49.8-54.3%; n = 985) of men and 35.5% (95% CI 33.5-37.5%; n = 821) of women were categorized in the 'treatment recommended' group, while the 'treatment considered' group included 14.2% (95% CI 12.6-15.8%; n = 269) of men and 14.1% (95% CI 12.7-15.6%; n = 326) of women. The 'no treatment' category included the remaining 33.8% (95% CI 31.7-35.9%; n = 640) of men and 50.4% (95% CI 48.4-52.5%; n = 1168) of women (Tables 12.2 and 12.4).

Based on the ESC guideline,[309] 66.1% (95% CI 64.0-68.3%; n = 1253) of men and 39.1% (95% CI 37.1-41.2%; n = 906) of women were included in the 'treatment recommended' category. The 'treatment considered' group comprised 31.6% (95% CI 29.5-33.7%; n = 598) of men and 51.4% (95% CI 49.3-53.4%; n = 1189) of women. Only 2.3% (95% CI 1.6-2.9%; n = 43) of men and 9.5% (95% CI 8.3-10.8%; n = 220) of women were assigned to the 'no treatment' category (Tables 12.2 and 12.5).

While all men and women with prevalent CVD were categorized in the 'treatment recommended' group by the ACC/AHA guideline (Table 12.3), 12.9% of men and 4.2% of women with clinical CHD and CHD risk equivalents were categorized in the 'treatment considered' or 'no treatment' category based on the ATP III guideline (Table 12.4). Using the ESC guideline, a small group of individuals with clinical CVD and its risk equivalents (0.6% of men and 0.4% of women) were categorized in the 'treatment considered' group (Table 12.5).

The treatment recommendations based on the 3 guidelines for the populations younger than 65 years and aged 65 years or older are detailed in the online supplement of the original publication.[119] The data suggest that almost all men older than 55 years and nearly all women older than 65 years are recommended for statin treatment based on the new ACC/AHA guideline.

Discrimination and calibration

The online supplement of the original publication provides the detailed description of the proportion of the population to whom each risk estimation model was applied.[119] Among 1513 men and 1920 women included for ASCVD risk prediction (ACC/AHA), 192 men and 151 women developed hard ASCVD over 10-year follow-up. Among 1431 men and 1976 women included for CHD risk prediction (ATP III), hard CHD occurred in 98 men and 62 women over 10-year follow-up. Among 1366 men and 1816 women included for CVD mortality risk prediction (ESC), 50 men and 37 women died of atherosclerotic CVD over 10-year follow-up. For all outcomes studied, follow-up time was truncated at 10 years for individuals with a longer follow-up time than 10 years.

After calculating the 10-year risk for individuals based on each risk prediction model, we first assessed the discriminative ability of each model. The c-statistic for the ACC/AHA model was 0.67 (95% CI 0.63-0.71) for men and 0.68 (95% CI 0.64-0.73) for women for hard ASCVD. Use of the ATP III risk prediction model resulted in a c-statistic of 0.67 (95% CI 0.62-0.72) for men and

Table 12.4 – Treatment recommendations based on the ATP III guidelines

Hard CHD risk	LDL cholesterol				
	< 100 mg/dL (< 2.5 mmol/L)	100-130 mg/dL (2.5-3.4 mmol/L)	130-160 mg/dL (3.4-4.1 mmol/L)	160-190 mg/dL (4.1-4.9 mmol/L)	> 190 mg/dL (> 4.9 mmol/L)
Men (n = 1894):					
< 2 risk factors (< 10% risk)	36 (1.9)	133 (7.0)	160 (8.5)	92 (4.9)	36 (1.9)
≥ 2 risk factors (< 10% risk)	14 (0.7)	24 (1.3)	15 (0.8)	2 (0.1)	1 (0.1)
≥ 2 risk factors (10-20% risk)	35 (1.8)	155 (8.2)	226 (11.9)	137 (7.2)	41 (2.2)
CHD or CHD risk equivalent (> 20% risk) [a]	68 (3.6)	177 (9.3)	278 (14.7)	194 (10.2)	70 (3.7)
Women (n = 2315):					
< 2 risk factors (< 10% risk)	77 (3.3)	228 (9.8)	358 (15.5)	249 (10.8)	109 (4.7)
≥ 2 risk factors (< 10% risk)	36 (1.6)	147 (6.3)	274 (11.8)	205 (8.9)	100 (4.3)
≥ 2 risk factors (10-20% risk)	6 (0.3)	20 (0.9)	51 (2.2)	56 (2.4)	62 (2.7)
CHD or CHD risk equivalent (> 20% risk) [a]	22 (0.9)	77 (3.3)	148 (6.4)	78 (3.4)	12 (0.5)

Values are counts (percentages) in each recommended treatment category.[27] Dark gray, grey, and light grey colors denote the 'treatment recommended', 'treatment considered', and 'no treatment' categories, respectively. Risk factors include smoking, hypertension, high-density lipoprotein cholesterol levels < 40 mg/dL (1.04 mmol/L), family history of CHD, and age (≥ 45 years in men; ≥ 55 years in women).[27] 10-year risk for hard CHD based on the ATP III Framingham risk score. Individuals receiving statin treatment at baseline (n = 315 men and n = 330 women) were excluded. ATP III = Adult Treatment Panel III; CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.

[a] CHD risk equivalents include clinical cardiovascular disease or diabetes mellitus.[27]

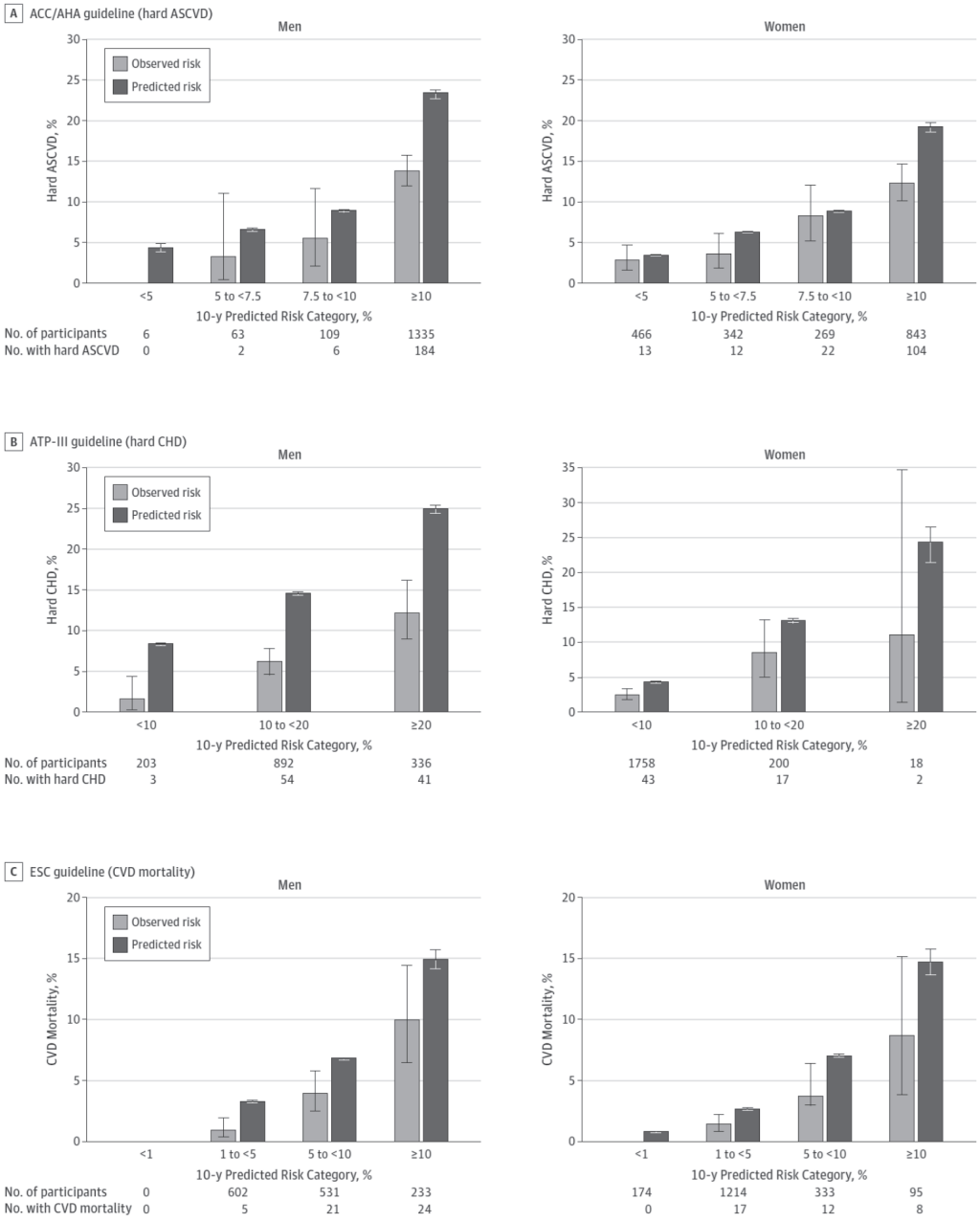
Table 12.5 – Treatment recommendations based on the ESC guidelines

Cardiovascular mortality risk	LDL cholesterol				
	< 1.8 mmol/L	1.8-2.5 mmol/L	2.5-4.0 mmol/L	4.0-4.9 mmol/L	> 4.9 mmol/L
Men (n = 1894):					
< 1%	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1-5%	5 (0.3)	38 (2.0)	371 (19.6)	152 (8.0)	36 (1.9)
5-10%	4 (0.2)	24 (1.3)	279 (14.7)	171 (9.0)	53 (2.8)
≥ 10% or very high risk equivalent [a]	11 (0.6)	45 (2.4)	426 (22.5)	214 (11.3)	65 (3.4)
Women (n = 2315):					
< 1%	3 (0.1)	18 (0.8)	105 (4.5)	43 (1.9)	5 (0.2)
1-5%	6 (0.3)	45 (1.9)	613 (26.5)	396 (17.1)	154 (6.7)
5-10%	2 (0.1)	9 (0.4)	151 (6.5)	114 (4.9)	58 (2.5)
≥ 10% or very high risk equivalent [a]	10 (0.4)	24 (1.1)	303 (13.1)	179 (7.7)	77 (3.3)

Values are counts (percentages) in each recommended treatment category.[309] Dark gray, grey, and light grey colors denote the 'treatment recommended', 'treatment considered', and 'no treatment' categories, respectively. 10-year risk for atherosclerotic cardiovascular mortality based on the SCORE project equations.[5] Individuals receiving statin treatment at baseline (n = 315 men and n = 330 women) were excluded. ESC = European Society of Cardiology; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Evaluation.

[a] Very high risk equivalents were defined as the presence of CVD, diabetes mellitus, or chronic kidney disease.

Figure 12.2 – Observed versus predicted risks by the ACC/AHA, ATP III, and SCORE risk prediction models



A. Comparison of average observed hard ASCVD risk over 10-year follow-up (i.e. cumulative incidence of hard ASCVD) versus average predicted 10-year hard ASCVD risk by the ACC/AHA risk prediction model [6] across categories of risk for men (n = 1513) and women (n = 1920). Individuals receiving statin treatment at baseline, with a history of CVD, or with low-density lipoprotein cholesterol levels ≥ 190 mg/dL (4.9 mmol/L) were excluded.

B. Comparison of average observed hard CHD risk over 10-year follow-up (i.e. cumulative incidence of hard CHD) versus average predicted 10-year hard CHD risk by the ATP III risk prediction model across categories of risk for men (n = 1431) and women (n = 1976). Individuals receiving statin treatment at baseline and those with a history of CVD or diabetes mellitus were excluded.
C. Comparison of average observed CVD mortality risk over 10-year follow-up (i.e. cumulative incidence of CVD mortality) versus average predicted 10-year CVD mortality risk by the SCORE equation [5] across categories of risk for men (n = 1366) and women (n = 1816). Individuals receiving statin treatment at baseline and those with history of CVD, diabetes mellitus, or chronic kidney disease were excluded.
ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; ATP III = Adult Treatment Panel III; CHD = coronary heart disease; CVD = cardiovascular disease; ESC = European Society of Cardiology; SCORE = Systematic Coronary Risk Evaluation.

0.69 (95% CI 0.63-0.75) for women for hard CHD. Using the SCORE equation (ESC), the c-statistic was 0.76 (95% CI 0.70-0.82) for men and 0.77 (95% CI 0.71-0.83) for women for CVD mortality.

We then assessed the calibration of each risk prediction model. Figure 12.2 displays the comparison of the average 10-year risks predicted by the ACC/AHA, ATP III, or SCORE (ESC) risk prediction models with the observed 10-year risks (i.e. cumulative incidence of events) in each risk category. Calibration was poor for all 3 models; the ACC/AHA (Figure 12.2A), the ATP III (Figure 12.2B), and the SCORE equation (Figure 12.2C) overestimated the 10-year risk among men and women across all risk categories. Details regarding the percentages of the study population at different categories of risk using each risk prediction model are available in online supplement of the original publication.[119] The average predicted risks versus observed cumulative incidence of hard ASCVD events were 21.5% (95% CI 20.9-22.1%) versus 12.7% (95% CI 11.1-14.5%) for men and 11.6% (95% CI 11.2-12.0%) versus 7.9% (95% CI 6.7-9.2%) for women using the ACC/AHA risk model. The average predicted versus observed cumulative incidences of hard CHD events were 16.1% (95% CI 15.8-16.5%) versus 6.8% (95% CI 5.6-8.3%) for men and 5.4% (95% CI 5.2-5.5%) versus 3.1% (95% CI 2.4-4.0%) for women based on the ATP III. Using the SCORE equation, the average predicted versus observed cumulative incidences of CVD mortality were 6.8% (95% CI 6.5-7.1%) versus 3.7% (95% CI 2.7-4.8%) for men and 3.8% (95% CI 3.7-4.0%) versus 2.0% (95% CI 1.4-2.8%) for women. Calibration plots for the ACC/AHA, the ATP III, and the ESC risk prediction models are presented in the online supplement of the original publication.[119]

Discussion

In this European population-based prospective cohort study of healthy men and women without previous CVD (i.e. primary prevention population) aged 55 years or older, we found that nearly all men and more than 65% of women were recommended for drug treatment based on the recent ACC/AHA guideline.[9]

Regarding secondary prevention of CVD, the ACC/AHA guidelines clearly recommend drug treatment for all persons with clinical CVD and its risk equivalents.[9] Based on the ATP III and ESC guidelines, however, it is possible that some individuals with clinical CVD are categorized into 2 groups of 'treatment considered' or 'no treatment' based on their LDL cholesterol levels.[27, 309]

For primary CVD prevention, based on the evidence from clinical trials of statins,[320] the new ACC/AHA guidelines modified clinical decision making and proposed to recommend statin treatment

solely based on a 10-year ASCVD risk > 7.5%.[9] This departure from previous guidelines in the U.S. and from the current ESC guideline represents a fairly straightforward approach that deviates from risk functions of 10-year hard CHD or CVD mortality combined with blood concentrations of LDL cholesterol.[27, 309]

The new ACA/AHA guideline recommendations [9] resulted in a larger 'treatment recommended' group in our population in contrast to the larger 'treatment considered' group based on the ESC guidelines.[309] This raises questions about the use of a risk assessment calculator for treatment decisions when so large a proportion of the older population is among the 'treatment recommended' group. A decade ago, Wald and Law described a strategy to prevent CVD by prescribing a daily polypill to everyone aged 55 years or older without requiring risk factors to be measured.[321] Our results suggest that by inclusion of stroke as an outcome and applying the lowered evidence-based risk threshold of 7.5% for treatment,[320, 322] the new ACC/AHA guidelines have approached this age-based strategy. In our population, almost all men older than 55 years and almost all women older than 65 years qualified for statin treatment based on the ACC/AHA guidelines.[9]

The clinical usefulness of a risk prediction tool is determined by a combination of its discrimination and calibration. In our study, the c-statistic for the 3 risk prediction models ranged between 0.67 and 0.77, indicating moderate to good discrimination, with the SCORE equation providing the highest c-statistic among the 3 models. Theoretically, if a model has near perfect discrimination (i.e. the c-statistic exceeds 0.98) and calibration, the cut-off threshold for treatment can be set at any level. However, the modest discrimination ability of the risk prediction models in our study indicates that there is a substantial overlap in the risk distributions of the individuals with and without the events. Therefore, given the current performance of the ACC/AHA risk prediction model, the place of the cut-off threshold for treatment is essential.

When an individual's absolute risk prediction is used for clinical decision making regarding initiation of treatment, accurate calibration is very important. As also evident from our analyses, concerns regarding model calibration are pertinent to all 3 of the risk prediction models; to the Framingham risk score that formed the basis for the ATP III,[229, 230, 323, 324] to the SCORE equation,[325] and recently to the new ACC/AHA risk calculator.[264] Miscalibration of the risk prediction models, once applied in other populations rather than derivation sets, is expected.[326] Imperfect calibration could partly be explained by differences in the characteristics of the new populations, i.e. different levels of baseline risk, for which the risk prediction model is applied. Furthermore, if the application cohorts are more contemporary to the cohorts used in the derivation sets, temporal improvements in overall health could partly be responsible for poor calibration. The risk prediction models underlying all 3 guidelines overestimated the risk among men and women in our study. About 17% of men and 16% of women included in the ASCVD risk assessment in our study were eventually prescribed statins over the course of follow-up. Based on the premise that healthy lifestyle and therapeutic measures would reduce the CVD burden, statin prescription together with improvement of high blood pressure treatment, higher and other lifestyle modifications over the follow-up period might have contributed to the observed overestimations to some extent.

Related closely to the calibration issue is the threshold for making clinical decisions. The new ACC/AHA guidelines substantially lowered the cut-off for treatment to an evidence-based

threshold of 7.5%.[320, 322] If the new ACC/AHA risk prediction model led to overestimation among individuals at high levels of actual CVD risk (e.g. > 20% estimated 10-year risk), it would not necessarily affect the eventual proportion of people recommended for consideration of statin use. However, among individuals with lower actual CVD risks, overestimation by the risk prediction models is of much greater concern. Inaccuracy of the prediction models at the lower levels of risk could indeed result in many more individuals recommended for statins than were intended. While not explicitly stated in the new ACC/AHA guideline, setting of thresholds typically involves both an awareness of clinical benefit of the treatment in the target population combined with a judgment about cost-effectiveness. Different countries and settings may decide on very different thresholds based on cost-effectiveness or resource considerations, which is another reason to look critically at the clinical implications of the risk estimation tool and the risk threshold in other non-U.S. settings. Beyond the need for improving the risk predictions and setting appropriate population-wide thresholds to facilitate better clinical decision making, the large proportion of the population recommended for statin treatment based on new guidelines should be a concerning signal. These large numbers point out the need for (a) preventing risk factor aggregation and (b) conveying information to individuals in ways that effectively lower their risk, in an era when cardiovascular disease remains a worldwide public health challenge.

Limitations

An important limitation is that our cohort includes predominantly white individuals aged 55 years or older. Therefore, the generalizability of our findings to younger and nonwhite populations remains uncertain. Furthermore, this study had relatively small numbers of events for some outcomes.

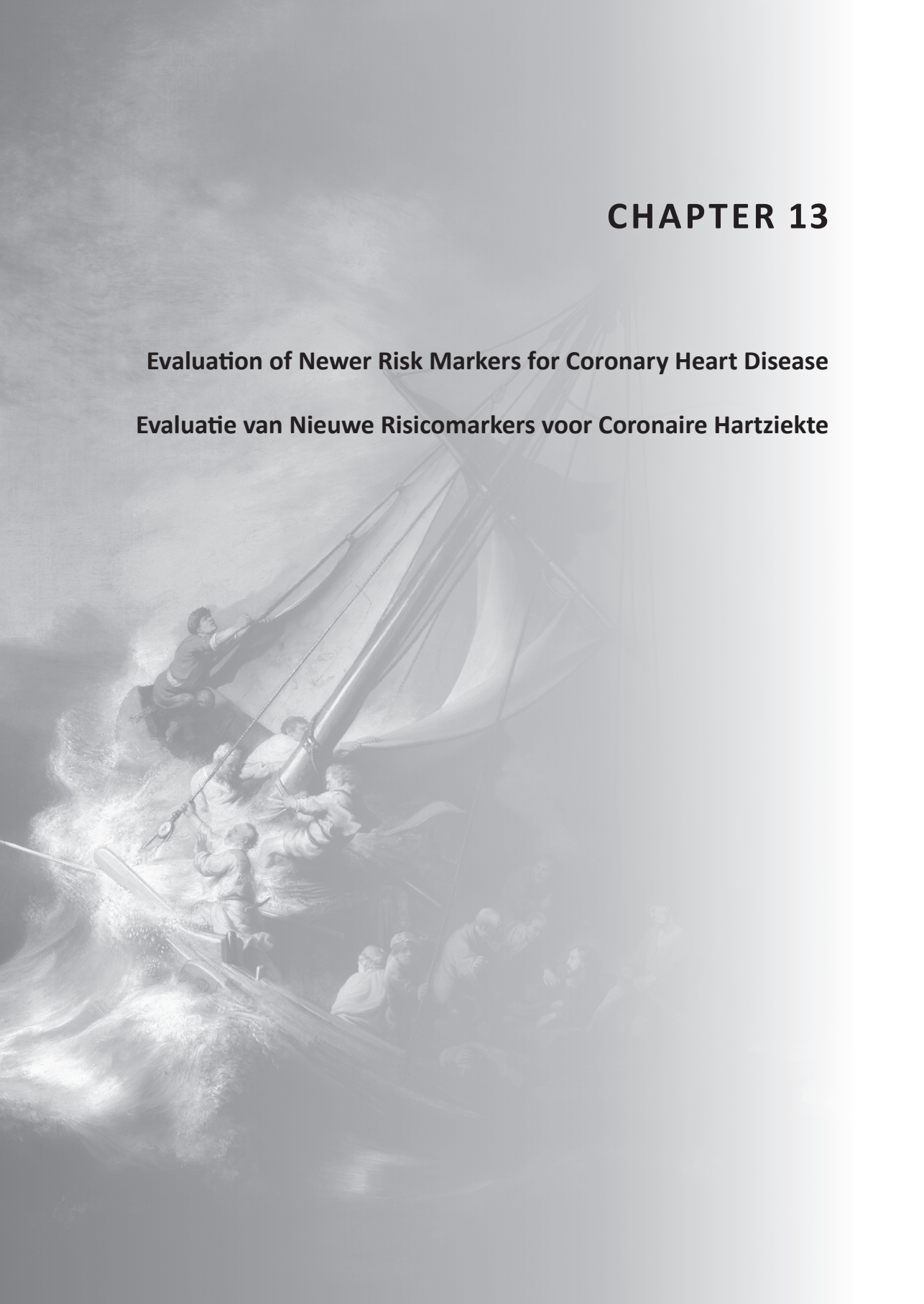
Conclusions

With application of the recent ACC/AHA guidelines in a healthy European population-based cohort, nearly all men and the majority of women aged 55 years or older were candidates for drug treatment. Application of the ACC/AHA, ATP III, and ESC risk prediction models led to overestimation of the risk. Given the modest discrimination and poor calibration of the ACC/AHA risk prediction model, the choice of treatment threshold becomes central.

CHAPTER 13

Evaluation of Newer Risk Markers for Coronary Heart Disease

Evaluatie van Nieuwe Risicomarkers voor Coronaire Hartziekte



Objective

To evaluate the value of a number of the newer risk markers used to improve the risk classification for coronary heart disease (CHD) in asymptomatic persons.

Design

Prospective cohort study in the general population of Rotterdam, the Netherlands (The Rotterdam Study).

Methods

Data on measurements taken between 1997 and 2001 in 5933 persons free of CHD (40.6% men; mean age 69.1 years) were collected. We studied the predictive ability of 12 newer risk markers (N-terminal pro-brain natriuretic peptide [NT-proBNP] levels, von Willebrand factor antigen levels, fibrinogen levels, chronic kidney disease, leukocyte count, C-reactive protein levels, homocysteine levels, uric acid levels, coronary artery calcification [CAC] scores obtained by means of CT, carotid intima-media thickness, peripheral arterial disease, and aortic pulse wave velocity). The predictive value was determined by adding a newer marker to a prediction model that was based on traditional cardiovascular risk factors.

Results

Risk discrimination improved the most with the addition of CAC scores. A net 23.5% of the individuals who developed CHD were reclassified to a higher risk category, but also 4.2% of those who did not develop CHD. This resulted in a net reclassification improvement (NRI) of 0.193. The CAC score was followed by NT-proBNP (NRI 0.076) in terms of the most improvement to risk classification. Improvements in risk predictions with the other newer markers were marginal.

Conclusions

Classification of CHD risk predictions improved most with the addition of the CAC scores to the risk model. Further research is needed to assess whether refinements in risk prediction will actually lead to more effective prevention of cardiovascular disease together with justifiable costs and efforts.

Doel

Het evalueren van de waarde van een aantal nieuwe risicomarkers voor de verbetering van de risicoclassificatie van coronaire hartziekte bij asymptomatische personen.

Opzet

Prospectief cohortonderzoek van de algemene bevolking in Rotterdam (het Erasmus Rotterdam Gezondheid Onderzoek).

Methode

Gegevens werden verzameld van metingen verricht in de periode 1997 tot 2001 bij 5933 personen die vrij waren van coronaire hartziekte (40,6% man; gemiddelde leeftijd: 69,1 jaar). Wij onderzochten de voorspellende waarde van de volgende 12 nieuwe risicomarkers voor het optreden van coronaire hartziekte: N-terminaal pro-breinnatriuretisch peptide (NT-proBNP), antigeen tegen von Willebrand-factor, fibrinogeen, chronische nierziekte, leukocytenaantal, C-reactieve proteine, homocysteïne, urinezuur, coronaire calcium (CAC)-score middels CT, intima-mediadikte van de A. carotis, perifeer vaatlijden en aortale polsgolfsnelheid. De voorspellende waarde werd vastgesteld door een nieuwe marker toe te voegen aan een predictiemodel dat was gebaseerd op klassieke cardiovasculaire risicofactoren.

Resultaten

Het onderscheidend vermogen nam het sterkste toe door toevoeging van de CAC-score. Hierdoor werd netto 23,5% van de personen die coronaire hartziekte ontwikkelde naar een hogere risicocategorie gereclassificeerd, maar ook 4,2% van de personen die geen coronaire hartziekte ontwikkelde. Dit resulteerde in een 'net reclassification improvement' (NRI) van 0,193. Na de CAC-score gaf NT-proBNP de sterkste verbetering van de risicoclassificatie (NRI 0,076). De overige nieuwe markers gaven minimale verbeteringen in de risicovoorspellingen.

Conclusies

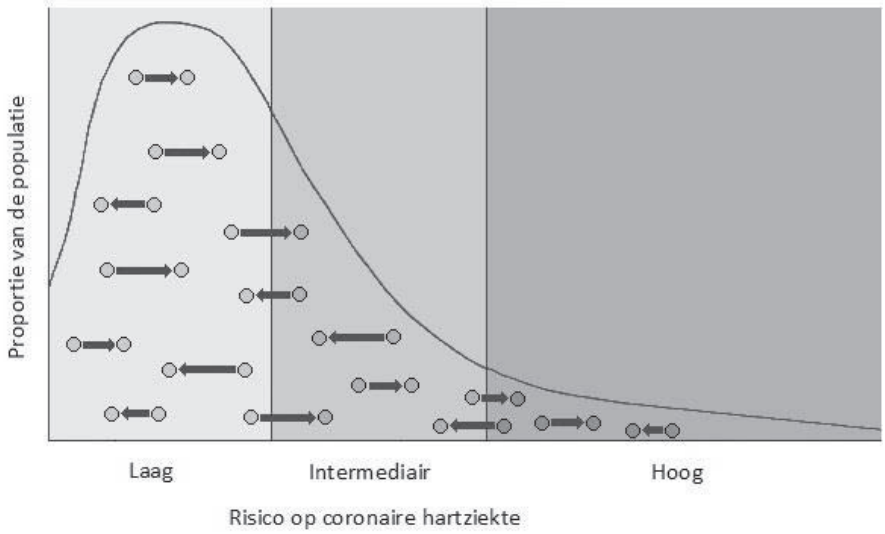
De classificatie van het risico op coronaire hartziekte verbeterde het meest na toevoeging van de CAC-score aan het predictiemodel. Vervolgonderzoek is noodzakelijk om te bepalen of de verbeterde risicovoorspellingen daadwerkelijk resulteren in effectievere preventie van cardiovasculaire ziekte tegen verantwoorde kosten en inspanningen.

Het identificeren van personen met een verhoogd risico op hart- en vaatziekten faciliteert gerichte leefstijladviezen en preventieve behandeling. Daarmee vormt het de basis voor de preventie van coronaire hartziekte. Nationale en internationale richtlijnen propageren daarom het gebruik van zogenoemde risicotabellen op basis van bekende klassieke cardiovasculaire risicofactoren.[8, 27, 327] Bij een hoog voorspeld risico kan laagdrempeliger gestart worden met intensieve bloeddruk- en cholesterolverlagende behandeling. Hoe beter het voorspellend vermogen van een risicotabel, hoe gerichter de preventieve behandeling kan worden gegeven aan degenen die hier het meeste baat bij hebben.

De afgelopen decennia is een overvloed aan nieuwe risicomarkers aangedragen om risicotabellen te kunnen verbeteren. In de studies die deze markers hebben aandragen zijn echter niet altijd de optimale methoden gebruikt en de resultaten zijn daarom soms misleidend.[197] Een klinisch relevant criterium is dat toevoeging van een nieuwe marker voor een substantieel deel van de populatie betekent dat zij een ander advies krijgen over het al dan niet starten van een preventieve behandeling.[114] De behandeladviezen gaan in richtlijnen samen met bepaalde afkapwaarden van het voorspelde risico;[8, 27, 327] daardoor kan een verandering in voorspeld risico voor een individu direct gevolgen hebben voor het behandeladvies (Figuur 13.1). Om deze veranderingen te kwantificeren zijn de afgelopen jaren maten voor reclassificatie ontwikkeld die snel aan populariteit hebben gewonnen.[16, 137, 328]

In dit hoofdstuk evalueren wij middels een groot prospectief onderzoek onder de Rotterdamse algemene bevolking de toegevoegde waarde van 12 nieuwe markers voor het classificeren

Figuur 13.1 – Het principe van reclassificatie van personen in klinische risicocategorieën door 2 achtereenvolgende voorspellingen van het risico op coronaire hartziekte



De meerderheid van de algemene bevolking, afgebeeld als de oppervlakte onder de curve, heeft op basis van klassieke cardiovasculaire risicofactoren een laag voorspeld risico op coronaire hartziekte (lichtgrijs). Een kleiner aantal personen heeft een intermediair risico (grijs) of hoog risico (donkergrijs) op coronaire hartziekte. Toevoeging van een nieuwe risicomarker aan het predictiemodel kan resulteren in veranderingen in voorspeld risico (pijlen). Hierdoor verandert voor een aantal personen de risicoclassificatie; zij worden gereclassificeerd.

van het risico op coronaire hartziekte. De gekozen markers representeren de verschillende processen die bijdragen aan het ontstaan van atherosclerose en atherotrombose of reflecteren de ernst van reeds opgetreden subklinische cardiovasculaire schade.

Methode

Onderzoekspopulatie

De studie is onderdeel van het Erasmus Rotterdam Gezondheid Onderzoek (ERGO, 'the Rotterdam Study'), een prospectief cohort gevormd door inwoners van 45 jaar of ouder van de wijk Ommoord te Rotterdam.[32-37, 329] De werving van het initiële cohort vond plaats in de periode 1990 tot 1993 (RS-I). In 2000 werd dit cohort uitgebreid met personen die naar Ommoord waren verhuisd na 1990 of inwoners die de leeftijd van 55 hadden bereikt (RS-II) (Figuur 1.1). Van deze twee subcohorten samen participeerde 75% (10.994 van 14.687) van de aangeschreven inwoners. De gegevens die gepresenteerd worden in dit hoofdstuk zijn verzameld bij 6498 deelnemers van 55 jaar of ouder tijdens de derde ronde van het initiële cohort (RS-I-3; 1997 tot 1999) en de eerste ronde van de uitbreiding van het cohort (RS-II-1; 2000 tot 2001) (Figuur 1.1). In totaal werden 565 deelnemers, die al bekend waren met coronaire hartziekte (gedefinieerd als een myocardinfarct of coronaire revascularisatie), geëxcludeerd voor deze analyse.[105] Dit resulteerde in een studiepopulatie van 5933 deelnemers.

Risicofactoren en markers

We verzamelden informatie over de volgende klassieke cardiovasculaire risicofactoren: leeftijd, geslacht, roken, BMI, bloeddruk, lipidenspectrum, diabetes mellitus en medicatiegebruik.

Daarnaast werden nieuwe risicomarkers bepaald in het bloed: N-terminaal pro-breinnatriuretisch peptide (NT-proBNP), antigeen tegen von Willebrand-factor, fibrinogeen, chronische nierziekte (gedefinieerd als een geschatte glomerulaire filtratiesnelheid van < 60 mL/min per 1,73 m^2), leukocytenaantal, hoog-sensitieve test op C-reactieve proteïne (CRP), homocysteïne en urinezuur. Ook werden de volgende maten van subklinische atherosclerose gemeten: coronaire calcium (CAC)-score (zie Figuur 13.3 [330]), intima-mediadikte van de A. carotis (cIMT) en perifeer vaatlijden (gedefinieerd als enkel-arm-index ≤ 0,9). Als maat voor de aortastijfheid werd de polsgolfsnelheid in de aorta gemeten tussen de A. carotis en A. femoralis. Metingen van de CRP-concentratie (n = 3029) en CT-scans met CAC-score (n = 3678) waren beschikbaar bij kleinere aantallen deelnemers; zij verschilden niet in kenmerken van de gehele studiepopulatie.

Details ten aanzien van de gebruikte methoden, assays en apparatuur voor zowel klassieke risicofactoren als nieuwe markers zijn na te lezen in een eerdere publicatie.[165]

Klinische uitkomstmaten

Informatie over de uitkomstmaten werd verkregen via de huisartsen en uit ontslagbrieven van ziekenhuisopnames en werd vervolgens gecodeerd door arts-onderzoekers en superviserende

medisch specialisten.[105] Incidente coronaire hartziekte was gedefinieerd als het optreden van de volgende harde coronaire uitkomstmaten: zeker fataal of niet-fataal myocardinfarct of overlijden door coronaire hartziekte.[105] Alleen de eerst opgetreden coronaire uitkomst van iedere deelnemer werd geanalyseerd; van 20 deelnemers was de follow-up incompleet.

Data-analyse

We evalueerden de onafhankelijke associatie van iedere marker met coronaire hartziekte met behulp van Coxregressieanalyse. Multivariabele gecorrigeerde hazardratio's (HRs) voor continue markers werden berekend voor de vergelijkingen van het hoogste versus het laagste kwartiel; het laagste kwartiel diende als referentie.

Vervolgens modelleerden we een Weibull-regressiemodel op basis van de variabelen uit de Framingham-risicoscore (leeftijd, geslacht, systolische bloeddruk, bloeddruk verlagende behandeling, totaal cholesterol, HDL cholesterol, diabetes mellitus en roken).[331] We refereren naar dit model als het 'basismodel'. We vergeleken het basismodel met de 12 nieuwe-marker-modellen aan de hand van de toename in onderscheidend vermogen.[28, 233, 328] Een verbetering van het onderscheidend vermogen is af te lezen aan een toename in c-statistiek. De c-statistiek is een variant van de 'area under the receiver operating characteristic curve' (AUC) voor prospectieve data. De AUC is de kans op correcte voorspelling van een ziekte of uitkomst bij een willekeurig paar personen, van wie 1 met en 1 zonder de ziekte of uitkomst die voorspeld moet worden. Meestal neemt de AUC maar weinig toe door een marker toe te voegen aan een predictiemodel. Wil toevoeging van een marker de risicoclassificatie van een individu—en daarmee de adviezen voor behandeling—veranderen, dan moet die extra marker zorgen dat het voorspelde risico op coronaire hartziekte voor dit individu over de afkapwaarde heen gaat, naar boven of naar beneden (Figuur 13.1). Om die reden is de toename in c-statistiek van beperkte waarde voor de beoordeling of een nieuwe marker het klinisch handelen zal veranderen.

Daarom evalueerden we ook de risico-reclassificatie zoals uitgedrukt in de 'net reclassification improvement' (NRI).[16, 137, 328] De NRI is de netto verbetering van het aantal correct geclassificeerde personen in risicocategorieën door toevoeging van een marker aan een model. De NRI vereist 1 of meer afkappunten voor classificatie (in dit hoofdstuk: laag, intermediair en hoog risico op coronaire hartziekte) (Figuur 13.1). De NRI wordt uitgedrukt als een statistiek zonder eenheid, omdat het de optelsom is van 2 percentages met verschillende delers: (a) het netto beter geclassificeerde percentage personen bij wie de uitkomstmaat is opgetreden; en (b) het netto beter geclassificeerde percentage personen zónder die uitkomst. Daarom heeft de NRI een theoretisch bereik van -2 tot 2. De NRI kwantificeert de verbetering in risicoclassificatie door toevoeging van een variabele (in dit hoofdstuk de 12 nieuwe risicomarkers) aan een voorspellend model. De berekening van de NRI was gebaseerd op klinisch relevante categorieën van het 10-jaarsrisico op coronaire hartziekte volgens Amerikaanse richtlijnen voor preventie van coronaire hartziekte: laag risico (< 10%), intermediair risico (10 tot 20%) en hoog risico (> 20%).[27]

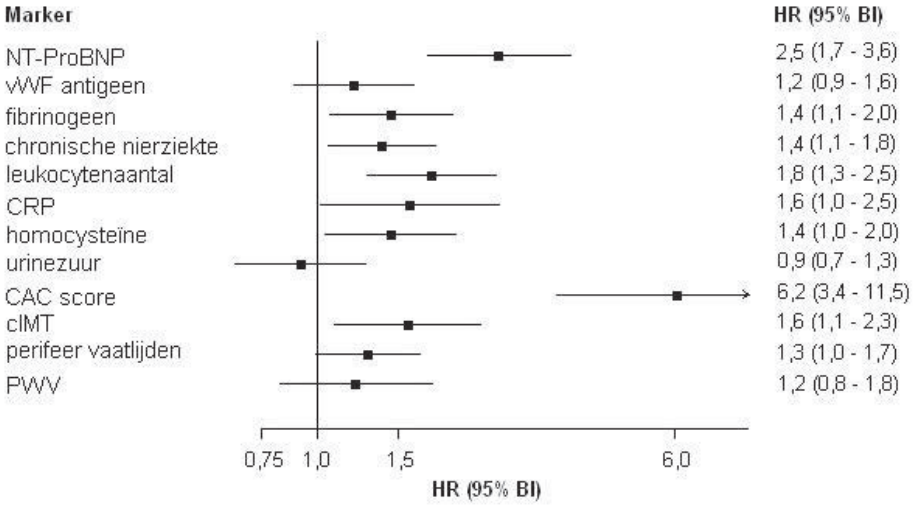
Voor een gedetailleerdere bespreking van de data-analyse en resultaten verwijzen we naar de oorspronkelijke publicatie.[165]

Resultaten

De kenmerken van de studiepopulatie voor zowel de klassieke risicofactoren als de nieuwe markers staan in Tabel 13.1. Gedurende een mediane follow-upduur van 6,8 jaar (25e en 75e percentiel: 5,8 en 8,1 jaar) deden zich 347 eerste manifestaties van coronaire hartziekte voor; bij 190 deelnemers ging het om een niet-fataal myocardinfarct en 157 deelnemers overleden door de coronaire hartziekte. Dit correspondeert met een incidentiecijfer van 8,77 per 1000 persoonsjaren.

De HRs voor de nieuwe risicomarkers, gecorrigeerd voor klassieke risicofactoren, zijn weergegeven in Figuur 13.2. De meeste markers waren statistisch significant geassocieerd met het optreden van coronaire hartziekte. De sterkste associaties werden gevonden voor de CAC-score (HR 6,2; 95% BI 3,4-11,5), NT-proBNP (HR 2,5; 95% BI 1,7-3,6), leukocytenaantal (HR 1,8; 95% BI 1,3-2,5), CRP (HR 1,6; 95% BI 1,0-2,5) en cIMT (HR 1,6; 95% BI 1,1-2,3).

Figuur 13.2 – Multivariabele gecorrigeerde hazardratio's van nieuwe risicomarkers voor het optreden van coronaire hartziekte



De hazard ratio's zijn gecorrigeerd voor leeftijd, geslacht, systolische bloeddruk, antihypertensieve behandeling, totaal cholesterol, HDL cholesterol, diabetes mellitus en roken. Vergelijkingen van continue markers worden gepresenteerd als het hoogste versus het laagste kwartiel (als referentie). CAC = coronaire calcium; cIMT = intima-mediadikte van de A. carotis; CRP = C-reactieve proteïne; NTproBNP = N-terminaal pro-breinnatriuretisch peptide; PWV = aortale polsgolfsnelheid; vWF = von Willebrand-factor.

Het onderscheidend vermogen van het basismodel zonder toevoeging van nieuwe risicomarkers was redelijk, met een c-statistiek van 0,73 (95% BI 0,71-0,75). Door toevoeging van de nieuwe markers aan het predictiemodel werden maximale toenames in c-statistiek gezien voor de CAC-score (0,05; 95% BI 0,02-0,06) en voor NT-proBNP (0,02; 95% BI 0,01-0,04) (Tabel 13.2).

De verbetering in classificatie van personen in risicocategorieën was ook het grootst na toevoeging van de CAC-score (Tabel 13.2). De NRI voor de CAC-score wordt berekend door de som van het netto percentage beter geclassificeerde personen met coronaire hartziekte

Tabel 13.1 – Kenmerken van de studiepopulatie

Meting	Waarde
Klassieke cardiovasculaire risicofactoren:	
Man	40,6%
Leeftijd, jaren	69,1 (8,5)
Systolische bloeddruk, mmHg	143 (21)
Diastolische bloeddruk, mmHg	77 (11)
Bloeddrukverlagende behandeling	23,5%
Quetelet-index, kg/m^2	27,0 (4,0)
Totaal cholesterol, mmol/L	5,8 (1,0)
HDL cholesterol, mmol/L	1,4 (0,4)
Triglycerides, mmol/L	1,5 (0,8)
Cholesterolverlagende behandeling	10,2%
Glucose, mmol/L	5,9 (1,5)
Diabetes mellitus	12,9%
Roker	17,5%
Nieuwe cardiovasculaire risicomarkers:	
NT-proBNP, pmol/L [a]	9,5 (5,1-18,1)
vWF antigeen, IU/mL [a]	1,2 (0,9-1,6)
Fibrinogeen, µmol/L [a]	11,2 (9,7-12,9)
eGFR, mL/min/1,73 m^2 [a]	76 (67-87)
Chronische nierziekte	12,2%
Leukocytenaantal, per L	6,8 x 10^9 (1,9 x 10^9)
CRP, mg/L [a,b]	2,3 (1,2-4,4)
Homocysteïne, µmol/L [a]	13,5 (11,4-16,6)
Urinezuur, µmol/L [a]	300 (260-360)
CAC score [a,c]	66 (4-323)
cIMT, mm [a]	1,0 (0,9-1,1)
Enkel-arm-index	1,1 (0,2)
Perifeer vaatlijden	14,0%
PWV, m/s [a]	12,6 (10,9-14,8)

Waardes zijn percentages of gemiddelden (standaard deviaties). CAC = coronaire calcium; cIMT = intima-mediadikte van de A. carotis; CRP = C-reactieve proteïne; eGFR = geschatte glomerulaire filtratiesnelheid; NT-proBNP = N-terminaal pro-breinnatriuretisch peptide; PWV = aortale polsgolfsnelheid; vWF = von Willebrand-factor.

[a] Mediaan (interkwartielafstand) vanwege een scheve verdeling.

[b] Metingen beschikbaar van 3029 deelnemers.

[c] Metingen beschikbaar van 3678 deelnemers.

Tabel 13.2 – Onderscheidend en reclassificerend vermogen van nieuwe risicomarkers voor het optreden van coronaire hartziekte

Risicomarker	Toename in c-statistiek (95% BI) [a]	Netto percentage personen beter geclassificeerd Met CHZ	Zonder CHZ	NRI (95% BI) [b]
NT-proBNP	0,02 (0,01-0,04)	5,3%	2,3%	0,076 (0,028-0,125)
vWF antigeen	0,00 (0,00-0,00)	0,6%	-0,2%	0,004 (-0,017-0,025)
Fibrinogeen	0,00 (0,00-0,01)	3,1%	-0,2%	0,029 (-0,002-0,060)
Chronische nierziekte	0,00 (0,00-0,00)	2,2%	0,5%	0,027 (-0,002-0,057)
Leukocytenaantal	0,01 (0,00-0,02)	1,9%	-0,4%	0,015 (-0,015-0,046)
CRP [c]	0,00 (-0,01-0,00)	2,1%	-0,1%	0,020 (-0,023-0,064)
Homocysteïne	0,00 (0,00-0,00)	- 0,4%	0,1%	-0,003 (-0,030-0,023)
Urinezuur	0,00 (0,00-0,00)	0,6%	0,2%	0,008 (-0,005-0,021)
CAC score [d]	0,05 (0,02-0,06)	23,5%	-4,2%	0,193 (0,125-0,262)
cIMT	0,00 (0,00-0,00)	0,2%	-0,4%	0,016 (-0,011-0,044)
Perifeer vaatlijden	0,00 (0,00-0,00)	0,6%	0,0%	0,006 (-0,018-0,029)
PWV	0,00 (0,00-0,00)	0,3%	-0,3%	0,000 (-0,021-0,021)

CAC = coronaire calcium; CHZ = coronaire hartziekte; cIMT = intima-mediadikte van de A. carotis; CRP = C-reactieve proteine; NRI = 'net reclassification improvement'; NT-proBNP = N-terminaal pro-breinnatriuretisch peptide; PWV = aortale polsgolfsnelheid; vWF = von Willebrand-factor.

[a] Toename in c-statistiek in het uitgebreide model (met klassieke risicofactoren en de nieuwe risicomarker) versus het basismodel (met alleen klassieke risicofactoren).

[b] De NRI voor het uitgebreide model (met klassieke risicofactoren en de nieuwe risicomarker) versus het basismodel (met alleen klassieke risicofactoren) met 10-jaarsrisico-categorieen van < 10%, 10 tot 20% en > 20%.

[c] Metingen beschikbaar van 3029 deelnemers.

[d] Metingen beschikbaar van 3678 deelnemers.

(23,5%) en zonder coronaire hartziekte (-4,2%). De toevoeging van CAC-score gaat dus gepaard met een NRI van 0,193 (95% BI 0,125-0,262). Na de CAC-score is NT-proBNP de meest opvallende marker: na toevoeging van NT-proBNP aan het basismodel werd netto 5,3% van de personen met coronaire hartziekte en 2,3% van de personen zonder coronaire hartziekte beter geclassificeerd (NRI 0,076; 95% BI 0,028-0,125). Tabellen 13.3 en 13.4 zijn de volledige risico-reclassificatietabellen voor het toevoegen van respectievelijk de CAC-score en NT-proBNP aan het basismodel. Het reclassificerend vermogen van de overige markers was minimaal.

De associaties en het onderscheidend vermogen waren iets sterker bij mannen dan bij vrouwen voor de meeste nieuwe risicomarkers. Voor gedetailleerdere resultaten van de geslachtsspecifieke analyse verwijzen we naar de oorspronkelijke publicatie.[165]

Tabel 13.3 – Risico-reclassificatietabel voor 10-jaars risico op coronaire hartziekte voor het toevoegen van de coronaire calciumscore aan een basismodel gebaseerd op klassieke risicofactoren

A. Personen met CHZ, n (%)

Basismodel	Basismodel en CAC score			
	Laag risico (< 10%)	Intermediair risico (10-20%)	Hoog risico (> 20%)	Totaal
Laag risico (< 10%)	71 (20,6)	50 (14,5)	4 (1,2)	125 (36,2)
Intermediair risico (10-20%)	19 (5,5)	75 (21,7)	55 (15,9)	149 (43,2)
Hoog risico (> 20%)	0 (0)	9 (2,6)	62 (18,0)	71 (20,6)
Totaal	90 (26,1)	134 (38,8)	121 (35,1)	345 (100)

Personen met CHZ gereclassificeerd, n (%)

Onveranderd	208 (60,3)
Naar hoger risico	109 (31,6)
Naar lager risico	28 (8,1)

B. Personen zonder CHZ, n (%)

Basismodel	Basismodel en CAC score			
	Laag risico (< 10%)	Intermediair risico (10-20%)	Hoog risico (> 20%)	Totaal
Laag risico (< 10%)	2015 (60,5)	315 (9,5)	16 (0,5)	2346 (70,4)
Intermediair risico (10-20%)	262 (7,9)	364 (10,9)	144 (4,3)	770 (23,1)
Hoog risico (> 20%)	17 (0,5)	60 (1,8)	140 (4,2)	217 (6,5)
Totaal	2294 (68,8)	739 (22,2)	300 (9,0)	3333 (100)

Personen zonder CHZ gereclassificeerd, n (%)

Onveranderd	2519 (75,6)
Naar hoger risico	475 (14,3)
Naar lager risico	339 (10,1)

Gehele studiepopulatie gereclassificeerd, n (%)

Onveranderd	2727 (74,1)
Naar hoger risico	584 (15,9)
Naar lager risico	367 (10,0)

De reclassificatietabel zet de risicoclassificatie van het basismodel (rijen) uit tegen de risicoclassificatie van het basismodel na toevoeging van de CAC-score (kolommen) voor (A) personen met CHZ en (B) personen zonder CHZ tijdens follow-up. Personen die CHZ ontwikkelden worden als correct gereclassificeerd beschouwd als ze door toevoeging van de CAC-score een hogere risicocategorie toebedeeld krijgen (lichtgrijs) terwijl reclassificatie naar een lagere risicocategorie als incorrect wordt beschouwd (donkergrijs). Voor personen zonder CHZ geldt het tegenovergestelde: een lagere classificatie is correct (lichtgrijs) en een hogere classificatie is incorrect (donkergrijs). CAC = coronaire calcium; CHZ = coronaire hartziekte.

Tabel 13.4 – Risico-reclassificatietabel voor 10-jaars risico op coronaire hartziekte voor het toevoegen van NT-proBNP aan een basismodel gebaseerd op klassieke risicofactoren

A. Personen met CHZ, n (%)

Basismodel	Basismodel en NT-proBNP			
	Laag risico (< 10%)	Intermediair risico (10-20%)	Hoog risico (> 20%)	Totaal
Laag risico (< 10%)	155 (28,2)	28 (5,1)	10 (1,8)	193 (35,2)
Intermediair risico (10-20%)	36 (6,6)	121 (22,0)	64 (11,7)	221 (40,3)
Hoog risico (> 20%)	3 (0,5)	34 (6,2)	98 (17,9)	135 (24,6)
Totaal	194 (35,3)	183 (33,3)	172 (31,3)	549 (100)

Personen met CHZ gereclassificeerd, n (%)

Onveranderd	374 (68,1)
Naar hoger risico	102 (18,6)
Naar lager risico	73 (13,3)

B. Personen zonder CHZ, n (%)

Basismodel	Basismodel en NT-proBNP			
	Laag risico (< 10%)	Intermediair risico (10-20%)	Hoog risico (> 20%)	Totaal
Laag risico (< 10%)	3622 (67,3)	210 (3,9)	16 (0,3)	3848 (71,5)
Intermediair risico (10-20%)	339 (6,3)	671 (12,5)	110 (20,4)	1120 (20,8)
Hoog risico (> 20%)	3 (0,1)	119 (2,2)	294 (54,6)	416 (7,7)
Totaal	3964 (73,6)	1000 (18,6)	420 (7,8)	5384 (100)

Personen zonder CHZ gereclassificeerd, n (%)

Onveranderd	4587 (85,2)
Naar hoger risico	336 (6,2)
Naar lager risico	461 (8,5)

Gehele studiepopulatie gereclassificeerd, n (%)

Onveranderd	4961 (83,6)
Naar hoger risico	438 (7,4)
Naar lager risico	534 (9,0)

De reclassificatietabel zet de risicoclassificatie van het basismodel (rijen) uit tegen de risicoclassificatie van het basismodel na toevoeging van NT-proBNP (kolommen) voor (A) personen met CHZ en (B) personen zonder CHZ tijdens follow-up. Personen die CHZ ontwikkelden worden als correct gereclassificeerd beschouwd als ze door toevoeging van NT-proBNP een hogere risicocategorie toebedeeld krijgen (lichtgrijs) terwijl reclassificatie naar een lagere risicocategorie als incorrect wordt beschouwd (donkergrijs). Voor personen zonder CHZ geldt het tegenovergestelde: een lagere classificatie is correct (lichtgrijs) en een hogere classificatie is incorrect (donkergrijs). NT-proBNP = N-terminaal pro-breinnatriuretisch peptide; CHZ = coronaire hartziekte.

Beschouwing

Van 12 nieuwe risicomarkers voor coronaire hartziekte gaf de mate van coronaire verkalking op een CT-scan de sterkste verbetering in de voorspelling van het risico op coronaire hartziekte als een marker werd toegevoegd aan een model met klassieke cardiovasculaire risicofactoren. Netto zou een kwart van de personen die coronaire hartziekte ontwikkelden met behulp van de CAC-score in een hogere risicoklasse zijn ingedeeld. Op grond daarvan zouden zij voor intensievere preventieve behandeling in aanmerking gekomen zijn.

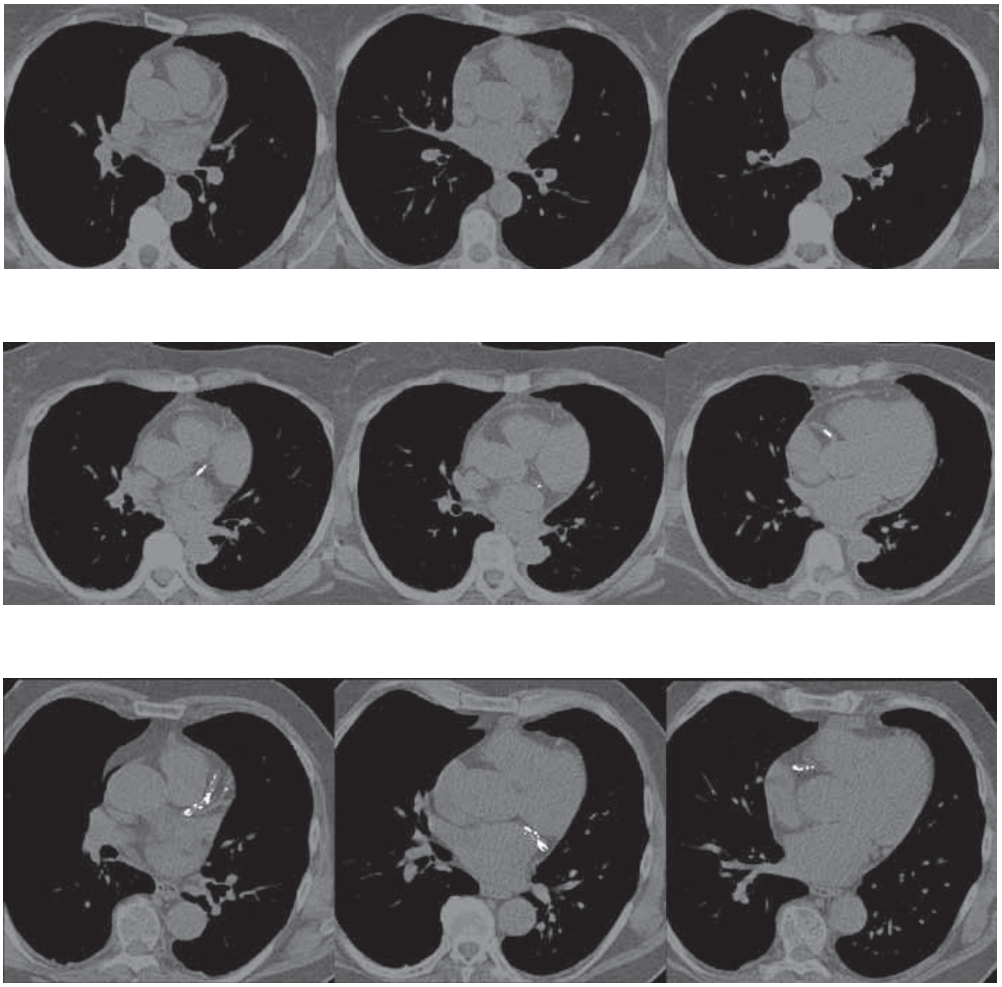
Andere vasculaire risicomarkers, zoals cIMT, enkel-arm-index en aortale polsgolfsnelheid, waren in verscheidene populaties sterke voorspellers van coronaire hartziekte,[332-334] maar deze waren van beperkte toegevoegde waarde in ons onderzoek. Hierbij moet worden aangetekend dat directe vergelijkingen met deze studies bemoeilijkt worden door de variatie in het aantal risicocategorieën, de afkappunten van deze categorieën en de selectie van uitkomstmaten.[211] De CAC-score is een directe en zeer nauwkeurige afspiegeling van de ernst van atherosclerose in het coronaire vaatbed (Figuur 13.3 [330]). Dit kan de zeer goede prestaties verklaren van de CAC-score vergeleken met de vasculaire maten elders in de vaatboom, zoals cIMT, enkel-arm-index en aortale polsgolfsnelheid. In ons onderzoek was de NT-proBNP-concentratie de bloedwaarde die het sterkste verband vertoonde met coronaire hartziekte en het grootste reclassificerende vermogen had. Al eerder was aangetoond dat verhoogde concentraties van dit peptide in het bloed een sterke voorspeller zijn voor cardiovasculaire uitkomsten en overlijden.[178, 203] NT-proBNP wordt aangemaakt door cardiomyocyten onder invloed van mechanische rek. Stijgingen in concentraties van NT-proBNP zijn dan ook sterk gecorreleerd met subklinische en manifeste hartziekte. Ook neemt de voorspellende waarde van NT-proBNP toe met het vorderen van de leeftijd.[335] Daarom is deze marker waarschijnlijk het bruikbaarst voor het voorspellen van coronaire hartziekte bij ouderen. Onze studie maakt het verschil tussen statistische significantie en klinische relevantie duidelijk voor een aantal andere bloedwaarden, zoals fibrinogeen, homocysteïne en CRP. In termen van risico-reclassificatie was de meerwaarde van deze markers minimaal wanneer ze werden toegevoegd aan het basismodel met klassieke risicofactoren.

Beperkingen

Het deel van het ERGO-cohort dat in dit hoofdstuk wordt beschreven, bestaat vrijwel volledig uit blanke deelnemers die allen 55 jaar of ouder zijn. Hierdoor zijn de resultaten van dit onderzoek niet te generaliseren naar jongere en niet-blanke bevolkingsgroepen. Ook is niet duidelijk of onze resultaten te extrapoleren zijn naar het model dat door het CBO en de NHG wordt geadviseerd;[327] dat model voorspelt onder andere ook cerebrovasculaire uitkomsten en hartfalen.[225, 257, 337]

Voor de klinische praktijk zouden ook een aantal alternatieve algoritmen met CAC-score overwogen kunnen worden, zoals het in eerste instantie inschatten van het cardiovasculaire risico met de CAC-score en in een tweede stap de risicostratificatie te verfijnen met behulp van klassieke risicofactoren. Ook zou de afwezigheid van coronaire verkalkingen (CAC-score = 0; 14,2% van de studiepopulatie) bij screening van asymptomatische personen gebruikt kunnen worden om het 10-jaarsrisico op coronaire hartziekte vrijwel uit te sluiten.[338] Deze alternatieven hebben wij buiten beschouwing gelaten in dit hoofdstuk.

Figuur 13.3 – Coronaire calciumscore



CT-scans zonder contrast van verschillende deelnemers met uiteenlopende mate van coronaire verkalking: (A) geen tot lichte verkalking, (B) matige verkalking en (C) uitgebreide coronaire verkalking. Met behulp van dit soort scans wordt de coronaire calciumscore als volgt vastgesteld: 2 of meer aangrenzende pixels in het epicardiale coronaire vaatbed met een signaalintensiteit > 130 Hounsfield-units worden geïdentificeerd als verkalking; daarna wordt volgens de methode van Agatston [336] het product berekend van de verkalkte oppervlakte (in mm^2) en de attenuatiefactor (1 tot 4), afhankelijk van de densiteit van de verkalking. De totale coronaire calciumscore, die kan variëren van 0 tot ver boven 1000, wordt verkregen door het optellen van de scores van alle coupes. Gemodificeerd overgenomen uit een eerdere publicatie.[330]

Implementatie in de praktijk?

Ons onderzoek is een eerste stap in het identificeren van relevante nieuwe markers voor het voorspellen van coronaire hartziekte in de klinische praktijk. Op dit moment is er nog niet voldoende wetenschappelijke onderbouwing voor het invoeren van CAC-scores in risicovoorspellingen van coronaire hartziekte.[339, 340] Het opstellen van een cardiovasculair risicoprofiel met daarin CAC-scores zal duurder zijn dan de huidige strategieën. Ook moet de

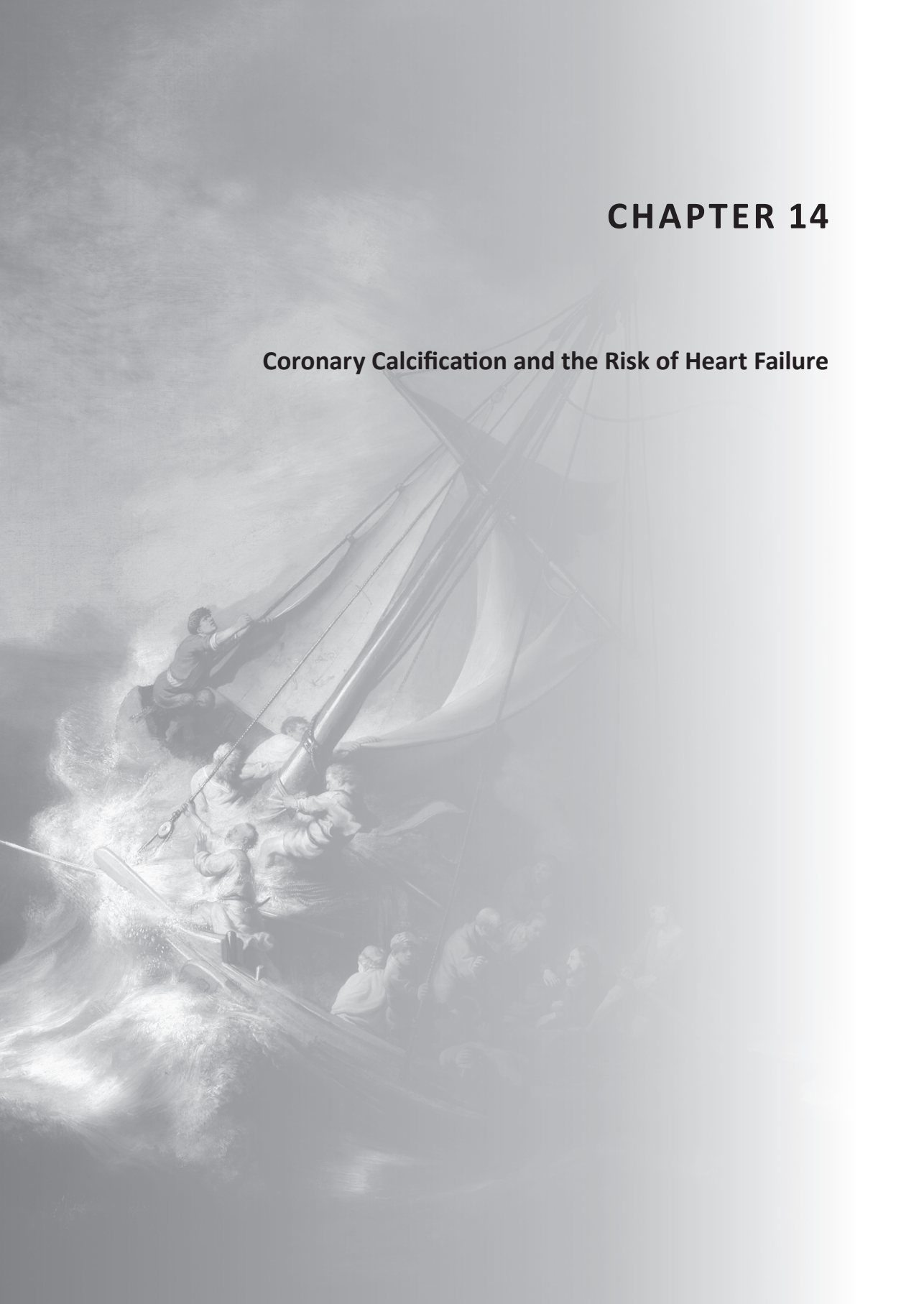
stralingsbelasting van een CT-scan bij gezonde personen afgewogen worden tegen de verbeterde classificatie,[341] en moeten bovenal de effectiviteit en kosteneffectiviteit nog vast komen te staan. De onderbouwing voor een gunstige kosteneffectiviteit van de CAC-score bestaat op dit moment alleen uit de resultaten van een Amerikaans gerandomiseerd onderzoek. Daarin concludeerde men dat CAC-screening een bijdrage kan leveren aan de primaire preventie van harten vaatziekten: 4 jaar na randomisatie tussen wel of niet een CT-scan ondergaan hadden de deelnemers van wie de CAC-score was bepaald een beter cardiovasculair risicoprofiel dan de controlegroep, tegen vergelijkbare kosten.[342]

Conclusies

In dit prospectieve onderzoek onder de algemene Nederlandse bevolking waren verbeteringen in classificatie van het risico op coronaire hartziekte het meest statistisch significant en klinisch relevant na toevoeging van de CAC-score aan het predictiemodel. Gerandomiseerd vervolgonderzoek is noodzakelijk om te bepalen of de verbetering in risicovoorspellingen aan de hand van coronaire verkalkingen—gemeten met CT—ook daadwerkelijk resulteert in minder hart- en vaatziekten tegen maatschappelijk verantwoorde kosten, inspanningen en stralingsbelasting bij asymptomatische ouderen.[114, 339, 340]

CHAPTER 14

Coronary Calcification and the Risk of Heart Failure



Objectives

The purpose of this study was to determine the association of coronary artery calcification (CAC) with incident heart failure in the elderly and examine its independence of overt coronary heart disease (CHD).

Background

Heart failure is often observed as a first manifestation of coronary atherosclerosis rather than a sequela of overt CHD. Although numerous studies have shown that CAC, an established measure of coronary atherosclerosis, is a strong predictor of CHD, the association between CAC and future heart failure has not been studied prospectively.

Methods

In the Rotterdam Study, a population-based cohort, 1897 asymptomatic participants (mean age, 69.9 years; 58% women) underwent CAC scoring and were followed for the occurrence of heart failure and CHD.

Results

During a median follow-up of 6.8 years, there were 78 cases of heart failure and 76 cases of nonfatal CHD. After adjustment for cardiovascular risk factors, increasing CAC scores were associated with heart failure (P for trend = 0.001), with a HR of 4.1 (95% CI 1.7-10.1) for CAC scores > 400 compared with CAC scores of 0 to 10. After censoring participants for incident nonfatal CHD, increasing extent of CAC remained associated with heart failure (P for trend = 0.046), with a HR of 2.9 (95% CI 1.1-7.4) for CAC scores > 400. Moreover, adding CAC to cardiovascular risk factors resulted in an optimism-corrected increase in the c-statistic by 0.030 (95% CI 0.001-0.050) to 0.734 (95% CI 0.698-0.770) and continuous net reclassification improvement of 0.340(95% CI 0.114-0.567).

Conclusions

CAC has a clear association with the risk of heart failure, independent of overt CHD. Because heart failure is highly prevalent in the elderly, it might be worthwhile to include heart failure as an outcome in future risk assessment programs incorporating CAC.

Coronary artery calcification (CAC), an established measure of subclinical coronary atherosclerosis, is a strong and independent predictor of future coronary heart disease (CHD).[70, 257, 343, 344] Furthermore, calcium scoring appears to improve CHD risk prediction beyond risk scoring algorithms such as the Framingham risk score and is considered useful in persons at intermediate risk of CHD (i.e. a 10-year absolute risk of 10 to 20%).[165, 188, 343, 345, 346]

It is well known that heart failure is a highly prevalent disease in the elderly, associated with reduced life expectancy and ever increasing costs.[31, 78, 347] Especially in the elderly, coronary atherosclerosis is the current leading cause of heart failure and heart failure is often observed as a first manifestation of coronary atherosclerosis rather than a sequela of overt coronary insufficiency or myocardial infarction (MI).[22, 348]

In this light, heart failure could be considered an additional outcome in cardiovascular risk assessment programs using CAC. As a prerequisite, it is important to examine the strength of the association between CAC and incident heart failure, independent of cardiovascular risk factors and overt CHD. In the Rotterdam Study, a prospective population-based cohort study among elderly individuals, we investigated the association between CAC, as detected by electron-beam computed tomography (CT) and the risk of heart failure and examined whether this association is independent of incident overt CHD during follow-up.

Methods

Study design, setting, and population

This study is embedded in the Rotterdam Study, a prospective population-based cohort study among persons older than 55 years of age that started in 1990. Starting in 2000, the original cohort (RS-I) was extended with a second cohort (RS-II) of persons who reached the age of 55 years and persons who had moved to the research area (Figure 1.1). The rationale and design of the Rotterdam Study were described elsewhere.[32-37]

For both cohorts, identical examinations took place from 1997 to 2001 (Figure 1.1), and participants through 85 years of age were invited to undergo a CT scan in a separate visit. Scans were obtained in 2349 participants (61% response rate). Clinical characteristics of responders and non-responders were highly comparable.[349] Due to several causes, image acquisition data could not be analyzed in 57 participants. Therefore, data were available for 2292 participants. For the present study, we excluded 79 participants with known heart failure and 10 participants with incomplete data concerning heart failure status at the time of CT scanning. Furthermore, we excluded the subset of the study population with a documented history of CHD (n = 306), defined as a recognized or unrecognized MI, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). This left a total of 1897 coronary asymptomatic individuals eligible for the present study. The median duration between the examination at the Rotterdam Study research center and CT scanning was 44 days.

Coronary artery calcification measurement

We assessed CAC in the epicardial coronary arteries detected on electron-beam CT scans, as described in detail previously.[70] Briefly, imaging was performed with a C-150 Imatron scanner (GE Imatron Inc., South San Francisco, CA, U.S.). From the level of the root of the aorta through the heart, 38 images were obtained with a 100-ms scan time and 3-mm slice thickness. A calcification was defined as a minimum of 2 adjacent pixels (0.65 mm^2 area) with a density > 130 Hounsfield units. CAC scores were calculated according to Agatston's method.[336] See Figure 13.3 for examples of CAC imaging.[221, 330] Conforming to the study protocol, approved by the medical ethics committee, participants were not informed about their CAC score, nor were their treating physicians.

Assessment of covariables

In the Rotterdam Study, assessment of anthropometrics, cardiovascular risk factors, and use of medication was described previously.[350] We defined diabetes mellitus as a fasting serum glucose level of ≥ 7.0 mmol/L, a nonfasting serum glucose level of ≥ 11.1 mmol/L (only if fasting serum was unavailable), or the use of oral blood glucose-lowering medication or insulin.

Assessment of outcomes

Follow-up started at the date of CT scanning. Cases of prevalent and incident heart failure and CHD were obtained by continuously monitoring participants of the Rotterdam Study during follow-up as described previously.[105] CHD events were defined as MI, PCI, CABG, or CHD mortality. Assessment of heart failure and CHD events was described in detail previously.[105] Two research physicians independently classified all potential events. Heart failure was classified as definite, probable, possible, or unlikely. In case of disagreement, consensus was reached in a separate session. Afterward, a cardiologist reviewed all events. Definite heart failure was defined as a combination of the presence of at least 1 of the typical symptoms or signs, such as breathlessness, ankle edema, and pulmonary crepitations, and confirmation by objective evidence of cardiac dysfunction. Also, for definite heart failure, the diagnosis had to have been made by a cardiologist or an internist. Heart failure was classified as probable when at least 2 typical symptoms are present, and at least 1 of the following: history of cardiovascular disease (e.g. MI, valvular heart disease, hypertension), positive response to initiated treatment for heart failure, or objective evidence of cardiac dysfunction. In accordance with the criteria of the European Society of Cardiology, only definite and probable cases were included in the analysis.[76]

Statistical analysis

CAC scores were divided into 4 categories: 0 to 10, 11 to 100, 101 to 400, and > 400, adapted from the categorization as proposed by Rumberger and colleagues.[351] We used Cox proportional hazards models to construct age- and sex-adjusted heart failure-free survival curves and to calculate hazard ratios (HRs) for the risk of heart failure for the natural logarithm

of the continuous CAC scores [log(CAC + 1)] and the different CAC score categories.[107] Before logarithmic transformation, we added 1 to all CAC scores to deal with participants who had a CAC score of 0. In model 1, we adjusted for age and sex. In model 2, we additionally adjusted for the following traditional cardiovascular risk factors: systolic blood pressure, current smoking, diabetes mellitus, total cholesterol to high-density lipoprotein cholesterol ratio, and body mass index. Participants with a CAC score of 0 to 10 served as the reference category. The P value for trend was obtained by entering CAC score categories into the Cox models as a continuous variable. Participants were censored at the date of death, loss to follow-up, or the end of the study period, defined as the last date of follow-up. In addition, we repeated the analyses after censoring participants when incident clinical nonfatal CHD occurred during follow-up (model 3 and additionally adjusted for cardiovascular risk factors in model 4). This was done to examine the association between CAC and risk of future heart failure, independent of incident CHD. We assessed the interaction terms between sex and the natural logarithm of the continuous CAC scores in all 4 models, which were all not significant (all P values > 0.30).

Next, we examined the added discriminative ability of log(CAC + 1) when added to the aforementioned cardiovascular risk factors. This was done by calculating optimism-corrected c-statistics as well as the optimism-corrected difference in c-statistic of a model including the cardiovascular risk factors and log(CAC + 1) compared with a model including the cardiovascular risk factors only.[352] These analyses were performed using 100 bootstrap repetitions.[28, 233] To further quantify the discriminative ability of CAC, we estimated the integrated discrimination improvement as a measure of the improvement in sensitivity with the addition of log(CAC + 1), corrected for the decrease in specificity (i.e. the difference in discrimination slopes).[16] Finally, we computed the true improvement in risk classification by addition of log(CAC + 1), by calculating the continuous net reclassification improvement.[137, 194]

In 83 (4.4%) of the participants, 1 or more cardiovascular covariables were missing. These missing values were handled by single imputation using an expectation-maximization algorithm.[109] With the exception of the baseline characteristics (Table 14.1), results are reported for imputed data. All measures of association are presented with 95% confidence intervals (CIs). We used the level of significance of P < 0.05. Data were analyzed using the PASW Statistics package, version 17.0.2 (SPSS Inc., Chicago, Ill, U.S.).The measures of discrimination and reclassification were computed using R version 2.10.1.[110]

Results

The baseline characteristics of the study population by category of CAC are shown in Table 14.1. For the total population, the median CAC score was 78 (interquartile range: 7 to 351). During a median follow-up time of 6.8 years (interquartile range: 6.3 to 7.5 years), there were 78 cases of incident heart failure, 76 cases of nonfatal incident CHD (46 MIs, 19 PCIs, and 11 CABG procedures), and 29 cases of fatal CHD. These 183 events occurred in 160 participants. Nonfatal incident CHD preceded heart failure in 14 of 78 participants (18%). Heart failure represented 64 of 160 (40%) of the first cardiac events observed. In all but 1 participant, in whom heart failure developed during follow-up, coronary calcifications were detected (98.7%). Figure 14.1 shows the association between CAC score categories and incident heart failure, adjusted for age and sex. The event-free survival decreased with increasing CAC scores, with an age- and

Table 14.1 – Characteristics of the study population

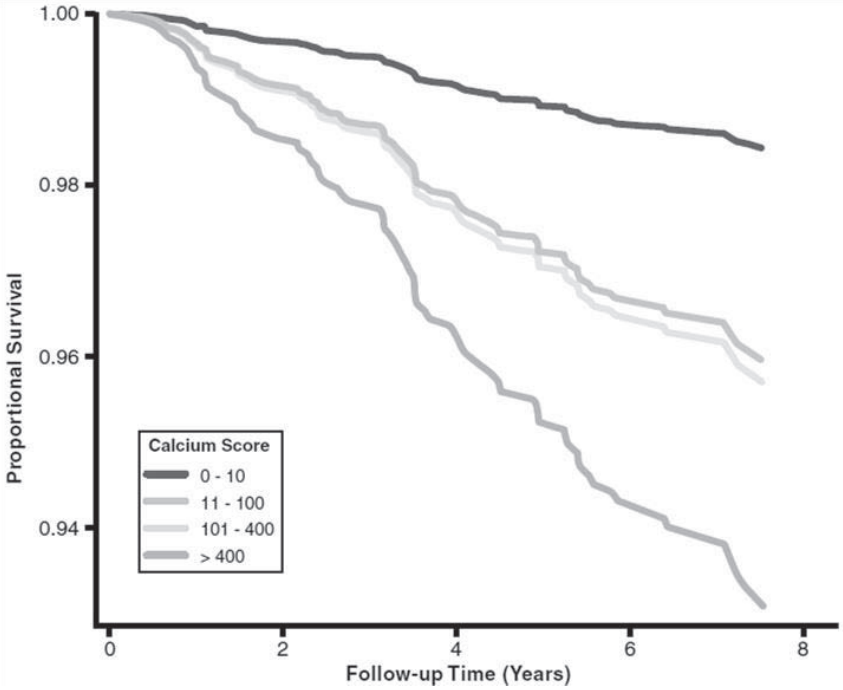
	Total population	CAC score categories			
		0-10	11-100	101-400	> 400
	n = 1897	n = 528	n = 498	n = 435	n = 436
Age, y	69.9 (6.5)	67.3 (6.0)	69.8 (6.3)	70.9 (6.2)	72.3 (6.2)
Men	41.9%	24.1%	39.4%	47.6%	60.6%
Systolic blood pressure, mmHg	143 (21)	138 (21)	144 (21)	144 (22)	147 (21)
Diastolic blood pressure, mmHg	76 (11)	75 (10)	77 (11)	76 (11)	77 (11)
Use of blood pressure-lowering medication	32.4%	24.4%	29.7%	34.5%	43.3%
Electrocardiographic LVH	4.7%	3.6%	4.6%	5.6%	5.2%
Smoking:					
Current	16.9%	12.0%	15.9%	20.3%	20.6%
Former	51.4%	45.8%	50.8%	51.6%	58.8%
Never	31.7%	42.4%	33.3%	28.1%	20.6%
Total cholesterol, mmol/L	5.9 (0.9)	5.9 (1.0)	5.9 (0.9)	5.9 (1.0)	5.8 (0.9)
HDL cholesterol, mmol/L	1.4 (0.4)	1.5 (0.4)	1.4 (0.4)	1.4 (0.3)	1.4 (0.4)
Diabetes mellitus	11.5%	6.5%	9.8%	14.4%	16.6%
Body mass index, kg/m^2	27.1 (4.0)	26.5 (3.6)	27.6 (4.2)	26.9 (4.1)	27.1 (3.9)
CAC score [a]	78 (7-351)	1 (0-4)	38 (20-66)	197 (145-264)	820 (578-1422)
CAC score > 0	89.4%	61.7%	100%	100%	100%

Values are percentages or means (standard deviations); unimputed data. CAC = coronary artery calcification; HDL = high-density lipoprotein; LVH = left ventricular hypertrophy.
[a] Median (interquartile range) because of its skewed distribution.

sex-adjusted cumulative incidence at 6 years of 1.4%, 3.3%, 3.5%, and 5.7% for CAC scores of 0 to 10, 11 to 100, 101 to 400, and > 400, respectively.

Increasing CAC score categories, adjusted for age and sex, were all significantly associated with heart failure (P for trend < 0.001), with an HR of 4.6 (95% CI 1.9-11.2) for CAC scores > 400 (model 1) (Table 14.2). Additional adjustment for cardiovascular risk factors lowered these estimates slightly but remained significant (P for trend = 0.001), with an HR of 4.1 (95% CI 1.7-10.1) in the CAC score category of > 400 (model 2). Further adjustment for measures of long-standing hypertension (i.e. use of antihypertensive medication and electrocardiographic left ventricular hypertrophy) resulted in minor attenuation of the associations, with an HR of 1.25 (95% CI 1.10-1.41) for continuous CAC scores.

Figure 14.1 – Heart failure-free survival, by coronary artery calcification score category



As the extend of coronary calcification increases, heart failure-free survival adjusted for age and sex decreases over time (P for trend < 0.001).

When repeating these analyses with additional censoring of participants with the occurrence of an MI or coronary revascularization procedure during follow-up, estimates of the HRs for increasing CAC score categories decreased but remained associated (P for trend = 0.027) and significant in the upper CAC score category (model 3). Even after adjustment for cardiovascular risk factors (model 4), every 1-unit increase in log(CAC + 1) corresponded to an HR of 1.17 (95% CI 1.02-1.33). Furthermore, increasing CAC score categories remained associated with the risk of heart failure (P for trend = 0.046) and a CAC score > 400 remained significantly elevated, with an HR of 2.9 (95% CI 1.1-7.4).

In our population free of heart failure and CHD at baseline, the prediction model based on the cardiovascular risk factors performed satisfactorily with a c-statistic of 0.705 (95% CI 0.666-0.754). CAC scores, when added to the model, increased the c-statistic by 0.030 (95% CI 0.001-0.050) and resulted in a c-statistic of 0.734 (95% CI 0.698-0.770). The integrated discrimination improvement was 0.011 (95% CI 0.001-0.020). Addition of the continuous CAC scores to the model containing cardiovascular risk factors led to a continuous net reclassification improvement of 0.340 (95% CI 0.114-0.567).

Table 14.2 – Hazard ratios for the developing heart failure, by coronary artery calcification score category

			Model 1 [a]	Model 2 [b]		Model 3 [a,c]	Model 4 [b,c]
	At risk, n	Events, n	HR (95% CI)	HR (95% CI)	Events, n [c]	HR (95% CI)	HR (95% CI)
Per 1-unit increase in log(CAC + 1)	1897	78	1.27 (1.13-1.44)	1.26 (1.11-1.42)	64	1.18 (1.04-1.35)	1.17 (1.02-1.33)
CAC score categories:							
0-10	528	6	1.0 (reference)	1.0 (reference)	6	1.0 (reference)	1.0 (reference)
11-100	498	19	2.6 (1.0-6.6)	2.4 (0.9-6.0)	18	2.5 (1.0-6.3)	2.3 (0.9-5.8)
101-400	435	19	2.8 (1.1-7.1)	2.6 (1.0-6.5)	17	2.5 (1.0-6.5)	2.4 (0.9-6.1)
> 400	436	34	4.6 (1.9-11.2)	4.1 (1.7-10.1)	23	3.2 (1.2-8.1)	2.9 (1.1-7.4)
P for trend			< 0.001	0.001		0.027	0.046

CAC = coronary artery calcification.
[a] Adjusted for age and sex.
[b] Adjusted for age, sex, systolic blood pressure, current smoking, diabetes mellitus, total cholesterol to high-density lipoprotein cholesterol ratio, and body mass index.
[c] After censoring participants when nonfatal coronary heart disease occurred during follow-up.

Discussion

Our results indicate a clear and graded association between the extent of CAC and the risk of heart failure in a population of Dutch elderly. All but a single participant in our study in whom heart failure developed had CAC detected, and participants in the highest CAC score category (> 400) were more than 4 times more likely to develop heart failure compared with participants with a 0 or very low CAC score, independent of cardiovascular risk factors. After censoring participants with the occurrence of incident nonfatal CHD, a 3-fold increased risk of heart failure persisted for this CAC score category, indicating a clear association between CAC and risk of heart failure apart from overt CHD. Moreover, adding continuous CAC scores to the cardiovascular risk factors increased the discriminative ability of the prediction model and improved the classification of the risk estimation.

Thus far, numerous large population-based studies investigating CAC and future cardiovascular disease only examined the risk of MI, coronary revascularization, stroke, death, or a combination of these outcomes.[70, 188, 257, 343-346] Recently, increasing CAC scores have been cross-sectionally associated with self-reported history of heart failure, with odds ratios adjusted for age and sex of 1.3 (95% CI 0.7-2.2) for CAC scores of 10 to 99, 1.9 (95% CI 1.1-3.3) for CAC scores of 100 to 399, and 2.2 (95% CI 1.2-4.1) for CAC scores > 399.[353] The strength of the associations of CAC with heart failure is substantially lower compared with the associations with CHD events in the elderly that we reported previously.[70, 165, 257, 345] For instance, we showed that log(CAC + 1) yielded a multivariable adjusted HR of 1.33 (95% CI 1.21-1.47) with hard CHD compared with 1.26 (95% CI 1.11-1.42) for heart failure (Table 14.2).[345] This is most likely explained by the heterogeneous etiology of heart failure in the general population. Nonetheless, we show that CAC measurements are of added value in predicting future heart failure in the elderly, regardless of the underlying etiology.

In our study, heart failure represented 40% (64 of 160) of the first cardiac events observed. This is in agreement with numbers from a recent report of the Framingham Heart Study showing in an elderly subpopulation that 48% of the participants with a cardiac event had heart failure as their initial presentation.[334] This reinforces heart failure as an additional outcome measure in studies on cardiovascular risk prediction in the elderly, in addition to hard coronary outcomes. Although abundant research indicates that CAC screening in the elderly has additive value for CHD risk prediction over traditional risk factors, its effect on clinical outcomes and its cost-effectiveness in large-scale randomized trials are much awaited.[339, 354-357] Given our study results, heart failure should be considered an additional outcome measure in possible future cardiac risk assessment programs using CAC screening.

Strengths and limitations

The strengths of our study include the standardized measurements of cardiovascular risk factors in a population-based setting with long and virtually complete follow-up. Furthermore, due to the fact that both participants of our study and their treating physicians were not informed about the CAC scores, our cohort is one of few in the world in which an unbiased association between CAC and future heart failure can be investigated. Awareness of a high CAC score may motivate patients to make beneficial lifestyle changes and results in superior risk factor control

with increased downstream medical testing in patients with CAC scores > 400.[342, 358]

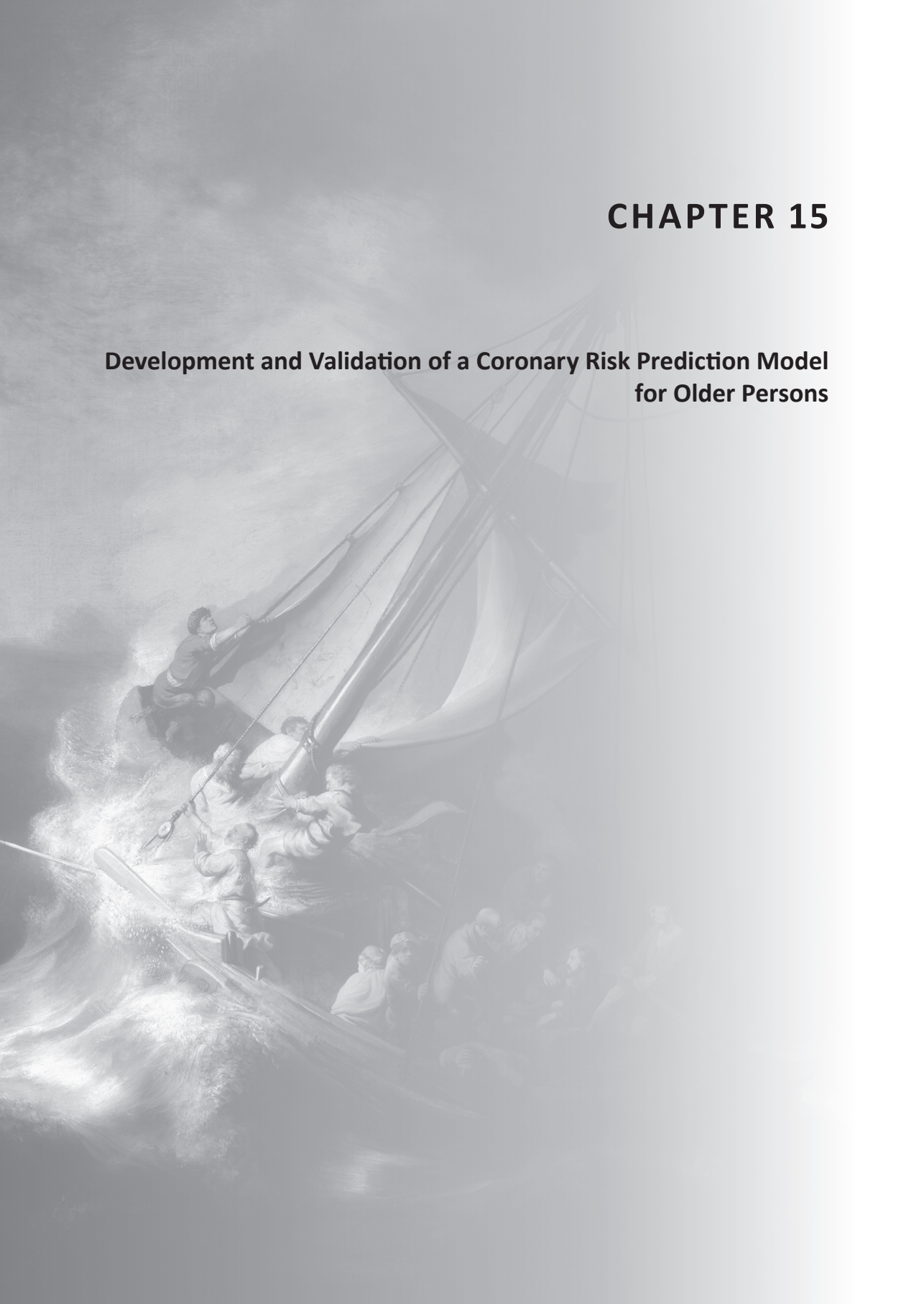
Our study also has some limitations that need to be addressed. First, heart failure diagnosis was based on the occurrence of symptoms and response to heart failure therapy, usually supported by concurrent echocardiography or chest X-ray. Unfortunately, additional information on the presence of objective cardiac dysfunction was not present in all cases, especially not for nursing home residents. This might have led to some misclassification and thereby underestimation of the associations. Second, our results were derived from an elderly population. In this age group, CHD is the most important risk factor for heart failure among many others, such as long-standing hypertension, atrial fibrillation, valvular heart disease, and various cardiomyopathies.[359] This may not hold true for younger individuals. The strength of associations of traditional coronary risk factors (e.g. cholesterol and hypertension) diminishes with increasing age, whereas increasing extent of CAC can be seen as a cumulative measurement of a lifetime exposure to cardiovascular risk factors.[29, 30] Therefore, our results cannot be generalized to middle-aged individuals. Furthermore, as in all prognostic studies in aging populations, competing causes of death (e.g. death due to other cardiovascular diseases or cancer) may have interfered with our estimation of the event-free survival. Last, because of the limited number of heart failure cases, we could not assess differences in prognosis of CAC in subgroups, such as women and those with diabetes or hypertension.

Conclusions

The extent of CAC has a clear association with the risk of the development of heart failure, independent of overt CHD. Because heart failure is highly prevalent in the elderly, it might be worthwhile to include heart failure as an outcome if future risk assessment programs incorporate CAC screening.

CHAPTER 15

Development and Validation of a Coronary Risk Prediction Model for Older Persons



Background

Risk scores for prediction of coronary heart disease (CHD) in older adults are needed.

Objective

To develop a sex-specific CHD risk prediction model for older adults that accounts for competing risks for non-coronary death.

Design

2 observational cohort studies, using data from 4946 participants aged 65 years or older who were free of cardiovascular disease from the Cardiovascular Health Study (CHS) and 4303 participants in the Rotterdam Study (RS).

Main outcomes

A composite of nonfatal myocardial infarction and coronary death.

Results

During a median follow-up of 16.5 and 14.9 years, 1166 CHS and 698 RS participants had CHD events, respectively. Deaths from non-coronary causes largely exceeded the number of CHD events, complicating accurate CHD risk predictions. The prediction model had moderate ability to discriminate between events and nonevents (c-statistic, 0.63 in both U.S. and European men and 0.67 and 0.68 in U.S. and European women). The model was well calibrated; predicted risks were in good agreement with observed risks. Compared with the Framingham point score, the prediction model classified elderly U.S. persons into higher risk categories but elderly European persons into lower risk categories. Differences in classification accuracy were not consistent and depended on cohort and sex. Adding newer cardiovascular risk markers to the model did not substantially improve performance.

Conclusions

A CHD risk prediction model that accounts for deaths from non-coronary causes among older adults provided well-calibrated risk estimates but was not substantially more accurate than Framingham point score. Moreover, adding newer risk markers did not improve accuracy. These findings emphasize the difficulties of predicting CHD risk in elderly persons and the need to improve these predictions.

Specialist societies recommend initiating preventive treatment of cardiovascular disease on the basis of a person's 10-year risk for coronary heart disease (CHD).[216, 247, 360] Well-known prognostic models to estimate this risk originate from the Framingham Heart Study,[331, 361-363] the Women's Health Study,[364] the Prospective Cardiovascular Münster (PROCAM) study,[365] and the Systematic Coronary Risk Evaluation (SCORE) project.[5]

Demographic changes have increasingly led to an extension of primary prevention strategies for CHD to elderly persons.[25, 366] However, these persons are underrepresented or neglected in well-known CHD prediction models. Several studies show that existing CHD prediction models may extrapolate poorly to persons older than 70 years [367] and that the predictive associations of risk factors for CHD may diminish with increasing age.[28-30, 216, 323] A CHD prediction model for elderly persons should also take into account that with growing age and frailty, CHD events may be increasingly precluded by death from competing non-coronary causes. A valid risk prediction approach in this situation must account for competing causes of death to prevent inflated predictions of limited practical use.[294, 368-371]

The purpose of this study was to develop and evaluate a population-based algorithm to predict coronary risk in elderly persons on the basis of traditional risk factors. We also examined model performance after the addition of newer risk markers for cardiovascular disease. Our study is the result of a collaboration between 2 large and similarly designed cohort studies on cardiovascular disease in elderly persons, the Cardiovascular Health Study (CHS) in the U.S. [72] and Rotterdam Study (RS) in the Netherlands.[32-35]

Methods

Study design, setting, and population

The CHS is a prospective population-based study in adults aged 65 years or older with the main objective of identifying risk factors related to the onset and course of CHD and stroke. Eligible participants were sampled from Medicare eligibility lists in 4 U.S. communities. The rationale and design of the CHS have been described elsewhere.[72] The RS is a prospective population-based cohort study of persons aged 55 years or older living in a suburb of Rotterdam, the Netherlands. This study aims to assess the determinants of cardiovascular and other diseases in elderly persons.[32-37]

We selected all participants aged 65 years or older who were free of definite CHD and cerebrovascular disease at enrollment. After participants with a history of myocardial infarction (MI); electrocardiography results consistent with past MI; or a history of percutaneous or surgical coronary revascularization procedures, stroke, or carotid endarterectomy were excluded, 4946 CHS and 4303 RS participants remained in the analyses. Previous publications detail the procedures for assessing medical history at baseline.[72, 105, 372]

Measurement of coronary risk factors

Participants were categorized in groups of current, former, or never smokers. Former smoking

was defined as having abstained from smoking for at least 2 years. Blood pressure was measured by using a random-zero sphygmomanometer at the right brachial artery in sitting position after a 5-minute rest. The average of 2 consecutive blood pressure measurements was used. In the CHS, participants were asked to fast for 12 h before coming to their clinical appointments and fasting plasma lipid levels were measured by an Olympus Demand system (Olympus, Lake Success, NY, U.S.). In the RS, serum total cholesterol level was determined by an automated enzymatic procedure by using the CHOD-PAP reagent agent (Roche Diagnostics, Basel, Switzerland) and serum HDL cholesterol level was measured with the HDL cholesterol assay (Roche Diagnostics, Basel, Switzerland) by using polyethylene glycol-modified enzymes and dextran sulfate. Diabetes mellitus was defined as current use of blood glucose-lowering medication or a random or postload serum glucose level of ≥ 11.1 mmol/L.

A 12-lead resting electrocardiogram (ECG) was obtained and stored electronically in both cohorts. In the CHS, the ECG reading center used the Novacode ECG measurement and classification system [72, 373] to analyze ECG data. In the RS, ECG data were computer-analyzed by the MEANS program.[54, 105] The presence of ECG-LVH was defined according to the Sokolow-Lyon voltage criteria.[374] In the CHS, fasting serum chemistry analyses were done with the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY, U.S.). In the RS, CRP was measured by Rate Near Infrared Particle Immunoassay (Immage Immunochemistry System; Beckman Coulter, Brea, CA, U.S.).[375] The ABI was calculated as the ratio of the systolic blood pressure of the posterior tibial artery, as assessed by an 8-MHz continuous wave Doppler probe and a random-zero sphygmomanometer, to the systolic blood pressure at the right arm. The lowest ABI of the left- and right-side readings was used for analysis.[376] Duplex ultrasonography of both carotid arteries was performed with a 5.0 MHz transducer (SSA-270A; Toshiba America Medical Systems, Tustin, CA, U.S.) in the CHS and a 7.5-MHz transducer (UltraMark IV; Advanced Technology Laboratories, Bothell, WA, U.S.) in the RS. Common cIMT was determined as described elsewhere.[41] The maximum common cIMT was determined as the average of the maximum cIMT of near- and far-wall measurements over a length of 1 cm, and the average of left and right maximum common cIMT was computed and used for analysis.

End points

The outcome for this study was time to first CHD event, a composite of nonfatal MI and fatal CHD. Appendix Table 15.1 compares the very similar standardized definitions of CHD events for the 2 cohorts and Appendix Table 15.2 provides the incidence of CHD end points (nonfatal MI and coronary death).

In the CHS, events were ascertained through regular surveys (surveillance calls, annual visits, newspaper obituaries, and reviews of medical records and Medicare data) from the field centers or by participants contacting the sites. Potential events were classified by a study-wide review committee on the basis of death certificates; autopsy and coroner forms; hospital records; and interviews with attending physicians, next of kin, and witnesses.[72, 94] In the RS, information on end points was obtained from general practitioners and discharge reports from medical specialists. All events were classified independently by 2 research physicians. If the physicians disagreed, a consensus was reached in a special session. Finally, all events were verified by a medical specialist affiliated with the study.[105]

For the CHS, the first examination cycle began in 1989, with annual examinations through 1999. A second cohort was enrolled in 1992 with the additional recruitment of African Americans. In the RS, baseline examinations were conducted from 1990 to 1993 (RS-I-1; Figure 1.1). The censoring date was 30 June 2006 in the CHS and 1 January 2007 in the RS. For our analysis, only 1 CHS participant and 6 RS participants were lost to follow-up after 10 years.

Statistical analysis

We developed prespecified and sex-specific CHD prediction models using age; systolic blood pressure, with separate effects for treated and untreated participants; presence of diabetes mellitus; levels of total and high-density lipoprotein (HDL) cholesterol; and smoking status as covariables. We used a competing risk method based on the Fine and Gray model, using the approach by Ruan and Gray.[296, 377, 378]

We pooled data from both cohorts into 2 sex-specific data sets. Regression models included cohort-stratified baseline hazard functions; that is, we assumed that baseline risk for CHD may differ but that risk factors act equally on U.S. and European persons [5] and assessed this assumption by testing for cohort-risk factor interactions. Appendix Table 15.3 provides details about the development steps of the model and the testing of the assumptions.

We assessed prognostic accuracy by evaluating the pooled model on each cohort individually and by cross-validation, in which models were fit to one cohort and evaluated in the other. We quantified the discriminative ability up to 10 years of follow-up with an adaptation of the Harrell's c-statistic [28] to the competing risks setting.[370] Calibration was assessed by plotting 10-year predicted risk against observed risk.[370]

Next, we computed 10-year risk predictions based on the original Adult Treatment Panel III (ATP III) Framingham point score (FPS),[27] which predicts the same composite CHD end point, and compared the accuracy of FPS predictions with predictions from our model by using the c-statistic [370] and risk classification methods with recommended cut-off values.[27] Because head-to-head comparisons of different non-nested prediction models, particularly those that have not been fitted on the same population, are hard to interpret with single measures (such as the net reclassification improvement [NRI][16]), we used summary metrics based on the margins of the reclassification table proposed by Janes and Pepe.[160, 209, 212] We focused on differences between the 2 models in proportions of events and nonevents classified into the high-risk (> 20%) or low-risk (< 10%) categories. In these categories, decisions to test or treat are more established than in the intermediate-risk category, in which appropriate clinical actions are sometimes less certain. The comparisons are summarized as changes in the true- and false-positive and true- and false-negative rates. Because the FPS is intended for non-diabetic persons, we also refit and reexamined our model in non-diabetic participants.

In a further step, we examined the incremental value of extending the competing risks model based on traditional risk factors with the single addition of body mass index, C-reactive protein (CRP) levels, carotid intima-media thickness (cIMT), ankle-brachial index (ABI), or the presence of left ventricular hypertrophy on electrocardiography (ECG-LVH).[16] We evaluated the added value of these markers on the basis of statistically significant overall model improvement and the

increase in the c-statistic.[28] Because we compared nested models, we used the NRI to present reclassification accuracy. We computed the NRIs by adapting the suggestion of Steyerberg and Pencina for survival data [16, 194] to the competing risks setting. Appendix Table 15.3 provides details of the evaluation of extended models.

In a sensitivity analysis, we excluded participants aged 80 years or older because the FPS are developed for adults up to age 79 years; there were few meaningful changes in our results so we do not report them.

We report estimates of hazard ratios and c-statistics with 95% CIs. All hypothesis tests are 2-sided, and the significance level was set to 5%. Data were analyzed using R version 2.14.2 .[110] The Appendix to this chapter provides more detailed descriptions of our statistical analysis and methods.

Results

Baseline characteristics are presented in Table 15.1. In the CHS cohort, 15.5% of men and 11.5% of women were aged 80 years or older. In the RS cohort, the corresponding proportions were 19.7% and 33.3%. The median duration of follow-up was 16.5 years (interquartile range, 13.5 to 16.7 years) in the CHS and 14.9 years (interquartile range, 14.1 to 15.7 years) in the RS. We observed 563 CHD events in men and 603 in women in the CHS; in the RS, we observed 283 events in men and 415 in women. This corresponded with 10-year cumulative incidences of 19.9% and 15.8% in men in the CHS and the RS, respectively, and similar incidences in women (11.5% and 10.4%, respectively). In both cohorts, the number of competing non-coronary deaths exceeded the number of CHD events over the entire age range; we observed 2000 and 2244 non-coronary deaths in the CHS and the RS, respectively (Appendix Tables 15.1 and 15.2). The incidence of competing non-coronary death increased more rapidly with age than did the incidence of CHD (Figure 15.1).

Coronary heart disease prediction

Coronary risk factors were associated with CHD about equally in men and women (Table 15.2). However, total cholesterol level was predictive of CHD in European but not in U.S. women, so we accounted for cholesterol– cohort interaction in our final prediction model. We also note that systolic blood pressure in men treated for hypertension was not statistically significant and smoking was borderline statistically significant in the multivariable model (Table 15.2). In women, the positive association of age with CHD was nonlinear and decreased with increasing age. We refer to our model based on established risk factors as the coronary risk in the elderly (CORE) model for the remainder of the text.

The discriminatory performance of the CORE model was moderate and lower in men than in women (c-statistic, 0.63 in both U.S. and European men and 0.68 and 0.67 in U.S. and European women, respectively) (Table 15.3). Cross-validation led to loss of discrimination compared with the pooled model (Table 15.3). Predicted 10-year risks were in good agreement with observed risks in each cohort, indicating good calibration (Figure 15.2). The Appendix to this chapter

Table 15.1 – Characteristics of study populations

	Cardiovascular Health Study		Rotterdam Study	
	Men	Women	Men	Women
	n = 1917	n = 3029	n = 1454	n = 2849
Age, y	72 (69-77)	71 (68-76)	73 (69-78)	76 (70-83)
White ethnicity	1628 (85)	2505 (83)	1301 (99)	2444 (99)
Use of blood pressure-lowering medication	750 (39)	1353 (45)	394 (31)	1095 (45)
Systolic blood pressure, mmHg:				
Treated	137 (123-153)	140 (126-156)	142 (128-158)	147 (132-163)
Untreated	132 (119-146)	130 (118-145)	138 (126-154)	142 (128-156)
Smoking:				
Current	221 (12)	377 (12)	414 (30)	342 (13)
Former	1065 (56)	895 (30)	876 (63)	636 (24)
Never	628 (33)	1754 (58)	106 (8)	1639 (63)
Total cholesterol, mmol/L	5.1 (4.5-5.7)	5.6 (5.0-6.3)	6.1 (5.3-6.8)	6.7 (5.9-7.5)
HDL cholesterol, mmol/L	1.2 (1.0-1.4)	1.5 (1.2-1.8)	1.2 (1.0-1.4)	1.4 (1.2-1.6)
Diabetes mellitus	318 (17)	391 (13)	143 (10)	336 (12)
ECG-LVH	77 (4)	123 (4)	72 (5)	126 (6)
Body mass index, kg/m^2	26 (24-29)	26 (23-30)	26 (24-27)	27 (24-29)
C-reactive protein, nmol/L	0.23 (0.12-0.42)	0.14 (0.27-0.48)	0.22 (0.10-0.44)	0.21 (0.10-0.38)
Ankle-brachial index	1.2 (1.1-1.2)	1.1 (1.0-1.2)	1.2 (1.0-1.3)	1.2 (1.0-1.2)
cIMT, mm	1.1 (1.0-1.2)	1.0 (0.9-1.2)	1.1 (0.9-1.2)	1.0 (0.9-1.1)

Values are counts (percentages) or medians (interquartile range); unimputed data. cIMT = carotid intima-media thickness; ECG-LVH = electrocardiographic left ventricular hypertrophy; HDL = high-density lipoprotein.

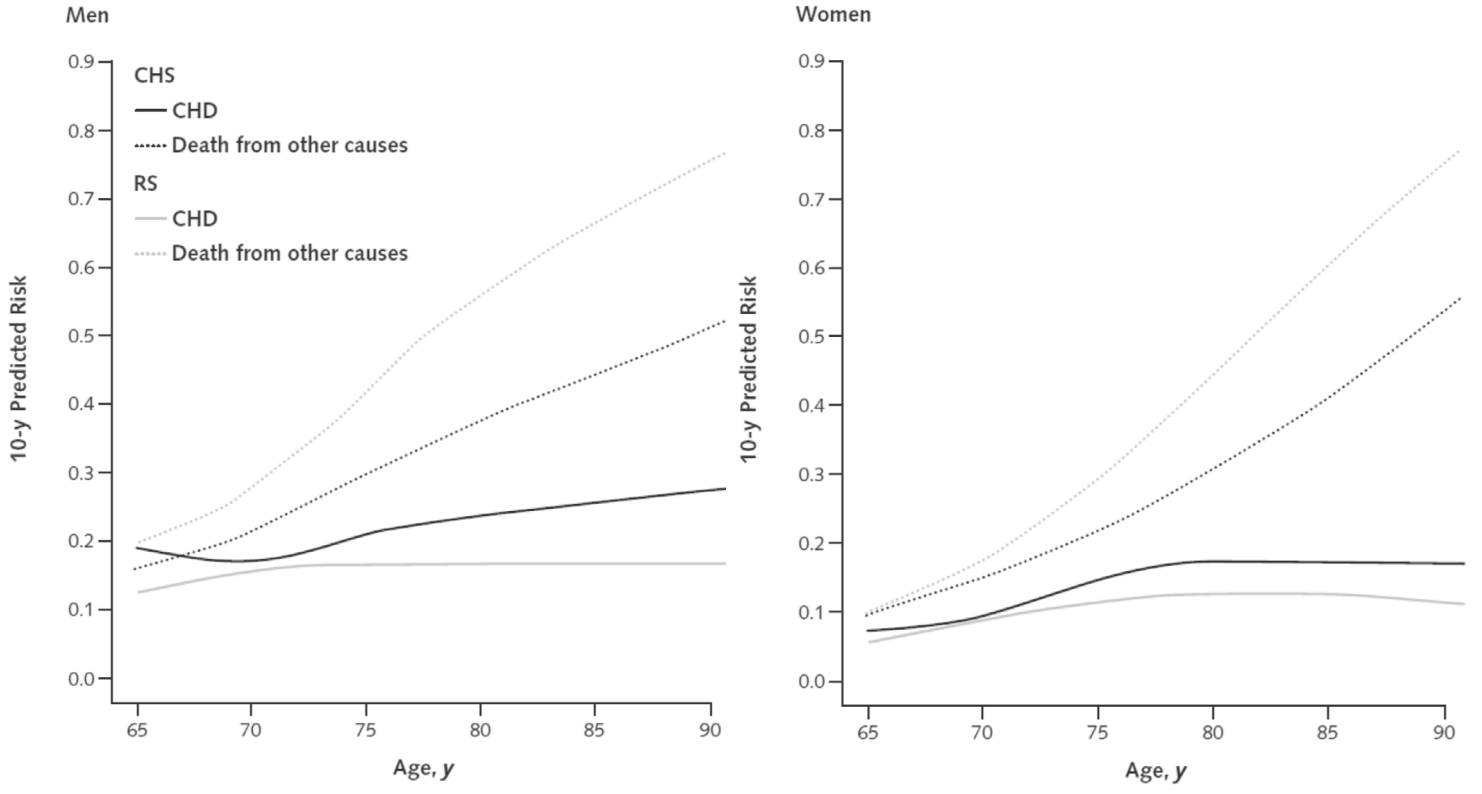
includes an example that explains how the CORE model can be applied to derive predicted risks by using the coefficients and subdistribution hazards from Appendix Tables 15.4 and 15.5, respectively. A risk calculator developed from our model for the prediction horizons of 3, 5, 7, and 10 years is available online at www.ceb-institute.org/evibox/chd/.

Comparison with the Framingham point score

We compared the CORE model with the FPS. The c-statistic of the FPS was 0.02 to 0.03 units lower than that of the CORE model in both cohorts Table 15.3.

In U.S. men, the CORE model classified many more persons into the high-risk group than did

Figure 15.1 – Association of age with 10-year actual risk for coronary heart disease and the 10-year risk for competing non-coronary death



CHD = coronary heart disease; CHS = Cardiovascular Health Study; RS = Rotterdam Study.

Table 15.2 – Multivariable-adjusted hazard ratios for coronary heart disease risk factors

Risk factor	Pooled CHS and RS data for men			Pooled CHS and RS data for women		
	HR (95% CI) [a]	P value	P for interaction with cohort [b]	HR (95% CI) [a]	P value	P for interaction with cohort [b]
Age (per 10-y)	1.23 (1.10-1.37)	< 0.001	0.176	1.68 (1.47-1.91)	< 0.001	0.68 [c]
Use of blood pressure-lowering treatment [d]	1.51 (1.29-1.76)	< 0.001	0.183	1.33 (1.15-1.55)	< 0.001	0.41
Systolic blood pressure (per 10-mmHg):						
Treated	1.00 (0.96-1.04)	0.56	0.61	1.08 (1.04-1.12)	< 0.001	0.49
Untreated	1.11 (1.07-1.16)	< 0.001	0.106	1.14 (1.09-1.18)	< 0.001	0.68
Total cholesterol (per 1-mmol/L)	1.12 (1.04-1.20)	< 0.001	0.068	CHS: 1.04 (0.96-1.13) RS: 1.22 (1.13-1.31)	CHS: 0.31 RS: < 0.001	0.004 [e]
HDL cholesterol (per 1-mmol/L)	0.69 (0.55-0.86)	< 0.001	0.60	0.65 (0.55-0.77)	< 0.001	0.74
Ever smoking	1.14 (0.97-1.35)	0.114	0.26	1.13 (1.00-1.29)	0.058	0.175
Diabetes mellitus	1.36 (1.14-1.62)	< 0.001	0.69	1.39 (1.18-1.64)	< 0.001	0.22

CHS = Cardiovascular Health Study; CORE = coronary risk in the elderly; HDL = high-density cholesterol; RS = Rotterdam Study.

[a] Hazard ratios for the subdistribution hazards of the Fine and Gray model.[296]

[b] Test of whether the effect of a risk factor differed between the CHS and the RS.

[c] Because of the nonlinear association of age with coronary heart disease in women, the age effect was best modeled with a quadratic polynomial and only the effect of age 79 versus 69 years is displayed for simplicity. Appendix Table 15.4 provides details and exact regression coefficients of the CORE model. The P value for the cohort-age interaction refers to an overall test of the linear and the quadratic age term.

[d] Shown for participants with a systolic blood pressure of 130 mmHg.

[e] In the CORE model, a total cholesterol-cohort interaction term was added.

Table 15.3 – Discriminatory performance of the CORE model and Framingham point score

Model	C-statistic (95% CI)	
	Men	Women
Model derived from pooled CHS and RS data:		
Evaluated in CHS	0.63 (0.60-0.65)	0.68 (0.65-0.70)
Evaluated in RS	0.63 (0.59-0.66)	0.67 (0.64-0.70)
Cross-validation performance:		
Model derived in RS evaluated in CHS	0.60 (0.57-0.63)	0.67 (0.64-0.69)
Model derived in CHS evaluated in RS	0.62 (0.58-0.65)	0.65 (0.62-0.68)
Framingham point score predictions:		
Evaluated in CHS	0.60 (0.57-0.63)	0.66 (0.64-0.69)
Evaluated in RS	0.60 (0.56-0.63)	0.65 (0.62-0.69)

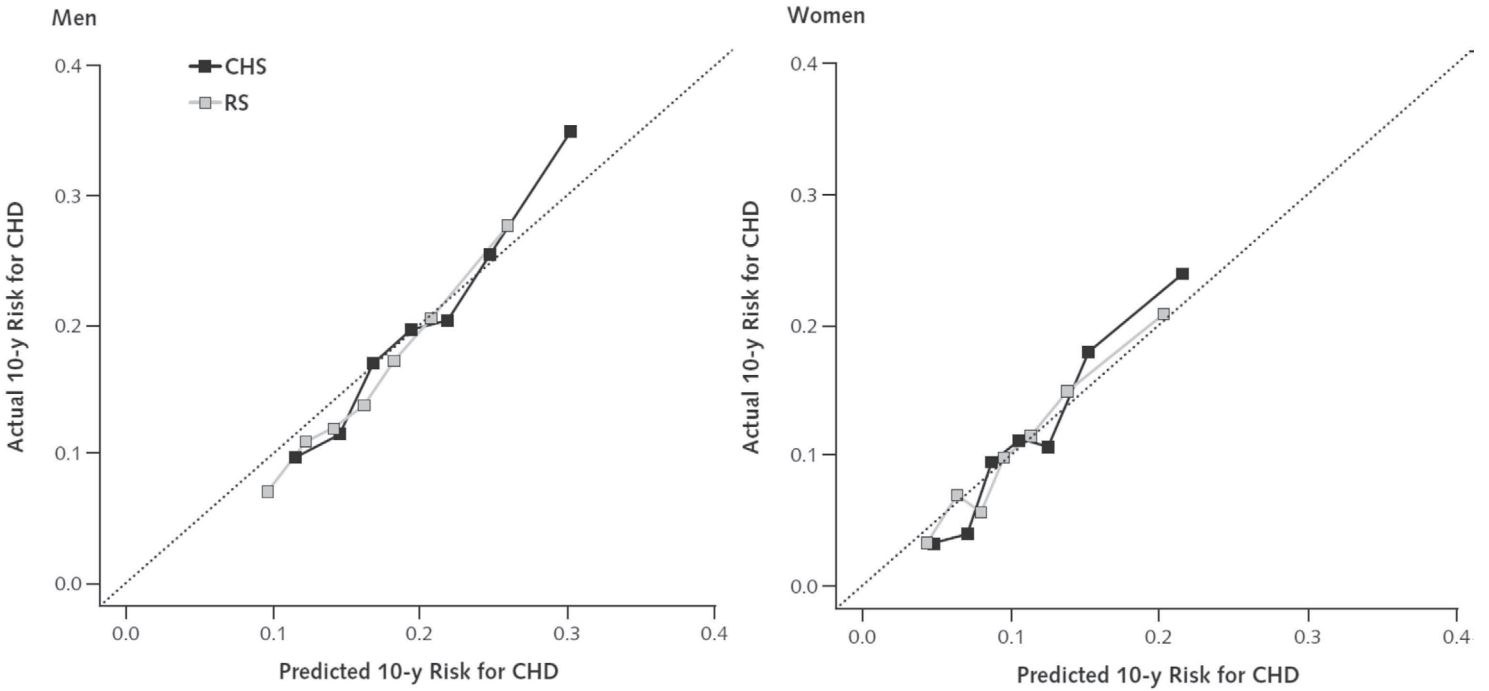
CHS = Cardiovascular Health Study; CORE = coronary risk in the elderly; RS = Rotterdam Study.

the FPS (47.7% versus 22.5%) (Table 15.4). More specifically, compared with the FPS, the CORE model increased classification of events and nonevents as high-risk by 30.6 and 23.8 percentage points, respectively. Similar results were seen for non-diabetic U.S. men (increases in true- and false-positive rates of 24.0 and 16.6 percentage points, respectively). Of note, observed risks in high-risk non-diabetic men were almost identical in the 2 models (24.6% in the CORE model and 24.8% for the FPS), whereas the number of events classified as high-risk in the CORE model was nearly double that of the FPS (51.4% versus 27.4%). Therefore, the increase in the true-positive rate can be ascribed at least in part to better discriminative properties of the CORE model. The reclassification table for the comparison of the CORE model to the FPS in non-diabetics is presented in the online supplement of the original publication.[104]

In U.S. women, the CORE model classified fewer events and nonevents as low-risk than the FPS (differences of 20.7 and 19.0 percentage points, respectively) (Table 15.4). In Europeans, the CORE model generally classified more persons into lower risk categories than the FPS (Table 15.5).

In European men, the CORE model classified fewer nonevents as high-risk (a difference of 14.2 percentage points) but at the expense of a 10.5-percentage point increase in events misclassified in lower risk strata (Table 15.5). The general downward movement of persons with the CORE model was due to systematic overestimation of risk in RS participants with the FPS. For example, observed risks were 11.1% and 19.7% in the intermediate- and high-risk categories using the FPS in European women.

Figure 15.2 – Calibration of the CORE model



CHD = coronary heart disease; CHS = Cardiovascular Health Study; CORE = coronary risk in the elderly; RS = Rotterdam Study.

Table 15.4 – Coronary heart disease risk classification according to the CORE model and Framingham point score in the Cardiovascular Health Study

Model	Men				Women			
	< 10% risk	10-20% risk	> 20% risk	Total	< 10% risk	10-20% risk	> 20% risk	Total
CORE:								
Total, n (%)	35 (1.8)	968 (50.5)	914 (47.7)	1917 (100)	1395 (46.1)	1392 (46.0)	242 (8.0)	3029 (100)
Events, n (%)	2 (0.5)	142 (37.2)	238 (62.3)	382 (100)	78 (22.4)	206 (59.2)	64 (18.4)	348 (100)
Nonevents, n (%)	33 (2.2)	826 (53.8)	676 (44.0)	1535 (100)	1317 (49.1)	1186 (44.2)	178 (6.6)	2681 (100)
Observed risk	5.7%	14.7%	26.0%		5.6%	14.8%	26.4%	
FPS:								
Total, n (%)	230 (12.0)	1255 (65.5)	432 (22.5)	1917 (100)	1976 (65.2)	833 (27.5)	220 (7.3)	3029 (100)
Events, n (%)	24 (6.3)	237 (62.0)	121 (31.7)	382 (100)	150 (43.1)	144 (41.4)	54 (15.5)	348 (100)
Nonevents, n (%)	206 (13.4)	1018 (66.3)	311 (20.3)	1535 (100)	1826 (68.1)	689 (25.7)	166 (6.2)	2681 (100)
Observed risk	10.4%	18.9%	28.0%		7.6%	17.3%	24.6%	
Difference (= CORE – FPS):								
Change in true-positive rate [a]	30.6% (= 62.3% – 31.7%)				2.9% (= 18.4% – 15.5%)			
Change in false-positive rate [b]	23.8% (= 44.0% – 20.3%)				0.4% (= 6.6% – 6.2%)			
Change in true-negative rate [c]	-5.8% (= 0.5% – 6.3%)				-20.7% (= 22.4% – 43.1%)			
Change in false-negative rate [d]	-11.3% (= 2.2% – 13.4%)				-19.9% (= 49.1% – 68.1%)			

CORE = coronary risk in the elderly; FPS = Framingham point score.
[a] Difference in proportion of events categorized as > 20% risk.
[b] Difference in proportion of nonevents categorized as > 20% risk.
[c] Difference in proportion of events categorized as < 10% risk.
[d] Difference in proportion of nonevents categorized as < 10% risk.

Table 15.5 – Coronary heart disease risk classification according to the CORE model and Framingham point score in the Rotterdam Study

Model	Men				Women			
	< 10% risk	10-20% risk	> 20% risk	Total	< 10% risk	10-20% risk	> 20% risk	Total
CORE:								
Total, n (%)	102 (7.0)	975 (67.1)	377 (25.9)	1454 (100)	1540 (54.1)	1149 (40.3)	160 (5.6)	2849 (100)
Events, n (%)	8 (3.5)	127 (55.5)	94 (41.0)	229 (100)	94 (31.6)	164 (55.2)	39 (13.2)	297 (100)
Nonevents, n (%)	94 (7.7)	848 (69.2)	283 (23.1)	1225 (100)	1445 (56.7)	986 (38.6)	121 (4.7)	2552 (100)
Observed risk	7.8%	13.0%	24.9%		6.1%	14.3%	24.6%	
FPS:								
Total, n (%)	76 (5.2)	803 (55.2)	575 (39.5)	1454 (100)	1155 (40.5)	1159 (40.7)	535 (18.8)	2849 (100)
Events, n (%)	4 (1.8)	107 (46.7)	118 (51.5)	229 (100)	64 (21.5)	128 (43.1)	105 (35.4)	297 (100)
Nonevents, n (%)	72 (5.9)	696 (56.8)	457 (37.3)	1225 (100)	1091 (42.8)	1031 (40.4)	430 (16.8)	2552 (100)
Observed risk	5.3%	13.3%	20.5%		5.5%	11.1%	19.7%	
Difference (= CORE – FPS):								
Change in true-positive rate [a]	-10.5% (= 41.0% – 51.5%)				-22.2% (= 13.2% – 35.4%)			
Change in false-positive rate [b]	-14.2% (= 23.1% – 37.3%)				-12.1% (= 4.7% – 16.8%)			
Change in true-negative rate [c]	1.7% (= 3.5% – 1.8%)				10.1% (= 31.6% – 21.5%)			
Change in false-negative rate [d]	1.8% (= 7.7% – 5.9%)				13.9% (= 56.7% – 42.8%)			

CORE = coronary risk in the elderly; FPS = Framingham point score.
[a] Difference in proportion of events categorized as > 20% risk.
[b] Difference in proportion of nonevents categorized as > 20% risk.
[c] Difference in proportion of events categorized as < 10% risk.
[d] Difference in proportion of nonevents categorized as < 10% risk.

Additional risk markers

Of the additional risk markers we evaluated, only the presence of ECG-LVH and low ABI were significantly associated with CHD in both sexes. There was negligible improvement in predictive accuracy when we added ECG-LVH and ABI to the CORE model (an increase in the c-statistic of only 0.019 with an NRI of 0.039 in U.S. men and an increase of only 0.010 with an NRI of 0.025 in European men) (Table 15.6). In women, adding cIMT, CRP, ABI, and ECG-LVH led to limited improvements in CHD prediction beyond established risk factors. Combining these 4 markers into an extended model resulted in small to moderate predictive improvements in both the U.S. and European populations (the c-statistic increased to 0.69 in both populations with NRIs of 0.068 and 0.096, respectively) (Table 15.6). Reclassification tables for the addition of the separate markers to the CORE model are presented in the online supplement of the original publication.[104]

Table 15.6 – Improvements in discrimination and risk classification for extensions of the CORE model

Additional risk marker	HR (95% CI)	Improvement in c-statistic		NRI	
		CHS	RS	CHS	RS
Men:					
ABI (per 0.1-unit)	0.58 (0.41-0.81)	0.013	-0.004	0.033	0.003
BMI (per 5-kg/m^2)	1.01 (0.99-1.03)	NA	NA	NA	NA
cIMT (per 1-unit on log-transformed scale)	1.22 (0.91-1.66)	NA	NA	NA	NA
CRP (per 1-unit on log-transformed scale)	1.00 (1.00-1.01)	NA	NA	NA	NA
ECG-LVH	2.17 (1.71-2.76)	0.009	0.011	0.017	0.021
ABI and ECG-LVH		0.019	0.010	0.039	0.025
Women:					
ABI (per 0.1-unit)	0.93 (0.90-0.96)	0.001	0.014	0.001	0.036
BMI (per 5-kg/m^2)	1.01 (0.99-1.02)	NA	NA	NA	NA
cIMT (per 1-unit on log-transformed scale)	2.81 (1.96-4.02)	0.010	0.013	0.022	0.061
CRP (per 1-unit on log-transformed scale)	1.08 (1.03-1.13)	0.003	0.004	0.024	0.008
ECG-LVH	1.63 (1.31-2.02)	0.005	0.007	0.041	0.019
ABI, cIMT, CRP, and ECG-LVH		0.016	0.026	0.068	0.096

ABI = ankle-brachial index; BMI = body mass index; CHS = Cardiovascular Health Study; cIMT = carotid intima-media thickness; CORE = coronary risk in the elderly; CRP = C-reactive protein; ECG-LVH = electrocardiographic left ventricular hypertrophy; NA = not applicable because of a nonsignificant improval in global model fit; NRI = net reclassification improvement; RS = Rotterdam Study.

Discussion

In this study, we report the performance of a sex-specific CHD prediction model tailored for an older population, based on 2 large population-based cohort studies of cardiovascular disease in the elderly. The model accounts for the fact that death from other causes often precludes CHD occurrence. Predicted risks for the presented model were well calibrated, and risk factors generally showed consistent effects across U.S. and European persons. However, our model had moderate discrimination, its accuracy was not substantially better than the FPS, and adding newer coronary risk markers did not substantially improve risk prediction.

Healthy elderly persons have been promoted as a target for primary prevention of CHD.[25, 26] According to the ATP III guideline, risk models assessing absolute CHD risk should guide primary preventive measures.[216] However, existing risk stratification approaches have not considered important characteristics of elderly persons, especially their considerable risk for dying of competing causes rather than CHD. The CORE model addresses this gap, and the 10-year CHD risk it predicts can be used in accordance with the ATP III guideline. In contrast to risk scores based on models that ignore or censor competing events, our model provides real-life and therefore more meaningful estimates of CHD risk for elderly patients and physicians. The 10-year risk for CHD did not exceed approximately 20% in men or 15% in women, and the occurrence of non-coronary death dominated the occurrence of CHD (Figure 15.1). This observation refutes the perception that all elderly men are at high risk for CHD.[379]

Competing risks

The discriminatory performance of the CORE model was modest compared with those based on younger age ranges; c-statistics of ≥ 0.80 have been reported for models based on similar established risk factors.[364, 365] However, such comparisons must be interpreted with caution, because inappropriately neglecting a substantial risk for competing non-coronary death leads to apparently high but uninterpretable c-statistics.[371] Comparison with the well-known ATP III FPS [27] in the competing risks setting of our model showed that the FPS had slightly lower accuracy.

Several studies have observed that associations of traditional risk factors with CHD diminish with age.[28-30, 216, 323] For example, smoking is one of the most influential CHD risk factors but had only borderline statistical significance in our cohorts when we used the competing risk method. The strong association of smoking with death from other causes (such as cancer or chronic obstructive pulmonary disease) competes with the observation and predictability of CHD.[380] Considering competing causes of death naturally leads to impairment of nonspecific risk factors (such as age) in predicting CHD,[371] in the same way that the benefit of treating a disease may be reduced by other causes of death.

Framingham point score

In elderly U.S. persons, improved predictions with the CORE model (such as the 30.6-percentage point increase in true-positive classifications for men) were often paired with risk

misclassifications (such as the 23.8-percentage point increase in false-positive classifications for men) (Table 15.4). In U.S. women, the models primarily differed in classifications of low-risk, in which decreases in the false-negative rate were paired with similar decreases in the true-negative rate. However, the decision to use a risk prediction model depends not only on the balance of improved and decreased risk classification but also on the costs and benefits of correct and incorrect classifications, and therefore on such factors as the cost of medication and side effects of treatment. For example, because of the availability of effective treatment for CHD prevention with limited side effects, the increase in the true-positive rate (those who would correctly qualify for treatment) in U.S. men with the CORE model may outweigh the increase in the false-positive rate (those who would receive unnecessary preventive treatment). At the same time, very few U.S. women were classified as high-risk in both models, and therefore only a few women with future CHD events would have received preventive treatment. This raises the question of whether current risk thresholds for treatment allocation need to be reevaluated for elderly women, as has been suggested for younger women.[206]

Compared with earlier Framingham risk functions,[331, 362] the FPS risk prediction tool is more appropriate for use in older populations because it includes interaction terms for total cholesterol level and smoking with age and has an upper age limit of 79 rather than 74 years.[216] Our U.S. study population included a modest proportion of participants aged 80 years or older (15.5% of men and 11.5% of women in the CHS). However, excluding these participants did not lead to meaningful changes in our results. This is consistent with the observation that absolute risk for CHD stabilizes after age 80 years (Figure 15.1).

In elderly European persons, the interpretation of model differences was dominated by substantial risk overestimation with the FPS, corresponding with earlier findings of overestimation of Framingham functions in lower-risk European populations.[229, 230, 367]

Additional risk markers

Measures that integrate risk factor information over time, such as measures of abnormal cardiac function, subclinical measures of atherosclerosis, or markers of inflammation, have been suggested to be more promising than traditional risk factors for predicting CHD at older age.[290] Our model yielded statistically significant improvements in risk prediction when we added ABI and ECG-LVH for men and ABI, cIMT, CRP, and ECG-LVH for women. However, clinical improvement in risk prediction was small in men and moderate in women (NRIs of up to 0.094 in women in the RS). An improvement of this extent does not outweigh the additional effort required to integrate multiple non-traditional markers into clinical practice. Therefore, we did not include these additional risk markers in our final model. Other markers, such as coronary artery calcification, may perform better in elderly persons, but evaluations in large elderly populations are still lacking.

Limitations

Our study has limitations. First, the cohorts differed ethnically, particularly in the number of African Americans (who have higher cardiovascular risk). Second, despite the highly similar CHD

end point definitions in both cohorts, subtle differences in end point ascertainment may have led to unknown differences in CHD incidence (Appendix Table 15.1).[94, 105] Third, the CORE model was developed and compared in the same population. However, because the model was largely prespecified by using 2 large cohorts, and the model derived from pooled data showed similar performance in both cohorts, we consider it unlikely that over-optimism has a major effect on the comparison of the CORE model with the FPS. Fourth, our approach to reclassification did not distinguish between persons with competing events and those without an event (both are classified as not having the event of interest). Fifth, the FPS is designed for persons up to age 79 years but was used for older persons in our study as well. Sixth, we examined only a few additional variables in extended models. Finally, we used the recommended cut-off values for risk classification,[216] but the appropriateness of these cut-offs in elderly persons is uncertain. Using different values could have affected the results of our reclassification analyses and subsequent clinical implications.

Conclusions

Deaths from non-coronary causes dominate CHD events in elderly persons and therefore pose a challenge to CHD prediction. We developed a model for predicting CHD risk in elderly persons that provides meaningful real-life estimates of absolute CHD risk. The CORE model showed good generalizability in aging U.S. and European populations, but only moderate discrimination and no consistent improvements in risk classification compared with the FPS. Moreover, adding promising newer cardiovascular markers did not substantially improve CHD risk prediction of the model. This emphasizes the need for further work to improve cardiovascular risk prediction in an elderly population.

Appendix

Appendix Table 15.1 – Definitions of coronary heart disease end points used

End point	Cardiovascular Health Study	Rotterdam Study
Nonfatal MI	ECG and/or cardiac enzyme changes.	ECG and cardiac enzyme changes.
Fatal MI	MI ≤ 28 days before death and no known non-atherosclerotic cause of death.	MI ≤ 28 days before death and no known non-atherosclerotic cause of death.
Atherosclerotic CHD death	Chest pain ≤ 72 hours before death and no known non-atherosclerotic cause of death.	Chest pain ≤ 72 hours before death and no known non-atherosclerotic cause of death.
	History of chronic ischemic heart disease in the absence of valvular heart disease or non-ischemic cardiomyopathy and no known non-atherosclerotic cause of death.	History of chronic ischemic heart disease in the absence of valvular heart disease or non-ischemic cardiomyopathy and no known non-atherosclerotic cause of death.
	Death certificate consistent with atherosclerotic CHD death and no known non-atherosclerotic cause of death.	Mode of death consistent with CHD in the absence of significant valvular heart disease or non-ischemic cardiomyopathy and no known non-atherosclerotic cause of death.
	Coronary death related to CHD procedures, such as CABG or PCI.	Coronary death related to CHD procedures, such as CABG or PCI.

CABG = coronary artery bypass grafting; CHD = coronary heart disease; ECG = electrocardiography; MI = myocardial infarction; PCI = percutaneous coronary intervention. Adapted from Ives and colleagues [94] and Leening and colleagues.[105]

Appendix Table 15.2 – Incidence of coronary heart disease and competing non-coronary death

	Cardiovascular Health Study		Rotterdam Study	
	Men	Women	Men	Women
	n = 1917	n = 3019	n = 1454	n = 2849
Overall CHD	563 (19.9%)	603 (11.5%)	283 (15.8%)	415 (10.4%)
Nonfatal MI	343 (12.6%)	338 (7.0%)	128 (7.3%)	121 (3.0%)
Fatal MI	47 (1.5%)	51 (1.0%)	24 (1.4%)	49 (1.3%)
Atherosclerotic CHD death	173 (5.8%)	214 (3.5%)	131 (7.1%)	245 (6.1%)
Competing non-coronary death	839 (26.6%)	1161 (19.1%)	777 (38.5%)	1467 (35.5%)
Total folow-up, pys	19,664	36,845	12,965	27,876
Median follow-up, y	16.6	16.5	14.8	14.9

Values are number of events (10-year cumulative incidence) unless noted otherwise. CHD = coronary heart disease; MI = myocardial infarction.

Additional details about the statistical analysis

Competing risk methods were used throughout, and model development was based on the Fine and Gray model [296] as implemented in the kmi package for R.[377, 378] The cumulative incidence function, which describes the absolute risk for failing from CHD as time progresses,[368] is of primary prognostic significance in competing risk analyses. In line with this function, we used the Fine and Gray model, a multivariable regression model that directly associates covariable effects with the cumulative incidence function via the subdistribution hazard. Hence, the regression coefficients of the model have a direct prognostic interpretation for CHD events.[370, 381, 382]

Possible cohort-risk factor interactions were assessed by introducing interaction terms. Total cholesterol level showed a stronger association with CHD among women in the RS than those in the CHS (P = 0.004); we therefore introduced an interaction term in the final competing risks model in women (Table 15.3 and Appendix Tables 15.3 and 15.4). Nonlinearity of predictors was assessed by comparing natural cubic splines (with 4 and 5 degrees of freedom) with the linear fit by using a likelihood ratio test.[28] Because strong evidence indicated a nonlinear effect of age on CHD incidence in women, we included a linear and a quadratic age term in the model,[331] which fitted the model equally well in terms of the Akaike Information Criterion as a more complex model using a natural cubic spline function. We tested the proportional subdistribution hazards assumption on the basis of scaled Schoenfeld residuals.

Appendix Table 15.3 – Steps in development, assessment, and extension of the CORE model

Assumption / modelling step	Test / comparison / predictor	Men	Women	Decision
Linearity assumption of continuous predictors	Restricted cubic spline transformation, 4 to 5 knots. Likelihood ratio test against non-transformed linear term:			
	Age	P = 0.60	P < 0.001	Men: accept linearity
				Women: reject linearity; age + age^2 appropriate
	Total cholesterol	P = 0.98	P = 0.21	Accept linearity
	HDL cholesterol	P = 0.60	P = 0.72	Accept linearity
	Systolic blood pressure	P = 0.22	P = 0.25	Accept linearity
Risk factor-cohort interaction	Total cholesterol	P > 0.05	P = 0.004	Add total cholesterol-cohort interaction term for women
	Remaining predictors	P > 0.05	P > 0.05	
Proportional subdistribution hazard assumption	Age	P < 0.001		Interpret as weighted average effect over follow-up
	Age + age^2		P < 0.001	Interpret as weighted average effect over follow-up
	Remaining predictors	P > 0.05	P > 0.05	
Model extension	Ankle-brachial index	P = 0.001 [a]	P < 0.001 [a]	Retain term
	ECG-LVH	P < 0.001	P < 0.001	Retain term
	cIMT	P > 0.05	P < 0.001 [b]	Men: reject term
				Women: retain term
	C-reactive protein	P > 0.05	P < 0.001 [b]	Men: reject term
				Women: retain term
	Body mass index	P > 0.05	P > 0.05	Reject term

Tables 15.3 and 15.6 and Appendix Tables 15.4 and 15.5 provide more details. cIMT = carotid intima-media thickness; CORE = coronary risk in the elderly; ECG-LVH = electrocardiographic left ventricular hypertrophy; HDL = high-density lipoprotein; NA = not applicable.

[a] Best fit as a linear term.

[b] Best fit as a log-transformed term.

Fewer than 1% of the values for traditional risk factors were missing in CHS participants and up to 4.4% were missing in RS participants who visited the research center at baseline (7153 participants). For variables used as additional risk markers in our extended model, values were missing for up to 11.6% of the variables in the RS, with the exception of cIMT (23.0%). We imputed missing covariables separately for men and women and for the CHS and RS cohorts, defining imputation models that included the outcomes of CHD and competing non-coronary death.[383] Multiple imputation of missing data was performed with the contributed mice package in R, and analyses were based on 5 imputed data sets.[384] All analyses were additionally done on complete cases to check for potential differences between results based on imputed data and those based on complete cases. With the exception of the baseline characteristics (Table 15.1), results are reported for imputed data. When calculating the c-statistic, we used multiple imputation of potential censoring times for competing events [377, 378] instead of treating competing events as 'censored at infinity'.[370]

For graphical display, the actual 10-year risk for the mutually exclusive CHD and competing non-coronary death events was estimated on the basis of the Fine and Gray models with age (included as a natural cubic spline) as the only covariable. Figure 15.1 displays the actual predicted risks.

Statistical assessments of the model showed that in men and women, the proportional hazards assumption was violated for age but for none of the remaining covariables. The reported age effects should therefore be interpreted as the weighted average effect over the entire follow-up.[381]

We used the cumulative incidence function to estimate the number of events and nonevents presented in Tables 15.4 and 15.5.

The FPS is designed for persons aged 79 years or younger. Participants aged 80 years or older were assigned an age of 79 years for the purpose of calculating their predicted risks using the FPS. Because the highest possible risk category of the FPS is denoted as ≥ 30% but not in terms of a single value, we used a value of 35% for participants with a predicted risk of ≥ 30%.

Appendix Table 15.4 – Coefficients in the CORE model

Risk factor	Scaling	Men	Women
Age, y:			
Linear	(Age – 75) / 10	0.205	0.463
Quadratic	$[(Age – 75) / 10]^2$		-0.262
Use of blood pressure-lowering medication		0.410	0.288
Systolic blood pressure, mmHg:			
Treated	(SBP – 130) / 10	-0.0005	0.080
Untreated	(SBP – 130) / 10	0.107	0.127
Total cholesterol, mmol/L	TC – 5	0.112	U.S.: 0.041 European: 0.198
HDL cholesterol, mmol/L	HDL-C – 1	-0.372	-0.432
Ever smoking		0.134	0.125
Diabetes mellitus		0.306	0.330

CORE = coronary risk in the elderly; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol.

Appendix Table 15.5 – Cumulative baseline subdistribution hazard for different time horizons

Population	3 years	5 years	7 years	10 years
U.S. elderly:				
Men	0.049	0.086	0.120	0.174
Women	0.025	0.046	0.074	0.125
European elderly:				
Men	0.040	0.065	0.074	0.125
Women	0.019	0.032	0.047	0.064

Example of coronary heart disease risk computation

We show the computation of the predicted risks for CHD at 3, 5, 7, and 10 years for a U.S. or European man or woman aged 65 years or older. Given the advanced age and limited life expectancy of this population, the risk prediction horizon can be adapted flexibly (Appendix Table 15.5). The baseline cumulative subdistribution hazard refers to a U.S. or European man or woman aged 75 years whose systolic blood pressure is 130 mmHg, total cholesterol level is 5 mmol/L, and HDL cholesterol level is 1 mmol/L and who does not smoke, is not receiving blood pressure-lowering medication, and is not diabetic.

The actual probability or predicted risk for an individual to have a CHD event at time *t* depends on the covariable vector (x_{i1}, …, x_{ip}) and on the baseline cumulative subdistribution hazard [370]: $I_i(t \mid x_i) = 1 - \exp[-\exp(\sum_{k=1}^{p}\beta_k * x_{ik}) * \int_0^t \overline{\lambda}_{1,0}(s)ds]$ where $\int_0^t \overline{\lambda}_{1,0}(s)ds$ refers to the cumulative baseline subdistribution hazard (given for different time points in Appendix Table 15.5), β refers to the vector of coefficients from the Fine and Gray model [296] provided in Appendix Table 15.4, and exp(β) refers to the hazard ratios given in Table 15.2.

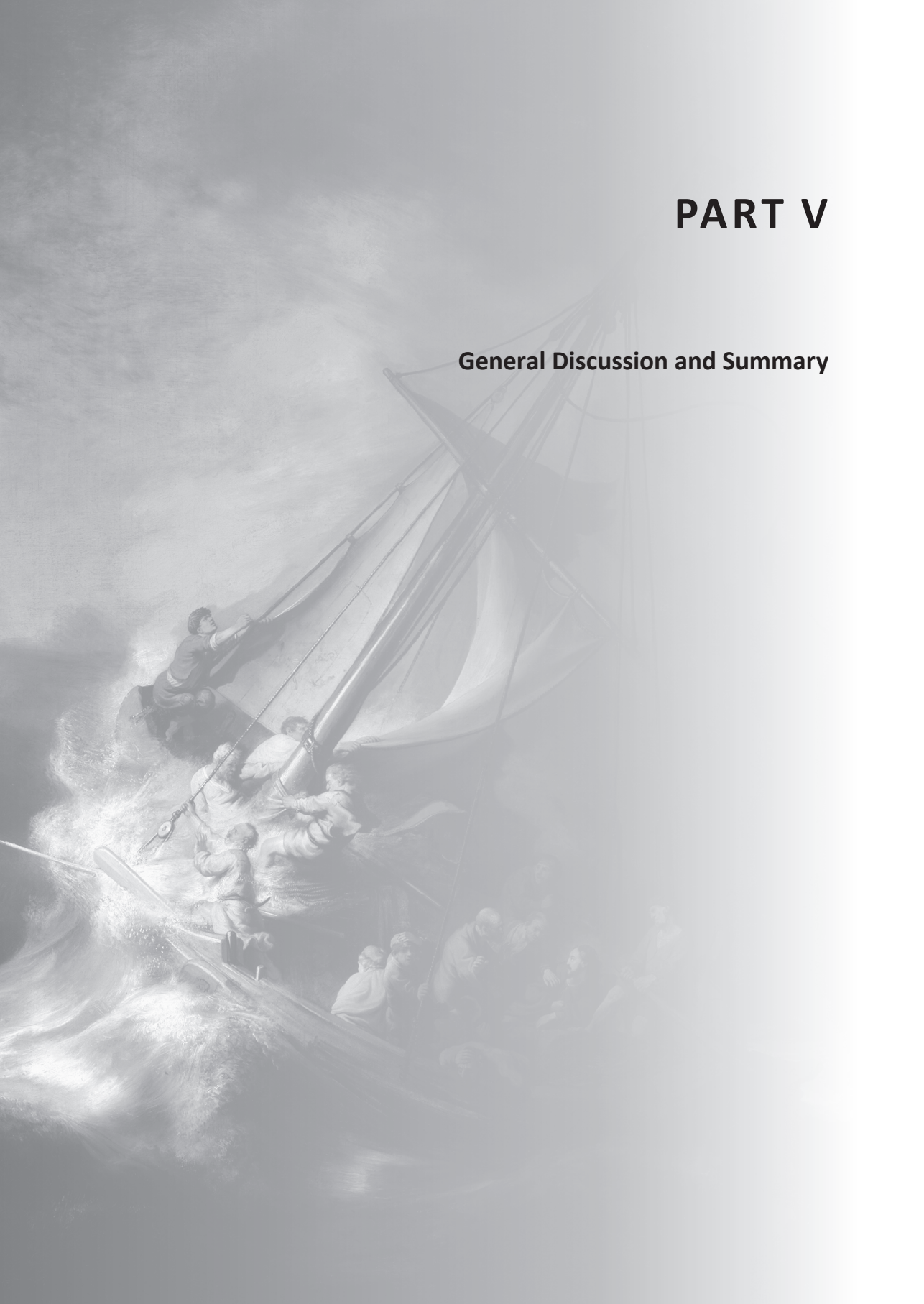
The following example illustrates the computation of the 10-year CHD risk for a U.S. man aged 72 years who is receiving blood pressure-lowering medication; whose systolic blood pressure is 136 mmHg, total cholesterol level is 4.4 mmol/L, and HDL cholesterol level is 1.56 mmol/L; who is not diabetic; and who is a current smoker.

Linear Predictor = $\sum_{k=1}^{p}\beta_k * x_{ik}$ = [0.205 * (72 − 75) / 10] + [0.410 * 1 (use of blood pressure-lowering medication) + [−0.0005 * (136 − 130) / 10] + [0.112 * (4.4 − 5)] + [−0.372 * (1.56 − 1)] + [0.306 * 0 (absence of diabetes)] + [0.134 * 1 (current smoking) = 0.2067
Predicted 10-year risk for CHD = 1 − exp[-0.174 * exp(0.2067)] = 0.192 = 19.2%.

A risk calculator developed from our model for the prediction horizons of 3, 5, 7, and 10 years is available online at www.ceb-institute.org/evibox/chd/.

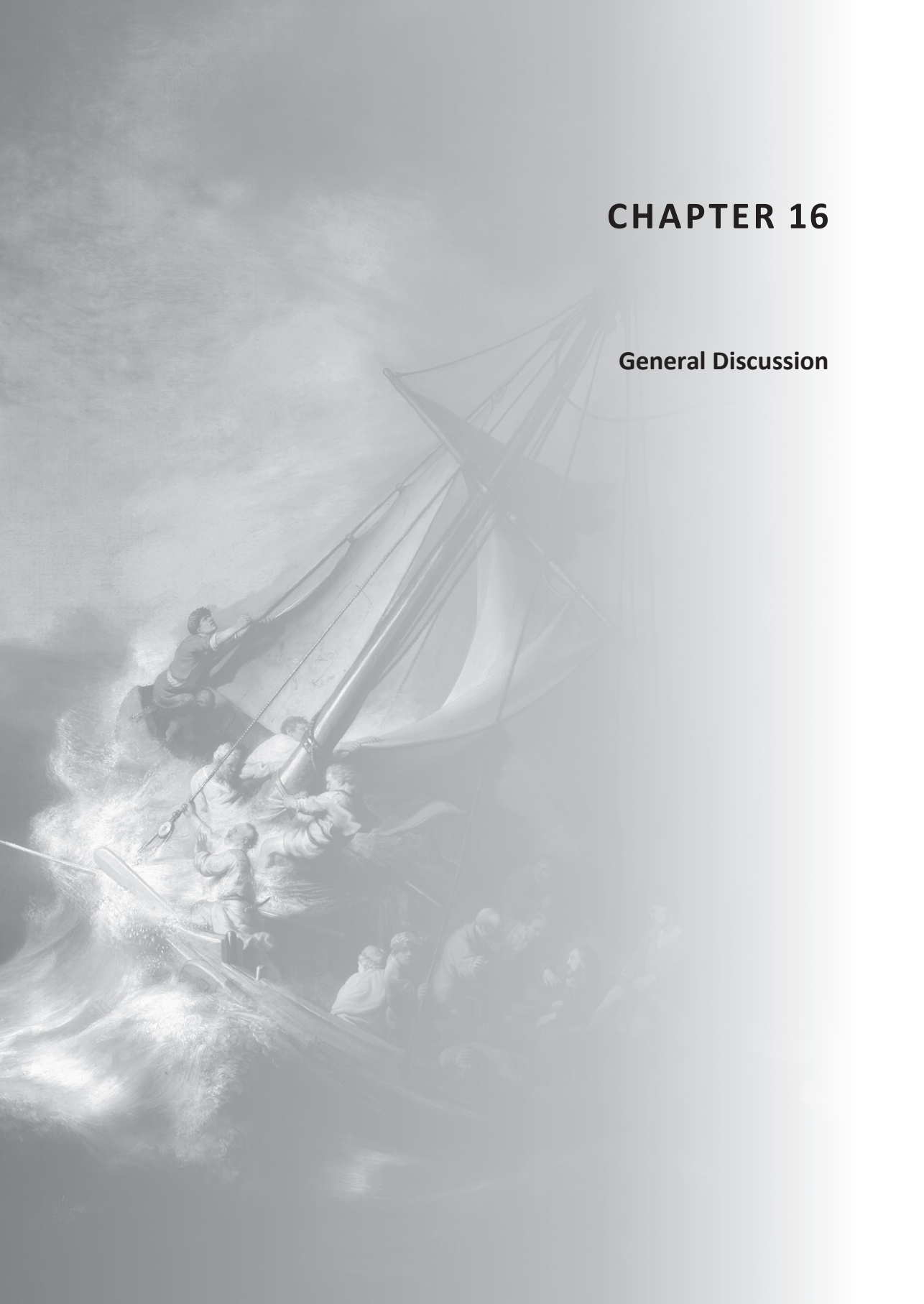
Old age is associated with disease, but does not cause it.

- Sir Richard Peto and Sir W. Richard S. Doll (1912 – 2005)
There is no such thing as aging
BMJ 1997;315(7115):1030-2



PART V

General Discussion and Summary



CHAPTER 16

General Discussion

The marked reduction in coronary heart disease (CHD) mortality has been one of the most impressive achievements in the history of modern medicine.[20] Notable contributions in invasive treatment of patients with CHD were made by René Favaloro introducing coronary artery bypass grafting (CABG) in 1967,[385] Andreas Grüntzig introducing percutaneous coronary interventions (PCI) in 1977,[386] and the Thrombolysis In Myocardial Infarction (TIMI) study group, led by Eugene Braunwald, championing the 'open artery' principle in 1985.[387] Long-term reductions in CHD mortality also come from the introduction of pharmacological agents to reduce mortality after a myocardial infarction, including β blockers,[388] aspirin,[389, 390], ACE inhibitors,[391] and statins.[392]. However, improvements in treatment for patients with manifest CHD is only part of the explanation why CHD mortality has plummeted.[393] It is estimated that half of the deaths prevented can be attributed to primary prevention through risk factor modification.[394-396] Notable achievements include marked reductions in tobacco consumption,[397, 398] improved blood pressure control,[398] and population interventions on caloric and salt intake.[398] Nonetheless, the sobering data presented in *Part III* of this thesis indicate there is a lot more work to be done in the field of primary prevention of cardiovascular disease (CVD).

To further optimize primary prevention of CVD, 2 tiers of commitment are required. First, we need stronger population measures to increase cardiovascular health in the overall population, for instance through expanding smoking bans, raising taxes on tobacco and unhealthy foods, and encouraging physical activity. Second, at individual patient level we need to better understand and identify which patient will benefit most from individualized preventive efforts, and, most importantly, act accordingly. The work described in this thesis is focused on improving identification of individuals free of CVD – but at an increased risk for CVD – who may benefit from preventive treatment.

In this chapter the focus is on some of the methodological considerations pertaining to the work described in this thesis, and how the work described in this thesis can be used to potentially enhance or nurture entirely different approaches for primary prevention strategies.

Methodological considerations

Specific limitations to the study design and analyses presented in this thesis are discussed in the individual chapters. Nonetheless, a number of general points with respect to the Rotterdam Study data can be made.

First, internal validity of the findings is likely to be high given that: no exclusion criteria were specified at baseline, loss to follow-up was low, and data collection of determinants and outcomes was done independently using calibrated devices and protocols. Nonetheless, self-selection of participants (e.g. by health status, as discussed in *Chapter 3*) may have introduced selection bias and – despite a wide gauntlet of risk factors measured – unmeasured confounding might be present. In large data sets, such as the Rotterdam Study and the Cardiovascular Health Study, improved external validity is traded-off with respect to the available measurements.

Next, external validity (i.e. generalizability) is mostly limited to older, suburban, white, Western European (Rotterdam Study) and U.S. (Cardiovascular Health Study) populations. This is clearly illustrated by the lower background incidence of CVD in the Rotterdam Study when compared to

U.S. data in *Chapters 12* and *15*. However, it should be noted that the observed relative effects of cardiovascular risk factors were highly similar in the Rotterdam Study and the Cardiovascular Health Study (*Chapter 15*).

Future perspectives and challenges for risk-based treatment allocation in primary prevention of cardiovascular disease

The emerging field of 'Preventive Cardiology' is vast and holds great promise. As improvements in prognosis for clinically manifest CVD with novel treatment get smaller and smaller, more eyes turn towards the preclinical stages of CVD, i.e. primary prevention. Rather than briefly touching upon a large number of avenues for future research in primary prevention of CVD, I rather discuss two important issues in greater detail.

For decades, clinical practice guidelines have emphasized the value of considering the additive effect of multiple risk factors on 10-year cardiovascular risk. First, a similar evolution seems needed in order to transition to a longitudinal lifetime perspective, by moving away from single measurements of risk factors to a broader appreciation for the influence of the entire range of risk factor burden on lifetime risk of a broad spectrum of CVD. I aim to describe how this transition could be made in more detail below.

Second, a major challenge for contemporary risk-based strategies is the oppressive role of age on recommendations for statin allocation in primary prevention of CVD. Using a number of examples I will try to set forth dilemmas in clinical practice resulting from age-driven risk prediction models. Over the last decade a number of alternative strategies for statin allocation have been proposed and I aim to put these into perspective.

Lifetime perspectives on cardiovascular disease risk in primary prevention

The discordance between short-term (10-year) and long-term (30-year to lifetime) cardiovascular risk is well established and is now reflected in the most recent clinical practice guidelines from the ACC/AHA on lipid-lowering treatment for primary prevention of atherosclerotic CVD (ASCVD).[6, 9] Specifically, these guidelines recommend that lifetime risk estimation can be used as a communication strategy for adults younger than 60 years free of ASCVD and not candidates for lipid-lowering therapy. Although a high lifetime ASCVD risk has not been recommended as a class I indication for lipid-lowering treatment, the acknowledgement of lifetime risk in the guidelines indicates a more comprehensive awareness of the importance of prevention of ASCVD over a lifespan. Yet, cut-points indicating a high lifetime risk of CVD have not been established.[399]

Risk estimation remains an imperfect science. However, by focusing on the key elements of risk prediction over a lifetime – the treatment thresholds, risk factors trajectories, and predicted outcome – advances can be made to more accurately identify individuals at an increased lifetime ASCVD risk to tailor optimal primary prevention strategies.

Treating a 'lifetime risk equivalent'

For decades, guidelines have recommended lipid-lowering therapy for individuals with an low-density lipoprotein (LDL) cholesterol level ≥ 190 mg/dL (4.9 mmol/L), irrespective of short-term risk, because these individuals have a "high lifetime risk for ASCVD".[9] Treatment is recommended for these individuals because of the cumulative effects of a lifetime exposure to high LDL cholesterol. This recommendation is *not* based on clinical trial data, as no primary prevention trial testing the effect of statin therapy on cardiovascular endpoints has included only individuals with an LDL cholesterol level ≥ 190 mg/dL.[9] In addition, this recommendation is also *not* based on a strategy to identify patients with heterozygous familial hypercholesterolemia.[400]

Although a high lifetime risk represents the primary rationale for treatment of an LDL cholesterol level ≥ 190 mg/dL, an elevated LDL cholesterol is not the only cause for a high lifetime risk. Hypertension, diabetes, and smoking are also associated with substantial differences in risk of ASCVD across the lifespan.[2] This well-established fact creates a dilemma. For example, a 45-year old non-smoking white man with a systolic blood pressure of 120 mmHg, no diabetes, and normal high-density lipoprotein (HDL) cholesterol level (40 mg/dL, 1.0 mmol/L) but with an LDL cholesterol level of 190 mg/dL (corresponding to a total cholesterol of 260 mg/dL, 6.7 mmol/L) would have a 10-year risk of hard ASCVD events (coronary death, myocardial infarction, stroke) of just 3.7% (Online calculator: http://tools.acc.org/ascvd-risk-estimator/).[6] However, current guidelines would indicate a class I recommendation for statin therapy because of this patient's LDL cholesterol level.[9] In contrast, another 45-year old non-smoking white man with a systolic blood pressure of 138 mmHg, no diabetes, normal HDL cholesterol, and an LDL cholesterol level of 150 mg/dL (3.9 mmol/L; corresponding to a total cholesterol level of 220 mg/dL, 5.7 mmol/L), would have a similar 10-year risk of ASCVD events of 3.6%, but current guidelines would not recommend lipid-lowering therapy for this patient.[9]

However, using the Framingham Heart Study 30-year risk calculator (Online calculator: https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/30-year-risk.php#), these individuals have identical 30-year risks for hard ASCVD events, approximately 24%.[218] Given the clinical trial evidence of a similar relative benefit of lipid-lowering therapy across a broad range of LDL cholesterol in the short-term, it would be reasonable that lipid-lowering therapy should be considered in both cases, and the second patient should be treated because of the presence of a 'lifetime risk equivalent'.

Lifetime risk factor trajectories

Understanding the lifetime risk for ASCVD requires not only a measure of current risk factor levels, but should also account for the accumulated long-term exposure to risk factors. However, current CVD risk prediction algorithms are limited to single, cross-sectional measures of risk factor levels. Most often these risk prediction algorithms are applied for patients later in life, at the time of increasing absolute ASCVD risk. However, the adverse effects of risk factors accumulate over the lifetime and, thus, long-term patterns in risk factor levels provide greater ability to identify individuals at high risk of experiencing an cardiovascular event. Given the rapid expansion of electronic health records, the increasing use of data within the electronic health record, and clinical decision support systems to calculate an individual's ASCVD risk, addition of

these long-term risk factor patterns into risk prediction algorithms has now become feasible.

Prospective epidemiologic studies have consistently found that risk factor levels measured early in life are more strongly associated with cardiovascular outcomes compared to contemporary levels later in life. Recently, a growing body of evidence demonstrates that the long-term patterns of risk factor levels, including blood pressure and cholesterol levels, provide additional information above and beyond single measurements to identify individuals at increased risk of future CVD.[401, 402] This cumulative exposure over a lifetime is not captured in current risk prediction algorithms and, as a consequence, risk estimates may be overestimated or underestimated depending on whether risk factors were accrued recently or earlier in life. Incorporating long-term risk factor patterns into risk prediction algorithms may improve the performance of these equations and would provide patients with a more accurate estimate of their future risk.

Cardiovascular disease manifestations over a lifetime

Traditional cardiovascular prediction algorithms were limited to predicting the risk of CVD mortality or CHD. The most recent iteration of the ACC/AHA prevention guidelines adds stroke to hard CHD events to form a composite ASCVD outcome of the 10-year risk calculators.[6] This is a major step forward, as this better reflects the overall burden of CVD in women and African Americans, among whom the stroke-to-CHD ratio is known to be greater.[116] However, limiting predicted ASCVD risk to endpoints of hard CHD and stroke does not reflect the entire risk of developing ASCVD over a lifetime. Most first manifestations of ASCVD are not hard endpoints with fatal or incapacitating consequences and include angina, transient ischemic attacks, or intermittent claudication.[116] These 'soft' endpoints should be incorporated in global ASCVD risk prediction algorithms as they represent a greater portion of the events in women and, particularly, younger individuals.[116] The latter is also reflected by the substantially greater case fatality of a first CVD event with increasing age.[116] Therefore, the effect of age on the overall burden of ASCVD in risk prediction algorithms is greater when solely predicting hard outcomes or CVD mortality compared with a broader outcome.

Incorporating soft atherosclerotic outcomes (and potentially also ischemic heart failure) into the outcome of risk calculators would generate higher lifetime risks than calculators restricted to hard outcomes.[116, 218] Calculators with more inclusive outcomes would yield more realistic estimates for patients on their risk of ASCVD, as, on average, 2 out of 3 will develop some form of ASCVD during their lifespan, whereas less than 1 out of 3 will die of ASCVD.[2, 116] Experiencing an ASCVD event and its consequences during life may be of greater importance to patients than their mode of death when balancing the risks and benefits of preventive measures.

Existing Resources

All of the suggested modifications to more accurately identify asymptomatic individuals at increased ASCVD risk over a lifetime can be made using existing resources. Most high-quality population-based studies have collected outcome data on a wide range of cardiovascular outcomes over decades with repeated measurement of traditional and novel risk factors.

Therefore, creativity, commitment, and persistence of researchers and clinicians will be instrumental in finding and implementing optimal strategies to quantify lifetime risk and subsequent potential benefit from preventive treatment to further lower the burden of ASCVD.

The role of age in treatment allocation for primary prevention of cardiovascular disease

Since CVD is highly age-related, age is universally the strongest predictor for CVD in risk calculators. In the most recent revisions of American and British prevention guidelines, risk thresholds for initiation of pharmacological treatment, to reduce LDL cholesterol, have been substantially lowered. This decision has been driven by the accumulating data on the

Table 16.1 – Age (years) at which persons with recommended optimal risk factor profiles exceed recommended cardiovascular risk thresholds for lipid-lowering treatment

Prevention guidelines		Men	Women
ESC 2012			
Treatment considered	LDL ≥ 2.5 mmol/L (≥ 97 mg/dL) [a]	55	62
	LDL < 2.5 mmol/L (< 97 mg/dL) [b]	74	79
Treatment recommended	LDL ≥ 2.5 mmol/L (≥ 97 mg/dL) [c]	74	79
	LDL < 2.5 mmol/L (< 97 mg/dL) [d]	85	88
ACC/AHA 2013			
Treatment considered [e]	White	59	67
	African-American	56	66
Treatment recommended [f]	White	63	71
	African-American	66	70
NICE 2014			
Treatment recommended [g]	White	64	69

The Appendix to this chapter provides detailed descriptions of recommended optimal risk factor profiles for each guideline and methods for age threshold calculations. ACC/AHA, American College of Cardiology/American Heart Association; CVD, cardiovascular disease; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health Care and Excellence.

[a] ≥ 1% to < 5% 10-year risk of CVD mortality.[8]

[b] ≥ 5% to < 10% 10-year risk of CVD mortality.[8]

[c] ≥ 5% 10-year risk of CVD mortality.[8]

[d] ≥ 10% 10-year risk of CVD mortality.[8]

[e] ≥ 5% to < 7.5% 10-year risk of atherosclerotic CVD.[9]

[f] ≥ 7.5% 10-year risk of atherosclerotic CVD.[9]

[g] ≥ 10% 10-year risk of CVD.[10]

efficacy [320, 403] and safety profile [404, 405] of statins in primary prevention, as well as the low costs of generic statins. However, by lowering the thresholds, otherwise healthy older adults with minimal or no risk factors are now considered candidates for statin treatment solely by virtue of their age. Doctors are recommended to discuss statin initiation with men who have optimal risk factor levels at an age between 63 and 66 in the U.S. or U.K. (Table 16.1). For women this is the case around the age of 70. As a consequence, the vast majority of individuals aged 55-65 and almost everyone aged ≥ 65 in the general population is currently considered a candidate for statin treatment in both the U.S. and Europe.[119, 406, 407]

This dominant role of age on the guideline recommendations changes the clinical question to *when* rather than *whether* an individual will qualify for lipid-lowering treatment. This raises a number of fundamental questions: Do we want to treat all healthy older persons in the absence of risk factors? Can we identify younger persons at low short-term risk but high long-term risk, and how long should we wait before we initiate treatment to mitigate their risk? And how can we effectively communicate to patients the contribution of cardiovascular risk factors to overall CVD risk?

Adaptations to risk-based strategies

Cardiovascular risk is overestimated in older populations, due to competition of non-cardiovascular causes of death.[104] This leads to inflated risk estimates and thereby potentially overtreatment. For instance, smoking substantially increases risk of CVD, but also the risk of a number of other conditions, including various types of cancer and pulmonary disease, which may result in death prior to the occurrence of CVD. Some of the advocated risk calculators try to accommodate this by including interaction terms of risk factors with age or (age)^{2}.[6, 7] Others have suggested to improve the accuracy of the calculators using competing risk regression.[104, 408] Such methods account for the overestimation and improve the agreement between predicted and observed risk. However, changes in treatment recommendations are generally minimal, since most of the overestimation due to competing risks occurs in those with very high predicted risks, rather than in healthy elderly without risk factors.[104, 408] Therefore, competing risk models appear to have limited clinical application.

A more recently proposed approach to reduce overtreatment is imaging of subclinical atherosclerosis to 'de-risk' older individuals with minimal or no cardiovascular risk factors.[409] Absence of coronary artery calcifications for example, has consistently been accompanied with very low probabilities of developing CVD and mortality,[410] especially in those with optimal risk factors according to current guidelines.[411] Results from ongoing trials on the use of coronary calcium screening in primary prevention of CVD are therefore much awaited.[412, 413] This strategy, however, also requires further careful evaluation with regards to points like cost-effectiveness, radiation exposure, and consequences of incidental findings in older individuals.

On the other end of the spectrum there are younger individuals with multiple cardiovascular risk factors who are at low absolute short-term (e.g. 10-year) risk of CVD. For instance, a young woman who smokes and has moderate hypercholesterolemia will have a 10-year risk that does not qualify her for lipid-lowering treatment, but at some point later in life she will qualify for treatment. Substantial amounts of atherosclerosis will likely have built up by that

time. Therefore, recent U.S. and British guidelines have incorporated the concept of 'lifetime risk' along with the traditional 10-year risk estimates in treatment recommendations, to guide treatment in younger individuals with substantial risk factor burden, who do not yet have a high 10-year risk of CVD.[9, 298] In conjunction with lowering the treatment thresholds, the inclusion of a high lifetime risk as a treatment indication ensures that a greater proportion of especially younger and middle-aged individuals with a high risk factor burden are recommended for early preventive treatment. This will result in small absolute risk reductions at younger ages, but the pay-off with early intervention may be substantially larger over the lifespan.

The role of age in alternative treatment allocation strategies

Since the early 1990s prevention strategies have revolved around risk-based strategies, yet multiple other approaches have been advocated. The role of age in each of these strategies varies greatly.

First of all, the strategy that solely relies on age. More than a decade ago Wald and Law suggested to initiate drug treatment for prevention of CVD in everyone above age 55, irrespective of risk factor burden.[321] Despite inherent overtreatment of a substantial proportion of the population, this age-based strategy has been reported to be more cost-effective than screening for risk factors in current risk-based strategies.[414] The age-based approach was considered "radical" by the authors upon its introduction, yet, with the recent lowering of the treatment thresholds, current guidelines also have inherent sex-specific upper age-thresholds at which basically everyone qualifies for drug treatment, irrespective of risk factor burden (Table 16.1).

A completely different approach would be to provide treatment recommendations solely based on available evidence from randomized clinical trials.[415] This approach does not rely on age, but rather aims to answer the question "what works in whom?".[416] For allocation of statins in primary prevention this would imply treating all persons who would have been eligible for enrollment in trials that showed a favorable outcome with statin therapy (Table 16.2). A hybrid strategy of risk-based and trial-based approaches was recently proposed and may seem more feasible in the absence of evidence in a substantial part of the population.[417] A key advantage of incorporating trial evidence into clinical recommendations is the transparency of these recommendations: for the majority of middle-aged persons for whom preventive treatment with statins is recommended, evidence from randomized clinical trials is available.[417] Providing clear insight into this, should discourage practicing clinicians to withhold treatment in whom statins have been proven to be effective and moreover augment the informed discussions between patients and clinicians on initiation of treatment.

Absolute risk is considered a direct proxy for the absolute benefit from lipid-lowering treatment. However, ideally the field should evolve from allocating treatment based on estimated risk to allocation based on anticipated benefit. The recent British CVD prevention guidelines have made important steps towards implementing anticipated treatment benefit into an online decision aid for clinicians and patients in order to facilitate informed shared decision making.[298] This third strategy would involve integrating CVD risk prediction, life-expectancy, and treatment efficacy (all based on age and risk factor levels). Preventing a CVD event does not translate into similar gains in (CVD free) life-expectancy in persons with identical predicted

Table 16.2 – Randomized clinical trials on primary prevention of cardiovascular disease using statins

Randomized clinical trial	Study drug	Participants	Events	Mean age	Age range	Target population
		n	n	years	years	
WOSCOPS, 1995	Pravastatin 40 mg	6595 [a]	422 [a]	55	45-64	Men with moderate hypercholesterolemia
AFCAPS/ TexCAPS, 1998	Lovastatin 20-40 mg	6605	419	58	45-73	Persons with below average cholesterol levels
PROSPER, 2002	Pravastatin 40 mg	3239 [b]	381 [b]	75	70-82	Older persons with risk factors
ALLHAT-LLT, 2002	Pravastatin 40 mg	10,355 [a]	801 [a]	66	51-81	Persons with hypertension, moderate hypercholesterolemia, and ≥ 1 other risk factor
ASCOT-LLA, 2003	Atorvastatin 10 mg	10,305 [a]	254 [a]	63	40-79	Persons with hypertension, below average cholesterol levels, and ≥ 3 other risk factors
MRC/BHF HPS, 2003	Simvastatin 40 mg	2912 [b]	329 [b]	NR	40-80	Persons with diabetes mellitus
CARDS, 2004	Atorvastatin 10 mg	2838	210	62	40-75	Persons with diabetes mellitus, low LDL cholesterol, and ≥ 1 other risk factor
ASPEN, 2006	Atorvastatin 10 mg	1905 [b]	147 [b]	61	40-75	Persons with diabetes mellitus and low LDL cholesterol
MEGA, 2006	Pravastatin 10-20 mg	7832	167	58	40-70	Persons with hypercholesterolemia
JUPITER, 2008	Rosuvastatin 20 mg	17,802	393	66	50-97	Persons with elevated CRP and low LDL cholesterol
HOPE-3, 2016	Rosuvastatin 10 mg	12,705	539	66	55-NR	Persons with ≥ 1 risk factor

Selection of trials was based on previously published meta-analyses on statins for primary prevention of cardiovascular disease,[322, 403] supplemented with the recently published HOPE-3 trial.[418] NR, not reported.

[a] Up to 15% of the participants had a history of cardiovascular disease at baseline; no data presented on subgroup of participants free of cardiovascular disease.

[b] Data from persons free of cardiovascular disease at baseline.

risks, and differences in gains in life-expectancy with statin therapy are generally smaller than the differences in cardiovascular risk between individuals.[304] Three important reasons for this can be identified. First, relative risk reduction of CVD with statins varies by levels of risk, with greater benefit at lower predicted risks.[320] Secondly, important determinants of predicted cardiovascular risk, such as age and smoking, are also strongly related to non-cardiovascular mortality, which competes with the incidence of CVD.[304] Third, absolute risk reduction of statin therapy is dependent on the achieved reduction in LDL cholesterol, which in turn is directly proportional to the pretreatment LDL cholesterol levels.[419] So, for valid estimation of individual benefits of statin treatment, all these factors need to be taken into account and long-term efficacy data in persons with a wide spectrum risk factor combinations (preferably including those without risk factors) are needed to avoid having to rely on assumptions or extrapolations of existing data. In such calculations similar anticipated benefits of smoking cessation and blood pressure control could be incorporated. This allows for better insight in the risk reduction that can be achieved by multifactorial interventions, which may show that in persons with certain risk factor combinations, time and resources may be better allocated to motivating individuals to quit smoking and intensifying blood pressure treatment rather than prescribing lipid-lowering treatment.

Age in communicating cardiovascular risk

Clinician-patient discussion on CVD risk, prior to making a decision on initiating therapy, has an important role in the current clinical practice guidelines.[9, 298] Whereas most clinicians who work in the field of CVD prevention are accustomed to probability estimates from CVD risk calculators, patients are generally not. As such, placing risk in context of everyday risks with which the patient is familiar can be challenging.[420]

A way to convey absolute cardiovascular risk estimates to patients, is by conversion of risk to vascular age. An individual's vascular age is defined as the age at which someone of the same sex with recommended optimal risk factors would have had the same absolute risk of CVD.[363] However, vascular age is still only a sex-specific transformation of absolute risk and its interpretation depends on an individual's calendar age and sex. The age thresholds in Table 16.1 are a direct transformation of the absolute risk thresholds from the guidelines. Let us examine vascular age using the example patients in Table 16.3. Patient 1 is a 65-year old man with optimal risk factors. His vascular age thus equals his calendar age. Note that solely because of his age he would be recommended for statin therapy under the current U.S. guidelines.[9] Patient 2 represents a 40-year old woman with a suboptimal risk factor burden, but without extreme levels of blood pressure or cholesterol that would qualify her for immediate pharmacological intervention. Her vascular age, however, is somewhat higher than that of a 50-year old man with less pronounced risk factor levels, who would qualify for statin treatment.

Can we get age out of the equation?

How can the effects of age be taken out of the equation when expressing cardiovascular risk? Let us consider two complementary measures of expressing cardiovascular risk, either relative to a man or woman of the same age with optimal risk factors ('relative risk factor burden'), or

Table 16.3 – Examples of vascular age, vascular ageing ratio, and relative risk factor burden

Calendar age	10-year ASCVD risk [a]		Vascular age	Vascular ageing ratio	Relative risk factor burden
	Predicted	Optimal			
Patient 1: 65-year old white man, non-smoker, non-diabetic, untreated SBP 110 mmHg, TC 4.4 mmol/L (170 mg/dL), HDL-C 1.3 mmol/L (50 mg/dL)					
65 year	8.8%	8.8%	65 year	65 year / 65 year = 1.0	8.8% / 8.8% = 1.0
Patient 2: 40-year old white women, smoker, non-diabetic, untreated SBP 135 mmHg, TC 5.7 mmol/L (220 mg/dL), HDL-C 1.2 mmol/L (45 mg/dL)					
40 year	4.7%	0.4%	67 year	67 year / 40 year = 1.7	4.7% / 0.4% = 12.8 [b]
Patient 3: 50-year old white man, smoker, non-diabetic, treated SBP 120 mmHg, TC 5.4 mmol/L (210 mg/dL), HDL-C 1.4 mmol/L (55 mg/dL)					
50 year	7.7%	2.1%	63 year	63 year / 50 year = 1.3	7.7% / 2.1% = 3.7

The Appendix to this chapter provides detailed descriptions of recommended optimal risk factor profile and vascular age calculations. ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.

[a] Based on 2013 ACC/AHA guideline on the assessment of cardiovascular risk.[6]

[b] Due to rounding in 10-year predicted and recommended optimal 10-year ASCVD risk.

relative to a man or woman of the same risk with optimal risk factors ('vascular ageing ratio'). Both can be readily calculated from existing risk prediction models and may be best explored using the example patients from Table 16.3.

The relative risk factor burden is the predicted risk of an individual divided by the risk for a person of the same age and sex with optimal risk factor levels (as defined by current guidelines). Example patient 1 has a relative risk factor burden of 1, consistent with his optimal risk factor levels. The man representing patient 3 has a 3.7-fold higher risk compared to the other 50-year old man with optimal risk factors, despite having only a borderline treatment recommendation, based on 10-year ASVCD risk. Patient 2, the 40-year old woman with a low 10-year risk of ASCVD, has a nearly 13-fold increased risk as compared to women of her age with optimal risk factors, which reflects her high propensity of long-term risk of CVD when her risk factor profile remains unmodified. Other measures with similar intent have been proposed previously, including age-specific relative lifetime risks for younger individuals,[421] comparisons of absolute risk estimates of the individual versus optimal risk,[422] and relative risk estimates relative to the average risk factor burden in the population.[298, 423] The advantage of the relative risk factor burden is that it can be derived from existing risk models and it is not depending on the risk factor burden in the general population.

Vascular ageing ratio can be computed by dividing an individual's vascular age by his or her

calendar age. All three example patients have a similar vascular age, yet the vascular ageing ratio is very different due to differences in calendar age and sex. The vascular age of a person with optimal risk factor levels (as defined by current guidelines) is identical to his or her calendar age (patient 1). Consequently the vascular ageing ratio is 1.Patient 2, the 40-year old woman, has a vascular age of 67: this corresponds to a vascular ageing ratio of 1.7. Whereas the 50-year old man with a vascular age of 63 has a much lower vascular ageing ratio of 1.3.

None of these measures require new modelling efforts and can be directly incorporated into existing online calculators and applications on hand-held electronic devices. Another advantage is that these measures are less prone to the effects of systematic over- or underestimation of risk (i.e. miscalibration), for instance due to differences in underlying event rates in populations where models were derived as compared to where they will be applied.[119, 264] However, the proposed measures do not mend all shortcomings of current strategies that greatly rely on age, but at least the contribution of age can be better distinguished from the contribution of other risk factors. Both relative risk factor burden and vascular ageing ratio require further evaluation in population studies, as well as more rigorous exploration of their mathematical properties. Before these measures can be implemented in prevention strategies, correlation with absolute risk at different ages, and selection of thresholds are issues that need to be addressed in future research. Also, the definition of optimal risk factor levels warrants further evaluation in the light of recent results demonstrating even lower CVD event rates when LDL cholesterol is reduced beyond levels that are currently considered to be optimal in the guidelines.[424] Therefore, measures expressing cardiovascular risk relative to optimal risk factor levels are subject to change when optimal cholesterol levels are redefined by guideline committees. Nonetheless, vascular ageing ratio and relative risk factor burden can be informative in adjunct to absolute risk estimates in clinician-patient discussion on cardiovascular risk.

Reconsidering the role of age

Back in the 17th century, British physician Thomas Sydenham wrote “a man is as old as his arteries”.[425] More than 3 centuries later, cumulative length of exposure to known and unknown cardiovascular risk factors is only reflected by calendar age. Yet, the effects of age can be decomposed into time-related effects that affect everyone and cumulative exposure to the risk factors that affect some more than others.[426] Therefore, primordial prevention of accruing CVD risk factors and subsequent atherosclerosis is the key to reduce the impact of age on cardiovascular risk. However, adopting and maintaining a healthy lifestyle is challenging in our contemporary society and some individuals will accrue cardiovascular risk factors, irrespective of their lifestyle. Given that the accumulation of risk factors and atherosclerosis starts early in life [427] and benefits of lipid-lowering treatment extend for decades after actual treatment,[428] we may need to reconsider the current role of age in allocating lipid-lowering medication.

Concluding remarks

Risk-based strategies have become the cornerstone of personalized CVD prevention. Yet, despite great progress made, there is plenty of opportunity for further improvement and as discussed above risk-based approaches to allocation of preventive treatment should not necessarily

be considered a dictum for the future. Each approach to primary prevention of CVD has its different pros and cons to consider, which highlights the challenges in constructing guidance for optimal use of resources to reduce the global burden of CVD.

Appendix

Optimal risk factor profiles, age threshold calculations, and vascular age

The European Society of Cardiology defines optimal risk factors as a total cholesterol of 4.0 mmol/L (155 mg/dL), systolic blood pressure of 120 mmHg, no current smoking, and absence of diabetes mellitus.[8] Age thresholds were calculated for low-risk countries (Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, the Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, U.K.), using the published Systematic Coronary Risk Evaluation (SCORE) equations.[5]

The ACC/AHA define optimal risk factors as a total cholesterol of 170 mg/dL (4.4 mmol/L), HDL cholesterol of 50 mg/dL (1.3 mmol/L), untreated systolic blood pressure of 110 mmHg, no current smoking, and absence of diabetes mellitus.[6] Age thresholds were calculated using the Pooled Cohort equations calculator (Online calculator: http://tools.acc.org/ascvd-risk-estimator/).[9] Vascular age was calculated using the according to the sex-specific Pooled Cohorts equations as described previously: the predicted risk of an individual is transformed to the calendar age of a man or woman with the same absolute 10-year risk, but with all risk factors set to optimal levels.[363] For an individual with optimal risk factors according to the guidelines, the vascular age equals the calendar age.

The 3rd Joint British Societies recommendations define optimal risk factors as a total cholesterol/HDL cholesterol ratio of 3.5, untreated systolic blood pressure of 120 mmHg, body mass index of 25.8 kg/m^2 for women and 26.3 kg/m^2 for men, no current smoking, absence of diabetes mellitus, atrial fibrillation, chronic kidney disease, rheumatoid arthritis, and family history of premature coronary heart disease.[298] Age thresholds were calculated using the QRISK2 calculator (Online calculator: http://www.qrisk.org/index.php).[7]

Note that vascular age for men and women are not to be interpreted on the same scale because they derive from sex-specific formulas. This reflects the lower incidence of CVD in women as compared to men, hence identical absolute 10-year risks in men and women translate into a higher heart age in women.

Summary

Despite great improvements in treatment, cardiovascular diseases (CVD) remain among the leading causes of death and disability in almost all societies. Since atherosclerosis – subclinical vascular alterations leading to CVD – accumulates over decades and the mechanisms though which atherosclerosis develops are reasonably well understood, there is great opportunity for prevention of atherosclerotic CVD (ASCVD). Current individualized primary prevention strategies focus on pharmacological treatment of modifiable ASCVD risk factors in individuals at high risk for ASCVD in the following 10 years, mostly with lipid-lowering medication (i.e. statins). Since decisions on initiating lipid-lowering medication are in part based on ASCVD risk estimates, adequate risk stratification is of great importance. Improving risk stratification for the development of ASCVD has the potential to translate into more effective and efficient prevention of ASCVD.

Chapter 1 summarizes the contemporary prevention strategies recommended by leading clinical societies in Europe and the U.S. as well as the outline and aims of the research described in this thesis. A brief description of the main study population, the Rotterdam Study, is provided. The Rotterdam Study is a prospective population-based cohort study of the community-dwelling population of a suburb of Rotterdam, the Netherlands.

In Part I of this thesis several methodological aspects of working with population-based data are discussed. Specific issues that are addressed include the methods and definitions on the follow-up of cardiac outcomes in the Rotterdam Study (*Chapter 2*), the healthy volunteer effect (*Chapter 3*), and comparisons to data obtained from population registries (*Chapter 4*). In *Chapter 3*, we confirm the existence of the healthy volunteer effect in the Rotterdam Study. This indicates that those invitees who agree to participate in a population-based study, have a lower cardiovascular risk factor burden and subsequent lower risk of dying compared to those who decline the invitation to participate. These differences diminished with increasing follow-up time.

Part II of this thesis is focused on a relatively novel statistical measure, net reclassification improvement (NRI), used to quantify differences in risk stratification when comparing 2 strategies. In *Chapter 5* of this thesis, we provide an overview of the history and definitions of NRI, and practical applications in 67 research papers published in top-medical journals. The results from this analysis highlight several challenges and limitations of NRI. Therefore, we constructed an educational part on NRI specifically for clinicians with examples from the literature and clear clinical applications. Some of the pitfalls identified in *Chapter 5* are worked out further in the subsequent chapters using examples from the medical literature. In *Chapter 6*, we delineate how NRI incorporates an implicit weighing factor for the frequency of occurrence of the studied outcome. The clinical and statistical importance of the placement of risk thresholds in NRI analyses are discussed in *Chapter 7*. The results from *Chapter 8* demonstrate that subtle differences in the selection of the studied outcome, in this particular instance coronary heart disease (CHD) versus CVD, can influence the estimates and subsequent interpretation of NRI for a newer risk marker. Last, *Chapter 9* of this thesis highlights the important role of model calibration on the interpretation of NRI.

The next part of this thesis, Part III, contains data on the contemporary burden of CVD in the general population. In *Chapter 10* we summarize the most recent Dutch nation-wide statistics. Over the past 50 years cardiovascular mortality has plummeted, yet the burden of heart disease

remains high. More recently, we have observed dramatic increases in the overall number of cardiac interventions, including percutaneous coronary interventions and implantations of pacemakers and ICDs. In *Chapter 11* of this thesis, we present the lifetime risk of CVD and the distribution of its first manifestations for men and women from the Rotterdam Study. This provided insight into the relative contribution of various types of CVD (i.e. CHD, cerebrovascular disease, and heart failure) among men and women. Two-thirds of all men and women will develop some form of CVD during their life. However, women generally developed CVD at a later age and were more likely to have it present as a cerebrovascular disease event or heart failure compared to men. This may have bearing on prioritizing specific preventive efforts in men and women.

Part IV of this thesis is entirely focused on cardiovascular risk estimation within the framework of the Rotterdam Study. In *Chapter 12*, we compare the implications of the contemporary European and U.S. clinical practice guidelines for primary prevention of CVD in the Rotterdam Study population. Following the U.S. guidelines would result in almost all men aged 55 and over to be recommended for statin treatment, as well as the majority of women. Also, the underlying models used to identify individuals at increased CVD risk performed suboptimal in the Rotterdam Study population. *Chapters 13* through *15* focus on ways to improve cardiovascular risk estimation. In *Chapter 13*, we compare the added predictive ability of 12 putative CVD risk markers, including blood biomarkers and measures to quantify subclinical atherosclerosis. Coronary artery calcification (CAC), measured by non-contrast computed tomography, yielded the strongest improvements in discrimination and subsequent risk classification to identify individuals at increased risk of future CHD. The results from *Chapter 14* indicate that CAC score does not only predict CHD, but also heart failure, even in the absence of clinical manifest CHD. As such, it would be worthwhile to consider heart failure as an additional outcome in ongoing screening trials using CAC for allocation of preventive treatment. In *Chapter 15*, we present the coronary risk in the elderly (CORE) model, a CHD prediction tool developed and validated for older populations. The CORE model is based on data from participants aged 65 years and older from the Rotterdam Study and the Cardiovascular Health Study (CHS) and uses competing risks regression in order to account for censoring due to death from non-coronary causes. The CORE model showed good generalizability in European and U.S. populations, but only moderate discrimination and no consistent improvements in risk classification compared with an existing CHD prediction model. Moreover, adding promising newer cardiovascular markers to the model did not substantially improve CHD risk prediction. These results emphasize the need for further work to improve cardiovascular risk prediction in an elderly population.

The general discussion in *Chapter 16* is focused on the limitations of the work described in this thesis, and how the same work can contribute to future strategies for primary prevention of ASCVD and preventive cardiology at large. This discussion can be broken down into two main focal points. First, a transition should be made in cardiovascular risk assessment from 10-year risk of hard ASCVD based on a single measurement of risk factor levels, to remaining lifetime risk of a broad spectrum of ASCVD based on trajectories of risk factor levels. This can be done using existing data resources. The second part of the discussion focusses on a critical point of current risk-based strategies, namely the dominant role of age in CVD prediction models. We discuss a number of potential adaptations, as well as entirely alternative strategies that do not depend on cardiovascular risk calculations. As such, many challenges remain in constructing guidance for optimal use of resources to reduce the global burden of CVD.

Samenvatting

Ondanks de verbeterde behandeling van hart- en vaatziekten blijft dit de belangrijkste oorzaak voor overlijden en lichamelijke beperkingen in vrijwel alle samenlevingen. Atherosclerose, de subklinische vasculaire veranderingen die leiden tot hart- en vaatziekten, ontwikkelt zich over tientallen jaren. De onderliggende mechanismen waardoor atherosclerose ontstaat, zijn redelijk goed in kaart gebracht. Hierdoor bestaat er de mogelijkheid om atherosclerotische hart- en vaatziekten te voorkomen. De huidige geïndividualiseerde preventiestrategieën richten zich op de medicamenteuze behandeling van modificeerbare risicofactoren voor het ontwikkelen van atherosclerose. Geldende richtlijnen adviseren personen met een hoog 10-jaars risico op atherosclerotische hart- en vaatziekten te behandelen, meestal met cholesterolverlagende medicatie (statines). Aangezien de keuze om iemand te gaan behandelen mede bepaald wordt door een risicoschatting, is adequate risicostratificatie van groot belang. Het verbeteren van deze risicostratificatie heeft de potentie om zich uiteindelijk te vertalen in effectievere en efficiëntere preventie van hart- en vaatziekten.

Hoofdstuk 1 is een inleiding op dit proefschrift en begint met een korte introductie in de huidige preventiestrategieën die aangeraden worden door de gezaghebbende beroepsverenigingen in Europa en de V.S. Daarnaast staan in dit hoofdstuk de opzet en doelen van het onderzoek dat in dit proefschrift beschreven wordt. Als laatste volgt een korte beschrijving van de belangrijkste onderzoekspopulatie waarop de meeste resultaten, beschreven in dit proefschrift, zijn gebaseerd: het Erasmus Rotterdam Gezondheid Onderzoek (ERGO, 'The Rotterdam Study'). ERGO is een langlopend prospectief cohort onderzoek in de algemene bevolking van Ommoord, een buitenwijk van Rotterdam.

In Deel I van dit proefschrift worden verschillende aspecten uitgelicht van het werken met gegevens verkregen uit bevolkingsonderzoeken. In het bijzonder beschrijven we de methoden en definities van hartaandoeningen welke gebruikt worden in ERGO (*Hoofdstuk 2*), het 'gezonde vrijwilligers effect' (*Hoofdstuk 3*) en vergelijkingen met gegevens verzameld uit digitale huisartsendossiers (*Hoofdstuk 4*). In *Hoofdstuk 3* bevestigen we het bestaan van het gezonde vrijwilligers effect in ERGO. Dit betekent dat de mensen die uitgenodigd zijn en vervolgens ook daadwerkelijk deelnemen aan een bevolkingsonderzoek een beter cardiovasculair risicoprofiel en lagere sterftecijfers hebben vergeleken met degenen die de uitnodiging afsloegen. De verschillen in sterftecijfers namen af naarmate deelnemers langer gevolgd werden.

Deel II van dit proefschrift is volledig gewijd aan een nieuwere statistische maat genaamd 'net reclassification improvement' (NRI). Deze maat wordt gebruikt om het verschil te kwantificeren tussen twee strategieën van risicoclassificatie. In *Hoofdstuk 5* van dit proefschrift geven we een overzicht van de totstandkoming en de definities van NRI. Daarnaast beschrijven we de toepassing van NRI in 67 wetenschappelijke publicaties, gepubliceerd in medische toptijdschriften. Deze resultaten leggen meerdere uitdagingen en beperkingen bloot ten aanzien van het gebruik van NRI. Daarom hebben we een educatief stuk geschreven, specifiek voor clinici met voorbeelden uit de medische literatuur. Een aantal van de valkuilen in het gebruik van NRI die we in *Hoofdstuk 5* hebben geïdentificeerd zijn verder uitgewerkt in de daaropvolgende hoofdstukken naar aanleiding van voorbeelden uit de literatuur. In *Hoofdstuk 6* zetten we uiteen hoe NRI een impliciete weging bevat voor de frequentie van optreden van de uitkomst die bestudeerd wordt. De klinische en statistische relevantie van het bepalen van NRI afkapwaarden wordt beschreven in *Hoofdstuk 7*. De resultaten uit *Hoofdstuk 8* tonen aan dat puntschattingen, en daaruit volgende interpretaties, van NRI voor een nieuwere risicomarker beïnvloed kunnen

worden door subtiele verschillen in de keuze van de bestudeerde uitkomst. In dit hoofdstuk hebben we dat uitgewerkt aan de hand van het voorbeeld van coronaire hartziekte versus atherosclerotische hart- en vaatziekten. Als laatste, in *Hoofdstuk 9*, benadrukken we het belang van kalibratie van risicomodellen in de context van de interpretatie van NRI.

Het volgende deel van dit proefschrift, Deel III, bevat gegevens over de hedendaagse ziektelast van hart- en vaatziekten in de algemene bevolking. In *Hoofdstuk 10* vatten we de meest recente Nederlandse landelijke statistieken samen. De afgelopen 50 jaar is de sterfte aan hart- en vaatziekten zeer sterk gedaald, echter de ziektelast van hartaandoeningen blijft nog altijd hoog. De afgelopen decennia hebben we een dramatische stijging van het aantal ingrepen aan het hart waargenomen, onder andere percutane coronaire interventies (dotterbehandelingen) en implantaties van pacemakers en ICDs. In *Hoofdstuk 11* van dit proefschrift presenteren we het risico op het ontwikkelen van hart- en vaatziekten over de gehele levensspan. Daarnaast beschrijven we hoe hart- en vaatziekten zich als eerste manifesteren in mannen en vrouwen binnen ERGO. Dit geeft inzage in de relatieve bijdrage van verschillende typen hart- en vaatziekten (d.w.z. coronaire hartziekte, cerebrovasculaire aandoeningen en hartfalen) in mannen en vrouwen. Twee derde van alle mannen en vrouwen ontwikkelt op enig moment tijdens het leven een vorm van hart- en vaatziekten. Echter bij vrouwen manifesteren hart- en vaatziekten zich op hogere leeftijd en vaker in de vorm van cerebrovasculaire aandoeningen of hartfalen. Dit kan consequenties hebben voor het prioriteren van specifieke preventieve zorg in mannen en vrouwen.

Deel IV van dit proefschrift is volledig gericht op cardiovasculaire risicoschattingen binnen het raamwerk van ERGO. In *Hoofdstuk 12* vergelijken we de implicaties van de hedendaagse Europese en Amerikaanse klinische richtlijnen voor primaire preventie van hart- en vaatziekten in de ERGO populatie. Het navolgen van de Amerikaanse richtlijnen zou betekenen dat vrijwel alle mannen van 55 jaar en ouder een statine wordt aanbevolen, evenals de meerderheid van de vrouwen. Daarnaast functioneren de onderliggende modellen suboptimaal met het oog op het identificeren van personen met een verhoogd risico op hart- en vaatziekten binnen de ERGO populatie. *Hoofdstukken 13* tot en met *15* zijn gericht op het verbeteren van cardiovasculaire risicomodellen. In *Hoofdstuk 13* vergelijken we 12 vermeende risicomarkers voor hart- en vaatziekten ten aanzien van de toegevoegde waarde op de precisie van risicoschattingen. Hierbij vergeleken we onder andere verschillende bloedwaarden en methoden om subklinische atherosclerose te kwantificeren. De coronaire calcium (CAC) score, gemeten met CT zonder contrastmedia, toonde de sterkste verbetering in discriminerend vermogen om personen met toekomstige coronaire hartziekte te identificeren en deze correct te classificeren. De resultaten uit *Hoofdstuk 14* tonen aan dat de CAC score niet alleen coronaire hartziekte voorspelt, maar ook hartfalen, zelfs in de afwezigheid van klinisch manifeste coronaire hartziekte. Daarom zou het interessant zijn om hartfalen mee te nemen als een additioneel eindpunt in reeds lopende screeningsstudies die gebruik maken van CAC om preventieve behandeling toe te wijzen. In *Hoofdstuk 15* presenteren we het coronaire risico bij ouderen (CORE, 'coronary risk in the elderly') model. Dit is een predictiemodel voor coronaire hartziekte ontwikkeld en gevalideerd bij ouderen. Het CORE model is gebaseerd op gegevens verzameld bij deelnemers van 65 jaar en ouder uit ERGO en 'the Cardiovascular Health Study' (CHS). Het model is ontwikkeld met behulp van regressietechnieken die rekening houden met concurrerende risico's op dood door niet-coronaire aandoeningen. Het CORE model toonde goede generaliseerbaarheid in zowel Europese als Amerikaanse populaties. Echter het discriminerend vermogen was matig

en het model toonde geen consistente verbeteringen in risicoclassificatie vergeleken met een bestaand predictiemodel voor coronaire hartziekte. Het toevoegen van veelbelovende nieuwere risicomarkers aan het CORE model resulteerde niet in een substantiële verbetering in risicoschattingen. Deze bevindingen benadrukken dat meer gericht onderzoek noodzakelijk is om cardiovasculaire risicoschattingen bij ouderen te kunnen verbeteren.

De algemene beschouwing in *Hoofdstuk 16* is gericht op de beperkingen van de verschillende onderzoeken beschreven in dit proefschrift, alsmede hoe deze onderzoeken bij kunnen dragen aan de toekomst van primaire preventie van hart- en vaatziekten en preventieve cardiologie in brede zin. De algemene beschouwing kan onderverdeeld worden in twee grote punten. Ten eerste lijkt een transitie nodig van 10-jaars risico op harde atherosclerotische eindpunten, gebaseerd op een enkele meting van risicofactoren, naar een risicoschatting voor het gehele leven op een breed spectrum van atherosclerotische hart- en vaatziekten, gebaseerd op trends in herhaalde metingen van risicofactoren. Dit is allemaal te realiseren met reeds verzamelde onderzoeksgegevens. Het tweede deel van de beschouwing richt zich op een zorgwekkend fenomeen binnen hedendaagse risico-gedreven preventiestrategieën, namelijk de dominante rol van leeftijd in predictiemodellen voor hart- en vaatziekten. Hiertoe beschrijven we een aantal potentiële aanpassingen aan predictiemodellen en alternatieve strategieën die niet gebaseerd zijn op dergelijke risicoschattingen. Hieruit valt te concluderen dat er nog vele uitdagingen zijn in het opstellen van het richtlijnen voor het optimale gebruik van mankracht en middelen om de wereldwijde ziektelast van hart- en vaatziekten te reduceren.

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MJG Leening, SE Elias-Smale, JF Felix, JA Kors, JW Deckers, A Hofman, BHCh Stricker, and JCM Witteman. Unrecognised myocardial infarction and long-term risk of heart failure in the elderly: the Rotterdam Study. *Heart* 2010;96(18):1458-62.

* These authors contributed equally to this work.

It has been my good fortune to have been in the right place, at the right time, and most importantly, with the right people.

- Eugene Braunwald
Eur Heart J 2015;36(22):1350-1

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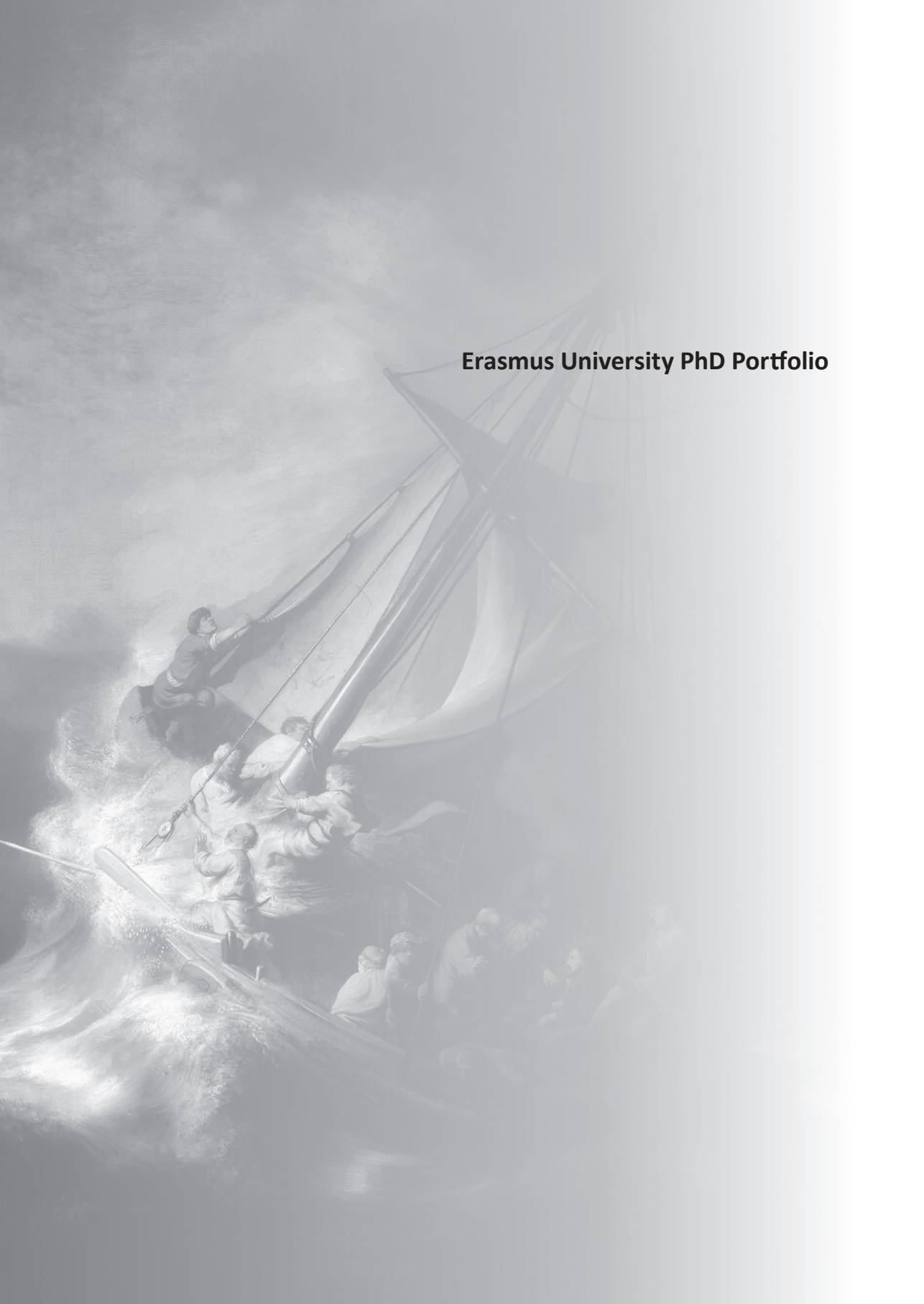

Erasmus University PhD Portfolio

Identifying Persons at Increased Risk of Cardiovascular Disease
Methodological Considerations and Practical Applications in the General Population

Maarten J.G. Leening

Departments	Epidemiology, Erasmus MC – University Medical Center Rotterdam
	Cardiology, Erasmus MC – University Medical Center Rotterdam
Research schools	Netherlands Institute for Health Sciences (NIHES)
	Cardiovascular Research School Erasmus University Rotterdam (COEUR)
Promotors	Prof. dr. B.H.Ch. Stricker
	Prof. dr. J.W. Roos-Hesselink

Training	**ECTS**	**Year**
MSc in Clinical Epidemiology	121.7	2006-2009
- NIHES, Erasmus MC, Rotterdam, the Netherlands		
- Harvard School of Public Health, Boston, MA, U.S.		
In-debt courses, short courses, and seminars	12.0	2011-2015
Scientific conferences		
- American Heart Association Scientific Sessions, Orlando, FL, U.S.[a,a]	1.2	2015
- American Heart Association Scientific Sessions, Chicago, IL, U.S.[a]	1.2	2014
- Cardiometabolic Health Congress, Boston, MA, U.S.	0.3	2014
- European Society of Cardiology Congress, Barcelona, Spain [a]	1.2	2014
- Netherlands Epidemiology Society Congress (WEON), Leiden, the Netherlands [a]	0.3	2014
- European Society of Cardiology Congress, Amsterdam, the Netherlands [a,a,b]	1.2	2013
- Netherlands Epidemiology Society Congress (WEON), Utrecht, the Netherlands [a,a]	0.6	2013
- European Society of Cardiology Congress, Munich, Germany [b]	1.2	2012
- Netherlands Epidemiology Society Congress (WEON), Rotterdam, the Netherlands [a]	0.6	2012
- Netherlands Association for Medical Education (NVMO) Congress, Egmond aan Zee, the Netherlands	0.6	2010

[a] oral presentation; [b] poster presentation

Teaching	**ECTS**	**Year**
Lecturing		
- Harvard Program in Cardiovascular Epidemiology, Boston, MA, U.S.	1.0	2015
- Markers and Prediction Research (ESP62) Erasmus Summer Programme. NIHES, Erasmus MC, Rotterdam, the Netherlands.	3.5	2014
- Study Design in Clinical Epidemiology (EPI210) Annual Summer Sessions for Public Health Studies. Harvard T.H. Chan School of Public Health, Boston, MA, U.S.	7.0	2014-2015
- Cardiovascular Epidemiology and Principles of Prevention Clinical cardiology residents training program. Erasmus MC, Rotterdam, the Netherlands.	0.5	2014
- Epidemiology of Coronary Heart Disease and Heart Failure Advanced minor in cardiology (GENMIN05). COEUR, Erasmus MC, Rotterdam, the Netherlands.	1.0	2012
- Co-chairing a workshop on the evaluation of prediction models Invited speaker: Prof. dr. M.J. Pencina. Departments of Public Health and Epidemiology, Erasmus MC, Rotterdam, the Netherlands.	0.5	2012
Assisting		
- Fundamentals of Epidemiology (EPI500) Annual Summer Sessions for Public Health Studies. Harvard School of Public Health, Boston, MA, U.S.	7.0	2012, 2014
- Pharmaco-epidemiology and Drug Safety (EWP03) Erasmus Winter Programme. NIHES, Erasmus MC, Rotterdam, the Netherlands.	0.5	2014
- Principles of Research in Medicine and Epidemiology (ESP01) Erasmus Summer Programme. NIHES, Erasmus MC, Rotterdam, the Netherlands.	1.5	2011-2013
- Statistics in Medical Research and Working with Statistical Software Core medical curriculum. Erasmus MC, Rotterdam, the Netherlands.	0.5	2008
(Co-)supervising MSc and DSc students		
- K.H.J. Ultee	1.0	2014-2015
- M. Stojković	1.0	2014
- J. Pavlović	1.0	2013-2015
- R.J. Billar	2.0	2013-2014
- S.K.L. Darweesh	2.0	2012-2013
- D. Nanchen	1.0	2012

Research visit		
Department of Epidemiology, Harvard School of Public Health, Boston, MA, U.S.		2014-2015
Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, U.S.		2014-2015

Miscellaneous	**ECTS**	**Year**
Peer review		
- JAMA	0.3	2016
- JAMA Cardiol	0.3	2016
- Circ Res	0.3	2016
- Stat Med	0.3	2016
- BMJ	0.9	2015-2016
- Circulation	0.6	2015-2016
- Circ: Heart Fail	0.3	2015
- Ann Intern Med	1.2	2014-2015
- Prev Med	0.3	2014
- Neth J Med	0.3	2014
- J Am Coll Cardiol: Cardiovasc Img	0.3	2014
- J Am Coll Cardiol	0.3	2014
- Biometrics	0.3	2013
- N Engl J Med	0.3	2013
- Eur J Epidemiol	2.8	2012-2015
Rotterdam Study management team	3.0	2013-2014
Organizing committee 36th annual congress of the Netherlands Epidemiology Society (VvE): WEON 2012	2.0	2011-2012
Awards		
- Annals of Internal Medicine Outstanding Reviewer 2014		2015
- American Heart Association (AHA) Elizabeth Barrett-Connor Research Award in Epidemiology and Prevention		2014
- Netherlands Epidemiology Society (VvE) Young Investigator Award: Best Publication 2014		2014
- European Society of Cardiology (ESC) Young Investigator Award Population Sciences		2013
- European Society of Cardiology (ESC) Congress Best Moderated Poster Award		2013
Grants		
- Stichting De Drie Lichten international research project grant		2014
- Prins Bernhard Cultuurfonds fellowship for international research		2014
- Erasmus Trustfonds international research grant		2014
- Erasmus Trustfonds travel grant		2012
- Erasmus Trustfonds travel grant		2008

The families and friends of most researchers have learned that they need to share their loved ones with the researchers' other demanding priority, science.

- J. Michael Gaziano and Eric Peterson
The cardiovascular disease researcher
JAMA 2013;310(19):2048-9

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I have learned that success in research is built on three important pillars: opportunities, collaboration, and unconditional support.

Opportunities

Life is about recognizing opportunities and to make the most out of these opportunities. However, it all starts with being offered opportunities, and I feel privileged to have been offered many by such a diverse group of people over the past decade.

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Boston, January 2015

About the Author

Maarten Leening was born and raised on the outskirts of Halsteren, a quiet little town in the southern part of the Netherlands. He attended Gymnasium (Latin school) at RSG 't Rijks in Bergen op Zoom. During those years he found out that he was not talented enough to become a professional basketball player. Therefore, after graduating cum laude in 2004, he pursued his passion for human biology and moved to Rotterdam to study Medicine at the Erasmus University. During this period he was invited to participate in a parallel Master of Science (MSc) program in Clinical Epidemiology (chair: Prof. dr. A. Hofman). As a part of this program, he was given the opportunity to attend courses at the Harvard School of Public Health in 2008. Aligning with his ever growing interests in cardiology and quantitative research, Maarten wrote his MSc thesis on subclinical coronary artery disease and subsequent risk of heart failure at the Department of Epidemiology of the Erasmus MC in 2009 (supervisor: Prof. dr. J.C.M. Witteman). Before embarking on a PhD in Epidemiology, he obtained his medical degree (MD) cum laude in 2011. During the following three years he worked on the research described in this thesis at the Departments of Epidemiology and Cardiology of the Erasmus MC (supervisors: Prof. dr. J.C.M. Witteman, Prof. dr. B.H.Ch. Stricker, and Prof. dr. J.W. Roos-Hesselink). In 2014, Maarten returned to Boston on a Prins Bernhard Cultuurfonds fellowship grant to work at the Center for Cardiovascular Disease Prevention of the Brigham and Women's Hospital (chair: Prof. dr. P.M. Ridker, supervisor: Prof. dr. N.C. Cook) and the Department of Epidemiology of the Harvard School of Public Health (chair: Prof. dr. M.A. Williams). After moving back to the Netherlands in 2015, he started clinical residency at the Department of Cardiology (chair: Prof. dr. F. Zijlstra) and got accepted into the cardiology training program (chairs: Prof. dr. J.W. Deckers and Dr. T.W. Galema). As a part of this program, Maarten currently works at the Department of Internal Medicine of the Albert Schweitzer Hospital in Dordrecht (chair: Dr. E.F.H. van Bommel). Besides his clinical work, Maarten has remained actively involved in preventive cardiology research as a postdoctoral research fellow at the Department of Epidemiology of the Erasmus MC (chair: Prof. dr. A. Hofman). Maarten lives in Rotterdam with his beloved wife Brenda, with whom he enjoys travelling the world.

All we know is still infinitely less than all that still remains unknown.

- William Harvey (1578 – 1657)
Exercitatio anatomica de motu cordis et sanguinis in animalibus, 1628