Chapter 1

Introduction

GENERAL INTRODUCTION

Cardiovascular disease is highly prevalent worldwide and a major cause of morbidity and mortality. For example, in the Netherlands, about one third of annual deaths is due to cardiovascular disease. Also, in 2014, the estimated number of disability adjusted life-years (DALYs) lost were 282,834 for coronary heart disease and 191,320 for stroke, indicating the magnitude of the burden of cardiovascular disease.[1] In the USA, in 2014, an estimated 85.6 million American adults (> 1 in 3) had one or more types of cardiovascular disease.[2] Of these adults, 43.7 million (≈ 50%) are estimated to be aged over 60 years. In very old age, absolute risk increases progressively, as the average annual rate of first cardiovascular events rises from 3 per 1000 men at 35-44 years of age, to 74 per 1000 men at 85-94 years of age. For women, comparable rates occur 10 years later in life, although this age gap tends to narrow with advancing age.[2]

Therefore, it is not surprising that cardiovascular disease is the leading contributor to global burden of disease in older people.[3] In the Netherlands, costs of care for people with cardiovascular disease rise with age and are highest in the group aged 65 years and over. Especially for women, peak cardiovascular disease-related costs occur in the age group 80-90 years.[4]

Due to improved treatment options, an increasing number of patients survive their first cardiovascular event. From then onwards many of them have 'chronic' cardiovascular disease, e.g. chronic heart failure as a result of myocardial infarction, or chronic disability after a stroke. Patients with a history of cardiovascular disease are also at high risk for recurrent events and are an important risk group in clinical practice.

Given this enormous burden of disease and the impact of cardiovascular disease on society, prevention of (recurrent) cardiovascular disease in our aging population is important. Therefore, this thesis addresses the prevention of cardiovascular disease in old age with a focus on patients with a history of cardiovascular disease, as they are at highest risk for future events.

First, to illustrate the dilemmas faced by physicians when implementing secondary cardiovascular prevention in daily practice, this introduction presents two older patients with a history of cardiovascular disease (in Chapter 8 these patients are discussed in a broader perspective). Then, an overview of risk assessment tools used in guidelines for both primary and secondary prevention will be presented. Subsequently, potential candidates for risk prediction in old age are introduced and current knowledge on prescription rates in secondary cardiovascular prevention in old age are reviewed. Finally, the aims of this thesis are formulated, followed by an outline of the studies performed to address the research questions posed.

1. CLINICAL DILEMMAS

To illustrate the challenges faced by clinicians in secondary cardiovascular prevention in old age, two 85-year-old patients are presented that reflect clinical differences that can occur in old age:

Ms Anne
Ms Anne is an 85-year-old woman visiting her general practitioner for follow-up after the transient ischemic attack she experienced one year ago. She was widowed two years ago and, although she lives alone, has a lively social network. She regularly cycles or wanders around the village, carrying her groceries. She is very punctual, never misses an appointment at the general practice, and takes her medications regularly. This time she visits the practice because for the last few months she has been feeling dizzy and has muscle pains. These symptoms affect her quality of life, because she is afraid to go out and the muscle pains prevent her from doing the shopping herself.

Mr John
Mr John is an 85-year-old man who is visited by his general practitioner at home for follow-up after a myocardial infarction three years earlier, complicated by heart failure last year. Besides the cardiovascular problems, he suffers from chronic obstructive pulmonary disease and osteoarthritis. He still smokes. Last year he was admitted to hospital with gastrointestinal bleeding. Since then he has shown non-adherence to his cardiovascular preventive medications; he thinks the medications are only making him sick and that they will not improve his quality of life.

In both these cases the main questions are: What do we clinicians tell these patients? What do we know about their risks for recurrence and future functional decline? What do we know about the possible benefits and risks of treatment?

2. RISK ASSESSMENT

Risk assessment plays an important role in the selection of eligible patients for cardiovascular preventive medication.

2.1. Risk assessment in primary prevention

The Framingham risk score was presented in 1991 and was the first risk score used worldwide for patients *without* a history of cardiovascular disease. The items included were age, sex, systolic blood pressure, cholesterol, smoking, and a history of diabetes. Various amendments were made over the years; a new Framingham risk score was introduced by the American College of Cardiology and the American Heart Association, that also includes ethnic background and treatment for hypertension.[5] For individual risk estimation, an online risk calculator can be used. In Europe, the SCORE risk chart, including more or less the same traditional risk markers, can be used to estimate risk.[6]

In the Netherlands, the Dutch College of General Practitioners (NHG) developed a risk chart including age, smoking status, systolic blood pressure, and a total cholesterol/high density cholesterol ratio.[7] In intermediate risk individuals the family history, degree of physical activity, body mass index (BMI) and renal function are also taken into consideration. In the United Kingdom, the online JBS3 risk calculator[8] has recently been developed, including traditional risk markers plus treatment for blood pressure, ethnic group, BMI, the Townsend quintile (as a marker of socioeconomic status), family history of cardiovascular disease, and a history of atrial fibrillation or rheumatoid arthritis.

With regard to preventive treatment specifically for old age, risk estimation becomes more difficult. The risk calculator of the American College of Cardiology and the American Heart Association provides risk estimations only for individuals aged 20 up to 79 years.[9] The American Guidelines state that for older individuals or those with limited life expectancy, clinical considerations should dictate the intensity of risk assessment and prevention efforts.[5] When using the Dutch risk chart, physicians are faced with 'red blocks' for all patients aged 75 years and over, indicating that all these older persons are eligible for preventive treatment with antihypertensive drugs as well as lipid-lowering drugs, due to their high estimated 10-year risk for the development of cardiovascular disease. The JBS3 risk calculator cannot be used for patients older than 85 years. The guideline from the National Institute for Health and Care Excellence (NICE: 2008, amended 2014) recommends to consider all people aged 85 and older to be at increased risk of cardiovascular disease based on age alone, particularly individuals who smoke or have raised blood pressure; however, the decision as to whether or not to start statin therapy, should be made after informed discussion between the clinician and the individual about the risks/benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy.

Thus, when implementing guidelines for primary prevention in old age clinicians are faced with serious challenges, because estimation of the risks/benefits for each older individual is complicated by multimorbidity, polypharmacy and various side-effects, as well as (on a societal level) general priorities of health care.

2.2. Risk assessment in secondary prevention

In patients with a history of cardiovascular disease, guidelines worldwide advocate lifelong preventive treatment regardless of age,[10-12] Risk prediction in secondary prevention in old age is difficult, since traditional cardiovascular risk markers lose their predictive value with age[13;14], and most risk scores are either complex or are for restricted subgroups of vascular hospitalized patients[15;16]. In a cohort of primary care patients with a history of cardiovascular disease (mean age 60 years), the SMART risk score calculator was developed to predict recurrent cardiovascular events.[17] It includes traditional cardiovascular

risk markers plus the history of cardiovascular disease, time since first cardiovascular disease, high sensitivity C-reactive protein, and kidney function. However this SMART risk score was developed in a population with a mean age of 60 years, and has not yet been validated in older age groups. Therefore, it remains uncertain whether it can be used in (very) old age as well, leaving physicians empty handed when trying to estimate risk for patients with a history of cardiovascular disease in the general older population.

This is undesirable because, in old age, risk assessment for recurrent cardiovascular disease is mandatory in order to help physicians and patients decide whether or not to start, stop or continue secondary preventive medication. Especially in old age these decisions are complex due to co-morbidity, side-effects and polypharmacy. Prevention of functional decline and improvement in quality of life may become even more important than preventing recurrent cardiovascular disease or prolonging life - and these aspects also have to be taken into account. This implies that 'one size fits all' is not applicable and that, in their consultations with each individual patient, clinicians need to know the current cardiovascular risk and possible benefits of treatment and treatment priorities. Especially in old age, benefits may be less clear whereas possible risks (e.g. development of side-effects or drug interactions, that can lead to adverse events/hospital admissions) become more prominent.

In conclusion, assessment of individual risk with regard to recurrent cardiovascular events, as well as with regard to (further) functional decline, is complicated, since no validated risk scores for secondary cardiovascular prevention in old age are available. Also, because traditional risk markers lose their predictive value with age, there is need for studies exploring new risk markers for older persons.

The following section elaborates on possible predictors of risk for (recurrent) cardiovascular disease and functional decline, that might be effective in secondary cardiovascular prevention in old age.

3. CANDIDATES FOR RISK PREDICTION IN OLD AGE

3.1. Severity of cardiovascular disease history

In a younger age group, the severity of prior cardiovascular disease was shown to be related to cardiovascular recurrence risk, i.e. patients with no history of cardiovascular disease had the lowest risk, patients with a history of transient ischemic attack or angina had intermediate risk, whereas patients with a history of myocardial infarction of stroke had the highest future risk for cardiovascular disease.[18] Accordingly, the severity of the history of cardiovascular disease might also be a useful predictor in old age. In some specified risk scores for risk for mortality after myocardial infarction[19] and risk for recurrence of stroke[20], the presence of previous cardiovascular disease (yes/no) is already

included. However, because those risk scores were developed in younger age groups, the predictive value of the severity of the history of cardiovascular disease in old age is still unknown.

3.2. New biomarkers

Several new biomarkers have emerged for prediction of cardiovascular events and mortality: markers of inflammation, including C-reactive protein (CRP), interleukin-6, markers of cardiac injury (e.g. brain natriuretic peptide (BNP) and N-terminal-pro brain natriuretic peptide (NT-proBNP)), markers of oxidative stress (e.g. homocysteine (HCY), troponin), and markers of renal injury (e.g. kidney function calculated as modification of diet in renal disease formula (MDRD) or estimated glomerular filtration rate (eGFR)). Since the traditional risk markers lose their predictive value with age, these easily available biomarkers may have considerable potential to improve prediction of cardiovascular disease in old age.

For primary prevention the American guideline recommends highly selective C-reactive protein (hs-CRP) as an optional screening test when risk-based advice about initiation of pharmacological therapy is uncertain after quantitative risk assessment, especially for those at intermediate risk. However, predictive value of hs-CRP seems to attenuate with age[21], and further studies in old age are mandatory.

Homocysteine has proven to be superior to traditional risk markers in primary prevention in very old age[22] and may also be a valuable predictor for recurrent cardiovascular disease and mortality in secondary prevention.

Another promising candidate for cardiovascular risk prediction in old age is NT-proBNP, a polypeptide belonging to the natriuretic peptide family. The main source of synthesis and secretion of NT-proBNP is the ventricular myocardium, which is initiated by ventricular wall stress caused by pressure, hypoxia and/or volume overload.[23] In a review of available prospective studies, strong associations were found between circulating concentration of natriuretic peptides and cardiovascular disease risk, under a range of different circumstances.[24] Further investigations in large general population studies are recommended to clarify any predictive utility and to better control for publication bias. Since NT-proBNP is so closely related to (sometimes) subtle and subclinical cardiovascular damage, it might prove especially promising in prediction of cardiovascular risk in old age.

3.3. Other new risk markers

The coronary artery calcium (CAC) score is new risk marker that can be used in primary prevention in persons at intermediate risk.[5;25;26] Reference values are available online.[27] However for old age the CAC score has some disadvantages, i.e. it is expensive, patients have to attend hospital for the scan, and most older patients with a history of cardiovas-

cular disease already have high coronary calcium scores. Therefore, this score seems less suitable for risk assessment in secondary prevention in very old age.

Carotid intima media thickness (IMT) has also been proposed as a new risk marker. However, its use in primary prevention (even in intermediate risk persons) is not recommended.[5] In secondary prevention, increased IMT is associated with increased risk for recurrent stroke.[28] However, IMT has not yet been advocated for general use in older persons with a history of cardiovascular disease and the application of IMT measurements is costly and not easily applied at home.

In conclusion, in old age, readily available biomarkers seem to be the most attractive for further investigation with regard to their predictive value in secondary cardiovascular prevention.

3.4. Prediction of treatment effect

In very old age, although prediction of recurrent cardiovascular events is very important, prediction of treatment effect might be even more important, especially when a patient has to decide whether or not to start, stop, or continue preventive treatment. Moreover, literature on prediction of effectiveness of preventive treatment in very old age is scarce. New biomarkers may help to facilitate treatment decisions, if they are predictive for recurrent cardiovascular disease and for a positive treatment effect.

4. UNDER TREATMENT IN SECONDARY CARDIOVASCULAR PREVENTION IN OLD AGE

Prescription rates of cardiovascular preventive medication decline with increasing age[29;30]; however, little is known about the underlying mechanisms for this lack of preventive prescriptions in old age. Doubts about benefits in old age, vulnerability, disease severity, life expectancy, comorbidity, polypharmacy, as well as side-effects, might lead to decreased secondary preventive treatment prescriptions in old age. In addition, forgetfulness may lead to unintentional non-adherence. Especially in secondary prevention, this might imply that older persons are at unnecessary high risk for future events and functional decline.

Qualitative research on the dilemmas faced by clinicians in daily practice related to secondary cardiovascular prevention in old age, might help unravel the reasons for the low prescription rates observed in secondary cardiovascular prevention in old age.

5. AIMS OF THIS THESIS

In view of these complexities and problems, the main aim of this thesis is to improve medical care for older patients with a history of cardiovascular disease.

The first aim is to investigate current practice regarding secondary cardiovascular prevention in general practice in the Netherlands, and investigate how general practitioners (GPs) deal with these dilemmas in daily practice.

The second aim is to find predictors of risk for recurrent cardiovascular disease and of functional decline in old age. These predictors can help physicians deal with the difficult decisions related to starting, stopping or continuing secondary cardiovascular preventive treatment in old age.

The third aim is to examine whether new risk predictors can also predict treatment effect and, thereby, offer additional clinical benefit for old patients with a history of cardiovascular disease.

Therefore, in **part one** of this thesis, the following topics are investigated:

- First: current prescription rates of secondary cardiovascular preventive treatment in old age and possible associations of prescription rates with disease severity and/or GPs' judgment of vulnerability (Chapter 2)
- Second: GP' perspectives on secondary cardiovascular prevention in old age and the dilemmas encountered in daily practice (Chapter 3)

Part two investigates the predictive value of severity of the history of cardiovascular disease, and the predictive value of new biomarkers:

- First: the predictive value of clinical information on the presence/severity of the history of cardiovascular disease for the development/recurrence of cardiovascular disease, and for functional decline in very old age, is explored (Chapter 4)
- Second, the predictive value for recurrent cardiovascular disease of new readily available biomarkers (CRP, HCY, MDRD and NT-proBNP) in secondary prevention in very old age is examined (Chapter 5)
- Third, the predictive value of the identified new biomarker (Chapter 3) with regard to the development/recurrence of cardiovascular disease and with regard to functional decline in very old age is investigated (Chapter 6)

Part three presents the final study:

- the relevance and clinical implication of measuring NT-proBNP, not only for its use in existing risk prediction models for prediction of recurrent cardiovascular disease, but also for the prediction of the treatment effect of statins (Chapter 7)

5.1. Part one

For the first aim, Chapter 2 investigates current prescription rates of antithrombotic and lipid-lowering drugs. Data from the ISCOPE study, a cluster randomized trial among persons aged ≥ 75 years from 59 general practices in and around the city of Leiden (the Netherlands, inclusion period September 2009 to September 2010) are available, because (after one year in this study) complete electronic medical records for 4361 participants were collected. These data enabled us to investigate current prescription rates in secondary prevention in old age. Since the severity of the prevalent cardiovascular disease and the GPs' judgment of vulnerability were also registered, we also had the opportunity to investigate possible associations of prescription rates with disease severity and vulnerability.

Second, to investigate dilemmas that GPs encounter in daily practice with regard to implementation of guidelines for secondary cardiovascular prevention in old age, focus-group discussions with GPs and GP trainees (Chapter 3) were organized. Focus-group discussions are suitable for this kind of research because they allow participants to have in-depth discussions about their experiences and ideas on this topic.

5.2. Part two

With regard to the second aim, finding predictors of (recurrent) cardiovascular disease and functional decline in old age, the Leiden 85-plus Study offered an appropriate study population. This study included a cohort of 85-year-old inhabitants of the city of Leiden, enrolled in the years 1997-1999, with 5-year complete follow-up for functional status and cardiovascular morbidity and mortality, and 10-year follow-up for cause-specific mortality. This study population provided the opportunity to observe prognosis in a time frame when statin treatment was very uncommon, thus a 'statin naive population'.

First, associations of the severity of the cardiovascular disease history with prognosis for future cardiovascular disease and for functional status over time, are explored in Chapter 4. The Leiden 85-plus Study has 5-year complete annual follow-up for functional status, with measurements of cognition (Mini Mental State Examination (MMSE)), activities of daily living (ADL), wellbeing (Cantril's ladder), and depression (Geriatric Depression Scale (GDS)).

Second, in participants with a history of cardiovascular disease, prognostic value with regard to the development of recurrent cardiovascular disease over time was investigated for new biomarkers such as C-reactive protein, homocysteine, kidney function as estimated by the modification of diet in renal disease formula (MDRD), and/or N-terminal pro-B type natriuretic peptide (NT-proBNP) (Chapter 5).

Third, in Chapter 6, research focuses on associations of NT-proBNP (measured at age 85 years) with incident cardiovascular disease and mortality, and with functional status,

over time. These associations are examined in the entire inception cohort of the Leiden 85-plus Study, including participants who had no history of cardiovascular disease.

5.3. Part three

Finally, (Chapter 7) the possible clinical value of NT-proBNP for recurrent cardiovascular disease and for the treatment effect of statins is investigated within the PROSPER study, in participants with a history of cardiovascular disease. The PROSPER study is a randomized, double-blind, placebo-controlled trial designed to investigate the effect of pravastatin in prevention of vascular events in older persons. Between December 1997 and May 1999, a total of 5804 individuals were screened and enrolled in Scotland, Ireland and the Netherlands. Men and women aged 70-82 years were recruited. Of these participants, 2565 participants had a history of cardiovascular disease (including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction and vascular surgery). In this secondary prevention population, predictive value of NT-proBNP is investigated with regard to recurrent cardiovascular disease. NT-proBNP is added to the three risk prediction models: a model with age and sex, a model with traditional risk markers, and a model with the SMART risk score.

Finally, the treatment effect of pravastatin across different risk groups, as identified by NT-proBNP, is examined.

6. WHAT THIS THESIS MAY CONTRIBUTE TO MEDICAL PRACTICE

The work presented here may help reveal the underlying reasons for the low prescription rates in old age. In addition, more guidance might be provided for the estimation of risk for recurrent cardiovascular disease and for functional decline, as well as for estimation of the possible treatment effect of statins. Thereafter, recommendations for potential improvements regarding secondary cardiovascular prevention in old age can be formulated.

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