Chapter 8

Discussion

1. MAIN FINDINGS

The main aim of this thesis was to search for possible improvements in medical care for older persons with a history of cardiovascular disease. First, we aimed to investigate current practice regarding secondary cardiovascular prevention in general practice in the Netherlands and to unravel the underlying reasons for the low prescription rates observed. Then, we aimed to provide more guidance for risk estimation in secondary cardiovascular prevention in old age, not only for recurrence risk and the risk for functional decline, but also for the treatment effect of statins. Because cardiovascular disease in old age is accompanied by major morbidity and mortality, optimisation of care for these old patients remains a challenge in our ageing society. In younger age groups, preventive treatment of patients with a history of cardiovascular disease has improved over the decades but, for unknown reasons, preventive treatment uptake in old age lags behind.[1] Since absolute cardiovascular risk increases with age this might needlessly increase the burden of cardiovascular disease, as well as related disability and dependency.

The first aim, described in part one, was to investigate current practice regarding secondary cardiovascular prevention in general practice in the Netherlands. We observed that, in old age, the prescription rates of secondary cardiovascular preventive treatment with lipid-lowering and antithrombotic medications are still low (Chapter 2). Only half of all participants that were eligible for secondary preventive treatment within the ISCOPE study (patients aged 75 years and over) received both a statin and an antithrombotic prescription. In patients aged 85 years and over, this proportion was even smaller. Interestingly, the general practitioners' (GPs) judgement of patients' vulnerability was not independently related to prescription rates in old age, with chronological age itself being the strongest predictor, i.e. the older the individuals, the lower the prescription rates.

In the focus-group discussions with GPs regarding implementation of guidelines for secondary cardiovascular prevention in old age, the main theme to emerge was that of 'uncertainty' (Chapter 3). GPs are uncertain about the risks and benefits of secondary preventive treatment in old age. Specific guidelines and risk charts for secondary cardiovascular prevention in old age are lacking. To reduce uncertainty, GPs use a 'shared decision-making' strategy with their old patients. They mentioned that prevention of symptoms, anticipated regret, and high vitality facilitated implementation of the guidelines, whereas lag time to benefit, side-effects, vulnerability and a long period since the initial event, hindered implementation. Because GPs mentioned that the overriding aim of secondary cardiovascular prevention was to improve quality of life, treatment decisions were highly individualised. This might partly explain the reduced prescription rates currently observed. According to these GPs, implementation of the guidelines for secondary cardiovascular prevention in old age might be optimised by structured

ICPC coding and the presence of a practice nurse, as well as organising proactive annual follow-up. This might prevent patients 'falling into the gap' between primary and secondary care.

In conclusion, treatment uptake in (very) old age is still low. Highly individualised care with the ultimate aim to improve in quality of life seems to underlie these low prescription rates; however, according to our focus-group discussions, improvements might be expected from age-specific guidelines and the identification of patients that have fallen into the gap between primary and secondary care.

For the second aim (described in part two), predictors for (recurrent) cardiovascular disease and for functional decline were investigated in a population-based sample of 85-year-old participants from the Leiden 85-plus Study. Traditional risk markers are known to lose their predictive value with age and, therefore, new easily available predictors were investigated, i.e. the severity of the cardiovascular disease history, and new biomarkers.

First, we observed that the severity of the cardiovascular disease history was associated with unfavourable prognosis, not only with regard to (recurrent) cardiovascular disease and mortality, but also for future disability and cognitive decline (Chapter 4). Participants with no history of cardiovascular disease had a chance of about 1 in 5 to develop a myocardial infarction, stroke or die of a cardiovascular cause during 5-year follow-up, whereas participants with a history of angina, transient ischaemic attack, claudication or heart failure (minor cardiovascular disease) had a chance of about 1 in 3. In participants with a history of myocardial infarction, stroke or surgery for peripheral artery disease (major cardiovascular disease), this chance was about 1 in 2.

Both minor and major cardiovascular disease were associated with an accelerated decline in cognitive function and an accelerated increase of disability score, albeit most pronounced in participants with major cardiovascular disease.

Second, of the four new risk markers, C-reactive protein (CRP), kidney function (MDRD), homocysteine (HCY) and N-terminal pro B-type natriuretic peptide (NT-proBNP), the latter was the strongest predictor of cardiovascular events and mortality in the secondary prevention population of the Leiden 85-plus Study (Chapter 5). Interestingly, we observed that CRP (an inflammatory marker that can be used in intermediate risk persons in primary prevention) appeared to lose its predictive value with age. Homocysteine, a strong predictor in primary prevention in very old age [2] improved reclassification but did not improve the C-statistic. NT-proBNP was the strongest new predictor: when added to traditional risk markers it markedly improved the C-statistic and correctly reclassified about 40% of the participants.

Third, in the entire population of the Leiden 85-plus Study (primary plus secondary prevention), NT-proBNP was found to predict not only incident cardiovascular disease and mortality, but also the development of cognitive and functional decline (Chapter 6)

In conclusion, with regard to the second aim, this thesis reveals that the severity of cardiovascular disease history and NT-proBNP levels are useful predictors in very old age, not only for recurrent cardiovascular disease and mortality, but also for cognitive decline and disability in activities of daily living (ADL), both of which are increasingly important in old age.

For the third aim, in the search for possible clinical benefit, we studied the predictive value of the addition of NT-proBNP to currently used prediction models in a different study population (comprising patients aged 75 years and over) with a history of cardiovascular disease (sampled from the PROSPER study). A model with age, sex and NT-proBNP predicted recurrent cardiovascular disease and mortality as effectively as the more complex risk scores, including all the traditional risk markers and the SMART risk score. Moreover, high-risk persons, as identified with the model with age, sex and NT-proBNP, gained more benefit from treatment with statins (number needed to treat (NNT) = 12 for 2.5 years to prevent one cardiovascular endpoint (cardiovascular event or cardiovascular death)) as compared to the low-risk group identified by the same model (NNT = 115). This underlines the promising clinical value of NT-proBNP for our ageing population.

In conclusion, this thesis reveals that in secondary cardiovascular prevention in old age, treatment uptake is low, partly because of highly individualised care for these often complex patients and partly because some patients have disappeared into the gap between primary and secondary care. According to our focus-group discussions, treatment guidelines need to address the heterogeneity of older patients with a history of cardiovascular disease for whom tailored guidelines should be developed. In the meantime, with regard to the difficult decision-making related to starting, stopping, or continuing secondary cardiovascular preventive treatment in old age, the severity of the cardiovascular disease history and NT-proBNP can help physicians estimate the future risk for recurrent cardiovascular disease, and for cognitive and functional decline. Moreover, NT-proBNP levels can help estimate the expected treatment effect of statins.

In the light of these findings, we now discuss the clinical dilemmas that arise in secondary cardiovascular prevention in old age. Frequently encountered problems (such as side-effects, polypharmacy, adverse reactions, and adherence problems) as well as the role of patient vulnerability in secondary cardiovascular prevention in old age, are reviewed and illustrated by means of two hypothetical patients: Ms Anne and Mr John (both already introduced in Chapter 1).

2. CONSIDERATIONS CONCERNING MS ANNE AND MR JOHN

We earlier introduced Ms Anne and Mr John, both of whom are eligible for secondary cardiovascular prevention in old age. This part of the discussion considers the dilemmas related to these two patients and discusses the results of this thesis in relation to clinical practice.

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.

2.1. Ms Anne and side effects in old age

As mentioned by the GPs in our focus-group discussions (Chapter 3), side-effects often hamper the provisions of prescriptions for preventive medications in old age.

Ms Anne complains of dizziness, which might be caused by the antihypertensive drugs she is taking. This raises a clinical challenge because, with regard to antihypertensive treatment, caution is required with the elderly. Elderly patients are not only at risk for the development of electrolyte disturbance, but are also more likely to develop orthostatic hypotension with subsequent falls.[3] In a Cochrane review on pharmacotherapy for hypertension in the elderly, withdrawals due to adverse effects increased by more than 50% in old age.[4]

Ms Anne also complains of muscle pains. Because she is a punctual and serious woman, she takes her secondary cardiovascular medication, including a statin, very cautiously. In clinical practice, according to the GPs in the focus-group discussions, muscle complaints were often a reason to discontinue preventive treatment with statins. In contrast to this clinical experience, in a recent systematic review/meta-analysis on unintended effects of statins from observational studies in the general population, the absolute excess risk of the observed harmful unintended effects of statins was very small compared to the beneficial effects of statins on major cardiovascular events.[5] However, there was evidence for an increased risk of myopathy, raised liver enzymes, and diabetes. In another systematic review of randomised placebo-controlled trials, only a small minority of symptoms reported on statins were considered to be genuinely due to the statins: almost all would occur just as frequently on placebo.[6] Muscle pains were reported in 7.9% of patients on a statin and by 7.6% of patients receiving placebo. However, the reliability of these findings might be undermined by the poor reporting of side-effects in clinical trial reports in

scientific journals.[7] Also, the nocebo effect (i.e. that patients on placebo tend to describe the same side-effects that are mentioned as possible side-effects of the drugs in the trial) may have influenced these results. With regard to Ms Anne, it remains uncertain as to whether her muscle pains are truly the result of her medication.

It also remains uncertain whether or not she might benefit from statin treatment, because no randomised clinical trials (RCTs) of statin or any other hypocholesterolemic medication have included persons older than 80 years at baseline.[8] However, findings from patients aged 75-80 years enrolled in RCTs, as well as information from observational studies, support statin treatment for secondary prevention of atherosclerotic cardiovascular disease. Harms from statin drugs were not found to be increased in older patients. Because people older than 80 years are biologically heterogeneous with varying life expectancy, and may have frailty or comorbid conditions, and may take multiple medications, the decision to treat with statins should be individualised and, ideally, treatment of hypercholesterolemia for patients at risk of atherosclerotic cardiovascular disease should start before they turn 80 years of age. The STOPP/START criteria do not advise to *start* statin treatment beyond 85 years of age, but also do not advise to *stop* statins in very old age.[9] For the development of appropriate guidelines for statin prescription in the very old, life expectancy, time to benefit, functional status, medication-related adverse events, polypharmacy, and adherence to treatment, are factors that need to be considered.[10] Well-designed clinical trials that account for the heterogeneity of this population are needed and, meanwhile, better clinical guidelines should be developed to address this issue.

With regard to Ms Anne, for secondary cardiovascular prevention, antihypertensive treatment and statin treatment might still be advisable, taking into account her vitality and life expectancy. However, it is reasonable to discuss with her, in shared decision-making, the possibility of a trial period reducing her antihypertensive treatment in order to prevent falls, and/or stopping her statin to find out whether her muscle pains disappear. In this conversation, risk assessment plays an important role. Besides the known traditional risk markers that have limited value in secondary prevention in old age, the results of studies in this thesis now offer additional options to estimate future risk. For Ms Anne, because the severity of her cardiovascular disease is mild her risk for recurrent disease, and cognitive and functional decline, is relatively low. A measurement of NT-proBNP might be considered. If the NT-proBNP level is low, then the risk for recurrent cardiovascular disease is low and the expected benefit of statin treatment is probably limited. However, if the NT-proBNP level is high, the risk for recurrent cardiovascular disease and for functional decline is also high, and Mme Anne will most likely benefit from statin use. This information can be very useful for clinicians, especially when considering whether or not to stop statin treatment.

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.

2.2. Mr John, polypharmacy and adverse drug reactions in old age

Mr John is an example of an old patient with multimorbidity, as is often encountered in general practice. Medication for cardiovascular disease and for all comorbidities, is likely to result in polypharmacy, thereby increasing the risk for drug interactions and adverse reactions.

In the Netherlands, about 30-45% of persons aged 65 years and over use five or more different drugs. For a fifth of the persons aged 75 years and over, the number of drugs prescribed increases to nine. Also in nursing homes, about 40% of persons is either overtreated or undertreated, and drug interactions are common.[11] In older persons, adverse drug reaction- related hospital admissions show a rapidly increasing trend and the incidence is still rising, warranting sustained focus on this problem.[12] Patients aged 75 years and over showed a more than 4-fold increased risk of being hospitalised, compared with those aged 55-64 years. Even when taking into account the number of dispensings, elderly are at an increased risk of being hospitalised for adverse drug reactions.[13] An international review of potentially avoidable hospital admissions showed that the 'top 5' of drug classes involved was (in descending order) antiplatelets, diuretics, NSAIDs, anticoagulants, and opioids.[14] The HARM-WRESTLING report (from the expert group for medication safety interventions to enhance the extramural safety of medication prescriptions in the Netherlands), describes that the most the frequent avoidable medication-related hospital admissions are gastrointestinal bleeding (due to antiplatelets, anticoagulants or NSAIDs), and electrolyte disturbances or dehydration (due to diuretics or ACE/ARB blockers).[15]

The question remains: what advice should be given to Mr John. In secondary cardiovascular prevention, antithrombotic treatment is advised regardless of age. Gastroprotective drugs should be provided in very old age in order to prevent bleeding. With regard to Mr John's traditional risk markers, it is still advisable to encourage him to quit smoking. With regard to the assessment of risk for recurrent cardiovascular disease, the study in Chapter 4 shows that Mr John, with a history of major cardiovascular disease, might have an estimated 5-year risk for development of cardiovascular disease and mortality as high as 50%, as well as an increased risk for cognitive and functional decline. Additional measurement of NT-proBNP level can be helpful (as shown in Chapters 5 and 6). Risk for recurrent cardiovascular disease, cognitive decline and decline in ADL func-

tioning, is even higher when NT-proBNP levels are high. Also, NT-proBNP can be used to optimise treatment for his heart failure. Finally, the findings in Chapter 7 suggest that, if NT-proBNP level is high, the expected benefit of treatment with statins is also high. All this information may encourage the treating physician and Mr John to fully implement secondary cardiovascular preventive medications.

2.3. Mr John and adherence problems

"*Drugs don't work in patients who don't take them*" C. Everett Koop, M.D.

A possible explanation for the observed low prescription rates in old age [1;16;17] may be reduced adherence in old age. Research on adherence in general has shown the following major predictors of poor adherence to medication: depression, cognitive impairment, asymptomatic disease, inadequate follow-up, side-effects of medication, patients' lack of belief in the benefit of treatment, patients' lack of insight into the illness, poor provider-patient relationship, presence of barriers to care or medications, missed appointments, complexity of treatment, and costs of medication.[18] Because these predictors are often highly prevalent in old age, drug adherence in old age generally remains a challenge. A study on non-adherence to chronic prescription medications showed that most patients forgot to take a medication, had run out of the medication, or were careless about taking the medication.[19] However, it appeared that unintentional non-adherence was not random, but predicted by medication beliefs, burden of chronic disease, and sociodemographics.

For Mr John this implies that, when visiting him at home for follow-up, his views and beliefs about medication need to be elucidated. Giving him details about the disease, the risks and benefits, and the proper use of medications, might result in improved adherence. In his case, multi-dose drug dispensing systems might increase adherence, although they have the disadvantage of leading to decreased knowledge about medications in older patients.[20] According to the findings in the focus-group discussions (Chapter 3) and in the literature, Mr John might benefit from individualised, systematic and guideline-based, nurse-based case management, as this often translates into a clinically meaningful reduction in cardiovascular-related morbidity and mortality.[21] Regular proactive follow-up might lead to improvement in treatment uptake. Since his absolute risk for recurrent cardiovascular disease and disability is high (severe history of cardiovascular disease complicated by heart failure, most likely also resulting in high NT-proBNP levels), optimising treatment might considerably reduce his risks.

2.4. Mr John and vulnerability in secondary cardiovascular prevention

Mr John lives alone, is not outgoing, is inactive and is most likely a vulnerable old man.

In the focus-group discussions, the GPs mentioned that 'vulnerability' influences their treatment decisions. In the case of very frail elderly patients they had more doubts as to whether or not to start or continue secondary preventive treatment. Life expectancy and lag time to benefit may contribute to these considerations. However, we observed (Chapter 2) that prescription rates were not independently associated with GPs' judgement of vulnerability; this might be due to the observed strong association of age itself with prescription rates. Also, the use of a more comprehensive frailty instrument might yield different results. However, studies on the association between GPs' judgement of vulnerability, and scores on questionnaires in the four domains of the ISCOPE study, showed that the association between GPs' judgement of vulnerability and scores in the somatic and psychological domains was reliable, although variability was found in scores on the social and functional domains.[22-24]

That GPs' judgement of vulnerability was not associated with reduced prescription rates, might be considered a positive finding. Especially in vulnerable patients, prevention of the recurrence of cardiovascular disease might help preserve independency. However, in already vulnerable patients with polypharmacy, it is important to provide close follow-up for possible adverse effects and be extra vigilant regarding e.g. drug interactions, dehydration, and comorbidity. Ultimately, frailty should not be seen as a reason to withhold care, but rather as a means of delivering it in a more patient-centred fashion.[25]

With regard to our patient, Mr John, a vulnerable person at high risk for recurrent cardiovascular disease, cognitive and functional decline, re-initiation of treatment should be considered. According to the focus-group discussions (Chapter 3) possible benefits and harms of treatment should be discussed, keeping in mind the main aim of secondary cardiovascular prevention in very old age, i.e. to improve quality of life.

3. METHODOLOGICAL CONSIDERATIONS

Several methodological features of the studies in this thesis are now addressed: namely, comparison of risk prediction models, recalibration of risk prediction models, net reclassification improvement (NRI), prediction versus causation, and the possible additional value of the use of directed acyclic graphs (DAGs).

3.1. Comparing risk prediction models

In this thesis we investigated associations between relatively new cardiovascular risk makers and several cardiovascular/functional outcomes in old age. We focused on new risk markers that might be effective for use in secondary cardiovascular prevention in old age. These markers were added to prediction models with the traditional risk markers, and the incremental predictive value was calculated.

Predictive model performance is mostly reported using area under the receiver-operating curves (AUCs) and C-statistics. However, improvements in model performance do not necessarily imply meaningful improvements on a patient level. Also, the better the existing model already performs, the more difficult it is to show significant improvements.[26] A systematic review on comparisons of established risk prediction models for cardiovascular disease showed that authors always report better AUCs for their own models, and that outcome selection bias was often present.[27] Optimism bias was observed in articles in which at least one of the authors was previously involved in the development of one of the models compared in the new research article.

In Chapter 7, we explored the predictive value of NT-proBNP in the secondary prevention population of the PROSPER study. First, the SMART risk score was validated using the same outcome as in the original SMART study population. Also, because we were not involved in the development of the SMART risk score, the possibility of optimism bias was avoided. However, we might have had an overoptimistic view on the performance of NT-proBNP, since we had observed its positive predictive value in the Leiden 85-plus Study. On the other hand, predictive value is often less in a RCT [28], e.g. the PROSPER study, than in observational studies. To validate the observed predictive value of NT-proBNP (Chapters 5 and 6) we tested the performance of NT-proBNP in a different study population. We found that the predictive performance was comparable, thereby strengthening our observation that NT-proBNP is a promising predictor of cardiovascular risk in old age.

In secondary cardiovascular prevention, C-statistics of models with traditional risk markers are often modest, leaving room for improvement.[29] Thompson et al. found C-statistics of 0.60 and 0.62 for the Essen stroke Risk Score and for the Stroke Prognosis Instrument, respectively.[29] Compared to these latter C-statistics, the incremental predictive value of NT-proBNP in this thesis was consistently better, with an AUC of 0.66 (Δ

AUC 0.05) in the PROSPER study population, and 0.67 (Δ AUC 0.08) in the Leiden 85-plus Study. This is in line with a review (including studies in younger populations) by di Angelantonio et al., in which AUCs ranged from 0.65 to 0.80 after addition of NT-proBNP to varying existing risk prediction models in secondary cardiovascular prevention (delta AUC with addition of NT-proBNP ranging from 0.02 to 0.10).[30]

This underlines that NT-proBNP might be very useful in risk prediction in the ageing population. However, as stated, improvement in model prediction does not necessarily mean improvement on the individual patient level. Therefore, we discuss below the net reclassification improvement (NRI), a calculation of the number of patients that are correctly reclassified by adding a new risk marker to a (traditional) model. However, we first address the use of risk prediction models and the need for recalibration of risk prediction models in different study populations.

3.2 Recalibration

In this thesis the incremental predictive value of new biomarkers was investigated. We added new biomarkers to the currently used risk prediction models. For example, in Chapter 7 we describe the performance of a model with age and sex, a model with traditional risk markers, and a model with the recalibrated SMART risk score. This SMART risk score includes traditional risk markers, high sensitive C-reactive protein, kidney function, history of coronary heart disease, history of cerebrovascular disease, and history of abdominal aortic aneurism. The SMART risk score had to be recalibrated for the PROSPER study population. Age differences might have contributed to the difference in performance of the SMART model, as the PROSPER study population is generally older than the population in which the SMART risk score was originally developed. In the PROSPER study population the SMART risk score overestimated risk for recurrent cardiovascular disease, especially in patients identified as higher risk patients.

The new AHA-ACC-ASCVD risk score has also been shown to overestimate risk in a different study population. This emphasises the need for calibration of newly developed risk scores in different populations, as the score will always predict best in the population for which it was developed.[31]

In general, when assessing the impact of the addition of new biomarkers to standard risk scores, the method used to control for standard predictors influences the apparent incremental performance.[32] Specifically, adding a new biomarker to a model with a published risk score usually leads to a greater increase in the C-statistic. Reliance on a published risk score might give an overly optimistic view of the true predictive ability of the biomarker. Therefore, assessment of the incremental yield of a new biomarker for cardiovascular disease should be performed by re-estimating the coefficients for the standard predictors using the current study data, as opposed to using coefficients

of the formerly published risk score. Therefore, in Chapter 7 we used the re-estimated coefficients for the traditional risk markers, and the recalibrated SMART risk score.

With the use of this proper technique, NT-proBNP still improved the AUC when added to a simple model including only age and sex, the traditional model and the SMART risk score, indicating its robust association with the cardiovascular endpoint, independent of the traditional risk markers and the SMART risk score.

3.3. Net Reclassification Index (NRI)

The additional predictive value of NT-proBNP with regard to incident cardiovascular disease and mortality was investigated in Chapter 5 to 7. NT-proBNP was added to the currently used risk prediction models and improvement in C-statistics was calculated. However, for clinicians it is crucial that the addition of new risk markers also improves risk classification on the individual level. Therefore, in this thesis, reclassification improvements are also presented (Chapters 5 to 7). Unlike primary prevention, in secondary prevention there are no risk categories with definite percentages of predicted risk and, therefore, the category-free net reclassification improvement (category-free NRI) was calculated.[33;34] This is a more objective reclassification and easy to compare across studies. The choice of risk cut-offs and the number of categories can have a considerable impact on the NRI, and only a limited number of categories should be used if categories have a strong clinical importance.[35;36] The category-free NRI represents how many participants are correctly reclassified when a new predictor is added to a risk prediction model. First, risk is calculated for each individual participant with a model including the established predictors and, thereafter, risk is calculated with the addition of the new predictor to the model. Participants with a higher calculated risk after addition of the new predictor are reclassified up, and participants with a lower predicted risk after addition of the new risk marker are reclassified down. In the group that actually experiences the endpoint, correctly reclassified persons are participants with a higher predicted risk after addition of the new risk marker, whereas participants with a lower predicted risk are incorrectly reclassified down. For calculation of net benefit within the group that experiences the endpoint, these participants are subtracted from the participants that are correctly reclassified up. In the group that does not experience the endpoint, correctly reclassified persons are participants with a lower predicted risk after addition of the new risk marker, whereas the participants with a higher predicted risk after addition of the new risk marker are incorrectly reclassified up. Thereafter, the net reclassification improvement NRI is calculated as follows:

$$NRI = P(up|event) - P(down|event) + P(down|nonevent) - P(up|nonevent)$$

In our population-based sample of participants with a history of cardiovascular disease in the Leiden 85-plus Study (Chapter 5), category-free NRI for addition of the severity of the cardiovascular disease history to the traditional risk markers was 27%. For addition of NT-proBNP this was 39% (58.7% of participants reclassified up, minus 41.3% reclassified down in the group that experienced the endpoint, plus 61.3% reclassified down, minus 38.7% reclassified up in the group that did not experience the endpoint). These numbers indicate that 16.4% was correctly reclassified up and 22.6% correctly reclassified down, indicating that NT-proBNP can be used both ways, i.e. it better identifies high as well as low risk persons. In the PROSPER study population (including patients aged 75 years and over) the category-less NRI with the addition of NT-proBNP to the minimal model, including only age and sex, was similar (41%)

In conclusion, the addition of NT-proBNP to simple or more complex risk prediction models not only improves model performance, but also improves risk prediction on the individual patient level. This implies that NT-proBNP can be useful in clinical practice when estimating individual risk for (recurrent) cardiovascular disease in old age.

3.4. Prediction versus causation

Our study in Chapter 6 shows that NT-proBNP was associated with cognitive decline over time. Although the exact cause or mechanism underlying this association remains unknown, the question arises as to whether these associations also have a causal relationship.

To address this question we need more insight into NT-proBNP itself: what it is and where it originates from. As described in Chapter 6, proBNP (split into the biologically active brain natriuretic peptide (BNP) and the biologically inactive N-terminal pro-brain natriuretic peptide), is secreted by the muscle cells of the heart in response to ventricular wall stress. BNP leads to increased diuresis, relaxation of vascular smooth muscle cells and inhibition of the renin-angiotensin-aldosterone axis, causing a reduction in blood pressure and ventricular preload. NT-proBNP is highly elevated in heart failure patients. Levels of NT-proBNP are also increased in acute coronary syndrome, stable angina pectoris, pulmonary embolism, atrial fibrillation, left ventricular hypertrophy, chronic obstructive pulmonary disease, and renal dysfunction.[37;38] In the elderly, including the presumed 'healthy' elderly, plasma levels of NT-proBNP are generally elevated and alterations in cardiac structure or function (such as age-related myocardial fibrosis and subtle diastolic dysfunction not detectable by current techniques) as well as reduced renal clearance, are suggested to be involved.[39;40]

In a study on possible biomarkers for the development of dementia, NT-proBNP was found to be a stable candidate protein for both the diagnosis and progression of Alzheimer dementia, as it was significantly higher in participants with mild cognitive impairment and in those with Alzheimer dementia.[41] In the PROSPER study, NT-proBNP

was also associated with cognitive decline.[42] Although this confirms the association, we still lack information on possible causal mechanisms.

Several mechanisms have been suggested regarding the association between cardiovascular disease and cognitive impairment. Abete et al. describe a heart-brain continuum hypothesis and suggest that the cardiovascular disease continuum begins with the traditional risk markers, initiating the process that leads to tissue damage; thereafter, the presence of hypertension during middle age represents the key point for the development of left ventricular hypertrophy and atrial fibrillation and all these conditions, together with coronary artery disease, may lead to chronic heart failure, cerebral hypoperfusion and embolic stroke, eventually leading to cognitive decline at the end of this cardiovascular continuum.[43] NT-proBNP might be a sensitive marker of this cascade as it is elevated in heart failure. This is supported by a study in an older population of patients with heart failure, showing that ejection fractions below 30% were indeed associated with worse memory function.[44] In patients with severe heart disease and congestive heart failure, a high frequency of cognitive abnormalities has been reported.[45;46] In further support of this possible pathophysiologic mechanism, a meta-analysis showed that both Alzheimer disease and vascular dementia are associated with decreased cerebral blood flow velocities.[47] In our study, exclusion of participants with clinical heart failure did not change the results; perhaps subclinical heart failure also affects the brain.

Intermittent atrial fibrillation in persons with high NT-proBNP, with subsequent embolic brain infarcts impairing cognitive function, has also been suggested as a causal mechanism.[48] This might be supported by our data (Chapter 6, as we also observed high NT-proBNP levels in persons with atrial fibrillation, as well as a high incidence of atrial fibrillation during 5-year follow-up in the highest tertile of NT-proBNP.

The possible association between vascular disease in general and cognitive impairment is also suggested by the finding that patients with both vascular disease and Alzheimer pathology have poorer intellectual function than patients with Alzheimer abnormalities only.[49;50] As NT-proBNP is associated with both atherosclerosis and (via heart failure) with decreased perfusion of the brain, these could be underlying causal mechanisms of the observed association between NT-proBNP and cognition.

In conclusion, although an association between NT-proBNP and cognition was observed, more research is needed to clarify the causal mechanisms. In the ageing society, prevention of cognitive decline is important and the promising role of NT-proBNP in the prediction of cognitive decline needs to be clarified. It will be interesting to investigate the presence of macro, micro and subcortical brain infarcts, lacunae, white matter lesions, and Alzheimer pathology in brain specimens of patients whose cardiac conditions, BNP, and NT-BNP were measured during life, and also to perform MRI during life to quantify these pathologies to some extent.[48]

3.5. Directed acyclic graphs (DAGs)

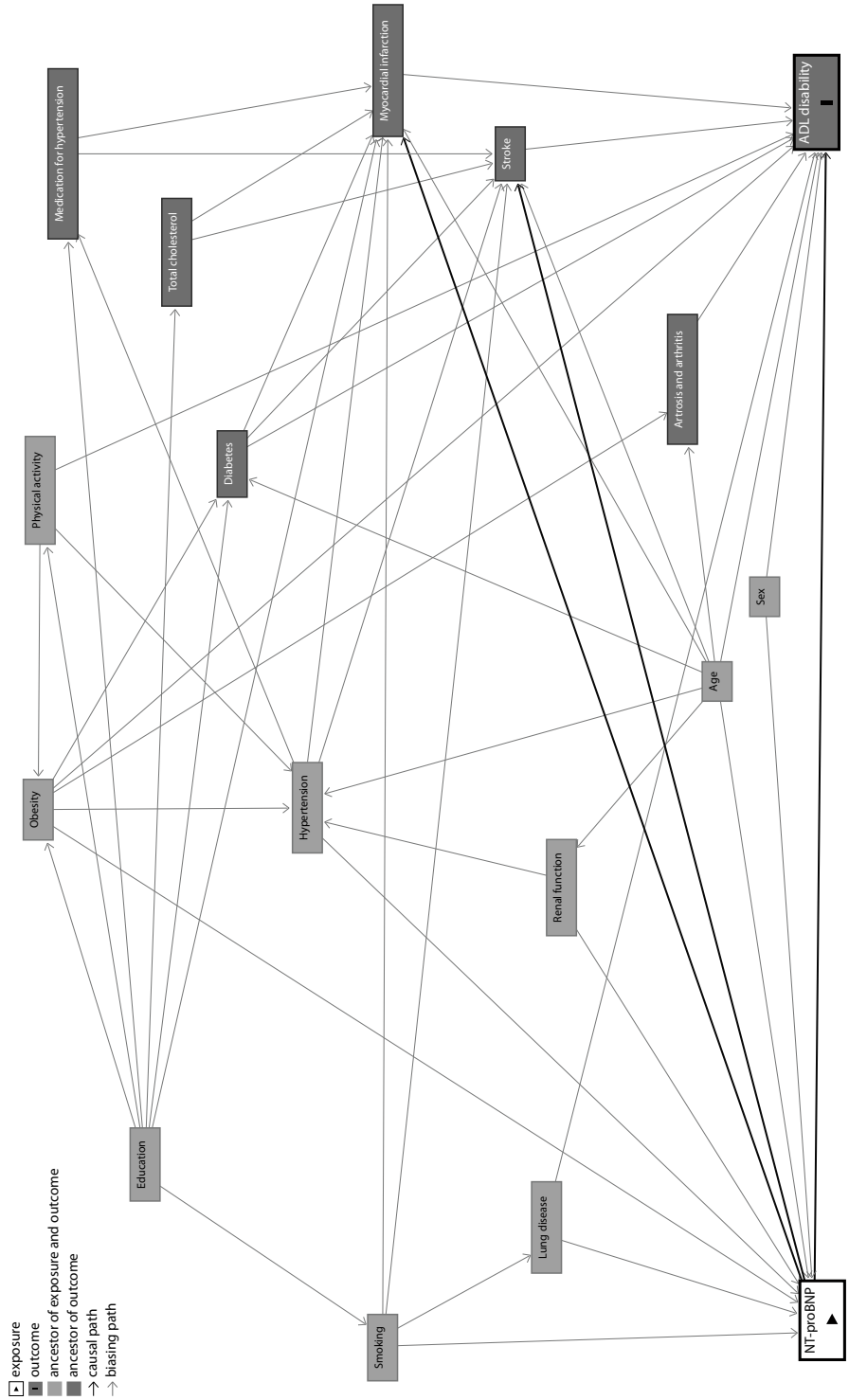
When estimating the consequence of an exposure on a health outcome, estimation of its effect is often complicated by confounding bias.[51;52] Although this can often be dealt with by controlling for the variables causing the confounding (if measured) in the statistical analysis, residual confounding is always possible due to currently unknown confounders. Common statistical methods to address confounding include multivariable regression models with adjustment for selected confounding variables, or stratification on those variables.

For example, in the association between NT-proBNP and ADL disability (Chapter 6), we first analysed crude associations of gender-specific tertiles of NT-proBNP and ADL disability and then presented associations adjusted for the traditional risk markers, BMI, kidney function, use of medication for hypertension, as well as additionally adjusting for prevalent cardiovascular and cerebrovascular disease. However, the results remained basically the same.

The question remains as to which measured variables need to be controlled for in order to remove confounding. One approach to confounder selection is based on causal diagrams. A directed acyclic graph (DAG) is a visual representation of the causal relationships believed to exist between the variables of interest, including the exposure, outcome and potential confounding variables. After creating a causal diagram for the research question, an intuitive and easy-to-use set of rules can be applied, based on a foundation of rigorous mathematics, to decide which measured variables must be controlled for in the statistical analysis to remove confounding to the extent possible using the available data. [53] We illustrate this by constructing a concept of a causal diagram for our research question: 'Does NT-proBNP independently affect the risk for the development of ADL disability?'

First, we have to define possible confounders. Age, sex, smoking, diabetes, cholesterol, hypertension, medication for hypertension, obesity, kidney function, physical activity, arthrosis and arthritis, chronic lung disease, myocardial infarction, and stroke, are all potential confounders when exploring the association between NT-proBNP and ADL disability. In our analysis in Chapter 6, we adjusted for known cardiovascular risk predictors, but did not include arthrosis and arthritis, or chronic lung disease. Although the presence of chronic lung disease might lead to ADL disability, chronic lung disease is also associated with higher NT-proBNP levels.

We added all these confounders in a DAG, using Daggitty (http://www.dagitty.net/) and defined the associations between the variables using common sense and known associations. It should be noted that we did not elaborate on finding evidence for all the arrows in the current DAG, so it is still possible to discuss possible associations and the directions of the arrows in the graph in order to optimise this causal diagram. Our first try-out resulted in the following DAG.


exposure
outcome
ancestor of exposure and outcome
ancestor of outcome
causal path
biasing path
NT-proBNP
ADL disability
Myocardial infarction
Stroke
Medication for hypertension
Total cholesterol
Diabetes
Physical activity
Obesity
Hypertension
Education
Smoking
Lung disease
Renal function
Artrosis and arthritis
Age
Sex

On the left, NT-proBNP is the determinant and, on the right, ADL disability is the outcome. All possible confounders (with arrows indicating their associations) are added to the graph.

Then, a computerised system automatically composes all possible minimal adjustment sets that prevent over-adjustment for interrelated variables. According to the arrows in this DAG, two minimal sufficient adjustment sets for estimating the total effect of NT-proBNP on ADL disability are identified:

– age, sex, hypertension, obesity, physical activity, smoking and lung disease
– age, sex, hypertension, obesity, renal function, smoking and lung disease

In conclusion, DAGs can help researchers to identify a minimal adjustment set, thereby preventing over adjustment. Also, it revealed a limitation of the study in Chapter 6, i.e. we could have made a minimal adjustment set for the association between NT-proBNP and ADL functioning over time, with a small selection of traditional risk markers and cardiovascular disease history, but with inclusion of lung disease.

4. OVERALL PERSPECTIVE

Finally, we present some points related to patient perspectives, societal perspectives, clinical implications, and some recommendations for future research.

4.1. Secondary cardiovascular prevention: what is the patient's perspective?

In this thesis, although we did not address patients' perspectives on secondary cardiovascular prevention in old age, this could be an interesting item for future research. In a survey among persons at increased risk for stroke, many elderly individuals were of the opinion that they currently experienced a high quality of life, but feared development of a major stroke; many considered this to be worse than death.[54] In our focus-group discussions (Chapter 3) GPs also mentioned that 'anticipated regret' (i.e. fearing the development of stroke after stopping preventive treatment) was a strong motivator to continue treatment.

Historically, patient-centred outcomes are often ignored in cardiovascular research. A review on the reporting of patient-centred outcomes in heart failure trials showed that of all trials, about 60% also measured outcomes in the functional, psychological and social domain.[55] That review showed increasing attention for more patient-relevant outcomes over time. Although this is promising, patients' individual goal attainments were universally absent. For continued progress in patient-centred care, we need to develop these outcomes, study their merits and pitfalls, and intensify their use in research.

Patient views on secondary cardiovascular prevention in old age are important, particularly since older persons' willingness to take medication for primary cardiovascular disease prevention is relatively insensitive to its benefit but highly sensitive to its adverse effects.[56] Therefore, clinical guidelines and decisions about prescribing these medications to older persons need to focus on both the benefits and harms [56]; this idea was confirmed by our focus-group study (Chapter 3). With respect to the burden of taking daily medications, it was reported that of 1,000 residents in the USA aged 30 years and over, about a third was willing to trade some time at the end of life to avoid taking daily medicine for cardiovascular disease.[57] This implies that more research on patients' views of secondary cardiovascular preventive medication in old age might reveal novel and unexpected viewpoints, and might further explain underlying reasons for the low prescription rates observed.

4.2. Perspectives for the ageing society: uncertainty

Although older patients that have survived their cardiovascular disease are at high risk of future events, cognitive and ADL decline, only half receive at least a lipid-lowering drug and an antithrombotic drug. Prescription rates decline even more with increasing age (Chapter 2), which might lead to unnecessary morbidity and mortality. In the focus-group discussions with GPs about secondary cardiovascular prevention in old age (Chapter 3), the main theme that emerged was 'uncertainty' , which is often difficult for physicians. As Alexander Smith argues in his report 'Uncertainty: the other side of prognosis', there is increased interest in prognosis as it plays a central role in medical decision-making. Patients mention that understanding prognosis is important for making life choices. However, there will always be some uncertainty in prognosis and this uncertainty is difficult to deal with. Worrying about the future may impede the ability to enjoy the present. Clinicians may also have trouble with prognostic uncertainty. Smith believes that physicians need to recognise their reaction to uncertainty and recognise how these reactions may influence their conversations with patients. In many respects, the primary communication task of clinicians is the management of uncertainty and, perhaps, nowhere is this clearer than in communication about prognosis. By normalising uncertainty and attending to the affective response to living in the face of an uncertain future, we may help our patients and their families to enjoy the time they have now.[58] Openness about uncertainty and shared decision-making can help physicians in their conversations with old patients with a history of cardiovascular disease.

Iona Heath recently stated that '… uncertainty exists in the gap between the territory of human suffering and the map of biomedical science…' and that '…the task of making the medical map useful to those trapped within the territory of suffering is, and will always be, fraught with uncertainty, because of the vast extent and infinite variation in the territory and because of the comparatively rudimentary nature of the map. But the

uncertainty and doubt that clinicians experience every day are also what makes new knowledge and understanding possible…'. [59]

Specifically with regard to uncertainty in secondary cardiovascular prevention in old age, in this thesis we may have created 'a mark on the medical map'. Information on the severity of the cardiovascular disease history and the use of NT-proBNP may help physicians when facing dilemmas in the treatment of old patients with a history of cardiovascular disease. However, because of the uncertainty about the benefits and harms in each individual (with their unique comorbidities, side-effects, and cardiovascular disease history) shared decision-making between clinician and patient is mandatory; moreover, decisions should always be re-evaluated when the patient's status changes.[60] Appropriate medications often depend on the remaining life expectancy, time to benefit, treatment targets, and goals of care.[61] All these aspects need to be taken into account for our older patients. Clinical decision-making requires judgement because the evidence is imperfect and treatment decisions have to consider all the patient's circumstances and preferences. It may sometimes be better to stop or even not start preventive medications. Also, deprescribing in older patients is receiving more attention [62-69] and might have possible benefits, such as improved adherence by means of reducing polypharmacy, increased medication knowledge, increased engagement in medication management, and resolution of adverse drug reactions. In view of all the uncertainty that comes with complex morbidity in old age, treatment decisions should be highly individualised with the ultimate aim not only to prolong life, but to improve the patient's quality of life.

4.3. Guidelines in the ageing society

As described in Chapter 3, GPs are hindered by the lack of age-specific guidelines for secondary cardiovascular prevention in old age. The ageing society would benefit from guidelines that provide more guidance about which treatments are most likely to benefit and least likely to harm in old age, also taking multi-morbidity into account. A qualitative study among staff physicians and nurse practitioners on the influence of patient age and comorbid burden on the usefulness of national heart failure guidelines, showed that clinicians perceive these guidelines to be substantially less useful in patients of older age and with greater comorbid burden.[70] Concerns about the clinical and pharmacologic complexity of these patients and the expected benefits of drug therapy were commonly invoked as reasons for this scepticism. Simple versions of guidelines only recommending treatments to consider starting, avoiding, or stopping, would be useful as a potential starting point, while more complex fully cross-referenced versions should be developed, with explicit guidance about treatments most likely to benefit and least likely to harm in old age, informed by the patterns of comorbidity that are most

common).[71] Guidelines should focus on providing recommendations and promoting choice, but leaving room for opinions about how to interpret the evidence.[72]

4.4. Ageing and secondary cardiovascular prevention in general

With regard to the overall scope, if the results of this thesis do help to improve clinical practice and the prescription of secondary cardiovascular preventive medications increases, this will probably result in more patients surviving up to very old age, which may pose a problem for society. However, since secondary cardiovascular prevention is probably as effective in older people as it is in younger people, with benefits increased in view of raised levels of absolute risk [73], it may help to reduce individual and societal effects on disability and dependence. A possible hopeful finding for future generations is that a Danish cohort study reported improvement of physical and cognitive functioning of people aged over 90 years over the last decade, which suggests that more people are living to older ages with better overall functioning.[74]

Improved identification and follow-up of patients eligible for secondary preventive measures in old age, seems worthwhile. If these patients are invited for a consultation, the benefits and harms can be evaluated individually and treatment decisions can be taken accordingly. Then we will be more certain that there is no 'under treatment' in old age, and more timely and appropriate treatment for each individual patient.

4.5. Clinical implications

The results of the studies described in this thesis give rise to the following recommendations related to aspects of secondary cardiovascular prevention in old age:

Organisation of care:

- To prevent patients falling into the gap between secondary and primary care, GPs are advised to regularly check whether they have correctly registered (ICPC) all their old patients with a history of cardiovascular disease in the electronic medical records
- Annual follow-up of these patients, preferably organised by a practice nurse, is mandatory. Computerised systems can help identify the (unintentional) non-adherence, untreated patients, and patients not showing for follow-up. Thereafter, in shared decision-making with each individual old patient, the pros and cons of secondary preventive treatment can be carefully weighed, taking into account the individual preferences, vulnerability, comorbidities, polypharmacy, lag time to benefit, side-effects, vitality, expected benefit of treatment, and priorities of care.

Risk assessment:

- The severity of the cardiovascular disease history should be taken into account when estimating the risk for recurrent cardiovascular disease and cardiovascular mortality in old age
- NT-proBNP values can be used as a predictor of recurrent cardiovascular disease in old age
- GPs should be aware that the SMART risk score overestimates risk in old age

Prognosis:

- The severity of the cardiovascular disease history and use of NT-proBNP levels can help estimate the risk for cognitive decline and ADL disability

Treatment:

- When in doubt as to whether or not to continue, start, or stop statin treatment, NT-proBNP levels can be helpful. However, before the results concerning NT-proBNP and prediction of treatment effect of statins (Chapter 7) can be generally applied in guidelines for secondary prevention in old age, replication of these results in different study populations is required
- Specified guidelines should be developed for old patients with a history of cardiovascular disease, including advice on frequently encountered problems with polypharmacy and comorbidity

4.6. Recommendations for future research

Patients' perspectives on secondary preventive treatment should be further investigated. Underlying reasons for not starting or stopping secondary preventive medication, as well reasons for non-adherence in old age, need to be further explored. Establishing whether non-adherence is intentional or unintentional, particularly among frail or isolated patients, might shed more light on the observed low prescription rates in old age. Research on the decision-making processes of physicians and patients leading to non-prescribing or selective intentional non-adherence amongst older adults with multiple medical problems and a history of cardiovascular disease, will provide more insight into the processes underlying the low prescription rates observed.

Research on ways to improve adherence in old age will help optimise treatment. Evaluating whether structural involvement of a practice nurse in evaluation and follow-up of all old patients with a history of cardiovascular disease indeed improves prescription rates is a first step to be taken and, ideally, this should be accompanied by the qualitative research described above.

Future dedicated research, that accounts for the heterogeneity of older patients with a history of cardiovascular disease, is necessary to collect evidence and data for

the development of tailored guidelines. Inclusion of old and multi-morbid patients in clinical trials is of pivotal importance, in order to reveal the real-life benefits of secondary preventive medication in community-dwelling patients with multi-morbidity in very old age.

Additionally, a new approach to research might be to embed randomisation in a large, free-living cohort of persons that spans the entire life spectrum. This would allow to test interventions at various stages of the cardiovascular disease process and provide sufficient power to reliably assess treatment. Randomisation would minimise bias and confounding. Nowadays, this can be easily undertaken, since randomisation can be included in the electronic medical records, which become the case report form for an RCT. Also, electronic sources of data might be used in clinical investigations.[75]

Our finding that NT-proBNP is associated with treatment effect of statins in old age should be further investigated in different study populations in old age.

Finally, further implementation studies with addition of NT-proBNP in risk assessment and subsequent treatment decisions, will help clarify whether this strategy indeed improves the prognosis of very old patients with a history of cardiovascular disease.

REFERENCES

1 Koopman C, Vaartjes I, Heintjes EM et al. Persisting gender differences and attenuating age differences in cardiovascular drug use for prevention and treatment of coronary heart disease, 1998-2010. *Eur Heart J* 2013;34:3198-3205.

2 de Ruijter W, Westendorp RG, Assendelft WJ et al. Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. *BMJ* 2009;338:a3083.

3 Mohebi R, Mohebi A, Ghanbarian A, Momenan A, Azizi F, Hadaegh F. Is systolic blood pressure below 150 mm Hg an appropriate goal for primary prevention of cardiovascular events among elderly population? *J Am Soc Hypertens* 2014;8:491-497.

4 Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. *Cochrane Database Syst Rev* 2009;CD000028.

5 Macedo AF, Taylor FC, Casas JP, Adler A, Prieto-Merino D, Ebrahim S. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. *BMC Med* 2014;12:51.

6 Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *Eur J Prev Cardiol* 2014;21:464-474.

7 Goldacre B. Meta-analysis of side effects of statins shows need for trial transparency. *BMJ* 2014; 348:g2940.

8 Strandberg TE, Kolehmainen L, Vuorio A. Evaluation and treatment of older patients with hypercholesterolemia: a clinical review. *JAMA* 2014;312:1136-1144.

9 O'mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213-218.

10 Noaman S, Ibrahim JE, Grenfell R. Prescribing Statins for Cardiovascular Disease Prevention in the Old: an Absence of Evidence and an Absence of Guidelines. *Heart Lung Circ* 2014;23:619-624.

11 Rijksinstituut voor Volksgezondheid en Milieu, polypharmacy report. Available from: URL: http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2013/juli/Polyfarmacie_bij_kwetsbare_ouderen_Inventarisatie_van_risico_s_en_mogelijke_interventiestrategie%C3%ABn

12 Hartholt KA, van d, V, Looman CW et al. Adverse drug reactions related hospital admissions in persons aged 60 years and over, The Netherlands, 1981-2007: less rapid increase, different drugs. *PLoS One* 2010;5:e13977.

13 Ruiter R, Visser LE, Rodenburg EM, Trifiro G, Ziere G, Stricker BH. Adverse drug reaction-related hospitalizations in persons aged 55 years and over: a population-based study in the Netherlands. *Drugs Aging* 2012;29:225-232.

14 Howard RL, Avery AJ, Slavenburg S et al. Which drugs cause preventable admissions to hospital? A systematic review. *Br J Clin Pharmacol* 2007;63:136-147.

15 Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, Harm-Wrestling report. Available from: URL: http://www.knmp.nl/downloads/harmwrestlingrapportdefnov2009.pdf

16 Eissa A, Krass I, Bajorek BV. Use of medications for secondary prevention in stroke patients at hospital discharge in Australia. *Int J Clin Pharm* 2014;36:384-393.

17 Hanlon JT, Schmader KE, Ruby CM, Weinberger M. Suboptimal prescribing in older inpatients and outpatients. *J Am Geriatr Soc* 2001;49:200-209.

18 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487-497.

19 Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? *BMC Health Serv Res* 2012;12:98.

20 Kwint HF, Stolk G, Faber A, Gussekloo J, Bouvy ML. Medication adherence and knowledge of older patients with and without multidose drug dispensing. *Age Ageing* 2013;42:620-626.

21 Berra K. Does nurse case management improve implementation of guidelines for cardiovascular disease risk reduction? *J Cardiovasc Nurs* 2011;26:145-167.

22 Drewes YM, Blom JW, Assendelft WJ, Stijnen T, den Elzen WP, Gussekloo J. Variability in vulnerability assessment of older people by individual general practitioners: a cross-sectional study. *PLoS One* 2014;9:e108666.

23 Drewes YM, Koenen JM, de Ruijter W et al. GPs' perspectives on preventive care for older people: a focus group study. *Br J Gen Pract* 2012;62:e765-e772.

24 Drewes YM, den Elzen WP, Mooijaart SP, de Craen AJ, Assendelft WJ, Gussekloo J. The effect of cognitive impairment on the predictive value of multimorbidity for the increase in disability in the oldest old: the Leiden 85-plus Study. *Age Ageing* 2011;40:352-357.

25 Afilalo J, Alexander KP, Mack MJ et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014;63:747-762.

26 Tzoulaki I, Liberopoulos G, Ioannidis JP. Assessment of claims of improved prediction beyond the Framingham risk score. *JAMA* 2009;302:2345-2352.

27 Siontis GC, Tzoulaki I, Siontis KC, Ioannidis JP. Comparisons of established risk prediction models for cardiovascular disease: systematic review. *BMJ* 2012;344:e3318.

28 Tzoulaki I, Siontis KC, Ioannidis JP. Prognostic effect size of cardiovascular biomarkers in datasets from observational studies versus randomised trials: meta-epidemiology study. *BMJ* 2011;343: d6829.

29 Thompson DD, Murray GD, Dennis M, Sudlow CL, Whiteley WN. Formal and informal prediction of recurrent stroke and myocardial infarction after stroke: a systematic review and evaluation of clinical prediction models in a new cohort. *BMC Med* 2014;12:58.

30 Di Angelantonio E, Chowdhury R, Sarwar N et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. Circulation 2009;120:2177-2187.

31 DeFilippis AP, Young R, Carrubba CJ et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 2015;162: 266-275.

32 Xanthakis V, Sullivan LM, Vasan RS et al. Assessing the incremental predictive performance of novel biomarkers over standard predictors. *Stat Med* 2014;33:2577-2584.

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

34 Pencina MJ, d'Agostino RB, Vasan RS. Statistical methods for assessment of added usefulness of new biomarkers. *Clin Chem Lab Med* 2010;48:1703-1711.

35 Muhlenbruch K, Heraclides A, Steyerberg EW, Joost HG, Boeing H, Schulze MB. Assessing improvement in disease prediction using net reclassification improvement: impact of risk cut-offs and number of risk categories. *Eur J Epidemiol* 2013;28:25-33.

36 Leening MJ, Cook NR. Net reclassification improvement: a link between statistics and clinical practice. *Eur J Epidemiol* 2013;28:21-23.

37 Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 2006;92:843-849.

38 DeFilippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. *Am J Cardiol* 2008;101:82-88.

39 Alehagen U, Goetze JP, Dahlstrom U. Reference intervals and decision limits for B-type natriuretic peptide (BNP) and its precursor (Nt-proBNP) in the elderly. *Clin Chim Acta* 2007;382:8-14.

40 Rutten FH, Hoes AW. B-type natriuretic peptide assays for detecting heart failure in the elderly: same value as those in the younger? *Int J Cardiol* 2008;125:161-165.

41 Marksteiner J, Imarhiagbe D, Defrancesco M, Deisenhammer EA, Kemmler G, Humpel C. Analysis of 27 vascular-related proteins reveals that NT-proBNP is a potential biomarker for Alzheimer's disease and mild cognitive impairment: a pilot-study. *Exp Gerontol* 2014;50:114-121.

42 Wijsman LW, Sabayan B, van Vliet P et al. N-terminal pro-brain natriuretic peptide and cognitive decline in older adults at high cardiovascular risk. *Ann Neurol* 2014;76:213-222.

43 Abete P, Della-Morte D, Gargiulo G et al. Cognitive impairment and cardiovascular diseases in the elderly. A heart-brain continuum hypothesis. *Ageing Res Rev* 2014;18:41-52.

44 Festa JR, Jia X, Cheung K et al. Association of low ejection fraction with impaired verbal memory in older patients with heart failure. *Arch Neurol* 2011;68:1021-1026.

45 Zuccala G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. *J Neurol Neurosurg Psychiatry* 1997;63:509-512.

46 Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 2007;9:440-449.

47 Sabayan B, Jansen S, Oleksik AM et al. Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: a meta-analysis of transcranial Doppler studies. *Ageing Res Rev* 2012;11:271-277.

48 Caplan LR. Cognitive decline and brain natriuretic peptide: how are they related? *Ann Neurol* 2014;76:165-167.

49 Gorelick PB, Scuteri A, Black SE et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011;42:2672-2713.

50 Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA* 1997;277:813-817.

51 Williamson EJ, Aitken Z, Lawrie J, Dharmage SC, Burgess JA, Forbes AB. Introduction to causal diagrams for confounder selection. *Respirology* 2014;19:303-311.

52 Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008;8: 70.

53 Rohrig N, Strobl R, Muller M et al. Directed acyclic graphs helped to identify confounding in the association of disability and electrocardiographic findings: results from the KORA-Age study. *J Clin Epidemiol* 2014;67:199-206.

54 Samsa GP, Matchar DB, Goldstein L et al. Utilities for major stroke: results from a survey of preferences among persons at increased risk for stroke. *Am Heart J* 1998;136:703-713.

55 Blom JW, El AM, Wopereis DM, Glynn L, Muth C, van Driel ML. Reporting of patient-centred outcomes in heart failure trials: are patient preferences being ignored? *Heart Fail Rev* 2015;20: 385-392.

56 Fried TR, Tinetti ME, Towle V, O'Leary JR, Iannone L. Effects of benefits and harms on older persons' willingness to take medication for primary cardiovascular prevention. *Arch Intern Med* 2011;171: 923-928.

57 Hutchins R, Viera AJ, Sheridan SL, Pignone MP. Quantifying the Utility of Taking Pills for Cardiovascular Prevention. *Circ Cardiovasc Qual Outcomes* 2015;8:155-63

58 Smith AK, White DB, Arnold RM. Uncertainty--the other side of prognosis. *N Engl J Med* 2013;368: 2448-2450.

59 Heath I. Role of fear in overdiagnosis and overtreatment—an essay by Iona Heath. *BMJ* 2014;349.

60 Tinetti ME. The gap between clinical trials and the real world: extrapolating treatment effects from younger to older adults. *JAMA Intern Med* 2014;174:397-398.

61 Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med* 2006;166:605-609.

62 Schuling J, Gebben H, Veehof LJ, Haaijer-Ruskamp FM. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. *BMC Fam Pract* 2012;13: 56.

63 Frank C, Weir E. Deprescribing for older patients. *CMAJ* 2014;86:1369-1376.

64 Scott IA, Gray LC, Martin JH, Pillans PI, Mitchell CA. Deciding when to stop: towards evidence-based deprescribing of drugs in older populations. *Evid Based Med* 2013;18:121-124.

65 Reeve E, Wiese MD, Hendrix I, Roberts MS, Shakib S. People's attitudes, beliefs, and experiences regarding polypharmacy and willingness to Deprescribe. *J Am Geriatr Soc* 2013;61:1508-1514.

66 Hilmer SN, Gnjidic D, Le Couteur DG. Thinking through the medication list - appropriate prescribing and deprescribing in robust and frail older patients. *Aust Fam Physician* 2012;41:924-928.

67 Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Review of deprescribing processes and development of an evidence based, patient-centred deprescribing process. *Br J Clin Pharmacol* 2014.

68 Reeve E, Wiese MD. Benefits of deprescribing on patients' adherence to medications. *Int J Clin Pharm* 2014;36:26-29.

69 Topinkova E, Baeyens JP, Michel JP, Lang PO. Evidence-based strategies for the optimization of pharmacotherapy in older people. *Drugs Aging* 2012;29:477-494.

70 Steinman MA, Sudore RL, Peterson CA, Harlow JB, Fried TR. Influence of patient age and comorbid burden on clinician attitudes toward heart failure guidelines. *Am J Geriatr Pharmacother* 2012;10: 211-218.

71 Guthrie B, Payne K, Alderson P, McMurdo ME, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. *BMJ* 2012;345:e6341.

72 Krumholz HM. The new cholesterol and blood pressure guidelines: perspective on the path forward. *JAMA* 2014;311:1403-1405.

73 Prince MJ, Wu F, Guo Y et al. The burden of disease in older people and implications for health policy and practice. *Lancet* 2015;385:549-62.

74 Christensen K, Thinggaard M, Oksuzyan A et al. Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. *Lancet* 2013;382: 1507-1513.

75 Antman EM, Jessup M. Clinical practice guidelines for chronic cardiovascular disorders: a road-map for the future. *JAMA* 2014;311:1195-1196.