Secondary cardiovascular prevention in old age

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Chapter 9

Summary

In old age cardiovascular disease is highly prevalent and a major cause of morbidity, functional decline and mortality (**Chapter 1**). In secondary cardiovascular prevention all guidelines advocate life-long preventive treatment. However, current literature on prescription rates in secondary cardiovascular prevention in very old age shows that prescription rates of secondary preventive medications in old age are low, despite a high absolute risk. This might lead to unnecessary recurrence of cardiovascular disease and functional decline, posing a huge burden on society.

Identification of high-risk persons might help to select patients that might benefit most from secondary cardiovascular preventive treatment. However, risk scores for the prediction of recurrent risk for the general old population are lacking and, since traditional risk markers lose predictive value with age, physicians are 'empty handed' when trying to estimate the risk for old patients with a history of cardiovascular disease. This thesis investigates predictors for recurrent cardiovascular disease and functional decline in old age. Available information, such as the severity of the cardiovascular disease history, or new easily available biomarkers, such as estimated glomerular filtration rate (MDRD), C-reactive protein (CRP), homocysteine and N-terminal pro B-type natriuretic peptide (NT-proBNP), are promising candidates for risk estimation in old persons with a history of cardiovascular disease.

The main aim of this thesis is to search for possible improvements in medical care for older patients with a history of cardiovascular disease. In part one we investigate current practice regarding secondary cardiovascular prevention in general practice in the Netherlands and try to unravel underlying reasons for low prescription rates. In part two we aim to find predictors that can help physicians to estimate risk for recurrent cardiovascular disease, as well as for functional decline in secondary cardiovascular prevention in old age. In part three we examine whether new risk predictors can predict treatment effect and, thereby, offer additional clinical benefit for old patients with a history of cardiovascular disease.

Part 1
Current practice regarding secondary cardiovascular prevention

Chapter 2 presents a study on current prescription rates of secondary cardiovascular preventive medications in old age, and investigates associations between the general practitioner's (GP) judgement of vulnerability and the severity of cardiovascular disease using these prescription rates. In a population-based observational study within the ISCOPE study (patients aged 75 years and older, enrolled in 2009-2010, in 46 general practices), one-year prescription rates were obtained from 1350 participants with a history of cardiovascular disease (median age 81 years, 50% female). Optimal treatment

was defined as prescription of a lipid-lowering drug as well as antithrombotic medication. GPs made a judgement regarding the patient's vulnerability. The severity of cardiovascular disease was expressed as major cardiovascular disease, including myocardial infarction, stroke and/or arterial surgery, versus minor cardiovascular disease, including angina, transient ischaemic attack and/or claudication.

Half of all the participants received optimal prescription, whereas in participants aged 85 years and over only a third received optimal prescription. In multivariate analysis (including age, sex and history of cardiovascular disease), GPs' judgement of vulnerability was not independently associated with lower prescription rates, whereas the history of minor cardiovascular disease was. Age itself remained the strongest predictor of optimal treatment.

In conclusion, treatment uptake of secondary cardiovascular preventive medication in old age is low and declines even further with age, independent from the GP's judgement of vulnerability.

In **Chapter 3** we aimed to find explanations for the low prescription rates of medications for secondary cardiovascular prevention that are reported in the literature, and present a qualitative study consisting of five focus groups with purposefully sampled GPs and GP trainees. With regard to secondary cardiovascular preventive treatment in old age, the main theme emerging from these focus-group discussions was that of 'uncertainty'. Within this uncertainty, four important features were identified: the guidelines themselves, physician-related factors, patient-related factors, and organisation-related factors. Regarding the guidelines, GPs reported that barriers related to the implementation of guidelines were often based on a perceived lack of scientific background and a lack of precise data on the benefits and risks in old age. Regarding physician-related factors, GPs mentioned that shared decision-making, and prevention of symptoms, helped them to implement the guidelines for secondary cardiovascular prevention in old age. Anticipated regret, especially the prevention of stroke after a transient ischaemic attack, was also mentioned as a facilitator by the GPs; however, this item was not mentioned by GP trainees. Patient-related barriers were lag time to perceived benefit, side-effects, vulnerability, and having had a cardiovascular event many years ago. An important patient-related facilitator was vitality and (expected) improvement in quality of life. All GPs agreed that the ultimate aim of secondary cardiovascular prevention in old age, was (expected) improvement in quality of life. Concerning the organisation of care, GPs realised that patients sometimes fall into the 'gap' between primary and secondary care. To optimise the organisation of secondary cardiovascular prevention in general practice, the following items were considered to be necessary: the presence of a practice nurse, structured ICPC coding, identification of patients that have fallen into the gap between primary and secondary care, and proactive annual follow-up.

In view of the presence of the 'uncertainty' described above, GPs consciously weigh and consider all aspects in close dialogue with the individual patient, with the ultimate aim to improve quality of life. This highly individualised care may, for a great part, explain the reduced prescriptions rates that were observed. However, to enhance shared decision-making, GPs favoured the development of specified risk/benefit charts for secondary cardiovascular prevention in old age. Identification of patients that have fallen into the gap between primary and secondary care, as well as the organisation of proactive annual follow-up, will probably help to optimise care for older patients with a history of cardiovascular disease.

Part 2
Predictors of risk for recurrent cardiovascular disease and functional decline in very old age

To explore whether the history of cardiovascular disease can predict bad outcomes in very old age, in **Chapter 4** we investigate the prognosis of very old people, depending on their history of cardiovascular disease, in the Leiden 85-plus Study. The Leiden 85-plus Study is an observational prospective cohort study (inclusion 1997-1999), with 5-year complete follow-up data for cardiovascular disease, functional status and mortality. At baseline, participants (n=570) were assigned to three groups according to the history of cardiovascular disease: no cardiovascular disease, 'minor' cardiovascular disease (angina pectoris, transient ischaemic attack, intermittent claudication and/or heart failure), or 'major' cardiovascular disease (myocardial infarction, stroke and/or arterial surgery). Follow-up data were collected on cardiovascular events (myocardial infarction and stroke), functional status and cause-specific mortality. The composite endpoint included cardiovascular events (myocardial infarction, stroke) and cardiovascular mortality. At baseline, 47% of the participants had no history of cardiovascular disease, 22% minor and 30% major cardiovascular disease. Compared to the group without clinical cardiovascular disease at age 85 years, the group with minor cardiovascular disease had a 1.5-fold, and the group with major cardiovascular disease had an almost 3-fold increased risk for the development of recurrent cardiovascular events or cardiovascular mortality. Both minor and major cardiovascular disease were associated with an accelerated decline in cognitive function and accelerated increase of disability score, albeit most pronounced in participants with major cardiovascular disease.

In conclusion, in the general population of persons aged 85 years and over the history of cardiovascular disease is an important prognostic factor. Also, compared to patients with a history of minor cardiovascular disease, patients with a history of major cardio-

vascular disease have a doubled risk of poor outcomes. This provided a strong rationale to further investigate the severity of cardiovascular disease history in very old age.

Since traditional cardiovascular risk markers lose their predictive value with age, in **Chapter 5** we investigate new (bio)markers for risk prediction in secondary cardiovascular prevention in very old age. In a population-based sample of 85-year-old participants with established cardiovascular disease from the Leiden 85-plus Study, we studied predictive values of traditional cardiovascular risk markers, the history of major cardiovascular disease (myocardial infarction, stroke or arterial surgery), and new cardiovascular biomarkers [estimated glomerular filtration rate (MDRD), C-reactive protein (CRP), homocysteine and N-terminal pro B-type natriuretic peptide (NT-proBNP)], in relation to the 5-year risk of recurrent cardiovascular events and mortality (composite endpoint). During the 5-year follow-up period, 56% of the participants died and 39% had a cardiovascular event or died from cardiovascular causes. Individually related to the composite endpoint were: a history of major cardiovascular disease, CRP, homocysteine and NT-proBNP. A prediction model including all traditional risk markers yielded a C-statistic of 0.59. Of all five new markers, only the addition of NT-proBNP improved the C-statistic. The category less net reclassification improvement was 39% for the addition of NT-proBNP, and 27% for the addition of a history of major cardiovascular disease to the traditional risk markers.

In conclusion: when estimating risk in secondary prevention in very old age, especially the use of NT-proBNP should be taken into consideration.

Preserving independency becomes very important in old age. Therefore, in the full inception cohort of the Leiden 85-plus Study (**Chapter 6**) we investigated whether plasma NT-proBNP levels in very old age can also predict change in functional status. Median NT-proBNP level for men was 351 pg/ml and for women it was 297 pg/ml. During the 5-year follow-up, participants with high NT-proBNP had an accelerated cognitive decline and an increase of disability in activities of daily living. Also, risks for heart failure, atrial fibrillation, myocardial infarction, stroke, cardiovascular mortality, non-cardiovascular mortality and all-cause mortality were increased 2-5 fold, irrespective of other known risk markers.

In conclusion: in very old age high NT-proBNP levels predict accelerated cognitive and functional decline, as well as cardiovascular morbidity and mortality. Therefore, NT-proBNP can probably help clinicians to identify very old people at high risk of functional impairment and incident cardiovascular morbidity and mortality.

Part 3
Can NT-proBNP improve prediction of recurrent events and cardiovascular mortality, and additionally predict treatment effect of pravastatin?

Chapter 7 presents a post-hoc analysis in participants (n=2348, age 70-82 years, median age 75 years) with a history of cardiovascular disease within the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a randomised placebo-controlled study (inclusion 1997-1999). First we assessed the predictive values of models including age and sex, traditional cardiovascular risk markers and the currently available SMART risk score (developed in a younger cohort (mean age 60 years)), with and without N-terminal pro-B-type natriuretic peptide (NT-proBNP), regarding recurrent cardiovascular disease (myocardial infarction and stroke) and cardiovascular mortality during the 2.5-year follow-up period. Then we assessed the treatment effect of pravastatin across the low-risk and high-risk groups identified by these models. The models with age and sex, traditional risk markers and SMART risk score, had a comparable predictive value for recurrent cardiovascular events and mortality [area under the curve (AUC) 0.58, 0.61 and 0.59, respectively]. The addition of NT-proBNP to these models improved AUCs and improved classification (NRI: 41%, 39% and 25%, respectively). Regarding treatment effect we observed that, in order to prevent one cardiovascular event or cardiovascular death, the number needed to treat (NNT) with pravastatin for 2.5 years for participants in the higher third of predicted risk of the simple model (including age, sex and NT-proBNP) was 12, compared to 115 for participants in the lower third of predicted risk of this model.

In conclusion: in secondary cardiovascular prevention in old age the predictive value of traditional risk markers and SMART risk score is poor. Including NT-proBNP in the prediction models improves the prediction of recurrent cardiovascular disease and mortality. A minimal model including age, sex and NT-proBNP makes as good a prediction as complex risk models including NT-proBNP. When confronted with difficult dilemmas regarding starting, continuing, or safely stopping preventive treatment in old age, NT-proBNP can help clinicians to identify patients who will probably benefit most from proactive follow-up.

Chapter 8 is the general discussion. First, the main findings of this thesis are presented. Then, we elaborate on clinical dilemmas and on frequently encountered problems in secondary cardiovascular prevention in old age, such as side- effects, polypharmacy, adverse reactions and adherence problems, as well as the role of vulnerability in secondary cardiovascular prevention in old age.

In addition, the following methodological aspects are addressed: comparison of risk prediction models, recalibration of risk prediction models, net reclassification improve-

ment prediction versus causation, and the possible additional value of directed acyclic graphs.

Finally, we discuss patient perspectives, perspectives for society in general, clinical implications, and some recommendations for future research.

In conclusion, this thesis reveals that in secondary cardiovascular prevention in old age treatment uptake is low, partly because of the highly individualised care for these (often complex) patients, and partly because some patients get lost in the gap between primary and secondary care. According to the focus-group discussions with GPs, treatment guidelines need to address the heterogeneity of older patients with a history of cardiovascular disease, and tailored guidelines need to be developed.

In the meantime, in the difficult decision-making process concerning starting, stopping, or continuing secondary cardiovascular preventive treatment in old age, the findings in this thesis indicate that the severity of the cardiovascular disease history, and especially the use of NT-proBNP, can help physicians estimate the future risk for recurrent cardiovascular disease, as well as for cognitive and functional decline. Moreover, NT-proBNP levels can help estimate the expected treatment effect of statins.

To meet the ongoing aim of improving patient care in older age, the following are recommended: vigorous ICPC coding, pro-active follow-up of all older patients with a history of cardiovascular disease, individualised optimisation of secondary cardiovascular prevention by risk prediction, and by together consciously weighing all the pros and cons of preventive treatment.