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Title: New perspectives on cardiovascular risk prediction in old age

Issue Date: 2015-09-17

NEW PERSPECTIVES ON
**CARDIOVASCULAR
RISK PREDICTION
IN OLD AGE**

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New perspectives on cardiovascular risk prediction in old age

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Cover design: Yorick Poortvliet and Rosalinde Poortvliet

Layout and Printing: Optima Grafische Communicatie (www.ogc.nl)

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ISBN: 978-94-6169-704-2

New Perspectives on Cardiovascular Risk Prediction in Old Age

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 17 september 2015
klokke 15.00 uur

door

Rosalinde Klazina Elisabeth Poortvliet

geboren te Aalsmeer
in 1981

PROMOTIECOMMISSIE

Promotor	Prof. dr. J. Gussekloo
Co-promotor	Dr. W. de Ruijter
Overige leden	Prof. dr. Y.M. Smulders, Vrije Universiteit Amsterdam Prof. dr. T. Stijnen Dr. E.P. Moll van Charante, Universiteit van Amsterdam

The research project presented in this thesis was funded by the SBOH (employer of GP trainees in the Netherlands). Financial support for printing of this thesis was kindly provided by the SBOH and the NVG-knows (Dutch Association for Gerontology).

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Chapter 1

General introduction

Cardiovascular disease is the leading cause of death worldwide. In 2012, an estimated 18.2 million people died from cardiovascular diseases (ischemic heart disease, stroke and hypertensive heart disease), representing 30% of all global deaths.¹ With increasing age, mortality from cardiovascular disease increases exponentially (Figure 1).²⁻⁴ Moreover, as populations age due to worldwide population growth and increasing longevity, annual cardiovascular disease mortality is projected to raise even further.⁵

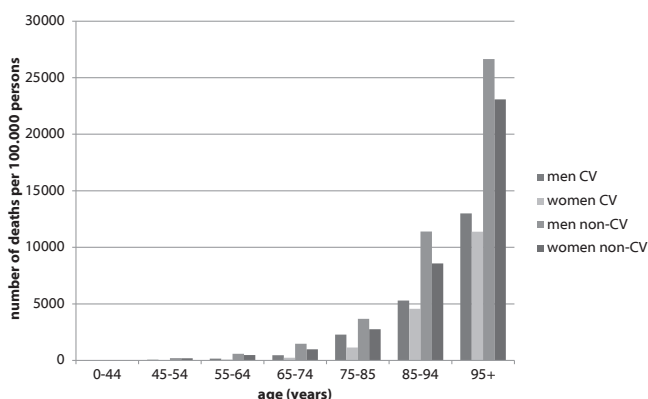


Figure 1. Number of cardiovascular (CV) and non-cardiovascular (non-CV) deaths per 100,000 persons in the Netherlands grouped by age and sex (2012)

Source: Statistics Netherlands

In the Netherlands, on average, 57 women and 50 men die every day from cardiovascular diseases: 32 (56%) of these women and 15 (30%) of these men are aged 85 years and older.⁶ The majority of cardiovascular deaths in old age is caused by ischemic heart disease in men and stroke and heart failure in women.⁶ The greatest amount of cardiovascular mortality took place in the 1970s and since then, cardiovascular mortality has declined.⁷ Between 1980 and 2012, the standardized mortality rate decreased by 43% in men and women aged 85 years and over.⁶ The decline in fatality rates reflects the improvements in treatment strategies in the past decades. More people (both young and old), will continue to survive their acute cardiovascular event. As a result, there is a projected increase in prevalence of cardiovascular disease over the coming decades, especially for coronary heart disease. This also applies for other common diseases in old age, such as diabetes and osteoarthritis (Figure 2).

However, this increase in survival rates of acute cardiovascular events is also associated with a loss of functional status and quality of life. Disability-adjusted life-years (DALYs) reflect the 'burden of disease'. It is a time-based measure that combines years of life lost due to premature mortality and years of life lost due to time lived in a state of less than full health. In the Netherlands, coronary heart disease causes the greatest bur-

den of disease resulting in 282,834 DALYs, compared to 194,312 DALYs for diabetes and 123,509 DALYs for osteoarthritis (Figure 2).^{9,10} From age 65 years onward, cardiovascular disease causes the highest number of DALYs, followed by cancer.¹¹

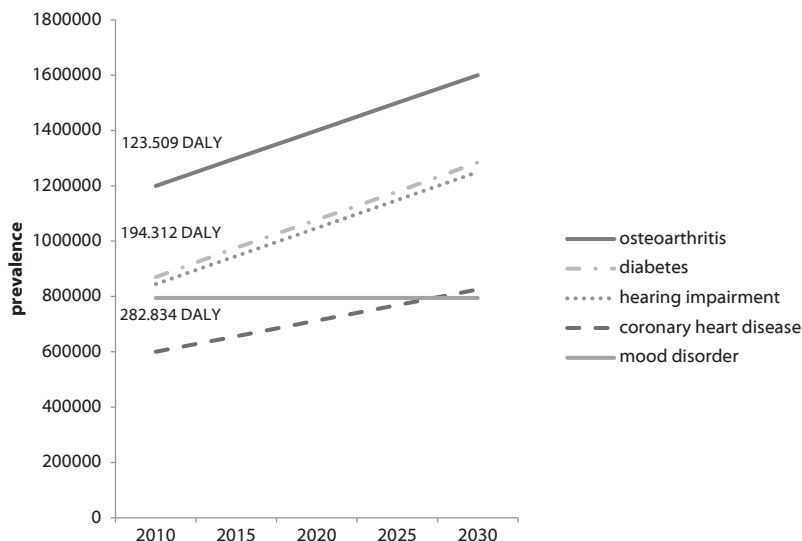


Figure 2. Predicted increase in prevalence and impact of the five most common diseases in the Dutch population between 2010 and 2030

Source: Ned Tijdschr Geneesk. 2014;158:A7819⁹ and Nationaal Kompas Volksgezondheid⁹

In conclusion, cardiovascular disease has a large impact in old age and will probably have an even greater impact in the future.

PREVENTION OF CARDIOVASCULAR DISEASE IN OLD AGE

Prevention of cardiovascular disease aims to prevent the development of cardiovascular disease in individuals without a history of cardiovascular disease (primary prevention), and recurrences and complications in those with established disease (secondary prevention). Besides advice concerning a healthy lifestyle (such as smoking cessation, healthy diet, weight control and exercise), a regimen of statins, blood pressure-lowering and antiplatelet agents (the latter only in secondary prevention) may significantly reduce the risk of death from cardiovascular disease in people at high cardiovascular risk. Eligible for prevention are those with a 10-year cardiovascular risk equal to or above 20%, and those who have survived a previous cardiovascular event.^{12,13}

There is evidence that blood pressure-lowering agents and statins, although less robust, are effective in older age. Blood pressure-lowering agents are effective in the

prevention of (especially) stroke and heart failure in persons aged 80 years and over.¹⁴ Statin therapy is safe and effective in older people to reduce the risk for cardiovascular events, whereas no effect was found on all-cause mortality.¹⁵ However, no clinical trials have addressed the prevention of coronary events using statins in people aged 85 years and older.¹⁶

When taking into account the current threshold to start preventive medication in individuals with a 10-year cardiovascular (absolute) risk equal or above 20%, then virtually all persons aged 75 years and over are eligible for preventive medication when applying traditional risk scores, i.e. the age-related absolute risk. This means that older people may be prescribed preventive medication based on predominantly age-related absolute risk. Indeed, some have suggested that preventive cardiovascular treatment should be offered to everyone over a specified age, without measuring other risk factors.¹⁷ Others have different opinions and suggest, for example, to start preventive medication in persons with the highest relative risk.

The evidence that i) preventive medication is beneficial up to old age on the one hand, and that ii) adverse drug-drug interactions and potential clinically significant adverse effects lead to poorer quality of life on the other, can argue both in favour and also against starting preventive cardiovascular medication in old age. This dilemma was reflected by the debate in the Journal of American Geriatric Society regarding whether or not to start statin therapy.^{18,19} Either way, physicians are often reluctant to start preventive medication in order to avoid either polypharmacy or overmedication, not only in apparently healthy older people but also in vulnerable older people.

CARDIOVASCULAR RISK PREDICTION IN OLD AGE

To help physicians decide whether to advise preventive medication to their older patients, prediction of those at highest or lowest (relative) risk is of pivotal importance. This also emphasizes the need for risk stratification in old age. Relatively easy methods to distinguish high-risk patients from low-risk patients may, therefore, contribute to better targeting of preventive strategies of cardiovascular disease in old age.

The most important independent predictor for cardiovascular disease is age: as we get older, our risk of cardiovascular disease increases.²⁰ Increasing age is a proxy for the aging process of the body, including blood vessels and organs such as the heart. In middle age, many other risk predictors for cardiovascular disease are known, such as high blood pressure, high cholesterol level, smoking, obesity and a history of diabetes, all of which are very common.²¹⁻²⁴

Cardiovascular risk models in old age

Because the risk for cardiovascular disease is considered to be multifactorial, risk factors are considered in conjunction when developing clinical risk scores. Clinical cardiovascular risk scores, such as the Framingham Risk Score²⁵ and the Systematic Coronary Risk Evaluation (SCORE),²⁶ are used worldwide to select those at high cardiovascular risk.

Their accuracy to predict risk of cardiovascular outcomes declines with advancing age, because the individual risk predictors have a different predictive value in old age compared to middle age.²⁷⁻³² Between age 70 and 80 years, classical cardiovascular risk factors appear to reverse their association with clinical outcomes, such that they no longer predict adverse events but, rather, predict good health outcomes. High blood pressure, high cholesterol and obesity are no longer risk factors for mortality and, in some studies, are even associated with better survival in old age.²⁷⁻³² These paradoxical observations have also been referred to as 'reverse epidemiology', 'inverse epidemiology' or 'risk factor paradox'. Therefore, in older people, established classic risk factors and corresponding risk scores (e.g. the Framingham Risk Score and the SCORE risk function) do not qualify for adequate risk prediction. The Leiden 85-plus Study showed that the Framingham Risk Score in no way predicts cardiovascular risk in persons aged 85 years and over.³³

Emerging cardiovascular risk factors

In old age there is a lack of good cardiovascular risk predictors, as the classical cardiovascular risk factors tend to lose their predictive value. Therefore, there is a need to identify new cardiovascular risk factors. In addition, the classical cardiovascular risk factors age, current cigarette smoking, hypertension, family history of premature coronary heart disease, low high density lipoprotein (HDL) levels and high low density lipoprotein (LDL) levels, when present, cannot explain the total variation in cardiovascular risk. Other factors, yet to be identified, might also influence cardiovascular risk. There has been intensive research to identify new cardiovascular risk factors in middle age, in order to improve cardiovascular risk prediction. These so-called 'emerging risk factors'³⁴ can be divided into serological biomarkers, and (imaging) tests for subclinical atherosclerotic disease.

1. Serological emerging risk factors

Little is known about the use of serological emerging risk factors in old age. Much research has focused on predominantly middle-aged populations. Several *lipid risk factors* have been studied in middle-aged adults. Lipoprotein(a) has an independent predictive power to predict coronary heart disease risk.³⁵ However, several prospective studies do not confirm this independent prediction.³⁶ Although apolipoprotein B

has been proposed as an alternative to LDL cholesterol as a risk factor, there is limited evidence to support this additional value on cardiovascular risk prediction.³⁷ Low apolipoprotein A-I is associated with an increased cardiovascular risk, but the independent predictive power of apolipoprotein A-I remains unclear.^{37,38} *Inflammatory markers* such as C-reactive protein, interleukin-6 and lipoprotein-associated phospholipase A₂ have been studied as separate markers, but also in combination with other emerging risk factors. In older persons, lipoprotein-associated phospholipase A₂ is a potential biomarker for vascular events.³⁹ C-reactive protein was included in multiple risk models and found to be one of the best predictors of cardiovascular events among the emerging risk factors in middle age.^{40,41} A higher level of high sensitivity C-reactive protein is associated with higher cardiovascular risk; however, it minimally enhances cardiovascular disease prediction beyond established vascular risk factors in older age.⁴² This might be explained by the decreasing predictive value of C-reactive protein with age.^{43,44} Several *hemostatic/thrombosis factors* are associated with coronary heart disease risk in middle age. For example, a high level of fibrinogen associates with increased risk for coronary events.^{45,46} Other hemostatic/thrombosis factors have been mentioned, such as tissue plasminogen activator, D-dimer, von Willebrand factor, factor V Leiden and protein C.⁴⁶ Sensitive troponin T, a marker for myocardial damage, is associated with cardiovascular events both in men and women.⁴¹ However, the evidence in old age is lacking for most of these factors. Moderately elevated *amino acid* homocysteine levels are associated with increased risk of first,^{47,48} as well as recurrent myocardial infarction.⁴⁹ It has also been shown that homocysteine is predictive of cardiovascular events in old age.^{33,50} Recent study showed that high homocysteine levels not only identify older persons at high risk for coronary heart disease and mortality, but also identify those with the highest absolute risk reduction by statin treatment and the lowest number needed to treat to prevent coronary heart disease.⁵¹ It is unknown whether there is an underlying biological pathway to explain the predictive value of homocysteine. Evidently, risk prediction based on homocysteine is valid up to high age. However, general practitioners (or physicians in general) might be reluctant to order a blood test for homocysteine since the causal relationship between homocysteine and cardiovascular disease is not clear for moderately elevated homocysteine levels. The *neuro-humoral factor* N-terminal pro-brain natriuretic peptide (NT-proBNP) is also a strong predictor in risk models with emerging risk factors in middle age.^{40,41} NT-proBNP might also be relevant in cardiovascular risk prediction in old age. Therefore, NT-proBNP might be a promising serological marker in old age.

2. (Imaging) tests for subclinical atherosclerotic disease

Advanced subclinical atherosclerotic disease is associated with a greater risk for major coronary events, up to the very old. The ankle-brachial blood pressure index is a simple

and non-invasive test to confirm lower extremity peripheral arterial disease. A lower ankle-brachial blood pressure index is associated with a higher risk of mortality in old age.⁵² Imaging techniques are also used to test for atherosclerotic plaque burden, including the coronary calcium score⁵³ and carotid artery intima media thickness.⁵⁴ The calcium score can be useful in cardiovascular risk prediction; a score of zero excludes coronary artery disease. Because atherosclerosis increases with age, the likelihood a person has a low calcium score decreases with advancing age. Therefore, use of the calcium score in older patients (>65 years) is generally not recommended.⁵⁵ The severity of the intimal medial thickness of the carotid arteries correlates with risk for major coronary events.⁵⁶

In conclusion, for many of the emerging risk factors the association with cardiovascular disease has been studied, both separately and in combination.^{40,41,46,57,58} However, their optimal use in routine screening and risk stratification, especially in old age, remains to be determined. In addition, many of these new risk factors, especially the imaging techniques, are costly and time consuming, and not easily available in primary care. Moreover, use of the calcium score is generally not recommended in old age. Therefore, we could argue that cardiovascular risk prediction in old age, especially in primary care, should be based on easily accessible risk predictors.

PROMISING WAYS TO PREDICT CARDIOVASCULAR RISK IN OLD AGE

Blood pressure measurements; single versus multiple measurements

Average (systolic) blood pressure is part of all cardiovascular risk scores used in daily practice^{25,26,59-61} and considered to be the key or most important blood pressure modality when determining risk of cardiovascular disease. Although these risk scores are validated for people up to age 65-75 years, in daily practice they are also applied to older people. However, until now, data on the association between blood pressure and mortality in very old age are conflicting.^{28,29,62-64} In a large meta-analysis of observational data from 61 studies,⁶² both high systolic and diastolic blood pressure were independently predictive of cardiovascular mortality (stroke and coronary heart disease) in all age groups. However, this association attenuated considerably with age. In contrast, observational studies in exclusively very older populations have shown that low, and not high blood, pressure is associated with increased mortality in very old age.^{28,29,63,64} Besides mortality, low blood pressure is also associated with morbidity, such as a decreased cognitive function,⁶⁵ decreased renal function,⁶⁶ grip strength⁶⁷ and increased depressive and anxiety symptoms.^{68,69} Thus, in very old age, low blood pressure changes from a favorable to an unfavorable predictive factor. The etiological mechanisms behind this association are not yet completely unravelled.

Systolic blood pressure rises with age until age 75 years,^{28,70} then decreases in very old age.^{28,63,70,71} Although a decreasing trend in systolic blood pressure in very old age is associated with an increased mortality risk, data from these studies are not consistent.^{28,63,70-72} There is limited information about the clinical significance and predictive value of decreasing systolic blood pressure in the individual over time

Blood pressure not only rises with age up to the very old, it also varies over time within individuals, resulting in variability in blood pressure.^{73,74} Studies in middle-aged persons suggest that this variability in blood pressure (assessed across multiple visits) is itself a predictor of incident cardiovascular disease⁷⁵⁻⁷⁷ and may have an important additional role in increasing the risk of vascular events, in particular stroke. In addition, the adverse effects of variability in blood pressure may extend beyond stroke. In a population-based study of adults in the USA, higher levels of visit-to-visit variability in systolic blood pressure was associated with increased all-cause mortality.⁷⁶

It is still unknown whether the use of multiple blood pressure measurements expressed in the *trends* or *variability* in blood pressure have any clinical significance in old age with regard to prediction of mortality and morbidity. Selection of high risk blood pressure patterns in old age could be an important and easily available step in the successful prediction of mortality and cardiovascular morbidity in this age group.

N-terminal pro-brain natriuretic peptide

Ventricular myocytes release prohormone pro-brain natriuretic peptide (BNP) in reaction to ventricular wall stress and hypoxia.^{78,79} Pro-BNP is then split into the active BNP and inactive NT-proBNP. NT-proBNP is known to increase with age, even in the absence of heart failure or cardiovascular disease,⁸⁰ and is mainly cleared through renal excretion.⁸¹ NT-proBNP is a diagnostic sensitive, but not highly specific, biomarker for heart failure, but also a prognostic marker for incident cardiovascular morbidity and mortality in middle-aged^{82,83} and older persons.^{84,85} Also, it was part of multiple panels of biomarkers tested to improve risk stratification for (death from) cardiovascular disease beyond risk stratification on a model based only on established risk factors, mainly in a middle-aged population.^{41,46,57} However, the optimal use of NT-proBNP in risk stratification in old age remains to be determined.

In conclusion, in cardiovascular risk prediction in old age there is a need for inexpensive and easy to use risk factors that not only distinguish high-risk from low-risk patients, but also help to identify effective preventive strategies. NT proBNP could be an interesting candidate.

AIM AND OUTLINE OF THIS THESIS

Aim

The general aim of this thesis is to study classical and new cardiovascular risk predictors in old age, in order to optimize risk stratification and subsequent prevention of cardiovascular disease in older persons.

Study populations

PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)

The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) 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 if they had either pre-existing vascular disease (including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction, and vascular surgery) or raised risk of such disease because of one or more major cardiovascular risk factors, defined as hypertension, cigarette smoking, or diabetes mellitus. Individuals with poor cognitive function (Mini-Mental State Examination score <24 points) were excluded. The primary outcome of the study was the combined endpoint of definite or suspected death from coronary heart disease, non-fatal myocardial infarction, and fatal or non-fatal stroke during a mean follow-up of 3.2 years. At baseline, and every 3 months thereafter, participants were reviewed with a maximum follow-up of 4 years. A 12-lead electrocardiogram was recorded annually. Cognition tests and disability assessment were assessed every year.

Leiden 85-plus Study

The Leiden 85-plus Study is a population based prospective follow-up study. All inhabitants of the city of Leiden, the Netherlands, turning 85 years old between September 1997 and September 1999 were invited to participate. Of the 705 people that were eligible to participate in the study, a total of 599 (87%) people gave informed consent and were enrolled. No exclusion criteria were used. Participants were visited at baseline and yearly thereafter by a research nurse at their place of residence until the age of 90 was reached or the participant died. During these visits, information on sociodemographic characteristics was collected and participants underwent face-to-face interviews, blood samples were drawn, and biometrical measurements and electrocardiography were taken. The participant's general practitioner (or, if applicable, nursing home physician) was interviewed annually about the participant's medical history, and the pharmacist provided detailed information on all medication used by each participant. Mortality

data were obtained from the municipal registry. Causes of death were classified into standardized ICD10 codes based on complete death certificates.

Brief description of chapters

This thesis is divided in two parts.

Part 1 Multiple blood pressure measurements in cardiovascular risk prediction in old age

Chapters 2 and 3 focus on visit-to-visit blood pressure variability. Chapter 2 describes the association between visit-to-visit variability in blood pressure and cardiovascular disease in older persons in the PROSPER study. In Chapter 3 an attempt was made to identify biological factors associated with visit-to-visit variability in blood pressure to help elucidate the biological mechanisms underlying high levels of visit-to-visit-variability in blood pressure in older persons.

Chapters 4 and 5 focus on blood pressure trends. Chapter 4 describes whether the absence or presence of heart failure influences the prognostic value of low systolic blood pressure with regard to mortality in the oldest old in the Leiden 85-plus Study. There is limited information about the clinical significance of decreasing systolic blood pressure in the individual over time. Therefore, in Chapter 5, the association between blood pressure trends and mortality in the oldest old is investigated.

Part 2 N-terminal pro-brain natriuretic peptide levels in cardiovascular risk prediction in old age

The second part of this thesis focuses on the use of NT-proBNP levels in older patients as a prognostic instrument for cardiovascular mortality and morbidity, and evaluates the added value of NT-proBNP in the prediction of treatment effect in old age. The use of NT-proBNP in the prediction of the treatment effect in secondary prevention is evaluated in Chapter 6. Chapter 7 describes whether an increase in NT-proBNP levels over time is still associated with cardiac disease and mortality in very old age and the effect of the change in renal function on this association.

By addressing these questions, this thesis will contribute to improved clinical management of cardiovascular risk in old age. In addition, the studies can contribute to adequate communication regarding cardiovascular risks and treatment benefits, and shared decision-making between physicians (general practitioners) and patients by providing evidence-based information on cardiovascular risk factors and the predicted treatment effect. In this way, this thesis will contribute to the prevention of one of the most important diseases worldwide with its related high disease burden and mortality rate in old age.

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PART 1

MULTIPLE BLOOD PRESSURE
MEASUREMENTS IN
CARDIOVASCULAR RISK
PREDICTION IN OLD AGE



Chapter 2

Blood pressure variability and cardiovascular risk in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)

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PLoS One 2012;7(12):e52438.

ABSTRACT

Variability in blood pressure predicts cardiovascular disease in young- and middle-aged subjects, but relevant data for older individuals are sparse. We analysed data from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study of 5804 participants aged 70–82 years with a history of, or risk factors for cardiovascular disease. Visit-to-visit variability in blood pressure (standard deviation) was determined using a minimum of five measurements over 1 year; an inception cohort of 4819 subjects had subsequent in-trial 3 years follow-up; longer-term follow-up (mean 7.1 years) was available for 1808 subjects. Higher systolic blood pressure variability independently predicted long-term follow-up vascular and total mortality (hazard ratio per 5 mmHg increase in standard deviation of systolic blood pressure = 1.2, 95% confidence interval 1.1–1.4; hazard ratio 1.1, 95% confidence interval 1.1–1.2, respectively). Variability in diastolic blood pressure associated with increased risk for coronary events (hazard ratio 1.5, 95% confidence interval 1.2–1.8 for each 5 mmHg increase), heart failure hospitalisation (hazard ratio 1.4, 95% confidence interval 1.1–1.8) and vascular (hazard ratio 1.4, 95% confidence interval 1.1–1.7) and total mortality (hazard ratio 1.3, 95% confidence interval 1.1–1.5), all in long-term follow-up. Pulse pressure variability was associated with increased stroke risk (hazard ratio 1.2, 95% confidence interval 1.0–1.4 for each 5 mmHg increase), vascular mortality (hazard ratio 1.2, 95% confidence interval 1.0–1.3) and total mortality (hazard ratio 1.1, 95% confidence interval 1.0–1.2), all in long-term follow-up. All associations were independent of respective mean blood pressure levels, age, gender, in-trial treatment group (pravastatin or placebo) and prior vascular disease and cardiovascular disease risk factors. Our observations suggest variability in diastolic blood pressure is more strongly associated with vascular or total mortality than is systolic pressure variability in older high-risk subjects.

INTRODUCTION

In daily practice and all major clinical guidelines,¹⁻⁵ 'usual' or average blood pressure is considered to be the key or most important measure determining risk of cardiovascular disease (CVD); reductions in average blood pressure are generally thought to account for the benefits of antihypertensive drugs.¹⁻⁹ However, recently Rothwell *et al.*¹⁰ has questioned the usual blood-pressure hypothesis, suggesting that visit-to-visit variability in blood pressure (assessed across multiple visits) may have an important additional role in increasing risk of vascular events, and in particular stroke. Visit-to-visit variability in blood pressure is increased in cohorts at high risk of stroke.^{11,12} A secondary analysis of several randomised controlled trials found that visit-to-visit variability in systolic blood pressure and episodic hypertension were strong predictors of stroke, independent of mean systolic blood pressure.¹³ In addition the adverse effects of variable blood pressure may stretch beyond stroke. In a population-based study of US adults, higher levels of visit-to-visit variability in systolic blood pressure were associated with increased all-cause mortality.¹⁴

However the risks associated with visit-to-visit variability of blood pressure in older age are less clear; some investigators have suggested such associations with visit-to-visit variability in systolic blood pressure may decrease with advancing age.¹³ Therefore, we aimed to establish whether visit-to-visit variability in blood pressure in older patients is associated with increased risk of incident CVD. We performed an analysis of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) cohort.¹⁵

METHODS

Study design

Details of the design and outcome of PROSPER have been Published elsewhere.¹⁵⁻¹⁷ 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 if they had either pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension or diabetes. Plasma total cholesterol was required to be 4.0–9.0 mmol/L and triglyceride concentrations ≤ 6.0 mmol/L. Individuals with poor cognitive function (Mini-Mental State Examination score < 24 points) were excluded. The level of blood pressure was not part of the inclusion or exclusion criteria. The institutional ethics review boards of all centres approved the protocol and all participants gave written informed consent. The protocol adhered to the principles of the Declaration of Helsinki.

Blood pressure measurements

Sitting blood pressure was measured once at baseline and at follow-up visits every three months during the randomised phase of the trial (mean follow-up 3.2 years) with a fully automatic electronic sphygmomanometer (Omron M4®) by trained research nurses.

Outcomes and follow-up

The outcomes for this study were incidence of cardiovascular events, including definite or suspected death from coronary heart disease or non-fatal myocardial infarction (CHD/MI), fatal or non-fatal stroke, heart failure hospitalisation, vascular mortality and total mortality.

All in-trial endpoints were assessed by the PROSPER Endpoints Committee, which was blinded to study medication. For this study the in-trial outcomes occurring over a maximum of 3 years (mean 2.3 years), following *one* year of blood pressure observations (i.e. five blood pressure measurements) were analysed. This follow-up was considered 'short-term'.

Routine health data on morbidity and mortality for the Scottish sub-group (including post-trial follow-up) were obtained from the Information Services Division, a division of National Services Scotland, part of *National Health Service* Scotland. The data obtained included the Scottish Morbidity Records (SMR) - SMR00 outpatient attendances; SMR01 general acute inpatient and day case discharges; SMR04 psychiatric admissions, residents and discharges; SMR06 cancer registrations, and General Register Office for Scotland death registrations. The outcomes for the Scottish sub-group were followed up over a maximum of 9.3 years (mean 7.1), following *two* years of blood pressure observations (with nine blood pressure measurements). This was considered the 'long-term follow-up'.

Statistical analysis

Baseline summary characteristics are reported as means with standard deviations (SD) for continuous variables and as numbers with percentage (%) for categorical variables. Variability of blood pressure was quantified using the standard deviation (SD) and the coefficient of variation (SD/mean; CV). The results for SD and CV were qualitatively the same; therefore the results for SD are presented. *F*-tests were used to test the difference in blood pressure variability between participants receiving pravastatin and those receiving placebo. The association of visit-to-visit variability in blood pressure in relation to the different endpoints was assessed separately for short- and long-term follow-up, the latter restricted to the Scottish sub-cohort. For short-term follow-up blood pressure variability was calculated from measurements made at visits 1 to 5 (0–12 months). In the Scottish sub-cohort which, in addition, has longer-term follow-up, blood pressure

variability was calculated from measurements made from visit 1 to 9 (0–24 months). Participants who had a CVD event during the blood pressure variability measurement period (0–12 months for short-term follow-up and 0–24 months for long-term follow-up) were excluded from relevant analysis. Participants with one or more missing blood pressure measurements, including those who died during the blood pressure variability measurement period, were excluded from the analyses. The agreement in blood pressure variability was assessed for the short-term inception cohort by analysing the Spearman Rank Correlation between the first three blood pressure measurements and the last two measurements. For the long-term Scottish sub-cohort, agreement in blood pressure variability was assessed by analysing the Spearman Rank Correlation between the first five blood pressure measurements and the last four measurements.

The associations between measures of blood pressure variability and time to occurrence of clinical outcomes were assessed using Cox proportional hazards models. Measures of blood pressure variability used were standard deviations and these were split into quarters of their distributions and hazard ratios (HRs) and corresponding 95% confidence intervals were calculated in relation to the lowest quarter of SD (referent); homogeneity across the quartiles was assessed using a general test of heterogeneity.

Analyses were adjusted for country (short-term analyses only), randomized treatment group (pravastatin or placebo) and the respective mean blood pressure measure during the period blood pressure variability was assessed (mean systolic blood pressure for systolic blood pressure variability; mean diastolic blood pressure for diastolic blood pressure variability and mean pulse pressure for pulse pressure variability) (Model 1). A second model (Model 2) included additional adjustment for age, gender, smoking status, and prior histories of diabetes, hypertension, cardiovascular disease, cerebrovascular disease or peripheral vascular disease, as well as body mass index (BMI), high density lipoprotein cholesterol (HDL) and low density lipoprotein cholesterol (LDL). The results for Models 1 and 2 were qualitatively the same; therefore the results for Model 2 are presented in the main tables.

We performed a number of sensitivity analyses, including using continuous values of the blood pressure variability measurements to evaluate the influence of the splitting the blood pressure variability measurements by quartiles. In this case continuous measures of variability of blood pressure were reported as HRs per 5 mmHg increase in SD of systolic and diastolic blood pressure and pulse pressure. HRs for one SD difference in baseline blood pressure, mean blood pressure and blood pressure variability, for systolic and diastolic blood pressure and pulse pressure were calculated. Further subgroup analyses were conducted for gender, the use of antihypertensive medication at baseline, baseline blood pressure above and below the median and for patients with/without a history of a stroke or transient ischaemic attack.

RESULTS

Of the initial cohort of 5804 PROSPER participants, 5054 were alive and had a full blood pressure profile up to 12 months (five measurements); 235 of these participants were excluded from analyses as having had a CVD event during this period, giving 4819 participants as an inception cohort to be included in the short-term (in trial) follow-up analyses (Figure 1). For the long-term follow-up (including post-trial) analyses only the Scottish sub-cohort was eligible ($n = 2520$); 625 of these participants were excluded because they did not have a full blood pressure profile (up to two years, nine measure-

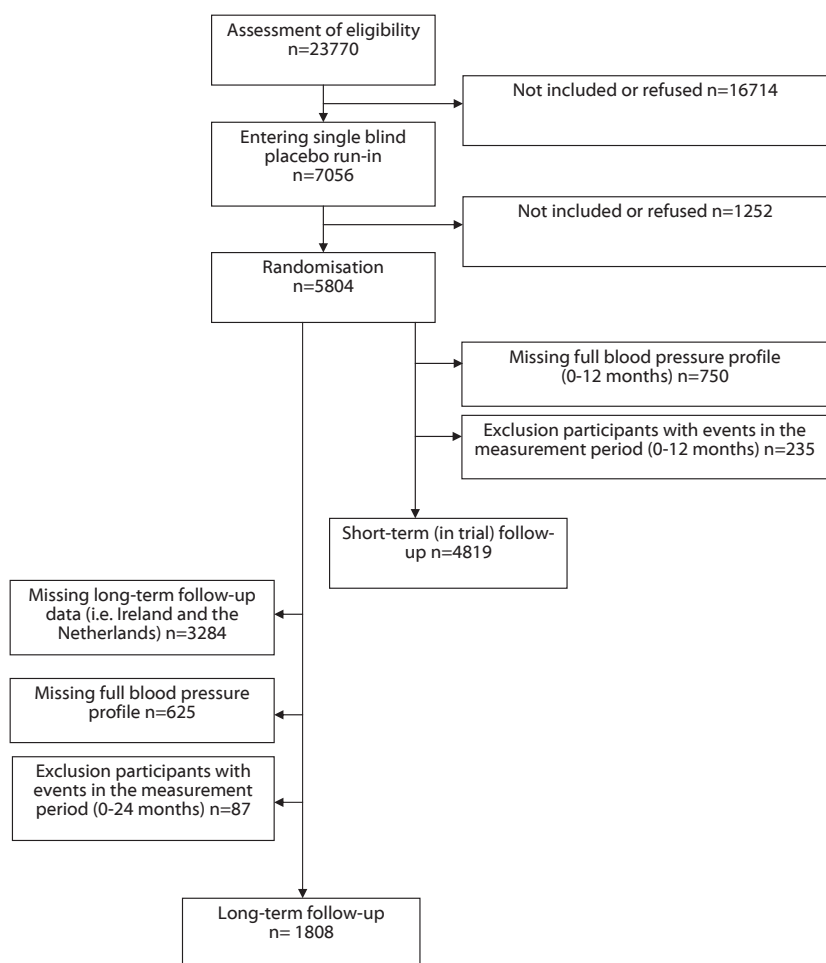


Figure 1. Flow chart

ments); an additional 87 of these participants were excluded as they had a CVD event during this period, giving 1808 Scottish participants to be included in the inception cohort for the long-term follow-up analyses (Figure 1).

Table 1 presents the baseline characteristics for the participants in the short- and long-term follow-up. Of the 4819 participants in the short-term follow-up 2339 (48.5%) were men, the mean age was 75.2 years (SD 3.3) and 2086 (43.3%) had a history of cardiovascular disease. Of the 1808 participants in the long-term follow-up 876 (48.5%) were men, the mean age was 75.2 years (SD 3.4) and 865 (47.8%) had a history of cardiovascular disease.

We initially examined whether there was a difference in variability in blood pressure between participants receiving pravastatin and those receiving placebo. There was no significant difference for short-term and long-term follow up, systolic and diastolic

Table 1. Baseline characteristics of participants with a short-term and long-term follow-up

	Follow-up	
	Short-term (whole cohort) (n=4819)	Long-term (Scottish sub-cohort) (n=1808)
Continuous variates (mean, SD)		
Age (years)	75.2 (3.3)	75.2 (3.4)
Systolic blood pressure (mmHg)	154.7 (21.6)	153.7 (20.8)
Diastolic blood pressure (mmHg)	83.9 (11.4)	82.9 (10.8)
Pulse pressure (mmHg)	70.8 (18.1)	70.9 (17.7)
Body mass index (kg/m ²)	26.9 (4.2)	26.8 (4.1)
Alcohol (units per week)*	5.3 (9.4)	4.6 (8.2)
Total cholesterol (mmol/L)	5.7 (0.9)	5.7 (1.0)
Low-density lipoprotein cholesterol (mmol/L)	3.8 (0.8)	3.8 (0.8)
High-density lipoprotein cholesterol (mmol/L)	1.3 (0.4)	1.3 (0.4)
Triglycerides (mmol/L)	1.5 (0.7)	1.6 (0.7)
Mini-Mental State Examination (pts)	28.1 (1.5)	28.3 (1.4)
Barthel index (pts)	13.7 (1.0)	13.8 (0.8)
Instrumental activities of daily-living (pts)	19.8 (0.7)	19.8 (0.6)
Categorical variates (n, %)		
Men	2339 (48.5)	876 (48.5)
Current smoker	1262 (26.2)	472 (26.1)
History of diabetes mellitus	492 (10.2)	144 (8.0)
History of hypertension	3016 (62.6)	1077 (59.6)
History of cardiovascular disease†	2086 (43.3)	865 (47.8)

SD Standard deviation.

*1 unit = 60 ml distilled spirits, 170 ml wine or 300 ml beer.

†Any of stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction, peripheral arterial disease surgery, or amputation for vascular disease more than 6 months before study entry.

blood pressure and pulse pressure (range of p-values 0.288–0.868); therefore, data from both groups were combined; however all subsequent analyses were adjusted for randomized treatment group because of the effect of the pravastatin on CVD outcomes.

Blood pressure variability was reproducible for short-term and long-term follow up, for systolic and diastolic blood pressure and pulse pressure (p-value <0.0001). The Spearman Rank Correlation was higher when more blood pressure measurements were added in the model.

Visit-to-visit variability in systolic blood pressure

Across the first five blood pressure measurements in the short-term follow-up cohort the mean SD for variability of systolic blood pressure was 13.6 mmHg. The mean SD for variability of systolic blood pressure across the first nine blood pressure measurements in the long-term follow-up cohort was 14.1 mmHg. Table 2 shows the results of the time-to-event analyses for the different quartiles of SD of systolic blood pressure for all endpoints in the short-term and long-term follow-up.

In the long-term follow-up, risk of vascular and total mortality increased across quartiles for SD of systolic blood pressure in the fully adjusted model. SD of systolic blood pressure per 5 unit change (mmHg) was associated with coronary events (HR 1.1, 95% CI 1.0–1.3); vascular mortality (HR 1.2, 95% CI 1.1–1.4) and total mortality (HR 1.1, 95% CI 1.1–1.2) in the long-term follow-up. The predictive value of visit-to-visit variability in systolic blood pressure was similar in all subgroup analyses, including in participants with and without the use of antihypertensive medication (data not shown).

Visit-to-visit variability in diastolic blood pressure

Across the first five measurements in the whole cohort the mean SD of diastolic blood pressure was 7.3 mmHg. The mean SD of diastolic blood pressure across the first nine measurements in the Scottish sub-cohort was 7.4 mmHg. Table 3 shows the results of the time-to-event analyses for the different quartiles of diastolic blood pressure for all endpoints in the short-term and long-term follow-up. In both short-term and long-term follow-up, high visit-to-visit variability in diastolic blood pressure was associated with increased risk of coronary events, heart failure hospitalisation and vascular and total mortality. The HRs for heart failure hospitalization and coronary events in the long-term follow-up were 1.9 (95% CI 1.3–2.8) for the highest quarter versus lowest quarter of SD of diastolic blood pressure and 1.8 (95% CI 1.3–2.6), respectively in the fully adjusted model (Table 3). SD of diastolic blood pressure per 5 unit change (mmHg) predicted coronary events (HR 1.1, 95% CI 1.0–1.3) and heart failure hospitalization (HR 1.3, 95% CI 1.1–1.6) in the short-term follow-up. In the long-term follow-up SD of diastolic blood pressure per 5 unit change predicted coronary events (HR 1.5, 95% CI 1.2–1.8); heart failure hospitalisa-

Table 2. Hazard Ratio's for the endpoints associated with quartiles of the standard deviation (SD) of systolic blood pressure

Short-term follow-up (n=4819)					
Quartile of SD of systolic blood pressure, range in mmHg					
Outcomes	Group 1 (n=1139) ≤9	Group 2 (n=1194) >9- ≤12.5	Group 3 (n=1266) >12.5-≤17	Group 4 (n=1220) >17	P for heterogeneity
Coronary events (n=407)	1 (ref)	0.8 (0.6-1.1)	1.0 (0.7-1.3)	1.0 (0.8-1.3)	0.563
Fatal/non-fatal stroke (n=158)	1 (ref)	1.0 (0.6-1.6)	1.1 (0.7-1.8)	1.2 (0.8-1.9)	0.764
Heart failure hospitalisation (n=144)	1 (ref)	0.5 (0.3-0.8)	0.8 (0.5-1.3)	1.0 (0.7-1.5)	0.019
Vascular mortality (n=172)	1 (ref)	0.8 (0.5-1.2)	1.0 (0.6-1.5)	0.9 (0.6-1.3)	0.741
Total mortality (n=330)	1 (ref)	1.0 (0.7-1.3)	1.1 (0.8-1.6)	1.0 (0.8-1.4)	0.676
Long-term follow-up (n=1808)					
Quartile of SD of systolic blood pressure, range in mmHg					
Outcomes	Group 1 (n=412) ≤10.5	Group 2 (n=428) >10.5-≤13	Group 3 (n=471) >13-≤16.5	Group 4 (n=497) >16.5	P for heterogeneity
Coronary events (n=248)	1 (ref)	0.9 (0.6-1.3)	1.3 (0.9-1.9)	1.2 (0.8-1.7)	0.155
Fatal/non-fatal stroke (n=245)	1 (ref)	1.0 (0.7-1.5)	1.3 (0.9-2.0)	1.3 (0.9-1.8)	0.329
Heart failure hospitalisation (n=216)	1 (ref)	0.8 (0.5-1.3)	1.4 (1.0-2.1)	1.2 (0.8-1.8)	0.044
Vascular mortality (n=315)	1 (ref)	1.1 (0.7-1.5)	1.5 (1.0-2.1)	1.6 (1.1-2.2)	0.016
Total mortality (n=735)	1 (ref)	1.2 (1.0-1.5)	1.4 (1.1-1.7)	1.5 (1.2-1.8)	0.006

Data are presented as Hazard Ratios and 95% Confidence Intervals.

Adjustment for randomized treatment, country (short-term follow-up only), mean systolic blood pressure, age, gender, current smoker, histories of diabetes, hypertension, cardiovascular disease, cerebrovascular disease & peripheral vascular disease, body mass index, high-density lipoprotein and low-density lipoprotein.

tion (HR 1.4, 95% CI 1.1–1.8); vascular mortality (HR 1.4, 95% CI 1.1–1.7) and total mortality (HR 1.3, 95% CI 1.1–1.5).

Variability in diastolic blood pressure was more predictive for coronary events in male participants (p for interaction = 0.008) and for vascular mortality in male participants and participants with systolic blood pressure below median (p for interaction = 0.043 and 0.028, respectively) in long-term follow-up.

Table 3. Hazard Ratio's for the endpoints associated with quartiles of the standard deviation (SD) of diastolic blood pressure

Short-term follow-up (n=4819)					
Outcomes	Quartile of SD of diastolic blood pressure, range in mmHg				P for heterogeneity
	Group 1 (n=1127) ≤4.8	Group 2 (n=1157) >4.8-≤6.5	Group 3 (n=1319) >6.5-≤9	Group 4 (n=1216) >9	
Coronary events (n=407)	1 (ref)	1.0 (0.8-1.4)	1.0 (0.8-1.4)	1.3 (1.0-1.8)	0.096
Fatal/non-fatal stroke (n=158)	1 (ref)	0.8 (0.5-1.2)	1.0 (0.6-1.5)	0.6 (0.4-1.0)	0.211
Heart failure hospitalisation (n=144)	1 (ref)	1.1 (0.7-1.9)	1.1 (0.7-1.9)	1.8 (1.1-3.0)	0.027
Vascular mortality (n=172)	1 (ref)	0.8 (0.5-1.2)	1.3 (0.8-1.9)	1.3 (0.9-2.1)	0.056
Total mortality (n=330)	1 (ref)	0.7 (0.5-1.0)	1.0 (0.8-1.4)	1.2 (0.9-1.6)	0.035
Long-term follow-up (n=1808)					
Outcomes	Quartile of SD of diastolic blood pressure, range in mmHg				P for heterogeneity
	Group 1 (n=431) ≤5.5	Group 2 (n=452) >5.5-≤7	Group 3 (n=460) >7-≤8.8	Group 4 (n=465) >8.8	
Coronary events (n=248)	1 (ref)	1.3 (0.9-1.9)	1.1 (0.7-1.6)	1.8 (1.3-2.6)	0.002
Fatal/non-fatal stroke (n=245)	1 (ref)	1.1 (0.7-1.5)	1.0 (0.7-1.4)	1.3 (0.9-1.8)	0.470
Heart failure hospitalisation (n=216)	1 (ref)	1.7 (1.1-2.5)	1.2 (0.8-1.8)	1.9 (1.3-2.8)	0.005
Vascular mortality (n=315)	1 (ref)	1.3 (0.9-1.8)	1.1 (0.8-1.5)	1.6 (1.2-2.2)	0.020
Total mortality (n=735)	1 (ref)	1.2 (0.9-1.5)	1.1 (0.9-1.3)	1.4 (1.1-1.7)	0.012

Data are presented as Hazard Ratios and 95% Confidence Intervals.

Adjustment for randomized treatment, country (short-term follow-up only), mean diastolic blood pressure, age, gender, current smoker, histories of diabetes, hypertension, cardiovascular disease, cerebrovascular disease & peripheral vascular disease, body mass index, high-density lipoprotein and low-density lipoprotein.

Visit-to-visit variability in pulse pressure

Across the first five measurements in the whole cohort the mean SD of pulse pressure was 12.2 mmHg. Across the first nine measurements in the Scottish sub-cohort the mean SD of pulse pressure was 12.6 mmHg.

Table 4 shows the results of the time-to-event analyses for the different quartiles of pulse pressure for all endpoints in the short-term and long-term follow-up. In the short-term follow-up, there was no association between the SD of pulse pressure and the risk of CVD events or mortality. In the long-term follow-up, high visit-to-visit variability in

pulse pressure was associated with increased risk of stroke (HR for the highest quartile versus lowest quartile 1.6, 95% CI 1.1–2.4); vascular and total mortality (HR 1.3, 95% CI 1.0–1.8 and HR 1.3, 95% CI 1.1–1.6 respectively). When the analyses were repeated for the continuous values of pulse pressure, SD of pulse pressure per 5 unit change (mmHg) predicted stroke (HR 1.2, 95% CI 1.0–1.4), vascular mortality (HR 1.2, 95% CI 1.0–1.3) and total mortality (HR 1.1, 95% CI 1.0–1.2) in the long-term follow-up. Variability in pulse pressure was more predictive for total mortality in participants with systolic blood pressure below the median (p for interaction = 0.024).

Table 4. Hazard Ratio's for the endpoints associated with quartiles of the standard deviation (SD) of pulse pressure

Short-term follow-up (n=4819)					
Quartile of SD of pulse pressure, range in mmHg					
Outcomes	Group 1 (n=1158) ≤8	Group 2 (n=1149) >8-≤11	Group 3 (n=1231) >11-≤15	Group 4 (n=1281) >15	P for heterogeneity
Coronary events (n=407)	1 (ref)	0.8 (0.6-1.1)	0.9 (0.7-1.2)	0.8 (0.6-1.0)	0.287
Fatal/non-fatal stroke (n=158)	1 (ref)	0.9 (0.5-1.4)	0.9 (0.6-1.4)	1.2 (0.8-1.8)	0.526
Heart failure hospitalisation (n=144)	1 (ref)	1.3 (0.8-2.1)	1.0 (0.6-1.6)	1.1 (0.7-1.7)	0.575
Vascular mortality (n=172)	1 (ref)	1.1 (0.7-1.7)	1.2 (0.8-1.8)	1.0 (0.6-1.5)	0.761
Total mortality (n=330)	1 (ref)	1.3 (0.9-1.8)	1.3 (0.9-1.8)	1.2 (0.9-1.7)	0.415
Long-term follow-up (n=1808)					
Quartile of SD of pulse pressure, range in mmHg					
Outcomes	Group 1 (n=459) ≤9.5	Group 2 (n=422) >9.5-≤12	Group 3 (n=475) >12-≤15	Group 4 (n=452) >15	P for heterogeneity
Coronary events (n=248)	1 (ref)	0.9 (0.6-1.3)	1.0 (0.7-1.5)	1.1 (0.8-1.6)	0.727
Fatal/non-fatal stroke (n=245)	1 (ref)	1.1 (0.7-1.6)	1.5 (1.0-2.1)	1.6 (1.1-2.4)	0.024
Heart failure hospitalisation (n=216)	1 (ref)	0.8 (0.6-1.3)	1.1 (0.7-1.6)	1.2 (0.8-1.7)	0.357
Vascular mortality (n=315)	1 (ref)	0.8 (0.6-1.2)	1.1 (0.8-1.6)	1.3 (1.0-1.8)	0.031
Total mortality (n=735)	1 (ref)	1.1 (0.9-1.3)	1.2 (1.0-1.5)	1.3 (1.1-1.6)	0.068

Data are presented as Hazard Ratios and 95% Confidence Intervals.

Adjustment for randomized treatment, country (short-term follow-up only), mean pulse pressure, age, gender, current smoker, histories of diabetes, hypertension, cardiovascular disease, cerebrovascular disease & peripheral vascular disease, body mass index, high-density lipoprotein and low-density lipoprotein.

Sensitivity analyses

Table 5 shows the result of the analyses with one SD difference in baseline, mean and variability in blood pressure in the long-term Scottish cohort. One SD difference in baseline systolic and diastolic blood pressure, but not pulse pressure, was associated with an increased risk of stroke. One SD difference in mean systolic and diastolic blood pressure and pulse pressure was associated with an increased risk of stroke.

One SD difference in variability in systolic and diastolic blood pressure predicted an increased risk of vascular and total mortality, but was not associated with an increased risk of stroke.

In the analyses with one SD difference in baseline, mean and variability in blood pressure in the short-term follow-up cohort, one SD difference in variability in diastolic blood pressure predicted an increased risk in coronary events and heart failure hospitalisation (HR 1.11, 95% CI 1.01–1.21 and 1.20, 95% CI 1.05–1.38, respectively), no other associations were found (data not shown).

DISCUSSION

This study shows that in older subjects visit-to-visit variability in systolic blood pressure, diastolic blood pressure and pulse pressure are associated with an increased long-term risk for cardiovascular and total mortality. In addition variability in diastolic blood pressure was predictive of coronary events and heart failure hospitalisation; variability in systolic blood pressure was predictive of heart failure hospitalisations. Variability in pulse pressure (but not diastolic blood pressure or systolic blood pressure) was somewhat associated with long-term stroke risk. These associations were independent of respective mean blood pressure values, the use of antihypertensive medication and other risk factors. The association of intra-individual variability in blood pressure measurements with adverse clinical outcomes was first recognized in the early 1990s.^{18–21} Subsequent studies have investigated the predictive value of visit-to-visit variability in blood pressure in middle-aged people.^{19,22–25} In contrast the present study population consists of an older population (aged ≥ 70 years) with high risk of vascular events and deaths. Therefore, the present study gives new insight into the clinical significance of blood pressure variability with regard to morbidity and mortality in later life. It has been suggested that the association between increased variability in blood pressure and the risk of stroke is strongest in younger age groups.^{10,13}

The reliability of blood pressure variability increased with the number of measurements included, this is in line with previous research in younger age groups.^{10,13} It is possible that our measures of blood pressure variability, although based on a reason-

Table 5. Hazard Ratio's for the endpoints associated with one SD change in each blood pressure parameter (a-c) for the long-term follow-up (n=1808)

a. Systolic blood pressure						
Outcomes	Change of one standard deviation					
	Baseline SBP (SD = 20.80 mmHg)		Mean SBP (SD = 15.53 mmHg)		SD SBP (SD = 4.88 mmHg)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Coronary events	1.1 (0.9-1.2)	0.390	1.2 (1.0-1.32)	0.030	1.1 (1.0-1.3)	0.044
Fatal / non-fatal stroke	1.2 (1.0-1.3)	0.030	1.2 (1.1-1.4)	0.003	1.1 (1.0-1.3)	0.084
Heart failure hospitalisation	1.1 (0.9-1.2)	0.514	1.1 (0.9-1.2)	0.426	1.1 (1.0-1.3)	0.135
Vascular mortality	1.1 (1.0-1.2)	0.082	1.2 (1.1-1.3)	0.005	1.2 (1.1-1.4)	>0.001
Total mortality	1.0 (1.0-1.1)	0.255	1.1 (1.0-1.2)	0.056	1.1 (1.1-1.2)	>0.001
b. Diastolic blood pressure						
Outcomes	Change of one standard deviation					
	Baseline DBP (SD = 10.80 mmHg)		Mean DBP (SD = 7.13 mmHg)		SD DBP (SD = 3.66 mmHg)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Coronary events	1.0 (0.9-1.1)	0.989	1.0 (0.9-1.1)	0.939	1.2 (1.1-1.4)	0.001
Fatal / non-fatal stroke	1.2 (1.0-1.3)	0.019	1.2 (1.1-1.4)	0.008	1.1 (1.0-1.2)	0.141
Heart failure hospitalisation	0.9 (0.8-1.0)	0.181	0.9 (0.8-1.0)	0.060	1.2 (1.0-1.3)	0.014
Vascular mortality	1.0 (0.9-1.2)	0.558	1.0 (1.0-1.2)	0.234	1.2 (1.1-1.3)	0.003
Total mortality	1.0 (1.0-1.1)	0.465	1.0 (1.0-1.1)	0.459	1.1 (1.1-1.2)	>0.001
c. Pulse pressure						
Outcomes	Change of one standard deviation					
	Baseline PP (SD = 17.70 mmHg)		Mean PP (SD = 12.38 mmHg)		SD PP (SD = 4.33 mmHg)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Coronary events	1.1 (0.9-1.2)	0.314	1.2 (1.1-1.4)	0.006	1.1 (1.0-1.2)	0.199
Fatal / non-fatal stroke	1.1 (0.9-1.2)	0.284	1.2 (1.0-1.3)	0.031	1.2 (1.0-1.3)	0.018
Heart failure hospitalisation	1.1 (1.0-1.3)	0.118	1.2 (1.0-1.3)	0.043	1.1 (0.9-1.2)	0.271
Vascular mortality	1.1 (1.0-1.2)	0.094	1.2 (1.1-1.3)	0.005	1.2 (1.0-1.3)	0.008
Total mortality	1.0 (1.0-1.1)	0.375	1.1 (1.0-1.2)	0.053	1.1 (1.0-1.2)	0.008

Data are presented as Hazard Ratios and 95% Confidence Intervals.

Adjustment for randomized treatment, mean systolic blood pressure (a), mean diastolic blood pressure (b) and mean pulse pressure (c), age, gender, current smoker, histories of diabetes, hypertension, cardiovascular disease, cerebrovascular disease & peripheral vascular disease, body mass index, high-density lipoprotein and low-density lipoprotein.

ably large number of individual measurements, may still have underestimated the true magnitude of effect of variability on clinical outcomes.

The association between visit-to-visit variability in systolic blood pressure and increased total mortality found in older persons in this present study is generally in line with previous research in younger age-groups.^{13,14} Visit-to-visit variability in systolic

blood pressure has also been claimed to be a predictor of stroke^{10,13,24,26} and coronary events,^{13,27} however in the present study visit-to-visit variability in systolic blood pressure was not associated with an increased risk of stroke or coronary events. In contrast, sensitivity analyses in this present study showed that one SD difference in baseline and mean systolic and diastolic blood pressure was associated with an increased risk of stroke.

In our cohort, variability in pulse pressure was the only measure that was associated with an increased risk of stroke, albeit modestly so; systolic blood pressure variability may be a more powerful predictor of stroke in younger cohorts; Rothwell *et al.*¹³ found an adjusted HR for stroke of 12.1 (95% CI 7.4–19.7; highest vs. lowest decile) in a population aged 40–79 years. Such differences between our study and other cohorts might be caused by higher mean systolic blood pressure levels in our older cohort. However there was no meaningful difference in average blood pressure between our study and other relevant cohorts (e.g. mean systolic blood pressure 150 mmHg in the UK-TIA and 164 mmHg at baseline and 148 mmHg on treatment in the ASCOT-BPA¹³ compared to 154/155 mmHg in the present study).

In previous research, in predominantly younger populations compared to the present study, no associations were present between visit-to-visit variability in diastolic blood pressure and all-cause mortality and CVD.^{13,14,27} In contrast, our data suggest that in older subjects diastolic blood pressure variability is more strongly associated with coronary events and vascular or total mortality than is systolic pressure variability, especially in male subjects and those with systolic blood pressure below median. The mechanisms for why diastolic blood pressure variability should be more strongly associated with risk in elderly remain uncertain but could speculatively include a bigger drop off in diastolic blood pressure as marker of risk. In addition, it is also not clear why such associations appear to be significantly stronger in men compared to women. Clearly, our results suggest these issues merit further study.

The present study reveals some differences in the association between variability in the different blood pressure measurement and outcomes and shows some differences with previous research. One of the major differences between the present study and previous research is the age of the participants. Although the present study was not aimed to investigate etiological mechanisms behind the observed associations, it is tempting to hypothesize that the mechanisms involved in the association between variability in blood pressure and stroke are different in younger and older persons. In previous studies, greater variability in blood pressure was related to older age and pulse pressure,^{13,14} which both correlate with arterial stiffness. Arterial stiffness may play a role in the found associations between variability in blood pressure and CVD events. While variability increases with age, the association with CVD events is not found to increase correspondingly with similar analysis. The variability in systolic blood pressure found

in the present study was indeed higher than the variability in systolic blood pressure found in younger populations (mean SD of systolic blood pressure 14.1 mmHg vs. 7.7 mmHg¹⁴), while the associated risk for total mortality was not higher. This could indicate that there might be more competing mechanisms in older persons than in younger persons.

This study has a number of strengths. Blood pressure was not part of the inclusion or exclusion criteria for the PROSPER trial. Therefore, people with the full range of baseline blood pressure and variability in blood pressure were included. The estimation of visit-to-visit variability should be reasonably reliable because of the frequency of measurements. The large sample size allowed us to conduct several subgroup analyses and investigating different outcomes. However a limitation of this study is that long-term follow-up was not assessed in the total PROSPER trial population and it was only available for the Scottish sub-cohort. Another potential limitation is that the participants were randomized to an intervention (pravastatin vs. placebo), however, we found no difference in variability in blood pressure between randomized groups and all analyses were adjusted for the randomized treatment. Third, we had no data on the use of antihypertensive medications during the follow-up after the randomized control trial ended. PROSPER was not designed to assess the effect of blood pressure on outcomes and the accuracy of measurement of blood pressure was reduced. By not having the perfect blood pressure measurement we may have underestimated the true effect of variability in blood pressure on clinical outcomes.

The present study aimed only to establish whether there is an association between of visit-to-visit variability in blood pressure and adverse CVD outcomes in older patients; however if these associations are causal the results may have implications in the management and treatment of blood pressure in the older population. Besides the aim of lowering the usual level of blood pressure in hypertensive patients, it is possible that additional benefit might be obtained from reducing variability in blood pressure. In a recent meta-analysis it was suggested that the use of calcium channel blockers and non-loop diuretics results in less systolic blood pressure variability than the use of ACE inhibitors and angiotensin 2 receptor antagonists. Calcium channel blockers have shown to reduce visit-to-visit variability compared with placebo.²⁸ However, currently it is not certain whether differential effects of various antihypertensives on variability in blood pressure will also lead to clinical gains.

In conclusion, in older subjects at risk of CVD events variability in systolic blood pressure is predictive for the risk of heart failure hospitalisations and cardiovascular and total mortality; variability in diastolic blood pressure is predictive for the risk of coronary events, and vascular and total mortality; variability in pulse pressure is predictive of stroke.

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Chapter 3

Biological correlates of blood pressure variability in elderly at high risk of cardiovascular disease

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Am J Hypertens. 2015;28(4):469-479.

ABSTRACT

Background

Visit-to-visit variability in blood pressure is an independent predictor of cardiovascular disease. This study investigates biological correlates of intra-individual variability in blood pressure in older persons.

Methods

Nested observational study within the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) among 3,794 male and female participants (range 70–82 years) with a history of, or risk factors for cardiovascular disease. Individual visit-to-visit variability in systolic and diastolic blood pressure and pulse pressure (expressed as 1 SD in mm Hg) was assessed using nine measurements over 2 years. Correlates of higher visit-to-visit variability were examined at baseline, including markers of inflammation, endothelial function, renal function and glucose homeostasis.

Results

Over the first 2 years, the mean intra-individual variability (1 SD) was 14.4 mm Hg for systolic blood pressure, 7.7 mm Hg for diastolic blood pressure, and 12.6 mm Hg for pulse pressure. After multivariate adjustment a higher level of interleukin-6 at baseline was consistently associated with higher intra-individual variability of blood pressure, including systolic, diastolic, and pulse pressure. Markers of endothelial function (Von Willebrand factor, tissue plasminogen activator), renal function (glomerular filtration rate) and glucose homeostasis (blood glucose, homeostatic model assessment index) were not or to a minor extent associated with blood pressure variability.

Conclusion

In an elderly population at risk of cardiovascular disease, inflammation (as evidenced by higher levels of interleukin-6) is associated with higher intra-individual variability in systolic, diastolic, and pulse pressure.

Blood pressure varies over time within individuals, resulting in variability in blood pressure.¹⁻⁴ Until the 1990s variability in blood pressure was merely regarded as a random phenomenon and an obstacle to determine the usual blood pressure.^{1,5-7} Usual or average blood pressure was considered to be the main determinant in the cause of cardiovascular disease and accounting for the benefits of antihypertensive drugs.^{1,5-7} However, recent data suggest that variability in blood pressure assessed across several visits (i.e., visit-to-visit variability) is reproducible and not a random phenomenon,^{8,9} and that visit-to-visit variability in blood pressure itself is a predictor of incident cardiovascular disease.¹⁰⁻¹⁸ Long-term visit-to-visit variability in systolic blood pressure has been claimed to be associated with increased risk of stroke,^{10,12-14} coronary events^{10,15,18} and all-cause mortality,^{11,17,18} all in middle-aged persons. In older age, visit-to-visit variability blood pressure is associated with an increased long-term risk for cardiovascular and total mortality and cognitive decline.^{16,19} In addition, variability in diastolic blood pressure is predictive of coronary events and heart failure hospitalization.¹⁶

Higher visit-to-visit variability in blood pressure might result from biological factors. Possible mechanisms underlying high levels of visit-to-visit-variability of blood pressure include impaired baroreceptor function,^{5,20} arterial stiffness,^{11,21} impaired endothelial function,^{22,23} inflammation,^{21,24,25} and renal impairment.²⁶ Identifying factors associated with intra-individual variability in blood pressure may help elucidate the underlying mechanisms. It is unknown which factors correlate most strongly with variability of blood pressure in older people. We hypothesized that inflammation, impaired endothelial function, renal function, and glucose metabolism might be important biological pathways underlying visit-to-visit variability of blood pressure in older age, based on previous studies on correlates of higher variability of blood pressure in middle-aged populations.^{10,21-26} We tested these hypotheses in 3,794 subjects participating in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER).²⁷

METHODS

Study design

Details of the design and outcome of PROSPER have been published elsewhere.²⁷⁻²⁹ In short, between December 1997, and May 1999 a total of 5,804 individuals were screened and enrolled in Scotland (n = 2,520), Ireland (n = 2,184) and the Netherlands (n = 1,100). Men and women aged 70–82 years were recruited if they had either pre-existing vascular disease (coronary, cerebral, or peripheral) or increased risk of such disease because of smoking, hypertension, or diabetes. Their plasma total cholesterol was required to be 4.0–9.0 mmol/L and their triglyceride concentrations ≤6.0 mmol/L. Individuals with poor cognitive function (Mini-Mental State Examination score <24 points) were

excluded. Blood pressure was not part of the inclusion or exclusion criteria. In total, 5,804 participants were randomized to either placebo or pravastatin; 2,913 assigned placebo and 2,891 assigned pravastatin.²⁷ During the pre-randomization visits, baseline participant characteristics were collected.²⁸ The institutional ethics review boards of all centers approved the protocol, and all participants gave written informed consent.

Blood pressure measurements

Sitting blood pressure was measured once at baseline and at follow-up visits every 3 months during the trial (mean follow-up 3.2 years) with a fully automatic electronic sphygmomanometer (Omron M4).

Biomarkers

Markers of inflammation. Saved biobank of baseline K2EDTA samples were used to assay interleukin-6 in 2007 using a high-sensitivity enzyme-linked immunosorbent assay (R&D Systems) with inter- and intra-assay coefficients of variation of <6% and sensitivity of <0.16 pg/mL.³⁰ High sensitivity C-reactive protein levels were measured on stored K2EDTA (at -80 °C) baseline samples by automated particle-enhanced immunoturbidimetric assay (Roche UK, Welwyn Garden City, UK), with inter- and intra-assay coefficients of variation of <3% and a lower limit of sensitivity of 0.1 mg/L.³¹ The laboratory participates in a national external quality control for high-sensitivity C-reactive protein. All laboratory analyses were conducted by technicians blind to the identity of samples.

Markers of endothelial function. In baseline blood samples from the biobank (stored at <80 °C) tissue plasminogen activator antigen was measured in citrated plasma using an enzyme-linked immunosorbent assay (Biopool AB) and VonWillebrand factor antigen level was measured in citrated plasma using an enzyme-linked immunosorbent assay with rabbit antihuman polyclonal antibodies (Dako).³²

Markers of renal function. Baseline serum creatinine levels were measured at central laboratories, one in each of the three participating countries. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation³³:

$$\text{eGFR} = 186 \times \text{serum creatinine level (mg dl)}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)}$$

Markers of glucose metabolism. Body mass index and detailed medical history was collected at baseline. Fasting glucose levels were assessed at baseline, using routine methods.²⁹ Diabetes at baseline was defined by self-reported history, a fasting blood glucose concentration of 7.0 mmol/L or greater or a blood glucose measurement of 11.1 mmol/L or greater when fasting status was uncertain, or self-reported use of anti-diabetic drugs (any oral hypoglycemic agent or insulin). Data on fasting glucose and fasting insulin levels were used to calculate the degree of insulin resistance according to homeostatic model assessment (HOMA).³⁴ The HOMA score was calculated using

the HOMA index³⁴ by dividing the product of fasting levels of glucose and insulin by a constant.

Statistical analysis

Variability of blood pressure was defined as the SD of the mean per person over 9 visits (0–24 months). Variability was assessed for systolic blood pressure, diastolic blood pressure and pulse pressure. Participants with one or more missing blood pressure measurements in the first 24 months ($n = 1,403$); those who had a cardiovascular event in the measurement period (0–24 months, $n = 316$) and those with atrial fibrillation ($n = 4$) were excluded. A total of 487 participants had missing data for one or more of the biomarkers and were also excluded (some participants had more than one exclusion criteria) (Figure 1). Variability of systolic blood pressure was also quantified using the coefficient

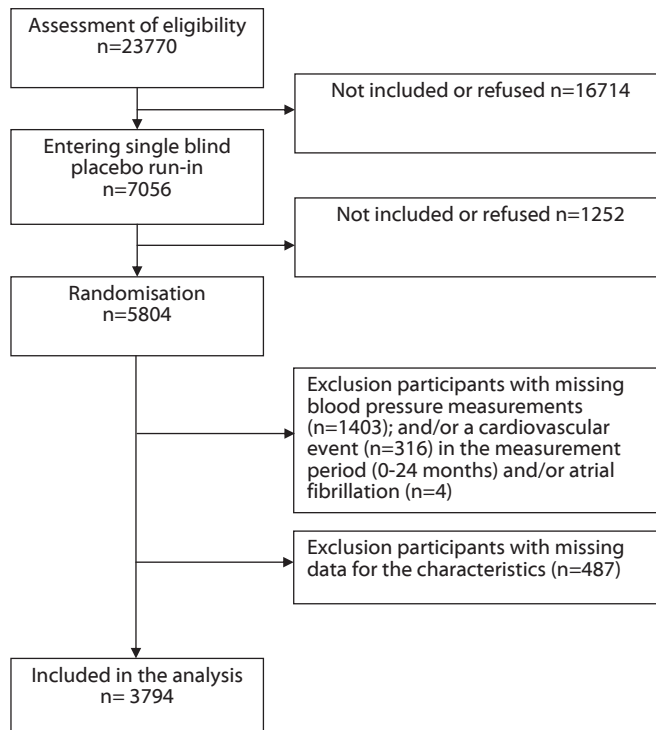


Figure 1. Flow chart

of variation (SD/ mean). The results for SD and coefficient of variation were qualitatively the same; therefore the results for SD are presented.

F-tests were used to test the variability in blood pressure variability between participants receiving pravastatin and those receiving placebo. Variability variables were split into quartiles. Baseline characteristics were calculated by quartile of SD of variability variables; they are reported as mean with SD for continuous variables and as numbers with percentage (%) for categorical variables. The association between the characteristics at baseline (independent variable) with the variability variables (dependent variable) was assessed using linear regression. The distribution of the variables C-reactive protein and interleukin-6 was skewed, therefore, these variables were log-transformed.

The markers of inflammation, endothelial function, renal function, and glucose metabolism were first analyzed separately, and then combined. The initial “minimally adjusted” regression model included adjustment for country and randomized treatment. In a subsequent model adjustment for age, gender, current smoking, average blood pressure during follow-up (systolic and diastolic blood pressure and pulse pressure), history of cardiovascular disease, history of hypertension, total cholesterol, high-density lipoprotein, and low-density lipoprotein was made. In the final model, the multivariable analysis, all biomarkers were combined to determine the subset of characteristics that were independently associated with variability in blood pressure. The beta’s from the linear regression analyses for the variables C-reactive protein and interleukin-6 are not easy to interpret as these variables were log-transformed. Therefore, the change in SD per doubling of these variables was calculated. In addition, the *R*-squared values for the models were calculated. In an additional analysis we excluded interleukin-6 from the final model to assess what effect this would have on the parameter estimates of the other variables.

A change in antihypertensive drug treatment could have influenced the SD in blood pressure. We therefore performed a sensitivity analysis in all participants that remained on the same antihypertensive treatment throughout the first 24 months.

RESULTS

Table 1 presents the baseline characteristics for the participants. Of the 3,794 participants 1,810 (47.7%) were men, the mean age was 75.2 years (SD 3.3) and 1,603 (42.3%) had a history of cardiovascular disease. The mean intra-individual SD of 9 measurements of systolic blood pressure was 14.4 mm Hg; the mean SD of diastolic blood pressure was 7.7 mm Hg and the mean SD of pulse pressure was 12.6 mm Hg. There was no significant difference in variability in blood pressure between participants receiving pravastatin

and those receiving placebo (P values 0.31, 0.92, 0.15); therefore, data from both groups were combined and all analyses were adjusted for treatment.

Table 1. Characteristics of study participants (n=3,794)

Characteristic	
Categorical variates (n, %)	
Men	1,810 (47.7%)
Current smoker	937 (24.7%)
Country	
Scotland	1,582 (41.7%)
Ireland	1,437 (37.9%)
Netherlands	775 (20.4%)
History of cardiovascular disease ^a	1,603 (42.3%)
History of hypertension	2,412 (63.6%)
Continuous variates (mean, SD)	
Age (years)	75.21 (3.32)
Average systolic blood pressure (mmHg)	153.78 (16.32)
Variability in systolic blood pressure (mmHg)	14.38 (5.11)
Average diastolic blood pressure (mmHg)	83.25 (7.54)
Variability in diastolic blood pressure (mmHg)	7.68 (2.97)
Average pulse pressure (mmHg)	70.53 (12.96)
Variability in pulse pressure (mmHg)	12.64 (4.56)
Baseline total cholesterol (mmol/L)	5.69 (0.90)
Baseline Low-density lipoprotein cholesterol (mmol/L)	3.79 (0.80)
Baseline High-density lipoprotein cholesterol (mmol/L)	1.28 (0.35)

^a Any of stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction, peripheral arterial disease surgery, or amputation for vascular disease more than 6 months before study entry.

Biological correlates of systolic blood pressure variability

Table 2 shows the baseline characteristics per quartile of variability in systolic blood pressure. Higher levels of C-reactive protein, interleukin-6 and creatinine and lower estimated glomerular filtration rate, all at baseline, were associated with higher quartiles of intra-individual variability of systolic blood pressure in the minimally adjusted analysis. Baseline levels of Von Willebrand Factor and tissue plasminogen activator were not associated with intra-individual variability in systolic blood pressure, nor was there an association between the glucose metabolism characteristics and intra-individual variability in systolic blood pressure.

Table 2. Baseline biomarkers by quartile of intra-individual systolic blood pressure variability (measured as SD of 9 measurements over 24 months)

Pathway	Baseline biomarker	Quartile of SD of systolic blood pressure					P value minimally adjusted analysis ^a
		All Subjects (n = 3794)	Q1	Q2	Q3	Q4	
			≤ 10.8 (n = 947)	>10.8 - ≤13.6 (n = 951)	>13.6 - ≤17.2 (n = 948)	>17.2 (n = 948)	
Inflammation	Log(C-reactive protein)	1.08 (1.10)	1.03 (1.07)	0.98 (1.09)	1.13 (1.12)	1.19 (1.11)	<0.001
	Log(Interleukin-6)	0.95 (0.65)	0.91 (0.66)	0.90 (0.62)	0.98 (0.65)	1.00 (0.66)	<0.001
Endothelial function	Von Willebrand factor	139.7 (45.80)	141.0 (45.87)	139.3 (45.18)	139.2 (45.71)	139.2 (46.46)	0.31
	Tissue plasminogen activator	10.93 (4.01)	10.91 (3.82)	10.92 (3.78)	10.92 (4.10)	10.97 (4.31)	0.15
Renal function	Creatinine	100.5 (21.66)	99.68 (20.17)	101.5 (21.77)	100.2 (22.03)	100.6 (22.59)	<0.01
	Estimated glomerular filtration rate	60.27 (14.14)	61.12 (13.37)	60.12 (14.26)	60.19 (14.18)	59.64 (14.69)	<0.001
Glucose metabolism	Body mass index	26.90 (4.08)	26.97 (4.07)	26.98 (4.07)	26.91 (4.15)	26.75 (4.02)	0.23
	Glucose	5.44 (1.38)	5.48 (1.40)	5.48 (1.39)	5.39 (1.35)	5.38 (1.39)	0.84
	History of diabetes	391 (10.3%)	104 (11.0)	100 (10.5)	95 (10.0)	92 (9.7)	0.67
	Log(HOMA)	0.65 (0.70)	0.67 (0.70)	0.69 (0.70)	0.61 (0.70)	0.61 (0.71)	0.26

Mean and corresponding SDs and numbers and corresponding percentage.

Abbreviation: HOMA, homeostatic model assessment.

^aAdjusted for randomised treatment code and country by linear regression. *P* for trend across quartiles.

Biological correlates of diastolic blood pressure variability

Table 3 shows the baseline characteristics per quartile of variability in diastolic blood pressure. Higher levels of C-reactive protein and interleukin-6, were associated with higher quartiles of intra-individual variability of diastolic blood pressure. In contrast to systolic blood pressure variability, higher estimated glomerular filtration rate was associated with a higher variability in diastolic blood pressure. Higher levels of tissue plasminogen activator, higher body mass index and higher level of HOMA were all associated with higher variability in diastolic blood pressure in the minimally adjusted analysis.

Table 3. Baseline biomarkers by quartile of intra-individual diastolic blood pressure variability (measured as SD of 9 measurements over 24 months)

Pathway	Baseline biomarker	Quartile of SD of diastolic blood pressure					P value minimally adjusted analysis ^a
		All Subjects (n = 3794)	Q1	Q2	Q3	Q4	
			≤ 5.7 (n = 965)	>5.7- ≤7.2 (n = 916)	>7.2 -≤ 9.1 (n = 959)	> 9.1 (n = 954)	
Inflammation	Log(C-reactive protein)	1.08 (1.10)	0.99 (1.10)	1.07 (1.08)	1.09 (1.10)	1.18 (1.11)	<0.001
	Log(Interleukin-6)	0.95 (0.65)	0.89 (0.64)	0.92 (0.64)	0.93 (0.63)	1.04 (0.68)	<0.001
Endothelial function	Von Willebrand factor	139.7 (45.80)	139.4 (43.15)	138.1 (46.04)	140.0 (46.90)	141.1 (47.05)	0.04
	Tissue plasminogen activator	10.93 (4.01)	10.96 (4.11)	10.68 (3.75)	10.94 (4.07)	11.12 (4.07)	<0.01
Renal function	Creatinine	100.5 (21.66)	101.4 (21.15)	100.1 (21.35)	100.7 (21.63)	99.71 (22.49)	0.66
	Estimated glomerular filtration rate	60.27 (14.14)	60.18 (13.60)	60.07 (13.71)	60.30 (14.19)	60.52 (15.02)	0.04
Glucose metabolism	Body mass index	26.90 (4.08)	26.81 (3.96)	26.90 (4.08)	26.93 (4.04)	26.97 (4.24)	0.03
	Glucose	5.44 (1.38)	5.43 (1.27)	5.44 (1.42)	5.46 (1.31)	5.40 (1.52)	0.65
	History of diabetes	391 (10.3%)	100 (10.4)	98 (10.7)	95 (9.9)	98 (10.3)	0.51
	Log(HOMA)	0.65 (0.70)	0.65 (0.69)	0.63 (0.67)	0.64 (0.72)	0.65 (0.72)	0.03

Mean and corresponding SDs and numbers and corresponding percentage.

Abbreviation: HOMA, homeostatic model assessment.

^aAdjusted for randomised treatment code and country by linear regression. *P* for trend across quartiles.

Biological correlates of pulse pressure variability

Higher levels of C-reactive protein ($P < 0.001$), interleukin-6 ($P < 0.001$) and tissue plasminogen activator at baseline ($P < 0.01$) were also associated with higher variability of pulse pressure in the minimally adjusted analyses (Supplementary Table 1). Moreover, lower estimated glomerular filtration rate ($P < 0.001$), higher body mass index ($P < 0.001$) and higher level of HOMA at baseline ($P < 0.01$) were also associated higher intra-individual variability in pulse pressure.

Adjusted multivariable analysis

In the adjusted multivariable analysis, the association between higher levels of interleukin-6 and higher variability of systolic and diastolic blood pressure and pulse pressure remained significant (all $P < 0.01$) (Table 4). Every doubling of interleukin-6 was associ-

ated with 0.26 higher intra-individual SD (i.e., variability) systolic blood pressure and 0.21 (higher intra-individual SD diastolic blood pressure. *R*-squared value for the adjusted multivariate model was 8.2% for systolic blood pressure variability and 4.8% for diastolic blood pressure, and 8.2% for pulse pressure variability.

Table 4. Change in intra-individual SD (of 9 measurements over 24 months) systolic and diastolic blood pressure per doubling of C-reactive protein and interleukin-6, multivariable analysis per pathway

Baseline characteristic	Systolic blood pressure				Diastolic blood pressure			
	Change in SD ^a	<i>P</i> value ^a	Change in SD ^b	<i>P</i> value ^b	Change in SD ^a	<i>P</i> value ^a	Change in SD ^b	<i>P</i> value ^b
C-reactive protein	0.10 (-0.01, 0.22)	0.09	0.07 (-0.05, 0.18)	0.25	0.06 (-0.01, 0.12)	0.10	0.04 (-0.03, 0.11)	0.22
Interleukin-6	0.28 (0.08, 0.48)	<0.01	0.26 (0.06, 0.46)	0.01	0.20 (0.09, 0.32)	<0.001	0.21 (0.09, 0.33)	<0.001

^aAdjusted for country and treatment by linear regression; *P* value calculated by linear regression.

^bAdjusted for age, gender, country, treatment, current smoking, average SBP over 2 years for variability in SBP and average DBP over 2 years for variability in DBP, history of cardiovascular disease, history of hypertension, total, HDL- and LDL- cholesterol by linear regression; *P* value calculated by linear regression.

Table 5 shows that there was no independent association between tissue plasminogen activator and variability in systolic and diastolic blood pressure in the adjusted multivariable analysis. A higher level of tissue plasminogen activator was associated with higher pulse pressure variability, every point higher of tissue plasminogen activator was associated with 0.05 (95% CI 0.01–0.09) higher SD pulse pressure. *R*-squared value for the adjusted multivariable analysis was 8.0%.

The associations between renal function and variability in blood pressure disappeared when adjusted for age, gender, current smoking, average blood pressure during follow-up (systolic and diastolic blood pressure and pulse pressure), history of cardiovascular disease, history of hypertension, and cholesterol in the multivariable analysis.

The association between body mass index and pulse pressure variability remained significant in the multivariable analysis (parameter estimate 0.06, 95% CI 0.02–0.10). *R*-squared value for the multivariate model was 8.0%.

In the final step of the analysis, all biomarkers were included in the same adjusted multivariable model. In this model, only higher levels of interleukin-6 were associated with higher variability of systolic and diastolic blood pressure and pulse pressure (all *P* < 0.02). Every doubling of interleukin-6 was associated with 0.24 higher SD systolic blood pressure, 0.19 higher SD diastolic blood pressure and 0.23 higher SD pulse pressure. Moreover, every point higher of body mass index was associated with a 0.045 (95% CI 0.004, 0.087) higher SD pulse pressure. The *R*-squared value for this adjusted multivariable model including all biomarkers was 9.0% for systolic blood pressure variability, 5.0% for diastolic blood pressure variability and 8.7% for pulse pressure variability.

Table 5. Associations with systolic and diastolic blood pressure variability (intra-individual SD of 9 measurements over 24 months), multivariable analysis per pathway

Pathway	Baseline characteristic	Systolic blood pressure			Diastolic blood pressure		
		Beta (95% CI) ^a	P value	Beta (95% CI) ^b	Beta (95% CI) ^a	P value	Beta (95% CI) ^b
Endothelial function	Von Willebrand factor	-0.003 (-0.006, 0.001)	0.17	-0.003 (-0.006, 0.001)	0.002 (-0.001, 0.004)	0.14	0.002 (-0.001, 0.004)
							0.16
Renal function	Tissue plasminogen activator	0.04 (-0.01, 0.08)	0.09	0.04 (-0.01, 0.08)	0.03 (0.01, 0.05)	0.01	0.02 (-0.01, 0.05)
	Creatinine	-0.004 (-0.016, 0.008)	0.47	0.024 (-0.002, 0.051)	-0.005 (-0.012, 0.002)	0.15	0.014 (-0.002, 0.030)
Glucose metabolism	Estimated glomerular filtration rate	-0.041 (-0.059, -0.022)	< 0.01	0.011 (-0.029, 0.051)	-0.014 (-0.025, -0.003)	0.013	0.020 (-0.004, 0.044)
	Body mass index	-0.02 (-0.06, 0.03)	0.46	-0.04 (-0.08, 0.01)	0.01 (-0.01, 0.04)	0.18	0.02 (-0.01, 0.04)
	Glucose	-0.01 (-0.18, 0.16)	0.88	0.00 (-0.17, 0.17)	-0.04 (-0.14, 0.06)	0.44	-0.01 (-0.11, 0.09)
	History of diabetes	-0.24 (-0.95, 0.46)	0.50	-0.29 (-0.98, 0.40)	-0.12 (-0.53, 0.29)	0.56	-0.27 (-0.68, 0.14)
	Log (HOMA)	-0.11 (-0.40, 0.19)	0.48	-0.16 (-0.46, 0.14)	0.12 (-0.05, 0.29)	0.18	0.08 (-0.10, 0.25)

Abbreviation: HOMA, homeostatic model assessment.
^aAdjusted for country and treatment by linear regression.
^bAdjusted for age, gender, country, treatment, current smoking, average SBP over 2 years for variability in SBP and average DBP over 2 years for variability in DBP, history of cardiovascular disease, history of hypertension, total, HDL- and LDL- cholesterol by linear regression.

In an additional analysis we excluded interleukin-6 from the final multivariable model. In this model, higher level of C-reactive protein was associated with higher systolic and diastolic blood pressure variability as well as higher pulse pressure variability (all $P < 0.01$).

In a sensitivity analysis we explored the effect of excluding those participants ($n = 1,816$) with a change in antihypertensive drug treatment (defined as a change in listed antihypertensive drugs), and repeating the analysis for only those participants ($n = 1,978$) who remained on the same antihypertensive drugs throughout the first 24 months; in these analyses there was no material change in the relationships observed in the whole cohort.

DISCUSSION

This study shows that higher interleukin-6 levels are associated with visit-to-visit variability in systolic and diastolic blood pressure as well as pulse pressure in an older population at high risk for cardiovascular disease. In addition, higher body mass index was associated with higher visit-to-visit variability in pulse pressure. These associations were independent of various cardiovascular risk factors and average blood pressure and remained present when all participants that had a change in antihypertensive drug treatment were excluded.

Previously it has already been suggested that visit-to-visit variability in blood pressure is not a random phenomenon.⁸ Several underlying mechanisms have been proposed with regard to higher levels of visit-to-visit variability in blood pressure.^{8,35,36} Some have suggested that higher blood pressure variability might identify people with subclinical inflammation.²⁵ In animal models, variability of blood pressure has been associated with higher levels of C-reactive protein.^{21,24} In the present study elevated interleukin-6 was indeed associated with variability in systolic and diastolic blood pressure as well as pulse pressure. In contrast, elevated C-reactive protein was not independently associated with higher visit-to-visit variability in blood pressure, in line with other studies.¹¹ However, when we excluded interleukin-6 from the final multivariable analysis, higher level of C-reactive protein became associated with higher variability in systolic and diastolic blood pressure as well as pulse pressure. This effect is biologically plausible; adjusting for interleukin-6 implies adjusting in the causal pathway, since interleukin-6 stimulates the production of C-reactive protein. Interleukin-6 and C-reactive protein were measured at baseline, prior to the measure of variability, therefore, we could not assess causal relationships. We hypothesize that subclinical inflammation may lead to higher blood pressure variability and as a result, is associated with higher risk of cardiovascular disease. Another explanation is that subclinical inflammation itself

causes higher risk of cardiovascular disease and higher blood pressure variability. Higher blood pressure variability could then be regarded as a marker of the association between subclinical inflammation and cardiovascular disease.

Recent evidence in a small sample of African Americans indicates that higher blood pressure variability is linked with endothelial injury, decreased endothelial functioning and disturbances in vascular smooth muscle functioning.^{22,23} It has been suggested that tissue plasminogen activator, which is synthesized mainly in the vascular endothelium, is a marker for endothelial function, with higher levels of tissue plasminogen activator indicating endothelial dysfunction.³⁷⁻³⁹ In our study, the associations between tissue plasminogen activator and blood pressure variability was only observed for pulse pressure variability in the adjusted analysis. The evidence suggesting that impaired endothelial function underlies the higher blood pressure variability presented in our study is therefore only limited and less convincing as compared to the inflammation pathway. We have previously shown that, pulse pressure variability was somewhat associated with long-term stroke risk in an older population at risk for cardiovascular disease, while systolic and diastolic blood pressure variability were not.¹⁶ This could indicate that different underlying mechanism might play a role. Endothelial injury, resulting in endothelial dysfunction could be a result of variability in pulse pressure. Whether higher levels of tissue plasminogen activator are just a marker of higher variability of pulse pressure or a true mediator in the relation between variability in pulse pressure and cardiovascular disease is uncertain. The association between estimated glomerular filtration rate and blood pressure variability disappeared when adjusted for age, gender, current smoking, average blood pressure, history of cardiovascular disease, history of hypertension, and cholesterol. This could indicate that impaired renal function does not underlie high levels of visit-to-visit-variability of blood pressure. The previously observed association between history of diabetes and blood pressure variability¹⁰ was not replicated in our study. We only found a low parameter estimate between body mass index and variability in pulse pressure, suggesting that glucose metabolism might not be relevant in an older population at risk for cardiovascular disease. Furthermore, it has been suggested that higher blood pressure variability may be a manifestation of baroreflex regulation of blood pressure.^{5,20} However, decreased heart rate variability is associated with an increased risk of mortality in a previous study,⁴⁰ suggesting that heart rate variability does not play a role in the association between variability in blood pressure and mortality.

Another explanation may lie in cognitive decline. Both interleukin-6 levels⁴¹ and C-reactive protein levels⁴² and blood pressure variability¹⁹ have been associated with cognitive decline. A common explanation may be that either cardiovascular burden, as measured in an increased level of interleukin-6 and C-reactive protein as well as increased blood pressure variability cause cognitive decline. Conversely, cognitive

decline may cause increased inflammatory markers (as a result of altered lifestyle, such as eating) and blood pressure variability.

The differences found in the associations between the different biomarkers and the variability in systolic and diastolic blood pressure and pulse pressure might reflect the differences in the associations with cardiovascular disease which were previously shown.¹⁶

Identifying inflammation as a factor associated with intra-individual variability in blood pressure and excluding other factors such as glucose, may help elucidate the underlying mechanisms of intra-individual variability in blood pressure. The model explains up to 9% of the variability in blood pressure, this modest fit could be considered to be a weakness of the study, despite small *P* values that reflect the large sample size. However, since we have only one baseline measure of biomarkers, this could be an underestimation of the true association due to regression dilution bias. We argue that part of the observed association could also be attributed to the fact that blood pressure was measured once every 3 months and the time of the day could vary between these measurements. The season of measurement could also influence the variability in blood pressure. This exogenous introduced variability however is unlikely to be of any effect on the influence of blood pressure variability on the pathogenesis of cardiovascular disease. Inflammation is one of the possible biological pathways of higher variability in blood pressure not explained by these exogenous factors. Other potential biological mechanisms remain unknown up to now. The change in drugs used as antihypertensive treatment could have influenced the blood pressure variability. This is, however, not expected to influence the association between interleukin-6 and blood pressure variability. The results did not materially changed when all participant that had a change in antihypertensive drug treatment (defined as a change in listed antihypertensive drugs) were excluded. It would be interesting to know if baseline variability in blood pressure predicts subsequent changes in inflammation biomarkers using longitudinal data. Metabolomics might also be a potential direction for further research to explore novel mechanisms of blood pressure variability.

This study was embedded in the PROSPER trial, a large double-blinded randomized placebo-controlled trial in older persons. This landmark clinical trial with older participants was performed following guidelines of good clinical practice. Blood pressure was not part of the inclusion or exclusion criteria for the PROSPER trial, therefore, people with the full range of baseline blood pressure and variability in blood pressure were included. The estimation of visit-to-visit variability should be reasonably reliable because of the frequency of measurements (nine measurements). The large sample size is another strength of this study. This study has certain limitations. A potential limitation is that the participants were randomized to an intervention (pravastatin vs. placebo), however, we found no difference in variability in blood pressure between both ran-

domized groups and all analyses were adjusted for the randomized treatment. Second, given the cross-sectional design of the study, we cannot conclude whether variability in blood pressure lead to subclinical inflammation, or vice versa. Third, we were lacking measures of baroreflex sensitivity, therefore this potential biological mechanism underlying individual variability in blood pressure in older persons could not be analyzed in this study. In addition, some of the associations between variability in blood pressure and baseline biomarkers may not be linear, however, we do not have sufficient power in our data to explore this fully. The trend or slope of blood pressure over time may have influenced the SD of blood pressure and thus can be considered as a potential confounding variable. The analysis was not adjusted for the trend or slope in blood pressure as we believe that this is beyond the scope of this paper. The final analysis were adjusted for randomized treatment code, country, age, gender, current smoking, average blood pressure, history of cardiovascular disease, history of hypertension, and cholesterol. One could argue that when adjusting for all these additional variables one might have introduced confounding instead of the intended adjustment for confounding. The step wise analysis approach was chosen to provide the most transparent results. Finally, there was no correction for multiple testing. These corrections could have resulted in type II errors and therefore prematurely discarding potentially useful observations which may help to elucidate the underlying mechanisms of intra-individual variability in blood pressure.

For the interpretation of the results it is important to note that the excluded patients are intrinsically different due to the criteria used for selection. The excluded patients include those with events in the measurement period (0–24 months, $n = 316$) and therefore differed in a systematic manner. They likely include the “sicker” patients. Another of our criteria is the requirement to have blood pressure measured at each of the nine time points during the 24 months. This excludes the non-attenders.

In conclusion, in this study of older population at risk, higher levels of interleukin-6 were independently associated with visit-to-visit variability in systolic and diastolic blood pressure and pulse pressure. Additional research is needed to confirm these results and to evaluate their potential clinical significance and potential mechanisms to reduce visit-to-visit variability.

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APPENDIX

Supplemental Table 1. Baseline biomarkers by quartile of intra-individual pulse pressure variability (measured as SD of 9 measurements over 24 months)

Pathway	Baseline biomarker	Quartile of SD of pulse pressure					P value minimally adjusted analysis ^a
		All Subjects (n= 3794)	Q1 ≤ 9.4 (n = 959)	Q2 >9.4 - ≤12.1 (n = 946)	Q3 >12.1 - ≤15.2 (n = 943)	Q4 >15.2 (n = 946)	
Inflammation	Log(C-reactive protein)	1.08 (1.10)	0.99 (1.08)	0.99 (1.10)	1.16 (1.12)	1.19 (1.09)	<0.001
	Log(Interleukin-6)	0.95 (0.65)	0.90 (0.65)	0.89 (0.64)	0.98 (0.66)	1.01 (0.64)	<0.001
Endothelial function	Von Willebrand factor	139.7 (45.80)	139.5 (45.13)	139.4 (46.16)	140.0 (45.62)	139.8 (46.34)	0.95
	Tissue plasminogen activator	10.93 (4.01)	10.77 (3.87)	10.94 (3.90)	10.84 (4.06)	11.17 (4.19)	<0.01
Renal function	Creatinine	100.5 (21.66)	100.2 (21.11)	100.6 (20.69)	101.1 (21.94)	100.1 (22.87)	0.10
	Estimated glomerular filtration rate	60.27 (14.14)	61.22 (13.66)	60.24 (13.67)	59.74 (14.13)	59.86 (15.03)	<0.001
Glucose metabolism	Body mass index	26.90 (4.08)	26.68 (3.88)	26.85 (4.17)	26.70 (3.94)	27.39 (4.27)	<0.001
	Glucose	5.44 (1.38)	5.46 (1.38)	5.47 (1.48)	5.40 (1.27)	5.41 (1.40)	0.20
	History of diabetes	391 (10.3%)	100 (10.4)	99 (10.5)	90 (9.5)	102 (10.8)	0.07
	Log(HOMA)	0.65 (0.70)	0.63 (0.71)	0.63 (0.68)	0.64 (0.70)	0.68 (0.71)	<0.01

Mean and corresponding SDs and numbers and corresponding percentage.

Abbreviation: HOMA, homeostatic model assessment.

^aAdjusted for randomised treatment code and country by linear regression. P for trend across quartiles.



Chapter 4

Low blood pressure predicts increased mortality in very old age even without heart failure: the Leiden 85-plus Study

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Eur J Heart Failure 2013;15:528-533.

ABSTRACT

Aims

To investigate whether low systolic blood pressure is predictive for increased mortality risk in 90-year-old subjects without heart failure, defined by low levels of NT-proBNP, as well as in 90-year-old subjects with high levels of NT-proBNP.

Methods and results

This study was embedded in the Leiden 85-plus Study, an observational population-based prospective study. All 90-year-old participants ($n = 267$) were included between 2002 and 2004 and followed up for mortality for at least 5 years. Differences in mortality risks were compared between participants with low systolic blood pressure (≤ 150 mmHg) and high systolic blood pressure (> 150 mmHg) within strata of low NT-proBNP (< 284 pg/mL for women and > 306 pg/mL for men = lowest tertile) vs. high NT-proBNP (middle and highest tertile) at age 90 years. During maximal follow-up of 7.2 years, 212 participants (79%) died. Among participants with low NT-proBNP, low systolic blood pressure gave a two-fold increased risk (hazard ratio 2.0, 95% confidence interval 1.1–3.4) compared with participants with high systolic blood pressure. For participants with high NT-proBNP, low systolic blood pressure provided a 1.7 increased mortality risk (95% confidence interval 1.2–2.3) compared with high systolic blood pressure.

Conclusion

Low systolic blood pressure is predictive for increased mortality risk in 90-year-old subjects, irrespective of the NT-proBNP level. Therefore, the absence or presence of heart failure as determined by NT-proBNP does not influence the prognostic value of low systolic blood pressure with regard to mortality in the oldest old.

INTRODUCTION

High systolic blood pressure is an established risk factor for cardiovascular disease and mortality in middle-aged persons. In contrast, observational data on the predictive relationship between systolic blood pressure and mortality in very old age are less consistent.¹⁻⁴ One large meta-analysis showed that high systolic blood pressure predicts increased mortality risk in all age groups, but also that this relationship was considerably attenuated with age.¹ Others, especially observational studies in exclusively elderly populations, have shown that not high, but low systolic blood pressure predicts increased mortality.²⁻⁴ To date, it remains unknown which mechanism(s) are responsible for this 'inversion of risk prediction'.

A plausible explanation is that (subclinical) heart failure may, at least in part, underlie this 'inversion of risk prediction'.^{2,4-7} Prolonged and uncontrolled hypertension can lead to heart failure that might lower blood pressure.⁸ Indeed, patients with heart failure tend to have lower blood pressure values. Our group previously reported that very old subjects with low systolic blood pressure have an impaired cardiac function.⁵ Therefore, we hypothesized that in very old subjects without heart failure, low systolic blood pressure is not predictive for increased mortality risk compared with those with high systolic blood pressure, but, instead, still follows the usual pattern (low systolic blood pressure associated with low risk, and high systolic blood pressure associated with high risk).

Diagnosing heart failure in old age is challenging. Symptoms and signs in combination with NT-proBNP reliably identify the presence or absence of heart failure in the vast majority of patients.⁹ NT-proBNP alone is a sensitive but not highly specific marker of heart failure. The negative predictive value of low levels of NT-proBNP is robust, and low levels of NT-proBNP are reported to exclude heart failure.¹⁰⁻¹² Also, within the Leiden 85-plus Study, it was shown that low NT-proBNP levels exclude echocardiographic abnormalities in very old age.¹³

The present study investigates the predictive relationship between systolic blood pressure and mortality in a population-based cohort of nonagenarians without heart failure as evidenced by low levels of NT-proBNP, as well as in nonagenarians with high levels of NT-proBNP.

METHODS

Study population

The Leiden 85-plus Study is a prospective population-based study in 85-year-old inhabitants of the city of Leiden (The Netherlands). The study design and characteristics of the cohort have been described in detail.^{14,15} Between September 1997 and September 1999,

705 people in the 1912–1914 birth cohort reached the age of 85 years and were eligible to participate in the study. No exclusion criteria were used. Fourteen people died before enrolment; a total of 599 (87%) people gave informed consent and were enrolled. Of the 599 participants enrolled in the study at age 85 years, 295 died before the age of 90, and 37 refused further participation or refused blood sampling. Thus, for the present study, 'baseline measurements at age 90 years', including systolic blood pressure and NT-proBNP levels, were available for 267 participants, all 'included' between 2002 and 2004. Participants were visited by a research nurse at their place of residence to collect information on socio-demographic characteristics, as well as a venous blood sample. The Medical Ethics Commission of the Leiden University Medical Center approved the study, and all participants gave informed consent. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Blood pressure and blood pressure categories

At age 90, blood pressure was measured twice with an interval of 2 weeks. Blood pressure was measured using a mercury sphygmomanometer, in the seating position after at least 5 min rest without having performed vigorous exercise during the preceding 30 min. The systolic value was measured at the onset of phase 1 of the Korotkoff sounds. For the analysis, we used the mean of the two systolic values at age 90 years.

Systolic blood pressure values were divided into two categories, 'low' and 'high' systolic blood pressure. Low systolic blood pressure was defined as a systolic blood pressure ≤ 150 mmHg, and high systolic blood pressure was defined as a systolic blood pressure >150 mmHg. This cut-off was based on the target value used in studies assessing the risks and benefits of treating hypertension in individuals aged ≥ 80 years.¹⁶

N-terminal pro brain natriuretic peptide and categories of heart failure

Serum levels of NT-proBNP were measured for all participants at age 90 in one batch using the NT-proBNP assay of Roche Diagnostics (Mannheim, Germany) on a Roche Modular E-17 automated immunoanalyser. The within-run coefficient of variation was $\leq 2\%$ and total variation was $\leq 6\%$ at all levels measured (400–13 500 pg/mL). Low levels of NT-proBNP can be used to rule out the diagnosis of heart failure.^{10–12} Since clinical cut-offs for NT-proBNP in very old age are still the subject of debate,¹² in the present study we used gender-specific tertiles of NT-pro-BNP levels. Heart failure was considered absent in all participants in the lowest NT-proBNP tertile (NT-proBNP <284 pg/mL for women and <306 pg/mL for men). Heart failure was considered to be probably present in the participants in the middle and highest NT-proBNP tertile (NT-proBNP ≥ 284 pg/mL for women and ≥ 306 pg/mL for men).

Other clinical characteristics

Each participant's general practitioner (or, if applicable, nursing home physician) was interviewed annually about the participant's medical history, using standardized questionnaires, including questions on present and past cardiovascular¹⁷ and non-cardiovascular morbidities.

Mortality

All participants were followed for mortality from age 90 years onwards. Dates of death were obtained from municipality records, with the censoring date 31 December 2009 (until ages 95–97 years). Specific data on cause of death were obtained from Statistics Netherlands, where all national death certificates are coded according to the International Classification of Diseases and Related Disorders, 10th revision (ICD-10).¹⁸ Causes of death were divided into two groups: cardiovascular mortality (ICD codes I00–I99) and non-cardiovascular mortality (all other ICD codes).

Statistical analysis

Participants were divided into two groups based on the NT-proBNP levels (lowest gender-specific tertile vs. middle and highest gender-specific tertile). Baseline summary characteristics are reported as mean with standard deviation (SD) for continuous variables and as numbers with percentage for categorical variables. Distributions of categorical clinical characteristics were compared using χ^2 tests, and continuous data were compared using independent t-tests. Time to event curves were constructed with the Kaplan–Meier method and compared using log rank test. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were calculated with Cox proportional hazard models. The analysis of the mortality risk for the lowest tertile NT-proBNP compared with the middle/highest tertiles NT-proBNP was adjusted for the continuous systolic blood pressure value. The analysis of the mortality risk for low systolic blood pressure compared with high systolic blood pressure was adjusted for the continuous NT-proBNP value. The HRs for the two NT-proBNP groups were calculated with Cox proportional hazard models, containing the systolic blood pressure category (low or high) as a categorical variable. These HRs were adjusted for sex only, because the present study focused on the question of whether the predictive value of low systolic blood pressure for mortality in very old age is dependent on the presence of (subclinical) heart failure and not on in-depth aetiology.¹⁹ All participants were 90 years of age, so no adjustment for age was made. HRs per increase in SD for systolic blood pressure at age 90 years and NT-proBNP at age 90 years, respectively, were also analysed with Cox proportional hazard models. In the additional model, the HRs were adjusted for the use of antihypertensive medication and history of diabetes, cardiac morbidity, other vascu-

lar morbidity, non-cardiovascular morbidity (including history of COPD, malignancies, arthritis, Parkinson's disease, and hip fracture), and hypertension. To explore whether the predicted difference in mortality risk was attributable to terminally ill patients, participants who died within 3 months after baseline were excluded in an additional sensitivity analysis. To evaluate the influence of the choice to combine the middle and highest tertile of NT-proBNP in the analyses, the analyses were repeated including only the lowest and highest tertile of NT-proBNP in the analyses.

Data analysis was performed using SPSS 17 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Study population

Table 1 presents the baseline characteristics according to NT-proBNP values. At age 90 years, < 30% of the participants were male, and almost 40% of the participants were institutionalized. Half of the study population had a history of cardiac morbidity, and almost half of the population used antihypertensive drugs. At age 90, mean systolic blood pressure was 152 mmHg (range 105–203 mmHg). There was no difference in systolic blood pressure at age 90 between participants with high NT-proBNP and those with low NT-proBNP. Participants with high NT-proBNP more often had a history of cardiac disease compared with those with low NT-proBNP (56% vs. 36%, $P = 0.002$). There were no differences in other clinical and socio-demographic characteristics between participants with low and high NT-proBNP ($P \geq 0.05$).

Mortality

During maximal follow-up of 7.2 years (median 3.6), 212 (79%) of the 267 participants died from age 90 years onwards. Participants with high NT-proBNP had a 2.9 increased mortality risk (95% CI 2.1–4.0) compared with those with low NT-proBNP, adjusted for the continuous systolic blood pressure value at age 90 years (HR 2.5, 95% CI 1.7–3.5 when adjusted for the use of antihypertensive medication and concomitant diseases mentioned in Table 1). A 1 SD increase in NT-proBNP (1915 pg/mL) was associated with an increased mortality risk (HR 1.39, 95% CI 1.25–1.55). Participants with low systolic blood pressure had a 1.6-fold increased mortality risk (95% CI 1.2–2.1) compared with participants with high systolic blood pressure, adjusted for the continuous NT-proBNP value at age 90; and HR 2.0 (95% CI 1.4–2.7) when adjusted for the use of antihypertensive medication and concomitant diseases mentioned in Table 1. A 1 SD increase in systolic blood pressure (18 mmHg) was associated with a decreased mortality risk (HR 0.77, 95% CI 1.25–1.55).

Table 1. Baseline sociodemographic and clinical characteristics at age 90 years, according to N-terminal pro-brain natriuretic peptide (NT-proBNP) value (n=276)

		NT-proBNP ^a	
	Overall (n=267)	Low (n=90)	High (n=177)
Sociodemographics			
Male (%)	73 (27%)	25 (28%)	48 ^b (27%)
Institutionalized (%)	100 (38%)	32 (36%)	68 ^b (38%)
Primary school only (%)	167 (63%)	55 (61%)	112 ^b (64%)
State pension only (%)	41 (15%)	10 (11%)	31 ^b (18%)
Systolic blood pressure (SD)	152 (18)	152 (17)	151 ^c (18)
History of (non)cardiovascular comorbidity			
Cardiac morbidity ^d (%)	131 (49%)	32 (36%)	99 ^e (56%)
Other vascular morbidity ^f (%)	44 (17%)	15 (17%)	29 ^b (16%)
Non-cardiovascular morbidity ^g (%)	170 (64%)	55 (61%)	115 ^b (65%)
Hypertension (missing n=5) (%)	145 (55%)	44 (50%)	101 ^b (58%)
Use of antihypertensive drugs (missing n=46) (%)	104 (47%)	30 (41%)	74 ^b (50%)
Diabetes	47 (18%)	11 (13%)	36 ^b (21%)

SD, standard deviation.

^a Low NT-proBNP <284 pg/mL for women and <306 pg/mL for men; high NT-proBNP ≥284 pg/mL for women and ≥306 pg/mL for men.^b χ^2 $P \geq 0.05$.^c t -test $P \geq 0.05$.^d Presence of a medical history of myocardial infarction, angina pectoris, arrhythmias, or heart failure.^e χ^2 $P = 0.002$.^f Including history of stroke and peripheral arterial disease.^g Including history of chronic obstructive pulmonary disease, malignancies, arthritis (including arthrosis, rheumatoid arthritis and polymyalgia rheumatica), Parkinson's disease, and hip fracture.

Figure 1 presents the Kaplan–Meier analysis of time to all-cause mortality depending on the systolic blood pressure at age 90 years for those in the low and high NT-proBNP category. It shows that low systolic blood pressure was associated with an increased cumulative all-cause mortality compared with high systolic blood pressure, in both the low and high NT-proBNP categories. In participants with low and in participants with high NT-proBNP, those with low systolic blood pressure had an increased all-cause mortality risk compared with participants with high systolic blood pressure (Table 2). The same was seen after analysis of the data with full adjustments for the use of antihypertensive medication and a range of concomitant diseases (HR 2.6, 95% CI 1.3–5.3 in participants with low NT-proBNP and low systolic blood pressure compared with those with low NT-proBNP and high systolic blood pressure, and HR 2.1, 95% CI 1.5–3.1 in participants with high NT-pro-BNP and low systolic blood pressure compared with those with high NT-proBNP and high systolic blood pressure). When the same analysis was carried out

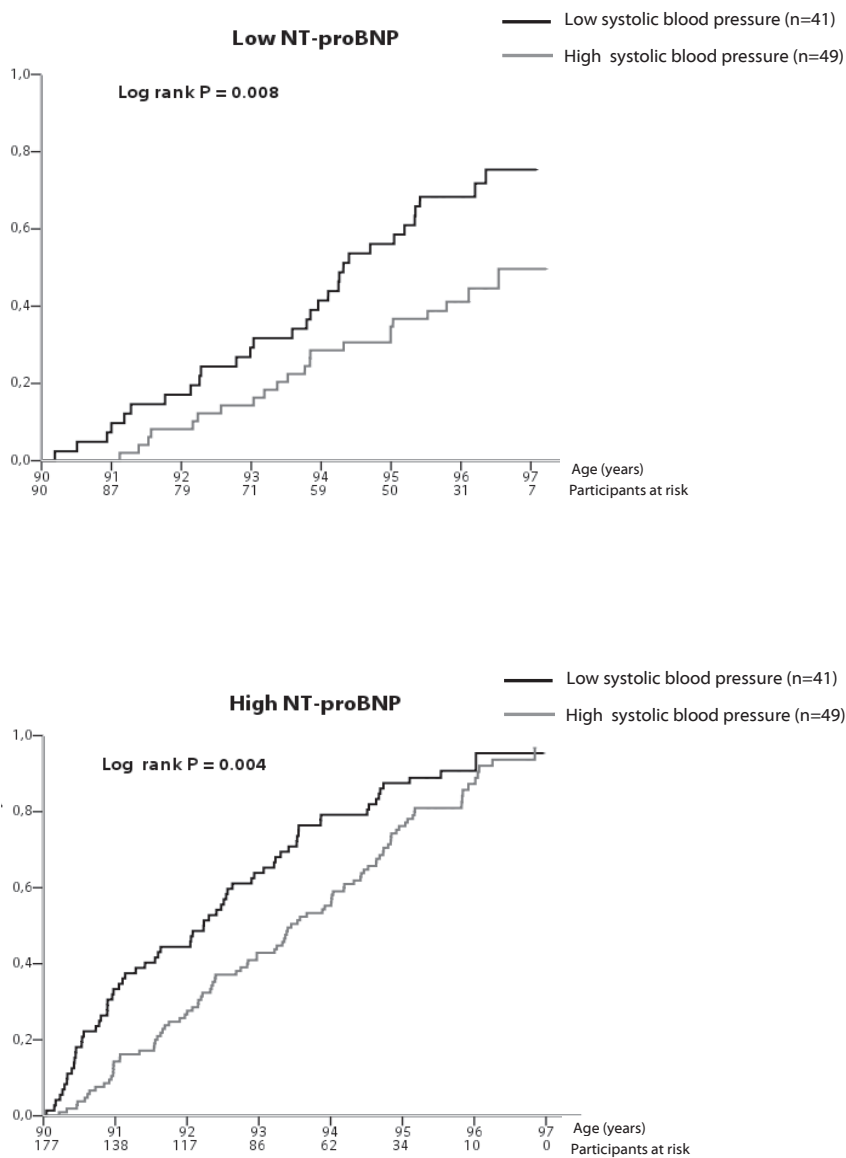


Figure 1. Cumulative all-cause mortality depending on the systolic blood pressure at age 90 years for (a) participants from age 90 years onwards with low NT-proBNP(<284 pg/mL for women and <306 pg/mL for men); and (b) for participants with high NT-proBNP (≥284 pg/mL for women and ≥306 pg/mL for men)

for cause-specific mortality, the same risk patterns were observed for cardiovascular and non-cardiovascular mortality (Table 2).

When participants who died within 3 months after baseline were excluded, similar increased mortality risks were seen. In both those with low and those with high NT-proBNP, low systolic blood pressure still predicted increased mortality risk (HR 1.9, 95% CI 1.0–3.3 and HR 1.6, 95% CI 1.1–2.2, respectively).

When the analyses were repeated including only the lowest and the highest NT-proBNP tertile, the same results emerged (data not shown).

Table 2. Mortality in low/high N-terminal pro-brain natriuretic peptide categories, depending on systolic blood pressure at age 90 years (n=267)

	Cumulative 5-year mortality		HR (95% CI) ^c
	Low systolic blood pressure ^a (93/113) ^b	High systolic blood pressure (116/154) ^b	
All-cause mortality ^d			
Low NT-proBNP ^e	30/41	22/49	2.0 (1.1-3.4)
High NT-proBNP ^e	66/72	94/105	1.7 (1.2-2.3)
Cardiovascular mortality			
Low NT-proBNP	9/40	6/49	2.5 (0.9-7.2)
High NT-proBNP	22/72	35/101	1.4 (0.8-2.4)
Non-cardiovascular mortality			
Low NT-proBNP	20/40	16/49	1.7 (0.9 -3.3)
High NT-proBNP	44/72	58/104	1.8 (1.2 -2.6)

CI, confidence interval; HR, hazard ratio.

^a Low systolic blood pressure ≤ 150 mmHg; high systolic blood pressure >150 mmHg.

^b Number of deceased/total.

^c Sex-adjusted hazard ratios (95% CI); hazard ratios express risk of mortality associated with low blood pressure compared to high blood pressure (as a reference category).

^d Complete cause-specific mortality data were missing for five participants.

^e Low NT-proBNP <284 pg/mL for women and <306 pg/mL for men; high NT-proBNP ≥ 284 pg/mL for women and ≥ 306 pg/mL for men.

DISCUSSION

This study shows that, in nonagenarians, low systolic blood pressure defined as ≤ 150 mmHg is predictive for an almost doubled mortality compared with high systolic blood pressure, in those without (subclinical) heart failure based on low NT-proBNP levels as well as in those with high NT-proBNP levels. Therefore, we could not confirm the hypothesis that impaired cardiac function with concomitant low systolic blood pressure, in part, underlies the association between low blood pressure and increased mortality. The potential clinical relevance of these findings, after replication in another cohort,

may become clearer when alternative explanations for the observed inversion of risk prediction of low systolic blood pressure in very old age have been studied.

Strengths and limitations of study

The use of tertiles of NT-proBNP could potentially introduce misclassification. At age 90 years, heart failure was considered absent based on low NT-proBNP values, but, vice versa, no explicit diagnosis of heart failure was made based on higher NT-proBNP values. The level of the lowest tertile in the present study (<284 pg/mL for women and <306 pg/mL for men) is, however, in line with cut-off points used to exclude heart failure in earlier studies.^{10,12,13} Also, there was no difference in the predictive value of low systolic blood pressure in the analysis adjusted for the continuous NT-proBNP value, confirming that the chosen cut-off value did not influence our results. Misclassification by using tertiles of NT-proBNP is therefore minimal.

We chose the cut-off value of 150 mmHg for high systolic blood pressure at age 90 years. This could be seen as an arbitrary choice. However, this value is based on the target value of systolic blood pressure used in the 2011 revision of the Dutch Guideline on Cardiovascular Risk Management,²⁰ as well as studies assessing the risks/benefits of treating hypertension in individuals aged ≥ 80 years,¹⁶ indicating that this cut-off value may be clinically more relevant than the formal cut-off value of 140 mmHg as incorporated in the World Health Organization (WHO) definition of hypertension.²¹ This was supported by the fact that there was no difference in the predictive value of high NT-proBNP in the analysis adjusted for the continuous systolic blood pressure value.

It may be considered a limitation of the present study that only participants aged 90 years were evaluated. Since our study population was a selection of strong survivors, we cannot extrapolate our conclusions to younger people. Still, our general population-based study is well suited to show the 'proof of principle' of our research question. Nevertheless, replication in other, preferably larger, study populations is warranted.

Comparison with other studies

The relationship between high NT-proBNP and increased mortality risk, as well as the relationship between low systolic blood pressure and increased mortality risk described in the present study are in line with earlier observational studies in the elderly population showing that high (NT-pro)BNP²²⁻²⁵ and low systolic blood pressure²⁻⁴ are each associated with an increased mortality risk. The present study shows that, in nonagenarians, low systolic blood pressure remains associated with a doubled mortality risk even when (subclinical) heart failure is ruled out and regardless of the use of antihypertensive medication and concomitant diseases. To our knowledge, no other study has analysed

the association between low systolic blood pressure and increased mortality in participants in whom heart failure was excluded based on their NT-proBNP level.

Implications

Although the present study was not aimed at investigating aetiological mechanisms behind the observed associations, it is tempting to hypothesize that the increased all-cause mortality risk associated with low systolic blood pressure as well as the increased all-cause mortality risk associated with heart failure are two unrelated phenomena. This finding warrants additional studies on the underlying mechanism(s). Also, instead of focusing on a monocausal explanation (e.g. heart failure,⁵ atrophy of the brain, or chronic hypoperfusion), low systolic blood pressure in very old age could also be a marker of an underlying syndrome that is associated with increased mortality (such as general wasting, inflammation, and sarcopenia). Also, the 'inversion of risk prediction' of high blood pressure in old age is not a unique phenomenon. In old age, high cholesterol²⁶ and obesity²⁷ are no longer risk factors for mortality, and in some studies have even been shown to be associated with better survival. These paradoxical observations have also been referred to as 'reverse epidemiology', 'inverse epidemiology', or 'risk factor paradox'. In chronic dialysis patients, the reverse epidemiology of high blood pressure,²⁸ high body mass index,²⁹ and high serum cholesterol or serum creatinine concentration²⁹ has also been described. The same reverse epidemiology was observed in other chronic diseases such as chronic heart failure,³⁰ advanced COPD,³¹ and rheumatoid arthritis.³²

Conclusion

In conclusion, the present study shows that in very old age, low systolic blood pressure is associated with an almost doubled mortality risk, even when there is no evidence of underlying heart failure. Thus, heart failure does not underlie the 'inversion of risk prediction' of systolic blood pressure in very old age. Future studies are needed to replicate these findings, and to gain more insight into the aetiological mechanisms and clinical implications.

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Chapter 5

Blood pressure trends and mortality: the Leiden 85-plus Study

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J Hypertens 2013;31:63-70.

ABSTRACT

Objective

To evaluate the independent contributions of both the trend in SBP and the SBP value at age 90 to the prediction of mortality in nonagenarians.

Methods

The trend in SBP between 85 and 90 years and SBP at age 90 years were assessed in a population-based sample of 271 participants (74 men and 197 women) aged 90 years of the Leiden 85-plus Study, an observational population-based prospective follow-up study (started 1997). Primary endpoint, followed up over 5 years (median 3.6 years), was all-cause mortality.

Results

A decreasing trend in SBP between 85 and 90 years (decline ≥ 2.9 mmHg/year) was associated with increased mortality compared to an average SBP trend (hazard ratio 1.45, 95% confidence interval 1.02–2.06), independent of SBP at age 90. The effect was stronger in institutionalized participants compared to those living independently [hazard ratio 1.87 (1.10–3.19) and hazard ratio 1.30 (0.81–2.09)]. After analysis with a fully adjusted model, the estimate approached unity [hazard ratio 1.08 (0.60–1.86)]. Overall, 90-year-old participants with SBP of 150 mmHg or less had a 1.62 times increased mortality risk compared to those with SBP more than 150 mmHg (1.21–2.20), independent of the SBP trend in preceding years. This applied to those with and without antihypertensive drugs and those with and without history of cardiovascular disease or noncardiovascular disease. In the fully adjusted model, the estimate was 1.47 (0.90–2.40).

Conclusion

In very old age, both decreasing trend in SBP over the previous 5 years and the current SBP value independently contribute to prediction of all-cause mortality. Therefore, in individual patients, all available preceding SBP measurements should be taken into account.

INTRODUCTION

Hypertension is a common condition with increasing age,^{1,2} but, so far, data on the association between a single blood pressure measurement and mortality in very old age are surprisingly conflicting.³⁻¹³ In a large meta-analysis of observational data from 61 studies,³ both high SBP and DBP were independently predictive of cardiovascular mortality in all age groups. However, this association attenuated considerably with age. In contrast, several observational studies in exclusively very old populations have shown that low, and not high blood pressure, is associated with increased mortality in very old age.⁴⁻¹³ Following a steady rise during earlier life, SBP decreases in very old age.^{5,14-17} There is limited information about the clinical significance of this decreasing SBP in the individual over time. Decreasing trend in SBP in very old age has been associated with an increased mortality risk, but data from these studies are not consistent.^{5,14,15,17-19}

In view of these conflicting data on the associations of different blood pressure values and trends over time with mortality, we investigated the association between SBP trends and mortality in a cohort of nonagenarians from the Leiden 85-plus Study. The present study evaluates the independent contributions of both current SBP value at age 90 and the trend in preceding SBP measurements to the prediction of mortality in nonagenarians.

PARTICIPANTS AND METHODS

Study population

The Leiden 85-plus Study is a prospective population-based study among 85-year-old inhabitants of the city of Leiden (the Netherlands). Study design and cohort characteristics have been described in detail.^{20,21} In brief, between September 1997 and September 1999, 705 people in the 1912–1914 birth cohort reached the age of 85 years and were eligible to participate. No exclusion criteria were used. Fourteen people died before enrollment; a total of 599 (87%) people gave informed consent and were enrolled. At baseline and yearly up to the age of 90 participants were visited at their place of residence. Figure 1 presents the flowchart of the present study, approved by the Medical Ethics Commission of the Leiden University Medical Center.

In this study, the cohort of interest consists of all participants who were alive at age 90 and for whom blood pressure was measured at age 90 years ($n = 271$).

Blood pressure and blood pressure categories

Each year up to age 90 years blood pressure was measured twice with an interval of 2 weeks. Blood pressure was measured using a mercury sphygmomanometer, in seating

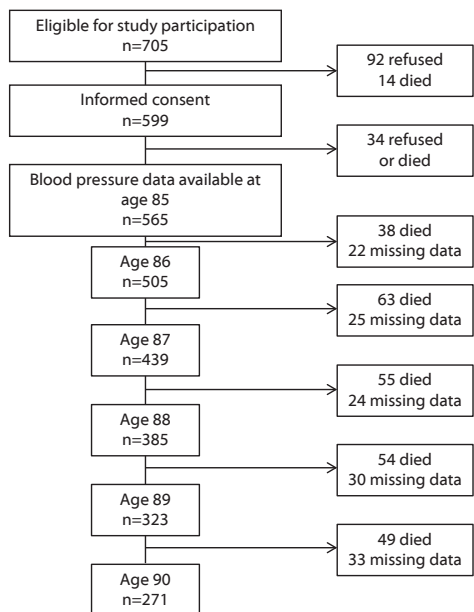


Figure 1. Flowchart of participants in the Leiden 85-plus Study

position, after at least 5 min of rest without having performed vigorous exercise during the preceding 30 min. The systolic value was measured at the onset of phase 1 of the Korotkoff sounds. For the analysis, the mean of the two systolic values for each year was used.

As there was no evidence that the relation between SBP and mortality was U-shaped, the SBP values at age 90 years were dichotomized into categories, ‘low’ and ‘high’ SBP. Low SBP was defined as a SBP of 150 mmHg or less and high as a SBP more than 150 mmHg. This cut-off was based on the target value used in studies assessing the risks and benefits of treating hypertension in individuals aged at least 80 years.^{22,23}

Blood pressure trends

A linear regression of SBP against time was used to assess the individual regression coefficient (β) of the blood pressure trend over the 5 preceding years (90–85 years) for each participant. Participants were divided into tertiles based on the beta from their individual model to describe the trend in SBP. The lowest tertile was considered as a ‘decreasing trend in SBP’; the highest tertile was considered as an ‘increasing trend in SBP’; and the average tertile was considered as an ‘average trend in SBP’.

Mortality

All participants were followed for mortality for 5 years from age 90 years onward. Dates of death were obtained from municipality records.

Sociodemographic, functional, and clinical characteristics

At age 90 years, participants were visited at their place of residence for face-to-face interviews, to perform several tests^{24–27} and to collect information on sociodemographic characteristics. Each participant's general practitioner (or, if applicable, nursing-home physician) was interviewed about the participant's medical history, using standardized questionnaires, including questions on present and past cardiovascular²⁸ (including presence of a medical history of myocardial infarction, angina pectoris, arrhythmias, or heart failure, or an ECG at age 90 revealing a prior myocardial infarction, atrial fibrillation or left ventricular hypertrophy, history of stroke, and peripheral arterial disease) and noncardiovascular morbidities (including history of chronic obstructive pulmonary disease, malignancies, arthritis, Parkinson's disease, and hip fracture). Pharmacists provided detailed information on all medication used by participants.

Statistical analysis

Baseline summary characteristics at age 90 years are reported as medians with interquartile ranges (IQRs) or means with standard deviation (SD) for continuous variables and as numbers with percentage (%) for categorical variables. A linear regression of SBP against time was used to assess the individual regression coefficient (β) of the blood pressure trend over the 5 preceding years (90–85 years) for each participant. Differences in change in SBP between men and women were compared using the Mann–Whitney U-test. Time-to-event curves were constructed with the Kaplan–Meier method. Hazard ratios and corresponding 95% confidence intervals (CIs) were calculated in Cox proportional-hazard models, including the blood pressure category (low or high) or trend in SBP (average, decreasing, increasing) as a categorical variable. The independent contributions of both SBP value at age 90 and trend in preceding SBP measurements to the prediction of mortality were calculated in Cox proportional-hazard models, including both blood pressure category (low or high) and category of trend in SBP (average, decreasing, increasing). In the sex-adjusted model, all hazard ratios were adjusted for sex only, because the present study focused on prediction²⁹ and not cause. In the additional models, the hazard ratios were subsequently adjusted for baseline characteristics from Table 1. The fully adjusted model included adjustment for sex, place of residence (institutionalized or not institutionalized), level of education, income, Activities of Daily Living Score, history of noncardiovascular disease, Mini-Mental State Examination Score, Geriatric Depression Scale Score, Instrumental Activities of Daily Living Score, smoking

status, history of diabetes, history of hypertension, use of antihypertensive drugs, total plasma cholesterol, history of cardiac or other vascular morbidity, hemoglobin and body weight, all at age 90 years, and SBP at age 85 and 90 years.

As sensitivity analysis, stratified analyses were performed for sex, place of residence (institutionalized or not institutionalized), use of antihypertensive drugs, history of cardiovascular disease, and history of noncardiovascular disease, all at age 90 years. To evaluate the influence of the arbitrary choice to use the blood pressure trend over the 5 preceding years, the analyses with blood pressure trend were repeated over 1 (90–89 years), 2 (90–88 years), 3 (90–87 years), and 4 years (90–86 years), respectively.

Data analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Study population

Of the initial cohort of 599 participants (87% response) at age 85 years, 304 individuals survived up to the age of 90 years. Blood pressure measurement at age 90 was missing for 33 (11%) participants. Therefore, the current analyses included 271 participants. Table 1 presents the baseline characteristics. At age 90 years, less than 30% of the participants were men, and almost 40% of the participants were institutionalized. Median Mini-Mental State Examination Score was 25 points. More than 60% of the study population had a history of cardiac morbidity, the majority had a history of hypertension (56%), and almost half of the population used antihypertensive drugs.

Blood pressure at age 90 and SBP trends between age 85 and 90 years

At age 90 years, median SBP was 153 mmHg. The number of participants with a low SBP (<150 mmHg) was 116 (42.8%); 155 (57.2%) had a high blood pressure.

Overall, the average change in SBP was -1.5 (SD 3.4) mmHg per year (-2.2 mmHg per year in men and -1.3 mmHg per year in women; $P=0.060$), resulting in a mean decrease in SBP per participant of 7.3 (SD 29.2) mmHg over the 5 years between the ages of 85 and 90 years (range -10.8 mmHg to +7.5 mmHg per year). The tertile limits (33 and 67%) of the change in SBP were -2.9 and -0.09 mmHg/year.

Mortality

SBP trends between age 85 and 90 years related to mortality after 90

From age 90 years onward, 187 (69%) of the 271 participants died during a median follow-up of 3.6 (range 0.04–5) years. Figure 2 presents the Kaplan–Meier analysis of time to all-

Table 1. Baseline characteristics of the participants at age 90 years (n=271^a)

	n (%), mean (SD) or median (IQR)			
	Total (n=271)	Decreasing (n=90)	Average (n=91)	Increasing (n=90)
Sociodemographic				
Men	74 (27.3)	33 (36.7)	22 (24.2)	19 (21.1)
Smoking	32 (11.9)	15 (16.9)	8 (8.9)	9 (10.0)
Institutionalized	101 (37.5)	42 (46.7)	33 (36.3)	28 (31.1)
Low level of education (primary school only)	167 (62.1)	56 (62.2)	52 (57.1)	60 (66.7)
Low income (state pension only)	41 (15.2)	15 (16.9)	12 (13.3)	14 (15.6)
Functional status				
Mini-Mental State Examination score (range 0-30, 30 optimal)	25 (18-28)	22 (15-27)	26 (20-28)	25 (20-28)
Activities of daily living score (range 9-36, 9 optimal)	13 (9-21)	16 (10-25)	15 (9-20)	12 (9-20)
Instrumental activities of daily living score (range 9-36, 9 optimal)	29 (21-36)	31 (24-36)	30 (23-35)	26 (19-35)
Geriatric Depression Scale ^b (range 0-15, 0 optimal)	2 (0-5)	2 (1-4)	3 (0-6)	1 (0-4)
(Non)cardiovascular comorbidity				
History of cardiac morbidity ^c	165 (61.3)	59 (66.3)	57 (63.3)	49 (54.4)
History of other vascular morbidity ^d	43 (16.3)	17 (19.5)	14 (15.9)	12 (13.5)
History of non-cardiovascular morbidity ^e	171 (63.6)	50 (56.2)	57 (63.3)	64 (71.1)
History of diabetes	48 (18.3)	13 (15.1)	17 (18.9)	18 (20.7)
History of hypertension	147 (55.7)	59 (67.8)	44 (50.0)	44 (49.4)
Use of antihypertensive drugs	105 (46.7)	36 (48.6)	41 (51.9)	28 (38.9)
Total cholesterol	5.3 (1.1)	5.1 (0.9)	5.3 (1.1)	5.4 (1.1)
Hemoglobin	8.2 (0.9)	8.1 (0.9)	8.1 (1.0)	8.3 (1.0)
Body weight	66.3 (12.9)	65.4 (13.7)	66.8 (12.1)	66.4 (13.0)
SBP at age 85 years	157.7 (17.6)	165.9 (18.5)	156.8 (16.2)	150.4 (14.6)
SBP at age 90 years	151.4 (18.1)	141.9 (17.1)	150.7 (16.7)	161.5 (15.1)

IQR, interquartile range; SD, standard deviation.

^aMissings range from n=0 to n=8, and n=46 for use of antihypertensive drugs.^bIn participants with Mini-Mental State Examination score >18, n=196.^cPresence of a medical history of myocardial infarction, angina pectoris, arrhythmias or heart failure, or an ECG at age 90 revealing a prior myocardial infarction (Minnesota Code 1-1 or 1-2, excluding 1-2-8), atrial fibrillation (Minnesota Code 8-3-1) or left ventricular hypertrophy (Minnesota Code 310, 330 or 340).^dIncluding history of stroke and peripheral arterial disease.^eIncluding history of chronic obstructive pulmonary disease, malignancies, arthritis (including arthrosis, rheumatoid arthritis and polymyalgia rheumatica), Parkinson's disease, and hip fracture.

cause mortality depending on the 5-year trend in SBP for the participants who survived up to the age of 90 years. It shows that a decreasing 5-year trend (≥ 2.9 mmHg/year) was associated with an increased cumulative all-cause mortality compared to an increasing or average 5-year trend. Participants with a decreasing 5-year trend in SBP had a 1.5-fold increased all-cause mortality risk compared to those with an average SBP trend (hazard ratio 1.51, 95% CI 1.07–2.15). When excluding participants who died within 3 months of follow-up (to avoid this increased risk being a reflection of terminally ill patients only), this increased mortality risk remained unchanged (hazard ratio 1.53, 95% CI 1.07–2.18). To evaluate the independent contribution of the trend in the SBP measurements between age 85 and 90 years, we analyzed mortality risk of the trends in SBP over 5 years, adjusted for SBP at age 90. Participants with a decreasing 5-year trend in SBP had an increased all-cause mortality risk (hazard ratio 1.45, 95% CI 1.02–2.06) compared to those with an average SBP trend, adjusted for SBP at age 90. There was no difference in mortality risk between participants with an average SBP trend and those with an increasing 5-year trend in SBP (hazard ratio 1.04, 95% CI 0.72–1.50; hazard ratio 1.18, 95% CI 0.81–1.71 after adjustment for SBP at age 90). After analysis of the data with a fully adjusted model, including all baseline characteristics mentioned in Table 1, the estimate for the decreas-

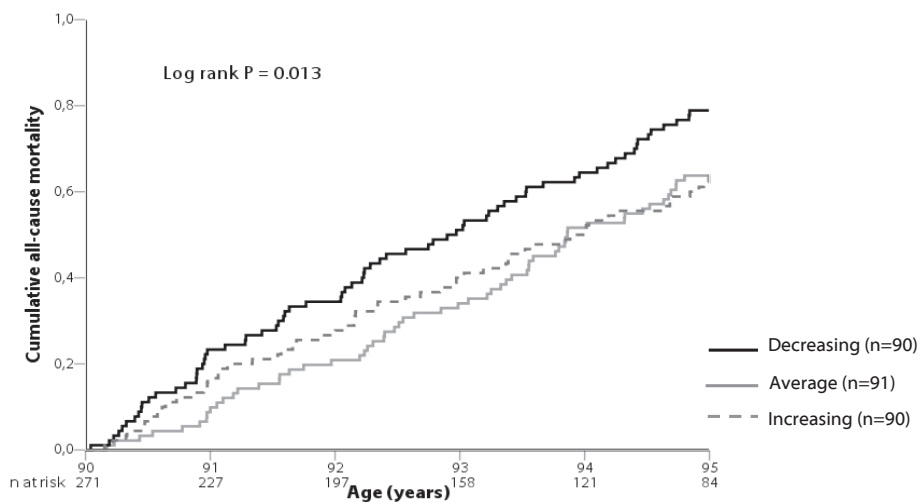


Figure 2. Cumulative all-cause mortality depending on the 5-year trend in SBP for the participants from age 90 years onward (decreasing trend = -10.8 to -2.9 mmHg/year; average trend = -2.8 to -0.09 mmHg/year; increasing trend = -0.08 to +7.5 mmHg/year). The number of participants alive at each year of age is represented by the n at risk

ing 5-year trend in SBP versus average SBP trend was 1.08 (95% CI 0.60–1.86) and 0.79 (95% CI 0.46–1.37) for increasing 5-year trend in SBP versus average SBP trend.

Low versus high SBP at age 90 years

Participants with a low SBP at age 90 had an increased all-cause mortality risk compared to those with a high SBP (hazard ratio 1.57, 95% CI 1.18–2.09). To evaluate the independent contribution of SBP at age 90 years, we analyzed mortality risk of low versus high SBP at age 90 years adjusted for SBP trends. Participants with a low SBP at age 90 had a 1.6-fold increased all-cause mortality risk compared to those with a high SBP, adjusted for SBP trends (hazard ratio 1.62, 95% CI 1.21–2.20). After analysis of the data with a fully adjusted model, including all baseline characteristics mentioned in Table 1 and SBP trends, participants with a low SBP at age 90 had a 1.5-fold increased all-cause mortality risk compared to those with a high SBP at age 90 years (hazard ratio 1.47, 95% CI 0.90–2.40).

SBP trends stratified by low and high SBP at age 90

To investigate the effect of the trend in SBP in conjunction with SBP at age 90, we analyzed mortality risk of the trends in SBP over 5 years dependent on SBP at age 90 years. Participants with a high SBP at age 90 and an average 5-year trend were considered the reference group. Participants with a low SBP at age 90 in combination with a decreasing trend in SBP in the preceding 5 years had a more than doubled all-cause mortality risk compared to the reference group (sex-adjusted model hazard ratio 2.39, 95% CI 1.48–3.88, fully adjusted model hazard ratio 1.62, 95% CI 0.74– 3.52; Table 2). This was most prominent in participants with an already low SBP at age 85 years, at the onset of the decrease in SBP (Appendix Table a1).

Table 2. All-cause mortality risks for various 5-year trends in SBP, depending on SBP at age 90 years (n=271)

5-year trend in SBP (between 85 and 90 years)	SBP at age 90 years	
	High (>150mmHg)	Low (≤150 mmHg)
Decreasing	1.44 (0.83-2.51)	2.39 (1.48-3.88)
Average	1 (Ref)	1.68 (0.99-2.82)
Increasing	1.32 (0.82-2.13)	1.45 (0.70-3.02)

Data are presented as sex-adjusted hazard ratios (95% confidence interval).

Sensitivity analyses

As sensitivity analyses for the association between a decreasing 5-year trend in SBP and mortality, the analyses were stratified for sex, place of residence, use of antihypertensive drugs, history of cardiovascular disease, and history of noncardiovascular

disease. Overall, decreasing 5-year trend in SBP predicted an increased mortality risk in the different subgroups (Table 3). The effect was stronger in women than in men (hazard ratio 1.67, 95% CI 1.08–2.58 and hazard ratio 1.18, 95% CI 0.66–2.11, respectively), although there was no significant interaction between the mortality risk associated with sex and the risk associated with the trend in SBP between the ages of 85 and 90 years ($P=0.12$). The effect was stronger in participants who were institutionalized than in those living independently (hazard ratio 1.87, 95% CI 1.10–3.19 and hazard ratio 1.30, 95% CI 0.81–2.09). The interaction between mortality risk associated with place of residence and the risk associated with the trend in SBP between the ages of 85 and 90 years was significant ($P=0.01$). The average change in SBP was -1.1 mmHg for independently living participants and -2.3 mmHg in those who were institutionalized (Mann–Whitney U -test, $P=0.01$). Although the average change in SBP was different between participants

Table 3. All-cause mortality risks for 90-year-old participants with a decreasing 5-year trend in SBP ($n=90$) compared to participants with average SBP ($n=91$) as well as 90-year-old participants with low SBP (≤ 150 mmHg, $n=116$) compared to participants with high SBP (>150 mmHg, $n=155$) by subgroup

Strata	n ^a (decreasing/ average)	Hazard ratio (95% CI)	n ^b (low/high)	Hazard ratio (95% CI)
Overall	181 (90/91)	1.51 (1.07–2.15)	271 (116/155)	1.57 (1.18–2.09)
Sex				
Men	55 (33/22)	1.18 (0.66–2.11)	74 (38/36)	1.65 (0.99–2.76)
Women	126 (57/69)	1.67 (1.08–2.58)	197 (78/119)	1.53 (1.08–2.17)
Place of residence				
Institutionalised	75 (42/33)	1.87 (1.10–3.19) ^c	103 (65/38)	1.30 (0.82–2.07)
Not institutionalised	106 (48/58)	1.30 (0.81–2.09)	168 (51/117)	1.40 (0.94–2.10)
Use of antihypertensive drugs				
Yes	77 (36/41)	1.46 (0.85–2.51)	105 (41/64)	1.76 (1.09–2.86)
No	76 (38/38)	1.75 (1.03–2.96)	120 (53/67)	2.09 (1.37–3.20)
History of cardiovascular disease				
Yes	123 (63/60)	1.43 (0.94–2.16)	177 (82/95)	1.49 (1.04–2.11)
No	52 (24/28)	1.64 (0.82–3.27)	87 (29/58)	1.38 (0.81–2.38)
History of non-cardiovascular disease				
Yes	107 (50/57)	1.54 (0.98–2.42)	171 (66/105)	1.45 (1.01–2.08)
No	69 (39/30)	1.50 (0.84–2.67)	98 (48/50)	1.74 (1.06–2.85)

Data are presented as sex-adjusted hazard ratios [95% confidence interval (CI)] except the analysis of the subgroup 'sex'.

^aMissings range from $n=0$ to $n=6$, and $n=28$ for use of antihypertensive drugs.

^bMissings range from $n=0$ to $n=8$, and $n=46$ for use of antihypertensive drugs.

^cInteraction between mortality risk associated with place of residence and the risk associated with the trend in SBP between the ages of 85 and 90 years, $p=0.01$.

without a history of cardiovascular disease and those with a history of cardiovascular disease (-0.9 and 1.8 mmHg, respectively; $P=0.04$), there was no difference in association between a decreasing 5-year trend in SBP and mortality. The same sensitivity analysis was performed for the association between low SBP and mortality. Low SBP at age 90 predicted an increased mortality risk in all different subgroups (Table 3).

As an additional sensitivity analyses, we analysed mortality risks associated with trends in SBP over 1–4 years (average, decreasing, increasing). A decreasing trend in SBP in the preceding years was still associated with an increased all-cause mortality risk when the trend was assessed over 4 years, but not when they were assessed over 1, 2, or 3 years.

DISCUSSION

In this prospective, population-based study in nonagenarians, we report a strong association between decreasing 5-year trend in SBP and an increased all-cause mortality risk. This observation was more pronounced in institutionalized participants. Additionally, we replicated the earlier observed association between low SBP at age 90 and an increased all-cause mortality risk. Both the 5-year trend in SBP measurements and the SBP value at age 90 contribute independently to the prediction of mortality. This applied to those with and without antihypertensive drugs at age 90 and in those with and without history of cardiovascular disease or noncardiovascular disease. The most striking observation is that a decreasing trend in SBP in the preceding 5 years in those participants with a low SBP at age 90 predicted a more than doubled mortality risk compared to participants with an average 5-year trend in SBP and high SBP at age 90. Therefore, repeated blood pressure measurement may contribute to identification of older people at risk. This implies looking at the global trend in SBP measurements over previous years when interpreting a single blood pressure measurement in very old persons in daily practice, and weighing both the absolute current value and the existing trend in SBP when making treatment or withdrawal decisions. The full potential clinical relevance of these findings may become clearer when biological explanations for the observed association have been studied.

The results of previous studies assessing the association between decreasing blood pressure and increased mortality risk in old age are not consistent.^{5,14,15,17–19} In the present study, decreasing 4-year and 5-year trend in SBP were associated with an increased mortality risk, whereas, in contrast, there was no significant difference in all-cause mortality risk associated with shorter term trends (up to 3 years) in SBP. It has been suggested that declining blood pressure is associated with declining health.¹⁹ In the present study, the association between decreasing trend in SBP and increased mortality risk was stronger in

institutionalized participants, yet this association was equally present in participants with and without history of cardiovascular disease or noncardiovascular disease. The estimated mortality risk associated with the trend in SBP did not change after adjustment for SBP at age 90, sex, place of residence (institutionalized or not institutionalized), level of education, income, Activities of Daily Living Score, and history of noncardiovascular disease (data not shown). After additional adjustments for Mini-Mental State Examination Score, Geriatric Depression Scale Score, Instrumental Activities of Daily Living Score, smoking status, history of diabetes, history of hypertension, use of antihypertensive drugs, total plasma cholesterol, body weight, hemoglobin, SBP at age 85 and 90 years, and history of cardiac or other vascular morbidity, the estimates approached unity. Although this could indicate that declining cardiovascular and cognitive health are true confounders, it is more likely that the adjustments for cardiovascular, cerebral, and cognitive characteristics were made within the causal pathway. Therefore, no interpretation regarding cause or causality was made in this study. This warrants additional studies on the underlying mechanisms. A new finding of the present study is that in nonagenarians, both the trend in preceding SBP measurements and SBP value at age 90 independently contribute to the mortality risk; decreasing trend in SBP in the preceding 5 years with a low SBP at age 90 predicted the highest mortality risk. The observed association between low SBP and an increased mortality risk is in contrast with a large meta-analysis of observational data from 61 studies;³ however, it is in line with earlier studies in exclusively very old populations.^{4-13,15} Some suggested that this association is caused by poor health status,^{4,5} whereas in the present study, the association between low SBP and increased mortality risk was equally present in participants with and without history of cardiovascular disease or noncardiovascular disease, as reported in other studies.^{8-12,15} After adjustment for the baseline characteristics in the fully adjusted model, the estimated mortality risk associated with low SBP remained similar (initial model hazard ratio 1.62, 95% CI 1.21–2.20 and fully adjusted model hazard ratio 1.47, 95% CI 0.90–2.40). The observed association between SBP at age 90 years and mortality in the present study is linear until it reaches a plateau from SBP 160–170mmHg onward. Therefore, it seems that ‘the lower the SBP, the worse’ rather than ‘the higher the blood pressure, the better’. In addition to the association between a decreasing trend in preceding SBP measurements and increased mortality, there might also be a trend for increased mortality with an increasing trend in SBP, especially when SBP at age 85 years is low (appendix Table a1). This could indicate that variability in blood pressure is also associated with increased mortality. Previous studies showed that higher variability in blood pressure is associated with an increased risk of cardiovascular events and mortality in middle-aged individuals.³⁰⁻³² Relevant data for older individuals on blood pressure variability are scarce; whether blood pressure variability is associated with increased mortality in very old age is, therefore, subject for further research.

A strength of the present study is that we used a population-based sample of nonagenarians. There were no exclusion criteria for participation in the Leiden 85-plus Study: 87% of

the general population aged 85 years living in Leiden participated and there was a complete follow-up for mortality. Furthermore, a blood pressure pattern was established over 5 years, with annual per-protocol measurements within the study. Also, use of the mean SBP values of two separate measurements annually, reduced regression to the mean. The present study focuses on prediction in clinical practice; SBP, being the most used blood pressure value in clinical practice, is therefore, the relevant blood pressure value to investigate. The choice of a cut-off value used for SBP at age 90 and the use of tertiles to describe the trends in SBP can be considered arbitrary. However, as there are no clinical cut-offs for these values and trends in very old age, it seems sensible to adhere to the target value used in studies assessing the risks/benefits of treating hypertension in individuals aged at least 80 years.^{22,23} Furthermore, there was no evidence for a U-shaped relationship between mortality and SBP at age 90 years, indicating that dichotomization of the blood pressure range can be considered correct. In addition, our relatively small number of participants reduced the statistical power to detect differences in mortality risk in subgroup analyses, creating the possibility of type-II errors. Due to a lack of power, we were unable to analyze the effects of declining SBP and low SBP on cause-specific mortality. Finally, as our study population included only strong survivors, thus a selected study population, we cannot extrapolate our conclusions to younger age groups.

In conclusion, at age 90 years, both the trend in SBP over the preceding 5 years and current SBP value independently contribute to all-cause mortality risk; the combination of a decreasing trend in SBP in the preceding 5 years and low SBP at age 90 predicts the highest mortality risk. Therefore, in very old age, all available preceding SBP measurements contribute to a more accurate prediction of mortality and should be taken into account. In addition, repeated blood pressure measurement may contribute to identification of older people at risk.

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APPENDIX

Table a1. All-cause mortality risks for various 5-year trends in SBP, depending on SBP at age 85 and 90 years (n=271)

5-year trend in SBP (between 85 and 90 years)	SBP at age 90 years		
	SBP at age 85 years	High (>150mmHg)	Low (≤150 mmHg)
Decreasing	High (>150mmHg)	1.50 (0.85-2.64) n=33	1.98 (1.15-3.41) n=39
	Low (≤150 mmHg)	x	4.30 (2.32-7.96) n=11
Average	High (>150mmHg)	1 (ref) n=45	1.70 (0.83-3.49) n=16
	Low (≤150 mmHg)	2.09 (0.49-8.89) n=2	1.78 (0.99-3.20) n=28
Increasing	High (>150mmHg)	1.16 (0.67-2.00) n=48	x
	Low (≤150 mmHg)	1.85 (1.02-3.36) n=27	1.56 (1.14-2.14) n=15

Data are presented as sex-adjusted hazard ratios (95% confidence interval)



PART 2

N-TERMINAL PRO-BRAIN
NATRIURETIC PEPTIDE LEVELS
IN CARDIOVASCULAR RISK
PREDICTION IN OLD AGE



Chapter 6

Risk stratification and
treatment effect of statins
in secondary cardiovascular
prevention in old age:
additive value of NT-proBNP

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ABSTRACT

Aims

To assess predictive values for recurrent cardiovascular disease, of models with age and sex, traditional cardiovascular risk markers, and SMART risk score, with and without N-terminal pro-B-type natriuretic peptide (NT-proBNP). To assess treatment effect of pravastatin across low and high risk groups identified by these models.

Methods and Results

Post-hoc analysis in participants ($n=2348$, age 70-82 years) with a history of cardiovascular disease within the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a randomized placebo-controlled study. Primary endpoint was recurrent cardiovascular event (myocardial infarction and/or stroke) or cardiovascular mortality. The models with age and sex, traditional risk markers and SMART risk score had comparable predictive values (area under the curve (AUC) 0.58, 0.61 and 0.59, respectively). Addition of NT-proBNP to these models improved AUCs with 0.07 ($p_{\text{diff}}=0.003$), 0.05 ($p_{\text{diff}}=0.009$) and 0.06 ($p_{\text{diff}} < 0.001$), respectively, and net reclassification improvements were 41% ($p < 0.001$), 39% ($p < 0.001$) and 25% ($p=0.002$), respectively. For the model with age, sex and NT-proBNP, the hazard ratio for the primary endpoint with pravastatin treatment compared to placebo was 0.67 (95%CI 0.48-0.96) for participants in the high third of predicted risk and 0.94 (0.65-1.36) in the low third, number needed to treat 16 (8.7-121) and 116 (17- ∞), respectively.

Conclusion

In secondary cardiovascular prevention in old age predictive value of traditional risk markers and SMART risk score is poor. Addition of NT-proBNP improves prediction of recurrent cardiovascular disease and mortality. A minimal model including age, sex and NT-proBNP predicts as good as complex risk models including NT-proBNP.

INTRODUCTION

Persons with known cardiovascular disease are at high risk of recurrent events, and guidelines worldwide advise statins for secondary prevention,¹⁻³ even in old age.⁴ Yet, prescription of secondary preventive treatment decreases with age.^{5,6} This might be caused by dilemmas regarding starting, continuing, or safely stopping preventive treatment, as physicians have to weigh postponed benefit versus current harm and priorities of care in old age. As many more patients are surviving their initial cardiovascular event, prediction of recurrent events becomes increasingly important. Ideally, the risk markers or risk models used, not only predict recurrence risk, but predict treatment effect as well. In secondary prevention in old age, traditional cardiovascular risk markers lose predictive value^{7,8} and most risk scores are either too complex or only apply to restricted subgroups of hospitalized patients.^{9,10} To date, for the general older population, no risk scores for prediction of recurrence risk and/or treatment effect exist. Recently the SMART risk score was developed to predict recurrent cardiovascular events in a younger cohort of patients with a history of cardiovascular disease (mean age 60 years),¹¹ but this risk score has not been validated in older age.

A new promising predictor of cardiovascular risk in old age is N-terminal pro-brain natriuretic peptide (NT-proBNP),^{8,12-15} a polypeptide released in reaction to myocardial wall stress or ischemia. Addition of NT-proBNP to a model with the traditional cardiovascular risk markers or SMART risk score might improve predictive performance, especially in older patients.

Therefore, we first validated the SMART risk score in 1157 old subjects (mean age 75 years, placebo group) with a history of cardiovascular disease participating in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER).¹⁶ We compared the predictive value for recurrent cardiovascular events and mortality of the SMART risk score, with a model with traditional cardiovascular risk markers and with a minimal model including only age and sex. Second, we investigated whether addition of NT-proBNP to these prediction models could improve prediction. Third, we studied whether treatment effect of pravastatin was different across groups with low and high risk, calculated with the different models.

METHODS

Study design

Data in this study were obtained from the PROSPER study, a randomized, double-blind, placebo-controlled trial designed to investigate the effect of pravastatin in prevention of vascular events in older persons. Details of the design and outcome of PROSPER have

been published elsewhere.¹⁶⁻¹⁸ 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. A total of 2565 participants had a history of cardiovascular disease (including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction and vascular surgery), and were included in the present study.

Individuals with congestive heart failure (New York Heart Association functional class III and IV) or poor cognitive function (Mini-Mental State Examination score <24 points) were excluded from PROSPER.¹⁸ Participants were randomized into a group who received 40 mg pravastatin a day and a control group receiving placebo and were followed 3.2 years on average. Throughout the study, all study personnel was unaware of the allocated study medication status of the participants. The institutional ethics review boards of all centres approved the protocol and all participants gave written informed consent. The protocol adhered to the principles of the Declaration of Helsinki.

Traditional cardiovascular risk markers and SMART risk score variables

During the pre-randomization visits, baseline participant characteristics were collected,¹⁷ including a detailed medical history with date(s) of last cardiovascular events, smoking status and current medication use. Participants weight, height and blood pressure were measured and fasting venous blood samples were taken including biobank samples. A history of diabetes was defined as a known diabetes mellitus or fasting blood glucose >7 mmol/L. Baseline serum creatinine levels were measured at central laboratories. Estimated glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease equation¹⁹:

$$\text{eGFR} = 186 \times \text{serum creatinine level (mg/dl)}^{(-1.154)} \times \text{age}^{(-0.203)} \times 0.742 \text{ [if female]}$$

Data of eGFR was missing for 5 included participants. High sensitivity C-reactive protein (hsCRP) levels were measured on stored K₂EDTA (at -80°C) baseline samples.²⁰ Data of hsCRP was missing for 41 included participants due to technical problems. All laboratory analyses were conducted by technicians blind to the identity of samples and outcomes. Time since last cardiovascular event was calculated from the recorded date(s) of last cardiovascular event.

NT-proBNP measurements

Blood samples were taken at 6 months after baseline in EDTA tubes.¹⁸ The venous blood samples were stored in the biobank. From biobank samples NT-proBNP was determined using electrochemiluminescence immunoassay on a Roche Modulator E170. NT-proBNP measurements were missing for 167 participants due to technical problems.

Outcomes

For the present study the primary outcome of the trial was used: the combination of definite or suspect death from coronary heart disease, non-fatal myocardial infarction and fatal or non-fatal stroke.¹⁸ The PROSPER Endpoints Committee assessed all endpoints. The Endpoints Committee was blinded for study medication, and for plasma levels of NT-proBNP.

Statistical analysis

From the 2565 participants with a history of cardiovascular disease, participants with coronary events or who died in the first 6 months of the study (n=50) and participants with missing NT-proBNP values at 6 months (n=167) were excluded. Baseline summary characteristics are reported as median with interquartile range (IQR) for continuous variables and as numbers with percentage (%) for categorical variables for all participants (n=2348) and for participants on placebo and those on pravastatin separately. Follow-up for the outcomes was calculated from 6 months onward up to a maximum of 2.5 years.

Calibration of the SMART risk score

For calculation of the SMART risk score the SMART formula¹¹ was used (Supplement 1). Calibration of the SMART risk score for the PROSPER trial population was investigated by comparing the predicted versus observed cardiovascular disease risks. Participants taking placebo were divided into five categories of 2.5-year predicted risk, <10%, 10 to <20%, 20 to <30%, 30 to <40%, and ≥40%. Within each category, predicted risk was compared to actual observed Kaplan-Meier cardiovascular disease free survival at 2.5 year follow-up (Supplement 2). In addition, the fitted regression coefficient (beta) was assessed in a Cox proportional hazard model fit, using only the linear prognostic score (A) as variable.²¹ The continuous predictive SMART prognostic risk score was multiplied with the calculated regression coefficient to recalibrate the SMART risk score for the PROSPER population, as the calibrated regression coefficient significantly differed from 1 (0.466, p<0.001).

Risk prediction with three models in the placebo group

The 2.5-year cardiovascular disease risk (%) was predicted for all participants using a Cox proportional hazards models (complete case analysis) fit based on 1) age and sex (minimal model); 2) age, sex, smoking, systolic blood pressure, high density lipoprotein and total cholesterol, history of diabetes, history of hypertension, history of myocardial infarction, history of stroke/transient ischaemic attack and history of surgery for peripheral artery disease (all as assessed at baseline; traditional model); and 3) recalibrated SMART risk score (SMART model). Using the continuous predicted risks from the three

models, area under the curves (AUCs) and receiver operating characteristic (ROC) curves with p-values (level of significance 5%) and 95% confidence intervals for difference were calculated.

Additional value of NT-proBNP in the placebo group

NT-proBNP was non-normally distributed and therefore log transformed. Cox proportional hazards models for the occurrence of the primary endpoint were fitted based on three additional models including 1) minimal model plus NT-proBNP; 2) traditional model plus NT-proBNP; and 3) SMART model plus NT-proBNP. AUCs and ROC curves were calculated and compared to the reference models without NT-proBNP (STATA 12.1). Cross validation method was used for comparison of optimism-corrected estimates.²²

Net Reclassification Improvement

We calculated the category-less Net Reclassification Improvement (NRI) for the primary endpoint with logistic regression, comparing the models including NT-proBNP to the reference models without NT-proBNP.^{23,24}

Treatment effect comparing placebo and treatment group

Predicted risk for the primary endpoint was calculated for all participants using the regression coefficients from the models developed in the placebo group. The treatment effect of pravastatin according to the thirds of predicted risk for the primary endpoint of the three models including NT-proBNP was assessed in three ways. First, the presence of multiplicative interaction was tested by adding the interaction term 'treatment x thirds of predicted risk' in the Cox model. Second, per third of predicted risk, the absolute numbers of events in the pravastatin group and the placebo groups were calculated and the absolute risk reduction (ARR) by pravastatin was calculated using the life-table method. Differences in ARR between the thirds of predicted risk, were tested using a z-test. Numbers needed to treat (NNT) were calculated over 2.5 years based on the difference in cumulative proportion surviving in the pravastatin and placebo groups. Finally, the hazard ratio (HR) for the occurrence of cardiovascular events in the pravastatin group versus placebo group was calculated using the Cox proportional hazard model per third of predicted risk.

RESULTS

Table 1 presents the baseline characteristics for the participants. Of the 2348 participants 57% (n=1334) were men, 73% (n=1713) had a history of cardiac disease, 25% (n=594)

had a history of cerebrovascular disease and 17% (n=408) had a history of peripheral disease. The median NT-proBNP level was 176 ng/L (IQR 96-359).

Table 1 Baseline characteristics of the participants stratified for non-treatment and treatment group

	Total group n=2348	Placebo n=1157	Pravastatin n=1191
Age (years)	75 (73-78)	75 (73-78)	75 (73-78)
Male Sex	1334 (57)	658 (57)	676 (57)
Current smoker	427 (18)	214 (19)	213 (18)
Systolic blood pressure (mm Hg)	152 (138-168)	151 (136-168)	153 (138-168)
High-density lipoprotein cholesterol (mmol/L)	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.2 (1.0-1.4)
Total cholesterol (mmol/L)	5.6 (5.0-6.3)	5.6 (5.0-6.2)	5.6 (5.0-6.3)
History of diabetes mellitus	200 (9)	99 (9)	101 (9)
History of coronary artery disease ^a	1713 (73)	831 (72)	882 (74)
History of myocardial infarction	701 (30)	365 (32)	336 (28)
History of cerebrovascular disease ^b	594 (25)	299 (26)	295 (25)
History of peripheral artery disease ^c	408 (17)	204 (18)	204 (17)
History of surgery for peripheral artery disease	113 (5)	53 (5)	60 (5)
Time since first diagnose	6.0 (3.0-11.0)	6.0 (3.0-11.3)	7.0 (3.0-11.0)
Creatinine clearance ^d	52 (43-63)	52 (43-63)	52 (43-63)
High-sensitivity C-reactive protein (mg/L) ^e	3.1 (1.6-6.3)	3.1 (1.7-6.1)	3.2 (1.6-6.5)
N-terminal pro-brain natriuretic peptide (ng/L) ^f	176 (96-359)	174 (96-354)	177 (95-367)

Data are presented as median with interquartile range (IQR) for continuous variables and as numbers with percentage (%) for categorical variables.

^a History of angina, myocardial infarction, coronary artery bypass surgery or percutaneous transluminal coronary angioplasty.

^b History of transient ischemic attack or stroke.

^c History of claudication or surgery for peripheral disease.

^d Calculated with the Cockcroft-Gault formula, missing n=5.

^e Missing n=41.

^f Measured at 6 months after study entrance.

Traditional cardiovascular risk markers and SMART risk score

During the maximum follow-up of 2.5 years, 16% (n=187) of participants in the placebo group (n=1157) developed a cardiovascular event or died of cardiovascular disease (primary endpoint). We calculated AUCs and created ROC curves for the minimal model, the traditional model and the SMART model, with the primary endpoint at 2.5-year (Figure 1). The three models had similar AUCs: 0.58 (95% CI 0.54-0.63) for the minimal model; 0.61 (95%CI 0.57-0.66) for the traditional model; and 0.59 (95% CI 0.54-0.63) for the SMART model (Table 2).

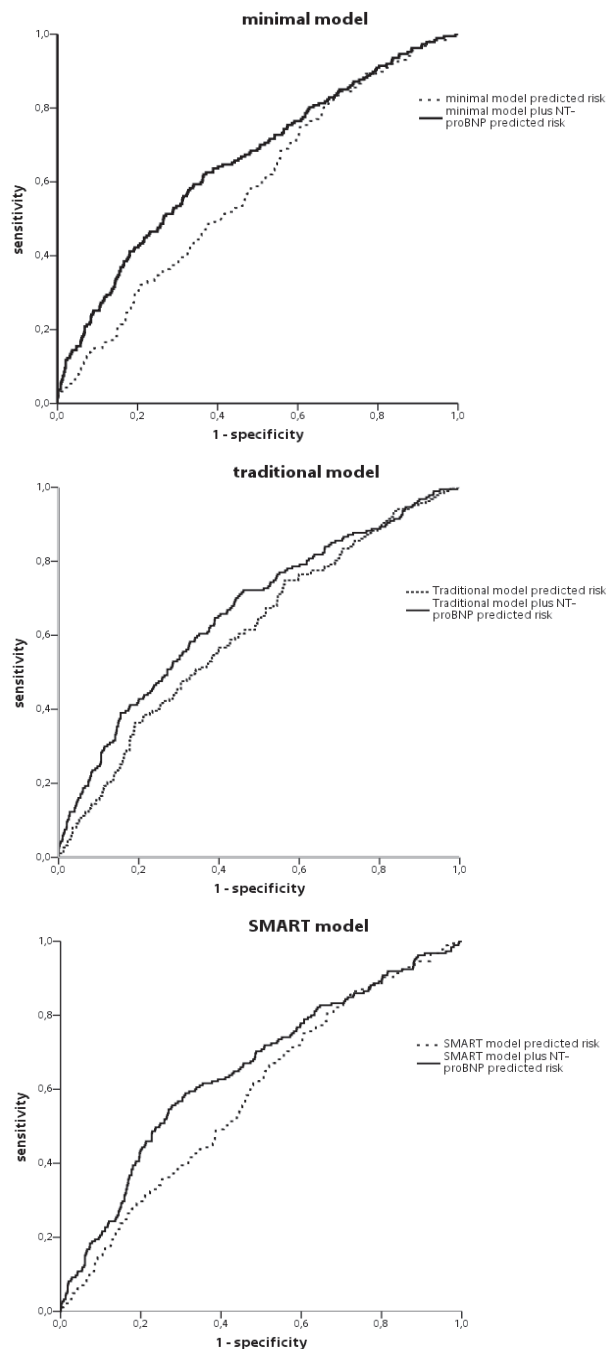


Figure 1. Receiver operating characteristic curves for three models without NT-proBNP (dotted lines) and with NT-proBNP (black lines) for cardiovascular events and cardiovascular mortality. Model with age and sex (top, minimal model) model with traditional risk markers (middle, traditional model) and model with SMART risk score (bottom, SMART model) ($p \Delta 0.003$, 0.003 and < 0.001 , respectively)

Addition of NT-proBNP

Figure 1 shows that the addition of NT-proBNP improved the AUC of all three models similarly. Addition of NT-proBNP to the minimal model increased the AUC from 0.58 to 0.65 (95% CI 0.6-0.70), Δ 0.07, p for difference (p_{diff}) = 0.003. The increase in AUC was similar for both the traditional and the SMART model (Δ 0.05, p_{diff} = 0.009 and Δ 0.06, p_{diff} < 0.001, respectively) (Table 2).

The minimal model with addition of NT-proBNP performed similarly to the traditional model with addition of NT-proBNP (p_{diff} = 0.26) as well as to the SMART model plus NT-proBNP (p_{diff} = 0.87).

Cross validation of the minimal model led to an AUC of 0.56 (95%CI 0.52-0.61) and for the minimal model with addition of NT-proBNP to an AUC of 0.64 (95%CI 0.60-0.69). The difference between these two cross validated AUCs was 0.08 (p = 0.0016). Cross validation of the other models showed similar results (data not shown).

Table 2. Absolute number of events in tertiles of predicted risk of the different models, with area under the curve (AUC), delta AUC with addition of NT-proBNP, and category free net reclassification improvement (NRI) for the primary endpoint

Risk models	Absolute numbers of events in tertiles of risk			AUC (95%CI)	Δ AUC	$p \Delta$	NRI (%)	p value
	Low	Medium	High					
Minimal model	43 (11.2)	68 (17.8)	76 (19.4)	0.58 (0.54-0.63)				
Minimal model plus NT-proBNP	58 (14.8)	56 (14.4)	73 (19.4)	0.66 (0.61-0.70)	0.07	0.0026	41	<0.001
Traditional model	42 (11.0)	56 (14.6)	89 (22.7)	0.61 (0.57-0.65)				
Traditional model plus NT-proBNP	35 (9.0)	54 (13.7)	98 (26.1)	0.66 (0.62-0.70)	0.05	0.0091	39	<0.001
SMART model	60 (15.8)	60 (16.0)	65 (16.9)	0.59 (0.54-0.63)				
SMART model plus NT-proBNP	53 (14.4)	65 (16.0)	67 (18.3)	0.65 (0.61-0.70)	0.06	0.0006	25	0.002

Primary endpoint: 2.5-year risk for cardiovascular morbidity and mortality in the placebo group.

Minimal model including age and sex.

Traditional model including age, sex, smoking, systolic blood pressure, high density lipoprotein and total cholesterol, history of diabetes, history of hypertension, history of myocardial infarction, history of cerebrovascular disease and history of surgery for peripheral artery disease.

SMART model including age in years, age in years², sex, sex, smoking, systolic blood pressure, histories of diabetes, coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm and peripheral artery disease, years since first diagnosis of vascular disease, estimated glomerular filtration rate and high sensitive C-reactive protein.

NRI

The category-less NRI with addition of NT-proBNP to the minimal model was 41% ($p < 0.001$, 57% of participants reclassified up, minus 43% reclassified down in the group that experienced the endpoint, plus 63% reclassified down, minus 37% reclassified up in the group that did not experience the endpoint). The category-less NRI with addition of NT-proBNP to the traditional model was 39% ($p < 0.001$). Addition of NT-proBNP to the SMART model had an NRI of 25% ($p = 0.002$) (Table 2).

Treatment effect

Overall, in the 2348 participants with a history of cardiovascular disease within the PROSPER study population, the ARR by pravastatin treatment was 3.6% for 2.5 year. After, the 2.5-year HR for the development of the primary endpoint was 0.77 (95% CI 0.62-0.95) in the pravastatin group compared to the placebo group.

We divided participants according to thirds of predicted risk. Multiplicative interaction between treatment and thirds of predicted risks of all models was not significant (all $p > 0.1$). Table 3 shows the treatment effect (2.5-year) of pravastatin according to thirds of predicted risk of cardiovascular disease and mortality for three risk models, all with NT-proBNP, including number of events (primary endpoint), ARR and HR. The ARR in primary endpoint with 2.5-year pravastatin treatment in the low predicted risk group of the minimal model plus NT-proBNP was 0.86% (95% CI -4.1-5.9) and in the high predicted risk group 6.2% (95% CI 0.8-11.5), difference=5.3% (95% CI 2.0-12.6, $p_{diff} = 0.07$). (Figure 2) In this model, participants with the highest predicted risk (highest third) and pravastatin treatment had a HR of 0.67 (95% CI 0.48-0.96) for the development of the primary endpoint compared to those on placebo. The NNT during 2.5 years with pravastatin was 16 (95% CI 8.7-121). HR for participants in the lowest third of predicted risk was 0.94 (95% CI 0.65-1.36), with a NNT of 116 (95% CI 17- ∞).

DISCUSSION

This study shows that the predictive value of traditional cardiovascular risk markers and the (recalibrated) SMART risk score is poor in older people with a history of cardiovascular disease, and comparable to prediction with a model including only age and sex. Addition of NT-proBNP improved prediction of recurrent cardiovascular disease and mortality. We observed that a model with age, sex and NT-proBNP predicts as good as more complex risk models including NT-proBNP. Moreover in high risk individuals as identified by age, sex plus NT-proBNP level, NNT for 2.5-year pravastatin treatment was 16, whereas, in patients with a low predicted risk in this model, NNT was 116. As many

Table 3. Treatment effect after 2.5-year of treatment with pravastatin according to tertiles of predicted risk of cardiovascular disease and mortality for three risk models including NT-proBNP

	Events in pravastatin group	Events in placebo group	ARR (95%CI)	HR (95% CI)
Minimal model plus NT-proBNP				
Low	54 (13.9)	58 (14.8)	0.86 (-4.14-5.86)	0.94 (0.65-1.36)
Medium	41 (10.3)	56 (14.4)	4.2 (-0.48-8.86)	0.70 (0.47-1.05)
High	55 (13.5)	73 (19.4)	6.2 (0.83-11.54)	0.67 (0.48-0.96)
Traditional model plus NT-proBNP				
Low	26 (6.6)	35 (9.0)	2.5 (-1.28-6.33)	0.73 (0.44-1.20)
Medium	45 (11.6)	54 (13.7)	2.0 (-2.73-6.77)	0.83 (0.56-1.24)
High	79 (19.4)	98 (26.1)	7.2 (1.18-13.29)	0.71 (0.53-0.95)
SMART model plus NT-proBNP				
Low	45 (11.3)	53 (14.4)	3.0 (-1.86-7.78)	0.78 (0.52-1.15)
Medium	42 (11.6)	65 (16.0)	4.5 (-0.43-9.45)	0.72 (0.49-1.06)
High	60 (14.9)	67 (18.3)	4.0 (-1.45-9.43)	0.78 (0.55-1.11)

Minimal model including age and sex.

Traditional model including age, sex, smoking, systolic blood pressure, high density lipoprotein and total cholesterol, history of diabetes, history of hypertension, history of myocardial infarction, history of cerebrovascular disease and history of surgery for peripheral artery disease.

SMART model including age in years, age in years², sex, sex, smoking, systolic blood pressure, histories of diabetes, coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm and peripheral artery disease, years since first diagnosis of vascular disease, estimated glomerular filtration rate and high sensitive C-reactive protein.

more patients are surviving their initial cardiovascular event, prediction and prevention of recurrent events becomes increasingly important and according to our study NT-proBNP is a promising risk predictor in old age.

Comparison with the literature

The combination of prediction of recurrent events and treatment effect has seldom been examined in secondary cardiovascular prevention. Our findings contrast with the findings in the CORONA and Heart Protection Study in patients with chronic heart failure, where the benefit of rosuvastatin was higher in the low NT-proBNP group. However, this relationship might have been modified by other patient characteristics in this specific population of ischemic heart failure patients.²⁵

Previously, Sattar et al. have investigated within the entire PROSPER study population whether hsCRP could predict treatment effect and they observed that hsCRP did not predict response to statin therapy.²⁰ In contrast, Drewes et al. found a positive relation of homocysteine levels with treatment effect.²⁶ However, physicians are perhaps

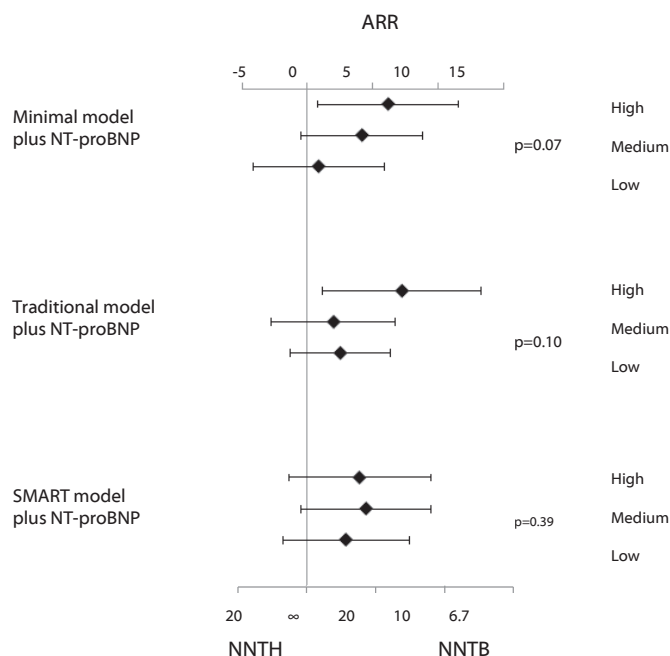


Figure 2. Absolute risk reduction (ARR) and number needed to treat to benefit (NNTB) and number needed to harm (NNTH) with pravastatin for 2.5 years, according to tertiles of predicted risk, p-value of difference between lowest and highest predicted risk group for NNTB, estimated using z-test

more inclined to determine serological biomarkers that have a direct association with cardiac strain such as NT-proBNP.

With regard to prediction of recurrent events, the predictive value of NT-proBNP has been described in primary as well as in secondary prevention,¹² even in very old age^{8,13,15} and in persons with²⁷ and without clinical heart failure.²⁸ In the literature, addition of NT-proBNP to traditional cardiovascular risk markers results in an improvement of the AUC ranging from 0.01-0.1.^{8,12,29} The HOPE study findings²⁹ showed that of all biomarkers added to traditional risk markers in secondary prevention, NT-proBNP was the strongest (increase in AUC 0.05 as compared to traditional risk markers, $p<0.001$). This is consistent with the present study in a secondary prevention population. The SMART risk score, which includes hsCRP, was not superior to the model including age and sex. This might be explained by the decreasing predictive value of hsCRP with age,^{30,31} as our study population was older by around 15 years on average, than the population in which the original SMART risk score was developed. Also, even if the true risks are the same in both populations, shrinkage can be expected when a prediction model is validated in a different population.

Implications for clinical practice and future research

In our cohort of older persons the SMART risk score had to be recalibrated as it overestimated actual risk for recurrent cardiovascular disease and cardiovascular mortality, especially in persons assigned to the high risk category. Physicians should be aware of the derivation cohort characteristics, before applying new risk scores to their patients.

Our result suggest than in secondary cardiovascular prevention in old age, measuring NT-proBNP helps physicians and patients better estimate recurrence risk. A more complex model including traditional cardiovascular risk markers including the history of cardiovascular disease, or the SMART risk score, is not required as predictive value was the same in a model with age and sex only. However this requires further validation and then evaluation of clinical impact, especially regarding treatment effect, before it can be implemented. Nevertheless, the wide availability of NT pro-BNP assays in routine laboratories means clinical translation is ultimately possible, although current assays remain expensive.

Strengths and limitations

To analyse NT-proBNP levels in the well-defined secondary prevention population within the PROSPER study population, and to calculate treatment effect accordingly, was a tempting opportunity, since placebo controlled RCT's concerning treatment effect of statins are ethically impossible to perform in the present era.

PROSPER is a randomised controlled trial, therefore, the participants were selected using more strict criteria than in a cohort study, like the SMART study. The observed risks could have been influenced. NT-proBNP was measured at 6 months, not at baseline due to limited plasma availability in latter. Therefore, follow-up was calculated from 6 months onward. Pravastatin treatment had no effect on NT-proBNP levels in the first 6 months, which is in line with previous studies.³² Since NT-proBNP was measured at 6 months from baseline, we had to exclude participants that already died or experienced a cardiac event in the first 6 months of the study. As these participants are likely to be high risk individuals in the models, exclusion may have led to an underestimation of the true magnitude of predictive value of the models. Finally, the relatively low AUCs might be considered as a limitation. However, an AUC between 0.65 and 0.70 is common in studies in older populations.^{8,33}

Conclusions

Due to increased survival following an acute cardiovascular event, prediction of recurrent events is becoming increasingly important and according to our study NT-proBNP is a promising risk predictor. Addition of NT-proBNP to (traditional) risk models improves prediction in old age and a minimal model with age, sex and NT-proBNP is as good as complex risk models including NT-proBNP.

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APPENDIX

Supplement 1

SMART formula:

$$2.5\text{-year cardiovascular disease risk (\%)} = (1 - 0.9488765^{\exp[A + 2.099]}) \times 100\%$$

Where A is the prognostic risk score:

$A = -0.0850 \times \text{age in years} + 0.00105 \times (\text{age in years})^2 + 0.156 \text{ [if male]} + 0.262 \text{ [if current smoker]} + 0.00429 \times \text{systolic blood pressure in mmHg} + 0.223 \text{ [if diabetic]} + 0.140 \text{ [if history of coronary artery disease]} + 0.406 \text{ [if history of cerebrovascular disease]} + 0.558 \text{ [if abdominal aortic aneurysm]} + 0.283 \text{ [if peripheral artery disease]} + 0.0229 \times \text{years since first diagnosis of vascular disease} - 0.426 \times \text{HDL-cholesterol in mmol/L} + 0.0959 \times \text{total cholesterol in mmol/L} - 0.0532 \times \text{eGFR in mL/min/1.73m}^2 + 0.000306 \times (\text{eGFR in mL/min/1.73m}^2)^2 + 0.139 \times \log(\text{hsCRP in mg/L})$

Supplement 2

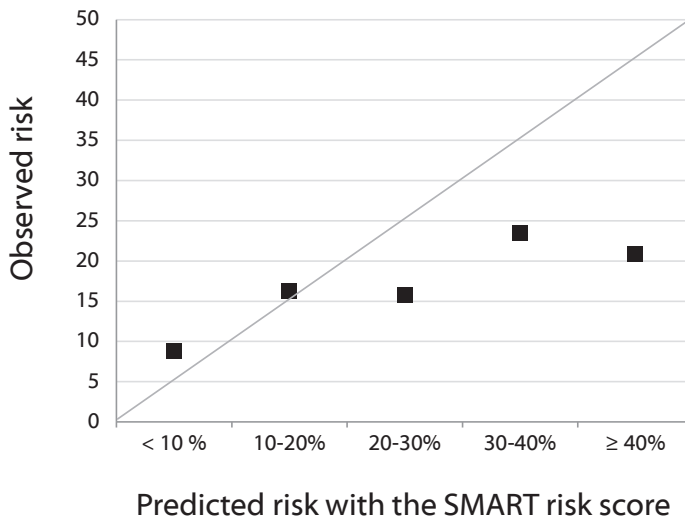


Figure 1. Calibration plot of 2.5-year predicted risk with the SMART risk score versus observed risk of cardiovascular events and cardiovascular mortality in PROSPER study participants



Chapter 7

Increase in N-terminal pro-brain natriuretic peptide levels, renal function and cardiac disease in the oldest old

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Accepted Age and Ageing, 2015

ABSTRACT

Background

The impact of renal function and its changes and the occurrence of cardiovascular events on changes in N-terminal pro-brain natriuretic peptide levels (NT-proBNP) is unknown in very old age.

Objective

To assess whether increase in NT-proBNP levels over time is still associated with cardiac disease and mortality in very old age, independent of renal function.

Methods

Changes in NT-proBNP levels between age 85 and 90 years and their associations with incident cardiac disease, (cardiovascular) mortality and renal function were assessed in 252 nonagenarian participants from a population-based sample of the Leiden 85-plus Study.

Results

Median NT-proBNP increase over five years was 154 pg/mL (inter-quartile range: 29-549), while in the same period estimated glomerular filtration rate (eGFR) decreased by 5.8 mL/min/1.73m² (standard deviation 7.5). Participants with increasing NT-proBNP levels more frequently developed heart failure and atrial fibrillation (Odds Ratio 2.79, 95% confidence interval (CI) 1.11-7.02 and 2.63, 95% CI 1.02-6.79, respectively, adjusted for eGFR at age 85 and change in eGFR) between age 85 and 90 years. Increasing NT-proBNP between age 85 and 90 years was associated with an increased cardiovascular mortality risk after age 90 years compared to not-increasing NT-proBNP levels (hazard ratio 1.62, 95% CI 1.04-2.51, adjusted for eGFR at age 90 years and change in eGFR).

Conclusion

In the oldest old, increase in NT-proBNP is associated with incident heart failure and atrial fibrillation and risk for cardiovascular mortality, independent of decreasing renal function.

INTRODUCTION

Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are the two fragments of the prohormone proBNP, which is released by ventricular myocytes in reaction to ventricular wall stress and hypoxia,¹⁻³ and by the atrial myocytes in reaction to highly frequent atrial myocyte contraction in atrial fibrillation.⁴ Thus, natriuretic peptide levels, especially NT-proBNP levels, are diagnostic blood-based biomarkers for heart failure, but also prognostic markers for incident cardiovascular morbidity and mortality in middle-aged⁵⁻⁷ and older persons.⁸⁻¹¹

Few studies are available on the course of the NT-proBNP levels over time, their association with cardiovascular risk and the underlying conditions related to changes in NT-proBNP in older age, although not in the oldest old.^{12,13} One prospective observational cohort study of cardiovascular disease in older people (mean age 73 years) found that NT-proBNP levels frequently change over time, reflecting a dynamic change in subsequent cardiovascular risk concordant with the direction of change of NT-proBNP.¹³ Moreover, a community-based study of subjects aged 70 years and over, found that not only single NT-proBNP levels, but also their changes over time, are predictive of all-cause and cardiovascular mortality.¹² Changes in NT-proBNP levels were associated with cardiovascular risk indicators such as male gender, ischemic electrocardiogram (ECG) changes, renal dysfunction, and lower left ventricle ejection fraction, together with intercurrent cardiovascular events.¹²

NT-proBNP levels increase with age, even in the absence of heart failure or cardiovascular disease.¹⁴ NT-proBNP is mainly cleared through renal excretion.¹⁵ Impaired renal function, which is common in old age and is a strong predictor for cardiovascular disease as well, is associated with higher levels of NT-proBNP.¹⁶ Therefore, declining renal function could, at least in part, underlie the increase in NT-proBNP over time. There are currently no studies available that address this hypothesis in the oldest old. It has been suggested that, besides symptoms, signs and patients' history, decline in renal function should also be considered when interpreting NT-pro-BNP values in old age.^{16,17}

We hypothesized that an increase in NT-proBNP level still reflects cardiac morbidity and risk for cardiovascular mortality in old age, independent of decreasing renal function. Therefore, we assessed whether 1) increase of NT-proBNP levels over five years is associated with incident cardiovascular disease during these five years; 2) whether this association is independent of the renal function; and 3) whether persons with an increase in NT-proBNP over five years have a higher mortality risk after these five years. Our analyses were performed in a population-based cohort of nonagenarians of the Leiden 85-plus Study, where NT-proBNP levels and estimated glomerular filtration rate (eGFR) levels were available at both 85 and 90 years of age.

METHODS

Study population

The Leiden 85-plus Study is a prospective population-based study in 85-year-old inhabitants of the city of Leiden, the Netherlands.¹⁸ Between September 1997 and September 1999, 705 people in the 1912-14 birth cohort reached the age of 85 years and were eligible to participate in the study. No exclusion criteria were used. Fourteen people died before enrolment; a total of 599 (87%) people gave informed consent and were enrolled. The Medical Ethics Commission of the Leiden University Medical Center approved the study and all participants gave informed consent.

Characteristics

Participants were visited yearly by a research nurse at their place of residence until death or the age of 90. During these visits information on sociodemographic characteristics was collected and participants underwent face to face interviews, blood sampling and electrocardiography.¹⁹

Of the 599 participants enrolled in the study at age 85 years, 295 died before the age of 90, and 32 refused blood sampling. An additional 20 participants missed creatinine clearance values at age 85 and/or 90 years. Thus, for the present study NT-proBNP levels and creatinine clearance at age 85 and 90 years were available for 252 participants (Flow chart Supplemental Figure 1).

NT-proBNP

Non-fasting blood samples were drawn before 11 a.m. Plasma samples were stored at -80°C . Serum levels of NT-proBNP were measured for all participants at age 85 and 90 years using the NT-proBNP assay of Roche Diagnostics (Mannheim, Germany) on a Roche Modular E-17 automated immunoanalyzer. Predefined change patterns were used to analyse the change in NT-proBNP levels from 85 to 90 years. These change patterns were defined considering the biological variability of NT-proBNP in healthy populations and were based on change patterns used in previous studies:^{12,20} 1) *increasing*: change in NT-proBNP levels $\geq +100\%$ [i.e. NT-proBNP level at least doubled]; or 2) *not-increasing*: change in NT-proBNP levels $< +100\%$.

Renal function

Plasma creatinine concentrations were measured according to the Jaffe method using a fully automated Hitachi 747 analyzer (Hitachi, Tokyo, Japan). Creatinine clearances were estimated using the Cockcroft–Gault formula.²¹

Incident cardiovascular events

Incident cardiovascular events were recorded *between the age of 85 and 90 years*. Each participant's general practitioner (or, if applicable, nursing home physician) was interviewed annually about the participant's medical history. ECGs were recorded yearly. Incident atrial fibrillation was defined as the appearance of Minnesota Code 8-3-1 on the ECG. Incident myocardial infarction was defined by newly diagnosed myocardial infarction according to the general practitioner and incident myocardial infarction on the ECG. Information about incident stroke and heart failure was collected from the general practitioner.

Mortality

All participants were followed for mortality *from age 90 years onwards*. Dates of death were obtained from municipality records, with censoring date 31 December 2011 (until ages 97 – 99 years). Specific data on cause of death were obtained from Statistics Netherlands, where all national death certificates are coded according to the International Classification of Diseases and Related Disorders, 10th revision (ICD-10).²² Causes of death were divided into two groups: cardiovascular mortality (ICD codes I00–I99) and non-cardiovascular mortality (all other ICD codes).

Statistical analysis

Summary characteristics are reported as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables and as numbers with percentage (%) for categorical variables. Relations between the two groups of NT-proBNP change and various clinical characteristics were explored using chi-squared tests and independent t-test as appropriate.

Differences in incident events that occurred between age 85 and 90 years between the two groups of NT-proBNP change were analysed using logistic regression analysis. We performed our analysis in three steps. First, crude analyses were performed. Second, we added eGFR at age 85 years. Third, change in eGFR between age 85 and 90 years was added. For incident atrial fibrillation and heart failure, subjects with a history of this event at age 85 years were excluded in this analysis.

For mortality after age 90, time to event curves were constructed with the Kaplan-Meier method, adjusted for competing risks. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were calculated with Cox proportional-hazard models. We performed our analyses in four steps. First, crude analyses were performed. Second, we added eGFR at age 85 years. Third, the change in eGFR between age 85 and 90 years was added. Furthermore, in a fully adjusted model we also added sex, smoking, total cholesterol and high-density lipoprotein cholesterol, systolic blood pressure, hyperten-

sion, body mass index, plasma creatinine, history of diabetes, myocardial infarction, stroke, atrial fibrillation and heart failure and the use of antihypertensive medication, loop diuretics and/or digoxin. All participants were 90 years of age, so no adjustment for age was made.

Data analysis was performed using SPSS 20 for Windows (SPSS Inc., Chicago, IL, USA).

Sensitivity analysis

First, analyses were performed excluding all participants with atrial fibrillation and/or heart failure at baseline ($n=38$). Second, analyses for mortality after age 90 were repeated excluding participants with atrial fibrillation and/or heart failure at baseline, or incident atrial fibrillation and/or heart failure between the age of 85 and 90 years, since these incident events could have influenced both the change in NT-proBNP as well as the mortality risk from age 90 years onwards. Third, to evaluate the additional value of the use of serial NT-proBNP values, analyses were adjusted for NT-proBNP levels at baseline. Fourth, analyses were performed in a subsample of participants with an $eGFR >30$ mL/min/1.73m² at age 90 years and in a subsample of participants with a decrease in $eGFR$ of less than 15% over five years ($< one$ SD of change in $eGFR$ between 85 and 90 years compared to $eGFR$ at age 85 years). Finally, to evaluate the influence of the choice to use two categories of change, the analyses with change in NT-proBNP were repeated using four categories of change in NT-proBNP (reduction in NT-proBNP, rise by 0-50%, rise by 50-100% and rise by more than 100%), respectively.

RESULTS

Study population

Change in NT-proBNP and $eGFR$ levels was available for 252 nonagenarian participants, 67 (26.6%) men and 185 (73.4%) women. Median NT-proBNP increase over five years was 154 pg/mL (IQR 29-549). Participants were divided into two groups based on the NT-proBNP change pattern (increasing levels $n=119$ and not-increasing levels $n=133$).

Renal function decreased between the age of 85 and 90 years, with a mean $eGFR$ decrease of 5.6 mL/min/1.73m² over five years (SD 7.5).

Table 1 shows the relations between the two change patterns of NT-proBNP and various clinical characteristics. History of hypertension and lower $eGFR$ at age 85 years were associated with an increasing NT-proBNP level over time ($p=0.025$ and $p=0.023$, respectively). Participants with atrial fibrillation on the baseline ECG ($n=17$) had higher median levels of NT-proBNP at age 85 years compared to those without atrial fibrillation on the baseline ECG (1228.4 pg/mL [751.1-1673.8] and 225.8 pg/mL [134.5-391.1], respec-

Table 1. Characteristics at age 85 and 90 years dependent on NT-proBNP change pattern (85-90 years) (n=252)

Characteristics	NT-proBNP change pattern (85-90 years)			P value
	All (n=252)	Increasing (n=119)	Not-increasing (n=133)	
Men (%)	67 (26.6)	38 (31.9)	29 (21.8)	0.069
Characteristics at age 85				
Smoking (%)	27 (10.7)	10 (8.4)	17 (13.0)	0.551
Systolic blood pressure (mmHg)	157.9 (17.3)	158.7 (18.0)	157.2 (16.7)	0.498
Diastolic blood pressure (mmHg)	78.5 (8.6)	78.4 (9.0)	78.6 (8.1)	0.845
Hypertension ^a (%)	152 (60.3)	81 (68.1)	71 (54.2)	0.025
Diabetes Mellitus ^b (%)	34 (13.5)	24 (20.2)	10 (7.6)	0.004
Body mass index (kg/m ²)	27.4 (4.5)	27.2 (4.4)	27.6 (4.5)	0.452
History of myocardial infarction (clinical or on ECG) (%)	26 (10.3)	15 (12.6)	11 (8.3)	0.267
History of heart failure (%)	21 (8.3)	13 (10.9)	8 (6.0)	0.165
History of arrhythmia (%)	41 (16.3)	18 (15.1)	23 (17.3)	0.741
History of stroke (%)	15 (6.0)	5 (4.2)	10 (7.5)	0.274
Atrial fibrillation on ECG (%)	17 (6.7)	3 (2.5)	14 (10.5)	0.011
NT-proBNP (pg/mL)	239 (141-429)	208 (116-363)	270 (153-524)	0.006
Estimated glomerular filtration rate (mL/min/1.73m ²)	46.7 (10.5)	45.1 (9.7)	48.1 (11.0)	0.023
Total cholesterol (mmol/L)	5.8 (1.0)	5.8 (1.0)	5.9 (1.0)	0.266
High-density lipoprotein cholesterol (mmol/L)	1.4 (0.4)	1.3 (0.4)	1.4 (0.4)	0.046
C-reactive protein (mg/L)	3.0 (1.0-5.0)	3.0 (1.0-5.0)	3.0 (0.25-6.0)	0.819
Characteristics at age 90 years				
NT-proBNP (pg/mL)	431 (231-1137)	762 (369-2216)	287 (178-544)	<0.001
Estimated glomerular filtration rate (mL/min/1.73m ²) at age 90 years	40.7 (11.7)	38.3 (11.0)	42.9 (11.9)	0.002
Change in NT-proBNP (pg/mL) (between 85 and 90 years)	154 (29-549)	519 (229-1753)	33 (-57-124)	-
Change in estimated glomerular filtration rate (mL/min/1.73m ²) (between 85 and 90 years)	-5.6 (7.5)	-6.7 (8.4)	-5.0 (6.6)	0.078

Categorical data are presented as frequencies (%); continuous data as mean (SD) or median (IQR). Missings n=0-6.

^aHistory of hypertension and/or systolic blood pressure >160mmHg and/or antihypertensive medication.

^bHistory of diabetes and/or glucose >11.0 and/or diabetic drugs.

tively, $p < 0.001$). However, participants with an increasing NT-proBNP level less often had atrial fibrillation on the ECG at age 85 years ($p = 0.011$).

Incident cardiovascular events

Between age of 85 and 90 years a total of 23 participants (9.1%) had an incident myocardial infarction. A total of 26 participants (11.1%) had incident atrial fibrillation, eleven participants (4.4%) experienced an incident stroke and 25 (10.9%) developed incident heart failure. Table 2 shows that increasing NT-proBNP was associated with incident atrial fibrillation (HR 3.11, 95% CI 1.25-7.70) and newly developed heart failure (HR 2.77, 95% CI 1.14-6.71), but not with incident myocardial infarction or stroke. The adjustment for eGFR at age 85 years and the change in eGFR between age 85 and 90 years did not alter the observed associations. The sensitivity and specificity of increasing NT-proBNP in identifying participants with atrial fibrillation were 73% and 53%, respectively, with a positive predictive value of 16.4% and a negative predictive value of 94.1%. For the identification of participants with heart failure, sensitivity of increasing NT-proBNP was 68% and specificity 57%, with a positive predictive value of 16.0% and a negative predictive value of 93.5%.

Table 2. NT-proBNP change pattern and incident cardiovascular events

	NT-proBNP change pattern (85-90 years)		Odds Ratio (95% CI)		
	Increasing (n=119)	Not-increasing (n=133)	Crude	Model 2 ^a	Model 3 ^a
Myocardial infarction ^{bc}	13 (10.9%)	10 (7.5%)	1.50 (0.63-3.55)	1.54 (0.64-3.69)	1.44 (0.59-3.50)
Atrial fibrillation on ECG ^d	19 (16.4%)	7 (5.9%)	3.11 (1.25-7.70)	3.26 (1.30-8.20)	2.63 (1.02-6.79)
Heart failure ^e	17 (16.0%)	8 (6.5%)	2.77 (1.14-6.71)	3.08 (1.24-7.63)	2.79 (1.11-7.02)
Stroke ^f	4 (3.4%)	7 (5.3%)	0.63 (0.18-2.23)	0.76 (0.21-2.75)	0.80 (0.22-2.95)

For incident heart failure and incident atrial fibrillation, subjects with a history of the relevant event were excluded in this analysis.

^a Model 2 adjusted for eGFR at age 85 years; model 3 adjusted for eGFR at age 85 years and change in eGFR over five years.

^b Data from general practice (or, if applicable, nursing home physician) and ECG recordings.

^c Missing n=1.

^d Excluded n= 17; missing n=1.

^e Excluded n=21; missing n=1.

^f Missing n=11.

Time to death from age 90 years onwards by NT-proBNP change pattern is shown in Figure 1. Participants with an increasing NT-proBNP level over five years had an 1.6 fold increased all-cause mortality risk compared to those with an not-increasing NT-proBNP level when adjusted for eGFR at age 90 years and change in eGFR between age 85 and 90 years (HR 1.57, 95% CI 1.20-2.05) (Figure 1a). Increasing NT-proBNP level over five years

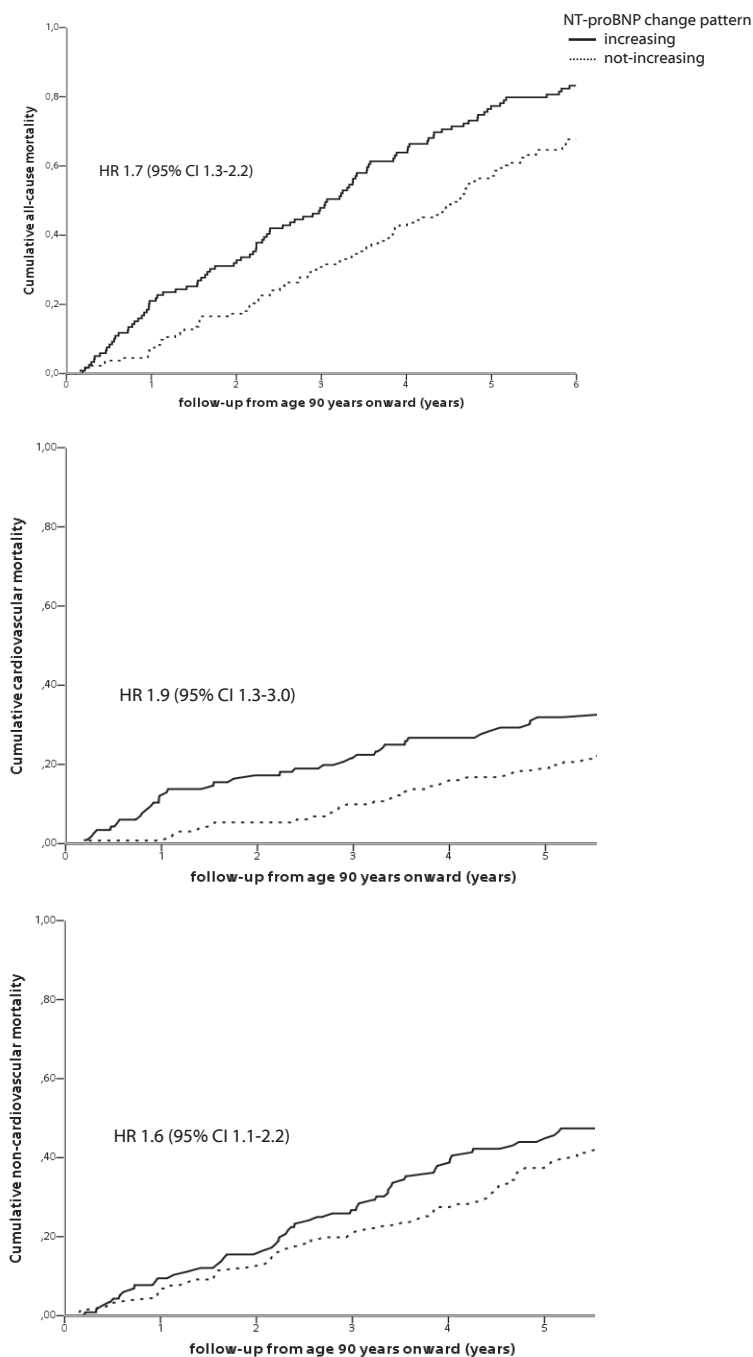


Figure 1. Cumulative mortality from age 90 years onward in relation to the relative change in NT-proBNP levels (n=252) a.) all-cause mortality; b) cardiovascular mortality; c) non-cardiovascular mortality

was associated with an increased cardiovascular mortality risk (HR 1.62, 95% CI 1.04-2.51) (Figure 1b) and non-cardiovascular mortality risk (Figure 1c). The same trend was seen for the fully adjusted model (Supplemental Table 1).

Sensitivity analysis

First, when the analyses were repeated in a subgroup of participants without heart failure or atrial fibrillation at baseline ($n=252-38=214$), the same results emerged (data not shown). Second, after exclusion of participants with atrial fibrillation and/or heart failure at baseline or incident atrial fibrillation and/or heart failure between the age of 85 and 90 years, the association of increasing NT-proBNP with higher mortality remained similar (all-cause mortality HR 2.02, 95% CI 1.39-2.92; cardiovascular mortality HR 1.93 95% CI 1.04-3.58; non-cardiovascular mortality HR 1.99 95%CI 1.24-3.20). Third, when the analyses were adjusted for NT-proBNP levels at baseline, the results did not materially changed (data not shown). Fourth, in participants with relatively normal and stable renal function ($eGFR >30$ mL/min/1.73m² at age 90 years and a decrease in $eGFR$ of less than 15% over five years, respectively), increasing NT-proBNP level over five years was still associated with an increased cardiovascular mortality risk compared to a not-increasing NT-proBNP level (data not shown). Finally, we analysed the association of incident cardiovascular events and mortality risks with four categories of change in NT-proBNP (reduction in NT-proBNP, rise by 0-50%, rise by 50-100% and rise by more than 100%). Participants with a rise by >100% more frequently had incident atrial fibrillation and heart failure compared to the other change categories (data not shown). Finally, only participants with a rise by >100% had an increased cardiovascular mortality risk (HR 2.03, 95% CI 1.04-3.94), adjusted for $eGFR$ at age 90 years and change in $eGFR$ between age 85 and 90 years, compared to participants with a reduction in NT-proBNP.

DISCUSSION

This study shows that in the oldest old an increase in NT-proBNP level, as compared to a not-increasing NT-proBNP level, is predictive for an increased cardiovascular mortality risk, independent of (change in) renal function. An increase in NT-proBNP in this group is also associated with incident atrial fibrillation and newly developed heart failure, irrespective of the renal function. Thus, interpretation of NT-proBNP and NT-proBNP changes over time in the oldest old is challenging, as they do not only reflect parallel changes in renal function.

In line with the literature, we found a predictive value of increasing NT-proBNP levels for increased mortality risk. This has been reported earlier in two observational studies in an elderly population.^{12,13} As described previously, NT-proBNP levels were found to

increase with advancing age.^{5,12,14,23} Present study investigates two possible biological pathways related to increasing NT-proBNP levels over time in old age: 1) decreasing renal function and 2) cardiovascular pathology. There is some evidence in the literature suggesting that, in old age, decreasing renal function could, in part, underlie increasing NT-proBNP levels over time.¹⁶ In an observational study among subjects aged 70 years,¹² increasing NT-proBNP levels were associated with lower eGFR. In line with these finding, the present study found that, in the oldest old, lower eGFR is related to increase in NT-proBNP levels over time. However, in line with the second possible pathway, the present study found that incident atrial fibrillation is independently related to increasing NT-proBNP levels over time in the oldest old. This concurs with a study by Patton et al.²⁴ that reported that NT-proBNP is a remarkable predictor of incident atrial fibrillation. In the present study atrial fibrillation at baseline was inversely associated with increasing NT-proBNP levels. This is probably due to already higher baseline levels in participants with atrial fibrillation compared to those without atrial fibrillation. When the level of NT-proBNP is already high, this value is less likely to double (increase of $\geq 100\%$). It is known from literature that patients with atrial fibrillation have markedly higher levels of NT-proBNP.^{24,25}

This study provides insight into the biology and clinical applicability of NT-proBNP in very old age. To our knowledge, ours is the first to evaluate the relation between increasing NT-proBNP levels and cardiac morbidity and mortality independent of the change in renal function in the oldest old. We show that an increase in NT-proBNP of at least 100% is driven by cardiac abnormalities causing increased wall stress or highly frequent atrial contraction, in the oldest old mainly heart failure and atrial fibrillation, and that this association is independent of renal function. Although a decline in renal function should still be considered when interpreting NT-pro-BNP values in old age, our results call for the awareness of physicians to consider the presence of (so far unrecognized) atrial fibrillation and/or heart failure when observing an increase in NT-proBNP in the oldest old. Future studies are needed to evaluate the appropriate time intervals for NT-proBNP testing, to evaluate the clinical thresholds for changes in NT-proBNP levels over time and to evaluate the use of NT-proBNP in risk assessment in the oldest old in clinical practice, as well as its cost effectiveness.

This study has several strengths: a large group of oldest-old individuals who were recruited from the general population without exclusion criteria, complete long-term follow-up for cause-specific mortality and a low attrition rate. Nevertheless, this study has a number of limitations. We included a specific population in our cohort, namely participants with NT-proBNP measurements at both age 85 and 90 years, a selection of strong survivors. There was a significant difference in almost all baseline characteristics between participants alive at age 90 years and those who died between ages 85 and 90 years (Supplemental Table 2). Participants alive at age 90 years and included in our analyses less

frequently had a history of cardiovascular disease and had higher systolic and diastolic blood pressure and total cholesterol, all factors associated with better survival in very old age.²⁶⁻²⁸ Persons with serious heart failure at age 85 were likely to have died before they could reach the age of 90 years, and were therefore not included in our study. The selection of strong survivors has most likely led to an underestimation of the found association (odds ratios) between the increase in NT-proBNP and incident events. Second, the diagnosis of heart failure and myocardial infarction in the present study was based solely on the information from the participant's general practitioner and electrocardiography, respectively. No echocardiography was available to confirm the diagnosis of heart failure. Misclassification may have played a role. However, this is a representation of routine clinical practice during the time the study was conducted. Still, our general population-based study is well suited to show the determinants associated with changes in NT-proBNP in the oldest old and therefore generalizable to the older population.

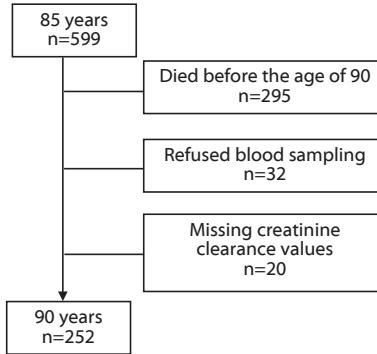
In conclusion, the present study shows that in the oldest old, an increase in NT-proBNP is associated with incident heart failure and atrial fibrillation, independent of changes in renal function. Also, this increase still reflects increased risk for (cardiovascular) mortality, independent of decreasing renal function.

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APPENDIX

**Supplemental Figure 1.** Flow chart**Supplemental Table 1.** Hazard ratio for mortality for participants with increasing NT-proBNP (n=119) compared to those without an increase in NT-proBNP (n=133)

	All-cause mortality	Cardiovascular mortality	Non-cardiovascular mortality
Unadjusted	1.7 (1.3-2.2)	1.9 (1.3-3.0)	1.6 (1.1-2.2)
Adjusted for sex and eGFR at age 90	1.6 (1.2-2.1)	1.6 (1.1-2.5)	1.5 (1.1-2.2)
Adjusted for sex, eGFR at age 90 and change in eGFR between 85 and 90 years	1.6 (1.2-2.1)	1.6 (1.0-2.5)	1.5 (1.1-2.2)
Adjusted for sex, renal function and risk factors for and history of cardiovascular disease ^a	1.8 (1.3-2.3)	1.8 (1.1-2.9)	1.7 (1.2-2.5)

Hazard Ratio and corresponding 95% confidence intervals.

^a Risk factors for and history of cardiovascular disease include smoking, total cholesterol and high-density lipoprotein cholesterol, systolic blood pressure, hypertension, body mass index, plasma creatinine, history of diabetes, myocardial infarction, stroke, atrial fibrillation and heart failure and the use of antihypertensive medication, loop diuretics and/or digoxin.

Supplemental Table 2. Baseline characteristics for participants that reached the age of 90 years and those who died before they could reach the age of 90 years

Characteristics at age 85 years	Reached the age of 90 years		P value
	Yes (n=252)	No (n=308)	
Men (%)	67 (26.6)	120 (39.0)	0.002
Smoking (%)	27 (10.7)	58 (18.8)	0.006
Systolic blood pressure (mmHg)	157.9 (17.3)	152.9 (19.6)	0.001
Diastolic blood pressure (mmHg)	78.5 (8.6)	75.3 (10.1)	<0.001
Hypertension ^a (%)	152 (60.3)	172 (55.8)	0.238
Diabetes Mellitus ^b (%)	34 (13.5)	56 (18.2)	0.134
Body mass index (kg/m ²)	27.4 (4.5)	26.9 (4.5)	0.191
History of myocardial infarction (clinical or on ECG) (%)	26 (10.3)	65 (21.1)	<0.001
History of heart failure (%)	21 (8.3)	49 (15.9)	0.007
History of arrhythmia (%)	41 (16.3)	75 (24.4)	0.021
History of stroke (%)	15 (6.0)	41 (13.3)	0.004
Atrial fibrillation on ECG (%)	17 (6.7)	39 (12.7)	0.019
NT-proBNP (pg/mL)	239 (141-429)	461 (192-1320)	<0.001
Creatinine (umol/L)	92.8 (19.9)	103.5 (41.4)	<0.001
Estimated glomerular filtration rate (mL/min/1.73m ²)	46.7 (10.5)	44.3 (12.3)	0.019
Total cholesterol (mmol/L)	5.8 (1.0)	5.6 (1.2)	0.017
High-density lipoprotein cholesterol (mmol/L)	1.4 (0.4)	1.3 (0.4)	0.003
C-reactive protein (mg/L)	3.0 (1.0-5.0)	5.0 (2.0-10.0)	0.003

Categorical data are presented as frequencies (%); continuous data as mean (SD) or median (IQR).

Missings n=0-17.

^a History of hypertension and/or systolic blood pressure >160mmHg and/or antihypertensive medication.

^b History of diabetes and/or glucose >11.0 and/or diabetic drugs.



FINAL

CHAPTERS



Chapter 8

General discussion

The studies presented in this thesis address new possibilities in cardiovascular risk prediction in old age. This general discussion describes the context of cardiovascular risk prediction and prevention, research among an older population and important epidemiological themes emerging from this thesis, then makes recommendations for future research and, finally, highlights key points arising from this thesis.

1. CARDIOVASCULAR RISK PREDICTION AND PREVENTION

Cardiovascular disease already has a substantial impact in old age and will probably have an even greater impact on society due to the projected increase in the prevalence of cardiovascular disease in the coming decades. To manage the expected epidemic of cardiovascular disease, it is essential to study (prediction) models that identify those individuals at highest or lowest (relative) risk and, when preventive strategies are proven effective, that these strategies be implemented, especially in older populations.

1.1 Prevention paradox

The prevention paradox, first formally described in 1981 by Sir Geoffrey Rose, describes the apparently contradictory situation where the majority of cases of cardiovascular disease occur among the population with mild to moderate increased risk, and only a minority of cases come from the minority of people at high risk.¹ This should be taken into account when considering primary prevention of cardiovascular disease, because it leads to the use of two distinct and complementary strategies: the ‘low-risk population approach’ and the ‘high-risk individual approach’. Interventions with the goal to improve health at the population level aim to produce small changes in a large number of people and have relatively little influence on the health of the majority of people. That is, for one person to benefit, many people have to change their behavior even though they receive no benefit. These interventions include, for example, promoting non-smoking, a healthy diet and physical exercise, and are usually implemented by the public health sector. No studies have focused on the effect of these interventions in the older population. However, prevention by promoting a healthy lifestyle starting early in life remains important.

The high-risk approach aims to identify individuals at highest risk, followed by appropriate interventions that may lower individual risk. However, this strategy has limited potential for population health improvement; moreover, focusing exclusively on those at high absolute risk overlooks the burden of events that will occur among the average majority. The Dutch Guideline Cardiovascular Risk Management more or less recommends screening for individuals at high cardiovascular risk.² However, there is no evidence that this approach is effective in old age. The first step in this high-risk

approach in old age is to identify new possibilities in cardiovascular risk prediction in order to select high-risk older individuals - as described in this thesis.

1.2 Use of classic and new cardiovascular risk predictors in old age

The risk of cardiovascular disease is considered to be multifactorial. However, in older people, established classic risk factors and corresponding risk scores, such as the Framingham Risk Score and the SCORE risk function, do not qualify for adequate risk prediction. The Leiden 85-plus Study showed that the Framingham Risk Score in no way predicts cardiovascular risk in persons aged 85 years and over.³ Therefore, the study on classic and new cardiovascular risk predictors in old age, as described in this thesis, is a first step to optimize risk stratification and subsequent prevention of cardiovascular disease in older persons.

Part 1 of this thesis shows that the use of multiple blood pressure measurements, expressed as variability in blood pressure or trend in blood pressure, can identify older persons at high risk for (cardiovascular) mortality (**Chapters 2 and 4**). Blood pressure is one of the most frequently recorded measurements in the medical file, at least in general practice. Therefore, the use of multiple blood pressure measurements in cardiovascular risk prediction is expected to be easy to implement. Additional research is needed to assess whether risk stratification based on multiple blood pressure measurements is effective and whether additional benefit might be obtained from reducing variability in blood pressure. Identifying the association between inflammation (evidenced by higher levels of interleukin-6) and blood pressure variability (**Chapter 3**) might help to elucidate the underlying mechanisms of variability in blood pressure. Observational studies in exclusively older populations have shown that not high, but low systolic blood pressure predicts increased mortality.⁴⁻⁶ It is suggested that low blood pressure is merely a proxy for heart failure and is, therefore, associated with increased mortality. If that is the case, then it is better to evaluate the absence or presence of heart failure when assessing cardiovascular risk, rather than (low) blood pressure. Low blood pressure, however, does predict increased mortality in very old age even without heart failure (**Chapter 4**).

Part 2 of this thesis addresses the use of N-terminal pro-brain natriuretic peptide (NT-proBNP) in old age. NT-proBNP has predictive value in cardiovascular prevention in old age.⁷⁻¹¹ In older patients with a history of cardiovascular disease, NT-proBNP not only predicts recurrent cardiovascular disease and cardiovascular mortality, but also predicts treatment effect of pravastatin (**Chapter 6**).

Risk prediction based on (risk prediction models including) serological biomarkers such as homocysteine¹² and NT-proBNP, in combination with statin treatment in persons with high levels of these serological biomarkers, is likely to result in better targeting of preventive medication in older people with truly increased risks of cardiovascular

disease (**Chapter 6**). General practitioners may be more inclined to determine serological biomarkers linked to cardiac damage, such as and NT-proBNP and troponin T. These markers of cardiac damage provide more information for the general practitioner, in addition to the cardiovascular risk prediction. For NT-proBNP it was shown that the change in NT-proBNP can also be informative. Changes in NT-proBNP do not merely reflect changes in renal function; an increase in NT-proBNP is associated with incident heart failure and atrial fibrillation, as well as a risk for cardiovascular mortality, independent of decreasing renal function (**Chapter 7**).

1.3 Treatment-risk paradox in the prevention of cardiovascular risk

Research has shown a treatment-risk paradox for primary and secondary prevention of cardiovascular disease.^{13,14} Patients become less likely to receive appropriate treatment the older they get. For example, in a study from Ontario in secondary prevention, the likelihood of a statin prescription was 6% lower for each year of increase in age.¹³ A study from the United Kingdom showed that in primary prevention for people aged 75 years and older, the odds of receiving a statin prescription decreased every five-year increment in age and that many older people did not receive anti-hypertensive drugs.¹⁴ Both polypharmacy and underprescribing are common among older people.¹⁵ It is difficult to determine whether there is a true under-utilisation of preventive treatment in older people; whether low use of preventive treatments in older people is just or unjust. Not prescribing these drugs might reflect a considered decision, taking into account factors associated with age such as multiple comorbidities, polypharmacy, cognitive decline, drug-drug interactions and side-effects such as serious fall injuries associated with antihypertensive medications¹⁶ and musculoskeletal pain associated with statin use¹⁷; all of these can make the physician reluctant to prescribe preventive drugs. The patient's choice also plays a role. Nevertheless, there is a striking contrast between use of statins and use of antihypertensive drugs in older people, which does indicate a possible underuse of statins.¹⁴ This could reflect the limited evidence for a benefit from the use of statins in the oldest old. The treatment-risk paradox highlights the need for a stronger evidence base and clearer guidelines for older people, especially for those aged 75 years and over.

1.4 Cardiovascular preventive strategies in old age

With the increasing proportion of older persons in the population, physicians will be increasingly challenged to make therapeutic decisions about cardiovascular risk and cardiovascular disease in old age. When older patients at high predicted cardiovascular risk are identified, physicians need to decide whether or not to advise preventive medication to their older high-risk patients. The evidence for cardiovascular risk reduction

in the oldest old is sparse. Therefore, more research involving the oldest old is needed before evidence-based recommendations can be formulated.

Lifestyle changes like dietary changes, exercise and smoking cessation, can be seen as individual or population-based preventive strategies. There is little evidence for the benefit of these lifestyle changes in the oldest old in the reduction of cardiovascular risk. However, there are benefits beyond cardiovascular disease risk, e.g. the benefits of exercise with regard to osteoporosis, quality of life and fall prevention¹⁸ and the benefits in relation to pulmonary diseases. Reports on centenarians have shown that a healthy lifestyle initiated at young age, including caloric restriction, abundant intake of vegetables rich in antioxidants and moderate intake of alcohol, is associated with longevity.¹⁹

The evidence supporting prescription of antihypertensive drugs in older patients is relatively well established, although few studies have focused on the outcomes of control of hypertension in old age compared to middle-aged. Antihypertensive drugs are generally considered safe and effective in older patients when aiming for a systolic blood pressure of no less than 150 mmHg. The HYVET study showed that antihypertensive treatment with a target systolic blood pressure of 150 mmHg in independently living patients over the age of 80 years with or without previous cardiovascular disease reduces risk of cardiovascular events and increases life expectancy with a benefit of treatment in the first year.²⁰ This is indirectly supported by another study that showed no evidence of a J-shaped increased risk at lower blood pressure in old age in patients without a history of cardiovascular disease.²¹

The effect of high blood pressure does vary by cardiovascular endpoint. Heart failure contributed to a substantial part of the estimated loss of years free of cardiovascular disease associated with hypertension. One study discussed whether a blood pressure target below 150 mmHg, but not less than 140 mmHg, could be of potential benefit.²² However, the reduction in cardiovascular events associated with antihypertensive treatment is most likely driven by the decrease in blood pressure and not by achieving the target blood pressure of less than 150 mmHg.²³ A meta-analysis of individual patient data showed that lowering blood pressure provides similar relative protection at all levels of baseline cardiovascular risk, but provides greater absolute risk reductions as baseline risk increases.²⁴ Nevertheless, when deciding to initiate or continue antihypertensive treatment, the potential harms and benefits should be weighed. In another study antihypertensive drugs were associated with an increased risk of serious fall injuries.¹⁶

The evidence for use of statins in older persons is less clear. There is insufficient evidence regarding statin treatment beyond the age of 85 years. A statin trial in the oldest old is needed.²⁵ Lipid lowering for those with a history of cardiovascular disease and high risk of cardiovascular events can be advised up to the age of 85 years. In this thesis

it was shown that older persons identified as high risk benefit the most from pravastatin treatment (**Chapter 6**).

Due to the increasing heterogeneity, it is essential to consider each person as an individual when decisions are made regarding initiating risk prediction and when preventive strategies are made. Patients' wishes and individual preferences, functional status, cognition, comorbidities, goal of care, possible side-effects, and the likelihood and duration of the preventive treatment to benefit need to be incorporated in decision-making, as well as the risk factors. The relatively new risk factor trends and variability in blood pressure and/or (change in) NT-proBNP can be useful regarding prediction of cardiovascular risk and treatment effect - as described in this thesis.

2. RESEARCH AMONG AN OLDER POPULATION

Research among an older population has important theoretical and methodological characteristics that need to be recognized and addressed.

2.1 What is 'old age'?

The term 'old age' has a broad interpretation. Traditionally, one is considered old when reaching the age of 65 years, reflected in multiple domains of society and economics. In PubMed, a database for healthcare literature, the MeSH (Medical Subject Headings) -term 'aged' is used for persons 65 through 79 years of age. For a person older than 79 years, the term 'aged, 80 and over' is used. However, references to older people may range from 60 up to 100 years. Increasing heterogeneity in medical complexity, function and cognition, one of the most striking features of ageing, may not be apparent in the word 'elderly' or 'old'. The introduction of sub-populations like the terms used in PubMed, or the three subpopulations 'young old' for those aged 65-74 years; 'old' for those 75-84 years and 'oldest old' for those aged 85 years and over can help to describe distinct populations. Nowadays, subgroup analyses for age groups are used more frequently in healthcare literature, however, most literature still summarizes results for those aged 65 years and older using the term 'elderly' or 'old'. Some of the terms used to describe an older population have a negative connotation. The use of the term 'elderly' is considered most undesirable.²⁶ The use of the term 'older' is preferred by both older people themselves²⁷ and the Human Rights Commission of the United Nations.²⁸

2.2 Heterogeneity in an older population

Even if subgroups on age are being considered, heterogeneity still plays a role. Many 80-year-old individuals are healthy, while others have serious medical issues and dis-

abilities. Take, for example, a vigorous 80-year-old person who is an informal caregiver, independently living and swimming three times a week; compared with an 80-year-old person living in a long-term care facility with severe dementia and wheelchair-bound due to a stroke; and, again, an 80-year-old person with a life expectancy of less than one year due to metastasized cancer. Whereas a generalized approach is suitable for 25-year-old individuals who are physiologically relatively similar, it is clear from these three examples that in older age a different, individual approach is needed. Subgroups within the same age group of, for example, multiple comorbidities might be the next step - like the sensitivity analyses described in various chapters of this thesis.

2.3 Generalizability of study results

Oldest old (aged 85 years and over) is the fastest-growing segment of the total population. The proportion of the population aged 85 years and older is projected to increase to 151% by 2030.²⁹ However, the evidence base for the older population is sparse when compared to younger populations. It can be said that with increasing age, less evidence-based decisions can be made. The most conclusive evidence for the effectiveness of preventive risk stratification and preventive risk factor modifications is derived from randomized controlled trials. It is important to note that most of the randomized trials exclude older individuals, especially individuals with complex and multiple chronic conditions.³⁰ With increasing age the number of comorbidities increases and therefore especially the oldest old are underrepresented in these trials.

Nevertheless, results from these trials are being extrapolated to older individuals, assuming that the same risk reduction applies to the older population. This assumption implies that older people, for example, experience the same treatment response as younger adults. However, it is known that most older people experience a change in physiology and have multiple chronic conditions that may affect pharmacokinetics and pharmacodynamics. Polypharmacy is most common in older persons and the use of multiple 'other' treatments may also affect treatment response due to drug-drug interactions. In addition, the presence of one disease may lessen the effect of preventing another. For example, the functional benefit of preventing a stroke through blood pressure control might be compromised by the presence of advanced multiple sclerosis. Therefore, we cannot assume that the same risk reduction would apply to an older population. The same applies to preventive risk stratification. Therefore, extrapolating evidence from younger populations to older populations is probably not appropriate.

Thus, although there is an urgent need for research in the older population, there are some difficulties concerning inclusion of the oldest old in clinical research. As mentioned before, comorbidities make it difficult to include older individuals in trials. The capacity to give informed consent with an increasing prevalence of cognitive impairment in the oldest old raises ethical dilemmas. Also, older people may have difficulty complying

with study requirements. This can, however, often be overcome by (for example) making home visits instead of requesting visits at the research center. Alternatives for randomized controlled trials, such as observational studies of representative populations with complete health records could provide useful information. The Leiden 85-plus Study is a good example of such an observational population-based study (**Chapters 4, 5 and 7**).

2.4 Competing risk

The statistical analysis of the data of an old age population also raises several methodological issues, such as 'competing risk'. Survival analysis provides valuable insight into how the risk of interest depends on time.³¹ When analysing survival data in which each patient can experience only one of several different types of events over follow-up, e.g. cardiovascular mortality, the probabilities of the other events are referred to as 'competing risks'.³² The commonly used approach in healthcare literature is to consider all events of all other causes as censored, as well as the true censored observations due to end of the study or loss to follow-up. This assumes that all patients at risk at a certain point in time are representative for all patients alive at this point in time; censoring distribution is considered independent. In other words, the censoring is not associated with an altered chance of the event occurrence at any given moment.³¹ This assumption is questionable, other events might have occurred which prevents occurrence of the event of interest. When the event of interest is death due to cardiovascular disease, but the patient is censored due to death from another cause such as cancer, the chance of death is now zero, therefore the censoring assumption is violated. This is the competing risk problem; other risks are competing with cardiovascular disease to produce the event death.

The competing risk problem is especially true in old age where death from other causes plays a large role. However, we can never explicitly prove that competing risks are or are not independent. It cannot be determined whether a patient that died from cardiovascular disease would have died from e.g. cancer if he/she had not died from cardiovascular disease. Non-independent censoring can lead to biased results in a survival analysis. When competing risks are present, cause-specific hazard is interpretable but the interpretation of the survival curve for a cause-specific mortality may be difficult or questionable.³² A better approach is to acknowledge that patients may die from causes other than cardiovascular disease and adjust for the competing risks in the analysis - as described in **Chapter 7**. There is no clear cut-off point when you should adjust for competing risks. It is clear that when two unadjusted survival curves add up to > 100%, competing risk is definitely an issue in the analysis and direct interpretation of these curves is erroneous. The longer the follow-up and the higher the incidence of the competing risks, the more important the adjustment for competing risks will be.

In conclusion, there is an urgent need for research among the older population. It is important to recognize the heterogeneity in this population regarding study design and the analysis, interpretation and extrapolation of the results. In addition, it is important to be aware of competing risks. This requires special research groups with experience, skills and interest in research among the older population.

3. EPIDEMIOLOGICAL CONSIDERATIONS

Epidemiology studies the distribution and determinants of disease frequency in different groups of people. Several epidemiological concepts are mentioned in this thesis or where considered in the analysis cited in this thesis. 'Prediction', 'causation' and 'confounding' are some important concepts.

3.1 Prediction versus causation

Being able to predict future health is important for both patients and physicians. That is probably why there is increasing interest in (the methodology of) clinical prediction research. Prediction research includes both diagnostic prediction research and prognostic research. Diagnostic prediction research investigates the ability of certain test results or variables to predict the presence or absence of a certain disease. Prognostic prediction research investigates the ability of various factors to predict a specific outcome - as described in this thesis. Both types of prediction research may include a single variable/predictor or multiple variables/multiple predictors. Prediction studies aim to find (independent contributing) predictors or develop and validate prediction models. A prediction model does not infer causal relationships of the risk factors included with the outcome of interest.

A framework of four distinct but inter-related prognosis research themes have been proposed³³:

1. Fundamental prognosis research: the course of health-related conditions in the context of the nature and quality of current care.
2. Prognostic factor research: specific factors (such as biomarkers) that are associated with prognosis.
3. Prognostic model research: the development, validation, and impact of statistical models that predict individual risk of a future outcome.
4. Stratified medicine research: the use of prognostic information to help tailor treatment decisions to an individual or group of individuals with similar characteristics.

Chapters 2, 5 and 7 of this thesis can be considered as ‘prognostic factor research’. Variability in blood pressure over time, a decreasing trend in systolic blood pressure over time, and higher and increasing NT-proBNP levels are identified as predictors of cardiovascular mortality and morbidity in old age. ‘Prognostic model research’ is described in **Chapter 6**, in which prognostic models for cardiovascular morbidity and mortality are compared. **Chapter 6** use prognostic information to help tailor treatment decisions and could therefore also be seen as ‘stratified medicine research’. Subgroups of older persons are identified who would benefit the most (or the least) from pravastatin therapy to prevent (subsequent) cardiovascular events.

Etiologic epidemiologic research aims to find causal associations. It is research into the causes of a health outcome, i.e. to understand the factors that influence the incidence, distribution and control of certain diseases. In **Chapter 3** of this thesis, factors associated with intra-individual variability in blood pressure are identified. The study design described in **Chapter 3** does not allow to assess causal relationships, but is, however, a first step in elucidating the underlying mechanisms of variability in blood pressure and its association with cardiovascular morbidity, mortality and cognition. In the current medical literature, etiologic and prediction research aims are frequently confused. Investigators tend to use principles from prediction research for their etiologic research questions, which results in misleading interpretation of risk factor findings at hand.

3.2 Confounding in prediction and etiologic research

Confounding is the ‘disturbance of the true effect’ and is a type of bias. Potential confounders may or may not distort the relationship between the determinant of interest and the outcome in the data, depending on the presence or absence of associations between these variables. If a factor is related to both the determinant and the outcome in an occurrence relation, the factor is a confounder. It should, however, not be a part of the causal relationship or causal chain between the determinant and the outcome.

In prediction research there is no central determinant for which the relationship to the outcome should be causally isolated from other outcome predictors as in causal research. Thus, confounding thus is not an issue in prediction research,³⁴ and adjusting for confounding in prediction research is therefore erroneous. Nevertheless, multiple predictors can be analysed together to assess whether a predictor makes an independent contribution.

In contrast, confounding plays an important role in etiological research. A determinant is believed to be causally related to an outcome if the association remains when confounding is excluded. However, residual confounding by some unidentified factors needs to be excluded. A causal association is difficult to establish and is more probable when a large number of independent studies show consistent results; e.g. a temporal

relationship where the cause precedes the outcome; when there is a strong association; when there is a dose-response relationship; and when there is biological plausibility.³⁵

3.3 Directed acyclic graphs

The structure of confounding can be represented by using causal diagrams or directed acyclic graphs (DAGs). A DAG is a graphical tool to represent qualitative expert knowledge and a priori assumptions about the causal structure of interest and was first described by Judea Pearl in 2009.³⁶ DAGs can be helpful in identifying confounding, selection bias, and strategies for the selection of variables of interest for e.g. regression analysis. A factor can be seen as a confounder that needs to be eliminated from a causal model, but may be an important component in a prediction model. In both cases, DAGs can be useful. Figure 1 shows three examples of DAGs. It is called 'directed' because the edges imply a direction. The arrow from, e.g., heart disease to aspirin (use) may cause aspirin use, but not the other way around. It is called 'acyclic' because there are no cycles: a variable cannot cause itself, either directly or through another variable.³⁷ Figure 1a shows an example of confounding. The effect of aspirin on the risk (reduction) of stroke is confounded if aspirin is more likely to be prescribed to individuals with heart disease that is both an indication for aspirin and a risk factor for stroke. Both heart disease and stroke are caused by atherosclerosis, an unmeasured variable. In this graph, heart disease is a confounder in the association between aspirin and stroke.

Causation and prediction can be linked. When it is known what causes a disease or event, it would be helpful in predicting its behavior. Causal thinking can help to develop accurate prediction models. However, a predictor does not have to be causally related to the outcome. An example may help to clarify this. In Figure 1b cigarette smoking has a causal effect on both nicotine-stained fingers and lung cancer. The absence of an arrow between nicotine-stained fingers and lung cancer indicates that having nicotine-stained fingers does not have a causal effect on lung cancer. Nevertheless, nicotine-stained fingers could still be a good predictor for lung cancer. Another example is the predictor homocysteine (Figure 1c). There is no causal relation between homocysteine and cardiovascular disease. Although the common factor is still unknown, homocysteine is a good predictor for cardiovascular disease.¹²

In conclusion, prediction and etiologic research are two distinct but related fields of research in which different methodological aspects apply. Confounding is one of these aspects. DAGs can help to select important variables for both etiologic and prediction research. However, to avoid confusion and misinterpretation, it is of utmost importance to describe whether the research is aimed at identifying predictors (or prediction models) or identifying causal associations.

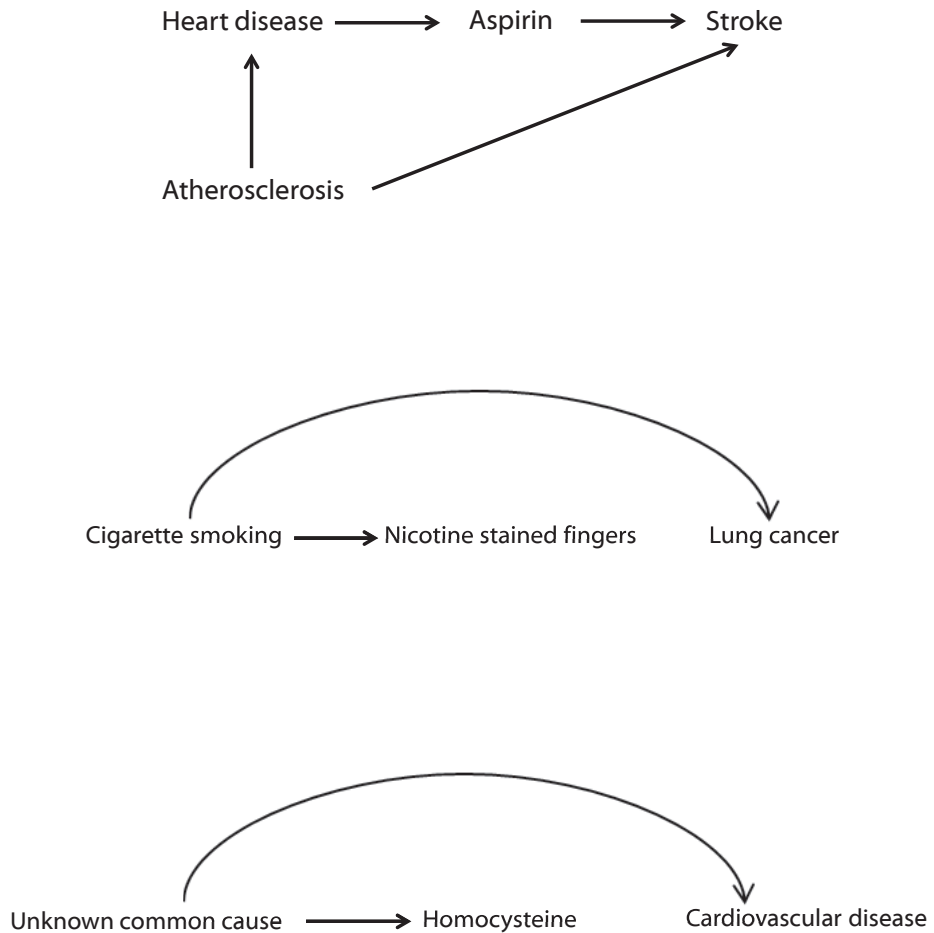


Figure 1. Directed acyclic graphs

4. RECOMMENDATIONS FOR FUTURE RESEARCH

There is a need for a stronger evidence base and clearer guidelines for older people as a whole, and for cardiovascular risk prevention in old age in particular. Future research among older people, especially involving people aged 75 years and older, is needed before evidence-based recommendations on cardiovascular risk prevention can be formulated for general practitioners and physicians in general.

With regard to cardiovascular risk prediction in old age, an important step is to develop and validate risk prediction models in the oldest old in order to select high-risk older individuals. The inclusion of (multiple) NT-proBNP measurements and possibly other emerging risk factors such as troponin T might be promising. Serological risk factors might be more relevant in an older population than imaging techniques that test for subclinical atherosclerotic disease, like the use of the calcium score which is generally not recommended older patients.³⁸ More studies are needed to evaluate the appropriate time intervals for NT-proBNP testing, to evaluate the clinical thresholds for changes in NT-proBNP levels over time, and to evaluate the use of NT-proBNP in risk assessment in the oldest old. The second step is to study the effectiveness of the preventive strategies including the (new) risk prediction models in the older population and, when proven effective, to study how these strategies can be implemented.

With regard to the prevention of cardiovascular disease, future research on the effectiveness of statin therapy in the oldest old, and possibly also the differential effects of various antihypertensive drugs on variability in blood pressure and cardiovascular risk and mortality, is warranted. Besides the aim of lowering the level of blood pressure in hypertensive patients, additional benefit might be obtained from reducing variability in blood pressure. This requires additional studies on the underlying mechanisms of blood pressure variability; for this, the association between the trend in interleukin-6 and variability in blood pressure could be a target for future research.

5. WHAT DOES THIS THESIS ADD?

By studying classical and new cardiovascular risk predictors in old age in an observational and a clinical trial, this thesis contributes to improved knowledge about cardiovascular risk prediction in old age. This can help to optimize risk stratification and subsequent prevention of cardiovascular disease in older persons. The use of multiple blood pressure measurements in cardiovascular risk prediction and risk stratification in old age is promising. Not only low systolic blood pressure, but also a decreasing trend in systolic blood pressure independently contribute to a prediction of mortality in the oldest old. The association between low systolic blood pressure and increased mortality risk found in old age is not influenced by the absence or presence of heart failure. In addition, blood pressure variability is associated with increased risk for coronary heart disease and mortality in older high-risk populations. Since blood pressure is one of the most frequently recorded measurements in medical files, the use of multiple blood pressure measurements in cardiovascular risk prediction in old age is also feasible.

In addition, in old age, the serological biomarker NT-proBNP may play an important role in the prediction of cardiovascular events and mortality, as well as treatment ef-

fect. The cardiovascular risk factors identified in this thesis can provide evidence-based information about cardiovascular risk factors and predicted treatment effect. This can help physicians (mainly general practitioners) in their discussions with patients on the cardiovascular risks and treatment benefits when considering the difficult decision to start or (dis)continue preventive treatment.

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Chapter 9

Summary

Cardiovascular disease is the leading cause of death worldwide. With increasing age, incidence and prevalence of cardiovascular disease increase as well. Therefore, the impact of cardiovascular disease is high in old age. Due to the expected increasing longevity and the aging population in the Netherlands, the number of older persons and therefore the impact of cardiovascular disease is projected to raise even further. Therefore, focus on prevention and risk prediction of cardiovascular disease in old age is of interest. Many physicians face the dilemma whether or not to start preventive treatment in old age, especially in primary prevention. To help physicians decide whether to advise preventive medication to their older patients, prediction of those at highest or lowest (relative) risk using (preferably) inexpensive and easy to use cardiovascular risk factors is important. However, in old age there is a lack of good cardiovascular risk predictors, as the classical cardiovascular risk factors tend to lose their predictive value. For many serological biomarkers the association with cardiovascular disease has been studied predominantly in middle age and not in old age. The use of multiple blood pressure measurements expressed in the variability or trends in blood pressure and the serological biomarker N-terminal pro-B-type natriuretic peptide (NT-proBNP) could be interesting candidates in cardiovascular risk prediction in old age. Selection of high risk blood pressure patterns or high risk NT-proBNP levels in old age could be an important and easily available step in the successful prediction of mortality and cardiovascular morbidity in this age group. Therefore, the general aim of this thesis is to study classical and new cardiovascular risk predictors in old age, in order to optimize risk stratification and subsequent prevention of cardiovascular disease in older persons (**Chapter 1**).

Part 1 Multiple blood pressure measurements in cardiovascular risk prediction in old age

Variability in blood pressure predicts cardiovascular disease in young- and middle-aged subjects, but relevant data for older individuals are sparse. Therefore, **Chapter 2** studied the impact of visit-to-visit variability in blood pressure in older patients. We examined the association between visit-to-visit variability in blood pressure and incident cardiovascular disease in the PROSPER study. Higher visit-to-visit variability in systolic blood pressure, diastolic blood pressure and pulse pressure was associated with an increased long-term risk of (vascular) death, even after adjustment for respective mean blood pressure levels, the use of antihypertensive medication and other risk factors. Persons with higher variability in diastolic blood pressure also had an increased risk for coronary events and hospitalization for heart failure. Variability in pulse pressure (but not diastolic blood pressure or systolic blood pressure) was somewhat associated with long-term risk of stroke. The principal finding of this study was that in old age, variability in diastolic blood pressure is more strongly associated with incident cardiovascular disease and (vascular) death than systolic pressure variability. To elucidate the

underlying mechanisms of variability in blood pressure in old age, **Chapter 3** studies the association between biological factor(s) and variability in blood pressure. Markers of inflammation, endothelial function, renal function and glucose homeostasis were included in the analysis. Inflammation (as evidenced by higher levels of interleukin-6) at baseline was consistently associated with higher variability in systolic blood pressure, diastolic blood pressure, and pulse pressure, even when adjusted for cardiovascular risk factors. Markers of endothelial function, renal function and glucose homeostasis were not or to a minor extent associated with blood pressure variability.

Observational studies have shown that not high, but low systolic blood pressure predicts increased mortality in old age. A plausible explanation is that (subclinical) heart failure may, at least partly, underlie this 'inversion of risk prediction'. The aim of **Chapter 4** was to investigate whether low systolic blood pressure is predictive for increased risk of death in the oldest old without heart failure, defined by low levels of NT-proBNP, as well as in the oldest old with high levels of NT-proBNP. This study was performed within the Leiden 85-plus Study, but restricted to the nonagenarian participants. We compared differences in risk of death between 90-year old persons with low systolic blood pressure and high systolic blood pressure for persons with low NT-proBNP (i.e. without heart failure) and for persons with high NT-proBNP. Persons with low systolic blood pressure had a two-fold increased risk of death compared to persons with high systolic blood pressure, both in the group with low NT-proBNP and in the group with high NT-proBNP. The main finding of this study was that in the oldest old, the absence or presence of heart failure does not influence the prognostic value of low systolic blood pressure regarding risk of death.

In **Chapter 5** the use of multiple blood pressure measurements to assess the trend in systolic blood pressure in cardiovascular risk prediction in the oldest old was studied in the Leiden 85-plus Study. We examined the association between the trend in systolic blood pressure between the age of 85 and 90 years, and systolic blood pressure at age 90 years and risk of death. The role of comorbidities and the use of antihypertensive medication in these associations were also investigated. Participants who had a decreasing trend in systolic blood pressure had a higher risk of death, independent of their blood pressure at age 90 years. Participants with low systolic blood pressure at age 90 years also had an increased risk of death, independent of the preceding trend in systolic blood pressure. Both for participants with and without antihypertensive medication and with or without (cardiovascular) comorbidities. Therefore, it was concluded that, in very old age, both decreasing trend in systolic blood pressure over the previous 5 years and the current systolic blood pressure value independently contribute to prediction of risk of death.

Part 2 N-terminal pro-brain natriuretic peptide levels in cardiovascular risk prediction in old age

As many more patients are surviving their initial cardiovascular event, prediction of recurrent events becomes increasingly important. However, no risk scores for prediction of recurrence risk and/or treatment effect exist for the general older population. Therefore, the aim of **Chapter 6** was to assess predictive values for recurrent cardiovascular disease, of models with age and sex, traditional cardiovascular risk markers, and SMART risk score, with and without NT-proBNP in old age. Also, to assess treatment effect of pravastatin across low and high risk groups identified by these models. This study was again performed within the PROSPER study, but restricted to those participants with a history of cardiovascular disease at baseline. The models with age and sex, traditional risk markers and SMART risk score had comparable predictive values. Addition of NT-proBNP to these models improved area under the curves, and net reclassification improvements were 41%, 39% and 25%, respectively. For the model with age, sex and NT-proBNP, the absolute risk reduction in cardiovascular morbidity and mortality was 0.86% (number needed to treat 116) in the low third of predicted risk and 6.2% (number needed to treat 16) in the high third of predicted risk. The principal finding of this study was that NT-proBNP is a promising cardiovascular risk predictor in old age. A minimal model with age, sex and NT-proBNP improves prediction of recurrent cardiovascular disease and mortality, and is as good as complex risk models including NT-proBNP.

An increase of NT-proBNP over time is further studied in **Chapter 7**. The aim of this study was to assess whether an increase in NT-proBNP level over time is still associated with cardiac disease and death in very old age, independent of (a change in) renal function. Within the Leiden 85-plus Study changes in NT-proBNP levels between age 85 and 90 years and their associations with incident cardiac disease, risk of (cardiovascular) death and renal function was studied. Participants with increasing NT-proBNP levels more frequently developed heart failure and atrial fibrillation between the age of 85 and 90 years, even when adjusted for renal function. Increasing NT-proBNP level between age 85 and 90 years was also associated with an increased risk of (cardiovascular) death after the age of 90 years, even when adjusted for renal function. In conclusion, in the oldest old, increase in NT-proBNP is associated with incident heart failure and atrial fibrillation, independent of renal function. Also, this increase still reflects increased risk of (cardiovascular) death, independent of decreasing renal function.

Chapter 8 is a general discussion and describes the context of cardiovascular risk prediction and prevention and highlights the themes discussed in this thesis. Due to the increasing heterogeneity, it is essential to consider each person as an individual when decisions are made regarding initiating risk prediction and when preventive strategies are made. The risk factors described in this thesis can be useful. Next, research among

an older population is discussed including its challenges resulting in a recommendation for special research groups with experience, skills and interest in research among the older population. In addition, important epidemiological themes emerging from this thesis, including the differences between prediction and causation and the concept of confounding, are explored. Prediction and etiologic research are two distinct but related fields of research in which different methodological aspects apply. To avoid confusion and misinterpretation, it is of utmost importance to describe whether the research is aimed at identifying predictors (or prediction models) or identifying causal associations. After the recommendations for future research, which highlights the need for a stronger evidence base and clearer guidelines for older people as a whole, and for cardiovascular risk prevention in old age in particular.



Chapter 10

Dutch Summary

Hart- en vaatziekten zijn doodsoorzaak nummer één wereldwijd. Met het stijgen van de leeftijd, stijgt ook het aantal nieuwe en bestaande gevallen van hart- en vaatziekten waardoor de impact van hart- en vaatziekten op hoge leeftijd groot is. Door de te verwachten toenemende vergrijzing, zal ook in Nederland het aantal (oudste) ouderen met hart- en vaatziekten toenemen en zal de impact hiervan alleen maar groter worden. Aandacht voor preventie en risicopredictie van hart- en vaatziekten is daarom zeker ook op hoge leeftijd van belang. Er bestaat bij veel (huis)artsen een dilemma om al dan niet te starten met preventieve medicatie bij oudere patiënten, zeker als het gaat om oudere patiënten die geen hart- en vaatziekten hebben gehad (primaire preventie).

Het kennen van de mate van risico (risicopredictie) kan (huis)artsen ondersteunen in hun keuze om al dan niet preventieve medicatie te adviseren aan hun oudere patiënten. Het voorspellen van patiënten met het hoogste of juist laagste (relatieve) risico op het krijgen van hart- en vaatziekten is hierbij belangrijk. Het ontbreekt echter aan goede risicofactoren op hoge leeftijd. De erkende klassieke risicofactoren verliezen hun voorspellende waarde bij het stijgen van de leeftijd. De nieuwe risicofactoren zijn vooral onderzocht op middelbare leeftijd en niet op hoge leeftijd. Dit betekent dat het op dit moment niet goed mogelijk is om het risico op hart- en vaatziekten voor ouderen in te schatten. Interessante potentiële nieuwe risicofactoren op hoge leeftijd zijn het gebruik van meerdere bloeddrukmetingen uitgedrukt in bloeddrukvariabiliteit of bloeddrukpatroon en het gebruik van N-terminaal pro-'brain natriuretic peptide' (NT-proBNP). Selectie van hoog risico patiënten door gebruikmakend van deze nieuwe risicofactoren kan een belangrijke stap zijn in de succesvolle voorspelling van toekomstige hart- en vaatziekten (**hoofdstuk 1**).

Het doel van dit proefschrift is het bestuderen van klassieke en nieuwe risicofactoren voor hart- en vaatziekten op hoge leeftijd, ten einde de risicostratificatie en daarmee uiteindelijk ook preventie van hart- en vaatziekten op hoge leeftijd te verbeteren.

Deel 1 Gebruik van meerdere bloeddrukmetingen in de cardiovasculaire risicopredictie op hoge leeftijd

De 'bezoek-tot-bezoek'-bloeddrukvariabiliteit is een risicofactor voor hart- en vaatziekten bij jongeren en personen van middelbare leeftijd. Het was onbekend of dit ook geldt op hogere leeftijd, daarom was het doel van **hoofdstuk 2** om te onderzoeken of 'bezoek-tot-bezoek'-bloeddrukvariabiliteit voorspellend is voor hart- en vaatziekten en/of sterfte aan hart- en vaatziekten op hoge leeftijd. De associatie tussen 'bezoek-tot-bezoek'-bloeddrukvariabiliteit en incidentie hart- en vaatziekten werd onderzocht in de PROSPER studie. Hogere 'bezoek-tot-bezoek'-bloeddrukvariabiliteit in systolische bloeddruk, diastolische bloeddruk en polsdruk was op lange termijn geassocieerd met een hoger risico op sterfte (aan hart- en vaatziekten), ook na correctie voor gemiddelde

bloeddruk, gebruik van bloeddrukverlagende medicatie en andere risicofactoren. Deelnemers met een hogere variabiliteit in diastolische bloeddruk hadden daarnaast ook een hoger risico op het krijgen van een hartinfarct en ziekenhuisopname voor hartfalen. De belangrijkste bevinding van dit onderzoek was dat variabiliteit in diastolische bloeddruk op hoge leeftijd sterker geassocieerd is met hart- en vaatzieken en/of sterfte aan hart- en vaatziekten dan variabiliteit in systolische bloeddruk.

Om de onderliggende mechanismen van bloeddrukvariabiliteit op te helderen werden in **hoofdstuk 3** de associaties tussen biologische factoren en bloeddrukvariabiliteit onderzocht. Markers van ontsteking, endotheelfunctie, nierfunctie en de glucose homeostase werden geïncorporeerd in de analyses. Ontsteking (gemeten door hogere niveaus van interleukine-6) bij aanvang van de studie was consequent geassocieerd met hogere variabiliteit in systolische en diastolische bloeddruk en polsdruk, ook wanneer werd gecorrigeerd voor klassieke risicofactoren voor hart- en vaatziekten. Markers van endotheelfunctie, nierfunctie en de glucose homeostase waren niet of slechts in geringe mate geassocieerd in bloeddrukvariabiliteit.

In tegenstelling tot in jongere leeftijdsgroepen is op zeer hoge leeftijd niet een hoge, maar juist een lage systolische bloeddruk geassocieerd met verhoogd sterfterisico. Mogelijk is (subklinisch) hartfalen verantwoordelijk voor deze 'omdraaiing van risicopredictie'. Het doel van **hoofdstuk 4** was om te onderzoeken of lage systolische bloeddruk voorspellend is voor een hoger risico op sterfte bij de oudste ouderen, ook als er geen sprake is van hartfalen, blijkend uit een laag-normaal NT-proBNP. De studie was onderdeel van de Leiden 85-plus Studie, maar beperkte zich tot de 90-jarige deelnemers. Wij vergeleken het sterfterisico van 90-jarigen met een lage systolische bloeddruk met het sterfterisico van 90-jarigen met een hoge systolische bloeddruk, zowel in de groep deelnemers met een laag-normaal NT-proBNP (waarbij hartfalen uitgesloten kon worden) als in de groep met een hoog NT-proBNP. Negentigjarige deelnemers met een lage systolische bloeddruk hadden een twee maal verhoogd sterfterisico ten opzichte van 90-jarigen met een hoge systolische bloeddruk, zowel in de groep met een laag-normaal NT-proBNP als in de groep met een hoog NT-proBNP. Concluderend kan worden gesteld dat ook als er geen sprake is van hartfalen een lage systolische bloeddruk geassocieerd is met een verdubbeld sterfterisico bij de oudste ouderen. De aan- of afwezigheid van hartfalen beïnvloedt de prognostische waarde van lage systolische bloeddruk wat betreft sterfterisico niet.

Het doel van **hoofdstuk 5** was om bij 90-jarigen in de Leiden 85-plus Studie na te gaan of het gebruik van een 5-jaars patroon van metingen van de systolische bloeddruk toegevoegde waarde heeft voor de voorspelling van de sterfte in vergelijking met een enkelvoudige bloeddrukmeting op de leeftijd van 90 jaar. Wij onderzochten de

associatie tussen systolische bloeddruk op 90 jaar en de vijf voorafgaande jaren (bloeddrukpatroon 85-90 jaar) en het sterfterisico. De mogelijke invloed van comorbiditeit en gebruik van bloeddrukverlagende medicatie op deze associaties werd ook onderzocht. Negentigjarige deelnemers met een dalende systolische bloeddruk hadden een hoger sterfterisico in vergelijking met deelnemers met een stabiele systolische bloeddruk over 5 jaar, onafhankelijk van hun systolische bloeddruk op 90 jaar. Een lage bloeddruk op 90 jaar was ook geassocieerd met een hoger sterfterisico, ongeacht het bloeddrukpatroon in de vijf voorgaande jaren. Dit gold voor zowel deelnemers met en zonder bloeddrukverlagende medicatie, en voor deelnemers met en zonder comorbiditeit. De belangrijkste bevinding van dit onderzoek was dat zowel een dalende systolische bloeddruk over vijf jaar als de huidige systolische bloeddruk beiden onafhankelijk bijdragen aan de voorspelling van het sterfterisico op zeer hoge leeftijd.

Deel 2 N-terminaal pro-'brain natriuretic peptide' in de cardiovasculaire risicopredictie op hoge leeftijd

Steeds meer patiënten zullen hun eerste hart- of vaatziekte overleven, daarom wordt het voorspellen van herhaalde hart- of vaatziekte en sterfte steeds belangrijker. Er is voor ouderen met een voorgeschiedenis van hart- en vaatziekten echter geen gevalideerde risicoscore voor herhaalde hart- en vaatziekte en/of sterfte. Mogelijk is NT-proBNP hierin bruikbaar. Daarom werd in **hoofdstuk 6** onderzocht in hoeverre modellen met leeftijd en geslacht, traditionele risicofactoren en de SMART risicoscore herhaalde hart- en vaatziekten adequaat voorspellen op hogere leeftijd. Daarnaast werd onderzocht of de voorspellende waarde van deze modellen verbeterd door het toevoegen van NT-proBNP aan deze modellen. Tot slot werd onderzocht of deze modellen ook het behandel-effect met pravastatine voorspellen. Deze studie was onderdeel van de PROSPER studie, maar beperkte zich tot de deelnemers met een voorgeschiedenis van hart- en vaatziekten bij aanvang van de studie. De modellen met leeftijd en geslacht, traditionele risicofactoren en de SMART risicoscore hadden vergelijkbare voorspellende waarden. Het toevoegen van NT-proBNP aan deze modellen verbeterde de voorspellende waarde. Voor het model met leeftijd, geslacht plus NT-proBNP was de absolute risicoreductie in hart- en vaatziekten en sterfte 0,86% in het laagste tertiel van voorspeld risico en 6,2% in het hoogste tertiel. Dat betekent dat 16 mensen met een hoog voorspeld risico behandeld moeten worden ('number needed to treat') met pravastatine gedurende 2,5 jaar om één hart- en vaatziekte of sterfte te voorkomen. Om ditzelfde resultaat te behalen moeten in de groep met een laag voorspel risico 116 mensen 2,5 jaar behandeld worden met pravastatine. Deze studie liet zien dat NT-proBNP een veelbelovende risicopredictor is op hoge leeftijd. Een eenvoudig model met leeftijd, geslacht plus NT-proBNP presteert net zo goed als meer complexe modellen met NT-proBNP.

In **hoofdstuk 7** werd bestudeerd of een stijging in NT-proBNP over tijd geassocieerd is met totale en oorzaakspecifieke sterfte en incidente hart- en vaatziekten bij de oudste ouderen. Hierbij was een belangrijke vraag wat de rol is van (verandering in) nierfunctie. Binnen de Leiden 85-plus Studie werden de veranderingen in NT-proBNP tussen de leeftijd van 85 en 90 jaar en de associaties met het optreden van hart- en vaatziekten, sterfte en nierfunctie onderzocht. Deelnemers met een stijgend NT-proBNP over 5 jaar ontwikkelden vaker hartfalen en atriumfibrilleren tussen 85 en 90 jaar, ook wanneer gecorrigeerd werd voor de nierfunctie. Een stijging in NT-proBNP tussen 85 en 90 jaar was ook geassocieerd met een hoger sterfterisico na 90 jaar, zelfs na correctie voor de nierfunctie. Concluderend kan worden gesteld dat een stijging in NT-proBNP is geassocieerd met incident hartfalen en atriumfibrilleren, onafhankelijk van de nierfunctie. Daarnaast is een stijging in NT-proBNP ook op zeer hoge leeftijd nog steeds voorspellend voor een hoger sterfterisico, onafhankelijk van de (verandering in) nierfunctie.

Hoofdstuk 8 is een algemene discussie waarin de belangrijkste thema's worden besproken die uit dit proefschrift naar voren kwamen. Het beschrijft de context van de predictie en preventie van hart- en vaatziekten op hoge leeftijd. Door de toename van heterogeniteit met het toenemen van de leeftijd is het essentieel om iedere persoon als individu te beschouwen en te behandelen als het gaat om beslissingen rond risicopredictie en preventieve behandeling. De risicofactoren zoals beschreven in dit proefschrift kunnen hierbij een rol spelen. Vervolgens wordt het doen van wetenschappelijk onderzoek in een oudere populatie in zijn algemeenheid besproken. Er is dringend behoefte aan onderzoek binnen de oudere populatie. Onderzoek naar en binnen deze doelgroep brengt uitdagingen met zich mee, wat resulteert in een aanbeveling voor specifieke onderzoeksgroepen met ervaring, vaardigheden en interesse in het onderzoek doen binnen een oudere populatie. Aansluitend worden belangrijke epidemiologische thema's die uit dit proefschrift naar voren komen besproken, waaronder het verschil tussen predictie-onderzoek, waarbij je onderzoekt of je met bepaalde metingen iets kan voorspellen, en etiologisch onderzoek, waarbij gezocht wordt naar een onderliggende oorzaak. Predictie-onderzoek en etiologisch onderzoek zijn twee verschillende, maar gerelateerde onderzoeksgebieden waarbij verschillende methodologische aspecten van belang zijn. Om misverstanden te voorkomen is het belangrijk om te beschrijven of een onderzoek als doel heeft om voorspellers of oorzakelijke factoren te identificeren. Daarnaast worden aanbevelingen gedaan voor vervolgonderzoek op het gebied van hart- en vaatziekten bij ouderen, waarin het belang van een sterkere empirische onderbouwing van richtlijnen en duidelijkere richtlijnen benadrukt wordt voor ouderen in zijn algemeenheid en op gebied van hart- en vaatziekten in het bijzonder.

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DANKWOORD

Onderzoek doe je niet alleen. Zonder de steun, inspiratie en kritische blikken van velen om mij heen was dit proefschrift nooit tot stand gekomen. Dit dankwoord geeft mij de gelegenheid iedereen te bedanken die op enige wijze bij dit onderzoek betrokken is geweest.

Naast het eigenlijke werk tijdens het promotietraject is de plek waar je werkt voor mij minstens zo belangrijk gebleken. Daarom wil ik ook alle collega's van de afdeling Public Health en Eerstelijns geneeskunde van het LUMC bedanken voor de fijne werksfeer, inspirerende gesprekken, hun enthousiasme en hun betrokkenheid. Een aantal mensen wil ik nog in het bijzonder noemen. Wendy, samenwerken aan TRUST gaf een andere dimensie aan het werk als onderzoeker. Wat een fijne collega was je en een lieve vriendin ben je. Jeanet, Petra en Yvonne, onderzoek op het gebied van cardiovasculaire ziekten bij ouderen leverde ons vanaf het begin een betekenisvolle band op, nu is er zo veel meer. Bedankt dat jullie er zijn.

De onderzoeksperiode in Glasgow heeft mijn wetenschappelijke blik verruimd. Dear David, thank you for your support to come to Glasgow. I am grateful for the opportunity to work with you and your team. Our collaboration was and is inspiring and intellectually stimulating for me.

Om een promotietraject tot een succesvol einde te brengen is een goede samenwerking met promotor en co-promotor essentieel. Jacobijn, jouw kritische wetenschappelijke blik heeft mij gestimuleerd. Jij steunde mij niet alleen op wetenschappelijk, maar ook op persoonlijk vlak. Ik ben blij dat wij voorlopig nog samen kunnen blijven werken. Wouter, wat heb jij mij veel geleerd de afgelopen jaren. Mijn promotietraject in combinatie met de huisartsopleiding vergde hier en daar behoorlijk wat flexibiliteit en jij steunde mij daarin. Door jou ben ik de afgelopen jaren gegroeid in mijn werk als onderzoeker. Jouw enthousiasme voor het vak is aanstekelijk. Mijn 'ex-promotor' Pim wil ik ook bedanken. Jouw visie op de huisartspraktijk was een aanvulling tijdens het begin van mijn promotietraject.

Daarnaast wil ik mijn dank betuigen aan de leden van mijn promotiecommissie prof. dr. Yvo Smulders, prof. dr. Theo Stijnen en dr. Eric Moll van Charante voor de tijd die zij vrij wilden maken om mijn proefschrift te beoordelen en met mij van gedachten te willen wisselen tijdens de verdediging ervan.

Al mijn opleiders, huisartsbegeleiders en gedragswetenschappers van de huisartsopleiding wil ik bedanken voor de ruimte die zij mij hebben gegeven om naast mijn opleiding ook mijn promotieonderzoek voort te zetten. In het bijzonder wil ik Paul Jonas en Ans

van der Salm bedanken. Paul, aan het einde van mijn eerste jaar in de huisartsenopleiding heb jij mij het laatste zetje gegeven te gaan solliciteren voor de AIOTHO plek. Ans, bij jou in de praktijk ben ik echt de huisarts-onderzoeker geworden die ik nu ben. Daarnaast wil ik de SBOH bedanken voor de mogelijkheid mijn promotieonderzoek te combineren met de opleiding tot huisarts.

Antonette, wat bijzonder dat ik jouw paranimf mocht zijn en wat fijn dat jij mijn paranimf wilt zijn op deze dag. Wat hebben wij samen gezwoegd op 'onze kamer'. Bedankt voor alles.

Lieve Yorick, ik ben blij dat jij mij als paranimf bij wilt staan. Ik ben er trots op jouw zus te zijn. Wij steunen elkaar door dik en dun en dat vind ik heel bijzonder. Bedankt voor het mooie ontwerp van de omslag van mijn proefschrift, dit betekent veel voor mij.

Lieve pap en mam, dank voor jullie onvoorwaardelijke steun en vertrouwen. Jullie hebben mij altijd gestimuleerd om mijn ambities waar te maken. Wat fijn om te beseffen dat ik uit zo'n warm nest kom. Bedankt dat jullie er altijd voor mij zijn.

Familie en vrienden, bedankt voor jullie interesse, steun en vertrouwen. Bij jullie vond ik de ontspanning en het klankbord dat ik nodig had. Oma's en opa, wat bijzonder dat jullie dit nog mee mogen maken.

En ten slotte natuurlijk Remco, wat een geluk dat jij in mijn leven bent gekomen. Bedankt voor jouw steun, betrokkenheid en de ruimte die jij mij geeft mijn ambities waar te maken. Wat fijn dat jij mij daarin begrijpt en dat wij er voor elkaar zijn.

CURRICULUM VITAE

Rosalinde Poortvliet was born on February 15 1981 in Aalsmeer, the Netherlands. She passed her Gymnasium examination at the Nieuwer Amstel in Amstelveen in 1999. She studied Biomedical Sciences at Leiden University Medical Center from 1999 through 2006. In 2001 she started medical school at the University of Leiden where she obtained her medical degree in 2007. Subsequently, she worked as a resident at the Department of Psychiatry at GGZ inGeest (2007-2009). Between 2009 and 2013 she completed her vocational training for general practice at the Department of Public Health and Primary Care of the Leiden University Medical Center. During this vocational training, in 2010, she started the research project described in this thesis at the same department. In 2011 she worked for three months at the Academic Section of Geriatric Medicine (University of Glasgow, Faculty of Medicine, Glasgow, UK). From 2013 onwards she worked as a part-time general practitioner.

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