Cover Page

Universiteit Leiden

Author: Wijsman, L.W.
Title: Blood pressure, cardiac biomarkers and cognitive function in old age
Issue Date: 2016-10-11

Blood pressure, cardiac biomarkers and cognitive function in old age

Liselotte Willemijn Wijsman

Blood pressure, cardiac biomarkers and cognitive function 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 dinsdag 11 oktober 2016, klokke 15.00 uur

door

Liselotte Willemijn Wijsman

geboren te Brunei
in 1985

Contents

Chapter 1

General introduction

Introduction

With the increase in life expectancy, the prevalence of cognitive disorders is expected to further rise the coming years.(1) The number of people suffering from dementia worldwide is estimated to almost double every 20 years, with prevalence numbers of 65.7 million in 2030 and 115.4 million in 2050.(1) Accumulating evidence of the last years highlights the role of cardiovascular risk factors in the pathogenesis of cognitive disorders.(2-4) Epidemiological, pathological and neuroimaging studies show that cardiovascular risk factors in middle age associate with an increased risk of brain aging and cognitive impairment in later life.(5, 6) In older people, however, the contribution of cardiovascular risk factors in the development of cognitive impairment is still a matter of debate.(7) Furthermore, although a variety of mechanisms have been proposed to explain the association of cardiovascular risk factors with cognitive disorders, the underlying pathways have not been fully understood.

An example of a cardiovascular risk factor in middle age that is associated with cognitive impairment in later life, is high blood pressure.(8) Numerous studies demonstrate that midlife high blood pressure is a risk factor for cardiovascular events, brain atrophy, and cognitive decline.(9-12) In addition, some randomized controlled trials show favorable effects of midlife antihypertensive treatment on risk of cognitive impairment.(13, 14) However, recent evidence shows that this association attenuates with increasing age and it has even been reported that in older age, low instead of high blood pressure relates with increased risk of cognitive disorders and cardiovascular events.(6, 15-17) In particular people who are biologically older seem to suffer from low blood pressure values.(18-20)

Besides blood pressure, cardiac disease is associated with increased risk of cognitive disorders and dementia. Patients with coronary artery disease, atrial fibrillation, and chronic heart failure have worse cognitive function and a higher risk of progression to dementia. (3, 21-23) A possible explanation behind this association is reduced cardiac output, leading to cerebral hypoperfusion and subsequently to impairment of delivery of oxygen and nutrients to the brain.(3) Concordantly, it has been shown that in patients with severe systolic heart failure, cognitive function significantly improved after a cardiac transplantation, or after implantation of a left ventricular assist device.(24, 25) However, whether people with early signs of cardiac disease are also at increased risk of cognitive impairment, has poorly been studied.

The aims of this thesis are 1) to further investigate whether blood pressure in older people is a risk factor for cardiovascular events and cognitive impairment; 2) to study whether early markers of cardiac disease are related with cognitive impairment; and 3) to evaluate the feasibility of home blood pressure monitoring using smartphone-assisted technology, which might eventually assist to prevent cognitive impairment.

Outline of this thesis

This thesis is divided in three parts. The first part consists three studies evaluating the association of blood pressure and blood pressure variability with cardiovascular events and cognitive function in older age, respectively. **Chapter 2** evaluates whether the association between (diastolic) blood pressure and cardiovascular events differs in people with and without a history of cardiovascular disease. Besides average blood pressure, visit-to-visit blood pressure variability has been associated with cardiovascular events and cognitive impairment. In **chapter 3**, we therefore study the association of visit-to-visit blood pressure variability with cognitive function. Furthermore, we investigate potential explanations behind this association in a magnetic resonance substudy. **Chapter 4** further elaborates on this topic by studying how blood pressure lowering medication is related to both visit-to-visit blood pressure variability and cognitive function; and whether blood pressure lowering medication could explain the relation between visit-to-visit blood pressure variability and cognitive impairment.

The second part of this thesis consists of two studies addressing the association between early markers of cardiac disease and cognitive function. In **chapter 5**, we evaluate the relation of N-terminal pro-brain natriuretic peptide (NT-proBNP), a neurohormone that is commonly used in the diagnosis of clinical heart failure, with cognitive function and decline. Furthermore, **chapter 6** investigates whether cardiac troponin T (cTnT), routinely used in the diagnosis of acute myocardial infarction, associates with cognitive function.
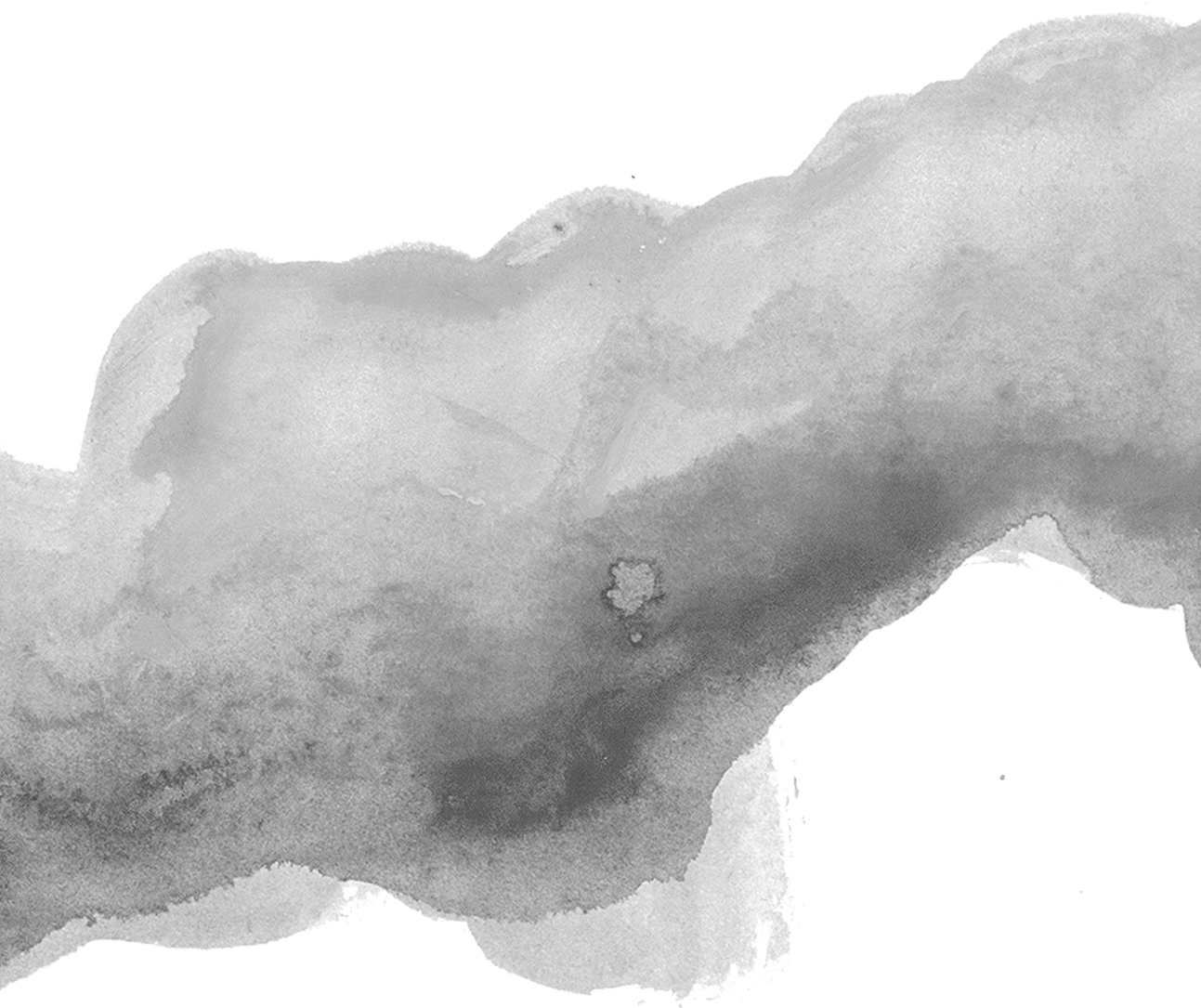
Part three includes the translation of results of previous studies into an innovative method, focused on the prevention of cognitive impairment. The online research platform iVitality, that comprises a website, a smartphone-based application and health sensors, was designed to perform large-scale studies in an aging population at risk for cognitive impairment. **Chapter 7** describes the first results of a proof-of-principle study, in which we evaluated the feasibility of home blood pressure monitoring using iVitality.

In **chapter 8** the main conclusions of this thesis are summarized and discussed, and future perspectives are proposed.

References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013;9(1):63-75.
2. Abete P, Della-Morte D, Gargiulo G, Basile C, Langellotto A, Galizia G, Testa G, Canonico V, Bonaduce D, Cacciatore F. Cognitive impairment and cardiovascular diseases in the elderly. A heart-brain continuum hypothesis. *Ageing Res Rev* 2014;18:41-52.
3. Eggermont LH, de BK, Muller M, Jaschke AC, Kamp O, Scherder EJ. Cardiac disease and cognitive impairment: a systematic review. *Heart* 2012;98(18):1334-1340.
4. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011;42(9):2672-2713.
5. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, Wolf PA, Decarli C. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology* 2011;77(5):461-468.
6. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360(9349):1903-1913.
7. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* 2005;4(8):487-499.
8. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and the risk for dementia: a double edged sword. *Ageing Res Rev* 2009;8(2):61-70.
9. den Heijer T, Launer LJ, Prins ND, van Dijk EJ, Vermeer SE, Hofman A, Koudstaal PJ, Breteler MM. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* 2005;64(2):263-267.
10. Korf ES, White LR, Scheltens P, Launer LJ. Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. *Hypertension* 2004;44(1):29-34.
11. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 2001;322(7300):1447-1451.
12. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, Havlik RJ. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging* 2000;21(1):49-55.
13. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, Bossini A, Fagard R, Gil-Extremera B, Laks T, Kobalava Z, Sarti C, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Birkenhager WH. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* 2002;162(18):2046-2052.
14. in't Veld BA, Ruitenberg A, Hofman A, Stricker BH, Breteler MM. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. *Neurobiol Aging* 2001;22(3):407-412.
15. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. *Ann Intern Med* 2002;136(6):438-448.
16. Protogerou AD, Safar ME, Iaria P, Safar H, Le DK, Filipovsky J, Henry O, Ducimetiere P, Blacher J. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. *Hypertension* 2007;50(1):172-180.
17. Voko Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JC, Breteler MM. J-shaped relation between blood pressure and stroke in treated hypertensives. *Hypertension* 1999;34(6):1181-1185.
18. Muller M, Maier AB, Smulders YM. [High blood pressure and mortality in the elderly: what does gait speed tell?]. *Ned Tijdschr Geneeskd* 2013;157(7):A5801.

19. Post HG, Smulders YM, Maier AB, Deeg DJ, Muller M. Relation between blood pressure and mortality risk in an older population: role of chronological and biological age. *J Intern Med* 2014.

20. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. *Arch Intern Med* 2012;172(15):1162-1168.

21. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med* 2006;166(9):1003-1008.

22. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 2007;9(5):440-449.

23. Zuccala G, Marzetti E, Cesari M, Lo Monaco MR, Antonica L, Cocchi A, Carbonin P, Bernabei R. Correlates of cognitive impairment among patients with heart failure: results of a multicenter survey. *Am J Med* 2005;118(5):496-502.

24. Zimpfer D, Wieselthaler G, Czerny M, Fakin R, Haider D, Zrunek P, Roethy W, Schima H, Wolner E, Grimm M. Neurocognitive function in patients with ventricular assist devices: a comparison of pulsatile and continuous blood flow devices. *ASAIO J* 2006;52(1):24-27.

25. Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, Aldershvile J. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke* 2001;32(11):2530-2533.

Part I

Blood pressure, cognitive function and mortality
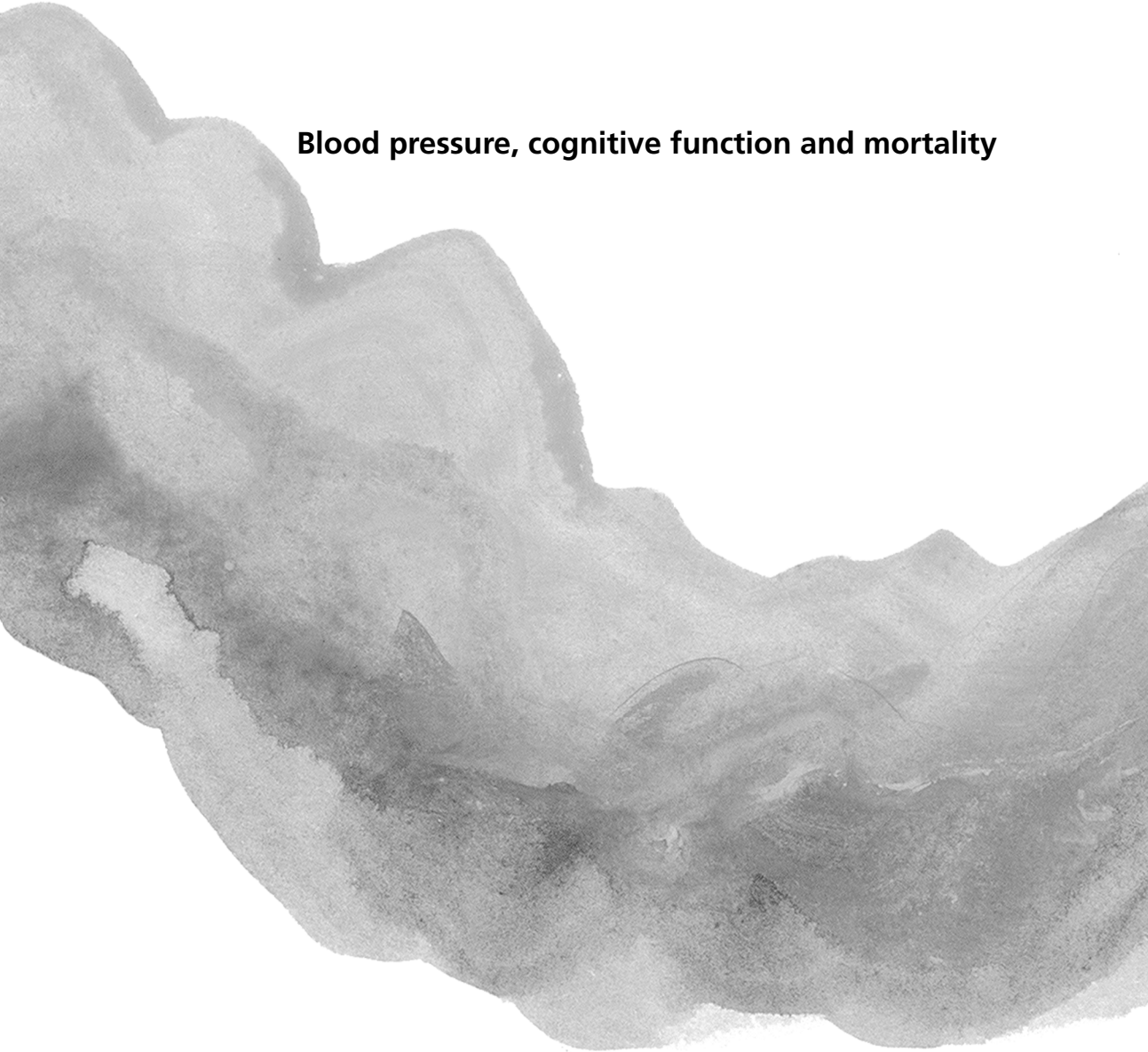
Chapter 2

Association of diastolic blood pressure with cardiovascular events in older people varies upon cardiovascular history

Liselotte W Wijsman, Majon Muller, Anton JM de Craen, J Wouter Jukema,
Rudi GJ Westendorp, Simon P Mooijaart

Abstract

Background In older age, a low diastolic blood pressure (DBP) has been associated with increased risk of cardiovascular events, especially in frail older people. A potential mechanism might be that low DBP leads to inadequate perfusion of vital organs. Here, we tested the hypothesis that low DBP is associated with a high risk of cardiovascular events in people with a previous history of cardiovascular disease, as a proxy of vascular impairment.

Methods We included 5,804 participants (mean age 75 years) from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) who as part of the trial were intensively monitored for an average period of 3.2 years. Baseline DBP was categorized in low (<70 mmHg), normal (70-90 mmHg) or high (>90 mmHg). Cox proportional hazards analyses were used to estimate hazard ratio (HR) with 95% confidence intervals (CI) for the association of DBP with cardiovascular events. Analyses were stratified for cardiovascular history.

Results We show that participants with low DBP had an 1.24-fold (95% CI 1.04; 1.49) increased risk of cardiovascular events compared to those with normal DBP. After further adjusting for cardiovascular factors, this association attenuated to 1.05 (95% CI 0.86; 1.28). A previous history of cardiovascular disease significantly modified the relation between DBP and risk of cardiovascular events (p for interaction=0.042). In participants without a history of cardiovascular disease, DBP was marginally significant associated with an increased event risk (HR (95% CI) per 10 mmHg increase in DBP 1.08 (0.99; 1.18), p-value=0.07), whereas in participants with a history of cardiovascular disease higher DBP was associated with a decreased risk of cardiovascular events (HR (95% CI) per 10 mmHg increase in DBP 0.92 (0.85; 0.99, p-value=0.018). These risk estimates were independent of potential confounders, including classical cardiovascular risk factors.

Conclusion The association of DBP with cardiovascular events in older people varies upon their previous history, showing that in participants with pre-existing cardiovascular disease a higher DBP associates with a decreased risk of future cardiovascular events.

Introduction

The association between blood pressure and cardiovascular events has been studied in numerous observational studies.(1-11) Despite a large body of evidence showing that high systolic and diastolic blood pressure are risk factors for cardiovascular disease in middle-aged people, the association is less evident in older age.(10, 12) Several studies in older people showed an attenuating relation between blood pressure and occurrence of myocardial infarction, stroke, and vascular and all-cause mortality.(2, 3, 5, 9, 12)

Recent data found that the risk associated with lower levels of blood pressure was even reversed in frail older people.(6, 8, 10, 13, 14) A population-based study including 599 of the oldest old (85 years or older) showed that blood pressure values below 140/90 mmHg were associated with excess mortality.(10) Furthermore, observational studies found that low blood pressure was associated with higher risk of cardiovascular events, but only in people with impaired physical and cognitive function, used as a marker of vascular impairment.(6, 8, 14) This finding was in particular the case for low diastolic blood pressure. (6, 8) This poses the hypothesis that instead of chronological age, it might be vascular impairment that explains that the association between low diastolic blood pressure and cardiovascular risk reverses.

We therefore hypothesized that low diastolic blood pressure, independent of systolic blood pressure, is associated with an increased risk of cardiovascular events in people with a previous history of cardiovascular disease, as a proxy of vascular impairment. The aims of this study were 1) to investigate the association of diastolic blood pressure with cardiovascular events, and 2) to study whether this association differed in people with and without a previous cardiovascular history. We used data of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), which included older participants (70-82 years) with a cardiovascular history and participants without a cardiovascular history, but with one or more risk factors defined as hypertension, cigarette smoking or diabetes mellitus.

Methods

Study design and participants

We used data from the PROspective Study of Pravastatin in the Elderly at Risk (PROS-PER), a randomized, placebo-controlled trial designed to investigate whether treatment with pravastatin would diminish the occurrence of vascular events in participants with pre-existing cardiovascular diseases or risk factors thereof. PROSPER included 5,804 participants, aged 70-82 years, from three collaborating centers in Ireland, Scotland and the Netherlands.15 Approximately 50% of all participants had a history of cardiovascular diseases, including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction, and vascular surgery. The rest of the participants had one or more major cardiovascular risk factors, defined as hypertension, cigarette smoking, or diabetes mellitus. Primary outcome of the trial is the composite outcome of coronary heart disease death, non-fatal myocardial infarction, and fatal or non-fatal stroke. Details of the design and outcome of the PROSPER have been published elsewhere.(15)

Blood pressure measurements

Blood pressure was measured at two consecutive moments at baseline, in sitting position, with a fully automatic electronic sphygmomanometer (Omron M4H) by trained research nurses. Baseline blood pressure was defined as the mean value of the two blood pressure measurements. Diastolic blood pressure was categorized based on three clinically relevant cutoff level: low (<70 mmHg), normal (70-90 mmHg) and high (>90 mmHg).

Outcomes

Information on the occurrence of cardiovascular events was collected during the course of PROSPER, which had a mean follow-up period of 3.2 years. Cardiovascular events were defined as definite or suspect death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal stroke / transient ischemic attack, coronary artery bypass graft or percutaneous transluminal coronary angioplasty or peripheral arterial surgery or angioplasty.(16)

Statistical analysis

Baseline characteristics were calculated for all participants and for participants with low, normal and high diastolic blood pressure at baseline. Baseline differences in continuous variables were tested with linear regression models; Chi-squared tests were used to test differences in categorical variables.

We used Cox proportional hazards analyses to estimate hazard ratio's (HR) with 95% confidence intervals (CI) for the association of diastolic blood pressure with risk of cardiovascular events. Participants with normal diastolic blood pressure (70-90 mmHg) were taken as reference category. To investigate the association of diastolic blood pressure with cardiovascular events in participants with and without a cardiovascular history, we stratified our analyses for history of cardiovascular disease. To study whether the trend for cardiovascular events among the diastolic blood pressure groups was significant, we calculated a probability (p) value by using diastolic blood pressure as a continuous variable. Furthermore, we analysed whether the association between diastolic blood pressure and cardiovascular events differed in participants with and without cardiovascular history. For this, we calculated the interaction term between diastolic blood pressure (as a continuous variable) and history of cardiovascular disease; and included this interaction term together with diastolic blood pressure (as a continuous variable) and history of cardiovascular disease in the Cox proportional hazards analyses. All Cox regression analyses were adjusted for the following sociodemographic variables: sex, age, country and treatment during follow-up of the study (pravastatin or placebo). We additionally adjusted the analyses for potential cardiovascular confounders, including systolic blood pressure, histories of hypertension, diabetes, smoking, body mass index (BMI), estimated glomerular filtration rate (eGFR), N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiac troponin T, and high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride levels at baseline.

In addition, we explored the association between systolic blood pressure with cardiovascular events. Again, participants with normal systolic blood pressure (120-140 mmHg) were taking as a reference category. All Cox regression analyses were adjusted for sociodemographic variables (sex, age, country and treatment during follow-up of the study) and additionally for potential cardiovascular confounders, including diastolic blood pressure, histories of hypertension, diabetes, smoking, body mass index (BMI), estimated glomerular filtration rate (eGFR), N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiac troponin T, and high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride levels at baseline.

All analyses were performed using SPSS software (version 20.0.0, SPSS Inc., Chicago, IL). Supplemental tables are available on request.

Results

Table 1 shows the baseline characteristics for all 5,804 study participants and in groups of diastolic blood pressure at baseline. Mean age of all participants was 75.3 years; participants with higher diastolic blood pressure were younger; 3,000 participants (51.7%) were female. Participants with a higher diastolic blood pressure had higher systolic blood pressure, higher pulse pressure, and a higher prevalence of hypertension. Participants with lower diastolic blood pressure had a higher prevalence of cardiovascular disease, history of

Table 1. Baseline characteristics in categories of diastolic blood pressure

	Diastolic blood pressure			
	Low <70 mmHg N=698	Normal 70-90 mmHg N=3701	High ≥90 mmHg N=1405	P-value[1]
Blood pressure (mmHg)				
Systolic blood pressure	133.2 (0.7)	153.0 (0.3)	169.6 (0.5)	<0.001
Diastolic blood pressure	65.5 (0.2)	81.7 (0.1)	98.3 (0.2)	
Pulse pressure	67.7 (0.7)	71.3 (0.3)	71.3 (0.5)	0.023
Demographics				
Age (years)	75.6 (0.1)	75.4 (0.1)	75.1 (0.1)	0.024
Female, n (%)	344 (49.3%)	1958 (52.9%)	698 (49.7%)	0.048
Vascular risk factors				
History of hypertension, n (%)	292 (41.8%)	2275 (61.5%)	1025 (73.0%)	<0.001
History of diabetes mellitus, n (%)	73 (10.5%)	375 (10.1%)	175 (12.5%)	0.055
History of stroke or TIA, n (%)	69 (9.9%)	428 (11.6%)	152 (10.8%)	0.384
History of MI, n (%)	150 (21.5%)	491 (13.3%)	135 (9.6%)	<0.001
History of vascular disease, n (%)	412 (59.0%)	1647 (44.5%)	506 (36.0%)	<0.001
Current smoker, n (%)	221 (31.7%)	1001 (27.0%)	336 (23.9%)	0.001
Body mass index (kg/m²)	25.7 (0.2)	26.8 (0.1)	27.6 (0.1)	<0.001
LDL cholesterol (mmol/L)	3.8 (0.0)	3.8 (0.0)	3.8 (0.0)	0.581
HDL cholesterol (mmolL)	1.3 (0.0)	1.3 (0.0)	1.3 (0.0)	0.482
Triglycerides (mmol/L)	1.5 (0.0)	1.5 (0.0)	1.6 (0.0)	0.247
Blood pressure lowering medication, n (%)				
Diuretics	251 (36.0%)	1517 (41.0%)	590 (42.0%)	0.022
Ace-inhibitors	105 (15.0%)	562 (15.2%)	284 (20.2%)	<0.001
Beta-blockers	199 (28.5%)	947 (25.6%)	356 (25.3%)	0.235
Calcium channel blockers	218 (31.2%)	947 (25.6%)	293 (20.9%)	<0.001
Biochemistry				
eGFR (ml/min/1.73m²)	59.5 (0.6)	59.8 (0.2)	60.8 (0.4)	0.025
NT-proBNP (ng/L)	375.7 (21.5)	279.1 (9.3)	293.7 (15.1)	0.547
Cardiac troponin T (ng/L)	10.1 (1.4)	9.2 (0.6)	13.4 (1.0)	0.021

Data represent mean (standard error), unless stated otherwise. Abbreviations: TIA, transient ischemic attack; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide. [1]P-value for continuous variables was calculated by using DBP as continuous variable.

myocardial infarction and smoking. No differences existed in prevalence of diabetes mellitus and stroke or transient ischemic attack between the diastolic blood pressure groups.

A total number of 977 participants (16.8%) experienced a cardiovascular event during the mean follow-up period of 3.2 years. Across the total population, participants with low diastolic blood pressure (<70 mmHg) had a 1.24-fold (1.04; 1.49) increased risk of cardiovascular events (HR (95% CI) compared to those with normal diastolic blood pressure). After adjusting for cardiovascular risk factors, the association between diastolic blood pressure and cardiovascular events attenuated to 1.11 (0.90; 1.37). When compared to normal diastolic blood pressure, high diastolic blood pressure (>90 mmHg) was not associated with an increased cardiovascular event risk (0.91 (0.76; 1.107)).

To further study the association between diastolic blood pressure and cardiovascular events, we investigated whether the association differed in participants with and without a previous history of cardiovascular disease as a marker of vascular impairment. History of cardiovascular disease significantly modified the relation between diastolic blood pressure and risk of cardiovascular events (p for interaction=0.042) (table 3 and figure 1). In participants without a history of cardiovascular disease, DBP was marginally significant associated with an increased event risk (HR (95%) per 10 mmHg increase in DBP 1.08 (0.99; 1.18), p-value=0.07), whereas in participants with a history of cardiovascular disease higher DBP was associated with a decreased risk of cardiovascular events (HR (95%) per 10 mmHg increase in DBP 0.92 (0.85; 0.99, p-value=0.018). Associations were independent of potential confounders, including classical cardiovascular risk factors.

Table 2. Association of diastolic blood pressure with cardiovascular events in all participants

	Diastolic blood pressure							
Cardiovascular events	Low <70 mmHg N=698		Normal 70-90 mmHg N=3701		High ≥90 mmHg N=1405		Change per 10 mmHg DBP[1]	
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	HR (95% CI)	P-value
Adjusted for sociodemographic factors	143	1.24 (1.04; 1.49)*	609	1 (ref)	225	0.98 (0.84; 1.14)	0.95 (0.90; 1.01)	0.077
Additionally adjusted for cardiovascular factors	143	1.11 (0.90; 1.37)	609	1 (ref)	225	0.91 (0.76; 1.12)	0.93 (0.87; 1.00)	0.049

Abbreviations: HR, Hazard Ratio; CI, confidence interval. *p-value <0.05 [1]value represents the change in log-hazard per 10 mmHg increase in DBP. Sociodemographic factors included sex, age, country and treatment during follow-up of the study (pravastatin or placebo). Cardiovascular factors included systolic blood pressure, histories of hypertension, diabetes, smoking, BMI, eGFR, NT-proBNP, cardiac troponin T, HDL, LDL and triglyceride levels at baseline.

Table 3. Association of diastolic blood pressure with cardiovascular events stratified by cardiovascular history

Cardiovascular events		Diastolic blood pressure						Change per 10 mmHg DBP[1]		
		Low <70 mmHg N=698		Normal 70-90 mmHg N=3701		High ≥90 mmHg N=1405				
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	HR (95% CI)	P-value	P for interaction
Adjusted for sociodemographic factors									
No cardiovascular history	40	1.19 (0.85; 1.66)	246	1 (ref)	126	1.19 (0.96; 1.47)	1.08 (0.99; 1.18)	0.074	0.008
Cardiovascular history	103	1.14 (0.91; 1.42)	363	1 (ref)	99	0.89 (0.71; 1.11)	0.92 (0.85; 0.99)	0.018	
Additionally adjusted for cardiovascular factors									
No cardiovascular history	40	0.97 (0.67; 1.41)	246	1 (ref)	126	1.12 (0.89; 1.41)	1.03 (0.93; 1.15)	0.541	0.042
Cardiovascular history	103	1.05 (0.83; 1.34)	363	1 (ref)	99	0.84 (0.66; 1.07)	0.87 (0.79; 0.96)	0.004	

Abbreviations: HR, Hazard Ratio; CI, confidence interval.

*p-value <0.05   [1]value represents the change in log-hazard per 10 mmHg increase in DBP. Sociodemographic factors included sex, age, country and treatment during follow-up of the study (pravastatin or placebo). Cardiovascular factors included systolic blood pressure, histories of hypertension, diabetes, smoking, BMI, eGFR, NT-proBNP, cardiac troponin T, HDL, LDL and triglyceride levels at baseline.
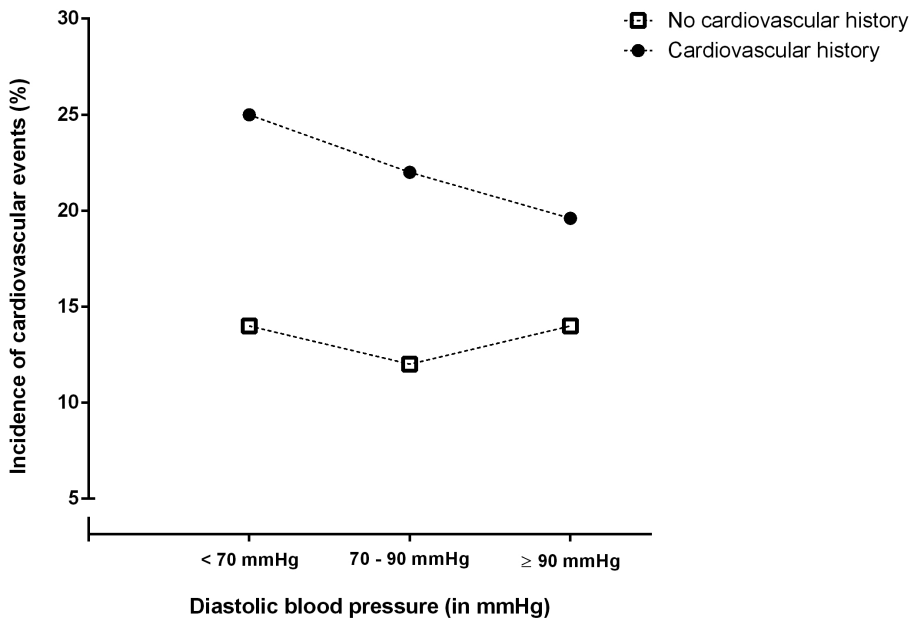
Figure 1. Incidence of cardiovascular events in different diastolic blood pressure groups, stratified by cardiovascular history. Data represent point estimates of incidence (in percentage) of cardiovascular events.

Furthermore, we performed additional analyses in which we explored the association between systolic blood pressure with cardiovascular events. Participants with a higher systolic blood pressure had an increased risk of cardiovascular events, independent of sociodemographic and cardiovascular factors (change in log-hazard per 10 mmHg systolic blood pressure (95% CI)=1.04 (1.00;1.08) (supplemental table 1). When stratifying for cardiovascular history, the same trend as for diastolic blood pressure was seen, showing that higher systolic blood pressure was associated with an increased risk of cardiovascular events in participants with and without a previous history of cardiovascular disease (p for interaction=0.490) (supplemental table 2).

Discussion

In this prospective cohort study including 5,804 participants with a mean age of 75 years, we show that history of cardiovascular disease modified the relation between diastolic blood pressure and cardiovascular event risk: in participants without a history of cardiovascular disease, there was no association between diastolic blood pressure and cardiovascular

events, whereas participants with a history of cardiovascular disease showed a decreased risk of cardiovascular events with higher diastolic blood pressure.

Previous studies that showed an association between high diastolic blood pressure and decreased cardiovascular risk have predominantly been performed in frail older populations in which all participants suffered from cardiovascular disease.(1-3, 5, 7, 9-11) Only few have studied whether biological age might determine the association between diastolic blood pressure and worse outcomes.(6, 8, 17) Recently, a population-based cohort study including 4,057 people investigated if the association of late-life blood pressure with brain atrophy and brain functioning differed in people with and without chronic hypertension. They found that in participants with a history of midlife hypertension, lower late-life diastolic blood pressure was associated with increased brain atrophy and worse cognitive function.(17) Furthermore, two prospective studies including 2340 and 1466 participants showed that the association of blood pressure with mortality risk was higher in biologically older people, defined as those with decreased psychical and cognitive function.(6, 8) To our knowledge, we are the first to investigate whether cardiovascular history as a proxy of vascular impairment could modulate the association between low diastolic blood pressure and cardiovascular risk in older people.

There are several pathophysiological mechanisms that can explain our finding that history of cardiovascular disease modified the relation between diastolic blood pressure and cardiovascular event risk. First, low diastolic blood pressure might be a reflection of deteriorating health status, leading to increased cardiovascular events and mortality.(18) Previous studies have demonstrated that a decreasing trend in blood pressure independently predicts cardiovascular events and mortality in older people.(4, 7) This is in line with results from a community based study of 835 subjects of 85 years and older, showing that the relation of low blood pressure with mortality disappeared after adjusting for indicators of poor health.(1) Indeed, our results demonstrate that risk factors for cardiovascular events and mortality such as older age, history of myocardial infarction and smoking status were more present in participants with lower diastolic blood pressure. However, adjusting our results for these indicators did not essentially change our findings. A second explanation is that both low diastolic blood pressure and cardiovascular events share a common cause, which most likely would be aging of the arterial system including atherosclerosis. Previous studies showed that progression of atherosclerosis is accompanied by a decrease in diastolic blood pressure.(19, 20) Instead of being causally related, low diastolic blood pressure might therefore be a reflection of widespread atherosclerosis, which itself associates

with increased risk of cardiovascular disease and mortality.(21) However, this might not be true for the population under study since pulse pressure, which reflects arterial aging and atherosclerosis best, was lower instead of higher in participants with low diastolic blood pressure.(22) Finally, there might be a causal relation between low diastolic blood pressure and cardiovascular events and mortality rates. In this scenario, low diastolic blood pressure, which is an important contributor of the perfusion pressure of an organ, might predispose to vascular hypoperfusion of vital organs, particularly in people who already suffer from increased arterial stiffness.(23, 24) It has been shown that diastolic blood pressure is more important than systolic blood pressure with respect to adequate perfusion of an organ. (5) Therefore, low perfusion pressure could also explain why we did not find a consistent association between systolic blood pressure with cardiovascular events. Furthermore, it suggests that excessive reduction of diastolic blood pressure in these people should be avoided, and has an experimental underpinning.(5)

Major strengths of the current study include the large sample size and the detailed monitoring during a mean follow-up period of 3.2 years. Furthermore, because of the inclusion criteria of PROSPER, all participants had cardiovascular disease or were at risk thereof, which provided us the unique opportunity to investigate the hypothesis whether people with a vascular impairment would suffer more from a lower diastolic blood pressure. However, this study also has several weaknesses. First, the study population consisted of older participants at risk of cardiovascular diseases with relatively preserved cognitive function (MMSE≥24 points), which might limit the extrapolation of our findings to the elderly population in general. A second limitation is that the design of the study is observational. Future trials investigating whether people with a cardiovascular history benefit from discontinuation of blood pressure lowering therapy are needed to provide definite answers.(25)

In conclusion, our study demonstrates that the association of diastolic blood pressure with cardiovascular events in older people varies upon previous cardiovascular history, showing that in participants with cardiovascular history higher diastolic blood pressure associates with a decreased risk of cardiovascular events. Randomized controlled trials are needed to investigate whether increasing diastolic blood pressure levels by discontinuation of blood pressure lowering therapy will lead to less recurrent events in people with a cardiovascular history. Eventually, this may result in moving from a 'one size fits all' concept of achieving normal blood pressure to an individualized approach and specific guidelines in blood pressure management for older people.

References

1. Boshuizen HC, Izaks GJ, van BS, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older: community based study. *BMJ* 1998; 316(7147):1780-1784.
2. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. *Ann Intern Med* 2002; 136(6):438-448.
3. Dorresteijn JA, van der Graaf Y, Spiering W, Grobbee DE, Bots ML, Visseren FL. Relation between blood pressure and vascular events and mortality in patients with manifest vascular disease: J-curve revisited. *Hypertension* 2012; 59(1):14-21.
4. Langer RD, Criqui MH, Barrett-Connor EL, Klauber MR, Ganiats TG. Blood pressure change and survival after age 75. *Hypertension* 1993; 22(4):551-559.
5. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006; 144(12):884-893.6.   Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. *Arch Intern Med* 2012; 172(15):1162-1168.
7. Poortvliet RK, de RW, de Craen AJ, Mooijaart SP, Westendorp RG, Assendelft WJ et al. Blood pressure trends and mortality: the Leiden 85-plus Study. *J Hypertens* 2013; 31(1):63-70.
8. Post HG, Smulders YM, Maier AB, Deeg DJ, Muller M. Relation between blood pressure and mortality risk in an older population: role of chronological and biological age. *J Intern Med* 2015;277(4):488-97
9. Protogerou AD, Safar ME, Iaria P, Safar H, Le DK, Filipovsky J et al. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. *Hypertension* 2007; 50(1):172-180.
10. van Bemmel T, Gussekloo J, Westendorp RG, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. *J Hypertens* 2006; 24(2):287-292.
11. Voko Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JC, Breteler MM. J-shaped relation between blood pressure and stroke in treated hypertensives. *Hypertension* 1999; 34(6):1181-1185.
12. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360(9349):1903-1913.
13. Muller M, Smulders YM, de Leeuw PW, Stehouwer CD. Treatment of hypertension in the oldest old: a critical role for frailty? *Hypertension* 2014; 63(3):433-441.
14. Sabayan B, van VP, de RW, Gussekloo J, de Craen AJ, Westendorp RG. High blood pressure, physical and cognitive function, and risk of stroke in the oldest old: the Leiden 85-plus Study. *Stroke* 2013; 44(1):15-20.
15. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM et al. The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. *Am J Cardiol* 1999; 84(10):1192-1197.
16. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360(9346):1623-1630.
17. Muller M, Sigurdsson S, Kjartansson O, Aspelund T, Lopez OL, Jonnson PV et al. Joint effect of mid- and late-life blood pressure on the brain: the AGES-Reykjavik study. *Neurology* 2014; 82(24):2187-2195.
18. Satish S, Zhang DD, Goodwin JS. Clinical significance of falling blood pressure among older adults. *J Clin Epidemiol* 2001; 54(9):961-967.
19. Bots ML, Witteman JC, Hofman A, de Jong PT, Grobbee DE. Low diastolic blood pressure and atherosclerosis in elderly subjects. The Rotterdam study. *Arch Intern Med* 1996; 156(8):843-848.

20. Witteman JC, Grobbee DE, Valkenburg HA, van Hemert AM, Stijnen T, Burger H et al. J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. *Lancet* 1994; 343(8896):504-507.
21. O'Leary DH, Polak JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson SK, Jr. et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. *Stroke* 1992; 23(12):1752-1760.
22. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension* 1994; 23(3):395-401.
23. Muller M, van der Graaf Y, Visseren FL, Vlek AL, Mali WP, Geerlings MI. Blood pressure, cerebral blood flow, and brain volumes. The SMART-MR study. *J Hypertens* 2010; 28(7):1498-1505.
24. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. *Brain* 2011; 134(Pt 11):3398-3407.
25. Moonen JE, Foster-Dingley JC, de RW, van der Grond J, Bertens AS, van Buchem MA et al. Effect of Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning-the DANTE Study Leiden: A Randomized Clinical Trial. *JAMA Intern Med* 2015; 175(10):1622-1630.

2

Chapter 3

Association of visit-to-visit blood pressure variability with cognitive function in old age: a prospective cohort study

Behnam Sabayan*, Liselotte W Wijsman*, Jessica Foster-Dingley, David J Stott, Ian Ford, Brendan M Buckley, Naveed Sattar, J Wouter Jukema, Matthijs van Osch, Jeroen van der Grond, Mark A van Buchem, Rudi GJ Westendorp, Anton JM de Craen, Simon P Mooijaart

* Authors contributed equally to this work

Abstract

Background Visit-to-visit blood pressure variability has been related to cerebrovascular damage. The aim of this study was to assess the association between visit-to-visit blood pressure variability and cognitive function in older subjects.

Methods We included 5,461 subjects from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study. Blood pressure was measured every three months during an average period of 3.2 years. Blood pressure variability was defined as the standard deviation of visit-to-visit blood pressure measurements. Four domains of cognitive function including selective attention, processing speed, immediate and delayed memory were assessed and a compound cognitive score was computed by averaging the four standardized z-scores. In an MRI substudy of 553 participants, structural brain volumes, cerebral microbleeds, infarcts, and white matter hyperintensities were measured.

Results Participants with higher visit-to-visit variability in systolic blood pressure had worse performance on all cognitive tests: attention (mean difference high versus low thirds) 3.08 seconds (95% confidence interval (CI) 0.85 to 5.31), processing speed -1.16 digits coded (95% CI-1.69 to -0.63), immediate memory -0.27 pictures remembered (95% CI -0.41 to -.13), and delayed memory -0.30 pictures remembered (95% CI -0.49 to -0.11). Furthermore, higher variability in both systolic and diastolic blood pressure was associated with lower hippocampal volume and cortical infarcts, and higher variability in diastolic blood pressure was associated with cerebral microbleeds (all p-values<0.05). All associations were adjusted for average blood pressure and cardiovascular risk factors.

Conclusion Higher visit-to-visit variability in blood pressure independent of average blood pressure was associated with impaired cognitive function in old age.

Introduction

Visit-to-visit variability in blood pressure independent of average blood pressure is related to cerebrovascular damage.(1) It has been shown that higher blood pressure variability increases the risk of stroke and that antihypertensives, which decrease both variability in blood pressure and mean blood pressure, more effectively reduce the risk of stroke.(2) In addition, observational studies have shown associations of variability in blood pressure, independent of average blood pressure, with white matter hyperintensities, carotid artery intima media thickness, and atherosclerosis in older people (≥55 years).(3-5)

The relation between increased variability in blood pressure and end organ damage is well established.(6) Recent evidence indicates that higher visit-to-visit variability is linked with microvascular damage, endothelial injury, and disturbances in vascular smooth muscle functioning.(7, 8) Indicators of cerebral small vessel disease, including white matter hyperintensities, cortical microinfarcts, and cerebral microbleeds are implicated in the pathogenesis of cognitive impairment.(9-11) Several pathological, observational, and experimental studies have shown that disruption of the blood-brain barrier due to microvascular damage results in neuronal injury and accelerates neuronal loss and brain atrophy.(12) Hence higher variability in blood pressure might potentially lead to cognitive impairment through changes in the brain structures and development of cerebral small vessel disease.

We investigated the association of variability in blood pressure between visits independent of average blood pressure with cognitive function in older participants (>70 years) at high risk of cardiovascular disease. Additionally, we investigated possible explanations behind this association in a magnetic resonance imaging substudy.

Methods

Study design and participants

The data in this study were obtained from PROSPER (The PROspective Study of Pravastatin in the Elderly at Risk), a randomized, double blind, placebo controlled trial designed to investigate the effect of pravastatin in the prevention of vascular events in elderly people with pre-existing, or risk factors for, cardiovascular disease. This trial included 5,804 people aged 70-82 years who were enrolled from three collaborating centers in Ireland, Scotland, and the Netherlands. Approximately 50% of the participants showed evidence of cardiovascular disease, including stable angina, intermittent claudication, stroke (the type,

hemorrhagic or ischemic, was unknown), transient ischemic attack, myocardial infarction, and vascular surgery. The rest of the participants had one or more major cardiovascular risk factors, defined as hypertension, cigarette smoking, or diabetes mellitus. The primary outcome of the PROSPER 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 period of 3.2 years. In the present study we included 5461 participants for whom data on variability in blood pressure and cognitive function were available. Additionally, participants from the Netherlands were invited to participate in an MRI substudy. Participants were included from both the pravastatin and placebo groups as we previously reported that treatment with pravastatin did not influence cognitive function, structural brain volumes, or indicators of cerebral small vessel disease.(13-15)

Blood pressure measurements

We measured systolic and diastolic blood pressure at baseline and every three months. Blood pressure was measured with participants in the sitting position and using a fully automatic electronic sphygmomanometer (Omron M4, Kyoto, Japan). All measurements were performed in the same clinical setting. In the analyses we used the average values of these blood pressure measurements. We defined visit-to-visit variability in blood pressure as the standard deviation of blood pressure measurements during the study period. We report the variability in blood pressure using only the standard deviation. Variance and coefficient of variation, which are two other measures of variability, are strongly correlated with the standard deviation (supplemental table 1) and they showed similar associations with cognitive and magnetic resonance imaging outcomes (data not shown).

Cognitive function

The Mini-Mental State Examination (MMSE) was used to evaluate global cognitive function at baseline; to exclude participants with poor cognitive function at baseline we used a cut-off score of 24 points or more (out of 30) as an inclusion criterion. In the present study we used data on cognitive function assessed at the end of the study, after a mean follow-up of 3.2 years, by a cognitive test battery consisting of four different tests. The Stroop colour and word test was used to assess selective attention and reaction time. The participants were asked to read the name of a colour, which appeared in a colour different from that being named. The outcome variable was the total number of seconds to complete the test; a higher score indicating worse performance. General cognitive speed was tested by the letter-digit coding test. The participants had to match certain digits with letters according to a provided key. The outcome variable was the total number of correct entries

in 60 seconds, with higher scores indicating better performance. The picture-word learning test was used to assess immediate and delayed memory. The participants were shown 15 pictures and were then asked to recall as many pictures as possible in three trials. After 20 minutes they were asked to repeat the test to measure their delayed recall. The outcome variable was the accumulated number of correct recalled pictures, immediately and after 20 minutes, with higher scores indicating better performance. A detailed description of the cognitive tests and the procedures has been published previously.[16]

Magnetic resonance imaging substudy

Overall, 646 of the 1100 Dutch participants in the PROSPER study consented to participate in the magnetic resonance imaging substudy. Forty of the 646 original study participants died during the follow-up period. Magnetic resonance imaging was performed at the end of the follow-up period in the remaining 606 participants. Data on visit-to-visit variability in blood pressure and magnetic resonance imaging were available for 553 participants. Details of individually magnetic resonance imaging scanning have been published previously.[13]

All imaging was performed on a magnetic resonance system operating at a field strength of 1.5 Tesla (Philips Medical Systems, Best, Netherlands). We used the SIENAX technique to calculate grey and white matter volumes. In short, SIENAX starts by extracting brain and skull images from input data for the whole head. The brain image is then affine registered to Montreal Neurological Institute 152 space (by using the skull image to determine the registration scaling), done primarily to obtain the volumetric scaling factor to be used as normalisation for head size. Next we carried out tissue type segmentation with partial volume estimation to calculate the total volume of brain tissue (including separate estimates of volumes of grey matter, white matter, peripheral grey matter, and ventricular cerebrospinal fluid).[17] The algorithm FIRST (the Oxford Centre for Functional MRI of the Brain's (FMRIB) integrated registration and segmentation tool) was applied to estimate the volume of hippocampus. In addition, we estimated the volume of six other subcortical regions, including nucleus accumbens, globus pallidus, amygdala, putamen, caudate nucleus, and thalamus. FIRST is part of FSL (FMRIB's software library) and performs both registration and segmentation of the mentioned subcortical regions.[18] To assess cerebral microbleeds, two experienced raters blinded to the participants' clinical history read all the magnetic resonance imaging scans in consensus. Cerebral microbleeds were defined as focal areas of signal loss on T2 weighted gradient echo pulse sequence ("blooming effect") that were invisible or smaller on T2 weighted magnetic resonance imaging.[19] For each participant we recorded the number and location (cortical, subcortical, and infratentorial) of the cerebral microbleeds. Segmenta-

tion of white matter hyperintensities volume was performed automatically using software for Neuro-Image Processing in Experimental Research (SNIPER), an in-house developed program for image processing.(20) This segmentation was based on the T2-weighted and fluid attenuated inversion recovery (FLAIR) images. Cerebral infarcts were defined as parenchymal defects seen on FLAIR images with the same signal intensity as cerebrospinal fluid and a surrounding rim of high signal intensity following a vascular distribution.

Personal and clinical characteristics
We recorded the personal, medical, and anthropometric data of the participants at baseline. A fasting venous blood sample was taken for biochemical and hematological assessment. Western blotting was used on the plasma samples to determine apolipoprotein E epsilon 2/3/4 phenotype.(21)

Statistical analysis
Characteristics of the study participants are reported as mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. We used Pearson's correlation coefficient to calculate the correlation between variability in blood pressure and average blood pressure. Linear regression models were used to assess the association of variability in blood pressure and average blood pressure with cognitive function. Dependent variables were the mean scores of the cognitive tests. In the tables these scores are presented in thirds of systolic and diastolic blood pressure and blood pressure variability. In the magnetic resonance imaging substudy, we used logistic regression models to estimate the odds ratio and 95% confidence interval of the presence of microbleeds or infarcts in different thirds of blood pressure variability as well as average blood pressure. We used multivariable linear regression models to test the association between blood pressure variability and average blood pressure with volume of white matter hyperintensities and structural brain volumes. P-values in all the analyses were calculated using systolic and diastolic blood pressure variability as continuous variables.

We performed our analyses in three steps. In the first step, we carried out crude analyses, in which we only adjusted for cognitive test version where appropriate. In the second step, we added age, sex, education, and country as covariates to investigate the potential influence of these factors on the associations (model 1). In the final model (model 2), we further adjusted the analyses for the following potential confounders: cardiovascular diseases and risk factors (history of vascular disease, history of hypertension, history of diabetes mellitus, smoking status, cholesterol levels, body mass index), average blood pressure, statin treat-

ment, and apolipoprotein E genotype. We adjusted the analyses of systolic blood pressure variability with cognitive function and magnetic resonance imaging outcomes for average systolic blood pressure. The analyses of variability in diastolic blood pressure with cognitive function and magnetic resonance imaging outcomes were adjusted for average diastolic blood pressure. Since the associations did not essentially change in different models, results of the second model are presented in the manuscript and results from the other models are presented in a supplementary file (available on request). All analyses were performed using SPSS software (version 20.0.0, SPSS Inc., Chicago, IL).

Results

Table 1 shows the characteristics of participants in the whole group and in the magnetic resonance imaging substudy. Blood pressure was measured in an average number of 12.7 visits in the whole group and 12.9 visits in the magnetic resonance substudy. Average systolic and diastolic blood pressure over the period of blood pressure measurements were 153.1 mm Hg and 82.5 mm Hg, respectively. The corresponding mean standard deviation values during this period were 14.8 mm Hg and 7.1 mm Hg.

There was a weak but significant correlation between average systolic blood pressure and standard deviation of systolic blood pressure measurements (r=0.20, p-value<0.001). Similarly, average diastolic blood pressure was weakly but statistically significantly correlated with standard deviation of diastolic blood pressure measurements (r=0.12, p-value<0.001).

Table 2 shows the association of visit-to-visit variability in systolic and diastolic blood pressure with cognitive function. Higher variability was associated with worse performance on the Stroop test (both p-values<0.001), letter-digit coding test (both p-values<0.001), immediate picture-word learning test (both p-values<0.001), and delayed picture-word learning test (both p-values=0.001). All associations were independent of average blood pressure and cardiovascular diseases and risk factors, as all analyses were adjusted for these factors. The figure presents the mean cognitive scores (95% confidence intervals) in each third of systolic and diastolic blood pressure variability. Data on the association of blood pressure variability with cognitive function from crude and minimally adjusted models are shown in the supplemental tables 2 and 3. Furthermore, we found a significant association of higher average systolic and diastolic blood pressure with worse performance in different domains of cognitive function (all p-values<0.05), except for the association

3

between higher average systolic blood pressure and performance on the picture-word learning tests (p-values>0.05) (supplementary table 4).

Table 1. Characteristics of study participants in whole group and MRI substudy

	All (n=5461)	MRI substudy (n=553)
Demographics		
Number of visits, mean (SD)	12.7 (2.4)	12.9 (1.5)
Age, years, mean (SD)	75.3 (3.3)	74.9 (3.2)
Female, n (%)	2822 (51.7)	241 (43.6)
Age left school, years, mean (SD)	15.1 (2.1)	15.5 (2.9)
Vascular risk factors		
History of hypertension, n (%)	3399 (62.2)	341 (63.1)
History of diabetes mellitus, n (%)	576 (10.5)	91 (16.5)
History of stroke or TIA, n (%)	606 (11.1)	89 (16.1)
History of myocardial infarction, n (%)	714 (13.1)	67 (12.1)
History of vascular disease, n (%)	2404 (44.0)	240 (43.4)
Current smoker, n (%)	1433 (26.2)	115 (20.8)
Body mass index , kg/m^2, mean (SD)	26.9 (4.2)	26.7 (3.6)
Total cholesterol, mmol/L, mean (SD)	5.7 (0.9)	5.7 (0.8)
Blood pressure, mean (SD)		
Systolic blood pressure, mm Hg*	153.1 (16.1)	156.1 (16.4)
Diastolic blood pressure, mm Hg *	82.5 (7.5)	85.1 (7.3)
Variability in systolic blood pressure, mm Hg**	14.8 (5.0)	13.9 (4.6)
Variability in diastolic blood pressure, mm Hg**	7.1 (2.9)	7.4 (2.3)
Cognitive function, mean (SD)*		
Stroop test score, seconds	69.4 (31.6)	56.9 (23.3)
Letter-Digit Coding test score, digits coded	21.8 (8.0)	26.3 (7.4)
PLTi score, pictures remembered	9.2 (2.2)	10.1 (2.2)
PLTd score, pictures remembered	9.8 (3.1)	11.1 (3.0)
MRI features		
Grey matter, ml, mean (SD)	---	590 (44)
White matter, ml, mean (SD)	---	768 (38)
Hippocampus, ml, mean (SD)	---	7.5 (1.1)
Micro-bleeds, n (%)	---	124 (24.0)
Infarcts, n (%)	---	180 (33.6)
Cortical	---	65 (12.1)
Lacunar	---	112 (21.0)
WMH volume, ml, mean (SD)	---	7.2 (1.1)

Abbreviations: SD, standard deviation; n, number; TIA, transient ischemic attack; PLTi, Picture-Word Learning Test immediate; PLTd, Picture-Word Learning Test delayed; WMH, white matter hyperintensity. * defined as the mean of all blood pressure measurements during follow-up. ** defined as the standard deviation of all blood pressure measurements during follow-up. *** defined as the cognitive test score at the end of follow-up.

Table 3 shows the association of visit-to-visit variability in systolic and diastolic blood pressure with structural brain volumes. Higher variability was associated with lower hippocampal volume (both p-values=0.01). There was no association between blood pressure variability and volume of the other brain structures (all p-values>0.05), except for the association between higher variability in systolic blood pressure and lower amygdala and putamen volumes (both p-values=0.04). Analyses were adjusted for average systolic and diastolic blood pressures, which themselves were not associated with structural brain volumes (all p-values>0.05) (supplemental table 5).

Table 2. Cognitive function in thirds of visit-to-visit blood pressure variability

| | Third of visit-to-visit blood pressure variability | | | |
	Low (n=1820)	Middle (n=1821)	High (n=1820)	P-value
Systolic blood pressure				
Range of SD, mm Hg	0.7-12.2	12.3-16.2	16.3-64.4	
Stroop, seconds	68.46 (0.79)	68.75 (0.79)	71.54 (0.82)	<0.001
LDCT, digits coded	22.40 (0.19)	21.82 (0.19)	21.24 (0.19)	<0.001
PLTi, pictures remembered	9.37 (0.05)	9.28 (0.05)	9.10 (0.05)	<0.001
PLTd, pictures remembered	10.00 (0.07)	9.89 (0.07)	9.70 (0.08)	0.001
Diastolic blood pressure				
Range of SD, mm Hg	0-6.5	6.6-8.5	8.6-33.1	
Stroop, seconds	68.28 (0.79)	68.89 (0.79)	71.34 (0.80)	<0.001
LDCT, digits coded	22.35 (0.19)	21.93 (0.19)	21.27 (0.19)	<0.001
PLTi, pictures remembered	9.41 (0.05)	9.22 (0.05)	9.13 (0.05)	<0.001
PLTd, pictures remembered	10.01 (0.07)	9.88 (0.07)	9.74 (0.07)	0.001

Abbreviations: SD, standard deviation; n, number; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning Test immediate; PLTd, Picture-Word Learning Test delayed. Data are adjusted values of the mean (standard error) of each cognitive function test. Adjustments were made for age, sex, body mass index, Statin treatment, apoE genotype, country, education, test version where appropriate, smoking, cholesterol levels, history of vascular diseases, history of hypertension, history of diabetes mellitus, and average blood pressure measures.

Table 3. Structural brain volumes in three groups of visit-to-visit blood pressure variability

| | Three groups of visit-to-visit blood pressure variability | | | |
	Low	Middle	High	P-value
Systolic blood pressure	(n=194)	(n=210)	(n=149)	
Range of SD, mm Hg	0.7-12.2	12.3-16.2	16.3-64.4	
Grey matter	593 (3)	590 (3)	589 (3)	0.21
White matter	770 (3)	770 (3)	765 (3)	0.19
Hippocampus	7.6 (0.07)	7.6 (0.07)	7.4 (0.08)	0.01
Diastolic blood pressure	(n=178)	(n=184)	(n=191)	
Range of SD, mm Hg	0-6.5	6.6-8.5	8.6-33.1	
Grey matter	591 (3)	594 (3)	587 (3)	0.18
White matter	768 (3)	772 (3)	764 (3)	0.62
Hippocampus	7.6 (0.07)	7.5 (0.07)	7.4 (0.07)	0.01

Data are structural brain volumes presented in mean (standard error) ml. Analyses were adjusted for age, sex, body mass index, Statin treatment, smoking, cholesterol level, history of vascular diseases, history of hypertension, history of diabetes mellitus, and average blood pressure measures.

Table 4 shows the association between visit-to-visit variability in blood pressure and cerebral microbleeds, infarcts, and white matter hyperintensities. Higher variability in systolic and diastolic blood pressure was associated with a higher risk of cortical infarcts (both p-values=0.02). Prevalence of cortical infarcts in participants with low, middle, and high variability in systolic blood pressure was 9.2%, 12.0%, and 16.2%, respectively. Prevalence of cortical infarcts in participants with low, middle, and high variability in diastolic blood pressure was 7.9%, 13.3%, and 16.2%, respectively. Furthermore, higher variability in diastolic blood pressure was associated with a higher risk of all types of microbleeds (p-value=0.01) as well as subcortical microbleeds (p-value=0.004). Prevalence of microbleeds in participants with low, middle, and high variability in systolic blood pressure was 21.2%, 23.9%, and 28.4%, respectively. Prevalence of cortical infarcts in participants with low, middle, and high variability in diastolic blood pressure was 17.8%, 27.5%, and 28.9%, respectively. Variability in systolic and diastolic blood pressure was not associated with white matter hyperintensities (both p-values>0.05). We found no association of average systolic and diastolic blood pressure with cerebral microbleeds, infarcts, and white matter hyperintensities (all p-values>0.05) (supplemental table 6).

Table 4. Microbleeds, infarcts and white matter hyperintensities in three groups of visit-to-visit blood pressure variability

	Three groups of visit-to-visit blood pressure variability			
	Low	Middle	High	P-value
Systolic blood pressure	(n=207)	(n=191)	(n=137)	
Range of SD, mm Hg	0.7-12.2	12.3-16.2	16.3-64.4	
Microbleeds, OR (95% CI)	1 (ref)	1.13 (0.69-1.85)	1.30 (0.77-2.21)	0.39
Infarcts, OR (95% CI)	1 (ref)	0.95 (0.61-1.48)	1.26 (0.78-2.04)	0.40
Cortical	1 (ref)	1.34 (0.68-2.64)	2.22 (1.09-4.54)	0.02
Lacunar	1 (ref)	0.79 (0.48-1.31)	0.84 (0.48-1.46)	0.97
WMH volume, ml, mean (SE)	8.12 (1.02)	7.34 (1.08)	7.79 (1.19)	0.98
Diastolic blood pressure	(n= 215)	(n= 166)	(n= 154)	
Range of SD, mm Hg	0-6.5	6.6-8.5	8.6-33.1	
Microbleeds, OR (95% CI)	1 (ref)	1.75 (1.05-2.91)	1.77 (1.06-2.96)	0.01
Infarcts, OR (95% CI)	1 (ref)	0.99 (0.63-1.56)	1.32 (0.84-2.06)	0.43
Cortical	1 (ref)	1.87 (0.93-3.76)	2.19 (1.10-4.37)	0.02
Lacunar	1 (ref)	0.95 (0.57-1.60)	1.17 (0.70-1.95)	0.75
WMH volume, ml, mean (SE)	7.65 (1.05)	8.27 (1.11)	7.93 (1.10)	0.55

Abbreviations: SD, standard deviation; n, number; OR, odds ratio; CI, confidence interval; WMH, white matter hyperintensity; SE, standard error. Analyses were adjusted for sex, age, body mass index, Statin treatment, smoking, cholesterol levels, history of vascular diseases, history of hypertension, history of diabetes mellitus, and average blood pressure measures. Data for microbleeds, infarcts and white matter hyperintensities were available for 535 participants.
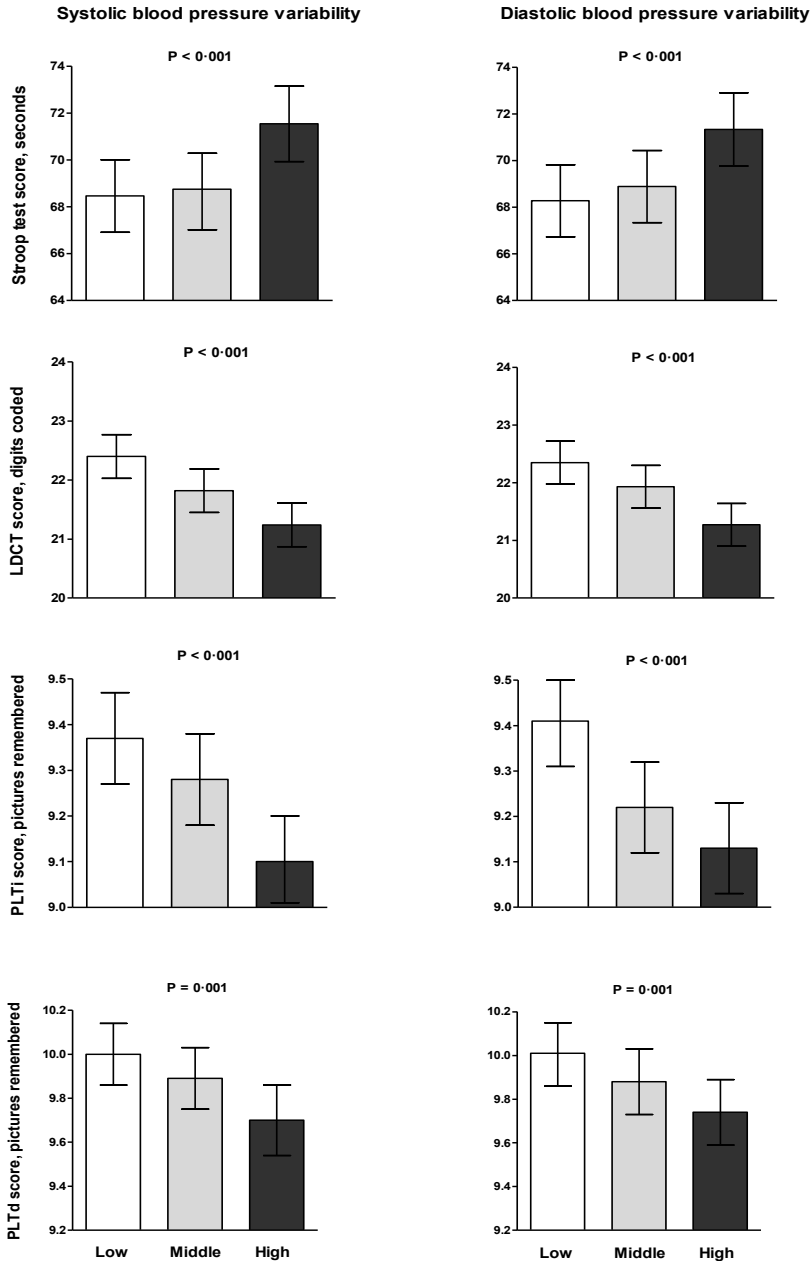
Figure 1. Cognitive function in thirds of visit-to-visit blood pressure variability
Stroop test, Letter-Digit Coding Test (LDCT), immediate Picture-Word Learning Test (PLTi) and delayed Picture-Word Learning Test (PLTd) scores in low, middle and high thirds of systolic and diastolic visit-to-visit blood pressure variability. Bars represent mean and 95% confidence interval. All analyses were adjusted for age, sex, body mass index, Statin treatment, apo E genotype, country, education, test version where appropriate, smoking, cholesterol level, history of vascular diseases, history of hypertension, history of diabetes mellitus, and average blood pressure measures

We performed four sensitivity analyses to explore whether the association of visit-to-visit variability in blood pressure with the studied outcomes could be affected by participants with a history of clinical stroke or transient ischemic attack (n=606) and cardiovascular disease (n=2404), participants with new or a change in antihypertensive therapy during the study period (n=2733), participants who developed vascular events (n=872) or arrhythmia (n=506) during the study period, and participants with a high average blood pressure (defined as average systolic blood pressure of ≥140 mm Hg and diastolic blood pressure of ≥80 mm Hg during the study period) (n=830). These sensitivity analyses showed that the results did not materially change. In an overall sensitivity analysis we excluded all participants with the aforementioned conditions (n=4654) and the results remained essentially unchanged (data not shown).

Discussion

Higher visit-to-visit variability in systolic and diastolic blood pressure was associated with worse performance in different domains of cognitive function and lower hippocampal volume and risk of cortical infarcts. Higher variability in diastolic blood pressure was associated with risk of cerebral microbleeds. These associations were independent of various cardiovascular risk factors, in particular average systolic and diastolic blood pressures.

Although hypertension is a well-established risk factor for cardiovascular diseases, increasing evidence indicates that the predictive value of conventional blood pressure measurement for cardiovascular diseases attenuates with increasing age.(22-24) Recent studies have shown that higher visit-to-visit variability in blood pressure increases the risk of cardiovascular events, stroke, and carotid artery atherosclerosis in older people, independent of average blood pressure.(1, 24-26) Given the link between neurovascular dysfunction and cognitive impairment, a recent study on 201 elderly participants (mean age 79.9 years) at high risk of cardiovascular disease showed that high visit-to-visit variability in blood pressure during 12 months was associated with worse performance in the mini-mental state examination and global deterioration scale.(27, 28) Consistent with this finding, by using a population of over 5000 participants and over three years of blood pressure measurements, we showed that high visit-to-visit variability in both systolic and diastolic blood pressure was associated with worse performance in different domains of cognitive function, including selective attention, processing speed, immediate verbal memory, and delayed verbal memory.

The magnitude of associations in this study, reflected as differences in cognitive scores between top and bottom thirds of variability in systolic and diastolic blood pressure, are comparable with the observed differences in cognitive function between groups of apolipoprotein E genotype on cognitive function.(29) The apolipoprotein E4 genotype is a well-recognized risk factor for the development of dementia in later life and it has been shown that people who carry this risk factor have a four times higher risk of developing late onset Alzheimer`s disease.(30) Similar differences in cognitive test scores in apolipoprotein E groups and variability in blood pressure implies that the observed associations can be considered clinically relevant.

Different explanations can be proposed for the observed association between high visit-to-visit variability in blood pressure and impaired cognitive function. Firstly, both blood pressure variability and cognitive impairment could stem from a common cause, without themselves being causally related. Cardiovascular risk factors are the most likely candidate. (31) Nevertheless, we reported our analyses adjusted for different cardiovascular risk factors and we performed a sensitivity analysis, by separately excluding those with a history of cardiovascular diseases. This did not change our estimates, although we accept that residual confounding could remain from unmeasured risk factors for cardiovascular disease. As a second explanation, high visit-to-visit variability in blood pressure might reflect a long term hemodynamic instability in the systemic circulation that puts stress on the vascular endothelium.(7, 32) This hemodynamic stress may lead to endothelial dysfunction and micro-vascular damage with consequent alterations in brain structure and function. (33) Thirdly, exaggerated fluctuations in systemic blood pressure could result in repeated episodes of cerebral hypoperfusion causing neuronal injury and cell death, particularly in vulnerable brain regions such as the hippocampus.(4) In line with latter explanations, we found that higher visit-to-visit variability in blood pressure is related to lower hippocampal volume and the presence of cerebral microbleeds and cortical infarcts. Given the well described association of hippocampal atrophy and cerebral small vessel disease with cognitive impairment, our findings may suggest that decreased hippocampal volume, cerebral microbleeds, and cortical infarcts are potential pathogenic mechanisms behind the association between variability in blood pressure and cognitive impairment.(10, 34)

Current evidence on the association of blood pressure variability with structural brain damage and cerebral small vessel disease mainly comes from studies that focused on ambulatory blood pressure rather than visit-to-visit variability. These studies showed that higher variability in ambulatory blood pressure is associated with brain atrophy and white

matter lesions.(35-37) In the present study, we only observed the association of visit-to-visit variability in blood pressure with lower hippocampal volume, cerebral microbleeds, and cortical infarcts. This might imply that different measures of blood pressure variability carry different predictive values for brain outcomes.(24) Data on the association between visit-to-visit variability and manifestations of small vessel diseases are scarce. Consistent with our findings, a recent study showed that higher visit-to-visit variability in blood pressure in people with a history of ischemic stroke was associated with progression of cerebral microbleeds but not with white matter lesions.(38) It is, however, still unclear whether higher variability in blood pressure is a cause or consequence of brain disease. It has been suggested that higher variability itself could originate from previously established brain diseases disturbing central autonomic control.(39) While clinical trials have shown conflicting findings on the benefit of antihypertensive therapy on reducing the risk of dementia, calcium channel blockers, the most effective drug class to reduce variability in blood pressure, showed significant efficacy in lowering the risk of vascular cognitive impairment.(40, 41) This might highlight potential clinical implications of agents reducing blood pressure variability in lowering the risk of brain vascular disease and cognitive impairment in old age. Collectively, we are not able to make a causal inference from our observation, and future long term investigations are warranted to examine whether strategies to reduce variability in blood pressure can effectively decrease the risk of cognitive impairment as well as of brain vascular disease.

The major strengths of this study include a large sample size and application of an extended standardized cognitive test battery to assess cognitive function. In addition, availability of neuroimaging data provided us with a unique opportunity to investigate potential biological pathways linked to the association between variability in blood pressure and cognitive function. However, this study has certain limitations. Firstly, we included elderly participants at risk of cardiovascular diseases with relatively preserved cognitive function (mini-mental state examination ≥24 points), which might limit the extrapolation of our findings to a general elderly population. However, this restriction has possibly resulted in a homogeneous study population who are among the main target groups for preventing cognitive decline.(42) Secondly, the outcomes of this study were evaluated at one time point, and long term longitudinal studies are needed to test whether lowering variability in blood pressure could lead to decelerated cognitive decline and lower the burden of brain diseases. Thirdly, owing to the limited number of participants in the magnetic resonance imaging substudy, we had limited power in several outcome measures. This means that the absence of significant associations for several outcome measures should be interpreted

with caution. There are reports indicating that higher visit-to-visit variability in blood pressure is related to a higher risk of stroke and cerebrovascular damage, however, the exact mechanisms behind these associations are still unclear.(1) This problem needs to be addressed in future magnetic resonance imaging studies with larger number of participants. Fourthly, although we adjusted our analyses for different potential confounding factors, some other confounders may exist that we did not consider in our analyses. Future studies investigating the determinants of visit-to-visit variability in blood pressure might help to understand better the association between variability in blood pressure and neurocognitive outcomes.

In conclusion, our findings suggest that higher visit-to-visit variability in blood pressure independent of average blood pressure is associated with worse cognitive performance in older people at high risk of cardiovascular disease. Changes in hippocampal volume and occurrence of cortical infarcts and cerebral microbleeds might be candidate pathogenic mechanisms behind this association. This observation merits further interventional studies to determine whether reducing variability in blood pressure can decrease the risk of cognitive impairment in old age.

3

References

1. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010;375(9718):895-905.
2. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, et al. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol* 2010;9(5):469-80.
3. Gunstad J, Cohen RA, Tate DF, Paul RH, Poppas A, Hoth K, et al. Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. *Blood Press* 2005;14(6):353-8.
4. Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol* 2010;67(5):564-9.
5. Havlik RJ, Foley DJ, Sayer B, Masaki K, White L, Launer LJ. Variability in midlife systolic blood pressure is related to late-life brain white matter lesions: the Honolulu-Asia Aging study. *Stroke* 2002;33(1):26-30.
6. Mancia G, Parati G. The role of blood pressure variability in end-organ damage. *J Hypertens Suppl* 2003;21(6):S17-23.
7. Diaz KM, Veerabhadrappa P, Kashem MA, Feairheller DL, Sturgeon KM, Williamson ST, et al. Relationship of visit-to-visit and ambulatory blood pressure variability to vascular function in African Americans. *Hypertens Res* 2012;35(1):55-61.
8. Diaz KM, Veerabhadrappa P, Kashem MA, Thakkar SR, Feairheller DL, Sturgeon KM, et al. Visit-to-visit and 24-h blood pressure variability: association with endothelial and smooth muscle function in African Americans. *J Hum Hypertens* 2013 [Epub ahead of print].
9. van Es AC, van der Grond J, de Craen AJ, Westendorp RG, Bollen EL, Blauw GJ, et al. Cerebral microbleeds and cognitive functioning in the PROSPER study. *Neurology* 2011;77(15):1446-52.
10. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010;9(7):689-701.
11. Kovari E, Gold G, Herrmann FR, Canuto A, Hof PR, Michel JP, et al. Cortical microinfarcts and demyelination significantly affect cognition in brain aging. *Stroke* 2004;35(2):410-4.
12. Wardlaw JM, Sandercock PA, Dennis MS, Starr J. Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? *Stroke* 2003;34(3):806-12.
13. ten Dam VH, Box FM, de Craen AJ, van den Heuvel DM, Bollen EL, Murray HM, et al. Lack of effect of pravastatin on cerebral blood flow or parenchymal volume loss in elderly at risk for vascular disease. *Stroke* 2005;36(8):1633-6.
14. ten Dam VH, van den Heuvel DM, van Buchem MA, Westendorp RG, Bollen EL, Ford I, et al. Effect of pravastatin on cerebral infarcts and white matter lesions. *Neurology* 2005;64(10):1807-9.
15. Trompet S, van Vliet P, de Craen AJ, Jolles J, Buckley BM, Murphy MB, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *J Neurol* 2010;257(1):85-90.
16. Houx PJ, Shepherd J, Blauw GJ, Murphy MB, Ford I, Bollen EL, et al. Testing cognitive function in elderly populations: the PROSPER study. PROspective Study of Pravastatin in the Elderly at Risk. *J Neurol Neurosurg Psychiatry* 2002;73(4):385-9.
17. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* 2004;23 Suppl 1:S208-19.
18. Widya RL, de Roos A, Trompet S, de Craen AJ, Westendorp RG, Smit JW, et al. Increased amygdalar and hippocampal volumes in elderly obese individuals with or at risk of cardiovascular disease. *Am J Clin Nutr* 2011;93(6):1190-5.
19. Altmann-Schneider I, Trompet S, de Craen AJ, van Es AC, Jukema JW, Stott DJ, et al. Cerebral microbleeds are predictive of mortality in the elderly. *Stroke* 2011;42(3):638-44.
20. Admiraal-Behloul F, van den Heuvel DM, Olofsen H, van Osch MJ, van der Grond J, van Buchem MA, et al. Fully automatic segmentation of white matter hyperintensities in MR images of the elderly. *NeuroImage* 2005;28(3):607-17.

21. Havekes LM, de Knijff P, Beisiegel U, Havinga J, Smit M, Klasen E. A rapid micromethod for apolipoprotein E phenotyping directly in serum. *J Lipid Res* 1987;28(4):455-63.

22. Olindo S, Cabre P, Deschamps R, Chatot-Henry C, Rene-Corail P, Fournerie P, et al. Acute stroke in the very elderly: epidemiological features, stroke subtypes, management, and outcome in Martinique, French West Indies. *Stroke* 2003;34(7):1593-7.

23. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360(9349):1903-13.

24. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 2010;375(9718):938-48.

25. Eguchi K, Hoshide S, Schwartz JE, Shimada K, Kario K. Visit-to-visit and ambulatory blood pressure variability as predictors of incident cardiovascular events in patients with hypertension. *Am J Hypertens* 2012;25(9):962-8.

26. Dellasega C, Morris D. The MMSE to assess the cognitive state of elders. Mini-Mental State Examination. *J Neurosci Nurs* 1993;25(3):147-52.

27. Kim YS, Immink RV, Stok WJ, Karemaker JM, Secher NH, van Lieshout JJ. Dynamic cerebral autoregulatory capacity is affected early in Type 2 diabetes. *Clin Sci (Lond)* 2008;115(8):255-62.

28. Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K. Visit-to-visit blood pressure variations: new independent determinants for cognitive function in the elderly at high risk of cardiovascular disease. *J Hypertens* 2012;30(8):1556-63.

29. Packard CJ, Westendorp RG, Stott DJ, Caslake MJ, Murray HM, Shepherd J, et al. Association between apolipoprotein E4 and cognitive decline in elderly adults. *J Am Geriatr Soc* 2007;55(11):1777-85.

30. Sadigh-Eteghad S, Talebi M, Farhoudi M. Association of apolipoprotein E epsilon 4 allele with sporadic late onset Alzheimer`s disease. A meta-analysis. *Neurosciences (Riyadh)* 2012;17(4):321-6.

31. Parati G, Lantelme P. Blood pressure variability, target organ damage and cardiovascular events. *J Hypertens* 2002;20(9):1725-9.

32. Kim KI, Lee JH, Chang HJ, Cho YS, Youn TJ, Chung WY, et al. Association between blood pressure variability and inflammatory marker in hypertensive patients. *Circ J* 2008;72(2):293-8.

33. Cecchi E, Giglioli C, Valente S, Lazzeri C, Gensini GF, Abbate R, et al. Role of hemodynamic shear stress in cardiovascular disease. *Atherosclerosis* 2011;214(2):249-56.

34. Barnes J, Bartlett JW, van de Pol LA, Loy CT, Scahill RI, Frost C, et al. A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. *Neurobiol Aging* 2009;30(11):1711-23.

35. Goldstein IB, Bartzokis G, Guthrie D, Shapiro D. Ambulatory blood pressure and the brain: a 5-year follow-up. *Neurology* 2005;64(11):1846-52.

36. Goldstein IB, Bartzokis G, Guthrie D, Shapiro D. Ambulatory blood pressure and brain atrophy in the healthy elderly. *Neurology* 2002;59(5):713-9.

37. Gomez-Angelats E, de La Sierra A, Sierra C, Parati G, Mancia G, Coca A. Blood pressure variability and silent cerebral damage in essential hypertension. *Am J Hypertens* 2004;17(8):696-700.

38. Liu W, Liu R, Sun W, Peng Q, Zhang W, Xu E, et al. Different Impacts of Blood Pressure Variability on the Progression of Cerebral Microbleeds and White Matter Lesions. *Stroke* 2012;43(11):2916-22.

39. Kario K, Motai K, Mitsuhashi T, Suzuki T, Nakagawa Y, Ikeda U, et al. Autonomic nervous system dysfunction in elderly hypertensive patients with abnormal diurnal blood pressure variation: relation to silent cerebrovascular disease. *Hypertension* 1997;30(6):1504-10.

40. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet* 2010;375(9718):906-15.

41. Lopez-Arrieta JM, Birks J. Nimodipine for primary degenerative, mixed and vascular dementia. *Cochrane Database Syst Rev* 2002;(3):CD000147.

42. Alagiakrishnan K, McCracken P, Feldman H. Treating vascular risk factors and maintaining vascular health: is this the way towards successful cognitive ageing and preventing cognitive decline? *Postgrad Med J* 2006;82(964):101-5.

3

Chapter 4

Blood pressure lowering medication, visit-to-visit blood pressure variability and cognitive function in old age

Liselotte W Wijsman, Anton JM de Craen, Majon Muller, Behnam Sabayan, David Stott, Ian Ford, Stella Trompet, J Wouter Jukema, Rudi GJ Westendorp, Simon P Mooijaart

Abstract

Background Visit-to-visit blood pressure variability is associated with cognitive impairment. We assessed to what extent the association between blood pressure variability and cognitive impairment is mediated by the association of blood pressure lowering mediation with both blood pressure variability and cognition.

Methods We studied 5,606 participants from the PROspective Study of Pravastatin in the Elderly at Risk. Blood pressure was measured every three months during 3.2 years; blood pressure variability was defined as the standard deviation of blood pressure measurements during follow up. Cognitive function was assessed at baseline and during follow-up using the Stroop test, Letter-Digit Coding test, immediate and delayed Picture-Word Learning tests. Multivariate regression models were used with and without adjustments for blood pressure lowering medication to calculate the percentage to which blood pressure lowering medication mediated the association between blood pressure variability and cognition.

Results Participants taking calcium-antagonists had a higher score in baseline Letter-Digit Coding test (mean difference (95% confidence interval (CI) 0.45 (0.06; 0.88). Participants taking beta-blockers had a steeper decline in Stroop test (additional change per year (95% CI) 0.40 (0.09; 0.70) and Letter-Digit Coding test (0.08 (-0.15; -0.02)). Furthermore, a steeper decline in Stroop test was found in participants taking RAS-inhibitors (0.50 (0.16; 0.85). Systolic blood pressure variability was higher in participants taking beta-blockers and RAS-inhibitors (mean difference in systolic blood pressure variability in mmHg (95% CI) 0.75 (0.45; 1.04) and 1.37 (1.04; 1.71) respectively). Participants taking diuretics, calcium antagonists and RAS-inhibitors had a higher diastolic blood pressure variability (mean difference in diastolic BP variability in mmHg (95% CI) 0.27 (0.04; 0.49), 0.37 (0.12; 0.62) and 0.65 (0.37; 0.93) SD, respectively). Beta estimates remained essentially the same when we adjusted for blood pressure lowering medication in the association of blood pressure variability with cognitive function.

Conclusion The association between blood pressure variability and cognitive impairment was not mediated by blood pressure lowering medication.

Introduction

Visit-to-visit blood pressure variability independent of average blood pressure is associated with higher cardiovascular risk in older adults. Several observational studies have shown that higher levels of blood pressure variability are related with increased risk of stroke, coronary events, heart failure hospitalization and cardiovascular and all-cause mortality. (1-5) Furthermore, blood pressure variability has been associated with white matter hyperintensities, intima media thickness and carotid artery atherosclerosis in older adults. (6-8) Recent evidence has shown that older subjects with higher levels of blood pressure variability have worse cognitive function.(9-11) Again, these findings were independent of average blood pressure.

Besides average blood pressure, reducing the variability of blood pressure might therefore be of importance. Blood pressure lowering medication may have class-specific effects on blood pressure variability, but evidence on the association of blood pressure lowering medication with blood pressure variability is limited. A recent meta-analysis of clinical trials showed that compared with other drugs, systolic blood pressure variability was reduced the most in subjects using calcium-channel blockers and non-loop diuretics; systolic blood pressure variability was higher in subjects using angiotensin-converting enzyme (ACE) inhibitors and beta-blockers.(12) Besides the effects on blood pressure variability, blood pressure lowering medication, especially calcium channel blockers, also seem to have class-specific effects in decreasing the risk of dementia.(13-16) Therefore, we hypothesized that the association between blood pressure variability and cognitive impairment might partially be caused by different effects of blood pressure lowering medication on both blood pressure variability and cognitive function.

We have previously described the association between blood pressure variability and cognitive function within this study population. Now, we evaluated whether the association between blood pressure variability and cognitive function could be mediated by blood pressure lowering medication.(9) We used data from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a multicenter trial including 5,804 participants with a mean age of 75 years, who all had repeated measurements of blood pressure and different domains of cognitive function over a mean follow-up period of 3.2 years.

4

Methods

Study design

Data in this study were obtained from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER): a randomized, double-blind, placebo-controlled trial designed to investigate the effect of pravastatin treatment to prevent vascular events in elderly men and women with pre-existing cardiovascular disease or risk factors thereof.(17) Primary outcome of this trial was the combined endpoint of definite or suspect death from coronary heart disease, non-fatal myocardial infarction and fatal or non-fatal stroke during a mean follow-up period of 3.2 years. PROSPER included 5,804 individuals aged 70-82 years old who were enrolled from three collaborating centers in Ireland, Scotland and the Netherlands.(17) In the present study we included 5,606 participants for whom data on blood pressure lowering medication and blood pressure variability were available. The institutional ethics committees of the three collaborating centers approved the study and all participants gave written informed consent.

Blood pressure lowering medication

Information about use and type of blood pressure lowering medication was self-recorded at baseline. A research nurse reported change in blood pressure lowering medication during every three-monthly study visit. Dosage of blood pressure lowering medication was unknown. For the present study, we only investigated participants who used one or more of the following classes of blood pressure lowering medication: diuretics, beta-blockers, calcium antagonists and renin-angiotensin system (RAS)-inhibitors (including angiotensin-converting-enzyme and angiotensin-receptor antagonists).

Blood pressure measurements

Blood pressure was measured at baseline and every three months during a mean 3.2 year follow-up period. Blood pressure was measured in sitting position using a fully automatic electronic sphygmomanometer (Omron M4®). All measurements were performed in the same clinical setting. Average blood pressure was calculated for each participant as the mean value of all blood pressure measurements during follow-up. Blood pressure variability was defined as the standard deviation of all blood pressure measurements during follow-up for each participant.

Cognitive function

The Mini-Mental State Examination (MMSE) was used to evaluate global cognitive function at baseline; a cutoff score of 24 points or more (out of 30) was used as an inclusion criterion to exclude subjects with poor cognitive function at baseline.(18) Cognitive function was tested at baseline, after 9, 18, 30 months and at the end of the study by a cognitive test battery consisting of four different tests.(18) For the current study, we used data on cognitive function assessed at the end of follow-up; to ensure that the determinant (blood pressure variability during follow-up) preceded the outcome variable (cognitive function). The time point of the measurement at the end of the study varied between 36 months and 48 months. The Stroop-Colour-Word-Test was used to test selective attention and reaction time of the participants. The participants were asked to read a color name which was displayed in a color different from the color it actually names. The outcome parameter was total number of seconds to complete the test; a higher score therefore indicates worse performance. General cognitive speed was tested by the Letter-Digit Coding Test. The participants had to match certain digits with letters according to a provided key. The outcome variable was the total number of correct entries in 60 seconds, and therefore higher scores represent better performance. The Picture-Word Learning Test was used to assess immediate and delayed memory performance. Fifteen pictures were presented at the participants, and they were asked to recall as many pictures as possible in three trials. After 20 minutes they were asked to repeat the test to measure their delayed recall. The outcome parameter is the accumulated number of correct recalled pictures, immediate and after 20 minutes. Higher scores thus indicate better performance. A detailed description of the cognitive tests and the procedures has been published previously.(18)

Statistical analyses

In the present study, we compared participants using the specific class of blood pressure lowering medication with participants not using this specific medication class. Baseline characteristics of the study participants are reported as mean (standard deviation) for continuous variables and number (percentage) for categorical variables. We used an independent t-test (for continuous variables) and a Chi-square test (for categorical variables) to assess whether there was a difference in baseline characteristics between participants using a specific medication class compared to participants not using this medication class.

We first investigated the association between blood pressure lowering medication and blood pressure variability by multivariate linear regression models. Independent variables were blood pressure lowering medication class; systolic and blood pressure variability were

the dependent variables. Second, we assessed the association between blood pressure lowering medication and cognitive function at baseline and cognitive decline during follow-up. For the baseline associations, we used multivariate linear regression models, with class of blood pressure lowering medication as an independent variable and cognitive tests as dependent variables. Furthermore, for the association of blood pressure lowering medication with cognitive decline over time,. linear mixed models were used, which included class of blood pressure lowering medication, time (in years) and the interaction term between class of blood pressure lowering medication and time. We performed our analyses according to two different models. In a minimally adjusted model, we adjusted our analyses for age, sex and country. In the final model (fully adjusted model), we additionally adjusted our analyses for the following potential confounders: study treatment, cardiovascular diseases and risk factors (history of vascular disease, history of hypertension, history of diabetes mellitus, smoking status, cholesterol levels, body mass index), estimated glomerular filtration rate (eGFR), number of blood pressure lowering medications, and average blood pressure during follow-up. Concerning the association between blood pressure lowering medication and blood pressure variability, we additionally adjusted for use of other blood pressure lowering medications. Furthermore, the analyses between blood pressure lowering medication and cognition were adjusted for education (defined as age left school).

In a third statistical analysis, we determined whether blood pressure lowering medication mediated the association of blood pressure variability and cognitive function. For this, we added class of blood pressure lowering medication to the model which examined the association between blood pressure variability and cognitive function. Each class of blood pressure lowering medication was first included separately in the analysis; however we also included combinations of blood pressure lowering medication and all blood pressure lowering medication. We did not incorporate interaction between blood pressure lowering medication and blood pressure variability in the model. Finally, we calculated the percentage of the association explained by blood pressure lowering medication.(19) We defined a percentage of 10% or greater as evidence of potential medication. To account for change in blood pressure lowering medication during follow-up, we performed an additional sensitivity analysis in which we excluded all participants who changed their blood pressure lowering medication during follow-up.

All analyses were performed using SPSS (version 20.0.0, SPSS Inc., Chicago, IL).

Results

Out of the 5,804 participants of PROSPER, we excluded 198 participants who had only one or two blood pressure measurements during follow-up. This resulted in a final study sample of 5,606 participants.

Table 1 shows the baseline characteristics in different classes of blood pressure lowering medication. Participants taking RAS-inhibitors had the lowest age and participants taking loop diuretics had the highest age at baseline. Prevalence of vascular diseases and risk factors varied among the groups, most probably reflecting differences in indications for which blood pressure lowering medication was prescribed. Systolic blood pressure was lowest

Table 1. Baseline characteristics in different classes of blood pressure lowering medication

	Blood pressure lowering medication			
	Diuretics	Beta-blockers	Calcium antagonists	RAS-inhibitors
	N=2266	N=1451	N=1406	N=1032
Demographics				
Age (years)	75.63 (3.41)**	75.29 (3.37)	75.41 (3.28)	75.35 (3.35)
Female, n (%)	1457 (64.3%)**	792 (54.6%)*	684 (48.6%)*	565 (54.7%)*
Country, n (%)				
The Netherlands	326 (15.4%)**	321 (22.1%)*	224 (15.9%)**	286 (27.7%)**
Ireland	932 (41.4%)**	538 (37.1%)*	428 (30.4%)**	467 (45.3%)**
Scotland	1008 (44.5%)**	592 (40.8%)*	754 (53.6%)*	279 (27.0%)**
Education (age left school)	15.12 (1.96)	15.15 (2.09)	15.04 (1.92)*	15.28 (2.24)*
Total number of medications	4.29 (2.26)**	4.21 (2.11)**	4.81 (2.29)**	4.47 (2.29)**
Total number of BP measurements during follow-up	11.24 (2.83)	11.38 (2.64)	11.22 (2.87)	11.16 (2.74)
Vascular risk factors				
History of hypertension, n (%)	1998 (88.2%)**	1192 (82.2%)**	1069 (76.0%)**	952 (92.2%)**
History of diabetes mellitus, n (%)	174 (7.7%)**	120 (8.3%)**	138 (9.8%)	173 (16.8%)**
History of stroke or TIA, n (%)	234 (10.3%)	137 (9.4%)*	170 (12.1%)	133 (12.9%)*
History of MI, n (%)	253 (11.2%)**	232 (16.0%)*	267 (19.0%)**	173 (16.8%)*
History of vascular disease, n (%)	880 (38.8%)**	710 (48.9%)**	853 (60.7%)**	443 (42.9%)
Current smoker, n (%)	339 (15.0%)**	182 (12.5%)**	216 (15.4%)**	136 (13.2%)**
Body mass index (kg/m^2)	27.82 (4.43)**	27.31 (4.02)**	27.19 (4.13)**	27.67 (4.37)**
Total cholesterol (mmol/L)	5.78 (0.91)**	5.72 (0.89)	5.67 (0.89)	5.68 (0.91)
Blood pressure				
Systolic blood pressure (mmHg)	154.97 (21.24)*	155.52 (23.33)	153.83 (21.71)**	158.77 (23.52)**
Diastolic blood pressure (mmHg)	84.28 (11.41)*	83.69 (0.30)	82.40 (11.47)**	85.53 (12.33)**
Estimated glomerular filtration rate (ml/min/1.73m^2)	56.86 (14.06)**	58.69 (15.23)**	58.00 (13.44)**	59.19 (14.19)*

Data are presented as mean (standard deviation) unless stated otherwise. Abbreviations: n, number; BP, blood pressure; TIA, transient ischemic attack; MI, myocardial infarction. **p<0.001 *p<0.05 representing the differences in characteristics between participants taking a specific blood pressure lowering medication class, and participants not taking this specific class.

Table 2. Association between blood pressure variability and blood pressure lowering medication

	Systolic BPV				Diastolic BPV			
	Minimally adjusted		Fully adjusted		Minimally adjusted		Fully adjusted	
	Unstd. Beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value
Diuretics	-0.15 (-0.42; 0.12)	0.281	-0.52 (-0.84; -0.21)	0.001	0.27 (0.04; 0.49)	0.020	0.23 (-0.04; 0.50)	0.089
Beta-blockers	0.75 (0.45; 1.04)	<0.001	0.59 (0.28; 0.91)	<0.001	-0.08 (-0.32; 0.17)	0.530	-0.09 (-0.36; 0.18)	0.530
Calcium antagonists	0.15 (-0.15; 0.45)	0.327	-0.05 (-0.38; 0.28)	0.778	0.37 (0.12; 0.62)	0.004	0.38 (0.10; 0.67)	0.008
RAS-inhibitors	1.37 (1.04; 1.71)	<0.001	0.98 (0.62; 1.35)	<0.001	0.65 (0.37; 0.93)	<0.001	0.53 (0.21; 0.84)	0.001

Abbreviations: BPV, blood pressure variability; Unstd., unstandardized; CI, confidence interval. Data represent difference in blood pressure variability (BPV) when compared to participants not taking the class of blood pressure lowering medication as unstandardized beta (95% confidence interval). Minimally adjusted: adjusted for age, sex, country. Fully adjusted: minimally adjustments + use of other blood pressure lowering medication, treatment (pravastatin/placebo), body mass index, ldl, hdl, triglycerides, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, average blood pressure during follow-up, eGFR, number of medications.

Table 3. Association of blood pressure lowering medication with cognitive function and decline

		Stroop		Letter-Digit Coding test		PLTi		PLTd	
		Unstd. beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value	Unstd. beta (95% CI)	P-value
Diuretics	Baseline	0.47 (-1.06; 1.99)	0.547	-0.06 (-0.47; 0.36)	0.790	0.03 (-0.09; 0.14)	0.661	0.06 (-0.10; 0.22)	0.431
	Annual change	0.04 (-0.23; 0.32)	0.767	0.04 (-0.02; 0.10)	0.147	0.00 (-0.03; 0.02)	0.744	0.00 (-0.04; 0.03)	0.953
Beta-blockers	Baseline	-1.09 (-2.62; 0.45)	0.165	0.27 (-0.15; 0.69)	0.204	0.04 (-0.08; 0.15)	0.530	0.05 (-0.11; 0.21)	0.547
	Annual change	0.40 (0.09; 0.70)	0.009	-0.08 (-0.15; -0.02)	0.013	-0.02 (-0.05; 0.01)	0.160	-0.02 (-0.06; 0.02)	0.231
Calcium antagonists	Baseline	-0.43 (-2.02; 1.16)	0.596	0.45 (0.06; 0.88)	0.042	0.05 (-0.07; 0.16)	0.425	0.09 (-0.07; 0.26)	0.272
	Annual change	0.20 (-0.11; 0.51)	0.211	0.00 (-0.06; 0.07)	0.977	-0.02 (-0.04; 0.01)	0.219	-0.02 (-0.06; 0.02)	0.375
RAS-inhibitors	Baseline	1.36 (-0.43; 3.14)	0.136	-0.02 (-0.51; 0.47)	0.935	-0.05 (-0.18; 0.08)	0.443	-0.02 (-0.20; 0.17)	0.857
	Annual change	0.50 (0.16; 0.85)	0.004	0.06 (-0.01; 0.14)	0.090	-0.01 (-0.04; 0.02)	0.439	0.00 (-0.04; 0.05)	0.872

Abbreviations: LDCT, letter-digit coding test; PLTi, picture-learning test, immediate; PLTd, picture-learning test, delayed; Unstd., unstandardized; CI, confidence interval. Data represent mean (95% confidence interval) of each baseline cognitive test score. For the longitudinal analyses, estimates represent the additional change in each cognitive function test per year in the different blood pressure lowering medication groups. Adjustments were made for age, sex, country, education, systolic and diastolic blood pressure at baseline, body mass index, ldl, hdl, triglycerides, history of vascular disease, history of diabetes mellitus, history of hypertension, history of diabetes mellitus, current smoking, eGFR, number of medications, and where appropriate for test version and treatment code.

in participants taking loop diuretics and highest in participants taking RAS-inhibitors. Participants taking calcium antagonists had the lowest mean diastolic blood pressure and participants taking RAS-inhibitors had the highest mean diastolic blood pressure.

The association between blood pressure lowering medication and visit-to-visit blood pressure variability is shown in table 2. Participants taking beta-blockers and RAS-inhibitors had a higher variability in systolic blood pressure (mean difference in systolic blood pressure variability when compared to participants not taking this medication class in mmHg (95% CI) 0.75 (0.45; 1.04) and 1.37 (1.04; 1.71) respectively). Results remained significant when further adjusting for use of other blood pressure lowering medication, number of blood pressure lowering medications, average systolic blood pressure during follow-up and cardiovascular diseases and risk factors. Participants taking diuretics, calcium antagonists and RAS-inhibitors had a higher diastolic blood pressure variability (mean difference in diastolic blood pressure variability when compared to participants not taking this medication class in mmHg 0.27 (0.04; 0.49), 0.37 (0.12; 0.62) and 0.65 (0.37; 0.93) SD, respectively). Results remained materially the same when further adjusting for use of other blood pressure lowering medication, number of blood pressure lowering medications, average diastolic blood pressure during follow-up and cardiovascular diseases and risk factors.

Table 3 shows the association of blood pressure lowering medication with cognitive function and decline. At baseline, there were no differences in Stroop test, Letter-Digit Coding test, and immediate and delayed Picture-Word Learning tests between participants taking diuretics, beta-blockers and RAS-inhibitors when compared to participants taking not this medication class. Participants taking calcium-antagonists had a higher score in Letter-Digit Coding test at baseline (mean difference (95% CI) 0.45 (0.06; 0.88). Participants taking beta-blockers had a steeper decline in Stroop test (additional change in seconds per year (95% CI) 0.40 (0.09; 0.70) and in Letter-Digit Coding test (additional change in digits coded per year (95% CI) -0.08 (-0.15; -0.02). Furthermore, participants taking RAS-inhibitors had a worse performance in Stroop test during follow-up (additional change in seconds per year (95% CI) 0.50 (0.16; 0.85). No differences in cognitive decline were found between participants using diuretics and calcium antagonists when compared to participants not using these medication classes.

Furthermore, we investigated whether the association between blood pressure variability and cognition was mediated by blood pressure lowering medication (table 4). When we additionally adjusted for each different class of blood pressure lowering medication, beta

4

Table 4. Association between blood pressure variability and cognitive function mediated through different combinations of blood pressure lowering medication

Difference in cognitive test score	Stroop test		Letter-Digit Coding test		Picture-Word Learning test, immediate		Picture Word Learning test, delayed	
	Unstd. beta (95% CI)	Mediated (%)	Unstd. beta (95% CI)	Mediated (%)	Unstd. Beta (95% CI)	Mediated (%)	Unstd. beta (95% CI)	Mediated (%)
Systolic BPV	0.47 (0.31; 0.64)	--	-0.09 (-0.13; -0.06)	--	-0.02 (-0.03; -0.01)	--	-0.02 (-0.04; -0.01)	--
+ all BPLM	0.49 (0.32; 0.66)	3.8%	-0.10 (-0.13; -0.06)	1.1%	-0.02 (-0.03; -0.01)	0.0%	-0.02 (-0.04; -0.01)	0.0%
+ diuretics	0.48 (0.31; 0.65)	1.7%	-0.09 (-0.13; -0.06)	0.0%	-0.02 (-0.03; -0.01)	0.0%	-0.02 (-0.04; -0.01)	0.0%
+ beta-blockers	0.48 (0.31; 0.65)	1.5%	-0.10 (-0.14; -0.06)	2.1%	-0.02 (-0.03; -0.01)	0.0%	-0.03 (-0.04; -0.01)	0.1%
+ calcium antagonists	0.47 (0.30; 0.64)	0.3%	-0.09 (-0.13; -0.06)	1.1%	-0.02 (-0.03; -0.01)	4.8%	-0.02 (-0.04; -0.01)	0.0%
+ RAS-inhibitors	0.48 (0.31; 0.65)	1.3%	-0.09 (-0.13; -0.06)	1.1%	-0.02 (-0.03; -0.01)	0.0%	-0.03 (-0.04; -0.01)	0.1%
Diastolic BPV	0.34 (0.15; 0.53)	--	-0.06 (-0.10; 0.01)	--	-0.02 (-0.03; 0.00)	--	-0.02 (-0.04; 0.00)	--
+ all BPLM	0.35 (0.15; 0.54)	2.1%	-0.06 (-0.11; 0.02)	1.7%	-0.02 (-0.03; 0.00)	5.9%	-0.02 (-0.04; 0.00)	5.9%
+ diuretics	0.34 (0.15; 0.53)	0.3%	-0.06 (-0.10; 0.01)	0.0%	-0.02 (-0.03; 0.00)	0.0%	-0.02 (-0.04; 0.00)	0.0%
+ beta-blockers	0.34 (0.15; 0.53)	0.9%	-0.06 (-0.10; 0.01)	1.7%	-0.02 (-0.03; 0.00)	0.0%	-0.02 (-0.04; 0.00)	5.9%
+ calcium antagonists	0.34 (0.15; 0.54)	1.5%	-0.06 (-0.10; 0.01)	3.4%	-0.02 (-0.03; 0.00)	0.0%	-0.02 (-0.04; 0.00)	0.0%
+ RAS-inhibitors	0.34 (0.15; 0.53)	0.6%	-0.06 (-0.10; 0.02)	1.7%	-0.02 (-0.03; 0.00)	0.0%	-0.02 (-0.04; 0.00)	0.0%

Abbreviations: BPV, blood pressure variability; Unstd., unstandardized; CI, confidence interval. Data represent change of cognitive function with each 1 mmHg increase in blood pressure variability as unstandardized beta (95% confidence interval). Adjusted for age, sex, country, treatment (pravastatin/placebo), body mass index, education, ldl, hdl, triglycerides, history of vascular disease, history of hypertension, history of diabetes mellitus, current smoking, average blood pressure during follow-up, eGFR, number of medications.

estimates for cognitive function did not essentially change. Furthermore, when we adjusted for all blood pressure lowering medication, beta estimates also remained essentially the same.

An additional sensitivity analysis in which we excluded all participants (n=2,766) who changed their blood pressure lowering medication during follow-up, revealed materially the same results (supplemental tables 1, 2 and 3; available on request).

Discussion

In this prospective cohort study including 5,606 men and women with a mean age of 75 years, we showed that blood pressure lowering medication, including diuretics, beta-blockers, calcium-channel blockers and RAS inhibitors, did not mediate the association between high levels of blood pressure variability and cognitive impairment.

The last few years, visit-to-visit blood pressure variability has received increasing attention, especially in the association with cardiovascular diseases and cognitive impairment. The association between blood pressure lowering medication and visit-to-visit blood pressure variability has previously been investigated by Rothwell and colleagues.(4) They hypothesized that class-specific differences of antihypertensive medication in preventing stroke might be due to their different effects on visit-to-visit blood pressure variability.(5) In their systematic review and meta-analysis, they showed that inter-individual systolic blood pressure variability was reduced the most by calcium-antagonists and non-loop diuretic drugs, and increased by ACE-inhibitors, angiotensin-2-receptor blockers and beta-blockers.(12) Besides the association with lower systolic blood pressure variability, these findings are in line with our results, in which we also showed higher systolic blood pressure variability in participants taking beta-blockers and RAS-inhibitors.

The underlying mechanism by which blood pressure lowering medication is associated with blood pressure variability, has not been fully understood. Although most blood pressure lowering medications have an effect on reducing blood pressure variability, there is evidence that the most effective are those acting on the arterial baroreflex and calcium channel.(20) Furthermore, previous studies showed that calcium antagonists and diuretics have arterial effects, including reduction of arterial stiffness and vasoconstriction, by which blood pressure variability is also reduced.(21, 22) Cumulative evidence from animal studies shows that higher levels of blood pressure variability produce lesions of arterial endothelial

cells, activation of the renin-angiotensin system, and inflammation.(20) Subsequently, this may lead to impaired cerebral microvasculature and hemodynamics, with comprised cerebral flow and eventually, impaired cerebral function. Future studies are needed to identify underlying mechanisms of the effects of blood pressure lowering medication on blood pressure variability.

Although this study provides evidence for an association between classes of blood pressure lowering medication and higher blood pressure variability, we found no proof that blood pressure lowering medication mediates the previously demonstrated relation of blood pressure variability with cognitive impairment. A possible explanation for this might be that the magnitude of effect of blood pressure lowering medication on blood pressure variability was relatively low, and only accounts for a small proportion of all variability. A second explanation might be that blood pressure lowering medication itself did not associate with cognitive function, which strengthens the finding that blood pressure variability, independent of blood pressure lowering medication, is associated with cognitive impairment.

One important issue that merits further discussion is the principle of confounding by indication, in which allocation of treatment may reflect a decision influenced by patient characteristics and prognostic factors.(23) Indeed, we found that characteristics of the study participants differed across classes of blood pressure lowering medication in the population under study, of which the high prevalence of diabetes mellitus in participants taking RAS-inhibitors is an example. In addition, besides blood pressure lowering medication, many other factors influence blood pressure variability, such as incident diseases, inflammation pathways and baroreceptor regulation.(3, 24) Although adjusting for possible confounders like histories of cardiovascular diseases and risk factors did not essentially change our results, our findings could still have been affected by unknown or unmeasured factors. Furthermore, another limitation could be that the combination of several drugs of one participant may be modifying the associations of blood pressure lowering medication with both blood pressure variability and cognitive function. However, when we adjusted our analyses for number of blood pressure lowering medications, our results did not materially change. Strength of our study is the large sample of participants taking blood pressure lowering medication, who all had repeated measures of blood pressure over a mean follow-up period of 3.2 years. Furthermore, the prospective nature of this study allowed us to study our research question in a clinical setting, rather than a trial context. In conclusion, we found that use of beta-blockers and RAS-inhibitors was associated with higher levels of blood pressure variability. Furthermore, blood pressure lowering medica-

tion did not mediate the association between high levels of blood pressure variability and cognitive impairment.

References

1. Brunelli SM, Thadhani RI, Lynch KE, Ankers ED, Joffe MM, Boston R, Chang Y, Feldman HI. Association between long-term blood pressure variability and mortality among incident hemo-dialysis patients. Am J Kidney Dis 2008;52:p 716-726.
2. Hata Y, Kimura Y, Muratani H, Fukiyama K, Kawano Y, Ashida T, Yokouchi M, Imai Y, Ozawa T, Fujii J, Omae T. Office blood pressure variability as a predictor of brain infarction in elderly hypertensive patients. Hypertens Res 2000;23:p 553-560.
3. Poortvliet RK, Ford I, Lloyd SM, Sattar N, Mooijaart SP, de Craen AJ, Westendorp RG, Jukema JW, Packard CJ, Gussekloo J, de RW, Stott DJ. Blood pressure variability and cardiovascular risk in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PLoS One 2012;7:p e52438.
4. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Poulter NR, Sever PS. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol 2010;9:p 469-480.
5. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375:p 895-905.
6. Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, Decarli C, Brown TR, Mayeux R. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. Arch Neurol 2010;67:p 564-569.
7. Gunstad J, Cohen RA, Tate DF, Paul RH, Poppas A, Hoth K, Macgregor KL, Jefferson AL. Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. Blood Press 2005;14:p 353-358.
8. Havlik RJ, Foley DJ, Sayer B, Masaki K, White L, Launer LJ. Variability in midlife systolic blood pressure is related to late-life brain white matter lesions: the Honolulu-Asia Aging study. Stroke 2002;33:p 26-30.
9. Sabayan B, Wijsman LW, Foster-Dingley JC, Stott DJ, Ford I, Buckley BM, Sattar N, Jukema JW, van Osch MJ, van der Grond J, van Buchem MA, Westendorp RG, de Craen AJ, Mooijaart SP. Association of visit-to-visit variability in blood pressure with cognitive function in old age: prospective cohort study. BMJ 2013;347:p f4600.
10. Epstein NU, Lane KA, Farlow MR, Risacher SL, Saykin AJ, Gao S. Cognitive dysfunction and greater visit-to-visit systolic blood pressure variability. J Am Geriatr Soc 2013;61:p 2168-2173.
11. Nagai M, Hoshide S, Nishikawa M, Masahisa S, Kario K. Visit-to-visit blood pressure variability in the elderly: associations with cognitive impairment and carotid artery remodeling. Atherosclerosis 2014;233:p 19-26.
12. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet 2010;375:p 906-915.
13. Forette F, Seux ML, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998;352:p 1347-1351.
14. Yasar S, Xia J, Yao W, Furberg CD, Xue QL, Mercado CI, Fitzpatrick AL, Fried LP, Kawas CH, Sink KM, Williamson JD, DeKosky ST, Carlson MC. Antihypertensive drugs decrease risk of Alzheimer disease: Ginkgo Evaluation of Memory Study. Neurology 2013;81:p 896-903.
15. Trompet S, Westendorp RG, Kamper AM, de Craen AJ. Use of calcium antagonists and cognitive decline in old age. The Leiden 85-plus study. Neurobiol Aging 2008;29:p 306-308.
16. Alrawi YA, Panerai RB, Myint PK, Potter JF. Pharmacological blood pressure lowering in the older hypertensive patients may lead to cognitive impairment by altering neurovascular coupling. Med Hypotheses 2013;80:p 303-307.
17. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, Ford I, Jukema JW, Hyland M, Gaw A, Lagaay AM, Perry IJ, Macfarlane PW, Meinders AE, Sweeney BJ, Packard CJ, Westendorp RG, Twomey C, Stott DJ. The design of a prospective study of Pravastatin in

the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. Am J Cardiol 1999;84:p 1192-1197.

18. Houx PJ, Shepherd J, Blauw GJ, Murphy MB, Ford I, Bollen EL, Buckley B, Stott DJ, Jukema W, Hyland M, Gaw A, Norrie J, Kamper AM, Perry IJ, Macfarlane PW, Meinders AE, Sweeney BJ, Packard CJ, Twomey C, Cobbe SM, Westendorp RG. Testing cognitive function in elderly populations: the PROSPER study. PROspective Study of Pravastatin in the Elderly at Risk. J Neurol Neurosurg Psychiatry 2002;73:p 385-389.

19. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:p 1173-1182.

20. Su DF. Treatment of hypertension based on measurement of blood pressure variability: lessons from animal studies. Curr Opin Cardiol 2006;21:p 486-491.

21. Ichihara A, Kaneshiro Y, Sakoda M, Takemitsu T, Itoh H. Add-on amlodipine improves arterial function and structure in hypertensive patients treated with an angiotensin receptor blocker. J Cardiovasc Pharmacol 2007;49:p 161-166.

22. Zhu Z, Zhu S, Liu D, Cao T, Wang L, Tepel M. Thiazide-like diuretics attenuate agonist-induced vasoconstriction by calcium desensitization linked to Rho kinase. Hypertension 2005;45:p 233-239.

23. Signorello LB, McLaughlin JK, Lipworth L, Friis S, Sorensen HT, Blot WJ. Confounding by indication in epidemiologic studies of commonly used analgesics. Am J Ther 2002;9:p 199-205.

24. Poortvliet RK, Lloyd SM, Ford I, Sattar N, de Craen AJ, Wijsman LW, Mooijaart SP, Westendorp RG, Jukema JW, de RW, Gussekloo J, Stott DJ. Biological Correlates of Blood Pressure Variability in Elderly at High Risk of Cardiovascular Disease. Am J Hypertens 2014.
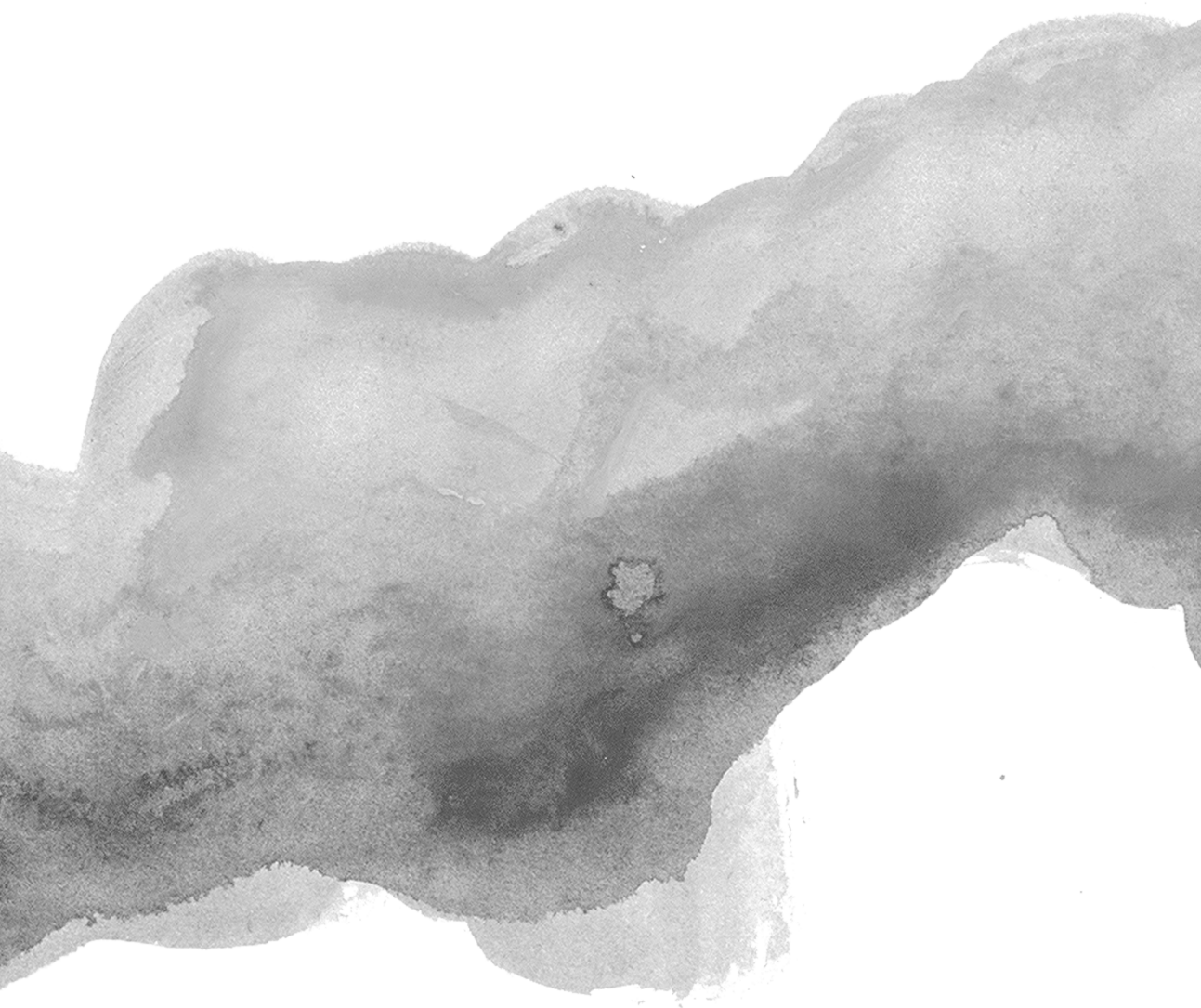
Part II

Cardiac biomarkers in cognitive function
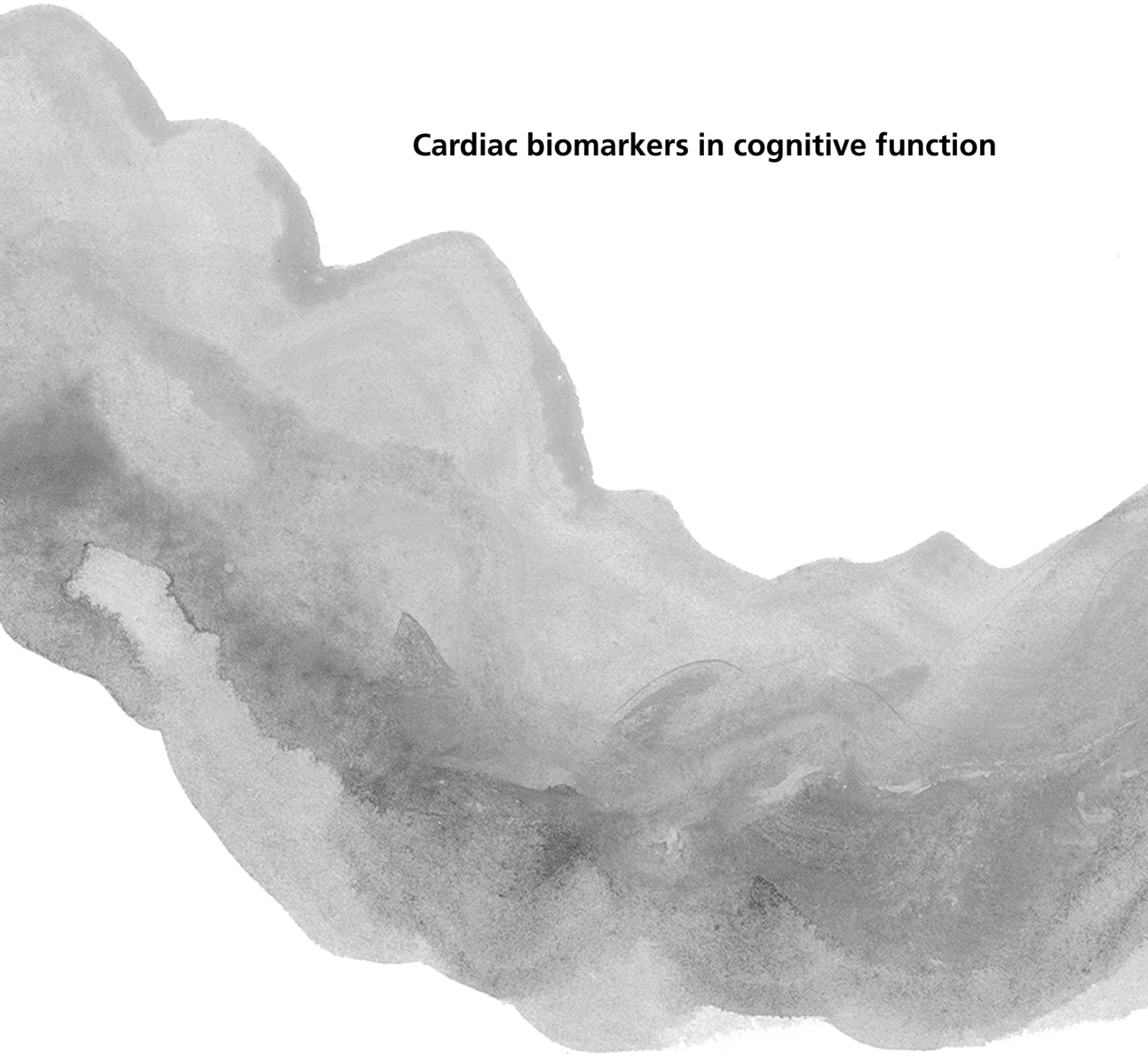
Chapter 5

N-terminal pro-brain natriuretic peptide and cognitive decline in older adults at high cardiovascular risk

Liselotte W Wijsman, Behnam Sabayan, Peter van Vliet, Stella Trompet, Wouter de Ruijter, Rosalinde KE Poortvliet, Petra G van Peet, Jacobijn Gussekloo, J Wouter Jukema, David J Stott, Naveed Sattar, Ian Ford, Rudi GJ Westendorp, Anton JM de Craen, Simon P Mooijaart

Abstract

Background Elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are associated with cognitive impairment, which might be explained by cardiovascular diseases or risk factors. The aim of this study was to investigate the association of NT-proBNP with cognitive function and decline in older adults at high risk of cardiovascular disease.

Methods We studied 5,205 men and women (mean age 75 years) who were included in the PROspective Study of Pravastatin in the Elderly at Risk. All participants had pre-existing cardiovascular disease or risk factors thereof. Four domains of cognitive function were tested at baseline and repeated during a follow-up period of 3.2 years.

Results Participants with higher NT-proBNP (≥450 ng/L) had worse baseline cognitive function including reaction time (mean difference high vs. low group=3.07 seconds, 95% confidence interval (CI)=0.83 to 5.32), processing speed (-1.02 digits coded, 95% CI=-1.65 to -0.39) and immediate memory (-0.13 pictures remembered, 95% CI=-0.29 to 0.04). There was no significant difference in delayed memory (-0.14 pictures remembered, 95% CI =-0.38 to 0.10) between the NT-proBNP groups. Participants with higher NT-proBNP had a steeper cognitive decline, including reaction time (mean annual change high vs. low group=0.60 seconds, 95% CI=0.14 to 1.07), processing speed (-0.15 digits coded, 95% CI=-0.25 to -0.05), immediate memory (-0.05 pictures remembered, 95% CI=-0.09 to 0.00), and delayed memory (-0.05 pictures remembered, 95% CI=-0.11 to 0.01). Associations were independent of cardiovascular diseases and risks.

Conclusion Higher NT-proBNP levels associate with worse cognitive function and steeper cognitive decline in older adults, independent of cardiovascular diseases and risks. Further studies to unravel the underlying mechanisms are warranted.

Introduction

Higher levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a neurohormone produced by cardiomyocytes in response to ventricular stretch, have been associated with cognitive impairment.(1-4) Evidence comes from several cross-sectional studies, which show that among community-dwelling older adults, higher NT-proBNP levels were associated with worse cognitive function, in particular memory.(1-4) There are limited numbers of longitudinal studies with relatively small sample sizes, which demonstrate that higher NT-BNP levels are also associated with steeper declines in Mini-Mental State Examination (MMSE) scores and higher incidence of dementia.(5, 6) A potential mechanism behind the relationship between higher NT-proBNP levels and cognitive function is clinical heart failure, resulting in left ventricular dysfunction with subsequent reduced cardiac output. It is hypothesized that reduced cardiac output causes inadequate cerebral perfusion, leading to a higher risk of cognitive impairment.(7-9) Improvements in cognitive function in patients following cardiac transplantation suggests that impaired cardiac function might be a reversible risk factor for cognitive impairment.(10, 11)

Recent evidence demonstrates that higher NT-proBNP levels in older adults are strongly associated with cardiovascular diseases and risk factors and predict an increased risk of atrial fibrillation, stroke, transient ischemic attack, myocardial infarction and mortality, even in the absence of clinical heart failure.(12-15) In addition, higher NT-proBNP levels have been related to left ventricular hypertrophy and systolic and diastolic dysfunction in adults without clinical heart failure.(16, 17) The relationship of cardiovascular diseases and risk factors with cognitive impairment is well-established.(18, 19) Hence, cognitive impairment might already be present in asymptomatic older adults at early stages of reduced cardiac function.

We hypothesized that elevated levels of NT-proBNP are associated with a steeper cognitive decline in older adults, which might be explained by cardiovascular diseases or risk factors. Therefore, we studied the cross-sectional and longitudinal association of NT-proBNP with cognitive function in a cohort of older men and women from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), in which all participants had either preexisting cardiovascular disease or were at risk of developing this condition.

5

Methods

Study design

Data were obtained from the PROspective Study of Pravastatin in the Elderly at Risk (PROS-PER), a randomized, double-blind, placebo-controlled trial designed to investigate the effect of pravastatin in prevention of vascular events in older individuals with pre-existing cardiovascular disease or risk factors thereof. This trial was conducted between 1997 and 2002 and included 5,804 men and women aged 70-82 years old who were enrolled from three collaborating centers in Ireland, Scotland and the Netherlands. Approximately 50% of the participants had cardiovascular disease including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction and/or vascular surgery. The rest of participants had one or more cardiovascular risk factor, defined as hypertension, smoking or diabetes mellitus. Primary outcome of the trial was the combined endpoint of definite or suspect death from coronary heart disease, non-fatal myocardial infarction and fatal or non-fatal stroke during a mean follow-up period of 3.2 years. The institutional ethics committees of the three collaborating centers approved the study and all participants gave written informed consent.[20, 21]

Study participants

All participants had pre-existing cardiovascular disease or risk factors thereof (defined as a history of hypertension, diabetes mellitus or current smoking). Participants with congestive heart failure, defined as New York Heart Association functional class III or IV, were excluded from the original PROSPER trial.[20] No information on NYHA class I or II was available. For the present study, we additionally excluded participants with heart failure hospitalization during follow-up (n=205).

NT-proBNP measurements

Blood samples were taken at 6 months after follow-up in EDTA tubes.[20] NT-proBNP was determined using electrochemiluminescence immunoassay on a Roche Modulator E170. A number of 394 participants had missing NT-proBNP measurements. In line with existing literature on cutoff values in this age group, we defined three groups of NT-proBNP: low (<100 ng/L), middle (100-450 ng/L) and high NT-proBNP (≥450 ng/L).[1] Furthermore, these cutoff values were chosen from a pragmatic approach, to allow direct interpretation for clinical practice.

Cognitive function

The MMSE was used to evaluate global cognitive function; participants with a baseline score below 24 points were not included in PROSPER. Cognitive function was tested at baseline and at 9, 18, 30 months and at the end of the study. The time-point of the measurement at the end of the study varied between 36 and 48 months; therefore, we performed the analysis with their individually varying time point, but report the results for the mean of these time points (at 42 months). Since PROSPER was conducted in three countries with in total two languages (Dutch and English), care was taken to select tests that are not sensitive to language. Furthermore, all analyses were adjusted for country.(22) Four different neuropsychological tests were used to assess executive function, attention, and immediate and delayed memory. The Stroop-Colour-Word-Test was used to test selective attention and reaction time. Participants were asked to read a color name which was displayed in a color different from the color it actually names. Outcome parameter was the total number of seconds to complete the test; a higher score indicates worse performance. General cognitive speed was tested by the Letter-Digit Coding Test. Participants had to match certain digits with letters according to a provided key. Outcome variable was the total number of correct entries in 60 seconds, therefore higher scores represented better performance. The Picture-Word Learning Test was used to assess immediate and delayed memory. Fifteen pictures were presented, and participants were asked to recall as many pictures as possible in three trials. After 20 minutes they were asked to repeat the pictures they remembered to measure their delayed recall. Outcome parameter was the accumulated number of correct recalled pictures, immediate and after 20 minutes. Higher scores thus indicate better performance. A detailed description of the cognitive tests has been published previously.(22) Since treatment with pravastatin did not influence cognitive function during follow-up, we included participants from both pravastatin and placebo groups.(23)

Statistical analysis

Baseline characteristics of the study participants are reported as number (percentage) for categorical variables and mean (standard deviation) for continuous variables for each group of NT-proBNP. Differences in categorical variables were tested by Chi-squared tests. Differences in continuous variables were tested with linear regression models. Since NT-proBNP levels were not normally distributed, we used log-transformed NT-proBNP levels to calculate p-values for continuous variables. To investigate the cross-sectional association of NT-proBNP with cognitive function, we used linear regression models. Log-transformed NT-proBNP levels were included as independent variable; outcome variable was the mean baseline score on each of the four cognitive function tests. Linear mixed models were

5

used to examine the association between NT-proBNP and cognitive decline over time. The models included log-transformed NT-proBNP levels, time (in years) and the interaction term between time and log-transformed NT-proBNP levels.

We performed our analyses in three steps. In the first step, crude analyses were performed, in which we only adjusted for cognitive test version where appropriate. In the second step, we added the variables age, sex, education (age left school), country and Apo E genotype to the model to investigate the potential influence of these factors on the associations (minimally adjusted model). Furthermore, in a fully adjusted model we also added the following potential confounders: cardiovascular diseases and risk factors at baseline (history of cerebrovascular and cardiovascular disease, hypertension, diabetes mellitus, smoking status, HDL and LDL cholesterol levels, triglycerides, systolic and diastolic blood pressure, body mass index), statin treatment and estimated glomerular filtration rate (eGFR). Since the associations did not essentially change in various models, we present the results of the minimally and fully adjusted models only.

To further explore the influence of cardiovascular diseases and risk factors, additional analyses were performed in which we stratified for history of cardiovascular diseases and risk factors. To test whether the difference between participants with or without a history of cardiovascular disease or risk factor was significant, we calculated a p-value for interaction by using linear regression models. Furthermore, we performed additional sensitivity analyses in which we excluded 1) participants taking pravastatin treatment during follow-up; 2) participants with incident stroke and/or transient ischemic attack; 3) participants with incident myocardial infarction; 4) participants with incident atrial fibrillation; 5) participants with vascular events, including coronary heart disease death, nonfatal myocardial infarction, nonfatal and fatal stroke and/or TIA; 6) participants with NT-proBNP of ≥450 ng/L; and 7) participants taking loop diuretics, beta blockers or ace-inhibitors at baseline.

Results

Participants with heart failure hospitalization during follow-up were excluded (n=205). A number of 394 participants had missing NT-proBNP measurements, resulting in a total number of 5205 participants for the present study.

Table 1 shows characteristics of participants grouped by NT-proBNP levels. Participants with higher NT-proBNP levels were older and had a higher prevalence of hypertension,

myocardial infarction, vascular disease and smoking (all p-values <0.001). Body mass index was lower in participants with higher NT-proBNP levels (p-value <0.001). Systolic blood pressure, pulse pressure and mean arterial blood pressure were higher among participants with higher NT-proBNP levels (p-values <0.001, p<0.001 and p=0.001 respectively). Furthermore, participants with higher NT-proBNP levels had a steeper decline in systolic and diastolic blood pressure during follow-up (p-values <0.001 and 0.001 respectively). Use of loop diuretics, beta blockers and ace-inhibitors was higher in participants with higher NT-proBNP levels (p-values <0.001, p<0.001 and p=0.031 respectively). Participants with higher NT-proBNP levels had lower eGFR (p <0.001).

Table 1. Characteristics of study participants grouped by NT-proBNP

	NT-proBNP			
	Low N=1818 <100 ng/L	Middle N=2698 100-450 ng/L	High N=689 ≥450 ng/L	P-value*
Demographics				
Age (years), mean (SD)	74.42 (3.04)	75.53 (3.37)	76.59 (3.40)	<0.001
Female, n (%)	850 (46.8)	1490 (55.2)	360 (52.2)	<0.001
Education (age left school), mean (SD)	15.17 (2.06)	15.15 (2.06)	15.10 (2.08)	0.083
Vascular risk factors				
History of hypertension, n (%)	1056 (58.1)	1736 (64.3)	444 (64.4)	<0.001
History of diabetes mellitus, n (%)	245 (13.5)	245 (9.1)	57 (8.3)	<0.001
History of stroke or TIA, n (%)	189 (10.4)	301 (11.2)	85 (12.3)	0.371
History of myocardial infarction, n (%)	120 (6.6)	369 (13.7)	177 (25.7)	<0.001
History of vascular disease, n (%)	630 (34.7)	1246 (46.2)	393 (57.0)	<0.001
Current smoker, n (%)	536 (29.5)	667 (24.7)	175 (25.4)	0.001
Body mass index (kg/m^2), mean (SD)	27.22 (4.02)	26.69 (4.21)	26.17 (4.20)	<0.001
Total cholesterol (mmol/L), mean (SD)	5.68 (0.90)	5.68 (0.91)	5.70 (0.93)	0.461
Systolic blood pressure (mmHg), mean (SD)[#]	152.60 (20.25)	155.11 (21.75)	158.75 (23.50)	<0.001
Diastolic blood pressure (mmHg), mean (SD)[#]	84.02 (10.95)	83.73 (11.33)	83.38 (12.01)	0.158
Pulse pressure (mmHg), mean (SD)	68.58 (0.42)	71.38 (0.35)	75.37 (0.68)	<0.001
Mean Arterial Pressure (mmHg), mean (SD)	106.88 (0.30)	107.53 (0.25)	108.51 (0.49)	0.001
Systolic blood pressure trend (mmHg), mean (SD)	-0.97 (7.94)	-1.49 (9.60)	-2.88 (12.44)	<0.001
Diastolic blood pressure trend (mmHg), mean (SD)	-1.25 (4.70)	-1.52 (5.25)	-1.93 (7.03)	0.001
Blood pressure lowering medication, n (%)				
Diuretics	650 (35.8)	1067 (39.5)	269 (39.0)	<0.001
Loop	153 (8.4)	327 (12.1)	107 (15.5)	<0.001
Other	497 (27.3)	740 (27.4)	162 (23.5)	
Calcium channel blockers	459 (25.2)	692 (25.6)	151 (21.9)	0.125
Beta blockers	241 (13.3)	831 (30.8)	273 (39.6)	<0.001
Ace-inhibitors	279 (15.3)	421 (15.6)	134 (19.4)	0.031
eGFR, mean (SD)	62.77 (13.79)	59.64 (14.48)	55.54 (14.99)	<0.001

*Probability values were calculated using log-transformed NT-proBNP levels for continuous variables and chi-squared tests for categorical variables. [#]Defined as the regression coefficient per year. Abbreviations: ACE=angiotensin-converting enzyme; eGFR=estimated glomerular filtration rate; NT-proBNP=N-terminal pro-brain natriuretic peptide; SD=standard deviation ; TIA=transient ischemic attack.

5

Table 2 shows the association of NT-proBNP levels with cognitive function at baseline. In the minimally adjusted model, participants with higher NT-proBNP levels had worse performance on the Stroop test (p=0.003) and the Letter-Digit Coding test (p<0.001). The same trend was observed for immediate and delayed Picture-Word Learning tests, showing that participants with higher NT-proBNP levels had worse performance, albeit these associations were not significant (p-value=0.060 and p=0.066 respectively). When further adjusting for prevalent cardiovascular diseases or risk factors at baseline, the estimates of the difference in cognitive function between the groups remained essentially the same. The association of NT-proBNP levels with the Stroop test and Letter-Digit Coding test in the fully adjusted model remained significant (p-value=0.003 and p<0.001 respectively), whereas for immediate and delayed Picture-Word Learning tests the associations were not significant (p-value=0.091 and p=0.062 respectively). Data on the association of NT-proBNP with cognitive function from crude models did not materially differ from minimally and fully adjusted models (data not shown).

Table 3 and Figure 1 show the association of NT-proBNP levels with changes in cognitive function during a mean follow-up period of 3.2 years. Participants with higher NT-proBNP

Table 2. Association of NT-proBNP with baseline cognitive function

Cognitive tests (mean, SE)	NT-proBNP			
	Low N=1818 <100 ng/L	Middle N=2698 100-450 ng/L	High N=689 ≥450 ng/L	P-value*
Stroop, seconds				
Minimally adjusted model	64.37 (1.46)	64.15 (1.42)	67.40 (1.63)	0.003
Fully adjusted model	66.23 (1.56)	66.09 (1.53)	69.30 (1.72)	0.003
LDCT, digits coded				
Minimally adjusted model	23.94 (0.41)	23.54 (0.40)	23.02 (0.46)	<0.001
Fully adjusted model	23.33 (0.44)	22.88 (0.43)	22.31 (0.48)	<0.001
PLTi, pictures remembered				
Minimally adjusted model	9.58 (0.11)	9.52 (0.11)	9.44 (0.12)	0.060
Fully adjusted model	9.49 (0.12)	9.44 (0.12)	9.37 (0.13)	0.091
PLTd, pictures remembered				
Minimally adjusted model	10.43 (0.16)	10.40 (0.15)	10.29 (0.17)	0.066
Fully adjusted model	10.22 (0.17)	10.19 (0.16)	10.08 (0.18)	0.062

Data represent mean (standard error) score of each cognitive function test. Minimally adjusted model: adjusted for age, sex, country, education (age on leaving school), ApoE genotype, treatment group, test version for LDCT and PLT. Fully adjusted model: minimally adjusted model + adjustments for history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index, and estimated gloermular filtration rate. *Probability values were calculated using the continuous value of log-transformed NT-proBNP levels. Abbreviations: LDCT=Letter-Digit Coding Test; NT-proBNP=N-terminal pro-brain natriuretic peptide; test; PLTd=Picture-Word Learning test, delayed; PLTi=Picture-Word Learning test, immediate.

levels had a steeper cognitive decline on the Stroop test, Letter-Digit Coding test and immediate and delayed Picture-Word Learning tests (all p-values≤0.001). Again, further adjustments for prevalent cardiovascular diseases or risk factors at baseline did not appreciably alter the observed associations (all p-values≤0.001). The association of NT-proBNP levels with cognitive decline from crude models did not materially differ from adjusted models (data not shown).

To further explore the influence of cardiovascular diseases and risk factors, we performed additional analyses in which we stratified for history of various cardiovascular diseases and risk factors, and tested for interaction. Figure 2 shows the association of NT-proBNP levels with cognitive decline, stratified by history of cardiovascular diseases and risk factors. There was no significant difference in change in cognitive function during follow-up between participants with and without cardiovascular diseases or risk factors, except on the Letter-Digit Coding test for participants with a history of stroke and/or transient ischemic attack (TIA) and myocardial infarction. Participants with previous stroke and/or TIA had a less steep decline on Letter-Digit Coding test (p for interaction=0.003), while participants with previous myocardial infarction had a steeper decline on Letter-Digit Coding test (p

Table 3. Association of NT-proBNP with cognitive decline during follow-up

Cognitive tests (mean annual change, SE)	NT-proBNP			
	Low N=1818 <100 ng/L	Middle N=2698 100-450 ng/L	High N=689 ≥450 ng/L	P-value*
Stroop, seconds				
Minimally adjusted model	0.46 (0.11)	0.71 (0.09)	1.04 (0.26)	0.001
Fully adjusted model	0.47 (0.11)	0.72 (0.09)	1.04 (0.26)	0.001
LDCT, digits coded				
Minimally adjusted model	-0.32 (0.02)	-0.36 (0.02)	-0.46 (0.04)	0.001
Fully adjusted model	-0.32 (0.02)	-0.35 (0.02)	-0.47 (0.04)	<0.001
PLTi, pictures remembered				
Minimally adjusted model	-0.00 (0.01)	-0.03 (0.01)	-0.05 (0.02)	<0.001
Fully adjusted model	0.00 (0.01)	-0.02 (0.01)	-0.04 (0.02)	<0.001
PLTd, pictures remembered				
Minimally adjusted model	-0.05 (0.01)	-0.06 (0.01)	-0.10 (0.03)	0.001
Fully adjusted model	-0.03 (0.01)	-0.05 (0.01)	-0.10 (0.03)	0.001

Data represent mean annual change (standard error) in each cognitive function test. Minimally adjusted model: adjusted for age, sex, country, education (age on leaving school), ApoE genotype, treatment group, test version for LDCT and PLT.Fully adjusted model: minimally adjusted model + adjustments for history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index, and estimated glomerular filtration rate. *Probability values were calculated using the interaction term of time and log-transformed NT-proBNP levels.Abbreviations: LDCT=Letter-Digit Coding test; NT-proBNP=N-terminal pro-brain natriuretic peptide; PLTd, Picture-Word Learning test, delayed; PLTi=Picture-Word Learning test, immediate

5

for interaction=0.008). However, no such differences were observed for participants with previous stroke and/or TIA or myocardial infarction on any of the other cognitive tests.

Furthermore, we performed additional sensitivity analyses to investigate whether the association between NT-proBNP levels and cognitive function and decline could be affected by 1) participants taking pravastatin treatment during follow-up (n=2,588); 2) participants with incident stroke and/or TIA during follow-up (n=355); 3) participants with incident myocardial infarction during follow-up (n=339); 4) participants with incident atrial fibrillation during follow-up (n=421); 5) participants with vascular events, including coronary heart disease death, nonfatal myocardial infarction, nonfatal and fatal stroke and/or TIA during follow-up (n=648); 6) participants with NT-proBNP levels of $\geq$ 450 ng/L; and 7) participants taking loop diuretics (n=588), beta blockers (n=1,345) or ace-inhibitors (n=834) at baseline. Exclusion of these participants did not essentially change our results (data available on request).
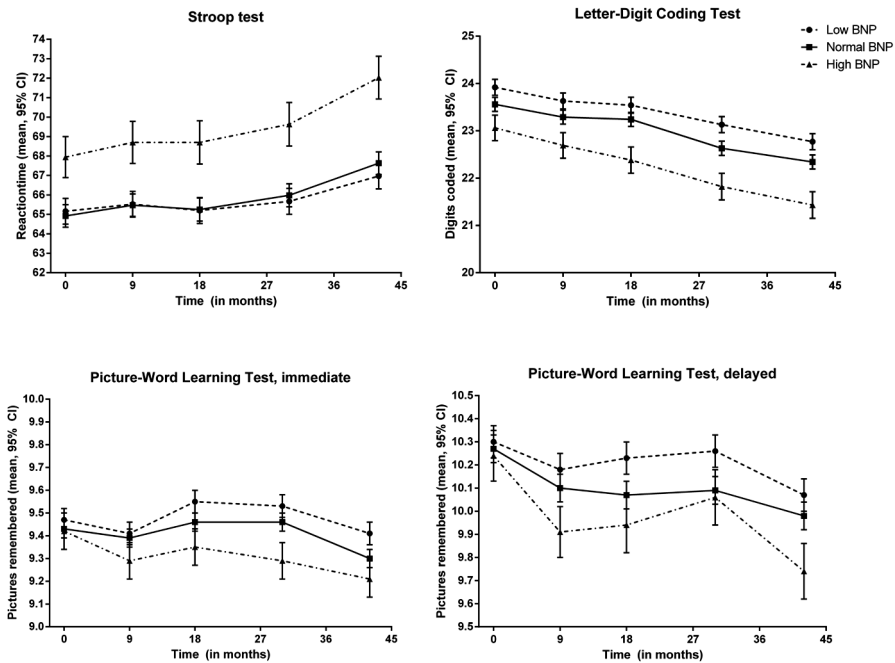
Figure 1. Association of NT-proBNP with cognitive decline during follow-up
Data represent mean score (95% confidence interval) of each cognitive test during follow-up, in each group of NT-proBNP. Because the time-point of the measurement at the end of the study varied between 36 and 48 months, the mean of these time points (42 months) is reported. Probability values were calculated using the interaction term of time and log-transformed NT-proBNP levels. Adjustments were made for age, sex, country, education, ApoE genotype, treatment group and test version where appropriate.
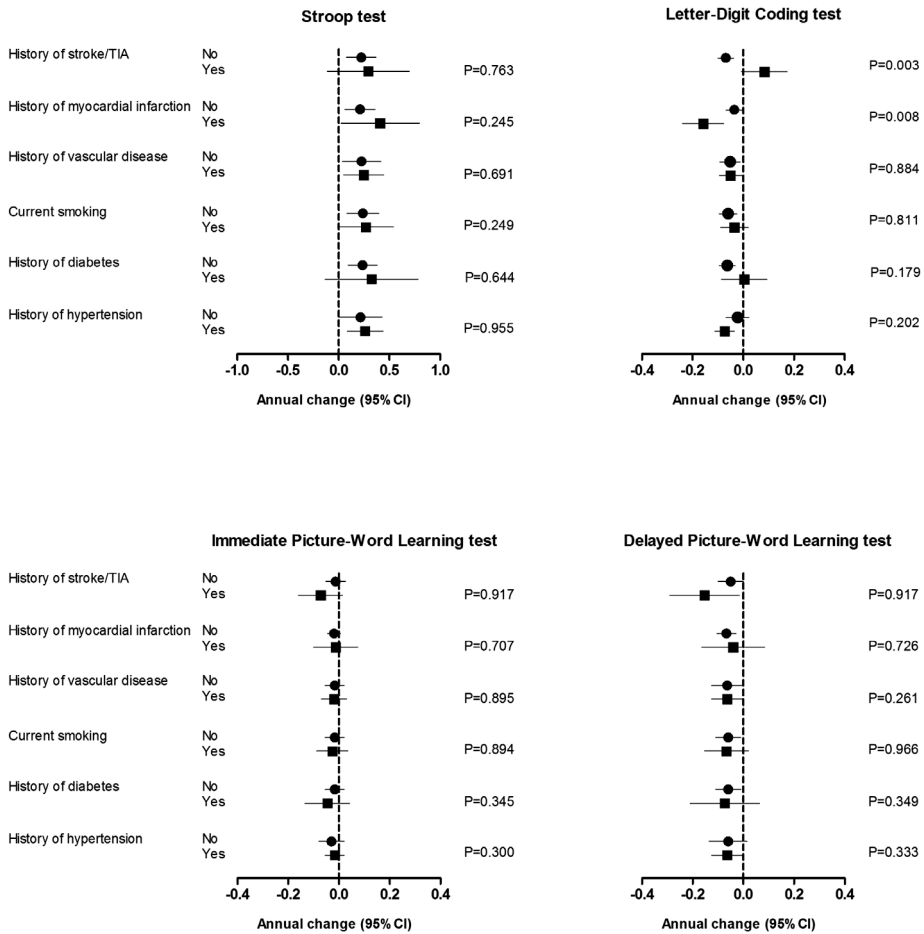
Figure 2. Association of NT-proBNP with cognitive decline during follow-up, stratified by cardiovascular diseases and risk factors

Data represent mean annual change (95% confidence interval) per 1 ng/L increase in log-transformed NT-proBNP for each cognitive test, stratified by cardiovascular diseases. Probability values were calculated using the interaction term of cardiovascular disease and log-transformed NT-proBNP level and represent the statistical difference in annual change in cognitive function between participants with and without cardiovascular disease or risk factors. Adjusted for age, sex, country, education, ApoE genotype, treatment group and test version where appropriate. Abbreviation: TIA=transient ischemic attack.

Discussion

In this prospective cohort study including over 5,000 men and women with mean age of 75 years, we showed that participants with higher NT-proBNP levels had worse cognitive

function and steeper cognitive decline during a mean period of 3.2 years. These associations were independent of cardiovascular diseases and risk factors.

Our findings are in line with previous cross-sectional studies, showing that higher NT-proBNP levels were associated with worse memory and with lower global and executive cognitive function.(1-4) Only few longitudinal studies with limited number of participants investigated the association between NT-proBNP and cognition during follow-up. They showed that higher NT-proBNP levels are associated with a steeper decline in Mini-Mental State Examination (MMSE) scores and a higher incidence of dementia during a mean follow-up period of 5 years.(5, 6) To our knowledge, this is the first study reporting on the association of NT-proBNP and cognitive function and decline, using an extended standardized test battery over a mean follow-up period of 3.2 years, in a large cohort of older adults with pre-existing cardiovascular disease or risk factors thereof.

Brain natriuretic peptide (BNP) and the biologically inactive N-terminal pro-brain natriuretic peptide are secreted by the ventricles of the heart in response to excessive stretching of cardiomyocytes.(24) BNP has favorable physiological properties, including increased natriuresis and diuresis, relaxation of vascular smooth muscle cells and inhibition of the renin-angiotensin-aldosterone-axis, eventually causing a reduction in blood pressure and ventricular preload.(24) Our results showed that higher NT-proBNP levels were associated with higher systolic blood pressure. Initially, higher systolic blood pressure might increase the ventricular stress of cardiomyocytes and therefore causes an increased release of NT-proBNP. In case of chronic ventricular stress, this might further proceed to reduced cardiac function and heart failure. Subsequently, cardiac output will be reduced and blood pressure will be lower.(9)

Different explanations can be proposed for the observed association of NT-proBNP with cognitive decline. First, NT-proBNP and cognitive decline are highly likely to reflect underlying cardiovascular damage and therefore stem from common causes. Previous studies have shown that NT-proBNP levels have a prognostic value for the occurrence of cardiovascular events, such as myocardial infarction, atrial fibrillation, coronary heart disease, unstable angina, stroke and transient ischemic attack.(12, 15, 25, 26) This has also been demonstrated in subjects with elevated NT-proBNP levels, but without clinical heart failure. (27) Furthermore, NT-proBNP levels provide predictive information for use of risk stratification in nonfatal cardiac events, stroke and mortality in range of populations including diabetes.(26, 28-30) These cardiovascular and metabolic diseases are closely linked to

cognitive dysfunction and dementia.(18, 19) This is in line with the finding that high NT-proBNP levels are associated with an increased prevalence of cardiovascular diseases and risk factors in the population under study. However, when adjusting and stratifying our analyses for cardiovascular diseases and risk factors, our results did not appreciably alter. Furthermore, excluding participants with incident myocardial infarction, stroke and/or TIA showed the same results. Nevertheless, we cannot rule out the possibility that unmeasured cardiovascular risk factors resulted in both increased NT-proBNP and cognitive decline. Second, impaired cardiac function may activate the renin-angiotensin system which in turn has been associated with cognitive decline.(31) In line with this evidence, observational studies have suggested that subjects receiving angiotensin receptor blockers may have a lower risk of developing dementia.(32, 33) Since only a small number of participants used angiotensin receptor blockers in the population under study (n<100), we could not further investigate this issue. Third, since natriuretic peptides have first been identified in porcine brain extract, one could hypothesize that NT-proBNP could have a direct effect in the brain. Although there is evidence that natriuretic peptides have receptors on endothelial cells, it is, to our knowledge, unknown whether NT-proBNP alters cerebral autoregulation.(7, 34) A fourth explanation might be that high NT-proBNP levels in subjects without advanced stages of heart failure indicate a suboptimal left ventricular functioning with subsequent decreased cardiac output and cerebral hypoperfusion.(9, 16) Cerebral hypoperfusion, which impairs the delivery of oxygen and nutrients to the brain, has been associated with cognitive dysfunction and dementia.(7-9) Although this explanation seems plausible, there is a need for interventional studies investigating the influence of improvement in cardiac function with its subsequent influence on cerebral perfusion, and eventually the prevention of cognitive decline in old age.

The present study found that participants with previous stroke and/or TIA had a less steep decline on Letter-Digit Coding test, which is unexpected and not in line with previous literature. Nevertheless, no differences were observed for participants with previous stroke and/or TIA on the Stroop test, immediate Picture-Word Learning test and delayed Picture Word Learning test. Furthermore, as there was no significant association between NT-proBNP levels and history of stroke and/or TIA, we could not explain this association from a biologically perspective. Therefore, we believe that the most likely explanation for this finding is chance.

Major strengths of this study include the large sample size of over 5000 older participants and the repeated use of an extended standardized cognitive test battery to assess cognitive

function over a mean follow-up period of 3.2 years. Furthermore, in contrast to previous studies, participants with NYHA functional class III/IV were excluded, which gave us the opportunity to investigate NT-proBNP in relation with cognitive function and decline in participants without advanced stages of clinical heart failure. However, a limitation of the study is that there was no information on the incidence of dementia during follow-up, nor was there information on cardiac functioning or NYHA class I or II. We might therefore have included participants with (beginning stages of) clinical heart failure, without ever being diagnosed with this condition. However, excluding participants with NT-proBNP levels of ≥ 450 ng/L showed essentially the same results. As high NT-proBNP levels have been recognized as predictor of heart failure, this finding further suggests an association between NT-proBNP and cognitive decline.(35) Furthermore, our study population consisted of older participants at risk of cardiovascular diseases with relatively preserved cognitive function (MMSE ≥ 24 points), which might limit extrapolation of our findings to a general population of older subjects.

In conclusion, higher NT-proBNP levels associate with worse cognitive function and steeper cognitive decline in older adults, independent of cardiovascular diseases and risks. Further studies to unravel the underlying mechanisms are warranted.

References

1. Daniels LB, Laughlin GA, Kritz-Silverstein D, Clopton P, Chen WC, Maisel AS, et al. Elevated natriuretic peptide levels and cognitive function in community-dwelling older adults. Am J Med 2011 Jul;124(7):670-8.
2. Feinkohl I, Sattar N, Welsh P, Reynolds RM, Deary IJ, Strachan MW, et al. Association of N-terminal pro-brain natriuretic peptide with cognitive function and depression in elderly people with type 2 diabetes. PLoS One 2012;7(9):e44569.
3. Gunstad J, Poppas A, Smeal S, Paul RH, Tate DF, Jefferson AL, et al. Relation of brain natriuretic peptide levels to cognitive dysfunction in adults > 55 years of age with cardiovascular disease. Am J Cardiol 2006 Aug 15;98(4):538-40.
4. van den Hurk K, Reijmer YD, van den Berg E, Alssema M, Nijpels G, Kostense PJ, et al. Heart failure and cognitive function in the general population: the Hoorn Study. Eur J Heart Fail 2011 Dec;13(12):1362-9.
5. Feinkohl I, Keller M, Robertson CM, Morling JR, Williamson RM, Nee LD, et al. Clinical and subclinical macrovascular disease as predictors of cognitive decline in older patients with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes Care 2013 Sep;36(9):2779-86.
6. Kerola T, Nieminen T, Hartikainen S, Sulkava R, Vuolteenaho O, Kettunen R. B-type natriuretic peptide as a predictor of declining cognitive function and dementia--a cohort study of an elderly general population with a 5-year follow-up. Ann Med 2010 Apr;42(3):207-15.
7. Georgiadis D, Sievert M, Cencetti S, Uhlmann F, Krivokuca M, Zierz S, et al. Cerebrovascular reactivity is impaired in patients with cardiac failure. Eur Heart J 2000 Mar;21(5):407-13.
8. Zuccala G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. J Neurol Neurosurg Psychiatry 1997 Oct;63(4):509-12.
9. Zuccala G, Onder G, Pedone C, Carosella L, Pahor M, Bernabei R, et al. Hypotension and cognitive impairment: Selective association in patients with heart failure. Neurology 2001 Dec 11;57(11):1986-92.
10. Bornstein RA, Starling RC, Myerowitz PD, Haas GJ. Neuropsychological function in patients with end-stage heart failure before and after cardiac transplantation. Acta Neurol Scand 1995 Apr;91(4):260-5.
11. Grimm M, Yeganehfar W, Laufer G, Madl C, Kramer L, Eisenhuber E, et al. Cyclosporine may affect improvement of cognitive brain function after successful cardiac transplantation. Circulation 1996 Sep 15;94(6):1339-45.
12. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. JAMA 2005 Apr 6;293(13):1609-16.
13. Pedersen F, Raymond I, Kistorp C, Sandgaard N, Jacobsen P, Hildebrandt P. N-terminal pro-brain natriuretic peptide in arterial hypertension: a valuable prognostic marker of cardiovascular events. J Card Fail 2005 Jun;11(5 Suppl):S70-S75.
14. Vaes B, de Ruijter W, Degryse J, Westendorp RG, Gussekloo J. Clinical relevance of a raised plasma N-terminal pro-brain natriuretic peptide level in a population-based cohort of nonagenarians. J Am Geriatr Soc 2009 May;57(5):823-9.
15. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004 Feb 12;350(7):655-63.
16. Mishra RK, Li Y, Ricardo AC, Yang W, Keane M, Cuevas M, et al. Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC]). Am J Cardiol 2013 Feb 1;111(3):432-8.
17. Uraizee I, Cheng S, Hung CL, Verma A, Thomas JD, Zile MR, et al. Relation of N-Terminal Pro-B-Type Natriuretic Peptide With Diastolic Function in Hypertensive Heart Disease. Am J Hypertens 2013 Jun 22.

5

18. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 2011 Sep;42(9):2672-713.

19. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010 Jul;9(7):689-701.

20. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, et al. The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. Am J Cardiol 1999 Nov 15;84(10):1192-7.

21. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002 Nov 23;360(9346):1623-30.

22. Houx PJ, Shepherd J, Blauw GJ, Murphy MB, Ford I, Bollen EL, et al. Testing cognitive function in elderly populations: the PROSPER study. PROspective Study of Pravastatin in the Elderly at Risk. J Neurol Neurosurg Psychiatry 2002 Oct;73(4):385-9.

23. Trompet S, van Vliet P, de Craen AJ, Jolles J, Buckley BM, Murphy MB, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. J Neurol 2010 Jan;257(1):85-90.

24. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003 Jul 26;362(9380):316-22.

25. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. Circulation 2012 Apr 3;125(13):1605-16.

26. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Christersson C, Ezekowitz J, et al. N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation). J Am Coll Cardiol 2013 Jun 4;61(22):2274-84.

27. Di AE, Chowdhury R, Sarwar N, Ray KK, Gobin R, Saleheen D, et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. Circulation 2009 Dec 1;120(22):2177-87.

28. de Lemos JA, Morrow DA, Gibson CM, Murphy SA, Sabatine MS, Rifai N, et al. The prognostic value of serum myoglobin in patients with non-ST-segment elevation acute coronary syndromes. Results from the TIMI 11B and TACTICS-TIMI 18 studies. J Am Coll Cardiol 2002 Jul 17;40(2):238-44.

29. Hillis GS, Welsh P, Chalmers J, Perkovic V, Chow CK, Li Q, et al. The relative and combined ability of high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide to predict cardiovascular events and death in patients with type 2 diabetes. Diabetes Care 2014 Jan;37(1):295-303.

30. Welsh P, Doolin O, Willeit P, Packard C, Macfarlane P, Cobbe S, et al. N-terminal pro-B-type natriuretic peptide and the prediction of primary cardiovascular events: results from 15-year follow-up of WOSCOPS. Eur Heart J 2013 Feb;34(6):443-50.

31. Unger T. The role of the renin-angiotensin system in the development of cardiovascular disease. Am J Cardiol 2002 Jan 24;89(2A):3A-9A.

32. Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ 2010;340:b5465.

33. Muller M, van der Graaf Y, Visseren FL, Mali WP, Geerlings MI. Hypertension and longitudinal changes in cerebral blood flow: the SMART-MR study. Ann Neurol 2012 Jun;71(6):825-33.

34. Kuhn M. Endothelial actions of atrial and B-type natriuretic peptides. Br J Pharmacol 2012 May;166(2):522-31.

35. Wannamethee SG, Welsh P, Whincup PH, Lennon L, Papacosta O, Sattar N. N-terminal pro brain natriuretic peptide but not copeptin improves prediction of heart failure over other routine clinical risk parameters in older men with and without cardiovascular disease: population-based study. Eur J Heart Fail 2013 Jul 30.

Chapter 6

High-sensitivity cardiac troponin T is associated with cognitive decline in older adults at high cardiovascular risk

Liselotte W Wijsman, Anton JM de Craen, Stella Trompet, Behnam Sabayan, Majon Muller, David J Stott, Ian Ford, Paul Welsh, Rudi GJ Westendorp, J Wouter Jukema, Naveed A Sattar*, Simon P Mooijaart*

Abstract

Background Cardiac troponin T (cTnT), measured with a high-sensitivity (hs) assay, is associated with cognitive decline, but the underlying mechanism is unknown. We investigated the association of hs-cTnT with cognitive function and decline, and studied whether this association was independent of cardiovascular diseases or risk factors, and N-terminal pro-brain natriuretic peptide (NT-proBNP).

Methods We studied 5,407 participants (mean age 75.31 years) from the PROspective Study of Pravastatin in the Elderly at Risk, who all had cardiovascular diseases or risk factors thereof. Participants with pre-existent advanced clinical heart failure were excluded. Hs-cTnT and NT-proBNP obtained after 6 months of follow-up were related with cognitive function, which was tested repeatedly during a mean follow-up of 3.2 years.

Results Participants with higher hs-cTnT performed worse at baseline on Stroop test (mean baseline score (standard error (SE)) lowest vs. highest third 65.91 (1.16) vs. 69.40 (1.10) seconds, p<0.001), Letter-Digit Coding test (23.35 (0.32) vs. 22.40 (0.31) digits coded, p<0.001), immediate Picture-Word Learning test (9.45 (0.09) vs. 9.31 (0.08) pictures remembered, p=0.002) and delayed Picture-Word Learning test (10.33 (0.12) vs. 10.10 (0.12) pictures remembered, p=0.013). Furthermore, participants with higher hs-cTnT had steeper decline on Stroop test (mean annual change (SE) lowest vs. highest third 0.34 (0.12) vs. 1.06 (0.12) seconds, p=0.013), Letter-Digit Coding test (-0.29 (0.03) vs. -0.46 (0.03) digits coded, p<0.001), immediate Picture-Word Learning test (0.01 (0.01) vs. -0.06 (0.01) pictures remembered, p<0.001) and delayed Picture-Word Learning test (-0.03 (0.01) vs. -0.12 (0.02) pictures remembered, p=0.001). Associations were independent of cardiovascular diseases risk factors or apoE genotype. Further adjusting for NT-proBNP levels revealed the same results.

Conclusion Higher levels of hs-cTnT associate with worse cognitive function and steeper cognitive decline in older adults independent of cardiovascular diseases, risk factors and NT-proBNP.

Introduction

Cardiac troponin T (cTnT) is a protein that is released in response to cardiomyocyte necrosis, and is routinely used in the diagnosis of acute myocardial infarction.(1) In patients with cardiovascular disease, higher levels of cTnT, measured with a high-sensitivity (hs) assay, are associated with higher risk of incident coronary heart disease, heart failure and stroke. (1, 2) Moreover, in patients free from cardiovascular disease, raised levels of hs-cTnT have also been associated with higher risk of all-cause mortality and myocardial infarction.(3)

Cardiovascular diseases are important risk factors for cognitive impairment and dementia. (4) Recent evidence shows that in subjects without cardiovascular disease, higher levels of hs-cTnT are associated with silent brain infarcts and white matter lesion progression.(5) Hs-cTnT might therefore be a sensitive systemic marker for structural brain damage, which is associated with decreased cognitive function and dementia.(6) Hs-cTnT has recently also been associated with cognitive function, but the underlying mechanism is unknown.(7) Besides the fact that cardiac disease and cognitive dysfunction share common risk factors there may be an alternative explanation. Myocardial ischemia or infarction, as detected by increased hs-cTnT, may lead to clinical heart failure or decreased cardiac function, which in turn leads to cognitive decline.(8) Given the predicted increase in prevalence of cognitive dysfunction in the coming decades, unravelling early predictors of cognitive decline is of importance.(9)

The aims of this study were to investigate 1) whether subjects with higher levels of hs-cTnT are at increased risk of worse cognitive function and steeper cognitive decline; 2) whether this was independent of cardiovascular diseases or its risk factors, and 3) whether this was independent of N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker used in the diagnosis of clinical heart failure.(10-12) We used data from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), which included 5804 older men and women who all had a cardiovascular disease or cardiovascular risk factors thereof.

Methods

Study design and participants
Data were obtained from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a randomized, double-blind, placebo-controlled trial designed to investigate the effect of pravastatin in prevention of vascular events in older individuals with pre-existing

cardiovascular disease or risk factors thereof.(13) Briefly, main inclusion criteria were that participants had either pre-existing vascular disease (coronary, cerebral or peripheral) or an elevated level of developing vascular disease because of smoking, diabetes mellitus or hypertension. Furthermore, their total cholesterol level was required to be between 4.0-9.0 mmol/L and their triglyceride concentration <6.0 mmol/L. Participants with congestive heart failure, defined as New York Heart Association functional class III or IV, were not included in the PROSPER study, nor were participants who were previously diagnosed with atrial fibrillation.(13) Furthermore, poor cognitive function at baseline, defined as a Mini-Mental Score Examination below 24 points, was an exclusion criteria. Participants with congestive heart failure, defined as New York Heart Association functional class III or IV, were not included in the PROSPER study, nor were participants who were previously diagnosed with atrial fibrillation.(13) This trial included 5,804 men and women aged 70-82 years old who were enrolled from three collaborating centers in Ireland, Scotland and the Netherlands. Approximately 50% of the participants had cardiovascular disease including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction and/or vascular surgery. The rest of participants had one or more cardiovascular risk factor, defined as hypertension, smoking or diabetes mellitus. Participants with congestive heart failure, defined as New York Heart Association functional class III or IV, were not included in the PROSPER study.(13) The primary outcome of the trial was the combined endpoint of definite or suspect death from coronary heart disease, non-fatal myocardial infarction and fatal or non-fatal stroke during a mean follow-up period of 3.2 years.(14) The institutional ethics committees of the three collaborating centers approved the study and all participants gave written informed consent.

cTnT and NT-proBNP measurements

cTnT and NT-proBNP were measured in blood samples obtained after 6 months of follow-up in EDTA tubes. Both proteins were measured using an electrochemiluminiscence immunoassay on a Roche Modular Analytics E170. The Roche cTnT measurement was performed with a high-sensitivity assay, which has a limit of detection of 0.003 ug/L and a 99th percentile cutoff of 0.014 ug/L. Furthermore, the Elecsys Troponin T hs assay used had a CV of 10.38% at a cTNT concentration of 0.010 ug/L, thus the assay is able to differentiate reasonably well at lower concentrations. For those patients who had a level below the detection limit, we have assumed these values to be distributed anywhere between zero and 0.003, of which the average is 0.0015. Hs-cTnT levels below detection level were therefore set to 0.0015 ug/L in the statistical analyses. To further investigate whether the association of cTnT with cognitive function and decline was independent of clinical heart

failure, we studied participants with low and high NT-proBNP levels more in detail. To be sure that participants had no clinical heart failure, we chose a conservative cut-off of 200 ng/L for NT-proBNP. Furthermore, we stratified our analyses by a less conservative cut-off of low (<400 ng/L) and high (≥400 ng/L) NT-proBNP, based on relevant guidelines.(15)

Cognitive function

The MMSE was used to evaluate global cognitive function; participants with a baseline score below 24 points were not included in PROSPER.(13) Cognitive function was tested at baseline and at 9, 18, 30 months and at the end of the study. The time-point of the measurement at the end of the study varied between 36 and 48 months; therefore, we performed the analysis with their individually varying time point, but report the results for the mean of these time points (at 42 months). Four different neuropsychological tests were used to assess executive function, attention, and immediate and delayed memory. The Stroop-Colour-Word-Test was used to test selective attention and reaction time. Participants were asked to read a color name which was displayed in a color different from the color it actually names. Outcome parameter was the total number of seconds to complete the test; a higher score indicates worse performance. Processing speed was tested by the Letter-Digit Coding Test. Participants had to match certain digits with letters according to a provided key. Outcome variable was the total number of correct entries in 60 seconds, therefore higher scores represented better performance. The Picture-Word Learning Test was used to assess immediate and delayed memory. Fifteen pictures were presented, and participants were asked to recall as many pictures as possible in three trials. After 20 minutes they were asked to repeat the pictures they remembered to measure their delayed recall. Outcome parameter was the accumulated number of correct recalled pictures, immediate and after 20 minutes. Higher scores thus indicate better performance. A detailed description of the cognitive tests has been published previously.(16) Since treatment with pravastatin did not influence cognitive function during follow-up, we included participants from both pravastatin and placebo groups.(17)

Statistical analyses

We present our results in thirds of cTnT. Baseline characteristics of the study participants are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables for each third of cTnT. Differences in continuous variables were tested with linear regression models; differences in categorical variables were tested by Chi-squared tests. Because of the skewed distribution of cTnT levels and log-transformed cTnT levels, all analyses were performed using the square root of cTnT, which was normally

distributed (supplemental figure 2). To investigate the cross-sectional association of cTnT with cognitive function, we used linear regression models. The square root levels of cTnT were included as independent variable; outcome variable was the mean baseline score on each of the four cognitive function tests. Linear mixed models were used to examine the association between cTnT and cognitive decline over time. The models included the square root of cTnT level, time (in years) and the interaction term between time and the square root of cTnT level.

We performed our analyses according to two different adjustment models. In the first model, we only adjusted for the variables age, sex, country, education, treatment with pravastatin or placebo and cognitive test version where appropriate (minimally adjusted model). In the second model, we further adjusted for ApoE genotype, history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol levels, triglycerides, body mass index and estimated glomerular filtration rate (eGFR), to investigate the potential influence of these factors on the associations. Since the observed associations did not materially differ, we chose to present the results from comprehensive adjusted models. Results from minimally adjusted models are included as supplemental material. Concerning the longitudinal analyses, we further studied the effects of potential confounders on the slope of the association by additionally including the interaction terms between time, square root of troponin level and potential confounder in the linear mixed models. These results did not materially affect the slope of the analyses and we therefore present the results of the simple models. Finally, to explore the influence of cardiovascular diseases and risk factors in more details, we performed additional analyses in which we stratified for history of cardiovascular diseases and risk factors.

To further investigate whether the association of cTnT with cognitive function and decline was independent of clinical heart failure, we stratified our analyses by low (<200 ng/L) and high (≥200 ng/L) NT-proBNP level and calculated a p-value for interaction to test whether the difference was significant. In addition, we 1) further adjusted our analyses for continuous levels of NT-proBNP and 2) stratified our analyses by a less conservative cut-off of low (<400 ng/L) and high (≥400 ng/L) NT-proBNP, was based on relevant guidelines.(15) Moreover, we performed additional analyses in which we excluded both participants with heart failure hospitalization during follow-up and participants who used loop diuretics at baseline, since those participants are likely to suffer from clinical heart failure. Furthermore,

we performed several sensitivity analyses in which we separately excluded participants who, during follow-up, had 1) a stroke and / or transient ischemic attack (TIA); 2) coronary events; 3) atrial fibrillation; 4) cardiovascular events; and 5) a sign of previous myocardial infarction (defined as pathological Q or QS-waves on their baseline ECG). In addotion, we excluded participants with high cTnT levels (defined conform 99th percentile as hs-cTnT levels >0.014 μg/L), to investigate the association of normal levels of cTnT with cognitive function and decline. Furthermore, to further investigate whether left ventricular dysfunction might have confounded our results, we excluded participants using diuretics and ace-inhibitors. Supplemental material is available on request.

Results

Out of the total number of 5,804 PROSPER participants, we excluded n=397 participants with missing cTnT measurements. The final sample of the present study included n=5,407 participants with a mean (standard deviation) age of 75.31 (3.36) years (supplemental figure 1).

Participants with higher cTnT were older, less frequently female and had a higher prevalence of hypertension, diabetes mellitus, stroke or transient ischemic attack, myocardial infarction and vascular disease (all p-values<0.05) (table 1). No difference in total cholesterol, high-density lipoprotein and low-density lipoprotein levels were found between the thirds of cTnT (all p-values>0.05). Systolic and diastolic blood pressure at baseline were higher in participants with higher cTnT levels (both p-values<0.001). Furthermore, participants with higher cTnT had a lower eGFR and higher NT-proBNP levels (both p-values<0.001).

6

The association of cTnT with cognitive function at baseline and cognitive decline during follow-up is shown in table 2. At baseline, participants with higher cTnT had worse cognitive function on Stroop test, Letter-Digit Coding test, immediate Picture-Word Learning test and delayed Picture-Word Learning test (all p-values<0.05). Longitudinally, participants with higher cTnT had a steeper decline on Stroop test, Letter-Digit Coding test, immediate Picture-Word Learning test and delayed Picture-Word Learning test (all p-values<0.05). Results were independent of cardiovascular diseases or risk factors, since all analyses were adjusted for histories of cardiovascular diseases and risk factors thereof. Data on the association of cTnT with cognitive function and decline from minimally adjusted models did not materially differ from comprehensive adjusted models (supplemental table 1).

Figure 1 shows the results of the association of cTnT with cognitive decline, stratified by cardiovascular diseases and risk factors. Participants with a history of hypertension had a steeper decline on Letter-Digit Coding test and immediate Picture-Word Learning test (both p-values for interaction=0.011).

Table 1. Baseline characteristics of study participants by thirds of cardiac troponin T

	Thirds of cardiac troponin T			
	Low 0.002-0.004 µg/L N=1584	Middle 0.005-0.009 µg/L N=1972	High 0.010-1.840 µg/L N=1851	P-value
Demographics				
Age (years), mean (SD)	74.37 (3.18)	75.17 (3.11)	76.27 (3.44)	<0.001
Female, n (%)	1114 (70.3)	977 (49.5)	693 (37.4)	<0.001
Education (age left school), mean (SD)	15.14 (1.99)	15.16 (2.22)	15.12 (2.15)	0.829
Pravastatin treatment, n (%)	778 (49.1)	983 (49.8)	921 (49.8)	0.898
Vascular risk factors				
History of hypertension, n (%)	952 (60.2)	1202 (61.0)	1199 (64.8)	0.011
History of diabetes mellitus, n (%)	120 (7.6)	209 (10.6)	247 (13.3)	<0.001
History of stroke or TIA, n (%)	147 (9.3)	207 (10.5)	248 (13.4)	<0.001
History of myocardial infarction, n (%)	140 (8.8)	252 (12.8)	330 (17.8)	<0.001
History of vascular disease, n (%)	620 (39.1)	861 (43.7)	916 (49.5)	<0.001
Current smoker, n (%)	451 (28.5)	535 (27.1)	441 (23.8)	0.006
Body mass index (kg/m$^{2)}$, mean (SD)*	26.12 (4.38)	26.82 (4.00)	27.41 (4.30)	<0.001
Total cholesterol (mmol/L), mean (SD)*	5.71 (0.80)	5.65 (0.89)	5.66 (0.86)	0.112
High density lipoprotein* (mmol/L), mean (SD)	1.29 (0.40)	1.28 (0.44)	1.27 (0.43)	0.404
Low density lipoprotein* (mmol/L), mean (SD)	3.83 (0.80)	3.76 (0.89)	3.77 (0.86)	0.083
Systolic blood pressure (mmHg), mean (SD)*	151.17 (22.29)	155.11 (21.32)	157.39 (22.37)	<0.001
Diastolic blood pressure (mmHg), mean (SD)*	82.76 (11.94)	84.02 (11.55)	84.44 (11.62)	<0.001
Blood pressure lowering medication, n (%)				
Diuretics	572 (36.1)	755 (38.3)	851 (46.0)	<0.001
ACE-inhibitors	185 (11.7)	292 (14.8)	409 (22.1)	<0.001
Beta-blockers	408 (25.8)	523 (26.5)	462 (25.0)	0.544
Calcium channel blockers	413 (26.1)	475 (24.1)	476 (25.7)	0.334
ApoE genotype				0.783
E2 carriers	14 (0.9)	12 (0.6)	9 (0.5)	
E3/E3 carries	984 (62.1)	1226 (62.2)	1123 (60.7)	
E4 carriers	389 (24.6)	482 (24.4)	452 (24.4)	
Biochemistry, mean (SD)				
eGFR (ml/min/m1.73m^2)	61.07 (14.33)	60.86 (14.65)	58.24 (14.63)	<0.001
NT-proBNP level (ng/L)* #	159.39 (549.23)	230.77 (525.78)	475.51 (542.09)	<0.001
Fasting glucose level (mmol/L)*^	5.41 (1.49)	5.45 (1.25)	5.49 (1.58)	0.362

Abbreviations: SD, standard deviation; n, number; TIA, transient ischemic attack; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide. P-values were calculated using the continuous value of the square root of troponin levels for continuous variables and Chi-squared tests for categorical variables.
*adjusted p-value for age and sex #measured at 6 months   ^missing data for n=716 participants

Figure 2 shows the association of cTnT with cognitive function at baseline in participants with low (<200 ng/L) and high (≥ 200 ng/L) NT-proBNP levels. For participants with low NT-proBNP levels, we observed that higher cTnT was associated with worse cognitive function on the Stroop test, Letter-Digit Coding test, immediate Picture-Word Learning test and delayed Picture-Word Learning test (all p-values <0.05). Although this trend was less marked on all four cognitive function tests for participants with high NT-proBNP levels, there was no significant difference between low and high NT-proBNP levels in the association of cTnT with cognitive function (all p-values for interaction>0.05). Table 3 shows the longitudinal association of cTnT with cognitive decline in participants with low and high NT-proBNP levels. Again, a trend was found showing that in participants with low NT-proBNP levels, higher levels of cTnT were associated with steeper decline on all four cognitive function tests. This association remained significant for the immediate Picture-Word Learning test. However, this difference between low and high NT-proBNP levels in the association of cTnT with cognitive function was not significant (all p-values for interaction>0.05). When further adjusting for continuous levels of NT-proBNP and when stratifying our analyses according to the less conservative cut-off of NT-proBNP < and ≥ 400 ng/L, the association between cTnT and cognitive function and decline remained essentially the same (supplemental tables 2 and 3). Furthermore, participants with a history of diabetes mellitus had a steeper decline in immediate Picture-Word learning test. In addition, the observed associations of cTnT with cognitive function and decline did not materially change when excluding participants with heart failure hospitalization during follow-up (n=205) and participants who used loop diuretics (n=588) (supplemental table 4).

6

Furthermore, we investigated whether incident cardiovascular diseases might confound our results, by performing sensitivity analyses in which we separately excluded participants who, during follow-up, had 1) a stroke or TIA (n=378); 2) coronary events (n=575); 3) atrial fibrillation (n=507); 4) cardiovascular events (n=872); and finally 5) a sign of previous myocardial infarction (defined as pathological Q or QS-waves on their baseline ECG) (n=1211). In general, exclusion of these participants did not affect the association of cTnT with cognitive function and decline (supplemental tables 5 and 6). In addition, we investigated the association of normal values of cTnT with cognitive function and decline, by excluding participants with cTnT>0.014 µg/L, conform 99th percentile (n=1002). Results from these analyses did not essentially differ (supplemental table 7). Furthermore, when we adjusted our results for use of diuretics and ace-inhibitors, our results remained broadly similar (data not shown).
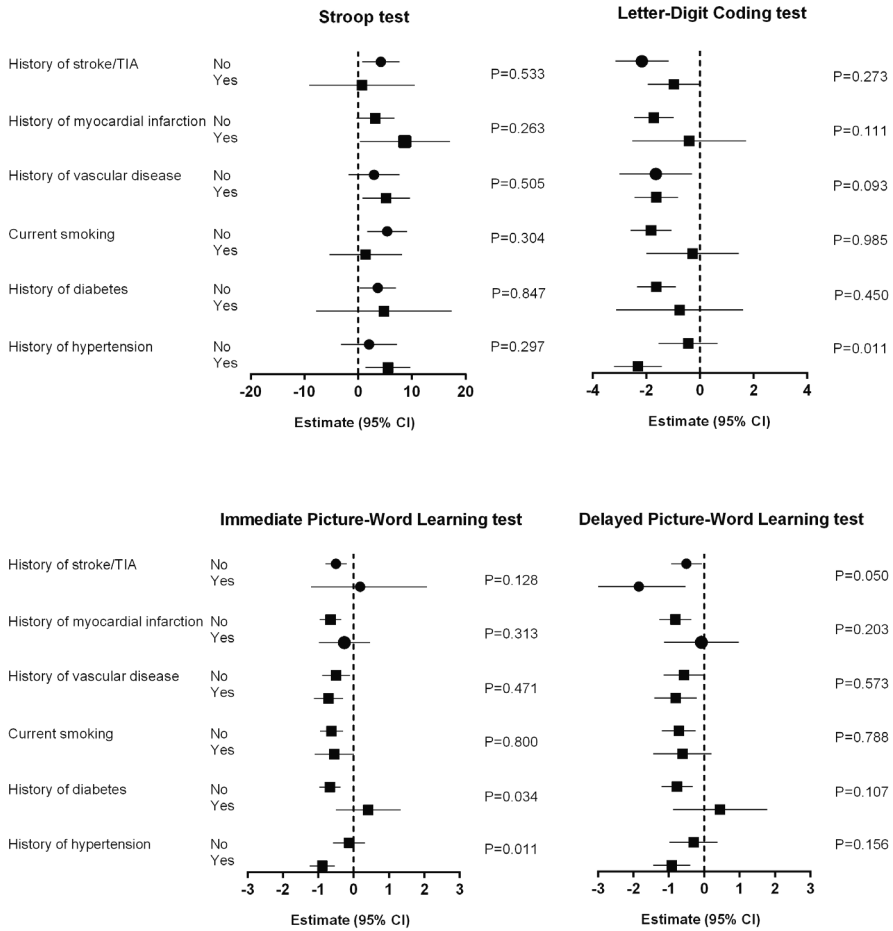
Figure 1. Association of cardiac troponin T with cognitive decline during follow-up, stratified by cardiovascular diseases and risk factors

Data represent mean annual change (95% confidence interval) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive test, stratified by cardiovascular diseases. Higher annual change indicates less decline in cognitive function over time; expect for the Stroop test, where higher annual change means more decline in cognitive function over time. P-values were calculated using the interaction term of cardiovascular disease, square root of cardiac troponin T, and time. They represent the statistical difference in annual change in cognitive function between participants with and without cardiovascular disease or risk factors. Adjusted for age, sex, country, education, treatment with pravastatin or placebo and test version where appropriate.

Low NT-proBNP (< 200 ng/L)　　　　　　**High NT-proBNP (≥ 200 ng/L)**
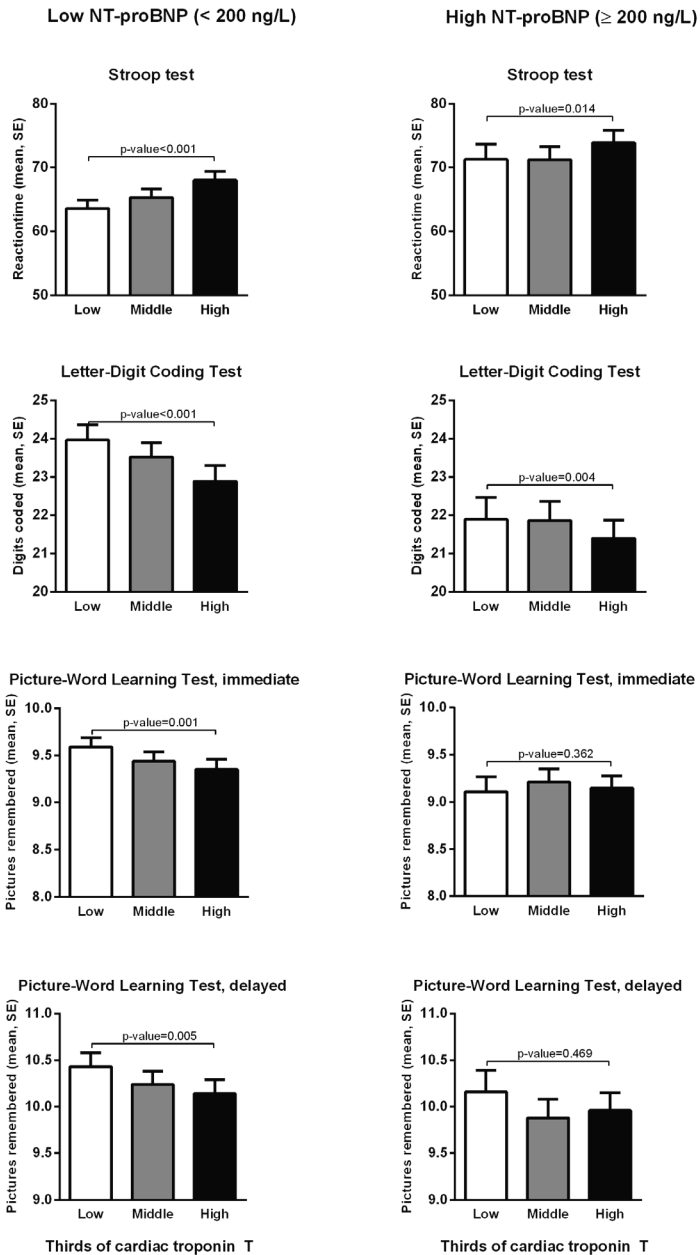

Figure 2. Association of cardiac troponin T with baseline cognitive function, stratified by NT-proBNP
Abbreviations: SE, standard error. Higher scores indicate better cognitive performance; expect for the Stroop test, where a higher score indicates worse performance.

Table 2. Association of cardiac troponin T with cognitive function at baseline and during follow-up

Cognitive tests (mean, SE)		Thirds of cardiac troponin T			
		Low 0.002-0.004 µg/L	Middle 0.005-0.009 µg/L	High 0.010-1.840 µg/L	
					P-value*
Stroop, seconds	Baseline score	65.91 (1.16)	67.26 (1.10)	70.09 (1.10)	<0.001
	Annual change	0.34 (0.12)	0.59 (0.11)	1.06 (0.12)	0.013
LDCT, digits coded	Baseline score	23.36 (0.32)	22.94 (0.30)	22.28 (0.30)	<0.001
	Annual change	-0.29 (0.03)	-0.34 (0.02)	-0.46 (0.03)	<0.001
PLTi, pictures remembered	Baseline score	9.45 (0.09)	9.36 (0.08)	9.28 (0.08)	0.002
	Annual change	0.01 (0.01)	-0.02 (0.01)	-0.06 (0.01)	<0.001
PLTd, pictures remembered	Baseline score	10.31 (0.12)	10.09 (0.12)	10.05 (0.11)	0.013
	Annual change	-0.03 (0.01)	-0.06 (0.01)	-0.12 (0.02)	0.001

Data represent model-based adjusted means (standard error) of each cognitive function test concerning the baseline associations. For the longitudinal analyses, data represent model-based adjusted mean annual change (standard error) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive function test. Cardiac troponin T was measured after 6 months of follow-up. *Adjusted p-values were calculated using the continuous value of the square root of troponin levels. Abbreviations: SE, standard error; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed.

Table 3. Association of cardiac troponin T and NT-proBNP with cognitive decline during follow-up

NT-proBNP	Thirds of cardiac troponin T			
	Low 0.002-0.004 µg/L	Middle 0.005-0.009 µg/L	High 0.010-1.840 µg/L	P-value*
Low (<200 ng/L)	N=1254	N=1279	N=826	
Stroop, seconds	0.27 (0.13)	0.64 (0.13)	0.71 (0.17)	0.076
LDCT, digits coded	-0.27 (0.03)	-0.34 (0.03)	-0.38 (0.04)	0.287
PLTi, pictures remembered	0.01 (0.01)	-0.01 (0.01)	-0.05 (0.02)	0.001
PLTd, pictures remembered	-0.02 (0.02)	-0.06 (0.02)	-0.09 (0.02)	0.176
High (≥ 200 ng/L)	N=330	N=693	N=1025	
Stroop, seconds	0.59 (0.29)	0.45 (0.21)	1.48 (0.19)	0.540
LDCT, digits coded	-0.37 (0.06)	-0.34 (0.04)	-0.53 (0.04)	0.001
PLTi, pictures remembered	0.01 (0.02)	-0.04 (0.02)	-0.07 (0.02)	0.070
PLTd, pictures remembered	-0.06 (0.04)	-0.06 (0.03)	-0.14 (0.02)	0.120

Abbreviations: SE, standard error; n, number; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning test, immediate; PLTd, Picture-Word Learning test, delayed. Data represent model-based adjusted mean annual change (standard error) per 1 square root (ng/L) increase of cardiac troponin T for each cognitive function test. Cardiac troponin T and NT-proBNP were measured after 6 months of follow-up. *Adjusted p-values were calculated using the interaction term of time x square root of troponin levels.

Discussion

In this large prospective cohort study, we found that among 5,407 older men and women, higher levels of hs-cTnT were associated with worse cognitive function at baseline and steeper cognitive decline. Results were independent of cardiovascular diseases or risk factors. Similar trends were observed in participants with lower NT-proBNP levels below levels which might be indicative of clinical heart failure.

Our findings are in line with a previous study by Schneider et al., investigating the association of hs-cTnT with cognitive function.(7) This prospective follow-up study, which included 9,472 community-dwelling participants with a mean age of 63 years, showed that higher levels of hs-cTnT were associated with lower scores on a digit symbol substitution test and a word fluency test, indicating worse cognitive function. Furthermore, during a median follow-up period of 13 years, higher baseline concentrations of hs-cTnT were associated with an increased risk for dementia hospitalizations.(7) Although these results did not appreciably alter when analyses were additionally adjusted for left ventricular hypertrophy and carotid intima media thickness, no information on NT-proBNP was available. In addition, this study did not consider apolipoprotein E4 genotype, a well-known risk factor for the development of cognitive impairment, as a potential confounder in the association between hs-cTnT and cognitive function.(18) Another difference between the present study and the study by Schneider et al. was the cognitive test battery. Both studies used measures of delayed word memory and the digit symbol substitution test, which measures processing speed and executive function. The only difference is that the ARIC study used the Word Fluency Test, whereas we used the Stroop test, although both measure executive function and processing speed. We think it is unlikely that this difference in choice of tests is significant enough to make different inferences about the outcome. To our knowledge, our study is the first examining the association of hs-cTnT and cognitive function in older adults at high cardiovascular risk, which tested the potential role of cardiovascular diseases, risk factors and NT-proBNP, and adjusted for apolipoprotein E4 genotype as well.

Several mechanisms can be proposed to explain the association of cTnT with worse cognitive function and steeper cognitive decline. First, cTnT might be a reflection of underlying myocardial injury as well as cerebral damage, rather than being causally related. It is well known that cardiovascular and cerebrovascular disease share the same risk factors, including hypertension, diabetes mellitus and smoking. These risk factors for cognitive decline clearly also cause myocardial disease, resulting in increased levels of cTnT. The finding that

6

participants with a history of hypertension and diabetes mellitus had a steeper decline on Picture-Word immediate test in stratified analyses, further supports this hypothesis. Second, although our results were found in participants without NYHA functional class stage III or IV, we do not have echocardiography data to rule out the possibility that higher levels of cTnT indicate suboptimal cardiac functioning with subsequent decreased cardiac output and cerebral hypoperfusion.(19, 20) Cerebral hypoperfusion has previously been associated with a higher risk of dementia.(21) However, this explanation is less likely since in the current study, participants with NT-proBNP levels <200 ng/L showed the same results, and additional adjustment for NT-proBNP levels did not change the results. Third, cTnT might have a direct effect in the brain, causing decreased cerebral function. However, no evidence has been provided for this explanation yet. Fourth, although it is generally believed that cTnT is only expressed in striated muscle cells, animal studies have revealed expression of troponin proteins, including troponin T, in smooth muscle cells of rats and mice as well.(22, 23) In addition, a recent report has shown the existence of cTnT in vascular smooth muscle cells of humans, and also found that cTnT contributes to calcium-mediated contraction of smooth muscle cells in mice experiments.(24) Although it has been reported that cTnT is highly specific for cardiomyocytes, these recent findings suggest that cTnT might also be a reflection of smooth muscle cell involvement.(24) Higher levels of cTnT may therefore indicate vascular smooth muscle cell damage in an early stage, before the manifestation of clinical or even subclinical diseases. This might also explain the observation that higher levels of cTnT are associated with subclinical brain disease, including silent brain infarcts and white matter hyperintensities.(5) Speculatively, cTnT is not only released by cardiomyocytes but also by smooth muscle cells in the brain vasculature, and may therefore mark structural brain damage as a cause of cognitive decline.

The magnitude of the association between cTnT and cognitive decline we report, is comparable in magnitude to associations of known risk factors of cognitive decline, such as apolipoprotein E4 carriership, smoking status and history of diabetes, indicating that the effects are clinically relevant.

A limitation of this study might be that all participants had cardiovascular diseases or risk factors thereof, which might restrict the extrapolation of our findings to a general population of older individuals. However, at the same time this is an advantage of our study, since it allows us to perform several sensitivity analyses to investigate the influence of cardiovascular diseases and risk factors on the association between cTnT and cognitive function. Second, although we adjusted our analyses for potential confounders, it is uncertain if this

fully accounts for the differences between the troponin groups. In addition, there might still be other factors which we did not consider in our analyses. Furthermore, the lack of extensive information on cardiac functioning is a weakness of our study. Strength of this study is the large sample size of 5,407 participants, who all underwent repeated extensive neuropsychological examination including four different cognitive function tests, during a mean follow-up period of 3.2 years, and, critically, inclusion and adjustment for NT-proBNP measures. Furthermore, cTnT measurements were performed using a high-sensitivity assay, which can detect 10-fold lower concentrations than the usual assay, and therefore allows detection of already very minor damage of the myocardial tissue.

Higher levels of hs-cTnT associate with worse cognitive function and steeper cognitive decline in older adults independent of cardiovascular diseases and risk factors and NT-proBNP.

6

References

1. Gravning J, Askevold ET, Nymo SH, Ueland T, Wikstrand J, McMurray JJ, Aukrust P, Gullestad L, Kjekshus J. Prognostic effect of high-sensitive troponin T assessment in elderly patients with chronic heart failure: results from the CORONA trial. *Circ Heart Fail* 2014;7(1):96-103.
2. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011;123(13):1367-1376.
3. Hochholzer W, Valina CM, Stratz C, Amann M, Schlittenhardt D, Buttner HJ, Trenk D, Neumann FJ. High-sensitivity cardiac troponin for risk prediction in patients with and without coronary heart disease. *Int J Cardiol* 2014;176(2):444-449.
4. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011;42(9):2672-2713.
5. Dadu RT, Fornage M, Virani SS, Nambi V, Hoogeveen RC, Boerwinkle E, Alonso A, Gottesman RF, Mosley TH, Ballantyne CM. Cardiovascular biomarkers and subclinical brain disease in the atherosclerosis risk in communities study. *Stroke* 2013;44(7):1803-1808.
6. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010;9(7):689-701.
7. Schneider AL, Rawlings AM, Sharrett AR, Alonso A, Mosley TH, Hoogeveen RC, Ballantyne CM, Gottesman RF, Selvin E. High-sensitivity cardiac troponin T and cognitive function and dementia risk: the atherosclerosis risk in communities study. *Eur Heart J* 2014.
8. Jefferson AL, Beiser AS, Himali JJ, Seshadri S, O'Donnell CJ, Manning WJ, Wolf PA, Au R, Benjamin EJ. Low Cardiac Index is Associated with Incident Dementia and Alzheimer's Disease: The Framingham Heart Study. *Circulation* 2015.
9. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013;9(1):63-75.
10. Wijsman LW, Sabayan B, van VP, Trompet S, de RW, Poortvliet RK, van Peet PG, Gussekloo J, Jukema JW, Stott DJ, Sattar N, Ford I, Westendorp RG, de Craen AJ, Mooijaart SP. N-terminal pro-brain natriuretic peptide and cognitive decline in older adults at high cardiovascular risk. *Ann Neurol* 2014;76(2):213-222.
11. Daniels LB, Laughlin GA, Kritz-Silverstein D, Clopton P, Chen WC, Maisel AS, Barrett-Connor E. Elevated natriuretic peptide levels and cognitive function in community-dwelling older adults. *Am J Med* 2011;124(7):670-678.
12. Kerola T, Nieminen T, Hartikainen S, Sulkava R, Vuolteenaho O, Kettunen R. B-type natriuretic peptide as a predictor of declining cognitive function and dementia--a cohort study of an elderly general population with a 5-year follow-up. *Ann Med* 2010;42(3):207-215.
13. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, Ford I, Jukema JW, Hyland M, Gaw A, Lagaay AM, Perry IJ, MacFarlane PW, Meinders AE, Sweeney BJ, Packard CJ, Westendorp RG, Twomey C, Stott DJ. The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. *Am J Cardiol* 1999;84(10):1192-1197.
14. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, MacFarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360(9346):1623-1630.
15. National Institute for Health and Clinical Excellence. Chronic Heart Failure - national clinical guideline for diagnosis and management in primary and secondary care. 2010.
16. Houx PJ, Shepherd J, Blauw GJ, Murphy MB, Ford I, Bollen EL, Buckley B, Stott DJ, Jukema W, Hyland M, Gaw A, Norrie J, Kamper AM, Perry IJ, MacFarlane PW, Meinders AE, Sweeney BJ, Packard CJ, Twomey C, Cobbe SM, Westendorp RG. Testing cognitive function in elderly

populations: the PROSPER study. PROspective Study of Pravastatin in the Elderly at Risk. *J Neurol Neurosurg Psychiatry* 2002;73(4):385-389.

17. Trompet S, van VP, de Craen AJ, Jolles J, Buckley BM, Murphy MB, Ford I, MacFarlane PW, Sattar N, Packard CJ, Stott DJ, Shepherd J, Bollen EL, Blauw GJ, Jukema JW, Westendorp RG. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *J Neurol* 2010;257(1):85-90.

18. Sadigh-Eteghad S, Talebi M, Farhoudi M. Association of apolipoprotein E epsilon 4 allele with sporadic late onset Alzheimer`s disease. A meta-analysis. *Neurosciences (Riyadh)* 2012;17(4):321-326.

19. Mishra RK, Li Y, Ricardo AC, Yang W, Keane M, Cuevas M, Christenson R, deFilippi C, Chen J, He J, Kallem RR, Raj DS, Schelling JR, Wright J, Go AS, Shlipak MG. Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC]). *Am J Cardiol* 2013;111(3):432-438.

20. Zuccala G, Onder G, Pedone C, Carosella L, Pahor M, Bernabei R, Cocchi A. Hypotension and cognitive impairment: Selective association in patients with heart failure. *Neurology* 2001;57(11):1986-1992.

21. Zuccala G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. *J Neurol Neurosurg Psychiatry* 1997;63(4):509-512.

22. Moran CM, Garriock RJ, Miller MK, Heimark RL, Gregorio CC, Krieg PA. Expression of the fast twitch troponin complex, fTnT, fTnI and fTnC, in vascular smooth muscle. *Cell Motil Cytoskeleton* 2008;65(8):652-661.

23. Pinet F, Poirier F, Fuchs S, Tharaux PL, Caron M, Corvol P, Michel JB, Joubert-Caron R. Troponin T as a marker of differentiation revealed by proteomic analysis in renal arterioles. *FASEB J* 2004;18(3):585-586.

24. Kajioka S, Takahashi-Yanaga F, Shahab N, Onimaru M, Matsuda M, Takahashi R, Asano H, Morita H, Morimoto S, Yonemitsu Y, Hayashi M, Seki N, Sasaguri T, Hirata M, Nakayama S, Naito S. Endogenous cardiac troponin T modulates Ca(2+)-mediated smooth muscle contraction. *Sci Rep* 2012;2:979.

6

Part III

Towards prevention of cognitive impairment
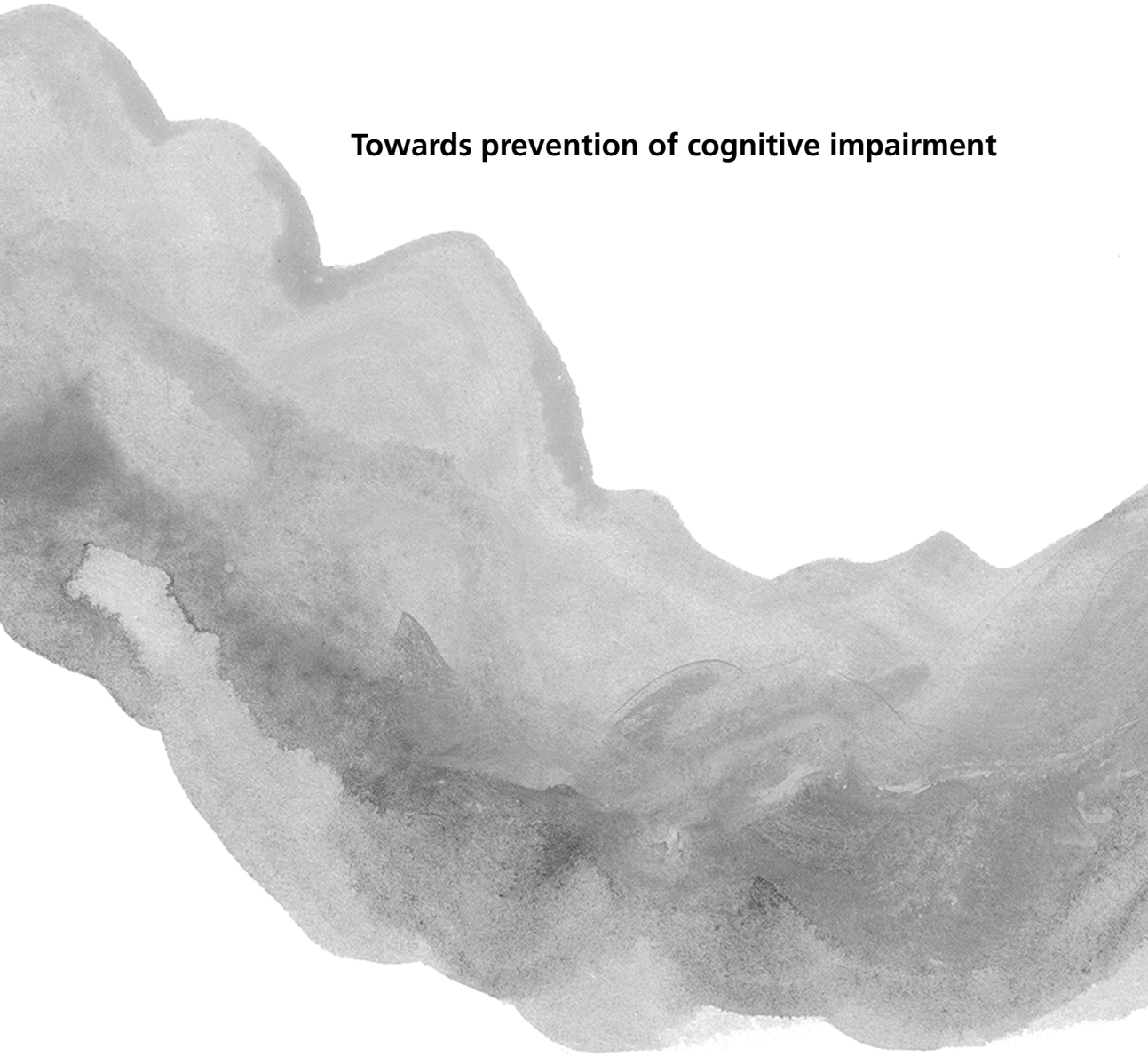
Chapter 7

Evaluation of the use of home blood pressure measurement using mobile phone-assisted technology: the iVitality proof-of-principle study

Liselotte W Wijsman, Edo Richard, Ricardo Cachucho, Anton JM de Craen,
Susan Jongstra, Simon P Mooijaart

Abstract

Background Mobile phone-assisted technologies provide the opportunity to optimize the feasibility of long-term blood pressure (BP) monitoring at home, with the potential of large-scale data collection. In this proof-of-principle study, we evaluated the feasibility of home BP monitoring using mobile phone-assisted technology, by investigating 1) the association between study center and home BP measurements; 2) adherence to reminders on the mobile phone to perform home BP measurements; and 3) referrals, treatment consequences and BP reduction after a raised home BP was diagnosed.

Methods We used iVitality, a research platform that comprises a Website, a mobile phone-based app, and health sensors, to measure BP and several other health characteristics during a six-month period. BP was measured twice at baseline at the study center. Home BP was measured on four days during the first week, and thereafter, at semimonthly or monthly intervals, for which participants received reminders on their mobile phone. In the monthly protocol, measurements were performed during two consecutive days. In the semimonthly protocol, BP was measured at one day.

Results We included 151 participants (mean age (standard deviation) 57.3 (5.3) years). BP measured at the study center was systematically higher when compared with home BP measurements (mean difference systolic BP (standard error) 8.72 (1.08) and diastolic BP 5.81 (0.68) mm Hg, respectively). Correlation of study center and home measurements of BP was high (R=0.72 for systolic BP and 0.72 for diastolic BP, both p-values<0.001). Adherence was better in participants measuring semimonthly (71.4%) compared with participants performing monthly measurements (64.3%, p=0.008). During the study, 41 (27.2%) participants were referred to their general practitioner because of a high BP. Referred participants had a decrease in their BP during follow-up (mean difference final and initial (standard error) -5.29 (1.92) for systolic BP and -2.93 (1.08) for diastolic BP, both p-values<0 .05).

Conclusion Mobile phone-assisted technology is a reliable and promising method with good adherence to measure BP at home during a six-month period. This provides a possibility for implementation in large-scale studies and can potentially contribute to BP reduction.

Introduction

High blood pressure contributes to the global burden of disease, accounting for 9.4 million deaths per year.(1) With a prevalence as high as 78% among the 65-plus population in Europe, it is one of the most common chronic conditions in primary care.(2) Although the prevalence is predicted to further increase over the coming years, only 70% of all hypertensive patients are aware of having hypertension.(3, 4) In spite of widely available effective ways to reduce blood pressure, rates of hypertension control are still far from optimal.(2, 5-7) In one study including 5,296 participants, blood pressure control was achieved in only 30% of patients, who were aged 60 years or older.(8)

The increasing availability of the Internet, mobile phones, and health sensors provides the potential to interactively administer health interventions at home. Recent surveys show that at least 75% of the European population uses the Internet on a regular basis, with almost half of them using a mobile phone to access the Internet (smartphone).(9) Adults aged 65 years and older are the fastest-growing group of Internet users.(10) Older adults have a high interest in self-assessment health tools.(11) This enables people to measure blood pressure at home, with the potential of direct feedback and treatment adjustments. Furthermore, previous studies show that home blood pressure measurements, when compared with clinic blood pressure measurements, are in fact a stronger prognostic indicator of cardiovascular events.(12-14) It could therefore be effective to identify patients at risk of cardiovascular events and thereby prevent the occurrence of cardiovascular complications. (12, 15) In addition, it provides a potential for large-scale implementation and data collection. However, data on feasibility of long-term home blood pressure measurements, using the Internet and mobile phones, are scarce.(16-18)

The aim of this proof-of-principle study was to evaluate home blood pressure measurements using mobile phone-assisted technology. For this, we investigated 1) the association between study center and home blood pressure; 2) the adherence to perform home blood pressure measurements according to a monthly or semimonthly measurement protocol; and 3) referrals, treatment consequences and blood pressure reduction after a raised home blood pressure was diagnosed.

7

Methods

Study design

iVitality is a Web-based research platform that consists of a Website, a mobile phone-based app, and sensors that are connected with or already integrated in the mobile phone to measure blood pressure.(19) This iVitality study is a proof-of-principle study in which participants were randomized to perform home blood pressure measurements according to a monthly or semimonthly measurement protocol, during a period of six months. The different measurement protocols are described in more detail in the "Follow-Up Measurements" paragraph below.

We chose to perform this study in people with a parental history of dementia because 1) they have a higher risk of both hypertension and dementia, making them a potentially suitable target group for large-scale preventive studies and 2) they are highly motivated to participate in preventive studies.(13, 14, 15) Other inclusion criteria were 1) age 50 years and older; 2) familiar with and in possession of a mobile phone with iOS or Android (version, 2.3.3 or higher) software; and 3) motivated to measure health characteristics at home several times a month, during a six-month period. Exclusion criteria were a medical diagnosis of dementia and/or any other cognitive disorder and a medical history of stroke and/or transient ischemic attack.

Participants were recruited through advertisements in memory outpatient clinics, nursing homes, general practices, and on the Website, and in the newsletter of the Dutch Alzheimer Foundation (Alzheimer-Nederland). If all of the inclusion criteria were met, participants received detailed study information in print. They visited the study center at Leiden University Medical Center or Academic Medical Center Amsterdam at baseline, where they received information about the study and baseline measurements were performed by a study physician or research nurse. Written informed consent was obtained from all participants. The medical ethical committee of Leiden University Medical Center, the Netherlands, approved the study.

Baseline measurements

Enrolment and follow-up took place from September 2013 to January 2015. In preparation for the first visit to the study center, all participants completed a Web-based questionnaire on education, medical history, and medication use. During the visit to the study center, detailed information about the iVitality app and instructions on how to use it were

given. History of hypertension and medication use was self-reported. Blood pressure was measured twice at baseline on the upper left arm, in sitting position with a fully automatic electronic blood pressure monitor. Participants were instructed in the use of the home blood pressure monitor.

Follow-up measurements

During a six-month period, participants received automatic messages on preprogrammed days at self-chosen time points on their mobile phone, which reminded them to measure blood pressure. Participants with an Android mobile phone used an A&D blood pressure monitor (A&D Company, Ltd; model UA 767 Bluetooth) which was connected to the mobile phone and automatically transferred the results to the iVitality app by Bluetooth.(20) Participants with an iPhone used an OMRON (OMRON Healthcare Company, Ltd, model M6W and M6AC (HEM-7322-E)); they manually typed their blood pressure values and heart rate in the iVitality app.(21) During the first week and the last week of the study, all participants performed blood pressure measurements according to the guideline of the European Society of Hypertension.(13) In short, participants were asked to measure their blood pressure twice at both morning and evening, at least for four days during the first week of the study, with day one being discarded.(13) For the rest of the study period, blood pressure was measured according to two different study protocols, to which participants were randomly assigned by a computerized program at baseline. Randomization was performed in a 1:1 manner stratified for sex. In the monthly protocol, participants performed measurements in the morning and evening of two consecutive days. In the semimonthly protocol, blood pressure was measured in the morning and evening of only one day. Blood pressure was measured twice at each measurement; the mean of both measurements was used. Reminders to perform blood pressure measurements were sent the evening before the measurement day and at the actual day on which the participant was expected to perform the blood pressure measurements. When participants did not perform their blood pressure measurements, they received a reminder the day after. This reminder was sent automatically by the Website of the iVitality research platform, and therefore, was a standardized procedure. The measured blood pressure was sent as a message to the mobile phone. Blood pressure measurements were also graphically visible in the app. Participants with a mean systolic home blood pressure above 135 mm Hg and/or 85 mm Hg for diastolic home blood pressure during these days were considered as possibly having hypertension and therefore referred to their general practitioner (GP).(13)

7

Statistical analysis

Characteristics of the study participants are reported as mean with standard deviation for continuous variables and as number with percentage for categorical variables. We used Pearson's correlation coefficient to calculate the correlation between home and study center blood pressure measurements. To investigate agreement between study center and home blood pressure measurements, we computed the mean and the difference in study center and home blood pressure measurements and visualized this in a Bland–Altman plot.

Adherence was defined as the actual performance of all blood pressure measurements within one week of the time point they were expected to perform their measurements and for which the participant received reminders through the mobile phone app. For each participant, we calculated the percentage of adherence during follow-up. Difference in adherence between the monthly and semimonthly measurement protocol was assessed using a Mann–Whitney U test. In this proof-of-principle study, only participants who completed the six-month period were used in the primary analysis. In a sensitivity analysis, we included all participants who were included at baseline.

We investigated the difference in blood pressure during the first week and the final week after six months using a paired t-test. For both blood pressure during the first week and final blood pressure, we calculated the mean values of all blood pressure measurements performed during the first and last week, with day one of both weeks being discarded. (13) All analyses were performed using SPSS (version 22.0.0, SPSS Inc., Chicago, IL, USA).

Results

Figure 1 shows the inclusion flowchart of participants. A total of 195 participants registered on the Web to participate. Of those, 27 did not meet inclusion criteria and 17 registered after recruitment had been completed because of a time lag between registration on the Web and baseline visits. Our study population therefore included 151 participants. A number of 66 (43.7%) participants were assigned to perform blood pressure measurements at a monthly interval; 85 (56.3%) participants were assigned to perform semimonthly blood pressure measurements (figure 1).

Baseline characteristics are shown in table 1. Mean age was 57.3 (standard deviation (SD) 5.3) years; 107 (70.9%) participants were female. Of all participants, 56 (37.1%) used iPhone and 59 (39.1%) used Samsung. Mean systolic and diastolic blood pressure

measured at the study center was 137.8 (SD 18.2) and 85.4 (SD 10.8) mm Hg, respectively. Participants within the monthly protocol had a higher body mass index, systolic blood pressure, and diastolic blood pressure at baseline (data not shown). A number of 32 (21.2%) participants had a history of hypertension and used antihypertensive medication, most
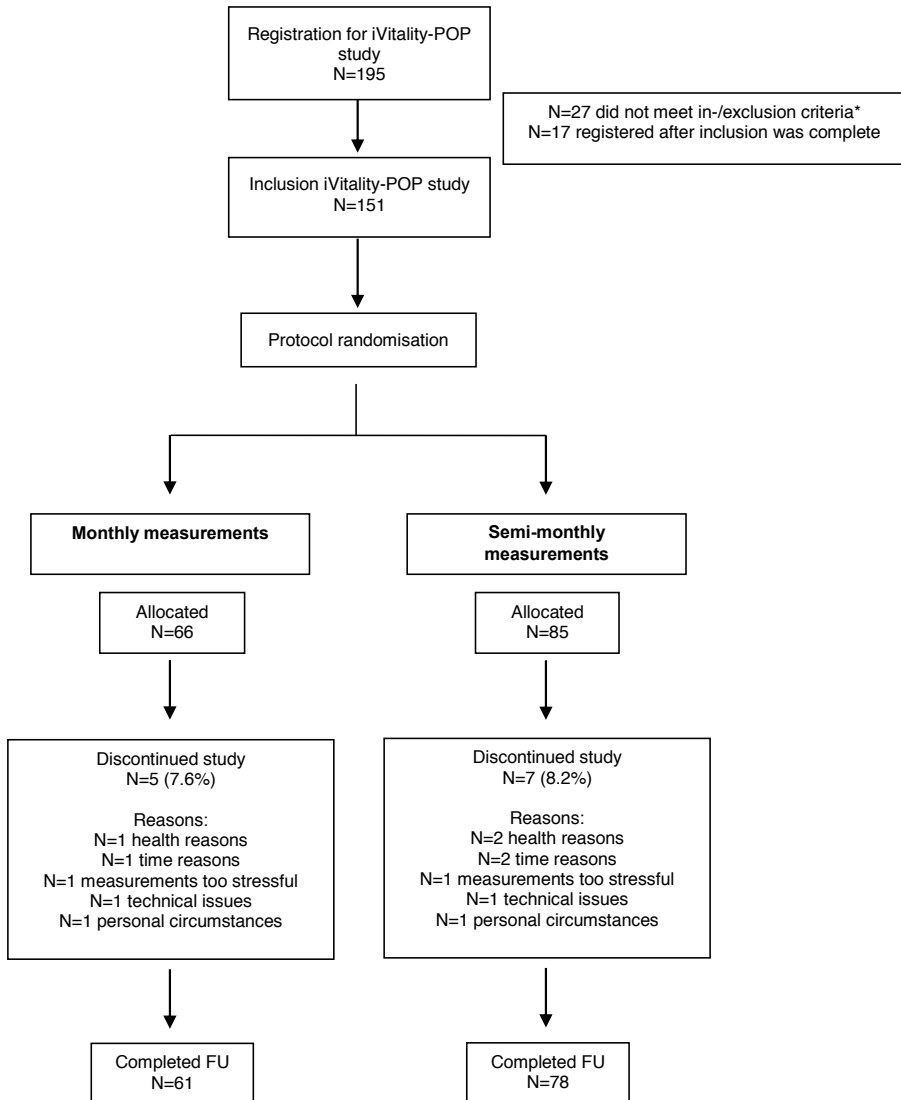

Figure 1. Flowchart of study participants
*reasons why participants did not meet in-/exclusion criteria were as follows: n=4 did not have the correct software version of the smartphone; n=6 did not have parents with dementia; n=6 were on holidays during the inclusion period; n=7 were not interested to participate after reading the study information; n=4 because of other reasons.

commonly diuretics (15 participants (46.9% of hypertensive participants)). This did not differ between the monthly and semimonthly protocol.

Table 1. Baseline characteristics of iVitality participants

	All participants N=151
Demographics	
Age (years)	57.3 (5.3)
Female, n (%)	107 (70.9%)
Body mass index	26.4 (4.0)
Highest education level, n (%)*	
Low	16 (10.6%)
Middle	44 (29.1%)
High	88 (58.3%)
Study center, n (%)	
Academic Medical Center Amsterdam	55 (36.4%)
Leiden University Medical Center	96 (63.6%)
Type of phone, n (%)	
iPhone	56 (37.1%)
Samsung	59 (39.1%)
HTC	15 (9.9%)
Other	21 (13.9%)
Blood pressure	
Systolic blood pressure (mmHg)	137.8 (18.2)
Diastolic blood pressure (mmHg)	85.4 (10.8)
Heart rate (beats per minute)	67.2 (10.2)
Vascular risk factors, n (%)	
History of hypertension	32 (21.2%)
History of diabetes mellitus	2 (1.3%)
History of MI	4 (4.6%)
History of arrhythmia	11 (7.3%)
History of heart failure	3 (2.0%)
Hypercholesterolemia	14 (9.3%)
Current smoker	14 (9.3%)
Antihypertensive medication, n (%)	
Diuretics	15 (9.9%)
Ace-inhibitors	6 (4.0%)
Beta-blockers	11 (7.3%)
Calcium antagonists	6 (4.0%)
Other	9 (6.0%)
N. of antihypertensive medication, n (%)	
One	21 (65.6%)
Two or more	11 (34.4%)

Data represent mean (standard deviation) unless stated otherwise. Abbreviations: n, number; MI, myocardial infarction; MMSE, mini-mental state examination. *Missing data for n=3 participants. Low: primary education, lower education, MAVO/MULO. Intermediate: high general secondary education (HAVO, HBS), Preparatory Scientific Education (VWO), intermediate professional education (MBO). High: higher professional education (HBO), academic education (university).

The association between study center and home blood pressure during the first week is shown in figure 2. The correlation between study center and home measurements was high for both systolic (R=0.72, p-value<0.001) and diastolic blood pressure (R=0.72, p-value<0.001, panel A). Systolic blood pressure at the study center was systematically 8.72 mm Hg higher (standard error (SE) 1.08) and diastolic blood pressure was 5.81 (0.68) mm Hg higher when compared with home blood pressure measurements (panel B). The Bland–Altman plot shows that the difference between the measurements was randomly distributed over the mean of the measurements, indicating that there was no systematic bias in agreement between the study center and home measurements. The 95% limits of
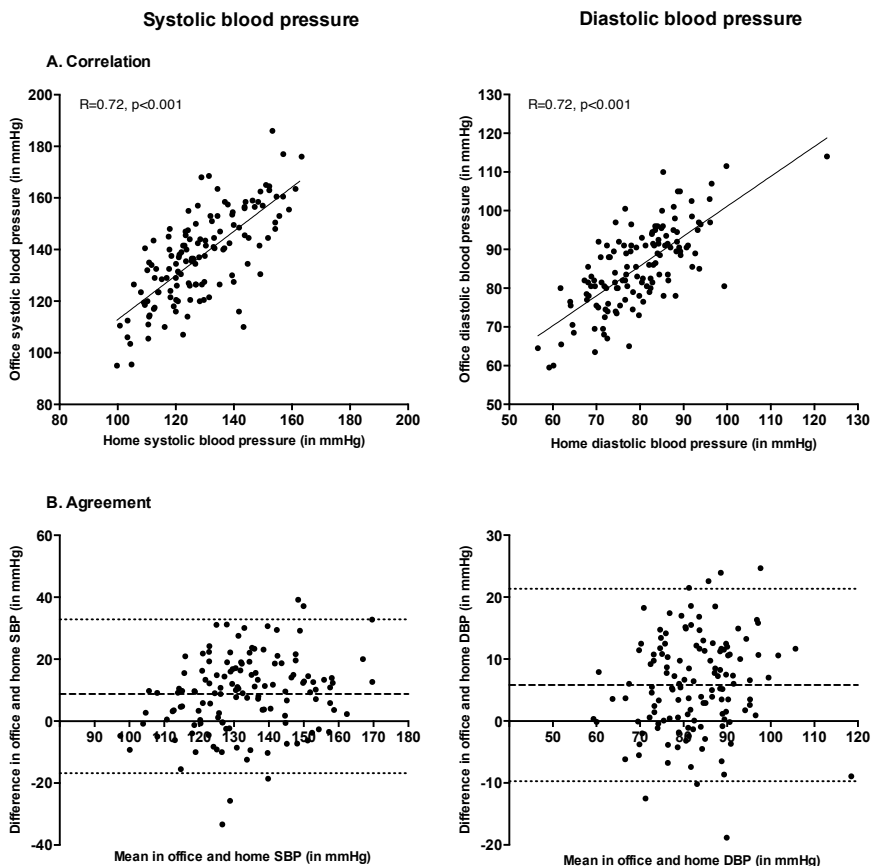
Figure 2. Association between blood pressure measurements at home and in the study center
Abbreviations: R, Pearson's correlation coefficient; SBP, systolic blood pressure; DBP, diastolic blood pressure. Panel A shows the home blood pressure (mean of two consecutive measurements in both morning and evening at day 2, 3 and 4, x-axis) and corresponding study center blood pressure measurements (mean value of two consecutive measurements, y-axis) for each participant. Panel B shows the agreement between study center and home systolic and diastolic blood pressure measurements.

agreement for the comparison were –16.82 to 32.82 mm Hg for systolic blood pressure and –9.71 to 21.33 mm Hg for diastolic blood pressure.

Adherence to the monthly and semimonthly blood pressure measurement protocols is shown in figure 3. In total, 12 participants did not complete follow-up: 5 (7.6%) participants in the monthly measurement protocol and 7 (8.2%) participants in the semimonthly measurement protocol. Median adherence to perform blood pressure measurements was 71.4% (figure 3). Participants performing semimonthly blood pressure measurements were more adherent (median adherence 71.4%) when compared with participants performing monthly blood pressure measurements (64.3%, p-value=0.008). There was no difference in adherence between participants who entered their blood pressure measurements manually and participants who used a Bluetooth connection to transfer the measurements (data not shown). Furthermore, a sensitivity analysis in which we investigated the adherence of all 151 participants who were included at baseline, showed similar results: adherence was higher in participants who performed semimonthly blood pressure measurements (median adherence 85.7%) when compared with participants performing monthly measurements (71.4%, p-value=0.002, data not shown). Discontinuation was highest within the first weeks of follow-up for both measurement protocols.

Table 2 presents the difference in final and initial home blood pressure measurements. Among all participants, there was no difference between final and initial blood pressure, for both systolic (mean difference (SE) -1.30 (1.10) mm Hg, *P*=.240) and diastolic (-0.90 (0.51)
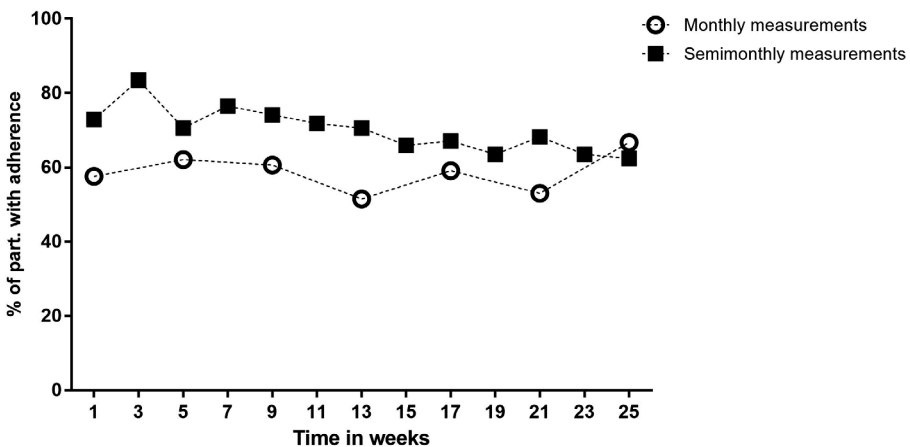

Figure 3. Adherence of participants to monthly and semi-monthly measurement protocol
Data represent the percentage of participants who are adherent to perform the expected blood pressure measurements.

Table 2. Difference between first and last home blood pressure measurement

	Systolic blood pressure				Diastolic blood pressure			
	First	Last	Diff. (SE)	P-value	First	Last	Diff. (SE)	P-value
All participants*	128.22 (1.45)	126.92 (1.31)	-1.30 (1.10)	0.240	79.30 (0.90)	78.40 (0.73)	-0.90 (0.51)	0.081
By protocol								
Monthly measurements, n=45	128.23 (2.25)	128.15 (2.25)	-0.08 (1.98)	0.968	80.08 (1.38)	78.87 (1.18)	-1.21 (0.84)	0.156
Bi-weekly measurements, n=58	128.20 (1.91)	125.96 (1.54)	-2.25 (1.20)	0.068	78.70 (1.20)	78.02 (0.92)	-0.67 (0.64)	0.304
By referral								
Not referred, n=78	122.61 (1.27)	122.59 (1.28)	-0.02 (1.29)	0.987	76.71 (0.91)	76.45 (0.80)	-0.25 (0.56)	0.654
Referred, n=25	145.72 (1.96)	140.43 (1.91)	-5.29 (1.92)	0.011	87.22 (1.66)	84.44 (1.02)	-2.93 (1.08)	0.012
Referred and visited GP, n=23	146.02 (2.03)	140.98 (2.00)	-5.04 (2.07)	0.023	87.22 (1.66)	84.44 (1.02)	-2.79 (1.17)	0.027
Referred and changed/started BP med., n=5	153.73 (3.93)	141.62 (4.83)	-12.12 (6.65)	0.142	90.62 (2.64)	83.79 (1.55)	-6.83 (2.29)	0.080

Data represent the mean difference (standard error) in mmHg of final and initial blood pressure. Abbreviations: Diff, difference; SE, standard error; n, number; GP, general practitioner; BP, blood pressure. *missing data for n=48 participants

7

mm Hg, p-value=0.081) blood pressure. There were 41 out of 151 (27.2%) participants who were referred to their GP because of a high blood pressure, of whom 35 (85.2%) actually visited their GP. In referred participants, blood pressure decreased significantly during the study, both systolic (mean difference (SE) -5.29 (1.92) mm Hg, p-value=0.011) and diastolic (-2.93 (1.08) mm Hg, p-value=0.012). Furthermore, no difference was found between final and initial blood pressure for both systolic and diastolic blood pressure between the monthly and semimonthly protocol (data not shown). In 7 out of 41 (17.1%) participants, blood pressure lowering medication had been started or changed.

Discussion

This proof-of-principle study, in which we evaluated the feasibility of home blood pressure measurements during a six-month intervention period using mobile phone-assisted technology, has three main findings. First, study center and home blood pressure were highly correlated, although blood pressure measured at the study center was systematically higher when compared with home blood pressure. Second, adherence of all participants to perform blood pressure measurements was high and persisted during six months with better adherence in participants measuring semimonthly compared with participants who performed monthly measurements. Third, in participants who were referred to their GP because of a high blood pressure, systolic and diastolic blood pressure decreased significantly during the study, especially for those who started medication.

Our finding that systolic and diastolic blood pressure at the study center was systematically higher when compared with home blood pressure measurements is in line with previous literature.(22) A well-known explanation for this is the "white-coat effect", meaning that blood pressure is higher because of stress and anxiety that patients experience during a clinical setting.(22, 23) Literature shows that home blood pressure measurements, instead of office or clinic blood pressure measurements, are in fact a stronger prognostic indicator of cardiovascular events and even have their own (lower) reference values.(12-14) A participant-level meta-analysis including 5,008 participants (mean age 57 years, not treated with antihypertensive medication), showed that in participants with an optimal office blood pressure (<120/<80 mm Hg), a 10-mm Hg higher systolic home blood pressure increased the risk of any cardiovascular event by nearly 30%.(12) In addition, previous studies on cost-effectiveness show that compared with usual care, home blood pressure monitoring is very useful for reducing health care costs. In view of the low burden of measuring and established treatment options, home blood pressure monitoring could therefore be an

important strategy to further prevent cardiovascular complications, especially in people at risk.(13)

Previous studies on adherence to perform home blood pressure measurements show similar results to our findings.(17, 24) In a study on telemonitoring including 213 hypertensive patients, who were asked to measure their blood pressure at least six times a week during six months, mean adherence was 73%.(17) Another study including only patients with heart failure (mean age 61 years) showed adherence of 55%.(24) Furthermore, in this study, we found that participants using the semimonthly measurement protocol showed higher adherence compared with participants using the monthly measurement protocol. A possible explanation could be that the fact that participants received a reminder twice a month (instead of once a month), might have kept participants more engaged in the study and therefore increased their adherence.(19) Furthermore, the burden of measuring for one day every two weeks may have been perceived lower than measuring during two consecutive days, albeit with monthly intervals.

Home-based blood pressure measurements using mobile phone-based technology may have several potential opportunities. First, other parameters derived from repeated blood pressure measurements, can easily be calculated, especially in a home-based setting. An example of such a parameter is blood pressure variability, of which we recently showed its association with cognitive decline.(25) Second, the combination with other parameters and measurements may reveal additional targets for blood pressure control. Physical activity, sleep, and other lifestyle factors can be measured using a mobile phone. This offers the potential for interventions, for instance aimed at increasing physical activity, that also beneficially affect blood pressure. The iVitality platform offers the opportunity to assess these lifestyle factors. Third, mobile phone-based technology might be a cost-effective alternative in the control of hypertension. It was previously shown that ambulatory blood pressure monitoring as a diagnostic strategy for hypertension saves costs, mainly because additional costs from ambulatory monitoring are counterbalanced by cost savings from better targeted treatment.(26) As mobile phone-based technology only requires a standard blood pressure monitor, which is much cheaper when compared with an ambulatory blood pressure monitor, we believe it has the potential of saving health care costs.

In our study, blood pressure was lower at the end of follow-up when the participant was referred to the GP because of a high blood pressure at baseline. There are two possible explanations for this finding. First, the decrease in blood pressure may be the result of

regression to the mean. This phenomenon occurs when repeated measurements tend to be followed by measurements that are closer to the mean. Although our baseline measurements were defined on repeated blood pressure measurements, it is still expected that the mean blood pressure during follow-up will go down, owing to regression toward the mean. Second, it may reflect a true effect of monitoring and subsequent treatment of blood pressure. Blood pressure lowering interventions by the GP and higher awareness of participants may all have contributed to a lower blood pressure. Although the fact that the effect on blood pressure was highest in those who initiated medication suggests the second explanation, we have not collected enough information on interventions in this proof-of-principle study to draw definite conclusions. An adequately powered randomized controlled trial may help to establish the effects of the interventions.

For this proof-of-principle study, we selected highly motivated participants with a parental history of dementia. This may have introduced a selection bias toward better adherence and treatment effects, which reduces the external validity for other, broader defined populations. The strength of this study is that mobile phone technology was used to collect study data on blood pressure. This innovative method reduces the need for face-to-face contact and stimulates self-management. Now that this proof-of-principle study is promising, broader and larger populations can be included in future studies.

This proof-of-principle study demonstrates that mobile phone-assisted technology can be used as a reliable and promising method to measure blood pressure at home during a six-month period. This provides a possibility for implementation in large-scale studies and can potentially lead to blood pressure reduction and eventually reduction of cardiovascular disease.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006;367(9524):1747-1757.
2. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, Kastarinen M, Poulter N, Primatesta P, Rodriguez-Artalejo F, Stegmayr B, Thamm M, Tuomilehto J, Vanuzzo D, Vescio F. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* 2003;289(18):2363-2369.
3. Banegas JR, Segura J, Ruilope LM, Luque M, Garcia-Robles R, Campo C, Rodriguez-Artalejo F, Tamargo J. Blood pressure control and physician management of hypertension in hospital hypertension units in Spain. *Hypertension* 2004;43(6):1338-1344.
4. Gutierrez-Misis A, Sanchez-Santos MT, Banegas JR, Zunzunegui MV, Castell MV, Otero A. Prevalence and incidence of hypertension in a population cohort of people aged 65 years or older in Spain. *J Hypertens* 2011;29(10):1863-1870.
5. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *JAMA* 2005;294(4):466-472.
6. Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. *Arch Intern Med* 2007;167(2):141-147.
7. Banegas JR, Segura J, Ruilope LM, Luque M, Garcia-Robles R, Campo C, Rodriguez-Artalejo F, Tamargo J. Blood pressure control and physician management of hypertension in hospital hypertension units in Spain. *Hypertension* 2004;43(6):1338-1344.
8. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *JAMA* 2005;294(4):466-472.
9. Seybert H, Reinecke P. Survey on ICT usage in households and by individuals. http://ec.europa.eu/eurostat/statistics-explained/index.php/internet_use_statistics_-_individuals ed. 2013.
10. Akkermans M.Central Department of Statistics. Ouderen maken inhaalslag op het internet. http://www.cbs.nl/nl-NL/menu/themas/vrije-tijd-cultuur/publicaties/artikelen/archief/2011/2011-3537-wm.htm. ed. 2011.
11. Kummervold PE, Chronaki CE, Lausen B, Prokosch HU, Rasmussen J, Santana S, Staniszewski A, Wangberg SC. eHealth trends in Europe 2005-2007: a population-based survey. *J Med Internet Res* 2008;10(4):e42.
12. Asayama K, Thijs L, Brguljan-Hitij J, Niiranen TJ, Hozawa A, Boggia J, Aparicio LS, Hara A, Johansson JK, Ohkubo T, Tzourio C, Stergiou GS, Sandoya E, Tsuji I, Jula AM, Imai Y, Staessen JA. Risk stratification by self-measured home blood pressure across categories of conventional blood pressure: a participant-level meta-analysis. *PLoS Med* 2014;11(1):e1001591.
13. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21(5):821-848.
14. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005;111(14):1777-1783.
15. Niiranen TJ, Asayama K, Thijs L, Johansson JK, Hara A, Hozawa A, Tsuji I, Ohkubo T, Jula AM, Imai Y, Staessen JA. Optimal Number of Days for Home Blood Pressure Measurement. *Am J Hypertens* 2014.
16. Green BB, Cook AJ, Ralston JD, Fishman PA, Catz SL, Carlson J, Carrell D, Tyll L, Larson EB, Thompson RS. Effectiveness of home blood pressure monitoring, Web communication, and pharmacist care on hypertension control: a randomized controlled trial. *JAMA* 2008;299(24):2857-2867.

7

17. Kerby TJ, Asche SE, Maciosek MV, O'Connor PJ, Sperl-Hillen JM, Margolis KL. Adherence to blood pressure telemonitoring in a cluster-randomized clinical trial. *J Clin Hypertens (Greenwich)* 2012;14(10):668-674.

18. Kumar N, Khunger M, Gupta A, Garg N. A content analysis of smartphone-based applications for hypertension management. *J Am Soc Hypertens* 2015;9(2):130-136.

19. van Osch M, Rovekamp A, Bergman-Agteres SN, Wijsman LW, Ooms SJ, Mooijaart SP, Vermeulen J. User preferences and usability of iVitality: optimizing an innovative online research platform for home-based health monitoring. *Patient Prefer Adherence* 2015;9:857-867.

20. Rogoza AN, Pavlova TS, Sergeeva MV. Validation of A&D UA-767 device for the self-measurement of blood pressure. *Blood Press Monit* 2000;5(4):227-231.

21. Topouchian J, Agnoletti D, Blacher J, Youssef A, Chahine MN, Ibanez I, Assemani N, Asmar R. Validation of four devices: Omron M6 Comfort, Omron HEM-7420, Withings BP-800, and Polygreen KP-7670 for home blood pressure measurement according to the European Society of Hypertension International Protocol. *Vasc Health Risk Manag* 2014;10:33-44.

22. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D. Call to action on use and reimbursement for home blood pressure monitoring: executive summary: a joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension* 2008;52(1):1-9.

23. Staessen JA, Thijs L, Ohkubo T, Kikuya M, Richart T, Boggia J, Adiyaman A, Dechering DG, Kuznetsova T, Thien T, de LP, Imai Y, O'Brien E, Parati G. Thirty years of research on diagnostic and therapeutic thresholds for the self-measured blood pressure at home. *Blood Press Monit* 2008;13(6):352-365.

24. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, Phillips CO, Hodshon BV, Cooper LS, Krumholz HM. Telemonitoring in patients with heart failure. *N Engl J Med* 2010;363(24):2301-2309.

25. Sabayan B, Wijsman LW, Foster-Dingley JC, Stott DJ, Ford I, Buckley BM, Sattar N, Jukema JW, van Osch MJ, van der Grond J, van Buchem MA, Westendorp RG, de Craen AJ, Mooijaart SP. Association of visit-to-visit variability in blood pressure with cognitive function in old age: prospective cohort study. *BMJ* 2013;347:f4600.

26. Lovibond K, Jowett S, Barton P, Caulfield M, Heneghan C, Hobbs FD, Hodgkinson J, Mant J, Martin U, Williams B, Wonderling D, McManus RJ. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. *Lancet* 2011;378(9798):1219-1230.

Chapter 8

General discussion

This thesis aimed to 1) further investigate whether blood pressure in older people is a risk factor for cardiovascular events and cognitive impairment; 2) study whether early markers of cardiac disease are related with cognitive impairment; and 3) to evaluate the feasibility of home blood pressure monitoring using smartphone-assisted technology, which might eventually assist to prevent cognitive impairment.

Main findings

The first part of this thesis consists of three studies that evaluated the association of blood pressure and blood pressure variability with cardiovascular events and cognitive function in older age. In **chapter 2**, we investigated the association of blood pressure with the risk of cardiovascular events. We found that the association of diastolic blood pressure with cardiovascular events in older people varied upon cardiovascular history: in participants without a history of cardiovascular disease, there was no association between diastolic blood pressure and cardiovascular events, whereas participants with a cardiovascular history showed a decreased risk of cardiovascular events with higher diastolic blood pressure. **Chapter 3** assessed the association between visit-to-visit blood pressure variability and cognitive function in older people. Visit-to-visit blood pressure variability has previously been related to cerebrovascular damage. We showed that higher visit-to-visit systolic and diastolic blood pressure variability, independent of average blood pressure, was associated with worse cognitive function. Furthermore, we found that higher blood pressure variability was related to lower hippocampal volume and higher risk of cortical infarcts and cerebral microbleeds. We hypothesized that blood pressure lowering medication might mediate the association of blood pressure variability with cognitive function, possibly through its previously found effect on blood pressure variability.(1) In **chapter 4**, we found that use of beta-blockers and inhibitors of the renin-angiotensin system was associated with higher systolic blood pressure variability. However, the association between blood pressure variability and cognitive impairment was not mediated by blood pressure lowering medication. This strengthens the finding that blood pressure variability, independent of blood pressure lowering medication, is associated with cognitive impairment.

The second part of this thesis consists of two studies that addressed the association between early markers of cardiac disease and cognitive function. In **chapter 5**, we presented an association of N-terminal pro-brain natriuretic peptide (NT-proBNP), a neurohormone that is commonly used in the diagnosis of clinical heart failure, with worse cognitive function and steeper cognitive decline. **Chapter 6** showed that participants with high but

within normal ranges levels of cardiac troponin T (cTnT), routinely used in the diagnosis of acute myocardial infarction, had worse cognitive function and steeper cognitive decline. These results were independent of cardiovascular diseases or risk factors. Furthermore, similar trends were found in participants with lower NT-proBNP levels below which might be indicative of clinical heart failure, suggesting that hs-cTnT is an independent predictor of cognitive impairment.

In the last part of this thesis, we introduced the innovative research technology iVitality, which comprises a website, a smartphone-based application and health sensors to measure health characteristics at home (**chapter 7**). In a proof of principle study including 151 people, we evaluated the feasibility of home blood pressure monitoring using iVitality during six months. We showed a high correlation between office and home blood pressure measurements. In addition, adherence of participants to perform blood pressure measurements was high. Furthermore, we found a significant decrease in home blood pressure when participants were referred to their general practitioner in case of a high blood pressure. We therefore concluded that smartphone-based technology is a reliable and promising method with good adherence. This provides a possibility for implementation in large-scale studies and can potentially contribute to blood pressure reduction, eventually helping to prevent cognitive impairment.

Discussion

Previous studies showed that the association between high diastolic blood pressure and increased risk of cardiovascular events attenuated with older age, and even reversed in the oldest old or biologically old.(2-7) Our finding that low blood pressure associates with a higher risk of cardiovascular events in people with previous cardiovascular disease further supports the hypothesis that in older people, biological or vascular age might be more important than calendar age per se. In this manner, low diastolic blood pressure, which is an important contributor of the perfusion pressure of an organ, might predispose to vascular hypoperfusion of vital organs, particularly in people who already suffer from increased arterial stiffness or obstruction.(8, 9) Besides average blood pressure, we showed that variability in sufficiently high blood pressure might be important in older people, especially concerning cognitive function.

Blood pressure variability may reflect a long-term hemodynamic instability in the systemic circulation that puts stress on the vascular endothelium.(10, 11) This hemodynamic

stress may lead to endothelial dysfunction and micro-vascular damage with consequent alterations in brain structure and function.(12) Furthermore, exaggerated fluctuations in systemic blood pressure could result in repeated episodes of cerebral hypoperfusion causing neuronal injury and cell death, particularly in vulnerable brain regions such as the hippocampus.(13) Blood pressure management in older people might therefore be more complicated then what current guidelines include. In addition, a conservative approach in the treatment of high blood pressure in older people might be appropriate, especially in those with a cardiovascular history. All this underlines the importance of an individualized approach in blood pressure management, in particular for older people.

Our findings that NT-proBNP and cTnT associate with worse cognitive function and decline, is in line with earlier studies which suggest a connection between cardiac function and brain structures. A possible explanation might be that higher NT-proBNP and cTnT levels indicate suboptimal left ventricular functioning with subsequent decreased cardiac output and cerebral hypoperfusion.(14) Cerebral hypoperfusion has previously been associated with a higher risk of dementia.(15) In line with this, earlier studies showed that patients with clinical heart failure have an increased risk of cognitive impairment, and that patients following cardiac transplantation showed an improvement in cognitive function.(16-20) Nevertheless, the finding that in participants with NT-proBNP levels within the normal range and below those indicative of clinical heart failure, cTnT was also associated with worse cognition, merits further speculations on underlying pathways. Although it is generally believed that cTnT is only expressed in striated muscle cells, animal studies have revealed expression of troponin proteins, including troponin T, in smooth muscle cells of rats and mice as well.(21, 22) This suggest that cTnT might also be a reflection of smooth muscle cell involvement.(23) Higher levels of cTnT may therefore indicate vascular smooth muscle cell damage in an early stage, before the manifestation of clinical or even subclinical diseases. This might also explain the observation that higher levels of cTnT are associated with subclinical brain disease, including silent brain infarcts and white matter hyperintensities.(24) Speculatively, cTnT is not only released by cardiomyocytes but also by smooth muscle cells in the brain vasculature, and may therefore mark structural brain damage as a cause of cognitive decline. These findings emphasize that people with early signs of cardiac or vascular disease are already at increased risk of cognitive impairment. Furthermore, it supports the importance of early recognition and treatment of cardiovascular risk factors in the prevention of cognitive decline.

The findings of this thesis strengthen the potential to prevent cognitive decline by early control of modifiable risk factors, including blood pressure, blood pressure variability and

8

cardiac or vascular disease. Since treatment of early stages of cognitive impairment or dementia is still lacking, prevention is currently the only option to diminish the burden of these disorders. Recently, it has been shown that elevated blood pressure as measured in the home situation is a stronger prognostic indicator of cardiovascular events than elevated office blood pressure.(25-27) In view of the cost-effectiveness, the low burden of measuring, and manifold established treatment options, home blood pressure monitoring could therefore be an important strategy to further prevent cardiovascular complications, including cognitive disorders and dementia.(28) The evidence of the last part of this thesis, in which we showed that smartphone-assisted technology is a reliable and promising method with good adherence to measure blood pressure at home, offers new opportunities.

Future perspectives

The work described in this thesis tried to provide new insights in the relation of blood pressure and cardiac function with cognitive impairment. Most of the data in this study were obtained from the PROspective Study of Pravastatin in the Elderly at Risk, a randomized, double blind, placebo controlled trial with a mean follow-up period of 3.2 years. The longitudinal nature of this study provided the opportunity to study relations between (changes in) determinants and subsequent changes in cognitive function. However, a limitation of the design used in our studies, is the observational nature, which does not allow to make conclusions about causality.

As for the association between diastolic blood pressure and cardiovascular events, it could be that both low diastolic blood pressure and cardiovascular events share a common cause, which most likely would be aging of the arterial system, including atherosclerosis. Previous studies showed that progression of atherosclerosis is accompanied by a decrease in diastolic blood pressure.(29, 30) Instead of being causally related, low diastolic blood pressure might therefore be a reflection of widespread atherosclerosis, which itself associates with increased risk of cardiovascular disease and mortality. Another possibility might be that low diastolic blood pressure is a reflection of deteriorating health status, leading to increased risk of cardiovascular events and mortality.(31) So far, only one randomized controlled trial investigated whether older people benefit from higher blood pressure values. The Discontinuation of Antihypertensive Treatment in Elderly People (DANTE) study examined whether discontinuation of antihypertensive medication in patients aged 75 years or older decreased the risk of cognitive decline.(32) In 385 participants with mild cognitive deficits, they found no differences in cognitive, psychological or general daily functioning during a 16-week follow-up period.(32) However, the short follow-up and the (unintentionally)

selection of participants with relatively intact cerebral autoregulation might explain the lack of effect of the discontinuation of antihypertensive medication. Future randomized controlled trials should include longer follow-up and biologically older people with impaired autoregulation. Furthermore, although most trials study the effect of medication, the focus of research in older people should be whether discontinuation of medication results in better outcomes.

Doubts on the causal nature also holds for the relation between blood pressure variability and cognitive impairment: both could stem from a common cause, for instance cardiovascular risk factors, without themselves being related. In line with this, previous literature showed that cardiovascular and cerebrovascular disease share the same risk factors, including hypertension, diabetes mellitus and smoking.(16, 20) In addition, increased levels of cTnT and NT-proBNP might reflect underlying myocardial damage caused by cardiovascular risk factors, which themselves also cause cognitive decline.(16, 17) Therefore, randomized controlled trials could help to draw conclusions about causality and interventions to prevent cerebral damage. These trials should examine whether lowering blood pressure variability, for example by calcium-channel blockers, an effective drug-class in lowering blood pressure variability, diminishes the risk of cognitive impairment. Furthermore, to unravel biological mechanisms concerning cerebral autoregulation, future investigations should examine the role of blood pressure variability, NT-proBNP and cTnT with respect to perfusion, volumes and small vessel disease of the brain.

Finally, we showed the feasibility of home blood pressure measurements using smartphone-assisted technology during six months of follow-up. Results of this study are promising in light of an alternative research method to study relevant health characteristics at home. Besides blood pressure, new technologies allow home-based measurement of other lifestyle characteristics, such as physical activity, blood glucose concentration, gait speed and sleep parameters. Furthermore, this also provides interesting opportunities for implementation in prevention programs, in particular in a primary care setting. In addition, engaging people to measure their own health could further stimulate awareness and involvement. This might contribute to a more home-based, self-management approach, which is a welcoming alternative for the current hospital centered paradigm. Future studies should therefore investigate the potential of smartphone-assisted technology to prevent or manage cardiovascular risk factors and whether this results in less events. Eventually, this might lead to a reduction of cardiovascular diseases and may help in the prevention of cognitive decline.

8

References

1. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet* 2010;375(9718):906-915.
2. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. *Ann Intern Med* 2002;136(6):438-448.
3. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360(9349):1903-1913.
4. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;144(12):884-893.
5. Muller M, Maier AB, Smulders YM. [High blood pressure and mortality in the elderly: what does gait speed tell?]. *Ned Tijdschr Geneeskd* 2013;157(7):A5801.
6. Protogerou AD, Safar ME, Iaria P, Safar H, Le DK, Filipovsky J, Henry O, Ducimetiere P, Blacher J. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. *Hypertension* 2007;50(1):172-180.
7. van Bemmel T, Gussekloo J, Westendorp RG, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. *J Hypertens* 2006;24(2):287-292.
8. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. *Brain* 2011;134(Pt 11):3398-3407.
9. Muller M, van der Graaf Y, Visseren FL, Vlek AL, Mali WP, Geerlings MI. Blood pressure, cerebral blood flow, and brain volumes. The SMART-MR study. *J Hypertens* 2010;28(7):1498-1505.
10. Diaz KM, Veerabhadrappa P, Kashem MA, Thakkar SR, Feairheller DL, Sturgeon KM, Ling C, Williamson ST, Kretzschmar J, Lee H, Grimm H, Babbitt DM, Vin C, Fan X, Crabbe DL, Brown MD. Visit-to-visit and 24-h blood pressure variability: association with endothelial and smooth muscle function in African Americans. *J Hum Hypertens* 2013;27(11):671-677.
11. Kim KI, Lee JH, Chang HJ, Cho YS, Youn TJ, Chung WY, Chae IH, Choi DJ, Park KU, Kim CH. Association between blood pressure variability and inflammatory marker in hypertensive patients. *Circ J* 2008;72(2):293-298.
12. Cecchi E, Giglioli C, Valente S, Lazzeri C, Gensini GF, Abbate R, Mannini L. Role of hemodynamic shear stress in cardiovascular disease. *Atherosclerosis* 2011;214(2):249-256.
13. Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, Decarli C, Brown TR, Mayeux R. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol* 2010;67(5):564-569.
14. Mishra RK, Li Y, Ricardo AC, Yang W, Keane M, Cuevas M, Christenson R, deFilippi C, Chen J, He J, Kallem RR, Raj DS, Schelling JR, Wright J, Go AS, Shlipak MG. Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC]). *Am J Cardiol* 2013;111(3):432-438.
15. Zuccala G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. *J Neurol Neurosurg Psychiatry* 1997;63(4):509-512.
16. Georgiadis D, Sievert M, Cencetti S, Uhlmann F, Krivokuca M, Zierz S, Werdan K. Cerebrovascular reactivity is impaired in patients with cardiac failure. *Eur Heart J* 2000;21(5):407-413.
17. Zuccala G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. *J Neurol Neurosurg Psychiatry* 1997;63(4):509-512.

18. Zuccala G, Onder G, Pedone C, Carosella L, Pahor M, Bernabei R, Cocchi A. Hypotension and cognitive impairment: Selective association in patients with heart failure. *Neurology* 2001;57(11):1986-1992.

19. Bornstein RA, Starling RC, Myerowitz PD, Haas GJ. Neuropsychological function in patients with end-stage heart failure before and after cardiac transplantation. *Acta Neurol Scand* 1995;91(4):260-265.

20. Eggermont LH, de BK, Muller M, Jaschke AC, Kamp O, Scherder EJ. Cardiac disease and cognitive impairment: a systematic review. *Heart* 2012;98(18):1334-1340.

21. Moran CM, Garriock RJ, Miller MK, Heimark RL, Gregorio CC, Krieg PA. Expression of the fast twitch troponin complex, fTnT, fTnI and fTnC, in vascular smooth muscle. *Cell Motil Cytoskeleton* 2008;65(8):652-661.

22. Pinet F, Poirier F, Fuchs S, Tharaux PL, Caron M, Corvol P, Michel JB, Joubert-Caron R. Troponin T as a marker of differentiation revealed by proteomic analysis in renal arterioles. *FASEB J* 2004;18(3):585-586.

23. Kajioka S, Takahashi-Yanaga F, Shahab N, Onimaru M, Matsuda M, Takahashi R, Asano H, Morita H, Morimoto S, Yonemitsu Y, Hayashi M, Seki N, Sasaguri T, Hirata M, Nakayama S, Naito S. Endogenous cardiac troponin T modulates Ca(2+)-mediated smooth muscle contraction. *Sci Rep* 2012;2:979.

24. Dadu RT, Fornage M, Virani SS, Nambi V, Hoogeveen RC, Boerwinkle E, Alonso A, Gottesman RF, Mosley TH, Ballantyne CM. Cardiovascular biomarkers and subclinical brain disease in the atherosclerosis risk in communities study. *Stroke* 2013;44(7):1803-1808.

25. Asayama K, Thijs L, Brguljan-Hitij J, Niiranen TJ, Hozawa A, Boggia J, Aparicio LS, Hara A, Johansson JK, Ohkubo T, Tzourio C, Stergiou GS, Sandoya E, Tsuji I, Jula AM, Imai Y, Staessen JA. Risk stratification by self-measured home blood pressure across categories of conventional blood pressure: a participant-level meta-analysis. *PLoS Med* 2014;11(1):e1001591.

26. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21(5):821-848.

27. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005;111(14):1777-1783.

28. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21(5):821-848.

29. Bots ML, Witteman JC, Hofman A, de Jong PT, Grobbee DE. Low diastolic blood pressure and atherosclerosis in elderly subjects. The Rotterdam study. *Arch Intern Med* 1996;156(8):843-848.

30. Witteman JC, Grobbee DE, Valkenburg HA, van Hemert AM, Stijnen T, Burger H, Hofman A. J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. *Lancet* 1994;343(8896):504-507.

31. Satish S, Zhang DD, Goodwin JS. Clinical significance of falling blood pressure among older adults. *J Clin Epidemiol* 2001;54(9):961-967.

32. Moonen JE, Foster-Dingley JC, de RW, van der Grond J, Bertens AS, van Buchem MA, Gussekloo J, Middelkoop HA, Wermer MJ, Westendorp RG, de Craen AJ, van der Mast RC. Effect of Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning--the DANTE Study Leiden: A Randomized Clinical Trial. *JAMA Intern Med* 2015;175(10):1622-1630.

8

Chapter 9

Nederlandse samenvatting
List of co-authors
List of publications
Curriculum vitae
Dankwoord

Nederlandse samenvatting

Introductie

Door de toename in levensverwachting stijgt het aantal ouderen met cognitieve stoornissen. Het aantal mensen dat wereldwijd lijdt aan dementie zal de komende 20 jaar naar verwachting verdubbelen; in 2030 wordt het aantal mensen met dementie geschat op 65.7 miljoen, in 2050 ligt dit rond de 115.4 miljoen.(1) De afgelopen jaren is in toenemende mate aangetoond dat cardiovasculaire risicofactoren bijdragen aan het ontstaan van cognitieve stoornissen.(2-4) Met name bij mensen van middelbare leeftijd hebben studies laten zien dat cardiovasculaire risicofactoren het risico op hersenveroudering en cognitieve stoornissen op oudere leeftijd verhogen.(2, 5) Dit is met name het geval bij mensen van middelbare leeftijd; bij oudere mensen wordt deze relatie veel minder sterk aangetoond.(6) Het is tot nu toe onduidelijk welk onderliggend mechanisme de relatie tussen cardiovasculaire risicofactoren en cognitieve achteruitgang kan verklaren.

Een voorbeeld van een cardiovasculaire risicofactor op middelbare leeftijd die geassocieerd is met cognitieve stoornissen op oudere leeftijd, is het hebben van een hoge bloeddruk. (7) Verschillende studies tonen aan dat een hoge bloeddruk op middelbare leeftijd een risicofactor is voor cardiovasculaire ziekten, hersenatrofie en cognitieve achteruitgang. (8-11) Een aantal gerandomiseerde klinische studies laat daarnaast zien dat bloeddrukverlagende medicatie het risico op cognitieve stoornissen vermindert.(12, 13) Recent bewijs toont echter dat deze relatie afneemt met toenemende leeftijd; en dat op oudere leeftijd een lage bloeddruk juist gerelateerd is aan een hoger risico op cardiovasculaire ziekten en cognitieve achteruitgang.(5, 14-16) Deze studie toont ook dat het voornamelijk de mensen met een hoge biologische leeftijd zijn, die meer nadelen ondervinden van een lage bloeddruk.(17-19)

Behalve bloeddruk is hartschade gerelateerd aan een hoger risico op cognitieve stoornissen en dementie. Patiënten met een coronaire hartziekte, boezemfibrilleren en chronisch hartfalen hebben een slechtere cognitie en een hoger risico op het ontwikkelen van dementie. (3, 20-22) Deze bevindingen kunnen verklaard worden door een verminderde hartfunctie wat leidt tot een verminderde perfusie van de hersenen en een verstoring van de toevoer van zuurstof en voedingsstoffen naar de hersenen.(3) Daarnaast is aangetoond dat bij patienten met ernstig hartfalen, de cognitieve functies verbeterden na een harttransplantatie. (23, 24) Het is nog onduidelijk of mensen met vroege tekenen van hartschade ook een verhoogd risico hebben op cognitieve achteruitgang.

9

Doel van dit proefschrift

Dit proefschrift heeft tot doel 1) te onderzoeken of bloeddruk bij oudere mensen een risicofactor is voor het optreden van cardiovasculaire ziekten en cognitieve stoornissen; 2) te analyseren of vroege markers van hartziekte gerelateerd zijn aan cognitieve stoornissen; en 3) te evalueren of smartphone-technologie bruikbaar is bij het langdurig monitoren van bloeddruk gemeten in de thuissituatie, met als uiteindelijk doel om hersenschade en cognitieve achteruitgang te voorkomen.

Overzicht van het beschreven onderzoek

Het eerste deel van dit proefschrift bevat drie studies die de relatie tussen bloeddruk en variabiliteit in bloeddruk met cardiovasculaire ziekten en cognitieve functie bij oudere mensen tonen. In **hoofdstuk 2** toonden we aan dat de relatie tussen diastolische bloeddruk en cardiovasculaire ziekten bij oudere mensen afhangt van cardiovasculaire ziekten in de voorgeschiedenis. Bij mensen zonder een cardiovasculaire voorgeschiedenis, vonden we geen relatie tussen diastolische bloeddruk en het optreden van cardiovasculaire ziekten. Bij mensen met cardiovasculaire ziekten in de voorgeschiedenis vonden we een lager risico op het opnieuw optreden van cardiovasculaire ziekten bij een hogere bloeddruk. Dit komt overeen met studies die deze relatie eerder onderzochten en aantoonden dat de 'oudste ouderen' een lager risico op cardiovasculaire ziekten hadden bij een hogere diastolische bloeddruk.(5, 14, 15, 17, 25, 26) Bovendien sluit het aan bij de hypothese dat een lage diastolische bloeddruk, welke een belangrijke bijdrage aan de perfusie van een orgaan levert, leidt tot vasculaire hypoperfusie van een orgaan, voornamelijk bij mensen die al aan arteriële vaatstijfheid lijden. Dit zou kunnen resulteren in een meer voorzichtige aanpak van de behandeling van hoge diastolische bloeddruk bij oudere mensen met een voorge-schiedenis van cardiovasculaire ziekten. Gerandomiseerde onderzoeken die bestuderen of een verhoging van diastolische bloeddruk, door bloeddrukverlagende medicatie (deels) te staken, leidt tot minder cardiovasculaire ziekten bij mensen met een hoger vasculaire leeftijd, zouden hier meer inzicht in kunnen geven. Daarnaast zijn MRI-studies nodig die meer inzicht kunnen geven in biologische mechanismen, zoals bijvoorbeeld cerebrale hypoperfusie, die deze relatie kunnen verklaren. **Hoofdstuk 3** toonde aan dat een hogere variabiliteit in systolische en diastolische bloeddruk gerelateerd is aan een slechtere cog-nitieve functie, ongeacht de waarde van de gemiddelde bloeddruk. Verder lieten we zien dat hogere bloeddrukvariabiliteit gepaard ging met een lager volume van de hippocampus en een hoger risico op corticale infarcten en cerebrale microbloedingen. Aangezien be-kend is dat een lager hippocampus volume en meer schade in de kleine vaten van de hersenen samengaat met cognitieve achteruitgang, kan dit een mogelijke verklaring van

onze resultaten zijn.(27, 28) Omdat eerdere studies lieten zien dat bloeddrukverlagende medicatie leidt tot veranderingen in bloeddrukvariabiliteit, veronderstelden we dat bloeddrukverlagende medicatie de relatie tussen bloeddrukvariabiliteit en cognitief functioneren zou kunnen mediëren.(29) In **hoofdstuk 4** lieten we zien dat het gebruik van bètablokkers en renine-angiotensine-systeem remmers gepaard gaat met een hogere variabiliteit in systolische bloeddruk. Echter, bloeddrukverlagende medicatie had geen invloed op de relatie tussen bloeddrukvariabiliteit en cognitief functioneren. Dit ondersteunt onze bevinding dat bloeddrukvariabiliteit, onafhankelijk van bloeddrukverlagende medicatie, gerelateerd is aan een slechtere cognitieve functie. Omdat deze relatie slechts op één tijdspunt geanalyseerd werd, is longitudinaal onderzoek nodig om de causaliteit te kunnen onderzoeken.

In het tweede deel van dit proefschrift laten we twee studies zien die de relatie tussen vroege markers van hartschade in relatie tot cognitief functioneren onderzochten. In **hoofdstuk 5** toonden we aan dat N-terminal pro-brain natriuretic peptide (NT-proBNP), een neurohormoon dat gebruikt wordt bij het diagnosticeren van klinisch hartfalen, gerelateerd was aan slechtere cognitieve functie op baseline en een snellere achteruitgang in cognitie tijdens een studieperiode van ongeveer drie jaar. Een mogelijke verklaring hiervoor is dat hogere waarden van NT-proBNP kunnen duiden op een suboptimale contractie van de linkerventrikel, met verminderde cerebrale hypoperfusie tot gevolg.(30) **Hoofdstuk 6** onderzocht de relatie tussen cardiaal troponine T (cTnT), een proteïne dat gebruikt wordt bij de diagnose van een acuut myocardinfarct, en cognitief functioneren. We toonden aan dat mensen met hogere waarden van cTnT een slechtere cognitie op baseline hadden en tevens een snellere achteruitgang in cognitief functioneren lieten zien. Het feit dat we dezelfde resultaten vonden bij mensen met een laag NT-proBNP, maakt het minder waarschijnlijk dat een verminderde linkerventrikelfunctie leidend tot verminderde cerebrale hypoperfusie hieraan ten grondslag ligt. Dit geeft aanleiding tot verdere speculatie over andere mechanismen. Omdat cTnT recent is aangetoond in vasculaire gladde spiercellen, kunnen we hypothetiseren dat hoge cTnT waarden wijzen op schade aan vasculaire gladde spiercellen in een vroege fase, vóór de manifestatie van (subklinische) ziekten.(31) Hierbij kunnen we speculeren dat cTnT niet alleen door cardiomyocyten wordt afgegeven, maar ook door gladde spiercellen van bijvoorbeeld de microvasculatuur van de hersenen. Hoge cTnT waarden zouden daardoor een aanwijzing kunnen zijn voor structurele hersenschade, wat cognitieve stoornissen veroorzaakt. Dit onderzoek laat in ieder geval zien dat vroege identificatie en behandeling van hartschade en microvasculaire schade belangrijk zijn om uiteindelijke cognitieve veroudering te vertragen of voorkomen. Toekomstig onderzoek dat zich richt op de relatie van NT-proBNP en cTnT met hersenperfusie, hersenvolume en

9

structuur van de kleine vaten is raadzaam om meer te weten te komen over het onderliggende mechanisme.

In het laatste deel van dit proefschrift introduceerden we een nieuwe onderzoekstechniek, genaamd iVitality (**hoofdstuk 7**). iVitality bestaat uit een website, een smartphone applicatie en gezondheidssensoren, die het mogelijk maken om indicatoren van gezondheid thuis te kunnen meten. In een proof-of-principle studie includeerden we 151 mensen en evalueerden we of smartphone-technologie bruikbaar is bij het langdurig monitoren van bloeddruk gemeten in de thuissituatie. We toonden aan dat 1) de correlatie tussen thuis gemeten bloeddruk en bloeddruk gemeten in de kliniek hoog was; 2) het aantal deelnemers dat de bloeddrukmetingen thuis uitvoerde, hoog was; en 3) de systolische en diastolische bloeddruk van deelnemers die naar de huisarts werden verwezen in verband met een hoge bloeddruk, significant verbeterde. Deze bevindingen zijn veelbelovend in het kader van een alternatieve onderzoeksmethode om op grote schaal gezondheidskarakteristieken thuis te kunnen meten. Omdat het opsporen en controleren van een hoge bloeddruk hersencomplicaties voorkomt, zou het daarnaast gebruikt kunnen worden als preventieve methode om uiteindelijk cognitieve achteruitgang te voorkomen. Deze mogelijkheden dienen verder uitgezocht te worden in een grotere onderzoekspopulatie.

References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013;9(1):63-75.
2. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, Wolf PA, Decarli C. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology* 2011;77(5):461-468.
3. Eggermont LH, de BK, Muller M, Jaschke AC, Kamp O, Scherder EJ. Cardiac disease and cognitive impairment: a systematic review. *Heart* 2012;98(18):1334-1340.
4. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011;42(9):2672-2713.
5. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360(9349):1903-1913.
6. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* 2005;4(8):487-499.
7. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and the risk for dementia: a double edged sword. *Ageing Res Rev* 2009;8(2):61-70.
8. den Heijer T, Launer LJ, Prins ND, van Dijk EJ, Vermeer SE, Hofman A, Koudstaal PJ, Breteler MM. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* 2005;64(2):263-267.
9. Korf ES, White LR, Scheltens P, Launer LJ. Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. *Hypertension* 2004;44(1):29-34.
10. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 2001;322(7300):1447-1451.
11. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, Havlik RJ. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging* 2000;21(1):49-55.
12. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, Bossini A, Fagard R, Gil-Extremera B, Laks T, Kobalava Z, Sarti C, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Birkenhager WH. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* 2002;162(18):2046-2052.
13. in't Veld BA, Ruitenberg A, Hofman A, Stricker BH, Breteler MM. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. *Neurobiol Aging* 2001;22(3):407-412.
14. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. *Ann Intern Med* 2002;136(6):438-448.
15. Protogerou AD, Safar ME, Iaria P, Safar H, Le DK, Filipovsky J, Henry O, Ducimetiere P, Blacher J. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. *Hypertension* 2007;50(1):172-180.
16. Voko Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JC, Breteler MM. J-shaped relation between blood pressure and stroke in treated hypertensives. *Hypertension* 1999;34(6):1181-1185.
17. Muller M, Maier AB, Smulders YM. [High blood pressure and mortality in the elderly: what does gait speed tell?]. *Ned Tijdschr Geneeskd* 2013;157(7):A5801.
18. Post HG, Smulders YM, Maier AB, Deeg DJ, Muller M. Relation between blood pressure and mortality risk in an older population: role of chronological and biological age. *J Intern Med* 2014.

9

19. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. *Arch Intern Med* 2012;172(15):1162-1168.

20. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med* 2006;166(9):1003-1008.

21. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 2007;9(5):440-449.

22. Zuccala G, Marzetti E, Cesari M, Lo Monaco MR, Antonica L, Cocchi A, Carbonin P, Bernabei R. Correlates of cognitive impairment among patients with heart failure: results of a multicenter survey. *Am J Med* 2005;118(5):496-502.

23. Zimpfer D, Wieselthaler G, Czerny M, Fakin R, Haider D, Zrunek P, Roethy W, Schima H, Wolner E, Grimm M. Neurocognitive function in patients with ventricular assist devices: a comparison of pulsatile and continuous blood flow devices. *ASAIO J* 2006;52(1):24-27.

24. Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, Aldershvile J. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke* 2001;32(11):2530-2533.

25. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;144(12):884-893.

26. van Bemmel T, Gussekloo J, Westendorp RG, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. *J Hypertens* 2006;24(2):287-292.

27. Barnes J, Bartlett JW, van de Pol LA, Loy CT, Scahill RI, Frost C, Thompson P, Fox NC. A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. *Neurobiol Aging* 2009;30(11):1711-1723.

28. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010;9(7):689-701.

29. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet* 2010;375(9718):906-915.

30. Mishra RK, Li Y, Ricardo AC, Yang W, Keane M, Cuevas M, Christenson R, deFilippi C, Chen J, He J, Kallem RR, Raj DS, Schelling JR, Wright J, Go AS, Shlipak MG. Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC]). *Am J Cardiol* 2013;111(3):432-438.

31. Kajioka S, Takahashi-Yanaga F, Shahab N, Onimaru M, Matsuda M, Takahashi R, Asano H, Morita H, Morimoto S, Yonemitsu Y, Hayashi M, Seki N, Sasaguri T, Hirata M, Nakayama S, Naito S. Endogenous cardiac troponin T modulates Ca(2+)-mediated smooth muscle contraction. *Sci Rep* 2012;2:979.

List of co-authors

Mark A van Buchem, Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands

Brendan M Buckley, Department of Pharmacology and Therapeutics, University College Cork, Cork, Ireland

Ricardo Cachucho, Leiden Institute of Advanced Computer Science, University of Leiden, Leiden, the Netherlands

Anton JM de Craen, Department of Gerontology & Geriatrics, Leiden University Medical Center, Leiden, the Netherlands. *Deceased 17 January 2016*.

Jessica C Foster-Dingley, Department of Psychiatry, Leiden University Medical Center, Leiden, the Netherlands

Ian Ford, Robertson Center for Biostatistics, University of Glasgow, Glasgow, United Kingdom

Jeroen van der Grond, Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands

Jacobijn Gussekloo, Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands

Susan Jongstra, Department of Neurology, Academic Medical Center Amsterdam, Amsterdam, the Netherlands

J Wouter Jukema, Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands

Simon P Mooijaart, Department of Gerontology & Geriatrics, Leiden University Medical Center, Leiden, the Netherlands; and Institute for Evidence-Based Medicine in Old Age, Leiden, the Netherlands

Majon Muller, Department of Gerontology & Geriatrics, VU Medical University Amsterdam, Amsterdam, the Netherlands

9

Mathias JP van Osch, Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands

Petra G van Peet, Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands

Rosalinde KE Poortvliet, Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands

Edo Richard, Department of Neurology, Radboud University Medical Center, Nijmegen, the Netherlands; and Academic Medical Center Amsterdam, Department of Neurology, Amsterdam, Netherlands

Wouter de Ruijter, Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands

Behnam Sabayan, Department of Gerontology & Geriatrics, Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands

Naveed Sattar, British Heart Foundation, Glasgow Cardiovascular Research Center, University of Glasgow, Glasgow, United Kingdom

David J Stott, Academic Section of Geriatric Medicine, Faculty of Medicine, University of Glasgow, Glasgow, United Kingdom

Stella Trompet, Department of Gerontology & Geriatrics, Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands

Peter van Vliet, Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands

Paul Welsh, British Heart Foundation, Glasgow Cardiovascular Research Center, University of Glasgow, Glasgow, United Kingdom

Rudi GJ Westendorp, Department of Public Health and Center for Healthy Aging, University of Copenhagen, Copenhagen, Denmark

List of publications

Wijsman LW, de Craen AJ, Trompet S, Sabayan B, Muller M, Stott DJ, Ford I, Welsh P, Westendorp RGJ, Jukema JW, Sattar NA, Mooijaart SP. *High-sensitivity cardiac troponin T is associated with cognitive decline in older adults at high cardiovascular risk.* Eur J Prev Cardiol 2016; epub ahead of print.

Wijsman LW, Richard E, Cachucho R, de Craen AJM, Jongstra S, Mooijaart SP. *Evaluation of the use of home blood pressure measurement using mobile phone-assisted technology: the iVitality proof-of-principle study.* J Med Internet Res 2016; 13; 4(2): e67.

Broekhuizen K, de Gelder J, Wijsman CA, Wijsman LW, Westendorp RG, Verhagen E, Slagboom PE, de Craen AJ, van Mechelen W, van Heemst D, van der Ouderaa F, Mooijaart SP. *An internet-based physical activity intervention to improve quality of life of inactive older adults: a randomized controlled trial.* J Med Internet Res 2016; 27; 18(4): e74.

Wijsman LW, de Craen AJ, Muller M, Sabayan B, Stott DJ, Ford I, Trompet S, Jukema JW, Westendorp RGJ, Mooijaart SP. *Blood pressure lowering medication, visit-to-visit blood pressure variability, and cognitive function in old age.* Am J Hypertension 2016; 29(3): 311-8.

Poortvliet RKE*, van Peet PG*, de Craen AJM, Mertens BJA, Mooijaart SP, Wijsman LW, Drewes YM, Ford I, Sattar N, Jukema JW, Stott DJ, Ruijter W, Gussekloo J. *Risk stratification and treatment effect of statins in secondary cardiovascular prevention in old age: additive value of NT-proBNP.* Eur J Prev Cardiol 2016; 23(10): 1104-13. *both authors contributed equally.

Blum MR*, Wijsman LW*, Virgini VS, Bauer DC, den Elzen WPJ, Jukema JW, Buckley BM, de Craen AJM, Kearney PM, Stott DJ, Gussekloo J, Westendorp RGJ, Mooijaart SP, Rodondi R. *Subclinical thyroid dysfunction and depressive symptoms among elderly: a prospective cohort study.* Neuroendocrinology 2016; 103(3-4): 291-9. *both authors contributed equally.

Wijsman LW, den Elzen W, Virgini VS, Rodondi N, Bauer D, Kearney P, Jukema JW, Westendorp RGJ, Ford I, Stott DJ, Gussekloo J, Mooijaart SP. *Subklinische schildklierafwijkingen en dagelijks functioneren bij ouderen.* Huisarts Wet 2015; 58(1):12-15.

9

van Osch M, Rovekamp AJM, Bergman-Agteres SN, Wijsman LW, Ooms SJ, Mooijaart SP, Vermeulen J. *User preferences and usability of iVitality: optimizing an innovative online research platform for home-based health monitoring.* Patient Prefer Adherence 2015; 30(9): 857-67.

Poortvliet RK, Lloyd SM, Ford I, Sattar N, de Craen AJ, Wijsman LW, Mooijaart SP, Westendorp RGJ, Jukema JW, de Ruijter W, Gussekloo J, Stott DJ. *Biological correlates of blood pressure variability in elderly at high risk of cardiovascular disease.* Am J Hypertens 2014; 76(2): 213-22.

van Vliet P, Sabayan B, Wijsman LW, Poortvliet RK, Mooijaart SP, de Ruijter W, Gussekloo J, de Craen AJ, Westendorp RGJ. *NT-proBNP, blood pressure, and cognitive decline in the oldest old: The Leiden 85-plus Study.* Neurology 2014; 83(13): 1192-9.

Wijsman LW, Sabayan B, van Vliet P, Trompet S, de Ruijter W, Poortvliet RK, van Peet PG, Gussekloo J, Jukema JW, Stott DJ, Sattar N, Ford I, Westendorp RGJ, de Craen AJ, Mooijaart SP. *N-terminal pro-brain natriuretic peptide and cognitive decline in older adults at high cardiovascular risk.* Ann Neurol 2014; 76(2): 213-22.

Virgini VS*, Wijsman LW*, Rodondi N, Bauer DC, Kearney PM, Gussekloo J, den Elzen WP, Jukema JW, Westendorp RGJ, Ford I, Stott DJ, Mooijaart SP. *Subclinical thyroid dysfunction and functional capacity among elderly.* Thyroid 2014; 24(2): 208-14. *both authors contributed equally.

Sabayan B*, Wijsman LW*, Foster-Dingley JC, Stott DJ, Ford I, Buckley BM, Sattar N, Jukema JW, van Osch MJ, van der Grond J, van Buchem MA, Westendorp RGJ, de Craen AJ, Mooijaart SP. *Association of visit-to-visit variability in blood pressure with cognitive function in old age: prospective cohort study.* BMJ 2013; 347: 4600. *both authors contributed equally.

Wijsman LW, de Craen AJ, Trompet S, Gussekloo J, Stott DJ, Rodondi N, Welsh P, Jukema JW, Westendorp RGJ, Mooijaart SP. *Subclinical thyroid dysfunction and cognitive decline in old age.* PLoS One 2013; 8(3): e59199.

Curriculum vitae

Liselotte Willemijn Wijsman was born on January 5, 1985 in Seria, Brunei. She graduated in 2003 at the Da Vinci College in Leiden. After she studied Education and Child Studies for one year, she started her study Medicine in 2004 at the Leiden University Medical Center (LUMC). During her scientific internship at the department of Gerontology and Geriatrics at the LUMC (dr. A.J.M. de Craen and dr. S. Trompet), she investigated the association between subclinical thyroid function and cognitive function in older people. She then became enthusiastic in ageing research, with a specific interest in the determinants of cognitive decline in older people. After obtaining her medical degree in the beginning of 2011, she started her PhD on blood pressure, cardiac biomarkers and cognitive function in old age at the department of Gerontology and Geriatrics (LUMC) under supervision of prof. dr. R.G.J. Westendorp and dr. S.P. Mooijaart. The results of her study are presented in this thesis and have been published in several international journals. From 2015 till 2016 she worked as a resident (anios) internal medicine at the Medical Center Alkmaar. She currently works as a resident psychiatry at Mentrum in Amsterdam. Eventually, she would like to become a general practitioner.

9

Dankwoord

Dit proefschrift was niet tot stand gekomen door de vrijwillige bijdrage van alle deelnemers aan wetenschappelijk onderzoek. Ik ben hen veel dank verschuldigd, met name de deelnemers van de PROSPER en de iVitality-studie.

Daarnaast wil ik mijn promotor professor Westendorp en mijn co-promotor Simon Mooijaart bedanken. Beste Rudi, jouw altijd scherpe commentaar en gedrevenheid waren gedurende mijn promotietraject een grote inspiratie. Simon, door jouw enthousiasme en positieve visie ben ik uiteindelijk gaan promoveren. Bedankt voor jullie vertrouwen en alle begeleiding de afgelopen jaren.

Ton, mijn wetenschappelijke pad begon met een door jou voorgestelde wetenschapsstage. Bedankt voor al je hulp en relativering; ik vind het ontzettend jammer dat je mijn promotie niet kan meemaken.

De leden van de promotiecommissie wil ik hierbij hartelijk bedanken voor het beoordelen van dit proefschrift.

Beste Edo en Carin, de uitvoering van de iVitality-studie was mede dankzij jullie een waardevolle toevoeging aan mijn promotietijd. Dank voor de goede samenwerking en de gezelligheid.

Alle medewerkers van de afdeling Ouderengeneeskunde waarmee ik heb samengewerkt wil ik graag bedanken voor hun bijdrage. Daarnaast dank aan de afdeling ICT voor hun onmisbare hulp bij de ontwikkeling van de iVitality-applicatie. Mijn collega-onderzoekers wil ik naast alle leerzame momenten tijdens Methode uur, Happy hour en de wetenschapsbespreking bedanken voor alle humor en gezelligheid in de 'trein' en tijdens lunch, ijs-momenten, borrels en etentjes. Dit heeft er voor gezorgd dat ik een onvergetelijke promotietijd heb gehad. Stella, dank voor al je inhoudelijke hulp, maar zeker ook voor alle gezellige gesprekken die niet over werk gingen. Heel fijn dat je mijn paranimf bent!

Van mijn vriendinnen wil ik in het bijzonder Soof, Jet, Chris, Lies, Laar en Daf bedanken voor jullie belangstelling en luisterend oor, en voor alle afleiding en ontspanning!

9

Lieve Neel en Maarten, bij jullie thuis waren mijn proefschrift-zorgen altijd ver weg, waarvoor dank. Maart, veel dank voor je hulp bij de lay-out van de kaft. Lieve Kaat, bij twijfel, tegenslagen, geluksmomenten; over grote of kleine dingen kan ik altijd bij je terecht. Dank voor al je lieve peptalks de afgelopen jaren.

Lieve pap en mam, jullie hebben mij altijd gestimuleerd om mijzelf te ontwikkelen. Dank voor jullie onvoorwaardelijke steun, grote interesse en dat jullie er altijd voor mij zijn.

Lieve Erik, je geduld, relativeringsvermogen en humor stelt mij altijd weer gerust en maakt mij altijd weer aan het lachen. Veel dank hiervoor; ik heb zin in de rest van ons leven samen!