Hypertensive organ damage in patients with vascular disease

Anneloes Vlek

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Hypertensieve orgaanschade bij patiënten met manifest vaatlijden
(met een samenvatting in het Nederlands)

Proefschrift

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door

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geboren op 28 augustus 1982 te Leusden

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Co-promotor: Dr. F.L.J. Visseren

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Manuscripts based on the studies presented in this thesis

Chapter 2.1

Vlek ALM, van der Graaf Y, Spiering W, Visseren FLJ and the SMART study group. Effect of metabolic syndrome or type 2 diabetes mellitus on the occurrence of recurrent vascular events in hypertensive patients. *Journal of Human Hypertension 2008;22:358-365*.

Chapter 2.2

Vlek ALM, van der Graaf Y, Sluman MA, Moll FL, Visseren FLJ and the SMART study group. Metabolic syndrome and vascular risk in patients with peripheral arterial occlusive disease: a 5.5-year follow-up study. *Journal of Vascular Surgery 2009 Feb 14 [epub ahead of print]*.

Chapter 3.1

Vlek ALM, van der Graaf Y, Braam B, Moll FL, Nathoe HM, Visseren FLJ and the SMART study group. Decline in renal function and the influence of blood pressure in patients with atherosclerotic vascular disease. A cohort study. *In revision American Journal of Kidney Diseases*.

Chapter 3.2

Vlek ALM, van der Graaf Y, Spiering W, Algra A, Visseren FLJ and the SMART study group. Cardiovascular events and all-cause mortality by albuminuria and decreased glomerular filtration rate in patients with vascular disease. *Journal of Internal Medicine 2008;264:351-360*.

Chapter 4.1

Vlek ALM, Visseren FLJ, Kappelle LJ, Witkamp TD, Vincken KL, Mali WP, van der Graaf Y and the SMART study group. Blood pressure and white matter lesions in patients with vascular disease: the SMART-MR study. *Submitted*.

Chapter 4.2

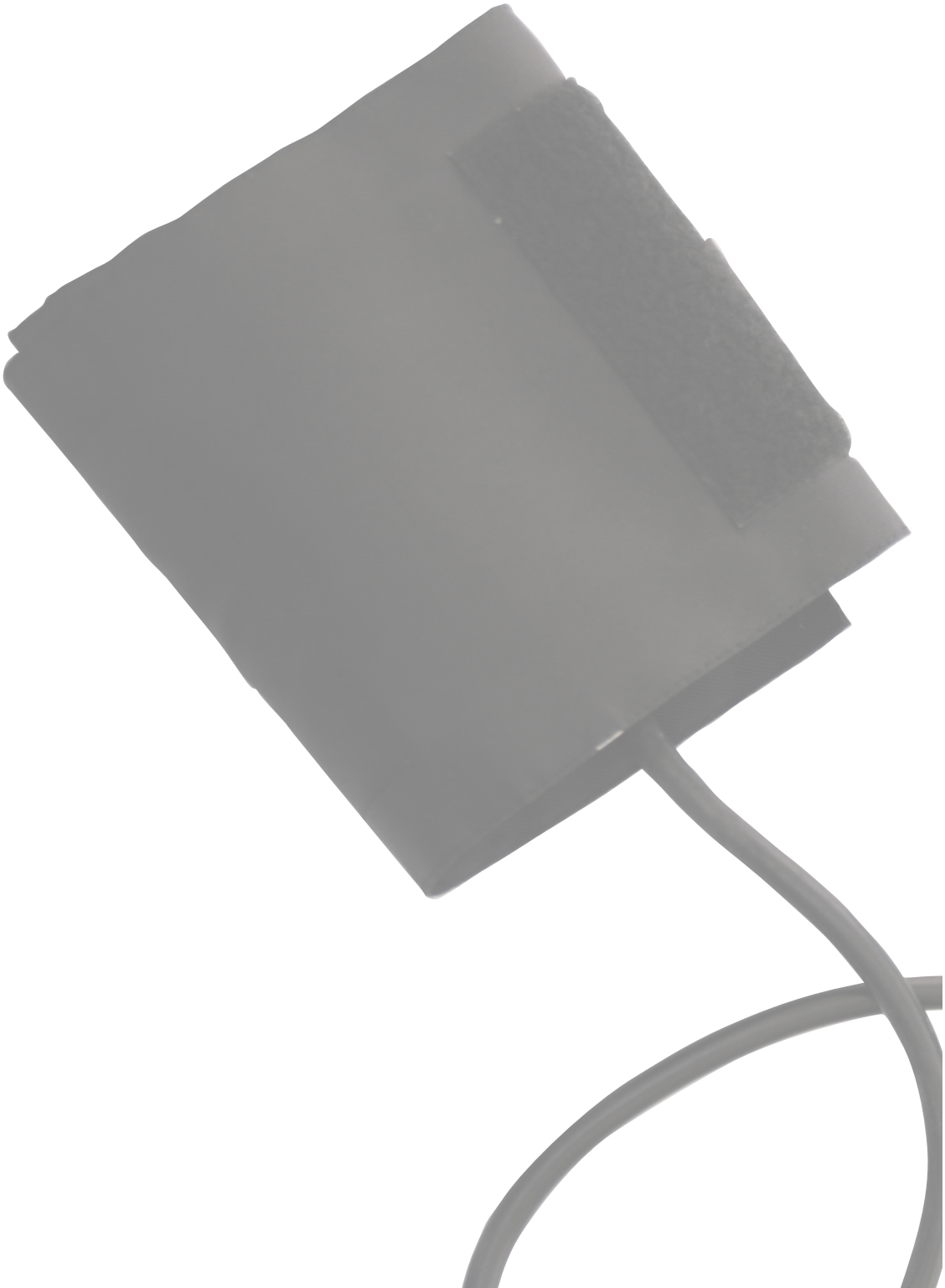
Vlek ALM, Visseren FLJ, Kappelle LJ, Geerlings MI, Vincken KL, Mali WP, van der Graaf Y and the SMART study group. Progression of cerebral atrophy and the association with blood pressure in patients with vascular disease: the SMART-MR study. *Submitted*.

Chapter 5

Vlek ALM, Visseren FLJ, Algra A, Soedamah-Muthu SS, Moll FL, Doevendans PA, Kappelle LJ, van der Graaf Y and the SMART study group. Trends in vascular risk factors and medication use in patients with various manifestations of vascular diseases or type 2 diabetes mellitus from 1996 to 2007: the Second Manifestation of ARTerial disease study. *In revision European Heart Journal*.

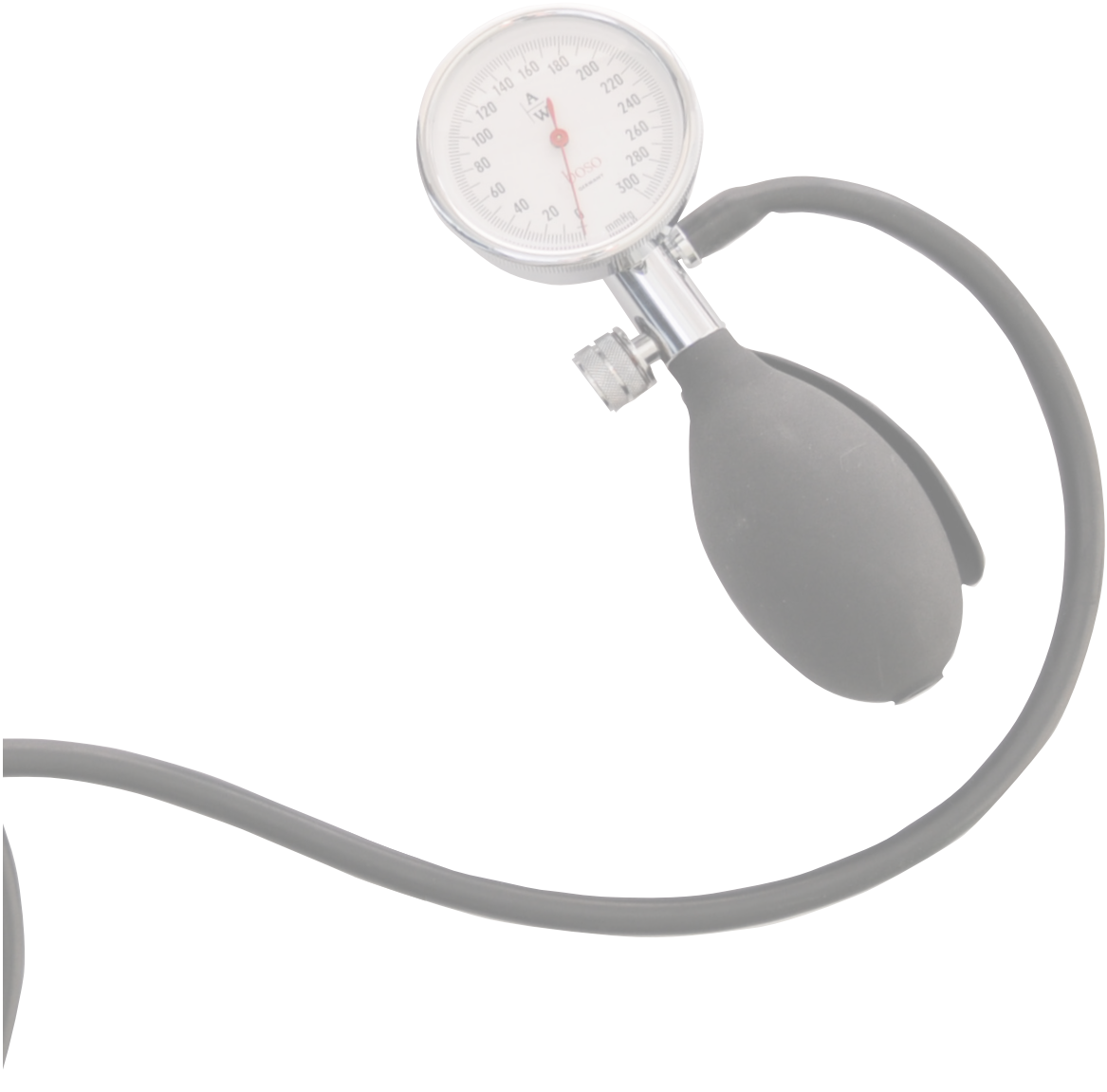
Members of the SMART study group are listed in the Appendix.

Contents



Chapter 1

General Introduction



Hypertension is one of the most common worldwide diseases afflicting humans. When hypertension is defined as an average systolic blood pressure (BP) of 140 mmHg or greater, diastolic BP of 90 mmHg or greater or the use of BP-lowering medication for earlier diagnosed hypertension, 26% of the world´s adult population in the year 2000 had hypertension. In economically developed countries, hypertension prevalence was even higher with 37% of the adult population fulfilling the hypertension criteria.[1] The high prevalence of hypertension worldwide has contributed to the present pandemic of cardiovascular disease. Of leading global risk factors, hypertension accounted for the largest number of attributable deaths.[2] About 54% of stroke and 47% of ischemic heart disease worldwide were attributable to high BP.[3]

Hypertension is one of the components that constitute the metabolic syndrome. The metabolic syndrome is a clustering of vascular risk factors, closely related to abdominal obesity and insulin resistance, including impaired glucose tolerance, elevated BP, dyslipidemia and abdominal obesity.[4, 5] The metabolic syndrome is frequent, with prevalences reported of 20 to 30% of the adult population, depending on the criteria used.[6, 7] In patients with atherosclerotic vascular diseases, prevalences are much higher. In patients with peripheral arterial occlusive disease, the prevalence exceeds 50%.[8] Hypertension is considered one of the key features of the metabolic syndrome and is the most prevalent of metabolic syndrome components.[9] The metabolic syndrome is an important risk factor for cardiovascular morbidity and mortality, as well as for the development of type 2 diabetes mellitus.[10, 11] Whether the metabolic syndrome is also associated with an increased risk of vascular events in high-risk patients who already have hypertension and a history of vascular diseases or in patients with peripheral arterial occlusive disease is not clear. Also the course of the metabolic syndrome over time in these patients has not been extensively studied.

Hypertension, among other vascular risk factors, is detrimental to kidney structure and function.[12] When kidney damage has developed, glomerular filtration rate declines and urinary albumin excretion can occur. Apart from pathogenic renal function decline, renal function also seems to show a physiologic decline during life, but the extent of this renal function deterioration is not entirely clear and differs across populations.[13, 14] A strong relation between BP and the development of end-stage renal disease has been shown, and a large proportion of cases of end-stage renal disease is attributed to hypertension.[15] A decreased renal function in itself is also associated with an increased mortality risk and with an increased risk for the development of vascular diseases.[16] To reduce the burden of atherosclerotic kidney disease in a population with increasing numbers of patients with overt vascular diseases, information on the extent of renal function decline and on the influence of BP on this decline is required. Knowledge on the separate and combined effects of albuminuria and of a decreased estimated glomerular filtration rate on the development of vascular diseases is needed to optimize vascular risk management in patients with decreased renal function.

Also the brain suffers from elevated levels of vascular risk factors including elevated BP levels. Besides the risk of ischemic and hemorrhagic stroke, vascular risk factors are also associated with cognitive impairment and dementia,[17] and may be involved in the etiology of white matter lesions and brain atrophy.[18, 19] White matter lesions are often seen on

cerebral MRI scans of elderly people and are attributed to degenerative changes of small vessels. Brain atrophy is characterized by sulcal widening, gyral narrowing and enlargement of the brain ventricles. A better understanding of the role of vascular pathology and individual vascular risk factors in the development and progression of different manifestations of cerebral damage may add to the admission of treatment strategies.

Objectives of this thesis

The main aim of this thesis is to determine the burden of hypertension-related vascular diseases and end-organ damage in patients with vascular diseases. The objectives of this thesis are

- to investigate the influence of the metabolic syndrome on the occurrence of future vascular events in high-risk patients with vascular diseases.
- to evaluate the effect of BP on renal function decline in patients with vascular diseases, and to examine the separate and combined effects of albuminuria and kidney function on vascular disease risk.
- to investigate the association of BP with presence and progression of cerebral damage.
- to assess trends in vascular risk factors and medication use over time in patients referred with vascular diseases.

Outline of this thesis

First, in *chapter 2.1* the prevalence of the metabolic syndrome in patients with hypertension and manifest vascular disease is described, and the influence of the metabolic syndrome and of type 2 diabetes mellitus on the future occurrence of vascular events is evaluated. In *chapter 2.2*, the association between presence of the metabolic syndrome and the risk of vascular events in patients with peripheral arterial occlusive disease is investigated, as well as the course of metabolic syndrome components over time. In *chapter 3.1*, the rate of renal function deterioration in patients with vascular diseases is examined, and the effect of BP on renal function decline is assessed. The separate and combined effects of decreased estimated glomerular filtration rate and of albuminuria on the occurrence of future vascular events and on mortality are presented in *chapter 3.2*. In *chapter 4.1*, the association between BP and cerebral white matter lesion volume in patients with manifest vascular disease is investigated. In *chapter 4.2*, the rate of cerebral atrophy progression in patients with vascular diseases is evaluated, as well as the association between BP and annual change in brain volume measures. *Chapter 5* describes trends in risk factors and in medication use over a 12-year period in patients who were referred to a vascular specialist because of a vascular disease, and compares these trends between patients with different manifestations of vascular diseases. In *chapter 6*, the findings of this thesis are discussed, and in *chapter 7*, the findings of the different studies described in this thesis are summarized.

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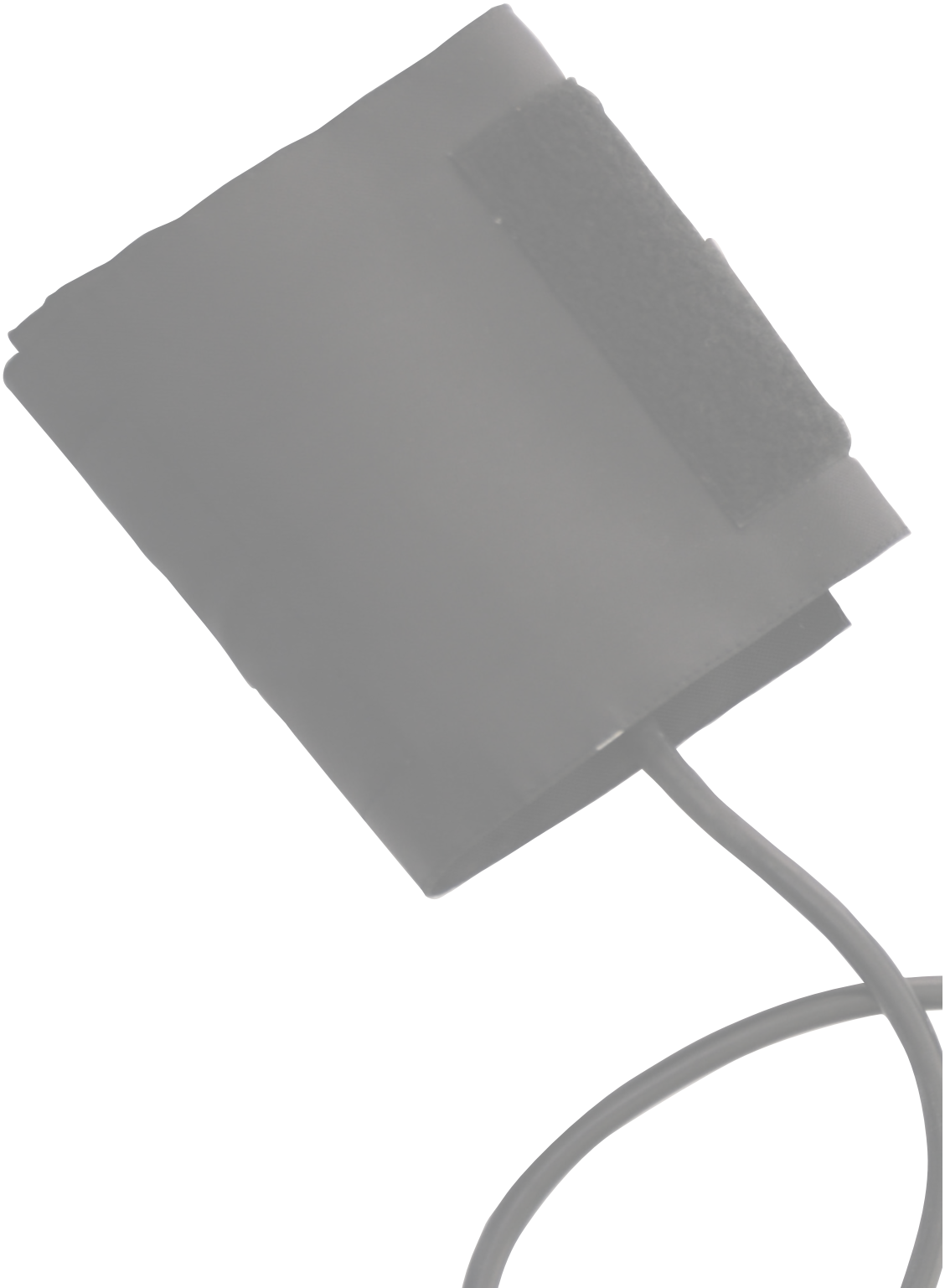
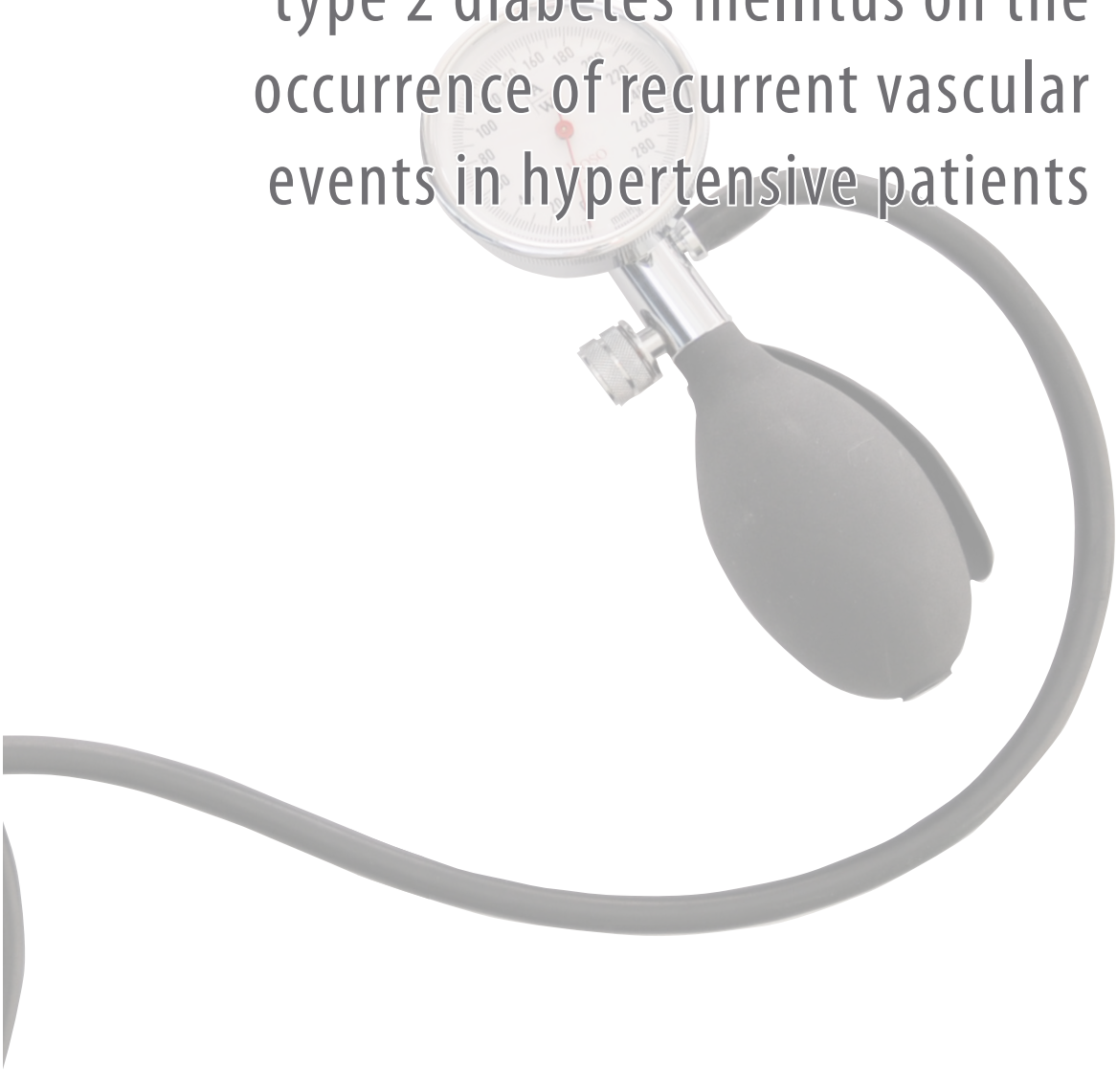


Chapter 2.1

Effect of metabolic syndrome or type 2 diabetes mellitus on the occurrence of recurrent vascular events in hypertensive patients



Abstract

Background

Patients with hypertension and manifest vascular disease are at high risk for recurrent cardiovascular diseases. It is unknown if the metabolic syndrome further increases vascular risk in these patients. This study aims to quantify the effect of metabolic syndrome and type 2 diabetes on cardiovascular events in hypertensive patients with vascular disease.

Methods

A total of 2196 hypertensive patients with vascular disease (cerebrovascular disease (34%), coronary heart disease (50%), peripheral arterial disease (28%), abdominal aortic aneurysm (13%)) from the Second Manifestations of ARTerial disease study were followed for up to 10 years (mean 3.9 years) for death, stroke and myocardial infarction. Age- and sex-adjusted hazard ratios (HR) were calculated for hypertensive patients with metabolic syndrome but without diabetes (n=775) and for hypertensive patients with type 2 diabetes (n=381), compared to merely hypertensive patients (n=1040).

Results

Forty-nine percent had metabolic syndrome (NCEP ATPIII definition) and 17% had type 2 diabetes. Metabolic syndrome predicted vascular death (HR 1.41, 95% confidence interval (CI) 1.01-1.98), stroke (HR 1.36, 95% CI 0.85-2.16) and myocardial infarction (HR 1.40, 95% CI 0.97-2.01). Type 2 diabetes accounted for even higher risks of vascular endpoints (HR 1.41-1.64). The effect of metabolic syndrome on future events could not be explained by the presence of type 2 diabetes.

Conclusions

Even in high-risk patients with hypertension and vascular disease, presence of metabolic syndrome or type 2 diabetes identifies patients at high risk for future cardiovascular events. Identifying metabolic syndrome patients may direct therapy focusing on treatment of insulin resistance by reducing weight and increasing physical activity.

Introduction

Patients with clinically manifest vascular disease are at increased risk of developing recurrent vascular events. A considerable proportion of these patients has hypertension as well, which is also a well-established cardiovascular risk factor.[1] Patients with both manifest vascular disease and hypertension make up a high-risk population for recurrent vascular disease.[1,2] In about half of patients with hypertension insulin resistance can be found and hypertension tends to cluster with metabolic risk factors.[3,4] Therefore, hypertension is considered one of the key features of the metabolic syndrome.[5,6]

The clustering of cardiovascular risk factors, often referred to as metabolic syndrome, is closely associated with central obesity and insulin resistance.[7,8] Metabolic syndrome is a highly prevalent condition with a prevalence around 20% in the general population[8-10] and 45% in patients with clinical manifestations of atherosclerosis,[11,12] while diabetes is present in 5% of the overall adult population.[13]

Presence of metabolic syndrome amplifies the risk of developing type 2 diabetes mellitus 3- to 30-fold, depending on the criteria used.[14-18] In populations free of cardiovascular disease at baseline, cardiovascular morbidity and mortality increased 1.5- to 3-fold in the presence of metabolic syndrome[10,19-21] and 2- to 4-fold in the presence of type 2 diabetes.[22] In spite of the use of different and modified definitions, the metabolic syndrome is associated with more extensive vascular damage and increased risk for subsequent events in patients with prevalent cardiovascular disease.[12,23,24] In hypertensive patients without manifest vascular disease, the metabolic syndrome has been shown to be associated with increased intima-media thickness and left ventricular hypertrophy as well as with increased incidence of cardiovascular events.[25-29]

It is not yet known whether the metabolic syndrome still is a predictor of new cardiovascular events in hypertensive patients with already clinically manifest cardiovascular disease. If the risk for future cardiovascular events in patients with hypertension and the metabolic syndrome is higher compared to those without the metabolic syndrome, these patients may benefit from more aggressive treatment of blood pressure and other risk factors. In parallel, it has been shown that patients with coronary heart disease and metabolic syndrome benefit from achieving lower LDL-cholesterol levels compared to patients with coronary heart disease without metabolic syndrome.[30]

The aim of this study is to quantify the risk of new vascular events associated with the metabolic syndrome and type 2 diabetes in patients with hypertension and manifest vascular disease.

Methods

Study design and population

The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective follow-up study in the University Medical Center Utrecht. Since 1996, more than 7000 newly referred patients aged 18-80 years with clinically manifest atherosclerotic vascular disease (cerebrovascular disease, coronary heart disease, peripheral arterial disease or abdominal aortic aneurysm) or risk factors for atherosclerosis (hyperlipidemia, type 1 diabetes, type 2 diabetes or hypertension) have been included. Patients with terminal

malignant disease, those not independent in daily activities or insufficiently familiar with the Dutch language are not included. All patients are assessed for atherosclerotic risk factors and arterial diseases by non-invasive means. The local Ethics Committee approved the study and all participants gave their written informed consent. Important objectives of the SMART study are to evaluate the presence of additional arterial disease and risk factors in patients with manifest vascular disease or a vascular risk factor. The rationale and design of the SMART study have been described in detail elsewhere.[31]
This analysis is based on patients included in the screening period from January 1996 to March 2005 and contains data on 2196 patients with clinically manifest vascular disease (at inclusion or in past history), who also had hypertension at inclusion. Normotensive patients with manifest vascular disease (n=1090) and patients with type 1 diabetes mellitus (n=22) were not included in data analyses. Clinically manifest vascular disease was defined as cerebrovascular disease, coronary heart disease, abdominal aortic aneurysm or peripheral arterial disease at inclusion or in past history. Cerebrovascular disease included transient ischemic attack, cerebral infarction, amaurosis fugax or retinal infarction; coronary heart disease included myocardial infarction and admission for percutaneous transluminal coronary angioplasty or coronary artery bypass graft; abdominal aortic aneurysm included abdominal aortic aneurysm ≥3.0 cm or aneurysm surgery; peripheral arterial disease included claudication of the legs, which was symptomatic and confirmed by a resting ankle-brachial pressure index <0.9 in at least one leg, percutaneous transluminal angioplasty or leg amputation. A description of the composition of the study population is shown in *Figure 1*.

Measurements

All patients who entered the SMART study underwent a diagnostic screening-protocol for detection of manifestations of atherosclerotic disease and vascular risk factors. Physical examination included assessments of height, weight, waist and hip circumferences and blood pressure. Blood pressure was measured by sphygmomanometry at the right and left upper arm and repeated on the side with the highest values. The mean of all obtained measurements was used in the analyses.[31] This assessment seems to be reliable as in a sample of 211 patients who underwent a second blood pressure measurement after 5.5 ± 1.3 years, 94% of newly diagnosed hypertensive subjects at inclusion were still hypertensive or receiving blood pressure-lowering agents at the second measurement.
Fasting blood samples were taken to ascertain levels of lipids, glucose, creatinine and homocysteine. Urinary albumin and creatinine concentrations were determined and duplex scanning of the carotid arteries, ultrasonography of the abdomen, electrocardiography and ankle-brachial pressure index were performed. The techniques of the baseline examinations have been published formerly.[31] All subjects completed a health questionnaire on cardiovascular history, risk factors, familial vascular history and medication use.

Definitions

Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or use of blood pressure-lowering drug therapy. According to the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treat-

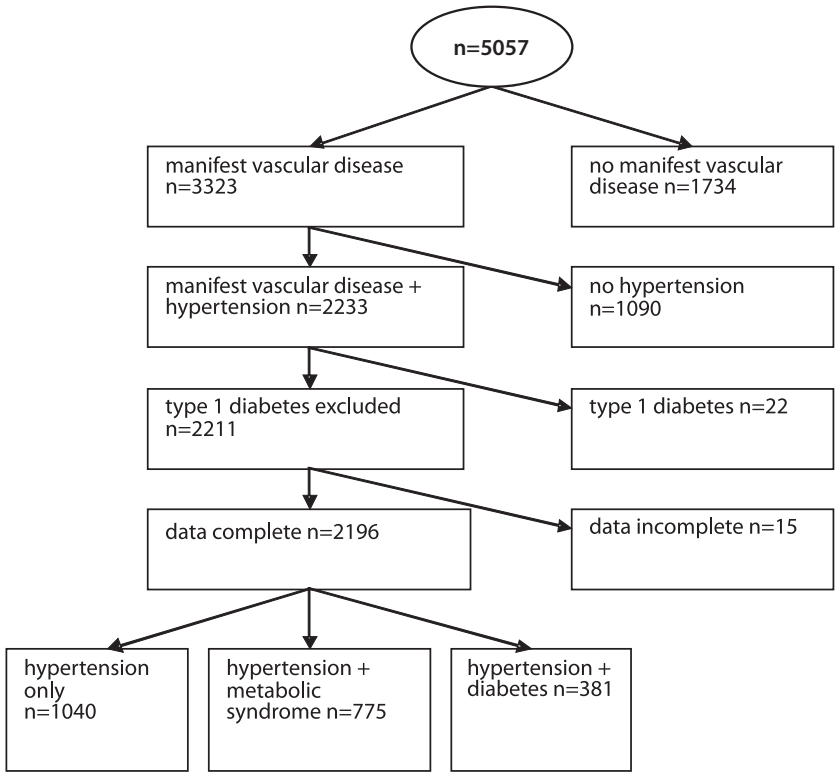


Figure 1 Composition of study population.

ment Panel III),[7] metabolic syndrome is defined as the presence of 3 or more of the following: 1) waist circumference >88 cm in women and >102 cm in men; 2) fasting triglycerides ≥1.70 mmol/l (150 mg/dl); 3) HDL-cholesterol <1.29 mmol/l (50 mg/dl) in women and <1.04 mmol/l in men (40 mg/dl); 4) blood pressure ≥130/85 mmHg or use of blood pressure-lowering drug therapy; and 5) fasting glucose ≥6.1 mmol/l (110 mg/dl) or use of glucose-lowering agents. As all patients in this study satisfy the blood pressure criterion, the metabolic syndrome was diagnosed when 2 or more of the other criteria were present in addition to the blood pressure criterion. Type 2 diabetes was diagnosed as self-reported type 2 diabetes or use of glucose-lowering therapy. On the basis of these definitions, study subjects were divided into 3 separate groups. Those diagnosed with type 2 diabetes made up the diabetic group, irrespective of additional presence of the metabolic syndrome. The second group consisted of non-diabetic patients fulfilling the metabolic syndrome criteria, and remaining patients constituted the reference group of non-diabetic hypertensive patients without the metabolic syndrome.

Follow-up procedure and endpoint evaluation

On a half-yearly basis, information on hospitalization and outpatient clinic visits was obtained by questionnaires and telephone interviews with patients. For the subjects who reported a cardiovascular event, original source documents were retrieved and reviewed

to determine the occurrence of cardiovascular disease. Additional information was collected on vascular interventions and death from other causes.
Outcome events used in our study include 1) vascular death; 2) non-fatal and fatal stroke; 3) non-fatal and fatal myocardial infarction and sudden death and 4) combined vascular events (non-fatal and fatal stroke, non-fatal and fatal myocardial infarction and sudden death). Vascular death was defined as sudden death (unexpected cardiac death occurring within 1 hour after onset of symptoms or within 24 hours given convincing circumstantial evidence) or death from stroke, myocardial infarction, congestive heart failure or rupture of abdominal aortic aneurysm. Patients with stroke had relevant clinical features causing an increase in impairment of at least one grade on the modified Rankin scale, accompanied by an infarction or hemorrhage on a repeat CT-scan. Myocardial infarction was defined by at least two of the following criteria: 1) chest pain for at least 20 minutes, not disappearing after administration of nitrates; 2) ST-elevation >1 mm in two following leads or a left bundle branch block on the electrocardiogram; 3) creatine kinase elevation of at least two times the normal value of creatine kinase and a myocardial band fraction >5% of the total creatine kinase. All possible events were audited independently by 3 members of the Endpoint Committee.

Statistical analysis

Results are expressed as mean ± standard deviation (SD) for continuous variables and as percentages with the number of patients in brackets for categorical variables. Survival free from vascular mortality, myocardial infarction and sudden death, stroke and combined vascular events was evaluated with the use of a Cox proportional hazards model separately for hypertensive patients with metabolic syndrome but not type 2 diabetes and for hypertensive patients with type 2 diabetes. Merely hypertensive patients served as the reference category in the analyses. Any first occurrence of an event during the follow-up period was used in the model. As all patients already had manifest vascular disease, these were all recurrent vascular events. The extent of confounding was assessed by comparing the crude hazard ratio (HR) derived from the initial model with the adjusted HR derived from the model that contained the potential confounding variable. HRs were adjusted for age and sex. All statistical analyses were performed with SPSS 14.0 for Windows (SPSS, Chicago, Illinois, USA).

Results

Baseline characteristics

From the total study population of 2196 patients, 1040 patients (48%) had hypertension and did not have metabolic syndrome or type 2 diabetes, 775 patients (35%) had hypertension in combination with metabolic syndrome but not type 2 diabetes and 381 patients (17%) had hypertension and type 2 diabetes (*Table 1*). In type 2 diabetic patients, 78.5% did also meet the metabolic syndrome criteria.
In the total study population of hypertensive patients with manifest vascular disease, the prevalence of metabolic syndrome was 49%. After hypertension (100%), the criterion for triglycerides was most frequently present (76%) in patients with metabolic syndrome, followed by the criteria for HDL-cholesterol (69%), waist circumference (54%) and fasting

Table 1 Baseline characteristics of the study population.

	MetS[a] – DM[b] – n=1040	MetS[a] + DM[b] – n=775	DM[b] + n=381
Ever cerebrovascular disease	36 (375)	30 (230)	41 (157)
Ever coronary heart disease	49 (507)	51 (393)	53 (202)
Ever peripheral arterial disease	23 (238)	30 (231)	31 (119)
Ever abdominal aortic aneurysm	14 (140)	16 (120)	8 (30)
Male gender	76 (795)	72 (557)	71 (270)
Age (years)	61.9 ± 10.0	60.3 ± 10.1	62.9 ± 9.1
Smoking, current or past[c]	81 (844)	84 (649)	78 (295)
Body mass index (kg/m^2)	25.4 ± 3.2	28.4 ± 4.1	28.0 ± 4.1
Waist circumference (cm)	92 ± 10	101 ± 11	100 ± 11
Triglycerides (mmol/l)	1.43 ± 0.86	2.59 ± 2.37	2.05 ± 1.01
HDL-cholesterol (mmol/l)	1.41 ± 0.37	1.05 ± 0.28	1.10 ± 0.30
Glucose (mmol/l)	5.6 ± 0.7	6.4 ± 1.5	9.0 ± 3.0
Systolic blood pressure (mmHg)	153 ± 20	150 ± 19	154 ± 21
Diastolic blood pressure (mmHg)	86 ± 11	84 ± 11	83 ± 11
Duration of hypertension (years)	10.2 ± 12.7	11.0 ± 12.0	12.5 ± 13.5
Creatinine (µmol/l)	104.9 ± 89.9	99.9 ± 52.0	105.2 ± 89.8
Creatinine clearance[d] (ml/min/1.73m^2)	72.8 ± 19.4	72.7 ± 19.6	73.9 ± 22.6
Albuminuria[e]	17 (166)	20 (141)	29 (103)
Use of lipid-lowering drugs	48 (497)	48 (371)	54 (203)
Use of glucose-lowering agents	0 (0)	0 (0)	94 (355)
Use of blood pressure-lowering agents	62 (647)	71 (552)	73 (277)
Amount of antihypertensive agents			
0 agents	38 (393)	29 (223)	27 (104)
1 agent	33 (340)	31 (238)	28 (105)
2 agents	20 (205)	28 (218)	29 (110)
3 or more agents	9 (102)	12 (96)	16 (62)
Type of antihypertensive agents			
Beta blockers	37 (389)	47 (366)	39 (150)
Diuretics	14 (143)	20 (158)	24 (90)
Ca channel blockers	20 (203)	25 (193)	22 (82)
ACE inhibitors	23 (239)	25 (190)	40 (153)
ATII antagonists	6 (64)	7 (53)	8 (29)
Rest group[f]	4 (33)	3 (19)	5 (21)

[a] metabolic syndrome according to the ATPIII criteria; [b] self-reported type 2 diabetes and/or use of glucose lowering agents; [c] smoking or previously smoking; [d] Modification of Diet in Renal Disease formula; [e] albumin-to-creatinine ratio >3 mg/mmol; [f] combination preparations, centrally active agents, alpha blockers
Continuous variables are expressed as mean ± SD and categorical variables as percentages with the number of patients between parentheses.

glucose (53%). Mean blood pressure in treated hypertensives was 150/84 mmHg compared to 155/85 mmHg in untreated subjects.

Incidence of vascular events

During a mean follow-up period of 3.9 years (range 0.5 to 8.5 years), 176 vascular deaths, 94 non-fatal and fatal strokes and 147 non-fatal and fatal myocardial infarctions and sudden deaths were recorded. In total, there were 283 recurrent vascular events.

Survival analysis

Event-free survival curves, derived from an age- and sex-adjusted Cox proportional hazards model, are shown for the endpoints vascular death, stroke, non-fatal and fatal myocardial infarction and sudden death and combined vascular events (*Figures 2a-d*). Metabolic syndrome was associated with a higher risk for vascular death (HR 1.41; 95% confidence interval (CI) 1.01-1.98) and for myocardial infarction and sudden death (HR 1.40; 95% CI 0.97-2.01), adjusted for age and sex in this hypertensive cohort (*Table 2*).

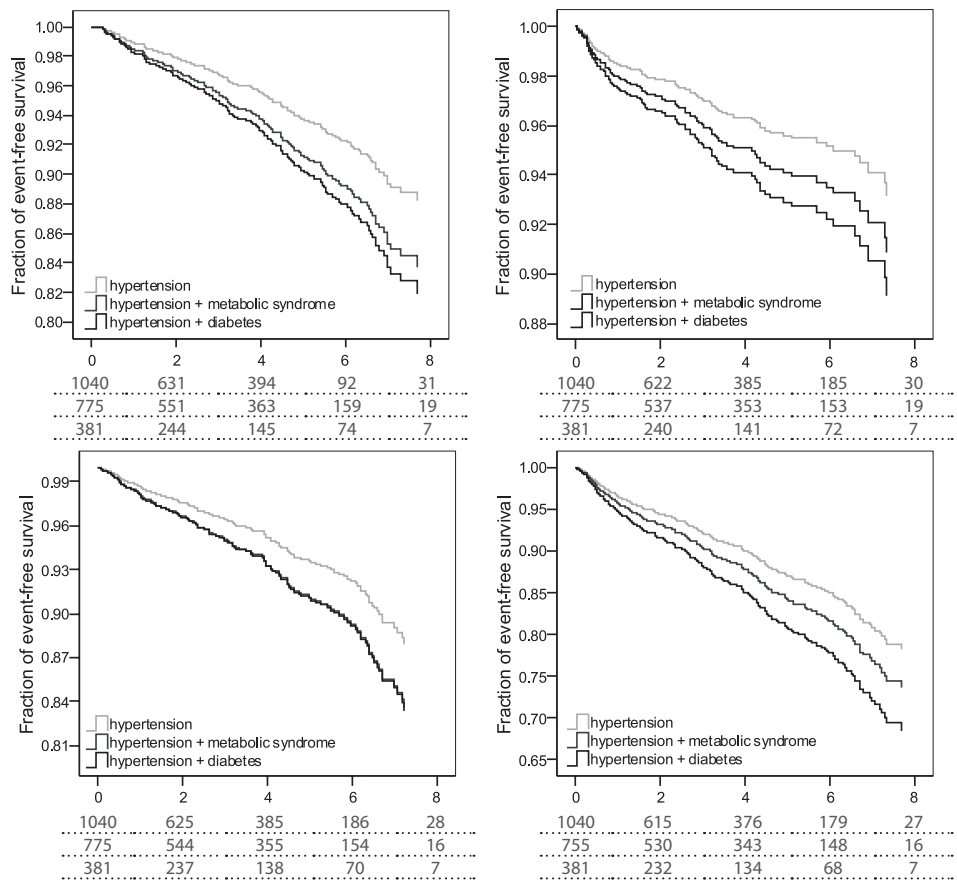


Figure 2 Fraction of hypertensive patients free from vascular death (a), stroke (b), myocardial infarction and sudden death (c) and combined vascular events (d) according to metabolic syndrome and type 2 diabetes, adjusted for age and sex. Lines for metabolic syndrome and type 2 diabetes overlap in (c).

Table 2 Hazard ratios (HRs) of metabolic syndrome and type 2 diabetes for categories of future events.

	Vascular death (n=176)	Stroke (n=94)	Myocardial infarction and sudden death (n=147)	Combined vascular endpoints (n=283)
	HR (95% CI;p-value)	HR (95% CI;p-value)	HR (95% CI;p-value)	HR (95% CI;p-value)
Hypertension only	1.00 (n=68)	1.00 (n=35)	1.00 (n=57)	1.00 (n=113)
Hypertension + MetS[a]	1.41 (1.01-1.98;0.046) (n=68)	1.36 (0.85-2.16;0.2) (n=37)	1.40 (0.97-2.01;0.07) (n=60)	1.24 (0.95-1.62;0.1) (n=105)
Hypertension + DM[b]	1.59 (1.07-.35;0.02) (n=40)	1.64 (0.96-.79;0.07) (n=22)	1.41 (0.91-2.20;0.1) (n=30)	1.54 (1.13-2.09;0.006) (n=65)

[a] metabolic syndrome according to the ATPIII criteria; [b] self-reported type 2 diabetes and/or use of glucose-lowering agents
HRs are adjusted for age and sex.

Although less explicit and not statistically significant, there was a distinct relation between metabolic syndrome and stroke (HR 1.36; 95% CI 0.85-2.16) and between metabolic syndrome and combined vascular events (HR 1.24; 95% CI 0.95-1.62). Type 2 diabetes was associated with an increased risk for vascular death (HR 1.59; 95% CI 1.07-2.35), stroke (HR 1.40; 95% CI 0.96-2.79) and the combined vascular endpoint (HR 1.54; 95% CI 1.13-2.09). For all analyses, additional adjustment for the amount and type of blood pressure-lowering agents did not substantially change the HRs.

Discussion

In a high-risk population of patients with hypertension and clinically manifest vascular disease, the presence of the metabolic syndrome entails a 1.41-fold greater risk for vascular death as well as a 1.40-fold greater risk for myocardial infarction and sudden death. In hypertensive patients with type 2 diabetes, the risk for vascular death (HR 1.59), combined vascular events (HR 1.54) and stroke (HR 1.64) is higher than for those without diabetes. Unless similar blood pressure and age at baseline, hypertensive patients with metabolic syndrome or diabetes are at higher risk for new cardiovascular events than hypertensive patients without metabolic syndrome or diabetes.

In studies among non-diabetic hypertensive subjects without cardiovascular disease, metabolic syndrome was present in 25-30% of patients.[25, 27, 29] In this study population, consisting of (treated) hypertensive patients with clinically manifest vascular disease, 49% of patients meet the metabolic syndrome criteria. In patients without diabetes this was 35%. The high prevalence of metabolic syndrome we observed is probably due to the fact that only hypertensive subjects with manifest vascular disease were included.

Several studies have demonstrated an association between metabolic syndrome and increased intima-media thickness, higher urinary albumin excretion and left ventricular hypertrophy in hypertensive subjects without manifest vascular disease.[25, 26, 29] In this population, presence of metabolic syndrome was also associated with an increased amount of cardiovascular events.[28] A few studies compared the effects of metabolic syndrome and diabetes on cardiovascular disease. The role of the metabolic syndrome in predicting all-cause and cardiovascular mortality in patients with established cardiovascular disease was

examined in the San Antonio Heart Study. After adjustment for diabetes and in subgroup analyses of non-diabetic and diabetic patients, the metabolic syndrome was no longer associated with both all-cause and cardiovascular mortality, which made the authors conclude that only diabetes accounted for the enhanced mortality in the metabolic syndrome group.[32] In NHANES III, participants with metabolic syndrome and diabetes showed the highest prevalence of cardiovascular disease, followed by those with metabolic syndrome without diabetes and patients with neither. However, in multivariate analysis metabolic syndrome was no longer a significant predictor of cardiovascular disease.[33] In patients with coronary heart disease, both metabolic syndrome without diabetes and diabetes alone were predictive of all-cause and cardiovascular mortality.[24] Similar to our population, diabetic patients had the highest mortality risk. A study among post-myocardial infarction patients showed a higher probability of death and cardiovascular events in both metabolic syndrome and diabetic patients.[34] In the Framingham Offspring Study, stroke risks were compared between metabolic syndrome and diabetic patients in a population in which some but not all patients had a history of cardiovascular disease. Patients with diabetes and metabolic syndrome were at greatest risk of stroke, followed by patients with diabetes alone and metabolic syndrome alone.[35] In our study, type 2 diabetes was associated with an increased risk of stroke, while an association between metabolic syndrome and stroke risk was evident but not statistically significant. This is probably due to the difference in study populations and the relatively small number of strokes (n=94) in our study.

In this study, metabolic syndrome is markedly associated with an increased risk of cardiovascular events. There are several mechanisms possibly underlying this association. The suggestion is made that the effect of the metabolic syndrome is primarily driven by the inclusion of diabetes in the definition.[32] Although the vascular risk caused by the metabolic syndrome is partly due to diabetes, as shown by studies where the effect of the metabolic syndrome was attenuated or disappeared after adjustment for diabetes or after subgroup analyses in diabetic and non-diabetic patients,[32, 33] it is not likely that the vascular risk associated with the metabolic syndrome is completely caused by the inclusion of diabetic patients, as our study still identifies an association between the metabolic syndrome and vascular events apart from diabetes. Other possible mechanisms causing an increased risk of vascular disorders in hypertensive patients with metabolic syndrome are insulin-mediated renal sodium reabsorption and vasoconstriction due to activation of the sympathetic nerve system and the renin-angiotensin-aldosterone system. Besides these mechanisms, there are other not routinely measured factors such as hypercoagulability, oxidative stress, pro-inflammatory state, hyperinsulinemia and impaired fibrinolysis associated with the metabolic syndrome, which may contribute in increasing cardiovascular risk. As the metabolic syndrome may precede diabetes, the vascular risk associated with the metabolic syndrome may also in part be mediated by the development of type 2 diabetes during follow-up. In this study, a gradual effect of metabolic syndrome and type 2 diabetes was seen on the risk of cardiovascular events. Metabolic syndrome can be seen as a pre-diabetic state with insulin resistance as the key feature. Owing to this central underlying pathophysiological mechanism, different combinations of the same number of metabolic syndrome traits are roughly comparable regarding vascular risk. Subjects who

developed type 2 diabetes during 8-year follow-up were found to have increased triglyceride levels, decreased HDL-cholesterol levels, increased systolic blood pressure, slightly increased fasting glucose levels and much higher insulin levels at baseline than subjects who did not develop diabetes.[36] Therefore, the cardiovascular risk accompanied by the metabolic syndrome is lower than that of type 2 diabetes patients and higher than that of non-metabolic syndrome patients.

We acknowledge several limitations of this study. The SMART database does not provide information on blood pressure values during follow-up, so we could only classify patients as hypertensive based on their baseline blood pressure and/or use of blood pressure-lowering medication. A white-coat effect may also be involved in the blood pressure measurements. However, in a sample of patients who underwent a second blood pressure measurement, 94% of newly diagnosed hypertensives were still hypertensive or receiving blood pressure-lowering agents. Inclusion of patients started in 1996, but the metabolic syndrome was defined retrospectively according to the NCEP criteria. In the group of patients with type 2 diabetes, there are both patients with and without the metabolic syndrome. Owing to the number of patients in this group, we were not able to separate these two subgroups.

In conclusion, even in a high-risk population of hypertensive patients with manifest vascular disease, it is still possible to differentiate between patients with lower and higher risks of recurrent vascular disease: metabolic syndrome increases the risk of vascular events with 25-40%, whereas type 2 diabetes shows a 40-65% increase in vascular risk. These results support the importance of aggressive treatment of blood pressure and other cardiovascular risk factors in high-risk patients. Besides aggressive treatment of individual risk factors, hypertensive patients with the metabolic syndrome may benefit from intensive lifestyle therapies such as stimulating physical activity and weight reduction aiming to decrease insulin resistance.

Table 3

What is known about the topic	What this study adds
Patients with hypertension and vascular disease are at high risk for recurrent vascular diseases	Even in a hypertensive population with manifest vascular disease the metabolic syndrome and diabetes are still predicitive of future cardiovascular disease
The metabolic syndrome and diabetes increase the risk of developing cardiovascular events in different populations	Based on their higher risk for future vascular events, hypertensive patients with the metabolic syndrome or diabetes may benefit from aggressive risk factor treatment and lifestyle changes

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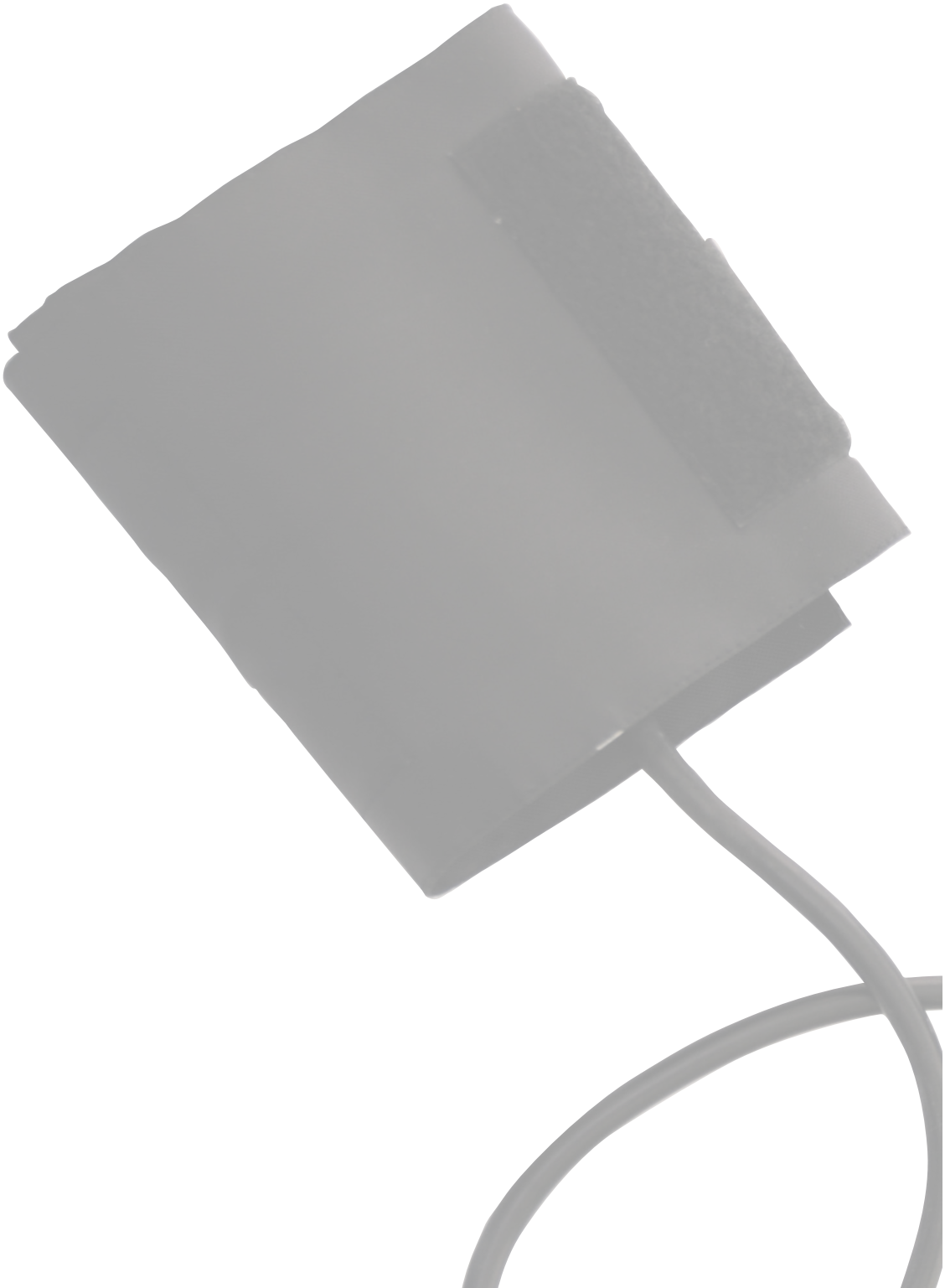
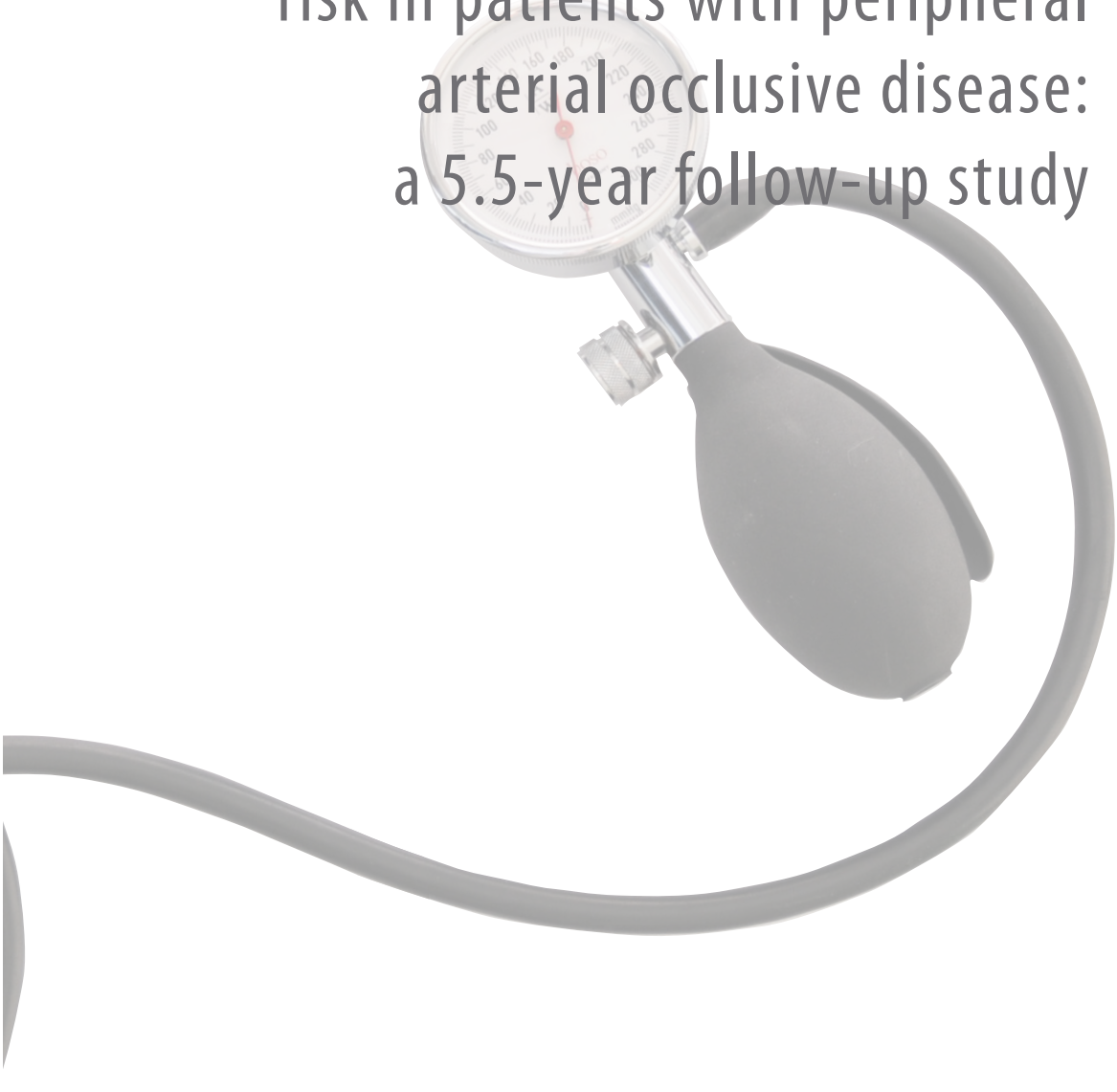


Chapter 2.2

Metabolic syndrome and vascular risk in patients with peripheral arterial occlusive disease: a 5.5-year follow-up study



Abstract

Background

Peripheral arterial occlusive disease (PAOD) is associated with a high risk of cardiovascular events. The metabolic syndrome is a frequent condition among patients with manifest vascular disease, but the influence of the metabolic syndrome on cardiovascular events in patients with PAOD is unknown. Also, progression and regression of the metabolic syndrome after follow-up are not extensively studied.

Methods

The study population consisted of 461 patients with symptomatic PAOD from the Second Manifestations of ARTerial disease study. Patients underwent vascular screening at baseline and after a mean follow-up of 5.5 ± 1.3 years. Hazard ratios (HR) with 95% confidence intervals (95% CI) for vascular events according to metabolic syndrome status (updated NCEP criteria) were calculated using Cox regression analysis. The course of the metabolic syndrome during follow-up and the influence of body mass index (BMI) on development or disappearance of the syndrome were assessed.

Results

During follow-up, 91 first vascular events were recorded. Cumulative 3-year survival free from vascular events was 84.7% in metabolic syndrome patients compared to 92.1% in participants without the syndrome. The metabolic syndrome was associated with an increased risk of vascular events (HR 1.51; 95% CI 1.01-2.30, age- and sex-adjusted). During follow-up, 128 patients died or were lost to follow-up and of 333 remaining patients, 221 participated in follow-up measurements. The metabolic syndrome disappeared in 16% of patients and was incident in 14% of patients during follow-up. Waist circumference increased with 10 ± 8 cm in those developing the syndrome. A BMI decrease of 1 kg/m^2 significantly decreased the risk of metabolic syndrome development by 23% (OR 0.77; 95% CI 0.62-0.96), and increased the chance to revert to a non-metabolic syndrome state by 32% (OR 1.32; 95% CI 1.03-1.71).

Conclusions

The metabolic syndrome is associated with a 1.5-fold increase in risk of vascular events in PAOD patients. Weight control reduces metabolic syndrome incidence and increases metabolic syndrome resolution during follow-up.

Introduction

Peripheral arterial occlusive disease (PAOD) is most often the result of atherosclerosis in the arteries of the lower extremities and is associated with a high risk of vascular events at other sites of the vasculature (myocardial infarction, stroke) and death.[1-4] Risk factors for developing vascular complications in PAOD patients are hypertension, hypercholesterolemia, diabetes, smoking and atherosclerotic vascular diseases in other vascular beds.[4] Often vascular risk factors cluster in single patients as the result of central obesity, referred to as metabolic syndrome.

The metabolic syndrome is defined as the clustering of at least three risk factors such as abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia and low HDL-cholesterol levels. The age-dependent prevalence of the metabolic syndrome is between 20% and 40% in healthy subjects,[5] whereas the metabolic syndrome is present in 45% of patients with manifest vascular disease.[6] In particular in patients with PAOD the condition is remarkably frequent, with prevalences of 52% and 58% reported for this population.[6, 7] Presence of metabolic syndrome in PAOD patients is associated with advanced vascular damage.[8]

In populations free of cardiovascular disease at baseline, cardiovascular morbidity and mortality increased 1.5- to 3-fold in the presence of the metabolic syndrome.[9, 10] Also in patients with a history of myocardial infarction or coronary heart disease, the metabolic syndrome was associated with increased risks of cardiovascular events or death.[9, 11-14]

Considering the high absolute risk of vascular morbidity and mortality in PAOD patients, the high prevalence of the metabolic syndrome in this population as well as the increased vascular risk accompanied by the metabolic syndrome, it might be an important condition in patients with PAOD.

Given the high prevalence of the metabolic syndrome in PAOD patients, it is also important to gain understanding about how the metabolic syndrome develops over time. No information is currently available on the course of the metabolic syndrome or on possible improvement or worsening in individual metabolic syndrome characteristics in patients with PAOD.

The aim of this prospective cohort study was to quantify the risk of vascular events associated with the metabolic syndrome in PAOD patients. Second, we studied determinants of incidence and disappearance of the metabolic syndrome during follow-up as well as the changes in individual metabolic syndrome components.

Methods

Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. The SMART study is an ongoing single-center prospective cohort study that was designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular disease or a vascular risk factor. Since 1996, more than 8000 patients aged 18-80 years with atherosclerotic vascular disease (cerebrovascular disease, coronary heart disease, PAOD or abdominal aortic an-

eurysm (AAA)) or risk factors for atherosclerosis (hyperlipidemia, diabetes or hypertension) have been included. The study was approved by the local Ethics Committee and all patients gave written informed consent. Rationale and design of the SMART study have been described previously.[15]

The current study was based on the data of SMART participants included because of PAOD. These patients were referred to the department of vascular surgery of the University Medical Center Utrecht with symptomatic PAOD (intermittent claudication, non-healing ulcers or gangrene) and had a resting ankle brachial pressure index (ABI) less than or equal to 0.90. The data of 461 consecutive patients included in the screening program between September 1996 and December 2000 were available for analysis.[16] Patients were invited to visit the hospital again for a follow-up measurement in the period between September 2003 and March 2005. In the intervening period, patients received usual care from their own general practitioner or vascular specialist.

Vascular screening

Patients underwent standardized screening for detection of manifestations of atherosclerotic disease and vascular risk factors both at baseline and after follow-up. Participants completed a questionnaire on cardiovascular history, medication use and risk factors. Severity of PAOD was classified according to the Fontaine classification.[17] After an overnight fast, patients visited the hospital where physical examination was carried out, consisting of measurements of weight, height, waist and hip circumferences and blood pressure. Measurements were performed according to a standardized protocol. Fasting blood was sampled to ascertain levels of glucose, total cholesterol, HDL-cholesterol, triglycerides, creatinine and homocysteine. LDL-cholesterol levels were calculated with Friedewald's formula. Morning urine samples were collected to measure albumin and creatinine concentrations. All assessments were performed at a single laboratory. ABI was assessed for each leg by calculating ratios of the highest systolic blood pressure measured at the ankle to the highest systolic blood pressure in both arms with the patient in supine position. Systolic blood pressure in the posterior tibial and dorsal pedal arteries (left and right) was measured with an 8-MHz continuous-wave Doppler probe connected to an IMEXLAB 9000 Vascular Diagnostic System (Imex Medical Systems Inc., Golden, Colorado, USA). Systolic blood pressure in both brachial arteries was determined with a semiautomatic oscillometric device (Omega 1400, Invivo Research Laboratories Inc., Broken Arrow, Oklahoma, USA). Screening also included duplex scanning of the carotid arteries, electrocardiography and ultrasonography of the abdomen with measurements of the anteroposterior aortic and juxtarenal diameter. Results of the screening and recommendations for treatment, formulated by a team of medical specialists, were reported to the general practitioner and other treating specialists. The techniques of the baseline examinations have been published formerly.[15]

Definitions

Metabolic syndrome was defined as the presence of 3 or more of the following: 1) waist circumference ≥88 cm in women and ≥102 cm in men; 2) fasting triglycerides ≥1.70 mmol/l (150 mg/dl) or drug treatment for elevated triglycerides; 3) HDL-cholesterol <1.30

mmol/l (50 mg/dl) in women and <1.03 mmol/l in men (40 mg/dl) or drug treatment for reduced HDL-cholesterol; 4) blood pressure ≥130/85 mmHg or use of blood pressure-lowering medication; and 5) fasting glucose ≥5.6 mmol/l (100 mg/dl) or use of glucose-lowering medication, according to the AHA/NHLBI updated National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) criteria.[18] If waist circumference was not available, a body mass index (BMI) ≥30 kg/m^2 was used as determinant for abdominal obesity.[19] Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or self-reported use of blood pressure-lowering medication.[20] Type 2 diabetes mellitus was defined as self-reported type 2 diabetes, use of glucose-lowering agents or fasting glucose ≥7.0 mmol/l at screening.[21] In this way, diabetes mellitus also included newly diagnosed patients with diabetes mellitus. Patients were classified as smoking when currently smoking or stopped smoking in the year of inclusion in the SMART study. The 4-variable Modification of Diet in Renal Disease (MDRD) equation was used to calculate estimated glomerular filtration rate (eGFR). At follow-up the homeostatic model assessment (HOMA) for insulin sensitivity was added to the measurements to estimate insulin resistance.[22]

Follow-up and outcome evaluation

Patients provided information on hospitalization and outpatient clinic visits in response to a short questionnaire every 6 months. When a cardiovascular event was reported, original source documents were retrieved and reviewed to determine the occurrence of cardiovascular disease. All possible events were audited independently by three members of the Endpoint Committee. Patients were followed until death or refusal of further participation. The main outcome of interest for this study was a composite of first occurrence of stroke, myocardial infarction or vascular death. Definitions of events are shown in *Table 1*.

Table 1 Definitions of events.

Vascular death	-	Sudden death (unexpected cardiac death occurring within 1 h after onset of symptoms, or within 24 h given convincing circumstantial evidence).
	-	Death from ischemic stroke, intracerebral hemorrhage, myocardial infarction, congestive heart failure or AAA[a] rupture.
Stroke	-	Definite: relevant clinical features causing an increase in impairment of at least one grade on the modified Rankin scale, accompanied by an infarction or hemorrhage on a repeat CT-scan.
	-	Probable: clinical deficits causing an increase in impairment of at least one grade on the modified Rankin scale, without CT documentation
Myocardial infarction	-	At least two of the following criteria: 1. chest pain for at least 20 minutes, not disappearing after administration of nitrates; 2. ST-elevation >1 mm in two following leads or a left bundle branch block on the electrocardiogram; 3. CK[b] elevation of at least two times the normal value of CK and a myocardial band fraction >5% of total CK.

[a] abdominal aortic aneurysm; [b] creatine kinase

Statistical analysis

Results are expressed as means with standard deviations or as percentages unless otherwise stated. Crude overall cumulative survival after 1 and 3 years was calculated using the Kaplan Meier method. Age- and sex-adjusted cumulative incidence of vascular events and of vascular interventions according to the presence or absence of the metabolic syndrome at baseline was evaluated with the use of the Cox proportional hazards model. Results are presented as hazard ratios (HR) with 95% confidence intervals (95% CI). Patients without the metabolic syndrome served as the reference category in the analyses. The presence and extent of confounding was assessed by comparing the crude HR with the adjusted HR derived from the model containing the potential confounding variable. Potential confounders were factors related to the determinant (metabolic syndrome) as well as to the outcome (occurrence of vascular events), but not part of the causal chain of the metabolic syndrome. No adjustment was made for variables part of the metabolic syndrome or highly correlated to (components of) the metabolic syndrome.
Patients who underwent follow-up measurements were classified into 4 categories according to the presence of metabolic syndrome at baseline and at follow-up: (1) patients without metabolic syndrome at baseline and at follow-up; (2) patients with metabolic syndrome at baseline but not at follow-up; (3) patients with metabolic syndrome at follow-up but not at baseline; (4) patients with metabolic syndrome at baseline and at follow-up. Changes in metabolic syndrome components are presented according to these groups. Logistic regression analysis was performed to evaluate the effect of baseline BMI and of change in BMI on development and resolution of the metabolic syndrome during follow-up. Adjustments were made for age and sex, and additionally for baseline BMI when change in BMI was studied. All statistical analyses were performed with SPSS 14.0 for Windows (SPSS, Chicago, IL, USA).

Results

Study population

In the period between September 1996 and December 2000, 461 patients were included based on a recent diagnosis of PAOD. The baseline characteristics of these patients are shown in *Table 2*. Of these 461 patients, 20 (4%) were lost to follow-up and 108 (23%) had died before the time of the follow-up visit. Of the remaining 333 patients, 112 (34%) refused further participation and 221 (66%) underwent follow-up measurements (*Figure 1*). Differences in baseline characteristics between patients who did and did not participate in the follow-up measurements are presented in *Table 3*. The largest differences were found between those who participated in the follow-up examination and those who died before the follow-up examination, but differences were also present between those who agreed and those who refused to participate. Participants were more often male (67% vs 61%), were generally younger (57 vs 60 years), less often had a history of cerebrovascular disease (9.5% vs 19.7%) or diabetes mellitus (14.9% vs 34.6%) and had lower mean glucose levels (6.0 vs 7.0 mmol/l). The proportion of patients using medication was lower in participants compared with non-participants.

Table 2 Baseline characteristics of 461 patients with PAOD according to metabolic syndrome presence.

	Metabolic syndrome - n=234	Metabolic syndrome + n=227
Male gender (%)	67.9	67.4
Age (years)	60 ± 11	60 ± 11
Fontaine classification 2 vs 3 or 4 (%)	87 vs 13	84 vs 16
Ankle-brachial index	0.83 ± 0.20	0.82 ± 0.21
Additional cerebrovascular disease (%)	12.4	20.7
Additional coronary heart disease (%)	28.2	27.3
Additional AAA[a] (%)	6.4	7.0
Diabetes mellitus[b] (%)	9.9	40.4
Smoking (%)	63	54
Packyears of smoking	27.2 ± 19.5	28.4 ± 20.3
Physical activity[c] (%)	22.7	17.5
Body mass index (kg/m^2)	24.0 ± 2.9	27.4 ± 4.1
LDL-cholesterol (mmol/l)	3.8 ± 1.0	3.9 ± 1.0
Homocysteine (µmol/l)	15.4 ± 11.3	14.5 ± 5.8
eGFR (ml/min/1.73m^2)[d]	76 ± 20	74 ± 21
Albuminuria[e] (%)	17.3	23.1
Subcutaneous fat (cm)	2.6 ± 2.5	2.8 ± 1.5
Intra-abdominal fat (cm)	8.5 ± 2.0	10.6 ± 2.1
Metabolic syndrome components		
Waist circumference (cm)	90 ± 8	99 ± 11
Systolic blood pressure (mmHg)	143 ± 22	151 ± 21
Diastolic blood pressure (mmHg)	78 ± 11	81 ± 11
HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.0 ± 0.2
Triglycerides (mmol/l)	1.6 ± 1.0	2.7 ± 1.6
Fasting glucose (mmol/l)	5.7 ± 1.5	7.2 ± 2.6
Treatment at baseline		
Glucose-lowering agents (%)	7.3	24.2
Lipid-lowering agents (%)	24.9	33.5
Blood pressure-lowering agents (%)	24.8	40.4
Antithrombotic agents (%)	42.7	41.9

Waist circumference was measured in 179 individuals, and measurements of intra-abdominal and subcutaneous fat were present for 51 patients. Continuous variables are expressed as means with standard deviations.
[a] abdominal aortic aneurysm; [b] defined as self-reported type 2 diabetes, use of glucose-lowering agents or fasting glucose ≥7.0 mmol/l; [c] self-reported exercising; [d] estimated glomerular filtration rate, calculated with MDRD equation; [e] albumin-to-creatinine rate >3 mg/mmol

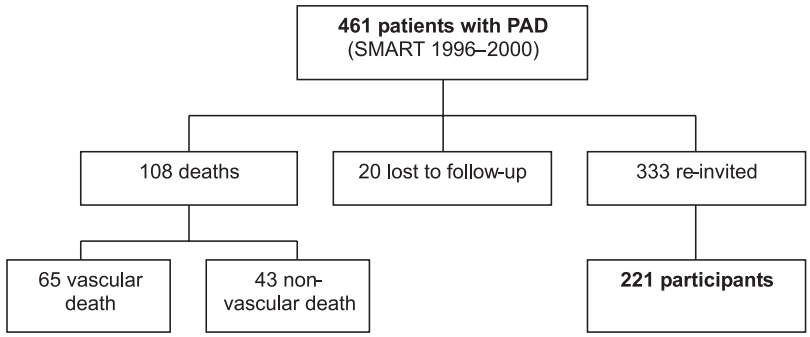


Figure 1 Composition of the study population.

Table 3 Differences in baseline characteristics between participants and non-participants in the follow-up examination.

	Participants follow-up	Non-participants and lost to follow-up	Died before follow-up	
	n=221	n=132	n=108	
Male gender (%)	67.0	61.4	76.9	*
Age (years)	57 ± 10	60 ± 11	67 ± 10	*
Fontaine classification 2 vs 3 or 4 (%)	88 vs 12	85 vs 15	81 vs 19	
Ankle-brachial index	0.85 ± 0.19	0.79 ± 0.19	0.80 ± 0.23	*
Additional cerebrovascular disease (%)	9.5	19.7	26.9	*
Additional coronary heart disease (%)	23.5	22.7	42.6	*
Additional AAA[a] (%)	5.0	4.5	13.0	*
Diabetes mellitus[b] (%)	14.9	34.6	33.6	*
Smoking (%)	58.6	60.8	55.1	
Packyears of smoking	26.6 ± 18.7	28.9 ± 21.9	29.0 ± 19.9	
Body mass index (kg/m^2)	25.6 ± 3.7	26.1 ± 4.2	25.2 ± 3.8	
LDL-cholesterol (mmol/l)	4.0 ± 1.0	3.8 ± 1.1	3.8 ± 1.0	
Waist circumference (cm)	95 ± 11	96 ± 12	95 ± 12	
Systolic blood pressure (mmHg)	144 ± 21	149 ± 21	152 ± 24	*
Diastolic blood pressure (mmHg)	80 ± 10	80 ± 11	78 ± 12	
HDL-cholesterol (mmol/l)	1.1 ± 0.3	1.2 ± 0.4	1.1 ± 0.4	
Triglycerides (mmol/l)	2.1 ± 1.4	2.4 ± 1.3	2.0 ± 1.4	
Fasting glucose (mmol/l)	6.0 ± 1.5	7.0 ± 2.7	6.7 ± 2.4	*
Glucose-lowering agents (%)	8.2	22.3	22.4	*
Lipid-lowering agents (%)	28.8	33.3	24.5	
Blood pressure-lowering agents (%)	26.8	33.1	43.0	*
Antithrombotic agents (%)	38.0	41.7	51.9	

Waist circumference was measured in 179 individuals. Continuous variables are expressed as means with standard deviations. * indicates p-value <0.05.
[a]abdominal aortic aneurysm; [b]defined as self-reported type 2 diabetes, use of glucose-lowering agents or fasting glucose ≥7.0 mmol/l

Metabolic syndrome and vascular events

The metabolic syndrome was present in 49% of the study population. Of the individual metabolic syndrome components, the blood pressure criterion was most frequent and was present in 83% of patients, followed by the criteria for HDL-cholesterol (54%), triglycerides (53%), and glucose (42%). The criterion for waist circumference was present in 19% of subjects.

During a mean follow-up of 5.6 ± 1.4 years, 91 patients experienced one or more vascular events (first event: 23 myocardial infarctions, 22 strokes and 46 vascular deaths). Crude cumulative one-year survival free from vascular events was 94.6% (92.4-96.8%) and declined to 88.4% (85.5-91.3%) after 3 years. In patients without the metabolic syndrome crude survival free from vascular events was 96.1% (93.6-98.6%) after 1 year and 92.1% (88.6-95.6%) after 3 years of follow-up, compared to 92.9% (89.6-96.2%) and 84.7% (80.0-89.4%) in patients with the metabolic syndrome. *Figure 2* shows the cumulative incidence of vascular events according to presence or absence of the metabolic syndrome, resulting from an age- and sex-adjusted Cox regression analysis. The metabolic syndrome increased the risk of vascular events after adjustment for age and sex (HR 1.51; 95% CI 1.01-2.30). There was no relation between presence of individual metabolic syndrome components and the occurrence of vascular events (*Table 4*).

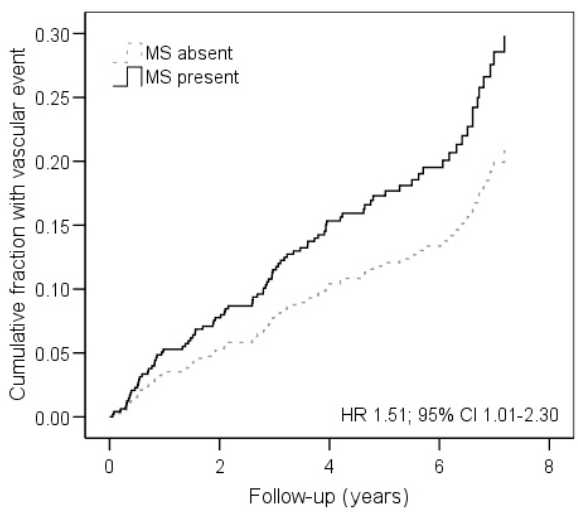


Figure 2 Cumulative incidence of vascular events according to presence or absence of the metabolic syndrome at baseline, adjusted for age and sex.

In additional analyses, no association was found between the metabolic syndrome and the occurrence of revascularization procedures to the legs during follow-up (age- and sex-adjusted HR 0.99; 95% CI 0.65-1.49) and between the metabolic syndrome and the occurrence of lower limb amputations (age- and sex-adjusted HR 1.59; 95% CI 0.84-3.01). The metabolic syndrome also did not influence the occurrence of surgical and endovascular aortic interventions (age- and sex-adjusted HR 1.11; 95% CI 0.59-2.10) or the occurrence of interventions to the carotid arteries (age- and sex-adjusted HR 1.20; 95% CI 0.49-2.95).

Table 4 Effect of metabolic syndrome and its components on the occurrence of vascular events.

	Prevalence		HR (95% CI)
Metabolic syndrome	49%	I	1.51 (1.00-2.30)
Blood pressure criterion[a]	83%	I	0.79 (0.46-1.35)
		II	0.75 (0.45-1.25)
HDL criterion[b]	54%	I	1.09 (0.72-1.65)
		II	1.00 (0.63-1.60)
Triglycerides criterion[c]	53%	I	1.13 (0.75-1.71)
		II	1.06 (0.67-1.70)
Waist criterion[d]	19%	I	1.07 (0.92-1.25)
		II	1.07 (0.91-1.24)
Glucose criterion[e]	42%	I	1.14 (0.89-1.47)
		II	1.18 (0.90-1.56)

Model I adjusted for age and sex; model II additionally adjusted for other metabolic syndrome components.
[a]blood pressure ≥130/85 mmHg or use of blood pressure-lowering medication; [b] HDL-cholesterol <1.30 mmol/l (50 mg/dl) in women and <1.03 mmol/l in men (40 mg/dl) or treatment for reduced HDL-cholesterol; [c] fasting triglycerides ≥1.70 mmol/l (150 mg/dl) or treatment for elevated triglycerides; [d] waist circumference ≥88 cm in women and ≥102 cm in men; [e] fasting glucose ≥5.6 mmol/l (100 mg/dl) or use of glucose-lowering agents

Change in metabolic syndrome status

Mean follow-up among the 221 PAOD patients with follow-up measurements was 5.5 ± 1.3 years. Metabolic syndrome was diagnosed in 45% of the population at baseline and in 43% at follow-up. The majority of patients (70%) remained at the same status: 91 patients (41%) did not meet the metabolic syndrome criteria at baseline and at follow-up and 64 patients (29%) had the metabolic syndrome at both measurements. In *Table 5* baseline characteristics and change in metabolic syndrome components and medication use are shown according to 4 groups of metabolic syndrome status at baseline and follow-up.
Patients with the metabolic syndrome at baseline and at follow-up were older and showed the highest values of waist circumference (100 ± 12 cm), systolic blood pressure (150 ± 19 mmHg), and triglycerides (2.8 ± 1.4 mmol/l) as well as the lowest HDL-cholesterol level (0.9 ± 0.2 mmol/l). Change in metabolic syndrome components according to metabolic syndrome status at baseline and follow-up is shown in *Figure 3*. HOMA-IR measured at follow-up correlated well with metabolic syndrome status and was highest among patients with persistent metabolic syndrome. HOMA-IR was also high in patients with incident metabolic syndrome.

Table 5 Baseline characteristics and changes in metabolic syndrome components and medication use according to metabolic syndrome status at baseline and after follow-up.

	Metabolic Syndrome				
Baseline	x	✓	x	✓	
Follow-up	x	x	✓	✓	
	n = 91	**n = 35**	**n = 31**	**n = 64**	**p-value**
Baseline characteristics[a]					
Male gender (%)	63.7	77.1	74.2	62.5	0.34
Age (years)	56 ± 10	55 ± 10	61 ± 8	60 ± 10	0.08
Smoking (%)	58.2	62.9	67.7	52.4	0.63
Diabetes mellitus (%)	1.1	25.7	19.4	26.6	<0.01
Waist circumference (cm)	88 ± 7	99 ± 10	96 ± 6	100 ± 12	<0.01
Systolic blood pressure (mmHg)	139 ± 20	147 ± 19	138 ± 22	150 ± 19	<0.01
Diastolic blood pressure (mmHg)	79 ± 10	84 ± 8	76 ± 9	82 ± 9	<0.01
HDL-cholesterol (mmol/l)	1.3 ± 0.3	1.0 ± 0.2	1.3 ± 0.3	0.9 ± 0.2	<0.01
Triglycerides (mmol/l)	1.5 ± 1.0	2.5 ± 2.0	1.9 ± 1.1	2.8 ± 1.4	<0.01
Fasting glucose (mmol/l)	5.3 ± 0.5	6.9 ± 2.7	5.9 ± 1.3	6.5 ± 1.4	<0.01
Glucose-lowering agents (%)	1.1	14.3	16.1	11.1	0.01
Lipid-lowering agents (%)	22.2	20.0	38.7	38.1	0.06
Blood pressure-lowering agents (%)	15.4	25.7	25.8	44.4	<0.01
Changes in metabolic syndrome components and medication use[b]					
Waist circumference (cm)	+3 ± 9	+1 ± 9	+10 ± 8	+6 ± 5	0.01
Systolic BP (mmHg)	+9 ± 20	+11 ± 21	+8 ± 25	+9 ± 22	0.94
Diastolic BP (mmHg)	+4 ± 12	+1 ± 10	+4 ± 12	+2 ± 10	0.45
HDL-cholesterol (mmol/l)	+0.3 ± 0.3	+0.3 ± 0.2	+0.2 ± 0.4	+0.2 ± 0.2	0.08
Triglycerides (mmol/l)	-0.2 ± 0.9	-1.0 ± 1.3	+0.2 ± 1.0	-0.4 ± 1.5	<0.01
Fasting glucose (mmol/l)	+0.1 ± 0.5	-0.8 ± 2.1	+1.1 ± 3.8	-0.1 ± 1.2	<0.01
Glucose-lowering agents	+1.1	+0	+3.3	+23.3	<0.01
Lipid-lowering agents	+38.2	+54.3	+29.0	+36.9	0.06
Blood pressure-lowering agents	+17.6	+17.2	+29.0	+18.1	0.15
ACE-inhibitors / AT II antagonists	+4.4	+14.3	+19.3	+26.6	0.12
Follow-up measurement					
HOMA-IR[c]	1.5 (1.1–2.3)	1.9 (1.6–3.2)	2.7 (2.0–6.4)	4.1 (3.1–5.8)	<0.01

[a] continuous variables are expressed as means with SD; [b] continuous variables are expressed as differences in mean ± SD, categorical variables are expressed as differences in percentages; [c] median with interquartile range

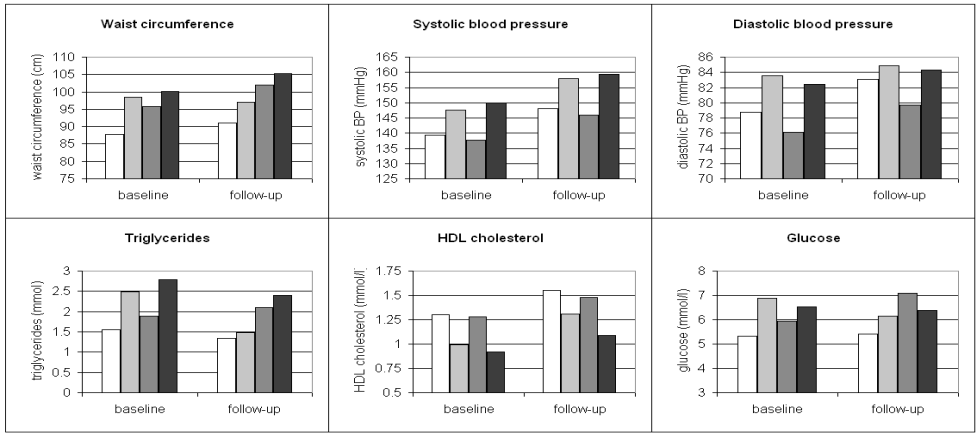


Figure 3 Changes in metabolic syndrome components according to metabolic syndrome status at baseline and at follow-up.
White bars represent patients without metabolic syndrome at baseline and follow-up; light grey bars represent patients with metabolic syndrome at baseline but not at follow-up; dark grey bars represent patients with metabolic syndrome at follow-up but not at baseline; black bars represent patients with metabolic syndrome at baseline and follow-up.

HDL-cholesterol was the criterion most frequently lost. 53.7% of patients fulfilling the HDL criterion at baseline lost it after follow-up. Also the triglycerides criterion was frequently lost (39.6%). The glucose criterion was no longer present in 21.8% of the baseline cases. Less patients were able to get their waist circumference below the metabolic syndrome cut-off (10.8%) and almost none lost the blood pressure criterion (2.3%). Of the patients without the blood pressure criterion at baseline, 84% did meet the blood pressure criterion at follow-up and of patients without the HDL criterion at baseline, 46% had the HDL criterion at follow-up. 36% of patients without the criterion for waist circumference at baseline did have the criterion for waist circumference at follow-up, and 20% of those without the triglycerides criterion and 16% of those without the glucose criterion at baseline fulfilled these criteria at follow-up.
Both baseline BMI and change in BMI during follow-up were significantly associated with the development or disappearance of the metabolic syndrome. Baseline BMI was related to incident metabolic syndrome (OR 1.53; 95% CI 1.23-1.90) and to resolution of metabolic syndrome at follow-up (OR 0.87; 95% CI 0.77-0.98) after adjustment for age and sex. Per kg/m^2 decrease in BMI during follow-up, patients without the metabolic syndrome at baseline decreased their risk to acquire the syndrome during follow-up with 23% (OR 0.77; 95% CI 0.62-0.96). Subjects with the metabolic syndrome at baseline showed a 32% (OR 1.32; 95% CI 1.03-1.71) increase in chance to lose the syndrome during follow-up when they lowered their BMI by 1 kg/m^2 (adjusted for age, sex and baseline BMI).

Discussion

The metabolic syndrome is a frequent condition in symptomatic PAOD patients with a prevalence of 49%. Cumulative 3-year survival free from vascular events was 84.7% in metabolic syndrome patients compared to 92.1% in participants without the metabolic syndrome. In the present study it was shown that the metabolic syndrome is associated with a 1.51-fold increased risk for the development of vascular events in patients with symptomatic PAOD. The metabolic syndrome was not associated to future vascular interventions, and presence of individual metabolic syndrome components was not associated with an increased vascular risk. BMI at baseline as well as change in BMI during follow-up had a large influence on incidence and resolution of the metabolic syndrome during follow-up.

The prevalence of metabolic syndrome in patients with PAOD is high in the present study (49%), and is comparable with other studies.[6, 7] In general, it is thought that abdominal obesity is the driving force for the development of insulin resistance resulting in the metabolic changes seen in the metabolic syndrome.[23, 24] As exercise has beneficial effects on insulin resistance[25, 26] and symptomatic PAOD reduces the ability to ambulate, a decrease in physical activity might be an important cause of insulin resistance in this population. Other possible causes of insulin resistance include genetic predisposition[27] and low birth weight.[28]

In this study with 5.5 years of follow-up it is shown that presence of the metabolic syndrome significantly increased the risk of vascular events in patients with PAOD by 51%. This is comparable with results from other studies among patients with coronary heart disease where the metabolic syndrome increased the risk of future vascular events by 23-63%.[9, 11, 29] In a previous study we showed that in patients with a history of vascular disease, the metabolic syndrome induced increased vascular risks. The metabolic syndrome was associated with a considerable vascular risk increment in patients with a history of PAOD or coronary heart disease, and to a lesser extent in patients with a history of AAA or cerebrovascular disease.[30] In patients without diabetes or overt cardiovascular disease at baseline, the risk of cardiovascular events was 2-3 times higher in the presence of the metabolic syndrome.[31] In this study, the individual metabolic syndrome components alone were not associated with future vascular events. In line with this observation, a number of studies found that most components of the syndrome were not or only marginally associated with vascular events,[9] coronary heart disease[32] or carotid stenosis[32] when considered individually, whereas the metabolic syndrome was associated with the outcomes examined. Also, the clustering of metabolic risk factors had excess influence on carotid intima-media thickness beyond what would have been expected from merely additive effects.[33] The results of the present study point towards an additional value of identifying the metabolic syndrome beyond recognition of its component traits. Probably cardiovascular risk increment is also caused by other factors associated with insulin resistance, like elevated inflammation, hypoadiponectinemia and coagulation disorders all seen in metabolic syndrome.[34, 35]

Although the prevalence of abdominal obesity at baseline was fairly low, in this study the development from a non-metabolic syndrome state to a metabolic syndrome state was

associated with a marked increase in waist circumference. This may suggest that an increase in insulin resistance is underlying the development to a metabolic syndrome state, supported by the high HOMA-IR values in patients developing the metabolic syndrome. However, since baseline HOMA-IR values were not available, conclusions on an increase in insulin resistance can not be drawn. Although the obesity criterion at baseline was the least frequent of the metabolic syndrome criteria, baseline BMI as well as change in BMI during follow-up significantly influenced the risk of development of the metabolic syndrome or reversion to a non-metabolic syndrome state. In parallel, a 1.22-fold increased risk of development of the syndrome was shown for every kg gained over 6 years among subjects from the DESIR cohort.[36] Maintaining stable weight from young adulthood into middle age has also been shown to prevent development of the metabolic syndrome.[37]

In cardiovascular risk prevention in PAOD patients, the importance of weight control should be emphasized, and specific interventions directed towards modulation of insulin resistance, such as increasing physical activity, may positively alter vascular prognosis in these patients at very high risk for cardiovascular events. Emphasis on weight control and physical activity are most important, as the present study showed a large effect of BMI decrease on the course of the metabolic syndrome during follow-up. Apart from lifestyle changes, treatment with insulin sensitizing agents, like metformin or thiazolidinediones can also be considered in PAOD patients with metabolic syndrome,[38] although the benefit of these interventions in this population should first be investigated in randomised controlled trials.

A reduction in the number of individual metabolic syndrome components in this study was mainly due to loss of the HDL-cholesterol or triglycerides criteria. These patients had lower HOMA-IR levels at follow-up compared to patients who kept the metabolic syndrome throughout the study. Possibly these changes in HDL-cholesterol and plasma triglyceride concentrations may be the result of increased insulin sensitivity, but information on HOMA-IR levels at baseline would be necessary to conclude on this possibility. Alternatively, the increased use of statins may also have affected plasma lipids, although statins only marginally influence HDL-cholesterol (+5%) and triglycerides (-15%).[39, 40]

Changes in metabolic syndrome components over time have also been studied in the French DESIR cohort.[41] Among 4293 healthy participants aged 30-64 years, the metabolic syndrome was present in 14% of the population. A quarter of patients with the metabolic syndrome at baseline were no longer classed as having the syndrome after 3 years of follow-up in that study, compared to 35% after 5.5 years in this study. This indicates that even in a high-risk population of patients with PAOD, it is possible to rid oneself of the metabolic syndrome. In the DESIR cohort, fasting glucose was the component that normalised most frequently (40%) after follow-up, whereas in our study this was the case for HDL-cholesterol and triglycerides, while the glucose criterion was only lost in 22% of patients. This difference might be caused by the baseline differences in glucose abnormalities: 10% in DESIR vs 42% in our study.

In the present cohort, vascular risk factors were not optimally treated. For example, less than half of the 221 patients were on statin therapy and the average blood pressure was high. Many patients did not reach treatment goals for vascular risk factors. This is in line with studies by others, also showing suboptimal treatment of risk factors in patients with

PAOD and coronary heart disease.[42, 43] Optimal treatment leads to a better cardiovascular prognosis in these high-risk patients. Patients with clinically evident coronary heart disease and the metabolic syndrome benefited the most from aggressive lipid-lowering therapy compared to patients without the metabolic syndrome, irrespective of the presence of diabetes.[44]

We acknowledge limitations in our study. Adequate measures for insulin resistance (e.g. fasting insulin) at baseline are lacking. It is therefore not possible to draw conclusions as to how insulin resistance is associated with cardiovascular prognosis in this study and development of insulin resistance over time could not be estimated. Also, changes in physical activity may have influenced the results. As we utilized measures of BMI instead of waist circumference in those patients who did not have waist circumference measured, it is possible we may have misclassified some individuals that would have been classified differently based on waist circumference measures that constitute the accepted criterion for the metabolic syndrome. Because the survivors of the cohort were invited and only part of them agreed to participate in the follow-up examination, possibly only the less severely affected and younger PAOD patients participated in the follow-up measurement. This could have led to an underestimation of the worsening of vascular risk factors and metabolic syndrome components during follow-up. As only symptomatic PAOD patients were included in this study, we were not able to pronounce upon the vascular risk in asymptomatic patients with PAOD.

In conclusion, patients with PAOD and the metabolic syndrome have a 51% higher risk of developing a vascular event compared to PAOD patients without the metabolic syndrome. Incident metabolic syndrome is associated with an increase in abdominal obesity, and a decrease in BMI was associated with resolution of metabolic syndrome in PAOD patients. It may be speculated that weight control in order to reduce incident metabolic syndrome may add to prevention of new vascular events in these high-risk patients.

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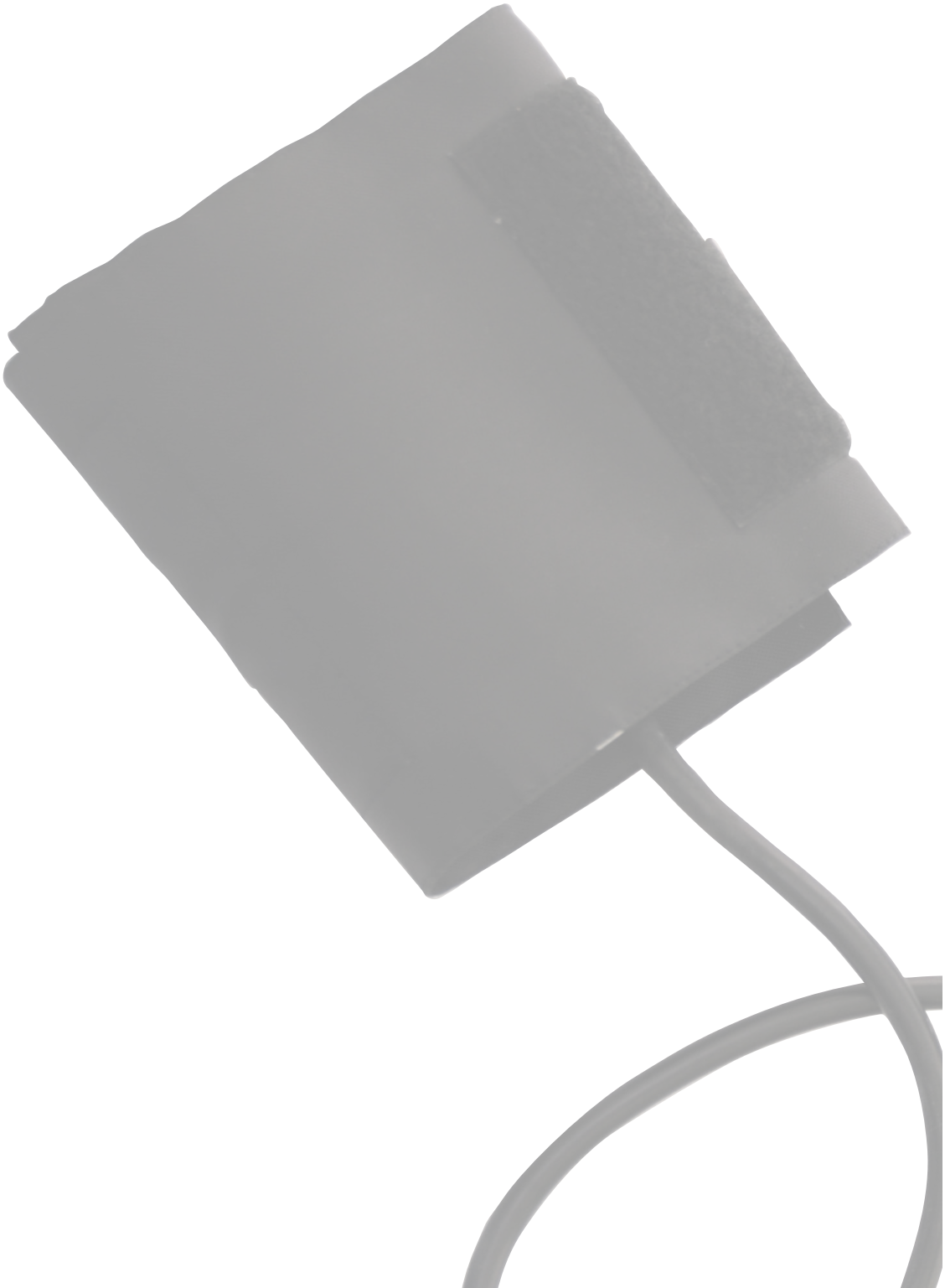
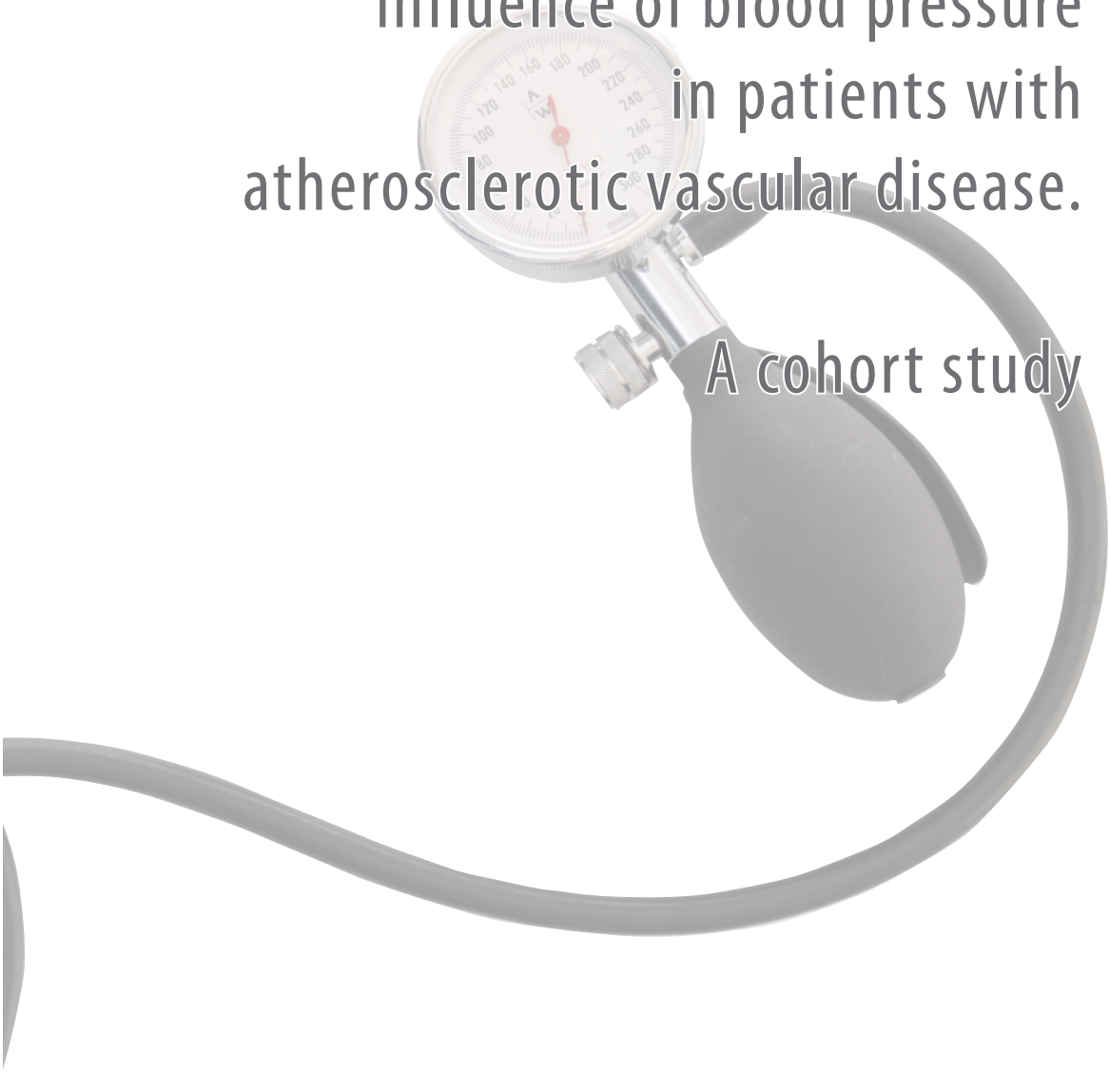


Chapter 3.1

Decline in renal function and the influence of blood pressure in patients with atherosclerotic vascular disease.

A cohort study



Abstract

Background

Elevated blood pressure (BP) is generally associated with renal function decline. Whether this is also the case in patients with atherosclerotic vascular disease is unclear. Also the absolute decline in renal function has not been studied in this population. We evaluated the rate of renal function decline in patients with atherosclerotic vascular disease, as well as the effect of BP on renal function deterioration.

Methods

This prospective study comprised 745 patients with vascular disease, enrolled in the Second Manifestations of ARTerial disease study. Participants underwent vascular screening at baseline and after 4.5 ± 1.0 years of follow-up. The rate of renal function decline was expressed as annual decline in estimated glomerular filtration rate (eGFR). Linear regression analysis was used to evaluate the relation between BP and eGFR decline.

Results

Mean baseline eGFR was 79.3 ± 16.3 ml/min/1.73m^2 and mean annual decrease in eGFR was 1.00 ± 2.71 ml/min/1.73m^2. In 35% of patients, eGFR remained stable during follow-up. In the presence of albuminuria, there was a positive association between BP and eGFR decline (β 1.29; 95% CI 0.73-1.85 for systolic BP, β 3.86; 95% CI 2.34-5.38 for hypertension presence). In patients without albuminuria, no association was found between BP and renal function decline.

Conclusions

Renal function decline among patients with vascular disease is considerable. BP is a strong and independent risk factor for eGFR decline in patients with atherosclerotic vascular disease and albuminuria. The need to prevent severe renal function deterioration dictates continued efforts to achieve early identification of patients with hypertension and albuminuria among vascular disease patients.

Introduction

Chronic kidney disease is a major health problem worldwide with rising numbers of patients with end-stage renal disease (ESRD).[1] Important risk factors for the development of ESRD are diabetes, hypertension and renovascular disease.[2]
In the general population renal mass and renal function are declining during life,[3, 4] but uncertainty exists about the exact rate of renal function decline and about which patients are at risk of progressive disease. Several factors associated with progression have been suggested, among which are hypertension,[5-8] obesity,[9, 10] proteinuria,[11, 12] smoking,[10] hyperlipidemia,[10, 13] diabetes[6, 10] and dietary protein intake.[14, 15] Hypertension is a common condition in a high-risk population of patients with manifest vascular disease and is associated with fatal as well as non-fatal outcomes involving the brain, heart and kidneys. The development of cerebrovascular and cardiovascular complications of hypertension has been described frequently, whereas less attention has been directed to concomitant renal disease. It is estimated that about 25% of cases of ESRD is caused by hypertension.[16] The relative contribution of elevated blood pressure (BP) to the progression of renal disease has not been investigated specifically in patients with overt vascular disease.
Vascular risk factors and presence of vascular disease have been associated with renal function decline and development of ESRD,[8, 17] and a significant portion of glomerulosclerosis occurring in aging has been linked to atherosclerosis.[18] It is not fully clear whether albuminuria may be a stronger predictor of progression to ESRD and whether BP can be proven to be an independent risk factor. In this respect, the renoprotective effect of BP-lowering treatment in patients with chronic kidney disease strongly depends on the effectiveness of BP lowering to lower proteinuria.[11] One could argue that in a diseased vascular system, BP affects progression independently from albuminuria (*Figure 1*). In particular, vascular disease results in increased vascular stiffening with more pronounced systolic BP elevation. Since systolic BP seems detrimental for the integrity of the glomerular filter, systolic BP in particular may represent an independent risk factor in this group.

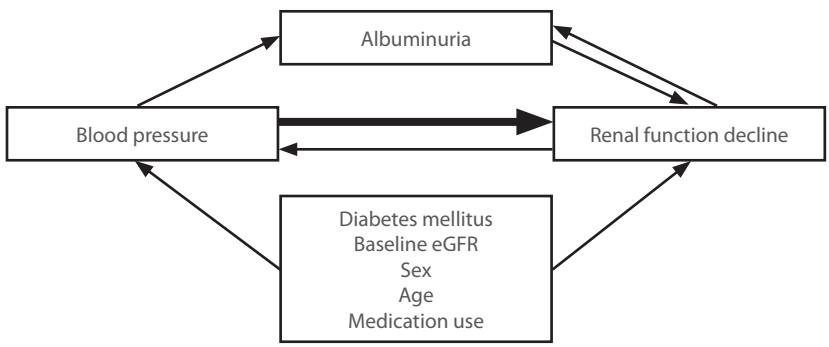


Figure 1 Conceptual framework of blood pressure, albuminuria and renal function decline. In bold the association investigated in this study.

For this reason, the rate of renal function decline and the predisposing factors contributing to progressive decline might be different in patients with vascular disease compared to other populations. Efforts to reduce the burden of kidney disease require reliable estimates of risks of progression to severe renal failure. In order to provide these estimates, insight in both the rate of renal function decline and the possible causes of accelerated decline are important, especially in patients with vascular disease.
We investigated the extent of renal function deterioration and the relation between BP and estimated glomerular filtration rate (eGFR) decline in a follow-up study of patients with manifest vascular disease.

Methods

Study design and population

The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective cohort study in the University Medical Center Utrecht. Since 1996, patients aged 18-80 years with clinically manifest atherosclerotic vascular disease (cerebrovascular disease, coronary heart disease, peripheral arterial disease or abdominal aortic aneurysm (AAA)) or risk factors for atherosclerosis (hyperlipidemia, diabetes mellitus or hypertension) are being included. Patients are referred by general practitioners or by medical specialists from other hospitals in the region. Not included are patients with terminal malignant disease, those not independent in daily activities or insufficiently familiar with the Dutch language. All patients are assessed for atherosclerotic risk factors and the extent of atherosclerosis by non-invasive means. The SMART study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent. The rationale and design of the SMART study have been described in detail elsewhere.[19]
The current study is a prospective cohort study within the SMART study.[19] A total of 755 patients with complete follow-up data were included. Between 2003 and 2005, 221 patients included in the SMART study between 1996 and 2000 with a diagnosis of peripheral arterial disease underwent a second vascular screening. Between 2006 and 2008, another 534 patients participated in a second screening program. These patients were included between 2001 and 2004 with clinically manifest atherosclerotic vascular disease (cerebrovascular disease, coronary heart disease, peripheral arterial disease or abdominal aortic aneurysm (AAA)). Cerebrovascular disease included transient ischemic attack, cerebral infarction, amaurosis fugax or retinal infarction; coronary heart disease included myocardial infarction and admission for percutaneous coronary intervention or coronary artery bypass grafting; AAA included AAA ≥3.0 cm or aneurysm surgery; peripheral arterial disease included claudication of the legs confirmed by a resting ankle-brachial pressure index <0.9 in at least 1 leg, percutaneous transluminal angioplasty or leg amputation. No patients with known primary renal diseases were included. Patients with missing data on renal function (n=10) were excluded leaving 745 patients for analyses.

Vascular screening

Participating patients underwent the same diagnostic screening-protocol at baseline and at follow-up. Participants completed a questionnaire on cardiovascular history, risk factors and medication use. Physical examination was carried out and consisted of measurements of height, weight, waist and hip circumferences and BP. BP was measured by sphygmomanometry at the right and left upper arm and repeated on the side with the highest values. The mean of all obtained measurements (≥3) was used in the analyses. Fasting blood was sampled to ascertain levels of glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine and homocysteine. Creatinine was measured with commercial enzymatic dry chemistry kits (Johnson and Johnson). Low-density lipoprotein (LDL) cholesterol levels were calculated with Friedewald's formula. Albumin and creatinine concentrations were measured in a morning urine portion. Urinary creatinine was measured with a commercial enzymatic dry chemistry kit (Johnson and Johnson) and albuminuria was determined with immunoturbidimetric assays (Boehringer-Mannheim). All assessments were performed at a single laboratory. Screening also included duplex scanning of the carotid arteries, electrocardiography, ankle-brachial pressure index and ultrasonography of the abdomen. Abdominal ultrasound consisted of measurements of the anteroposterior diameter of the aorta and the anteroposterior juxtarenal diameter. Measurement procedures were the same at baseline and at follow-up. Techniques of the examinations have been published formerly.[19]

Definitions

Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg or self-reported use of BP-lowering medication. As a reflection of the hemodynamic perfusion pressure of the organs, mean arterial pressure (MAP) was used as a measure of BP and was calculated as 2 times diastolic BP plus systolic BP divided by 3. Pulse pressure was the difference between systolic and diastolic BP. Type 2 diabetes mellitus was defined as self-reported type 2 diabetes, use of glucose-lowering agents or fasting glucose ≥7.0 mmol/l at screening. According to the Advisory from the American Heart Association Kidney and Cardiovascular Disease Council the 4-variable Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR and the albumin-to-creatinine ratio (ACR) was used to estimate albuminuria.[20] An ACR >3 mg/mmol was regarded as albuminuria while an ACR ≤3 mg/mmol was considered normal.

Statistical analysis

Results are expressed as means with standard deviations (SD) for continuous variables and as percentages with the absolute number of patients between parentheses for categorical variables. Yearly eGFR decline was calculated on patient level by determining the difference between baseline and follow-up values and dividing by the exact follow-up time recorded for that patient. Age- and sex-adjusted estimates of yearly eGFR decline for different subgroups separately were calculated with the use of a general linear model.
The influence of different measures of BP on eGFR decline was evaluated with the use of linear regression analysis. Results are presented as β coefficients with 95% confidence

intervals (95% CI). The extent of confounding was assessed by comparing the crude β coefficient derived from the initial model with the adjusted β coefficient derived from the model that contained the potential confounding variable. Potential confounders were factors which were related to eGFR decline as well as to BP. Analyses were performed with different levels of adjustment: 1) adjustment for age and sex and 2) adjustment for age, sex, diabetes mellitus and baseline eGFR. Additional adjustment for amount and type of BP-lowering medication was also made. The modifying effect of sex and albuminuria on the relationship of eGFR decline and BP was examined by entering product terms in the model. Interaction was considered present when the p-value of the interaction terms was below 0.05. Stratified analyses were performed using data of 696 patients with available measurements of urinary albumin. All statistical analyses were performed with SPSS, version 14.0 (Windows, Chicago, Illinois, USA).

Results

Study population

Baseline characteristics of the study population are shown in *Table 1*. Mean age was 57.7 ± 9.5 years. Mean systolic BP at baseline was 141 ± 20 mmHg and mean diastolic BP was 81 ± 10 mmHg. 63% of patients was hypertensive and this number rose to 80% among patients with eGFR <60 ml/min/1.73m^2. At baseline, 53% of hypertensive patients was treated with BP-lowering medication. Most of the patients receiving medication were treated with RAAS blockers (49.4%; ACE inhibitors 38.6% and angiotensin II antagonists 10.8%). Beta blockers were used by 41.8%, calciumantagonists by 19.7% and diuretics by 17.7% of patients. Of hypertensive patients with eGFR <60 ml/min/1.73m^2, 75% was treated with BP-lowering medication (31% monotherapy), but only 27% had their BP reduced to below 140/90 mmHg. A BP below 130/80 mmHg, as recommended for this category of patients,[21] was reached in 13% of hypertensives (17% of those receiving BP-lowering medication).

Change in eGFR

At baseline 3.9% of patients aged 40-60 years and 15.4% of those aged 60-70 years had eGFR values <60 ml/min/1.73m^2. Mean baseline eGFR was 79.3 ± 16.3 ml/min/1.73m^2 and declined to a mean value of 75.1 ± 16.8 ml/min/1.73m^2 after a mean follow-up period of 4.5 ± 0.99 years. It appeared that 35% of patients had the same or higher eGFR at follow-up compared to baseline, whereas 65% of patients showed a decline in eGFR. *Figure 2* shows the distribution of eGFR according to age at baseline and after follow-up. The mean yearly decrease in eGFR was 1.00 ± 2.71 ml/min/1.73m^2. When analyzing eGFR decrease in different subgroups, age- and sex-adjusted eGFR decrease was most pronounced in patients with AAA (2.02; 95% CI 1.23-2.81) and in patients with albuminuria (1.71; 95% CI 1.17-2.25) (*Table 2*).

Table 1 Baseline characteristics of the study population according to hypertension presence.

	All (n=745)	Hypertension[a] (n=471)	No hypertension[a] (n=274)
Age (years)	57.7 ± 9.5	59.1 ± 9.3	55.2 ± 9.3
Male gender (%)	79.5	78.6	81.0
Cerebrovascular disease (%)	19.5	22.9	13.5
Cononary heart disease (%)	51.4	47.3	58.4
Peripheral arterial disease (%)	40.3	40.6	39.8
AAA[b] (%)	6.0	7.2	4.0
Intima-media thickness (mm)	0.92 ± 0.29	0.96 ± 0.32	0.85 ± 0.22
Smoking (packyears)	23.6 ± 19.6	23.6 ± 19.8	23.7 ± 19.2
Body mass index (kg/m^2)	26.4 ± 3.7	26.8 ± 3.7	25.8 ± 3.5
Waist circumference (cm)	95.6 ± 10.6	96.3 ± 10.6	94.4 ± 10.5
Serum triglycerides (mmol/l)	1.87 ± 1.20	1.87 ± 1.23	1.85 ± 1.15
LDL-cholesterol (mmol/l)	3.21 ± 1.03	3.17 ± 0.96	3.28 ± 1.15
HDL-cholesterol (mmol/l)	1.24 ± 0.38	1.25 ± 0.40	1.23 ± 0.36
Use of lipid-lowering agents (%)	48.9	53.1	41.7
Diabetes mellitus[c] (%)	16.6	20.6	9.9
Glucose (mmol/l)	6.2 ± 1.8	6.3 ± 1.8	5.9 ± 1.9
Albumin-creatinine ratio (mg/mmol)[d]	0.7 (0.3-1.4)	0.8 (0.4-1.9)	0.6 (0.2-1.0)
Albuminuria[e] (%)	14.5	18.3	7.8
Baseline eGFR (ml/min/1.73m^2)	79.3 ± 16.3	77.4 ± 16.5	82.7 ± 15.3
Systolic BP (mmHg)	141 ± 20	151 ± 19	125 ± 9
Diastolic BP (mmHg)	81 ± 10	85 ± 10	75 ± 7
Mean arterial pressure (mmHg)	101 ± 12	107 ± 11	91 ± 7
Use of BP-lowering agents (%)	33.7	53.3	-
Amount of BP-lowering agents (%)			
0 agents	65.0	44.6	-
1 agent	18.9	29.9	-
2 agents	12.1	19.1	-
3 or more agents	4.0	6.4	-
Type of BP-lowering agents (%)			
β-blockers	19.3	30.6	-
Diuretics	7.0	11.0	-
ACE inhibitors	14.4	22.7	-
Angiotensin II antagonists	3.9	6.2	-
Calcium channel blockers	10.1	15.9	-

[a]diastolic BP ≥90 mmHg, systolic BP ≥140 mmHg or use of BP-lowering medication; [b]abdominal aortic aneurysm; [c]self-reported type 2 diabetes, use of glucose-lowering agents or fasting glucose ≥7.0 mmol/l; [d]median with interquartile range; [e]albumin-creatinine ratio >3 mg/mmol

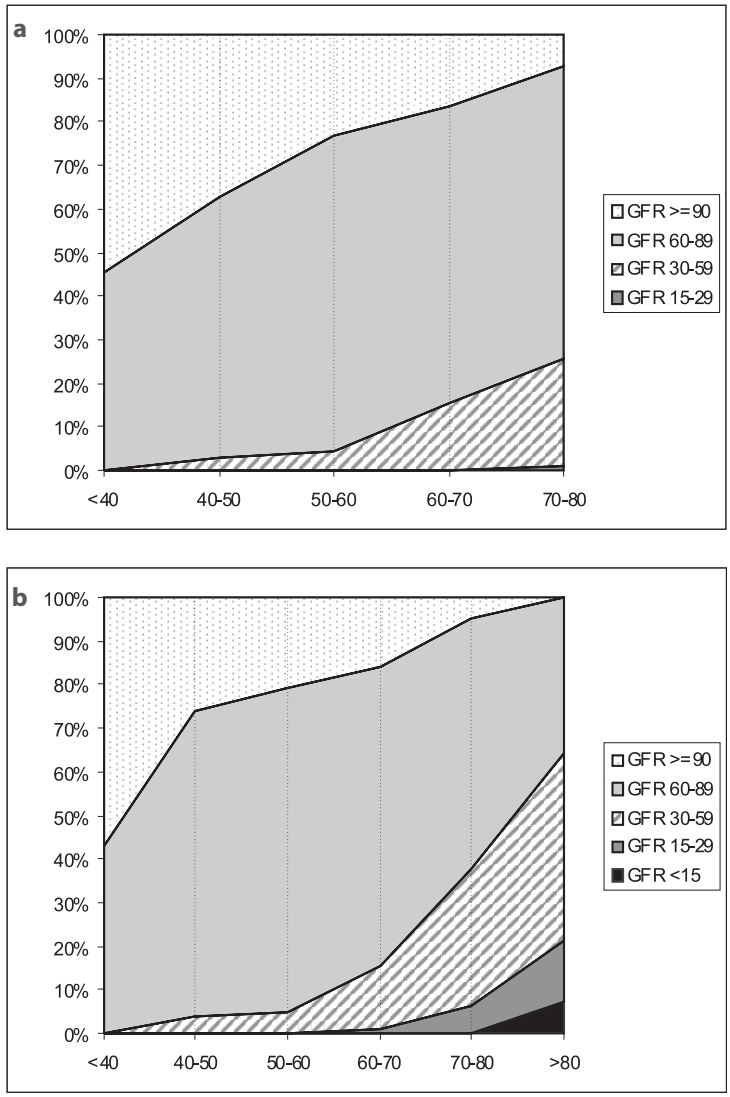


Figure 2 Distribution of eGFR across different age groups at baseline (a) and after follow-up (b).

Table 2 Annual eGFR decline according to different patient categories.

	eGFR decline per year	
	Absolute change ml/min/1.73m² per year (95% CI)	**Percentage change % (95% CI)**
Age (years)		
≤60 (n=463)	0.76 (0.52-1.01)	0.7 (0.4-1.0)
>60 (n=282)	1.38 (1.07-1.70)*	1.9 (1.5-2.3)*
Gender		
Female (n=153)	0.77 (0.34-1.20)	0.9 (0.4-1.4)
Male (n=592)	1.06 (0.84-1.28)	1.2 (0.9-1.5)
Localization of vascular disease[a]		
Cerebrovascular disease (n=145)	1.15 (0.71-1.59)	1.2 (0.7-1.8)
Coronary heart disease (n=383)	0.75 (0.48-1.02)*	0.8 (0.5-1.2)*
Peripheral arterial disease (n=300)	1.05 (0.74-1.36)	1.2 (0.8-1.6)
AAA disease (n=45)	2.02 (1.23-2.81)*	2.7 (1.7-3.7)*
Glycemic status		
No diabetes (n=621)	0.90 (0.69-1.11)	1.0 (0.8-1.3)
Diabetes (n=124)	1.48 (1.00-1.97)*	1.6 (1.0-2.2)
Metabolic syndrome[b]		
Absent (n=458)	0.94 (0.69-1.18)	1.0 (0.7-1.3)
Present (n=287)	1.10 (0.78-1.41)	1.3 (0.9-1.7)
Albuminuric status		
No albuminuria (n=596)	0.89 (0.67-1.11)	1.0 (0.7-1.3)
Albuminuria (n=100)	1.71 (1.17-2.25)*	2.1 (1.5-2.8)*
Hypertension status		
No hypertension (n=274)	0.78 (0.46-1.11)	0.8 (0.4-1.2)
Treated hypertension, BP <140/90 mmHg (n=90)	0.67 (0.11-1.23)	0.7 (0.1-1.4)
Untreated hypertension (n=222)	1.22 (0.86-1.57)	1.4 (0.9-1.8)*
Treated hypertension, BP ≥140/90 mmHg (n=159)	1.25 (0.83-1.68)	1.6 (1.1-2.1)*

[a]localizations of vascular disease are not exclusive categories; [b]NCEP-ATPIII criteria
Values are age- and sex-adjusted means, with age only adjusted for sex and sex only adjusted for age.
*p-value for difference <0.05; for vascular disease localization, the reference category was absence of the disease localization under study; for hypertension status the reference category was no hypertension.

Relation between BP and change in eGFR

Figure 3 shows the crude association between systolic BP (but not diastolic BP or MAP) and yearly eGFR decline according to albuminuric status. In this cohort of patients with vascular disease, there was a significant association between baseline systolic BP, diastolic BP and MAP and mean yearly decrease in eGFR, adjusted for age, sex, baseline eGFR and diabetes mellitus. The strongest association was found with systolic BP (β 0.39; 95% CI

0.20-0.58) (*Table 3*), indicating an accelerated annual eGFR decline of 0.39 ml/min/1.73m^2 for each SD increase in systolic BP. However, the relation between yearly eGFR decline and BP turned out to be modified by the presence of albuminuria (p-value of interaction term <0.05 for all measures of BP). Stratified analyses of patients with ACR >3 mg/mmol and patients with ACR ≤3 mg/mmol showed that there was no association between yearly eGFR decline and BP in patients without albuminuria (*Table 3*). In patients with albuminuria, a clear relation between yearly eGFR decline and BP was found. The strongest association was identified for systolic BP (β 1.29; 95% CI 0.73-1.85). In albuminuric patients, the presence of hypertension was associated with an accelerated annual eGFR decline of 3.86 (95% CI 2.34-5.38) ml/min/1.73m^2. Adjustment for amount and type of BP-lowering medication did not substantially affect the relationship between BP and renal function decline. Also additional adjustment for the localization of vascular disease did not change the associations (data not shown). No gender differences were present regarding the associations between BP and renal function decline.

Table 3 Associations between BP and annual decline in eGFR.

		β coefficient (95% confidence interval)		
		All patients n=745	Albuminuria n=100	No albuminuria n=596
SBP[a] (per SD)	I	0.39 (0.19-0.59)	1.39 (0.80-1.99)	0.11 (-0.11-0.34)
	II	0.39 (0.20-0.58)	1.29 (0.73-1.85)	0.15 (-0.05-0.36)
DBP[b] (per SD)	I	0.26 (0.06-0.45)	1.06 (0.43-1.69)	0.08 (-0.14-0.29)
	II	0.28 (0.10-0.46)	1.08 (0.51-1.66)	0.12 (-0.07-0.32)
MAP[c] (per SD)	I	0.34 (0.15-0.54)	1.32 (0.72-1.91)	0.10 (-0.12-0.32)
	II	0.36 (0.18-0.54)	1.27 (0.72-1.82)	0.15 (-0.05-0.34)
PP[d] (per SD)	I	0.34 (0.13-0.56)	1.17 (0.53-1.81)	0.09 (-0.14-0.33)
	II	0.32 (0.13-0.52)	1.01 (0.41-1.62)	0.11 (-0.10-0.33)
Hypertension[e] (yes vs no)	I	0.33 (-0.08-0.74)	4.25 (2.65-5.85)	-0.18 (-0.61-0.25)
	II	0.50 (0.12-0.88)	3.86 (2.34-5.38)	0.12 (-0.28-0.52)

[a] systolic BP; [b] diastolic BP; [c] mean arterial pressure; [d] pulse pressure; [e] diastolic BP ≥90 mmHg, systolic BP ≥140 mmHg or use of BP-lowering medication

Model I adjusted for age and sex; Model II adjusted for age, sex, diabetes mellitus and baseline eGFR.

Additional adjustment for the amount and type of BP-lowering medication or for the localization of vascular disease did not change the associations.

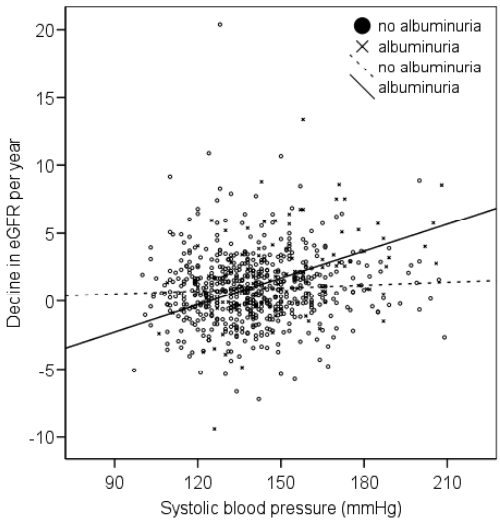


Figure 3 Crude association between systolic BP and annual eGFR decline, according to albuminuria presence.

Discussion

Renal function deteriorated during follow-up in the majority of patients. Mean decline in eGFR was 1.00 ± 2.71 ml/min/1.73m^2 per year, with the fastest deterioration in renal function found in patients with AAA and in patients with albuminuria. BP influenced the decline in eGFR in patients with albuminuria, but not in patients without albuminuria. Systolic BP showed the strongest association with eGFR decline.

The prevalence of lower eGFR in our study was higher compared with estimates in the general population.[22] For example, among SMART participants aged 60-70 years, 15.4% showed eGFR <60 ml/min/1.73m^2 compared to 6.2% in the same age group in the general population.[22] This is not unexpected given the fact that cardiovascular disease and chronic kidney diseases share many risk factors, like obesity, hypertension, diabetes and smoking. In addition, cardiovascular disease may have direct effects on the kidney that can promote initiation and progression of chronic kidney disease, including decreased renal perfusion and atherosclerosis of the renal arteries.

Before 1980 eGFR had already been shown to decline with age in a number of studies,[4, 23, 24] yet, it is not clear to what extent renal changes are the result of normal aging or the result of pathologic conditions. Cross-sectional estimates of eGFR decline with age show wide variation, but also results from longitudinal research are divergent. In a longitudinal study with 254 healthy adults, an annual decline of 0.75 ml/min/1.73m^2 was shown over a period of 5 up to 24 years.[3] Recently, large population-based cohort studies investigated eGFR decline rates. Among 4441 participants of the population based study of Tromsø (mean age 59 years), a yearly eGFR decline of 1.21 ml/min/1.73m^2 in men and 1.19 ml/min/1.73m^2 in women was reported (7 years of follow-up)[25] whereas in 120.727 healthy Japanese adults aged 40-79 years, eGFR declined with 0.36 ml/min/1.73m^2 per year over a period of 10 years.[26] In 5488 subjects from the PREVEND study, annual eGFR decline after a 6.5 year follow-up period was 0.55 ml/min/1.73m^2 for males compared to 0.33 ml/

min/1.73m^2 for females (mean age 49 years).[27] In the present study in patients with manifest vascular diseases, the annual decline in eGFR was 1.00 ml/min/1.73m^2, which is larger compared to the results of other studies in healthy adults at similar age.

In the Baltimore Longitudinal Study of Aging, one third of healthy elderly subjects displayed stability of renal function during follow-up[3] and also 27% of participants in the Tromsø study did not experience eGFR decline.[28] A comparable result was found in our study, where 35% of the study population did not show any deterioration of renal function during the follow-up period. None of the baseline parameters was significantly different between patients with stable renal function and patients showing renal function deterioration (data not shown). The large decrease in renal function of 2.02 ml/min/1.73m^2 per year among AAA patients, observed in the present study, may be due to differences in risk factor profile in those patients and to postoperative renal function deterioration associated with surgical AAA repair.[29]

Several studies found gender differences in renal function decline and in predictors of decline.[25, 27, 30] These differences possibly represent oestrogenic pre-menopausal protection.[31] We observed a slight gender difference in renal function decline, but gender did not modify the effect of BP on the annual decline in eGFR. This might be due to the fact that most women in our study were post-menopausal.

Whereas gender was not an effect modifier in this study, the association between BP and eGFR decline was present only in patients with albuminuria. This modifying effect of urinary albumin excretion is consistent with other studies.[8, 11, 32] In line with these observations, the MDRD study showed a greater beneficial effect of BP lowering in albuminuric patients compared to patients with lower levels of urinary protein excretion.[14] This study was unable to determine whether the presence of albuminuria in hypertensive patients was the consequence of a long-standing advanced hypertension or due to pre-existing intrinsic renal disease.

A relation between BP and future progression of renal disease has frequently been found in patients with pre-existing renal disease, hypertension, diabetes or in healthy populations. However, many studies focus on threshold values indicating renal disease progression, with a certain eGFR value[33] or the development of ESRD[5, 34] as the cut-off point. This can lead to misclassification of patients for whom the eGFR estimation equation is less reliable.[35] Additionally, in many ESRD studies, no detailed information on renal function is available and consequently it remains unknown whether the associations found are due to initiation of renal disease or to accelerated progression. An association between BP and renal function decline was also found in studies that used the preferable slope-based analysis,[13, 36] but none of these studies evaluated the relationship between BP and renal function change in patients with manifest vascular disease.

In the present study, systolic BP showed a stronger relation with eGFR decline compared to the other BP measures investigated in this study. Probably systolic BP elevations exceed the (often already impaired) renal autoregulatory threshold.[37] This finding is in concordance with other studies[11, 32, 36, 38] and is in line with the observation that systolic BP is of greater importance than diastolic BP in cardiovascular risk prediction.[21, 39]

In addition to BP, several other possible predisposing factors of renal function decline have been investigated. In the general population, systolic BP and plasma glucose pre-

dicted accelerated renal function decline in both genders, while albuminuria and waist circumference were only predictive in males. The direction of the association between cholesterol/HDL ratio and eGFR decline differed by gender.[27] In a large Japanese cohort, BP, proteinuria and baseline eGFR were significant risk factors for a faster decline in eGFR.[26] When using eGFR <60 ml/min/1.73m^2 to define renal function decline, age, baseline eGFR, body mass index, diabetes, smoking, hypertension and HDL-cholesterol were predictive.[10] In addition to these factors, the Tromsø study found significant relations with kidney disease stage, proteinuria, and uric acid levels.[40]

In this study, 80% of patients with eGFR <60 ml/min/1.73m^2 was hypertensive, compared to 70% in NHANESIII.[41] Of hypertensive patients with reduced eGFR, 75% was treated with BP-lowering medication, but only a minority of patients reached recommended BP levels (27% for 140/90 mmHg, 13% for 130/80 mmHg). These results correspond to NHANESIII, where 27% reached BP <140/90 mmHg and 11% reached BP <130/85 mmHg.[41] We also observed a large difference in age-adjusted eGFR decline between treated hypertensive patients with BP levels above and below 140/90 mmHg. Although we were not able to investigate the effect of treatment on eGFR decline in this study, these results point towards an important effect of hypertension treatment. In line with this observation, several studies showed that lower levels of achieved BP were associated with a slower decline in renal function.[42, 43]

We acknowledge study limitations. First, patients who participated in the follow-up study are survivors and possibly reflect a healthier subgroup of patients with vascular disease. Because of competing risks of renal failure and mortality we might have underestimated the renal function decline in this population. Second, the issue of whether hypertension precedes or is the result of underlying intrinsic renal insufficiency can not be resolved, and therefore complicates attempts to establish a causal relationship between hypertension and change in renal function. During follow-up, natural variation in the described variables might have occurred as well as prescription of medication. This could have influenced the associations between baseline variables and rate of renal function loss.

Strengths of the study are the prospective design and the choice of change in eGFR over time as estimation of renal function decline instead of using a certain threshold value. The possible systematic bias that is associated with the use of GFR estimating equations[35] is more important in the analysis of absolute eGFR values compared to the assessment of change in eGFR.

In conclusion, levels of renal function are in general lower in patients with vascular disease compared with healthy populations at similar age. Renal function declines at a mean annual rate of 1.00 ml/min/1.73m^2, which is higher than the rate of renal function loss that occurs with aging. Subjects with AAA, diabetes mellitus or albuminuria loose renal function at a higher rate. Only in patients with elevated levels of albuminuria, BP is associated to rate of renal function loss. These results support the importance of considering BP and albuminuric status and stress the importance to focus intensely on BP control in vascular patients regarding renal disease.

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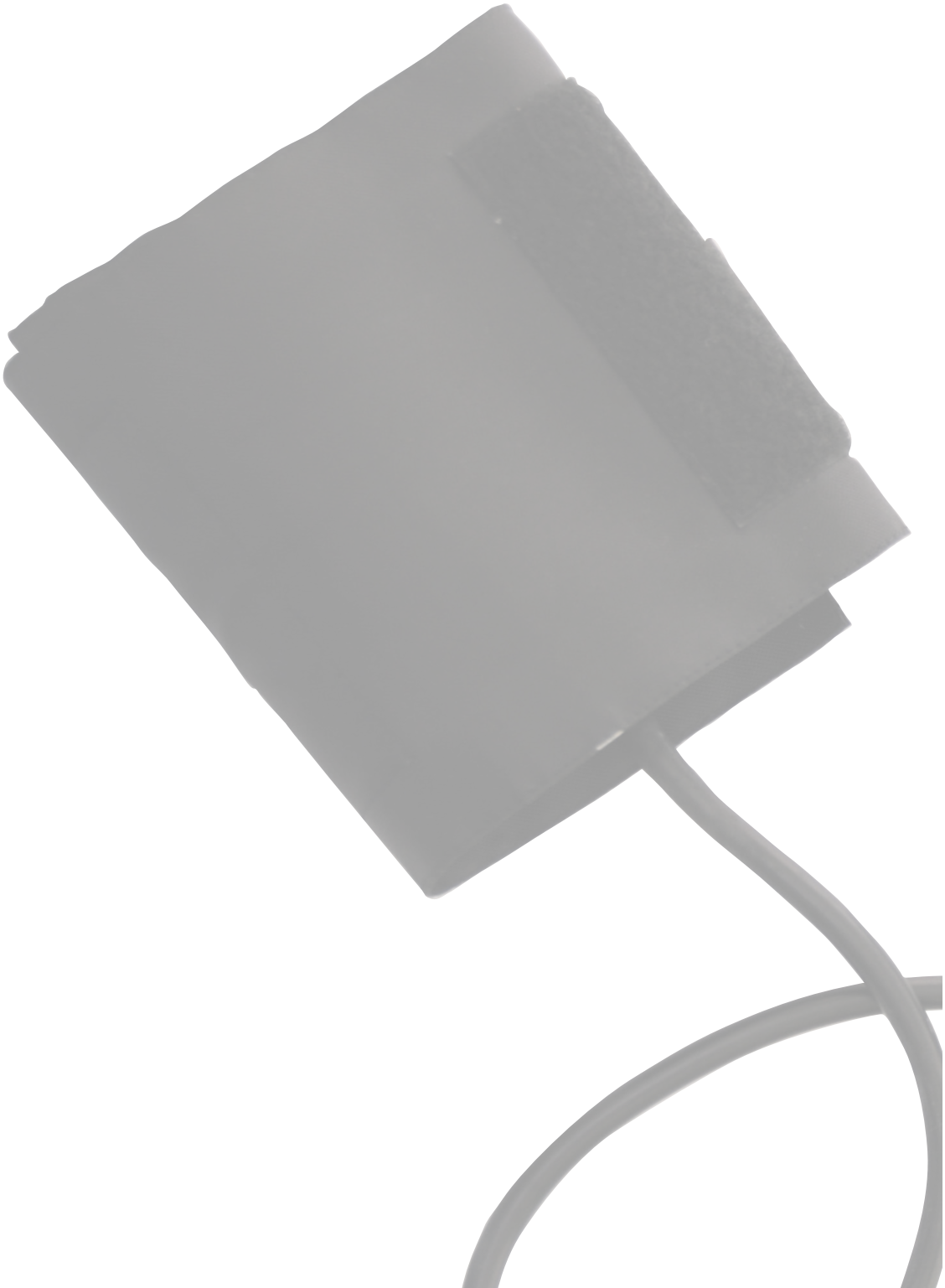
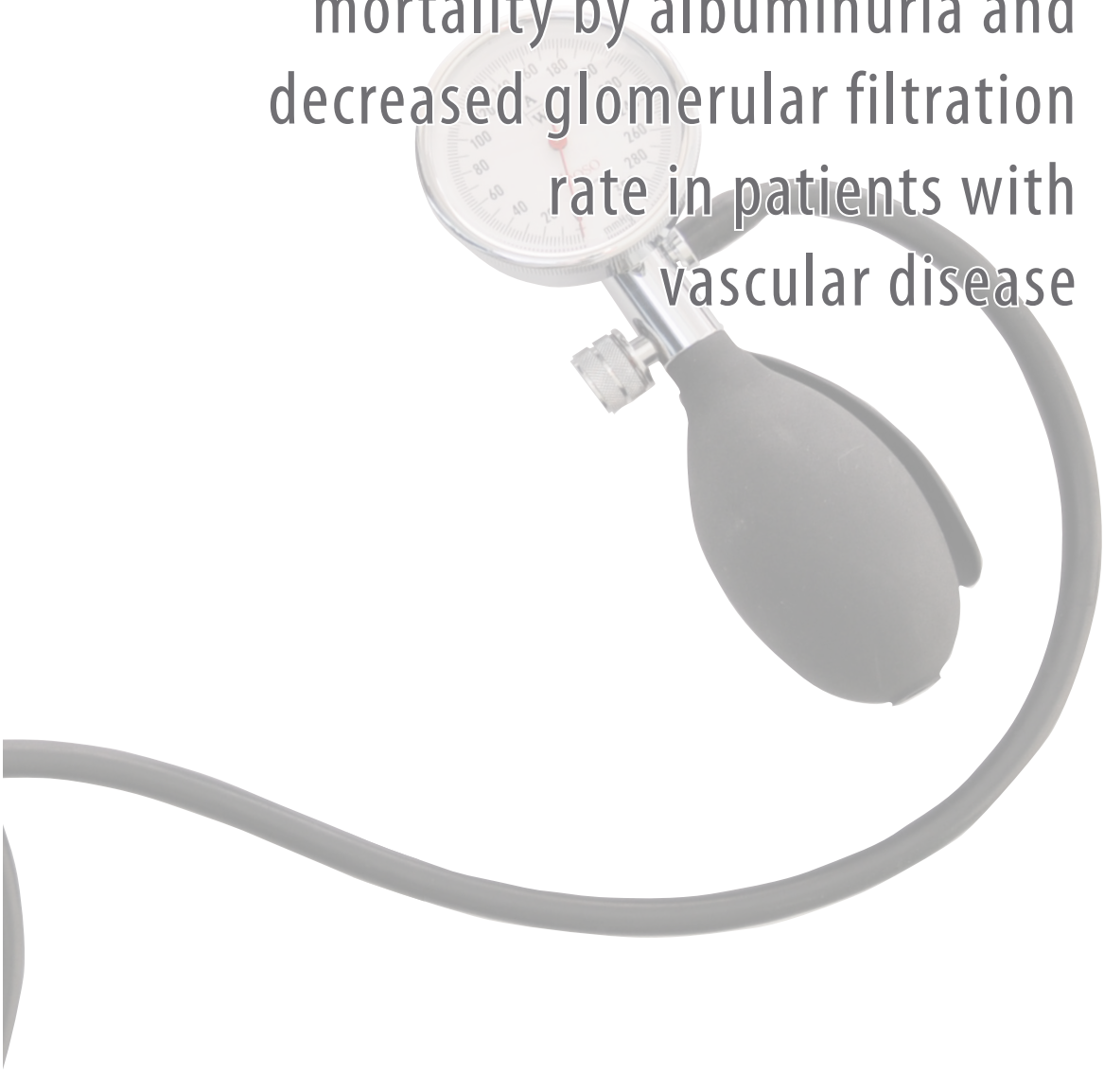


Chapter 3.2

Cardiovascular events and all-cause mortality by albuminuria and decreased glomerular filtration rate in patients with vascular disease



Abstract

Background

Albuminuria and decreased estimated glomerular filtration rate (eGFR) are associated with increased cardiovascular risk, but do not necessarily coexist and have different pathophysiological mechanisms. This study aims to evaluate separate and combined effects of decreased eGFR and albuminuria on the occurrence of vascular diseases and mortality in patients with vascular disease.

Methods

In this prospective cohort study, 2600 patients with vascular disease were followed for vascular events, vascular and all-cause mortality. Cox regression analysis was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI) according to eGFR (MDRD) and albuminuria (albumin-to-creatinine ratio >3mg/mmol).

Results

In this population, 14.0% had albuminuria, 15.6% had eGFR <60 ml/min/1.73m^2 and 5.2% had both. Nonalbuminuric decreased eGFR and albuminuria with normal eGFR generated moderately increased risks on all outcomes. eGFR <60 ml/min/1.73m^2 without albuminuria mainly influenced the risk of vascular events (HR 1.50; 95% CI 1.05-2.15) whilst albuminuria with eGFR ≥60 ml/min/1.73m^2 principally affected all-cause mortality (HR 1.53; 95% CI 1.04-2.26). The combination of eGFR <60 ml/min/1.73m^2 and albuminuria was associated with an increased risk for vascular events (HR 2.27; 95% CI 1.54-3.34), vascular mortality (HR 2.22; 95% CI 1.40-3.52) and all-cause mortality (HR 1.84; 95% CI 1.25-2.69). Comparable results were found in additional analyses amongst 759 diabetic patients.

Conclusions

The combination of decreased eGFR with albuminuria is associated with the highest risks of vascular events, vascular and all-cause mortality in patients with vascular diseases. To adequately estimate vascular risk associated with impaired renal function, both eGFR and urinary albumin should be considered.

Introduction

Albuminuria as well as decreased estimated glomerular filtration rate (eGFR) is associated with an increased risk for the development of cardiovascular diseases and an increased mortality risk. Decreased eGFR is associated with cardiovascular morbidity and mortality independent from other cardiovascular risk factors in hypertensive patients,[1] patients with diabetes mellitus and in nondiabetic patients with[2, 3] and without[4] previous cardiovascular disorders. Only in low-risk populations and in community studies, the relationship between eGFR level and outcomes has not been as clear.[5, 6] Albuminuria is related to cardiovascular disease in the general population[7] and in subgroups of diabetic and nondiabetic patients[8, 9] and in patients with prevalent vascular disease.[9] Even low-grade microalbuminuria is associated with increased cardiovascular risk.[9, 10]

Although both albuminuria and decreased eGFR reflect renal dysfunction and the prevalence of albuminuria increases with a decline in eGFR, the pathophysiological mechanisms leading to albuminuria and decreased eGFR as well as the mechanisms generating increased cardiovascular risk seem to be different.[11-13] A decrease in eGFR can lead to atherosclerosis and occurrence of cardiovascular events via retention of sodium and water, increased levels of various atherogenic factors and metabolic changes, whilst albuminuria is a reflection of vascular endothelial dysfunction. Both identify different patients at risk: data from the United States indicate that only 25% of subjects with albuminuria have low eGFR and around 33% of patients with reduced eGFR have microalbuminuria.[2, 14] Particularly amongst elderly subjects nonalbuminuric decreased eGFR is frequent. Amongst nondiabetic elderly with an eGFR <30 ml/min/1.73m^2, almost two-third does not have albuminuria.[14, 15]

Albuminuria and decreased eGFR have often been assessed separately as risk factors for cardiovascular outcomes but the combined effects of these factors have not been examined extensively.[13, 16] Because both are independently associated with the development of cardiovascular disease but do not necessarily exist together, we hypothesize that, in a high-risk population of patients with manifest vascular disease, the combination of albuminuria and decreased eGFR accounts for a larger cardiovascular risk increment than either of the two alone. In that case, measurement of either urinary albumin or eGFR alone would not be enough to properly estimate cardiovascular and mortality risks associated with impaired renal function.

The purpose of the present study is to describe the prevalence of decreased eGFR and albuminuria and the combination of both in patients with various clinical manifestations of vascular diseases but without diabetes. Furthermore, the effect of decreased eGFR and albuminuria alone and in combination on the occurrence of new cardiovascular events and mortality is evaluated.

Methods

Study design and population

The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective cohort study in the University Medical Center Utrecht. Since 1996, patients aged 18-80

years with clinically manifest atherosclerotic vascular disease (cerebrovascular disease, coronary heart disease, peripheral arterial disease or abdominal aortic aneurysm (AAA)) or risk factors for atherosclerosis (hyperlipidemia, diabetes mellitus or hypertension) are being included. Patients are referred by general practitioners or by medical specialists from other hospitals in the region. Not included are patients with terminal malignant disease, those not independent in daily activities or insufficiently familiar with the Dutch language. All patients are assessed for atherosclerotic risk factors and the extent of atherosclerosis by non-invasive means. The SMART study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent. The rationale and design of the SMART study have been described in detail elsewhere.[17]

For the current study the data of 2810 nondiabetic patients with clinically manifest vascular disease (at inclusion or in past history) included between 1996 and 2005 were available. Patients with eGFR <15 ml/min/1.73m^2 at inclusion (n=25) were excluded as they make up a highly specific group with different characteristics. Patients with missing data on renal function (n=185) were not included leaving 2600 patients for analyses. Diabetic patients (n=759) were studied separately because of their different renal pathology. Clinically manifest vascular disease was defined as cerebrovascular disease, coronary heart disease, AAA or peripheral arterial disease at inclusion or in history. Cerebrovascular disease included transient ischemic attack, cerebral infarction, amaurosis fugax or retinal infarction; coronary heart disease included myocardial infarction and admission for percutaneous transluminal coronary angioplasty or coronary artery bypass graft; AAA included AAA ≥3.0 cm or aneurysm surgery; peripheral arterial disease included claudication of the legs confirmed by a resting ankle-brachial pressure index <0.9 in at least one leg, percutaneous transluminal angioplasty or leg amputation.

Vascular screening

All patients who entered the SMART study underwent a diagnostic screening-protocol for detection of atherosclerotic disease and vascular risk factors. Participants completed a questionnaire on cardiovascular history, risk factors and medication use. Physical examination was carried out and consisted of measurements of height, weight, waist and hip circumferences and blood pressure according to a standardized diagnostic protocol. Fasting blood samples were taken to ascertain levels of glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine and homocysteine. Creatinine was measured with commercial enzymatic dry chemistry kits (Johnson and Johnson). Low-density lipoprotein (LDL) cholesterol levels were calculated with Friedewald's formula. Albumin and creatinine concentrations were measured in a morning urine portion. Urinary creatinine was measured with a commercial enzymatic dry chemistry kit (Johnson and Johnson) and albuminuria was determined with immunoturbidimetric assays (Boehringer-Mannheim). All assessments were performed at a single laboratory. Screening also included duplex scanning of the carotid arteries, electrocardiography, ankle-brachial pressure index and ultrasonography of the abdomen. Abdominal ultrasound consisted of measurements of the anteroposterior diameter of the aorta and the anteroposterior

juxtarenal diameter. The techniques of the baseline examinations have been published formerly.[17]

Definitions

According to the Advisory from the American Heart Association Kidney and Cardiovascular Disease Council the 4-variable Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR and the albumin-to-creatinine ratio (ACR) was used to estimate albuminuria.[18] eGFR was dichotomized at 60 ml/min/1.73m^2 because of the misclassification that exists above 60 ml/min/1.73m^2.[18, 19] An ACR >3 mg/mmol was regarded as albuminuria whilst an ACR ≤3 mg/mmol was considered normal. Diabetes mellitus was defined as self-reported diabetes at baseline and/or the use of glucose-lowering agents.

Follow-up and outcome evaluation

Patients provided information on hospitalization and outpatient clinic visits at a half-yearly basis. When a cardiovascular event was reported, original source documents were retrieved and reviewed to determine the occurrence of cardiovascular disease. Additional information was collected on vascular interventions and death from other causes. Outcome events used in this study included vascular events (non-fatal and fatal stroke, non-fatal and fatal myocardial infarction and sudden death), vascular mortality and all-cause mortality. Definitions of events are given in *Table 1*. All possible events were audited independently by 3 members of the Endpoint Committee. Patients were followed until death or refusal of further participation.

Table 1 Definitions of events.

Vascular death	-	Sudden death (unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence)
	-	Death from ischemic stroke, intracerebral hemorrhage, myocardial infarction, congestive heart failure or rupture of AAA[a].
Stroke	-	Definite: relevant clinical features causing an increase in impairment of at least one grade on the modified Rankin scale, accompanied by an infarction or hemorrhage on a repeat CT-scan.
	-	Probable: clinical deficits causing an increase in impairment of at least one grade on the modified Rankin scale, without CT documentation.
Myocardial infarction	-	At least two of the following criteria: 1. chest pain for at least 20 minutes, not disappearing after administration of nitrates; 2. ST-elevation >1 mm in two following leads or a left bundle branch block on the electrocardiogram; 3. CK[b] elevation of at least two times the normal value of CK and a myocardial band fraction >5% of total CK.

[a]abdominal aortic aneurysm; [b] creatine kinase

Statistical analysis

Patients were classified into 4 categories according to eGFR and ACR: 1) eGFR ≥60 ml/min/1.73m^2 and ACR ≤3 mg/mmol; 2) eGFR <60 ml/min/1.73m^2 and ACR ≤3 mg/mmol; 3) eGFR ≥60 ml/min/1.73m^2 and ACR >3 mg/mmol and 4) eGFR <60 ml/min/1.73m^2 and ACR >3 mg/mmol. Baseline characteristics are presented for these 4 categories.

Results are expressed as means with standard deviations (SDs) for continuous variables and as percentages with the absolute number of patients between parentheses for categorical variables. A Venn diagram was used to show the relation between albuminuria and eGFR.

The influence of different categories of eGFR and ACR on survival free from vascular events, vascular and all-cause mortality was evaluated with the use of the Cox proportional hazards model. We verified that the assumption of proportionality of hazards was satisfied. Results are presented as hazard ratios (HRs) and 95% confidence intervals (95% CIs). Patients with normal eGFR and no albuminuria served as the reference group in the analyses. The extent of confounding was assessed by comparing the crude HR derived from the initial model with the adjusted HR derived from the model that contained the potential confounding variable. Potential confounders were factors which were related to eGFR or albuminuria as well as to the occurrence of cardiovascular events and which were different across the groups of eGFR and ACR. HRs are shown according to different levels of adjustment: 1) HRs adjusted for age and sex; 2) HRs adjusted for age, sex, location of vascular disease (coronary heart disease, cerebrovascular disease, peripheral arterial disease and AAA), smoking, systolic blood pressure, diastolic blood pressure, HDL-cholesterol and LDL-cholesterol. Additional adjustment for the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II (ATII) antagonists was performed in a third model. Cox regression was also performed with eGFR and the natural logarithm of ACR as continuous variables. In these analyses the same abovementioned adjustments were made with additional adjustment for ACR when eGFR was analysed, and additional adjustment for eGFR in the analyses of ACR.

Survival analyses were repeated separately in a population of 759 diabetic patients from the SMART study. All statistical analyses were performed with SPSS, version 14.0 (Windows, Chicago, Illinois, USA).

Results

Baseline characteristics and prevalence of albuminuria and reduced eGFR

The study population consisted of 2600 patients with manifest vascular disease, of whom 28.5% had cerebrovascular disease, 54.3% had coronary heart disease, 25.0% had peripheral arterial disease and 12.4% had AAA at inclusion or in history. The majority of patients (75.6%) had a normal renal function (GFR ≥60 ml/min/1.73m^2 and ACR ≤3 mg/mmol). Of the total of 2600 participants, 365 patients (14.0%) had albuminuria, defined as ACR >3 mg/mmol, and 406 patients (15.6%) had an eGFR <60 ml/min/1.73m^2. A total of 136 patients had both albuminuria and eGFR <60 ml/min/1.73m^2, which is 37.3% of albuminuric patients and 33.5% of patients with eGFR <60 ml/min/1.73m^2 (*Figure 1*). Baseline characteristics according to 4 groups of eGFR and ACR are shown in *Table 2*.

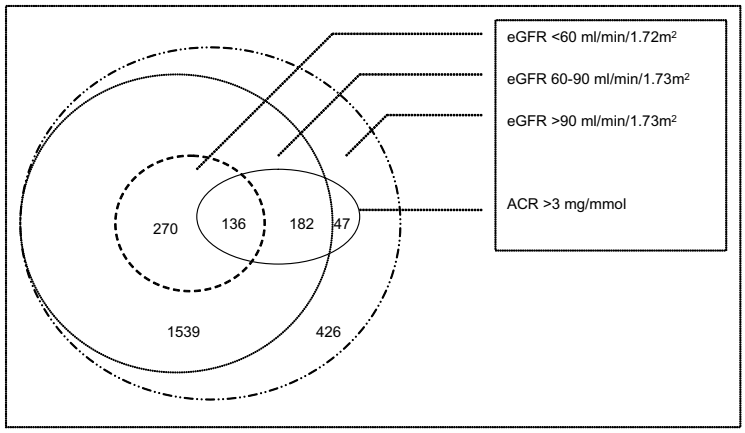


Figure 1 Venn diagram for the relation between estimated glomerular filtration rate and urine albumin-to-creatinine ratio (measured on a single occasion).

Table 2 Baseline characteristics of the study population of patients with vascular diseases according to estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR).

	eGFR[a] ≥60		eGFR[a] <60	
	ACR[b] ≤3 n=1965 (76%)	ACR[b] >3 n=229 (9%)	ACR[b] ≤3 n=270 (10%)	ACR[b] >3 n=136 (5%)
Cerebrovascular disease (%)	26.7	34.5	32.6	36.8
Coronary heart disease (%)	56.5	44.1	51.5	45.6
Peripheral arterial disease (%)	23.6	31.9	22.2	39.7
AAA[c] (%)	9.3	15.3	22.6	32.4
Male gender (%)	78.6	79.0	57.4	80.1
Age (years)	58 ± 10	62 ± 10	66 ± 9	68 ± 8
Smoking, current or past (%)	82.8	88.1	76.6	82.0
Body mass index (kg/m²)	26.4 ± 3.7	26.5 ± 4.0	26.6 ± 3.9	26.2 ± 4.2
Serum triglycerides (mmol/l)	1.9 ± 1.2	2.2 ± 3.8	1.9 ± 1.0	2.0 ± 1.6
LDL-cholesterol (mmol/l)	3.3 ± 1.0	3.3 ± 1.0	3.5 ± 1.0	3.5 ± 1.0
HDL-cholesterol (mmol/l)	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.4	1.2 ± 0.3
Use of lipid-lowering agents (%)	47.8	45.7	46.2	45.0
Systolic blood pressure (mmHg)	140 ± 39	150 ± 23	146 ± 22	156 ± 23
Diastolic blood pressure (mmHg)	82 ± 38	84 ± 11	81 ± 12	85 ± 13
Hypertension[d] (%)	58.5	79.0	80.7	88.2
Duration of hypertension (years)	6.4 ± 10.9	7.7 ± 11.8	10.5 ± 12.4	12.9 ± 13.5
Use of blood pressure-lowering agents (%)	33.9	38.1	59.8	67.9
ACE inhibitors or ATII antagonists[e] (%)	19.2	21.0	39.6	36.8
eGFR[f] (ml/min/1.73m²)	81 ± 13	81 ± 18	51 ± 8	45 ± 11

Continuous variables are expressed as means with standard deviations.
[a]in ml/min/1.73m2; [b]in mg/mmol; [c]abdominal aortic aneurysm; [d]blood pressure ≥140/90 mmHg or use of blood pressure-lowering medication; [e]use of angiotensin-converting enzyme inhibitors or angiotensin II antagonists; [f]estimated glomerular filtration rate

Albuminuria, reduced eGFR and the risk of new cardiovascular events in patients with vascular disease

During a median follow-up of 4.0 years (range 0.5-8.5 years) 274 vascular events occurred, of which 85 strokes, 161 myocardial infarctions and sudden deaths and 28 other vascular events. In total, 253 patients died of which 156 from a vascular cause.

In this cohort of patients with vascular disease, eGFR <60 ml/min/1.73m^2 without albuminuria only significantly influenced the risk of vascular events (HR 1.50; 95% CI 1.05-2.15), whilst the effect on vascular mortality was of the same magnitude but borderline significant (HR 1.43; 95% CI 0.90-2.29) and no significant association with all-cause mortality (HR 1.16; 95% CI 0.79-1.71) was found. On the contrary, albuminuria with eGFR ≥60 ml/min/1.73m^2 was only significantly associated with all-cause mortality (HR 1.53; 95% CI 1.04-2.26) and to a lesser extent with the occurrence of vascular mortality (1.56; 95% CI 0.94-2.60) and vascular events (HR 1.40; 95% CI 0.93-2.11) (*Table 3*, *Figure 2*).

Table 3 Hazard ratios and 95% confidence intervals for groups of estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) for future events in patients with vascular diseases and patients with diabetes mellitus.

	eGFR[a] >60 ACR[b] <3	eGFR[a] >60 ACR[b] >3	eGFR[a] <60 ACR[b] <3	eGFR[a] <60 ACR[b] >3
Patients with vascular diseases	n=1965	n=229	n=270	n=136
Vascular events	n=162	n=29	n=45	n=38
Model I[c]	1.00	1.41 (0.95-2.11)	1.64 (1.16-2.31)	2.55 (1.76-3.70)
Model II[d]	1.00	1.40 (0.93-2.11)	1.50 (1.05-2.15)	2.27 (1.54-3.34)
Vascular mortality	n=81	n=19	n=27	n=29
Model I[c]	1.00	1.58 (0.96-2.62)	1.53 (0.98-2.40)	2.81 (1.80-4.36)
Model II[d]	1.00	1.56 (0.94-2.60)	1.43 (0.90-2.29)	2.22 (1.40-3.52)
All-cause mortality	n=142	n=35	n=37	n=39
Model I[c]	1.00	1.70 (1.17-2.47)	1.22 (0.84-1.77)	2.25 (1.56-3.25)
Model II[d]	1.00	1.53 (1.04-2.26)	1.16 (0.79-1.71)	1.84 (1.25-2.69)
Patients with diabetes mellitus	n=488	n=149	n=73	n=49
Vascular events	n=48	n=17	n=15	n=13
Model I[c]	1.00	1.07 (0.61-1.87)	1.58 (0.87-2.89)	2.09 (1.10-3.96)
Model II[d]	1.00	1.17 (0.63-2.16)	1.56 (0.81-2.99)	2.14 (1.06-4.31)
Vascular mortality	n=18	n=8	n=12	n=11
Model I[c]	1.00	1.29 (0.56-2.99)	3.13 (1.45-6.73)	4.26 (1.93-9.42)
Model II[d]	1.00	1.53 (0.62-3.79)	3.64 (1.59-8.34)	4.64 (1.91-11.26)
All-cause mortality	n=39	n=13	n=15	n=15
Model I[c]	1.00	0.96 (0.51-1.80)	1.85 (0.99-3.44)	2.66 (1.42-4.98)
Model II[d]	1.00	0.98 (0.49-1.95)	1.85 (0.94-3.64)	2.74 (1.39-5.41)

[a] in ml/min/1.73m2; [b]in mg/mmol; [c] model I shows HRs adjusted for age and gender; [d] model II shows HRs adjusted for age, sex, vascular history, smoking, systolic blood pressure, diastolic blood pressure, HDL-cholesterol and LDL-cholesterol

Additional adjustment for the use of angiotensin-converting enzyme inhibitors or angiotensin II antagonists did not change the HRs

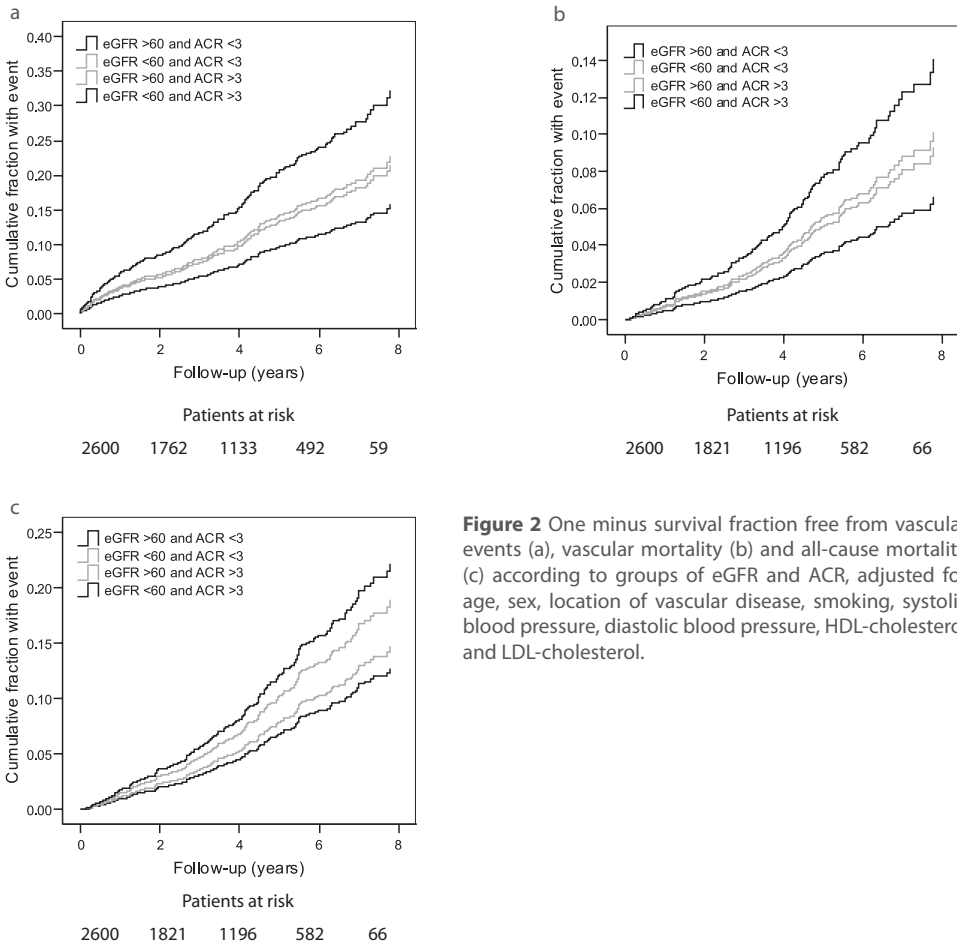


Figure 2 One minus survival fraction free from vascular events (a), vascular mortality (b) and all-cause mortality (c) according to groups of eGFR and ACR, adjusted for age, sex, location of vascular disease, smoking, systolic blood pressure, diastolic blood pressure, HDL-cholesterol and LDL-cholesterol.

The combination of decreased eGFR and albuminuria accounted for the highest risk on vascular events (HR 2.27; 95% CI 1.54-3.34), vascular mortality (HR 2.22; 95% CI 1.40-3.52) and all-cause mortality (HR 1.84; 95% CI 1.25-2.69). Presented HRs result from a Cox model that adjusted for age, sex, location of vascular disease, smoking, systolic blood pressure, diastolic blood pressure, HDL-cholesterol and LDL-cholesterol. Additional adjustment for the use of ACE inhibitors or ATII antagonists did not change the HRs in all analyses.

When continuous associations were examined, a clear relation was found between the natural logarithm of the ACR and vascular events (HR 1.14; 95% CI 1.05-1.24), vascular mortality (HR 1.19; 95% CI 1.09-1.30) and all-cause mortality (HR 1.22; 95% CI 1.10-1.36). HRs for every 10 ml/min/1.73m^2 decrease in eGFR were 1.11; 95% CI 1.02-1.20 for vascular disease, 1.06; 95% CI 0.95-1.17 for vascular mortality and 0.99; 95% CI 0.92-1.07 for all-cause mortality. Analyses of continuous relationships were performed with the same adjustments as were the analyses of categories of renal function, with additional adjustment for ACR when eGFR was analysed, and additional adjustment for eGFR in the analyses of ACR.

Albuminuria, reduced eGFR and the risk of new cardiovascular events in diabetic patients

Amongst diabetic patients, albuminuria with eGFR ≥60 ml/min/1.73m^2 was not significantly associated with any of the endpoints studied, whilst eGFR <60 ml/min/1.73m^2 without albuminuria showed a large influence on vascular mortality risk. The combination of decreased eGFR and albuminuria accounted for the highest risk on all endpoints, like in patients with vascular disease (*Table 3*).

Discussion

Renal impairment, as measured by eGFR <60 ml/min/1.73m^2 or albuminuria, was prevalent in a high-risk population of patients with manifest vascular disease. Nonalbuminuric decreased eGFR and albuminuria with normal eGFR generated moderately increased risks on the occurrence of vascular events, vascular mortality and all-cause mortality. Patients with decreased eGFR in combination with albuminuria were at the highest risk of vascular events and vascular and all-cause mortality. This effect was also seen in diabetic patients. Although there seems to exist a slight difference in vascular risk between albuminuric patients and patients with reduced eGFR this cannot be confirmed based on these data. A considerable proportion of patients only had albuminuria or decreased eGFR indicating that measuring only one of these indicators leaves patients unnoticed with renal dysfunction and thus at elevated cardiovascular and mortality risk.

The possible cause of these findings is the difference in pathophysiological mechanisms that can be considered for the association between both decreased eGFR and albuminuria and increased cardiovascular risk. First, a decreased eGFR is associated with increased oxidative stress,[11, 16] elevated plasma concentrations of inflammatory mediators (e.g. increased C-reactive protein),[4, 11, 16, 20, 21] homocysteine[4, 11, 16, 20] and uric acid,[11] abnormal levels of lipoprotein(a) and apolipoprotein A1,[4, 16, 20] decreased insulin sensitivity and hyperinsulinemia[22] and enhanced coagulability.[4, 11, 16, 20, 21, 23] In addition, changes in phosphate metabolism may also be involved.[11, 16, 23-25] All these factors may cause endothelial dysfunction and although these markers were not examined in this study, they may contribute to the development of atherosclerosis.[26] Apart from endothelial dysfunction, decreased eGFR can lead to volume expansion, which causes hypertension and an increased afterload[11, 16] and can eventually cause impairment of ventricular function.[11] Besides these mechanisms, therapeutical strategies may be different in patients with decreased eGFR (compared with those with albuminuria or with normal renal function) and part of the effect may also be due to residual confounding by traditional risk factors.[13]

Endothelial dysfunction most likely underlies the association between albuminuria and cardiovascular disease.[27, 28] Albuminuria is associated with vascular dysfunction and increased cardiovascular risk through a systemic increase in vascular permeability, allowing the entry of lipoproteins in the vessel wall, an early event in atherogenesis.[12, 29-32] Besides increased vascular permeability, vascular dysfunction also accounts for an increased adhesiveness of the endothelium with respect to leukocytes and platelets and endothelial production of vasoactive and inflammatory mediators.[12, 32] As a prediabetic state at base-

line may be present in some patients, the vascular risk associated with decreased renal function may also in part be mediated by the development of type 2 diabetes during follow-up.

Given the fact that albuminuria and decreased eGFR have distinct pathophysiological pathways contributing to atherogenesis, it is plausible that decreased eGFR and albuminuria add up to the cardiovascular risk and identify different patients, as shown in the present study. Although some patients (5.2% of patients in the present study) have albuminuria and decreased eGFR in combination, albuminuria is present in 14.0% of patients and decreased eGFR in 15.6% of the study population. In a study amongst patients with previous myocardial infarction, 9.3% had proteinuria, 17.3% had eGFR <60 ml/min/1.73m^2 and 4.2% had both.[33] Previous studies have shown that the HR of cardiovascular morbidity and mortality for albuminuria ranged from 1.8 in patients with previous vascular disease to 2.0 in type 2 diabetic patients and 2.9 in hypertensive patients.[9, 29, 34, 35] In the PREVEND study, a population based study, a doubling of urinary albumin concentration was associated with a 29% increased risk of cardiovascular mortality.[7] Albuminuria also caused a twofold increase in all-cause mortality in different populations.[9, 34, 35] The HR for cardiovascular morbidity and mortality for decreased eGFR was 1.4 in patients with vascular disease,[2, 3] 2.1 in hypertensive patients[1] and 1.2-3.4 in a healthy population.[3, 4] In a similar patient population as in the present study the combination of decreased eGFR and proteinuria was associated with high risk (HR 2.39) whilst patients with only proteinuria or only decreased eGFR were at intermediate risk (HR 1.69 and HR 1.41) for all cause mortality.[33] That study and others reveal similar results as our study.[2, 33, 36] As patients with the highest absolute cardiovascular risk will have the largest benefit of risk reducing interventions, measuring both albuminuria and eGFR as indicators of renal insufficiency should be considered. Early detection of these patients and aggressive risk factor reduction in combination with specific treatments for patients with renal impairment, as issued by the K/DOQI clinical practice guidelines, may reduce the burden of cardiovascular disease in this high-risk group.[37]

This study has several limitations. The single measurement of urinary albumin and serum creatinine might have led to an underestimation of the cardiovascular risk, and also the fact that we did not calibrate our GFR assay against the reference laboratory assay used to develop the GFR equation may have led to some misclassification.[38] Although the MDRD formula is recommended by the Advisory from the American Heart Association Kidney and Cardiovascular Disease Council as a reliable estimation of GFR which is applicable to patients with cardiovascular diseases, the accuracy of the GFR estimate might be reduced in persons with normal or only slightly diminished GFR and in woman younger than 65 years.[18, 19]

In conclusion, nonalbuminuric decreased eGFR and albuminuria with normal eGFR generated moderately increased risks on the occurrence of vascular events, vascular death and all-cause mortality in patients with clinically manifest vascular diseases. The combination of decreased eGFR and albuminuria is associated with the highest risk on subsequent vascular events, vascular mortality and all-cause mortality in patients with vascular disease as well as in diabetic patients. Thus, to adequately estimate the cardiovascular risk associated with impaired renal function, both eGFR and urinary albumin should be considered in patients with clinically manifest vascular diseases or diabetes.

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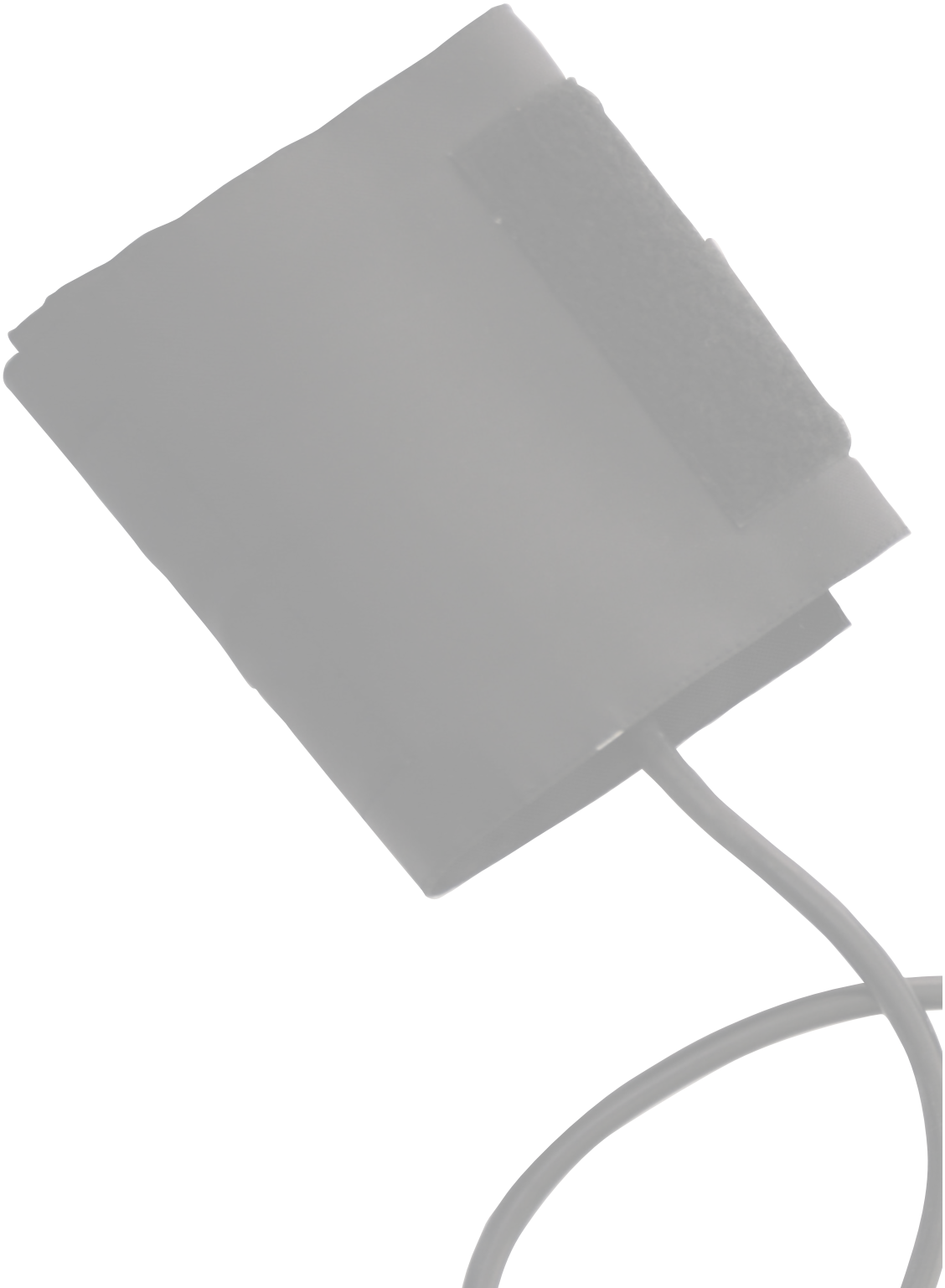
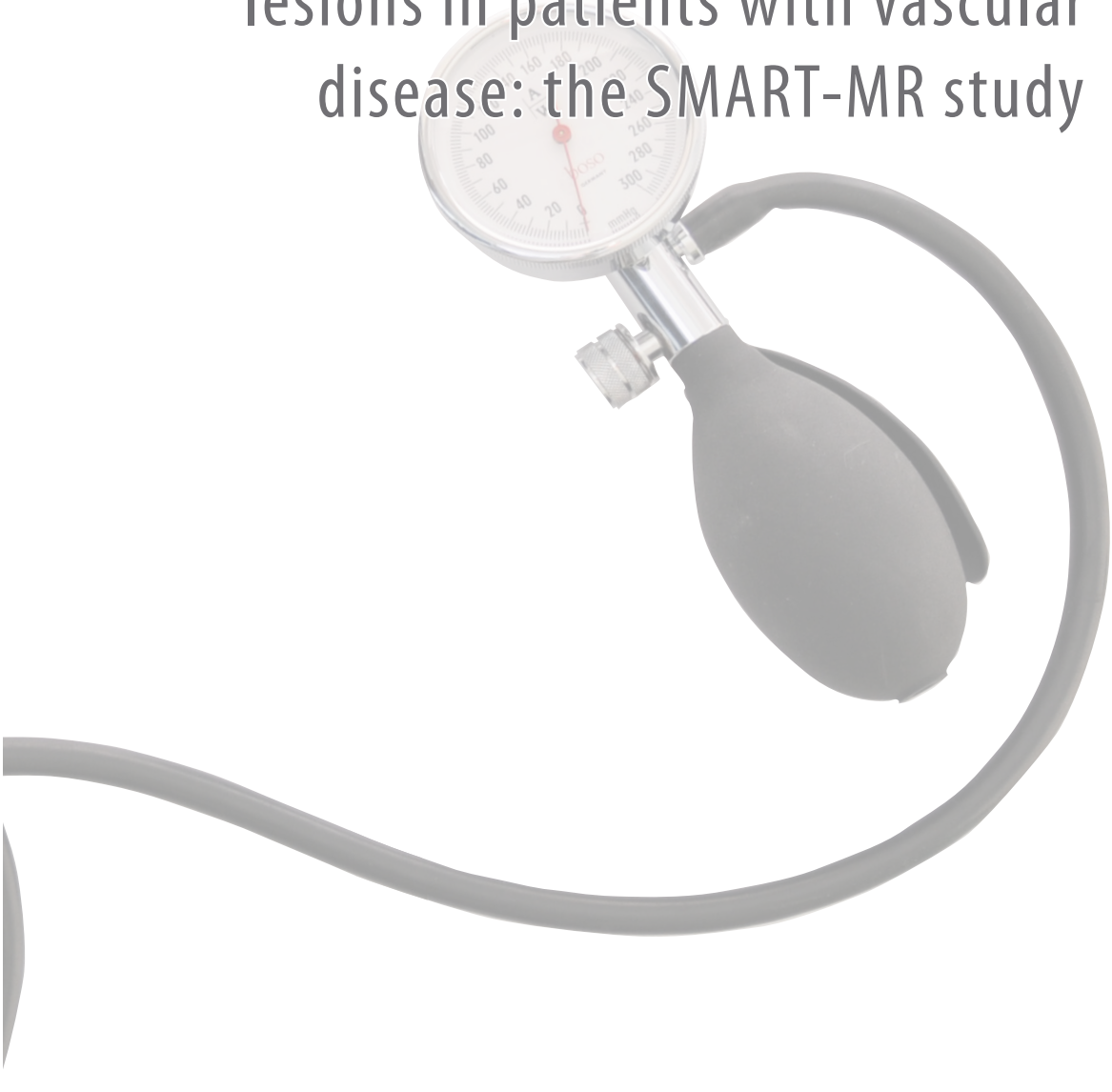


Chapter 4.1

Blood pressure and white matter lesions in patients with vascular disease: the SMART-MR study



Abstract

Background

White matter lesions (WML) are a frequent finding on brain magnetic resonance imaging scans. Elevated blood pressure (BP) is consistently identified as risk factor for WML. However, it is unknown whether BP still is associated with WML in patients with manifest vascular disease. The aim of this cross-sectional study was to investigate associations between BP and WML in patients with manifest vascular disease.

Methods

A total of 1030 patients with vascular disease (cerebrovascular disease (23%), coronary heart disease (59%), peripheral arterial disease (23%), abdominal aortic aneurysm (9%)) from the Second Manifestations of ARTerial disease study were included. WML volume was calculated using an automated quantitative volumetric method and subsequently divided into quartiles. We investigated associations between BP and WML, and examined whether relations between BP and WML were modified by the localization of the symptomatic site or by the presence of diabetes.

Results

Participants had a mean age of 58.7 years. Median volume of WML was 1.70 ml. Mean BP was 141/82 mmHg and 69% suffered hypertension. No significant associations between systolic BP, diastolic BP, mean arterial pressure (MAP) or hypertension presence and moderate or large WML volumes were present. The relation between BP and WML was not modified by the localization of vascular disease or by the presence of diabetes.

Conclusions

Among patients with manifest vascular disease, BP was not associated with the presence of WML, irrespective of the presence of diabetes or the localization of vascular disease.

Introduction

Cerebral white matter lesions (WML) are a frequent finding on brain magnetic resonance imaging (MRI) scans, especially in elderly subjects.[1] Different studies report a wide range of prevalences varying from 25% to 55%, which is probably caused by differences in age, vascular risk factors and method of WML assessment.[2-6] Scanty information is available on WML prevalence among patients with vascular disease. WML probably play an important role in the development of dementia and cognitive impairment,[1, 4, 5, 7, 8] and the presence of WML has also been related to development of stroke.[1, 9, 10]

Although the pathogenesis of WML is still poorly understood, age, hypertension, diabetes mellitus and several other vascular risk factors have been identified as possible predisposing factors.[1, 4, 9] In cross-sectional studies, hypertension has consistently been identified as a risk factor for WML in different categories of patients.[2, 3, 11-14] Longitudinal studies have also reported a relation between baseline blood pressure (BP) levels and WML at follow-up.[11, 12, 15, 16] In patients with hypertension, WML have been associated with BP levels and with both the duration[15] and the severity[2] of hypertension. Also the lack of BP control in patients treated with BP-lowering medication has been related to WML presence.[3, 12, 15, 17]

Most research investigating the association between BP and WML has been performed in population based studies[3, 11, 12, 15] or in patients with vascular risk factors,[2] whereas a substantial proportion of elderly patients who are at risk for developing WML already have a history of vascular disease. In addition, many of these previous studies used qualitative grading methods for WML assessment which can lead to inconsistencies across studies.[18]

It is unknown whether elevated BP levels are still related to WML presence in patients with manifest vascular disease. We investigated the association between BP and WML in a large cohort of patients with manifest vascular disease with the use of an automated quantitative volumetric method of WML assessment.

Methods

Study design and population

The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective cohort study carried out in the University Medical Center Utrecht, the Netherlands. Patients aged 18-80 years with manifest atherosclerotic disease or risk factors for atherosclerosis are being included and are evaluated for atherosclerotic risk factors and the extent of atherosclerosis by non-invasive means. The rationale and design of the SMART study have been described in detail elsewhere.[19]

In 2001, the SMART-MR study started as a part of the SMART study.[20] Until 2005, all patients without contraindications for MRI who were included with manifest vascular disease (cerebrovascular disease, coronary heart disease, abdominal aortic aneurysm (AAA) or peripheral arterial disease) were asked to participate. Patients underwent brain MRI investigation in addition to the baseline examinations. Cerebrovascular disease included transient ischemic attack, ischemic stroke, amaurosis fugax or retinal infarction. Coronary heart disease included myocardial infarction and admission for percutaneous transluminal coronary angioplasty or coronary artery bypass graft. AAA included AAA ≥3.0 cm or

aneurysm surgery. Peripheral arterial disease included claudication of the legs confirmed by a resting ankle-brachial pressure index <0.9 in at least 1 leg, percutaneous transluminal angioplasty or leg amputation. The SMART study and the SMART-MR study were approved by the local medical ethics committee and all participants gave written informed consent.

For the current study, data of 1030 patients with clinically manifest vascular disease and suitable MR images were available. From the original 1309 patients included in the SMART-MR study, 279 patients had to be excluded from the analyses because of missing MR sequences (n=192), irretrievable MR data (n=19), missing FLAIR images (n=14), artefacts (n=40) or absence of manifest vascular disease (n=14).

Baseline measurements

All patients who entered the SMART-MR study underwent a diagnostic screening-protocol for detection of atherosclerotic disease and vascular risk factors. Participants completed a questionnaire on cardiovascular history, risk factors and medication use. Physical examination consisted of anthropometric and BP measurements, with BP measured by sphygmomanometry at the right and left upper arm and repeated on the side with the highest values. The mean of all obtained measurements was used in the analyses.[19] Fasting blood samples were taken to ascertain levels of glucose, lipids, creatinine and homocysteine, and urinary albumin and creatinine concentrations were measured. All assessments were performed at a single laboratory. Screening also included duplex scanning of the carotid arteries, electrocardiography, ankle-brachial pressure index and ultrasonography of the abdomen. Abdominal ultrasound consisted of measurements of the anteroposterior diameter of the aorta and the anteroposterior juxtarenal diameter. Techniques of the baseline examinations have been published formerly.[19]

MR protocol

Brain MRI examinations were performed with a 1.5 T Philips Gyroscan (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The brain was imaged in the axial plane with 38 slices of 4 mm without slice gap, covering the entire brain, with a field of view of 230 x 230 mm and matrix size 180 x 256. In each patient, a T1-weighted gradient-echo sequence (repetition time (TR)/echo time (TE) 235 ms/2 ms; flip angle 80°), a T2-weighted turbo spin-echo sequence (TR/TE 2200/11 and 2200/100 ms; turbo factor 12), a T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/inversion time (TI) 6000/100/2000 ms), and an inversion recovery (IR) sequence (TR/TE/TI 2900/22/410 ms) were applied.

Analysis of white matter lesions

The volume of WML on MRI images was determined with an automated probabilistic segmentation procedure (*Figure 1*). This method has been described in more detail elsewhere.[21] Briefly, the algorithm is based on the K-Nearest Neighbour (KNN) classification technique and uses information from T1-weighted, IR and FLAIR scans to estimate the probability of voxels being part of a lesion. With this combination of images, optimal

performance of the KNN classification algorithm is achieved.[21] Before the KNN classification and analysis was performed, data were corrected for differences due to patient movement.[22] The region of interest for the segmentation process was defined by automated brain extraction.[23] The KNN classification method was then used to generate a probability map, containing the probabilities of voxels being part of a specific type of brain tissue (grey matter, white matter, WML, ventricles or cerebro-spinal fluid outside ventricles). Volumes were calculated by addition of all probability values.

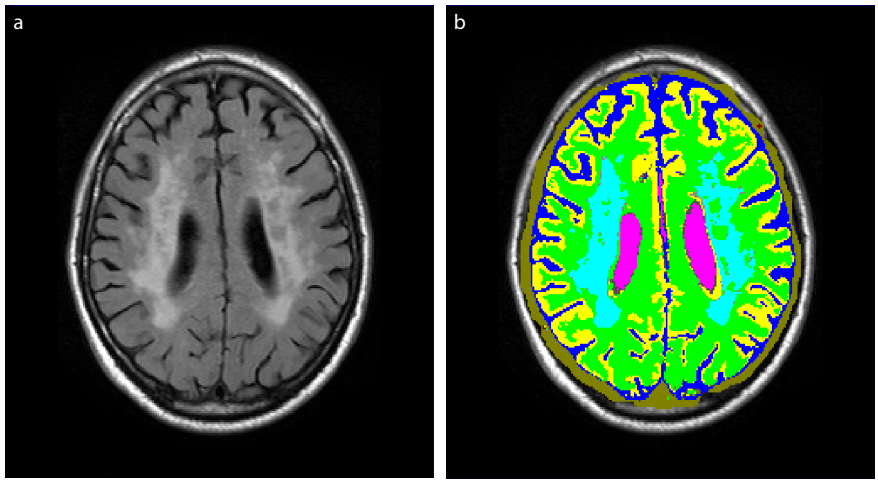


Figure 1 (a) MR FLAIR image of a patient with extensive WML, visible as white areas and (b) the result of segmentation based on the automated KNN-based algorithm.

Segmentation was accomplished on all images cranial to the foramen magnum. All images were analysed and interpreted blind to subject data and in all patients the accuracy of WML segmentation was checked visually. As the segmentation program is unable to differentiate WML from cerebral infarcts, manual correction was performed in scans with cerebral infarcts.

Definitions

Hypertension was defined as diastolic blood pressure (DBP) ≥90 mmHg, systolic blood pressure (SBP) ≥140 mmHg or self-reported use of BP-lowering medication. As a reflection of the hemodynamic perfusion pressure of the organs, mean arterial pressure (MAP) was used as a measure of BP and was calculated as 2 times DBP plus SBP divided by 3. Type 2 diabetes mellitus was defined as self-reported type 2 diabetes or use of glucose-lowering agents.

Statistical analysis

WML volumes were calculated for all subjects and were divided into quartiles. WML volume was normalised for total intracranial volume by dividing WML volume by the

patient's intracranial volume and multiplying by the population mean intracranial volume (1463 ± 129 ml).[24] Baseline characteristics are presented according to presence or absence of hypertension.

Polytomous logistic regression analysis was used to examine the association between BP and the different WML quartiles, with the first quartile serving as the reference category. In all analyses total WML volume was used, but deep and periventricular WML were also considered separately in the analyses. Deep WML include the deep white matter of the centrum semiovale extending into subcortical regions, and periventricular WML are contiguous to the margins of the ventricles.[25] Odds ratios (OR) with 95% confidence intervals (95% CI) were estimated at two different levels of adjustment: 1) adjustment for age and sex and 2) adjustment for age, sex and number and class of BP-lowering medication.

WML volume was not normally distributed and therefore was log-transformed for the linear regression analyses that were used to study the relation between BP and WML volume. In the linear regression analyses the same adjustments were used as in the polytomous logistic regression analyses.

The possible modifying effect of vascular disease localization and of diabetes mellitus on the relation between BP and WML was examined by entering product terms in the models. Interaction was considered present if p-values of the interaction terms were below 0.05. To check for the possibility of a J-shaped relationship between BP and WML, logistic regression analyses were performed with the upper WML quartile as the dependent variable and BP quartiles as the covariate. All analyses were repeated after exclusion of patients with non-lacunar cerebral infarcts on MR imaging. Statistical analyses were performed with SPSS, version 14.0 (Windows, Chicago, Illinois, USA).

Results

Of the 1030 patients included in the study, 59% had coronary heart disease, 23% had cerebrovascular disease, 23% had peripheral arterial disease and 9% had AAA. Fourteen percent of patients had more than 1 localization of vascular disease. Mean age was 58.7 ± 10.1 years.

In the total study population, WML quartile ranges consisted of first, 0.08 to 0.96 ml (median 0.66 ml); second, 0.96 to 1.70 ml (median 1.30 ml); third, 1.70 to 3.55 ml (median 2.42 ml); and fourth, 3.55 to 66.16 ml (median 6.58 ml). Median volume of WML lesions was 1.70 ml. WML burden was highest in patients with cerebrovascular disease (median volume 2.76 ml) or AAA (median volume 2.71 ml), and lower in patients with peripheral arterial disease (median volume 1.74 ml) or coronary heart disease (median volume 1.52 ml).

Table 1 presents baseline characteristics according to presence of hypertension. Overall, WML volumes, age, prevalence of diabetes and medication use were higher in hypertensive patients compared to patients without hypertension.

White matter lesions and blood pressure

Mean SBP was 141 mmHg and mean DBP was 82 mmHg. Mean MAP was 102 mmHg. In total 69.3% of the population suffered from hypertension according to our prespecified criteria.

Table 1 Baseline characteristics of patients according to hypertension presence.

	No hypertension[a] n=316	Hypertension[a] n=714
WML volume (ml)[b]	1.45 (0.93-2.66)	1.90 (0.97-4.01)
Male gender	84.8	76.5
Age (years)	56.3 ± 10.1	59.7 ± 9.9
Localization of vascular disease		
cerebrovascular disease	13.6	27.0
coronary heart disease	70.3	53.6
abdominal aortic aneurysm	8.5	9.7
peripheral arterial disease	18.4	24.8
Diabetes mellitus[c]	12.7	24.3
SBP (mmHg)	124 ± 10	149 ± 19
DBP (mmHg)	74 ± 7	85 ± 10
Packyears of smoking	21 ± 20	23 ± 21
Body mass index (kg/m^2)	26.1 ± 3.6	27.0 ± 3.8
Waist circumference (cm)	94.0 ± 11.0	95.8 ± 11.0
Triglycerides (mmol/l)	1.72 ± 1.19	1.76 ± 1.11
HDL-cholesterol (mmol/l)	1.23 ± 0.36	1.31 ± 0.40
LDL-cholesterol (mmol/l)	2.88 ± 0.94	2.85 ± 0.95
Glucose (mmol/l)	5.9 ± 1.1	6.4 ± 1.9
eGFR (ml/min/1.73m^2)[d]	82 ± 16	76 ± 18
Aortic diameter (cm)	1.91 ± 0.44	1.90 ± 0.45
Use of lipid-lowering agents	51.1	57.6
Use of glucose-lowering agents	5.4	16.7
Use of BP-lowering agents	0.0	62.4

Results are presented as mean ± SD or as percentage in case of categorical variables unless otherwise stated. [a] SBP ≥140 mmHg, DBP ≥90 mmHg or use of BP-lowering medication; [b] median (25th percentile-75th percentile), corrected for total intracranial volume; [c] self-reported type 2 diabetes or use of glucose-lowering agents; [d] estimated glomerular filtration rate, Modification of Diet in Renal Disease equation

BP did not show any significant associations with WML volume (*Table 2*). Even when analysing the upper quartile of WML volume, which contrasts strongly with the volume in the first quartile, there were no significant relations between BP and WML volume. ORs per SD increase were 1.12 (95% CI 0.91-1.37) for SBP, 1.07 (95 % CI 0.88-1.30) for DBP and 1.10 (95% CI 0.90-1.34) for MAP. Also the presence of hypertension or its treatment status were not associated with WML volume. After exclusion of patients with non-lacunar cerebral infarcts, results were essentially the same. The association between BP and WML did not differ significantly across different localizations of vascular disease (p-values for interaction terms >0.13 for all measures of BP). Relations between BP and WML were also not modified by diabetes presence (p-values for interaction terms >0.15 for all measures of BP).

Table 2 Relation between white matter lesions[a] and blood pressure reflected in odds ratios with 95% confidence intervals.

		WML volume in Q2	WML volume in Q3	WML volume in Q4
Systolic BP (per SD)	I	0.95 (0.78-1.14)	1.08 (0.90-1.30)	1.16 (0.96-1.42)
	II	0.95 (0.78-1.15)	1.04 (0.86-1.26)	1.12 (0.91-1.37)
Diastolic BP (per SD)	I	0.92 (0.77-1.10)	0.97 (0.81-1.16)	1.13 (0.93-1.36)
	II	0.93 (0.78-1.11)	0.93 (0.78-1.12)	1.07 (0.88-1.30)
MAP (per SD)	I	0.93 (0.78-1.11)	1.02 (0.85-1.22)	1.15 (0.95-1.40)
	II	0.93 (0.78-1.12)	0.98 (0.82-1.18)	1.10 (0.90-1.34)
Hypertension[b]	I	0.71 (0.49-1.03)	0.92 (0.62-1.35)	1.25 (0.81-1.95)
	II	0.75 (0.51-1.10)	0.80 (0.54-1.20)	1.06 (0.67-1.67)
Untreated hypertension	I	0.78 (0.52-1.15)	0.76 (0.51-1.13)	0.75 (0.49-1.15)
	II	0.69 (0.46-1.04)	0.75 (0.49-1.15)	0.78 (0.50-1.23)
Treated HT; BP <140/90[c]	I	0.80 (0.50-1.26)	0.80 (0.50-1.29)	1.16 (0.70-1.93)
	II	0.88 (0.54-1.42)	0.74 (0.45-1.22)	1.06 (0.63-1.81)
Treated HT; BP ≥140/90[d]	I	1.04 (0.68-1.61)	1.44 (0.95-2.20)	1.51 (0.97-2.36)
	II	1.17 (0.74-1.84)	1.34 (0.86-2.09)	1.31 (0.82-2.09)

[a] white matter lesion volume is normalised for total intracranial volume and divided into quartiles. The first quartile serves as the reference category; [b] SBP ≥140 mmHg, DBP ≥90 mmHg or use of BP-lowering medication; [c] treated hypertension with BP <140/90 mmHg; [d] treated hypertension with BP ≥ 140/90 mmHg
Model I adjusted for age and sex; Model II additionally adjusted for number and class of BP-lowering medication.

When WML volume was analysed as a continuous variable in linear regression analyses, again no significant relations were found with SBP (β coefficient per SD 0.03; 95% CI -0.03-0.09 per SD), DBP (β coefficient per SD 0.03; 95% CI -0.03-0.08 per SD), MAP (β coefficient per SD 0.03; 95% CI -0.03-0.09 per SD) or hypertension presence (β coefficient 0.04; 95% CI -0.08-0.17) (*Table 3*). Crude associations between MAP and ln WML volume are shown in *Figure 2*.

There were no differences in the effect of BP in separate analyses of periventricular and deep WML (data not shown). There were also no indications for a J-shaped relationship between MAP, SBP or DBP and WML (data not shown). To verify the reliability of the BP measurements we investigated whether there was an association between BP and albuminuria, a different manifestation of end-organ damage due to BP. The OR for the presence of albuminuria was 1.35 (95% CI 1.13-1.63) for every SD increase in SBP, whereas the same increase in DBP generated an OR of 1.24 (95% CI 1.04-1.48). One SD increase in MAP showed an OR of 1.32 (95% CI 1.10-1.58) on albuminuria presence, after adjustment for age and sex.

Table 3 Linear regression analysis of associations between ln WML volume and blood pressure.

		Regression coefficient (95% CI)
Systolic blood pressure (per SD)	I	0.04 (-0.02-0.10)
	II	0.03 (-0.03-0.09)
Diastolic blood pressure (per SD)	I	0.04 (-0.02-0.09)
	II	0.03 (-0.03-0.08)
Mean arterial pressure (per SD)	I	0.04 (-0.01-0.10)
	II	0.03 (-0.03-0.09)
Hypertension[a]	I	0.09 (-0.04-0.21)
	II	0.04 (-0.08-0.17)

[a]SBP ≥140 mmHg, DBP ≥90 mmHg or use of BP-lowering medication
Model I adjusted for age and sex; Model II additionally adjusted for number and class of BP-lowering medication.

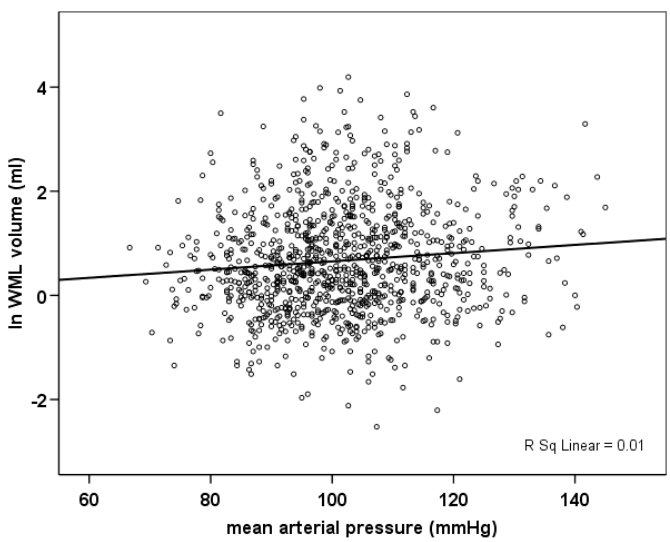


Figure 2 Crude association between ln WML volume and mean arterial pressure.

Discussion

In this study among patients with manifest vascular disease at entry, median volume of WML was 1.70 ml. No associations between BP and WML volume and between hypertension and WML volume were present. The relation between BP and WML volume was not modified by the presence of diabetes or the localization of vascular disease.
In previous studies an association between BP and WML has frequently been found. The underlying mechanism of this frequently found association is thought to consist of an acceleration of arteriosclerotic changes in the arterioles in the brain, which eventually

result in a reduction of luminal diameter and increased resistance to flow.[26, 27] Besides this, hypertension may also contribute to impairment of cerebral autoregulation.[26] The brain white matter is particularly vulnerable to ischemic damage because of its blood supply being dependent on end-arteries lacking appropriate anastomoses. Due to these changes, lacunar infarctions or white matter changes occur.

Median WML volume in this study was relatively small compared with that in other studies, possibly due to the relatively young age of our study population. In a study of 414 patients (mean age 73 years) of whom about half had vascular disease, median WML volume was 2.09 ml.[16] Median WML volume at baseline was 1.70 ml among 535 patients (mean age 75 years) with a history of or increased risk for vascular disease[28] and 2.30 ml among 61 stroke patients (mean age 65 years).[29]

In this study population, BP was not associated with WML volume. This finding is not in line with observations from other studies in healthy individuals and hypertensive patients that reported a pronounced relation between presence and severity of WML load and elevated SBP,[2-4, 12, 30, 31] elevated DBP[2, 3, 12, 31] and elevated MAP.[2] However, none of these studies was performed in patients with a history of vascular disease. There also was no association between treated or present hypertension and WML in this study while other studies showed a marked association between hypertension presence and WML and between hypertension treatment status and WML.[3, 11, 12, 15, 17]

In this study, comparable results were found when analyzing total WML compared to analyzing deep and periventricular WML separately. In previous studies, differences between deep and periventricular WML were not consistent which is probably due to the arbitrary distinction between periventricular and deep WML.[32]

In subjects with chronic hypertension, the threshold of BP needed to maintain adequate cerebral flow may move to a higher level when autoregulatory limits are shifted upward.[26, 33] This resulted in a J-shaped relation between change of DBP over 20 years and WML in 1077 patients, while the association between current DBP and WML was not J-shaped.[31] In the present study we did not demonstrate this J-shaped relation, which could possibly be explained by the cross-sectional design of our study. Another explanation would be that increased BP variability instead of casual BP levels particularly causes WML.[34]

No studies were found that investigated the association between hypertension or BP and the presence of WML in patients with different types of vascular disease. However, a few studies among patients with cerebrovascular disease showed that relations between WML and stroke[35] and between WML and intracranial bleeding[36] were not attenuated by adjustment for hypertension. When the predictive value of stroke and hypertension were simultaneously evaluated, stroke turned out to be more important than hypertension as a predictor of WML.[5, 37-40] In the LADIS study, no association between hypertension and WML was present among stroke patients.[14] One study was found that reported a relation between DBP and WML in patients of whom about half had cardiovascular disease.[16]

This study showed that the relation between BP and WML is not unequivocal, as we could not identify any associations between BP and WML volume among patients with established vascular disease. A possible explanation for this finding would be that BP does not further discriminate within a population already at high vascular risk. Another possibility is that BP measured earlier in life shows a clear association with the development of WML

later in life, while cross-sectional associations are weaker. For example, in the EVA MRI cohort the frequency of severe WML was higher in people who were hypertensive both at baseline and after 4 years of follow-up than in those who were hypertensive only at the second measurement.[11] Differences in study results may also be due to different methods of WML assessment used. To rule out the possibility that no associations between BP and WML were found due to invalidity of the BP measurements in this population, we verified whether there was an association between BP and albuminuria. Such a relation was clearly established, indicating that results can not be attributed to unreliability of BP measurements. Besides, BP values in our study are comparable with values in other studies that did find a clear association between BP and WML, indicating that the lack of an explicit relation between BP and WML is not due to the level of BP in our population.

Strengths of this study include the large number of participants drawn from a population of patients with manifest vascular disease. Also the use of a quantitative image analysis instead of rating scales which gave variable results for WML assessment[18] is a strength of this study. There are also some limitations in this study that must be considered. First, the cross-sectional design does not permit to determine causality. A longitudinal design would clarify whether the lack of associations at baseline is confirmed after follow-up and would allow to assess what risk factors possibly affect the progression of WML over time. Some misclassification of hypertension might have occurred as BP was measured only at a single occasion.

In a high-risk population of patients with manifest vascular disease, BP was not associated with the presence of WML, irrespective of the presence of diabetes or the localization of vascular disease. Longitudinal research is needed to confirm these findings.

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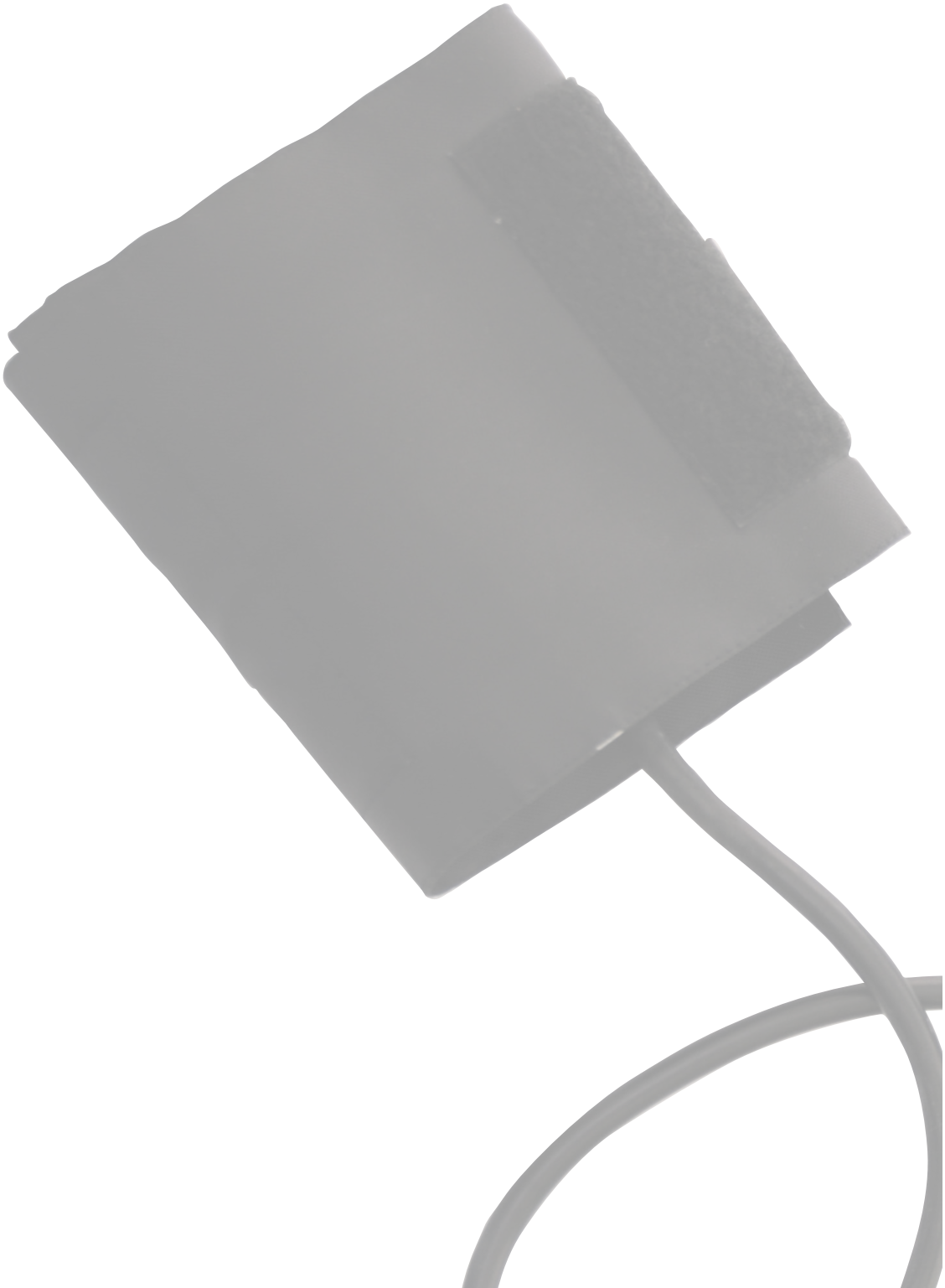
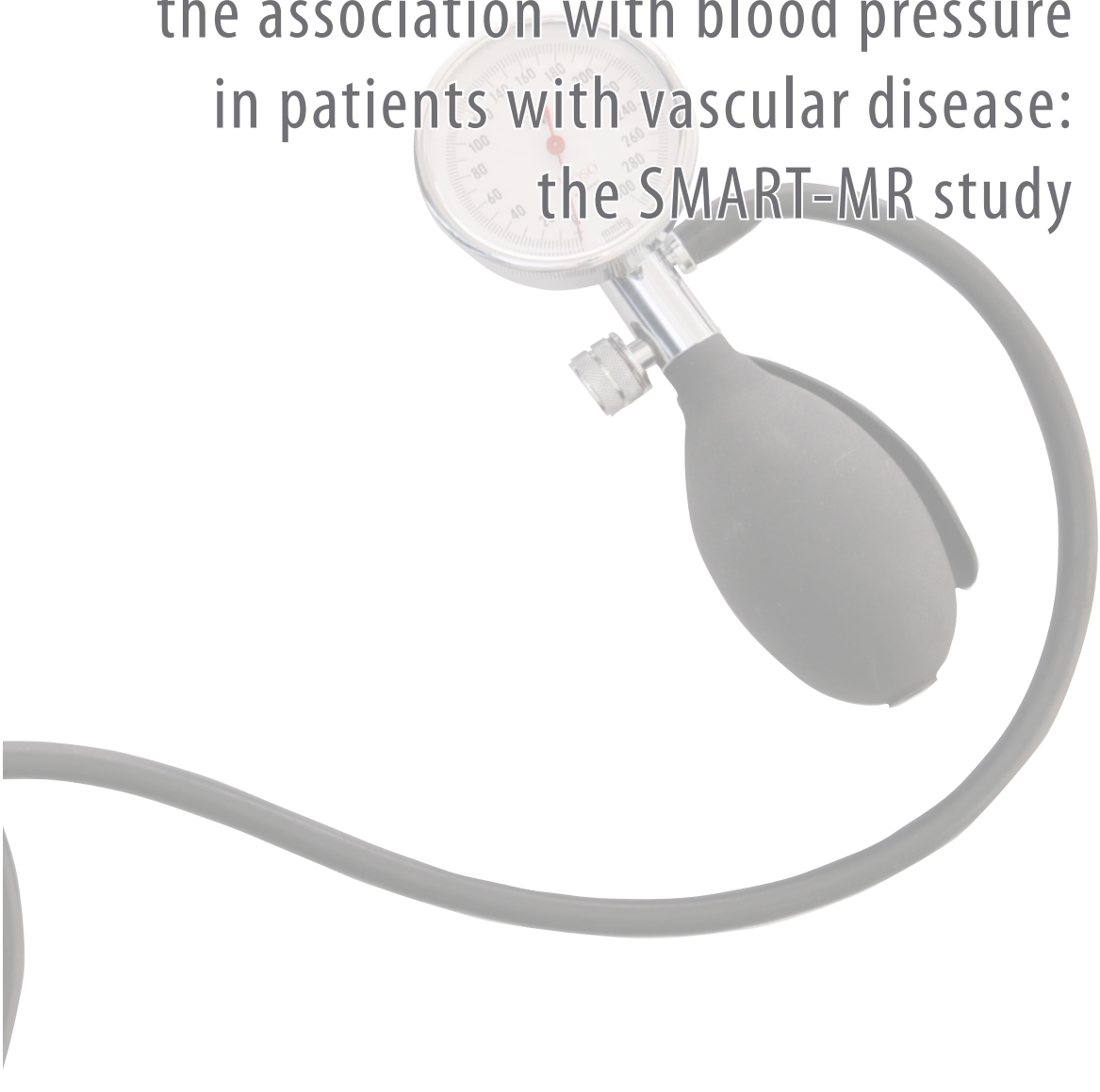


Chapter 4.2

Progression of cerebral atrophy and the association with blood pressure in patients with vascular disease: the SMART-MR study



Abstract

Background

Cerebral atrophy on brain MRI has been associated with vascular risk factors including hypertension. Progression of cerebral atrophy and its risk factors have not been studied in patients with vascular disease. This study aimed to assess the progression of cerebral atrophy and to evaluate possible associations with blood pressure (BP) in patients with pre-existing vascular disease.

Methods

A total of 331 patients with manifest vascular disease from the Second Manifestations of ARTerial disease study underwent baseline and follow-up MRI-scanning (mean follow-up 4.1 ± 0.3 years). The annual change in brain and ventricular volume was calculated with an automated quantitative volumetric method. Associations between BP and change in brain and ventricular volumes and between BP and the occurrence of lacunar infarcts were analyzed.

Results

At baseline mean age was 58 ± 9 years and mean BP was 138/80 mmHg. Mean annual decrease in brain tissue volume was 6.5 ± 3.8 ml and mean annual increase in ventricular volume was 1.0 ± 1.0 ml. There was no association between BP and annual change in brain or ventricular volume, but a clear association was found between BP and incident lacunar infarcts (OR 1.57; 95% CI 1.11-2.22 per SD increase in systolic BP).

Conclusions

The magnitude of changes in brain tissue and ventricular volume in patients with vascular disease was comparable to the physiological changes described in normal people at a much higher age. Progression of cerebral atrophy in this population may be associated with advanced physiological aging, but is probably not caused by elevated BP.

Introduction

Cerebral atrophy on brain magnetic resonance imaging (MRI) is a common finding and most elderly people have some degree of cerebral atrophy.[1] Accumulating evidence shows that cerebral atrophy is associated with cognitive impairment[2] and different degenerative pathologies.[3]

The decrease in brain tissue volume may be caused by degenerative processes, but vascular risk factors and presence of atherosclerotic vascular disease have also been associated with cerebral atrophy.[4-7] Elevated blood pressure (BP) has repeatedly been reported to be a risk factor for cerebral atrophy in cross-sectional studies,[8-10] but some evidence is available indicating that elevated BP is associated with cerebral atrophy and atrophy progression in follow-up studies.[11, 12] However, all of these latter studies were performed in populations of community-dwelling elderly or hypertensive patients without prevalent vascular diseases.

Cerebral atrophy progresses gradually over time although the extent of progression is unclear. Increased rates of progression of brain atrophy have been reported in people with dementia or older age.[13, 14] As a limitation, progression rates have been estimated mostly with either visual or semiquantitative techniques that are not well suited for measuring change in cerebral atrophy.[15, 16]

Despite the suggested possibility of a vascular etiology of cerebral atrophy, progression and risk factors of cerebral atrophy have not been studied in patients with overt vascular disease. Because a vascular origin of cerebral atrophy is suggested, one might argue that in patients with manifest vascular diseases, severity and progression rate of cerebral atrophy could be higher compared to healthy populations. Also risk factors associated with cerebral atrophy might not be the same in a diseased vascular system.

The aim of this study was to quantify the progression of cerebral atrophy during follow-up in patients with clinically manifest vascular diseases using automated volumetric methods, and to evaluate in a follow-up study of patients with overt vascular disease whether elevated BP levels are associated with progression of cerebral atrophy.

Methods

Study design and population

The SMART-MR study is a prospective cohort study in patients with manifest vascular disease whom participate in the Second Manifestations of ARTerial disease (SMART) study.[17] Between 2001 and 2005, all patients without contraindications for MRI who were included with clinically manifest vascular disease (cerebrovascular disease, coronary heart disease, abdominal aortic aneurysm (AAA) or peripheral arterial disease) were asked to participate. Patients underwent brain MRI investigation in addition to the baseline examinations. The SMART study and the SMART-MR study were approved by the local medical ethics committee and all participants gave written informed consent.

Starting from January 2006, all 1309 participants of the SMART-MR study were invited for follow-up examinations including a second MRI of the brain. In 2006 and 2007, a total of 499 patients underwent follow-up measurements. For the current study, data of 331

patients with manifest vascular diseases and suitable MR images at baseline and after follow-up were available. From the original 499 participants, 142 had to be excluded because of missing baseline information (missing MRI sequences n=126, irretrievable MRI data or artefacts n=13 or absence of manifest vascular disease n=3). Of the remaining 357 patients, another 26 patients had to be excluded because of missing follow-up data (refused follow-up MRI n=12, missing MRI sequences n=11, irretrievable MRI data or artefacts n=3).

Measurements

All patients who entered the SMART-MR study underwent a diagnostic screening-protocol for detection of atherosclerotic disease and vascular risk factors at baseline and after 4.1 ± 0.3 years of follow-up. Participants completed questionnaires on history, risk factors and medication use. Physical examination consisted of anthropometric and BP measurements, with BP measured by sphygmomanometry at the right and left upper arm and repeated on the side with the highest values. The mean of all measurements was used in the analyses.[17] Fasting blood samples were taken to ascertain levels of glucose, lipids, creatinine and homocysteine. All assessments were performed at a single laboratory.[18]

MR protocol

Brain MRI examinations were performed with a 1.5 T Philips Gyroscan (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The brain was imaged in the axial plane with 38 slices of 4 mm without slice gap, with a field of view of 230 x 230 mm and matrix size 180 x 256. In each patient, a T1-weighted gradient-echo sequence (repetition time (TR)/echo time (TE) 235 ms/2 ms; flip angle 80°), a T2-weighted turbo spin-echo sequence (TR/TE 2200/11 and 2200/100 ms; turbo factor 12), a T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/inversion time (TI) 6000/100/2000 ms), and an inversion recovery (IR) sequence (TR/TE/TI 2900/22/410 ms) were applied.

Brain segmentation and assessment of brain atrophy

The automated probabilistic segmentation procedure used for brain segmentation has been described in detail elsewhere.[19] Briefly, the algorithm is based on the K-Nearest Neighbour (KNN) classification technique and uses information from T1-weighted, IR and FLAIR scans to estimate the probability of voxels being part of a lesion.[19] Before the KNN analysis was performed, data were corrected for differences caused by patient movement.[20] The region of interest for the segmentation process was defined by automated brain extraction.[21] The KNN classification method was then used to generate a probability map, containing the probabilities of voxels being part of a specific type of brain tissue (grey matter, white matter, white matter lesions (WML), ventricles or cerebro-spinal fluid outside ventricles). Volumes were calculated by addition of probability values. As the segmentation program is unable to differentiate WML from cerebral infarcts, the results of the segmentation analysis were visually checked and manually corrected by a trained investigator and a neuroradiologist to distinguish between WML and infarct volumes. All images were analyzed and interpreted blind to subject data. Total volume of brain tissue

was calculated by summing the volumes of grey and white matter and, if present, the volumes of WML and infarcts.

Definitions

Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg or self-reported use of BP-lowering medication. Mean arterial pressure (MAP) was calculated as 2 times DBP plus SBP divided by 3. Type 2 diabetes mellitus (DM2) was defined as self-reported DM2, use of glucose-lowering agents or fasting glucose ≥7.0 mmol/l at screening.
Infarcts were defined as focal hyperintensities on T2-weighted images of at least 3 mm in diameter. Hyperintensities located in the white matter also had to be hypointense on T1-weighted images, in order to distinguish them from WML. We defined lacunar infarcts as infarcts sized 3-15 mm and located in the subcortical white matter, thalamus or basal ganglia.

Statistical analysis

Results are expressed as means with standard deviations (SDs) for continuous variables and as percentages for categorical variables. Yearly decline in brain tissue volume and yearly increase in ventricular volume were calculated on patient level by determining the difference between baseline and follow-up values and dividing by the follow-up time recorded for that patient. Age- and sex-adjusted estimates of yearly change in brain tissue and ventricular volume for different subgroups separately were calculated with a general linear model.
The influence of BP on brain tissue volume decrease and ventricular volume increase was evaluated with linear regression analysis. β Coefficients with 95% confidence intervals (95% CI) were estimated, and the extent of confounding was assessed by comparing crude β coefficients with adjusted β coefficients derived from the model containing the potential confounding variable. Full adjustment was made for age, sex, DM2, WML volume, BP-lowering medication use and baseline brain tissue volume or ventricular volume. The possible modifying effect of age and sex on the relation between BP and atrophy rate was examined by entering product terms in the models. All analyses were repeated after exclusion of patients with non-lacunar cerebral infarcts on MRI. The association between BP and incident lacunar infarcts was evaluated with logistic regression analysis using the same adjustment as in the analyses of brain atrophy progression.

Results

Of the 1309 patients with baseline measurements, 499 patients with follow-up measurements in 2006 and 2007 were available for this study. Of these 499 patients, 331 patients had suitable baseline and follow-up MR measurements and constituted the study population. There were differences in baseline characteristics between patients who did and did not participate in the follow-up measurements. Participants were more often male (85% vs 74%), generally younger (57.9 vs 61.3 years old), less often had DM2 (9.8% vs 17.3%) or hypertension (65% vs 73%) and had larger initial brain tissue volumes (1173 ml vs 1127 ml).

Mean baseline age was 58 ± 9 years. Mean SBP at baseline was 138 ± 19 mmHg and mean DBP was 80 ± 10 mmHg (*Table 1*). 63% of patients suffered from hypertension. At follow-up both SBP and DBP were higher compared to baseline (144/83 mmHg) and hypertension prevalence was 73%.

Table 1 Baseline characteristics of the study population according to hypertension presence.

	All (n=331)	Hypertension[a] (n=209)	No hypertension[a] (n=122)
Age (years)	58 ± 9	59 ± 9	56 ± 9
Male gender (%)	86.4	83.7	91.0
Cerebrovascular disease (%)	23.3	30.1	11.5
Cononary heart disease (%)	62.5	53.1	78.7
Peripheral arterial disease (%)	17.5	22.5	9.0
AAA[b] (%)	7.6	8.1	6.6
Smoking (packyears)	23.3 ± 20.0	25.0 ± 20.7	20.5 ± 18.4
Body mass index (kg/m^2)	26.6 ± 3.6	26.7 ± 3.6	26.5 ± 3.7
Serum triglycerides (mmol/l)	1.8 ± 1.1	1.7 ± 1.0	1.9 ± 1.2
LDL-cholesterol (mmol/l)	2.9 ± 0.9	2.9 ± 0.9	2.9 ± 1.0
HDL-cholesterol (mmol/l)	1.25 ± 0.40	1.27 ± 0.42	1.21 ± 0.34
Use of lipid-lowering agents (%)	58.8	62.3	52.9
Diabetes mellitus[c] (%)	9.1	11.5	4.9
Glucose (mmol/l)	6.3 ± 1.8	6.5 ± 2.1	6.0 ± 1.3
Albuminuria[d] (%)	14.4	17.8	8.8
Baseline eGFR[e] (ml/min/1.73m^2)	81.5 ± 17.3	79.6 ± 18.1	84.8 ± 15.4
Systolic blood pressure (mmHg)	138 ± 19	147 ± 17	123 ± 10
Diastolic blood pressure (mmHg)	80 ± 10	84 ± 9	74 ± 7
Mean arterial pressure (mmHg)	100 ± 12	105 ± 11	90 ± 7
Use of β-blockers	35.0	30.1	43.4
Use of diuretics	7.9	12.0	0.8
Use of ACE inhibitors	15.4	20.6	6.6
Use of angiotensin II antagonists	5.1	7.2	1.6
Use of calcium channel blockers	12.7	12.9	12.3

[a]systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg or use of blood pressure-lowering medication; [b]abdominal aortic aneurysm; [c]self-reported type 2 diabetes, use of glucose-lowering agents or fasting glucose ≥7.0 mmol/l; [d]albumin-creatinine ratio >3 mg/mmol; [e]estimated glomerular filtration rate, MDRD equation

Change in brain tissue volume

Mean baseline brain tissue volume was 1175 ± 102 ml and declined to a mean value of 1149 ± 104 ml after 4.1 ± 0.3 years of follow-up. Ventricular volume was 29.9 ± 13.4 ml at baseline and 33.8 ± 15.5 ml at follow-up. Mean yearly decrease in brain tissue volume was 6.5 ± 3.8 ml (0.55% of baseline volume) and mean increase in ventricular volume per year was 1.0 ± 1.0 ml (3.3% of baseline volume). When stability of brain tissue volume was defined as a yearly decrease of less than 1 SD of mean yearly brain tissue volume decrease (3.9 ml/year), 22.7% of patients had stable brain tissue volume, whereas 77.3% of patients showed a decline in brain tissue volume. Similarly, ventricular volume remained stable in 63.1% of patients and increased in 36.9%. When analyzing brain tissue volume change in different subgroups, age- and sex-adjusted brain tissue volume decrease as well as ventricular volume increase were most pronounced in patients ≥60 years, patients with cerebrovascular disease and patients with DM2 (*Table 2*).

Table 2 Age- and sex-adjusted annual change in cerebral volume measures.

	Brain tissue volume change per year		Ventricular volume change per year	
	Absolute change in ml (95% CI)	Percentage change (95% CI)	Absolute change in ml (95% CI)	Percentage change (95% CI)
Age (years)				
<60	-5.56 (5.04-6.09)*	0.47 (0.43-0.52)*	0.62 (0.50-0.75)*	2.52 (2.09-2.94)*
≥60	-7.75 (7.13-8.37)*	0.67 (0.62-0.73)*	1.42 (1.27-1.57)*	4.22 (3.71-4.72)*
Sex				
Female	-6.03 (4.97-7.08)	-0.57 (0.48-0.66)	0.80 (0.54-1.05)	3.16 (2.28-4.04)
Male	-6.55 (6.13-6.96)	-0.55 (0.52-0.59)	0.98 (0.88-1.08)	3.23 (2.89-3.58)
Localization of vascular disease[a]				
CVD[b]	-8.19 (7.40-8.98)*	-0.71 (0.64-0.78)*	1.19 (0.99-1.38)*	3.49 (2.81-4.16)
CHD[c]	-6.10 (5.61-6.60)*	-0.52 (0.48-0.57)*	0.86 (0.74-0.98)*	3.04 (2.63-3.46)
PAOD[d]	-6.66 (5.72-7.61)	-0.57 (0.49-0.66)	0.85 (0.62-1.08)	3.04 (0.25-3.83)
AAA[e]	-6.81 (5.37-8.25)	-0.58 (0.46-0.71)	1.03 (0.68-1.37)	3.22 (2.03-4.42)
Glycemic status				
No diabetes	-6.30 (5.90-6.71)*	-0.54 (0.50-0.57)*	0.91 (0.82-1.01)*	3.17 (2.83-3.51)
Diabetes	-8.15 (6.85-9.45)*	-0.72 (0.61-0.83)*	1.40 (1.09-1.72)*	3.81 (2.72-4.90)
Hypertension status				
No hypertension	-5.95 (5.30-6.59)*	-0.51 (0.45-0.56)*	0.94 (0.78-1.09)	3.35 (2.81-3.89)
Hypertension	-6.78 (6.29-7.27)*	-0.59 (0.54-0.63)*	0.97 (0.85-1.09)	3.15 (2.74-3.56)

[a]localizations of vascular disease are not exclusive categories; [b] cerebrovascular disease; [c] coronary heart disease; [d] peripheral arterial occlusive disease; [e] abdominal aortic aneurysm
Values are age- and sex-adjusted means, with age only adjusted for sex and sex only adjusted for age.
*p-value for difference <0.05; for vascular disease localization, the reference category was absence of the disease localization under study.

The difference in age- and sex-adjusted change in cerebral volume measures between normotensive and hypertensive patients was small whereas the incidence of both lacunar and cortical infarcts was larger in hypertensive as compared to normotensive patients (*Table 3, Figure 1*).

Table 3 Age- and sex-adjusted cerebral volume measures and presence of cerebral infarcts at baseline and after 4 years of follow-up.

	Mean total brain tissue volume (ml)	Mean ventricular volume (ml)	1 lacunar infarct (%)	≥2 lacunar infarcts (%)	Cortical infarcts (%)
Baseline					
All	1175 (1165-1184)	29.9 (28.6-31.2)	8.5 (5.5-11.5)	8.5 (5.5-11.5)	10.9 (7.5-14.2)
No HT[a]	1186 (1170-1202)	29.1 (26.9-31.2)	5.5 (0.5-10.5)	3.1 (-1.8-8.1)	5.9 (0.3-11.5)
HT[a]	1169 (1156-1181)	30.4 (28.7-32.0)	10.2 (6.4-14.0)	11.6 (7.8-15.3)	13.8 (9.5-18.0)
Follow-up					
All	1149 (1139-1158)	33.8 (32.4-35.2)	10.9 (7.6-14.3)	12.7 (9.2-16.3)	13.6 (9.9-17.3)
No HT[a]	1161 (1145-1178)	32.9 (30.5-35.3)	8.4 (2.9-14.0)	4.5 (-1.3-10.3)	7.1 (1.0-13.2)
HT[a]	1141 (1129-1154)	34.3 (32.5-36.1)	12.4 (8.1-16.6)	17.6 (13.2-22.0)	17.4 (12.7-22.0)

[a] hypertension

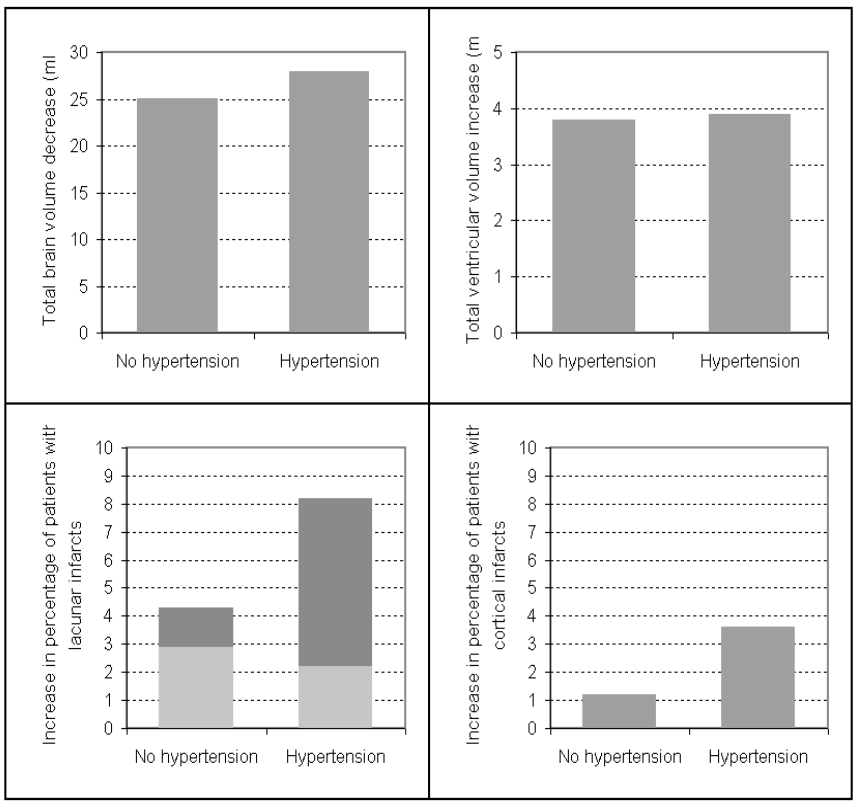


Figure 1 Change in cerebral volume measures and change in percentage of patients with lacunar and cortical infarcts. For lacunar infarcts: light grey represents 1 infarct, dark grey represents ≥2 infarcts.

BP and change in brain tissue volume measures

In this cohort of patients with vascular diseases, there was no association between baseline BP and mean annual change in brain tissue volume (MAP β -0.07; 95% CI -0.48-0.33, hypertension β -0.47; 95% CI -1.33-0.38) or ventricular volume (MAP β -0.04; 95% CI -0.13-0.05, hypertension β 0.00; 95% CI -0.20-0.20)(*Table 4*). The relation between annual change in cerebral volume measurements and BP was not modified by sex (interaction term p>0.21 for ventricular volume and p>0.18 for brain tissue volume) or age (interaction term p>0.31 for ventricular volume and p>0.48 for brain tissue volume). After exclusion of patients with non-lacunar infarcts, results were essentially the same. There was also no association between change in BP during follow-up and annual brain tissue volume decrease or ventricular volume increase (data not shown). After full adjustment, there were slight differences in annual brain tissue volume decrease between patients who were hypertensive both at baseline and follow-up and patients who were normotensive at both measurements (6.58 ml vs 6.04 ml, p=0.56).

Table 4 Association between BP and annual brain atrophy progression.

		Absolute change in brain tissue volume	Absolute change in ventricular volume
		β coefficient (95% CI)	β coefficient (95% CI)
SBP[a] (per SD)	I	-0.64 (-1.05--0.23)	0.16 (0.05-0.26)
	II	-0.28 (-0.68-0.13)	0.03 (-0.07-0.13)
	III	-0.18 (-0.59-0.24)	0.01 (-0.09-0.10)
DBP[b] (per SD)	I	-0.05 (-0.47-0.37)	-0.07 (-0.18-0.04)
	II	-0.07 (-0.47-0.32)	-0.06 (-0.16-0.03)
	III	0.03 (-0.37-0.43)	-0.08 (-0.17-0.02)
MAP[c] (per SD)	I	-0.36 (-0.78-0.05)	0.04 (-0.06-0.15)
	II	-0.18 (-0.57-0.22)	-0.02 (-0.12-0.08)
	III	-0.07 (-0.48-0.33)	-0.04 (-0.13-0.05)
Hypertension	I	-1.23 (-2.08--0.38)	0.17 (-0.05-0.39)
	II	-0.84 (-1.66--0.02)	0.03 (-0.17-0.23)
	III	-0.47 (-1.33-0.38)	0.00 (-0.20-0.20)

[a] systolic blood pressure; [b] diastolic blood pressure; [c] mean arterial pressure
Model I is unadjusted; model II is adjusted for age and sex; model III is adjusted for age, sex, diabetes mellitus, white matter lesion volume, blood pressure-lowering medication and baseline brain tissue volume / ventricular volume.

Contrary to atrophy progression, BP did show a clear association with the occurrence of incident lacunar infarcts. In total, 44 (13.3%) patients had incident lacunar infarcts during follow-up. The odds ratio for incident lacunar infarcts was 1.48 (95% CI 1.04-2.10) per SD increase in MAP and 2.74 (95% CI 1.13-6.65) for the presence of hypertension.

Discussion

Brain tissue volume declined during follow-up in the majority of patients. Ventricular volume showed an overall increase during follow-up but a large proportion of patients also had stable ventricular volumes. Mean annual brain tissue volume decrease was 6.5 ± 3.8 ml and mean ventricular volume increase was 1.0 ± 1.0 ml. BP did not influence the rate of brain tissue volume decline nor the rate of ventricular volume increase. A clear association between increase in BP and incident lacunar infarcts was present.

Previous cross-sectional imaging studies revealed age-associated global loss of brain tissue volume but yielded differential age effects.[22-24] Longitudinal studies were performed mostly in healthy elderly or in patients with dementia or cognitive impairment. In a study among healthy elderly with a mean age of 70 years, the annual rate of brain tissue volume loss was 5.4 ml, and ventricles increased by 1.4 ml per year.[1] Rates of brain tissue volume decrease were 0.32%, 0.40% and 0.48% per year in studies among healthy elderly with a mean age of 52, 60 and 66 years of age, respectively.[25-27] Brain tissue volume decreased at an annual rate of 0.55% in healthy elderly, 0.65% in cognitive impaired elderly and 1.01% in patients with Alzheimer's disease in a study population with a mean age of 78 years.[28] Ventricular volume increase was 2.2%, 3.1% and 5.4% per year for the aforementioned 3 patient categories.[28] In cognitively impaired patients brain tissue volume decreased at a rate of 0.64% per year with an increase in ventricular volume of 4.54% per year,[14] and in patients with mild Alzheimer's disease brain tissue volume loss reached 0.98% per year.[29] Progression of cerebral atrophy in patients with vascular disease may be associated with advanced physiological aging (*Figure 2*).

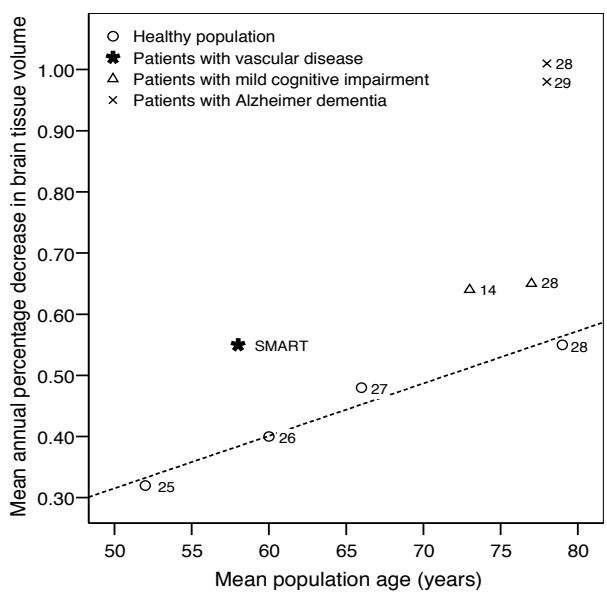


Figure 2 Mean annual percentage decrease in brain tissue volume in patients with vascular disease compared to populations from previous studies. Estimate for patients with vascular disease derived from this study, other estimates from previous studies.

We found higher atrophy rates among patients above 60 years, and in patients with cerebrovascular diseases or DM2 compared to patients without these conditions. Several studies have reported an association between DM2 and brain atrophy, and HbA1c has been linked to greater brain atrophy rates.[26, 30] Also prior stroke has been associated to measures of cerebral atrophy[4] and patients with transient ischemic attacks had increased atrophy rates over the subsequent year compared to healthy controls.[31]

A relation between BP and brain atrophy has been reported in cross-sectional studies among elderly people and among hypertensive patients.[8, 9, 32] In elderly subjects, baseline BP was associated with cerebral volume after follow-up.[12, 33] In longitudinal studies a relation has been shown between BP and rates of cerebral volume decrease over time in healthy adults,[6] hypertensive patients[11] and in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).[34] However, study populations were relatively small and recent advancements have been made in longitudinal structural brain MRI studies. None of these studies evaluated the relationship between BP and cerebral atrophy rate in patients with manifest vascular disease. High BP is thought to contribute to brain atrophy by reducing cerebral blood flow and by compromising the integrity of the blood-brain barrier.[4] These changes can disrupt nutrient delivery to the brain and promote cell death.[35] In addition, high BP may contribute to cerebral ischemia that may restrict regional cerebral blood flow.

Conflicting results on the association of conventional vascular risk factors (among which BP) with cerebral atrophy rates have been reported.[6, 26] We could not identify any association between BP and brain tissue volume change among patients with established vascular disease. A possible explanation for this finding may be that BP does not further discriminate within a population already at high vascular risk. Differences in study results may also be due to different methods of brain tissue volume assessment used. The clear association we found between BP and incident lacunar infarcts made the possibility unlikely that no associations with atrophy rate were found due to possible invalidity of BP measurements.

Strengths of this study include the large sample size of patients with manifest vascular disease, the large range of BP values, the prospective design with a long period of follow-up and the quantitative assessment of brain tissue volumes. Limitations in this study include the fact that atrophy measurements are limited to the whole brain so associations with regional atrophy remain unexplored. Also some misclassification of hypertension might have occurred as BP was measured at a single occasion, although BP was the mean of several measurements.

In conclusion, in patients with manifest vascular disease, total brain tissue volume decreased and ventricular volume increased at a rate comparable to the rate described in older patients without vascular disease. BP was not associated with brain tissue volume change, whereas a clear association with incident lacunar infarcts actually was present.

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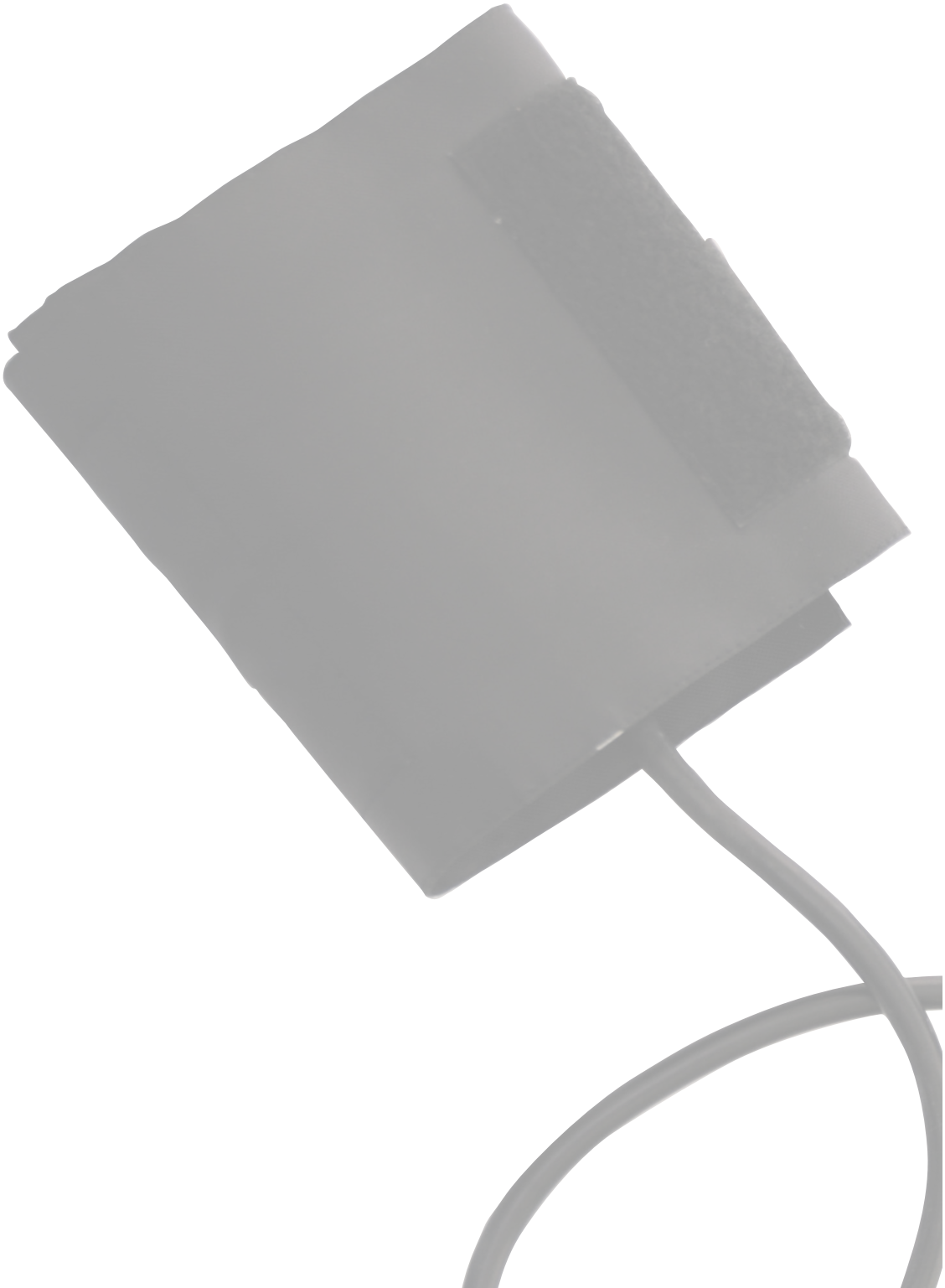
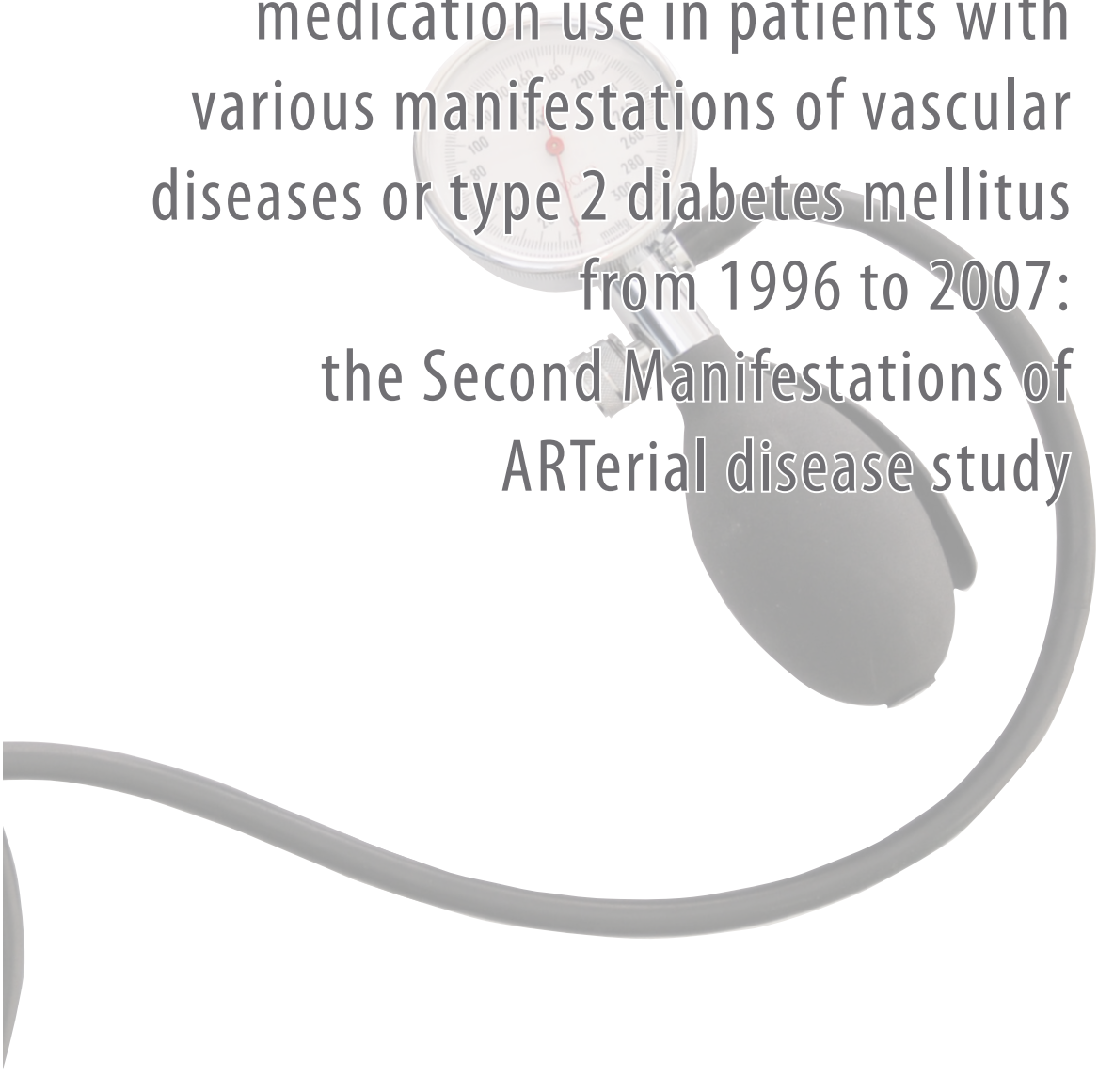


Chapter 5

Trends in vascular risk factors and medication use in patients with various manifestations of vascular diseases or type 2 diabetes mellitus from 1996 to 2007: the Second Manifestations of ARTerial disease study



Abstract

Background

Patients with established vascular disease or type 2 diabetes mellitus (DM2) are identified as the top priority for prevention because of their high risk of cardiovascular events. We investigated time trends in vascular risk factors and medication use for patients referred to a vascular specialist with manifest vascular disease or DM2.

Methods

Change in risk factor profile and medication use at referral over a 12-year period was evaluated and comparisons were made between patients with coronary heart disease, cerebrovascular disease, peripheral arterial occlusive disease, abdominal aortic aneurysm and DM2 who participated in the Second Manifestations of ARTerial disease study in the period of 1996 to 2007.

Results

A total of 4731 patients was included. Mean age was 59 ± 11 years and 75% was male. From 1996 to 2007, the prevalence of obesity (BMI ≥30 kg/m^2) increased from 14% to 24% and no change in smoking behaviour was observed. The prevalence of elevated lipid levels (total cholesterol ≥4.5 mmol/l or LDL-cholesterol ≥2.5 mmol/l) at referral declined from 92% in 1996-1997 to 45% in 2006-2007. The proportion of patients with blood pressure (BP) above 140/90 mmHg decreased from 66% to 51%. The largest decrease in both lipid and BP levels was seen in patients with cerebrovascular disease. The use of lipid-lowering, BP-lowering and antithrombotic medication at referral increased over a 12-year period.

Conclusions

An improvement in risk factor profile and medical treatment was seen in patients referred with manifest vascular disease or DM2 over a 12-year period. Nevertheless, the prevalence of modifiable risk factors is still high leaving patients at elevated risk for new vascular events.

Introduction

Vascular diseases are a leading cause of hospitalizations, death and loss of disability-adjusted life years.[1] The major risk factors for atherosclerotic vascular disease are well-established and include hypertension, dyslipidemia, hyperglycemia, abdominal obesity, smoking and physical inactivity.[2] Patients with previous clinical manifestations of vascular disease are at considerably increased risk of developing future vascular events due to the systemic nature of atherosclerosis.[3] Also type 2 diabetes mellitus (DM2) is considered a high-risk condition for development of vascular diseases and vascular mortality.[4, 5] The changes in mortality risk from coronary heart disease that have been reported for different countries were directly related to changes in major cardiovascular risk factors, as shown in the 40-year trend analyses in the Seven Countries Study.[6] Many clinical trials convincingly showed the efficacy of therapies aimed at lowering risk factors, but the implementation and application of guidelines in clinical practice is complicated and often delayed.[7-9]

The EUROASPIRE survey, which was undertaken in patients with coronary heart disease in 15 European countries, showed increases in the prevalence of hyperlipidemia, obesity and hypertension over the period 1995-2000,[7-9] and no change in smoking prevalence was observed.[10] However, the EUROASPIRE surveys were only done in patients with coronary heart disease, and a limited number of patients per country was investigated whereas the distribution of risk factors and change in risk factor profile over time can be quite different across different regions.[11] Apart from cardiovascular risk factors, medication use as well as adherence to the recommendations on pharmacological treatment that have been included in international guidelines changes over time.

Direct comparisons of time trends in the prevalence of vascular risk factors and medication use among high-risk patients with different manifestations of vascular diseases or DM2 are not available. Such data may provide tools for general practitioners, clinicians and decision makers and patients to further improve vascular risk management. The aim of this study was to investigate time trends in vascular risk factors and risk factor treatment at referral, in a large cohort of patients referred with various clinical manifestations of vascular disease (coronary heart disease, peripheral arterial occlusive disease (PAOD), cerebrovascular disease and abdominal aortic aneurysm (AAA)) or DM2 in the period from 1996 to 2007.

Methods

Study design and population

The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective cohort study in the University Medical Center Utrecht. Since 1996, patients aged 18-80 years with clinically manifest atherosclerotic vascular disease (cerebrovascular disease, coronary heart disease, PAOD or AAA) or risk factors for atherosclerosis (hyperlipidemia, DM2 or hypertension) are being included. Patients are referred by general practitioners or by medical specialists from other hospitals in the region. Not included are patients with terminal malignant disease, those not independent in daily activities or insufficiently familiar with the Dutch language. All patients are assessed for vascular risk factors and the

extent of atherosclerosis by non-invasive tests. The SMART study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent. The rationale and design of the SMART study have been described in detail elsewhere.[12]
Recruitment in the SMART study is ongoing, and 4731 patients with a referral diagnosis of DM2, coronary heart disease, cerebrovascular disease, PAOD or AAA have been included in the SMART study until January 2008. Cerebrovascular disease included transient ischemic attack, non-disabling ischemic stroke, amaurosis fugax or retinal infarction; coronary heart disease included myocardial infarction and admission for percutaneous coronary intervention or coronary artery bypass grafting; PAOD included claudication of the legs confirmed by a resting ankle-brachial pressure index <0.9 in at least 1 leg, percutaneous transluminal angioplasty or leg amputation; AAA included AAA ≥3.0 cm or aneurysm surgery.

Vascular screening

Participating patients underwent a diagnostic screening-protocol conducted on a single day in the University Medical Center Utrecht. This screening protocol is done in the first weeks after referral. Participants completed questionnaires on cardiovascular history, risk factors and medication use. Physical examination consisted of measurements of height, weight, waist and hip circumferences and blood pressure (BP). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. BP was measured by sphygmomanometry at the right and left upper arm and repeated on the side with the highest values. The mean of all obtained measurements (≥3) was used in the analyses. Fasting blood was sampled to ascertain levels of glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine and homocysteine. Low-density lipoprotein (LDL) cholesterol levels were calculated with Friedewald's formula. Albumin and creatinine concentrations were measured in a morning urine portion. All assessments were performed at a single laboratory. Techniques of the examinations have been published formerly.[12]

Definitions

According to current guidelines, cut-off points were defined for BP, fasting glucose and cholesterol. Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg or self-reported use of BP-lowering medication. Target levels for BP were defined as BP <140/90 mmHg.[13, 14] In patients with a referral diagnosis other than DM2, concomitant DM2 was defined as self-reported DM2, use of glucose-lowering agents or fasting glucose ≥7.0 mmol/l at screening. Treatment target for diabetic patients was fasting glucose ≤6.0 mmol/l.[5, 15] Hyperlipidemia was defined as total cholesterol ≥4.5 mmol/l, LDL-cholesterol ≥2.5 mmol/l or use of lipid-lowering medication, and target levels in patients with established cardiovascular disease or DM have been defined as cholesterol levels below these values.[5, 15]

Statistical analysis

The inclusion years from 1996 to 2007 were divided into 2-year periods and patients were grouped according to the year of inclusion in the SMART study. Vascular risk factors were presented according to vascular disease or DM2 as well as by time period of inclusion. Results are expressed as means with standard deviations (SDs) for continuous variables and as percentages for categorical variables. The prevalence of missing values was overall low (<1.5%), except for waist circumference which was only measured in 80.2% of patients. Complete case analyses were performed for all variables. The proportions of patients with elevated BP, elevated lipid levels and elevated glucose levels were calculated as well as the proportions of patients receiving treatment for these conditions.
The amount of change in risk factors and medication use over time was calculated according to referral diagnosis. For all inclusion periods, age- and sex-adjusted mean values of different risk factors were calculated with the use of a general linear model. Multivariable linear and logistic regression analyses were performed to estimate age- and sex-adjusted trends in risk factors and medication use over time. Age- and sex-adjusted mean values were calculated according to 2-year periods of inclusion, whereas in the linear and logistic regression analyses, annual changes in risk factors and medication use are presented. Results are presented as β coefficients with 95% confidence intervals (95% CI) for annual change in risk factors or as odds ratios (OR) with 95% CI for annual change in medication use.

Results

Baseline characteristics

The study population consisted of 4731 patients, of whom 45% (n=2128) with coronary heart disease (79% percutaneous coronary intervention, 14% coronary artery bypass grafting, 7% other), 20% (n=924) with cerebrovascular disease, 18% (n=842) with PAOD, 6% (n=282) with AAA and 12% (n=555) with DM2. Mean age of the population was 59.1 ± 11.3 years and 75% was male. Baseline characteristics of the study population according to referral diagnosis are described in *Table 1*. Patients with PAOD and AAA showed high prevalences of vascular diseases at other sites of the vasculature. Patients with DM2 were younger (49.6 ± 14.5 years) and had a lower prevalence of smoking (ever smoking 62%). Mean BMI was above 25 kg/m^2 in all groups.
Elevated BP was most prevalent in patients with cerebrovascular disease (61%) and hyperlipidemia was most frequent among AAA patients (88%) (*Table 2*). A considerable proportion of patients with elevated lipid levels did not receive any treatment (57%). Of patients with elevated BP levels, 48% was untreated. Of patients receiving BP-lowering medication, 35% had BP levels below the 140/90 mmHg target. Of patients taking lipid-lowering drugs, 35% reached total cholesterol <4.5 mmol/l and LDL-cholesterol <2.5 mmol/l.

Table 1 Baseline characteristics of the SMART study population (n=4731) by referral diagnosis at the time of referral by the general practitioner or other vascular specialist.

	CHD[a] n=2128	CVD[b] n=924	PAOD[c] n=842	AAA[d] n=282	DM2[e] n=555
Age (years)	59.6 ± 9.5	60.9 ± 10.8	59.2 ± 10.7	67.5 ± 7.3	49.6 ± 14.5
Male sex (%)	82	71	65	94	60
Concomitant disease					
Coronary heart disease (%)	100	15	21	37	11
Cerebrovascular disease (%)	3	100	8	7	4
Peripheral arterial disease (%)	3	6	100	6	2
Abdominal aortic aneurysm (%)	2	3	5	100	2
DM2[f] (%)	22	20	26	15	100
Modifiable risk factors					
Body mass index (kg/m^2)	27.3 ± 3.6	26.3 ± 3.8	26.0 ± 4.1	26.1 ± 3.4	28.8 ± 6.2
Waist circumference (cm)	96.6 ± 10.9	94.2 ± 11.8	94.2 ± 11.7	97.9 ± 11.3	97.7 ± 16.3
Systolic BP (mmHg)	138 ± 20	146 ± 22	146 ± 22	145 ± 19	138 ± 19
Diastolic BP (mmHg)	80 ± 11	83 ± 11	81 ± 11	85 ± 11	82 ± 11
Ever smoking (%)	77.0	82.1	90.9	89.7	61.6
Total cholesterol (mmol/l)	4.7 ± 1.1	5.2 ± 1.1	5.6 ± 1.2	5.4 ± 1.0	5.1 ± 1.2
LDL-cholesterol (mmol/l)	2.7 ± 0.9	3.1 ± 1.1	3.5 ± 1.1	3.5 ± 0.9	3.0 ± 0.9
HDL-cholesterol (mmol/l)	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.4
Fasting triglycerides (mmol/l)	1.7 ± 1.6	1.7 ± 1.4	2.0 ± 1.4	1.9 ± 1.1	2.0 ± 1.6
Fasting glucose (mmol/l)	6.3 ± 1.8	6.2 ± 1.8	6.4 ± 2.0	6.0 ± 1.1	10.0 ± 4.0
Medication use					
Glucose-lowering agents (%)	13	13	15	4	93
Lipid-lowering agents (%)	60	44	35	33	29
Blood pressure-lowering agents (%)	41	48	38	43	42
Antithrombotic medication (%)	79	75	44	37	15

Continuous variables are expressed as means with standard deviations.
[a] coronary heart disease; [b] cerebrovascular disease; [c] peripheral arterial occlusive disease; [d] abdominal aortic aneurysm; [e] type 2 diabetes mellitus; [f] self-reported type 2 diabetes mellitus, glucose-lowering medication use or fasting glucose ≥7.0 mmol/l at screening

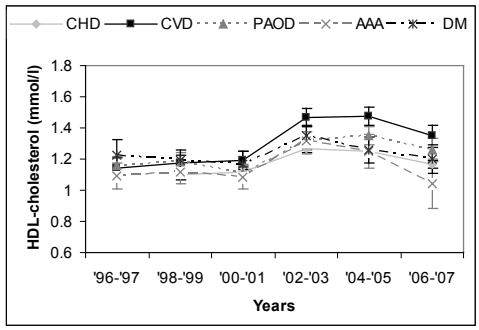
Table 2 Percentages of patients with abnormal levels of glucose, blood pressure and lipids and their treatment status in the SMART study population (n=4731) by referral diagnosis at the time of referral by the general practitioner or other vascular specialist.

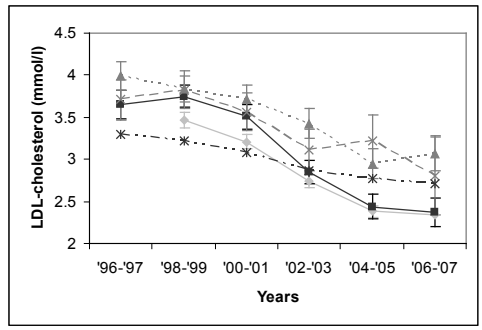
	All	CHD[a]	CVD[b]	PAOD[c]	AAA[d]	DM2[e]
	n=4731	n=2128	n=924	n=842	n=282	n=555
Blood pressure						
BP ≥ 140/90 mmHg	52 (2443)	45 (957)	61 (566)	58 (491)	60 (169)	47 (260)
Untreated	48 (1157)	46 (436)	46 (259)	55 (266)	50 (84)	44 (112)
Treated and uncontrolled	52 (1269)	54 (518)	54 (304)	45 (217)	50 (85)	56 (145)
Cholesterol						
Total cholesterol ≥ 4.5 mmol/l	66 (3099)	53 (1127)	71 (658)	83 (698)	83 (233)	69 (166)
LDL-cholesterol ≥ 2.5 mmol/l	62 (2939)	51 (1094)	68 (627)	77 (648)	80 (225)	62 (345)
Triglycerides ≥ 1.7 mmol/l	40 (1870)	37 (773)	36 (331)	48 (397)	43 (120)	45 (249)
Low HDL-cholesterol[f]	36 (1798)	39 (807)	33 (297)	43 (359)	39 (110)	41 (225)
Hyperlipidemia[g]	71 (3339)	60 (1270)	75 (692)	85 (717)	88 (248)	74 (412)
Untreated	57 (1892)	42 (528)	60 (407)	69 (484)	70 (171)	75 (302)
Treated and uncontrolled	43 (1405)	58 (734)	41 (277)	31 (217)	31 (75)	25 (102)
Glucose						
Glucose 6.0-6.9 mmol/l	22 (1020)	23 (498)	22 (204)	22 (186)	27 (76)	10 (56)
Glucose ≥ 7.0 mmol/l	24 (1146)	17 (369)	15 (135)	20 (167)	14 (39)	79 (436)
Untreated	31 (345)	44 (160)	41 (55)	46 (73)	77 (30)	6 (27)
Treated and uncontrolled	70 (788)	57 (208)	59 (80)	54 (87)	23 (9)	94 (404)

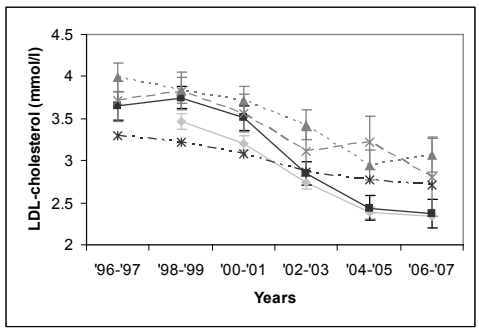
[a] coronary heart disease; [b] cerebrovascular disease; [c] peripheral arterial occlusive disease; [d] abdominal aortic aneurysm; [e] type 2 diabetes mellitus; [f] HDL-cholesterol ≤1.0 mmol/l (men) or ≤ 1.3 mmol/l (women); [g] total cholesterol ≥4.5 mmol/l or LDL-cholesterol ≥2.5 mmol/l

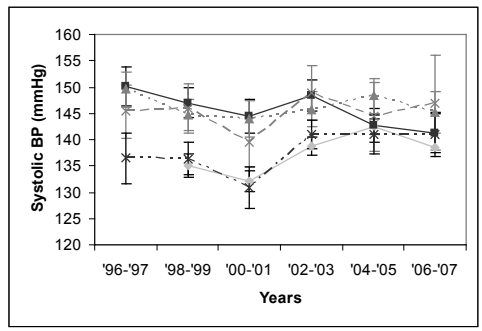
Trends in risk factors

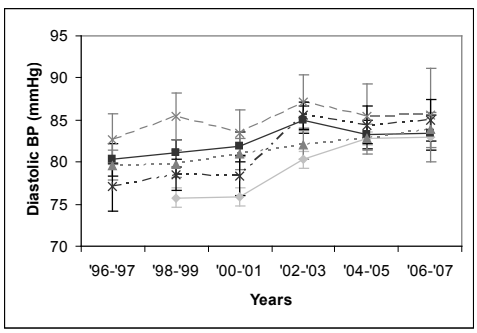
Trends for modifiable risk factor prevalences over time are shown in *Figure 1* and in *Figure 2* for medication use. Mean age of patients referred with vascular diseases or DM2 hardly changed during the period from 1996 to 2007 and was between 57 and 61 years at all time periods. From 1996 until 2007 improvements in LDL-cholesterol, HDL-cholesterol and triglyceride levels were seen in all diagnosis groups, with the largest decrease in LDL-cholesterol (β -0.17; 95% CI -0.19 to -0.15 mmol/l/year) and increase in HDL-cholesterol (β 0.04; 95% CI 0.03 to 0.04 mmol/l/year) observed in patients with cerebrovascular disease, and the largest decrease in triglycerides seen in patients with coronary heart disease (β -0.08; 95% CI -0.10 to -0.05 mmol/l/year) (*Table 3*). Average LDL-cholesterol concentration declined from 3.7 mmol/l to 2.4 mmol/l. Also HDL-cholesterol and triglycerides improved in all groups except for diabetic and AAA patients. Mean level of triglycerides declined from 2.0 mmol/l to 1.5 mmol/l and mean HDL-cholesterol increased from 1.16 mmol/l to 1.21 mmol/l. BMI increased for all diagnosis groups but the largest increase was observed in DM2 (β 0.19; 95% CI 0.02 to 0.36 kg/m2/year). Obesity (BMI ≥30 kg/m^2) prevalence increased from 14% in 1996-1997 to 24% in 2006-2007. Systolic BP showed a downward

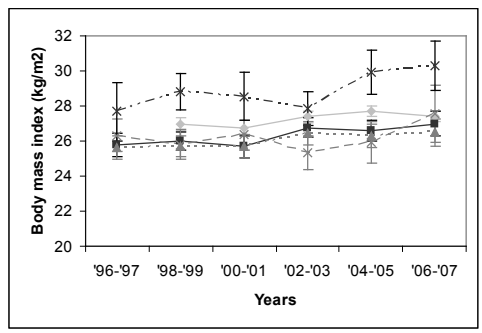












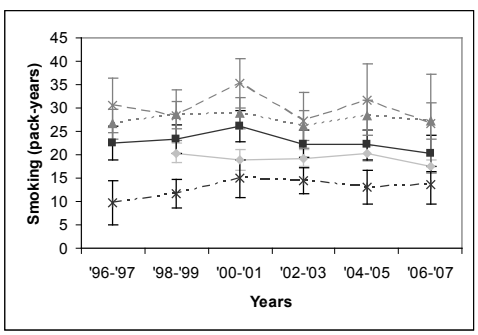


Figure 1 Trends in age-and sex-adjusted mean risk factor levels over time from 1996-2007.

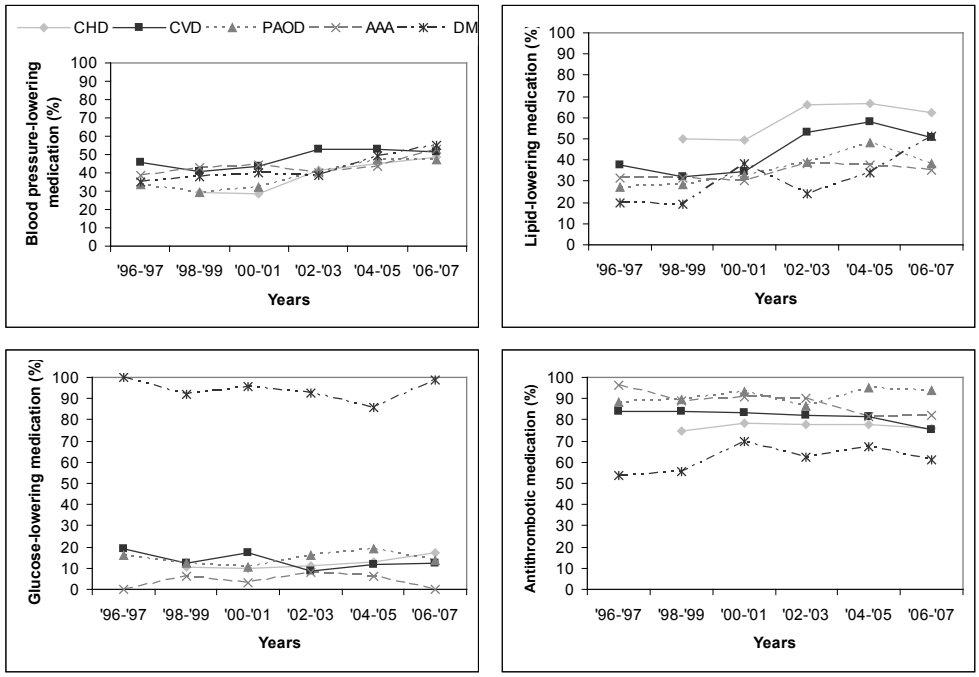


Figure 2 Trends in medication use over time from 1996-2007.

trend in patients with cerebrovascular disease (β -0.75; 95% CI -0.17 to -0.32 mmHg/year), remained stable in PAOD patients and increased in the other diagnosis groups, especially in DM2 patients (β 0.75; 95% CI 0.25 to 1.24 mmHg/year). Mean systolic pressure was 148 mmHg in 1996-1997 and 141 mmHg in 2006-2007. Smoking habits remained fairly constant over time, and none of the groups showed a change in pack-years over time. The proportion of smokers was highest in PAOD patients throughout the observation period. When analyses were repeated after exclusion of patients referred with amaurosis fugax or retinal infarction (n=136), results were essentially the same.

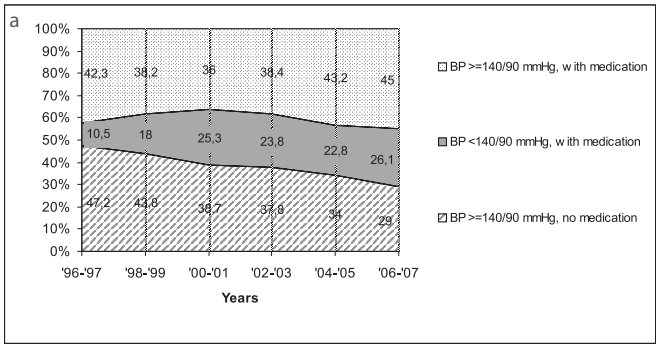
Trends in medication use

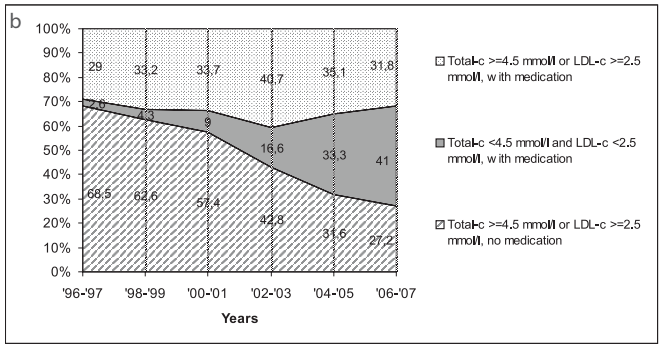
The use of BP-lowering and lipid-lowering medication increased over time in all diagnosis groups except for AAA patients. Only patients with coronary heart disease demonstrated an increase in use of glucose-lowering medication, whereas the use of antithrombotic medication increased in patients with coronary heart disease, PAOD and DM2 (*Table 3*).
The prevalence of BP ≥140/90mmHg declined from 66% to 51% while the overall prevalence of hypertension (BP ≥140/90 mmHg or use of BP-lowering medication) did not change considerably over time. The proportion of hypertensive patients with adequately controlled BP increased from 11% in 1996-1997 to 26% in 2006-2007 (*Figure 3*). In 2006-2007, 29% of hypertensive patients did not receive any BP-lowering treatment, compared with 47% in 1996-1997.

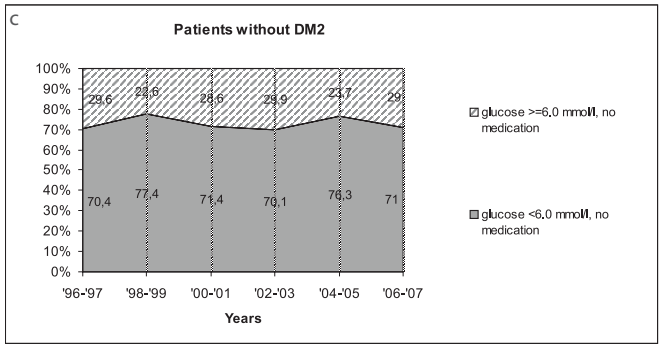
Table 3 Age- and sex-adjusted annual change in risk factors and medication use from 1996 until 2007, according to referral diagnosis.

	CHD[a]	CVD[b]	PAOD[c]	AAA[d]	DM[e]
Modifiable risk factors ß (95% CI)					
Systolic BP (mmHg)	0.71 (0.42-1.00)	-0.75 (-0.17--0.32)	-0.12 (-0.54-0.30)	0.23 (-0.54-0.99)	0.75 (0.25-1.24)
Diastolic BP (mmHg)	1.03 (0.87-1.19)	0.41 (0.18-0.65)	0.45 (0.23-0.67)	0.40 (-0.07-0.86)	1.00 (0.71-1.30)
Glucose (mmol/l)	-0.01 (-0.03-0.02)	-0.02 (-0.05-0.02)	-0.04 (-0.08-0.01)	0.03 (-0.02-0.07)	-0.03 (-0.14-0.08)
Total cholesterol (mmol/l)	-0.17 (-0.18--0.15)	-0.17 (-0.19--0.15)	-0.11 (-0.14--0.09)	-0.10 (-0.14--0.06)	-0.07 (-0.10--0.04)
LDL-cholesterol (mmol/l)	-0.15 (-0.16--0.14)	-0.17 (-0.19--0.15)	-0.11 (-0.13--0.09)	-0.10 (-0.13--0.06)	-0.07 (-0.10--0.05)
HDL-cholesterol (mmol/l)	0.01 (0.00-0.01)	0.04 (0.03-0.04)	0.02 (0.01-0.03)	0.02 (0.00-0.03)	0.01 (-0.00-0.02)
Triglycerides (mmol/l)	-0.08 (-0.10--0.05)	-0.07 (-0.10--0.04)	-0.05 (-0.08--0.02)	-0.04 (-0.09-0.00)	-0.00 (-0.05-0.04)
BMI (kg/m^2)	0.08 (0.03-0.14)	0.13 (0.05-0.21)	0.12 (0.03-0.20)	0.02 (-0.12-0.16)	0.19 (0.02-0.36)
Smoking (pack-years)	-0.28 (-0.57-0.01)	-0.29 (-0.73-0.14)	-0.05 (-0.98-0.79)	-0.10 (-0.20-0.77)	0.28 (-0.20-0.77)
Medication use OR (95% CI)					
BP-lowering medication use	1.11 (1.08-1.15)	1.05 (1.01-1.10)	1.09 (1.04-1.14)	1.03 (0.95-1.12)	1.10 (1.04-1.17)
Lipid-lowering medication use	1.10 (1.07-1.13)	1.11 (1.07-1.16)	1.09 (1.04-1.14)	1.02 (0.94-1.11)	1.15 (1.08-1.23)
Glucose-lowering medication use	1.07 (1.03-1.13)	0.96 (0.90-1.02)	1.03 (0.97-1.09)	1.07 (0.88-1.31)	0.95 (0.84-1.06)
Antithrombotic medication use	1.17 (1.13-1.22)	0.99 (0.95-1.04)	1.13 (1.08-1.18)	1.07 (0.99-1.17)	1.11 (1.02-1.21)

[a]coronary heart disease; [b]cerebrovascular disease; [c]peripheral arterial occlusive disease; [d]abdominal aortic aneurysm; [e]diabetes mellitus







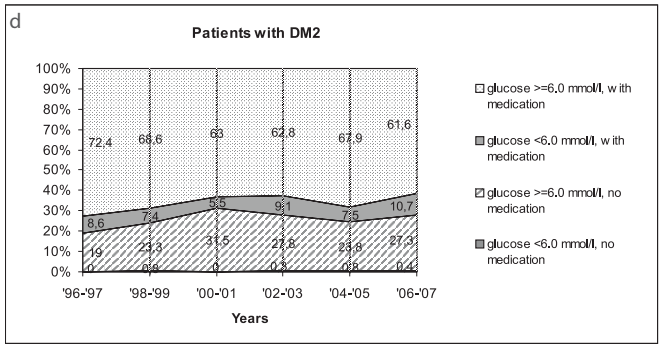


Figure 3 Trends in percentages of elevated BP and control (a), elevated lipids and control (b) and elevated glucose and control (c, d) from 1996 to 2007.

The proportion of patients with elevated lipid levels (total cholesterol ≥4.5 mmol/l or LDL-cholesterol ≥2.5 mmol/l) declined from 92% to 45%. Prevalence of hyperlipidemia (elevated lipid levels or lipid-lowering treatment) decreased from 95% to 78%. In 1996-1997 only 3% of patients with hyperlipidemia reached treament goals and this number increased to 41% in 2006-2007.

Discussion

In patients presenting with atherosclerotic vascular diseases or DM2 in the period 1996-2007 the highest prevalence of risk factors not at target was found in patients with PAOD or AAA. In the 12-year observation period improvements were shown in lipid levels, whereas improvements in BP were smaller. The use of BP-lowering, lipid-lowering and antithrombotic medication increased during the past decade. Despite improvements in risk factor management over time, still a considerable proportion of patients was not at target levels while receiving medication. These findings reflect clinical practice at the time patients were referred for further evaluation and treatment. In many patients, vascular risk factors were already treated before referral by a general practitioner or vascular specialist from an other hospital.

Several guidelines for high-risk cardiovascular patients have been published over the time period covered by this study. In 1994 and 1998, recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension identified patients with clinically manifest coronary heart disease, or other major atherosclerotic disease, as the top priority for prevention. According to these guidelines, total cholesterol should stay consistently below 4.5 mmol/l in this population.[16, 17] Treatment goals for HDL-cholesterol and triglycerides were not defined, although decreased HDL-cholesterol and elevated triglycerides are known markers of increased cardiovascular risk.[18, 19] In EUROASPIRE II, 89% of coronary heart disease patients had hyperlipidemia defined as total cholesterol ≥5.0 mmol/l or use of lipid-lowering medication. Of these patients, 68% received medication, and 51% of those using medication reached total cholesterol levels <5.0 mmol/l.[7] Prevalence of hyperlipidemia was comparable with our study, where hyperlipidemia (total cholesterol ≥4.5 mmol/l, LDL-cholesterol ≥2.5 mmol/l or use of lipid-lowering medication) was present in 88% of patients. However, less patients with hyperlipidemia received treatment (53%), and of those using medication 36% reached total cholesterol <4.5 mmol/l and LDL-cholesterol <2.5 mmol/l. These numbers differed considerably between the first and the last years of the observation period, suggesting a clear improvement in cholesterol management. After the year 2000, guidelines have been modified and target levels for patients with atherosclerotic vascular disease have been emphasized to total cholesterol <4.5 mmol/l and LDL-cholesterol <2.5 mmol/l.[5, 15] The implementation of these more stringent target levels may have led to the decrease in cholesterol and increase in lipid-lowering treatment observed from 1996 to 2007.

The percentage of patients diagnosed with elevated BP in our study was comparable with that in the EUROASPIRE II survey (52% vs 51%), while the percentage of patients with elevated BP among those taking BP-lowering medication was much higher in our study

(65%) than the 51% reported in EUROASPIRE II.[9] This difference might be due to the fact that only patients with coronary heart disease were included in the EUROASPIRE survey. Compared with EUROASPIRE I, the prevalence of elevated BP in the second EUROASPIRE survey remained at a high level and the proportion of patients treated and controlled had not changed between 1995-1996 and 1999-2000.[20] In a Croatian survey of patients with coronary heart disease, elevated BP was present in 66% of the population.[21] In Polish patients with ischemic heart disease, as many as 69% of hypertensive patients did not reach target levels while receiving BP-lowering medication.[22] The WHO MONICA project did show a decrease in the prevalence of hypertension between the early 1980s and the mid-1990s, together with an increase in use of BP-lowering medication and treatment control rate among 35-64 year old men and women from 21 different countries.[23] From all surveys it is clear that the majority of patients with established atherosclerotic disease has hypertension, and large proportions of hypertensive patients are not reaching treatment goals. Age and hypertension awareness[22] as well as presence of associated risk factors[24] have been associated with quality of BP control, but additional explanations are that treatment is started with low-dose prescriptions that are not titrated up, together with a possibly poor compliance.

All guidelines emphasize the urgency of smoking cessation in patients with cardiovascular disease. In patients with coronary heart disease, a persistent smoking rate of 21% was found despite a personal advice to stop smoking.[10] In the present study, especially in PAOD patients smoking rates were high and pack-years smoked remained almost unchanged for all diagnosis groups. Smoking cessation is a very important issue in secondary prevention and more effective smoking cessation programmes are needed.

The fast increase in obesity prevalence in this population is in line with the striking worldwide trends.[25] In 1996-1997, 14% of our study population was obese (BMI ≥30 kg/m^2), compared with 24% in 2006-2007. In the United States, 20% of the population was obese in 2003.[25] The adverse trends in obesity will also have unfavourable effects on BP, lipoprotein profile and propensity to hyperglycemia. Modification of an unhealthy lifestyle requires dietary intervention and increased physical activity.

The use of prophylactic medication was substantially higher in recent years compared with the late 1990s. Besides increases in lipid-lowering and BP-lowering medication use, there was also an increase in the use of antithrombotic medication which was especially seen after 2001. Changes in the major risk factors have been found to explain much of the decline in morbidity and mortality from cardiovascular diseases[26, 27] and these findings underline the need for an effective strategy of treatment of risk factors at the population level.

Strengths of this study include the large study population, the wide range of risk factors and treatments documented, the direct comparison of groups of patients with different vascular diseases and DM2 and the 12-year long observation period. We also acknowledge study limitations. First, some misclassification of risk factors might have occurred as all risk factors were measured on a single occasion. For this reason, also medication adherence could not be evaluated. Second, we did not have HbA1c measurements from all patients and consequently control rate of DM2 could only be based on fasting glucose levels. Waist circumference was only measured in 80% of patients. We used recent guide-

lines to define target values for BP, lipid and glucose levels. However, guidelines have been modified and target levels used were not standard care during the total study period. In this way, adaptations to guidelines might be partly responsible for trends in prevalence and control of hypertension and hyperlipidemia. Finally, in this study we used generally recommended BP targets of 140/90 mmHg for all patients,[16, 17] but BP targets have been lowered to levels below 130/80 mmHg in patients with DM2 and in patients with chronic kidney disease[5, 13, 14] because of the positive effect of vigorous BP-lowering therapy on cardiovascular outcomes and on deceleration of the progression rate to end-stage renal disease.[5, 13, 14, 28, 29]

In conclusion, trends in risk factors and use of medication reveal an improvement in risk factor management in patients referred with manifest vascular diseases or DM2 in the period 1996-2007. Nevertheless, the proportion of modifiable risk factors not at target is still high leaving many patients at elevated vascular risk.

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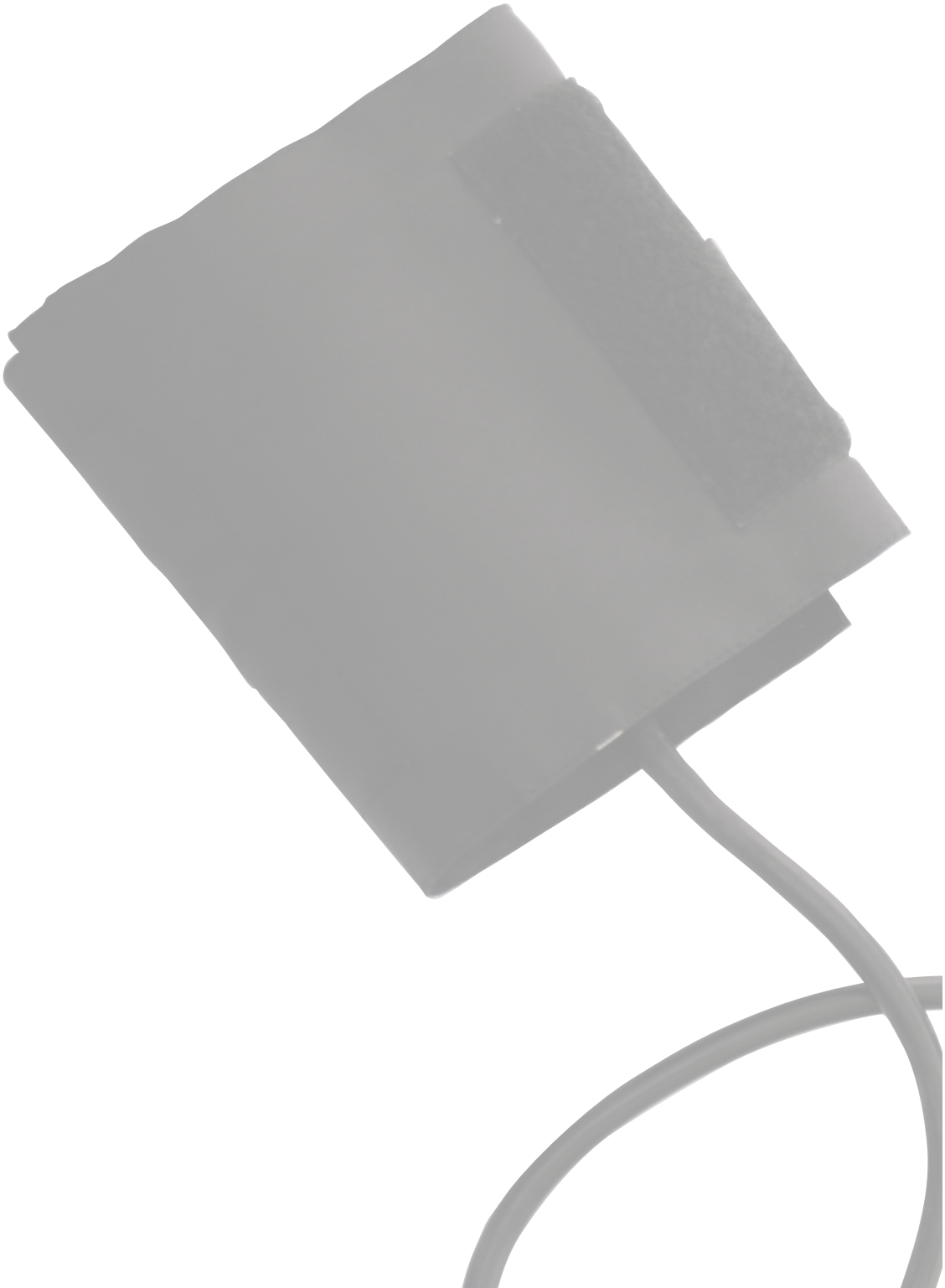
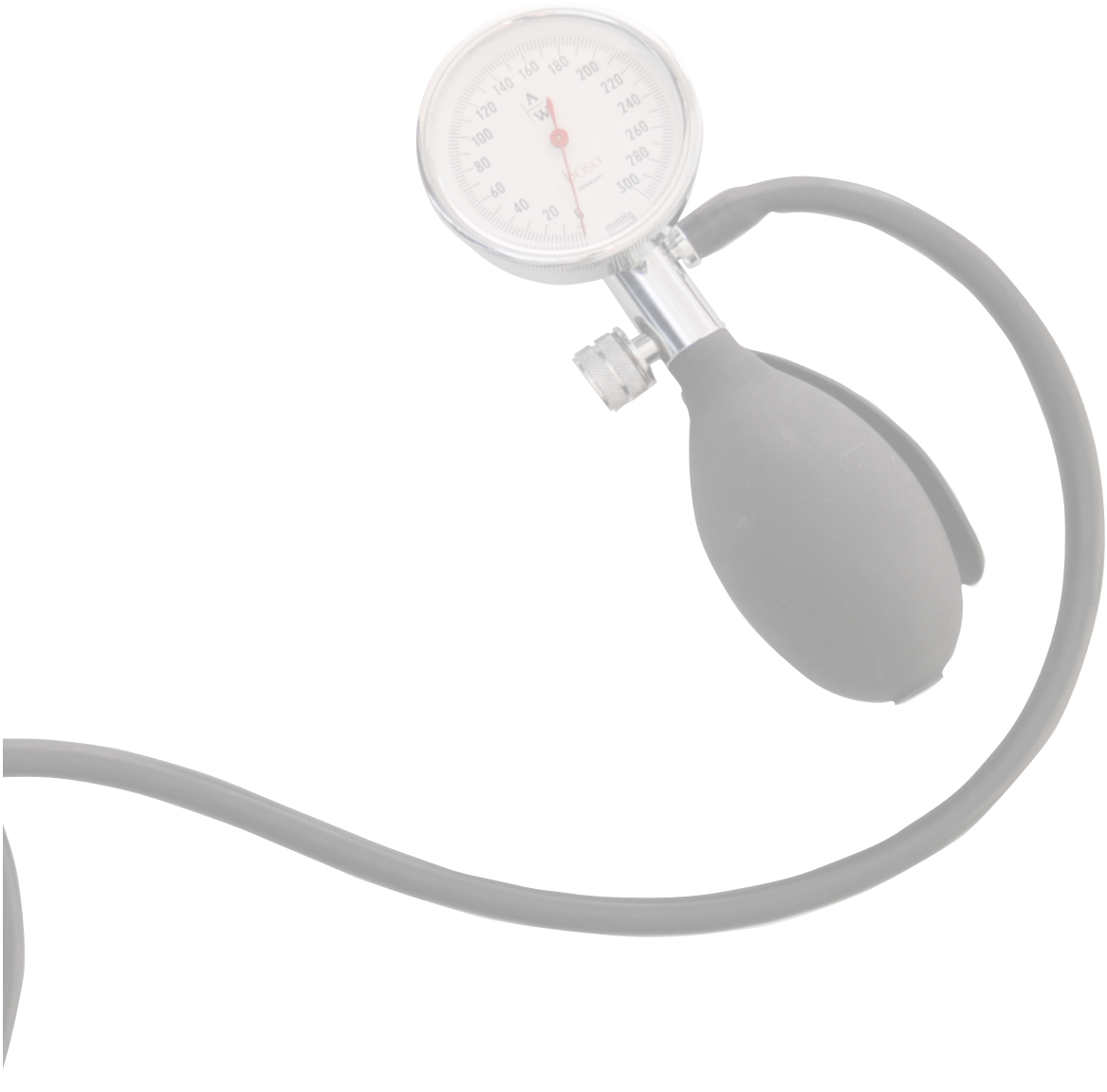


Chapter 6

General discussion



Progression of vascular risk to vascular disease in hypertension

Clinical research has established that blood pressure (BP) elevation is a common and powerful risk factor for the development of cardiovascular diseases, including coronary heart disease, stroke, peripheral arterial occlusive disease and abdominal aortic aneurysms, as well as of renal insufficiency and heart failure.[1] Besides the fact that systolic hypertension is more prevalent than diastolic hypertension, elevated systolic BP also contributes more to the burden of hypertensive disease than does elevated diastolic BP.[2] A continuous influence of BP is present even within what is regarded as the normotensive range.
Dependent on the other risk factors that are taken into account and the thresholds used for defining the risk factors, it is estimated that only 20-44% of hypertension occurs isolated, while the majority of hypertension cases occur in conjunction with one or more other vascular risk factors.[3, 4] Vascular risk factors that often tend to accompany hypertension are glucose intolerance, obesity and dyslipidemia. The clustering of these metabolic risk factors is also referred to as the metabolic syndrome and is attributed to insulin resistance and abdominal obesity. The term metabolic syndrome describes the combined presence of cardiovascular risk factors in a single patient: hypertension, abdominal obesity, dyslipidemia and hyperglycemia. Elevated BP is included as a component of the metabolic syndrome by all major definitions of the metabolic syndrome. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) guidelines used a cut-off point of 130/85 mmHg to define hypertension,[5] while the World Health Organization (WHO) used BP levels of 140/90 mmHg as the cut-off point.[6] Elevated BP in the context of metabolic syndrome is mediated through obesity-induced processes such as increased circulating plasma volume, activated renin angiotensin system and by increased sympathetic activity. A cluster of hypertension with two or more additional vascular risk factors (and thus fulfilling the metabolic syndrome criteria) occurs in about 50% of the hypertensive subjects.[3] In agreement with these numbers, it is estimated that about half of the patients with hypertension also have insulin resistance.[7, 8] In *chapter 2.1* of this thesis we showed that the prevalence of the metabolic syndrome was 49% in hypertensive patients with previous vascular disease. Both insulin resistance and abdominal obesity are associated with an increased BP and the metabolic syndrome is associated with development of hypertension in normotensive patients.[9, 10] Mechanisms for the development of hypertension in insulin resistance or hyperinsulinemia include stimulation of the sympathetic nervous system, renal sodium retention, altered transmembrane cation transport, vascular hyperreactivity and growth-promoting effects of vascular smooth muscle cells.[10-12] It is thought that leptin, free fatty acids and insulin may act individually and synergistically to stimulate sympathetic activity and vasoconstriction.[10] Hypertension has often been reported as being the most frequent of the metabolic syndrome components, with prevalences of elevated BP in patients with the metabolic syndrome being as high as 85% or even 95% of patients.[13, 14] One of the studies described in this thesis confirmed this high prevalence of elevated BP (83%) in patients with the metabolic syndrome (*chapter 2.2*).
Isolated hypertension is known to increase the risk of cardiovascular morbidity and mortality in different populations. In men with isolated hypertension (hypertension without associated risk factors like hypercholesterolemia, diabetes mellitus, smoking, obesity or

elevated heart rate), mortality rates from cardiovascular disease were twice as high compared to normotensive subjects.[15] Hypertension also emerged as the key factor leading to a significant increase in cardiovascular mortality risk in overweight subjects.[16] However, in both studies cardiovascular mortality rates increased dramatically in the presence of associated vascular risk factors in addition to hypertension.[15, 16] In the Framingham study it was shown that the risk of coronary heart disease as well as of stroke, peripheral arterial occlusive disease and heart failure in hypertensive individuals increases in proportion to the burden of associated risk factors.[17-20] One of the studies described in this thesis showed a clear effect of metabolic syndrome presence on cardiovascular morbidity and mortality in hypertensive patients with previous cardiovascular disease (*chapter 2.1*), and the same effect has been shown in patients without clinically evident cardiovascular disease.[21] Among all metabolic and hemodynamic risk factors, hypertension accounted for the greatest increase in risk of carotid plaque presence and again it applies that this risk continued to increase in the presence of more risk factors in addition to hypertension.[22]
Although isolated hypertension accounts for a clear increase in risk of cardiovascular events and mortality, it is the combination of hypertension with obesity, dyslipidemia and impaired fasting glucose that has the greatest influence on future cardiovascular risk. Determining global cardiovascular risk is more important than focusing entirely on BP elevation alone. With the use of multivariate risk assessment so as to arrive at a composite risk estimate, hypertensive patients are more appropriately targeted for therapy. The metabolic syndrome increased vascular risk in high-risk patients with hypertension and vascular disease and in patients with peripheral arterial occlusive disease (*chapter 2.1*, *chapter 2.2*). Because the metabolic syndrome is caused by underlying insulin resistance and the presence of the metabolic syndrome may affect the response to BP-lowering treatment,[23] non-pharmacologic interventions that increase sensitivity to insulin, including weight reduction and increased physical activity, should have a primary role. When pharmacological treatment is required, close follow-up and aggressive non-pharmacological treatment are still justified in these patients. Considering that the metabolic syndrome is related to an increased vascular risk, it is possible that high-risk hypertensive patients with vascular disease and the metabolic syndrome would obtain an additional benefit on vascular prognosis with the achievement of a more aggressive BP goal, similar to that of patients with diabetes mellitus.

Vascular diseases and progression of renal function decline and brain tissue volume decrease

There is solid evidence that estimated glomerular filtration rate (eGFR) decreases inexorably with aging. One of the first studies on this subject showed a linear decrease in inulin clearance beyond the age of 30 years.[24] Longitudinal studies confirmed such a decline in renal function in elderly patients, but also show that some patients do not have a decline in renal function. In the Baltimore Longitudinal Study of Aging renal function declined with increasing age, but also one third of all subjects had no decrease in renal function at all.[25] More recently, large prospective studies have found lower rates of renal function decline.[26, 27] These studies indicate that the morphological and functional changes of aging

tend to be less marked than previously thought. The rate of annual renal function decline was higher in patients with vascular disease (*chapter 3.1*) compared to previous studies among patients without vascular disease.

Aging also affects the brain and causes changes in brain size, vasculature and cognition. The brain shrinks with increasing age and incidences of stroke, white matter lesions and dementia rise. Brain tissue volume is found to decline with age after age 40, with the actual rate of decline possibly increasing with age particularly over age 70.[28] Also the presence of white matter lesions increases with age and may indicate subclinical ischemia. Brain volume reductions increase from about 0.1-0.2% per year at age 30-50 to 0.3-0.5% per year over the age of 70.[29, 30] In one of the studies described in this thesis, brain tissue volume decreased at a rate of 0.55% per year in a population with a mean age of 58 years (*chapter 4.2*).

Studies described in this thesis show that rates of annual renal function decline as well as rates of annual brain tissue volume decrease are higher in patients with vascular disease compared with rates described in previous studies among patients without vascular disease (*chapter 3.1*, *chapter 4.2*). It seems that the progression of renal function decline and of cerebral atrophy in patients with vascular disease may be associated with advanced physiological aging.

Small vessel disease may underlie this common finding between renal function deterioration and brain tissue volume changes. Unlike most organs, both kidney and brain are low resistance end-organs and are exposed to high-volume blood flow throughout the cardiac cycle. Both the blood vessels in the kidney and the brain are highly susceptible to fluctuations in BP and flow.

In support of the idea that both organs are interrelated, associations between renal function and MRI-findings of brain vascular disease have been found.[31-33] A possibility is that shared risk factors such as hypertension could lead to similar vascular injury in both kidney and brain and could explain these associations. In one of the studies described in this thesis, a clear relation between elevated BP and renal function decline was found (*chapter 3.1*). However, no association between BP and the volume of white matter lesions or between BP and progression of cerebral atrophy was present (*chapter 4.1*, *chapter 4.2*). This suggests that other factors must be present leading to cerebral small vessel disease and explaining the association with kidney disease. Apart from shared insults, impairments of kidney function may lead to brain injury directly or indirectly by modifying the effects of other risk factors like endothelial dysfunction.

A link between vascular disease of the kidney and the brain exists, but whether kidney and brain share unique susceptibilities to vascular injury or whether impaired kidney function in itself contributes to brain injury is unclear. The suggested vascular origin of both renal function decline and brain tissue volume decrease makes it a potentially treatable condition to prevent or decelerate the deterioration of renal function and the progression of cerebral atrophy. Because patients with vascular disease show higher rates of progression of renal function decline and cerebral atrophy, this population will benefit most from implementation of any interventions to prevent renal function decline or atrophy progression.

Management of hypertension in vascular disease patients

Contrary to the reported decrease in hypertension prevalence between 1960 and 1991, hypertension prevalence has increased in recent years.[34] Suboptimal levels of systolic BP are responsible for a large proportion of morbidity and mortality due to vascular diseases. There is a continuous, incremental risk of cardiovascular disease, stroke and renal disease across levels of both systolic and diastolic BP.[35-37] During the last decade, guidelines for defining hypertension have been modified to lower levels of BP. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) which was published in 2003, defined normal BP as a BP <120/80 mmHg. Hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg.[38] In those patients with hypertension, the target of BP-lowering treatment is to lower BP to a level <140/90 mmHg.[38]

From a clinical perspective, hypertension might be defined as that level of BP at which the institution of BP-lowering therapy leads to a reduction in associated morbidity and mortality. The Hypertension Optimal Treatment trial aimed to assess the optimum target BP in hypertensives aged 50-80 years. The lowest incidence of cardiovascular events and mortality occurred at a mean diastolic pressure between 80 mmHg and 90 mmHg, comparable to the optimum target found in patients with coronary heart disease.[39] In diabetic patients a further reduction in major events was present in the group with target pressure <80 mmHg.[40] Most of the benefit in terms of prevention of major cardiovascular events is achieved by lowering systolic BP to about 140 mmHg and diastolic BP to about 90 mmHg, and only a small further benefit is obtained by any further reduction of BP. The target for BP-lowering treatment is below 140/90 mmHg, but there is no clearly defined critical BP that distinguishes normal from abnormal.

BP-lowering treatment to levels below the recommended target values decrease cardiovascular morbidity and mortality. Trials showed that lowering systolic BP by 10 to 12 mmHg and diastolic BP by 5 to 6 mmHg reduces stroke risk by 40%, risk of coronary heart disease by 16% and risk of vascular mortality by 20%.[41, 42] Despite these known benefits of BP lowering, BP goals are achieved in only 25-40% of patients taking BP-lowering medication. In the most recent NHANES survey (1999-2000), BP control rate was 31% and among individuals with both diabetes and hypertension only 25% had their BP controlled.[34] During the past decade, only a small increase in hypertension control has been observed.[34] In the study described in *chapter 5* of this thesis, comparable rates of BP control were found, but both treatment and control increased during the past decade.

Poor control of hypertension can be attributed to several factors. Long-term adherence to treatment for any chronic condition can be problematic, and this is also true for hypertension. From the prescribed BP-lowering medication, approximately 50% is discontinued after a year.[43] Physicians' knowledge of hypertension and ideas about BP-lowering treatment are also important in BP control.[44] Different studies were designed to identify patient characteristics associated with BP control. Advanced age, diabetes mellitus, isolated systolic hypertension, lower frequency of BP measurements and lower frequency of visits to the general practitioner were related to worse BP control.[45-49] Patients with a history of vascular events showed better BP control compared to patients without vascular disease.[46,

[47] The presence of diabetes mellitus was found to be associated with poorer BP control, and control rates tend to be lower among diabetic populations. In those patients with hypertension in combination with insulin resistance, lifestyle modification is probably even more important in lowering BP compared to other populations.

The goal of the US Department of Health and Human Services that 50% of patients with hypertension have their BP controlled by the year 2000 was not met, and this goal has been re-established to be achieved by 2010.[50] Several strategies to increase BP control have been developed and investigated. A treatment advice, sent out to both the patient and the general practitioner was effective to improve the use of BP-lowering drugs, although the advice was only followed in about a third of hypertensive patients.[51] In the decision to follow the advice, the general practitioner was influenced by the level of BP but not by the presence of concomitant risk factors. Both at patient level and at community level, strategies for hypertension control should address overall cardiovascular risk instead of exclusively BP control. An extensive implementation program with both passive and active strategies aimed at improving hypertension management in Canada resulted in more aggressive BP management.[52] Also strategies to prevent obesity are likely to have an impact on hypertension prevalence, and greater emphasis must clearly be placed on managing systolic hypertension instead of diastolic hypertension.

Effective BP control can be achieved in most hypertensive patients, but the majority will require 2 or more BP-lowering drugs.[53] Despite more effort to control hypertension, there are patients in whom BP control is not possible despite the use of more than 3 BP-lowering drugs, or because of too many adverse effects. The fact that the population is becoming older and more obese also makes it more difficult to reach treatment goals.

The control rate of 50% that was defined as the goal for the year 2010 by the US Department of Health and Human Services could be achieved by raising hypertension awareness to 80% of all hypertensives, guaranteeing treatment in 90% of aware hypertensive patients and controlling BP (levels below 140/90 mmHg) in 70% of all treated patients.[50] Educational interventions directed to either patients or physicians alone are not likely to generate important BP reductions. Effective hypertensive care requires regular review of patients and intensified BP-lowering treatment when BP goals are not being met. An organized system of registration, recall and regular review allied to a vigorous stepped care approach to BP-lowering drug treatment appears the most likely way to improve the control of elevated BP.[54]

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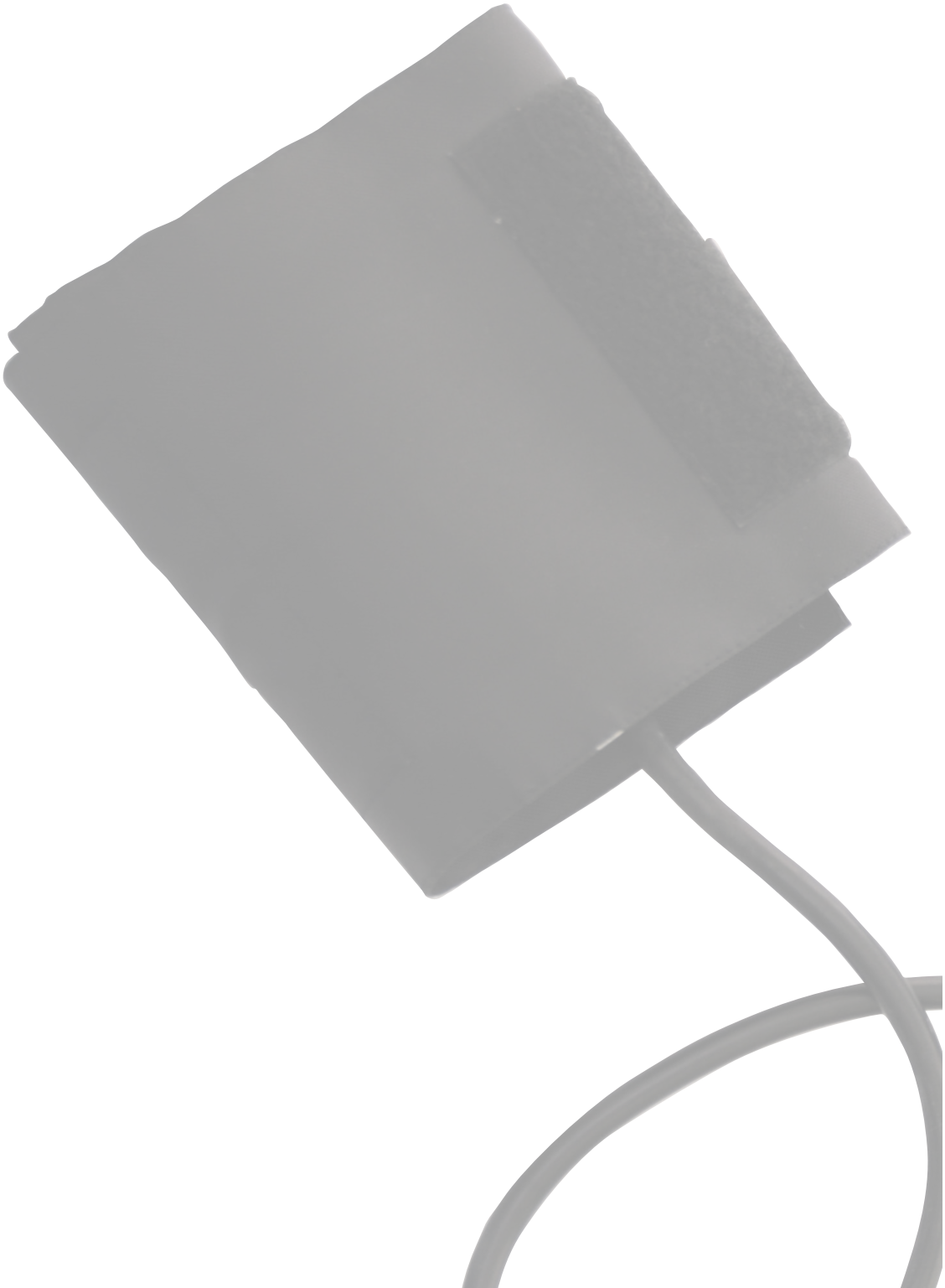

Chapter 7

Summary
Samenvatting
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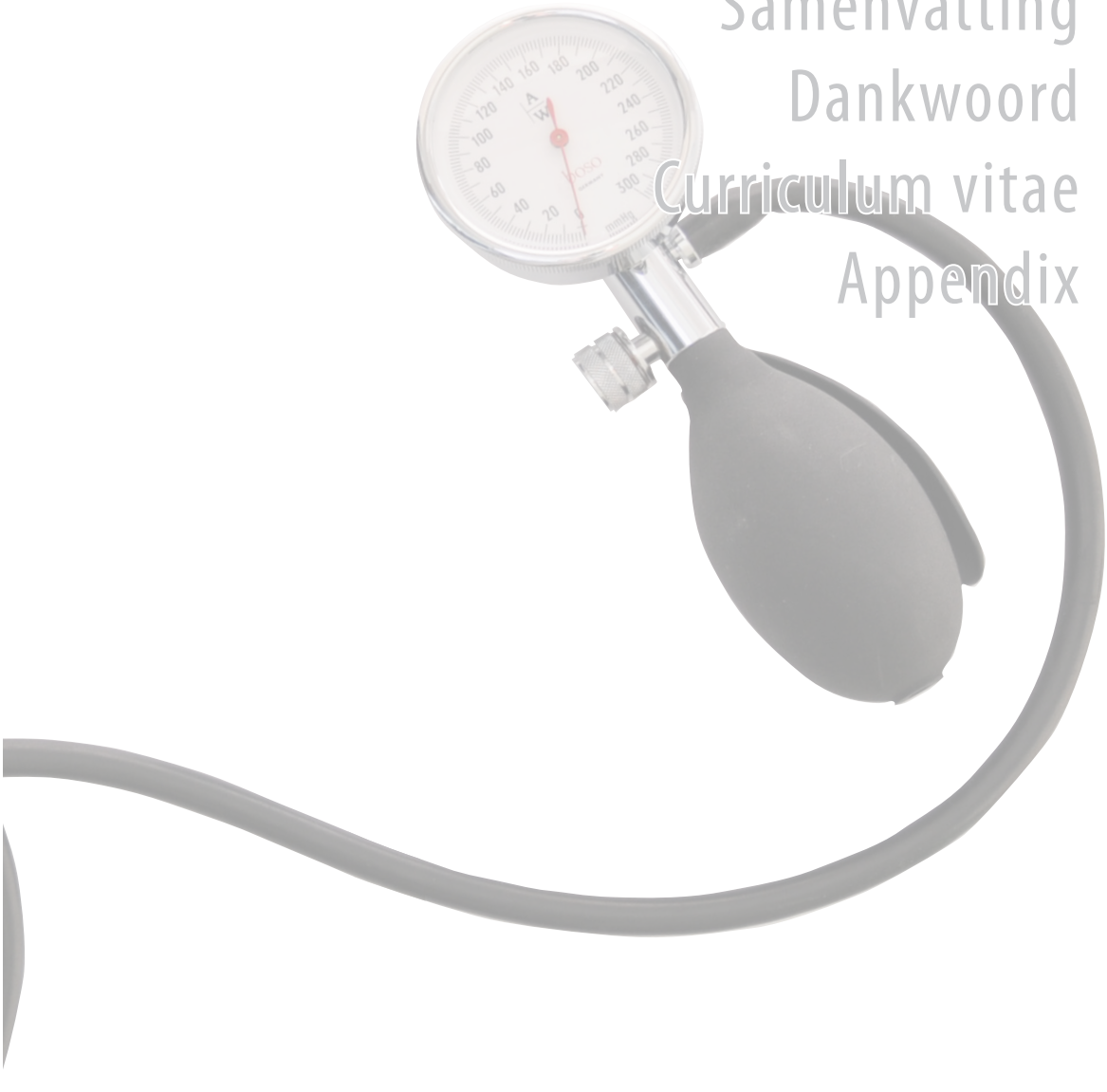
Appendix



Hypertension is one of the most common vascular risk factors, and is an important cause of development of different vascular diseases. Besides a role for elevated blood pressure in the development of coronary heart disease, cerebrovascular disease, peripheral arterial occlusive disease and abdominal aortic aneurysm, hypertension is also detrimental to kidney structure and function, and may be involved in the etiology of cerebral damage including atrophy and white matter lesions. The main aim of this thesis was to determine the burden of hypertension-associated vascular diseases and end-organ damage in patients with manifest vascular disease. The population studied in this thesis consisted of paticipants of the Second Manifestations of ARTerial disease study, an ongoing prospective cohort study carried out in the University Medical Center Utrecht, the Netherlands.

Patients with clinical manifestations of vascular diseases are at high risk for recurrent vascular diseases. The effect of the metabolic syndrome and type 2 diabetes mellitus on the occurrence of cardiovascular events in patients with hypertension and manifest vascular disease was studied in *chapter 2.1*. The metabolic syndrome was present in 49% of the 2196 patients included in this study. The prevalence of type 2 diabetes mellitus was 17%. During a mean follow-up time of 3.9 years, 283 vascular events were recorded. Patients with the metabolic syndrome but without type 2 diabetes mellitus (n=775) had a 41% higher risk of vascular death (age- and sex adjusted hazard ratio (HR) 1.41; 95% confidence interval (CI) 1.01-1.98) and a 40% higher risk of myocardial infarction and sudden death (HR 1.40; 95% CI 0.97-2.01). The association between the metabolic syndrome and stroke and between the metabolic syndrome and combined vascular events was less explicit. Presence of type 2 diabetes mellitus (n=381) was associated with a further increase in risk of vascular death (HR 1.59; 95% CI 1.07-2.35), stroke (HR 1.40; 95% CI 0.96-2.79) and combined vascular events (HR 1.54; 95% CI 1.13-2.09). Thus, even in high-risk patients with hypertension and vascular disease, presence of the metabolic syndrome or type 2 diabetes mellitus identifies patients at higher risk for future vascular events. Identifying metabolic syndrome patients may direct therapy focusing on treatment of insulin resistance by stimulating intensive lifestyle therapies.

It has been shown that patients with peripheral arterial occlusive disease are at very high risk for new vascular events. The metabolic syndrome is known to be a frequent condition in these patients. In *chapter 2.2*, the influence of the metabolic syndrome on the occurrence of cardiovascular events in patients with symptomatic peripheral arterial occlusive disease was investigated, as well the course of the metabolic syndrome and the changes in individual metabolic syndrome components during follow-up. In this prospective study, 91 of 461 patients had a new vascular event during a mean follow-up of 5.6 years. Patients with the metabolic syndrome (prevalence 49%) had a 51% higher risk of vascular events compared to patients without the metabolic syndrome (age- and sex adjusted HR 1.51; 95% CI 1.01-2.30). In 221 of 461 patients, a follow-up screening was performed after a mean follow-up time of 5.5 years. At the second measurement, the metabolic syndrome had disappeared in 16% of patients and was incident in 15% of patients. A decrease in body mass index (BMI) of 1 kg/m^2 during follow-up decreased the risk of development of the metabolic syndrome by 23% (odds ratio (OR) 0.77; 95% CI 0.62-0.96), and increased

the chance to revert to a non-metabolic syndrome state by 32% (OR 1.32; 95% CI 1.03-1.71). Thus, the metabolic syndrome is a frequent and important condition in patients with peripheral arterial occlusive disease. Changes in BMI have a large influence on both metabolic syndrome development and disappearance at follow-up. Weight control in order to reduce incident metabolic syndrome may add to prevention of new vascular events in these high-risk patients.

In the general population, renal mass and renal function are declining during life, and elevated blood pressure is generally associated with renal function decline. In *chapter 3.1*, we evaluated the absolute rate of renal function decline in patients with atherosclerotic vascular disease, as well as the effect of blood pressure on renal function deterioration. In our prospective study comprising 745 patients with different manifestations of vascular diseases, mean estimated glomerular filtration rate (eGFR) was 79.3 ± 16.3 ml/min/1.73m^2 at baseline and declined to a mean value of 75.1 ± 16.8 ml/min/1.73m^2 after a mean follow-up period of 4.5 years. Mean annual decrease in eGFR was 1.00 ml/min/1.73m^2. In 35% of patients, eGFR remained stable during follow-up. In the presence of albuminuria, there was a positive association between blood pressure and eGFR decline (β 1.29; 95% CI 0.73-1.85 per standard deviation increase in systolic blood pressure, β 3.86; 95% CI 2.34-5.38 for hypertension presence). In patients without albuminuria, no association was present between blood pressure and renal function decline. Renal function decline among patients with vascular diseases is considerable and blood pressure is a strong risk factor for eGFR decline in patients with albuminuria and atherosclerotic vascular disease. These results stress the importance of considering blood pressure and albuminuric status in patients with vascular disease.

Both albuminuria and decreased eGFR are associated with an increased cardiovascular risk, but do not necessarily coexist and have different pathophysiological mechanisms. In *chapter 3.2*, the separate and combined effects of decreased eGFR and albuminuria on the occurrence of vascular diseases and mortality in patients with manifest vascular disease are investigated. Of 2600 patients with vascular disease, 14.0% had albuminuria, 15.6% had eGFR <60 ml/min/1.73m^2 and 5.2% had both. Patients who only had albuminuria and patients with only decreased eGFR demonstrated moderately increased risks of vascular events, vascular mortality and all-cause mortality. The combination of eGFR <60 ml/min/1.73m^2 and albuminuria accounted for a 2.27-fold increased risk for vascular events (HR 2.27; 95% CI 1.54-3.34), a 2.22-fold increased risk of vascular mortality (HR 2.22; 95% CI 1.40-3.52) and a 1.84-fold increased risk for all-cause mortality (HR 1.84; 95% CI 1.25-2.69). Comparable results were found amongst 759 patients with type 2 diabetes mellitus. The combination of decreased eGFR and albuminuria is associated with the highest risks of vascular events, vascular and all-cause mortality in patients with manifest vascular disease. To adequately estimate vascular risk associated with impaired renal function, both eGFR and urinary albumin should be considered.

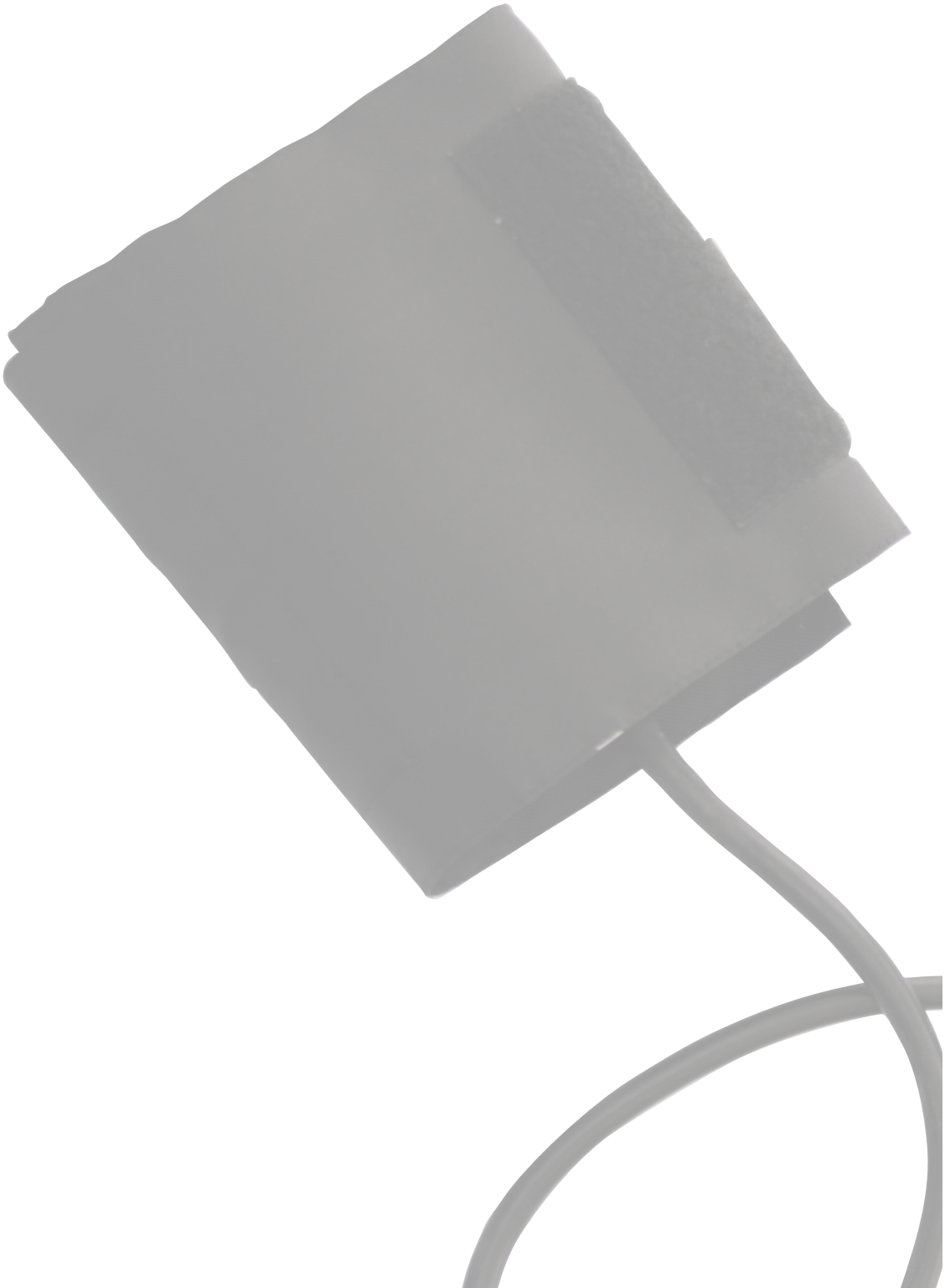
Cerebral white matter lesions (WML) are a frequent finding on brain magnetic resonance imaging scans, especially in elderly subjects. Elevated blood pressure has been identified as risk factor for WML. In *chapter 4.1*, we investigated the association between blood pressure and WML in patients with manifest vascular disease. Using an automated quantitative volumetric method, WML volume was calculated for 1030 patients with cerebrovascular disease, coronary heart disease, peripheral arterial occlusive disease or abdominal aortic aneurysm. The median volume of WML was 1.70 ml. No significant associations were present between systolic blood pressure, diastolic blood pressure, mean arterial pressure or hypertension presence and moderate or large volumes of WML. The localization of vascular disease and the presence of type 2 diabetes mellitus did not modify these relations. Thus, among patients with manifest vascular disease, BP was not associated with the presence of WML, irrespective of the presence of diabetes or the localization of vascular disease. Within a population already at high vascular risk, blood pressure does not further discriminate between patients at low and high risk of WML.

Cerebral atrophy on brain magnetic resonance imaging has been associated with vascular risk factors including hypertension. In *chapter 4.2*, the progression of cerebral atrophy and the possible associations with blood pressure were studied in patients with clinically evident vascular diseases. Baseline and follow-up examinations were performed in 331 patients with a mean follow-up time of 4.1 years. The annual decrease in brain tissue volume was 6.5 ± 3.8 ml and the annual increase in ventricular volume was 1.0 ± 1.0 ml. No associations were found between blood pressure and annual changes in brain or ventricular volume, but a clear association between blood pressure and incident lacunar infarcts was present (OR 1.57; 95% CI 1.11-2.22 per SD increase in systolic blood pressure). These results show that the magnitude of changes in brain tissue volume and ventricular volume in patients with vascular disease was comparable to the physiological changes described in normal people at a much higher age. Progression of cerebral atrophy in this population may be associated with advanced physiological aging, but is probably not caused by elevated blood pressure.

Patients with previous clinical manifestations of vascular disease are at considerably increased risk of developing future vascular events due to the systemic nature of atherosclerosis. Also type 2 diabetes mellitus is considered a high-risk condition for development of vascular disease and vascular mortality. Changes in vascular disease mortality have been directly related to changes in vascular risk factor prevalence. In *chapter 5*, we examined time trends in vascular risk factors and medication use in patients referred to a vascular specialist at the University Medical Center Utrecht with manifest vascular disease or type 2 diabetes mellitus in the period of 1996 to 2007. Mean age of the population (n=4731) was 59 years. From 1996 to 2007, the prevalence of obesity (BMI ≥30 kg/m^2) increased from 14% to 24%, and no change in smoking behaviour was observed. The prevalence of hyperlipidemia (total cholesterol ≥4.5 mmol/l or LDL-cholesterol ≥2.5 mmol/l) at referral declined from 92% in 1996-1997 to 45% in 2006-2007. The proportion of patients with blood pressure above 140/90 mmHg decreased from 66% to 51%. The use of lipid-lowering, blood pressure-lowering and antithrombotic medication at referral increased

over the observation period. An improvement in risk factor profile was seen in patients referred with manifest vascular disease or type 2 diabetes mellitus over a 12-year period. Nevertheless, the prevalence of modifiable risk factors is still high leaving patients at elevated vascular risk.

Finally, in the general discussion in *chapter 6*, main conclusions of this thesis were presented and our findings were discussed in the context of hypertension-associated vascular risk and hypertension management.



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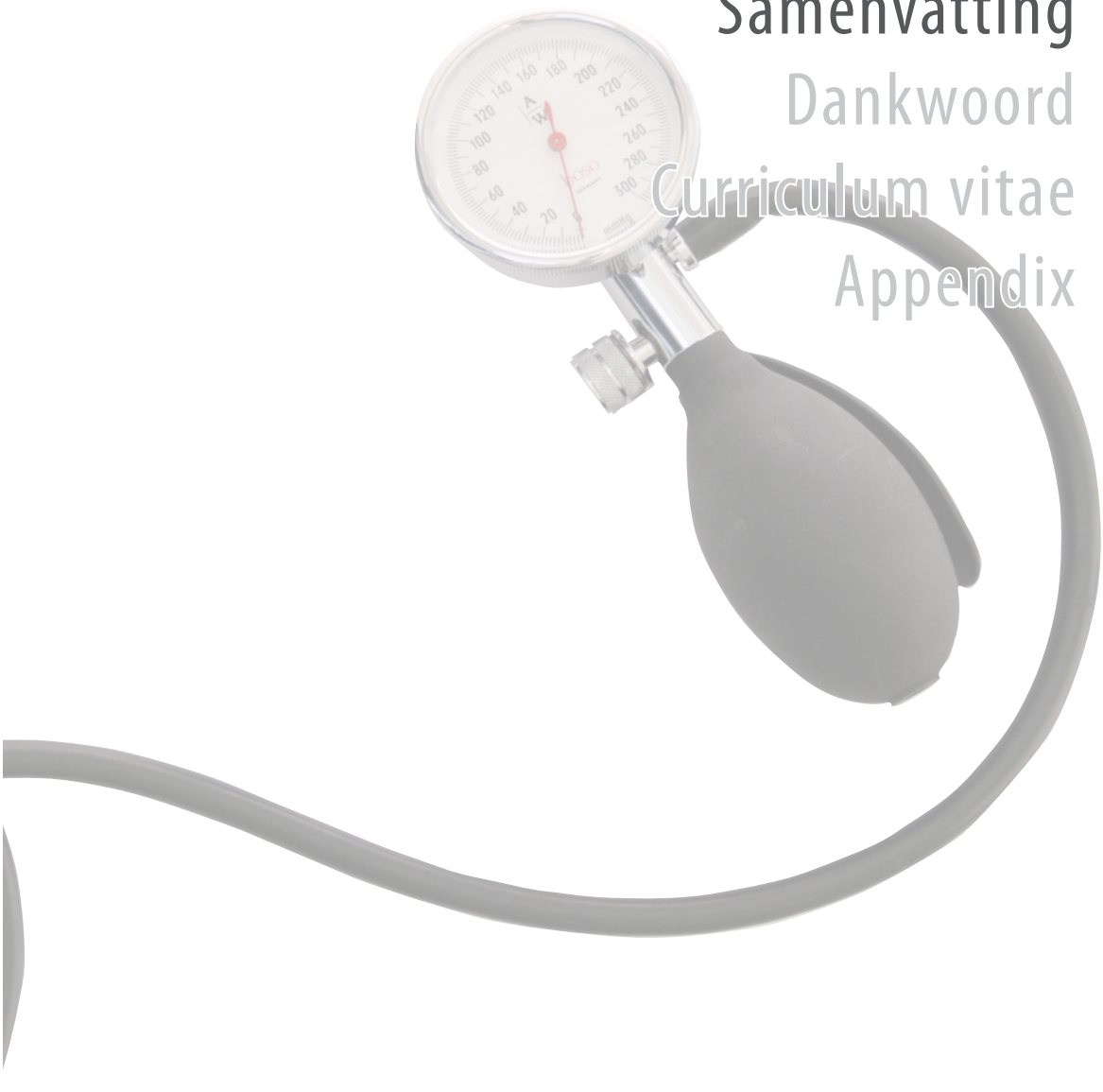


Hypertensie is één van de meest voorkomende vasculaire risicofactoren, en vormt een belangrijke oorzaak voor het ontwikkelen van verschillende hart- en vaatziekten. Hypertensie draagt bij aan het ontstaan van coronair vaatlijden, cerebraal vaatlijden, perifeer vaatlijden en aneurysmata van de abdominale aorta. Daarnaast heeft hypertensie ook schadelijke effecten op de nieren, en kan hypertensie leiden tot cerebrale schade waaronder hersenatrofie en witte stof afwijkingen. Het voornaamste doel van dit proefschrift was een beter te inzicht te krijgen in het optreden van hypertensie gerelateerde vasculaire aandoeningen en orgaanschade bij patiënten met klinisch manifest vaatlijden.
De onderzoeken die zijn beschreven in dit proefschrift zijn uitgevoerd met gegevens van patiënten die deelnemen aan de Second Manifestations of ARTerial Disease (SMART) studie. De SMART studie is een prospectief cohort onderzoek dat wordt uitgevoerd in het Universitair Medisch Centrum Utrecht.

Patiënten met klinisch manifest vaatlijden lopen een hoog risico om opnieuw een vasculaire aandoening te krijgen. In *hoofdstuk 2.1* is de invloed van het metabool syndroom en van type 2 diabetes mellitus op het optreden van vasculaire aandoeningen bij patiënten met zowel hypertensie als klinisch manifest vaatlijden onderzocht. Het metabool syndroom kwam voor bij 49% van de 2196 patiënten die in deze studie onderzocht werden. De prevalentie van type 2 diabetes mellitus was 17%. Na een gemiddelde duur van 3,9 jaar hadden 283 patiënten opnieuw een vasculaire aandoening doorgemaakt. Patiënten met het metabool syndroom maar zonder type 2 diabetes mellitus (n=775) hadden een 41% hoger risico om te overlijden door een vasculaire oorzaak dan patiënten zonder het metabool syndroom. Ook het risico op een myocardinfarct of plotselinge dood was 40% hoger onder patiënten die voldeden aan de criteria voor het metabool syndroom. Het verband tussen aanwezigheid van het metabool syndroom en het optreden van cerebrovasculaire aandoeningen was minder uitgesproken, evenals de relatie tussen het metabool syndroom en het gecombineerde eindpunt van vasculaire aandoeningen en overlijden. Patiënten met type 2 diabetes mellitus hadden een nog sterker verhoogd vasculair risico. Type 2 diabetes mellitus verhoogde het risico op vasculaire dood met 59%, het risico op cerebrovasculaire aandoeningen met 40% en het risico op het gecombineerde eindpunt van vasculaire aandoeningen en overlijden met 54%. Zelfs in een populatie van patiënten met een hoog vasculair risico kan het vaststellen van de diagnose metabool syndroom of type 2 diabetes mellitus bijdragen aan de risicostratificatie van deze patiënten. Het diagnosticeren van het metabool syndroom kan een juiste behandeling bevorderen, welke gericht is op het bestrijden van insulineresistentie door middel van het verbeteren van de leefstijl.

Patiënten met perifeer arterieel vaatlijden lopen een zeer hoog risico op het ontwikkelen van nieuwe vasculaire aandoeningen elders in het lichaam. Het is bekend dat het metabool syndroom bij deze patiënten veel voorkomt. In *hoofdstuk 2.2* is de invloed van het metabool syndroom op het optreden van vasculaire aandoeningen onderzocht bij patiënten met symptomatisch perifeer arterieel vaatlijden. Ook het verloop van het metabool syndroom en de veranderingen in afzonderlijke componenten van het metabool syndroom over de tijd zijn geëvalueerd. Uit dit prospectieve onderzoek bleek dat 91 van

de 461 patiënten een nieuwe vataandoening ontwikkelden gedurende gemiddeld 5,6 jaar. Patiënten met het metabool syndroom (49% van de populatie) hadden een 51% hoger risico op het ontwikkelen van vasculaire aandoeningen dan patiënten zonder het metabool syndroom. Na een gemiddelde duur van 5,5 jaar namen 221 patiënten deel aan een vervolgmeting. Ten tijde van deze tweede meting voldeed 16% van de patiënten niet meer aan de criteria voor het metabool syndroom, terwijl zij bij de eerste meting wel het metabool syndroom hadden. Bij 15% van de patiënten was het metabool syndroom na 5,5 jaar juist ontstaan. Een daling van de body mass index (BMI) van 1 kg/m^2 tussen de eerste en de tweede screening verlaagde het risico op ontwikkeling van het metabool syndroom met 23%. Tegelijkertijd werd hierdoor de kans om het metabool syndroom kwijt te raken met 32% verhoogd. Het metabool syndroom komt veel voor bij patiënten met perifeer arterieel vaatlijden en heeft belangrijke consequenties in deze populatie. Veranderingen in BMI kunnen zowel het ontstaan als het kwijtraken van het metabool syndroom over de tijd sterk beïnvloeden. Bij deze hoog-risico patiënten kan gewichtsreductie een belangrijke rol spelen bij het voorkomen van vasculaire aandoeningen door het risico op het metabool syndroom te verminderen.

In de algemene populatie neemt de nierfunctie af naarmate de leeftijd stijgt. Er is een relatie tussen de bloeddruk en de snelheid van deze achteruitgang in nierfunctie. In *hoofdstuk 3.1* is de mate van nierfunctie achteruitgang bij patiënten met klinisch manifest vaatlijden onderzocht, evenals de invloed van de bloeddruk op verslechtering van de nierfunctie. In dit prospectieve onderzoek onder 745 patiënten met verschillende uitingen van vaatlijden daalde de gemiddelde geschatte glomerulaire filtratie snelheid (eGFR) van 79.3 ± 16.3 ml/min/1.73m^2 aan het begin van de studie tot 75.1 ± 16.8 ml/min/1.73m^2 na een gemiddelde duur van 4,5 jaar. De gemiddelde eGFR daling per jaar was 1.00 ± 2.71 ml/min/1.73m^2. Bij 35% van de patiënten bleef de eGFR echter stabiel gedurende de studie. Bij patiënten met albuminurie was er een duidelijke relatie tussen een verhoogde bloeddruk en een snellere eGFR daling. Bij patiënten met hypertensie daalde de eGFR per jaar 3.86 ml/min/1.73m^2 (95% betrouwbaarheidsinterval (BI) 2.34-5.38) meer dan bij patiënten zonder hypertensie. Bij patiënten zonder albuminurie was deze relatie niet aanwezig. De snelheid van nierfunctie verslechtering bij patiënten met manifest vaatlijden is aanzienlijk, en bloeddruk is een sterke risicofactor voor nierfunctie achteruitgang bij patiënten met albuminurie en vasculaire aandoeningen. De resultaten van dit onderzoek benadrukken het belang van het beoordelen van bloeddruk en albuminurie bij patiënten met klinisch manifest vaatlijden.

Zowel albuminurie als een verminderde eGFR veroorzaken een verhoogd vasculair risico. Beide uitingen van nierschade komen echter niet altijd samen voor en hebben een verschillende pathofysiologie. In *hoofdstuk 3.2* zijn de afzonderlijke en gecombineerde effecten van een verminderde eGFR en albuminurie op het optreden van vasculaire aandoeningen en mortaliteit onderzocht bij patiënten met klinisch manifest vaatlijden. Van de 2600 patiënten had 14,0% albuminurie, 15,6% een eGFR <60 ml/min/1.73m^2 en 5,2%

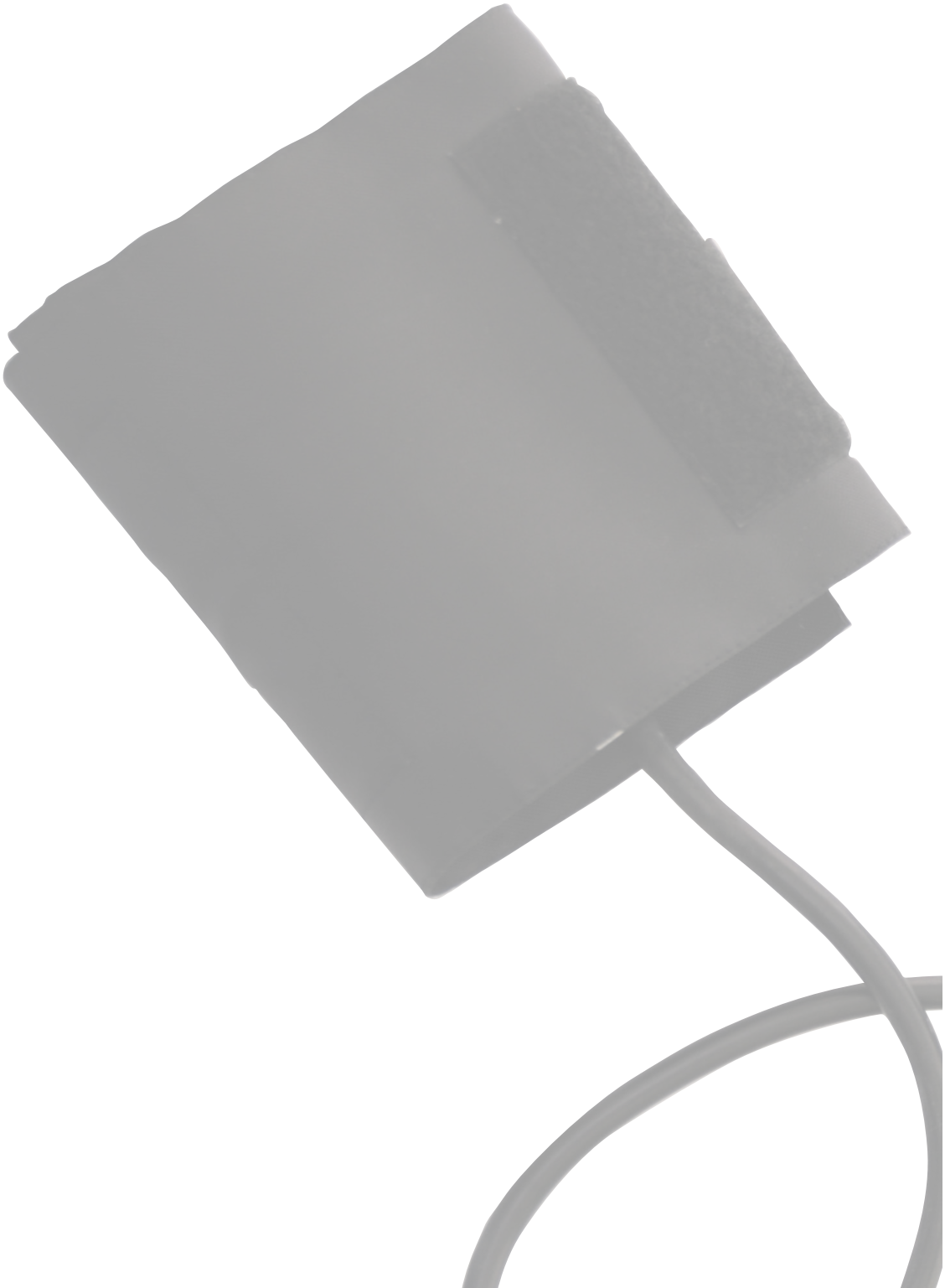
beide. Patiënten met alleen albuminurie of alleen een verminderde eGFR hadden een matig verhoogd risico op vasculaire aandoeningen, vasculaire mortaliteit en algemene mortaliteit. Patiënten met zowel albuminurie als een eGFR <60 ml/min/1.73m^2 hadden een 2,27 maal verhoogd risico op vasculaire aandoeningen, een 2,22 maal verhoogd risico op vasculaire mortaliteit en een 1,84 maal verhoogd risico op algemene mortaliteit. Vergelijkbare resultaten werden gevonden bij 759 patiënten met type 2 diabetes mellitus. De combinatie van een verminderde eGFR en albuminurie veroorzaakt de sterkste stijging in het risico op vasculaire aandoeningen, vasculaire en algemene mortaliteit bij patiënten met manifest vaatlijden. Om een adequate schatting te maken van het vasculaire risico dat gepaard gaat met een verminderde nierfunctie zijn metingen van zowel eGFR als albuminurie noodzakelijk.

Op MRI scans van de hersenen worden regelmatig witte stof afwijkingen (WML) gezien, voornamelijk bij oudere patiënten. Een verhoogde bloeddruk is regelmatig genoemd als een van de risicofactoren voor WML. In *hoofdstuk 4.1* is de relatie tussen bloeddruk en WML bij patiënten met manifest vaatlijden onderzocht. Met behulp van een geautomatiseerde kwantitatieve volumetrische techniek werd het volume van WML berekend van 1030 patiënten met cerebraal vaatlijden, coronair vaatlijden, perifeer arterieel vaatlijden of een aneurysma van de abdominale aorta. Het mediane volume van WML was 1.70 ml. In deze populatie werd geen relatie gevonden tussen systolische bloeddruk, diastolische bloeddruk, gemiddelde arteriële druk of de aanwezigheid van hypertensie en een bovengemiddeld of groot volume van WML. De lokalisatie van het vaatlijden en de aan- of afwezigheid van type 2 diabetes mellitus hadden geen invloed op deze relatie. Er is geen duidelijke relatie tussen bloeddruk en WML, ongeacht de lokalisatie van het vaatlijden of de aanwezigheid van type 2 diabetes mellitus. De bloeddruk biedt geen mogelijkheid om verder te differentiëren tussen patiënten met een laag en een hoog risico op WML binnen een populatie met een al sterk verhoogd vasculair risico.

De aanwezigheid van cerebrale atrofie op MRI scans van de hersenen is gerelateerd aan verschillende vasculaire risicofactoren, waaronder hypertensie. In *hoofdstuk 4.2* zijn de snelheid van progressie van hersenatrofie en de mogelijke relatie tussen bloeddruk en progressie van hersenatrofie onderzocht bij patiënten met klinisch manifest vaatlijden. In totaal werden 331 patiënten twee maal onderzocht met gemiddeld 4,1 jaar tussen deze metingen. De gemiddelde jaarlijkse afname van het breinvolume was 6,5 ± 3,8 ml, en de jaarlijkse toename van het ventrikelvolume was 1.0 ± 1.0 ml. De bloeddruk was niet gerelateerd aan de jaarlijkse veranderingen in brein- of ventrikelvolume, terwijl er wel een duidelijk verband aanwezig was tussen de bloeddruk en de incidentie van lacunaire infarcten. De resultaten van dit onderzoek laten zien dat de omvang van de veranderingen in breinvolume en ventrikelvolume bij patiënten met manifest vaatlijden vergelijkbaar is met de fysiologische veranderingen die gezien worden bij gezonde personen met een hogere leeftijd. De progressie van hersenatrofie in deze populatie houdt mogelijk verband met een versnelde fysiologische veroudering, maar wordt waarschijnlijk niet veroorzaakt door een verhoogde bloeddruk.

Patiënten met manifest vaatlijden in de voorgeschiedenis hebben een aanzienlijk verhoogd risico om in de toekomst opnieuw vasculaire aandoeningen te ontwikkelen. Ook patiënten met type 2 diabetes mellitus vallen in de hoogste risico categorie voor de ontwikkeling van vaatziekten of het overlijden door een vasculaire oorzaak. De veranderingen die in de tijd zijn opgetreden in de mortaliteit door vasculaire aandoeningen houden direct verband met de veranderingen in vasculaire risicofactoren over dezelfde periode. In *hoofdstuk 5* zijn de trends in vasculaire risicofactoren en medicatiegebruik beschreven bij patiënten die verwezen werden naar een vasculair specialist in het Universitair Medisch Centrum Utrecht wegens manifest vaatlijden of type 2 diabetes mellitus in de periode van 1996 tot en met 2007. Deze patiënten (n=4731) waren gemiddeld 59 jaar oud. Tussen 1996 en 2007 steeg de prevalentie van obestias (BMI ≥30 kg/m^2) van 14% naar 24%. Duidelijke veranderingen in rookgedrag waren niet aanwezig. De prevalentie van hyperlipidemie (totaal cholesterol ≥4,5 mmol/l of LDL-cholesterol ≥2,5 mmol/l) ten tijde van verwijzing daalde van 92% in 1996-1997 tot 45% in 2006-2007. Ook het percentage patiënten met een bloeddruk boven 140/90 mmHg daalde van 66% naar 51%. Het gebruik van zowel cholesterolverlagende medicatie, bloeddrukverlagende medicatie als antithrombotica op het moment van verwijzing naar een vasculair specialist nam toe over de duur van de observatie periode. Er is een duidelijke verbetering zichtbaar in het vasculaire risicoprofiel van patiënten die worden verwezen met manifest vaatlijden of type 2 diabetes mellitus. Ondanks deze verbetering is de prevalentie van risicofactoren nog altijd hoog, waardoor veel patiënten een verhoogd vasculair risico hebben.

Ten slotte wordt in de discussie in *hoofdstuk 6* ingegaan op de interpretatie van de resultaten van de in dit proefschrift beschreven onderzoeken. Zowel de metabole effecten van hypertensie, de invloed van hypertensie op de nieren en de hersenen als de behandeling van hypertensie bij patiënten met vaatlijden worden besproken en geïntegreerd met de bevindingen van de studies in dit proefschrift.



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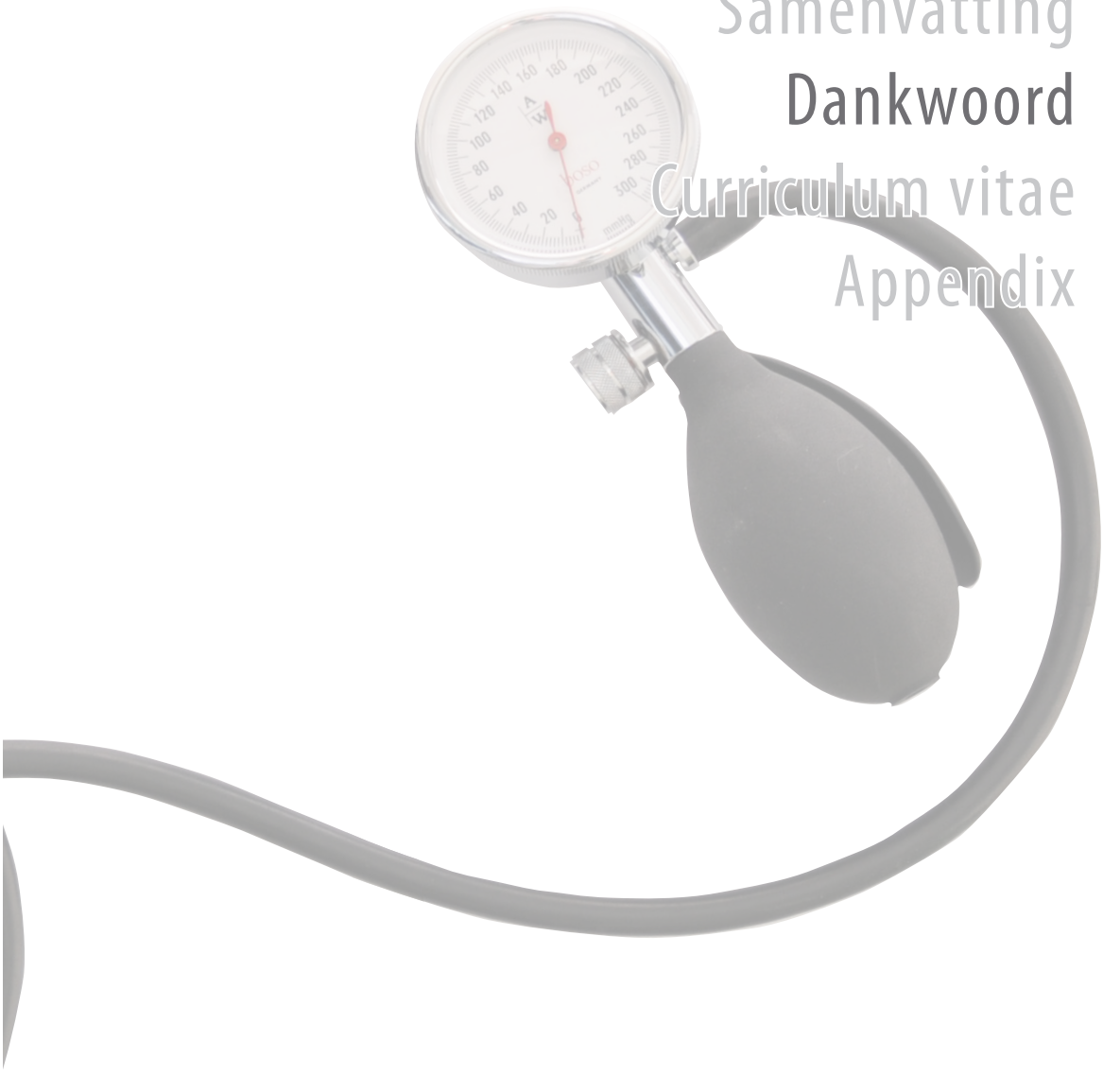

Bij de uitvoering van de in dit proefschrift beschreven onderzoeken heb ik hulp ondervonden van vele mensen. Ik ben blij dat ik nu in de gelegenheid ben al die mensen te bedanken die de afgelopen jaren zo leuk en interessant hebben gemaakt.

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Lieve Janneke, beste! Zonder dat ik je iets hoef te vragen weet je altijd precies wat ik nodig heb. Ik ga je zeker missen, maar ik wens jou en Chris de meest fantastische tijd in Buenos Aires. Reken maar dat ik langskom (geen afspraak in vreugde)!

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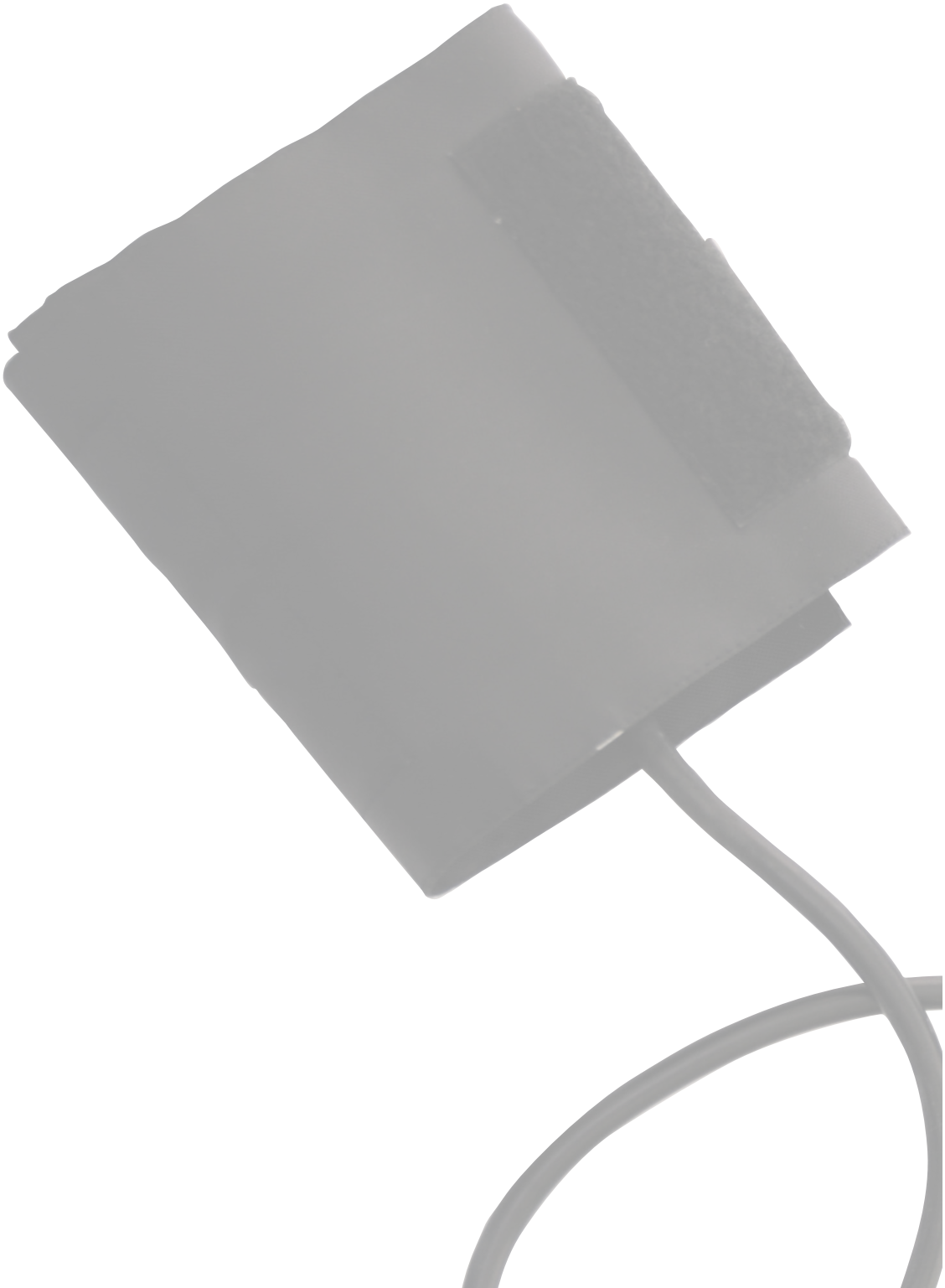
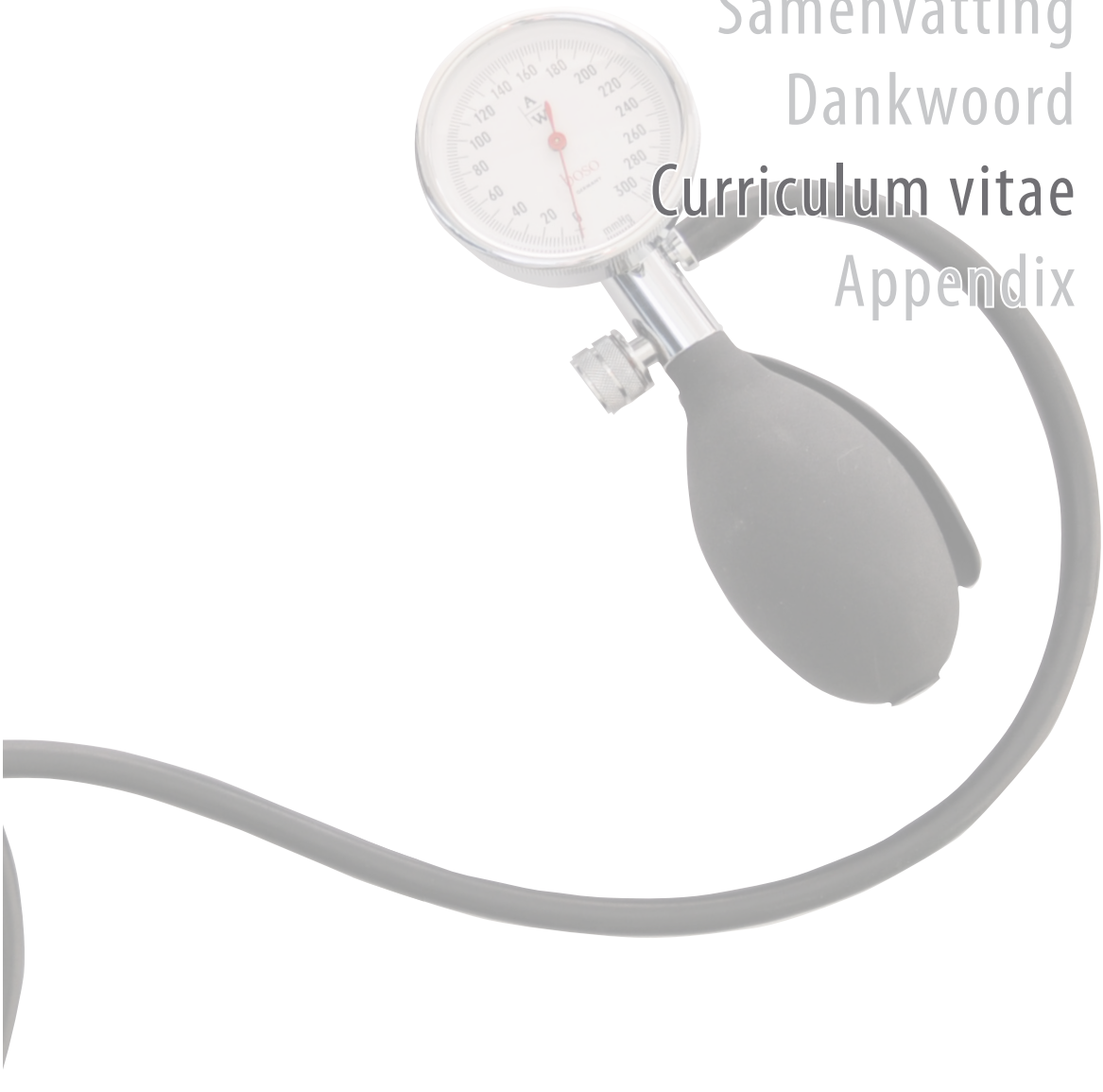
Louis en Martine Vlek, lieve pap en mam, wat jullie voor mij over hebben is heel erg veel. Niets fijner dan thuiskomen bij jullie, afgesloten met een ritje tussen Amersfoort en Utrecht. Bedankt voor zoveel gezelligheid, lieve woorden en interesse. Weet dat ik het nog altijd niet zonder jullie kan.

Lieve, lieve Werner, heel erg bedankt voor alles wat je voor mij hebt gedaan. Ik wens je de allermooiste zomers.



Chapter 7



Anne Louise Martine Vlek was born on the 28th of August, 1982 in Leusden, the Netherlands. In 2000, after graduating from secondary school at the Johan van Oldenbarneveltgymnasium in Amersfoort, she started her medical training at the University of Utrecht. In 2006 she participated in a research project concerning hypertension and the metabolic syndrome in patients with manifest vascular disease under supervision of prof. dr. Y. van der Graaf (Julius Center for Health Sciences and Primary Care) and dr. F.L.J. Visseren (Department of Vascular Medicine). After obtaining her medical degree in August 2006, she started the research descibed in this thesis at the Julius Center for Health Sciences and Primary Care, again under supervision of prof. dr. Y. van der Graaf and dr. F.L.J. Visseren. She obtained her Master of Science degree in Clinical Epidemiology at the University of Utrecht in June 2008.

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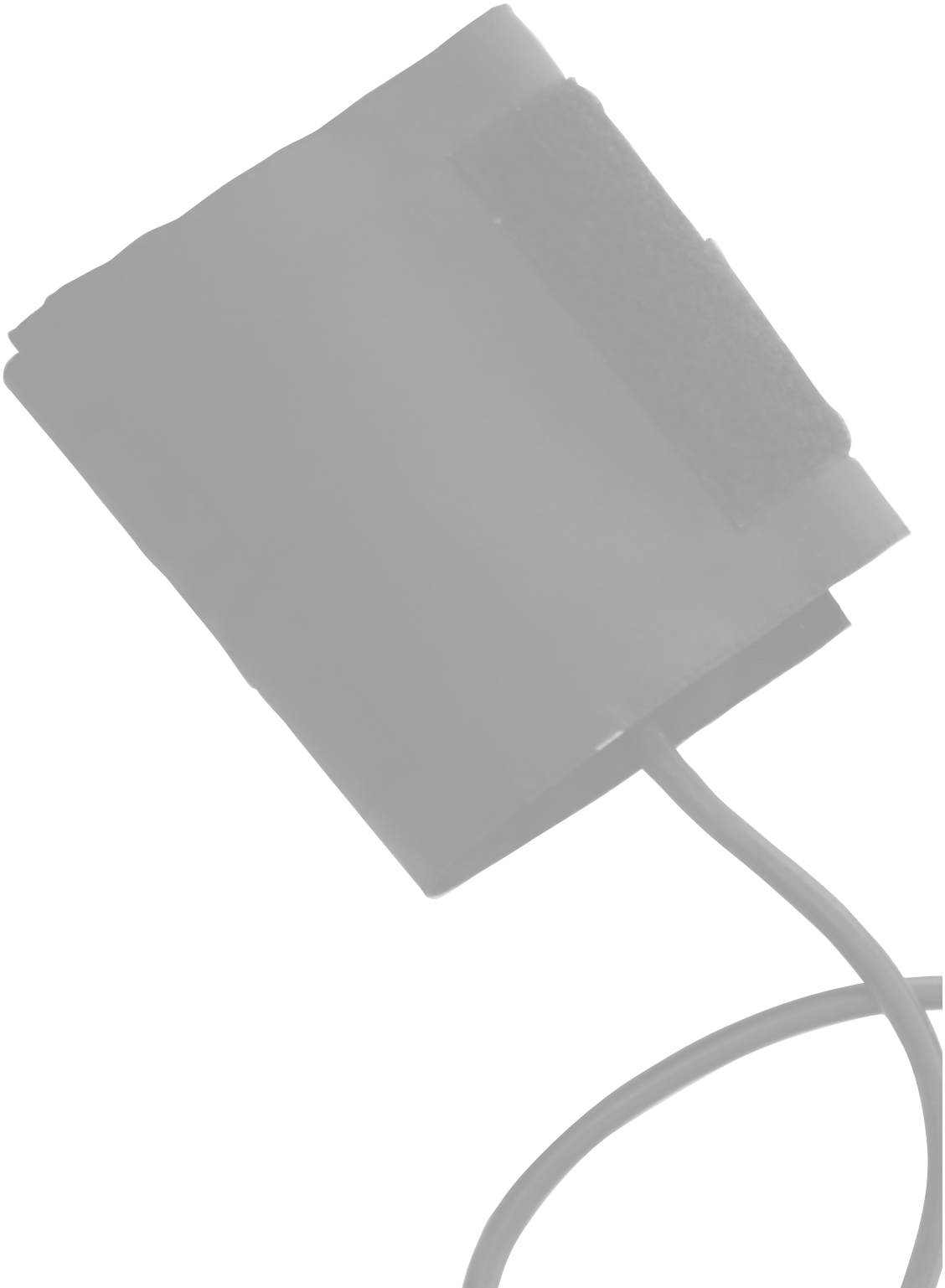
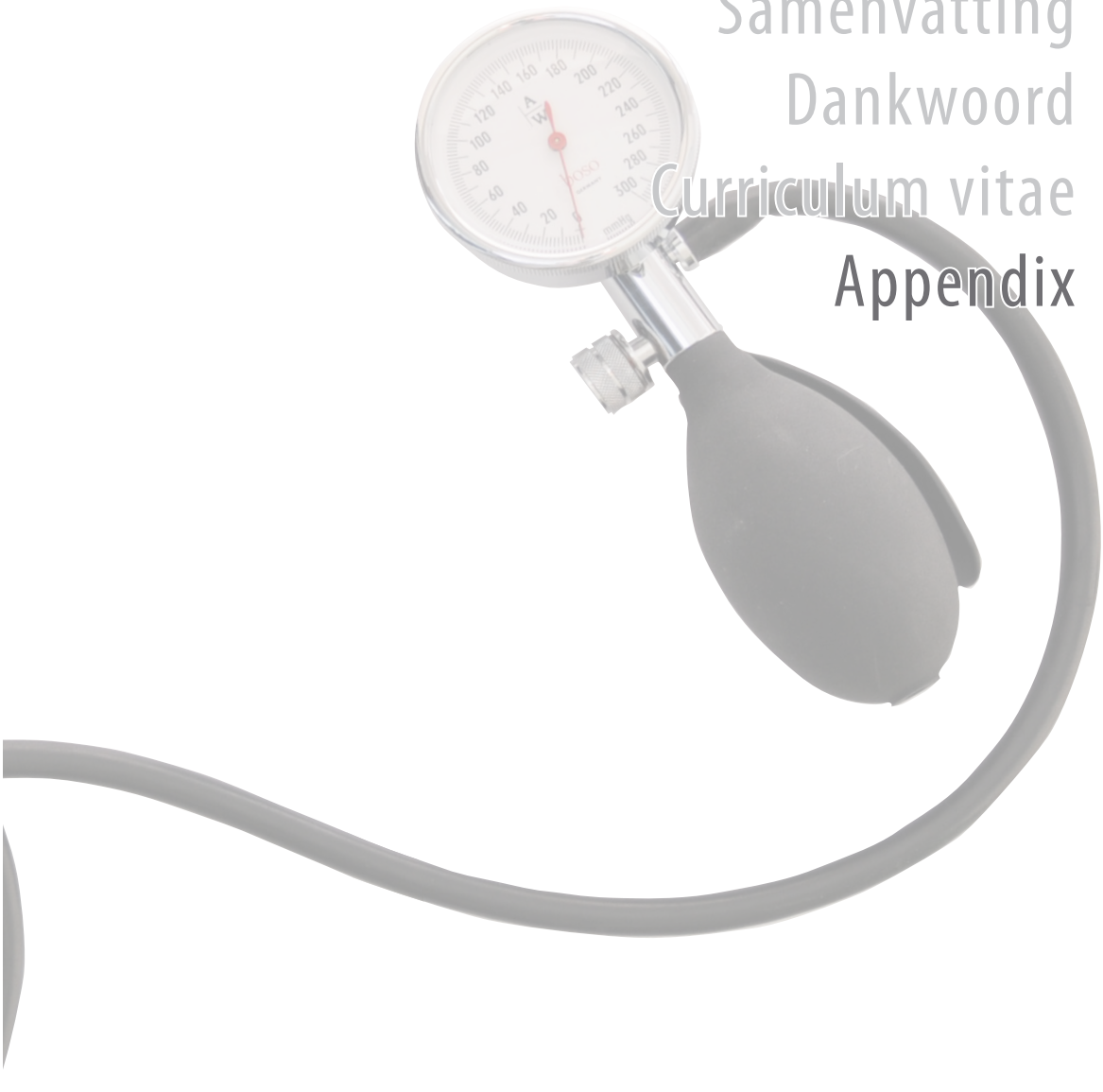


Chapter 7



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