SMART risk factor screening in patients at high vascular risk

Beate Geraldina Brouwer

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(met een samenvatting in het Nederlands)

Proefschrift

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Beate Geraldina Brouwer

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Promotor : Prof.dr. Y. van der Graaf

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

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General introduction

Despite an overall reduction in cardiovascular mortality over the past decade, an aging population has seen a shift in risk for cardiovascular disease to the older adult; vascular disease will still be the leading cause of death world-wide in 2020.[1;2] The underlying pathophysiology of vascular disease is atherosclerosis, affecting the endothelial surface of the arteries throughout the human body. Therefore, atherosclerotic vascular disease can become clinically evident at several sites in the arterial system, leading to coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. Patients who have survived a vascular event are at high risk for developing new vascular events at the same or another site.[3] Classical risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking, abdominal obesity, and physical inactivity are important causes of vascular morbidity and mortality in this high-risk population.[2] Fortunately, reduction of these risk factors can decrease the risk of a subsequent vascular event in patients with clinically manifest arterial disease.[4] Since these patients seldom have only one risk factor, and the presence of multiple risk factors has a multiplicative effect on vascular risk,[5] it is especially important to investigate which strategies are effective in improving their vascular risk profile.

Lifestyle changes

Lifestyle factors, such as an unhealthy diet, physical inactivity and abdominal obesity, all associated with an increased risk for the development of vascular diseases and diabetes mellitus, have gained increased attention. Governments' awareness is rising and World Health Organization launched the "Global Strategy on Diet, Physical Activity and Health' to mobilize countries in an effort to stimulate healthy lifestyle at global, national, regional, and local levels.[6] The increased burden of cardiovascular disease and type 2 diabetes can partly be attributed to the increase in prevalence of sedentary lifestyle and abdominal obesity associated with insulin resistance.[7-9] Physical inactivity and obesity lead to insulin resistance and as a consequence to other vascular risk factors like hypertension and hyperlipidemia and eventually to an increased incidence of diabetes and vascular disease (Figure 1). Thus, lifestyle changes, including increased physical activity and weight reduction, substantially contribute to decreased vascular risk.[10] Physical activity interventions, in the form of exercise training, have been shown to reduce vascular risk factors, such as high blood pressure,[11] high blood glucose,[12] high plasma triglycerides and low HDL-cholesterol.[13]

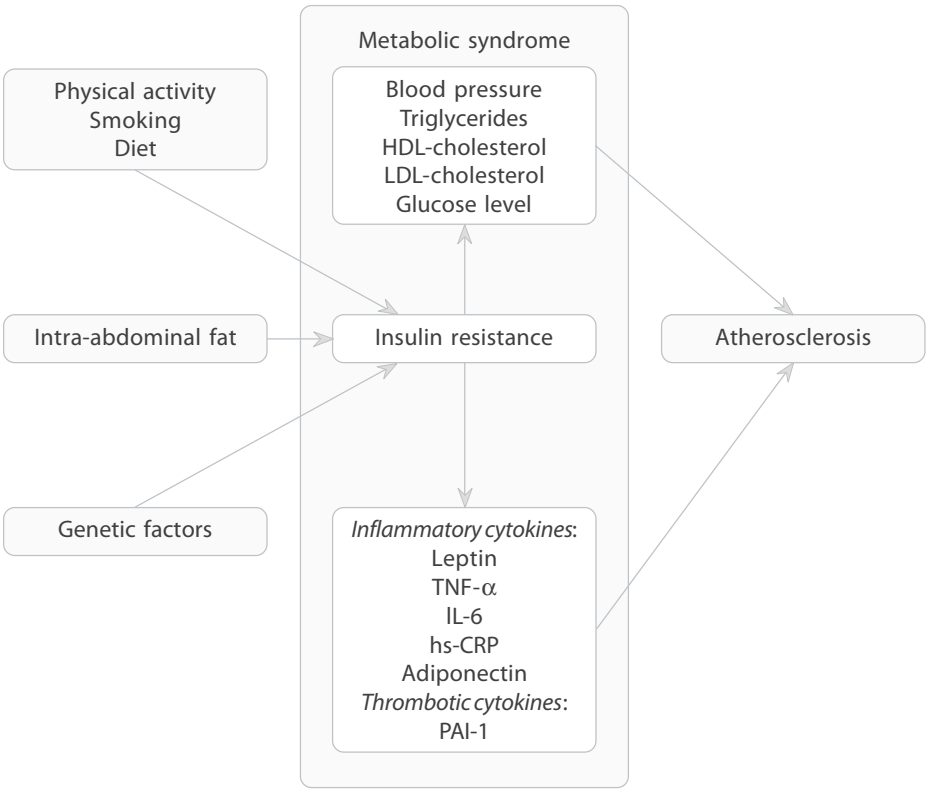

Figure 1. HDL: high-density lipoprotein, LDL: low-density lipoprotein, TNF-α: tumor necrosis factor-α, IL-6: interleukin-6, hs-CRP: high sensitive C-reactive protein, PAI-1: plasminogen activator inhibitor-1

However, physical training usually is part of a comprehensive cardiac rehabilitation program under supervision in a specialized centre and it is difficult to identify the relative importance of each preventive measure.[14] The importance of physical activity in daily life as modifier of vascular risk is unclear in some groups of patients, in particular in patients with symptomatic vascular diseases.

Risk factor management

Screening individuals for vascular risk factors may help focus secondary preventive measures aimed at improving a person's vascular risk profile, in order to prevent new vascular events in already high-risk patients. Yet, it is difficult to reduce these vascular

risk factors, and to sustain this reduction, in clinical practice.[15-17] Many patients with coronary heart disease,[15] peripheral arterial disease,[18;19] cerebrovascular disease,[20] abdominal aortic aneurysm[21] do not reach the treatment goals for important vascular risk factors. Treatment is usually done by the general practitioner or vascular specialist and is mainly focussed on modification of high LDL-cholesterol, elevated blood pressure, or elevated glucose by pharmacological interventions. Although treatment guidelines recommend the simultaneous adoption of lifestyle and starting pharmacological interventions targeted at multiple risk factors,[4;22;23] less attention is given to lifestyle changes. However, shifting even late in life from a sedentary lifestyle to a more active one confers a reduction in vascular risk.[24;25]

Universal improvements in disease management and public health measures have led to an aging population in whom these risk factors have more time to cause vascular disease. Therefore effective and efficient comprehensive management of risk factors is needed. Adequate treatment of vascular risk factors starts with (1) risk factor identification which is depending upon the diagnostic work up. Levels of individual risk factors are (2) to be weighed against current (inter)national guidelines, and if appropriate (3) pharmacological and lifestyle treatment needs to be started. And lastly (4) risk factors should be monitored. Nevertheless, the implementation of strategies to prevent vascular risk factors remains far from optimal. Multidisciplinary collaboration and continuity of care is required.

Objectives

The objectives of this thesis are

- to investigate the relationship between the presence of coronary heart disease and intra-abdominal fat (**chapter 2)**, and the relationship between leisure-time physical activity and the presence of metabolic syndrome, incidence of type 2 diabetes and recurrence of vascular events in high-risk patients (**chapters 3, 4, and 5**), and
- to evaluate vascular risk factor management strategies for risk factor reduction in patients with established vascular disease or type 2 diabetes (**chapters 6 and 7**).

Outline of this thesis

Patients with peripheral arterial disease have an increased risk of death from coronary heart disease. Intra-abdominal fat is an important determinant of the risk of coronary heart disease but the relative importance of intra-abdominal fat in patients with peripheral

arterial disease is unknown. Therefore, we investigate, in **chapter 2**, whether the presence of coronary heart disease can be explained by the accumulation of intra-abdominal fat and compare different measures of adiposity as predictors of coronary heart disease in patients with peripheral arterial disease. Although considerable research and clinical interest has focused on the incidence of vascular disease in individuals with metabolic syndrome or diabetes, much less is known about the converse relationship, namely the development of metabolic syndrome or type 2 diabetes in patients with manifest vascular disease. Awareness of the importance of physical activity has increased in the face of sedentary lifestyle and obesity. The association between leisure-time physical activity and the presence of metabolic syndrome and insulin resistance is examined in **chapter 3** and the relationship between physical activity and the incidence of type 2 diabetes is investigated in **chapter 4**. Although both insulin resistance and metabolic syndrome are important factors in the development of new vascular events, there is uncertainty regarding the role of physical activity in this relationship. In **chapter 5**, we will describe the relationship between leisure-time physical activity and the risk of new vascular events and all-cause mortality in patients with manifest arterial disease. The Risk management in Utrecht and Leiden Evaluation (RULE) study is presented in **chapter 6**. The aim is to compare the effects of a hospital setting with a multidisciplinary vascular screening program and a hospital setting without such a program on the vascular risk profile in patients with established vascular disease or type 2 diabetes. Another study of a vascular risk factor reduction strategy, BEST, is described in **chapter 7**. The aim of this randomized controlled trial is to investigate whether a written agreement on risk factor treatment between general practitioner and hospital compared with usual care will lead to improvement of the vascular risk profile in patients with manifest arterial disease after 1 year. The main findings of the different studies described in this thesis are discussed in the general discussion, **chapter 8**, and summarized in **chapter 9**.

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Abdominal fat and risk of coronary heart disease in patients with peripheral arterial disease

Beate G. Brouwer, Frank L.J. Visseren, Ronald P. Stolk, Yolanda van der Graaf, for the SMART Study Group

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Abstract

Background

We investigated whether the presence of concomitant coronary heart disease (CHD) in patients with peripheral arterial disease (PAD) can be explained by intra-abdominal fat accumulation and compared different measures of adiposity as predictors of CHD in patients with PAD.

Methods

Data were collected from patients enrolled in the Second Manifestations of ARTerial disease (SMART), an ongoing prospective cohort study of patients with manifest vascular disease or vascular risk factors at the University Medical Centre Utrecht. The current analysis includes 315 patients, mean age 59 ± 10 years, who had PAD with (n=79) or without CHD (n=236). Parameters of adiposity were measured, and intra-abdominal fat and subcutaneous fat were measured ultrasonographically. Metabolic syndrome was defined according to Adult Treatment Panel III.

Results

The prevalence of metabolic syndrome was higher among patients with CHD (63%) than among patients without CHD (48%). All parameters of adiposity indicated more fat in patients with CHD, except for subcutaneous fat. Waist circumference was associated with 64% higher prevalence of CHD (confidence interval, 20% to 123%) per 1 standard deviation increase in waist circumference after adjustment for age and sex. The odds ratio for waist circumference remained virtually the same after additional adjustment for the components of the metabolic syndrome and smoking.

Conclusion

An increased waist circumference, a crude measure of intra-abdominal fat, is associated with an increased risk of concomitant CHD in patients with PAD.

Introduction

Peripheral arterial disease (PAD) coexists with other manifestation of atherosclerotic disease at other locations in the vasculature. The risk of a fatal or non-fatal myocardial infarction or stroke is high in patients with PAD, whereas the incidence of complications associated with ischaemia of the lower extremities is rather limited.[1] The 5-year mortality due to cardiovascular diseases in PAD patients is about ~30%. Moreover, these patients have a 3.1-fold increase in all-cause mortality compared to patients without PAD and a 6.6-fold increased risk of death from coronary artery disease. [2-4]

Metabolic syndrome, the clustering of risk factors associated with central obesity, is prevalent in 58% of PAD patients[5] and is associated with increased vascular damage.[6] In general, patients with metabolic syndrome are at increased risk of developing type 2 diabetes and of cardiovascular morbidity and mortality.[7-10] The high prevalence of metabolic syndrome in patients with PAD may contribute to the high incidence of cardiovascular events in these patients. Intra-abdominal fat is a major driver of insulin resistance and, therefore, plays, an important role in the development of metabolic disorders, including hyperglycemia, hypertension, hypertriglyceridaemia, and low high-density lipoprotein (HDL)-cholesterol.[11] Furthermore, intra-abdominal fat accumulation causes dysregulation of adipocyte function, leading to oversecretion of tumor necrosis factor-α (TNF-α), free fatty acids, plasminogen activator inhibitor-1 (PAI-1), interleukin-6 (IL-6) and growth factors, as well as hyposecretion of adiponectin, all of which may participate in the development of metabolic dysfunction.[12] Patients with metabolic syndrome have a 3-4 fold increased risk of mortality due to coronary heart disease (CHD),[10] and intra-abdominal fat is an important determinant of the risk of CHD,[13-15] but the relative importance of intra-abdominal fat in patients with PAD is unknown. In addition, little is known about which of the various measurements of obesity show the strongest relation with the risk of CHD in patients with an arterial disease. Previous studies were done primarily in healthy persons and provided conflicting results.[16-21] Therefore, in the present study, we investigated whether the presence of concomitant CHD can be explained by intra-abdominal fat accumulation and compared different measures of adiposity as predictors of CHD in patients with PAD.

Methods

Study population

In this study, we used data from patients enrolled in the Second Manifestations of ARTerial disease (SMART) study. The SMART study is an ongoing prospective cohort study of patients with manifest vascular disease or vascular risk factors. From 1996, patients aged 18 to 80 years old, newly referred to the University Medical Center Utrecht with manifest vascular disease or a cardiovascular risk factor, underwent a vascular screening including a questionnaire, laboratory assessments, ankle-brachial pressure index (ABPI), duplex scan of the carotid arteries, and ultrasonography of the abdomen. All participants gave their informed consent and the local Ethics Committee approved the study. Study design and definitions have been described in detail previously.[22]

For this cross-sectional study, analyses were based on the inclusion period from May 2000 to April 2004 and were limited to patients with a qualifying diagnosis or medical history of PAD. For the current study, 315 consecutive patients with PAD, aged 18-80 years, were enrolled.

PAD category

The presence of PAD was based on referral diagnosis. Patients with typical symptoms of intermittent claudication (IC) (cramping pain in the lower leg(s) during exercise) and a resting ABPI $\leq$ 0.90 or with rest pain, non-healing ulcers, or gangrene were referred by the general practitioner (GP) to the outpatient clinic of the Department of Vascular Surgery at the University Medical Center Utrecht, the Netherlands. If the vascular surgeon confirmed the diagnosis PAD, patients were asked by their vascular surgeon to participate in the SMART study.

Patients with a history of peripheral artery bypass surgery, or confirmed intermittent claudication (Fontaine II and III) or rest pain/ ulcer or amputation of the leg could also be included.

CHD

Patients with PAD were categorized according to the presence of CHD (past and current). The presence of a history of CHD was based on referral diagnosis and medical history. Patients who had one of the referral diagnosis, angina pectoris or myocardial infarction, and had an elective percutaneous transluminal coronary angioplasty or coronary bypass surgery, or who stated a history of one of these diagnosis in the questionnaire were considered as having a history of CHD.

Angina pectoris was defined as chest pain with or without documented ischemia on the electrocardiogram (ECG) and with documented stenoses on angiography. All patients had indication for percutaneous transluminal coronary angioplasty. Myocardial infarction was defined as having at least two of the following: chest pain for at least 20 minutes, not disappearing after administration of nitrates; sinus tachycardia elevation >1 m in two following leads or a left bundle branch block on the ECG; and/or creatine kinase (CK) elevation of at least two times the normal value of CK and a myoglobin fraction >5% of the total CK.

Anthropometric and ultrasonography measurements

Intra-abdominal fat thickness was estimated anthropometrically and ultrasonographically. The subjects' height and weight were measured while they wore indoor clothes and no shoes. Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Waist circumference was measured halfway between the lower rib and the iliac crest, and hip circumference was measured at the level of the greater trochanter. Both measurements were taken in standing position. Sagittal diameter was measured at the level halfway between the lower rib and the iliac crest while the patient was in a supine position. Ultrasonographic measurements were taken in supine position with an HDI 3000 (Philips Medical Systems, Eindhoven, Netherlands) with a C 4-2 transducer. There was no bowel prep performed before the ultrasound measurement. For the ultrasound measurement of intra-abdominal fat, we used electronic calipers to measure the distance between the peritoneum and the lumbar spine or psoas muscles. For determining subcutaneous fat, the distance between the linea alba and the skin was measured. This means that the abdominal muscles were excluded for both measurements. A strict protocol, including the position of and pressure on the transducer, was used. For all images the transducer was placed on a straight line drawn between the left and right midpoints of the lower rib and the iliac crest. All measurements were performed at the end of a quiet inspiration, applying minimal pressure without displacement or compression of the abdominal cavity. Each distance was measured three times at three positions.[23]

Blood pressure

The blood pressure was measured two times at the right and left upper arm with a non-random sphygmomanometer, with a non-random sphygmomanometer, with the subject in a sitting position. The mean value of the two blood pressure measurements was taken as the blood pressure.

Vascular screening

All elements of the vascular screening were conducted during 1 day at the University Medical Center Utrecht. Patients were asked to complete a standardized health questionnaire covering medical history of vascular disease (CHD, PAD, abdominal aortic aneurysm and cerebrovascular disease), symptoms of cardiovascular disease, risk factors (type 2 diabetes, hypertension, hyperlipidemia, alcohol consumption, physical activity, current and former smoking habits), family history and current drug use. All patients underwent a standardized diagnostic protocol including physical examination (weight, height, waist circumference, systolic and diastolic blood pressure), non-invasive screening of asymptomatic atherosclerotic disease including ABPI, duplex scan of the carotid arteries, ultrasonography of the abdomen and laboratory tests to determine the lipid profile (serum triglycerides, serum total cholesterol, serum HDL-cholesterol) and glucose and creatinine levels. Blood samples were collected after an overnight fast. The laboratory techniques and screening have been described previously.[22]

Definitions

Metabolic syndrome was defined according to the Adult Treatment Panel III (ATP III) criteria. Three or more of the following metabolic abnormalities had to be present: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), high blood pressure (≥130 mmHg systolic or 85 mmHg diastolic), hypertriglyceridaemia (serum triglycerides ≥1.70 mmol/l (150 mg/dl)), low HDL-cholesterol (serum HDL-cholesterol <1.04 mmol/l (40 mg/dl) in men and <1.29 mmol/l (50 mg/dl) in women), and high fasting glucose (serum glucose ≥6.1 mmol/l (110 mg/dl).[24] When waist circumference was missing, we used the BMI as a measure of obesity, with a cut-off point of 30 kg/m^2.[25]

Subjects who did not meet the ATP III criteria for high blood pressure or high fasting glucose, but who were being treated with blood pressure-lowering agents or glucose-lowering agents or who had (self) reported type 2 diabetes were also considered to fulfil the criteria for high blood pressure or high fasting glucose, respectively. A fasting glucose ≥7.0 mmol/l in a patient without a history of diabetes mellitus was considered as newly diagnosed type 2 diabetes.

Statistical analysis

Values are given as percentages or as mean ± standard deviation (SD) for normally distributed variables. Differences between patients with and without CHD were tested with chi-square (categorical variables) or unpaired Student's *t* test (continuous normal distributed variables).

To adjust the mean of measures of adiposity for age and sex differences between patients with and without CHD, we used analysis of covariance (ANCOVA, general linear model procedure). Multiple logistic regression analysis was performed to investigate the independent association between the different measures of adiposity and the presence of CHD. Results are expressed as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). We estimated the ORs corresponding to a 1 SD increase in each measure of adiposity. Three models were used. The first model was adjusted for age and sex. In the second model, additional adjustment was performed for systolic blood pressure, glucose, triglycerides, HDL-cholesterol, and ever smoking, and in the third model, final additional adjustment was performed for use of glucose-lowering agents, lipid-lowering agents and blood pressure-lowering agents. The covariates were included as continuous variables. Only sex, smoking and use of glucose-lowering agents, lipid-lowering agents and blood pressure-lowering agents were included as categorical variable. The presence of CHD was taken as the dependent variable and age, sex, systolic blood pressure, glucose, triglycerides, HDL- cholesterol, ever smoking and the different measures of adiposity as the independent variables. All statistical analyses were performed with SPSS for Windows 12.0.1 (SPSS Inc., Chicago, IL).

Results

Study population

The baseline characteristics of the study population are given in Table 1. Seventy-nine of the 315 patients had CHD, most patients were men (71%) and the mean age was 59 years.

The group with CHD were mostly men, consisted of more patients with the metabolic syndrome (63%), and were slightly older than the patients without CHD. All components of the metabolic syndrome were more prevalent in the patients with CHD than in the patients without CHD, except for hypertension. Among all patients, 4% had no components of the metabolic syndrome, 21% had one component, 24% had two components, 27% had three components and 25% had four or more components.

Table 1. Baseline characteristics in 18-80 year-old patients with peripheral vascular disease

	Peripheral arterial disease (n=315)	
	Absence of CHD (n=236)	**Presence of CHD (n=79)**
Men (%)	67	85
Age (y)	58 ± 11	61 ± 10
Systolic blood pressure (mmHg)	142 ± 21	148 ± 24
Diastolic blood pressure (mmHg)	81 ± 9	84 ± 12
Triglycerides (mmol/l)	1.9 ± 1.3	2.4 ± 1.4
HDL-cholesterol (mmol/l)	1.2 ± 0.4	1.1 ± 0.3
Fasting serum glucose (mmol/l)	6.4 ± 2.2	6.8 ± 2.2
Creatinine clearance (Cockroft) (ml/min)	79 ± 25	74 ± 25
Type 2 diabetes (%)[a]	25	33
Previous cerebral vascular disease (%)	11	13
Diagnosis of CHD (years ago)	-	10.4 ± 9.3
Smoking, current, or past (%)[b]	88	94
Never smoked (%)	12	6
Recently stopped smoking (%)	25	19
Past smoking (%)	39	62
Still smoking (%)	24	13
ABPI	0.90 ± 0.21	0.92 ± 0.21
High fasting glucose* (%)	45	46
Hypertriglyceridemia† (%)	43	68
Low HDL- cholesterol‡ (%)	43	48
Abdominal obesity§ (%)	33	41
Hypertension‖ (%)	78	76
Metabolic syndrome# (%)	48	63
Glucose-lowering agents (%)	9	13
Anti-hypertensive drugs (%)	33	61
Lipid-lowering agents (%)	26	53

CHD: coronary heart disease, HDL: high density lipoprotein, ABPI: ankle brachial pressure index. All data expressed as means ± standard deviation or as indicated

[a] fasting serum glucose >7.0 mmol/l or treated for diabetes or self- reported diabetes mellitus

[b] still smoking, recently stopped or previously smoking

[*] fasting serum glucose ≥6.1 mmol/l or treated for diabetes

[†] serum triglycerides ≥1.70 mmol/l

[‡] serum HDL-cholesterol <1.04 mmol/l in men and <1.29 mmol/l in women

[§] waist circumference >102 cm in men and >88 cm in women or BMI >30 kg/m^2

[‖] ≥130 mmHg systolic or 85 mmHg diastolic or treated for hypertension

[#] according to Adult Treatment Panel III

Table 2. Measures of adiposity in patients with or without coronary heart disease

	Peripheral arterial disease (n=315)		
	Absence of CHD (n=236)	**Presence of CHD (n=79)**	**P-value**
BMI (kg/m^2)	26.0 ± 0.3	27.5 ± 0.5	<0.01
Waist circumference (cm)	94.0 ± 0.7	98.6 ± 1.2	<0.01
Hip circumference (cm)	103.1 ± 0.6	105.6 ± 1.1	0.052
Intra abdominal fat (cm)	9.3 ± 0.2	10.3 ± 0.3	<0.01
Subcutaneous fat (cm)	2.7 ± 0.1	2.7 ± 0.2	0.765
Waist-to-hip ratio	0.912 ± 0.004	0.934 ± 0.008	<0.01
Waist-to-height ratio	0.541 ± 0.004	0.566 ± 0.007	<0.01
Obesity (BMI ≥30 kg/m^2) (%)	15	20	0.261

CHD: coronary heart disease, BMI: body mass index
All data expressed as age-and sex-adjusted mean ± standard error

Intra-abdominal fat in PAD patients with and without CHD

Table 2 displays the measures of adiposity according to patients with and without CHD. All measures of adiposity were higher in patients with CHD than in patients without CHD, with the exception of the amount of subcutaneous fat (2.6 ± 1.7 cm in patients with CHD vs. 2.7 ± 1.8 cm in patients without CHD). In addition, more of the patients with CHD were obese (20%). In both groups, with and without CHD, 9% of the waist- and hip circumference, waist-to-hip ratio and waist-to-height ratio measurements were missing. For BMI and subcutaneous fat, 2% of the measurements were missing in the group without CHD and none were missing in the group with CHD. In both groups, no measurement of intra-abdominal fat was missing.

Relation between intra-abdominal fat measurements and CHD

The ORs for the presence of CHD in patients with PAD for each 1 SD increase in individual measures of adiposity, adjusted for age and sex, are shown in Table 3. Waist circumference and BMI showed the strongest association with the presence of CHD (OR 1.64; 95% CI 1.20-2.23) after adjustment for age and sex, whereas subcutaneous fat and hip circumference were not associated with the presence of CHD in these patients with

Table 3. The risk of the presence of coronary heart disease for each 1 standard deviation (SD) increase of different measurements of fat

		Odds Ratio (95% confidence interval)		
	1 SD	**Model I**	**Model II**	**Model III**
Waist circumference (cm)	11.07	1.64 (1.20 - 2.23)	1.61 (1.10 - 2.31)	1.41 (1.00 - 2.04)
BMI (kg/m^2)	4.09	1.57 (1.12 - 2.18)	1.41 (0.99 - 2.05)	1.35 (0.92 - 1.98)
Waist-to-hip ratio	0.079	1.55 (1.08 - 2.23)	1.30 (0.95 - 2.00)	1.28 (0.83 - 1.98)
Waist-to-height ratio	0.061	1.54 (1.15 - 2.08)	1.38 (0.99 - 2.20)	1.34 (0.95 - 1.91)
Intra-abdominal fat (cm)	2.66	1.48 (1.13 - 1.94)	1.40 (0.99 - 1.83)	1.27 (0.93 - 1.73)
Hip circumference (cm)	9.22	1.31 (0.99 - 1.73)	1.33 (0.99 - 1.82)	1.26 (0.93 - 1.70)
Subcutaneous fat (cm)	1.75	1.04 (0.80 - 1.35)	1.22 (0.86 - 1.99)	1.04 (0.77 - 1.41)

SD: standard deviation
BMI: body mass index
Model I: adjusted for age and sex
Model II: additionally adjusted for systolic blood pressure, HDL-cholesterol, triglycerides, glucose, and ever smoking
Model III: additionally adjusted for use of glucose-lowering agents, lipid-lowering agents, blood pressure-lowering agents

PAD. The OR for intra-abdominal fat was 1.48 (95% CI 1.13–1.94). To show whether there was an association between adiposity and CHD, we additionally adjusted for the components of the metabolic syndrome and smoking (Table 3). The OR for waist circumference was 1.61 (95% CI 1.10-2.31) after additional adjustment for the components of the metabolic syndrome and smoking. The OR for intra-abdominal fat after adjustment for the metabolic syndrome factors and smoking was 1.40 (95% CI 0.99-1.83). After additional adjustment for the use of glucose-lowering agents, lipid-lowering agents and anti-hypertensive drugs, only waist circumference remained significantly associated with CHD (OR 1.41; 95% CI 1.00-2.04).

To investigate whether the location of fat in the abdomen was most important in the association with CHD or whether total body fat mainly determined the risk, we additionally adjusted for a quantitative measure of body weight (BMI). However, due to collinearity these analyses were not interpretable.

Discussion

In this study, it is shown that for each SD increase in waist circumference, an indirect indicator of intra-abdominal fat, was associated with a 61% increase in the risk of concomitant CHD in patients with PAD. Moreover, the metabolic syndrome was more prevalent among patients with CHD (63%). Patients with recently established atherosclerotic arterial disease are at high risk of developing another vascular complication in the same or another part of the vascular system.

Patients with increased intra-abdominal fat are at increased risk of developing cardiovascular morbidity and mortality. Although most deaths among patients with PAD are due to CHD,[4] little is known about the relative importance of intra-abdominal fat in patients with PAD. In the present study, we found that the presence of CHD in patients with PAD was associated with abdominal fat accumulation, as evidenced by the strong association with waist circumference.

Several factors may explain the increased cardiovascular risk of cardiovascular events associated with abdominal obesity. First, abdominal fat is associated with a number of metabolic disturbances, such as elevated blood pressure, hypertriglyceridemia, low serum HDL-cholesterol, and elevated plasma glucose, all established risk factors for the development of CHD.[11] Secondly, visceral fat acts as an endocrine organ by secreting several hormones and cytokines, such as TNF-α, IL-6, PAI-1 and adiponectin.[26] These adipokines are directly or indirectly involved in the process of atherosclerosis, thus contributing to an increased cardiovascular risk. Metabolic syndrome, the clustering of risk factors associated with central obesity,[27-29] is associated with advanced vascular damage in patients with already clinical manifestations of vascular diseases,[6] indicating that metabolic syndrome may lead to more generalized atherosclerosis. Indeed, metabolic syndrome is highly prevalent among patients with atherosclerosis.[5]

Several previous studies have examined the association between different measures of adiposity (BMI, waist-to-hip ratio, or waist circumference) and CHD.[16-21] The results of these studies are conflicting. Some suggest that BMI is a good predictor of CHD risk, whereas other studies suggest that waist-to-hip ratio or waist circumference is a better indicator of vascular risk. Most of these studies compared only a few measures of adiposity, and the strength of the present study is that we used several measures and investigated their relation with CHD risk.

Our findings are in agreement with several studies[30] that found waist circumference to be more strongly associated with the risk of myocardial infarction than BMI. Some indicated that of the various anthropometric measures commonly used, waist circumference and waist-to-hip ratio showed the strongest relationship with the risk of CHD.[20] Because waist circumference is considered as a simple and crude measure of visceral obesity, we measured intra-abdominal fat by ultrasonography but found it to have a weaker association with CHD than waist circumference, waist-to-hip ratio and waist- to-height ratio. Although waist circumference and BMI both predicted an increased risk of CHD, they measure different aspects of body fatness. BMI is a measure of overall fatness but does not provide information about the distribution of fat or distinguish between lean and fat mass, whereas waist circumference is a measure of abdominal adiposity. A previous study[31] reported that waist circumference and BMI independently contributed to the prediction of abdominal subcutaneous, visceral, and non-abdominal fat. They found that waist circumference was a better predictor of visceral fat than BMI but recommended that both should be used in clinical practice.

Hence, it is in our view the intra-abdominal fat accumulation that plays an important role in the development of metabolic syndrome favours the development of generalized atherosclerosis in patients with PAD, increasing the risk of CHD. Thus, interventions aimed at reducing weight, and especially focused on the waist area, may reduce the CHD risk. Such interventions should be considered in combination with conventional medical treatment of risk factors clustered in the metabolic syndrome. Indeed, several interventions studies have shown that weight reduction leads to a better cardiovascular risk profile in patients with abdominal adiposity.[32;33]

We acknowledge some limitations in our study. It had a cross-sectional design, which means that we can only make assumptions about possible etiological relationship. Moreover, there were too few women in our sample to enable us to perform separate analyses for men and women, which would have been interesting because men and women have a different fat distribution.[34] Additionally, the study population was comprised of a selected group of patients with symptomatic PAD referred to an academic center, and only patients who wished to participate were included. Additional adjustment for BMI, a quantitative measure, to investigate whether there was an association between localization of fat and CHD was difficult to interpret given the collinearity. Finally, computed tomography has been considered the most accurate and reproducible technique for measuring intra-abdominal fat.[35] We determined intra-abdominal fat by ultrasonography because this method has been proposed as a suitable alternative

technique to accurately measure intra-abdominal fat.[23;36] Some studies have shown that measuring intra-abdominal fat by ultrasonography has low reproducibility,[37] but the method used in this article has been shown to be a good reproducible method to assess the amount of intra-abdominal fat using a strict protocol.[23]

We conclude that, of various measures of adiposity, waist circumference has the strongest association with CHD in patients with PAD. Reduction of abdominal adiposity may diminish the risk of vascular events in patients with PAD.

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The effect of leisure-time physical activity on the presence of metabolic syndrome in patients with manifest arterial disease. The SMART study.

Beate G. Brouwer, Frank L.J. Visseren, Yolanda van der Graaf, on behalf of the SMART Study Group

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Abstract

Background

Physical activity can influence insulin sensitivity and metabolic syndrome independent of weight loss. Therefore, we investigated the independent effect of leisure-time physical activity on the prevalence of metabolic syndrome and insulin resistance in patients with manifest arterial disease and the role of body fat and fat distribution on this relationship.

Methods

Data were collected from the Second Manifestations of ARTerial disease study, an ongoing prospective cohort study of patients with manifest vascular disease or vascular risk factors at the University Medical Center Utrecht. Data of 1097 patients, mean age 58.3 ± 10.4 years, with clinically manifest arterial disease were used. Information on leisure-time physical activity (sporting or other physical exercise) during the past year was collected using a questionnaire. Patients were classified according to the time spent doing leisure-time physical activities: 0 metabolic equivalent (MET)/hours (h) per week (64%), 1.0-14.9 MET/h/wk (16%), and >15.0 MET/h/wk (20%).

Results

The prevalence of metabolic syndrome was markedly lower (20%) in physically active patients (>15 MET/h/wk active) than in physically inactive patients (36%; odds ratio (OR) 0.50, 95% confidence interval (CI) 0.33-0.75) after adjustment for age, sex, BMI and smoking. After adjustment for age, sex, waist circumference and smoking the OR of having metabolic syndrome remained essentially the same (OR 0.59, 95% CI 0.38-0.90). Patients who were active (>15 MET/h/wk active) had a considerable lower risk of insulin resistance (HOMA-IR >2.38) than inactive patients (OR 0.40, 95% CI 0.25-0.64), after adjustment for age, sex, BMI, and smoking.

Conclusion

Patients with manifest arterial disease who are physically active are less likely to have metabolic syndrome and insulin resistance than physically inactive patients even though body weight is comparable between the groups.

Introduction

Obesity is a major lifestyle-related health problem throughout the world,[1] and awareness of the importance of physical activity has increased in the face of the epidemics of sedentary lifestyle, obesity and metabolic syndrome. The metabolic syndrome is a clustering of risk factors closely associated with central obesity, with insulin resistance as an important underlying mechanism.[2] The metabolic syndrome is associated with a 2-to 3-fold increased risk of the development of cardiovascular diseases and with a 3-to 4-fold increased risk of the development of type 2 diabetes mellitus.[3] The prevalence of metabolic syndrome in patients with clinical manifestations of atherosclerosis (coronary heart disease (CHD), cerebrovascular disease (CVD), and peripheral arterial disease (PAD)) ranges between 41% and 58%.[4] In these high-risk patients, the presence of metabolic syndrome is associated with an even higher cardiovascular risk.[5]

Several studies have shown that an increase in physical activity can improve, at least in the relatively short term, insulin sensitivity,[6] with a subsequent decrease in plasma triglyceride levels, increased high-density lipoprotein (HDL) cholesterol levels,[7] and reduced blood pressure.[8] Increased physical activity induces abdominal weight loss and improves weight maintenance,[9;10] and reduces the risk of developing metabolic syndrome[11] and type 2 diabetes.[12-14] There is increasing evidence indicating that the improvement of insulin sensitivity may not totally be explained by the influence of physical activity on body composition. However, even after controlling for traditional risk factors, physical inactivity has still been shown to be an independent risk factor for insulin sensitivity, indicating that physical activity can influence insulin sensitivity even without weight loss.[15]

It is under debate how physical activity influences the insulin signalling transduction pathways in liver, skeletal muscle, and adipose tissue. An exercise-induced increase in insulin sensitivity in muscle is related to increased expression or activity of key signalling proteins and gene expression of glucose transporter 4 (GLUT-4) involved in skeletal muscle glucose metabolism.[16] Exercise beneficially influences the production of cytokines and adipokines, such as high-sensitive C-reactive protein (hs-CRP), interleukin- 6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-10 (IL-10) by adipose tissue irrespective of changes in total body weight, leading to improvement of insulin sensitivity by improving insulin signal transduction after physical activity.[17;18] Moreover, physical activity reduces plasma concentrations of inflammatory markers, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM-1), P-selectin, which are associated

with endothelial dysfunction[19;20] and activate adenosine monophosphate-activated protein kinase (AMPK) in muscle and other tissues, leading to increased fat oxidation and glucose transport.[21]

Physical activity interventions reduce the prevalence of metabolic syndrome,[22] and physical activity is inversely associated with a number of components of the metabolic syndrome in apparently healthy men.[23] Additionally, leisure-time physical activity is associated with the extent of subclinical atherosclerosis.[24] In a cohort of patients with pre-existing ischemia, physical activity was associated with lower CHD mortality.[25;26] Current (inter)national guidelines for the prevention of cardiovascular diseases encourage the use of lifestyle changes such as increasing physical activity, to at least 30 minutes of moderate-intensity physical activity a day,[27;28] and reducing the dietary intake of saturated fat and cholesterol.[3;27;28]

In the present study, we investigated the independent effect of leisure-time physical activity on the prevalence of metabolic syndrome and insulin resistance in patients with manifest arterial disease and the role of body weight and fat distribution on this relationship.

Methods

Study population

This study was part of the Second manifestations of ARTerial disease (SMART) study. The SMART study is an ongoing prospective single-center cohort study of patients with cardiovascular risk factors or manifest arterial disease. Starting in 1996, consecutive patients aged 18 to 80 years, referred to the University Medical Center Utrecht (UMC Utrecht) with manifest arterial disease or a cardiovascular risk factor underwent vascular screening including a questionnaire, blood chemistry, and ultrasonography. Written informed consent was obtained from all participants. The study was approved by the medical ethics committee of the UMC Utrecht and has been described elsewhere.[29]

For the present cross-sectional study, the data of 1301 patients with clinical manifest arterial disease were used. These patients had been newly diagnosed as having coronary CHD, CVD, PAD or abdominal aortic aneurysm (AAA) and participated in the SMART study between January 2000 and December 2005. Patients who reported that they had been diagnosed with type 2 diabetes mellitus in the past or those who were being treated for type 2 diabetes mellitus were excluded (n=204). Finally the data of 1097 patients were analyzed.

Vascular screening

Extensive screening for vascular risk factors was performed on a single day at the UMC Utrecht. Blood samples were collected after an overnight fast. Total cholesterol, triglycerides, HDL-cholesterol, serum glucose, insulin, hs-CRP, and creatinine clearance (Cockroft) were measured. Low-density lipoprotein (LDL) cholesterol was calculated according to Friedewald's formula. Insulin was measured with an immunometric assay (Diagnostic Products Corporation, Los Angeles, USA), and hs-CRP with a quantitative enzyme immunoassay technique (R&D Systems, Minneapolis, USA).

Blood pressure was measured twice on both upper arms with the patient in sitting position using a nonrandom sphygmomanometer, and mean systolic and diastolic blood pressure were calculated. Height and weight were measured without shoes and heavy clothing. Body Mass Index (BMI) was calculated as weight to height squared. Waist circumference was measured halfway between the lower rib and the iliac crest, and hip circumference was measured at the level of the greater trochanter. Ultrasonography of the abdomen was performed to measure intra-abdominal fat and subcutaneous fat. For measurement of intra-abdominal fat, we used the distance between the peritoneum and the lumbar spine, and subcutaneous fat was measured as the distance between the linea alba and the skin. All measurements, including the position of and pressure on the transducer, were standardized.[30] Use of current medication, patient medical history, physical activity, occupational activity, and smoking habits were derived from a questionnaire.[29]

The patients were classified as never, former, and current smokers. Patients who quit smoking during the past year were categorized as current.

Definitions

The metabolic syndrome was defined according to the Adult Treatment Panel III (ATP III) criteria.[3] Subjects with 3 or more of the following criteria met the definition for metabolic syndrome: abdominal obesity (waist circumference >102 cm in men or >88 cm in women), high blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic or use of blood pressure-lowering agents), hypertriglyceridemia (serum triglycerides ≥1.70 mmol/l), low HDL-cholesterol (serum HDL-cholesterol <1.04 mmol/l in men or 1.29 mmol/l in women), high fasting glucose (fasting glucose ≥6.1 mmol/l or use of glucose-lowering agents). If waist circumference was not available (56 patients), we used the BMI as a measure of obesity, with a cut-off point of 30 kg/m^2.[31] Diabetes was defined as self-reported diabetes or a fasting glucose ≥7.0 mmol/l in patients without a history of

diabetes mellitus. Homeostasis model assessment determined insulin resistance (HOMA-IR) was used as quantitative estimate of insulin resistance. The HOMA-IR was calculated with the formula: HOMA-IR = (fasting serum glucose x fasting serum insulin) / 22.5.[32]

Physical activity

At screening, the patients completed a questionnaire about their usual pattern of physical activity (leisure-time physical activity and occupational physical activity) in the past year. Patients were asked how many hours per week they spent on sporting or other physical activities (e.g. jogging, swimming). The time spent on sport activities in hours per week was multiplied by the sport-specific energy expenditure, expressed in metabolic equivalents (METs).[33] The leisure-time physical activity was not a measure of total time spent on physical activity, but was a relative measure of how much energy was expended on physical activity. One MET is equivalent of the energy expenditure of 1-hour rest. We assessed physical activity according to the intensity and amount of exercise (MET hours per week (MET/h/wk)). Accordingly, all patients were classified into one of the following categories: no physical activity (0 MET/h/wk), moderate physical activity (1.0-14.9 MET/h/wk), and vigorous physical activity (>15.0 MET/h/wk).

Current physical activity at work was classified in 5 categories: not occupationally active, sedentary (e.g. driver, administrative officer), standing (e.g. hairdresser, shop assistant), physical work (e.g. nurse, housewife), and heavy manual work (e.g. docker, construction worker, and farmer).

Statistical analysis

Patients were divided into physical activity categories. All inactive patients were considered as one group (0 MET/h/wk), and all active patients were dichotomized into 2 groups: moderate physical active (1.0-14.9 MET/h/wk) and vigorous physical active (>15.0 MET/h/wk).

All values were expressed as means ± standard deviation (SD), medians (interquartile range) or as percentages. Differences across physical activity groups were tested with chi-square (categorical variables), analysis of variance (continuous normal distributed variables) or Kruskal-Wallis (continuous skewed variables). Multivariable logistic regression was performed to quantify the association between leisure-time physical activity and the presence of metabolic syndrome, where metabolic syndrome was taken as dependent variable and physical activity as independent variable. Physical inactivity was considered as the reference. Results are expressed as adjusted odds ratios

(ORs) with 95% confidence intervals (95% CIs). Four models were built. In the first model, the relationship between metabolic syndrome and physical activity was adjusted for age and sex; the second model included age, sex, waist circumference, and smoking; the third model included age, sex, BMI, and smoking; and in the fourth model, additional adjustment of occupational physical activity was performed to assess the independent effect of leisure-time physical activity. Most of the patients were retired, and therefore only a minority was occupationally physical active. The covariates were included as categorical variables, only age, waist circumference and BMI were included as continuous variables. Furthermore, a multivariable logistic regression analysis was used to estimate the relationship between the individual components of metabolic syndrome and physical activity adjusted for age, sex, and occupational activity.

Subsequently, multivariable logistic regression was performed to investigate the association between leisure-time physical activity and insulin resistance (HOMA-IR). The HOMA-IR was dichotomized according to its median. The HOMA-IR data were missing for 464 patients because it was not possible to calculate HOMA-IR for these patients due to the later start of the determination of insulin during the inclusion period. The hs-CRP of 458 patients was missing also due to later determination of hs-CRP during the inclusion period.

All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows 12.01 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

In total, 1097 patients participated in this study (mean age of 58.3 years, SD 10.4) and were predominantly male (75%). Of the patients, 699 (64%) spent 0 MET/h/wk on leisure-time physical activity, 180 (16%) 1.0-14.9 MET/h/wk; and 218 (20%) >15.0 MET/h/wk. In Table 1, the baseline characteristics of the study population are described according to the 3 physical activity levels. Men were more active than women, and the mean age was lower in the physical active group. Patients with AAA were the most inactive: they spent 4.7 ± 10.4 MET/h/wk on leisure-time physical activity compared with 6.7 ± 14.1, 7.3 ± 14.2, and 7.7 ± 14.0 MET/h/wk for patients with PAD, CVD, and CHD, respectively.

Patients who were physically active had lower hs-CRP plasma levels than their inactive counterparts (1.4 (0.5-3.2) mg/l vs 2.0 (1.0-4.6) mg/l). Adiposity was comparable between the physical activity categories, and intra-abdominal fat was lower in the physical active group (Table 1).

Table 1. Baseline characteristics of the study population according to leisure-time physical activity (n=1097)

	Physical activity in MET/h/wk		
Average physical activity (MET/h/wk)	**0 (n=699) 0**	**1.0-14.9 (n=180) 9.1**	**>15.0 (n=218) 30.6**
Male sex (%)	74	73	80
Age (years)[a]	59.2 ± 10.5	56.9 ± 10.1	56.6 ± 10.4
Total cholesterol (mmol/l)[b]	4.9 (4.3-5.7)	4.8 (4.3-5.4)	4.7 (4.0-5.5)
LDL-cholesterol (mmol/l)[b]	2.80 (2.25-3.50)	2.64 (2.21-3.36)	2.65 (2.08-.2.25)
Hs-CRP (mg/l)[b,*]	2.0 (1.0-4.6)	1.6 (0.7-3.1)	1.4 (0.5-3.2)
Creatinine clearance (Cockroft) (ml/min)[a]	78 ± 23	80 ± 23	80 ± 20
BMI (kg/m^2)[a]	26.9 ± 4.1	26.4 ± 3.6	26.5 ± 3.7
Waist-to-hip ratio[a]	0.92 ± 0.08	0.90 ± 0.08	0.89 ± 0.07
Subcutaneous fat (cm)[a]	2.5 ± 1.4	2.4 ± 1.1	2.5 ± 1.2
Intra-abdominal fat (cm)[a]	9.6 ± 2.7	8.8 ± 2.7	8.8 ± 2.4
Smoking status			
Never smoking (%)	15	18	29
History of smoking (%)	26	18	14
Current smoking (%)	59	64	57
Manifest vascular disease[†]			
Coronary heart disease (%)	58	63	58
Cerebrovascular disease (%)	28	27	29
Peripheral arterial disease (%)	21	16	17
Abdominal aortic aneurysm (%)	11	7	7

LDL-cholesterol: low-density lipoprotein cholesterol, hs-CRP: high-sensitive C-reactive protein, BMI: body mass index
[a] mean ± standard deviation or [b] median with interquartile range
[*] data on 458 patients missing
[†] ever or current diagnosis, a single patient can be classified into more than one disease category

Prevalence of components of metabolic syndrome in relation to physical activity

The overall prevalence of metabolic syndrome in this study population was 30% and was similar among men (30%) and women (32%). The prevalence of metabolic syndrome was markedly lower in physically active patients than in physically inactive patients (20% vs. 36%). The prevalence of the individual cardiovascular risk factors according to level of physical activity is shown in Table 2. The prevalence of high fasting glucose, hypertriglyceridemia, low HDL-cholesterol, and abdominal obesity decreased with increasing leisure-time physical activity.

Physical activity and metabolic syndrome

Results from the logistic regression analyses showed that the patients who were >15.0 MET/h/wk physically active had a strikingly lower risk of having metabolic syndrome than the least active patients (OR 0.50, 95% CI 0.33-0.75) after adjustment for age, sex, BMI, and smoking (Table 3). Leisure-time physical activity remained significantly associated with metabolic syndrome after additional adjustment for occupational activity (OR 0.49, 95% CI 0.33-0.75). To determine the effect of body fat and fat distribution on the relation between physical activity and metabolic syndrome, we adjusted in the second model, for waist circumference, and in the third model, for BMI. After additional adjustment for waist circumference the OR of having metabolic syndrome remained essentially the same (OR 0.59, 95% CI 0.38-0.90).
Physical activity was associated with a lower prevalence of individual components of the metabolic syndrome, expect for hypertension (Table 3).

Physical activity and insulin resistance

Patients who were physically active had a lower HOMA-IR than physically inactive patients (1.9 (1.3-2.7) vs. 2.6 (1.7-3.9)). The median HOMA-IR was 2.38. Of the 318 patients with HOMA >2.38, 155 (49%) had metabolic syndrome, and of the 315 patients with HOMA <2.38, 42 (12%) had metabolic syndrome. Patients who were physically active had a lower risk of being insulin-resistant (HOMA-IR >2.38) than those who were physically inactive (OR 0.40, 95% CI 0.25-0.64) after adjustment for age, sex, BMI, and smoking (Table 4). Similarly, after adjustment for age, sex, waist circumference, and smoking, the OR hardly changed (OR 0.49, 95% CI 0.31-0.79).

Table 2. Prevalence of metabolic syndrome and its components in relation to levels of leisure-time physical activity in patients with manifest arterial disease

	Physical activity in MET/h/wk		
	0	**1.0 - 4.9**	**>15.0**
Metabolic syndrome (%)	36	21	20
Fasting serum glucose (mmol/l)[b]	5.7 (5.3-6.2)	5.5 (5.2-6.0)	5.5 (5.1-6.0)
Triglycerides (mmol/l)[b]	1.52 (1.12-2.12)	1.29 (1.02-1.77)	1.26 (0.93-1.84)
HDL-cholesterol (mmol/l)[b]	1.28 (1.04-1.54)	1.34 (1.15-1.60)	1.32 (1.10-1.61)
Waist circumference (cm)[a]	95 ± 12	93 ± 12	93 ± 11
Systolic blood pressure (mmHg)[a]	143 ± 22	142 ± 22	143 ± 21
Diastolic blood pressure (mmHg)[a]	83 ± 12	84 ± 11	84 ± 12
Fasting serum insulin (mlU/l)[b]	10 (7-14)	10 (6-12)	8 (6-11)
HOMA-IR[*,b]	2.6 (1.7-3.9)	2.4 (1.5-3.2)	1.9 (1.3-2.7)
Components of metabolic syndrome			
Abdominal obesity (%)[†]	34	24	21
Hypertension (%)[‡]	96	96	97
Hypertriglyceridemia (%)[§]	42	28	28
Low HDL-cholesterol (%)[‖]	31	21	22
High fasting glucose (%)[#]	32	22	21

HDL-cholesterol: high-density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment determined insulin resistance (fasting serum glucose x fasting serum insulin /22.5)
[a] mean ± standard deviation or [b] median with interquartile range
[*] data on 464 patients are missing
[†] waist circumference >102 cm in men and >88 cm in women or BMI ≥30 kg/m^2
[‡] ≥130 mmHg systolic or 85 mmHg diastolic blood pressure or treated for hypertension
[§] serum triglycerides ≥1.70 mmol/l
[‖] serum HDL-cholesterol <1.04 mmol/l in men and <1.29 mmol/l in women
[#] fasting serum glucose ≥6.1 mmol/l ore treated for diabetes

Table 3. Relation (OR and 95% CI) between leisure-time physical activity and the presence of and components of metabolic syndrome with physical inactive patients as reference group

	Adjusted for	OR (95% CI)	
		1.0-14.9 MET/h/wk	>15.0 MET/h/wk
Presence of metabolic syndrome			
Metabolic syndrome	age and sex	0.48 (0.33-0.71)	0.45 (0.31-0.64)
	age, sex, WC, and smoking	0.55 (0.34-0.87)	0.59 (0.38-0.90)
	age, sex, BMI, and smoking	0.52 (0.34-0.79)	0.50 (0.33-0.75)
	age, sex, BMI, smoking, and occupational activity	0.52 (0.34-0.80)	0.49 (0.33-0.75)
Components of metabolic syndrome			
Abdominal obesity	age and sex	0.64 (0.44-0.93)	0.55 (0.38-0.79)
	age, sex, and occupational activity	0.65 (0.44-0.94)	0.56 (0.39-0.80)
Hypertension	age and sex	1.11 (0.41-3.06)	1.38 (0.51-3.80)
	age, sex, and occupational activity	1.11 (0.41-3.06)	1.33 (0.48-3.65)
Hypertriglyceridemia	age and sex	0.49 (0.34-0.71)	0.47 (0.34-0.71)
	age, sex, and occupational activity	0.49 (0.34-0.70)	0.47 (0.34-0.66
Low HDL-cholesterol	age and sex	0.55 (0.37-0.82)	0.59 (0.41-0.85)
	age, sex, and occupational activity	0.54 (0.36-0.81)	0.58 (0.40-0.83)
High fasting glucose	age and sex	0.63 (0.42-0.95)	0.58 (0.40-0.84)
	age, sex, and occupational activity	0.67 (0.44-1.01)	0.62 (0.42-0.92)

WC: waist circumference, BMI: body mass index

Table 4. Relation (OR and 95% CI) between physical activity and insulin resistance (HOMA-IR >2.38) with physical inactive patients as reference group

Adjusted for	OR (95% CI)	
	1.0-14.9 MET/h/wk	>15.0 MET/h/wk
age and sex	0.75 (0.49-1.16)	0.39 (0.26-0.60)
age, sex, WC, and smoking	1.02 (0.62-1.68)	0.49 (0.31-0.79)
age, sex, BMI, and smoking	0.87 (0.54-1.41)	0.40 (0.25-0.64)
age, sex, BMI, smoking and occupational activity	0.86 (0.53-1.40)	0.40 (0.25-0.63)

HOMA-IR: homeostasis model assessment determined insulin resistance, WC: waist circumference, BMI: body mass index

Discussion

The present study showed that patients with manifest arterial disease who were physically active in their leisure time were more than 50% less likely to have metabolic syndrome than inactive patients, even after adjustment for important cardiovascular risk factors. Furthermore, the prevalence of metabolic syndrome was lower in the physically active patients, although body weight was comparable between the different physical activity groups. Physical activity was also associated with a lower prevalence of the individual components of metabolic syndrome, except for hypertension. In addition, leisure-time physical activity was inversely associated with insulin resistance (OR 0.40, 95% CI 0.25-0.63).

Low physical activity has been related to insulin resistance independent of adiposity and fat distribution. Increased regular exercise has been shown to improve insulin resistance without concomitant changes in body weight or body composition in obese men.[15] Whether or not higher levels of physical activity may play a role in preventing metabolic syndrome, which is often induced by central obesity, is shown in this study. Although physical activity improves insulin sensitivity as a result of weight loss,[34;35] little is known about the direct effect of physical activity on insulin resistance. Physical activity-induced improvements in glucose homeostasis may be caused by up-regulation of the expression or activity of GLUT-4,[16] and the exercise-induced increase in insulin-mediated glucose transport appears to be associated with enhanced signal transduction at the

level of insulin receptor substrate (IRS) protein and phosphatidylinositol 3 (PI3) kinase.[36] Two longitudinal studies showed that regular training induces a reduction in hs-CRP level[37;38] and indicate that physical activity as such may suppress systemic low-grade inflammation. In the present study, levels of hs-CRP were lower in the physically active patients than in the inactive patients with a similar weight and fat distribution. The exercise-induced decrease in plasma hs-CRP concentrations has been shown not to be mediated by changes in body weight.[39]

Metabolic syndrome may improve as a result of the favourable effect of physical activity on insulin resistance. Cross-sectional,[3;23;40;41] and prospective studies[11;42] in healthy individuals have shown that this effect of physical activity on the metabolic syndrome is sex-dependent,[41] probably because of hormonal differences and different patterns of fat distribution in men and women. In the present study, we could not perform separate analyses for men and women because of relatively small number of women in our study population.

The results of the present study support the NCEP ATP III recommendations[3] promoting lifestyle changes (including physical activity) in individuals with multiple risk factors. Increasing physical activity may be an important treatment option for patients with metabolic syndrome and insulin resistance having already clinically manifest arterial disease.

This approach is likely to reduce the risk of new cardiovascular events as well as the development of type 2 diabetes mellitus.

Some limitations of this study must be mentioned. It had a cross-sectional design, which means that we can only make assumptions about etiological relationship. Although we obtained information on leisure-time physical activity, the fact that questionnaires were self-administered and that we measured physical activity only at enrolment into the study might have caused misclassification of physical activity. Moreover, it may be important to obtain information on all types of activity over the person's lifetime because physical activity during different lifetime periods may influence insulin resistance later in life. It is possible that the patients who reported low levels of physical activity may have reduced their activity because they had cardiovascular disease. Although, it is not feasible to obtain physical activity of person's lifetime, physical activity of person's past year is reliable. Misclassification, particularly overreporting of physical activity and changes in the activity during the disease period, probably leads to an underestimation of the association between physical activity and the outcome, especially in patients with CVD and PAD.

In conclusion, in patients with manifest arterial disease, more leisure-time physical activity is associated with a lower risk of having metabolic syndrome and insulin resistance irrespective of total body fat. Regular physical activity is likely to improve components of the metabolic syndrome and insulin resistance in patients with clinical manifest vascular disease leading to a lower risk of developing (new) cardiovascular events and type 2 diabetes mellitus.

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4

Leisure-time physical activity and risk of type 2 diabetes in patients with established vascular disease or poorly controlled vascular risk factors

Beate G. Brouwer, Yolanda van der Graaf, Sabita S. Soedamah-Muthu, Annemarie M.J. Wassink, Frank L.J. Visseren, on behalf of the SMART study group

Submitted

Abstract

Objective

To investigate the effect of leisure-time physical inactivity on the incidence of type 2 diabetes in patients with various manifestations of arterial disease, or poorly controlled risk factors.

Methods

Data were used of 3940 patients from the Second Manifestations of ARTerial disease (SMART) study, a prospective cohort. Patients had manifest arterial disease, hypertension or hyperlipidemia and were aged 55.2±12.2 years. Patients with diabetes at baseline were excluded from analyses. Leisure-time physical activity was measured by a questionnaire and metabolic equivalent (MET) hours per week (h/wk) were calculated. Incident type 2 diabetes was evaluated by a specific diabetes questionnaire sent to all patients.

Results

Most patients (65%) were physically inactive (<2.5 MET·h/wk) and 35% were physically active (≥2.5 MET·h/wk). During a mean follow-up of 4.7 years, 194 (5%) incident cases of type 2 diabetes occurred. Physically inactive patients had a higher incidence of diabetes (hazard ratio(HR) 1.6, 95% confidence interval (CI) 1.2-2.2). Additional adjustment for BMI partly explained the relation (HR 1.4, 95% CI 1.0-1.9). Patients who were physically inactive and obese (BMI ≥30 kg/m^2) were at the highest risk for developing type 2 diabetes (HR 5.6, 95% CI 3.6-8.6) in comparison with patients who are physically active and not obese. The relative excess risk due to interaction of physical activity and obesity on an additive scale was 1.0 (95% CI -1.5-3.5).

Conclusion

Leisure-time physical inactivity is independently associated with an increased risk of type 2 diabetes in patients with manifest arterial disease, or poorly controlled risk factors. The combined effect of physical inactivity and obesity poses an even greater risk for development of type 2 diabetes.

Introduction

Diabetes is a major independent risk factor for coronary heart disease (CHD)[1] and is considered a CHD-risk equivalent in risk assessment and management guidelines.[2] Patients with clinical manifest vascular disease are at high risk for developing a new vascular event. Moreover, patients with clinical manifest vascular disease and diabetes mellitus have an even higher risk of cardiovascular morbidity and mortality.[3] Optimal treatment of vascular risk factors such as hypertension, hyperlipidemia, smoking and hyperglycemia reduces cardiovascular morbidity and mortality.[4-6]

Physical inactivity and obesity are both risk factors associated with an increased risk for incident type 2 diabetes and cardiovascular disease.[7] Physical activity improves insulin sensitivity,[8] glucose tolerance,[9] and lipid profiles,[10] decreases blood pressure,[11] body weight and visceral fat accumulation,[12] and has a protective effect on the development of metabolic syndrome.[13] However, even after controlling for traditional risk factors, physical inactivity has still been shown to be an independent risk factor for insulin sensitivity, and it was demonstrated that physical activity can influence insulin sensitivity even without weight loss.[14] Physical activity could potentially play a role in insulin resistance and skeletal glucose metabolism by increased expression of glucose transporter 4 (GLUT-4) and beneficially influencing the production of inflammatory cytokines and adipokines, such as high-sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and interleukin-10 (IL-10) irrespective of weight loss.[15;16] In addition, leisure-time physical activity is associated with a lower prevalence of subclinical atherosclerosis. In a cohort of patients with coronary artery disease, physical activity was associated with a lower cardiovascular mortality rate.[17]

It is well known that physical activity reduces the risk of developing diabetes in healthy populations[18] and in patients with impaired glucose tolerance[19] but whether physical activity reduces the onset of diabetes in patients at high risk for developing (new) vascular diseases is not known.

Therefore, we investigated the independent effect of physical inactivity on incidence of type 2 diabetes in patients with various clinical manifestations of vascular diseases, hypertension or hyperlipidemia. Second, we considered the combined effect of physical inactivity and obesity on the incidence of type 2 diabetes.

Methods

Study population

Data were obtained from patients enrolled in the SMART (Second Manifestation of ARTerial disease) study, an ongoing prospective single-centre cohort study of patients with manifest arterial disease or poorly controlled cardiovascular risk factors. Starting in 1996, consecutive patients aged 18-79 years, referred to the University Medical Center (UMC) Utrecht with manifest arterial disease or a cardiovascular risk factor, were screened non-invasively for manifestations of arterial disease and risk factors other than the qualifying diagnosis. The rationale and design of the SMART study have been described in detail previously.[20] The Ethics Committee of the UMC Utrecht approved the study and written informed consent was obtained from all patients.

In the present study, patients with coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease (PAD), abdominal aortic aneurysm (AAA), or hypertension or hyperlipidemia included in the SMART study between January 1996 and June 2006 were considered (n=5695). Patients who reported that they had been diagnosed with diabetes mellitus in the past, those who were treated for diabetes mellitus and those with a glucose ≥7.0 mmol/l and a diagnosis of diabetes one year after baseline (n=1065), patients who died (n=529), and were lost to follow-up (n=161) before June 2006 were excluded (see follow-up). The final study population for analysis therefore consisted of 3940 patients.

Physical activity

At screening patients completed a questionnaire about their usual pattern of leisure-time physical activity in the past year. Patients were asked how many hours per week they spent on sporting or other physical activities. In order to quantify the intensity of each activity, a specific metabolic equivalent (MET) value was assigned to each reported activity derived from the 'Compendium of Physical Activity'.[21] Men and women were assigned the same MET value for a given subjective intensity of a given physical activity. The time spent on sport activities in hours per week was multiplied by the computed sport-specific energy expenditure, expressed in MET hours per week (MET·h/wk). One MET represents the energy expenditure for an individual at rest, whereas a 10-MET activity requires 10 times the resting energy expenditure (brisk walking is estimated to be about 3.5-4.0 METs). For example, 3.5 hours per week brisk walking (3.8 MET) is 13.3 MET·h/wk. We assessed physical activity according to the intensity and amount of exercise and classified the patients into one of the following categories: physical inactive patients (<2.5 MET·h/wk), and physical active patients (≥2.5 MET·h/wk).

Risk factors

Measurement of vascular risk factors was conducted on a single day at the UMC Utrecht. Blood samples were collected after an overnight fast. Total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and serum glucose were measured and low-density lipoprotein (LDL) cholesterol was calculated with Friedewald's formula.

Blood pressure was measured twice in sitting position on both upper arms with a non-randomized sphygmomanometer and mean systolic and diastolic blood pressures were calculated. Height and weight were measured without shoes and heavy clothing. Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in metres. Waist circumference was measured halfway between the lower rib and the iliac crest and hip circumference was measured at the level of the trochanter. Information on medical history, use of current medication, current and past cigarette smoking behaviour and alcohol consumption were obtained by questionnaire.[20] The patients were classified as never, former and current smokers. Patients who quit smoking during the past year were categorized as current. Alcohol consumption was classified as 0, 1-10, 11-30, or ≥31 glasses per week.

Follow-up

The main outcome of interest for this study was new onset type 2 diabetes. In order to assess the presence of diabetes, all 3940 patients without baseline diabetes who were still being followed on the 1st of June 2006 were asked to answer two questions on diabetes ("do you suffer from diabetes?" and "are you currently being treated for diabetes?") Those who answered "yes" to one of these questions were asked to complete an additional postal questionnaire with more detailed questions on their diabetes, including the date since when they suffered from diabetes, how they initially had been treated (oral medication or insulin), current treatment and family history of diabetes. If the answers were incomplete or unclear, patients were phoned for explanation. If necessary their general practitioner was consulted for supplementary information. Based on this information, all diabetes cases were audited by two physicians from the SMART study. Diabetes was defined as a positive answer to either one of the questions (self-reported diabetes or use of glucose-lowering agents) and was classified on the basis of the extensive questionnaire (type 1, type 2 diabetes or other). Duration of follow-up (years) was defined as the period between study inclusion and new onset of diabetes, or the preselected closing date of March 1, 2007.

Definitions

The metabolic syndrome was defined according to the Adult Treatment Panel III (ATPIII) criteria.[2] Subjects with 3 or more of the following criteria met the definition for metabolic syndrome: abdominal obesity (waist circumference >102 cm in men or >88 cm in women), high blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic or use of blood pressure lowering agents), hypertriglyceridemia (≥1.70 mmol/l), low HDL-cholesterol (<1.04 mmol/l in men or <1.29 mmol/l in women), high fasting glucose (≥6.1 mmol/l or use of glucose lowering agents). If waist circumference was not available (n=639), BMI was used as a measure of obesity, with a cut-off point of 30 kg/m^2.[22]

Diabetes at baseline was defined as either a referral diagnosis for diabetes, self-reported diabetes (use of glucose-lowering agents), known history of diabetes mellitus at the time of enrolment or fasting glucose levels ≥7.0 mmol/l combined with the physician diagnosis of diabetes within one year.

Data analysis

All values were expressed as means ± standard deviation (SD), medians (25th – 75th percentile) or as percentages. Cox proportional hazard analysis was used to estimate the independent effect of physical activity on the incidence of diabetes mellitus. Results are expressed as hazard ratios (HR) with 95% confidence intervals (95% CI). In the first model, in which we estimated the effect of leisure-time physical activity on incidence of diabetes, we adjusted for age and sex, and in the second model, additionally adjustment was performed for other lifestyle risk factors: alcohol consumption (0, 1-10, 11-30, ≥31 drinks per week) and smoking (never, former, current smoking). To determine whether body fat confounded the relation between leisure-time physical activity and the incidence of type 2 diabetes, we additionally adjusted for BMI (continuously). To examine if the presence of metabolic syndrome at baseline affected this relationship, we built a model in which we also adjusted for the presence of metabolic syndrome. In the final model, we adjusted for location of vascular disease, to investigate whether location of vascular disease influenced the relation between physical activity and the incidence of type 2 diabetes.

To assess whether leisure-time physical inactivity according to international guidelines[23] (adults not engaging in at least 30 minutes of moderate-intensity physical activity five days per week) still showed an increased risk of the incidence of type 2 diabetes, we set the cut-off point at 10.5 MET·h/wk. Physically active was defined as ≥10.5 MET·h/wk.

Finally, the joint effects of physical activity and obesity on the incidence of type 2 diabetes were measured on both multiplicative and additive scales. Patients were categorized according to physical activity (physically inactive (<2.5 MET·h/wk) and active group (≥2.5 MET·h/wk)) and BMI (BMI <30 and ≥30 kg/m^2): active normal-weighted, active obese, inactive normal-weight and inactive obese. The active normal-weight patients served as the reference group. The interaction term calculated by multiplying the indicators for 2 risk factors were added into the main effect model, and their significance was tested by -2 log likelihood chi-square between models with and without interaction term of physical activity and obesity measures. Interaction estimated on an additive scale was calculated with the formula for the relative excess risk due to interaction (RERI = RR(AB) – RR(A) – RR(B) + 1)[24] and a 95% confidence limit was calculated.[25]

Results

Study population

In total, 3940 patients were included in this study (mean age of 55.2 ± 12.2 year; predominantly male (68%)). Most patients were physically inactive, namely 2550 (65%) compared to 35% active patients. Baseline characteristics of the study population according to physical activity are presented in Table 1. Patients were on average overweight (mean BMI 26.6 kg/m^2), and 16% was obese (BMI ≥30 kg/m^2). Mean BMI was comparable in the two physical activity groups but waist circumference was lower in the physically active group than in the inactive group (age and sex adjusted mean 92±12 vs. 94±12 cm, respectively). Patients who were active smoked less often and drank more often moderate amounts of alcohol (1-10 drinks per week).

The overall prevalence of metabolic syndrome in this population was 32% and was comparable among men and women, and was most prevalent in the inactive group (35%). The mean fasting glucose concentrations, triglycerides, waist circumference and systolic blood pressure were lower in physically active patients. HDL-cholesterol was higher in the physically active group.

Leisure-time physical activity and incidence of diabetes mellitus

The mean follow-up time was 4.7 years (range 0.03 – 10.5). In total, 194 incident cases of type 2 diabetes were registered between 1996 and 2006. Physically inactive patients had a higher risk of incident type 2 diabetes with age- and sex-adjusted HR 1.63, 95% CI 1.17-2.28 compared with physically active patients (table 2). Additional adjustment for smoking, and alcohol consumption did not change the hazard ratio. Additional

Table 1. Baseline characteristics of study population according to leisure-time physical activity at baseline (n=3940)

	Physical activity in MET·hours/wk	
	Active (≥2.5 MET·h/wk) (n=1390)	**Inactive (<2.5 MET·h/wk) (n=2550)**
Median physical activity (MET·h/wk)†	**14 (8 - 24)**	**0**
Male sex (%)	67	68
Age (years)*	53.4 ± 12.5	56.3 ± 12.0
Cholesterol (mmol/l)†	5.2 (4.4 - 6.2)	5.4 (4.5 - 6.2)
LDL-cholesterol (mmol/l)†	3.1 (2.4 - 4.0)	3.2 (2.5 - 4.1)
BMI (kg/m^2)*	26.2 ± 3.7	26.8 ± 4.2
Obesity (BMI ≥30 kg/m^2) (%)	13	17
Smoking status		
never smoking (%)	29	22
former smoking (%)	51	47
current smoking (%)	20	32
Alcohol consumption		
abstainer (%)	15	22
1-10 drinks per week (%)	57	49
11-30 drinks per week (%)	27	27
≥31 drinks per week (%)	2	3
Medication use		
Lipid-lowering agents (%)	47	46
Blood pressure lowering agents (%)	57	59
Antiplatelet agents (%)	51	54
Metabolic syndrome		
Metabolic syndrome (%)	26	35
Fasting serum glucose (mmol/l)†	5.5 (5.1 - 5.9)	5.6 (5.2 - 6.0)
Triglycerides (mmol/l)†	1.4 (1.0 - 2.0)	1.6 (1.1 - 2.3)
HDL-cholesterol (mmol/l)†	1.27 (1.02 - 1.56)	1.26 (0.97 - 1.46)
Waist circumference (cm)*	91 ± 11	94 ± 12
Systolic blood pressure (mmHg)*	141 ± 21	143 ± 22
Diastolic blood pressure (mmHg)*	84 ± 12	84 ± 13

LDL-cholesterol: low density lipoprotein cholesterol, HDL: high density lipoprotein cholesterol, BMI: body mass index
* mean ± standard deviations or †median (25th percentile - 75th percentile) or unless indicated otherwise

Table 2. Hazard ratios for physical activity and the occurrence of type 2 diabetes in patients with manifest arterial disease or risk factor

	Physical activity	
	Active (≥2.5 MET·h/wk) (n=1390)	**Inactive (<2.5 MET·h/wk) (n=2550)**
Incidence of diabetes (n=194)	46	148
Model I	1.00	1.63 (1.17 - 2.28)
Model II	1.00	1.57 (1.12 - 2.22)
Model III	1.00	1.37 (0.97 - 1.93)
Model IV	1.00	1.39 (0.96 - 1.94)

Model I: adjusted for age and sex
Model II: model I, additionally adjusted for smoking and alcohol consumption
Model III: model II, additionally adjusted for BMI
Model IV: model III, additionally adjusted for location of vascular disease (coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm)

adjustment for BMI revealed that BMI partly explained the association between physical activity and risk of diabetes because the HR decreased (HR 1.37, 95% CI 0.97-1.93). Adjustment for the presence of metabolic syndrome did not change the HR (HR 1.37, 95% CI 0.98-1.93). Furthermore, additional adjustment of location of vascular disease did not modify the effect estimate.

Changing the cut-off point for MET-hours per week higher or lower did not change the overall results. Leisure-time physical inactivity (<10.5 MET·h/wk) according to international guidelines still showed an increased risk of the onset of type 2 diabetes (age-and sex adjusted HR 1.81, 95% CI 1.19-2.56). After additional adjusting for BMI, the HR decreased (HR 1.62, 95% CI 1.01-2.26).

Joint effect of BMI and physical activity on incidence of diabetes mellitus

Table 3 shows the combined effect of physical activity and BMI on the incidence of type 2 diabetes. High risk patients who are physical inactive and obese had the highest risk for type 2 diabetes (HR 5.55, 95% CI 3.57-8.63) in comparison with patients who are physical active and have a BMI <30 kg/m^2. Inactive patients with a BMI <30 kg/m^2 had a HR for diabetes of 1.6 compared to active patients with a BMI <30 kg/ m^2. Additional

adjustment for smoking and alcohol consumption in the model did not essentially alter the strengths of the associations. The joint effects for physical activity and BMI were described well by a non-interaction multiplicative model (chi-square likelihood ratio test: 2.276; p >0.05).

The excess risk of type 2 diabetes that could be attributed to the interacting effect on an additive scale of BMI ≥30 kg/m^2 and physical inactivity was 5.6 – 4.0 – 1.6 + 1 = 1.0 (95% CI -1.52 to 3.52).

Discussion

In this prospective cohort study, physical inactivity was independently associated with an increased risk of type 2 diabetes in high risk patients. The prevalence of metabolic syndrome was lower in physically active patients. Obesity partly explained the relation between physical inactivity and incidence of type 2 diabetes. Physical inactivity and obesity may interact to increase the risk of diabetes on an additive scale, indicating that the combination of the two risk factors has a greater effect than the sum of the two separate conditions.

It has been shown that physical activity is one of the most important modifiable factors in the prevention of type 2 diabetes, because physical training, even in absence of weight loss, is associated with an increase in insulin sensitivity and improvement in glucose intolerance.[9;18] It has been suggested that it is acceptable, from a health risk standpoint, to be overweight as long as a patient is 'fit'.[26;27] In healthy persons it has been shown that fitness level did not override body fatness.[28] Our data indicate that the risk of diabetes is the highest in inactive and obese patients. Presumably, at any given BMI, it is better to be active than inactive. Although physical activity has multiple beneficial effects that can improve insulin and glucose delivery to muscle,[29] it may not fully eliminate the adverse effects of obesity in high risk patients.[30] Similarly, physical activity decreased the risk for type 2 diabetes within the BMI ≥30 category, although the risk was still 6-fold among physically active obese versus physically active normal-weighted patients in the present study. There may be an interaction on an additive scale between physical inactivity and obesity. The 95% CI of RERI included 0, but statistical evaluation of interaction is not well established. Some consider every departure from a RERI of 0 as interaction, and the method we used is conservative.[31] Moreover, there are studies in healthy persons that showed a combined effect of physical inactivity and obesity but the magnitude of risk caused by obesity is much greater than that of physical inactivity.[32;33]

Table 3. Hazard ratios for the joint effect of physical activity and BMI on the incidence of type 2 diabetes (n=3940)

	Physical activity category			
	Active (≥2.5 MET·h/wk)		Inactive (<2.5 MET·h/wk)	
	BMI <30	BMI ≥30	BMI <30	BMI ≥30
Total (n (%))	1205 (31)	186 (5)	2105 (53)	444 (11)
Incidence type 2 diabetes (n (%))	31 (3)	15 (8)	93 (4)	55 (12)
Model I	1.00	3.98 (2.14 - 7.40)	1.57 (1.04 - 2.36)	5.55 (3.57 - 8.63)
Model II	1.00	4.08 (2.18 - 7.62)	1.51 (0.99 - 2.30)	5.49 (3.50 - 8.61)

Model I: adjusted for age and sex
Model II: additionally adjusted for smoking and alcohol consumption

It is under debate how physical activity influences the insulin transduction pathways in liver, skeletal muscle, and adipose tissue. First, prior studies have demonstrated favourable effects of physical activity on traditional risk factors.[9-11] Physical activity has also an direct effect on glycemic control,[34] and insulin sensitivity.[14] Physical activity has a positive effect on the cellular expression of GLUT-4 involved in skeletal muscle glucose metabolism.[16] Physical activity beneficial influences the production of cytokines and adipokines, such as TNF-α, CRP, IL-6, IL-10 by adipose tissue, irrespective of changes in total body weight, leading to improvement of insulin sensitivity by improving signal transduction.[15;35] Moreover, physical activity reduces plasma concentrations of inflammatory markers which are associated with endothelial dysfunction.[36] Physical activity is associated with a lower presence of metabolic syndrome,[37] considered to be a pre-diabetic state. Although physical activity has direct beneficial effects on insulin sensitivity and improved glucose metabolism, it may not fully reverse the effects of obesity.[30] Physical activity and with weight loss are 2 separate goals with combined effects on insulin sensitivity.

This study has several limitations that need to be considered. Some underreporting of the incidence of diabetes may have occurred because diabetes was self-reported. Information on leisure-time physical activity was also obtained by self-report and we measured physical activity only at enrolment into the study, so it is not known whether

patients sustained this level of physical activity during the follow up. It may be important to obtain information on all types of activity over a person's lifetime because physical activity at different times of life may influence the risk of diabetes. Although, the effect of physical activity in decreasing insulin resistance is likely to last only a few days.[38]

In conclusion, the present study shows that physical inactivity is associated with an increased incidence of type 2 diabetes in patients with vascular disease or poorly controlled risk factors. The benefit of physical activity was present at any level of BMI.

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Leisure-time physical activity, metabolic syndrome, and the risk of new vascular events in patients with established vascular disease

Beate G. Brouwer, Frank L.J. Visseren, Pieter A. Doevendans, Frans L. Moll, Yolanda van der Graaf, for the SMART Study Group

Submitted

Abstract

Objective

To investigate whether leisure-time physical activity affects the occurrence of new vascular events in patients with manifest arterial disease and whether metabolic syndrome, body fat and fat distribution modify this relationship.

Methods

This prospective study involved 3875 patients with manifest arterial disease enrolled in the Second Manifestations of ARTerial (SMART) study. Leisure-time physical activity was measured by questionnaire. The outcomes of interest were all-cause mortality, a composite of first recurrence of vascular events and organ-specific endpoints (coronary ischemic events plus coronary interventions, stroke plus carotid interventions, and lower-limb vascular interventions).

Results

During follow-up (3.9±2.6 years), 12% of the patients had new vascular events. The risk of all-cause mortality was lowest in physically active patients. Compared with inactive patients, the hazard ratios (HR) of a recurrent vascular event were 0.70 (95% confidence interval (CI) 0.52-0.84 and 0.88 (95% CI 0.65-1.18) in moderately and vigorously active patients, respectively. The risk of ischemic stroke and carotid interventions and lower-limb vascular interventions was lower in moderately (HR 0.71, 95% CI 0.45-1.12 and 0.55, 95% CI 0.38-0.81, respectively) and vigorously physically active patients (HR 0.54, 95% CI 0.30-0.95 and 0.52, 95% CI 0.33-0.81, respectively) than in inactive patients. Metabolic syndrome, body fat, and fat distribution did not modify the relationships between physical activity and outcomes.

Conclusion

Moderate and vigorous leisure-time physical activity are associated with a lower risk of vascular events, vascular death, and all-cause mortality in patients with manifest arterial disease. Physical activity is also related to a lower risk of ischemic stroke, carotid interventions, and vascular interventions of the lower extremities. The presence of metabolic syndrome does not modify this relationship.

Introduction

All-cause mortality and mortality from cardiovascular disease (CVD) is higher in persons with metabolic syndrome and in patients with established CVD than in persons without metabolic syndrome and CVD.[1] The prevalence of metabolic syndrome in patients with clinical manifestations of arterial disease ranges between 41% and 58%.[2] Moreover, in these high-risk patients, the presence of metabolic syndrome is associated with an even higher risk of CVD.[3] Physical activity decreases the risk of cardiovascular events and extends the life expectancy of healthy men and women.[4-7] It has been postulated that the beneficial influence of physical activity on cardiovascular events is due to a decrease in insulin resistance.[8] Regular physical activity results in lower blood pressure,[9] lower plasma cholesterol,[10] better endothelial dysfunction,[11] less inflammation, and reduced coagulation.[12] International guidelines recommend that all adults engage in at least 30 minutes of moderate-intensity physical activity at least 5 days a week to prevent chronic diseases, including type 2 diabetes and CVD.[13] While insulin resistance has several causes, including physical inactivity, it is conceivable that physical activity influences the occurrence of metabolic syndrome and may lead to a decreased risk of new vascular events. There is evidence from meta-analyses of cardiac rehabilitation under supervision that regular physical activity reduces cardiac and total mortality in patients with diagnosed coronary heart disease.[14;15] However, exercise was part of a comprehensive rehabilitation program. Further, among patients with peripheral arterial disease, higher levels of physical activity during daily life were associated with lower mortality and cardiovascular events.[16] However, if the relationship between leisure-time physical activity and recurrence of vascular events at different sites is influenced by metabolic syndrome, body fat or fat distribution is unknown.

In the present prospective study, we investigated whether physical activity is related with the occurrence of new vascular events in patients with clinically manifest arterial diseases and whether this relationship is modified by metabolic syndrome, body fat, and fat distribution.

Methods

Study population

Data were obtained from patients enrolled in the SMART (Second Manifestation of ARTerial disease) study. The SMART study is an ongoing prospective single-center cohort study of patients with manifest arterial disease. Starting in 1996, consecutive patients aged 18-79 years, referred to the University Medical Center Utrecht (UMC Utrecht) with

manifest arterial disease or a cardiovascular risk factor underwent a vascular screening including a questionnaire, blood chemistry, and ultrasonography of the abdomen. Written informed consent was obtained from all patients. The medical ethics committee of the UMC Utrecht study approved the study. The rationale and design of the SMART study have been described in detail previously.[17]

For the present study, the data of 3875 consecutive patients with symptomatic arterial disease (coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease (PAD) or abdominal aortic aneurysm (AAA)) who were included in SMART between September 1996 and March 2006 were used.

Physical activity

At screening, patients completed a questionnaire about their usual pattern of physical activity (leisure-time physical activity) in the past year. Patients were asked how many hours per week they spent on sporting or other physical activities. In order to quantify the intensity of each activity, a specific metabolic equivalent (MET) value was assigned to each reported activity derived from the 'Compendium of Physical Activity'.[18] The time spent on sport activities in hours per week was multiplied by the computed sport-specific energy expenditure, expressed in MET hours per week (MET·h/wk). One MET represents the energy expenditure for an individual at rest, whereas a 10-MET activity requires 10 times the resting energy expenditure (brisk walking is estimated to be about 3.5-4.0 METs). We assessed physical activity according to the intensity and amount of exercise (MET hours per week (MET·h/wk)) and classified the patients into one of the following categories: no physical activity (0 MET·h/wk), moderate physical activity (1.0–14.9 MET·h/wk) and vigorous physical activity (≥15.0 MET·h/wk). The median is 15.0 MET·h/wk, which is crudely equivalent to a brisk walk (3.8 MET) for 30 minutes every day per week. Moving the cut-off point a few MET-hours per week higher or lower did not change the overall interpretation of the results.

Risk factors

Vascular risk factors were measured on a single day at the UMC Utrecht. Blood samples were collected after an overnight fast. Total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, serum glucose, insulin, and high-sensitive C-reactive protein (hs-CRP) were measured and low-density lipoprotein (LDL) cholesterol was calculated with Friedewald's formula. Insulin was measured with an immunometric assay (Diagnostic Products Corporation, Los Angeles, USA) and hs-CRP with a quantitative enzyme immunoassay technique (R&D Ayatems, USA).

Blood pressure was measured twice in sitting position on both upper arms with a non-randomized sphygmomanometer and mean systolic and diastolic blood pressures were calculated. Height and weight were measured without shoes and heavy clothing. Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured halfway between the lower rib and the iliac crest and hip circumference was measured at the level of the greater trochanter. Ultrasonography of the abdomen was performed to measure intra-abdominal- and subcutaneous fat. Intra-abdominal fat was measured as the distance between the peritoneum and the lumbar spine, and subcutaneous fat as the distance between the linea alba and the skin. All measurements, including the position of and pressure on the transducer, were standardized.[19] Information on medical history, use of current medication, and current and past cigarette smoking behavior were obtained by questionnaire.[17] The patients were classified as never, former, and current smokers. Patients who quit smoking during the past year were categorized as current smokers.

Follow-up

Patients were asked to complete biannually a questionnaire on hospitalizations and outpatient clinic visits. The outcomes of interest for this study were all-cause mortality, a composite of vascular death and first recurrence of ischemic stroke, or myocardial infarction (all vascular events), and organ-specific endpoints. For the latter we combined coronary ischemic events and coronary interventions, stroke and carotid interventions, and lower-limb vascular interventions. Definitions of events and interventions are given in Table 1.[17] If a possible event was reported by the patient or relatives of the patients, the hospital discharge letter and the results of relevant laboratory and radiology examinations were obtained. Three members of the SMART study Outcome Event Committee, which consisted of physicians from different departments, independently audited all available information to establish the occurrence of the event of interest. If there was disagreement, consensus was reached by consulting other members of the Outcome Event Committee.

Follow-up duration (years) was defined as the period between study inclusion and first recurrence of cardiovascular event, date of loss to follow-up, date of death not due to cardiovascular causes or the pre-selected date of March 1, 2006. Sixty five of the 3875 participants (1.7%) were lost to follow-up due to emigration or discontinuation of the study.

Table 1. Definitions of fatal/non-fatal events

Vascular event	Vascular death (as defined below) Ischemic stroke (as defined below) Ischemic coronary event (as defined below) Intracerebral hemorrhage: relevant clinical features as in ischemic stroke , accompanied by a hemorrhage on a CT-scan Rupture of a abdominal aortic aneurysm confirmed by ultrasound, CT scan or laparotomy
Vascular death	Sudden death Death from ischemic stroke Death from intracerebral hemorrhage (hemorrhage on CT scan) Death from stroke of unspecified type Death from congestive heart failure Death from myocardial infarction Death from rupture of abdominal aortic aneurysm Vascular death from other cause, such as sepsis following stent placement
All-cause mortality	Death from any cause (both vascular and non-vascular causes)
Ischemic stroke	Definite: relevant clinical features that have caused an increase in impairment of at least one grade on the modified Rankin scale, accompanied by a fresh ischemic infarction on a repeat CT-scan Probable: clinical features that have caused an increase in impairment of at least one grade on the modified Rankin scale; without a fresh ischemic infarction on a repeat brain-scan
Coronary ischemic event	Sudden death: unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence Fatal or non-fatal 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 ECG 3. CK elevation of at least two times the normal value of CK and a MB-fraction >5% of the total CK
Coronary interventions	Percutaneous transluminal coronary angioplasty Coronary artery bypass grafting
Carotid interventions	Carotid endarterectomy Percutaneous transluminal angioplasty of carotid artery
Vascular interventions of low extremities	Amputation of low extremities Percutaneous transluminal angioplasty of iliaca or arteries of lower extremities

CT: computer tomography, ECG: electrocardiogram, CK: creatinine kinase, MB: myocardial band

Definitions

Metabolic syndrome was defined according to the Adult Treatment Panel III (ATPIII) criteria.[20] Subjects with three or more of the following criteria met the definition for metabolic syndrome: abdominal obesity (waist circumference >102 cm in men or >88 cm in women), high blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic or use of blood pressure lowering agents), hypertriglyceridemia (≥1.70 mmol/l), low HDL-cholesterol (<1.04 mmol/l in men or <1.29 mmol/l in women), high fasting glucose (≥6.1 mmol/l or use of glucose lowering agents). If waist circumference was not available, BMI was used as a measure of obesity, with a cut-off point of 30 kg/m^2 [21]. Diabetes was defined as self-reported diabetes, use of glucose-lowering agents or glucose ≥7.0 mmol/l. Homeostasis model assessment determined insulin resistance (HOMA-IR) was used as a quantitative estimate of insulin resistance. HOMA-IR was calculated with the formula: HOMA-IR=(fasting serum glucose x fasting serum insulin)/22.5.[22]

Data analysis

Patients were classified into physical activity categories. All inactive patients were considered as one group (0 MET/h/wk) and all active patients were dichotomized into two groups based on the median score, namely moderately physically active (1.0-14.9 MET·h/wk) and vigorously physically active (≥15.0 MET·h/wk). Baseline characteristics were classified by the three categories of leisure-time physical activity. Cox proportional hazard analysis was used to estimate the relation between different levels of physical activity and the different future events. Results are expressed as hazard ratios (HR) with 95% confidence intervals (95% CI). If a patient experienced more than one recurrent event, the first was used in the analysis.

In the first model, in which we estimated the relation between leisure-time physical activity and all-cause mortality, vascular death, and vascular events, we adjusted for age and sex. To determine whether the presence of metabolic syndrome mediated the associations between leisure-time physical activity and all-cause mortality, vascular death and vascular events, we additionally adjusted for smoking and metabolic syndrome in the second model. In the third and fourth model, we adjusted for age, sex, smoking and waist circumference or BMI, to investigate whether fat distribution or body fat confounded the relation between physical activity and the risk of all-cause mortality, vascular death and vascular events. To investigate if the presence of metabolic syndrome modified the relation between physical activity and all-cause mortality and future events, we compared -2 log likelihood chi-square between models with and without metabolic syndrome and physical activity as interaction terms. We also investigated if body fat or fat distribution

Table 2. Baseline characteristics of the study population according to leisure-time physical activity (n=3875)

	Physical activity in MET·hours/wk		
	0 (n=2699)	**1.0 - 14.9 (n=600)**	**≥15.0 (n=576)**
Average physical activity (MET·h/wk)	**0**	**9.2 ± 3.5**	**30.6 ± 16.9**
Male sex (%)	75	69	81
Age (years)*	60.4 ± 10.4	58.2 ± 10.3	57.3 ± 11.0
Cholesterol (mmol/l)†	5.2 (4.4-6.0)	5.0 (4.3-5.9)	4.9 (4.1-5.7)
LDL-cholesterol (mmol/l)†	3.1 (2.4-3.9)	2.9 (2.3-3.8)	2.8 (2.2-3.6)
Hs-CRP (mg/l)	2.2 (1.0-5.0)	1.8 (0.8-3.9)	1.6 (0.7-3.3)
Weight (kg)	81.1 ± 14.2	79.9 ± 13.8	81.8 ± 12.6
BMI (kg/m^2)*	26.8 ± 4.0	26.5 ± 3.7	26.4 ± 3.5
Subcutaneous fat (cm)*	2.5 ± 1.5	2.5 ± 1.2	2.5 ± 1.4
Intra-abdominal fat (cm)*	9.6 ± 2.6	9.0 ± 2.7	8.8 ± 2.5
HOMA-IR†,‡	2.7 (1.7-4.4)	2.4 (1.6-3.7)	2.2 (1.5-3.5)
Diabetes mellitus type 2 (%)	25	16	15
Smoking status			
Never smoking (%)	16	20	25
History of smoking (%)	71	72	67
Current smoking (%)	13	8	8
Manifest vascular disease§			
Coronary heart disease (%)	54	60	61
Cerebrovascular disease (%)	31	27	28
Peripheral arterial disease (%)	27	20	17
Abdominal aortic aneurysm (%)	12	7	8
Metabolic syndrome			
Metabolic syndrome (%)	43	33	28
Fasting serum glucose (mmol/l)†	5.8 (5.3-6.6)	5.7 (5.3-6.3)	5.6 (5.2-6.2)
Triglycerides (mmol/l)†	1.6 (1.2-2.3)	1.4 (1.0-2.0)	1.4 (1.0-1.9)
HDL-cholesterol (mmol/l)†	1.2 (0.9-1.4)	1.2 (1.0-1.5)	1.2 (1.0-1.5)
Waist circumference (cm)*	96 ± 12	93 ± 11	93 ± 11
Systolic blood pressure (mmHg)*	143 ± 22	141 ± 23	141 ± 20
Diastolic blood pressure (mmHg)*	81 ± 11	82 ± 12	82 ± 11

LDL: low density lipoprotein, hs-CRP: high-sensitive C-reactive protein, BMI: body mass index
* mean ± standard deviations or †median (25^{th} percentile, 75^{th} percentile)
‡ HOMA-IR: homeostasis model assessment determined insulin resistance (fasting serum glucose x fasting serum insulin)/22.5
§ ever or current diagnosis, a single patient can be classified into more than one disease category

modified the relation between physical activity and all-cause mortality and vascular events. Measurement of hs-CRP, insulin, waist circumference, hip circumference, intra-abdominal fat and subcutaneous fat was started in May 2000, and thus these data were missing for patients included before this date. To reduce bias and increase statistical efficiency, missing values in the data were imputed, using S-plus.[23]

Results

Baseline characteristics

Of the total study population, 2699 (70%) patients were inactive, 600 (15%) were moderately active, and 576 (15%) patients were vigorously active. The mean age was 59.6±10.5 years, the BMI was 26.7± 3.7 kg/m^2, and the waist circumference was 95± 11 cm (Table 2). Of the patients with CHD, 67% were inactive, 17% moderately active, and 16% vigorously active. Of the patients with cerebrovascular disease and PAD 72% and 77% were inactive, 14% and 12% moderately active, and 14% and 10% vigorously active, respectively. Patients who were vigorously physically active had lower hs-CRP plasma levels than their inactive counterparts (1.6 (0.7-3.3) mg/l vs. 2.2 (1.0-5.0) mg/l).

The overall prevalence of metabolic syndrome was 39% (38% among men and 43% among women) but was markedly lower in vigorously physically active patients than in physically inactive patients (28% versus 43%). The prevalence of type 2 diabetes mellitus was higher in patients who were physically inactive than in their moderately active and vigorously active counterparts (25% versus 16% and 15%, respectively).

All-cause mortality, vascular death, and vascular events and physical activity

During a mean follow-up of 3.9±2.6 years, 434 (11%) of the 3875 patients died with 278 (64%) deaths being attributable to a vascular event. Of the total study population, 113 (3%) patients had an ischemic stroke, 273 (7%) patients had a myocardial infarction, and 466 patients had vascular death, myocardial infarction or ischemic stroke (combined endpoint).

Moderately and vigorously physically active patients had a lower risk of all-cause mortality with age- and sex-adjusted HR of 0.52 (95% CI 0.36-0.74) and of 0.72 (95% CI 0.51-1.01), respectively (Table 3). Additional adjustment for smoking and the presence of metabolic syndrome did not influence the hazard ratios. To investigate whether fat distribution or body fat confounded the relation between moderate physical activity and the risk of all-cause mortality, we additionally adjusted for waist circumference or BMI. However, the point estimates remained essentially the same (HR 0.52, 95% CI

Table 3. Relation (hazard ratio and 95% CI) between leisure-time physical activity and all-cause mortality, physical activity and vascular death, and between physical activity and the combined endpoint

		Physical activity category in MET·hours/week		
	Model	**0**	**1.0 - 14.9**	**≥15.0**
All vascular events* (n=466)		n=366	n=49	n=51
	I	1.00	0.70 (0.52 - 0.94)	0.88 (0.65 - 1.18)
	II	1.00	0.73 (0.54 - 0.98)	0.95 (0.70 - 1.27)
	III	1.00	0.71 (0.52 - 0.95)	0.90 (0.67 - 1.21)
	IV	1.00	0.72 (0.53 - 0.97)	0.92 (0.68 - 1.23)
Vascular death (n=278)		n=231	n=21	n=26
	I	1.00	0.51 (0.34 - 0.78)	0.75 (0.52 - 1.08)
	II	1.00	0.53 (0.36 - 0.79)	0.83 (0.57 - 1.20
	III	1.00	0.52 (0.35 - 0.77)	0.79 (0.55 - 1.14)
	IV	1.00	0.53 (0.36 - 0.79)	0.81 (0.56 - 1.18)
All-cause mortality (n=434)		n=364	n=33	n=37
	I	1.00	0.52 (0.36 - 0.74)	0.72 (0.51 - 1.01)
	II	1.00	0.53 (0.37 - 0.76)	0.77 (0.55 - 1.09)
	III	1.00	0.52 (0.36 - 0.74)	0.73 (0.52 - 1.04)
	IV	1.00	0.54 (0.37 - 0.77)	0.77 (0.54 - 1.08)

Model I: age and sex
Model II: model I additionally adjusted for smoking and metabolic syndrome
Model III: model I additionally adjusted for smoking and BMI
Model IV: model I additionally adjusted for smoking and waist circumference
* including vascular death, first recurrence of ischemic stroke, or myocardial infarction

0.36-0.74, and HR 0.54, 95% CI 0.37-0.77, respectively). Moderate and vigorous physical activity were associated with a lower risk of vascular death (age-and sex-adjusted HR 0.51, 95% CI 0.34-0.78 and HR 0.75, 95% CI 0.52-1.08, respectively). Adjustment for smoking and BMI, waist circumference or metabolic syndrome did not affect the association between moderate and vigorous physical activity and vascular death. Moderate and vigorous physical activity were inversely associated with all vascular events after adjustment for age and sex (HR 0.70, 95% CI 0.52-0.94 and HR 0.88, 95% CI 0.65-1.18, respectively).

Table 4. Relation (hazard ratio and 95% CI) between leisure-time physical activity and organ specific vascular events and interventions

		Physical activity category in MET·hours/week		
	Model	**0**	**1.0 - 14.9**	**≥15.0**
Coronary ischemic event and		n=445	n=87	n=89
coronary interventions (n=621)	I	1.00	0.97 (0.77 - 1.22)	1.18 (0.93 - 1.48)
	II	1.00	0.98 (0.78 - 1.24)	1.18 (0.94 - 1.49)
	II	1.00	0.97 (0.77 - 1.23)	1.16 (0.92 - 1.45)
	IV	1.00	0.97 (0.77 - 1.23)	1.17 (0.92 - 1.47)
Ischemic stroke and carotid		n=154	n=21	n=13
interventions (n=188)	I	1.00	0.66 (0.42 - 1.05)	0.48 (0.27 - 0.84)
	II	1.00	0.71 (0.45 - 1.12)	0.54 (0.30 - 0.95)
	III	1.00	0.68 (0.43 - 1.07)	0.50 (0.28 - 0.89)
	IV	1.00	0.69 (0.43 - 1.09)	0.51 (0.29 - 0.90)
Vascular interventions of		n=266	n=29	n=21
low extremities (n=316)	I	1.00	0.49 (0.34 - 0.73)	0.43 (0.28 - 0.67)
	II	1.00	0.55 (0.38 - 0.81)	0.52 (0.33 - 0.81)
	III	1.00	0.53 (0.36 - 0.77)	0.48 (0.31 - 0.75)
	IV	1.00	0.42 (0.25 - 0.73)	0.54 (0.32 - 0.90)

Model I: age and sex
Model II: model I additionally adjusted for smoking and metabolic syndrome
Model III: model I additionally adjusted for smoking and BMI
Model IV: model I additionally adjusted for smoking and waist circumference

Organ-specific outcomes and physical activity

After vascular events were classified into organ-specific vascular events and interventions, moderate and vigorous physical activity were no longer associated with a lower risk of coronary ischemic events and interventions (HR 0.98, 95% CI 0.78-1.24 and HR 1.18, 95% CI 0.94-1.49, respectively) (Table 4). Moreover, patients who were vigorously physically active had an increased risk of coronary artery bypass grafting (CABG) (HR 1.81, 95% CI 1.10–2.98 adjusted for age, sex, metabolic syndrome, and smoking). There was no association between vigorous physical activity and percutaneous transluminal coronary angioplasty (PTCA) (HR 0.98, 95% CI 0.76–1.54 adjusted for age, sex, metabolic

syndrome, and smoking). Moderate and vigorous physical activity was associated with a lower risk of ischemic stroke or carotid interventions (HR 0.71 95% CI 0.45-1.12 and HR 0.54, 95% CI 0.30-0.95, respectively). Comparable lower risks were seen when the relation between activity levels and lower limb interventions were quantified. Hazard ratios adjusted for age, sex, smoking, and metabolic syndrome were 0.55 (95% CI 0.38-0.81) and 0.52 (95% CI 0.33-0.81), respectively. Fat distribution and body fat did not influence this relationship.

Metabolic syndrome, fat distribution and body fat and the relation between physical activity and future events

The presence of metabolic syndrome did not modify the relationship between physical activity and all-cause mortality and vascular events. Interaction terms were not statistically significant (p- value for the interaction was 0.24 for all-cause mortality and 0.71 for all vascular events). In addition, the relation between physical activity and all-cause mortality, and the relation between physical activity and vascular events were not modified by fat distribution and body fat (p-value for the interaction was 0.17 and 0.13 for all-cause mortality and 0.29 and 0.09 for all vascular events, respectively).

Discussion

In the present study, we found moderate or vigorous leisure-time physical activity to be associated with a decreased risk of new vascular events, vascular death, and all-cause mortality in patients with manifest arterial disease. In addition, patients who were moderately or vigorously physically active had a lower risk of ischemic stroke or carotid interventions, or lower-limb vascular interventions. These relations were independent of fat distribution, body fat and presence of metabolic syndrome.

Several studies have shown that regular physical activity has beneficial effects on many risk factors for CVD, including decreasing body weight,[24] enhancing insulin sensitivity,[8] and lowering blood pressure,[9] improving dislipidemia,[10] lowering inflammation,[12] and improving endothelial dysfunction.[11] Thus, the protective role of physical activity on cardiovascular morbidity and mortality is, at least in part, mediated by its favourable effects on several traditional and novel risk factors.[7] In the present study, we found physical activity to be associated with a better risk factor profile, and this improved risk factor profile is probably responsible, at least in part, for the lower vascular risk. Surprisingly, this effect was independent of presence of metabolic syndrome, BMI, or waist circumference.

Physical activity may reduce low-grade systemic inflammation, as measured by lower concentrations of hs-CRP.[25] In the present study, CRP was much lower in vigorously physically active patients. Physical activity also has a direct effect on endothelial function by stimulating the production of nitric oxide (NO).[11;26] Training reduces peripheral resistance by ameliorating endothelial dysfunction, thus improving muscular perfusion.[27]

In healthy subjects, higher amount of physical activity are associated with lower all-cause and cardiovascular disease mortality.[4;5] Physical activity also reduces the risk of mortality in patients with CHD,[28] cerebrovascular disease[29] and PAD.[16] In fact, it is well-known that physical activity reduces mortality rates[30] and is more effective than percutaneous coronary intervention for event-free survival.[31] In the present study, we found that physical activity was not associated with a lower risk for ischemic coronary artery events and coronary interventions. These results are in line with the conclusion of meta-analysis of studies with patients with CHD[14;30] It is possible that physically active patients have a better health and are more likely to undergo a CABG than other patients because of their better physical condition or that coronary artery disease becomes clinically manifest in an earlier stage in these patients. However, vigorous physical activity may also affect platelet function, heart rate, and blood pressure[32;33] thereby increasing the risk of a coronary event.

Interventions of lower extremities were less frequent in patients who are physically active. Physical activity is an important therapeutic strategy for improving walking distance in patients with intermittent claudication, because it improves collateral formation in the lower extremities and adds to better control of vascular risk factors.[34] Our finding of a decreased risk of lower extremities interventions among moderately and vigorously physically active patients is in line with this study. Moreover, the finding that the risk of ischemic stroke or carotid intervention was decreased in moderately and vigorously physically active patients is consistent with earlier studies.[35] Hypertension is, after age, the most important risk factor for stroke,[36] and thus the reduction in blood pressure induced by physical activity, probably underlies the observed decreased risk of ischemic stroke.[9] Furthermore, as carotid artery stenosis is usually not treated when asymptomatic, but is treated in the presence of neurological symptoms, the lower risk of stroke seen in patients who were physically active may also explain the lower risk of carotid interventions seen in our study.

The prevalence of metabolic syndrome is about 50% in patients with clinical manifestations of arterial disease,[2] and patients with metabolic syndrome have an increased risk of cardiovascular events and mortality.[37] Several studies have reported that physical activity is associated with a reduced risk of the development of metabolic

syndrome,[38] and that it decreases the risk of all-cause and cardiovascular mortality in fit patients with metabolic syndrome. In the present study, we found that the presence of metabolic syndrome did not modify the relation between physical activity and all-cause mortality and vascular events in patients with manifest vascular diseases. Abdominal obesity, assessed by waist circumference, has been found to be a better predictor of total, CHD, and cerebrovascular disease mortality than BMI.[39] Apparently, physical activity appears to overcome the risk of abdominal obesity. We found that the physically active patients had less abdominal fat than the inactive patients and had the lowest prevalence of metabolic syndrome and risk factors associated with insulin resistance. Moreover, the vigorously active patients had the least intra-abdominal fat, and the lowest prevalence of metabolic syndrome and risk factors associated with insulin resistance.

Our study had some limitations. Information on leisure-time physical activity was obtained by self-report and concerned the leisure-time activity that the patients spent the most time doing each week. Thus, patients who took part in several sports or physical activities may have underestimated their amount of physical activity. Moreover, we measured physical activity at enrolment into the study only, so it is not known whether patients sustained this amount of physical activity during the follow up. It may be important to obtain information on all types of activity over a person's lifetime because physical activity at different times of life may influence the risk of vascular events later in life.[4]

In conclusion, moderate and vigorous leisure-time physical activity are associated with a decreased risk of new vascular events, vascular death and all-cause mortality independent of the presence of metabolic syndrome, fat distribution or body fat in patients with clinically established arterial diseases. Moreover, moderate and vigorous leisure-time physical activity are associated with a lower risk of ischemic stroke, carotid interventions and vascular interventions of the lower extremities.

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Effectiveness of a hospital-based vascular screening program (SMART) on risk factor reduction after 16 months in patients with established vascular disease or type 2 diabetes

B.G. Brouwer, F.L.J. Visseren, A. Algra, J.H. van Bockel, E.L.E.M. Bollen, P.A. Doevendans, L.J. Kappelle, F.L. Moll, H. Pijl, J.A. Romijn, E.E. van der Wall, Y. van der Graaf.

Submitted

Abstract

Background

Modification of vascular risk factors is effective in reducing mortality and morbidity in patients with symptomatic atherosclerosis, however, it is difficult to achieve and maintain. In the Risk management in Utrecht and Leiden Evaluation(RULE) study, a prospective, parallel group, comparative study, we compared the effects of a hospital setting with a multidisciplinary vascular screening program (intervention group) and a hospital setting without such a program (reference group) on the improvement of the cardiovascular risk profile of high-risk patients.

Methods

Patients with type 2 diabetes, coronary artery disease, cerebrovascular disease, or peripheral arterial disease referred to medical specialists by general practitioners were enrolled. Blood pressure, lipids, glucose, creatinine, weight, waist circumference, and smoking status were measured in the two hospitals 12-18 months after referral. Differences were adjusted for age, sex and baseline-value of the risk factor.

Results

At baseline the intervention (n=604) and the reference (n=566) group had similar vascular risk profiles(mean age 61±10 years). After a median of 16 months systolic blood pressure (139±19 vs. 142±20 mmHg, difference 2.3, 95%CI 0.7-4.3) and LDL-cholesterol (2.4±0.8 vs. 2.7±1.0 mmol/l, difference 0.3, 95%CI 0.2-0.4) were lower in the intervention group. Patients in the intervention group more often reached the treatment goal for LDL-cholesterol (59 vs. 48%, difference 11%, 95% CI 6-17).

Conclusion

Systematic screening of risk factors contributed to slightly better risk factor reduction in patients with established vascular disease or type 2 diabetes. However, a large proportion did not reach the treatment goals according to (inter)national treatment guidelines. Only systematic screening of vascular risk factors is not enough for adequate risk factor management in high-risk patients.

Introduction

After a first clinical manifestation of an atherosclerotic vascular disease patients have a considerable increased risk of a recurrent event at the same or at another location in the vascular system.[1] Therefore, interventions aimed at secondary prevention are warranted in these patients. Several risk factors are involved in the process of atherosclerosis such as hypertension, hypercholesterolemia, smoking, hyperglycemia and obesity. Modification of these risk factors is effective in reducing mortality and morbidity in patients with symptomatic atherosclerosis.[2-4] Nevertheless, reduction of risk factors is difficult to achieve and maintain in clinical practice.[5-8]

Treatment of vascular risk factors in high-risk patients is usually done by the general practitioner or medical specialists such as internists, cardiologists, vascular surgeons, and neurologists. Trivial treatment of vascular risk starts with (a) assessment of all relevant risk factors. Individual risk factors are then (b) to be weighted against current (inter)national guidelines on vascular prevention and, if needed, (c) pharmacological treatment or lifestyle changes need to be initiated and to be monitored.

Several programs for risk assessment and treatment have been developed.[9-14] In addition, there are (inter)national guidelines on cardiovascular disease prevention to assist vascular risk factor management.[15;16] However, the clinical reality is that not all relevant vascular risk factors are measured in individual patients.[17] The aim of the Risk management in Utrecht and Leiden Evaluation (RULE) study was to evaluate whether risk factor management in a setting with a multidisciplinary hospital-based vascular screening program was associated with better risk factor treatment compared to a setting without such a program in patients with established vascular diseases or type 2 diabetes.

Methods

Study design

The RULE study is a two-center prospective, nonrandomized, parallel group comparative study. Patients were referred to either the University Medical Center Utrecht (UMC Utrecht) or the Leiden University Medical Center (Leiden UMC) by general practitioners. The intervention group was treated in the UMC Utrecht, a setting with a vascular screening program for risk factor management in patients with established vascular disease or type 2 diabetes and the reference group was treated in Leiden UMC, a setting without such a formalised program.

Study population

All patients, aged 18-80 years, referred by their general practitioner to the UMC Utrecht or the Leiden UMC because of transient ischaemic attack (TIA), minor ischaemic stroke, peripheral arterial disease (PAD), type 2 diabetes mellitus, angina pectoris or myocardial infarction referred for elective percutaneous transluminal coronary angioplasty (PTCA) were invited to participate in the RULE study. Patients were enrolled between May 2005 and August 2007. The Ethics Committee of the two institutions approved the study and written informed consent was obtained from all participants.

Selection of patients

At the UMC Utrecht, patients who were enrolled in the vascular screening program or those who were identified with use of the hospital registration system (Diagnosis Related Group (DRG) registration) were potential participants in RULE. Not all patients at the UMC Utrecht participated in the vascular screening program and received regular care. These patients fulfilled the inclusion criteria but were not enrolled into the Second Manifestations of ARTerial disease (SMART) screening program because of logistical reasons, or physicians did not propose the screening program to the patients or the patient refused to participate. We took a random sample of these patients and pragmatically decided that the number of patients in the sample would total 20% of all patients evaluated for the RULE project in Utrecht. Thus 80% of the evaluated patients at the UMC Utrecht followed the vascular screening program in addition to regular care.
At the Leiden UMC, patients were also identified through the DRG and received for vascular risk factor management regular care by their vascular specialist or general practitioner.

Risk factor treatment in the intervention group (UMC Utrecht)

In addition to regular care, patients were offered the opportunity to participate in the multidisciplinary vascular screening and prevention program SMART, which started in 1996. This program is offered to patients with recently diagnosed vascular disease (coronary heart disease, transient ischemic attack, stroke, peripheral arterial disease, abdominal aortic aneurysm) or diabetes mellitus and is now part of regular care at the UMC Utrecht. Participating patients completed questionnaires on medical history, family history, symptoms of cardiovascular disease and risk factors, lifestyle habits and quality of life.[18] Blood pressure was measured twice in sitting position on both upper arms with a non-randomized sphygmomanometer and mean systolic and diastolic blood pressures

were calculated. Height and weight were measured without shoes and heavy clothing. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured halfway between the lower rib and the iliac crest. Blood and urine samples were collected after an overnight fast for measuring glucose, creatinine, total cholesterol, triglycerides, HDL-cholesterol, and homocysteine concentrations. LDL-cholesterol was calculated with Friedewald's formula. An early-morning urine sample was collected to measure albumin and creatinine concentrations.

The results of the screening program of each patient were discussed at a weekly meeting of a multidisciplinary team consisting of an internist, vascular surgeon, cardiologist, neurologist, and nurse practitioner and an individualized treatment advice regarding vascular risk factors was made for each patient. The results of the screening program together with the treatment advice were reported in writing to the treating vascular specialist and general practitioner. Treatment recommendations were given according to the Dutch treatment guidelines[16] based on the Third Joint Task Force of European Societies recommendations[15] for the treatment of risk factors, in particular hypertension, hyperlipidemia, diabetes mellitus, obesity, and smoking. Further action was left to the discretion of the general practitioner and the treating vascular specialist.

Risk factor treatment in the reference group (Leiden UMC)

Patients in the reference group received regular care from their treating medical specialist (internist, cardiologist, neurologist or vascular surgeon) or by their general practitioner. Risk factor assessment was done according to the Dutch guidelines on Cardiovascular risk management 2006, largely based on the European Guidelines on Cardiovascular disease prevention.[15] The organisation of risk factor management was organised by each physician for each individual patient. There was no overall screening or prevention program. Patients might have been treated by the medical specialist or a nurse practitioner in the outpatient clinic or by the general practitioner.

Baseline examinations

For all patients in the intervention group and in the reference group, baseline data were retrieved from the DRG system and medical records by independent physician assistants. The disease stage was documented for cerebrovascular disease with the modified Rankin grade[19], for PAD with the Fontaine classification[20], for coronary heart disease (CHD) the number of stenotic (>70%) or occluded coronary arteries, and for type 2 diabetes the

duration of the disease was recorded. Age, gender, additional medical history besides the inclusion diagnosis, any vascular interventions, blood pressure, weight, waist circumference, plasma concentrations of glucose, creatinine, homocysteine, LDL-cholesterol, HDL-cholesterol, total cholesterol and triglycerides, smoking status and current use of medication were recorded, if available, for all patients.

Follow-up examinations

All patients were asked to return between 12 and 18 months after their initial visit for assessment of their risk factor profile. All measurements were done by physician assistants. Fasting blood was sampled to determine concentrations of total cholesterol, HDL-cholesterol, triglycerides, serum glucose, homocysteine and creatinine. LDL-cholesterol was calculated with Friedewald's formula. Fasting urine was collected to determine creatinine and albumin concentrations. Height, weight and waist circumference were measured and BMI was calculated. Medical history, current medication use, smoking- and physical activity behaviour, and alcohol use were derived from a questionnaire.

Data analysis

Continuous variables are presented as means with standard deviation (SD) or as median with interquartile range (IQR) and dichotomous variables as percentages. We calculated mean differences between the intervention and reference group with corresponding 95% confidence intervals (95% CI) based on the independent sample t-test. To adjust the mean differences in the level of risk factors for age, sex and baseline-value between patients in the intervention and reference group we used analysis of covariance (ANCOVA, general linear model procedure).

For dichotomous variables, differences between intervention and reference group in proportions of patients who achieved the treatment goals were determined with the corresponding 95% CI. To adjust for age, sex and baseline-value linear regression was used.

Primarily, analyses were based on the intention-to-treat-principles. On treatment analyses were done for patients who underwent the screening program in the UMC Utrecht.

To compare the severity of disease of the patients between the intervention and reference group, the disease stage in each patient was documented. Data on risk factors at baseline were not available for all patients. Because missing data might lead to bias and thus affect our findings, we imputed missing values at baseline for these patients with regression imputation,[21] and used these to calculate baseline-adjusted differences

in the risk factor levels and proportions of achieved treatment goals. Missing values for the following risk factors were imputed: systolic and diastolic blood pressure, glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, creatinine, homocysteine, weight, and smoking status.

Results

Study population

A total of 2348 patients was invited for follow-up examinations (1123 in the intervention and 1225 patients in the reference group) of whom 1170 patients participated in the RULE study (604 patients in the intervention group and 566 patients in the reference group) with a median follow-up of 16 months (Figure 1). In the intervention group, 136 (23%) patients did not participate in the vascular screening program.

Of the total study population, 70% was male, with a mean age of 61±10 years. Baseline characteristics of the patients in the four inclusion diagnosis categories are shown in Table 1. There were no relevant differences between the intervention and reference group with regard to the stage or severity of the qualifying disease. In the reference group a large number of risk factors were not recorded at baseline (Table 2). The group of patients with coronary artery disease consisted of patients undergoing a PTCA. The hospital stay for patients referred from other hospitals for PTCA was very short which may have influenced risk factor measurement.

Differences in risk factors between intervention and reference group at follow-up

In the intervention compared with the reference group there were statistically significant differences in systolic blood pressure (139±19 vs. 142±20 mmHg; age- and sex-adjusted difference: -2.5 mmHg (-4.6 to -0.3)), diastolic blood pressure (82±10 vs. 85±11 mmHg; age- and sex-adjusted difference: -3.2 mmHg (-4.4 to -1.9)), LDL-cholesterol (2.4±0.8 vs. 2.7±1.0 mmol/l; age- and sex-adjusted difference: -0.3 mmol/l (-0.4 to -0.2)), HDL-cholesterol (1.3±0.4 vs. 1.5±0.4 mmol/l; age- and sex-adjusted difference: -0.1 mmol/l (-0.2 to -0.1)), homocysteine (11.3±4.3 vs. 13.2±5.0 µmol/l; age- and sex-adjusted difference: -1.9 mmol/l (-2.4 to -1.3)) (Table 3). Additional adjustment for baseline-values did not materially change the mean differences.

Mean differences in risk factors between the two study groups are given separately for the four patient categories in Appendices 1A-1D. The patterns in the subgroups are not essentially different when compared with the total group.

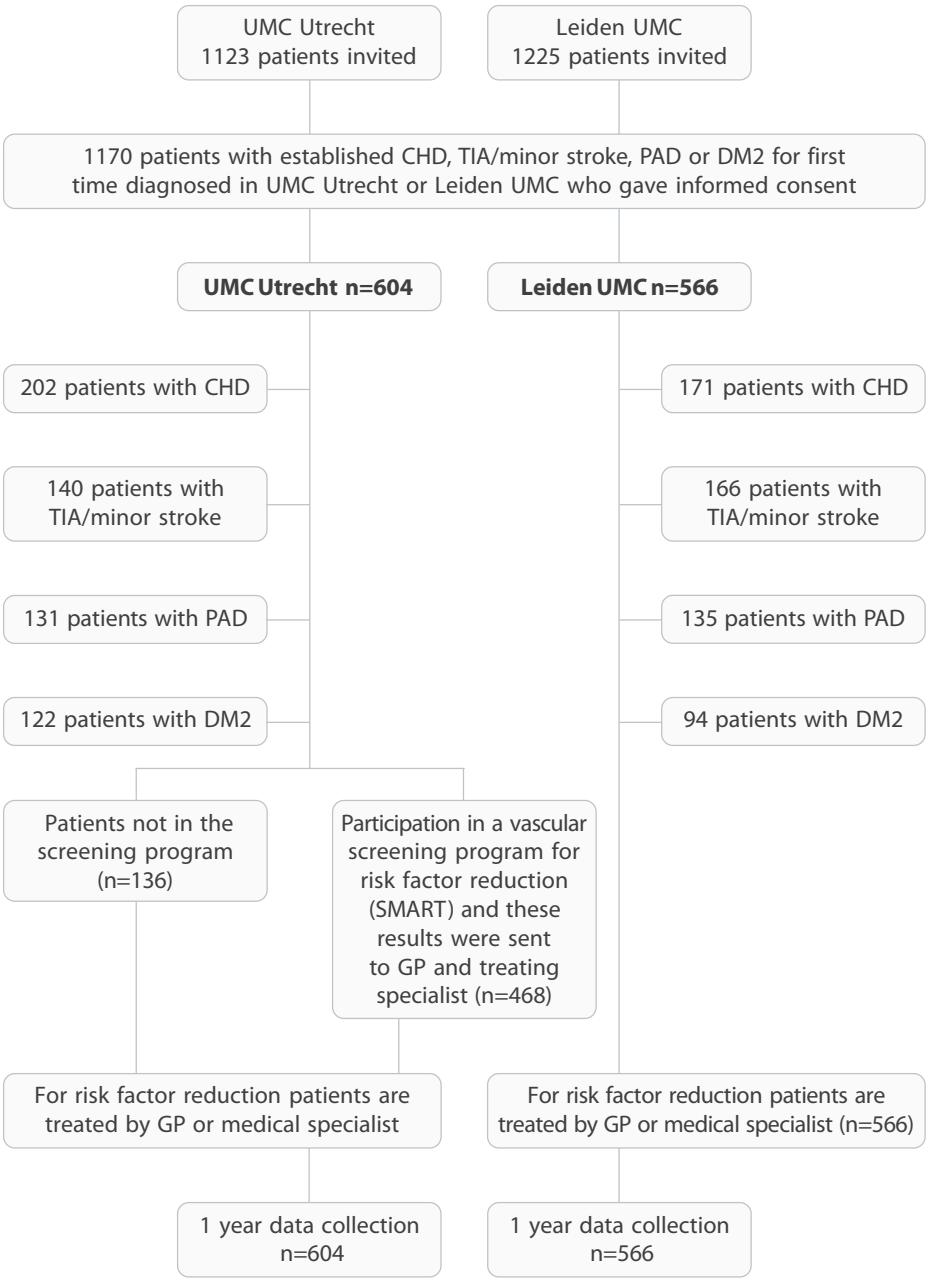

Figure 1. Flowchart of RULE study. UMC Utrecht: University Medical Center Utrecht, Leiden UMC: Leiden University Medical Center, CHD: coronary heart disease, TIA/minor stroke: transient ischaemic attack or minor ischaemic stroke, PAD: peripheral arterial disease, DM2: type 2 diabetes, GP: general practitioner

Table 1. Baseline characteristics of the study population (n=1170)

	Intervention group (n=604)	Reference group (n=566)
Age (years)	60 ± 10	61 ± 10
Male (%)	73	66
Coronary heart disease (N)	202	171
Severity (>70% diameter) of coronary vessel disease		
1-vessel disease (%)	46	65
2-vessel disease (%)	34	28
3-vessel disease (%)	19	7
Cerebrovascular disease (N)	149	166
Rankin grade		
0 (%)	43	38
1 (%)	37	35
2 (%)	13	19
3 (%)	6	4
4 (%)	1	4
Peripheral arterial disease (N)	132	135
Fontaine classification		
1 + 2 (%)	94	87
3 + 4 (%)	6	13
Ankle brachial index	0.70 ± 0.21	0.70 ± 0.16
Type 2 diabetes mellitus (N)	121	94
Median duration of diabetes (years)	2.5 (0.3-7.0)	5.0 (1.0-9.0)
Use of insulin (%)	7	17
Prevalence of vascular disease		
Coronary heart disease (%)	43	40
Cerebrovascular disease (%)	29	33
Peripheral arterial disease (%)	25	28
Risk factors		
Systolic blood pressure (mmHg)	144 ± 21	145 ± 22
Diastolic blood pressure (mmHg)	83 ± 11	82 ± 12
Glucose (mmol/l)	6.6 ± 2.3	7.8 ± 3.5
Total cholesterol (mmol/l)	4.9 ± 1.2	5.0 ± 1.4
HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.4 ± 0.7
LDL-cholesterol (mmol/l)	2.8 ± 1.0	2.9 ± 1.2
Triglycerides (mmol/l)	1.8 ± 1.1	2.4 ± 2.2
Creatinine clearance (Cockroft)	79 ± 24	79 ± 23
BMI (kg/m^2)	27.4 ± 4.2	27.5 ± 5.6
Current smoking (%)	21	33

HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
Mean ± standard deviation or unless indicated otherwise

Table 2. Proportion of risk factors in intervention and reference group documented at baseline

	Intervention group (n=604)	Reference group (n=566)
Systolic blood pressure (%)	96	77
Diastolic blood pressure (%)	96	76
Glucose (%)	94	61
Total cholesterol (%)	91	50
HDL-cholesterol (%)	87	42
LDL-cholesterol (%)	84	37
Triglycerides (%)	88	40
Creatinine clearance (%)	86	43
BMI (%)	93	53
Waist circumference (%)	75	5
Smoking (%)	93	74

LDL: low-density lipoprotein, HDL: high-density lipoprotein, BMI: body mass index

Proportion of patients achieving treatment goals of risk factors at follow-up

More patients in the intervention than in the reference group achieved their treatment goals for some of their risk factors at follow-up (Table 4). After adjustment for age, sex and baseline-value, there was a statistically significant difference between the proportion of patients achieving treatment goals between intervention and reference group for diastolic blood pressure (9%, 95% CI 4–14), LDL-cholesterol (11%, 95% CI 6-17) and HDL-cholesterol (-7%, 95% CI -3 to -11) in the whole study population.

Appendices 2A-2D provide data on proportions of achieved treatment goals according to disease category. The patterns in the subgroups are not essentially different compared with the total group.

Use of medication at follow-up

In patients with vascular diseases there were no differences in the proportion of patients using medication at follow-up (Table 5). Patients with type 2 diabetes in the reference group used more glucose-lowering agents (96 vs. 88%, difference -8, 95% CI -16 to -0.3)

compared with the intervention group, due to more frequent use of insulin in the reference group (61 vs. 29%, difference -31, 95% CI -44 to -19). In Appendix 3 data are presented on medication use according to disease category.

On treatment analysis

Of all patients in the intervention group (n=604), 468 patients underwent the vascular screening. The mean age was 60.0±9.8 years and most patients were male (74%). Compared with the reference group there were statistically significant differences between the intervention and reference group with regard to systolic and diastolic blood pressure (138±18 vs. 142±20; age- and sex-adjusted difference: -3.3 mmHg (-5.6 to -1.0), and 81±10 vs. 85±11; age- and sex-adjusted difference: -3.6 mmHg (-4.9 to -2.3)), LDL-cholesterol (2.4±0.8 vs. 2.7±1.0; age- and sex-adjusted difference: -0.3 mmHg (-0.4 to -0.2)) and homocysteine 11.2±4.4 vs. 13.2±5.0; age- and sex-adjusted difference: -2.0 mmHg (-2.5 to -1.4)) (Appendix 4).

Discussion

The results of our study show that in a hospital setting with the availability of a vascular screening program, patients with manifest arterial disease or type 2 diabetes mellitus had statistically significant lower levels of systolic blood pressure and LDL-cholesterol compared with the patients treated in a setting without such a program. In the reference group, risk factors were not measured or documented in two third of the patients at baseline. Although treatment goals for vascular risk factors were achieved more frequently in the intervention group, in at least one third of patients systolic blood pressure, LDL-cholesterol and other vascular risk factors were still not at target according to international guidelines.

Patients with a history of cardiovascular events are at high risk for recurrence of a vascular event. The importance of modifying risk factors is supported by previous studies, which showed that a reduction in 5 mmHg diastolic blood pressure is associated with one third lower risk of stroke[22;23] and 2 mmHg lower usual systolic blood pressure would involve about 10% lower stroke mortality and about 7% lower mortality of ischemic heart disease.[24] A reduction of 1 mmol/L LDL-cholesterol is accompanied by a 10% reduction of CHD events during the first year.[3] For patients with diabetes a 50% reduction in the risk of cardiovascular events during follow-up period of 8 years is seen in a study with multifactorial treatment of hyperglycemia, hypertension, and dyslipidemia.[14] In the intervention group in this study the reduction of blood pressure and LDL-cholesterol

Table 3. Risk factor measurements and mean differences of risk factors between intervention and reference group at follow-up examinations (n=1170)

	Intervention group (n=604)	Reference group (n=566)	Mean difference*	95% CI	Mean difference†	95% CI
Systolic blood pressure (mmHg)	139 ± 19	142 ± 20	-2.5	-4.6 to -0.3	-2.3	-4.3 to -0.7
Diastolic blood pressure (mmHg)	82 ± 10	85 ± 11	-3.2	-4.4 to -1.9	-3.3	-4.5 to -2.1
Glucose (mmol/l)	6.5 ± 1.9	6.6 ± 3.0	-0.2	-0.5 to 0.1	0.1	-0.1 to 0.4
Total cholesterol (mmol/l)	4.4 ± 1.0	4.5 ± 1.1	-0.02	-0.14 to 0.10	-0.01	-0.12 to 0.10
HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.5 ± 0.4	-0.1	-0.2 to -0.1	-0.1	-0.2 to -0.1
LDL-cholesterol (mmol/l)	2.4 ± 0.8	2.7 ± 1.0	-0.3	-0.4 to -0.2	-0.3	-0.4 to -0.2
Triglycerides (mmol/l)	1.6 ± 1.1	1.6 ± 1.1	-0.1	-0.2 to 0.1	-0.01	-0.13 to 0.11
Creatinine clearance (Cockroft)	75 ± 22	76 ± 23	-2.0	-4.1 to 0.1	-3.0	-4.7 to -1.3
Homocysteine (µmol/l)	11.3 ± 4.3	13.2 ± 5.0	-1.9	-2.4 to -1.3	-1.8	-2.3 to -1.3
BMI (kg/m^2)	27.9 ± 4.6	28.0 ± 4.7	-0.1	-0.6 to 0.4	-0.3	-0.7 to 0.1
Waist circumference (cm)	99 ± 12	99 ± 14	-0.4	-1.8 to 1.0	-	-
Current smoking (%)	20	22	-3‡	-8 to 1	1§	-3 to 4

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in mean ± standard deviation
* mean difference adjusted for age and sex: follow-up value in intervention group - follow-up value in reference group
† mean difference adjusted for age, sex and baseline-value: follow-up value in intervention group - follow-up value in reference group
‡ difference of two proportions adjusted for age and sex
§ difference of two proportions adjusted for age, sex and baseline-value

Table 4. Proportion of patients who achieved treatment goals at follow-up examinations

	Intervention group (n=604)	Reference group (n=566)	Absolute difference*	95% CI	Absolute difference†	95% CI
Systolic blood pressure <140 mmHg	55	51	3	-3 to 9	3	-3 to 8
Diastolic blood pressure <90 mmHg	78	69	8	3 to 13	9	4 to 14
Total cholesterol <4.5 mmol/l	56	56	-1	-7 to 5	-1	-7 to 4
HDL-cholesterol men >1.0, women >1.2 mmol/l	77	86	-8	-4 to -13	-7	-3 to -11
LDL-cholesterol <2.5 mmol/l	59	48	11	5 to 17	11	6 to 17
Triglycerides <1.7 mmol/l	67	67	0	-5 to 5	-0.2	-8 to 3
Glucose <7.0 mmol/l	78	75	4	-1 to 9	-1	-5 to 3
Patients with diabetes: glucose <7.0 mmol/l	39	35	4	-5 to 14	2	-8 to 12
Patients without diabetes: glucose <7.0 mmol/l	96	95	1	-2 to 4	-0.2	-3.0 to 2.6
BMI <25 kg/m^2	23	27	-3	-8 to 2	-1	-6 to 3
BMI <30 kg/m^2	75	72	3	-2 to 8	4	-2 to 8
Waist circumference men <102, women <88 cm	51	46	3	-3 to 8	-	-
No smoking	80	78	3	-1 to 8	-1	-4 to 3

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in percentages
* absolute differences of proportions adjusted for age and sex
† absolute differences of proportions adjusted for age, sex and baseline-value

Table 5. Medication use in the intervention and reference group in patients with manifest arterial disease or type 2 diabetes at follow-up examinations

	Patients with arterial disease			Patients with type 2 diabetes		
	Intervention group (n=483)	Reference group (n=472)	Absolute difference (95% CI)	Intervention group (n=121)	Reference group (n=94)	Absolute difference (95% CI)
Blood pressure-lowering agents (%)	75	79	-3 (-9 to 2)	83	78	4 (-7 to 14)
1 idem (%)	42	36	6 (-1 to 13)	23	34	-12 (-25 to 2)
2 idem (%)	36	37	-1 (-8 to 6)	32	40	-8 (-23 to 6)
3 idem (%)	16	22	-6 (-11 to -0)	32	22	10 (-3 to 23)
>4 idem (%)	6	6	0 (-3 to 4)	14	5	10 (2 to 18)
Beta-blocking agents (%)	47	48	-2 (-8 to 5)	40	30	10 (0 to 22)
Diuretics (%)	26	30	-3 (-8 to 3)	53	32	21 (7 to 34)
ACE inhibitor or AII-antagonist (%)	48	50	-2 (-8 to 5)	74	65	7 (-5 to 20)
Calcium-antagonist (%)	17	24	-7 (-12 to 2)	23	19	3 (9 to 14)
Lipid-lowering agents (%)	86	83	2 (-3 to 6)	71	70	3 (-10 to 15)
1 lipid-lowering agent (%)	92	97	-5 (-8 to -2)	90	100	-11 (-17 to -4)
>2 lipid-lowering agent (%)	8	3	5 (2 to 8)	10	0	11 (4 to 17)
Statins (%)	83	81	1 (-4 to 6)	67	69	-5 (-17 to 8)
Cholesterol absorption inhibitor (%)	7	4	3 (0.3 to 6)	7	0	7 (2 to 11)
Fibrates (%)	2	0.4	1 (-0.1 to 3)	3	1	2 (-2 to 7)
Glucose-lowering agents (%)	14	18	-3 (-8 to 1)	88	96	-8 (-16 to -0.3)
Oral glucose-lowering agents (%)	13	15	-2 (-7 to 2)	75	73	1 (-11 to 13)
Insulin (%)	4	7	-3 (-6 to 0.1)	29	61	-31 (-44 to -19)
Anti-thrombotic agents* (%)	85	93	-8 (-12 to 4)	39	40	-6 (-19 to 7)
Antiplatelet agents	76	80	-5 (-10 to 0.4)	31	38	-11 (-23 to 2)

ACE-inhibitor: angiotensin converting enzyme-inhibitor, AII-antagonist: angiotensin II-antagonist; Data are presented as percentages of users
* anticoagulant and antiplatelet agents

is clinically relevant. Although the reductions of 2 mmHg systolic blood pressure, 3 mmHg diastolic blood pressure and 0.3 mmol/L LDL-cholesterol in the intervention group compared with the reference group seem to be relatively small, every decrease in risk factors is beneficial.

The data of the present study indicate that a vascular screening program adds to better vascular risk factor treatment. However, still a large proportion of risk factors is not treated optimally in these high-risk patients, and, consequently, a single systematic screening of risk factors followed by an interdisciplinary treatment advice is not enough for adequate risk reduction in patients with established vascular diseases or type 2 diabetes mellitus. In the vascular screening and prevention program SMART in the UMC Utrecht, the patients themselves were not informed about the results and subsequent recommendations of the program, however, their vascular specialist and general practitioner were. The efficacy of the program may be enhanced by active involvement of the patients. This may also lower the likelihood of patients not consulting their vascular specialist or general practitioner for risk factor management. However, the treatment advice may have stimulated the physician to comply with the guidelines[25] and to take a greater responsibility for the treatment plan. Patients should be encouraged to take responsibility of their own health; therefore, patients now also receive the results on risk factors and the treatment advice.

In the intervention group part of the patients (23%) did not undergo the vascular screening program. Although the screening program is presented to all patients referred to the UMC Utrecht, it is not possible to include all patients in the program due to logistical reasons. Moreover, not all patients participate because of co-morbidities, no interest or the distance of their residency to the hospital. Thus, patients who did and did not undergo the program are likely to be incomparable. In the present study about 80% participation to the screening program was investigated. In current practice at the UMC Utrecht the participation to the screening program is lower awaiting the results of the present study. If the cost-effectiveness analysis of the program turns out to be positive, a higher participation level is warranted. In an on-treatment analysis, reflecting 100% participation, the risk factor levels at follow-up were lower in the patients participating in the vascular screening than in those who did not. The results of the present study should be interpreted considering a participation level of about 80%.

The differences in risk factors between intervention and reference group were not explained by the number of drugs used by the patients. To improve control of LDL-cholesterol and blood pressure, there are various options, including increasing the dose, prescribing a more effective drug or use of combination therapy.[26-29] The proportion of patients using medication was similar in both groups, but the dose of medication may

have differed leading to differences in efficacy. Furthermore, physicians of patients in the intervention group may also have been more triggered to achieve optimal treatment of risk factors by non-pharmacological ways (exercise, salt-intake, quit smoking). Another explanation may be differences in adherence of patients to prescribed medication regimes. Patients participating in a prevention program may be more motivated to adhere to medication as a result of the screening program and this may also be the reason for participation in the program. Unfortunately, we could not determine from our data whether patients complied poorly with medication. Multidrug treatment is a common therapy to reduce multiple cardiovascular risk factors in patients with cardiovascular disease, and adherence decreases with each additionally prescribed drug.[30;31].

Our results indicate that only systematic screening of risk factors followed by a multidisciplinary treatment advice is not enough for achieving adequate risk factor management. A vascular screening program with individual treatment advice may be a good starting point to facilitate risk factor management for vascular specialists, but apparently should also be followed by actual treatment. The question remains how this should be done. Treatment of vascular risk factors by nurse practitioners has proven to be more effective than usual care.[10;12;13;32] An internet-based treatment program may also be an effective and efficient way to improve risk factor treatment.[11;33;34] In other studies, time constraints were identified as the largest single barrier to risk factor and lifestyle treatment by physicians.[25;35] In patients, lack of awareness of the importance of risk factors is one of the most crucial factors.[25] Therefore active involvement of patients in risk reduction programs may be of key importance by starting self-management programs.

The strengths of the present study are that patients with various localisations of clinical manifest arterial diseases were analysed. Furthermore, only patients referred by general practitioners were included; therefore we think that these findings have a broad generalisability. We did not attempt to impose specific treatments but we evaluated risk factor management as a complete strategy. This is a non-randomised study and hence the comparability of the two groups may be compromised. In our opinion this study design was the only feasible option to assess the efficacy of a broad hospital-based risk factor management strategy. If randomisation were used it should have been at patient level, but the vascular screening program is already implemented in care, and, therefore, this was neither an ethically justifiable nor feasible option. It is unlikely that a physician will practice both strategies simultaneously in different patients during the study period. Mortality rates for vascular disease, coronary heart disease and stroke are comparable between the catchments areas of the two hospitals (see Table 6), indicating that comparability of prognosis of patients in the two areas was not an issue in our study.

Table 6. Mortality rate per 10,000 inhabitants adjusted for age and sex between 2001-2004*

	Public Health Institute region Utrecht	Public Health Institute region Middle of the Netherlands	Public Health Institute region south-Holland north	Public Health Institute region South-Holland west	Netherlands
Total vascular disease	28.3	26.1	26.2	26.2	28.9
Acute myocardial infarction	6.4	5.7	6.0	6.2	6.9
Coronary heart disease	9.0	8.1	8.5	8.43	9.6
Stroke	6.9	6.8	6.7	6.6	7.2
Diabetes mellitus	2.7	2.0	2.4	2.0	2.5

* source Statistics Netherlands (http://www.rivm.nl/vtv/object_class/atl_sterfteoorzaak.html)

The severity, extent or duration of diseases were similar in intervention and reference groups. It is therefore not likely that referral patterns by general practitioners were different in both regions.

We acknowledge some limitations of our study. It was not possible to confirm the self-reported medication use by checking pharmacy records. Neither a questionnaire nor pharmacy records can be considered as golden standard with regard to true pharmacotherapy.[36] Furthermore, the study population might be viewed as complex high-risk patients because the patients were referred to university medical centres. However, patients were referred by general practitioners and were not tertiary referrals and patients were able to visit the outpatient clinics indicating that they were in reasonable good physical condition.

In conclusion, systematic screening of risk factors contributed to slightly better risk factor reduction in patients with established vascular disease or type 2 diabetes. In spite of screening, a large proportion of these patients did not reach the treatment goals according to (inter)national treatment guidelines. Only screening of risk factors in a systematic program is not enough for adequate risk factor management in high-risk patients.

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Appendix 1A. Risk factor measurements and mean differences of risk factors between intervention and reference group at follow-up examinations in patients with coronary heart disease

	Intervention group (n=202)	Reference group (n=171)	Mean difference*	95% CI	Mean difference†	95% CI
Systolic blood pressure (mmHg)	137 ± 19	141 ± 19	-3.3	-7.1 to 0.5	-3.3	-6.9 to 0.4
Diastolic blood pressure (mmHg)	81 ± 10	85 ± 11	-3.9	-6.1 to-1.8	-3.9	-6.0 to-1.7
Glucose (mmol/l)	5.9 ± 1.0	6.2 ± 2.3	-0.2	-0.5 to 0.2	-0.2	-0.5 to 0.2
Total cholesterol (mmol/l)	4.3 ± 0.8	4.2 ± 0.9	0.1	-0.1 to 0.3	0.2	-0.01 to 0.3
HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.5 ± 0.4	-0.2	-0.2 to -0.1	-0.1	-0.2 to -0.1
LDL-cholesterol (mmol/l)	2.3 ± 0.7	2.5 ± 0.8	-0.2	-0.3 to -0.003	-0.1	-0.3 to 0.02
Triglycerides (mmol/l)	1.5 ± 0.9	1.6 ± 1.1	-0.1	-0.3 to 0.1	-0.1	-0.3 to 0.1
Creatinine clearance (Cockroft)	75 ± 18	77 ± 21	-3.5	-6.4 to -0.7	-3.4	-6.0 to -0.9
Homocysteine (µmol/l)	11.1 ± 3.3	12.5 ± 3.8	-1.3	-2.0 to -0.6	-1.2	-1.9 to -0.6
BMI (kg/m^2)	27.7 ± 3.4	28.3 ± 4.2	-0.6	-1.4 to 0.2	-0.8	-1.4 to -0.2
Waist circumference (cm)	99 ± 10	100 ± 13	-2.2	-4.4 to 0.1	-	-
Current smoking (%)	13	12	1‡	-6 to 8	-2§	-8 to 4

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in mean ± standard deviation
* mean difference adjusted for age and sex: follow-up value in intervention group - follow-up value in reference group
† mean difference adjusted for age, sex and baseline-value: follow-up value in intervention group - follow-up value in reference group
‡ difference of two proportions adjusted for age and sex
§ difference of two proportions adjusted for age, sex and baseline-value

Appendix 1B. Risk factor measurements and mean differences of risk factors between intervention and reference group at follow-up examinations in patients with cerebrovascular disease

	Intervention group (n=149)	Reference group (n=166)	Mean difference*	95% CI	Mean difference†	95% CI
Systolic blood pressure (mmHg)	136 ± 17	140 ± 18	-3.3	-7.2 to 0.6	-2.1	-5.6 to 1.4
Diastolic blood pressure (mmHg)	81 ± 9	86 ± 11	-5.3	-7.6 to -3.1	-5.2	-7.4 to -3.1
Glucose (mmol/l)	6.0 ± 1.3	5.5 ± 1.7	0.5	0.1 to 0.8	0.7	0.4 to 1.0
Total cholesterol (mmol/l)	4.4 ± 1.0	4.5 ± 1.1	-0.1	-0.3 to 0.1	-0.02	-0.24 to 0.20
HDL-cholesterol (mmol/l)	1.5 ± 0.5	1.5 ± 0.4	-0.1	-0.2 to 0.04	-0.01	-0.1 to 0.1
LDL-cholesterol (mmol/l)	2.4 ± 0.9	2.8 ± 1.0	-0.4	-0.6 to -0.2	-0.4	-0.6 to -0.2
Triglycerides (mmol/l)	1.3 ± 0.8	1.5 ± 0.8	-0.2	-0.3 to 0.03	-0.1	-0.3 to 0.1
Creatinine clearance (Cockroft)	72 ± 20	74 ± 23	-5.5	-9.6 to -1.5	-3.7	-7.0 to -0.4
Homocysteine (µmol/l)	10.6 ± 2.7	13.1 ± 5.4	-2.4	-3.4 to -1.4	-2.4	-3.4 to -1.5
BMI (kg/m^2)	26.9 ± 3.8	27.4 ± 4.7	-0.6	-1.6 to 0.4	-0.5	-1.2 to 0.2
Waist circumference (cm)	96 ± 12	96 ± 14	-0.8	-3.5 to 1.9	-	-
Current smoking (%)	21	20	1‡	-8 to 10	-2§	-2 to 15

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in mean ± standard deviation
* mean difference adjusted for age and sex: follow-up value in intervention group - follow-up value in reference group
† mean difference adjusted for age, sex and baseline-value: follow-up value in intervention group - follow-up value in reference group
‡ difference of two proportions adjusted for age and sex
§ difference of two proportions adjusted for age, sex and baseline-value

Appendix 1C. Risk factor measurements and mean differences of risk factors between intervention and reference group at follow-up examinations in patients with peripheral arterial disease

	Intervention group (n=132)	Reference group (n=135)	Mean difference*	95% CI	Mean difference†	95% CI
Systolic blood pressure (mmHg)	145 ± 20	144 ± 22	0.9	-4.0 to 5.8	0.7	-4.0 to 5.3
Diastolic blood pressure (mmHg)	81 ± 9	82 ± 12	-0.4	-3.0 to 2.1	-0.9	-3.4 to 1.6
Glucose (mmol/l)	6.2 ± 1.4	6.6 ± 3.2	-0.4	-1.0 to 0.2	-0.2	-0.8 to 0.3
Total cholesterol (mmol/l)	4.6 ± 1.2	4.7 ± 1.2	-0.2	-0.5 to 0.1	-0.2	-0.5 to 0.04
HDL-cholesterol (mmol/l)	1.4± 0.4	1.5 ± 0.5	-0.2	-1.3 to -0.1	-0.2	-0.3 to -0.1
LDL-cholesterol (mmol/l)	2.5 ± 0.9	2.9 ± 1.1	-0.5	-0.7 to -0.2	-0.5	-0.8 to -0.3
Triglycerides (mmol/l)	1.6 ± 1.3	1.6 ± 0.9	0.01	-0.26 to 0.28	0.02	-0.2 to 0.3
Creatinine clearance (Cockroft)	71 ± 22	71 ± 23	1.7	-2.8 to 6.1	-0.1	-3.8 to 3.6
Homocysteine (µmol/l)	12.3 ± 6.6	14.3 ± 5.2	-2.1	-3.5 to -0.7	-2.1	-3.5 to -0.8
BMI (kg/m^2)	27.0 ± 4.2	26.7 ± 3.7	0.3	-0.7 to 1.2	0.04	-0.72 to 0.81
Waist circumference (cm)	97 ± 11	97 ± 12	0.3	-2.3 to 2.9	-	-
Current smoking (%)	28	39	-10‡	-21 to 1	-6§	-15 to 2

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in mean ± standard deviation
* mean difference adjusted for age and sex: follow-up value in intervention group - follow-up value in reference group
† mean difference adjusted for age, sex and baseline-value: follow-up value in intervention group - follow-up value in reference group
‡ difference of two proportions adjusted for age and sex
§ difference of two proportions adjusted for age, sex and baseline-value

Appendix 1D. Risk factor measurements and mean differences of risk factors between intervention and reference group at follow-up examinations in patients with type 2 diabetes

	Intervention group (n=121)	Reference group (n=94)	Mean difference*	95% CI	Mean difference†	95% CI
Systolic blood pressure (mmHg)	140 ± 19	144 ± 21	-4.7	-10.1 to 0.6	-5.5	-10.5 to -0.4
Diastolic blood pressure (mmHg)	84 ± 12	87 ± 11	-1.5	-4.5 to 1.6	-2.1	-5.0 to 0.8
Glucose (mmol/l)	8.3 ± 2.9	9.4 ± 3.8	-1.0	-1.9 to -0.1	-0.2	-1.0 to 0.7
Total cholesterol (mmol/l)	4.5 ± 1.1	4.5 ± 1.0	0.1	-0.2 to 0.4	0.03	-0.2 to 0.3
HDL-cholesterol (mmol/l)	1.2 ± 0.4	1.3 ± 0.4	-0.1	-0.2 to -0.03	-0.1	-0.2 to -0.03
LDL-cholesterol (mmol/l)	2.5 ± 1.0	2.7 ± 0.9	-0.2	-0.4 to 0.1	-0.3	-0.5 to -0.02
Triglycerides (mmol/l)	1.9 ± 1.3	2.0 ± 1.6	-0.1	-0.5 to 0.3	0.03	-0.3 to 0.4
Creatinine clearance (Cockroft)	83 ± 28	87 ± 24	0.6	-5.3 to 6.5	-5.3	-9.7 to -1.0
Homocysteine (µmol/l)	11.6 ± 4.0	13.1 ± 5.5	-1.8	-3.1 to -0.5	-1.6	-2.8 to -0.3
BMI (kg/m^2)	30.5 ± 6.2	30.6 ± 5.9	0.2	-1.3 to 1.8	0.5	-1.3 to 1.4
Waist circumference (cm)	105 ± 12	105 ± 15	0.4	-3.2 to 4.0	-	-
Current smoking (%)	22	22	-0.2‡	-11 to 11	-2§	-10 to 7

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in mean ± standard deviation
* mean difference adjusted for age and sex: follow-up value in intervention group - follow-up value in reference group
† mean difference adjusted for age, sex and baseline-value: follow-up value in intervention group - follow-up value in reference group
‡ difference of two proportions adjusted for age and sex
§ difference of two proportions adjusted for age, sex and baseline-value

Appendix 2A. Proportion of patients who achieved treatment goals at follow-up examinations in patients with coronary heart disease

	Intervention group (n=202)	Reference group (n=171)	Absolute difference*	95% CI	Absolute difference†	95% CI
Systolic blood pressure <140 mmHg	57	54	3	-8 to 13	1	-9 to 11
Diastolic blood pressure <90 mmHg	79	72	7	-2 to 15	6	-2 to 15
Total cholesterol <4.5 mmol/l	59	64	-5	-15 to 5	-6	-16 to 3
HDL-cholesterol men >1.0, women >1.2 mmol/l	81	91	-10	-17 to -2	-9	-16 to -2
LDL-cholesterol <2.5 mmol/l	63	56	11	5 to 17	4	-6 to 14
Triglycerides <1.7 mmol/l	70	67	4	-6 to 13	1	-8 to 11
Glucose <7.0 mmol/l	91	84	7	0 to 14	6	-0.3 to 13
BMI <25 kg/m^2	18	21	-2	-10 to 7	0.4	-7 to 8
BMI <30 kg/m^2	78	70	8	-1 to 17	10	2 to 18
Waist circumference men <102, women <88 cm	54	46	6	-5 to 16	-	-
No smoking	87	88	1	-6 to 8	-2	-8 to 4

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in percentages
* absolute differences of proportions adjusted for age and sex
† absolute differences of proportions adjusted for age, sex and baseline-value

Appendix 2B. Proportion of patients who achieved treatment goals at follow-up examinations in patients with cerebrovascular disease

	Intervention group (n=149)	Reference group (n=166)	Absolute difference*	95% CI	Absolute difference†	95% CI
Systolic blood pressure <140 mmHg	66	55	11	-0.2 to 22	8	-2 to 18
Diastolic blood pressure <90 mmHg	84	65	19	9 to 29	19	9 to 28
Total cholesterol <4.5 mmol/l	54	55	-2	-13 to 9	-4	-15 to 7
HDL-cholesterol men >1.0, women >1.2 mmol/l	87	88	-2	-9 to 6	0.2	-7 to 7
LDL-cholesterol <2.5 mmol/l	60	46	14	3 to 25	13	2 to 24
Triglycerides <1.7 mmol/l	76	72	6	-4 to 16	1	-8 to 11
Glucose <7.0 mmol/l	90	90	-1	-8 to 6	-6	-12 to 1
BMI <25 kg/m^2	32	31	3	-8 to 13	2	-8 to 11
BMI <30 kg/m^2	86	78	8	-1 to 16	7	-1 to 11
Waist circumference men <102, women <88 cm	56	54	0.3	-11 to 11	-	-
No smoking	79	80	1	-8 to 10	-2	-9 to 5

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in percentages
* absolute differences of proportions adjusted for age and sex
† absolute differences of proportions adjusted for age, sex and baseline-value

Appendix 2C. Proportion of patients who achieved treatment goals at follow-up examinations in patients with peripheral arterial disease

	Intervention group (n=132)	Reference group (n=135)	Absolute difference*	95% CI	Absolute difference†	95% CI
Systolic blood pressure <140 mmHg	43	48	-4	-16 to 7	-4	-15 to 7
Diastolic blood pressure <90 mmHg	81	79	2	-7 to 12	4	-6 to 14
Total cholesterol <4.5 mmol/l	50	49	1	-11 to 13	4	-8 to 15
HDL-cholesterol men >1.0, women >1.2 mmol/l	76	82	-6	-16 to 4	-6	-16 to 4
LDL-cholesterol <2.5 mmol/l	52	38	14	2 to 27	16	5 to 29
Triglycerides <1.7 mmol/l	67	70	-3	-14 to 8	-4	-14 to 7
Glucose <7.0 mmol/l	83	79	4	-5 to 14	2	-6 to 11
BMI <25 kg/m^2	34	34	1	-11 to 12	3	-7 to 13
BMI <30 kg/m^2	78	82	-3	-13 to 6	-2	-11 to 7
Waist circumference men <102, women <88 cm	55	50	6	-5 to 18	-	-
No smoking	72	62	10	-1 to 21	6	-2 to 15

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in percentages
* absolute differences of proportions adjusted for age and sex
† absolute differences of proportions adjusted for age, sex and baseline-value

Appendix 2D. Proportion of patients who achieved treatment goals at follow-up examinations in patients with type 2 diabetes

	Intervention group (n=121)	Reference group (n=94)	Absolute difference*	95% CI	Absolute difference†	95% CI
Systolic blood pressure <140 mmHg	49	44	9	-5 to 22	10	-3 to 23
Diastolic blood pressure <90 mmHg	65	61	2	-11 to 15	4	-9 to 17
Total cholesterol <4.5 mmol/l	58	54	2	-12 to 15	3	-10 to 16
HDL-cholesterol men >1.0, women >1.2 mmol/l	62	78	-17	-30 to -5	-15	-25 to -4
LDL-cholesterol <2.5 mmol/l	59	50	7	-7 to 21	11	-2 to 23
Triglycerides <1.7 mmol/l	51	56	-6	-19 to 8	-10	-22 to 3
Glucose <7.0 mmol/l	37	28	8	-5 to 21	3	-10 to 17
BMI <25 kg/m^2	9	18	-10	-19 to -1	-11	-19 to -2
BMI <30 kg/m^2	53	52	-2	-15 to 11	-4	-14 to 6
Waist circumference men <102, women <88 cm	33	29	2	-10 to 14	-	-
No smoking	79	78	2	-11 to 11	-2	-10 to 7

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in percentages
* absolute differences of proportions adjusted for age and sex
† absolute differences of proportions adjusted for age, sex and baseline-value

Appendix 3. Medication use in patients with coronary heart disease, cerebrovascular disease, peripheral arterial disease, and type 2 diabetes at follow-up examinations

	Coronary heart disease		Cerebrovascular disease		Peripheral arterial disease		Type 2 diabetes	
	Intervention group (n=202)	Reference group (n=171)	Intervention group (n=149)	Reference group (n=166)	Intervention group (n=132)	Reference group (n=135)	Intervention group (n=121)	Reference group (n=94)
Blood pressure-lowering agents (%)	89	93	62	74	70	69	83	78
Lipid-lowering agents (%)	93	95	81	81	80	71	71	70
Glucose-lowering agents (%)	13	15	14	13	17	27	88	96
Anti-thrombotic agents* (%)	84	96	85	95	87	88	39	40
Beta-blocking agents (%)	75	74	24	31	28	36	40	30
Diuretics (%)	19	21	28	41	34	28	53	32
ACE inhibitor or AII-antagonist (%)	46	57	44	43	54	49	74	65
Calcium-antagonist (%)	21	29	10	17	20	27	23	19
Statins (%)	91	92	79	79	76	70	67	69
Fibrates (%)	2	0	1	1	2	1	3	1
Oral hypoglycaemic drugs (%)	12	15	12	10	15	20	75	73
Insulin (%)	3	2	5	6	5	13	29	61
Antiplatelet agents	78	88	74	80	74	71	31	38

ACE-inhibitor: angiotensin converting enzyme-inhibitor, AII-antagonist: angiotensin II-antagonist; Data are presented as percentages of users
* anticoagulant and antiplatelet agents

Appendix 4. On treatment analyses of risk factors in intervention and reference group at follow-up examinations

	Intervention group (n=468)	Reference group (n=566)	Mean difference*	95% CI	Mean difference†	95% CI
Systolic blood pressure (mmHg)	138 ± 18	142 ± 20	-3.3	-5.6 to -1.0	-3.0	-5.1 to -0.8
Diastolic blood pressure (mmHg)	81 ± 10	85 ± 11	-3.6	-4.9 to -2.3	-3.8	-5.1 to -2.5
Glucose (mmol/l)	6.5 ± 1.8	6.6 ± 3.0	-0.2	-0.5 to 0.1	0.2	-0.1 to 0.4
Total cholesterol (mmol/l)	4.4 ± 1.0	4.5 ± 1.1	-0.1	-0.2 to 0.04	-0.1	-0.2 to 0.1
HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.5 ± 0.4	-0.1	-0.2 to -0.1	-0.1	-0.2 to -0.1
LDL-cholesterol (mmol/l)	2.4 ± 0.8	2.7 ± 1.0	-0.3	-0.4 to -0.2	-0.3	-0.4 to -0.2
Triglycerides (mmol/l)	1.5 ± 1.0	1.6 ± 1.1	-0.1	-0.3 to 0.01	-0.04	-0.17 to 0.08
Creatinine (µmol/l)	95 ± 37	93 ± 40	1.2	-3.4 to 5.8	1.9	-2.0 to 5.7
Creatinine clearance (Cockroft)	76 ± 22	76 ± 23	-1.9	-4.1 to 0.3	-3.0	-4.8 to -1.2
Homocysteine (µmol/l)	11.2 ± 4.4	13.2 ± 5.0	-2.0	-2.5 to -1.4	-1.9	-2.4 to -1.3
Weight (kg)	84.2 ± 14.7	84.4 ± 16.0	-1.3	-3.1 to 0.4	-2.0	-3.3 to -0.8
BMI (kg/m^2)	27.8 ± 4.5	28.0 ± 4.7	-0.2	-0.8 to 0.4	-0.4	-0.8 to -0.05
Waist circumference (cm)	99 ± 11	99 ± 14	-0.4	-1.9 to 1.1	0.3	-0.9 to 1.6
Hip circumference (cm)	105 ± 9	106 ± 10	-1.0	-2.2 to -0.1	-1.2	-2.2 to -0.3
Current smoking (%)	19	22	-4‡	-9 to 1	2§	-2 to 6

CI: confidence interval, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMI: body mass index
All data in mean ± standard deviation
* mean difference: follow-up value intervention group - follow-up value reference group adjusted for age and sex
† mean difference: follow-up value intervention group - follow-up value reference group adjusted for age, sex and baseline-value
‡ difference of two proportions adjusted for age and sex
§ difference of two proportions adjusted for age, sex and baseline-value

7

A written agreement between general practitioner and hospital on risk factor treatment slightly improves vascular risk profiles of patients with manifest arterial disease. A randomized controlled trial

Beate G. Brouwer, Frank L.J. Visseren, Guy E.H. Rutten, Sophie M.C. Hickox, Berna G.M. Sol, Yolanda van der Graaf.

Submitted

Abstract

Objective

Treatment goals for vascular risk factors are often not reached without the use of effective (pharmacological or lifestyle) interventions. High-risk patients remain at high risk of developing new vascular events. In the present study, we investigated whether a clearly written agreement on risk factor management between general practitioners (GP) and hospital improved the vascular risk profile of high-risk patients compared with usual care after 1 year.

Methods

Patients aged 18-79 years referred for symptomatic manifestations of coronary artery disease, cerebrovascular disease, or peripheral arterial disease entered a screening program for vascular risk factors. The GPs of these patients were asked to participate in the study and, if they consented, GPs were randomized to the intervention or the control group. The GPs in the intervention group signed an agreement in which they explicitly stated which risk factors they intended to treat and which were to be treated by nurse practitioners in the hospital. All patients of one GP were assigned to the same arm of the trial. After 1 year risk factors were measured again. The primary outcome was the achievement of treatment goals for different vascular risk factors.

Results

Eighty-seven of the 122 patients of the GPs in the intervention (n=96) group participated in the study as did 98 of 126 patients of the GPs in the control group (n=101). The GPs indicated in the agreement to take responsibility for treatment of most vascular risk factors. Patients in the intervention group achieved treatment goals for total cholesterol (differences: 9%, 95% CI 2-17) and LDL-cholesterol (8%, 95% CI 0.5-16) more often than did patients in the control group.

Conclusion

A written risk factor treatment agreement between GP and hospital for individual patients who had been screened for vascular risk factors resulted in slightly better management of vascular risk factors in patients with manifest arterial diseases after 1 year.

Introduction

Modification of vascular risk factors is known to be effective in reducing the incidence of (new) vascular events and death,[1] yet risk factor treatment is often not successful in a large proportion of patients. Indeed, risk factor management has improved slightly in Europe between 1996 and 2007.[2-5] Patients are not treated at all or do not reach treatment goals for individual risk factors according to (inter)national guidelines.[6] While the systematic identification of risk factors is often done adequately,[7;8] the subsequent treatment of these risk factors appears to be difficult in daily clinical practice.[3;9;10] Physicians report that time constraints are the largest single barrier to the treatment of lifestyle such as smoking cessation, weight loss, increasing consumption of fruit and vegetables, increasing physical activity, and decreasing intake of salt and saturated fats.[11;12]

Medical specialists are mainly focused on the diagnosis and treatment of the clinical manifestations of vascular diseases and are perhaps less focused on preventive aspects. Risk factors are often not measured routinely and data are often incomplete.[13] Moreover, communication between general practitioner (GP) and vascular specialist about the treatment of risk factors is often not structured and it often remains unclear 'who is doing what'.[14] Optimal risk factor management for individual patients requires a tailored, co-ordinated approach, involving the GP, vascular specialist(s), and patient. A systematic review showed that shared care across the primary-speciality interface is not effective in the management of chronic diseases, although shared care might be more effective in certain patients groups, for example patients with high levels of morbidity. However, shared care significantly improved the prescribing and use of medications.[15] There are few studies of shared care models, based on written protocols, for patients with vascular diseases.[15;16] Yet close collaboration between the GP and the vascular specialist(s) on the management of vascular risk factors in their patients may improve the treatment of risk factors and hence improve the prognosis of high-risk patients. In the BEST (BEtter risk factor treatment with STructured agreement) study, we investigated whether clearly written agreements about risk factor management between GPs and hospital improved the vascular risk profile of patients with manifest arterial disease, compared with usual care, after 1 year.

Methods

Study design

In this randomized controlled trial, GPs were assigned after informed consent to the intervention or control group by a computerized randomization program, specially developed for this study. The randomization program was designed with blocking into 4 groups that allowed orderly recruitment into both groups and reduced the risk of uneven recruitment later in the study and was managed by the researcher. Some participating GPs had more than one patient in the study; these GPs were randomized only once. The GPs needed to give informed consent for each separate patient. While the patients of GPs who assigned to the intervention group were asked to give informed consent before the start of the study, those of GPs assigned to the control group were asked for their informed consent when they came for follow-up measurements. This approach was necessary to achieve sufficient internal validity[17] and was approved by the Ethics Committee of the UMC Utrecht.

Patients

A vascular risk factor screening programme was routinely offered to patients aged 18-79 years with symptomatic manifestations of transient ischaemic attack, stroke, myocardial infarction, angina pectoris, or peripheral arterial disease (PAD) referred to the University Medical Center Utecht (UMC Utrecht), The Netherlands. The vascular screening and prevention program (Second Manifestations of ARTerial disease (SMART) study) is described in detail elsewhere.[18] In short, information on medical history, current medication use, smoking behaviour, alcohol use, and health-related quality of life (SF-36) was obtained by a questionnaire. Blood pressure was measured twice in sitting position at the right and left upper arm with a non-random sphygmomanometer, and mean systolic and diastolic blood pressure were calculated. Height and weight were measured without shoes and heavy clothing, and Body mass index (BMI) was calculated. Waist circumference was measured halfway between the lower rib and the iliac crest, and hip circumference was measured at the level of the greater trochanter. Blood and urine samples were collected after an overnight fast. Serum glucose, total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol levels were measured, and low-density lipoprotein (LDL) cholesterol was calculated with Friedewald's formula. An early-morning urine sample was collected to measure albumin and creatinine

concentrations. A multidisciplinary team of in-hospital specialists (cardiologist, neurologist, internist, vascular surgeon) formulated treatment recommendations (such as repeat measurements, start or adjust current medication, or change lifestyle) for the management of elevated individual risk factors based on (inter)national guidelines.[1;19] The results and the treatment recommendations were reported in writing to the treating vascular specialist and the GP within 1 month of screening. Patients were eligible for the BEST study when at least two modifiable vascular risk factors were present: hypertension, overweight, hypercholesterolaemia, hyperglycaemia, microproteinuria, or current smoking. Patients with terminal malignant disease or a life expectancy shorter than 2 years were excluded. The GPs of the patients eligible for the BEST study were asked to participate at the moment they received the results and the treatment recommendations about a patient. The results of the vascular screening were used as baseline measurements in the BEST study. GPs of the eligible patients were approached in the period September 2004 to November 2006.

Intervention group

The patients of GPs randomized to the intervention group were informed about the BEST study by letter. After patients gave their informed consent, GPs received a written agreement in which they indicated which vascular risk factor(s) of that patient they considered themselves responsible for. This was duly signed and a copy returned to the UMC Utrecht. The other risk factors, if any, were treated by a nurse practitioner under supervision of an internist at the outpatient clinic of the department of Vascular Medicine of UMC Utrecht. The GP and the patient received confirmation of the agreement regarding the treatment of the indicated risk factors. According to the agreement and according to Dutch guidelines on cardiovascular disease prevention, the patient then was treated by both, his/her GP or the nurse practitioner at the outpatient clinic. The Dutch guidelines on cardiovascular disease prevention are based on the European Guidelines on Cardiovascular Disease prevention.[1] Until January 2006, when a new Dutch cardiovascular guideline was launched, the treatment goals of the old guidelines were used for inclusion of the patients. According to guidelines the following goals were set: total cholesterol <4.5 mmol/l, LDL-cholesterol <2.5 mmol/l, triglycerides <1.7 mmol/l, HDL-cholesterol for men >1.0 mmol/, and women >1.2 mmol/l,[20] blood pressure <140/90 mmHg,[21] fasting glucose <6.1 mmol/l,[22] microproteinuria <3.0 mg/mmol kreat, BMI<25 kg/m^2,[23] and complete smoking cessation.[24]

Control group

The patients of the GPs assigned to the control group received care as usual, so further actions was left to the discretion of the GP or the treating vascular specialist. Both physicians received the results of the vascular screening program in writing, together with treatment recommendations, similarly as those in the intervention group.

Follow-up measurements

The follow-up measurements were scheduled about 12 months after GPs in the control group gave their informed consent and 14 months the GPs in the intervention group gave their informed consent, resulting in a similar 'active' follow-up period of 12 months in both groups.

Fasting blood samples were collected for the measurement of total cholesterol, HDL-cholesterol, triglycerides, and serum glucose levels. LDL-cholesterol was calculated with Friedewald's formula. Fasting urine was collected to measure creatinine and micro-albumin levels. Weight was measured and BMI was calculated. Waist and hip circumference were measured. Current medication use, smoking, physical activity and alcohol use were established with a questionnaire. Quality of life was assessed with the Medical Outcomes Study 36-items Short-Form Health Survey (SF-36).[25]

Outcome parameters

The proportion of achieved treatment goals for each risk factor achieved before and after the intervention was compared for the intervention group and control group.

Analyses

The unit-of-analysis was the patients. The data of patients who withdrew (n=32), were lost to follow-up (n=7), were non-responders (n=22) or whose GP did not do the intervention (n=2) were not included in the final analysis. Continuous variables are presented as means with standard deviation (SD) or as medians with interquartile range (IQR), and dichotomous variables are presented as percentages. The baseline characteristics of the randomized GPs and patients are presented to show if intervention and control group were comparable. Differences between the intervention and the control group are expressed as differences in the proportion of patients who achieved the treatment goal(s) at baseline and follow-up and are presented with the corresponding 95% CI.

To determine whether there were changes in quality of life, mean differences in any scale of overall scores between the groups were calculated.

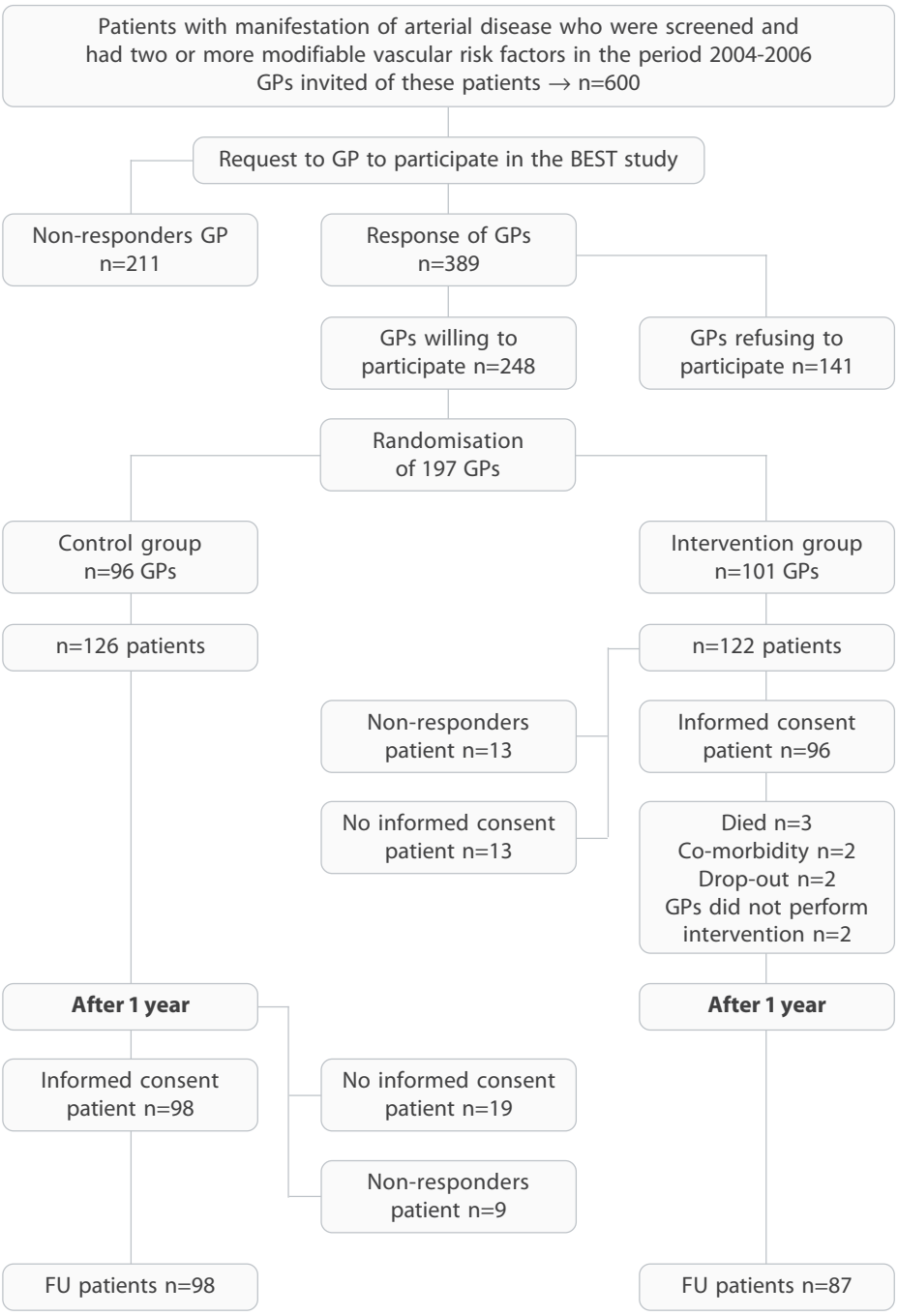

Figure 1. Flow of general practitioners and patients through the study. GP: general practitioner, FU: follow-up.

Results

Study population

The response rate of the GPs was 65%; 197 GPs were randomized between September 2004 and November 2006. These GPs corresponded with 248 eligible patients (Figure 1). Informed consent was not obtained for 28 patients in the control group and 26 patients in the intervention group, because of other comorbidity, no interest, or distance of their residence to the hospital. During the study, three patients died, two patients were not able to continue the study, one patient had a severe stroke, and one patient was diagnosed with HIV and decided not to continue the study. Although initially consenting, two GPs assigned to the intervention group did not sign the risk factor treatment agreement. Therefore, the main analyses were based on data for 87 (71%) of the 122 patients in the intervention group and 98 (78%) of the 126 patients in the control group. Follow-up ended in November 2007. The median follow-up was 13 (IQR 12-15) months in the intervention group and 14 (IQR 13-15) months in the control group.

The baseline characteristics of GPs are shown in Table 1. The GPs who were randomized were well balanced in terms of practice characteristics and the number of patients per participating GP. The mean age of GPs was 48.4±7.4 years and 75% were male. The mean number of patients per GP was 1.2 (range, 1-3) for the intervention group and 1.3 (range, 1-3) for the control group. Baseline characteristics of the patients in the intervention and control groups were comparable (Table 2). The baseline characteristics of the patients eligible for inclusion and those who gave informed consent were comparable, except that the patients in the intervention group used blood pressure-lowering and lipid-lowering drugs more often than the eligible patients.

Risk factor treatment agreement between general practitioner and vascular specialist

Among the 87 patients in the intervention group, elevated blood pressure (56%) and BMI ≥25 kg/m^2 (77%) were the most prevalent risk factors measured at baseline. The GPs indicated that they would take responsibility for the management of most vascular risk factors; almost a third of the GPs asked the hospital to take responsibility for the weight reduction and smoking cessation treatment goals (Table 3). The most GPs indicate that they would be responsible for treatment of all risk factors of their patients (51%). Only 7% of all GPs indicated that the hospital should take responsibility for treatment of all risk factors.

Table 1. Baseline characteristics of general practitioners

	Intervention group (n=101)	Control group (n=96)
Men (%)	74	70
Age (years)	47.5 ± 7.7	49.6 ± 7.1
Years practicing as GP	18.0 ± 8.7	16.4 ± 9.2
Number of GPs in that practice	2.5 ± 1.7	2.6 ± 1.4
Number of patients per GP in study		
1 patient (%)	81	87
2 patients (%)	12	10
3 patients (%)	5	3
4 patients (%)	2	0
Practice form		
solo (%)	34	28
duo (%)	23	28
group* (%)	44	44
Location of GP practice		
urban (%)	43	29
semi-rural (%)	46	47
rural (%)	12	23

GP: general practitioner
* ≥3 general practitioners in one practice

Differences in proportion of achieved treatment goals in the intervention and control groups

The median number of times patients visited their GP was the same in the two groups (2; range, 0-7). A slightly higher proportion of patients in the intervention group compared with the control group achieved their treatment goals for risk factors at follow-up (Table 4); this difference was statistically significant for total cholesterol (difference: 9%, 95% CI 2 to 17) and LDL-cholesterol (difference: 8%, 95% CI 0.5 to 16) treatment goals. For all other risk factors, there were no significant differences in proportion of achieved treatment goals between intervention and control group.

Table 2. Baseline characteristics of eligible and participating patients

	Intervention group (n=122)	Control group (n=126)	Informed consent Intervention group (n=87)	Informed consent Control group (n=98)
Men (%)	72	83	74	85
Age (years)	59.0 ± 8.9	60.6 ± 9.7	58.1 ± 8.1	60.9 ± 9.8
Systolic blood pressure (mmHg)	144 ± 21	144 ± 20	142 ± 21	144 ± 19
Diastolic blood pressure (mmHg)	82 ± 11	83 ± 11	82 ± 11	83 ± 10
Total cholesterol (mmol/l)	4.7 ± 1.0	4.5 ± 1.0	4.6 ± 1.0	4.5 ± 1.0
HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.3 ± 0.3	1.3 ± 0.4	1.3 ± 0.3
LDL-cholesterol (mmol/l)	2.7 ± 0.9	2.5 ± 0.9	2.6 ± 0.9	2.5 ± 0.9
Triglycerides (mmol/l)	1.7 ± 1.1	1.7 ± 1.1	1.7 ± 1.1	1.7 ± 1.2
Glucose (mmol/l)	6.1 ± 1.7	6.1 ± 1.3	5.9 ± 1.2	6.1 ± 1.4
Body Mass Index (kg/m^2)	27.7 ± 3.9	27.7 ± 3.8	27.6 ± 3.8	27.6 ± 3.8
Waist circumference (cm)	95 ± 12	97 ± 12	95 ± 12	96 ± 12
Current smokers (%)	24	22	20	15
Diabetes mellitus* (%)	18	22	18	22
Prevalence of arterial disease†				
Coronary heart disease (%)	69	69	72	70
Cerebrovascular disease (%)	16	20	18	19
Peripheral arterial disease (%)	27	16	21	16
Medication use				
Blood pressure-lowering drugs (%)	77	80	81	83
Lipid-lowering drugs (%)	75	78	81	81
Antiplatelet drugs (%)	82	87	87	86
Glucose-lowering drugs (%)	12	14	9	13

Data are expressed as mean ± standard deviation or as percentages
* fasting glucose ≥7.0 mmol/l or glucose-lowering agents
† recent diagnosis or in medical history. A single patient can be classified into more than one disease category

Table 3. Proportion of patients (number) with a risk factor not at target at baseline, and the preference of the general practitioner for management of the different risk factors

		Treated by	
	Patients (n=87)	**GP**	**Hospital**
Blood pressure ≥140/90 mmHg	56 (49)	94 (46)	6 (3)
Total cholesterol ≥4.5 mmol/l	20 (17)	88 (15)	12 (2)
HDL-cholesterol men ≤1.0, women 1.2 mmol/l	16 (14)	86 (12)	14 (2)
Triglycerides ≥1.7 mmol/l	32 (28)	86 (24)	14 (4)
LDL-cholesterol ≥2.5 mmol/l	39 (34)	79 (27)	21 (7)
Glucose ≥6.1 mmol/l	30 (26)	92 (24)	8 (2)
Albumin/creatinine ratio ≥3.0 mg/mmol	24 (21)	81 (17)	19 (4)
BMI ≥25 kg/m^2	77 (67)	72 (48)	28 (19)
Smoking*	38 (33)	73 (24)	27 (9)

GP: general practitioner
* current smoking or stopped smoking previous year

Quality of life was not significantly different between the groups at baseline or at follow-up on any scale or overall scores (data not shown).

Medication use

More patients in the intervention group than in the control group used blood pressure-lowering drugs (difference in proportion 6%, 95% CI 2 to 14) (Table 5).

Discussion

A written agreement between GP and hospital regarding the treatment of individual patient's risk factors identified during a screening program resulted in slightly better reduction of risk factors compared to screening alone in patients known with an arterial disease. There was a statistically significant difference in the achievement of treatment goals for LDL-cholesterol and total cholesterol between the intervention and the control group. Blood pressure-lowering drugs were used more often in the intervention group.

The ageing of the population and the improved survival of patients after acute vascular events has led to a considerable increase in the number of patients in the chronic phase of vascular disease who require treatment and monitoring of vascular risk

Table 4. Proportion of patients who achieved treatment goals at baseline and follow-up (n=185)

	Baseline		Follow-up*			
	Intervention group (n=87)	Control group (n=98)	Intervention group (n=87)	Control group (n=98)	Absolute difference†	95% CI‡
Systolic blood pressure <140 mmHg	46	40	59	56	-3	-10 to 4
Diastolic blood pressure <90 mmHg	75	74	82	83	-2	-9 to 5
Total cholesterol <4.5 mmol/l	45	51	59	56	9	2 to 17
HDL-cholesterol men >1.0, women >1.2 mmol/l	76	72	75	66	5	-2 to 12
Triglycerides <1.7 mmol/l	64	63	72	69	2	-5 to 9
LDL-cholesterol <2.5 mmol/l	43	49	55	53	8	0.5 to 16
BMI <25 kg/m^2	23	18	16	17	-6	-13 to 1
BMI <30 kg/m^2	79	80	76	76	1	-5 to 5
Waist circumference men <102, women <88 cm	73	68	59	46	8	0 to 14
No smoking	80	85	83	83	5	-3 to 11

* median follow-up of 14 months (interquartile range 12-15)
† differences in proportions: (follow-up value - baseline value in intervention group) - (follow-up value - baseline value in control group)
‡ 95% confidence interval of difference in proportion

Table 5. Medication use at baseline and at follow-up (n=185)

	Baseline		Follow-up*		
	Intervention group (n=87)	Control group (n=98)	Intervention group (n=87)	Control group (n=98)	Difference in proportions† (95% CI)
Blood pressure-lowering drugs (%)	81	83	88	84	6 (2 to 14)
Lipid-lowering drugs (%)	81	81	91	87	4 (-2 to 10)
Antiplatelet drugs (%)	87	86	80	73	6 (-1 to 13)
Glucose-lowering drugs (%)	9	13	13	14	3 (-3 to 9)

95% CI: 95% confidence interval of the difference
* median follow-up of 14 months (interquartile range 12-15)
† difference in proportions: (follow-up value - baseline value in intervention group) - (follow-up value - baseline value in control group)

factors. Delivering care to this group of patients requires the combined efforts of a variety of professionals (vascular specialist, GP, nurse practitioner), in order to integrate the different aspects of this complex care. While structured screening of vascular risk factors is feasible in practice, achieving a reduction in identified vascular risk factors is more complex. Various interventions have been conducted with the aim of improving vascular risk factor management in primary care[26;27] and secondary care settings.[28] It is assumed that shared care is the way to deliver optimal care, and that it is more effective than either primary or speciality care alone.[15] However, studies of patients with vascular diseases that support this concept are lacking. One study of an integrated care model of service delivery for vascular risk factor management for post-stroke patients showed only a trend towards significant changes in blood pressure control, cholesterol levels and physical activity compared to the control group receiving usual care.[16]

Communication between the GP and vascular specialist about who should take action in vascular risk management is often suboptimal.[14] To improve the dialogue between physicians in primary and secondary care, we developed a risk factor treatment agreement that can be viewed as a contract between GP and vascular specialists. This agreement specified who is responsible for the management of which risk factor in individual patients. Currently, the professional collaboration and communication between primary and secondary care physicians is mainly based on written communication as referral and discharge letters. Studies have shown an insufficient quality and delayed process in written communication about coordination or transferral of duties and obligations from one responsible physician to the other[14;29-31] In the present study, vascular risk factors were evaluated in the hospital and both the GP and vascular specialist received, at the same, a written report of the patient's risk factor profile and the treatment recommendations. In this way, all physicians involved in the care of a specific patient received the same information about that patient. This study showed that a written risk factor treatment agreement adds slightly to better risk factor treatment but was not adequate for ensuring that all risk factors met the targets set by international guidelines for patients with vascular disease. Interestingly, while the patients in the intervention group used blood pressure-lowering drugs more often than the patients in the control group, their blood pressure control was not better. Physicians in the control could have promoted more non-pharmacological therapy (exercise, salt intake) to achieve optimal treatment of blood pressure.

The physicians in this study received written information but it might be more efficient and effective to share electronic medical records, which requires a safe Internet environment. Studies in which joint (tele)consultations of GPs and specialists were

investigated reported a substantial reduction in number of follow-up outpatient appointments, referrals, and number of diagnostic tests.[32;33] However, these studies did not involve patients with vascular disease. Another way to improve risk factor management may be to involve patients more.[34] In the present study, the selections of the risk factors to be treated by the GP or specialists were sent to the patient, so that they would know which physician they would need to consult about those risk factors. Thus, patients were more involved in their risk factor management.

Nevertheless, opinions vary among physicians about the importance of risk factor treatment and how aggressively they should be managed. Moreover, there are barriers to the translation of research findings into clinical practice.[2] Whether this can be attributed to a lack of awareness of relevant evidence or resistance to change in clinical practice is not known. A study of possible barriers indicated that physicians will not implement guidelines if there are unfamiliar, if there are no available tools, such as reminder system, and if they are unconvinced that a guideline will have an impact on patient outcome.[12] However, physicians should know for each individual patient the best way to treat vascular risk factor. Not every risk factor management intervention will be suitable for each patient. Furthermore, the use of modern information technology such as a reminder system in electronic medical records, may promote more efficient risk factor management.[35]

The study had some strong points, namely its randomized design and the variety of patients with regard to the location of the clinical manifestations of arterial diseases. However, the study has some potential limitations. The study population could be considered as complex high-risk patients because the patients were seen in an academic setting, which would limit the generalizability of our findings. However, the patients were referred by GPs and were not tertiary referrals. Halfway through the study, the treatment goals were handled according to the new Dutch cardiovascular guideline.[19] The GPs might have consented because of their particular interest in cardiovascular care, which could dilute the difference between intervention and control group. Lastly, GPs could indicate which risk factor they would take responsibility for, but some risk factors require multifactorial treatment.

In conclusion, a written agreement between GP and hospital for the management of the risk factors of individual patients, identified in a vascular risk factor screening program, resulted in slightly better management of vascular risk factors in patients with manifest arterial disease after 1 year of follow-up.

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Appendix

Behandelovereenkomst

Patiëntenprofiel
Patiëntnummer : 7777666/ 47
Naam : Dhr. G. Smarties
Geb. datum : 08-08-1958
Geslacht : M
Huisarts : dr. J. Janssen

Reden (en) van verwijzing:
Angina pectoris

Risicofactor	**Huidige situatie**	**Welke behandelaar gaat samen met de patiënt aan de slag om het behandeldoel te bereiken?**	
		Huisarts[1]	Nurse Practitioner (onder supervisie van specialist)
Bloeddruk	148/ 92 mmHg	☐	☐
Lengte	1.79 m		
Gewicht	95 kg		
BMI	29.7 kg/m^2	☐	☐
LDL- cholesterol	2.99 mmol/l	☐	☐
Roken	ja	☐	☐

Therapieadvies
Zie bijlage

Streefwaarden
Bloeddruk <140 / 90 mmHg, <130 / 85 mmHg bij hartfalen, diabetes mellitus of nierinsufficiëntie
BMI <25 kg/m^2
LDL- cholesterol <2.5 mmol/l
Roken = stoppen met roken

[1] Wilt u aankruisen welke risicofactoren u samen met de patiënt wilt gaan behandelen. Dit kan variëren van niets, enkele risicofactoren of alles. Daarna kunt u de behandelovereenkomst terugsturen in de bijgevoegde antwoordenvelop.

BEST Behandelovereenkomst Eerste lijn in Samenwerking met Tweede lijn

Written agreement on risk factor treatment

Patient profile

Patient number	: 7777666/ 47
Name	: G. Smarties
Date of birth	: 08-08-1958
Sex	: M
General practitioner (GP)	: dr. J. Janssen

Reason of referral
Angina pectoris

Risk factor	**Current status**	**Who is responsible for management of which vascular risk factor in order to reach the treatment goals?**	
		GP[1]	Nurse Practitioner (supervised by a vascular specialist)
Blood pressure	148/ 92 mmHg	☐	☐
Length	1.79 m		
Weight	95 kg		
BMI	29.7 kg/m^2	☐	☐
LDL- cholesterol	2.99 mmol/l	☐	☐
Smoking	yes	☐	☐

Therapy advice
See enclosure

Treatment goals
Blood pressure <140 / 90 mmHg, <130 / 85 mmHg for patients with heart failure, diabetes mellitus or kidney insufficiency
BMI <25 kg/m^2
LDL-cholesterol <2.5 mmol/l
Smoking = stop smoking

[1] Would you like to tick which risk factor you are going to treat together with your patient. This can be no, a few or all risk factors. Can you send the written agreement back to the researcher. Thank you.

BEST BEtter risk management with STructured agreement

Dear colleges,

Patient G. Smarties, born 08-08-1958 is referred for: Angina pectoris.

We offered the patient, on top of the regular care, to participate in the vascular screening and prevention program SMART, and these gave informed consent. Therefore, information is collected by questionnaire, echography of carotids arteries and aorta, ankle-brachial index, ECG and blood and urine measurements (the results of the vascular screening program are enclosed).

Below follows the results of the screening program together with the treatment advice. These advices are based on (inter)national guidelines.

Blood pressure

Result: - high blood pressure (>140/90 mmHg)
Advice: - consider titration of medication
- if necessary, lifestyle and diet adjustments

Body weight

Result: - BMI 25-30: overweight
risk of co-morbidities moderate increased
Advice: - weight reduction
- if necessary, lifestyle and diet adjustments

Lipids

Result: - increased LDL-cholesterol
Advice: - consider titration of medication

Smoking

Result: - Patient is smoking
Advice: - Stop smoking, consider the possibility of guidance/treatment

The above described advices were formulated in collaboration with:
F.L.J. Visseren, MD, PhD; W. Spiering, MD: internists, P.A.F.M. Doevendans, MD, PhD: cardiologist and L.J. Kappelle, MD, PhD: neurologist.

Kind regards, on behalf of involved specialists,

F.L.J. Visseren, internist.

Enclosure

Patient profile date: 02-06-2006

Pat.nr.	: 7777666
Patient	: G. Smarties
City	: Blokzijl
Gender	: M
Date of birth	: 08-08-1958

Reason of referral:
Angina pectoris

Referred by: Dr. McDreamy, cardiologist, University Medical Center Utrecht

Medical history:
2006 Heart: PTCA

Medication:

selokeen zoc 50	50 mg	1x daily
plavix 75mg tablet	75 mg	1x daily
lipitor 10mg tablet	10 mg	1x daily
ascal cardio 100mg	100 mg	1x daily

Smoking:
Smoking: Yes. Packyears: 14.4.

Results additional examination:

Examination	Results	Date
Duplex of right internal carotid artery	<30% stenosis	16-05-2006
Duplex of left internal carotid artery	no stenosis or plaque	16-05-2006
Ultrasound abdominal aorta maximal diameter proximal	2 cm	16-05-2006
Ultrasoound abdominal aorta maximal diameter distal	1.6 cm	16-05-2006
Kidney measurement, length right	11.7 cm	16-05-2006
Kidney measurement, volume right	126 cc	16-05-2006
Kidney measurement, length left	11 cm	16-05-2006
Kidney measurement, volume left	116 cc	16-05-2006
Ankle-brachial index in rest, right	1.16	16-05-2006
Ankle-brachial index in rest, left	1.17	16-05-2006

ECG:
Old lateral myocardial infarction 20-03-2006

Blood pressure: 148 / 92 mmHg
Length: 1.79 m **Weight**: 95 kg **BMI**: 29.7 kg/m^2
Waist: 103 cm **Hip**: 111 cm **WHR**: 0.93

Blood and urine measurements*:

Examination	Results	Treatment goal	Date
Cholesterol	4.1 mmol/l	<4.5 mmol/l	16-05-2006
Triglycerides	1.21 mmol/l	<1.7 mmol/l	16-05-2006
HDL-cholesterol	0.86 mmol/l	>1.0 mmol/l [Man] >1.2 mmol/l [Women]	16-05-2006
LDL-cholesterol (Friedewald)	2.99 mmol/l	<2.5 mmol/l	16-05-2006
Glucose	5.6 mmol/l	<6.1 mmol/l	16-05-2006
Plasma creatinine	78 µmol/l	<90 µmol/l	16-05-2006
Creatinine clearance	73.61 ml/min/1.73m^2	>90 ml/min/1.73m^2	
Microproteïnuria	1.196 mg/mmol kreat	<3 mg/mmol kreat	16-05-2006
Homocysteine	9.3 µmol/l	<15 µmol/l	16-05-2006
TSH	1.2 mIE/L	0.45 - 4.5 mIE/L	16-05-2006
Hs-CRP	0.9 mg/l	<3.0 mg/l	16-05-2006
Insulin	21 mIE/L		16-05-2006

* after an overnight fast
The calculated microproteinuria is measured on basis of a micro-albumin of <8.

8

General discussion

Physical activity in patients with manifest arterial disease

Cardiovascular disease is the leading cause of death and loss of disability-adjusted year of life.[1] Patients with symptomatic arterial disease or type 2 diabetes are at considerably increased risk of developing a (new) vascular event.[2] The major risk factors for atherosclerotic disease are well-established, namely hypertension, dyslipidemia, hyperglycemia, abdominal obesity, smoking, decreased consumption of fruit and vegetables, and physical inactivity.[3] Current risk factor management is mainly focused on specific risk factors such as hypertension and hyperlipidemia, which can be treated with pharmacological agents, leading to a decreased cardiovascular risk.[2;4-9] The high incidence and prevalence of cardiovascular diseases and type 2 diabetes can partly be attributed to the increased prevalence of abdominal obesity associated with insulin resistance.[10-12] Abdominal obesity, in combination with insulin resistance, is strongly related with the presence of metabolic syndrome, a clustering of cardiovascular risk factors. This health problem is exacerbated by a sedentary lifestyle and the dietary intake of saturated fat. Physical activity has the potential to contribute to a decreased cardiovascular risk,[13;14] with an increase in physical activity leading to improved insulin sensitivity and a subsequent decrease in triglycerides levels, increase in HDL-cholesterol levels and decrease in blood pressure. One of the studies described in this thesis showed that leisure-time physical activity was related to a lower prevalence of metabolic syndrome, independent of body weight or fat distribution (chapter 3). Physical activity may directly influence the insulin signalling transduction pathways in skeletal muscle, leading to increased expression of the glucose transporter GLUT-4, which is involved in the cellular uptake of glucose.[15] Furthermore, physical activity influences the production of adipokines (hs-CRP, IL-6, TNF-α, IL-10, adiponectin) by adipose tissue, irrespective of weight loss, leading to an improvement of insulin sensitivity.[16-18] Insulin resistance is considered to be the major driver underlying the clustering of vascular risk factors and increases the risk of vascular events.[19] The presence of metabolic syndrome is accompanied by a 2- to 3–fold increased risk of the development of cardiovascular diseases and by a 3- to 4-fold increased risk of type 2 diabetes.[20] Patients with clinical manifestations of arterial disease at different sites have a higher prevalence of metabolic syndrome and this is associated with an even higher cardiovascular risk.[21;22] Studies described in this thesis showed that high-risk patients who are physically active have a decreased risk of future vascular events, mortality, and type 2 diabetes (chapters 4 and 5).

The protective role of physical activity against type 2 diabetes, vascular morbidity, and mortality is probably mediated by its favourable effects on traditional and novel risk factors (chapter 2)[13] but particularly by its positive effect on insulin sensitivity (chapter 3). Increasing physical activity and weight reduction are two important lifestyle changes that reduce abdominal obesity and insulin resistance and therefore modify vascular risk and type 2 diabetes. A study investigating the relationship between leisure-time physical activity and the incidence of type 2 diabetes in high-risk patients showed that being physical inactive was associated with an increased risk of type 2 diabetes (chapter 5). The combination of obesity and physical inactivity had a greater effect on the incidence of diabetes than the sum of the effect of the two conditions separately. The importance of these metabolic risk factors from both a clinical and public health perspective is that they can be influenced by weight reduction and increased physical activity, thereby preventing the development of vascular diseases and type 2 diabetes.[23]

Managing vascular risk in patients with vascular disease: is there need for change?

There are evidence-based guidelines for the diagnosis and treatment of vascular risk factors for the prevention of new or recurrent vascular events. However, there is a gap between what is recommended and what is practised.[24] The European Society of Cardiology (ESC) EUROASPIRE I, II and III surveys[25;26] clearly indicated that cardiovascular risk factors are insufficiently managed in patients with coronary heart disease in Europe. The Reduction of Atherothrombosis for Continued Health (REACH) Registry extends the EUROASPIRE findings to include other groups of patients, such as patients with cerebrovascular disease or peripheral arterial disease.[27] These studies revealed that in clinical reality patients with vascular disease continue to have a burden of vascular risk factors. One of the studies described in this thesis not only confirms the high prevalence of vascular risk factors in patients with established vascular disease but also demonstrates that there is a difference between the vascular disease groups (chapter 6). More than 45% of the patients with vascular disease or type 2 diabetes had an increased systolic blood pressure and LDL-cholesterol level.

EUROASPIRE III showed that the increased number of patients with obesity, overweight, diabetes and uncontrolled high blood pressure clearly reflects the failure of preventive strategies. Nevertheless, over the years there has been an increase in the use of drugs (antiplatelet agents, ACE inhibitors and β-blockers, and statins) known to be

of value in vascular prevention or in delaying events in patients with coronary heart disease. Moreover, physical activity affects multiple risk factors such as obesity,[28] insulin resistance,[29] hypertension,[30] hyperlipidemia,[31] and inflammation,[32] and strongly reduces the prevalence of metabolic syndrome and independent components of metabolic syndrome (chapter 3). The changes in individual risk factors brought about by physical activity tend to be modest, in the order of 5% for blood lipids,[33;34] and 3-5 mmHg for blood pressure.[30;35] Physical activity was recently shown to reduce cardiovascular risk by 59% in healthy women, which to a large extent could be explained by changes in inflammation, hemostasis, blood pressure, lipids, and body mass index (BMI).[13] Even taking up physical activity later in life is associated with a reduction in vascular risk factors.[36] There is evidence that lifestyle modification, thus eating more fruit and vegetables, taking exercise, and not smoking, could potentially prevent more than three-quarters of the risk of coronary heart disease (CHD) and stroke.[3] While a range of clinical trials have shown that various drugs for the treatment of individual risk factors reduce the incidence of vascular events,[5-7;37] polypharmacy is needed to influence the major risk factors; however, adherence to drug regimens decreases with each additionally prescribed drug. [38;39] The idea of a 'polypill' containing low doses of multiple drugs has generated much interest, with a simultaneous intervention targeting four risk factors being estimated to reduce cardiovascular mortality by 88%.[40] The effectiveness of lifestyle changes was demonstrate in the theoretical concept of a polymeal.[41]

A substantial proportion of patients use drugs for hypertension and hyperlipidemia, but the proportion of patients achieving treatment goals for these risk factors is disappointingly low (chapter 6 and 7). The same was found for the achievement of treatment goals for lifestyle factors such as obesity and smoking. The vascular screening program, SMART, does not give recommendations for lifestyle changes, which could be considered an omission. The findings presented in this thesis indicate the urgent need to promote lifestyle changes focused on increasing physical activity. This should be done together with weight reduction and smoking cessation. Such an approach would inevitably have beneficial consequences on vascular risk factors. Vascular disorders need to be treated with a combination of lifestyle recommendations/changes and medical management of major cardiovascular risk factors in a more comprehensive risk factor management strategy.[42] An important challenge for physicians involved in the treatment of high-risk patients is how to achieve an optimal vascular risk factor profile to lower vascular risk.

Multiple risk factor interventions in patients with established arterial disease

A potentially effective and efficient way to manage vascular risk factors involves (a) measuring all relevant risk factors, (b) comparing risk factor levels against those laid in current (inter)national guidelines on vascular prevention, (c) implementing therapy, if necessary, and (d) monitoring risk factors. Therefore, several interventions for reducing multiple risk factors will be discussed.

Various programs to improve risk factor awareness and treatment of risk factors in primary or secondary care, or both have been tested among patients at increased risk of developing recurrent vascular events. However, most of these programs focussed on only one or two risk factors and assessment of risk factors in clinical practice is often incomplete. The vascular prevention program SMART provides for the systematic measurement of relevant vascular risk factors. Two strategies for improving relevant vascular risk factors were evaluated in the studies described in this thesis. The RULE study showed that mean blood pressure and LDL-cholesterol were lower 16 months after patients had undergo vascular screening of risk factors than in patients who had not undergo such screening (chapter 6). Furthermore, a written risk factor treatment agreement between general practitioner and hospital, in addition to the vascular screening protocol, resulted in a marginally reduction in levels of LDL-cholesterol and total cholesterol between baseline and follow-up (chapter 7). Although two-thirds of the patients reached the treatment goals for important risk factors, a substantial proportion of patients did not. Vascular screening in combination with individual treatment advice and a written risk factor treatment agreement may be a good starting point to facilitate risk factor management for general practitioners and vascular specialists but should be followed by intensive coaching, monitoring, and follow-up.

Multiple risk factor intervention strategies for patients with a vascular disease are conducted in different ways (*Table 1*). Nurse-led treatment is frequently used for vascular risk factor management. Studies have shown that the reduction in mean levels of risk factors is greater with intensive nurse-led interventions[43;44] than with nurse-led interventions focused on co-ordinating, supporting follow-up, and improving communication between hospital and general practice.[45] In the study described in chapter 7, the written risk factor treatment agreement was the only intervention. Apparently there is need for interventions that go beyond the mere transfer of information and the sending of reminders. Education should be followed by empowerment and monitoring, with iteration of this process until the target risk factor levels are achieved.[44]

Table 1. Multiple risk factor interventions for risk factor reduction in patients with established arterial disease

First author	N	Mean age	Type of patients	Intervention group	Follow-up	Outcome estimates (intervention vs. control between baseline and follow-up)
Web-based intervention						
Southard 2003[53]	104	62 years (range, 37-86)	patients with cardiovascular disease	internet program managed by nurses to provide risk factor management, support, education, and monitoring services	6 months	weight (-3.6 vs. +0.47 lb, p=0.003) BMI (-0.6 vs. -0.1 kg/m^2, p=0.003) No significant differences in changes for SBP, DBP , TC, LDL, HDL, and TG
Coaching by telephone and mail						
Vale 2003[44]	792	58.5 years (range, 24-87)	patients with coronary heart disease	coach program which provide coaching via telephone and mailings managed by dieticians and nurses	6 months	TC (-0.54 vs. -0.18 mmol/l, p=0.0001) LDL (-0.55 vs. 0.21 mmol/l, p=0.0001) weight (-1.3 vs. -0.4 kg, p=0.001) BMI (-0.5 vs. 0.1 kg/m^2, p=0.001) SBP (+0.1 vs. +4.5 mmHg, p=0.001) DBP (0.4 vs. +2.8 mmHg, p=0.005) taken up walking (69% vs. 44%, p<0.05)
Joint consultation						
Vlek 2003[46]	396	58 years (range, 0-97)	patients with suspected cardiac disease	joint consultation with GP and cardiologist	1.25 years	referral to cardiologist (33 vs. 52%, p=0.001) further diagnostic procedures (7 vs. 16%, p<0.05) No risk factors were mentioned
Nurse-led intervention *nurses coordinating existing services*						
Jolly 1999[45]	597	mean 63.5 years	patients with coronary heart disease	specialist nurse coordinate care by improving com-munication between hospital and GP and encou-raging GP nurse to provide structured follow-up visits	12 months	TC at FU (5.8 vs. 5.9 mmol/l, dif -0.1(-0.3 to 0.1)) SBP at FU (137 vs. 139 mmHg, dif -2.2 (-5.9 to 1.5)) DBP at FU (84 vs. 85 mmHg, dif -1.3 (-3.6 to 0.9)) BMI at FU (27.4 vs. 28.2 kg/m^2, dif -0.3 (-0.6 to 0.0)) stopped smoking at FU (19 vs. 20%, dif -1 (-13 to 11)

Table 1. Continued

First author	N	Mean age	Type of patients	Intervention group	Follow-up	Outcome estimates (intervention vs. control between baseline and follow-up)
Nurse-led intervention *more intensive care by nurse*						
McHugh 2001[43]	120	I: 61.1 (range, 35-77) C: 63.0 (range, 42-76)	patients on waiting list for CABG	health education and motivational interviews by nurses at patients' home	15 months	TC (-0.7 vs. 0 mmol/l, p=0.003) BMI (-1.0 vs. 0.2 kg/m^2, p=0.000) SBP (-9.1 vs. 0 mmHg, p=0.000) DBP (-5.4 vs. 2.8 mmHg, p=0.048) mean min/wk exercise (+75.4 vs. -30.6 min, p=0.00) smoking (-25 vs. -2%, p=0.001)
Ellis 2005[57]	205	I: 64.3 years (range, 62.4-66.1) C: 65.8 years (range, 64.0-67.5)	patients with stroke, TIA or amaurosis fugax	stroke nurse specialist promote lifestyle, medication compliance and relevance of secondary prevention	5 months	TC (-0.96 vs. -0.87 mmol/l, p=0.63) SBP (-9.3 vs. -1.0 mmHg, p=0.039) DBP (-2.1 vs. -1.2 mmHg, p=0.71) smoking (-1.6 vs. -0.4 cigarettes/day, p=0.61)
Murchie 2003[58]	1343	I: 66.1 years C: 66.1 years	patients with coronary heart disease	nurse-run secondary prevention clinics promote lifestyle and medical aspects in general practices	4.7 years	TC (OR 1.22 (0.93 to 1.58) BP (OR 1.48 (0.91 to 2.42) exercise (OR 1.26 (0.88 to 1.81) non-smoking (OR 0.73 (0.40 to 1.34)
Cupples 1999[59]	688	63±7 years	patients with angina pectoris	personal health education/ promotion and follow-up every 4 months in general practice	5 years	TC (-0.35 vs. -0.21 mmol/l, p>0.05) SBP (+7.3 vs. +8.6 mmHg, p>0.05) DBP (-8.6 vs. -6.8 mmHg, p>0.05) BMI (-0.4 vs. -0.4 kg/m^2, p>0.05) episode/wk 20 min exercise (-0.6 vs. -1.0 p>0.05) stopped smoking at FU (17 vs. 25%, p>0.05)

Table 1. Continued

First author	N	Mean age	Type of patients	Intervention group	Follow-up	Outcome estimates (intervention vs. control between baseline and follow-up)
Nurse-led intervention *more intensive care by nurse*						
Goessens 2006[60]	236	60.1±10.3 years	patients with cerebrovascular disease, aortic abdominal aneurysm, or peripheral arterial disease	treatment by nurse practitioners	14 months	TC (-0.9 vs. -0.5 mmol/l, p<0.05) LDL (-0.8 vs. -0.4 mmol/l, p<0.05) TG (-0.4 vs. -0.1, p<0.05) HDL (0 vs. +0.1 mmol/l, p=0.05) SBP (-8 vs. -6 mmHg, p>0.05) DBP (-6 vs. -3 mmHg, p>0.05) BMI (+0.2 vs. +0.7 kg/m^2, p>0.05) WC (0 vs. -1 cm, p>0.05) current smoking (+3 vs. +7%, p>0.05)
telehealth counselling						
Wister 2007[61]	296	not mentioned	patients with coronary heart disease	health report card with Telehealth counselling by a lifestyle counsellor (kinesiologist)	12 months	TC (-0.10 vs. -0.08 mmol/l, p>0.05) HDL (+0.01 vs. -0.02 mmol/l, p>0.05) SBP (-5.64 vs. -1.98 mmHg, p>0.05) BMI (-0.09 vs. -0.03 kg/m^2, p>0.05) WC (-0.18 vs. -1.23 cm, p>0.05) stopped smoking (0 vs. 0%, p>0.05)
case management[*]						
Lear 2006[62]	302	I: 64.8 years C: 63.4 years	patients with ischemic heart disease	risk factor and lifestyle counselling after cardiac rehabilitation by case manager	4.1 years	TC (-0.21 vs. -0.0 mmol/l, p=0.051) LDL (-0.15 vs. +0.01 mmol/l, p=0.093) TG (-0.15 vs. -0.10, p=0.75) HDL (+0.03 vs. +0.041 mmol/l, p=0.42) SBP (-2 vs. +6 mmHg, p=0.005) DBP (+2 vs. +5 mmHg, p=0.10) BMI (+0.3 vs. +0.4 kg/m^2, p=0.48) WC (+1.6 vs. +2.6 cm, p=0.24) current smoking (-0.7 vs. +0.9%, p>0.05)

Table 1. Continued

First author	N	Mean age	Type of patients	Intervention group	Follow-up	Outcome estimates (intervention vs. control between baseline and follow-up)
Nurse-led intervention *case management*[*]						
DeBusk 1994[63]	585	I: 57 years C: 57 years	patients with coronary heart disease (only myocardial infarction)	physician-directed, nurse-managed, home-based case management system	12 months	TC at FU (4.8 vs. 5.4 mmol/l, p<0.001) LDL at FU (2.8 vs. 3.4 mmol/l, p<0.001) TG at FU (1.93 vs. 1.93 mmol/l, p>0.05) stopped smoking at FU (70 vs. 53%, p=0.03) No significant differences in changes for HDL, TG
Haskell 1994[49]	300	56±7 years	patients with coronary heart disease	comprehensive multiple risk factor reduction program by telephone, mail, visits (every 2-3 months to the clinic) By physician-supervised, nurse case manager	4 years	TC (-1.0 vs. -0.1 mmol/l, p=0.001) LDL (-1.0 vs. -0.2 mmol/l, p=0.001) HDL (+0.14 vs. +0.06 mmol/l, p=0.001) TG (-0.34 vs. -0.01, p=0.002) SBP (-0.6 vs. +3.1 mmHg, p=0.008) DBP (-1.3 vs. +0.4 mmHg, p=0.07) BMI (-1.0 vs. +0.3 kg/m^2, p=0.0001) current smoking (0 vs. +1%, p=0.47)
case-management of medium intensity[†]						
Nordmann 2001[48]	201	I: 61±10 years C:62±9 years	patients with coronary heart disease (only myocardial infarction)	hospital-based case-management and outreach program, limited to counselling by a clinician	18 months	TC (-0.6 vs. -0.3 mmol/l, p=0.2) LDL (-0.1 vs. +0.1 mmol/l, p>0.2) HDL (0 vs. 0 mmol/l, p>0.2) SBP (+8 vs. +5 mmHg, p=0.2) DBP (+5 vs. +4 mmHg, p=0.2) BMI (+0.2 vs. -0.4 kg/m^2, p>0.2) smoking (28 vs. 20%, p>0.2)

Table 1. Continued

First author	N	Mean age	Type of patients	Intervention group	Follow-up	Outcome estimates (intervention vs. control between baseline and follow-up)
Nurse-led intervention *co-ordinated care‡ post-discharge*						
Middleton 2005[64]	133	70.4 years	patients having carotid endarterectomy	telephone liaison by nurse combined with education about risk factor management and structured contact with surgeon and GP	3 months	TC (+11.1 vs. -4.5 mgl/dl, p>0.05) DBP (-3.1 vs. -3.1 mmHg, p>0.05) current smoking (-3.4 vs. -4.7%, p>0.05) exercise (+20.3 vs. +15.2 min, p=0.11)
shared care§						
Joubert 2006[65]	97	I: 64.7 years C: 68.2 years	patients with stroke or TIA	integrated care model of service delivery for vascular risk factors management by neurologist	12 months	TC (-0.3 vs. -0.4 mmol/l, p=0.16) SBP (-2 vs. +4 mmHg, p=0.07) no of walks/wk (+1.4 vs. -0.1, p=0.048) No significant differences in changes for TC, TG

BMI: body mass index, TC: total cholesterol, LDL: LDL-cholesterol, HDL: HDL-cholesterol, TG: triglycerides, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, CABG: coronary artery bypass grafting, GP: general practitioner, I: intervention group, C: control group, TIA: transient ischemic attack, N: number of patients randomized

* case-management system refers to a system in which a nurse case-manager, working with different health care specialists (a psychiatrist, a cardiologist, a nutritionist, and a nurse coordinator), managed coronary risk factors

† case -management of medium intensity= program that does not prolonged duration of hospitalization and is restricted to a few follow-up contacts by phone or mail

‡ co-ordinated care models=case management

§ shared care=primary and secondary care clinicians having joint contemporaneous responsibility for patient care, including routine management and monitoring

Intensive individual-tailored counselling by health-care professionals is essential to achieve treatment goals, not only for medication but also for lifestyle changes. One way to improve communication between primary and secondary care and to facilitate effective management is to hold joint (tele)consultations.[46;47] More intensive involvement of the general practitioner and specialist is needed in this structure. Better communication between general practitioner and hospital, which was achieved with a clear written agreement about who was responsible for specific treatment goals resulted in a slightly reduction in risk factors (chapter 7). A greater use of telemedicine could lead to better risk factor management. Undoubtedly, intensive risk factor management strategies or drastic changes in lifestyle are not easily implemented on a large scale and should be tailored to the local situation. Unfortunately, while simple low-intensity interventions for modifying multiple vascular risk factors improves awareness, they seldom result in clinical benefit.[45;48] More intensive coaching and management of risk factors are necessary to achieve long-term compliance with lifestyle changes and medication use.[49] In patients with type 2 diabetes, a target-driven, long-term intensive multifactorial intervention has been shown to reduce the risk of cardiovascular events.[50;51] Importantly, although differences in clinical parameters were small, the differences in outcome were substantial, showing that better outcomes can be achieved by reducing multiple risk factors to a modest extent rather than by maximally reducing a single risk factor. However, is such a time-consuming approach cost effective? A nurse-led clinic for secondary prevention in primary care seems to be cost effective.[52] Moreover, new digital technologies, such a e-health counselling,[53] short message service (SMS),[54;55] or telehealth[56] have the potential to be an efficient and effective way for providing follow-up and for encouraging the active involvement of patients. Further research is required to gain knowledge of the long-term consequences of different interventions and treatments.

Evaluating these studies, a thorough risk factor screening protocol is an effective means to support physicians because in clinical practice the majority of risk factors are not measured or documented properly. However, physicians in different care settings appear to experience problems in sharing risk factor management. Implementation of a written risk factor treatment agreement could prove beneficial, if established by Internet communication, providing a better way to treat all risk factors simultaneously. This approach should be integrated into the existing healthcare system. Subsequently, one physician, general practitioner, or treating specialist, should be responsible for the management of risk factors. Primary care is probably better suited to provide adequate

follow-up of these patients. Intensive treatment and follow-up management are needed to increase patient awareness of the importance of attaining treatment goals to improve long-term adherence with lifestyle changes and medication compliance. However, the 'optimal' approach for effective risk factor management will be different for each individual patient.

Main conclusions of this thesis:

- Waist circumference, an indirect indicator of intra-abdominal fat, has the strongest association with the presence of coronary heart disease in patients with peripheral arterial disease.
- Patients with manifest arterial disease who are physically active in their leisure time are less likely to have metabolic syndrome or insulin resistant than inactive patients, independent of body weight or fat distribution.
- Moderate or vigorous leisure-time physical activity is associated with a decreased risk of vascular events, vascular death, and all-cause mortality, independent of metabolic syndrome in patients with manifest arterial disease.
- Leisure-time physical inactivity is independently associated with an increased risk of type 2 diabetes in patients with manifest arterial disease, or poorly controlled risk factors. Obesity partly explains the relationship between physical inactivity and the incidence of type 2 diabetes.
- The combined effect of physical inactivity and obesity poses a greater risk for the development of type 2 diabetes than the sum of physical inactivity and obesity independently.
- Patients with manifest arterial disease or type 2 diabetes have a lower level systolic blood pressure and lower LDL-cholesterol levels when treated in a hospital with a vascular screening program than when treated in a hospital without such a program.
- Systematic screening for risk factors followed by multidisciplinary treatment advice is not enough for achieving adequate risk factor management in patients with established vascular disease or type 2 diabetes.
- A written risk factor treatment agreement slightly improves risk factor management in patients with arterial disease.

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Summary

Cardiovascular disease continues to impose a heavy burden because of its associated morbidity and mortality. Atherosclerotic vascular disease can become clinically evident at several sites in the arterial system leading to coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. Patients with evident vascular disease are particularly prone to develop (new) vascular diseases. There are several risk factors (hypertension, dyslipidemia, hyperglycemia, smoking, abdominal obesity, and physical inactivity) for the development of atherosclerotic vascular diseases, of which abdominal obesity and its associated insulin resistance are of great importance. Obesity-induced insulin resistance is a major driver behind the clustering of vascular risk factors (metabolic syndrome) and is promoted by a sedentary lifestyle and the dietary intake of saturated fat. Treatment of these risk factors with medication and improvement of lifestyle factors (such as increasing physical activity) can reduce the future risk of vascular events. Currently, risk factor management in patients with vascular disease is not optimal.

The studies presented in this thesis focused on the relationship between the presence of coronary heart disease and intra-abdominal fat (**chapter 2**), and the relationship between leisure-time physical activity and the presence of metabolic syndrome, incidence of type 2 diabetes and recurrence of vascular events in high-risk patients (**chapters 3, 4, and 5**). In addition, risk factor management strategies in patients with clinical manifest vascular disease were evaluated (**chapters 6 and 7**).

MET•hours per week

In the studies described in **chapters 3, 4, and 5,** we asked patients about their usual pattern of leisure-time physical activity and used this information to classify patients into categories according to MET•hours per week. MET means METabolic equivalent and is the total, individual energy expenditure at rest. The amount of energy used depends on a person's weight. One MET represents the energy expenditure for an individual at rest, whereas a 10-MET activity requires 10 times the resting energy expenditure. The time spent on sport activities in hours per week was multiplied by the computed sport-specific energy expenditure, expressed in MET hours per week (MET•h/wk). For example, walking (5 km/h) is 4 MET, so a person who walks 3 hours per week has a leisure-time physical activity of 12 MET•hours per week.

Peripheral arterial disease coexists with other manifestations of atherosclerotic disease at other locations in the arterial system especially coronary heart disease. Intra-abdominal fat, which is associated with metabolic syndrome, is an important determinant of the risk of coronary heart disease. In **chapter 2**, we demonstrated that metabolic syndrome was more prevalent (63%) in patients with coronary heart disease than in patients without coronary heart disease (48%). Furthermore, a 1 standard deviation increase in waist circumference was associated with a 64% (confidence interval (CI) 20% to 123%) higher prevalence of coronary heart disease after adjustment for age and sex in patients with peripheral arterial disease. Additional adjustment for the components of metabolic syndrome and smoking did not influence the results. This suggests that waist circumference, a crude measure of intra-abdominal fat, is associated with an increased risk of concomitant coronary heart disease in patients with peripheral arterial disease. Thus, a reduction of abdominal adiposity may diminish the risk of vascular events in these patients.

It has been shown that metabolic syndrome is highly prevalent in patients with clinical manifestations of arterial disease. Physical activity can influence insulin sensitivity and metabolic syndrome independent of weight loss. In **chapter 3,** we investigated whether leisure-time physical activity was independently associated with the prevalence of metabolic syndrome and insulin resistance in patients with manifest arterial disease, and the role of body fat and fat distribution in this relationship. We demonstrated that the prevalence of metabolic syndrome was markedly lower (20%) in physically active patients (>15 MET•h/wk) than in physically inactive patients (36%, odds ratio 0.49, 95% CI 0.33-0.75) after adjustment for age, sex, body mass index (BMI), smoking, and occupational activity. Patients who were physically active in their leisure time had a considerably lower risk of insulin resistance than inactive patients (OR 0.40, 95% CI 0.25-0.64) after adjustment for age, sex, BMI, and smoking. Thus, regular physical activity is likely to improve components of the metabolic syndrome and insulin resistance in patients with clinical manifest arterial disease, leading to a lower risk of development of new vascular events and type 2 diabetes.

While the incidence of vascular disease in diabetic individuals has been given great attention, much less is known about the converse relationship: the development of type 2 diabetes in patients with manifest vascular disease, and the role of physical activity in this relationship. In **chapter 4,** we investigated the effect of physical inactivity on the incidence of type 2 diabetes in 3940 patients with manifestations of arterial

disease, hypertension, or hyperlipidemia. During a mean follow-up of 4.7 years, 194 (5%) incident cases of type 2 diabetes occurred. Physically inactive patients (<2.5 MET•h/wk) had a higher incidence of type 2 diabetes than physically active patients (≥2.5 MET•h/wk) after adjustment for age, sex, smoking, alcohol consumption, and BMI (hazard ratio, HR, 1.6, 95% CI 1.2-2.2). Patients who were physically inactive and obese (BMI ≥30 kg/m^2) were at greater risk of developing type 2 diabetes (HR 5.6, 95% CI 3.6-8.6) than patients who were physically active and not obese (BMI <30 kg/m^2). We concluded that leisure-time physical activity is independently associated with an increased risk of type 2 diabetes. In addition, the relative excess risk due to interaction of physical inactivity and obesity on an additive scale was 1.0 (95% CI -1.5-3.5). Thus the combined effect of physical inactivity and obesity poses an even greater risk for the development of type 2 diabetes than either condition alone.

In **chapter 5,** we studied the relationship between leisure-time physical activity and the recurrence of vascular events in patients with manifest arterial disease and determined whether metabolic syndrome, body fat, and fat distribution modified this relationship. In a prospective study, 466 of 3875 patients (12%) had a new vascular event during a mean follow-up of 3.9 years. Patients who were moderately (1.0-14.9 MET•h/wk) and vigorously (>15.0 MET·h/wk) physically active had a 30% and 22% lower risk of a recurrent vascular event (age- and sex-adjusted HR 0.70, 95% CI 0.52-0.94 and 0.88, 95% CI 0.65-1.18) and a 48% and 28% lower risk of all-cause mortality (age- and sex-adjusted HR 0.52, 95% CI 0.36-0.74 and 0.72, 95% CI 0.51-1.01), respectively. Metabolic syndrome, body fat, and fat distribution did not modify these relationships. The risk of ischemic stroke, carotid interventions, and lower-limb vascular interventions was lower in moderately and vigorously physically active patients than in inactive patients. Thus, physical activity is associated with a lower risk of non-fatal and fatal vascular events and all-cause mortality in patients with manifest arterial disease. Additionally, physical activity prevents recurrent events and the need for vascular interventions at different vascular sites, except in the coronary arteries.

Modification of vascular risk factors is effective in reducing mortality and morbidity in patients with symptomatic atherosclerosis; however, it is difficult to achieve and maintain. The results of the Risk management in Utrecht and Leiden Evaluation (RULE) study are presented in **chapter 6.** In the RULE study, we compared the effects of a hospital setting with a multidisciplinary vascular screening program and a hospital setting without such a structured program on the improvement in vascular risk profile of patients with

established vascular disease or type 2 diabetes. Eleven hundred seventy patients were enrolled (604 patients in the intervention group and 566 patients in the reference group). After a median follow-up of 16 months, systolic blood pressure (139±19 vs. 142±20 mmHg, difference 2.3 mmHg, 95% CI 0.7-4.3) and LDL-cholesterol (2.4±0.8 vs. 2.7±1.0 mmol/l, difference 0.3 mmol/l, 95% CI 0.2-0.4) were lower in the intervention group than in the reference group. Moreover, patients in the intervention group reached the treatment goal for LDL-cholesterol more often than patients in the reference group (59 vs. 48%, difference 11%, 95% CI 6-17). Systematic screening for risk factors contributed to a slightly better reduction of risk factors in patients with established vascular disease or type 2 diabetes. However, a large proportion of the patients did not reach the treatment goals according to (inter)national treatment guidelines. Thus, systematic screening alone, without adequate monitoring of vascular risk factors, is not enough for risk factor management in high-risk patients.

The results of the BEST study are presented in **chapter 7**. In this randomized controlled trial, we investigated whether a written risk factor treatment agreement between general practitioner and hospital led to improvement of the vascular risk profile compared with usual care in patients with established vascular disease. Patients with manifestation of a vascular disease and who had more than one modifiable risk factor were eligible for the study. Of these patients, 197 general practitioners consented and were randomized to one of two strategies. In one strategy the general practitioners signed an agreement in which they explicitly stated which risk factors they intended to treat and which were left for treatment in the hospital by nurse practitioners (intervention group). In the other strategy care as usual (control group) was given. Eighty-seven of the 122 patients of the GPs in the intervention group (n=96) participated in the study, as did 98 of 126 patients of the GPs in control group (n=101). After a median follow-up of 14 months, the patients in the intervention group achieved the treatment goals for total cholesterol (differences: 9%, 95% CI 2-17) and LDL-cholesterol (8%, 95% CI 0.5-16) significantly more often than did the patients in the control group. The between-group changes in the other risk factors were not significantly different. This study revealed that a written agreement on risk factor treatment between general practitioner and hospital for individual patients, in whom vascular risk factors have been screened, results in slightly better management of vascular risk factors in patients with manifest arterial diseases after 1 year.

Lastly, in the general discussion in **chapter 8,** we discussed our findings in the context of physical activity and vascular risk factor management in patients with established vascular disease and presented the main conclusions of this thesis.

Samenvatting

Hart- en vaatziekte is de belangrijkste oorzaak van ziekte en sterfte en is meestal het gevolg van slagaderverkalking (atherosclerose). Atherosclerotische vaatvernauwingen kunnen optreden in vrijwel alle slagaders maar vooral in de vaten van de benen (perifeer), de hersenen (cerebraal) en het hart (coronair) en leiden dan tot klachten omdat de bloedstroom wordt belemmerd. Patiënten met een klinische uiting van atherosclerotisch vaatlijden hebben een verhoogd risico op een nieuwe uiting van vaatziekte op dezelfde of andere plaats in het vaatstelsel. Verschillende risicofactoren zoals verhoogde bloeddruk, dislipidemie (verstoring in de samenstelling van vet- en cholesterolwaarden), roken, diabetes mellitus (suikerziekte), overgewicht, en weinig lichaamsbeweging zijn verantwoordelijk voor de ontwikkeling van atherosclerose. De clustering van risicofactoren (verhoogde glucose (bloedsuiker), verhoogde bloeddruk, verhoogde triglyceridenconcentratie (vetten), verlaagde HDL-cholesterolconcentratie (goed cholesterol) en overgewicht, met name rond de buik), wordt het metabool syndroom genoemd. Dit metabool syndroom hangt samen met insuline resistentie. Insulineresistentie betekent dat weefsels in het lichaam minder gevoelig zijn voor insuline. Medicamenteuze behandeling (bloedplaatjesremmers, bloeddruk- en cholesterolverlagende medicijnen, en ACE-remmers) en leefstijlverandering (gezondere voeding, meer bewegen, stoppen met roken) kunnen risicofactoren verminderen en de kans op toekomstig atherosclerotisch vaatlijden verkleinen. Helaas is de behandeling van risicofactoren bij veel patiënten die dit verhoogde risico hebben nog niet optimaal.

In dit proefschrift hebben wij gekeken naar de relatie tussen buikvet en de aanwezigheid van coronair vaatlijden (**hoofdstuk 2**), en hebben de relatie tussen lichamelijke activiteit en de aanwezigheid van metabool syndroom, de kans op type 2 diabetes en nieuwe uitingen van vaatziekten bij hoogrisico patiënten onderzocht (**hoofdstukken 3, 4, en 5**). In de laatste hoofdstukken laten we zien wat de effecten zijn van twee nieuwe risicomanagement strategieën bij patiënten met klinisch vaatlijden of type 2 diabetes (**hoofdstukken 6 en 7**).

MET•uren per week

In de **hoofdstukken 3, 4 en 5** worden de patiënten ingedeeld op grond van hun beweegpatroon. Hiervoor worden patiënten geclassificeerd in categorieën van het aantal MET•uren per week dat zij verbruiken. MET is de afkorting voor METabolic equivalent en is het totale, individuele energieverbruik in rust. De hoeveelheid energie die verbruikt wordt is afhankelijk van het gewicht van een persoon. De MET-waarde in rust is 1. Een

MET-waarde van 2 geeft aan dat er 2 maal de energie verbruikt wordt die normaal tijdens rust nodig is. Bijvoorbeeld wandelen (5 km/uur) heeft de MET-waarde 4 dus als een persoon 3 uur per week wandelt dan is dat 12 MET•uren per week.

Patiënten met perifeer vaatlijden hebben een verhoogd risico op coronair vaatlijden. Buikvet en de metabole risicofactoren die hiermee samenhangen zouden het risico op coronair vaatlijden bij patiënten met perifeer vaatlijden kunnen vergroten. In **hoofdstuk 2** laten we zien dat het metabool syndroom vaker voorkomt bij patiënten met coronair vaatlijden dan bij patiënten zonder coronair vaatlijden. Verder was de taille omtrek geassocieerd met de aanwezigheid van coronair vaatlijden. Een standaarddeviatie tailleomtrek was geassocieerd met een meer dan 1.5 keer verhoogd risico. Metabool syndroom en roken hadden geen invloed op de relatie tussen buikvet en de aanwezigheid van coronair vaatlijden.

Het metabool syndroom komt veel voor bij patiënten met klinisch vaatlijden. Insuline gevoeligheid van de cellen en het metabool syndroom worden positief gestimuleerd door lichaamsbeweging zonder dat er sprake hoeft te zijn van gewichtsverlies. In **hoofdstuk 3** wordt de relatie tussen lichamelijke activiteit en de prevalentie van metabool syndroom en insuline resistentie onderzocht bij patiënten met klinisch vaatlijden, en wat de rol van lichaamsgewicht en vetverdeling hierin is. Bij patiënten die lichamelijk meer dan gemiddeld actief waren (≥15 MET•uren per week) in hun vrije tijd kwam het metabool syndroom minder voor (20%) in vergelijking met patiënten die niet actief (0 MET•uren per week) waren (36%). Actieve patiënten hadden 50% minder kans op het ontwikkelen van het metabool syndroom dan inactieve patiënten. Verder bleek uit deze studie dat lichamelijk actieve patiënten 60% minder kans hadden op insuline resistentie dan de inactieve patiënten. Lichaamsgewicht en vetverdeling hadden geen invloed op deze relaties. Regelmatig bewegen zou belangrijk kunnen zijn voor het voorkomen van het metabool syndroom en insuline resistentie bij patiënten met klinisch vaatlijden.

Er zijn veel studies gedaan naar het ontwikkelen van arterieel vaatlijden bij patiënten met type 2 diabetes maar er is minder bekend over het ontwikkelen van diabetes bij patiënten met klinisch vaatlijden. In **hoofdstuk 4** behandelen we de relatie tussen lichaamsbeweging en het ontwikkelen van type 2 diabetes bij patiënten met klinisch vaatlijden, hypertensie of hyperlipidemie. Uit de resultaten bleek dat na een gemiddelde duur van 4.7 jaar lichamelijk inactieve patiënten (<2.5 MET•uren per week) een hoger

risico hadden om type 2 diabetes te ontwikkelen in vergelijking met lichamelijk actieve patiënten (≥2.5 MET•uren per week) (hazard ratio 1.6, 95% betrouwbaarheidsinterval (BI) 1.2-2.2). Deze relatie werd gedeeltelijk verklaard door de body mass index (BMI). In vergelijking met actieve patiënten zonder obesitas (<30 kg/m^2) hadden inactieve patiënten met obesitas (≥30 kg/m^2) een bijna 6 keer groter risico op type 2 diabetes. Verder bleek dat de combinatie van lichamelijke inactiviteit en obesitas een groter effect had dan de som van de 2 risicofactoren. Dit effect suggereert dat lichaamsbeweging en gewichtreductie een grote bijdrage zou kunnen leveren bij het voorkomen van type 2 diabetes bij hoogrisico patiënten.

In **hoofdstuk 5** wordt de relatie tussen lichamelijke activiteit en nieuwe uitingen van vaatlijden op verschillende locaties in het vaatstelsel onderzocht en gaan we na of metabool syndroom, lichaamsgewicht en vetverdeling deze relatie beïnvloeden. In dit onderzoek werden 3875 patiënten met klinisch vaatlijden betrokken. Uit dit prospectief onderzoek van gemiddeld 3.9 jaar bleek dat 12% van de patiënten een nieuwe vaataandoening ontwikkelde. Patiënten die meer dan gemiddeld lichamelijk actief waren in hun vrije tijd (≥15 MET•uren per week) hadden minder risico (30%) op nieuwe uitingen van vaataandoeningen in vergelijking met lichamelijk inactieve patiënten. Patiënten die gemiddeld lichamelijk actief waren (1-14.9 MET•uren per week) en meer dan gemiddeld lichamelijk actieve patiënten (≥15 MET•uren per week) hadden een lager risico, respectievelijk 48% en 28%, om binnen 4 jaar te overlijden in vergelijking met lichamelijk inactieve patiënten. Verder bleek de aanwezigheid van metabool syndroom, lichaamsgewicht en vetverdeling geen invloed op deze relaties te hebben. Daarnaast was het risico op het ontwikkelen van cerebraal vaatlijden, de noodzaak van interventie van de halsslagaders en beenvaten lager bij patiënten die lichamelijk gemiddeld en meer dan gemiddeld actief waren. Dit suggereert dat lichaamsbeweging kan bijdragen in de preventie van niet-fatale en fatale vaataandoeningen en vaatinter-venties bij patiënten met klinisch vaatlijden.

Behandeling van risicofactoren kan de kans op nieuwe uitingen van slagaderverkalking verkleinen bij patiënten met klinisch vaatlijden, maar in de praktijk blijkt dit moeilijk te zijn. In **hoofdstuk 6** wordt de effectiviteit van een risicofactor screening en preventie-programma (SMART) op de vermindering van risicofactoren bij patiënten met klinisch vaatlijden of type 2 diabetes onderzocht. In de Risk management in Utrecht en Leiden Evaluation (RULE) studie waren in totaal 1170 patiënten (604 patiënten in de interventiegroep en 566 in de controle groep) met klinisch vaatlijden of type 2 diabetes

1 jaar na de eerste verwijzing voor hun ziekte teruggekomen voor metingen van hun risicofactoren. Patiënten in de interventiegroep hadden het SMART screenings-programma doorlopen (UMC Utrecht), waarbij de resultaten van deze screening en de bijbehorend behandeladviezen van nieuw opgespoorde of onvoldoende behandelde risicofactoren naar de huisarts en de behandeld specialist werden gestuurd. Verdere behandeling werd overgelaten aan de huisarts en behandeld specialist. Patiënten in de controle groep kregen standaard zorg (LUMC).

De resultaten van het onderzoek laten zien dat systematisch screenen bijdroeg aan het gestructureerd in kaart brengen van de risicofactoren. Bij patiënten die geen screeningsprogramma hadden doorlopen (controle groep) bleek dat een groot deel van de risicofactoren niet was gedocumenteerd. Verder bleek dat na een gemiddelde van 16 maanden de gemiddelde systolische bloeddruk en LDL-cholesterol significant lager waren in de interventiegroep in vergelijking met de referentiegroep. Meer patiënten in de interventiegroep behaalden het behandeldoel voor LDL-cholesterol in vergelijking met de referentiegroep (59% vs. 48%, verschil 11%, 95% BI 6-17). We kunnen hieruit concluderen dat systematisch screenen van vasculaire risicofactoren voor een deel bijdraagt aan beter risicofactormanagement bij patiënten met klinisch vaatlijden of type 2 diabetes. Verder behaalt één derde van de patiënten de behandeldoelen niet volgens de (inter)nationaal richtlijnen. Het systematische screenen zonder monitoring van de risicofactoren is echter nog niet voldoende voor een adequaat risicofactormanagement bij hoogrisico patiënten.

In **hoofdstuk 7** worden de resultaten van de Behandelovereenkomst Eerste lijn in Samenwerking Tweede lijn (BEST) studie beschreven. In deze gerandomiseerde studie werden de effecten van duidelijke afspraken over risicofactor behandeling tussen huisarts en ziekenhuis vergeleken met alleen de huidige zorg. Voor deze studie werden 197 huisartsen gerandomiseerd in de groep waarbij de huisarts in een behandelovereenkomst aangaf voor welke risicofactor hij/zij verantwoordelijk wilde zijn (interventiegroep) of in de groep waarin de zorg benaderd werd volgens de 'gebruikelijk methode' (controle groep). Van de 96 huisartsen in de interventiegroep wilden 87 van de gevraagde 122 patiënten meedoen en van de 101 huisartsen in de controle groep namen 98 van de 126 patiënten deel aan de studie. Uit de resultaten bleek dat na een gemiddelde van 14 maanden meer patiënten in de interventiegroep de behandeldoelen voor totaal cholesterol, triglyceriden en LDL-cholesterol behaalden dan in de controlegroep. Concluderend kan gezegd worden dat het maken van afspraken over de risicofactor behandeling tussen huisarts en ziekenhuis voor een deel bijdraagt aan beter risicofactor management bij patiënten met klinisch vaatlijden.

Ten slotte wordt in de algemene discussie in **hoofdstuk 8** het onderwerp 'Lichaamsbeweging en risicofactormanagement bij patiënten met klinisch arterieel vaatlijden' besproken en geïntegreerd met bevindingen van de verschillende studies in dit proefschrift. Daarnaast worden de belangrijkste conclusies van dit proefschrift genoemd.

Conclusies van dit proefschrift:

- Taille omtrek, een indirecte indicator van hoeveelheid buikvet, heeft de sterkste associatie met de aanwezigheid van coronair vaatlijden bij patiënten met perifeer vaatlijden.
- Patiënten met klinisch vaatlijden die lichamelijk actief zijn in hun vrije tijd hebben een lager risico op de aanwezigheid van metabool syndroom en insuline resistentie in vergelijking met inactieve patiënten, onafhankelijk van lichaamsgewicht en vetverdeling.
- Gemiddelde of meer dan gemiddelde lichamelijke activiteit in de vrije tijd is geassocieerd met een verlaagd risico op zowel nieuwe niet-fatale en fatale vaataandoeningen, als sterfte. Dit wordt niet beïnvloed door de aanwezigheid van het metabool syndroom bij patiënten met klinisch vaatlijden.
- Lichamelijk inactiviteit in de vrije tijd is onafhankelijk geassocieerd met een hoger risico op het ontwikkelen van type 2 diabetes bij patiënten met klinisch vaatlijden, hypertensie of hyperlipidemie. Deze associatie wordt voor een deel verklaard door overgewicht.
- Het gecombineerde effect van lichamelijke inactiviteit en obesitas heeft een synergistisch effect op het ontwikkelen van type 2 diabetes.
- In een ziekenhuis met een risicofactor screeningsprogramma worden alle belangrijke risicofactoren gestructureerd gemeten en in kaart gebracht in vergelijking met een ziekenhuis zonder een vergelijkbaar programma.
- In een ziekenhuis met een screeningsprogramma van risicofactoren hebben patiënten met klinisch vaatlijden of type 2 diabetes na een periode van 16 maanden een lagere systolische bloeddruk en LDL-cholesterol in vergelijking met patiënten in een ziekenhuis zonder een dergelijk programma.
- Alleen het systematisch screenen van risicofactoren, gevolgd door een therapieadvies is niet voldoende voor adequaat risicofactormanagement bij hoogrisico patiënten.
- Een behandelovereenkomst over risicofactormanagement verbetert het risicofactorprofiel marginaal bij patiënten met klinisch vaatlijden.

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Curriculum Vitae

Beate Geraldina Brouwer was born on March 16th, 1977, in Steenwijk, the Netherlands. In 1995, after graduating from secondary school at CSG Dingstede in Meppel, she studied at the School of Human Movement & Sports at the Hogeschool Windesheim in Zwolle and graduated in June 1999. Subsequently, she studied Health Sciences at the Maastricht University. As part of the specialization Movement Sciences, she performed a research project at Human Biology department on effects of high-intensity intermittent and continuous training on substrate utilization in untrained subjects under supervision of Prof. Dr. M.A. van Baak and Dr. J.M. Oomen. She obtained her Master of Science degree in Health Sciences in June 2002. After travelling 6 months through South America, she worked as quality controller at Kendle from March 2003 until January 2004. In February 2004, she started working on the studies described in this thesis at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, under supervision of Prof. Dr. Y. van der Graaf and Dr. F.L.J. Visseren. She obtained her Master of Science degree in Epidemiology at the Netherlands Institute of Health Sciences, Erasmus Medical Center Rotterdam, in June 2007.

Appendix

Members of the SMART Study Group (alphabetically):

- A. Algra, MD, PhD, Julius Center for Health Sciences and Primary Care, Rudolph Magnus Institute of Neuroscience, department of Neurology, and Leiden University Medical Center, department of Clinical Epidemiology
- P.A.F.M. Doevendans, MD, PhD, department of Cardiology
- Y. van der Graaf, MD, PhD, Julius Center for Health Sciences and Primary Care
- D.E. Grobbee, MD, PhD, Julius Center for Health Sciences and Primary Care
- L.J. Kappelle, MD, PhD, department of Neurology
- W.P.Th.M. Mali, MD, PhD, department of Radiology
- F.L. Moll, MD, PhD, department of Vascular Surgery
- G.E.H.M. Rutten, MD, PhD, Julius Center for Health Sciences and Primary Care
- F.L.J. Visseren, MD, PhD, department of Vascular Medicine and Julius Center for Health Sciences and Primary Care