Risk prediction and risk reduction in patients with manifest arterial disease

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Risk prediction and risk reduction in patients with manifest arterial disease

Risicovoorspelling en risicoverlaging bij patiënten met manifest vaatlijden

(met een samenvatting in het Nederlands)

Proefschrift

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Manuscripts based on the studies presented in this thesis

Chapter 2 Goessens BMB, Visseren FLJ, van der Graaf Y. Life expectancy in the elderly with and without vascular disease: review of the current literature. In *"Vascular procedures in the elderly patient"* ISBN-13: 978-0-9553015-0-6.

Chapter 3 Goessens BMB, Visseren FLJ, Algra A, Banga JD, van der Graaf Y. Screening for asymptomatic cardiovascular disease with non-invasive imaging in patients at high risk and low risk according to the European Guidelines on Cardiovascular Disease Prevention. The SMART study. *J Vasc Surg*. 2006;43:525-32.

Chapter 4 Goessens BMB, Visseren FLJ, Kappelle LJ, Algra A, van der Graaf Y. Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease. The SMART study. In revision *Stroke*.

Chapter 5 Goessens BMB, Visseren FLJ, Edlinger M, Zuithoff NPA, Algra A, van der Graaf Y. Performance of the Framingham, PROCAM, and SCORE algorithms in predicting recurrent vascular events in patients with clinical manifestations of arterial disease and the development of a new risk model. The SMART Study. *Submitted.*

Chapter 6 Goessens BMB, van der Graaf Y, Olijhoek JK, Visseren FLJ. The course of vascular risk factors and the occurrence of vascular events in patients with symptomatic peripheral arterial disease. Accepted for publication in *J Vasc Surg*.

Chapter 7 Goessens BMB, Visseren FLJ, Olijhoek JK, Eikelboom BC, van der Graaf Y. Multidisciplinary vascular screening program modestly improves the medical treatment of vascular risk factors. *Cardiovasc Drugs Ther.* 2005;19 (6):429-35.

Chapter 8 Goessens BMB, Visseren FLJ, Sol BGM, de Man - van Ginkel JM, van der Graaf Y. A randomized controlled trial for risk factor reduction in patients with symptomatic vascular disease: the multidisciplinary Vascular prEvention by NUrses Study. Accepted for publication in *Eur J Cardiovasc Prev Rehabil.*

Chapter 9 Goessens BMB, Visseren FLJ, de Nooijer J, van den Borne HW, Algra A, Wierdsma J, van der Graaf Y. Self-management of vascular Patients Activated by the Internet and Nurses (SPAIN) study: Rationale and Design. Based on a short paper published as proceeding in *Lecture Notes in Computer Science* 2006; 3962:162-166.

Contents

General introduction

General introduction

Despite a better understanding of the aetiology and pathophysiology of atherothrombotic vascular disease, and the availability of effective treatment modalities, the burden of vascular disease is likely to increase rather than decrease in the next 20 years (1). The life expectancy of men and women is increasing and will contribute to a higher prevalence of chronic diseases. The global burden of coronary heart disease, cerebrovascular disease, peripheral arterial disease, and abdominal aortic aneurysm is not only increasing, but also shifting from developed to developing countries as a result of increased life expectancy and lifestyle changes in these regions (2). Abnormal lipid profiles, smoking, hypertension, abdominal obesity, psychosocial factors, diminished consumption of fresh fruit and vegetables, excessive alcohol use, and less physical activity are the major risk factors for vascular disease worldwide in both sexes and at all ages (3). Historically, intervention thresholds for the treatment of these vascular risk factors have been based on variable and arbitrary cut-off points for individual risk factors. Indeed, international and national guidelines were often developed for the diagnosis and treatment of a single risk factor (4-6). However, because patients seldom have only one risk factor (7) and multiple risk factors have a multiplicative effect on cardiovascular risk (8), most international guidelines for vascular disease prevention now use an absolute risk approach, taking all major risk factors into account (9-11). Absolute risk is the probability of developing a vascular event in a finite period, e.g. within the next 10 years. For most countries, the threshold for aggressive medical treatment in the general population is a 20% risk of developing a myocardial infarction, ischemic stroke, or vascular death in the coming 10 years. Patients with clinically manifest arterial disease are already at high risk of future vascular events in the same or different arterial bed (12). In these patients intensive risk factor management is needed to reduce the vascular risk.

There are two main approaches to reduce the risk of vascular events. The first is to focus interventions on patients likely to benefit the most, the so-called individual high-risk approach. This approach should be integrated in everyday clinical practice. The second is to aim to reduce risk in the entire population regardless of each individual's level of risk and potential benefits. This approach focuses on diet, transport, employment, education, health, and other policies at international, national, regional, and local levels (13).

It is well established that the occurrence of vascular disease is strongly associated with lifestyle and modifiable factors. Despite the fact that guidelines and recommendations exist for the treatment of the several forms of vascular disease and their associated risk factors, many patients with peripheral arterial disease (14;15), coronary heart disease (16-18), cerebrovascular disease (19), abdominal aortic aneurysm (20;21), and vascular disease in general (22) do not reach treatment goals.

Incomplete implementation of appropriate therapy may be one cause of this failure. Three groups of barriers to the implementation of evidence-based guidelines have been suggested: physician-related, patient-related, and healthcare-related (23). Physician-related barriers include lack of knowledge of the best current evidence, lack of agreement with specific guidelines, or insufficient belief that an intervention will lead to an improved outcome (24). Patient-related barriers include poor compliance with prescribed drugs, time, financial constraints, and lack of motivation to make lifestyle changes (quit smoking, increase physical activity, adopt a healthy diet) that are crucial for vascular risk reduction. In a study examining the patterns and predictors of compliance with concomitant antihypertensive and lipid-lowering agents, only 1 in 3 patients in a group of 8406 patients were compliant with both medications at 6 months (25). Patients were more likely to be compliant if antihypertensive and lipid-lowering agents were initiated simultaneously, if they had a higher absolute cardiovascular risk, or if they took fewer other medications. Lastly, healthcare-related barriers include the lack of systematic approaches to the care of chronic illnesses. With the shift from short-stay acute tertiary hospital care to patient-centred, home-based, and team-driven care, new skills, multidisciplinary collaboration, and continuity of care (follow-up arrangements) are required (26).

Objectives

The objective of the studies described in this thesis is twofold. To examine additional interventions aimed at reducing the vascular risk of patients with clinical manifestations of arterial disease, and to distinguish high-risk from low-risk patients by predicting the risk of a recurrent vascular event at the same or at another site of the vascular tree.
The study population consisted of participants of the Second Manifestations of ARTerial disease (SMART) study, an ongoing single-centre prospective cohort study of the University Medical Center Utrecht. The aim of the SMART study is to investigate the prevalence and incidence of additional vascular diseases in patients who already have a

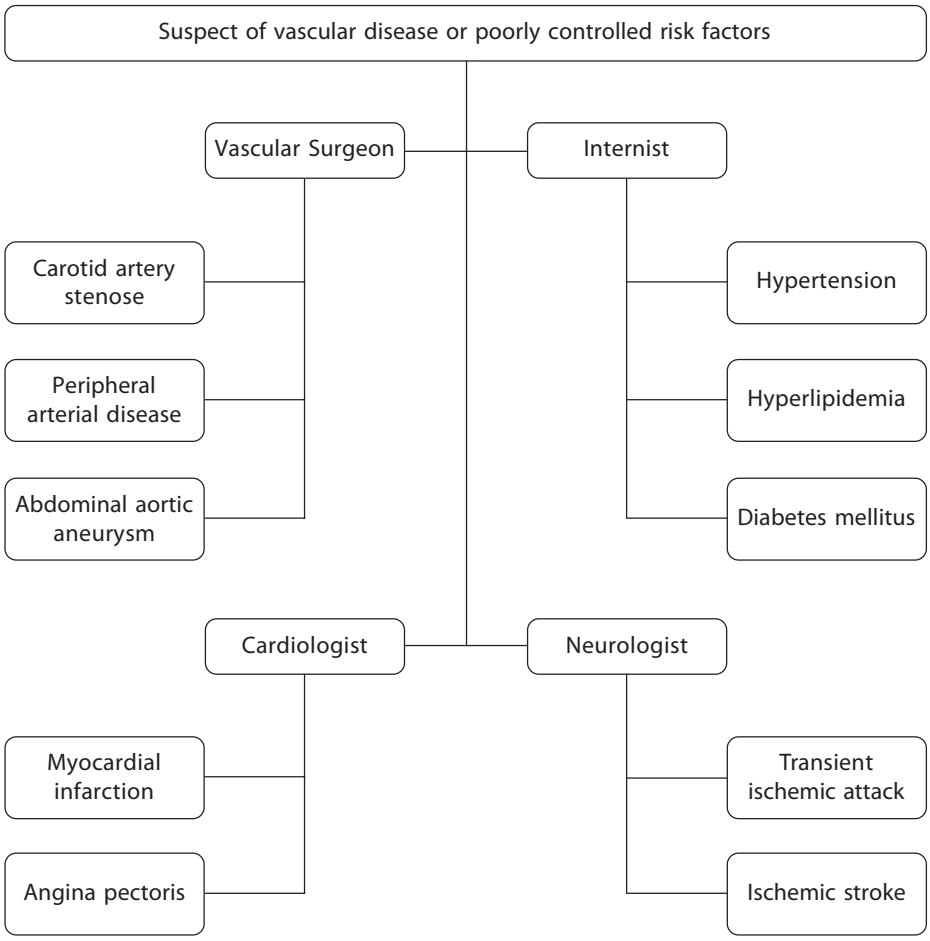

Figure 1. Disease categories of the SMART study

clinical manifestation of arterial disease or who are otherwise at high risk (type 1 or 2 diabetes mellitus, hypertension, hyperlipidemia) of developing symptomatic arterial disease (27). Patients were referred by general practitioners or by medical specialists from other hospitals. All referral diagnoses were confirmed by vascular specialists at the outpatient clinics. Patients were classified into disease categories on the basis of their referral diagnosis and vascular history. The different disease categories are represented in Figure 1. Parallel to the medical treatment or intervention given by the treating

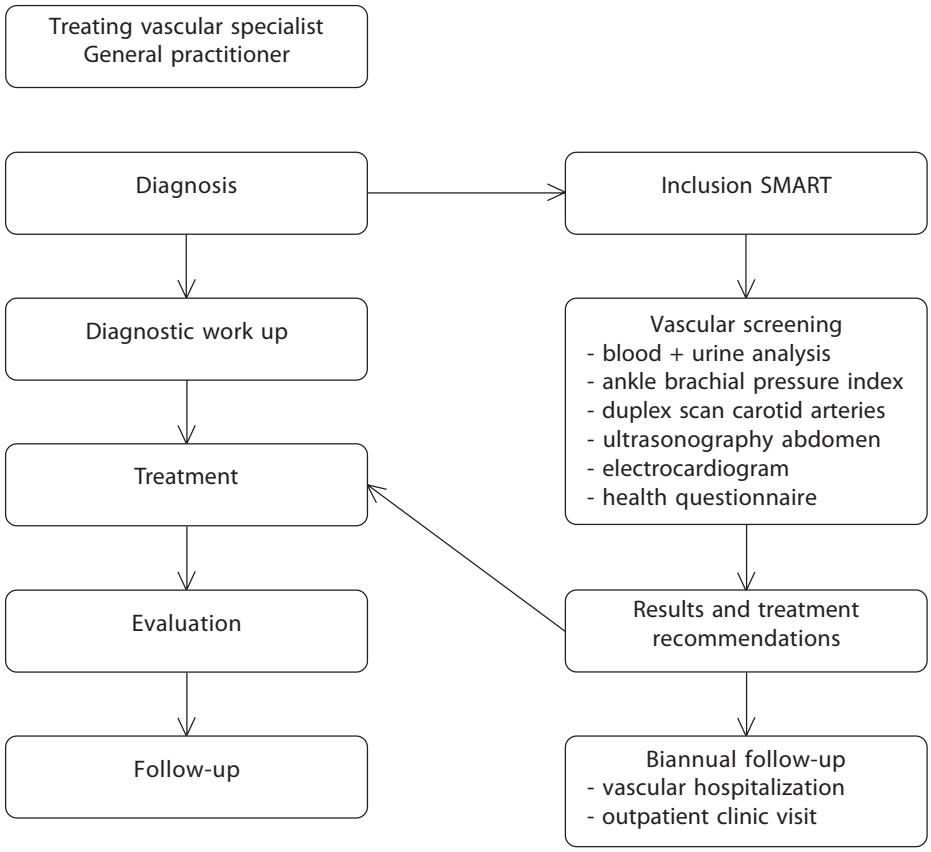

Figure 2. Workflow of vascular screening

vascular specialist, patients included in the SMART study underwent a standardized non-invasive vascular screening program. The results of the screening program and treatment recommendations were discussed at weekly meetings of a multidisciplinary team and were reported in writing to the treating specialist and the general practitioner, with further action being left to their discretion (Figure 2). Patients included in the SMART study were asked to complete a questionnaire on hospitalizations and outpatient clinic visits biannually, in order to detect non-fatal and fatal vascular events.

Outline of this thesis

The outline of this thesis is as follows. The review, described in **chapter 2**, outlines the consequences of important vascular risk factors and the impact of various manifestations of arterial disease on life expectancy. The prevalence of risk factors and the additional benefit of non-invasive screening to detect asymptomatic arterial disease in patients at low risk or high risk of experiencing (new) vascular events, according to the European Guidelines of Cardiovascular Disease Prevention, are discussed in **chapter 3**. In the study reported in **chapter 4,** the relationship between asymptomatic carotid artery stenosis and the risk of new vascular events was established. In **chapter 5** the performance of Framingham, PROCAM, and Systematic COronary Risk Evaluation (SCORE) prediction models in the SMART population is discussed, and the development of a new risk model for the prediction of recurrent vascular events in patients with manifest arterial disease is described. In **chapter 6,** a longitudinal study, also called 'second vascular screening', to establish the relationship between baseline variables and subsequent vascular events in patients with symptomatic peripheral arterial disease is described. Thereafter, the changes and the amount of vascular risk factors were studied between baseline and 5.5 years follow-up. The study described in **chapter 7** investigated whether the recommendations given to the treating vascular specialist and the general practitioner by a multidisciplinary team of vascular specialists regarding the medical treatment of risk factors (based on international guidelines) led to changes in medication use in a high-risk population. The randomized controlled trial "Vascular prEvention by NUrses Study" (VENUS) is presented in **chapter 8.** This study investigated whether the extra care of a nurse practitioner plus usual care compared to usual care alone was beneficial for the cardiovascular risk profile of patients with clinical manifestations of arterial disease. **Chapter 9** presents the rationale and design of a feasibility study, the Self-management of vascular Patients Activated by the Internet and Nurses study (SPAIN). The aim of this study was to develop and test a safe patient-specific website to provide patients with clinical manifestations of arterial disease additional treatment and individual coaching by a nurse practitioner regarding several vascular risk factors. In the general discussion, **chapter 10,** the main findings of the different chapters are presented and discussed. Finally, a summary of the results presented in this thesis is given in **chapter 11**.

Figure 3 gives an overview of the different study samples that were used for the different studies described in this thesis.

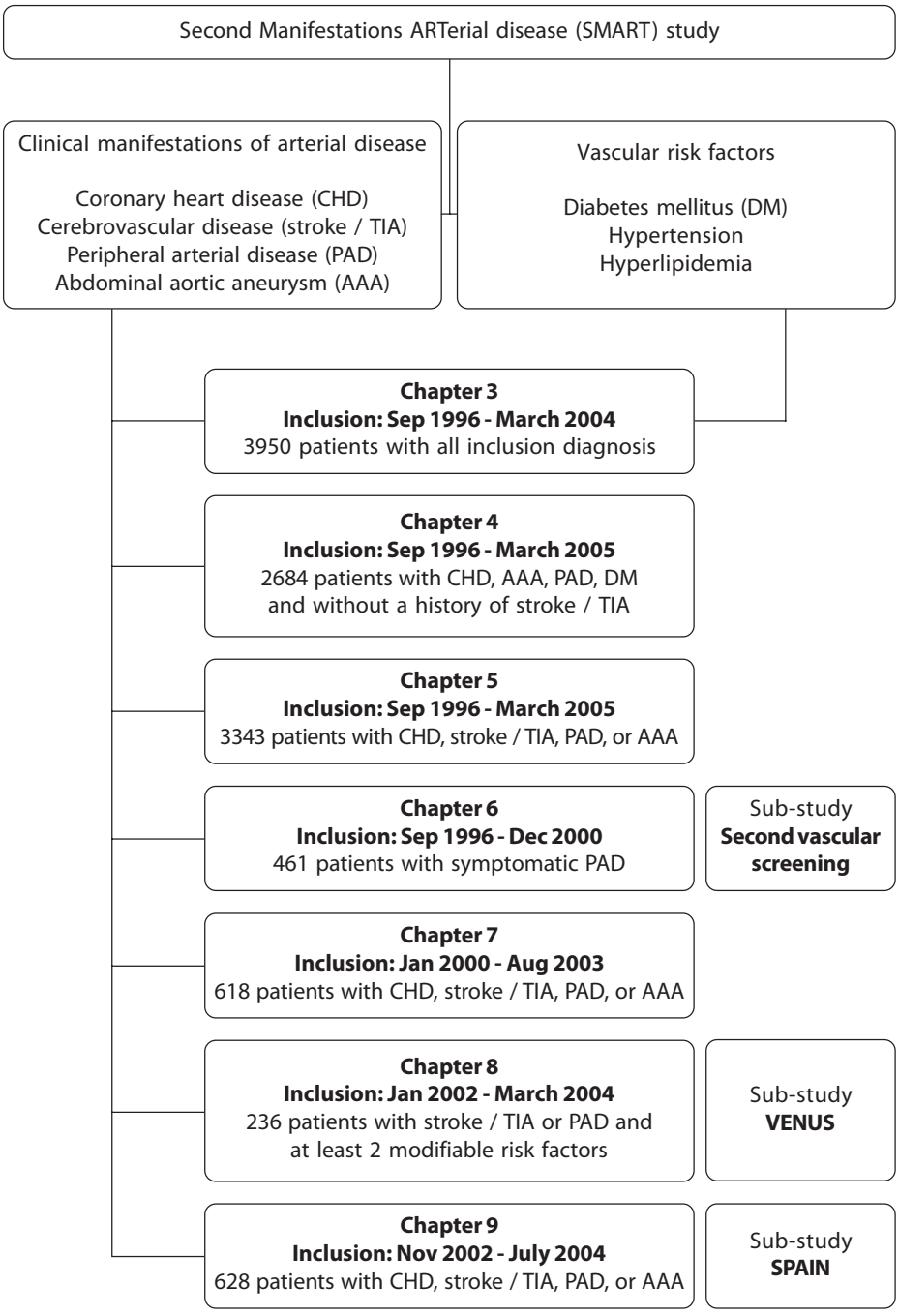

Figure 3. Overview of the different study samples

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Life expectancy in the elderly with and without vascular disease: review of the current literature

Chapter 2

Abstract

Background

The life expectancy (LE) of people in the Western countries increases and contributes to a higher prevalence of chronic conditions. Cardiovascular disease (CVD) patients, however, differ from the general population in the presence of atherosclerosis and related ischemic symptoms. This review seeks to summarize the consequences of important vascular risk factors and set out the impact of various manifestations of atherosclerosis on LE.

Methods and results

A literature search was performed on the influence of vascular risk factors and the effect of symptomatic arterial disease on total LE and LE with and without CVD. Due to the longevity, more people are at a higher risk to develop clinical manifestations of atherosclerosis. One in two men and one in three women will develop coronary heart disease (CHD) and one out of six men and one out of five women will suffer a stroke after 50 years of age. Moderate and high physical activity, normal bodyweight, normal blood pressure level, not having diabetes and being a non-smoker contributed to longer total LE and disability free LE. With more adverse levels of risk factors, lifetime risk increased and median survival decreased. Clinical manifestations of atherosclerosis reduced LE eight to twelve years in a 60 year old patient depending on the location of the vascular event. At age 70, a man with CHD may expect to live 8.9 years and a similar woman 11.7 years. A man of 70 year who survived a stroke is expected to live 5.5 years and a woman 7.1 years.

Conclusion

Available studies show convincingly the impact of various vascular risk factors and clinical manifestations of atherosclerosis on LE. A broad range of primary and secondary prevention strategies is important in adults at high risk, but also in the elderly because of the expanding growth of people in this age-category.

Introduction

Life expectancy (LE) has increased for many decades in the developed countries and is accompanied by an increased burden of age-associated medical conditions (coronary heart disease, stroke, arthritis, osteoporosis, Alzheimer disease) (1). In the developed countries, smoking, high blood pressure, obesity, high cholesterol, and alcohol use are the leading causes of chronic diseases (2). Whereas, in the developing countries where 85% of the global population lives, childhood underweight and HIV/AIDS contributed absolutely more to the loss of healthy life than all diseases in the developed countries (3).

As longevity increases, the time exposure to vascular risk factors is prolonged and results in a greater probability of cardiovascular disease (CVD). It becomes more and more obvious that the burden of CVD in elderly is considerable. However, little attention has been paid to preventive medicine in elderly until recent years; probably because of a misconception that taking preventive measures (lifestyle and / or drug treatment of risk factors) at older age is too late to be effective (4).

In this paper we summarize the consequences of important vascular risk factors and set out the impact of various manifestations of atherosclerosis on LE, with special emphasis on the elderly.

Search strategy

Data for this review were identified by the use of a Dutch textbook (5) and by searches in PubMed (1966 to April 2006) using the search terms 'life expectancy' in combination with the search terms or text words hypertension, hyperlipidemia, diabetes mellitus, smoking, overweight, physical inactivity, coronary heart disease, cerebrovascular disease, peripheral arterial disease, vascular disease, or atherosclerosis. The following keywords and possible related search terms of life-expectancy were also used: total or healthy life expectancy, longevity, lifespan, life-course, survival, and aging. There was a restriction on English-language full-length articles, and an elimination of letters, meeting abstracts, and animal research by using PubMed limits features. Titles and abstracts of the retrieved studies were scanned to exclude studies that were clearly irrelevant. Relevant articles not identified by this strategy, but referenced in the bibliographies of these selected papers, were also included.

Life expectancy at different ages

LE has increased since the eighteenth century in European countries (6). In the Netherlands reduction of mortality started in the nineteenth century. From 1840 to 1990 LE increased from 36.1 to 74.2 years in men and from 38.5 to 80.2 years in women (http://epp.eurostat.cec.eu.int). Changes in the cause of death from mainly infectious diseases to chronic diseases were accompanied by a shift in age pattern of mortality to older ages. In 2000, the LE at birth for men was 75.5 years and for women 80.6 years, at age 65 for men 15.3 years and for women 19.2 years, and at age 80 the LE was 6.5 years for men and 8.4 years for women in 2000 in the Netherlands (Table 1) (5). The difference in LE between men and women is 5 years at birth and diminishes during life to 1.9 years at age 80 in 2000. In the period 1980-2000, the LE increased in men with 3.1 years and in women with only 1.4 year due to the decreased mortality of vascular disease in all age-groups, including the oldest (85+). A possible explanation of the higher increase of LE in men than in women could be that men have more benefit from recent advances in medical care or that women adopt more unfavorable lifestyles (7). In the last two decades the decline in vascular mortality in Europe was highest in England, Wales and France and lowest in Norway, the Netherlands and Denmark (8).

In 2004, the proportion of people aged 65 and over was 17% in the Euro-zone and 14% in the Netherlands (http://epp.eurostat.cec.eu.int). It is predicted based on data of Netherlands Central Bureau of Statistics that the LE in men will increase from 75.5 years in 2000 to 78.0 years at birth in 2020 and to 79.5 in 2050 (Table 1). For women an increase is expected from 80.6 years in 2000 to 81.1 in 2020 and 82.6 years at birth in 2050 (5). Longevity has been mostly determined by genetic and environmental factors. The influence of both genetic and environmental factors on longevity can potentially be modified by drug treatment (for instance introduction of vaccination programs, antiplatelet agents, blood pressure- and cholesterol-lowering agents), behavioral changes (quit smoking, improved nutrition) and environmental improvements (less crowded and better living conditions, water sterilization, and growing income). People living in Japan have the highest estimated average healthy LE of 74.5 years, 77.2 years for women and 71.9 years for men, at birth in 1999 (1). After Japan, in second and third places, are Australia and France, 73.2 years and 73.1 years, followed by a number of other industrialized countries of Western Europe. The countries with LE at birth less than 35 years are all sub-Saharan Africa, where the HIV/AIDS epidemic is most prevalent.

Table 1. Life expectancy in years at birth, 65 and 80 years of age in the general population in the Netherlands at different points in time

	1980		2000		2020		2050	
	Men	women	Men	Women	Men	Women	Men	Women
At birth	72.5	79.2	75.5	80.6	78.0	81.1	79.5	82.6
Age 65 years	14.0	18.8	15.3	19.2	16.6	19.6	17.6	20.1
Age 80 years	5.9	8.1	6.5	8.4	7.2	8.6	7.6	8.8

There are two views on future developments in LE. The first is known as the proportions of the 'limited-lifespan paradigm', and describes that the average LE will not increase beyond 85 years of age (9). It is indicated that the human lifespan is fixed, and that the great changes in LE have occurred in the early years of life. Mortality patterns were dominated by acute, usually infectious disease and were replaced by chronic disease as major health threats. These chronic diseases are approached most effectively with a strategy of 'postponement' rather than of cure. The second view is known as proponents of the 'mortality-reduction paradigm', and speculates on the fact that the decline in mortality will continue and may even accelerate, including in the most advanced ages (10). The observed decrease in mortality at advanced ages, the progress in effective drug treatment, and the very low mortality rates in subpopulations with healthy lifestyles were used as arguments in favor of substantial future increase in LE.

Influence of vascular risk factors on life expectancy

Atherosclerosis is a potentially life-threatening generalized disease process that affects all arteries. Myocardial infarction (MI) and stroke, the principal manifestations of atherosclerosis, are the first and second most common causes of death worldwide (11). Secondary prevention, including lifestyle modification and drug treatment of risk factors, are important for all patients and also for elderly patients because of the impact on morbidity and mortality and quality of life (12). Data from randomized controlled trials to guide pharmaceutical decisions in the very elderly are scarce. Relevant clinical treatment strategies in elderly with CVD are given in Table 2 (13-20).

We will consider the influence of risk factors for vascular disease on LE in detail below and a summary is given in Table 3.

Table 2. Preventive measures in elderly with cardiovascular disease*

Antiplatelet therapy use after evaluation of individual's trombotic and haemorrhagic risk	(13)
Lipid-lowering with statins	(15;16)
ACE-inhibitors and calcium channel blockers	(17)
Smoking cessation	(14)
Salt reduction	(18)
Decreased alcohol intake	
Dietary counseling	
Light to moderate physical activity	(19)
Interventions directed at depression, social isolation	(20)

* Based on knowledge from the literature

Physical activity

Physical activity has a positive impact on vascular risk factors such as obesity, hypertension and insulin resistance, also in patients older than 75 years (12). Being physically active can be the result and the cause of a better health status and consequently of survival to an advanced age. The consequences of different physical activity levels on LE were calculated in the Framingham Heart Study cohort (21). A daily physical activity score was obtained by adding the sum of the weighted hours for each level of activity. The minimum theoretical possible score was 24 for somebody sleeping 24 hours a day. Moderate (score 30-33) and high physical activity levels (> 33) led to an additional 1.3 (95% confidence interval (95% CI) 0.3 – 2.3) and 3.7 (95% CI 2.6 – 4.8) years on the total LE and 1.1 (95% CI -0.02 – 2.1) and 3.2 (95% CI 1.9 – 4.3) more years lived without CVD, respectively, for men aged 50 years or older compared with those maintained at low physical activity level. For women the differences were 1.5 (95% CI 0.4 – 2.5) years and 3.5 (95% CI 2.4 – 4.6) years of the total LE and 1.3 (95% CI 0.1 – 2.4) and 3.3 (95% CI 2.0 – 4.5) more years lived free of CVD, respectively (21). The benefit of higher levels of physical activity on total LE in men and women was nearly equal and was the result of the larger number of years lived without CVD and a slightly larger LE with CVD. The role that physical activity plays in vascular risk management should be emphasized with at least half an hour of daily physical activity at 60-75% of the average maximum heart rate on most of the days of the week (22). Physical activity is associated with a decreased risk of arterial disease, and is associated with a beneficial effect on the inflammatory response potentially involved in athero-genesis (23).

Table 3. Effect of risk factors on life expectancy in years at age 50 years for subpopulations with and without a history of cardiovascular disease in the Framingham Heart Study cohort

	Blood pressure*			Physical activity			Obesity†			Smoking		Diabetes mellitus‡	
Males	Normal	Normal-high	High	High	Moderate	Low	Normal	Overweight	Obese	Never	Always	No	Yes
with CVD	5.2	6.7	7.4	7.1	6.8	6.6	NR	NR	NR	7.3	4.8	NR	NR
free of CVD	24.5	21.3	17.3	22.8	20.8	19.7	26.8	24.8	20.8	30.4	21.8	27.2	23.8
Females													
with CVD	4.7	5.7	7.0	6.6	6.6	6.4	NR	NR	NR	6.2	3.6	NR	NR
free of CVD	29.5	27.6	22.4	29.4	27.4	26.1	25.4	23.9	19.8	34.1	26.6	33.8	24.3

Data represent reduced years to live with CVD and further years to live free of CVD, NR: not reported
* normal blood pressure: < 120/80 mmHg, high-normal: ≥ 120-139 mmHg / ≥ 80-89 mmHg, high: ≥ 140/90 mmHg
† normal weight: BMI < 25 kg/m^2, overweight: BMI ≥ 25 and < 29.9 kg/m^2, obese: BMI ≥ 30kg/m^2
‡ diabetes if random blood sample ≥ 200mg/dL or use of hypoglycemic agent

Hypertension

Elevated blood pressure (> 140/90 mmHg) is a risk factor for heart failure, chronic kidney disease, CHD, and cerebrovascular disease in both men and women and is present in more than two third of patients older than 65 years of age. Elderly are more likely than younger patients to have poorly controlled blood pressure as found in 16,095 adults of at least 25 years of age who participated in the third NHANES Survey (24). Among persons who were being treated, hypertension was controlled in 65% of those who were 25 to 44 years old, in 52% of those who were 45 to 64 years old, and in 34% of those who were 65 or older. Nonpharmacological therapy, including weight reduction and decreased sodium intake, was effective in the treatment of hypertension in 975 elderly patients involved in a randomized controlled trial (25). The combined outcome measure (diagnosis of high blood pressure at follow-up, or treatment with antihypertensive drugs, or a cardiovascular event during follow-up) was less frequent among those assigned to reduced sodium intake and weight loss, hazard ratio (HR) 0.47, 95% CI 0.35 – 0.64, versus not assigned. Increased levels of blood pressure at age 50 (independent of antihypertensive drugs) are associated with large decrease in total LE and LE free of CVD. Having hypertension (> 140/90 mmHg) and being free of CVD at age 50 was associated with a reduction of total LE of 5.1 (95% CI -3.5 – 6.7) for men and 4.9 years (95% CI -3.4 – 6.4) for women (26). Presence of hypertension was remarkably associated with two more years lived with CVD compared with normotensives (< 120/80 mmHg) irrespective of gender (26). A possible explanation of this result could be that a low blood pressure is related with heart failure, and patients with heart failure have a high mortality rate.

Since most randomized controlled trials have been conducted in subjects under 80 years of age, concern remained about the efficacy of antihypertensive drugs in very old hypertensive patients. A meta-analysis of the effect of reduction of blood pressure in hypertensive patients ≥ 80 years of age was conducted (27). For the primary outcome stroke, treatment reduced the risk with 34% (RR 0.66 (95% CI 0.48 – 0.92)). The number of cardiovascular events and heart failure as secondary outcomes were significantly decreased with 22% (RR 0.78 (95% CI 0.61 – 0.97)) and with 39% (RR 0.61 (95% CI 0.42 – 0.84)), respectively.

Obesity

Obesity (body mass index ≥ 30 kg/m^2) in adulthood is associated with an increased risk of disability throughout life (28). Obesity at ages 30 to 49 years is associated with a 2.21-fold (95% CI 0.97 – 5.07) increased odds of mobility only-limitations and a 2.01-fold (95% CI 1.01 – 4.03) increased odds of activities daily living (ADL)-limitations after 46 years of follow-up, compared with normal weight subjects (BMI > 18 - < 24.5 kg/m^2). The LE of an obese population at age 50 is 5.9 years (95% CI 4.1 – 7.3) shorter for men and 5.6 years (95% CI 3.8 – 7.3) for women compared with those with normal bodyweight. Overweight males (BMI> 25 and ≤ 29.9 kg/m^2) at age 50 live 2.5 years (95% CI 1.1 – 3.8) less and overweight females 2.3 years (95% CI 0.9 – 3.5) less than subjects with normal bodyweight (28). If the prevalence of obesity continues to rise, especially at younger ages, the negative effect on health and longevity in the coming decades could be markedly worse than it is for current generations.

Smoking

Smoking is associated with a shorter duration of life free of CVD (similar to hypertension, physical activity and obesity) and also associated with the duration of life with CVD (29). A 50 year old non-smoking man, lives 8.7 years (95% CI 7.6 – 9.6) more free of CVD than a smoker, and a 50 year old non-smoking woman lives 7.6 years (95% CI 6.3 – 8.9) more. Never-smokers live more years after the diagnosis of CVD than smokers, for men 2.4 years (95% CI 1.7 – 3.2) and for women 2.7 years (95% CI 1.9 – 3.4). Former smokers have more years lost between 40 and 70 years of age than never-smokers, after adjusting for marital status, duration of education, county of residence, and physical activity (30). The years lost increased progressively with increasing consumption. A former male smoker loses 1.6 years compared with a never smoker, men who smoked 1-9 cigarettes/ day lose 3.0 years and heavy smokers (≥ 20 cigarettes/ day) 3.8 years. A former female smoker loses 1.0 years compared with a never smoking woman. Those who smoked 1-9 cigarettes/ day lose 1.6 years and 20 or more cigarettes/ day is accompanied by a reduction of 2.1 years of life between 40 and 70 years. Quitting smoking leads to an increase in total LE for older smokers in whom CVD has already developed. The reduction in relative risk of death or MI in elderly patients with CHD who quit smoking is comparable with that in younger patients (14). Thus, it is worthwhile to encourage elderly patients with CVD to quit smoking because advanced age does not attenuate the benefits of quitting.

Hyperlipidemia

In middle aged persons, the role of total cholesterol and LDL-cholesterol levels have been established as risk factors for CVD but the role of plasma cholesterol in persons 65 years of age and over remains controversial. A meta-analysis of 33 studies showed the association between total cholesterol and mortality of CHD in people aged 65 years and above (31). In men, the relative risk for CHD mortality, due to a 1.0 mmol/L increase in total cholesterol, was 1.22 (95% CI 1.15 – 1.28) and in women 1.04 (95% CI 0.85 – 1.23) Only two large-scale, randomized trials have investigated the effects of statins in elderly subjects. The Prospective Study of Pravastatin in the Elderly at Risk trial conducted in 5,804 subjects 70-80 years of age with a history of risk factors for CVD found that treatment with a statin reduced the incidence of the primary endpoint (composite of coronary death, non-fatal MI, and fatal or non-fatal stroke) compared with placebo (RR 0.85; 95% CI 0.74 – 0.97) (15). In the Heart Protection Study, which included 20,536 individuals 40-80 years of age (of whom 5,806 subjects were ≥ 70 years of age) with CHD, occlusive arterial disease and/or diabetes, treatment with simvastatin was associated with a 24% (95% CI 19 – 28) reduction in the event rate of major vascular events irrespective of age (16).

Diabetes mellitus

The incidence of type 2 diabetes has increased considerably over the past two decades, an increase that is due almost entirely to the obesity epidemic and to physical inactivity. Type 2 diabetes is associated with long-term complications and a high burden of morbidity (32). Older adults with diabetes are also at a greater risk than older persons without diabetes for depression, cognitive impairment, urinary incontinence and persistent pain (33).

The mean LE of men between 45 and 50 years with newly diagnosed type 2 diabetes and without a vascular history was 25.5 years (95% CI 21.9 – 29.7) compared with 30.1 years for non-diabetic men of that age-category who participated in the United Kingdom Prospective Diabetes Study (34). Diagnosing diabetes between ages 60 – 64 years resulted in a mean LE of 13.9 years (95% CI 12.6 – 15.3) for men and 17.7 years (95% CI 16.6 – 19.7) for women with no reported LE of non-diabetic patients in that age-range. Participants of the Framingham Heart Study at age 50 years had a total LE of 27.2 (men) and 33.8 (women) years, of which 25.5 and 32.1 years, respectively, were spent without diabetes and 1.7 years (both sexes) with diabetes. In contrast, LE of 50

year old individuals with type 2 diabetes is 23.8 and 24.3 years for men and women, respectively (35). These two cohort-studies showed that a diagnosis of type 2 diabetes at middle age has been estimated to result in the loss of 5 to 10 years of life.

Other influences on life expectancy

Besides the traditional vascular risk factors, the social surrounding of elderly (family situation, social relations) influences the LE of elderly (36). People expect to live longer when they receive social and emotional support than those without (36). Married people are healthier than others, have lower mortality rates and might be expected to live longer as a consequence. People in a higher social economic status with a higher degree of education have on average a better LE than people at the lower end of the socioeconomic scale. Moreover, despite their longer total LE, these persons live shorter with disability or ill health than persons in lower socioeconomic groups (37). Elderly living in disadvantaged neighborhoods have a 1.5 times higher risk of cardiovascular death (HR 1.5, 95% CI 1.2 – 1.9) after adjustment for income, education and lifetime occupation compared with those who live in advanced neighborhoods (38).

Approximately 20 – 30% of the overall variation in adult lifespan is accounted for by genetic factors. It seems that genetic influences on lifespan are minimal prior to age 60 but moderate thereafter as shown in an almost extinct cohort of twins with more than 90 years of follow-up (39).

Life expectancy among patients with vascular disease

Atherosclerosis is associated with a poor prognosis, significantly reducing LE in a 60 year old patient by 8-12 years depending on the type of vascular event (40).

Coronary heart disease

The prevalence of CHD increases with age and it occurs in almost 25% of the elderly population. The case-fatality rates following MI are markedly higher in older compared with younger patients. Contributions to increased MI mortality at an elderly age include an increased presence of co-morbid conditions, more extensive CHD, and a lesser use of beneficial therapies, including substantial underuse of drugs shown to improve CVD survival (e.g. aspirin, ß-blocking drugs and ACE-inhibitors) (41). A recent analysis of data from the Framingham Heart Study, clearly demonstrates that atherosclerosis reduces

LE (42). Healthy males aged 70 years were expected to live for a further 13.5 years; while 70 year old males with a history of CHD had a LE of 8.9 years. Healthy women aged 70 years had 17.2 more years to live while women of the same age with CHD had 11.7 years left. Table 4 shows the LE at other ages for persons with and without CHD. A CHD-event at younger age has more impact on LE than a CHD-event at older age. An explanation could be that smoking and diabetes is much more prevalent in younger than in older patients with CHD. Also low ejection fraction and family history of CHD are prominent risk factors in young adults.

Patients with previous MI (n=15,590) and a mean age of 66.9 years were expected to live 12.9 years. A subsequent MI halves the LE to 6.4 years, and a new ischemic stroke in individuals with a previous MI decreases the LE to 7.4 years (43). Thus the already shortened LE in individuals with MI was further and substantially reduced in patients with more than one event.

Cerebrovascular disease

Mortality data underestimate the true burden of cerebrovascular disease (ischemic stroke) since, in contrast to CHD or cancer, the major burden of stroke is chronic disability rather than death. About a third of cerebrovascular disease survivors are functionally dependent after one year. Women at the age of 50 have a higher risk of developing a stroke (1 in 5) than men (1 in 6). Female survivors of cerebrovascular disease live longer than male survivors, but the difference between the sexes decreases with time (44). Females with cerebrovascular disease at age 75 lived 6.2 years in 1983 and LE increased to 7.0 years in 1994. Men with cerebrovascular disease at age 75 lived 4.8 years in 1983 and 6.0 years in 1994. LE among survivors of 75 years of age of precerebral occlusion and stenosis (8.4 years) was significantly better than it was among survivors of intracerebral hemorrhage (7.2 years) or occlusion of intracranial vessels (6.5 years). The increase in LE is not only the result of the implementation of stroke units in care (45) but also of increased availability of imaging (CT, MRI) which lead to more accurate diagnosis of cerebrovascular disease. Blood pressure is a strong determinant of the lifetime risk of cerebrovascular disease, and promotion of normal blood pressure levels in the community might be expected to substantially reduce the risk (46). In addition to above mentioned LE, another article showed that LE was reduced by 8.9 years in patients with cerebrovascular disease and a subsequent ischemic stroke, and in individuals with cerebrovascular disease and a subsequent MI LE was reduced with 4.1 years (43).

Table 4. State-specific life expectancy in years for subpopulations with or without a history of disease at each given age

Age	Healthy*	Cardiovascular disease	Coronary heart disease	Acute myocardial infarction	Stroke	Congestive heart failure
Males						
50	26.7 (0.27)	15.9 (0.75)	16.4 (0.88)	13.9 (1.1)	N/A†	N/A†
60	20.0 (0.24)	12.3 (0.39)	12.6 (0.44)	10.8 (0.53)	7.98 (0.98)	4.00 (0.62)
70	13.5 (0.22)	8.78 (0.26)	8.85 (0.31)	7.48 (0.33)	5.50 (0.44)	4.43 (0.41)
80	8.29 (0.25)	5.26 (0.28)	5.15 (0.34)	4.30 (0.35)	3.75 (0.36)	2.17 (0.29)
Females						
50	32.3 (0.26)	20.3 (1.3)	22.8 (1.9)	14.9 (3.3)	N/A†	N/A†
60	24.5 (0.23)	16.1 (0.46)	17.6 (0.57)	11.6 (0.86)	9.81 (0.86)	8.26 (0.84)
70	17.2 (0.22)	11.0 (0.31)	11.7 (0.42)	7.18 (0.51)	7.11 (0.48)	5.45 (0.50)
80	10.8 (0.22)	7.02 (0.27)	7.66 (0.38)	5.34 (0.48)	4.96 (0.39)	3.30 (0.37)

Data represent further years to live with standard error
* Without a history of cardiovascular disease
† Based on a risk set with less than 10 people
Source: A. Peeters, A.A. Mamun, F. Willekens and L. Bonneux for NEDCOM. Eur Heart J 2002; 23:458-466. Reproduced with permission by Oxford University Press

Analysis of survival after stroke between ethnic groups showed that black people with good morbidity (expressed as prior Barthel index 15-20) before a stroke and older black people (> 65 years) have a better survival (3.3 years) over similar white people (2.6 years), even after adjustment for age, socio-economic status and stroke subtype (47).

Peripheral arterial disease

PAD is chronic arterial occlusive disease of the lower extremities caused by atherosclerosis. The prevalence of PAD increases with advancing age, male gender, a history of diabetes and smoking. In a study of 16,440 patients diagnosed with symptomatic PAD between 1985 and 1995 with an average follow-up of 5.9 years, subsequent MI or stroke occurred in 17.1 and 16.8 per 1000 patient years and the five–year death rate among these patients was 82.4 deaths per 1000 patients years (43). The mean LE of

these 16,440 patients with a mean age of 67.3 years was 13.6 years. In those who developed a new MI or ischemic stroke, LE decreased to 4.4 and 4.7 years (43). A minority of the patients with intermittent claudication suffer from worsening leg symptoms (rest pain, ischemia ulceration or gangrene). Disease severity may be directly related to mortality, and patients with critical ischemia have the worst prognosis.

Vascular disease

The lifetime risks for total atherosclerotic vascular disease (MI, angina pectoris, coronary insufficiency, stroke, claudication) were recently estimated in the Framingham Heart Study for men and women (48). At 50 years of age, lifetime risks were 51.7% (95% CI 49.3 – 54.2) for men and 39.2% (95% CI 37.0 – 41.4%) for women. The lifetime risk for developing "severe" CVD (MI, stroke, or either vascular death) at 50 years of age, were 41.2% (95% CI 38.8 – 43.7) in men and 28.8% (95% CI 26.6 – 30.8) in women. Thus more than 40% of men and nearly 30% of women will develop severe CVD during their remaining lifespan. Diabetes at 50 years of age conferred the highest lifetime risk for CVD of any single risk factor, 67% of the men and 57% of the women with diabetes will have developed CVD at 75 years of age. With more advanced levels of single risk factors, lifetime risks increased and median survivals decreased. The lifetime risks for developing vascular disease are among the highest published for any disease to date. The lifetime risks for all types of cancer in the United States are lower, 47% in men and 36% in women, compared with the lifetime risks for total atherosclerotic vascular disease (49). At 50 years of age, the most common types are breast cancer in women, with a lifetime risk of 12.5%, and prostate cancer in men, with a lifetime risk of 19%.

Risk factor management and life expectancy

Mortality due to CVD has gradually declined and caused an increase in LE in many developed countries since the 1980s. There is clear evidence that a combination of long-term, tailored drug treatment provides effective secondary prevention (13;50-54), next to life style changes. An estimation of life-years gained from treatment and vascular risk factor changes was done in England and Wales between 1981 and 2000 (55). Each death avoided by drug treatment, lifestyle changes or revascularization gained an additional 7.5 years of life in patients with recognized CHD, and each death avoided by primary prevention yielded an average additional 20 years of life.

The decrease in the number of vascular deaths is attributable to population-wide improvements in the major vascular risk factors (less smoking, improved nutrition) to treatment such as angioplasty, and to the introduction of statins, aspirin, and ACE-inhibitors for example. On the other hand, the longer survival of patients with CVD results in a large amount of patients at high risk for subsequent vascular events and a higher prevalence of chronic conditions. Cardiovascular prevention is not only important in middle-aged patients but should also be implemented in the expanding population of elderly (≥ 75 years of age) who are at a more advanced stage of atherosclerosis. Worldwide, more than 580 million people are 60 years of age or older at the moment; and the number is estimated to increase to 1 billion by 2020. The challenge is to get more elderly to make appropriate lifestyle changes, and to deliver drug treatment to the vast majority of the elderly.

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Screening for asymptomatic cardiovascular disease with non-invasive imaging in patients at high risk and low risk according to the European Guidelines on Cardiovascular Disease Prevention. The SMART study

Abstract

Objective

To assess the prevalence of atherosclerotic risk factors and to investigate the added value of noninvasive imaging in detecting asymptomatic cardiovascular diseases in patients at low risk and high risk according to the European Guidelines on Cardiovascular Disease Prevention.

Methods

In the vascular screening program of the University Medical Center Utrecht, patients, aged 18-79 years, recently diagnosed with manifest vascular disease (coronary heart disease (CHD), cerebrovascular disease, abdominal aortic aneurysm (AAA), peripheral arterial disease (PAD) or had a risk factor (hypertension, hyperlipidemia, diabetes mellitus) were assessed for atherosclerotic risk factors and (other) arterial diseases by non-invasive means. The European guidelines were applied to quantify the number of high risk patients.

Results

Eighty-eight percent of 3950 patients were considered to be at high risk. More than 80% had hyperlipidemia, about 50% had hypertension, 21% had diabetes mellitus, and 31% were current smokers. An asymptomatic reduced ankle brachial index (≤ 0.90) was most frequently observed in patients diagnosed with cerebrovascular disease (21%), an asymptomatic AAA (≥ 3.0 cm) in patients with PAD (5%) or cerebrovascular disease (5%), and an asymptomatic carotid stenosis ($\geq 50\%$) in patients with PAD (15%). Based on non-invasive measurements, 73 (13%) of 545 patients initially considered low risk were reclassified as high risk.

Conclusion

This study confirmed a high prevalence and clustering of modifiable atherosclerotic risk factors in high risk patients. The yield of non-invasive vascular measurements was relatively low but identified a sizable number of high risk patients. Standard screening for asymptomatic atherosclerotic disease identified a limited number of vascular abnormalities requiring immediate medical attention in patients already identified as high risk patients.

Introduction

Cardiovascular disease (CVD) is a leading cause of death worldwide and accounts for almost 17 million deaths annually. Nearly 80% of these deaths occur in developed countries, mainly as a result of ageing of the population (1).

In 1994, the first European guidelines for the prevention of coronary heart disease (CHD) were published (2), and these were later revised to include lifestyle factors, atherosclerotic risk factors, and therapeutic goals. In 2003, the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice issued the latest European guidelines on CVD in clinical practice in detail (3) and in summary (4). Patients are categorized as high risk on the basis of well-defined conditions or on the SCORE (Systematic COronary Risk Evaluation) mortality risk table (5) (Table 1). A high absolute cardiovascular risk calls for drastic lifestyle changes and medical treatment of atherosclerotic risk factors, whereas patients at low to moderate risk are mainly advised to adhere to a healthy lifestyle. The European guidelines discuss the opportunities of non-invasive vascular measurements for identifying patients initially considered to have a low vascular risk, but by detecting an asymptomatic atherosclerotic disease to reconsider these patients high vascular risk. Patients with a (recent) clinical manifestation of an atherosclerotic disease are already classified as high risk but non-invasive vascular imaging may be useful in detecting vascular abnormalities that necessitate immediate medical attention (e.g. aortic aneurysms, carotid artery stenosis). Because of the generalized nature of atherosclerosis, the prevalence of asymptomatic vascular diseases is high in these patients (6).

One of the aims of the Second Manifestations of ARTerial disease (SMART) study is to establish a protocol for multidisciplinary care of vascular patients. The SMART-study, initiated in 1996, is an ongoing, single-centre, prospective cohort study. Patients referred to the University Medical Center Utrecht because of clinical manifestations of vascular disease, therapy refractory hypertension, hyperlipidemia or diabetes mellitus all underwent a standardized evaluation of atherosclerotic risk factors and non-invasive diagnostic measurements.

In this cross-sectional study, we assess the prevalence of atherosclerotic risk factors and investigate the added value of non-invasive imaging in detecting asymptomatic CVD in patients initially considered at low risk and in patients already at high risk according to the European guidelines on Cardiovascular Disease Prevention (4).

Table 1. The European guidelines

Individuals who fulfill criteria 1, 2, or both are defined as at high risk
1) Patients with established CHD, PAD and cerebrovascular disease
2) Asymptomatic individuals who are at high-risk of developing CVD because of:
a) Multiple risk factors resulting in a 10 year risk of ≥ 5% (SCORE) for developing a fatal cardiovascular event
b) Markedly raised levels of single risk factors: cholesterol ≥ 8.0 mmol/L LDL-cholesterol ≥ 6.0 mmol/L, blood pressure ≥ 180/110 mmHg
c) Diabetes type 2 and diabetes type 1 with microalbuminuria
3) Close relatives (first degree relatives) of:
a) Patients with early-onset of CVD
b) Asymptomatic individuals at particularly high risk
4) Other individuals met in connection with ordinary clinical practice

Source: De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J et al. Eur Heart J 2003; 24:1601-1610

Methods

Study setting, patients and design

The SMART study started in 1996. This ongoing single-centre prospective cohort study has enrolled more than 5000 patients referred to the University Medical Center Utrecht (UMCU) for the treatment of clinical manifestations of atherosclerosis (internal carotid artery stenosis; transient ischemic attack or minor stroke; peripheral arterial disease; aortic abdominal aneurysm; renal artery stenosis; angina pectoris; or myocardial infarction) or for the treatment of major atherosclerotic risk factors, including therapy refractory hypertension, genetic hyperlipidemia, and type 1 or 2 diabetes mellitus. Patients were referred by general practitioners or by medical specialists from other hospitals in the Utrecht region. All referral diagnoses were conformed by a vascular surgeon, internist, neurologist, nephrologist or cardiologist at an outpatient clinic. Patients were classified into disease categories based on referral diagnosis and vascular history. For definitions, see Table 2. Asymptomatic patients were those without symptoms of clinically manifest atherosclerosis.

Table 2. Classification of disease categories based on referral diagnosis and vascular history

Disease category	Inclusion diagnosis	Vascular history*
Cerebrovascular disease	Cerebral ischemia, transient ischemic attack, amaurosis fugax, minor ischemic stroke, retinal infarction, or asymptomatic carotid artery stenosis with diameter reduction ≥ 30%	Transient ischemic attack Stroke
Coronary heart disease	Myocardial infarction at least 2 of the following criteria: 1. chest pain for at least 20 minutes, not disappearing after administration of nitrates 2. ST-elevation > 1mm 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 Angina pectoris: chest pain with or without documented ischemia on the ECG and with documented stenosis on the angiography.	Myocardial infarction Angina pectoris CABG or PTCA
Peripheral arterial disease	Intermittent claudication, rest pain, gangrene, ulcers, resting ABI ≤ 0.90	Arterial operation, PTA Amputation leg
Aneurysm abdominal aorta	Distal aortic anteroposterior diameter ≥ 3.0 cm and/ or distal/proximal ratio ≥ 1.5 cm	Surgery for aneurysm
Hypertension	Systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg or antihypertensive agents use	
Hyperlipidemia	Total cholesterol ≥ 5.0 mmol/l, LDL-cholesterol ≥ 3.0 mmol/l or lipid-lowering drugs use	
Diabetes mellitus type 1 and 2	Fasting glucose ≥ 7.0 mmol/l, non-fasting glucose ≥ 11.0 mmol/l or oral antidiabetic drugs or insulin use	

ECG: elektrocardiogram, CK: creatinine kinase, MB: myocardial band, CABG: coronary artery bypass graft, PTCA: percutaneous transluminal coronary angioplasty, PTA: percutaneous transluminal angioplasty, ABPI: ankle brachial pressure index, BP: blood pressure
* Ever or current diagnosis

Patients, aged 18 to 79 years, who gave their written informed consent were included. Patients with a life expectancy shorter than 2 years, those with terminal malignant disease, those dependent in daily activities (Rankin grade > 3), and those not proficient in Dutch were excluded. The Ethics Committee of our institution approved the study. The rationale and design of the SMART-study have been described in detail elsewhere (7). For the current cross-sectional study, the data were used of the first consecutive 3950 patients included from September 1996 to March 2004.

Vascular screening

All included patients underwent a standardized non-invasive screening (ankle-brachial pressure index (ABPI), duplex scan of carotid arteries, ultrasonography of abdomen, electrocardiogram (ECG)) and laboratory assessment (blood and urine analyses). Patients completed questionnaires on history of CVD (CHD, PAD, and cerebrovascular disease), and risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking, alcohol consumption, physical activity, and familial vascular history), and current medication use. The self-reported data were compared with information of the physician's letter and missing information was added by research nurses. Height, weight, waist circumference, and blood pressure were measured according to a standardized diagnostic protocol. Fasting blood was sampled to determine serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine and homocysteine levels. Glucose, total cholesterol, triglycerides, and creatinine were measured with a commercial enzymatic dry chemistry kit (New Brunswick: Johnson & Johnson), HDL-cholesterol was measured with a commercial enzymatic kit (Mannheim: Boehringer) and homocysteine was analyzed with Shipchandler and Moore method (8). The low-density lipoprotein (LDL) cholesterol level was calculated with Friedewald's formula. An early morning urine portion was collected to measure the albumin and creatinine concentrations. A twelve-lead resting ECG was recorded and ultrasonography was performed to assess the presence of asymptomatic atherosclerosis. Ultrasound examinations were performed by well-trained registered vascular technologists in a certified vascular laboratory. Ultrasonography of the abdomen was performed with an ATL 3000 HDI (Advanced Technology Laboratories) equipped with a 4 MHz curved array transducer to measure the anteroposterior juxtarenal diameter and the distal anteroposterior diameter of the aorta. The presence of plaques and stenosis of the common and internal carotid arteries at both sides was assessed with color Doppler-

assisted Duplex scanning. The left and right ABPIs at rest were determined by taking the ratios of the highest systolic blood pressure measured at the ankle to the highest systolic blood pressure in both arms with the patient in supine position.
All patients visited the hospital after an overnight fast of at least 8 hours and underwent the total vascular screening program within 2 hours. The direct costs of the vascular screening were approximately €900,00 ($1098,00) per patient in 2004.

Multidisciplinary treatment recommendations

The results of the vascular screening program were discussed at weekly meetings of a multidisciplinary team that consisted of an internist, vascular surgeon, cardiologist, nurse practitioner, and, on request, a neurologist. The target goals for patients with established CVD were quitting smoking and achieving a body mass index (BMI) less than 25 kg/m^2, blood pressure less than 140/90 mmHg, total cholesterol less than 5.0 mmol/L, LDL-cholesterol less than 3.0 mmol/L, and plasma glucose level less than 7.0 mmol/L. If these targets were exceeded, treatment was given according to the Third Joint Task Force of European Societies recommendations (4) and the best available evidence for the treatment of atherosclerotic risk factors, namely, hypertension (9;10), diabetes mellitus / insulin resistance, hyperlipidemia, hyperhomocysteinaemia (11;12), obesity (13), smoking (14;15), and microproteinuria (16;17), as well as for asymptomatic arterial disease (AAA (18), carotid stenosis (19-21), and low ABPI (22)). The results of the vascular screening and the treatment recommendations were reported in writing to the treating specialist and the GP, and further action was left to their discretion. Patients were not informed by mail.

European Guidelines on Cardiovascular Disease Prevention

The objective of the European guidelines on CVD prevention in clinical practice is to reduce the incidence of first event or recurrent clinical events (4). Preventive efforts are most efficient in those at highest risk. Patients with established atherosclerotic disease, asymptomatic individuals with a 10-year mortality risk of 5% or more with the SCORE chart, those with markedly raised levels of single risk factors, and those with type 2 diabetes or type 1 diabetes with micro-albuminuria are considered at high risk, as are asymptomatic patients with pre-clinical evidence of atherosclerosis. There are two SCORE charts, one for low risk regions and one for high risk regions (5). The

Netherlands is classified as a high risk region in Europe. Although there are no studies to date comparing the Framingham risk equation with the SCORE algorithm, the 10-year mortality risk of 5% by SCORE is considered to be roughly equal to the 10-year vascular event risk (including vascular mortality) of 20% by the Framingham risk equation.

Data analysis

Continuous variables are presented as means with standard deviation. The prevalence of atherosclerotic risk factors and asymptomatic arterial disease is expressed as a percentage with corresponding 95% confidence interval (CI). The 10-year risk estimate for fatal CVD was calculated for the potentially low risk patients with the high risk SCORE chart.

Results

From 1 September 1996 to 31 March 2004, 3950 patients were enrolled in the SMART study with the following confirmed referral diagnoses: PAD (15%), cerebrovascular disease (17%), CHD (26%), AAA (6%), diabetes mellitus (10%), hyperlipidemia (13%), or hypertension (13%). Table 3 describes the baseline characteristics and medication use of the population. Sixty-nine percent of the patients were male; the mean age was 57 ± 12 years for men and 54 ± 14 years for women. The prevalence of "ever smokers" was highest among patients presenting with AAA (90%). A history of CHD was most common among patients referred with AAA (38%). A previous diagnosis of AAA was relatively uncommon. Drug treatment of risk factors was most common in patients with CHD and relatively sparse in patients with other forms of clinically manifest disease.

Table 4 shows the prevalence of atherosclerotic risk factors according to the presenting disease. A total of 3448 (87%) of the 3950 patients had hypercholesterolemia (TC ≥ 4.5 mmol/L or LDL-C ≥ 2.5 mmol/L), of which 34% used lipid-lowering medication at baseline. A total of 2131 patients were hypertensive (≥ 140/90 mmHg) and 58% were taking antihypertensive medication. Diabetes mellitus (fasting glucose ≥ 7.0 mmol/L) was detected in 841 (21%) of the 3950 patients, and exactly half of these patients used glucose-lowering medication at baseline. An increased level of homocysteine (≥ 15.0 μmol/L) was most prevalent in patients with AAA (43%). Approximately 93% of the patients had at least one risk factor for CVD (hypertension, hyperlipidemia, diabetes, elevated homocysteine level, or current smoking), and 73% had two or more risk factors (data not shown).

Table 3. Baseline characteristics of the study population (n= 3950)

	Referral diagnosis							
	PAD (n = 604)	Cerebro (n = 650)	CHD (n = 1034)	AAA (n = 239)	DM (n = 403)	Hyperlipidemia (n = 528)	Hypertension (n = 492)	Total (n=3950)
Gender, male	397 (66)	485 (75)	854 (83)	226 (95)	231 (57)	316 (60)	229 (47)	2738 (69)
Age in years (SD) male	59 (10)	62 (10)	58 (9)	68 (7)	49 (15)	45 (11)	52 (12)	57 (12)
Age in years (SD) female	59 (12)	60 (11)	61(10)	69 (8)	49 (14)	47 (14)	49 (14)	54 (14)
Systolic BP in mmHg (SD)	146 (22)	148 (22)	135 (19)	145 (19)	136 (19)	135 (17)	154 (22)	142 (21)
Diastolic BP in mmHg (SD)	80 (10)	82 (11)	78 (10)	85 (11)	81 (11)	81 (11)	95 (13)	82 (12)
BMI in kg/m^2 (SD)	26 (4)	26 (4)	27 (4)	26 (3)	28 (6)	26 (4)	27 (5)	27 (4)
Ever smoking	525 (87)	527 (81)	769 (74)	215 (90)	154 (39)	175 (34)	191 (40)	2556 (65)
History of vascular events *								
- PAD		43 (7)	37 (4)	12 (5)	10 (3)	8 (2)	8 (2)	118 (4)
- Cerebrovascular	48 (8)		21 (2)	18 (8)	14 (4)	18 (3)	32 (7)	151 (5)
- CHD	127 (21)	104 (16)		91 (38)	41 (10)	47 (9)	29 (6)	439 (15)
- AAA	26 (4)	25 (4)	15 (2)		9 (2)	6 (1)	18 (4)	99 (3)
Anti-hypertensive drugs	241 (40)	308 (47)	844 (82)	122 (51)	154 (38)	120 (23)	335 (68)	2124 (54)
Lipid-lowering agents	149 (25)	235 (36)	586 (57)	65 (27)	79 (20)	234 (44)	79 (16)	1427 (36)
Glucose-lowering agents	67 (11)	74 (11)	88 (9)	7 (3)	292 (73)	28 (5)	32 (7)	588 (15)
Anti-platelet agents	272 (45)	504 (78)	761 (74)	101 (42)	59 (15)	78 (15)	70 (14)	1845 (47)

Data represent number of patients with percentages (%) or mean with standard deviation
PAD: peripheral arterial disease, CHD: coronary heart disease, AAA: aortic aneurysm abdominal, DM: diabetes mellitus
* Documented as PAD, cerebrovascular disease, CHD or AAA in history and other than the referral diagnosis

Table 4. Risk factors of the study population (n= 3950).

	Referral diagnosis							
	PAD (n = 604)	Cerebro (n = 650)	CHD (n = 1034)	AAA (n = 239)	DM (n = 403)	Hyperlipidemia (n = 528)	Hypertension (n = 492)	Total (n=3950)
Total cholesterol ≥ 4.5 mmol/l	527 (87)	533 (82)	735 (71)	201 (84)	291 (72)	478 (91)	421 (86)	3185 (81)
LDL-cholesterol ≥ 2.5 mmol/l	528 (87)	532 (82)	735 (71)	206 (86)	293 (73)	474 (90)	414 (84)	3182 (81)
Systolic BP ≥ 140 mmHg and/or Diastolic BP ≥ 90 mmHg	339 (58)	408 (65)	382 (38)	139 (60)	273 (69) *	207 (40)	383 (80)	2131 (54)
Impaired glucose tolerance > 6.1 - < 6.9 mmol/l	119 (20)	121 (19)	189 (18)	49 (21)	29 (7)	55 (10)	75 (15)	637 (16)
Plasma glucose ≥ 7.0 mmol/l	125 (21)	107 (17)	157 (15)	31 (13)	322 (80)	52 (10)	47 (10)	841 (21)
Homocysteine ≥ 15.0 µmol/l	146 (24)	181 (28)	261 (25)	103 (43)	67 (17)	80 (15)	136 (28)	974 (25)
Creatinine clearance								
< 60 mL/min/1.73 m^2	128 (21)	156 (24)	123 (12)	102 (43)	39 (10)	14 (3)	69 (14)	631 (16)
60-90 mL/min/1.73 m^2	298 (49)	352 (54)	587 (57)	116 (49)	121 (30)	215 (41)	211 (43)	1900 (48)
Microalbumin > 30.0 mg/mmol	102 (17)	97 (15)	71 (7)	48 (20)	67 (17)	35 (7)	73 (15)	493 (13)

Data represent number of patients with percentages (%)
PAD: peripheral arterial disease, CHD: coronary heart disease, AAA: abdominal aorta aneurysm, DM: diabetes mellitus
* Blood pressure <130/80 mmHg in patients with DM

The prevalence of a reduced ABPI (≤ 0.90) was highest in patients with cerebrovascular disease (21%), a carotid stenosis of 50% or more was most frequently found in patients with PAD (15%) and a dilated abdominal aorta of 3.0 cm or more was found in 5% of the patients with PAD or cerebrovascular disease (Table 5). An AAA of 5.5 cm or more was rare (only in five patients with CVD). In patients referred for the treatment of major atherosclerotic risk factors, a reduced ABPI was most prevalent in patients with diabetes (5%), carotid stenosis of 50% or more, in patients with hypertension (4%) and an AAA of 3 cm or more, in patients with hypertension (2%).

In the Figure, the distribution of high risk versus low risk patients is shown. Patients with established CVD (n= 2527), individuals referred with a risk factor and a vascular history (n= 151), or patients with type 2 diabetes (n= 275) or type 1 diabetes with microalbuminuria (n= 22) are immediately considered at high risk. The low risk patients with markedly raised levels of single risk factors (total cholesterol ≥ 8.0 mmol/L, LDL-cholesterol ≥ 6.0 mmol/L (n= 165), or blood pressure ≥ 180/110 mmHg (n= 106)), or a 10-year mortality risk of 5% or more calculated with the high risk SCORE-chart (n= 159) were also considered to be at high risk. Patients referred with an atherosclerotic risk factor and with asymptomatic atherosclerosis (reduced ABPI (n= 5), carotid stenosis of ≥ 50% (n= 10), an AAA of ≥ 3 cm (n= 1), a mean carotid intima-media thickness (CIMT) > 1.0 mm (N= 19)), or signs of left ventricular hypertrophy (n= 38) were also considered high risk patients. Hence, we identified 3478 (88%) high risk patients who required the most intensive lifestyle intervention and drug therapy according to international guidelines.

The number of high risk patients receiving medication at baseline is given in Table 6. The most infrequent use of antiplatelet agents was in patients with AAA (32%) and the most frequent use in patients with cerebrovascular disease (72%). Anti-hypertensive drugs were the most used category of medication. Patients with CHD used more lipid-lowering agents (57%) than did patients with PAD (25%). Less than 6% of patients with established CVD or a risk factor for atherosclerosis used folic acid.

Discussion

This study confirmed a high prevalence and clustering of modifiable atherosclerotic risk factors in high risk patients. The yield of non-invasive vascular measurements was relatively low but identified a sizable number of patients who were initially considered as low risk but who, by detection of asymptomatic atherosclerotic vascular disease, could be considered as high risk patients. Standard screening for asymptomatic atherosclerotic disease identified a limited number of vascular abnormalities that

Table 5. Prevalence (%) of new ultrasonographic and ankle brachial index findings (n=3950)

	Referral diagnosis							
	PAD (n = 604)	Cerebro (n = 650)	CHD (n = 1034)	AAA (n = 239)	DM (n = 403)	Hyperlipidemia (n = 528)	Hypertension (n = 492)	Total (n=3950)
Ankle brachial index ≤ 0.90*		137	64	47	19	13	15	295
		21: 18 - 24	6: 5 - 8	20: 15 - 25	5: 3 - 7	3: 1 - 4	3: 2 - 5	8: 7 - 8
A. carotis stenosis ≥ 50% †	93		63	28	11	13	19	227
	15: 13 - 18		6: 5 - 8	12: 8 -16	3: 1 - 5	3: 1 - 4	4: 2 - 6	6: 5 - 7
A. carotis stenosis ≥ 70% †	67		32	20	5	8	12	144
	11: 9 -14		3: 2 - 4	8: 5 - 13	1: 0 - 3	2: 1 - 3	2: 1 - 4	4: 3 - 4
AAA distal aorta ≥ 3.0 cm ‡	27	32	23		5	2	12	101
	5: 3 - 6	5: 3 - 7	2: 1 - 3		1: 0 - 3	0: 0 - 1	2: 1 - 4	3: 2 - 3
AAA distal aorta ≥ 5.5 cm ‡	1	3	1	-	-	-	2	7
	0	1	0				0	0

Data represent number of patients with percentages (%) and 95% confidence intervals (CIs)
PAD: peripheral arterial disease, CHD: coronary heart disease, AAA: abdominal aortic aneurysm, DM: diabetes mellitus
* Measurement of the systolic BP in left and right brachial arteries and both posterior tibial and dorsalis pedis arteries
† Duplex ultrasound of both carotid internae arteries and based on peak systolic velocity > 150cm/s
‡ Utrasound of the anteroposterior juxtarenal and the distal anteroposterior diameter of the aorta

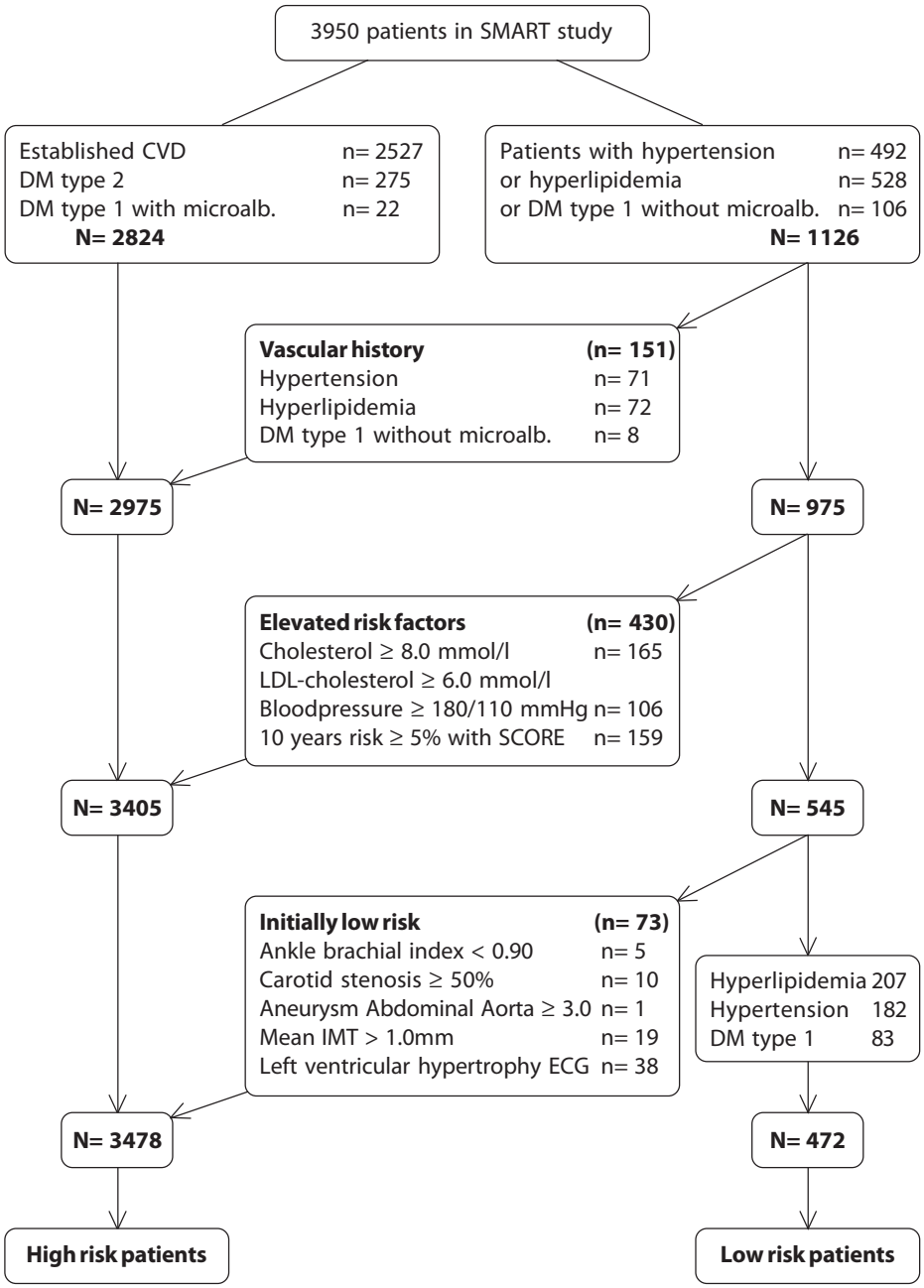

Figure 1. Categorization of Second Manifestation of ARTerial Disease (SMART) patients into high and low risk. CVD: cardiovascular disease, DM: diabetes mellitus, microalb: microalbuminuria, LDL: low-density lipoprotein, SCORE: Systematic COronary Risk Evaluation, IMT: intima-media thickness, ECG: electrocardiogram

Table 6. Medication use at baseline according to referral diagnosis (n= 3478)

	Referral diagnosis							
	PAD (n = 604)	Cerebro (n = 650)	CHD (n = 1034)	AAA (n = 239)	DM (n = 320)	Hyperlipidemia (n = 321)	Hypertension (n = 310)	Total (n= 3478)
Antiplatelet agents	221 (37)	469 (72)	712 (69)	77 (32)	44 (14)	57 (18)	54 (17)	1634 (47)
Vitamin K-antagonist agents	58 (10)	49 (8)	78 (8)	26 (11)	16 (5)	8 (3)	5 (2)	240 (7)
Lipid-lowering agents	149 (25)	235 (36)	586 (57)	65 (27)	75 (23)	148 (46)	60 (19)	1318 (38)
Glucose-lowering agents	67 (11)	74 (11)	88 (9)	7 (3)	236 (74)	19 (6)	27 (9)	518 (15)
Anti-hypertensive drugs	241 (40)	308 (47)	844 (82)	122 (51)	145 (54)	89 (28)	218 (70)	1967 (57)
Folic-acid use	15 (3)	33 (5)	21 (2)	-	9 (3)	9 (3)	16 (5)	103 (3)

Data represent number of patients with percentages (%)
PAD: peripheral arterial disease, CHD: coronary heart disease, AAA: abdominal aorta aneurysm, DM: diabetes mellitus

necessitated immediate medical attention in patients already identified as high risk patients.

The high prevalence and clustering of major atherosclerotic risk factors in our study were in agreement with previously reported findings of high prevalences of atherosclerotic risk factors among patients with PAD (23;24), CHD (25-27), cerebrovascular disease (28), and AAA (29).

New imaging methods, such as magnetic resonance imaging and computed tomography to detect coronary calcifications, or ultrasound to measure CIMT, can be used to detect asymptomatic individuals at high risk of cardiovascular events. The European guidelines refer to these methods as an extra option to identify patients at high risk for new cardiovascular events. In our cohort, we were able to use a set of vascular diagnostic modalities that were all non-invasive, validated, safe, and relatively inexpensive. All included patients underwent the complete vascular screening protocol, and no selection was made in patients who could benefit more or less from the screening. The yield of screening for a reduced ABPI, carotid artery stenosis, AAA, increased mean CIMT, or left ventricular hypertrophy was low in patients referred for poorly controlled risk factors (diabetes mellitus, hyperlipidemia, or hypertension). On the basis of non-invasive measurements, 73 patients (13%) could be reclassified from the initially low risk group to the high risk category (Figure). The measurement with the highest yield of newly detected high risk patients was ECG fulfilling criteria of left ventricular hypertrophy (38 out of 545 patients). In patients with hypertension, hyperlipidemia, or diabetes, the overall prevalence of carotid artery stenosis (≥ 50%) was 3%. Jones et al (30) detected 2 carotid stenoses in 92 patients with diabetes and Sutton et al. (31) found a prevalence of 25% in 187 hypertensive participants. We detected only 1 AAA (≥ 3 cm) in 545 low risk patients. Others found 24 (3%) AAA among 918 patients with hypertension (32). We found a reduced ABPI in five low risk patients. The prevalence of PAD was much higher (~ 20%) among 6880 primary care patients in Germany (33). The discrepancies between our ultrasound findings and other results can be partly explained by differences in diagnostic criteria or from differences in study populations and ultrasound methods. We found a mean CIMT of greater than 1 mm in 19 out of 545 low risk patients. An increased CIMT is associated with both CVD risk factors and atherosclerosis elsewhere in the arterial system (34). CIMT could be a suitable indicator of atherosclerotic burden in asymptomatic patients but further research is needed to confirm this.

The clinical and prognostic relevance of asymptomatic atherosclerosis detected with additional screening in low risk patients is not known. To our knowledge, no other comparable studies published results of additional non-invasive vascular screening in

low risk patients, and the cost-effectiveness remains to be determined. Carotid endarterectomy is well established as a beneficial procedure for reducing the risk of stroke among patients with symptomatic high-grade carotid artery disease (35). Screening for asymptomatic carotid artery stenosis may be relevant now some trials show that carotid endarterectomy in asymptomatic patients resulted in small reductions in the incidence of transient cerebral ischemia (21), non-disabling stroke (19) and fatal or disabling stroke (20). In patients with an asymptomatic AAA smaller than 5.5 cm, ultrasonographic surveillance is to be preferred to surgical or endovascular treatment (18). Asymptomatic PAD, as indicated by a reduced ABPI, points to diffuse atherothrombotic disease and to the need for treatment. Successful treatment strategies include atherosclerotic risk factor modification, particularly smoking cessation; initiation of regular exercise; control of hypertension, diabetes, and hyperlipidemia; and use of antiplatelet agents to reduce the risk of atherothrombotic events (18).

The prevalence of severe asymptomatic vascular abnormalities was more common in patients already known to be at high risk compared to the lower risk patients. An asymptomatic reduced ABPI was found most often in patients who were included with cerebrovascular disease (21%) or AAA (20%). A carotid stenosis of $\geq$ 50% was mostly found in patients with PAD (15%) as well as a carotid stenosis of 70% or more (11%), and a dilated abdominal aortic of 3.0 cm or more was found in only 5% of the patients with PAD and in 5% of the patients with cerebrovascular disease. The additional screening to detect concomitant asymptomatic atherosclerosis (carotid stenosis > 50% and < 70%, AAA $\geq$ 3.0 and $\leq$ 5.5) is not of clinical relevance in patients already known to be at high risk. These patients already require the most intensive lifestyle intervention, and where appropriate drug treatment of atherosclerotic risk factors. Additional screening would only be justified if it could identify severe asymptomatic vascular disorders, such as AAA 5.5 cm or more. In 3478 already high risk patients, we identified only 7 (0.2%) patients with an AAA of 5.5 cm or more (Table 5).

The prevalence of asymptomatic vascular abnormalities requiring immediate medical attention was low in high risk patients. Besides the fact that in our study the prevalence of asymptomatic vascular abnormalities was also low in low risk patients, the prognostic relevance of asymptomatic vascular abnormalities in low risk patients is not known. It is therefore questionable whether the detection of such vascular abnormalities justifies shifting these initially low risk patients to the high risk category. A cost-effectiveness analysis was not performed but the yield of screening seems not worth the effort. Still, this needs to be further studied. For the moment, it would seem more appropriate to focus on the management of major atherosclerotic risk factors

(hypertension, hyperlipidemia, diabetes), the use of antithrombotic therapy, and to repeatedly address the role of lifestyle changes (quit smoking, adopt a healthy diet, and increase physical activity).

In conclusion, the prevalence of modifiable risk factors in high risk patients is high. Although the yield of non-invasive vascular measurements was relatively low in patients referred for a poorly controlled risk factor, it led to additional identification of high risk patients. Standard screening for asymptomatic atherosclerotic disease identified a limited number of vascular abnormalities that necessitated immediate medical attention and intervention in patients already identified as high risk patients. The results of this study indicate that standard non-invasive vascular screening in patients at already high risk for the development of vascular diseases has little added benefit and can not be recommended in general practice.

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Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease. The SMART study

Chapter 4

Abstract

Background

The frequency of asymptomatic carotid artery stenosis (CAS) increases with age from 0.5% in individuals below 50 to 5 - 10% in individuals over 65 years of age in the general population. Its prognostic value has been examined in the general population, but less often in patients with clinical manifestations of arterial disease other than retinal or cerebral ischemia. We examined the relationship between asymptomatic CAS and the risk of subsequent events in this specific group of patients.

Methods

This study involved 2,684 consecutive patients with clinical manifestations of arterial disease or type 2 diabetes mellitus, but without a history of cerebral ischemia enrolled in the SMART study (Second Manifestations of ARTerial disease). The degree of asymptomatic CAS was assessed with Duplex scanning and defined on basis of the blood flow velocity patterns at baseline in both carotid arteries. None of the patients underwent carotid endarterectomy or endovascular intervention. During the follow-up period, vascular events (vascular death, ischemic stroke and myocardial infarction (MI)) were documented in detail. Data were analyzed with Cox proportional hazards regression and adjusted for age, gender and classical vascular risk factors.

Results

Asymptomatic CAS of ≥ 50% was present in 221 (8%) patients. During a mean follow-up of 3.6 years (SD 2.3), a first vascular event occurred in 253 patients (9%). The cumulative incidence rate for the composite of subsequent vascular events after 5 years was 12.3% (95% CI 10.7 – 13.9), for cerebral infarction 2.2% (95% CI 1.4 – 2.8) and for MI 8.0% (95% CI 6.6 – 9.4). Adjusted for age and gender, asymptomatic CAS of ≥ 50% was related to a higher risk of subsequent vascular events (hazard ratio (HR) 1.5, 95% CI 1.1 – 2.1), in particular of vascular death (HR 1.8, 95% CI 1.2 – 2.6). After additional adjustment for vascular risk factors the hazard ratios remained essentially the same.

Discussion

Asymptomatic carotid artery stenosis is an independent predictor of vascular events, especially vascular death, in patients with clinical manifestations of arterial disease or type 2 diabetes but without a history of cerebral ischemia.

Introduction

Carotid artery stenosis (CAS) is defined as a narrowing of the common or internal carotid artery. A stenosis is considered symptomatic when ipsilateral retinal or cerebral ischemia has occurred, and asymptomatic when these symptoms did not take place. Between 5 and 10% of the general population over 65 years of age has an asymptomatic CAS of ≥ 50% (1;2). Recently we reported a 10% (95% CI 9 – 12) prevalence of asymptomatic CAS of ≥ 50% in a cohort of patients with clinical manifestations of arterial diseases in other vascular territories than the CAS (3). The prevalence of asymptomatic CAS ≥ 50% was highest in patients with peripheral arterial disease (15%, 95% CI 13 - 15) and abdominal aortic aneurysm (12%, 95% CI 8 – 16).

Three large trials have been conducted to examine the efficacy of carotid endarterectomy (CEA) in patients with asymptomatic CAS (4-6). A short description of these trials is given in Table 1. The three trials with a total of 5,223 patients (3,579 males and 1,644 females) and 17,037 person-years of follow-up were included in a Cochrane - review (7). For the primary outcome of perioperative stroke or death or any subsequent stroke, patients undergoing CEA fared better than those treated medically (relative risk (RR) 0.69, 95% CI 0.57 – 0.83). The absolute risk reduction, however, is small (approximately 1% per annum over the first few years of follow-up). Nineteen patients with an asymptomatic CAS of at least 60% needed to undergo CEA to prevent one stroke or death in the coming 5 years, while 6 patients with a symptomatic CAS of 70 - 99% needed to undergo CEA to prevent one event in five years (8).

The degree of asymptomatic CAS is related to various vascular risk factors, including age, smoking, systolic blood pressure, and cholesterol (9). A higher degree of asymptomatic CAS was predictive for future stroke in patients with a large-artery or small vessel atherosclerotic disease, but not in patients with a cardio-embolic stroke in a study among 1,820 patients (10). Moreover, asymptomatic CAS has been related to future myocardial infarction (MI) and vascular death (Table 1). Most of these studies have been performed in the general population. Two studies, restricted to patients with coronary heart disease (CHD) or abdominal aortic aneurysm (AAA), also reported an increased risk of vascular death or MI in patients with asymptomatic CAS (11;12).

The aim of the present large prospective cohort study was to examine the relation between asymptomatic carotid artery stenosis and the risk of vascular events in patients with various clinical manifestations of arterial disease or presence of type 2 diabetes mellitus but without a history of cerebrovascular disease.

Table 1. Summary of prospective studies examining the relationship between asymptomatic carotid artery stenosis and vascular events

First author	N	Type of patients	FU (years)	Age at entry	Adjusted risk estimate
ACST-trial (6)	3120	CAS ≥ 60% randomized deferral of any CEA	3.4	~ 68	Immediate CEA 6.4% vs deferred CEA 11.8% of any type of stroke or death within 5 years
VA-trial (4)	444	CAS ≥ 50% randomized to surgery or medical treatment	4.0	~ 65	12.8% in surgical compared with 24.5% in the medical group for neurologic events in 4 years
ACAS-trial (5)	1662	CAS ≥ 60% randomized to surgery or medical treatment	2.7	~ 67	Surgery 5.1 % and medical treatment 11.0% for stroke or death in 5 years
Held (11)	809	Stable angina pectoris	3.0	< 70	Any type of plaque for vascular death / MI HR 1.83 (0.96 – 3.51) Plaque grade ≥ 50% for vascular death / MI HR 1.85 (0.77 – 4.46)
Liapis (12)	208	Operative repair AAA	4.2	49 - 80	Carotid stenosis ≥ 50% for vascular mortality HR 3.61 (1.28 – 10.14)
Bertges (19)	1004	Asymptomatic* general population, history of MI 35%	2.7	~ 66	Baseline stenosis RR 1.29 (p=0.01) for TIA/CVA Change in stenosis RR 1.68 (p=<0.01) for TIA/CVA
Joakimsen (15)	248	Asymptomatic* general population, with CVD history of 44%	4.2	> 24	Stenosis > 45% - ≤ 74% RR 2.22 (0.81 – 6.12) for death Stenosis ≥ 75% - ≤ 99% RR 3.24 (1.12 – 9.35) for death Occlusion RR 5.50 (1.63 – 18.52) for death
Dick (21)	525	Asymptomatic* general population with ≥ 70%, history of MI of 21% and PAD of 40%	3.2	~ 73	Male vs Female HR 1.96 (1.13 - 3.38) for CVD Male vs Female HR 2.48 (1.57 - 3.93) for vascular death Male vs Female HR 1.70 (1.15 - 2.49) for mortality
Nadareishvili (18)	106	Asymptomatic* general population	10	~ 64	Stenosis ≥ 50% HR 1.59 (0.43 - 5.94) for ipsilateral stroke Stenosis ≥ 50% HR 2.80 (1.06 - 7.41) for MI, nonstroke vascular death Stenosis ≥ 50% HR 2.11 (0.95 - 4.66) for stroke, MI, vascular death

FU: follow-up, CAS: carotid artery stenosis, HR: hazard ratio, RR: relative risk, ~: approximately, TIA: transient ischemic attack, CVA: cerebrovascular accident, CVD: cardiovascular disease, MI: myocardial infarction, PAD: peripheral arterial disease, CEA: carotid endarterectomy, * asymptomatic: without a history of neurological events

Methods

Study population

This study is part of the Second Manifestations of ARTerial disease (SMART) study. Patients aged 18-79 years, newly referred to the University Medical Center Utrecht, the Netherlands with risk factors for arterial disease (hypertension, hyperlipidemia, diabetes mellitus) or with symptomatic arterial disease (coronary heart disease (CHD), cerebrovascular disease, abdominal aortic aneurysm (AAA), or peripheral arterial disease (PAD), were included in the SMART study. A detailed description of the study was published previously (13). Briefly, patients who gave their written informed consent, underwent a standardized vascular screening including a health questionnaire, laboratory assessment and ultrasonography to investigate the prevalence and incidence of additional vascular diseases. The Ethics Committee of the University Medical Center Utrecht approved the study.

For the current study the data of 3,722 consecutive patients presenting with symptomatic arterial disease or type 2 diabetes mellitus were available. Of those patients, 996 were excluded from the analysis because of a history of cerebrovascular disease. 42 patients had missing values on the carotid artery duplex scanning (due to logistic reasons) and were excluded. Thus, 2,684 patients without cerebrovascular disease at baseline remained in the study.

Vascular screening

All patients visited the hospital after an overnight fast of at least 8 hours and underwent the total vascular screening within 2 hours. Patients completed questionnaires on history of vascular disease (CHD, PAD, AAA, and cerebrovascular disease), and risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking, alcohol consumption, physical activity, and familial vascular history), and current medication use. Height, weight, waist circumference, and blood pressure were measured according to a standardized diagnostic protocol. Fasting blood was sampled to determine serum glucose, total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, creatinine and homocysteine levels. Low density lipoprotein (LDL) cholesterol was calculated according to Friedewald's formula. An early morning urine sample was collected to measure albumin and creatinine concentrations.

Carotid artery stenosis

Ultrasound examinations were performed by well-trained and certified ultrasound technicians at the department of Radiology. The degree of the asymptomatic CAS at both sides was assessed with color Doppler-assisted Duplex scanning. The severity of CAS was evaluated on basis of the blood flow velocity patterns (14). The greatest stenosis observed on the right or the left side of the common or internal carotid artery was taken as the severity of carotid artery disease. Accordingly, all patients were classified into one of the following categories: absence of stenosis; mild stenosis (< 50% diameter stenosis, peak systolic velocity (PSV) > 100 - ≤ 150 cm/s); moderate stenosis (≥ 50 to 69% diameter stenosis, PSV > 150 - ≤ 210 cm/s); severe stenosis (≥ 70 to 99% diameter stenosis, PSV > 210 cm/s or pre-occlusion PSV > 210 cm/s and distal PSV < 40 cm/s or subtotal PSV < 50 cm/s and severe plaque); and occlusion (100% diameter stenosis, no flow) (14).

Follow-up

Patients were biannually asked to complete a questionnaire on hospitalizations and outpatient clinic visits. The endpoint of interest for this study was a composite of first occurrence of a vascular event, namely vascular death, ischemic stroke, and myocardial infarction. Definitions of events are given in Table 2. If patients or family recorded such an event, we retrieved hospital discharge letters and the results of relevant laboratory and radiology examinations. Three members of the SMART study Endpoint Committee independently audited all events on the basis of available information. This committee consisted of physicians from different departments. In case of disagreement, consensus was reached by consulting other members of the Endpoint Committee.

Data-analysis

The baseline characteristics were adjusted for age between patients with and without an asymptomatic CAS with covariance analysis (ANCOVA, general linear model procedure). Differences between patients with and without an asymptomatic CAS were tested with chi-square (categorical variables), unpaired T-test (continuous normal distributed variables) or Mann-Whitney U (continuous skewed variables).

Cox proportional hazard analysis was performed to estimate hazard ratios and 95% confidence intervals (CI) for the occurrence of vascular events (composite vascular outcome, and separate for vascular death, ischemic stroke and MI) associated with the

Table 2. Definitions of fatal / non-fatal events

Vascular death	Sudden death: unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence
	Death from ischemic stroke (22)
	Death from intracerebral hemorrhage (hemorrhage on CT-scan) (22)
	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
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 brain-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
Myocardial infarction	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

ECG: electrocardiogram, CK: creatinine kinase, MB: myocardial band

presence of asymptomatic CAS. If a patient had multiple events, the first was used in the analysis. The unadjusted association of asymptomatic CAS of ≥ 50% and vascular events was examined in model I. In model II, this association was adjusted for age and gender. In model III, additional adjustments were made for systolic and diastolic blood pressure, current smoking, diabetes, use of antiplatelet agents, blood pressure-lowering agents,

and lipid-lowering agents at baseline. Furthermore, the extent of asymptomatic CAS (30 - 49%, 50 - 69%, 70 - 99%, 100% versus no asymptomatic CAS in that category as reference group) was examined in relation to the composite vascular outcome and separate for vascular death, ischemic stroke and MI.

Analyses were performed in SPSS version 12.0.1. (SPSS, Chicago, Illinois, USA).

Results

Study population

The age-adjusted baseline characteristics of the study population are presented in Table 3. Asymptomatic CAS of ≥ 50% was present in 221 (8%) of the 2684 patients. Patients with asymptomatic CAS were older (mean age 65 versus 57 years), had a higher systolic blood pressure (144 versus 139 mmHg), were more often ever-smokers (90 versus 78%), and had more often a history of PAD (19 versus 7%) and AAA (19 versus 11%).

Fatal and non-fatal events during follow-up

During a mean follow-up of 3.6 years (SD 2.3), 239 of the 2684 (9%) patients died (147 of a vascular event), 49 (2%) patients suffered from an ischemic stroke, and 165 (6%) patients had an MI. Compared with patients without an ischemic stroke during the follow up, the 49 patients who suffered an ischemic stroke were older (62 versus 57 years), had an impaired renal function (creatinine clearance 68 versus 82 ml/min), used more often blood pressure-lowering agents (82 versus 59%), and had more often a history of PAD (43 versus 26%) and AAA (25 versus 11%). Compared with patients without a myocardial infarction during follow up, the 165 patients who had a MI were older (62 versus 57 years), had an impaired renal function (creatinine clearance 69 versus 82 ml/min), used more often blood pressure-lowering agents (84 versus 59%), and had more often a history of CHD (69 versus 59%), PAD (35 versus 26%) and AAA (24 versus 11%). The composite of ischemic stroke, MI, or vascular death occurred in 253 patients (9%). An ipsilateral ischemic stroke occurred in 5 patients with an asymptomatic CAS of ≥ 50%, 5 other strokes could not be classified: 2 were hemorrhagic strokes, 2 were ischemic strokes in the cerebellum or brain stem and on one ischemic stroke insufficient information was available. Seventeen patients (1%) underwent carotid endarterectomy and 2 patients an endovascular intervention during follow-up. The

Table 3. Age-adjusted baseline characteristics of the study population (n= 2684)

	CAS ≥ 50% n= 221	No CAS n= 2463	P-value
Male gender (%)	73	75	0.7
Age (years)	64.5 ± 8.3	56.9 ± 11.7	<0.001
Systolic blood pressure (mmHg)	144 ± 20	139 ± 20	<0.001
Diastolic blood pressure (mmHg)	78 ± 11	81 ± 11	<0.001
Body mass index (kg/m^2)	26.4 ± 4.4	27.1 ± 4.3	0.01
Waist circumference (cm)	96 ± 14	96 ± 13	0.1
Total cholesterol (mmol/L)	5.5 ± 1.2	5.3 ± 1.2	<0.001
LDL-cholesterol (mmol/L)	3.4 ± 1.1	3.2 ± 1.0	<0.001
HDL-cholesterol (mmol/L)	1.2 ± 0.4	1.2 ± 0.4	0.7
Triglycerides (mmol/L)	2.1 ± 1.7	2.0 ± 1.7	0.07
Homocysteine (µmol/L)	14.7 ± 7.4	14.0 ± 9.7	<0.001
Fasting glucose (mmol/L)	7.2 ± 2.8	6.8 ± 2.7	0.3
Diabetes Mellitus* (%)	21	20	0.7
Serum creatinine (µmol/L)	102 ± 62	97 ± 73	<0.001
Creatinine clearance (Cockroft) (ml/min)	81 ± 22	78 ± 25	<0.001
Current smoking (%)	42	30	<0.001
Ever smoking (%)	90	78	<0.001
Medication use			
Antiplatelet agents (%)	63	54	<0.001
Blood pressure-lowering agents (%)	63	61	0.5
Lipid-lowering agents (%)	45	42	0.4
ACE-inhibitor and/or AIIA (%)	29	23	0.05
Vascular disease†			
Coronary heart disease (%)	59	59	1.0
Peripheral arterial disease (%)	45	26	<0.001
Abdominal aortic aneurysm (%)	20	12	<0.001

Data represent mean (SD) or percentages, CAS: carotid artery stenosis
* Patients on glucose-lowering agents
† Ever or current diagnosis, a single person can be classified into more than one disease category

Table 4. Relation between asymptomatic carotid artery stenosis (CAS) and vascular events

Vascular event	Model	Hazard ratio (95% CI)	
		CAS ≥ 50 - 99% n= 221	CAS ≥ 70 - 99% n= 147
All first vascular events (n= 253)	I	2.0 (1.5 - 2.8)	2.1 (1.5 - 3.1)
	II	1.5 (1.1 - 2.1)	1.5 (1.0 - 2.1)
	III	1.5 (1.1 - 2.1)	1.5 (1.0 - 2.2)
Vascular death (n= 147)	I	2.8 (1.9 - 4.2)	2.6 (1.7 - 4.1)
	II	1.8 (1.2 - 2.6)	1.5 (1.0 - 2.4)
	III	2.0 (1.3 - 3.0)	1.7 (1.1 - 2.8)
Ischemic stroke (n= 49)	I	1.3 (0.6 - 3.1)	1.7 (0.7 - 4.2)
	II	1.1 (0.5 - 2.6)	1.3 (0.5 - 3.4)
	III	1.2 (0.5 - 3.0)	1.6 (0.6 - 4.2)
Myocardial infarction (n= 165)	I	2.0 (1.3 - 3.0)	2.0 (1.2 - 3.2)
	II	1.5 (1.0 - 2.3)	1.4 (0.9 - 2.3)
	III	1.5 (1.0 - 2.3)	1.4 (0.8 - 2.3)

Model I: unadjusted, model II: adjusted for age and gender, model III: additionally adjusted for systolic and diastolic blood pressure, current smoking, diabetes, use of antiplatelet agents, blood pressure-lowering agents, and lipid-lowering agents at baseline

cumulative incidence after 5 years was 12.3% (95% CI 10.7 – 13.9) for the composite of subsequent vascular events, 2.2% (95% CI 1.4 – 2.8) for cerebral infarction and 8.0% (95% CI 6.6 – 9.4) for MI. In 647 (24%) of the 2684 patients an MRI of the brain was performed. Asymptomatic carotid stenosis of ≥ 50% were found in 38 (6%) of the 647 patients. In the 38 patients with an asymptomatic CAS, silent infarcts were present in 8 (21%) and in 90 (15%) of the 609 patients without an asymptomatic CAS (relative risk of silent infarction 1.42, 95%CI 0.75 - 2.71). Thus, the prevalence of silent infarcts is non-significantly higher in patients with asymptomatic CAS compared with patients without asymptomatic CAS in this sub sample of patients. In 38 patients with asymptomatic CAS 2 (5%) new vascular events occurred and in 609 patients without asymptomatic CAS 29 (5%) new vascular events occurred during a mean follow-up of 2.1 years. Thus, the recurrent vascular event rate is the same in patients with and without asymptomatic CAS.

Table 5. Risk of any vascular event in relation to the extent of asymptomatic CAS

	Hazard ratios adjusted for age and gender with 95% CI			
	All first vascular events	**Vascular death**	**Ischemic stroke**	**MI**
Asymptomatic CAS extent †	n= 253	n= 147	n= 49	n= 165
30 - 49% (n= 172)	1.0 (0.6 - 1.5)	0.8 (0.4 - 1.4)	0.7 (0.2 - 2.1)	1.2 (0.7 - 1.9)
50 - 69% (n= 74)	1.4 (0.8 - 2.5)	2.1 (1.1 - 3.8)	0.6 (0.1 - 4.1)	1.5 (0.7 - 3.0)
70 - 99% (n= 96)	1.4 (0.9 - 2.2)	1.5 (0.9 - 2.5)	0.7 (0.2 - 3.0)	1.7 (0.9 - 2.8)
100% occlusion (n= 51)	1.5 (0.8 - 2.7)	1.5 (0.7 - 3.2)	2.6 (0.8 - 8.4)	1.0 (0.4 - 2.5)

† no carotid artery stenosis is reference category

Vascular events in patients with asymptomatic CAS

In Table 4, the hazard ratios of different vascular events are given for asymptomatic CAS of ≥ 50% and of ≥ 70%. Adjusted for age and gender, the presence of asymptomatic CAS of ≥ 50% and of ≥ 70% was related to a higher risk of subsequent vascular events (HR 1.5, 95% CI 1.1 – 2.1) and (HR 1.5, 95% CI 1.0 -2.1), respectively. When the vascular events were separated into vascular death, ischemic stroke and MI, the relative risk of vascular death (HR 1.8, 95% CI 1.2 - 2.6) and (HR 1.5, 95% CI 1.0 - 2.4) associated with the presence of asymptomatic CAS of ≥ 50% and of ≥ 70% was slightly higher. After adjustment for vascular risk factors known to be associated with the degree of CAS and with vascular risk, the strength of the relations for any vascular event, vascular death, ischemic stroke, and MI remained essentially the same. Relationships of asymptomatic CAS with outcomes were similar in patients with and without peripheral arterial disease (data not shown). The 857 patients with diabetes mellitus and the presence of asymptomatic CAS of ≥ 50% and of ≥ 70% had the highest increased risk of vascular death (HR 3.2, 95% CI 1.6 - 6.4) and (HR 2.6, 95% CI 1.1 - 6.1), respectively, compared with patients without diabetes. The extent of asymptomatic CAS and the risk of a subsequent event adjusted for age and gender are presented in Table 5. Patients with 30 - 49% asymptomatic CAS had a 1.2 increased risk of MI (HR 1.2, 95% CI 0.7 - 1.9), those with 50 - 69% CAS had the highest risk of vascular death (HR 2.1, 95% CI 1.1 - 3.8), and those with 70-99% CAS had a HR 1.7 , 95% CI 0.9 - 2.8 of MI. Patients with an occlusion of one of the carotid arteries detected at screening had a 2.6 increased risk of ischemic stroke (HR 2.6, 95% CI 0.8 - 8.4). The strength of the relations for any vascular event remained essentially the same after adjustment for vascular risk factors.

Discussion

In patients with a previous clinical manifestation of arterial disease or type 2 diabetes mellitus, the presence of asymptomatic carotid artery stenosis (≥ 50%) was related to a higher risk of subsequent vascular events, in particular of vascular death. Moreover, the relative risk for any recurrent vascular event was greater when the extent of asymptomatic CAS increased. The associations were independent of age and gender.

To the best of our knowledge, only two other studies examined the prognostic value of asymptomatic CAS in patients with clinical manifest arterial disease. A study of 809 patients with stable CHD showed that asymptomatic CAS of ≥ 50% was related to an increased risk of vascular death or MI in a univariate Cox regression analysis (HR 3.4, 95% CI 1.5 – 7.8) (11). After adjustment for age, sex, smoking, hypertension, diabetes mellitus, lipid status and history of previous MI, asymptomatic CAS tended to predict vascular death or MI (HR 1.9, 95% CI 0.8 – 4.5). In another study it was shown that in 208 patients electively operated for an AAA, the presence of an asymptomatic CAS of ≥ 50% was independently associated with vascular mortality (HR 3.6, 95% CI 1.3 – 10.1) and morbidity (HR 4.0, 95% CI 1.8 – 9.0) (12). These studies and our present study indicate that, overall, in patients with clinical manifestations of arterial disease, the presence of asymptomatic CAS (≥ 50%) is a risk indicator of new vascular events. One of the differences between the previous studies and this study is that our study was conducted in a large prospective cohort of patients with well-defined diagnostic inclusion criteria of manifest arterial disease.

A study conducted in subjects with a mean age of 67 years showed that the death rate in 109 patients with self-reported cardiovascular disease or diabetes was only slightly higher (3.61 deaths per 100 person-years) than that in 139 patients with asymptomatic CAS who did not report cardiovascular disease or diabetes (3.14 deaths per 100 person-years) (15). The relative risks of vascular events associated with asymptomatic CAS seemed to be higher in the general population than in patients with clinical manifestations of arterial disease (Table 1). This may be caused by management of vascular risk factors and the use of antithrombotic medication, but different approaches used by investigators to define the study population and the degree of CAS may also play a role.

In the present study we showed that the risk of vascular death is greater than the risk of stroke. This is consistent with previous studies in the general population (1;16;17). The annual risk of stroke from asymptomatic CAS is about 1% per year in the general population (18), 2% in the medical treatment group of the CEA-trials (5;6), and we

found an annual stroke risk of less than 1%. This is probably due to the fact that our patients had no history of cerebral ischemia or had another clinical vascular disease or were otherwise at high risk.

Screening 2,684 patients for detecting asymptomatic CAS resulted in a prevalence of 8%. The clinical consequence of the identification of an asymptomatic CAS in patients with already clinical manifestations of arterial disease, however, is limited, and the cost-effectiveness remains to be determined. Asymptomatic CAS is an independent predictor of vascular events in particular of vascular death in patients with clinical manifest arterial disease as shown in this study. Management of these patients should concentrate on a reduction of the total vascular risk rather than on the stroke risk only. Medical treatment (use of antiplatelet agents, lipid- and blood pressure-lowering agents), lifestyle changes (quit smoking, increase physical activity, appropriate diet), and close monitoring or follow-up measurements of existing vascular risk factors are essential to reduce the vascular risk in these patients. With advances in effective risk management, the benefit of CEA in patients with asymptomatic CAS may be further narrowed.

Follow-up of asymptomatic CAS with duplex-ultrasound for detecting progression of the degree of stenosis may identify patients with high risk for developing cerebral ischemia and may be a tool in selecting patients for CEA (19). However, the cost-effectiveness of this strategy is unknown. New guidelines from the American Academy of Neurology support the use of CEA for patients aged 40 to 75 years with asymptomatic CAS of 60 to 99%, if the patient has at least a 5-year life expectancy and if the surgery / complication rate is low (< 3%) (8). The level of surgical expertise with CEA is related with the surgical risk. Surgeons with less expertise have a higher perioperative risk and this reverses the benefit of CEA (7). So, in our view effective treatment of the established vascular risk factors is the first treatment step to reduce vascular risk and if the degree of asymptomatic CAS progresses than surgery may be considered. Patients with an asymptomatic CAS but without cerebral ischemia do not have an increased risk of ischemic stroke but do have an increased risk of MI or vascular death, as shown in Table 4. Therefore, CEA in patients with asymptomatic CAS of ≥ 50% may be of lesser benefit to reduce the risk of a recurrent vascular event. Whether this is also true for progressive asymptomatic CAS is not known.

We acknowledge some limitations of the study. The study population consisted of those patients who had survived their first vascular event, could be located and were willing to participate. Thus, it could be that our patients were healthier than those not referred to our hospital, which may have led to an underestimation of the association

between asymptomatic CAS and the risk of subsequent vascular events. Secondly, because in patients with asymptomatic CAS, the ipsilateral neurologic event rate may be dependent on plaque characteristics (20), we collected data about the structure of the carotid arterial wall and the characteristics of the atherosclerotic plaque. Unfortunately these data were missing or not retrievable in about half of the patients. Therefore we could not perform reliable analyses.

In conclusion asymptomatic carotid artery stenosis of ≥ 50% is an independent predictor of vascular events, in particular of vascular death, in patients with already clinical manifest arterial disease or type 2 diabetes but without a history of cerebrovascular ischemia.

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Performance of the Framingham, PROCAM, and SCORE algorithms in predicting recurrent vascular events in patients with clinical manifestations of arterial disease and the development of a new risk model. The SMART Study

Abstract

Background

Knowledge of patient's absolute vascular risk can guide physicians and patients in treatment decision making. We investigated the performance of the Framingham, PROCAM, and SCORE prediction rules and developed a risk model for prediction of subsequent vascular events after 1, 3, and 5 years in patients with symptomatic vascular disease.

Methods

We used the data of 3343 patients with symptomatic vascular disease and a mean age of 59.7 years (SD 10.6); they had 392 recurrent vascular events (myocardial infarction, ischemic stroke, and vascular death) within a mean follow-up of 3.6 years. Performance of existing risk scores was investigated by evaluating calibration and discrimination in the SMART data. New risk models were derived with Cox proportional hazards regression analysis. Three models were pre-specified based on literature, including traditional risk factors, location of vascular disease, and the extent of atherosclerosis (intima media thickness, creatinine, and the presence of carotid artery stenosis).

Results

Predicted risk was considerably lower than observed risk with the existing prediction rules and the area under the ROC-curve was poor for framingham 0.45 (95% CI 0.42 – 0.49) and moderate for SCORE 0.70 (95% CI 0.66 – 0.74) at 1, 3, and 5 years of follow-up. A new risk model predicted well at 1 year follow-up but poorly at 3 and 5 years, underestimating the absolute number of events. Discrimination was moderate, with a ROC area of 0.67 (0.62 - 0.71) at 1 year, 0.69 (0.66 - 0.73) at 3 years, and 0.70 (0.67 - 0.73) at 5 years.

Conclusions

Existing primary prevention algorithms do not accurately predict risk in patients with symptomatic vascular disease. A new risk model combining traditional risk factors, location, and extent of vascular disease performed much better and was accurate at 1 year but not at 3 or 5 years.

Introduction

The decision to initiate drug treatment of risk factors (e.g. impaired glucose tolerance, dyslipidemia, hypertension) and appropriate lifestyle changes (quit smoking, weight loss, exercise) is preferably based on appropriate estimation of the absolute vascular risk of an individual patient. Several prediction models for middle-aged people without clinically evident vascular disease exist to assess absolute cardiovascular risk (1-8). All these prediction models are based on traditional risk factors known to contribute to the development of atherosclerosis. The Framingham Heart Study (FHS) prediction model has been externally validated frequently, and tends to overestimate the absolute risk in southern (9;10) and in northern European populations (11-13). Two external validation studies of the PROCAM prediction model show overestimation in healthy UK, Irish, and French men (13;14), and also for the Systematic COronary Risk Evaluation (SCORE) overestimation of the predicted risk versus the observed mortality pattern was observed in a large Austrian population (15). The decline in coronary heart disease mortality over the past decades and improvements in the management of hypertension, dyslipidemia, and other risk factors might explain these systematic overestimations (16). Prediction models tend to perform better when derived than in new populations. Little is known about the performance of the FHS, PROCAM, and SCORE prediction models in patients with clinical manifest arterial disease. The ability to determine the risk of these patients, who are already considered to be at high vascular risk, may help clinicians in their decision to adopt a more aggressive approach to treatment goals for blood pressure and LDL-cholesterol. Moreover, insight into their risk may motivate patients to change inappropriate lifestyles and to comply with their medication regimen.

In the present study we investigated how accurate the FHS, PROCAM, and SCORE prediction models predict the risk of future vascular events in patients with already clinically evident vascular disease. Also, a new prediction model was developed in a large cohort of patients with manifest vascular diseases.

Methods

Study setting and population

The data were derived from patients participating in the Second Manifestations of ARTerial disease (SMART) study (17). This ongoing single-center prospective cohort study started in 1996 and enrolled over 6000 patients referred to the University Medical Center Utrecht (UMC Utrecht), the Netherlands, for treatment of clinical manifestations of atherosclerosis (transient ischemic attack, ischemic stroke, peripheral arterial disease

(PAD), abdominal aortic aneurysm (AAA), coronary heart disease (CHD)) or who are otherwise at high risk of developing symptomatic arterial disease (diabetes mellitus, hypertension, hyperlipidemia). Patients were aged 18-79 years and gave their written informed consent. The Ethics Committee of the UMC Utrecht approved the study.

For the current study the data of 3343 participants with clinical manifestations of arterial disease included between September 1996 and March 2005 were used.

Vascular screening

Vascular screening was conducted on a single day at the UMC Utrecht. A questionnaire was completed on lifestyle habits, smoking, and current medication use. Height and weight were measured without shoes and heavy clothing. Blood pressure was measured twice in sitting position at the right and left upper arm with a non-random sphygmomanometer. Fasting blood was sampled to determine serum glucose, total cholesterol, HDL-cholesterol, triglycerides, and creatinine levels by standard enzyme methods. LDL-cholesterol level was calculated with Friedewald's formula. An early morning urine sample was collected to measure albumin and creatinine concentrations. Common intima-media thickness (IMT) was measured at the left and right common carotid arteries with an ATL Ultramark 9 (Advanced Technology Laboratories, Bethel, WA, USA) equipped with a 10-MHz linear array transducer. Color Doppler-assisted Duplex scanning of the carotid arteries was performed to detect common or internal carotid artery stenosis. The degree of stenosis was classified according to blood flow velocity (18).

Follow-up

Patients were biannually asked to complete a questionnaire on hospitalizations and outpatient clinic visits. Event of interest was model specific for the existing prediction rules, and a composite of first occurrence of vascular events was used for the new risk models, namely vascular death, ischemic stroke, and myocardial infarction (MI). Definitions of all vascular events used in each prediction model are given in Table 1. When a potential event was recorded by the patient or family, hospital discharge letters and the results of relevant laboratory and radiology examinations were collected. Three members of the SMART study Endpoint Committee audited all events on the basis of this information. This committee consisted of physicians from different departments. If there was disagreement, consensus was reached by consulting other members of the Endpoint Committee.

Table 1. SMART-definitions of fatal / non-fatal events by Framingham, PROCAM, SCORE, and the new prediction model

FHS	Fatal / non-fatal coronary ischemic event
	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
	Sudden death: unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24h given convincing circumstantial evidence
	Angina pectoris: all registrated CABG and PTCA interventions occurred in the follow-up
PROCAM	Fatal / non-fatal coronary ischemic event, same definition as for FHS except angina pectoris
SCORE	Vascular death
	Sudden death: unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24h given convincing circumstantial evidence
	Fatal myocardial infarction / congestive heart failure
	Death from ischemic stroke: relevant clinical features, lasting more than 24h, 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 brain-scan.
	Death from intracerebral hemorrhage: hemorrhage on brain-scan
	Death from rupture of abdominal aortic aneurysm: rupture on echography, CT-scan or laparotomy
	Vascular death from other cause, such as sepsis following stent placement
Newly derived model	Fatal or non-fatal coronary ischemic event, same definition as for PROCAM
	Fatal or non-fatal ischemic stroke
	Definite: relevant clinical features causing an increase in impairment of at least one grade on the modified Rankin scale, accompanied by a fresh ischemic infarction on a repeat brain-scan
	Probable: clinical features causing an increase in impairment of at least one grade on the modified Rankin scale, without a fresh ischemic infarction on a repeat brain-scan
	Vascular death, same definition as for SCORE

CT: computer tomography, ECG: electrocardiogram, CK: creatinine kinase, MB: myocardial band, CABG: coronary artery bypass graft, PTCA: percutaneous transluminal coronary angioplasty, FHS: Framingham Heart Study

Existing prediction models

The independent predictors and events used in the FHS, PROCAM, SCORE models are summarized in Table 2. The FHS prediction model is based on the data of 2489 men and 2856 women aged 30 to 74 years with no overt CHD (1) and estimates the probability of developing fatal / non-fatal MI, angina pectoris, or coronary death within 10 years. The PROCAM prediction model is based on the Prospective Cardiovascular Münster Study (PROCAM) involving 5389 healthy working men aged 35 to 65 years (6). We used the scoring scheme of PROCAM to calculate the 10 year predicted risk of coronary events (nonfatal / fatal MI, or sudden cardiac death). The SCORE chart is based on pooled data from 12 European prospective cohort studies involving 205,178 people aged 45 to 64 years, among whom there were 7934 vascular deaths during follow-up (8). A chart of high risk and low risk regions was prepared; the Netherlands are classified as a high risk region. In contrast to the previously mentioned prediction rules, SCORE predicts the 10 year individual absolute risk of fatal vascular events only.

Development of new prediction models

Vascular mortality has decreased during the last decades but the incidence of non-fatal vascular disease is likely to increase rather than decrease (19). It is conceivable that patients who have experienced a previous MI or an ischemic stroke have high absolute risks. We assumed that risk in patients with symptomatic vascular disease is not only related to the traditional risk factors but also to the site and extent of atherosclerosis. Thus, we built 3 models based on: (1) data on traditional risk factors (age, gender, systolic and diastolic blood pressure, HDL-cholesterol, LDL-cholesterol, presence of diabetes mellitus, current smoking); (2) data on traditional risk factors and the site of symptoms (based on the referral diagnosis or the presence of other clinically manifest arterial disease (CHD, cerebrovascular disease, PAD, and / or AAA)); and (3) data on traditional risk factors, disease location, and the extent of atherosclerosis (presence of carotid artery stenosis $\geq$ 50%, and the continuous variables IMT and serum creatinine).

Data analysis

Validation of existing prediction rules

Because there were few missing values (1%) in our sample of 3343 patients, we imputed the estimated mean of a particular variable if a value was missing (20). We used the PROCAM scoring scheme without using the variable MI of relatives because we did not have this information.

Table 2. Independent predictors and events used in the prediction models

Independent predictor	Framingham	PROCAM	SCORE
Age	+	+	+
Gender	+		+
Systolic blood pressure	+	+	+
Diastolic blood pressure	+		
Total cholesterol			+
LDL-cholesterol	+	+	
HDL-cholesterol	+	+	
Triglycerides		+	
Diabetes mellitus	+	+	
Family history of myocardial infarction		+	
Current smoking	+	+	+
Vascular event			
Vascular mortality			+
Fatal or non-fatal myocardial infarction	+	+	
Sudden death	+	+	+
Angina pectoris (stable AP)	+		
Coronary insufficiency (unstable AP)	+		

+: present

The predictive ability of each model was assessed after 1, 3, and 5 years of follow-up in two ways. First, calibration was assessed, i.e. the fit of predicted with observed risk. For this purpose predicted and observed risks in each decile were compared, and the goodness of fit was assessed with the Hosmer-Lemeshow test (21), in which a p-value < 0.05 indicates poor calibration. Second, discrimination was assessed with the area under the Receiver Operating Characteristic (ROC) curve with its 95% confidence interval (95% CI). The area under the ROC curve measures the proportion of case/non-case pairs that are correctly ordered (22). It may range from 0.5 (no discrimination) to 1.0 (perfect discrimination).

Derivation of new models

The association between the presence or absence of a recurrent vascular event and potential prognostic factors was quantified with Cox proportional hazard models. The

proportional hazards assumption was satisfied based on survival curves for dichotomous variables and for tertiles of continuous variables. The pre-specified predictors were retained in the final models without attaining a certain level of significance. We evaluated the three models, in terms of calibration and discrimination, at 1, 3, and 5 years of follow-up. To test the contribution of the pre-specified predictors to the model, we tested the differences between the -2 log likelihood function.

The analyses were performed with SPSS version 14.0 (SPSS, Chicago, Illinois, USA).

Results

Study population

The baseline characteristics of the study population are described according to gender in Table 3. Male patients were less often smokers (31 versus 36%), and more often had a history of CHD (59 versus 41%) and AAA (14 versus 7%) than female patients. Medication use (all categories) was comparable between men and women.

Follow-up

During a mean follow-up of 3.6 years (SD 2.3), data on 12,020 person-years were available: of the 3343 patients included at baseline, 350 (11%) died (228 of a vascular event), 224 (7%) had an MI, and 117 (4%) had an ischemic stroke. We evaluated the performance of the existing models with 2842 patients who had ≥ 1 year follow-up, in 1986 patients with ≥ 3 years, and in 1342 patients who had ≥ 5 years of follow-up. The composite outcome event occurred in 445 patients according to the FHS model and in 178 patients according to the PROCAM model at 5-year follow-up. Vascular mortality, as defined in the SCORE model, occurred in 188 of the 1211 patients who had ≥ 5 years of follow-up. The composite event for the newly derived prediction model (MI, ischemic stroke, or vascular death) occurred in 392 patients, and also there we evaluated the performance of the existing models with 2705 patients who had ≥ 1 year follow-up, 1720 patients with ≥ 3 years, and 962 patients who had ≥ 5 years of follow-up.

Performance of the three existing prediction models

The ranking of the predicted probabilities of PROCAM yielded less than 10 equal groups because there was little variation in the prediction probabilities. Half of the patients after 1 year follow-up had a predicted risk higher than the model could classify. Therefore,

Table 3. Baseline characteristics of the study population according to sex (n= 3343)

	Male (n= 2518)	Female (n= 825)
Age (years)	59.9 ± 10.2	59.2 ± 11.6
Systolic blood pressure (mmHg)	142 ± 21	144 ± 23
Diastolic blood pressure (mmHg)	82 ± 11	80 ± 12
Total cholesterol (mmol/L)	5.3 ± 1.1	5.5 ± 1.2
LDL-cholesterol (mmol/L)	3.3 ± 1.0	3.3 ± 1.1
HDL-cholesterol (mmol/L)	1.2 ± 0.3	1.4 ± 0.4
Triglycerides (mmol/L)	2.0 ± 1.6	1.8 ± 1.1
Diabetes mellitus * (%)	11	14
Current smoking (%)	31	36
Medication use		
Antiplatelet agents (%)	67	66
Blood pressure-lowering agents (%)	61	61
Lipid-lowering agents (%)	45	46
ACE-inhibitor and/or AIIA (%)	24	26
Vascular disease †		
Coronary heart disease (%)	59	41
Cerebrovascular disease (%)	28	35
Peripheral arterial disease (%)	23	33
Abdominal aortic aneurysm (%)	14	7

Data represent mean (SD) or percentages
* Patients using glucose-lowering medication
† Vascular disease in medical history and/or a recent diagnosis. A single person can be classified into more than one disease category

only the predicted risk by FHS and SCORE and the observed events are given for those patients with 1, 3, and 5 years follow-up (Table 4). The predicted risk was much lower than the observed risk in each decile, indicating that the FHS and SCORE prediction models underestimate the risk of a recurrent vascular event. The Hosmer-Lemeshow test statistics were significant for both models at the three follow-up moments, indicating poor calibration. ROC analyses showed poor to moderate discriminatory performance for the FHS and SCORE models at 1, 3, and 5 years of follow-up (Table 4).

Table 4. Observed versus predicted risk of FHS and SCORE prediction models in the SMART study at 1, 3, and 5 years of follow-up

	1 year follow-up						3 years follow-up						5 years follow-up					
	N	n	O-risk	P-risk	HL-test*	ROC† (95%CI)	N	n	O-risk	P-risk	HL-test*	ROC† (95%CI)	N	n	O-risk	P-risk	HL-test*	ROC† (95%CI)
FHS: prediction of fatal and non-fatal coronary ischemic events																		
1	284	20	7.04	0.16			198	34	17.17	0.94			134	45	33.58	1.84		
2	284	30	10.56	0.32			200	53	26.50	1.72			134	58	43.28	3.34		
3	284	31	10.92	0.44			197	42	21.32	2.31			134	51	38.06	4.45		
4	285	33	11.58	0.57			199	40	20.10	2.97			135	50	37.04	5.77		
5	284	22	7.75	0.72			199	34	17.09	3.74			134	41	30.6	7.34		
6	284	21	7.39	0.93			199	36	18.09	4.64			134	45	33.58	8.95		
7	285	22	7.72	1.17			198	26	13.13	5.78			135	36	26.67	11.02		
8	284	18	6.34	1.51			198	33	16.67	7.17			134	39	29.10	13.58		
9	284	22	7.75	1.99			200	28	14.00	9.17			134	41	30.60	17.09		
10	284	14	4.93	3.44			198	27	13.64	15.17			134	39	29.10	26.22		
					X^2= 3619	0.45					X^2= 2034	0.44					X^2= 2295	0.45
Total	2842	233			p< 0.001	(0.41 - 0.48)	1986	353			p< 0.001	(0.41 - 0.48)	1342	445	445		p< 0.001	(0.42 - 0.49)
SCORE: prediction of vascular death																		
1	282	1	0.35	0.02			192	5	2.60	0.08			121	8	6.61	0.18		
2	283	2	0.71	0.08			192	3	1.56	0.31			121	5	4.13	0.63		
3	283	2	0.71	0.15			192	6	3.13	0.58			121	9	7.44	1.17		
4	283	2	0.71	0.23			193	6	3.11	0.88			121	12	9.92	1.79		
5	282	4	1.42	0.33			192	10	5.21	1.22			121	9	7.44	2.44		
6	283	2	0.71	0.45			192	13	6.77	1.66			122	24	19.67	3.36		
7	283	11	3.89	0.63			193	12	6.22	2.32			121	21	17.36	4.76		
8	283	4	1.41	0.90			192	16	8.33	3.26			121	23	19.01	6.55		
9	283	5	1.77	1.35			192	18	9.38	4.79			121	35	28.93	9.44		
10	282	16	5.67	2.79			192	32	16.67	9.47			121	42	24.71	17.69		
					X^2= 110	0.70					X^2= 299	0.69					X^2= 660	0.70
Total	2827	49			p< 0.001	(0.63 - 0.78)	1922	121			p< 0.001	(0.64 - 0.74)	1211	188			p< 0.001	(0.66 - 0.74)

N: number of patients at baseline, n: number of events, O-risk: observed risk, P-risk: predicted risk,
* Hosmer-Lemeshow goodness-of-fit test with 8 degrees of freedom
† area under the Receiver Operating Characteristics curve with 95% confidence interval

A new prediction model for recurrent vascular events

The distribution of all candidate predictors according to the presence of a recurrent vascular event is listed in Table 5: 392 out of 3343 patients (12%) had a recurrent event. As expected, patients with a recurrent vascular event had less favorable levels of traditional risk factors, had a higher prevalence of other vascular disease, and more extensive atherosclerosis than the patients without a recurrent vascular event.
In table 6 regression coefficients, their standard error, and corresponding hazard ratios are presented. Neither systolic nor diastolic blood pressure was related with an increased risk of recurrent vascular events, whereas the presence of other vascular disease was.

The performance of the three new prediction models in patients with 1, 3, and 5 years of follow-up is presented in Table 7. Calibration of all models decreased as the follow-up duration became longer. As seen in Figure 1 the predicted risk fitted the actual risk better at 1 year than at 3 and 5 years (model III). The area under the ROC increased marginally by adding more predictors to the model: the classical model had an area of 0.62 (95% CI 0.58 - 0.67) at 1 year and model III had an area of 0.67 (95% CI 0.62 - 0.71) (Table 7). The -2 log likelihood test showed a significant difference between model II and model III ($X^2 = 40.8$, $p < 0.001$). Thus, the additional predictors of model III contributed to a better fit of the new prediction model. To be able to predict the absolute risk of a recurrent vascular event for an individual patient, a risk score was developed containing the beta coefficients of the pre-specified predictors (Appendix).

Discussion

We applied the Framingham Heart Study, PROCAM, and SCORE prediction algorithms to data from a population of patients with clinical manifestations of arterial disease. All models underestimated the predicted risk compared with the observed incidence. Direct comparison of the performance of FHS, PROCAM, and SCORE is not possible because different outcome events are used in each prediction rule. The PROCAM scoring scheme performed the worst, predicting a high probability of vascular events in half of the patients in the study sample. SCORE performed better than the other models at 5 years, with an area under the ROC of 0.70 (95% CI 0.66 – 0.74), but this model also underestimated the predicted risk in the SMART cohort.

There are several possible explanations for the lack of accuracy of the existing prediction models within the SMART cohort. Firstly, the FHS, PROCAM, and SCORE rules were developed for vascular risk prediction in middle-aged individuals without pre-existing symptomatic vascular disease rather than in patients with clinical manifestations of arterial disease. Most often overestimation of the predicted risk is seen if these

Table 5. Distribution of candidate predictors according to a recurrent vascular event (n= 3343)

	Recurrent vascular event	
	Yes (n= 392)	**No (n= 2951)**
Age (yrs)	64.4 ± 10.4	59.1 ± 10.4
Male gender (%)	81	75
Current smoking (%)	40	31
Diabetes mellitus * (%)	18	11
Systolic blood pressure (mmHg)	148 ± 23	142 ± 22
Diastolic blood pressure (mmHg)	81 ± 11	81 ± 13
HDL-cholesterol (mmol/L)	1.2 ± 0.4	1.1 ± 0.3
LDL-cholesterol (mmol/L)	3.5 ± 1.0	3.2 ± 1.0
Coronary heart disease † (%)	51	55
Cerebrovascular disease † (%)	37	29
Peripheral arterial disease † (%)	31	25
Abdominal aortic aneurysm † (%)	23	10
Serum creatinine (µmol/L)	122 ± 115	97 ± 70
Intima media thickness (mm)	1.1 ± 0.4	0.9 ± 0.3
Carotid artery stenosis (≥ 50%)	36	19

Data represent mean (SD) or percentages
* Patients using glucose-lowering agents
† Ever or current diagnosis, a single patient can be classified into more than one disease category

models were validated in the general population, probably because of better risk factor management and increasing knowledge about diagnosis, therapy, and management of vascular disease (23). An underestimation of the predicted risk, as found in our study, is seldom seen. The FHS rule was derived before widespread use of medical therapy (e.g. antihypertensive agents, statins), PROCAM was initially developed for men only, and SCORE was developed to predict the risk of vascular mortality within a narrow age range (45 to 64 years) whereas the life expectancy in western European countries is steadily increasing.

Given the correlation between increasing age and vascular disease incidence and the fact that more patients survive an acute (first) clinical manifestation of a vascular disease, it is likely that the incidence of vascular events will increase exponentially rather than linearly the coming decades (24). This means that more patients will develop

clinical manifestations of arterial disease and for this reason it is important to identify those patients at the highest risk of a recurrent fatal or non-fatal vascular event because they are likely to benefit the most from aggressive riskfactor treatment.

The major vascular risk factors that are important in primary prevention are also important in secondary pevention (25;26). For better risk prediction, we added information about co-morbid vascular disease and extent of atherosclerosis to the new prediction models. In a prospective study of 766 adults with manifest arterial disease, serum creatinine, albumin, and IMT in the highest quartile (vs. lowest quartile) and carotid plaque (vs. no plaque) were independently associated with recurrent vascular events in addition to established vascular risk factors (27). While. some novel risk factors, such as plasma concentrations of hsCRP, lipoprotein(a), fibrinogen, provide more insight into the pathophysiology of atherosclerosis, their use in risk prediction may be limited because of the high correlation with traditional risk factors (28). In a recent study assessing the association of 19 novel risk markers with incident CHD in 15,792 adults, none of the novel risk factors were found to improve the area under the ROC curve of a prediction model consisting of traditional risk factors (29). Another study of 3199 patients with previous CHD showed that traditional risk factors were the best predicors of recurrent vascular events. Addition of information about the plasma concentration of N-terminal pro-brain natriuretic peptide increased prediction accuracy (30).

We found that the new models were better in predicting vascular events in the short term (1 year) than in the long term (3 and 5 years). It is questionable whether long-term prediction is possible in already high risk patients. In a cohort study of 1336 patients with TIA and minor stroke, it was shown that the risk was highest shortly after an ischemic event, was lowest after 3 years and gradually increased thereafter (31). The same pattern was recorded for the risk of stroke during the first 3 years, whereas the risk of mortality increased gradually throughout the study. Researchers from the North American Symptomatic Carotid Endarterectomy Trial also reported the falling risk of new events (especially that of strokes) over the first 3 years after the index event (32). The increased risk directly after an event may be due to the instability of atherosclerotic plaques, suboptimal medication use, and inappropriate lifestyle. It is possible that unstable plaques become more stable as a result of risk factor management and lifestyle changes (31).

Furthermore, we found that model III with 15 predictors fitted better than model II with 12 predictors because of a significant difference between the models using the -2 log likelihood test. Thus, model III had the best fit in our dataset, showed a good agreement between the predicted and observed risk, and had a moderate discriminatory performance in predicting recurrent vascular events after 1 year.

Table 6. Multivariable associations between predictors and recurrent vascular events in three models (n= 3343)

	Model I			Model II			Model III		
	ß†	SE‡	HR§	ß†	SE‡	HR§	ß†	SE‡	HR§
Age in years	0.05	0.01	1.05 (1.04 - 1.07)	0.04	0.01	1.05 (1.03 - 1.06)	0.04	0.01	1.04 (1.03 - 1.05)
Gender (female)	-0.26	0.14	0.77 (0.59 - 1.01)	-0.18	0.14	0.84 (0.64 - 1.10)	-0.08	0.14	0.93 (0.70 - 1.22)
Smoking (current)	0.45	0.11	1.56 (1.26 - 1.93)	0.41	0.11	1.50 (1.21 - 1.87)	0.38	0.11	1.46 (1.17 - 1.82)
Diabetes mellitus (present)	0.33	0.12	1.39 (1.11 - 1.75)	0.33	0.12	1.39 (1.11 - 1.75)	0.32	0.12	1.38 (1.10 - 1.74)
Systolic blood pressure per 10 mmHg	0.02	0.03	1.02 (0.95 - 1.08)	0.02	0.03	1.02 (0.95 - 1.09)	-0.02	0.03	0.98 (0.92 - 1.05)
Diastolic blood pressure per 10 mmHg	0.08	0.06	1.08 (0.96 - 1.21)	0.07	0.06	1.07 (0.95 - 1.21)	0.11	0.06	1.11 (0.99 - 1.26)
HDL-cholesterol per 0.1 mmol/L	-0.04	0.02	0.96 (0.93 - 0.99)	-0.03	0.02	0.97 (0.94 - 1.00)	-0.03	0.02	0.97 (0.94 - 1.01)
LDL-cholesterol per 0.5 mmol/L	-0.01	0.03	0.99 (0.94 - 1.05)	-0.01	0.03	0.99 (0.94 - 1.05)	0.00	0.03	1.00 (0.95 - 1.06)
Coronary heart disease (present) *				0.39	0.12	1.48 (1.17 - 1.86)	0.36	0.12	1.44 (1.14 - 1.81)
Cerebrovascular disease (present) *				0.49	0.12	1.63 (1.28 - 2.07)	0.34	0.14	1.41 (1.08 - 1.84)
Peripheral arterial disease (present) *				0.36	0.12	1.43 (1.12 - 1.82)	0.29	0.13	1.33 (1.04 - 1.70)
Abdominal aortic aneurysm (present) *				0.69	0.13	2.00 (1.55 - 2.59)	0.64	0.13	1.90 (1.47 - 2.46)
Serum creatinine per 10 µmol/L							0.03	0.00	1.03 (1.02 - 1.03)
Intima media thickness per 0.1 mm							0.05	0.01	1.05 (1.02 - 1.08)
Carotid artery stenosis (≥ 50%) (present)							0.21	0.13	1.23 (0.96 - 1.58)

* Ever or current diagnosis, a single patient can be classified into more than one disease category
† Regression coefficients were calculated using Cox proportional hazards models
‡ Standard error
§ Hazard ratios with corresponding 95% confidence interval

Table 7. Discrimination and calibration of the new prediction models in patients with manifest arterial disease

	Prediction after 1 year follow-up N= 2705, n= 144		Prediction after 3 years follow-up N= 1720, n= 254		Prediction after 5 years follow-up N= 962, n= 343	
	ROC-area (95% CI)	**HL-test**	**ROC-area (95% CI)**	**HL-test**	**ROC-area (95% CI)**	**HL-test**
Model I *	0.62 (0.58 - 0.67)	X^2= 18.0, p= 0.02	0.64 (0.60 - 0.67)	X^2= 44.3, p < 0.001	0.65 (0.62 - 0.69)	X^2= 133.6, p < 0.001
Model II †	0.65 (0.60 - 0.69)	X^2= 8.4, p= 0.40	0.66 (0.63 - 0.70)	X^2= 33.9, p < 0.001	0.67 (0.64 - 0.71)	X^2= 127.1, p < 0.001
Model III ‡	0.67 (0.62 - 0.71)	X^2= 10.0, p= 0.27	0.69 (0.66 - 0.73)	X^2= 35.8, p < 0.001	0.70 (0.67 - 0.73)	X^2= 117.5, p < 0.001

N: number of patients at baseline, n: number of events, ROC area: area under the receiver operating characteristics curve, 95% CI: 95% confidence interval, HL-test: Hosmer-Lemeshow goodness of fit test with 8 degrees of freedom

* Age, gender, systolic and diastolic blood pressure, HDL-cholesterol, LDL-cholesterol, current smoking, presence of diabetes

† Model 1 and co-morbidity of coronary heart disease, cerebrovascular disease, abdominal aortic aneurysm and/ or peripheral arterial disease

‡ Model 2 and carotid artery stenosis of ≥ 50%, intima-media thickness, serum creatinine

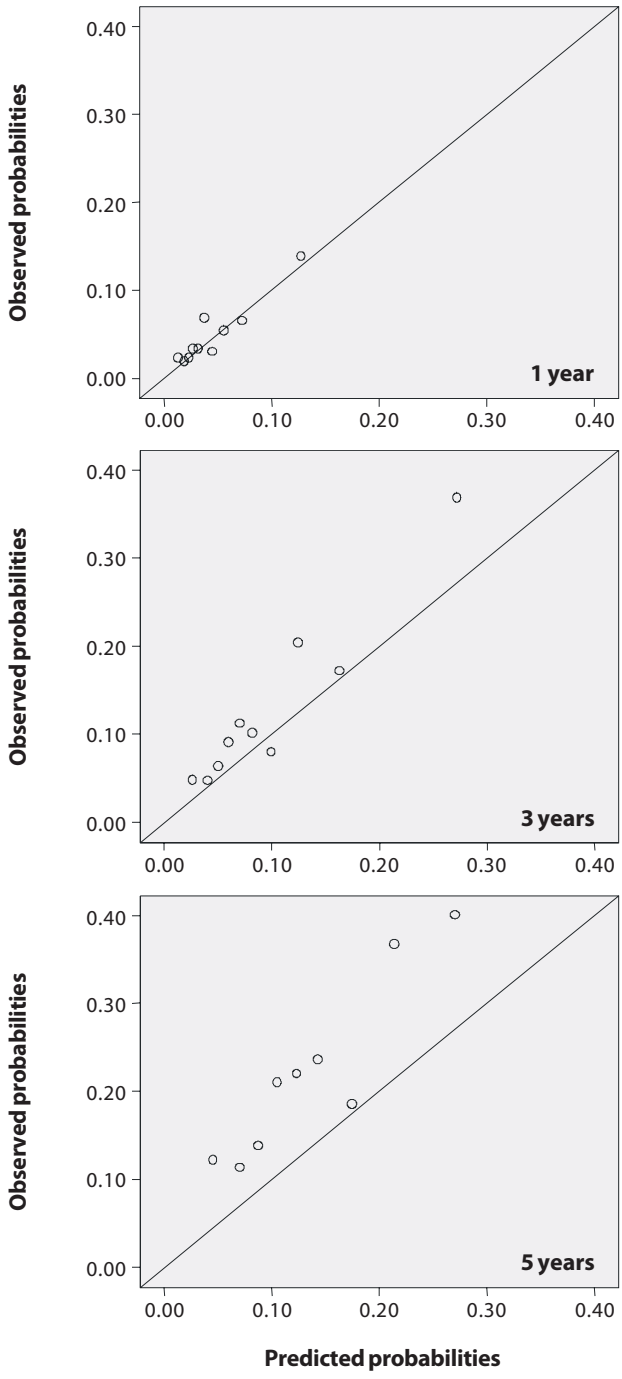

Figure 1. Observed and predicted probabilities of Model III at 1, 3, and 5 years of follow-up

Our study had some limitations. Firstly, the mean follow-up to evaluate existing primary prevention algorithms was limited (3.6 years). Although, we should realize that prediction of recurrent vascular events in patients with clinical manifest arterial disease was more accurate in the short term (1 year after the index event) rather than in the long term (3 or more years after the index event). Secondly, we used data, obtained using standardized procedures, for a single clinic visit. It could be that regression-dilution bias occurred, by which the real association between disease rates and risk factors is underestimated as a result of a high intra individual variability (33). Repeated measurements could increase the validity of the risk estimation. Finally, we estimated the PROCAM score for each SMART participant without having information about MI in relatives. However, we do not think that this influenced the predicted probability because we observed in half of the patients too high predicted probabilities after 1 year of follow-up. As strong points, the study was done in a relatively large cohort with a small proportion of missing values. Moreover, the new prediction model for recurrent vascular events was based on well-known predictors from the literature. The accuracy of this new model should be assessed in a separate sample of patients with clinically manifest arterial disease before being used in clinical practice.

In conclusion, the existing algorithms for predicting vascular events in patients without previous vascular diseases are not applicable for accurate risk prediction in patients with symptomatic vascular disease. The new risk model performed rather well, having an accurate predicted probability and a moderate discriminative ability. With the new model it is possible to predict the risk of recurrent vascular events after 1 year but not at 3 or 5 years in patients with symptomatic vascular disease.

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Appendix

The mathematical details for using the new prediction model III are presented here; model I and II can be estimated on the same manner. The presentation will allow one to estimate the probability of a recurrent vascular event for a period of 1, 3, or 5 years for men and women. The Cox model provides a simple formula for estimating the probabilities of a recurrent vascular event for specified levels of risk factors, the presence of co-morbidity of vascular disease, and the extent of atherosclerosis.

In Table 6 all pre-specified predictors are defined and their ß-coefficients are given. From these, a linear function is computed.

L= 0.039 * age - 0.075 * gender - 0.002 * SBP + 0.011 * DBP + 0.322 * DM – 0.265 * HDL + 0.005 * LDL + 0.381 * smoking + 0.343 * cerebro + 0.363 * CHD + 0.642 * AAA + 0.287 * PAD + 0.209 * CAS + 0.509 * IMT + 0.003 * creatinine.

Where gender is 0 if male and 1 if female, SBP is systolic blood pressure, DBP is diastolic blood pressure, DM is 1 if diabetes mellitus is present, HDL is high-density lipoprotein, cerebro is 1 if cerebrovascular disease is present, CHD is 1 if coronary heart disease is present, AAA is 1 if abdominal aortic aneurysm is present, PAD is 1 if peripheral arterial disease is present, CAS is 1 if carotid artery stenosis ≥ 50% is present, and IMT is intima-media thickness.

This function is next evaluated at the values of the means for each predictor.

M= 0.039 * 59.69 - 0.075 * 1.25 - 0.002 * 142.7 + 0.011 * 81.1 + 0.322 * 0.22 – 0.265 * 1.22 + 0.005 * 3.26 + 0.381 * 0.32 + 0.343 * 0.30 + 0.363 * 0.54 + 0.642 * 0.12 + 0.287 * 0.26 + 0.209 * 0.21 + 0.509 * 0.95 + 0.003 * 100.1= 4.0049

This value M is next subtracted from the function L to produce a function we will call A.

A= L – M= L – 4.0049

The function A is then exponentiated, and we will call this function B, $B= e^{A}$

Now we choose a value that is the estimated probability of surviving without a recurrent vascular event for patients whose risk factors values are equal to the mean values of those observed in the data. These are called S(t), whereas the S is to indicate survival without a recurrent vascular event and t is to index the number of years.

t	S(t)
1	0.964
3	0.926
5	0.877

We are now ready to obtain the predicted probabilities that a patient with clinical manifest arterial disease will develop a recurrent vascular event within t years. This is obtained by computing the value B defined above for the selected predictors and then computing the desired probability as $p= 1 - (S(t))^{B}$.

An example, consider a non-smoking man 71 years of age with a systolic blood pressure of 185 mmHg, diastolic blood pressure of 86 mmHg, diabetic, HDL-level of 0.94 mmol/L, LDL-level of 4.03 mmol/L, does not have a carotid artery stenosis and no previous cerebrovascular disease and abdominal aortic aneurysm but has a history of coronary heart disease and peripheral arterial disease. The intima-media thickness was 0.82 mm and the serum creatinine level was 95 µmol/L.

The value of L for this individual is L= 0.039 * 71 - 0.075 * 0 - 0.002 * 185 + 0.011 * 86 + 0.322 * 1 – 0.265 * 0.94 + 0.005 * 4.03 + 0.381 * 0 + 0.343 * 0 + 0.363 * 1 + 0.642 * 0 + 0.287 * 1 + 0.209 * 0 + 0.509 * 0.82 + 0.003 * 95= 4.7904

The values for A and B are A= L – 4.0049= 4.7904- 4.0049= 0.7855 and B= $e^{A} = e^{0.7855}$= 2.1936.

Finally, the predicted probability that this patient will develop a recurrent vascular event within 1 year is P= 1 - $0.964^{2.1936}$= 1- 0.9227 = 0.0773 or 7.73%.

The course of vascular risk factors and the occurrence of vascular events in patients with symptomatic peripheral arterial disease

Chapter 6

Abstract

Background

Previous studies have documented an undertreatment of vascular risk factors, while patients with symptomatic peripheral arterial disease (PAD) are at increased risk of recurrent vascular events. We examined which baseline variables are related to future vascular events, investigated the course of vascular risk factors, and compared the number of vascular risk factors at baseline and at follow-up in order to determine whether risk factor management could be further improved.

Methods

This study involved 461 patients with Fontaine classification II – IV, enrolled in the SMART study (Second Manifestations of ARTerial disease) in the period September 1996 to December 2000. Patients underwent a standardized screening program for risk factors and were invited for a follow-up measurement in the period September 2003 to March 2005, after a mean follow-up of 5.5 years (SD 1.3). In the interim period between baseline and follow-up measurement, patients received usual care. During follow-up, vascular events (mortality, ischemic stroke and myocardial infarction) and PAD-related events (vascular surgery, interventions, amputations) were documented in detail.

Results

In 2739 person-years of follow-up, 91 vascular events occurred resulting in a 29.1% (95% CI 22.8 – 35.4) cumulative incidence proportion of recurrent vascular events. Older age, elevated homocysteine levels, impaired renal function, and a history of coronary heart disease at baseline were related with an increased risk of new vascular events. Of the 461 patients, 108 patients died, 20 patients were lost to follow-up, and 333 patients were eligible for follow-up measurement of which 221 (66%) patients wished to participate. In 8 of the 221 patients a non-fatal vascular event occurred during follow-up.

The prevalence of hypertension increased from 51 to 70%; 95% CI 10 – 28, obesity from 54 to 67%; 95% CI 3 – 21, and the prevalence of diabetes mellitus increased from 8 to 16%; 95% CI 2 – 14. At follow-up, fewer patients were current smokers (59 to 37%; 95% CI -13 ; -31) and fewer patients had elevated lipid levels (96 to 73%; 95% CI -29 ; -16). Medication use increased in all drug categories during follow-up.

Conclusion

Age, raised homocysteine levels, impaired renal function, and a history of CHD were independent risk factors for vascular events in patients with symptomatic PAD. The prevalence of most risk factors increased over a 5.5-year period, except for smoking and hyperlipidemia, even though medication use had increased over the same period.

Introduction

The first clinical signs of peripheral arterial disease (PAD) are usually intermittent claudication (IC), which affects 2-3% of men and 1-2% of women older than 60 years in primary care settings (1). The frequency of IC increases dramatically with advancing age, ranging from 0.6% in individuals aged 45-54 years, to 8.8% in patients aged 65-74 years (2). Progression to severe ischemia or amputation is unusual in patients with IC, occurring in approximately 1.4% of patients per year (3). IC not only limits functional capacity and adversely affects quality of life but is also associated with a 3- to 6-fold increased risk of coronary heart disease (CHD) and stroke, and a 3- to 5-fold increased risk of death due to cardiovascular disease (CVD) compared with patients without PAD (4). Patients with multi-vessel PAD have a particularly poor long-term prognosis, with a 15-fold increased risk of cardiovascular mortality after 10 years compared with patients without PAD (4). Although patients with PAD have a lower cumulative occurrence of non-fatal vascular events compared with patients with stroke or myocardial infarction (MI) (6.5% vs. 11.8% and 8.5%), they experience the highest fatality due to stroke, MI, or other vascular causes (24% vs. 6% in patients with stroke vs. 7% in patients with MI) after 3 years (5).

The aim of treatment in patients with symptomatic PAD is to relieve lower-extremity symptoms by interventions such as regular exercise, endovascular therapy, or surgery and to reduce the risk of generalized atherosclerosis by treatment of risk factors (2). Risk modification to minimize the risk of vascular morbidity and mortality requires major changes in lifestyle and behavior and drug therapy, such as smoking cessation and medical treatment with antithrombotic, lipid- and blood pressure-lowering agents, which should be continued lifelong. There is clear evidence that a combination of long-term, tailored medical treatment provides effective secondary prevention (6-11). Yet, despite the proven benefits, patients with symptomatic PAD appear to receive treatment for hypertension and hyperlipidemia and antiplatelet therapy less often than patients with CHD or cerebrovascular disease (12-14).

The purpose of this study was threefold. First to determine which patient characteristics were related to the occurrence of fatal and non-fatal vascular events in patients with symptomatic PAD in order to specify determinants of increasing risk of recurrent vascular events. Second, to investigate the course of risk factors in order to evaluate the change of risk factors in patients who attended a vascular screening at baseline and after a mean follow-up of 5.5 years. Finally, to determine the difference in risk factors between follow-up and baseline based on treatment goals for the different risk factors according to the European Guidelines of Cardiovascular Disease Prevention (15) in order to determine whether risk factor management could be further improved in patients with symptomatic PAD.

Methods

Study population

Most patients with typical symptoms of IC (cramping pain in the lower leg(s) during exercise) or with rest pain, non-healing ulcers, or gangrene were referred by general practitioners (GPs) of the province Utrecht to the outpatient clinic of the Department of Vascular Surgery at the University Medical Center Utrecht, the Netherlands. If the vascular surgeon diagnosed IC (typical symptoms and a resting ankle brachial pressure index (ABI) ≤ 0.90), patients were asked to participate in the SMART study (Second Manifestations of ARTerial disease). The SMART study runs in parallel to the care given by the vascular surgeon for PAD, decisions on revascularization procedures were independently made by the vascular surgeon. The SMART study is an ongoing single-centre prospective cohort study with the purpose to investigate the prevalence and incidence of additional vascular diseases in patients who already have a manifestation of arterial disease or who are otherwise at high risk (diabetes mellitus, hypertension, hyperlipidemia) of developing symptomatic arterial disease. The rationale and the study design have been described previously (16). Briefly, patients, aged 18-79 years, who were willing to participate and gave their written informed consent, underwent a standardized vascular screening including a health questionnaire, laboratory assessment, and ultrasonography. The Ethics Committee of our institution approved the study.

For the current study the data of 461 consecutive patients presenting with symptomatic PAD who were included in the vascular screening program in the period September 1996 to December 2000 were used. Patients were invited to visit the hospital again for a follow-up measurement in the period September 2003 to March 2005. Patients received usual care from a GP or a vascular specialist in the period between baseline and follow-up measurement.

Vascular screening

Participating patients visited the hospital after an overnight fast of at least 8 hours, and underwent the same screening at baseline and at follow-up. Patients completed a health questionnaire on history and symptoms of CVD, current medication use, and atherosclerotic risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking, diet, physical activity, familial vascular history). The items on CHD and PAD were based on the Rose Questionnaire (17). Severity of PAD was classified according to the Fontaine classification (18). 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 limb and the iliac crest. Blood pressure was measured two times in sitting position on the right and left upper arm with a non-random sphygmomanometer. Fasting blood was sampled to determine serum glucose, total cholesterol, HDL-cholesterol, triglycerides, creatinine, and homocysteine concentrations. LDL-cholesterol was calculated with Friedewald's formula. An early morning urine sample was collected to measure albumin and creatinine concentrations. Resting ABI was measured for each leg by taking the ratios of the highest systolic blood pressure measured at the ankle to the highest systolic blood pressure in both arms with the patient in supine position. The systolic blood pressure in the posterior tibial and dorsal pedal arteries (left and right) was measured with an 8-MHz continuous-wave Doppler probe connected to an IMEXLAB 9000 Vascular Diagnostic System (Imex Medical Systems Inc., Golden, Colorado, USA) and that in both brachial arteries with a semiautomatic oscillometric device (Omega 1400, Invivo Research Laboratories Inc., Broken Arrow, Oklahoma, USA). The results of the vascular screening were discussed at weekly meetings of a multidisciplinary team consisting of an internist, vascular surgeon, cardiologist, vascular nurse practitioner, and on request a neurologist. An internist evaluated the results of the follow-up measurement. If risk factors were not within the target range, treatment was given according to the European Guidelines of Cardiovascular Disease Prevention (15). The vascular screening results and treatment recommendations were reported in writing to the treating vascular specialist (most often the vascular surgeon) and the GP, with further action being left to their discretion. The patients were informed on the results of the follow-up measurement by telephone.

Difference in risk factors

One of our aims was to quantify how risk factors changed over time. Therefore, we determined the prevalence of hypertension, hyperlipidemia, diabetes mellitus, obesity, and smoking at baseline and at follow-up. The cut-offs for the different risk factors were according to the European Guidelines (15) and were as follows: hypertension (> 140 / 90 mmHg), hyperlipidemia (total cholesterol > 4.5 mmol/L or LDL-cholesterol > 2.5 mmol/L), diabetes mellitus (patients on glucose-lowering agents), obesity (BMI > 25 kg/m^2), and current smoking. The change in number of risk factors was calculated by subtracting the number of risk factors at follow-up from the number at baseline.

Table 1. Definitions of fatal / non-fatal events

Vascular death	Sudden death: unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence
	Death from ischemic stroke
	Death from intracerebral hemorrhage (hemorrhage on CT-scan)
	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
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 brain-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
Myocardial infarction	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

ECG: electrocardiogram, CK: creatinine kinase, MB: myocardial band

Follow-up

Patients were biannually asked to complete a questionnaire on hospitalizations and outpatient clinic visits. If a patient did not return the questionnaire, a research-nurse phoned to the patient, family, or otherwise to the GP to inform about the health status. The endpoint of interest for this study was a composite of first occurrence of vascular events, namely mortality, ischemic stroke, and MI. Definitions of events are given in Table 1. PAD-related amputation, surgical procedures (bypass), and percutaneous

transluminal angioplasty were also recorded during follow-up. If a patient or family recorded such an event, we retrieved hospital discharge letters and the results of relevant laboratory and radiology examinations. Three members of the SMART study Endpoint Committee independently audited all events on the basis of available information. This committee consisted of physicians from different departments. In case of disagreement, consensus was reached by consulting other members of the Endpoint Committee. The patients were followed until they died or refused further participation.

Data analysis

Data are presented as means with standard deviations or as percentages.
Cox proportional hazards analysis was used to assess the effect of risk factors on vascular events and presented as hazard ratios and 95% confidence intervals (95% CIs). If a patient had multiple events, the first was used in the analysis. In model I, the age-adjusted association between baseline risk factors and vascular events was examined. Additional adjustments for systolic and diastolic blood pressure, smoking, HDL-cholesterol, and diabetes were made in model II.

Differences between participants and those refused to participate at follow-up measurement were tested with chi-square (categorical variables), unpaired T-test (continuous normal distributed variables) or Mann-Whitney U (continuous skewed variables).

Changes in the proportion of patients in whom risk factor values were higher than the relevant cut-off level were determined and reported with the corresponding 95% CIs.

Calculations were performed with SPSS version 12.0.1 (SPSS, Chicago, Illinois, USA).

Results

Study population

Patients were screened for the first time between September 1996 and December 2000. Baseline characteristics of the study population are given in Table 2. The 461 patients with symptomatic PAD had a mean age of 60.2 years and were predominantly male (68%). Eighty-seven percent of the patients were classified as having Fontaine II and 13% as Fontaine III / IV, and the mean ABI value of the 461 patients was 0.82.

Table 2. Baseline characteristics of the patients with symptomatic PAD (n= 461)

Age (years)	60.2 ± 10.9
Male gender (%)	68
Body mass index (kg/m^2)	25.7 ± 3.9
Systolic blood pressure (mmHg)	147 ± 22
Diastolic blood pressure (mmHg)	80 ± 11
Total cholesterol (mmol/L)	5.9 ± 1.2
Glucose (mmol/L)	6.5 ± 2.2
Homocysteine (µmol/L)	15.0 ± 9.0
Creatinine clearance (Cockroft) (ml/min)	74 ± 23
Hypertension* (%)	60
Diabetes mellitus type 2† (%)	14
Current smokers (%)	58
Ankle brachial pressure index	0.82 ± 0.2
Medication use	
Antiplatelet agents (%)	53
Blood pressure-lowering agents (%)	46
Lipid-lowering agents (%)	25
ACE-inhibitor and/or AIIA (%)	21
Fontaine classification	
II (%)	87
III + IV (%)	13
Previous cardiovascular disease‡	
Abdominal aortic aneurysm (%)	7
Cerebrovascular disease (%)	12
Coronary heart disease (%)	27

Data are mean (SD) or percentages
* Systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg
† Patients on glucose-lowering agents
‡ Not mutually exclusive

Fatal and non-fatal events during follow-up

During follow-up (till September 1, 2004) 108 of the 461 (23%) patients died (66 of a vascular event). The mean age of those who died was 66.9 years (SD 9.7). Twenty- seven of the 461 (6%) patients experienced an ischemic stroke, and 57 of the 461 (12%) patients had an MI. The composite of ischemic stroke, MI, or vascular death occurred in 91 patients. There were 2739 person-years of follow-up. The cumulative incidence proportion was 29.1% (95% CI 22.8 – 35.4) for the composite of subsequent vascular events, 22.1% (95% CI 16.4 - 27.8) for vascular death and 19.6% (95% 13.9 – 25.3) for MI.

Amputation occurred in 38 legs of 35 patients during follow-up. Surgical procedures (bypass or endarterectomy) were performed the first time in 97 of the 461 (21%) patients involving the aorta / iliac, iliac, or femoral / popliteal arteries. Re-surgical procedures occurred most often (n= 30) in the femoral / popliteal segment and in two patients at the iliac artery segment. Percutaneous transluminal angioplasty was performed the first time in 61 of the 461 patients (13%), 32 times in the iliac segment and 29 times in the femoral / popliteal segment. Endovascular re-interventions occurred 5 times in treated iliac arteries and 3 times in femoral / popliteal arteries.

Older age, elevated homocysteine levels, impaired renal function, and a history of CHD age-adjusted were associated with an increased risk of fatal or non-fatal vascular events (Table 3). Male gender and decreased HDL-levels were borderline significantly related with vascular events. The strengths of the relations for a first vascular event remained essentially the same after adjustment for classical risk factors (data not shown). By analyzing the data separately for each single event outcome, we found results in the same direction but based on rather small number of events.

Follow-up measurement

At the follow-up visit, 108 of the 461 patients (23%) had died and 20 (4%) patients were lost to follow-up. Of the remaining 333 (72%) patients, 221 (66%) came for follow-up measurement and 112 (34%) patients did not participate because of co-morbidity, lack of time, lack of motivation, travel distance. In 8 of the 221 patients a non-fatal vascular event occurred, 2 suffered from an ischemic stroke and 6 patients had an MI. A PAD-related amputation occurred in 12 of the 221 (5%) between baseline and follow-up measurement. Percutaneous transluminal angioplasty was performed the first time in 35 of the 221 (16%), and surgical procedures (bypass) were performed the first time in 42 of the 221 (19%) patients involving the aorta / iliac, iliac, or femoral / popliteal arteries.

Table 3. Hazard ratios (HR) and 95% CI of baseline characteristics for vascular events (n= 461)

Continuous variables	**HR**	**95% CI**	**P-value**
Age per 10 years	1.85	1.48 - 2.30	< 0.001
Total cholesterol per 0.5 mmol/L	0.92	0.84 - 1.01	0.07
HDL-cholesterol per 0.1 mmol/L	0.94	0.89 - 1.00	0.06
LDL-cholesterol per 0.5 mmol/L	0.94	0.85 - 1.04	0.9
Triglycerides per 0.5 mmol/L	1.01	0.94 - 1.08	0.8
Systolic blood pressure per 10 mmHg	1.01	0.91 - 1.11	0.9
Diastolic blood pressure per 10 mmHg	1.00	0.81 - 1.22	1.0
Serum glucose per 1.0 mmol/L	1.06	0.98 - 1.15	0.2
Homocysteine per 1.0 µmol/L	1.03	1.02 - 1.05	< 0.001
Body mass index per 1.0 kg/m^2	1.01	0.96 - 1.07	0.6
Creatinine clearance (Cockroft) per 10 ml/min	0.79	0.69 - 0.91	0.001
Dichotomous variables			
Gender (female)	0.64	0.40 - 1.03	0.07
Diabetes mellitus type 2 (present)	1.49	0.89 - 2.51	0.1
Smoking (current smoking)	1.13	0.98 - 1.31	0.09
History of cerebrovascular disease	1.46	0.85 - 2.52	0.2
History of coronary heart disease	2.30	1.51 - 3.51	< 0.001
History of abdominal aortic aneurysm	1.52	0.76 - 3.03	0.2

HR: hazard ratio adjusted for age, 95% CI: 95% confidence interval, references in parenthesis

There were small differences between the baseline characteristics of the participants and those who refused to participate at follow-up measurement. Participants were younger (57.1 vs. 60.5, p-value 0.01), less often had a history of cerebrovascular disease (7 vs. 16%, p-value 0.01), had a lower mean glucose-level (6.0 vs. 7.0 mmol/L, p-value 0.02), and a lower mean systolic blood pressure (144 vs. 150 mmHg, p-value 0.01). The mean follow-up of the participants was 5.5 years (SD 1.3).

Risk factors at baseline and follow-up

The characteristics of the 221 patients who completed the baseline and follow-up measurements are given in Table 4. The mean ABI value was 0.85 at baseline and 0.89 at

Table 4. Characteristics of patients with symptomatic PAD at baseline and follow-up

	Baseline (n= 221)	Follow-up (n= 221)
Age (years)	57.1 ± 9.9	62.6 ± 10.0
Male gender (%)	67	67
Total cholesterol (mmol/L)	6.0 ± 1.1	5.2 ± 1.2
LDL-cholesterol (mmol/L)	4.0 ± 1.0	2.9 ± 1.0
HDL-cholesterol (mmol/L)	1.1 ± 0.3	1.4 ± 0.4
Triglycerides (mmol/L)	2.1 ± 1.4	1.8 ± 1.0
Systolic blood pressure (mmHg)	144 ± 21	152 ± 23
Diastolic blood pressure (mmHg)	80 ± 10	83 ± 11
Fasting serum glucose (mmol/L)	6.0 ± 1.5	6.0 ± 1.7
Diabetes mellitus type2* (%)	8	16
Homocysteine (µmol/L)	13.9 ± 5.2	14.5 ± 10.5
Body mass index (kg/m^2)	25.6 ± 3.8	26.6 ± 4.2
Waist circumference (cm)	95 ± 11	98 ± 12
Current smoking (%)	59	37
Creatinine clearance (Cockcroft) (ml/min)	78 ± 20	82 ± 29
Albuminuria ≥ 3.0 mg/mmol (%)	14	25
Ankle brachial pressure index	0.85 ± 0.2	0.89 ± 0.2
Medication use		
Antiplatelet agents (%)	47	80
Blood pressure-lowering agents (%)	31	44
Lipid-lowering agents (%)	22	66
ACE-inhibitor and/or AIIA (%)	20	35
Folic acid (%)	2	11

Data are mean (SD) or percentages
* Patients on glucose-lowering agents

follow-up measurement. Mean serum glucose level (6.0 mmol/L) was comparable at both measurements, but more patients quantified for the diagnosis diabetes mellitus type 2 at follow-up (8 vs. 16%). The mean levels of total cholesterol (6.0 vs. 5.2 mmol/L), LDL-cholesterol (4.0 vs. 2.9 mmol/L), HDL-cholesterol (1.1 vs. 1.4 mmol/L), and triglycerides (2.1 vs. 1.8 mmol/L) were more favorable at follow-up. The percentage

Table 5. Difference in risk factors and use of drugs between follow-up and baseline (n= 221)

	% (n) at baseline	% (n) at follow-up	% increase follow-up baseline	95% CI	P-value
Hypertension*	51 (113)	70 (155)	19	10 - 28	< 0.001
Hyperlipidemia†	96 (211)	73 (161)	-23	-29 - -16	< 0.001
Diabetes mellitus‡	8 (17)	16 (35)	8	2 - 14	< 0.001
Obesity§	54 (120)	67 (147)	12	3 - 21	< 0.001
Current smoking	59 (130)	37 (82)	-22	-13 - -31	< 0.001
Antiplatelet agents	47 (99)	79 (167)	32	24 - 41	< 0.001
Blood pressure-lowering agents	31 (67)	44 (95)	13	4 - 22	< 0.001
Lipid-lowering agents	22 (47)	66 (139)	44	35 - 52	< 0.001
ACE-inhibitor and/or AIIA	20 (43)	35 (75)	15	7 - 23	< 0.001

* Systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg
† Total cholesterol > 4.5 mmol/L or LDL-cholesterol > 2.5 mmol/L
‡ Patients on glucose-lowering agents
§ BMI > 25 kg/m^2

current smokers had decreased from 59 to 37%. The mean systolic and diastolic blood pressure, homocysteine level, BMI and waist circumference had increased after a mean follow-up of 5.5 years (Table 4).

During this period, the number of risk factors in individual patients remained the same in 93 (42%) patients, decreased in 71 (32%) patients, and increased in 57 (26%) patients. The decrease in risk factors was mainly caused by patients who quit smoking (from 59 to 37%, 95% -13 - -31) and by fewer patients with elevated lipid levels (from 96 to 73%, 95% CI -29 - -16) (Table 5). The increase in risk factors was caused by more hypertension 19% (95% CI 10 – 28), obesity 12% (95% CI 3 – 21), and by more diabetes mellitus 8% (95% CI 2 - 14). Medication use in all categories increased with time (Table 5).

Discussion

In this study we showed that older age, elevated homocysteine levels, impaired renal function and a history of CHD age-adjusted were related with an increased risk of future vascular events in patients with PAD. In addition, we demonstrated that after a mean follow-up of 5.5 years, mean blood pressure, homocysteine levels, and BMI had increased, whereas mean lipid-levels and the prevalence of smoking decreased. Furthermore,

comparison of risk factors at baseline and at follow-up showed that risk factors had increased in 26% of patients (mainly due to increased prevalence of hypertension, followed by obesity and diabetes), remained stable in 42% and decreased in 32% of the patients.

Atherosclerosis is a systemic disease affecting multiple arteries sites simultaneously. Management of patients with symptomatic PAD requires not only local treatment to decrease limb-specific symptoms but also lifestyle changes and treatment of risk factors in order to decrease the absolute vascular risk. Despite overwhelming evidence of the benefit of risk reduction, most risk factors are inadequately managed in patients with PAD (12;14;19-22). This could have two causes, firstly treating physicians may be not aware of the increased cardiovascular risk of these patients and therefore less keen on starting aggressive risk factor management and the necessary lifestyle changes (23). Second, patients may be not aware of the implications of PAD and their prognosis. Several previous studies reported progression of atherosclerosis in patients with symptomatic PAD, with a high case fatality of vascular deaths (4;5;24;25), that was not influenced by the sites of the original symptoms (26). In our study, 108 of the 461 patients (23%) died, and 66 of 108 (61%) of these deaths were caused by CVD within a mean follow-up of 5.5 years. In a large database study, involving 16,440 patients diagnosed with PAD between 1985 and 1995 without reported Fontaine classification, with an average follow-up of 5.9 years, 7973 deaths (48%) were reported and numbers of vascular deaths were not published (24). In a 10-year prospective follow-up study of 67 patients with diagnosed PAD, 32 deaths were reported due to all causes (48%), 22 (69%) of which were caused by CVD (4). It appears that the number of all cause death, and of deaths associated with vascular disease, decreases in time in PAD patients with a mean age between 60 and 67 years.

In the present study, we found that several baseline risk factors were associated or borderline significantly associated with an increased risk of future vascular events, independently of classical risk factors. Some predictors, such as gender, age and medical history, are not modifiable. Others are potentially modifiable and these changed over time. The mean plasma HDL-cholesterol concentration increased by 0.3 mmol/L during follow-up, the creatinine clearance remained essentially the same, while the plasma homocysteine concentration increased, although the increase was rather small (0.6 µmol/L). The pathophysiological pathway of the effect of renal function on subsequent events remains unclear. Decreased renal function may be a reflection of advanced and diffuse atherosclerosis. On the other hand, metabolic changes accompanied with renal insufficiency (inflammation, endothelial dysfunction) may contribute to future vascular

events. Homocysteine has been suggested as a risk indicator of an increased risk of CVD (27) but treatment of homocysteine with folic acid or vitamins has shown not to prevent future vascular events (28). The two strongest risk factors for the development of PAD, smoking and diabetes, were not predictive for subsequent cardiovascular events. One other study also found that smoking is not a risk factor for new vascular events in PAD patients (25), while other studies reported a relation between smoking and clinical progression of PAD (26;29). A possible explanation of the fact that smoking at baseline was not predictive for future vascular events in our study could be the reduced risk of a future vascular event during follow-up because of a substantial percentage of patients that stopped smoking (59 to 37%). A recent study indicated that diabetes was more predictive in small vessel disease than in large vessel disease (29), while another study showed that diabetes is a prognostic factor in the years after a nonfatal MI (30). A low number of patients with diabetes (n= 63) at baseline and thus a lack of power could be a reason why we did not found diabetes to be an independent predictor.

Under-treatment of existing risk factors was confirmed in our study, despite the fact that all patients were screened and treatment advice was given to the treating vascular specialist and the GP about medical treatment and lifestyle changes. The prevalence of diabetes mellitus, a major risk factor for PAD (2), increased during the follow-up period. However, the prevalence of another strong risk factor, current smoking decreased, possibly as a result of advice given to the treating physicians or the strong public health campaign against smoking.

In general, medication use was higher at follow-up than at baseline. We reported earlier that treatment recommendations sent to the treating vascular specialist and general practitioner led to a marginal increase in medication use compared to usual care (31). In this study, an increase in the use of antiplatelet-agents was noticed, although, 20% of the patients did not use antiplatelet agents at follow-up, even though these drugs provide on average 19% relative risk reduction in major vascular events in patients with arterial disease (8). ACE inhibitors were used by only 20% of the patients at baseline and by 35% at follow-up. Use of ACE inhibitors reduces the cardiovascular risk in high-risk patients who are not known to have a low ejection fraction or heart failure (6), although no statistically significant benefits were found in the PEACE trial who included patients with stable CHD and preserved left ventricular function (32). In addition to reduce cardiovascular complications in patients with PAD (33), there is evidence that statins may also specifically limit PAD progression (34) and improve pain-free walking distance (35). In our study, lipid-lowering agent use increased from 22 to 66% at follow-up, and this may contribute to the decrease in prevalence of hyperlipidemia.

Studies like ours emphasize the need to pay attention to effective risk factor management because of the burden of PAD and its complications on patients and society. Treatment of acute vascular complications by a doctor and management of risk factors by a nurse practitioner has been shown to initiate behavioural changes and to help patients to cope with illness and vascular risk. This approach led to a reduction in vascular risk in patients with manifestations of CVD within the same study cohort (36). Therefore, spending more time for education about existing risk factors, medication use, and about absolute vascular risk may result in better treatment of risk factors.

Our study had some limitations. The study population might be a selected group of patients with symptomatic PAD referred to an academic center, and only patients who whished to participate were included. Because the survivors of our cohort were invited to participate in the follow-up measurement after a mean of 5.5 years, it is possible that less severely affected, younger patients with PAD participated in the follow-up measurement. A strength of our study is that we used data collected from patients with symptomatic PAD over a long period and examined risk determinants associated with fatal and non-fatal vascular events.

In conclusion, in patients with symptomatic PAD, older age, elevated homocysteine levels, impaired renal function, and a history of CHD age-adjusted were associated with an increased risk of future vascular events. The prevalence of most risk factors increased over a 5.5 -year period, except for smoking and hyperlipidemia, even though medication use also increased in this time period.

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Multidisciplinary vascular screening program modestly improves the medical treatment of vascular risk factors

Abstract

Purpose

This study investigated whether recommendations given to the treating vascular specialist and the general practitioner (GP) by a multidisciplinary team of vascular specialists concerning the medical treatment of risk factors, based on international guidelines, led to an increased medication use in a high-risk population.

Methods

Data were obtained from 618 patients enrolled in the SMART study, an ongoing single-center prospective cohort study of patients referred to the University Medical Center Utrecht for atherosclerotic vascular diseases. All patients underwent a vascular screening and their physicians received recommendations concerning the medical treatment of newly detected or not yet sufficiently treated vascular risk factors. After a median follow-up of 29 months, questionnaires about medication use were sent to 618 patients; 534 (86%) questionnaires were returned. Actual use of medication was compared with medical treatment recommendation given at baseline.

Results

The proportion of patients on antihypertensive medication with hypertension (≥ 140/90 mmHg) and not diagnosed with coronary heart disease increased from 56% to 68% (95% confidence interval (95% CI) 2 – 23). The frequency of lipid-lowering medication use increased substantially from 47% to 69% (95% CI 17 - 28). The frequency of glucose-lowering medication use increased slightly from 11% to 14% (95% CI -1 – 7). The use of folic acid increased from 2% to 14% (95% CI 9 – 15) in patients with hyperhomocysteinemia.

Conclusion

Medical treatment recommendations, formulated by a multidisciplinary team, led to a significant increase in medication use. The increase is marginal compared with trends in medication use without this intervention in usual care.

Introduction

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in Western countries (1). Patients with manifest vascular diseases (cerebral, coronary, peripheral) are at a considerably increased risk of non-fatal and fatal events at the same or at another location in the arterial tree. Optimal screening and treatment of vascular risk factors, such as hypertension, hyperlipidemia, smoking, and diabetes mellitus, can reduce cardiovascular morbidity and mortality, and improve quality of life (2-5). Despite overwhelming evidence of the benefit of risk reduction, most cardiovascular risk factors are inadequately managed. The prevalence of treatable risk factors is still high in high-risk patients (6-8). The acute treatment of patients with vascular diseases is focused on the primary, and often life-threatening, presenting vascular disorder, and too little attention is given to lifestyle changes and risk factor management in the chronic phase. Treatment goals are often not met because too few follow-up appointments are scheduled, too few appointments are kept, and there is poor patient compliance or attitude to reduce risk factors (9). The integration of secondary vascular prevention into hospital and primary care has only been marginally successful (6-8). Programs or strategies to improve treatment of important vascular risk factors and to ensure long-term compliance are urgently needed because risk factors continue to contribute to disease progression and impaired prognosis (10).

In this article, we report on the effects of individualised medical treatment recommendations given by a multidisciplinary team of vascular specialists and based on international guidelines (11). The aim of the multidisciplinary treatment advices is to improve the medical treatment of vascular risk factors and to improve compliance with guidelines among specialists and general practitioners (GPs) treating patients with established CVD.

Methods

Vascular screening and prevention program

All patients in the present analysis are participants of Second Manifestation of ARTerial disease study. This is an ongoing single-center, prospective cohort study among patients aged 18-80 with atherosclerotic vascular disease. The Ethics Committee of our institution approved the study and written informed consent was obtained from all participants. The design and criteria used to define the different manifestations of atherosclerotic vascular diseases have been described in detail elsewhere (12). Briefly, all included patients underwent a standardised non-invasively screening and laboratory assessment

to determine the prevalence of risk factors and concomitant asymptomatic arterial disease. Beforehand, the GP and the treating vascular specialist were in writing informed about the participation of their patient and the content of the vascular screening. Patients completed extensive questionnaires on medical history, symptoms of CVD, and risk factors and lifestyle habits. Height, weight, waist circumference, and blood pressure were measured according to a standardised diagnostic protocol. A fasting venous blood sample was taken for the determination of serum glucose, total cholesterol, HDL-cholesterol, triglycerides, creatinine, and homocysteine levels. LDL-cholesterol level was calculated using the Friedewald formula. An early-morning urine sample was collected to measure the albumin concentration and creatinine excretion.

Multidisciplinary treatment recommendations

The results of the vascular screening program were discussed at weekly meetings of a multidisciplinary team consisting of an internist, vascular surgeon, cardiologist, nurse practitioner, and on request a neurologist. The knowledge and experience of these disciplines were combined to discuss the various aspects of risk factor management of these high-risk vascular patients. The treatment goals for patients with established CVD were quitting smoking, BMI < 25 kg/m^2, blood pressure < 140/90 mmHg, total cholesterol < 5.0 mmol/l (195 mg/dl), LDL-cholesterol < 3.0 mmol/l (115 mg/dl), and fasting glucose < 6.1 mmol/l (110 mg/dl). If these targets were exceeded, treatment recommendation was given according to Third Joint Task Force of European Societies recommendations (11) and the best available evidence for the treatment of risk factors, namely, hypertension (13;14), hyperlipidemia (15), diabetes mellitus / insulin resistance (16), and hyperhomocysteinemia (17;18).

Table 1 provides an overview of the definitions of risk factors used and standardised treatment recommendations given. The results of the vascular screening, the treatment recommendations, and the treatment goals were reported in writing to the treating vascular specialist and the GP. The vascular screening and treatment advice per patient was a single action at 1 moment in time. No follow-up or monitoring was done by the multidisciplinary team. Therefore, further action was left to the discretion of the GP and the treating vascular specialist. Patients were not informed.

In this article, we report on the medical treatment advice of hypertension, hyperlipidemia, hyperglycemia, and hyperhomocysteinemia. Medical treatment advice for other disorders is not presented because of the small number of patients involved.

Table 1. Treatment recommendations for elevated vascular risk factors in patients with established cardiovascular disease

Antiplatelet agents	All patients should use it	
Hypertension	Blood pressure ≥ 140/90 mmHg	Repeat measurement; Change diet and lifestyle Start drug treatment to achieve <140/90 mmHg Adapt current drug use to achieve <140/90 mmHg For the time being no consequence; Refer to internist
Hyperlipidemia	Total cholesterol ≥ 5.0 mmol/l or LDL-cholesterol ≥ 3.0 mmol/l or HDL-cholesterol < 1.0 mmol/l or Triglycerides > 2.0 mmol/l	Repeat fasting measurement; Change diet and lifestyle Start statin to achieve TC < 5.0, LDL-C < 3.0, HDL-C ≥ 1.0, or trig ≤ 2.0 mmol/l Adapt current drug use to achieve TC < 5.0, LDL-C < 3.0, HDL-C ≥ 1.0, or trig ≤ 2.0 mmol/l Start fibrate; Refer to internist
Hyperglycemia	Glucose between 6.1 - 6.9 mmol/l	Repeat fasting measurement; Change diet and lifestyle
	Glucose ≥ 7.0 mmol/l	Start drug treatment to achieve < 6.1 mmol/l Adapt current drug use to achieve < 6.1 mmol/l Refer to internist
Hyperhomocysteinemia	Homocysteine (male) 11.3 - 18.7 µmol/l	Repeat measurement and if then still elevated homocysteine plasma level: start folic acid 5 mg once daily
	Homocysteine (male) > 18.7 µmol/l	Start folic acid 5 mg once daily to achieve < 15.0 µmol/l
	Homocysteine (female) 9.4 - 16.2 µmol/l	Repeat measurement and if then still elevated homocysteine plasma level: start folic acid 5 mg once daily
	Homocysteine (female) > 16.2 µmol/l	Start folic acid 5 mg once daily to achieve < 15.0 µmol/l

Data collection

For the current study the data of 618 patients with clinical manifestations of atherosclerosis who were included between January 1 2000 and December 31 2001 were considered. Baseline data on vascular risk factors and medication use were available for all patients. In May 2003, a structured questionnaire was sent to the participants to investigate the change in medication use. The questionnaire enquired about current medication use, generic name, total daily dose, and year of prescription.

Data-analysis

Medication use at follow-up was compared with that at baseline and expressed as percentage and corresponding 95% confidence interval (CI). In this way, actual use of medication was compared with the medical treatment recommendation.

Results

The study population consisted of 485 men, aged 61 years (SD 10.0), and 133 women aged 60 years (SD 10.6), with coronary heart disease (CHD) (43%), abdominal aortic aneurysm (AAA) (9%), peripheral arterial disease (PAD) (22%), or cerebrovascular disease (26%). Table 2 describes the baseline characteristics of the 618 participants. The mean plasma concentrations of total cholesterol (5.5 mmol/l ± 1.0) (211 mg/dl ± 40), LDL-cholesterol (3.5 mmol/l ± 0.9) (135 mg/dl ± 36), and fasting glucose (6.4 mmol/l ± 2.0) (116 mg/dl ± 37) were raised.

The median follow-up time between vascular screening and completion of the questionnaire was 29 months (range 16 to 40 months). During the follow-up, 13 patients died (11 male and 2 female) due to a vascular cause and 2 male patients died due to a non-vascular cause. Five hundred thirty-four (86%) patients completed the questionnaire. Non-responders (N= 84) did not differ from responders in age (64 years (SD 9.6; range 40 to 77 years) or sex (67% male).

Medication use at baseline and at follow-up is given in Table 3. Use of antihypertensive medication was analysed without patients with CHD (n= 242), because it is difficult to distinguish for which indication, hypertension or anginal therapy, antihypertensive medication was prescribed in these patients. At baseline, 175 of 242 (72%) patients took β-blockers and / or calcium antagonists but no longer used these after percutanous transluminal coronary angioplasty (at follow-up 142 of 175 (81%) patients took antihypertensive medication). The self-reported use of medication for all categories of vascular risk factors increased during the study period. The multidisciplinary team

Table 2. Baseline characteristics of the study sample (n= 618)

Age (yrs)	60.7 ± 10.1
Men (%)	79
Systolic blood pressure (mmHg)	139 ± 19
Diastolic blood pressure (mmHg)	79 ± 9
Total cholesterol (mmol/l)	5.5 ± 1.0
HDL-cholesterol (mmol/l)	1.1 ± 0.3
LDL-cholesterol (mmol/l)	3.5 ± 0.9
Triglycerides (mmol/l)	1.9 ± 1.2
Fasting glucose (mmol/l)	6.4 ± 2.0
Homocysteine (µmol/l)	13.5 ± 5.7
Microproteinuria*	
0-3 (mg/mmol) (%)	82
3-30 (mg/mmol) (%)	12
30-200 (mg/mmol) (%)	2
Current smoking (%)	38
Body mass index (kg/m^2)	26.4 ± 3.7
Waist circumference (cm)	95 ± 10
Vascular disease†	
Peripheral arterial disease (%)	25
Abdominal aortic aneurysm (%)	12
Cerebrovascular disease (%)	28
Coronary heart disease (%)	55

Data represent mean with standard deviation or percentages (%)
* Microproteinuria = albumin / creatinine ratio
† Not mutually exclusive

recommended medical treatment of newly detected or poorly treated vascular risk factors 358 times, 286 recommendations for male and 72 for female. Compliance of the medical treatment recommendations was equal in males (69%) and in females (68%).

Table 4 shows compliance to the start medical treatment recommendation. The effects of 122 treatment recommendations to change the medication regimen for individual risk factors at follow-up are listed in Table 5.

Table 3. Difference between medication use at baseline and follow-up

Type of drug	N	P1 %	P2 %	P2-P1	95% CI Δ
Antihypertensive*	292	50	59	9	2 – 18
Hypertension†	164	56	68	12	2 – 23
Lipid-lowering	534	47	69	22	17 – 28
Hyperlipidemia‡	356	35	65	30	24 – 38
Glucose-lowering	534	11	14	3	-1 – 7
Diabetes mellitus§	95	48	63	15	1 – 29
Folic acid	534	2	14	12	9 – 15
Antiplatelet	534	82	87	5	1 – 9

P1: proportion at baseline, P2: proportion at follow-up, P2-P1: difference in proportions, Δ 95% CI: 95% confidence interval of the difference
* without patients with CHD
† Patients with hypertension at baseline (blood pressure ≥ 140/90 mmHg)
‡ Patients with hyperlipidemia at baseline (TC ≥ 5.0 mmol/l or LDL-C ≥ 3.0 mmol/l)
§ Patients with diabetes mellitus at baseline (fasting glucose ≥ 7.0 mmol/l)

The proportion of patients on antihypertensive medication with hypertension (blood pressure ≥ 140/90 mmHg) increased from 56% at baseline to 68% at follow-up (P<0.001) (Table 3). For 13 (4%) of 292 patients, the treating vascular specialist and the GP were advised to start medication for newly detected hypertension and this recommendation was followed for 10 (77%) patients (Table 4). The treating vascular specialist and the GP were advised to change the current antihypertensive medication of 43 (15%) patients because of poorly controlled hypertension (blood pressure ≥ 140/90 mmHg). At follow-up, 23 (53%) patients were taking a higher dose of antihypertensive medication, 2 (5%) patients were taking a lower dose, 15 (35%) patients were taking the same dose, and 1 patient (2%) was no longer taking antihypertensive medication (Table 4).

The frequency of lipid-lowering medication use increased substantially from 47% to 69% (P<0.001), the increase in medication use was equal distributed in the different diagnose groups. High total cholesterol concentrations (≥ 5.0 mmol/l) (≥ 195 mg/dl) or high LDL-cholesterol concentration (≥ 3.0 mmol/l) (≥ 115 mg/dl) and the use of lipid-lowering medication were found in 35% of the patients at baseline and in 65% at follow-up (Table 3). Table 4 shows the start lipid-lowering regimen for 146 (27%) of 534 patients with elevated lipid levels. At follow-up, 82 (56%) of 146 patients were using

Table 4. 'Start medication advise' at baseline and compliance at follow-up

Type of drug	N with start advice (%) at baseline	User (%) at FUP	Non-user (%) at FUP
Antihypertensive*	13 of 292 (4)	10 (77)	3 (23)
Lipid-lowering	146 of 534 (27)	82 (56)	64 (44)
Glucose-lowering	13 of 534 (2)	4 (31)	9 (69)
Folic acid	64 of 534 (12)	35 (55)	29 (45)

Data represent number of patients with percentage (%)
FUP: follow-up, * without patients with CHD

lipid-lowering medication. The drug dose had been increased in 25 of 73 (34%) patients with poorly treated hyperlipidemia, but the drug dose was unchanged in 44 (60%) patients (Table 5).

The frequency of glucose-lowering drug use increased from 11% to 14% (P=0.07) (Table 3). The treating vascular specialist and the GP of 13 patients were advised to start glucose-lowering medication because of diabetes mellitus (fasting glucose level ≥ 7.0 mmol/l) (≥ 125 mg/dl), but at follow-up only 4 patients were taking such drugs (Table 4). The frequency of folic acid use for high homocysteine levels increased from 2% to 14% (P<0.001) (Table 3). The treating vascular specialist and the GP of 64 (12%) patients were advised to prescribe folic acid for hyperhomocysteinemia in their patients. At follow-up, 35 (55%) of these patients used folic acid (Table 4).

The frequency of antiplatelet agent usage increased from 82% to 87% (p=0.01) (Table 3), but 69 (13%) patients were not on antiplatelet therapy.

Discussion

In the present study, we investigated the effects of a hospital-wide vascular screening and prevention program on medication use for existing risk factors in patients with a recent clinical manifestation of atherosclerosis. Patients were enrolled in a standardised, vascular screening program for the detection of new or poorly controlled vascular risk factors. A multidisciplinary team guided the treating vascular specialist (cardiologist, vascular surgeon, neurologist, or internist) and the GP by giving up-to-date and evidence-based treatment recommendations. This approach may be a good starting point to facilitate and stimulate individualised and tailored risk interventions. The focus is to

Table 5. 'Change medication advice' at baseline and compliance at follow-up

Type of drug	N with change advice (%) at baseline	↑dosage (%) at FUP	↓dosage (%) at FUP	Same dosage (%) at FUP	Stop (%) at FUP	Replace (%) at FUP
Antihypertensive*	43 of 292 (15)	23 (53)	2 (5)	15 (35)	1 (2)	2 (5)
Lipid-lowering	73 of 534 (14)	25 (34)	-	44 (60)	2 (3)	2 (3)
Glucose-lowering	6 of 534 (1)	1	-	3	1	1

Data represent number of patients with percentage (%)
FUP: follow-up, * without patients with CHD

combine treatment of the vascular disorder with lifestyle changes and medical management of major cardiovascular risk factors (19). At least for lipid lowering drugs, in-hospital initiation of therapy has been shown to be a more effective strategy compare to out-of-hospital initiation (20). The question is how this is effectively and efficiently implemented for a broad range of high-risk vascular patients.

We focused in this article on the medical treatment of risk factors, while we had given lifestyle recommendations, stop smoking, reduce weight, increase in physical activity and change diet, and acknowledge that lifestyle changes are the first and most important step in decreasing cardiovascular risk (7). In our study at follow-up, medical treatment for all risk factors had increased substantially. The medical treatment recommendations for newly detected or poorly treated vascular risk factors led to (a change in) pharmacotherapy in approximately 52% of the instances in which advice was given. The start folic acid recommendation was followed in more than half of the recommendations while evidence of the effect of folic acid is along the way. The compliance with the start or to change medical recommendations for hypertension and hyperlipidemia was higher compared to the recommendations of hyperglycemia / diabetes mellitus. Treatment recommendations for hyperglycemia were given if a single fasting glucose measurement was ≥ 7.0 mmol/l. Repeated fasting glucose measurements by the treating physician ultimately has lead to the decision whether or not to start or change medical treatment with glucose-lowering agents. Drug treatment is only one of the treatment options, next to weight reduction and exercise, for management of newly detected diabetes mellitus or to better treat diabetes mellitus patients. We did not measure lifestyle changes and changes in weight which may have led to better glycemic control making (changes in) drug use unnecessary.

In order to place the results in perspective, we compared our findings with results of studies among patients who had evidence of a CVD. The HOPE- as well as the EUROASPIRE II- study reported aspirin or other antiplatelet agents usage of 76% and 84% in usual care (2;7). In our study slightly more patients were on antiplatelet drugs at follow up (87%).

At entry of the Heart Protection Study between July 1994 and May 1997, only 12% of the 20,536 patients were treated for hypertension (21). Data of the Oxford Vascular Study showed an upward trend from 19.8% to 47.3% in the use of antihypertensive medication from 1981 to 2004 among patients with cerebrovascular disease (22). The EUROASPIRE study showed very frequent use of antihypertensive medication in patients with CHD in 1995-1996 (84.1%) as well as in 1999-2000 (89.9%). We have not observed such an enormous use of antihypertensive medication although there was some increase between baseline and follow-up.

McDermott et. al. (23) reported about the use of lipid-lowering medication among patients with PAD or CHD 36% (n= 136) versus 51.4% (n= 70). In patients with cerebrovascular disease the use of lipid-lowering agents was less common 11.1% (n= 262) (22). The use of lipid-lowering medication among patients with CHD increased from 59.8% in VIC-I in 1996-1998 to 86.8% in VIC-II in 1999-2000 (24). Similarly, there was an increase from 32% in EUROASPIRE I to 62.9% in EUROASPIRE II. In our cohort the use of lipid-lowering medication increased from 47% in 2000-2001 to 69% in 2003.
Comparison of our results with those of usual care studies, especially EUROASPIRE I and II, showed that while advising the treating vascular specialist and the GP about medical therapy, this did not lead to a great therapeutic benefit. We did not inform the patients. Possibly, patients missed the impulse to consult the treating vascular specialist or the GP for information. It could also be that the treating vascular specialist or the GP ignored the recommendation. Atthobari et al. (25) showed that a letter about the intervention sent to participants and GPs improved the use of antihypertensive and lipid-lowering drugs. Similarly, Rascati et al. (26) found that an intervention letter to GPs was effective to change prescribing behaviour.

We acknowledge some limitations of our study. Vascular risk factors were not measured at follow-up. Although not likely, it is possible that medical treatment no longer was necessary for some risk factors because treatment goals had been achieved by other lifestyle modifications (weight reduction, smoking cessation, increase of physical activity). However, EUROASPIRE II showed that despite an increase in medical treatment, the proportion of patients that reached the treatment goals was disapprovingly low (8). In our study, the results are based on self-reported medication use per patient and it was not possible to verify this by checking pharmacy records. Klungel et al. (27) found that

neither a questionnaire nor the pharmacy records can be considered as the "gold standard" with regard to true pharmacotherapy. Also patients may have started medication as a result of the treatment recommendation but may have stopped, for what reason, in the period between medical treatment recommendation and follow-up. Side-effects and contraindications were not known to the multidisciplinary advice team and could be reasons of non-compliance of the recommended drugs therapy which wasn't asked in the follow-up questionnaire. The last limitation is that there is no control group, so it is not easy to check whether the observed change in medication use in a 3-year period occurred because of historical trend rather than because of specific interventions. However, all patients are at high-risk and medical treatment recommendations may be alert treating physicians for better treatment of vascular risk factors.

Unfortunately, despite the multidisciplinary approach of our vascular prevention program, medical treatment recommendations may not have provided a sufficient impulse to treat risk factors more aggressively by medical therapy. A possibility to consult the multidisciplinary team in case of uncertainly or contraindications for the suggested therapy may be a stimulus for the treating physicians to implement the recommendation easier. The treatment recommendations were given in general terms, but this may have been to a specific. The choice for specific (class of) drugs and dosages was left to the discretion of the treating physician. Better communication between physicians (e.g. medical specialists in the hospital and GP) about who is expected to take action could lead to better implementation of vascular risk factor treatment. Also providing information simultaneously to the patient about the medical treatment recommendations may be more effective for initiating and maintaining therapy. As a result of the present study each individual patient receives now in our hospital, in a visit to a vascular nurse practitioner, the results and treatment recommendations and individualized treatment goals for each risk factor. By giving this information together with general information on atherosclerosis and vascular risk, the nurse practitioner aims to motivate a patient to take and remain on a medication regimen (28). Giving sufficient information and regular feedback to the patient may enhance adherence to medication.

In conclusion, a written, once-given treatment recommendation led to a significant but small increase in medication use for cardiovascular risk factor treatment in vascular patients. Therefore this strategy, in the present form, cannot be recommended for general application.

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A randomized controlled trial for risk factor reduction in patients with symptomatic vascular disease: the multidisciplinary Vascular prEvention by NUrses Study

Chapter 8

Abstract

Background

Patients with manifest vascular disease are at high risk of a new vascular event or death. Modification of classical risk factors is often not successful. We determined whether the extra care of a nurse practitioner could be beneficial to the cardiovascular risk profile of high-risk patients.

Design

We conducted a randomized controlled trial based on the Zelen design.

Methods

Two hundred thirty-six patients with manifestations of a vascular disease and with two or more modifiable vascular risk factors were pre-randomized to receive treatment by a nurse practitioner plus usual care or usual care alone. After 1 year, risk factors were remeasured. The primary endpoint was achievement of treatment goals for blood pressure, lipid, glucose and homocysteine levels, body mass index, and smoking.

Results

Of the pre-randomized patients, 95 of 119 (80%) in the intervention group and 80 of 117 (68%) in the control group participated in the study. After a mean follow-up of 14 months, the patients in the intervention group achieved significantly more treatment goals than did the patients in the control group (systolic blood pressure 63% versus 37%, total cholesterol 79% versus 61%, LDL-cholesterol 88% versus 67%, and body mass index 38% versus 24%). Medication use was increased in both groups and no differences were found in patients' quality of life (SF-36) at follow-up.

Conclusion

Treatment delivered by nurse practitioners, in addition to a vascular risk factor screening and prevention program, resulted in a better management of vascular risk factors than usual care alone in vascular patients after 1 year follow-up.

Introduction

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in Western countries (1). It is the result of atherosclerosis and is influenced by multiple risk factors, such as smoking, obesity, physical inactivity, hypertension, dyslipidemia, and diabetes. Patients with manifest vascular diseases are at a considerably increased risk of fatal and non-fatal events at the same or another location in the vascular tree (2). Modification of classical risk factors is known to reduce the risk of vascular events (3), yet despite this vascular risk factors are often poorly managed. Secondary prevention care improved only slightly in Europe between 1996/97 and 1999/2000 (4-6), and many patients are not treated at all or have not reached treatment goals for hypertension or dyslipidemia. Physicians adhere poorly to CVD prevention guidelines for several reasons, such as lack of time and difficultly determining which of several treatment guidelines is best (7). Physicians have also indicated that it is the patient him or herself that forms the greatest barrier to adequate CVD prevention (8). Lifestyle changes are an important component of vascular risk reduction strategies, and not all physicians have enough time or the appropriate training to advise about lifestyle changes (e.g. quit smoking, weight loss, increased consumption of fruit and vegetables, increased physical activity, decreased intake of salt and saturated fats) (7). New strategies, such as organizational changes or specialist healthcare, need to be developed to achieve better risk factor management in high-risk patients. Nurse practitioners have the skills in medical and behavioural sciences needed for successful risk management (9). A number of randomized controlled trials have shown that nurse practitioner-guided treatment for patients with coronary heart disease (CHD) results in better risk factor management than achieved with usual care (10-20). Most of these trials, however, were conducted in a primary care setting, whereas high-risk patients are often treated in the hospital, where medical specialists are responsible for risk factor management.

We investigated in the multidisciplinary Vascular prEvention by NUrsus Study (VENUS) whether risk factor management in the hospital improved with nurse practitioner care plus usual care compared with usual care. Beforehand, all patients underwent an institutionalized vascular screening.

Methods

Study design

Patients were randomized before informed consent was obtained, according to the Zelen design (21), to either nurse practitioner care plus usual care (intervention group) or usual care alone (control group). Randomization was carried out by telephone with a computer-generated list. Within 24 h, a research nurse mailed patients information about the treatment they would receive. Informed consent was obtained immediately from the patients in the intervention group and after 6 months from the patients in the control group.

We aimed to detect a 20% difference between the two groups in achievement of treatment goals (e.g. hypertension, dyslipidemia) at follow-up. With a power of 80% (β= 0.2) and an α value of 0.05, 79 patients were needed in each group. To allow for drop-outs, we decided to enroll 236 patients; the estimated study duration was 18 months.

Study population

Dutch-speaking patients between 18 and 79 years referred to University Medical Center Utrecht (UMC Utrecht), The Netherlands, with symptomatic manifestations of transient ischemic attack, stroke, aortic abdominal aneurysm (AAA) or peripheral artery disease (PAD) are routinely offered a vascular screening and prevention program (described below). Patients were eligible for VENUS when two or more of the following modifiable vascular risk factors were detected: smoking, hypertension, dyslipidemia, diabetes mellitus, obesity, or hyperhomocysteinemia. Patients with a life expectancy shorter than 2 years, those with terminal malignant disease, those dependent in daily activities (Rankin grade >3) (22) were excluded. The Ethics Committee of our institution approved the study. Before participating in the VENUS study, patients underwent a vascular screening program. This institutionalized screening program was offered to patients with recently diagnosed vascular diseases or severe risk factors and is part of regular care. The program was supported by the departments of Internal Medicine, Nephrology, Vascular Surgery, Neurology, Radiology, Cardiology, and Epidemiology at the UMC Utrecht. Patients were screened for vascular risk factors and for asymptomatic arterial disease. 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. Blood pressure was measured two times in sitting position at the right and left upper arm with a non-random sphygmomanometer. Medical history, current use of medication, current

and past smoking behavior and current and past alcohol use were derived from a standardized questionnaire described elsewhere (23). Fasting blood was sampled to determine serum glucose, total cholesterol, HDL-cholesterol, triglycerides, and homocysteine levels. LDL-cholesterol was calculated with Friedewald's formula. A multidisciplinary team of specialists formulated treatment recommendations (such as repeat measurement, start medication, adapt current medication, stop smoking, or change lifestyle) for the management of individual risk factors and/or vascular disorders. The results and the treatment recommendations were reported in writing to the treating vascular specialist and the general practitioner (GP) approximately one month before the start of VENUS. This procedure was identical in the control as in the intervention group and further action was left to the discretion of the treating physicians. The results of the vascular screening were considered as baseline measurements in the VENUS study.

The intervention group

Patients assigned to the intervention group were invited by a nurse practitioner to attend the risk-factor management clinic. At the first visit, patients were told about their vascular risk factors and individualized, realistic goals were set in cooperation with the patients. Action plans were made for lifestyle changes; smoking cessation, regular exercise, healthy diets, and medical treatment of risk factors (antiplatelet agents, blood pressure-, lipid-, and glucose-lowering agents, or folic acid). These action plans were created to raise awareness and motivation and created in such a way that goals were attainable. A study physician prescribed or changed medication because a nurse practitioner in The Netherlands is formally not allowed to do this. At subsequent visits the nurse practitioner provided support, encouragement and reassurance in changing or maintaining the desired lifestyle and in their adherence to the prescribed medication. The nurse practitioner interventions were based on written protocols for each vascular risk factor. The length and frequency of the visits were determined by the needs of patients and nurse practitioner in order to achieve the individual treatment goals. The nurse practitioner documented for each patient the applied interventions and visit duration.

The control group

Patients assigned to the control group received care provided by the GP and the treating vascular specialist (in this study a vascular surgeon or neurologist).

Treatment goals

The formulated treatment recommendation and the nurse intervention of the VENUS study are based on international guidelines for the treatment of vascular risk factors. According to guidelines at the time of the start of the study, the following goals were set: total cholesterol < 5.0 mmol/L, LDL-cholesterol ≤ 3.1 mmol/L, triglycerides < 1.7 mmol/L, HDL-cholesterol for men > 1.0 mmol/L and women > 1.3 mmol/L (24), blood pressure < 140/90 mmHg (25), fasting glucose < 6.1 mmol/L (26), homocysteine for men <11.3 µmol/L and women < 9.4 µmol/L (27;28), BMI < 25 kg/m^2 (29), and complete smoking cessation (30;31).

Follow-up

Follow-up visits were at 6 months and 1 year after randomization. In this article, we provide data of the 1-year follow-up only. At both follow-up evaluations, data were collected on current medication use and smoking behavior. The vascular risk factor levels were again determined by physical examination and a fasting blood sample. Quality of life was assessed by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (32).

Outcome assessment

The primary outcome was the cardiovascular risk profile at 1 year after randomization. We measured change in risk factors and medication usage. The proportion of achieved treatment goals for each risk factor before and after the intervention was compared for the intervention and the control group.

Data analysis

All comparisons between groups were performed according to the intention-to-treat principle. The data of patients who withdrew their consent before the beginning of the randomized controlled trial (n= 61) or who were lost to follow-up (n= 10) were not analyzed. Continuous variables are presented as means with standard deviation and categorical variables as percentages. Differences between the groups were tested by the independent sample t-test for continuous variables and the X^2 test for categorical variables; the corresponding 95% confidence intervals (95 % CI) are reported. Changes within each group were assessed by paired samples t-test. The association between the

proportion of treatment goals achieved and treatment arm was determined with logistic regression and adjusted for the baseline values of the vascular risk factors. Analyses were performed in SPSS version 12.0.1. (SPSS, Chicago, Illinois, USA).

Results

Patient flow and follow-up

Two hundred and thirty-six consecutive patients were recruited and randomized in the study between May 2002 and October 2003 (Fig. 1). During this time, 61 patients refused to participate, eight died (four in each group), one moved abroad and one developed severe pulmonary disease and was not able to continue the study. One patient was crossed over from the control to the intervention group. Hence, the main analyses were based, without those lost to follow-up, on data from 90 (76%) of the 119 patients in the intervention group and 75 (64%) of the 117 control patients. Follow-up ended on December 27, 2004. The mean follow-up was 14 months (range, 10 - 22 months); 14 months (range, 10 - 22) for the intervention group and 14 months (range, 12 - 23) for the control group.

Randomization was considered successful because the two groups were not different with respect to important risk factors (Table 1). Of the total study population, 77% was male, with a mean age of 60.1 ± 10.3 years. Patients assigned to the intervention group more often had PAD, CHD, and cerebrovascular disease in history than those in the control group. Medication use was similar in the two groups at baseline, with most patients using antiplatelet therapy, blood pressure and lipid lowering agents. There were no conspicuous differences between the baseline characteristics of the patients who did or did not participate in the study (Table 2).

The mean values for the different vascular risk factors at baseline and at 1 year are shown in Table 3. The intervention group achieved a mean reduction in total cholesterol of 0.9 mmol/L (95% confidence interval (95% CI) 0.7 - 1.1) compared to 0.5 mmol/L (95% CI 0.3 - 0.7) in the control group. For systolic blood pressure, the intervention group achieved a mean reduction of 8 mmHg (95% CI 5 - 13) compared to 6 mmHg (95% CI 2 - 11) in the control group. Diastolic blood pressure, LDL-cholesterol, and glucose levels improved ($P<0.001$) from baseline to 1 year in each group. The levels of triglycerides decreased 0.4 mmol/L (95% CI 0.2 - 0.5) and homocysteine decreased 2.4 µmol/L (95% CI 1.4 - 3.1) in the intervention group but not in the control group. The mean BMI increased 0.7 kg/m^2 (95% CI 0.4 - 1.0) in the control group after 1 year. The prevalence of smoking increased in both groups.

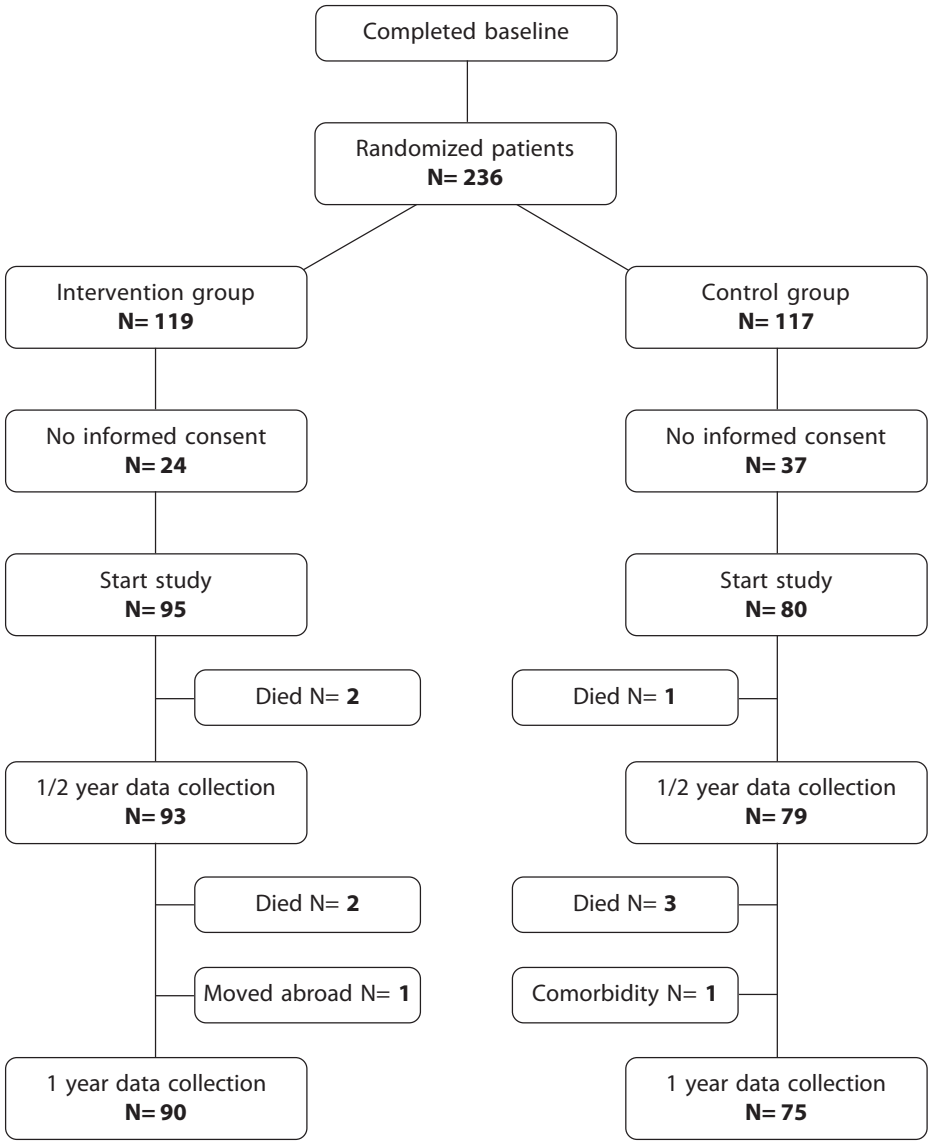

Figure 1. Flow of patients through the trial

Table 1. Baseline characteristics of the randomized patients

	Intervention group N=119	Control group N=117
Age (years)	60.6 (10.2)	61.6 (10.4)
Male sex (%)	73	81
Total cholesterol (mmol/L)	5.4 (1.1)	5.2 (1.0)
HDL-cholesterol (mmol/L)	1.3 (0.4)	1.3 (0.4)
LDL-cholesterol (mmol/L)	3.3 (1.0)	3.1 (1.0)
Triglycerides (mmol/L)	1.8 (1.0)	1.8 (0.9)
Body mass index (kg/m^2)	26.7 (3.9)	26.8 (4.1)
Waist circumference (cm)	97 (11)	99 (11)
Systolic blood pressure (mmHg)	146 (21)	149 (21)
Diastolic blood pressure (mmHg)	84 (12)	84 (11)
Homocysteine (µmol/L)	15.1 (6.1)	16.0 (8.9)
Glucose (mmol/L)	6.7 (2.0)	6.7 (2.2)
Current smokers (%)	38	32
Prevalence of CVD*		
Peripheral arterial disease (%)	45	37
Abdominal aortic aneurysm (%)	17	21
Cerebrovascular disease (%)	45	40
Coronary heart disease (%)	24	18
Medication use		
Antiplatelet agents (%)	45	49
Blood pressure-lowering agents (%)	40	39
Lipid-lowering agents (%)	39	40
Glucose-lowering agents (%)	10	9
ACE-inhibitor and/or AIIA (%)	17	19
Folic acid (%)	3	5

Data are mean (SD) or percentages

* Ever or current diagnosis, a single patient can be classified into more than one disease category

Table 2. Baseline characteristics of participants vs non-participants

	Informed consent N= 175	No informed consent intervention group N= 24	No informed consent control group N= 37
Age (years)	61.5 (9.9)	62.5 (10.3)	62.9 (11.9)
Male sex (%)	72	63	78
Total cholesterol (mmol/L)	5.3 (1.0)	5.5 (1.0)	5.3 (1.1)
HDL-cholesterol (mmol/L)	1.3 (0.4)	1.4 (0.4)	2.1 (1.3)
LDL-cholesterol (mmol/L)	3.2 (1.0)	3.4 (0.9)	3.2 (1.0)
Triglycerides (mmol/L)	1.8 (1.0)	1.5 (0.6)	1.8 (0.9)
Body mass index (kg/m^2)	26.8 (3.9)	26.3 (3.3)	26.8 (4.6)
Waist circumference (cm)	98 (11)	96 (9)	98 (10)
Systolic blood pressure (mmHg)	149 (21)	141 (20)	146 (21)
Diastolic blood pressure (mmHg)	85 (12)	81 (13)	82 (9)
Homocysteine (µmol/L)	14.7 (5.1)	15.4 (7.2)	19.5 (14.2)
Glucose (mmol/L)	6.7 (2.0)	6.6 (2.1)	6.7 (2.6)
Current smokers (%)	32	35	50
Prevalence of CVD*			
Peripheral arterial disease (%)	45	13	3
Abdominal aortic aneurysm (%)	17	13	27
Cerebrovascular disease (%)	43	17	19
Coronary heart disease (%)	21	17	22
Medication use			
Antiplatelet agents (%)	49	46	41
Blood pressure-lowering drugs (%)	43	29	30
Lipid-lowering agents (%)	43	25	26
Glucose-lowering agents (%)	11	4	5
ACE-inhibitor and/or AIIA (%)	21	8	19
Folic acid (%)	3	4	5

Data are mean (SD) or percentages

* Ever or current diagnosis, a single patient can be classified into more than one disease category

The levels of total cholesterol decreased 0.4 mmol/L (95% CI 0.1 - 0.7), LDL-cholesterol 0.4 mmol/L (95% CI 0.1 - 0.7), triglycerides 0.3 mmol/L (95% CI 0.1 - 0.5), homocysteine 1.9 µmol/L (95% CI 0.6 - 3.3) more in the intervention group and HDL-cholesterol increased -0.1 mmol/L (95% CI -0.2 - -0.0) more in the intervention group.

The proportion of patients who had already reached their target for individual risk factors at baseline or who achieved treatment goals after 1 year, separated per group, is shown in Table 4. More patients in the intervention group than in the control group achieved their treatment goals at follow-up. After adjustment for the baseline values, the proportion of patients who achieved treatment goals was significantly higher in the intervention group than in the control group (odds ratio for systolic blood pressure 2.7 (1.3 - 5.4), total cholesterol 3.3 (1.5 - 7.3), LDL-cholesterol 3.5 (1.5 - 8.6) and BMI 4.0 (1.2 - 13.1). This indicated that patients in the intervention group more often achieved treatment goals for instance systolic blood pressure below 140 mmHg than patients in the control group, taken the baseline blood pressure into account.

Change in medication use

Regardless of group, more patients used medication at follow-up than that at baseline (Table 5). At follow-up, more patients in the intervention group than in the control group used lipid-lowering drugs (89% versus 73%), ACE-inhibitor and/or AIIA (76% versus 53%) and folic acid (61% versus 28%).

Quality of life

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).

Nurse intervention

Eighty-three of the 90 (92%) patients in the intervention group visited the nurse practitioner risk factor management clinic, making a mean of 4 visits (range, 1 to 15 times) during the follow-up period. One person died and six patients only participated in the follow-up visits. The first visit was longest, with a mean duration of 48 minutes (min) (range, 15 - 105 min): 10 min was spent on hypertension, 5 min on hyperglycemia, 9 min on hyperhomocysteinemia, 11 min on dyslipidemia, 6 min on smoking, and 7 min

Table 3. Changes in risk factors and differences between the changes in the intervention and the control group (n=165)

	Baseline		Follow-up*			
	Intervention group N= 90	Control group N= 75	Intervention group N= 90	Control group N= 75	Mean difference †	95% CI ‡
Age (years)	59.8 ± 9.9	60.7 ± 9.6	61.3 ± 9.9	62.0 ± 9.5		
Male sex (%)	76	83	76	83		
Total cholesterol (mmol/L)	5.3 ± 1.1	5.2 ± 0.9	4.4 ± 0.8	4.7 ± 1.0	0.4	0.1 - 0.7
HDL-cholesterol (mmol/L)	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	-0.1	-0.2 to -0.0
LDL-cholesterol (mmol/L)	3.2 ± 1.0	3.1 ± 1.0	2.4 ± 0.7	2.7 ± 0.9	0.4	0.1 - 0.7
Triglycerides (mmol/L)	1.9 ± 1.1	1.8 ± 1.0	1.5 ± 0.7	1.7 ± 1.0	0.3	0.1 - 0.5
Body mass index (kg/m^2)	26.7 ± 3.9	27.1 ± 3.8	26.9 ± 3.9	27.8 ± 3.8	0.5	-0.0 - 1.0
Waist circumference (cm)	97 ± 11	100 ± 11	97 ± 14	99 ± 10	-0.6	-2.6 - 1.4
Systolic blood pressure (mmHg)	146 ± 21	150 ± 21	138 ± 15	144 ± 18	2.3	-3.6 - 8.2
Diastolic blood pressure (mmHg)	84 ± 11	85 ± 11	78 ± 9	82 ± 11	2.4	-1.0 - 5.8
Homocysteine (µmol/L)	14.7 ± 5.2	14.2 ± 4.3	12.3 ± 4.2	13.9 ± 5.2	1.9	0.6 - 3.3
Glucose (mmol/L)	6.7 ± 2.0	6.7 ± 1.9	6.0 ± 1.7	6.2 ± 1.3	0.2	-0.4 - 0.7
Current smokers (%)	38	25	41	32	4	-3 - 9§

Data are mean (SD) or percentages

* Mean follow-up of 14 months (range 10 - 22)

† Mean difference: (baseline value - follow-up value in intervention group) - (baseline value - follow-up value in control group)

‡ 95% confidence interval of unpaired t test

§ 95% confidence interval of difference in proportion

Table 4. Proportion of patients who achieved treatment goals at baseline and at follow-up and odds ratio's (n=165)

	Baseline		Follow-up*		
Achieved targets	**Intervention group N= 90 (%)**	**Control group N= 75 (%)**	**Intervention group N= 90 (%)**	**Control group N= 75 (%)**	**OR (95% CI)†**
Systolic blood pressure < 140 mmHg	43	33	63	37	2.7 (1.3 - 5.4)
Diastolic blood pressure < 90 mmHg	80	70	90	81	1.8 (0.7 - 4.6)
Total cholesterol < 5.0 mmol/L	40	40	79	61	3.3 (1.5 - 7.3)
LDL-cholesterol ≤ 3.1 mmol/L	43	53	88	67	3.5 (1.5 - 8.6)
HDL- cholesterol (men > 1.0 + women > 1.3) mmol/L	71	76	76	76	1.3 (0.5 - 3.4)
Triglycerides < 1.7 mmol/L	52	56	63	61	1.3 (0.6 - 3.0)
Fasting glucose < 6.1 mmol/L	47	51	73	61	1.7 (0.8 - 3.5)
Homocysteine (men < 11.3 + women < 9.4) µmol/L	21	20	39	28	1.4 (0.7 - 2.8)
Body Mass Index < 25 kg/m^2	39	32	38	24	4.0 (1.2 - 13.1)
Waist circumference (men < 102 + women < 88) cm	54	49	62	55	1.0 (0.4 - 2.2)
No smoking	59	69	50	67	0.7 (0.3 - 1.5)

Data are proportions, * mean follow-up of 14 months (range 10 - 22), † OR: odds ratio, 95% CI: 95% confidence interval
Model adjusted for baseline-value

Table 5. Medication usage in the intervention group and in the control group

	Baseline		Follow-up*	
	Intervention N= 90	Control N= 75	Intervention N= 90	Control N= 75
Antiplatelet agents	66 (73)	57 (76)	81 (90)	68 (91)
Blood pressure-lowering agents	49 (54)	42 (56)	69 (77)	52 (69)
Lipid-lowering agents	44 (49)	42 (56)	80 (89)	55 (73)
Glucose-lowering agents	11 (12)	9 (12)	17 (19)	12 (16)
ACE-inhibitor and/or AIIA	28 (31)	28 (37)	57 (76)	40 (53)
Folic acid	4 (4)	6 (8)	55 (61)	21 (28)

Data are number of users with % in brackets, * Mean follow-up of 14 months (range 10 - 22)
ACE-inhibitor: Angiotensin Converting Enzyme inhibitor, AIIA: Angiotensin II-Antagonist

on overweight. The second and third visits lasted 27 min (range, 10 - 60 min). In these visits less attention was paid to risk factors than during the first visit: 6 min on hypertension, 2 min on hyperglycemia, 3 min on hyperhomocysteinemia, 6 min on dyslipidemia, 4 min on smoking, and 6 min on overweight.

Discussion

In this randomized controlled trial, we investigated whether nurse practitioner-care plus usual care instead of usual care alone improved the cardiovascular risk profile of high-risk patients who underwent a vascular screening and prevention program beforehand. We found that nurse practitioner-assisted risk factor management resulted in more frequent achievement of treatment goals for systolic blood pressure (OR 2.7 (1.3 - 5.4)), total cholesterol (OR 3.3 (1.5 - 7.3)), LDL-cholesterol (OR 3.5 (1.5 - 8.6)) and BMI (OR 4.0 (1.2 -13.1)). All patients used more medication at follow-up than at baseline, and the quality of life was not different in the two groups. The prevalence of smoking was higher in both groups at follow-up compared to baseline. This was partly unexpected, because of the no-smoking policies in governmental buildings, in working environment and strong anti-smoking messages from healthcare providers. At the start of the study smokers had quitted smoking but a considerable number of them started smoking again. Our findings confirm that in patients with recent clinical manifestations of a vascular disease, a relapse of smoking is a serious threat that needs continuous attention from healthcare professionals.

Earlier randomized controlled trials of nurse practitioner care for patients with established CHD reported contradictory findings (Table 6). These studies differed from our study in sample size, study population, and some focused on a single risk factor (e.g. plasma lipids). Two longer studies showed that differences in improvements in medical and lifestyle components between intervention and control groups diminished over a 4-year period (14;17). For example, the OR for blood pressure diminished from 5.3 (3.0 - 9.4) at 1 year to 1.5 (0.9 - 2.4) at 4 years follow-up, however, nurse-led secondary prevention clinics led to fewer total deaths and probably fewer coronary events. A systematic review of 12 different randomized controlled trials involving 9803 patients with CHD concluded that in five of seven trials nurse practitioner intervention improved the risk factor profile, reduced hospital admissions, and enhanced quality of life (33).

In contrast to many other studies, we chose a tailored and individualized intervention for vascular risk factor management in patients with PAD and cerebrovascular disease. Although their manifestation of atherosclerosis is different, they share many common risk factors. Patients were screened for vascular risk factors, and a multidisciplinary team formulated treatment advice, which formed the basis of the nurse practitioner intervention. In addition, this study was conducted in the hospital instead of primary care. We think that a setting of an outpatient clinic attached to a hospital, integrating treatment of the (acute) clinical manifestation of the vascular disease and initiating risk factor treatment, is an optimal environment for successful risk management in these high-risk patients. For long term follow-up patients can then be seen by their GP. Communication between the GP and the vascular specialist in the hospital about who is expected to take action in vascular risk management, is often suboptimal (34).

An integrated approach to vascular risk reduction in which a doctor treats the vascular problems and a nurse practitioner treats risk factors initiates behavioral change and helps patients to cope with illness and vascular risks should be effective on vascular risk reduction in all patients with manifestations of CVD (9). Other investigators suggest that a community approach to the prevention of CVD may be worthwhile (35). In our opinion, risk management can only be successful if patients are given feedback on their progress by trained healthcare professionals. On average, the patients of our study visited the nurse practitioner-clinic four times over a 14 month period. While such an approach is time consuming nurse-led clinics for the secondary prevention of CHD in primary care are cost effective (36).

Our study has some potential limitations. It was conducted in a single academic medical centre, and thus the results may reflect not only the effects of the nurse practitioner intervention but also the hospital setting. Moreover, VENUS was carried out

Table 6. Randomized Controlled Trials among patients with CHD

First author	N	Intervention group versus control group of usual care	FU	Estimate of the difference in risk factors (intervention vs control)		
				Cholesterol (mmol/L)	Blood pressure (mmHg)	Non-smoking
Cupples (1994) (13)	688	Personal health education and FU every 4 months in GP	24	0.09 (-0.10 - 0.28)	SBP 2.0 (-1.8 - 5.7) DBP 0.4 (-1.5 - 2.4)	3.8%
Carlsson (1996) (12)	168	Individual and group education and training by a nurse at the hospital	12	NR	NR	21%
Campbell (1998) (11)	1343	Nurse run clinics promoted lifestyle and medical aspects in GP	12	OR 3.2 (2.4 - 4.3)*	OR 5.3 (3.0 - 9.4)*	OR 0.8 (0.5 - 1.3)
Cupples (1999) (14)	688	Personal health education and FU every 4 months in GP	60	0.06 (-0.15 - 0.26)	SBP -0.8 (-5.2 - 3.5) DBP -1.3 (-3.6 - 1.0)	-8.4%
Jolly (1999) (15)	597	Nurse coordinating care by improving communication and FU visits in GP	12	-0.14 (-0.33 - 0.06)	SBP -2.2 (-5.9 - 1.5) DBP -1.3 (-3.6 - 0.9)	-1 (-13 - 11)
McHugh (2001) (16)	121	Health education and motivational interviews by nurses at patients' home	15	-0.70*	SBP -9.1* DBP -8.2*	23%*
Allen (2002) (10)	228	Individualized lifestyle and medical intervention by nurses at the hospital	12	0.40*	NR	NR
Murchie (2003) (17)	1343	Nurse run clinics promoted lifestyle and medical aspects in GP	48	OR 1.2 (0.9 - 1.6)	OR 1.5 (0.9 - 2.4)	OR 0.7 (0.4 - 1.3)
Quist-Paulsen (2003) (18)	240	Booklet to prevent relapses and telephone contact by nurses	12	NR	NR	20 (6 - 33)*
Ellis (2005) (20)	205	Stroke Nurse Specialist promoting lifestyle changes at the hospital	5	-0.09 (-0.06 - 0.1)	SBP -8.3 (-8.7 - -7.8)* DBP -0.9 (-1.2 - 3.0)	-1.2 (-1.4 - 1.0)

FU: follow-up in months, GP: general practice, SBP: systolic blood pressure, DBP: diastolic blood pressure, NR: not reported, OR: odds ratio with 95% confidence interval in brackets, * significant difference (P<0.05) between intervention and control group

in addition to a vascular screening and prevention program. Before the start of the study, the treating physicians and the GPs of all patients received a letter detailing the cardiovascular risk profile of their patient, which may have motivated them to make an extra effort to alter their patients' cardiovascular risk profile. We did not attempt to control for the type of treatment the patients received from usual care during the study. Nevertheless, we found a statistically significant improvement in risk factor management in the intervention group compared with the control group. It should be noted that the sample size in both groups was rather small to detect differences between dichotomous outcome variables. As a consequence differences may be missed due to lack of power. We used the Zelen design instead of a conventional design because detailed knowledge of the trial and its exact purposes would have been likely to bias or influence the results of both groups of patients (37). The Zelen design probably reduces non-compliance and drop-out considerably, thus increasing validity (38). Furthermore, Schellings et al. suggest that the design has a wider applicability, particularly when potential participants would find being in the experimental group more attractive rather than being in the control group, which receives standard treatment (38). The number of people who refused participation in our study, however, was not lower (n= 61) than in other studies, although we had fewer drop-outs (n= 10). Those who refused to participate can introduce a difference in prognostic factors but in the VENUS-study hardly any differences between the baseline characteristics of the patients who did or did not participate was observed. Finally, medication use and smoking behavior were self-reported. It was not possible to confirm this by checking pharmacy records and by assessing a salivary sample for cotinine levels. Klungel et al. (39) found that neither a questionnaire nor pharmacy records can be considered as the "gold standard" with regard to true pharmacotherapy.

In conclusion, our findings show that care provided by a nurse practitioner in addition to usual care and on top of a vascular screening and prevention program improved the management of important risk factors in patients with a recent clinical manifestation of a vascular disease. Adequately managed risk factors will contribute to a reduction in vascular morbidity and mortality in this group of high-risk patients.

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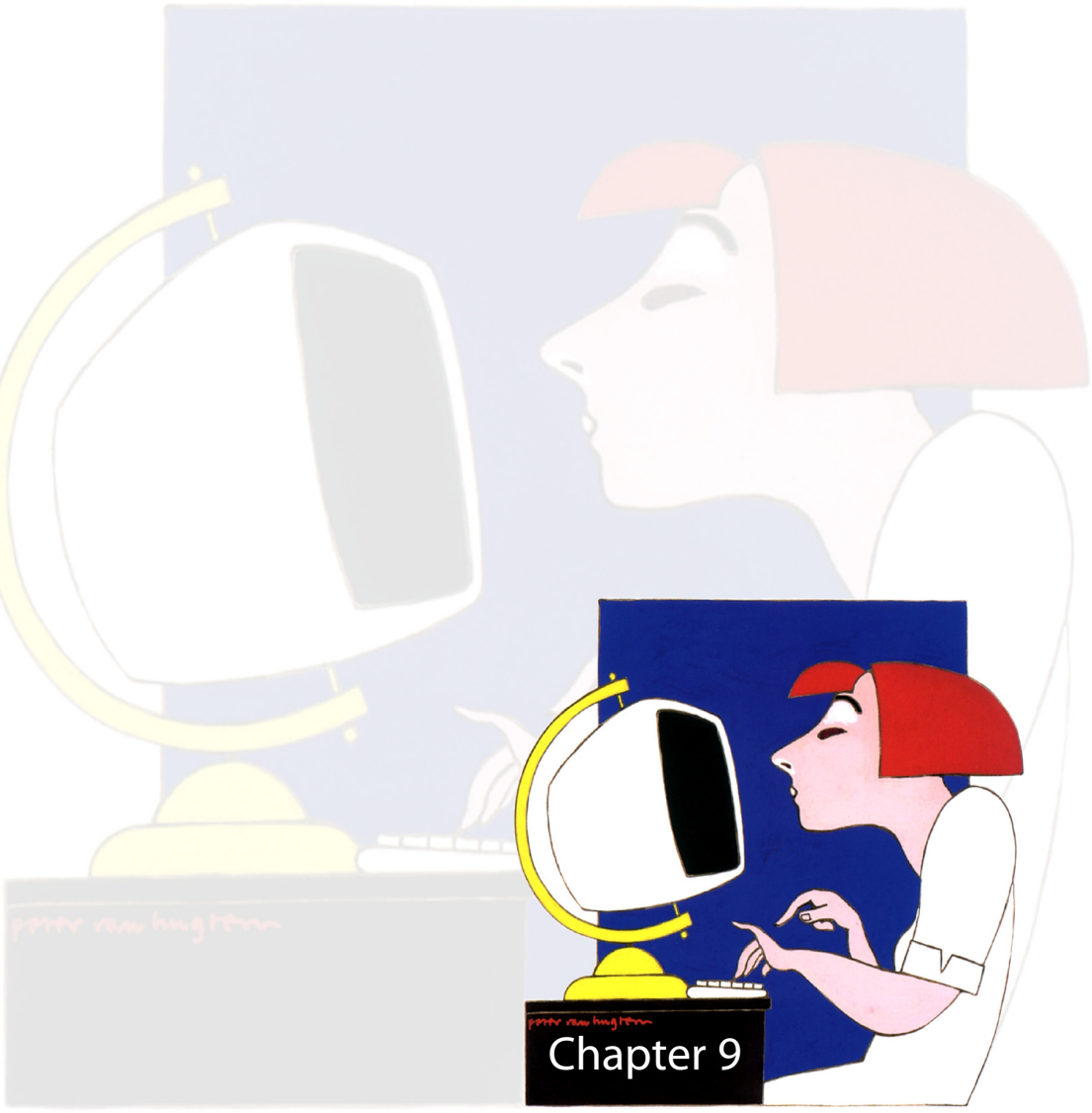
Self-management of vascular Patients Activated by the Internet and Nurses (SPAIN) study: Rationale and Design



Chapter 9

Abstract

Background

Vascular risk factors are often poorly managed in high-risk patients. A medical and behavioural approach by nurse practitioners (NPs) is shown to be more successful in vascular risk reduction than compared with usual care in patients with manifest arterial disease. Lifestyle changes, medical treatment and increased self-management capacity of patients are important to establish effective and lasting risk factor management.

Aims

The overall aim of the SPAIN pilot-study is to develop and test a secure personalized website and treatment by a NP for vascular risk factors in addition to usual care in patients with clinical manifestations of arterial disease.

Methods

Fifty patients with a recent clinical manifestation of arterial disease are going to use the patient-specific website for six months, replacing frequent visits to the outpatient NP-clinic. Each patient receives a password to access his/her records on the website. At the start of the study realistic treatment goals are set for each risk factor (hypertension, hyperlipidemia, diabetes mellitus, overweight, smoking) in a dialogue between patient and the NP, based on European Guidelines. Patients and NP enter new measurements and are stimulated to keep frequent e-mail contact. The NP replies during working days and gives regular, protocol driven, treatment advice, feedback and support. Data are collected on login attempts, number of messages, risk factor levels before and after intervention, and on the level of self-management (problem solving skills and self-efficacy).

Results

The results can be expected at the beginning of 2007.

Conclusion

This pilot-study will give insight in feasibility, satisfaction, and determinants of patients in treatment of vascular risk factors using a website. Also information on the course of risk factors will be available.

Introduction

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in Western countries (1). It is the result of atherosclerosis and is influenced by multiple risk factors, such as smoking, obesity, hypertension, hyperlipidemia, and diabetes mellitus. Lifestyle changes are an important component of vascular risk reduction strategies. Not all physicians have enough time or the appropriate training to advice about lifestyle changes (e.g. quit smoking, weight loss, increased consumption of fruit and vegetables, increased physical activity, decreased intake of salt and saturated fats). Lack of awareness on the importance of vascular risk factors by patients with atherosclerosis usually originates from the invisibility of most risk factors like elevated blood pressure and dyslipidemia (2).

New strategies are required to address the high prevalence and suboptimal control of vascular risk factors in high risk patients. The Council on Cardiovascular Nursing of the American Heart Association and the European Society of Cardiology's Working Group on Cardiovascular Nursing have begun to collaborate in education/training, research and practice initiatives in order to increase the capacity and contributions of nurse practitioners (NPs) to primary and secondary prevention of CVD worldwide (3). A number of randomized controlled trials show that the aid of NPs is more beneficial for achieving treatment goals and reducing events than achieved with usual care in patients with CVD (4-8). NPs have skills in medical and behavioural sciences needed for intensive and prolonged coaching to achieve successful risk management.

Rationale

An innovative way of risk factor management may be NP treatment with the aid of Internet communication in addition to usual care. Appealing language, visual effects, 24 h accessibility and speed makes the Internet very attractive for patients to receive medical information. Another advantage is that information can be tailored to the characteristics, needs and interests of the recipient. However, the large volume of information available on the World Wide Web makes it difficult for patients to select proper information that pertains to their particular needs. Many patients are interested in using e-mail to communicate with their physicians and in receiving online health information from their doctor's office (9). Among the diseases for which Internet users seek information most often, heart disease ranks third behind allergies and cancer (10). However, there is also a non-online group of patients including a disproportionate number of ethnic minorities, people with a low standard of education, those with a low family income, elderly, and often these people are at high risk of developing CVD (11).

Until now, a few, mainly American based, studies have published results on the possible effects of behaviour e-counseling for single risk factors e g. quitting smoking, losing weight, management of type 2 diabetes or drug compliance. These studies show a beneficial effect compared with a control group without the use of e-counseling (12-16). A study among patients with congestive heart failure showed improved adherence of drugs and feasible access to an online medical record but demonstrated no effect on health (17). One study showed no favourable effects of web-based nutrition counselling and social support for 146 patients with an increased cardiovascular risk after 8 months (18). Overall, most studies showed promising results of Internet-use for single risk factors but more evidence is required concerning the treatment of multiple vascular risk factors for CVD. In patients with manifest arterial disease, a cluster of risk factors referred to as metabolic syndrome, is very common and therefore a comprehensive approach is needed (19).

In the "Self-management of vascular Patients Activated by the Internet and Nurses" (SPAIN) pilot-study, we aim to develop and test a secure patient-specific website and treatment by a NP for vascular risk factors in addition to usual care in patients with clinical manifestations of arterial disease. The aims of the SPAIN-study are threefold: (1) to investigate the use of the specific website and the satisfaction of patients and NP after six months; (2) to study the change in existing vascular risk factors, and (3) to study which determinants predispose a change in risk factors in patients with clinical manifestations of atherosclerosis.

Here, the rationale and design of the SPAIN-study is presented.

Methods

Study population

Patients with clinical manifestations of arterial disease (coronary heart disease, cerebrovascular disease, abdominal aortic aneurysm; or peripheral arterial disease), aged 18-79 years, with a computer and Internet access, being proficient in Dutch reading and writing, and participating in the Second Manifestations of ARTerial disease study (SMART) are eligible subjects. The SMART study is a single-centre prospective cohort to investigate the prevalence of additional vascular diseases in patients who already have a manifestation of arterial disease or who otherwise are at high risk to develop symptomatic arterial disease (20).

Before the start of the SPAIN-study, we surveyed computer use and Internet access of 628 patients participating in the SMART-study. Five hundred (80%) patients completed the questionnaire (Table 1). 325 respondents who indicated their unwillingness to

Table 1. Response questionnaire computer and Internet use (n= 628)

	Interest in participation n= 175	**No computer/ Internet/interest n= 325**	**Non-response n= 128**
Male gender (%)	82	69	74
Age (male), years	54.8 ± 9.4	60.9 ± 9.5	55.3 ± 10.9
Age (female), years	54.2 ± 11.8	61.1 ± 10.7	57.6 ± 14.1
History of vascular disease*			
Coronary heart disease	50	52	45
Cerebrovascular disease	17	11	18
Abdominal aortic aneurysm	9	12	14
Peripheral arterial disease	7	6	4
Number of risk factors†	**2.3 ± 1.0**	**2.5 ± 1.1**	**2.7 ± 1.0**
0	3	3	2
1	15	14	10
2	40	27	28
3	32	38	40
4	9	17	18
5	1	1	2
Hypertension	68	79	72
Hyperlipidemia	75	81	85
Diabetes mellitus	18	23	25
Obesity	68	67	71
Current smoking	17	15	36

Data represent mean with standard deviation or percentages

* In history and other than the referral diagnosis

† Hypertension (> 140/90 mmHg or on blood pressure-lowering agents), hyperlipidemia (total cholesterol > 5.0 mmol/L, LDL-cholesterol > 3.2 mmol/L or on lipid-lowering agents), diabetes (fasting glucose ≥ 7.0 mmol/L, non-fasting glucose ≥ 11.1 mmol/L or on glucose-lowering agents), obesity (body mass index > 25 kg/m^2), or current smoking

participate were older (61 versus 55 years); were more often female (31% vs 18%) and had more vascular risk factors (2.5 ± 1.1) than the 175 respondents who were interested in participation (2.3 ± 1.0). Because of restricted personal capacity, 50 of the 175 patients were randomly selected for participation in the SPAIN-study. The SPAIN study is carried out in agreement with the principles of the'Declaration of Helsinki' (21). Its study protocol has been approved by the medical ethical review board of the University Medical Center Utrecht (UMC Utrecht).

Baseline measurement

Patients are invited to visit the UMC Utrecht for baseline examination. They are informed about the study and written informed consent will be obtained. Current medication use and smoking behaviour are asked and fasting venous blood is taken to determine serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides concentrations. Low-density lipoprotein (LDL) cholesterol concentration is calculated with Friedewald's formula. Height, weight and waist circumference are measured without shoes and heavy clothing. Body mass index (BMI) is calculated as weight to height squared (kg/m^2). Blood pressure is measured twice in sitting position at the right and left upper arm with a non-random sphygmomanometer.

Nurse practitioner intervention

The history, physical measurements and results of blood chemistry are the starting point for the intervention. The patient receives information about the vascular risk profile and individualised realistic treatment goals based on European Guidelines of Cardiovascular Disease Prevention (22) are discussed with the patient. According to the guidelines, the following goals are aimed for as closely as possible: total cholesterol < 4.5 mmol/L, LDL-cholesterol ≤ 2.5 mmol/L, triglycerides < 1.7 mmol/L, HDL-cholesterol > 1.0 mmol/L for men and > 1.2 mmol/L for women, blood pressure < 140/90 mmHg, fasting glucose < 6.1 mmol/L, BMI < 25 kg/m^2, and complete smoking cessation. To achieve these goals self-management is stimulated by teaching patients problem-solving skills and thereby enhancing self-efficacy. The NP can help achieve these goals in close collaboration with the patient. The personal treatment goal(s) and appointment(s) how to reach the goal(s) are set in five separate action plans for hypertension, hyperlipidemia, diabetes mellitus, obesity, and smoking. Also regular exercise, healthy diet, and adherence to medical treatment are part of the total intervention. Action plans should give patients confidence in managing their disease and encourage internal motivation which is more likely to result in improved clinical outcomes compared with only providing information about the disease (23).

When the action plan for each elevated risk factor is formulated, information about access to and use of the patient specific website is given to the patient. The personal data, relevant medical information and the action plan(s) needed to achieve the treatment goal(s) are registered in the patient-specific website. The patient receives a personal login and password in order to communicate with the NP by e-mail via the website. The NP tries to make optimal benefit from the website instead of outpatient visits or telephone contact. The frequency of e-mail contact is determined by the needs of the patient. It is for instance possible that a patient enters his/ her own weight or a new blood pressure measurement, apart from the regular exchange information with the responding NP through e-mail messages at the website. The NP personally replies as quickly as possible during working days and gives frequent protocol driven feedback, support, and recommendations to the patient in changing or maintaining the desired lifestyle and in their adherence to the prescribed medication. When the deadline of an appointment is passed or when for example a new fasting cholesterol measurement is entered by the patient, the NP checks the data and medical treatment can be adapted if necessary. A study physician prescribes or changes medication because a nurse practitioner in The Netherlands is formally not allowed to do this.

The website guided treatment by a NP will end if a patient achieves the treatment goal for a risk factor or after six months of use because of the end of the pilot-study. Telephone contact is only established by the NP after a patient has failed to login within a month. The NP intervention is based on written protocols for each vascular risk factor (24). The general practitioner and the treating vascular specialist are informed at the start of the study about the additional risk factor treatment and coaching but they do not have access to the patients' website.

Website design

The SPAIN website contains a secure, password protected, web based application for both patients and NP. Patients can only be identified through an independent number and no possible identifiers appear on the website screen because of security considerations. The application facilitates e-mail communication between patient and NP, the entry and storage of medication use and laboratory or physical data, the sharing of information like general news and relevant links to other websites and the use of reminders and past agreements. Data entered and created during the use of the application are stored and available for further analysis. The application has been developed in Visual C# .NET using Microsoft Visual Studio .NET. The back-end database is a Microsoft SQL Server database.

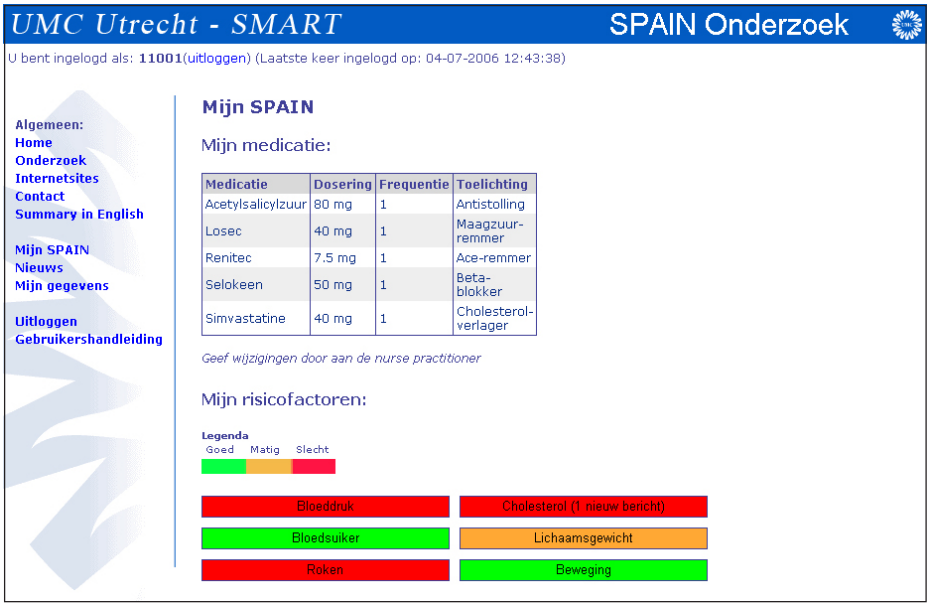


Figure 1. Homepage of the SPAIN web-application. Translation in English, left column: back to homepage, research, additional Internet sites, contact, news messages, my data, log off, instructions for use. Right column: last time log-in, my medication use, section for sub-pages of hypertension, hyperlipidemia, diabetes mellitus, obesity, smoking, physical activity in traffic light colours.

The patient-specific website contains a homepage "MY SPAIN" and six separate pages for hypertension, hyperlipidemia, diabetes mellitus, obesity, smoking, and physical activity. The homepage contains current medication use, general news on atherosclerosis and six links to the separate risk factor pages (Figure 1). The links are visualised using "traffic light" colours. Green corresponds with an adequate level of that particular risk factor, orange with a dangerous zone for a risk factor and red means clearly elevated level(s) of that risk factor and an indication for treatment. The risk factor pages all have the same lay-out and functions. They display tabular real-time laboratory and physical data, sent and received e-mail messages, facilities to describe the treatment appointments, and links to additional risk factor specific education facilities (Figure 2). Information of a physical or laboratory measurement entered by the patient automatically receive a corresponding colour (red, orange, green) by which changes in positive or negative direction are immediately visible.

The NP application offers the two above mentioned pages and an additional overview page with lists of all patients under treatment, date of last login, unread messages or entered laboratory or physical measurements, and a to-do list.

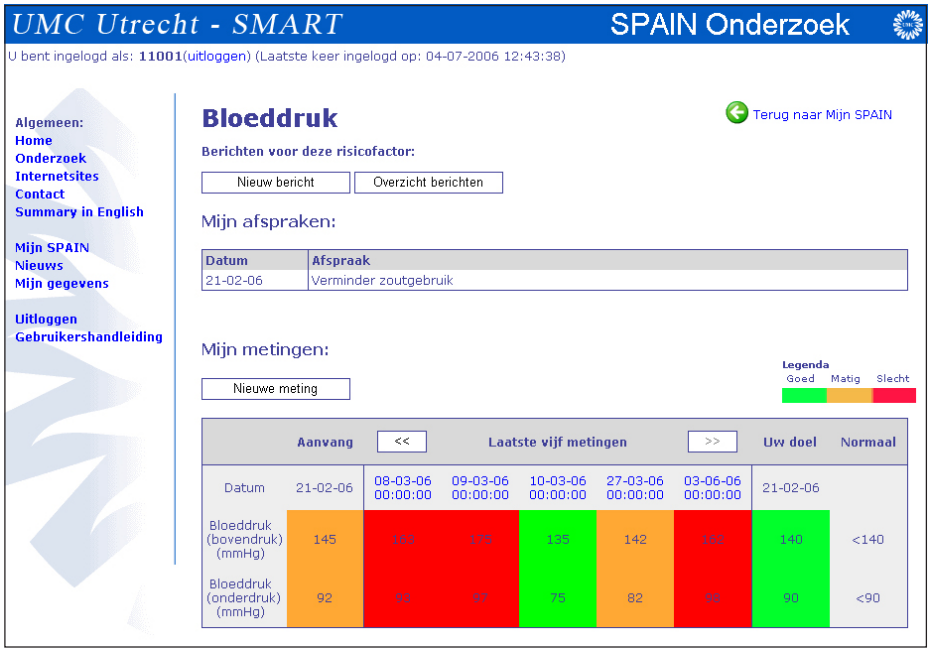


Figure 2. Treatment-page for hypertension. Translation in English, left column: see legend Figure 1. Right column: from up to down: send e-mail message to the nurse practitioner (NP) and received e-mail messages of the NP, appointments between patient and NP, and measurements of blood pressure; left is the value of systolic and diastolic blood pressure at study begin, several additional measurements in time, and right the personal goal and the standard treatment goal of blood pressure.

Questionnaires

Patient's health related behaviours are partly affected by social cognitive factors they hold (25). Such factors are influenced by more than information provision from health care professionals and may be inconsistent with these.

With several standardized questionnaires before and after the intervention we assess the specific determinants of behavioural change in patients. These questionnaires include assessments of quality of life, social problem solving, self-efficacy, mastery, social support, and self-reported behaviour. Quality of life is assessed with the SF-36 (26). Social problem solving is assessed with a 25 items containing self-reported instrument that measures the constructs coping and adaptation (27). Self-efficacy is measured with the adapted diabetes mellitus type II self efficacy scale (28), which measures the level of confidence people have about their ability to take the medication as prescribed, to stop smoking, to choose healthy food, to take a proper amount of exercise, and to control their weight. Mastery refers to the extent to which people see

themselves as being in control of the forces that affect their lives importantly (29). Degree of physical activity and fruit and vegetable intake is obtained via self-reported validated questionnaires (30;31).

Follow-up measurement

After six months of Internet-based treatment by the NP, the participating patients (n= 50) are asked to visit the hospital again for follow-up evaluation. Data are collected on current medication use, smoking behaviour, weight, blood pressure, and on fasting glucose- and lipid-levels. The website-guided NP treatment of patients finished at follow-up. Instructions to continue with lifestyle changes are given to the participating patients and the treating physicians are informed by letter about the course of vascular risk factors at the end of the study. With a random sample of the participants and the NP focus-group interviews are planned to evaluate user-friendliness and satisfaction.

Outcome measures

The intensity of the website use is determined by the number of logins, entered data of new measurements, and a categorization of e-mail messages based on content of both patients and NP. By means of focus-group interviews data are collected on patient and NP experiences, preferences, and time of work.

From the baseline and follow-up data of vascular risk factors, we create a series of dichotomous measures indicating whether treatment goals for cardiovascular risk management have been attained according to the European Guidelines (22). We aim to detect a 10% difference between the baseline and follow-up measurement in achievement of treatment goals for weight, blood pressure, lipid spectrum, glucose-level, smoking and medication use. With a power of 80% (β=0.2) and an α value of 0.05, 31 patients will be needed to detect a difference.

To evaluate the determinants of changing behaviour the characteristics of those who changed their behaviour (achieved treatment goals) will be compared with those who do not change their behaviour (not achieved treatment goals) in an adjusted Logistic regression model.

A randomized controlled trial is needed to examine the real effect on risk factors and to evaluate the cost-effectiveness of this intervention compared with usual care.

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General discussion: risk prediction and risk reduction

General discussion: vascular risk prediction and risk reduction

The number of patients with clinical manifestations of arterial disease is increasing because the population is ageing. There is widespread evidence of effective risk reduction by long-term, individual tailored drug therapy, and lifestyle and behaviour change. When treating patients with clinical manifestations of an atherosclerotic vascular disease, clinicians tend to focus on revascularization and often give low priority to the management of vascular risk factors, which could leave patients at increased risk. Several national and international cardiovascular guidelines emphasize that clinicians should focus on the aggressive management of traditional modifiable vascular risk factors such as, smoking, blood pressure, LDL-cholesterol levels, sedentary lifestyle, and obesity, in patients with cardiovascular disease (CVD) (1-3). Despite publication of these guidelines, medical treatment of risk factors remains suboptimal (4). Furthermore, the increased intake of total and saturated fat and the lack of physical activity in modern societies have led to an increased prevalence of obesity and type 2 diabetes, and inevitably CVD (5).

The studies presented in this thesis not only confirm the high prevalence of vascular risk factors in high-risk patients (chapter 3 and 6), but also demonstrate the relevance of non-invasive screening for asymptomatic arterial disease (chapter 3), and evaluate new interventions aimed at better risk factor management in order to delay or prevent the progression of atherosclerotic vascular disease (chapters 7, 8, and 9). These interventions were additional to a vascular screening and prevention programme. But first of all, we want to discuss the topic of vascular risk prediction in patients with clinical manifest arterial disease which is addressed in chapter 5.

Vascular risk prediction

Several risk algorithms have been developed to predict cardiovascular risk in middle-aged individuals without pre-existing symptomatic CVD or diabetes mellitus, in order to differentiate individuals at low or high risk of developing a vascular event over a finite period (6-8). These prediction models are based on traditional vascular risk factors known to contribute to the chronic development of atherosclerotic vascular disease.

Cardiovascular risk prediction in patients without pre-existing symptomatic CVD can be approached in two ways: the prediction of risk within a specific period, e.g. 10 years, and the prediction of lifetime risk. Estimates of lifetime risk take into account the risk of the disease of interest and the competing risk of death from other causes, and provide a simple conceptual basis for estimating the absolute risk of developing disease over the remaining lifespan (9). An advantage of lifetime risk prediction is that it makes

possible to identify individuals with a low short-term risk but a high lifetime risk, for example due to a sedentary lifestyle at a young age or because of a single risk factor which causes cumulative damage and markedly shortens survival. A study investigating whether the Framingham 10-year risk equation could reliably stratify lifetime risk for coronary heart disease showed that the Framingham risk function was very effective at stratifying the remaining lifetime risk of women of all ages, but performed less well in younger men, although performance improved in older ages as the remaining life expectancy approached 10 years (9). So, the technique of estimating long-term risk is particularly relevant to younger patients, in whom attention focused solely on low short-term risk may discourage initiation of or compliance with lifestyle modification and medical treatment.

Considerable effort has been invested in the development of methods to predict cardiovascular risk in patients without pre-existing CVD or diabetes. Most existing risk algorithms overestimate the predicted risk in populations without existing CVD worldwide, although regional recalibration methods are promising (10). Patients with clinical manifestations of arterial disease and patients with diabetes mellitus are generally considered to be at high risk of developing (new) vascular events. Nevertheless, it seems reasonable to assume that there is a spectrum of risk, ranging in severity from moderate to very high, in this high-risk patient group. We investigated in chapter 5 how existing prediction models, intended for patients without symptomatic CVD or diabetes, performed in a cohort of patients with clinical manifestations of arterial disease. The framingham, PROCAM, and SCORE prediction models underestimated the predicted risk in our study population. A new prediction model that incorporated traditional vascular risk factors (age, gender, systolic and diastolic blood pressure, LDL-cholesterol, HDL-cholesterol, diabetes, and smoking) performed reasonably with an area under the receiver operating characteristics (ROC) curve of 0.62 (95% CI 0.58 - 0.67) after 1 year of follow-up. While some predictors, such as age and gender, are not modifiable, others become the focus of therapy once a patient's high-risk status has been established (11). Currently, there is ongoing debate whether novel risk factors, if any, should be added to existing CVD prediction models. An important step beyond merely reporting the relative risk of a novel risk factor is to evaluate its prognostic value, whether the area under the ROC curve increases after a novel risk factor is added to a model incorporating the traditional vascular risk factors. Few studies have compared the ability of novel risk factors and traditional risk factors to differentiate persons at low- or high risk of cardiovascular events. A study in the general population concluded that none of the 19 novel risk factors could improve the area under the ROC curve of a prediction model

consisting of traditional risk factors (12). In another study of patients with manifest arterial disease, levels of N-terminal pro-brian natriuretic peptide enhanced the prediction of recurrent CVD events only (13). Results from our own group indicate that in patients with manifest arterial disease, homocysteine, high-sensitive C-reactive protein, microalbuminuria, creatinine, carotid intima-media thickness (CIMT), and carotid stiffness do not have additional value over traditional risk factors in distinguishing between patients at low-or high risk (14).

What can be done to improve risk prediction in patients already at increased risk of developing recurrent vascular events? The occurrence of an arterial ischemic event due to atherosclerosis implies that other arterial sites may also be affected, although clinically silent, by the same pathophysiological process (15). The largest ever long-term cohort study of patients with a transient ischemic attack (TIA) or minor ischemic stroke, recently reported that 54% of the 1336 patients had had at least one major vascular event during a mean follow-up of 10 years (16). Patients with symptomatic peripheral arterial disease have a 4-fold higher risk of myocardial infarction than those without such disease (17), and the risk of ischemic stroke after myocardial infarction is substantial, with about 1 in 40 patients suffering from an ischemic stroke within 6 months of discharge (18). Thus, it is tempting to speculate that patients with (previous) clinical manifestations of arterial disease in other locations of the arterial tree (cerebral, coronary, peripheral) have a higher risk of future vascular events than those with clinical manifestations of arterial disease restricted to only one location of the arterial system. Therefore, we included the presence of other vascular disease (cerebrovascular disease, coronary heart disease, abdominal aortic aneurysm, peripheral arterial disease) in our new prediction model. The area under the ROC curve was 0.65 (95% CI 0.60 - 0.69) compared with an area of 0.62 (95% CI 0.58 - 0.67) for the prediction model consisting of traditional risk factors, after 1-year of follow-up. Thus, the discriminative ability of the model was increased only slightly by adding co-morbidity of vascular disease to a prediction model consisting of traditional risk factors.

Measurement of the extent of atherosclerosis may help to contribute to differentiate low risk from high risk patients. In this thesis, we found that the presence of asymptomatic carotid artery stenosis of ≥ 50% was associated with a 50% increased risk of recurrent vascular events (hazard ratio (HR) 1.5, 95% CI 1.1 – 2.1) during a mean follow-up of 3.6 years of patients with clinical manifestations of arterial disease or type 2 diabetes but without a history of cerebral ischemia (chapter 4), which agrees with results from two other studies involving smaller population samples (19;20). Thus, the presence of asymptomatic carotid artery stenosis of ≥ 50% is indicative of a higher risk in patients already known to be at high risk.

We also looked at the relationship between several baseline characteristics and the risk of developing new vascular events in patients with symptomatic peripheral arterial disease (chapter 6). We found that older age, impaired renal function, elevated homocysteine levels, and a history of coronary heart disease were associated with an increased risk of new vascular events. Thus, these characteristics are indicators of a higher cardiovascular risk in patients with symptomatic peripheral arterial disease.

Furthermore, we showed that additional non-invasive vascular screening to detect asymptomatic arterial disease in patients at low- and high risk according to the criteria of the European Guidelines on Cardiovascular Disease Prevention (2) has little added benefit (chapter 3). In individuals identified as being at low risk of fatal CVD, e.g. patients included in the SMART study with a single risk factor (hypertension, hyperlipidemia, diabetes mellitus), additional screening for the detection of an asymptomatic reduced ankle brachial pressure index, carotid artery stenosis of ≥ 50%, abdominal aortic aneurysm of ≥ 3 cm, increased mean CIMT, or left ventricular hypertrophy resulted in the reclassification of 73 of the 545 (13%) from low to high risk. It is not known whether the detection of such vascular abnormalities justifies shifting these initially low risk patients to the high risk category because the prognostic relevance of these abnormalities is not known. This is a subject for further research. Additional vascular screening of patients with a manifestation of arterial disease, patients with diabetes type 1 or 2 or markedly raised levels of single risk factors, or patients with a 10-year mortality risk ≥ 5% resulted in the identification of a small number of patients with severe vascular disorders, such as an abdominal aortic aneurysm ≥ 5.5 cm (found in 7 of the 3950 patients). These patients already required the most intensive lifestyle intervention and medical treatment of vascular risk factors. So, further screening to detect asymptomatic arterial disease in patients at already high risk cannot be recommended in general practice.

Vascular risk reduction

All patients included in the SMART study underwent a standardized non-invasive vascular screening programme to investigate the prevalence and incidence of additional vascular diseases. According to the SMART study protocol, the course of detected vascular risk factors was not further monitored and actual treatment of risk factors was left to the discretion of the general practitioner (GP) and the vascular specialist. One of the purposes of a longitudinal study described in this thesis was to investigate the course of vascular risk factors by inviting patients with symptomatic peripheral arterial disease for a

follow-up evaluation (chapter 6). We demonstrated that after a mean follow-up of 5.5 years, mean blood pressure, homocysteine levels, body mass index, and the prevalence of diabetes had increased, whereas mean lipid levels and the prevalence of smoking had decreased. So, even though these patients were screened and treatment advice was given to the treating vascular specialist and the GP about medical treatment and lifestyle changes, the treatment goals for important risk factors were often not reached. Appropriate lifestyle changes and aggressive pharmaceutical interventions reduce vascular risk.

In general, two approaches can be taken to reduce vascular risk: a population approach and an individualized approach. The concept of the polypill, a pill combining six drugs to reduce four risk factors that can be given to all people aged 55 years and older or to adults of any age with diabetes or existing CVD, is an example of a potential population approach (21). However, this is hypothetical and needs to be tested further before such a polypill can be considered a valid alternative to the prevention and treatment of CVD. Increasing taxation on cigarettes, no-smoking policies in governmental buildings and the working environment, and wide provision of exercise facilities and activities are other examples of health-promoting activities (22). A Dutch community intervention to reduce vascular risk by reducing fat intake, increasing physical activity and stopping smoking showed that a regional strategy requires a lot attention and effort to ensure long-term benefit (23).

Patients at very high risk (patients with clinical manifestations of atherosclerosis and patients with diabetes) may benefit the most from an individualized approach to modifying vascular risk factors like hypertension, hyperlipidemia, type 2 diabetes, smoking, and obesity. Patients with a recent clinical manifestation of atherosclerosis are most often seen by medical specialists (vascular surgeon, neurologist, cardiologist, internist), and patients at increased risk in the chronic phase of vascular disease are most often seen by the GP, although, other healthcare professionals may be involved in the treatment of these patients (e.g. dieticians, nurses, pharmacists, exercise physiotherapists). Multidisciplinary treatment calls for excellent communication between healthcare professions, but in practice this is often suboptimal. A crucial element of long-term secondary prevention is the surveillance of vascular risk factors, which can be achieved by providing regular follow-up assessments, feedback, psychosocial and emotional support, and education and motivation in a systematic manner to achieve tailored and high-quality care (24).

In this thesis, we investigated additional interventions to reduce vascular risk. A letter sent to the patient's GPs and vascular specialists about the results of a single vascular screening and related medical treatment recommendations if newly or poorly controlled risk factors were detected resulted in a marginal increase in medication use for several risk factors compared with medication use without this intervention (usual care) (chapter 7). Opportunities to consult the multidisciplinary team who formulates medical treatment recommendations, communication with the patient in question, and clarifying who should take action could contribute to better risk reduction. We also found that in patients with clinical manifestations of arterial disease, extra care given by a vascular nurse practitioner in addition to usual care and on top of a vascular screening and prevention programme resulted in an improved cardiovascular risk profile compared with usual care alone (chapter 8). In the VENUS-study, we found that nurse practitioner-assisted risk factor management resulted in the achievement of more treatment goals for systolic blood pressure, total cholesterol, LDL-cholesterol, and body mass index. The care delivered by a nurse practitioner was characterized by medical, nursing, and especially educational interventions regarding vascular risk factors and was supervised by an internist. A systematic review of twelve different randomized controlled trials involving 9803 patients with coronary heart disease concluded that in five of seven trials the nurse practitioner intervention improved the treatment of blood pressure, cholesterol, and smoking (although an overall-effect size was not presented), reduced hospital admissions (shorter length of stay), and led to a small improvement in quality of life (25). One of these trials investigated the experiences of health professionals that had been involved in a nurse-led secondary prevention clinic (26). While many GPs and nurses were convinced that these clinics were of benefit to patients, they mentioned several barriers to the implementation of nurse practitioner clinics, such as lack of training, time, resources (especially staff), and difficulties in team working. Often GPs were hesitant about handing over their responsibility for continuing care. In our view the extra care provided by a nurse practitioner is supplemental to the medical care provided by treating vascular specialist and GP because all three health professionals have their own specialties. With the addition of a vascular nurse practitioner to a multidisciplinary team, to provide chronic care, treating physicians are still, but less actively, involved in the intervention and can leave lifestyle issues to the nurse practitioner. Nurse practitioners are also increasingly involved in the medical treatment of vascular risk factors such as hypertension and hyperlipidemia. The nurse practitioner can give more intensive

individual-tailored counseling, which is not always feasible during a consultation with the doctor because of limited time available and lack of training in behaviour modification. Other tasks of nurse practitioners are to encourage compliance with medication and to lifestyle changes, to listen to patients, and to review the levels of risk factors regularly. We believe that nurse-guided care should be started directly after the occurrence of a vascular event. Once treatment goals are achieved, long-term follow-up to recheck achieved targets and to support the patient can be done by a vascular nurse practitioner or practice nurse in primary care, close to patient. This necessitates close collaboration and excellent communication between the different caregivers. Another essential advantage of additional nurse practitioner care is that it appears to be more cost effective than most healthcare interventions (27). At the moment, a nurse practitioner is formally not allowed to prescribe or change medication in The Netherlands, whereas in other countries a nurse is legally allowed to prescribe supplementary drugs to patients with chronic conditions (asthma, diabetes, and coronary heart disease) (28). So, a nurse practitioner is not independent in practice and should always approach a physician about medical treatment decisions. Another obstacle for implementing the supplemental care provided by a nurse practitioner is that the care given is not covered yet by national Dutch health insurance schemes, although, the relevant legislation is expected to be adapted soon (29).

A potentially effective and efficient way to manage risk factors is for nurse practitioners to provide additional guidance by communicating with patients via the Internet, as described in chapter 9 of this thesis. Goal-setting to change behaviour and the online-relationship between nurse practitioner and patient can continue for many years because of the repeated episodic nature of the atherosclerotic vascular disease process. Appealing language, visual effects, 24-h accessibility, and tailoring to individual needs make the Internet a very attractive means for patients to receive medical information about themselves. The Self-management of vascular Patients Activated by Internet and Nurses (SPAIN) pilot study was set up within the SMART study and will soon provide information about the feasibility, intensity of website use, satisfaction of the patients and nurse practitioner involved and the course of vascular risk factors after 6 months of website usage. In a future study, preferably a randomized trial, the effect of this Internet-based treatment programme on the treatment of vascular risk factors should be evaluated before its widespread implementation can be recommended.

Main conclusions of this thesis

- Adverse levels of vascular risk factors and the presence of arterial disease reduce life-expectancy.
- Additional non-invasive screening for asymptomatic atherosclerotic disease has limited value in identifying vascular conditions requiring immediate intervention in patients at low and high risk as defined by the European Guidelines.
- Asymptomatic carotid artery stenosis of ≥ 50% is an independent predictor of vascular events in patients with arterial disease or type 2 diabetes and without cerebral ischemia.
- The existing primary prevention algorithms underestimate the risk of recurrent vascular events.
- A recently developed risk prediction model is better at estimating the 1-year probability of a recurrent vascular event in patients with manifest arterial disease than in estimating the long-term probability.
- Predictors of new vascular events in patients with symptomatic peripheral arterial disease are older age, elevated homocysteine levels, impaired renal function, and a history of coronary heart disease.
- In patients with peripheral arterial disease, the prevalence of most risk factors increases despite the increase in medication use.
- Medical treatment recommendations given to treating physicians of patients with manifest vascular disease leads to a marginal increase in medication use compared with medication use without this advice.
- Treatment delivered by nurse practitioners results in a better management of several vascular risk factors than usual care alone in patients with manifest arterial disease.
- An effective and efficient way to manage vascular risk factors may be nurse practitioner guided treatment via Internet communication with individual patients.

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Chapter 11

Summary

Cardiovascular diseases are the most common chronic illnesses in developed countries, causing many deaths and a high morbidity rate. The term cardiovascular disease (CVD) includes clinical manifestations of arterial disease or atherosclerosis, such as peripheral arterial disease, abdominal aortic aneurysm, cerebrovascular disease, and coronary heart disease. Patients with clinical manifest arterial disease have an increased risk of a new vascular event in the same or different arterial bed. Several lifestyle measures (healthy diets, exercise, quit smoking) and treatment of risk factors with medication (antiplatelet agents, blood pressure-, and lipid-lowering agents, beta-blockers, and ACE-inhibitors) can reduce the future vascular risk in patients with clinical manifestations of arterial disease.

The work presented in this thesis focused on new intervention strategies aiming at better risk factor management in patients with clinical manifestations of arterial disease. Furthermore, the aim was to distinguish high risk form low risk patients by predicting the risk of a recurrent vascular event using existing prediction models, intended for patients without CVD or diabetes. A new prediction model was developed in an effort to improve cardiovascular risk prediction in patients with clinical manifestations of symptomatic arterial disease.

The study population consisted of participants of the Second Manifestations of ARTerial disease (SMART) study, an ongoing single-centre prospective cohort study of the University Medical Center Utrecht, the Netherlands in which since 1996 over 6000 patients were included.

The consequences of the presence of traditional (vascular) risk factors and the impact of various manifestations of atherosclerosis on life-expectancy are summarized in **chapter 2**. Life-expectancy increased for many decades in the developed countries. Due to the longevity, more people are at a higher risk to develop clinical manifestations of atherosclerosis. The absence of overweight, high blood pressure, smoking, physical inactivity, and diabetes mellitus contributed to longer total life-expectancy and disability free life-expectancy. With more adverse levels of risk factors, lifetime risk of CVD increased and median survival decreased. Clinical manifestations of atherosclerosis reduced life-expectancy 8 to 12 years in a 60 year old patient depending on the location of the vascular event. At age 70, a man with coronary heart disease may expect to live 8.9

years and a similar woman 11.7 years. A man of 70 year who survived a stroke is expected to live 5.5 years and a woman 7.1 years. We concluded that a broad range of primary and secondary prevention strategies to reduce vascular risk is important in adults at high risk, but also in the elderly (≥ 75 years) because of the expanding number of people in this age-category.

In **chapter 3** we evaluated the additional value of non-invasive screening to detect asymptomatic arterial disease in 3950 patients at low- and high risk of experiencing (new) vascular events, according to criteria of the European Guidelines of Cardiovascular Disease Prevention. Eighty-eight percent of the 3950 patients were considered to be at high risk and 13% of the patients initially considered low risk were reclassified as high risk based on non-invasive measurements. Twenty-one percent of the patients with cerebrovascular disease had an asymptomatic reduced ankle brachial index (≤ 0.90), 5% of the patients with peripheral arterial disease or cerebrovascular disease had an asymptomatic abdominal aortic aneurysm (≥ 3.0 cm), and 15% of the patients with peripheral arterial disease had an asymptomatic carotid artery stenosis (≥ 50%). The results suggest that the yield of non-invasive vascular measurements was relatively low but identified a sizable number of high risk patients. Standard screening for asymptomatic arterial disease identified a limited number of vascular abnormalities that necessitated immediate medical attention in patients already identified as high risk patients.

In **chapter 4** the relation between presence of asymptomatic carotid artery stenosis and risk of a recurrent vascular event (myocardial infarction, ischemic stroke, or vascular death) was assessed in patients with clinical manifestations of arterial disease or type 2 diabetes but without a history of cerebral ischemia. Asymptomatic carotid artery stenosis of ≥ 50% was present in 221 (8%) of the 2684 patients. Adjusted for age and gender, an asymptomatic carotid artery stenosis of ≥ 50% was associated with a 50% increased risk of recurrent vascular events (hazard ratio (HR) 1.5, 95% CI 1.1 – 2.1) and in particular an increased risk of vascular death (HR 1.8, 95% CI 1.2 – 2.6). After additional adjustment for vascular risk factors the hazard ratios remained essentially the same, suggesting that asymptomatic carotid artery stenosis is an independent predictor of vascular events in patients with clinical manifestations of arterial disease or type 2 diabetes but without a history of cerebral ischemia.

In **chapter 5** the results of the performance of the Framingham, PROCAM and SCORE prediction models in 3343 patients with clinical manifestations of arterial disease are presented. These models were initially intended for patients without CVD or diabetes. The three models underestimated the risk observed in our population. The SCORE prediction rule discriminated better than the others, with an area under the ROC curve of 0.70 (95% CI 0.66 – 0.74) at 5 years of follow-up. We developed new risk models for the prediction of recurrent vascular events (myocardial infarction, ischemic stroke, and vascular death). Based on 392 recurrent vascular events, Cox proportional hazard analysis were derived with pre-specified information on traditional vascular risk factors, location of vascular disease, and extent of atherosclerosis (creatinine levels, intima-media thickness, carotid artery stenosis). The performance of the final model was rather good at 1 year follow-up but at 3 or 5 years the number of events was underestimated. Discrimination was moderate with a ROC area of 0.67 (95% CI 0.62 – 0.71) at 1 year, 0.69 (95% CI 0.66 – 0.73) at 3 years, and 0.70 (0.66 – 0.73) at 5 years. We concluded that the existing primary prevention algorithms are not suitable for accurate risk prediction in patients with symptomatic CVD. The new risk model performed rather good with accurate predicted probabilities and moderate discriminative abilities. Prediction the risk of recurrent vascular events is possible after 1 year but not at 3 or 5 years in patients with symptomatic CVD.

In **chapter 6** the relation between baseline variables and risk of new vascular events was assessed in 461 patients with symptomatic peripheral arterial disease. Moreover, after a mean follow-up of 5.5 years, patients were invited for a follow-up measurement to examine the amount and the course of risk factors between baseline and follow-up. The cumulative incidence after 5.5 years was 29.1% (95% CI 22.8 – 35.4) for the composite of new vascular events. Higher age (HR 1.85, 95% CI 1.48 – 2.30), elevated homocysteine levels (HR 1.03, 95% CI 1.02 – 1.05), impaired renal function (HR 0.79, 95% CI 0.69 – 0.91), and a history of coronary heart disease (HR 2.30, 95% CI 1.51 – 3.51) at baseline were related with an increased risk of new vascular events. Of the 461 patients, 333 patients were still alive and not lost for follow-up measurement and 221 (66%) patients were willing to participate. The prevalence of most risk factors increased, except for smoking and hyperlipidemia, even though medication use had increased over a 5.5-year period.

Chapter 7 deals with the question whether individualized medical treatment recommendations given by a multidisciplinary team to the treating physicians, led to changes in medication use. Patients included in the SMART study underwent a vascular screening. The results and treatment recommendations concerning the medical treatment of newly detected or not yet sufficiently treated vascular risk factors were reported to the treating physicians. After a mean follow-up of 2.4 years, questionnaires about medication use were sent to an a-selective group of 618 patients resulting in a response-rate of 86%. The medical treatment recommendations led to (a change in) pharmacotherapy in approximately 52% of the instances in which advice was given. The compliance with the start medication recommendations for hypertension (77%) and hyperlipidemia (56%) was higher compared with the recommendations of hyperglycemia / diabetes mellitus (34%). We concluded that medical treatment recommendations led to a marginal increase compared with trends in medication use without this intervention in usual care.

The results of the randomized controlled trial Vascular prEvention by NUrses Study (VENUS) were presented in **chapter 8**. This study investigated whether the extra care of a nurse practitioner plus usual care compared to usual care alone was beneficial for the cardiovascular risk profile of patients with clinical manifestations of arterial disease. Two hundred thirty-six patients with manifestations of a vascular disease and who had ≥ 2 modifiable vascular risk factors were pre-randomized to receive treatment by a nurse practitioner plus usual care (intervention group) or usual care alone (control group). Patients assigned to the intervention could attend the nurse practitioner guided risk factor management clinic. After a mean follow-up of 1.2 year, vascular risk factors were measured again. The patients in the intervention group achieved significantly more treatment goals for systolic blood pressure (odds ratio (OR) 2.7, 95% CI 1.3 – 5.4), total cholesterol (OR 3.3, 95% CI 1.5 – 7.3), LDL-cholesterol 3.5, 95% CI 1.5 – 8.6), and body mass index (OR 4.0, 95% CI 1.2 – 13.1) than did the patients in the control group. Medication use was increased in both groups and no differences were found in quality of life of these patients at follow-up. The findings showed that treatment delivered by nurse practitioners resulted in a better management of several vascular risk factors than usual care alone.

Chapter 9 describes the rationale and design of the ongoing Self-management of vascular Patients Activated by the Internet and Nurses (SPAIN) study. Final results can be expected at the beginning of 2007. Development and use of a safe personalized website are study-aims. During a face to face dialogue between a nurse practitioner and a patient, realistic treatment goals are set for elevated risk factors (hypertension, hyperlipidemia, diabetes mellitus, overweight, smoking, physical inactivity). Each of the 50 participating patients receives a password to access his/her records on the website, can enter new measurements and is stimulated to keep frequent e-mail contact. The nurse practitioner replies during working days and gives regular, protocol driven, treatment advice, feedback, and support. After 6 months, the participating patients are asked to visit the hospital again for follow-up evaluation of the risk factors. Based on login attempts, number of messages, risk factor levels before and after intervention, and on the level of self-management (problem solving skills and self-efficacy), insight in feasibility, satisfaction, and determinants of patients in risk factor management using a website will be given.

Finally, in the general discussion in **chapter 10**, the topics of risk prediction and risk reduction were integrated with our own study findings and interpreted. Main conclusions of this thesis were also presented.

Samenvatting

Hart- en vaatziekten zijn de meest voortkomende ziekten in ontwikkelde landen en veroorzaken het hoogste sterftepercentage. De term hart- en vaatziekten omvat alle klinische uitingen van slagaderverkalking (atherosclerose), zoals perifeer vaatlijden van de benen, verwijding van de grote buikslagader, TIA of een herseninfarct (cerebraal vaatlijden), en pijn op de borst of een hartinfarct (coronair lijden). Patiënten met een klinische uiting van slagaderverkalking hebben een verhoogd risico op een nieuwe uiting van vaatziekte op dezelfde of andere plaats in het vaatstelsel. Verschillende leefstijlfactoren (gezonde voeding, voldoende beweging, niet roken) en medicamenteuze behandeling (bloedplaatjesremmers, bloeddruk- en cholesterol verlagende medicijnen, beta-blockers, en ACE-remmers) kunnen het risico op een nieuwe vaatziekte van patiënten met arterieel vaatlijden verlagen.

In dit proefschrift hebben we gekeken naar een aantal nieuwe strategieën om het risico op een nieuwe uiting van vaatlijden te verlagen. Tevens hebben we met behulp van drie bestaande modellen om nieuwe vaataandoeningen te voorspellen, die bestemd zijn voor gezonde mensen, het absolute risico voorspeld op een nieuwe uiting van vaatlijden. Daarnaast is een nieuw model ontwikkeld om het ontstaan van nieuwe vaatziekten te voorspellen voor patiënten met arterieel vaatlijden.

Om de onderzoeksvragen te beantwoorden, hebben we gebruik gemaakt van gegevens van patiënten met arterieel vaatlijden deelnemend aan het Second Manifestations of ARTerial disease (SMART) onderzoek. Dit is een lopend onderzoek bij personen met ernstige risicofactoren voor hart- en vaatziekten of met een uiting van vaatziekte die verwezen zijn naar het Universitair Medisch Centrum Utrecht. Bij deelname aan het SMART onderzoek vindt een uitgebreide screening plaats bestaande uit bloed- en urineonderzoek, echografie van de hals-, buik-, en beenvaten, bloeddruk- en gewichtmeting, en het invullen van een vragenlijst over leefstijlfactoren en medicatiegebruik.

De consequenties van het hebben van belangrijke (klassieke) risicofactoren van hart- en vaatziekten en de invloed van arterieel vaatlijden op de levensverwachting van mensen zijn samengevat in **hoofdstuk 2**. De levensverwachting is de laatste jaren in ontwikkelde landen toegenomen. Hierdoor neemt de tijdspanne om vasculaire risicofactoren te ontwikkelen toe en draagt hiermede bij aan een grotere kans op arterieel vaatlijden. Weinig beweging, overgewicht, hoge bloeddruk, diabetes mellitus

(suikerziekte), en roken dragen bij aan een kortere totale levensverwachting en een kortere levensverwachting zonder lichamelijke beperkingen. Bij het toenemen van het aantal risicofactoren neemt de kans op arterieel vaatlijden toe en neemt de levensverwachting af. Een klinische uiting van arterieel vaatlijden heeft tot gevolg dat bij een 60-jarige patiënt de levensverwachting acht tot twaalf jaar afneemt, afhankelijk van de plaats van optreden. We concludeerden dat de risicofactoren niet alleen bij volwassenen maar ook bij ouderen (≥ 75 jaar) behandeld moeten worden vanwege de enorme toename van het aantal mensen in deze leeftijdscategorie.

In **hoofdstuk 3** evalueerden we de aanvullende rol van beeldvormende technieken in het opsporen van niet symptomatisch (zonder ziekteverschijnselen) vaatlijden. 3950 patiënten werden ingedeeld in een laag- of hoogrisico groep volgens de Europese richtlijn voor hart- en vaatziekten preventie. Van de 3950 patiënten werd 88% beschouwd als hoogrisico groep en 13% van de oorspronkelijk laagrisico patiënten werd geclassificeerd als hoogrisico op basis van beeldvormende technieken. Eenentwintig procent van de patiënten met cerebraal vaatlijden had een verlaagde niet symptomatische enkel-arm index (≤ 0.90), 5% van de patiënten met perifeer arterieel vaatlijden of cerebraal vaatlijden had een verwijde lichaamsslagader van de buik (≥ 3.0 cm), en 15% van de patiënten met perifeer arterieel vaatlijden had een niet symptomatische vernauwing van de halsslagader (≥ 50%). Hieruit blijkt dat de prevalentie van niet symptomatisch vaatlijden op andere plaatsen laag is maar identificeert een aantal hoogrisico patiënten. Standaard diagnostiek voor het opsporen van niet symptomatisch vaatlijden beperkt zich tot een gering aantal ernstige vaataandoeningen, die meteen medische aandacht vergen.

In **hoofdstuk 4** bekeken we de relatie tussen de aanwezigheid van een niet symptomatische vernauwing van de halsslagader en het optreden van een nieuwe uiting van vaatziekte (hartinfarct, beroerte, of dood door hart- en vaatziekten) bij patiënten met arterieel vaatlijden of type 2 diabetes mellitus en zonder een voorgeschiedenis van cerebraal vaatlijden. In 221 (8%) van de 2684 patiënten werd een niet symptomatische vernauwing van de halsslagader waargenomen met echografie. Uit deze studie bleek dat de kans op het ontwikkelen van een nieuwe uiting van vaatziekte 50% groter was bij de aanwezigheid van een niet symptomatische halsslagadervernauwing. De kans op het overlijden aan hart- en vaatziekten was het grootst (80%) bij de aanwezigheid van

een niet symptomatische halsslagadervernauwing. Het verhoogde risico was niet het gevolg van het vaker voorkomen van traditionele risicofactoren bij deze groep patiënten. We concludeerden daarom dat een niet symptomatische halsslagadervernauwing een onafhankelijke voorspeller is voor het optreden van een nieuwe uiting van vaatziekte bij patiënten met arterieel vaatlijden of type 2 diabetes mellitus en zonder een voorgeschiedenis van cerebraal vaatlijden.

Met behulp van een voorspellingsmodel hebben vaatspecialisten en huisartsen een extra hulpmiddel om het risico te schatten op een uiting van vaatlijden. In **hoofdstuk 5** werden de voorspellende waarden van drie bestaande modellen Framingham, PROCAM en SCORE, bestemd voor gezonde mensen, bestudeerd voor een nieuwe uiting van vaatziekte bij 3343 patiënten met arterieel vaatlijden. De drie bestaande modellen vertoonden een slechte overeenkomst tussen het werkelijk ontstaan van een nieuwe uiting van vaatziekte en de door de regels voorspelde kans hierop. Ook het onderscheidend vermogen tussen laag- en hoogrisico groepen was slecht tot matig. Daarom werd een nieuw model ontwikkeld met, naast de voorspellende traditionele risicofactoren, een toevoeging van vaatlijden op één of meerdere plaatsen, vaatwanddikte, creatinine concentratie in het bloed (maat voor nierfunctie), en vernauwing van de halsslagaders. De voorspelling van een nieuwe uiting van vaatziekte is beter na 1 jaar dan op langere termijn (3 of 5 jaar). Voordat het uiteindelijke voorspellingsmodel in de praktijk kan worden gebruikt, dient dit voorspellingsmodel in een andere dataset getoetst te worden.

In **hoofdstuk 6** werd bij 461 symptomatische patiënten met perifeer arterieel vaatlijden de relatie tussen verschillende risicofactoren en het optreden van een nieuwe uiting van vaatziekte (hartinfarct, beroerte, of dood door hart- en vaatziekten) bestudeerd. Bovendien werden na een gemiddelde duur van 5,5 jaar de patiënten uitgenodigd voor een vervolgmeting om het aantal en het verloop van risicofactoren van vaatlijden in de tijd te bestuderen. Het 5,5-jaarsrisico op een nieuwe uiting van vaatziekte was 29.1% . Een hogere leeftijd, een verhoogd homocysteine gehalte in het bloed, een slechte nierfunctie, en een voorgeschiedenis van coronair lijden bleken verband te houden met een hoger risico op het optreden van een nieuwe uiting van vaatlijden. Van de 461 oorspronkelijke patiënten waren 333 nog in leven of traceerbaar voor een vervolgmeting en daarvan wilden 221 (66%) patiënten deelnemen. Bij veel patiënten werden meer

traditionele risicofactoren (hoge bloeddruk, overgewicht, diabetes mellitus) vastgesteld, terwijl het medicatiegebruik toenam. Dyslipidemie (afwijkend vet- en cholesterolgehalte) werd minder vastgesteld en er waren minder rokers ten tijde van de vervolgmeting.

In **hoofdstuk 7** onderzochten we of een individueel medicatie-therapieadvies, opgesteld door een multidisciplinair team van vaatspecialisten en gebaseerd op internationale behandelrichtlijnen, leidde tot een toename in medicatiegebruik. Patiënten die deelnamen aan de SMART-studie, ondergingen een vasculaire screening. Behandelende artsen ontvingen schriftelijk de resultaten van deze screening en medimencateuze behandeladviezen voor nieuw opgespoorde of onvoldoende behandelde risicofactoren. Na een gemiddelde duur van 2,4 jaar, vroegen we schriftelijk aan een aselecte steekproef van 618 patiënten naar het medicatiegebruik waarvan 534 patiënten een ingevulde vragenlijst retourneerden. Het voorgestelde medicatie-therapieadvies leidde tot een nieuw of veranderd medicatiegebruik bij 52% van de patiënten. De volgzaamheid voor het start medicatie-advies was hoger voor hoge bloedruk (77%) en cholesterol (56%) medicatie dan voor glucose-verlagende medicatie (34%). Concluderend lijkt het geven van medicatie-therapieadvies tot een toename van medicatiegebruik, maar deze toename is marginaal in vergelijking met de trends van toename in de huidige zorg.

In **hoofdstuk 8** werden de effecten van aanvullende zorg van gespecialiseerde verpleegkundigen naast huidige zorg (interventiegroep) vergeleken met alleen de huidige zorg (controlegroep) in het Vascular prEvention by NUrses Study (VENUS) onderzoek. Hiervoor werden 236 patiënten met arterieel vaatlijden en tenminste twee beïnvloedbare traditionele risicofactoren aselect toegewezen tot één van beide groepen. Patiënten in de interventiegroep konden deelnemen aan begeleidingsspreekuren voor leefstijlaanpassing en risicofactor behandeling. Na een gemiddelde duur van 1,2 jaar werden beide patiëntgroepen uitgenodigd voor een meting van risicofactoren. De patiënten in de interventiegroep behaalden meer behandeldoelen voor de bloeddruk, totaal cholesterol, LDL-cholesterol, en de body mass index dan de patiënten in de controlegroep. Het medicatiegebruik nam in beide groepen toe en de kwaliteit van leven bleef gelijk. We concludeerden daarom dat de extra behandeling door gespecialiseerde verpleegkundigen leidt tot een betere behandeling van diverse risicofactoren dan zorg alleen door artsen bij patiënten met arterieel vaatlijden.

In **hoofdstuk 9** worden de beweegredenen en de opzet van het Self-management of vascular Patients Activated by the Internet and Nurses (SPAIN) onderzoek beschreven, waarbij de resultaten in het voorjaar van 2007 worden verwacht. Bij het SPAIN onderzoek staat de ontwikkeling en het gebruik van een beveiligde persoonlijke website centraal. Tijdens een poliklinisch bezoek aan een gespecialiseerde verpleegkundige, worden bij 50 individuele patiënten risicofactoren van hart- en vaatziekten bepaald en maakt elke patiënt met de gespecialiseerde verpleegkundige afspraken over behandeldoelen voor de verhoogde risicofactoren. Tevens ontvangen alle patiënten een gebruikersnaam en wachtwoord voor toegang tot de persoonlijke webpagina's. Patiënten kunnen thuis zelfstandig nieuwe metingen invoeren bij de risicofactoren die vastgesteld zijn en worden tevens gestimuleerd om gebruik te maken van de e-mail faciliteit. De gespecialiseerde verpleegkundige beantwoordt e-mail berichten op werkdagen en geeft digitale ondersteuning en behandeling om de behandeldoelen te bereiken. Na zes maanden, worden de risicofactoren nogmaals bepaald tijdens een poliklinisch bezoek. Op basis van inlogpogingen, e-mail correspondentie, voor- en nameting van de risicofactoren, en gedragsbeïnvloedende factoren geeft dit onderzoek inzicht in de haalbaarheid van risicofactor-begeleiding door een gespecialiseerde verpleegkundige via het Internet.

Ten slotte worden in de algemene discussie in **hoofdstuk 10** de onderwerpen risicovoorspelling en risicoverlaging geïntegreerd met bevindingen van studies in dit proefschrift. Daarnaast worden de belangrijkste conclusies van dit proefschrift opgesomd. Deze zijn:

- Door de aanwezigheid van ongunstige risicofacoren en / of arterieel vaatlijden neemt de levensverwachting af.
- De prevalentie van niet symptomatisch vaatlijden op andere plaatsen is laag, gestandaardiseerde diagnostiek is geen meerwaarde in het opsporen van niet symptomatisch vaatlijden.
- De aanwezigheid van een niet symptomatische vernauwing van de halsslagader is een onafhankelijke voorspeller voor een nieuwe uiting van vaatziekte.
- De bestaande modellen om nieuwe vaataandoeningen te voorspellen, bestemd voor gezonde mensen, onderschatten het risico bij patiënten met arterieel vaatlijden.

- Het nieuw ontworpen model kan een nieuwe uiting van vaatziekte bij patiënten met arterieel vaatlijden beter schatten op korte termijn (1 jaar) dan op een langere termijn (3 of 5 jaar).
- Hogere leeftijd, verhoogd homocysteine gehalte, slechte nierfunctie, en coronair lijden geven een verhoogd risico op een nieuwe uiting van vaatziekte bij patiënten met perifeer arterieel vaatlijden.
- Na een periode van 5,5 jaar, worden bij veel patiënten meer risicofactoren vastgesteld met uitzondering van roken en dyslipidemie.
- Het geven van een medicatie-therapieadvies leidt tot een geringe toename in medicatiegebruik ten opzichte van het medicatiegebruik in de huidige zorg zonder deze interventie.
- De inzet van gespecialiseerde verpleegkundigen naast de huidige zorg, resulteert in een betere behandeling van risicofactoren.
- Patiënt-communicatie met een gespecialiseerde verpleegkundige via het Internet, kan een nieuwe manier van risicofactor behandeling zijn.

Dankwoord

Één van de laatste klusjes maar zeker niet het minst belangrijke!
Naast een computer, begeleiding, patiëntgegevens, en literatuur kunnen ook doorzettingsvermogen en ontspanning niet ontbreken om tot een voldaan einde te komen.

Prof. dr. Y. van der Graaf en dr. F.L.J. Visseren, samen zijn jullie een goed team dat elkaar aanvult en ondanks het frequente contact blijft er altijd nog voldoende gespreksstof over.
Beste Yolanda, ik ben je eerste "niet echte" SMART dokter maar al snel werd ik als echte SMART dokter gezien. Dank voor het vertrouwen dat je in me had en ook voor de complimentjes als ik het eens donker inzag.
Beste Frank, ondanks je vele werkzaamheden stond je deur wagenwijd open. Door jouw enthousiasme crossten we samen op de derde en vierde kerstdag in de sneeuw door het land om ook de laatste patiëntgegevens te verzamelen. Van een cholesterolarme lunch in Meppel tot een met rook doortrokken leefkamer in Lochem, zagen we hoe de SMART-patiënten echt leven.

De beoordelingscommissie bestaande uit Prof. dr. W.P.Th.M. Mali, Prof. dr. L.J. Kappelle, Prof. dr. F.L. Moll van het UMC Utrecht en Prof. dr. R.J.G. Peeters van het AMC, wil ik graag danken voor hun bereidheid om plaats te nemen in de commissie.

Mijn dank gaat ook uit naar de SMART-patiënten, of het nu gaat om het invullen van één of meerdere vragenlijsten, een enquête, de komst naar het UMC Utrecht voor een meting of een afspraak bij de nurse practitioner, jullie laten het niet afweten!

De Smarties, of het nu een front- of een back-office wordt, hopelijk blijft het nog lang zo'n gezellig en goedwerkend geheel. Van arts-onderzoekers (Jeroen, Joke, Martijn, Fleur, Beate, Auke, Audrey, Petra, Arnoud), verpleegkundigen (Loes, Hettie, Vera, Anneke, Lies, Ursula), doktersassistente (Cindy), werkstudenten, hoogbegaafde secretaresse (Kim), duizendpoot (Sabita) tot ristelende manager (Harry) allen met een bijzondere persoonlijkheid. Ik heb veel van jullie geleerd en genoten van de warmte, mooie pen, en natuurlijk de traditionele (non)-alcoholische etentjes. Ook dank voor alle hulp bij kopieer- en verzendklusjes.

Collega-promovendi zijn er vele, afkomstig uit alle windstreken en ieder met zijn of haar eigen werkwijze maar allemaal met hetzelfde doel: promoveren. Ik kan jullie helaas niet allemaal noemen. Kamer 6.118 introduceerde me in het leventje van een fulltime onderzoeker. Al snel kreeg ik handige tips en voelde ik me thuis. Dank voor de gezelligheid en ons jaarlijks kano-uitje of variant daarop. Het is leuk om ieders ingeslagen wegen te volgen.
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Martijn, bijna alle varianten van snoep hebben we gehad, de gesprekken varieerden van welke kleur tot de kilo-verwekkende varianten. Ik weet dat je een halve pagina over jezelf wilt lezen maar weinig woorden zeggen vaak meer!
Esther, ook al zit je op de buurkamer, je bijna dagelijks "bakje" behoren toch wel tot de rituelen van 6.103.
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Curriculum Vitae

Nadine Goessens was born as part of a twin on 30th of December 1976, in Geleen (L). She graduated from the MAVO at the Stedelijke Scholengemeenschap in Roermond in 1993 and from the HAVO at the Walram College in Sittard in 1995. She started her training in Diagnostic Imaging and Radiation Therapy at the Fontys Hogeschool Eindhoven and graduated in June 1999. She continued studying at the University Maastricht, faculty of Health Sciences. During this period she performed a research-project involved a product and process evaluation of the care planning system for people with intellectual disability at the Stichting Pepijn in Echt under supervision of Dr. M. Maaskant, G. Brouns and N. de Jong. She obtained her Master of Science degree in Health Sciences, specialization Health Care Studies, in November 2001. From July 2002 until November 2002, she worked as a research assistant at the Netherlands Cancer Institute. In February 2003 she started working as a PhD-student on the studies described in this thesis at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, under supervision of Dr. F.L.J. Visseren and Prof. Dr. Y. van der Graaf. She obtained her Master of Science in Epidemiology at the Netherlands Institute of Health Sciences, Erasmus Medical Center Rotterdam in June 2005.

Appendix

Members of the SMART Study Group are (alphabetically):

- A. Algra, MD, PhD, Julius Center for Health Sciences and Primary care and Rudolf Magnus Institute for Neurosciences, department of Neurology
- P.A. Doevendans, MD, PhD, department of Cardiology
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