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

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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 to 79 years who had recently received a diagnosis of manifest vascular disease (coronary heart disease, cerebrovascular disease, abdominal aortic aneurysm, or peripheral arterial disease [PAD]) or had a risk factor (hypertension, hyperlipidemia, or diabetes mellitus) were assessed for atherosclerotic risk factors and (other) arterial diseases by noninvasive 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, approximately 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 with cerebrovascular disease (21%); an asymptomatic abdominal aortic aneurysm (≥3.0 cm) in patients with PAD (5%) or cerebrovascular disease (5%); and an asymptomatic carotid stenosis (≥50%) in patients with PAD (15%). On the basis of noninvasive measurements, 73 (13%) of 545 patients initially considered as low risk were reclassified as high risk.**

Conclusions: **This study confirmed a high prevalence and clustering of modifiable atherosclerotic risk factors in high-risk patients. The yield of noninvasive 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 that necessitated immediate medical attention in patients already identified as high-risk patients. (J Vasc Surg 2006; 43:525-32.)**

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 the aging 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 (Table I).[5] 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 noninvasive 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 noninvasive vascular imaging may be useful in detecting vascular abnormalities that necessitate immediate medical attention (eg, aortic aneurysms and 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

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Table I. 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.

study, initiated in 1996, is an ongoing single-center 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 noninvasive diagnostic measurements.

In this cross-sectional study, we assessed the prevalence of atherosclerotic risk factors and investigated the added value of noninvasive imaging for 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]

METHODS

Study setting, patients, and design. The SMART study started in 1996. This ongoing single-center prospective cohort study has enrolled more than 5000 patients referred to the University Medical Center Utrecht for the treatment of clinical manifestations of atherosclerosis (internal carotid artery stenosis, transient ischemic attack or minor stroke, peripheral arterial disease [PAD], aortic abdominal aneurysm [AAA], 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 II. Asymptomatic patients were those without symptoms of clinically manifest atherosclerosis.

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 noninvasive screening (ankle-brachial pressure index [ABPI], duplex scan of the carotid arteries, ultrasonography of the abdomen, electrocardiogram [ECG]) and laboratory assessment (blood and urine analyses). Patients completed questionnaires on the history of CVD (CHD, PAD, and cerebrovascular disease), 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 from 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 the 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 12-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 on 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 the 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 (US$1098.00) per patient in 2004.

Multidisciplinary treatment recommendations. The results of the vascular screening program were discussed at

Table II. 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 min not disappearing after administration of nitrates 2. ST elevation >1 mm in 2 following leads or a left bundle branch block on the ECG 3. CK elevation of at least 2 times the normal value of CK and an 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 ABPI ≤0.90	Arterial operation; PTA leg; amputation leg
Aneurysm of abdominal aorta	Distal aortic anteroposterior diameter ≥3.0 cm and/or distal/proximal ratio ≥1.5 cm	Surgery for aneurysm
Hypertension	Systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or antihypertensive agent use	
Hyperlipidemia	Total cholesterol ≥5.0 mmol/L, LDL cholesterol ≥3.0 mmol/L, or lipid-lowering drug use	
Diabetes mellitus type 1 and 2	Fasting glucose ≥7.0 mmol/L, nonfasting glucose ≥11.0 mmol/L, or oral antidiabetic drug or insulin use	

ECG, Electrocardiogram; *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; *LDL,* low-density lipoprotein.
*Ever or current diagnosis.

weekly meetings of a multidisciplinary team that consisted of an internist, vascular surgeon, cardiologist, nurse practitioner, and, on request, neurologist. The target goals for patients with established CVD were quitting smoking and achieving a body mass index less than 25 kg/m^2, blood pressure less than 140/90 mm Hg, 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, hyperhomocysteinemia,[11,12] obesity,[13] smoking,[14,15] and microproteinuria[16,17]—as well as 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 general practitioner, and further action was left to their discretion. Patients were not informed by mail.

European guidelines on CVD prevention. The objective of the European guidelines on CVD prevention in clinical practice is to reduce the incidence of the 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 increased levels of single risk factors, and those with type 2 diabetes or type 1 diabetes with microalbuminuria are considered at high risk, as are asymptomatic patients with preclinical 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 deviations. The prevalence of atherosclerotic risk factors and asymptomatic arterial disease is expressed as a percentage with corresponding 95% confidence interval. The 10-year risk estimate for fatal CVD was calculated for the potentially low-risk patients with the high-risk SCORE chart.

RESULTS

From September 1, 1996, to March 31, 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 III 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 who presented with AAA (90%). A history of CHD was most common among patients who were referred with AAA (38%). A previous diagnosis of AAA was relatively uncommon. Drug treatment of risk factors was most common in patients with

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

	Referral diagnosis							
Variable	*PAD (n = 604)*	*Cerebro (n = 650)*	*CHD (n = 1034)*	*AAA (n = 239)*	*DM (n = 403)*	*Hyperlipidemia (n = 528)*	*Hypertension (n = 492)*	*Total (n = 3950)*
Male sex	397 (66)	485 (75)	854 (83)	226 (95)	231 (57)	316 (60)	229 (47)	2738 (69)
Age (male), y (SD)	59 (10)	62 (10)	58 (9)	68 (7)	49 (15)	45 (11)	52 (12)	57 (12)
Age (female), y (SD)	59 (12)	60 (11)	61(10)	69 (8)	49 (14)	47 (14)	49 (14)	54 (14)
Systolic BP, mm Hg (SD)	146 (22)	148 (22)	135 (19)	145 (19)	136 (19)	135 (17)	154 (22)	142 (21)
Diastolic BP, mm Hg (SD)	80 (10)	82 (11)	78 (10)	85 (11)	81 (11)	81 (11)	95 (13)	82 (12)
BMI, kg/m^2 (SD)	26 (4)	26 (4)	27 (4)	26 (3)	28 (6)	26 (4)	27 (5)	27 (4)
Ever smoker	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)
Antihypertensive 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)
Antiplatelet agents	272 (45)	504 (78)	761 (74)	101 (42)	59 (15)	78 (15)	70 (14)	1845 (47)

PAD, Peripheral arterial disease; *CHD,* coronary heart disease; *AAA,* abdominal aortic aneurysm; *DM,* diabetes mellitus; *BMI,* body mass index.
Data represent the number of patients (%) or mean (SD); cerebro: cerebrovascular disease.
*Documented as PAD, cerebrovascular disease, CHD, or AAA in history and other than the referral diagnosis.

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

	Referral diagnosis							
Variable	*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 mm Hg and/ or diastolic BP ≥90 mm Hg	339 (58)	408 (65)	382 (38)	139 (60)	273 (69)*	207 (40)	383 (80)	2131 (54)
Impaired glucose tolerance >6.1 to <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 per 1.73 m^2	128 (21)	156 (24)	123 (12)	102 (43)	39 (10)	14 (3)	69 (14)	631 (16)
60-90 mL/min per 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)

PAD, Peripheral arterial disease; *CHD,* coronary heart disease; *AAA,* abdominal aortic aneurysm; *LDL,* low-density lipoprotein; *DM,* diabetes mellitus; *BP,* blood pressure; cerebro: cerebrovascular disease.
Data represent the number of patients (%) or mean (SD).
*Blood pressure <130/80 mm Hg in patients with DM.

CHD and was relatively sparse in patients with other forms of clinically manifest disease.

Table IV shows the prevalence of atherosclerotic risk factors according to the presenting disease. A total of 3448 (87%) of the 3950 patients had hypercholesterolemia (total cholesterol ≥4.5 mmol/L or LDL cholesterol ≥2.5 mmol/L), of which 34% were taking lipid-lowering medication at baseline. A total of 2131 patients were hypertensive (≥140/90 mm Hg), 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 were taking 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, increased homocysteine level, or current smoking), and 73% had two or more risk factors (data not shown).

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 V). An AAA of 5.5 cm or more was rare (in only five patients with CVD). In patients

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

	Referral diagnosis							
Variable	*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
%: 95% CI		21: 18-24	6: 5-8	20: 15-25	5: 3-7	3: 1-4	3: 2-5	8: 7-8
A. carotid stenosis ≥50%†	93		63	28	11	13	19	227
%: 95% CI	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
%: 95% CI	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
%: 95% CI	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
%: 95% CI	0	1	0				0	0

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

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

Variable	*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)
Antihypertensive 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)

PAD, Peripheral arterial disease; *CHD,* coronary heart disease; *AAA,* abdominal aorta aneurysm; *DM,* diabetes mellitus.
Data represent the number of patients (%); cerebro: cerebrovascular disease.

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 increased levels of single risk factors (total cholesterol ≥8.0 mmol/L, LDL cholesterol ≥6.0 mmol/L [n = 165], or blood pressure ≥180/110 mm Hg [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], or 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 VI. The most infrequent use of antiplatelet agents was in patients with AAA (32%), and the most frequent use was in patients with cerebrovascular disease (72%). Antihypertensive 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 took folic acid.

DISCUSSION

This study confirmed a high prevalence and clustering of modifiable atherosclerotic risk factors in high-risk patients. The yield of noninvasive 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 necessitated immediate medical attention in patients already identified as high-risk patients. The high prevalence and clustering of

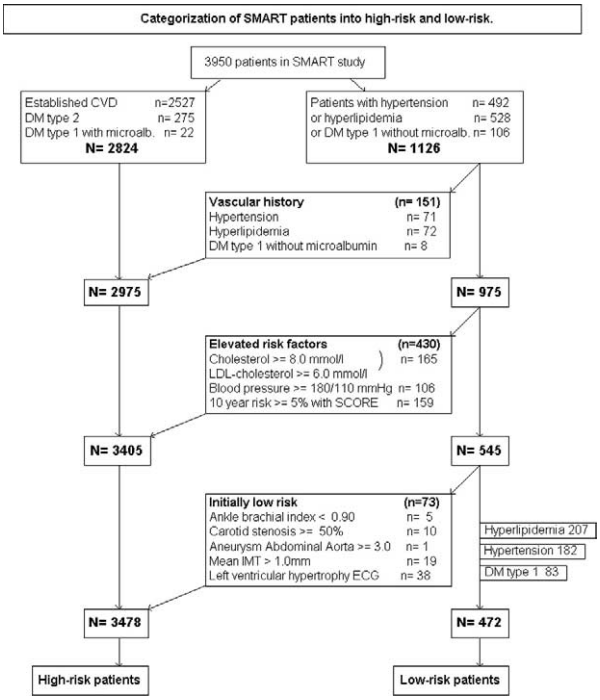

Fig 1. Categorization of Second Manifestations of ARTerial disease *(SMART)* patients into high and low risk. *CVD,* cardiovascular disease; *DM,* diabetes mellitus; *microalb,* microalbuminuria; *LDL,* low-density lipoprotein; *SCORE,* Systematic COronary Risk Evaluation; *IMT,* intima-media thickness;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

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 ultrasonography 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 noninvasive, 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 noninvasive measurements, 73 patients (13%) could be reclassified from the initially low-risk group to the high-risk category (Fig). The measurement with the highest yield of newly detected high-risk patients was an ECG fulfilling the criteria of left ventricular hypertrophy (38 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%) AAAs among 918 patients with hypertension.[32] We found a reduced ABPI in five low-risk patients. The prevalence of PAD was much higher (approximately 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 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 have published results of additional noninvasive 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 that some trials have shown that carotid endarterectomy in asymptomatic patients resulted in small reductions in the incidence of transient cerebral ischemia,[21] nondisabling 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 with 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 ≥50% was mostly found in patients with PAD (15%) as well as a carotid stenosis of 70% or more (11%), and a dilated abdominal aorta 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 ≥3.0 cm and ≤5.5 cm) 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 be justified only 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 V).

The prevalence of asymptomatic vascular abnormalities necessitating 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, and diabetes) and 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 noninvasive 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 noninvasive vascular screening in patients already at high risk for the development of vascular diseases has little added benefit and cannot be recommended in general practice.

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AUTHOR CONTRIBUTIONS

Conception and design: BMBG, FLJV, YvdG
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Data collection: BMBG, FLJV, AA, JDB, YvdG
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Critical revision of the article: FLJV, AA, JDB, YvdG
Final approval of the article: FLJV, YvdG
Statistical analysis: BMBG
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APPENDIX

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