Hypertension–related organ damage and vascular disease

Joris Vernooij

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Hypertension-related organ damage and vascular disease

Hoge bloeddruk gerelateerde orgaanschade en vaatziekten
(met een samenvatting in het Nederlands)

Proefschrift

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Joris Willem Pieter Vernooij

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Promotoren
Prof.dr. F.L.J. Visseren
Prof.dr. Y. van der Graaf

Co-promotor
Dr. W. Spiering

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Contents

Chapter 1

General introduction

Blood pressure and hypertension

Hypertension received worldwide attention starting April 12th, 1945. That day Franklin Roosevelt, the 32nd president of the United States, died while he had been in excellent health according to his treating physicians.[1] His blood pressure had been methodically recorded and rose to 300/190 mmHg at the time he died from a cerebral hemorrhage. Those days it was clear that enough blood pressure was essential for a person's well being and the common principle was that "Hypertension may be an important compensatory mechanism which should not be tampered with."[2] The death of a president initiated a paradigm shift from high blood pressure being essential to perfuse organs to hypertension as a separate disease entity.[3]

On a global scale hypertension is a leading cause of the global burden of disease.[4] Approximately 2/3 of stroke and 1/2 of ischemic heart disease is attributable to high blood pressure. It is estimated that 13.5% of the global deaths and 6.0% of the disability-adjusted life years are due to high blood pressure.

In healthy subjects the optimal systolic blood pressure is thought to be around 115 mmHg, as this blood pressure is associated with the lowest risk of vascular (and overall) mortality in cohort studies[5] and is the mean systolic blood pressure in populations with very low prevalence of vascular disease.[6,7] Blood pressure is normally distributed in the population and there is no natural cut-off point above were blood pressure is too high and can be considered to be hypertension and below which can be considered normal. The threshold for defining hypertension has been progressively lowered over the past 50 years based on cohort studies and based on trial data, showing benefit at reducing vascular morbidity and mortality with progressively lower blood pressure thresholds. More than a quarter of the world population is already hypertensive (RR >140/90 and/or use of blood pressure-lowering medication) and this number is likely to increase.[8] In the Netherlands 42% of the general population has hypertension (RR >140/90 and/or use of blood pressure-lowering medication) with a control rate of only 35%, based on observational data from 2008.[9] Thus there is a dire need for research on the causes of hypertension and more effective treatment strategies.

Causes of hypertension

Blood pressure is the product of cardiac output and peripheral arterial resistance (Ohms law). Regulation of the blood pressure involves cross talk between the kidney, the heart and the brain via neurohumoral systems and local paracrine and intracellular feedback loops. The nervous system has baroreceptors in high and low pressure zones and via the autonomic nervous system efferent signals go to the heart, the peripheral arteries and the kidney.[10] Most likely the kidney also has afferent autonomic nerve signals to the brain.[11] Hormonal systems involved in blood pressure regulation are the renin-angiotensin-aldosterone system (RAAS), the natriuretic peptide system, the adrenals, endothelium-derived hormones (like endothelin) and more. The final common pathway of all systems is the sodium-fluid balance and vasomotor tone. The pathophysiology of hypertension involves

multiple genetic, environmental and behavioral factors involved in the various regulating systems.[12,13] Many secondary causes of hypertension can be distinguished, among which impaired renal function[14] and obesity.[15] Impaired renal function in the end results in sodium and fluid retention,[16] activation of the RAAS and the sympathetic nervous system,[17] thus increasing both the cardiac output and the peripheral arterial resistance. Obesity results in a state of chronic inflammation[18,19] by adipose tissue dysfunction and inflammatory adipokines.[20] Like in impaired renal function this stimulates both the sympathetic nervous system[21] and the RAAS. There are indications that adipose tissue has its local RAAS that is stimulated in obesity.[22] The final result is again sodium and fluid retention and increased peripheral resistance.

Hypertension-related organ damage

Hypertension may result in organ damage of the heart, arteries, the kidney and the brain. The pathophysiology of hypertension-induced organ damage is complex. As a result of long lasting elevated blood pressure in large arteries, the elastin fibers degrade from fatigue failure, being replaced by stiffer collagen.[23] This results in loss of elasticity or compliance which can be noticed by an increased pulse wave velocity.[24]

For the heart increased pressure results in an increased workload and a compensating increase in size and number of cardiomyocytes[25] to reduce the increased wall stress. In pathologic cardiac hypertrophy a maladaptive cardiac hypertrophy develops[26] where interstitial edema in the cardiac tissue, interstitial infiltrates, and fibrosis of the left ventricle can be seen.[27] This contributes to increased left ventricular stiffness and reduced compliance, with diastolic dysfunction as a consequence.[28] The changed cardiac tissue is prone to dysrhythmias and sudden death,[29] with an increased oxygen demand and impaired coronary flow.[30] This maladaptive cardiac hypertrophy seems to be the result of a stimulated RAAS,[31] hyperinsulinemia,[32] and a stimulated sympathetic nervous system.[33] As shown above, these pathophysiologic conditions can be the result of obesity. It is not clear whether obesity is directly related to the maladaptive hypertrophy with both an increase in cardiac mass and a change in cardiac histology.

In the kidney hypertension leads to global glomerulosclerosis, tubular atrophy, interstitial fibrosis, and renal arteriosclerosis.[34] With the development of kidney damage, glomerular filtration rate declines and pathologic urinary albumin excretion may occur. Chronic kidney disease is strongly associated with (recurrent) vascular morbidity and mortality.[35,36] Hypertension-induced damage to the kidney is not only the result of an elevated intrarenal blood pressure. Insulin resistance and hyperinsulinemia directly stimulate the rate of protein synthesis, as well as in an alteration in the type of interstitial and basement membrane collagens excreted by mesangial renal cells.[37,38] Insulin also enhances the proliferative action of angiotensin II in the kidney and impairs the insulin-mediated endothelium-dependent vasodilation.[39]

Hypertension induced cardiac and kidney disease share causal factors and both lead to vascular morbidity and mortality. It is not yet clear whether they have an independent or additive relation to vascular morbidity and mortality.

Clinical manifest vascular disease and hypertension

Hypertension is the most important risk factor for all types of stroke: ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage.[40] The vascular stress of high intraluminal pressure can enhance permeability over the blood-brain barrier. Chronic hypertension also impairs cerebral endothelium-dependent dilation and alters the cerebral blood pressure autoregulation.[41] This could be the result of endothelial damage by hypertension-induced chronic shear stress.[42] The alterations in the blood-brain barrier and the changed autoregulation makes the brain in particular vulnerable to chronic hypertension.[43] Endothelial damage and altered blood cell–endothelium interaction can lead to local thrombus formation and ischemic lesions. Endothelial damage makes the vessels prone to atherosclerosis[44] and thus to changes in vessel lumen and thrombus formation.
The strong relation of hypertension with stroke is in contrast to the weaker relation of hypertension with myocardial infarction, 20 mmHg increase in systolic blood pressure is related to a HR of 2.04 (95%CI 1.96 to 2.08) for stroke mortality compared to a HR of 1.75 (95%CI 1.72 to 1.79) for ischemic heart disease mortality.[5] Also, blood pressure-lowering treatment is more efficacious in preventing stroke than in preventing coronary artery disease, a systolic blood pressure reduction of 10 mmHg is related to a HR of 0.59 (95%CI 0.52 to 0.67) for stroke and a HR of 0.78 (95%CI 0.73 to 0.78) for coronary heart disease.[45] Other risk factors play a more important role in the risk for coronary heart disease as 90% of population-attributable risk for acute myocardial infarction is accounted for by hypertension and the other risk factors smoking history, fruit and vegetables consumption, exercise, alcohol, presence of diabetes, abdominal diabetes, psychosocial factors and cholesterol concentration.[46] The difference in vascular hemodynamics between the cerebral and cardiac circulation appears to make the cardiac circulation more prone to atherosclerosis and other risk factors than hypertension alone. Therefore, prevention of myocardial infarction lies even more in treatment of all risk facors.[47]
Treatment of these risk factors, alone or in combination, is proven to be very effective in reducing the risk of all recurrent vascular events (myocardial infarction and ischemic stroke) and death.[48,49] However, in daily clinical practice, treatment goals are often not reached,[50,51] and a large proportion of patients with a clinical manifestation of a vascular disease still are at high residual vascular risk by not reaching treatment targets as advocated in (inter)national guidelines. Therefore there is a need for extra treatment strategies and options. Treatment of vascular risk factors by nurse practitioners has proven to be effective in some extra reduction of cardiovascular riskfactors[52] and vascular risk[53] but this treatment is costly and time-consuming for patients and healthcare professionals, as frequent visits to the outpatient clinic are required. The use of internet is a low-cost method compared to a regular outpatient clinic. Stimulating self-management is shown

to have an extra blood pressure-lowering effect[54] and supporting self-management with an internet-program may add to the effectiveness and cost-effectiveness of a nurse practitioner intervention.

Objectives of this thesis

The aim of this thesis is to determine the prevalence and the risk for vascular events of the combination of hypertension and obesity and several forms of hypertension-related organ damage in patients with clinically manifest vascular disease. Furthermore we aim to determine the effect of an integrated approach to risk factor management with a nurse-led internet-based vascular risk management program for patients with vascular disease. The objectives of this thesis are:

- To determine the prevalence and vascular risk of obesity-related hypertension in patients with vascular disease (chapter 2)
- To determine the relation of abdominal obesity and ECG criteria for LVH and anatomical criteria for LVH in patients with vascular disease (chapter 3)
- To determine the prevalence and the vascular risk of different criteria for left ventricular hypertrophy, impaired renal function and albuminuria in patients with vascular disease (chapter 4 and 5)
- To determine the effect and cost-effectiveness of an internet-based, nurse-led vascular risk factor management program on vascular risk and vascular risk factors (chapter 6 and 7)

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Chapter 2

The prevalence of obesity-related hypertension and risk for new vascular events in patients with vascular diseases

J.W.P. Vernooij

Y. van der Graaf

F.L.J. Visseren

W. Spiering

Obesity, 2012 March 26th

Abstract

Objectives

Higher bodyweight is associated with an increased prevalence of vascular risk factors. Obesity leads to hypertension by various mechanisms, often referred to as obesity-related hypertension. Aim of the present study was to evaluate the prevalence and the vascular risk of the combination of obesity and hypertension in patients with vascular diseases.

Methods

A cohort of patients with various clinical manifest vascular diseases (n=4,868) was screened for vascular risk factors and followed (median follow-up 4.2 years) for the occurrence of vascular events (stroke, myocardial infarction, and vascular death).

Results

The prevalence of obesity was 18% (95%CI 17 to 19%) and the prevalence of hypertension was 83% (95%CI 82 to 84%). The prevalence of the combination of obesity and hypertension was 16% (95%CI 15 to 17%). Patients with high blood pressure combined with a high weight (highest tertile systolic blood pressure (SBP) in the highest tertile BMI) were not at higher risk for new vascular events (HR 1.29; 95%CI 0.89 to 1.88) or mortality (HR 1.18; 95%CI 0.81 to 1.73) compared to patients without high SBP and high BMI (patients in the lowest tertile of SBP in the lowest tertile of BMI). Patients with only high weight did not have an elevated risk either for vascular events (HR 1.34; 95%CI 0.91 to 1.98) or mortality (HR 1.22; 95%CI 0.81 to 1.83) compared to patients without high blood pressure and high weight.

Conclusions

The prevalence of the combination of hypertension and obesity is low in patients with vascular diseases and does not confer a higher risk for recurrent vascular diseases and mortality than each risk factor alone.

Introduction

Obesity is associated with multiple co-morbidities, including hypertension, type 2 diabetes mellitus, dyslipidemia, obstructive sleep apnea, cancer, and vascular diseases.[1,2] Data from the National Health and Nutrition Examination Survey (NHANES) III indicate that the prevalence of hypertension increases progressively with increasing body mass index (BMI) from about 15% among people with a body mass index <25 kg/m^2 to approximately 40% among those with a BMI of ≥30 kg/m^2.[3] Several pathophysiological mechanisms contribute to the occurrence of hypertension in obese patients such as increased sympathetic nervous system activity and up-regulated renin-angiotensin system.[4] Both obesity and hypertension are important risk factors for vascular morbidity and mortality.[5-7]
In patients with vascular diseases the vascular risk of the combination of obesity and hypertension is unclear. An 'obesity paradox' has been reported in patients with heart failure, coronary heart disease, and peripheral arterial disease,[8-10] referring to the inverse relation between bodyweight and the risk of vascular diseases and mortality.[11] How this protective effect of obesity can be explained is subject of debate. Nevertheless, intentional weight loss undoubtedly decreases the risk for future vascular events in these patients.[12,13]
In this study we evaluated in patients with manifest vascular disease, the prevalence and vascular risk of the presence of obesity and hypertension, both apart and combined.

Patients and Methods

Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. Rationale and design of the SMART study have been described previously.[14] In short, the SMART study is an ongoing single-center prospective cohort study that was designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular diseases or a vascular risk factor. The study was approved by the ethics committee of the UMC Utrecht and all patients gave written informed consent. The current study was based on the data of SMART participants included with manifest vascular diseases.

Measurements

Blood pressure was measured with a sphygmomanometric device at both arms and repeated on the side with the highest values. The mean of all obtained measurements was used in the analysis. A standard bladder (12–13 cm long and 35 cm wide) was used and according to the patient a larger or a smaller bladder was chosen. Glucose, insulin, lipids, and creatinine were obtained after an overnight fast. Urine albumin/creatinine ratio was determined in a first morning-void urine sample.

Definitions

Type 2 diabetes mellitus was defined as a referral diagnosis of type 2 diabetes mellitus, use of glucose-lowering medication, or fasting glucose ≥7.0 mmol/l at screening and receiving treatment with glucose-lowering medication within 1 year after inclusion. In this way, type 2 diabetes mellitus also included newly diagnosed patients with type 2 diabetes mellitus. The four-variable Modification of Diet in Renal Disease (MDRD) equation was used to calculate estimated glomerular filtration rate (eGFR).[15]

Microalbuminuria was defined as an urine albumin/creatinine ratio between 2.5 and 25 mg/mmol in men and between 3.5 and 35 mg/mmol in women. Macroalbuminuria was defined as an urine albumin/creatinine ratio of ≥25 mg/mmol in men and ≥35 mg/mmol in women.[16]

Follow-up and outcome evaluation

Patients provided information on hospitalization and out-patient clinic visits in response to a short questionnaire every 6 months. When a vascular event was reported, original source documents were retrieved and reviewed to determine the occurrence of vascular diseases. All possible events were audited independently by three members of the Endpoint Committee. Patients were followed until death or refusal of further participation. The main outcome of interest for this study was all-cause mortality and a composite of first occurrence of non-fatal stroke, non-fatal myocardial infarction or vascular death (vascular events). The study period was from 1996 to 2008 with a median follow-up of 4.2 years (interquartile range 2.1 to 7.1 years) and a total of 22,682 patients years of follow-up in which 605 vascular events occurred and 593 patients died.

Definitions of events

Myocardial infarction: At least two of the following criteria: (1) chest pain for at least 20 minutes, not disappearing after administration of nitrates; (2) ST-elevation >1 mm in two following leads or a left bundle branch block on the electrocardiogram; (3) creatine kinase elevation of at least two times the normal value of creatine kinase and a myocardial band-fraction >5% of the total creatine kinase.

Stroke: relevant clinical features causing an increase in impairment of at least one grade on the modified Rankin scale, accompanied by an infarction or hemorrhage on a CT scan and clinical deficits causing an increase in impairment of at least one grade on the modified Rankin scale, without CT documentation. Vascular death: sudden death (unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence), death from ischemic stroke, intracerebral hemorrhage, myocardial infarction, congestive heart failure, or acute aorta aneurysm rupture.

Vascular events is a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death.

Data analysis

Results are expressed as means with standard deviations or as absolute numbers and percentages unless otherwise stated. Prevalence of high blood pressure and high weight was assessed by presenting the crude data. Confidence intervals were calculated using the Wald statistic. Linearity was assessed by visual inspection of a plot with deciles of BMI and systolic blood pressure (SBP) versus endpoints. Baseline data of BMI and SBP for the continuous analysis were truncated at 1% and 99% to avoid unproportional influence of the extremes.[17] Age- and gender-adjusted risk for vascular events was estimated with the Cox proportional hazards model and presented as hazard ratios (HR) with 95% confidence intervals (95% CI). The occurrence of vascular events and mortality was equally distributed during the follow up period. The relation of weight and blood pressure was assessed with linear regression analysis. Blood pressure-lowering medication was considered a confounder as it could influence SBP, BMI and outcome.

To investigate whether the relation between BMI and vascular events was modified by SBP, the interaction term (product of BMI and SBP) was included in the regression analyses. Interaction between BMI and SBP was assessed for BMI continuous and the analyses within tertiles of BMI. If the p-value of the interaction term was ≤0.05 effect-modification was considered to be present. All statistical analyses were performed with SPSS 15.0.1.1 for Windows (SPSS, Chicago, Illinois, USA).

Results

Baseline characteristics

Baseline characteristics of the 3,615 men and 1,253 women with manifest vascular diseases are shown in Table 1. The study population was middle aged (60 ± 10 years), predominantly male (74%), most frequent had a history of coronary artery disease (59%) and 16% of the study population had type 2 diabetes mellitus. Mean BMI was 26.8 ± 3.8 kg/m^2 and the mean SBP was 142 ± 21 mmHg. 64% of the patients used up to one blood

Figure 1
Prevalence of the combination of hypertension and body mass index categories

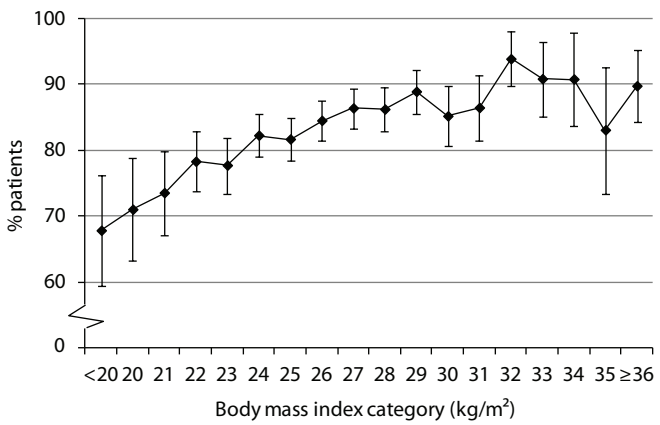

Table 1
Baseline characteristics

			Body mass index		
			Tertile 1	Tertile 2	Tertile 3
			(n=1,624)	(n=1,624)	(n=1,620)
Body mass index, kg/m^2			22.9 (1.6)	26.4 (0.9)	31.1 (2.7)
Body mass index range			18.9-25.0	25.0-28.0	28.0-38.4
Age, years			60 (11)	61 (10)	59 (10)
Male gender, n (%)			1,148 (71)	1,285 (79)	1,182 (73)
Ever smoking, n (%)			1,305 (80)	1,317 (81)	1,294 (80)
Total cholesterol, mmol/l			5.1 (1.2)	5.0 (1.3)	5.0 (1.2)
HDL-cholesterol, mmol/l			1.3 (0.4)	1.2 (0.3)	1.1 (0.3)
Triglycerides, mmol/l			1.3 [1.0-1.8]	1.5 [1.1-2.1]	1.7 [1.2-2.4]
LDL-cholesterol, mmol/l			3.1 (1.1)	3.0 (1.1)	2.9 (1.0)
Glucose, mmol/l			5.5 [5.1-6.1]	5.7 [5.3-6.4]	6.0 [5.5-7.0]
Systolic blood pressure, mmHg			141 (22)	142 (21)	143 (20)
Diastolic blood pressure, mmHg			81 (12)	82 (11)	83 (11)
eGFR, ml/min/1.73 m^2			75.5 (19.8)	75.1 (17.8)	76.4 (18.5)
Albuminuria	-micro, n (%)		267 (16)	221 (14)	270 (17)
	-macro, n (%)		45 (3)	40 (2)	42 (3)
Metabolic syndrome, n (%)			368 (23)	637 (39)	1,105 (68)
Coronary artery disease, n (%)			795 (49)	1,015 (63)	1,057 (65)
Cerebrovascular disease, n (%)			525 (32)	448 (28)	413 (25)
Peripheral arterial disease, n (%)			579 (36)	450 (28)	413 (25)
Type 2 diabetes mellitus, n (%)			167 (10)	241 (15)	369 (23)
Number of blood pressure- lowering medication, n (%)		0	685 (42)	525 (32)	393 (24)
		1	479 (29)	537 (33)	490 (30)
		2	332 (20)	364 (22)	451 (28)
		≥3	128 (8)	198 (12)	286 (18)
		Total	1.0 (1.0)	1.2 (1.1)	1.4 (1.1)
Platelet aggregation inhibitors, n (%)			1,126 (69)	1,201 (74)	1,243 (77)
Lipid lowering medication, n (%)			776 (48)	932 (57)	1,009 (62)

eGFR: estimated glomerular filtration rate
Metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III criteria
Data are expressed as mean (standard deviation), as number (percentage), or as median [interquartile range]

pressure-lowering medication, mostly a beta-blocker (47%). Across tertiles of BMI, triglycerides, glucose and presence of metabolic syndrome appeared to increase but LDL-cholesterol and blood pressure were similar. Confounders like age, gender and smoking appeared not to differ across BMI tertiles and so were parameters about severity of disease (eGFR, albuminuria and medical history).

Prevalence of hypertension and obesity

The prevalence of hypertension (SBP ≥140 mmHg and/or use of blood pressure-lowering medication) was 83% (95%CI 82 to 84%), the prevalence of overweight (BMI ≥25 kg/m^2) was 66% (95%CI 65 to 67%) and the prevalence of obesity (BMI ≥30 kg/m^2) was 18% (95%CI 17 to 19%). The prevalence of the combined presence of overweight and hypertension was 57% (95%CI 56 to 58%). The prevalence of the combined presence of obesity and hypertension was 16% (95%CI 15 to 17%) and was mainly determined by the prevalence of obesity. Adding diastolic blood pressure criterion to the definition of hypertension did not alter the prevalence of the combination of obesity and hypertension.

The prevalence of hypertension stratified per unit BMI varied from 71% (95%CI 63 to 79%) in BMI category 20-20.9 kg/m^2 to 85% (95%CI 73 to 93%) in BMI category 34-34.9 kg/m^2 (Figure 1). Linear regression analysis also showed a small increase of SBP with increasing BMI: per unit BMI (1 kg/m^2) SBP increased with 0.3 mmHg (ß=0.28 95%CI 0.13 to 0.42, adjusted for age and gender).

Risk for vascular events or mortality of obesity and hypertension

There was a 2% lower risk per 1 kg/m^2 increase in BMI for vascular events (HR 0.98; 95%CI 0.96 to 1.01), and a 3% statistically different lower risk per 1 kg/m^2 increase in BMI for all-cause mortality (HR 0.97; 95%CI 0.94 to 0.99) (Table 2). Additional adjustment for smoking did not alter the results. Per 10 mmHg increase in SBP the risk for vascular events increased by 4% (HR 1.04; 95%CI 1.00 to 1.08) and for all-cause mortality with 3% (HR 1.03; 95%CI 0.99 to 1.07), although the latter was not statistically significant. There was no interaction between BMI and SBP on the occurrence of vascular events (p=0.10) and all-cause mortality (p=0.09). Results for the patients with type 2 diabetes mellitus did not differ (data not shown).

To investigate whether the results were driven by one form of vascular disease we stratified for coronary artery disease, cerebrovascular disease and peripheral arterial disease (Table 3). The results showed that the risk of SBP for vascular events and all-cause mortality was mainly increased in patients with cerebrovascular disease. The risk of BMI for vascular events and all-cause mortality was mainly decreased in patients with peripheral arterial disease. These results should be viewed with caution as the number of events in strata of vascular disease are limited.

Table 2
Risk of systolic blood pressure and body mass index for vascular events and all-cause mortality

					Excluding events first 6 months*	
	events (n)	model	Systolic blood pressure per 10 mmHg HR (95%CI)	Body mass index per 1 kg/m^2 HR (95%CI)	events (n)	Body mass index per 1 kg/m^2 HR (95%CI)
Vascular events	608	I	1.04 (1.00 to 1.08)	0.98 (0.96 to 1.01)	517	0.99 (0.96 to 1.01)
		II	1.04 (1.00 to 1.08)	0.98 (0.96 to 1.00)		0.98 (0.96 to 1.01)
		III	-	0.98 (0.96 to 1.01)		0.98 (0.96 to 1.01)
		IV	1.04 (1.00 to 1.08)	-		-
		V	1.02 (0.99 to 1.07)	0.98 (0.95 to 1.00)		0.98 (0.95 to 1.00)
All-cause mortality	591	I	1.03 (0.99 to 1.07)	0.97 (0.94 to 0.99)	542	0.97 (0.94 to 0.99)
		II	1.03 (0.99 to 1.07)	0.97 (0.94 to 0.99)		0.97 (0.94 to 0.99)
		III	-	0.97 (0.94 to 0.99)		0.97 (0.94 to 0.99)
		IV	1.03 (0.99 to 1.07)	-		-
		V	1.02 (0.98 to 1.06)	0.96 (0.93 to 0.98)		0.96 (0.93 to 0.98)

model I: adjusted for age and gender

model II: model I + smoking and blood pressure-lowering medication

model III: model I + systolic blood pressure

model IV: model I + body mass index

model V: model I + number of vascular manifestations at inclusion

Vascular events is a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death.

HR indicates the increase or decrease in risk for an event. For example: per 10 mmHg increase in systolic blood pressure the risk for vascular events increases with 4%.

*To address the issue of potential reverse causality in the relation of body mass index and occurrence of vascular events or mortality, patients with an endpoint in the first 6 months were excluded in these analyses.

Table 3
Risk of systolic blood pressure and body mass index for vascular events and all-cause mortality in patients with different forms of vascular disease

		events (n)	Systolic blood pressure per 10 mmHg HR (95%CI)	Body mass index per 1kg/m^2 HR (95%CI)
Vascular events	Coronary artery disease	171	0.94 (0.87 to 1.02)	1.01 (0.97 to 1.06)
	Cerebrovascular disease	166	1.10 (1.02 to 1.18)	1.00 (0.96 to 1.05)
	Peripheral arterial disease	272	1.01 (0.95 to 1.07)	0.98 (0.95 to 1.01)
All-cause mortality	Coronary artery disease	127	0.96 (0.87 to 1.05)	1.04 (0.98 to 1.09)
	Cerebrovascular disease	161	1.10 (1.02 to 1.19)	1.01 (0.96 to 1.06)
	Peripheral arterial disease	303	0.97 (0.92 to 1.03)	0.94 (0.91 to 0.97)

Vascular events is a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death.

Hazard ratios are adjusted for age and gender.

Analyzing the risk of SBP for new vascular events and mortality within tertiles of BMI revealed that within each tertile of BMI the HRs for the vascular events and all-cause mortality were equal (Figure 2). Only in the first BMI tertile high SBP was associated with a higher risk for vascular events (HR 1.64; 95%CI 1.16 to 2.32) and mortality (HR 1.55; 95%CI 1.10 to 2.20), compared to the first SBP tertile (reference).

Discussion

In the present study we found a low prevalence of the combined presence of hypertension and obesity in patients with clinical manifest vascular diseases. Blood pressure increased only marginally with increasing BMI. The combination of obesity and hypertension did not add to the risk for vascular events and all-cause mortality compared to none or one of these risk factors. Increasing BMI was related to a lower risk for vascular events and all-cause mortality, pointing towards an 'obesity paradox'. Increase in blood pressure was associated with marginally higher risk for vascular events and all-cause mortality.
Our study population consisted of patients with a (recent) clinical manifestation of a vascular disease. The low prevalence of hypertension in combination with obesity is mainly caused by the low prevalence of obesity. In the patients with obesity the prevalence of hypertension is high. Comparing our data with the Dutch data from EUROASPIRE I to III our data showed a somewhat lower prevalence of obesity (18% vs. 19 to 27%) and a somewhat higher prevalence of hypertension (83% vs. 56 to 63%).[18] These differences are probably due to differences in study population.

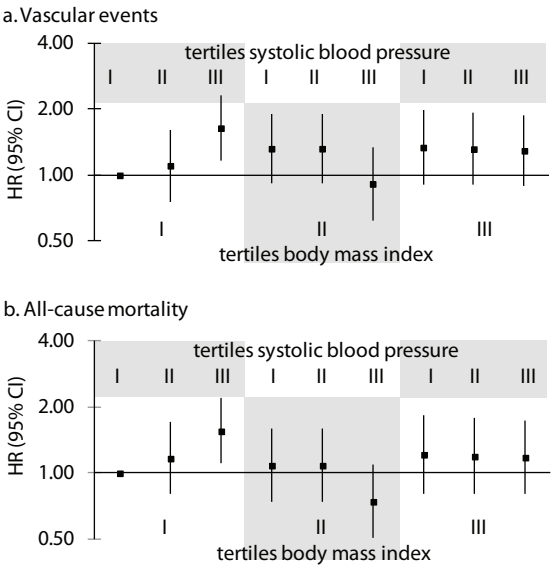

Figure 2
Risk for vascular events and all-cause mortality for combinations of body mass index and systolic blood pressure

Tertiles body mass index and tertiles systolic blood pressure within the tertiles body mass index. Hazard ratio's (HR) adjusted for age and gender compared to the first tertile of systolic blood pressure within the first tertile of body mass index (reference).
Vascular events is a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death.

It should also be noted that there is room for improvement of blood pressure treatment as 64% of the patients only used no or one class of blood pressure-lowering medication. A recent analysis of the same cohort showed increased use of blood pressure-lowering medication over the years.[19]

The absence of a clear relation between BMI and the prevalence of hypertension was unexpected. There are several arguments for a causal relation between weight and blood pressure. Observational data from the NHANES showed a steep rise in prevalence of hypertension from 18% to 52% with increasing body weight categories.[3] The difference between the finding in NHANES and our study may be explained by the lower mean age in the NHANES cohort and the fact that the NHANES cohort predominantly consisted of subjects without vascular diseases. In the NHANES cohort the prevalence of hypertension in subjects over 50 years of age was 41% to 74% with increasing bodyweight categories, closer to the prevalence in our cohort. A study in the general (Danish) population showed per 10% increase in BMI a 3.85 mmHg rise in systolic blood pressure.[20] This study used mendelian randomisation, strengthening the argument for a causal relation.

If obesity is a cause of hypertension, the relation between obesity and hypertension may change over time. Long standing hypertension may lead to arterial stiffening and glomerulosclerosis, both causes of hypertension itself. Many patients with vascular diseases are likely to already have hypertension, irrespective of the underlying cause, for a long period leading to arterial stiffening and impaired renal function which caused hypertension independent of obesity. There was also a high prevalence of hypertension in non-obese patients in our cohort. The different association of weight with blood pressure found in our study compared to other studies could therefore be explained by our selection of patients with vascular disease.

The inverse relation between BMI and the risk for vascular events and all-cause mortality points towards an 'obesity paradox': the higher the weight the lower the risk. This has been shown in some subgroups of patients with vascular diseases and is now demonstrated in a population of patients with various vascular diseases. The explanation for this finding is subject of debate. The positive relation of overweight with vascular disease in people without vascular disease shown in other studies could be mediated by progressive insulin resistance, inflammation and changes in adipokine profiles leading to organ damage. It could be that the prognosis of patients with vascular diseases is determined by the organ damage itself and not anymore by the underlying cause of the organ damage.[11] Smoking is a possible confounder in the relation of weight and vascular events or mortality, because smoking is associated with lower bodyweight and increased vascular events and mortality. Nevertheless, in the analysis of the Prospective Studies Collaboration adjusting and stratification for smoking status did not change the relations between overweight or obesity and mortality.[6] In the present study, adjusting for smoking status did not affect the relation between BMI and vascular events or mortality.

Another possible explanation for our discrepant findings may be selection. Patients with overweight have a higher risk of earlier death and are therefore likely to be underrepresented in cohort studies than lean patients.[21] In the present study, adjusting for the num-

ber of vascular diseases at inclusion did not change the results. Exclusion of patients with endpoints within 6 months after inclusion did not change the results either. This does not rule out the possibility of selection of lean high risk patients, but makes this less likely.
In our study there was only a weak association between SBP and vascular events and all-cause mortality. In another study, a twofold increase for the occurrence of vascular diseases was seen for every 20 mmHg elevation of SBP in patients without vascular disease.[5] It could be argued that in our population of patients with vascular diseases the risk for a subsequent vascular disease could be more determined by the disease itself and not by SBP and other vascular risk factors leading to the primary manifestation of vascular disease.
In the lowest BMI tertile (BMI 19 to 25 kg/m^2) of our study there was an increasing risk for vascular events and all-cause mortality with increasing SBP. Although no interaction between SBP and BMI for the occurrence of new vascular events and all-cause mortality was demonstrated, these results cannot exclude the possibility that in lean patients hypertension does confer to a higher risk for new vascular events and all-cause mortality.
Based on the results of our study the concept of obesity-related hypertension in patients with vascular diseases may be questioned. The mechanisms leading to or sustaining hypertension in patients with vascular disease might not be weight-related. In an early stage of atherosclerotic disease overweight could be a cause of increasing blood pressure, but in advanced vascular disease, hypertension is rather the consequence of the vascular disease than of overweight.
A strength of this study is the large prospective cohort of patients with various clinical manifestations of vascular diseases. We also acknowledge study limitations. Patients in the SMART study were referred to a tertiary (academic) referral centre and could have more severe vascular disease than patients referred to a general hospital. Adjusting for severity of disease (number of manifestations of vascular disease) did not change the results. In our definition of hypertension the use of blood pressure-lowering medication was taken into account. Blood pressure-lowering medication may also be prescribed for other indications than hypertension, such as post-myocardial infarction or albuminuria. This could have lead to an overestimation of the prevalence of hypertension. Analysis of the data with exclusion of patients with a cardiac history or with albuminuria or adjusting for the use of blood pressure-lowering medication did not change the prevalence estimates.
In conclusion, we found a low prevalence of the combination of hypertension and obesity in patients with vascular diseases and the combination of hypertension and obesity does not confer a higher risk for recurrent vascular diseases and mortality than each risk factor alone.

Acknowledgments

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Chapter 3

Relation between abdominal obesity, insulin resistance and left ventricular hypertrophy diagnosed by electrocardiogram and magnetic resonance imaging in hypertensive patients

J.W.P. Vernooij

M.J.M. Cramer

F.L.J. Visseren

M.J. Korndewal

M.L. Bots

M.F.L. Meijs

P.A.F.M. Doevendans

W. Spiering

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Abstract

Objective

Obesity is related to left ventricular hypertrophy (LVH). Whether LVH criteria on ECG are a result of increased cardiac electrical activity, or due to increased left ventricular mass (LVM) remains to be determined. Intent of the present study was to investigate the relation between obesity and LVH criteria on ECG (ECG-LVH) and LVM by MRI (MRI-LVM) in patients with hypertension and to investigate the relation of insulin resistance (IR) and LVH.

Methods

Patients with hypertension (n=421) were evaluated by Sokolow-Lyon voltage, Cornell voltage and by cardiac MRI. Waist was used as a measurement of abdominal obesity.

Results

Linear regression analysis revealed an inverse relation (adjusted β -0.02; 95%CI -0.02 to -0.01) between waist and Sokolow-Lyon voltage. This indicates a decrease of 0.02 mV per cm increase of waist. There was a positive relation between waist and MRI-LVM (β 0.49; 95%CI 0.32-0.67). Patients in the highest quartile of LVM had a worse metabolic profile than patients with the Sokolow-Lyon voltage criterion. The relations of IR with ECG-LVH and MRI-LVM were similar to those of waist in relation to ECG-LVH and MRI-LVM.

Conclusions

There is an inverse relation between waist and ECG-LVH and a positive relation between waist and MRI-LVM. This study indicates that obesity has a different relation to voltage criteria for LVH as to anatomical criteria for LVH, supporting the hypothesis that IR decreases ECG voltages, despite an increase in MRI-LVM. The clinical implication will be that especially in patients with IR the Sokolow-Lyon voltage is low in contrast to a high MRI-LVM.

Introduction

Insulin acts as a growth factor in many tissues, including the heart, leading to hypertrophy.[1] In an insulin resistant (IR) state, plasma concentrations of insulin are usually elevated, together with changes in plasma adipokines, inflammation and the thrombotic system which may all influence cardiac tissue histology.[2] Hypertension is more prevalent in obesity[3] and in IR states[4] and is a key component in the clustering of vascular risk factors closely associated with abdominal obesity, which is also known to be associated with left ventricular hypertrophy (LVH).[5,6] Myocardial fatty acid oxidation, as measured with cardiac positron emission tomography, is decreased in LVH patients pointing to a changed myocardial fatty acid metabolism as seen in IR in other organs.[7] Therefore, it is likely that IR contributes to the changes in cardiac tissue seen in LVH. Our hypothesis is that abdominal obesity has a different relation to electrical criteria for LVH as to anatomical criteria for LVH in patients with hypertension. In the present study we evaluated the relation between electrical (ECG) and anatomical (MRI) LVH and obesity as measured by waist circumference, as well as the relations between LVH and visceral fat and between LVH and IR.

Methods

Patients originate from the SMART cohort (Second Manifestations of Arterial diseases). The SMART study cohort consists of patients referred to the University Medical Center Utrecht with clinical manifest cardiovascular disease (cardiac, cerebral and peripheral vascular disease or aneurysm of the abdominal aorta) or marked risk factors for cardiovascular disorders (e.g. hypertension, diabetes mellitus, dyslipidemia).[8] All patients underwent extensive screening for cardiovascular risk factors at inclusion. The local Medical Ethics Committee approved the SMART-study and all subjects gave their written informed consent. For this study we randomly selected 1,273 subjects from the SMART population having had hypertension for at least 3 years and who were free from previous symptomatic coronary or valvular heart disease. Subjects with severe concomitant illness (n=8), or contraindications to MRI examination (including claustrophobia; n=34) were excluded. Five-hundred and thirty-six subjects agreed to participate.

For this analysis patients were included in the period of January 1999 to July 2006 with routine measurement of waist circumference. Exclusion followed in case of missing crucial parameters (i.e. ECG; n=32, waist circumference; n=61) or an ECG where LVH could not be evaluated because of a bundle branch block (QRS duration >120 msec; n=22). This left a study population of 421 patients. Measurement of visceral fat was available from May 2000 onward (n=346) and measurement of fasting insulin from July 2003 onwards. Patients with type 2 diabetes mellitus were excluded because the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) as a measure of IR is not reliable in these patients.[9] In this subset of patients with available data on fasting insulin levels 117 patients were evaluated.

Waist circumference was measured halfway between the lower rib and iliac crest and was taken in standing position. A well-trained registered vascular technologist in a certified vascular laboratory performed ultrasonographic measurements (without a bowel preparation) in supine position using an ATL HDI 3000 (Philips Medical Systems, Eindhoven, Netherlands) with a C 4-2 transducer. Intra-abdominal visceral fat was measured as the distance between the peritoneum and the lumbar spine or psoas muscles using electronic calipers at the end of a quiet inspiration, applying minimal pressure without displacement or compression of the abdominal cavity.

A 12-lead ECG was recorded at 25 mm/s and 1 mV/cm calibration. QRS-duration was calculated by the ECG-device according to a standardized formula. Two independent readers manually obtained the voltage- amplitude of R-waves and S-deflections used for the LVH criteria, as well as the cardiac rhythm and T-top flattening or inversion. Differences were discussed and corrected. LVH on ECG was determined with Sokolow-Lyon voltage (S in V_1 + R in V_5 or V_6 whichever is larger) and the Sokolow-Lyon voltage criterion with a cut-off value of ≥3.5 mV;[10] Sokolow-Lyon voltage product is calculated as the Sokolow-Lyon voltage x QRS duration (ms).[11] Cornell voltage was calculated as S(V_3) + R(aVL) and the Cornell voltage criterion with a cut-off value of >2.8 mV in men and >2.0 mV in women.[12] Cornell voltage product was calculated as the Cornell voltage x QRS-duration (ms).[11]

Plasma glucose, insulin, lipids, and creatinine aswell as urine albumin and creatinine were obtained after an overnight fast. Laboratory assessment of insulin was by immunometric assay (Diagnostic Products Corporation, Los Angeles, USA).

Cardiac MRI was done with a 1.5T Philips Achieva MRI Scanner (Philips Medical Systems, Best, The Netherlands) using a steady state free precession pulse sequence for optimal blood myocardium contrast. These measurements were performed on serial short axis views, using offline dedicated software (ViewForum, Philips Medical Systems) as described previously.[13] The reproducibility of the cardiac MRI readings was determined by calculating in a set of 50 duplicate readings the intraclass correlation coefficient. For intra-observer errors in left ventricular mass (LVM) the intraclass correlation coefficient was 99%, and for inter-observer errors in left ventricular mass it was 97%. For intra-observer errors in LVM the mean difference was 1.1±2.1 g, and for inter-observer errors it was 10.3±5.8 g. With MRI the left ventricular end-diastolic volume was computed using a modified Simpson's rule algorithm. LVM on MRI was calculated as 1.05 x (epicardial volume – endocardial volume) as described earlier.[14] LVM on MRI was used as a continuous variable. There is a body of great writing about partition values for LVH with MRI[14] and values are influenced by differences in technique. In studies using cardiac echo LVH was seen in 15-50% of different populations[15] with a prevalence of around 25% a hypertensive population.[16] Therefore dichotomization was done by using the gender-pooled upper quartile as LVH on MRI. LVM-index was calculated as LVM (g)/height $(m)^{2.7}$. HOMA-IR was calculated by fasting plasma insulin (mU/L) x fasting plasma glucose (mmol/l) / 22.5.[9]

Analysis of the relation between waist circumference and LVH was done by linear regression analysis using SPSS Statistics, version 18.0.2 for Windows. Confounders in the relation between waist circumference and LVH/LVM were age, gender, blood pressure, and use

Table 1
Baseline characteristics

Waist circumference tertiles*	1	2	3
	(n=139)	(n=145)	(n=137)
Waist circumference (cm)	82 (8)	93 (7)	109 (9)
Waist circumference range (cm)	(65-93)	(80-103)	(93-139)
Age (years)	52 (13)	53 (12)	52 (11)
Male gender, n (%)	83 (60)	81 (56)	80 (58)
Systolic blood pressure (mmHg)	150 (19)	149 (21)	149 (20)
Diastolic blood pressure (mmHg)	89 (11)	90 (12)	92 (11)
Body mass index (kg/m^2)	23.9 (2.9)	26.6 (2.6)	32.1 (4.7)
Visceral fat (cm)	7.2 (1.9)	8.4 (2.2)	11.2 (2.8)
Total cholesterol (mmol/l)	5.5 (1.2)	5.6 (1.3)	5.4 (1.2)
HDL-cholesterol (mmol/l)	1.5 (0.5)	1.3 (0.4)	1.2 (0.4)
Triglycerides (mmol/l)	1.4 [1.0-2.0]	1.5 [1.1-2.6]	2.0 [1.4-2.9]
LDL-cholesterol (mmol/l)	3.3 (1.2)	3.4 (1.0)	3.1 (1.1)
Glucose (mmol/l)	5.4 [5.1-5.9]	5.7 [5.2-6.2]	5.9 [5.5-7.5]
Insuline (mU/l)	9 (8)	11 (8)	19 (17)
Homeostasis model assessment of insulin resistance	2.1 (1.8)	3.1 (3.0)	6.0 (7.4)
eGFR (ml/min/1.73m2)	79 (17)	77 (17)	82 (19)
Albuminuria -micro, n (%)	14 (10)	16 (11)	27 (20)
-macro, n (%)	4 (3)	2 (1)	8 (6)
Cerebrovascular disease, n (%)	35 (25)	48 (33)	42 (31)
Peripheral arterial disease, n (%)	9 (6)	10 (7)	11 (8)
Type 2 diabetes mellitus, n (%)	11 (8)	25 (17)	36 (26)
Hypertension, n (%)	122 (88)	131 (90)	130 (95)
Smoking current or previously, n (%)	92 (66)	106 (73)	97 (71)
β-blocker, n (%)	40 (29)	45 (31)	42 (31)
ACE inhibitor or ARB, n (%)	60 (43)	73 (50)	72 (53)
Diuretic, n (%)	19 (14)	18 (12)	25 (18)
Other blood pressure-lowering medication, n (%)	41 (29)	36 (25)	51 (37)
Lipid lowering medication, n (%)	47 (34)	46 (32)	54 (39)
Platelet aggregation inhibitors, n (%)	47 (34)	53 (37)	50 (36)

eGFR indicates estimated glomerular filtration rate, ACE: angiotensin converting enzyme, ARB: angiotensin-II receptor blocker

*Gender pooled tertiles

Data are expressed as mean (standard deviation), as number (percentage), or as median [interquartile range]

of β-blockers and/or ACE-inhibitors and/or angiotensin-II receptor blockers. Models were created with age and gender and with all confounders. A third explorative model was added with BMI as confounder to determine the change in relation of abdominal obesity and LVH when adding another measurement of obesity.

Results

Most patients had hypertension (91%) with 69% using blood pressure-lowering medication and 17% of the patients had albuminuria. Baseline measurements were divided in gender-pooled tertiles of waist circumference showing increasing glucose, triglycerides and prevalence of type 2 diabetes mellitus but no change in blood pressure or medication use per increasing tertile of waist circumference (Table 1). Per increasing tertile of waist circumference both Sokolow-Lyon voltage and the percentage of patients with a positive Sokolow-Lyon voltage criterion were lower (Table 2), whereas Cornell voltage and the percentage of a positive Cornell voltage criterion were comparable per increasing tertile of waist circumference. MRI-LVM appeared to increase per increasing tertile of waist circumference.

Waist circumference showed an inverse relation with Sokolow-Lyon voltage (Table 3a). A cm increase in waist circumference was associated with a decrease in Sokolow-Lyon voltage of 0.02 mV (0.2 mm) (95%CI -0.02 to -0.01mV). The relation of waist circumference with Sokolow-Lyon voltage product was inverse as well. In contrast, the relation between waist circumference with MRI-LVM was a positive relation. Every cm increase in waist circumference was associated with an increase of 0.49g MRI-LVM (95%CI 0.32 to 0.67). No clear relation was found for waist circumference with Cornell voltage and with Cornell

Table 2
Left ventricular hypertrophy by tertiles of waist circumference

Waist circumference tertiles*	1	2	3
Electrocardiogram			
Sokolow-Lyon voltage criterion, n (%)	23 (17)	11 (8)	7 (5)
Sokolow-Lyon voltage (mV)	2.7 (0.9)	2.5 (0.7)	2.2 (0.8)
Cornell voltage criterion, n (%)	8 (6)	13 (9)	10 (7)
Cornell voltage (mV)	1.5 (0.6)	1.6 (0.6)	1.5 (0.5)
Magnetic Resonance Imaging			
Left ventricular mass (g)	101 (27)	104 (28)	114 (29)
Upper quartile left ventricular mass, n (%)*	21 (15)	35 (24)	54 (39)
Left ventricular mass-index (g/$m^{2.7}$)	22 (5)	23 (5)	26 (6)

*Gender pooled

Data are expressed as mean (standard deviation) or as number (percentage)

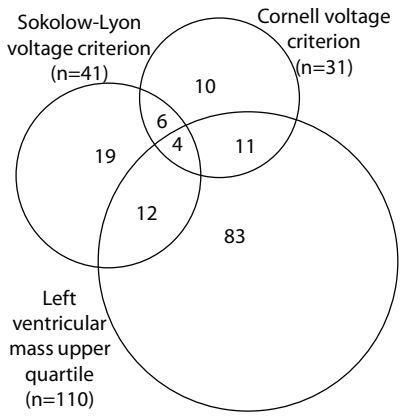

Figure 1
Venn diagram with overlap in left ventricular hypertrophy on electrocardiogram and high left ventricular mass on magnetic resonance imaging

Table 3
Relations between waist circumference and visceral fat and left ventricular hypertrophy

a: Relation between waist circumference and left ventricular hypertrophy (n=421)

	model 1 β (95%CI)	model 2 β (95%CI)	model 3 β (95%CI)
Electrocardiogram			
Sokolow-Lyon voltage (mV)	-0.02 (-0.02 to -0.01)	-0.02 (-0.02 to -0.01)	-0.01 (-0.02 to 0.00)
Sokolow-Lyon product (mV·ms)	-1.66 (-2.26 to -1.06)	-1.69 (-2.27 to-1.12)	-1.13 (-2.08 to -0.19)
Cornell voltage (mV)	-0.001 (-0.005 to 0.003)	-0.001 (-0.005 to 0.003)	-0.004 (-0.010 to 0.003)
Cornell product (mV·ms)	-0.22 (-0.67 to 0.23)	-0.26 (-0.71 to 0.18)	-0.53 (-1.25 to 0.20)
Magnetic Resonance Imaging			
Left ventricular mass (g)	0.49 (0.32 to 0.67)	0.50 (0.33 to 0.67)	0.17 (-0.11 to 0.45)
Left ventricular mass-index (g/m$^{2.7}$)	0.11 (0.07 to 0.15)	0.11 (0.07 to 0.15)	-0.04 (-0.10 to 0.02)

b: Relation between visceral fat and left ventricular hypertrophy (n=346)

	model 1 β (95%CI)	model 2 β (95%CI)	model 3 β (95%CI)
Electrocardiogram			
Sokolow-Lyon voltage (mV)	-0.06 (-0.09 to -0.03)	-0.06 (-0.09 to -0.03)	-0.02 (-0.06 to 0.01)
Sokolow-Lyon product (mV·ms)	-6.27 (-9.57 to -2.97)	-6.50 (-9.68 to -3.32)	-3.15 (-7.14 to 0.85)
Cornell voltage (mV)	0.007 (-0.016 to 0.030)	0.007 (-0.016 to 0.029)	0.018 (-0.010 to 0.047)
Cornell product (mV·ms)	-0.17 (-2.58 to 2.25)	-0.18 (-2.57 to 2.21)	0.83 (-2.20 to 3.85)
Magnetic Resonance Imaging			
Left ventricular mass (g)	1.57 (0.62 to 2.51)	1.63 (0.68 to 2.58)	0.00 (-1.17 to 1.17)
Left ventricular mass-index (g/m$^{2.7}$)	0.45 (0.23 to 0.67)	0.46 (0.24 to 0.69)	0.01 (-0.26 to 0.28)

model 1: age, gender

model 2: model 1 plus systolic blood pressure, use of β-blocker, ACE-inhibitor or angiotensin-II receptor blocker

model 3: model 2 plus body mass index

Intra abdominal visceral fat was measured in cm by abdominal echography
The β indicates the negative or positive relation of a determinant with the outcome. A β of -0.02 for Sokolow-Lyon voltage indicates a decrease of 0.02 mV per cm increase of waist circumference.

Table 4
Clinical characteristics of patients according to left ventricular hypertrophy criteria

	Sokolow-Lyon voltage criterion	Cornell voltage criterion	Upper quartile left ventricular mass*
n (%)	41 (10)	31 (7)	110 (26)
Age (years)	51 (14)	54 (9)	49 (12)
Male gender, n (%)	23 (56)	8 (26)	63 (57)
Systolic blood pressure (mmHg)	153 (24)	159 (22)	149 (21)
Diastolic blood pressure (mmHg)	92 (12)	97 (12)	91 (11)
Body mass index (kg/m^2)	25.1 (4.0)	27.1 (4.5)	29.8 (5.6)
Waist circumference (cm)	88 (12)	91 (11)	99 (13)
Visceral fat (cm)	7.9 (2.7)	8.6 (2.7)	9.5 (2.9)
Triglycerides (mmol/l)	1.4 [1.0-2.2]	1.4 [1.1-2.5]	1.8 [1.2-2.8]
Glucose (mmol/l)	5.6 [5.0-6.1]	5.6 [4.8-6.0]	5.8 [5.2-6.6]
Insuline (mU/l)	8 (6)	15 (14)	14 (17)
Homeostasis model assessment of insulin resistance	2.2 (2.3)	4.5 (5.6)	4.3 (7.2)
eGFR (ml/min/1.73m^2)	74 (20)	75 (18)	83 (18)
Albuminuria -micro, n (%)	6 (15)	6 (19)	22 (20)
-macro, n (%)	2 (5)	2 (6)	5 (5)
Cerebrovascular disease, n (%)	11 (27)	6 (19)	30 (27)
Peripheral arterial disease, n (%)	4 (10)	3 (10)	12 (11)
Type 2 diabetes mellitus, n (%)	2 (6)	6 (21)	22 (22)

*Gender pooled

eGFR indicates estimated glomerular filtration rate

Data are expressed as mean (standard deviation), as number (percentage) or as median [interquartile range]

voltage product. When adding BMI to the model the point estimates did not change. The relation between visceral fat and ECG-LVH criteria and MRI-LVM were in general comparable to the results of the analyses with waist circumference (Table 3b).

To better understand the discrepant findings with different ECG-LVH criteria, we evaluated the distribution of the ECG-LVH criteria (Figure 1). The Venn diagram illustrates that there is only limited overlap between the patients with positive Sokolow-Lyon voltage criterion and positive Cornell voltage criterion. Of the 62 patients with a positive ECG criterion, only 10 patients had both criteria positive (15%). Similarly, the overlap between ECG-LVH criteria and high MRI-LVM (gender-pooled upper quartile LVM) was also limited. In this study 141 patients had a positive criterion on either ECG or MRI and only 4 patients (2%) had all criteria positive. When we calculate the correlation between both ECG-LVH measures with MRI-LVM, we found Pearson correlation coefficients of 0.23 (Sokolow-Lyon voltage) and 0.17 (Cornell voltage). The differences in patient characteristics per ECG-LVH

Table 5
Relation between insulin resistance and left ventricular hypertrophy (n=117)

	model 1 β (95%CI)	model 2 β (95%CI)
Electrocardiogram		
Sokolow-Lyon voltage (mV)	-0.10 (-0.20 to -0.00)	-0.12 (-0.22 to -0.02)
Sokolow-Lyon product (mV·ms)	-12.11 (-22.71 to -1.51)	-13.50 (-23.80 to -3.20)
Cornell voltage (mV)	0.002 (-0.066 to 0.070)	0.001 (-0.065 to 0.067)
Cornell product (mV·ms)	-1.25 (-8.50 to 6.00)	-1.40 (-8.33 to 5.54)
Magnetic Resonance Imaging		
Left ventricular mass (g)	1.20 (-1.45 to 3.84)	1.23 (-1.50 to 3.96)
Left ventricular mass-index ($g/m^{2.7}$)	0.43 (-0.13 to 0.99)	0.45 (-0.12 to 1.03)

model 1: age, gender

model 2: model 1 plus systolic blood pressure, use of β-blocker, ACE-inhibitor or angiotensin-II receptor blocker

Insulin resistance measured with the Homeostasis Model Assessment of Insulin Resistance

criterion are shown in Table 4. Patients with a high MRI-LVM compared to patients with a positive Sokolow-Lyon voltage criterion had a worse metabolic profile with higher bodyweight, higher triglycerides and more organ damage shown in albuminuria and medical history. Patients with a positive Cornell voltage criterion were in between those extremes. To further analyze the causal relation between waist circumference and ECG-LVH we analyzed the relation between IR and LVH in a subpopulation (n=117) (Table 5). HOMA-IR was closely related to waist circumference in our study population with β = 0.15 (95%CI 0.09 to 0.21) adjusted for age and gender. The Pearson correlation coefficients of HOMA-IR were 0.74 (waist circumference) and 0.41 (visceral fat), both $p<0.05$. The relation of HOMA-IR with Sokolow-Lyon voltage was inverse β -0.10 (95%CI -0.20 to -0.00) and with MRI-LVM there was a trend for a positive relation β 1.20 (95%CI -1.45 to 3.84), comparable with the results of the relation of waist circumference with ECG-LVH.

Since the distance between the precordial electrodes and the cardiac mass is different in women and men, there could be another relation between waist circumference and precordial voltages in women than in men. Therefore all the analyses in Table 3 and 5 were tested for interaction of waist circumference, visceral fat and HOMA with gender in the relation with left ventricular hypertrophy. All interactions were not statistical significant ($p>0.2$).

Discussion

The present study showed that there is an inverse relation between waist circumference and ECG-LVH (defined as Sokolow-Lyon voltage) and a positive relation between waist circumference and a high MRI-LVM. The overlap of LVH on ECG and high LVM on MRI in hypertensive patients was limited. Patients with high MRI-LVM compared to patients with positive Sokolow-Lyon voltage criterion had a worse metabolic profile and more organ damage. There was also an inverse relation between IR and ECG-LVH.

Various studies, using different measures of IR and ECG-LVH in different populations report comparable or different results, but evaluations of ECG-LVH or MRI-LVM and IR in a single study were lacking.[17-19] An explanation for the findings in the present study might be that electrical changes in a hypertrophied heart are different from anatomical changes. Given the changes in anatomy and histology in LVH it is not unexpected that different diagnostic modalities give different results.

ECG leads V_5 and V_6 appear to have a close relation with changes in left ventricular position and filling.[20] This may explain why IR has a relation with Sokolow-Lyon voltage and Cornell voltage shows no relation with IR.

Discrepancies in changes of ECG voltages and anatomical mass have been reported before. In a cross-sectional human study 189 healthy subjects and 54 subjects with hypertension LVM was measured using echocardiogram and the magnitude of the approximated maximum QRS spatial vector (QRSmax) was calculated from the amplitudes of R(aVF), R(V_5) and S(V_2), representing the electrical activity of the left ventricle. Higher echo-LVM values were found in the hypertensive subjects, but the QRSmax values were significantly lower as compared to healthy subjects.[21] This study showed net lower cardiac electrical activity per cm^3 cardiac tissue with increasing cardiac left ventricular mass. This indicates that either physiologic increase in cardiac mass (exercise) or pathologic increase in cardiac mass (hypertension) leads to (relative) decreasing electrical activity. A necropsy study of 30 patients showed adipose tissue in the heart could constitute up to 50% of the cardiac weight. The greater amounts of cardiac adipose tissue were associated with lower total 12-lead QRS voltages.[22] The intracellular signaling pathway of insulin PI3K/PKB/Akt is involved in the pathways leading to physiologic hypertrophy.[23] IR is characterized by an alteration of this signaling pathway, leading to a decrease in glucose uptake and glucose oxidation and an increase in fatty acid uptake. Fatty acid oxidation is enhanced as well, but this is not sufficient to prevent lipid accumulation.[24] Furthermore it is shown that chronic hyperinsulinemia stimulates the angiotensin II signaling that is involved in pathological hypertrophy.[25] Thus IR leads to lipid accumulation and stimulation of the angiotensin II signaling, both leading to pathologic left ventricular hypertrophy.

In the present study we showed a positive relation between waist circumference, visceral fat and IR and high LVM on MRI, which was expected based on pathophysiological knowledge described above. The negative relation between IR and Sokolow-Lyon voltage on ECG is supported by the concept that cardiac hypertrophy leads to a diminished voltage. Our study population is a cohort of middle aged hypertensive patients. Our result of a

positive relation of IR with MRI-LVM and a negative relation of IR with Sokolow-Lyon voltage matches the worse metabolic profile in patients with a high MRI-LVM compared to patients with a positive Sokolow-Lyon voltage criterion.
The results of the present study contribute to our understanding of several problems: the lower than expected voltage with an anatomical large cardiac mass and the low correlation of ECG-LVH and high LVM on MRI. As is well known obese patients have lower precordial voltages, effecting Sokolow-Lyon voltages. A common explanation is that anatomical change in the precordium or the increased chest wall thickness.[26,27] A mathematical model of the heart and the thorax showed that changes in body surface potentials (precordial voltages) and changes in epicardial potentials are different with increasing left ventricular mass.[28] However, these changes are not easily to predict since they depend on whether the increase in ventricular mass is concentric or eccentric with or without dilatation, and could be influenced by changes in the orientation and position of the heart in the thorax. The analysis in this paper showed that high IR could be another explanation why obese patients are likely to have a low Sokolow-Lyon voltage. On the contrary, our analysis showed that a high IR is associated with an increased left ventricular mass on MRI, indicating important pathological changes with consequences for prognosis and treatment. The clinical implication could be that treatment or prevention of LVH may be achieved by reducing IR.
A strength of our study is the combined and precise measurement of ECG-LVH and MRI-LVM in a clinical relevant group of patients. We also acknowledge study limitations. This is a cross-sectional study and it is unknown whether morphologic changes and electrical changes of the myocardium have the same time path. Further research might focus on the sequence of events. The comparison of patients with positive ECG criteria and patients with a high MRI-LVM is difficult. The partition values of both could be subject to discussion, especially the high MRI-LVM values. MRI values for LVH vary considerable between groups.[14] Therefore the relative measure of the upper quartile was chosen. The reference test for insulin resistance is the hyperinsulinemic euglycemic clamp measuring the glucose uptake. The HOMA-IR value has a reasonable correlation with the hyperinsulinemic euglycemic clamp.[29]

Conclusion

There is an inverse relation between waist circumference and ECG-LVH and a positive relation between waist circumference and MRI-LVM. The relations of visceral fat and IR with ECG-LVH and MRI-LVM were similar. These data explain (part of) the low correlation of electrical and anatomical LVH especially in patients with obesity and high IR. When IR is indeed causally related with LVH, than treatment or prevention of LVH may be achieved by reducing IR.

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Chapter 4

The risk of different ECG criteria for left ventricular hypertrophy on vascular events and all-cause mortality in patients with vascular disease

J.W.P. Vernooij

Y. van der Graaf

R.H.H. Bemelmans

H.M. Nathoe

F.L.J. Visseren

W. Spiering

Submitted for publication

Abstract

Objective

Presence of left ventricular hypertrophy (LVH) on ECG can be assessed with multiple criteria. We evaluated the vascular risk and all-cause mortality related to 2 traditional (Sokolow-Lyon and Cornell voltage criterion) and 2 recently developed ECG criteria (Perugia and LIFE criterion) for LVH in patients with vascular disease.

Methods

A cohort of patients with clinical vascular diseases (n=4,556) was followed (median 4.5; interquartile range 2.3-7.4 years) for the occurrence of vascular events (stroke, myocardial infarction and vascular death) and all-cause mortality.

Results

The prevalence of the Sokolow-Lyon, Cornell voltage, Perugia and the LIFE criterion was 8%, 4%, 12% and 12% respectively. 11% of the patients had LVH according to multiple criteria. The risk for vascular events and mortality was increased with presence of each LVH-criterion, but most notably with the Perugia criterion for vascular events (HR 2.03, 95%CI 1.65 to 2.49) and for all-cause mortality (HR 1.69, 95%CI 1.36 to 2.09), adjusted for age and gender. Patients with coronary artery disease and women had comparable risks for vascular events and mortality compared to patients without coronary artery disease and men.

Conclusions

ECG-LVH is prevalent in patients with clinical manifest vascular diseases and confers an independent risk for vascular events and mortality. The Perugia ECG-LVH criterion is related to the highest risk for vascular events and all-cause mortality combined with a high prevalence.

Introduction

Hypertensive target organ damage can be assessed with several measures of renal, cardiac and vascular function. Damage by hypertension to the heart can be evaluated with the assessment of LVH on ECG (ECG-LVH). ECG-LVH is an independent risk factor for vascular events.[1] LVH on ECG has a modest specificity and sensitivity compared to anatomical measurements of left ventricular size with echocardiography or cardiac MRI,[2] but the associated risk for vascular events and mortality is comparable.[1] The information of ECG-LVH might even be of additional value after echocardiography.[3] LVH on ECG can be assessed with multiple diagnostic criteria.[4] ECG criteria can be simple or may require an extensive scoring system involving computation of various measurements. Traditionally used LVH criteria are the Sokolow-Lyon criterion[5] and the Cornell voltage criterion.[6] Both are associated with an increased risk for development of vascular diseases and mortality,[1,7] although the prognostic value of the Sokolow-Lyon criterion is debated.[8] In studies evaluating the relation between LVH criteria and the risk for vascular diseases and mortality, patients with a previous myocardial infarction are usually excluded and the vascular risk of the separate and combined effect of those criteria in patients with vascular disease is unclear.[8] The LIFE LVH criterion was specifically developed and evaluated in the LIFE study.[9] The Perugia LVH criterion is also recently introduced and consists of an adjusted Cornell voltage criterion with or without a left ventricular strain pattern.[8,10]

Guidelines address the importance of LVH on ECG, but do not recommend the use of a specific ECG criterion,[11,12] except the 2007 ESH/ESC Guideline for the management of hypertension, which recommends the use of the LIFE-LVH criterion.[13] A comparison of 7 ECG criteria for LVH and the risk for vascular events in a hypertensive population is done before,[8] but is lacking in patients with a vascular disease and patients with coronary artery disease (CAD). In the present study we compared the vascular risk and risk for all-cause mortality for 2 traditional and 2 recently developed ECG criteria of LVH in a cohort of patients with clinical manifest vascular disease.

Patients and Methods

Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. Rationale and design of the SMART study have been described previously.[14] In short, the SMART study is an ongoing single-center prospective cohort study that was designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular diseases or a vascular risk factor. The study was approved by the Institutional Review Board of the University Medical Center Utrecht and all patients gave written informed consent. The current study was based on the data of SMART participants with clinically manifest vascular diseases (n=5,280). Patients with no ECG available (n=362) and patients (n=378) with a bundle branch block on the ECG (QRS ≥120 ms) were excluded from analyses, leaving a study population of

4,556 patients. Of these patients 2,750 (60%) had CAD, 1,291 (28%) cerebrovascular disease (CVD) and 1,217 (27%) peripheral arterial disease and/or abdominal aortic aneurysm (PAD/AAA).

Measurements

Blood pressure was measured with a sphygmomanometric device at both arms and repeated on the side with the highest values. The mean of all obtained measurements was used in the analysis. A standard bladder (12–13 cm long and 35 cm wide) was used and according to the arm circumference a larger or smaller bladder was chosen. Glucose, insulin, lipids, and creatinine were obtained after an overnight fast. The four-variable Modification of Diet in Renal Disease (MDRD) equation was used to estimate glomerular filtration rate (eGFR).[15] Urine albumin/creatinine ratio was determined in a first morning-void urine sample. At study inclusion, a 12-lead 10 seconds ECG was obtained after 5 minutes rest with the patient in supine position. Measurements of R- and S-amplitudes and QRS timing was performed using the Marquette 12SL analysis program (General Electric Healthcare, Hoevelaken, The Netherlands).

Definitions

Type 2 diabetes mellitus was defined as a referral diagnosis of type 2 diabetes mellitus, use of glucose-lowering agents, or the combination of fasting glucose ≥7.0 mmol/L at screening and receiving treatment within 1 year after inclusion. In this way, diabetes mellitus also included newly diagnosed patients with type 2 diabetes mellitus. Definitions of LVH criteria used are shown in Table 1.

Follow-up and outcome evaluation

Patients provided information on hospitalization and outpatient clinic visits in response to a short questionnaire every 6 months. When a vascular event was reported, original source documents were retrieved and reviewed to determine the occurrence of vascu-

Table 1
Definitions of LVH criteria

Criterion	Description	Cut-off
Sokolow-Lyon[5]	S in V_1 + (R in V_5 or V_6, whichever is larger)	≥3.5 mV
Cornell voltage[6]	S in V_3 + R in aVL	men >2.8 mV women >2.0 mV
Perugia[8]	left-ventricular-strain pattern* S in V_3 + R in aVL	strain or men >2.4 mV women >2.0 mV
LIFE[16]	(S in V_3 + R in aVL (+0.6 in women)) x QRS duration S in V_1 + (R in V_5 or V_6, whichever is larger)	>244 mV·ms or >3.8 mV
*Strain	ST-J segment depression ≥0.05 mV and inverted T wave in any of leads I, II, aVL or V_2 to V_6	

lar events. All possible events were evaluated independently by three members of the Endpoint Committee. Patients were followed until death or refusal of further participation. The main outcome of interest for this study was all-cause mortality and a composite of first occurrence of non-fatal stroke, non-fatal myocardial infarction or vascular death (vascular events). The study period was from 1996 to 2010 with a median follow-up of 4.5 years (interquartile range 2.3-7.4 years) and a total of 22,645 person years, in which 536 vascular events occurred and 511 patients died. Due to migration or discontinuation of the study, 136 (3.0%) patients were lost to follow-up.

Definitions of outcome events

Myocardial infarction: At least two of the following criteria: (1) chest pain for at least 20 minutes, not disappearing after administration of nitrates; (2) ST-elevation >1 mm in two following leads or a left bundle branch block on the electrocardiogram; (3) creatine kinase elevation of at least two times the normal value of creatine kinase and a myocardial band-fraction >5% of the total creatine kinase.

Stroke: relevant clinical features causing an increase in impairment of at least one grade on the modified Rankin scale, accompanied by an infarction or hemorrhage on a CT scan and clinical deficits causing an increase in impairment of at least one grade on the modified Rankin scale, without CT documentation. Vascular death: sudden death (unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence), death from ischemic stroke, intracerebral hemorrhage, myocardial infarction, congestive heart failure, or acute aorta aneurysm rupture. Vascular events are a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death.

Data-analyses

Data were expressed as mean with standard deviation. Not-normal distributed variables were expressed as median with the interquartile range. Categorical data were expressed as absolute numbers and percentages. Risk for vascular events and mortality was estimated with the Cox proportional hazards model and presented as hazard ratios (HR) with 95% confidence intervals (95%CI). The proportional hazard assumption was confirmed by plotting the survival curves and by testing the correlations between scaled Schoenfeld residuals and time. No significant non-proportionality ($p<0.05$) was observed. Age and gender were considered confounders in the relation of LVH and vascular events and mortality. Body mass index (BMI), blood pressure and blood pressure-lowering medication were also considered confounders, but could be in the causal pathway as well. Type 2 diabetes mellitus and CAD most likely are in the causal pathway and were added as confounders in an explorative model. Because of the importance of presenting vascular risks in women and in a population with CAD we tested for interaction of gender and history of CAD with vascular events and all-cause mortality. Single imputation methods were used to reduce missing covariate data for BMI (n=7), albuminuria (n=219), HDL-cholesterol (n=37), triglycerides (n=32), LDL-cholesterol (n=217), glucose (n=32), systolic blood pressure (SBP) (n=7)

and diastolic blood pressure (n=10), since complete case analysis leads to loss of statistical power and possibly to bias.[16] To assess the relevance of the different ECG criteria for LVH in our population a study population attributable risk was calculated. This gives an estimate of the proportion of events that can be directly attributed to the predictive factor under examination by taking into account its prevalence and adjusted HR. It was calculated as [(prevalence (HR - 1)) / (prevalence x (HR -1) + 1)] x 100.

All statistical analyses were performed with SPSS 18.0.2 for Windows (IBM Corporation, Chicago, Illinois, USA).

Table 2
Baseline characteristics

Total population n=4,556		No left ventricular hypertrophy	Sokolow-Lyon criterion	Cornell voltage criterion	Perugia criterion	LIFE criterion
n (%)		3,700 (81)	355 (8)*	202 (4)*	567 (12)*	526 (12)*
Age (years)		59 (10)	61 (11)	62 (11)	63 (10)	62 (11)
Male gender, n (%)		2,729 (74)	283 (80)	76 (38)	395 (70)	374 (71)
Systolic blood pressure (mmHg)		140 (21)	152 (25)	153 (26)	152 (25)	152 (25)
Body mass index (kg/m^2)		27.0 (4.0)	25.2 (3.6)	26.8 (4.3)	26.8 (3.9)	26.3 (3.9)
Current or previous smoking, n (%)		3,125 (84)	321 (90)	188 (93)	531 (94)	485 (92)
HDL-cholesterol (mmol/l)		1.2 (0.4)	1.3 (0.4)	1.3 (0.4)	1.2 (0.4)	1.3 (0.4)
Triglycerides (mmol/l)		1.5 [1.1-2.1]	1.3 [1.0-1.8]	1.5 [1.0-2.2]	1.5 [1.0-2.2]	1.4 [1.0-2.0]
LDL-cholesterol (mmol/l)		2.9 (1.1)	3.1 (1.1)	3.0 (1.1)	3.0 (1.1)	3.0 (1.1)
Glucose (mmol/l)		6.2 (1.8)	6.3 (2.0)	6.8 (2.7)	6.8 (2.4)	6.6 (2.3)
eGFR (ml/min/1.73m^2)		77.1 (17.8)	74.4 (18.6)	70.3 (21.1)	72.0 (19.4)	73.2 (20.2)
Albuminuria, n (%)	-micro	518 (14)	79 (22)	53 (26)	137 (24)	127 (24)
	-macro	77 (2)	18 (5)	14 (7)	32 (6)	27 (5)
History of vascular disease, n (%)						
Coronary artery disease		2,236 (60)	191 (54)	110 (54)	355 (63)	307 (58)
Cerebrovascular disease		1,002 (27)	136 (38)	76 (38)	187 (33)	182 (35)
Peripheral arterial disease		985 (27)	98 (28)	60 (30)	162 (29)	157 (30)
Type 2 diabetes mellitus		562 (15)	47 (13)	54 (27)	139 (25)	104 (20)
Hypertension		3,125 (84)	321 (90)	188 (93)	531 (94)	485 (92)
Medication use, n (%)						
β-blocker		1,948 (53)	172 (48)	97 (48)	309 (54)	259 (49)
ACEi or ARB		1,197 (32)	128 (36)	99 (49)	263 (46)	235 (45)
Diuretic		605 (16)	87 (25)	60 (30)	174 (31)	146 (28)
Other blood pressure-lowering medication		42 (0)	5 (0)	6 (0)	15 (0)	11 (0)
Lipid lowering mediction		2,348 (63)	198 (56)	122 (60)	336 (59)	306 (58)
Platelet aggregation inhibition		2,978 (80)	282 (79)	159 (79)	467 (82)	418 (79)

eGFR indicates estimated glomerular filteration rate, ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker

*498 (11%) Patients with more than one criterion

Data are expressed as mean (standard deviation), as number (percentage) or as median [interquartile range]

Results

Prevalence of LVH according to different ECG criteria

Patients had a mean age of 60 ± 10 years and 73% of the population was male (Table 2). The prevalence of LVH in the study population ranged from 4% (Cornell voltage criterion) to 12% according to the Perugia and LIFE criteria. The distribution of gender according to LVH criteria ranged from 38% male in patients with Cornell voltage criterion to 80% male in the group of patients with Sokolow-Lyon criterion. SBP was higher in patients with LVH (150 ± 24 mmHg), compared to patients without any LVH criterion (140 ± 20 mmHg). In patients without LVH the prevalence of CAD was 60%, compared with 54% (Cornell voltage), 54% (Sokolow-Lyon), 58% (LIFE), and 63% (Perugia) in patients with LVH. There was poor concordance between different LVH criteria. Only 11% of patients had LVH according to ≥2 LVH criteria (Figure 1). The Cornell criterion was congruent with the Perugia criterion, as expected from the definitions. Between the LIFE criterion and the Cornell criterion was an agreement of 86%, while the other criteria had an agreement ranging between 15 and 67%.

Relation between LVH criteria and risk for vascular events and all-cause mortality

The risk for vascular events of the 2 traditional criteria, Sokolow-Lyon and Cornell voltage, was comparable. For Sokolow-Lyon the hazard ratio was 1.49 (95%CI 1.14-1.94) and for Cornell voltage criterion the hazard ratio was 1.83 (95%CI 1.30-2.57). The LIFE criterion was in the same range (HR 1.90, 95%CI 1.53-2.36), but the Perugia criterion was associated with a higher risk (HR 2.03, 95%CI 1.65-2.49) (Table 3). The risk for all-cause mortality followed the same pattern for Sokolow-Lyon (HR 1.27, 95%CI 0.96-1.68), Cornell voltage (HR 1.68, 95%CI 1.17-2.41), LIFE criterion (HR 1.68, 95%CI 1.34-2.10) and Perugia criterion (HR 1.69, 95%CI 1.36-2.09). Adding blood pressure or other potential confounding factors to the models did not alter the effect estimates.

Figure 1
Venn diagram with overlap between left ventricular hypertrophy criteria

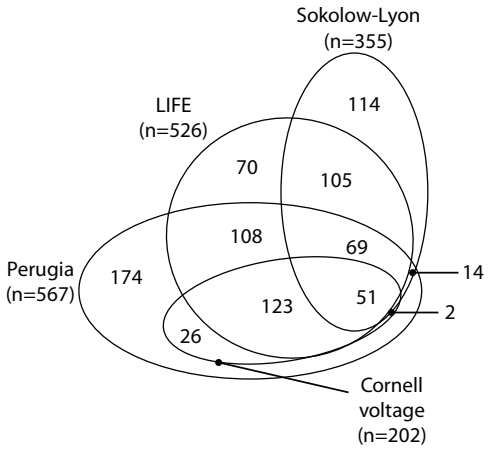

Table 3
Left ventricular hypertrophy criteria and risk for vascular events and all-cause mortality

n=4,556	Sokolow-Lyon criterion	Cornell voltage criterion	Perugia criterion	LIFE criterion
Vascular events* (n=536)				
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
I	1.49 (1.14 to 1.94)	1.83 (1.30 to 2.57)	2.03 (1.65 to 2.49)	1.90 (1.53 to 2.36)
II	1.40 (1.07 to 1.84)	1.77 (1.26 to 2.50)	1.98 (1.61 to 2.44)	1.83 (1.47 to 2.28)
III	1.42 (1.08 to 1.87)	1.72 (1.22 to 2.43)	1.97 (1.60 to 2.43)	1.81 (1.45 to 2.25)
Study population attributable risk	4%	4%	11%	9%
All-cause mortality (n=511)				
I	1.27 (0.96 to 1.68)	1.68 (1.17 to 2.41)	1.69 (1.36 to 2.09)	1.68 (1.34 to 2.10)
II	1.18 (0.89 to 1.57)	1.64 (1.14 to 2.35)	1.68 (1.35 to 2.08)	1.62 (1.29 to 2.03)
III	1.20 (0.90 to 1.60)	1.63 (1.13 to 2.34)	1.71 (1.37 to 2.12)	1.62 (1.29 to 2.04)
Study population attributable risk	2%	3%	8%	7%

model I age and gender
model II model I + body mass index, blood pressure, blood pressure-lowering medication
model III model II + type 2 diabetes mellitus, coronary artery disease
*Vascular events is a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death

Table 4
Left ventricular hypertrophy criteria and risk for vascular events and all-cause mortality with respect to gender

		Sokolow-Lyon criterion	Cornell voltage criterion	Perugia criterion	LIFE criterion
Men (n=3,344)	n	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Vascular events*	425	1.39 (1.04 to 1.87)	1.77 (1.10 to 2.84)	2.12 (1.68 to 2.67)	1.91 (1.50 to 2.43)
All-cause mortality	413	1.17 (0.86 to 1.59)	1.53 (0.94 to 2.49)	1.68 (1.32 to 2.13)	1.62 (1.27 to 2.08)
Women (n=1,212)					
Vascular events*	111	2.23 (1.25 to 4.00)	1.92 (1.18 to 3.12)	1.79 (1.15 to 2.77)	2.01 (1.28 to 3.15)
All-cause mortality	98	2.11 (1.12 to 3.96)	2.02 (1.20 to 3.38)	1.83 (1.15 to 2.92)	2.00 (1.24 to 3.22)

Hazard ratio's adjusted for age
*Vascular events is a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death

The LVH criterion with the highest study population attributable risk (PAR) was the Perugia criterion with a PAR of 11% for vascular events and 8% for all-cause mortality. PARs for the other criteria were 9% and 7% (LIFE), 4% and 3% (Cornell voltage), and 4% and 2% (Sokolow-Lyon) for vascular events and all-cause mortality, respectively.
Different LVH criteria and risk for vascular events and all-cause mortality were comparable for both men and women and for both patients with and without CAD (Table 4 and 5), with a p for interaction >0.16.

Discussion

In this study in patients with vascular diseases we have studied the prevalence and associated (vascular) risk of LVH according to 2 often used criteria (Sokolow-Lyon and Cornell voltage) and 2 recently introduced criteria (Perugia and LIFE). We found that in our study population the prevalence of LVH ranged from 4% (Cornell voltage criterion) to 12% for the Perugia and LIFE criteria. LVH according to ≥2 LVH criteria was found in 11% of patients. The risk for vascular events and all-cause mortality was increased for all 4 LVH criteria, with the Perugia criterion conferring the highest risk and independent of blood pressure. No interactions for gender or CAD with the risk for vascular events and mortality were found.
In patients with hypertension a prevalence of ECG-LVH was observed ranging from 9.1% for the Cornell voltage criterion, 13.1% for the Sokolow-Lyon criterion to 17.3% for the Perugia criterion.[8] Another study showed a prevalence of 22% for the LIFE criterion in patients with hypertension.[17] In patients with an acute myocardial infarction the prevalence

Table 5
Left ventricular hypertrophy criteria and risk for vascular events and all-cause mortality with respect to presence of history of coronary artery disease

		Sokolow-Lyon criterion	Cornell voltage criterion	Perugia criterion	LIFE criterion
	n	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Patients with coronary artery disease (n=2,750)					
Vascular events*	285	1.41 (0.97 to 2.05)	1.92 (1.18 to 3.13)	1.82 (1.37 to 2.41)	1.99 (1.49 to 2.66)
All-cause mortality	237	1.32 (0.88 to 1.98)	2.01 (1.19 to 3.37)	1.55 (1.14 to 2.11)	1.78 (1.29 to 2.44)
Patients without coronary artery disease (n=1,806)					
Vascular events*	251	1.61 (1.11 to 2.32)	1.81 (1.14 to 2.89)	2.38 (1.77 to 3.19)	1.86 (1.36 to 2.54)
All-cause mortality	274	1.24 (0.85 to 1.80)	1.56 (0.97 to 2.51)	1.97 (1.47 to 2.63)	1.64 (1.21 to 2.22)

Hazard ratio's adjusted for age and gender
*Vascular events is a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death

of LVH on the admission ECG was 5.3% according to the Sokolow-Lyon criterion, 7.1% according to the Cornell voltage criterion.[18] In another study in patients with an acute myocardial infarction 7.9% of patients had LVH according to the Cornell voltage criterion.[19] In the present study in patients with clinical manifestations of vascular diseases the prevalence of LVH was comparable.

In a cohort of patients with hypertension, presence of LVH according to the Sokolow-Lyon criterion and the Cornell voltage criterion was not related to an elevated risk for vascular events (RR 0.99, 95% CI 0.67–1.44 and RR 1.33, 95% CI 0.99–1.96 respectively).[8] In that study LVH according to the Perugia criterion was related to an increased risk for vascular events (RR 1.89, 95%CI 1.44–2.49). This risk is comparable with the results in the present study.

In patients with an acute myocardial infarction the Cornell product criterion was related to an increased risk (RR 2.52, 95%CI 1.19-5.35) for death, reinfarction, severe angina or heart failure.[18] In another study in patients with acute myocardial infarction presence of LVH according to the Cornell voltage criterion was associated with a no increased risk (HR 1.22, 95%CI 0.95–1.56) for mortality within 1 year.[19] These studies were limited by a low number of patients or a short follow-up time. These limitations were overcome in the present analyses. The risk for vascular events and all-cause mortality of the LIFE criterion is not known. In the present study it is shown that LVH according to LIFE criterion is also related to an elevated risk for vascular events and mortality.

In the present study the Perugia criterion for ECG-LVH was related to the highest risk vascular risk and mortality risk. Also Perugia criterion had the highest population attributable risk, as a result of the relatively high prevalence in patients with vascular diseases. The Perugia criterion is fairly simple and easy to use in daily clinical practice. The population attributable risk of the LIFE criterion is comparable with Perugia criterion, but the LIFE criterion for the diagnosis of ECG-LVH requires some calculation of ECG values which limits clinical applicability.

Detecting LVH on ECG has consequences for therapy. The LIFE study showed regression of LVH (every 1050 mm·ms decrease in Cornell product) was associated with a decrease in vascular events (HR 0.86, 95%CI 0.82-0.90); and HR 0.83 (95%CI 0.78-0.88) for every 10.5 mm decrease in Sokolow-Lyon voltage.[20] Losartan based therapy compared to atenolol based therapy induced more regression of LVH as was shown already after 6 month (reduction of Cornell product with -200 versus -69 mm x ms and Sokolow-Lyon voltage -2.5 versus -0.7 mm, both P<0.01).[21] A trial with ramipril also showed that patients who had regression/prevention of LVH had a lower risk for vascular events compared with those who had development/persistence of LVH (12.3% versus 15.8%, P<0.01), independent of blood pressure changes.[22]

Patients identified with ECG-LVH, irrespective of their blood pressure, should be treated with aggressive blood pressure lowering, preferably with blockade of the renin-angiotensin-aldosterone system.

Strengths of this study include the large sample size of patients with vascular disease (especially the large number of patients with CAD) and the large number of follow-up years and number of hard clinical endpoints. Some study limitations need to be considered. LVH was measured on ECG. LVH-ECG does have a low sensitivity LVH compared to anatomical measurements of LVH like cardiac-MRI.[2] However, ECG is readily available at low cost.
In conclusion, ECG-LVH is prevalent in patients with clinical manifest vascular diseases and confers an independent risk for vascular events and mortality. The Perugia criterion was related with the highest risk for vascular events and all-cause mortality and the highest population attributable risk.

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Chapter 5

Hypertensive target organ damage and the risk for vascular events and all-cause mortality in patients with vascular disease

J.W.P. Vernooij

Y. van der Graaf

H.M. Nathoe

R.H.H. Bemelmans

F.L.J. Visseren

W. Spiering

Submitted for publication

Abstract

Objective

Presence of hypertensive target organ damage is related to increased vascular risk and mortality. Whether combined presence of hypertensive target organ damage confers higher vascular risk compared to single presence is unknown. This study evaluates the separate and combined effects of impaired renal function, albuminuria and LVH on the occurrence of vascular events and mortality in patients with vascular disease (coronary artery disease, cerebrovascular disease and peripheral arterial disease).

Methods

A cohort of patients with vascular diseases (n=4,319) was followed (median 4.4 years; interquartile range 2.3-7.4 years) for the occurrence of vascular events and mortality.

Results

LVH was present in 11%, impaired renal function in 15% and albuminuria in 18% of patients. Presence of ≥2 hypertensive target organ damage was prevalent in 8% of patients. The risk for vascular events was HR 1.5 (95%CI 1.2 to 1.9) for presence of 1 hypertensive target organ damage and HR 3.8 (95%CI 2.3 to 6.3) for 3 manifestations of hypertensive target organ damage (adjusted for age, gender). For mortality this was HR 1.4 (95%CI 1.1 to 1.7) and HR 3.2 (95%CI 1.9 to 5.2). Hazard ratios for single presence of different types of organ damage were comparable and independent of the presence of hypertension.

Conclusions

Impaired renal function, albuminuria and LVH are prevalent in patients with vascular disease and confer independent and additive risk for vascular events and mortality.

Introduction

Impaired renal function, albuminuria and/or left ventricular hypertrophy (LVH) are manifestations of hypertensive target organ damage and are each associated with increased risk for vascular events and for mortality.[1,2] Guidelines recommend to routinely assess target organ damage by measuring renal function, albuminuria and LVH on ECG when evaluating vascular risk in patients.[3,4] Many more optional and advanced measurements of target organ damage, like intima-media thickness and pulse wave velocity, could be performed but are not regularly available in routine clinical practice. Although these manifestations of target organ damage are most often the result of hypertension, the exact pathophysiological mechanisms by which they contribute to increased vascular risk are poorly understood. Microalbuminuria for example, not only indicates specifically an impairment in glomerular permeability due to blood pressure load, but also more generalized and widespread endothelial dysfunction.[5]

Guidelines recommend screening for LVH with electrocardiography (ECG), although sensitivity in detecting LVH with this technique is low. Nonetheless ECG-detected LVH is an independent predictor of vascular events.[6,7] In healthy subjects the presence of subclinical target organ damage, including LVH and albuminuria, as well as the number of organs damaged was associated with increased cardiovascular risk independently of the Systematic COronary Risk Evaluation (SCORE risk) algorithm.[8] A meta-analysis of studies in the general population indicated that an impaired renal function (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2) and albuminuria (albumin/creatinine-ratio >1.1 mg/mmol) are independent predictors of premature mortality risk.[9] Presence of an impaired renal function and albuminuria identifies individuals at vascular risk in the general population.[10] We previously showed that in patients with clinical manifestations of vascular disease, both impaired renal function (eGFR <60 mL/min/1.73 m^2) and albuminuria (albumin/creatinine-ratio >3.0 mg/mmol) were independent vascular risk factors, with the highest risk in patients with the combined presence of albuminuria and impaired renal function.[2] In the present study we evaluated the prevalence of separate and combined presence of impaired renal function, albuminuria and LVH and evaluated the risk of the separate and combined presence of these signs of hypertensive target organ damage on the occurrence of vascular events and mortality in patients with clinically manifest vascular disease.

Patients and Methods

Study population

The patients included in this study originated from the Second Manifestations of ARTerial disease (SMART) study. Rationale and design of the SMART study have been described previously.[11] In short, the SMART study is an ongoing single-center prospective cohort study that was designed to establish the presence of additional arterial disease and risk factors for atherosclerosis in patients with manifest vascular diseases or a vascular risk factor. The study was approved by the ethics committee of the University Medical Center Utrecht and all patients gave written informed consent. The current study was based on

the data of SMART participants with clinically manifest vascular diseases (n=5,280). Patients with no ECG available (n=362), without measurement of creatinine or albuminuria at inclusion (n=262) and patients with a bundle branch block on the ECG (QRS ≥120 ms) (n=378) were excluded from analyses, leaving a study population of 4,319 patients. Of these patients 2,613 (61%) had coronary artery disease, 1,221 (28%) cerebrovascular disease and 1,153 (27%) peripheral arterial disease and/or abdominal aortic aneurysm.

Measurements

Blood pressure was measured with a sphygmomanometric device at both arms and repeated on the side with the highest values. The mean of all obtained measurements was used in the analysis. A standard bladder (12–13 cm long and 35 cm wide) was used and according to the arm circumference a larger or smaller bladder was chosen. Glucose, insulin, lipids, and creatinine were obtained after an overnight fast. The four-variable Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR.[12] Urine albumin/creatinine ratio was determined in a first morning-void urine sample. At study inclusion, a 12-lead 10 seconds ECG was obtained after 5 minutes rest with the patient in supine position. Measurements of R- and S-amplitudes and QRS timing was performed using the Marquette 12SL analysis program (General Electric Healthcare, Hoevelaken, The Netherlands).

Definitions

Hypertension was defined as a systolic blood pressure (SBP) ≥140 mmHg and/or the use of blood pressure-lowering medication. Type 2 diabetes mellitus was defined as a referral diagnosis of type 2 diabetes mellitus, use of glucose-lowering medication, or the combination of fasting glucose ≥7.0 mmol/l at screening and receiving treatment within 1 year

Table 1
Definitions of hypertensive target organ damage

Left ventricular hypertrophy	
Sokolow-Lyon criterion[32]	
S in V_1 + (R in V_5 or V_6, whichever is larger)	≥3.5 mV
and/or Cornell voltage criterion[33]	
S in V_3 + R in aVL	men >2.8 mV
	women >2.0 mV
Impaired renal function[34]	
eGFR using the MDRD formula[12]	
186 x (creatinine (µmol)/88.4)$^{-1.154}$x age$^{-0.203}$(women x 0.742)	≤60 mL/min/1.73 m^2
Albuminuria[34]	
urine morning sample	
albumin (mg/L)/creatinine (mmol/l) ratio	men ≥2.5 mg/mmol
	women ≥3.5 mg/mmol

eGFR indicates estimated glomerular filtration rate, MDRD: Modification of Diet in Renal Disease

after inclusion. In this way, diabetes mellitus also included newly diagnosed patients with type 2 diabetes mellitus. Definitions of impaired renal function, albuminuria and LVH are shown in Table 1.

Follow-up and outcome evaluation

Patients provided information on hospitalization and out-patient clinic visits in response to a short questionnaire every 6 months. When a vascular event was reported, original source documents were retrieved and reviewed to determine the occurrence of vascular events. All possible events were audited independently by three members of the Endpoint Committee. Patients were followed until death or refusal of further participation. The main outcome of interest for this study was all-cause mortality and a composite of first occurrence of non-fatal stroke, non-fatal myocardial infarction or vascular death (combined vascular endpoint). The study period was from 1996 to 2009 with a median follow-up of 4.4 years (interquartile range 2.3 to 7.4 years), with a total of 21,320 person years, in which 605 vascular events occurred and 593 patients died. Due to migration or discontinuation of the study, 125 (2.9%) patients were lost to follow-up.

Definitions of outcome events

Myocardial infarction: At least two of the following criteria: (1) chest pain for at least 20 minutes, not disappearing after administration of nitrates; (2) ST-elevation >1 mm in two following leads or a left bundle branch block on the electrocardiogram; (3) creatine kinase elevation of at least two times the normal value of creatine kinase and a myocardial band-fraction >5% of the total creatine kinase.

Stroke: relevant clinical features causing an increase in impairment of at least one grade on the modified Rankin scale, accompanied by an infarction or hemorrhage on a CT scan and clinical deficits causing an increase in impairment of at least one grade on the modified Rankin scale, without CT documentation. Vascular death: sudden death (unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence), death from ischemic stroke, intracerebral hemorrhage, myocardial infarction, congestive heart failure, or acute aorta aneurysm rupture.

Data analyses

Data were expressed as mean with standard deviation. Not-normal distributed variables were expressed as median with the interquartile range. Categorical data were expressed as absolute numbers and percentages. Risk for vascular events and mortality was estimated with the Cox proportional hazards model and presented as hazard ratios (HR) with 95% confidence intervals (95%CI). The proportional hazard assumption was confirmed by plotting the survival curves and by testing the correlations between scaled Schoenfeld residuals and time. No significant non-proportionality ($p<0.05$) was observed. Age and gender were considered confounders in the relation of hypertensive target organ damage and the composite vascular endpoint and mortality. Body mass index (BMI), blood pressure and blood pressure-lowering medication were also considered confounders, but could

be in the causal pathway as well. Type 2 diabetes mellitus and coronary artery disease most likely are in the causal pathway and were added as confounders in an explorative model. Single imputation methods were used to reduce missing covariate data for BMI (n=7), smoking status (n=17), SBP (n=7), diastolic blood pressure (n=10), HDL-cholesterol (n=13), triglycerides (n=11), LDL-cholesterol (n=175) and glucose (n=21) since complete case analysis leads to loss of statistical power and possibly to bias.[13] Effect modification for the relation of hypertensive target organ damage with vascular events or all-cause mortality by SBP was assessed by comparing the adjusted model with and without a blood pressure interaction term on the basis of Akaike information criterion ($p<0.154$)[14] and by stratification. All statistical analyses were performed with SPSS 18.0.2 for Windows (IBM Corporation, Chicago, Illinois, USA).

Results

Prevalence of hypertensive target organ damage

Of the study population 34% had at least 1 manifestation of target organ damage (Table 2). The combined presence of ≥2 manifestation of hypertensive target organ damage was found in 345 patients (8%), as is shown in Figure 1. All 3 target organ damages were present in 47 patients (1%). Albuminuria was most prevalent (18%), followed by impaired renal function (15%) and LVH (11%). In male patients albuminuria was most frequently present (18%), whereas in female patients impaired renal function (22%) was most often

Figure 1
Prevalence of the three different types of hypertensive target organ damage

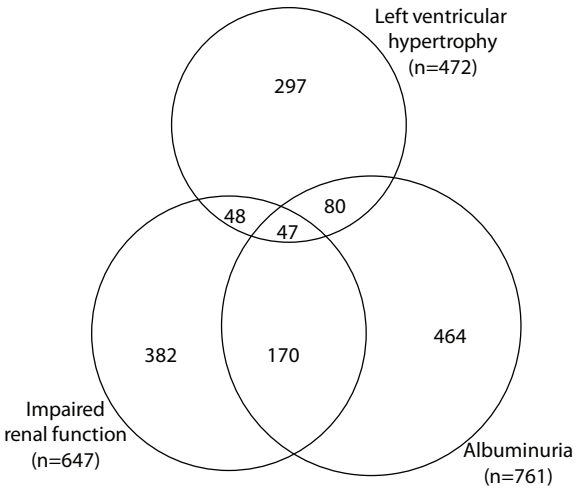


Table 2
Baseline characteristics

Total population n = 4,319		No other target organ damage (n = 2,831)	Left ventricular hypertrophy (n = 472)*	Impaired renal function (n = 647)*	Albuminuria (n = 761)*
Age (years)		58 (10)	61 (11)	65 (9)	63 (10)
Male gender, n (%)		2,157 (76)	308 (65)	396 (61)	578 (76)
Systolic blood pressure (mmHg)		138 (20)	152 (25)	147 (24)	150 (23)
Body mass index (kg/m^2)		26.9 (3.9)	25.8 (3.9)	26.8 (4.0)	27.0 (4.3)
Current smoking, n (%)		948 (33)	150 (32)	180 (28)	275 (36)
HDL-cholesterol (mmol/l)		1.2 (0.4)	1.3 (0.4)	1.2 (0.4)	1.2 (0.4)
Triglycerides (mmol/l)		1.4 [1.0-2.0]	1.3 [1.0-1.8]	1.6 [1.2-2.3]	1.6 [1.1-2.3]
LDL-cholesterol (mmol/l)		3.0 (1.1)	3.0 (1.1)	3.0 (1.1)	2.9 (1.1)
Glucose (mmol/l)		6.2 (1.8)	5.7 (5.3)	5.8 (5.4)	5.9 (5.4)
eGFR (mL/min/1.73m^2)[†]		81 (14)	74 (19)	49 (10)	71 (23)
Albuminuria	-micro, n (%)	0 (0)	103 (22)	169 (26)	657 (86)
	-macro, n (%)	0 (0)	24 (5)	48 (7)	104 (14)
History of vascular disease, n (%)					
Coronary artery disease		1,784 (63)	253 (54)	372 (57)	412 (54)
Cerebrovascular disease		720 (25)	181 (38)	214 (33)	253 (33)
Peripheral artery disease		684 (24)	129 (27)	229 (35)	270 (35)
Type 2 diabetes mellitus, n (%)		398 (14)	81 (17)	114 (18)	198 (26)
Hypertension[‡], n (%)		2,348 (83)	424 (90)	606 (94)	692 (91)
Hypertension duration (years)		10 (12)	12 (13)	13 (13)	12 (13)
Use of blood pressure-lowering medication, n (%)		1,999 (71)	348 (74)	558 (86)	573 (75)
β-blockers		1,515 (54)	225 (48)	359 (55)	369 (48)
ACE-inhibitors or Angiotensin-I-receptor antagonists		831 (29)	190 (40)	338 (52)	318 (42)
Diuretics		382 (13)	120 (25)	260 (40)	189 (25)
Other blood pressure-lowering medication		22 (1)	7 (1)	22 (3)	18 (2)
Lipid-lowering medication, n (%)		1,806 (64)	270 (57)	406 (63)	443 (58)
Platelet inhibitor medication, n (%)		2,325 (82)	380 (81)	534 (83)	595 (78)

*345 (8%) patients in multiple categories
[†]eGFR = Glomerular Filtration Rate, estimated by the Modification of Diet in Renal Disease equation
[‡]Hypertension = Systolic Blood Pressure ≥140 mmHg and/or the use of blood pressure-lowering medication
ACE indicates angiotensin converting enzyme
Data are expressed as mean (standard deviation), as number (percentage), or as median [interquartile range]

Table 3
Relation of different types of hypertensive target organ damage with vascular events and all-cause mortality

Left ventricular hypertrophy		-	+	-	-	+	-	+	+
Impaired renal function		-	-	+	-	-	+	+	+
Albuminuria		-	-	-	+	+	+	-	+
n (%)		2,831 (66)	297 (7)	382 (9)	464 (11)	80 (2)	170 (4)	48 (1)	47 (1)
Combined vascular endpoint*, n		251	37	59	66	15	43	12	17
		HR	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
model	I	1	1.5 (1.0 to 2.1)	1.5 (1.1 to 2.0)	1.6 (1.2 to 2.1)	2.0 (1.2 to 3.4)	2.5 (1.8 to 3.4)	2.7 (1.5 to 4.8)	3.8 (2.3 to 6.3)
	II	1	1.4 (1.0 to 2.0)	1.5 (1.1 to 2.0)	1.6 (1.2 to 2.1)	2.0 (1.2 to 3.3)	2.5 (1.8 to 3.5)	2.6 (1.5 to 4.7)	3.7 (2.2 to 6.1)
	III	1	1.4 (1.0 to 2.0)	1.5 (1.1 to 2.0)	1.5 (1.1 to 2.0)	1.9 (1.1 to 3.2)	2.5 (1.8 to 3.5)	2.7 (1.5 to 4.8)	3.5 (2.1 to 5.9)
All-cause mortality, n		233	33	57	66	20	49	5	17
model	I	1	1.3 (0.9 to 1.9)	1.3 (0.9 to 1.7)	1.6 (1.2 to 2.1)	2.3 (1.4 to 3.6)	2.4 (1.8 to 3.3)	1.0 (0.4 to 2.5)	3.2 (1.9 to 5.2)
	II	1	1.3 (0.9 to 1.9)	1.3 (1.0 to 1.8)	1.6 (1.2 to 2.1)	2.2 (1.4 to 3.5)	2.6 (1.9 to 3.5)	1.0 (0.4 to 2.4)	3.0 (1.8 to 5.0)
	III	1	1.3 (0.9 to 1.9)	1.3 (0.9 to 1.7)	1.5 (1.2 to 2.0)	2.2 (1.4 to 3.6)	2.6 (1.9 to 3.5)	1.0 (0.4 to 2.5)	2.9 (1.7 to 4.8)

model I age, gender
model II model I + body mass index, systolic blood pressure, blood pressure-lowering medication
model III model II + type 2 diabetes mellitus, coronary artery disease
*Combined vascular endpoint is a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death

observed. In patients with type 2 diabetes mellitus the overall prevalence of albuminuria was 28% and of LVH 12%. The prevalence of impaired renal function, albuminuria and LVH was comparable in the group of patients with CAD, CVD or PAD/AAA.

Hypertensive target organ damage and risk for combined vascular endpoint and mortality

Compared with no target organ damage, the single presence of target organ damage was associated with an increased risk for combined vascular endpoints (LVH: HR 1.5, 95%CI 1.0-2.1; impaired renal function: HR 1.5, 95%CI 1.1-2.0; albuminuria: HR 1.6, 95%CI 1.2-2.1) (Table 3). Comparable risks were found for all-cause mortality (LVH: HR 1.3, 95%CI 0.9-1.9; impaired renal function: HR 1.3, 95%CI 0.9-1.7; albuminuria: HR 1.6, 95%CI 1.2-2.1). Compared with no target organ damage, double and triple combinations of target organ damage were associated with an even higher risk for the combined vascular endpoint, as well as for all-cause mortality (Table 3). The triple combination of hypertensive target organ damage represented the highest risk for the combined vascular endpoint (HR 3.8, 95%CI 2.3-6.3) and all-cause mortality (HR 3.2, 95%CI 1.9-5.2), compared to no target organ damage. Adjustment for potential confounding factors in model 2 and 3 did not affect the point estimates.

Different types of target organ damage were incorporated in a score from 0 to 3 types of target organ damage. Patients with all 3 target organs affected had an elevated risk for myocardial infarction (HR 3.0, 95%CI 1.5-6.2), had a 5.3 times higher risk for stroke (HR 5.3, 95%CI 2.2-12.3) and a 3.2 times higher risk for all-cause mortality (HR 3.2, 95%CI 1.9-5.2), compared to patients without signs of target organ damage (Table 4).

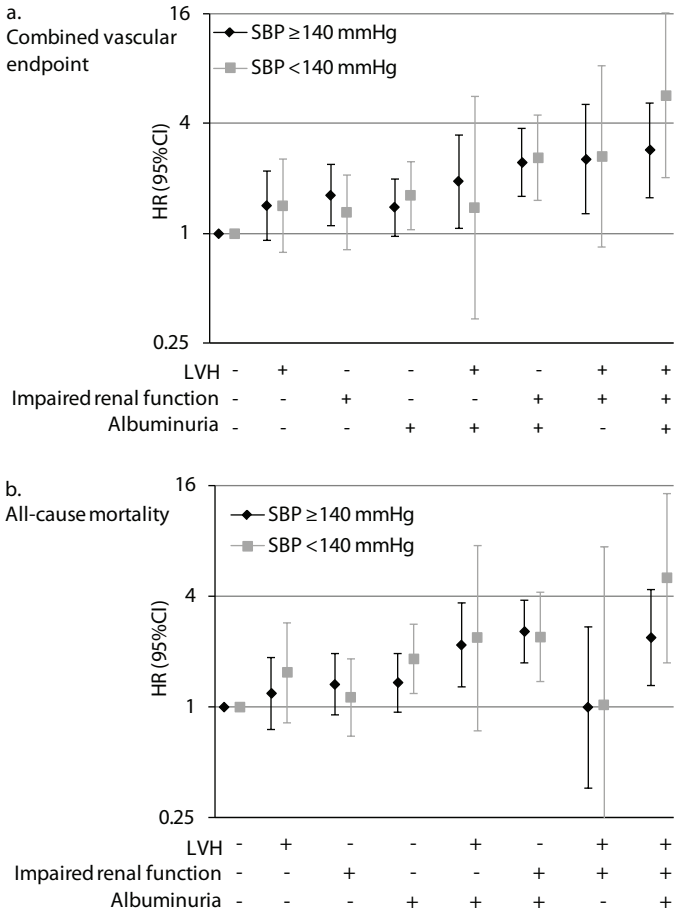
Effect modification of hypertension

As impaired renal function, albuminuria and LVH are most often the consequence of hypertension the potential effect modification of elevated blood pressure on the relation between target organ damage and the combined vascular endpoint and all-cause mortality was investigated. These analyses revealed that presence or absence of elevated blood pressure did not affect the relation between target organ damage and combined vascular endpoints and mortality (Figure 2 and model II in Table 3).

Discussion

In the present study it is shown that in patients with clinically manifest vascular disease impaired renal function, albuminuria or LVH was present in 34% of the patients and conferred an independent and additive risk for combined vascular endpoint and all-cause mortality. With increasing number of target organs damaged, the risk for stroke was higher compared to the risk for myocardial infarction. Although these measures of target organ damage are mostly the result of hypertension, the risk was independent of the present blood pressure.

Figure 2
Relation of the three different hypertensive target organ damage with combined vascular endpoints and all-cause mortality in patients with and without elevated blood pressure



LVH: left ventricular hypertrophy; SBP: systolic blood pressure
Model with age, gender, body mass index, systolic blood pressure, blood pressure-lowering medication, type 2 diabetes mellitus and coronary artery disease
Combined vascular endpoint is a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death

Table 4
Relation of increasing number of types of hypertensive target organ damage and vascular events or all-cause mortality

Number of hypertensive target organ damage		0	1	2	3
Left ventricular hypertrophy, n (%)		0 (0)	297 (26)	128 (21)	47 (33)
Impaired renal function, n (%)		0 (0)	382 (33)	218 (37)	47 (33)
Albuminuria, n (%)		0 (0)	464 (41)	250 (42)	47 (33)
n (%)		2,831 (66)	1,143 (26)	298 (7)	47 (1)
Myocardial infarction, n		155	72	27	8
		HR	HR (95%CI)	HR (95%CI)	HR (95%CI)
model	I	1	1.1 (0.8 to 1.5)	1.5 (1.0 to 2.3)	3.0 (1.5 to 6.2)
	II	1	1.1 (0.8 to 1.5)	1.5 (1.0 to 2.3)	2.9 (1.4 to 6.0)
	III	1	1.1 (0.8 to 1.5)	1.5 (1.0 to 2.3)	2.9 (1.4 to 6.0)
Stroke, n		68	54	28	6
model	I	1	2.0 (1.4 to 2.8)	3.8 (2.4 to 5.9)	5.3 (2.2 to 12.3)
	II	1	1.9 (1.3 to 2.8)	3.7 (2.3 to 5.8)	4.5 (1.9 to 10.9)
	III	1	1.8 (1.3 to 2.7)	3.6 (2.2 to 5.7)	4.3 (1.8 to 10.3)
Vascular death, n		120	96	45	14
model	I	1	1.7 (1.3 to 2.2)	2.6 (1.8 to 3.7)	5.0 (2.9 to 8.9)
	II	1	1.7 (1.3 to 2.2)	2.6 (1.8 to 3.7)	4.9 (2.7 to 8.7)
	III	1	1.6 (1.2 to 2.1)	2.6 (1.8 to 3.7)	4.6 (2.6 to 8.2)
Combined vascular endpoint*, n		251	162	70	17
model	I	1	1.5 (1.2 to 1.9)	2.4 (1.8 to 3.1)	3.8 (2.3 to 6.3)
	II	1	1.5 (1.2 to 1.9)	2.4 (1.8 to 3.1)	3.7 (2.2 to 6.1)
	III	1	1.5 (1.2 to 1.8)	2.4 (1.8 to 3.1)	3.5 (2.1 to 5.9)
All-cause mortality, n		233	156	74	17
model	I	1	1.4 (1.1 to 1.7)	2.2 (1.7 to 2.9)	3.2 (1.9 to 5.2)
	II	1	1.4 (1.1 to 1.7)	2.2 (1.7 to 2.9)	3.0 (1.8 to 5.0)
	III	1	1.4 (1.1 to 1.7)	2.2 (1.7 to 3.0)	2.9 (1.8 to 4.9)

model I age, gender
model II model I + body mass index, systolic blood pressure, blood pressure-lowering medication
model III model II + type 2 diabetes mellitus, coronary artery disease
*Combined vascular endpoint is a composite of non-fatal myocardial infarction, non-fatal stroke or vascular death

The prevalence of impaired renal function (15%) and albuminuria (18%) in our study was comparable with other studies in patients with symptomatic vascular disease. In patients with a previous myocardial infarction, 9.3% had albuminuria, 17.3% had impaired renal function (eGFR <60 mL/min/1.73 m^2) and 4.2% had both.[15] As there are various definitions of ECG-LVH and most studies are performed in populations without previous coronary artery disease, the reported prevalences of LVH are difficult to compare. In the present study a prevalence of ECG-LVH of 11% was observed, which is lower than the prevalence in a hypertensive population (22%)[16] and a population with acute non-Q-wave myocardial infarction (23%).[17]
We show that the combined presence of impaired renal function, albuminuria and ECG-LVH in a cohort of patients with manifest vascular disease is high. Therefore, these results confirm current guidelines where it is recommended to screen every patient with vascular disease for these forms of hypertensive target organ damage.[18-20] Screening is also recommended in patients with vascular diseases without hypertension, and in patients with cardiac disease.

In patients with a previous myocardial infarction the combined presence of both an impaired renal function and albuminuria was associated with an elevated risk for myocardial infarction (HR 1.8, 95%CI 1.3-2.5), for stroke (HR 1.7, 95%CI 0.9-2.0) and for all-cause mortality (HR 2.4, 95%CI 1.7-3.3).[15] A previous study in a smaller cohort of patients showed that the combined presence of impaired renal function and albuminuria is associated with the highest risks of vascular events, vascular mortality and all-cause mortality.[2] In the present study, addition of ECG-LVH as a measure of target organ damage identifies 297 (7%) patients with very high risk for vascular events and mortality who would not be identified using only measurements of renal function and albuminuria. Therefore, measurement of ECG-LVH should not be omitted in the assessment of hypertensive target organ damage in patients with vascular disease. The number of events in this study made it possible to analyze the association of hypertensive target organ damage and the risk for myocardial infarction and stroke and to analyze effect modification by the presence or absence of hypertension on hypertensive target organ damage and the risk for vascular events or all-cause mortality. ECG-LVH has a low sensitivity for detecting LVH, but is an independent risk factor for vascular events.[6,7] During the first year after an acute myocardial infarction, presence of ECG-LVH was related to increased mortality risk (HR 1.7, p=0.4) and for re-infarction (HR 2.1, p<0.005) compared with no ECG-LVH.[17]
The fact that the risks associated with presence of hypertensive organ damage are additive may indicate different pathological mechanisms or may reflect the extent of damage as a result of prolonged exposure to elevated blood pressure. LVH, impaired renal function and albuminuria are all the result of longstanding exposure to hypertension.[21-23] Renin-angiotensin-aldosterone system (RAAS) activation, activation of the sympathetic nervous system and insulin resistance are all entangled effects and causes of LVH, impaired renal function and albuminuria.[24-26] Although the pathological pathway leading to hypertensive target organ damage may be the same, the pathological effects of LVH,

impaired renal function and albuminuria may exacerbate each other. Impaired renal function can lead to volume expansion by RAAS activation, which causes hypertension and an increased afterload and can eventually cause impairment of ventricular function.[27] There is strong evidence that patients with chronic kidney disease as demonstrated with impaired renal function and/or albuminuria[28,29] and LVH[30] benefit from aggressive blood pressure-lowering, especially with RAAS blockade. Thus it could be argued that patients with vascular disease with hypertensive target organ damage should have lower blood pressure treatment targets including RAAS blockade. Our analyses showed that the increased risk of LVH, impaired renal function and albuminuria is independent of hypertension which implicates that also patients without hypertension might benefit from blood pressure-lowering therapy and from RAAS blockade.

Strengths of the present study include the large sample size and the large number of follow-up years and large number of relevant clinical endpoints. Addition of potential confounders did not influence the results. Some study limitations need to be considered. Urinary albumin and serum creatinine were measured on a single occasion, which may introduce some inaccuracy and misclassification that could have led to an underestimation of the risk for vascular events and mortality.[31] The use of angiotensin converting enzyme-inhibitors and angiotension-II receptor blockers for blood pressure treatment and post myocardial infarction influences albuminuria and could give an underestimation of the presence of albuminuria. LVH was measured on ECG. LVH-ECG does have a low sensitivity to detect LVH compared to anatomical measurements of LVH like cardiac-MRI.[32] However, it is readily available at low cost and recommended in guidelines. Due to the low sensitivity to detect LVH the impact of LVH on vascular endpoints and mortality could be underestimated.
In conclusion, the single and combined presence of impaired renal function, albuminuria and LVH is highly prevalent in patients with clinical manifest vascular disease and confers independent and additive risks for the combined vascular endpoints and mortality. Routine measurement of hypertensive target organ damage identifies patients at the highest risk and may direct treatment of blood pressure.

Acknowledgments

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Chapter 6

Internet-based vascular risk factor management for patients with clinical manifest vascular disease; a randomized controlled trial

J.W.P. Vernooij

H.A.H. Kaasjager

Y. van der Graaf

J. Wierdsma

H.M.H. Grandjean P.C.

M.M.C. Hovens

G.A. de Wit

F.L.J. Visseren

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Abstract

Objective

To investigate whether an internet-based, nurse-led vascular risk factor management program promoting self-management on top of usual care is more effective than usual care alone in reducing vascular risk factors in patients with clinical manifest vascular disease.

Methods

A prospective multicentre randomized controlled trial comparing intervention via internet plus usual care to usual care alone. Included were patients diagnosed with a recent clinical manifestation of atherosclerosis in the coronary, cerebral or peripheral arteries and with ≥2 treatable risk factors not at goal. The intervention consisted of a personalized website with an overview and actual status of patients' risk factors and mail communication via the website with a nurse practitioner for 12 months.

Results

A total of 330 patients were randomized. After 1 year we found a relative change of -14% (95%CI -25 to -2%) in Framingham Heart Risk (FHR) score of the intervention group compared to the usual care group. At baseline, the FHR score was higher in the intervention group than in the usual care group (16.1 SD 10.6 versus 14.0 SD 10.5). Therefore we adjusted the outcome for the separate variables of the FHR score and for the baseline FHR score. This showed a relative change of -12% (95%CI -22 to -3%) respectively -8% (95%CI -18 to 2%).

Conclusion

An internet-based nurse-led treatment program on top of usual care of vascular risk factors has a small effect on lowering vascular risk and on lowering of some vascular risk factors in patients with vascular disease.

Trial registration

ClinicalTrials.gov identifier NCT00785031.

Introduction

Patients with a recent clinical manifestation of a vascular disease (e.g. myocardial infarction, stroke, peripheral arterial disease) are at increased risk for developing a new vascular event or death.[1] Nowadays more patients survive an acute vascular event and as a consequence the total number of patients in the chronic phase of vascular disease is increasing. Established strategies to reduce vascular risk are to treat hypertension, to lower LDL-cholesterol, to use platelet inhibitors, weight-control, cessation of smoking and increasing physical exercise.[2-5] Treatment of these risk factors, alone or in combination, is proven to be very effective in reducing the risk of recurrent vascular events (myocardial infarction, ischemic stroke) and death.[6] However, in daily clinical practice, treatment goals are often not reached. In a prospective cohort study in patients with established vascular disease or type 2 diabetes, 1.5 years after referral to the hospital and even after participating in a risk factor screening program, the prevalence of hypertension was 43%, hypercholesterolemia 40%, obesity 24% and smoking 19%.[7] Comparable numbers are seen in patients with coronary artery disease,[8] indicating that a large proportion of patients with a clinical manifestation of a vascular disease still are at high residual cardiovascular risk by not reaching treatment targets as advocated in (inter)national guidelines.
Treatment of vascular risk factors by nurse practitioners has proven to be effective in reducing cardiovascular riskfactors[9] and vascular risk[10] but this treatment is costly and time-consuming for patients and healthcare professionals, as frequent visits to the outpatient clinic are required. Stimulating self-management is shown to be effective in lowering blood pressure[11] and supporting self-management with an internet-program may add to the effectiveness of the nurse practitioner intervention. The use of internet is a low-cost method compared to a regular outpatient clinic. There is already experience and evidence for effective internet-based treatment of depression,[12,13] physical activity in patients with rheumatoid arthritis,[14] pain reduction in patients with fibromyalgia,[15] reduced mortality and hospitalisation in patients with heart failure[16] and glucose control in patients with type 2 diabetes.[17-19] In a small, single-centre, uncontrolled, pilot study, an internet-based and nurse-led vascular risk reduction program on top of usual care, was feasible and showed beneficial effects on risk factor levels after 6 months.[20] The objective of the present multicentre, randomized trial was to evaluate the 1-year effect of an internet-based, nurse-led vascular risk factor management program on vascular risk and vascular risk factors in patients with clinical manifest vascular disease.

Methods

Trial design

The study was a multicentre, prospective, randomized controlled trial comparing intervention via internet plus usual care to usual care. Randomization was done by the local study coordinator using an online randomization procedure with a printed confirmation. Participant assignment was checked by the overall study coordinator with the printed confirmation.

Study population

All patients were diagnosed with a recent clinical manifestation of atherosclerosis in the coronary, cerebral or peripheral arteries and were referred by their vascular specialist (vascular surgeon, cardiologist, neurologist) and/or the general practitioner in the Rijnstate Hospital Arnhem, The Netherlands, a teaching hospital, and at the University Medical Center Utrecht, Utrecht, The Netherlands. The study was approved by the medical ethics committee of the UMC Utrecht (No. 08-119/O) and the local medical ethics committee of the Rijnstate Hospital Arnhem and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent.

As part of routine clinical practice vascular risk factors were measured. Patients between 18 and 80 years were eligible for participation in the present study if ≥2 of the following 6 treatable risk factors were not at target: systolic blood pressure >140 mmHg; LDL-cholesterol >2.5 mmol/l; triglycerides >1.7 mmol/l; BMI >25 kg/m^2; diabetes or fasting glucose >6.1 mmol/l; and smoking. Patients had to be able to read and write Dutch, to be independent in daily activities (Rankin score <3),[21,22] and to have access to internet at home. Patients with an estimated life expectancy less than 2 years or a malignant disease were not included in the study.

Internet-based nurse-led risk factor program and usual care

Patients meeting the inclusion criteria and not meeting the exclusion criteria were invited to participate in the study. After obtaining informed consent, patients were randomized to receive either internet-based care or usual care.

Patients randomized to the internet program received an internet-based vascular risk factor management program on top of usual care during 1 year. For this purpose a website was constructed and tested in a pilot study[20] and based on evaluation of the website by patients in the pilot study several improvements were made. The website has been developed using Microsoft Visual Studio 2005 (development environment) in Visual C# (programming language). The website uses a Microsoft SQL Server 2005 database for data storage. The scripts for the website can be obtained via the corresponding author. At the start patients were invited for a visit to the outpatient clinic of the nurse practitioner in the hospital during 1 hour. At this visit patients received information on their risk factor levels and received instructions about the internet program and received a username and password for their personalized website. Subsequent contacts between patient and nurse practitioner were through the internet and no further outpatient clinic visits were scheduled. Depending on presence of risk factors that needed (additional) treatment, the website was personalized for each individual patient by the nurse practitioner on average taking 10 minutes. The opening page showed an overview of the actual status of all risk factors (green=at goal, yellow=close to goal, red=needs attention) and medication use (Supplementary figure A). Within the personalized website, each risk factor was displayed on a separate internet page containing a history of risk factor measurements (e.g. blood pressure or LDL-cholesterol, etc), medication use, treatment goal, advices from the nurse, correspondence between nurse and patient, and news items for that particular risk factor

(Supplementary figure B). Patients were instructed to use the website as frequent as considered convenient and necessary at their own discretion and to login at least every other week to submit new measurements (blood pressure, weight, smoking status, cholesterol) and to read and send messages.
The internet program was linked to the website of the University Medical Center Utrecht for general information on risk factors and vascular diseases. The nurse practitioner was able to view all files and pages from all patients and had access to pages with a total overview of the current status of risk factors, last log-in attempts of each patient and new messages sent by patients. The treating nurse practitioner logged-in every working day and replied to messages sent by patients and sent messages to patients not using the program at least every other week. In case of non response by a patient the nurse contacted patients by phone. Patients were encouraged to self-measure blood pressure at home or ask the general practitioner to measure blood pressure. Patients were free to use their own device as this a reflection of daily clinical practice. For measuring plasma lipids and/or glucose patients received laboratory forms from the nurse by mail for drawing blood in their own city or at the University Medical Center Utrecht or Rijnstate Hospital Arnhem, whichever was convenient for the patient. The nurse practitioner worked according to the Dutch cardiovascular risk management guideline 2006[23], which is closely related to the 2003 ESC/EAS guidelines,[24] for the diagnosis and treatment of vascular risk factors. The nurse practitioners were supervised by internists. Changes in medication regimen were made by sending pharmacy-recipes to patients by regular mail. The care delivered by the nurse practitioner with the internet program was on top of usual care and did not replace the care given by the treating physician in the hospital and the general practitioner.

The usual care given by medical specialist and/or general practitioner was also based on the Dutch cardiovascular risk management guideline 2006. The guideline was applicable for primary care and hospital care. Patients randomized to usual care were asked and to contact their treating physician in the hospital (vascular surgeon, cardiologist, neurologist) and/or the general practitioner for risk factor management. The treating physician and the general practitioner were also informed in writing on the risk factor status. The treating physician was free to determine the frequency of control. This could differ from a once a year visit for a stable coronary artery disease patient to every 3 months for a type 2 diabetes mellitus patient to his general practitioner.

Study measurements

At baseline medication use, exercise, and smoking were registered, blood pressure, weight, height, and waist circumference were measured, and fasting blood was drawn for measurement of lipids, glucose, and creatinine, and urine analysis for albuminuria was performed. After 12 months all patients in both groups were asked to return to the clinic for the same measurements. Follow-up measurements were performed by independent research nurses not aware of the treatment allocation of the patients. The four-variable Modification of Diet in Renal Disease (MDRD) equation was used to calculate estimated

glomerular filtration rate (eGFR).[25] Albuminuria was defined as an urine albumin/creatinine ratio ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women.[26] Type 2 diabetes mellitus was defined as a referral diagnosis of type 2 diabetes mellitus, use of glucose-lowering medication, or fasting glucose ≥7.0 mmol/L at screening.

Primary endpoint and secondary endpoints

The primary endpoint was the relative change in Framingham Heart Risk score after 1 year.[27] This is calculated as the difference between the groups in change in Framingham Heart Risk score between baseline and after 1 year follow up: (baseline Framingham Heart Risk minus follow up Framingham Heart Risk in usual care group) - (baseline Framingham Heart Risk minus follow up Framingham Heart Risk in intervention group) divided by the mean Framingham Heart Risk score at baseline. The Framingham Heart Risk score was calculated for each individual patient at baseline and after 1 year follow up based on actual risk factor levels. The Framingham Heart Risk score represents the predicted 10-year risk for coronary heart disease. The Framingham Heart Risk score is developed for patients free of vascular disease. In the present study the Framingham Heart Risk score is used as a summary score of vascular risk factors.[28] The estimated absolute risk level by Framingham Heart Risk cannot be regarded as a precise reflection of actual risk,[29] but absolute change in Framingham Heart Risk over time is likely to reflect absolute changes in risk.

The secondary endpoints were the differences between intervention group and usual care group in the absolute changes in the levels of risk factors (level at 1 year minus level at baseline) and the differences between groups in the change in proportion of patients reaching treatment goals for each risk factor.

Sample size calculation

For the primary outcome we aimed to detect a 10% relative difference in the Framingham Heart Risk score between the two groups based on a pilot study.[20] We considered this a minimal difference to be clinically relevant. In the pilot study (n=50) we found a change in Framingham Heart Risk score from 11.2 standard deviation (SD) 7.8 to 9.0 SD 5.8, difference -2.2 SD 6.0. For the present study patients were recruited among participants from an ongoing cohort study with a higher mean age compared to the patients in the pilot study and a higher Framingham Heart Risk score of 20%. For the sample size calculation we used an absolute change in Framingham Heart Risk Score of -2.0 SD 6.0, an alpha of 0.05 and a power of 80%. The calculated sample size was 146 patients in each group.

Adverse events and clinical endpoints

During follow-up, patients were asked to fill out a questionnaire by internet every 3 months, to report newly diagnosed diseases and hospital admissions. When suspected for a cardiovascular event, patients' medical records and documentation were retrieved from their treating specialist or general practitioner. Suspected vascular events and mortality were assessed separately by 3 independent non-treating specialists. Registered events included vascular interventions (for example percutaneous coronary artery interven-

tions), stroke, myocardial infarction, vascular mortality and other severe adverse events (all events causing death, life-threatening events, requiring at least one night of hospital stay or prolonged hospital stay or causing significant invalidity or labour incapacity) and non-severe adverse events (any reported event).

Data analyses

Results were expressed as means with standard deviations or as absolute numbers and percentages. Not-normal distributed variables were expressed as median and interquartile range. Absolute changes in Framingham Heart Risk score and individual risk factors between baseline and follow up are presented with 95% confidence intervals (CI) in complete case analyses. Also, the change in percentages of patients that achieve treatment goals for individual risk factors were calculated for both groups. Differences in absolute changes in Framingham Heart Risk and risk factors between groups between baseline and 12 months follow up and differences between groups in proportion of patients achieving treatment goals were tested with independent sample t-test. Sensitivity analyses were done by imputing the missing values with the last observation carried forward, truncation of extreme values and calculation of the intervention result by linear regression with adjustment for baseline risk. All statistical analyses were performed with SPSS statistics 18.0.2 (IBM Corp., New York, USA).

Results

Baseline characteristics

Patients were recruited between October 2008 and March 2010. A total of 638 patients fulfilling inclusion criteria were invited for participation of which 330 patients were randomized (Figure 1). The mean age was 59.9 SD 8.4 years and most patients were male (75%) (Table 1). All patients had a recent manifestation of vascular disease, most frequently this was coronary artery disease (49%). Mean LDL-cholesterol was 2.8 SD 0.9 mmol/l and mean systolic blood pressure was 140 SD 18 mmHg.

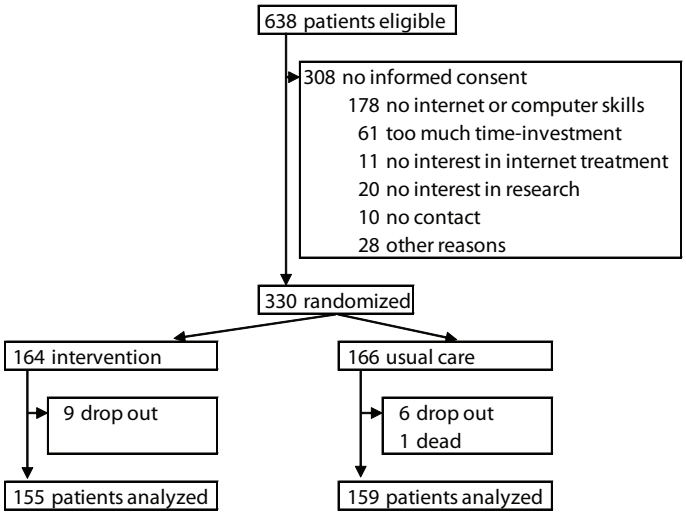
The main reason not to participate in the study was the absence of internet access or basic computer skills (58%). Patients not randomized were slightly older (62.1 SD 10.7 vs. 59.9 SD 8.4 years) and more often female (33% vs. 25%) (Supplementary table A).

During the study 16 patients (4.8%) dropped out and did not have a follow-up measurement. Those patients appeared to be of equal age compared to the patients with complete follow-up (59.6 SD 8.0 vs. 59.9 SD 8.4 years), were more often female (37% vs. 25%) and appeared to have a worse risk factor profile (Framingham Heart Risk score 18.1 SD 19.1 vs. 15.0 SD 10.6) (Table 2).

Difference in change in Framingham Heart Risk score between intervention group and control group

After 1 year we found a relative change of -14% (95%CI -25 to -2%) in Framingham Heart Risk score of the intervention group compared to the usual care group. At baseline, the Framingham Heart Risk score was higher in the intervention group than in the usual care group (16.1 SD 10.6 versus 14.0 SD 10.5). Therefore we adjusted the outcome for the separate variables of the Framingham Heart Risk score (age, gender, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, type 2 diabetes mellitus and current smoking) and for the baseline level of the Framingham Heart Risk score using linear regression analysis. This showed a relative change of -12% (95%CI -22 to -3%) respectively -8% (95%CI -18 to 2%) in Framingham Heart Risk score of the intervention group compared to the usual care group adjusted for the separate variables of the Framingham Heart Risk score and adjusted for the baseline level of the Framingham Heart Risk score, the latter being not statistically significant. The range of the Framingham Heart Risk score was 0.7 to 60.0. The difference in change in LDL-cholesterol was -0.3 mmol/l (95%CI -0.5 to -0.1, p<0.001). This translated in a difference between groups in patients reaching the LDL-cholesterol goal <2.5 mmol/l of 18.4% (95%CI 5.9 to 30.9, p=0.004). In the intervention group from the 42 smokers 8 (19%) stopped smoking compared to the usual care group were 4 patients (10%) started smoking, a difference in change between groups in patients that quit smoking of 7.7% (95%CI 0.4 to 14.9, p=0.038) (Table 4). Some other risk factors tended to improve (BMI, triglycerides, systolic blood pressure, renal function) or tended to worsen (glucose, albuminuria).

Figure 1
Flowchart



Truncation of extreme values of the Framingham Heart Risk score (<1% and >99% percentiles) or imputation of missing values with the last observation carried forward revealed similar differences in change of Framingham Heart Risk score between groups (Table 5). Stratification for gender, age, type 2 diabetes mellitus, BMI or smoking status revealed similar results.

Use of the website by patients

From the patients in the intervention group (n=155) 152 patients actually logged in, a median of 56 times (interquartile range (IQR) 35 to 83) during 1 year (Supplementary table B). Patients (n=134) sent median 14 (IQR 7 to 22) messages and 131 patients entered median 7 (IQR 3 to 14) measurements during 1 year. Measurements most entered considered blood pressure (111 patients, median 2, IQR 2 to 6) and weight (114 patients, median 3, IQR 1 to 6). The monthly number of logins decreased during intervention period with a maximum in the 3rd month with 1099 logins to 435 login in the 12th month (Supplementary figure C). Patients in the highest tertile of website use had the highest Framingham Heart Risk score (17.6 SD 10.7) compared to patients in the lowest tertile of website use (Framingham Heart Risk score 14.1 SD 9.1). Patients in the highest tertile of website use had the largest change in Framingham Heart Risk score during intervention (-3.8 (95%CI -6.3 to -1.3) compared to those in the lowest tertile of website use (change in Framingham Heart Risk score -1.4 (95%CI -3.6 to 0.8) (Supplementary table C). During the 1-year intervention period the time spent by nurse practitioners was on average 23 SD 12 minutes/month/patient.

Vascular events and other severe adverse events

Forty patients reported a total of 50 vascular events (Table 6). The intervention was safe as the HR for a subsequent vascular event was 0.66 (95%CI 0.35 to 1.24) and this was HR 0.64 (95%CI 0.34 to 1.21) after adjustment of baseline Framingham Heart Risk score. Vascular events occurred equally throughout the study period as shown in the Kaplan-Meier curve (Figure 2). Thirty-eight patients reported 47 other severe adverse events of which 5 severe bleeding events.

Discussion

This study showed that an internet-based nurse-led vascular prevention program on top of usual care compared to usual care alone resulted in a small relative reduction in the Framingham Heart Risk score of 14% after 12 months in patients with clinical manifest vascular disease. At baseline, the Framingham Heart Risk score was higher in the intervention group than in the usual care group. Therefore the primary outcome was adjusted for the separate variables of the Framingham Heart Risk score and for the baseline Framingham Heart Risk score. The difference in the primary outcome was not statistically significant after adjusting for baseline Framingham Heart Risk score. The clinical importance of

Table 1
Baseline characteristics

	Intervention (n=164)	Usual care (n=166)
Age (years)	60.7 (7.8)	59.2 (8.9)
Male gender, n (%)	128 (78)	118 (71)
Body mass index (kg/m^2)	28.2 (4.1)	27.4 (3.9)
Total cholesterol (mmol/l)	4.7 (1.1)	4.7 (1.0)
HDL-cholesterol (mmol/l)	1.2 (0.3)	1.2 (0.3)
Triglycerides (mmol/l)	1.8 (1.1)	1.7 (1.1)
LDL-cholesterol (mmol/l)	2.8 (0.9)	2.8 (0.9)
Glucose (mmol/l)	6.3 (1.4)	6.3 (1.5)
Systolic blood pressure (mmHg)	140 (18)	139 (18)
Diastolic blood pressure (mmHg)	81 (10)	80 (10)
eGFR (ml/min/1.73m^2)	80 (18)	80 (17)
Albuminuria, n (%)	20 (12)	20 (12)
Vascular disease at inclusion, n (%)		
Coronary artery disease	75 (46)	69 (42)
Cerebral vascular disease	44 (27)	51 (31)
Abdominal aortic aneurysm	7 (4)	8 (5)
Peripheral vascular disease	38 (23)	38 (23)
Medical history, n (%)		
Coronary artery disease	86 (52)	77 (46)
Cerebral vascular disease	40 (24)	51 (31)
Abdominal aortic aneurysm	3 (2)	5 (3)
Peripheral vascular disease	26 (16)	23 (14)
Type 2 diabetes mellitus	43 (26)	34 (20)
Current smoking	43 (26)	44 (27)
Family history of cardiovascular disease	77 (48)	92 (56)
Medication use, n (%)		
Platelet aggregation inhibitor	154 (94)	153 (92)
Lipid-lowering medication	142 (87)	140 (84)
Blood pressure-lowering medication	130 (79)	113 (68)
Glucose-lowering medication	29 (18)	23 (14)

eGFR indicates estimated glomerular filtration rate
Data are expressed as mean (standard deviation)or as number (percentage)

Table 2
Baseline characteristics of drop outs versus analyzed patients

	Drop outs (n=16)	Analyzed (n=314)
Age (years)	59.6 (8.0)	59.9 (8.4)
Male gender, n (%)	10 (63)	236 (75)
Body mass index (kg/m^2)	27.5 (4.1)	27.8 (4.0)
LDL-cholesterol (mmol/l)	3.1 (1.0)	2.7 (0.9)
Systolic blood pressure (mmHg)	149 (22)	139 (18)
Current smoking, n (%)	4 (25)	83 (26)
Framingham Heart Risk score	18.1 (19.1)	15.0 (10.6)

Data are expressed as mean (standard deviation) or as number (percentage)

this effect is small and limited. A larger reduction in LDL-cholesterol and a larger proportion of patients that stopped smoking was observed in the intervention group compared to the usual care group.

Comparison with other studies

Randomized controlled trials on lowering overall vascular risk with the use of internet interventions are scarce. In primary prevention, a 2-year randomized controlled trial with the use of a website with education modules and personal tailored counselling support in 276 healthy overweight subjects showed no effect on vascular risk factors, although several risk factors tended to improve.[30] A cluster-randomized controlled trial in 163 patients with type 2 diabetes who received the combined intervention of behavioural mobile phone and internet coaching with presentation of blood glucose levels, lifestyle measurements, and self-management support was effective in reducing glycated haemoglobin levels after 1 year by 1.2% (95%CI 0.6 to 1.8) compared to a control group.[17] In that study, no differences in blood pressure or plasma lipid levels were observed between groups. In a small randomized controlled study (n=15) in patients after a myocardial infarction a virtual cardiac rehabilitation program, consisting of on-line intake forms, one-on-one chat sessions with a nurse, dietician, and exercise specialist, downloadable exercise heart rate monitoring, education and data monitoring of blood pressure, weight, and glucose, resulted in significant changes in HDL-cholesterol, triglycerides, exercise capacity and weekly physical activity after 12 weeks.[31] Evaluation of a web-based cardiac rehabilitation program for patients with vascular disease, consisting of e-mail contact with a case manager, education modules assigned by the case manager, and entering data (e.g., number of minutes of exercise, blood pressure measurements), in combination with the option of participating in an online discussion group, resulted in a decrease in BMI of 0.7 kg/m^2 compared to a control group after 6 months.[32] In that study blood pressure, lipid values and physical exercise improved as well but this was not statistically significant.

Table 3
Difference in change in Framingham Heart Risk score and vascular risk factors between intervention group and usual care group

	Intervention (n=155)		Usual care (n=159)			
	Baseline	Follow-up	Baseline	Follow-up	Difference intervention and usual care* (95%CI)	Relative change† (95% CI)
Framingham Heart Risk score	16.1 (10.6)	13.2 (8.9)	14.0 (10.5)	13.2 (9.4)	-2.1 (-3.8 to -0.3)	**-14% (-25 to -2%)**
					-1.8 (-3.3 to -0.4)‡	**-12% (-22 to -3%)**‡
					-1.2 (-2.7 to 0.3) §	**-8% (-18 to 2%)**§
Age (years)	60.8 (7.9)		59.1 (8.9)			
Male gender	121 (78)		115 (72)			
Body mass index (kg/m^2)	28.2 (4.2)	28.6 (4.1)	27.5 (3.9)	27.9 (4.2)	-0.1 (-0.5 to 0.4)	
Total cholesterol (mmol/l)	4.7 (1.0)	4.3 (0.9)	4.7 (1.0)	4.5 (1.0)	**-0.3 (-0.5 to -0.1)**	
HDL-cholesterol (mmol/l)	1.2 (0.3)	1.3 (0.4)	1.2 (0.3)	1.3 (0.4)	0.0 (-0.1 to 0.0)	
Triglycerides (mmol/l)	1.8 (1.1)	1.6 (1.2)	1.7 (1.2)	1.4 (0.7)	0.1 (-0.1 to 0.4)	
LDL-cholesterol (mmol/l)	2.8 (0.9)	2.3 (0.7)	2.7 (0.9)	2.6 (0.9)	**-0.3 (-0.5 to -0.1)**	
Glucose (mmol/l)	6.3 (1.5)	6.4 (1.5)	6.3 (1.4)	6.3 (1.7)	0.1 (-0.1 to 0.4)	
HbA1c	5.8 (0.7)	5.9 (0.9)	5.7 (0.7)	5.9 (0.7)	0.0 (-0.1 to 0.1)	
SBP (mmHg)	140 (17)	137 (18)	138 (18)	140 (19)	-3.7 (-7.6 to 0.2)	
DBP (mmHg)	81 (10)	80 (9)	79 (10)	80 (10)	-2.0 (-4.4 to 0.4)	
eGFR (ml/min/1.73m^2)	80 (18)	80 (18)	80 (17)	79 (17)	0.9 (-1.6 to 3.4)	
Albuminuria	20 (13)	25 (17)	18 (11)	18 (12)	0.7 (-6.6 to 8.1)	

SBP indicates systolic blood pressure, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate

*Difference between groups: (baseline value–follow-up value in usual care group)-(baseline value–follow-up value in intervention group)

†Relative change was calculated by dividing by the mean FHR at baseline x 100%

‡Adjusted for baseline age, gender, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, type 2 diabetes mellitus, current smoking

§Adjusted for baseline FHR score

Data are expressed as mean (standard deviation) or as number (percentage)

Table 4
Difference in change in risk factors at target and medication use between intervention group and usual care group

	Intervention (n=155)		Usual care (n=159)		Difference intervention and usual care* (95% CI)
Risk factors	Baseline	Follow-up	Baseline	Follow-up	
Systolic blood pressure <140 mmHg (%)	48	54	50	54	2.0 (-10.5 to 14.5)
LDL-cholesterol <2.5 mmol/l (%)	39	65	41	48	**18.4 (5.9 to 30.9)**
HDL-cholesterol women ≥1.30, men ≥1.0 mmol/l (%)	60	66	69	72	2.0 (-7.7 to 11.8)
Triglycerides <1.7 mmol/l (%)	55	68	64	71	5.9 (-5.4 to 17.2)
Fasting glucose <6.1 mmol/l (%)	55	52	55	58	-6.4 (-16.7 to 3.9)
Body mass indexl <25.0 kg/m^2 (%)	16	17	26	23	3.9 (-1.8 to 9.6)
Waist women <88, men <102 cm (%)	45	42	53	44	2.5 (-7.0 to 12.0)
No smoking (%)	73	78	74	72	**7.7 (0.4 to 14.9)**
Type 2 diabetes mellitus, n(%)	26	28	20	22	0.0 (-5.0 to 5.1)
HbA1c <7%, <53 mmol/mol (%)	69	67	78	74	1.0 (-22.2 to 24.1)
Fasting glucose <8 mmol/l (%)	60	60	41	57	-18.9 (-46.4 to 8.6)
Glucose-lowering medication (%)	65	72	69	74	-2.5 (-18.9 to 13.8)
Number of risk factors on target†	2.9 (1.2)	3.4 (1.2)	3.1 (1.2)	3.3 (1.2)	**0.4 (0.1 to 0.6)**
Medication use					
Medication vascular disease‡ (%)	97	99	97	97	2.6 (-2.1 to 7.3)
Platelet aggregation inhibitor (%)	94	98	93	94	2.7 (-3.7 to 9.1)
Lipid-lowering medication (%)	86	90	86	88	0.8 (-7.7 to 9.2)
Blood pressure-lowering medication (%)	79	80	69	75	-5.0 (-11.7 to 1.6)

*Difference: (baseline value-follow-up value in usual care group)-(baseline value-follow-up value in intervention group)
†Risk factors: Systolic blood pressure, LDL-cholesterol, triglycerides, glucose, body mass index, smoking
‡Medication vascular disease: platelet aggregation inhibitors, lipid-lowering medication, blood pressure-lowering medication
Date are expressed as percentage or as mean (standard deviation)

Table 5
Sensitivity analyses

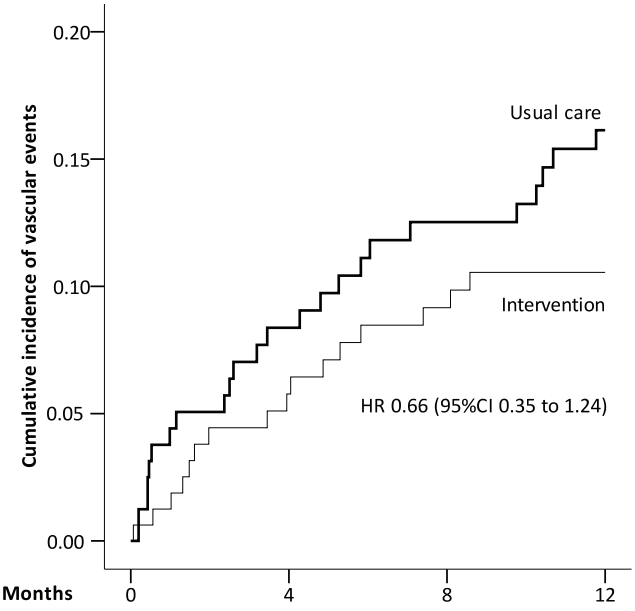
	Difference FHR intervention and usual care (95%CI)
No adjustments	**-2.1 (-3.8 to -0.3)**
Adjusted for baseline age, gender, SBP, LDL-c, HDL-c, T2DM, current smoking	**-1.8 (-3.3 to -0.4)**
Adjusted for baseline FHR score	**-1.2 (-2.7 to 0.3)**
FHR truncated at 1 and 99%	-1.8 (-3.5 to -0.2)
Last observation carried forward	-2.1 (-3.8 to -0.4)
Men	-2.1 (-4.3 to 0.2)
Women	-1.8 (-3.9 to 0.3)
Age under 61 years*	-1.7 (-3.5 to 0.1)
Age over 61 years	-2.5 (-5.8 to 0.8)
No T2DM	-1.9 (-3.6 to -0.2)
T2DM	-2.1 (-7.2 to 3.1)
Body mass index under 27 kg/m^2*	-1.5 (-3.7 to 0.8)
Body mass index over 27 kg/m^2	-2.6 (-5.2 to 0.0)
No smoking	-2.7 (-4.3 to -1.0)
Smoking	-0.2 (-4.7 to 4.3)

FHR indicates Framingham Heart Risk score, SBP: systolic blood pressure, LDL-c: LDL-cholesterol, HDL-c: HDL-cholesterol, T2DM: type 2 diabetes mellitus
*Stratified at median value

The present multicentre randomized controlled trial is the largest study conducted in this field to date. Sensitivity analysis showed a comparable result in subgroups and it is likely that the intervention can be widely implemented. The results of the present study can be generalized to patients with access to internet at home and with sufficient computer skills. It is likely that the number of patients without internet access or no computer skills will decrease in the coming years, also in the older age groups.[33] This could broaden the applicability of the intervention in the future. In the present study there was an age limit of 80 years. More widespread use of internet by elderly could make this an effective and efficient intervention by those less able to frequently travel to outpatient clinics. To use this intervention in other populations we think it would be very well possible to adapt the website but it would require careful planning and testing. Different populations should be addressed differently. For example a study about designing a cardiovascular disease

prevention website for Latinos.[34] This study showed that Latinos prefer a website that is culturally appropriate, with photos of a multigenerational family and available in Spanish. Using internet for the treatment of vascular risk factors, which is considered to be a chronic condition, is based on the chronic care model.[35,36] Crucial elements in this model are support of self-management, support of informed consent and organizing the health care process. Via internet all elements can be combined and is the patient is able to manage his own health in the place where it should be managed, namely in the own environment at time of choice. Some patients reported technical difficulties assessing the website. This might be due to inexperience of participating patients. Also, there was no screening of computer skills beforehand. Screening of computer skills or extra training might enhance use of the website. Every other week a summary of a news item was sent by email to all intervention patients and the whole news message could be read on the website. This was done to stimulate patients to visit the website and their personal pages on the website. It could be considered to start a (supervised) forum or a chat function to attract patients to the website and to further stimulate self management. Use of the study website on tablet computers or on smart-phones might increase adherence and could make the intervention accessible to a larger group of patients.

Figure 2
Kaplan-Meier curve for vascular events



Strengths and limitations of study

A summary score for vascular risk was used. We realize that the Framingham Heart Risk score is not developed for estimating the vascular risk in patients with clinical manifest vascular disease.[27] As yet, there is no such a validated score for patients with vascular diseases. The Framingham Heart Risk score is not accurate in estimating the absolute vascular risk in these patients, but can be used to evaluate relative differences and changes between groups. Secondly, the endpoint in the study was difference in change in Framingham Heart Risk score which is a surrogate measure. Although it is likely that this will translate into a lower vascular event rate and mortality rate, this can only be investigated in a clinical endpoint study. The changes in risk factors during the 1-year intervention period were extrapolated to change in 10-year cardiovascular risk. A permanent change in risk factors is assumed, but to maintain changes in risk factors the intervention should also cover the 10-year period. Third, an internet-based and nurse-led intervention might be cost-effective as the intervention is at least equally effective and could partly replace more expensive care by medical doctors. Nevertheless cost-effectiveness will be evaluated in a formal cost-effective analysis. Fourth, the duration of the intervention including the follow-up was 1 year and thus the time of smoking cessation was per definition less than 1 year. This is a short period to ensure a patient really stopped smoking. Accuracy could be enhanced by extending the follow-up period. Fifth, at baseline there was an imbalance in risk factors between groups, translating in a difference in the baseline level of the Framingham Heart Risk score. The intervention had a small effect on lowering the

Table 6
Adverse events

	Intervention		Usual care	
	n events	n patients	n events	n patients
All vascular events	18	16	32	24
Myocardial infarction	0	0	6	6
Fatal cerebrovascular event	0	0	1	1
Vascular intervention	18	16	25	20
Other severe adverse events	26	22	21	16
Severe bleeding	1	1	4	4
Total severe adverse events	44	38	53	40
Other adverse events	17	15	14	4

All vascular events is a composite of vascular interventions, stroke, myocardial infarction, vascular mortality

Other severe adverse events is a composite of death, life-threatening events, events requiring at least one night of hospital stay or prolonging of hospital stay, events causing significant invalidity or labour incapacity

Other adverse events are any reported event

absolute level of the Framingham Heart Risk score. This effect was statistical significant after adjustment for the separate variables of the Framingham Heart Risk score and not statistically significant adjusted for the baseline Framingham Heart Risk score. Nevertheless we feel that the results are important and consistent also considering the results of the secondary endpoints and subgroup analyses.

Conclusions and policy implications

An internet-based nurse-led treatment program on top of usual care of vascular risk factors has a small effect on lowering vascular risk and on lowering of some vascular risk factors in patients with vascular disease. The intervention used in the present study is easy to implement in clinical practice at low costs and could be used for various groups of patients at high cardiovascular risk.

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Supplementary figure A
Personal homepage

My Home Page UMC Utrecht and Rijnstate Hospital

Welcome mister Jansen. Your nurse practitioner is Anne de Vries.
Last time you used the website at November 7th 17:00h

My medication

	dose	frequency	
carbasalaat calcium	100 mg	once daily	blood clotting
ramipril	5 mg	once daily	high blood pressure
Simvastatin	20 mg	once daily in the evening	high cholesterol

Report changes to your nurse practitioner Anne de Vries

My risk factors

optimal | almost at goal… | not under control

Blood pressure	Cholesterol
Blood sugar	Body weight
Smoking	Exercise

My nurse practitioner

Your nurse practitioner is Anne de Vries

Name is fictitious and picture is of one of the authors.

Supplementary figure B
Personal risk factor page of smoking

UMC Utrecht and Rijnstate Hospital

Welcome mister Jansen. Your nurse practitioner is Anne de Vries.
Last time you used the website at November 7th 17:00h

Smoking

Messages for this risk factor

New message		Overview messages

My appointments

Date	Appointments
15-07-2011	Plan stop day
07-11-2011	Plan stop date

My measurements

New measurement		Print measurements

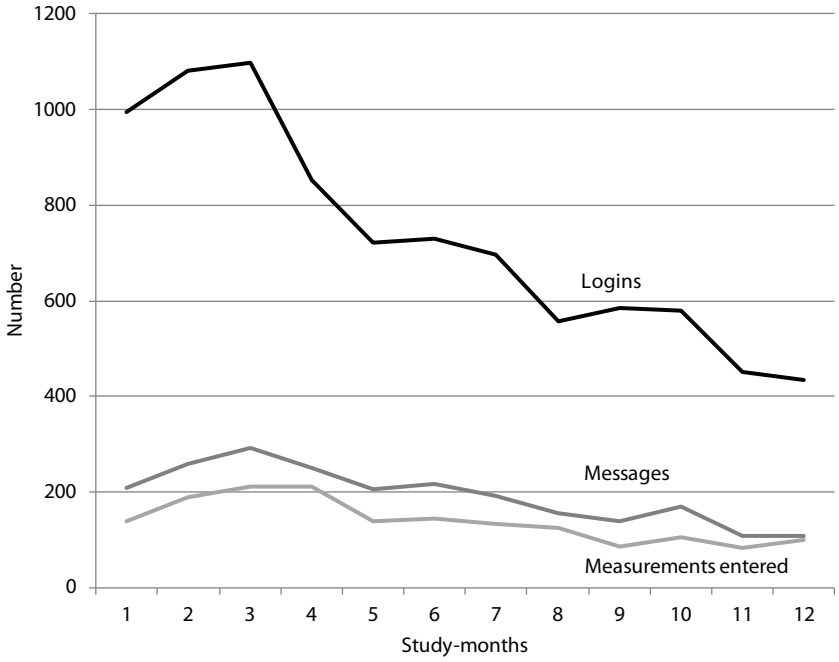
optimal | almost at goal… | not under control

	Start	<<	Last four measurements			>>	My goal	Normal
Date	15-05-2011	11-06-2011	12-07-2011	01-10-2011	07-11-2011		01-01-2012	
Amount			1	6	3		0	0
	Per day	Per week	Per day	Per week	Per week		Per day	Per day

Websites for this risk factor

www.stivoro.nl	Smoking
www.hulpbijstoppenmetroken.nl	Smoking
www.ikstop.nl	smoking

Supplementary figure C
Website use by patients per study-month



Supplementary table A
Baseline characteristics of non-randomized patients versus randomized patients

	Non-randomized (n=308)	Randomized (n=330)
Age (years)	62.1 (10.7)	59.9 (8.4)
Male gender, n (%)	205 (67)	246 (75)
Body mass index (kg/m^2)	27.6 (4.6)	27.8 (4.0)
Total cholesterol (mmol/l)	4.8 (1.1)	4.7 (1.0)
Glucose (mmol/l)	6.2 (1.4)	6.3 (1.5)
Systolic blood pressure (mmHg)	142 (20)	140 (18)
Type 2 diabetes mellitus, n (%)	64 (21)	77 (23)
Current smoking, n (%)	99 (32)	87 (26)
Diagnosis at inclusion, n (%)		
Coronary artery disease	125 (41)	144 (44)
Cerebral vascular disease	80 (26)	95 (29)
Abdominal aortic aneurysm	13 (4)	15 (5)
Peripheral vascular disease	78 (25)	76 (23)
Medical history, n (%)		
Coronary artery disease	147 (48)	163 (49)
Cerebral vascular disease	73 (24)	91 (28)
Abdominal aortic aneurysm	20 (7)	8 (2)
Peripheral vascular disease	44 (14)	49 (15)

Data are expressed as mean (standard deviation) or as number (percentage)

Supplementary table B
Website use by patients

Intervention group n=155	No. of patients	n per patient
Logins	152	56 [35 to 83]
Messages sent	134	14 [7 to 22]
Measurements entered	131	7 [3 to 14]
Blood pressure	111	3 [2 to 6]
Lipids	41	1 [1 to 2]
Glucose	35	1 [1 to 3]
Weight	114	3 [1 to 6]
Smoking	27	1 [1 to 4]
Excercise	48	2 [1 to 3]

Number of patients actually using the internet program and use of the internet program by these patients

Data are expressed as median [interquartile range] or as number

Supplementary table C
Intervention result stratified by website use patients

	tertiles of logins		
	1	2	3
	(n=51)	(n=52)	(n=52)
Logins	21.7 (12.1)	54.0 (8.7)	96.5 (20.9)
Range	0-38	39-68	69-166
Messages sent	4.0 (4.3)	12.9 (7.6)	26.8 (14.0)
Measurements	4.3 (5.5)	6.4 (5.3)	21.4 (28.2)
Age (years)	58.6 (8.3)	61.6 (6.9)	62.1 (8.1)
Male gender, n (%)	38 (75)	40 (77)	43 (83)
Body mass index (kg/m^2)	27.5 (4.1)	28.4 (3.6)	28.6 (4.8)
LDL-cholesterol (mmol/l)	2.8 (1.0)	2.7 (0.7)	2.8 (1.0)
Systolic blood pressure (mmHg)	135 (17)	140 (14)	144 (21)
Current smoking, n (%)	34 (67)	39 (75)	40 (77)
Framingham Heart Risk score	14.1 (9.1)	16.5 (11.6)	17.6 (10.7)
Change in Framingham Heart Risk score during intervention, (95%CI)	-1.4 (-3.6 to 0.8)	-3.3 (-5.4 to -1.1)	-3.8 (-6.3 to -1.3)

Data are expressed as mean (standard deviation) or as number (percentage)

Chapter 7

Cost-effectiveness of a nurse-led internet-based vascular risk factor management program: economic evaluation of a randomized controlled clinical trial

J.W.P. Vernooij

J.P. Greving

H.A.H. Kaasjager

J. Wierdsma

H.M.H. Grandjean P.C.

Y. van der Graaf

G.A. de Wit

F.L.J. Visseren

Submitted for publication

Abstract

Objective

To assess the cost-effectiveness of an internet-based, nurse-led vascular risk factor management program promoting self-management on top of usual care compared to usual care alone in patients with clinical manifest vascular disease.

Methods

Incremental cost-effectiveness analysis alongside a randomized controlled trial. Included were 330 patients with a recent clinical manifestation of vascular disease (myocardial infarction, stroke or peripheral arterial disease) and with ≥2 treatable vascular risk factors not on target. The intervention consisted of a personalized website with an overview and actual status of patients' risk factors and mail communication via the website with a nurse practitioner for 12 months.

Results

The intervention yields both improvements in number of QALYs (0.865 for the intervention group and 0.853 for the control group) and less societal costs (€4,460 for the intervention group and €4,723 for the usual care group) and thus, the intervention dominates usual care. The probability that the intervention is cost-effective at a threshold of €20,000 per QALY, was 66%. At mean annual cost of €155 per patient, the intervention was relatively cheap.

Conclusion

A one-year internet-based intervention to improve vascular risk factors in patients with a recent clinical manifestation of vascular disease on top of usual care is a cost-effective intervention.

Trial registration

ClinicalTrials.gov identifier NCT00785031.

Introduction

Patients with a recent clinical manifestation of a vascular disease (e.g. myocardial infarction, stroke, peripheral arterial disease) are at increased risk for developing a new vascular event or death.[1] Nowadays more patients survive an acute vascular event and as a consequence the total number of patients in the chronic phase of vascular disease is increasing. Established strategies to reduce vascular risk are to treat hypertension, to lower LDL-cholesterol, to use platelet inhibitors, to control weight, to stop smoking and to increase physical activity.[2-5] Treatment of these risk factors, alone or in combination, is proven to be very effective in reducing the risk of recurrent vascular events (myocardial infarction, ischemic stroke) and death.[6] However, in daily clinical practice, treatment goals are often not reached. In a prospective cohort study patients with established vascular disease or type 2 diabetes, the prevalence of hypertension was 43%, hypercholesterolemia 40%, obesity 24% and smoking 19%, even after participating in a risk factor screening program.[7] Comparable numbers are seen in patients with coronary artery disease,[8] indicating that a large proportion of patients with a clinical manifestation of a vascular disease still are at high residual cardiovascular risk by not reaching treatment targets as advocated in (inter)national guidelines.

Treatment of vascular risk factors by nurse practitioners has proven to be effective in reducing cardiovascular risk factors[9] and vascular risk[10] but this treatment is costly and time-consuming for patients and healthcare professionals, as frequent visits to the outpatient clinic are required. Treatment of vascular risk factors and supporting self-management with an internet-program may add to the effectiveness of the nurse practitioner intervention. The use of internet is a low-cost method compared to regular visits to the outpatient clinic, and therefore, it is anticipated that internet-based support by nurse practitioners is more cost-effective than a more traditional intervention.

The cost-effectiveness of internet-based interventions have been shown in a low vascular risk population,[11,12] in diabetes management[13] and in secondary prevention of heart disease.[14] The interpretation of the results and the generalizability of these studies are hampered by a short duration of the intervention, limited effect size, or a highly selected population.

The objective of the present multicentre, randomized, controlled trial was to evaluate the cost-effectiveness of an internet-based, nurse-led vascular risk factor management program on vascular risk and vascular risk factors in patients with clinical manifest vascular disease for the study duration of 1 year and for the patients' life span.

Methods

Study design and patients

A detailed description of the design and intervention of the Risk factor Intervention and Selfmanagement (IRIS) study have been described in chapter 6. Briefly, the trial was a multicentre randomised clinical trial. Patients diagnosed with a recent clinical manifestation of atherosclerosis in the coronary, cerebral or peripheral arteries underwent a standard-

ized vascular risk screening program as part of usual care. Consenting patients who were considered eligible for the study and who had ≥2 treatable vascular risk factors not on target were randomized to receive either internet-based care on top of usual care or usual care alone.

Internet-based nurse-led risk factor program and usual care

Patients randomized to the intervention group received an internet-based vascular risk factor management program on top of usual care during 1 year. At the start patients were invited for a visit to the outpatient clinic of the nurse practitioner in the hospital. At this visit patients received information on their risk factor levels and received instructions about the internet program and received a username and password. Subsequent contacts between patient and nurse practitioner were through the internet and no further outpatient clinic visits were scheduled. Depending on presence of risk factors that needed (additional) treatment, tailored, personalized web-pages were made for each individual patient. The nurse practitioner was able to view all files and pages from all patients and had access to a total overview of the current status of risk factors, last log-in attempts of each patient and new messages sent by patients. In general, the nurse practitioner logged-in every working day and replied to messages sent by patients and sent messages to patients not actively using the program at least every other week. Using internet for the treatment of vascular risk factors was based on the chronic care model.[15,16] Crucial elements in this model are support of self-management, support of informed consent and organizing the health care process. Via internet all elements can be combined thus supporting patient self-management in the place where it should be managed, namely in the own environment, at their own time of choice. The care delivered by the nurse practitioner with the internet program was on top of usual care and did not replace the care given by

Table 1
Schematic representation of planned measurements

	baseline (inclusion)	3 months	6 months	9 months	12 months
Time point	1	2	3	4	5
Health care use questionnaire	x	x	x	x	x
EQ-5D	x	x	x	x	x
SF-36 health questionnaire	x				x
SF-HLQ	x		x		x

EQ-5D: EuroQol 5-dimensions health status questionnaire ; SF-36 : Short-Form-36 ; SF-HLQ : Short-Form Health and Labour Questionnaire

the treating physician in the hospital and the general practitioner. The results of the vascular screening programme and a treatment advice according to Dutch guidelines[17] were sent to the treating physicians and the general practitioners of all participating patients. Patients randomized to usual care were stimulated to contact their treating physician in the hospital (vascular surgeon, cardiologist, neurologist) and/or the general practitioner for risk factor management.

Resource use

We collected data on the use of resources at the level of individual participants. Several methods were used to collect data (Table 1). In a diary patients recorded the frequency of visits to the medical specialist, nurse practitioner, general practitioner, paramedics or complementary medicine. Questionnaires were completed 5 times: at baseline and at 3, 6, 9 and 12 months. Furthermore, hospital admission and use of medications was recorded

Table 2
Unit costs

Resource	Unit costs (€)	Source
Consultations		
General practitioner	28.00	Costing manual[20]
Complementary medicine practitioner	28.00	Assumption
Paramedic health care professional*	30.00	Costing manual
Specialist	72.00	Costing manual
Pharmacy compensation per drug per period	5.50	Costing manual
Medication costs per month		Weighted mean based on medication use (GIP database) and medication price (Z-index taxe November 2009)
Platelet aggregation inhibitor	4.60	
Lipid-lowering medication	10.50	
Blood pressure-lowering medication	7.30	
Glucose-lowering medication	9.30	
Inpatient hospital days		
University hospital	575.00	Costing manual
General hospital	435.00	Costing manual
1 Year internet-based vascular risk factor management program	155.10	Own costing research based on time assessment
Travelling costs (per km)	0.20	Costing manual
Parking costs	3.00	Costing manual
Reduced productivity (absence from paid work, per hour)	By individual patient†	Costing manual
Absence from unpaid work (per hour)	12.50	Costing manual

All unit costs are based on or adjusted to the price level of 2009

*Weighted mean price of different paramedic health care professionals

†Depending on age and gender, Statistics Netherlands

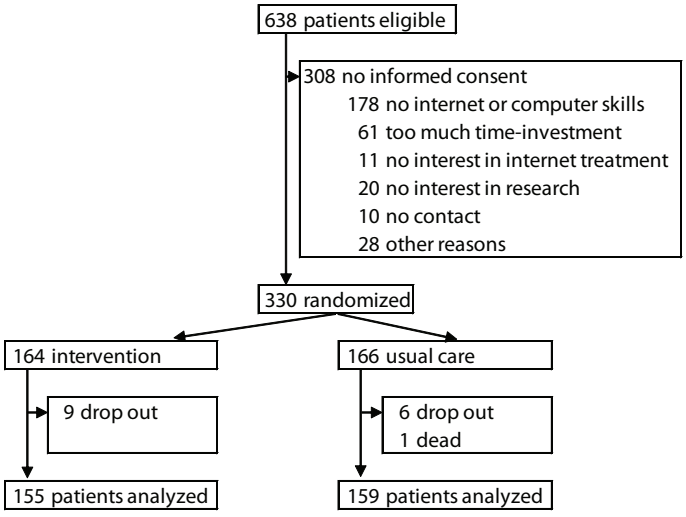
through electronic patient files. In order to record patients' absence from work and reduced productivity while at work, patients completed the Short-Form Health and Labor Questionnaire (SF-HLQ) at baseline and at 6 and 12 months.[18,19]

Costs

Table 2 shows the various types of resources and their unit costs. All costs were assessed from the societal perspective and were calculated per patient by multiplying the volume of resource use by the unit costs. Unit costs were taken from the Dutch manual for costing research in economic evaluations, issued by the Dutch healthcare insurance board (CVZ).[20] Costs were estimated for the year 2009.

Complementary medicine costs were assumed to equal costs of a visit to a general practitioner. Costs of vascular medication were valued by calculating a weighted mean of different classes of medication (platelet aggregation inhibitors, lipid-lowering medication, blood pressure-lowering medication and glucose-lowering medication) based on aggregate medication use in the Netherlands in 2009 (The Drug Information System of the Health Care Insurance Board[21]) and medication price (Z-index taxe November 2009[22]). The costs of the internet-based vascular management program mainly consisted of staff involvement. The program was managed by specialized nurse practitioners. All nurse practitioners in the program were asked to keep diaries about the time they spent on patients participating in the study. Over the year of the intervention, the total number of patient contacts for 11 nurses involved was related to total time spent on the intervention. Hence, average time spent per patient (in minutes per month) in the intervention arm was estimated. For the costing study, this was valued following recommendations from the Dutch costing manual, but it was assumed that nurse practitioners, being highly specialized and well-educated, receive a higher compensation (€ 33.50 per hour) than other nurses.

Figure 1
Study flowchart



All costs of lost productivity (absence from work and reduced productivity while at work) were calculated by applying mean hourly productivity costs varying with age and gender (data from Statistics Netherlands) and using the friction cost approach.[23]

Quality of life

Quality of life was assessed using both Short-Form-36 (SF-36)[24] and EuroQol-5D (EQ-5D)[25,26] questionnaires (Table 1). The EQ-5D was used as a basis for quality adjusted life year (QALY) estimates, based on a Dutch value set.[26] We imputed single missing utility scores using linear interpolation between the two known values on either side.

Data analyses

Initially, we analyzed cost and health benefits separately. We calculated mean total costs (i.e. the sum of direct health care costs, direct non-health care costs and indirect non-health care costs) and mean QALYs with their standard deviations for both treatment groups. Mean differences between both groups are presented with their 95% confidence

Table 3
Baseline characteristics

	Intervention (n=164)	Usual care (n=166)
Age, years	60.7 (7.8)	59.2 (8.9)
Male gender, n (%)	128 (78)	118 (71)
Body mass index, kg/m^2	28.2 (4.1)	27.4 (3.9)
Medical history, n (%)		
Coronary artery disease	75 (46)	69 (42)
Cerebral vascular disease	44 (27)	51 (31)
Abdominal aortic aneurysm	7 (4)	8 (5)
Peripheral vascular disease	38 (23)	38 (23)
Type 2 diabetes mellitus	43 (26)	34 (20)
Medication use, n (%)		
Platelet aggregation inhibitor	154 (94)	153 (92)
Lipid-lowering medication	142 (87)	140 (84)
Blood pressure-lowering medication	130 (79)	113 (68)
Glucose-lowering medication	29 (18)	23 (14)
Employment, n (%)	77 (49)	79 (49)
Part-time job	19 (12)	31 (19)
Temporarily unable to work	10 (6)	11 (7)
Educational level, n (%)		
Primary school	61 (39)	74 (46)
Secondary education	48 (31)	42 (26)
University education	46 (30)	45 (28)

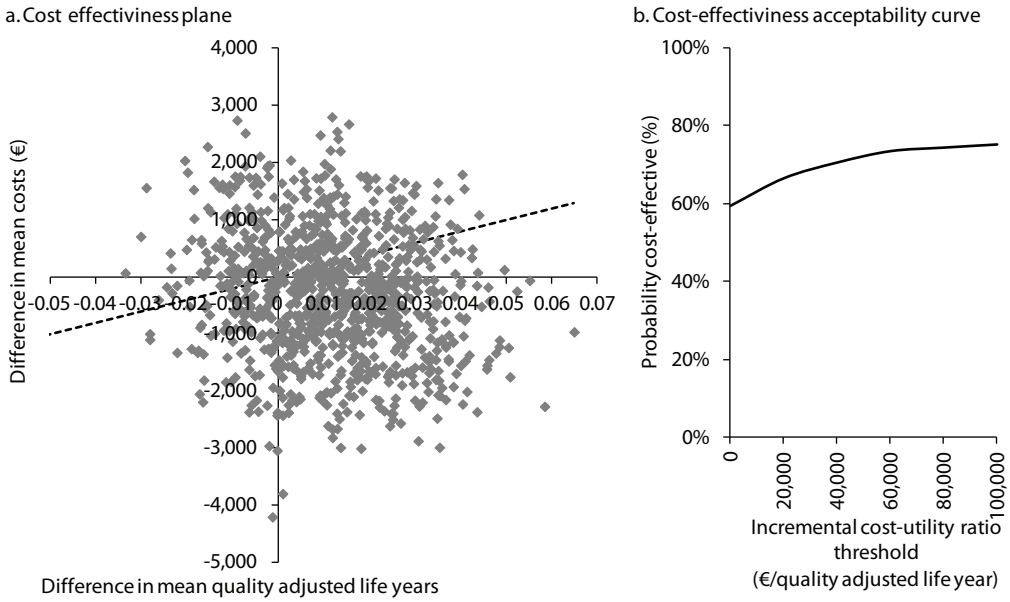
Data are expressed as mean (standard deviation) or as number (percentage)

intervals. After that, we combined differences in total costs with differences in QALYs (cost utility analyses). By dividing the incremental costs by the incremental health benefits, we estimated the incremental cost effectiveness ratio (ICER) in terms of costs per QALY gained. We estimated uncertainty around the ICER using bootstrapping, generating 1000 replications of each ratio (replicated ICERs). We depicted these replicated ICERs in a cost effectiveness plane. Furthermore, we present results in the form of a cost-effectiveness acceptability curve (CEAC). A CEAC presents the probability that the intervention is cost-effective for different thresholds levels for cost-effectiveness (acceptable cost per QALY gained by the intervention).

Scenario analyses

A Markov model was used to estimate the effect of the intervention for the life time of patients. It was estimated that the usual care group had a 14% standard mortality rate (SMR) for death by other causes (2 times the SMR of the general population). After a coronary artery event the SMR was estimated at 4 times the SMR of the general population. The relative risk of the intervention group compared to the usual care group for coronary

Figure 2
Incremental costs and quality adjusted life years



Cost effectiveness plane for incremental costs and quality adjusted life years, with cost effectiveness threshold line (€20,000/quality adjusted life year) and corresponding cost-effectiveness acceptability curve.

artery disease was 0.86 according to the result of the clinical trial. To calculate the relative risk for stroke we used the Framingham Stroke Risk score.[27] This showed a mean risk for stroke of 14.5% (SD 9.1) in 10 years with a risk reduction by the intervention compared to usual care of 1.7% (0.7 to 2.7%), a relative risk of 0.88. With these assumptions, the life expectancy of a 61 years old male was about 12 years.

Table 4
Quality of life scores

	Intervention	Usual care	Difference
Baseline	0.85 (0.14)	0.81 (0.21)	0.04
3 months	0.87 (0.14)	0.87 (0.15)	0.00
6 months	0.87 (0.16)	0.88 (0.17)	-0.01
9 months	0.87 (0.17)	0.87 (0.17)	0.00
12 months	0.85 (0.17)	0.82 (0.20)	0.03

Scores of the Dutch value set of the EuroQol 5-dimensions health status questionnaire (EQ-5D)

Data are expressed as mean (standard deviation)

Table 5
Units of resource use per patient

	Intervention	Usual care
Consultations, n per year		
General practitioner	5.4 (5.2)	5.1 (4.6)
Complementary medicine practitioner	0.5 (2.5)	0.2 (1.2)
Paramedic health care professional	6.4 (4.4)	9.8 (17.9)
Specialist	4.9 (5.8)	4.6 (4.8)
Inpatient hospital, days per year		
University hospital	0.4 (1.7)	1.6 (7.8)
General hospital	1.0 (3.6)	1.1 (4.4)
Number of medication	5.4 (2.6)	5.0 (2.4)
Loss of productivity, hours/year		
Absence from paid work	132 (263)	97 (251)
Reduced productivity while at paid work	20 (91)	31 (93)
Absence from unpaid work	13 (37)	13 (47)
Time spent by nurse practitioner, minutes/month	23 (12)	

Data are expressed as mean (standard deviation)

We estimated 2 scenarios. In scenario I the intervention stops after 1 year and from the second year onward there are no differences in costs and effects due to the internet-intervention. Only costs and effects of new vascular events are calculated. In scenario II the intervention lasts 5 years. Costs and effects are conform the first scenario plus a relative risk for coronary artery disease diminishing from 0.86 to 1 in year 2 to 5 plus costs (€155) for 4 years intervention extra (Figure 3).
All data were analyzed according to the intention to treat principle. All analyses were performed with SPSS statistics 18.0.2 (IBM Corp., New York, USA) and Microsoft Office Excel 2003 SP3.

Table 6
Cumulative costs per patient in 1 year

	Intervention	Usual care	Difference
	€	€	€
Direct medical costs			
Consultation			
General practitioner	151	142	9
Complementary medicine practitioner	13	6	7
Paramedic health care professional	192	294	-102
Specialist	353	333	20
Inpatient hospital days			
University hospital	249	935	-685
General hospital	421	462	-41
Medication	451	464	-13
Internet-based vascular risk factor management program	155	0	155
Subtotal	1,987	2,635	-648
Direct non-medical costs			
Visits			
General practitioner	1	1	0
Complementary medicine practitioner	0	0	0
Paramedic health care professional	3	4	-1
Specialist	22	20	1
Inpatient hospital	6	12	-6
Subtotal	32	38	-6
Indirect non-medical costs			
Absence from paid work	2,289	1,675	614
Reduced productivity while at paid work	326	566	-240
Absence from unpaid work	159	164	-4
Subtotal	2,775	2,405	370
Total costs	**4,794**	**5,078**	**-284**

Results

Baseline characteristics

Patients were recruited between October 2008 and March 2010. A total of 638 patients fulfilling inclusion criteria were invited for participation of which 330 patients were randomized (Figure 1). 16 patients were lost to follow-up. The mean age was 59.9 standard deviation (SD) 8.4 years and most patients were male (75%) (Table 3). All patients had a recent manifestation of vascular disease, most frequently this was coronary artery disease (49%). Of the study population 49% was employed.

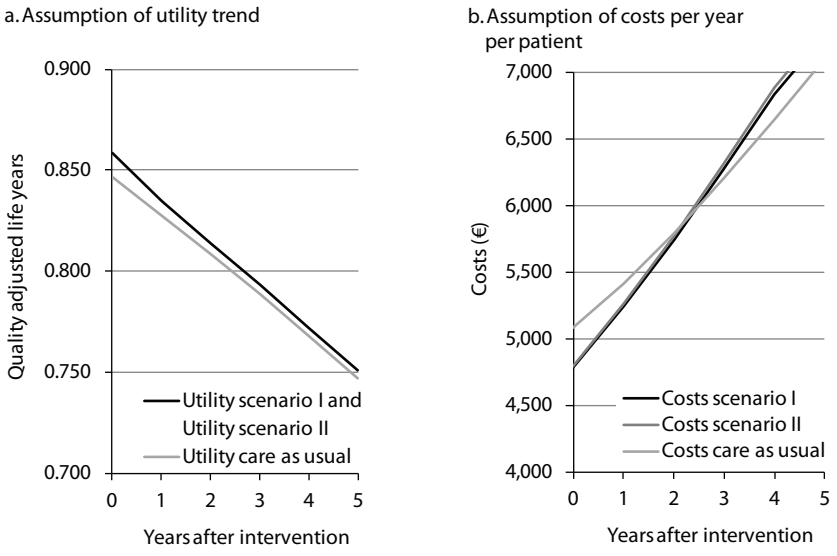
Clinical outcomes

After 1 year, the absolute difference between the intervention group and usual care group in change in Framingham Heart Risk score[28] was -2.1 (95%CI-3.8 to -0.3). This relates to a relative decrease of 14% in 10-year risk for coronary heart disease. Of the individual risk factors a difference between groups was observed in LDL-cholesterol (-0.3 mmol/l; 95%CI -0.5 to -0.1) and smoking (-7.7%; 95%CI -14.9 to -0.4).

During the trial the experienced quality of life in the intervention group (0.865 SD 0.129 QALYs) was comparable to the usual care group (0.853 SD 0.154 QALYs) which translates in a difference of 0.012 QALYs (95%CI -0.020 to 0.043), (Table 4).

The nurse practitioners spent an average of 23 SD 12 minutes per month per patients on the intervention (Table 5). Patients in the intervention group appeared to have the same number of consultations during the 1 year follow up period with the general practitioner

Figure 3
Scenario analysis with utility and costs



compared to the patients in the usual care group (5.4 SD 5.2 vs. 5.1 SD 4.6 visits), with complementary medicine practitioners (0.5 SD 2.5 vs. 0.2 SD 1.2 visits), with paramedic health care professionals (6.4 SD 14.4 vs. 9.8 SD 17.9 visits) and with medical specialists (4.9 SD 5.8 vs. 4.6 SD 4.8 visits). Patients in the intervention group spent on average 1.4 SD 4.0 days admitted to hospitals and patients in the usual care group 2.6 SD 10.0 days.

Economic evaluation

Absence from paid work in the intervention group was 132 SD 263 hours compared to the usual care group 97 SD 251 hours (Table 5). The higher number of inpatient hospital days in the usual care group resulted in higher direct medical costs (€648) of the usual care group compared to the intervention group (Table 6). The indirect non-medical costs were €370 higher in the intervention group. This resulted in a costs benefit of the intervention group of €284 compared to the usual care group (Table 7a).

Cost utility analyses

Since there was a benefit for the intervention group of both costs and quality of life the ICER was dominant. Repeating the ICER 1000 times was done using the bootstrapping technique and plotted together with the cost effectiveness threshold line of €20,000 per QALY (2a). Cost acceptability (proportion of replicated ICERs below the line) was 66%. Figure 2b shows the CEAC of 1 year internet-intervention, showing the probability of cost-

Table 7
Incremental cost effectiveness ratio

a

	Intervention	Usual care	Difference
Costs (€)	4,794	5,078	-284
QALY	0.865	0.853	0.012
Costs per QALY			dominant

b: Scenario I: Lifetime results 1 year intervention and effect.

Costs (€)	11,840	12,150	-310
QALY	9.227	9.201	0.026
Costs per QALY			dominant

c: Scenario II: Lifetime results 5 year intervention and effect diminishing from year 2 to 5.

Costs (€)	12,322	12,150	172
QALY	9.247	9.201	0.047
Costs per QALY			3,697

QALY: Quality adjusted life year

effectiveness of cost per QALY. For example, if policymakers are prepared to pay €20,000 for each QALY gained, then they can be 66% sure that the internet-intervention is cost effective.

Scenario analyses

The lifetime results after 1 year intervention (Scenario I) compared to usual care alone showed the intervention dominant (Table 7b). When prolonging the intervention for 5 years and a gradually diminishing effect on coronary and stroke events (Scenario II) the intervention is no longer dominant but requires costs of €3,697 per QALY (Table 7c).

Discussion

The results of the clinical study indicate that a nurse-led and internet-based risk factor intervention program is effective in lowering the Framingham Heart Risk score in patients with vascular disease with 14%. The present economic evaluation showed that this is a cost-effective intervention with €284 benefit in 1 year intervention and a higher quality of life during the trial (0.012 QALY). At €20,000 there is a 66% probability that the intervention is cost-effective. Scenario analysis showed the intervention to be dominant for a life time, and with prolonging the intervention to a total of 5 years costing €3,697 per QALY.
In another study evaluating the cost-effectiveness of an internet intervention to prevent vascular disease in primary intervention, a tailored website, medical advice and psychological training was given to 208 participants of a health insurance company during 1 year and compared to 106 controls.[11] When adjusting for baseline utility differences, the incremental cost was €433 and the incremental effectiveness was 0.016 QALYs. The incremental cost-effectiveness ratio was €26,910 per QALY. In this study no effectiveness data on vascular outcomes are available yet. In a retrospective, quasi-experimental design participants of the DASH for Health were analysed for health care costs.[29] DASH for Health is an Internet-based nutrition and exercise behaviour modification program with a duration of 1 year. Among the cardiovascular risk study subjects, health care costs were US$827 lower year (p=0 .05, adjusted for baseline year costs, vascular risk, and demographic variables) compared to non-DASH participants, on average, during the study. In a randomized controlled trial a behavioural internet treatment program for weight management in overweight, but otherwise healthy, adults serving in the US Air Force (n=227) was compared with usual care (n=215).[30] Intervention participants lost 1.9 kg compared to usual care at an intervention cost of $25.92 per kilogram of weight loss and $28.96 per centimetre loss of waist circumference. A randomized controlled trial evaluating the effects of a nurse-led secondary prevention clinic for patients with coronary heart disease with a follow-up of 4 years, revealed that the cost of the intervention was €195 accompanied with a reduction in NHS costs of €334.[31] This is comparable with the results of the present study. These trials indicate that vascular risk reduction by internet-based care might be cost-effective. The results of the present study show robust cost-effectiveness of internet-based care of vascular risk factors in patients with clinical manifest vascular disease.

The intervention in our study is easily implemented in the care for secondary prevention, either in secondary care or in primary care as well. An increasing proportion of patients has access to internet at home and nurse practitioners can easily implement internet-based care in their clinical practice. Implementation costs for software are relatively low. To be effective and cost-effective we believe there are some key elements of our internet intervention that need special attention. The internet-based care needs to be tailored at the clinical situation, at the risk factor levels and to personal goals of each individual patient. Personal goal setting is an essential element in a self-management program. At start of the study each patients and has seen the treating nurse practitioner in person and discussed personal goals and priorities. Nurse practitioners need to be trained in supporting self-management according to the chronic care model.

Strength of the present study is that the economic evaluation is part of the largest, randomized controlled clinical trial on internet-based treatment of patients with vascular disease to date. The drop-out rate was only 5% and data collection was almost complete. Some study limitations need to be considered. A summary score for vascular risk was used. We realize that the Framingham Heart Risk score is not developed for estimating the vascular risk in patients with clinical manifest vascular disease.[28] As yet, there is no such a validated score for patients with vascular diseases. The Framingham Heart Risk score is not accurate in estimating the absolute vascular risk in these patients, but can be used to evaluate relative differences and changes between groups. Secondly, the difference in QALY between the intervention group and the usual care group in 1 year intervention was not huge and not statistically significant (difference of 0.012; 95%CI -0.020 to 0.043 QALY). With bootstrapping and ICER analyses we accounted for these uncertainties and showed a probability 66% of the intervention being cost effective (for €20,000/QALY). Third, the Framingham Stroke Risk score was no pre-specified endpoint in this trial. Together with assumptions about the SMR of coronary and stroke events the scenario analysis should be viewed with caution. We did not construct the scenario analysis for primary presentation of our data but to hypothesise about the long term effects.

In conclusion, a 1-year nurse-led and internet-based vascular risk program on top of usual care is cost-effective in the treatment of vascular risk factors in patients with a recent clinical manifestation of vascular disease.

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Chapter 8

General discussion

Hypertension is a very common condition with an overall prevalence of 42% in the general population in the Netherlands[1], rising to a prevalence of 60-70% beyond the seventh decade of life.[2] Usually, hypertension is a symptomless disease but attributes to approximately 2/3 of stroke and 1/2 of ischemic heart disease.[3] The proportion of patients with an adequately controlled hypertension in the general population in the Netherlands is only 35% and also in a population with vascular disease other risk factors like hypercholesterolemia, obesity and smoking are only under control for 67% to 85%.[4,5] Treatment of these risk factors, alone or in combination, is proven to be very effective in reducing the risk of all recurrent vascular events (myocardial infarction and ischemic stroke) and death.[6,7] Therefore there is a need for research into the causes of hypertension and better treatment strategies with more efficacy and less side-effects.

Obesity-related hypertension in patients with vascular disease

In the general population there is a strong relation of obesity with hypertension[8,9] and the combination of both confers an extra high risk for the occurrence of vascular disease.[10] From pathophysiologic point of view obesity is an important cause of hypertension. Adipose tissue dysfunction[11] and inflammatory adipokines herald a cascade on mechanisms leading to hypertension.[12] In chapter 2 we showed that (1) in contrast to patients without vascular disease, the combination of hypertension and obesity had a low prevalence in patients with vascular diseases, that (2) there was a weak relation between obesity and hypertension and that (3) the combination of hypertension and obesity did not confer a higher risk for recurrent vascular events and mortality than each risk factor alone. When analysing separately the risk factors hypertension and obesity and the relation with recurrent vascular events and mortality we found that per 10 mmHg increase in systolic blood pressure the risk for vascular events increased by 4% (HR 1.04; 95%CI 1.00-1.08) and for all-cause mortality with 3% (HR 1.03; 95%CI 0.99-1.07). This is in contrast with a study in patients without vascular disease where a twofold increase for the occurrence of vascular diseases was seen for every 20 mmHg elevation of systolic blood pressure.[13] When analysing weight we showed that in patients with vascular disease an increase in weight is related to a lower risk for vascular morbidity and mortality. This in contrast with patients without vascular disease, where in case of a body mass index >25 kg/m^2 the mortality increased with higher weight.[14]

What could be the explanation for these discrepancies? First, most patients after a manifestation of vascular disease have a high level of risk factors. This leads to organ damage, and organ damage is a much stronger determinant of recurrent events and mortality than the risk factors itself. The relation between risk factors, i.e. obesity and hypertension, is than lost. In many patients, the blood pressure has been treated for years before the event and this could influence the relation of hypertension with obesity and the relation of hypertension with vascular events and mortality. Second, selection on having a vascular disease manifestation could induce index event bias.[15] When a certain high level risk factor causes an event in a patient, this patient most likely has other risk factors with lower levels. Thus the high level risk factor could be 'protective' for other risk factors. This

could create negative associations between risk factors even if those risk factors were not associated with each other before the event. Because risk factors often have overlapping effects on the outcome and recurrent events, this negative association will tend to bias any estimation of the effect of a risk factor on recurrence risk toward null, unless there is a thorough accounting for all shared risk factors. In a recent study, the inverse relation of weight with recurrent events was eliminated when many risk factors were accounted for.[16] Yet, the observed associations in chapter 2 remained after adjustment for most known risk factors for cardiovascular disease, making index event bias a less likely explanation. Third, reverse causality could be an explanation. Low blood pressure could be a sign of a failing heart and low weight a sign of cachexia due to severe disease and therefore leading to early events or mortality. However, when excluding patients with vascular events or mortality in the first 6 months after inclusion the relations did not change, making this a less plausible explanation.

There are other studies showing that obesity and hypertension in subjects without vascular disease have a different relation with vascular events and mortality than in patients with vascular disease. The inverse relation between obesity and the risk of vascular diseases and mortality has been called the 'obesity paradox' and has been reported in patients with heart failure, coronary heart disease, and peripheral arterial disease.[17-20] Whether this is an inverse causal relation or due to methodical issues, is subject of debate, as discussed above. Nevertheless, intentional weight loss decreases the risk for future vascular events in these patients.[21,22] In a study in patients with vascular disease, the relation of hypertension with vascular events and mortality was J-shaped with a nadir in events at a blood pressure of about 140/80 mmHg.[23] This in contrast with a meta-analysis in subjects without vascular disease showing a continuous linear relation of hypertension with (vascular) mortality.[13] This also illustrates that the relation between a vascular risk factor, such as hypertension, and occurrence of vascular events and mortality may be different in patients with or without clinical manifest vascular disease.

Thus the question arises whether obesity-related hypertension exist in patients with vascular disease or not. The epidemiological relations of obesity, hypertension and the combination of both and the occurrence relations with vascular disease are not as clear as in subjects without vascular disease, but therapy for both groups of patients is related to lower vascular risk. If obesity is a cause of hypertension, the relation between obesity and hypertension may change over time. Longstanding hypertension may lead to arterial stiffening and nephrosclerosis, both causes of hypertension itself. Many patients with vascular diseases are likely to already have hypertension, irrespective of the underlying cause, for a long period leading to arterial stiffening and impaired renal function which caused hypertension independent of obesity. Still the effects of blood pressure-lowering therapy show benefit in terms of vascular risk reduction. Thus the term obesity-related hypertension could still be used in patients without vascular disease because obesity is an important determinant of hypertension in these patients. In patients with vascular disease the existence of obesity-related hypertension is debated above and is probably not an important disease entity.

Left ventricular hypertrophy on electrocardiogram

Hypertension is causally related to cardiac pathology, among which left ventricular hypertrophy (LVH), atrial fibrillation, coronary artery disease and congestive heart failure. All are considered to be the result of hemodynamic overload as a result of elevated blood pressure.

Anatomical information about the heart can be obtained by imaging with ultrasound, CT or MRI and electrical information can be obtained with electrocardiography. These different diagnostic approaches may contain different information about the heart. The most accessible diagnostic modality is the electrical information obtained by electrocardiogram (ECG). For the detection of LVH on ECG many criteria have been developed.[24] As shown in chapter 3 there is a weak relation between ECG criteria for LVH (Sokolow-Lyon and Cornell voltage) and LVH on MRI. Other studies confirmed the weak relation between LVH on ECG and LVH on ultrasound or MRI.[25,26] Thus anatomical mass, as measured by ultrasound or MRI, is not an important determinant of LVH on ECG. In LVH there is a structural and functional change of cardiac tissue. On the cellular level cardiomyocytes increase in size[27] and number and type of connections.[28] Furthermore, edema, interstitial infiltrates, and fibrosis can be identified.[29] On the molecular level a reduction and redistribution of gap junction channels (due to diminished connexion expression) is shown.[30] These changes affect electrical activity and conductivity of cardiac tissue[31] and body surface potentials shown on ECG, leading to less and diminished ECG voltage despite an increase in left ventricular mass (LVM) on MRI.[32]

In a study in treated hypertensive patients without vascular disease, determinants of the Sokolow-Lyon criterion of ECG-LVH were male gender, black race and systolic blood pressure.[33] Another study in patients with high cardiovascular risk roughly showed the same determinants for the Sokolow-Lyon criterion and determinants of the Cornell voltage duration product were increased diastolic blood pressure, higher BMI, increased age, and female gender.[34] As there is a poor correlation with ECG criteria for LVH and high left ventricular mass on imaging and hypertension is a determinant of ECG criteria for LVH it would be better to rename the diagnosis of LVH on ECG to 'hypertensive ECG changes' or 'hypertension-related changes on ECG'.

To determine the value of the different criteria for hypertensive ECG changes one could consider the relation with anatomy and the relation with clinical outcome such as vascular disease and mortality. As discussed above the relation between LVH on ECG and left ventricular anatomy is weak, but there is a strong relation between hypertensive ECG changes and vascular morbidity and mortality.[35,36] In chapter 4 we showed that presence of hypertensive ECG changes is related with an increased risk for vascular events and mortality in patients with vascular disease. We compared the Sokolow-Lyon criterion, the Cornell voltage criterion, the Perugia criterion and the LIFE criterion on prevalence, congruence and the relation with vascular events and mortality. The prevalence of positive criteria in the study population ranged from 4% (Cornell voltage criterion) to 12% according to the Perugia and LIFE criterion. We showed that to some extend different criteria identify different patients. All criteria do have a positive relation with vascular events and mortality but

the Perugia and LIFE criterion conferred the highest risk for vascular events and mortality. To combine the prevalence of a positive criterion and the relation with vascular events and mortality we calculated a study attributable risk of the different ECG criteria. In our cohort the highest attributable risk for vascular events is the Perugia criterion with 11% and an attributable risk for mortality of 8%. The LIFE criterion showed comparable numbers for the attributable risk with 9% and 7%, respectively. The ease of visual inspection with the Perugia criterion adds to the accessibility of this ECG criterion. Computer-aided analysis of ECG is also daily practice and when the calculated scores of the LIFE criterion is incorporated in the computer algorithms this would add to the usability. Interestingly, the ECG criteria for evaluating LVH according that are advocated in current clinical guidelines (Sokolow-Lyon and Cornell voltage), performed less well than the 'newer' Perugia and LIFE criteria for LVH.

The relevance of hypertensive target organ damage

Apart from hypertensive target organ damage in the heart, such as left ventricular hypertrophy, hypertension may also lead to damage to the kidneys, as measured by impaired renal function and/or albuminuria. Albuminuria may not only indicate specifically an impairment in glomerular permeability due to blood pressure load, but also a more generalized and widespread endothelial dysfunction.[37] There is a clear relation between hypertensive ECG changes and elevated risk for vascular events and mortality and this is also true for impaired renal function and albuminuria.[38] In chapter 5 we showed that impaired renal function, albuminuria and hypertensive ECG changes conferred independent and additive risks for vascular events and mortality in patients with vascular disease. The importance of hypertensive target organ damage has several aspects. First, hypertensive target organ damage could not only be a consequence of hypertension, but could also maintain hypertension and may be a separate risk factor for vascular events and mortality in patients with vascular disease. Direct hypertensive damage to the large arteries leads to the degradation of the elastic fibers in the large arteries due to fatigue failure[39] resulting in stiffening of the arteries and decreasing vascular compliance. This induces an acceleration of the pulse wave over the arteries causing the reflection wave to augment the systolic pressure, rather than the diastolic pressure and in doing so being a factor that maintains hypertension.[40] Another form of hypertensive organ damage maintaining hypertension is hypertension-induced nephrosclerosis and impaired renal function activating the renin-angiotensin-aldosterone system, elevating the blood pressure and inducing even more damage to the kidney in the long term.[41] Thus hypertension-related target organ damage could induce a positive feedback loop increasing blood pressure and could be an important cause of sustained, longstanding hypertension or organ damage-related hypertension.

Second, identification of hypertensive target organ damage identifies patients at very high risk, even in a population with clinical manifest vascular disease. Guidelines recommend to routinely assess target organ damage when evaluating vascular risk in patients[42,43] and our analyses confirm that it is relevant to assess at least hypertensive ECG changes, renal function and albuminuria.

The consequences for therapy of the presence of hypertensive target organ damage could be debated. Prevention of organ damage-related hypertension in subjects without vascular disease could be in early and aggressive treatment of hypertension. This is supported by the continuous and linear relation of blood pressure with vascular events and mortality down to at least 115/75 mmHg[13] and the consistent and linear treatment effects of blood pressure-lowering medication, irrespective of the patients' pre-treatment blood pressure, even when pre-treatment blood pressures were as low as 110/70 mmHg.[44] This would imply the treatment of subjects with so called pre-hypertension and subjects with a low risk for vascular disease. This concept requires prospective testing in a large group of subjects and a long follow-up time to properly define the balance between efficacy and safety.

Progressive lowering of the blood pressure in patients with vascular disease and hypertensive target organ damage could cause a rise in vascular morbidity and mortality as shown by the J-curve in the relation of blood pressure with vascular events and mortality,[23] a post-hoc analysis of a trial in patients with hypertensive ECG changes[45] and a randomized controlled trial comparing a standard and a low blood pressure target in patients with type 2 diabetes mellitus.[46] It is not clear what the optimal blood pressure target is in patients with vascular disease and if there is a difference in long standing and recently developed hypertension. Apart from blood pressure-lowering the blockade of the renin-angiotensin-aldosterone system could be of benefit in patients with manifest vascular disease and hypertensive target organ damage. A direct comparison an angiotensin converting enzyme inhibitor and an angiotensin II receptor antagonist with a β-blocker showed equal reductions in blood pressure but more regression of LVH and less vascular events or mortality for the renin-angiotensin-aldosterone blockers.[47,48] However, it appears that extra blockade with two blockers of the renin-angiotensin-aldosterone system does not result in extra lowering of vascular events or mortality,[49,50] and the evidence of one drug therapy over another drug therapy is not shown in meta-analysis.[44,51]

Are there other strategies to lower the high risk for vascular events and mortality in patients with hypertensive target organ damage? One of the factors commonly found in hypertensive target organ damage is a sympathetic overdrive.[52] This might be a target to effectively reduce the very high risk for recurrent vascular disease in patients with already vascular disease and hypertension-related organ damage. Effectively reducing the sympathetic tone has been shown by baroreceptor stimulation[53] and by renal sympathetic nerve ablation.[54] Both therapies showed to reduce blood pressure[55,56] by attenuating the sympathetic overdrive, but also showed regression of left ventricular hypertrophy,[57,58] and

reduction of albuminuria.[59] It has to be proven whether this results in lowering vascular events and mortality, but improving the autonomic nerve system balance seems promising, especially in very high risk patients.

Management of risk factors in patients with vascular disease

In chapter 6 and 7 we evaluated the effectiveness and cost-effectiveness of an internet-based nurse-led risk factor management program in patients with clinical manifest vascular disease. We showed that an internet-based nurse-led treatment program on top of usual care of vascular risk factors has a small effect on lowering vascular risk and on lowering of some vascular risk factors in patients with vascular disease and that this program is a cost-effective intervention. The intervention used is easy to implement in clinical practice at low costs. The intervention was developed based on the chronic care model.[60,61] Elements in this model are support of self-management, support of informed consent and organizing the health care process. Via internet all elements can be combined and the patient is able to manage his/her own health in the place where it should be managed, namely in the own environment at time of choice. However, the effectiveness of the intervention was limited. This could be due to a sub-optimal use of the internet program by the patients as shown by the rapidly decreasing log-in attempts over time and the limited number of messages sent by patients. Some patients reported technical difficulties accessing the website and this could have been overcome by better computer training of the patients and by more strict selection of patients with adequate computer skills. The effectiveness of the intervention could probably be improved by introducing more modern methods of health promotion like group consults, peer patient contact[62] and the use of webcam technologies. Also a connection to patients own medical records[63] and the current medical information systems are obvious improvements.

The internet-based and nurse-led vascular risk factor intervention in our study was on top of usual care. It can also be considered to replace current usual care by this intervention. That was not investigated in the study. The internet-based nurse-led risk factor management program provides an extra tool in the optimalisation of risk factor management especially in the secondary care environment. Patients with vascular disease are high risk patients with complex problems best managed by specialists. The secondary care is usually (relatively) far away from home and long lasting and intensive care in secondary care is expensive. These limitations are overcome by the use of internet and nurse practitioners supervised by a specialist in vascular medicine. We show this is a cost-effective intervention and this justifies implementation of an internet-based risk factor intervention in other outpatient clinics caring for patients with vascular disease and financial support to do so by insurance companies.

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Chapter 9

Summary

Samenvatting

Hypertension-related organ damage and vascular disease

Hypertension is a very common condition with an overall prevalence of 42% in the general population in the Netherlands, rising to a prevalence of 60-70% beyond the seventh decade of life. Usually, hypertension is asymptomatic, but as a risk factor attributes to approximately 2/3 of stroke and 1/2 of ischemic heart disease.
Regulation of blood pressure involves cross talk between the kidney, the heart and the brain via neurohumoral systems and local paracrine and intracellular feedback loops. The various regulating systems are influenced by multiple genetic, environmental and behavioral factors and these are involved in the pathophysiology of hypertension. Many secondary causes of hypertension can be distinguished, among which impaired renal function and obesity.
Hypertension may result in organ damage of the heart, arteries, the kidney and the brain and may result in vascular disease as stroke and myocardial infarction. Together with other risk factors hypertension accounts for 90% of the population attributable risk for myocardial infarction. Treatment of these risk factors, alone or in combination, is proven to be very effective in reducing the risk of all recurrent vascular events (myocardial infarction and ischemic stroke) and death. However, in daily clinical practice, treatment goals are often not reached and there is a need for extra treatment strategies and options.

Higher bodyweight is associated with an increased prevalence of vascular risk factors including hypertension. Obesity leads to hypertension by various mechanisms, often referred to as obesity-related hypertension. In **chapter 2** we evaluated the prevalence and the vascular risk of the combination of obesity and hypertension in patients with vascular diseases. The prevalence of the combination of obesity and hypertension was only 16% (95%CI 15 to 17%). Patients with high blood pressure combined with a high weight (highest tertile SBP in the highest tertile BMI) were not at higher risk for new vascular events or mortality compared to patients without high blood pressure and high weight (patients in the lowest tertile of SBP in the lowest tertile of BMI). Patients with only high weight did not have an elevated risk either for vascular events or mortality either compared to patients without high blood pressure and high weight. Thus the prevalence of the combination of hypertension and obesity is low in patients with vascular diseases and does not confer a higher risk for recurrent vascular diseases and mortality than each risk factor alone.

Obesity is also related to cardiac left ventricular hypertrophy (LVH). A consequence of obesity is insulin resistance (IR), which can effect remodelling of vascular structures. Whether LVH criteria on ECG are a result of increased cardiac electrical activity, or due to increased left ventricular mass (LVM) remains to be determined. In **chapter 3** we investigated the relation between obesity and LVH criteria on ECG (ECG-LVH) and LVM by MRI (MRI-LVM) in patients with hypertension and investigated the relation of IR and LVH.
Linear regression analysis revealed an inverse relation between waist and Sokolow-Lyon voltage and a positive relation between waist and MRI-LVM. Patients in the highest quartile of LVM had a worse metabolic profile than patients with the Sokolow-Lyon voltage

criterion. The relations of IR with ECG-LVH and MRI-LVM were similar to those of waist in relation to ECG-LVH and MRI-LVM. Therefore, waist circumference and hypertensive ECG changes are inversely related, whereas waist circumference is positively related to cardiac left ventricular mass on MRI in patients with hypertension. This indicates that obesity has a different relation to voltage criteria for LVH as to anatomical criteria for LVH, supporting the hypothesis that IR decreases ECG voltages, despite an increase in MRI-LVM.

Presence of LVH on ECG can be assessed with multiple criteria. In **chapter 4** we evaluated the vascular risk and all-cause mortality related to 2 traditional (Sokolow-Lyon and Cornell voltage criterion) and 2 recently developed ECG criteria (Perugia and LIFE criterion) for LVH in patients with vascular disease. The prevalence of the Sokolow-Lyon, Cornell voltage, Perugia and the LIFE criterion was 8%, 4%, 12% and 12%, respectively. The risk for vascular events and mortality was increased with presence of each LVH-criterion, but most notably with the Perugia criterion for vascular events and for all-cause mortality. Patients with coronary artery disease and women had comparable risks for vascular events and mortality compared to patients without coronary artery disease and men. Concluding, ECG criteria for LVH are prevalent in patients with clinical manifest vascular diseases and confer an independent risk for vascular events and mortality. The Perugia criterion for LVH is highly prevalent in these patients and is related to the highest risk for vascular events and all-cause mortality.

Presence of hypertensive target organ damage is related to increased vascular risk and mortality. Whether combined presence of hypertensive target organ damage confers higher vascular risk compared to single presence is unknown. In **chapter 5** we evaluated the separate and combined effects of impaired renal function, albuminuria and LVH on the occurrence of vascular events and mortality in patients with vascular disease. LVH was present in 11%, impaired renal function in 15% and albuminuria in 18% of the patients. Presence of ≥2 manifestations of hypertensive target organ damage was prevalent in 8% of patients. The risk for vascular events had a HR of 1.5 (95%CI 1.2 to 1.9) for presence of 1 manifestation of hypertensive target organ damage and HR 3.8 (95%CI 2.3 to 6.3) for 3 manifestations of hypertensive target organ damage (adjusted for age and gender). For mortality this was HR 1.4 (95%CI 1.1 to 1.7) and HR 3.2 (95%CI 1.9 to 5.2). Hazard ratios for single presence of different types of organ damage were comparable and independent of the presence of hypertension. In conclusion, impaired renal function, albuminuria and LVH are prevalent in patients with vascular disease and confer independent and additive risk for vascular events and mortality. Presence of hypertensive target organ damage in patients with vascular disease identifies patients at very high risk.

In **chapter 6 and 7** we investigated the effect and cost-effectiveness of an internet-based, nurse-led vascular risk factor management program on vascular risk and vascular risk factors.

Therefore we conducted a prospective multicentre randomized controlled trial comparing intervention via internet plus usual care to usual care alone. Patients were diagnosed with a recent clinical manifestation of atherosclerosis in the coronary, cerebral or peripheral arteries and with ≥2 treatable risk factors not at goal. The intervention consisted of a personalized website with an overview and actual status of patients' risk factors and mail communication via the website with a nurse practitioner for 12 months. After 1 year we found a relative change of -14% (95%CI -25 to -2%) in Framingham Heart Risk score of the intervention group compared to the usual care group. The intervention yields both improvements in number of QALYs (0.865 for the intervention group and 0.853 for the control group) and less societal costs (€4,460 for the intervention group and €4,723 for the usual care group) and thus, the intervention dominates usual care. The probability that the intervention is cost-effective at a threshold of €20,000 per QALY, was 66%. At annual cost of €155, the intervention was relatively cheap.
An internet-based nurse-led treatment program on top of usual care of vascular risk factors has a small effect on lowering vascular risk and on lowering of some vascular risk factors in patients with vascular disease and is a cost-effective intervention.

Finally in **chapter 8** we discussed the main findings in of thesis. Obesity and hypertension are important causes of vascular disease and mortality. The term obesity-related hypertension is adequate in patients without vascular disease because obesity is an important determinant of hypertension in these patients. In patients with vascular disease the existence of obesity-related hypertension could be questioned and is probably not an important disease entity. Obesity and hypertension are also causes of cardiac changes. These changes affect probably electrical activity and conductivity of cardiac tissue and body surface potentials shown on ECG, leading to less and diminished ECG voltage despite an increase in left ventricular mass on imaging. As there is a poor correlation with ECG criteria for LVH and high left ventricular mass on imaging and hypertension is a strong determinant of ECG criteria for LVH it would be better to rename the diagnosis of LVH on ECG to 'hypertensive ECG changes' or 'hypertension-related changes on ECG'. The hypertension-related target organ damage could induce a positive feedback loop increasing blood pressure and could be an important cause of sustained, longstanding hypertension or organ damage-related hypertension.
The internet-based nurse-led risk factor management program provides an extra tool in the optimalisation of risk factor management especially in the secondary care environment. Options for improvement and implementation of the intervention are discussed.

In final conclusion, the studies presented in this thesis showed that:

- The prevalence of the combination of hypertension and obesity is low in patients with vascular diseases and does not confer a higher risk for recurrent vascular disease and mortality than each risk factor alone.

- Waist circumference and hypertensive ECG changes are inversely related, whereas waist circumference is positive related to cardiac left ventricular mass on MRI in patients with hypertension. This indicates that obesity has a different relation to voltage criteria for LVH as to anatomical criteria for LVH, supporting the hypothesis that obesity via insulin resistance decreases ECG voltages, despite an increase in MRI-LVM.
- Hypertensive ECG changes are prevalent in patients with clinical manifest vascular diseases and confer an independent risk for vascular events and mortality. The Perugia criterion for LVH is highly prevalent in these patients and is related to the highest risk for vascular events and all-cause mortality.
- Impaired renal function, albuminuria and LVH are prevalent in patients with vascular disease and confer independent and additive risk for vascular events and mortality. Presence of hypertensive target organ damage in patients with vascular disease identifies patients at very high risk.
- An internet-based nurse-led treatment program on top of usual care of vascular risk factors has a small effect on lowering vascular risk and on lowering of some vascular risk factors in patients with vascular disease and is a cost-effective intervention.

Hoge bloeddruk gerelateerde orgaanschade en vaatziekten

Hoge bloeddruk komt in Nederland bij 42% van alle mensen voor. Van alle mensen met hoge bloeddruk in Nederland is dit bij ongeveer 35% onder controle. Het is over het algemeen een aandoening zonder klachten, maar draagt bij aan ongeveer 2/3 van alle beroertes en 1/2 van alle hartinfarcten.
Steeds meer mensen overleven het eerste hartinfarct en beroerte en dus zijn er steeds meer mensen die vaatziekten hebben. Het is duidelijk dat veel nieuwe vaatziekten voorkomen kunnen worden door behandeling van hoge bloeddruk, hoog cholesterol, suikerziekte en bloedverdunning. Toch worden mensen met vaatziekten in Nederland nog onvoldoende behandeld en zijn er in deze groep mensen veel nieuwe hartinfarcten en beroertes.
Daarom is onderzoek naar de oorzaken van nieuwe hartinfarcten en beroertes en betere behandelingen in de groep mensen belangrijk.

Overgewicht is een belangrijke oorzaak van hoge bloeddruk. Maar in patiënten met vaatziekten komt overgewicht en hoge bloeddruk niet vaak samen voor en geeft het ook geen hogere kans op nieuwe vaatziekten. Hoge bloeddruk en overgewicht geven ook verdikking van de hartspier. In ons onderzoek laten wij dit ook zien, maar tegelijkertijd geeft dit op een hartfilmpje minder signaal. Dit is een aanwijzing dat het hartspierweefsel zelf veranderd door overgewicht en hoge bloeddruk. Schade door hoge bloeddruk kan op meerdere plaatsen in het lichaam voorkomen. Wij laten zien dat op hoe meer plaatsen schade wordt gevonden de kans op nieuwe vaatziekten sterk toeneemt.
Oorzaken van vaatziekten als hoge bloeddruk en overgewicht zijn belangrijk voor het eerste hartinfarct en beroerte. Maar bij mensen die al vaatziekten hebben doorgemaakt is de schade die ontstaan is in het lichaam belangrijker voor het ontwikkelen van nieuwe vaatziekten dan de oorzaken van de eerdere vaatziekten.
De kennis dat de schade door vaatziekten belangrijker is dan de oorzaken daarvan kan belangrijk zijn om de behandeling te verbeteren en de resultaten van behandeling te begrijpen. Behandeling van de schade door vaatziekten is maar beperkt mogelijk, maar in de toekomst is het mogelijk dat daar nieuwe behandelingen voor ontwikkeld worden.

Om de nu beschikbare behandelingen beter te gebruiken is internetbegeleiding een mogelijkheid. Het is goed mogelijk dit in te zetten in veel ziekenhuizen in Nederland en wij hebben laten zien dat dit kostenbesparend is.
Gebruik van internet in de begeleiding van mensen met vaatziekten is in korte tijd te regelen. De techniek om een website te maken is niet ingewikkeld en kan overal worden toegepast. Begeleiding via internet is voor medewerkers in de gezondheidszorg wel even aanpassen, maar is snel te leren. Deze extra begeleiding vraagt een investering maar ons onderzoek toont aan dat de extra begeleiding kosten bespaard en patiëntvriendelijk is.

Chapter 10

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Appendix

Participants of the SMART Study Group

Curriculum Vitae

Abbreviations

Participants of the SMART Study Group

A. Algra, MD, PhD, Julius Center for Health Sciences and Primary care
Y. van der Graaf, MD, PhD, Julius Center for Health Sciences and Primary care
D.E. Grobbee, MD, PhD, Julius Center for Health Sciences and Primary care
G.E.H.M. Rutten, MD, PhD, Julius Center for Health Sciences and Primary care
F.L.J. Visseren, MD, PhD, Department of Vascular Medicine
F.L. Moll, MD, PhD, Department of Vascular Surgery
L.J. Kappelle, MD, PhD, Department of Neurology
W.P.Th.M. Mali, MD, PhD, Department of Radiology
P.A.F.M. Doevendans, MD, PhD, Department of Cardiology

Curriculum Vitae

Birth date	December 9th 1972, The Hague, The Netherlands
Married	September 7th 2002 to Annette Vernooij-van Langen
Children	September 20th 2005, Merel
	July 21st 2008, Joppe
	July 23rd 2011, Floor
E-mail	jwp.vernooij@gmail.com

Education

1979-1985	Rudolf Steinerschool Alkmaar
1985-1991	Adriaan Roland Holstschool Bergen
1991-1993	Cornelis Drebbel college Alkmaar
1993-2000	VU University Amsterdam, Medicine
2002-2012	Internship Internal Medicine, Maastricht, Eindhoven, Utrecht
September 2009	European Society of Hypertension Summer School in Slovakia

Research

1997	Scientific training for 5 months at the University of Newcastle upon Tyne: Mitochondria and Diabetes, Prof. D.M. Turnbull, M. Walker, Prof. E.A. van der Veen
2008-2011	PhD student: Hypertension–related organ damage and vascular disease

Work

1994-1998	teaching-student philosophy, physiology, chemistry
2000-2001	emergency physician Waterland Ziekenhuis Purmerend
2001-2002	resident internal medicine Laurentius Hospital Roermond
2002-2004	resident internal medicine Academic Hospital Maastricht
2004-2006	resident internal medicine Catharina Hospital Eindhoven
2006-2012	fellow vascular medicine University Medical Center Utrecht

Abbreviations

AAA	abdominal aortic aneurysm
ACEi	angiotensin converting enzyme inhibitor
ARB	angiotensin II receptor blocker
BMI	body mass index
CAD	coronary artery disease
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CT	computed tomography
CVD	cerebrovascular disease
CVZ	college voor zorgverzekeringen
DBP	diastolic blood pressure
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol-5D
FHR	Framingham Heart Risk
HDL	high-density lipoprotein
HOMA-IR	homeostasis model assessment of insulin resistance
HR	hazard ratio
ICER	incremental cost effectiveness ratio
IQR	interquartile range
IR	insulin resistance
IRIS	Internet-based vascular Riskfactor Intervention and Selfmanagement
LDL	low-density lipoprotein
LIFE	Losartan Intervention For Endpoint reduction
LVH	left ventricular hypertrophy
LVM	left ventricular mass
MDRD	modification of diet in renal disease
MRI	magnetic resonance image
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PAD	peripheral arterial disease
QALY	quality adjusted life years
RAAS	renin-angiotensin-aldosterone system
RR	Riva Rochi or relative risk
SBP	systolic blood pressure
SCORE	Systematic COronary Risk Evaluation
SD	standard deviation
SF-36	Short-Form-36
SF-HLQ	Short-Form Health and Labour Questionnaire
SMART	Second Manifestations of Arterial diseases
SMR	standard mortality rate
SPSS	statistical package for the social sciences
T2DM	type 2 diabetes mellitus