

ORIGINAL ARTICLE

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

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Patients with hypertension and manifest vascular disease are at high risk for recurrent cardiovascular diseases. It is unknown if the metabolic syndrome further increases the risk in these patients. This study aims to quantify the effect of metabolic syndrome and type II diabetes on cardiovascular events in hypertensive patients with vascular disease. A total of 2196 hypertensive patients with vascular disease (cerebrovascular disease (34%), coronary heart disease (50%), peripheral arterial disease (28%), abdominal aortic aneurysm (13%)) from the Second Manifestations of Arterial Disease study were followed for up to 10 years (mean 3.9 years) for death, stroke and myocardial infarction. Age and sex adjusted hazard ratios (HR) were calculated for hypertensive patients with metabolic syndrome but without diabetes ($n=775$) and for hypertensive patients with type II diabetes ($n=381$), compared to merely hypertensive patients ($n=1040$).

Forty-nine percent had metabolic syndrome (NCEP ATP III definition) and 17% had type II diabetes. Metabolic syndrome predicted vascular death (HR 1.41, 95% confidence interval (CI) 1.01–1.98), stroke (HR 1.36, 95% CI 0.85–2.16) and myocardial infarction (HR 1.40, 95% CI 0.97–2.01). Type II diabetes accounted for even higher risks of vascular end points (HR 1.41–1.64). The effect of metabolic syndrome on future events could not be explained by the presence of type II diabetes. Even in high-risk patients with hypertension and vascular disease, presence of metabolic syndrome or type II diabetes identifies patients at high risk for future cardiovascular events. Identifying metabolic syndrome patients may direct therapy focusing on treatment of insulin resistance by reducing weight and increasing physical activity.

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Introduction

Patients with clinically manifest vascular disease are at increased risk of developing recurrent vascular events. A considerable proportion of these patients has hypertension as well, which is also a well-established cardiovascular risk factor.¹ Patients with both manifest vascular disease and hypertension make up a high-risk population for recurrent vascular disease.^{1,2} In about half of patients with hypertension insulin resistance can be found and hypertension tends to cluster with metabolic risk

factors.^{3,4} Therefore, hypertension is considered one of the key features of the metabolic syndrome.^{5,6}

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

Presence of metabolic syndrome amplifies the risk of developing type II diabetes mellitus 3- to 30-fold, depending on the criteria used.^{14–18} In populations free of cardiovascular disease at baseline, cardiovascular morbidity and mortality increased 1.5- to 3-fold in the presence of metabolic syndrome^{10,19–21} and two- to fourfold in the presence of type II diabetes.²² In spite of the use of different and modified definitions, the metabolic syndrome is

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associated with more extensive vascular damage and increased risk for subsequent events in patients with prevalent cardiovascular disease.^{12,23,24} In hypertensive patients without manifest vascular disease, the metabolic syndrome has been shown to be associated with increased intima-media thickness and left ventricular hypertrophy as well as with increased incidence of cardiovascular events.^{25–29}

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

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

Materials and methods

Study design and population

The Second Manifestations of Arterial Disease (SMART) study is an ongoing prospective follow-up study in the University Medical Center Utrecht. Since 1996, more than 7000 newly referred patients aged 18–80 years with clinically manifest atherosclerotic vascular disease (cerebrovascular disease, coronary heart disease, peripheral arterial disease or abdominal aortic aneurysm) or risk factors for atherosclerosis (hyperlipidemia, type I diabetes, type II diabetes or hypertension) are included. Patients with terminal malignant disease, those not independent in daily activities or insufficiently familiar with the Dutch language are not included. All patients are assessed for atherosclerotic risk factors and arterial diseases by non-invasive means. The local Ethics Committee approved the study and all participants gave their written informed consent. Important objectives of the SMART study are to evaluate the presence of additional arterial disease and risk factors in patients with manifest vascular disease or a vascular risk factor. The rationale and design of the SMART study have been described in detail elsewhere.³¹

This analysis is based on patients included in the screening period from January 1996 to March 2005 and contains data on 2196 patients with clinically manifest vascular disease (at inclusion or in past history), who also had hypertension at inclusion. Normotensive patients with manifest vascular

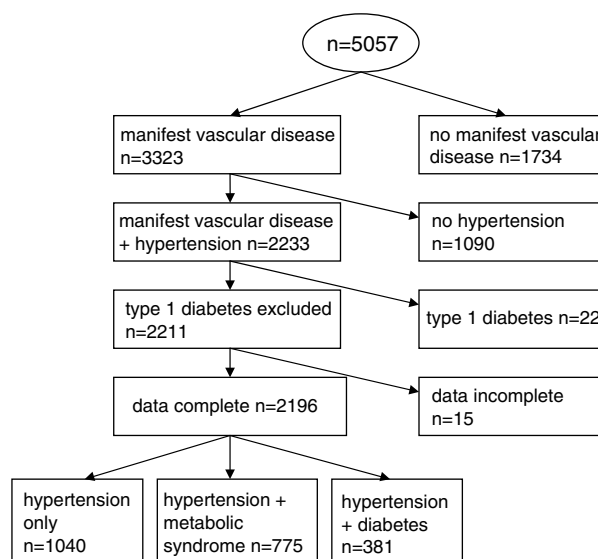


Figure 1 Composition of the study population.

disease ($n = 1090$) and patients with type I diabetes mellitus ($n = 22$) were not included in data analyses. Clinically manifest vascular disease was defined as cerebrovascular disease, coronary heart disease, abdominal aortic aneurysm or peripheral arterial disease at inclusion or in past history. Cerebrovascular disease included transient ischaemic attack, cerebral infarction, amaurosis fugax or retinal infarction; coronary heart disease included myocardial infarction and admission for percutaneous transluminal coronary angioplasty or coronary artery bypass graft; abdominal aortic aneurysm included abdominal aortic aneurysm ≥ 3.0 cm or aneurysm surgery; peripheral arterial disease included claudication of the legs, which was symptomatic and confirmed by a resting ankle-brachial pressure index < 0.9 in at least one leg, percutaneous transluminal angioplasty or leg amputation. A description of the composition of the study population is shown in Figure 1.

Measurements

All patients who entered the SMART study underwent a diagnostic screening-protocol for detection of manifestations of atherosclerotic disease and vascular risk factors. Physical examination included assessments of height, weight, waist and hip circumferences and blood pressure. Blood pressure was measured by sphygmomanometry at the right and left upper arm and repeated on the side with the highest values. The mean of all obtained measurements was used in the analysis.³¹ This assessment seems to be reliable as in a sample of 211 patients who underwent a second blood pressure measurement after 5.5 ± 1.3 years, 94% of newly diagnosed hypertensive subjects at inclusion were still

hypertensive or receiving blood pressure lowering agents at the second measurement.

Fasting blood samples were taken to ascertain levels of lipid, glucose, creatinine and homocysteine. Urinary albumin and creatinine concentrations were determined and duplex scanning of the carotid arteries, ultrasonography of the abdomen, electrocardiography and ankle-brachial pressure index were performed. The techniques of the baseline examinations have been published formerly.³¹ All subjects completed a health questionnaire on cardiovascular history, risk factors, familial vascular history and medication use.

Definitions

Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg and/or use of antihypertensive drug therapy. According to the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III),⁷ metabolic syndrome is defined as the presence of three or more of the following: (1) waist circumference > 88 cm in women and > 102 cm in men; (2) fasting triglycerides ≥ 1.70 mmol⁻¹ (150 mg per 100 ml); (3) high-density lipoprotein cholesterol < 1.29 mmol⁻¹ (50 mg per 100 ml) in women and < 1.04 mmol⁻¹ in men (40 mg per 100 ml); (4) blood pressure $\geq 130/85$ mmHg or use of antihypertensive drug therapy and (5) fasting glucose ≥ 6.1 mmol⁻¹ (110 mg per 100 ml) or use of hypoglycaemic agents. As all patients in this study satisfy the blood pressure criterion, the metabolic syndrome was diagnosed when two or more of the other criteria were present in addition to the blood pressure criterion. Type II diabetes was diagnosed as self-reported type II diabetes or use of glucose-lowering therapy. On the basis of these definitions, study subjects were divided into three separate groups. Those diagnosed with type II diabetes made up the diabetic group, irrespective of additional presence of the metabolic syndrome. The second group consisted of non-diabetic patients fulfilling the metabolic syndrome criteria, and remaining patients constituted the reference group of non-diabetic hypertensive patients without the metabolic syndrome.

Follow-up procedure and end point evaluation

On a half-yearly basis, information on hospitalization and outpatient clinic visits was obtained by questionnaires and telephone interviews with patients. For the subjects who reported a cardiovascular event, original source documents were retrieved and reviewed to determine the occurrence of cardiovascular disease. Additional information was collected on vascular interventions and death from other causes.

Outcome events used in our study include (1) vascular death; (2) non-fatal and fatal stroke; (3) non-fatal and fatal myocardial infarction and sudden death and (4) combined vascular events (non-fatal and fatal stroke, non-fatal and fatal myocardial infarction and sudden death). Vascular death was defined as sudden death (unexpected cardiac death occurring within 1 h after onset of symptoms or within 24 h given convincing circumstantial evidence) or death from stroke, myocardial infarction, congestive heart failure or rupture of abdominal aortic aneurysm. Patients with stroke had relevant clinical features causing an increase in impairment of at least one grade on the modified Rankin scale, accompanied by an infarction or haemorrhage on a repeat CT scan. Myocardial infarction was defined by at least two of the following criteria: (1) chest pain for at least 20 min, not disappearing after administration of nitrates; (2) ST-elevation > 1 mm in two following leads or a left bundle branch block on the electrocardiogram; (3) creatine kinase elevation of at least two times the normal value of creatine kinase and a myocardial band-fraction $> 5\%$ of the total creatine kinase.

All possible events were audited independently by three members of the Endpoint Committee.

Data analysis

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

Results

Baseline characteristics

From the total study population of 2196 patients, 1040 patients (48%) had hypertension and did not have metabolic syndrome or type II diabetes, 775 patients (35%) had hypertension in combination with metabolic syndrome but not type II diabetes

and 381 patients (17%) had hypertension and type II diabetes (Table 1). In type II diabetic patients, 78.5% did also meet the metabolic syndrome criteria.

In the total study population of hypertensive patients with manifest vascular disease, the prevalence of metabolic syndrome was 49%. After hypertension (100%), the criterion for triglycerides was most frequently present (76%) in patients with metabolic syndrome, followed by high-density lipoprotein cholesterol (69%), waist circumference (54%) and fasting glucose (53%).

Mean blood pressure in treated hypertensives was 150/84 mm Hg compared to 155/85 mm Hg in untreated subjects.

Incidence of vascular events

During a mean follow-up period of 3.9 years (range 0.5–8.5 years), 176 vascular deaths, 94 non-fatal and

fatal strokes and 147 non-fatal and fatal myocardial infarctions and sudden deaths were recorded. In total, there were 283 recurrent vascular events.

Survival analysis

Event-free survival curves, derived from an age- and sex-adjusted Cox proportional hazards model, are shown for the end points vascular death, stroke, non-fatal and fatal myocardial infarction and sudden death and combined vascular events (Figures 2a–d). Metabolic syndrome was associated with a higher risk for vascular death (HR 1.41; 95% confidence interval (CI) 1.01–1.98) and for myocardial infarction and sudden death (HR 1.40; 95% CI 0.97–2.01), adjusted for age and sex in this hypertensive cohort (Table 2). Although less explicit and not statistically significant, there was a distinct relation between metabolic syndrome and stroke

Table 1 Baseline characteristics of the study population

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

^aMetabolic syndrome according to the ATPIII criteria.

^bSelf-reported type II diabetes and/or use of glucose-lowering agents.

^cSmoking or previously smoking.

^dModification of diet in renal disease formula.

^eAlbumin-to-creatinine ratio > 3 mg mmol⁻¹.

^fCombination preparations, centrally active agents, α-blockers.

Continuous variables are expressed as mean ± s.d. and categorical variables as percentages with the number of patients between parentheses.

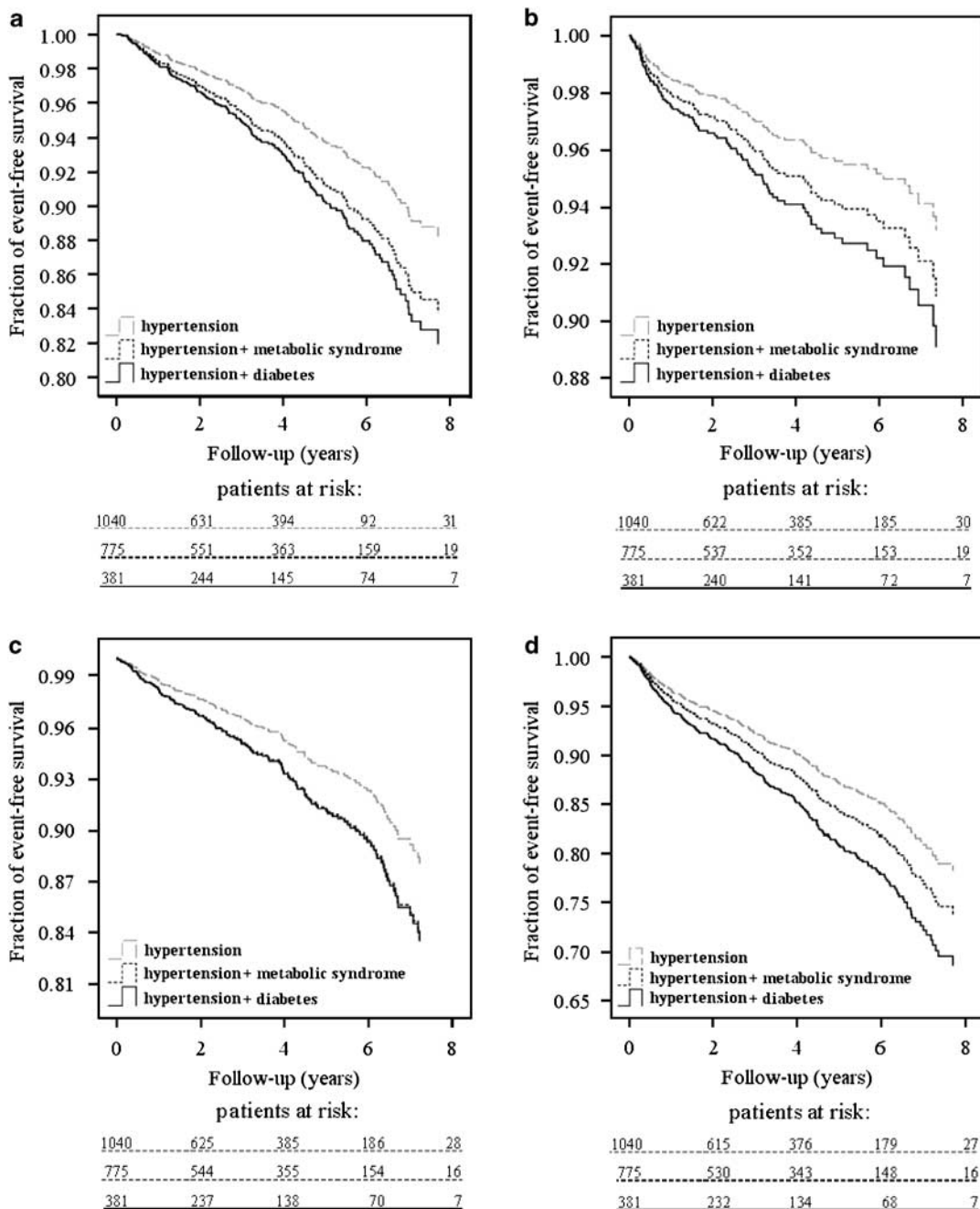


Figure 2 Fraction of hypertensive patients free from vascular death (a), stroke (b), myocardial infarction and sudden death (c) and combined vascular events (d) according to metabolic syndrome and type II diabetes, adjusted for age and sex. Lines for metabolic syndrome and type II diabetes overlap in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

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

Discussion

In a high-risk population of patients with hypertension and clinically manifest vascular disease, the presence of the metabolic syndrome entails a 1.41-fold greater risk for vascular death as well as a 1.40-fold greater risk for myocardial infarction and sudden death. In hypertensive patients with type II diabetes, the risk for vascular death (HR 1.59), combined vascular events (HR 1.54) and stroke

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

	<i>Vascular death (n = 176)</i> <i>HR (95% CI; P-value)</i>	<i>Stroke (n = 94)</i> <i>HR (95% CI; P-value)</i>	<i>Myocardial infarction and</i> <i>sudden death (n = 147)</i> <i>HR (95% CI; P-value)</i>	<i>Combined vascular end</i> <i>points (n = 283)</i> <i>HR (95% CI; P-value)</i>
Hypertension only	1.00 (n = 68)	1.00 (n = 35)	1.00 (n = 57)	1.00 (n = 113)
Hypertension+MetS ^a	1.41 (1.01–1.98; 0.046) (n = 68)	1.36 (0.85–2.16; 0.2) (n = 37)	1.40 (0.97–2.01; 0.07) (n = 60)	1.24 (0.95–1.62; 0.1) (n = 105)
Hypertension+DM ^b	1.59 (1.07–2.35; 0.02) (n = 40)	1.64 (0.96–2.79; 0.07) (n = 22)	1.41 (0.91–2.20; 0.1) (n = 30)	1.54 (1.13–2.09; 0.006) (n = 65)

^aMetabolic syndrome according to the ATPIII criteria.

^bSelf-reported type II diabetes and/or use of glucose-lowering agents. HRs are adjusted for age and sex.

(HR 1.64) is higher than for those without diabetes. Unless similar blood pressure and age at baseline, hypertensive patients with metabolic syndrome or diabetes are at higher risk for new cardiovascular events than hypertensive patients without metabolic syndrome or diabetes.

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

Several studies have demonstrated an association between metabolic syndrome and increased intima-media thickness, higher urinary albumin excretion and left ventricular hypertrophy in hypertensive subjects without manifest vascular disease.^{25,26,29} In this population, presence of metabolic syndrome was also associated with an increased amount of cardiovascular events.²⁸ A few studies compared the effects of metabolic syndrome and diabetes on cardiovascular disease. The role of the metabolic syndrome in predicting all-cause and cardiovascular mortality in patients with established cardiovascular disease was examined in the San Antonio Heart Study. After adjustment for diabetes and in subgroup analyses of non-diabetic and diabetic patients, the metabolic syndrome was no longer associated with both all-cause and cardiovascular mortality, which made the authors conclude that only diabetes accounted for the enhanced mortality in the metabolic syndrome group.³² In NHANES III, participants with metabolic syndrome and diabetes showed the highest prevalence of cardiovascular disease, followed by those with metabolic syndrome without diabetes and patients with neither. However, in multivariate analysis metabolic syndrome was no longer a significant predictor of cardiovascular disease.³³ In patients with coronary heart disease, both metabolic syndrome without diabetes

and diabetes alone were predictive of all-cause and cardiovascular mortality.²⁴ Similar to our population, diabetic patients had the highest mortality risk. A study among post-myocardial infarction patients showed a higher probability of death and cardiovascular events in both metabolic syndrome and diabetic patients.³⁴ In the Framingham Offspring Study, stroke risks were compared between metabolic syndrome and diabetic patients in a population in which some but not all patients had a history of cardiovascular disease. Patients with diabetes and metabolic syndrome were at greatest risk of stroke, followed by patients with diabetes alone and metabolic syndrome alone.³⁵ In our study, type II diabetes was associated with an increased risk of stroke, while metabolic syndrome and stroke risk was evident but not statistically significant. This is probably due to the difference in study populations and the relatively small number of strokes ($n = 94$) in our study.

In this study, metabolic syndrome is markedly associated with an increased risk of cardiovascular events. There are several mechanisms possibly underlying this association. The suggestion is made that the effect of the metabolic syndrome is primarily driven by the inclusion of diabetes in the definition.³² Although the vascular risk caused by the metabolic syndrome is partly due to diabetes, as shown by studies where the effect of the metabolic syndrome was attenuated or disappeared after adjustment for diabetes or after subgroup analysis in diabetic and non-diabetic patients,^{32,33} it is not likely that the vascular risk associated with the metabolic syndrome is completely caused by the inclusion of diabetic patients, as our study still identifies a large association between the metabolic syndrome and vascular events apart from diabetes. Other possible mechanisms causing an increased risk of vascular disorders in hypertensive patients with metabolic syndrome are insulin-mediated renal sodium reabsorption and vasoconstriction due to activation of the sympathetic nerve system and the renin-angiotensin-aldosterone system. Besides these mechanisms, there are other not routinely measured factors such as hypercoagulability, oxidative stress,

proinflammatory state, hyperinsulinaemia and impaired fibrinolysis associated with the metabolic syndrome, which may contribute in increasing cardiovascular risk. As the metabolic syndrome may precede diabetes, the vascular risk associated with the metabolic syndrome may also in part be mediated by the development of type II diabetes during follow-up. In this study, a gradual effect of metabolic syndrome and type II diabetes was seen on the risk of cardiovascular events. Metabolic syndrome can be seen as a pre-diabetic state with insulin resistance as the key feature. Owing to this central underlying pathophysiological mechanism, different combinations of the same number of metabolic syndrome traits are roughly comparable regarding vascular risk. Subjects who developed type II diabetes during 8-year follow-up were found to have increased triglyceride levels, decreased high-density lipoprotein cholesterol levels, increased systolic blood pressure, slightly increased fasting glucose levels and much higher insulin levels at baseline than subjects who did not develop diabetes.³⁶ Therefore, the cardiovascular risk accompanied by the metabolic syndrome is lower than that of type II diabetes patients and higher than that of non-metabolic syndrome patients.

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

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

What is known about the topic

- Patients with hypertension and vascular disease are at high risk for recurrent vascular diseases
- The metabolic syndrome and diabetes increase the risk of developing cardiovascular events in different populations

What this study adds

- Even in a hypertensive population with manifest vascular disease the metabolic syndrome and diabetes are still predictive of future cardiovascular disease
 - Based on their higher risk for future vascular events, hypertensive patients with the metabolic syndrome or diabetes may benefit from aggressive risk factor treatment and lifestyle changes
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Acknowledgements

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Appendix

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