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Prognostic Value of the Metabolic Syndrome in Essential Hypertension

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OBJECTIVES We sought to determine the prognostic significance of the metabolic syndrome in hypertension.

BACKGROUND Increased cardiovascular risk in hypertensive patients might be partially attributable to metabolic disturbances.

METHODS We prospectively followed for up to 10.5 years (mean 4.1 years) a total of 1,742 hypertensive patients without cardiovascular disease (55% men; blood pressure [BP] 154/95 mm Hg; age 50 ± 12 years). A modified National Cholesterol Education Program definition for metabolic syndrome was used, with body mass index in place of waist circumference.

RESULTS During follow-up, 162 patients developed cardiovascular events (2.28 events/100 patient-years). Event rates in the groups with one to five characteristics of the metabolic syndrome were 1.54, 1.96, 2.97, 3.35, and 5.27 per 100 patient-years, respectively ($p < 0.001$). A total of 593 patients (34%) had the metabolic syndrome. Patients with the syndrome had an almost double cardiovascular event rate than those without (3.23 vs. 1.76 per 100 patient-years, $p < 0.001$). After adjustment for age, gender, total cholesterol, creatinine, smoking, left ventricular hypertrophy, and 24-h systolic BP, the risk of developing cardiovascular events was still higher in patients with the metabolic syndrome (hazard ratio [HR] 1.73, 95% confidence interval [CI] 1.25 to 2.38). The syndrome was an independent predictor of both cardiac and cerebrovascular events (HRs 1.48 and 2.11, respectively). The adverse prognostic value of the metabolic syndrome was attenuated but still significant among the 1,637 patients without diabetes (HR 1.43, 95% CI 1.02 to 2.08).

CONCLUSIONS In hypertensive subjects, the metabolic syndrome amplifies cardiovascular risk associated with high BP, independent of the effect of several traditional cardiovascular risk factors. (J Am Coll Cardiol 2004;43:1817–22) © 2004 by the American College of Cardiology Foundation

The metabolic syndrome represents a cluster of cardiovascular risk factors closely linked to insulin resistance (1), whose prevalence is high and rapidly rising in the Western population (2,3). The working definition of the metabolic syndrome proposed in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) (4) is based on the presence of three or more of the following characteristics: abdominal obesity, high blood pressure (BP), high fasting glucose, high triglycerides, and reduced levels of high-density lipoprotein cholesterol. Recently, a modification of the ATP-III definition has been developed (5,6), in which waist circumference as a measure of adiposity was replaced by body mass index (BMI), which has been shown to predict metabolic disturbances as strongly as waist circumference (7–9). According to the latter definition, the metabolic syndrome is a predictor of future coronary heart disease in hypercholesterolemic men (5) and of cardiovascular morbidity in women without a history of cardiovascular disease (6).

High BP is considered one of the key features of the syndrome (4,10), and the recent European Society of Hypertension/European Society of Cardiology clinical guidelines for the management of hypertension underscore the importance of identifying hypertensive patients with the metabolic syndrome as a group at high risk for the development of cardiovascular disease (11). Although the problem is now thought to be of paramount importance, no systematic study has been performed to determine the prognostic importance of the metabolic syndrome in the hypertensive population. In the setting of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, we had the opportunity to investigate the relationship between the metabolic syndrome and incident cardiovascular disease in subjects with essential hypertension without prevalent cardiovascular disease, who underwent a thorough clinical work-up at the baseline examination and were then prospectively followed for up to 10 years.

METHODS

The PIUMA study is a prospective follow-up study of Caucasian adult subjects with essential hypertension (12,13), carried out in Umbria, Italy. A total of 1,750 white subjects enrolled between 1988 and 1996 were included in the present analysis. All study subjects fulfilled the following criteria: 1) office systolic BP ≥140 mm Hg, diastolic BP

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Abbreviations and Acronyms

ATP-III = Adult Treatment Panel III of the National Cholesterol Education Program
BMI = body mass index
BP = blood pressure
CI = confidence interval
HR = hazard ratio
LV = left ventricular
PIUMA = Progetto Ipertensione Umbria Monitoraggio Ambulatoriale

≥90 mm Hg, or both, on three or more visits at one-week intervals; 2) no previous treatment for hypertension (70%) or withdrawal from antihypertensive drugs at least four weeks before the study; 3) no clinical or laboratory evidence of heart failure, coronary heart disease, previous stroke, valvular defects, secondary causes of hypertension, or important concomitant disease; and 4) one or more valid BP measurement per hour over 24 h. At the baseline evaluation, hypertensive patients were classified by the presence or absence of the metabolic syndrome on the basis of the modified ATP-III criteria (4–6). By selection, all patients were hypertensive and hence fulfilled at least one of the ATP-III criteria.

The remaining cut-off values were: 1) serum triglyceride levels ≥1.69 mmol/l (150 mg/dl); 2) serum high-density lipoprotein cholesterol <1.04 mmol/l (40 mg/dl) in men and <1.30 mmol/l (50 mg/dl) in women; 3) fasting plasma glucose ≥6.11 mmol/l (110 mg/dl); and 4) BMI >29.3 kg/m^2 in men and >27.0 kg/m^2 in women. Hypertensive patients were classified as having the metabolic syndrome if they fulfilled two or more of the aforementioned criteria, in addition to hypertension. The BMI cut-off values were equivalent in a regression analysis to a waist circumference of 102 cm in men and 88 cm in women in a subgroup of 254 hypertensive patients from the PIUMA data base, in whom BMI showed a strong direct association with waist circumference ($r = 0.78$, $p < 0.001$). Compared with the original ATP-III definition, the modified definition resulted in misclassification of only 5.1% of the patients (13 of 254 patients). Diabetes mellitus was diagnosed by a fasting glucose level ≥7.0 mmol/l (126 mg/dl) or a clinical diagnosis of diabetes with dietary, oral, or insulin treatment. All subjects gave oral or written informed consent to participate in the study, which was approved by the institutional review board.

Baseline measurements. Office BP was measured by a physician in the hospital clinic, using a mercury sphygmomanometer, after the subject sat for ≥10 min. The average of six or more measurements for two or more sessions was considered for the analysis. Ambulatory BP was recorded with an oscillometric device (models 90202 and 90207; SpaceLabs, Redmond, Washington), which was set to take a reading every 15 min throughout 24 h (14). The BMI was calculated as weight in kilograms divided by the square of height in meters. Electrocardiographic (ECG) left ventricular (LV) hypertrophy was defined according to the Perugia criterion (S-wave in lead V_3 + R-wave in lead aVL = >2.4 mV in men and >2.0 mV in women, or typical LV strain, or a Romhilt-Estes score of ≥5 points) (15), which shows a greater attributable risk for cardiovascular morbidity and mortality than do other criteria (16).

Follow-up procedures and end-point evaluation. All subjects were followed by their family physicians, in cooperation with the outpatient clinic of the referring hospital. At the follow-up visit, 70% of the study patients were taking antihypertensive drugs, and 30% were receiving lifestyle measures only. Aspirin and hypolipidemic drugs were being used in 3% and 9% of the population, respectively. Contacts with family physicians and telephone interviews were periodically undertaken to determine the occurrence of cardiovascular disease. For the subjects who developed a cardiovascular event, hospital record forms and other available original source documents were reviewed in conference by the authors. Cardiovascular events included new-onset coronary artery disease (myocardial infarction, unstable angina with documentation of ischemic ECG changes, sudden cardiac death, or coronary revascularization procedure), congestive heart failure that required hospitalization, stroke, transient cerebral ischemia, and symptomatic aorto-iliac occlusive disease verified by angiography (12).

Statistical analysis. Survival curves were compared with the use of the Mantel (log-rank) test. For those subjects who experienced multiple events, survival analysis was restricted to the first event. The effect of prognostic factors on survival was evaluated with the use of the stepwise Cox semiparametric regression model. The assumption of proportionality for the Cox model was tested through visual inspection, and no violation of proportional hazards was found. We tested the variables of age (years), gender, office and 24-h systolic BP (mm Hg), serum total cholesterol (mmol/l), smoking habits (previous, never, or current smokers), family history of premature cardiovascular disease (yes, no), and antihypertensive treatment at the time of follow-up contact (lifestyle measures only, diuretics and/or beta-blockers, angiotensin-converting enzyme inhibitors and/or Ca^{2+}-channel blockers, other drugs or other antihypertensive drug combinations). Although at the follow-up visit only a small number of hypertensive patients were taking either aspirin or hypolipidemic drugs, the effects of those therapies were also evaluated in the regression model. The SPSS statistical package, release 9.0 (SPSS Inc., Chicago, Illinois), was used to perform the analyses.

RESULTS

Follow-up data were available for 1,742 (99.5%) of the 1,750 hypertensive patients, and only 0.5% were lost to follow-up. A total of 593 patients (34.0%) had the metabolic syndrome. Subjects with the metabolic syndrome were older and had a longer duration of hypertension and higher systolic BP (Table 1). The two groups did not differ in terms

Table 1. Clinical Characteristics of Study Subjects by Metabolic Pattern

Data	Metabolic Syndrome Absent (n = 1,149)	Metabolic Syndrome Present (n = 593)	p Value
Age (yrs)	49.8 ± 12	51.4 ± 11	0.009
Men (%)	55	55	0.86
Body mass index (kg/m^2)	25.6 ± 3	29.1 ± 4	<0.001
Current smokers (%)	24	27	0.12
Diabetes (%)	2	14	<0.001
Duration of hypertension (yrs)	3.4 ± 5	4.8 ± 7	<0.001
Office systolic BP (mm Hg)	153 ± 19	157 ± 21	<0.001
Office diastolic BP (mm Hg)	96 ± 10	97 ± 11	0.27
24-h systolic BP (mm Hg)	135 ± 14	138 ± 17	<0.001
24-h diastolic BP (mm Hg)	86 ± 10	86 ± 11	0.70
Total cholesterol (mmol/l)	5.51 ± 1.1	5.60 ± 1.1	0.08
HDL cholesterol (mmol/l)	1.35 ± 0.3	1.07 ± 0.3	<0.001
LDL cholesterol (mmol/l)	3.56 ± 0.9	3.55 ± 1.0	0.78
Triglycerides (mmol/l)	1.17 (0.87–1.54)	1.96 (1.51–2.59)	<0.001
Left ventricular hypertrophy (%)	16	18	0.22

Data are presented as the mean value ± SD, percentage, or median value (interquartile range).
BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

of gender distribution, smoking habits, total and low-density lipoprotein cholesterol concentrations, and LV hypertrophy.

Survival analysis. During follow-up of 4.1 ± 2 years (range 1.0 to 10.5 years), 162 patients had a new cardiovascular morbid event (2.28 events/100 patient-years). Specifically, there were 39 subjects with myocardial infarction, 7 with sudden cardiac death, 1 with cardiac death from other causes, 20 with unstable angina, 9 with coronary revascularization procedures, 14 with heart failure that required hospitalization, 43 with stroke, 16 with transient cerebral ischemia, and 13 with new-onset aorto-iliac occlusive disease that required revascularization. As shown in Figure 1, the event rate increased progressively with an increasing number of components of the metabolic syndrome (1.54, 1.96, 2.97, 3.35, and 5.27, respectively, per 100 patient-years in the groups with 1 to 5 characteristics; $p < 0.001$). Overall, there were 80 first cardiovascular events in the group with the metabolic syndrome (3.23 events per 100 patient-years) and 82 events in the group without (1.76 events per 100 patient-years). Event-free survival curves differed significantly among the two groups (log-rank value = 45.4, $p < 0.001$) (Fig. 2).

In a multivariate analysis, the metabolic syndrome maintained an association with subsequent cardiovascular events after adjustment for several potential confounders (Table 2). Patients with the metabolic factors had a 73% greater age- and risk factor-adjusted excess cardiovascular risk (hazard ratio [HR] 1.73, 95% confidence interval [CI] 1.25 to 2.38; $p < 0.001$). The metabolic syndrome was also an independent risk factor for "hard" cardiovascular events (i.e., after the exclusion of angina, coronary revascularizations, and congestive heart failure [HR 1.62, 95% CI 1.13 to 2.32; $p < 0.01$]). The prevalences of the single components of the metabolic syndrome are shown in Table 3, along with their risk factor–adjusted HR.

Men versus women. Event-free survival analysis was performed separately in men and women. In a multivariate Cox

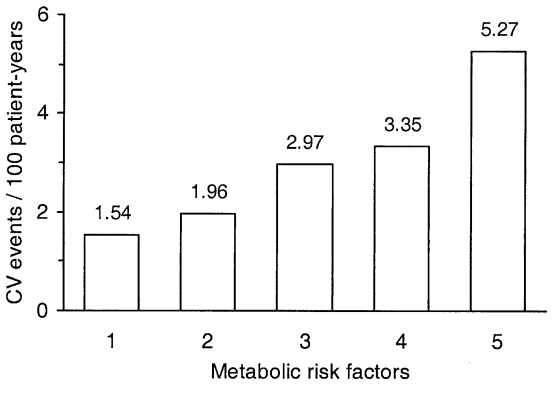

Figure 1. Cardiovascular (CV) event rate among 1,742 hypertensive patients grouped by number of characteristics of the metabolic syndrome. See text for details.

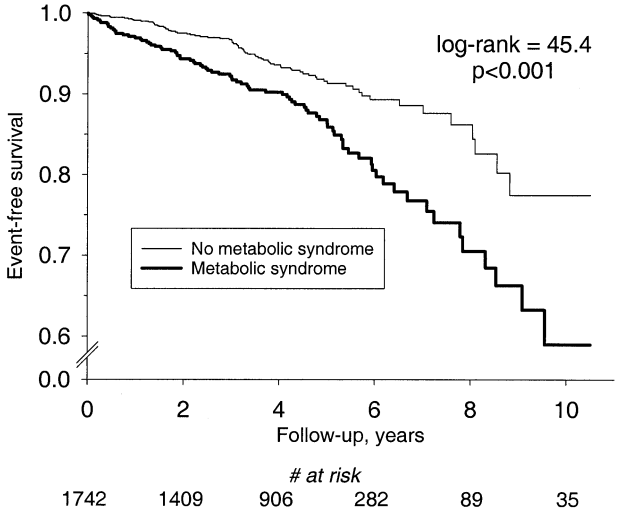

Figure 2. Cardiovascular event-free survival curves in hypertensive patients with **(thick line)** or without **(thin line)** the metabolic syndrome.

Table 2. Predictors of Cardiovascular Morbidity in a Multivariate Cox Model in 1,742 Hypertensive Patients

Variable	Adjusted HR* (95% CI)	p Value
Metabolic syndrome (yes vs. no)	1.73 (1.25–2.38)	0.001
Age (12 yrs)	2.17 (1.81–2.59)	<0.001
Gender (male vs. female)	1.61 (1.11–2.33)	0.01
Cigarette smoking (yes vs. no)	1.60 (1.12–2.28)	0.009
24-h systolic BP (15 mm Hg)	1.40 (1.21–1.61)	<0.001
Serum cholesterol (1 mmol/l)	1.20 (1.01–1.43)	0.04
Serum creatinine (18 μmol/l)	1.15 (1.06–1.24)	0.002
Left ventricular hypertrophy (yes vs. no)	1.88 (1.29–2.73)	<0.001

*For continuous variables, the adjusted hazard ratio associated with each standard deviation increase is reported. A family history of premature cardiovascular disease, office blood pressure, heart rate, and treatment status (antihypertensive, hypolipidemic and aspirin) failed to enter the final equation.

BP = blood pressure; CI = confidence interval; HR = hazard ratio.

regression model, the metabolic syndrome independently predicted cardiovascular events in men (HR 1.63, 95% CI 1.11 to 2.39; p = 0.02), as well as in women (HR 1.80, 95% CI 1.02 to 3.15; p = 0.048).

Cardiac versus cerebrovascular events. We also evaluated the prognostic impact of the metabolic syndrome on cardiac and cerebrovascular events taken separately. Compared with patients without the metabolic syndrome, patients with it had a higher rate of both cardiac events (1.77 vs. 1.07 events/100 patient-years; log-rank = 4.95, p = 0.026) and cerebrovascular events (1.41 vs. 0.59 events/100 patient-years; log-rank = 14.96, p < 0.001). Both differences remained significant in a multivariate Cox model (HR 1.48, 95% CI 1.01 to 2.27, p = 0.04 for cardiac events; HR 2.11, 95% CI 1.27 to 3.50, p < 0.001 for cerebrovascular events).

Influence of diabetes. To further explore whether the relationship between the metabolic syndrome and prognosis was independent of the presence of diabetes mellitus, we repeated the survival analysis after exclusion of patients with diabetes mellitus (n = 105). In the 1,637 hypertensive patients without diabetes, the relationship between the metabolic syndrome and cardiovascular morbidity was attenuated, but the event rate was still significantly higher in the presence of the metabolic syndrome (2.42 vs. 1.66 events per 100 patient-years, log-rank = 5.91, p = 0.02). In this group (Table 4), patients with the metabolic syndrome had a significantly higher age- and risk factor–adjusted rate of cardiovascular events than did patients without it (HR 1.43, 95% CI 1.02 to 2.08; p = 0.03).

DISCUSSION

The new finding of this prospective study is that the metabolic syndrome is an independent predictor of subsequent cardiovascular disease in initially untreated men and women with essential hypertension who had no clinically overt cardiovascular disease at the baseline examination. The adverse prognostic effect of the metabolic syndrome was independent of traditional cardiovascular risk factors, including LV hypertrophy (15,16) and 24-h BP, which is a better risk marker than office BP (12). Most notably, the association between the metabolic syndrome and future cardiovascular morbidity also held in patients without diabetes mellitus at the baseline examination. Hence, this study provides evidence that the metabolic syndrome may be useful as an integrating index of the overall burden imposed by metabolic factors on the cardiovascular system in hypertensive patients.

Several studies have shown that insulin resistance/hyperinsulinemia, a hallmark of the metabolic syndrome (1), is a predictor of ischemic heart disease in the population at large (17–21) and in patients with type II diabetes (22). In people with a family history of type II diabetes, individuals who had the metabolic syndrome, according to the World Health Organization (WHO) (23), had a higher mortality (24). However, patients with the metabolic syndrome had a higher prevalence of cardiovascular disease and diabetes at baseline, and no adjustment for those confounding factors was allowed in that study. In middle-aged Finnish men, the metabolic syndrome, based on definitions by the ATP-III and WHO, predicted an increased all-cause and cardiovascular mortality (3). Using a modified ATP-III definition with BMI in place of waist circumference, the metabolic syndrome was found to predict coronary heart disease in hypercholesterolemic men (5) and in apparently healthy women (6). Still, in the latter study, plasma glucose levels were not collected, and no adjustment was made for important risk factors, such as smoking status.

Taken together, the available studies do not provide an answer to the question regarding the clinical significance of the metabolic syndrome in hypertension. High BP is a

Table 3. Prevalence and Prognostic Significance of the Single Components of the Metabolic Syndrome in 1,742 Hypertensive Patients

Variable	Prevalence (%)	Adjusted HR* (95% CI)	p Value
High serum triglycerides (≥1.69 mmol/l)	34	1.75 (1.26–2.42)	<0.001
Low HDL cholesterol (<1.04 mmol/l in men, <1.30 mmol/l in women)	35	1.71 (1.24–2.36)	<0.001
High fasting plasma glucose (≥6.11 mmol/l)	19	1.38 (1.00–1.93)	<0.05
Obesity (body mass index >29.3 kg/m^2 in men, >27.0 kg/m^2 in women)	29	0.96 (0.72–1.27)	0.80

*Adjusted for age, gender, smoking, 24-h systolic blood pressure, serum total cholesterol concentration, serum creatinine, and left ventricular hypertrophy.

Abbreviations as in Tables 1 and 2.

Table 4. Independent Predictors of Cardiovascular Morbidity and All-Cause Mortality in 1,637 Nondiabetic Hypertensive Patients in a Multivariate Cox Model

Variable	Adjusted HR* (95% CI)	p Value
Metabolic syndrome (yes vs. no)	1.43 (1.02–2.08)	0.03
Age (12 yrs)	2.10 (1.72–2.55)	<0.001
Gender (male vs. female)	1.80 (1.18–2.75)	0.007
Cigarette smoking (yes vs. no)	1.92 (1.31–2.82)	<0.001
24-h systolic BP (15 mm Hg)	1.36 (1.16–1.60)	<0.001
Serum cholesterol (1 mmol/l)	1.20 (1.00–1.45)	0.05
Serum creatinine (18 μmol/l)	1.11 (1.01–1.23)	0.04
Left ventricular hypertrophy (yes vs. no)	1.96 (1.28–3.00)	0.002

*For continuous variables, the adjusted hazard ratio associated with each 1-SD increase is reported. A family history of premature cardiovascular disease, office blood pressure, heart rate, and treatment status (antihypertensive, hypolipidemic and aspirin) failed to enter the final equation.

Abbreviations as in Table 2.

major (25) and independent (26) cardiovascular risk factor. On the other hand, hypertension tends to cluster with metabolic risk factors, and about half of patients with essential hypertension are insulin-resistant (10,27). Coronary risk continues to be higher in drug-treated hypertensive patients than in normotensive individuals (28,29), and some of this difference might be due to the presence in hypertensive patients of additional metabolic risk factors, which have been collectively identified as the metabolic syndrome.

The ATP-III guidelines recognize that the metabolic syndrome enhances the risk of coronary heart disease (4), and the prognostic value of the metabolic syndrome for incident coronary heart disease (5), cardiovascular disease (6), cardiovascular mortality (7,24), and all-cause mortality (3) has been established in different clinical settings. In the Helsinki Policemen Study (30), risk factor clustering of insulin resistance syndrome predicted both coronary heart disease and stroke. In our study, we found, for the first time, that the metabolic syndrome, defined by ATP-III, is an independent predictor of cerebrovascular and cardiac events. Our finding of an increased risk of two different manifestations of atherosclerotic disease in hypertensive patients with the metabolic syndrome is in agreement with the hypothesis that insulin resistance, per se, might accelerate the development of atherosclerosis. As a matter of fact, the metabolic syndrome has been associated with progressive carotid atherosclerosis (31), as well as to coronary atherosclerosis (32). On the other hand, individuals with the metabolic syndrome tend to have systemic endothelial dysfunction (33) and chronic subclinical inflammation (34), which are increasingly recognized as powerful risk factors for cardiac and cerebrovascular events (35–37).

Study limitations. The present study has some limitations. Because our findings have been obtained in initially untreated white subjects, the results may not be extended to different ethnic groups or to subjects receiving antihypertensive treatment at the time of the qualifying examination. The PIUMA data base does not include information on BP control during follow-up in the whole population; these data were available in about 30% of the study subjects. Another limitation inherent to observational cohort studies is the lack of control for occasional changes in the antihypertensive regimen over time.

Perspectives. Our findings suggest that the metabolic syndrome represents a strong, independent risk factor for future cardiovascular disease in hypertensive patients. Over and above the prognostic information provided by all other traditional cardiovascular risk markers (11), the simple, inexpensive assessment of the metabolic syndrome may contribute to further refine cardiovascular risk stratification in hypertension. Hypertensive patients with the metabolic syndrome are at increased risk of coronary and cerebrovascular disease and require a more vigorous nondrug and pharmacologic preventive approach. The present finding of a synergistic impact of the metabolic syndrome and hypertension on cardiovascular disease strongly indicates the need for metabolic screening in all hypertensive patients at the first diagnosis.

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