Prognostic Relevance of Metabolic Syndrome in Hypertensive Patients at Low-to-Medium Risk

Sante D. Pierdomenico, Domenico Lapenna, Roberta Di Tommaso, Silvio Di Carlo, Maria P. Caldarella, Matteo Neri, Andrea Mezzetti, and Franco Cuccurullo

Background: The prognostic impact of metabolic syndrome (MetS) in the hypertensive population at low-medium risk is unknown. In this study, we evaluated the prognostic relevance of MetS in hypertensive patients at low-medium risk.

Methods: The occurrence of nonfatal and fatal cardiac and cerebrovascular events was evaluated in 802 patients with mild to moderate essential hypertension at low-medium risk according to the 2003 World Health Organization/International Society of Hypertension statement on the management of hypertension. Among these patients, 218 (27.2%) had MetS according to a modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition (body mass index in place of waist circumference).

Results: During follow-up (6.9 ± 3.1 years; range, 0.5 to 13.1 years, mean ± SD), 58 first cardiovascular events occurred. The event rates per 100 patient-years in patients without and with MetS were 0.87 and 1.51, respectively. Event-free survival was significantly different between groups (P = .03). After adjustment for several covariates, Cox regression analysis showed that cardiovascular risk was significantly higher in patients with than in patients without MetS (relative risk, 2.64; 95% confidence interval, 1.52 to 4.58; P = .001). Other independent predictors of outcome were age, smoking habit, 24-h systolic BP, and LDL cholesterol.

Conclusions: Hypertensive patients at low-medium risk with MetS are at higher cardiovascular risk than those without MetS. Metabolic syndrome may be a useful tool for clinicians to identify subjects who are at increased risk when traditional assessment may indicate low-medium risk. Am J Hypertens 2007;20:1291–1296 © 2007 American Journal of Hypertension, Ltd.

Key Words: Metabolic syndrome, essential hypertension, prognosis.
Methods

Subjects

We studied 802 mild-to-moderate essential hypertensive patients (untreated at baseline) at low-medium cardiovascular risk according to the 2003 WHO/ISH statement on the management of hypertension (ie, those with up to two risk factors, and without diabetes, target-organ damage, and associated clinical conditions). These patients were selected from a larger population that included 1859 hypertensive subjects. Six hundred and sixty-four patients at high risk (ie, those with ≥3 risk factors, diabetes, target-organ damage, and associated clinical conditions) were excluded from this study. Three hundred and ninety-three patients aged <40 years were also excluded. In this population, we employed a modified definition of the NCEP ATP III to identify MetS, ie, hypertension plus any two of the following: (1) body mass index >28.6 kg/m² in men and >26.5 kg/m² in women, (2) blood glucose ≥100 mg/dL (as recently updated), (3) triglycerides ≥150 mg/dL, and (4) HDL cholesterol <40 mg/dL in men and <50 mg/dL in women. The body mass index cutoff 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 357 hypertensive subjects, in whom body mass index had a strong, direct association with waist circumference (r = 0.80 and P < .0001 in both men and women). The study population came from the same geographic area (Chieti and Pescara, Abruzzo, Italy). The study was in accordance with the Second Declaration of Helsinki, and was approved by our institutional committee on human research. Subjects gave informed consent.

Procedures

All patients had undergone clinical evaluation and laboratory and instrumental investigations. Clinical evaluation included medical history, physical examination, and BP measurement. Clinic BP recording was performed by a physician with subjects in supine position after 10 min of rest, by using a mercury sphygmomanometer. Laboratory tests included glucose, total cholesterol, HDL cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol calculated by Friedewald’s formula, creatinine, potassium, and urinalysis (in the present study, we included subjects with at least two urinalyses indicating absent proteins). Instrumental investigations included electrocardiogram, echocardiogram, carotid ultrasound, and noninvasive ambulatory BP monitoring. Echocardiographic left-ventricular (LV) mass was calculated using the formula introduced by Devereux et al. Individual values for LV mass were indexed by height².7 and LV hypertrophy was defined as LV mass/height² >50 g/m² in men and >47 g/m² in women.7 Carotid ultrasonography was performed to evaluate vascular damage in the carotid arteries. Plaque was defined as a localized lesion encroaching on the lumen, at a thickness >1.5 mm. Ambulatory BP monitoring was performed on a day of typical activity. Technical aspects were previously described.7 Daytime, nighttime, and 24-h BP were evaluated. Recordings were automatically edited.16

Follow-Up

Subjects were followed in our hospital outpatient clinic or by their family doctors. Patients’ characteristics and the occurrence of cardiovascular events were recorded during follow-up visits or by telephone interview of the patient, followed by a clinic visit. Hospital record forms were collegially reviewed by the authors of this study.

Cardiovascular events included fatal and nonfatal myocardial infarction (at least two of three standard criteria: typical chest pain, electrocardiogram changes, or transient elevation of conventional myocardial enzymes by more than twofold the upper normal limits), coronary revascularization (bypass surgery or angioplasty), heart failure requiring hospitalisation (at least two major or one major plus two minor Framingham criteria),17 and fatal and nonfatal stroke (rapid onset of localizing neurologic deficit lasting ≥24 h according to computer tomography evidence).

Statistical Analysis

Data are expressed as mean ± SD or percentage. Groups were compared with an unpaired t test, Mann-Whitney U test, or χ² test, as appropriate. Event rates are expressed as number of events per 100 patient-years, based on the ratio of the observed number of events to the total number of patient-years of exposure up to the terminating event or censor. Survival curves were estimated using the Kaplan-Meier product-limit method and compared by Mantel-log-rank test.18 The effect of various covariates on survival was evaluated by using a backward, stepwise, Cox regression model (significance levels for inclusion and exclusion were .05 and .1, respectively).18 Covariates included in the Cox model were: age (years), sex (men versus women), family history of premature cardiovascular disease (yes versus no), smoking habit (yes versus no), BP (mm Hg; entered as either clinic systolic or diastolic BP or 24-h systolic or diastolic BP, and retaining in the model the BP measure that was the best predictor of risk), LDL cholesterol (mg/dL), creatinine (mg/dL), LV mass index (g/m².7), MetS (yes versus no), aspirin use (yes versus no), statin use (yes versus no), and antihypertensive drug class. Adjusted relative risks and 95% confidence intervals were calculated for the significant Cox model factors. Statistical significance was defined as P < .05. Analyses were performed with the SPSS-12 software package (SPSS, Inc., Chicago, IL).

Results

In this mildly-to-moderately hypertensive population, 278 and 524 subjects, respectively, were at low and medium risk. According to the definition used, 218 patients (27.2%)
had MetS. The main characteristics and BPs of the study groups are reported in Table 1. Body mass index, glucose, and triglycerides were significantly higher in patients with MetS than in those without MetS. High-density lipoprotein cholesterol was significantly lower in the group with MetS. Total cholesterol was significantly higher in patients with MetS. A family history of premature cardiovascular disease tended to be more common in patients with MetS, but did not attain statistical significance (P = .06). Left-ventricular mass index (although in normal range) was slightly but significantly higher in subjects with MetS. Sex distribution, age, smoking habit, LDL cholesterol, creatinine, and clinic and ambulatory BP were not significantly different between groups.

Antihypertensive drug classes of the study groups at follow-up are described in Table 2. The use of diuretics, beta-blockers, angiotensin-converting enzyme (ACE)-inhibitors, calcium antagonists, sartans, and alpha-blockers was not significantly different between patients with and without MetS. At follow-up, about 84% of individuals in each group were receiving drug therapy. Aspirin and statin use at follow-up did not differ between patients without and with MetS (1.7% v 1.4%, respectively, and 1.5% v 1.0%, respectively).

During follow-up (6.9 ± 3.1 years; range, 0.5 to 13.1 years), 58 first cardiovascular events occurred. Specifically, there were 17 myocardial infarctions, 8 coronary revascularizations, 2 heart failures requiring hospitalization, and 31 strokes. In the groups without and with MetS, 36 and 22 subjects, respectively, had a cardiovascular event. The event rates per 100 patient-years and event-free survival curves in subjects without and with MetS are given in Fig. 1. Event rates in the study groups according to number of components of MetS are given in Fig. 2. The event rate increased progressively with an increasing number of components.

To identify independent predictors of outcome, a Cox regression analysis was performed. Age, smoking habit, LDL cholesterol, 24-h systolic BP, and MetS provided independent predictors of cardiovascular events. The main results are listed in Table 3. The prognostic contributions of single components of MetS were also evaluated. The main results are given in Table 4.

### Discussion

This study shows that MetS is an independent predictor of cardiovascular risk in hypertensive patients at low-me-
medium risk, even after adjustment for traditional risk factors and ambulatory BP. It was reported that MetS is associated with increased cardiovascular morbidity and mortality in both men and women, in different clinical settings.\textsuperscript{5–11} However, at present, there is only a single study\textsuperscript{12} specifically regarding the prognostic relevance of MetS in the hypertensive population. Schillaci et al\textsuperscript{12} reported that MetS is an independent predictor of risk in initially untreated hypertensive patients. In the aforementioned study, after excluding diabetic subjects, hypertensive patients with MetS had a higher risk for future events than those without MetS (relative risk, 1.43; 95% confidence interval, 1.02 to 2.03; \( P = .03 \)). That study\textsuperscript{12} included hypertensive patients at low, medium, and high risk.

The present study indicates that MetS is associated with increased cardiovascular risk in the subset of hypertensive patients at low-medium risk. Thus, our data confirm and extend the previous findings\textsuperscript{12} in the hypertensive population.

Several mechanisms could explain the increment of risk in hypertensive patients with MetS. Increased glucose levels induce the glycosylation of proteins, free radical generation, glycosylation of LDL particles (making them more oxidizable and more atherogenic), and alteration of the coagulation process.\textsuperscript{19} Mixed dyslipidemia (ie, hypertriglyceridemia, low HDL cholesterol, preponderance of small, dense LDL, and accumulation of cholesterol-rich remnant particles) is emerging as an important lipid risk factor for cardiovascular disease.\textsuperscript{20,21} Low HDL cholesterol may also be associated with less anti-inflammatory, antithrombotic, and antiproliferative activity.\textsuperscript{22} In addition, expanded adipose tissue mass may produce a variety of substances with proinflammatory and prothrombotic activity.\textsuperscript{1,23} Finally, various MetS features are associated with an increase in sympathetic activity, which in turn induces functional and structural cardiovascular alterations.\textsuperscript{24}

Certainly, the clustering of the aforementioned factors, associated with the synergistic, detrimental impact of high BP, amplifies injuries to the vascular system and increases the probability of developing cardiovascular disease.

In the present study, drug therapy at follow-up was not significantly different between subjects with and without MetS. The pathophysiology of MetS is incompletely un-

### Table 3. Independent predictors of cardiovascular events by Cox regression analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>RR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 years)</td>
<td>2.29 (1.74–3.02)</td>
<td>.0001</td>
</tr>
<tr>
<td>Smoking habit (yes vs no)</td>
<td>2.49 (1.31–4.74)</td>
<td>.005</td>
</tr>
<tr>
<td>LDL cholesterol (1 SD)</td>
<td>2.13 (1.06–1.76)</td>
<td>.02</td>
</tr>
<tr>
<td>24-h systolic BP (10 mm Hg)</td>
<td>2.12 (1.64–2.73)</td>
<td>.0001</td>
</tr>
<tr>
<td>Metabolic syndrome (yes vs no)</td>
<td>2.64 (1.52–4.58)</td>
<td>.001</td>
</tr>
</tbody>
</table>

BP = blood pressure; CI = confidence interval; LDL = low-density lipoprotein; RR = relative risk.

One standard deviation (SD) of LDL cholesterol is 26 mg/dL.

### Table 4. Prognostic relevance of single components of metabolic syndrome

<table>
<thead>
<tr>
<th>Predictor</th>
<th>RR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ( &gt;28.6 \text{ kg/m}^2 ) (M) and ( &gt;26.5 \text{ kg/m}^2 ) (W)</td>
<td>1.64 (0.95–2.81)</td>
<td>.07</td>
</tr>
<tr>
<td>Glucose ( \geq 100 \text{ mg/dL} )</td>
<td>1.59 (0.89–2.85)</td>
<td>.12</td>
</tr>
<tr>
<td>HDL cholesterol ( &lt;40 \text{ mg/dL} ) (M) and ( &lt;50 \text{ mg/dL} ) (W)</td>
<td>2.27 (1.22–4.23)</td>
<td>.01</td>
</tr>
<tr>
<td>Triglycerides ( \geq 150 \text{ mg/dL} )</td>
<td>2.25 (1.24–4.07)</td>
<td>.007</td>
</tr>
</tbody>
</table>

BMI = body mass index; CI = confidence interval; HDL = high-density lipoprotein; M = men; RR = relative risk; W = women.

Adjusted for age, smoking habit, low-density lipoprotein cholesterol, and 24-h systolic blood pressure.
nderstood, but insulin resistance seems to be an important component leading to various metabolic alterations. It was previously reported that high-dose diuretics and some beta-blockers may decrease insulin sensitivity and worsen glucose and lipid metabolism.\textsuperscript{25–27} On the other hand, ACE inhibitors and angiotensin receptor blockers exert a positive influence on glucose metabolism and lipid profile by improving insulin sensitivity.\textsuperscript{28,29} Indeed, Lindholm et al\textsuperscript{30} reported that antihypertensive treatment with old drugs may be associated with an aggravated metabolic profile, whereas this complication does not seem to be present when new drugs are used. Thus, the long-term metabolic effects of antihypertensive therapy should be taken into account in general, and especially in hypertensive patients with MetS who should receive drugs with a favourable metabolic profile.

The present study has some limitations. First, we used body mass index in place of waist circumference, which was not available in all subjects. However, we employed body mass index values corresponding in a regression analysis to the waist circumference cutoff values used for the definition of MetS according to NCEP ATP III. Second, we included patients with at least two urinalyses indicating absent proteins; the lower detection limit of this method is 5 mg/dL. Thus, it cannot be completely ruled out that some patients had urinary albumin values at the low end of the microalbuminuric range. Third, peripheral (femoral) ultrasound was not performed in the vast majority of these patients. However, no subject had signs of peripheral vascular disease or developed peripheral vascular events. Fourth, fundoscopy was not performed in all subjects. However, grade 1 and 2 retinal changes are no longer considered signs of organ damage by WHO/ISH guidelines,\textsuperscript{13} and grades 3 and 4 tended to be present in patients with severe hypertension who were excluded from this study. Finally, we studied only white subjects, and our results cannot be applied to other ethnic groups.

In conclusion, hypertensive patients at low-medium risk with MetS are at higher cardiovascular risk than those without MetS. Metabolic syndrome may be a useful tool for clinicians to identify subjects who are at increased risk when traditional assessment may indicate low-medium risk. These patients should receive a more aggressive therapeutic approach, targeting the control of both BP and metabolic factors.

References