Adult Treatment Panel III 2001 but Not International Diabetes Federation 2005 Criteria of the Metabolic Syndrome Predict Clinical Cardiovascular Events in Subjects Who Underwent Coronary Angiography

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OBJECTIVE — The International Diabetes Federation (IDF) has recently established a worldwide consensus definition of the metabolic syndrome. No prospective data are available on the cardiovascular risk associated with this new metabolic syndrome definition.

RESEARCH DESIGN AND METHODS — In a prospective study of 750 coronary patients, we recorded vascular events over 4 years.

RESULTS — From our patients, 37.3% ($n = 280$) had the metabolic syndrome according to the Adult Treatment Panel III (ATPIII) definition and 45.5% ($n = 341$) according to the IDF definition. The metabolic syndrome as defined by the ATPIII criteria significantly predicted vascular events (adjusted hazard ratio 1.745 [95% CI 1.255–2.427]; $P = 0.001$), but the metabolic syndrome as defined by IDF criteria did not (1.189 [0.859–1.646]; $P = 0.297$). Accordingly, event-free survival was significantly lower among patients who fulfilled the ATPIII but not the IDF criteria than among those who met the IDF but not the ATPIII criteria ($P = 0.012$). The metabolic syndrome as defined by ATPIII criteria remained significantly predictive of vascular events after adjustment for type 2 diabetes but not after additional adjustment for the metabolic syndrome components high triglycerides and low HDL cholesterol. These lipid traits in turn proved significantly predictive of vascular events even after adjustment for the metabolic syndrome.

CONCLUSIONS — The ATPIII definition of the metabolic syndrome confers a significantly higher risk of vascular events than the IDF definition. However, among angiographied coronary patients, even the ATPIII definition of the metabolic syndrome does not provide prognostic information beyond its dyslipidemic features.

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The term metabolic syndrome refers to a cluster of cardiovascular risk factors associated with insulin resistance (1,2). During the past decade, there have been various attempts to standardize the definition of the metabolic syndrome as a diagnostic category, with several institutions proposing various criteria (3–7).

The definition of the metabolic syndrome that has most often been used in the literature was proposed by the National Cholesterol Education Program's Adult Treatment Panel III (ATPIII) 4 years ago (4). According to this definition, the metabolic syndrome is diagnosed in the presence of any three of five markers: central obesity, high triglycerides, low HDL cholesterol, high fasting glucose, and high blood pressure.

Recently, the concept of the metabolic syndrome as an entity with clinical implications over and above its single constituents has been challenged (8,9). However, efforts continue to integrate the individual metabolic syndrome traits into an overall diagnosis, and the International Diabetes Federation (IDF) has now established a worldwide consensus definition of the metabolic syndrome (10,11).

This new definition basically agrees with the component features of the ATPIII definition but introduces some important changes: the cutoff for a waist circumference defining central obesity has been considerably lowered for both men (from 102 to 94 cm) and women (from 88 to 80 cm), and the presence of central obesity is mandatory in this new definition. Also, the cutoff for elevated fasting glucose has been lowered in accordance with the American Diabetes Association's recommendation (12), and, importantly, patients receiving treatment for metabolic syndrome components are considered to meet the respective criteria, whereas therapy was not explicitly considered in the ATPIII definition.

The metabolic syndrome as defined by ATPIII criteria confers a strongly increased risk of vascular events (13–19). However, no prospective data are available on the cardiovascular risk associated with the new IDF definition. We therefore aimed at investigating the power of the ATPIII and IDF definitions of the metabolic syndrome as predictors of future vascular events in a high-risk cohort of coronary patients. Further, we intended to investigate whether the integral diagnosis of the metabolic syndrome is a better predictor of vascular events than

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Abbreviations: ATPIII, Adult Treatment Panel III; CAD, coronary artery disease; IDF, International Diabetes Federation.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

the individual metabolic syndrome components.

RESEARCH DESIGN AND METHODS

— The design of this prospective cohort study has been described in detail earlier (19,20). In brief, we enrolled 756 consecutive Caucasian patients referred to coronary angiography for routine evaluation of established or suspected coronary artery disease (CAD). Six patients with type 1 diabetes (C-peptide negative) were excluded from the analyses. The ethics committee of the University of Innsbruck approved the present study, and all participants gave written informed consent.

At baseline, coronary angiography was performed with the Judkins technique. Stenoses ≥50% were considered significant, and coronary arteries were defined as angiographically normal in the absence of any visible lumen narrowing at angiography, as described previously (21,22).

From the 750 patients included in the analyses, 164 had diabetes according to World Health Organization criteria (23) and 586 did not have diabetes. Among patients with diabetes, 42.7% were not receiving any antidiabetic medication and 34.8, 32.3, 24.4, and 1.2% were receiving—alone or in combination—sulfonylurea, biguanides, insulin, and α-glucosidase inhibitors, respectively. Overall, 64.7% of our patients were on aspirin, 31.3% on statins, 2.9% on fibrates, 12.1% on calcium antagonists, 47.1% on β-blocking agents, 36.0% on ACE inhibitors, and 3.9% on angiotensin II blocking agents.

According to ATPIII criteria (4), the metabolic syndrome was diagnosed in the presence of any three of the following: waist circumference >102 cm in men and >88 cm in women, triglycerides ≥150 mg/dl (1.7 mmol/l), HDL cholesterol <40 mg/dl (1.0 mmol/l) in men and <50 mg/dl (1.3 mmol/l) in women, blood pressure ≥130/≥85 mmHg, or fasting glucose ≥110 mg/dl (6.1 mmol/l). Using IDF criteria (10), the metabolic syndrome was diagnosed in patients who had a high waist circumference (≥94 cm in men and ≥80 cm in women) plus any two of the following: triglycerides ≥150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality, HDL cholesterol <40 mg/day (1.0 mmol/l) in men and <50 mg/dl (1.3 mmol/l) in women or specific treatment for this lipid abnormality, systolic blood pressure ≥130 or diastolic blood pressure ≥85 mg/dl or treatment of previously diagnosed hypertension, and fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes.

Prospective study

During a follow-up period of 3.9 ± 0.8 years, we recorded fatal and nonfatal cardiovascular events, including coronary death (fatal myocardial infarction, sudden cardiac death, and mortality from congestive heart failure due to CAD), fatal ischemic stroke, nonfatal myocardial infarction, nonfatal ischemic stroke, and need for coronary artery bypass grafting, percutaneous coronary intervention, or noncoronary revascularization. Angina pectoris per se was not included among the end points.

Statistical analysis

Differences in baseline characteristics were tested for statistical significance with the χ^2 test and the Mann-Whitney *U* test for categorical and continuous variables, respectively. The Wilcoxon-Gehan statistic was used to compare differences in the cumulative incidence rates of vascular events. Adjusted hazard ratios (HRs) for the incidence of vascular events were derived from Cox proportional hazards models; for these calculations, continuous variables were z transformed. Results are given as means ± SD if not denoted otherwise. All statistical analyses were performed with the software package SPSS 11.0 for Windows.

RESULTS

Baseline characteristics with respect to metabolic syndrome status

From the total study population, 280 patients (37.3%) met the ATPIII criteria and 341 patients (45.5%) the IDF criteria for the metabolic syndrome. Baseline characteristics of patients with respect to the metabolic syndrome status according to the ATPIII and IDF definitions are summarized in Table 1.

Prevalence of the individual metabolic syndrome criteria

From the individual ATPIII metabolic syndrome criteria, the blood pressure criterion was most frequently (in 85.4%) met in patients with the metabolic syndrome according to the ATPIII definition, followed by the criteria for triglycerides (75.0%), fasting plasma glucose (70.4%), HDL cholesterol (68.9%), and waist circumference (59.3%). From the patients with the metabolic syndrome according to the IDF definition, 100, 89.4, 83.9, 59.2, and 52.2% fulfilled the IDF criteria for waist circumference, blood pressure, fasting plasma glucose, triglycerides, and HDL cholesterol, respectively.

Concordance of the two definitions

Concordance between the ATPIII and IDF definitions was moderate (Cohen-κ coefficient = 0.522; $P < 0.001$). From our 280 patients (37.3% of the total study population) with the metabolic syndrome according to the ATPIII definition, 223 (79.6%) also had the metabolic syndrome according to the IDF definition; from the 470 patients who did not have the ATPIII metabolic syndrome (62.7% of the total study population), 352 (74.9%) also did not fulfil the criteria of the IDF definition (online appendix [available from http://care.diabetesjournals.org]). Thus, 57 patients (7.6% of the total study cohort) fulfilled the ATPIII criteria but not the IDF criteria (ATPIII+/IDF− group), and 118 patients (15.7% of the total study cohort) fulfilled the IDF criteria but not the ATPIII criteria (ATPIII−/IDF+ group).

Differences between the discordant groups

By definition, all ATPIII−/IDF+ patients met the IDF waist criterion. No ATPIII+/IDF− patient fulfilled the ATPIII waist criterion. ATPIII−/IDF+ patients less frequently than ATPIII+/IDF− patients met the respective triglycerides (30.5 vs. 86.0%; $P < 0.001$) and HDL (24.6 vs. 77.2%; $P < 0.001$) criteria. There were no significant differences in the prevalence of the respective blood pressure (83.9 vs. 84.2%; $P = 0.958$) and glucose (78.0 vs. 68.4%; $P = 0.173$) criteria between these subgroups.

Incidence of vascular events

During a mean (±SD) follow-up time of 3.9 ± 0.8 years, we recorded 160 vascular end points, encompassing 42 coronary deaths, 12 fatal ischemic strokes, 13 nonfatal myocardial infarctions, 14 nonfatal ischemic strokes, 23 coronary artery bypass graftings, 33 percutaneous coronary interventions, and 23 revascularizations at the carotid ($n = 6$) or peripheral ($n = 17$) arteries. Thus, the overall incidence rate was 21.3%.

Table 1—*Baseline characteristics in patients with and in patients without the metabolic syndrome*

	ATPIII definition			IDF definition		
	Metabolic syndrome	No metabolic syndrome	*P* value	Metabolic syndrome	No metabolic syndrome	*P* value
n	280	470		341	409	
Age (years)	61.6 ± 10.5	63.3 ± 10.6	0.002	62.6 ± 10.3	62.7 ± 10.5	0.878
Male sex (%)	70.0	66.6	0.334	66.3	69.2	0.394
Type 2 diabetes (%)	40.0	11.1	<0.001	32.8	12.7	<0.001
Smoking (%)	67.5	52.6	<0.001	62.8	54.3	0.019
BMI (kg/m²)	29.1 ± 4.2	25.9 ± 3.7	<0.001	29.1 ± 3.8	25.4 ± 3.8	<0.001
Waist circumference (cm)	102 ± 11	90 ± 10	<0.001	101 ± 10	88 ± 10	<0.001
HbA_{1c} (%)	6.6 ± 1.4	5.9 ± 0.8	<0.001	6.4 ± 1.2	5.9 ± 1.1	<0.001
Fasting plasma glucose (mg/dl)	134 ± 45	105 ± 28	<0.001	125 ± 39	108 ± 35	<0.001
Homeostasis model assessment of insulin resistance	4.94 ± 4.04	2.30 ± 2.09	<0.001	4.16 ± 3.3	2.55 ± 2.95	<0.001
Triglycerides (mg/dl)	225 ± 126	127 ± 70	<0.001	197 ± 120	138 ± 84	<0.001
Total cholesterol (mg/dl)	216 ± 47	220 ± 41	0.085	215 ± 45	221 ± 42	0.037
LDL cholesterol (mg/dl)	125 ± 37	135 ± 35	0.001	127 ± 36	134 ± 35	0.015
HDL cholesterol (mg/dl)	41 ± 11	54 ± 14	<0.001	44 ± 12	52 ± 15	<0.001
Apolipoprotein A1 (mg/dl)	136 ± 26	153 ± 28	<0.001	141 ± 27	152 ± 28	<0.002
Apolipoprotein B (mg/dl)	117 ± 26	112 ± 24	0.006	114 ± 26	114 ± 25	0.658
LDL peak particle diameter (Å)	256 ± 6	261 ± 5	<0.001	257 ± 6	260 ± 5	<0.001
Systolic blood pressure (mmHg)	143 ± 20	133 ± 21	<0.001	141 ± 21	133 ± 21	<0.001
Diastolic blood pressure (mmHg)	82 ± 12	77 ± 11	<0.001	82 ± 12	77 ± 11	<0.001
Any coronary lumen narrowing (%)	85.4	80.0	0.065	84.5	80.0	0.110
Significant coronary stenoses (%)	65.0	58.3	0.069	63.3	58.7	0.193
Waist criterion (%)	59.3	11.7	<0.001	100.0	23.9	<0.001
Blood pressure criterion (%)	85.4	52.8	<0.001	89.4	60.1	<0.001
HDL cholesterol criterion (%)	68.9	14.5	<0.001	52.2	20.3	<0.001
Triglyceride criterion (%)	75.0	20.2	<0.001	59.2	28.1	<0.001
Glucose criterion (%)	70.4	19.4	<0.001	83.9	45.2	<0.001

Data are means ± SD, unless otherwise indicated. To convert values for fasting plasma glucose to mmol/l multiply by 0.0555, to convert values for triglycerides to mmol/l multiply by 0.0113, and to convert values for total cholesterol, LDL cholesterol, or HDL cholesterol to mmol/l multiply by 0.0259.

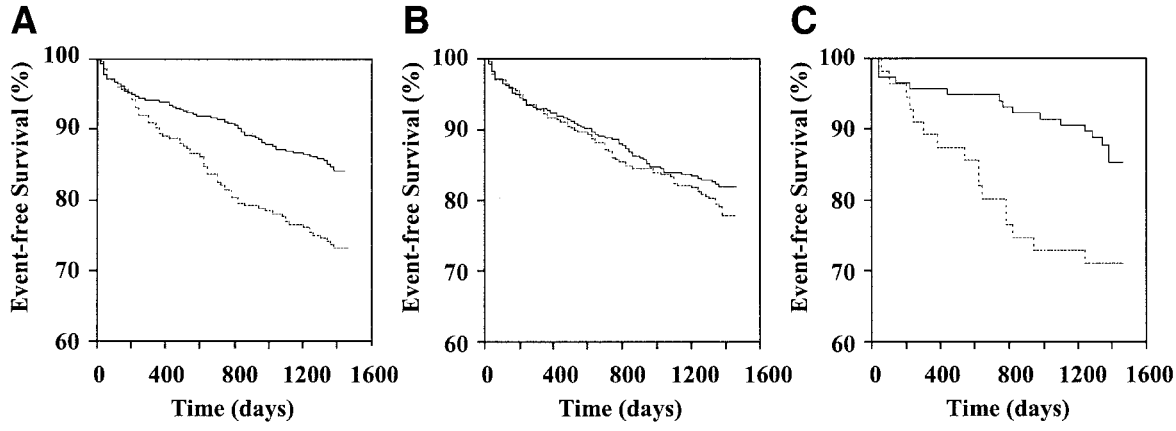

Figure 1—A: *Event-free survival with respect to the presence of the metabolic syndrome according to the National Cholesterol Education Program's ATPIII definition* (P < *0.001). Solid line denotes no metabolic syndrome according to the ATPIII definition. Broken line denotes metabolic syndrome according to the ATPIII definition.* B. *Event-free survival with respect to the presence of the metabolic syndrome according to the IDF's definition* (P = *0.283). Solid line denotes no metabolic syndrome according to the IDF definition. Broken line denotes metabolic syndrome according to the IDF definition. C: Event-free survival in patients who meet the National Cholesterol Education Program's ATPIII criteria but not the IDF's criteria for the diagnosis of the metabolic syndrome and in patients who conversely meet the IDF's criteria but not the ATPIII criteria for the diagnosis of the metabolic syndrome* (P = *0.012). Solid line denotes ATPIII−/IDF+. Broken line denotes ATPIII+/IDF−.*

Table 2—*Cardiovascular risks related to the dichotomous diagnosis of the metabolic syndrome and to its single components*

	ATPIII category	IDF category	Continuous variable
Diagnosis of the metabolic syndrome			
Model 1	1.745 (1.255–2.427); $P = 0.001$	1.189 (0.859–1.646); $P = 0.297$	
Model 2	1.578 (1.114–2.234); $P = 0.010$	1.102 (0.791–1.534); $P = 0.566$	
Model 3	1.576 (1.099–2.258); $P = 0.013$	1.064 (0.755–1.500); $P = 0.723$	
Waist circumference			
Model 1	0.981 (0.679–1.417); $P = 0.917$	0.889 (0.640–1.234); $P = 0.482$	1.107 (0.904–1.355); $P = 0.327$
Model 2	0.925 (0.639–1.341); $P = 0.682$	0.853 (0.613–1.186); $P = 0.344$	1.060 (0.864–1.299); $P = 0.578$
Model 3	0.961 (0.658–1.404); $P = 0.838$	0.831 (0.593–1.165); $P = 0.283$	1.109 (0.894–1.376); $P = 0.345$
Blood pressure*			
Model 1	1.389 (0.967–1.995); $P = 0.075$	1.389 (0.920–2.097); $P = 0.118$	1.181 (0.992–1.406); $P = 0.062$
Model 2	1.336 (0.929–1.922); $P = 0.118$	1.317 (0.870–1.993); $P = 0.193$	1.171 (0.983–1.396); $P = 0.078$
Model 3	1.345 (0.927–1.950); $P = 0.119$	1.302 (0.841–2.016); $P = 0.236$	1.174 (0.983–1.401); $P = 0.076$
Triglycerides			
Model 1	1.767 (1.266–2.467); $P = 0.001$	1.699 (1.217–2.372); $P = 0.002$	1.227 (1.090–1.382); $P = 0.001$
Model 2	1.689 (1.208–2.636); $P = 0.002$	1.630 (1.166–2.280); $P = 0.004$	1.188 (1.051–1.343); $P = 0.006$
Model 3	1.639 (1.163–2.309); $P = 0.005$	1.617 (1.144–2.288); $P = 0.007$	1.174 (1.033.10.334); $P = 0.014$
HDL cholesterol			
Model 1	1.963 (1.398–2.756); $P < 0.001$	1.963 (1.398–2.756); $P < 0.001$	0.722 (0.579–0.900); $P = 0.004$
Model 2	1.852 (1.314–2.611); $P < 0.001$	1.852 (1.314–2.611); $P < 0.001$	0.755 (0.605–0.942); $P = 0.013$
Model 3	1.838 (1.293–2.612); $P = 0.001$	1.838 (1.293–2.612); $P = 0.001$	0.765 (0.610–0.960); $P = 0.021$
Glucose			
Model 1	1.524 (1.102–2.109); $P = 0.011$	1.547 (1.074–2.229); $P = 0.019$	1.176 (1.027–1.348); $P = 0.019$
Model 2	1.304 (0.898–1.893); $P = 0.163$	1.336 (0.896–1.992); $P = 0.155$	1.055 (0.879–1.266); $P = 0.565$
Model 3	1.279 (0.874–1.871); $P = 0.205$	1.296 (0.866–1.938); $P = 0.207$	1.041 (0.858–1.262); $P = 0.648$

Data are adjusted HR (95% CI). Model 1 adjusts for age, sex, smoking, LDL cholesterol, and CAD at baseline. Model 2 adjusts for the covariates included in model 1 and additionally for type 2 diabetes. Model 3 adjusts for the covariates included in model 2 and additionally for treatment with medications (statins, fibrates, ACE inhibitors, angiotensin II inhibitors, aspirin, β-blockers, diuretics, and calcium antagonists). *Standardized adjusted HRs for the continuous variable are given for systolic blood pressure; for diastolic blood pressure, the respective standardized adjusted HRs were 1.068 (0.897–1.272), $P = 0.462$, in model 1; 1.070 (0.901–1.270), $P = 0.443$, in model 2; and 1.075 (0.906–1.276), $P = 0.409$, in model 3.

Impact of new and old criteria of the metabolic syndrome on the incidence of vascular events

Event-free survival was significantly lower ($P < 0.001$) in patients with the metabolic syndrome according to the ATPIII definition than in patients who did not meet the ATPIII criteria for the diagnosis of the metabolic syndrome (Fig. 1*A*). In Cox regression analyses adjusting for age, sex, smoking, LDL cholesterol, and baseline CAD, the ATPIII metabolic syndrome proved strongly and independently predictive of vascular events, with an adjusted HR of 1.745 (95% CI 1.255–2.427; $P = 0.001$). After additional adjustment for type 2 diabetes, this HR decreased, but the metabolic syndrome (ATPIII definition) remained predictive of vascular events (1.578 [1.114–2.234]; $P = 0.010$). Further adjustment for treatment with medications did not substantially change the power of the metabolic syndrome (ATPIII definition) as a predictor of vascular events (Table 2).

When patients receiving treatment for individual metabolic syndrome traits were considered to meet the respective criteria for these traits, the thus-modified ATPIII definition of the metabolic syndrome significantly predicted vascular events after adjustment for age, sex, smoking, LDL cholesterol, and baseline CAD (adjusted HR 1.810 [95% CI 1.299–2.520]; $P < 0.001$). Also, a modified ATPIII definition that was recently proposed by the American Heart Association and the National Heart, Lung, and Blood Institute (7), which considers treatment and uses a fasting glucose of 100 mg/dl as a cutoff for the high-glucose criterion, significantly predicted vascular events in our patient cohort (1.634 [1.173–2.276]; $P = 0.004$). Further, the metabolic syndrome as defined by World Health Organization criteria (3) proved significantly predictive of vascular events (1.405 [1.011–1.953]; $P = 0.043$).

In patients with the metabolic syndrome according to the IDF definition, event-free survival was not significantly different ($P = 0.283$) from patients who did not fulfil the IDF criteria for the diagnosis of the metabolic syndrome (Fig. 1*B*). Also, in Cox regression analysis adjusting for age, sex, smoking, LDL cholesterol, and baseline CAD, the IDF metabolic syndrome was not significantly associated with vascular events, with an adjusted HR of 1.189 (95% CI 0.859–1.646; $P = 0.297$).

The incidence of vascular events was significantly lower ($P = 0.012$) among ATPIII−/IDF+ patients than among ATPIII+/IDF− patients (Fig. 1*C*). Cox regression analysis adjusting for age, sex, smoking, LDL cholesterol, diabetes status, and baseline CAD confirmed that ATPIII+/IDF− patients had a significantly worse prognosis than ATPIII−/IDF+ patients, with an adjusted HR of 2.073 (95% CI 1.012–4.246; $P = 0.046$).

The metabolic syndrome, its individual components, and vascular risk

Table 2 summarizes the cardiovascular risks related to the dichotomous diagnosis of the metabolic syndrome and to its single components. In Cox regression analyses adjusting for age, sex, smoking,

LDL cholesterol, diabetes, baseline CAD, and for the presence of individual metabolic syndrome component features, the metabolic syndrome as defined by ATPIII criteria remained significantly predictive of vascular events after adjustment for the ATPIII metabolic syndrome traits high fasting glucose (HR 1.530 [95% CI 1.045–2.239]; $P = 0.029$), high blood pressure (1.500 [1.041–2.163]; $P = 0.030$), and high waist circumference (1.865 [1.265–2.747]; $P = 0.002$). However, after adjustment for the metabolic syndrome traits high triglycerides or low HDL cholesterol, the ATPIII metabolic syndrome no longer was predictive of vascular events (1.251 [0.825–1.899]; $P = 0.292$ and 1.205 [0.806–1.801], respectively; $P = 0.363$). In contrast, the individual metabolic syndrome traits high triglycerides and low HDL cholesterol significantly predicted vascular events even after adjustment for the overall diagnosis of the ATPIII metabolic syndrome, with adjusted HRs of 1.502 (1.006–2.244); $P = 0.047$ and 1.686 (1.130–2.514); $P = 0.011$, respectively. In a multivariate analysis including both the clinical category of the metabolic syndrome (ATPIII definition) and at the same time all component features from the ATPIII definition, no significant association remained between the metabolic syndrome and vascular events (adjusted HR 1.167 [95% CI 0.626–2.178]; $P = 0.627$). From the individual metabolic syndrome criteria, only the low HDL feature independently predicted vascular events in this model (1.755 [1.156–2.664]; $P = 0.008$).

Specific study end points

In analyses focusing on specific secondary study end points, the ATPIII metabolic syndrome after adjustment for age, sex, smoking, LDL cholesterol, and baseline CAD proved significantly predictive of end points related to CAD ($n = 111$), with an adjusted HR of 1.708 (1.158–2.519; $P = 0.007$). The IDF metabolic syndrome in contrast was not associated with CAD-related end points (0.945 [0.642–1.389]; $P = 0.772$). We did not observe significant associations between either metabolic syndrome category and the smaller number ($n = 32$) of end points related to cerebrovascular disease (1.333 [0.553–3.213]; $P = 0.521$ and 0.758 [0.311–1.848]; $P = 0.542$ for the ATP and IDF definitions, respectively).

Subgroup analyses

Among the 509 men included in our analyses, 196 (38.5%) fulfilled the ATPIII criteria for the definition of the metabolic syndrome and 226 (44.4%) fulfilled the IDF criteria. Among women ($n = 241$), 84 (34.9%) and 115 (47.7%) met the ATPIII and IDF metabolic syndrome definitions, respectively. The metabolic syndrome as defined by ATPIII criteria after adjustment for age, smoking, LDL cholesterol, and baseline CAD proved significantly predictive of vascular events among both men (adjusted HR 1.625 [95% CI 1.111–2.377]; $P = 0.012$) and women (2.321 [1.179–4.567]; $P = 0.015$). In contrast, the metabolic syndrome as defined by the IDF criteria predicted vascular events neither in men nor in women (1.204 [0.829–1.748], $P = 0.330$, and 1.276 [0.648–2.513], $P = 0.481$, respectively). There was no significant difference in the impact of the metabolic syndrome on vascular events between men and women, irrespective of whether the ATPIII criteria or the IDF criteria were applied ($P_{interaction} = 0.313$ and 0.903, respectively).

When patients with diabetes ($n = 164$) were excluded from the analyses, of the remaining 586 nondiabetic patients, 168 (28.7%) had the metabolic syndrome according to ATPIII criteria and 229 (39.1%) met the IDF criteria for the diagnosis of the metabolic syndrome. Consistent with the total study cohort, the metabolic syndrome as defined by ATPIII criteria significantly predicted vascular events in nondiabetic patients (HR 1.531 [95% CI 1.007–2.328]; $P = 0.046$), whereas the metabolic syndrome as defined by IDF criteria did not significantly predict vascular events in these patients (1.139 [0.765–1.695]; $P = 0.522$).

CONCLUSIONS — From our results, we conclude that among angiographied coronary patients the ATPIII definition and the IDF definition of the metabolic syndrome do not identify the same patients. The metabolic syndrome as defined by ATPIII criteria confers a higher risk of vascular events than the metabolic syndrome as defined by IDF criteria.

The prevalence of the metabolic syndrome defined according to the IDF definition in our investigation was higher than the metabolic syndrome defined according to the ATPIII definition. Concordantly, Athyros et al. (24) have found a higher prevalence of the metabolic syndrome diagnosed according to IDF criteria in a Greek population–based study, and Ford (25) described a higher prevalence of the IDF metabolic syndrome among adults in the U.S. A recent investigation from northern Mexico reported a high concordance between the ATPIII and IDF definitions of the metabolic syndrome (26). However, in 23.3% of our Caucasian patients the two metabolic syndrome definitions led to discordant diagnoses; thus, concordance was moderate.

The IDF wanted its new definition to encourage the identification of patients at increased risk of cardiovascular events (10). However, in our study population, we did not find a significant association between vascular events and the IDF metabolic syndrome, whereas the metabolic syndrome as defined according to ATPIII criteria was strongly predictive of future vascular events. The incidence of vascular events was significantly higher in patients who met the ATPIII criteria but not the IDF criteria for the diagnosis of the metabolic syndrome than in patients who met the IDF criteria but not the ATPIII criteria.

There are important differences between the ATPIII and IDF definitions of the metabolic syndrome that may explain the weaker association of the IDF metabolic syndrome with vascular events. First, the lowering of the cutoff value for waist circumference leads to the inclusion of patients with a relatively lower level of this risk factor in the IDF category of the metabolic syndrome. Second, the mandatory status of the waist criterion in the new definition results in a relatively lower prevalence of other (potentially stronger) metabolic syndrome risk factors in patients with the metabolic syndrome. In particular, the high triglycerides and low HDL cholesterol metabolic syndrome components are relatively underrepresented in patients with the IDF metabolic syndrome. However, the greatest vascular risk in our investigation was conferred by these lipid traits. Concordant with this finding, high triglycerides and low HDL cholesterol were the only metabolic syndrome components that were independently associated with myocardial infarction and stroke in an evaluation of data from the third National Health and Nutrition Examination Survey (27). Consistent with their less pronounced dyslipidemia, patients with the metabolic syndrome according to the IDF definition had a lower degree of homeostasis model assessment of insulin resistance (Table 1), which is a strong cardiovascular risk factor among coronary patients (19). Third,

in the IDF definition, patients receiving treatment for metabolic syndrome components are considered to meet the respective criteria, whereas therapy was not explicitly considered in the ATPIII definition. Treatment of risk factors possibly could dilute their effects on prognosis and thus weaken their prognostic power. However, in our investigation, a modification of the ATPIII category in which treatment was considered still proved strongly predictive for vascular events. Thus, the consideration of treatment in the IDF definition of the metabolic syndrome does not appear to account for its weak association with vascular events.

A recent report from a population with a high proportion of Mexican Americans suggested that the increased vascular risk of patients with the metabolic syndrome is entirely due to the high prevalence of patients with diabetes among subjects with the metabolic syndrome (28). However, in our population of Caucasian coronary patients, the metabolic syndrome defined according to ATPIII criteria conferred an increased vascular risk independent from the diabetic state.

Importantly, the cardiovascular risk associated with the ATPIII metabolic syndrome in our patients resided basically in its lipid components. Moreover, our data suggest that these lipid traits are better predictors of vascular events than the clinical category of the metabolic syndrome itself and thus lend support to recent criticism of the use of the metabolic syndrome as a clinical category in cardiovascular risk stratification (8,9). Of note, the decisive role of the dyslipidemic metabolic syndrome features in cardiovascular risk prediction is well in line with our recent report on the paramount impact of the low HDL/high triglyceride pattern on the short-term incidence of vascular events in patients with type 2 diabetes (20).

In conclusion, patients with the metabolic syndrome according to the ATPIII definition are at a significantly higher risk of vascular events than patients with the metabolic syndrome diagnosed according to IDF criteria. However, as even the ATPIII definition of the metabolic syndrome did not provide prognostic information beyond its dyslipidemic features, physicians in the care of coronary patients should pay more attention to the high triglyceride/low HDL pattern of dyslipidemia. Evaluations of new and old criteria for the metabolic syndrome in other populations as well as interventional data on the potential of cardiovascular risk reduction residing in an improvement of the high triglycerides and low HDL traits in patients with the metabolic syndrome are urgently needed.

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References

1. Hanley AJ, Karter AJ, Festa A, D'Agostino R Jr, Wagenknecht LE, Savage P, Tracy RP, Saad MF, Haffner S: Factor analysis of metabolic syndrome using directly measured insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *Diabetes* 51:2642–2647, 2002
2. Eckel RH, Grundy SM, Zimmet PZ: The metabolic syndrome. *Lancet* 365:1415–1428, 2005
3. World Health Organization: *Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus: Report of a WHO consultation*. Alwan A, King H, Eds. Geneva, World Health Org., Department of Noncommunicable Disease Surveillance, 1999, p. 1–59
4. Executive summary of 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). *JAMA* 285:2486–2497, 2001
5. Balkau B, Charles MA, Drivsholm T, Borch-Johnsen K, Wareham N, Yudkin JS, Morris R, Zavaroni I, van Dam R, Feskins E, Gabriel R, Diet M, Nilsson P, Hedblad B: Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. *Diabetes Metab* 28: 364–376, 2002
6. Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW, Seibel JA, Smith DA, Wilson PW: American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract* 9:237–252, 2003
7. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 112:2735–2752, 2005
8. Reaven GM: The metabolic syndrome: requiescat in pace. *Clin Chem* 51:931–938, 2005
9. Kahn R, Buse J, Ferrannini E, Stern M: The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 28:2289–2304, 2005
10. International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome [article online], 2005. Available from http://www.idf.org/webdata/docs/metac_syndrome_def.pdf. Accessed on 19 October 2005
11. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome: a new worldwide definition. *Lancet* 366:1059–1062, 2005
12. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26:3160–3167, 2003
13. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288: 2709–2716, 2002
14. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Bonadonna RC, Muggeo M: Carotid atherosclerosis and coronary heart disease in the metabolic syndrome: prospective data from the Bruneck Study. *Diabetes Care* 26:1251–1257, 2003
15. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 108:414–419, 2003
16. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 107:391–397, 2003
17. Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN: Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. *Diabetes Care* 28:391–397, 2005
18. Marroquin OC, Kip KE, Kelley DE, Johnson BD, Shaw LJ, Bairey Merz CN, Sharaf BL, Pepine CJ, Sopko G, Reis SE: Metabolic syndrome modifies the cardiovascular risk associated with angiographic

coronary artery disease in women: a report from the Women's Ischemia Syndrome Evaluation. *Circulation* 109:714–721, 2004
19. Saely CH, Aczel S, Marte T, Langer P, Hoefle G, Drexel H: The metabolic syndrome, insulin resistance, and cardiovascular risk in diabetic and nondiabetic patients. *J Clin Endocrinol Metab* 90:5698–5703, 2005
20. Drexel H, Aczel S, Marte T, Benzer W, Langer P, Moll W, Saely CH: Is atherosclerosis in diabetes and impaired fasting glucose driven by elevated LDL cholesterol or by decreased HDL cholesterol? *Diabetes Care* 28:101–107, 2005
21. Drexel H, Amann FW, Rentsch K, Neuenschwander C, Luethy A, Khan SI, Follath F: Relation of the level of high-density lipoprotein subfractions to the presence and extent of coronary artery disease. *Am J Cardiol* 70:436–440, 1992
22. Drexel H, Amann FW, Beran J, Rentsch K, Candinas R, Muntwyler J, Luethy A, Gasser T, Follath F: Plasma triglycerides and three lipoprotein cholesterol fractions are independent predictors of the extent of coronary atherosclerosis. *Circulation* 90: 2230–2235, 1994
23. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
24. Athyros VG, Ganotakis ES, Elisaf M, Mikhailidis DP: The prevalence of the metabolic syndrome using the National Cholesterol Educational Program and International Diabetes Federation definitions. *Curr Med Res Opin* 21:1157–1159, 2005
25. Ford ES: Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 28:2745–2749, 2005
26. Guerrero-Romero F, Rodriguez-Moran M: Concordance between the 2005 International Diabetes Federation definition for diagnosing metabolic syndrome with the National Cholesterol Education Program Adult Treatment Panel III and the World Health Organization definitions (Letter). *Diabetes Care* 28:2588–2589, 2005
27. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS: Association of the metabolic syndrome with history of myocardial infarction and stroke in the third National Health and Nutrition Examination Survey. *Circulation* 109:42–46, 2004
28. Stern MP, Williams K, Hunt KJ: Impact of diabetes/metabolic syndrome in patients with established cardiovascular disease. *Atheroscler Suppl* 6:3–6, 2005