Metabolic Syndrome and Risk of Restenosis in Patients Undergoing Percutaneous Coronary Intervention

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OBJECTIVE — Patients with metabolic syndrome have increased risk of cardiovascular events. The number of patients with metabolic syndrome is rapidly increasing, and these patients often need revascularization. However, only limited data are available on the effect of metabolic syndrome on restenosis in patients undergoing percutaneous coronary intervention (PCI).

RESEARCH DESIGN AND METHODS — To assess the role of metabolic syndrome in the development of restenosis, we performed an analysis in a population of patients from the GENetic DEterminants of Restenosis (GENDER) study. The GENDER project, a multicenter prospective study, included consecutive patients after successful PCI and was designed to study the predictive value of various genetic and other risk factors for subsequent clinical restenosis, defined as target vessel revascularization (TVR) or combined end point of death, myocardial infarction, and TVR. This subpopulation of GENDER consisted of 901 patients, 448 of whom (49.7%) had metabolic syndrome.

RESULTS — On multivariable Cox regression analysis, controlling for age, sex, previous myocardial infarction, stent length, current smoking, and statin therapy, there was no association between increased risk of TVR (hazard ratio 1.03 [95% CI 0.68–1.57]) or the combined end point (1.05 [0.71–1.55]) and the presence of metabolic syndrome.

CONCLUSIONS — This study demonstrates that metabolic syndrome is not associated with TVR or the combined end point after PCI. Furthermore, accumulating characteristics of metabolic syndrome were neither associated with increased risk of TVR nor with the combined end point. Therefore, PCI has equal beneficial results in patients with or without metabolic syndrome. This is important information in light of the pandemic proportion of metabolic syndrome that the medical community will face.

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Abbreviations: CAD, coronary artery disease; GENDER, GENetic DEterminants of Restenosis; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

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

The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) has stressed the importance of targeting prevention strategies for individuals with metabolic syndrome (1,2). Moreover, metabolic syndrome was recently found to be a predictor of 4-year cardiovascular risk only when it was associated with significant angiographic coronary artery disease (CAD) (3). However, the consequences of metabolic syndrome on clinical restenosis in patients who undergo percutaneous coronary intervention (PCI) and coronary stent placement remain unknown.

Clinical restenosis remains a problem after PCI. Diabetes and insulin resistance have already been shown to be independent predictors of early restenosis after coronary stenting (4–6). However, only limited information is available on metabolic syndrome, as a whole and its components, with regard to clinical restenosis. The aim of our study was to examine whether the presence of metabolic syndrome constitutes a risk factor for clinical restenosis.

RESEARCH DESIGN AND METHODS

— The GENetic DEterminants of Restenosis (GENDER) study was designed as a prospective multicenter follow-up study to evaluate various genetic risk factors in association with clinical restenosis. The study design has been reported previously (7). In brief, patients were eligible for inclusion if they were successfully treated for stable angina, non–ST-elevation acute coronary syndromes, or silent ischemia with PCI. Patients treated for acute ST-elevation myocardial infarction were excluded. The overall inclusion period lasted from March 1999 until June 2001. To study the effect of metabolic syndrome as a risk factor for restenosis, we determined the lipid profile (serum triglyceride, serum total cholesterol, and serum HDL cholesterol levels) and fasting serum glucose level in a

Table 1—*Prevalence of metabolic syndrome characteristics*

	Metabolic syndrome absent	Metabolic syndrome present
n	453 (50.3)	448 (49.7)
BMI >28.8 kg/m^2	37 (8.2)	207 (46.2)
Triglyceride level ≥1.7 mmol/l	128 (28.3)	370 (82.6)
HDL cholesterol level <1.04 mmol/l in men and <1.3 mmol/l in women	128 (28.3)	324 (72.3)
Systolic blood pressure ≥130 and diastolic blood pressure ≥85 mmHg	273 (60.3)	383 (85.5)
Fasting glucose level ≥5.55 mmol/l	115 (25.4)	329 (73.4)

Data are *n* (%).

subpopulation of patients for whom plasma was collected. The study protocol conforms to the Declaration of Helsinki and was approved by the ethics committees of the participating institutions. Written informed consent was obtained from each participant before the PCI procedure.

Angioplasty and stenting procedure

Balloon angioplasty and intracoronary stenting were performed with standard techniques using the radial or femoral approach. The use of intracoronary stents and additional medication, such as glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. If a stent was implanted, patients received either ticlopidine or clopidogrel for at least 1 month after the procedure, depending on local practice. Intracoronary brachytherapy or drug-eluting stents were not used in this study. The total length of the stented segment and the minimal diameter of the stents were calculated per patient.

Data collection

At inclusion, medical history, symptoms of cardiovascular disease and risk factors, current and former smoking habits, the presence of vascular diseases in first-degree relatives, and information about the use of current medical treatment of the patients were collected. Furthermore, patients underwent a physical examination that included measurements of body weight, height, and blood pressure. Laboratory tests were performed to determine the lipid profile (serum triglyceride, serum total cholesterol, and serum HDL cholesterol levels) and fasting serum glucose level. Blood was drawn before the PCI procedure. Serum cholesterol, glucose, and triglyceride levels were measured with a fully automated Hitachi 747 (Hitachi, Tokyo, Japan). HDL cholesterol was determined with a turbidimetric assay on a Hitachi 911, and insulin was measured with an immunoradiometric assay (Biosource, Nivelles, Belgium). BMI was calculated as weight in kilograms divided by the square of height in meters.

Follow-up and study end points

Patients were followed for at least 9 months. The primary end point was the incidence of target vessel revascularization (TVR) either by repeat PCI or coronary artery bypass grafting, which was considered clinical restenosis. The secondary combined end point was defined as death presumably from cardiac causes, myocardial infarction not attributable to a coronary artery other than the target vessel, and TVR. An independent clinical events committee of experienced cardiologists adjudicated the clinical events. The committee members did not review patients treated in their own center. Events occurring within 1 month were classified and analyzed separately, because these events are more likely attributable to subacute stent thrombosis or occluding dissections and not to restenosis (7).

Definitions

Patients were defined as having metabolic syndrome by presence of three or more of the following criteria: *1*) triglyceride level ≥1.7 mmol/l (150 mg/dl); *2*) HDL cholesterol level <1.04 mmol/l (40 mg/dl) in men and <1.3 mmol/l (50 mg/dl) in women; *3*) systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg; *4*) obesity, defined as BMI >28.8 kg/m^2, which was equivalent to a waist circumference of 102 cm in a cross-sectional study and similar to the BMI value (28.2 kg/m^2) calculated in a regression of BMI on waist circumference in a large population of Scottish men (8,9); and *5*) fasting glucose level ≥5.55 mmol/l (100 mg/dl), above which patients have either pre-diabetes (impaired fasting glucose) or diabetes. This level was recently established by the American Diabetes Association and suggested as the new cut point for identifying the lower boundary to define an elevated glucose level as one criterion for the metabolic syndrome (1,2,10).

Statistical methods

All data are presented as means ± SD, unless stated otherwise. Time to the first clinical event was compared between (sub)groups of patients with the log-rank test. The prognostic value of clinical and procedural variables was assessed with the Cox proportional hazards model. All event rates were calculated from Kaplan-Meier survival analysis. We used multivariable Cox regression models to examine the association of metabolic syndrome with the risk of TVR and the combined end point after adjustment for potentially confounding factors. The covariates included in the baseline multivariable model were age, sex, previous myocardial infarction, stent length, current smoking, and statin therapy. Subgroup analysis was performed in subgroups of patients with or without diabetes and for men and women. A two-sided value of $P < 0.05$ was considered statistically significant. Analyses were performed with SPSS for Windows version 11.5 (SPSS, Chicago, IL).

RESULTS — The GENDER study included 3,146 unselected consecutive patients treated with successful PCI. Two of the four participating centers (Leiden University Medical Center and Academic Hospital Maastricht) systemically collected extra blood samples to perform additional laboratory measurements to examine other predictors of restenosis. In 901 patients, data were sufficient to establish absence or presence of metabolic syndrome. Patients were followed for at least 9 months, except when a coronary event occurred. The overall follow-up of the patients had a median duration of 9.6 months (interquartile range 3.9). Of these patients, 448 (49.7%) had metabolic syndrome (three or more of the five characteristics). Of the five characteristics used to define metabolic syndrome, the prevalence of increased blood pressure was

Table 2—*Baseline characteristics by metabolic syndrome status* (n = *901*)

	Metabolic syndrome		
	Absent	Present	*P* value*
n	453	448	
Baseline characteristics			
Age (years)	63 ± 10	61 ± 11	0.003
BMI (kg/m^2)	25.4 ± 3.0	28.7 ± 4.1	<0.001
Women	127 (28)	131 (29)	0.69
Diabetes	32 (7)	108 (24)	<0.001
Current smoking	80 (18)	94 (21)	0.21
Family history of myocardial infarction	150 (33)	159 (36)	0.45
Previous myocardial infarction	174 (38)	183 (41)	0.45
Previous percutaneous transluminal coronary angioplasty	77 (17)	86 (19)	0.39
Previous coronary artery bypass grafting	59 (13)	63 (14)	0.64
Baseline medication			
β-Blocker	345 (76)	363 (81)	0.08
Calcium antagonist	199 (43)	221 (49)	0.10
Aspirin/ASA	369 (82)	370 (83)	0.66
ACE inhibitors	112 (25)	107 (24)	0.77
Insulin therapy	13 (3)	32 (7)	0.003
Statins	231 (51)	265 (59)	0.014
Angiographic data			
Stent placement	376 (80)	373 (83)	0.92
Total stent length (mm)	23.4 ± 18.5	23.0 ± 19.0	0.53
Biochemical data			
Erythrocyte sedimentation rate (mm/h)	10.0 (15)	12.0 (20)	0.006
Total cholesterol (mmol/l)	4.91 ± 1.05	5.01 ± 1.12	0.32
Fibrinogen (g/l)	3.73 ± 1.62	3.82 ± 1.19	0.22
Insulin (mU/l)	12 (9)	20 (20)	<0.001

Data are means ± SD or *n* (%). Erythrocyte sedimentation rate and insulin are presented as median (interquartile range). *P value from the nonparametric Mann-Whitney *U* test or χ^2 test.

highest (85.5%), whereas increased BMI was the least prevalent characteristic (46.2%) (Table 1). The most common combination of metabolic abnormalities in the 448 patients with metabolic syndrome (309 patients [69%]) was high triglyceride levels and high blood pressure. The presence of one or more components of the metabolic syndrome was common in both sexes: 16.3% had one component, 29.6% had two components, 26.9% had three components, 15.9% had four components, and 7.0% had all five components (see Table 4). Among the patients with diabetes in our cohort ($n = 140$), 5% had one component, 17.9% had two components, 32.9% had three components, 26.4% had four components, and 17.9% had all five components.

As expected, patients in whom metabolic syndrome was present were more likely to be younger, to have diabetes, and to have increased BMI (Table 2). There was no significant difference in the number of coronary stents placed between patients with metabolic syndrome (83%) compared with those without metabolic syndrome (80%). Patients with metabolic syndrome received more statin therapy ($P = 0.014$) and were more likely to be insulin dependent ($P = 0.003$). Regarding biochemical data, patients with metabolic syndrome had significantly higher erythrocyte sedimentation rates and insulin levels at baseline.

On multivariable Cox regression analysis, there was an expected trend toward increased risk of death and myocardial infarction in patients with metabolic syndrome compared with those without; however, the results were not statistically significant (Table 3). Interestingly, there was no association whatsoever between increased risk of TVR (hazard ratio [HR] 1.03 [95% CI 0.68–1.57]) or the combined end point (1.05 [0.71–1.55]) and the presence of metabolic syndrome. The Kaplan-Meier curves are presented in Fig. 1.

In the subgroup of patients with 0, 1, 2, 3, 4, or 5 metabolic syndrome–defining characteristics, the incidence of TVR was 5, 13, 27, 27, 13, and 7, respectively ($P = 0.77$) (Table 4). On multivariable Cox regression analysis, there was no significant increase in risk of TVR in patients with metabolic syndrome or any number of its components compared with patients without metabolic syndrome or with no characteristics of metabolic syndrome.

We performed subgroup analysis to evaluate risk analysis of metabolic syndrome in subgroups of patients with or without diabetes. The adjusted HR for TVR was 2.83 (95% CI 0.62–12.69, $P = 0.17$) in the subgroup of patients with diabetes, whereas the HR was 0.84 (0.52–1.35, $P = 0.47$) in the group of patients without diabetes. This difference in HR was, however, not significant ($P = 0.15$). The same result was obtained for the combined end point (overall $P = 0.12$).

When we analyzed the difference in

Table 3—*HRs of cardiovascular events according to presence of metabolic syndrome* (n = *901*)

	Metabolic syndrome absent	Metabolic syndrome present	HR (95% CI)*
Death of cardiac origin	4 (0.9)	8 (1.8)	2.52 (0.75–8.48)
Death from other causes	3 (0.7)	3 (0.7)	1.12 (0.22–5.72)
Death all causes	7 (2)	11 (3)	1.97 (0.76–5.10)
Myocardial infarction	2 (0.4)	6 (1.3)	2.72 (0.54–13.63)
TVR	45 (9.9)	47 (10.5)	1.03 (0.68–1.57)
Combined end point†	51 (11.3)	54 (12.1)	1.05 (0.71–1.55)

Data are *n* (%) unless otherwise indicated. *Adjusted for age, sex, previous myocardial infarction, stent length, current smoking, and statin therapy; †combined end point was defined as death presumably from cardiac causes, myocardial infarction not attributable to a coronary artery other than the target vessel, and TVR either by repeat PCI or coronary artery bypass grafting.

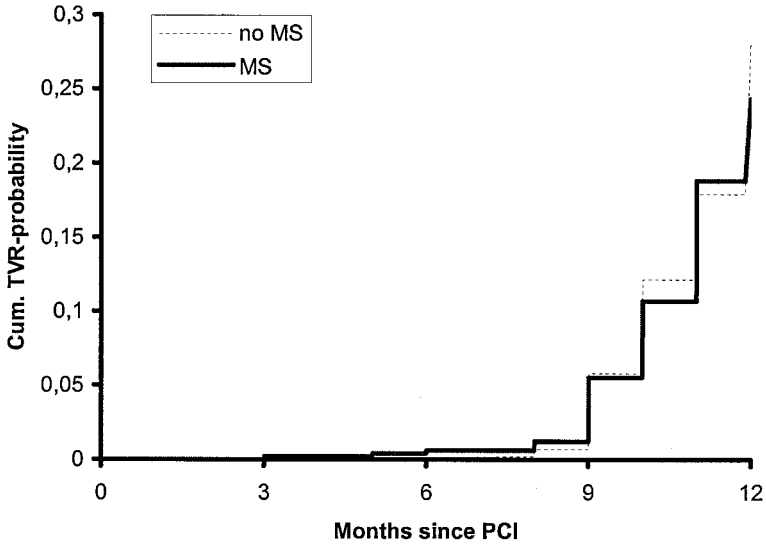

Figure 1—*Kaplan-Meier curve of the cumulative probability of TVR. ——, patients with metabolic syndrome; - - - -, patients without metabolic syndrome.*

TVR risk for men compared with women, we found that the HR for TVR was 0.99 (0.61–1.58, $P = 0.99$) for men and 0.87 (0.42–1.84, $P = 0.72$) for women. This difference in HR was also not significant ($P = 0.85$).

CONCLUSIONS — Previously, patients with metabolic syndrome have been shown to have higher prevalence of angiographic CAD and to have higher cardiovascular risk only when associated with significant angiographic CAD (3,5,11). However, the effect of metabolic syndrome, present in a rapidly increasing patient population, on clinical restenosis in patients undergoing PCI and coronary stent placement was thus far unknown.

The results of our prospective follow-up study of patients who underwent PCI demonstrate that metabolic syndrome is neither associated with TVR nor with the combined end point. Furthermore, accumulating characteristics of metabolic syndrome were neither associated with increased risk of TVR nor with the combined end point. Similar to a previous study showing increased risk for cardiovascular disease (3) in patients with metabolic syndrome compared with those without, we observed an expected trend toward increased risk of death and myocardial infarction; however, the results were not statistically significant because of the low number of instances of death and myocardial infarction on follow-up.

Of the various components of metabolic syndrome, the presence of diabetes has been shown to be associated with increased risk of restenosis after PCI and coronary stent placement (12). However, a recent meta-analysis showed that, although the published literature suggests that diabetes is a risk factor for restenosis in patients after PCI and coronary stent placement, this effect is overestimated because it is partly related to the older age of the patients, which is an important factor for restenosis (13). In our study, the mean age of our population with metabolic syndrome was lower than that for those without metabolic syndrome. Because age has been found to be a confounding factor of metabolic syndrome, we have controlled for age in the multivariable analysis; however, a residual protective effect of younger age in the patients with metabolic syndrome cannot be fully excluded.

Furthermore, in the recent meta-analysis (13), rates of restenosis were higher in patients treated with insulin, which in turn, may be a marker for disease duration and severity (14,15). How-

Table 4—*HRs of TVR and clinical restenosis according to presence of accumulating characteristics of metabolic syndrome*

	Patients	TVR	HR (95% CI)*	Combined end point†	HR (95% CI)*
n	901	92		105	
Number of metabolic syndrome characteristics					
0	39 (4.3)	5 (5.4)	1 (reference)	6 (5.7)	1 (reference)
1	147 (16.3)	13 (14.1)	0.61 (0.22–1.71)	14 (13.3)	0.55 (0.21–1.44)
2	267 (29.6)	27 (29.3)	0.68 (0.26–1.76)	31 (29.5)	0.66 (0.27–1.57)
3	242 (26.9)	27 (29.3)	0.79 (0.30–2.05)	32 (30.5)	0.78 (0.33–1.87)
4	143 (15.9)	13 (14.1)	0.52 (0.19–1.46)	14 (13.3)	0.47 (0.18–1.23)
5	63 (7.0)	7 (7.6)	0.79 (0.25–2.50)	8 (7.6)	0.76 (0.26–2.18)
Overall ANOVA		$P = 0.77$		$P = 0.81$	

Data are *n* (%) unless otherwise indicated. *Adjusted for age, sex, previous myocardial infarction, stent length, current smoking, and statin therapy; †combined end point was defined as death presumably from cardiac causes, myocardial infarction not attributable to a coronary artery other than the target vessel, and TVR either by repeat PCI or coronary artery bypass grafting.

ever, in our study, despite an increased frequency of insulin therapy among our patients with metabolic syndrome, there was no difference in risk of clinical restenosis between patients with metabolic syndrome with or without insulin therapy.

Previously, we have reported that in the GENDER population, diabetes is indeed an independent predictor for clinical restenosis (7). However, in the present study, metabolic syndrome did not seem to be a similar risk for restenosis. One of the reasons for this could be that the presence of diabetes is only one of the five criteria used to define metabolic syndrome and only 24% of the patients with metabolic syndrome had overt diabetes in our population. Moreover, our reference group or the group without metabolic syndrome also had 7% of patients with diabetes, which could have further minimized any HR conferred by diabetes in the group with metabolic syndrome. Therefore, we would like to present the hypothesis that although the presence of diabetes along with old age is a risk factor for restenosis, the presence of metabolic syndrome per se is not associated with an increased risk of clinical restenosis.

Limitations of the study

One of the limitations of our study is that we did not have waist circumference as per criteria of ATP-III. Therefore, we substituted waist circumference with a variable of obesity defined by BMI >28.8 kg/m^2. This cutoff was equivalent to a waist circumference of 102 cm in a cross-sectional study and similar to the BMI value (28.2 kg/m^2) calculated in a regression of BMI on waist circumference in a large population of Scottish men (8,9). Furthermore, we cannot exclude the possibility of some misclassification bias on the presence or absence of some of the components of metabolic syndrome due to effective pharmacological therapy at the time of diagnosis. Of note, the presence or absence of statin therapy did not influence restenosis rates.

In conclusion, the results of this prospective follow-up study of patients who underwent PCI demonstrate that metabolic syndrome is associated with neither TVR nor with the combined end point. Furthermore, accumulating characteristics of metabolic syndrome were not associated with increased risk of TVR or the combined end point. Therefore, PCI is an option to treat symptomatic CAD in patients with metabolic syndrome as well as in patients without metabolic syndrome. This is important information in light of the pandemic proportion of metabolic syndrome that will confront the medical community.

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