The metabolic syndrome and its components and the long-term risk of death in patients with coronary heart disease

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Background The metabolic syndrome confers an increased risk of major cardiovascular events in individuals initially free from coronary heart disease (CHD). Presently, approximately 25% of the US population possesses the metabolic syndrome as defined using the National Cholesterol Education Program (NCEP) criteria. We sought to assess the impact of the metabolic syndrome and its individual components on intermediate-term and long-term outcomes in patients with CHD.

Methods The CASS registry represents a database of 24958 patients with suspected or proven CHD who underwent cardiac catheterization between 1974 and 1979. Mean long-term follow-up was 12.6 ± 5.1 years. Metabolic syndrome was defined using modified definitions of the NCEP and World Health Organization (WHO) because high-density lipoprotein cholesterol measures were not available.

Results We identified 3279 and 1080 patients with metabolic syndrome using our modified NCEP and WHO definitions, respectively. Adjusted long-term all-cause death was higher in patients with metabolic syndrome (hazard ratio [HR] 1.21, 95% CI 1.14-1.29; HR 1.56, 95% CI 1.43-1.70 for NCEP and WHO criteria, respectively). Similarly, long-term adjusted risk of cardiovascular death and intermediate-term risk of morbidity and mortality were higher in patients with the metabolic syndrome. Fasting blood glucose ≥110 mg/dL was responsible for most of the increased risk associated with the metabolic syndrome (adjusted HR 1.47, 95% CI 1.39-1.56).

Conclusions The metabolic syndrome confers a higher risk of long-term death in patients with preexisting CHD, and dysglycemia appears to be responsible for most of the associated risk. (Am Heart J 2006;151:514-21.)

The metabolic syndrome refers to a constellation of coronary heart disease (CHD) risk factors including obesity and abdominal fat distribution, disorders of glucose and lipid metabolism, and hypertension. Although each of these risk factors individually has been shown to increase cardiovascular risk,[1-5] the metabolic syndrome itself has been shown to increase cardiovascular and all-cause mortality in subjects without known heart disease.[6-8] The recently published INTERHEART study showed that among traditional risk factors, diabetes, hypertension, and abdominal obesity together account for approximately 50% of the risk of a first myocardial infarction.[5] The effect of the metabolic syndrome on outcomes in patients with preexisting CHD has not been well studied. Obese patients with acute myocardial infarction are generally younger than nonobese patients at presentation[9] and would appear to have worse long-term outcomes.[10] In addition, elevated body mass index (BMI) has been shown to be a risk factor for acute coronary syndromes in patients with angiographically documented CHD.[11] The impact of the metabolic syndrome on fatal and nonfatal events in patients with stable coronary artery disease has not been studied. We therefore sought to evaluate the effect of the metabolic syndrome on intermediate-term and long-term outcomes in patients with suspected or proven CHD and to determine whether specific features of the metabolic syndrome contribute more significantly than others to the long-term risk of death.

Methods

Patient population and follow-up

The CASS registry includes 24958 patients with suspected or proven CHD who were initially enrolled at 15 centers throughout North America between 1974 and 1979. Patients had annual scheduled follow-up until 1982, and afterward, vital status was obtained through a mail-in survey completed between 1989 and 1991. Vital status for nonresponders was

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Table I. Baseline characteristics for entire CASS registry cohort, patients with and without metabolic syndrome, and those dying from any cause

Characteristics	Entire cohort (n = 24958)	Metabolic syndrome, modified WHO definition (n = 1080)	Metabolic syndrome, modified NCEP definition (n = 3279)	No modified NCEP metabolic syndrome or diabetes (n = 21079)	All-cause death (n = 10302)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age (y)	52.9 ± 9.3	54.5 ± 8.4	52.9 ± 8.8	52.8 ± 9.4	55.9 ± 9.0*
Body weight (kg)	75.9 ± 13.5	86.8 ± 14.9	85.8 ± 12.9	74.4 ± 13.0	76.1 ± 13.4*
BMI (kg/m2)	25.9 ± 3.8	29.1 ± 4.4	29.7 ± 3.5	25.3 ± 3.6	25.9 ± 3.9
LVEF (%)	59.3 ± 15.5	58.7 ± 15.1	59.8 ± 14.6	59.4 ± 15.6	54.1 ± 17.5*
Systolic blood pressure (mm Hg)	130 ± 20.3	145.6 ± 19.1	142.1 ± 17.9	128.3 ± 20.0	131.9 ± 21.7*
Diastolic blood pressure (mm Hg)	80.5 ± 11.9	87.5 ± 11.6	86.5 ± 11.6	79.7 ± 11.7	80.7 ± 12.4
Serum total cholesterol (mg/dL)	230.9 ± 50.4	242.4 ± 53.2	240.2 ± 54.0	229.4 ± 49.4	232.9 ± 53.5*
Serum triglycerides (mg/dL)	203.1 ± 160.2	295.6 ± 209.9	278.0 ± 176.0	186.2 ± 151.4	210.4 ± 196.6*
FPG (mg/dL)	104.4 ± 32.4	140.6 ± 44.9	122.5 ± 42.4	98.7 ± 23.1	110.4 ± 40.7*
Serum creatinine (mg/dL)	0.51 ± 0.66	0.56 ± 0.62	0.57 ± 0.62	0.49 ± 0.66	0.55 ± 0.72*
	n (%)	n (%)	n (%)	n (%)	n (%)
Male sex	18876 (75.6)	802 (74.3)	2577 (78.6)	15860 (75.2)	8361 (81.2)*
Active smokers	8202 (32.9)	288 (26.7)	1000 (30.5)	7054 (33.5)	3622 (35.2)*
Family history for premature CHD	10836 (43.4)	471 (43.6)	1451 (44.3)	9140 (43.4)	4272 (41.5)
Medical history of hypertension	8433 (33.8)	577 (53.4)	1580 (48.2)	6624 (31.4)	4073 (39.5)*
Medical history of diabetes	2613 (10.5)	520 (48.2)	847 (25.8)	1195 (5.7)	1608 (15.6)*
Abnormal coronary angiogram	20460 (82.0)	952 (88.2)	2824 (86.2)	17074 (81.0)	9679 (94.0)*
Extent of coronary disease					*
0-Vessel disease	6844 (27.7)	211 (19.7)	753 (23.1)	6028 (28.8)	1213 (11.9)
1-Vessel disease	5062 (25.5)	186 (17.4)	669 (20.6)	4299 (20.6)	1777 (17.5)
2-Vessel disease	5582 (22.6)	250 (23.4)	753 (23.1)	4687 (22.4)	2678 (26.3)
3-Vessel disease	7266 (29.4)	423 (39.5)	1079 (33.2)	5891 (28.2)	4509 (44.3)
Antihypertensive therapy	2126 (8.5)	217 (20.1)	504 (15.4)	1561 (7.4)	1094 (10.6)*
β-Blocker use	11392 (45.7)	514 (47.6)	1579 (48.2)	9524 (45.2)	4728 (45.9)
Aspirin use	1076 (4.3)	47 (4.4)	118 (3.6)	935 (4.4)	451 (4.4)
Lipid-lowering therapy	1064 (4.3)	60 (5.6)	195 (6.0)	832 (3.9)	513 (5.0)*
	n (%)	n (%)	n (%)	n (%)	n (%)
All antidiabetic agents	1103 (4.4)	359 (33.3)	517 (15.8)	0	820 (8.0)*
Oral hypoglycemic agents	627 (2.5)	215 (19.9)	319 (9.7)	0	455 (4.4)*
Insulin therapy	491 (2.0)	152 (14.1)	208 (6.3)	0	376 (3.7)*

LV, Left ventricle.
*Univariate predictors of all-cause mortality with $P < .0001$ for all variables.

obtained from the National Death Index for patients in the United States and in Canada by next of kin, medical records, and death certificates. Follow-up was complete for 96% of patients in the registry by the closing date of December 31, 1992. Patients without death records available by the closing date were considered alive. Mortality from cardiovascular disease in the registry and in the National Death Index was defined according to the *International Classification of Diseases, Eighth Revision* using codes 390 to 458. Intermediate-term end points were defined as those occurring by the end of scheduled follow-up in 1982, whereas long-term end points were defined as those occurring by the December 1992 closing date. Data on nonfatal events were available until 1982 from scheduled follow-up visits and are included in the intermediate-term end points. Nonfatal events studied included hospitalization for acute myocardial infarction, stroke, or congestive heart failure.

Clinical variables

The clinical variables used are derived from the CASS registry, were obtained at the time of enrolment in the study, and included age, sex, family history of premature CHD, medical history of diabetes, hypertension, hypercholesterolemia and smoking, and medication use. Additional variables studied were systolic and diastolic blood pressure, serum cholesterol, triglycerides, fasting plasma glucose (FPG) and creatinine levels, left ventricular ejection fraction (LVEF), and

Table II. Intermediate-term and long-term risk of cardiovascular and all-cause death and complications according to presence or absence of metabolic syndrome

	HR (95% CI)			
	Long-term all-cause death	**Long-term CV death**	**Intermediate-term risk of all-cause death, MI, CHF, or stroke**	**Intermediate-term risk of CV death, MI, CHF, or stroke**
Metabolic syndrome—modified NCEP definition (unadjusted models)	1.23 (1.16-1.29)	1.26 (1.19-1.35)	1.21 (1.13-1.30)	1.22 (1.14-1.31)
Metabolic syndrome—modified NCEP definition (adjusted models*)	1.21 (1.14-1.29)	1.22 (1.14-1.31)	1.21 (1.13-1.31)	1.23 (1.13-1.33)
Metabolic syndrome—modified WHO definition (unadjusted models)	1.63 (1.50-1.77)	1.67 (1.52-1.83)	1.53 (1.38-1.70)	1.54 (1.38-1.72)
Metabolic syndrome—modified WHO definition (adjusted models*)	1.56 (1.43-1.70)	1.55 (1.40-1.71)	1.50 (1.35-1.68)	1.52 (1.35-1.70)

CV, Cardiovascular; *MI*, myocardial infarction; *CHF*, congestive heart failure.
*Adjusted for age, sex, smoking status, lipid-lowering therapy, and serum total cholesterol levels.

extent of coronary disease. Serum high-density lipoprotein (HDL) cholesterol and insulin were not measured in CASS. The number of diseased coronary arteries was based upon whether the left anterior descending artery, the left circumflex artery, or the right coronary artery had ≥70% diameter stenoses, or whether the left main artery had a ≥50% diameter stenosis. Left main artery disease was considered 2-vessel disease in the presence of a right-dominant coronary circulation and 3-vessel disease in the presence of a left-dominant coronary circulation. Coronary angiograms were interpreted using visual estimation in the CASS registry.

Definitions of metabolic syndrome

The National Cholesterol Education Program (NCEP) definition of the metabolic syndrome requires the presence of ≥3 of 5 criteria, namely, abdominal obesity (waist circumference >102 cm in men and >88 cm in women), triglycerides ≥150 mg/dL, decreased HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, and FPG ≥110 mg/dL.[12] Data on waist circumference, serum HDL cholesterol, and insulin levels, however, were not available in the CASS registry. We therefore modified the NCEP definition for the purpose of the current study which consisted of possessing ≥3 of the 4 following characteristics: (1) FPG ≥110 mg/dL or a diagnosis of diabetes with use of either oral hypoglycemic agents or insulin (n = 3936/24958 or 15.8%), (2) abdominal obesity defined as BMI ≥27.5 kg/m^2 (n = 7075/24855 or 28.5%), (3) dyslipidemia defined as serum triglycerides ≥150 mg/dL (n = 9118/24958 or 36.5%), and (4) hypertension defined as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or use of antihypertensive medication (n = 14849/24958 or 59.5%). We also used a validated definition of the metabolic syndrome used for epidemiological studies based upon World Health Organization (WHO) criteria and requiring the presence of either hyperinsulinemia, impaired FPG ≥110 mg/dL or diabetes, and ≥2 of the following: (1) abdominal obesity (waist/hip ratio >0.90 or BMI ≥30 kg/m^2), (2) dyslipidemia (triglycerides ≥150 mg/dL or HDL cholesterol <35 mg/dL), and (3) hypertension defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication.[13-15] Because waist/hip ratio, insulin, and HDL-cholesterol levels were not available in CASS, we used modified WHO criteria for the diagnosis of the metabolic syndrome requiring the presence of FPG ≥110 mg/dL or a diagnosis of diabetes with use of either oral agents or insulin (n = 3936/24958 or 15.8%), and at least 2 of the following: (1) abdominal obesity defined as BMI ≥30 kg/m^2 (n = 3076/24855 or 12.4%), (2) dyslipidemia defined as serum triglycerides ≥150 mg/dL (n = 9118/24958 or 36.5%), and (3) hypertension defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication (n = 11133/24958 or 44.6%). By using the above criteria, from the entire cohort of 24958 patients in the registry, we were able to identify 3279 patients (13.1%) and 1080 patients (4.3%) with metabolic syndrome using the modified NCEP and modified WHO criteria, respectively.

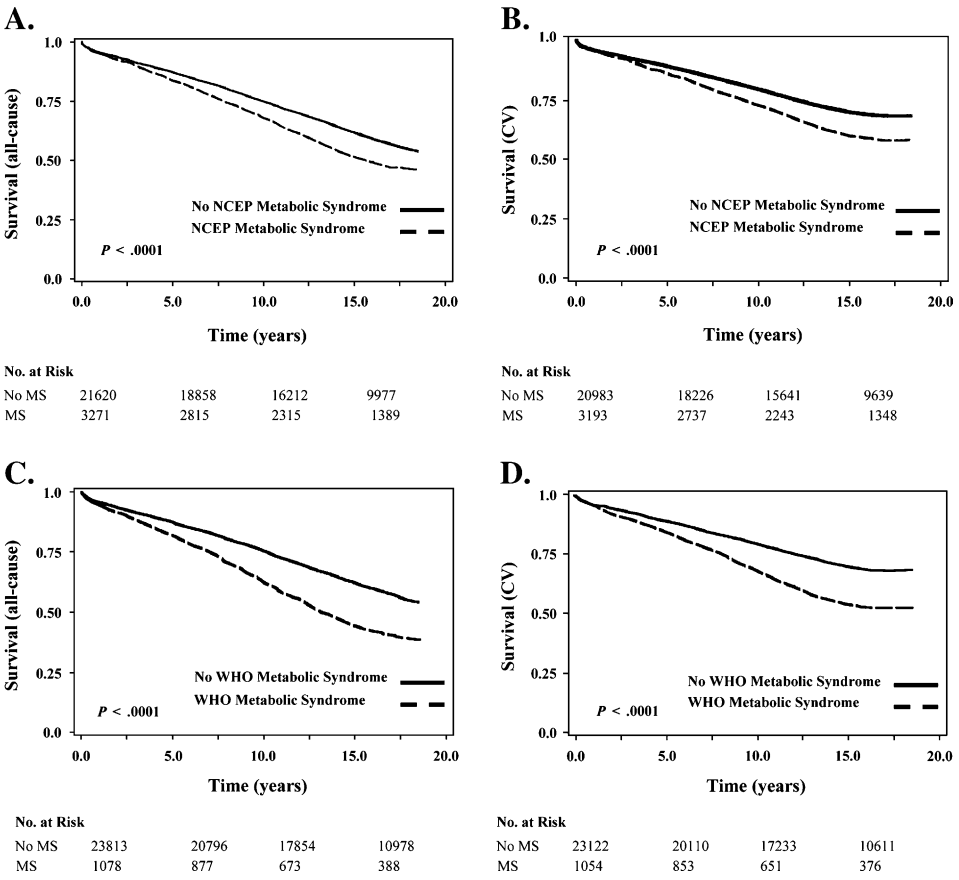
Statistical methods

The results are expressed as mean ± SD for continuous variables and as percentages for categorical variables. Univariate analyses (*t* test or Wilcoxon test for continuous variables and Pearson χ^2 test for categorical variables) were used to compare patients with and without metabolic syndrome and to determine which variables were related to the outcomes. Freedom from long-term all-cause and cardiovascular mortality and intermediate-term combined end points was evaluated using the Kaplan-Meier method and log-rank test and was modeled and adjusted for potential confounders using the Cox regression. A *P* value <.05 was considered statistically significant. Statistical analyses were done with SAS version 8.2.

Results

Baseline characteristics for the entire CASS registry cohort, those with and without the metabolic syndrome, and those dying from all causes are described in Table I. Mean long-term follow-up was 12.6 ± 5.1 years, whereas

Figure 1



Cumulative survival according to metabolic syndrome definition. **A**, Modified NCEP definition and freedom from long-term all-cause death. **B**, Modified NCEP definition and freedom from long-term CV death. **C**, Modified WHO definition and freedom from long-term all-cause death. **D**, Modified WHO definition and freedom from long-term CV death. *MS*, Metabolic syndrome; *CV*, cardiovascular.

mean intermediate-term follow-up was 5.4 ± 1.8 years. Univariate predictors of long-term all-cause mortality in the CASS registry included age, sex, smoking status, LVEF, systolic blood pressure, higher body weight, fasting glycemia, total cholesterol, serum triglyceride, and serum creatinine levels (all P values < .0001). BMI itself was not a predictor of all-cause mortality. Patients with and without metabolic syndrome using the modified NCEP definition were similar with respect to age, sex, family history of premature CHD, and LVEF, although fewer patients with metabolic syndrome were active smokers (30.5% vs 33.2%; P = .0068). Using the modified WHO criteria, patients with metabolic syndrome were significantly older (54.5 ± 8.4 vs 52.8 ± 9.4 years; P < .0001) and less likely to be active smokers (26.7% vs 33.2%; P < .0001) but otherwise were similar to those without metabolic syndrome.

In univariate analyses, both modified NCEP and WHO metabolic syndrome definitions were associated with increased long-term all-cause and cardiovascular mortality and an increase in the combined end points of intermediate-term mortality, or hospitalization for acute myocardial infarction, stroke, or congestive heart failure (Table II, Figure 1). Multivariate models were created adjusting for prognostic factors (Table II). After adjustment, all fatal and nonfatal events remained significantly more frequent in patients with metabolic syndrome. We did not adjust for LVEF in our principal models given that a large proportion of patients were missing data for this variable. However, in a separate analysis in which LVEF was included, hazard ratios (HRs) remained similar to those reported here (data not shown). Patients with modified WHO metabolic syndrome criteria had a 1.5-fold increased risk of having long-term cardiovascular or all-cause death, respectively, whereas patients with metabolic syndrome using the modified NCEP definition had a 1.2-fold increased risk of long-term death irrespective of cause. Similar

Table III. Adjusted risk of cardiovascular and all-cause death and complications according to the presence of NCEP metabolic syndrome excluding diabetes, and diabetes alone, relative to subjects with neither metabolic syndrome or diabetes

	HR (95% CI)			
	Long-term all-cause death	**Long-term CV death**	**Intermediate-term risk of all-cause death, MI, CHF, or stroke**	**Intermediate-term risk of CV death, MI, CHF, or stroke**
Metabolic syndrome—modified NCEP definition without diabetes*	1.15 (1.08-1.22)	1.15 (1.07-1.24)	1.15 (1.06-1.24)	1.16 (1.07-1.25)
Diabetes mellitus*	2.36 (2.17-2.58)	2.39 (2.16-2.65)	2.19 (1.96-2.44)	2.22 (1.98-2.49)

*Adjusted for age, sex, smoking status, lipid-lowering therapy and serum total cholesterol levels.

Table IV. Long-term risk of all-cause death according to components of the metabolic syndrome

HRs*	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
FPG ≥110 mg/dL	1.33 (1.25-1.41)	–	–	–	–
FPG ≥110 mg/dL and/or antidiabetic treatment	–	1.48 (1.40-1.56)	1.47 (1.39-1.56)	1.47 (1.39-1.56)	1.47 (1.39-1.56)
BMI ≥27.5 kg/m^2	–	–	1.07 (1.02-1.12)	1.07 (1.02-1.12)	1.07 (1.02-1.12)
Triglycerides ≥150 mg/dL	–	–	–	1.01 (0.97-1.06)	1.01 (0.97-1.06)
BP ≥130/85 or antihypertensive therapy	–	–	–	–	1.01 (0.97-1.06)

Model 1 = FPG ≥110 mg/dL; model 2 = FPG ≥110 mg/dL and/or antidiabetic treatment; model 3 = FPG ≥110 mg/dL and/or antidiabetic treatment + BMI ≥27.5 kg/m^2; model 4 = FPG ≥110 mg/dL and/or antidiabetic treatment + BMI ≥27.5 kg/m^2 + triglycerides ≥150 mg/dL; model 5 = FPG ≥110 mg/dL and/or antidiabetic treatment + BMI ≥27.5 kg/m^2 + triglycerides ≥150 mg/dL + BP ≥130/85 or antihypertensive therapy. *BP*, Blood pressure.
*Adjusted for age, sex, smoking status, lipid-lowering therapy and serum total cholesterol levels.

HRs were obtained for the intermediate-term end points (Table II).

As an additional analysis, we evaluated clinical outcomes in (1) patients with treated diabetes alone and (2) patients with our modified NCEP metabolic syndrome definition but excluding treated patients with diabetes, relative to patients with neither metabolic syndrome or diabetes (Table III). The metabolic syndrome excluding patients with diabetes was still associated with a significantly increased risk of intermediate-term and long-term end points, although HRs were slightly reduced relative to our primary definition that included diabetic patients. Treated patients with diabetes had the highest risk of morbidity and mortality with a 2-fold increased risk of having an intermediate-term or long-term end point. In models tested, no interaction was found between metabolic syndrome and diabetes.

Finally, we created a graduated model to evaluate the relative contributions of the individual components to the overall risk associated with the metabolic syndrome (Table IV). FPG ≥110 mg/dL was the major factor responsible for the long-term risk of death in the metabolic syndrome, whereas BMI ≥27.5 kg/m^2 was associated with a small but significantly increased risk of fatal events after adjustment for age, sex, smoking status, total cholesterol levels, and lipid-lowering therapy. All components of the metabolic syndrome demonstrated significant correlations between each other (data not shown).

Discussion

Recent trends have demonstrated a dramatic rise in the prevalence of both obesity and metabolic syndrome in the general North American population.[16,17] The metabolic syndrome profile is known to increase the risk of both all-cause and cardiovascular death in individuals initially free from CHD.[6-8] In a Finnish cohort of 1209 men free from cardiovascular disease, diabetes, or cancer and followed up for approximately 12 years, the metabolic syndrome was associated with a 1.5- to 2.5-fold increase in cardiovascular mortality, and a similar 1.5- to 2-fold increase in all-cause mortality.[6] In the Botnia Study, which included 4483 men and women free from CHD, the metabolic syndrome was associated with a 1.8-fold increase in the adjusted risk of cardiovascular mortality using the WHO definition.[7]

Approximately 4% and 13% of patients of the entire CASS registry fit the criteria for metabolic syndrome according to our modified WHO and NCEP definitions.

The true prevalence of metabolic syndrome in this cohort may have been underestimated, however, given our use of BMI instead of waist circumference for the definition of abdominal obesity in our modified criteria. Our data indicate that individuals with metabolic syndrome and CHD have a higher likelihood of death or recurrent cardiovascular events relative to individuals without this disorder after adjustment for other major risk factors including age, sex, smoking status, hypercholesterolemia, and lipid-lowering therapy. HR estimates for all end points considered were slightly higher using the modified WHO criteria relative to the modified NCEP criteria for the diagnosis of metabolic syndrome. This finding is consistent with data from the primary prevention setting[6] and is presumably due to the fact that the WHO definition of the metabolic syndrome requires the presence of impaired glucose metabolism (hyperinsulinemia, impaired fasting glycemia, or diabetes), whereas the NCEP definition does not. Both our modified NCEP and WHO definitions were able to identify a high-risk subgroup of CHD patients in the absence of HDL-cholesterol levels. Data from the WISE study which included 755 patients referred for coronary angiography and followed up over a 4-year period would also indicate that women with significant CHD and the metabolic syndrome are at increased risk of death.[18] Analysis of our survival curves for both all-cause and cardiovascular mortality, with a much larger population and a longer follow-up period relative to the WISE study, reveals that patients with CHD and metabolic syndrome possess a progressively increasing risk of death over time as the survival curves of those with and without metabolic syndrome began to separate early on and continued to separate by the end of the follow-up period.

Exclusion of treated patients with diabetes from our modified NCEP definition resulted in a slight reduction in HRs, but the metabolic syndrome was nevertheless associated with an increased risk of both intermediate-term and long-term morbidity and mortality (Table III). As expected, treated patients with diabetes possessed the highest risk of death among the cohorts we examined, with HRs for death that were comparable to those noted in previous studies in CHD patients.[19,20]

Our data would also suggest that in this CHD cohort, the presence of dysglycemia was responsible for most of the long-term risk of death, whereas elevated BMI as a surrogate for abdominal obesity played a less important role. Our modified NCEP population contained only 15% treated diabetic patients, with a mean FPG of 122 mg/dL. Even by excluding diabetic patients from our modified NCEP definition, the metabolic syndrome was still associated with significantly increased risk of death. FPG $\geq$110 mg/dL alone was associated with 1.3-fold increased risk of death, whereas patients with treated diabetes or FPG $\geq$110 mg/dL had a 1.5-fold increased risk of long-term death after adjustment for other potential confounders (Table IV). These findings would indicate that elevated FPG in the nondiabetic range can greatly influence the overall risk associated with the metabolic syndrome in a CHD population. Our data are consistent with a recent observational study in 3128 subjects undergoing angiography, in which FPG $\geq$110 mg/dL was predictive of angiographic CHD and a higher risk of death or myocardial infarction during a mean follow-up period of 2.8 years (adjusted HR 1.46, 95% CI 1.17-1.82, including diabetic patients).[21] Elevated BMI and other features of the metabolic syndrome, however, were not predictive of future clinical events in this same study.

Several pathophysiological mechanisms may explain why CHD patients are more susceptible to the effects of dysglycemia. Insulin resistance, a key component of the metabolic syndrome, is known to impair endothelial function in human studies[22] and is associated with both hypertension[23] and hypertriglyceridemia.[24] Obesity per se is an independent risk factor for CHD[25] and is associated with a proinflammatory state which may contribute to the increased risk.[26,27] Furthermore, obesity is associated with a prothrombotic state that includes enhanced platelet aggregation,[28] increased thrombosis, and decreased fibrinolysis.[29] All of these factors conceivably play a role in worsening the prognosis of CHD individuals with metabolic syndrome.

Several limitations exist in the current study. First, the CASS registry did not include data on HDL-cholesterol levels; however, we believe that our modified definitions do capture most individuals with the metabolic syndrome. Low HDL levels are known to correlate strongly with hypertriglyceridemia in the metabolic syndrome.[30] In addition, the current WHO definition of the metabolic syndrome requires the measurement of either HDL cholesterol or triglyceride levels, but not both.[13-15] Second, we did not have data on waist circumference; however, use of BMI $\geq$30 kg/m^2 has been accepted by the WHO for defining obesity in patients with metabolic syndrome.[13-15] For our modified NCEP definition, we used a BMI $\geq$27.5 kg/m^2 in lieu of waist circumference as a lower BMI cutoff appears to capture more individuals with elevated waist circumference using NCEP criteria.[27] Third, in CASS, serum insulin was not measured and could therefore not be used in our modified WHO definition; however, HRs for intermediate-term and long-term outcomes we obtained are similar to those reported in individuals without CHD[6,7] and presumably would have only increased had this information been available. Fourth, diabetes mellitus was not classified by type in this study; however, few type I patients with diabetes are likely to have been included in our population because diabetes was necessarily accompanied by hypertension, obesity, and/or hypertriglyceridemia in our definitions of the metabolic syndrome. Finally, outcomes in patients

included in the CASS registry necessarily reflect management practices at the time the study was undertaken. Nevertheless, we do believe that the current study is informative and is consistent with data in the primary prevention setting. In addition, perhaps it provides some insight into the natural history of the metabolic syndrome in patients with CHD. Only 4% to 5% of patients in the CASS registry were receiving aspirin or available lipid-lowering therapy, including the subgroup of patients with metabolic syndrome. Except for antihypertensive and diabetes medication, patients with metabolic syndrome were treated in a similar fashion to those without the disorder. Presumably more aggressive medical management focused on measures to improve glycemic control including weight loss would have led to better long-term outcomes.

Clinical implications

During the 20th century, public health policies promoting risk factor reduction including exercise and smoking cessation programs contributed to the decline in CHD death rates. Currently, however, dietary habits and a lack of physical activity appear to be fuelling the ongoing and expanding obesity and metabolic syndrome epidemics. As a result, both incident and prevalent CHD will likely continue to increase in the next decades with significant socioeconomic consequences. CHD patients with metabolic syndrome must be identified and managed aggressively including an emphasis on glucose control to reduce both morbidity and mortality for what is in large part a preventable condition.

References

1. McGill HC, McMahan A, Herderick EE, et al. Obesity accelerates the progression of coronary atherosclerosis in young men. Circulation 2002;105:2712-8.
2. The DECODE Study Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? Diabetes Care 2003;26:688-96.
3. Eberly LE, Stamler J, Neaton JD, et al. Relation of triglyceride levels, fasting and nonfasting, to fatal and nonfatal coronary heart disease. Arch Intern Med 2003;163:1077-83.
4. Grundy SM, Balady GJ, Criqui MH, et al. Primary prevention of coronary heart disease: guidance from Framingham. A statement for healthcare professionals from the AHA Task Force on Risk Reduction. Circulation 1998;97:1876-87.
5. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:953-62.
6. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709-16.
7. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683-9.
8. Trevisan M, Liu J, Bahsas FB, et al. Syndrome X and mortality: a population-based study. Risk factor and life expectancy research group. Am J Epidemiol 1998;148:958-66.
9. Suwaidi JA, Wright RS, Grill JP, et al. Obesity is associated with premature occurrence of acute myocardial infarction. Clin Cardiol 2001;24:542-7.
10. Rea TD, Heckbert SR, Kaplan RC, et al. Body mass index and the risk of recurrent coronary events following acute myocardial infarction. Am J Cardiol 2001;88:467-72.
11. Wolk R, Berger P, Lennon RJ, et al. Body mass index: a risk factor for unstable angina and myocardial infarction in patients with angiographically confirmed coronary artery disease. Circulation 2003;108:2206-11.
12. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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 2001;285:2486-97.
13. 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 1998;15:539-53.
14. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 1999;16:442-3.
15. Laaksonen DE, Laaka H-M, Niskanen LK, et al. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol 2002;156: 1070-7.
16. National Center for Health Statistics. Prevalence of overweight and obesity among adults: United States, 1999. Hyatsville, MD: Centers for Disease Control. Available at http://www.cdc.gov/nchs/ products/pubs/pubd/hestats/obese/obse99t2.htm [accessed September 4, 2003].
17. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third national health and nutrition examination survey. JAMA 2002;287:356-9.
18. Marroquin OC, Kip KE, Kelley DE, et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women. A report from the women's ischemia syndrome evaluation. Circulation 2004;109:714-21.
19. Mukamal KJ, Nesto RW, Cohen MC, et al. Impact of diabetes on long-term survival after acute myocardial infarction. Diabetes Care 2001;24:1422-7.
20. Aguilar D, Solomon SD, Kober L, et al. Newly diagnosed and previously known diabetes mellitus and 1-year outcomes of acute myocardial infarction. The Valsartan in Acute Myocardial Infarction (VALIANT) Trial. Circulation 2004;110:1572-8.
21. Anderson JL, Horne BD, Jones HU, et al. Which features of the metabolic syndrome predict the prevalence and clinical outcomes of angiographic coronary artery disease. Cardiology 2004;101: 185-93.
22. Arcaro G, Cretti A, Balzano S, et al. Insulin causes endothelial dysfunction in humans: sites and mechanisms. Circulation 2002;105:576-82.
23. Tezcan H, Yavuz D, Toprak A, et al. Effect of angiotensin-converting enzyme inhibition on endothelial function and insulin sensitivity in hypertensive patients. J Renin Angiotensin Aldosterone Syst 2003;4: 119-23.
24. Olefsky JM, Farquhar JW, Reaven GM. Reappraisal of the role of insulin in hypertriglyceridemia. Am J Med 1974;57:551-60.

25. Wilson PWF, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97: 1837-47.
26. Grundy SM. Obesity, metabolic syndrome and coronary atherosclerosis. Circulation 2002;105:2696-8.
27. Ridker PM, Buring JE, Cook NR, et al. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. An 8-year follow-up of 14719 initially healthy American women. Circulation 2003;107:391-7.
28. Konstantinides S, Schäfer K, Koschnick S, et al. Leptin-dependent platelet aggregation and arterial thrombosis suggests a mechanism for atherothrombotic disease in obesity. J Clin Invest 2001;108: 1533-40.
29. De Pergola G, Pannacciulli N. Coagulation and fibrinolysis abnormalities in obesity. J Endocrinol Invest 2002;25:899-904.
30. Rashid S, Uffelman KD, Lewis GF. The mechanism of HDL lowering in hypertriglyceridemic, insulin-resistant states. J Diabetes Complications 2002;16:24-8.

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Effects of clopidogrel on soluble CD40 ligand and on high-sensitivity C-reactive protein in patients with stable coronary artery disease

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Background Antiplatelet therapy with clopidogrel decreases ischemic complication especially in patients with acute coronary syndromes or after percutaneous coronary interventions. Our study was designed to test the effects of clopidogrel on soluble CD40 ligand (sCD40l) and on high-sensitivity C-reactive protein (hs-CRP) in patients with stable coronary artery disease (CAD).

Methods This is a randomized, double-blind, placebo-controlled study. A total of 73 patients with stable CAD for >6 months were randomized to receive either clopidogrel (loading dose 300 mg followed by 75 mg/d) for 8 weeks or placebo. Soluble CD40 ligand and hs-CRP were measured at baseline and at completion of the study.

Results All patients were on aspirin therapy, and 74% were on statins. Median and interquartile ranges (IQR) of sCD40l decreased from 64 pg/mL (43-99) at baseline to 53 pg/mL (35-77) at 8 weeks (P = .03) in the clopidogrel group and remained unchanged in the placebo group (59 pg/mL, IQR 35-77 vs 55 pg/mL, IQR 35-78) (P = non significant). Levels of hs-CRP were not affected by therapy and remained unchanged in both groups.

Conclusions In patients with stable CAD, clopidogrel inhibits the release of sCD40l by platelets, which may contribute to the clinical benefit provided by this drug. This, however, does not translate in a reduction of subclinical inflammation, as measured by hs-CRP. (Am Heart J 2006;151: 521.e1-521.e4.)