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Impact of Metabolic Syndrome on the Long-Term Survival of Patients With Acute Myocardial Infarction

—— Potential Association With C-Reactive Protein ——

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Background Population-based cohort studies demonstrate that metabolic syndrome (MeS) is associated with increased risk for cardiovascular diseases and related mortalities. The present study was designed to investigate the prognostic impact of MeS in patients with acute myocardial infarction (AMI).

Methods and Results The study group was 461 AMI patients without a history of previous myocardial infarction. On the basis of the National Cholesterol Education Program Adult Treatment Panel III criteria, MeS was defined having at least 3 of the following 5 conditions: dysglycemia (impaired fasting glucose, current use of insulin or oral hypoglycemic drugs), hypertriglyceridemia, low high-density lipoprotein-cholesterol level, hypertension and obesity. The prevalence of MeS was 37% (n=172). C-reactive protein (CRP) levels increased with the increase in the number of conditions of MeS. During follow-up at a median of 17.6 months, the incidence of major adverse cardiovascular events (MACE) was significantly different between patients with and without MeS. Furthermore, after adjustment of predictive factors (age, sex, Killip class, multivessel coronary artery disease, low ejection fraction and high CRP level), MeS was an independent risk factor for MACE.

Conclusions In patients with AMI, MeS is associated with systemic inflammation and is an important predictor for MACE, which suggests the need for early identification and medical intervention for secondary prevention of MeS. (*Circ J* 2008; **72:** 415–419)

Key Words: Glucose; Inflammation; Metabolic syndrome; Myocardial infarction

Several population-based studies have shown that metabolic syndrome (MeS) is an independent predictor of cardiovascular diseases, including acute myocardial infarction (AMI).[1–3] It has also become clear that MeS is strongly associated with systemic inflammation characterized by high levels of C-reactive protein (CRP).[4,5]

Although the number of deaths caused by AMI has declined over the past decade, the incidence of recurrent myocardial infarction (MI) is unchanged[6,7] which indicates the importance of understanding the underlying risk factors that lead to secondary cardiac events. Therefore, this study was designed to investigate the long-term prognostic impact of MeS in patients with AMI.

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Methods

Study Patients

From January 2000 to December 2002, 465 patients who had an AMI without a previous MI were admitted to the coronary care unit of the National Cardiovascular Center, Japan. Four patients complicated with severe inflammatory diseases such as sepsis, pneumonia and pyelonephritis were excluded, leaving a total of 461 patients who were retrospectively analyzed in the present study. The study protocol was approved by the institutional review board.

Definitions

AMI was defined as the presence of any 2 of the following 3 conditions: typical chest pain for at least 30 min, typical electrocardiogram changes (ST elevation, ST depression, T inversion and new pathological Q waves in at least 2 adjacent leads) and elevation of serum creatine kinase level to more than twice the upper normal limit.

Significant coronary artery stenosis was defined as stenosis in more than 75% of the vessels. Multivessel coronary disease was defined as a significant stenosis of 1 or more vessels other than the infarct-related artery. Left main coronary disease was considered to be double vessel involvement. Left ventricular ejection fraction (LVEF) was measured by the Simpson's method on left ventriculography or echocardiography, and left ventricular dysfunction was defined as a LVEF <40%. Congestive heart failure at admission was diagnosed on the basis of physical examination, such as presence of moist rales on chest auscultation and

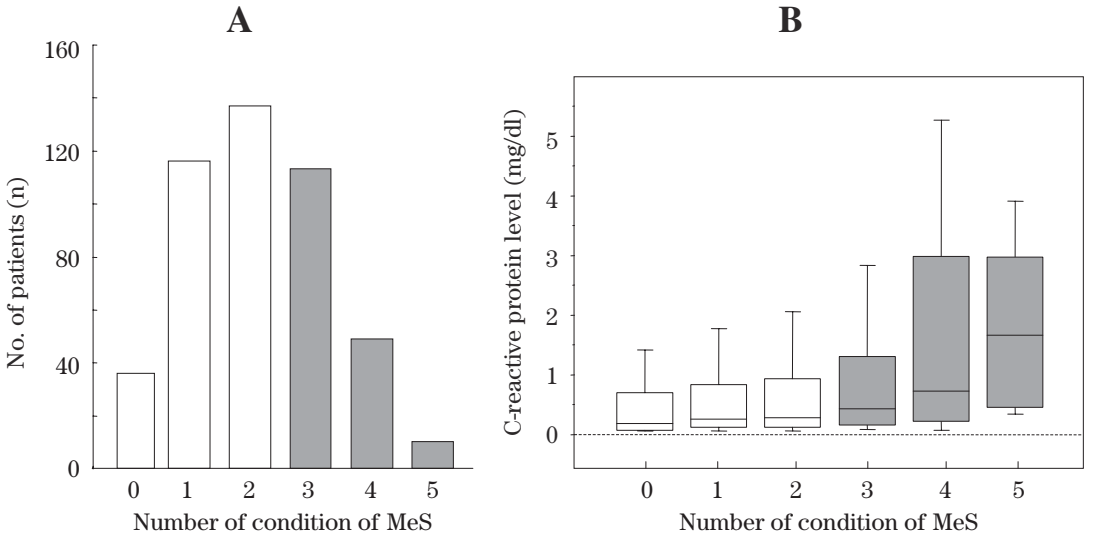

Fig 1. (A) Distribution of the number of conditions of metabolic syndrome (MeS) among 461 patients with acute myocardial infarction. (B) Distribution of C-reactive protein level according to the number of conditions of MeS. Box plots demonstrate median, and 25th, and 75th percentile values for C-reactive protein.

pulmonary congestion on the chest roentgenogram.

The presence of atherosclerotic disease was confirmed by a history of cerebral infarction, presence of arteriosclerosis obliterans or aortic aneurysm.

MeS was defined as having at least 3 of the following 5 conditions set by the recent National Cholesterol Education Program (NCEP) Adult Panel III (ATP-III) report[8] with modifications: dysglycemia, hypertension, hypertriglyceridemia, decreased level of high-density lipoprotein (HDL)-cholesterol, and obesity. Dysglycemia was defined as a fasting glucose >6.11 mmol/L; for the purpose of this analysis, the dysglycemia definition was also met by current use of insulin or oral hypoglycemic drugs. Hypertension was defined as a systolic blood pressure >130 mmHg and/or a diastolic blood pressure >85 mmHg; for the purpose of this analysis, hypertension was also met by current use of antihypertensive drugs. Hypertriglyceridemia was defined as a serum triglyceride level >1.69 mmol/L. Low HDL-cholesterol was defined as a serum level <1.03 mmol/L in men and <1.29 mmol/L in women. Obesity was defined as a body mass index >25 kg/m^2 according to the guidelines of the Japan Society for the Study of Obesity, because the body structure of Japanese is smaller than that of Caucasians and Africans and therefore the World Health Organization criteria appear to be inappropriate for Japanese[9,10]

In addition, the CRP level was defined as high if >0.3 mg/dl, on the basis of previous studies[4,11,12]

Laboratory Measurements

To assess the glycemic and lipid profiles, venous blood samples were drawn in the morning during fasting conditions in the stable phase of AMI (median: 9 days from the onset of AMI). Serum glucose concentration was measured using a glucose oxidase method (Glucose GA-1140; Arkray, Kyoto, Japan). Total cholesterol, triglyceride and HDL-cholesterol concentrations were determined by enzymatic methods using a Toshiba TBA 80M analyzer (Toshiba, Japan). Low-density lipoprotein was calculated using Friedewald's formula.

Serum CRP level was measured by the N Latex CRP II monoassay using a nephelometric technique with a nephelometric analyzer (BN II, Dade Behring, Germany). Additional measurements of CRP level were also performed in the acute phase (median: 2 days from the onset of AMI) and just before discharge (median: 15 days from the onset of AMI). The lower detection limit of this test was 0.06 mg/dl.

Blood samples were analyzed in the hospital central laboratory in a blinded fashion.

Follow-up Study

A follow-up study by reviewing medical records or by telephone interview was carried out for all patients. The endpoints were death from any cause and major adverse cardiovascular events (MACE), which included cardiac death, nonfatal MI, heart failure, and the need for percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). The follow-up period for each patient was calculated from the onset of AMI.

Statistical Analysis

Means are expressed with SD for continuous variables, and medians are presented with 25–75th percentiles for skewed variables. Differences in categorical variables between 2 groups were evaluated with χ^2 test. Differences between means or medians for continuous variables were evaluated with t-test or Mann-Whitney U-test, as appropriate. Survival and event-free survival curves were analyzed by the Kaplan-Meier method and comparison between curves was carried out by log-rank test. Multivariate analysis of death and MACE was evaluated with Cox's proportional hazard model. Results were considered significant when the p-value was <0.05. Statistical analysis was performed with StatView 5.0 software (SAS Institute, Cary, NC, USA).

Results

Prevalence and Characteristics of Patients With MeS

Among the 461 AMI patients (326 men, 135 women), 172 had MeS (Fig 1A), a prevalence of 37%. Patients with MeS were more likely to be young and female and to have a history of systemic atherosclerotic disease than patients

Table 1 Comparison of the Patients' Clinical and Angiographic Characteristics

	MeS(+)	MeS(−)	p value
Age (years)	65.9±11.8	68.2±11.6	0.04
Female, % (n)	35% (61)	26% (74)	0.02
Dysglycemia	61% (105)	18% (52)	<0.01
Hypertriglyceridemia	49% (84)	10% (28)	<0.01
Low HDL-cholesterol	94% (161)	40% (117)	<0.01
Hypertension	86% (148)	54% (156)	<0.01
Obesity (BMI ≥25 kg/m^2)	49% (84)	13% (39)	<0.01
Atherosclerotic disease, % (n)	28% (49)	20% (57)	0.04
Smoking, % (n)	73% (125)	70% (201)	0.53
LDL-cholesterol (mmol/L)	3.28 (2.73–3.90)	3.42 (2.75–3.79)	0.56
CRP (mg/dl)	0.54 (0.18–1.57)	0.26 (0.12–0.82)	<0.01
Killip class ≥2, % (n)	15% (26)	15% (43)	0.99
Multivessel disease, % (n)	52% (85)	46% (131)	0.33
Anterior MI, % (n)	43% (73)	48% (139)	0.25
PCI, % (n)	71% (122)	75% (216)	0.39
Stent use, % (n) to no. of PCI	79% (96)	78% (168)	0.42
CABG, % (n)	11% (19)	9% (25)	0.42
Peak CK (U/L)	1,953 (1,125–3,477)	1,841 (973–3,142)	0.43
LVEF <40%, % (n)	31% (53)	30% (85)	0.75
Medications during follow-up period			
Oral hypoglycemics, % (n)	28% (48)	7% (21)	<0.01
Insulin, % (n)	15% (25)	4% (12)	<0.01
β-blocker, % (n)	58% (100)	44% (127)	<0.01
Statin,% (n)	40% (68)	33% (96)	0.16
Aspirin, % (n)	97% (166)	94% (271)	0.28
ACEI, % (n)	65% (112)	57% (164)	0.08
ARB, % (n)	11% (18)	8% (24)	0.50

Data are mean±SD, percentage, or median value (interquartile range).
MeS, metabolic syndrome; HDL, high-density lipoprotein; BMI, body mass index; LDL, low-density lipoprotein; CRP, C-reactive protein; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; CK, creatine kinase; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

without MeS (Table 1). However, Killip class, incidence of multivessel coronary artery disease and the proportion of coronary revascularization by PCI or CABG, peak creatine kinase, left ventricular dysfunction and anterior wall MI were similar between the 2 groups.

The CRP data for the acute phase was available for 449 patients (median, 2 days after onset of MI). Because 20 patients died in hospital (including 11 patients who died within 3 days of admission because of cardiogenic shock) and 7 patients did not undergo data sampling just before discharge, the CRP data for the chronic phase was available in 422 patients. Although the serum CRP level in the acute phase was similar between the 2 groups (median CRP level of patients with MeS: 1.2 mg/dl vs that of patients without MeS: 1.5 mg/dl, p=0.70), those measured just before discharge (median, 15 days after the onset of infarction) were higher in the patients with MeS than in the patients without MeS (median, 0.54 vs 0.26 mg/dl, p<0.01). As shown in Fig 1B, there was a linear increase in the CRP level as the number of conditions of MeS increased; the median CRP levels for patients with 0, 1, 2, 3, 4, and 5 conditions were 0.19, 0.26, 0.29, 0.43, 0.73, and 1.66 mg/dl, respectively. In the multivariate analysis, CRP level was significantly associated with MeS, but not with infarct size or left ventricular dysfunction.

Medications during the follow-up period, such as insulin, oral hypoglycemic drugs and β-blockers were frequently used in the patients with MeS (Table 1). However, both patient groups similarly received other cardiovascular medications, including statins, aspirin, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers.

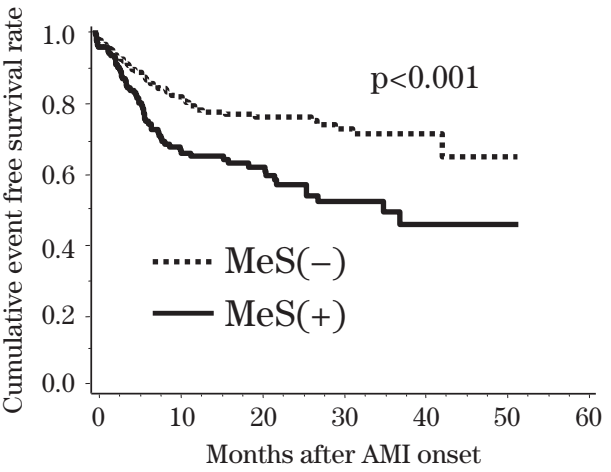

Fig 2. Cumulative event-free survival curves in acute myocardial infarction (AMI) patients with (solid line) and without (dotted line) metabolic syndrome (MeS).

Long-Term Mortality and MACE

During follow-up of a median of 17.6 months (interquartile range: 6.3–30.1), 33 patients died from various causes and 124 patients had at least 1 MACE: cardiac death in 20, heart failure in 24, nonfatal MI in 11 and revascularization in 69 patients. Regarding the occurrence of MI, there were 13 cases of fatal and non-fatal MI during the follow-up. Fig 2 shows that the cumulative-event-free survival rate of patients with MeS was significantly lower than that of the patients without MeS. In the unadjusted Cox's proportional hazard model analysis, the hazard ratio (HR) for MACE in

Table 2 Multivariate Analysis of Predictors of Clinical Outcome

	Death		MACE	
	HR (95%CI)	p value	HR (95%CI)	p value
Age >70 years	3.31 (1.13–9.66)	0.02	1.15 (0.77–1.73)	0.48
Female	3.06 (1.27–7.34)	0.01	1.21 (0.79–1.87)	0.36
Multivessel disease	1.29 (0.45–3.63)	0.62	1.35 (0.90–2.02)	0.14
Killip class ≥2	1.86 (0.76–4.71)	0.16	2.10 (1.29–3.43)	<0.01
LVEF <40%	7.06 (2.50–19.9)	<0.001	1.44 (0.96–2.18)	0.07
CRP ≥0.3 mg/dl	5.57 (1.62–19.2)	<0.01	1.41 (0.94–2.07)	0.09
MeS	1.27 (0.54–3.04)	0.58	1.83 (1.24–2.70)	<0.01

HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiac events. Other abbreviations see in Table 1.

Table 3 Prognostic Value of MeS for MACE

MACE	HR (95%CI)	p value
Cardiac death	0.96 (0.30–3.03)	0.95
Fatal and nonfatal MI	0.84 (0.23–2.70)	0.76
Nonfatal MI	1.02 (0.28–3.69)	0.97
CHF (Killip class ≥2)	2.60 (1.01–6.66)	0.04
Coronary revascularization	2.10 (1.27–3.47)	<0.01

Adjusted for age >70 years, female gender, multivessel disease, Killip class ≥2, LVEF <40, and CRP >0.3 mg/dl.
CHF, congestive heart failure. Other abbreviations see in Tables 1,2.

patients with MeS was 2.05. When we performed multivariate Cox's proportional hazard model analysis for several potential confounders, including age >70 years, female gender, Killip class ≥2, multivessel coronary disease, left ventricular dysfunction (LVEF <40%) and CRP >0.3 mg/dl, MeS remained an independent risk factor for MACE (HR 1.83, 95% confidence interval (CI) 1.24–2.70; p<0.01) after adjustment (Table 2). Multivariate analysis also demonstrated that elevated CRP level even in the stable period, appeared to be a potential determinant of death (HR 5.57, 95% CI 1.61–19.2; p<0.01) and of MACE (HR 1.40, 95% CI 0.94–2.07; p=0.09). To further explore the synergic effect of MeS and CRP, we divided the study patients into 4 groups on the basis of the presence or absence of MeS and on the basis of CRP levels less than or greater than 0.3 mg/dl[4] When setting patients without MeS and with a low CRP level (<0.3 mg/dl) as the reference, the relative risks of future cardiovascular events following AMI were 1.82 (95% CI 1.12–2.95) in patients without MeS and with a high CRP level (≥0.3 mg/dl), 2.24 (95% CI 1.21–4.16) in patients with MeS and a low CRP level, and 2.56 (95% CI 1.56–4.20) in patients with MeS and a high CRP level. These findings suggest there is a synergistic effect between MeS and CRP for experiencing cardiovascular events in patients following AMI.

We then assessed individual cardiac events among the MACE that were associated with MeS. In the multivariate analysis, MeS was significantly associated with repeated coronary revascularization and congestive heart failure (Table 3). Furthermore, we assessed the individual conditions of MeS for MACE and of the 5 components, only dysglycemia was found to be a significant risk factor for MACE after adjustment (Table 4).

Discussion

The major findings of the present study are that MeS is associated with MACE and that a high CRP level is independently associated with mortality after AMI during a 17.6-month follow-up. Moreover, of the 5 conditions of MeS, dysglycemia is the most important factor in mortality and MACE.

The Observatoire des Infarctus de Cote-d'Or Survey demonstrated that the prevalence of MeS in patients with AMI was 46% and that MeS was associated with in-hospital outcome (eg, development of heart failure several days after the onset of AMI)[13] In that survey population (n=633), only 20–25% of patients underwent reperfusion therapy, so the impact of MeS on long-term prognosis (after discharge) remains unknown, particularly in the recent reperfusion era.

In our study, the AMI patients with MeS had a higher incidence of atherosclerotic disease and a higher CRP level measured during the stable period (median, 15 days after onset) than AMI patients without MeS. In patients with AMI, the CRP level reaches its peak approximately 2–4 days after AMI onset[14,15] in accordance with the extent of myocardial necrosis[16] Independent of infarct size, the CRP level measured in the stable period (25 days after AMI onset) has been reported to be significantly associated with long-term mortality in patients with AMI[17] Taken together with the present result by multivariate analysis that CRP level measured in the stable period of AMI was associated only with MeS, but not with infarct size and cardiac func-

Table 4 Incidence and Significance of Each Condition of the MeS for Clinical Outcomes

	Prevalence	Death		MACE	
		HR (95%CI)	p value	HR (95%CI)	p value
Dysglycemia	34.2%	2.39 (0.93–6.11)	0.07	1.61 (1.07–2.41)	0.02
Hypertriglyceridemia	24.3%	0.93 (0.23–3.67)	0.91	1.30 (0.84–2.02)	0.24
Low HDL-cholesterol	60.3%	1.64 (0.55–4.92)	0.37	1.38 (0.89–2.15)	0.15
Hypertension	65.9%	1.27 (0.41–4.00)	0.68	0.83 (0.54–1.24)	0.37
Obesity (BMI ≥25 kg/m^2)	26.9%	0.35 (0.11–1.13)	0.08	1.26 (0.84–1.90)	0.09

Adjusted for age >70 years, female gender, multivessel disease, Killip class ≥2, LVEF <40, and CRP >0.3 mg/dl.
Abbreviations see in Tables 1,2.

tion, it appears that systemic inflammation may be part of the pathophysiology of MeS.[18] Therefore, an understanding of the interactions between metabolic and inflammatory pathways may be important with regard to secondary prevention of MACE after AMI.

We found that MeS is significantly associated with repeated coronary revascularization and congestive heart failure, a finding that may be related to the development of new coronary stenosis or restenosis during the follow-up period, leading to myocardial ischemia and left ventricular dysfunction. Previous studies also show that a persistent inflammatory response plays an important role in the post infarction remodeling process.[16]

As shown in Table 2, dysglycemia, defined as impaired fasting glucose or previous diabetic medication, is the most important among the 5 conditions of MeS, which may be related to a previous observation that the onset of diabetes follows elevated levels of atherosclerotic risk factors.[19] Therefore, it is therapeutically important to simultaneously improve glucose intolerance, abnormal lipid metabolism, blood pressure level and inflammation.[20–22]

Controversy exists as to whether the MeS is more than the sum of its independent metabolic components. An important finding in the present study is that MeS is closely associated with elevation of CRP. Moreover, MeS seems to have a synergistic effect on CRP. Because inflammation participates centrally in the process of atherosclerosis,[23] MeS may indicate a potential risk for future cardiovascular diseases. Further studies are needed to address this issue.

In conclusion, MeS is associated with a high CRP level and is an important predictor for MACE following AMI. This finding suggests the need for early identification and medical intervention of this underlying disease for preventing future adverse cardiac events.

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References

1. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; **288:** 2709–2716.
2. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American adolescents: Findings from the third national health and nutrition examination survey. *Circulation* 2004; **110:** 2494–2497.
3. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: Prevalence and associated risk factor findings in the US population from the third national health and nutrition examination survey, 1988–1994. *Arch Intern Med* 2003; **163:** 427–436.
4. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, et al. 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* 2003; **108:** 414–419.
5. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham offspring study. *Circulation* 2004; **110:** 380–385.
6. American Heart Association. Heart and stroke statistical update. Dallas, Tex: AH; 2003.
7. Guidry UC, Evans JC, Larson MG, Wilson PW, Murabito JM, Levy D. Temporal trends in event rates after Q-wave myocardial infarction: The Framingham Heart Study. *Circulation* 1999; **100:** 2054–2059.
8. 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). *JAMA* 2001; **285:** 2486–2497.
9. Examination Committee of Criteria for 'obesity disease' in JAPAN; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; **66:** 987–992.
10. Anuurad E, Shiwaku K, Nogi A, Kitajima K, Enkhmaa B, Shimono K, et al. The new BMI criteria for Asians by the regional office for the Western Pacific region of WHO are suitable for screening of overweight to prevent metabolic syndrome in elder Japanese workers. *J Occup Health* 2003; **45:** 335–343.
11. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; **347:** 1557–1565.
12. 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 14719 initially healthy American women. *Circulation* 2003; **107:** 391–397.
13. Zeller M, Steg PG, Ravisy J, Laurent Y, Janin-Manificat L, L'Huillier I, et al; Observatoire des Infarctus de Cote-d'Or Survey Working Group. Prevalence and impact of metabolic syndrome on hospital outcomes in acute myocardial infarction. *Arch Intern Med* 2005; **165:** 1192–1198.
14. Kushner I, Broder ML, Karp D. Control of the acute phase response: Serum C-reactive protein kinetics after acute myocardial infarction. *J Clin Invest* 1978; **61:** 235–242.
15. de Beer FC, Hind CR, Fox KM, Allan RM, Maseri A, Pepys MB. Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. *Br Heart J* 1982; **47:** 239–243.
16. Anzai T, Yoshikawa T, Shiraki H, Asakura Y, Akaishi M, Mitamura H, et al. C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. *Circulation* 1997; **96:** 778–784.
17. Kinjo K, Sato H, Ohnishi Y, Hishida E, Nakatani D, Mizuno H, et al; Osaka acute coronary insufficiency study (OACIS) group. Impact of high-sensitivity C-reactive protein on predicting long-term mortality of acute myocardial infarction. *Am J Cardiol* 2003; **91:** 931–935.
18. Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy R, Haffner S. Chronic subclinical inflammation as part of the insulin resistance syndrome: The Insulin resistance atherosclerosis study (IRAS). *Circulation* 2000; **102:** 42–47.
19. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 1992; **41:** 715–722.
20. van Wijk JP, de Koning EJ, Martens EP, Rabelink TJ. Thiazolidinediones and blood lipids in type 2 diabetes. *Arterioscler Thromb Vasc Biol* 2003; **23:** 1744–1749.
21. Ryan MJ, Didion SP, Mathur S, Faraci FM, Sigmund CD. PPARγ agonist rosiglitazone improves vascular function and lowers blood pressure in hypertensive transgenic mice. *Hypertension* 2004; **43:** 661–666.
22. Nesto R. C-reactive protein, its role in inflammation, type 2 diabetes and cardiovascular disease, and the effects of insulin-sensitizing treatment with thiazolidinediones. *Diabet Med* 2004; **21:** 810–817.
23. Libby P. Inflammation and cardiovascular disease mechanisms. *Am J Clin Nutr* 2006; **83:** 456S–460S.