Impact of metabolic syndrome on the outcome of patients with stable coronary artery disease: 2-year follow-up of the MASS II study

Neuza H. Lopes, Felipe S. Paulitsch, Alexandre C. Pereira, Aécio F. Góis, Antônio Gagliardi, Cibele L. Garzillo, João F. Ferreira, Noedir A. Stolf and Whady Hueb

Objective **We characterized the impact of the metabolic syndrome (MetS) and its components on cardiovascular adverse events in patients with symptomatic chronic multivessel coronary artery disease, which have been followed prospectively for 2 years.**

Methods **Patients enrolled in the MASS II study were evaluated for each component of the MetS, as well as the full syndrome.**

Results **The criteria for MetS were fulfilled in 52% of patients. The presence of MetS ($P<0.05$), glucose intolerance ($P=0.007$), and diabetes ($P=0.04$) was associated with an increased mortality in our studied population. Moreover, despite a clear tendency for each of its components to increase the mortality risk, only the presence of the MetS significantly increased the risk of mortality among nondiabetic study participants in a multivariate model ($P=0.03$, relative risk 3.5, 95% confidence interval 1.1–6). Finally, MetS was still associated with increased mortality even after adjustment for diabetes status. These results indicate a strong and consistent relationship of the MetS with mortality in patients with stable coronary artery disease.**

Conclusion **Although glucose homeostasis seems to be the major force driving the increased risk of MetS, the operational diagnosis of MetS still has information for stratifying patients when diabetes information is taken into account.** ***Coron Artery Dis*** **19:383–388 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Coronary Artery Disease 2008, **19**:383–388

Keywords: coronary disease, metabolic syndrome, prognosis, risk factor

Heart Institute (InCor) of the University of Sao Paulo, Sao Paulo, Brazil

Correspondence to Neuza Lopes, MD, PhD, Heart Institute (InCor) University of Sao Paulo, Av. Dr Eneas de Carvalho Aguiar, 44, Sala AB sala 114 05403-000 Sao Paulo, Brazil
Tel: +55 11 3069 5032; fax: +55 11 3069 5188; e-mail: mass@incor.usp.br

Received 10 December 2007 **Revised** 2 April 2008
Accepted 14 April 2008

Introduction

Metabolic syndrome (MetS) refers to a clustering of lipid and nonlipid factors of metabolic origin associated with insulin resistance and leading to higher cardiovascular risk. It is characterized by the presence of insulin resistance, abdominal obesity, dyslipidemia, and hypertension [1].

MetS has a high prevalence, with approximately 44% of the US population over 50 years of age meeting the National Cholesterol Education Program (NCEP) criteria [2]. Two recent reports, one by the NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) [3] and the other from the World Health Organization (WHO) [4] give special attention to the diagnosis of MetS mainly because its components [especially obesity and diabetes mellitus (DM)] on industrialized countries are rising over the decades.

Patients with MetS are at increased risk for cardiovascular disease (CVD) as a result of multiple risk factors at any given low-density lipoprotein (LDL) cholesterol level [5,6]. All of the main components of the MetS have been associated independently with atherosclerosis [7–10].

Recently, MetS was also associated with an increased incidence of cardiovascular events, including increased risk for both cardiovascular and all causes of mortality [11–14]. The impact of MetS on the outcome of patients with chronic coronary artery disease (CAD), however, is less well defined. In this study, we investigated the association between the MetS and its components with the incidence of cardiovascular events in stable CAD

Methodology

Study population

The participants for this study were selected from the prospective, randomized, and controlled clinical trial, The Medicine, Angioplasty, or Surgery Study (MASS II Study). It was designed to compare medical treatment (MT), angioplasty/stent (PCI), and surgical myocardial revascularization (CABG) for patients with multivessel stable CAD

0954-6928 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/MCA.0b013e328306aa8a

with preserved left ventricular function [15]. From May 1995 to May 2000, 2076 candidates who had indications for myocardial revascularization were evaluated. Of these, 611 patients were eligible and met all entry criteria to be assigned randomly to one of the three therapeutic groups: MT ($n = 203$), PCI (205), or CABG (203).

The inclusion criteria included symptomatic multivessel coronary disease, preserved left ventricular function, and the presence of coronary lesions (> 70% of stenosis) amenable to angioplasty. The primary endpoint of this study is to compare the incidence of the major cardiac events, such as acute myocardial infarction, cardiac death, or refractory angina requiring revascularization procedures among the three therapeutic options.

The beginning of the treatment was considered to be randomized date, and patients were studied by the intention-to-treat principle. The follow-up time for all patients will be 5 years. All patients gave informed consent, and the ethics committee of the Heart Institute of the University of Sao Paulo, Brazil approved this study.

Data collection

The collected demographic and laboratory data included age, sex, angiographic findings, and traditional risk factors, such as history of earlier coronary events, hypertension, DM, body mass index, severity of angina, smoking status, and cholesterol and triglycerides profile.

We applied the condition-specific cut points for the MetS from the revised NCEP ATP-III report, with minor modifications as noted [16]. The five-component conditions are insulin resistance defined as a fasting plasma glucose (FPG) greater than or equal to 100 mg/dl (5.6 mmol/l), hypertension, as systolic blood pressure greater than or equal to 130 mmHg, and/or diastolic blood pressure greater than or equal to 85 mmHg or the use of antihypertensive drugs; hypertriglyceridemia, as serum triglicerides greater than or equal to 150 mg/dl (1.7 mmol/l), low HDL cholesterol (HDL-C), as serum HDL-C less than 40 mg/dl (1.03 mmol/l) in men or less than 50 mg/dl (1.29 mmol/l) in women, and abdominal obesity as body mass index greater than or equal to 30 kg/m^2. MetS was defined if the patient had at least three or more of the components above.

Statistical analysis

Differences in baseline characteristics among groups were analyzed by *t*-tests for continuous variables, and χ^2 tests for categorical variables. Survival curves were calculated with the Kaplan–Meier method, and differences between the curves were evaluated with the log-rank statistic. We assessed the relationship between baseline variables and composite endpoints of overall and cardiac-related death, myocardial infarction, and refractory angina requiring revascularization using a Cox proportional hazards survival model. Models were stratified by MetS and adjusted for age, sex, cholesterol levels, DM, race, cigarette smoking, number of vessel disease, and randomization treatment. Hazard ratios with 95% confidence intervals (CI) demonstrate the risk of mortality.

A *P* value of less than 0.05 was considered significant for comparisons. Statistical analyses were performed with the statistical package StatView for Windows ver.5.0 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Baseline clinical characteristics according to metabolic syndrome

Of the 611 patients enrolled in the MASS II Trial Study, we were able to obtain complete information regarding baseline MetS-defining variables of 589 patients. Of these, 308 (52%) fulfilled the criteria for MetS and 281 (48%) did not fulfil the criteria for MetS (NmetS). The clinical and disease characteristics were similar in both groups, except for higher prevalence of hypertension, DM, obesity, FPG, and higher LDL cholesterol and triglycerides, and lower HDL-C levels in MetS patients. Additionally, more female and fewer smoker patients were found in the MetS group (Table 1). No difference among treatment randomization (medical, surgery or angioplasty) was verified regarding MetS status

Table 1 Cardiovascular risk variables in individuals with coronary artery disease stratified by metabolic syndrome

	NMetS	MetS	
Characteristics	(n=281)	(n=308)	*P* value
Demographic profile			
Age (years)	59.57 (9.5)	60.07 (8.8)	NS
Sex male (%)	76.9	60.6	<0.001
Current smoker (%)	38.8	28.2	0.004
White ethnicity (%)	84.7	85.2	NS
Medical history (%)			
Diabetes mellitus	29.3	48.2	<0.001
Hypertension	32.6	88.7	<0.001
Angina pectoris II or III	78.3	73.1	NS
Higher triglycerides	37.6	77.7	<0.001
FPG ≥ 100 mg/dl	42.8	90.5	<0.001
Lower HDL cholesterol	29.7	49.1	<0.001
BMI >30 kg/m^2	6.8	37.7	<0.001
Laboratory values (mmol/l)			
Total cholesterol (mg/dl) (± SD)	214.25 (45)	233.34 (46)	<0.001
LDL cholesterol (mg/dl) (± SD)	142.93 (42)	152.43(42)	0.008
Angiographic findings (%)			
Two-vessel coronary disease	41.4	41.5	0.51
Three-vessel coronary disease	58.6	58.5	
Positive treadmill test	44.7	43.8	NS
Positive scintigraphy	15.8	16.5	NS
Ejection fraction	65.2 (18)	66.1 (11.8)	NS
LAD disease	90%	93%	NS
Randomization (%)			
Medical treatment	50.5	49.5	
Percutaneous coronary intervention	50.8	49.2	0.66
Coronary artery bypass grafting	51.9	48.1	

Continuous variables presented as mean (standard deviation, SD)
BMI, body mass index; LAD, left artery descendent; MetS, metabolic syndrome; NMetS, nonmetabolic syndrome; NS, nonsignificant; FPG, fasting plasma glucose.

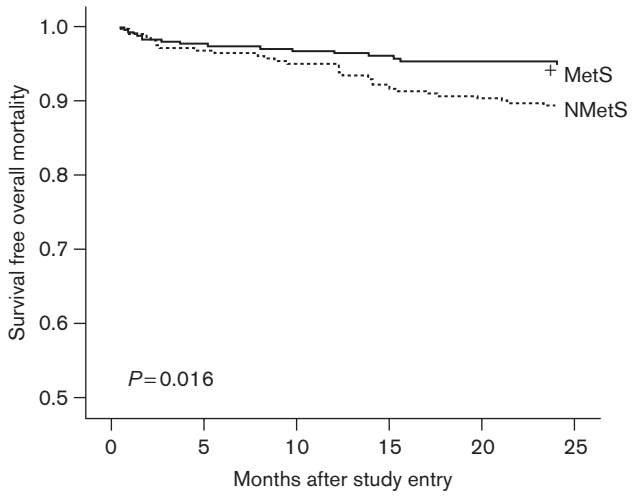
($P = 0.24$), nor its components ($P = 0.42$ for FPG; $P = 0.89$, for low HDL; $P = 0.78$ for high tryglicerides; $P = 0.22$ for hypertension; and $P = 0.06$, for obesity). No difference in lipid-lowering therapy, antihypertensive, and aspirin use were observed between groups at baseline (data not shown).

Cardiovascular endpoints related to metabolic syndrome

Mortality was significantly associated with MetS in our analysis considering a 2-year follow-up period ($P = 0.016$) (Fig. 1). The probability of death was 89.4% and 94.8% in MetS and NMetS patients, respectively. This effect was not seen when analyzing myocardial infarction, or the necessity of a new revascularization procedure (data not shown). We observed the incidence of cardiac or overall mortality of 8.1 and 10.6% in MetS patients compared with 3.6 and 5.2% in NMetS patients, respectively ($P = 0.014$ and 0.011).

In a multivariate Cox proportion hazards survival model, presence of the MetS was associated with an increased mortality even after adjustment for age, sex, smoking status, total cholesterol, ethnicity, treatment allocation, lipid-lowering therapy, and number of diseased vessels ($P = 0.021$; relative risk = 2.5, 95% CI = 1.152–5.472). Interestingly, only MetS and FPG as dependent variables, were significantly associated with mortality, but none of MetS' other components. FPG of more than 5.6 mmol/l was the major factor responsible for the mortality risk in the MetS. Of note, DM itself, also caused a significant 1.86-fold increased risk of mortality (Table 2).

Fig. 1



Probability of event-free survival among patients with or without metabolic syndrome (MetS) at 2 years. NMetS, nonmetabolic syndrome.

Table 2 Adjusting risk of overall mortality according to the presence of metabolic syndrome, each of its component and diabetes alone, relative to patients with neither metabolic syndrome or diabetes

Syndrome model	HR	CI 95%[a]	*P* value
Metabolic syndrome	2.5	1.152–5.472	0.02
Hypertension	1.6	0.828–3.058	0.16
Impaired glucose (100 mg/dl)	4.2	1.601–18.586	0.007
High triglycerides	1.7	0.898–3.433	0.10
Low HDL cholesterol	0.6	0.323–1.327	0.24
Obesity	0.7	0.332–1.705	0.49
DM	1.86	1.030–3.367	0.04

[a]Estimated from separate Cox proportion hazards models for metabolic syndrome and for each of its component adjusted for age, sex, smoking status, ethnicity, total cholesterol number of disease, and treatment allocation.
CI, confidence interval; DM, diabetes; HR, hazard ratio.

Table 3 Effect of metabolic syndrome on all cause of mortality in patients with established CAD

	Model 1[a]		Model 2[b]	
Variable	Hazard ratio	*P* value	Hazard ratio	*P* value
Age (years)	1.067	0.001	1.066	0.001
Number of vessel disease	2.105	0.04	2.125	0.001
MetS	2.307	0.013	2.094	0.34
Diabetes	–	–	1.508	0.189

CAD, coronary artery disease; MetS, metabolic syndrome.
[a]Adjusted for age, sex, smoking status, ethnicity, total and LDL cholesterol, number of disease, and treatment allocation.
[b]Adjusted for age, sex, smoking status, ethnicity, total and LDL cholesterol, number of disease, treatment allocation, and diabetes.

Furthermore, to assess the role of DM in the driven mortality risk of MetS, we analyzed in a multivariate model, the impact of MetS among DM and non-DM patients. Surprisingly, the MetS imposed a significant 3.57 increased risk for mortality in non-DM patients, but not on DM patients (Table 3). Finally, when we adjusted our overall analysis to the presence of DM, MetS was still associated with a significant 2.09-fold increased risk for mortality, but DM was not associated with overall mortality in this model (Table 4).

Figure 2 clearly illustrates that the presence of the MetS was associated with incremental risk of mortality even when one takes DM information into account. Presence of glucose intolerance, defined as a fasting blood glucose level between 5.6 and 6.9 mmol/l, but without DM, also seemed to confer a significant increase in the mortality risk. The probability of mortality stratified by glucose intolerance in patients with MetS is 96.3% (absence) and 88.3% (presence), and 98.7% (absence) and 91.8% (presence) in patients without MetS ($P = 0.007$).

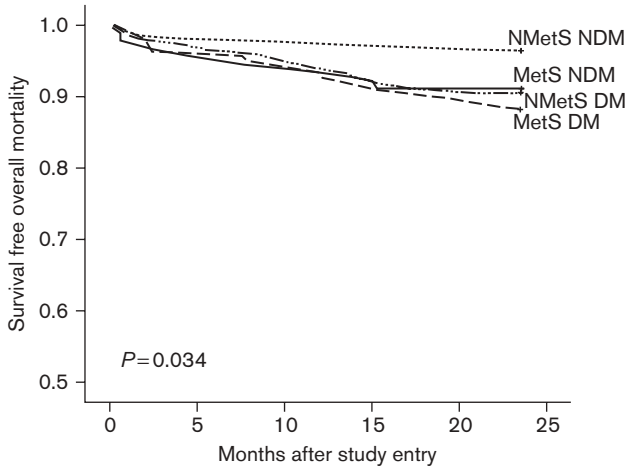
Finally, when we analyzed comparatively the risk of mortality among the three therapeutic options received, there was no statistical difference among MetS patients.

Table 4 Effect of metabolic syndrome on all cause of mortality in nondiabetic and diabetic patients with established CAD

	All patients			Nondiabetic patients			Diabetic patients		
Variable	Hazard ratio	CI	*P* value	Hazard ratio	CI	*P* value	Hazard ratio	CI	*P* value
Age (years)	1.067	1.027–1.109	0.001	1.077	1.017–1.141	0.01	1.019	1.011–1.1128	0.019
Number of vessel disease	2.105	1.027–4.317	0.042	1.255	0.491–3.209	0.63	4.968	1.435–17.203	0.011
MetS	2.307	1.189–4.477	0.013	3.565	1.383–9.186	0.008	1.057	0.384–2.906	0.91

CAD, coronary artery disease; CI, confidence interval; MetS, metabolic syndrome.
Adjusted for age, sex, smoking status, ethnicity, total and LDL cholesterol, number of disease, and treatment allocation.

Fig. 2



Cumulative probability of mortality according to metabolic subgroups. DM, diabetes mellitus; MetS, metabolic syndrome; NMetS, nonmetabolic syndrome; NDM, nondiabetes mellitus.

We observed a mortality incidence of 11.2, 10.3, and 10.6% in PCI, CABG, and MT, respectively in the MetS group ($P = 0.965$); as well as 3, 8, and 5.2% in PCI, CABG, and MT, respectively, in NMetS group ($P = 0.269$). In a Cox proportional hazards adjusted survival model (including antilowering lipid therapy and antihypertensive), considering the impact of MetS on mortality separately in each of treatment options, we found a higher risk of the mortality only in the PCI group ($P = 0.025$; relative risk = 5.906, 95% CI = 1.255–27.782).

Discussion

We found a strong association with MetS and a worse outcome in a 2-year follow-up period of patients with stable multivessel CAD. The presence of MetS conferred a significant 2.5-fold increase in the mortality risk regardless of age, sex, smoking status, LDL cholesterol, ethnicity, type of treatment allocated, and number of vessel disease. A great component of this risk might be driven by impaired fasting glucose. When we compared the three therapeutic strategies, we did not observe a particularly higher mortality among any treatment in MetS patients.

The survival rate of patients with stable coronary and preserved left ventricular function is usually good, regardless of treatment as we and others already had demonstrated [15,17–20]. The subsets of patients, such as diabetic patients, however, might have a worse survival rate as demonstrated by the 7 years of follow-up of bypass angioplasty revascularization investigation study, even when these patients were submitted to surgical treatment [21]. Our findings suggest that MetS patients may have such a worse prognosis in the context of stable coronary disease and preserved ventricular function.

We have demonstrated that the patients with MetS presented a 10.6% rate of mortality in 2 years, significantly superior to 5.2% seen in patients without MetS. This effect was not completely dependent on the presence of DM, because in the Cox proportion hazard model the presence of MetS was associated with a higher risk of mortality even when adjusted by the presence of DM in this subset of patients. Interestingly, the MetS also conferred higher risk for mortality in non-DM population. This should be explained because DM is in itself a well-recognized and strong risk factor for mortality. MetS did not impose an additional risk on diabetic patients in this study. This fact highlighted the importance of the MetS and dysglycemia on mortality risk assessment in patients with preexisting CAD, once it is disentangled from its relationship with DM.

Unlike earlier reports that relied on cross-sectional data to estimate the mortality or CAD risk, our study is one of the few conducted as a prospectively long-term cardiovascular outcome trial in patients with chronic CAD to assess the risk of major coronary events associated with the MetS.

Lakka *et al.* [22] reported the association of the MetS using the proposed definitions (NCEP and WHO with modification) with coronary heart disease (CHD) and overall mortality. They reported an approximately three times higher risk of death from CHD over 10 years in

patients with MetS. Only men free from CVD at baseline were, however, studied. Our report adds information by bringing follow-up data on a sample of multivessel CAD patients.

Girman *et al.* [23] analyzed the placebo data from the Scandinavian Simvastatin Survival Study (4S), using post-hoc analysis to estimate the long-term relative risk of major coronary events (fatal and nonfatal myocardial infarction, sudden cardiac death, and unstable angina) associated with the MetS. All patients had clinically established CHD and high LDL cholesterol levels with 5.4 years of follow-up. Placebo-treated patients with MetS were 1.4 (95% CI = 1.04–1.9) times more likely to have major coronary events than those without it.

Echahidi *et al.* [24] more recently reported in a retrospective analysis that MetS based on NCEP-Adult Treatment Panel III criteria, is a highly prevalent (46%) and powerful risk factor for operative mortality in 5304 consecutive patients who underwent an isolated CABG procedure between 2000 and 2004.

In the literature, there are no data assessing the impact of MetS on cardiovascular prognosis in context of comparing therapeutic strategies for stable chronic coronary disease. Surprisingly, considering the impact of MetS on mortality separately in each of the treatment options, we found a higher risk of five-fold of mortality only in the PCI group. These findings might be related to the fact that dysglycemia seems to be responsible for most of the associated risk in this study. Insulin resistance, a key component of the MetS, is known to impair endothelial function, proinflammatory [25] and prothrombotic state that enhanced platelet aggregation, increased thrombosis, and decreased fibrinolysis [26]. All of these factors conceivably play a role in worsening the prognosis on CAD patients with MetS, mainly for those who underwent PCI. In addition, we cannot rule out other factors related to the worse prognosis observed in PCI, such as creatinine levels, as well as the absence of use of coated stents, and adequate antiplatelets therapy in those subsets of patients in this study. When we compared the three therapeutic options, however, there was no difference in mortality regardless of the presence or not of MetS.

To our knowledge, this is the first prospective cardiovascular outcome trial reporting the association of the MetS and mortality in patients with chronic coronary artery disease. Further studies should look at the impact of MetS on risk of mortality in PCI strategy.

Clinical implications

These findings highlight the clinical importance of the MetS as a significant risk factor for CVD and the need of applied strategies for controlling this syndrome and its component conditions. Thus, it might be important that cardiologists and cardiac interventionists are aware of the MetS and its associated risk, considering strategies to minimize morbidity and mortality, including strict control of risk factors and aggressive preventive therapy.

Conclusion

In summary, MetS conferred an independent higher mortality risk in patients with stable CAD, mainly driven by dysglycemia.

Acknowledgement

Research grant from Zerbini Foundation, SP, Brazil.

References

1 Grundy SM, Brewer JR, Bryan CJI, Smith JR, Sidnet C, Lenfant C. For the conference participants. Definition of Metabolic Syndrome Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation* 2004; **109**:433–438.
2 Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults. *J Am Med Assoc* 2002; **287**:356–359.
3 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). *J Am Med Assoc* 2001; **285**:2486–2497.
4 Ford ES, Giles WH. A comparison of the prevalence of the metabolic syndrome using two proposed definitions. *Diabetes Care* 2003; **26**:575–581.
5 Alexander CM, Landsman PB, Teutsch SM, Haffner SM; Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 2003; **52**:1210–1214.
6 Bos G, Dekker JM, Nijpels G, de Vegt F, Diamant M, Stehouwer CD, et al, Hoorn Study. A combination of high concentrations of serum triglyceride and non-high-density-lipoprotein-cholesterol is a risk factor for cardiovascular disease in subjects with abnormal glucose metabolism–the Hoorn Study. *Diabetologia* 2003; **46**:910–916.
7 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* 2004; **109**:42–46.
8 Kannel WB, Neaton JD, Wentworth D, Thomas HE, Stamler J, Hulley SB, Kjelsberg MO. Overall and coronary heart disease mortality rates in relation to major risk factors in 325.348 men screened for the MRFIT: Multiple Risk Factor Intervention Trial. *Am Heart J* 1986; **112**:825–836.
9 Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, *et al.* Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; **24**:683–689.
10 Park Y-M, Shankuan Z, 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.
11 Scott CI. Diagnosis, prevention and intervention for the metabolic syndrome. *Am J Cardiol* 2003; **92** (**Suppl**):35i–42i.
12 Deedwania PC. Metabolic syndrome and vascular disease: is nature or nurture leading the new epidemic of cardiovascular disease? *Circulation* 2004; **109**:2–4.
13 Marroquin OC, Kip KE, Kelley DE, Johnson BD, Shaw LJ, Bairey Merz CN, *et al.* Women's Ischemia Syndrome Evaluation Investigators. 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**:714–721.
14 Isomaa B, Henricsson M, Almgren P, Tuomi T, Taskinen M-R, Groop L. The metabolic syndrome influences the risk of chronic complications in patients with type ii diabetes. *Diabetologia* 2001; **44**:1148–1154.

15 Hueb W, Soares PR, Gersh BJ, Cesar LA, Luz PL, Puig LB, *et al*. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. *J Am Coll Cardiol* 2004; **43**:1743–1751.
16 Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute American Heart Association conference on scientific issues related to definition. *Arterioscler Thromb Vasc Biol* 2004; **24**:e13–e18.
17 Chaitman BR, Ryan TJ, Kronmal RA, Foster ED, Frommer PL, Killip T. Coronary Artery Surgery Study (CASS): comparability of 10 year survival in randomized and randomizable patients. *J Am Coll Cardiol* 1990; **16**:1071–1078.
18 Sculpher MJ, Seed P, Henderson RA. Health service costs of coronary angioplasty and coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. *Lancet* 1994; **344**: 927–930.
19 Serruys PW, Unger F, Sousa JE. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001; **344**:1117–1124.
20 BARI Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996; **335**:217–225.
21 BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *JACC* 2000; **35**:1122–1129.
22 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. *J Am Med Assoc* 2002; **288**:21.
23 Girman CJ, Rhodes TM, Michele P, Kalevi K, John P, Terje R, *et al*. For the 4S group and the afcaps/texcaps research group. The metabolic syndrome and risk of major coronary events in the scandinavian simvastatin survival study (4S) and the air force/texas coronary atherosclerosis prevention study (afcaps/texcaps). *Am J Cardiol* 2004; **93**:136–141.
24 Echahidi N, Pibarot P, Després JP, Daigle JM, Mohty D, Voisine P, *et al*. Metabolic syndrome increases operative mortality in patients undergoing coronary artery bypass grafting surgery. *J Am Coll Cardiol* 2007; **50**:843–851.
25 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* 2003; **107**: 391–397.
26 Schneider DJ. Abnormalities of coagulation, platelet function, and fibrinolysis associated with syndromes of insulin resistance. *Coron Artery Dis* 2005; **16**:473–476.