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Scott M. Grundy, H. Bryan Brewer, Jr, James I. Cleeman, Sidney C. Smith, Jr, Claude Lenfant and for the Conference Participants

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## Definition of Metabolic Syndrome

### Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition

Scott M. Grundy, MD, PhD; H. Bryan Brewer, Jr, MD; James I. Cleeman, MD; Sidney C. Smith, Jr, MD; Claude Lenfant, MD; for the Conference Participants\*

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III)<sup>1</sup> identified the metabolic syndrome as a multiplex risk factor for cardiovascular disease (CVD) that is deserving of more clinical attention. The cardiovascular community has responded with heightened awareness and interest. ATP III criteria for metabolic syndrome differ somewhat from those of other organizations. Consequently, the National Heart, Lung, and Blood Institute, in collaboration with the American Heart Association, convened a conference to examine scientific issues related to definition of the metabolic syndrome. The scientific evidence related to definition was reviewed and considered from several perspectives: (1) major clinical outcomes, (2) metabolic components, (3) pathogenesis, (4) clinical criteria for diagnosis, (5) risk for clinical outcomes, and (6) therapeutic interventions.

#### Clinical Outcomes of Metabolic Syndrome

ATP III viewed CVD as the primary clinical outcome of metabolic syndrome. Most individuals who develop CVD have multiple risk factors. In 1988, Reaven<sup>2</sup> noted that several risk factors (eg, dyslipidemia, hypertension, hyperglycemia) commonly cluster together. This clustering he called *Syndrome X*, and he recognized it as a multiplex risk factor for CVD. Reaven and subsequently others postulated that insulin resistance underlies Syndrome X (hence the commonly used term *insulin resistance syndrome*). Other researchers use the term *metabolic syndrome* for this clustering of metabolic risk factors. ATP III used this alternative term. It avoids the implication that insulin resistance is the primary or only cause of associated risk factors. Although ATP III identified CVD as the primary clinical outcome of the metabolic syndrome, most people with this syndrome have insulin resistance, which confers increased risk for type

2 diabetes. When diabetes becomes clinically apparent, CVD risk rises sharply. Beyond CVD and type 2 diabetes, individuals with metabolic syndrome seemingly are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer.

#### Components of Metabolic Syndrome

ATP III<sup>1</sup> identified 6 components of the metabolic syndrome that relate to CVD:

- Abdominal obesity
- Atherogenic dyslipidemia
- Raised blood pressure
- Insulin resistance  $\pm$  glucose intolerance
- Proinflammatory state
- Prothrombotic state

These components of the metabolic syndrome constitute a particular combination of what ATP III terms *underlying*, *major*, and *emerging* risk factors. According to ATP III, *underlying* risk factors for CVD are obesity (especially abdominal obesity), physical inactivity, and atherogenic diet; the *major* risk factors are cigarette smoking, hypertension, elevated LDL cholesterol, low HDL cholesterol, family history of premature coronary heart disease (CHD), and aging; and the *emerging* risk factors include elevated triglycerides, small LDL particles, insulin resistance, glucose intolerance, proinflammatory state, and prothrombotic state. For present purposes, the latter 5 components are designated *metabolic risk factors*. Each component of the metabolic syndrome will be briefly defined.

- *Abdominal obesity* is the form of obesity most strongly associated with the metabolic syndrome. It presents clinically as increased waist circumference.

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\*Conference Participants: Robert O. Bonow, MD; H. Bryan Brewer, Jr, MD; Robert H. Eckel, MD; Daniel Einhorn, MD; Scott M. Grundy, MD, PhD; Steven M. Haffner, MD; Rury R. Holman, MD; Edward S. Horton, MD; Ronald M. Krauss, MD; Claude Lenfant, MD; Daniel Levy, MD; Xavier Pi-Sunyer, MD; Daniel Porte, Jr, MD; Gerald M. Reaven, MD; Frank M. Sacks, MD; Neil J. Stone, MD; and Peter W.F. Wilson, MD.

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- *Atherogenic dyslipidemia* manifests in routine lipoprotein analysis by raised triglycerides and low concentrations of HDL cholesterol. A more detailed analysis usually reveals other lipoprotein abnormalities, eg, increased remnant lipoproteins, elevated apolipoprotein B, small LDL particles, and small HDL particles. All of these abnormalities have been implicated as being independently atherogenic.
- *Elevated blood pressure* strongly associates with obesity and commonly occurs in insulin-resistant persons. Hypertension thus commonly is listed among metabolic risk factors. However, some investigators believe that hypertension is less “metabolic” than other metabolic-syndrome components. Certainly, hypertension is multifactorial in origin. For example, increasing arterial stiffness contributes significantly to systolic hypertension in the elderly. Even so, most conference participants favored inclusion of elevated blood pressure as one component of the metabolic syndrome.
- *Insulin resistance* is present in the majority of people with the metabolic syndrome. It strongly associates with other metabolic risk factors and correlates univariately with CVD risk. These associations, combined with belief in its priority, account for the term *insulin resistance syndrome*. Even so, mechanisms underlying the link to CVD risk factors are uncertain, hence the ATP III’s classification of insulin resistance as an emerging risk factor. Patients with longstanding insulin resistance frequently manifest *glucose intolerance*, another emerging risk factor. When glucose intolerance evolves into diabetes-level hyperglycemia, elevated glucose constitutes a major, independent risk factor for CVD.
- A *proinflammatory state*, recognized clinically by elevations of C-reactive protein (CRP), is commonly present in persons with metabolic syndrome. Multiple mechanisms seemingly underlie elevations of CRP. One cause is obesity, because excess adipose tissue releases inflammatory cytokines that may elicit higher CRP levels.
- A *prothrombotic state*, characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen, also associates with the metabolic syndrome. Fibrinogen, an acute-phase reactant like CRP, rises in response to a high-cytokine state. Thus, prothrombotic and proinflammatory states may be metabolically interconnected.

### Pathogenesis of Metabolic Syndrome

The metabolic syndrome seems to have 3 potential etiological categories: obesity and disorders of adipose tissue; insulin resistance; and a constellation of independent factors (eg, molecules of hepatic, vascular, and immunologic origin) that mediate specific components of the metabolic syndrome. Other factors—aging, proinflammatory state, and hormonal changes—have been implicated as contributors as well.

### Obesity and Abnormal Body Fat Distribution

ATP III considered the “obesity epidemic” as mainly responsible for the rising prevalence of metabolic syndrome. Obesity contributes to hypertension, high serum cholesterol, low HDL cholesterol, and hyperglycemia, and it otherwise associates with higher CVD risk. Abdominal obesity especially

correlates with metabolic risk factors. Excess adipose tissue releases several products that apparently exacerbate these risk factors. They include nonesterified fatty acids (NEFA), cytokines, PAI-1, and adiponectin. A high plasma NEFA level overloads muscle and liver with lipid, which enhances insulin resistance. High CRP levels accompanying obesity may signify cytokine excess and a proinflammatory state. An elevated PAI-1 contributes to a prothrombotic state, whereas low adiponectin levels that accompany obesity correlate with worsening of metabolic risk factors. The strong connection between obesity (especially abdominal obesity) and risk factors led ATP III to define the metabolic syndrome essentially as a clustering of metabolic complications of obesity.

### Insulin Resistance

A second category of causation is insulin resistance. Many investigators place a greater priority on insulin resistance than on obesity in pathogenesis.<sup>2,3</sup> They argue that insulin resistance, or its accomplice, hyperinsulinemia, directly causes other metabolic risk factors. Identifying a unique role for insulin resistance is complicated by the fact that it is linked to obesity. Insulin resistance generally rises with increasing body fat content, yet a broad range of insulin sensitivities exists at any given level of body fat.<sup>4</sup> Most people with categorical obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) have postprandial hyperinsulinemia and relatively low insulin sensitivity,<sup>5</sup> but variation in insulin sensitivities exists even within the obese population.<sup>4</sup> Overweight persons (BMI 25 to 29.9 kg/m<sup>2</sup>) likewise exhibit a spectrum of insulin sensitivities, suggesting an inherited component to insulin resistance. In some populations (eg, South Asians), insulin resistance occurs commonly even with BMI  $< 25$  kg/m<sup>2</sup> and apparently contributes to a high prevalence of type 2 diabetes and premature CVD. South Asians and others who manifest insulin resistance with only mild-to-moderate overweight can be said to have *primary insulin resistance*. Even with primary insulin resistance, however, weight gain seems to enhance insulin resistance and metabolic syndrome. Thus, dissociation of obesity and primary insulin resistance in patients with metabolic syndrome is difficult.

This is not to say that insulin resistance per se does not play a significant role in causation of metabolic syndrome. When insulin-resistant muscle is already overloaded with lipid from high plasma NEFA levels, some excess NEFA presumably is diverted to the liver, promoting fatty liver and atherogenic dyslipidemia. Hyperinsulinemia may enhance output of very-low-density lipoprotein triglycerides, raising triglycerides. Insulin resistance in muscle predisposes to glucose intolerance, which can be worsened by increased hepatic gluconeogenesis in insulin-resistant liver. Finally, insulin resistance may raise blood pressure by a variety of mechanisms.

### Independent Factors That Mediate Specific Components of the Metabolic Syndrome

Beyond obesity and insulin resistance, each risk factor of the metabolic syndrome is subject to its own regulation through both genetic and acquired factors. This leads to variability in expression of risk factors. Lipoprotein metabolism, for instance, is richly modulated by genetic variation; hence,

**TABLE 1. ATP III Clinical Identification of the Metabolic Syndrome**

Risk Factor	Defining Level
Abdominal obesity, given as waist circumference*†	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL‡

\*Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated BMI. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

†Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, eg, 94 to 102 cm (37 to 39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

‡The American Diabetes Association has recently established a cutpoint of ≥100 mg/dL, above which persons have either prediabetes (impaired fasting glucose) or diabetes.<sup>14</sup> This new cutpoint should be applicable for identifying the lower boundary to define an elevated glucose as one criterion for the metabolic syndrome.

expression of dyslipidemias in response to obesity and/or insulin resistance varies considerably. The same holds for blood pressure regulation. Moreover, glucose levels depend on insulin-secretory capacity as well as insulin sensitivity. This variation in distal regulation cannot be ignored as an important factor in causation of metabolic syndrome.

**Other Contributing Factors**

Advancing age probably affects all levels of pathogenesis, which likely explains why prevalence of the metabolic syndrome rises with advancing age.<sup>6</sup> Recently, a *proinflammatory state* has been implicated directly in causation of insulin resistance, as well as atherogenesis. Finally, several *endocrine factors* have been linked to abnormalities in body-fat distribution and hence indirectly to metabolic syndrome. Thus, pathogenesis of the metabolic syndrome is complex and ripe with opportunities for further research.

**Criteria for Clinical Diagnosis of Metabolic Syndrome**

At least 3 organizations have recommended clinical criteria for the diagnosis of the metabolic syndrome.<sup>1,7-9</sup> Their criteria are similar in many aspects, but they also reveal fundamental differences in positioning of the predominant causes of the syndrome. Each will be reviewed briefly.

**ATP III**

Criteria of ATP III<sup>1</sup> are shown in Table 1. When 3 of 5 of the listed characteristics are present, a diagnosis of metabolic syndrome can be made. The primary clinical outcome of metabolic syndrome was identified as CHD/CVD. Abdomi-

**TABLE 2. WHO Clinical Criteria for Metabolic Syndrome\***

Insulin resistance, identified by 1 of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:

- Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
- Plasma triglycerides ≥150 mg/dL (≥1.7 mmol/L)
- HDL cholesterol <35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women
- BMI >30 kg/m<sup>2</sup> and/or waist:hip ratio >0.9 in men, >0.85 in women
- Urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g

\*Derived from Alberti et al.<sup>7,8</sup>

nal obesity, recognized by increased waist circumference, is the first criterion listed. Its inclusion reflects the priority given to abdominal obesity as a contributor to metabolic syndrome. Also listed are raised triglycerides, reduced HDL cholesterol, elevated blood pressure, and raised plasma glucose. Cutpoints for several of these are less stringent than usually required to identify a categorical risk factor, because multiple marginal risk factors can impart significantly increased risk for CVD. Explicit demonstration of insulin resistance is not required for diagnosis; however, most persons meeting ATP III criteria will be insulin resistant. Finally, the presence of type 2 diabetes does not exclude a diagnosis of metabolic syndrome.

**World Health Organization**

In 1998, a World Health Organization (WHO) consultation group outlined a provisional classification of diabetes that included a working definition of the metabolic syndrome.<sup>7</sup> This report was finalized in 1999 and placed on the WHO website<sup>8</sup> (see Table 2). The guideline group also recognized CVD as the primary outcome of the metabolic syndrome. However, it viewed insulin resistance as a required component for diagnosis. Insulin resistance was defined as 1 of the following: type 2 diabetes; impaired fasting glucose (IFG); impaired glucose tolerance (IGT), or for those with normal fasting glucose values (<110 mg/dL), a glucose uptake below the lowest quartile for background population under hyperinsulinemic, euglycemic conditions. In addition to insulin resistance, 2 other risk factors are sufficient for a diagnosis of metabolic syndrome. A higher blood pressure was required than in ATP III. BMI (or increased waist:hip ratio) was used instead of waist circumference, and microalbuminuria was listed as one criterion. The requirement of objective evidence of insulin resistance should give more power to predict diabetes than does ATP III, but like ATP III, the presence of type 2 diabetes does not exclude a diagnosis of metabolic syndrome. A potential disadvantage of the WHO criteria is that special testing of glucose status beyond routine clinical

**TABLE 3. AACE Clinical Criteria for Diagnosis of the Insulin Resistance Syndrome\***

Risk Factor Components	Cutpoints for Abnormality
Overweight/obesity	BMI $\geq$ 25 kg/m <sup>2</sup>
Elevated triglycerides	$\geq$ 150 mg/dL (1.69 mmol/L)
Low HDL cholesterol	
Men	<40 mg/dL (1.04 mmol/L)
Women	<50 mg/dL (1.29 mmol/L)
Elevated blood pressure	$\geq$ 130/85 mm Hg
2-Hour postglucose challenge	>140 mg/dL
Fasting glucose	Between 110 and 126 mg/dL
Other risk factors	Family history of type 2 diabetes, hypertension, or CVD Polycystic ovary syndrome Sedentary lifestyle Advancing age Ethnic groups having high risk for type 2 diabetes or CVD

\*Diagnosis depends on clinical judgment based on risk factors.

assessment may be necessary to diagnose metabolic syndrome.

### American Association of Clinical Endocrinologists

The American Association of Clinical Endocrinologists (AACE)<sup>9</sup> proposes a third set of clinical criteria for the *insulin resistance syndrome* (Table 3). These criteria appear to be a hybrid of those of ATP III and WHO metabolic syndrome. However, no defined number of risk factors is specified; diagnosis is left to clinical judgment. When a person develops categorical diabetes, the term *insulin resistance syndrome* no longer applies. In patients without IFG, a 2-hour postglucose challenge is recommended when an abnormality is clinically suspected. Finding abnormal 2-hour glucose will improve prediction of type 2 diabetes.

### Issue of Oral Glucose Tolerance Test

Both WHO and AACE include IGT, detected by oral glucose tolerance test (OGTT) or 2-hour postglucose challenge, among the risk factors for metabolic syndrome. ATP III did not include it because of the added inconvenience and cost of OGTT in clinical practice. Its added value for CVD risk prediction appears small. However, several conference participants suggested adding OGTT at the physician's discretion in nondiabetic patients with ATP III-defined metabolic syndrome or  $\geq$ 2 metabolic risk factors (Table 1). Several potential benefits were noted. First, in the absence of IFG, IGT could count as one metabolic risk factor defining metabolic syndrome. If IGT were to be added to ATP III criteria, metabolic syndrome prevalence over age 50 years would increase by  $\approx$ 5% (Table 4). Second, IGT carries increased risk for type 2 diabetes. Third, postprandial hyperglycemia in a patient with IFG denotes diabetes, a high-risk condition for CVD.

### Metabolic Syndrome as a Risk Condition

It seems self-evident that a condition characterized by multiple risk factors will carry a greater risk for adverse clinical

outcomes than will a single risk factor. This conclusion is implicit in Framingham risk equations, which incorporate many of the components of the metabolic syndrome. For this conference, Framingham investigators examined their extensive database for the relation between metabolic syndrome and future development of both CVD and diabetes. Their analysis was carried out on 3323 Framingham offspring men and women (mean age, 52 years) in 8 years of follow-up.

### Metabolic Syndrome as a Predictor of CVD

Individuals with metabolic syndrome are at increased risk for CHD.<sup>10</sup> In Framingham, the metabolic syndrome alone predicted  $\approx$ 25% of all new-onset CVD. In the absence of diabetes, the metabolic syndrome generally did not raise 10-year risk for CHD to  $>$ 20%; this is the threshold for ATP III's CHD risk equivalent. Ten-year risk in men with metabolic syndrome generally ranged from 10% to 20%. Framingham women with metabolic syndrome had relatively few CHD events during the course of the 8-year follow-up; this was due in part to the high proportion of women who were under 50 years of age. Although the metabolic syndrome in these women appeared to be accompanied by higher risk for CVD/CHD, the confidence interval was wide, and differences between those with and without metabolic syndrome were not statistically significant. Of note, the 10-year risk for CHD in most women in this relatively young cohort did not exceed 10%.

Framingham investigators then examined whether the metabolic syndrome carries incremental risk beyond the usual risk factors of the Framingham algorithm. Analyses were carried out both including and excluding patients with diabetes. Several models were tested. Results were compared as *C* statistics. The *C* statistic is the probability that the model used will place a person in the right order, giving the higher probability to the one who develops the disease than to the one who does not. Some investigators consider this approach to have limitations, particularly because of the high contribution of age alone to the *C* statistic. Nonetheless, this is a standard method for evaluating the power of adding new risk factors to multiple-risk factor equations. Various models were tested. These included (1) the standard Framingham algorithm,<sup>11</sup> (2) ATP III metabolic syndrome risk factors alone, (3) metabolic syndrome risk factors + age, (4) usual Framingham risk factors + unique metabolic syndrome risk factors (obesity, triglycerides, glucose), and (5) usual Framingham risk factors + metabolic syndrome as a single variable. When usual risk factors and unique metabolic syndrome risk factors were combined, either on a continuous or categorical basis, the reliability of prediction (*C* statistic) increased only marginally. The results of this analysis indicated that no advantage is gained in risk assessment by adding the unique risk factors of the ATP III metabolic syndrome to the usual Framingham risk factors in risk assessment. It is likely that most of the risk associated with the metabolic syndrome is captured by age, blood pressure, total cholesterol, diabetes, and HDL cholesterol. Beyond these, obesity, triglycerides, and glucose levels (in the absence of diabetes) provided little additional power of prediction. Repetition of the analysis including patients with diabetes had little impact on the *C* statistic. Serum CRP possibly

**TABLE 4. Impact on Prevalence of Metabolic Syndrome if Impaired Glucose Tolerance Plus 2 or More Risk Factors Is Added to the National Cholesterol Education Program Definition\***

Demographic Characteristics	% Meeting Current National Cholesterol Education Program Definition	% Meeting Revised Definition
Overall	37.9	43.5
Race/ethnicity		
Non-Hispanic white	38.2	43.6
Non-Hispanic black	34.6	38.9
Mexican American	43.5	53.4
Other	35.9	43.1
Age group, y		
50–59	30.6	36.5
60–69	41.5	48.1
70–79	42.6	48.4
80+	43.3	43.3

\*Data derived from NHANES III. Data analysis provided by Dr Steven Haffner.

has independent predictive power beyond usual risk factors and/or metabolic syndrome; however, the absolute increment in risk associated with elevated CRP has not been adequately tested.

### Metabolic Syndrome as a Predictor of Diabetes

When the risk for new-onset diabetes was examined for the Framingham cohort, in both men and women, the presence of metabolic syndrome was highly predictive of new-onset diabetes. Almost half of the population-attributable risk for diabetes could be explained by the presence of ATP III metabolic syndrome.

### Diabetes as a Predictor of CVD

Framingham data showed that most men with diabetes had a 10-year risk for CHD >20%; in contrast, women rarely exceeded the 20% level. Some authorities believe that improved risk assessment in individuals with diabetes would be clinically useful in risk management. Oxford investigators therefore have developed a risk engine (available on the World Wide Web)<sup>12</sup> based on the large UK Prospective Diabetes Study (UKPDS) database, which had >500 hard CHD events. It differs from the Framingham algorithm in that it includes a measure of glycemia and duration of diabetes. Surveys of other diabetic populations by UKPDS investigators found that Framingham equations considerably underestimate risk for CHD and stroke, whereas the UKPDS Risk Engine provides a more robust estimate.

## Therapeutic Implications

### Obesity and Body Fat Distribution as Targets of Therapy

ATP III recommended that obesity be the primary target of intervention for metabolic syndrome. First-line therapy should be weight reduction reinforced with increased physical activity. Weight loss lowers serum cholesterol and triglycerides, raises HDL cholesterol, lowers blood pressure and

glucose, and reduces insulin resistance. Recent data further show that weight reduction can decrease serum levels of CRP and PAI-1. Most conference participants held that obesity contributes significantly to development of the metabolic syndrome in the general population. They further acknowledged that clinical management should focus first on lifestyle changes—particularly weight reduction and increased exercise. Even participants who emphasized the role of insulin resistance in the pathogenesis of the metabolic syndrome acknowledged that therapeutic lifestyle changes deserve priority. Some participants questioned whether such changes could successfully be implemented in clinical practice. Still, the potential for benefit certainly exists; implementation is the challenge.

### Insulin Resistance as Target of Therapy

If insulin resistance, whether primary or secondary to obesity, is in the chain of causation of metabolic syndrome, it would be an attractive target. Certainly, weight reduction and increased physical activity will reduce insulin resistance. Insulin resistance as a target has caught the imagination of the pharmaceutical industry, and drug discovery is underway. Two classes of drugs are currently available that reduce insulin resistance. These are metformin and insulin sensitizers such as thiazolidinediones (TZDs).

Metformin has long been used for treatment of type 2 diabetes. In UKPDS, metformin apparently reduced new-onset CHD in obese patients with diabetes. In the Diabetes Prevention Program, metformin therapy prevented (or delayed) onset of type 2 diabetes in persons with IGT. There are, however, no CVD end-point studies on metformin-treated patients with metabolic syndrome. Thus, at present, metformin cannot be recommended for the express purpose of reducing risk for CVD in persons with the metabolic syndrome.

TZDs currently are approved for treatment of type 2 diabetes. They reduce insulin resistance, favorably modify several metabolic risk factors, and reverse abnormal arterial responses. Nonetheless, no clinical trial data yet exist to document benefit in CVD risk reduction. Thus, in spite of promise, TZDs cannot be recommended at present for preventing CVD in patients with either metabolic syndrome or diabetes.

### Specific Metabolic Risk Factors as Targets of Therapy

#### Atherogenic Dyslipidemia

Although statins typically are recognized to be LDL-lowering drugs, they reduce all apolipoprotein B-containing lipoproteins. Recent subgroup analyses of statin trials reveal that statins reduce risk for CVD events in patients with metabolic syndrome. Fibrates also favorably modify atherogenic dyslipidemia and may directly reduce atherogenesis. Post hoc analysis of recent fibrate trials strongly suggests that they reduce CVD end points in patients with atherogenic dyslipidemia and metabolic syndrome.<sup>13</sup> Moreover, clinical studies demonstrate that abnormal lipoprotein patterns are doubly improved by combined statin-fibrate therapy, but just how

much this combination reduces CVD events beyond statins alone awaits demonstration with controlled clinical trials.

#### **Elevated Blood Pressure**

There is full agreement that hypertensive patients with metabolic syndrome deserve lifestyle therapies to reduce blood pressure. In addition, antihypertensive drugs should be used as recommended by hypertension guidelines. No class of antihypertensive drugs has been identified as being uniquely efficacious in patients with metabolic syndrome.

#### **Prothrombotic State**

No drugs are available that target PAI-1 and fibrinogen. An alternative approach to the prothrombotic state is antiplatelet therapy. For example, low-dose aspirin reduces CVD events in both secondary and primary prevention. Thus, use of aspirin for primary prevention in patients with metabolic syndrome is promising. According to current recommendations, low-dose aspirin therapy has a favorable efficacy/side effect ratio when 10-year risk for CHD is  $\geq 10\%$ .

#### **Proinflammatory State**

There is growing interest in development of drugs to dampen the proinflammatory state. Several lipid-lowering drugs will reduce CRP levels, which could reflect an antiinflammatory action.

#### **Hyperglycemia**

When patients with metabolic syndrome develop type 2 diabetes, they are at high risk for CVD. All CVD risk factors should be intensively reduced. In addition, glucose levels should be appropriately treated with lifestyle therapies and hypoglycemic agents as needed to keep hemoglobin A1c levels below guideline targets.

### **Conclusions**

Conference participants agreed that CVD is the primary clinical outcome of metabolic syndrome. Additionally, risk for type 2 diabetes is higher, and diabetes is a major risk factor for CVD. ATP III criteria provide a practical tool to identify patients at increased risk for CVD. WHO and AACE criteria require further oral glucose testing if IFG and diabetes are absent. IGT on OGTT denotes greater risk for diabetes than does metabolic syndrome without elevated fasting glucose. Several potential benefits make OGTT in such patients an attractive option for use at the discretion of the physician. First, in the absence of IFG, IGT could count as one metabolic risk factor defining metabolic syndrome, besides carrying increased risk for type 2 diabetes. Moreover, postprandial hyperglycemia in a patient with IFG denotes diabetes, a high-risk condition for CVD.

Regardless of diagnostic criteria used, there is full agreement that therapeutic lifestyle change, with emphasis on weight reduction, constitutes first-line therapy for metabolic syndrome. Drug treatment to directly reduce insulin resistance is promising, but clinical trials to prove reduction of CVD are lacking. In patients in whom lifestyle changes fail to reverse metabolic risk factors, consideration should be given to treating specific abnormalities in these risk factors with drugs. Use of drugs to target risk factors should be in accord with current treatment guidelines.

### **References**

1. 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). Final report. *Circulation*. 2002;106:3143–3421.
2. Reaven GM. Banting lecture 1988: role of insulin resistance in human disease. *Diabetes*. 1988;37:1595–1607.
3. Ferrannini E, Haffner SM, Mitchell BD, et al. Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia*. 1991; 34:416–422.
4. Abbasi F, Brown BW, Lamendola C, et al. Relationship between obesity, insulin resistance, and coronary heart disease risk. *J Am Coll Cardiol*. 2002;40:937–943.
5. Bogardus C, Lillioja S, Mott DM, et al. Relationship between degree of obesity and in vivo insulin action in man. *Am J Physiol*. 1985;248(3 pt 1):e286–e291.
6. 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;287:356–359.
7. 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;15:539–553.
8. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO Consultation. Part 1: diagnosis and classification of diabetes mellitus. Geneva, Switzerland: World Health Organization; 1999. Available at: [http://whqlibdoc.who.int/hq/1999/WHO\\_NCD\\_NCS\\_99.2.pdf](http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf). Accessed December 12, 2003.
9. Einhorn D, Reaven GM, Cobin RH, et al. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract*. 2003;9:237–252.
10. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288:2709–2716.
11. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.
12. The Oxford Centre for Diabetes, Endocrinology, and Metabolism Diabetes Trials Unit. UKPDS Risk Engine. Available at: <http://www.dtu.ox.ac.uk/riskengine>. Accessed December 12, 2003.
13. Rubins HB. Triglycerides and coronary heart disease: implications of recent clinical trials. *J Cardiovasc Risk*. 2000;7:339–345.
14. Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2003;26:3160–3167.

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