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AHA/NHLBI Scientific Statement

Diagnosis and Management of the Metabolic Syndrome

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The metabolic syndrome has received increased attention in the past few years. This statement from the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) is intended to provide up-to-date guidance for professionals on the diagnosis and management of the metabolic syndrome in adults.

The metabolic syndrome is a constellation of interrelated risk factors of metabolic origin—*metabolic risk factors*—that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD).[1] Patients with the metabolic syndrome also are at increased risk for developing type 2 diabetes mellitus. Another set of conditions, the *underlying risk factors*, give rise to the metabolic risk factors. In the past few years, several expert groups have attempted to set forth simple diagnostic criteria to be used in clinical practice to identify patients who manifest the multiple components of the metabolic syndrome. These criteria have varied somewhat in specific elements, but in general they include a combination of both underlying and metabolic risk factors.

The most widely recognized of the metabolic risk factors are atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose. Individuals with these characteristics commonly manifest a prothrombotic state and a proinflammatory state as well. Atherogenic dyslipidemia consists of an aggregation of lipoprotein abnormalities including elevated serum triglyceride and apolipoprotein B (apoB), increased small LDL particles, and a reduced level of HDL cholesterol (HDL-C). The metabolic syndrome is often referred to as if it were a discrete entity with a single cause. Available data suggest that it truly is a syndrome, ie, a grouping of ASCVD risk factors, but one that probably has more than one cause. Regardless of cause, the syndrome identifies individuals at an elevated risk for ASCVD. The magnitude of the increased risk can vary according to which components of the syndrome are present plus the other, non–metabolic syndrome risk factors in a particular person.

Underlying Risk Factors and Metabolic Syndrome

The predominant underlying risk factors for the syndrome appear to be abdominal obesity[2–4] and insulin resistance[5,6]; other associated conditions can be physical inactivity,[3,7] aging,[8] and hormonal imbalance.[9] An atherogenic diet (eg, a diet rich in saturated fat and cholesterol) can enhance risk for developing cardiovascular disease in people with the syndrome, although this diet is not listed specifically as an underlying risk factor for the condition.[1] One theory holds that insulin resistance is the essential cause of the metabolic syndrome.[10] There is no doubt that insulin resistance predisposes to the hyperglycemia of type 2 diabetes mellitus. Multiple metabolic pathways have also been proposed to link insulin resistance and compensatory hyperinsulinemia to the other metabolic risk factors.[10,11] It is recognized that some people who are not obese by traditional measures nevertheless are insulin resistant and have abnormal levels of metabolic risk factors. Examples are seen in individuals with 2 diabetic parents or 1 parent and a first- or second-degree relative[12]; the same is true for many individuals of South Asian ethnicity.[13,14] Although insulin-resistant individuals need not be clinically obese, they nevertheless commonly have an abnormal fat distribution that is characterized by predominant upper body fat. Upper-body obesity correlates

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strongly with insulin resistance. Excess upper body fat can accumulate either intraperitoneally (visceral fat) or subcutaneously. Many investigators claim that excess visceral fat is more strongly associated with insulin resistance than any other adipose tissue compartment[4,15–21]; other workers find that excess subcutaneous abdominal (or truncal) fat also carries a significant association with insulin resistance.[22–27] Regardless of the relative contributions of visceral fat and abdominal subcutaneous fat to insulin resistance, a pattern of abdominal (or upper-body) obesity correlates more strongly with insulin resistance and the metabolic syndrome than does lower-body obesity.[28] An interesting feature of upper-body obesity is an unusually high release of nonesterified fatty acids from adipose tissue[12,14,28]; this contributes to accumulation of lipid in sites other than adipose tissue. Ectopic lipid accumulation in muscle and liver seemingly predisposes to insulin resistance[29] and dyslipidemia.[30]

According to many experts, the increasing burden of obesity in the United States is the driving force behind the rising prevalence of the metabolic syndrome.[1–4,31,32] This view needs to be harmonized with the insulin resistance hypothesis. Abnormalities in adipose tissue metabolism may be the crux of the issue. Adipose tissue in obese people is insulin resistant, which raises nonesterified fatty acid levels, worsening insulin resistance in muscle[29,33] and altering hepatic metabolism[31]; in addition, the adipose tissue of obesity exhibits abnormalities in the production of several adipokines that may separately affect insulin resistance and/or modify risk for ASCVD.[34] These include increased production of inflammatory cytokines,[35,36] plasminogen activator inhibitor-1,[37] and other bioactive products[38–40]; at the same time the potentially protective adipokine, adiponectin, is reduced.[41,42] All of these changes have been implicated as causes of the metabolic risk factors. Indeed, as mentioned before, some individuals exhibit the metabolic syndrome with only a moderate degree of total body obesity.[43,44] Notable are many South Asians who appear to be inherently insulin resistant,[45] a condition that is exacerbated by mild abdominal obesity.[14] Moreover, the population of the United States varies considerably in degree of insulin resistance[46]; those having more inherent insulin resistance can develop the metabolic syndrome with only moderate excess in abdominal fat,[43,44] but even people with little or no inherent insulin resistance can develop the metabolic syndrome if they accumulate marked abdominal obesity.[3,8] These findings support the idea that body fat distribution, particularly excess abdominal fat, plays an important role in the etiology of the syndrome.

Recently, this syndrome has been noted to be associated with a state of chronic, low-grade inflammation.[47,48] Some researchers speculate that inflammation of this type underlies or exacerbates the syndrome. For example, inflammatory cytokines reportedly induce insulin resistance in both adipose tissue and muscle.[48–51] In the presence of obesity, adipose tissue indeed produces cytokines in excess, whereas output of adiponectin is diminished; these responses appear to heighten the connection between obesity and inflammation.[35] Interestingly, insulin-resistant people manifest evidence of low-grade inflammation even without an increase of total body fat.[52]

Finally, considerable individual and ethnic variation exists in the clinical pattern of metabolic risk factors in obese/insulin-resistant subjects.[53,54] It is likely that the expression of each metabolic risk factor falls partially under its own genetic control, which influences the response to different environmental exposures. For example, a variety of polymorphisms in genes affecting lipoprotein metabolism are associated with worsening of dyslipidemia in obese people.[55,56] Similarly, a genetic predisposition to defective insulin secretion when combined with insulin resistance can raise plasma glucose to abnormal levels.[57]

Although the metabolic syndrome unequivocally predisposes to type 2 diabetes mellitus,[48,58–62] many investigators of cardiovascular diseases consider this syndrome to be a multidimensional risk factor for ASCVD.[1,58] Several recent reports show that the metabolic syndrome is associated with greater risk for cardiovascular disease,[63–73] but once type 2 diabetes mellitus emerges, cardiovascular risk increases even more.[74] Finally, insulin resistance and the metabolic syndrome are associated with a variety of other conditions[75–77]; some of these are fatty liver,[30,78] polycystic ovary syndrome,[79] cholesterol gallstones,[80] sleep apnea,[81] lipodystrophies,[82] and protease-inhibitor therapy for HIV.[83] These associations are generating considerable interest in several other fields of medicine.

Metabolic Risk Factors, ASCVD, and Type 2 Diabetes Mellitus

The metabolic risk factors consist of those factors that seemingly have a direct effect on atherosclerotic disease. Among these, as stated earlier, *atherogenic dyslipidemia* consists of an aggregation of lipoprotein abnormalities including elevated serum triglyceride and apoB, increased small LDL particles, and a reduced level of HDL-C.[1] Among triglyceride-rich lipoproteins, remnant lipoproteins almost certainly are the most atherogenic.[1] Many studies further suggest that the smallest particles in the LDL fraction carry the greatest atherogenicity.[84] The atherogenic potential of lipoprotein remnants and small LDL could be confounded in part by their common association with an increased total number of apoB-containing lipoproteins in circulation; this increased number is reflected by an elevation of serum total apoB.[85–89] Finally, the lipoprotein field widely holds that low levels of HDL are independently atherogenic[1]; multiple mechanisms are implicated to explain this relationship.[90]

Other metabolic risk factors likewise appear individually to be atherogenic. Among these are *hypertension, elevated plasma glucose,* a *prothrombotic state,* and a *proinflammatory state*. Indeed, 3 of the metabolic risk factors—elevated apoB-containing lipoproteins,[1] low HDL-C levels,[1] and hypertension[91]—are well established, major risk factors. Each imparts increased risk even when only marginally abnormal, as often observed in the metabolic syndrome. A growing body of data additionally implicates high circulating levels of prothrombotic factors in the causation of ASCVD events, possibly by predisposing to thrombotic episodes.[92–94] Many reports also show that the presence of a proinflammatory state, as revealed by increased inflammatory markers,[95,96] denotes a higher risk for acute cardiovascular syndromes.

TABLE 1. Previous Criteria Proposed for Clinical Diagnosis of Metabolic Syndrome

Clinical Measure	WHO (1998)	EGIR	ATP III (2001)	AACE (2003)	IDF (2005)
Insulin resistance	IGT, IFG, T2DM, or lowered insulin sensitivity* **plus any 2 of the following**	Plasma insulin >75th percentile **plus any 2 of the following**	None, **but any 3 of the following 5 features**	IGT or IFG **plus any of the following based on clinical judgment**	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m^2	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women†	BMI ≥25 kg/m^2	Increased WC (population specific) **plus any 2 of the following**
Lipid	TG ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TG ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL or on TG Rx HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)‡	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)
Other	Microalbuminuria			Other features of insulin resistance§	

T2DM indicates type 2 diabetes mellitus; WC, waist circumference; BMI, body mass index; and TG, triglycerides. All other abbreviations as in text.

*Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

†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 lifestyle habits, similar to men with categorical increases in waist circumference.

‡The 2001 definition identified fasting plasma glucose of ≥110 mg/dL (6.1 mmol/L) as elevated. This was modified in 2004 to be ≥100 mg/dL (5.6 mmol/L), in accordance with the American Diabetes Association's updated definition of IFG.[46,47,77]

§Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus.

Finally, a variety of mechanisms to explain how elevated plasma glucose may promote atherosclerosis are postulated.[97] Regardless, once type 2 diabetes mellitus compounds the metabolic syndrome, risk for ASCVD events increases still more.

Clinical Diagnosis of Metabolic Syndrome

Many investigations confirm that multiple cardiovascular risk factors of endogenous origin commonly aggregate in one individual. Although this aggregation was originally observed many years ago,[98,99] more recently, several terms have been proposed to describe this clustering: metabolic syndrome,[100] syndrome X,[101] the "deadly quartet,"[102] insulin-resistance syndrome,[103,104] and hypertriglyceridemic waist.[105] The term *metabolic syndrome* is most commonly used in the cardiovascular field. Although the metabolic syndrome is often referred to as a discrete entity, it is important to recognize, as noted earlier, that it is a *syndrome* and not a defined uniform entity. No single pathogenesis has been elucidated, nor may one exist. Thus, the syndrome could range from a cluster of unrelated risk factors to a constellation of risk factors linked through a common underlying mechanism. From a clinical standpoint, presence of the metabolic syndrome identifies a person at increased risk for ASCVD and/or type 2 diabetes mellitus. Eventually, a better understanding of the specific cause(s) of the syndrome may provide an improved estimate of risk of developing ASCVD or type 2 diabetes mellitus for individuals. For now, however, the presence of the syndrome is a more general indicator of higher risk for these conditions. Because of a documented high relative risk for ASCVD events and type 2 diabetes mellitus, the metabolic syndrome undoubtedly carries a relatively high lifetime risk for these disorders even when shorter-term (10-year) risk is in the low-to-moderate range.[63–73]

In the effort to introduce the metabolic syndrome into clinical practice, several organizations have attempted to formulate simple criteria for its diagnosis (Table 1). The first proposal came in 1998 from a consultation group on the definition of diabetes for the World Health Organization (WHO).[106] This group emphasized insulin resistance as the major underlying risk factor and required evidence of insulin resistance for diagnosis. This followed on the widely held belief that insulin resistance is the primary cause of the syndrome. A diagnosis of the syndrome by WHO criteria could thus be made when a patient exhibited one of several markers of insulin resistance plus 2 additional risk factors. Although insulin resistance is difficult to measure directly in a clinical setting, several types of indirect evidence were accepted, ie, impaired glucose intolerance [IGT], impaired fasting glucose [IFG], type 2 diabetes mellitus, or impaired disposal of glucose under hyperinsulinemic, euglycemic conditions. The other risk factors used for diagnosis included obesity, hypertension, high triglycerides, reduced HDL-C level, or microalbuminuria. The consultation group suggested categorical cutpoints to define each of these factors. Importantly, the WHO group allowed the term *metabolic syndrome* to be used in patients with type 2 diabetes mellitus who otherwise met the requirements for the syndrome. They reasoned that patients with type 2 diabetes mellitus often have a clustering of ASCVD risk factors, which puts them at particularly high risk for ASCVD.[69,70]

In 1999, the European Group for Study of Insulin Resistance (EGIR) proposed a modification of the WHO definition.[107] This group used the term *insulin resistance syndrome*

rather than metabolic syndrome. They likewise assumed that insulin resistance is the major cause and required evidence of it for diagnosis. By their criteria, plasma insulin levels in the upper quartile of the population defined insulin resistance. An elevated plasma insulin plus 2 other factors—abdominal obesity, hypertension, elevated triglycerides or reduced HDL-C, and elevated plasma glucose—constituted a diagnosis of the insulin-resistance syndrome. Notably, EGIR focused more on abdominal obesity than did WHO, but in contrast to WHO, EGIR excluded patients with type 2 diabetes mellitus from their syndrome because insulin resistance was viewed primarily as a risk factor for diabetes.

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) introduced alternative clinical criteria for defining the metabolic syndrome.[1] In so doing, the purpose of ATP III was to identify people at higher long-term risk for ASCVD who deserved clinical lifestyle intervention to reduce risk. The ATP III criteria did not require demonstration of insulin resistance per se. It was noted that direct measures of insulin resistance are laborious and not well standardized. Moreover, less-specific measures, such as glucose tolerance tests, are not routinely used in clinical practice. Although the ATP III panel recognized the phenomenon of clustering of metabolic risk factors, it did not draw conclusions on mechanistic pathogenesis. The ATP III criteria thus required no single factor for diagnosis, but instead made the presence of 3 of 5 factors the basis for establishing the diagnosis; these were abdominal obesity (also highly correlated with insulin resistance), elevated triglycerides, reduced HDL-C, elevated blood pressure, and elevated fasting glucose (IFG or type 2 diabetes mellitus).

Although ATP III did not make any single risk factor (eg, abdominal obesity) a requirement for diagnosis, it nonetheless espoused the position that abdominal obesity is an important underlying risk factor for the syndrome. Its cutpoints for abdominal obesity came from the definition in the 1998 National Institutes of Health obesity clinical guidelines[108]; they were a waist circumference of ≥102 cm (≥40 in) for men and ≥88 cm (≥35 in) for women. These cutpoints identify approximately the upper quartile of the US population. Abdominal obesity at these cutpoints was not made a prerequisite for diagnosis because lesser degrees of abdominal girth often associate with other ATP III criteria. In fact, some individuals or ethnic groups (eg, Asians, especially South Asians) appear to be susceptible to development of the metabolic syndrome at waist circumferences below ATP III cutpoints. Thus, ATP III specifically noted that some individuals having only 2 other metabolic syndrome criteria appear to be insulin resistant even when the waist circumference is only marginally elevated, eg, 94 to 101 cm in men or 80 to 87 cm in women. If so, they should benefit from clinical intervention similarly to many others who have greater increases in waist circumference, ie, ≥102 cm (≥40 in) for men and ≥88 cm (≥35 in) for women. ATP III, like WHO, allowed for a diagnosis of metabolic syndrome in the presence of type 2 diabetes because of the high risk for ASCVD among multiple-risk factor patients with diabetes. When type 2 diabetes mellitus is present, concomitant metabolic risk factors must not be overlooked because of strong evidence that intervention on them can substantially reduce risk for ASCVD.

In 2003, the American Association of Clinical Endocrinologists (AACE) modified ATP III criteria to refocus on insulin resistance as the primary cause of metabolic risk factors.[109] Like the EGIR,[107] they used the name *insulin resistance syndrome*. Major criteria were IGT, elevated triglycerides, reduced HDL-C, elevated blood pressure, and obesity. No specified number of factors qualified for diagnosis, which was left to clinical judgment. Other factors used to inform clinical judgment were a family history of ASCVD or type 2 diabetes mellitus, polycystic ovary syndrome, and hyperuricemia. By the AACE's definition, once a person develops type 2 diabetes mellitus, the term insulin resistance syndrome no longer applies.

In 2005, the International Diabetes Foundation (IDF) published new criteria that again modified the ATP III definition.[110] The IDF writing group included several members of the original WHO consultation group. They liked the ATP III definition because of its clinical simplicity. They furthermore considered that abdominal obesity is so highly correlated with insulin resistance that other, more laborious measures of insulin resistance are unnecessary. The IDF clinical definition thus makes the presence of abdominal obesity necessary for diagnosis. When such is present, 2 additional factors originally listed in the ATP III definition are sufficient for diagnosis. IDF recognized and emphasized ethnic differences in the correlation between abdominal obesity and other metabolic syndrome risk factors. For this reason, criteria of abdominal obesity were specified by nationality or ethnicity based on best available population estimates. For people of European origin (Europid), the IDF specified thresholds for abdominal obesity to be waist circumferences ≥94 cm in men and ≥80 cm in women. These thresholds apply to Europids living in the Americas as well as Europe. For Asian populations, except for Japan, thresholds were ≥90 cm in men and ≥80 cm in women; for Japanese they were ≥85 cm for men and ≥90 cm for women.

The present AHA/NHLBI statement, in contrast to IDF, maintains the ATP III criteria except for minor modifications (Table 2). This decision is based on the conclusion that ATP III criteria are simple to use in a clinical setting and have the advantage of avoiding emphasis on a single cause. No compelling reasons were found for making a change. In addition, a large number of studies have been carried out to evaluate the ATP III criteria for the metabolic syndrome.[35,111–133] The majority of these reports are supportive of the present structure of ATP III criteria. It must be noted in Table 2, however, that the threshold for IFG was reduced from 110 to 100 mg/dL; this adjustment corresponds to the recently modified American Diabetes Association (ADA) criteria for IFG.[134] Otherwise, the statement maintains that continuity with the original ATP III definition, which has been widely adopted in the United States and elsewhere, is appropriate in the absence of new evidence to the contrary.

Present diagnostic criteria thus accord with ATP III by defining abdominal obesity as a waist circumference of ≥102 cm (≥40 in) for men and ≥88 cm (≥35 in) for women. As noted in ATP III,[1] some people will manifest features of

TABLE 2. Criteria for Clinical Diagnosis of Metabolic Syndrome

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Categorical Cutpoints
Elevated waist circumference*†	≥102 cm in men ≥88 cm in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or On drug treatment for elevated triglycerides‡
Reduced HDL-C	<40 mg/dL (0.9 mmol/L) in men <50 mg/dL (1.1 mmol/L) in women or On drug treatment for reduced HDL-C‡
Elevated blood pressure	≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL or On drug treatment for elevated glucose

*To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration.

†Some US adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94–102 cm [37–39 inches] in men and 80–88 cm [31–35 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cutpoint (eg, ≥90 cm [35 inches] in men and ≥80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

‡Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking one of these drugs are presumed to have high TG and low HDL.

insulin resistance and the metabolic syndrome with only moderate increases in waist circumference (ie, between 94 and 101 cm in men or 80 and 87 cm in women). Among the characteristics that may predispose to insulin resistance and metabolic syndrome in such individuals are the following: (1) type 2 diabetes mellitus in first-degree relatives before age 60 years,[109] (2) polycystic ovary disease,[9] (3) fatty liver,[135] (4) C-reactive protein (CRP) >3 mg/L (if measured),[96] (5) microalbuminuria (if detected),[136–141] (6) impaired glucose tolerance (if measured),[109] and (7) elevated total apoB (if measured).[88,89] In addition, some populations are predisposed to insulin resistance, metabolic syndrome, and type 2 diabetes mellitus, with only moderate increases in waist circumference (ie, populations from South Asia, China, Japan, and other Asian countries).[127,130,131,142] None of these phenotypic features or ethnic differences was included in the ATP III diagnostic criteria; but if individuals with such characteristics have only moderate elevations of waist circumference plus at least 2 ATP III metabolic syndrome features, then consideration should be given to managing them similarly to people with 3 ATP III risk factors.

The recent IDF definition of metabolic syndrome is similar in practice to the modified ATP III definition adopted in the present statement. Obvious differences are 2-fold: IDF requires abdominal obesity as 1 factor and sets lower thresholds for abdominal obesity than used in the United States. Even so, most subjects with waist circumference ≥94 cm in men or ≥80 cm in women plus 2 other risk factors (IDF definition) will in fact have 3 risk factors (ATP III definition). The defining third risk factor will be either a higher waist circumference (≥102 cm for men and ≥88 cm for women) or 1 other risk component. For this reason, in the United States, for the most part the same individuals will be identified by either definition. At the same time, when applying ATP III criteria in Asian countries, lower waist circumferences, as defined by IDF for these populations, appear to be appropriate as 1 risk factor.[127,130,131,142] The same waist criteria are reasonable for Asians living in the United States (Table 2).

Clinical Management of the Metabolic Syndrome

Goals of Clinical Management

The primary goal of clinical management in individuals with the metabolic syndrome is to reduce risk for clinical atherosclerotic disease. Even in people with the metabolic syndrome, first-line therapy is directed toward the major risk factors: LDL-C above goal, hypertension, and diabetes. Prevention of type 2 diabetes mellitus is another important goal when it is not present in a person with the metabolic syndrome. For individuals with established diabetes, risk factor management must be intensified to diminish their higher risk for ASCVD. The prime emphasis in management of the metabolic syndrome per se is to mitigate the modifiable, underlying risk factors (obesity, physical inactivity, and atherogenic diet) through lifestyle changes. Effective lifestyle change will reduce all of the metabolic risk factors. Then, if absolute risk is high enough, consideration can be given to incorporating drug therapy to the regimen. The priority of drug therapy is elevations of LDL-C, blood pressure, and glucose; current guidelines for their management should be followed. Moreover, efforts should be made to bring about smoking cessation in any cigarette smokers.

Table 3 summarizes the current goals and recommendations for management of each of the risk factors of the metabolic syndrome. These recommendations are derived in large part from existing NHLBI, AHA, and ADA guidelines for management of specific risk factors. It is important to note that individuals who have established ASCVD and/or diabetes can still have the metabolic syndrome. The evidence bases for most of the recommendations have been presented in background documents for obesity,[108] physical inactivity,[143] lipids,[1] high blood pressure,[91] and diabetes.[134] The present

statement attempts to provide an integrated approach to the management of a multidimensional risk factor condition.

Risk Assessment

ASCVD

A series of studies[63–73] have found that many middle-aged people with the metabolic syndrome are at increased absolute risk for ASCVD in the near future (eg, 10-year risk). Moreover, as stated previously, because of the high relative risk for ASCVD, long-term (lifetime) risk for ASCVD is increased even when 10-year risk is not considered to be high, eg, in young adults who develop the syndrome. An exacerbating factor raising lifetime risk for ASCVD is an increased likelihood for developing premature type 2 diabetes mellitus.

To reduce lifetime risk for ASCVD, all individuals found to have the metabolic syndrome deserve long-term management and follow-up in the clinical setting. The primary aim is to reduce the underlying risk factors. Such individuals need to be categorized according to *absolute* 10-year risk.[1] Individuals with any clinical form of ASCVD or with diabetes belong in the *high-risk* category.[1] For metabolic syndrome patients without ASCVD or diabetes, Framingham risk scoring should be performed to estimate 10-year risk for coronary heart disease (CHD).[1] This assessment triages patients into 3 risk categories based on 10-year risk for CHD: *high risk* (10-year risk >20%), *moderately high risk* (10-year risk 10% to 20%), or *lower to moderate risk* (10-year risk <10%).

Thus, detecting metabolic syndrome is only one part of overall risk assessment for cardiovascular disease. The metabolic syndrome per se is not an adequate tool to estimate 10-year risk for CHD. Although patients with the metabolic syndrome are at higher lifetime risk, in the absence of diabetes they do not necessarily have a high 10-year risk. Estimating 10-year risk entails key risk factors beyond those of the syndrome, ie, age, sex, smoking, and total cholesterol. Moreover, risk factors of the metabolic syndrome are not graded for severity as are the risk factors contained in Framingham scoring. Framingham investigators find little or no increase in predictive power for CHD by adding abdominal obesity, triglycerides, or fasting glucose to their 10-year risk algorithm.[58,144] These factors come into play in the longer term. Whether adding still other factors—apoB, small LDL, CRP, and insulin levels—will enhance shorter-term prediction of ASCVD has not been rigorously tested in multivariable models.

Type 2 Diabetes Mellitus

In individuals with diabetes, the coexistence of other metabolic syndrome factors denotes a higher risk for future development of ASCVD.[69] Compared with other metabolic risk factors, IFG (fasting glucose 100 to 125 mg/dL) carries the greatest predictive power for diabetes.[112] A closely related measure is IGT, defined as a 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL observed during a standard oral glucose tolerance test (OGTT). The ADA has introduced the term "prediabetes" to apply to individuals with either IFG or IGT.[134] Some investigators recommend OGTT for normoglycemic subjects who have the metabolic syndrome to detect IGT or occult diabetes. IGT in fact exceeds IFG in frequency; it consequently uncovers more individuals at increased risk for diabetes. In part to reduce the need for OGTT in routine practice, the ADA recently reduced the threshold for IFG to 100 mg/dL, from its previous 110 mg/dL.[134] People who have fasting glucose in the range of 100 to 110 mg/dL are now said to have IFG; many such people would have IGT if tested by OGTT. OGTT nonetheless remains an option in normoglycemic individuals who appear to be at elevated risk for developing diabetes. In fact, performing OGTT in people with IFG will identify some individuals who already have type 2 diabetes mellitus. Intensive lifestyle management of individuals with IFG (or IGT) will delay conversion to type 2 diabetes mellitus.[145]

Management of Underlying Risk Factors

Although many people may be genetically susceptible to the metabolic syndrome, rarely does it become clinically manifested in the absence of some degree of obesity and physical inactivity. Consequently, therapies to mitigate these underlying risk factors constitute first-line intervention. If cigarette smoking, another risk factor for ASCVD, is present, then it likewise deserves intensive cessation effort. The reason to modify underlying risk factors is to prevent or delay onset of ASCVD; and if type 2 diabetes mellitus is not already present, a concomitant goal is to prevent it as well.

Abdominal Obesity

Weight reduction deserves first priority in individuals with abdominal obesity and the metabolic syndrome.[108,146] Both weight reduction and maintenance of a lower weight are best achieved by a combination of reduced caloric intake and increased physical activity and the use of principles of behavior change. The first aim of weight loss is to achieve a decline of about 7% to 10% from baseline total body weight during a period of 6 to 12 months. This will require decreasing caloric intake by 500 to 1000 calories per day. Greater physical activity helps to enhance caloric deficit. Achieving the recommended amount of weight loss will reduce the severity of most or all of the metabolic risk factors. Maintenance of a lower weight is just as important; this requires long-term follow-up and monitoring.[108]

Currently available weight-loss drugs possess limited utility in the management of obesity. Nevertheless, in some patients they may be helpful. Bariatric surgery is being used increasingly in the United States for severe obesity. Individuals at high risk for the complications of obesity may benefit. Weight-loss surgery is not without risk, however. Selection of patients must be made with a team of healthcare professionals who are qualified to make appropriate clinical judgments about the pros and cons of this approach.

Physical Inactivity

Increasing physical activity assists in weight reduction; it also has beneficial effects on metabolic risk factors; and importantly, it reduces overall ASCVD risk.[147] Current recommendations for the public call for accumulation of ≥30 minutes of moderate-intensity exercise, such as brisk walking, on most, and preferably all, days of the week[77,143]; even more exercise adds more benefit. Thus, going beyond current recommendations will be particularly beneficial for people

TABLE 3. Therapeutic Goals and Recommendations for Clinical Management of Metabolic Syndrome

Therapeutic Target and Goals of Therapy	Therapeutic Recommendations
Lifestyle risk factors	Long-term prevention of CVD and prevention (or treatment) of type 2 diabetes mellitus
Abdominal obesity	
Reduce body weight by 7% to 10% during year 1 of therapy. Continue weight loss thereafter to extent possible with goal to ultimately achieve desirable weight (BMI <25 kg/m^2)	Consistently encourage weight maintenance/reduction through appropriate balance of physical activity, caloric intake, and formal behavior-modification programs when indicated to maintain/achieve waist circumference of <40 inches in men and <35 inches in women. Aim initially at slow reduction of $\approx$7% to 10% from baseline weight. Even small amounts of weight loss are associated with significant health benefits.
Physical inactivity	
Regular moderate-intensity physical activity; at least 30 min of continuous or intermittent (and preferably $\geq$60 min) 5 d/wk, but preferably daily	In patients with established CVD, assess risk with detailed physical activity history and/or an exercise test, to guide prescription. Encourage 30 to 60 min of moderate-intensity aerobic activity: brisk walking, preferably daily, supplemented by increase in daily lifestyle activities (eg, pedometer step tracking, walking breaks at work, gardening, housework). Longer exercise times can be achieved by accumulating exercise throughout day. Encourage resistance training 2 d/wk. Advise medically supervised programs for high-risk patients (eg, recent acute coronary syndrome or revascularization, CHF).
Atherogenic diet	
Reduced intake of saturated fat, *trans* fat, cholesterol	Recommendations: saturated fat $<$7% of total calories; reduce *trans* fat; dietary cholesterol <200 mg/dL; total fat 25% to 35% of total calories. Most dietary fat should be unsaturated; simple sugars should be limited.
Metabolic risk factors	Shorter-term prevention of CVD or treatment of type 2 diabetes mellitus
Atherogenic dyslipidemia	
Primary target: elevated LDL-C (see Table 4 for details)	Elevated LDL-C (see Table 4 for details)
Secondary target: elevated non-HDL-C	Elevated non-HDL-C
High-risk patients*: <130 mg/dL (3.4 mmol/L) (optional: <100 mg/dL [2.6 mmol/L] for very high-risk patients†)	Follow strategy outlined in Table 4 to achieve goal for LDL-C First option to achieve non-HDL-C goal: Intensify LDL-lowering therapy Second option to achieve non-HDL-C goal: Add fibrate (preferably fenofibrate) or nicotinic acid if non-HDL-C remains relatively high after LDL-lowering drug therapy Give preference to adding fibrate or nicotinic acid in high-risk patients Give preference to avoiding addition of fibrate or nicotinic acid in moderately high-risk or moderate-risk patients All patients: If TG is $\geq$500 mg/dL, initiate fibrate or nicotinic acid (before LDL-lowering therapy; treat non-HDL-C to goal after TG-lowering therapy)
Moderately high-risk patients‡: <160 mg/dL (4.1 mmol/L)	
Therapeutic option: <130 mg/dL (3.4 mmol/L)	
Moderate-risk patients§: <160 mg/dL (4.1 mmol/L)	
Lower-risk patients‖: <190 mg/dL (4.9 mmol/L)	
Tertiary target: reduced HDL-C	Reduced HDL-C
No specific goal: Raise HDL-C to extent possible with standard therapies for atherogenic dyslipidemia	Maximize lifestyle therapies: weight reduction and increased physical activity Consider adding fibrate or nicotinic acid after LDL-C-lowering drug therapy as outlined for elevated non-HDL-C
Elevated BP	
Reduce BP to at least achieve BP of $<$140/90 mm Hg (or $<$130/80 mm Hg if diabetes present). Reduce BP further to extent possible through lifestyle changes.	For BP $\geq$120/80 mm Hg: Initiate or maintain lifestyle modification in all patients with metabolic syndrome: weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products For BP $\geq$140/90 mm Hg (or $\geq$130/80 mm Hg for individuals with chronic kidney disease or diabetes): As tolerated, add BP medication as needed to achieve goal BP
Elevated glucose	
For IFG, delay progression to type 2 diabetes mellitus. For diabetes, hemoglobin A_{1C} $<$7.0%	For IFG, encourage weight reduction and increased physical activity. For type 2 diabetes mellitus, lifestyle therapy, and pharmacotherapy, if necessary, should be used to achieve near-normal HbA1C ($<$7%). Modify other risk factors and behaviors (eg, abdominal obesity, physical inactivity, elevated BP, lipid abnormalities).
Prothrombotic state	
Reduce thrombotic and fibrinolytic risk factors	High-risk patients: Initiate and continue low-dose aspirin therapy; in patients with ASCVD, consider clopidogrel if aspirin is contraindicated. Moderately high-risk patients: Consider low-dose aspirin prophylaxis
Proinflammatory state	Recommendations: no specific therapies beyond lifestyle therapies

TG indicates triglycerides; BP, blood pressure; CVD, cardiovascular disease; CHF, congestive heart failure; BMI, body mass index; IFG, impaired fasting glucose; and ASCVD, atherosclerotic cardiovascular disease.

*High-risk patients are those with established ASCVD, diabetes, or 10-year risk for coronary heart disease $>$20%. For cerebrovascular disease, high-risk condition includes TIA or stroke of carotid origin or $>$50% carotid stenosis.

†Very high-risk patients are those who are likely to have major CVD events in next few years, and diagnosis depends on clinical assessment. Factors that may confer very high risk include recent acute coronary syndromes, and established coronary heart disease + any of following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), and metabolic syndrome.

‡Moderately high-risk patients are those with 10-year risk for coronary heart disease 10% to 20%. Factors that favor therapeutic option of non-HDL-C <100 mg/dL are those that can raise individuals to upper range of moderately high risk: multiple major risk factors, severe and poorly controlled risk factors (especially continued cigarette smoking), metabolic syndrome, and documented advanced subclinical atherosclerotic disease (eg, coronary calcium or carotid intimal-medial thickness $>$75th percentile for age and sex).

§Moderate-risk patients are those with 2+ major risk factors and 10-year risk $<$10%.

‖Lower-risk patients are those with 0 or 1 major risk factor and 10-year risk $<$10%.

with the metabolic syndrome. Sixty minutes or more of continuous or intermittent aerobic activity, preferably done every day, will promote weight loss or weight-loss maintenance. Preference is given to 60 minutes of moderate-intensity brisk walking to be supplemented by other activities.[77] The latter include multiple short (10- to 15-minute) bouts of activity (walking breaks at work, gardening, or household work), using simple exercise equipment (eg, treadmills), jogging, swimming, biking, golfing, team sports, and engaging in resistance training[148]; avoiding common sedentary activities in leisure time (television watching and computer games) is also advised. Self-monitoring of physical activity can help to achieve adherence to an activity program.

Current AHA guidelines[143] call for clinical assessment of risk for future ASCVD events before initiating a new exercise regimen. This includes a detailed history of physical activity. For high-risk patients (eg, those with recent acute coronary syndromes or recent revascularization), physical activity should be carried out under medical supervision. AHA guidelines[143] further recommend exercise testing before vigorous exercise in selected patients with cardiovascular disease and other patients with symptoms or those at high risk. It is not necessary, however, that all individuals beginning an exercise program of moderate intensity that is moderately progressive undergo an exercise stress test, although this issue remains controversial.

Atherogenic and Diabetogenic Diets

Beyond weight control and reduction of total calories, the diet should be low in saturated fats, *trans* fats, cholesterol, sodium, and simple sugars.[1,149] In addition, there should be ample intakes of fruits, vegetables, and whole grains; fish intake should be encouraged with recognition of concerns about the mercury content of some fish (see the Food and Drug Administration web site, www.cfsan.fda.gov/~dms/admehg3.html).[91,150,151] Very high carbohydrate intakes can exacerbate the dyslipidemia of the metabolic syndrome. ATP III[1] recommended that for individuals entering cholesterol management the diet should contain 25% to 35% of calories as total fat. If the fat content exceeds 35%, it is difficult to sustain the low intakes of saturated fat required to maintain a low LDL-C. On the other hand, if the fat content falls below 25%, triglycerides can rise and HDL-C levels can decline[152]; thus, very-low-fat diets may exacerbate atherogenic dyslipidemia. To avoid any worsening of atherogenic dyslipidemia in patients with the metabolic syndrome, some investigators favor fat intakes in the range of 30% to 35%; others, however, are concerned about possible weight gain resulting from long-term ingestion of higher fat intakes and thus prefer intakes in the range of 25% to 30%.

There has long been an interest in the question of whether changing the macronutrient content of the diet can promote weight reduction. For many years, a low-fat diet was advocated because the high caloric density of fat could increase the likelihood of obesity. More recently, interest has grown in the possibility that high-protein, low-carbohydrate diets will enhance weight reduction.[153] The rationale seems to be that fat and protein offer satiety that is absent with carbohydrates. That this effect of fat and protein on satiety makes the diet more effective for producing weight loss is a disputable hypothesis. Moreover, research documenting that high-fat/high-protein/low-calorie diets can achieve long-term maintenance of a lower body weight is lacking. In fact, after 1 year of consumption of low-carbohydrate diets, severely obese patients show no more weight reduction than those eating a conventional weight-loss diet.[154] High-fat diets not only tend to be higher in saturated fat but they often are deficient in fruits, vegetables, and whole grains—all of which are important components in currently recommended diets. High-protein diets of any sort are not well tolerated by individuals with chronic renal disease who have markedly reduced glomerular filtration rate; excess protein enhances phosphorus load, which can cause acidosis and worsen insulin resistance.[155,156] Finally, preoccupation with macronutrient composition to promote weight loss fails to identify the key factors affecting body weight. Effective weight loss requires a combination of caloric restriction, physical activity, and motivation; effective lifelong maintenance of weight loss essentially requires a balance between caloric intake and physical activity.

Management of Metabolic Risk Factors

Beyond lifestyle therapies directed toward underlying risk factors, attention must be given to the metabolic risk factors. If ASCVD or diabetes is present, or if the 10-year risk as determined by Framingham risk factors is relatively high, then drug therapies for risk factors may be required as defined by current guidelines.[1,91,134] Recommended principles of management for each of the metabolic risk factors are also considered in Table 3.

Atherogenic Dyslipidemia

As noted before, this condition consists of abnormal levels of triglycerides and apoB, small LDL particles, and low HDL-C. According to ATP III,[1] atherogenic dyslipidemia can become a target for lipid-lowering therapy *after* the goal for LDL-C has been attained. In other words, as long as LDL-C remains above goal level, LDL-C is the primary target of therapy even in the metabolic syndrome. Other lipid risk factors are secondary. The LDL-C goals depend on estimates of absolute risk. Table 4 reviews LDL-C goals that are consistent with recommendations of ATP III[1] and its recent update.[157] In patients with atherogenic dyslipidemia in whom serum triglyceride levels are ≥200 mg/dL, non-HDL-C becomes the next target of treatment after the LDL-C goal is reached (Table 3). A related and potential secondary target is an elevated total apoB[158]; this measure denotes the number of atherogenic lipoproteins in circulation.[85–89] Some investigators hold that total apoB is superior to non-HDL-C as a target of lipid-lowering therapy.[89,159,160] ATP III nonetheless identified non-HDL-C rather than total apoB as a secondary target (after LDL-C) because accurate measurement of non-HDL-C is more readily available in clinical practice. Goals for non-HDL-C parallel those for LDL-C except that the former are 30 mg/dL higher (Table 3).

When triglycerides are ≥500 mg/dL, triglyceride-lowering drugs should be considered to prevent the development of acute pancreatitis.[1] To achieve non-HDL-C goals at triglyc-

TABLE 4. Elevated LDL-C: Primary Target of Lipid-Lowering Therapy in People at Risk for ASCVD

Goals of Therapy	Therapeutic Recommendations
High-risk patients*: <100 mg/dL (2.6 mmol/L) (for very high-risk patients‡ in this category, optional goal <70 mg/dL)	High-risk patients: lifestyle therapies† plus LDL-C-lowering drug to achieve recommended goal If baseline LDL-C ≥100 mg/dL, initiate LDL-lowering drug therapy If on-treatment LDL-C ≥100 mg/dL, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination) If baseline LDL-C <100 mg/dL, initiate LDL-lowering therapy based on clinical judgment (ie, assessment that patient is at very high risk)
Moderately high-risk patients§: <130 mg/dL (3.4 mmol/L) (for higher-risk patients‖ in this category, optional goal is <100 mg/dL (2.6 mmol/L)	Moderately high-risk patients: lifestyle therapies+LDL-lowering drug if necessary to achieve recommended goal when LDL-C ≥130 mg/dL (3.4 mmol/L) after lifestyle therapies If baseline LDL-C is 100 to 129 mg/dL, LDL-lowering therapy can be introduced if patient's risk is assessed to be in upper ranges of this risk category
Moderate-risk patients¶: <130 mg/dL (3.4 mmol/L)	Moderate risk patients: lifestyle therapies+LDL-C lowering drug if necessary to achieve recommended goal when LDL-C ≥160 mg/dL (4.1 mmol/L) after lifestyle therapies
Lower-risk patients#: <160 mg/dL (4.9 mmol/L)	Lower-risk patients: lifestyle therapies+LDL-C lowering drug if necessary to achieve recommended goal when LDL-C ≥190 mg/dL after lifestyle therapies (for LDL-C 160 to 189 mg/dL, LDL-lowering drug is optional)

*High-risk patients are those with established ASCVD, diabetes, or 10-year risk for coronary heart disease >20%. For cerebrovascular disease, high-risk condition includes transient ischemic attack or stroke of carotid origin or >50% carotid stenosis.

†Lifestyle therapies include weight reduction, increased physical activity, and antiatherogenic diet (see Table 3 for details).

‡Very high-risk patients are those who are likely to have major CVD events in next few years, and diagnosis depends on clinical assessment. Factors that may confer very high risk include recent acute coronary syndromes, and established coronary heart disease+any of following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), and multiple risk factors of metabolic syndrome.

§Moderately high-risk patients are those with 10-year risk for coronary heart disease 10% to 20%.

‖Factors that can raise individuals to upper range of moderately high risk are multiple major risk factors, severe and poorly controlled risk factors (especially continued cigarette smoking), metabolic syndrome, and documented advanced subclinical atherosclerotic disease (eg, coronary calcium or carotid intimal-medial thickness >75th percentile for age and sex).

¶Moderate-risk patients are those with 2+ major risk factors and 10-year risk <10%.

#Lower-risk patients are those with 0 or 1 major risk factor and 10-year risk <10%.

erides <500 mg/dL, triglyceride-lowering drugs may be useful in combination with LDL-lowering therapy. Beyond lowering of non-HDL-C, a tertiary aim in patients with atherogenic dyslipidemia is to raise HDL-C when it is reduced. No specific goal of therapy is recommended for low HDL-C, but HDL-C should be raised to the extent possible after attaining goals for LDL-C and non-HDL-C.

If non-HDL-C remains elevated after the LDL-C goal is reached (Table 4), at least 2 therapeutic options are available. First, intensification of LDL lowering often also reduces non-HDL-C. For example, statins lower both LDL-C and non-HDL-C by a similar percentage; moreover, statins reduce risk for ASCVD events in patients with the metabolic syndrome.[161] Second, a triglyceride-lowering drug can be added to LDL-lowering therapy. Both fibrates and nicotinic acid reduce non-HDL-C and reportedly decrease risk for ASCVD in patients with the metabolic syndrome/type 2 diabetes mellitus.[162–164] For this reason, combining a fibrate or nicotinic acid with LDL-C-lowering treatment becomes an option.[165,166] Both fibrates and nicotinic acid raise HDL-C as well as reduce triglycerides and small LDL particles. If a statin is being used for LDL-C lowering, fenofibrate seems preferable to gemfibrozil because risk for severe myopathy appears to be lower for fenofibrate in combination with statins.[167] One recent report,[168] however, failed to find a difference in myopathy risk between gemfibrozil and fenofibrate when either was used in combination with statins (other than cerivastatin, which is no longer available). Patients with IFG, IGT, or diabetes who are treated with nicotinic acid deserve careful monitoring for worsening of hyperglycemia.[169] Lower doses of nicotinic acid lessen this risk. Whether adding a fibrate or nicotinic acid to statin therapy will reduce cardiovascular events more than a statin alone has not been evaluated adequately in randomized clinical trials; consequently the use of this combination probably should be limited largely to high-risk individuals who stand to gain the most from it. If a fibrate or nicotinic acid is used with a statin, higher doses of the statin generally should be avoided to minimize risks for myopathy or hepatic effects.

Elevated Blood Pressure

When overt hypertension is present without diabetes or chronic kidney disease, the goal for antihypertensive therapy is a blood pressure of <140/90 mm Hg.[91] In the presence of diabetes or chronic kidney disease, the blood pressure goal is <130/80 mm Hg.[91] Beyond these specific treatment goals, lifestyle changes deserve increased emphasis in people with the metabolic syndrome; the goals here are to reduce blood pressure as much as possible even in the absence of overt hypertension and to obtain other metabolic benefits of lifestyle change. Mild elevations of blood pressure often can be effectively controlled with lifestyle therapies: weight control, increased physical activity, alcohol moderation, sodium reduction, and increased consumption of fresh fruits and vegetables and low-fat dairy products, in accord with the Dietary Approaches to Stop Hypertension (DASH) diet.[91] If hypertension cannot be adequately controlled by lifestyle

therapies, antihypertensive drugs usually are necessary to prevent long-term adverse effects, eg, myocardial infarction, stroke, and chronic kidney disease.[91] The benefits of therapy extend to patients with type 2 diabetes mellitus whose blood pressure is above goal level, and presumably to hypertensive patients with the metabolic syndrome. Some investigators support angiotensin-converting enzyme (ACE) inhibitors as first-line therapy for hypertension in the metabolic syndrome, especially when either type 2 diabetes mellitus or chronic renal disease is present.[170] Indeed, inhibition of the renin-angiotensin system with ACE inhibitors or angiotensin receptor blockers (ARBs) may lower risk for diabetes itself.[171] ARBs may be used in those who cannot tolerate ACE inhibitors or as an alternative to ACE inhibitors in people who have left ventricular dysfunction.[172] Debate persists about the latter strategy. The results of a large clinical trial[173] raised the possibility that use of diuretics in patients with IFG or IGT may increase the likelihood of progression to type 2 diabetes mellitus, although diuretics do in fact lower the risk for cardiovascular events.[91,173] Most investigators in the hypertension field believe that the potential benefit of low-dose diuretics in combination antihypertensive therapy outweighs their risk.

Elevated Fasting Glucose

In the metabolic syndrome diagnosis, elevated fasting glucose (≥100 mg/dL) includes both IFG and type 2 diabetes mellitus. In metabolic syndrome patients with IFG (or IGT if assessed), weight reduction, increased physical activity, or both will delay (or prevent) the onset of type 2 diabetes mellitus.[145,174] In addition, metformin,[145] thiazolidinediones,[175,176] and acarbose[177] will lower risk for type 2 diabetes mellitus in people with IFG or IGT. Except for a preliminary trial with acarbose,[178] no clinical trial evidence is yet available to document that oral hypoglycemic agents will lessen risk for cardiovascular events. Moreover, neither metformin nor thiazolidinediones are recommended in this statement solely for the purpose of preventing diabetes because their cost-effectiveness and long-term safety have not been documented.

For patients with established type 2 diabetes mellitus, clinical trials confirm a reduction in cardiovascular risk from treatment of dyslipidemia[161–163,179–181] and hypertension.[91] Glycemic control to a hemoglobin A_{1c} of <7% reduces microvascular complications and may decrease risk for macrovascular disease as well.[182]

Prothrombotic State

People with the metabolic syndrome typically manifest elevations of fibrinogen, plasminogen activator inhibitor-1, and other coagulation factors. These abnormalities, however, are not routinely detected in clinical practice. For primary prevention, the only available long-term approach to counter their contribution to arterial thrombosis is low-dose aspirin or other antiplatelet agents. These agents, especially aspirin, are recommended in patients with established ASCVD provided they are not contraindicated. Their efficacy in individuals with type 2 diabetes mellitus without ASCVD has not been established conclusively through clinical trials, although they are widely recommended in such individuals. In metabolic syndrome patients who are at moderately high risk for ASCVD events, aspirin prophylaxis is an attractive therapeutic option to lower vascular events.[183]

TABLE 5. Additional Measures Reported to Be Associated With Metabolic Syndrome and in Need of More Research

Abnormal body fat distribution
General body fat distribution (dual-energy x-ray absorptiometry [DXA])
Central fat distribution (CT/MRI)
Adipose tissue biomarkers: leptin, adiponectin
Liver fat content (magnetic resonance spectroscopy)
Myocellular fat (magnetic resonance spectroscopy)
Atherogenic dyslipidemia (beyond elevated triglyceride and non-HDL-C and low HDL)
Apolipoprotein B
Small LDL particles
Triglycerides/HDL-C ratios
Dysglycemia
Fasting glucose
OGTT
Insulin resistance (other than elevated fasting glucose)
Fasting insulin/proinsulin levels
Homeostasis model assessment for insulin resistance (HOMA-IR)
Insulin resistance by Bergman Minimal Model
Elevated free fatty acids (fasting and during OGTT)
Vascular dysregulation (beyond elevated blood pressure)
Measurement of endothelial dysfunction
Microalbuminura
Chronic renal disease
Proinflammatory state
Elevated high-sensitivity CRP
Elevated inflammatory cytokines (eg, interleukin-6)
Low levels of adiponectin
Prothrombotic state
Fibrinolytic factors (plasminogen activator inhibitor-1, etc)
Clotting factors (fibrinogen, etc)
Hormonal factors
Corticosteroid axis
Polycystic ovary syndrome

Proinflammatory State

People with the metabolic syndrome frequently have a proinflammatory state as shown by elevated cytokines (eg, tumor necrosis factor-α and interleukin-6) and acute-phase reactants (eg, CRP, fibrinogen).[96,184] Measurement of CRP is the simplest way to identify a proinflammatory state in clinical practice. CRP levels >3 mg/L can be taken to define such a state in a person without other detectable causes.[95] If CRP is measured, the finding of an elevated level supports the need for lifestyle changes. The latter, particularly weight reduction, will reduce CRP levels and presumably will mitigate the underlying inflammatory stimulus.[185] No drugs that act exclusively through this mechanism are available for reducing cardiovascular risk. However, several drugs used to

treat other metabolic risk factors have been reported to reduce CRP levels (eg, statins, nicotinic acid, fibrates, ACE inhibitors, thiazolidinediones).[186–188] At present, these drugs cannot be recommended specifically to reduce a proinflammatory state independent of their indications for other risk factors.

Future Research

This statement recognizes several issues related to the metabolic syndrome that require additional research for clarification. Foremost is the need for improved strategies to achieve and sustain long-term weight reduction and increased physical activity. Moreover, a lack of understanding of the genetic and metabolic contributions to the causation of the syndrome stands in the way of developing new therapeutic approaches. The need exists, therefore, for additional basic and clinical research designed to better understand pathophysiology from the standpoint of genetics, molecular biology, and cellular signaling. At present, tools to assess short-term risk for ASCVD and diabetes in patients with the metabolic syndrome need significant improvement. Although statins and other LDL-lowering drugs effectively reduce the risk for ASCVD, adequate therapies for remaining dyslipidemias either are not available or have not yet been proved to reduce risk in combination with LDL-lowering drugs. Insulin resistance is an attractive target for prevention of ASCVD; clinical trials to date, however, have not been carried out to confirm ASCVD risk reduction from decreasing insulin resistance per se. The emerging relationship between a proinflammatory state and the development of both ASCVD and diabetes deserves much additional investigation. Finally, the cost-effectiveness of various drugs, both alone and in combination therapies, requires more extensive evaluation.

The metabolic syndrome can be clinically manifested in a variety of ways. A sizable number of metabolic changes thus occur in people with clinical evidence of the syndrome. Identification of these changes should provide a broader picture of the metabolic status of an affected individual. They may also give insights into pathogenesis. At present, many of these factors cannot be readily identified in routine clinical practice. Nevertheless, several factors appear to overlap with alternative measures of the same underlying or metabolic risk factor. For example, there are several ways to estimate body fat distribution. In addition, multiple tests for insulin resistance have been proposed; each examines a different aspect of the insulin-resistance phenomenon. The IDF report lists many of these factors as important targets for research even when they are not used for routine clinical diagnosis. Table 5 presents a list of research targets similar to those proposed by the IDF. Epidemiological, metabolic, and genetic studies directed to a broad profile of parameters related to the metabolic syndrome should provide new insights into the responsible pathways. It is not expected that these measures will be used in routine clinical practice because the incremental value of measurement is uncertain. Their study at present is expected to be mainly for research, ie, metabolic and epidemiological studies.

Conclusions

In summary, the following points should be emphasized:

1. The metabolic syndrome is a term for a constellation of endogenous risk factors that increase the risk of developing both ASCVD and type 2 diabetes mellitus.
2. The syndrome is not a discrete entity known to be caused by a single factor. Moreover, it shows considerable variation in the components among different individuals. This variation is even greater among different racial and ethnic groups.
3. In the United States, the syndrome is strongly associated with the presence of abdominal obesity.
4. The metabolic syndrome is a secondary target for reducing cardiovascular events. Smoking cessation, lowering the levels of LDL-C, and blood pressure management are primary targets for risk reduction.
5. Lifestyle interventions are the initial therapies recommended for treatment of the metabolic syndrome. If lifestyle change is not sufficient, then drug therapies for abnormalities in the individual risk factors may be indicated.
6. To date, there is insufficient evidence for primary use of drugs that target the underlying causes of the metabolic syndrome.
7. Considerable additional research is needed to better refine the most appropriate therapies for individuals with the metabolic syndrome.

TABLE 6. Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers Bureau/ Honoraria	Ownership Interest	Consultant/Advisory Board	Other
James I. Cleeman	National Heart, Lung, and Blood Institute	None	None	None	None	None	None
Fernando Costa	American Heart Association	None	None	None	None	None	None
Stephen R. Daniels	Cincinnati Children's Hospital Medical Center	Pfizer, Astra-Zeneca, Inamed	None	None	None	Abbott Laboratories	None
Karen A. Donato	National Heart, Lung, and Blood Institute	None	None	None	None	None	None
Robert H. Eckel	University of Colorado Health Sciences Center	None	None	None	None	None	None
Barry A. Franklin	William Beaumont Hospital	None	None	Pfizer	None	None	None
David Gordon	National Heart, Lung, and Blood Institute	None	None	None	None	None	None
Scott M. Grundy	University of Texas Southwestern Medical Center	Abbott, GlaxoSmithKline, Merck, KOS	Department of Veterans Affairs, Reynolds, National Institutes of Health	None	None	Pfizer, Sanofi, Abbott Laboratories	None
Ronald M. Krauss	Children's Hospital Oakland Research Institute	None	None	Abbott, Merck	None	Abbott, AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer	None
Peter J. Savage	National Heart, Lung, and Blood Institute	None	None	None	None	None	None
Sidney C. Smith, Jr.	University of North Carolina Medical School	None	None	None	Johnson & Johnson, Medtronic, Intuitive Surgery	None	None
John A. Spertus	Saint Luke's Hospital of Kansas City	CV Therapeutics	National Heart, Lung, and Blood Institute	None	CV Outcomes, Outcomes Instruments, Inc	CV Therapeutics	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.

TABLE 7. Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
George Alberti	University of Newcastle Upon Tyne	None	None	AstraZeneca; GlaxoSmithKline; Novartis	None	AstraZeneca Galida board; Pfizer Global	None
John Brunzell	University of Washington	None	None	None	None	None	None
Harold Franch	Emory University; Atlanta VA Medical Center	National Institutes of Health; Department of Veterans Affairs	AHA Kidney Foundation	None	None	None	None
Daniel Porte, Jr.	Independent consultant	None	None	None	Abbott Laboratories; Amcyte; Diamedica Inc; Merck	Amcyte; Amylin; Aventis; Bristol-Myers Squibb; Diamedica Inc; Johnson & Johnson; Kowa Research Institute; Mankind Corporation; Novartis; Sanyko; Sanofi-Synthelabo; Sanofi Aventis; Sanwa Kaguku Kenkyusho; Takeda	None
Paul Thompson	Hartford Hospital	Otsuka; Merck; Pfizer; AstraZeneca; Schering-Plough; KOS	None	Merck; Pfizer; Schering-Plough; AstraZeneca	Pfizer; Schering-Plough; Zoll; Merck	Merck; Pfizer; Schering-Plough; AstraZeneca; Bristol-Myers Squibb; Reliant; KOS; Sanyko	None

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References

1. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Almeras N, Bergeron J, Gaudet D, Tremblay G, Prud'homme D, Nadeau A, Despres JP. Hypertriglyceridemic waist: a marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? *Circulation*. 2000;102:179–184.
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. Carr DB, Utzschneider KM, Hull RL, Kodama K, Retzlaff BM, Brunzell JD, Shofer JB, Fish BE, Knopp RH, Kahn SE. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes*. 2004;53:2087–2094.
5. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595–1607.
6. Ferrannini E, Haffner SM, Mitchell BD, Stern MP. Hyperinsulinemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia*. 1991;34:416–422.
7. Gustat J, Srinivasan SR, Elkasabany A, Berenson GS. Relation of self-rated measures of physical activity to multiple risk factors of insulin resistance syndrome in young adults: the Bogalusa Heart Study. *J Clin Epidemiol*. 2002;55:997–1006.
8. 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.
9. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2004;90:1929–1935.
10. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *Endocrinol Metab Clin North Am*. 2004;33:283–303.
11. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415–1428.
12. Perseghin G, Ghosh S, Gerow K, Shulman GI. Metabolic defects in lean nondiabetic offspring of NIDDM parents: a cross-sectional study. *Diabetes*. 1997;46:1001–1009.
13. McKeigue PM, Ferrie JE, Pierpoint T, Marmot MG. Association of early-onset coronary heart disease in South Asian men with glucose intolerance and hyperinsulinemia. *Circulation*. 1993;87:152–161.
14. Abate N, Chandalia M, Snell PG, Grundy SM. Adipose tissue metabolites and insulin resistance in nondiabetic Asian Indian men. *J Clin Endocrinol Metab*. 2004;89:2750–2755.
15. Brochu M, Starling RD, Tchernof A, Matthews DE, Garcia-Rubi E, Poehlman ET. Visceral adipose tissue is an independent correlate of glucose disposal in older obese postmenopausal women. *J Cin Endocrinol Metab*. 2000;85:2378–2384.
16. Rendell M, Hulthen UL, Tornquist C, Groop L, Mattiasson I. Relationship between abdominal fat compartments and glucose and lipid metabolism in early postmenopausal women. *J Clin Endocrinol Metab*. 2001;86:744–749.
17. Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. *J Clin Endocrinol Metab*. 2001;86:5366–5371.
18. Ross R, Freeman J, Hudson R, Janssen I. Abdominal obesity, muscle composition and insulin resistance in premenopausal women. *J Clin Endocrinol Metab*. 2002;87:5044–5051.
19. Nyholm B, Nielsen MF, Kristensen K, Nielsen S, Ostergard T, Pedersen SB, Christiansen T, Richelsen B, Jensen MD, Schmitz O. Evidence of increased visceral obesity and reduced physical fitness in healthy insulin-resistant first-degree relatives of type 2 diabetic patients. *Eur J Endocrinol*. 2004;150:207–214.
20. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahn SE, Fujimoto WY. Visceral adiposity and the risk of impaired glucose tolerance: a prospective study among Japanese Americans. *Diabetes Care*. 2003;26:650–655.
21. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahn SE, Fujimoto WY. Visceral adiposity is an independent predictor of incident hypertension in Japanese Americans. *Ann Intern Med*. 2004;140:992–1000.
22. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest*. 1995;96:88–98.
23. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B, Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. *Diabetes*. 1996;45:1684–1693.
24. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes*. 1997;46:1579–1585.
25. Kelley DE, Thaete FL, Troost F, Huwe T, Goodpaster BH. Subdivisions of subcutaneous abdominal adipose tissue and insulin resistance. *Am J Physiol Endocrinol Metab*. 2000;278:E941–E948.
26. Sites CK, Calles-Escandon J, Brochu M, Butterfield M, Ashikaga T, Poehlman ET. Relation of regional fat distribution to insulin sensitivity in postmenopausal women. *Fertil Steril*. 2000;73:61–65.
27. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. *J Clin Invest*. 2004;113:1582–1588.
28. Jensen MD, Haymond MW, Rizza RA, Cryer PE, Miles JM. Influence of body fat distribution on free fatty acid metabolism in obesity. *J Clin Invest*. 1989;83:1168–1173.
29. Petersen KF, Shulman GI. Pathogenesis of skeletal muscle insulin resistance type 2 diabetes mellitus. *Am J Cardiol*. 2002;90:11G–18G.
30. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology*. 2004;40:1387–1395.
31. Bergman RN, Van Citters GW, Mittelman SD, Dea MK, Hamilton-Wessler M, Kim SP, Ellmerer M. Central role of the adipocyte in the metabolic syndrome. *J Investig Med*. 2001;49:119–126.
32. Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. *J Clin Endocrinol Metab*. 2004;89:2595–2600.
33. Yu C, Chen Y, Cline GW, Zhang D, Zong H, Wang Y, Bergeron R, Kim JK, Cushman SW, Cooney GJ, Atcheson B, White MF, Kraegen EW, Shulman GI. Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)–associated phosphatidylinositol 3-kinase activity in muscle. *J Biol Chem*. 2002;277:50230–50236.
34. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr*. 2004;92:347–355.
35. You T, Yang R, Lyles MF, Gong D, Nicklas BJ. Abdominal adipose tissue cytokine gene expression: relationship to obesity and metabolic risk factors. *Am J Physiol Endocrinol Metab*. 2005;288:E741–E747.
36. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*. 2003;112:1796–1808.
37. Juhan-Vague I, Alessi MC, Mavri A, Morange PE. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. *J Thromb Haemost*. 2003;1:1575–1579.
38. Morton NM, Paterson JM, Masuzaki H, Holmes MC, Staels B, Fievet C, Walker BR, Flier JS, Mullins JJ, Seckl JR. Novel adipose tissue–mediated resistance to diet-induced visceral obesity in 11 beta-hydroxysteroid dehydrogenase type 1–deficient mice. *Diabetes*. 2004;53:931–938.
39. Kannisto K, Pietilainen KH, Ehrenborg E, Rissanen A, Kaprio J, Hamsten A, Yki-Jarvinen H. Overexpression of 11beta-hydroxysteroid dehydrogenase-1 in adipose tissue is associated with acquired obesity and features of insulin resistance: studies in young adult monozygotic twins. *J Clin Endocrinol Metab*. 2004;89:4414–4421.
40. Ruan H, Lodish HF. Regulation of insulin sensitivity by adipose tissue–derived hormones and inflammatory cytokines. *Curr Opin Lipidol*. 2004;15:297–302.
41. Hara T, Fujiwara H, Shoji T, Mimura T, Nakao H, Fujimoto S. Decreased plasma adiponectin levels in young obese males. *J Atheroscler Thromb*. 2003;10:234–238.
42. Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. *Diabetes*. 2003;52:1779–1785.
43. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. *Diabetes*. 1998;47:699–713.

44. Dvorak RV, DeNino WF, Ades PA, Poehlman ET. Phenotypic characteristics associated with insulin resistance in metabolically obese but normal-weight young women. *Diabetes*. 1999;48:2210–2214.
45. Chandalia M, Abate N, Garg A, Stray-Gundersen J, Grundy SM. Relationship between generalized and upper body obesity to insulin resistance in Asian Indian men. *J Clin Endocrinol Metab*. 1999;84:2329–2335.
46. McLaughlin T, Allison G, Abbasi F, Lamendola C, Reaven G. Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals. *Metabolism*. 2004;53:495–499.
47. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. 2004;53:693–700.
48. Hanley AJ, Festa A, D'Agostino RB Jr, Wagenknecht LE, Savage PJ, Tracy RP, Saad MF, Haffner SM. Metabolic and inflammation variable clusters and prediction of type 2 diabetes: factor analysis using directly measured insulin sensitivity. *Diabetes*. 2004;53:1773–1781.
49. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest*. 2000;106:171–176.
50. Hotamisligil GS. Inflammatory pathways and insulin action. *Int J Obes Relat Metab Disord*. 2003;27(suppl 3):S53–S55.
51. Ruan H, Lodish HF. Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor-alpha. *Cytokine Growth Factor Rev*. 2003;14:447–455.
52. Chandalia M, Cabo-Chan AV Jr, Devaraj S, Jialal I, Grundy SM, Abate N. Elevated plasma high-sensitivity C-reactive protein concentrations in Asian Indians living in the United States. *J Clin Endocrinol Metab*. 2003;88:3773–3776.
53. Okosun IS, Liao Y, Rotimi CN, Prewitt TE, Cooper RS. Abdominal adiposity and clustering of multiple metabolic syndrome in White, Black and Hispanic Americans. *Ann Epidemiol*. 2000;10:263–270.
54. Martin LJ, North KE, Dyer T, Blangero J, Comuzzie AG, Williams J. Phenotypic, genetic, and genome-wide structure in the metabolic syndrome. *BMC Genet*. 2003;4(suppl):S95.
55. Laakso M. Gene variants, insulin resistance, and dyslipidaemia. *Curr Opin Lipidol*. 2004;15:115–120.
56. Ruel IL, Gaudet D, Perron P, Bergeron J, Julien P, Lamarche B; Quebec LipD Study. Effect of obesity on HDL and LDL particle sizes in carriers of the null P207L or defective D9N mutation in the lipoprotein lipase gene: the Quebec LipD Study. *Int J Obes Relat Metab Disord*. 2003;27:631–637.
57. Poulsen P, Levin K, Petersen I, Christensen K, Beck-Nielsen H, Vaag A. Heritability of insulin secretion, peripheral and hepatic insulin action, and intracellular glucose partitioning in young and old Danish twins. *Diabetes*. 2005;54:275–283.
58. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr., Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. 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.
59. Hanson RL, Imperatore G, Bennett PH, Knowler WC. Components of the "metabolic syndrome" and incidence of type 2 diabetes. *Diabetes*. 2002;51:3120–3127.
60. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. 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;156:1070–1077.
61. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care*. 2004;27:2676–2681.
62. Bhargava A. A longitudinal analysis of the risk factors for diabetes and coronary heart disease in the Framingham Offspring Study. *Popul Health Metr*. 2003;1:3.
63. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683–689.
64. 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. *JAMA*. 2002;288:2709–2716.
65. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J. 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.
66. Girman CJ, Rhodes T, Mercuri M, Pyorala K, Kjekshus J, Pedersen TR, Beere PA, Gotto AM, Clearfield M; 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.
67. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*. 2004;110:1245–1250.
68. Olijhoek JK, van der Graaf Y, Banga JD, Algra A, Rabelink TJ, Visseren FL; the SMART Study Group. The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm. *Eur Heart J*. 2004;25:342–348.
69. 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.
70. 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.
71. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, Ballantyne CM, Heiss G. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care*. 2005;28:385–390.
72. Solymoss BC, Bourassa MG, Lesperance J, Levesque S, Marcil M, Varga S, Campeau L. Incidence and clinical characteristics of the metabolic syndrome in patients with coronary artery disease. *Coron Artery Dis*. 2003;14:207–212.
73. Turhan H, Yasar AS, Basar N, Bicer A, Erbay AR, Yetkin E. High prevalence of metabolic syndrome among young women with premature coronary artery disease. *Coron Artery Dis*. 2005;16:37–40.
74. Nesto RW. Correlation between cardiovascular disease and diabetes mellitus: current concepts. *Am J Med*. 2004;116(suppl 5A):11S–22S.
75. Pi-Sunyer FX. Medical hazards of obesity. *Ann Intern Med*. 1993;119(7 pt 2):655–660.
76. Casey DE Metabolic issues and cardiovascular disease in patients with psychiatric disorders. *Am J Med*. 2005;118(suppl 2):15S–22S.
77. Grundy SM, Hansen B, Smith SC Jr, Cleeman JI, Kahn RA; American Heart Association; National Heart, Lung, and Blood Institute; American Diabetes Association. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. *Circulation*. 2004;109:551–556.
78. Choudhury J, Sanyal AJ. Clinical aspects of fatty liver disease. *Semin Liver Dis*. 2004;24:349–362.
79. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2005;90:1929–1935.
80. Grundy SM. Cholesterol gallstones: a fellow traveler with metabolic syndrome? *Am J Clin Nutr*. 2004;80:1–2.
81. Coughlin SR, Mawdsley L, Mugarza JA Calverley PM, Wilding JP. Obstsructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J*. 2004;25:735–741.
82. Garg A, Misra A. Lipodystrophies: rare disorders causing metabolic syndrome. *Endocrinol Metab Clin North Am*. 2004;33:305–331.
83. Jerico C, Knobel H. Montero M, Ordonez-Llanos J, Guelar A, Gimeno JL, Saballs P, Lopez-Colomes JL, Pedro-Botet J. Metabolic syndrome among HIV-infected patients: prevalence, characteristics, and related factors. *Diabetes Care*. 2005;28:132–137.
84. Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. *J Lipid Res*. 2002;43:1363–1379.
85. Sniderman AD. Applying apoB to the diagnosis and therapy of the atherogenic dyslipoproteinemias: a clinical diagnostic algorithm. *Curr Opin Lipidol*. 2004;15:433–438.
86. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated

with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
87. Lamarche B, Tchernof A, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, Despres JP. Small, dense low-density lipoprotein particles as predictor of the risk of ischemic heart disease in men: prospective results from the Quebec Cardiovascular Study. *Circulation*. 1997;95:69–75.
88. Carr MC, Brunzell JD. Abdominal obesity and dyslipidemia in the metabolic syndrome: importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. *J Clin Endocrinol Metab*. 2004;89:2601–2607.
89. Brunzell JD. Increased apo B in small dense LDL particles predicts premature coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2005;25:474–475.
90. von Eckardstein A, Hersberger M, Rohrer L. Current understanding of the metabolism and biological actions of HDL. *Curr Opin Clin Nutr Metab Care*. 2005;8:147–152.
91. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
92. Vague P, Rarccah D, Scelles V. Hypofibrinolysis and the insulin resistance syndrome. *Int J Obes Relat Metab Disord*. 1995;19(suppl 1):S11–S15.
93. De Pergola G, Pannacciulli N. Coagulatioin and fibrinolysis abnormalities in obesity. *J Endocrinol Invest*. 2002;25:899–904.
94. Juhan-Vague I, Morange PE, Alessi MC. The insulin resistance syndrome: implications for thrombosis and cardiovascular disease. *Pathophysiol Haemost Thromb*. 2002;32:269–273.
95. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511.
96. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive proteion, the metabolic syndrome, and the risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation*. 2003;107:391–397.
97. Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: molecular mechanisms. *Cardiovasc Diabetol*. 2002;1:1.
98. Kylin E. Studien uber das Hypertonie-Hyperglyka "mie-Hyperurika" miesyndrom. *Zentralbl Innere Med*. 1923;44:105–127.
99. Vague J. La differenciation sexuelle, facteur determinant des formes de l;obesite. *Presse Med*. 1947;30:339–140.
100. Bjorntorp P. Abdominal obesity and the metabolic syndrome. *Ann Med*. 1992;24:465–468.
101. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annu Rev Med*. 1993;44:121–131.
102. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med*. 1989; 149:1514–1520.
103. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14: 173–194.
104. Stern MP. The insulin resistance syndrome: the controversy is dead, long live the controversy! *Diabetologia*. 1994;37:956–958.
105. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Almeras N, Bergeron J, Gaudet D, Tremblay G, Prud'homme D, Nadeau A, Despres JP. Hypertriglyceridemic waist: a marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? *Circulation*. 2000;102:179–184.
106. 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.
107. 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;16:442–443.
108. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—the Evidence Report. National Institutes of Health. *Obes Res*. 1998;6(suppl 2):51S–209S.
109. Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW, Seibel JA, Smith DA, Wilson PW. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract*. 2003;9:237–252.
110. International Diabetes Federation. Worldwide definition of the metabolic syndrome. Available at: http://www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf. Accessed August 24, 2005.
111. Ford ES, Giles WH. A comparison of the prevalence of the metabolic syndrome using two proposed definitions. *Diabetes Care*. 2003;26: 575–581.
112. Liao Y, Kwon S, Shaughnessy S, Wallace P, Hutto A, Jenkins AJ, Klein RL, Garvey WT. Critical evaluation of adult treatment panel III criteria in identifying insulin resistance with dyslipidemia. *Diabetes Care*. 2004; 27:978–983.
113. Marchesini G, Forlani G, Cerrelli F, Manini R, Natale S, Baraldi L, Ermini G, Savorani G, Zocchi D, Melchionda N. WHO and ATPIII proposals for the definition of the metabolic syndrome in patients with type 2 diabetes. *Diabet Med*. 2004;21:383–387.
114. Meigs JB, Wilson PW, Nathan DM, D'Agostino RB Sr, Williams K, Haffner SM. Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. *Diabetes*. 2003;52:2160–2167.
115. Rodriguez A, Muller DC, Engelhardt M, Andres R. Contribution of impaired glucose tolerance in subjects with the metabolic syndrome: Baltimore Longitudinal Study of Aging. *Metabolism*. 2005;54:542–547.
116. Duncan GE, Li SM, Zhou XH. Prevalence and trends of a metabolic syndrome phenotype among U.S. adolescents, 1999–2000. *Diabetes Care*. 2004;27:2438–2443.
117. Carnethon MR, Loria CM, Hill JO, Sidney S, Savage PJ, Liu K; Coronary Artery Risk Development in Young Adults Study. Risk factors for the metabolic syndrome: the Coronary Artery Risk Development in Young Adults (CARDIA) study, 1985–2001. *Diabetes Care*. 2004;27: 2707–2715.
118. McNeill AM, Rosamond WD, Girman CJ, Heiss G, Golden SH, Duncan BB, East HE, Ballantyne C. Prevalence of coronary heart disease and carotid arterial thickening in patients with the metabolic syndrome (The ARIC Study). *Am J Cardiol*. 2004;94:1249–1254.
119. Wyszynski DF, Waterworth DM, Barter PJ, Cohen J, Kessaniemi YA, Mahley RW, McPherson R, Waeber G, Bersot TP, Sharma SS, Nolan V, Middleton LT, Sundseth SS, Farrer LA, Mooser V, Grundy SM. Relation between atherogenic dyslipidemia and the Adult Treatment Program-III definition of metabolic syndrome (Genetic Epidemiolgoy of Metabolic Syndrome Project). *Am J Cardiol*. 2005;95:194–198.
120. Al-Lawati JA, Mohammed AJ, Al-Hinai HQ, Jousilahti P. Prevalence of the metabolic syndrome among Omani adults. *Diabetes Care*. 2003;26: 1781–1785.
121. Jaber LA, Brown MB, Hammad A, Zhu Q, Herman WH. The prevalence of the metabolic syndrome among Arab Americans. *Diabetes Care*. 2004;27:234–238.
122. Anderson JL, Horne BD, Jones HU, Reyna SP, Carlquist JF, Bair TL, Pearson RR, Lappe DL, Muhlestein JB; Intermountain Heart Collaborative (IHC) Study. Which features of the metabolic syndrome predict the prevalence and clinical outcomes of angiographic coronary artery disease? *Cardiology*. 2004;101:185–193.
123. Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care*. 2004;27:1182–1186.
124. Jacobson TA, Case CC, Roberts S, Buckley A, Murtaugh KM, Sung JC, Gause D, Varas C, Ballantyne CM. Characteristics of US adults with the metabolic syndrome and therapeutic implications. *Diabetes Obes Metab*. 2004;6:353–362.
125. 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.
126. Ozsahin AK, Gokcel A, Sezgin N, Akbaba M, Guvener N, Ozisik L, Karademir BM. Prevalence of the metabolic syndrome in a Turkish adult population. *Diabetes Nutr Metab*. 2004;17:230–234.
127. Enkhmaa B, Shiwaku K, Anuurad E, Nogi A, Kitajima K, Yamasaki M, Oyunsuren T, Yamane Y. Prevalence of the metabolic syndrome using the Third Report of the National Cholesterol Education Program Expert

Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) and the modified ATP III definitions for Japanese and Mongolians. *Clin Chim Acta*. 2005;352:105–113.
128. Leoncini G, Ratto E, Viazzi F, Vaccaro V, Parodi D, Falqui V, Tomolillo C, Deferrari G, Pontremoli R. Metabolic syndrome is associated with early signs of organ damage in nondiabetic, hypertensive patients. *J Intern Med*. 2005;257:454–460.
129. Thomas GN, Ho SY, Janus ED, Lam KS, Hedley AJ, Lam TH; Hong Kong Cardiovascular Risk Factor Prevalence Study Steering Committee. The US National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) prevalence of the metabolic syndrome in a Chinese population. *Diabetes Res Clin Pract*. 2005;67:251–257.
130. Shah T, Jonnalagadda SS, Kicklighter JR, Diwan S, Hopkins BL. Prevalence of metabolic syndrome risk factors among young adult Asian Indians. *J Immigr Health*. 2005;7:117–126.
131. Shiwaku K, Nogi A, Kitajima K, Anuurad E, Enkhmaa B, Yamasaki M, Kim JM, Kim IS, Lee SK, Oyunsuren T, Yamane Y. Prevalence of the metabolic syndrome using the modified ATP III definitions for workers in Japan, Korea and Mongolia. *J Occup Health*. 2005;47:126–135.
132. Lorenzo C, Serrano-Rios M, Martinez-Larrad MT, Gabriel R, Williams K, Gomez-Gerique JA, Stern MP, Haffner SM. Central adiposity determines prevalence differences of the metabolic syndrome. *Obes Res*. 2003;11:1480–1487.
133. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP; San Antonio Heart Study. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation*. 2004;110:1251–1257.
134. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*. 2003;26:3160–3167.
135. Angelico F, Del Ben M, Conti R, Francioso S, Feole K, Fiorello S, Cavallo MG, Zalunardo B, Lirussi F, Alessandri C, Violi F. Insulin resistance, the metabolic syndrome and non-alcoholic fatty liver disease. *J Clin Endocrinol Metab*. 2005;90:1578–1582.
136. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J. The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med*. 2004;140:167–174.
137. Liese AD, Hense HW, Doring A, Stieber J, Keil U. Microalbuminuria, central adiposity and hypertension in the non-diabetic urban population of the MONICA Augsburg survey 1994/95. *J Hum Hypertens*. 2001;15:799–804.
138. Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH. Increased urinary albumin excretion, endothetlial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes*. 2002;51:1157–1165.
139. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension*. 2003;42:1050–1065.
140. Cuspidi C, Meani S, Fusi V, Severgnini B, Valerio C, Catini E, Leonetti G, Magrini F, Zanchetti A. Metabolic syndrome and target organ damage in untreated essential hypertensives. *J Hypertens*. 2004;22:1991–1998.
141. Vidal J, Morinigo R, Codoceo VH, Casamitjana R, Pellitero S, Gomis R. The importance of diagnostic criteria in the association between the metabolic syndrome and cardiovascular disease in obese subjects. *Int J Obes Relat Metab Disord*. 2005;29:668–674.
142. Choi SH, Ahn CW, Cha BS, Chung YS, Lee KW, Lee HC, Huh KB, Kim DJ. The prevalence of the metabolic syndrome in Korean adults: comparison of WHO and NCEP criteria. *Yonsei Med J*. 2005;46:198–205.
143. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, Wenger NK; Am Heart Association Council on Clinical Cardiology Subcommittee on Exercise, Rehabilitation, and Prevention; American Heart Association Council on Nutrition, Physical Activity, and Metabolism Subcommittee on Physical Activity. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation*. 2003;107:3109–3116.
144. Wilson PW. Estimating cardiovascular disease risk and the metabolic syndrome: a Framingham view. *Endocrinol Metab Clin North Am*. 2004;33:467–481.
145. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
146. Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, Hong Y, Eckel RH; American Heart Association Council on Nutrition, Physical Activity, and Metabolism; American College of Cardiology Foundation. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation*. 2004;110:2952–2967.
147. Franklin BA, Kahn JK, Gordon NF, Bonow RO. A cardioprotective "polypill"? Independent and additive benefits of lifestyle modification. *Am J Cardiol*. 2004;94:162–166.
148. Pollock ML, Franklin BA, Balady GJ, Chaitman BL, Fleg JL, Fletcher B, Limacher M, Pina IL, Stein RA, Williams M, Bazzarre T. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation*. 2000;101:828–833.
149. Krauss RM, Eckel RH, Howard B, Appel LJ, Daniels SR, Deckelbaum RJ, Erdman JW Jr, Kris-Etherton P, Goldberg IJ, Kotchen TA, Lichtenstein AH, Mitch WE, Mullis R, Robinson K, Wylie-Rosett J, St. Jeor S, Suttie J, Tribble DL, Bazzarre TL. AHA Dietary Guidelines: revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation*. 2000;102:2284–2299.
150. US Department of Health and Human Services and US Department of Agriculture. *Dietary Guidelines for American 2005*. 6th ed. Washington, DC: US Government Printing Office; Jan 2005.
151. Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002;106:2747–2757.
152. Garg A, Bantle JP, Henry RR, Coulston AM, Griver KA, Raatz SK, Brinkley L, Chen YD, Grundy SM, Huet BA. Effects of varying carbohydrate content of diet in patients with non-insulin-dependent diabetes mellitus. *JAMA*. 1994;271:1421–1428.
153. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS, Klein S. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med*. 2003;348:2082–2090.
154. Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams M, Gracely EJ, Samaha FF. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med*. 2004;140:778–785.
155. Mitch WE, Maroni BJ. Nutritional considerations in the treatment of patients with chronic uremia. *Miner Electrolyte Metab*. 1998;24:285–289.
156. Mitch WE. Beneficial responses to modified diets in treating patients with chronic kidney disease. *Kidney Int Suppl*. 2005;94:S133–S135.
157. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239.
158. Grundy SM. Low-density lipoprotein, non-high-density lipoprotein, and apolipoprotein B as targets of lipid-lowering therapy. *Circulation*. 2002;106:2526–2529.
159. Sniderman AD. Applying apoB to the diagnosis and therapy of the atherogenic dyslipoproteinemias: a clinical diagnostic algorithm. *Curr Opin Lipidol*. 2004;15:433–438.

160. Sattar N, Williams K, Sniderman AD, D'Agostino R Jr, Haffner SM. Comparison of the associations of apolipoprotein B and non-high-density lipoprotein cholesterol with other cardiovascular risk factors in patients with the metabolic syndrome in the Insulin Resistance Atherosclerosis Study. *Circulation*. 2004;110:2687–2693.
161. Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. *Circulation*. 2001;104:3046–3051.
162. Rubins HB. Triglycerides and coronary heart disease: implications of recent clinical trials. *J Cardiovasc Risk*. 2000;7:339–345.
163. Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, Faas FH, Anderson JW. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med*. 2002;162:2597–2604.
164. Canner PL, Furberg CD, Terrin ML, McGovern ME. Benefits of niacin by glycemic status in patients with healed myocardial infarction (from the Coronary Drug Project). *Am J Cardiol*. 2005;95:254–257.
165. Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). *Am J Cardiol*. 2005;95:462–468.
166. Bays HE, Dujovne CA, McGovern ME, White TE, Kashyap ML, Hutcheson AG, Crouse JR; ADvicor Versus Other Cholesterol-Modulating Agents Trial Evaluation. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADvicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol*. 2003;91:667–672.
167. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol*. 2005;95:120–122.
168. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA*. 2004;292:2585–2590.
169. Grundy SM, Vega GL, McGovern ME, Tulloch BR, Kendall DM, Fitz-Patrick D, Ganda OP, Rosenson RS, Buse JB, Robertson DD, Sheehan JP; Diabetes Multicenter Research Group. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch Intern Med*. 2002;162:1568–1576.
170. Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med*. 2004;351:1952–1961.
171. Scheen AJ. Prevention of type 2 diabetes mellitus through inhibition of the renin-angiotensin system. *Drugs*. 2004;64:2537–2565.
172. Ball SG, White WB. Debate: angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers—a gap in evidence-based medicine. *Am J Cardiol*. 2003;91:15G–21G.
173. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group; The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981–2997.
174. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343–1350.
175. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes*. 2002;51:2796–2803.
176. Knowler WC, Hamman RF, Edelstein SL, Barrett-Connor E, Ehrmann DA, Walker EA, Fowler SE, Nathan DM, Kahn SE; Diabetes Prevention Program Research Group. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. *Diabetes*. 2005;54:1150–1156.
177. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trail Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359:2072–2077.
178. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA*. 2003;290:486–494.
179. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) Trial. The Care Investigators. *Circulation*. 1998;98:2513–2519.
180. Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyorala K. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med*. 1999;159:2661–2667.
181. Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005–2016.
182. American Diabetes Assocation. Standards of medical care in diabetes. *Diabetes Care*. 2005;38:S4–S36.
183. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Greenland P, Grundy SM, Hong Y, Miller NH, Lauer RM, Ockene IS, Sacco RL, Sallis JF Jr, Smith SC Jr, Stone NJ, Taubert KA. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation*. 2002;106:388–391.
184. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation*. 2004;109:2818–2825.
185. van Dielen FM, Buurman WA, Hadfoune M, Nijhuis J, Greve JW. Macrophage inhibitory factor, plasminogen activator inhibitor-1, other acute phase proteins, and inflammatory mediators normalize as a result of weight loss in morbidly obese subjects treated with gastric restrictive surgery. *J Clin Endocrinol Metab*. 2004;89:4062–4068.
186. Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S. Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation*. 2001;103:1933–1935.
187. Schieffer B, Bunte C, Witte J, Hoeper K, Boger RH, Schwedhelm E, Drexler H. Comparative effects of AT1-antagonism and angiotensin-converting enzyme inhibition on markers of inflammation and platelet aggregation in patients with coronary artery disease. *J Am Coll Cardiol*. 2004;44:362–368.
188. 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.

KEW WORDS: AHA/NHLBI Scientific Statements ■ metabolic syndrome ■ cardiovascular disease ■ obesity ■ diabetes ■ lifestyle therapy

Correction

In the version of "Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement" that published online ahead of print on September 12, 2005 (DOI: 10.1161/CIRCULATIONAHA.105.169404), the following changes have been made to Table 2:

1. The value for categorical cut points in elevated waist circumference for men should have added "(≥40 inches)" after "≥102 cm."
2. The value for categorical cut points in elevated waist circumference for women should have added "(≥35 inches)" after "≥88 cm."
3. The conversion of mg/dL to mmol/L for reduced HDL-C is incorrect. The correct value for men should be 1.03 mmol/L and the correct value for women should be 1.3 mmol/L.
4. In the footnotes, the values for marginally increased waist circumference should read "(eg, 94–101 cm [37–39 inches] in men and 80–87 cm [31–34 inches] in women)."

These changes were incorporated into the version of the article printed in the October 25, 2005, issue (*Circulation*. 2005;112:2735–2752) and the current online version of the article. (If needed, the original version of the article posted online on September 12, 2005, is available by selecting the "Previous Version of This Article" link.)

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