REVIEW

A Practical "ABCDE" Approach to the Metabolic Syndrome

Michael J. Blaha, MD, MPH; Sandeep Bansal, MD, MPH; Rosanne Rouf, MD; Sherita H. Golden, MD, MHS; Roger S. Blumenthal, MD; and Andrew P. DeFilippis, MD, MSc

The metabolic syndrome comprises a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus that are due to abdominal obesity and insulin resistance. This increasingly important proinflammatory condition remains both underrecognized and undertreated. To aid physicians in their approach to the metabolic syndrome, we assessed and synthesized the literature on cardiovascular risk assessment and early intervention for risk reduction. We performed a comprehensive search of MEDLINE and the Cochrane database for peer-reviewed clinical studies published from January 1, 1988, to December 31, 2007, augmented by consultation with content experts. We used the search terms *metabolic syndrome*, *abdominal obesity*, *waist circumference*, *insulin resistance*, *cardiovascular disease*, *prediabetes*, *diabetes*, *treatment*, *prevention*, *aspirin*, *hypertension*, *cholesterol*, *atherogenic dyslipidemia*, *lifestyle therapy*, *diet*, and *exercise*. Criteria used for study review were controlled study design, English language, relevance to clinicians, and validity based on experimental design and appropriateness of conclusions. Although growing evidence supports early intervention in patients with the metabolic syndrome, many physicians do not recognize the risk associated with this condition and fail to initiate early treatment. A comprehensive management plan can be assembled through an "ABCDE" approach: "A" for assessment of cardiovascular risk and aspirin therapy, "B" for blood pressure control, "C" for cholesterol management, "D" for diabetes prevention and diet therapy, and "E" for exercise therapy. This ABCDE approach provides a practical and systematic framework for encouraging metabolic syndrome recognition and for implementing a comprehensive, evidence-based management plan for the reduction of cardiovascular risk.

***Mayo Clin Proc.* 2008;83(8):932-943**

ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin receptor blocker; CI = confidence interval; DREAM = Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; GL = glycemic load; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; PPAR = peroxisome proliferator-activated receptor; VLDL-C = very low-density lipoprotein cholesterol

Increased caloric intake, increased consumption of refined carbohydrates, and physical inactivity have led to an explosion in the incidence of abdominal obesity and an emerging epidemic of insulin resistance. Abdominal obesity has tripled in the United States during the past 4 decades,[1] currently affecting half of all adults.[2] More than one quarter of the US population has the metabolic syndrome,[3] and the incidence is increasing.[4]

The metabolic syndrome is a multiplex risk factor for type 2 diabetes mellitus and cardiovascular disease that reflects the clustering of individual risk factors due to abdominal obesity and insulin resistance. This multiplex comprises the following interrelated metabolic risk conditions: atherogenic dyslipidemia, glucose intolerance, hypertension, proinflammatory state, and prothrombotic state[5] (Table 1).

The metabolic syndrome is a predictor of type 2 diabetes mellitus and future cardiovascular events. The incidence of diabetes mellitus is increased at least 7-fold[6]; however, increased cardiovascular risk is present long before the development of overt diabetes.[7] A recent meta-analysis of nearly 175,000 patients showed that the metabolic syndrome confers a relative risk of 1.54 for cardiovascular events and death after adjustment for traditional risk factors.[8]

Several groups have operationalized the metabolic syndrome, choosing risk factors and cut points that are readily measurable, correlate with insulin resistance, and can be integrated with guidelines for primary prevention of cardiovascular disease[9-12] (Table 2). Despite these available clinical definitions, the metabolic syndrome remains underdiagnosed.[13] While debate continues as to whether this risk factor clustering represents a true syndrome,[14-17] physicians may be missing the opportunity for early identification of a disease process and comprehensive intervention aimed at risk reduction.

Recognizing the widespread failure to address fully the risk associated with this condition, we present a practical ABCDE approach to the metabolic syndrome for primary prevention of cardiovascular events.

METHODS

We performed a comprehensive search of MEDLINE and the Cochrane database for clinical studies published from January 1, 1988, to December 31, 2007, using combinations of the following terms in their titles or abstracts: *metabolic syndrome*, *abdominal obesity*, *waist circumference*, *insulin resistance*, *cardiovascular disease*, *prediabetes*, *diabetes*, *treatment*, *prevention*, *aspirin*, *hypertension*, *cholesterol*, *atherogenic dyslipidemia*, *lifestyle therapy*, *diet*, and *exercise*. After screening the titles of all

From the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD.

Dr Golden is a member of the Merck Clinical Diabetes Advisory Board.

Individual reprints of this article are not available. Address correspondence to Michael J. Blaha, MD, MPH, Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Blalock 524C, Division of Cardiology, 600 N Wolfe St, Baltimore, MD 21287 (mblaha1@jhmi.edu).

7920 identified articles, we evaluated abstracts for pertinence to the study objective, selecting more than 460 articles for full text review. Bibliographies from these references were examined, and additional studies were identified by content experts. Criteria used for study selection were controlled study design, English language, relevance to clinicians, and validity based on experimental design and appropriateness of conclusions.

MECHANISMS OF INCREASED RISK

The term *metabolic syndrome* evolved from observations that cardiovascular risk factors cluster in obese, insulin-resistant people; in its current use, it also refers to metabolically obese people of normal weight.[18] The concept of the metabolic syndrome is useful because of its emphasis on underlying dysmetabolism and the attention it calls to coexisting cardiovascular risk factors.

Advances in adipocyte biology, subclinical inflammation, and oxidative stress have added to the original mechanistic understanding of how obesity and insulin resistance contribute to the metabolic syndrome.[19] Abdominal fat, as determined by measures such as waist circumference and waist:hip ratio, is highly correlated with insulin resistance, prothrombotic factors, and inflammation, as well as hypertension, dyslipidemia, and hyperglycemia.[20] Adipose tissue, particularly in the abdominal compartment, is a powerful endocrine organ that is the main source of free fatty acids and of several important biologically active adipokines.[21,22]

Excessive caloric intake and insulin resistance increase free fatty acid release, further inhibiting insulin action, causing lipotoxicity of the β-cell and leading to formation of an atherogenic lipoprotein profile.[21,22] Levels of adiponectin, an adipokine that normally increases insulin sensitivity and is anti-inflammatory, decrease with abdominal obesity. Interleukin 6, tumor necrosis factor α, and C-reactive protein, all of which are secreted in association with abdominal obesity, increase inflammation and further insulin resistance. Secretion of plasminogen activator inhibitor 1 by adipose tissue increases thrombosis. Leptin, a metabolic signal of energy sufficiency, is increased with obesity and can lead to hypertension as well as leptin resistance, with associated loss of feedback on appetite centers.[23] The obesity-driven dysregulation of the endocannabinoid system is associated with worsening insulin resistance, dyslipidemia, and further obesity.[24]

TABLE 1. **Five Metabolic Risk Conditions That Constitute the Metabolic Syndrome and Their Clinical Markers**[a]

Metabolic risk condition	Clinical markers
Atherogenic dyslipidemia	↑ Triglycerides, VLDL-C, non–HDL-C ↓ HDL-C, LDL-C particle size
Glucose intolerance	↑ Fasting glucose, HbA_{1c} Impaired glucose tolerance
Hypertension	Elevated blood pressure
Proinflammatory state	↑ WBC, hs-CRP, IL-6
Prothrombotic state	↑ Fibrinogen, vWF, PAI-1

[a] HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor 1; VLDL-C= very low-density lipoprotein cholesterol; vWF = von Willebrand factor; WBC = white blood cell count.

TABLE 2. **Current Clinical Definitions of the Metabolic Syndrome**[a,b]

WHO,[9] 1999	NCEP ATP III,[10,11] 2001	IDF,[12] 2005
Insulin resistance, identified as	At least 3 of the following 5 criteria	Abdominal obesity, identifed as
Type 2 diabetes mellitus	Waist circumference	Waist circumference
Impaired fasting glucose	Men ≥102 cm (≥40 in)	European men ≥94 cm (≥37 in)
Impaired glucose tolerance	Women ≥88 cm (≥35 in)	European women ≥80 cm (32 in)
Abnormal findings of hyperinsulinemic euglycemic clamp	Triglycerides ≥150 mg/dL[c]	Ethnicity-specific values for other groups
Plus any 2 of the following	HDL-C[c]	Plus any 2 of the following
Hypertension ≥140/90 mm Hg	Men <40 mg/dL	Triglycerides ≥150 mg/dL[c]
Plasma triglycerides	Women <50 mg/dL	HDL-C
Men <35 mg/dL or	Hypertension ≥130/85 mm Hg[c]	Men <40 mg/dL
Women <39 mg/dL	Fasting glucose ≥100 mg/dL	Women <50 mg/dL
BMI >30 and/or		Blood pressure ≥130/85 mm Hg
Waist:hip ratio		Fasting glucose >100 mg/dL
Men >0.9		
Women >0.85		
Microalbuminuria		

[a] BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; WHO = World Health Organization.
[b] SI conversion factors: To convert triglyceride value to mmol/L, multiply by 0.0113; to convert HDL-C value to mmol/L, multiply by 0.0259; and to convert glucose value to mmol/L, multiply by 0.0555.
[c] Or taking medication for treatment of this risk factor.

Insulin itself is thought to act as an anti-inflammatory protein, inhibiting nuclear factor κB and stimulating inhibitor of nuclear factor κB.[19] Therefore, changes in the adipocyte that increase insulin resistance also exacerbate underlying inflammation. All these dysmetabolic changes occur more often in the proinflammatory milieu of the Western diet, and most can be reversed with dietary restriction.[25]

DEFINITION OF THE METABOLIC SYNDROME

Clinical definitions of the metabolic syndrome use commonly measured patient data to identify people who are sufficiently insulin resistant to be at increased cardiovascular risk (Table 2). Although the World Health Organization, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and International Diabetes Federation definitions vary slightly, all identify a similar population of insulin-resistant people in need of risk modification. The conclusions of this review apply only to patients who are free of known coronary artery disease and overt diabetes mellitus and who have the metabolic syndrome by any of these definitions.

Although the risk factors that comprise the metabolic syndrome are generally recognized as important, the usefulness of the metabolic syndrome diagnosis has been the subject of substantial debate.[26] Much of this debate has been driven by imperfections in the clinical definitions of the metabolic syndrome and by the resulting confusion about how to apply the definitions in the clinical setting.[17] Indeed, because a single pathophysiologic defect for the metabolic syndrome has not yet been identified, current definitions lack a central risk variable that must be abnormal for diagnosis. Instead, current definitions are a combination of both causes (abdominal obesity) and consequences (dysglycemia) of insulin resistance.

Current clinical definitions of the metabolic syndrome do not include all features of the disease, leaving out prothrombotic and proinflammatory markers. Moreover, current definitions are weakened by the somewhat arbitrary dichotomization of risk variables. To be sure, the metabolic syndrome should be considered a continuum of risk. However, as will be discussed, the metabolic syndrome is not intended to be a comprehensive risk-scoring equation, but rather a tool to identify people at increased lifetime risk of developing diabetes mellitus and cardiovascular disease because of abdominal obesity and insulin resistance.

CARDIOVASCULAR RISK PREDICTION

A diagnosis of metabolic syndrome allows early identification of patients with excessive adipose tissue and insulin resistance; as such, it can be considered a tool for the selection of patients who may have an increased *lifetime* risk of *cardiovascular disease*. Although the diagnosis should not be confused with a precise risk-scoring instrument, current definitions of the metabolic syndrome may identify a population of patients at greater cardiovascular risk than predicted by traditional risk factors alone.[27-31]

For example, a middle-aged woman with abdominal obesity, atherogenic dyslipidemia, and a fasting glucose of 110 mg/dL (to convert to mmol/L, multiply by 0.0555) is classified as low risk in the Framingham model. Yet there is ample evidence that abdominal obesity,[32] elevated triglyceride levels,[33] the small dense high-density lipoprotein cholesterol (HDL-C)/low-density lipoprotein cholesterol (LDL-C) phenotype,[34] insulin resistance,[35] and impaired fasting glucose[36] are all risk factors for coronary artery disease. Indeed, patients with the metabolic syndrome considered low-risk by Framingham often show a substantial burden of subclinical atherosclerosis and may have event rates characteristic of those in higher-risk groups.[37-39]

In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, men classified as having low cardiovascular risk (10-year risk, <5%) by the European Systematic Coronary Risk Evaluation (SCORE) model who had the metabolic syndrome experienced nearly 3 times as many fatal cardiovascular events as those without the syndrome.[40] A comparable increased event rate among patients with the metabolic syndrome and low calculated risk was seen in a pooled analysis of 2 large lipid-lowering trials.[41] Although it is less clear if the metabolic syndrome improves risk prediction across an entire high-risk population,[42,43] there appears to be a benefit in discriminating increased risk among otherwise lower-risk groups.

The metabolic syndrome therefore represents risk not accounted for by traditional models and a missed opportunity for aggressive lifestyle and medical management. Clinical diagnosis of the metabolic syndrome can be used as a complementary tool for "correcting" the risk calculated by instruments such as the Framingham risk score. Precedence for advancing a calculated risk score comes from the 2003 American College of Cardiology (ACC) Bethesda conference on atherosclerosis imaging, which endorsed an expanded intermediate risk category (10-year risk, 6%-20%) when coronary calcium imaging predicts increased risk not fully captured by the Framingham risk equation.[44]

Similarly, a practical approach to accounting for the unmeasured risk due to the metabolic syndrome would be to reclassify patients with the syndrome and a calculated Framingham 10-year event rate between 6% and 10% as intermediate risk, equivalent to patients without the meta-

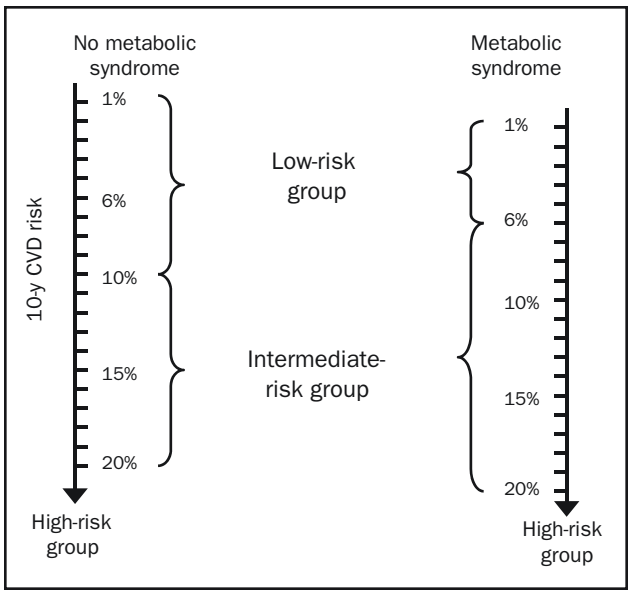

FIGURE. Proposed reclassification of cardiovascular disease (CVD) risk categories for patients with the metabolic syndrome. An augmented intermediate risk group (from 10%-20% to 6%-20% 10-year risk) adjusts for the unaccounted risk present with the metabolic syndrome.

bolic syndrome and a calculated Framingham 10-year risk of 10% to 20% (Figure). Physicians can then use these adjusted risk estimates to guide more aggressive lifestyle changes, lower blood pressure goals, and intervene earlier with aspirin and LDL-C–lowering drugs.

ABCDE APPROACH

In 2001, our center proposed an "ABC" approach to the implementation of ACC/American Heart Association (AHA) primary prevention guidelines,[45] and we have since adopted an "ABCDE" approach to secondary prevention[46] and the treatment of non–ST-segment elevation acute coronary syndromes.[47] This review adapts this practical approach to the metabolic syndrome (Table 3).

Assessment

The first step in treatment is recognition of the condition. Clinical definitions of the metabolic syndrome vary only slightly (Table 2), with little evidence to suggest that one is superior to another.

Treatment of the metabolic syndrome requires a multidisciplinary approach, including physicians and health educators skilled in nursing, nutrition, and exercise physiology. Therefore, a formal diagnosis recorded in the medical record may improve clinical communication. The *International Classification of Diseases, Ninth Revision* code is 277.7.

After diagnosis, all patients should have their 10-year risk calculated using a traditional scoring tool, such as the

TABLE 3. **ABCDE Approach for Treating the Metabolic Syndrome**[a,b]

A	Assessment	Make metabolic syndrome diagnosis, *ICD-9* code 277.7 Calculate Framingham risk score
	Aspirin	All patients with >6% 10-y Framingham risk
B	Blood pressure control	Goal blood pressure is <130/80 mm Hg if intermediate risk (≥6% 10-y risk) First-line therapy: ACEI or ARB β-Blockers, thiazide diuretics may increase risk of diabetes
C	Cholesterol management	
	First target: LDL-C	Statins to achieve LDL-C <100 mg/dL in high-risk, <130 mg/dL in intermediate-risk (≥6% 10-y risk) patients per the NCEP ATP III
	Second target: non-HDL-C	Statin intensification Fenofibrate to achieve target non–HDL-C <130 mg/dL in high-risk, <160 mg/dL in intermediate-risk patients per NCEP ATP III Consider omega-3 fatty acids
	Third target: HDL-C	Long-acting niacin, although insufficient evidence for wide use of niacin at this time due to concern for increased glucose intolerance
D	Diabetes prevention	Intensive lifestyle modification for all patients; pharmacotherapy is second line Metformin Consider pioglitazone
	Diet	Weight loss Mediterranean diet: increase omega-3 fatty acids, fruits, vegetables, fiber, nuts Low glycemic load diet
E	Exercise	Daily vigorous activity Recommend use of pedometer with goal >10,000 steps/d

[a] ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HDL-C = high-density lipoprotein cholesterol; *ICD-9 = International Classification of Diseases, Ninth Revision*; LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.
[b] SI conversion factors: To convert LDL-C, HDL-C, and non–HDL-C values to mmol/L, multiply by 0.0259.

Framingham risk score. We propose that patients with the metabolic syndrome and a 10-year risk of a hard coronary artery disease event (myocardial infarction, cardiovascular death) of 5% or less should be considered low risk; those with a 6% to 20% 10-year risk, intermediate risk; and those with more than a 20% risk, high risk (Figure).

Aspirin

Patients with the metabolic syndrome are at increased risk of thrombosis because of increased platelet aggregation, increased fibrinogen, increased vitamin K–dependent clotting factors, and decreased fibrinolysis via increased levels of plasminogen activator inhibitor 1.[48] Aspirin decreases platelet aggregation and effectively reduces the risk of initial thrombotic events.

The benefits of aspirin must be weighed against the risks of bleeding.[49] The ACC/AHA gives a class I recommendation for 75 to 162 mg of aspirin for primary prevention in men with intermediate risk,[50] a class IIa recommendation for women aged 65 years and older with intermediate risk, and a class IIb recommendation for women younger than 65 years with intermediate risk.[51] The Third US Preventive Services Task Force recommends aspirin for all those with a 10-year risk greater than 6%.[52] A recent systematic review indicates that aspirin doses of 75 to 81 mg are noninferior to higher doses and have fewer bleeding risks.[53]

Therefore, to treat the increased thrombogenicity and cardiovascular risk seen with the metabolic syndrome, we think that all patients in the augmented intermediate-risk category (calculated 10-year risk, 6%-20%) and all high-risk patients with the metabolic syndrome should be treated with 75 to 81 mg/d of aspirin in the absence of contraindications.

Blood Pressure

Blood pressure with the metabolic syndrome may be increased because of reduced bioavailability of nitric oxide secondary to obesity-induced oxidative stress, increased sodium reabsorption secondary to increased angiotensinogen production by adipocytes, and increased sympathetic activity secondary to hyperinsulinemia, as well as the vasoconstrictive effects of fatty acids and other adipokines.[54]

New AHA guidelines recommend a goal of less than 130/80 mm Hg for all patients with known coronary artery disease or with a 10-year cardiovascular risk of 10% or greater.[55] Although data are insufficient to set specific blood pressure goals for patients with the metabolic syndrome, it is reasonable, given the increased risk of cardiovascular events, to aim for a blood pressure of less than 130/80 mm Hg in patients with the metabolic syndrome who have an augmented intermediate risk (10-year risk, ≥6%).

β-Blockers should be avoided as initial agents in patients with the metabolic syndrome without known cardiovascular disease on the basis of data from several clinical trials indicating worsening glucose intolerance and decreased efficacy.[56] The new British National Institute for Health and Clinical Excellence (NICE) guidelines state that traditional types of β-blockers are associated with an "unacceptable risk of provoking type 2 diabetes,"[57] and have removed these drugs as potential first-line blood pressure agents. New AHA guidelines have also removed these drugs as options for initial therapy in the primary prevention population.[55]

Higher doses of thiazide diuretics may also increase the risk of diabetes. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), chlorthalidone was shown to have the same efficacy for mortality reduction as other antihypertensive agents but led to a significant increase in glucose intolerance.[58] Patients taking a combination of a β-blocker and a thiazide are at higher risk of diabetes. Indeed, current clinical guidelines specifically advise against this combination in patients with impaired glucose tolerance.[57]

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) do not worsen glucose intolerance and may improve glycemia. A predefined substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial first suggested this salutary effect. This study examined 5720 patients without diabetes and with known vascular disease, showing that patients with features of the metabolic syndrome who received the ACEI ramipril had a 34% reduction in new diabetes in the 4.5 years of follow-up compared with placebo (3.6% vs 5.4%; $P<.001$).[59]

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial showed similar diabetes reduction with an ARB compared with placebo.[60] Reductions in diabetes have also been observed in secondary analyses of large head-to-head trials comparing ARBs with β-blockers[61] and ARBs with calcium channel blockers.[62] Although the recent Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) trial failed to show a significant reduction in the incidence of diabetes among glucose-intolerant patients randomized to ramipril (18.1% vs 19.5%; $P=.15$), glucose values were more likely to return to the euglycemic range in these patients (hazard ratio, 1.16; $P=.001$).[63]

We suggest that ACEIs and ARBs be used for initial treatment of hypertension with the metabolic syndrome because they have been consistently shown to improve glycemic control, whereas evidence suggests that other common antihypertensive agents do not improve or may even worsen glucose intolerance. Data are insufficient to recommend specific combination therapies in patients requiring additional agents for blood pressure control.

Cholesterol

Low-Density Lipoprotein Cholesterol. Although not part of the metabolic syndrome, LDL-C has an integral role in the pathophysiology of atherosclerosis, and targeting LDL-C remains an important component of any strategy to reduce cardiovascular risk. Cholesterol synthesis can be blocked by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), leading to a reduction in LDL-C concentration and the total number of atherogenic apolipoprotein B–containing particles. Several clinical trials support the effectiveness of statins in reducing cardiovascular risk in patients with risk factors characteristic of the metabolic syndrome.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was a primary prevention trial of 6605 patients with moderately elevated LDL-C and low HDL-C.[64] Almost half of all participants (46%) had the metabolic syndrome. In this trial, lovastatin reduced first major coronary events by 37% (183 vs 116 first events; 95% confidence interval [CI], 0.50-0.79) during an average 5.2 years of follow-up, with patients with the metabolic syndrome receiving the greatest benefit.

The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA) enrolled 10,305 participants with average levels of LDL-C (133 mg/dL) (to convert to mmol/L, multiply by 0.0259), hypertension, and 3 or more other risk factors, most of which were characteristic of the metabolic syndrome.[65] Because of the relatively low baseline LDL-C levels, many of these patients would not have been candidates for LDL-lowering therapy using the Framingham risk score and current guidelines. Nonetheless, the study was stopped early after a mean of 3.3 years of follow-up, with atorvastatin lowering the primary end point of nonfatal myocardial infarction and fatal coronary heart disease by 36% (154 vs 100 events; 95% CI, 0.50-0.83).

Similar to NCEP ATP III guidelines, statin therapy should be considered in all patients with the metabolic syndrome and an augmented intermediate 10-year cardiovascular risk (10-year risk, ≥6%) if LDL-C remains above goal after intensive lifestyle intervention. Patients at intermediate risk should have a goal of less than 130 mg/dL with an optional goal of less than 100 mg/dL, and patients at high risk should have LDL-C lowered to less than 100 mg/dL.

Atherogenic Dyslipdemia. Low-density lipoprotein cholesterol has long been considered the principal lipoprotein determinant of atherosclerosis, particularly small, dense LDL particles that more efficiently transport cholesterol into the vessel wall and have greater susceptibility for oxidation. Although LDL-C is a potent risk factor for cardiovascular disease, more than half of all events occur in patients with "normal" LDL-C levels. In the setting of elevated triglycerides, other lipoproteins become important determinants of atherosclerosis.

Atherogenic dyslipidemia, which includes fasting and postprandial hypertriglyceridemia, elevated levels of very low-density lipoprotein cholesterol (VLDL-C), low HDL-C levels, and an atherogenic small dense LDL profile, is associated with the metabolic syndrome and likely accounts for much of the residual risk after LDL-C lowering. Several other lipoprotein measures, including the apolipoprotein B:apolipoprotein A-I ratio, correlate well with insulin resistance and lipid abnormalities in the metabolic syndrome but are less routinely measured.[66] Although combination lipid-lowering therapy targeting atherogenic dyslipidemia may result in additional cardiovascular risk reduction in these patients, definitive trial data are currently lacking. On a routine lipid profile, atherogenic dyslipidemia can be most easily quantified using 2 measures: (1) non–HDL-C (total cholesterol – HDL-C); and (2) HDL-C.

Non–High-Density Lipoprotein Cholesterol. In epidemiologic studies, non–HDL-C predicts cardiovascular disease better than LDL-C, particularly when triglycerides are high.[67] Non–HDL-C offers the benefit of being an aggregate measure that includes the concentrations of *all* apolipoprotein B–containing lipoproteins currently thought to contribute to atherosclerosis. Indeed, non–HDL-C includes LDL and lipoprotein(a), as well as triglyceride-rich lipoproteins, such as VLDL, intermediate-density lipoprotein, and chylomicron remnants. Not surprisingly, as triglycerides increase, non–HDL-C correlates with apolipoprotein B much better than does LDL-C.[68]

Very low-density lipoprotein cholesterol, the chief contributor to non–HDL-C levels after LDL-C, is a triglyceride-rich apolipoprotein B–containing particle that is particularly sensitive to increases in abdominal obesity, insulin resistance, free fatty acid flux to the liver, and the resultant hypertriglyceridemia. Because VLDL-C is the principal carrier of plasma triglycerides, routine triglyceride measurements can be considered surrogate measures for VLDL-C concentration.

Triglyceride and non–HDL-C levels can be lowered with fibrate drugs, which are agonists of the peroxisome proliferator-activated receptor (PPAR) α transcriptional factor. Fibrates also modestly raise HDL-C and increase the size of LDL particles via pathways downstream of PPAR-α.[69] Trials have shown that gemfibrozil therapy may reduce initial and subsequent cardiovascular events.

The Helsinki Heart Study randomized 4081 men with non–HDL-C of 200 mg/dL (to convert to mmol/L, multiply by 0.0259) or more to the fibrate gemfibrozil or placebo.[70] Gemfibrozil reduced the primary end point of first nonfatal

myocardial infarction or cardiac death by 34% (2.7% vs 4.1%; $P<.02$), with a larger 66% reduction in patients with triglyceride levels of 200 mg/dL (to convert to mmol/L, multiply by 0.0113) or more and HDL-C levels of less than 42 mg/dL (to convert to mmol/L, multiply by 0.0259).[71] A similar result was seen in the Bezafibrate Infarction Prevention (BIP) study, with a 42% reduction in fatal and nonfatal cardiac events in patients with triglyceride levels of 200 mg/dL or more and HDL-C levels of less than 35 mg/dL ($P=.02$).[72]

More recently, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomized 9795 patients with type 2 diabetes mellitus to micronized fenofibrate or placebo.[73] This study showed a nonsignificant reduction in first myocardial infarction or death from coronary heart disease (5.2% vs 5.9%; $P=.16$). However, fenofibrate use resulted in a significant 24% reduction in nonfatal myocardial infarction ($P=.01$) and a significant 21% reduction in revascularization ($P=.004$); post hoc analyses adjusting for statin use revealed a 19% reduction in coronary heart disease events ($P=.01$).

When used in combination with statin therapy, fibrates provide incremental improvements in triglyceride, LDL-C, apolipoprotein B, and HDL-C levels.[74] However, the benefits of combination therapy must be weighed against the elevated risk of myalgias, myositis, and rhabdomyolysis. This risk may be reduced by combining statins with fenofibrate, which does not affect statin pharmacokinetics, rather than with gemfibrozil.[75]

Currently, no completed clinical trial has shown reduced cardiovascular events with combination statin-fibrate therapy. This approach is currently under study with fenofibrate in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which will be completed in 2009.[76]

Omega-3 fatty acids are useful in the treatment of hypertriglyceridemia. In large doses, these fatty acids reduce hepatic secretion of triglyceride-rich lipoproteins. Lovaza, an omega-3 fatty acid supplement, has received an Food and Drug Administration indication for treatment of primary hypertriglyceridemia. Omega-3 fatty acid therapy has also been shown to provide additional triglyceride reduction in statin-treated individuals.[77]

In summary, patients with the metabolic syndrome are likely to have elevated triglyceride levels and thus elevated non–HDL-C levels. In accordance with NCEP ATP III guidelines, non–HDL-C should be a secondary goal of treatment. Non–HDL-C targets are 30 mg/dL higher than the corresponding LDL-C goal for a given risk group.[10] Given the increased risk conferred by atherogenic dyslipidemia, it is appropriate to consider fibrate therapy and/or omega-3 fatty acid therapy to achieve non–HDL-C goals after lifestyle modification and intensification of statin therapy.

High-Density Lipoprotein Cholesterol. High-density lipoprotein cholesterol is critical for reverse cholesterol transport, and increased levels have a protective effect against atherosclerosis. Levels of HDL-C, which are inversely correlated with abdominal obesity and insulin resistance, can be improved with lifestyle modification.

Niacin inhibits hepatic uptake of apolipoprotein A-I and thus increases plasma pre-β HDL-C levels. It is the most efficacious agent for raising HDL-C levels, leading to 20% to 35% increases in plasma, while also reducing triglycerides. Niacin has been shown to reduce secondary cardiovascular events in the Coronary Drug Project.[77] In combination with a statin, the drug seems to slow atherosclerosis progression.[78,79] Use of higher doses of niacin (>1500 mg/d) in patients with the metabolic syndrome has been limited by data indicating mild worsening of glucose tolerance.[80,81] The ongoing Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial, which combines niacin with simvastatin for the treatment of atherogenic dyslipidemia, will help clarify the risks and benefits of niacin for patients with the metabolic syndrome.[82]

Niacin can be considered adjunctive therapy for patients with the metabolic syndrome who have low HDL-C or high triglyceride levels despite maximal lifestyle modification and therapy with statins and/or fibrates. At this time, safety in patients with glucose intolerance is not clearly established.

Diabetes Prevention

Dysglycemia results when the pancreas fails to produce adequate compensatory hyperinsulinemia for the degree of insulin resistance. Vascular damage can be evident long before a patient is overtly hyperglycemic. Clinical trial data indicate that early treatment of abnormal glucose metabolism with aggressive lifestyle therapy can delay or prevent frank diabetes. Currently, the use of pharmacotherapy for this indication is controversial.

The Diabetes Prevention Program randomized 3234 high-risk patients without diabetes who had elevated fasting and postload plasma glucose concentrations to placebo, metformin (850 mg twice daily), or an intensive lifestyle modification program with specific weight loss and exercise goals.[83] During 2.8 years of follow-up, the incidence of diabetes was 11 cases per 100 person-years in the placebo group vs 7.8 cases per 100 person-years in patients receiving metformin. An even greater decrease was noted in the lifestyle group with 4.8 cases per 100 person-years, corresponding to a 58% reduction (95% CI, 0.48-0.66)

compared with placebo. Multiple cost-benefit analyses have confirmed the feasibility of implementing such an intervention in higher-risk patients, such as those with the metabolic syndrome.[84]

The thiazolidinedione class of drugs are agonists of the PPAR-γ transcription factor and have pleiotropic effects, including improved insulin sensitivity, pancreatic β-cell preservation, improved HDL-C levels, decreased triglyceride levels, and increased LDL particle size.[85] Troglitazone, the first thiazolidinedione, was shown to reduce cases of new-onset diabetes but was withdrawn from the market because of hepatotoxicity.[86] In the DREAM trial, 5269 patients with abnormal glucose levels were randomized to rosiglitazone or placebo and followed up for a median of 3 years.[87] Patients who received rosiglitazone were 62% less likely (10.6% vs 25.0%; $P<.001$) to develop diabetes.

Despite the reduction in diabetes, the safety profile of rosiglitazone is not completely clear. In secondary analyses of several clinical trials, rosiglitazone increased cardiovascular events.[88] However, the only prospective study specifically examining rosiglitazone and cardiovascular events found it to be no more associated with cardiovascular events than were other common hypoglycemic agents.[89] In contrast, data from a meta-analysis and a recent large clinical trial suggest a neutral or possible modest salutary effect of pioglitazone on cardiovascular disease.[90,91] Data from the ongoing Pioglitazone in the Prevention of Diabetes (PIPOD)[92] and Actos Now for Prevention of Type 2 Diabetes (ACT-NOW)[93] will help determine if pioglitazone is indeed safe and effective for the prevention of diabetes.

Physicians should therefore concentrate on lifestyle interventions for the prevention of diabetes. Pharmacotherapy with metformin or pioglitazone may be considered if further glucose control is required. Fasting glucose levels should be measured periodically throughout treatment to monitor for progression to overt diabetes mellitus.

Diet

Weight loss has been shown to reduce oxidative stress[25] and to improve each of the components of the metabolic syndrome.[94] Unfortunately, emphasis on low-fat diets during the past half-century has led to a proportional increase in refined carbohydrate intake, contributing to insulin resistance, the metabolic syndrome, and diabetes.[95] Many readily available refined carbohydrates lead to more rapid increases and decreases in blood sugar levels, and this high glycemic load (GL) produces more insulin resistance.

Epidemiologic evidence from 2 large studies has linked high-GL diets with cardiovascular events, noting a greater effect on obese women.[96,97] Similar conclusions were reached in a recent clinical trial by Ebbeling et al.[98] In that study, 73 obese young adults were randomized to a low-GL diet or a low-fat diet. Patients in the low-GL group had greater increases in HDL-C levels ($P=.002$) and greater reductions in triglyceride levels ($P=.02$) at 6 months. Despite equivalent caloric intake and physical activity, the insulin-resistant patients in the low-GL group lost significantly more weight at 18 months ($P=.004$), suggesting specific benefit of the low-GL diet in hyperinsulinemic patients with the metabolic syndrome.

Inflammation is an integral part of the metabolic syndrome that is made worse by the proinflammatory macronutrient profile of the Western diet.[99] Strong data suggest that diets rich in omega-3 fatty acids and other unsaturated fats, natural antioxidants in fruits and vegetables, and fiber in nuts and whole grains provide specific benefit for patients with the metabolic syndrome.

The Mediterranean diet, based on the macronutrient profile of Mediterranean cultures, is rich in anti-inflammatory agents and antioxidants and was shown to reduce incidence of myocardial infarctions in the Lyon Diet Heart Study.[100] Adherence to a Mediterranean diet has been directly associated with lower total and cardiovascular mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC) study,[101] as well as decreased incidence of the metabolic syndrome in the large Seguimiento University of Navarra (SUN) cohort.[102]

Recently, Esposito et al[103] randomized 180 patients with the metabolic syndrome to the Mediterranean diet or a traditional heart-healthy low-fat diet. After 2 years, greater reductions in both insulin resistance and proinflammatory cytokines were observed in the Mediterranean diet group—56% of patients in the Mediterranean diet group had the metabolic syndrome at the end of the study vs 87% of those in the low-fat group ($P<.001$).

Recent clinical trial evidence points to supplementation with omega-3 fatty acids as a promising approach for the prevention of major coronary events, even in patients with adequate consumption of these oils.[104] These fatty acids decrease thrombosis, decrease oxidative stress, and decrease inflammation. In the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), statin-treated patients consuming an extra 1800 mg of eicosapentaenoic acid experienced a 19% relative reduction in major coronary events during a 5-year follow-up (2.8% vs 3.5%; $P=.011$), despite identical LDL-C concentrations.[105]

Rimonabant, an endocannabinoid inhibitor available in Europe but not in the United States, is an emerging therapy that encourages weight loss. In the Rimonabant In Obesity (RIO) trials, rimonabant was shown to improve cardiovascular risk factors.[106] In the Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant—the Intravascular Ultrasound Study (STRADIVARIUS), rimonabant slowed the progression of atherosclerosis.[107]

We conclude that a Mediterranean diet rich in omega-3 fatty acids, fruits, vegetables, and fiber that provides a low overall GL is appropriate for patients with the metabolic syndrome. Supplementation with omega-3 fatty acids is an emerging treatment modality and should be strongly considered in patients unable to consume goal amounts of omega-3 fatty acids. Additionally, referral to a nutritionist should be strongly considered for long-term reinforcement and follow-up.

Exercise

Cardiorespiratory fitness is associated with improved cardiovascular risk factors, increased insulin sensitivity,[108] decreased incidence of the metabolic syndrome,[109] and decreased cardiovascular mortality independently of measures of obesity.[110,111] Exercise is the primary determinant of fitness and of course is also effective for reducing fatness (obesity).[112]

Physical activity appears to have an even greater effect on patients with the cluster of abnormalities associated with insulin resistance. In a subgroup analysis of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study, levels of HDL-C increased with exercise only in patients with abdominal obesity and lipid components of the metabolic syndrome.[113]

A healthy exercise program can comprise many different activities. Simple, daily, vigorous walking can significantly improve cardiac risk factors and glucose metabolism.[114] A recent meta-analysis suggested that regular use of pedometers can motivate patients to increase their physical activity if daily goals are set.[115] A specific step goal such as 10,000 steps/d is associated with a significant increase in physical activity, decreased body mass index, and decreased systolic blood pressure.[115]

Despite changing guidelines, the optimal "dose" of exercise is unknown. Recent data from the Dose-Response to Exercise in Women Aged 45-75 Years (DREW) study reveals that there is a graded, dose-response improvement across levels of exercise training.[116] Patients exercising as little as 4 kcal/kg per week experienced significant increase in fitness and reduction in waist circumference compared with the no-exercise control group. Patients in the 12 kcal/kg per week group showed the greatest improvements.

These findings suggest that current guidelines are somewhat arbitrary and that, with regard to exercise and the metabolic syndrome, "a little is good, more is better."[117] Physicians may find pedometers a useful tool for motivating patients and monitoring their exercise habits.

CONCLUSION

An underrecognized and undertreated condition caused by abdominal obesity and insulin resistance, the metabolic syndrome predisposes people to the development of cardiovascular disease and diabetes. A clinical diagnosis of metabolic syndrome can be used as a tool to identify patients in need of comprehensive cardiovascular risk reduction therapy. A simple ABCDE approach is both easily accessible and comprehensive and can assist physicians by encouraging identification of patients with the metabolic syndrome and encouraging appropriate initiation and maintenance of treatment.

REFERENCES

1. Okosun IS, Chandra KM, Boev A, et al. Abdominal adiposity in U.S. adults: prevalence and trends, 1960-2000. *Prev Med.* 2004;39(1):197-206.
2. Li C, Ford ES, McGuire LC, Mokdad AH. Increasing trends in waist circumference and abdominal obesity among US adults. *Obesity (Silver Spring).* 2007;15(1):216-224.
3. 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(3):356-359.
4. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. *Diabetes Care.* 2004;27(10):2444-2449.
5. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *J Am Coll Cardiol.* 2006 Mar 21;47(6):1093-1100. Epub 2006 Feb 23.
6. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation.* 2005 Nov 15;112(20):3066-3072. Epub 2005 Nov 7.
7. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA.* 1990;263(21):2893-2898.
8. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol.* 2007 Jan 30;49(4):403-414. Epub 2007 Jan 12.
9. 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(7):539-553.
10. 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(25):3143-3421.
11. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [published corrections appear in *Circulation.* 2005;112(17):e297 and 2005;112(17):e298]. *Circulation.* 2005 Oct 25;112(17):2735-2752. Epub 2005 Sep 12.
12. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome—a new worldwide definition. *Lancet.* 2005;366(9491):1059-1062.
13. Ford ES. Rarer than a blue moon: the use of a diagnostic code for the metabolic syndrome in the U.S. *Diabetes Care.* 2005;28(7):1808-1809.
14. Kahn R. Metabolic syndrome: is it a syndrome? does it matter? *Circulation.* 2007;115(13):1806-1810.
15. Grundy SM. Does the metabolic syndrome exist? *Diabetes Care.* 2006; 29(7):1689-1692.
16. Reaven GM. The individual components of the metabolic syndrome: is there a raison d'etre? *J Am Coll Nutr.* 2007;26(3):191-195.
17. Blaha M, Elasy TA. Clinical use of the metabolic syndrome: why the confusion? *Clin Diabetes.* 2006;24:125-131.
18. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. *Diabetes.* 1998;47(5):699-713.

19. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation.* 2005;111(11):1448-1454.

20. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*. 2000;11(8):327-332.

21. Bulcão C, Ferreira SR, Giuffrida FM, Ribeiro-Filho FF. The new adipose tissue and adipocytokines. *Curr Diabetes Rev*. 2006;2(1):19-28.

22. Kong AP, Chan NN, Chan JC. The role of adipocytokines and neurohormonal dysregulation in metabolic syndrome. *Curr Diabetes Rev*. 2006; 2(4):397-407.

23. Yang R, Barouch LA. Leptin signaling and obesity: cardiovascular consequences. *Circ Res*. 2007;101(6):545-559.

24. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. The emerging role of the endocannabinoid system in endocrine regulation of energy balance. *Endocr Rev*. 2006 Feb;27(1):73-100. Epub 2005 Nov 23.

25. Dandona P, Mohanty P, Ghanim H, et al. The suppressive effect of dietary restriction and weight loss in the obese on the generation of reactive oxygen species by leukocytes, lipid peroxidation, and protein carbonylation. *J Clin Endocrinol Metab*. 2001;86(1):355-362.

26. Johnson LW, Weinstock RS. The metabolic syndrome: concepts and controversy. *Mayo Clin Proc.* 2006;81(12):1615-1620.

27. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 2001;24(4): 683-689.

28. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288(21):2709-2716.

29. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation*. 2003 Jul 29;108(4):414- 419. Epub 2003 Jul 14.

30. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K, DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in non-diabetic European men and women. *Arch Intern Med*. 2004;164(10):1066-1076.

31. McNeill AM, Rosamond WD, Girman CJ, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the Atherosclerosis Risk in Communities study. *Diabetes Care*. 2005;28(2):385-390.

32. Rexrode KM, Carey VJ, Hennekens CH, et al. Abdominal adiposity and coronary heart disease in women. *JAMA*. 1998;280(21):1843-1848.

33. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation.* 2007 Jan 30;115(4):450-458. Epub 2006 Dec 26.

34. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol.* 2002;90(8A):22i-29i.

35. Jeppesen J, Hansen TW, Rasmussen S, Ibsen H, Torp-Pedersen C, Madsbad S. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease: a population-based study. *J Am Coll Cardiol*. 2007 May 29;49(21):2112-2119. Epub 2007 May 17.

36. Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? a meta-analysis of prospective studies. *Arch Intern Med.* 2004;164(19):2147-2155.

37. Kullo IJ, Cassidy AE, Peyser PA, Turner ST, Sheedy PF II, Bielak LF. Association between metabolic syndrome and subclinical coronary atherosclerosis in asymptomatic adults. *Am J Cardiol.* 2004;94(12):1554-1558.

38. Ingelsson E, Sullivan LM, Murabito JM, et al. Prevalence and prognostic impact of subclinical cardiovascular disease in individuals with the metabolic syndrome and diabetes. *Diabetes.* 2007Jun;56(6):1718-1726. Epub 2007 Mar 16.

39. Santos RD, Nasir K, Tufail K, Meneghelo RS, Carvalho JA, Blumenthal RS. Metabolic syndrome is associated with coronary artery calcium in asymptomatic white Brazilian men considered low-risk by Framingham risk score. *Prev Cardiol.* 2007;10(3):141-146.

40. Diabetes Epidemiology: Collaborative analysis Of Diagnostic Criteria in Europe (DECODE) Study Group. Does diagnosis of the metabolic syndrome detect further men at high risk of cardiovascular death beyond those identified by a conventional cardiovascular risk score? the DECODE Study. *Eur J Cardiovasc Prev Rehabil.* 2007;14(2):192-199.

41. Girman CJ, Rhodes T, Mercuri M, et al, 4S Group, 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(2):136-141.

42. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med.* 2005;165(22):2644-2650.

43. 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 [published correction appears in *Diabetes Care.* 2005;28(1):238]? *Diabetes Care.* 2004;27(11):2676-2681.

44. Taylor AJ, Merz CN, Udelson JE. 34th Bethesda Conference: Executive summary—can atherosclerosis imaging techniques improve the detection of patients at risk for ischemic heart disease? *J Am Coll Cardiol.* 2003;41(11): 1860-1862.

45. Braunstein JB, Cheng A, Fakhry C, Nass CM, Vigilance C, Blumenthal RS. ABCs of cardiovascular disease risk management. *Cardiol Rev.* 2001;9(2): 96-105.

46. Gluckman TJ, Baranowski B, Ashen MD, et al. A practical and evidence-based approach to cardiovascular disease risk reduction [published correction appears in *Arch Intern Med.* 2004;164(27):1832]. *Arch Intern Med*. 2004;164(14):1490-1500.

47. Gluckman TJ, Sachdev M, Schulman SP, Blumenthal RS. A simplified approach to the management of non-ST-segment elevation acute coronary syndromes [published correction appears in *JAMA.* 2005;293(14):1728]. *JAMA.* 2005;293(3):349-357.

48. Devaraj S, Rosenson RS, Jialal I. Metabolic syndrome: an appraisal of the pro-inflammatory and procoagulant status. *Endocrinol Metab Clin North Am.* 2004;33(2):431-453.

49. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ.* 2004;329(7456):15-19.

50. Pearson TA, Blair SN, Daniels SR, et al. 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. *Circulation.* 2002;106(3):388-391.

51. Mosca L, Banka CL, Benjamin EJ, et al. Expert Panel/Writing Group. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update [published correction appears in *Circulation.* 2007;115(15):e407]. *Circulation.* 2007 Mar 20;115(11):1481-1501. Epub 2007 Feb 19.

52. US Preventative Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med.* 2002;136(2):157-160.

53. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA.* 2007; 297(18):2018-2024.

54. Reaven GM. Insulin resistance/compensatory hyperinsulinemia, essential hypertension, and cardiovascular disease. *J Clin Endocrinol Metab*. 2003; 88(6):2399-2403.

55. Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention [published correction appears in C*irculation.* 2007;116(5):e121. *Circulation*. 2007 May 29;115(21):2761-2788. Epub 2007 May 14.

56. Mayor S. NICE removes β blockers as first line treatment for hypertension. *BMJ.* 2006;333(7557):8.

57. National Institute for Health and Clinical Excellence (NICE) Web site. http://www.nice.org.uk/CG34\. Accessed June 25, 2008.

58. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. 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) [published corrections appear in *JAMA*. 2003; 289(2):178 and 2004;291(18):2196]. *JAMA.* 2002;288(23):2981-2997.

59. Yusuf S, Gerstein H, Hoogwerf B, et al. Ramipril and the development of diabetes. *JAMA.* 2001;286(15):1882-1885.

60. Yusuf S, Ostergren JB, Gerstein HC, et al, Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity Program (CHARM) Investigatiors. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure [published correction appears in *Circulation.* 2005;112(7):e292]. *Circulation.* 2005 Jul 5; 112(1):48-53. Epub 2005 Jun 27.

61. Lindholm LH, Ibsen H, Borch-Johnsen K, et al, LIFE Study Group. Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. *J Hypertens.* 2002;20(9):1879-1886.

62. Kjeldsen SE, Julius S, Mancia G, et al, VALUE Trial Investigators. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. *J Hypertens.* 2006;24(7): 1405-1412.

63. DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med*. 2006 Oct 12;355(15):1551-1562. Epub 2006 Sep 15.

64. Downs JR, Clearfield M, Weis S, et al, AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA*. 1998;279(20):1615-1622.

65. Sever PS, Dahlof B, Poulter NR, et al, ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet.* 2003;361(9364):1149-1158.

66. Sierra-Johnson J, Romero-Corral A, Somers VK, Lopez-Jimenez F. The apolipoprotein b/apolipoprotein AI ratio in the metabolic syndrome-should we start using it? J *Cardiometab Syndr*. 2008 Winter;3(1):53-54.

67. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA*. 2005;294(3):326-333.

68. Ballantyne CM, Andrews TC, Hsia JA, Kramer JH, Shear C, ACCESS Study Group. Correlation of non-high-density lipoprotein cholesterol with apolipoprotein B: effect of 5 hydroxymethylglutaryl coenzyme A reductase inhibitors on non-high-density lipoprotein cholesterol levels. *Am J Cardiol.* 2001;88(3):265-269.

69. Vamecq J, Latruffe N. Medical significance of peroxisome proliferator-activated receptors. *Lancet.* 1999;354(9173):141-148.

70. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med.* 1987;317(20):1237-1245.

71. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation.* 1992;85(1):37-45.

72. BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation.* 2000;102(1):21-27.

73. FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial [published correction appears in *Lancet.* 2006;368(9545):1415 and 1420]. *Lancet*. 2005;366(9500):1849-1861.

74. 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) [published correction appears in *Am J Cardiol.* 2006;98(3):427-428]. *Am J Cardiol*. 2005;95(4):462-468.

75. Davidson MH. Statin/fibrate combination in patients with metabolic syndrome or diabetes: evaluating the risks of pharmacokinetic drug interactions. *Expert Opin Drug Saf.* 2006;5(1):145-156.

76. Ginsberg HN, Bonds DE, Lovato LC, et al, ACCORD Study Group. Evolution of the Lipid Trial Protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Am J Cardiol.* 2007 Jun 18;99(12A): 56i-67i. Epub 2007 Apr 12.

77. Chan DC, Watts GF, Barrett PH, Beilin LJ, Redgrave TG, Mori TA. Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. *Diabetes.* 2002;51(8):2377-2386.

78. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol.* 1986;8(6):1245-1255.

79. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med.* 2001;345(22):1583-1592.

80. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins [published corrections appear in *Circulation.* 2004;110(23):3615 and 2005;111(24):e466]. *Circulation.* 2004 Dec 7;110(23):3512-3517. Epub 2004 Nov 10.

81. Grundy SM, Vega GL, McGovern ME, et al, 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(14):1568-1576.

82. National Institutes of Health. AIM-HIGH: Niacin Plus Statin to Prevent Vascular Events. ClinicalTrials.gov Web site. http://clinicaltrials.gov/ct/show/NCT00120289. Accessed June 26, 2008.

83. Knowler WC, Barrett-Connor E, Fowler SE, et al, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346(6):393-403.

84. Herman WH, Hoerger TJ, Brandle M, et al, Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med.* 2005;142(5):323-332.

85. Yki-Jarvinen H. Thiazolidinediones. *N Engl J Med.* 2004;351(11):1106-1118.

86. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes.* 2002;51(9):2796-2803.

87. The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet.* 2006;368(9541):1096-1105.

88. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes [published correction appears in *N Engl J Med.* 2007;357(1):100]. *N Engl J Med.* 2007 Jun 14;356(24):2457-2471. Epub 2007 May 21.

89. Home PD, Pocock SJ, Beck-Nielsen H, et al, RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med*. 2007 Jul 5;357(1):28-38. Epub 2007 Jun 5.

90. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA*. 2007;298(10):1180-1188.

91. Nissen SE, Nicholls SJ, Wolski K, et al, PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA*. 2008 Apr 2;299(13):1561-1573. Epub 2008 Mar 31.

92. Xiang AH, Peters RK, Kjos SL, et al. Effect of pioglitazone on pancreatic β-cell function and diabetes risk in Hispanic women with prior gestational diabetes. *Diabetes.* 2006;55(2):517-522.

93. National Institutes of Health, Texas Diabetes Institute. Actos Now for Prevention of Diabetes (ACT NOW). ClinicalTrials.gov Web site. http://clinicaltrials.gov/ct2/show/NCT00220961?term=diabetes&rank=32. Accessed June 26, 2008.

94. Brook RD, Bard RL, Glazewski L, et al. Effect of short-term weight loss on the metabolic syndrome and conduit vascular endothelial function in overweight adults. *Am J Cardiol.* 2004;93(8):1012-1016.

95. Hu FB. Diet and cardiovascular disease prevention the need for a paradigm shift [editorial]. *J Am Coll Cardiol.* 2007 Jul 3;50(1):22-24. Epub 2007 Jun 18.

96. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr.* 2000;71(6):1455-1461.

97. Beulens JW, de Bruijne LM, Stolk RP, et al. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. *J Am Coll Cardiol.* 2007 Jul 3;50(1):14-21. Epub 2007 Jun 18.

98. Ebbeling CB, Leidig MM, Feldman HA, Lovesky MM, Ludwig DS. Effects of a low-glycemic load vs low-fat diet in obese young adults: a randomized trial [published correction appears in *JAMA*. 2007;298(6):627]. *JAMA.* 2007;297(19):2092-2102.

99. Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. *J Am Coll Cardiol.* 2006 Aug 15;48(4):677-685. Epub 2006 Jul 24.

100. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation.* 1999;99(6):779-785.

101. Trichopoulou A, Orfanos P, Norat T, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. *BMJ*. 2005 Apr 30;330(7498):991. Epub 2005 Apr 8.

102. Tortosa A, Bes-Rastrollo M, Sanchez-Villegas A, Basterra-Gortari FJ, Nuñez-Cordoba JM, Martinez-Gonzalez MA. Mediterranean diet inversely associated with the incidence of the metabolic syndrome: the SUN prospective cohort. *Diabetes Care.* 2007 Nov;30(11):2957-2959. Epub 2007 Aug 21.

103. Esposito K, Marfella R, Ciotola M, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA*. 2004;292(12):1440-1446.

104. Lee JH, O'Keefe JH, Lavie CJ, Marchioli R, Harris WS. Omega-3 fatty acids for cardioprotection. *Mayo Clin Proc.* 2008;83(3):324-332.

105. Yokoyama M, Origasa H, Matsuzaki M, et al, Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis [published correction appears in *Lancet.* 2007;370(9583):220]. *Lancet*. 2007;369(9567):1090-1098.

106. Van Gaal L, Pi-Sunyer X, Després JP, McCarthy C, Scheen A. Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program. *Diabetes Care.* 2008;31(suppl 2):S229-S240.

107. Nissen SE, Nicholls SJ, Wolski K, et al, STRADIVARIUS Investigators. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. *JAMA*. 2008 Apr 2;299(13):1547-1560. Epub 2008 Apr 1.

108. Nassis GP, Papantakou K, Skenderi K, et al. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metabolism*. 2005;54(11):1472-1479.

109. LaMonte MJ, Barlow CE, Jurca R, Kampert JB, Church TS, Blair SN. Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome: a prospective study of men and women. *Circulation.* 2005 Jul 26;112(4):505-512. Epub 2005 Jul 11.

110. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr*. 1999;69(3):373-380.

111. Church TS, Cheng YJ, Earnest CP, et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care.* 2004;27(1):83-88.

112. Lavie CJ, Milani RV. Cardiac rehabilitation and exercise training programs in metabolic syndrome and diabetes. *J Cardiopulm Rehabil*. 2005; 25(2):59-66.

113. Couillard C, Despres JP, Lamarche B, et al. Effects of endurance exercise training on plasma HDL cholesterol levels depend on levels of triglycerides: evidence from men of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study. *Arterioscler Thromb Vasc Biol.* 2001; 21(7):1226-1232.

114. Hu FB, Sigal RJ, Rich-Edwards JW, et al. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *JAMA.* 1999;282(15):1433-1439.

115. Bravata DM, Smith-Spangler C, Sundaram V, et al. Using pedometers to increase physical activity and improve health: a systematic review. *JAMA*. 2007;298(19):2296-2304.

116. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. *JAMA.* 2007;297(19):2081-2091.

117. Lee IM. Dose-response relation between physical activity and fitness: even a little is good; more is better [editorial]. *JAMA.* 2007;297(19):2137-2139.