

# Optimal Management of Hypertension and Obesity in the Metabolic Syndrome

*A Monograph for Continuing Medical Education Credit*

*Guest Editor*

**George L. Bakris, MD**



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Department of Continuing Medical Education  
Arlington Heights, Illinois

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Arlington Heights, Illinois 60004-1566

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**George L. Bakris, MD**

Professor of Preventive Medicine and Internal Medicine  
Director, Hypertension Research  
Rush-Presbyterian-St. Luke's Medical Center  
Chicago, Illinois

*Sponsored by: ACCESS Medical Group, Department of Continuing Medical Education*

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# Optimal Management of Hypertension and Obesity in the Metabolic Syndrome

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## *Goal and Learning Objectives*

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The goal of this activity is to educate physicians regarding the identification and treatment of patients with obesity, hypertension, and the metabolic syndrome.

This activity is intended for all general practitioners, cardiologists, endocrinologists, and other physicians interested in the management of obese or hypertensive patients with the metabolic syndrome.

After completing this CME activity, participants should be able to:

- Describe cardiovascular disease risks associated with hypertension and obesity in patients with the metabolic syndrome
- Recognize that hypertension and obesity patients with the metabolic syndrome need to be managed aggressively and comprehensively to minimize cardiovascular morbidity and mortality
- Explain recent recommendations of the Adult Treatment Panel (ATP) III and the Joint National Committee (JNC) VI regarding the management of obesity and hypertension in patients with the metabolic syndrome
- Discuss the role of therapeutic lifestyle changes in the treatment of hypertension and obesity
- Identify pharmacologic options and selection criteria for the treatment of obesity and hypertension in patients with the metabolic syndrome

# Optimal Management of Hypertension and Obesity in the Metabolic Syndrome

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## *Disclosure Statement*

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Current Guidelines state that participants in CME activities should be made aware of any affiliation or financial interest that may affect the editor's contributions. The editor has completed a statement of disclosure, which includes funding sources other than the honorarium received for this program. The editor has provided the following information on sources of funding that may be perceived as a potential conflict of interest.

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## *Inquiries Should Be Directed to*

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ACCESS Medical Group  
Department of Continuing Medical Education  
3395 N. Arlington Heights Road, Suite A  
Arlington Heights, IL 60004-1566  
Phone: 1-847-392-2227

# Optimal Management of Hypertension and Obesity in the Metabolic Syndrome

## *Introduction*

Clinical guidelines from the National Cholesterol Education Program (NCEP) provide an evidence-based approach to the prevention of cardiovascular disease (CVD) in at-risk patients.<sup>1</sup> NCEP Adult Treatment Panel (ATP) III is the first edition of the treatment guidelines to report the metabolic syndrome as an enhancer of cardiovascular risk beyond elevated low-density lipoprotein (LDL) cholesterol.<sup>1</sup> The metabolic syndrome is a condition that promotes atherosclerosis and increases the risk of cardiovascular events through the aggregation of independent metabolic disorders. The hallmark features of the metabolic syndrome include atherogenic dyslipidemia, a prothrombotic state, insulin resistance, hypertension, and abdominal obesity.<sup>2</sup> Other disorders associated with the metabolic syndrome include elevated microalbuminuria, increased fibrinogen, decreased plasminogen activator, elevated plasminogen activator inhibitor-1 (PAI-1), increased blood viscosity, and increased uric acid.<sup>3</sup> Each abnormality promotes atherosclerosis independently, but when clustered together, these metabolic disorders are increasingly atherogenic and enhance the risk of CVD at any LDL cholesterol level. In addition to increasing a patient's risk of CVD, the metabolic syndrome may hasten the development of stroke, type 2 diabetes,<sup>4</sup> diabetic nephropathy, retinopathy, and distal neuropathy.<sup>5</sup> The purpose of this educational monograph is to review major components of the metabolic syndrome and the importance of aggressive management of hypertension and abdominal obesity in patients with this condition.

## *Diagnostic Criteria*

The relationship between various metabolic abnormalities and CVD has been described by many different investigators over time,<sup>6</sup> though they used somewhat arbitrary criteria and terminology. In fact, the metabolic syndrome itself has been referred to variously as "syndrome X," "insulin resistance syndrome,"<sup>7</sup> "Reaven's syndrome,"<sup>8</sup> and "the metabolic cardiovascular risk syndrome."<sup>9</sup> In an effort to provide uniformity in the description of this phenomenon, the World Health Organization (WHO)<sup>10</sup> and ATP III<sup>1</sup> have proposed similar standards for the diagnosis of the metabolic syndrome.

**The metabolic syndrome is a condition that promotes atherosclerosis and increases the risk of cardiovascular events through the aggregation of independent metabolic disorders.**

According to the WHO, the metabolic syndrome can be diagnosed if the following components are present: 1) hypertension, defined as antihypertensive treatment and/or elevated blood pressure (>140 mm Hg systolic or >90 mm Hg diastolic); 2) dyslipidemia, defined as elevated plasma triglycerides ( $\geq 150$  mg/dL) and/or low high-density lipoprotein (HDL) cholesterol (<35 mg/dL in men, <39 mg/dL in women) concentrations; 3) obesity, defined as a high body mass index (BMI) ( $\geq 30$  kg/m<sup>2</sup>) and/or a high waist-to-hip ratio (>0.90 in men, >0.85 in women); and 4) microalbuminuria (urinary albumin excretion rate  $\geq 20$   $\mu$ g/min).<sup>10</sup> By this standard, individuals with type 2 diabetes must meet only 2 of the criteria in order to be diagnosed with the metabolic syndrome.

According to ATP III, a diagnosis of metabolic syndrome can be established if 3 or more of the following risk factors are present: (1) a waist circumference >102 cm (40 in) for men or >88 cm (37 in) for women; (2) a triglyceride level  $\geq 150$  mg/dL; (3) an HDL cholesterol level <40 mg/dL for men or <50 mg/dL for women; (4) blood pressure  $\geq 130/\geq 85$  mm Hg; or (5) a fasting glucose  $\geq 110$  mg/dL.<sup>1</sup> These guidelines assert that abdominal obesity rather than elevated BMI is more highly associated with the metabolic syndrome and suggest that all patients with abdominal obesity should be evaluated for the possibility of this disorder. In addition, ATP III has a lower diagnostic threshold level than the WHO for certain characteristics (ie, HDL cholesterol and hypertension). Therefore, a higher proportion of the population meets ATP III, rather than WHO, guidelines for the diagnosis of metabolic syndrome. [Table 1](#) compares current ATP III and WHO diagnostic standards.

**Table 1**

**COMPARISON OF ADULT TREATMENT PANEL (ATP) III AND WORLD HEALTH ORGANIZATION (WHO) CRITERIA FOR THE DIAGNOSIS OF THE METABOLIC SYNDROME.\***

Risk Factor	ATP III Defining Level	WHO Defining Level
1. Obesity	Waist circumference >102 cm (>40 in) for men and >88 cm (>35 in) for women	Body mass index (BMI) $\geq 30$ kg/m <sup>2</sup> and/or waist-to-hip ratio of >0.90 for men and >0.85 for women
2. Blood Pressure	$\geq 130/\geq 85$ mm Hg	>140/>90 mm Hg
3. Fasting Glucose	$\geq 110$ mg/dL	Not used for diagnosis
4. Microalbuminuria	Not used for diagnosis	Urinary albumin excretion rate $\geq 20$ $\mu$ g/min
5. Triglycerides	$\geq 150$ mg/dL	$\geq 150$ mg/dL
6. HDL Cholesterol	<40 mg/dL for men, <50 mg/dL for women	<35 mg/dL for men, <39 mg/dL for women

\*Under ATP III criteria, an individual must exhibit 3 of the risk factors from the ATP III column to be diagnosed with the metabolic syndrome. To meet WHO criteria, an individual must exhibit risk factors 1, 2, 4, and 5 or 6 from the WHO column.

## Prevalence

A substantial proportion of individuals living in Western nations are afflicted with multiple metabolic abnormalities. Using obesity, insulin resistance, dyslipidemia, impaired glucose tolerance (IGT), and hypertension as central features of the metabolic syndrome, one estimate suggests that as many as 50 to 75 million people in the United States may exhibit significant manifestations of the syndrome by 2010.<sup>6</sup> Using similar criteria, Kalff et al estimated that between 20% to 30% of middle-aged individuals living in highly industrialized countries may currently be affected by multiple features of the metabolic syndrome.<sup>11</sup> Ferrannini et al estimated that as few as 30% of all adults exhibit none of the major characteristics of the metabolic syndrome.<sup>12</sup> This data reflects the growing interest in the metabolic syndrome as a target for therapeutic intervention.

In a comprehensive epidemiological survey, Isomaa et al used WHO criteria to determine the prevalence of the metabolic syndrome.<sup>13</sup> This study included 4483 subjects between the ages of 35 years and 70 years from Finland and Sweden who were enrolled in the Botnia study. Subjects were divided into 3 groups, based on the results of a glucose tolerance test. Subjects with a fasting plasma glucose  $\geq 7.0$  mmol/l ( $\geq 126$  mg/dL) and/or a 2-hour plasma glucose  $\geq 11.1$  mmol/L ( $\geq 200$  mg/dL) were considered to have type 2 diabetes (n=1697). Subjects with a fasting plasma glucose between 6.1 and 6.9 mmol/L (110 to 126 mg/dL) and/or a 2-hour plasma glucose between 7.8 and 11.0 mmol/L (141 to 198 mg/dL) were considered to have impaired fasting glucose or impaired glucose tolerance (IFG/IGT, n=798). Subjects with a fasting plasma glucose  $< 6.1$  mmol/L (110 mg/dL) and a 2-hour plasma glucose  $< 7.8$  mmol/L ( $< 141$  mg/dL) were considered to have normal glucose tolerance (NGT, n=1988).

Using WHO criteria, the metabolic syndrome was observed in 10% of women and 15% of men with NGT, 42% of women and 64% of men with IFG/IGT, and 78% of women and 84% of men with type 2 diabetes.<sup>13</sup> Incidence of the metabolic syndrome increased with age. The frequency of metabolic abnormalities grouped by glucose tolerance and gender is shown in [Table 2](#). In this study, the prevalence of obesity was high in all groups, and especially high in male subjects. In addition, the prevalence of dyslipidemia and hypertension were both increased 2-fold in type 2 diabetic patients compared with subjects with normal glucose tolerance. Of the individual components of the metabolic syndrome, microalbuminuria conferred the strongest risk of cardiovascular death (relative risk=2.80;  $P=0.002$ ).<sup>13</sup>

The authors noted that the prevalence of metabolic syndrome and its components was strongly dependent on the definition used for the different components.<sup>13</sup> For example, obesity defined by a high waist-to-hip ratio was more common than obesity defined by a BMI  $> 30$  kg/m<sup>2</sup>. Increased awareness of the epidemiology of the metabolic syndrome will allow researchers to specifically target particular high-risk subgroups, based on gender, age, and glucose tolerance.

**As many as 50 to 75 million people in the United States may exhibit significant manifestations of the syndrome by 2010.<sup>6</sup>**

**Table 2****PREVALENCE OF THE METABOLIC SYNDROME AND THE DIFFERENT COMPONENTS OF THE METABOLIC SYNDROME IN MALE AND FEMALE SUBJECTS WITH NORMAL GLUCOSE TOLERANCE (NGT), ABNORMAL IMPAIRED FASTING GLUCOSE/IMPAIRED GLUCOSE TOLERANCE (IFG/IGT), AND DIABETIC GLUCOSE TOLERANCE (TYPE 2 DIABETES)<sup>13</sup>**

	NGT		IFG/IGT		Type 2 diabetes	
	Male	Female	Male	Female	Male	Female
Metabolic syndrome	15	10	64	42	84	78
Obesity	76	36	86	51	92	78
Dyslipidemia	29	16	45	31	54	56
Hypertension	23	24	31	35	55	59
Microalbuminuria	4	3	7	6	22	12
Insulin resistance*	25	25	58	59	87	89

Data are % and includes patients 35 to 70 years of age.

The definition of the metabolic syndrome was based on WHO criteria.

$P < 0.001$  for differences in all variables between subjects with diabetes and NGT/IFG/IGT when men and women were compared separately.

\* Highest quartile of the homeostasis model of insulin resistance (HOMAIR).

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The primary components of the metabolic syndrome (eg, obesity, atherogenic dyslipidemia, a prothrombotic state, insulin resistance, and hypertension) are highly related, involve multiple physiological systems, and exhibit a complex, multifactorial etiology.<sup>14,15</sup>

### *Components of the Metabolic Syndrome*

The primary components of the metabolic syndrome (eg, obesity, atherogenic dyslipidemia, a prothrombotic state, insulin resistance, and hypertension) are highly related, involve multiple physiological systems, and exhibit a complex, multifactorial etiology.<sup>14,15</sup> Contributors to the development of the metabolic syndrome may include genetics, a sedentary lifestyle, a Western diet (high in refined carbohydrates, low in fiber, and high in saturated fat), cigarette smoking,<sup>16</sup> and progressive weight gain.<sup>3</sup> This section briefly reviews the major risk factors of the metabolic syndrome.

#### *Atherogenic Dyslipidemia*

Population studies have established a clear link between elevated LDL cholesterol levels and CVD, and LDL cholesterol reduction is often a primary goal of therapeutic intervention.<sup>17</sup> Elevated LDL cholesterol, however, is usually considered to be an independent risk predictor for CVD and not a part of the metabolic syndrome. Atherogenic dyslipidemia, also known as the lipid triad, includes other lipid abnormalities more characteristic of the metabolic syndrome, such as moderately raised (often high-normal) triglycerides, an increased preponderance of small, dense LDL particles, and low levels of HDL cholesterol.<sup>17</sup>

The Framingham Heart Study established a correlation between low HDL cholesterol levels and increased risk of CVD at all LDL cholesterol levels,<sup>18</sup> and Kannel et al found that the risk of CVD decreased by 50% for each 10-mg/dL increase in low HDL levels.<sup>19</sup> The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) reported a 22% reduction in relative risk associated with a 6% increase in HDL cholesterol without lowering LDL cholesterol levels.<sup>20</sup> Most patients in the Québec Cardiovascular Study who developed CVD exhibited key features of atherogenic dyslipidemia.<sup>21</sup> In the study, small, dense LDL (peak particle diameter <25.64 nm) was a major predictor of CVD, increasing the risk by as much as 3.6-fold compared with patients who had morphologically normal LDL (peak particle diameter ≥26.05 nm).<sup>22</sup> Atherogenic dyslipidemia is thought to impart a risk for CVD at least equal to that of isolated, moderate hypercholesterolemia (eg, an isolated LDL cholesterol in the range of 160 to 220 mg/dL).

Atherogenic dyslipidemia and insulin resistance are related metabolic conditions.<sup>23,24</sup> The underlying metabolic abnormality driving dyslipidemia is believed to be an increased assembly and secretion of very low-density lipoprotein (VLDL) particles, leading to an increased plasma level of triglyceride.<sup>23,24</sup> As a result of increased VLDL production, increased transfer from HDL to VLDL occurs, resulting in decreased HDL levels. Growing evidence suggests that each of these lipoproteins independently promotes the development of atherosclerosis; when in combination, they rival LDL in atherogenic potential.<sup>3</sup> Despite the high risk of CVD conferred by these abnormalities, cholesterol-screening programs often overlook these lipoproteins.<sup>25</sup>

### *Prothrombotic State*

Insulin resistant patients often experience changes in coagulation factors that may promote arterial thrombosis and inflammation.<sup>14</sup> A procoagulant state may increase the formation of atherosclerotic plaques and the size of thrombi following the rupture of plaques. Commonly identified conditions in the metabolic syndrome that are related to a prothrombotic state include activation of endothelial cells, promotion of LDL oxidation, enhanced platelet aggregation, activation of factor VII, increased levels of factor IX, factor X, and prothrombin, and increased concentrations of PAI-1.<sup>26</sup>

Another factor that may play a role in atherogenic dyslipidemia and inflammation is peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ), a major regulator of intra- and extracellular lipid metabolism.<sup>27</sup> Activation of the PPAR- $\alpha$  ligand binding domain may facilitate fatty acid metabolism in the liver by promoting transcription of certain target genes, such as fatty acid binding protein. In addition, PPARs may play a central role in regulating the interaction between HDL cholesterol and apolipoprotein (apo) B-containing lipoproteins.<sup>28</sup>

## *Insulin Resistance*

Insulin is the primary hormone responsible for controlling the uptake, utilization, and storage of cellular nutrients.<sup>29</sup> Insulin's anabolic actions include the stimulation of intracellular utilization and storage of glucose, amino acids, and fatty acids, while it inhibits catabolic processes, such as the breakdown of glycogen, fat, and protein.<sup>29</sup> It accomplishes these functions by stimulating the transport of substrates and ions into cells, promoting the translocation of proteins between cellular compartments, activating and inactivating specific enzymes, and changing the amount of proteins by altering the rate of transcription of specific genes.<sup>29</sup>

Insulin-mediated glucose disposal varies approximately 10-fold in apparently healthy human beings.<sup>30</sup> Insulin resistance is an impaired response to normal levels of exogenous or endogenous insulin in cells, tissues (especially skeletal muscle and adipose tissue), the liver, or the whole body. Insulin resistance has been implicated in the pathogenesis of the metabolic syndrome.

In clinical practice, insulin resistance can usually be inferred from the presence of abdominal obesity. One of the major causes of insulin resistance is the overload of tissues with lipids. Obesity, especially upper body obesity, physical inactivity, fat-storage defects, male hormones, aging, and genetic factors may lead to the impairment of insulin action. Up to 79% of the variance in insulin sensitivity can be accounted for by central fat.<sup>30</sup> Patients with insulin resistance can also be identified through the following characteristics:<sup>31</sup>

- Impaired fasting glucose (fasting plasma glucose 111 to 125 mg/dL)
- Impaired glucose tolerance or type 2 diabetes (2-hr glucose on OGTT of 140 to 199 mg/dL; fasting plasma glucose  $\geq$ 126 mg/dL)
- Hypertriglyceridemia (fasting plasma triglycerides  $\geq$ 175 mg/dL)
- Low HDL cholesterol (fasting plasma HDL <45 mg/dL)
- Hyperuricemia or gout
- Family history of diabetes mellitus or coronary artery disease

In the Framingham Heart Study, at any level of blood pressure, the risk for a cardiac event was higher in both men and women with glucose intolerance compared with the risk in subjects without glucose intolerance.<sup>32</sup> The researchers noted that in either diabetic or hypertensive individuals, reducing the risk of cardiovascular disease events should be based on a comprehensive, multifactorial approach, since prevention requires more than normalization of either blood sugar or blood pressure. Prevention measures should include weight reduction, appropriate changes in diet, cessation of cigarette smoking, raising HDL, lowering LDL, and reduction of fibrinogen.<sup>32</sup>

Considerable overlap exists between features of insulin resistance and atherogenic dyslipidemia.<sup>24</sup> Patients with either condition tend to experience concomitant hypertension, obesity, hyperinsulinemia, diabetes, hypertriglyceridemia, elevated small, dense LDL, low HDL, and hypercoagulability. Central obesity often exacerbates the problem of insulin resistance and may increase the risk of atherosclerosis.<sup>24</sup>

## *Hypertension*

Many studies have shown that elevated systolic and diastolic blood pressure independently increases the risk for coronary heart disease (CHD).<sup>30,33</sup> Increased blood pressure independently increases the risk of atherosclerosis, presumably by promoting the entry of LDL into the subendothelial space, and may exacerbate other metabolic abnormalities.<sup>34</sup> WHO guidelines suggest that patients receiving antihypertensive treatment and/or having elevated blood pressure (>140 mm Hg systolic or >90 mm Hg diastolic) are at risk for the metabolic syndrome.<sup>10</sup>

Hypertension has been well established as a metabolic disorder and is predictive of insulin resistance.<sup>35</sup> As many as 50% of persons with hypertension have comorbid insulin resistance and hyperinsulinemia.<sup>31</sup> The use of an appropriate pharmacologic agent to reduce blood pressure may lessen the signs of insulin resistance in patients who exhibit both conditions. Lowering elevated blood pressure may also improve a patient's lipid profile.<sup>36</sup>

## *Identifying Patients With the Metabolic Syndrome*

Many of the abnormalities associated with the metabolic syndrome continue to be unrecognized and untreated by physicians.<sup>37</sup> Often, management of the metabolic syndrome is complicated by the complexity of differentiating patients who may be at the highest risk for CVD from low-to-moderate risk patients.<sup>37</sup> For example, patients with moderate levels of obesity based on a BMI measurement may exhibit a constellation of metabolic abnormalities, while patients with substantial levels of excess fat based on BMI may display a normal metabolic profile.<sup>37</sup> This is because intra-abdominal or visceral fat is a much greater predictor of cardiovascular risk than subcutaneous abdominal fat.<sup>38</sup>

Després et al have argued that the simple measurement of waist circumference in the clinic may be the easiest way to identify high-risk patients.<sup>37</sup> Such a measurement can suggest a high level of visceral adipose tissue accumulation in an overweight patient, a finding that can be confirmed via computed tomography. Up to 80% of patients with a waist measurement  $\geq 90$  cm ( $\geq 36$  in) and a triglyceride concentration  $\geq 177$  mg/dL may be characterized by an atherogenic triad of nontraditional markers (consisting of hyperinsulinemia, small, dense LDL particles, and elevated levels of apo B) that may increase the risk of CHD 20-fold.<sup>37</sup> Patients who have a high waist circumference and a preponderance of nontraditional risk factors express a phenotype known as the hypertriglyceridemic waist.<sup>39</sup>

Hyperinsulinemia, small, dense LDL particles, and elevated levels of apo B are important markers for the presence of the metabolic syndrome, even in patients who do not have an abnormally high level of visceral fat.<sup>40</sup> Evidence from the Sibutramine Trial in Obesity Reduction and Maintenance (STORM) study showed that weight-reduction intervention can positively affect metabolic abnormalities, including concentrations of serum triglycerides, VLDL cholesterol, insulin, C-peptide, and uric acid.<sup>41</sup>

**Up to 80% of patients with a waist measurement  $\geq 90$  cm ( $\geq 36$  in) and a triglyceride concentration  $\geq 177$  mg/dL may be characterized by an atherogenic triad of nontraditional markers (consisting of hyperinsulinemia, small, dense LDL particles, and elevated levels of apolipoprotein B) that may increase the risk of CHD 20-fold.<sup>37</sup>**

Obesity is correlated with increased insulin resistance and hyperinsulinemia, and increased cardiovascular risk.<sup>38</sup> Hyperinsulinemia and insulin resistance increase with weight gain and decrease with weight loss, suggesting a possible cause and effect relationship.<sup>42</sup> It has been suggested that the adipocyte may actively increase insulin resistance and impaired glucose tolerance by functioning as an endocrine organ.<sup>43</sup> Adipose tissue may regulate pathways responsible for energy balance through a complex network of hormonal and neuronal signals, and the recent isolation of the adipocyte hormone resistin in mice suggests that it may be an important link between abdominal obesity and insulin resistance.<sup>43</sup> Abdominal fat tissue could provide a signal for the chain of events leading to skeletal muscle and insulin resistance.<sup>44</sup>

The consequences of obesity are serious and include increased morbidity and mortality, reduced productivity and functioning, and increased health care costs (costs increase at older ages, and prevention of obesity at early ages could dramatically reduce these costs).<sup>45</sup> Patients with a higher BMI are at an increased risk of myocardial infarction (MI) and CHD; patients with a BMI  $\geq 29$  experience a 4-fold increased risk compared with patients who have a BMI  $< 21$ .<sup>46</sup> Clearly, abdominal obesity is a major clinical and public health issue that is an important indicator of the metabolic syndrome and an appropriate target for therapeutic intervention.

### *Management of Metabolic Abnormalities in the Metabolic Syndrome*

Because each independent factor of the metabolic syndrome can amplify the patient's risk of CVD, an integrated, multifaceted approach is indicated for patients with the syndrome. Often, by treating underlying cardiovascular risk factors, such as obesity or hypertension, other risk factors, such as IGT or atherogenic dyslipidemia, may also improve. Physicians should emphasize the use of diet and exercise as a first-line strategy to reduce signs of the metabolic syndrome in moderate-risk patients.<sup>1</sup> It should be noted, however, that viscerally obese middle-aged men with an atherogenic plasma lipoprotein profile (characterized by hyperinsulinemia, small, dense LDL particles, and elevated apo B) may be at a substantially increased risk of CHD. Patients exhibiting signs of the hypertriglyceridemic waist should be managed especially aggressively.

Because each independent factor of the metabolic syndrome can amplify the patient's risk of CVD, an integrated, multifaceted approach is indicated for patients with the syndrome.

## Case Study

To illustrate the importance of aggressive management in patients with multiple metabolic abnormalities including visceral obesity, the example of a 51-year-old white man presenting in the physician's office with a primary complaint of fatigue is summarized here.\* The patient regularly smoked fewer than 5 cigars per week and had not seen a physician in several years. When he had last visited a physician, he was prescribed an antihypertensive regimen, which was terminated after a few days because he felt poorly on the medication. His father had a heart attack at the age of 62 years. At the time of his visit, he had a hypertriglyceridemic waist and was more than 40 lbs overweight. He was unaware of his blood pressure, glucose, or lipid profile. His blood pressure was 160/98 mm Hg and his heart rate was 80 bpm. Cardiac examination revealed a regular rhythm without murmurs or gallops. Laboratory studies revealed an elevated fasting glucose of 136 mg/dL (normal range 60 to 110 mg/dL) with an elevated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) of 8% (normal range, 4.4% to 6.5%). Electrolytes, blood urea nitrogen (BUN), creatinine, and liver function tests were normal. Lipid profile measurements showed a triglyceride level of 250 mg/dL (normal range 30-150 mg/dL), total cholesterol of 220 mg/dL (normal range <200 mg/dL), LDL cholesterol of 105 mg/dL (normal range <100 mg/dL), and HDL cholesterol of 33 mg/dL (normal range >35 mg/dL).

### Diagnosis and Initial Treatment

The patient was diagnosed with multiple metabolic abnormalities that placed him at an increased risk of adverse cardiovascular outcomes. He was encouraged to quit smoking cigars and was initially prescribed 10 mg enalapril BID to control his elevated blood pressure. The use of an angiotensin converting enzyme (ACE) inhibitor was deemed most appropriate for this patient, because of concerns of fatigue and other side effects associated with beta blockers. In addition, he was prescribed 5 mg glyburide with a low-fat diet to improve glycemic control and simvastatin to improve his lipid profile. Sibutramine was also prescribed to help control weight. The patient was advised to maintain this pharmacologic regimen and return in 4 weeks for further evaluation.

### Follow-Up

The patient successfully quit smoking and maintained good home glucose readings due to administration of glyburide. In spite of the patient's difficulties with diet and twice-daily ACE inhibitor regimen compliance, he achieved successful weight reduction of 4 lbs with sibutramine. However, blood pressure was still unacceptably high (150/95 mm Hg), partially due to the difficulty of maintaining compliance with the regimen. Therefore, he was switched to once-daily trandolapril. In addition, while his LDL cholesterol was reduced to close to normal, triglycerides were high and HDL cholesterol was low. Lipid-modifying therapy with fenofibrate was recommended as an alternative to simvastatin, to improve lipid risk factors beyond elevated LDL.

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\*Case study adapted from: Levine JH. Managing multiple organ risk factors. In: Bakris GL, Mancia G, Messerli FH, Opie LH, eds. *Clinical Cases in Hypertension: Specific Treatment Strategies (Volume Two)*. Surry, UK: PAN Communications; 2000.

### *Therapeutic Lifestyle Changes*

According to NCEP-ATP III guidelines, therapeutic lifestyle changes (TLC) should be a part of any strategy to reduce the risk of CVD associated with the metabolic syndrome, regardless of whether or not the patient is receiving pharmacologic therapy. The essential features of the TLC approach include the following:<sup>1</sup>

- Reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg/d)
- Therapeutic options for enhancing LDL lowering such as plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d)
- Weight reduction
- Increased physical activity

While TLC is recommended as a necessary component of all treatment regimens for patients with the metabolic syndrome, it may not be sufficient to reduce the risk of CHD in all patients. Aggressive pharmacologic therapy is vital to patients who exhibit multiple metabolic abnormalities and to patients for whom compliance with TLC is an issue.

### *Managing Obesity in the Metabolic Syndrome*

Obesity may play a central role in the development of the metabolic syndrome. Increasing obesity is positively correlated with blood pressure, fasting insulin, glucose, and triglycerides, and negatively correlated with change in HDL cholesterol.<sup>47</sup> The primary goal of antiobesity drug therapy is to restore the balance between energy intake and expenditure. In order to achieve this goal, pharmacologic therapy may reduce energy intake by decreasing hunger, increasing satiety, or decreasing nutrient absorption. Energy equilibrium may also be achieved by increasing the metabolic rate of the patient, thereby increasing energy expenditure.

The use of long-term pharmacologic therapy can often facilitate and maintain modest weight loss with few adverse consequences. In addition, evidence from STORM suggests that weight-reduction intervention can positively affect multiple metabolic abnormalities, including concentrations of serum triglycerides, VLDL cholesterol, insulin, C-peptide, and uric acid.<sup>41</sup> The benefits of extended treatment appear to outweigh the risks for those patients who are unable to lose sufficient weight without pharmacologic therapy but who maintain adequate weight loss with long-term pharmacologic therapy.<sup>48</sup> Currently, sibutramine and orlistat are the only antiobesity drugs approved by the US Food and Drug Administration (FDA) for long-term use.

### **Sibutramine**

Regulation of feeding and satiety occurs in the region of the brain that includes the thalamus, hypothalamus, and pituitary gland. Sibutramine employs serotonin and norepinephrine blockade to reduce hunger, causing patients to feel full with less food. Active sibutramine metabolites inhibit the reuptake of serotonin and norepinephrine to modestly increase the concentration of the neurotransmitters at the synapses, prolonging their action at postsynaptic receptors. Sibutramine is the only medication that is approved for the long-term treatment of obesity that has once-daily dosing.

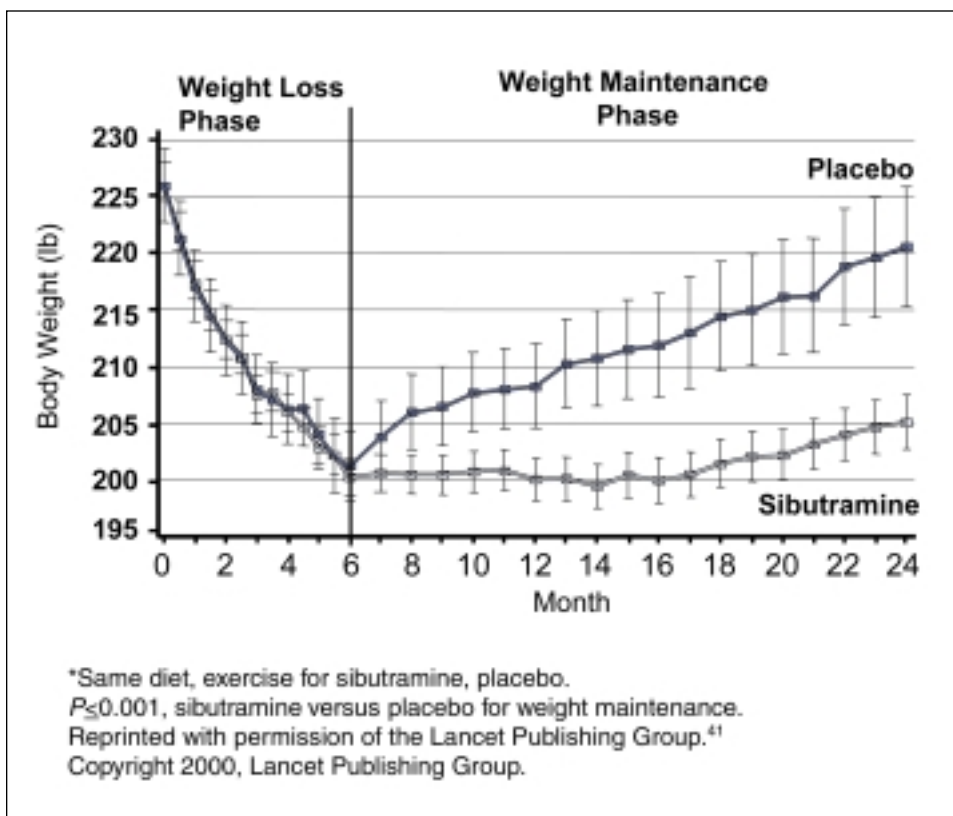
**Obesity may play a central role in the development of the metabolic syndrome. Increasing obesity is positively correlated with blood pressure, fasting insulin, glucose, and triglycerides, and negatively correlated with change in HDL cholesterol.<sup>47</sup>**

Sibutramine has been shown to induce dose-dependent weight loss and to enhance the effects of a low-calorie diet for up to a 2-year period.<sup>41</sup> The STORM study was a large, placebo-controlled trial designed to assess the ability of patients taking sibutramine to maintain long-term weight reductions and the effect of treatment on body composition, glycemic and serum lipid levels, and safety and tolerability. Patients who had successfully achieved weight loss over a 6-month period were randomized to receive either sibutramine or placebo for a subsequent 18-month period to test whether weight loss with sibutramine could be maintained over a 24-month period. The individualized management program employed in STORM achieved a 5% weight loss in 77% of obese patients. The average 6-month weight loss for all patients was 26 lbs, at which time patients were randomized to 2 groups. Of the 204 sibutramine-treated patients who completed the trial, 89 (43%) maintained 80% or more of their original 6-month weight loss and 142 (69%) maintained at least 5% weight loss 18 months after entering the study (see Figure 1). Nearly 3 times the number of patients maintained weight loss with sibutramine versus diet and exercise alone.

The STORM study was a large, placebo-controlled trial designed to assess the ability of patients taking sibutramine to maintain long-term weight reductions and the effect of treatment on body composition, glycemic and serum lipid levels, and safety and tolerability.<sup>41</sup>

**Figure 1**

Weight loss maintenance observed among patients on sibutramine versus placebo in the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) study.\*



In patients treated with sibutramine, there were substantial decreases in concentrations of serum triglycerides, VLDL cholesterol, insulin, C-peptide, and uric acid.<sup>41</sup>

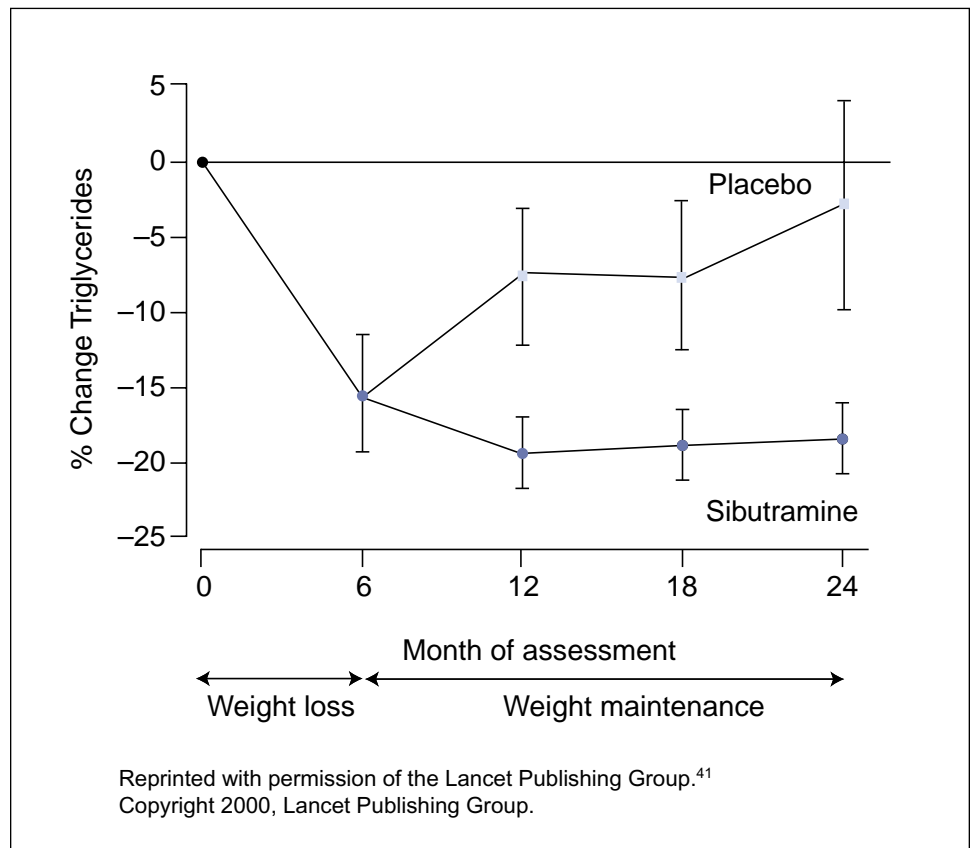
Weight loss was shown to correlate with metabolic improvements. In patients treated with sibutramine, there were substantial decreases in concentrations of serum triglycerides (see Figure 2a), VLDL cholesterol (see Figure 2b), insulin, C-peptide, and uric acid. In addition, there were significant changes in HDL cholesterol (a 19.9% increase, see Figure 2c) and total/HDL cholesterol ratio.<sup>41</sup> These changes were maintained up to 2 years and were proportional to weight loss.<sup>41</sup> In obese patients with type 2 diabetes, weight loss with sibutramine treatment has been shown to improve glycemic parameters.<sup>49</sup> Glycosylated hemoglobin (HbA<sub>1c</sub>) is an indicator of the average glucose level over time. Weight loss achieved with sibutramine was statistically significantly correlated with improvements in glycemic control, as indicated by HbA<sub>1c</sub>. For every 5% loss of weight associated with sibutramine, a 0.52 unit reduction in percent HbA<sub>1c</sub> was documented, resulting in a 20 mg/dL reduction in fasting plasma glucose. In addition, greater improvements were observed in patients who achieved the greatest loss of weight.<sup>49</sup>

**Figure 2**

Changes in concentration of selected blood lipids during weight-loss and weight-maintenance phases in the Sibutramine Trial of Obesity Reduction and Maintenance (STORM).

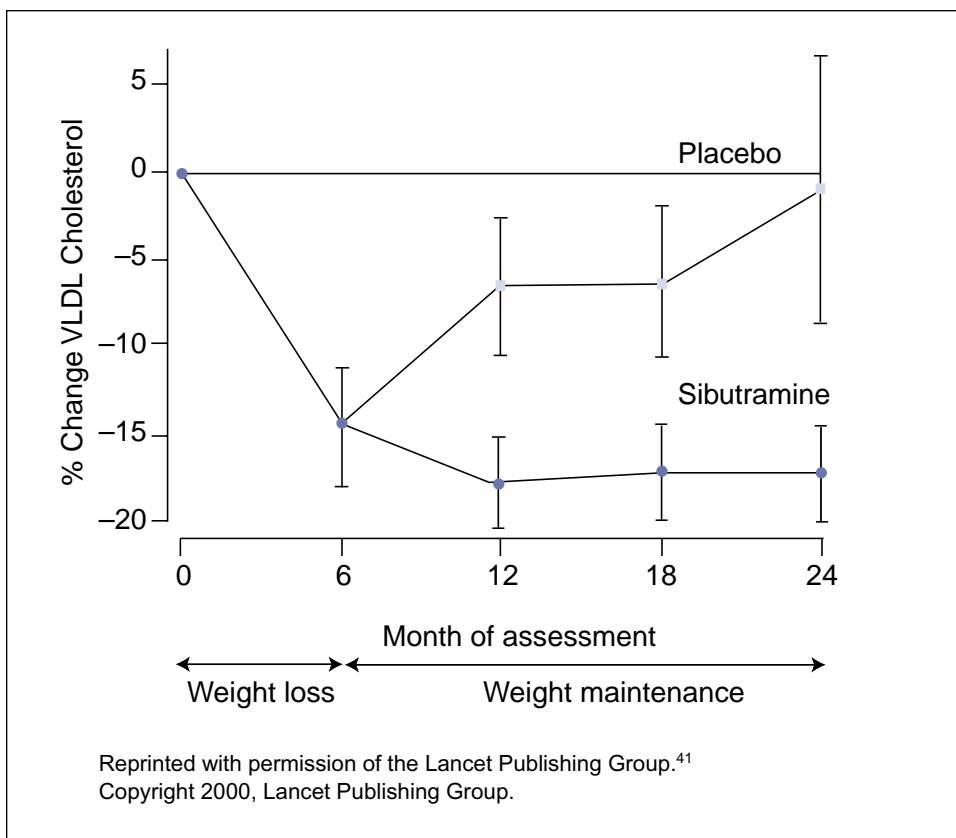
**Figure 2a**

Change in triglycerides with sibutramine.



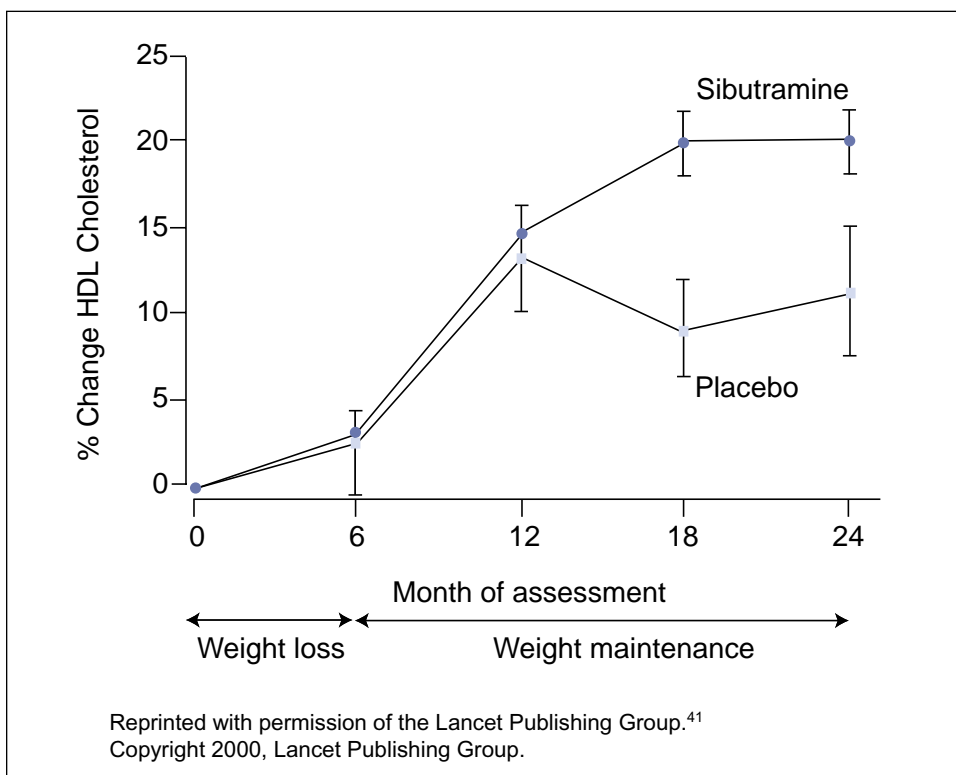
**Figure 2b**

Change in VLDL cholesterol with sibutramine.



**Figure 2c**

Change in HDL cholesterol with sibutramine.



Sibutramine has been shown to be an effective and well-tolerated weight loss treatment in hypertensive patients.<sup>50</sup> More randomized long-term obesity trials should be performed to evaluate the positive effects of STORM. As with most other weight-loss studies, over 80% of the participants in STORM were women. Therefore, the results of STORM may not be typical of what would be expected with the obesity phenotypes that typically affect men (ie, the hypertriglyceridemic waist).<sup>51</sup>

Common side effects associated with the use of sibutramine experienced by greater than 5% of patients compared with placebo include headache (30% versus 18%), dry mouth (17% versus 4%), anorexia (13% versus 3%), constipation (11% versus 6%), and insomnia (10% versus 4%).<sup>52</sup> Treatment with sibutramine is associated with mean increases in blood pressure of 1 to 3 mm Hg.<sup>52</sup> Regular monitoring of blood pressure is recommended when prescribing sibutramine. In mild-to-moderately obese hypertensive patients, weight loss with sibutramine has been shown to reduce diastolic blood pressure up to 4.0 mm Hg.<sup>53</sup>

## Orlistat

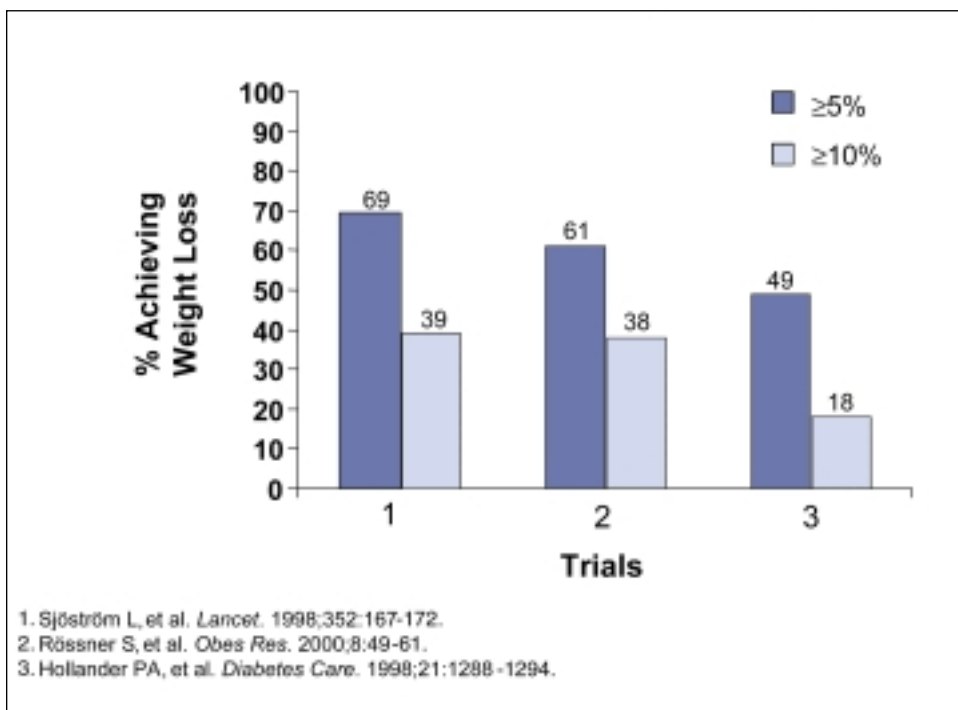
Orlistat is a selective lipase inhibitor approved for the long-term treatment of obesity. It has been evaluated in clinical trials for treatment of up to 2 years.<sup>54</sup> Orlistat works by inhibiting absorption of about 30% of dietary fat from the gut. When taken 3 times daily in conjunction with a low-calorie diet and multivitamin supplement, orlistat has been shown to maintain weight loss in the long term. [Figure 3](#) summarizes weight loss observed in placebo-controlled studies with orlistat. In one study, orlistat was evaluated in a double-blind multicenter study of 743 overweight patients. From the start of lead-in to the end of year 1, the orlistat group lost, on average, more bodyweight than the placebo group (10.2%, or 10.3 kg versus 6.1% or 6.1 kg; lifestyle modification difference 3.9 kg,  $P=0.001$  from randomization to the end of year 1).<sup>54</sup> During year 2, patients who continued with orlistat regained, on average, half as much weight as those patients switched to placebo ( $P=0.001$ ).<sup>54</sup> Patients switched from placebo to orlistat lost an additional 0.9 kg during year 2, compared with a mean regain of 2.5 kg in patients who continued on placebo ( $P=0.001$ ). This study found that calories derived from protein and carbohydrates were not affected by treatment with orlistat.<sup>54</sup>

Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis (impaired bile flow).<sup>55</sup> Gastrointestinal symptoms are the most commonly observed (incidence of 5% or more, and twice that of placebo) adverse events associated with the use of orlistat in the double-blind, placebo-controlled clinical trials, and are primarily a manifestation of the mechanism of action.<sup>55</sup> The most common of these adverse events were oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence.<sup>55</sup>

**From the start of lead-in to the end of year 1, the orlistat group lost, on average, more bodyweight than the placebo group (10.2%, or 10.3 kg versus 6.1% or 6.1 kg; lifestyle modification difference 3.9 kg,  $P=0.001$  from randomization to the end of year 1).<sup>54</sup>**

**Figure 3**

Percentage of patients losing  $\geq 5\%$  and  $\geq 10\%$  body weight in clinical trials involving orlistat.



### *Managing Hypertension in the Metabolic Syndrome*

Optimal management of hypertension in the metabolic syndrome through aggressive management may help to improve blood pressure, cholesterol levels, and insulin sensitivity.<sup>56</sup> According to The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) guidelines, patients with the metabolic syndrome should be managed differently than patients who do not have the disorder.<sup>56</sup> For example, corticosteroids and high-dose thiazides may be contraindicated in patients who are insulin resistant, because those therapies may exacerbate insulin resistance.<sup>57</sup> In addition, beta blockers and diuretics may not be well tolerated and may confer an increased risk of general side effects, and therefore may not be the appropriate first choice for patients with the metabolic syndrome.<sup>58</sup> The National Kidney Foundation (NKF) and the American Diabetes Association (ADA) have recommended a blood pressure goal of  $<130/80$  mm Hg for patients with diabetes.<sup>59</sup>

Angiotensin converting enzyme (ACE) inhibitors reduce elevated blood pressure through the process of vasodilation, which may actually improve insulin resistance by increasing insulin-mediated glucose uptake. Because of this action, ACE inhibitors may improve insulin sensitivity and may be especially appropriate for patients with the metabolic syndrome. Based on JNC VI, hypertensive patients with diabetes and proteinuria, congestive heart failure, and MI with systolic dysfunction should receive antihypertensive therapy with ACE inhibitors.<sup>56</sup> According to guidelines, ACE inhibitors may have favorable effects on comorbid diabetes mellitus (types 1 and 2) with proteinuria.

**ACE inhibitors may improve insulin sensitivity and may be especially appropriate for patients with the metabolic syndrome.**

The use of ACE inhibitors offers many cardiovascular benefits because they inhibit the formation of angiotensin II by ACE pathways and increase tissue bradykinin levels.<sup>60</sup> Angiotensin II is a potent vasoconstrictor, while bradykinin exerts positive effects on the endothelium by activating prostacyclin biosynthesis and stimulating release of nitric oxide. Angiotensin II directly affects the pathobiology of cardiovascular disease via growth promoting properties that can be observed as the proliferation of smooth muscle cells following vascular injury. Also, angiotensin II is involved in regulating the balance between fibrinolysis and thrombosis via modulation of PAI-1. Angiotensin II exerts a rapid, specific, and dose-dependent increase in PAI-1 expression in vivo in humans.<sup>60</sup> In addition, bradykinin serves as a potent stimuli for the release of tissue plasminogen activator (t-PA) and in patients treated with ACE inhibitors, bradykinin induces a dose-dependent increase in t-PA levels.

In contrast with ACE inhibitors, angiotensin receptor blockers (ARBs) act selectively to block the angiotensin II type 1 (AT1) receptor.<sup>61</sup> By acting at the level of the receptor, rather than the pathway, ARBs may be able to reduce side effects associated with other agents. However, because of their specificity, ARBs do not increase insulin sensitivity and may not be appropriate for patients with the metabolic syndrome. In addition, ARBs have not yet shown cardioprotective benefits in clinical trials.<sup>62</sup>

All of the ACE inhibitors currently available in the United States are approved for use in hypertension by the US Food and Drug Administration. These include benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril. Physicians should choose the appropriate ACE inhibitor on the basis of the drug's unique dosing, pharmacokinetic, and physical properties. According to JNC VI guidelines, the optimal formulation for effective blood pressure control should provide 24-hour efficacy with a once-daily dose.<sup>56</sup> In addition, at least 50% of the peak effect should be remaining at the end of the 24-hour dosing interval. Therefore, the trough-to-peak range should be at least 50%.<sup>56,63</sup> Table 3 summarizes dosing range and frequency of common ACE inhibitors and Table 4 summarizes reported trough-to-peak ratios.

**Table 3**

**DOSING RANGE AND FREQUENCY OF SELECTED ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS**

Drug	Dosage Range (mg)	Dosing Frequency
Captopril	12.5-150	BID-TID
Benazepril	5-40	QD-BID
Perindopril	4-8	QD
Quinapril	20-40	QD-BID
Ramipril	10-40	QD-BID
Lisinopril	5-40	QD*
Enalapril	5-40	QD-BID
Trandolapril	1-4	QD*

\* Recognized by JNC VI guidelines as the only true once-daily dosing ACE inhibitors.

Physicians should choose the appropriate ACE inhibitor on the basis of the drug's unique dosing, pharmacokinetic, and physical properties.

Table 4

**TROUGH-TO-PEAK RATIOS OF VARIOUS ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS AS DERIVED FROM 24-HOUR AMBULATORY BLOOD PRESSURE MONITORING MEASUREMENTS<sup>56</sup>**

Drug	Trough-to-Peak (%)
Captopril	0-40%
Benazepril	10-40%
Perindopril	30%
Quinapril	30-40%
Ramipril	40-50%
Lisinopril	40-70%
Enalapril	50-80%
Trandolapril	80-100%

### The TRACE Study

Trandolapril is indicated for the treatment of hypertension, post-MI congestive heart failure, and post-MI left ventricular dysfunction. ACE inhibition with trandolapril was evaluated in a randomized, double-blind, placebo-controlled study involving 1749 patients from 27 centers in Denmark.<sup>64</sup> The TRAndolapril Cardiac Evaluation (TRACE) study was designed to evaluate the role of ACE inhibition in a patient group that had reduced ventricular function shortly after MI, with or without symptoms of heart failure/ischemia.<sup>64</sup> Survival benefit was analyzed in all patients in the TRACE population with a minimum follow-up period of 6 years. The primary endpoint in the study was all-cause mortality. During the TRACE study, 34.7% of the trandolapril patients and 42.3% of the placebo patients died.<sup>65</sup>

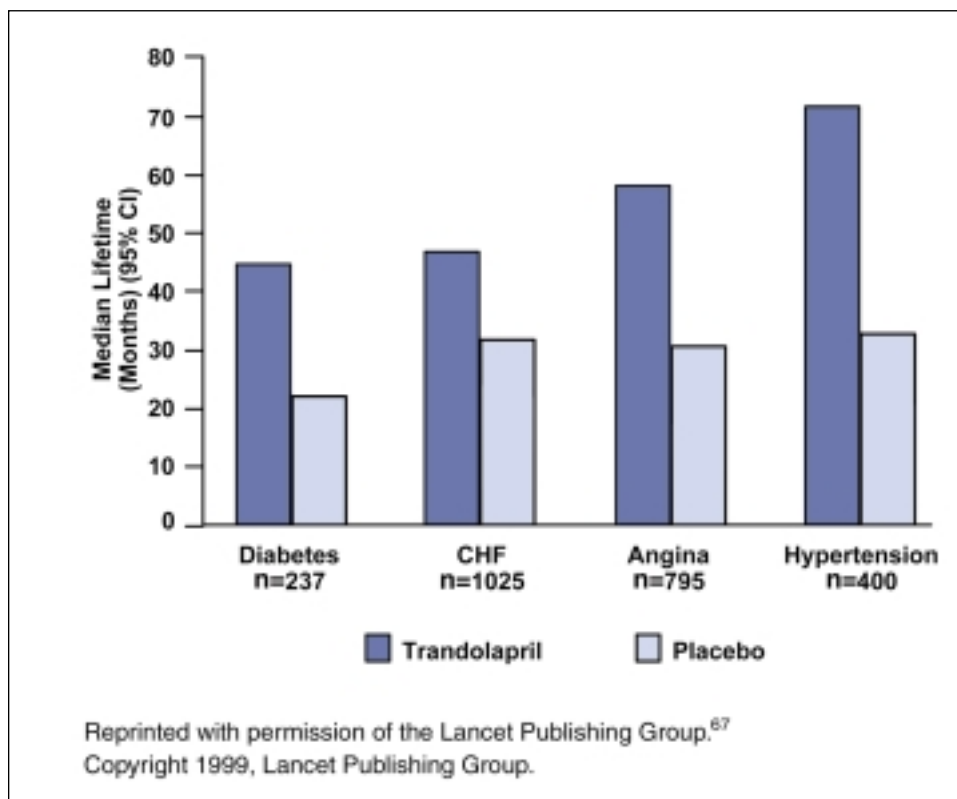
The beneficial effects of trandolapril in reducing the primary endpoint are summarized in Figure 4. They were observed 1 month after the start of therapy and continued throughout the study.<sup>65</sup> Trandolapril therapy was associated with a relative risk of death from any cause of 0.78 compared with placebo (95% confidence interval, 0.67 to 0.91;  $P=0.01$ ).

Trandolapril was associated with a 25% reduction in risk of death from cardiovascular causes compared with placebo. The beneficial effects of trandolapril therapy on overall mortality were consistent through all groups analyzed.<sup>65</sup> At the 2-year follow up, there was a 22% reduction in all-cause mortality and a trend toward decreased incidence of MI in the ACE inhibitor assigned group, and morbidity and mortality reductions were sustained at the 6-year follow-up. Cardiovascular mortality was reduced by 25%, progression to severe congestive heart failure was reduced by 29%, and sudden death, defined as death occurring within 1 hour after onset of new symptoms, was reduced by 24%. Trandolapril may be an effective therapeutic choice for patients with the metabolic syndrome because it has been shown to be equally effective at reducing elevated blood pressure, regardless of the patient's weight.<sup>66</sup>

**Trandolapril therapy was associated with a relative risk of death from any cause of 0.78 compared with placebo (95% confidence interval, 0.67 to 0.91;  $P=0.01$ ).<sup>65</sup>**

**Figure 4**

Survival rates among high-risk patients receiving trandolapril or placebo in the TRAndolapril Cardiac Evaluation (TRACE).



### The PEACE Study

Trandolapril was chosen as the ACE inhibitor to be tested in the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study, an 8100 patient, randomized, double-blind study designed to determine the usefulness of ACE inhibitors in treating coronary patients with left ventricular ejection fraction.<sup>66</sup> Members of the PEACE Steering Committee noted that trandolapril had established efficacy in morbidity and mortality in post-MI patients (TRACE), used an effective once-a-day dosing, and exhibited a side effect profile similar to other ACE inhibitors.<sup>66</sup>

The antihypertensive effects of trandolapril have been achieved in patients of many different weight levels. Trandolapril has also been shown to exhibit a high degree of lipophilicity,<sup>68</sup> or n-octanol water partition coefficient, which may be associated with an increased ability to penetrate tissues. The clinical significance of the lipophilic index, however, has not been established.

**Trandolapril has been shown to exhibit a high degree of lipophilicity.<sup>68</sup>**

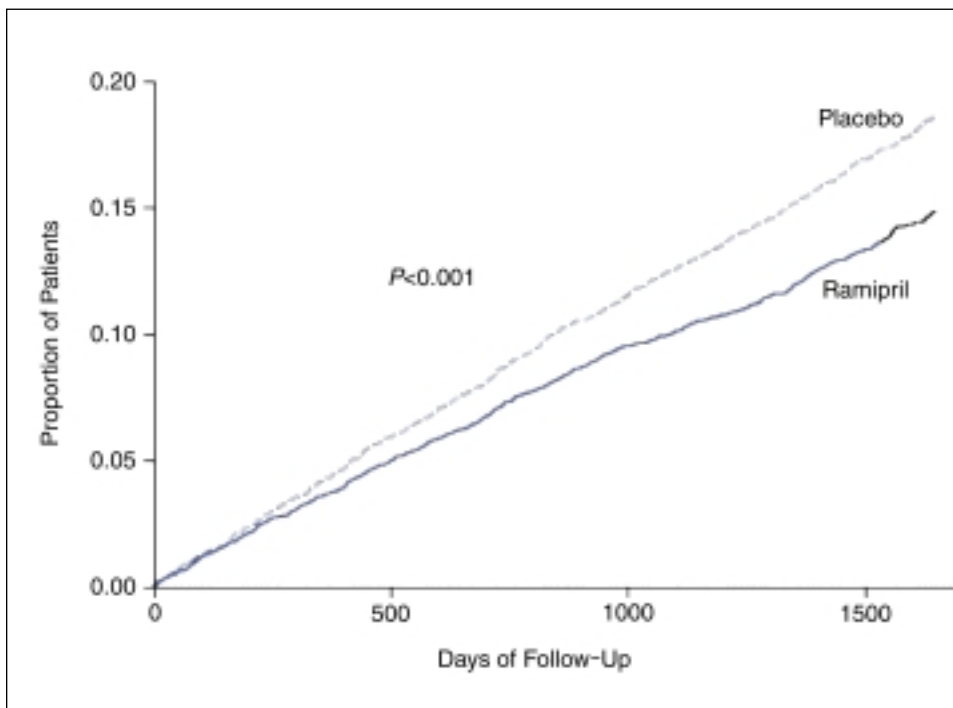
## The HOPE Study

The effects of ramipril and vitamin E in the treatment of patients with vascular disease or diabetes plus 1 other cardiovascular risk factor were reported in the Heart Outcomes Prevention Evaluation (HOPE) study.<sup>69</sup> This study involved a total of 9297 high-risk patients over 55 years of age. A total of 651 patients assigned to receive ramipril (14.0%) reached the primary end point, as compared with 826 patients who were assigned to receive placebo (17.8%) (relative risk, 0.78; 95% confidence interval, 0.70 to 0.86;  $P<0.001$ ). Figure 5 shows Kaplan-Meier estimates of composite outcomes evaluated in the study. Treatment with ramipril reduced the rates of death from cardiovascular causes (6.1% versus 8.1% in the placebo group; relative risk, 0.74;  $P<0.001$ ), myocardial infarction (9.9% versus 12.3%; relative risk, 0.80;  $P<0.001$ ), stroke (3.4% versus 4.9%; relative risk, 0.68;  $P<0.001$ ), death from any cause (10.4% versus 12.2%; relative risk, 0.84;  $P=0.005$ ), revascularization procedures (16.0% versus 18.3%; relative risk, 0.85;  $P=0.002$ ), cardiac arrest (0.8% versus 1.3%; relative risk, 0.63;  $P=0.03$ ), heart failure (9.0% versus 11.5%; relative risk, 0.77;  $P<0.001$ ), and complications related to diabetes (6.4% versus 7.6%; relative risk, 0.84;  $P=0.03$ ). The authors concluded that the spectrum of patients who would benefit from ACE inhibitor treatment is broad, and ACE inhibition is capable of preventing ischemia, atherosclerosis, heart failure, and left ventricular dysfunction.<sup>69</sup>

**Treatment with ramipril reduced the rates of death from cardiovascular causes, myocardial infarction, stroke, death from any cause, revascularization procedures, cardiac arrest, heart failure, and complications related to diabetes.<sup>69</sup>**

**Figure 5**

Kaplan-Meier estimates of the composite outcome of myocardial infarction, stroke, or death from cardiovascular causes in the ramipril group and the placebo group in the Heart Outcomes Prevention Evaluation (HOPE) study.<sup>69</sup>



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Patients receiving  
lisinopril had lower  
mortality than did  
control patients  
( $P=0.03$ ).<sup>70</sup>

### GISSI-3 Study

The Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI)-3 study evaluated the efficacy of lisinopril in the treatment of patients with acute MI.<sup>70</sup> This study included 200 coronary care units in Italy and 19,394 patients (78% men) with chest pain and ST-segment elevation or depression of  $\geq 1$  mm in  $\geq 1$  peripheral lead or  $\geq 2$  mm in  $\geq 1$  precordial lead who were admitted within the previous 24 hours and had no contraindications to the study treatments. Patients were assigned to oral lisinopril (5 mg/d at randomization and at 24 hours, then 10 mg/d thereafter), transdermal glyceryl trinitrate, both treatments, or neither. Main outcome measures included all-cause mortality and a combined end point of mortality and either congestive heart failure or left ventricular ejection fraction  $\leq 35\%$ . In this study, patients receiving lisinopril had lower mortality than did control patients ( $P=0.03$ ). Lisinopril also lowered the risk for the combined end point ( $P=0.01$ ).

### *Safety Considerations with ACE Inhibitors*

All ACE inhibitors approved by the FDA carry a black box warning regarding their use in the second and third trimesters of pregnancy. Several dozen cases of neuronal morbidity and death have been reported in the literature when ACE inhibitors have been administered during the second and third trimesters of pregnancy. Such adverse events do not appear to have resulted from intrauterine exposure to ACE inhibitor therapy that was limited to the first trimester; however, whenever patients become pregnant, ACE inhibitor therapy should be discontinued. Patients who have experienced angioedema with previous ACE inhibitor exposure should not receive ACE inhibitor therapy.

In controlled clinical trials of ACE inhibitors, a higher rate of angioedema was observed in black than in non-black patients. Angioedema has been reported in patients treated with ACE inhibitors. If laryngeal stridor or angioedema occurs, ACE inhibition should be discontinued. Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, emergency therapy should be promptly administered.

ACE inhibitors may cause symptomatic hypotension, especially in patients who are salt- or volume depleted. Volume and/or salt depletion should be corrected before initiating treatment with an ACE inhibitor. ACE inhibitors rarely have been associated with a syndrome involving cholestatic jaundice, fulminant hepatic necrosis, and death. Patients receiving ACE inhibitors who develop jaundice should discontinue the ACE inhibitor and be given appropriate medical follow-up.

### *Managing Dyslipidemia in the Metabolic Syndrome*

The majority of the patients with dyslipidemia and metabolic syndrome are overweight or obese and sedentary. NCEP-ATP III guidelines suggest that initiation of TLC can help to reduce triglycerides and raise HDL cholesterol in patients with the metabolic syndrome.<sup>1</sup> Weight reduction therapy for overweight or obese patients will enhance LDL lowering and may beneficially modify lipid and nonlipid risk factors. A portion of the population may require lipid-modifying drug intervention to reduce an elevated risk of CHD. The 4 main types of drugs used for managing dyslipidemia are hydroxymethyl-glutaryl coenzyme A (HMG CoA) reductase inhibitors (statins), fibric acid derivatives (fibrates), nicotinic acid, and bile acid sequestrants.

## Statins

This class of drugs reduces cholesterol synthesis by competitive inhibition of the rate-limiting enzyme HMG CoA reductase. HMG CoA reductase inhibitors reduce the cholesterol content of cells and stimulate synthesis of LDL receptors, especially in the liver. Increased hepatic LDL receptor activity leads to receptor-mediated clearance of LDL and VLDL remnants. These effects are associated with significant LDL cholesterol lowering and modest-to-moderate triglyceride lowering.<sup>71,72</sup> Drugs in this class include atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. Statins are not believed to effect glycemic control.<sup>73</sup>

## Fibric Acid Derivatives

The drugs in this class, which include gemfibrozil, clofibrate, and fenofibrate, lower lipids by reducing hepatic production of VLDL triglycerides. They also promote lipolysis of serum triglycerides by enhancing lipoprotein lipase activity. Fibric acid derivatives can raise HDL cholesterol levels, possibly by lowering triglyceride concentrations and by directly increasing synthesis of apo A-I.<sup>74</sup> In patients with normal triglyceride levels, fibric acids reduce LDL cholesterol concentrations by stimulating clearance of LDL from the circulation. Because these drugs have potent hypotriglyceridemic properties, they should be the drugs of first choice for patients with marked hypertriglyceridemia and for those with chylomicronemia who are at risk for acute pancreatitis.

In addition to potent hypotriglyceridemic properties, fibric acids (including gemfibrozil and fenofibrate) are recognized agonists of the PPAR- $\alpha$  system.<sup>75</sup> Therefore, fibric acids are capable of activating the PPAR- $\alpha$  ligand binding domain, which may facilitate fatty acid metabolism in the liver by promoting transcription of certain target genes, such as fatty acid binding protein. PPAR- $\alpha$  is considered a major regulator of intra- and extracellular lipid metabolism.<sup>27</sup> Upon fibrate activation, PPAR- $\alpha$  down-regulates hepatic apo C-III and increases lipoprotein lipase gene expression, key players in triglyceride metabolism.<sup>27</sup> In addition, PPAR- $\alpha$  activation increases plasma HDL cholesterol via the induction of hepatic apo A-I and apo A-II expression in humans.<sup>76</sup> Animal models have shown that PPAR- $\alpha$  agonists may directly improve insulin sensitivity and reduce adiposity.<sup>75</sup> This evidence suggests that the benefits of fibric acids may occur directly at a transcriptional level that may be in addition to the established hypotriglyceridemic effects of these agents.<sup>77</sup>

## Nicotinic Acid

Nicotinic acid reduces hepatic production of VLDL cholesterol, which results in lower levels of VLDL cholesterol and LDL cholesterol. It usually increases HDL cholesterol levels. Because elevated VLDL cholesterol and reduced HDL cholesterol are the characteristic lipoprotein patterns found in many patients with the metabolic syndrome, nicotinic acid would appear to be a viable treatment option for dyslipidemia.<sup>78,79</sup> However, in patients with type 2 diabetes, nicotinic acid therapy has been found to worsen glycemic control and raise plasma uric acid levels. It is not known how nicotinic acid therapy worsens hyperglycemia in patients with type 2 diabetes; this response may be due to accentuation of insulin resistance. Hyperuricemia from nicotinic acid therapy can precipitate gout and worsen renal function due to uric acid nephropathy.<sup>78,79</sup> For these reasons, nicotinic acid cannot be considered first-line therapy for dyslipidemia in type 2 diabetes, despite its actions to improve lipid and lipoprotein levels.

**Fibric acids are capable of activating the PPAR- $\alpha$  ligand binding domain, which may facilitate fatty acid metabolism in the liver by promoting transcription of certain target genes, such as fatty acid binding protein.<sup>75</sup>**

### *Bile acid sequestrants*

By binding to bile acids in the intestinal tract, these drugs interrupt their enterohepatic circulation, which results in more cholesterol converted to bile acids in the liver.<sup>79,80</sup> This depletion of hepatic cholesterol content stimulates hepatic LDL cholesterol receptor synthesis and promotes removal of LDL particles from the circulation. A problem with bile acid sequestrants, however, is that they tend to increase serum triglycerides, so their use cannot be recommended in patients with significant hypertriglyceridemia. Because of their effect on triglyceride levels and other side effects, the use of bile acid sequestrants should be limited to a select group of patients with type 2 diabetes who have an isolated increase in LDL cholesterol and normal serum triglyceride levels.

### *Managing Insulin Resistance in the Metabolic Syndrome*

Insulin sensitivity can often be improved through the management of obesity, hypertension, and dyslipidemia in the metabolic syndrome. Improvements in a patient's weight, blood pressure, and lipid profile correlate with improvements in a patient's glucose level.<sup>81</sup> In addition, therapies such as PPAR- $\alpha$  agonists (eg, fibrates)<sup>75</sup> and ACE inhibitors<sup>82</sup> may directly improve the insulin sensitivity of the patient. When TLC and other recommendations fail to lower the blood glucose level of the patient, drugs that directly improve the patient's insulin sensitivity should be considered. Therapies that do not directly affect hypertension, obesity, or atherogenic dyslipidemia but do affect insulin sensitivity include sulfonylureas, biguanides,  $\alpha$ -glucosidase inhibitors, and thiazolidinediones. Each of these drug classes utilizes a different mechanism and is summarized here.

#### *Sulfonylureas*

The sulfonylureas, a class of oral drugs designed to stimulate a release of insulin by the pancreas, were used in the United Kingdom Prospective Diabetes Study (UKPDS), one of the most comprehensive studies of patients with type 2 diabetes. A subsidiary trial of the study<sup>83</sup> showed that intensive blood-glucose control by either sulfonylureas or insulin substantially decreased the risk of microvascular complications, but not of macrovascular disease, in patients with type 2 diabetes.

The sulfonylureas can cause hypoglycemia that can be prolonged, dangerous, and often misdiagnosed. They also cause weight gain, a side effect that can exacerbate symptoms of the metabolic syndrome. Sulfonylureas are generally contraindicated for women who are pregnant or nursing. Some studies have shown the sulfonylureas to be effective as part of a combination regimen, rather than as a first-line monotherapy.

**Therapies that affect insulin sensitivity include sulfonylureas, biguanides,  $\alpha$ -glucosidase inhibitors, and thiazolidinediones.**

## *Biguanides*

Metformin, a biguanide, is often a therapy of choice for obese, insulin resistant patients with normal renal function. Metformin, unlike the sulfonylureas, does not cause weight gain, but may actually cause weight loss in patients. In addition, metformin does not cause hypoglycemia, because the drug diverts glucose in the gut wall to lactate through the anaerobic glycolysis pathway.

One subset of the UKPDS showed metformin to be an effective mono-therapy for the treatment of obese diabetic patients. In this study, metformin effectively improved insulin resistance, decreased insulin levels, decreased trigly- ceride and LDL levels, and did not cause hypoglycemia.<sup>84</sup> Another study showed that when oral agents alone do not provide adequate glucose control, the combina- tion of a single bedtime injection of insulin with 2 daily doses of metformin often normalizes blood glucose levels without the weight gain and hypoglycemia that may occur with other combined regimens.<sup>85</sup>

## *$\alpha$ -Glucosidase Inhibitors*

This class of drugs precludes enzymatic digestion of starches in the body, slowing the rate of blood sugar increase, especially after meals. A 24-week study of the  $\alpha$ -glucosidase inhibitor acarbose in 76 outpatients with type 2 diabetes and non- alcoholic liver cirrhosis showed a reduction in glycemia, post-prandial glycemia, mean glycemia, daily glucose variation, and other risk variables.<sup>86</sup> In addition, the study documented the tolerability of acarbose as well as the absence of toxic events on the liver with acarbose. This class of drugs is most effective when used in combination with other oral drugs, such as metformin or sulfonylurea.

## *Thiazolidinediones*

Thiazolidinediones increase the body's sensitivity to insulin by activating meta- bolism and fat synthesis genes. While clinical studies have shown these therapies to exert antihyperglycemic activity in a dose-dependent manner, the efficacy of these drugs may be challenged by their safety profile.<sup>87</sup> Concerns over hepatic safety led to the withdrawal of troglitazone from the market in March 2000. Rosiglitazone and pioglitazone, 2 other thiazolidinediones indicated for the improvement of glycemic control, were approved by the US FDA because the drugs demonstrated similar efficacy to troglitazone, with fewer safety concerns. Rosiglitazone is the most selective and potent thiazolidinedione.<sup>88</sup>

**One subset of the UKPDS showed that metformin effectively improved insulin resistance, decreased insulin levels, decreased triglyceride and LDL levels, and did not cause hypoglycemia.<sup>84</sup>**

## *Conclusions*

Recent NCEP-ATP III guidelines recognized the importance of the metabolic syndrome as an enhancer of cardiovascular risk beyond elevated LDL cholesterol. Major components of this condition include atherogenic dyslipidemia, hypertension, insulin resistance, obesity, and a prothrombotic state. The easiest method to identify patients at high risk is through the presence of the hypertriglyceridemic waist, which is characterized by the detection of visceral fat, rather than subcutaneous fat, along with nontraditional risk factors, such as hyperinsulinemia, small, dense LDL particles, and elevated levels of apo B.

According to ATP III, patients with the metabolic syndrome should be managed with a nonpharmacologic regimen of diet and exercise known as TLC. Because of the complicated etiology of the metabolic syndrome and issues with patient compliance, an aggressive pharmacologic approach is often necessary to reduce the CVD risk of the patient. The aggressive management of hypertension and obesity, central metabolic abnormalities in the syndrome, with pharmacologic intervention often improves other major risk factors. The only 2 therapies indicated for long-term weight reduction are sibutramine and orlistat. Due to the side effects of beta blockers and diuretics, ACE inhibitors may be the most appropriate choice for hypertensive patients with the metabolic syndrome. According to JNC VI guidelines, once-daily medications, such as trandolapril, can improve patient compliance. In the event that aggressive weight lowering and antihypertensive medication fails to control the syndrome, physicians may choose from a number of lipid-altering and insulin-sensitizing medications.

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# Optimal Management of Hypertension and Obesity in the Metabolic Syndrome

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## *Self-Assessment Questions*

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To receive up to **2.0 credit hours** in category 1 of the Physician's Recognition Award of the American Medical Association, please review this monograph carefully and answer the questions that follow. Answer ALL of the questions. Complete the enrollment form and mail, along with the completed post-test and the evaluation form, to ACCESS Medical Group, Department of Continuing Medical Education, 3395 N. Arlington Heights Road, Suite A, Arlington Heights, IL 60004-1566. Your corrected test, a copy of the answers, and a certificate (if appropriate) will be returned to you. Should you have any questions, call 1-847-392-2227.

To earn credit, a minimum score of 70% must be obtained. This test may be submitted only once for credit consideration and must be received by December 6, 2004. All test results are strictly confidential and intended for self-assessment only.

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## *CME Post-test*

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**1. Which of the following is NOT a feature of the hypertriglyceridemic waist?**

- a. Hyperinsulinemia
- b. Small, dense LDL particles
- c. Elevated levels of apolipoprotein B
- d. All of the above
- e. None of the above

**2. Adult Treatment Panel III guidelines define hypertension as a risk factor for the metabolic syndrome at what level?**

- a.  $\geq 140/\geq 85$  mm Hg
- b.  $> 140/> 90$  mm Hg
- c.  $\geq 130/\geq 85$  mm Hg
- d.  $> 130/> 90$  mm Hg

**3. Insulin-mediated glucose disposal varies approximately \_\_\_\_ fold in apparently healthy human beings.**

- a. 5-
- b. 10-
- c. 15-
- d. 20-

**4. Which of the following is a component of the therapeutic lifestyle changes diet recommended by the Adult Treatment Panel III guidelines?**

- a. Reduced intake of saturated fats ( $< 10\%$  of total calories)
- b. Reduced intake of viscous (soluble) fiber ( $< 10$  g/day)
- c. Reduced intake of cholesterol ( $< 200$  mg per day)
- d. All of the above
- e. None of the above

5. ***In the Heart Outcomes Prevention Evaluation (HOPE) study, trandolapril was associated with a 25% reduction in risk of death from cardiovascular causes, compared with placebo.***
- True
  - False
6. ***Which of the following classes of lipid-altering drugs may beneficially interact with PPAR- $\alpha$ ?***
- Bile acid
  - Nicotinic acid
  - Statins
  - Fibrates
7. ***GISSI-3 evaluated the use of which ACE inhibitor in the treatment of acute myocardial infarction?***
- Quinapril
  - Ramipril
  - Lisinopril
  - Enalapril
  - Trandolapril
8. ***Concerns over hepatic safety led to the withdrawal of which medication from the US market in March 2000?***
- Rosiglitazone
  - Moexipril
  - Troglitazone
  - Perindopril
  - Pioglitazone
9. ***Which of the following antihypertensive medications may exacerbate insulin resistance in patients with the metabolic syndrome?***
- Beta blockers
  - Corticosteroids
  - High-dose thiazides
  - All of the above
  - None of the above
10. ***In which of the following studies was weight loss positively correlated with improved concentrations of serum triglycerides, VLDL cholesterol, insulin C-peptide, and uric acid?***
- PEACE
  - STORM
  - AIPRI
  - All of the above
  - None of the above

# Optimal Management of Hypertension and Obesity in the Metabolic Syndrome

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## *Enrollment Form*

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(For CME Identification Purposes)

PLEASE PRINT CLEARLY

Name \_\_\_\_\_  
Last First MI Degree

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip code \_\_\_\_\_

Specialty \_\_\_\_\_ Social Security number \_\_\_\_\_

Medical Education number \_\_\_\_\_

Year medical degree was received \_\_\_\_\_

Phone number \_\_\_\_\_ Fax number \_\_\_\_\_

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I have read the CME monograph and completed the post-test in \_\_\_\_\_ hour(s).

(The smallest division of hours currently used by the AMA is 0.5 hours)

\_\_\_\_\_  
Participant Signature

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SCORE

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DATE CERT. SENT



# Optimal Management of Hypertension and Obesity in the Metabolic Syndrome

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## *Evaluation Form*

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After reviewing the monograph and completing the post-test, to what degree were the following objectives met?

**Scale: 1 = Low, 5 = High**

I am able to describe cardiovascular disease risks associated with hypertension and obesity in patients with the metabolic syndrome **1 2 3 4 5**

I am able to recognize the need for aggressive management of hypertension and obesity in the metabolic syndrome to minimize cardiovascular morbidity and mortality **1 2 3 4 5**

I am able to explain recent recommendations of the Adult Treatment Panel (ATP) III and the Joint National Committee (JNC) VI regarding the management of obesity and hypertension in patients with the metabolic syndrome **1 2 3 4 5**

I am able to discuss the role of therapeutic lifestyle changes in the treatment of hypertension and obesity **1 2 3 4 5**

I am able to identify pharmacologic options and selection criteria for the treatment of obesity and hypertension in patients with the metabolic syndrome **1 2 3 4 5**

Did you find the information contained herein to be clinically relevant?  Yes  No

Did you learn anything regarding the evaluation and treatment of the metabolic syndrome from this CME activity?  Yes  No

Provide specific examples:

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Can you apply this information to your clinical practice?  Yes  No

Provide specific examples:

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What topics would you like to see in future programs? \_\_\_\_\_

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How can we improve this monograph?

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