Overview of Metabolic Syndrome
By Ariane Conrad, PharmD

Upon successful completion of this article, the pharmacist should be able to:
1. Define metabolic syndrome.
2. Describe the risk factors associated with metabolic syndrome.
3. Describe the criteria used to diagnose metabolic syndrome.
4. Identify the goals of therapy for the management of the risk factors associated with metabolic syndrome.
5. Describe the management strategies for risk factors associated with metabolic syndrome.

INTRODUCTION
Metabolic syndrome has been extensively researched for more than 20 years. In 1988, Raven noted that patients who had glucose intolerance, hyperinsulinemia, high triglycerides, low HDL high cholesterol, and hypertension at the same time were at high risk of developing cardiovascular disease. He referred to this syndrome as “syndrome X.” In 1989, Kaplan published an article in which he identified upper body obesity, hypertension, hypertriglyceridemia, and glucose intolerance as the “deadly quartet” of metabolic risk factors that often coexist. His review of this coexistence of risk factors suggested that a shared pathology exists for those patients with more than one of these conditions. Since then, investigators have confirmed that multiple cardiovascular risk factors commonly do exist in one individual and that the presence of these multiple risk factors carry a greater risk for clinical adverse outcomes than a single risk factor.

Metabolic syndrome is sometimes referred to as if it was an individual diagnosis, but it is actually a clustering of multiple interrelated metabolic risk factors. Characteristics include abdominal obesity, dyslipidemia, elevated blood pressure, insulin resistance, and prothrombotic and proinflammatory states. Abdominal obesity (53 percent), hypertension (40 percent), and hyperglycemia (39 percent) have been identified as the most frequently occurring risk factors. This syndrome has received attention over the years because investigators have identified that cardiovascular disease is the primary risk factor.
clinical outcome associated with metabolic syndrome. The National Cholesterol Education Program Adult Treatment Panel III (ATP III) 2001 publication identified metabolic syndrome as a secondary target for risk reduction therapy, following LDL cholesterol, establishing the importance of addressing the increased CV risk associated with this cluster of factors.

**PATHOPHYSIOLOGY**

The underlying cause for metabolic syndrome is still not completely understood. However, insulin resistance and abdominal obesity are considered to be the most significant factors. Insulin resistance occurs when hepatic cells, skeletal muscle cells, and adipose tissue cells become less sensitive and resistant to the insulin produced by the pancreas. Glucose is unable to be transported into the cells due to the lack of response to insulin, so the glucose remains in the blood triggering more insulin production from the pancreas. This overproduction eventually leads to the wearing out of the pancreatic beta cells so the pancreas is no longer able to produce enough insulin. This leads to a diagnosis of type 2 diabetes. This insulin resistance is widely considered to be the most important contributor to metabolic syndrome. Obesity is closely associated with insulin resistance and it contributes to the development of hypertension, dyslipidemia, and hyperglycemia. Obesity has actually been found to be strongly associated with all CV risk factors. Obesity is defined as abnormal or excessive body fat accumulation and it occurs when food intake exceeds energy expended. Body mass index (BMI) is calculated by using weight (kg) divided by height (m^2) to classify adult patients as overweight and obese. A BMI of 25 to 29.9 classifies patients as overweight, and a BMI ≥ 30 classifies patients as obese. However, BMI is not an accurate measure to quantify body fat distribution so it is not useful for determining abdominal obesity. Abdominal obesity presents clinically as an increased waist circumference. The World Health Organization estimated, in 2008, that 1.5 billion adults were overweight and, of these, over 500 million can be classified as obese. They also estimate that the prevalence of worldwide obesity has more than doubled since 1980. For that reason, it is widely accepted that this increasing incidence of obesity is the major reason for the increasing prevalence of metabolic syndrome.

**RISK FACTORS**

There are three categories of risk factors for CVD, according to ATP III: major, life-habit, and emerging risk factors. The major risk factors include cigarette smoking, hypertension, low HDL cholesterol (<40 mg/dL), family history of premature coronary heart disease (CHD), and increased age (males > 45 and females > 55 years). These risk factors are also used in the Framingham risk assessment to determine the 10 year risk for developing CHD. The life-habit risk factors include obesity, physical inactivity, and atherogenic diet. The emerging risk factors include lipoprotein (a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease. The presence of life-habit risk factors and emerging risk factors can contribute to CVD and may be considered when making therapeutic decisions.

The following risk factors have been identified as components of the metabolic syndrome: abdominal obesity, atherogenic dyslipidemia (elevated triglyceride, small LDL particles, low HDL cholesterol), elevated blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. Each component is defined as follows.

- **Abdominal obesity** is considered to be a greater risk factor for CVD disease than excess fat in other areas. Clinically, it presents as a waist circumference greater than 40 inches for men and greater than 35 inches for women. Upper-body obesity is correlated more strongly with insulin resistance and the metabolic syndrome than lower-body obesity. ATP III considered abdominal obesity to be the risk factor primarily responsible for the increasing prevalence of metabolic syndrome, because obesity contributes to elevated blood pressure and blood cholesterol, low HDL cholesterol, and hyperglycemia.
• **Atherogenic dyslipidemia** presents as elevated triglycerides and low concentrations of HDL cholesterol on a routine lipoprotein analysis. Other lipoprotein abnormalities, including increased small LDL particles and elevated apolipoprotein B, may also be found on a detailed lipoprotein analysis. These abnormalities have been independently implicated as atherogenic.

• **Elevated blood pressure** is considered to be a major CVD risk factor. As blood pressure increases, the risk for myocardial infarction, stroke, heart failure, and kidney disease also increases.

• **Insulin resistance** rises with increasing body fat content and occurs in the majority of patients with metabolic syndrome. It is strongly associated with the other metabolic risk factors and it is sometimes considered to be one of the more important risk factors for CVD. Some guidelines place a greater priority on insulin resistance than other risk factors, so metabolic syndrome is sometimes referred to as the “insulin resistance syndrome.” It is argued that insulin resistance directly causes some of the other metabolic risk factors. However, since insulin resistance rises with increasing body fat content, it is not really clear which should be the priority. What is clear is that patients with longstanding insulin resistance generally do progress to glucose intolerance and eventually type 2 diabetes.

• **Prothrombotic state** is characterized by increased plasminogen activator inhibitor (PAI)-1 and fibrinogen. **Proinflammatory state** is characterized by elevations of C-reactive protein (CRP). In the presence of obesity, adipose tissue produces excess inflammatory cytokines leading to higher CRP and fibrinogen levels.

**EVALUATION**

There have been several criteria proposed for the diagnosis of metabolic syndrome. There are three tables that outline the diagnostic criteria:

### Table 1. Diagnostic Criteria for Metabolic Syndrome

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<thead>
<tr>
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<tbody>
<tr>
<td>Insulin Resistance</td>
<td>DMII, IFG, IGT, or lowered insulin sensitivity Plus 2 of the following:</td>
<td>None but must have any 3 of the following 5 components</td>
<td>None</td>
</tr>
<tr>
<td>Body Weight</td>
<td>Waist:Hip ratio &gt;0.9 in men, &gt;0.85 in women and/or BMI &gt;30 kg/m²</td>
<td>Waist circumference &gt;102 cm (&gt;40 in) in men, &gt;88 cm (&gt;35 in) in women</td>
<td>Increased waist circumference with ethnic specific values Plus 2 of the following:</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>HDL &lt;35 mg/dL in men or &lt;39 mg/dL in women and/or TG ≥150 mg/dL</td>
<td>HDL &lt;40 mg/dL in men or &lt;50 mg/dL in women and/or TG ≥150 mg/dL</td>
<td>HDL &lt;40 mg/dL in men or &lt;50 mg/dL in women or on specific treatment for ↑HDL or TG ≥150 mg/dL or on specific treatment for ↑TG</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>≥140/90 mmHg and/or antihypertensive meds</td>
<td>≥130/85 mmHg</td>
<td>≥130/85 mmHg or treatment for ↑BP</td>
</tr>
<tr>
<td>Glucose</td>
<td>DMII, IFG, or IGT*</td>
<td>Fasting glucose ≥110 mg/dL**</td>
<td>FPG ≥100 mg/dL or diagnosed with DMII</td>
</tr>
<tr>
<td>Other</td>
<td>Urinary excretion rate &gt;20 mcg/min or albumin:creatinine ratio ≥30mg/g</td>
<td></td>
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</tr>
</tbody>
</table>

DMII=type 2 diabetes, IFG=impaired fasting glucose, IGT=impaired glucose tolerance, HDL=high density lipoprotein, TG=triglycerides, FPG=fasting plasma glucose

* Impaired fasting glucose= fasting glucose 100-125 mg/dL; impaired glucose tolerance=2 hour post glucose in the oral glucose tolerance test of 140-199

** Fasting glucose level was changed to ≥100 mg/dL in 2004 after the ADA updated its definition of IFG.
major guidelines proposed: the World Health Organization (WHO) definition in 1998, the National Cholesterol Education Program-ATP III definition in 2001, and the International Diabetes Federation (IDF) definition in 2006. Each of these identifies CVD and CHD as the primary clinical outcomes of metabolic syndrome. The criteria proposed by each of these organizations are very similar to one another with the primary difference being the identified predominant cause of the syndrome. Criteria from each organization are detailed in Table 1.

The WHO guideline identified insulin resistance as the required component for diagnosis. Insulin resistance is identified by one of the following: type 2 diabetes, impaired fasting glucose, impaired glucose tolerance, or for patients with normal fasting glucose levels (<110 mg/dL), a glucose uptake below the lowest quartile for background population under hyperinsulinemic, euglycemic conditions. The oral glucose tolerance test (OGTT) is recommended to detect insulin resistance. In addition to insulin resistance, WHO criteria for metabolic syndrome require two other risk factors (obesity, hypertension, high triglycerides, low HDL cholesterol, or microalbuminuria) be present. For this guideline, obesity can be determined using BMI instead of waist circumference measurement. The major disadvantage of this guideline is that it requires that testing for hyperglycemia be performed before the diagnosis of metabolic syndrome can be made.

According to the criteria proposed by ATP III, three of the five characteristics listed must be present for a diagnosis to be made. This guideline lists abdominal obesity first, giving it priority over the other items listed. The other characteristics listed are elevated triglycerides, low HDL cholesterol, elevated blood pressure, and elevated fasting plasma glucose. For this guideline, a demonstration of insulin resistance is not required, but most patients that meet the ATP criteria will be insulin resistant. Also, type 2 diabetes does not exclude a diagnosis of metabolic syndrome. By these criteria, most patients with type 2 diabetes have the metabolic syndrome if they also have the metabolic abnormalities commonly associated with diabetes.

The diagnostic criteria proposed by the IDF identified central obesity (measured by waist circumference) as a requirement for the diagnosis of metabolic syndrome. Gender and ethnicity specific cut-points are provided for waist circumference measurement instead of the use of higher generalized cut-points used for all ethnic groups as with other guidelines. For example, the cut point for European males is ≥94 cm versus ≥90 cm for South Asian males. The cut point for both European and South Asian females is ≥80 cm. According to the IDF, ethnic group specific cut-points should be used for people of the same ethnic group regardless of the country of residence. In addition to central obesity, two of four characteristics listed must be present for a diagnosis to be made. The other diagnostic characteristics include elevated blood pressure, elevated fasting blood glucose, elevated triglycerides, and reduced HDL cholesterol. Insulin resistance is not a required characteristic per this guideline. Again, type 2 diabetes does not exclude a diagnosis of metabolic syndrome using these criteria and most patients with type 2 diabetes have the metabolic syndrome.

OVERVIEW OF MANAGEMENT

Risk Assessment

Risk should be assessed for all patients with metabolic syndrome before a treatment strategy can be determined. The standard Framingham risk assessment uses the following risk factors to determine the 10-year risk for developing CHD: cigarette smoking, hypertension, total cholesterol, low HDL cholesterol, and increased age. This assessment includes most of the risk factors for CVD in patients with metabolic syndrome. The addition of factors such as abdominal obesity, triglycerides, and glucose to the equation has not been proven to increase the prediction power of the scoring system, so the use of the standard risk factors alone is recommended. The Framingham risk assessment uses a point value system for each risk factor. It then divides patients with multiple risk factors into categories with a 10-year risk for CHD of >20 percent (high risk), 10–20
percent (moderate risk), or <10 percent (low risk). Those with a score of >20 percent are at the highest risk for CHD and CV events, meaning that more than 20 out of 100 people with this level of risk will have a CV event in the next 10 years. Using this system, patients with any clinical form of CVD or diabetes will likely belong to the high risk category (>20 percent). However, there is recent data that shows that not all patients with diabetes have high CV risk. Therefore, calculation of a risk score should still be performed on those patients to appropriately assess risk. For those patients with metabolic syndrome without CVD or diabetes, calculation of a risk score should definitely be performed to assess risk.

CVD is the primary clinical consequence of metabolic syndrome. Studies have shown that patients with metabolic syndrome have up to a 400 percent

<table>
<thead>
<tr>
<th>Therapy Target</th>
<th>Goal of Therapy</th>
<th>Therapeutic Recommendations</th>
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<tbody>
<tr>
<td>Obesity</td>
<td>Loss of 7–10% of body weight during year 1. Ultimate goal is to reach a desirable weight (BMI &lt;25 kg/m²).</td>
<td>Encourage calorie restriction; increase physical activity.</td>
</tr>
<tr>
<td>Physical Inactivity</td>
<td>30–45 minutes of moderate intensity activity 3–5 days/week. 60 minutes daily for weight loss. Resistance training at least 2 days/week.</td>
<td>Assess CV risk first in high risk patients; encourage gradual increase in activity intensity</td>
</tr>
<tr>
<td>Dietary Modification</td>
<td>Reduced intake of saturated fat, trans fat, cholesterol, sodium, &amp; simple sugars</td>
<td>Recommendations: saturated fat &lt;7%, reduced trans fat, total fat 25–35% of total calories, fiber 20–30g/day, carbohydrates 50–60% of total calories. Most dietary fat should be unsaturated.</td>
</tr>
<tr>
<td>Atherogenic Dyslipidemia</td>
<td>High risk: &lt;100 mg/dL (optional goal of &lt;70 mg/dL for some very high risk patients)*</td>
<td>Lifestyle modifications + LDL lowering agent to achieve the recommended goal</td>
</tr>
<tr>
<td>Secondary target: High non-HDL</td>
<td>High risk: &lt;130 mg/dL (optional goal of &lt;100 mg/dL for some very high risk patients with TG)*</td>
<td>Achieve LDL goal 1st. Intensify LDL lowering treatment (statin) to achieve non-HDL goal. Fibrate or nicotinic acid may be added if goal not reached on statin alone. If TG ≥500 mg/dL, start omega-3 fish oil before statin.</td>
</tr>
<tr>
<td>Tertiary target: Low HDL</td>
<td>No specific goal. Raise HDL as much as possible with standard LDL drug therapy.</td>
<td>Maximize lifestyle modifications. Consider fibrate or nicotinic acid as adjunct therapy with statin.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Reduce BP to &lt;140/90 (or &lt;130/80 if diabetes or chronic kidney disease is present)</td>
<td>Lifestyle modifications + BP lowering agent to achieve the recommended goal</td>
</tr>
<tr>
<td>Insulin Resistance &amp; Hyperglycemia</td>
<td>IFG: delay progression to T2DM T2DMi: HgA1c &lt;7%</td>
<td>Lifestyle modifications + glucose lowering agent, if needed to achieve HgA1c &lt;7%. Metformin is an option for IFG for patients at high risk for progressing to T2DM, unless impaired renal function present.</td>
</tr>
<tr>
<td>Prothrombotic State</td>
<td>Reduce levels of fibrinogen, PAI-1, &amp; other coagulation factors</td>
<td>Consider low-dose aspirin therapy in high risk patients; clopidogrel may be used if aspirin is contraindicated</td>
</tr>
<tr>
<td>Proinflammatory State</td>
<td>No specific recommendations</td>
<td>Lifestyle modifications (specifically weight loss)</td>
</tr>
</tbody>
</table>

LDL=low density lipoprotein, non-HDL=non-high density lipoprotein, HDL=high density lipoprotein, TG=triglycerides, BP=blood pressure, IFG=impaired fasting glucose, DMII=type 2 diabetes, PAI-1=plasminogen activator inhibitor

* Very high risk patients include those with recent acute coronary syndromes and established coronary heart disease with multiple major risk factors (e.g. diabetes).
increased risk of CVD. In patients with diabetes, the presence of the other metabolic syndrome risk factors increases that risk even more. Consequently, identifying patients at risk for diabetes is clinically important. The presence of impaired fasting glucose (fasting glucose 100-125 mg/dL) or impaired glucose tolerance (two-hour plasma glucose ≥140 mg/dL and <200 mg/dL during an oral glucose tolerance test) is termed prediabetes by the American Diabetes Association. Diagnosing and initiating intensive lifestyle modifications as treatment for patients with prediabetes can delay progression to type 2 diabetes and decrease CV risk. Therefore, early diagnosis of these patients is considered to be crucial for risk management.

**Goals of Therapy**

The primary goal for the management of metabolic syndrome is to reduce the risk for progression to atherosclerotic cardiovascular disease (ASCVD). The secondary goal is to prevent the development of type 2 diabetes for those patients that do not have it already. Effective lifestyle modifications are recommended to reduce all of the underlying risk factors for disease progression, specifically obesity, physical inactivity, and atherogenic diet. Therapy generally focuses on treating the individual components of the metabolic syndrome without regarding the syndrome as an identifiable target. A thorough risk assessment of all patients is necessary to determine if medication therapy should be considered. The recommended treatments for metabolic syndrome are summarized in Table 2 and detailed as follows.

**Management of Underlying Risk Factors**

**Obesity**

Weight reduction is the first priority for patients with metabolic syndrome and abdominal obesity. Loss of 7–10 percent of body weight is recommended over a period of six to 12 months. A reduced calorie diet consisting of a 500 to 1000 calorie per day reduction, along with increased physical activity, is recommended as a healthy regimen for weight loss. Emphasis should be placed on modifying behaviors that improve eating habits. Meal planning, reading food nutrition labels, eating regular meals, reducing portion sizes, and self-monitoring food intake are all behaviors that should be stressed to patients. Routine professional nutrition counseling is helpful also. Reaching the recommended weight loss goal will help to reduce the severity of most of the metabolic risk factors associated with metabolic syndrome.

Prescription weight loss medications are available as adjuncts to diet and exercise for patients with a BMI ≥30 without comorbid diseases, and for patients with a BMI≥27 with comorbidities. Most of these agents work as appetite suppressants. In general, these medications are only recommended for the short term treatment of patients at increased medical risk because of their weight. Unfortunately, medications are typically not appropriate for the treatment of obesity in patients with metabolic syndrome, as they are usually contraindicated in patients with CVD.

**Physical Inactivity**

Regular physical activity helps with weight loss and weight loss maintenance. It also affects metabolic risk factors and reduces CVD risk. Unfortunately, approximately 70 percent of the U.S. population live sedentary lifestyles and do not engage in the recommended amount of daily physical activity. The current recommendations for a standard exercise program are for 30 to 45 minutes of moderate intensity physical activity for three to five days per week. Increasing the amount and intensity level of activity beyond this provides further benefit. For patients with metabolic syndrome, 60 minutes or more of continuous or intermittent aerobic activity, preferably daily, is recommended for weight loss and weight loss maintenance. Resistance training should also be encouraged at least two days per week. While this may seem like a very intimidating goal for most sedentary patients, it is important to remember that physical activity should be initiated slowly and the intensity should be increased gradually. Initial activities can be small tasks like taking the stairs, walking, or swimming at a slow pace. With time, the patient may
engage in more strenuous activities like brisk walking, cycling, and aerobic dancing. Some other ideas for incorporating physical activities include engaging in multiple short (10–15 minute) stints of activity such as brisk walking, avoiding sedentary activities during leisure time (watching TV, playing video or computer games), purchasing simple exercise equipment for the home (treadmills and exercise bikes) and adding regular activity into the daily schedule (bike riding, swimming, walking, golfing, or team sports).

Patients should be evaluated by a physician for future CVD risk prior to initiating a new exercise regimen. Exercise stress testing before initiating a vigorous exercise regimen may be required for selected patients with CVD and in those patients with higher risk. For those high risk patients, physical activity may only be recommended under medical supervision. However, it is usually not necessary to test all patients starting a moderate intensity exercise program.

**Dietary Modification**

Beyond reducing the number of calories consumed, it is also recommended that the diet is low in saturated fat, trans fat, cholesterol, sodium, and simple sugars. The diet should also include increased amounts of whole grains, fruits, and vegetables. ATP III recommended certain dietary modifications as part of their Therapeutic Lifestyle Changes (TLC) diet. The recommendations that were provided are consistent with general dietary recommendations for patients with metabolic syndrome. The diet recommended that total dietary fat intake should be limited to 25–35 percent of the total calories consumed per day, assuming that the amounts of saturated fat and trans fat are kept low. This recommendation is significant because dietary fat intake greater than 35 percent can make it difficult to maintain a low LDL cholesterol. Also, if the fat intake is lower than 25 percent, triglycerides can increase and HDL cholesterol can decrease. Therefore, very low fat diets may actually worsen atherogenic dyslipidemia. Some data suggests that a lower limit of 25–30 percent may be more beneficial as this would avoid worsening of atherogenic dyslipidemia in metabolic syndrome patients, and it may lower the risk of weight gain associated with dietary fat intake. Other nutrient recommendations are as follows: carbohydrate intake limited to 50–60 percent of the total daily calories consumed, fiber intake increased to 20–30 grams/day, and protein intake should be approximately 15 percent of the total daily calories consumed.

Along with the composition of the diet, controlling food intake is a very important factor for the successful dietary treatment of obesity. Dietary modifications, including those recommended by ATP III, have been shown to be beneficial for weight loss in the short term, but long-term benefits on weight are unclear as patient adherence may wane over time. The regulation of appetite can be the determinant factor for the long-term success of a dietary modification program as patients are less likely to adhere to a program that leaves them with feelings of hunger. Therefore, the ideal diet needs to be patient specific and should include strategies that address nutrient requirements/limitations and issues with satiety.

Special low carbohydrate/high fat diets and extremely low calorie diets, while very popular, are generally not recommended. These diets have been shown to result in quick weight loss but the safety and long-term benefits of these diets remains unclear. On the other hand, the Mediterranean diet has some data suggesting that, over time, it is associated with lower levels of insulin resistance, fasting glucose, waist circumference, triglycerides, and higher HDL cholesterol levels. The principles of this diet are as follows: high fruit, vegetables, nuts, and cereal grain intake, use of olive oil for cooking and dressings, moderate fish and seafood intake, rare meat intake, low to moderate full-fat cheese and yogurt intake, and moderate consumption of wine with meals.

**Management of Metabolic Risk Factors**

**Atherogenic Dyslipidemia**

According to ATP III, atherogenic dyslipidemia can be considered a target for lipid lowering therapy only
after LDL cholesterol has been lowered to goal level. LDL cholesterol is considered the primary target for therapy even in patients with metabolic syndrome, and all other lipid risk factors are considered to be secondary. LDL cholesterol goals vary depending on the patient’s absolute risk for coronary heart disease. LDL cholesterol goals according to APT III and its 2004 update are detailed in Table 2. In patients with atherogenic dyslipidemia, non-HDL cholesterol (total cholesterol minus HDL cholesterol) is the secondary target when triglyceride levels are ≥200 mg/dL. When triglycerides are ≥500 mg/dL, triglyceride lowering becomes the initial goal of therapy (before LDL lowering) as these patients are at increased risk for pancreatitis. Beyond lowering non-HDL cholesterol, a tertiary goal is to raise HDL cholesterol levels but no specific goal is recommended.

Statins are the most effective medications available for achieving ATP III goals for LDL cholesterol and non-HDL cholesterol, so they are recommended as first line therapy for the treatment of atherogenic dyslipidemia. Statins have also been shown to reduce the risk for CVD events in patients with metabolic syndrome. Triglyceride lowering drug therapy can be used in conjunction with statin therapy, if indicated. Fibrates and niacin are effective adjunctive options for lowering triglycerides and LDL cholesterol, and they can raise HDL cholesterol levels.

Fenofibrate (Tricor®) is preferred over gemfibrozil (Lopid®), especially when used with statins, because the risk of pharmacokinetic interactions is less with fenofibrate (Tricor®). Niacin possibly worsens hyperglycemia so it should be used with caution in patients with insulin resistance or diabetes, but use of lower doses may lessen this effect. Omega-3-acid ethyl esters (Lovaza®) is the only medication that is Food and Drug Administration approved to treat severely elevated triglycerides (≥500 mg/dL), so this is the preferred treatment in those situations. However, there is no data that this agent reduces CVD risk.

**Hypertension**

According to the Joint National Committee (JNC 7) report on high blood pressure, hypertension is defined as a blood pressure >140/90 mmHg for most adults. Therefore, the blood pressure goal for most patients is <140/90 mmHg. In patients with diabetes or kidney disease, the blood pressure goal is <130/80 instead. Generally, the goal is to reduce the blood pressure as much as possible. Mild elevations in blood pressure can usually be controlled with lifestyle modifications: weight reduction, following the Dietary Approaches to Stop Hypertension (DASH) eating plan, dietary sodium reduction, increased physical activity, and moderation of alcohol consumption. If the blood pressure cannot be controlled by lifestyle modifications alone, antihypertensive medications are indicated to prevent the long-term adverse events associated with uncontrolled hypertension. Angiotensin-converting enzyme inhibitors (ACEIs) may be used as first line agents in patients with metabolic syndrome, especially when diabetes or chronic kidney disease is present. Angiotensin receptor blockers (ARBs) may be used as alternatives to ACEIs when intolerances to ACEIs exist. As combinations of two or more medications are usually required to reach blood pressure goals, thiazide diuretics, β-blockers, and calcium channel blockers are also recommended adjunctive agents.

**Insulin Resistance and Hyperglycemia**

As part of the diagnosis for metabolic syndrome, elevated fasting glucose may be present. Weight reduction, dietary modifications, and increased physical activity may delay progression to type 2 diabetes in metabolic syndrome patients with impaired fasting glucose. Even in the absence of insulin resistance, metabolic syndrome is considered to be a risk factor for diabetes. Therefore, delaying disease progression is a very important consideration when treating these patients. Metformin therapy may be indicated for prevention of type 2 diabetes in those patients at the highest risk for progressing. In addition, metformin has been shown to have beneficial effects on CVD outcomes. However, impaired renal function (serum creatinine > 1.5 mg/
dL for males and >1.4 mg/dL for females or abnormal creatinine clearance) is considered a contraindication to metformin use due to risk of lactic acidosis, so this must be considered prior to initiation. When patients with metabolic syndrome develop type 2 diabetes, they are at high risk for CVD, so all risk factors should be addressed. A hemoglobin A1c of <7 percent is recommended to reduce the risk of microvascular complications (such as retinopathy, nephropathy, and neuropathy) and possibly macrovascular complications (such as CHD and peripheral artery disease). Additionally, appropriate management of dyslipidemia and hypertension are necessary.

**Prothrombotic State**
A prothrombotic state in patients with metabolic syndrome manifests as elevated levels of fibrinogen, PAI-1, and some other coagulation factors. Unfortunately, these levels are not part of routine lab work so they are rarely checked in clinical practice. For primary prevention of thrombotic events, low dose aspirin therapy (75–162 mg/day) may be indicated. According to the 2010 American Heart Association position statement on aspirin use for primary prevention in diabetes, aspirin therapy is recommended for adults with diabetes and no history of vascular disease with a 10-year risk of CVD events of >10 percent (per Framingham risk scoring) and who are not at an increased risk for bleeding. Aspirin therapy is no longer recommended for CVD prevention for adults with low CVD risk (10 year risk of <5 percent) since the risk for bleeding outweighs the possible benefit of therapy. Aspirin therapy for patients with metabolic syndrome without diabetes may be considered for those patients with a 10-year risk of ≥10 percent.

**Proinflammatory State**
A proinflammatory state in patients with metabolic syndrome manifests as elevated levels of cytokines, CRP, and fibrinogen. CRP measurement is the most practical way to determine an inflammatory state because levels rise in response to inflammation. CRP levels are usually higher than normal in patients with metabolic syndrome. Levels >3 mg/L can indicate a proinflammatory state. Currently, there are no medications available to target elevated CRP levels, but lifestyle modifications, particularly weight loss, have been shown to reduce CRP levels. However, there are no specific recommendations regarding strategies to reduce inflammation at this time.

**CONCLUSION**
Regardless of the diagnostic criteria used, the number of patients diagnosed with metabolic syndrome is likely to continue to increase. With the increased incidence in obesity and diabetes, along with the increasing age of our population, metabolic syndrome will continue to be a clinically important diagnosis. Therefore, it is important to remember that CVD is the primary outcome associated with a diagnosis of metabolic syndrome. Additionally, the risk for type 2
diabetes is higher with the metabolic syndrome (with or without preexisting insulin resistance). The treatment strategy should focus on minimizing CV risk factors with the goal of slowing disease progression. Lifestyle modifications, specifically weight reduction, are considered as first line therapy for metabolic syndrome.

Medication therapy should be considered for those patients who fail to meet treatment goals on lifestyle modifications alone. Goals for medication therapy should be in accordance with the current treatment guidelines for each risk factor. Clinicians, including pharmacists, should encourage patients to follow the recommendations for primary prevention for CVD. Pharmacists, in particular, are in a position to provide support and education regarding the treatment options available.

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6. Which of the following medications has been shown to reduce CV risk in patients with metabolic syndrome?
   a. Fenofibrate (Tricor®)
   b. Niacin
   c. Atorvastatin (Lipitor®)
   d. Omega-3 fish oil (Lovaza®)

Refer to case for questions 7–9: IJ is a 60-year-old African American female with a medical history that includes hypertension, dyslipidemia, obesity, and current tobacco use. Her BMI is 45.3 and her most recent BP is 150/90. Recent labs include FPG=100 mg/dL, LDL=143 mg/dL, HDL=22 mg/dL, and TG=78.

7. Does this patient meet the criteria for metabolic syndrome, per ATP III?
   a. Yes
   b. No
   c. Cannot be determined

8. Based on the above case, how many major risk factors for cardiovascular disease does this patient possess?
   a. One
   b. Two
   c. Three
   d. Four

9. IJ has a Framingham risk assessment score of 16 percent. Based on the information provided in the above case, what is IJ’s LDL cholesterol goal?
   a. <160 mg/dL
   b. <130 mg/dL
   c. <100 mg/dL
   d. <70 mg/dL

10. What is the percentage of weight loss recommended for the management of obesity during the first six to 12 months of treatment?
    a. 20 percent
    b. 15 percent
    c. 10 percent
    d. 5 percent

11. Which of the following correctly indicates the percentage of total dietary fat intake recommended as part of a TLC diet?
    a. 0–10 percent
    b. 15–25 percent
    c. 25–35 percent
    d. >35 percent

12. Which of the following risk factors is considered the first priority for treatment/management?
    a. Hypertension
    b. Dyslipidemia
    c. Proinflammatory state
    d. Obesity

13. What is the primary goal of therapy for metabolic syndrome?
    a. Decrease overall CVD risk
    b. Prevent insulin resistance
    c. Weight loss
    d. Decrease blood pressure

14. Which of the following cholesterol medications is least likely to get LDL cholesterol to goal levels?
    a. Omega-3 fish oil (Lovaza®)
    b. Simvastatin (Zocor®)
    c. Gemfibrozil (Lopid®)
    d. Niacin

OA is a 62-year-old Hispanic male with a medical history that includes hypertension and type 2 diabetes. He is currently taking lisinopril (Prinivil® or Zestril®), atorvastatin (Lipitor®), and metformin (Glucophage®). His calculated BMI=28.3. Recent labs include FPG=118 mg/dL, TG=398 mg/dL, LDL=62 mg/dL, HDL=22 mg/dL, and HgA1c=6.5 percent.

15. Which of the following therapies would be most appropriate at this point?
    a. Maximize atorvastatin (Lipitor®) dosage
    b. Add fenofibrate (TriCor®) therapy
    c. Add omega-3 fish oil (Lovaza®)
    d. All of the above
16. Based on the information from OA’s patient case, does OA meet the WHO criteria for a diagnosis of metabolic syndrome?
   a. Yes
   b. No
   c. Cannot be determined

17. Which of the following risk factors is considered to be primarily responsible for the increased incidence of metabolic syndrome?
   a. Obesity
   b. Increased age of population
   c. Elevated LDL
   d. Cigarette smoking

18. A Framingham risk score of 11 percent indicates that the patient has a ________ risk for CVD.
   a. Low
   b. Moderate
   c. High

19. Which of the following lifestyle modifications are recommended for managing high blood pressure?
   a. Decrease dietary sodium
   b. Decrease alcohol consumption
   c. Increase physical activity
   d. All of the above

20. Which of the following therapeutic interventions is recommended for the management of the prothrombotic state seen in some patients with metabolic syndrome?
   a. Aspirin
   b. Weight reduction
   c. Ibuprofen
   d. Physical activity

Overview of Metabolic Syndrome
Feb. 1, 2012 (expires Feb. 1, 2015) • Activity Type: Knowledge-based

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Quiz: Shade in your choice

Quiz: Circle your choice

21. Is this program used to meet your mandatory C.E. requirements?
   a. Yes b. No

22. Type of pharmacist: a. owner b. manager c. employee

23. Age group: a. 21–30 b. 31–40 c. 41–50 d. 51–60 e. Over 60

24. Did this article achieve its stated objectives?
   a. Yes b. No

25. How much of this program can you apply in practice?
   a. All b. Some c. Very little d. None

How long did it take you to complete both the reading and the quiz? ______ minutes

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