

A Constellation of Complications: The Metabolic Syndrome

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The metabolic syndrome is a common cluster of risk factors for coronary heart disease and type 2 diabetes mellitus that includes obesity, elevated blood pressure, insulin resistance, and dyslipidemia. The diagnosis of metabolic syndrome itself appears to be an important risk factor for atherogenic cardiovascular disease and diabetes, and there is recent evidence that its components cluster, rather than occurring together by coincidence. A recent statement from the American Heart Association and the National Heart, Lung, and Blood Institute slightly modifies and clarifies the diagnostic criteria for the metabolic syndrome that are most widely used in the United States, along with giving practical guidance about management. Prompt therapeutic attention to the underlying risk factors—abdominal obesity, physical inactivity, and atherogenic/diabetogenic diet—is warranted for all patients with the metabolic syndrome, and drug therapy for specific metabolic risk factors should be considered for those at high or moderately high 10-year absolute risk of atherosclerotic cardiovascular disease. A new class of investigational drugs that block cannabinoid type 1 receptors have shown promise. This review also discusses issues that require additional research and new drugs that are considered promising for treatment of the metabolic syndrome itself. (*Clinical Cornerstone*. 2005;7[2/3]:36–45) Copyright © 2005 Excerpta Medica, Inc.

The metabolic syndrome is a cluster of metabolic abnormalities that increases the risk of coronary heart disease (CHD) and type 2 diabetes mellitus (DM). Since 1998, the World Health Organization (WHO)¹ and several professional societies have developed definitions of the metabolic syndrome that include somewhat different components and cutoff points. The definition most widely used in the United States was published by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program in 2001.² It calls for the metabolic syndrome to be diagnosed in adults when ≥ 3 of the following 5 risk factors are present: abdominal obesity (waist circumference), elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and high fasting glucose ≥ 110 mg/dL. In a recent joint statement the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) affirmed the ATP criteria with the following modifications: when individuals are prone to insulin resistance a lower waist circumference threshold should

be used; when an individual is using medication to control triglycerides, HDL-C levels, and blood pressure these would be counted as abnormal, clarifying that an elevated blood pressure is a level that exceeds the threshold for either systolic or diastolic pressure, and a reduction in the ≥ 110 mg/dL threshold for elevated fasting glucose to ≥ 100 mg/dL.³

The metabolic syndrome is highly prevalent in the United States. The Third National Health and Nutrition Examination Survey (NHANES III),⁴ a study conducted in 1988–1994 that is representative of the US population, indicated that 24% of adults had the metabolic syndrome based on the ATP III criteria. The prevalence was lowest (6.7%) among participants aged 20 to 29 years and highest (43.5%) among participants aged 60 to 69 years. A more recent analysis of NHANES III determined that 44% of Americans >50 years of age have the metabolic syndrome.⁵

For children and adolescents, no criteria for the diagnosis of the metabolic syndrome have been formally developed.⁶ However, NHANES III showed that 4% of

all adolescents and 29% of overweight adolescents met modified ATP III criteria for the metabolic syndrome.⁶ The magnitude and prevalence of childhood obesity have increased in the decade since NHANES III was conducted,⁷ and the metabolic syndrome, too, appears to have become more common. In a study of 439 obese and 31 overweight children and adolescents, the metabolic syndrome was diagnosed according to modified WHO and ATP III criteria in 39% of moderately obese subjects and 50% of severely obese subjects, although in none of the overweight subjects.⁷

KEY POINT

A recent analysis of NHANES III determined that 44% of Americans >50 years of age have the metabolic syndrome.

UPDATED DEFINITION OF THE METABOLIC SYNDROME

In September 2005, the AHA/NHLBI issued a statement that slightly modifies and clarifies the ATP III definition of the metabolic syndrome in adults (**Table I**).³ The statement specifies how waist circumference should be measured and suggests lower cutoff points for waist circumference in Asian Americans and individuals with a genetic propensity to insulin resistance. In keeping with the American Diabetes Association's recently modified definition,⁸ the cutoff point for elevated fasting glucose has been lowered from ≥ 110 mg/dL to ≥ 100 mg/dL. In addition, the statement explains that the definition of elevated blood pressure is met when either the threshold of ≥ 130 mm Hg systolic blood pressure or ≥ 85 mm Hg diastolic blood pressure is exceeded, and that triglycerides, HDL-C, and blood pressure are considered abnormal in patients who have these risk factors controlled with medication.

THE METABOLIC SYNDROME AND THE RISK OF CORONARY HEART DISEASE AND DIABETES

Analyses of data from large, prospective studies suggest that the metabolic syndrome itself is an important risk factor for CHD and type 2 DM, and that the metabolic

syndrome increases total mortality and cardiovascular mortality. For example, Sattar et al⁹ analyzed a database on hypercholesterolemic Scottish men who had participated in a study of a statin, with average follow-up of 5 years. They identified 6647 individuals who met ATP III criteria for the metabolic syndrome at baseline and did not have diabetes. Univariate analyses showed that the presence of the metabolic syndrome increased the risk of a CHD event by 76% and more than tripled the risk of developing diabetes. Even in a multivariate analysis that incorporated conventional risk factors, the metabolic syndrome was associated with a 30% greater risk of CHD events.

KEY POINT

Analyses of data from large, prospective studies suggest that the metabolic syndrome itself is an important risk factor for CHD and type 2 DM, and that the metabolic syndrome increases total mortality and cardiovascular mortality.

The Botnia study¹⁰ followed individuals from families with type 2 DM in Finland and Sweden. According to an analysis of 4483 subjects aged 35 to 70 years, the prevalence of the metabolic syndrome according to WHO criteria increased in a stepwise fashion with worsening glucose tolerance. Over a median follow-up period of 7 years, the presence of the metabolic syndrome tripled the risk of CHD and doubled the risk of myocardial infarction and stroke. The risk of cardiovascular mortality was 80% greater in subjects with the metabolic syndrome than in those without, and the risk of all-cause mortality was also significantly greater.

Lakka et al¹¹ examined 12-year follow-up data from a Finnish study of 2682 middle-aged men who did not have cardiovascular disease (CVD) or diabetes at baseline. Even when conventional risk factors were taken into account, death from CHD was 2.9 to 4.2 times more likely among men with the metabolic syndrome than among those without, depending on how the syndrome was defined. In addition, the presence of the metabolic syndrome doubled the risk of death from any cause.

TABLE 1. AMERICAN HEART ASSOCIATION/NATIONAL HEART, LUNG, AND BLOOD INSTITUTE CRITERIA FOR DIAGNOSIS OF THE METABOLIC SYNDROME.

| Measure* | Categoric Cutoff Points |
|--|--|
| Elevated waist circumference ^{†‡} | ≥102 cm in men ≥88 cm in women |
| Elevated triglycerides | ≥150 mg/dL (1.7 mmol/L) or On drug treatment for elevated triglycerides [§] |
| Reduced HDL-C | <40 mg/dL (0.9 mmol/L) in men <50 mg/dL (1.1 mmol/L) in women or On drug treatment for reduced HDL-C [§] |
| Elevated blood pressure | ≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or On antihypertensive drug treatment in a patient with a history of hypertension |
| Elevated fasting glucose | ≥100 mg/dL or On drug treatment for elevated glucose |

HDL-C = high-density lipoprotein cholesterol.

*The presence of any 3 of the 5 components constitutes a diagnosis of the metabolic syndrome.

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

[‡]In the United States, some adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94–102 cm [37–39 inches] in men and 80–88 cm [31–35 inches] in women) may have a strong genetic contribution to insulin resistance and should benefit from changes in lifestyle, similar to men with categoric increases in waist circumference. A lower waist circumference cutoff point (eg, ≥90 cm [35 inches] in men and ≥80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

[§]Fibrates and nicotinic acid are the drugs most commonly used to treat elevated triglycerides and reduced HDL-C. Patients taking 1 of these drugs are presumed to have high triglycerides and low HDL-C. Reprinted with permission.³

In the San Antonio Heart Study,¹² 2815 men and women were followed for an average of 13 years. Those with the metabolic syndrome according to the ATP III definition² were 2.53 times more likely to die of CVD and 1.47 times more likely to die of any cause than those without the metabolic syndrome. In a subgroup of 2372 individuals who had neither CVD nor diabetes at baseline, the metabolic syndrome doubled the risk of death from CVD.

Associations between the metabolic syndrome, CHD, and diabetes have also been established by an analysis of the cross-sectional NHANES III data on adults aged >50 years.⁵ As in the Botnia study,¹⁰ a stepwise increase in the prevalence of the metabolic syndrome was observed with worsening glucose tolerance, and 86% of people with diabetes had the metabolic syndrome. The prevalence of CHD was 19% in people with both the metabolic syndrome and diabetes versus 9% in those with neither and 7.5% in the small percentage of the study population that

had diabetes but not the metabolic syndrome. These results suggest that for most diabetic patients, cardiovascular risk is related not to diabetes itself but to the concomitant presence of the metabolic syndrome.¹³

CLUSTERING OF RISK FACTORS IN THE METABOLIC SYNDROME

Japanese researchers reported support for the view that components of the metabolic syndrome actually cluster, rather than occurring together by coincidence.¹⁴ In 119,412 adults from the general population, they studied the prevalence of ≥3 components of the metabolic syndrome as defined by ATP III,² except that they measured body mass index (BMI) instead of waist circumference. The actual prevalence of any combination of 3 to 5 risk factors of the metabolic syndrome was found to be more frequent than those expected to occur by coincidence (*P* < 0.001), based on a calculated probability of all possi-

ble combinations of 3 or more factors.¹⁴ This report and other cluster analyses leave little doubt that the metabolic syndrome exists as a clinical entity.

These findings and the data on the risk of progression to CHD and diabetes suggest that early diagnosis and intensive management of risk factors are important for patients with the metabolic syndrome.

MANAGEMENT OF THE METABOLIC SYNDROME

The primary goals of managing the metabolic syndrome are to reduce the risk of CHD and diabetes. Even in patients with established diabetes, intensive management of the metabolic syndrome will diminish the higher risk of CHD. All components of the metabolic syndrome can be improved through a global strategy¹⁵ addressing the underlying risk factors—abdominal obesity, physical inactivity, and atherogenic/diabetogenic diet. These should be managed as discussed below, independent of the patient's risk status. If necessary, patients should receive drug therapy for the specific metabolic risk factors, also discussed below, and counseling about smoking cessation.³

KEY POINT

All components of the metabolic syndrome can be improved through a global strategy addressing the underlying risk factors—abdominal obesity, physical inactivity, and atherogenic/diabetogenic diet.

In some patients, the metabolic syndrome confers a high or moderately high risk of major CVD events in the short term, whereas in others the short-term risk is relatively low but the longer-term risk is fairly high.¹⁶ The AHA/NHLBI statement³ recommends that certain components of the metabolic syndrome as well as other risk factors be targeted for drug therapy when a patient's 10-year absolute risk of atherosclerotic CVD is high or moderately high. Certainly patients with clinically apparent CVD or diabetes are considered at high risk. In patients with neither CVD nor diabetes, Framingham risk scoring is to be performed to classify the patient's risk as *high* (Framingham 10-year risk score >20%), *moderately high* (score 10%–20%), *mod-*

erate (score <10% and ≥2 major risk factors), or *lower* (score <10% and 0 or 1 major risk factor). All patients with the metabolic syndrome should undergo Framingham risk scoring. The procedure for scoring is published in the executive summary of the ATP III report.²

Management of Underlying Risk Factors

Abdominal Obesity

In patients with the metabolic syndrome who have abdominal obesity, weight reduction is the first priority.³ According to evidence-based National Institutes of Health (NIH) guidelines¹⁷ for the treatment of overweight and obesity, a reasonable initial goal is a 10% reduction in body weight over 6 months. To achieve this target, patients with a BMI of 27 to 35 kg/m² need to eliminate 300 to 500 kcal/d, and those with a BMI >35 kg/m² should eliminate 500 to 1000 kcal/d.

The NIH accepts pharmacotherapy for certain patients as an adjunct to a low-calorie diet, increased physical activity, and behavior therapy (eg, self-monitoring of eating habits and physical activity, stress management, stimulus control, and social support). Patients should have followed such a regimen for at least 6 months before pharmacotherapy is considered. Weight-loss drugs should be reserved for patients who have a BMI ≥30 kg/m² or those who have a BMI of 27 to 29.9 kg/m² and hypertension, dyslipidemia, CHD, type 2 DM, or sleep apnea. If medical therapy fails, weight-loss surgery is an option for motivated patients with complications of extreme obesity.¹⁷

KEY POINT

In patients with the metabolic syndrome who have abdominal obesity, weight reduction is the first priority.

Physical Inactivity

The AHA/NHLBI statement³ recommends 60 minutes of continuous or intermittent aerobic activity (preferably brisk walking) daily to promote or maintain weight loss. Walking should be supplemented by jogging, swimming, biking, golfing, team sports, resistance training, use of a treadmill or other simple exercise equipment, or multiple

10- to 15-minute sessions of activity (eg, walking breaks at work, gardening, or housework). Patients should also be advised to limit television viewing and other sedentary activities.³

Atherogenic/Diabetogenic Diet

The trend to focus on the macronutrient composition of a diet (eg, high protein, low cholesterol) misses the point that weight loss requires a combination of caloric restriction, physical activity, and changes in behavior. Patients should be counseled to choose foods that are low in saturated fat, trans fats, cholesterol, sodium, and simple sugars, and to eat plenty of fruits, vegetables, and whole grains.³

Management of Metabolic Risk Factors

Dyslipidemia

Elevated low-density lipoprotein cholesterol (LDL-C) is not a component of the metabolic syndrome, but it is the primary target of lipid-lowering therapy in ATP III guidelines.² **Table II**^{3,18} presents the LDL-C goals established in a recent update of ATP III.

Once the desired LDL-C level is reached, the next target of lipid-lowering therapy is non-HDL-C.³ The goals are 30 mg/dL higher than those for LDL-C (**Table II**). If triglycerides are ≥ 500 mg/dL, therapy with a fibrate or nicotinic acid should be considered to prevent acute pancreatitis. If triglycerides are 200 to 500 mg/dL, more intensive LDL-C lowering with a statin is appropriate. If non-HDL-C remains high, the addition of a fibrate or nicotinic acid can be considered. However, the benefit of

combining a fibrate or nicotinic acid with a statin has not been adequately evaluated in clinical trials. There is nonetheless suggestive evidence of benefit based on results of clinical trials with monotherapies; nevertheless, for the time being, it probably is prudent to reserve combined drug therapy for high-risk patients. Adding a fibrate (especially gemfibrozil) to therapy with a statin drug increases the risk of myopathy, so high statin doses should be avoided in this combination.¹⁹ Nicotinic acid should be given at a relatively low dose to patients with elevated fasting glucose, impaired glucose tolerance, or diabetes, with careful monitoring for worsening of hyperglycemia.³

Reduced HDL-C levels should be increased as much as possible with standard lipid therapies; there is no specific target.³ Fibrates and, to an even greater degree, nicotinic acid raise HDL-C levels,¹⁵ but have other favorable effects on the lipoprotein profile.

Blood Pressure

According to NHLBI guidelines,²⁰ the target for anti-hypertensive therapy is $<140/90$ mm Hg, or $<130/80$ mm Hg for patients with diabetes or renal disease. In patients with the metabolic syndrome, blood pressure should be reduced as much as possible through lifestyle therapies, even in the absence of overt hypertension.³ Lifestyle changes such as weight loss and sodium reduction may be adequate to control mildly elevated blood pressure. In individuals whose blood pressure remain >140 mm Hg systolic or >90 mm Hg diastolic on lifestyle therapies,

TABLE II. GOALS FOR LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C) AND NON-HIGH-DENSITY LIPOPROTEIN CHOLESTEROL (NON-HDL-C).

| Risk Category* | LDL-C Goal ¹⁸ | Non-HDL-C Goal ⁷ |
|---|---|--|
| Established CHD or otherwise at high risk | <100 mg/dL (optional goal for very high-risk patients: <70 mg/dL) [†] | <130 mg/dL (optional goal for very high-risk patients: <100 mg/dL) [†] |
| Moderately high risk | <130 mg/dL | <160 mg/dL |
| Moderate risk | <130 mg/dL | <160 mg/dL |
| Lower risk | <160 mg/dL | <190 mg/dL |

CHD = coronary heart disease.

*Based on Framingham 10-year risk score¹: high = $>20\%$; moderately high = 10% – 20% ; moderate = $<10\%$ and ≥ 2 major risk factors; or lower = $<10\%$ and 0 or 1 major risk factor.

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

Data derived with permission.^{3,18}

antihypertensive drugs often are required to achieve acceptable blood pressure levels.

In patients with the metabolic syndrome who are not diabetic, an angiotensin-converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker is an attractive choice. For example, they do not worsen hyperglycemia and may even help prevent type 2 DM.¹⁵ Some experts recommend ACE inhibitors as first-line therapy and use an angiotensin receptor blocker for patients who cannot tolerate ACE inhibitors or have left ventricular dysfunction.³ In reality, multiple drugs often are required to adequately control blood pressure. Whatever agents are chosen, factors other than blood pressure response should be monitored. Some evidence suggests that diuretics and β -blockers are associated with the development of diabetes, and weight gain can occur during β -blocker therapy.²¹ Even so, these drugs are not contraindicated in patients with the metabolic syndrome.

Elevated Fasting Glucose

In patients with type 2 DM, multiple drugs likewise may be required to control hyperglycemia. Whether to employ glucose-lowering drugs in persons with prediabetes to delay conversion to diabetes has not been resolved. Metformin and the thiazolidinediones (eg, pioglitazone, rosiglitazone) seemingly reduce the risk of conversion of prediabetes into diabetes. However, the AHA/NHLBI statement³ advises against their use solely for this purpose because the cost-effectiveness and long-term safety of this approach have not been established.

On the other hand, 2 large, randomized clinical trials have demonstrated that in patients with elevated fasting glucose, an intensive lifestyle modification program (frequent individualized counseling about weight loss and increased physical activity) reduces the incidence of diabetes in persons with prediabetes.^{22,23} In fact, 1 of these studies showed that lifestyle changes were significantly more effective than metformin in preventing diabetes.²²

At a 2003 AHA/NHLBI conference about the definition of the metabolic syndrome, some experts suggested using the oral glucose tolerance test for nondiabetic patients with at least 2 components of the metabolic syndrome.²⁴ The thinking is that, like elevated fasting glucose, impaired glucose tolerance denotes an increased risk for type 2 DM. In addition, the oral glucose tolerance test can detect occult type 2 DM.

Proinflammatory State and Prothrombotic State

Elevated levels of proinflammatory cytokines, C-reactive protein (CRP), and coagulation factors such as fibrinogen are typical in patients with the metabolic syndrome, although they are not established components of the syndrome.³ The AHA/NHLBI statement³ suggests aspirin prophylaxis for patients with the metabolic syndrome who are at moderately high or high risk of atherosclerotic CVD. The statement also indicates that measurement of CRP is an option in patients with the metabolic syndrome; if measured, lifestyle therapy is indicated for those with CRP >3 mg/L. Some investigators believe that elevations of CRP represent an additional component of the metabolic syndrome.²⁵ Elevations are taken to represent the presence of a prothrombotic state.

TOWARD THE FUTURE

In light of the recent AHA/NHLBI joint statement, all physicians are encouraged to give serious attention to the diagnosis and management of their patients with metabolic risk factors. The primary focus in clinical management is to mitigate the modifiable, underlying risk factors (obesity, physical inactivity, and atherogenic diet) through lifestyle changes. An integrated approach to the management of these metabolic risk factors is warranted.

The AHA/NHLBI statement identified several areas where additional research is needed. Some of the questions that deserve attention are the following:

- What new strategies can be developed to achieve and sustain long-term weight reduction and increased physical activity?
- What new genetic and metabolic contributions to the metabolic syndrome can be discovered that will support the development of new therapeutic approaches?
- How can short-term risk for both CVD and diabetes be better assessed so as to tailor therapies to maximize benefit and minimize costs and adverse effects?
- What drug combinations provide the greatest risk reductions?
- What is the relation between the proinflammatory state and the metabolic syndrome?

Another important question is whether a single drug can treat the cluster of factors that compose the metabolic syndrome. One promising candidate is rimonabant, the first in a new class of drugs that block cannabinoid type 1 receptors, which help regulate appetite, energy balance, and

nicotine dependence, and lipid and glucose metabolism in adipose tissue.²⁶ Preliminary results from Phase III clinical trials show that after 1 to 2 years of rimonabant therapy, the proportion of study patients who met the criteria for the metabolic syndrome decreased, reflecting significant improvements in waist circumference, triglycerides, and HDL-C.²⁷ Another new class of drugs, called dual peroxisome proliferator-activated receptor agonists, also targets both the glucose and lipid abnormalities associated with the metabolic syndrome.¹⁶ Two of them, GW409544 and tesaglitazar, are currently in Phase III trials.²⁸

SUMMARY

The metabolic syndrome can be diagnosed when any 3 of the 5 following criteria are met: elevated waist circumference, elevated triglycerides, reduced HDL-C, elevated blood pressure, and elevated fasting glucose. Its presence appears to identify patients at substantial additional risk of CHD and type 2 DM that is beyond the risk conferred by the components individually. Clinical management should first address the underlying risk factors of abdominal obesity, physical inactivity, and atherogenic/diabetogenic diet, regardless of the individual's absolute 10-year risk of CHD. If absolute risk is high enough, drug therapy for treatment of metabolic factors may be appropriate. New medications are being tested as potential therapy for the metabolic syndrome itself, but much work is still needed to elucidate the pathophysiology of the metabolic syndrome, the associated cardiovascular risk, and optimal treatments.

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Dialogue Box

EDITORIAL BOARD

With regard to the metabolic syndrome and cardiovascular (CV) risk, is the whole greater than the sum of the parts with respect to CV risk?

GRUNDY

That is a complicated question, although my feeling is, that is probably the case. Let's say you have a 50-year-old man with metabolic syndrome and that, based on his Framingham score, you determine his 10-year risk to be 15%, placing him in the moderately high-risk category. The question you are asking then is whether the fact that he has metabolic syndrome places him in the high-risk (>20%) category. The answer is that we don't know for sure. It's analogous to C-reactive protein (CRP). Is a patient in the moderately high-risk category who also has a high CRP level at higher risk than a patient with a normal CRP? Unfortunately, definitive studies addressing these questions have not yet been conducted. Regardless, it's important to appreciate that the presence or absence of metabolic syndrome itself is not a replacement for the Framingham score. The metabolic syndrome does not take into account age or gender, and it doesn't factor in total cholesterol levels and smoking. By itself, metabolic syndrome really provides no indication of 10-year risk. Nevertheless, patients with metabolic syndrome are definitely at higher long-term risk for the rest of their lives and are at higher risk for developing diabetes. The latter should not be ignored, since there is no other risk-assessment tool for diabetes.

EDITORIAL BOARD

Which should be accorded the higher priority—weight loss or dyslipidemia management?

GRUNDY

Weight reduction, definitely. The advantage of weight reduction is it improves not only dyslipidemia but all of the other metabolic risk factors such as blood pressure, glucose, and insulin levels across the board. As a result, we generally put a priority on lifestyle change as the up-front approach to all of the risk factors, particularly

metabolic syndrome. If this is not wholly successful, you then should step back and look at the remaining risk factors and make a decision regarding drug treatment for those conditions.

EDITORIAL BOARD

Please elaborate on the role of peroxisome proliferator-activated receptor (PPAR) agonists in metabolic syndrome.

GRUNDY

There are 2 kinds of PPAR agonists, the alpha and the gamma. The alpha agonists are fibrates, for example, fenofibrate and gemfibrozil. The gamma agonists are the glitazones, including pioglitazone and rosiglitazone. We have had more experience with the fibrates, since they have been around for 40 years. Generally speaking, clinical trials show that fibrates reduce CV risk by 15% to 20% in subjects who have the metabolic syndrome or type 2 diabetes. This is about half as much as the statins; thus, fibrates are best regarded as backup or second-line agents. For patients with diabetes, the glitazones are an option for treating hyperglycemia. A trial that was just completed, called ProActive, found a trend toward a reduction in heart attacks and coronary events with pioglitazone. Although there are some who favor the use of glitazones for diabetes prevention, this strategy is not widely accepted.

EDITORIAL BOARD

What are your thoughts regarding the role of niacin in the management of dyslipidemia in metabolic syndrome?

GRUNDY

Niacin has an effect similar to fibrates. It is a terrific drug from the lipid point of view. It is very good for raising high-density lipoprotein cholesterol (HDL-C) and lowering serum triglycerides, and it appears to be more potent than the fibrates. The downside is that it causes more side effects, including flushing and a tendency for glucose and uric acid levels to rise. Although

Dialogue Box

niacin is a very good drug and definitely occupies a niche in the management of dyslipidemia, it has to be used by people who are committed to it.

EDITORIAL BOARD

Should patients on lipid-lowering drugs be monitored regularly for myopathy?

GRUNDY

Creatine kinase (CK) levels should be monitored in patients who develop symptoms of myopathy. Although it is regarded as prudent to obtain a baseline CK when starting treatment with a statin, routine monitoring of CK levels is not recommended. The most important thing to do is educate patients about the symptoms of myopathy, such as muscle weakness, flu-like symptoms without fever, and brown-colored urine. By educating patients to be on the lookout for these symptoms, serious long-term side effects of lipid-lowering agents can be avoided. The problem in the past was that patients weren't taught to recognize the symptoms of myopathy and so continued to take the drugs. This led to the development of severe complications, such as renal failure, in some patients. It is also important to be aware of the risk factors for myopathy: older age and people with thin, small frames who may be prescribed a statin dose that is too high; the concomitant use of drugs that interact with statins; and underlying medical conditions such as chronic renal failure.

EDITORIAL BOARD

Do you favor the use of weight-loss medications as a means for "kick-starting" weight loss?

GRUNDY

It has been our position to take a more conservative stand on that and to give patients the chance to lose weight on their own. Weight reduction is a long-term proposition and there is no quick fix. As a general guideline, I think it is prudent to give the patient a period of time to make appropriate adjustments and then, if

it seems that they are not getting to goal, you could add a weight-loss agent to their regimen.

EDITORIAL BOARD

Can you offer readers any tips on facilitating weight loss in their patients?

GRUNDY

In 1998, we published weight-loss guidelines through the National Institutes of Health, which go into great depth on this subject. The guidelines are available online at http://www.nhlbi.nih.gov/guidelines/obesity/e_txtbk/intro/intro.htm

EDITORIAL BOARD

When managing dyslipidemia, once you achieve the desired low-density lipoprotein cholesterol (LDL-C) level using a statin, what are the options if serum triglycerides remain in the 200 to 500 mg/dL range?

GRUNDY

If dyslipidemia continues to be present after correcting LDL-C, you have 4 options. One is to increase the statin dose, further lowering LDL-C. Another would be to add ezetimibe to get the LDL-C and non-HDL-C levels lower. The third option would be to add nicotinic acid (ie, niacin), and option 4 would be to add a fibrate. Which of these you choose needs to be individualized because there is no clinical trial that tells you which one to use.

EDITORIAL BOARD

In a patient who continues to have an elevated CRP level despite adequate treatment of LDL-C with a statin, what other measures would you use to lower CRP?

GRUNDY

Besides increasing the statin dose, the best thing is weight reduction. Smoking cessation also lowers CRP. Although, perhaps surprisingly, aspirin does not lower CRP; however, niacin and fenofibrate do.