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Managing Cardiometabolic Risk: Will New Approaches Improve Success?

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Managing Cardiometabolic Risk: Will New Approaches Improve Success?

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Faculty Disclosures

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George Kunos, MD, PhD, reports nothing to disclose.
Managing Cardiometabolic Risk: Will New Approaches Improve Success?

Statement of Need
Common cardiovascular and metabolic (cardiometabolic) risk factors in high-risk patients include dyslipidemia, insulin resistance, hypertension, and abdominal adiposity. Abdominal adiposity is an important underlying risk factor for clinical atherosclerotic disease and, along with the other cardiometabolic risk factors, requires early identification and management. Overstimulation of the endocannabinoid (EC) system, a newly identified physiologic system involved in lipid and glucose metabolism, is associated with the development of various cardiometabolic risk factors. Cannabinoid (CB) receptors, specifically CB1 receptors, found in the brain and in various peripheral organs, play a pivotal role in regulating energy balance and body weight. Blockade of CB1 receptors has been shown to improve various cardiometabolic risk factors in obese or overweight patients, even in patients with preexisting diabetes mellitus and dyslipidemia.

Program Overview
This continuing medical educational (CME) activity examines how to improve outcomes in high-risk patients through targeted risk-reduction strategies aimed at each patient’s individual cardiometabolic risk factor profile. Current and new risk-reduction approaches are reviewed.

Educational Objectives
After taking part in this activity, participants will be able to:
- Identify the relation between abdominal adiposity and the development of cardiometabolic risk factors
- List the potential cardiometabolic risk factors caused by overstimulation of the EC system
- Assess the role of various clinical interventions for cardiometabolic risk reduction
- Apply cardiometabolic risk-reduction strategies aimed at each patient’s individual risk factor profile

Target Audience
This CME activity is designed for endocrinologists, cardiologists, primary care physicians, and other interested healthcare professionals.

Accreditation
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Method of Instruction
Participants should carefully review the entire activity, including the program overview, educational objectives, target audience description, and other material in this CME Information section. After review, read the text, and complete and submit answers to the CME Assessment Test, Registration Form, and Activity Evaluation Form.

Participants must achieve a passing grade of ≥70% to receive credit. Please be sure to complete and return both the Registration Form and the Activity Evaluation Form to receive the appropriate credit.

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Introduction

The rates of obesity and type 2 diabetes mellitus in the United States are approaching epidemic proportions. Currently, the majority of US adults (>56%) are overweight, and, according to a Centers for Disease Control and Prevention (CDC) surveillance study, in 2000 the prevalence of obesity (body mass index [BMI] ≥30) was 19.8%, and the prevalence of diabetes was 7.3%. These statistics, which are based on self-reported information, probably underestimate the true prevalence. A community-based sample of middle-aged adults reported that the incidence of diabetes doubled over the past 30 years. According to the Third National Health and Nutrition Examination Survey (NHANES III) 86% of patients aged >50 years with type 2 diabetes also have the metabolic syndrome, which is a clustering of atherogenic risk factors including dyslipidemia, elevated blood pressure, elevated blood glucose, a prothrombotic state, and a proinflammatory state, and is a precursor to cardiovascular disease (CVD). Despite widely disseminated management guidelines, the obesity and diabetes epidemics continue unabated and if the current trends continue, obesity and its associated complications (metabolic syndrome, type 2 diabetes, coronary heart disease [CHD], cancer, and other diseases) threaten to undermine gains in life expectancy in this century.

Early intervention strategies can prevent overweight and obesity (specifically abdominal obesity) from progressing to the cascade of cardiometabolic complications that begins with insulin resistance and border-line CVD risk factors and culminates in type 2 diabetes and CVD events. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and subsequent guidelines use metabolic syndrome criteria to facilitate the clinical simplification of cardiometabolic risk factor assessment in office practice. The term metabolic syndrome describes a constellation of metabolic risk factors that includes atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state. Individuals with the metabolic syndrome typically are overweight or obese with an “apple-shaped” body type characterized by a large waist circumference.

The primary treatment for the metabolic syndrome is lifestyle therapy—weight loss, increased physical activity, and an antiatherogenic diet—with the objective of preventing progression to diabetes and CVD. Risk factor assessment algorithms should be used to guide the intensity of therapy, particularly regarding use of drugs, for patients with the metabolic syndrome, as detailed in my article in this supplement to The American Journal of Medicine. Unfortunately, despite its proven potential to reduce the severity of cardiometabolic risk at every stage of progression, lifestyle intervention (alone or in combination with drug therapy) is often overlooked in routine clinical practice.

Currently, the drugs approved for the treatment of metabolic syndrome are those that target individual risk factors: lipid-lowering drugs, antihypertensive agents, hypoglycemic drugs, antiplatelet drugs, and weight-loss agents. However, the concept of reducing multiple risk factors with a single drug or a combination of drugs (thereby avoiding the risks associated with polypharmacy) has become increasingly attractive, particularly as the population prevalence of obesity and cardiometabolic risk continue to climb.

Sibutramine and orlistat, weight-loss agents approved for long-term use, improve cardiometabolic risk factors and produce moderate weight loss. The endocannabinoid (EC) system, a newly identified physiologic system involved in lipid and glucose metabolism, may be linked to the development of various cardiometabolic risk factors. Cannabinoid (CB) receptors, specifically CB1 receptors, found in the brain and in various peripheral organs, appear to play a pivotal role in regulating energy balance and body weight. Rimonabant, the first CB1 receptor antagonist, offers a new approach to reducing weight and abdominal adiposity and to improving various cardiometabolic risk factors. In the Rimonabant in Obesity (RIO) clinical trials program, rimonabant in combination with a hypocaloric diet caused sustained weight loss over 1- and 2-year periods and reduced cardiometabolic risk factors seemingly through both weight loss—dependent and weight loss—

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Recently, an FDA Advisory Committee recommended a delay in the approval of rimonabant because of safety issues that need to be addressed in further studies.
independent mechanisms, even in patients with preexisting diabetes and dyslipidemia.\textsuperscript{18,20}

The articles presented in this supplement are based on an educational program held during the 66th Scientific Session of the American Diabetes Association (ADA) Congress in Washington, DC, in June 2006, and address the issues of obesity and cardiometabolic risk, exploring new approaches to their management.

An estimated 47 million individuals in the United States have the metabolic syndrome,\textsuperscript{21} making its management a top clinical priority. In the first article, I discuss the importance of early identification of high-risk patients to implement risk-reduction strategies targeted toward each patient’s cardiometabolic risk factor profile. Next, Dr. Steven M. Haffner focuses on overweight and obesity, particularly abdominal adiposity, and other cardiometabolic risk factors that increase the risk of developing diabetes and CVD, emphasizing lifestyle intervention as an effective first-line management strategy. He also describes the association of obesity, the metabolic syndrome, insulin resistance, and type 2 diabetes with nonalcoholic fatty liver disease. Dr. George Kunos reports on both his research and that of other investigators regarding the role of the EC system in energy and fat metabolism, both through central and peripheral actions, with central sites within the hypothalamus and peripheral sites, including adipose tissue, skeletal muscle, and the liver. He concludes that preclinical studies demonstrate that CB\textsubscript{1} blockade reduces weight and adiposity, decreases hepatic lipogenesis, increases fatty acid oxidation, and improves glucose homeostasis. Finally, the clinical efficacy of CB\textsubscript{1} blockade with rimonabant in promoting weight loss and improvements in cardiometabolic parameters is covered by Dr. Michael D. Jensen in his review of data from the phase 3 RIO clinical trials.

The authors believe that the information presented in this supplement will help physicians improve outcomes for patients at high cardiometabolic risk. It is our hope that widespread early intervention with risk-targeted management approaches will reduce the prevalence of overweight and obesity and its associated cardiometabolic risks.

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References

Cardiovascular and Metabolic Risk Factors: How Can We Improve Outcomes in the High-Risk Patient?
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ABSTRACT

Risk assessment algorithms, such as that used in the third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) for treating low-density lipoprotein cholesterol, can be used to classify patients’ risk for cardiovascular and metabolic problems and to determine the appropriate level of therapeutic intervention. Patients at highest risk should receive the most intensive therapy. The presence of the metabolic syndrome, a clustering of atherogenic risk factors including dyslipidemia, elevated blood pressure, elevated blood glucose, and other problems, confers additional risk for diabetes mellitus and atherosclerotic cardiovascular disease at every level of risk. Pharmacotherapy with lipid-lowering, antiplatelet, antihypertensive, or insulin-sensitizing agents to modify specific risk factors is indicated in patients at higher risk, but lifestyle change (e.g., smoking cessation, weight reduction, increased physical activity, and “heart-healthy” dietary modifications) and blood pressure control can be used across all categories of risk. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Atherosclerotic cardiovascular disease; Framingham risk score; Lipid-lowering therapy; Metabolic syndrome; Primary prevention; Secondary prevention

The clinical approach to comprehensive cardiometabolic risk assessment and management is directed toward reducing short- and long-term risk for diabetes mellitus and atherosclerotic cardiovascular disease (ASCVD) in the settings of both primary and secondary prevention. Key risk factors are listed in Table 1 and include: (1) major risk factors (proven, direct causes); (2) emerging risk factors (less well defined, though supported by evidence as causative); and (3) underlying risk factors (the root causes of the emerging and major risk factors).

GLOBAL ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK ASSESSMENT: A GUIDE FOR THERAPY

In 2001 the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) incorporated a risk assessment algorithm for ASCVD. Patients with coronary heart disease (CHD), other atherosclerotic disease, or diabetes are considered to be at high risk. For other patients, risk stratification occurs in 2 steps. First, for the purpose of cholesterol management, the clinician counts the number of major risk factors. In this case only 5 major risk factors apply: cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or controlled with an antihypertensive medication), low high-density lipoprotein (HDL) cholesterol (<40 mg/dL [1 mg/dL = 0.02586 mmol/L]), family history of premature CHD, and age (≥45 years for men, ≥55 years for women). Low-density lipoprotein (LDL) cholesterol does not count as a separate risk factor in this algorithm because the point of the algorithm is to guide the management of LDL cholesterol. (Although the ATP III guidelines focus on modifying LDL cholesterol to prevent CHD, their approach is relevant to the management of other cardiovascular and metabolic disorders.) Patients with 0 or 1 risk factor are considered to be at lowest risk. For patients with ≥2 risk factors, Framingham or other predictive risk calculators can be used to estimate the global risk of developing CHD within a period of time, such as within 10 years.
years.\textsuperscript{1,4} Treatment strategy depends on the level of global risk and the patient’s LDL cholesterol level. Patients at highest risk receive the most intensive intervention, which usually involves drug therapies.

**THE METABOLIC SYNDROME**

In 2001, the ATP III introduced the metabolic syndrome as a clinically useful description of a commonly observed clustering of metabolic risk factors, including atherogenic dyslipidemia (e.g., high triglycerides and low HDL cholesterol), elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state.\textsuperscript{2,5,6} According to ATP III,\textsuperscript{1} a diagnosis of metabolic syndrome can be made when $\geq 3$ of 5 metabolic risk factors are present in an individual patient (Table 2). These criteria are not the only ones in use; however, composite risk estimators make use of the same cluster of variables.\textsuperscript{2} In patients with the metabolic syndrome, relative risk for ASCVD ranges from 1.5 to 3.0 depending on the stage of progression. When diabetes is not yet present, patient risk for progression to type 2 diabetes averages about a 5-fold increase compared with individuals without the syndrome. Once diabetes develops, cardiovascular risk increases further. A major clinical advantage of the recognition of the metabolic syndrome is that it brings the fields of CVD and diabetes together in an effort to reduce the risk for both diseases simultaneously.\textsuperscript{5}

Because metabolic syndrome raises the risk for both diabetes and ASCVD, it is important to identify such patients as early as possible to institute lifestyle therapy. All patients with the metabolic syndrome deserve global risk assessment for ASCVD in the short term (e.g., 10-year risk), whether by Framingham or other risk factor algorithms that include additional risk factors such as age, sex, total cholesterol, and smoking status or by atherosclerosis imaging, to identify candidates for preventive drug therapies.\textsuperscript{5}

**MODIFYING RISK FACTORS**

Lifestyle change is the first-line approach to the management of patients at high cardiovascular and metabolic risk. The therapeutic goal is to reduce underlying cardiovascular and metabolic risk factors such as overweight/obesity, physical inactivity, and atherogenic diet. Successful incorporation of healthy eating and fitness habits into a patient’s lifestyle can reduce every metabolic risk factor (Table 3).\textsuperscript{7} For patients at higher risk, specific lipid and metabolic risk factors are targets for pharmacotherapy with lipid-modifying, antiplatelet, antihypertensive, and antidiabetic agents.

**Lipid-Lowering Therapy**

In 2001, the ATP III reinforced its earlier recommendation that lowering elevated LDL cholesterol is the primary target of cholesterol-lowering therapy.\textsuperscript{1} Under these guidelines patients at high risk had the lowest LDL cholesterol goal ($<100 \text{mg/dL}$). Recent clinical trials indicate that patients at very high risk will benefit from even more intensive LDL cholesterol–lowering therapy.\textsuperscript{8} In very-high-risk patients with diabetes and CHD, The Treating to New Targets (TNT) study showed that lowering LDL cholesterol to mean levels of 77 mg/dL with atorvastatin 80 mg/day reduced the rate of major ASCVD events by 25% compared with atorvastatin 10 mg/day ($P = 0.026$).\textsuperscript{9} A similar result was reported for patients with CHD and the metabolic syndrome.\textsuperscript{10}

As Figure 1 shows, it now appears that for CHD risk reduction, the lower the LDL cholesterol level, the better the outcome. Thus, the American Heart Association/American College of Cardiology (AHA/ACC) guidelines for secondary prevention and the ATP III guidelines have been updated to note that treating to a target LDL cholesterol level of $<70 \text{mg/dL}$ is a reasonable goal for patients at very high risk (i.e., patients with CHD and other high-risk conditions).\textsuperscript{3,11} Figure 2 shows the most current ATP III algorithm.

### Antipla telet Therapy

Daily low-dose aspirin therapy is an effective and low-cost option for reducing thrombotic vascular events in high-risk patients. A meta-analysis of 287 randomized trials involving about 212,000 patients showed that antiplatelet therapy (predominantly aspirin) was associated with a reduction in the rates of CVD events and nonfatal stroke of approximately 25% and a reduction in the rate of nonfatal myocardial infarction (MI) of approximately 33%.\textsuperscript{11} In these patients, who had acute or previous vascular disease or some other predisposing condition, the benefits of low-dose aspirin (75 to 150 mg/day) significantly outweighed the risk of major extracranial bleeding.\textsuperscript{12} Thus, it has

### Table 1 Risk factor categories for atherosclerotic cardiovascular disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Risk Factors</td>
<td>Cigarette smoking, elevated BP, elevated LDL-C, low HDL-C, diabetes mellitus, metabolic syndrome, advanced atherosclerotic burden</td>
</tr>
<tr>
<td>Emerging Risk Factors</td>
<td>Prothrombotic state, proinflammatory state, insulin resistance</td>
</tr>
<tr>
<td>Underlying Risk Factors</td>
<td>Atherogenic diet, obesity, physical inactivity, family history</td>
</tr>
</tbody>
</table>

**BP** = blood pressure; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **VLDL-C** = very-low-density lipoprotein cholesterol.

Adapted from JAMA\textsuperscript{4} and Circulation.\textsuperscript{2,3}
been estimated that for most patients whose 10-year risk is ≥10%, low-dose aspirin therapy outweighs the risks of side effects. The question as to whether the benefits of aspirin therapy extend to lower-risk patients, who may still be at increased lifetime risk for MI or stroke, is currently under investigation.

**Antihypertensive Therapy**

Lowering blood pressure reduces the risk for CVD and stroke. During the past 2 decades, many researchers have concluded that, compared with diastolic pressure, systolic blood pressure better predicts the risk for CVD and renal disease. A meta-analysis of 10 randomized trials involving 18,542 patients showed that an average reduction of 12 to 13 mm Hg in systolic pressure over 4 years of follow-up was associated with a 21% reduction in CHD, a 37% reduction in stroke, a 25% reduction in total CVD mortality, and a 13% reduction in all-cause mortality. Hypertension guidelines recommend lifestyle intervention and antihypertensive drugs for patients with high blood pressure. Currently, no single class of antihypertensive agent has been recognized as a clear drug of choice for patients with the metabolic syndrome.

**Glucose Control**

The risk for CVD is substantially elevated not only in overt diabetes but also in patients with prediabetes (i.e., impaired glucose tolerance and other glycemic risk factors that can precede diabetes). The Nurses’ Health Study, a database of 177,629 women followed for 20 years, documented the relation of prediabetes to CVD risk. The higher risk for CVD in patients with prediabetes can be explained largely by concomitant metabolic syndrome. The subjects who had diabetes at baseline (n = 1,508) had a 5-fold increased risk for developing CVD (MI or stroke) compared with nondiabetic subjects (Figure 3). Similarly, compared with non-diabetic women, women who developed diabetes during follow-up were at elevated risk for CVD. Among these women, the risk for CVD was 3.71 after a diagnosis of diabetes and 2.82 before diagnosis. In other words, the risk for MI or stroke was substantially elevated both before and after the diagnosis of diabetes. The risk for CVD began

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**Table 2** Diagnosing the metabolic syndrome: National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>Men: &gt;102 cm (&gt;40.2 in) Women: &gt;88 cm (&gt;34.6 in)</td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C*</td>
<td>Men: &lt;40 mg/dL</td>
</tr>
<tr>
<td>BP</td>
<td>≥130/85 mm Hg</td>
</tr>
<tr>
<td>Fasting plasma glucose*</td>
<td>≥110 mg/dL††</td>
</tr>
</tbody>
</table>

BP = blood pressure; HDL-C = high-density lipoprotein cholesterol.

*To convert values to SI units: for triglycerides, 1 mg/dL = 0.01129 mmol/L; for cholesterol, 1 mg/dL = 0.02586 mmol/L; for fasting plasma glucose, 1 mg/dL = 0.05551 mmol/L.

††The American Diabetes Association uses a cutpoint of ≥100 mg/dL.

Adapted from JAMA.1

**Table 3** Therapeutic lifestyle changes for patients at high cardiovascular and metabolic risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Goal/Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>• 7%–10% loss of body weight from baseline</td>
</tr>
<tr>
<td></td>
<td>• Caloric deficit of 500–1,000 kcal* daily</td>
</tr>
<tr>
<td></td>
<td>• Physical activity</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>• 30–60 min of moderately intense aerobic activity daily</td>
</tr>
<tr>
<td>Atherogenic diet</td>
<td>• Saturated fat &lt;7% of total calories</td>
</tr>
<tr>
<td></td>
<td>• Reduce intake of trans fat</td>
</tr>
<tr>
<td></td>
<td>• Dietary cholesterol &lt;200 mg/dL*</td>
</tr>
<tr>
<td></td>
<td>• Total fat 25%–35% of total calories</td>
</tr>
</tbody>
</table>

To convert values to SI units, 1 kcal = 4.2 kJ; for cholesterol, 1 mg/dL = 0.02586 mmol/L.
to increase 15 years before the manifestation of overt diabetes.\textsuperscript{16}

The slow and insidious onset of diabetes makes it an ideal target for preventive interventions. The Diabetes Prevention Program (DPP) study demonstrated that the progression to diabetes can be delayed. In this trial, both intensive lifestyle intervention and metformin were shown to reduce the risk for diabetes in high-risk patients with impaired fasting glucose.\textsuperscript{17} Lifestyle intervention reduced the risk for diabetes to a greater extent (58\%) than did metformin (31\%).\textsuperscript{17} However, troglitazone (which was discontinued during the trial owing to liver toxicity and is no longer available) reduced the development of diabetes by more than placebo, lifestyle intervention, or metformin.\textsuperscript{18}

The DPP demonstrated the high effectiveness of intensive lifestyle intervention in preventing or delaying the onset of diabetes. Clearly, the therapeutic lifestyle changes recommended by the ATP III and other guidelines should be widely implemented for patients at all levels of cardiometabolic risk.

**A RISK GROUP–GUIDED APPROACH TO ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK MANAGEMENT**

Various management approaches are recommended for each of the different risk group categories of moderate risk, moderately high risk, high risk, and very high risk, as well
as for the metabolic syndrome. In general, therapy intensifies with increasing level of risk. However, therapeutic lifestyle changes (e.g., smoking cessation, weight reduction, and “heart-healthy” dietary modifications) and blood pressure control are recommended across all categories of risk.

Patients with the Metabolic Syndrome
The first-line approach to treating the metabolic syndrome is therapeutic lifestyle change directed toward weight reduction and increased physical activity.\textsuperscript{1,2} Weight loss improves metabolic syndrome by lowering serum cholesterol and triglycerides, raising HDL cholesterol, lowering blood pressure and glucose, and reducing insulin resistance, inflammation, and thrombotic tendency.\textsuperscript{2}

Effective weight-loss strategies involve behavior modification, caloric restriction, increased physical activity (30 minutes of moderate exercise daily), and a heart-healthy diet with reductions in dietary saturated fat, \textit{trans} fat, and cholesterol. All patients with the metabolic syndrome should receive intensive lifestyle therapy aimed at reducing their long-term cardiovascular risk. As mentioned previously, patients with the metabolic syndrome should have an ASCVD risk assessment such as Framingham risk scoring; those who turn out to be at high risk should receive the appropriate therapeutic interventions (\textbf{Figure 4}).

Patients at Moderate Risk
These patients have low short-term cardiometabolic risk, but their long-term risk may still be high. The therapeutic goal for these patients, therefore, is to reduce long-term risk, primarily through therapeutic lifestyle changes.\textsuperscript{3} The LDL cholesterol goal is <130 mg/dL. In moderate-risk patients with LDL cholesterol levels \geq 160 mg/dL, drug therapy can be considered in order to achieve an LDL cholesterol level <130 mg/dL.\textsuperscript{1} Smokers should receive therapy to help them quit, and patients with hypertension should have their blood pressure controlled with lifestyle changes or, possibly, drug therapy.

Patients at Moderately High Risk
Patients in this risk category are at higher short-term risk; the therapeutic goal is thus to reduce short-term as well as
long-term risk. As with moderate-risk patients, smoking cessation and blood pressure normalization are key. The LDL cholesterol goal for these patients is <130 mg/dL. However, for moderately high-risk patients with the metabolic syndrome, it is reasonable to reduce the LDL cholesterol level further to <100 mg/dL. Once blood pressure and LDL cholesterol goals have been achieved, the focus shifts to managing metabolic syndrome traits. For example, low-dose aspirin therapy should be considered for the treatment of prothrombotic states, and lifestyle therapy should be intensified to reduce weight and to control prediabetic states.

Patients at High Risk
This category applies to secondary prevention (i.e., patients who already have ASCVD or diabetes) and to patients with multiple risk factors who have high short-term risk (e.g., >20% 10-year risk for CHD). High-risk patients are candidates for intensified therapeutic interventions. For patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with chronic kidney disease or diabetes), blood pressure medication is indicated, as needed and as tolerated, to achieve blood pressure goals. In patients with diabetes, lifestyle interventions and pharmacotherapy should be initiated to achieve a near-normal hemoglobin A1c level <7%. Management of the metabolic syndrome in these high-risk patients requires intensification of lifestyle therapies, with frequent assessment of body mass index, waist circumference, and physical activity performance. In patients with ASCVD, antithrombotic therapy with low-dose aspirin is recommended.

Patients at Very High Risk
The recommendations for very-high-risk patients (i.e., patients with established CHD and other high-risk conditions) are identical to those for high-risk patients, with the exception that an increasing amount of evidence supports treating to an LDL cholesterol goal of 70 mg/dL in such individuals.

SUMMARY
In clinical practice, risk assessment is a valuable guide to optimizing outcomes in the settings of both primary and secondary prevention. In general, risk modification therapy should be “stepped up” according to risk category. Patients at high or very high risk should receive intensive intervention for risk reduction. For example, it is reasonable to treat very-high-risk patients to an LDL cholesterol goal of <70 mg/dL. However, at all levels of risk, therapeutic lifestyle changes (e.g., smoking cessation, weight reduction, and heart-healthy diet modification) and blood pressure control are recommended. Finally, to reduce long-term risk for ASCVD, all patients with the metabolic syndrome should receive intensive lifestyle therapy and, if risk algorithms so indicate, pharmacotherapy directed toward individual risk factors.

References
Discussion Following Dr. Grundy’s Presentation

Question: In the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and other guidelines, no explicit recommendation is given regarding how to modify risk factor management above and beyond global risk for patients who have the metabolic syndrome. Would you like to comment?

Scott M. Grundy, MD, PhD (Dallas, Texas, USA): Although the ATP III provides no explicit recommendation, the 2004 American Heart Association/American College of Cardiology (AHA/ACC) update of the guidelines states that more intensive management is required for patients with the metabolic syndrome. For example, within the context of primary prevention, the low-density lipoprotein (LDL) cholesterol goal is <130 mg/dL (1 mg/dL = 0.02586 mmol/L); however, in patients with the metabolic syndrome it is stated that it is reasonable to aim for an LDL cholesterol level <100 mg/dL. We are moving in the direction of formulating guidelines, but recommendations have not been defined precisely, perhaps because the data are not yet available.
Abdominal Adiposity and Cardiometabolic Risk: Do We Have All the Answers?

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ABSTRACT

Overweight and obesity, particularly abdominal adiposity, increase the risk for type 2 diabetes mellitus and cardiovascular disease (CVD). Metabolic syndrome, a constellation of risk factors that includes elevated triglycerides, low high-density lipoprotein cholesterol, elevated blood pressure, elevated fasting glucose, and abdominal obesity, predicts the development of CVD and diabetes to an even greater degree. Excess abdominal adipose tissue is associated with insulin resistance, the precursor to type 2 diabetes, and creates an atherogenic inflammatory milieu, characterized by high levels of C-reactive protein and other inflammatory markers (e.g., fibrinogen, plasminogen activator inhibitor–1, cytokines, and adhesion molecules). High levels of these biomarkers correlate with an increased incidence of diabetes and CVD. Recent evidence suggests that patients with nonalcoholic fatty liver disease have an increased incidence of obesity, metabolic syndrome, and insulin resistance and/or type 2 diabetes. Relatively small reductions in body weight may significantly reduce abdominal adipose tissue, reduce insulin resistance, lower triglycerides and low-density lipoprotein cholesterol, reduce inflammation, and decrease overall cardiometabolic risk.

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KEYWORDS: Abdominal adipose tissue; C-reactive protein; Cardiometabolic risk; Metabolic syndrome; Type 2 diabetes mellitus

During the past 2 decades, the rates of overweight (body mass index [BMI] ≥25) and obesity (BMI ≥30) in the United States have increased.1–3 An estimated 97 million adults are now overweight or obese, greatly heightening their risk for numerous diseases, including cardiovascular disease (CVD), type 2 diabetes mellitus, and certain forms of cancer.4 A prospective study of >1 million US adults showed a curvilinear relation between BMI and death from CVD and other causes, in which the very heavy and the very lean were at greatest risk.5 The lowest rates of death from all causes were observed among men with BMIs ranging from 23.5 to 24.9 and women with BMIs ranging from 22.0 to 23.4. The relative risk of death remained relatively low and stable across a wide spectrum of BMIs (ranging from 22.0 to 26.4 in men and from 20.5 to 24.9 in women), but the risk of death from CVD began to increase significantly when BMI exceeded the high end of those ranges (Figure 1). Two recent large, prospective, cohort studies confirm that even a moderate elevation in BMI is associated with an increased risk of death from CVD and other causes.6,7 More direct measures of abdominal adiposity, such as waist–hip ratio and waist circumference, may predict mortality risk as well as or better than BMI, particularly in the elderly.8

ABDOMINAL OBESITY AND INSULIN RESISTANCE

Insulin resistance is a precursor to impaired glucose tolerance and type 2 diabetes. It has been hypothesized to correlate with abdominal obesity (a marker of visceral fat). To test this hypothesis, Banerji and colleagues’ measured insulin action with the euglycemic insulin clamp (a direct measure of glucose disposal) and adipose tissue distribution with computed tomog-
raphy scans (a direct visualization of visceral fat) in 32 black men and 20 black women with non–insulin-dependent diabetes (type 2 diabetes). As depicted in Figure 2, the results showed an inverse correlation between glucose disposal and visceral (not subcutaneous or total) adipose tissue in both men and women whose visceral adipose tissue ranged from 500 to 2,500 mL/m² body surface area. This implies that even slight changes in intra-abdominal adipose tissue could have a significant effect on insulin-mediated glucose disposal in patients with type 2 diabetes. Extrapolating to clinical practice, simply losing a small amount of weight may be associated with a substantial reduction in insulin resistance.

CONCEPTUAL FRAMEWORK FOR METABOLIC SYNDROME

The metabolic syndrome is a constellation of cardiometabolic abnormalities that is correlated with increased risk for diabetes and CVD. The exact nature, causes, and treatments of the syndrome are still being debated (Table 1). The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III),¹⁰ the International Diabetes Federation (IDF),¹¹ and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)¹² all endorse first-line treatments such as weight reduction and increased physical activity to address underlying environmental causes of metabolic syndrome. The World Health Organization (WHO) views insulin resistance as the underlying pathophysiologic mechanism and recommends consideration of pharmacotherapy with insulin sensitizers to prevent high-risk individuals with insulin resistance from developing diabetes.¹⁰ A newly emergent third concept attributes the metabolic syndrome to inflammation, which expands treatment options for cardiometabolic risk to include agents with anti-inflammatory properties (e.g., 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors [statins], angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers) as well as insulin sensitizers.

EXPANDING THE DEFINITION OF METABOLIC SYNDROME

Data from the Insulin Resistance Atherosclerosis Study (IRAS),¹³ a multicenter population-based study of 1,008 healthy nondiabetic individuals (33% of whom had im-

![Figure 1](image1.png)

**Figure 1** Overweight and obesity increase the risk of cardiovascular disease mortality. Data are from 1 million men and women (average age, 57 years), followed for 14 years, who never smoked and had no history of disease at enrollment. (Reprinted from *N Engl J Med.*)³

![Figure 2](image2.png)

**Figure 2** Relation between visceral adipose tissue and insulin action. LBM = lean body mass. (Adapted from *Am J Physiol.*)⁹
paired glucose tolerance), demonstrated that subclinical inflammation (as measured by fibrinogen, C-reactive protein [CRP], and plasminogen activator inhibitor–1 [PAI-1]) was strongly correlated with metabolic disorders. In particular, increases in CRP levels were shown to parallel increases in the number of metabolic disorders. CRP and other surrogate markers of subclinical inflammation (such as fibrinogen and white blood cell count) also predicted the development of diabetes over a 5-year period. These findings support the inclusion of CRP, and perhaps other inflammatory markers, as a component of the metabolic syndrome.

Clinical and epidemiologic evidence suggests that obesity, type 2 diabetes, and hyperlipidemia are risk factors for nonalcoholic fatty liver disease (NAFLD). Likewise, the presence of NAFLD is an indicator of the metabolic syndrome, insulin resistance, and type 2 diabetes. Unchecked, NAFLD may progress from simple fat accumulation in hepatocytes to nonalcoholic steatohepatitis (NASH) and eventually culminate in advanced fibrosis or cirrhosis. Medical therapy is directed toward preventing NASH progression in those patients at highest risk for developing NASH and its complications. Recent clinical trial data have shown that insulin sensitizers (e.g., metformin) and lifestyle intervention may reduce liver fat and even reverse NASH to some degree.

The multicenter IRAS demonstrated a strong correlation between elevated liver enzymes (e.g., alanine aminotransferase and aspartate aminotransferase) and the risk for type 2 diabetes. In 906 individuals who were diabetes free at baseline, those with the highest elevations in liver enzymes were at significantly greater risk for developing diabetes. Notably, liver markers predicted diabetes risk across all subgroups, regardless of sex, ethnicity, obesity, glucose tolerance status, or insulin sensitivity (Figure 3). CRP, which appears to play a role in the development of NAFLD and NASH, also predicted diabetes risk independent of liver markers and to the same extent. Clinically, testing patients with both liver enzyme and CRP assays may add to the individual predictive powers of each of these markers. In a more recent IRAS analysis, liver enzymes were shown to predict the risk for metabolic syndrome independent of potentially confounding variables, such as insulin sensitivity and acute insulin response. This supports accumulating evidence suggesting that NAFLD should be recognized as a component of the metabolic syndrome.

### CLINICAL UTILITY OF METABOLIC SYNDROME FOR PREDICTING DIABETES AND CARDIOVASCULAR DISEASE RISK

In the large primary prevention arm of the San Antonio Heart Study (SAHS), the investigators assessed the risk for CVD mortality in relation to diabetes, metabolic syndrome, and sex in 2,372 individuals without CVD or diabetes at baseline using sex-specific hazard ratios (HRs). Patients were stratified according to diabetes and NCEP ATP III metabolic syndrome status (Table 2).

During the 12.7-year follow-up, patients with NCEP-defined metabolic syndrome who did not have diabetes had a 2-fold risk for CVD that was not modified by sex. The magnitude of risk conferred by metabolic syndrome was similar to that associated with other major risk factors, such as hypertension or smoking. By contrast, in individuals who had diabetes but who did not have metabolic syndrome, an uncommon clinical combination, the HR of CVD was higher in women than in men (3.53 and 2.34, respectively, compared with healthy patients). This sex-based trend became significant among patients who had both diabetes and metabolic syndrome, the more common clinical presentation. The risk of CVD doubled in women, increasing 8-fold, but increased only 3-fold in men (compared with individuals with no diabetes or metabolic syndrome). In nondiabetic persons, the metabolic syndrome modestly increased CVD risk to the same extent in both sexes, whereas in individuals with diabetes, the metabolic syndrome increased the risk for CVD most dramatically in women. Therefore, diabetes appears to be the factor responsible for the sex-associated modification in CVD risk.

Sex appeared to modify the predictive value of the metabolic syndrome for CVD mortality in the general population: the CVD mortality HRs for NCEP-defined metabolic
syndrome (Table 3) were 4.65 for women and 1.82 for men. Corresponding HRs for WHO-defined metabolic syndrome (Table 3) were 2.83 for women and 1.15 for men. Thus, in lower-risk individuals without diabetes or CVD at baseline, the simpler NCEP criteria better identified those at increased CVD risk than did the WHO criteria.18

The SAHS also evaluated the relation of metabolic syndrome to the risk for diabetes in individuals with normal and impaired glucose tolerance who were followed for about 7 years.19 Among individuals with normal glucose tolerance, metabolic syndrome (NCEP definition) increased the incidence of diabetes 4-fold, leading to a 7-year absolute risk of 15%. The risk rose to 25% in individuals without the metabolic syndrome who had impaired glucose tolerance. Individuals with the metabolic syndrome and impaired glucose tolerance had a 55% risk of developing diabetes within 7 years. According to the experience of the Diabetes Prevention Program (DPP), these risks could be roughly halved in obese patients using modest behavioral interventions. However, individuals with both the metabolic syndrome and impaired glucose tolerance would still be at substantial risk (25% to 30%); these individuals also should be considered candidates for drug therapy.22 Thus, in clinical practice, the metabolic syndrome is useful for risk stratification aimed at targeting more intensive preventive efforts to those at highest risk for diabetes.

Despite the controversies and criticisms that continue to surround the metabolic syndrome, it provides a simplified operational definition of cardiometabolic risk that is easier to apply in the clinical setting than is global risk assessment or multivariate predictive equations. Importantly, the metabolic syndrome encourages providers to look for additional risk factors and to use behavioral therapy to address the entire constellation of risk holistically rather than just treating each risk factor individually.

### Table 2
<table>
<thead>
<tr>
<th>Baseline Status</th>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−Diabetes/−metabolic syndrome</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>−Diabetes/+metabolic syndrome</td>
<td>2.07 (0.72–6.00)</td>
<td>1.96 (0.99–3.88)</td>
</tr>
<tr>
<td>+Diabetes/−metabolic syndrome</td>
<td>3.53 (0.75–16.7)</td>
<td>2.34 (0.70–7.82)</td>
</tr>
<tr>
<td>+Diabetes/+metabolic syndrome</td>
<td>8.19 (3.51–19.1)</td>
<td>3.09 (1.49–6.43)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
*Metabolic syndrome as defined by National Cholesterol Education Program Adult Treatment Panel III criteria.

Adapted from Circulation.18

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**Figure 3** Logistic regression analysis of markers of liver injury (e.g., alanine aminotransferase [ALT]) with risk for incident diabetes mellitus in nondiabetic subjects in the Insulin Resistance Atherosclerosis Study (IRAS) classified into subgroups by sex, ethnicity, obesity, glucose tolerance (normal glucose tolerance [NGT] and impaired glucose tolerance [IGT]), and insulin sensitivity (S1). Although associations between ALT and diabetes risk were not uniformly significant for all individual subgroups, the directions of the associations were almost entirely positive. Odds ratios refer to risk for incident type 2 diabetes associated with a standard deviation increase in the log of ALT. (Reprinted with permission from Diabetes.16)
A study of 56 healthy premenopausal obese women (BMI >30) showed that after 2 years, patients who maintained weight losses of 5% to 10% of initial weight still showed significant and sustained reductions in low-density lipoprotein cholesterol levels than did those who sustained weight reductions of 5% to 10% of initial weight. Long-term changes in lipids and lipoproteins were assessed in these biomarkers of CVD risk. A small study of 25 patients established that weight loss with rimonabant is associated with increased basal concentrations of tumor necrosis factor–α interleukin-6, P-selectin, intracellular adhesion molecule–1 (ICAM-1), and vascular adhesion molecule–1 (VCAM-1). After 1 year, the obese women lost ≥10% of their initial weight, which resulted in reductions in the levels of inflammatory cytokines and adhesion molecules (e.g., P-selectin, ICAM-1, VCAM-1) and improvements in vascular responses to L-arginine, a measure of improved endothelial function (Figure 4). Thus, it appears that weight loss effectively reduces inflammation in obese patients, thereby lowering CVD risk.

Weight loss of 5% to 10% of initial weight has been shown to reduce the risk for developing type 2 diabetes. In the DPP study,22 high-risk nondiabetic individuals (N = 3,234) with a mean BMI of 34.0 were randomized to receive placebo, metformin 850 mg bid, or a lifestyle modification program with goals of 7% weight loss and 150 minutes of physical activity per week. Over the 4-year study period, the average weight loss was 2.1 kg (2%) in the metformin group compared with 5.6 kg (6%) in the lifestyle intervention group (P <0.001), and the incidence of diabetes was reduced by 31% and 58%, respectively, compared with placebo (Figure 5). These results established that high-risk individuals can cut their risk of developing type 2 diabetes by >50% with a realistic loss of weight.

A recent analysis of data from the same study showed that lifestyle therapy and metformin also reduced the risk for metabolic syndrome.23 Some 53% of this high-risk population with high BMI and increased waist circumference had the metabolic syndrome at baseline. After 3 years, the incidence of metabolic syndrome in patients who did not have it at baseline was reduced by 41% in the lifestyle intervention group (P <0.001) and by 17% in the metformin group (P = 0.03) compared with placebo (Figure 5). In addition, treatment, particularly with lifestyle intervention, was also effective in resolving the metabolic syndrome. At 3 years, 18% of the placebo group, 23% of the metformin group, and 38% of the lifestyle group who had the metabolic syndrome at baseline no longer met the criteria.

**EFFECT OF WEIGHT REDUCTION ON CARDIOMETABOLIC RISK**

Excess adipose tissue creates an inflammatory milieu, characterized by high levels of CRP and other inflammatory biomarkers (e.g., cytokines and adhesion molecules), that promotes CVD. Studies have evaluated the effects of weight loss on these biomarkers of CVD risk. A small study of 25 patients assessed the effect of modest reductions in initial body weight on long-term changes in lipids and lipoproteins.20 The results showed that after 2 years, patients who maintained weight reductions >10% of initial weight had significantly greater decreases in low-density lipoprotein cholesterol levels than did those who sustained weight reductions of 5% to 10% of initial weight.

Sustained weight loss of ≥10% of initial body weight has also been shown to reduce the inflammation associated with endothelial dysfunction and CVD risk in obese individuals. In a study of 56 healthy premenopausal obese women (BMI >30) compared with nonobese women, obesity was associated with increased basal concentrations of tumor necrosis factor–α interleukin-6, P-selectin, intracellular adhesion molecule–1 (ICAM-1), and vascular adhesion molecule–1 (VCAM-1). After 1 year, the obese women lost ≥10% of their initial weight, which resulted in reductions in the levels of inflammatory cytokines and adhesion molecules (e.g., P-selectin, ICAM-1, VCAM-1) and improvements in vascular responses to L-arginine, a measure of improved endothelial function (Figure 4). Thus, it appears that weight loss effectively reduces inflammation in obese patients, thereby lowering CVD risk.

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**FUTURE DIRECTIONS**

The benefits of weight loss in reducing cardiometabolic risk have been evaluated primarily in short-term studies. Therefore, many questions remain unanswered.

Recently, the Rimonabant in Obesity (RIO)–Lipids trial24 showed that rimonabant,* a cannabinoid-1 receptor antagonist, reduced weight and waist circumference and improved the metabolic risk profile. The RIO–North America (NA) trial,25 although it did not evaluate cardiometabolic risk parameters in the same detail, established that weight loss with rimonabant is sustained for 2 years. The Look AHEAD (Action for Health in Diabetes) Study,26 a multicenter randomized clinical trial, recently completed enrollment of 5,145 obese patients with type 2 diabetes. The study is designed to evaluate the effects of a lifestyle intervention (caloric restriction and exercise) on

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*Recently, an FDA Advisory Committee recommended a delay in the approval of rimonabant because of safety issues that need to be addressed in future studies.
weight loss and CVD events during a long-term follow-up period of 11.5 years. A number of related Look AHEAD studies will address other areas, such as fatty liver disease, sleep apnea, and eating disorders in the Look AHEAD population.

**SUMMARY**

Obesity, especially abdominal obesity, increases the risk for metabolic syndrome, insulin resistance, type 2 diabetes, and CVD. Obesity also adversely affects several emerging biomarkers of diabetes and CVD risk, such as CRP and liver enzymes. The cause of the metabolic syndrome (environment, insulin resistance, inflammation) remains open to debate; however, lifestyle intervention is clearly the first-line treatment. Drug therapy with insulin sensitizers, statins, and antihypertensive agents can be used to treat individual components of the metabolic syndrome in high-risk patients and in those refractory to lifestyle interventions alone; another emerging possibility is the pharmacologic enhancement of weight loss.

**References**

Discussion Following Dr. Haffner’s Presentation

Question: Nonalcoholic fatty liver disease (NAFLD) is not only a predictor of insulin resistance but also a leading cause of cirrhosis. Therefore, should current definitions extend the concept of metabolic syndrome beyond cardio-metabolic risk to encompass cardiohepatometabolic risk?

Steven M. Haffner, MD (San Antonio, Texas, USA): That is an excellent question. In fact, the interest in NAFLD began with gastroenterologists, then reached endocrinologists and, finally, cardiologists. A major clinical trial is in the start-up phase. However, at this point, although debate has begun, I am not prepared to recommend a change in the start-up phase. However, at this point, although debate has begun, I am not prepared to recommend a change in the start-up phase. However, at this point, although debate has begun, I am not prepared to recommend a change in

This is an area of active investigation. It is possible that much of what we ascribe to visceral fat may actually be owing to fat in the muscle and the liver, and new studies are beginning to explore this phenomenon.

George Kunos, MD, PhD (Bethesda, Maryland, USA): I would like to add that fatty liver disease could be included as part of the treatment goal in regressing, or reversing, metabolic syndrome. In this regard, a recent French study published in Nature Medicine reported that rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight patients with dyslipidemia. N Engl J Med. 2005;353:2121–2134.

This is an area of active investigation. It is possible that much of what we ascribe to visceral fat may actually be owing to fat in the muscle and the liver, and new studies are beginning to explore this phenomenon.

This is an area of active investigation. It is possible that much of what we ascribe to visceral fat may actually be owing to fat in the muscle and the liver, and new studies are beginning to explore this phenomenon.
Dr. Haffner: That is a very dangerous question. In the questionnaire-based data we just published on diet versus exercise, the improvement was almost entirely attributable to diet. However, because a questionnaire is not the most reliable measure, it was difficult to accurately assess the relative contribution of each. The Look AHEAD (Action for Health in Diabetes) Study, in which 50% of participants will use accelerometers and have maximum-level stress tests initially and once yearly, will provide more information on the relative importance of diet versus exercise in terms of cardiovascular disease (CVD) risk.

The other often-misunderstood issue is that, in the acute phase, as opposed to the maintenance phase, of lifestyle intervention, weight loss is almost always owing to caloric restriction. However, exercise is vitally important in weight maintenance. In fact, you can make a case that weight maintenance is much more important than weight loss, because obese patients often lose thousands of pounds during their lifetimes. The problem is that they gain the weight back again. Therefore, although both diet and exercise are important strategies, physical activity is less important in the acute phase of weight loss.

Question: The DPP showed that modest weight loss reduced the risk for diabetes by >50%. To what extent did modest weight loss improve metabolic syndrome?

Dr. Haffner: It depends on how one interprets the data. In the incredibly obese group of patients (mean body mass index >35) evaluated in the DPP, although the majority had a fasting glucose abnormality, only 53% had the metabolic syndrome at baseline. In patients with the metabolic syndrome at study entry, metformin reduced it by about 17% and lifestyle modification by 41%. Conversely, in the patients who did not have the metabolic syndrome initially, the incidence of subsequently developing it was 53% in the placebo group, 47% in the metformin group, and 38% in the lifestyle group.

Question: It is amazing that relatively small, easily achievable amounts of weight loss can have such a dramatic effect. What is the mechanism? Is it insulin resistance through β-cell function?

Michael D. Jensen, MD (Rochester, Minnesota, USA): In the studies in which we have evaluated the effects of weight loss with respect to glucose tolerance, it does appear to improve insulin sensitivity, remarkably, on a percentage basis, probably owing to the insulin-induced regulation of adipose tissue lipolysis. As we know, it also improves adiponectin and many other parameters. Therefore, one could argue that weight loss corrects dysfunctional adipose tissue stores and that, even without achieving normal weight, it is possible to reduce dysfunction of existing fat cells. I am a proponent of the large fat cell hypothesis, which maintains that those with the largest fat cells have the worst prognosis. Fat cells may be better regulated when weight loss results in fat cell shrinkage.

Question: Should we include C-reactive protein (CRP) in the metabolic syndrome criteria?

Dr. Haffner: This is an interesting issue. The data for inclusion are stronger with respect to diabetes, and, again, it depends on how one interprets the data. Using Cox or logistic regression models, CRP independently predicts the metabolic syndrome. However, using a more stringent receiver-operator curve, CRP does not improve upon existing criteria. This type of data analysis must be done for CVD, because it is the major end point in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition. Within 1 or 2 years we may have enough new data to form a reasonable conclusion.

References
Understanding Metabolic Homeostasis and Imbalance: What Is the Role of the Endocannabinoid System?

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ABSTRACT

Endogenous endocannabinoids (ECs) (anandamide and 2-arachidonoyl glycerol) are part of the leptin-regulated neural circuitry involved in appetite regulation. One of the sites of the orexigenic action of ECs involves activation of cannabinoid-1 (CB₁) receptors in the lateral hypothalamus, from which neurons involved in mediating food reward project into the limbic system. In animal models of obesity, pharmacologic blockade or genetic ablation of CB₁ receptors causes a transient reduction in food intake accompanied by sustained weight loss, reduced adiposity, and reversal of hormonal/metabolic changes, such as elevated levels of plasma leptin, insulin, glucose, and triglyceride, and reduced levels of plasma adiponectin (Acrp30). However, the beneficial effects of CB₁ blockade on weight and metabolism cannot be explained by appetite suppression alone. Animal studies suggest that CB₁ blockade exerts a direct peripheral as well as a central effect on fat metabolism. CB₁ receptor blockade with rimonabant has been shown to not only reduce weight and adiposity but also to directly modulate fat metabolism at peripheral sites in skeletal muscle, adipose tissue, and the liver. Preclinical animal studies suggest that CB₁ blockade acts on adipocytes to increase Acrp30 expression, on hepatocytes to decrease de novo lipogenesis and increase fatty acid oxidation, and on skeletal muscle to reduce blood glucose and insulin levels. Extrapolating from animal studies to the clinic, CB₁ receptor blockade offers a promising strategy not only for reducing weight and abdominal adiposity but also for preventing and reversing its metabolic consequences. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Adiponectin; Cannabinoid-1 receptors; Endocannabinoid system; Fatty liver disease; Leptin; Rimonabant

The appetite-stimulating effects of cannabinoids (CBs), specifically Cannabis sativa (marijuana), have been recognized for centuries. In the 1980s, the discovery of specific CB receptors and their endogenous ligands (the endocannabinoids [ECs] anandamide and 2-arachidonoyl glycerol [2-AG]) in human and mammalian tissue catapulted a relatively obscure field of research into a major area of basic scientific and clinical investigation.

Mounting evidence suggests that the EC system is involved in the physiologic regulation of many functions in the central and peripheral nervous systems, including energy homeostasis and glucose and lipid metabolism. In addition to known physiologic systems and pathways that modulate energy balance and substrate metabolism—hypothalamic and leptin-regulated pathways in particular—the EC system appears to play a role in cardiovascular risk factors and metabolic profile.

Important central effects of CB₁ receptor activation are modulation of energy balance and feeding behavior. Injection of ECs into the hypothalamus or mesolimbic region stimulates food intake. Under normal conditions, feeding reduces EC levels in the hypothalamus, whereas starvation increases them. CB₁ deletion in animal models is associated with a lean phenotype and resistance to diet-induced obesity.

The influence of the EC system on energy homeostasis cannot be completely explained by central effects on feeding behavior. Emerging evidence suggests that weight gain associated with CB₁ receptor stimulation is attributable not only to food intake but also to metabolic processes, independent of food intake. Beyond central effects on feeding, data show that the EC system also functions periph-
erally in discrete tissues to modulate hepatic lipogenesis, glucose homeostasis, and adipose tissue metabolism.

The EC system normally is a silent physiologic system that becomes transiently activated, i.e., it is activated only when needed. However, in animal models of genetic and diet-induced obesity, it has been shown that the EC system is tonically overactivated. It is still not clear whether overactivation of the EC system precedes or is a consequence of the obese phenotype.

The EC system now provides the promise of a novel mechanistic pathway for modulating cardiometabolic processes, including energy intake and expenditure as well as lipid and glucose metabolism. Definitive evidence for the involvement of ECs in the control of food intake, reduced adiposity, and reversal of hormonal/metabolic changes has been provided by a number of animal-model studies, some of which are discussed in this review.

**MECHANISMS OF APPETITIVE BEHAVIOR: LEPTIN–ENDOCANNABINOID INTERACTION**

In collaboration with Di Marzo, a study in my laboratory demonstrated the effects of leptin and EC interaction on the maintenance of food intake in normal wild-type mice and CB1-deficient, or knockout, mice. After an 18-hour fast, a single intraperitoneal injection of rimonabant,* a CB1 receptor blocker, reduced the level of food intake in the normal mice to the level observed in vehicle-treated CB1 receptor knockout mice. The effects of rimonabant occurred within 1 hour of feeding, suggesting that rimonabant influenced the appetite, rather than the consummatory, aspects of food intake. These results indicate that the hunger-induced increase in food intake noted in wild-type mice may be mediated by endogenous ECs acting via CB1 receptors.

Further experimentation revealed that leptin, a known negative regulator of other orexigenic peptides and hormones, similarly downregulates ECs. In genetically obese animals deficient in the appetite-suppressing hormone leptin, rimonabant injection effectively reduced food intake (even without food restriction), suggesting that increased EC system activation had contributed to their hyperphagia. When obese mice with defective leptin receptors were treated with leptin, their elevated EC levels, particularly anandamide but also 2-AG, decreased dramatically in the hypothalamus, whereas anandamide levels in the cerebellum remained unchanged. These results show that leptin may downregulate ECs through an EC-specific mechanism located within the hypothalamus. Therefore, it appears that ECs, along with other leptin-regulated orexigenic signals, contribute to overeating and the development of obesity, although the precise mechanism by which ECs in the hypothalamus are connected with the motivational food reward and satiety circuitry within the limbic system could not be clearly defined.

Jo and colleagues recently elucidated the relation between the leptin-mediated synthesis of ECs in the hypothalamus and the mesolimbic reward pathway that governs the pleasurable aspects of food consumption. Their electrophysiologic analysis showed that hypothalamic ECs interact with leptin in the lateral hypothalamus, also known as the hunger center. In rodents, electrical stimulation of this area increases food intake, whereas a lessening of stimulation results in anorexia. Subsets of neurons in the lateral hypothalamus that contain the orexigenic peptides melanin-concentrating hormone (MCH) and orexin/hypocretin, project into the mesolimbic ventral tegmental area, the site of origin of the dopaminergic reward pathway, thereby connecting the hypothalamic sustenance appetite center with the mesolimbic hedonic appetite center in the brain. The MCH neurons receive tonic γ-aminobutyric acid (GABA)ergic inhibitory input, which controls food intake and appetite as well as mood. The investigators found that neurons identified as containing MCH synthesize and release ECs in response to a rise in intracellular calcium (Figure 1).

Subsequently, ECs are released and act as retrograde messengers to suppress GABA release via activation of presynaptic CB1 receptors on the GABAergic interneurons, leading to increased excitability of MCH-containing lateral hypothalamic neurons and to enhanced food intake.

Jo and colleagues also found that MCH neurons contain leptin receptors, the activation of which by leptin inhibits voltage-gated calcium channels, preventing the influx of calcium into cells and blocking EC release, which may contribute to the appetite-suppressing effect of leptin. Conversely, the hyperphagia of leptin-deficient genetically obese mice may be related to the increased EC production, leading to a CB1 receptor–mediated suppression of GABAergic transmission and activation of MCH neurons. When EC activity is prevented though blockade of CB1 receptors, the GABAergic inhibitory tone on MCH neurons remains high, resulting in decreased food intake, which may explain the appetite-reducing effect of rimonabant.

**DIRECT EFFECTS OF CANNABINOID-1 BLOCKADE ON FAT METABOLISM**

In animal models of obesity, pharmacologic blockade or genetic ablation of CB1 receptors causes a transient decline in food intake accompanied by sustained weight loss and metabolic improvements. Because appetite reduction alone cannot explain these antiobesity and metabolic effects, it has been hypothesized that CB1 blockade exerts direct peripheral, as well as central, effects on fat metabolism.

In a mouse model of diet-induced obesity, 5-week treatment with rimonabant produced a transient reduction in food intake and a significant and sustained reduction in body weight (−20%) and adiposity (−50%) (Figure 2). In this study and others, diet-induced obesity was associated

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*Recently, an FDA Advisory Committee recommended a delay in the approval of rimonabant because of safety issues that need to be addressed in future studies.*
with adverse metabolic changes, including increased levels of plasma insulin, triglycerides, and leptin, and decreased levels of plasma adiponectin (Acrp30). Pharmacologic CB1 blockade with rimonabant improved metabolic parameters, reversing insulin resistance and lowering plasma leptin, insulin, and free fatty acid levels. Similarly, CB1 receptor–deficient mice fed the same high-fat diet that promoted obesity in wild-type mice were resistant to obesity and its associated metabolic changes. These results show that additional mechanisms unrelated to centrally mediated food intake contribute to obesity in normal mice and to resistance to obesity and its related metabolic changes in CB1 knockout mice and in rimonabant-treated wild-type mice.

In a study by Poirier and coworkers, chronic CB1 receptor blockade with rimonabant reversed the adverse metabolic effects of obesity in mice. Mice fed a high-fat diet for 5 months were randomized to receive rimonabant, its vehicle, or a dietary switch to standard laboratory diet plus vehicle for 10 additional weeks. The rimonabant treatment resulted in a marked and sustained decrease in body weight similar to that obtained by switching obese mice from a high-fat to a standard laboratory diet during 10 weeks, and was associated with only transient (14 days) reduction in energy intake. Rimonabant treatment significantly reduced the adverse metabolic changes related to obesity, decreasing leptin (−81%), insulin (−78%), and glucose (−67%) (P < 0.001) compared with the vehicle treatment (Figure 3). In addition, rimonabant treatment resulted in a modest but significant increase in Acrp30 levels (+18%, P < 0.05), which decrease with weight gain and increase with weight loss. Although rimonabant had no effect on high-density lipoprotein (HDL) cholesterol and only modest effects on total cholesterol, it significantly reduced triglycerides and low-density lipoprotein (LDL) cholesterol and increased the HDL–LDL cholesterol ratio (P < 0.001).

A study by Liu and associates demonstrated for the first time that rimonabant has a direct effect on energy expenditure, suggesting that its antiobesity property is owing to activation of thermogenesis in addition to the initial hypophagia. A similar increase in energy expenditure was noted earlier in CB1-receptor knockout mice compared with wild-type mice. Genetically obese mice were treated with rimonabant (10 mg/kg once daily) or with vehicle for 1 week. The mice were then decapitated and glucose uptake was measured in the isolated soleus muscle in the presence of a physiologic concentration of insulin (10 nmol/L). In vivo blockade of CB1 receptors resulted in a significant 68% increase in the rate of glucose uptake in isolated soleus muscle of the rimon-
abant-treated mice compared with vehicle-treated controls ($P < 0.05$) (Figure 2).\textsuperscript{13} Cota and colleagues\textsuperscript{1} showed that CB\textsubscript{1}-receptor knock-out mice had a lighter and leaner body phenotype compared with their wild-type control littermates. The CB\textsubscript{1}-deficient mice spontaneously consumed fewer calories and, consequently, weighed slightly but significantly less than controls. Although the lean phenotype was the result of decreased caloric intake in young CB\textsubscript{1} knockout mice, it also was attributable to metabolic factors that increased energy expenditure in adult mice. Within the central hypothalamic circuitry, CB\textsubscript{1} was found to be coexpressed with appetite-modulating neuropeptides, such as corticotropin-releasing hormone, cocaine-amphetamine-regulated transcript, MCH, and prepro-orexin. Peripherally, CB\textsubscript{1} activation was shown to enhance lipogenesis in primary adipocyte cultures. The reduced body fat observed in CB\textsubscript{1} knockout mice appeared to be attributable to both central hypothalamic mechanisms

![Figure 2](https://example.com/image2.png) Transient reduction in food intake and long-lasting reduction in body weight by cannabinoid-1 receptor blockade. Rimonabant significantly decreased the body weight of mice fed a high-fat diet (HFD). When food consumption was corrected for differences in body weight, mice in the 2 vehicle (veh)-treated groups ate a mean $0.40 \pm 0.00$ kcal/g per day over the treatment period ($1 \text{ kcal} = 4.2 \text{ kJ}$). The relative energy intake of mice in the HFD-rimonabant group was reduced to a mean $0.23 \pm 0.01$ kcal/g per day during the first week of treatment. This effect then progressively reversed, and, at the end of the treatment period, the ratio increased to a mean $0.45 \pm 0.01$ kcal/g per day. STD = standard diet. *$P < 0.05$; †$P < 0.01$. (Reprinted with permission from Am J Physiol Regul Integr Comp Physiol.\textsuperscript{11})

![Figure 3](https://example.com/image3.png) Cannabinoid-1 blockade improves cardiac and metabolic risk factors in mice with diet-induced obesity. HDL-C = high-density lipoprotein cholesterol; HFD-veh = high-fat diet, vehicle treated; HFD-R = high-fat diet, rimonabant treated; LDL-C = low-density lipoprotein cholesterol; STD-veh = standard diet throughout, vehicle treated; swSTD-veh = switched from high-fat to standard diet, vehicle treated. *$P < 0.001$, HFD-veh vs. other groups; †$P < 0.05$, HFD-R vs. STD-veh; ‡$P < 0.05$, HFD-R vs. HFD-veh; §$P < 0.05$, swSTD-veh vs. STD-veh. (Adapted from Diabetes Obes Metab.\textsuperscript{16})
involving neuropeptides and peripheral mechanisms involving inhibition of lipogenesis due to impaired adipocyte function. These results confirm those of other studies in which CB1 blockade was found to promote a sustained reduction in adiposity independent of its transient suppression of food intake.11

In another study, conducted by Bensaid and colleagues,14 that explored the direct effects of CB1 blockade on fat cells, CB1 blockade with rimonabant increased Acrp30 expression in adipocytes. Rimonabant stimulated messenger RNA expression of Acrp30 and decreased hyperinsulinemia in obese Zucker rats (Figure 5).14 Reverse transcription–polymerase chain reaction (RT-PCR) analysis revealed that expression of CB1 receptors in adipose tissue of obese rats was 3 to 4 times greater compared with that of lean rats. These findings show that rimonabant regulates hormones implicated in lipid and glucose metabolism, which indicates that rimonabant could exert a metabolic “peripheral” action in addition to its known “central” effect on food intake. However, it should be kept in mind that peripheral metabolism may be influenced from central sites via descending autonomic innervation,17 and the findings discussed in this review do not exclude the possibility that such sites may also contribute to the metabolic effects of ECs.

ENDOCANNABINOID REGULATION OF HEPATIC FAT METABOLISM

Activation of CB1 receptors affects fat metabolism, not only by regulating Acrp30 levels but also by increasing fatty acid synthesis in the liver.12 In fact, the liver plays an even greater role in lipogenesis than does adipose tissue.18 In a mouse model, Osei-Hyiaman and coworkers12 examined the possible role of the liver as a peripheral target of the metabolic actions of ECs and explored the underlying molecular targets. The results showed that activation of CB1 receptors increased de novo fatty acid synthesis through the induction of the lipogenic transcription factor sterol response element binding protein–1c (SREBP-1c)19 and its target enzymes acetyl-coenzyme A carboxylase–1 (ACC1) and fatty acid synthase (FAS).

The expression of the genes involved in fat metabolism within the liver and adipose tissue of CB1 knockout and wild-type mice was analyzed using RT-PCR.12 Expression
of SREBP-1c was consistently lower in the livers of CB1 knockout mice compared with their wild-type counterparts. In agreement with this observation, treatment of wild-type mice with a CB1 agonist increased gene expression of SREBP-1c and its target enzymes, ACC1 and FAS, in liver and adipose tissue, whereas rimonabant, a CB1 antagonist, blocked these effects.

To assess de novo hepatic fatty acid synthesis in vivo, radiolabeled water was injected intrahepatically into live wild-type mice. Pretreatment of wild-type mice with a CB1 agonist more than doubled the rate of hepatic fatty acid synthesis, an effect attributed to CB1, as no increase was observed in rimonabant-pretreated mice or CB1 knockout mice.

In vitro, the investigators confirmed the presence of CB1 receptors in hepatocytes through various assays, including RT-PCR, immunohistochemistry, and Western blot. CB1 receptors were localized primarily around the central sinusoids in the liver. The Western blot findings showed increased CB1 receptor levels in the livers of wild-type mice fed a high-fat diet for 3 weeks compared with wild-type mice fed regular mouse chow. Similar increases in CB1 receptor expression in obesity have been detected in adipose tissue and in skeletal muscle. In vivo, the investigators evaluated the short-term effect of a high-fat diet on hepatic fatty acid synthesis in wild-type mice fed a high-fat diet for 3 weeks, a period too short for significant weight gain. After only 3 weeks, the basal rates of de novo fatty acid synthesis were markedly increased in mice on a high-fat diet compared with lean controls. By contrast, rimonabant treatment of wild-type mice significantly reduced the extent of the high-fat diet–induced increase in hepatic fatty acid synthesis, and no such increase was noted in CB1 knockout mice on the same high-fat diet. High-fat diet also induced fatty liver in wild-type mice (even before excessive eating resulted in obesity), but not in CB1 knockout mice or rimonabant-treated mice. Furthermore, in mice killed simultaneously, the hepatic levels of the endogenous EC anandamide increased 3-fold in those on the high-fat diet for 3 weeks compared with the controls on a normal diet. However, no difference in hepatic levels of 2-AG was detected between the 2 groups.

Together, these findings suggest that the hepatic EC system is activated during the early stages of high-fat diet–induced obesity, because both anandamide and CB1 receptor levels are increased in the liver. Furthermore, this activation is required for the development of obesity, primarily through an increase in de novo lipogenesis, although reduced energy expenditure is also likely to play a role. Although high dietary fat would be expected to suppress rather than induce de novo lipogenesis, evidence to the contrary has emerged in a number of recent studies in both mice and rats. This could suggest that in addition to substrate–product relations, endogenous factors including ECs are important in regulating de novo lipogenesis, particularly during the induction of diet-induced obesity. These findings also suggest that CB1 antagonists may be effective not only as weight loss drugs but also in preventing or reversing metabolic complications of obesity, such as fatty liver disease.

**SUMMARY**

Preclinical studies in rodents have shown that CB1 receptors are expressed centrally in various brain regions involved in appetite control, including the lateral hypothalamus, and peripherally in skeletal muscle, adipose tissue, and the liver. The net effect of CB1 activation on metabolism is anabolic. The activation of CB1 receptors in adipose tissue inhibits Acrp30 release. The activation of CB1 receptors in the liver increases lipogenic gene expression and de novo fatty acid synthesis. The development of diet-induced obesity and the associated hormonal and metabolic abnormalities may be related to upregulation and tonic activation of the EC system in adipose tissue and the liver.

The blockade or genetic deletion of CB1 receptors has the opposite effects and also increases insulin sensitivity and HDL cholesterol and decreases plasma triglycerides.

Extrapolating from animal studies to the clinic, the downregulation of the EC system with the CB1 antagonist rimonabant offers a promising strategy, not only for reducing weight and abdominal adiposity but also for preventing and reversing its metabolic consequences, including insulin resistance, dyslipidemia, and fatty liver disease.

**References**

Discussion Following Dr. Kunos’s Presentation

Question: What is the effect of the cannabinoid-1 (CB1) receptor pathway on behavioral factors other than appetite, such as mood?

George Kunos, MD, PhD (Bethesda, Maryland): The anxiolytic effect of CB1 receptor activation has generated interest. Of course, in this paradigm the desireable therapeutic goal would be a CB1 receptor agonist, and, in fact, a CB1 antagonist may actually aggravate underlying anxiety and depression. Because no medication is without side effects, we have to be aware of this possibility when treating obese individuals, who may have an underlying anxiety or depressive disorder, with a CB1 antagonist, particularly if dosage increase precipitates effects on mood. However, in certain animal models of depression, CB1 antagonists were reported to have an antidepressant effect, so the situation is complicated as far as depression is concerned. Conversely, preliminary animal studies suggest that amplification of the endogenous endocannabinoid (EC) system may unmask an anxiolytic effect mediated by CB1 receptors that could be further developed for therapeutic use.

Question: Is serotonin reuptake the mechanism responsible for the effects of CB1 receptor upregulation on mood?

Dr. Kunos: The downstream mechanisms have not yet been explored. However, because serotonin and catecholamines play fundamental roles in regulating mood, I would not be surprised if there was a link.

Question: Is the EC system involved in reinforcing or propagating addictive behavior?

Dr. Kunos: Because the cannabinoid marijuana is an addictive substance, it was not surprising to learn that ECs, as well as CB1 receptors, are components of the mesolimbic reward pathway. This pathway is activated not only by natural rewards, such as food and sex, but also by chemical rewards, such as drugs and alcohol. Animal studies indicate that the rewarding effects of opiates, nicotine, and alcohol are interrupted by rimonabant. In the case of nicotine addiction, this forms the basis for the potential usefulness of rimonabant as an adjunct to smoking-cessation therapy. In terms of alcoholism, we have almost completed the first North American study, which is evaluating whether rimonabant can reduce alcohol cravings. We expect to have the results next year.

*Recently an FDA Advisory Committee recommended a delay in the approval of rimonabant because of safety issues that need to be addressed in future studies.
What Is the Potential Role of Cannabinoid-1 Receptor Blockade in Glucose and Lipid Management?

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ABSTRACT

Interventions that reduce weight and abdominal adiposity have been shown to improve obesity-associated disorders of glucose and lipid metabolism, reduce blood pressure, and promote other beneficial effects on cardiometabolic risk parameters. When long-term adherence to diet/exercise recommendations is suboptimal, management of overweight and obese patients at high cardiometabolic risk includes the use of adjunctive pharmacologic agents to facilitate weight loss and weight loss maintenance. Rimonabant, a cannabinoid-1 (CB\textsubscript{1}) receptor blocker, has been shown to induce weight loss and improve cardiometabolic parameters, implying that the endocannabinoid system is a promising target for obesity-related health improvement. Herein we summarize the results of the Rimonabant in Obesity (RIO) studies, which have evaluated the effectiveness of CB\textsubscript{1} receptor blockade in facilitating weight loss and improving cardiometabolic health in >6,600 patients from the United States and Europe. As compared with placebo, 20 mg/day of rimonabant consistently produced greater reductions in weight and waist circumference, as well as improvements in dyslipidemia and parameters of glucose metabolism. The improvements that were noted for several cardiometabolic parameters with rimonabant were greater than what would be expected from the weight loss alone, suggesting there may be an independent effect of the drug on metabolic function. The results of these studies suggest that CB\textsubscript{1} receptor blockade may be a useful treatment for multiple cardiometabolic risk factors in overweight and obese patients. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Cannabinoid-1 blockade; Metabolic syndrome; Rimonabant; Rimonabant in Obesity program; Type 2 diabetes mellitus

The burden of cardiometabolic disease in the United States remains high, despite substantial advances in the management of individual risk factors. In overweight and obese patients, weight loss has a beneficial effect on multiple cardiometabolic risk factors. However, many individuals find long-term adherence to diet and exercise recommendations difficult. Therefore, the management of overweight and obese patients at high cardiometabolic risk includes the use of adjunctive pharmacologic agents to facilitate weight loss and weight maintenance.

Recent research has identified the endocannabinoid (EC) system, specifically blockade of the cannabinoid-1 (CB\textsubscript{1}) receptor, as a promising therapeutic target for the reduction of weight and the improvement of cardiometabolic risk factors.

EFFECTS OF CANNABINOID-1 RECEPTOR BLOCKADE

As reviewed elsewhere in this supplement, the EC system helps regulate energy balance, food intake, and lipid and glucose metabolism through both central and peripheral mechanisms. In animal models, CB\textsubscript{1} receptor activation acts in the central nervous system (CNS) to increase food intake and peripherally to enhance lipogenesis. Thus, one might predict that blockade of this system
would have the opposite effects. Consistent with this hypothesis, rimonabant, the first specific CB₁ receptor blocker to enter clinical development, reduces food intake and body weight in treated animals. This is accompanied by altered metabolic activity in adipose tissue, including the induction of adiponectin gene expression. It has also been shown to have a direct effect on glucose uptake in muscle. Thus, preclinical data support the potential usefulness of pharmacotherapy targeting the EC system for treating obesity and reducing cardiometabolic risk factors.

**CLINICAL TRIALS OF CANNABINOID-1 RECEPTOR BLOCKADE: THE RIMONABANT IN OBESITY PROGRAM**

The Rimonabant in Obesity (RIO) program enrolled >6,600 patients in 4 randomized, placebo-controlled, phase 3, multicenter studies designed to investigate the impact of rimonabant on cardiometabolic risk factors in overweight or obese individuals (Table 1).

The RIO-North America (NA) and RIO-Europe studies were 2-year studies that enrolled overweight patients (body mass index [BMI] >27) with treated or untreated hypertension and/or dyslipidemia, and obese patients (BMI ≥30) with or without comorbidities. The RIO-Lipids study was a 1-year study designed to evaluate rimonabant in overweight or obese patients with a BMI 27 to 40 and untreated dyslipidemia. The RIO-Diabetes study was a 1-year study conducted in overweight or obese patients (BMI 27 to 40) with type 2 diabetes mellitus who had been treated with metformin or sulfonylurea monotherapy for ≥6 months but who remained inadequately controlled.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIO-NA⁹</td>
<td>3,045</td>
<td>BMI &gt;27 + comorbidities (excluding DM) or BMI ≥30 + comorbidities</td>
<td>1 yr + 1 yr rerandomized</td>
</tr>
<tr>
<td>RIO-Europe⁸</td>
<td>1,507</td>
<td>BMI &gt;27 + comorbidities (excluding DM) or BMI ≥30 + comorbidities</td>
<td>2 yr</td>
</tr>
<tr>
<td>RIO-Lipids⁹</td>
<td>1,036</td>
<td>BMI 27–40 + untreated dyslipidemia (excluding DM)</td>
<td>1 yr</td>
</tr>
<tr>
<td>RIO-Diabetes¹¹</td>
<td>1,045</td>
<td>BMI ≥27 + treated type 2 DM</td>
<td>1 yr</td>
</tr>
</tbody>
</table>

*BMI = body mass index; DM = diabetes mellitus; NA = North America.

**Study Designs**

In all of the RIO trials, each volunteer underwent a single-blind, placebo, run-in that included a mild hypocaloric diet (600 kcal/day energy deficit [1 kcal = 4.2 kJ]) for 4 weeks before randomization. The diet was maintained throughout the double-blind treatment period. Patients were also encouraged to increase their level of physical activity throughout the study. Patients were stratified before randomization based on whether they had lost ≤2 kg or >2 kg during the run-in period. Patients in the RIO-Lipids study were also stratified according to their triglyceride levels (>4.5 vs. ≤4.5 mmol/L [400 mg/dL]), and patients in the RIO-Diabetes study¹¹ were stratified according to the class of antidiabetic treatment they had been taking (all patients continued to take their oral antidiabetic monotherapy throughout the trial). In the RIO-Europe² and RIO-NA¹⁰ studies, patients were randomized to receive placebo, rimonabant 5 mg/day, or rimonabant 20 mg/day in a 1:2:2 ratio, respectively. Randomization to the 3 treatment groups in the RIO-Lipids⁹ and RIO-Diabetes¹¹ studies was conducted in a 1:1:1 ratio, respectively.

The primary efficacy measure for all of the RIO trials was change in body weight; waist circumference and cardiometabolic parameters were also evaluated. Analyses were conducted on the modified intent-to-treat (ITT) population, which was defined as all randomized patients who received ≥1 dose of study drug and had ≥1 postbaseline assessment. In the 2-year trials, the modified ITT population for the analysis of efficacy over 2 years included patients who received the same double-blind study drug for the entire study (including those who discontinued study participation during the first year).²,⁹–¹¹

The design of the RIO-NA trial differed from that of the other RIO trials in that after 1 year, patients who received rimonabant were rerandomized to continue their current dosage of rimonabant or to switch to placebo for the second year. In this way, the RIO-NA study could evaluate the effects of rimonabant on change in weight and cardiometabolic risk factors at 1 year, on the maintenance of these effects in the second year, and on the impact of discontinuing the drug.

**Study Populations**

Baseline patient characteristics were similar across the treatment groups in all 4 RIO clinical trials. In the RIO-NA and RIO-Europe studies, women outnumbered men by approximately 4:1, whereas men and women were more equally represented in the RIO-Lipids and RIO-Diabetes studies. Most patients were white (>80% in all 4 studies).

The mean age of patients in the 4 studies ranged from 45 to 56 years (45 years in the RIO-NA and RIO-Europe studies, 48 years in the RIO-Lipids study, and 56 years in the RIO-Diabetes study).

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¹Recently, an FDA Advisory Committee recommended a delay in the approval of rimonabant because of safety issues that need to be addressed in future studies.
Modifying Cardiometabolic Risk: Results of the RIO Clinical Trials

The number of patients completing 12 months of follow-up varied between 53% to 66% in the 4 studies.²⁻⁹⁻¹¹ Although both rimonabant 5 mg/day and 20 mg/day showed statistically significant efficacy,¹ the effect of 5 mg was small compared with that of 20 mg. Thus, this review focuses on the efficacy results for the 20-mg dose compared with placebo.

Reduction in Weight and Waist Circumference. Weight and waist circumference were significantly reduced with rimonabant treatment in each study.²⁻⁹⁻¹¹ In the RIO-NA study,¹⁰ patients assigned to rimonabant 20 mg/day for both years had sustained weight loss compared with patients who received placebo (−7.4 kg vs. −2.3 kg; P < 0.001) (Figure 1). The 2-year mean reduction in waist circumference was also greater in patients assigned to rimonabant 20 mg/day for both years compared with patients who received placebo (−7.6 cm vs. −3.4 cm; P < 0.001) (Figure 2). In contrast, patients who received rimonabant in the first year but were switched to placebo for the second year regained most of their previous weight loss; a similar pattern was noted for waist circumference. This is not unexpected, given that successful pharmacotherapy of any chronic disease, such as diabetes or hypertension, requires continued use of the medication.

Of the patients assigned to rimonabant 20 mg/day for both years in the RIO-NA study,¹⁰ 40% lost ≥5% of their initial weight and 17% achieved a weight loss of ≥10%, compared with 19% and 8% of placebo-treated patients, respectively (P < 0.001). Similarly, in the RIO-Europe study² (for which only the first year's results have been reported), 51% of patients treated with rimonabant 20 mg/day achieved ≥5% weight loss and 27% achieved ≥10% weight loss; the rates for placebo-treated patients were 19% and 7%, respectively (P < 0.001). Thus, a sustained loss of 5% to 10% of body weight, a standard goal of pharmacotherapy, is achievable in a reasonable proportion of patients treated with rimonabant, provided that they remain on treatment.
Rimonabant and Cardiovascular Risk. Figure 3 shows the changes in high-density lipoprotein (HDL) cholesterol and triglycerides in the RIO-NA,10 RIO-Europe,2 and RIO-Lipids9 studies. In all of these studies, rimonabant 20 mg/day resulted in a greater (P < 0.001) increase in HDL cholesterol and reduction in triglycerides at 1 year. In the RIO-Lipids study,9 which examined several additional lipid parameters, rimonabant 20 mg/day produced beneficial effects on low-density lipoprotein (LDL) cholesterol particle size, fasting insulin concentrations, and serum concentrations of adiponectin and C-reactive protein (CRP). Although no changes in concentrations of LDL cholesterol were found in the rimonabant 20-mg/day group compared with the placebo group, the distribution of LDL particles shifted toward larger size in the rimonabant group (P < 0.001), and the proportion of small LDL particles was lower in the rimonabant 20-mg/day group compared with the placebo group (P = 0.002). Larger LDL particles are associated with less cardiovascular risk compared with smaller LDL particles. Fasting plasma insulin concentrations decreased by 1.7 μU/mL (1 μU/mL = 7.175 pmol/L) in the rimonabant 20-mg/day group versus 0.9 μU/mL in the placebo group (P = 0.016), whereas rimonabant 20 mg/day, as compared with placebo, increased plasma adiponectin concentrations by 46.2% (P < 0.001). Both of these findings imply improved insulin sensitivity in the group receiving rimonabant 20 mg/day. As expected because of the greater body fat loss, plasma leptin concentrations decreased by 4.1 ng/mL in the rimonabant group, compared with 0.3 ng/mL in the placebo group (P < 0.001). Finally, the prevalence of patients who met the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)2 criteria for the metabolic syndrome declined from 52.9% to 25.8% in the rimonabant 20-mg/day group compared with a decline from 51.9% to 41.0% in the placebo group (P < 0.001, rimonabant vs. placebo). In the RIO-NA study,10 the prevalence of metabolic syndrome in patients who received rimonabant 20 mg/day was reduced from 34.8% to 21.2% compared with 31.7% to 29.2% in the patients who received placebo (P < 0.001).

Rimonabant in Type 2 Diabetes. Recently published results of the 1-year RIO-Diabetes study11 (the only RIO study in which patients with diabetes were not excluded) showed that patients receiving rimonabant 20 mg/day had a weight loss of approximately 5.3 kg, which was slightly less than that observed in the other studies but still significantly more than the loss of 1.4 kg in the placebo group (P < 0.0001). The number of patients who achieved a weight loss of ≥5% and ≥10% was also significantly greater in the patients who received rimonabant 20 mg/day compared with those who received placebo (49.4 % vs. 14.5%, respectively, and 16.4% vs. 2.0%, respectively; P < 0.0001). Reduction in waist circumference was also significantly greater in patients who received rimonabant 20 mg/day compared with those who received placebo (−5.2 cm vs. −1.9 cm, respectively; P < 0.0001).

Patients in the RIO-Diabetes study11 had reasonably well-controlled disease at study entry (mean glycosylated hemoglobin [HbA1c] baseline value averaging 7.3% for the rimonabant 20-mg/day group and 7.2% for the placebo group). Treatment with rimonabant 20 mg/day reduced HbA1c by −0.6% compared with 0.1% for placebo (P < 0.0001). Twice as many patients in the rimonabant 20-mg group as in the placebo group achieved an HbA1c target <6.5% at 1 year (43% vs. 21%; P < 0.0001) (Figure 4), thereby meeting the treatment target for antidiabetic therapy proposed by the International Diabetes Federation (IDF) and the American Association of Clinical Endocrinologists (AACE). Similarly, more patients in the rimonabant 20-mg/day group as compared with the placebo group reached the American Diabetes Association (ADA) HbA1c target <7% (68% vs. 48%; P < 0.0001). Antidiabetic medication needed to be adjusted downward in more patients who received rimonabant 20 mg/day com-
pared with patients who received placebo (11.9% vs. 7.5%, respectively; \( P < 0.005 \)).

Improvements in fasting glucose concentrations and insulin resistance estimated by the homeostasis model assessment were greater in patients who received rimonabant 20 mg/day compared with those who received placebo (−0.64 vs. 0.33 mmol/L, \( P < 0.0001 \), and −0.5 vs. 0.6 mmol/L, \( P = 0.03 \), respectively). Greater improvements in HDL cholesterol (15.4% vs. 7.1%), triglyceride (−9.1% vs. 7.3%), and non–HDL cholesterol concentrations (−1.8% vs. 2.5%) were also seen with rimonabant 20 mg/day as compared with placebo (\( P < 0.0001 \) for all). At 1 year, the prevalence of persisting metabolic syndrome was less in the rimonabant 20-mg/day group as compared with the placebo group (18% vs. 26%, \( P = 0.02 \)). Additionally, rimonabant 20 mg/day resulted in lower supine systolic blood pressure measurements (−0.8 vs. 1.6 mm Hg, \( P = 0.02 \)), a greater decrease in high-sensitivity CRP levels (−1.4 vs. −0.0 mg/L, \( P = 0.02 \)), and lower plasma leptin concentrations (−0.3 vs. 3.1 ng/mL, \( P < 0.0001 \)) compared with placebo.\(^{11}\)

Moreover, improvements were noted for all food behavior parameters for patients in the rimonabant 20-mg/day group as compared with those in the placebo group at 1 year: patients reported decreased appetite (\( P < 0.0001 \)), less desire for high-fat food (\( P = 0.0003 \)), less desire for sweets (\( P = 0.04 \)), and said it was easier to follow the diet (\( P < 0.0001 \)).\(^{11}\)

**Weight Loss–Independent Effects of Rimonabant**

Because preclinical studies suggested that rimonabant affects metabolism independent of its effects on food intake, specific statistical analyses were conducted to test for this effect.\(^{4,13}\) In the RIO-Diabetes study,\(^{11}\) the investigators assessed the proportion of rimonabant-induced improvement in HbA\(_{1c}\) related to weight loss. The results showed that of the 0.7% treatment difference between rimonabant 20 mg/day and placebo, only 0.3% was attributable to weight loss according to multivariate linear regression analysis (Figure 5). The other portion of the effect (0.4%) was
not explained by change in weight, suggesting a direct, beneficial effect of the drug on metabolic function. This implies that rimonabant may improve glycemic control through both direct and indirect actions.

Pi-Sunyer and colleagues\textsuperscript{14} recently presented a linear regression analysis of clinical data from all the RIO studies to estimate the proportion of the drug’s effects on variables such as HbA\textsubscript{1c}, insulin, HDL cholesterol, and triglycerides that was due to weight loss–dependent versus weight loss–independent effects. After adjustment for weight loss, approximately half of the effect of rimonabant 20 mg/day on HDL cholesterol, triglycerides, HbA\textsubscript{1c} in patients with diabetes, fasting insulin in patients without diabetes, and adiponectin levels remained to be explained (Table 2), supporting the possibility of direct effects of the drug on these parameters.

### Overall Safety and Adverse Events

In all of the RIO studies, rimonabant was generally well tolerated, with adverse events that were mostly transient and mild or moderate in intensity.\textsuperscript{2,9–11} The 1-year rates of adverse events were similar across all studies. This discussion will focus on the RIO-NA study\textsuperscript{10} safety results, which are representative of the 1-year data in all RIO trials, and, in addition, include second-year safety data. As Table 3 shows, in the first year both the overall rate of adverse events and the rate of serious adverse events were increased in the rimonabant-treated groups in a dose-dependent fashion. More rimonabant-treated patients than placebo-treated patients discontinued owing to adverse events, mainly psychiatric, nervous system, and gastrointestinal tract adverse events. Compared with patients receiving placebo, adverse events (upper respiratory tract infection, nasopharyngitis, nausea, influenza, diarrhea, arthralgia, anxiety, insomnia, viral gastroenteritis, dizziness, depressed mood, and fatigue) were reported in \(\geq 5\%\) of patients receiving 20 mg/day of rimonabant. The Hospital Anxiety and Depression Scale (HADS), administered at baseline and every 3 months during the study, showed no difference in change over time among the treatment groups. Among patients who received the same treatment both years, rates of adverse events, serious adverse events, and discontinuations due to adverse events showed no pattern related to rimonabant dose. Thus, treatment-related adverse events were more likely to occur within the first year, and continuing treatment for a second year did not appear to increase the risk for adverse events.

#### Table 2  Rimonabant in Obesity (RIO) studies: mean (SEM) of metabolic parameters with and without adjustment for weight loss\textsuperscript{*}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall Treatment Effect ((\beta_1))</th>
<th>Effect Independent of Weight Loss ((\beta))</th>
<th>Overall Effect Not Explained by Weight ((\beta/\beta_1))</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA\textsubscript{1c} (%)</td>
<td>-0.67 (0.07), (P &lt; 0.001)</td>
<td>-0.37 (0.007), (P &lt; 0.001)</td>
<td>55%</td>
</tr>
<tr>
<td>HDL-C (%)</td>
<td>8.0 (0.6), (P &lt; 0.001)</td>
<td>3.6 (0.6), (P &lt; 0.001)</td>
<td>45%</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>-14.0 (1.4), (P &lt; 0.001)</td>
<td>-6.5 (1.4), (P &lt; 0.001)</td>
<td>46%</td>
</tr>
<tr>
<td>Fasting insulin ((\mu U/mL))\textsuperscript{†}</td>
<td>-2.74 (0.48), (P &lt; 0.001)</td>
<td>-1.34 (0.51), (P = 0.018)</td>
<td>49%</td>
</tr>
<tr>
<td>Adiponectin ((\mu g/mL))</td>
<td>1.5 (0.2), (P &lt; 0.001)</td>
<td>0.85 (0.21), (P &lt; 0.001)</td>
<td>57%</td>
</tr>
</tbody>
</table>

\(\text{HbA}_{1c}\) = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol.\textsuperscript{*}HDL-C and triglyceride data from all 4 RIO studies; HbA\textsubscript{1c} data from RIO–Diabetes; fasting insulin data from RIO–North America (NA) RIO–Europe, and RIO–Lipids.\textsuperscript{†}1 \(\mu U/mL = 7.175\) pmol/L.

Adapted from J Am Coll Cardiol.\textsuperscript{14}

#### Table 3  The Rimonabant in Obesity–North America (RIO-NA) study: safety profile

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th></th>
<th>Year 2*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 607)</td>
<td>Rimonabant 5 mg/day (n = 1,214)</td>
<td>Rimonabant 20 mg/day (n = 1,219)</td>
</tr>
<tr>
<td>Subjects with any AE</td>
<td>82.0%</td>
<td>83.4%</td>
<td>85.5%</td>
</tr>
<tr>
<td>Subjects with any serious AE</td>
<td>3.5%</td>
<td>3.8%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Subjects discontinued due to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>7.2%</td>
<td>9.4%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>2.3%</td>
<td>3.6%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>1.3%</td>
<td>2.1%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

AE = adverse event.\textsuperscript{*}Patients who received the same treatment both years.

Adapted from JAMA.\textsuperscript{10}
SUMMARY

The results of the RIO-NA, RIO-Europe, RIO-Lipids, and RIO-Diabetes studies were highly consistent in terms of both efficacy and tolerability/safety outcomes. Treatment with rimonabant 20 mg/day resulted in marked and significant improvements compared with placebo in body weight and waist circumference, as well as HDL cholesterol, triglycerides, HbA1c, insulin resistance, metabolic syndrome, and other cardiometabolic risk factors. Moreover, the cardiometabolic benefits achieved with rimonabant treatment were sustained for up to 2 years. Importantly, the magnitude of these benefits was greater than what would be expected from weight reduction alone, suggesting direct effects of the drug on cardiometabolic parameters.

Thus, rimonabant therapy as an adjunct to lifestyle modifications may significantly improve multiple cardiometabolic risk factors in overweight and obese patients in clinical practice. The potential of rimonabant to modulate multiple cardiometabolic risk factors may streamline therapy for overweight and obese patients by reducing the amount of polypharmacy currently required to treat each risk factor individually.

References


Discussion Following Dr. Jensen’s Presentation

Question: Referring to the linear regression analysis in the Rimonabant in Obesity (RIO) studies, would it have been more appropriate to use the change in waist circumference, as opposed to weight, to determine weight loss–independent effects?

Michael D. Jensen, MD (Rochester, Minnesota): If rimonabant<sup>•</sup> induced a greater reduction in waist circumference relative to the amount of weight loss, and was accompanied by a corresponding improvement in metabolic abnormalities, that would indicate that rimonabant had a preferential effect on the reduction in waist circumference. This would suggest that the beneficial effects were related to improved body fat distribution coincident with weight loss.

Question: In clinical trials, was rimonabant effective in nonobese, slightly overweight, patients with the metabolic syndrome?

Dr. Jensen: There were not enough patients in that particular subgroup to enable us to analyze and address that question.

Question: Cannabinoids (CBs) exert an antianxiety effect. Therefore, what is the effect of CB1 blockade on anxiety? Is rimonabant contraindicated in patients with a preexisting anxiety disorder?

George Kunos, MD, PhD (Bethesda, Maryland): No. However, careful screening is indicated, especially in pa-

*Recently, an FDA Advisory Committee recommended a delay in the approval of rimonabant because of safety issues that need to be addressed in future studies.
Supplement to
The American Journal of Medicine

Managing Cardiometabolic Risk: Will New Approaches Improve Success?

CME SECTION

ASSESSMENT TEST
AND EVALUATION FORM

Sponsored by Network for Continuing Medical Education (NCME) and supported by a grant from sanofi-aventis US Inc.

Release Date: September 2007
Expiration Date: September 30, 2008
CME ASSESSMENT TEST

Managing Cardiometabolic Risk: Will New Approaches Improve Success?

Please circle the correct response to each question on the Answer Sheet provided. A passing score of ≥70% must be achieved to receive CME credit. There is no fee for participation in this educational activity.

1. Which of the following is an emerging risk factor for atherosclerotic cardiovascular disease (ASCVD)?
   a. Low levels of high-density lipoprotein (HDL) cholesterol
   b. Elevated blood pressure
   c. Atherogenic diet
   d. Insulin resistance

2. Which of the following describes the 10-year risk of experiencing a cardiovascular disease (CVD) event for a patient at moderately high risk?
   a. <10%
   b. 10% to 20%
   c. ≥20%
   d. None of the above

3. Which of the following describes the risk for ASCVD in patients who are candidates for secondary prevention?
   a. <10%
   b. ≥20%
   c. 10% to 20%
   d. <20%

4. Which of the following describes the reduction in risk achieved by intensive lifestyle intervention in the Diabetes Prevention Program (DPP)?
   a. 17%
   b. 31%
   c. 58%
   d. 59%

5. Which of the following is the best clinical measure of abdominal adiposity?
   a. Waist–hip ratio
   b. Waist circumference
   c. Body mass index
   d. Euglycemic insulin clamp

6. Which of the following biomarkers of inflammation decreases in response to weight loss?
   a. Interleukin-6
   b. Vascular cell adhesion molecule-1
   c. C-reactive protein
   d. All of the above

7. Which of the following was associated with elevated risk for CVD among patients with diabetes mellitus and the metabolic syndrome in the San Antonio Heart Study (SAHS)?
   a. Smoking
   b. Elevated interleukin-12 levels
   c. Sex
   d. Genetic predisposition

8. Which of the following classes of agents has been associated with improvement in nonalcoholic fatty liver disease?
   a. Antihypertensive agents
   b. Insulin sensitizers
   c. Anti-inflammatory drugs
   d. All of the above

9. Which of the following occurs when endocannabinoids (ECs) act on cannabinoid-1 (CB₁) receptors in rodents?
   a. Increased food intake
   b. Decreased food intake
   c. Anorexia
   d. None of the above

10. Which of the following hormones regulates the EC system?
    a. Sex hormones (estrogen or testosterone)
    b. Leptin
    c. Insulin
    d. None of the above

11. Which of the following metabolic parameters increased in response to CB₁ receptor blockade in obese mice?
    a. Insulin sensitivity
    b. Adiponectin
    c. HDL cholesterol
    d. All of the above

12. Which of the following increases in response to CB₁ receptor activation?
    a. Adiponectin
    b. Lipogenic gene downregulation
    c. De novo hepatic fatty acid synthesis
    d. All of the above

13. Which of the following cardiometabolic risk factors improved in response to treatment with rimonabant 20 mg in the Rimonabant in Obesity (RIO) trials?
    a. Weight and waist circumference
    b. HDL cholesterol and triglycerides
    c. Glucose control
    d. All of the above

14. Which of the following describes the percentage of patients treated with rimonabant 20 mg in the RIO-
North America trial who achieved a weight loss ≥5%?

a. 17%
b. 19%
c. 40%
d. None of the above

15. Which of the following describes the percentage of patients treated with rimonabant 20 mg in the RIO-Diabetes trial who met the American Diabetes Association (ADA) hemoglobin $A_1c$ target goal of <7%?

a. 32.7%
b. 52.7%
c. 67.2%
d. None of the above

16. Which of the following adverse effects was related to drug discontinuation in the RIO trials?

a. Depressive disorders
b. Vomiting
c. Severe diarrhea
d. Sleep apnea
Managing Cardiometabolic Risk: Will New Approaches Improve Success?

INSTRUCTIONS: To obtain AMA PRA Category 1 credit, participants are required to: (1) Read the educational objectives, review the entire activity, and complete the posttest. (2) Complete the Registration Form and Activity Evaluation Form and record test answers on the posttest Answer Sheet below. (3) Retain a copy of your test answers. Your Answer Sheet will be graded and, if a passing score of ≥70% is achieved, a CME certificate will be mailed to you within 6 weeks. (4) A CME certificate is issued only upon receipt of your completed Registration and Activity Evaluation Forms. To receive a copy of the CME certificate, please mail or fax your completed Registration Form and Activity Evaluation Form to:

NCME
Attn.: CME Department
One Harmon Plaza
Secaucus, NJ 07094
Fax: (201) 867-2149

ANSWER SHEET (Circle the best answer to each question)

1. a b c d  5. a b c d  9. a b c d  13. a b c d
2. a b c d  6. a b c d  10. a b c d  14. a b c d
3. a b c d  7. a b c d  11. a b c d  15. a b c d
4. a b c d  8. a b c d  12. a b c d  16. a b c d

REGISTRATION FORM
I attest that I have completed the Managing Cardiometabolic Risk: Will New Approaches Improve Success? activity as designed and

☐ I participated in the entire activity and claim 2.0 credits.
☐ I participated in only part of the activity and only claim partial credits based on ___ hours of instruction (e.g., 1.0, 1.5, 1.75).

I certify that the above is true and correct.

______________________________
Signature

PLEASE PRINT CLEARLY

First Name __________________________ MI _____ Last Name __________________________

Degree __________________________ Specialty __________________________

Street Address __________________________ Room/Suite ________________

City __________________________ State __________________________ Zip Code __________________________

Phone No. __________________________ Fax No. __________________________ E-mail __________________________

Last 4 digits of your Social Security Number* __________________________

Signature __________________________ Date ________________

* Required for processing.

Please Note: The information obtained here will not be distributed to faculty or sold to any other commercial entity.

Activity #: 01604530001
Managing Cardiometabolic Risk: Will New Approaches Improve Success?

The Network for Continuing Medical Education (NCME) is committed to excellence in continuing education. Your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please reflect carefully and complete this Evaluation Form. Please note: a CME certificate will be issued only upon receipt of your completed Evaluation Form.

Please answer the following questions by circling or checking the appropriate rating:

Effectiveness in Meeting Identified Needs

Was the activity effective in meeting the educational needs as identified below? □ Yes □ No

Patients with cardiometabolic risk factors are at high risk for cardiovascular and metabolic disease. This activity examines how to improve outcomes in high-risk patients through targeted risk-reduction strategies aimed at each patient’s individual cardiometabolic risk factor profile.

Rating scale: 5 = Outstanding; 4 = Good; 3 = Satisfactory; 2 = Fair; 1 = Poor

Effectiveness of the Individual Faculty Members

<table>
<thead>
<tr>
<th>Knowledge of Subject Matter</th>
<th>Appropriateness of Teaching Strategies</th>
<th>Was the Presentation Free of Bias?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott M. Grundy, MD, PhD</td>
<td>5 4 3 2 1</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Steven M. Haffner, MD</td>
<td>5 4 3 2 1</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Michael D. Jensen, MD</td>
<td>5 4 3 2 1</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>George Kunos, MD, PhD</td>
<td>5 4 3 2 1</td>
<td>□ Yes □ No</td>
</tr>
</tbody>
</table>

Educational Objectives

| Identifying the relation between abdominal adiposity and the development of cardiometabolic risk factors | 5 4 3 2 1 |
| List the potential cardiometabolic risk factors caused by overstimulation of the endocannabinoid system | 5 4 3 2 1 |
| Assess the role of various clinical interventions for cardiometabolic risk reduction | 5 4 3 2 1 |
| Apply cardiometabolic risk-reduction strategies aimed at each patient’s individual risk factor profile | 5 4 3 2 1 |

Teaching Effectiveness

Degree to which this presentation provided you with knowledge or skills to implement in your practice

Learning Contract

State 1 practice change you are committed to making based on these objectives.

How certain are you that you will make this change?

☐ 1% to 20%      ☐ 21% to 40%      ☐ 41% to 60%      ☐ 61% to 80%      ☐ 81% to 99%      ☐ 100%

☐ You have permission to contact me in approximately 3 months to determine whether I was able to implement changes in my practice as a result of this CME activity. (Contact me by: ☐ e-mail    ☐ fax)

Future Educational Needs

Please list any other topics that would be of interest to you for future educational activities: