Contemporary Management of Cardiometabolic Risk
A continuing epidemic: 2 of 3 US adults are overweight or obese

- Most recent data from the National Health and Nutrition Examination Surveys (NHANES) show continued high levels of overweight or obese adults in this country.
- Proportions of overweight/obese adults were 64.5%, 65.7%, and 66.3% in 1999-2000, 2001-2002, and 2003-2004, respectively.
- Abbreviation used in slide:
  BMI = body mass index
Parallel epidemics of diabetes and obesity

- The Behavioral Risk Factor Surveillance System data demonstrate parallel rises in the prevalence of diabetes and obesity.
- In 1994, no states had obesity rates ≥20% whereas in 2004, 33 states had obesity rates of 20%-24%, and 9 states had rates ≥25%.
- Similarly, in 1994 only 2 states had diabetes rates of ≥6%, but within only 10 years 39 states had diabetes rates ≥6%.
Defining cardiometabolic risk

Risk factors linked to cardiovascular disease (CVD) and diabetes

- Adiposity
- Hypertension
- Dyslipidemia
- Dysglycemia

Cardiometabolic risk factors

- Excess body weight is associated with dysglycemia (abnormal fasting and/or postprandial glucose), hypertension, and dyslipidemia. In turn, these cardiovascular and metabolic risk factors (collectively referred to as “cardiometabolic” risk factors) interact to increase the potential risk for developing cardiovascular disease (CVD), stroke, and diabetes.

- This topic was addressed in a recent scientific statement jointly released by the American Diabetes Association (ADA) and the American Heart Association (AHA). The scientific statement stressed the importance of identifying and treating these cardiometabolic risk factors.

- The interaction of cardiometabolic risk factors, in addition to current and emerging management strategies, are reviewed in this kit.
Evidence implicates abdominal adiposity (specifically, excessive visceral fat deposition) as a more important determinant of cardiometabolic risk than overall weight as measured by BMI.

Excessive visceral adipose tissue is associated with numerous pathologic conditions that elevate CVD risk.

Abbreviation used in slide:
CAD = coronary artery disease
Adiposity predicts mortality

Adams KF et al prospectively examined the relationship between body weight and all-cause mortality in 527,265 US men and women enrolled in the National Institutes of Health-AARP Diet and Health Study.

Study participants were enrolled between 1995-1996, when they were 50 to 71 years of age. The study investigators monitored participant survival through December 31, 2005 via annual linkage of the cohort to the Social Security Administration Death Master File.

During follow-up, 42,173 men and 19,144 women died. Investigators observed a J-shaped relationship between BMI and risk of death (adjusted for age, race/ethnic group, education level, smoking, physical activity, and alcohol intake). Adiposity was independently associated with increased risk of death.
Adiposity associated with premature MI

- Suwaidi et al studied 906 consecutive patients admitted to the Mayo Clinic Coronary Care Unit with acute myocardial infarction (MI). An inverse relationship between age and body weight was observed.

- Specifically, study subjects with a BMI of >30 kg/m² presented with acute MI on average 10.6 years earlier than those with a normal body weight (BMI <25 kg/m²).
Majority of patients undergoing PCI are overweight or obese

- Gruberg et al studied 9633 consecutive patients who underwent percutaneous coronary intervention (PCI) between January 1994 and December 1999 at Washington Hospital Center, Washington, DC.
- Approximately 80% of study subjects had a BMI ≥25 kg/m².
Adverse consequences of chronic adiposity and ectopic fat

- As adiposity progresses, lipid deposition occurs in other organs (referred to as “ectopic” sites).
- Excessive accumulation of lipids in the liver and muscle may contribute to insulin resistance, while deposition in the heart causes structural and functional abnormalities.

FFA = free fatty acids  
NASH = nonalcoholic steatohepatitis

Epicardial adipose tissue may be increased in visceral obesity

- The slide shows magnetic resonance images (MRIs) taken in patients with visceral (left image) or peripheral (right image) obesity.
- In the patient with visceral adiposity, epicardial fat thickness was 19.9 mm in the right ventricular free wall and 27.2 mm around the left ventricular apex.
- In the patient with peripheral adiposity, epicardial fat thickness was 4.7 mm and 7.8 mm, respectively.

Adiposity in the development of NASH

- The slide depicts the pathogenesis of nonalcoholic fatty liver disease.
- Accumulation of fat in adipocytes is associated with development of insulin resistance, increased leptin levels, and decreased adiponectin levels. The lipolysis rate in adipocytes is also increased, leading to influx of fatty acids into the liver.
- Accumulation of fat in hepatocytes (steatosis) generates reactive oxygen species, enhances lipid peroxidation, and promotes generation of cytokines. Subsequent infiltration of inflammatory cells and activation of stellate cells marks the transition to steatohepatitis and, eventually, fibrosis.
Visceral vs subcutaneous adiposity

- Adipose depots are located throughout the body. Some have a structural function, e.g., fat pads in the hands and feet, and the periorbital fat supporting the eyes.¹
- Other adipocytes exist in loose association with the skin and are termed subcutaneous fat.¹
- Abdominal (visceral) adiposity refers to fat around the viscera and within the peritoneum, as well as at the dorsal border of the intestines, and the ventral surface of the kidney.
- BMI does not accurately measure intra-abdominal fat accumulation.
- This slide shows computerized tomography (CT) scans from 2 men with similar BMIs, but different adiposity phenotypes.
- The upper image is from a man with mostly intra-abdominal adiposity; this subject has at least 50% more visceral fat than the subject whose CT scan is indicated in the lower panel.

Neutral effect of liposuction on cardiometabolic risk factors

- Klein et al evaluated cardiometabolic risk factors in 15 obese women before and after liposuction to remove subcutaneous fat.

- This slide shows MRIs taken of 1 subject before and after the liposuction procedure. The volume of subcutaneous abdominal adipose tissue decreased by 44% in the 8 subjects with normal glucose tolerance, and by 28% in the 7 subjects with type 2 diabetes.

- However, despite this marked reduction in subcutaneous adipose tissue, no significant changes in the parameters listed on the slide were observed.

- This finding demonstrates that adipocyte function varies depending on the anatomic location.

- Abbreviations used in slide:
  BP = blood pressure
  Total-C = total cholesterol
  LDL-C = low-density lipoprotein cholesterol
  HDL-C = high-density lipoprotein cholesterol
  TG = triglycerides
  TNF = tumor necrosis factor
  IL = interleukin
  CRP = C-reactive protein
Central adiposity: Better marker of CVD than BMI

N = 8802 HOPE Study participants

Adjusted RR of CVD death

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>WHR</th>
<th>WC (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>P = 0.14</td>
<td>1</td>
</tr>
<tr>
<td>Second</td>
<td>P = 0.003</td>
<td>1.5</td>
</tr>
<tr>
<td>Third</td>
<td>P = 0.0127</td>
<td>1</td>
</tr>
</tbody>
</table>

WC = waist circumference
WHR = waist/hip ratio

Dagenais et al examined the relationship between BMI and abdominal adiposity (measured by either waist/hip ratio or waist circumference) and CVD death in 8802 Heart Outcomes Prevention Evaluation (HOPE) study participants.

Subjects were classified according to their tertile of BMI, waist/hip ratio, and waist circumference.

Compared with the first tertile, the third tertile of BMI increased the risk of CVD death by 16% (P = 0.14). The corresponding relative risk (RR) increases for waist/hip ratio and waist circumference were 34% (P = 0.003) and 27% (P = 0.0127), respectively.
A new vital sign: Waist circumference

- In summary, a new paradigm has emerged, with data supporting inclusion of waist circumference measurement in the standard physical examination.
Continued burden of disease

- Individuals with excessive central accumulation of fat are at higher risk of hypertension, dyslipidemia, and dysglycemia.
- In turn, these cardiovascular and metabolic abnormalities, collectively termed “cardiometabolic” risk, interact to increase the risk for cardiovascular morbidity and mortality.
- Since adiposity continues to be a major public health problem, new approaches to its prevention and management are needed.
Adiposity in CVD
Role of adipose tissue in atherogenesis

- Adipocytes are a source of bioactive molecules (adipokines) that act in either a paracrine or endocrine manner to modulate insulin sensitivity locally as well as in the liver and skeletal muscle.

- Adipose tissue is also a source of inflammatory mediators.

- Thus, adipose tissue promotes atherosclerosis through a number of pathologic mechanisms.
Elevated FFA contribute to hypertension, dyslipidemia, and insulin resistance

- Visceral adipose tissue is associated with a higher rate of free fatty acid (FFA) flux to the liver via the splanchnic circulation. In contrast, subcutaneous accumulation is not associated with direct effects in the liver, since FFA are released into the systemic circulation.

- FFA flux to the liver, in turn, is associated with a higher production of glucose, triglycerides, and VLDL; small, dense LDL particles, and lower HDL-C levels.

- Elevated FFA levels also inhibit glucose uptake by skeletal muscle, thereby contributing to impairment of insulin sensitivity, characteristic of the prediabetic state.

- Hyperinsulinemia, a result of reduced insulin sensitivity, enhances sodium reabsorption and increases sympathetic nervous system activity, resulting in elevated systolic blood pressure.
Energy homeostasis is linked to immune balance

- Metabolism and the immune system are closely linked. In particular, excess food intake relative to energy requirements is associated with immune activation and increasing risk for inflammatory conditions such as atherosclerosis.
- As the following slide indicates, this inflammatory response is initiated in the adipocytes themselves.
Weight gain induces inflammatory changes in adipose tissue

- Obesity is associated with a chronic state of low-grade inflammation. Models of inflammation in obesity include a major role for macrophages in molecular changes in adipose tissue.
  - Metabolic and endocrine function alterations in adipose tissue increase the release of free fatty acids, hormones, and proinflammatory molecules. Increasing adiposity produces physical changes and modification of adipocyte paracrine function. Adipocytes begin secreting TNF-alpha, an inflammatory cytokine.
  - TNF-alpha stimulates preadipocytes to produce monocyte chemoattractant protein-1 (MCP-1). Endothelial cells also respond to cytokines by secreting MCP-1; either endothelial cells or adipocytes could attract macrophages to adipose tissue.
  - Obesity induces leptin secretion (and/or decreases production of adiponectin) by adipocytes, which may promote macrophage accumulation. Oxidative damage in the endothelium due to an increasingly lipolytic environment may also increase macrophage recruitment.
- The presence and activity of macrophages in adipose tissue in the obese state perpetuates a vicious cycle of increased macrophage recruitment and inflammatory cytokine production, and impaired adipocyte function.
- Abbreviations used in slide:
  VEGF = vascular endothelial growth factor
  JNK = c-Jun amino-terminal kinase
  NF-kB = nuclear factor-kappa B
Adipose tissue: An endocrine organ

- Several bioactive molecules produced by adipocytes have been identified. These adipokines participate in diverse metabolic processes.
- Some adipokines (e.g., CRP, IL-6, MCP-1, components of the renin-angiotensin-aldosterone system (RAAS), serum amyloid A, and TNF-alpha) are well known proinflammatory, proatherogenic molecules.
- Other adipokines such as leptin promote satiety and increase metabolic expenditure. Alternatively, data suggest this adipokine may also have proliferative, proinflammatory, prothrombotic, and pro-oxidative effects.
- Unlike these other adipokines, adiponectin acts as an antiatherogenic and antidiabetic agent. The effects of adiponectin are reviewed in the next 2 slides.
- Abbreviation used in slide:
  PAI = plasminogen activator inhibitor

Adiponectin associated with decreased risk of MI

Using data from the Health Professionals Follow-up Study, Pischon et al conducted a case-control study to assess the relationship between adiponectin and CV risk.

N = 18,225 men were followed for a mean duration of 6 years.

As shown, subjects with adiponectin levels in the highest quintile demonstrate a significantly lower risk of MI compared with those in the lowest quintile (relative risk, 0.39; 95% confidence interval [CI], 0.23-0.64; P < 0.001).
Beneficial associations of adiponectin

- Adiponectin exhibits anti-inflammatory and antiatherosclerotic effects in vascular tissue, in addition to insulin-sensitizing effects in tissues involved in glucose and lipid metabolism.
- As such, adiponectin is a component of a complex signaling network connecting adipocytes and insulin-sensitive tissues, with potential implications for vascular function and CV risk reduction.
- The multiple effects of adiponectin in the vasculature are consistent with a protective impact on macrovascular disease.
- As visceral adipose mass increases, adiponectin secretion is markedly reduced—whereas secretion of other adipokines that reduce insulin sensitivity and contribute to endothelial dysfunction is increased—potentially promoting the CV risk associated with obesity and type 2 diabetes.
Low adiponectin in visceral adiposity

- Manigrasso et al measured plasma adiponectin levels in 64 women with abdominal (visceral) adiposity (BMI >28 kg/m² [mean 37.1 kg/m²] and waist/hip ratio <0.86), 20 women with lower-body (subcutaneous) adiposity (BMI >28 kg/m² [mean 33.4 kg/m²] and waist/hip ratio ≥0.86), and 20 normal-weight women (mean BMI of 25.2 kg/m²).

- Median adiponectin levels were lower in overweight/obese women compared with normal-weight subjects. The lowest levels were observed in those with visceral adiposity.

- The P values were obtained using a Kruskal-Wallis test followed by a Mann-Whitman U test.
Even moderate weight loss may improve cardiometabolic risk

- In summary, data suggest that the cardiometabolic benefits of weight loss are mediated, in part, by the reduction in visceral adipose tissue.

- Lipid storage in adipose tissue represents an excess in energy expenditure relative to energy consumption. This can be achieved through lifestyle modification (increased physical activity or caloric restriction).

- Small but consistent differences over time can result in substantial weight loss (or gain).

- Of high significance and contrary to widespread belief, cardiometabolic benefit may be accrued with moderate loss in body weight of 5% to 10%.

- Abbreviations used in slide:
  A1C = glycated hemoglobin
  IFG = impaired fasting glucose
  IGT = impaired glucose tolerance
Summary

- Adipose tissue is no longer viewed simply as a passive depot for fat. It is the source of a number of bioactive molecules that promote atherosclerosis.

- Expansion of visceral adipocytes is also accompanied by decreased secretion of adiponectin, a molecule with anti-inflammatory and antiatherogenic effects.

- The pathologic consequences of central adiposity are also mediated by elevated circulation levels of free fatty acids superimposed on a state of chronic inflammation.
The Endocannabinoid System

Role in energy homeostasis and peripheral lipid and glucose metabolism
- The first cannabinoid to be identified (in 1964) was Δ⁸-tetrahydrocannabinol (THC), the psychoactive factor in the marijuana plant. This is one of approximately 60 cannabinoids present in the plant. Many of these phytocannabinoids are bioactive but only THC is psychoactive.
- The discovery of these exogenous cannabinoids prompted the development of a number of synthetic analogs such as nabilone (shown on the slide).
- It was not until 1992 that the existence of endogenous cannabinoids (endocannabinoids) was reported. The most widely studied of these are anandamide and 2-arachidonoyl glycerol (2-AG).
ECS: Widely distributed with multiple cardiometabolic effects

- Cannabinoid receptor 1 (CB₁) activation modulates caloric intake centrally and peripherally. In the central nervous system, activation of these receptors in the hypothalamus increases appetite. Activation of these receptors in the limbic system increases motivation to eat, perhaps by stimulating orosensory reward.

- Activation of CB₁ receptors in the gastrointestinal (GI) tract blunts production of satiety signals to the brain.

- Data suggest that peripheral CB₁ receptors may also have direct metabolic action, regulating glucose and lipid metabolism.

- ECS in both central and peripheral tissues is overactivated in adiposity which plays a pathologic role.
### Potential therapeutic implications of CB₁ receptor blockade

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Mechanism(s)</th>
<th>Addresses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↓Food intake</td>
<td>Body weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Waist circumference</td>
</tr>
<tr>
<td></td>
<td>↑Adiponectin</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>↓Lipogenesis</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>↑Glucose uptake</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>↓Lipogenesis</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>↑Satiety signals</td>
<td>Body weight</td>
</tr>
</tbody>
</table>

Data indicate that CB₁ receptor blockade favorably improves central adiposity, insulin resistance, and dyslipidemia. Several sites of action are involved in these effects.

These data will be summarized in the following slides.
Circulating 2-AG elevated in persons with visceral vs sc adiposity

- Blüher et al measured levels of circulating 2-AG in 20 lean volunteers, 20 with subcutaneous adiposity, and 20 with visceral adiposity. The investigators used computed tomography scanning to distinguish adiposity type.
- Levels of 2-AG were higher in adipose vs lean subjects, and specifically in those with higher degrees of visceral adiposity.
- Differences between the groups were analyzed by ANOVA and post hoc Bonferroni-Holm test.
CB₁ receptor blockade blunts overeating in rats

Anandamide administered via injection to rat hypothalamus

- Presatiated rats who received an intrahypothalamic injection of anandamide exhibited significant hyperphagia, while injection of vehicle was associated with a very minor, nonsignificant increase in food intake.

- Pretreatment with the CB₁ receptor blocker rimonabant 30 minutes prior to anandamide injection blocked this effect.

- Differences between groups were analyzed by ANOVA, with post hoc Dunn Multiple Comparison test used if P < 0.05.
Ravinet Trillou et al assessed the effects of chronic treatment with rimonabant in a mouse adiposity model. Animals were fed a high-fat diet or standard chow (controls) for 12-17 weeks. High-fat-diet mice were then randomized to 1 of 2 groups for a further 40 days:
- Rimonabant (10 mg/kg/day po) in addition to the high-fat diet
- Drug vehicle in addition to the high-fat diet

The control group were fed standard laboratory chow plus drug vehicle throughout the randomized phase.

At the start of the randomized phase, animals fed the high-fat diet weighed 34% more than controls. Rimonabant treatment was associated with a marked and sustained weight reduction and was associated with a reduction in food intake that lasted for only the first 8 days of treatment. Thereafter, food intake was similar to that observed in the high-fat diet plus drug vehicle group.

The investigators concluded that their data suggest that reducing food intake may be the main initial cause of weight loss associated with rimonabant treatment. However, it may not be the only mechanism. They hypothesized that this additional mechanism may involve activation of metabolic processes.

Abbreviations used in slide:
HF = high-fat
veh = vehicle
R = rimonabant
ST = standard

CB₁ receptor blockade modulates adipocyte function in mice

- Studies of adipose tissue in a diet-induced mouse model of adiposity by Jbilo et al demonstrated favorable changes associated with CB₁ receptor blockade with rimonabant. These include:
  - Reduction in adipose mass, resulting from:
    - Enhanced lipolysis via stimulation of enzyme involved in beta-oxidation and tricarboxylic acid cycle
    - Increased energy expenditure mainly through futile cycle induction
    - Tight regulation of glucose via increased expression of glucose transporter-4
  - Increased expression of adiponectin mRNA and decreased expression of pro-inflammatory genes
- Overall, the investigators observed changes in gene expression suggesting that rimonabant had reversed the diet-induced alteration of the adipocyte phenotype.
- Previous studies in rats and mice have shown that adipocytes express CB₁ receptors and that rimonabant stimulates adipocyte production of adiponectin.¹ These results led Jbilo et al to speculate that their data were likely a result of a direct effect on adipocyte CB₁ receptors.

CB₁ receptors modulate liver lipogenesis in mice

- Osei-Hyiaman et al provided the first report of hepatic CB₁ receptor-mediated modulation of fatty acid synthesis in the liver.

- The investigators used uptake of tritium into fatty acids as a measure of fatty acid synthesis. Pretreatment of mice with a CB₁ receptor agonist (HU210) caused a >2-fold increase in tritium uptake. This increase was not observed in mice pretreated with rimonabant or in CB₁ receptor-knockout mice (data not shown).

- Wild-type mice fed a high-fat diet became obese and developed fatty liver (steatosis), as shown on the slide. CB₁ receptor-knockout mice remained lean and did not develop steatosis.

- These findings suggest that CB₁ receptor activation in the liver may play a key role in diet-induced obesity and steatosis.
CB₁ receptor blockade increases skeletal muscle glucose uptake in obese mice

- Liu et al studied the effect of CB₁ receptor blockade on glucose uptake in the isolated soleus muscle of genetically obese, leptin-deficient (Lep<sup>ob</sup>/Lep<sup>ob</sup>) mice.
- Following a 7-day treatment with rimonabant 10 mg/kg ip or drug vehicle, muscle tissue samples were obtained and incubated with 2-deoxy-[³H]-glucose and insulin. Rimonabant treatment was associated with a 68% greater uptake of tritium than control (P < 0.05).
- Differences between treatment groups were done using one-way analysis of variance followed by Dunett's multiple comparisons test and Student's unpaired t-test.
CB₁ receptor blockade and mood: Range of effects observed in animal models

Direct effects reported:
- Anxiolytic/antidepressant
- Neutral
- Anxiogenic

Studies with antidepressants:
- No acute interaction with SSRI (fluoxetine) or tricyclic antidepressant (desipramine)*
- Transient ↑anxiety with chronic desipramine + CB₁ blocker use†

*Porsolt forced swim test
†Elevated plus maze assay

- Understanding of the involvement of the ECS system in mood and emotional behavior continues to evolve.
- CB₁ receptor blockade studies in animal models of anxiety or depression have reported conflicting findings ranging from anxiolytic/antidepressant effects, no effect, or an anxiogenic effect.
- Studies in mice receiving either the tricyclic antidepressant desipramine or the selective serotonin reuptake inhibitor (SSRI) fluoxetine found that acute treatment with rimonabant did not appear to influence the efficacy of either antidepressant.
- Chronic (3-month) treatment with rimonabant in mice receiving desipramine appeared to be associated with a transient increase in anxiety-like behavior.
Endocannabinoid system overview

- CB₁ receptors are distributed in brain and peripheral tissue.
- Fasting triggers endocannabinoid synthesis and binding to the CB₁ receptor, with subsequent increase in food intake. Normally, the ECS is immediately downregulated; however, data suggest that this may not occur in obesity. In particular, excess visceral adipose tissue accumulation appears to be associated with upregulation of the ECS and subsequent hyperphagia.
- CB₁ receptor blockade modulates food intake and metabolic pathways through multiple mechanisms of action.
Managing Cardiometabolic Risk

Lifestyle modification and weight reduction strategies
NHLBI guidelines: Adiposity assessment

• Use BMI to assess body fat
  – Body weight alone can be used to track weight loss, and to determine efficacy of therapy (Evidence Category C)

• Use BMI to classify overweight/obesity
  – Estimate relative risk of disease compared to normal weight (Evidence Category C)

• Use waist circumference to assess abdominal fat content (Evidence Category C)


The National Heart, Lung, and Blood Institute (NHLBI) evidence-based guidelines on the identification, evaluation, and treatment of overweight and obesity in adults are available on the NHLBI website.

These guidelines were released in June 1998 and were based on a systematic review of the scientific literature published between January 1980 and September 1997.

BMI may be used to assess overall body fat, whereas, waist circumference may be used to assess abdominal fat.

Definitions of overweight and obese are based on BMI. These recommendations are given an evidence level of C, denoting that the evidence is from uncontrolled or nonrandomized trials or from observational studies. These are summarized on the next slide.
BMI classifications

- Recommended classifications for BMI adopted by the NHLBI obesity guidelines panel are summarized on the slide.
- These classifications were based on research on the relationship of BMI to morbidity and mortality.
Measuring waist circumference

- Locate upper hip bone and top of right iliac crest
- Place measuring tape horizontally around abdomen at level of iliac crest
- Tape should be snug without causing compression

Measuring waist circumference

- To measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place the measuring tape horizontally around the abdomen at the level of the iliac crest. The tape should be snug without causing compression.
- Measurement is made at the end of a normal expiration.
- Data are taken from *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*, which is available from the NHLBI website at: www.nhlbi.nih.gov
Diagnostic criteria for metabolic syndrome

Any 3 criteria

- **Adiposity**
  - WC (men) ≥35 (Asian) ≥40 (other ethnicities)
  - WC (women) ≥31 (Asian) ≥35 (other ethnicities)

- **Dyslipidemia**
  - HDL-C <40 mg/dL (men)
  - HDL-C <50 mg/dL (women)
  - TG ≥150 mg/dL

- **Hypertension**
  - BP ≥130/85 mm Hg

- **Dysglycemia**
  - FG ≥100 mg/dL

**WC** = waist circumference (inches)  

- Waist circumference is now recognized as an important component of risk assessment. In particular, abdominal adiposity is one of the key abnormalities that comprise the metabolic syndrome.
- US adults of Asian origin have a lower cutpoint for diagnosing abdominal adiposity than adults of other ethnicities.
- Abbreviation used in slide: FG = fasting glucose
NHLBI guidelines: Weight loss goals

• Goal is ~10% reduction from baseline weight (Evidence Category A)
• If successful, assess continued weight loss (Evidence Category A)
• Aim for weight loss ~1–2 lb/week for 6 months
  – Base subsequent strategies on the amount of weight lost (Evidence Category B)

The initial goal of weight loss therapy is a reduction of approximately 10% from baseline. Further weight loss can be attempted if necessary. These recommendations are given an evidence level of A, which are based on randomized, controlled trials.

A weight loss of 1-2 lbs per week is the target for the first 6 months. This recommendation is given an evidence level of B, indicating that it is based on evidence from a limited number of randomized clinical trials, or from post hoc or subgroup analyses.
Guide to adiposity management

- BMI classification and the presence or absence of comorbid conditions may be used as a guide to selecting the type of adiposity management.

- Comorbid conditions that confer high absolute risk include:
  - Established coronary heart disease or other atherosclerotic disease
  - Type 2 diabetes
  - Sleep apnea
  - Hypertension
  - Smoking
  - Dyslipidemia
  - Dysglycemia
  - Family history of early CVD
  - ≥45 years of age (if male) or ≥55 years (if female)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>25.0-26.9</th>
<th>27.0-29.9</th>
<th>30.0-34.9</th>
<th>35.0-39.9</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Physical activity</td>
<td>✓ With comorbidities</td>
<td>✓ With comorbidities</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Behavior therapy</td>
<td>✓ With comorbidities</td>
<td>✓ With comorbidities</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>✓ With comorbidities</td>
<td>✓ With comorbidities</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Surgery</td>
<td>✓ With comorbidities</td>
<td>✓ With comorbidities</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Lee M, Aronne LJ. Am J Cardiol. 2007;99(suppl):68B-79B.
NHLBI guidelines: Lifestyle modification

- Combined intervention of a calorie-deficit diet, ↑physical activity, and behavioral treatment is most successful for weight loss and maintenance (Evidence Category A)
  - 500-1000 kcal/day deficit
  - Moderate physical activity 30-45 min, 3-5 days/week, with eventual goal of ≥30 min on most (and preferably all) days of the week
- Maintain for ≥6 months before considering pharmacotherapy

Lifestyle modification includes the following components:
- Hypocaloric diet: A 500-1000 kcal per day deficit is recommended, which can translate to a weight loss goal of 1-2 lbs per week in most patients. Very low caloric diets are not recommended for weight loss since they require special monitoring and supplementation.
- Physical activity: Increasing energy expenditure through physical activity is recommended. Initially, 30-45 minutes of moderately-intense physical activity should be carried out 3-5 times per week. The long-term goal is ≥30 minutes on most, and preferably all, days of the week.

- Lifestyle modification should be maintained for at least 6 months before weight-loss pharmacotherapy is considered.
Some moderate-intensity physical activities

<table>
<thead>
<tr>
<th>Daily life</th>
<th>Sports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washing car, 45–60 min</td>
<td>Walking 3 mph, 35 min</td>
</tr>
<tr>
<td>Washing windows or floors, 45–60 min</td>
<td>Bicycling 10 mph, 30 min</td>
</tr>
<tr>
<td>Gardening, 30–45 min</td>
<td>Dancing, 30 min</td>
</tr>
<tr>
<td>Raking leaves, 30 min</td>
<td>Water aerobics, 30 min</td>
</tr>
<tr>
<td></td>
<td>Swimming, 20 min</td>
</tr>
<tr>
<td></td>
<td>Jogging 1 mile, 15 min</td>
</tr>
</tbody>
</table>

• The CV benefits of physical activity are cumulative. Thus, any physical activity carried out through the day counts towards the daily goal. That is, two 15-minute sessions will provide essentially the same benefit as a single 30-minute session.

• To minimize the risk of injury, patients should be advised to start off with low-intensity physical activity, gradually increasing the intensity over time.

• For weight loss, physical activity must be more vigorous to achieve a caloric deficit.
3-Week diet + exercise regimen yields favorable metabolic changes

N = 31 overweight/obese men; weight ↓8.4 lbs

- Roberts et al. demonstrated substantial benefits of an intensive, 21-day program combining diet and exercise in 31 overweight or obese men with metabolic risk factors (mean BMI 35 kg/m²; 13 with type 2 diabetes; all others had >1 metabolic risk factor; 5 with diagnosed CAD).

- The diet and aerobic exercise program was residential and supervised:
  - Diet: High-fiber, low-fat, moderate-protein diet with no caloric restrictions; but with restrictions on types of foods (whole grains, vegetables/fruit, and protein from nonfat dairy, plant sources, and fish/fowl)
  - Exercise: Treadmill walking 45-60 minutes/day at 70% to 85% maximum heart rate

- Although the men as a group remained obese (BMI >30 kg/m²), the number of individuals who were obese decreased from 22 (71%) to 18 (58%).

- Results showed significant improvements in lipid profiles:
  - Total-C decreased 21%
  - LDL-C decreased 26%
  - Triglycerides decreased 28%

- Insulin resistance and hyperinsulinemia were also decreased:
  - Insulin use decreased 30%
  - Homeostasis model assessment of insulin resistance (HOMA-IR) decreased 33% (data not shown)

- Preintervention and postintervention values were compared by matched t-tests.
Physical activity may reduce CV and all-cause mortality

- The NHANES I was conducted from 1971 to 1975. The NHANES I Epidemiological Follow-up Survey consisted of 4 additional surveys, the most recent of which was conducted in 1992.

- These data show that even moderate exercise is associated with a reduction in all-cause and CV mortality.

- The association was most robust in hypertensive subjects, although a trend to benefit was also seen at lower BP levels. This finding is consistent with other studies suggesting that the health benefits of increased physical activity extend beyond their effect on CV risk factors.¹

- Hazard ratios (HR) were adjusted for age, gender, race, BMI, education, diabetes, smoking, alcohol, diet, BP, and lipids.

---

Lifestyle modification associated with diabetes prevention

• Five randomized, controlled trials assessed the effects of lifestyle modification on new-onset diabetes in high-risk individuals. Yamaoka and Tango conducted a meta-analysis of these trials.

• Despite heterogeneity in the specific interventions, lifestyle modification consistently demonstrated a reduction in new-onset diabetes. The relative risk reduction calculated by 3 different models were similar:
  – Fixed-effects model: 0.55 (95% CI, 0.48-0.63)
  – Random-effects model: 0.55 (0.44-0.69)
  – Bayesian model: 0.55 (0.41-0.74)
DPP: Benefit of diet + exercise or metformin on diabetes prevention in at-risk patients

- The Diabetes Prevention Program (DPP) was the largest of the 5 trials included in the meta-analysis discussed on the previous slide.

- This trial randomized 3234 individuals with a BMI ≥24 kg/m², IFG, and IGT to placebo, lifestyle modification, or metformin 850 mg twice daily.

- Incidence of type 2 diabetes after average follow-up of 2.8 years was 11 cases/100 person-years in the placebo group vs 7.8 in the metformin and 4.8 in the lifestyle-intervention groups. This represented a reduction of 58% in diabetes incidence with lifestyle intervention and 31% with metformin.

- Lifestyle intervention was particularly effective—1 case of diabetes was prevented per 7 persons treated for 3 years.

- The effects were similar in both men and women and in all racial and ethnic groups. Intensive lifestyle intervention was at least as effective in older as in younger participants.

- In a follow-up analysis, metabolic syndrome was reduced by 41% in the lifestyle modification group (P < 0.001) and by 17% in the metformin group (P = 0.03).¹

- P values reported are nominal (unadjusted). Comparisons between treatment groups were made using the group-sequential log-rank test.

Popular dietary programs: Effective yet difficult to maintain

- Dansinger conducted a single-center, randomized trial of 4 well-known diets: Atkins, The Zone, Weight Watchers, and Ornish.
- These diets varied widely in their approaches, yet each resulted in comparable weight loss after 1 year. However, each was also associated with high recidivism.
Look AHEAD: Study design

Look Action for Health in Diabetes

N = 5145
45-74 years with T2DM, BMI ≥ 25 kg/m² (≥ 27 kg/m² if taking insulin)

Usual medical care + diabetes support and education for 4 years

Usual medical care + lifestyle intervention* for 4 years, with maintenance counseling thereafter

Total follow-up 11.5 years

Primary endpoint: CV death, nonfatal MI, nonfatal stroke

*≥7% mean weight loss with hypocaloric diet ± pharmacologic therapy + ≥175 min/week moderate physical activity
Diet = 1200-1500 kcal/day (<250 lbs) or 1500-1800 kcal/day (≥250 lbs)

Look AHEAD: Study design

- Look AHEAD is an NIH-sponsored trial assessing lifestyle modification in overweight individuals with type 2 diabetes (T2DM). A total of 5145 individuals were randomized to a diabetes support and education group or to a lifestyle intervention group.

- The diabetes support and education group received usual medical care from their own primary care physician plus 3 group educational sessions yearly for the first 4 years of the trial. One session was devoted to diet and nutrition, another to exercise, and the third to social support.

- The lifestyle intervention group received usual medical care plus an intensive 4-year program designed to increase physical activity and reduce weight by ≥7%. The 3 phases are as follows:
  - Months 1-12: Three group meetings weekly in addition to 1 individual counseling session per month
  - Months 13-48: A minimum of 2 contacts per month are targeted. One contact is on-site; the other will be conducted off-site by phone, post, or e-mail.
  - Month 49-trial end: Maintenance phase, with ≥2 on-site contacts yearly

- A total follow-up of 11.5 years is planned. Anticipated completion is in 2012.
NHLBI guidelines: Pharmacologic therapy

- FDA-approved drugs may be used as part of a comprehensive weight-loss program, including dietary therapy and physical activity (Evidence Category B) in these individuals:
  - BMI ≥30 kg/m² with no concomitant risk factors or diseases
  - BMI ≥27 kg/m² with concomitant risk factors or diseases (hypertension, dyslipidemia, CHD, T2DM, sleep apnea)

- Herbal preparations are not recommended. These preparations have unpredictable amounts of active ingredients and unpredictable, and potentially harmful, effects.


- Weight-loss drugs should only be used as part of a multifactorial intervention that includes lifestyle modification.

- Over-the-counter (OTC) preparations that are non-Food and Drug Administration (FDA) approved, that claim to aid weight loss, are not recommended and should not be taken. Such “neutraceuticals” are ineffective and can cause serious health consequences. The exception is orlistat, a prescription (Rx) weight-loss medication that has been approved by the FDA for over-the-counter use (discussed in next slide).

- Abbreviation used in slide:
  CHD = coronary heart disease
Pharmacologic weight management options

- In the US, sibutramine and orlistat are 2 drugs approved by the FDA as adjuncts to a hypocaloric diet for weight reduction.

- Sibutramine acts via NE and serotonin reuptake inhibition, which suppresses appetite. It may also stimulate thermogenesis. In 5 trials of 44- to 54-weeks duration conducted in obese adults (with or without comorbidities), Arterburn et al calculated that the mean placebo-corrected weight loss was 9.9 lbs. In these trials, there was a mean increase in blood pressure and heart rate of 4.6/2.8 mm Hg and 5.9 bpm in sibutramine patients vs placebo, limiting its use in patients with poorly controlled hypertension, pre-existing CVD, or tachycardia.1

- Orlistat acts via lipase inhibition, which prevents digestion and absorption of dietary fats. In twenty-two 1-year trials conducted in overweight/obese adults, Li et al calculated that the mean placebo-corrected weight loss was 6.4 lbs. The most frequent side effects were diarrhea (relative risk, 3.4), flatulence (relative risk, 3.10), and bloating/abdominal pain/dyspepsia (relative risk, 1.48).

- Orlistat over-the-counter is half the dose to that requiring a doctor’s prescription.

- Additional data on sibutramine and orlistat are provided in the following slides.

Efficacy of orlistat as adjunct to lifestyle modification

Torgerson et al randomized 3305 patients (mean BMI of 37 kg/m\(^2\)) to lifestyle modification plus placebo or orlistat for 4 years.

Lifestyle modification consisted of the following:
- Reduced-calorie diet (approximately 800 kcal/day deficit) containing 30\% of calories from fat and ≤300 mg cholesterol daily. The prescribed energy intake was readjusted every 6 months to account for any weight loss.
- Dietary counseling every 2 weeks for the first 6 months, and monthly thereafter.
- Encouragement to walk at least 1 extra kilometer daily in addition to their usual physical activities.

At 1 year, mean weight loss was significantly greater with lifestyle modification plus orlistat vs lifestyle modification alone: 10.6 kg vs 6.2 kg (23.3 lbs vs 13.6 lbs), P < 0.001. The difference between the groups remained significant at the end of the study: 5.8 kg vs 3.0 kg (12.8 lbs vs 6.6 lbs), P < 0.001 by last observation carried forward analysis.

Changes in weight were analyzed using an ANOVA model, with baseline values as covariates.
A recent sibutramine study by Wadden et al illustrates the benefit of a structured lifestyle modification program combined with pharmacologic therapy.

All subjects (N = 224) were prescribed a balanced diet of 1200-1500 kcal daily and encouraged to walk for 30 minutes on most days of the week.

The investigators randomized subjects to one of the following 4 groups:
- Sibutramine 15 mg
- Lifestyle modification, with weekly group meetings conducted during weeks 1-18, every other week during weeks 20-40, and a follow-up visit at study end (week 52). The session during weeks 1-18 followed the LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) Program for Weight Control. From weeks 20-40, sessions were conducted using the Weight Maintenance Survival Guide.
- Sibutramine and brief lifestyle modification counseling given by a primary care provider in 8 visits of 10-15 minutes each. They were also given the 2 manuals described above.

The combination of sibutramine plus lifestyle modification resulted in more weight loss (26.6 lbs) than either intervention alone (11.0 lbs and 14.7 lbs, respectively).

Interestingly, even the brief lifestyle modification counseling had an incremental benefit over sibutramine alone (weight loss of 16.5 lbs).

These findings reinforce the NHLBI recommendation for management of adiposity.

Differences in weight were compared with the use of analysis of variance with repeated measures. In cases of a significant treatment effect, Tukey’s significant difference test was used to identify differences among the 4 groups.

---

## Effects of sibutramine and lifestyle modification on cardiometabolic risk factors

In the study by Wadden et al described in the previous slide, both sibutramine and lifestyle modification were associated with improvements in several cardiometabolic risk factors.

• The largest changes were observed in the group receiving both pharmacologic and lifestyle interventions.
SCOUT: Study design

- SCOUT is a large, multinational clinical outcomes trial of sibutramine in patients with high-risk adiposity.
- Eligible subjects will enter a 6-week single-blind lead-in period, during which they will receive sibutramine 10 mg plus be instructed to the following lifestyle modification:
  - Diet: Individualized hypocaloric diet (600 kcal/day deficit)
  - Exercise: ≥150 minutes per week, moderately-intense physical activity
- The lifestyle modification program has been translated into the languages of all 16 participating countries, with adaptations to meet local dietary preferences and traditions.
- Participants will then be randomized to either placebo or sibutramine 10-15 mg.
- The first patient was randomized in February 2003. The investigators plan to randomize approximately 9000 patients. Study completion is anticipated in 2008.
NHLBI guidelines: Weight loss surgery

- An option for carefully selected patients when less-invasive methods have failed and the patient is at high risk for obesity-associated morbidity or mortality (Evidence Category B)
  - BMI $\geq 40 \text{ kg/m}^2$
  - BMI $\geq 35 \text{ kg/m}^2$ with comorbid conditions

According to the NHLBI guidelines, published in 1998, surgery is reserved for patients with class 2 or 3 obesity when less invasive methods have failed.

- Lifelong medical surveillance after surgery is necessary.
**SOS: Bariatric surgery-associated improvements in cardiometabolic risk**

- The Swedish Obese Subjects (SOS) Study was a prospective, nonrandomized, controlled trial conducted in obese subjects (BMI $\geq 34$ kg/m$^2$ [men] or $\geq 38$ kg/m$^2$ [women]).
- The surgery group underwent gastric surgery while the matched control group received usual care (lifestyle intervention and behavioral modification).
- At 2 years, weight increased by 0.1% in the control group, whereas it decreased by 23.4% in the surgery group ($P < 0.001$). Improvements in several cardiometabolic risk factors were noted in the surgery group.
- Abbreviations used in slide:
  - SBP = systolic blood pressure
  - DBP = diastolic blood pressure
  - FPG = fasting plasma glucose
This is the first study to quantify the decrease in cardiovascular risk associated with substantial and sustained weight loss.

Vogel et al reported on 109 consecutive patients who underwent laparoscopic Roux-en-Y gastric bypass surgery.

At follow-up, mean weight loss was 78 lbs in women and 80 lbs in men.

In agreement with the SOS findings, surgically-induced weight loss was associated with improvements in several cardiometabolic risk factors.

The investigators further calculated 10-year risk for CHD using the Framingham Risk Score. Both men and women showed a significant reduction in their risk score from baseline (P = 0.002 and P < 0.0001, respectively).
Clinical evaluation of $\text{CB}_1$ receptor blockade

Rimonabant clinical trial program
The RIO clinical trial program consisted of 4 trials in patients with varying levels of cardiometabolic risk.

Basal metabolic rates were estimated for each patient using the Harris Benedict formula; 600 kcal were subtracted to calculate a recommended daily energy intake. All participants were also encouraged to increase physical activity.

In each trial, all patients underwent a 4-week placebo run-in period on the hypocaloric diet prior to randomization (baseline assessment of cardiometabolic risk factors).

In addition to change in weight, waist circumference, and proportion of patients with metabolic syndrome, a broad range of cardiometabolic risk factors were assessed, such as lipids, glucose, blood pressure, adiponectin, leptin, and CRP.

Mood was assessed via the Hospital Anxiety and Depression (HAD) scale. HAD scores are derived from responses to a short, self-reported questionnaire that has been validated for use in the primary care setting for the presence of mood disorders in different patient populations, including those who are overweight/obese.

Abbreviation used in slide: N Am = North America

Citations used in slide:
Pi-Sunyer FX et al. JAMA. 2006;295:761-75.

RIO program: Improved cardiometabolic risk factors at 1 year

- Effects of rimonabant on cardiometabolic risk factors were generally consistent from trial to trial.
- At 1 year, rimonabant 20 mg was associated with reductions in waist circumference of 1.3-1.9 inches (3.3-4.7 cm), increases in HDL-C of 7.2%-8.9%, decreases in triglycerides of 12.4%-16.4%, and reductions in systolic BP of 0.2-2.4 mm Hg (all placebo-corrected).
RIO program: Decreased metabolic syndrome incidence

- At 1 year, in all 4 trials, rimonabant 20 mg was associated with significant reductions from baseline in the proportion of patients with metabolic syndrome.

- Abbreviation used in slide:
  ATP = Adult Treatment Panel (National Cholesterol Education Program)

- Citations used in slide:
  Pi-Sunyer FX et al. *JAMA*. 2006;295:761-75.
RIO program: Safety and tolerability

Rimonabant 20 mg

- CNS adverse effects*
  - Dizziness (5.6%–10.4%)
  - Insomnia (5.8%–6.4%)
  - Anxiety (5%–8.7%)
  - Depressed mood (5.2%)

- GI adverse effects*
  - Nausea (11.2%–12.9%)
  - Diarrhea (5.3%–7.2%)

- Adverse effect-related discontinuation rates
  - Rimonabant (12.8%–15%)
  - Placebo (5%–9.2%)

- Overall discontinuation rates
  - Rimonabant (32%–44.9%)
  - Placebo (33.6%–49.1%)

*Most common

In a review of the RIO program data, Padwal and Majumdar concluded that the most common central nervous system (CNS) effects were dizziness, insomnia, anxiety, and depression; the most common GI adverse effects were nausea and diarrhea.

Adverse effects tended to be mild, self-limiting, and occurred early.

Discontinuation rates related to adverse effects were higher in the rimonabant 20 mg group compared with placebo. Overall discontinuation rates were comparable with rimonabant 20 mg and placebo.

Citations used in slide:
Pi-Sunyer FX et al. JAMA. 2006;295:761-75.
RIO program: No significant effect on mood

HAD scale: 0–7 = normal; 8–10 = borderline symptoms; ≥11 = significant symptoms

- HAD scores between 0-7 are within the normal range; scores of 8-10 suggest anxiety and depression symptoms of borderline clinical significance; scores ≥11 suggest clinically significant symptoms.

- At 1 year, mean scores in the anxiety and depression HAD subscales tended to be higher in the rimonabant 20 mg group compared with placebo. However, all scores were well within the normal range.

- To more fully examine this issue, patients were classified according to their status at baseline and 1 year (next slide).

- Citations used in slide:
  Pi-Sunyer FX et al. JAMA. 2006;295:761-75.
RIO program: Mood at 1 year

- In both the rimonabant and placebo groups, most patients with a baseline score of 0-7 had a concluding score of 0-7, suggesting no development of depressive symptoms.

- Among patients with a baseline score of 8-10 (suggesting borderline depressive symptoms), similar proportions of patients in the rimonabant and placebo groups improved their score at follow-up, suggesting a small improvement in mood.
  - 39.6% of patients with a baseline HAD depression score of 8-10 improved their score to <8 during 1 year of rimonabant 20 mg.

- Among patients with a baseline score ≥11 (suggesting significant depressive symptoms), more patients in the rimonabant 20 mg group improved their score at 1 year compared with placebo.
  - 65.5% with a baseline HAD depression score of ≥11 improved their score to <11 during 1 year of rimonabant 20 mg.

- One year of rimonabant 20 mg was not associated with any overall impairment in the HAD depression score.
RIO clinical trial program efficacy summary

Rimonabant 20 mg combined with diet over 1 year

- Significant decreases in weight and waist circumference
  - 11.7–16.4 lbs absolute loss
  - 8.7–12.0 lbs placebo-corrected loss

- Improved cardiometabolic risk factor profile

- Weight loss only partially accounted for changes in lipids, glucose, and adipokines, consistent with direct actions in peripheral tissues

Pi-Sunyer FX et al. *JAMA*. 2006;295:761-75.

- One year of rimonabant 20 mg treatment was associated with significant reductions in weight and waist circumference and improvement in the overall cardiometabolic risk factor profile.

- Main results of the individual trials will be summarized in the following slides.

- Data strongly indicate that weight loss only partially accounts for the favorable changes observed in cardiometabolic risk factors with rimonabant 20 mg. The RIO program data are consistent with preclinical data, and suggest that rimonabant has direct actions on metabolic pathways in peripheral tissues.

- Citations used in slide:
  Pi-Sunyer FX et al. *JAMA*. 2006;295:761-75.
The SERENADE trial randomized 278 patients with type 2 diabetes (diagnosed at least 3 months but less than 3 years) and not previously treated with antidiabetic medication.

Insulin use was permissible if it was not within 6 months of study entry and only for management of gestational diabetes or to maintain glycemic control during hospitalization, medical procedures, or intervention.

Study subjects were randomized to rimonabant 20 mg or placebo, in addition to a mild hypocaloric diet (600 kcal/day deficit). Follow-up was 6 months.

Abbreviation used in slide:
PA = physical activity
Preliminary results were presented on December 5, 2006 at the International Diabetes Federation 19th World Diabetes Conference, in Capetown, South Africa; 85% of the study population completed the study.

At baseline, mean A1C was 7.9% in both groups. At 6 months, this value was 7.1% and 7.5% in the rimonabant and placebo groups, respectively (P = 0.0002).

The SERENAIDE data are consistent with the effects of rimonabant 20 mg on glucose control as demonstrated in RIO-Diabetes.
Summary

- **Multiple cardiometabolic risk factors increase CVD risk**
  - Abdominal adiposity, decreased HDL-C, increased TG, BP, glucose

- **Moderate weight loss decreases cardiometabolic risk**
  - Significantly improves cardiometabolic risk factors
  - Encourages continued health-promoting behaviors and adherence to management plan

- **CB₁ receptor blockade provides a novel approach to treat cardiometabolic risk factors**
  - Indirectly (via weight loss)
  - Directly (via actions in peripheral tissues)

---


---

**Summary**

- Abdominal adiposity, low HDL-C, and elevated levels of triglycerides, blood pressure, and glucose (collectively referred to as cardiometabolic risk factors), interact to increase CVD risk.

- Reducing abdominal adiposity (via overall weight loss) improves multiple cardiometabolic risk factors and usually encourages continued adherence to a healthy lifestyle.

- CB₁ receptor blockade appears to be a promising new pharmacologic option for managing multiple cardiometabolic risk factors associated with adiposity. The mechanism of benefit appears to include reduction in abdominal adiposity and direct actions in peripheral tissues such as adipocytes, skeletal muscle, and the liver.
Ongoing trials with rimonabant in abdominal adiposity

<table>
<thead>
<tr>
<th>Study</th>
<th>Concomitant conditions</th>
<th>Primary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAGIO-Lipids</td>
<td>Dyslipidemia</td>
<td>Change in HDL-C and TG</td>
</tr>
<tr>
<td>ARPEGGIO</td>
<td>T2DM</td>
<td>Change in A1C</td>
</tr>
<tr>
<td>AUDITOR</td>
<td>MetS</td>
<td>Progression of carotid atherosclerosis</td>
</tr>
<tr>
<td></td>
<td>Carotid atherosclerosis</td>
<td></td>
</tr>
<tr>
<td>CRESCENDO</td>
<td>High CV risk</td>
<td>MI, stroke, CV death</td>
</tr>
<tr>
<td>RAPSODI</td>
<td>IFG and/or IGT</td>
<td>Progression to T2DM</td>
</tr>
<tr>
<td>RIO-Asia</td>
<td>—</td>
<td>Change in weight</td>
</tr>
<tr>
<td>STRADIVARIUS</td>
<td>Smoking and/or MetS</td>
<td>Progression of coronary atherosclerosis (IVUS)</td>
</tr>
<tr>
<td>VICTORIA</td>
<td>MetS</td>
<td>Change in visceral fat</td>
</tr>
</tbody>
</table>

NIH. www.clinicaltrials.gov.

Ongoing clinical trials are assessing the effects of rimonabant 20 mg on cardiometabolic risk factors, atherosclerosis progression, clinical outcomes, and new-onset diabetes. Key inclusion criterion is abdominal adiposity. Most of the studies also specify comorbidities in inclusion criteria.

- CRESCENDO (Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes). Comorbidities: documented atherosclerotic disease of the coronary, cerebral, or peripheral arteries; type 2 diabetes; or multiple cardiometabolic risk factors. Primary outcome: composite of MI, stroke, and CV death. Length of follow-up is not available.
- RAPSODI (RimonAbant in Prediabetic Subjects to Delay Onset of Type 2 DIabetes). Comorbidities: impaired fasting glucose, impaired glucose tolerance, or both. Primary outcome: time to progression to type 2 diabetes. Length of follow-up is not available.
- RIO-ASIA is another trial in the RIO program and is being conducted in Asian patients. Follow-up is 9 months.
- STRADIVARIUS (Strategy To Reduce Atherosclerosis Development InVolving Administration of Rimonabant—the Intravascular Ultrasound Study). Comorbidities: metabolic syndrome, smoking, or both. Primary outcome: atherosclerosis progression as assessed by coronary intravascular ultrasound (IVUS). Follow-up will be 18-20 months.
- VICTORIA (Visceral Fat Reduction Assessed by CT-Scan On RImonabAnt). Comorbidity: metabolic syndrome. Primary outcome is change in visceral fat area at 1 year.
Current and emerging pharmacologic combinations for treating cardiometabolic risk

- Lifestyle modification (dietary intervention, weight loss, and increased physical activity) is the first-line therapy for managing cardiometabolic risk.\(^1\)\(^-\)\(^3\) However, its benefits are frequently compromised by poor patient adherence. Therefore, adjunctive pharmacologic therapy is frequently needed.

- Comprehensive pharmacologic management of cardiometabolic risk involves managing abdominal adiposity, glucose, blood pressure, and lipids, simultaneously, using multiple agents as necessary.\(^4\)

- \(\text{CB}_1\) receptor blockade is associated with a broad range of favorable cardiometabolic effects. As understanding of this new pharmacologic strategy evolves, its role in combination with other proven therapies will likewise evolve.

- Abbreviations used in slide:
  
  - ACEI = angiotension-converting enzyme inhibitor
  - ARB = angiotension receptor blocker
  - CCB = calcium channel blocker
  - DPP = dipeptidyl peptidase
  - GLP = glucagon-like peptide

Managing cardiometabolic risk

- Traditionally, clinicians have tended to focus CV risk reduction strategies on blood pressure and lipids. Newer strategies stress the importance of assessing all patient cardiometabolic risk factors.
- The key components of cardiometabolic risk can be remembered using a simple mnemonic.
**RIO-Europe: Study design**

- This placebo-controlled, parallel-group study enrolled patients with a high BMI with or without concomitant (treated or untreated) hypertension and/or dyslipidemia.
- Patients with diabetes, pre-existing CVD, hepatic or renal disease, or a history of depression were excluded.
- This was a 2-year trial, although only the results for 1-year of follow-up have been published.
In the intent-to-treat population, weight change from baseline was significantly greater in the rimonabant 5 mg (7.5 lbs, $P = 0.002$) and rimonabant 20 mg (14.6 lbs, $P < 0.001$) groups compared with placebo (4.0 lbs).

Waist circumference followed a similar pattern. Reductions from baseline were 1.5 inches (rimonabant 5 mg, $P = 0.002$ vs placebo), 2.6 inches (rimonabant 20 mg, $P < 0.001$ vs placebo), and 0.9 inches (placebo).

Analysis of the primary endpoints was performed using ANOVA, with treatment and randomization as fixed effects, followed by the modified Bonferroni procedure (Hochberg) to account for multiplicity of doses. For secondary endpoints, continuous variables were analyzed by one-way ANOVA, with treatment as fixed effect.
**RIO-Europe: Treatment effect on lipids**

- HDL-C increased from baseline by 10.0 mg/dL and 5.8 mg/dL in the rimonabant 20 mg and placebo groups, respectively (P < 0.001).

- Triglycerides decreased by 17.7 mg/dL and 0.89 mg/dL in the rimonabant 20 mg and placebo groups, respectively (P < 0.001).

- Changes in HDL-C and triglycerides with the 5-mg dose were not significantly different from baseline.

- Changes in LDL-C and total-C were not significantly different from placebo for either dose of rimonabant.

- Details of the statistical analysis are given on the previous slide.
### RIO-Europe: Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (%) (n = 305)</th>
<th>Rimonabant 20 mg (%) (n = 599)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>15.7</td>
<td>15.5</td>
</tr>
<tr>
<td>Influenza</td>
<td>10.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>7.9</td>
<td>8.5</td>
</tr>
<tr>
<td>Upper respiratory tract infection (URTI)</td>
<td>7.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Headache</td>
<td>13.4</td>
<td>9.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.3</td>
<td>12.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.0</td>
<td>7.2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6.9</td>
<td>7.8</td>
</tr>
<tr>
<td>Back pain</td>
<td>8.5</td>
<td>9.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.6</td>
<td>4.2</td>
</tr>
</tbody>
</table>


- The frequency of gastroenteritis, bronchitis, dizziness, nausea, diarrhea, arthralgia, and back pain were higher in the rimonabant 20 mg group compared with placebo.
- The frequency of nasopharyngitis, influenza, upper respiratory tract infection, sinusitis, headache, and fatigue were higher in the placebo group.
• This placebo-controlled, parallel-group study enrolled patients with a high BMI and untreated dyslipidemia.

• Among the exclusion criteria were diabetes, cardiovascular, hepatic, or renal disease, and history of depression.
RIO-Lipids: Treatment effect on weight and WC

- In the intent-to-treat population, weight change from baseline was significantly greater in the rimonabant 5 mg (6.9 lbs, \( P < 0.001 \)) and rimonabant 20 mg (15.2 lbs, \( P < 0.001 \)) groups compared with placebo (3.3 lbs).

- Waist circumference followed a similar pattern. Reductions from baseline were 1.4 inches (rimonabant 5 mg, \( P = 0.029 \) vs placebo), 2.8 inches (rimonabant 20 mg, \( P < 0.001 \) vs placebo), and 0.9 inches (placebo).

- Analysis of primary and secondary endpoints was performed using ANOVA, followed by the modified Bonferroni procedure (Hochberg) to adjust for multiple comparisons.
RIO-Lipids: Treatment effect on lipids

Intent-to-treat population

- HDL-C increased from baseline by 19.1% and 11% in the rimonabant 20 mg and placebo groups, respectively (P < 0.001).
- Triglycerides decreased by 12.6% and 0.2% in the rimonabant 20 mg and placebo groups, respectively (P < 0.001).
- Changes in triglycerides with the 5-mg dose were not significantly different from baseline.
- Changes in LDL-C and total-C were not significantly different from placebo for either rimonabant dose. The distribution of LDL particles shifted toward a larger particle size in the rimonabant 20 mg group (data not shown)—a beneficial effect.
- Details on the statistical analysis are given on the previous slide.
RIO-Lipids: Rimonabant weight-independent effect on adiponectin

- Plasma adiponectin levels increased by 57.7% from baseline in the rimonabant 20 mg group (P < 0.001 vs placebo).
- While the change in adiponectin correlated with weight loss, not all of the increase could be attributed to weight loss alone. For the same degree of weight loss, patients in the rimonabant 20 mg group consistently demonstrated greater increases in adiponectin compared with placebo.
RIO-Lipids: Adverse events

≥5% incidence in any group

<table>
<thead>
<tr>
<th></th>
<th>Placebo (%) (n = 342)</th>
<th>Rimonabant 20 mg (%) (n = 346)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>21.6</td>
<td>19.4</td>
</tr>
<tr>
<td>Headache</td>
<td>15.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.2</td>
<td>12.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.7</td>
<td>10.4</td>
</tr>
<tr>
<td>Influenza</td>
<td>5.3</td>
<td>9.5</td>
</tr>
<tr>
<td>URTI</td>
<td>9.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.8</td>
<td>8.7</td>
</tr>
<tr>
<td>Back pain</td>
<td>10.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>6.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.6</td>
<td>6.4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9.6</td>
<td>5.5</td>
</tr>
</tbody>
</table>


- Nausea, dizziness, influenza, anxiety, diarrhea, gastroenteritis, and insomnia occurred more frequently in the rimonabant 20 mg group compared with placebo.
- Nasopharyngitis, headache, upper respiratory tract infection, back pain, arthralgia, and fatigue occurred more frequently in the placebo group.
RIO-Diabetes: Study design

- This trial enrolled patients with a high BMI and type 2 diabetes treated with metformin or sulfonylurea. Thus, the RIO-Diabetes population was at higher baseline risk that the patients enrolled in either RIO-Europe or RIO-Lipids.

- RIO-Diabetes had the same placebo-controlled, parallel-group design as the other 2 trials.

- Among the exclusion criteria were severe microvascular or macrovascular complications of diabetes, or blood pressure >160/95 mm Hg.
RIO-Diabetes: Treatment effect on weight and waist circumference

- In the intent-to-treat population, weight change from baseline was significantly greater in the rimonabant 5 mg (5.1 lbs, P = 0.01) and rimonabant 20 mg (11.7 lbs, P < 0.0001) groups compared with placebo (3.1 lbs).

- Waist circumference followed a similar pattern. Reductions from baseline were 1.1 inches (rimonabant 5 mg, P = 0.02 vs placebo), 2.0 inches (rimonabant 20 mg, P < 0.0001 vs placebo), and 0.7 inches (placebo).

- Analysis of the primary endpoint was performed using ANOVA, followed by the modified Bonferroni procedure (Hochberg) to adjust for multiple doses. The three-way ANOVA included terms for treatment, and 2 randomization strata (weight loss of ≤4.4 lbs or >4.4 lbs, and diabetic therapy with metformin or sulfonylurea).
RIO-Diabetes: Treatment effect on lipids

- HDL-C increased from baseline by 15.4% and 7.1% in the rimonabant 20 mg and placebo groups, respectively (P < 0.0001).
- Triglycerides decreased by 9.1% in the rimonabant 20 mg group and increased by 7.3% in the placebo group (P < 0.0001).
- Changes in triglycerides with the 5-mg dose were not significantly different from placebo.
- Changes in LDL-C and total-C were not significantly different from placebo for either dose of rimonabant.
- Statistical analysis of secondary endpoints was similar to that used for the primary endpoints; however, randomization strata were excluded from the models.
RIO-Diabetes: Treatment effect on glucose metabolism

- A1C decreased by 0.6% in the rimonabant 20 mg group and increased by 0.1% in the placebo group (P < 0.0001). The rimonabant-associated decrease in patients taking metformin was comparable to that in patients taking sulfonylureas.

- An A1C of <7% was achieved by 68% of patients taking rimonabant 20 mg and by 48% of patients taking placebo (P < 0.0001, data not shown).

- HOMA-IR decreased by 0.5 in the rimonabant 20 mg group and increased by 0.6 in the placebo group (P = 0.03).

- Statistical analysis of secondary endpoints was similar to that used for the primary endpoints; however, randomization strata were excluded from the models.
RIO-Diabetes: Adverse events

≥5% incidence in any group

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (%) (n = 348)</th>
<th>Rimonabant 20 mg (%) (n = 339)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Back pain</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>URTI</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>


• Nausea, dizziness, arthralgia, vomiting, hypoglycemia, fatigue, and anxiety occurred more frequently in the rimonabant 20 mg group compared with placebo.

• Nasopharyngitis and upper respiratory tract infection occurred more frequently in the placebo group.
RIO-North America: Study design

- RIO-North America enrolled a similar patient population as RIO-Europe. Study subjects had high BMI and treated or untreated hypertension or dyslipidemia.
- Among the exclusion criteria were significant cardiac, renal, hepatic, gastrointestinal tract, neuropsychiatric, or endocrine disorders; or type 2 diabetes.
- RIO-America had a different design than the other 3 trials in the RIO program.
- Patients were initially randomized to placebo or 1 of 2 rimonabant groups (5 mg or 20 mg). After 1 year, patients in both rimonabant groups were rerandomized to placebo or continued treatment with rimonabant at the same dose.
RIO-North America: Weight change by treatment assignment

- During year 1, rimonabant 20 mg was associated with a placebo-corrected decrease in weight of 10.3 lbs (P < 0.001 vs placebo).
- During year 2, patients who continued treatment with rimonabant 20 mg maintained a mean absolute weight loss from baseline of 16.3 lbs (8.0 lbs placebo-corrected weight loss).
- Patients who were rerandomized to placebo from rimonabant for year 2 regained most of the weight they had lost the previous year.
During year 1, rimonabant 20 mg was associated with a placebo-corrected reduction in waist circumference of 1.4 inches (P < 0.001).

At the end of year 2, patients who continued on rimonabant 20 mg had a mean reduction in waist circumference of 1.1 inches (P < 0.001 vs placebo).

Waist circumference in patients who were rerandomized to placebo from rimonabant for year 2 steadily returned to baseline.

These findings demonstrate that the efficacy of rimonabant can be maintained over 2 years. They also demonstrate that, as for other chronic disorders such as hypertension, dyslipidemia, or diabetes, sustained treatment is required to maintain favorable changes in cardiometabolic risk factors.
• Effects of rimonabant 20 mg on lipid profiles were consistent with those from the other RIO program trials.

• HDL-C increased from baseline by 7.2% (placebo-corrected, P < 0.001).

• Triglycerides decreased by 13.2% (placebo-corrected, P < 0.001).

• Changes in triglycerides with the 5-mg dose were not significantly different from placebo.
**RIO-North America: Weight-independent and weight-dependent effects on lipids**

- To assess the extent by which changes in lipids could be attributed to weight loss alone, the investigators used standard regression analysis in which weight loss was introduced as a covariate.
- 58% of the effect on HDL-C and 47% of the effects on triglycerides could not be explained by weight loss.
- Abbreviation used in slide:
  ANCOVA = analysis of covariance
RIO-North America: Weight-independent and weight-dependent effects on insulin and IR

- At 1 year, fasting insulin decreased from baseline by 2.8 micro-IU/mL (placebo-corrected, P < 0.001). Analysis of covariance regression indicated that 50% of this effect could not be explained by weight loss.

- Also at 1 year, HOMA-IR decreased from baseline by 0.8 (placebo-corrected, P < 0.001). Analysis of covariance regression indicated that 51% of this effect could not be explained by weight loss alone.

- In summary, the effect of rimonabant 20 mg on HDL-C, triglycerides, fasting insulin, and insulin resistance (IR) was approximately twice that expected from the degree of weight loss achieved. This finding suggests a direct action of rimonabant on lipid and glucose metabolism.
RIO-North America: Adverse events

≥5% incidence in any group

<table>
<thead>
<tr>
<th></th>
<th>Placebo (%) (n = 498)</th>
<th>Rimonabant 20 mg (%) (n = 1042)</th>
</tr>
</thead>
<tbody>
<tr>
<td>URTI</td>
<td>15.2</td>
<td>18.5</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.8</td>
<td>11.2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8.2</td>
<td>8.8</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11.7</td>
<td>8.7</td>
</tr>
<tr>
<td>Headache</td>
<td>10.2</td>
<td>7.8</td>
</tr>
<tr>
<td>Back pain</td>
<td>6.1</td>
<td>5.9</td>
</tr>
<tr>
<td>Influenza</td>
<td>7.7</td>
<td>8.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Viral gastroenteritis</td>
<td>4.8</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Pi-Sunyer FX et al. JAMA 2006;295:761-75.

- Upper respiratory tract infection, nasopharyngitis, nausea, arthralgia, influenza, diarrhea, and viral gastroenteritis occurred more frequently with rimonabant 20 mg vs placebo.
- Sinusitis, headache, and back pain occurred more frequently in the placebo group.
### RIO-North America: Adverse events, cont’d

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (%)</th>
<th>Rimonabant 20 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 498)</td>
<td>(n = 1042)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>3.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.4</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Pi-Sunyer FX et al. JAMA. 2006;295:761-75.

- Dizziness, anxiety, depressed mood, fatigue, and insomnia occurred more frequently with rimonabant 20 mg vs placebo.
- Bronchitis occurred more frequently with placebo.
Obesity program* depression-related events: Overall incidences

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 2472) (%)</th>
<th>Rimonabant 5 mg (N = 2520) (%)</th>
<th>Rimonabant 20 mg (N = 2742) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood disorders and disturbances</td>
<td>4.5</td>
<td>6.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Mood alterations with depressive symptoms</td>
<td>2.8</td>
<td>3.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>1.7</td>
<td>2.8</td>
<td>3.9</td>
</tr>
</tbody>
</table>

*Obesity program (RIO-Europe, RIO-North America, RIO-Lipids, RIO-Diabetes, REBA, EFC5745 and ACT3801)
Data on file from sanofi-aventis.

- Safety data were combined from all 7 trials that have evaluated rimonabant in obese or overweight individuals. This analysis included all subjects who were randomized and received at least 1 dose of study medication.
- All adverse events were coded according to the MedDRA 9.0 dictionary.
- There was an increased incidence of depressed mood disorders and disturbances in rimonabant-treated subjects compared with placebo, although the overall incidence in all groups was relatively low.
- The MedDRA 9.0 definition of depressed mood disorders and disturbances includes the following terms:
  - Anhedonia
  - Decreased interest
  - Depressed mood
  - Feeling of despair
  - Feelings of worthlessness
  - Morose
  - Psychomotor retardation
  - Tearfulness
  - Feeling guilty
  - Depressive symptom
  - Negative thoughts
- The definition of depressive disorders includes the following terms:
  - Depression
  - Depression postmenopausal
  - Depression postoperative
  - Depression suicidal
  - Dysthymic disorder
  - Postpartum depression
  - Major depression
Completed phase 2 and 3 studies as of March 2007: All suicidality-related events

- Blinded reports of adverse events from completed studies were sent for assessment to the Columbia-Classification of Adult Suicidality Assessment (C-CASA). Independent, blinded assessment was categorized as follows:
  1. Completed suicide
  2. Suicide attempt
  3. Preparatory acts toward imminent suicide behavior
  4. Suicidal ideation
  5. Self-injurious behavior, intent unknown
  6. Not enough information (fatal)
  7. Self-injurious behavior, no suicidal intent
  8. Other: accident, psychiatric, medical
  9. Not enough information (nonfatal)

- The two categories summarized on the slide are as follows:
  - Definitely suicidal (suicidal behavior/ideation): ratings 1, 2, 3, 4
  - Possibly suicidal: ratings 5, 6, 9

- There was no difference between placebo and rimonabant 20 mg with regard to the incidence of either category. At other rimonabant doses, the incidence was lower compared with placebo.
Rimonabant clinical safety: Summary

• Safety assessment based on extensive exposure up to 2 years
• The most frequent adverse events that led to drug discontinuation were depression, mood alteration, nausea and anxiety
• Psychiatric events:
  – Increased incidence of depression-related events and anxiety with rimonabant vs placebo, overall incidence remained relatively low
  – Most adverse events were mild to moderate intensity
  – Similar qualitative characteristics between rimonabant 20 mg vs placebo
• No clinical changes in laboratory test, electrocardiogram, or vital signs
• Long-term exposure did not identify new or increased risks and supports its long term administration in overweight/obese patients with at least one cardiometabolic risk factor

Data on file from sanofi-aventis.

Rimonabant clinical safety: Summary

• Adverse events were generally mild to moderate in intensity and in trials of up to 2 years mainly involved the gastrointestinal tract and central nervous system.
• The most frequent adverse events that led to drug discontinuation were depression, mood alteration, nausea, and anxiety.
• There were no clinical changes in laboratory tests, electrocardiograms, or vital signs in rimonabant-treated subjects compared with placebo.
ACOMPLIA: European product information

Therapeutic indication

• As an adjunct to diet and exercise for treatment of patients with BMI ≥30 kg/m² or >27 kg/m² with associated risk factors such as T2DM or dyslipidemia

Adult dosing

• 20 mg daily, to be taken in the morning before breakfast
• No dosage adjustment in elderly, mild/moderate hepatic insufficiency, or mild/moderate renal impairment

In June 2006, the European Commission granted marketing authorization for rimonabant 20 mg as ACOMPLIA® in all 25 European member states. The marketing authorization was based on data from the RIO clinical trial program.

ACOMPLIA is indicated as an adjunct to diet and exercise for treatment of patients with a BMI ≥30 kg/m² or with a BMI >27 kg/m² in the presence of concomitant cardiometabolic risk factors such as type 2 diabetes or dyslipidemia.

Rimonabant is metabolized by the liver by both CYP3A and amidohydrolase pathways, but no dosage adjustment of ACOMPLIA is required for patients with mild or moderate hepatic impairment.

No dosage adjustment is required for patients with mild or moderate renal impairment.

The complete Summary of Product Characteristics is available on the European Medicines Agency website at: www.emea.europa.eu
ACOMPLIA: European product information, cont’d

<table>
<thead>
<tr>
<th>Contraindicated/Not recommended</th>
<th>Use with caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pregnant or breast-feeding women</td>
<td>• Receiving potent CYP3A4 inhibitors</td>
</tr>
<tr>
<td>• Children below age 18 years</td>
<td>– Ketoconazole</td>
</tr>
<tr>
<td>• Uncontrolled serious psychiatric illness such as major depression</td>
<td>– Itraconazole</td>
</tr>
<tr>
<td>• Taking antidepressant medication</td>
<td>– Ritonavir</td>
</tr>
<tr>
<td>• Severe renal or hepatic impairment</td>
<td>– Telithromycin</td>
</tr>
<tr>
<td>• Moderate hepatic impairment</td>
<td>– Clarithromycin</td>
</tr>
<tr>
<td>• Age &gt;75 years</td>
<td>– Nefazodone</td>
</tr>
<tr>
<td>• Treated for epilepsy</td>
<td></td>
</tr>
</tbody>
</table>

Because there are no adequate or well-controlled studies in pregnant women or in children <18 years of age, ACOMPLIA® is not recommended for use in these patients.

Therapy should not be initiated in patients with serious uncontrolled psychiatric illness. Appropriate treatment of this condition should be initiated first, and therapy with ACOMPLIA considered once the psychiatric condition is controlled. Use of ACOMPLIA is not recommended in patients taking antidepressant medication, as there are limited data available.

Use in patients with severe hepatic or renal impairment is contraindicated.

Because rimonabant is metabolized by the CYP3A pathway, caution is advised when ACOMPLIA is used in combination with potent CYP3A4 inhibitors.