ORIGINAL ARTICLE

Effects of Rimonabant on Metabolic Risk Factors in Overweight Patients with Dyslipidemia

Jean-Pierre Després, Ph.D., Alain Golay, M.D., and Lars Sjöström, M.D., Ph.D., for the Rimonabant in Obesity–Lipids Study Group*

ABSTRACT

BACKGROUND

Rimonabant, a selective cannabinoid-1 receptor (CB_1) blocker, has been shown to reduce body weight and improve cardiovascular risk factors in obese patients. The Rimonabant in Obesity–Lipids (RIO-Lipids) study examined the effects of rimonabant on metabolic risk factors, including adiponectin levels, in high-risk patients who are overweight or obese and have dyslipidemia.

METHODS

We randomly assigned 1036 overweight or obese patients (body-mass index [the weight in kilograms divided by the square of the height in meters], 27 to 40) with untreated dyslipidemia (triglyceride levels >1.69 to 7.90 mmol per liter, or a ratio of cholesterol to high-density lipoprotein [HDL] cholesterol of >4.5 among women and >5 among men) to double-blinded therapy with either placebo or rimonabant at a dose of 5 mg or 20 mg daily for 12 months in addition to a hypocaloric diet.

RESULTS

The rates of completion of the study were 62.6 percent, 60.3 percent, and 63.9 percent in the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively. The most frequent adverse events resulting in discontinuation of the drug were depression, anxiety, and nausea. As compared with placebo, rimonabant at a dose of 20 mg was associated with a significant (P<0.001) mean weight loss (repeated-measures method, −6.7±0.5 kg, and last-observation-carried-forward analyses, −5.4±0.4 kg), reduction in waist circumference (repeated-measures method, −5.8±0.5 cm, and last-observation-carried-forward analyses, −4.7±0.5 cm), increase in HDL cholesterol (repeated-measures method, +10.0±1.6 percent, and last-observation-carried-forward analyses, +8.1±1.5 percent), and reduction in triglycerides (repeated-measures method, −13.0±3.5 percent, and last-observation-carried-forward analyses, −12.4±3.2 percent). Rimonabant at a dose of 20 mg also resulted in an increase in plasma adiponectin levels (repeated-measures method, 57.7 percent, and last-observation-carried-forward analyses, 46.2 percent; P<0.001), for a change that was partly independent of weight loss alone.

CONCLUSIONS

Selective CB_1-receptor blockade with rimonabant significantly reduces body weight and waist circumference and improves the profile of several metabolic risk factors in high-risk patients who are overweight or obese and have an atherogenic dyslipidemia.

From the Quebec Heart Institute, Laval Hospital Research Center, and the Division of Kinesiology, Department of Social and Preventive Medicine, Laval University, Ste.-Foy, Que., Canada (J.-P.D.); the Service of Therapeutic Education for Chronic Diseases, University Hospital Geneva, Geneva (A.G.); and the Department of Body Composition and Metabolism, Sahlgrenska University Hospital, Göteborg, Sweden (L.S.). Address reprint requests to Dr. Després at the Quebec Heart Institute, Laval Hospital Research Center, Pavilion Marguerite-D'Youville, 4th Fl., 2725 Chemin Ste.-Foy, Ste.-Foy, QC G1V 4G5, Canada, or at jean-pierre.despres@crhl.ulaval.ca.

THE EPIDEMIC OF OBESITY IN DEVEL-
oped countries illustrates the inability of
homeostatic mechanisms to offset a sed-
entary lifestyle[1] and almost unlimited access to
processed, energy-dense foods of poor nutrition-
al value. Although modification of nutritional and
physical-activity habits is the cornerstone of ther-
apy for obesity, pharmacotherapy focusing on im-
provement of the metabolic risk profile in abdomi-
nally obese patients who are at high risk of diabetes
and cardiovascular disease may be required. The
newly discovered endocannabinoid (EC) system and
cannabinoid CB_1 receptor,[2] with their reported roles
in the regulation of energy balance and body com-
position, offer a new target to induce weight loss
and improve the metabolism of carbohydrates and
lipids.[2-4]

The EC system consists of a family of locally
produced, short-lived, endogenous, phospholip-
id-derived agonists (endocannabinoids)[5,6] and the
$G_{I/O}$-protein–coupled CB_1 receptor[7] that they acti-
vate. CB_1 receptors are expressed predominantly in
several areas of the brain and in peripheral organs,
including the autonomic nervous system, liver,
muscle, gastrointestinal tract, and adipose tissue.[2]
Administration of the first endocannabinoid dis-
covered, anandamide, in the hypothalamus or of
2-arachidonoyl-glycerol in the nucleus accumbens
can provoke food intake in satiated rodents.[8,9] As
compared with wild-type animals, CB_1-knockout
mice have leaner body composition, but this lean
phenotype is not fully explained by changes in food
intake.[3]

Stimulation of the CB_1 receptors in fat cells pro-
motes lipogenesis and inhibits the production of
adiponectin,[3,10] a cytokine derived from adipose
tissue that has potentially important antidiabetic
and antiatherosclerotic properties.[11] Rimonabant,
the first specific CB_1-receptor blocker to enter clin-
ical development, has been shown to reduce food
intake and body weight in treated animals and to
alter metabolic activity in adipose tissue[12] while in-
ducing the expression of the adiponectin gene.[13]
The results of a phase 3 study involving obese
patients (Rimonabant in Obesity–Europe [RIO-
Europe] study) showed that rimonabant induces
significant weight loss and improves metabolic risk
factors for diabetes and cardiovascular disease.[14]
However, the patients enrolled in the study were
selected only on the basis of excess weight. There-
fore, we examined the effects of rimonabant in per-
sons at higher risk of cardiovascular disease, such

as patients with dyslipidemia who were overweight
or obese. Also, since only traditional risk factors
for cardiovascular disease were measured in the
RIO-Europe study, we explored the effect of ri-
monabant on other key metabolic risk markers for
cardiovascular disease such as the size of particles
of low-density lipoprotein (LDL) and the plasma
levels of C-reactive protein and adiponectin.

METHODS

STUDY DESIGN

The primary objective of the study was to assess the
effect of 12 months of randomized, double-blind
treatment with rimonabant at a dose of 5 mg or 20
mg, as compared with placebo, in addition to a hy-
pocaloric diet (a deficit of 600 kcal per day in rela-
tion to the calculated daily intake to maintain body
weight), on the loss of body weight in patients who
are overweight or obese (body-mass index [BMI], 27
to 40, with BMI defined as the weight in kilograms
divided by the square of the height in meters), have
untreated dyslipidemia, and do not have diabetes.
Secondary measures included changes from base-
line (randomization) in levels of high-density lipo-
protein (HDL) cholesterol, triglycerides, glucose,
and insulin during an oral glucose-tolerance test
and the prevalence of the metabolic syndrome (ac-
cording to the criteria of the third report of the Na-
tional Cholesterol Education Program Adult Treat-
ment Panel [NCEP-ATPIII]).[15] Additional efficacy
measures included waist circumference, leptin and
adiponectin levels, and relevant biochemical cardio-
vascular risk markers. The safety assessment includ-
ed standard adverse-event reporting, vital signs, the
QT interval corrected for heart rate (QTc), and anxi-
ety and depression according to the hospital anxiety
and depression scales.[14,16] The range of scores for
each scale is 0 to 21, with higher scores indicating a
worse condition. Data were gathered by the spon-
sor (Sanofi Aventis) and were analyzed jointly by the
authors and the sponsor. The data analysis and the
final analyses were reviewed and validated by the
authors, who then wrote the manuscript.

The study was conducted between September
2001 and November 2003 and was in compliance
with the Helsinki Declaration. It was conducted at
67 sites in eight countries, with an independent,
unblinded data safety monitoring board compris-
ing five permanent members. At each meeting of
the data safety monitoring board, it was mandatory
to have at least three permanent independent mem-

bers, including a clinician, a safety expert, and a statistician. All patients gave written informed consent for participation in the study.

Inclusion criteria were age of 18 to 70 years; BMI of 27 to 40; fasting plasma triglyceride levels of 1.7 to 7.9 mmol per liter (150 to 700 mg per deciliter), a ratio of total cholesterol to HDL cholesterol higher than 5 (among men) and higher than 4.5 (among women), or both; and variation in body weight within the previous three months of less than 5 kg. Exclusion criteria were a history of pharmacologic treatment for dyslipidemia within six weeks before screening, pharmacologic treatment for weight loss within three months before screening, or treatment with a very-low-calorie diet within six months before screening; diabetes mellitus (type 1 or 2); clinically significant findings indicating cardiovascular, endocrine, pulmonary, neurologic, psychiatric, gastrointestinal, hepatic, hematologic, renal, or dermatologic disease; a positive result on a test for hepatitis B surface antigen, hepatitis C antibody, or both; an abnormal thyrotropin level (greater than the upper limit of the normal range or less than the lower limit of the normal range); one or more of the following: levels of alanine aminotransferase or aspartate aminotransferase greater than 2.5 times the upper limit of the normal range; hemoglobin levels less than 11 g per deciliter, neutrophil levels less than 1500 per cubic millimeter, platelet levels of less than 100,000 per cubic millimeter, and a creatinine level greater than 150 μmol per liter (1.7 mg per deciliter); a history of marijuana or hashish use; severe depression (depression requiring hospitalization or indicated by a suicide attempt); and treatment for epilepsy, an eating disorder, or a malignant disease except basal-cell skin cancers (within five years). Other grounds for exclusion included systolic or diastolic blood pressure at screening that was higher than 165 or 105 mm Hg, respectively; pregnancy or lactation; or less than 80 percent compliance with a hypocaloric diet and placebo during the postscreening four-week, single-blind run-in period.[14]

After enrollment, patients were stratified according to baseline triglyceride levels (>4.5 vs. ≤4.5 mmol per liter [400 mg per deciliter]) and weight loss during the run-in period (>2 vs. ≤2 kg) and assigned to double-blind therapy, receiving placebo or rimonabant at a dose of 5 mg or 20 mg in a ratio of 1:1:1. Follow-up visits with a consulting dietitian occurred every 2 weeks for the first two visits and monthly thereafter for 12 months; standardized assessments of body weight, blood pressure, waist circumference, smoking status, and concomitant medications were performed at each visit. Patients were not eligible if they had recently (within the past six months) quit smoking or were considering quitting. Patients who had undergone randomization were not allowed to change smoking status during the study, and smokers who quit during the study period were ruled out because of the known effects of smoking cessation on body weight.

ASSAYS

Standard laboratory tests were performed by ICON Laboratories (at sites in Farmingdale, New York, and Dublin). The peak size of LDL particles and the proportion of small (<255 Å) LDL particles were determined by means of nondenaturing 2 to 16 percent polyacrylamide-gradient–gel electrophoresis.[17] Apolipoprotein B and apolipoprotein A-I were quantified by nephelometry. Serum C-reactive protein levels were measured by immunoturbidimetric assay, glucose with the use of the hexokinase method, insulin by immunometric assay, leptin by radioimmunoassay,[18] and adiponectin by an enzyme-linked immunosorbent assay (B-Bridge International). A 75-g oral glucose-tolerance test was performed in the morning after an overnight fast, and glucose and insulin areas under the curve (AUCs) were calculated with the use of the trapezoid method.

STATISTICAL ANALYSIS

All statistical tests were two-sided, with an alpha level of 0.05. The prespecified analysis of the primary end point (change in weight from baseline at the last observation carried forward) was conducted with the use of analysis of variance with the modified Bonferroni procedure (Hochberg) for adjustment for multiple comparisons. The analysis of variance included terms for treatment and randomization subgroup. Because this analysis ruled out scheduled measurements collected during the study, a post-hoc repeated-measures approach was performed for changes in weight from baseline, which provided a better estimate of the true effect of the study drug. The repeated-measures model included the fixed effects (randomization subgroup, treatment, day [number of days after randomization], and treatment-by-day interaction) and a random effect (the patient). Similar methods were used for the analysis of other efficacy end points.

Table 1. Patients' Assignments, Values at Screening, and Baseline Efficacy and Safety Values.*

Variable	Placebo Group (N=342)	5-mg Rimonabant Group (N=345)	20-mg Rimonabant Group (N=346)
Patients' assignment — no. (%)			
Randomly assigned and exposed to medication	342 (100)	345 (100)	346 (100)
Intention-to-treat analysis†	334 (97.7)	340 (98.6)	344 (99.4)
Completed study	214 (62.6)	208 (60.3)	221 (63.9)
Reason for discontinuation	128 (37.4)	137 (39.7)	125 (36.1)
Lack of efficacy	2 (0.6)	4 (1.2)	3 (0.9)
All adverse events	31 (9.1)	29 (8.4)	56 (16.2)
Poor compliance	13 (3.8)	18 (5.2)	13 (3.8)
Patient's request	70 (20.5)	71 (20.6)	42 (12.1)
Lost to follow-up	12 (3.5)	10 (2.9)	8 (2.3)
Other	0	5 (1.4)	3 (0.9)
Screening values			
Sex — %			
Male	42.1	37.7	38.4
Female	57.9	62.3	61.6
Current smoker — %	17.8	16.8	15.3
Age — yr‡	47.0±10.1	48.1±10.2	48.4±10.0
Height — cm	168±9	168±9	167±10
Weight — kg	97.0±15.4	96.0±14.6	95.3±15.1
Body-mass index‡	34.0±3.5	34.1±3.5	33.9±3.3
Triglycerides — mmol/liter‡	2.26±1.61	2.36±1.13	2.42±1.14
Total cholesterol — mmol/liter	6.01±0.86	6.03±0.81	5.91±0.91
HDL cholesterol — mmol/liter	1.15±0.24	1.16±0.25	1.14±0.25
Total cholesterol:HDL cholesterol ratio‡	5.38±1.02	5.37±1.09	5.33±1.09
Baseline efficacy values			
Weight — kg	95.0±15.1	94.2±14.6	93.3±14.8
Waist circumference — cm	105.7±11.4	104.8±10.8	104.7±11.0
Triglycerides — mmol/liter	2.05±1.21	2.10±1.41	2.11±1.15
Total cholesterol — mmol/liter	5.65±0.94	5.63±0.96	5.59±1.00
LDL cholesterol — mmol/liter	3.58±0.78	3.52±0.79	3.46±0.86
Peak size of LDL particles — Å	259.3±5.0	260.0±5.0	259.1±4.8
Proportion of small LDL particles (<255Å) — %	26.2±21.4	25.2±20.2	25.8±21.0
HDL cholesterol — mmol/liter	1.10±0.25	1.10±0.23	1.11±0.24
Total cholesterol:HDL cholesterol ratio	5.31±1.13	5.29±1.11	5.19±1.10
LDL cholesterol:HDL cholesterol ratio	3.36±0.82	3.30±0.83	3.20±0.81
Apolipoprotein B:apolipoprotein A-I ratio§	0.73±0.15	0.73±0.18	0.72±0.16
Fasting glucose — mmol/liter	5.29±0.64	5.33±0.71	5.29±0.59
Fasting insulin — μU/ml	12.8±11.4	13.0±8.0	12.8±12.3
Metabolic syndrome — %	51.9	55.9	52.9
Adiponectin — μg/ml¶	5.7±2.5	5.8±2.9	5.9±2.9
Leptin — ng/ml	18±10	20±12	18±11
C-reactive protein — mg/liter	5.3±5.3	5.2±5.3	5.0±5.0

Table 1. (Continued.)

Variable	Placebo Group (N=342)	5-mg Rimonabant Group (N=345)	20-mg Rimonabant Group (N=346)
Baseline safety values			
Heart rate — bpm	65.7±9.7	65.9±9.8	64.7±8.5
Blood pressure — mm Hg			
Systolic	124.0±13.8	123.8±13.5	124.9±12.7
Diastolic	78.2±8.4	78.1±8.9	78.2±7.7
QTc — msec	402.1±20.2	403.9±19.3	406.5±21.0
Depression‖	3.0±2.7	3.2±3.1	3.0±2.6
Anxiety‖	5.1±3.8	5.6±4.1	5.3±3.3

* Plus–minus values are means ±SD. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, bpm beats per minute, and QTc the QT interval corrected for heart rate. To convert values for triglycerides to milligrams per deciliter, divide by 0.01129. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert values for glucose to milligrams per deciliter, divide by 0.05551. To convert values for insulin to picomoles per liter, multiply by 6.

† At least one post-baseline measurement of body weight was required for the analysis.

‡ The category was required according to the entry criteria of the study.

§ Measurements were performed in a subgroup of patients (231, 224, and 237 patients from the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively).

¶ Measurements were performed in a subgroup of patients (231, 222, and 238 patients from the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively).

‖ The disorder was measured according to the hospital anxiety and depression scales.[14,16] The range of scores for each scale is 0 to 21, with higher scores indicating a worse condition.

Patients were classified as having a response of a 5 percent weight loss if they had a reduction in body weight from baseline at the last observation carried forward of at least 5 percent; the identification of those with a response of a 10 percent weight loss at the last observation carried forward was performed in a similar manner. The incidences of patients who had a weight loss of 5 percent and 10 percent and of those with the metabolic syndrome at the last observation carried forward were analyzed with the use of logistic-regression models. The models for patients who had weight losses of 5 percent and 10 percent included terms for treatment and randomization subgroup, and the model for the metabolic syndrome included terms for treatment and the status of the metabolic syndrome at baseline. Because C-reactive protein values were not normally distributed, nonparametric analyses were substituted for parametric analyses for this specific marker. The effect of rimonabant independent of weight loss was tested with the use of analysis of covariance with weight loss as a covariate. The values in the tables are presented as means ±SD and presented in the figures as means ±SE for the intention-to-treat population.

RESULTS

About 40 percent of the patients in each of the three treatment groups dropped out during the 12-month study, with a higher dropout rate due to adverse events in the group receiving 20 mg of rimonabant and due to patients' requests in the placebo group and the group receiving 5 mg of rimonabant (Table 1). The characteristics of the patients in the three groups were similar both at screening and at baseline, and there were similar improvements during the four-week placebo run-in period in the three groups with regard to all efficacy measures except HDL cholesterol levels, which declined in all three groups (Table 1).

After a weight loss of approximately 2 kg in each group during the run-in period (Table 1), the placebo group had a further decline of 2.3 kg over the next 12 months, as compared with a weight loss of 4.2 kg and 8.6 kg in the group receiving 5 mg of rimonabant and the group receiving 20 mg of rimonabant, respectively (Table 2) (P<0.001 for both doses). Weight loss was generally greater among patients who completed the 12-month study. In the overall population, the proportion of patients who

Table 2. Changes from Baseline for the Efficacy and Safety End Points in the Intention-to-Treat Population, According to the Repeated-Measures (RM) Method and Last-Observation-Carried-Forward (LOCF) Analyses.*

End Point	Placebo Group	5-mg Rimonabant Group		20-mg Rimonabant Group	
			P Value		P Value
Efficacy end point					
Weight (kg)					
RM	−2.3±5.6	−4.2±5.3	<0.001	−8.6±6.0	<0.001
LOCF	−1.5±5.0	−3.1±4.8	<0.001	−6.9±6.1	<0.001
Waist circumference (cm)					
RM	−3.4±6.0	−4.9±6.2	0.016	−9.1±6.6	<0.001
LOCF	−2.4±5.7	−3.5±6.0	0.029	−7.1±6.8	<0.001
Triglycerides (%)					
RM	−3.6±36.4	0.0±40.5	NS	−15.8±38.0	<0.001
LOCF	−0.2±38.7	+1.2±39.4	NS	−12.6±41.2	<0.001
Total cholesterol (%)					
RM	+1.4±13.9	+2.3±12.6	NS	+2.2±14.9	NS
LOCF	+2.3±14.2	+2.9±12.7	NS	+1.6±14.4	NS
LDL cholesterol (%)					
RM	+6.1±22.2	+4.8±17.6	NS	+8.4±30.2	NS
LOCF	+7.0±22.4	+6.6±21.4	NS	+7.2±28.4	NS
Peak size of LDL particles (Å)					
RM	−0.5±1.4	−0.6±1.4	NS	−0.1±1.5	0.008
LOCF	−0.9±3.9	−1.0±4.1	NS	+0.3±3.8	<0.001
Proportion of small LDL (%)					
RM	+5.6±18.3	+3.9±13.7	NS	+0.4±15.8	0.007
LOCF	+3.2±18.8	+2.2±15.1	NS	−1.5±16.1	0.002
HDL cholesterol (%)					
RM	+12.2±15.5	+15.6±15.3	0.017	+23.4±21.8	<0.001
LOCF	+11.0±15.8	+14.2±17.6	0.025	+19.1±20.9	<0.001
Total cholesterol:HDL cholesterol ratio					
RM	−0.50±0.91	−0.57±0.81	NS	−0.84±0.93	<0.001
LOCF	−0.40±0.90	−0.47±0.82	NS	−0.72±0.93	<0.001
LDL cholesterol:HDL cholesterol ratio					
RM	−0.19±0.69	−0.31±0.62	NS	−0.41±0.76	<0.001
LOCF	−0.14±0.68	−0.23±0.65	NS	−0.35±0.76	<0.001
Apolipoprotein B:apolipoprotein A-I ratio†					
RM	0±0.13	−0.02±0.13	NS	−0.03±0.12	0.040
LOCF	0±0.12	−0.02±0.14	NS	−0.03±0.13	0.023
Fasting glucose (mmol/liter)					
RM	−0.02±0.60	+0.01±0.60	NS	−0.09±0.61	NS
LOCF	−0.05±0.62	−0.01±0.62	NS	−0.08±0.58	NS

had a weight loss equal to or greater than 5 percent was 19.5 percent in the placebo group and 58.4 percent in the group receiving 20 mg of rimonabant (P<0.001), whereas the proportion of those who had a weight loss equal to or greater than 10 percent was 7.2 percent in the placebo group and 32.6 percent in the group receiving 20 mg of rimonabant (P<0.001). Weight loss occurred during the first 9 months of the study period, after which body weight stabilized until the end of the 12th month

Table 2. (Continued.)

End Point	Placebo Group	5-mg Rimonabant Group		20-mg Rimonabant Group	
			P Value		P Value
Fasting insulin (μU/ml)					
RM	+0.7±17.5	+0.6±10.0	NS	−1.3±7.9	0.011
LOCF	+0.9±15.9	+0.4±10.3	NS	−1.7±12.4	0.016
Adiponectin (μg/ml)‡					
RM	+0.8±1.8	+1.1±1.9	0.049	+2.7±2.5	<0.001
LOCF	+0.7±1.9	+1.0±2.0	NS	+2.2±2.5	<0.001
Leptin (ng/ml)					
RM	−0.3±5.8	−2.4±7.0	0.002	−4.8±7.7	<0.001
LOCF	−0.3±6.0	−2.3±7.9	<0.001	−4.1±7.4	<0.001
C-reactive protein (mg/liter)§					
LOCF	−0.4	−0.2	NS	−0.9	0.020
Safety end point					
Heart rate (bpm)¶	+0.7±8.3	+0.2±7.5	ND	+0.9±7.2	ND
Blood pressure (mm Hg)					
Systolic					
RM	−0.7±9.1	−0.4±11.3	NS	−3.6±10.9	0.015
LOCF	−0.3±10.1	+0.4±11.8	NS	−2.1±12.3	0.048
Diastolic					
RM	−0.8±7.3	−0.5±7.9	NS	−2.9±7.6	0.002
LOCF	−0.2±7.4	+0.1±8.3	NS	−1.7±8.5	0.011
QTc (msec)¶	−1.8±15.3	−3.7±16.9	ND	−4.6±15.7	ND
Depression¶‖	+0.2±2.7	−0.2±2.8	ND	+0.1±3.1	ND
Anxiety¶‖	+0.1±2.7	−0.1±3.5	ND	+0.3±3.0	ND

* Plus–minus values are means ±SD. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, bpm beats per minute, NS not significant, and ND not determined. To convert values for glucose to milligrams per deciliter, divide by 0.05551. To convert values for insulin to picomoles per liter, multiply by 6.

† The analysis was performed on a subgroup of patients (231, 224, and 237 patients in the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively).

‡ The analysis was performed on a subgroup of patients (231, 222, and 238 patients in the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively).

§ Values for the change from baseline were not normally distributed and are presented as medians, with statistical significance assessed nonparametrically with the use of an analysis of variance on ranked values.
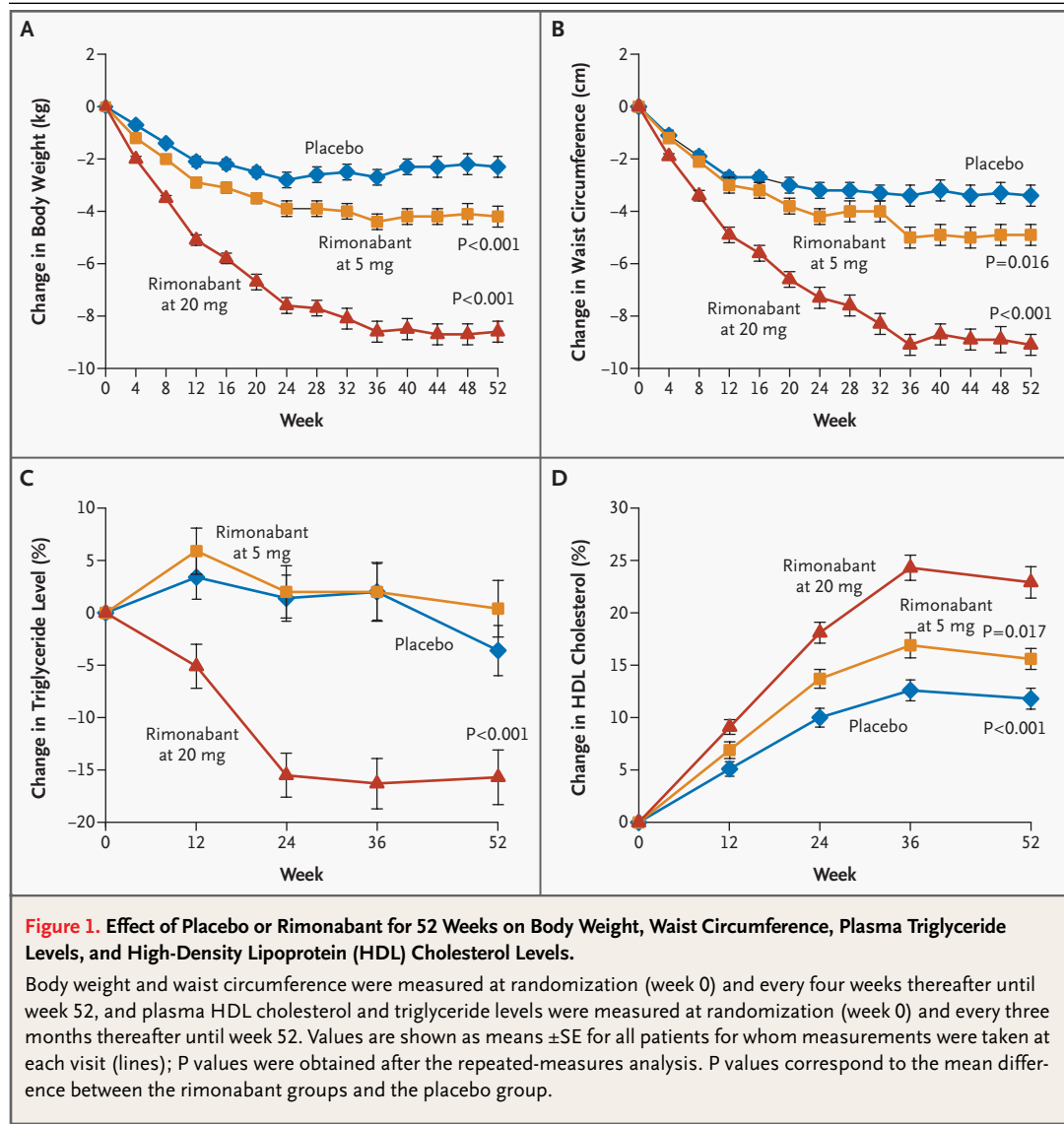
¶ No statistical test was performed.

‖ The disorder was measured according to the hospital anxiety and depression scales.[14,16]

without evidence of regain (Fig. 1A). Changes in waist circumference showed a similar dose response (Table 2) and temporal pattern (Fig. 1B).

The caloric restriction during the four-week run-in period produced reductions of 5.3±37.9 percent in triglycerides, 4.9±17.2 percent in LDL cholesterol, and 3.6±11.9 percent in HDL cholesterol, which resulted in a 0.11±0.76 decrease in the total cholesterol:HDL cholesterol ratio (Table 1). During treatment, triglycerides remained stable in both the placebo group and the group receiving 5 mg of rimonabant but fell an additional 15.8±38.0 per-

cent in the group receiving 20 mg of rimonabant (P<0.001) (Table 2 and Fig. 1C).

HDL cholesterol increased in a dose-dependent fashion, achieving an increase of 15.6±15.3 percent from baseline in the group receiving 5 mg of rimonabant (P=0.017) and of 23.4±21.8 percent in the group receiving 20 mg of rimonabant (P<0.001) (Table 2 and Fig. 1D). Although there was no change in levels of LDL cholesterol, the distribution of LDL particles shifted toward larger size in the group receiving 20 mg of rimonabant, as compared with placebo, with a difference of 1.1 Å in the peak

Figure 1. Effect of Placebo or Rimonabant for 52 Weeks on Body Weight, Waist Circumference, Plasma Triglyceride Levels, and High-Density Lipoprotein (HDL) Cholesterol Levels.

Body weight and waist circumference were measured at randomization (week 0) and every four weeks thereafter until week 52, and plasma HDL cholesterol and triglyceride levels were measured at randomization (week 0) and every three months thereafter until week 52. Values are shown as means ±SE for all patients for whom measurements were taken at each visit (lines); P values were obtained after the repeated-measures analysis. P values correspond to the mean difference between the rimonabant groups and the placebo group.

size of LDL particles (P=0.008) and a 4.6 percent lower proportion of small LDL particles (P=0.007) (Table 2). Changes in levels of HDL cholesterol translated into a dose-dependent reduction in the total cholesterol:HDL cholesterol ratio of −15.2 percent with 20 mg of rimonabant, which was greater than with placebo (P<0.001) (Table 2). Levels of fasting plasma insulin, the one-hour and two-hour plasma glucose and insulin levels, and the insulin and glucose AUCs during the 75-g oral glucose-tolerance test decreased significantly in the group receiving 20 mg of rimonabant (Fig. 2A and 2B; P=0.011 to <0.001).

At baseline, 54 percent of the patients who underwent randomization met the NCEP-ATPIII crite-

ria for the metabolic syndrome (Table 1). The prevalence of the metabolic syndrome fell to 25.8 percent, 40.0 percent, and 41.0 percent in the groups receiving 20 mg of rimonabant, 5 mg of rimonabant, and placebo, respectively; the reduction in the group receiving 20 mg of rimonabant was significantly greater (P<0.001) than in the placebo group and was attributed mainly to the reduction in waist circumference and the increase in HDL cholesterol levels.

Plasma adiponectin levels increased with rimonabant treatment (at a dose of 20 mg) by 57.7 percent — an increase significantly greater than that observed in the placebo group (Fig. 2C). The increase correlated with weight loss in each group
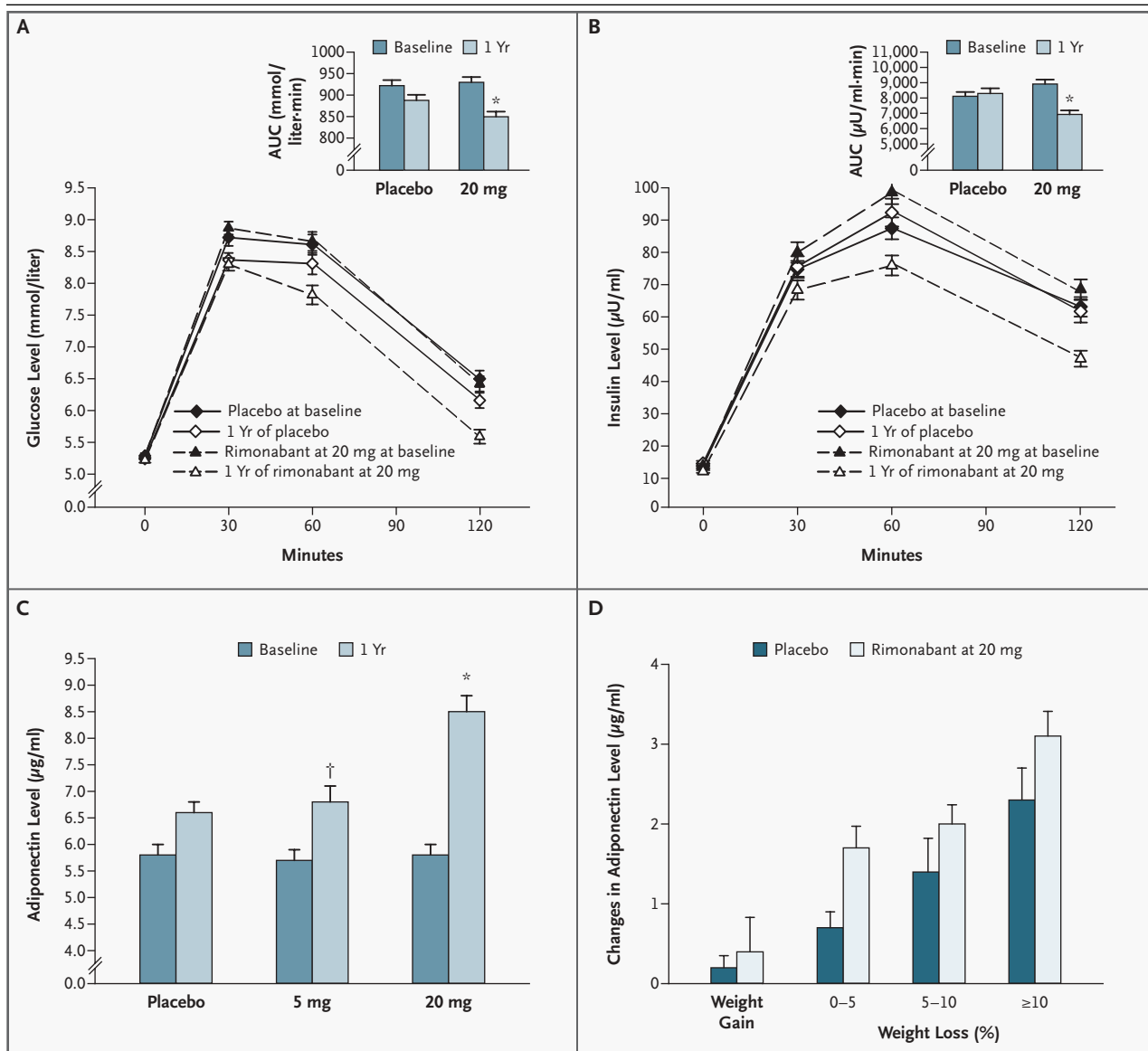
Figure 2. Effect of Placebo or 20 mg of Rimonabant for 52 Weeks on the Plasma Glucose and Insulin Responses to Oral Glucose Challenge (Panels A and B), and the Plasma Adiponectin Level (Panels C and D).

Values for plasma glucose and insulin were measured before the 75-g oral glucose challenge and 30, 60, and 120 minutes afterward, and values are shown for patients for whom measurements were available for each time point (Panels A and B). The integrated areas under the curves (AUCs) are shown in the insets with the P values obtained with the use of the repeated-measures analysis. Panel C shows the effect on plasma adiponectin levels, and Panel D shows the changes in adiponectin levels according to changes in body weight. P values correspond to the mean differences between the rimonabant groups and the placebo group. The asterisk denotes P<0.001, and the dagger P=0.049. To convert values for glucose to milligrams per deciliter, divide by 0.05551; to convert values for insulin to picomoles per liter, multiply by 6.

(r=−0.27, r=−0.30, and r=−0.26 in the placebo group, the 5-mg rimonabant group, and the 20-mg rimonabant group, respectively; P<0.001). However, 57 percent of the increase in adiponectin levels observed in the group receiving 20 mg of rimonabant could not be attributed to weight loss (Fig. 2D).

Changes in adiponectin levels produced by rimonabant at a dose of 20 mg also positively correlated with changes in levels of HDL cholesterol (r=0.27, P<0.001) and apolipoprotein A-I (r=0.38, P<0.001).

Plasma leptin levels decreased significantly in the groups receiving 5 mg of rimonabant (P=0.002)

Table 3. Adverse Events.

Event	Placebo Group (N=342)	5-mg Rimonabant Group (N=345)	20-mg Rimonabant Group (N=346)
Adverse events — %*			
Nasopharyngitis	21.6	26.4	19.4
Headache	15.8	15.4	15.3
Nausea	3.2	7.2	12.7
Dizziness	6.7	8.4	10.4
Influenza	5.3	6.1	9.5
Upper respiratory tract infection	9.9	8.7	8.7
Anxiety	3.8	2.9	8.7
Back pain	10.2	9.6	7.2
Diarrhea	4.1	6.4	7.2
Gastroenteritis	6.4	4.3	6.6
Insomnia	2.6	4.1	6.4
Arthralgia	9.6	7.0	5.5
Serious adverse events — no. (%)†			
Infections and infestations	1 (0.3)	1 (0.3)	2 (0.6)
Surgical and medical procedures	1 (0.3)	0	0
Immune system disorders	2 (0.6)	0	0
Psychiatric disorders	1 (0.3)	1 (0.3)	1 (0.3)
Nervous system disorders	2 (0.6)	0	2 (0.6)
Eye disorders	0	1 (0.3)	0
Cardiac disorders	0	2 (0.6)	1 (0.3)
Vascular disorders	1 (0.3)	0	0
Gastrointestinal disorders	1 (0.3)	3 (0.9)	1 (0.3)
Hepatobiliary disorders	0	2 (0.6)	0
Musculoskeletal and connective-tissue disorders	1 (0.3)	4 (1.2)	2 (0.6)
Renal and urinary disorders	0	0	1 (0.3)
Reproductive system and breast disorders	0	2 (0.6)	1 (0.3)
Investigations	0	0	1 (0.3)
Injury, poisoning, and procedural complications	0	0	1 (0.3)
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)	0	3 (0.9)	2 (0.6)

and 20 mg of rimonabant (P<0.001) in a dose-dependent fashion (Table 2). Plasma C-reactive protein levels decreased by 0.9 mg per liter in the group receiving 20 mg of rimonabant (P=0.020) (Table 2).

The proportions of patients who had treatment-related adverse events or serious adverse events were slightly higher in the group receiving 5 mg of rimonabant and the group receiving 20 mg of rimonabant than in the placebo group (treatment-related adverse events: 82.3 percent, 86.7 percent, and 81.6 percent, respectively; and serious adverse events: 5.2 percent, 4.0 percent, and 2.3 percent,

respectively). There were no deaths in any of the three groups. The treatment-related adverse events reported in 5 percent or more of the patients in either rimonabant group but more commonly among those receiving 20 mg of rimonabant were (in order of decreasing frequency) nausea, dizziness, influenza, anxiety, diarrhea, and insomnia; these occurred early in the treatment period (Table 3). Overall discontinuation rates were similar in the three groups, but more patients discontinued treatment because of adverse effects in the group receiving 20 mg of rimonabant (Table 1) than in the other groups. The most frequent adverse events resulting in discon-

Table 3. (Continued.)			
Event	Placebo Group (N=342)	5-mg Rimonabant Group (N=345)	20-mg Rimonabant Group (N=346)
Discontinuation — no. (%)‡			
Patients who discontinued participation	24 (7.0)	29 (8.4)	52 (15.0)
Reason for discontinuation			
Psychiatric disorders			
Depression	2 (0.6)	6 (1.7)	10 (2.9)
Anxiety	2 (0.6)	1 (0.3)	6 (1.7)
Major depression	0	2 (0.6)	2 (0.6)
Irritability	2 (0.6)	1 (0.3)	2 (0.6)
Aggression	0	1 (0.3)	2 (0.6)
Depressed mood	0	0	2 (0.6)
Sleep disorder	0	0	2 (0.6)
Insomnia	2 (0.6)	1 (0.3)	0
Nervous system disorders			
Dizziness	0	2 (0.6)	3 (0.9)
Amnesia	0	0	2 (0.6)
Headache	3 (0.9)	1 (0.3)	0
General disorders			
Fatigue	3 (0.9)	0	2 (0.6)
Gastrointestinal disorders			
Nausea	0	2 (0.6)	4 (1.2)
Dyspepsia	0	1 (0.3)	2 (0.6)
Upper abdominal pain	0	0	2 (0.6)
Vascular disorders			
Hypertension	1 (0.3)	2 (0.6)	1 (0.3)
Infections and infestations			
Pneumonia	2 (0.6)	0	0

* Adverse events are included if they occurred in at least 5 percent of either rimonabant group. They are listed according to preferred term.
† Serious adverse events are listed according to system organ class.
‡ Treatment-related adverse events are included if they occurred in at least 0.5 percent of any treatment group and resulted in a request to discontinue participation in the study. Events are listed according to system organ class and then preferred term for the event. Patients may have had more than one type of adverse event that led to discontinuation.

tinuation in the groups receiving rimonabant at 5 mg and 20 mg, as compared with placebo, included depression (1.7 percent and 2.9 percent, respectively, vs. 0.6 percent); anxiety (0.3 percent and 1.7 percent vs. 0.6 percent); and nausea (0.6 percent and 1.2 percent vs. 0 percent).

Values for laboratory safety measures linked to obesity (i.e., levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, and uric acid) decreased with rimonabant at a dose of 20 mg (data not shown). Other values for safety measures included heart rate, systolic and dia-

stolic blood pressure, QTc, and scores for anxiety and depression according to the hospital anxiety and depression scales (Table 1), and all except for blood pressure were similar in the three groups during the study period. Decreases in systolic and diastolic blood pressure with 20 mg of rimonabant were statistically significant (Table 2) and were greater among patients with hypertension at baseline (blood pressure, ≥140/90 mm Hg). For the 20-mg rimonabant versus placebo groups, the respective decreases in patients with hypertension were as follows: systolic pressure, 13.1±11.5

vs. 7.2±10.7 mm Hg, P=0.038; and diastolic pressure, 6.3±6.0 vs. 2.4±9.7 mm Hg, P=0.022. Finally, there were no interactions between treatment assignment and sex (data not shown).

DISCUSSION

The NCEP-ATPIII report and the recently published National Heart, Lung, and Blood Institute and American Heart Association consensus report highlighted abdominal obesity as assessed by waist circumference as an important cardiovascular risk marker and the primary target for the treatment of the metabolic syndrome.[15,19] Few tools exist to treat collectively the underlying pathophysiology in high-risk, abdominally obese patients, and most published obesity studies primarily enrolled patients who were at relatively low cardiovascular risk (i.e., obese women not selected for the presence of cardiovascular risk factors).[20] In the recent RIO-Europe study in obese patients, CB_1-receptor blockade with rimonabant was found to reduce body weight and waist circumference, improve plasma glucose–insulin homeostasis, and produce a substantial increase in plasma HDL cholesterol levels — a change that was greater than what could be expected from weight loss alone.[14] These findings suggested a weight-loss–independent effect of rimonabant on metabolic risk that may be mediated by the effect of rimonabant on adiponectin secretion by fat cells, as reported in studies in animals.[13]

Our study explored further the effect of rimonabant in a high-risk population of patients with dyslipidemia who are overweight or obese, with a focus on metabolic risk markers such as the size of LDL particles and levels of C-reactive protein and adiponectin. As compared with placebo, rimonabant at a dose of 20 mg per day induced significant weight loss and reduction in waist circumference, suggesting a substantial mobilization of abdominal fat, which, by itself, would predict an improved cardiovascular risk profile.[21] Additional effects of rimonabant at this dose, as compared with placebo, included significant improvements in plasma triglycerides, plasma HDL cholesterol, and the total cholesterol:HDL cholesterol ratio, as well as changes in LDL particle size, adiponectin levels, glucose tolerance, fasting and post-challenge insulin levels (markers for the risk of diabetes), and plasma C-reactive protein levels and in the proportion of patients meeting the NCEP-ATPIII criteria for the metabolic syndrome.

Rimonabant had no effect on LDL cholesterol levels. Patients with abdominal obesity and the metabolic syndrome generally do not have elevated levels of LDL cholesterol[22] but, rather, express the high triglyceride–low HDL cholesterol–small, dense LDL dyslipidemia associated with insulin resistance phenotype.[23] Although the LDL cholesterol level itself powerfully predicts cardiovascular risk,[24] the metabolic risk profile of abdominal obesity[23,25] further increases the risk of coronary heart disease for any level of LDL cholesterol.[26] In the RIO-Lipids study, the proportions of small and large LDL particles were altered with rimonabant, as compared with placebo, in the absence of any change in LDL cholesterol levels.

Although patients who meet the NCEP-ATPIII criteria for the metabolic syndrome have a distinct cardiovascular disease risk-factor profile, the clinical relevance of making the metabolic syndrome a treatable target beyond classic risk factors has been debated.[27] Therefore, the clinical relevance of reducing the proportion of patients meeting those NCEP-ATPIII criteria for the metabolic syndrome by the use of rimonabant can be questioned if it is not accompanied by favorable changes in markers for insulin resistance and abdominal obesity such as glucose tolerance and levels of insulin, adiponectin, and C-reactive protein, all of which, when abnormal, are linked to visceral obesity and the metabolic syndrome.[28,29] The results of the RIO-Lipids study with regard to C-reactive protein are thus consistent with the reported beneficial effect of weight loss on inflammation.[30,31] Whether the reduction in C-reactive protein levels will be additive to or synergistic with the reduction in C-reactive protein levels and the cardiovascular protection ascribed to statins and fibric acids[32,33] remains to be explored. Although regarded as the least prominent component of the metabolic syndrome,[34] hypertension is more prevalent among abdominally obese patients with insulin resistance, and the condition usually responds to weight loss.[35] Rimonabant at a dose of 20 mg reduced blood pressure overall, especially among patients with hypertension.

Finally, the results of the RIO-Lipids study provide evidence for a weight-loss–independent effect of rimonabant on adiponectin levels. This finding may be of clinical importance, since a high adiponectin level has been reported to be predictive of a reduced risk of diabetes and cardiovascular events.[36,37] Abdominal obesity is accompanied by reduced adiponectin levels, and such hypoadipo-

nectinemia is partly responsible for the low HDL cholesterol levels in abdominal obesity.[38] Since the changes in adiponectin levels observed in the present study correlated with changes in HDL cholesterol and apolipoprotein A-I, the stimulation of adiponectin production with CB_1-receptor blockade could explain the consistent and weight-loss-independent effect of rimonabant on HDL cholesterol levels in the RIO-Europe and RIO-Lipids studies.

In conclusion, although pharmacotherapy alone will not eradicate the epidemic of obesity, this study provides evidence that CB_1-receptor blockade may constitute a new, clinically relevant pharmacologic approach to improve the unfavorable cardiovascular risk profile in high-risk patients with dyslipidemia who are overweight or obese. The adverse-event profile of rimonabant observed in the RIO-Lipids study was found to be concordant with the results of the RIO-Europe study. Finally, the weight-loss–independent effect of rimonabant on plasma adiponectin levels is consistent with the reported in vitro effect of this CB_1-receptor blocker on adiponectin production by adipose cells.

APPENDIX

The following investigators and coinvestigators participated in the study: D. Carey, N. Wood, G. Wittert, D. Jesudason, P. Phillips, M.T. Kuruvila, A. Sverdlov, H. Sia, J. Proietto, K. Bate, P. Colman, L. Rando, M. Hooper, C. Ting, N. Kormas, T. Markovic, K. Steinbeck, I. Kormas, N. Caterson, S. Li, J. Hui, V. Wong, J.-P. Després, A. Tremblay, N. Alméras, P. Poirier, R. Aronson, M.E. Alexander, L.G. Goluboff, Y. Twum-Barima, P. Whitsitt, R. Verdonk, C. Li, J.-P. Ouellet, P. Marchand, M. Bezeau, R. Girard, F. Ross, R. Goldenberg, R. Schlosser, R. Aronson, M.-C. Audet, D. Bélanger, M. Boutin, A. Martel, R. Boucher, P.-P. Côté, G. Tellier, F. Cousineau, Y. Pesant, P. Chevalier, G. Laurin, G. Girard, A. Crépeau, L. Frenette, R. Bouchard, C. St.-Pierre, F. Turcotte, M. Loyer, M. Drapeau, P. Pelletier, A. Dugas, A. Rissanen, J. Puhakka, K. Pietilainen, P. Broas, S. Keinanen-Kiukaanniemi, M. Laakso, R. Pasquali, B. Ambrosi, L. Frittitta, C.M. Rotella, R. Vettor, X. Formiguera, A. Almenara, R. Gomis, M.J. Coves, J. Vidal, B. Moreno, J. Rivera, A. Jimenez, A. Zugasti, M.D. Rodriguez, J. Salas, M.J. Jimenez, L. Sjöström, A.M. Langkilde, K. Vikman-Adolfsson, C. Ehrnborg, U. Adamson, L. Adamson, A. von Dobeln, T. Kjellstrom, P. Katzman, R. Rosin, I. Lager, L. Eden, A. Pagnamenta, G. Noseda, C. Fragiacomo, J. Zerega, M. Ghielmetti, T. Reynaldos, A. Golay, V. Makoundou, C. Ries, G. Gastaldi, V. Giusti, M.A. Adamczyk, M.R. Modiano, C.L. Hannah, R.B. Salazar, R. Armbruster, F.E. Dunlap, D. Brune, E. Rufus, A.J. Heritch, J. Cavanaugh, A. Delpilar, M.A. Ziboh, S. Chipkin, B.L. Haag, M.P. Roy, R.J. Cooper, E. Cohen, S. Klugh, O.M. Quijano, V. Reddy, L. Metchick, B. Egan, W.H. Bestermann, K. Nashar, A. Jesri, D. Fiske, J.M. Houri, T. Evans, D.B. George, S.M. George, S. Polyhronopoulos, B.F. Scott, R.V. Steeves, J.L. Kantlehner, P.A. Warner, T.C. Harris, W.K. Kleinsteuber, G.T. Gerhard, S.J. Redmond, T. Passmore, E. Glover, C.R. Sullivan, P.N. Glover, C.L. Cerullo, J.H. Berry, S.C. Yerneni, R.M. Griffin, P.D. Nicholas, M.A. Borofsky, J.S. Weisberg, W. Santoro, C.H. Schmidley, J.A. Van Den Bosch, J.T. Lumley, D.F. Steffy, P.J. Baney, C.A. Wagner, E. Krishnan, L. Gringeri, A.F. Marchesani, C.W. Clark, D. Torelli, G.K. Phillips, L. Denton, S.M. Kneiss, L.G. Kelner, R. Rosenberg, S.B. Jones, D.B. Vine, A. Kivitz, S.P. Kafka, F.T. Murphy, V.M. Sommer, L.A. Krug, D.L. Rentz, S.K. Ritchey, M.J. Zumer, M. Dubeck, A. Maldonado, C. Cunningham, M.J. Koren, S. Greco, J.A. Jacqmein, D. Robinson, J.C. Hackenberg, D.M. Bartilluci, M.N. Lunde, M.J. Zarama-Medina, M.G. Somermeyer, E.A. Holum, S.L. McElroy, P.E. Keck, E. Nelson, R. Kotwal, S. Malhotra, L. Arnold, B. Martens, R. Kowatch, W.J. Mroczek, B.L. Berliner, J. Klein, A.R. George, W.P. Jennings, R. Nett, C.F. Serna, T.R. Weiss, M. Nides, D. Medway, H. Eisenbach, E. Marshall, S.E. Prohaska, R.E. Pruitt, D. Jacobus, R.W. Herring, J.B. Rosen, I.G. Carrasquilla, H.M. Silberman, C.K. Mitch-Gomez, S. Yahia, C.F. Yanes, S. Duncan-Garcia, S. Rosenblatt, J.M. Wilson, E.R. Lee, M.A. Flanagan, E.M. Lewiecki, E.W. Best, J. Chavez, I. Garcia, M. Gurule, L. Ierides, R.L. Romanik, G. Shockey, A.M. Germaine, K.L. Valderhaug, J.A. Brown, M. Smith, R. Laufer, L.D. Smith, R. Chan, C.R. Ellsworth, K.R. Becker, R.L. Goldman, W.B. Smith, A.B. Alper, G.M. Johnson, R.L. Gibson, R.K. Mautner, S.G. Swanson, J.J. Maly, P. Gillapsie, M.M. Snow, P. Railsback, J. Oden, R. Tanous, T.P. Hutchens, R.J. Bury, S.S. Bradley, J. Akhter, S.J. Scherr, K.R. Happel, M.J. Tonkon, E.R. Ross, N.C. Morcos, D.M. See, P. Rand, P.D. Toth, D.C. Weiser, J. Zavoral, J.M. Beard, C.J. Baumgartner, F.J. Zieve, J.R. Levy, S.K. Frederickson, D.I. Panebianco, K.A. Tidsel, B. Lindgren, and H. Zacur.

REFERENCES

1. Flier JS. Obesity wars: molecular progress confronts an expanding epidemic. Cell 2004;116:337-50.

2. Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. Nat Rev Drug Discov 2004;3:771-84.

3. Cota D, Marsicano G, Tschop M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. J Clin Invest 2003;112:423-31.

4. Horvath TL. Endocannabinoids and the regulation of body fat: the smoke is clearing. J Clin Invest 2003;112:323-6.

5. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258:1946-9.

6. Hanus L, Abu-Lafi S, Fride E, et al. 2-Arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor. Proc Natl Acad Sci U S A 2001;98:3662-5.

7. Howlett AC, Barth F, Bonner TI, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 2002;54:161-202.

8. Di Marzo V, Goparaju SK, Wang L, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature 2001;410:822-5.

9. Kirkham TC, Williams CM, Fezza F, Di Marzo V. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimula-

tion of eating by 2-arachidonoyl glycerol. Br J Pharmacol 2002;136:550-7.

10. Pagotto U, Pasquali R. Fighting obesity and associated risk factors by antagonising cannabinoid type 1 receptors. Lancet 2005; 365:1363-4.

11. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol 2004;24:29-33.

12. Jbilo O, Ravinet-Trillou C, Arnone M, et al. The CB1 receptor antagonist rimonabant reverses the diet-induced obesity phenotype through the regulation of lipolysis and energy balance. FASEB J 2005;19:1567-9.

13. Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. Mol Pharmacol 2003;63:908-14.

14. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005;365:1389-97.

15. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.

16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.

17. St-Pierre AC, Ruel IL, Cantin B, et al. Comparison of various electrophoretic characteristics of LDL particles and their relationship to the risk of ischemic heart disease. Circulation 2001;104:2295-9.

18. Laboratory test handbook. 4th ed. Hudson (Cleveland): Lexi-Comp, 1996.

19. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433-8.

20. Després JP. Drug treatment for obesity: we need more studies in men at higher risk of coronary events. BMJ 2001;322:1379-80.

21. Ross R, Dagnone D, Jones PJ, et al. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: a randomized, controlled trial. Ann Intern Med 2000;133:92-103.

22. Després JP, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 1990;10:497-511.

23. Tchernof A, Lamarche B, Prud'homme D, et al. The dense LDL phenotype: association with plasma lipoprotein levels, visceral obesity, and hyperinsulinemia in men. Diabetes Care 1996;19:629-37.

24. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999;282:2340-6.

25. Rainwater DL. Lipoprotein correlates of LDL particle size. Atherosclerosis 2000;148:151-8.

26. Assmann G. Pro and con: high-density lipoprotein, triglycerides, and other lipid subfractions are the future of lipid management. Am J Cardiol 2001;87:2B-7B.

27. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005;28:2289-304.

28. Lemieux I, Pascot A, Prud'homme D, et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. Arterioscler Thromb Vasc Biol 2001;21:961-7.

29. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation 2004;109:2818-25.

30. Tchernof A, Nolan A, Sites CK, Ades PA, Poehlman ET. Weight loss reduces C-reactive protein levels in obese postmenopausal women. Circulation 2002;105:564-9.

31. Heilbronn LK, Noakes M, Clifton PM. Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women. Arterioscler Thromb Vasc Biol 2001;21:968-70.

32. Staels B, Koenig W, Habib A, et al. Activation of human aortic smooth-muscle cells is inhibited by PPARalpha but not by PPAR-gamma activators. Nature 1998;393:790-3.

33. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001;286:64-70.

34. Meigs JB, D'Agostino RB Sr, Wilson PW, Cupples LA, Nathan DM, Singer DE. Risk variable clustering in the insulin resistance syndrome: the Framingham Offspring Study. Diabetes 1997;46:1594-600.

35. Kanai H, Tokunaga K, Fujioka S, Yamashita S, Kameda-Takemura KK, Matsuzawa Y. Decrease in intra-abdominal visceral fat may reduce blood pressure in obese hypertensive women. Hypertension 1996; 27:125-9.

36. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291:1730-7.

37. Spranger J, Kroke A, Mohlig M, et al. Adiponectin and protection against type 2 diabetes mellitus. Lancet 2003;361:226-8. [Erratum, Lancet 2002;361:1060.]

38. Côté M, Mauriège P, Bergeron J, et al. Adiponectinemia in visceral obesity: impact on glucose tolerance and plasma lipoprotein and lipid levels in men. J Clin Endocrinol Metab 2005;90:1434-9.

Copyright © 2005 Massachusetts Medical Society.

POWERPOINT SLIDES OF *JOURNAL* FIGURES AND TABLES

At the *Journal*'s Web site, subscribers can automatically create PowerPoint slides of *Journal* figures and tables. Click on a figure or table in the full-text version of any article at **www.nejm.org**, and then click on PowerPoint Slide for Teaching. A PowerPoint slide containing the image, with its title and reference citation, can then be downloaded and saved.