# Effect of Rimonabant on Progression of Atherosclerosis in Patients With Abdominal Obesity and Coronary Artery Disease

## The STRADIVARIUS Randomized Controlled Trial

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**Context** Abdominal obesity is associated with metabolic abnormalities and increased risk of atherosclerotic cardiovascular disease. However, no obesity management strategy has demonstrated the ability to slow progression of coronary disease.

**Objective** To determine whether weight loss and metabolic effects of the selective cannabinoid type 1 receptor antagonist rimonabant reduces progression of coronary disease in patients with abdominal obesity and the metabolic syndrome.

**Design, Setting, and Patients** Randomized, double-blinded, placebo-controlled, 2-group, parallel-group trial (enrollment December 2004-December 2005) comparing rimonabant with placebo in 839 patients at 112 centers in North America, Europe, and Australia.

**Interventions** Patients received dietary counseling, were randomized to receive rimonabant (20 mg daily) or matching placebo, and underwent coronary intravascular ultrasonography at baseline (n=839) and study completion (n=676).

**Main Outcome Measures** The primary efficacy parameter was change in percent atheroma volume (PAV); the secondary efficacy parameter was change in normalized total atheroma volume (TAV).

**Results** In the rimonabant vs placebo groups, PAV (95% confidence interval [CI]) increased 0.25% (–0.04% to 0.54%) vs 0.51% (0.22% to 0.80%) ($P=.22$), respectively, and TAV decreased 2.2 $mm^3$ (–4.09 to –0.24) vs an increase of 0.88 $mm^3$ (–1.03 to 2.79) ($P=.03$). In the rimonabant vs placebo groups, imputing results based on baseline characteristics for patients not completing the trial, PAV increased 0.25% (–0.04% to 0.55%) vs 0.57% (0.29% to 0.84%) ($P=.13$), and TAV decreased 1.95 $mm^3$ (–3.8 to –0.10) vs an increase of 1.19 $mm^3$ (–0.73 to 3.12) ($P=.02$). Rimonabant-treated patients had a larger reduction in body weight (4.3 kg [–5.1 to –3.5] vs 0.5 kg [–1.3 to 0.3]) and greater decrease in waist circumference (4.5 cm [–5.4 to –3.7] vs 1.0 cm [–1.9 to –0.2]) ($P<.001$ for both comparisons). In the rimonabant vs placebo groups, high-density lipoprotein cholesterol levels increased 5.8 mg/dL (4.9 to 6.8) (22.4%) vs 1.8 mg/dL (0.9 to 2.7) (6.9%) ($P<.001$), and median triglyceride levels decreased 24.8 mg/dL (–35.4 to –17.3) (20.5%) vs 8.9 mg/dL (–14.2 to –1.8) (6.2%) ($P<.001$). Rimonabant-treated patients had greater decreases in high-sensitivity C-reactive protein (1.3 mg/dL [–1.7 to –1.2] [50.3%] vs 0.9 mg/dL [–1.4 to –0.5] [30.9%]) and less increase in glycated hemoglobin levels (0.11% [0.02% to 0.20%] vs 0.40% [0.31% to 0.49%]) ($P<.001$ for both comparisons). Psychiatric adverse effects were more common in the rimonabant group (43.4% vs 28.4%, $P<.001$).

**Conclusions** After 18 months of treatment, the study failed to show an effect for rimonabant on disease progression for the primary end point (PAV) but showed a favorable effect on the secondary end point (TAV). Determining whether rimonabant is useful in management of coronary disease will require additional imaging and outcomes trials, which are currently under way.

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OBESITY HAS REACHED EPIdemic proportions in many developed countries, particularly the United States, where 66% of the adult population is considered overweight and 34% are obese, defined as a body mass index greater than 30.[1,2] Epidemiologists predict that the epidemic of obesity and its public health consequences will continue to increase over the next several decades, affecting both the developed and developing worlds.[3,4] An abdominal pattern of fat distribution produces

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the most profound metabolic abnormalities and is associated with an increased risk of atherosclerotic cardiovascular disease.[5-11] Metabolic and physiologic abnormalities associated with abdominal obesity include an increased incidence of type 2 diabetes or impaired glucose tolerance, hypertension, reduced levels of high-density lipoprotein cholesterol (HDL-C), and increased levels of triglycerides and biomarkers of systemic inflammation.[9-11]

Few strategies for management of obesity have yielded long-term success. Accordingly, there exists considerable interest in developing new pharmacological approaches to treatment of abdominal obesity and its metabolic consequences. One promising approach is inhibition of the cannabinoid type 1 ($CB_1$) receptors, which are present in both the central nervous system and peripheral tissues.[12] Inhibition of $CB_1$ receptors results in reduced food intake and decreased body weight and produces metabolic effects that include an increase in HDL-C levels and reductions in levels of triglycerides, high-sensitivity C-reactive protein (hsCRP), and glycated hemoglobin ($HbA_{1c}$) in patients with diabetes.[13-16]

The first $CB_1$ antagonist to reach the market is rimonabant, which is available in several countries but has not yet been approved by the US Food and Drug Administration (FDA). In June 2007, an FDA panel did not recommend approval of rimonabant pending clarification of safety issues, primarily psychiatric adverse effects, including anxiety and depression.[17,18]

Atherosclerosis progression is increased by various individual risk factors, including elevated levels of total or low-density lipoprotein cholesterol (LDL-C) and triglycerides, low levels of HDL-C, high systolic blood pressure, and diabetes.[19-24] Since a decrease in body weight and reduction in waist circumference are associated with favorable changes in the lipid profile, insulin sensitivity, and levels of hsCRP,[25,26] we sought to determine if administration of the $CB_1$ antagonist rimonabant could reduce the progression of coronary atherosclerosis in abdominally obese patients with the metabolic syndrome and preexisting coronary disease. The Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant—The Intravascular Ultrasound Study (STRADIVARIUS) used ultrasonographic coronary imaging to assess atherosclerosis progression. In recent years, this imaging modality has been commonly used in the serial assessment of atherosclerotic disease burden.[19]

## METHODS

### Study Design

The STRADIVARIUS trial was a prospective, multicenter, multinational, randomized, double-blinded, placebo-controlled, 2-group, parallel-group study. The trial involved 112 centers in North America (United States and Canada), Europe, and Australia. The institutional review boards of all participating centers approved the protocol, and all patients provided written informed consent.

Patients were eligible only if they also required coronary angiography for a clinical indication, which most often consisted of ischemic chest pain or an abnormal finding on a functional study, such as exercise testing or nuclear scintigraphy. Patients were eligible if they were 18 years of age or older, had a waist circumference greater than 88 cm (34.6 inches) for women or 102 cm (40.2 inches) for men, and either met prespecified criteria for the presence of the metabolic syndrome or were current smokers. The metabolic syndrome was defined as 2 or more of the following risk factors: triglyceride level greater than 150 mg/dL (to convert to millimoles per liter, multiply by 0.0113); HDL-C level less than 40 mg/dL (men) or 50 mg/dL (women) (to convert to millimoles per liter, multiply by 0.0259); fasting plasma glucose level greater than 110 mg/dL (to convert to millimoles per liter, multiply by 0.0555); or high blood pressure, defined as 140/90 mm Hg or greater or current use of antihypertensive medications. Current smoking was defined as consumption of more than 10 cigarettes per day. Patient eligibility required the clinically indicated angiogram to demonstrate at least 1 coronary obstruction with greater than 20% angiographic luminal diameter narrowing.

Major exclusion criteria included previous weight loss surgery, uncontrolled diabetes (defined as $HbA_{1c}$ level >10%), or a urine test result positive for tetrahydrocannabinol. Concomitant administration of other weight loss agents such as orlistat or sibutramine at baseline and during the trial was prohibited. To assess the safety of rimonabant in a broad population, the study intentionally did not exclude patients with a prior history of psychiatric disorders.

Race/ethnicity was assessed by the investigator or study coordinator. This information was collected to determine whether the response to therapy (efficacy and safety) differed among individuals with different racial or ethnic backgrounds.

### Baseline Catheterization and Intravascular Ultrasound

Prior publications have described the methods for intravascular ultrasound (IVUS) examination of the coronary arteries.[19-24,27,28] A single artery was selected for IVUS examination, generally the longest and least angulated major epicardial vessel. This artery must not have undergone prior revascularization, nor have greater than 50% luminal narrowing throughout a segment with a minimum length of 30 mm. Intracoronary nitroglycerin was administered to prevent vasospasm and standardize vessel tonicity. An ultrasonography catheter (Atlantis; Boston Scientific Scimed Inc, Maple Grove, Minnesota) was advanced into the target vessel and the imaging transducer positioned distal to an angiographically identifiable side branch.

The operator selected a starting point for the IVUS examination located as far distally as could be safely reached, to provide the longest possible vessel segment for quantitative analysis. Subsequently, the operator activated a motor drive that withdrew the transducer at a translation velocity of 0.5 mm/s. During this pullback, images were obtained at 30 frames/s and recorded on analog videotape. The study was screened for image quality in a core laboratory at the Cleveland Clinic, and only patients meeting prespecified im-

age quality requirements were eligible for inclusion in the study.

### Treatments and Clinic Visits

Following successful IVUS examination, all patients were scheduled for a randomization visit occurring within 2 weeks after baseline IVUS. During this visit, they were randomly assigned to receive either rimonabant, 20 mg daily, or a matching placebo, for 18 to 20 months. At the time of randomization, patients were referred to a dietician for instruction on a moderate reduced-calorie diet and, if appropriate, were counseled on smoking cessation. Investigators were instructed to institute appropriate risk factor modification according to local guidelines. The patients returned for scheduled clinic visits at baseline and at 3, 6, 12, and 18 months following randomization. Local laboratories performed routine biochemical measurements, and a central laboratory performed measurement of specialized biomarkers (Laval Hospital Laboratory, Quebec City, Quebec, Canada).

### Follow-up IVUS Examination

After an 18- to 20-month treatment period, actively participating patients underwent repeat IVUS examination, regardless of whether they continued to take study drug (intent-to-treat approach). If a patient required coronary angiography for a clinical indication between 12 and 18 months following enrollment, an end-of-study IVUS examination was performed to avoid subjecting patients to an additional invasive procedure at the final 18-month visit. During the follow-up study, IVUS examination was repeated using a motorized pullback procedure identical to that used in the initial study, beginning just distal to the originally selected distal side branch. This procedure was designed to obtain a series of cross-sectional images at sites identical to those in the original examination.

### Randomization and Allocation Concealment

The patients and all study personnel were blinded to treatment assignment. The randomization was performed using an interactive voice response system that used a preestablished randomization code of randomly permuted blocks. The study specified a balanced (1:1) treatment allocation, stratified by center.

### Core Laboratory Analysis

Images were analyzed in a core laboratory dedicated to measurement of IVUS studies. For each pullback sequence, a technician began analysis at the distal branch site originally selected by the investigator and continued by analyzing every 60th image in the sequence. Because the pullback speed was 0.5 mm/s, this procedure identified cross-sections spaced exactly 1.0 mm apart. Intravascular ultrasound measurements were performed in accordance with the standards of the American College of Cardiology and European Society of Cardiology.[29] Using customized software (ImageJ version 1.29w; National Institutes of Health, Bethesda, Maryland), the technician performed a calibration by measuring 1-mm grid marks in the image. Manual planimetry was used to trace the leading edges of the luminal and external elastic membrane (EEM) borders. Previous reports have established the accuracy and reproducibility of this method.[30]

### Calculation of IVUS Efficacy Parameters

The primary efficacy parameter, percent atheroma volume (PAV), was calculated as:

$$PAV = [\Sigma(EEM_{CSA} - LUMEN_{CSA})/\Sigma EEM_{CSA}] \times 100,$$

where $EEM_{CSA}$ is the EEM cross-sectional area and $LUMEN_{CSA}$ is the luminal cross-sectional area.

A secondary efficacy parameter, normalized total atheroma volume (TAV), was calculated by first determining the mean atheroma area per cross-section as:

$$\text{Mean atheroma area} = \Sigma(EEM_{CSA} - LUMEN_{CSA})/n,$$

where $EEM_{CSA}$ is the EEM cross-sectional area, $LUMEN_{CSA}$ is the luminal cross-sectional area, and n is the number of matched evaluable cross-sections in the pullback at baseline and follow-up.

Normalized TAV for each patient was calculated as the mean atheroma area multiplied by the median number of matched cross-sections in pullbacks for all patients completing the trial. This procedure adjusts for pullbacks with differing numbers of measured cross-sections, resulting in an equal weighting of each individual patient in computing efficacy results.

Percent atheroma volume was selected as the primary efficacy parameter because this end point has exhibited the least variability in multiple previous IVUS trials for a diverse set of therapeutic interventions.[20-24]

### Exploratory IVUS Analyses

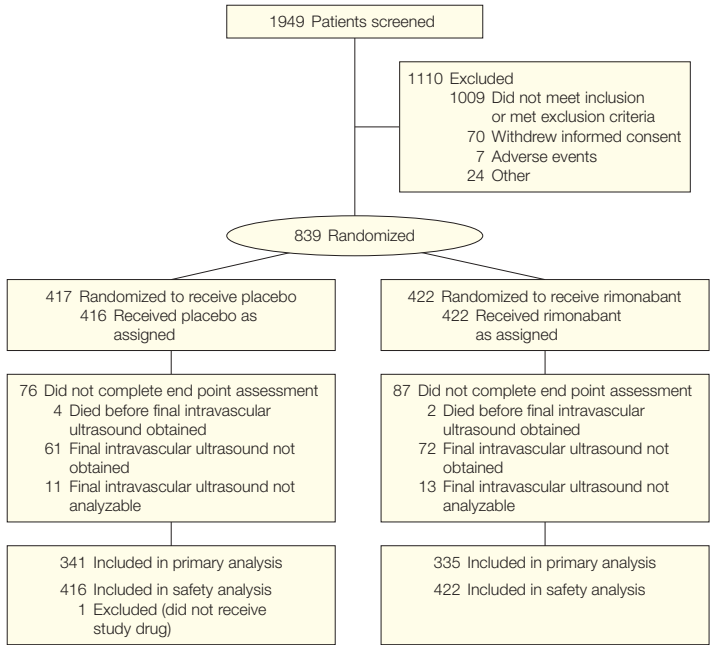
Two additional exploratory IVUS efficacy measures were calculated, the change in average maximum atheroma thickness and the change in atheroma volume in the most diseased 10-mm subsegment. Although not prespecified, both of these end points have been used in previous IVUS trials and were assessed to provide additional insight into the effects of rimonabant on coronary atherosclerosis.

### Clinical Outcomes and Safety Measures

Although the study was not powered to assess clinical outcomes, patients underwent follow-up for occurrence of major cardiovascular adverse events including myocardial infarction, stroke, cardiovascular death, and hospitalization for unstable angina, revascularization (surgical or via percutaneous intervention), or transient ischemic attack. The protocol specified inclusion of events beginning with first administration of study drug, with patients censored at the last known date of any contact. Other adverse events were assessed from first administration of study drug until 75 days following the final administration of study drug. All adverse events were investigator-reported using the standardized Medical Dictionary for Regulatory Activities.

After initiation of the trial, evolving data from other rimonabant studies indicated a potential for neurologic and

**Figure 1.** Flow of Patients Through Trial




psychiatric adverse events. Accordingly, a detailed questionnaire was developed and added to the patient assessment performed by personnel at each site during all subsequent study-related visits to standardize reporting (protocol amendment dated September 30, 2005).

### Statistical Methods

The study protocol and statistical analysis plan specified that the primary efficacy analysis include all randomized patients with an evaluable IVUS examination result both at baseline and after 12 or more months of treatment, regardless of whether the patient actually received study drug or complied with the study protocol (modified intent-to-treat approach including patients with evaluable baseline and follow-up IVUS results). The statistical analysis plan defined tests of normality for the efficacy parameters and specified nonparametric testing if the data were not normally distributed. Safety analyses included all patients who received at least 1 dose of study drug.

The primary efficacy parameter, the change in PAV, was analyzed using an analysis of covariance model, with treatment as a fixed effect and baseline as a covariate. The interaction between baseline value and treatment were also evaluated. A sensitivity analysis was performed using a multiple imputation procedure (PROC MI in SAS) to impute the IVUS end points for those who did not have follow-up IVUS performed. Changes in laboratory parameters were analyzed using a mixed model for repeated measures with terms for baseline value, treatment, visit, and the interaction between treatment and visit. Least-square means (95% confidence intervals [CIs]) are reported.

Power calculations assumed a treatment difference of 1.3% with a common SD of 4.9%, based on the outcomes for a previous IVUS trial comparing intensive vs moderate lipid lowering.[23] These assumptions provided 90% power for a sample size of 300 evaluable patients per treatment group. Invasive regression-progression trials routinely enroll excess patients to account for failure to obtain follow-up examinations in all patients. Based on prior experience, the STRADIVARIUS trial assumed that 25% of patients would not complete a final IVUS examination. Accordingly, the protocol specified randomization of 800 patients (400 per study group) to account for noncompleters. Analyses were performed using SAS Version 8.2 (SAS Institute, Cary, North Carolina).

## RESULTS

### Patient Population

Between December 2004 and December 2005, 1949 patients were screened at 126 sites in the United States, Canada, Europe, and Australia. The flow of patients in the trial is reported in FIGURE 1, including reasons for screening failures and noncompletion. Of the screened patients, 839 met all inclusion and exclusion criteria, including an acceptable baseline IVUS examination, and received study drug at 112 centers. A total of 676 patients had evaluable IVUS examinations at baseline and after the prespecified minimum of 320 days of follow-up.

Baseline demographic characteristics and concomitant medications for the 839 randomized patients are reported in TABLE 1. There were no major differences in baseline characteristics for the 676 patients who had evaluable IVUS examinations at both time points and the 163 patients who did not complete IVUS assessment (data not shown). On average, patients were younger than 60 years; approximately two-thirds were men. Patients were abdominally obese, with a mean waist circumference of approximately 117 cm (46 in) and a mean body mass index of 35 (calculated as weight in kilograms divided by height in meters squared). A high percentage of patients had obesity-related comorbid conditions specified in the inclusion criteria, including hypertension and dyslipidemia. There were no significant differences in baseline characteristics for patients randomized to the 2 treatment groups.

### Laboratory Outcomes

TABLE 2 summarizes laboratory values, body weight, waist circumference, and blood pressure at baseline and follow-up for the 676 patients who had evaluable baseline and follow-up IVUS examinations and who contributed to

the efficacy analysis. Patients randomized to rimonabant lost more weight and experienced a greater reduction in waist circumference compared with placebo-treated patients. Compared with placebo, there were also significant differences in the reduction in triglyceride and hsCRP levels, elevation of HDL-C levels, and change in levels of $HbA_{1c}$ and insulin. However, LDL-C levels and blood pressure changes did not differ significantly between treatment groups. The changes over time in weight, waist circumference, and levels of HDL-C, triglycerides, insulin, and $HbA_{1c}$ are illustrated in FIGURE 2. These data show significant differences in levels of HDL-C, triglycerides, hsCRP, $HbA_{1c}$, and insulin in the rimonabant treatment group at both 12 and 18 months following randomization.

### IVUS Efficacy Analyses

TABLE 3 reports the results for the IVUS analyses, showing baseline values, follow-up values, and changes from baseline during the study. The least-square mean (95% CI) change in the primary efficacy parameter, PAV, was 0.51% (0.22% to 0.80%) in the placebo group and 0.25% (–0.04% to 0.54%) in the rimonabant group ($P$=.22). The least-square mean (95% CI) change in the prespecified secondary efficacy parameter, normalized TAV, was 0.88 $mm^3$ (–1.03 to 2.79) in the placebo group and –2.2 $mm^3$ (–4.09 to –0.24) in the rimonabant group ($P$=.03). The –2.2-$mm^3$ change from baseline in TAV in the rimonabant group was statistically significant ($P$=.03).

### Subgroups

FIGURE 3 reports the results for the primary efficacy parameter in a variety of subgroups. Although most categories showed no heterogeneity, 2 subgroups showed statistically significant interactions. For patients not taking a statin at baseline, change in PAV was larger in the placebo group compared with the rimonabant group (least-square mean difference [95% CI], –1.31 [–2.29 to –0.33]), whereas patients taking a statin showed similar results in both treatment groups (least-square mean difference [95% CI], –0.06 [–0.51 to 0.39]) ($P$=.03 for subgroup interaction).

There was also a subgroup interaction for patients dichotomized by baseline triglyceride levels. For patients with median triglyceride levels (≥140.0 mg/dL), the least-square mean (95% CI) treatment difference was –0.77 (–1.35 to –0.18) favoring rimonabant, whereas patients with triglyceride levels less than median at baseline showed no treatment difference (0.16% [–0.40 to 0.72]) ($P$=.03 for subgroup interaction).

### Exploratory IVUS Analyses

Because the primary and secondary end points showed differing results, exploratory analyses were performed for additional efficacy parameters used in previous IVUS studies. The least-square mean (95% CI) change in mean

**Table 1.** Baseline Characteristics of the Study Population (n = 839)[a]

| Characteristic | Placebo (n = 417) | Rimonabant (n = 422) | *P* Value[b] |
|---|---|---|---|
| Age, mean (SD), y | 57.5 (9.8) | 57.9 (9.5) | .57 |
| Men, No. (%) | 271 (65.0) | 274 (64.9) | .99 |
| Race, No. (%)[c] | | | |
| White | 397 (95.2) | 407 (96.4) | .37 |
| Black | 17 (4.1) | 12 (2.8) | .33 |
| Waist circumference, mean (SD), cm | 117.5 (14.1) | 117.3 (13.6) | .82 |
| Weight, mean (SD), kg | 103.5 (21.7) | 103.5 (20.5) | .99 |
| Body mass index, mean (SD)[d] | 35.3 (6.2) | 35.3 (5.9) | .96 |
| Comorbid conditions, No. (%) | | | |
| Unstable angina/NSTEMI[e] | 95 (22.8) | 112 (26.5) | .21 |
| Hypertension | 366 (87.8) | 369 (87.4) | .89 |
| Prior MI | 115 (27.6) | 126 (29.9) | .47 |
| Psychiatric disease | 102 (24.5) | 108 (25.6) | .71 |
| Qualifying characteristics, No. (%)[f] | | | |
| Abdominal obesity | 415 (99.5) | 422 (100) | .25[g] |
| Metabolic syndrome | 382 (91.6) | 397 (94.1) | .17 |
| Current smoker | 111 (26.6) | 126 (29.9) | .30 |
| Metabolic syndrome + smoking | 79 (18.9) | 103 (24.4) | .06 |
| Metabolic risk factors, No. (%) | | | |
| Triglycerides ≥150 mg/dL | 250 (60.0) | 241 (57.1) | .40 |
| HDL-C <40 mg/dL | 268 (64.3) | 275 (65.2) | .79 |
| Fasting plasma glucose ≥110 mg/dL | 213 (51.1) | 223 (52.8) | .63 |
| Hypertension[h] | 369 (88.5) | 379 (89.8) | .54 |
| Baseline medications, No. (%) | | | |
| Aspirin | 380 (91.1) | 387 (91.7) | .77 |
| Clopidogrel or ticlopidine | 254 (60.9) | 252 (59.7) | .72 |
| β-Blockers | 294 (70.5) | 293 (69.4) | .74 |
| ACE inhibitors or ARBs | 286 (68.6) | 293 (69.4) | .79 |
| Statins | 341 (81.8) | 348 (82.5) | .79 |
| Insulin | 49 (11.8) | 47 (11.1) | .78 |
| Oral hypoglycemic agents | 124 (29.7) | 129 (30.6) | .79 |
| Benzodiazepines[i] | 197 (47.2) | 202 (47.9) | .86 |
| Antidepressants | 80 (19.2) | 77 (18.2) | .73 |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker ; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction.
SI conversion factors: To convert HDL-C values to mmol/L, multiply by 0.0259; triglyceride values to mmol/L, by 0.0113; and fasting plasma glucose values to mmol/L, by 0.0555.
[a] All randomized patients.
[b] $\chi^2$ test was performed for categorical variables and *t* test performed for continuous variables.
[c] Assessed by investigator or study coordinator.
[d] Calculated as weight in kilograms divided by height in meters squared.
[e] At the time of current admission.
[f] Inclusion criteria per investigator report.
[g] By Fisher exact test.
[h] Blood pressure ≥140/90 mm Hg or current use of antihypertensive medication.
[i] Includes acute administration during cardiac catheterization.

**Table 2.** Body Weight, Waist Circumference, Metabolic Outcomes, and Blood Pressure in Patients Completing the Trial (n = 676)[a]

| Parameter | Placebo (n = 341) | | Rimonabant (n = 335) | | *P* Value |
|---|---|---|---|---|---|
| | No. | Value | No. | Value | |
| **Baseline Values** | | | | | |
| Body weight, mean (SD), kg | | 103.4 (21.7) | | 103.2 (20.3) | .89 |
| Waist circumference, mean (SD), cm | 340 | 117.3 (14.3) | 335 | 116.9 (13.3) | .71 |
| LDL-C, mean (SD), mg/dL | 330 | 89.5 (32.2) | 328 | 91.9 (27.9) | .29 |
| HDL-C, mean (SD), mg/dL | 337 | 37.6 (9.9) | 332 | 38.5 (10.4) | .24 |
| Triglycerides, median (IQR), mg/dL | 337 | 140.0 (102.8 to 197.6) | 332 | 140.0 (101.9 to 200.2) | .77 |
| hsCRP, median (IQR), mg/L | 336 | 3.8 (1.9 to 7.2) | 332 | 3.4 (1.5 to 6.3) | .10 |
| $HbA_{1c}$, mean (SD), % | | | | | |
| All | 314 | 5.8 (1.1) | 301 | 5.8 (1.1) | .89 |
| With diabetes | 118 | 6.6 (1.1) | 107 | 6.7 (1.2) | .92 |
| Fasting insulin levels, median (IQR), pmol/L | 334 | 110.0 (71.1 to 162.3) | 331 | 111.3 (77.4 to 179.3) | .24 |
| Blood pressure, mean (SD), mm Hg | | | | | |
| Systolic | | 129.3 (17.1) | | 129.4 (15.1) | .94 |
| Diastolic | | 76.7 (9.9) | | 76.9 (9.8) | .75 |
| **End-of-Study (18-mo) Values** | | | | | |
| Body weight, mean (SD), kg | 340 | 102.8 (21.9) | 331 | 98.8 (20.9) | .01 |
| Waist circumference, mean (SD), cm | 333 | 116.4 (14.9) | 327 | 112.2 (14.9) | <.001 |
| LDL-C, mean (SD), mg/dL | 331 | 86.3 (30.3) | 319 | 87.6 (30.5) | .57 |
| HDL-C, mean (SD), mg/dL | 335 | 39.6 (11.2) | 323 | 44.2 (12.5) | <.001 |
| Triglycerides, median (IQR), mg/dL | 335 | 132.9 (95.7 to 189.6) | 323 | 112.5 (78.8 to 160.4) | <.001 |
| hsCRP, median (IQR), mg/L | 333 | 2.9 (1.2 to 5.5) | 320 | 1.6 (0.7 to 4.0) | <.001 |
| $HbA_{1c}$, mean (SD), % | | | | | |
| All | 314 | 6.2 (1.2) | 298 | 5.9 (1.0) | <.001 |
| With diabetes | 121 | 7.1 (1.3) | 109 | 6.5 (1.2) | .001 |
| Fasting insulin levels, median (IQR), pmol/L | 332 | 119.5 (73.2 to 191.6) | 322 | 103.3 (64.7 to 153.2) | .003 |
| On-treatment blood pressure, mean (SD), mm Hg | | | | | |
| Systolic | 341 | 132.3 (13.2) | 335 | 131.5 (13.2) | .43 |
| Diastolic | 341 | 77.5 (7.4) | 335 | 76.8 (7.4) | .23 |
| **Change From Baseline[b]** | | | | | |
| Body weight, LS mean (95% CI), kg | | −0.5 (−1.3 to 0.3) | | −4.3 (−5.1 to −3.5) | <.001 |
| Waist circumference, LS mean (95% CI), cm | | −1.0 (−1.9 to −0.2) | | −4.5 (−5.4 to −3.7) | <.001 |
| LDL-C, mg/dL | | | | | |
| LS mean (95% CI) | | −3.2 (−6.1 to −0.3) | | −3.8 (−6.7 to −0.8) | .78 |
| Percentage change (95% CI) | | 1.7% (−1.7 to 5.2) | | 0.44% (−3.1 to 3.9) | |
| HDL-C, mg/dL | | | | | |
| LS mean (95% CI) | | 1.8 (0.9 to 2.7) | | 5.8 (4.9 to 6.8) | <.001 |
| Percentage change (95% CI) | | 6.9% (−1.1 to 14.8) | | 22.4% (14.4 to 30.4) | |
| Triglycerides, mg/dL | | | | | |
| Median (95% CI)[c] | | −8.9 (−14.2 to −1.8) | | −24.8 (−35.4 to −17.3) | <.001 |
| Percentage change (95% CI)[d] | | −6.2% (−10.2 to −1.9) | | −20.5% (−24.0 to −16.8) | |
| hsCRP, mg/L | | | | | |
| Median (95% CI)[c] | | −0.9 (−1.4 to −0.5) | | −1.3 (−1.7 to −1.2) | <.001 |
| Percentage change (95% CI)[d] | | −30.9% (−37.7 to −23.3) | | −50.3% (−55.3 to −44.8) | |
| $HbA_{1c}$, LS mean (95% CI), % | | | | | |
| All | | 0.40 (0.31 to 0.49) | | 0.11 (0.02 to 0.20) | <.001 |
| With diabetes | | 0.42 (0.22 to 0.62) | | −0.13 (−0.34 to 0.09) | <.001 |
| Fasting insulin levels, pmol/L | | | | | |
| Median (95% CI)[c] | | 7.8 (−1.9 to 18.6) | | −13.7 (−23.0 to −4.2) | <.001 |
| Percentage change (95% CI)[d] | | 7.9% (0.60 to 15.7) | | −10.6% (−16.7 to −4.0) | |
| Blood pressure, LS mean (95% CI), mm Hg[e] | | | | | |
| Systolic | | 2.9 (1.7 to 4.1) | | 2.1 (0.8 to 3.3) | .34 |
| Diastolic | | 0.7 (−0.03 to 1.4) | | −0.09 (−0.8 to 0.6) | .13 |

Abbreviations: CI, confidence interval; $HbA_{1c}$, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LS, least-square.

SI conversion factors: To convert LDL-C and HDL-C values to mmol/L, multiply by 0.0259; triglyceride values to mmol/L, by 0.0113.

[a] Modified intent-to-treat population: all patients with a baseline and follow-up intravascular ultrasound examination who contributed to the primary efficacy parameter; n = 341 for placebo and n = 335 for rimonabant unless otherwise noted.

[b] Least-square means and 95% CIs estimated using a 2-way analysis of variance with terms for baseline value, treatment group, visit, and treatment × visit interaction.

[c] Calculated using bootstrap resampling.

[d] Estimated using the logarithm of the ratio of follow-up value to baseline value as the dependent variable.

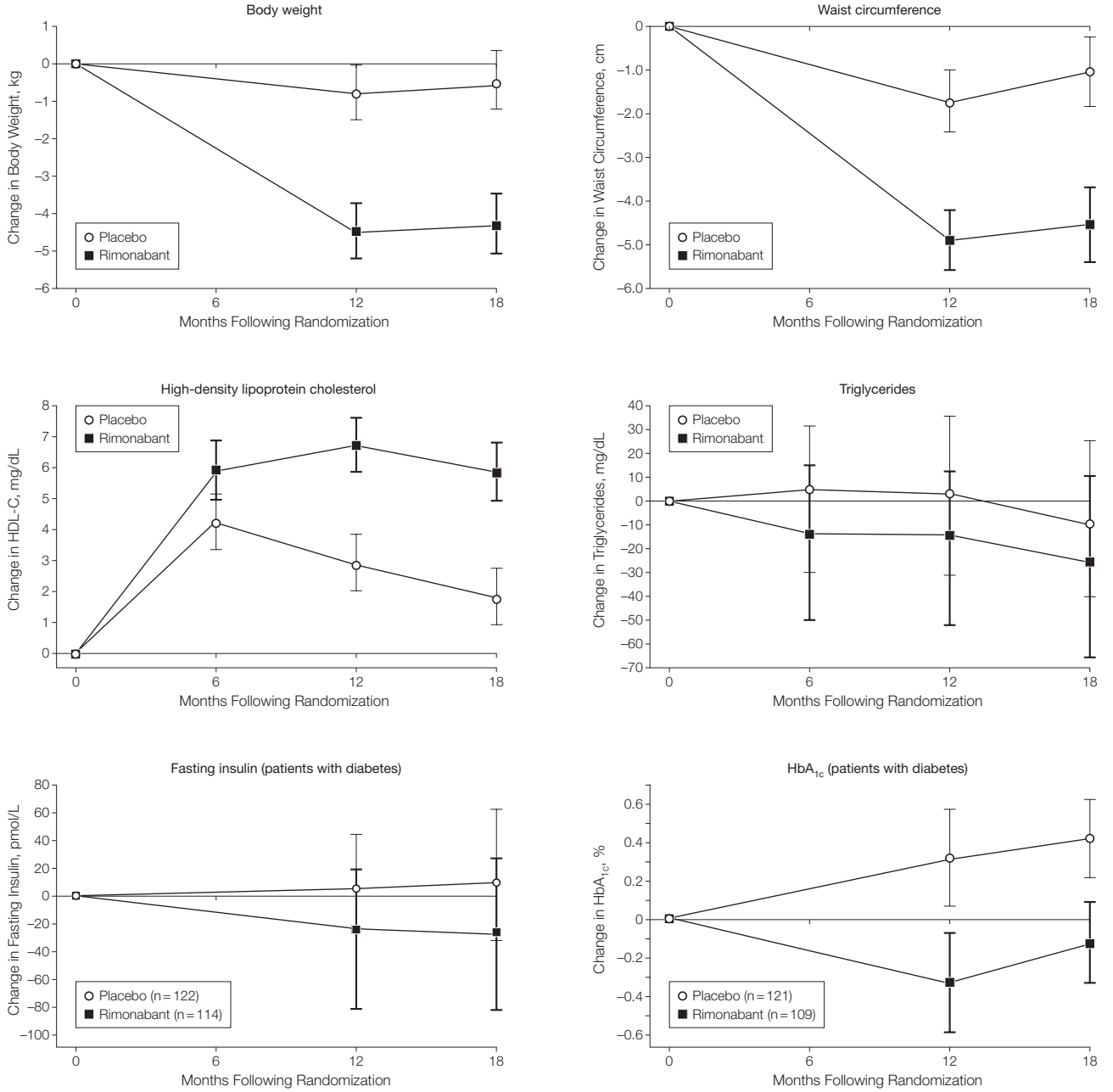
[e] Change in mean on-treatment blood pressure.

maximum atheroma thickness increased 0.01 mm (0.006 to 0.020) in the placebo group and decreased 0.0006 mm (–0.008 to 0.007) in the rimonabant group ($P$=.01). The change in atheroma volume in the 10-mm most severely diseased subsegment decreased 0.89 $mm^3$ (–1.791 to 0.018) for placebo and 1.47 $mm^3$ (–2.36 to –0.59) for rimonabant ($P$=.37).

### IVUS Results Imputing Noncompleters

To determine the potential influence of patients randomized in the trial who did not complete IVUS assessment, we per-

**Figure 2.** Effects of Rimonabant on Body Weight, Waist Circumference, and Levels of High-Density Lipoprotein Cholesterol (HDL-C), Triglycerides, Fasting Insulin, and Glycated Hemoglobin ($HbA_{1c}$)




Data markers and error bars indicate least-square means and 95% confidence intervals, respectively, for body weight, waist circumference, HDL-C, and $HbA_{1c}$ and medians and interquartile ranges for triglycerides and fasting insulin. SI conversion factors; To convert HDL-C values to mmol/L, multiply by 0.0259; triglyceride values to mmol/L, by 0.0113.

formed a post hoc sensitivity analysis in which values were imputed for noncompleters based on their baseline characteristics. The imputation technique assigned changes in these efficacy end points for each noncompleter based on the patient's baseline characteristics, including demographics, laboratory values, and baseline atheroma volumes. For the primary efficacy parameter, PAV, the placebo group showed a mean (95% CI) increase of 0.57% (0.29% to 0.84%), vs 0.25% (–0.04% to 0.55%) for the rimonabant group ($P$=.13). For the prespecified secondary efficacy parameter, TAV, the placebo group showed a mean (95% CI) increase of 1.19 $mm^3$ (–0.73 to 3.12), vs –1.95 $mm^3$ (–3.8 to –0.10) for the rimonabant group ($P$=.02).

## Cardiovascular Outcomes and Mortality

TABLE 4 reports the incidence of major cardiovascular adverse events, the most common treatment-emergent adverse events, and the most common reasons for discontinuation of study drug as a result of adverse events. The composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina, revascularization, or transient ischemic attack occurred in 46 placebo-treated patients (11%) and 44 rimonabant-treated patients (10.4%) ($P$=.79). The individual components of this end point did not show any consistent pattern suggesting differences between placebo and rimonabant. Eight deaths (2 cardiovascular and 6 noncardiovascular) occurred in placebo-treated patients, and 2 (noncardiovascular) occurred in rimonabant-treated patients ($P$=.06) (Table 4).

## Adverse Events

The most common treatment-emergent adverse events included psychiatric disorders, which occurred in 118 placebo-treated patients (28.4%) and 183 rimonabant-treated patients (43.4%) ($P$<.001). These adverse events consisted primarily of an increase in anxiety and depression. Severe psychiatric adverse effects, defined as major depression, suicidal ideation, or attempted or successful suicide occurred with similar frequency in the placebo- and

**Table 3.** Baseline, Follow-up, and Change from Baseline in Intravascular Ultrasound End Points in Patients Completing the Trial (n = 676)

| | Prespecified Primary and Secondary End Points | | | | |
|---|---|---|---|---|---|
| | Placebo (n = 341) | | Rimonabant (n = 335) | | |
| | Mean (SD) | Median (IQR) | Mean (SD) | Median (IQR) | *P* Value |
| Baseline examination | | | | | |
| PAV[a] | 37.5 (7.5) | 37.9 (32.1 to 43.3) | 37.5 (8.0) | 37.7 (31.2 to 42.4) | .58 |
| TAV,[b] $mm^3$ | 197.5 (82.0) | 184.8 (133.8 to 251.7) | 191.7 (81.4) | 183.9 (135.0 to 227.2) | .35 |
| Follow-up examination[c] | | | | | |
| PAV[a] | 38.0 (7.7) | 38.3 (32.8 to 43.6) | 37.7 (7.9) | 37.4 (31.8 to 42.7) | .40 |
| TAV,[b] $mm^3$ | 198.5 (85.5) | 184.9 (129.6 to 253.9) | 189.7 (78.8) | 187.1 (132.1 to 229.9) | .30 |
| | LS Mean (SE) [95% CI] | *P* Value (Change From Baseline) | LS Mean (SE) [95% CI] | *P* Value (Change From Baseline) | *P* Value[d] |
| Nominal change from baseline | | | | | |
| PAV[a] | 0.51 (0.15) [0.22 to 0.80] | <.001 | 0.25 (0.15) [–0.04 to 0.54] | .09 | .22 |
| TAV,[b] $mm^3$ | 0.88 (0.97) (–1.03 to 2.79) | .37 | –2.2 (0.98) [–4.09 to –0.24] | .03 | .03 |
| | Exploratory (Nonprespecified End Points) | | | | |
| | Mean (SD) | Median (IQR) | Mean (SD) | Median (IQR) | *P* Value |
| Baseline examination | | | | | |
| Mean maximum atheroma thickness, mm | 0.75 (0.22) | 0.77 (0.60 to 0.90) | 0.74 (0.23) | 0.75 (0.57 to 0.88) | .30 |
| Atheroma volume at 10-mm most diseased segment, $mm^3$ | 60.6 (26.3) | 60.1 (39.9 to 78.0) | 55.6 (28.1) | 52.6 (34.8 to 72.3) | .009 |
| Follow-up examination[c] | | | | | |
| Mean maximum atheroma thickness, mm | 0.77 (0.23) | 0.76 (0.60 to 0.92) | 0.74 (0.23) | 0.75 (0.57 to 0.88) | .16 |
| Atheroma volume in 10-mm most diseased segment, $mm^3$ | 59.6 (26.5) | 57.7 (39.6 to 75.0) | 54.3 (26.8) | 50.4 (34.5 to 70.8) | .01 |
| | LS Mean (SE) [95% CI] | *P* Value (Change From Baseline) | LS Mean (SE) [95% CI] | *P* Value (Change From Baseline) | *P* Value[d] |
| Nominal change from baseline | | | | | |
| Mean maximum atheroma thickness, mm | 0.01 (0.004) [0.006 to 0.020] | <.001 | –0.0006 (0.004) [–0.008 to 0.007] | .88 | .01 |
| Atheroma volume in 10-mm most diseased segment, $mm^3$ | –0.89 (0.46) [–1.791 to 0.018] | .05 | –1.47 (0.45) [–2.356 to –0.587] | .001 | .37 |

Abbreviations: IQR, interquartile range; LS, least-square; PAV, percent atheroma volume; TAV, nominal total atheroma volume.
[a] Primary efficacy parameter.
[b] Secondary efficacy parameter.
[c] Follow-up values are unadjusted.
[d] *P* values from 2-way analysis of variance (mixed model) with terms for treatment and baseline values.

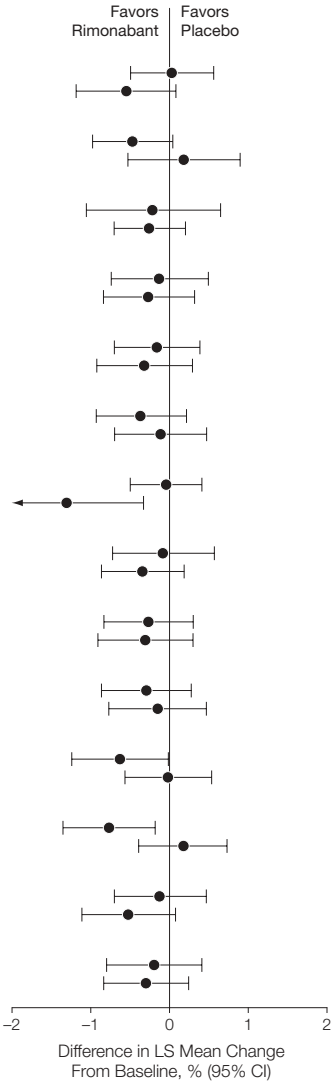
rimonabant-treated patients (3.8% vs 4.7%, respectively; $P=.52$). A single patient in the placebo group attempted suicide, and a single patient in the rimonabant group successfully completed suicide. Gastrointestinal tract disorders also showed an imbalance between the 2 groups, occurring in 74 placebo-treated patients (17.8%) and 142 rimonabant-treated patients (33.6%) ($P<.001$). Adverse events were more likely to lead to drug discontinuation in the rimonabant-treated patients compared with placebo-treated patients (74 [17.5%] vs 31 [7.5%], $P<.001$). The cumulative rates of drug discontinuation are shown in FIGURE 4.

## COMMENT

Abdominal obesity, even in the absence of type 2 diabetes, is associated with a constellation of metabolic and physiological abnormalities that amplify the risk for atherosclerotic cardiovascular disease.[11] The most relevant risk factors related to abdominal obesity include hypertension, low levels of HDL-C, increased levels of triglycerides and hsCRP, and impaired glucose tolerance. In recent years, this clustering of these risk factors has been termed the metabolic syndrome and is now recognized by guidelines as a sec-

**Figure 3.** Primary Efficacy Parameter (Percent Atheroma Volume) in Subgroups

| Baseline Characteristics | No. of Patients: Placebo | No. of Patients: Rimonabant | Percentage Atheroma Volume Mean LS Change From Baseline, % (SE): Placebo | Percentage Atheroma Volume Mean LS Change From Baseline, % (SE): Rimonabant | Treatment Difference, % (95% CI) | *P* Value |
|---|---|---|---|---|---|---|
| Age, y | | | | | | |
| ≥58 | 173 | 181 | 0.23 (0.19) | 0.25 (0.19) | 0.02 (–0.51 to 0.55) | .17 |
| <58 | 168 | 154 | 0.81 (0.22) | 0.25 (0.23) | –0.56 (–1.19 to 0.07) | |
| Sex | | | | | | |
| Male | 224 | 226 | 0.63 (0.18) | 0.16 (0.18) | –0.47 (–0.98 to 0.03) | .15 |
| Female | 117 | 109 | 0.28 (0.25) | 0.44 (0.26) | 0.16 (–0.54 to 0.87) | |
| Smoker | | | | | | |
| Yes | 94 | 98 | 0.69 (0.31) | 0.47 (0.30) | –0.22 (–1.08 to 0.63) | .96 |
| No | 247 | 237 | 0.43 (0.16) | 0.17 (0.17) | –0.26 (–0.72 to 0.19) | |
| Change in weight | | | | | | |
| ≥Median (–1.8 kg) | 211 | 126 | 0.55 (0.19) | 0.41 (0.25) | –0.13 (–0.75 to 0.48) | .75 |
| <Median | 129 | 208 | 0.45 (0.23) | 0.18 (0.18) | –0.27 (–0.85 to 0.31) | |
| Body mass index | | | | | | |
| ≥Median (34.3) | 175 | 164 | 0.47 (0.20) | 0.29 (0.20) | –0.17 (–0.72 to 0.37) | .71 |
| <Median | 166 | 171 | 0.55 (0.22) | 0.22 (0.22) | –0.33 (–0.94 to 0.28) | |
| Systolic blood pressure | | | | | | |
| ≥Median (130 mm Hg) | 177 | 167 | 0.78 (0.20) | 0.41 (0.21) | –0.37 (–0.94 to 0.21) | .55 |
| <Median | 164 | 168 | 0.22 (0.21) | 0.10 (0.21) | –0.12 (–0.70 to 0.46) | |
| Statin therapy | | | | | | |
| Yes | 287 | 273 | 0.29 (0.16) | 0.23 (0.16) | –0.06 (–0.51 to 0.39) | .03 |
| No | 54 | 62 | 1.66 (0.36) | 0.35 (0.34) | –1.31 (–2.29 to –0.33) | |
| Diabetes | | | | | | |
| Yes | 127 | 121 | 0.69 (0.23) | 0.61 (0.24) | –0.08 (–0.73 to 0.56) | .56 |
| No | 214 | 214 | 0.40 (0.19) | 0.06 (0.19) | –0.34 (–0.86 to 0.18) | |
| Baseline HDL-C | | | | | | |
| ≥Median (36.8 mg/dL) | 165 | 170 | 0.40 (0.20) | 0.13 (0.20) | –0.27 (–0.83 to 0.30) | .92 |
| <Median | 172 | 162 | 0.68 (0.21) | 0.37 (0.22) | –0.31 (–0.91 to 0.29) | |
| HDL-C increase | | | | | | |
| ≥Median (3.9 mg/dL) | 143 | 193 | 0.33 (0.22) | 0.02 (0.19) | –0.30 (–0.86 to 0.26) | .75 |
| <Median | 194 | 138 | 0.70 (0.20) | 0.53 (0.24) | –0.16 (–0.78 to 0.45) | |
| Baseline LDL-C | | | | | | |
| ≥Median (87.1 mg/dL) | 156 | 175 | 1.01 (0.22) | 0.39 (0.21) | –0.62 (–1.23 to –0.02) | .15 |
| <Median | 174 | 153 | 0.08 (0.19) | 0.06 (0.21) | –0.03 (–0.58 to 0.53) | |
| Baseline triglycerides | | | | | | |
| ≥Median (140 mg/dL) | 169 | 169 | 1.07 (0.21) | 0.30 (0.21) | –0.77 (–1.35 to –0.18) | .03 |
| <Median | 168 | 163 | 0.01 (0.20) | 0.17 (0.20) | 0.16 (–0.40 to 0.72) | |
| Baseline CRP | | | | | | |
| ≥Median (3.5 mg/L) | 178 | 156 | 0.33 (0.20) | 0.20 (0.21) | –0.13 (–0.70 to 0.45) | .34 |
| <Median | 158 | 176 | 0.80 (0.22) | 0.28 (0.21) | –0.53 (–1.12 to 0.07) | |
| Baseline PAV | | | | | | |
| ≥Median (37.8%) | 172 | 166 | 0.12 (0.22) | –0.07 (0.22) | –0.20 (–0.81 to 0.41) | .83 |
| <Median | 169 | 169 | 0.88 (0.19) | 0.59 (0.19) | –0.29 (–0.84 to 0.25) | |




*P* values shown are for subgroup interaction. Values in parentheses in "baseline characteristics" column indicate median value for each characteristic. CI indicates confidence interval; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least-square; PAV, percent atheroma volume.

ondary target for management of patients at high cardiovascular risk.[31,32]

Although specific pharmacological agents are effective at treating the individual components of the metabolic syndrome, few treatment options exist that directly address the underlying pathophysiology of this disorder, specifically abdominal obesity. One promising approach is based on the central and peripheral effects produced by inhibition of $CB_1$ receptors. The first of these agents to successfully reach the market, rimonabant, has been shown to reduce body weight and diminish abdominal obesity, while improving several components of the metabolic syndrome.[13-16]

We sought to determine whether rimonabant would slow the progression of coronary disease in abdominally obese patients with preexisting coronary disease. Administration of rimonabant, 20 mg daily, for 18 months did not significantly reduce the rate of progression of coronary disease for the primary IVUS end point, the change in PAV. However, the secondary end point, change in TAV, showed a statistically significant treatment effect favoring rimonabant. Because of the differing extent of rimonabant effects for the primary and secondary end points, we performed additional post hoc exploratory analyses using other efficacy measures commonly used in IVUS trials. The change in the mean maximum atheroma thickness was favorably affected by rimonabant. However, the change in atheroma volume in the most diseased 10-mm subsegment showed no significant difference between treatments.

Accordingly, although the trial failed to achieve significance for the primary end point, it did demonstrate favorable effects for other IVUS end points. These observations suggest that the strategy of using a $CB_1$ antagonist to reduce progression of coronary disease may be useful but will require further study to confirm an antiatherosclerotic effect.

There is no obvious explanation for the divergence in the primary and secondary IVUS end points, although it should be noted that PAV has proven the most reliable end point in previous studies examining LDL-C reduction with statins. However, the effects of rimonabant do not include LDL-C lowering but, rather, involve reductions in body weight and waist circum-

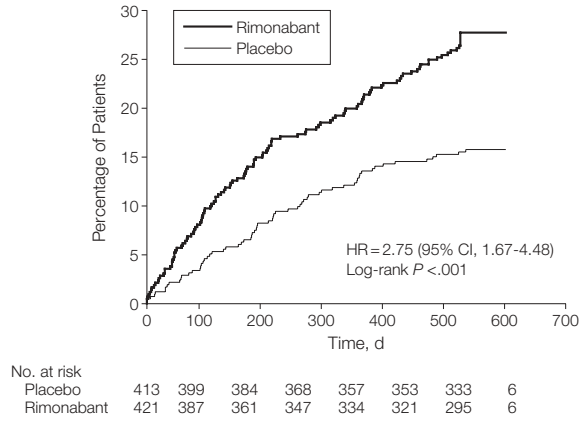
**Table 4.** Major Cardiovascular Adverse Events, Treatment-Emergent Adverse Events, and Reasons for Study Drug Discontinuation (Randomized Population, n = 839)

| Event | No. (%) Placebo | No. (%) Rimonabant | *P* Value |
|---|---|---|---|
| **Major Cardiovascular Adverse Events** | | | |
| No. | 417 | 422 | |
| Composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization (for revascularization, unstable angina, or TIA) | 46 (11.0) | 44 (10.4) | .79[a] |
| Composite of cardiovascular death, nonfatal MI, or nonfatal stroke | 7 (1.7) | 13 (3.1) | .18[a] |
| Cardiovascular death | 2 (0.5) | 0 | .25 |
| All-cause mortality | 8 (1.9) | 2 (0.5) | .06 |
| Nonfatal MI | 4 (1.0) | 9 (2.1) | .17 |
| Fatal or nonfatal stroke | 1 (0.2) | 4 (0.9) | .37 |
| Hospitalization for revascularization, unstable angina, or TIA | 40 (9.6) | 36 (8.5) | .59 |
| **Most Common Treatment-Emergent Adverse Events (Safety Population, n = 838)** | | | |
| No. | 416 | 422 | |
| Psychiatric disorders | 118 (28.4) | 183 (43.4) | <.001 |
| Anxiety | 49 (11.8) | 76 (18.0) | .01 |
| Depression | 47 (11.3) | 71 (16.8) | .02 |
| Insomnia | 38 (9.1) | 52 (12.3) | .14 |
| Depressed mood | 20 (4.8) | 29 (6.9) | .20 |
| Major depression | 9 (2.2) | 13 (3.1) | .41 |
| Suicidal ideation | 10 (2.4) | 7 (1.7) | .44 |
| Suicide attempt | 1 (0.2) | 0 | .50 |
| Completed suicide | 0 | 1 (0.2) | .50 |
| Severe psychiatric disorders[b] | 16 (3.8) | 20 (4.7) | .52 |
| Dizziness | 53 (12.7) | 61 (14.5) | .47 |
| Fatigue | 25 (6.0) | 46 (10.9) | .01 |
| Gastrointestinal tract disorders | 74 (17.8) | 142 (33.6) | <.001 |
| Nausea | 23 (5.5) | 63 (14.9) | <.001 |
| Diarrhea | 14 (3.4) | 33 (7.8) | .005 |
| Vomiting | 8 (1.9) | 23 (5.5) | .01 |
| Constipation | 8 (1.9) | 11 (2.6) | .51 |
| Erectile dysfunction (n=271 and 274 men) | 2 (0.7) | 9 (3.3) | .03 |
| Creatinine ≥150 µmol/L | 6/372 (1.6) | 12/361 (3.3) | .13 |
| **Most Common Reasons for Discontinuation of Study Drug Due to Adverse Events** | | | |
| Any adverse event leading to discontinuation | 31 (7.5) | 74 (17.5) | <.001 |
| Psychiatric disorders | 13 (3.1) | 40 (9.5) | <.001 |
| Depression | 5 (1.2) | 15 (3.6) | .03 |
| Anxiety | 3 (0.7) | 13 (3.1) | .01 |
| Insomnia | 1 (0.2) | 7 (1.7) | .07 |
| Depressed mood | 1 (0.2) | 4 (0.9) | .37 |
| Nervous system disorders | 4 (1.0) | 22 (5.2) | <.001 |
| Dizziness | 1 (0.2) | 7 (1.7) | .07 |
| Other | 3 (0.7) | 15 (3.6) | .005 |
| Gastrointestinal tract disorders | 4 (1.0) | 15 (3.6) | .01 |
| Nausea | 1 (0.2) | 13 (3.1) | .001 |
| Other | 3 (0.7) | 2 (0.5) | .68 |

Abbreviations: MI, myocardial infarction; TIA, transient ischemic attack.
[a] *P* value based on log-rank. Fisher exact test was performed if expected counts were less than 5; otherwise, $\chi^2$ test was used.
[b] Major depression, suicidal ideation, or attempted or successful suicide.

ference, increases in HDL-C levels, and reductions in levels of insulin and hsCRP. The responses of blood vessels to antiatherosclerotic therapies are complex and involve changes in both atheroma and EEM volumes. The PAV represents the ratio of atheroma volume to EEM volume, whereas TAV is solely a measure of change in atheroma volume. Conceivably, the mechanism of action of rimonabant produces effects on the atheroma and EEM volume different from those observed previously with statin therapy. More study is needed to determine if therapies that increase HDL-C levels act differently on vessel wall components than agents that lower LDL-C levels.

**Figure 4.** Cumulative Incidence of Drug Discontinuation




CI indicates confidence interval; HR, hazard ratio.

Although rimonabant has been approved in several countries, an FDA Advisory Panel did not recommend approval and requested additional safety data on psychiatric adverse effects.[17] In the current trial, to more fully characterize the safety of rimonabant in a broad population, we deliberately enrolled patients whether or not they had a history of psychiatric illness. In addition, we amended the protocol to include a questionnaire designed to standardize reporting of these adverse effects. Our findings confirm that inhibition of $CB_1$ receptors with rimonabant does increase psychiatric and gastrointestinal tract adverse effects, specifically anxiety, depression, and nausea. The inclusion of patients with a history of psychiatric illness and the use of a questionnaire increased the rate of reported psychiatric disorders in the placebo and rimonabant groups compared with prior studies. Although these adverse effects resulted in an increase in drug discontinuations, 73% of patients were able to successfully complete 18 months of rimonabant therapy, compared with 84% in the placebo group.

Severe psychiatric adverse effects, including major depression, suicidal ideation, and attempted or successful suicide were relatively uncommon, occurring with similar frequency in the placebo- and rimonabant-treated patients (3.8% vs 4.7%, respectively; $P = .52$). However, the study was not powered to assess severe psychiatric effects. One placebo-treated patient attempted suicide, and a single rimonabant-treated patient completed suicide. In interpreting these data, it should be noted that obesity and body weight reduction have been linked to an increased incidence of depression.[33] Overall, our findings demonstrate that rimonabant is associated with an increase in psychiatric symptoms.

The effects of rimonabant on body weight, waist circumference, and levels of serum lipids, hsCRP, and $HbA_{1c}$ observed in the STRADIVARIUS trial were similar in magnitude to previous studies conducted using this agent.[13-16] These included a 4.3-kg reduction in body weight, an 4.5-cm reduction in waist circumference, a 22.4% increase in HDL-C levels, and a 20.5% reduction in triglyceride levels (Table 2 and Figure 2). These changes were maintained for the 18-month duration of the trial (Figure 2).

An important question is why these changes did not result in a more robust reduction in the rate of progression of coronary atherosclerosis. One potential explanation is the high rates of administration of other beneficial therapies in the study population. More than 80% of patients were receiving statins at baseline and during the trial, with mean on-treatment LDL-C levels averaging approximately 87 mg/dL. Prior IVUS studies have demonstrated that LDL-C levels are a very strong predictor of progression rates.[21,23,24] It has been challenging to demonstrate an incremental benefit on a background of optimal medical therapy, particularly in patients with well-controlled LDL-C levels.[27,28] The relatively short duration of therapy also may represent a factor limiting the extent of benefit. It also remains possible that the biological effects of rimonabant are insufficient to produce an antiatherosclerotic benefit.

We performed analyses of outcomes in various subgroups in the current study (Figure 3). These analyses were not prespecified. Such analyses are always considered exploratory and hypothesis-generating but may offer insights into populations with a greater or lesser apparent benefit. Two of these subgroups exhibited statistically significant heterogeneity—patients taking statins compared with those not taking statins and patients with triglyceride levels above or below the median. The more substantial benefit observed in patients not taking statins suggests that rimonabant and statin treatment may have exhibited overlapping benefits. The more favorable results in the subgroup with elevated triglyceride levels suggest that patients with the greatest metabolic abnormalities may be af-

forded the greatest benefits of $CB_1$ antagonist therapy. Further clarification of these hypotheses will require additional post hoc analyses, including a multivariate analysis of the factors influencing outcomes.

Because the current study failed to achieve a statistically significant effect for the primary efficacy measure, additional studies will be required to further define the role of rimonabant in the treatment of abdominally obese patients with coronary disease and metabolic risk factors. Two placebo-controlled randomized trials are currently under way, the Atherosclerosis Underlying Development Assessed by Intima-Media Thickness in Patients on Rimonabant (AUDITOR) study (clinicaltrials.gov NCT00228176) and the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial (clinicaltrials.gov NCT00263042). AUDITOR is a 24-month study of the effects of rimonabant on carotid intimal-medial thickness, and CRESCENDO is a long-term cardiovascular outcomes trial in 17 000 patients with a high risk for cardiovascular events.

The current study has several important limitations. The study included a narrow population, specifically patients with at least 1 coronary stenosis identified by angiography. This population may not be representative of the broader population with coronary artery disease. Intravascular ultrasound is a measure of disease progression and there exist limited data regarding the ability of this efficacy measure to predict clinical outcomes. Morbidity and mortality trials are always the preferred approach to determining the clinical benefits of any intervention. In invasive imaging trials, some patients do not complete IVUS assessments at both baseline and follow-up. The absence of imaging information for noncompleting patients can potentially introduce biases into the analyses. Accordingly, we performed a post hoc sensitivity analysis in which values were imputed for noncompleters based on their baseline characteristics. Although all *P* values for IVUS efficacy parameters change slightly using the imputed results, the overall interpretation of the study was not altered. Finally, the duration of exposure to rimonabant was relatively short (18 months), which may have been inadequate to observe a treatment effect on the rate of progression of coronary atherosclerosis.

Despite these limitations, we believe that the STRADIVARIUS trial supports the following conclusions. Treatment with the $CB_1$ antagonist rimonabant for 18 months reduced body weight and waist circumference and improved lipid profiles, glycemic measures, and hsCRP levels, but did not significantly reduce atherosclerosis for the primary efficacy parameter, change in PAV. However, rimonabant treatment did show a statistically significant favorable effect for a secondary IVUS end point and an additional exploratory end point. Accordingly, this agent may favorably influence the progression of atherosclerosis. Significant psychiatric and gastrointestinal tract adverse effects were observed but were usually mild or moderate in severity. We believe that this approach to treatment of abdominal obesity, inhibition of $CB_1$ receptors with rimonabant, continues to hold promise in the treatment of patients with coronary disease and should be explored in further clinical trials.

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