

STRADIVARIUS

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

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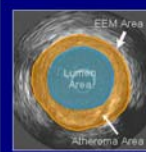
Background and Objectives

- Obesity is increasing at an alarming rate in developed countries; 34% in the US population have BMI >30.
- Abdominal obesity is associated with specific metabolic abnormalities that increase the risk of CAD.
- Rimonabant, a cannabinoid receptor (CB₁) antagonist, enhances weight loss and improves obesity-related metabolic abnormalities.
- We sought to determine if rimonabant could reduce progression of coronary atherosclerosis measured by IVUS in abdominally-obese CAD patients.

Methods

- Patients selected with abdominal obesity (defined as waist >102 cm for men or >88 cm for women) undergoing angiography for clinical indications.
- Inclusion criteria required two additional risk factors of the metabolic syndrome or current smoking.
- Intravascular ultrasound (IVUS) was performed to assess atheroma volume in 839 patients randomized to placebo or rimonabant 20 mg.
- After 18 months, repeat IVUS was performed in the 676 patients who completed the trial, regardless of whether they were still taking study drug.

Intravascular Ultrasound Endpoint Calculations



$$\text{Change in Percent Atheroma Volume} = \frac{\sum_n \text{Atheroma}_{\text{CSA}}}{\sum_n \text{EEM}_{\text{CSA}} (\text{Month 18})} - \frac{\sum_n \text{Atheroma}_{\text{CSA}}}{\sum_n \text{EEM}_{\text{CSA}} (\text{baseline})}$$

$$\text{Total Atheroma Volume} = \frac{\sum_n \text{EEM}_{\text{CSA}} - \sum_n \text{Lumen}_{\text{CSA}}}{\text{Number of slices in patient's pullback}} \times \text{Median number of slices in all pullbacks}$$

$$\text{Change in Atheroma Volume} = \text{Atheroma Volume (Month 18)} - \text{Atheroma Volume (baseline)}$$

Baseline Patient Characteristics (n=839)

	Placebo (n=417)	Rimonabant (n=422)
Age (years)	57.5	57.9
Male gender	65.0%	64.9%
Weight (kg)	103.5	103.5
Waist Circum. (cm) [in]	117.5 [46.3]	117.3 [46.2]
BMI	35.3	35.3
Diabetes	37.4%	38.4%
Metabolic Syndrome	91.6%	94.1%
Current Smoker	26.6%	29.9%
Psychiatric Disease	24.5%	25.6%

Medications at Randomization (n=839)

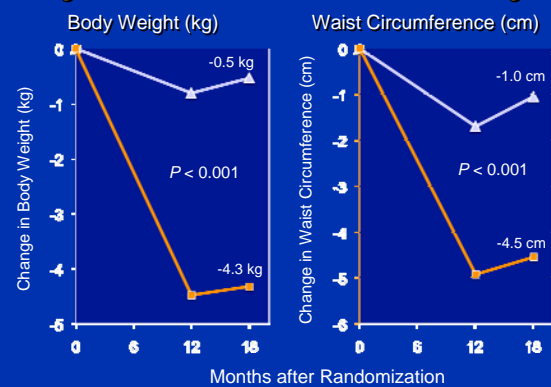
	Placebo (n=417)	Rimonabant (n=422)
Aspirin	91.1%	91.7%
β-blocker	70.5%	69.4%
ACEi or ARB	68.6%	69.4%
Statin	81.8%	82.5%
Oral hypoglycemia agent	29.7%	30.6%
Insulin	11.8%	11.1%
Antidepressant	19.2%	18.2%

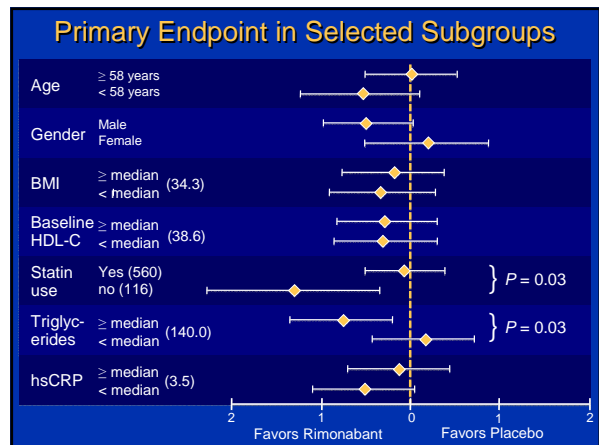
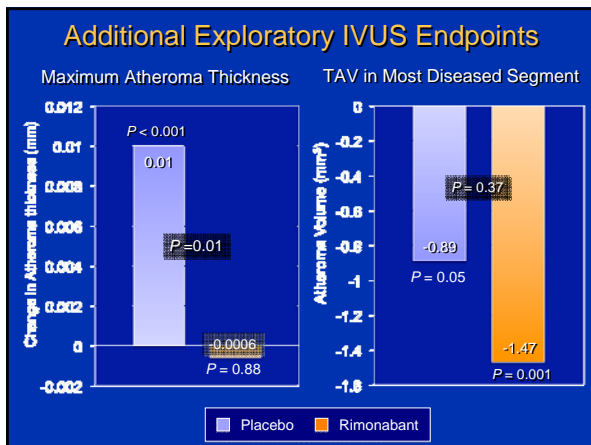
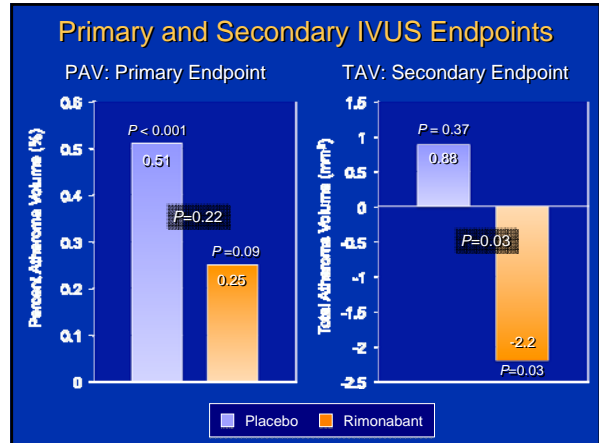
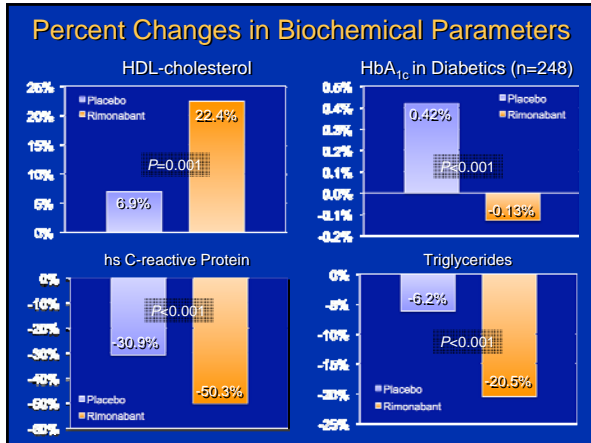
Baseline Lab Values & Blood Pressure (n=676)

	Placebo (n=341)	Rimonabant (n=335)
LDL-cholesterol (mg/dL)	89.5	91.9
HDL-cholesterol (mg/dL)	37.6	38.5
Triglycerides* (mg/dL)	140.0	140.0
hsCRP* (mg/L)	3.8	3.4
HbA _{1c} (%)	5.8	5.8
Systolic BP (mmHg)	129.3	129.4
Diastolic BP (mmHg)	76.7	76.9

*median values

Weight and Waist Circumference Changes





Major Adverse Cardiovascular Events

	Placebo (n=417)	Rimonabant (n=422)
Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for revascularization, unstable angina, TIA	11.0%	10.4%
Composite of CV death, nonfatal MI, or nonfatal stroke	1.7%	3.1%
Cardiovascular death	0.5%	0%
All cause mortality*	1.9%	0.5%
Nonfatal MI	1.0%	2.1%
Fatal or nonfatal stroke	0.2%	0.9%
Hospitalization for revascularization, unstable angina, or TIA	9.6%	8.5%

*P = 0.06

Psychiatric Adverse Effects

	Placebo (n=417)	Rimonabant (n=422)	P value
Psychiatric Disorders	28.4%	43.4%	<0.001
Anxiety	11.8%	18.0%	0.01
Depression	11.3%	16.8%	0.02
Insomnia	9.1%	12.3%	0.14
Depressed Mood	4.8%	6.9%	0.20
Major Depression	2.2%	3.1%	0.41
Suicidal ideation	2.4%	1.7%	0.44
Suicide Attempt – n (%)	1 (0.2%)	0 (0%)	0.50
Completed suicide – n (%)	0 (0%)	1 (0.2%)	0.50
Severe psychiatric disorders*	3.8%	4.7%	0.52

* Major depression, suicidal ideation, attempted or successful suicide

Other Treatment-Emergent Adverse Effects

	Placebo (n=417)	Rimonabant (n=422)	P value
GI Disorders	17.8%	33.6%	<0.001
Nausea	5.5%	14.9%	<0.001
Diarrhea	3.4%	7.8%	0.005
Vomiting	1.9%	5.5%	0.01
Erectile Dysfunction*	0.7%	3.3%	0.04
Dizziness	12.7%	14.5%	0.47
Fatigue	6.0%	10.9%	0.01

*n = 545 male patients

Conclusions

- Treatment of abdominally-obese coronary disease patients for 18 months with rimonabant:
 - Reduced body weight 4.3 kg and waist circumference 4.5 cm, increased HDL-C 22.4%, reduced triglycerides 20.5%, hsCRP 50.3%, and favorably affected HbA_{1c}.
- The study did not demonstrate an effect for rimonabant on the primary endpoint, PAV ($P = 0.22$), but a favorable effect for the secondary endpoint, TAV ($P = 0.03$).
- Psychiatric and GI adverse effects were more common with rimonabant, which resulted in a higher rate of drug discontinuation.

ORIGINAL CONTRIBUTION JAMA-EXPRESS

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-blind, 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 mm³ (−4.09 to −0.24) vs an increase of 0.68 mm³ (−1.03 to 2.79) ($P=.03$). In the rimonabant vs placebo groups, imputed 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 mm³ (−3.18 to −0.72) vs an increase of 1.19 mm³ (−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 (6.5 cm [−5.4 to −7.7] vs 1.0 cm [−1.9 to −0.2]) ($P<.001$ for both).

Some Final Thoughts

Development of effective and durable treatment strategies for management of obesity has proven a daunting challenge.

New approaches are greatly needed to reduce the burdens of this global epidemic and its metabolic consequences.

We believe CB₁ inhibition shows promise for treatment of atherosclerotic disease in patients with abdominal obesity, but these benefits will need to be confirmed in additional trials, currently underway.

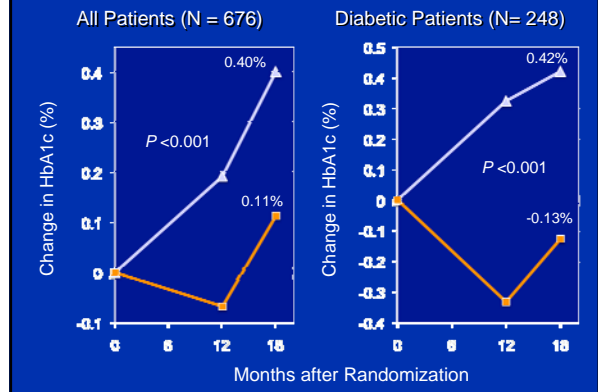


Back Up Slides

Changes: Lab Values and Obesity Measures

	Placebo(n=341)	Rimonabant(n=335)	P value
Body Weight	-0.5 kg	-4.3 kg	<0.001
Waist Circumference	-1.0 cm	-4.5 cm	<0.001
LDL-cholesterol	1.7%	0.4%	0.78
HDL-cholesterol	6.9%	22.4%	<0.001
Triglycerides	-6.2%	-20.5%	<0.001
hsCRP	-30.9%	-50.3%	<0.001
HbA _{1c}	0.40%	0.11%	<0.001

Changes in HbA_{1c}: All Patients and Diabetics



Time to Permanent Drug Discontinuation

