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**Review**

# Effect of blockage of the endocannabinoid system by CB<sub>1</sub> antagonism on cardiovascular risk

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**Abstract:**

The endocannabinoid system is a crucial player in the inflammatory processes underlying atherosclerosis. Recently, basic research studies and animal models have strongly supported the role of the endocannabinoid system not only in the regulation of classical cardiovascular risk factors (including lipid profile and glucose homeostasis), but also in the activation of immune cells and inflammatory mediators. Clinical trials investigating treatment with rimonabant (a selective antagonist of the cannabinoid type 1 receptor) have suggested a beneficial effect of this drug in the management of obesity. Further studies are needed to explore a possible use for rimonabant in treating type 2 diabetes and acute and chronic cardiovascular disease. Despite the slight increase in adverse events (mainly psychiatric), which has led to the recent withdrawal of rimonabant from the market, CB<sub>1</sub> receptor antagonism might represent a very promising therapeutic strategy to reduce the cardiovascular risk. In the present review, we focused on the most important experimental investigations into the role of the endocannabinoid system in atherosclerosis and cardiovascular risk.

**Key words:** rimonabant, endocannabinoids, cardiovascular risk

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## The endocannabinoid system

Atherosclerosis is a systemic inflammatory disease involving several immune cell types and organs [15]. Several inflammatory mediators (such as cytokines, growth factors and hormones) orchestrate atherosclerotic processes [5, 14, 15, 17]. Recently, the complex cross-talk between immune and vascular cells has been shown to be directly modulated by the endocannabinoid system. The endocannabinoid system comprises two distinct membrane receptors that have been identified by molecular cloning, CB<sub>1</sub> and CB<sub>2</sub>, their endogenous ligands (called endocannabinoids), such

as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), as well as enzymes for ligand biosynthesis and inactivation [6]. The CB<sub>1</sub> receptor is primarily localized in the central nervous system (CNS), but is also expressed in peripheral tissues and on immune cells. Conversely, CB<sub>2</sub> is predominantly expressed peripherally, in particular on immune cells, but is also present in the brain [16, 37]. Therefore, it is not surprising that activation or inactivation of CB<sub>1</sub> and CB<sub>2</sub> receptors have several central and peripheral effects [16]. In addition, there is emerging evidence suggesting that some cannabinoid effects may not be mediated by either CB<sub>1</sub> or CB<sub>2</sub> receptors, which implicates

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additional receptors involved in these actions [3]. Moreover, endocannabinoids can activate transient receptor potential vanilloid type-1 receptors (TRPV1), peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ) and the orphan G protein-coupled receptor GPR55 [3, 32, 35].

The most important pathway for AEA biosynthesis is mediated by the enzymatic hydrolysis of the precursor N-acyl-phosphatidylethanolamine (NAPE), which is catalyzed by the NAPE-selective phospholipase D (PLD), whereas degradation occurs through fatty acid amide hydrolase (FAAH) [6]. On the other hand, 2-AG is mainly released from membrane lipids by the sn-1-specific diacylglycerol lipase (DAGL), and is metabolized by FAAH as well as the catalytic action of a specific monoacylglycerol lipase (MAGL) [6]. It is now well established that endocannabinoids are synthesized and released “on demand” and that this process can be regulated both physiologically and under pathological conditions [6, 10].

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### **The endocannabinoid system and cardiovascular risk: evidence from basic research and animal models**

Synthetic and endogenous cannabinoids are known to exhibit complex cardiovascular actions by activating vascular and myocardial CB<sub>1</sub> receptors [25, 26]. Both increases and decreases in blood pressure in response to cannabinoid treatment have been reported, depending on the experimental model, species and/or concentration used [29]. The acute administration of cannabinoids in humans is typically associated with an increased pulse rate and acute rise in blood pressure, but also sudden falls in blood pressure in the orthostatic state [31]. On the other hand, endocannabinoid AEA and 2-AG released from endothelial cells, macrophages or platelets, induce hypotension in rodents [9, 20, 38]. In spontaneously hypertensive rats, prevention of endocannabinoid AEA degradation using an inhibitor of fatty acid amide hydrolase (FAAH) was shown to lower blood pressure and heart rate through reductions in both cardiac contractility and vascular resistance [1]. These effects were prevented by CB<sub>1</sub> antagonists. FAAH<sup>-/-</sup> mice, however, have normal blood pressure and cardiac function, indicating that under normal conditions AEA does not play

a major role in cardiovascular regulation [27]. These findings suggest that the endocannabinoid system has an influence on hypertension, which represents a major risk factor for atherosclerosis [26].

A more recent study investigated the age-associated decline of cardiac function and changes in inflammatory gene expression, oxidative stress and apoptosis in FAAH<sup>-/-</sup> mice as compared to wildtype mice [2]. Enhanced AEA levels in the FAAH<sup>-/-</sup> animals were protective, which further supports the protective role of endocannabinoids in inflammatory disorders such as atherosclerosis. Moreover, AEA dose-dependently attenuated TNF $\alpha$ -induced ICAM-1 and VCAM-1 expression in human coronary artery endothelial cells (HCAECs), and the adhesion of THP-1 monocytes to HCAECs in a CB<sub>1</sub> and CB<sub>2</sub>-dependent manner [2]. We have previously shown that activation of CB<sub>2</sub> receptors with delta-9-tetrahydrocannabinol (THC) inhibits atherosclerotic plaque progression in mice, mainly by reducing macrophage recruitment [34].

In contrast to the previously described potentially beneficial effects in treating cardiovascular disease, endocannabinoids might exhibit pro-thrombotic effects. Indeed, both AEA and 2-AG have been shown to activate rodent and human platelets [4, 19, 20]. Platelets are anucleated cellular fragments that circulate in the blood. In addition to their well-recognized role in hemostasis and acute thrombus formation, platelets are also thought to have proinflammatory and growth-regulatory properties that contribute to the progression of atherosclerosis [12, 23, 39]. Endothelial cells, macrophages or platelets themselves might increase their endocannabinoid synthesis during atherosclerosis, thus triggering platelet activation. On the other hand, these cells are also capable of metabolizing AEA and 2-AG, which may counterbalance enhanced endocannabinoid levels.

Obesity, characterized by an excess of adipose tissue mass, is closely associated with an increase in cardiovascular morbidity and mortality attributable to atherosclerosis [13]. The endocannabinoid system is known to play a crucial role in energy balance and substrate metabolism, in particular through central hypothalamic and leptin-regulated pathways [21]. The overactivity of the endocannabinoid system promotes excessive food intake and fat accumulation in animal models and humans [11, 21]. In rodents, pharmacologic blockade or genetic ablation of CB<sub>1</sub> receptors reduces appetite and weight and prevents obesity and insulin resistance [21]. In addition to central effects,

the EC system also regulates food intake and metabolic factors through peripheral CB<sub>1</sub> receptors located at multiple sites throughout the body [21, 40]. Thus, CB<sub>1</sub> blockade in rodents acts on adipocytes to increase adiponectin expression, on hepatocytes to decrease *de novo* lipogenesis and increase fatty acid oxidation and acts in the gastrointestinal tract to increase satiety [40].

### The endocannabinoid system and cardiovascular risk: evidence from clinical trials

Rimonabant is a selective antagonist of the CB<sub>1</sub> receptor and the first member of a new class of compounds targeting the endocannabinoid system with central and peripheral effects (Fig. 1 and 2). The first clinical studies performed with rimonabant have demonstrated its efficacy in obese subjects, as it improved weight, waist circumference, lipid profile and glucose homeostasis (Tab. 1 and 2) [7, 28, 33, 36]. On the basis of these promising early studies, several clinical trials with rimonabant have been designed and started. In 2008, the first study (STRADIVARIUS) targeting the efficacy of rimonabant against atherosclerosis and coronary artery disease (CAD) in obese subjects was published [24]. More recently (August

2008), the SERENADE study with rimonabant was performed in drug-naïve type 2 diabetes patients, with some encouraging effects. This 6-month, randomized, double-blind, placebo-controlled trial, which enrolled 281 patients, investigated if treatment with rimonabant (20 mg/day) induces any changes in HbA<sub>1C</sub>, body weight, waist circumference or lipid profile. Rimonabant treatment resulted in improved glycemic control, body weight and lipid profile relative to the base-line values [30]. Other phase IIIb clinical studies (including ARPEGGIO, ALLEGRO, ADAGIO-Lipids, AUDITOR, CRESCENDO) are currently ongoing [8]. In the following section we will discuss the available results of the five clinical trials already published, investigating the efficacy and tolerability of rimonabant in obese subjects.

#### RIO-Europe

This study [36] was conducted mainly in Europe, with a few patients in the United States. It included obese subjects with BMI ≥ 30 kg/m<sup>2</sup>, or > 27 kg/m<sup>2</sup> with comorbidity (hypertension or dyslipidemia) (Tab. 1). Importantly, exclusion criteria were diabetes mellitus, significant cardiovascular, pulmonary, hepatic as well as renal disorders and neurological and psychiatric diseases. Patients were excluded for the presence of two or more episodes of depression, a history of hospitalization for depression or suicide attempt. No treatment with antidepressive drugs was permitted

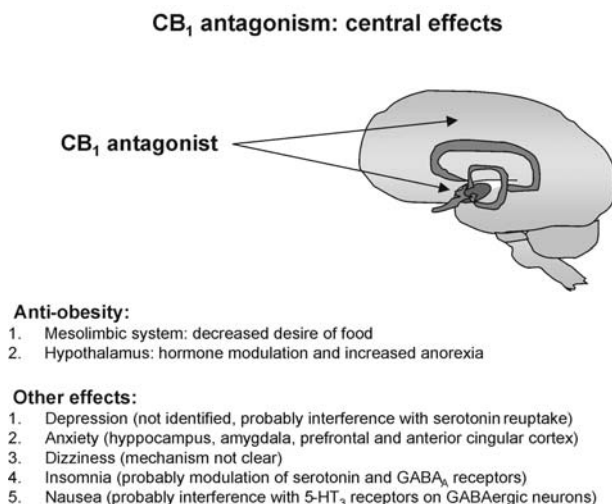


Fig. 1. Central effects of CB<sub>1</sub> antagonism

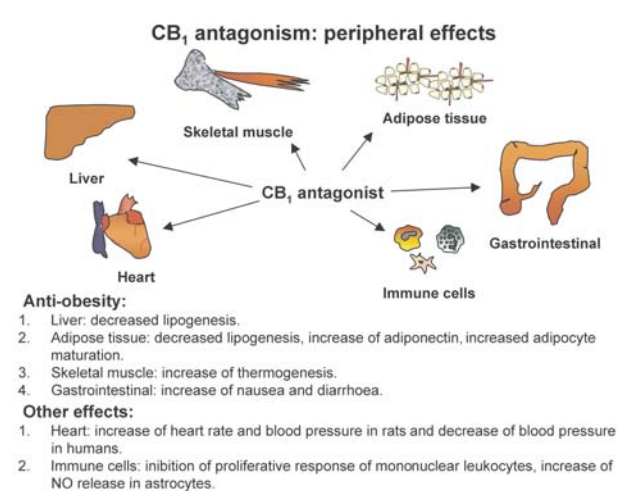


Fig. 2. Peripheral effects of CB<sub>1</sub> antagonism

during the study. After the exclusion of 158 patients during a 4-week placebo run, 1507 obese patients were enrolled and assigned randomly to the treatments with rimonabant (n = 599 subjects in the 20 mg/day group and n = 603 subjects in the 5 mg/day) or placebo (n = 305). A mild hypocaloric (600-kcal deficit) diet and moderate physical activity was assigned to all patients. Patients were mostly white (94%) and female (80%), with an average age of 45 years and an average weight of 101 kg. Furthermore, 41% exhibited hypertension, 61% exhibited dyslipidemia and 41% had a metabolic syndrome. Among 920 patients (61% of the total number of patients that started the study) completing one full year of treatment, 20 mg/day rimonabant induced a significant improvement of body weight, waist circumference, HDL-cholesterol, triglycerides, insulin resistance and prevalence of metabolic syndrome. A slight beneficial effect of rimonabant in weight loss was also observed in patients withdrawn before the end of the study. The effects of 5 mg/day rimonabant were of less clinical significance. Systolic and diastolic blood pressure as well as total cholesterol and LDL-cholesterol showed no significant amelioration under any treatments. The safety and efficacy of rimonabant was investigated in the present trial. No significant differences between the three groups were observed in the number of total adverse events (Tab. 2). Patients treated with rimonabant developed more nausea and dizziness than placebo. These adverse effects were more frequent upon treatment with 20 mg/day of rimonabant than 5 mg/day. Treatment with rimonabant did not significantly increase psychiatric adverse disorders, which were diagnosed by using the Hospital Anxiety and Depression Scale (HADS) [41].

### Rio-North America

This trial is the largest study investigating the effects of rimonabant in obese subjects [28]. It enrolled 3,500 obese but not type 1 or 2 diabetic patients at 72 centers in the United States and Canada. During an initial 4-week period with a hypocaloric diet (600 kcal/day deficit) and placebo, 455 patients were excluded for different reasons and a total of 3,045 patients were randomized to continue the diet and start the treatments with 20 mg/day rimonabant (n = 1,222), 5 mg/day rimonabant (n = 1,216) or placebo (n = 607) for one year (Tab. 1). The patients under examination were mainly white (84%) and female (81%), with an

average weight of about 105 kg and a BMI of 38. About half of the patients failed to complete the one-year treatment in the three groups. At the end of the first year of the study, patients (n = 299) treated with placebo continued the study for a second year under the same treatment. Patients (n = 602) that completed the treatment with 5 mg/day rimonabant during the first year were randomized and assigned to two new groups, treated with placebo (n = 300) or 5 mg/day rimonabant (n = 302) for another year. Also, patients (n = 660) that completed the treatment in the first year with 20 mg/day rimonabant, were randomized into placebo (n = 327) vs. 20 mg/day rimonabant (n = 333) groups in the second year of the study. At one year of follow-up, the same outcomes as in RIO-Europe were investigated. Treatment with 20 mg/day rimonabant induced a significant improvement in body weight, waist circumference, HDL-cholesterol, triglycerides and metabolic syndrome prevalence. After two years, patients re-randomized to placebo after the end of one year regained much of their weight, while patients receiving 20 mg rimonabant/day for two years maintained their weight loss and favorable changes in cardiometabolic risk factors. These findings suggest that 2 years of treatment with 20 mg/day rimonabant induces and helps to maintain weight loss in obese subjects. Therefore, the results of this study suggest that the rimonabant treatment should be prolonged for more than one year. Also, rimonabant was generally well tolerated in this study (Tab. 2). In the rimonabant groups, nausea and psychiatric disorders (including depression, anxiety and insomnia) were slightly increased in comparison to placebo.

### RIO-Lipids

This study was conducted at 67 sites in 8 countries [7]. It enrolled 1,036 obese patients with untreated dyslipidemia (Tab. 1). Patients who received pharmacological treatments for dyslipidemia within the 6 weeks of screening were excluded. Other exclusion criteria were type 1 and 2 diabetes and a history of depression requiring hospitalization or history of suicide attempts. After an initial 4-week placebo period, during which 135 more patients were excluded, patients were assigned to a placebo group (n = 342), 5 mg/day rimonabant (n = 345) or 20 mg/day rimonabant (n = 346). All these groups also started a hypocaloric diet (600-kcal deficit). The mean age was about 48 years, and 40% were men. The baseline average weight was

Tab. 1. Study design of already published clinical trial with rimonabant

Rimonabant treatment in Clinical Trials: study design				
Studies	Patients	Outcomes	Inclusion criteria	Ethnicity sex
RIO-EUROPE (2005) [28]	<b>1507</b> (men and women ≥ 18 years old)	<b>Study length:</b> 12 months <b>Primary:</b> Body weight change over 1 year <b>Secondary:</b> Waist circumference; HDL-C; LDL-C; Total C; Triglycerides; Fasting glucose; Fasting insulin; Insulin resistance (HOMA-IR); Blood pressure; Presence of metabolic syndrome (NCEP ATP III criteria)	BMI ≥ 30 or > 27 with hypertension or dyslipidemia	<b>White:</b> 1410 <b>Black:</b> 0 <b>Male:</b> 309 <b>Female:</b> 1198
RIO-North America (2006) [29]	<b>3045</b> (men and women ≥ 18 years old)	<b>Study length:</b> 24 months <b>Primary:</b> Body weight change over first year. Prevention of weight regain in the second year <b>Secondary:</b> Waist circumference; HDL-C; LDL-C; Total C; Triglycerides; Fasting glucose; Fasting insulin; Insulin resistance (HOMA-IR); Blood pressure; Presence of metabolic syndrome (NCEP ATP III criteria)	BMI ≥ 30 or > 27 with hypertension or dyslipidemia	<b>White:</b> 2553 <b>Black:</b> 339 <b>Male:</b> 588 <b>Female:</b> 2452
RIO-Lipids 2005) [30]	<b>1036</b> (men and women 18–70 years old)	<b>Study length:</b> 12 months <b>Primary:</b> Body weight change over 1 year <b>Secondary:</b> Waist circumference; HDL-C; LDL-C; Total C; Triglycerides; Fasting glucose; Fasting insulin; Blood pressure; Presence of metabolic syndrome (NCEP ATP III criteria); Proportion of small LDL particles; Peak size of LDL particles; Adiponectin; Leptin; C-reactive protein	BMI 27–40 and triglycerides > 1.69 mmol/L to 7.90 mmol/L and/or cholesterol/HDL-C ratio > 5 (men) or > 4.5 (women)	<b>White:</b> not known <b>Black:</b> not known <b>Male:</b> 407 <b>Female:</b> 626
RIO-Diabetes (2006) [31]	<b>1047</b> (men and women 18–70 years old)	<b>Study length:</b> 12 months <b>Primary:</b> Body weight change over 1 year <b>Secondary:</b> Waist circumference; HDL-C; LDL-C; Total C; Triglycerides; Fasting glucose; Fasting insulin; Insulin resistance (HOMA-IR); Blood pressure; Presence of metabolic syndrome (NCEP ATP III criteria); Change in HbA <sub>1c</sub> ; Leptin; C-reactive protein	BMI 27–40 with type 2 diabetes treated with metformin or sulfonylurea monotherapy for ≥ 6 months; HbA 1C 6.5–10%; fasting glucose 5.55–15.05 mmol/L	<b>White:</b> 925 <b>Black:</b> 57 <b>Male:</b> 513 <b>Female:</b> 536

about 96 kg and BMI 34. Half of the patients met the metabolic syndrome criteria. Approximately, 40% of the patients in each group did not complete the study (one-year follow up). Body weight, waist circumference, heart rate, blood pressure, QT duration, depression, anxiety, complete lipid profile, adiponectin, leptin and CRP were assessed. Compared with placebo, 20 mg/day rimonabant significantly improved weight, waist circumference, blood pressure, HDL cholesterol, triglycerides, adiponectin, leptin and CRP. Concerning blood pressure, improvements were seen in the statistical evaluations rather than clinical ameliorations of hypertension. Treatment with 20 mg/day rimonabant also significantly reduced metabolic syndrome in comparison with placebo (respectively

25.8% vs. 41%). Adverse events, such as nausea, dizziness, insomnia and anxiety were increased by high-dose rimonabant treatment in comparison with placebo (Tab. 2).

### Rio-Diabetes

This trial is the most recent study reported from the RIO phase III program. It was conducted in 151 centers in 11 countries [33] and enrolled 1,047 patients with type 2 diabetes and a BMI between 27 and 40 kg/m<sup>2</sup>. Half of the patients were women. To be enrolled, patients needed to have been treated with metformin or a sulfonylurea monotherapy for at least 6 months, to have fasting plasma glucose concentra-

**Tab. 2.** Results of already published clinical trial with rimonabant

Rimonabant treatment in Clinical Trials: results					
Studies	Outcomes				Adverse events
RIO-EUROPE (2005) [28]	Change in ITT	Placebo	Rimonabant 5 mg	Rimonabant 20 mg	Any adverse events: Placebo:84.3%; Rimonabant 5 mg:82.6%; Rimonabant 20 mg:87.1%. Serious adverse events: Placebo:7.5%; Rimonabant 5 mg:7.5%; Rimonabant 20 mg 8.7%. Psychiatric disorders: Placebo:5.2%; Rimonabant 5 mg:2.3%; Rimonabant 20 mg:7.0%. Nervous System disorders: Placebo:0.7%; Rimonabant 5 mg:1.3%; Rimonabant 20 mg:1.7%. Gastrointestinal disorders: Placebo:0.0%; Rimonabant 5 mg:0.8%; Rimonabant 20 mg:3.5%.
	Weight (kg)	-1.8 ± 6.4	-3.4 ± 5.7	-6.6 ± 7.2	
	Waist Circumference (cm)	-2.4 ± 6.9	-3.9 ± 6.3	-6.5 ± 7.4	
	HDL (mmol/L)	0.15 ± 0.23	0.19 ± 0.23	0.26 ± 0.26	
	Triglycerides (mmol/L)	-0.01 ± 0.68	-0.02 ± 0.77	-0.20 ± 0.64	
	Fasting glucose (mmol/L)	0.03 ± 0.77	-0.05 ± 0.68	-0.09 ± 0.65	
	Fasting insulin (mU/L)	1.8 ± 13	0.3 ± 11.2	-1.0 ± 8.8	
	HOMA-IR (%)	0.4 ± 3.5	0.0 ± 3.4	-0.3 ± 2.4	
Metabolic syndrome reduction (%)	21.3	30.6	53.6		
RIO-North America (2006) [29]	Change vs. placebo	Placebo	Rimonabant 5 mg	Rimonabant 20 mg	Any adverse events: Placebo:82%; Rimonabant 5 mg:83.4%; Rimonabant 20 mg:85.5%. Serious adverse events: Placebo:3.5%; Rimonabant 5 mg:3.8%; Rimonabant 20 mg:4.5%. Psychiatric disorders: Placebo:2.3%; Rimonabant 5 mg:3.6%; Rimonabant 20 mg:6.2%. Nervous System disorders: Placebo:1.0%; Rimonabant 5 mg:1.2%; Rimonabant 20 mg:2.2%. Gastrointestinal disorders: Placebo:0.7%; Rimonabant 5 mg:0.7%; Rimonabant 20 mg:1.6%.
	Weight change (kg)		-1.3 ± 0.3	-4.7 ± 0.3	
	Weight regain (kg)		-0.8 ± 0.3	-3.6 ± 0.3	
	Waist Circumference (cm)		-0.6 ± 0.3	-3.6 ± 0.3	
	Total C/HDL-C ratio		-0.14 ± 0.04	-0.28 ± 0.04	
	Triglycerides (%)		-4.2 ± 2.3	-13.2 ± 2.3	
	Fasting glucose (mg/dL)		-0.38 ± 0.59	-0.65 ± 0.59	
	Fasting insulin (mU/mL)		-1.7 ± 0.7	-2.8 ± 0.7	
RIO-Lipids (2005) [30]	Change	Placebo	Rimonabant 5 mg	Rimonabant 20 mg	Serious adverse events: Placebo:3.0%; Rimonabant 5 mg:5.7%; Rimonabant 20 mg:4.5%. Psychiatric disorders: Placebo:2.4%; Rimonabant 5 mg:3.5%; Rimonabant 20 mg:6.6%. Nervous System disorders: Placebo:0.9%; Rimonabant 5 mg:0.9%; Rimonabant 20 mg:1.5%. Gastrointestinal disorders: Placebo:0.0%; Rimonabant 5 mg:0.9%; Rimonabant 20 mg:2.4%.
	Weight change (kg)	-1.5 ± 5.0	-3.1 ± 4.8	-6.9 ± 6.1	
	Waist Circumference (cm)	-2.4 ± 5.7	-3.5 ± 6.0	-7.1 ± 6.8	
	HDL-C (%)	11.0 ± 15.8	14.2 ± 17.6	19.1 ± 20.9	
	Peak size LDL particles (A)	-0.9 ± 3.9	-1.0 ± 4.1	0.3 ± 3.8	
	Proportion of small LDL (%)	3.2 ± 18.8	2.2 ± 15.1	-1.5 ± 16.1	
	Triglycerides (%)	-0.2 ± 38.7	1.2 ± 39.4	-12.6 ± 41.2	
	Fasting insulin (%)	0.9 ± 15.9	0.4 ± 10.3	-1.7 ± 12.4	
	Adiponectin (mg/mL)	0.7 ± 1.9	1.0 ± 2.0	2.2 ± 2.5	
	Leptin (ng/mL)	-0.3 ± 6.0	-2.3 ± 7.9	-4.1 ± 7.4	
C-reactive protein (mg/L)	-0.4	-0.2	-0.9		
RIO-Diabetes (2006) [31]	Change	Placebo	Rimonabant 5 mg	Rimonabant 20 mg	Any adverse events: Placebo:79.0%; Rimonabant 5 mg:82.0%; Rimonabant 20 mg:85.0%. Serious adverse events: Placebo:4.0%; Rimonabant 5 mg:8.0%; Rimonabant 20 mg:8.0%. Psychiatric disorders: Placebo:0.9%; Rimonabant 5 mg:0.6%; Rimonabant 20 mg:3.6%. Nervous System disorders: Placebo:0.3%; Rimonabant 5 mg:0.3%; Rimonabant 20 mg:2.1%. Gastrointestinal disorders: Placebo:0.3%; Rimonabant 5 mg:0.0%; Rimonabant 20 mg:2.1%.
	Weight change (kg)	-1.4 ± 3.6	-2.3 ± 4.2	-5.3 ± 5.2	
	Waist Circumference (cm)	-1.9 ± 5.5	-2.9 ± 5.6	-5.2 ± 6.1	
	HBA <sub>1c</sub> (%)	0.1 ± 1.0	-0.1 ± 1.0	-0.6 ± 0.8	
	HDL level (%)	7.1 ± 13.5	9.2 ± 15.8	15.4 ± 17.4	
	Triglycerides (%)	7.3 ± 43.0	1.3 ± 35.1	-9.1 ± 44.3	
	Fasting glucose (mmol/L)	0.33 ± 2.32	0.3 ± 2.06	-0.64 ± 1.96	
	Metabolic syndrome reduction (%)	18	22	26	
	Systolic blood pressure (mmHg)	1.6 ± 13.2	-0.4 ± 12.9	-0.8 ± 12.8	
	Diastolic blood pressure (mmHg)	-0.7 ± 8.4	-0.4 ± 8.5	1.9 ± 8.2	
	hsCRP (mg/L)	0.0 ± 10.0	-0.5 ± 5.8	-1.4 ± 5.2	
	Leptin (ng/mL)	3.1 ± 7.5	1.9 ± 6.1	-0.3 ± 6.0	

tion between 100 and 271 mg/dl and HbA<sub>1C</sub> between 6.5% and 10% (Tab. 1). Approximately two-thirds of patients received concomitant metformin and one third sulfonylurea during the study in addition to a mild hypocaloric diet and an increase of physical activity. Under these treatments, patients were randomly assigned to three groups: placebo (n = 348), 5 mg/day rimonabant (n = 360) or 20 mg/day rimonabant (n = 339) for one year. About 60% patients completed the study in each group. Both rimonabant groups significantly improved weight loss in comparison with placebo. Treatment with 20 mg/day rimonabant also ameliorated HbA<sub>1C</sub> (-0.7%), HDL cholesterol and triglycerides. Importantly, 43% of all subjects treated with 20 mg/day rimonabant achieved an optimal HbA<sub>1C</sub> level (< 6.5%) compared to 21% of those receiving placebo. Treatment with 5 mg/day rimonabant induced smaller improvements in these parameters. Rimonabant was also well tolerated in this study. The incidence of adverse events that led to discontinuation was slightly greater in the 20 mg/day rimonabant group (mainly including depressed mood disorders, nausea and dizziness) (Tab. 2).

### STRADIVARIUS

The Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant – The Intra-vascular Ultrasound Study (STRADIVARIUS) was a prospective, multicenter, multinational, randomized, double-blind placebo-controlled two-group, parallel-group study, involving 112 centers in North America, Europe and Australia [24]. This study was performed to investigate if rimonabant reduces the progression of coronary artery disease in patients with abdominal obesity and metabolic syndrome. It enrolled 839 patients, all of whom were 18 years of age or older, had a waist circumference larger than 88 cm (for women) or 102 cm (for men), respectively, and either met criteria for the metabolic syndrome or were current smokers. Furthermore, they were also required to have had a coronary angiography for a clinical indication demonstrating at least one coronary obstruction with greater than 20% angiographic luminal diameter narrowing. Major exclusion criteria were previous weight loss surgery, uncontrolled diabetes (defined as HbA<sub>1C</sub> > 10%), or urine test that was positive for tetrahydrocannabinol. These patients were randomly assigned to two groups (placebo vs. 20 mg/day rimonabant) and followed for 18 months. Concomitant admi-

nistration of other weight loss agents was prohibited during the study. Although rimonabant ameliorated the normalized total atheroma volume (TAV, secondary endpoint), the study failed to show a decrease in percent atheroma volume (PAV, primary endpoint). These controversial results indicated that the use of rimonabant in the management of coronary disease in patients with central obesity or metabolic syndrome requires further investigation. In accordance with previous results from the RIO-trials, rimonabant ameliorated body weight, waist circumference, HDL cholesterol, triglycerides, CRP and HbA<sub>1C</sub>. On the other hand, this study showed a significant increase of psychiatric and gastrointestinal disorders in the rimonabant-treated group, which were the main reasons for discontinuation of the therapy. The elevated incidence of adverse events in this study (43.4% of psychiatric disorders in the rimonabant group vs. 28.4% in the placebo group) raised some concerns about rimonabant's safety.

### Conclusions

Basic research, animal models and clinical trials clearly show that the endocannabinoid system is a crucial player in inflammatory processes characterizing atherosclerosis. Endocannabinoids induce immunomodulatory effects on several organs and cell types at both central and peripheral levels (Fig. 1 and 2). The selective antagonists of the CB<sub>1</sub> receptors represent very promising therapies for treatment of obesity and related cardiovascular and metabolic disorders. Several studies are needed to examine a possible use for rimonabant in type 2 diabetes and acute and chronic cardiovascular diseases. Clinical trials with rimonabant, a selective antagonist of the CB<sub>1</sub> cannabinoid receptor, have suggested a beneficial effect of this drug in the management of obesity and cardio-metabolic risk factors in humans. These promising outcomes are contrasted by the safety concerns related to the increased incidence of psychiatric adverse events associated with this drug, which has led to the recent withdrawal of this drug from the market during the review process of this manuscript. In the future, selective targeting of peripheral CB<sub>1</sub> receptors may overcome the safety problems associated with currently available CB<sub>1</sub> antagonists such as rimonabant.

For instance, the peripherally restricted CB<sub>1</sub> cannabinoid receptor antagonist URB447 has been shown to reduce feeding and body-weight gain in mice [18]. Other therapeutic approaches targeting the endocannabinoid system may represent the FAAH uptake inhibitors leading to systemically elevated endocannabinoid levels, which are very promising for the treatment of hypertension. Finally, new experimental evidence suggests a therapeutic benefit of CB<sub>2</sub> activation with synthetic selective receptor agonists not only in chronic inflammatory conditions such as atherosclerosis, but also acute myocardial ischemia and reperfusion syndrome [22].

#### Acknowledgments:

This research was funded by EU FP7, Grant number 201668, AtheroRemo, and was supported by a grant from the Swiss National Science Foundation to Dr. F. Mach (# 310000-118245).

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**Received:**

September 25, 2008; in revised form: January 28, 2009.