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Scientific Update™

A Novel Way to Slow the Progression of Atherosclerosis: Inhibition of the Endocannabinoid Receptor

Originally presented by: Steven E. Nissen, MD, and simultaneously published in the *Journal of the American Medical Association*¹

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Reduction of cardiovascular (CV) risk by a multifaceted approach has had a substantial effect on diminishing mortality from coronary and cerebrovascular disease. A recent study by Ford et al² has attributed more than one-half of the reduction in CV mortality over the past 20 years to risk-factor modification. The INTERHEART study³ revealed that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, suboptimal consumption of fruits, vegetables, and alcohol, and lack of regular physical activity account for most of the risk of myocardial infarction (MI) worldwide in both sexes, at all ages. Since abnormal lipids have the greatest population-attributable risk for MI, it follows that cholesterol modification, and low-density lipoprotein cholesterol (LDL-C) reduction in particular, has an important impact on reducing CV events. Both primary- and secondary-prevention trials in patients treated with statins for up to 5 years demonstrate an approximate one-third reduction in morbidity and mortality.⁴ However, two-thirds of the patients in these studies continue to experience CV events despite LDL-C reductions. Lowering this residual risk is one of the greatest challenges in preventive cardiology today. The impact of visceral obesity on atherosclerotic CV disease likely remains an important component of this residual risk. This issue of *Cardiology Scientific Update* considers the link between visceral adiposity and atherosclerosis, and reviews a recent clinical trial examining whether the reduction of cardiometabolic risk with an endocannabinoid inhibitor, rimonabant, translates into slowing the progression of atherosclerosis.

Cardiometabolic risk

The lifestyle of a high proportion of the world's population, characterized by a lack of physical activity and an excessively

energy-dense and highly calorific diet, has led to the current epidemic of abdominal obesity and metabolic syndrome. The prevalence of overweight (body mass index [BMI] >25 kg/m²) and obese (BMI >30 kg/m²) individuals has increased substantially over the past 10-20 years. Approximately one-third of the population of the United States (US) is either overweight or obese.⁵ Epidemiological studies indicate that overweight and obesity are independent risk factors for the development of diabetes, CV disease, and future mortality.^{6,7} The rise in obesity is a major cause for the rapid increase of diabetes prevalence in Canada today. In Ontario, the prevalence of diabetes increased substantially during the past 10 years and, by 2005, had exceeded the global rate that was predicted for 2030.

The Nurses' Health Study demonstrated that BMI, waist circumference, and waist-to-hip ratio are independent predictors for the development of both diabetes⁸ and coronary heart disease (CHD).⁹ Waist circumference and waist-to-hip ratio, as measures of abdominal obesity, predict CV risk better than BMI alone. The INTERHEART study revealed that waist-to-hip ratio is an independent risk factor for MI³ and waist-to-hip ratio was a better predictor of risk across the range of BMI.¹⁰ Both the EPIC-Norfolk study¹¹ and the Dallas Heart study¹² also confirmed waist-to-hip ratio and waist circumference as better predictors of CHD events than BMI. Visceral obesity is associated with the development of insulin resistance,¹³ associated lipid abnormalities, diabetes, and an increased risk for atherosclerotic vascular disease.¹⁴

The endocannabinoid system and atherosclerosis

The endocannabinoid system is an endogenous physiological system that integrates intake, transport, metabolism, and storage of nutrients in the brain, gut, liver, adipose tissue, and muscle. Cannabinoid (CB1) receptors are expressed in the brain, as well as in adipose tissue, liver, gastrointestinal (GI) tract, and skeletal muscle. Increased circulating levels of the physiological

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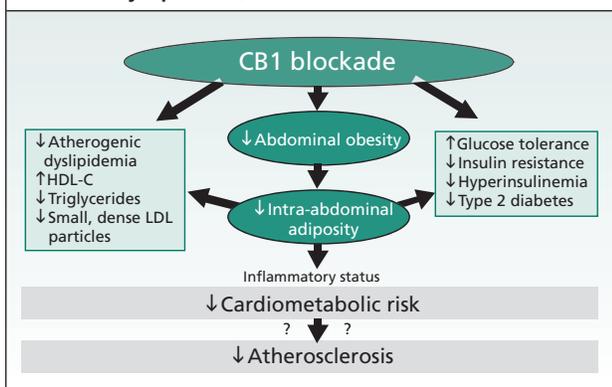
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Figure 1: Endocannabinoid receptor CB1 blockade reduces intra-abdominal adiposity, atherogenic dyslipidemia, and insulin resistance¹



endocannabinoid agonists, 2-arachidonylglycerol and anandamide, are found in subjects with abdominal obesity. Excessive activity of the endocannabinoid system results in increased body weight, increased lipogenesis with consequent dyslipidemia, and reduced insulin sensitivity. Adiponectin levels are reduced, with the consequent glucose intolerance, proinflammatory profile, and enhanced development of atherosclerosis.

Use of the CB1 receptor antagonist, rimonabant, results in weight loss, reduction of abdominal adiposity, and an improvement in cardiometabolic risk factors (Figure 1). The 4 Rimonabant in Obesity (RIO) trials assessed the efficacy and safety of rimonabant in >6,000 overweight and obese patients receiving rimonabant for 1-2 years.¹⁵⁻¹⁹ Not only was weight reduced by approximately 4 kg, but proatherogenic and proinflammatory risk was also diminished by rimonabant therapy. High-density lipoprotein cholesterol (HDL-C) levels increased, there was a shift in the distribution of LDL-C particles towards larger sizes, and a decrease in the inflammatory marker, C-reactive protein (CRP). Furthermore, these metabolic changes were 2-fold greater than would be expected from weight loss alone. These observations support a weight-independent effect of rimonabant in reducing metabolic risk factors for atherosclerosis.

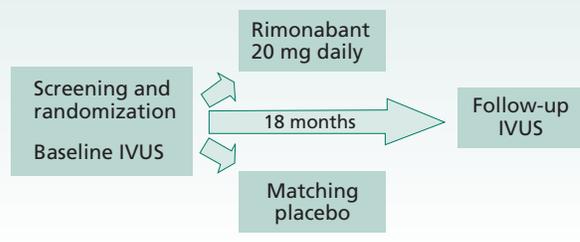
The increased prevalence of abdominal obesity and diabetes is projected to have a major impact on CV disease and associated costs of care. Yet even modest weight loss (5%–10%) can reduce cardiometabolic risk factors. However, current behavioural and dietary approaches to weight loss have limited success, and new approaches to weight loss are needed. Rimonabant produces not only sustained weight loss, but also reduces the metabolic components of cardiometabolic risk. Whether this translates into improved CV outcomes is unknown. The Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant – The Intravascular Ultrasound Study (STRADIVARIUS) is the first in a series of studies to investigate the impact of rimonabant on the progression of atherosclerotic arterial disease.

STRADIVARIUS

STRADIVARIUS¹ was a randomized, double-blind, placebo-controlled trial to evaluate the effect of the CB1 inhibitor,

Figure 2: STRADIVARIUS study design

- Abdominal obesity and features of metabolic syndrome
- Mild hypocaloric diet and smoking cessation counselling



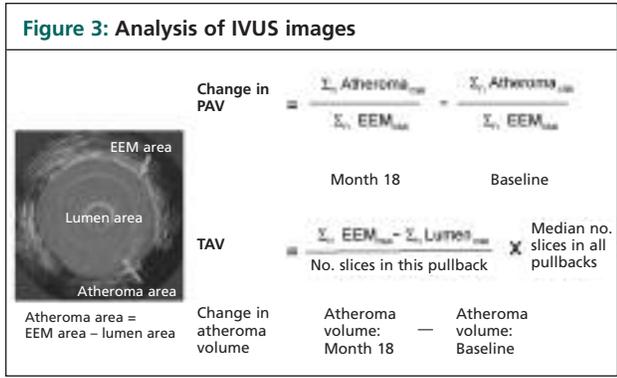
IVUS = intravascular ultrasound

rimonabant, on coronary artery atherosclerosis as assessed by ultrasonic intracoronary imaging (Figure 2). The study was performed at 112 sites in North America (including 6 Canadian centres), Europe, and Australia. Eligible patients had abdominal obesity (waist circumference: men >102 cm, women >88 cm), and 2 additional features of metabolic syndrome that could include: triglyceride level ≥ 1.7 mmol/L, HDL-C <1.04 mmol/L (men) or <1.30 mmol/L (women), fasting glucose ≥ 6.1 mmol/L, or hypertension (defined either by blood pressure $\geq 140/90$ mm Hg or receiving treatment with antihypertensive agents). Eligible patients undergoing a clinically indicated diagnostic coronary angiogram had to have at least 1 coronary luminal narrowing of at least 20%. Patients were excluded if they had uncontrolled diabetes or had undergone weight-loss surgery. Other weight-loss agents, such as orlistat or sibutramine, were not permitted during the study.

The operator selected a single artery for an intravascular ultrasound (IVUS) evaluation; the chosen artery was the longest and straightest vessel that had not undergone prior revascularization nor had a stenosis >50%. IVUS imaging was recorded in the longest possible vessel segment, and a core laboratory analyzed the recorded images. Following a successful baseline IVUS recording, the patients were randomized to receive either rimonabant (20 mg daily) or matching placebo for a period of 18-20 months. A follow-up IVUS examination of the identical coronary artery segment studied at baseline was repeated, either at 18-20 months or earlier if the patient needed coronary angiography between 12-18 months. The patients received the follow-up IVUS study on an intent-to-treat basis, whether or not they were continuing on the study medications.

The IVUS analysis is shown in Figure 3. The primary efficacy parameter was the change in percent atheroma volume (PAV) between baseline and month 18. A secondary efficacy parameter, normalized total atheroma volume (TAV), was calculated; first, the mean atheroma area per cross-section was determined and then normalized for the median number of slices for each artery in all the studies.

Baseline characteristics were well-matched between the treatment and placebo groups. The patients were typical of those with metabolic syndrome: average age 57.7 years; 65% male; waist circumference 117 cm; BMI 35.3 kg/m²; incidence of hypertension, 87%; triglycerides ≥ 1.7 mmol/L, 58%; HDL-C <1.03 mmol/L, 64%; and fasting blood glucose ≥ 6.1 mmol/L, 52%.

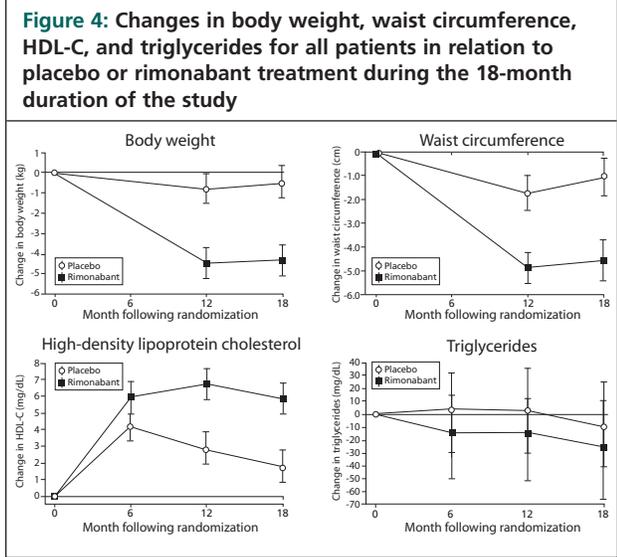


PAV = percent atheroma volume; EEM = external elastic membrane; CSA = cross-sectional area; TAV = total atheroma volume

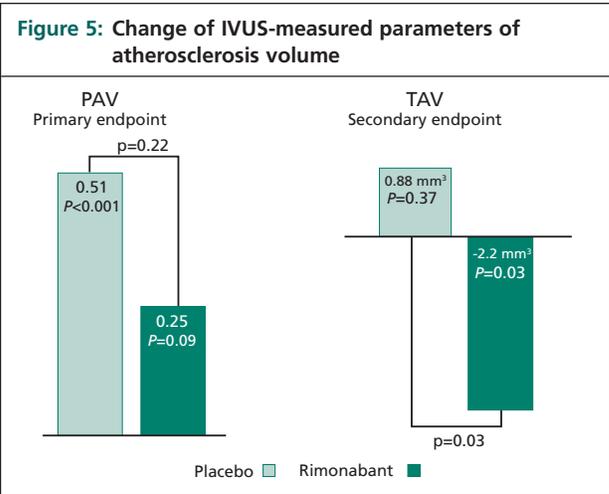
There was a high utilization of medications for the prevention of vascular disease that included acetylsalicylic acid (ASA) 91%, clopidogrel or ticlopidine 60%, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers 69%, statins 82%, and beta-blockers 70%. Oral hypoglycemic agents were used in 30%, and 11% of patients were taking insulin. A history of psychiatric disease was recorded in 25%, 47% were taking a benzodiazepine, and 19% used an antidepressant.

Rimonabant treatment for 18 months yielded improvements in cardiometabolic risk factors. Patients receiving rimonabant lost 4.3 kg weight (vs placebo -0.5 kg), and reduced their waist circumference 4.5 cm (vs placebo 1 cm; Figure 4). HDL-C increased 22.4% (placebo +6.9%) and triglycerides were reduced 20.5% (placebo -6.2%). Hemoglobin A_{1c} (HbA_{1c}) decreased 0.13% (vs placebo +0.43%), and high-sensitivity (hs) CRP decreased 50.3% (vs placebo -30.9%).

The change from baseline to follow-up for the primary (PAV) and secondary (TAV) efficacy endpoints of the trial are shown in Figure 5. There was a nonsignificant increase in PAV in the rimonabant group and a significant increase for the placebo



Adapted from Nissen SE et al. *JAMA*. 2008;299(13):1547-1560. Copyright © 2008 American Medical Association. Used with permission.



group. The difference in PAV between baseline and the final follow-up examination was not significantly different between the placebo- and rimonabant-treated patients. By contrast, the secondary efficacy endpoint, TAV, revealed significant differences between the placebo and treatment groups over the treatment period. In the placebo group, TAV did not change significantly (+0.88 mm³; 95% confidence interval [CI], -1.03 to 2.79 mm³); yet, in the rimonabant group TAV decreased by 2.2 mm³ (95% CI, -4.09 to -0.24 mm³). The difference between the TAV in the treatment and placebo groups was statistically significant (P=0.03). Further, IVUS analysis demonstrated that rimonabant significantly decreased the maximum atheroma thickness, whereas there was no change in the placebo-treated group. Nevertheless, there was no change in atheroma volume in the 10 mm of most severely diseased artery segment for either treatment group. Analyses performed to determine whether the study result was affected by the failure to complete the follow-up IVUS examination in all patients revealed no change in either primary (PAV) or secondary (TAV) IVUS outcomes.

Although the study was not adequately powered to examine clinical outcomes, no differences in mortality or CV events were observed between placebo- and rimonabant-treated patients. The most commonly observed adverse events in rimonabant-treated patients were GI and psychiatric in nature. There was an excess of anxiety (18% vs 11.8%, P=0.01) and depression (16.8% vs 11.3%, P=0.02), although major depression and suicidal ideation were similar in both groups. Nausea was more common in the rimonabant group (14.9% vs 5.5%, P<0.001). Erectile dysfunction was also reported more frequently by patients receiving rimonabant (3.3% vs 0.7%, P=0.03). Adverse effects resulting in discontinuation of the study medications were more frequent in the rimonabant group (17.5% vs 7.5%, P<0.001). Depression (3.6%), anxiety (3.1%), and nausea (3.1%) were the most common reasons why patients receiving rimonabant discontinued treatment.

Rimonabant and atherosclerosis

In STRADIVARIUS, rimonabant reduced weight (-4.3 kg) and waist circumference (-4.5 cm), improved the lipid profile

(22.4% increase of HDL-C and 20.5% reduction of triglycerides), and reductions in hsCRP and HbA_{1c} were consistent with those observed in previous trials. There was no change in atherosclerosis progression by the PAV measurement, but a significant reduction in the rate of progression was observed when TAV was used.

The PAV measurement represents the ratio of atheroma volume to external elastic membrane (EEM) volume and has been the most robust measurement in IVUS trials with statin therapy. In contrast, the secondary IVUS endpoint, TAV, is solely a measure of the atheroma volume. Consequently, if atheroma volume and EEM volume decreased, little change may be observed in PAV, but a significant reduction in TAV is seen. Based on experience with prior trials, however, it is unclear why the improvement in risk factors did not result in a more robust reduction for PAV. In subgroup analyses, it was observed that patients who were not on statins appeared to have slower atherosclerosis progression. This may suggest that an interaction between rimonabant and statins could have limited the benefits of rimonabant in the patients (80%) who were receiving statins. Atherosclerosis progression was also slower in subjects receiving rimonabant who had higher triglyceride levels. This observation may indicate greater benefits from CBI inhibition in subjects with the greatest metabolic derangement. In addition, the duration of treatment may not have been sufficiently adequate to observe a reduction in the progression of atherosclerosis. Furthermore, risk factors are not immediately optimized by rimonabant treatment. It is notable that HDL-C did not increase significantly after 6 months of treatment and was only increased at 1 year. Medication discontinuation was more frequent in the rimonabant group (~28%) compared with the placebo group (~16%). Since the analysis of the IVUS was on an intention-to-treat basis, an important number of patients received no treatment for long periods. This may have reduced the power of the study to observe a difference between groups.

STRADIVARIUS reveals that rimonabant resulted in weight loss and an improved cardiometabolic risk profile consistent with the findings from the RIO series of clinical trials. Although the primary endpoint of PAV was not changed after 18-20 months treatment with rimonabant, TAV was reduced significantly. To determine whether rimonabant is useful clinically will require further trials with both imaging and clinical outcomes. Currently, 2 clinical trials are examining the effects of rimonabant on atherosclerosis and outcomes. The Atherosclerosis Underlying Development Assessed by Intima-media Thickness in Patients on Rimonabant (AUDITOR) study will examine the effect of a 30-month treatment with rimonabant on carotid intima-media thickness. Effects on long-term clinical outcomes will be examined in the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial with 17,000 patients at high risk for CV events. Only with these trials will we know whether rimonabant favourably influences the progression of atherosclerosis and, thus, improves clinical outcomes.

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