Effect of rimonabant on carotid intima—media thickness (CIMT) progression in patients with abdominal obesity and metabolic syndrome: the AUDITOR Trial

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ABSTRACT

Objective The aim of this trial was to determine whether obese patients benefit from treatment with rimonabant in terms of progression of carotid atherosclerosis. Rimonabant, a selective cannabinoid-1 receptor blocker, reduces body weight and improves cardiometabolic risk factors in patients who are obese.

Design, setting, patients, interventions and results A prospective, double-blind, placebo-controlled trial (Atherosclerosis Underlying Development assessed by Intima—media Thickness in patients On Rimonabant (AUDITOR)) randomised 661 patients with abdominal obesity and metabolic syndrome to rimonabant or placebo for 30 months of treatment. The absolute change in the average value for six segments of far wall carotid intima—media thickness from baseline to month 30 was 0.010 ± 0.095 mm in the rimonabant group and 0.012 ± 0.091 mm in the placebo group ($p=0.67$). The annualised change was an increase of 0.005 ± 0.042 mm for the rimonabant-treated group and 0.007 ± 0.043 mm for the placebo-treated group ($p=0.45$).

Conclusions There was no difference in atherosclerosis progression between patients receiving rimonabant for 30 months and those receiving placebo for the primary efficacy measure (absolute change in carotid intima—media thickness). These findings are consistent with a similar study using coronary intravascular ultrasound and another study evaluating the occurrence of cardiovascular events. Our findings suggest that a 5% loss of body weight over a 30-month period with rimonabant is insufficient to modify atherosclerosis progression in the carotid artery in obese patients with metabolic syndrome.

Clinical trial registration information clinicaltrials.gov Identifier: NCT00228176.

INTRODUCTION

Because of a sedentary lifestyle and over-consumption of calories, an increasing proportion of the population is overweight or obese.[1][2] A particularly vulnerable subgroup is characterised by an excess of abdominal fat and by a constellation of metabolic abnormalities linked to insulin resistance, a condition commonly referred to as the metabolic syndrome.[3] Patients with metabolic syndrome are at higher risk of type 2 diabetes and cardiovascular disease.[4–7] Visceral obesity, closely associated with insulin resistance, is thought to play a crucial role in the underlying pathophysiology of the metabolic syndrome.[8] However, the component of the metabolic syndrome that is most resistant to intervention in clinical practice is abdominal obesity. This situation has stimulated the search for safe and effective pharmacological approaches to managing abdominal obesity and related metabolic abnormalities. One proposed strategy for treatment of obesity consists of inhibition of the endocannabinoid type 1 (CB1) receptors in both the central nervous system and peripheral tissues.[9]

Rimonabant was the first selective antagonist of CB1 cannabinoid receptors tested in large clinical trials. The efficacy and safety of rimonabant has been investigated in several multicentre, double-blind, placebo-controlled studies in non-diabetic obese patients and in a single trial in obese patients with type 2 diabetes.[10–14] Overall, significant weight loss and reduction in waist circumference have been reported with rimonabant accompanied by improvements in high-density lipoprotein cholesterol (HDL-c), triglycerides (TGs), glycosylated haemoglobin (HbA1c) and insulin sensitivity. The ADAGIO-Lipids Imaging Study reported a 16% loss of visceral fat and evidence of mobilisation of liver fat measured by CT in abdominally obese dyslipidaemic subjects treated with rimonabant for 1 year.[15] These findings suggest that rimonabant may have a beneficial effect on atherosclerosis in patients with excess visceral adiposity and/or liver fat and with the features of the metabolic syndrome. The AUDITOR Study was designed to test the hypothesis that 20 mg rimonabant would reduce progression of carotid intima—media thickness (CIMT) over 30 months of treatment when added to usual background therapy in abdominally obese patients with the metabolic syndrome.

METHODS
Study design

The AUDITOR Study was a prospective, multicentre, placebo-controlled, double-blind, randomised, two-arm parallel group study that compared

rimonabant 20 mg once daily with matching placebo in addition to usual care in patients with abdominal obesity and metabolic syndrome. It was conducted at 64 centres in North America (USA, Canada) and Europe (France, The Netherlands, Spain, UK) between August 2005 and April 2009. The institutional review boards of all participating centres approved the protocol. Written informed consent was obtained from all patients before enrolment in the trial. Inclusion criteria required that patients were ≥55 years old, had abdominal obesity (waist circumference >88 cm in women or >102 cm in men), and met two additional criteria for the Metabolic Syndrome as defined by National Cholesterol Education Program Adult Treatment Panel III guidelines. These criteria included: fasting TG concentrations of ≥150 mg/dl, HDL-c <40 mg/dl for men or <50 mg/dl for women, fasting glucose ≥110, high blood pressure (≥140 mm Hg systolic and/or ≥90 mm Hg diastolic, or current treatment by anti-hypertensive medication).[16] Inclusion also required that all six carotid artery segments during a screening ultrasound exam would allow CIMT measurement, a minimum thickness of ≥0.7 mm in at least one of the (common carotid artery) (CCA) far wall, and that the maximum CIMT measurement would be <3 mm in every segment of the carotid artery. Exclusion criteria precluded a history of surgical procedure for weight loss within the previous 6 months, uncontrolled diabetes (HbA1c >10%), severe renal dysfunction (creatinine concentration ≥2.0 mg/dl), active liver disease, obesity of known endocrine origin, significant haematology abnormalities, total occlusion of any carotid artery, a previous history of carotid intervention, or high likelihood of carotid intervention during the course of the study.

Two carotid ultrasounds were performed before randomisation. An initial study was completed and submitted to a single imaging core laboratory (Imagepace, Cincinnati, OH, USA). Within 2 weeks, a second scan was performed on patients meeting enrolment criteria. This second scan served as the baseline CIMT. Enrolled patients were centrally randomised in a 1:1 ratio to 30 months of double-blind treatment with rimonabant (20 mg daily) or placebo. Eligible patients were randomly assigned a treatment number at randomisation by using a central interactive voice response system, and were then provided with the corresponding kit box of study drug. A randomisation schedule, stratified by clinical centre, using balanced blocks was established by the sponsor before the start of the trial.

Patients were counselled to follow a mildly hypocaloric diet, to increase their physical activity level, and to stop smoking if applicable. During a randomisation visit, a fasting blood sample was obtained for baseline assessment of lipid and blood glucose concentrations. Investigators were instructed to treat patients for other risk factors according to local guidelines, including use of lipid-lowering, blood pressure-lowering, or glucose-lowering agents. During follow-up, patients were examined every 6 months for laboratory testing, clinical evaluation, and carotid ultrasound examination. The study was discontinued in November 2008, when the European Medicines Agency had suspended the drug because the benefits of rimonabant no longer outweighed its safety risks.

CIMT end points
The primary prespecified end point was the difference in absolute change in averaged per patient CIMT from baseline to month 30 between treatment groups. For each scan, a maximum of six sites were available for averaging: far wall of the right and left CCA, carotid bulb (CB) and internal carotid artery (ICA).

Readings from two image analysts were also averaged to derive the mean CIMT end point.

CIMT protocol
Among the 64 clinical centres, 29 were also designated as imaging centres because of their ability to perform carotid ultrasound studies. Three additional imaging centres were used where no recruitment was performed. All 32 imaging centres were equipped with the same ultrasound equipment (Acuson Sequoia and 8L5 linear array transducer; Acuson-Siemens, Mountainview, California, USA). Using a standardised imaging protocol, magnified, single, grayscale images of the carotid artery at three locations on the right and left were obtained in the distal CCA, CB and the proximal ICA. The images were obtained with the probe held at a standardised 45° angle at each location and the participant's head rotated 45° away from the side of study. Each segment was captured as a single or static image and was accompanied by a 3—5 s cine loop for two complete cardiac cycles. All static images were obtained at end diastole using EKG gating and were adjusted to optimally visualise the intima—media complex of the far and near wall of each segment over a 1 cm length of artery. Images were recorded on to two CDs, one maintained within the patient binder at the imaging centre and the other submitted to the imaging core laboratory. Qualitative review of the images was performed throughout the study to permit regular quality reports to be prepared for all sonographers. Like the screening scan, it was required that the month-30 scan had six measurable far wall segments. If this protocol requirement was judged not to have been fulfilled upon review of the end-of-trial scan by the imaging core laboratory, the sonographer was required to perform another rescan within 14 days. Off-line batch readings were performed after acceptance of the last CIMT study for each participant by the imaging core laboratory. CIMT measurements, defined as the distance between the leading edges of the lumen—intima and media—adventitia interfaces, were obtained on all images judged to display these structures. There were a maximum of six carotid segments per scan (CCA, ICA, and CB, right and left), and a maximum of seven scans (screening, baseline, month 6, month 12, month 18, month 24 and month 30 (original scan or potential rescan)) available for analysis for each participant.

Training and certification was performed for all sonographers before any subject scans were preformed. All sites were given a Siemens Acuson Sequoia that was configured exactly the same. All scans were performed according to predefined acquisition protocol and predefined study settings installed on the system. Sonographers were certified by Imagepace (imaging core laboratory) contracted by the sponsor. Certification was divided into several stages as described below:
1. Training: each sonographer participated in a training session before any subject scans were performed. Upon completion of the training, using the same equipment that would be used in the study, they submitted a training scan which demonstrated key components of the acquisition protocol.
2. Phase 1: single scan per protocol
3. Phase 2: one set of replicate scans (on the same subject performed within 7 days) meeting predefined criteria
4. Phase 3: three sequential pairs of replicate scans all meeting the predefined criteria
5. Phase 4: annual recertification submission of two sets of replicate scans meeting the same criteria.

In order to ensure ongoing proficiency of the sonographers during the course of the study, and in addition to the phase 4 process described above, a process was implemented to require

sonographers to submit periodic scans during periods in which no actual subject scans were being preformed based on the study enrolment and predefined imaging timelines. Moreover, low-activity scans were required if a sonographer had not performed study scans (subject or certification) within the previous 60 days. Sonographers submitted a replicate pair on a volunteer.

Threshold values for certification:

▶ Readers were certified if the SD of inter-reader mean—mean intima—media thickness difference ≤0.05 mm
▶ Sonographers were certified if phases 1, 2 and 3 had been passed
▶ Scans were performed per protocol
▶ Volunteer scan pairs each had a mean—mean intima—media thickness difference ≤0.15 mm

For each arterial segment, readers were trained to manually trace the far wall lumen—intima and media—adventitia interfaces using study-dedicated software for each arterial segment. All available studies for a single participant were displayed simultaneously in blinded random order on the workstation monitor. Each reader was blinded to treatment category, patient identification and assessment sequence, except that they were aware of which scan was the reference, it being either the baseline scan or the screening scan depending on which displayed the greater number of measurable segments. Every patient study was interpreted by two readers independently, with neither aware of the other's measurements. Upon completion of the interface tracings, an automated measurement algorithm calculated the distance between the lines and provided minimum, maximum, average and SD values. A total of six readers were involved in the batch-reading process. This number was selected to minimise reader variability while having sufficient numbers to complete the batch readings within the study-specific timeline. Before the batch readings were performed, 10 study patients were selected at random from all patients having the complete set of seven scans. Each reader was assigned the selected 10 patients' batches twice (20 batches total) in the same manner as the study batch process as detailed in the study-specific carotid ultrasound analysis protocol. The 70 replicate scans (10 patients×7 visits) were analysed for intra-reader variability based on the primary study efficacy variable (mean—mean CIMT). The combined mean of the mean of the three segments for the first reading for the six readers was 0.811 mm (SD±0.119 mm) and for the second reading was 0.808 mm (SD±0.124 mm). The interclass correlation coefficient was 0.931 for the reader's 70 replicate readings. The mean intrareader absolute difference was 0.031 mm (SD±0.033 mm).

Laboratory tests

At randomisation, 3 months, 6 months and subsequently every 6 months, blood was collected for metabolic risk factors (fasting glucose, HbA1c, TGs, HDL-c, low-density lipoprotein cholesterol (LDL-c), high-sensitivity C-reactive protein (hs-CRP)) and safety testing including liver and renal function tests, creatinine kinase, haematology (haemoglobin, packed cell volume, white blood cell differential, platelets), thyroid stimulating hormone, and urine analysis. All laboratory tests were performed in a certified, central clinical laboratory (MDS Pharma Services, Mississauga, Canada).

Clinical outcomes and safety assessment

Secondary, non-CIMT vascular end points included the first occurrence of any of the following events: stroke, myocardial infarction, hospitalisation for revascularisation procedure, unstable angina, transient ischaemic attack or cardiovascular

death. A Data and Safety Monitoring Board was established composed of academic members who were not otherwise participating in the trial. Participants were assessed at baseline for safety by clinical history, laboratory testing, ECG, blood pressure testing, vital signs, height and measurement of waist circumference. These studies were repeated every 6 months at the time of follow-up CIMT testing visits. Information on adverse reactions was obtained in person at baseline and at the time of each repeat CIMT visit, and by telephone at 3 months between clinic visits. In addition, there was a safety visit after the post-treatment period at 35 months to capture all adverse events, including those occurring within 75 days of study drug discontinuation.

Statistical analysis

The study protocol defined the primary efficacy end point as the absolute change in averaged per patient CIMT from baseline to month 30. For each ultrasound examination, CIMT measurements were combined for the six carotid segments. Therefore the dependent primary efficacy variable was the CIMT value from screening to month 30 at each of six insonated segments, by two independent readers. The primary efficacy analysis population was the intent-to-treat population, defined as all randomised patients having at least one post-randomisation CIMT measurement. The primary analysis was repeated-measurements analysis of covariance (ANCOVA) with time, treatment (rimonabant or placebo) and treatment-by-time interaction as fixed effects; the dependent variable was the averaged per patient CIMT measurement. The time in the model was a continuous variable, defined as the time elapsed from randomisation to CIMT measurement in years. The primary end point (change in averaged per patient CIMT in mm from baseline to month 30) was assessed using appropriate contrast within the framework of repeated-measurements ANCOVA. Patients with no valid CIMT measurements at month 30 (as well as any missing segment at any CIMT measurement) were handled by the use of the mixed-effect model with repeat measures described above. This model takes into account all available data for each patient to allow appropriate estimates from baseline to month 30, under the random framework. LS means and p value are from a linear mixed model (Laird—Ware model), which includes treatment as a factor, time as a covariate, and an interaction between treatment and time, with randomly varying intercepts and slopes. Sample size calculations were based on the ability to detect a 0.04 mm difference in CIMT progression between rimonabant and placebo over 24 months (later extended to 30 months). It was estimated that 297 patients/arm would support 90% power to detect a mean difference of 0.04 mm versus control, based on SD=0.15 mm, two-sided test, and α=5%. The scenario required a total of 600 patients. The time from randomisation to each cluster end point (stroke, myocardial infarction or cardiovascular death) was compared between the two treatment groups using a two-sided log rank asymptotic test. Cumulative incidence functions in each treatment group were calculated and plotted using Kaplan—Meier estimate. The corresponding 95% CI was computed at each scheduled time point of the protocol (month 3, month 6, and then every 6 months up to month 30) using Greenwood's variance estimation. The significance of the difference in terms of the incidences of treatment-emergent adverse events between the rimonabant and placebo group was examined with the Fisher exact test. To calculate differences in baseline characteristics between groups, χ^2 test was performed for categorical variables, and t test for continuous variables.

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Changes in laboratory variables were analysed using an ANCOVA model with treatment as a factor and baseline values as a covariate.

RESULTS
Baseline characteristics
Enrolment occurred between August 2005 and April 2006. The final participant completed the trial in April 2009. The flow of patients in the trial is reported in figure 1, including reasons for screening failures and non-completion. A total of 661 patients were randomised, 326 to rimonabant 20 mg daily and 335 to placebo. One participant from the rimonabant group was randomised but received no drug. Of the 661 participants randomised, 660 (99.8%) had post-baseline laboratory results on or off study drug and whether or not an end-of-study carotid ultrasound was obtained (325 (99.7%) in the rimonabant-treated group and 335 (100.0%) in the placebo-treated group). Among the 661 participants, 640 (96.8%) had at least one post-baseline CIMT (313 (96.0%) in the rimonabant-treated group and 327 (97.6%) in the placebo-treated group), and 566 (85.6%) had a final CIMT measurement at month 30, whether on or off study drug. A total of 440 (66.6%) patients (207 (63.5%) in the rimonabant group and 233 (69.6%) in the placebo group) completed the study treatment period and underwent month-30 CIMT ultrasound. The most common reason for discontinuing

the study drug was an adverse event, 74 (22.7%) in the rimonabant group versus 40 (11.9%) in the placebo group.

The two groups were well balanced for baseline characteristics (online supplementary table 1). Of the 661 patients randomised in AUDITOR, all met the protocol definition of abdominal obesity, and all but six (99%) met the criteria of metabolic syndrome. Metabolic syndrome risk factors were equally distributed. Diabetes was present in 126 (39%) of the rimonabant group and 124 (37%) of the placebo group. Weight was similar in both treatment groups (97.0±17.4 vs 97.5±17.7 kg, for rimonabant and placebo, respectively). Mean age was 62.8 years, and waist circumference was 112 cm in both groups. The use of statin medication was comparable in both groups (48% for the rimonabant-treated group vs 49% for the placebo-treated group). Because data from other studies suggested a potential for psychiatric and neurological adverse events from rimonabant, a detailed questionnaire was used at each patient visit to assess these. A history of psychiatric disease was reported at baseline by 83 (26%) of those receiving rimonabant and by 90 (27%) of those receiving placebo.

Effect of rimonabant on body weight, waist circumference and risk factors
All subjects saw the dietician once at the baseline visit. There was no difference in the number of visits to the dietician between the groups. Rimonabant treatment resulted in

Figure 1 Flow of patients through trial.

O'Leary DH, Reuwer AQ, Nissen SN, et al. Heart (2011). doi:10.1136/hrt.2011.223446
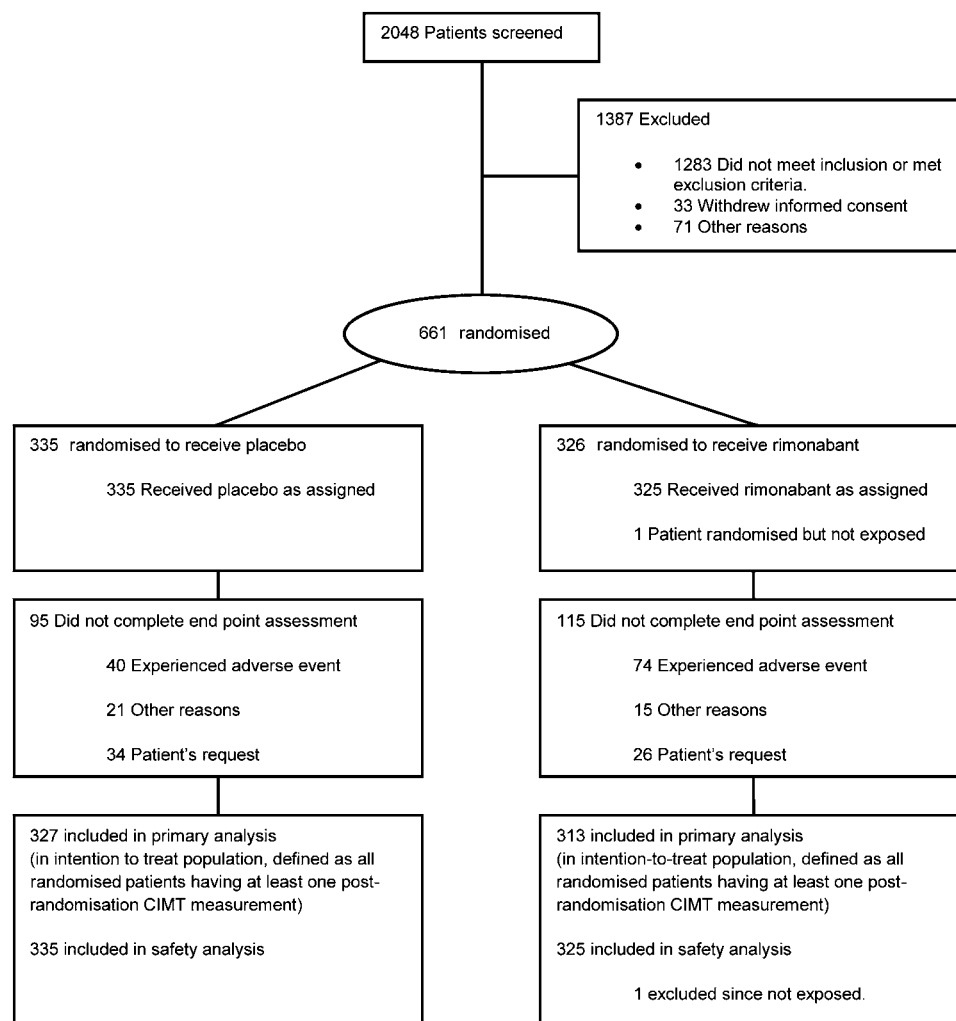
a decrease in body weight of 4.8±6.7 kg compared with 1.6±6.4 kg in the placebo group (4.9% vs 1.4%; p<0.0001), and a reduction in waist circumference of 4.9±6.7 cm compared with 2.0±6.6 cm in the placebo group (4.4% vs 1.6%; p<0.0001) after 30 months compared with baseline (table 1). HDL-c increased by 0.07±8.4 mg/dl (1.0%) in rimonabant-treated patients compared with a decrease of 3.3±7.6 mg/dl (−5.8%) in the placebo group (p<0.0001). Systolic blood pressure fell by 2.3±17.5 mm Hg (1.1%) in the rimonabant group compared with a decrease of 0.1±16.6 mm Hg (0.5%) in the placebo group (p=0.29). Diastolic blood pressure fell by 3.1±10.4 mm Hg (3.0%) in the rimonabant group compared with 2.2±10.3 mm Hg (2.0%) in the placebo group (p=0.48). There was no significant difference between LDL-c concentrations in both groups after treatment (rimonabant vs placebo −0.6±33.3 vs 0.2±34.0 mg/dl; −6.5% and 7.7%, respectively; p=0.73). In the rimonabant-treated group, there was a greater decrease in hs-CRP (0.31 (−1.50; 0.50) mg/l and 0.02 (−1.15; 0.90) mg/l; 18.8% vs 0.9%, respectively; p=0.03) and in HbA1c concentrations (0.1±0.7% vs 0.04±0.6%, respectively; p=0.08) than in placebo-treated patients. In the subgroup of patients with diabetes, there was no difference in terms of the decrease in HbA1c (absolute change 0.28% vs 0.13%; rimonabant vs placebo, respectively; p=0.17).

Effect of rimonabant on CIMT

Baseline CIMT was similar in the rimonabant-treated group and the placebo-group (0.816±0.167 mm vs 0.828±0.171 mm; p=0.38) (table 2). During the 30-month period, the absolute change in average per patient far wall CIMT over 30 months was 0.010±0.095 mm in the rimonabant group and 0.012±0.091 mm in the placebo group (p=0.67). The averaged per patient CIMT progressed from baseline to month 30 in both treatment groups, and there was no significant difference between these two groups, as shown in table 2 and figure 2. The average yearly progression for the rimonabant-treated group was 0.005±0.042 mm/year versus 0.007±0.043 mm/year for the placebo-treated group (p=0.45). The estimated difference in progression for the rimonabant-treated group versus the placebo-treated group was −0.002±0.003 mm (p=0.53).

Cardiovascular end points and adverse events

There was no difference between study groups for the time to new stroke, myocardial infarction or cardiovascular death in the intention-to-treat population (p=0.43) (figure 3). Adverse events were more common in the rimonabant group than in the placebo group for nervous system disorders (153 vs 129; 47% and 39%, respectively; p=0.03), psychiatric disorders (138 vs 104; 43% and 31%, respectively, p=0.003) and gastrointestinal disorders (132 vs 106; 41% and 32%, respectively, p=0.02), as were adverse events leading to permanent study drug discontinuation (74 vs 40; 23% vs 12%, respectively; p≤0.0001). In contrast, the incidence of serious adverse events as defined by study protocol were similar (57 vs 56; 18% and 17%, respectively; p=0.84), and there was an equal number of suicidal ideation (three in both groups). For a complete overview of treatment-emergent adverse events, please refer to online supplementary table 2. Any treatment-emergent adverse event leading to death occurred three times in the rimonabant group (0.9%) and twice in the placebo group (0.6%). In the rimonabant group, one patient died because of metastases of an oesophageal carcinoma, another died as a result of bladder carcinoma, and the third in this group died from non-small-cell carcinoma of the right lung. In the placebo group, one patient died as a result of

Table 1 Change from baseline for patients with post-baseline laboratory results (n=660)

Variable	Baseline		Month 30		Arithmetic change from baseline			% Change from baseline		
	Rimonabant (n=325)	Placebo (n=335)	Rimonabant (n=325)	Placebo (n=335)	Rimonabant (n=325)	Placebo (n=335)	p Value for change	Rimonabant (n=325)	Placebo (n=335)	p Value for % change
BMI (kg/m²)	33.7 (5.3)	34.1 (6.0)	32.0 (5.3)	33.5 (5.9)	−1.7 (2.4)	−0.5 (2.2)	<0.0001	−4.9 (6.4)	−1.4 (6.0)	<0.0001
Waist circumference (cm)	111.5 (11.8)	112.4 (12.2)	106.6 (12.5)	110.4 (12.0)	−4.9 (6.7)	−2.0 (6.6)	<0.0001	−4.4 (5.9)	−1.6 (5.6)	<0.0001
SBP (mm Hg)	140.8 (16.3)	138.7 (16.5)	138.4 (18.2)	138.6 (17.4)	−2.3 (17.5)	−0.1 (16.6)	0.29	−1.1 (12.2)	0.5 (12.2)	0.26
DBP (mm Hg)	82.0 (9.5)	81.2 (10.3)	78.9 (10.1)	79.0 (10.7)	−3.1 (10.4)	−2.2 (10.3)	0.48	−3.0 (13.3)	−2.0 (12.8)	0.54
Weight (kg)	96.7 (17.3)	97.6 (17.7)	91.9 (17.2)	96.1 (17.6)	−4.8 (6.7)	−1.6 (6.4)	<0.0001	−4.9 (6.4)	−1.4 (6.0)	<0.0001
HDL-c (mg/dl)	49.3 (11.3)	50.0 (12.8)	49.3 (12.6)	46.7 (13.0)	0.07 (8.4)	−3.3 (7.6)	<0.0001	1.0 (17.1)	−5.8 (15.2)	<0.0001
LDL-c (mg/dl)	111.5 (39.7)	111.6 (42.3)	111.0 (36.9)	111.8 (42.8)	−0.6 (33.3)	0.2 (34.0)	0.73	−6.5 (37.4)	7.7 (52.4)	0.70
Triglycerides (mg/dl)*	169.2 (118.7; 237.4)	175.4 (135.5; 241.8)	144.4 (105.4; 208.1)	153.2 (123.1; 217.9)	−19.5 (−63.8; 15.9)	−14.2 (−61.1; 21.3)	0.24	−15.1 (−33.5; 11.0)	−9.3 (−30.6; 14.9)	0.13
hs-CRP (mg/l)*	2.44 (1.30; 4.70)	2.60 (1.40; 5.32)	2.00 (1.06; 4.00)	2.50 (1.36; 4.60)	−0.31 (−1.50; 0.50)	−0.02 (−1.15; 0.90)	0.03	−18.8 (−48.4; 29.4)	−0.9 (−37.9; 45.0)	0.01
HbA1c (%)	6.3 (0.9)	6.3 (0.9)	6.2 (0.9)	6.3 (0.9)	−0.1 (0.7)	−0.04 (0.6)	0.08	−1.7 (9.0)	−0.2 (9.2)	0.05
Glucose (mg/dl)	122.8 (35.6)	121.6 (34.2)	121.1 (31.5)	119.9 (36.0)	−1.7 (28.2)	−1.7 (33.8)	0.81	0.9 (18.0)	0.9 (24.1)	0.87

Unless otherwise stated, values are mean (SD). p Values are from an analysis of covariance model with treatment as a factor and baseline values as a covariate.
*Results reported as median (Q1, Q3).
BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin; HDL-c, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

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Table 2 Baseline, month-30 follow-up, and change from baseline for averaged per patient carotid intima—media thickness (CIMT) for six segments for patients having at least one post-baseline CIMT study (n=640)

Variable	Rimonabant (n=313)	Placebo (n=327)	p Value
Baseline, mean (SD)	0.816 (0.167)	0.828 (0.171)	0.38
Month-30 end point, mean (SD)	0.827 (0.170)	0.840 (0.186)	0.33
Arithmetic change from baseline to month-30 end point, mean (SD)	0.010 (0.095)	0.012 (0.091)	0.67*
Progression/year, mean (SD)	0.005 (0.042)	0.007 (0.043)	0.45*
Month-30 end point, LS mean (SE)	0.825 (0.010)	0.845 (0.010)	
Progression/year, LS mean (SE)	0.004 (0.002)	0.006 (0.002)	
Difference in progression versus Placebo, LS mean (SE)		−0.002 (0.003)	0.53†

*p Value is from an analysis of covariance model with treatment as a factor and baseline CIMT as a covariate.

†LS means and p value are from a linear mixed model (Laird—Ware model) which includes treatment as a factor, time as a covariate and an interaction between treatment and time, with randomly varying intercepts and slopes.

extraovarian ovarian carcinoma and one patient died from pancreas carcinoma with metastases to the liver.

DISCUSSION

Rimonabant was the first potent and selective antagonist of CB1 receptors, and its use results in a reduced motivation to consume food.[9] In clinical studies, this CB1 receptor antagonist also reduced body weight, abdominal obesity, and improved several components of the metabolic syndrome.[10–15] Since abdominal obesity is associated with the metabolic syndrome and the latter condition increases the risk of atherosclerotic vascular disease,[4–6] we hypothesised that treatment with rimonabant would slow atherosclerosis progression and would ultimately result in a reduction of cardiovascular end points. However, in the AUDITOR Study, treatment with rimonabant over a 30-month period had no statistically significant effect on the progression of atherosclerosis as assessed by CIMT. It has been widely acknowledged that CIMT predicts the occurrence of cardiovascular events.[17 18]
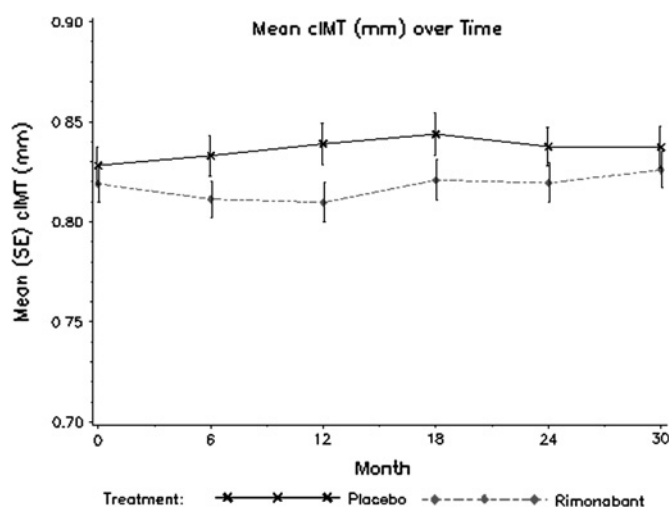
Figure 2 Averaged per patient carotid intima—media thickness (CIMT) from baseline to month 30. The primary efficacy analysis population was the intent-to-treat population, defined as all randomised patients having at least one post-randomisation CIMT measurement. The averaged per patient CIMT progressed from baseline to month 30 in both treatment groups, and there was no significant difference between these two groups.
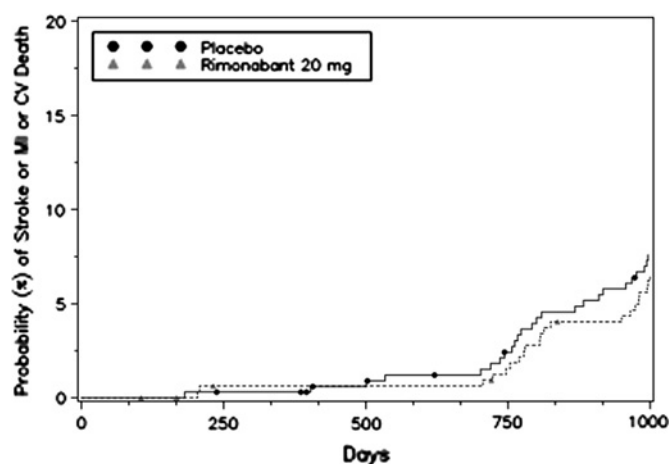
Figure 3 Probability of stroke, myocardial infarction (MI) or cardiovascular (CV) death. The time from randomisation to each cluster end point was compared between the two treatment groups using a two-sided log rank asymptotic test. Cumulative incidence functions in each treatment group were calculated and plotted using Kaplan—Meier estimate. The corresponding 95% CI was computed at each scheduled time point of the protocol (month 3, month 6, and then every 6 months up to month 30) using Greenwood's variance estimation.

On the other hand, treatment with rimonabant did result in significant reduction of weight and waist circumference and an increase in HDL-c, but was not accompanied by any clinically relevant changes in cardiovascular risk factors such as blood pressure, LDL-c or glucose concentrations. It is known that rimonabant has a small blood pressure-lowering effect.[15] Since 70% of patients were receiving blood pressure-lowering medication, we probably could not find any additional effect of rimonabant in this setting. In addition, although rimonabant has no effect on LDL-c, it decreases the proportion of small LDL particles.[15] Addition of an additional study arm in the present study with weight loss by lifestyle changes could have elucidated potential off-target toxicity of rimonabant on atherosclerosis, counteracting beneficial changes in cardiovascular risk factors.

The results of the present study are very reminiscent of those reported by Nissen et al in STRADIVARIUS (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant—The Intravascular Ultrasound Study), which used intravascular ultrasound to assess coronary artery atherosclerosis progression.[19] STRADIVARIUS was also a randomised, placebo-controlled study that compared rimonabant 20 mg daily with placebo in patients who underwent two intravascular ultra-sound examinations. After 18 months of treatment, the study failed to show an effect for rimonabant on disease progression for the primary end point (percentage atheroma volume). STRADIVARIUS and AUDITOR were designed to be parallel studies with considerable design overlap to permit meaningful comparison of results. Because of the shorter time period over which STRADIVARIUS was conducted, its findings were reported first. The results, as determined by the primary outcome measures in both studies, are essentially identical and support the conclusion that rimonabant does not have a signifi-cant effect on atherosclerosis progression even after a 30-month treatment period. In addition to AUDITOR and STADIVARIUS, a recent study named CRESCENDO assessed whether rimona-bant would improve major vascular event-free survival.[20] In this double-blind, placebo-controlled trial, 18 695 patients with previously manifest or increased risk of vascular disease were randomly assigned to receive either rimonabant or placebo.

In November 2008, all clinical studies involving rimonabant were discontinued because of regulatory directives that compromised the entire rimonabant development program. The treatment period in AUDITOR had already been completed for nearly all participants at that moment, so the impact of this decision on the study was negligible. As rimonabant was the first in its class of potentially important therapeutic compounds, the decision was made to complete the study in order to bring important information to the scientific community. Also, the post-treatment safety follow-up was maintained as planned for all patients. For CRESCENDO, all randomised participants were analysed at the moment the drug was suspended. At the close of the trial in November 2008, the composite primary end point of cardiovascular death, myocardial infarction, or stroke occurred in 364 (3.9%) patients assigned to rimonabant and 375 (4.0%) assigned to placebo (HR 0.97, 95% CI 0.84 to 1.12, p=0.68). With rimonabant, gastrointestinal (3038 (33%) vs 2084 (22%)), neuropsychiatric (3028 (32%) vs 1989 (21%)) and serious psychiatric (232 (2.5%) vs 120 (1.3%)) side effects were significantly increased compared with placebo. Four patients in the rimonabant group and one in the placebo group committed suicide. The AUDITOR Study has some limitations that merit discussion. First, not all patients completed CIMT assessments at follow-up and this absence of imaging information for non-completing patients may have introduced bias and reduced power to detect differences between groups. Accordingly, we repeated the analysis to estimate the difference in progression with imputation of missing numbers. This showed that, although all p values for CIMT slightly changed, the overall interpretation was similar (table 2). It also needs to be kept in mind that AUDITOR is a surrogate marker trial, which does not carry the weight for a definitive verdict regarding the benefit of this compound. Of note, differences in local arterial anatomy may result in differences between trial outcomes that investigate surrogate end points such as intima—media thickness.[21] It is unclear why the modest improvement in metabolic variables induced by rimonabant failed to result in a reduction in the progression of atherosclerosis. Although rimonabant clearly reduces visceral and liver fat and improves the cardiometabolic risk profile including inflammation,[15] these effects may not be sufficient to alter progression of atherosclerosis in this patient population. In the present study, the use of rimonabant did attenuate the rise of hs-CRP, presumably through reduced production of inflammatory cytokines by adipose tissue. Likewise, the slightly lower plasma TG concentration and a marginal increase in HDL-c may suggest an improvement in insulin resistance. Apparently, however, these changes were too modest to result in an effect on atherosclerosis progression. It is also of note that the majority of participants in STRADIVARIUS and CRESCENDO and about half of the participants in AUDITOR also received statin therapy.[19 20] This treatment may have already exerted such a favourable effect on the atherosclerotic process that the relatively small changes in cardiovascular risk factors induced by rimonabant treatment did not further affect CIMT progression.

When carrying out a number of post hoc analyses, we could not detect any heterogeneity in CIMT results. There was no difference in CIMT for the rimonabant group versus the placebo group in patients with or without diabetes (data not shown). The same holds true for patients receiving statins versus patients not receiving statins (data not shown). Two of the most common triads for meeting the definitions of the metabolic syndrome consist of the combination of a high waist circumference, high blood pressure plus hyperglycaemia, or the combination of low HDL, high blood pressure plus hypertriglyceridaemia. These triads are known to predict cardiovascular disease and mortality.[21 22] In fact, in AUDITOR, rimonabant did not attenuate CIMT progression in these two subgroups. In addition, in the subgroup of patients with higher than median TGs, rimonabant had similar efficacy towards CIMT progression. In contrast, it was shown in STRADIVARIUS that rimonabant significantly reduced mean atheroma volume in this subset of patients.[19]

In terms of the safety of this compound, our findings demonstrate that rimonabant is associated with an increase in psychiatric symptoms, nervous system disorders and gastrointestinal disorders. Suicidal ideation was relatively uncommon, occurring with similar frequency in the placebo- and rimonabant-treated patients. Safety results of AUDITOR are consistent with previous trials[11 13 14 19] and the recent trial CRESCENDO.[20]

We conclude that, despite a loss in weight, accompanied by a beneficial change in the cardiometabolic risk factor profile, there was no difference in CIMT progression between rimonabant and placebo in patients with abdominal obesity and metabolic syndrome, even after 30 months of treatment. These findings make it unlikely that other molecules of this class will be selected for clinical development and suggest that other approaches to safely reducing body weight will have to be pursued.

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Effect of rimonabant on carotid intima–media thickness (CIMT) progression in patients with abdominal obesity and metabolic syndrome: the AUDITOR Trial

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