Rosiglitazone and carotid IMT progression rate in a mixed cohort of patients with type 2 diabetes and the insulin resistance syndrome: main results from the Rosiglitazone Atherosclerosis Study

Short title: Rosiglitazone and carotid IMT progression rate

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ABSTRACT

Objective. Insulin resistance is associated with progression of atherosclerosis. We assessed the effect of 12 months treatment with rosiglitazone (RSG) on the progression of carotid intima-media thickness (IMT) in people with type-2 diabetes (T2DM) or the insulin resistance syndrome (IRS).

Design. Randomized, double-blind, placebo-controlled trial.

Setting. Malmö University Hospital, Malmö, Sweden.

Subjects. 555 subjects (200 with T2DM and 355 non-diabetics with IRS according to EGIR criteria), aged 35-80 years. 447 subjects (165 T2DM and 282 IRS) completed the study.

Intervention. Participants were allocated to placebo or RSG 4mg for 2 months and then 8mg daily.

Main outcome measure. Change in composite IMT [mean IMT in the common carotid (CCA) and maximal IMT in the bulb] was the primary and various other IMT measures were secondary outcome variables.

Results. There was no effect of RSG treatment in the mixed population**.** In T2DM patients there was a reduced progression of the composite IMT (mean change: 0.041 versus 0.070 mm, p=0.07), and of the mean IMT CCA (mean change: -0.005 mm versus 0.021 mm, p=0.007). RSG treatment led to significant reductions of HOMA-IR, fasting plasma glucose, $HbA1_C$, PAI-1 activity, fibrinogen, C-reactive protein and matrix metalloproteinase-9.

Conclusions. In a mixed study population of patients with T2DM and IRS RSG treatment was not associated with a statistically significant reduction of carotid IMT progression rate. Separate analyses of these two patients groups indicated however

a significant beneficial effect on common carotid IMT in T2DM patients but no similar effect in subjects with IRS.

Key words: Carotid arteries, drugs, rosiglitazone, trials, ultrasonics.

INTRODUCTION

The thiazolidinedione (TZD) rosiglitazone (RSG), a peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist, is an insulin-sensitizing agent and is used in the treatment of type-2 diabetes mellitus (T2DM). Recent data from animal experiments [1, 2], and studies in humans [3-5], suggest that TZDs may have anti-atherosclerotic properties. RSG has also been shown to improve impaired beta-cell function which along with insulin resistance (IR) is a fundamental characteristic of T2DM [6]. In addition to its effects on glycaemia, RSG has also been shown to exert positive effects on cardiovascular (CV) risk factors such as blood pressure (BP) [7,8], albuminuria [9], as well as on levels of plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA) and C-reactive protein (CRP) [10]. Markers of endothelial function and plaque stability may also be improved with RSG [11-13].

The primary objective of the "Rosiglitazone and Atherosclerosis Study" (RAS) was to assess whether in a cohort having either T2DM or the insulin resistance syndrome (IRS) the rate of progression of the carotid intima-media thickness (IMT) can be changed by treatment with RSG for 12 months.

METHODS

Eligibility and inclusion criteria's

Participants were recruited from the "Malmö Diet and Cancer" study population cardiovascular sub-cohort [14]. Five thousand five hundred and forty of these subjects have been evaluated in terms of IR using the homeostasis model assessment (HOMA-IR) [15]. Eleven hundred and eighty-nine non-diabetic subjects (25%) whose values exceeded the sex-specific 75th percentile (i.e. 1.80 for women

and 2.12 for men) were considered to have IR [16]. Both these subjects and patients with T2DM were invited to participate in the RAS trial. Eleven hundred and eighteen attended the enrollment examination (visit one), which included a two-dimensional B-mode ultrasound of the right carotid artery (Figure 1). Inclusion criteria at the screening visit were: i) patients, aged 35-80 years, with established T2DM as defined by WHO criteria [17], and fasting plasma glucose of $\geq$ 5.5 and $\leq$ 11.1 mmol/L^{-1} at the screening visit, and ii) non-diabetic subjects with IRS as defined by the European Group for the Study of Insulin Resistance (EGIR) criteria [18], i.e. with HOMA-IR value >1.80 for females or >2.12 for males in combination with at least two of the following conditions, plasma glucose between ≥6.1 mmol/L and <7.0 mmol/L^{-1}, BP ≥140/90 mmHg or current use of blood pressure-lowering medication, triglycerides >2.0 mmol/L or HDL-cholesterol <0.9 mmol/L^{-1} for men, and <1.0 mmol/L^{-1} for women or waist circumference ≥94 cm for men and ≥80 cm for women.

Exlusion criteria

The following exclusion criteria were used: use of two or more oral anti-hyperglycaemic agents during the 3 months preceding the date of randomization, use of anti-hypertensive or lipid-lowering therapy ≤ 6 months and increased dose of these drugs during the last 3 months, previous exposure to a TZDs or other PPAR-γ agonist, regular use of insulin, BP >170/>100 mmHg, unstable or severe angina, cardiac failure (NYHA class I-IV), history of acute myocardial infarction or stroke within the last 6 months, any history of surgical intervention in the right carotid artery, presence of clinically significant hepatic disease (i.e. alanine aminotransferase (AST), aspartate aminotransferase (ALT), total bilirubin, or alkaline phosphatase >2.5 times of the upper limit of the normal), haemoglobin concentration <11g/dL^{-1} for males or

<10g/dL^{-1} for females, creatinine clearance <40 ml/min^{-1} with the Cockcroft-Gault equation and a decreased glomerular filtration rate (e.g. <70 ml/min^{-1} for subjects aged ≤50 years, <60 ml/min^{-1} for subjects aged 51 - 69 years and <50 ml/min^{-1} for subjects aged ≥70 years), alcohol or drug abuse within the last 6 months, known hypersensitivity to RSG, or conditions which in the opinion of the investigator rendered the subject unsuitable for the trial.

Allocation

Five hundred and fifty-seven of the screened subjects (200 TDM2 and 357 IRS) accepted participation (Figure 1). All participants provided written informed consent. The Ethics Committee of Lund University approved the study. After a 4 week run-in period participants were double-blind and randomly allocated (GSK Coding Memo system and RAMOS) to receive placebo or RSG 4mg once daily respectively during the initial 8 weeks. This procedure was done separately for each of the two patient groups. After checking for normal transaminases the dosage was increased to placebo two tablets daily or RSG 8mg for the remaining 44 weeks. RSG and matching placebo tablets were supplied by GlaxoSmithKline (Greenford, UK). Compliance assessed by tablet count was >95%.

Outcome measures

The primary outcome measure was the change from baseline of the composite IMT [(mean IMT CCA plus maximal IMT in the carotid artery bifurcation) / 2] in the right carotid artery [19]. Secondary outcomes included the safety, tolerability and clinical benefit of RSG on various IMT measures (mean IMT CCA, intima-media area (IMA) in the CCA and maximal IMT in the carotid artery bifurcation), measures of HOMA-IR

and surrogate markers (high sensitive CRP, matrix metalloproteinase 9 (MMP-9), fibrinogen, plasminogen activator inhibitor (PAI-1) antigen, PAI-1 activity, tissue and plasminogen activator (tPA) antigen). Adverse events (AEs), laboratory findings (see below) and vital signs were closely monitored.

Baseline examination and follow-up visits

The first participant was randomized on 5 March 2002, and the 52-week treatment period was completed for all participants by 4 November 2004. Unless prematurely withdrawn from the study, each subject visited the clinic on a maximum of 8 occasions. Weight and waist- and hip circumference were measured every 6 months. All biochemical measurements were performed by Quest Diagnostics Clinical Trials, London UK. Fasting blood glucose and insulin and $HbA1_{C,}$ total cholesterol (TC), LDL cholesterol, HDL cholesterol and triglycerides were determined every two months. AST, ALT and creatine kinase (CK) were obtained at every visit. AST or ALT values ≥2.5 times and CK values ≥10 times the upper limit of normal were considered elevated during the study.

The carotid ultrasound investigation was performed twice at baseline and twice at the end after 52 weeks treatment. Where HbA1c targets were not achieved (i.e. HbA1c ≥7%), patients were uptitrated to a maximum of 15 mg of glibenclamide or 2 g of metformin daily. Patients who were already taking a maximum dose of anti-diabetic medication and whose $HbA1_C$ value exceeded the upper limit (>10% on two consecutive occasions) were withdrawn from the study. Use of insulin and agents known to significantly alter glycaemic control (e.g. oral corticosteroids) was prohibited during the study. For IRS subjects, if the HbA1c was ≥7% during the study,

glibenclamide at a starting dose of 2.5 mg or metformin was added and uptitrated as necessary to a maximum of 15 mg day^{-1} and 2 g day^{-1}, respectively.

Other conditions such as high BP, high blood lipids, congestive heart failure or other abnormal laboratory values during the trial, were dealt with in accordance with existing guidelines. Vital status was obtained for all subjects at termination of the study.

B-mode-ultrasound

An Acuson Sequoia Computed Tomograpy System (Acuson, Mountain View, CA, USA) with 8 MHz transducer was used. The examination procedure and image analysis, which have been described in detail previously [14, 19, 20], were performed by two specially trained sonographers certified upon completion of an extensive educational program. In brief, the right carotid bifurcation was scanned within a pre-defined window comprising 3 cm of the distal common carotid artery (CCA), the bifurcation and 1 cm of the internal and external carotid arteries, respectively, for the presence of plaques, defined as a focal IMT above 1.2 mm [19]. The thickness of the common carotid intima-media complex, i.e. the mean distance between the leading edges of the lumen-intima and the media-adventitia interfaces of the far wall (mean IMT CCA), was measured off-line and along 1 cm section in the longitudinal projection using a specially designed computer-assisted image analyzing system based on automated detection of the echo structures, but with the option to make manual corrections by the operator [21]. The maximum thickness of the intima-media (max IMT bifurcation) in the far wall of the carotid bifurcation was also measured off-line. Each image was analyzed without knowledge of the subject's randomization

group. Composite IMT in the carotid artery was defined as: (mean IMT CCA + max IMT bifurcation) / 2. The intima media area (IMA) in the far wall of the CCA was measured off-line as: $IMA = \pi \times \left(\left(\frac{d}{2} + \text{IMTmean CCA} \right)^2 - \left(\frac{d}{2} \right)^2 \right)$, where d is the luminal diameter. The sonographers were required to demonstrate proficiency and efficiency in performance of the protocol prior to initiation of the study, and their performance was monitored regularly during the course of the study. The mean of the absolute difference between the paired mean composite IMT, mean IMT CCA and max IMT bifurcation measurements were 0.07±0.05, 0.05±0.04 and 0.12±0.12 mm, respectively, for inter-observer variability and 0.05±0.05, 0.02±0.05, and 0.09±0.09 mm, respectively, for in intra-observer variability, which compares favourably with previous studies [19].

Statistical methods

The change from baseline in composite IMT was analyzed using parametric analysis of covariance (a linear model assuming normal errors). The assumptions of normality and homogeneity of variance underlying the statistical analysis were checked. If these assumptions were not met, additional non-parametric analyses were performed. Exploratory analyses to assess the robustness of the primary model were also undertaken. The interactions between treatment effects and baseline characteristics, and treatment effects and patients groups were investigated by adding the interaction terms separately to the primary model, and assessing the statistical significance at the 10% level.

From previous experience it was anticipated that the average progression of the composite IMT in the placebo group would be approximately 0.060 mm during the 12

months study period with a standard deviation (SD) of 0.079 mm [19]. The corresponding anticipated placebo values in the T2DM and IRS groups were 0.070±0.079 and 0.060±0.079 mm respectively. Based on a withdrawal rate of 20% and a sample size of 556 subjects (200 patients with T2DM and 356 subjects with IRS), the study had 90% power at 5 % significance level to detect a 40% difference (0.024 mm) of the composite IMT in the two groups, i.e. the placebo group and the mixed population of patients having T2DM or IRS. In a planned comparison with the T2DM patients and the IRS subjects the differences required to achieve similar power and significance level would have to be 51% (0.031 mm) and 60% (0.042 mm) respectively.

According to the protocol, the initial analysis was based on a comparison of placebo and RSG-treated patients having either T2DM or IRS. A secondary analysis evaluating the treatment effect in each of these two patient groups was also performed. In the event of a non-statistically significant outcome for the primary analysis, the results of the second analysis should be considered as exploratory only.

For those who withdrew from the study early, the last IMT assessment performed whilst on therapy was used to estimate the effect of treatment. A formal per-protocol (PP) analysis was also performed for the primary endpoint.

Post-hoc analyses were performed to assess the effect of RSG on change of composite IMT and mean IMT CCA after taking concomitant lipid-lowering and/or antihypertensive therapy into account and after including early withdrawn patients with IMT assessment after the study drug was discontinued. SAS software was used

for the statistical analysis, and the statistical team of the sponsor was involved in the final data analysis.

RESULTS

Baseline characteristics

Two hundred and thirty people in the placebo group (83 T2DM and 147 IRS) and 213 in the RSG group (80 T2DM and 133 IRS) took study medication and attended the ultrasound scan after week 52 (Fig. 1). One subject in each treatment group dropped out before receiving study drug. Of the 108 subjects (19.4%) who were withdrawn from therapy following randomization (three T2DM and one IRS) had a carotid IMT assessment performed whilst on-therapy.

The distribution of clinical characteristics in the placebo and RSG groups is illustrated in Table 1. Amongst the patients with T2DM, there were a higher proportion of men, smokers and a longer mean duration of disease in the placebo group compared to the RSG group. More than half the patients with T2DM were using oral anti-diabetic medication, 30% metformin, 23% sulphonylurea. Of the subjects with IRS, 96% had central obesity, 89% hypertension, 48% dyslipidaemia and 24% hyperglycaemia. Although slightly more women than men did not complete the study, there were limited differences in demographics, biological and current drug treatment between completers and non-completers (data not shown).

Treatment effect on carotid IMT progression

Baseline and follow-up ultrasound data after 52 weeks are given in Table 2. The 12-month mean increase of the combined IMT was lower in the RSG than it was in the placebo-treated groups. The mean difference between groups when taking patient

cohort and baseline IMT into account was: -0.010 mm, *P*=0.310. No significant interaction was observed between patient cohort and treatment effect in the combined model (*P*=0.174). The mean change IMT in the CCA and max IMT in the bifurcation was somewhat higher in the placebo treated group of patients having T2DM than the placebo treated group having IRS. When patients having T2DM were analysed separately, the adjusted mean difference in progression of composite IMT was: -0.029 mm, *P*=0.067 (Table 2 and Fig. 2). Furthermore, there was a statistically significant baseline-adjusted difference of the mean IMT CCA (Fig. 2) and IMA in the RSG compared to the placebo group [adjusted mean difference: -0.026 mm, *P*=0.007, and -0.850 mm^2, *P*=0.001 respectively]. In the IRS cohort, there was no corresponding effect (Table 2). Similar results were observed in a PP analysis of the primary endpoint which contained 173 RSG and 191 placebo-treated patients (data not shown). *Post-hoc* analysis of the change from baseline including post-treatment IMT values for early withdrawals was consistent with the primary efficacy results. Treatment effects remained unchanged when lipid-lowering and/or antihypertensive therapy was taken into account.

Metabolic and physiological effects of treatment

The metabolic effects of RSG treatment in different study cohorts are summarized in Table 3. RSG treatment led in patients having T2DM to a more pronounced reduction of fasting glucose than it did in subjects having IRS [baseline-adjusted mean difference: -1.9, and -0.4 $mmol/L^{-1}$ respectively]. $HbA1_C$ was significantly but moderately reduced in RSG treated T2DM patients (-0.41%) but remained rather unchanged in RSG treated IRS patients (0.03%). A significant baseline-adjusted difference in $HbA1_C$ levels between treatment groups was observed in T2DM patients

(-0.64 %, *P*<0.0001). The RSG related decrease in HOMA-IR was greatest in the T2DM group (baseline-adjusted mean difference, 95% CI, in T2DM: -2.05%, -2.66% to -1.43%, *P*<0.001, vs. -1.08%, -1.51% to -0.65%, *P*<0.001, in the IRS group).

The body weight increase associated with RSG treatment was, after adjustment for differences at baseline, at week fifty-two 3.1 kg (95% CI: 2.2 - 4.1 kg) in the T2DM and 1.3 kg (0.6 - 4.1 kg) in the IRS Cohort (Table 3). RSG treatment increased TC by 9.8%, LDL cholesterol by 9.1%, and triglycerides by 5.0% in patients having T2DM. In the IRS group corresponding increase in these blood lipids was 6.9%, 7.0% and 9.4% respectively (Table 3). A significant positive treatment effect of RSG on HDL cholesterol was only observed in T2DM patients. There was a small increase in TC/HDL and LDL/HDL ratios associated with RSG treatment in the IRS group (0.5±1.6 and 0.3±1.2 respectively), whereas there was no change in these ratios in the T2DM group (0.1±1.0 and 0.1±0.8 respectively). In both the T2DM and the IRS group, RSG treatment led to a significant decrease in free fatty acids (FFAs) [% change in T2DM: -17.5% (95% CI: -25.4 to -8.7 %), *P*=0.002), and in IRS: -14.9% (95% CI: -21.2 to -8.0 %), *P*<0.001].

Markers of inflammation (CRP, MMP-9) and fibrinolysis (fibrinogen, PAI-1 antigen) were in the mixed, T2DM and the IRS cohorts, at the end of the trial significantly lower in RSG-treated subjects than in the control group (Table 3). Similar findings were observed for PAI-1 activity and tPA (data not shown). Observed differences were greater in the T2DM than in the IRS Cohort (Table 3).

In the T2DM cohort, the office mean systolic (SBP) and diastolic (DBP) blood pressures remained rather unchanged at each on-therapy time point in both treatment groups (data not shown). At week 52, the mean increase from baseline in SBP was 1.4±1.3 mmHg in the RSG group and 2.7±1.3 mmHg in the placebo group. The corresponding change in DBP in the both treatment groups were -2.3±0.8 and -0.4±0.7 mmHg. None of these blood pressure changes were statistically significant.

In *post-hoc* analysis no significant correlations were observed between 52-week treatment changes in composite IMT or mean IMT CCA and changes from baseline in HbA1c, HOMA-IR, FFA, LDL, HDL, LDL-to-HDL ratio, MMP-9 and CRP (all correlation coefficients were < 0.3).

Tolerability

Adverse events were the main reasons for withdrawal in both treatment groups (RSG 18.1% and placebo 11.2%). In both the T2DM and the IRS cohort incidence of AEs was higher in the RSG group than in the placebo group (17.2% and 9.9%, and 19.0% vs 12.4% respectively). Overall, the incidence of dyslipidaemia, peripheral oedema, weight gain- and anaemia-related AEs was higher in the RSG (12.3%, 10.8%, 7.2% and 4.3% respectively) than it was in the placebo group (4.3%, 3.6%, 0.7% and 0.0% respectively). The most frequent AEs leading to withdrawal in the RSG group were peripheral oedema (3.6%), and headache (2.5%), and in the placebo group vertigo (1.8%) and fatigue (1.4%). Three T2DM subjects in the placebo group were withdrawn because of lack of glycaemic control. The majority of withdrawals due to an AE occurred before or at the week 26 visit. Five deaths occurred during the study,

two (0.7%) in the RSG group and three (1.1%) in the placebo group, none of which were considered to be causally related to study medication.

DISCUSSION

The incidence of stroke, myocardial infarction and other vascular events increases in a stepwise fashion with the thickness of the intima-media layer in the carotid artery [22]. T2DM and IR are both associated with enhanced rate of progression of IMT [23]. Similar relationships have been documented with age, male gender, smoking, hypertension, raised pulse pressure, hypercholesterolaemia and poor glycaemic control [24]. The most robust data demonstrating a reduced rate of progression of the IMT come from studies using statins [22] and antihypertensive agents [19, 25]. Improvements of glycaemic control in subjects with type 1 diabetes have similarly been associated with reduced progression rate [26]. Hence, it seems scientifically relevant to evaluate whether RSG treatment may have similar effect in patients having T2DM and subjects having IRS.

Rosiglitazone treatment during 12 months was, in this study, not associated with any statistically significant reduction of the carotid composite IMT progression rate. Whether the absence of an effect is related to the design of the study or methods used for evaluation can only be speculated upon. The study should, according to the protocol, be assessed using an intention-to-treat approach, however, since no final evaluation of carotid IMT progression was done for the 19% who dropped out or stopped taking medication, this was not possible to achieve. It should be pointed out, however, that although the magnitude of progression in the placebo group was as expected (0.060 mm in the mixed population and 0.070 mm in the T2DM cohort) the

observed variance was greater than expected (SD: 0.100 vs. 0.079 mm). Furthermore, the mixed study population, the use of two ultrasound-investigators and that the composite IMT is based on a single measurement of maximum IMT in the bulb are all important factors that may cause a method-driven larger variability of the primary endpoint [21] in comparison to other studies [3-5].

A separate analysis of patients with T2DM demonstrated a significantly lower rate of mean IMT CCA progression in the RSG group; this treatment effect was confirmed by determination of IMA. No effect was, however, demonstrated when the maximum IMT in the bifurcation was compared. Further studies are needed to assess whether the differences in the changes observed in the anatomical sites evaluated may be related to the duration of treatment. Although the changes in mean IMT CCA in the T2DM subgroup did not correlate with improvements of HbA1c, it is not possible to exclude an effect of glycaemic control. Others have reported that the progression rate in diabetes patients treated with TZD is related to changes in insulin sensitivity but not the degree of glycaemic control [4]. In the RSG-treated group of T2DM patients, there was not only an improvement in glycaemic control but also an increase in the mean HDL cholesterol levels and furthermore positive effects on some inflammatory markers (CRP and MMP-9). Whether the observed different effect of RSG on common carotid IMT in T2DM and IRS patients is related to differences with regard to treatment effect on blood lipids, inflammatory markers or to differences with regard to the level of insulin resistance remains to be evaluated.

Elevated systemic BP has been associated with more rapid IMT progression [19, 23]. Arterial vasodilators which lower systemic BP could in theory confound the

interpretation of IMT by contributing to an increase in arterial diameter with no reduction in arterial wall mass as determined using the IMA. However, there was no dilatation of the carotid artery in this study and therefore the reduction in mean IMT CCA and IMA progression observed in the T2DM subgroup is compatible with the idea of a structural change in the arterial wall.

Strengths and limitations

Besides the use of a composite endpoint, another potential criticism is that a larger proportion of subjects in the RSG than in the placebo group initiated statin therapy. The *post hoc* analyses in which use of statins are controlled for do not indicate that this could have confounded the results.

The lack of any treatment effect in subjects with IRS, contrasts with the results in a recently published study of non-diabetic patients with angiographically documented coronary artery disease [3]. The RSG effects on lipids and inflammatory markers were very similar in the two studies. The higher LDL cholesterol concentration in the IRS group in our study may have contributed to the absence of an effect of treatment. An additional potential explanation to the difference in outcome may be that the 12 months mean IMT CCA progression rate in the placebo group was almost twice as high in the Sidhu study as it was in our study, (0.031 mm vs. 0.018 mm respectively), which might be due to that the latter study included patients having coronary artery disease (CAD).

The significant improvements of surrogate CV risk biomarkers, specifically CRP, PAI-I antigen and fibrinogen following treatment with RSG are consistent with previous

studies [12]. The lowering effect of RSG on CRP has been shown to persist for at least 18 months in T2DM subjects on combination therapy [27]. RSG has also been shown to reduce MMP-9 and CRP in diabetic patients with [13] or without [12] CAD, to reduce CRP levels in hypertensive, nondiabetic subjects [28] and in nondiabetic CAD subjects [29], and to suppress proinflammatory cytokine production and reduce TNF-α levels in obese, nondiabetic subjects [30]. The anti-inflammatory effect of RSG thus appears to be independent of its blood glucose lowering effect.

Rosiglitazone was well tolerated and there were few withdrawals due to AEs. Oedema was frequently reported with RSG (11%), but there was also a high incidence in the placebo-treated group (4%) highlighting the investigators' awareness of this potential problem. The changes in the lipid profile are consistent with those reported in other studies with RSG. There was a 1- to 3-kg weight gain in subjects treated with RSG, in particular in the T2DM subgroup. This might be due to a combination of improved glycaemic control contributing to increased subcutaneous fat deposition, and a small degree of fluid retention.

In this double-blind, randomised, controlled trial of patients with T2DM or IRS, RSG treatment for 12 months was not associated with any significant differences compared to placebo treatment in composite measure of the carotid artery IMT. However, secondary analyses of these two groups of patients indicated a significant beneficial effect on common carotid IMT in patients with T2DM but no similar effect in subjects having IRS.

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Conflict of interest statement

Andrew Zambanini is employed by GlaxoSmithKline. There is no conflict of interest regarding all other authors.

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Legends to figures:

Figure 1: Trial profile.

Figure 2. Bar chart showing baseline-adjusted mean (SEM) change from baseline in composite IMT and mean CCA IMT at week 52 for T2DM patients treated with rosiglitazone (n=81, white bars) and placebo (n=84, grey bars).

Table 1. Baseline characteristics in 555 (200 T2DM and 355 IRS) randomized patients.

Variables	Mixed Cohort		T2DM Cohort		IRS Cohort	
	Rosiglitazone N=277	Placebo N=278	Rosiglitazone N=99	Placebo N=101	Rosiglitazone N=178	Placebo N=177
Age (years)	68±5	67±6	67±6	66±8	68±5	67±6
Male sex, %	45	47	51	59	41	41
BMI (kg/m^2)	30±4	30±5	30±4	29±5	30±4	30±4
Waist to hip ratio	0.91±0.07	0.91±0.07	0.92±0.07	0.92±0.06	0.91±0.07	0.91±0.07
Current smoker, %	14	12	10	19	16	7
Former smoker, %	44	42	52	44	39	41
Angina pectoris, %	6	8	7	8	5	7
Systolic blood pressure (mmHg)	141±13	142±14	138±13	139±14	143±12	144±14
Diastolic blood pressure (mmHg)	83±8	83±8	82±8	82±8	84±7	84±7
Use of anti-hypertensive agents						
ACE-inhibitors or ARBs, %	22	26	28	33	14	14
Beta-blockers, %	25	26	22	24	26	27
Calcium channel blockers, %	11	9	14	10	10	9
Diuretics, %	16	16	16	12	15	18
Total cholesterol (mmol/L)	5.5±1.0	5.4±1.1	5.1±0.9	5.0±0.9	5.7±1.0	5.7±1.2
HDL-cholesterol (mmol/L)	1.3±0.3	1.3±0.3	1.2±0.3	1.2±0.3	1.3±0.3	1.3±0.3
LDL-cholesterol (mmol/L)	3.5±0.9	3.4±1.0	3.1±0.8	3.0±0.8	3.7±0.9	3.6±1.0
Triglycerides (mmol/L)	1.7±0.7	1.7±0.7	1.7±0.7	1.7±0.7	1.7±0.7	1.8±1.0
Use of lipid reducing agents, %	26	26	35	32	21	22
On statins at baseline, %	24	25	29	30	19	21
Initiated statin therapy, %	11	5	10	2	11	6
T2DM and IRS (%)	36 / 64	36 / 64	-	-	-	-
Duration of diabetes (years)	-	-	3.7±4.6	4.5±6.6	-	-
Prior anti-diabetic medication, %	-	-	53	56	-	-
Biguanides, %	-	-	33	26	-	-
Sulphonylureas, %	-	-	19	26	-	-
Other, %	-	-	1	4	-	-
Components of IRS	-	-				
Central obesity, %	-	-	-	-	96	96
Hypertension, %	-	-	-	-	90	88
Dyslipidemia, %	-	-	-	-	46	50
Hyperglycemia, %	-	-	-	-	23	25

To convert values from mmol L^{-1} to mg L^{-1}, divided by 0.0551 for glucose, 0.02586 for cholesterol, and 0.01130 for triglycerides.

Table 2. Mean values of baseline and 52 weeks and mean adjusted change of carotid intima-media thickness (IMT) measurements in different treatment groups.

Variables	Mixed Cohort		T2DM Cohort		IRS Cohort	
	Rosiglitazone N=216	Placebo N=231	Rosiglitazone N=81	Placebo N=84	Rosiglitazone N=135	Placebo N=147
Carotid IMT						
Baseline composite IMT (mm)	1.46±0.42	1.43±0.40	1.47±0.42	1.40±0.39	1.45±0.42	1.46±0.41
Week 52 composite IMT (mm)	1.51±0.44	1.49±0.43	1.51±0.43	1.47±0.44	1.51±0.44	1.51±0.43
Adjusted mean change from baseline [a,b]	0.049±0.007	0.060±0.007	0.041±0.011	0.070±0.011	0.054±0.009	0.054±0.009
Adjusted mean difference (95% CI) versus PLA [a,b]	-0.010 (-0.030, 0.009)		-0.029 (-0.060, 0.002)		-0.0002 (-0.025, 0.026)	
p-value	0.310		0.067		0.987	
Baseline mean IMT CCA (mm)	0.97±0.22	0.96±0.19	0.95±0.22	0.93±0.18	0.99±0.23	0.97±0.19
Week 52 mean IMT CCA (mm)	0.99±0.23	0.98±0.20	0.95±0.21	0.95±0.20	1.01±0.24	0.99±0.20
Adjusted mean change from baseline [a,b]	0.010±0.005	0.017±0.005	-0.005±0.007	0.021±0.007	0.022±0.006	0.018±0.006
Adjusted mean difference (95% CI) versus PLA [a,b]	-0.007 (-0.019, 0.006)		-0.026 (-0.045, -0.007)		0.004 (-0.012, 0.021)	
p-value	0.280		0.007		0.614	
Baseline maximal IMT bifurcation (mm)	1.95±0.75	1.92±0.74	1.99±0.74	1.86±0.70	1.92±0.75	1.95±0.76
Week 52 maximal IMT bifurcation (mm)	2.03±0.78	2.01±0.79	2.08±0.76	1.98±0.78	2.01±0.79	2.03±0.80
Adjusted mean change from baseline*†	0.088±0.014	0.101±0.013	0.086±0.021	0.120±0.021	0.085±0.017	0.088±0.017
Adjusted mean difference (95% CI) versus PLA [a,b]	-0.014 (-0.050, 0.023)		-0.034 (-0.093, 0.025)		-0.003 (-0.050, 0.043)	
p-value	0.464		0.261		0.891	
Baseline mean IMT media area CCA	23.28±6.92	22.61±6.43	22.71±6.98	22.08±5.55	23.62±6.88	22.91±6.88
Week 52 mean IMT media area CCA	23.58±7.14	23.16±6.68	22.55±6.90	22.77±6.11	24.19±7.23	23.38±7.00
Adjusted mean change from baseline [a,b]	0.271±0.127	0.515±0.123	-0.155±0.187	0.696±0.183	0.085±0.017	0.464±0.157
Adjusted mean difference (95% CI) versus PLA [a,b]	-0.244 (-0.586, 0.098)		-0.850 (-1.367, -0.334)		0.109 (-0.339, 0.556)	
p-value	0.161		0.001		0.633	

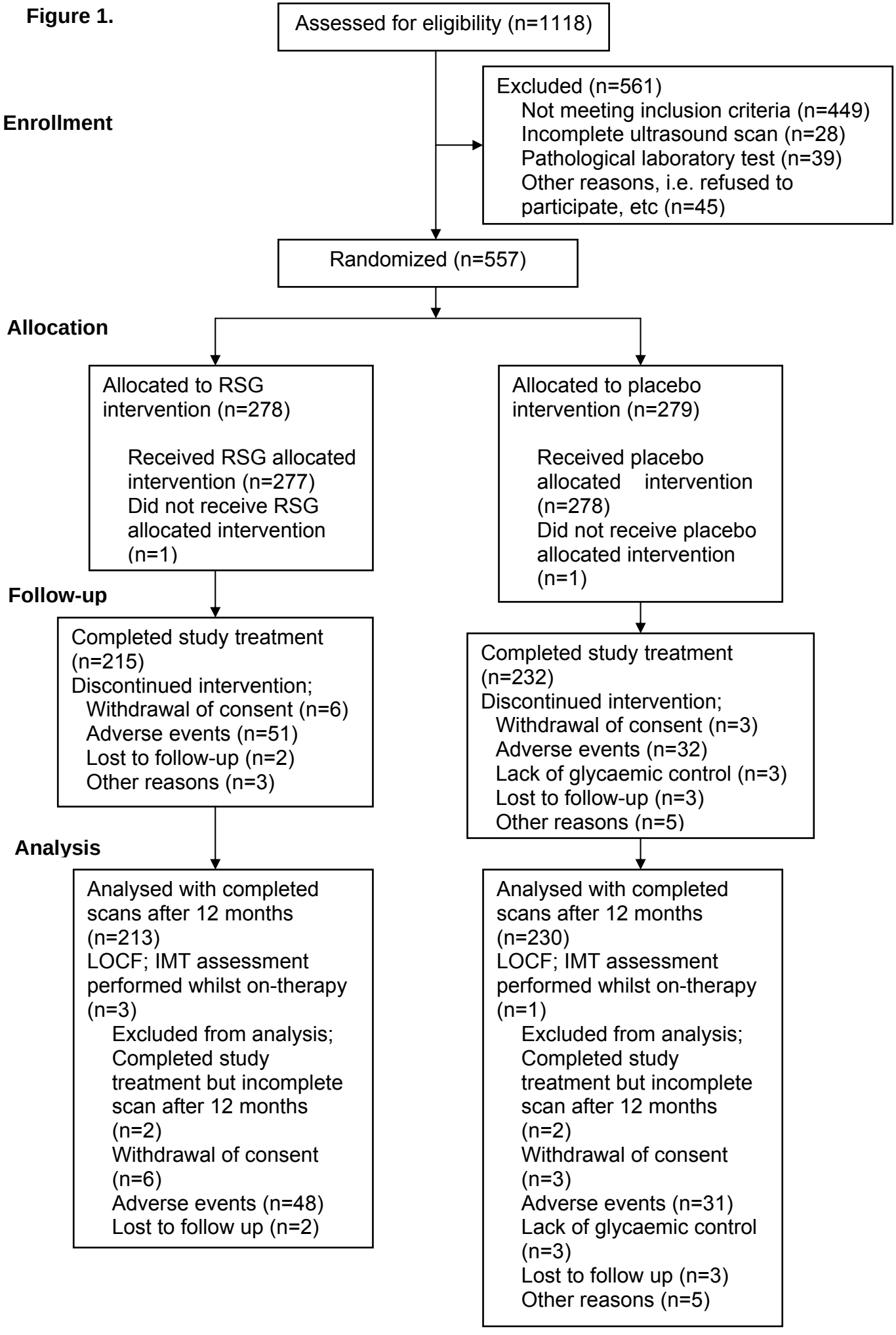
CCA, common carotid artery. PLA, placebo. Baseline and week 52 values are shown as mean±SD, change is shown as mean±SEM. [a]In mixed cohort adjusted for strata and baseline IMT. [b]In T2DM and IRS Cohort adjusted for baseline IMT.

Table 3. Mean baseline, mean week 52 and baseline-adjusted change of physiologic and metabolic parametes in different treatment groups.

	T2DM Cohort			IRS Cohort		
Variable	Rosiglitazone	Placebo	*P*[a]	Rosiglitazone	Placebo	*P*[a]
Glucose (mmol/L), n	85	89		144	145	
Baseline	7.99±1.39	7.96±1.51		5.59±0.63	5.62±0.72	
52 wk	6.26±1.08	8.27±1.58		5.24±0.46	5.65±0.70	
Adjusted change	-1.53±0.12	0.34±0.11	<0.001	-0.36±0.04	0.04±0.04	<0.001
HbA1c (%), n	92	97		164	165	
Baseline	6.93±0.83	6.94±0.83		5.97±0.44	5.90±0.41	
52 wk	6.52±0.65	7.16±0.89		5.99±0.39	5.87±0.44	
Adjusted change	-0.41±0.06	0.22±0.06	<0.001	0.03±0.02	-0.04±0.02	0.014
HOMA-IR (units), n	85	88		144	155	
Baseline	4.18±2.95	4.09±3.21		3.25±1.81	3.19±1.48	
52 wk	2.34±1.49	4.34±3.37		2.17±2.32	3.22±1.67	
Adjusted change	-1.85±0.22	0.22±0.22	<0.001	-1.06±0.16	0.03±0.15	<0.001
Weight (kg), n	85	89		145	155	
Baseline	86.8±14.2	86.9±18.4		84.4±13.0	85.0±12.2	
52 wk	89.6±15.1	86.6±18.9		85.4±13.9	84.7±12.8	
Adjusted change	2.84±0.35	-0.29±0.34	<0.001	1.01±0.26	-0.26±0.25	<0.001
CRP (mg/L), n	75	81		132	140	
Baseline	2.89±2.41	2.22±1.12		3.07±2.21	2.85±2.18	
52 wk	1.46±1.43	2.33±2.05		1.86±1.91	2.48±1.94	
Adjusted change	-1.23±0.18	0.07±0.017	<0.001	-1.14±0.15	-0.43±0.14	<0.001
MMP-9 (mg/mL), n	85	87		137	152	
Baseline	39.2 (37.1, 41.4)	39.2 (37.1, 41.4)		42.1 (40.2, 44.1)	39.2 (37.1, 41.4)	
52 wk	29.1 (26.7, 31.7)	36.9 (34.6, 39.4)		31.3 (29.7, 32.9)	33.8 (32.1, 35.6)	
Adjusted % change	-25.8 (-32.4, -18.6)	-5.5 (-11.2, 0.5)	0.020	-25.7 (-30.3, -20.8)	-18.2 (-22.8,- 13.3)	0.243
Fibrinogen (g/L), n	85	88		143	145	
Baseline	3.5 (3.4, 3.6)	3.2 (3.2, 3.3)		3.4 (3.4, 3.5)	3.4 (3.3, 3.4)	
52 wk	3.1 (3.1, 3.2)	3.2 (3.2, 3.3)		3.2 (3.1, 3.2)	3.3 (3.2, 3.3)	
Adjusted % change	-7.0 (-12.2, -1.5)	0.2 (-2.0, 2.4)	0.014	-7.7 (-9.6, -5.8)	-3.2 (-4.9, -1.5)	0.073
PAI-1 ant. (mg/mL), n	72	71		120	132	
Baseline	21.8 (20.9, 22.8)	22.4 (21.5, 23.4)		24.3 (23.6, 25.1)	18.0 (17.0, 19.1)	
52 wk	15.0 (14.1, 16.0)	22.7 (21.5, 23.9)		16.5 (15.8, 17.2)	22.6 (21.9, 23.5)	
Adjusted % change	-32.1 (-34.7, -27.4)	1.2 (-3.2, 5.7)	<0.001	-32.2 (-34.9, -29.4)	-8.9 (-11.6, -6.1)	<0.001
Total chol. (mmol/L), n	85	89		144	155	
Baseline	5.10±0.93	5.01±0.95		5.72±1.06	5.68±1.19	
52 wk	5.57±1.09	4.97±0.95		6.19±1.41	5.62±1.11	
% change	9.8 (7.9, 11.7)	1.2 (-0.1, 2.6)	<0.001	6.9 (5.3, 8.5)	-1.8 (-2.9, -0.6)	<0.001
LDL-chol (mmol/L), n	85	89		144	155	
Baseline	3.10±0.80	2.99±0.83		3.65±0.93	3.60±1.04	
52 wk	3.43±1.02	2.97±0.82		3.98±1.24	3.54±1.00	
% change	9.1 (6.2, 12.0)	0.1 (-1.7, 2.0)	<0.001	7.0 (4.6, 9.4)	-2.6 (-4.3, -1.0)	<0.001
HDL-chol (mmol/L), n	85	89		145	156	
Baseline	1.23±0.32	1.24±0.34		1.32±0.32	1.30±0.35	
52 wk	1.32±0.33	1.29±0.38		1.31±0.34	1.30±0.30	
% change	8.7 (6.9, 10.6)	2.2 (0.9, 3.6)	<0.001	-0.3 (-1.8, 1.2)	0.8 (-0.2, 1.8)	NS
Tg (mmol/L), n	85	89		145	156	
Baseline	1.71±0.74	1.67±0.74		1.73±0.69	1.78±1.02	
52 wk	1.84±0.97	1.71±0.91		1.99±1.06	1.76±0.75	
% change	5.0 (1.0, 9.2)	1.7 (-1.6, 5.0)		9.4 (5.8, 13.1)	0.1 (-2.3, 2.6)	

Chol, cholesterol; Tg, triglycerides; MMP-9, matrix metalloproteinase; PAI, plasminogen activator inhibitor. Baseline and week 52 values are shown as mean±SD, change as mean±SEM. MMP-9, fibrinogen and PAI-1 antigen are shown as geometric mean±SEM. [a]*P*-value for adjusted mean difference versus placebo.

Figure 1.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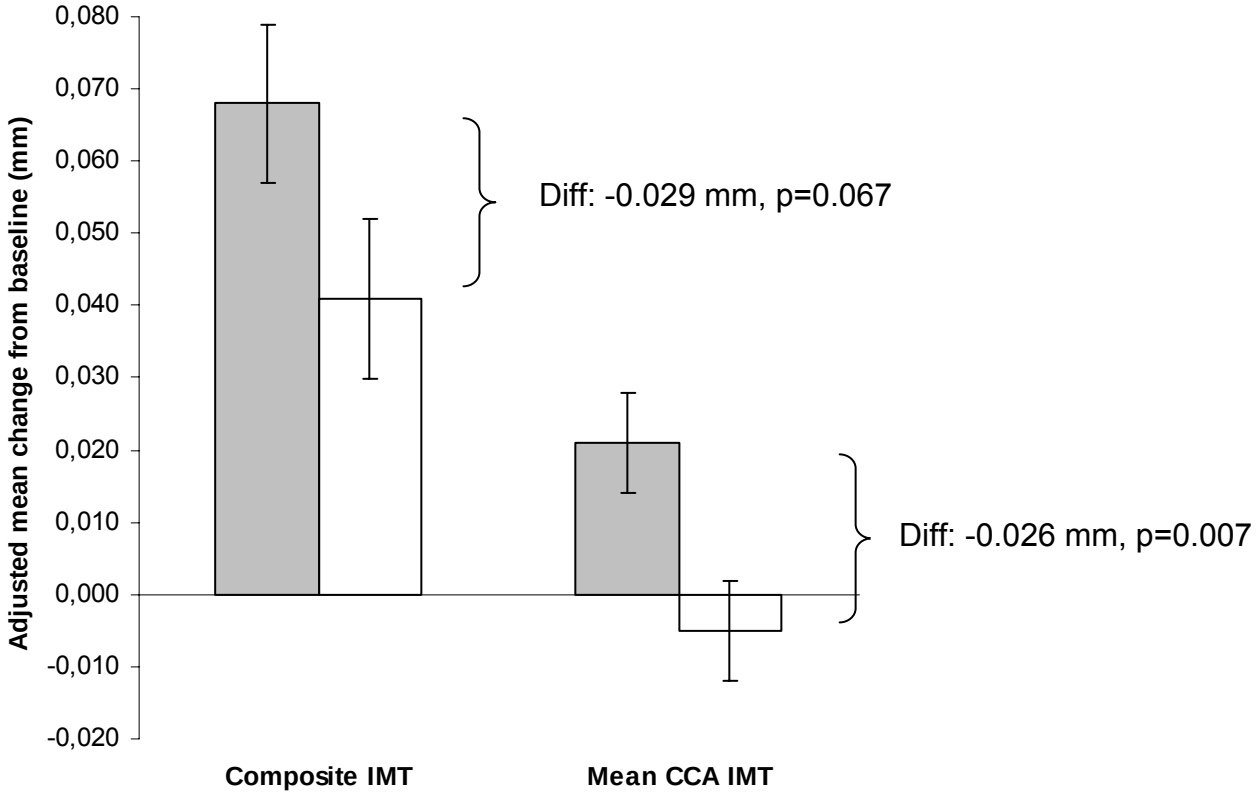
Enrollment
Excluded (n=561)
Not meeting inclusion criteria (n=449)
Incomplete ultrasound scan (n=28)
Pathological laboratory test (n=39)
Other reasons, i.e. refused to participate, etc (n=45)
Randomized (n=557)
Allocation
Allocated to RSG intervention (n=278)
Received RSG allocated intervention (n=277)
Did not receive RSG allocated intervention (n=1)
Allocated to placebo intervention (n=279)
Received placebo allocated intervention (n=278)
Did not receive placebo allocated intervention (n=1)
Follow-up
Completed study treatment (n=215)
Discontinued intervention;
Withdrawal of consent (n=6)
Adverse events (n=51)
Lost to follow-up (n=2)
Other reasons (n=3)
Completed study treatment (n=232)
Discontinued intervention;
Withdrawal of consent (n=3)
Adverse events (n=32)
Lack of glycaemic control (n=3)
Lost to follow-up (n=3)
Other reasons (n=5)
Analysis
Analysed with completed scans after 12 months (n=213)
LOCF; IMT assessment performed whilst on-therapy (n=3)
Excluded from analysis;
Completed study treatment but incomplete scan after 12 months (n=2)
Withdrawal of consent (n=6)
Adverse events (n=48)
Lost to follow up (n=2)
Analysed with completed scans after 12 months (n=230)
LOCF; IMT assessment performed whilst on-therapy (n=1)
Excluded from analysis;
Completed study treatment but incomplete scan after 12 months (n=2)
Withdrawal of consent (n=3)
Adverse events (n=31)
Lack of glycaemic control (n=3)
Lost to follow up (n=3)
Other reasons (n=5)

Figure 2.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Adjusted mean change from baseline (mm)
Diff: -0.029 mm, p=0.067
Diff: -0.026 mm, p=0.007
Composite IMT
Mean CCA IMT