



Published in final edited form as:

Diabetes Metab Res Rev. 2013 October ; 29(7): 582–591. doi:10.1002/dmrr.2433.

Effects of Acarbose to Delay Progression of Carotid Intima-Media Thickness in Early Diabetes

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Abstract

Background—The antidiabetic agent acarbose reduces postprandial glucose excursions. We have evaluated the effect of randomized treatment with acarbose on the progression of carotid intima-media thickness (IMT) in early diabetes.

Methods—The Early Diabetes Intervention Program (EDIP) was a randomized trial of acarbose versus placebo, in 219 participants with early diabetes characterized by glucose values over 11.1 mmol/L 2 hours after a 75g oral glucose load, and mean HbA1c 6.3%. IMT was measured at baseline and yearly. Follow-up was discontinued if participants progressed to the study glucose endpoints; IMT readings were available for a median of 2 years, with 72 subjects followed for 5 years.

Results—Progressive increases in IMT were seen in both treatment groups, but this was reduced in participants randomized to acarbose ($p=0.047$). In age, sex and smoking-adjusted analyses IMT progression was associated with greater fasting and OGTT-excursion glucose, fasting insulin, cholesterol, and glycated LDL concentrations. IMT progression was reduced with study-related changes in weight, insulin, and nonesterified fatty acids; these features were more strongly associated with reduced IMT progression than acarbose treatment. Despite strong associations of baseline glycemia with IMT progression, study-related changes in glucose were not important determinants of IMT progression.

Conclusions—Acarbose can delay progression of carotid intima-media thickness in early diabetes defined by an oral glucose tolerance test. Glucose, weight, insulin and lipids contributed to risk of progression but reductions in glycemia were not major determinants of reduced rate of IMT progression. Vascular benefits of acarbose may be independent of its glycemic effects.

Keywords

Diabetes; Acarbose; Atherosclerosis; Intima-Media Thickness

INTRODUCTION

Carotid intima-media thickness (IMT), a validated surrogate measure of cardiovascular risk [1], is increased in diabetes [2-9]. The Diabetes Control and Complications Trial (DCCT)

[10] glucose reduction interventions in a Type 1 diabetic cohort produced subsequent reductions in CVD event rates [11] which were heralded by reduced rates of IMT progression [12, 13]. Alpha-glucosidase inhibitors improve glucose control in part by delaying glucose digestion, thereby allowing better matching of the endogenous insulin response with glucose absorption. This in turn reduces overall glucose variability, which has been linked to overall CVD risk [14, 15]. In populations with Type 2 diabetes or prediabetes, slowed progression of IMT has been observed in randomized studies using the α -glucosidase inhibitors voglibose [16, 17] and acarbose [18-20]. In a meta-analysis of these 5 studies, alpha-glucosidase inhibition produced a reduction in the rate of progression of IMT of 0.06mm/yr [95% confidence interval 0.01 – 0.11 mm/yr] [21]. Also, acarbose was found to reduce CVD event rates in follow-up of the STOP-NIDDM trial of participants with prediabetes [22], concordant with the beneficial effects on IMT in that population [18]. Although these studies were predominantly in Asian populations, the result appears generalizable. However, the question of whether improved glycemia versus other beneficial effects of acarbose mediates beneficial effects on IMT have not been evaluated in detail.

The Early Diabetes Intervention Project (EDIP) was a randomized trial of acarbose versus placebo on a background of diet and exercise recommendations, targeting reduction in the rate of progression of fasting hyperglycemia in subjects with early type 2 diabetes [23]. EDIP recruited subjects with screen-detected early Type 2 diabetes characterized by diabetic post-challenge glucose concentrations, but with only modest elevations in fasting glucose concentrations. Final study visits took place in the fall of 2004. The EDIP population was on average obese and carried the associated increased prevalence of other cardiovascular risk factors. Here we report the 5-year follow-up of carotid IMT in the EDIP cohort, evaluating contributions of glucose versus other risk factors in progression of IMT in this obese population with early type 2 diabetes.

MATERIALS AND METHODS

The Early Diabetes Intervention Program (EDIP) trial was a double-blind, randomized, placebo-controlled 5-year study carried out at Indiana University School of Medicine and Washington University School of Medicine (registered on ClinicalTrials.gov, NCT01470937). This study was designed to assess effects of acarbose to delay worsening of fasting glucose values. The eligibility criteria, study design, methods and primary study results have been reported elsewhere [23]. Briefly, participants were recruited from a population at high-risk for diabetes, including men and women at least 25 years of age with obesity, a history of gestational diabetes, or a family history of diabetes. The diagnosis of diabetes was made during screening based on a 75 g oral glucose tolerance test. They were eligible for the study if they had fasting plasma glucose (FPG) measurement between 105 mg/dl (5.8 mmol/l) and 140 mg/dl (7.8 mmol/l), plus a 2-h plasma glucose \geq 200 mg/dl (11.1 mmol/l). Exclusion criteria included BMI $<$ 24 kg/m², acute or chronic infectious disease, a cardiac event within the previous 6 months, uncontrolled hypertension, use of β -blockers or thiazide diuretics at screening, or fasting plasma triglycerides $>$ 600 mg/dl (6.8 mmol/l) despite treatment.

Eligible participants received either acarbose or an identical placebo based on a blinded randomization stratified by site. Acarbose was titrated up to the maximum dose of 100 mg three times a day with meals, or the maximum tolerated dose. At initiation of randomized study treatment, all subjects received diet counseling by a registered dietitian, and were provided with standard of care recommendations for exercise [23].

At baseline, anthropomorphic, hemodynamic, and metabolic variables were measured. Participants were seen every 3 months by the study nurse for pill count and distribution, documentation of adverse events, and measurement of blood pressure and fasting plasma glucose concentration. Annually, each participant completed a visit which included a brief physical examination with standardized blood pressure measurement, oral glucose tolerance test, carotid ultrasonography, and blood lipid profile. Participants who met study criteria for progression of fasting glucose (to a value greater than 140 mg/dL) at quarterly visits were discontinued from the study, with no further measurements of secondary endpoints in view of the potential effect of additional glycemic therapy on these parameters. Study treatment did not delay progression of fasting glucose over the 5 year follow-up interval [23].

The study protocol was approved by the institutional review boards of both institutions, and each patient signed an informed consent form for screening and for the trial.

Assessment of Carotid IMT

Carotid IMT was a pre-specified secondary endpoint for the EDIP trial. Carotid ultrasonography was first performed at baseline before initiation of the study treatment and was repeated annually thereafter. High-resolution ultrasonographic imaging of the carotid arteries was performed by trained personnel blinded to study treatment assignment. Imaging of the extracranial common carotid artery and internal carotid artery in the neck was performed bilaterally. Carotid IMT was measured as the distance from the edge of the lumina-intima interface to the edge of the collagen-containing upper layer of the adventitia [24, 25], using semi-automated edge-detection software. Analyses were performed by personnel blinded to study assignment and to duration of participation in the study. Readings were taken for maximum thickness of each of the far walls of the common carotid artery (CCA), and the far, posterior and lateral walls of internal carotid artery (ICA). In accordance with recent recommendations from the American Society of Echocardiography [26], we prospectively identified the average of all 4 right side readings as the main endpoint for analysis.

Anthropomorphic and Laboratory measurements

Weight and height were measured with participants wearing light clothing, and the body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2). Blood pressure was measured 3 times on the right arm while sitting, using an automated blood pressure cuff, with the final 2 readings averaged to provide the blood pressure measurement used for analysis.

Glucose concentrations were determined using a glucose oxidase method (YSI, Yellow Springs, OH). Insulin was measured using a radioimmune assay (Linco, St. Louis MO) highly selective for insulin over pro-insulin. HbA1c and lipid concentrations were measured

by immunoturbidimetric assay and by an enzymatic endpoint assay respectively (both from Roche Diagnostics, Indianapolis IN). Non-esterified fatty acids were measured using a colorimetric method (Wako, Richmond VA). Beta cell function was quantified as the Insulinogenic Index, (IGI:[insulin(30)-insulin(0)]/[glucose(30)-glucose(0)]). Insulin resistance was estimated using HOMA-IR, calculated as insulin (μmL) time glucose (mmol/L) divided by 22.5 [27]. Incremental glucose and insulin area under the curve following the oral glucose challenge were calculated as the excursion above baseline, using the trapezoidal rule.

Statistical Analysis

The primary outcome for the current analysis was progression of carotid IMT, measured for each individual at yearly intervals across the available observation period. The primary analyses used linear mixed models to assess the effect of baseline and change in metabolic variables on this repeated measures outcome, allowing the use of different lengths of follow-up between individuals. Change was calculated as $[\text{Yr1} - \text{Yr0}]$, which allows assessment of the maximal on-study treatment effect. First, the univariate relationship of each variable with IMT progression was assessed. To select variables for subsequent inclusion in a multivariable model, we applied a threshold value for these univariate relationships of $p < 0.1$. Multivariable models were constructed using baseline variables, and then baseline and 1-year change variables that met these criteria. Carotid IMT was not normally distributed, even after applying logarithmic or square root transformations. Therefore, the untransformed data were used in the mixed modeling procedure, applying the Minimum Variance Quadratic Unbiased Estimation (MIVQUE) method, which does not require normally distributed data [28]. Pairwise associations of the metabolic variables at the baseline were assessed by nonparametric Spearman rank-order correlations.

A number of variables had significant univariate effects on progression of IMT, and were potentially affected by randomized treatment. Therefore we evaluated the effects of randomized treatment on change in metabolic variables, in order to explore potential mechanisms for the observed effects of acarbose on IMT progression. A MIVQUE method was applied for models incorporating glucose variables as these were not normally distributed. Other variables were normally distributed and in those cases we applied a Residual Estimation Maximum Likelihood (REML) method in mixed modeling analysis.

All statistical analyses were performed with SAS statistical software 9.2 SAS institute Inc. Cary, NC, applying a two-sided significance level of $p=0.05$.

RESULTS

Baseline characteristics of the EDIP population have been previously published [23]. For convenience pertinent baseline descriptive data are presented in Table 1. By protocol, subjects who met the main study fasting glucose endpoint at the quarterly visits (i.e. progression of fasting glucose) did not undergo further study measurements. Analyses incorporating change in baseline variables to year 1 of follow-up were possible with 163 subjects (76% of entry cohort). Median duration of randomized treatment exposure was 24

months; 72 participants had data through the full 60 months of the study. The number of subjects contributing data at each yearly interval is presented in Figure 1, upper panel.

Correlations and Univariate Relationships with IMT Progression

Table 2 shows the Spearman correlations at baseline between carotid IMT and variables of interest. We found significant cross-sectional associations of carotid IMT with older age, male gender, higher fasting plasma glucose, higher OGTT glucose values at 120 min and OGTT glucose AUC excursion, and lower values of fasting insulin and beta cell function. Blood pressure and lipid parameters were not associated with baseline carotid IMT in this study population.

Analyses of determinants of IMT progression used the mixed modeling procedure, incorporating available follow-up in all subjects. In univariate analyses, many baseline factors were associated with progression of carotid IMT over the observation period (Table 4). Treatment with acarbose reduced progression of carotid IMT, significant when evaluated as the mixed model or as an annualized rate of progression ($p=0.047$) (Table 4 and Figure 1). Other individually significant factors included higher age, higher OGTT-glucose measurements (120 min and excursion AUC), higher systolic blood pressure, and history of smoking (Table 2). Lower fasting insulin concentrations and lower baseline LDL cholesterol values were associated with IMT progression in univariate analyses in this population. Alcohol use, BP medication use, and lipid-lowering medication use were not different across treatment groups (Table 1) and were not significant determinants of IMT progression in univariate analyses (all $p>0.6$).

Study treatment induced significant changes in glucose and non-glucose parameters, maximal at Year 1 and then regressing with further follow-up (Figure 2). The values for relevant variables at Year 1 and the treatment-specific change in those variables are presented in Table 3. Univariate analysis of the association of progression of carotid IMT with changes from baseline to year 1 in relevant anthropomorphic and metabolic variables are presented in Table 4. Notable observations include associations of IMT progression with decreased weight, decreased OGTT glucose measurement at 30 min, increased fasting insulin, increased LDL cholesterol, decreased glycated LDL, and decreased fasting free fatty acids. There was no association of progression of IMT with change in fasting plasma glucose (despite a significant treatment-related reduction in fasting and 2 hour glucose), changes in beta cell function or changes in blood pressure (both of which exhibited study-related changes, not different by treatment; Figure 2). The association of progression in IMT with change in A1C to year 1 approached but did not reach significance ($p=0.051$).

Multivariable modeling of IMT progression

A multivariable analysis including nominally significant univariate baseline factors is presented as Multivariable Model 1 in Table 2. In order to avoid collinearity with FPG in the model, fasting insulin was used in lieu of HOMA-IR as an index of insulin resistance. Similarly, OGTT glucose AUC excursion was the only variable included to reflect the contribution of post-challenge glucose handling. In this model, many factors retained independent significance in association with progression of IMT. These included higher

OGTT glucose AUC, lower HDL cholesterol, and higher glycated LDL. Lower fasting glucose and lower LDL cholesterol remained associated with IMT progression in the multivariable models. Under this mutually adjusted model, the effect of acarbose treatment was no longer significant, suggesting either that the variables that retained significance accounted for the effect of acarbose or the relative strength of the acarbose effect was smaller than the effect of these other variables.

The multivariable mixed model analysis including nominally significant baseline and Year 1 change variables is presented as Multivariable Model 2 in Table 2. Baseline metabolic factors with persisting independent effects on IMT progression in this model included higher baseline OGTT AUC glucose excursion, higher baseline HbA1C, and lower baseline fasting plasma glucose. IMT progression was also associated independently with changes over the first year in weight, fasting insulin and fasting NEFA. There were no significant effects of baseline weight, lipid and blood pressure parameters, or changes in glucose, cholesterol or triglyceride parameters on IMT progression in this multivariable model.

The change variables evaluated change over the first year of randomized treatment, and represent the relationship of changes in IMT with maximal study effects. Our dataset also includes these measurements made concurrently with each yearly visit. We therefore undertook a further set of analyses incorporating all available time-dependent data against the time-dependent changes in IMT (not shown; Supplemental Tables 1 and 2). Many relevant variables exhibited initial improvement followed by reversion toward baseline over the course of the study (Figure 2), which reduces the sensitivity of this approach. The results were concordant with the above analyses but not identical, showing significant univariate relationships between IMT progression and the time course of weight, fasting glucose, and fasting insulin. In these analyses we also found associations of IMT progression with the time course of HDL cholesterol and systolic blood pressure. Multivariable modeling using these time-dependent variables differed from Model 2 above in that in after adjustment for age, sex, and smoking, only the time courses of weight, fasting glucose and HDL concentrations retained significance as predictors of IMT progression.

Mediators of Acarbose Effect on IMT

In univariate analysis, acarbose treatment slowed the progression of IMT relative to placebo. Multivariable modeling suggested that effects of acarbose on weight, fasting insulin, LDL cholesterol, glycated LDL and/or fasting NEFA could potentially be the mediators of this effect. We therefore undertook exploratory analyses, using mixed model analyses of the effect of study interventions on changes in these and other relevant parameters over time. In these analyses we observed changes over time in fasting glucose, OGTT glucose excursions, diastolic blood pressure, HDL cholesterol, and fasting non-esterified fatty acids, but these parameters did not differ by treatment (Figure 2). Only OGTT glucose at 60 minutes ($p=0.014$) and triglycerides ($p=0.013$) were significantly different by treatment. However, these parameters were not concordant with the results from the mixed modeling analyses of determinants of IMT progression as described above.

DISCUSSION

In this randomized trial we found a reduced rate of progression of carotid IMT among subjects with oral glucose tolerance test-defined early diabetes treated with acarbose. This result was seen in univariate analysis, but was lost when effects of glucose, insulin, and lipids were incorporated. In multivariate analyses, a mix of baseline and treatment-related factors proved independently related to IMT progression. Despite clear acarbose-related effects to improve glycemia, changes in glucose did not achieve significance in multivariable modeling of treatment effects on IMT progression. However, higher baseline OGTT excursion and higher HbA1c were associated with greater IMT progression, confirming the general concept that glycemic control is important in IMT progression. Reductions in weight, blood pressure, glucose, NEFA and lipid parameters were observed in both treatment arms, reflecting the general benefits of study participation. Acarbose-specific beneficial changes were seen in fasting and OGTT-excursion glucose, cholesterol, weight, insulin, and NEFA concentrations, although only the latter 3 contributed significantly in the fully adjusted model as determinants of IMT progression. Both treatment arms experienced reductions in blood pressure, but these changes did not contribute to the reduced rate of IMT progression. In sum, the current results suggest that effects of acarbose on IMT progression are not simply attributable to its effects to reduce glucose.

Our study confirms and extends the results of a recent meta-analysis that combined the 3 previously published studies of acarbose with 2 studies of voglibose on IMT progression [21]. The current study demonstrates a beneficial effect of acarbose on IMT in a largely Caucasian population with early diabetes as defined by an oral glucose tolerance test, and provides a more extensive analysis of the determinants of IMT progression with treatment than has been previously published. Beneficial effects of alpha-glucosidase inhibitors on carotid IMT have been previously reported in Asian [17, 19, 20, 30] and Caucasian [18] cohorts. A similar benefit of acarbose on carotid IMT was reported in a one-year, prospective, randomized, open-label, parallel-group study in Japanese adults with newly diagnosed impaired glucose tolerance or mild type 2 diabetes mellitus [19]. In that study a significant reduction of carotid IMT in acarbose-treated participants was observed concurrent with acarbose effects to improve glucose, cholesterol, and triglyceride concentrations, although a formal analysis for mediation was not performed. In a Japanese population with type 2 diabetes also treated with sulfonylurea [20], acarbose decreased the progression of carotid IMT after 12 months of treatment, with concurrent improvements in HbA1c, cholesterol, triglycerides, and lipoprotein lipase mass. Voglibose (another alpha-glucosidase inhibitor) reduced 3-year progression of carotid IMT in 101 type 2 diabetic patients who were already being treated with diet, sulfonylurea or insulin [17]. In a study comparing voglibose against pioglitazone, the alpha-glucosidase inhibitor effect on IMT did not reach statistical significance [16]. In a substudy cohort from the STOP-NIDDM randomized trial acarbose reduced the progression of carotid IMT compared to placebo in a cohort of 115 subjects with impaired glucose tolerance followed for an average of 3.9 years [18]. This was reflected in a reduced rate of CVD events in the full study cohort in a similar time frame [22], via effects that included reductions in blood pressure. The definition of CVD events in that study differs from what is now accepted as standard, and the total

number of events was small, so this study requires confirmation before accepting a beneficial effect of acarbose on CVD events. A large-scale study addressing this question is underway in China (Acarbose Cardiovascular Evaluation Trial, ClinicalTrials.gov NCT00829660).

The strengths of our study include the 5-year prospective design with yearly IMT determinations, and the analyses of determinants of change that allow separation of baseline, study-related, and treatment-specific contributors to IMT progression. The limitations of our study include incomplete 5-year IMT data, the application of multiple comparisons in our exploratory analyses, and the relatively narrowly defined study population. By design, the study stopped following participants who progressed to the primary glucose endpoints, resulting in a falling number of subjects available for carotid ultrasound analyses over the follow-up interval. The current analyses used a statistical approach that accounts for all available data but nevertheless longer follow-up of IMT measurements in more subjects would have been preferable. In the current analyses we evaluated effects of a number of variables of interest, with the goal of exploring major potential physiologic determinants of IMT progression. We did not adjust these analyses for multiple comparisons but simply applied the traditional $p < 0.05$ threshold. The consistency of results across multiple models supports the relevance of the present observation, arguing against spurious findings due simply to multiple comparisons. Our study population presents both a strength and a limitation for interpreting and applying the current observations. By design, these subjects exhibited narrowly defined early diabetic-level dysglycemia, and were also fairly uniformly obese with a relatively narrow range of related metabolic parameters. Nevertheless, our population exhibited clear and strongly significant relationships of IMT with traditionally associated factors including age, sex, and smoking [13, 31, 32]. Therefore these results are likely generalizable at least to obese, dysglycemic populations.

In summary, in a randomized trial of the effect of acarbose versus placebo on progression of hyperglycemia, we found a significant effect of acarbose to slow IMT progression. This effect was related to recognized baseline determinants of IMT including parameters of glycemic control, and to reductions in weight, insulinemia, and fasting NEFA. The current results suggest that the effects of acarbose on IMT progression cannot be simply attributed to associated reductions in glucose parameters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by an investigator-initiated grant from Bayer with additional support from the National Institutes of Health (grants P60 DK20542, P60 DK20579, GCRC M01RR00750, and M01RR00036). KM was supported by an award from the Sandra A. Daugherty Foundation. This work was presented in abstract form at the American Medical Association Medical Student Section, New Orleans LA 2011.

The conduct of the study, statistical analyses, and manuscript preparation were performed without influence of the commercial sponsor. The authors report no conflicts of interest in regard to this work.

YP co-wrote the manuscript and performed statistical analyses. MK researched data and reviewed/edited the manuscript. RC researched data and reviewed/edited the manuscript. TH contributed to the discussion and reviewed/edited the manuscript. KM co-wrote the manuscript. KM takes responsibility for the work presented here.

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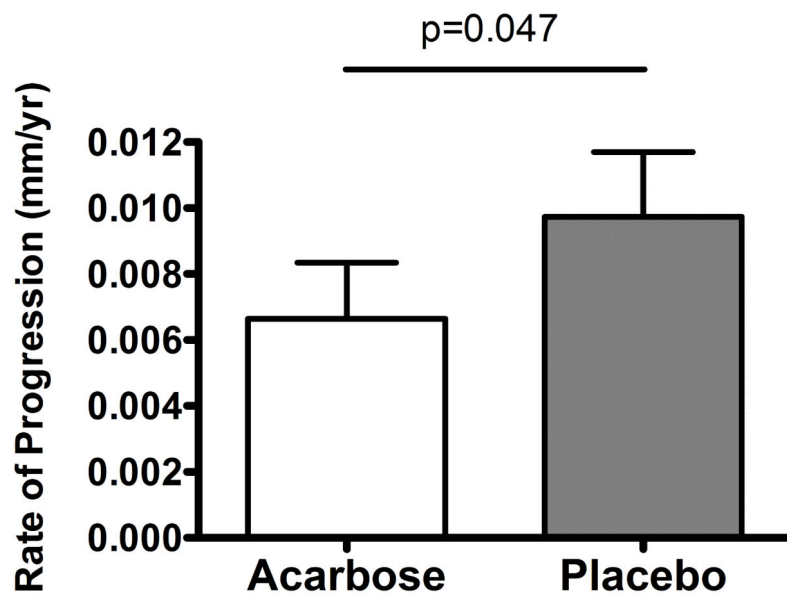
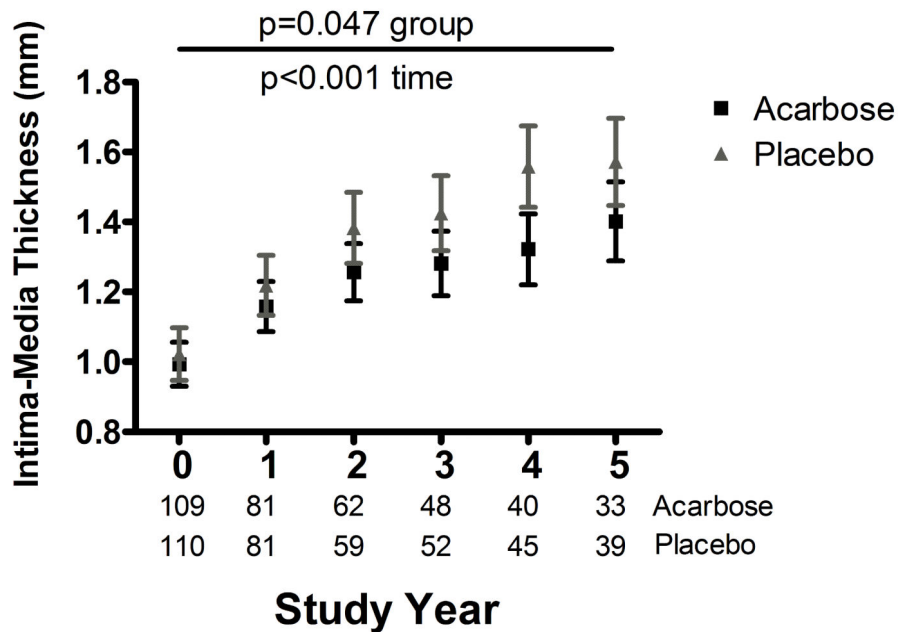


Figure 1. Effects of acarbose on carotid IMT. Upper panel, yearly measures; lower panel, annualized rate of change. Numbers of subjects available for measurement at each yearly interval are indicated below the x axis in the upper panel. Presented as mean±SEM

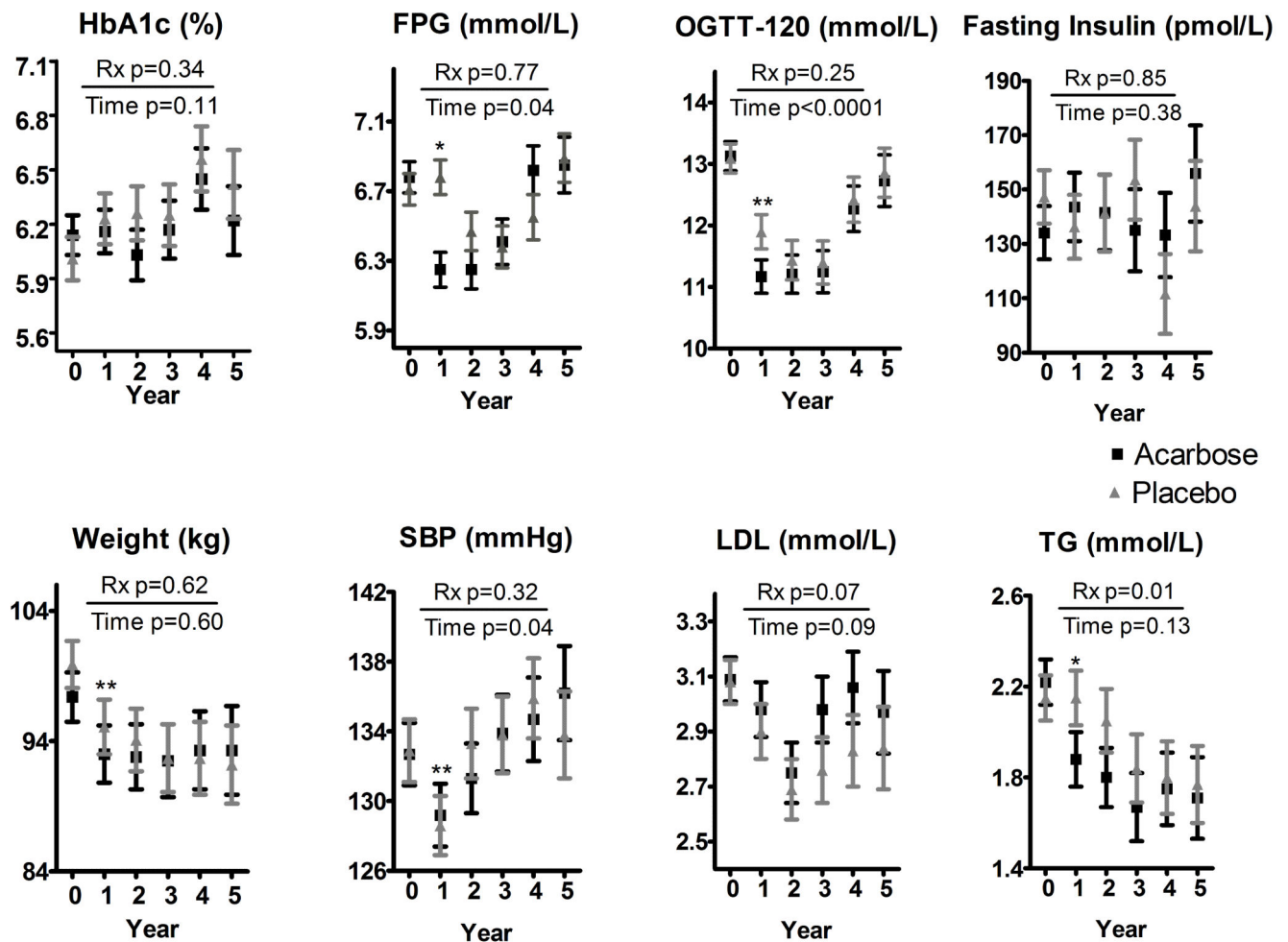


Figure 2.

Time course of determinants of carotid IMT. Statistical results represent the effect of treatment (Rx) or time; there were no statistically significant interactions of treatment and time in these parameters. Where parameters were significantly different between treatment groups within a particular study year, these are denoted individually as *($p < 0.05$) or **($p < 0.01$). Presented as mean \pm SEM.

Table 1

Baseline characteristics of the population

Baseline Characteristics	Acarbose (n=109)	Placebo (n=110)	p-value
	<u>N (%)</u>	<u>N (%)</u>	
Gender: Male/Female	36/73	38/72	0.85
Race: C/AA/AS/H/NA	84/21/2/2/1	85/20/1/2/2	0.67
EtOH intake Y/N (0/40/80/>80 g/d)	36/70 (70/29/2/5)	48/58 (58/42/3/3)	0.40
BP meds Y/N (RAS/CCB/BB/Other)	45/64 (19/8/10/8)	38/72 (11/5/5/17)	0.31
Lipid meds Y/N (Statin/Other)	11/98 (11/0)	9/101 (7/2)	0.63
	<u>Mean ± SD</u>	<u>Mean ± SD</u>	
Age (years)	53.6 ± 11.1	53.6 ± 11.7	0.60*
BMI (kg/m ²)	35.2 ± 7.3	35.3 ± 7.1	0.86*
Weight (kg)	96.9 ± 2.2	97.7 ± 2.3	0.79*
HbA1c (%)	6.13 ± 1.67	6.12 ± 1.65	0.86*
Fasting glucose (mmol/L)	6.78 ± 0.78	6.71 ± 0.74	0.43*
OGTT 120 min glucose (mmol/L)	13.09 ± 1.76	13.09 ± 1.69	0.99
Fasting NEFA (mmol/L)	586.2 ± 181.5	573.1 ± 211.6	0.63
Fasting insulin (pmol/L)	134.6 ± 86.8	148.1 ± 100.1	0.30
HOMA-IR (U)	5.90 ± 3.90	6.44 ± 4.47	0.51*
Systolic BP (mm Hg)	133.4 ± 16.5	131.7 ± 18.0	0.48
Diastolic BP (mm Hg)	75.4 ± 11.1	75.2 ± 11.1	0.87
Total cholesterol	5.00 ± 0.97	5.02 ± 1.03	0.88
HDL cholesterol	0.98 ± 0.21	1.00 ± 0.22	0.38
LDL cholesterol	3.06 ± 0.85	3.04 ± 0.90	0.91
Triglycerides	2.24 ± 1.34	2.19 ± 1.04	0.75*
IMT (mm)	1.082 ± 0.736	1.022 ± 0.544	0.55

P-values reported are from chi-square analysis for categorical variables, unpaired t-test for normally distributed continuous variables, and Wilcoxon Rank-Sum test for skewed distributed continuous variables (the latter denoted by *).

Abbreviations: AA, African American; AS, Asian American; BB, beta blockers; BMI, body mass index; BP, blood pressure; C, Caucasian; CCB, calcium channel blockers; HbA1C, hemoglobin A1C; HDL, high density lipoprotein; H, Hispanic; IMT, carotid intima-media thickness; LDL, low density lipoprotein; HOMA-IR, homeostasis model of insulin resistance; NA, Native American; NEFA, non-esterified fatty acids; OGTT, oral glucose tolerance test; RAS, renin-angiotensin system antagonists

Table 2

Spearman correlations between carotid IMT and variables of interest at baseline

Baseline parameter	r value	p-value
Age (yrs)	+ 0.435	<0.0001
Gender (M=0, F=1)	- 0.253	0.0002
Weight (kg)	- 0.107	0.12
Fasting glucose (mmol/L)	+ 0.863	0.012
OGTT glucose at 120 min (mmol/L)	+ 0.158	0.02
OGTT glucose AUC excursion (mmol/L*min)	+ 0.134	0.049
HbA1C (%)	+ 0.034	0.62
Insulinogenic Index (pmol/mmol)	- 0.154	0.029
Fasting insulin (pmol/L)	- 0.211	0.002
LDL cholesterol (mmol/L)	+ 0.076	0.31
HDL cholesterol (mmol/L)	- 0.021	0.77
Triglycerides (mmol/L)	+ 0.123	0.09
Fasting NEFA (mmol/L)	- 0.113	0.10
Systolic BP (mmHg)	+ 0.093	0.18
Diastolic BP (mmHg)	+ 0.099	0.15

Abbreviations: AUC, area under curve; BP, blood pressure; F, female; HbA1C, hemoglobin A1C; HDL, high density lipoprotein; IMT, intima media thickness; LDL, low density lipoprotein; M, male; NEFA, non-esterified fatty acids; OGTT, oral glucose tolerance test

Table 3

Status at Year 1 and change from baseline to year 1 in metabolic and hemodynamic parameters.

Variable	Acarbose (n=81)		Placebo (n=81)		P value change by group
	Year 1	Change	Year 1	Change	
Weight (kg)	93.0 ± 2.2	-3.9 ± 0.6	95.2 ± 2.3	-2.5 ± 0.7	0.14
HbA1c (%)	6.2 ± 0.1	-0.2 ± 0.1	6.2 ± 0.1	0.0 ± 0.1	0.04
Fasting glucose (mmol/L)	112.6 ± 1.9	-0.5 ± 0.1	116.2 ± 1.9	-0.3 ± 0.1	0.09
OGTT 120 min glucose (mmol/L)	201.3 ± 5.0	-1.9 ± 0.3	212.8 ± 5.5	-1.2 ± 0.3	0.129
Fasting NEFA (mmol/L)	1.95 ± 0.62	-0.19 ± 1.17	4.80 ± 0.47	-1.23 ±	0.14
Fasting insulin (pmol/L)	143.6 ± 17.5	6.1 ± 22.5	135.2 ± 12.4	-4.8 ± 14.9	0.68
HOMA-IR (U)	4.95 ± 0.62	-0.19 ± 1.17	4.80 ± 0.72	-1.23 ± 0.62	0.43
Systolic BP (mm Hg)	129.2 ± 1.6	-3.6 ± 1.8	128.5 ± 1.6	-4.4 ± 2.2	0.79
Diastolic BP (mm Hg)	71.1 ± 1.0	-3.4 ± 1.2	71.9 ± 1.0	-3.9 ± 1.4	0.78
Total cholesterol (mmol/L)	4.87 ± 0.09	-0.15 ± 0.08	4.88 ± 0.11	0.16 ± 0.08	0.94
HDL cholesterol (mmol/L)	1.03 ± 0.03	0.05 ± 0.02	1.03 ± 0.03	0.04 ± 0.02	0.77
LDL cholesterol (mmol/L)	2.98 ± 0.08	-0.15 ± 0.09	2.92 ± 0.10	-0.20 ± 0.10	0.73
Triglycerides (mmol/L)	1.88 ± 0.11	-0.26 ± 0.12	2.11 ± 0.12	-0.17 ± 0.11	0.15

Data from Abbreviations: AUC, area under curve; BP, blood pressure; HbA1C, hemoglobin A1C; HDL, high density lipoprotein; IMT, intima media thickness; LDL, low density lipoprotein; NEFA, non-esterified fatty acids; OGTT, oral glucose tolerance test

Table 4

Determinants of progression of carotid IMT

Variable	Univariate Models		Multivariable Model 1		Multivariable Model 2	
	β	p-value	β	p-value	β	p-value
Treatment group (P=0, A=1)	- 0.104	0.047	+ 0.069	0.20	- 0.027	0.72
Age (yrs)	+ 0.026	<0.0001	+ 0.021	< 0.0001	+ 0.017	< 0.0001
Gender (M=0, F = 1)	- 0.396	<0.0001	- 0.129	0.061	- 0.136	0.14
History of smoking (Yes=1)	+ 0.468	<0.0001	+ 0.345	< 0.0001	+ 0.415	< 0.0001
Weight (kg)	- 0.003	0.012	- 0.002	0.37	- 0.002	0.30
Weight	- 0.024	<0.0001			- 0.023	0.005
Fasting glucose (mmol/L)	- 0.062	0.073	- 0.078	0.045	- 0.287	< 0.0001
Fasting glucose	- 0.012	0.70				
OGTT glucose at 120 min (mmol/L)	+ 0.043	0.006				
OGTT glucose (120 min - 0 min)	- 0.013	0.28				
OGTT glucose AUC Excursion (mmol/L*min)	+ 0.001	0.0006	+ 0.0005	0.017	+ 0.0009	0.003
OGTT glucose AUC Excursion	- 0.0003	0.11				
HbA1c (%)	+ 0.033	0.05	+ 0.029	0.078	+ 0.222	0.019
HbA1c	- 0.091	0.051			- 0.017	0.84
Fasting insulin (pmol/L)	- 0.001	<0.0001	- 0.0009	0.001	+ 0.0006	0.23
Fasting insulin	+ 0.0007	0.003			+ 0.002	< 0.0001
Insulinogenic Index (pmol/mmol)	- 0.001	0.0002	- 0.0006	0.14	- 0.0003	0.50
Insulinogenic Index	+ 0.0006	0.13				
HDL cholesterol (mmol/L)	- 0.493	<0.0001	- 0.347	0.018	+ 0.109	0.59
HDL cholesterol	- 0.126	0.38				
LDL cholesterol (mmol/L)	- 0.107	0.0006	- 0.091	0.005	- 0.111	0.058
LDL cholesterol	+ 0.097	0.009			+ 0.062	0.31
Triglycerides (mmol/L)	+ 0.105	<0.0001	+ 0.033	0.32	+ 0.031	0.53
Triglycerides	+ 0.031	0.30				
Glycated LDL (mmol/L)	+ 0.084	0.002	+ 0.101	0.0001	+ 0.072	0.28
Glycated LDL	- 0.111	0.0001			- 0.128	0.054
Fasting NEFA (mmol/L)	- 0.0002	0.21				
Fasting NEFA	- 0.0003	0.01			- 0.0004	0.012

Variable	Univariate Models		Multivariable Model 1		Multivariable Model 2	
	β	p-value	β	p-value	β	p-value
Systolic BP (mmHg)	+ 0.003	0.023	- 0.0005	0.78	- 0.004	0.082
Systolic BP	- 0.002	0.15				
Diastolic BP (mmHg)	+ 0.001	0.71				
Diastolic BP	- 0.0005	0.82				

Parameter estimates represent the effect of 1 unit increment in the dependent variable on rate of progression of IMT. Model 1 presents an evaluation of baseline factors that determined progression of IMT. Model 2 presents an evaluation of baseline and treatment-induced changes in factors that determined progression of IMT. β indicates change in a parameter, calculated as Yr1-Yr0. Abbreviations: A, Acarbose; AUC, area under curve; BP, blood pressure; F, female; FPG, fasting plasma glucose; HbA1C, hemoglobin A1C; HDL, high density lipoprotein; IMT, intima media thickness; LDL, low density lipoprotein; M, male; NEFA, non-esterified fatty acids; OGTT, oral glucose tolerance test; P, Placebo.