Supplemental Material

Research Design and Methods:

Treatment algorithm: Participants randomized to Triple Therapy were started on metformin 1000 mg/day, pioglitazone 15 mg/day and exenatide 5 μg subcutaneously twice daily before breakfast and supper. At 1 month, metformin was increased to 2000 mg/day pioglitazone to 30 mg/day and exenatide to 10 μg twice daily. If, at 3 months, HbA1c was >6.5% (48 mmol/mol), pioglitazone was increased to 45 mg/day. Participants receiving Conventional Therapy were started on metformin 1000 mg/day. If, at 1 month, fasting plasma glucose (FPG) concentration was >6.1 mmol/l (110 mg/dl), metformin was increased to 2000 mg and glipizide started at 5 mg/day. If, at 2 months, FPG was >6.1 mmol/l (110 mg/dl) or HbA1c was >6.5% (48 mmol/mol), glipizide was increased to 10 mg/day and then to 20 mg/day. If, at 3 months, FPG was >6.1 mmol/l (110 mg/dl) or HbA1c >6.5% (48 mmol/mol), glargine insulin was started at 10 units before breakfast and escalated weekly by 1–5 units (based on FPG and HbA1c) to 60 units/day to maintain FPG at <6.1 mmol/l (110 mg/dl).

After 3 months, participants were seen every 3 months. During follow-up, patients were asked to measure their FPG daily and perform 7-point home blood glucose measurement one day per week on Wednesday. On each follow-up visit, patients were questioned about adverse events and home blood glucose levels were reviewed. FPG, body weight and HbA1c were measured at each follow-up visit and medication dose was adjusted to maintain FPG at <6.1 mmol/l (110 mg/dl) and HbA1c at <6.5% (48 mmol/mol), unless hypoglycemia (blood glucose <3.3 mmol/l [60 mg/dl] or symptoms was present. Hypoglycemia was defined as blood glucose concentration <3.3 mmol/l (60 mg/dl), with or without symptoms, or hypoglycemic symptoms that subsided after carbohydrate ingestion. Severe hypoglycemia was defined as hypoglycemia requiring third party assistance.

If HbA1c increased to >6.5% (48 mmol/mol) on two consecutive visits performed 3 months apart (to ensure that the deterioration in glycemic control was not attributable to transient factors) despite maximum antihyperglycemic therapy, treatment was defined as having failed, baseline studies were repeated, and rescue therapy was started. Rescue therapy in the Conventional Therapy group was 4-6 units of short-acting insulin before each meal and the dose was adjusted based on blood glucose measurements to maintain plasma glucose concentration <7.8 mmol/l (140 mg/dl) 2 hours after meals. Rescue therapy in the Triple Therapy arm was glargine insulin started at 6–10 units/day with dose increase to maintain FPG <6.1 mmol/l (110 mg/dl).

Oral Glucose Tolerance Test (OGTT):

Before the start of therapy and at study end (at year 3 or at the time of treatment failure), subjects received 2-hour 75-gram OGTT after 10-12 hour overnight fast. Blood samples were drawn before and every 30 minutes thereafter for the measurement of plasma glucose, insulin and C-peptide concentrations. In subjects receiving insulin therapy, insulin was not injected on the morning of the study. All other medications (other than insulin) were administered on the morning of study.

Carotid Intima Media Thickness (IMT)

Carotid IMT was measured with high-resolution B-mode carotid artery ultrasound to image the far wall of the right distal common carotid artery by the same certified technician as previously described (18). All ultrasound images were read blinded to treatment at the University of Southern California Atherosclerosis Research Unit Core Imaging and Reading Center (18).

Data Analysis: For the primary analysis (intention to treat analysis), patients who failed to achieve the treatment goal during follow-up (i.e. had HbA1c increase >6.5%), and were started on rescue therapy, the last HbA1c before starting rescue therapy (end of study value) was used for analysis. In patients who dropped of the study during follow-up (mean follow-up =19.1±1.8 and 17.6±1.6 months, in the

Conventional Therapy and Triple Therapy groups, respectively), the HbA1c value at the last visit (end of study value) was used for analysis. In patients who maintained the treatment goal for 36 months, the HbA1c at 36 months (end of study value) was used for analysis. The HbA1c at end of study was compared amongst the two treatment groups with 2-way ANOVA with time and treatment as factors.

For the intention to treat analysis, every subject who received therapy was included in the analysis (n=157, and n=161 for Triple Therapy and Conventional Therapy groups, respectively). For the as treated (or per protocol) analysis, only subjects with known outcome were included in the analysis (n=103, and n=114 for Triple Therapy and Conventional Therapy groups respectively).

Sample Size Calculation: In PROactive, at study end, participants who received pioglitazone had 0.5% lower HbA1c than participants who received placebo. Based on this, we assumed that participants who received Triple Therapy (which includes pioglitazone) would achieve ≥0.5% lower HbA1c than those receiving Conventional Therapy. We calculated that 76 completers per arm would provide 90% power to detect a 0.5% HbA1c difference between treatment arms at alpha value <0.05.

SUPPLEMENTAL TABLES

Supplemental Table 1: Baseline patient characteristics

	Conventional Therapy	Triple Therapy	P-Value
Age (years)	47±1	44±1	NS
Gender (% male)	42	51	NS
Ethnicity (%)			
Mexican Americans	75	73	NS
Caucasian	15	15	NS
Other	10	12	NS
Diabetes Duration (months)	5.2±0.5	4.8±0.5	NS
Fasting Plasma Glucose (mg/dl)	200±6	203±6	NS
HbA1c (%)	8.8±0.2	9.0±0.2	NS
BMI (kg/m^2)	36.1±1.1	36.4±1.1	NS
BP (mm Hg)	129/80	128/80	NS
Plasma Lipids (mg/dl)			
Total Chol	185±5	194±5	NS
LDL Chol	109±4	118±5	NS
HDL Chol	43±1	43±1	NS

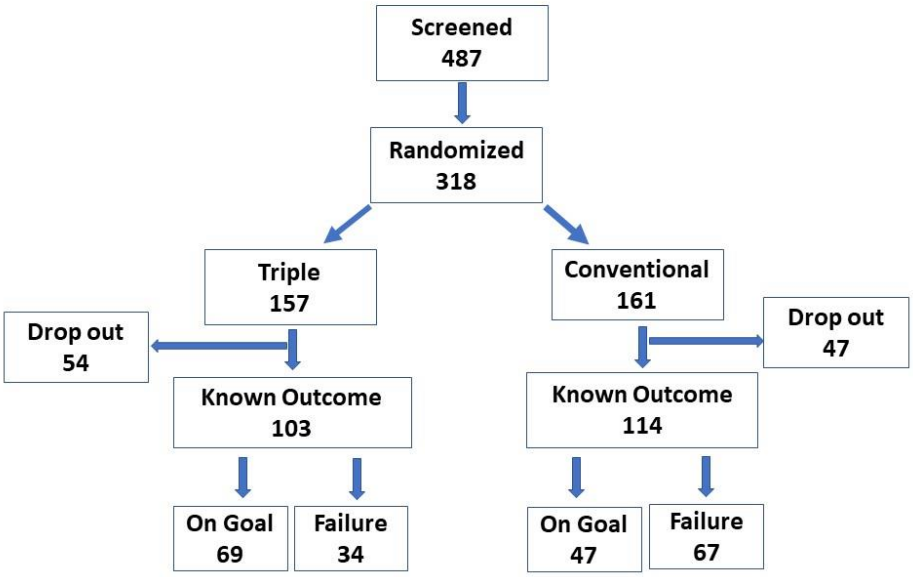
Triglyceride	182±13	175±12	NS

Supplemental Table 2: Baseline characteristics of subjects who dropped of the study and those whose outcome is known in the two treatment groups

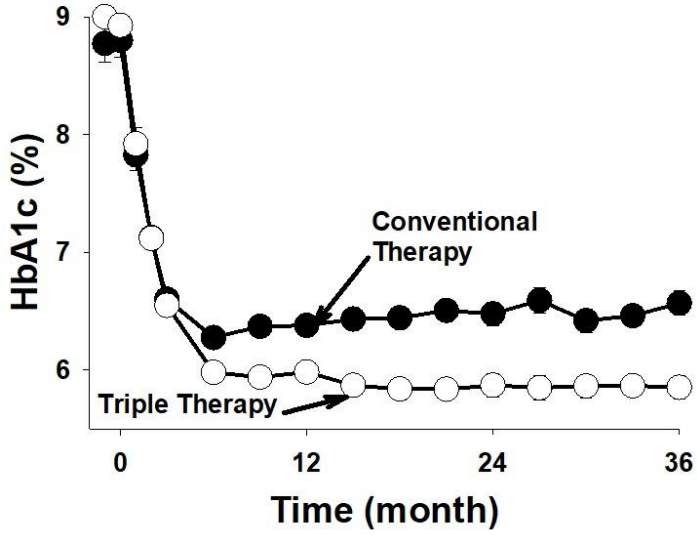
	Conventional Therapy		**Triple Therapy**	
	Dropped Out	**Outcome Known**	**Dropped Out**	**Outcome Known**
Age (year)	46± 2	48± 1	42 ±2	47± 2
Gender (%male)	44	41	51	50
BMI	34.7± 1.1	36.2 ±1.2	35.6 ±2.1	36.9 ±2.2
Diabetes Duration (month)	5.1± 0.9	4.7± 0.8	5.5± 0.9	5.0± 0.8
HbA1c (%)	9.0 ±0.4	8.9 ±0.4	9.1± 0.5	8.8± 0.4

SUPPLEMENTAL FIGURES

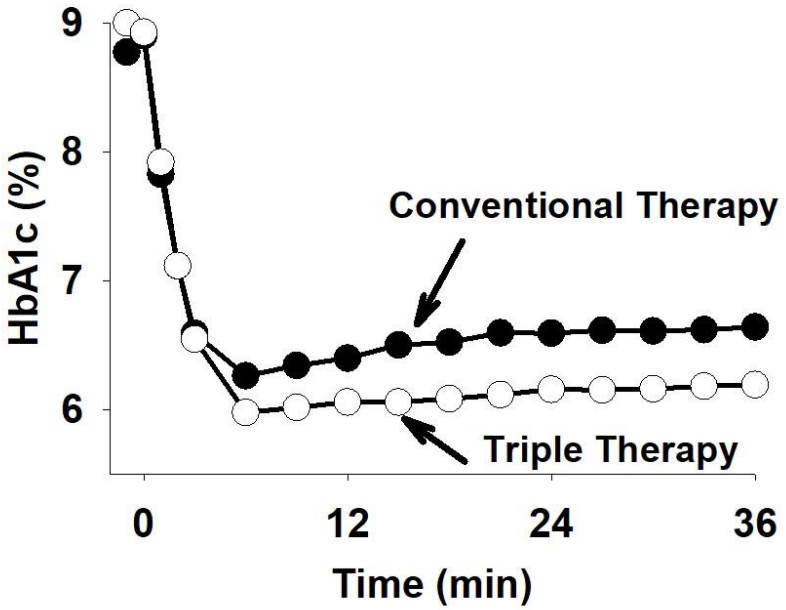
Suppl Figure 1. Study flow design.



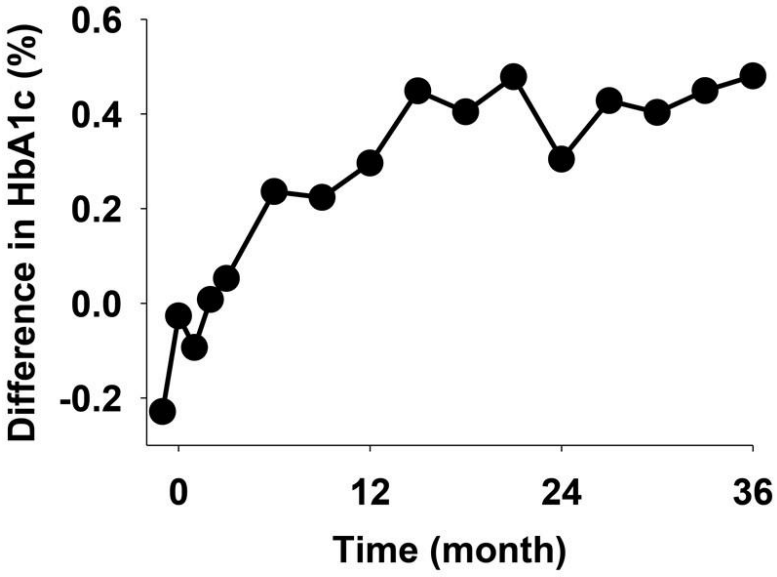
Suppl Figure 2: Time-related change in HbA1c: As-treated analysis;



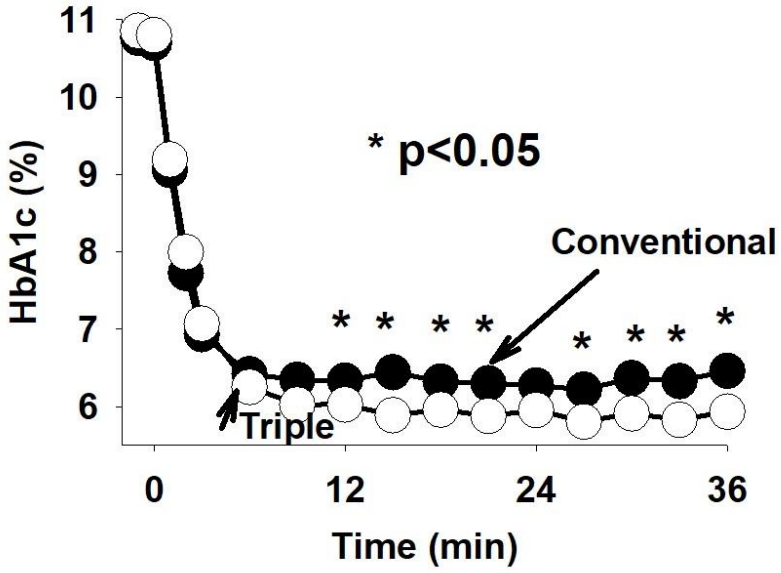
Suppl Figure 3. Time-related change in HbA1c: Last observation carried forward analysis.



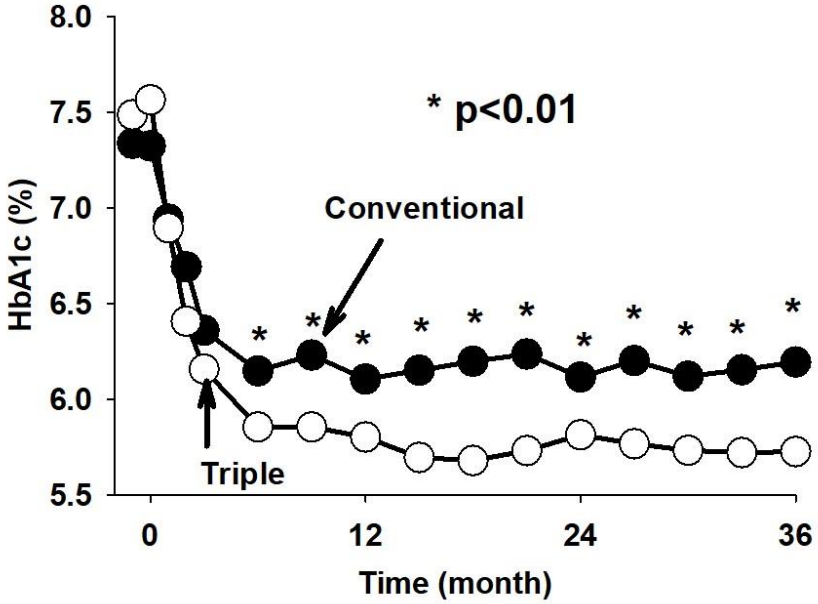
Suppl Figure 4. Time-related difference in HbA1c between Conventional and Triple Therapy groups. Values represent the HbA1c differences between the Conventional Therapy group minus the HbA1c in the Triple Therapy group. The HbA1c in Figure 1A was used for the analysis.



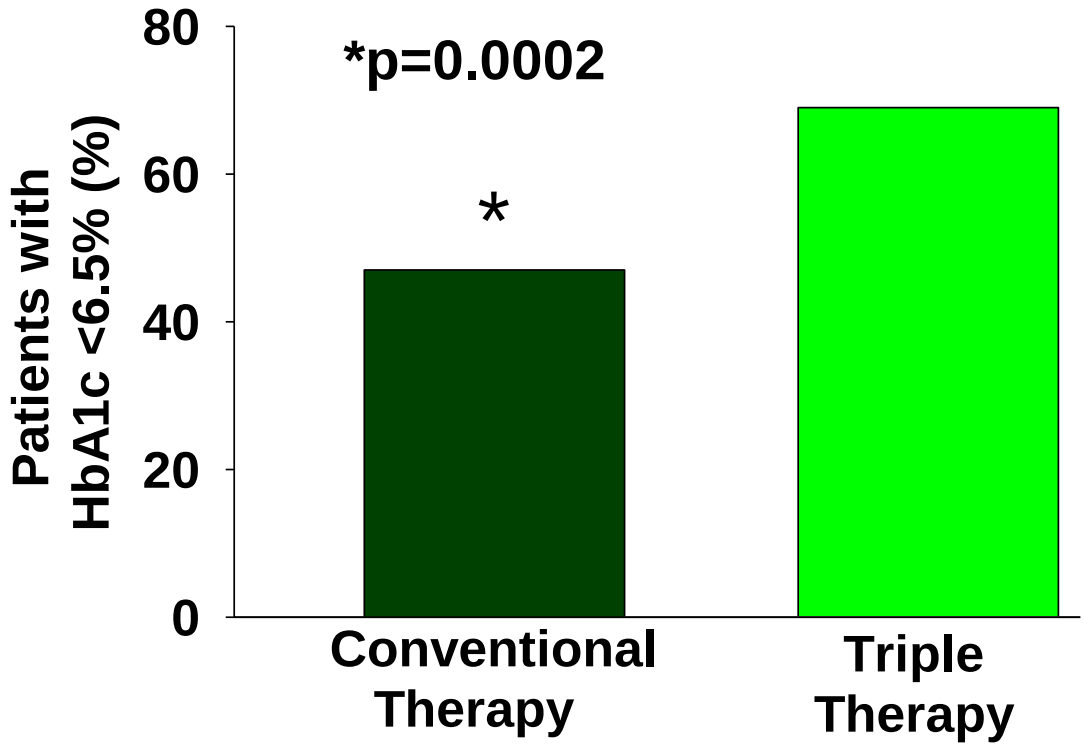
Suppl Figure 5. Time-related change in HbA1c in Conventional Therapy and Triple Therapy subjects with HbA1c ≥ 9.0%



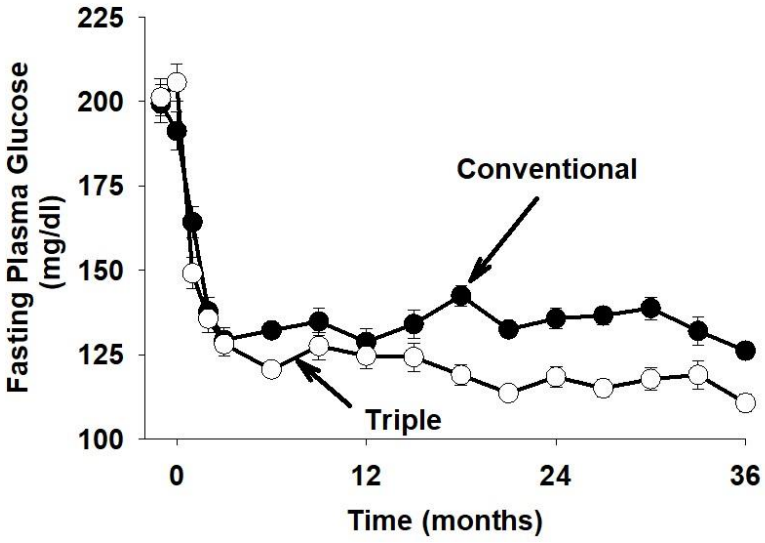
Suppl Figure 6. Time-related change in HbA1c in Conventional Therapy and Triple Therapy subjects with HbA1c < 9.0%



Suppl Figure 7: Percent of subjects in the Triple Therapy and Conventional Therapy groups who maintained HbA1c < 6.5%

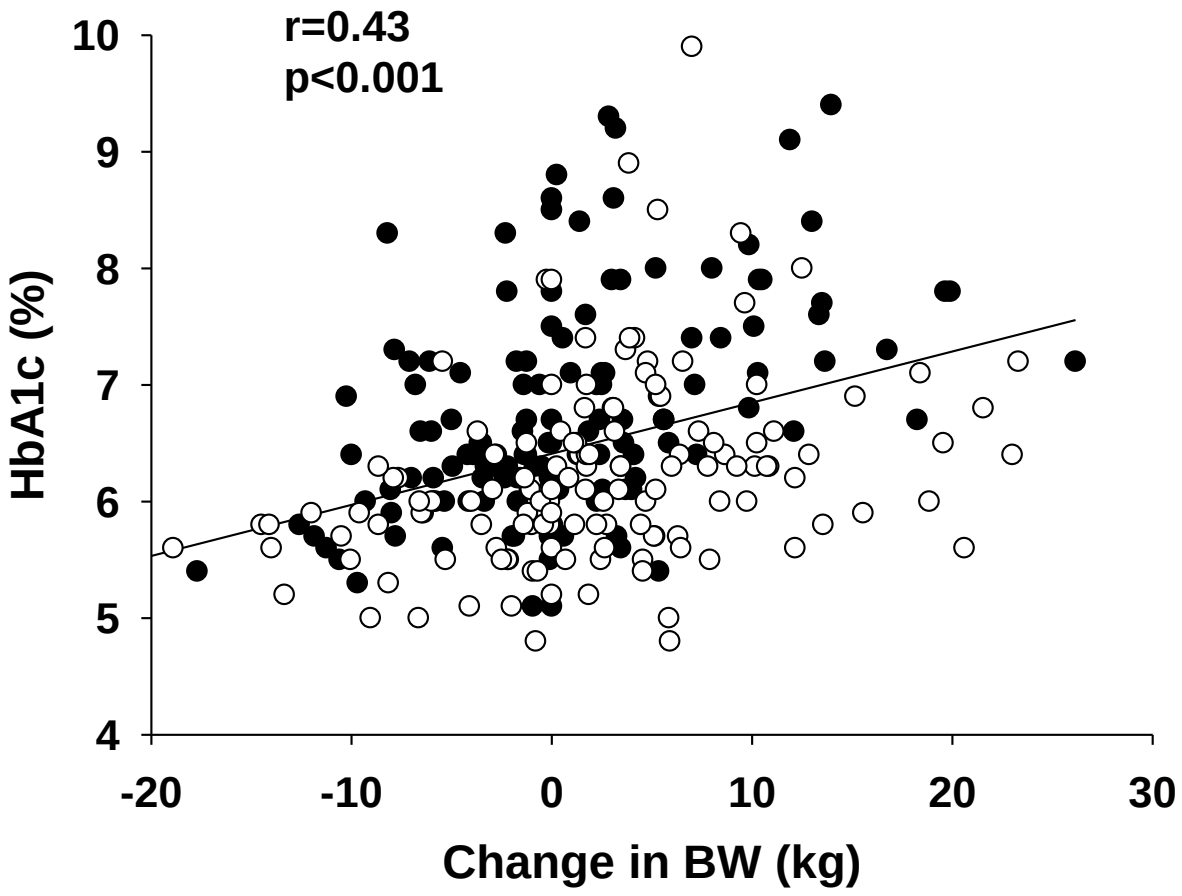


Suppl Figure 8: Time-related change in fasting plasma glucose concentration in Conventional Therapy and Triple Therapy groups.

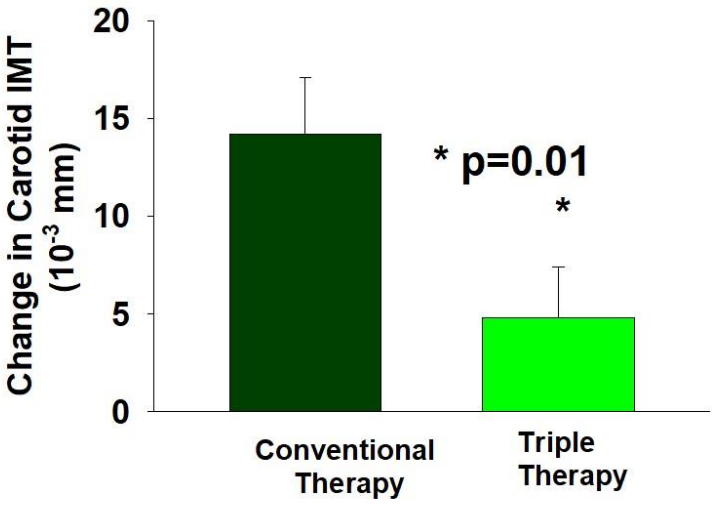


Suppl Figure 9: Relationship between HbA1c at study end and change in body weight during the 3 -years.

Open circles= Triple Therapy, closed circles= Conventional Therapy



Suppl Figure 10. Change in carotid intima medial thickness in Conventional Therapy and Triple Therapy groups.



Suppl Figure 11: Incidence of hypoglycemia at year 1, 2, and 3 in subjects receiving sulfonylurea or sulfonylurea plus insulin.