VICTORY: A Cardiometabolic Trial

Results of a Multicenter Randomized Double-blind Placebo-Controlled Study to Assess the Benefit and Safety of Rosiglitazone in Preventing Atherosclerosis Progression After Coronary Artery Bypass Surgery in Patients with Type 2 Diabetes

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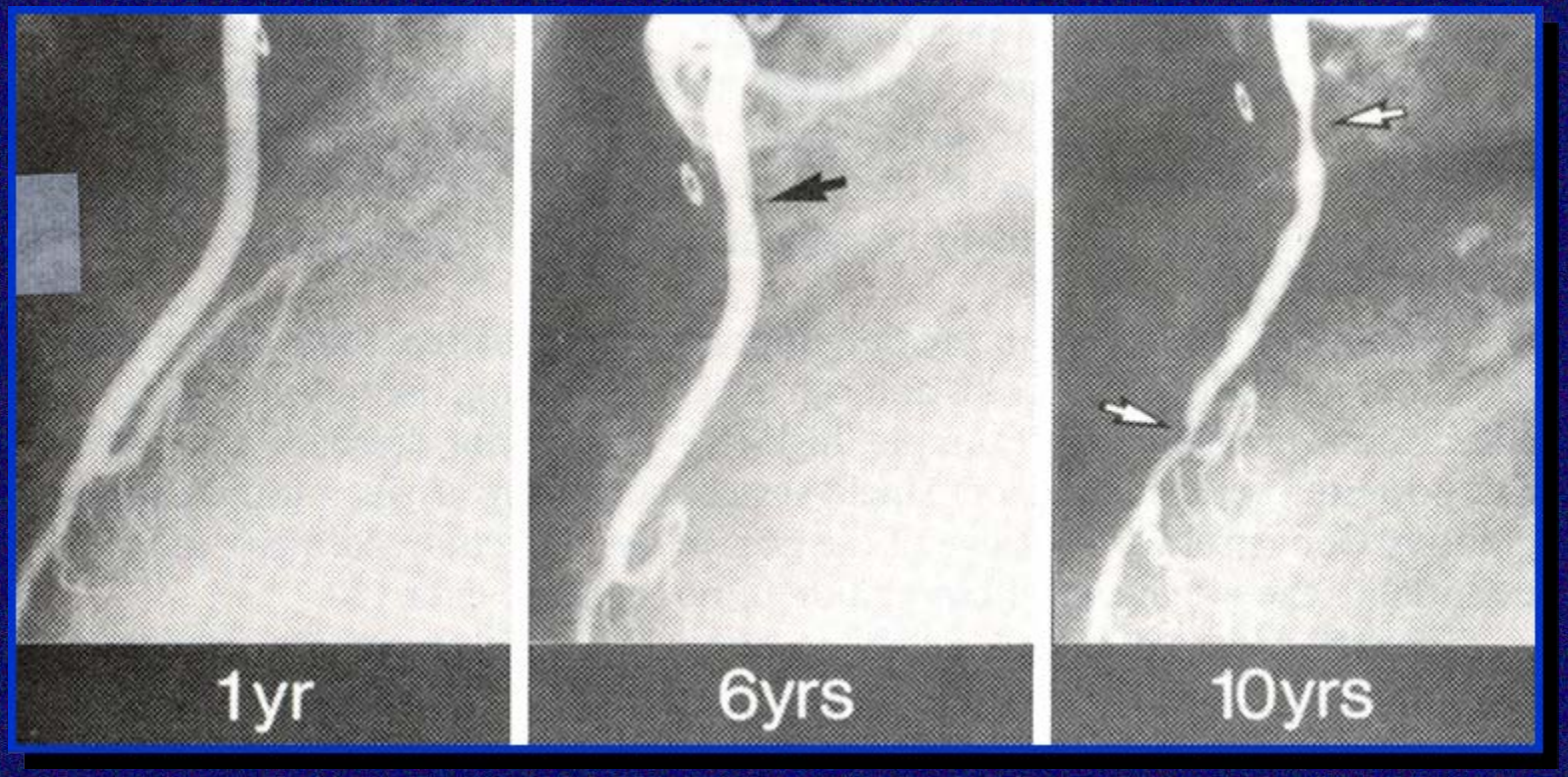
Background

- ✓ In the US, > 500,000 CABGs/year (~30% type 2 diabetes)
- ✓ Accelerated atherosclerosis in SVGs leads to significant stenosis/occlusion ≤ 10 years
- ✓ Although tight glycemic control has been associated with a significant reduction in microvascular complications of diabetes, no such evidence exists for the prevention of macrovascular complications
- ✓ Glitazones are PPAR-γ agonists with multiple and complex effects on metabolism and the cardiovascular system

Accelerated Atherosclerosis in SVG



From Miller DD
Cardiovascular Clinics (1991) chapter 8:137-167

The VICTORY trial

Objectives

- ✓ Efficacy and safety of rosiglitazone to reduce the progression of atherosclerosis in post-CABG patients with type 2 diabetes.
- ✓ Rosiglitazone effects on metabolic and morphologic parameters and biomarkers associated with cardiovascular risk in post-CABG patients with type 2 diabetes.

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Primary End-point: IVUS

✓ The change in plaque volume (12 month - Baseline) in a ≥ 40 mm segment in one SVG as measured by intravascular ultrasound (IVUS).

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Secondary End-points: Metabolic

✓ Changes in glucose-insulin homeostasis, lipids, pro-thrombotic and inflammatory markers of cardiovascular disease risk.

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Secondary End-points: Body Composition

- ✓ Abdominal areas of adipose tissue assessed by computed tomography (CT-scan).
- ✓ Body composition assessed by Dual Energy X-ray Absorptiometry (DEXA).
- ✓ Total body water by bio-impedance (BIA).

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Secondary End-points: Clinical Outcomes

- ✓ Any of the following:

Death, MI, TIA, stroke, ischemia-driven coronary intervention and hospitalization.

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Study Population

- ✓ Stable patients with type 2 Diabetes (HbA1c < 9%)
- ✓ Class 1-2 CCS patients, 1-10 years post-CABG
- ✓ Last ejection fraction > 35%
- ✓ Randomized, rosiglitazone up to 8 mg versus placebo
- ✓ Insulin not allowed

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6 Canadian and 3 Spanish Centers

- ✓ Laval Hospital, Quebec City (PI: OF Bertrand)
- ✓ CHUM-Notre-Dame Hospital, Montreal (PI: S Rinfret)
- ✓ Queen Elizabeth II Health Centre, Halifax, (PI: L Title)
- ✓ Toronto General Hospital, Toronto: (PI: V Dzavik)
- ✓ Hamilton Health Sciences, Hamilton (PI: M Natarajan)
- ✓ Bonaventure, (PI: R Audet)
- ✓ H Vall d'Hebron, Barcelona (PI: J Angel)
- ✓ H Sacrat Cor, Barcelona (PI: N Batalla)
- ✓ H del Mar, Barcelona (PI: A Serra)

- ✓ DSMB: H Gerstein, M Bourassa, J Brophy
- ✓ Monitoring: CATO Research
- ✓ Data Management: Montreal Heart Institute

Results:
Study Population (n = 193)

	Placebo (n = 95)	Rosiglitazone (n = 98)
Age	65 ± 7	64 ± 7
Males	92%	92%
Previous MI	60%	55%
Stroke	5%	8%
Hypertension	84%	84%
Current Smoking	8%	12%
DM with diet/oral Rx	13%/87%	13%/87%
DM duration (yrs)	8.4 ± 6.9	7.8 ± 6.4
Time since CABG (yrs)	3.7 ± 2.5	3.9 ± 2.5

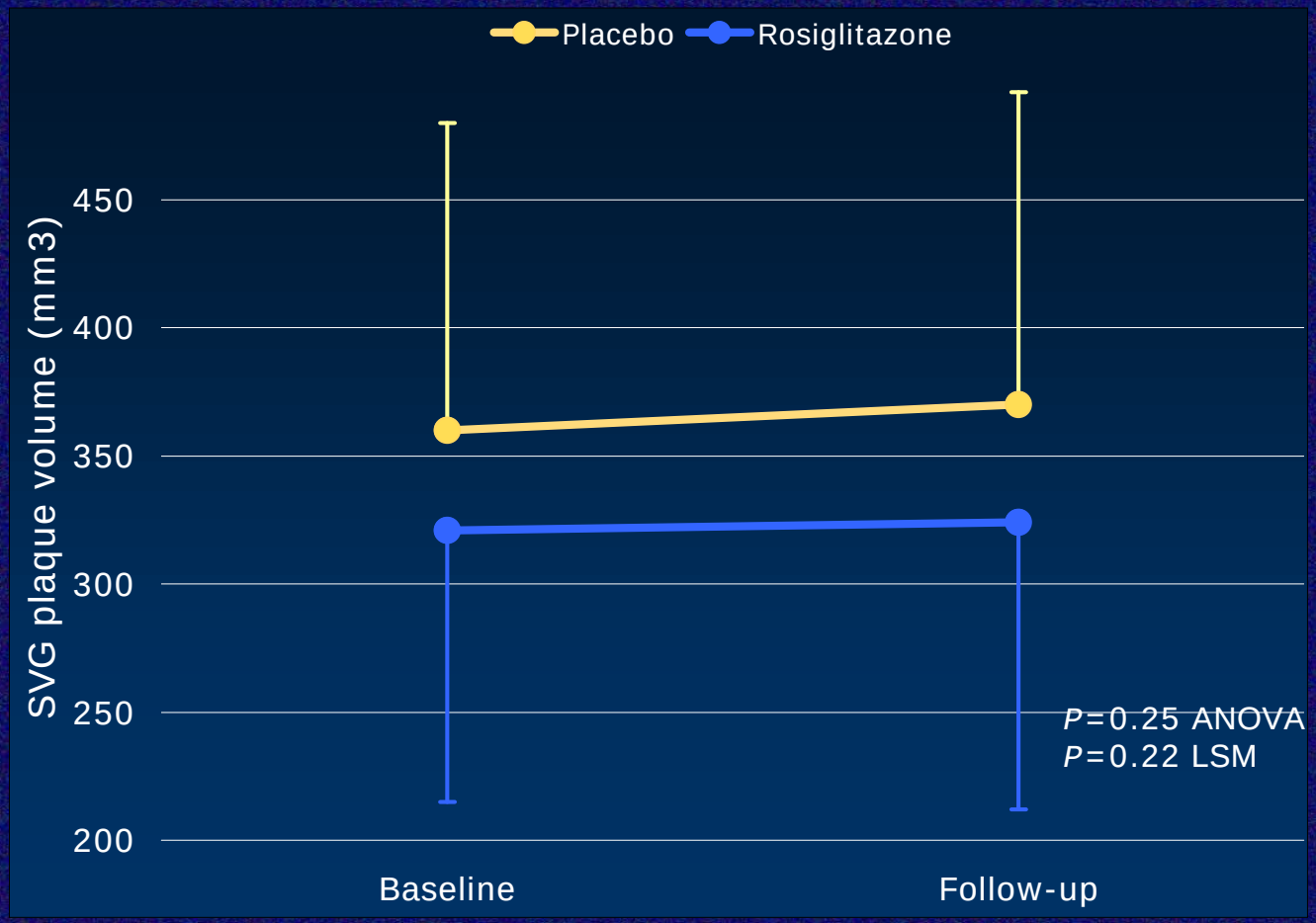
Results:
Medical Rx

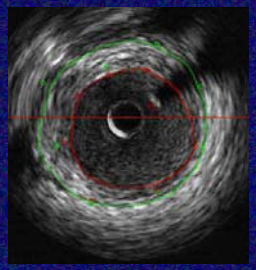
	Placebo (n = 95)	Rosiglitazone (n = 98)
Antiplatelet agent	95 (100%)	98 (100%)
ACEI/ARB	86 (90.5%)	85 (86.7%)
Beta-blockers	64 (67%)	69 (70%)
Ca channel blockers	75 (79%)	77 (79%)
Diuretics	24 (25%)	37 (38%)
Statins	91 (96%)	92 (94%)
Fibrates	19 (20%)	16 (16%)
Metformin	69 (73%)	75 (77%)
Sulfonylureas	46 (48%)	53 (54%)
Alpha-Glucosidase Inh.	2 (2%)	4 (4%)

Results:
Study Population

Variables	Placebo (n = 95)	Rosiglitazone (n = 98)
Weight (kg)	84 ± 15	86 ± 14
BMI	29.5 ± 4.6	30.2 ± 4.2
Systolic Pressure (mmHg)	129 ± 14	129 ± 13
Diastolic Pressure (mmHg)	73 ± 9	71 ± 9
Cholesterol (mg/dl)	151 ± 28	153 ± 31
LDL-Cholesterol (mg/dl)	88 ± 24	87 ± 26
HDL-Cholesterol (mg/dl)	41 ± 8	41 ± 9
TG (mg/dl)	142 ± 74	163 ± 81
Fasting Glucose (md/dl)	135 ± 30	139 ± 35
HbA_{1c} (%)	6.91 ± 0.78	6.92 ± 1.2
CRP (mg/L)	2.54 ± 3.79	3.31 ± 7.11

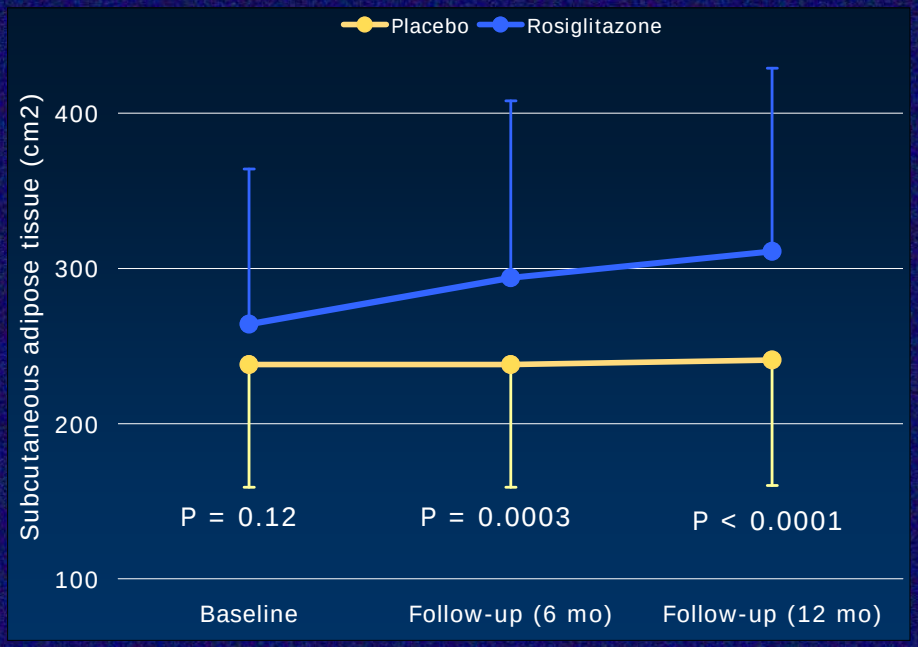
Results:
SVG Plaque Volume





Results:
Adipose Tissue Distribution (CT)

Subcutaneous



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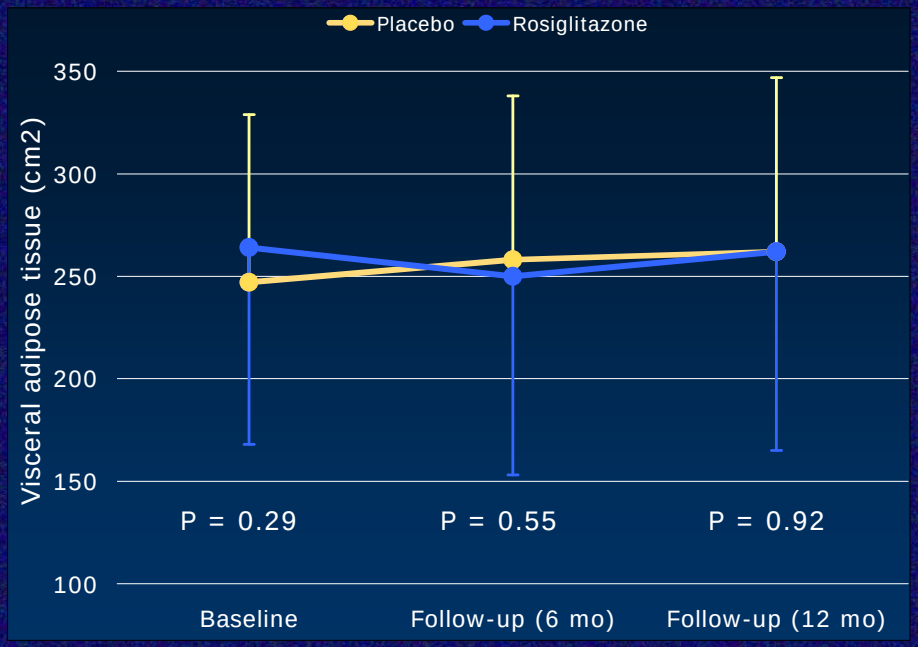
Visceral



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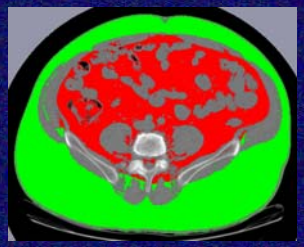
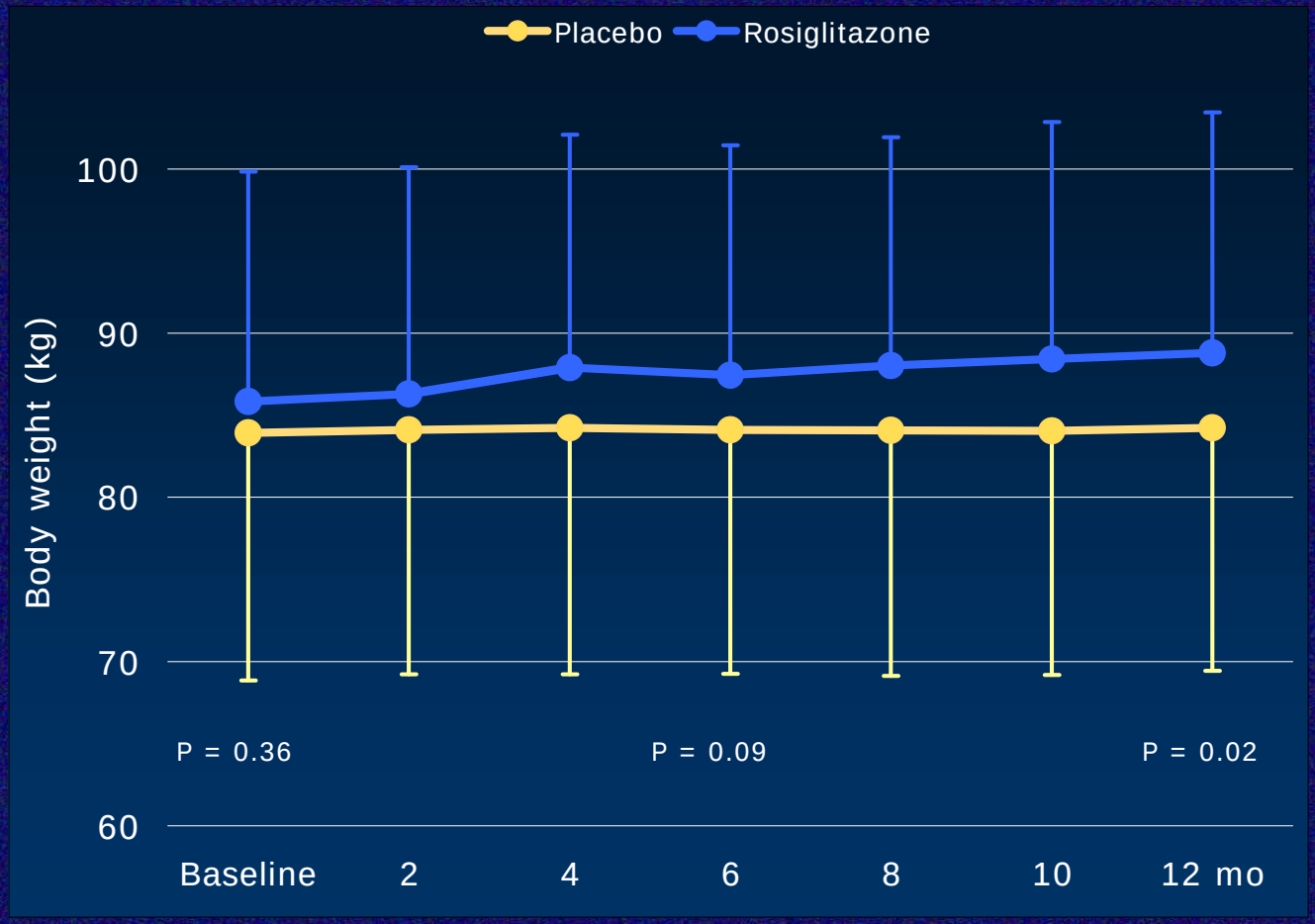


Results:
Body Weight



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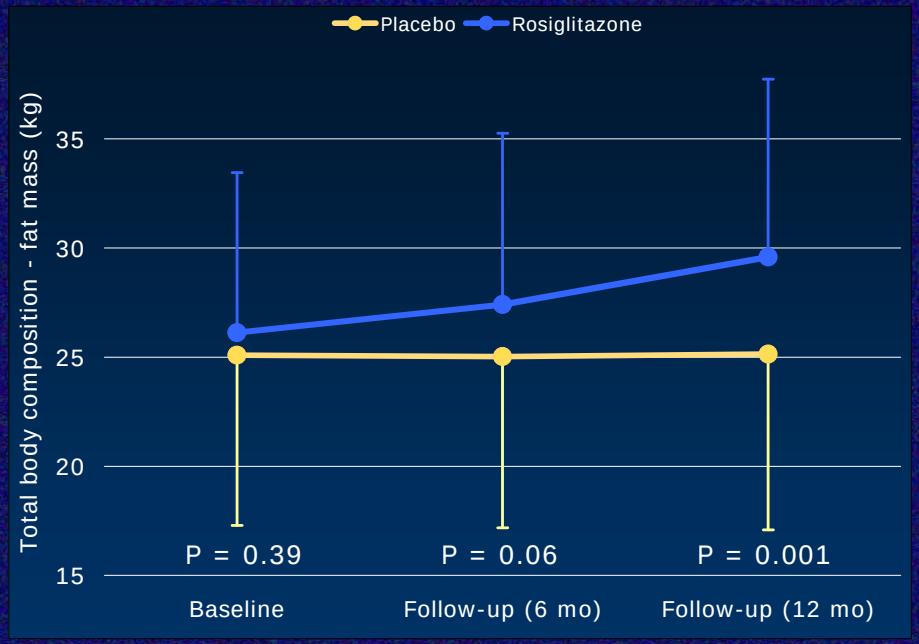
Results:
Body Composition

Body Fat (DEXA)



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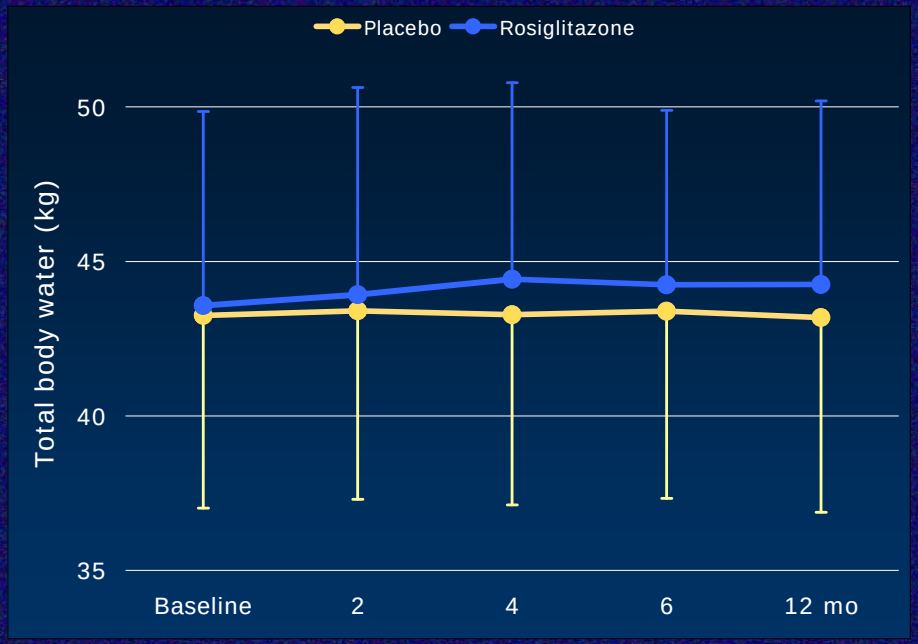
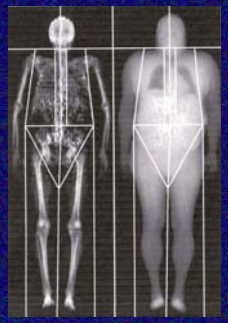
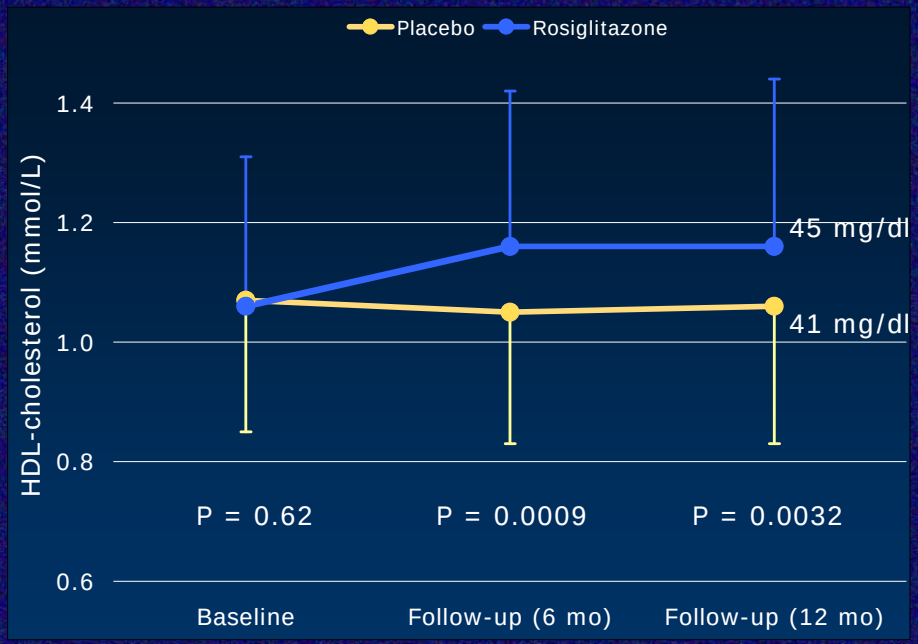
Total Body Water (BIA)





Results:
Lipid Parameters

HDL-Cholesterol



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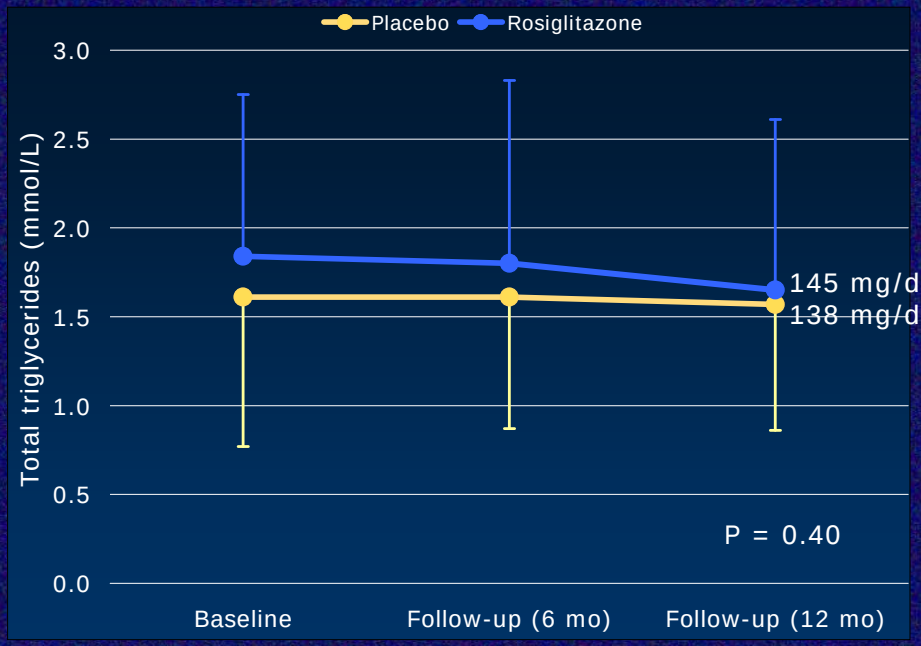
Triglycerides



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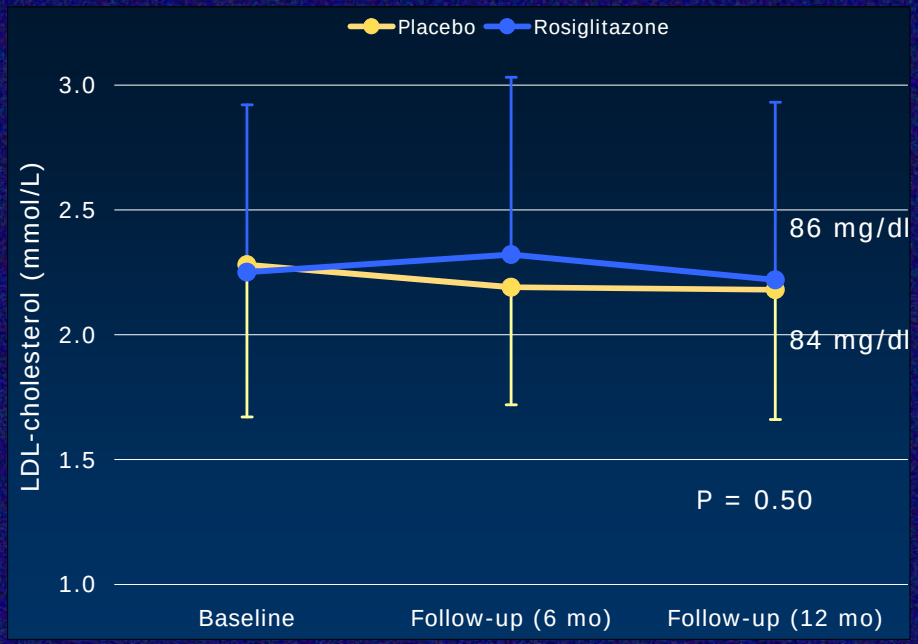
Results:
Lipid Parameters

LDL-Cholesterol



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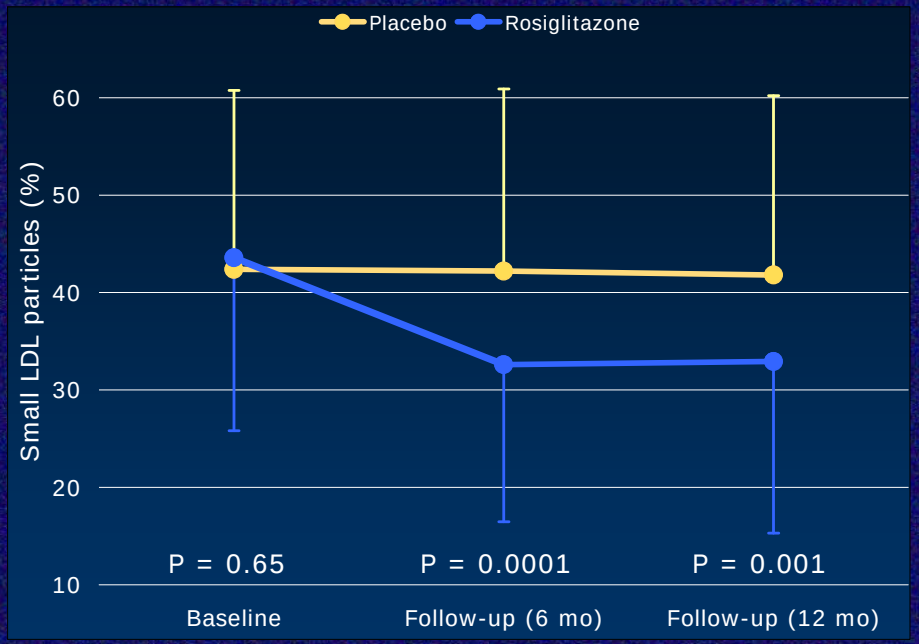
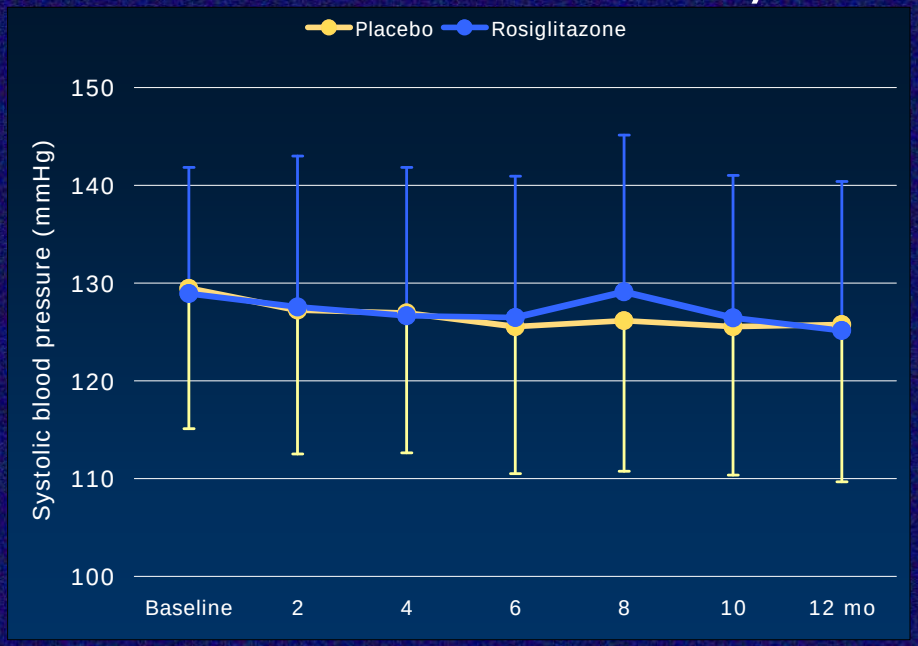
% Small LDL



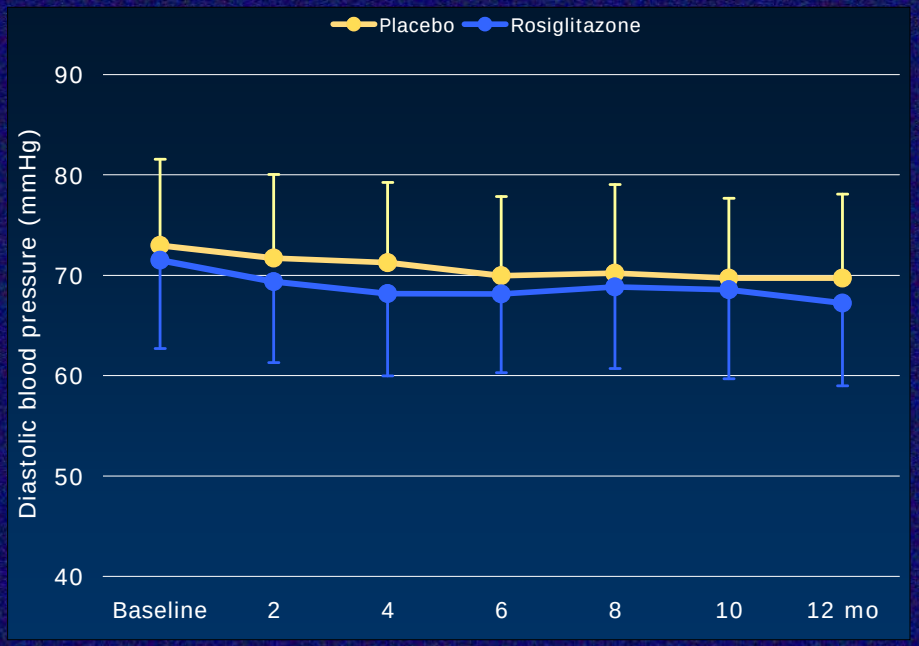
P<0.0001 interaction

Results:
Blood Pressure

Systolic

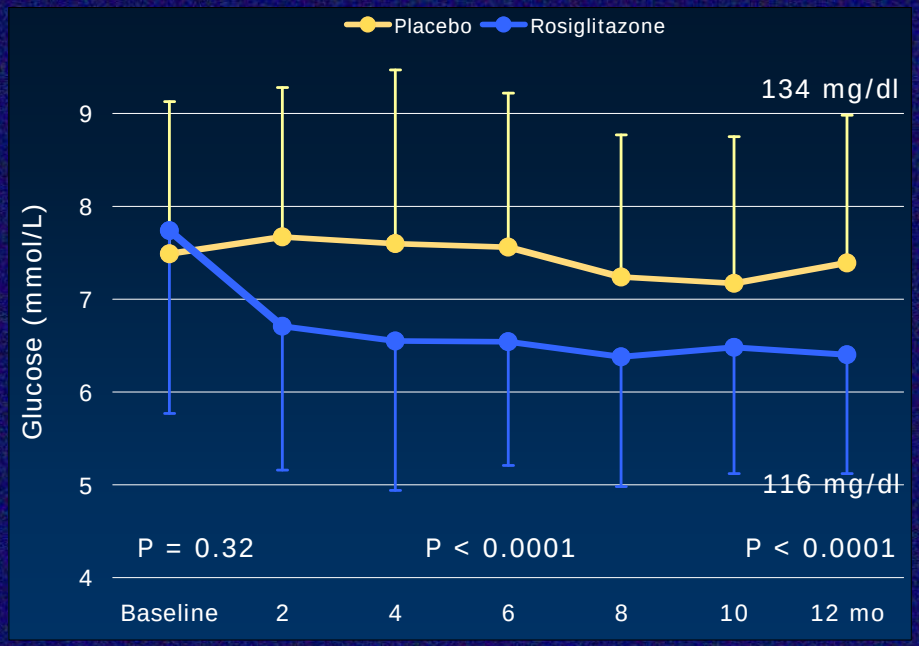


Diastolic



Results:
Glycaemic Control

Fasting Glucose



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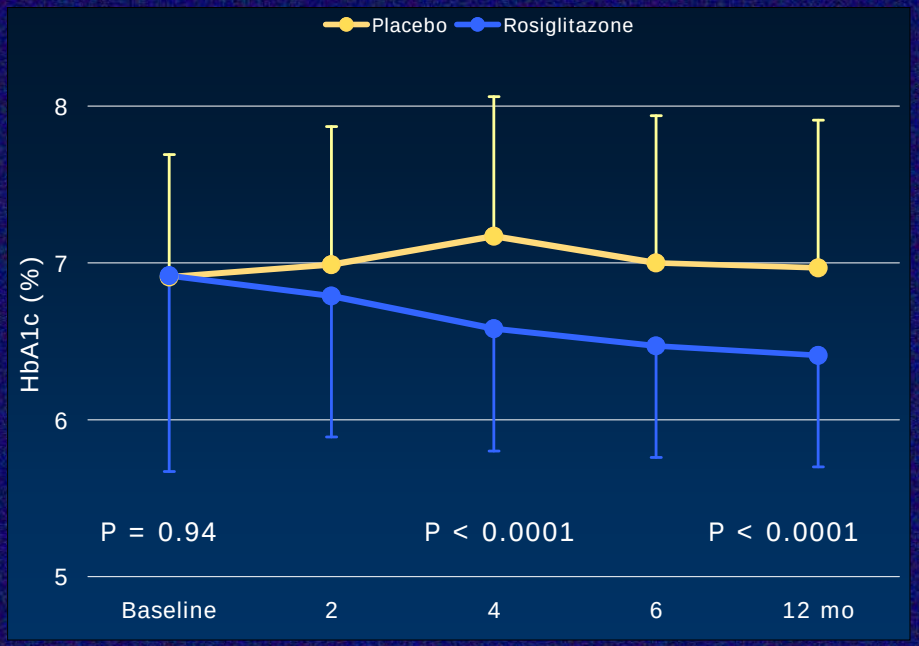
HbA_{1c}



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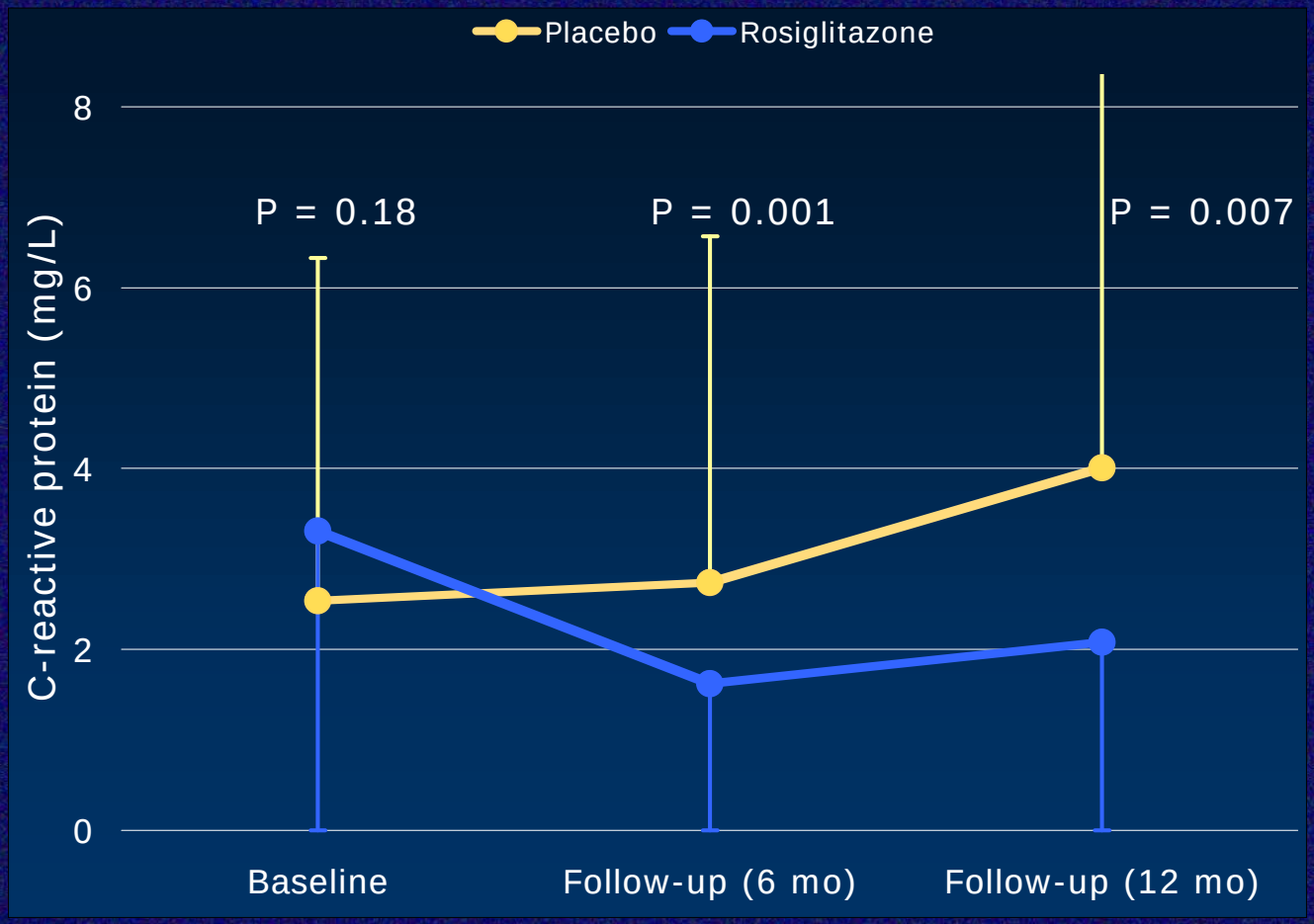
Results:
CRP



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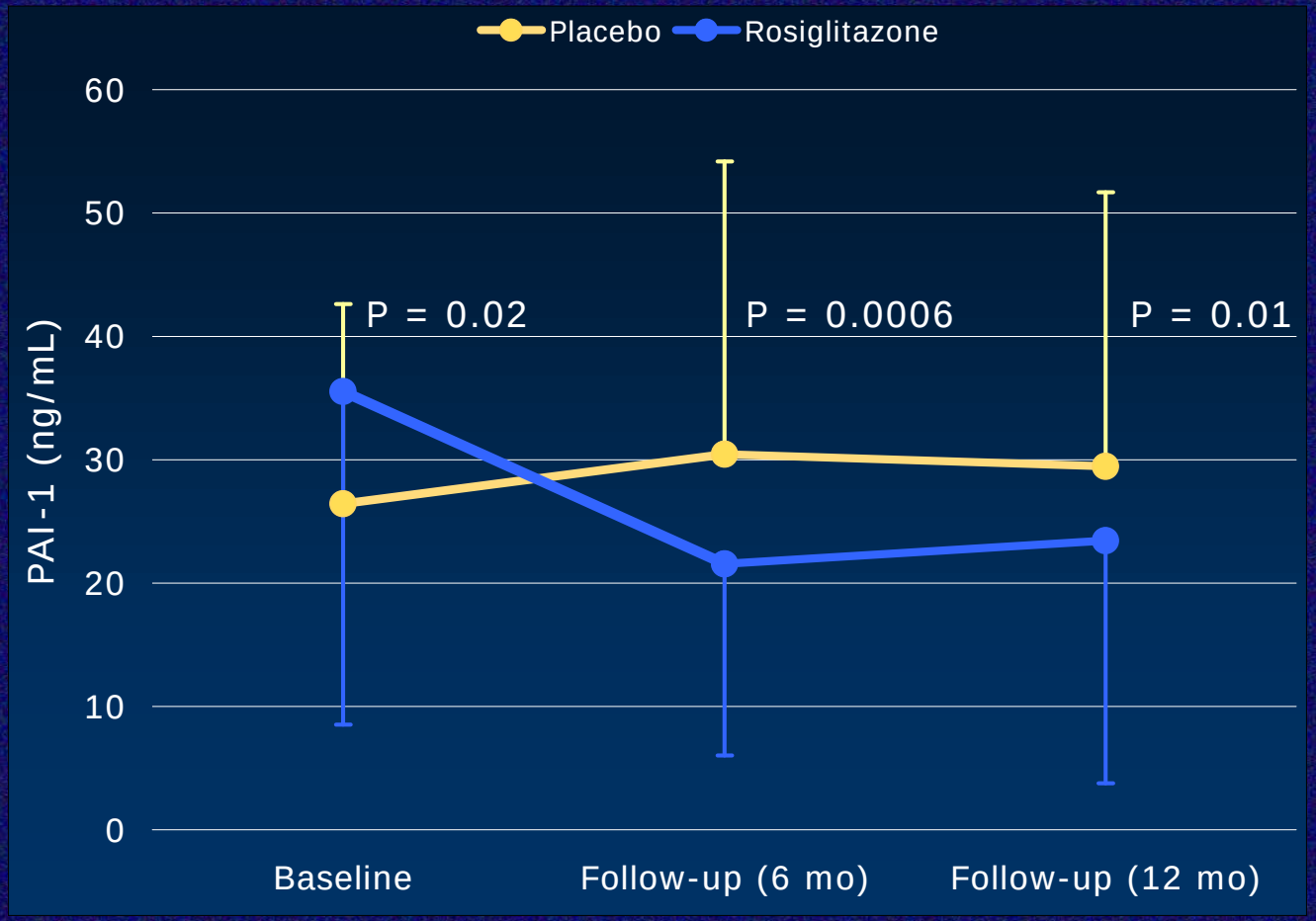
Results:
Thrombosis

PAI-I



P<0.0001 interaction

Results:
Clinical Events

Events	Placebo (n = 95)	Rosiglitazone (n = 98)
Death	0	0
MI	1 (1%)	0
Stroke	1 (1%)	1 (1%)
TIA*	2 (2%)	0
PCI	7 (7%)	6 (6%)
Hospitalization	11 (12%)	10 (10%)

*procedure-related

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Conclusion

✓ In post-CABG patients with optimally managed type 2 diabetes and traditional risk factors, rosiglitazone demonstrated

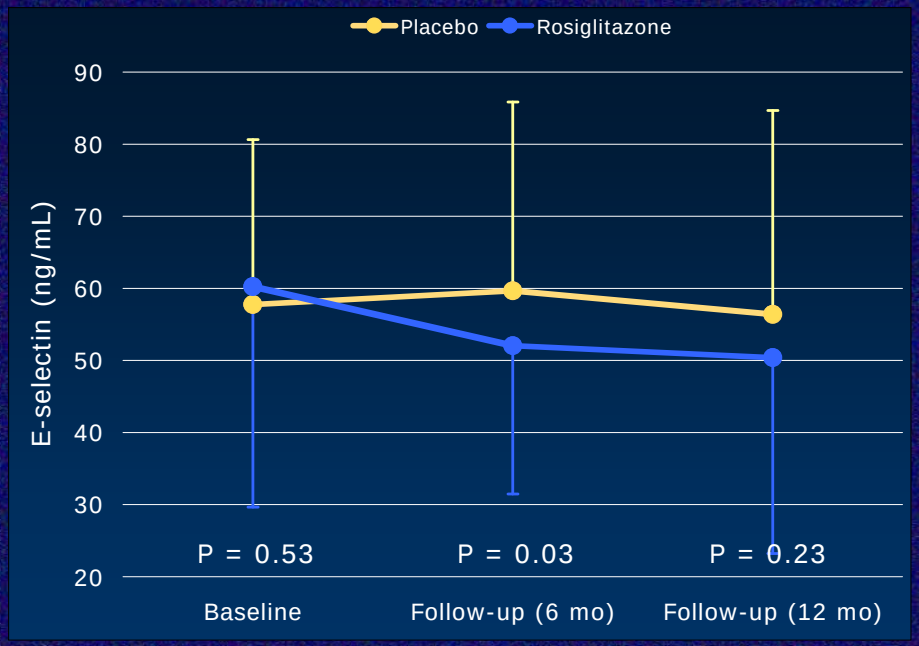
- ❑ A neutral effect on atherosclerosis at 12 months
- ❑ Significant improvement in glucose-insulin homeostasis
- ❑ Significant benefit on lipid, pro-thrombotic and inflammatory parameters

✓ Metabolic benefits of rosiglitazone appeared to be related to the expansion of subcutaneous adipose tissue which explained the moderate weight gain

✓ No safety issues were identified in this high cardiovascular risk population

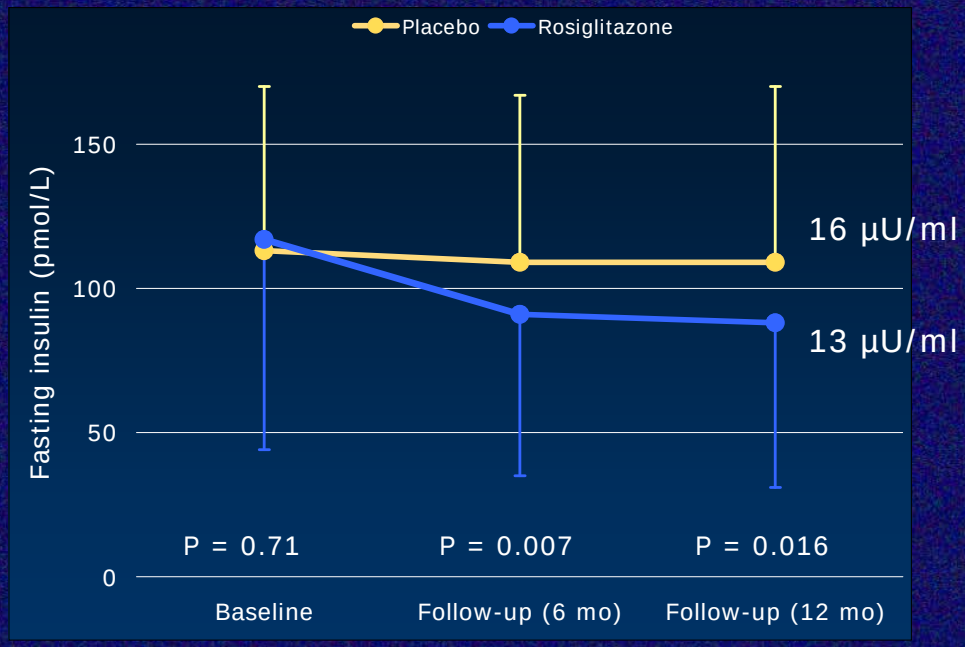
Results:
Thrombosis

E-Selectin



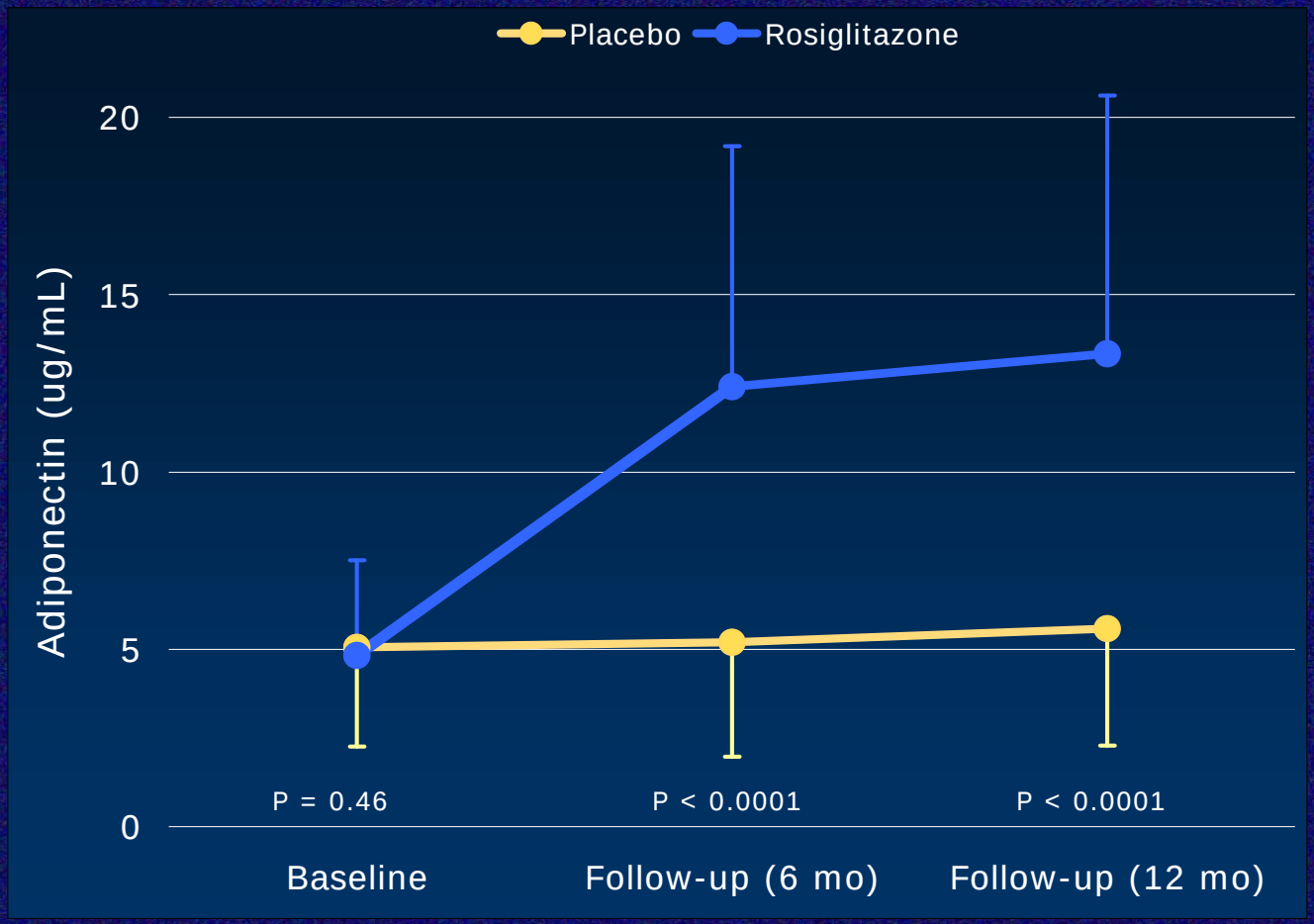
P=0.0037 interaction

Results:
Fasting Insulin



P<0.0001 interaction

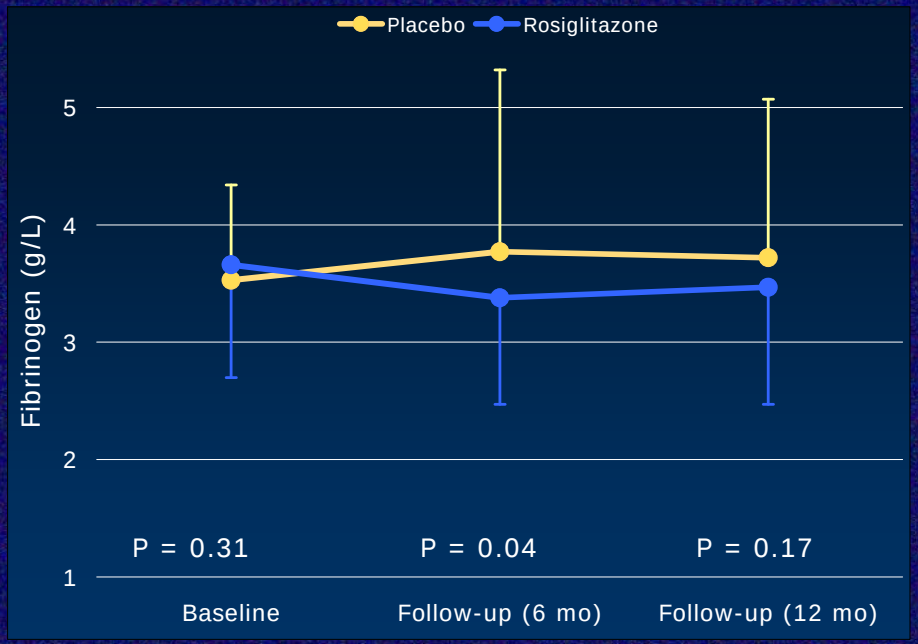
Results:
Adiponectin



P<0.0001 interaction

Results:
Inflammation

Fibrinogen



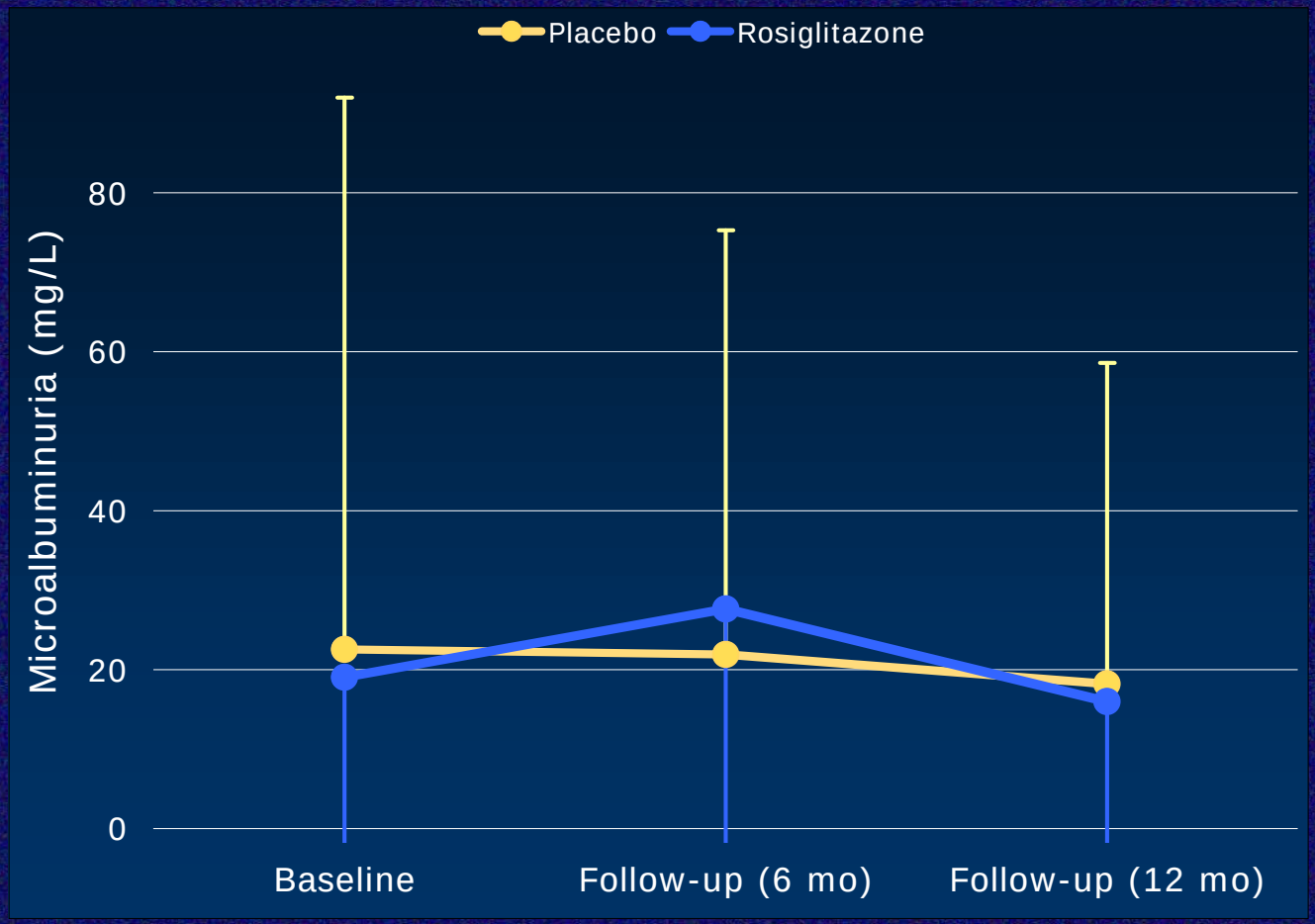
P=0.004 interaction

The VICTORY trial

Study Procedures

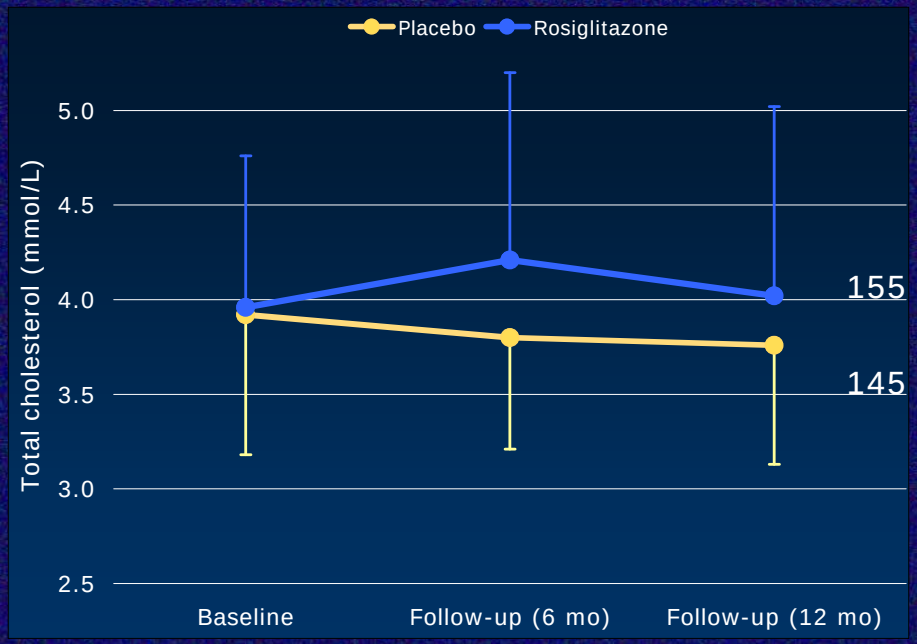
Clinical Follow-up
Angiography and IVUS examinations (B, 12M)
Fat distribution (CT) and
body composition (DEXA) (B, 6M, 12M)
Hematology, biochemistry, metabolic parameters
Microalbuminuria and urinanalysis
Bioelectrical impedance (BIA) (fluid retention)

Results:
Micro-Albumineria



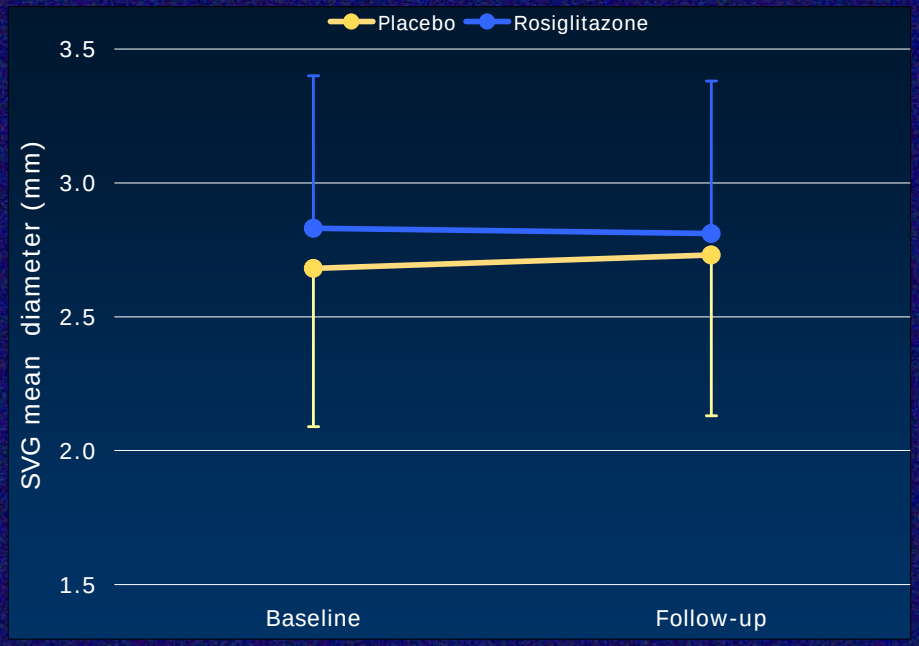
Results:

Total Cholesterol



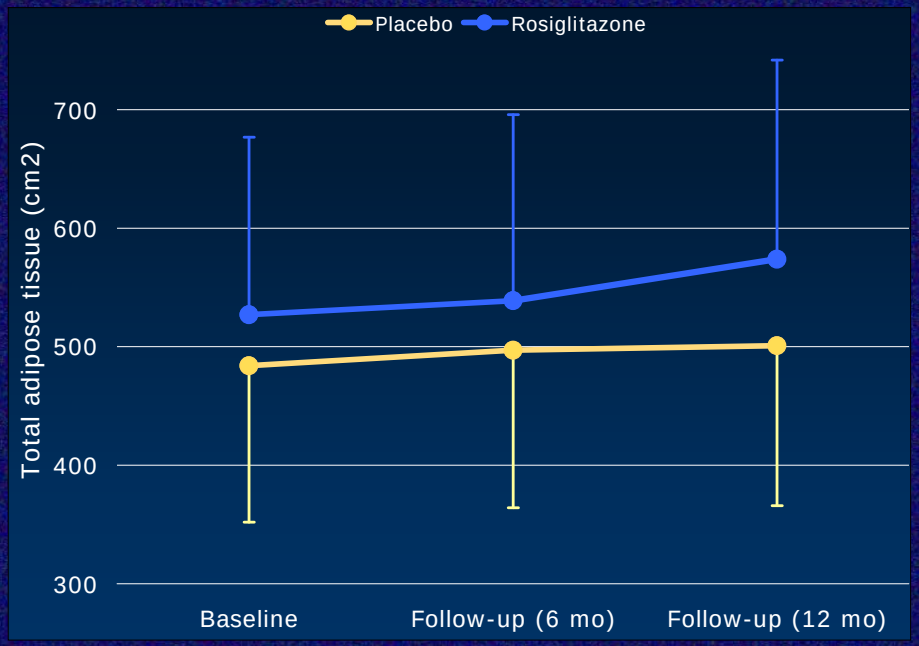
P=0.011 anova

Results (5):
QCA



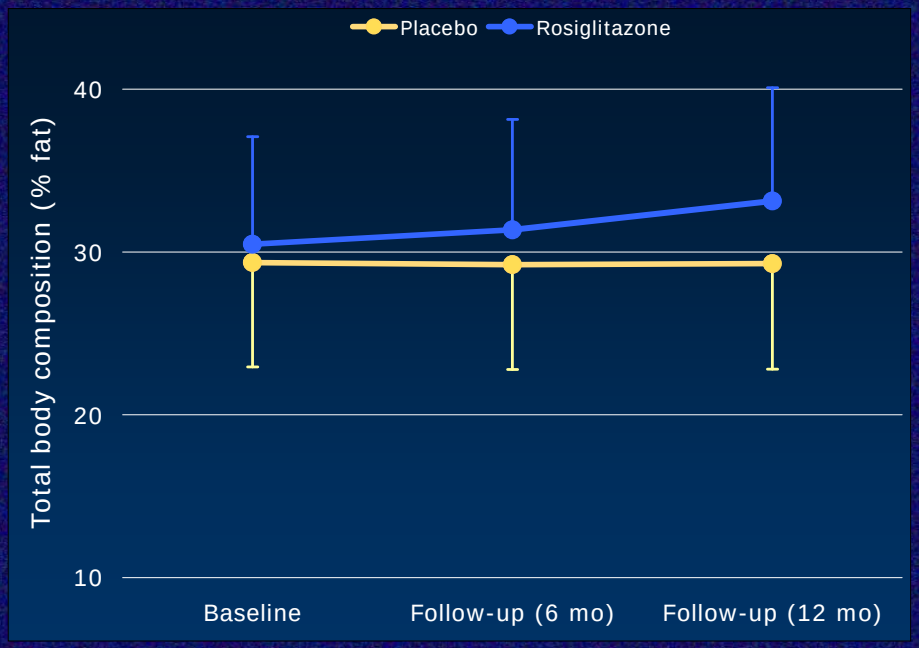
P=0.11 ANOVA

Results (5):
Adiponectin



P=0.0006 anova

Results (5):
Adiponectin

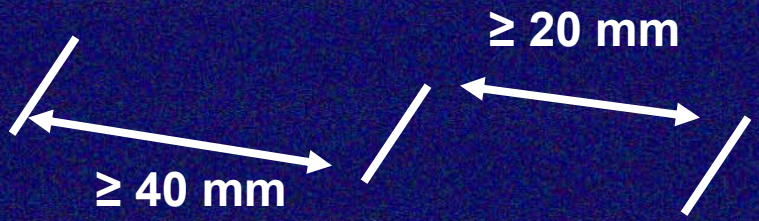


P<0.0001 anova

Exemple of IVUS in SVG: Case #1

No change in lumen diameter by Angio

QuickTime™ and a
TIFF decompressor
are needed to see this picture.
F J-C, M



QuickTime™ and a
TIFF decompressor
are needed to see this picture.
F J-C, M

Baseline

12 months

The VICTORY trial

Sample size and statistical power

✓ A sample size of 280 patients will provide a 80% power to detect a difference ≥ 10% in SVG plaque area and ≥ 20% in native coronary artery plaque volume between the 2 groups at 0.05 level.