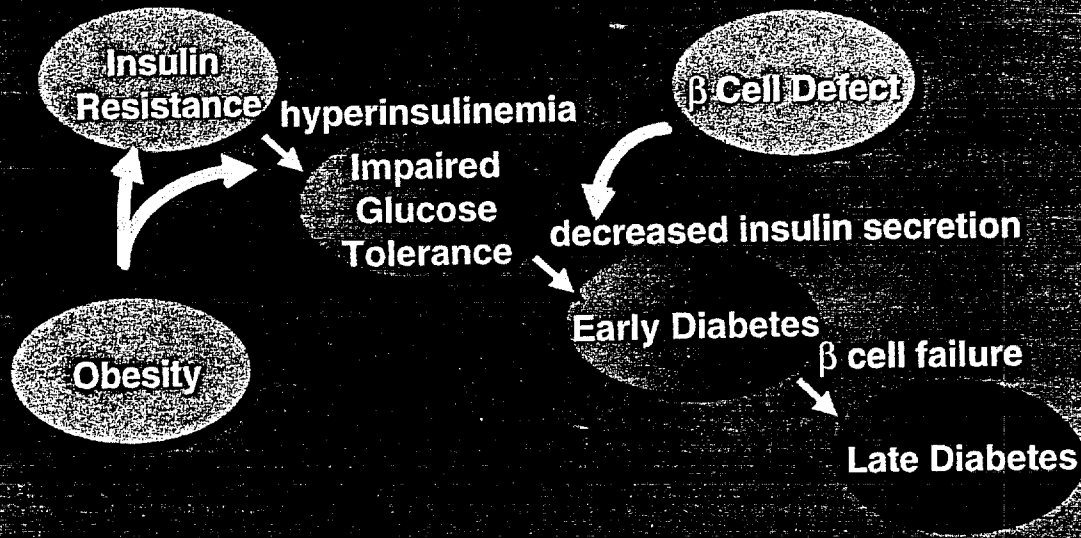


Benefits of Rezulin Therapy

Randall Whitcomb, MD

**Vice President, Clinical Research
Parke-Davis**

Metabolic Staging of Type 2 Diabetes



Troglitazone Efficacy

- Insulin – Combination
- Proposed - Triple Therapy Trog/SU/Met
- Sulfonylurea – Combination
- Monotherapy
- Impact on beta cell function and atherosclerotic risk factors
- Projected risk reduction for microvascular endpoints

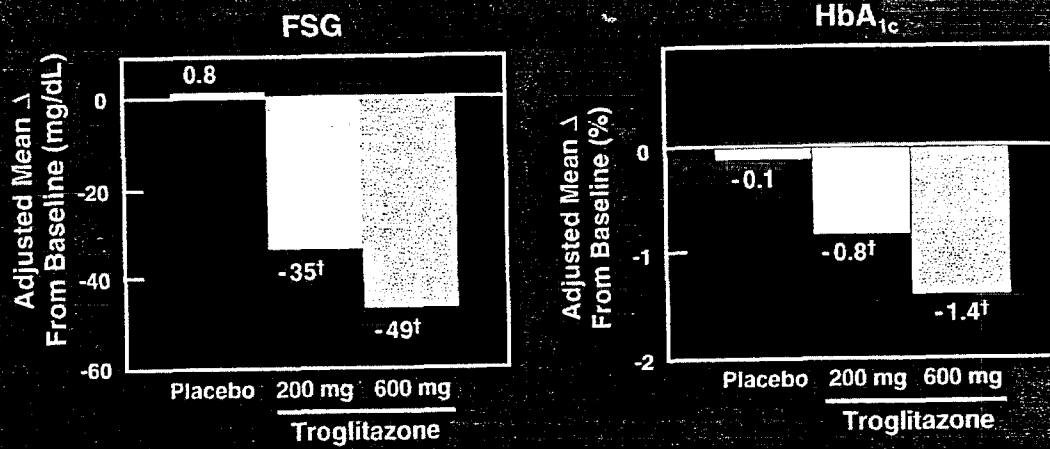
TROGLITAZONE COMBINATION WITH INSULIN

Patient Profile at Baseline

	Mean
Age	56 yr
BMI	35 kg/m ²
Years Diagnosed With Type 2 Diabetes	10.0 yr
Years on Insulin	5.0 yr
Insulin Dose	73 U/day
FSG	216 mg/dL
HbA _{1c}	9.4%

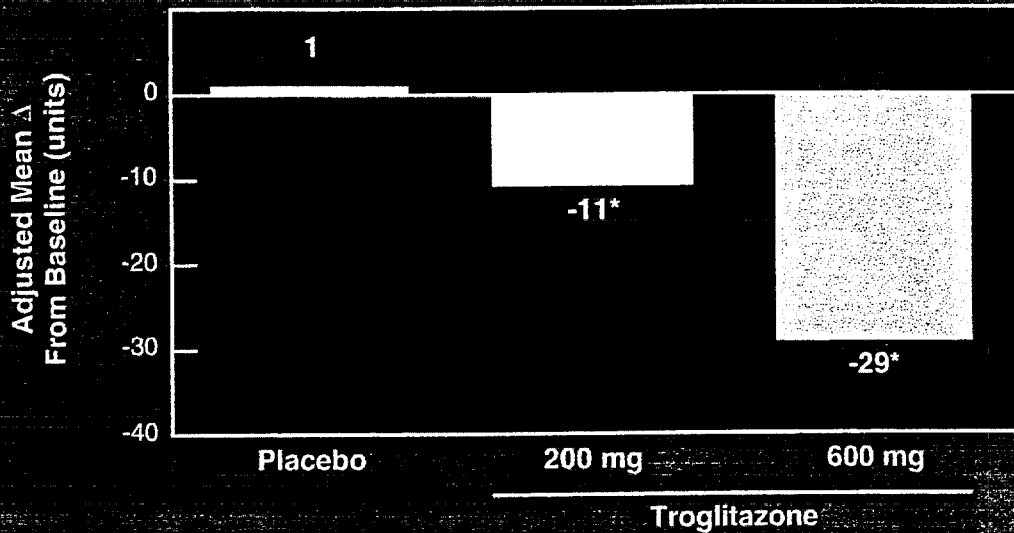
Schwartz S, et al. *NEJM*. 1998;338:861-866.

TROGLITAZONE COMBINATION WITH INSULIN
Adjusted Mean Change From Baseline Fasting Serum
Glucose (FSG) and HbA_{1c} at Month 6



† $P < 0.0001$ vs placebo (insulin-only group).
Schwartz S, et al. *NEJM*. 1998;338:861-866.

TROGLITAZONE COMBINATION WITH INSULIN
Insulin Dose at Month 6



* $P < 0.0001$ vs placebo (insulin-only group).
Schwartz S, et al. *NEJM*. 1998;338:861-866.

Significant Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin

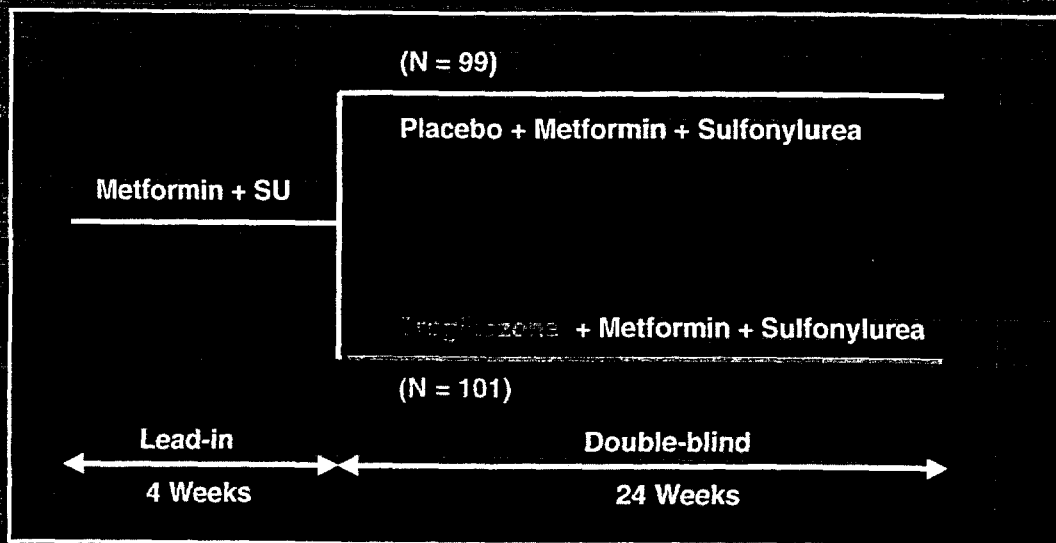
**Triple Therapy Study:
Combination Troglitazone /
Metformin / Sulfonylurea**

COMBINATION TROGLITAZONE / METFORMIN / SULFONYLUREA

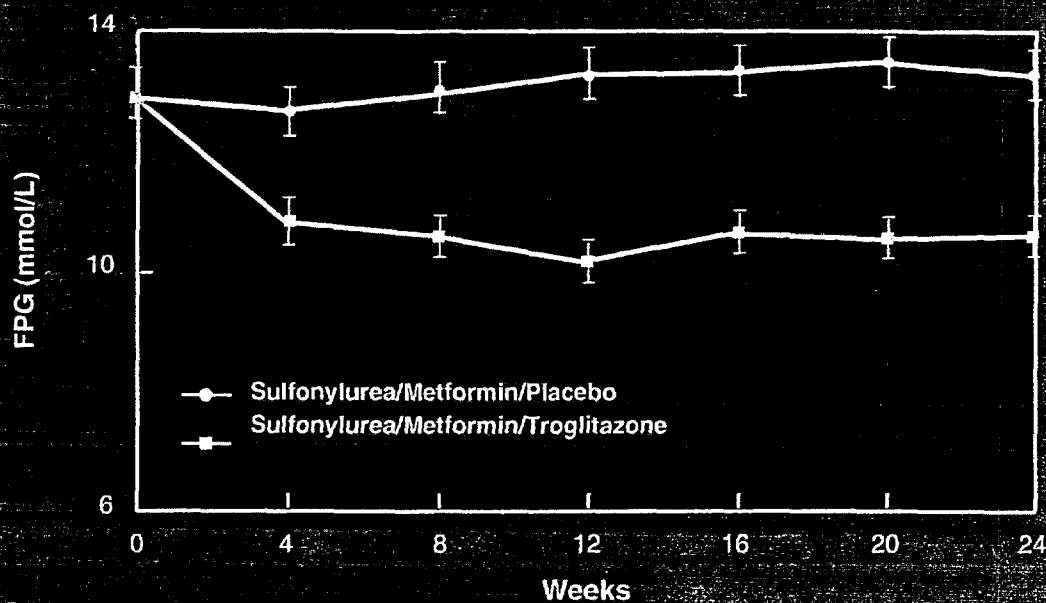
Base-Line Patients Characteristics

N	200
Age (yr \pm SD)	59 \pm 9
Duration of Diabetes (yr \pm SD)	11.3 \pm 7.1
Body-mass Index (\pm SD)	30.1 \pm 4.5
Fasting Plasma Glucose (mg/dL \pm SD)	234 \pm 56
HbA _{1c} (% \pm SD)	9.7 \pm 1.2
Fasting Plasma Insulin (μ U/mL \pm SD)	24 \pm 13
Fasting Plasma C-peptide (ng/mL \pm SD)	3.4 \pm 1.5

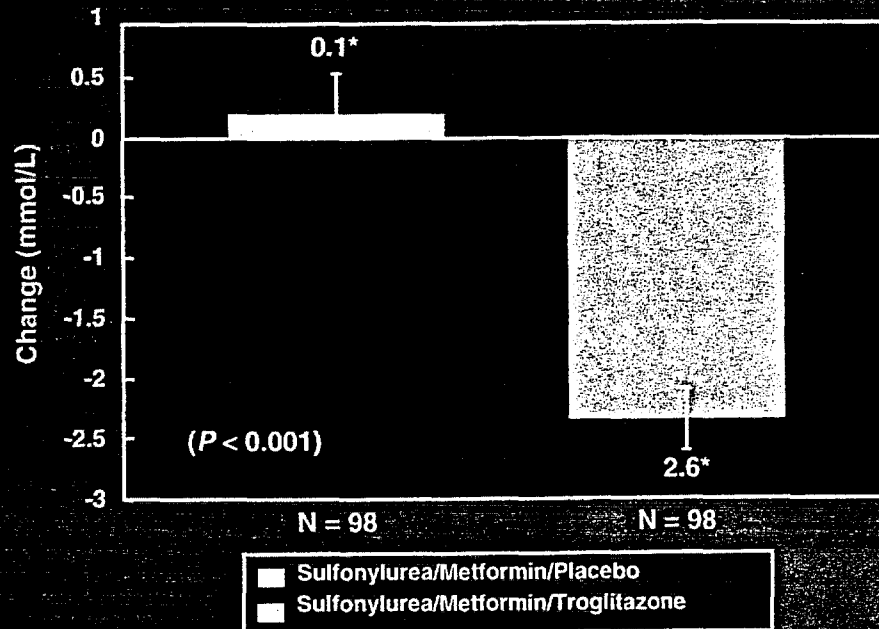
**COMBINATION TROGLITAZONE / METFORMIN / SULFONYLUREA
Triple Therapy (Study Design)**



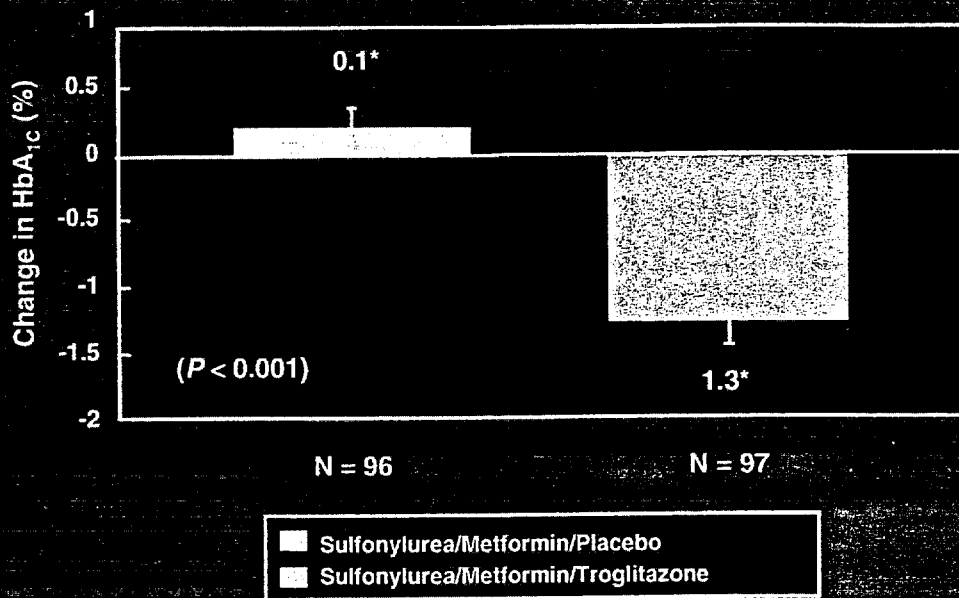
Mean (\pm SE) FPG Over Time



**Adjusted Mean Change (\pm SE)
From Baseline in FPG at Week 24**



**Adjusted Mean Change (\pm SE)
From Baseline in HbA_{1c} at Week 24**



**Frequency Distribution of Patients
With Target HbA_{1c} Levels $\leq 8\%$ or $\leq 7\%$**

	Sulfonylurea/Metformin		P-Value
	Placebo (n = 96)	Troglitazone (n = 97)	
	%	%	
HbA _{1c} Levels $\leq 8\%$	6	43	<0.001
HbA _{1c} Levels $\leq 7\%$	1	14	<0.001

Significant Benefits

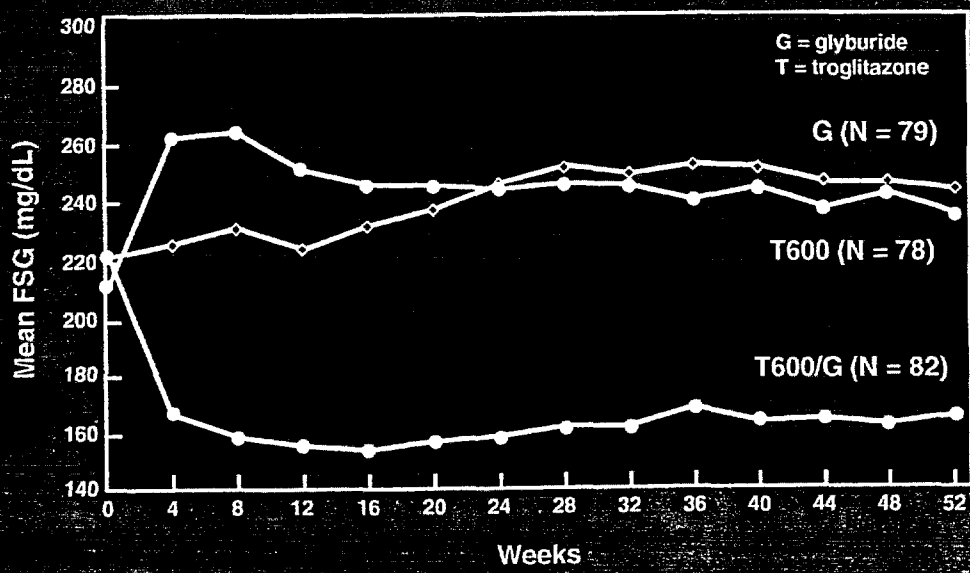
- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination

Troglitazone + Micronized Glyburide (12 Mg) in Type 2 Diabetes Patients

- 1-year, double-blind, active-control trial
- N = 552
- Sulfonylurea failures (FSG >140 mg/dL on maximum dose of glyburide)
- 200, 400, 600 mg troglitazone alone or with 12 mg micronized glyburide vs glyburide alone

Horton ES et al. *Diabetes Care*. 1998;21:1462-1469.

TROGLITAZONE + MICRONIZED GLYBURIDE (12 MG)
Fasting Serum Glucose
Mean Levels Over Time (ITT)

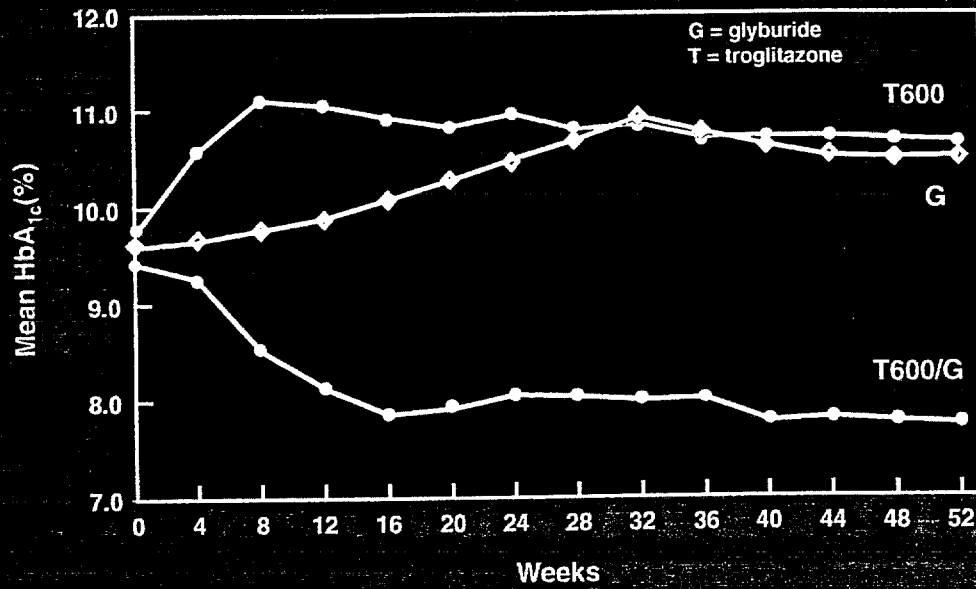


Horton ES et al. *Diabetes Care*. 1998;21:1462-1469.

TROGLITAZONE + MICRONIZED GLYBURIDE (12 MG)

HbA_{1c}

Mean Levels Over Time (ITT)

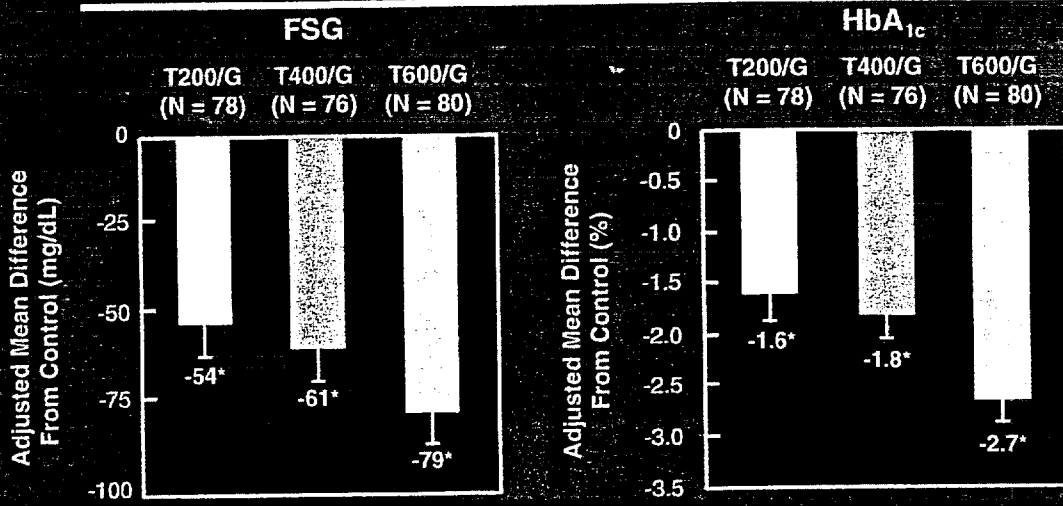


Horton ES et al. *Diabetes Care*. 1998;21:1462-1469.

TROGLITAZONE + MICRONIZED GLYBURIDE (12 MG)

FSG and HbA_{1c}

Mean Difference vs Control at 12 Months (ITT)



*P < 0.0001.

Horton ES et al. *Diabetes Care*. 1998;21:1462-1469.

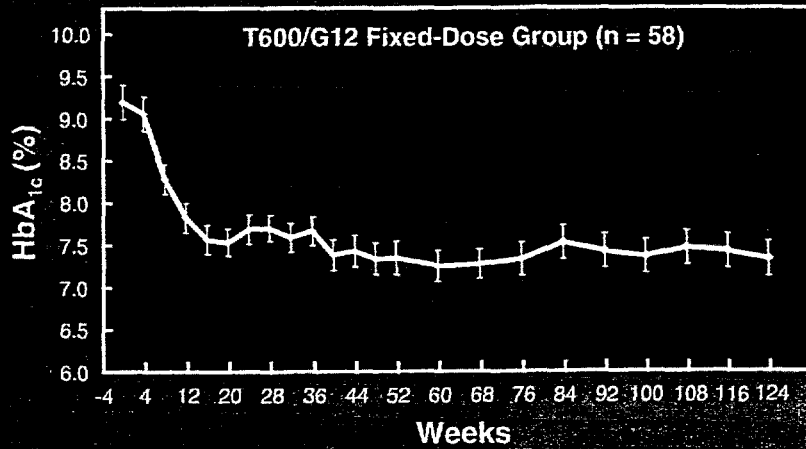
Frequency Distribution of Patients With Target HbA_{1c} Levels ≤8% or ≤7%

	Glyburide	Troglitazone/Glyburide		
		200 mg/ 12 mg	400 mg/ 12 mg	600 mg/ 12 mg
	%	%	%	%
HbA _{1c} Levels ≤8%	10	33	33	60
HbA _{1c} Levels ≤7%	1	22	21	41

Horton ES et al. *Diabetes Care*. 1998;21:1462-1469.

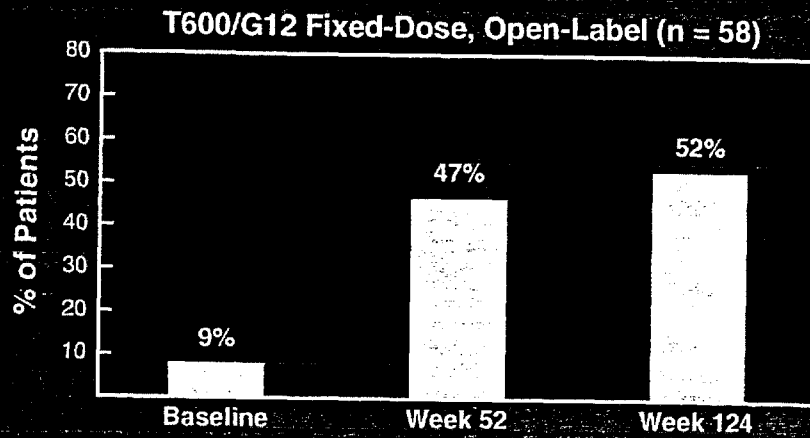
COMBINATION TROGLITAZONE/SULFONYLUREA OPEN-LABEL
EXTENSION STUDY

Mean HbA_{1c} Levels Over Time



Draznin B, et al. *Diabetes*. 1998;47;(suppl 1) AO330.

Percentage of Patients at HbA_{1c} Level ≤7%



Draznin B, et al. *Diabetes*. 1998;47;(suppl 1) AO330.

Significant Clinical Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination
- Significant and sustained glucose lowering in combination with sulfonylurea

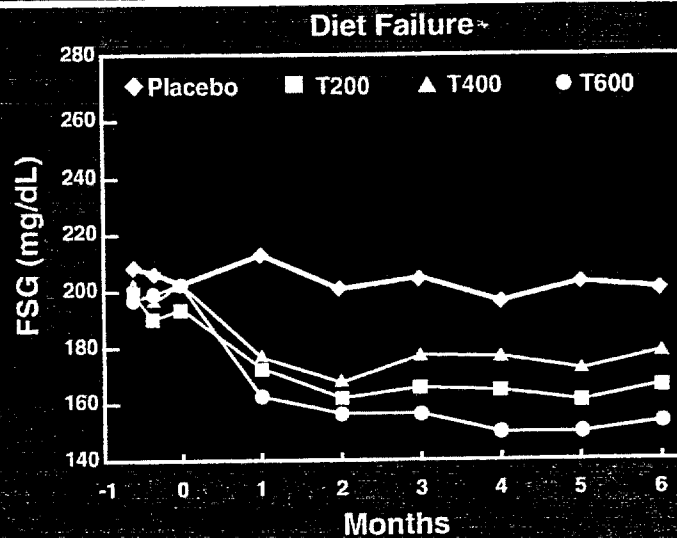
6-Month Monotherapy Study

- 6-month, double-blind, placebo-controlled study
- N = 402 (86 diet-only therapy)
- Mean HbA_{1c} 8.5 ± 1.7%
- 100 mg, 200 mg, 400 mg, 600 mg troglitazone

Fonseca VA. *J Clin Endocrinol Metab.* 1998;83:3169-3176.

TROGLITAZONE MONOTHERAPY

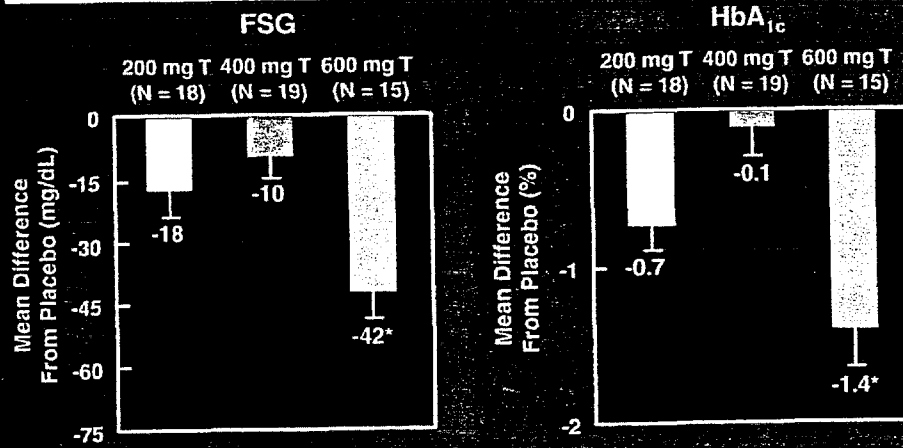
Fasting Serum Glucose Mean Levels Over Time (ITT)



Fonseca VA. *J Clin Endocrinol Metab.* 1998;83:3169-3176.

TROGLITAZONE MONOTHERAPY

Mean Difference in FSG and HbA_{1c} vs Placebo at Month 6 (ITT)

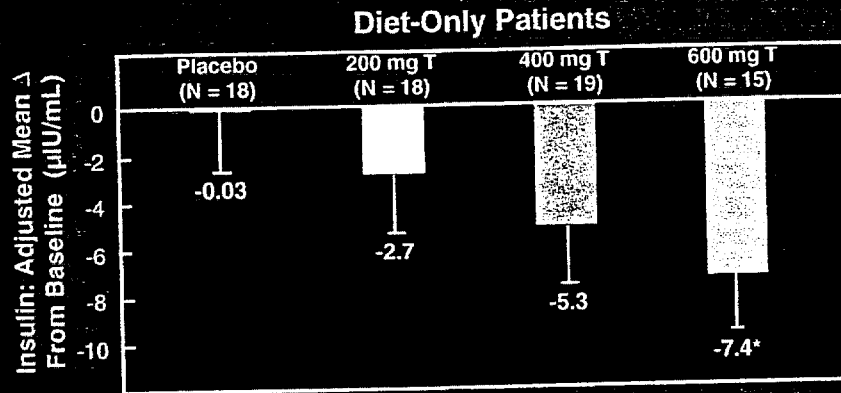


*P < 0.05.

Fonseca VA. *J Clin Endocrinol Metab.* 1998;83:3169-3176.

TROGLITAZONE MONOTHERAPY

Serum Insulin: Adjusted Mean Change From Baseline at Month 6 (ITT)

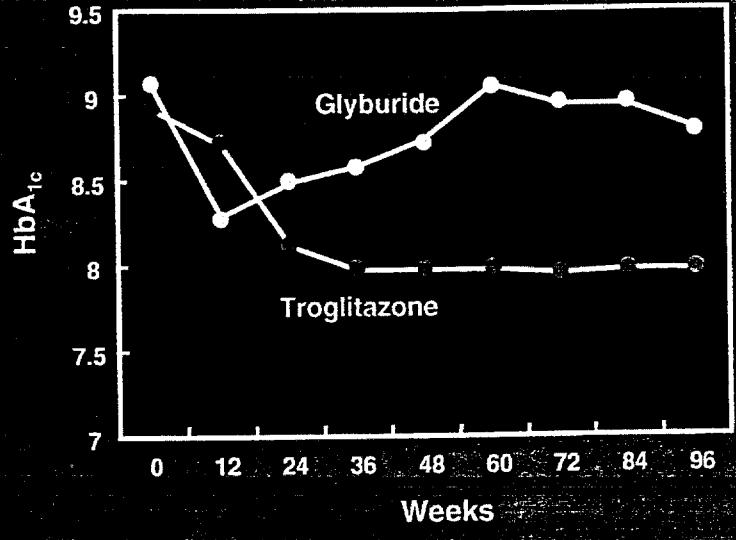


* $P \leq 0.01$ vs placebo.

Fonseca VA. *J Clin Endocrinol Metab.* 1998;83:3169-3176.

991-042

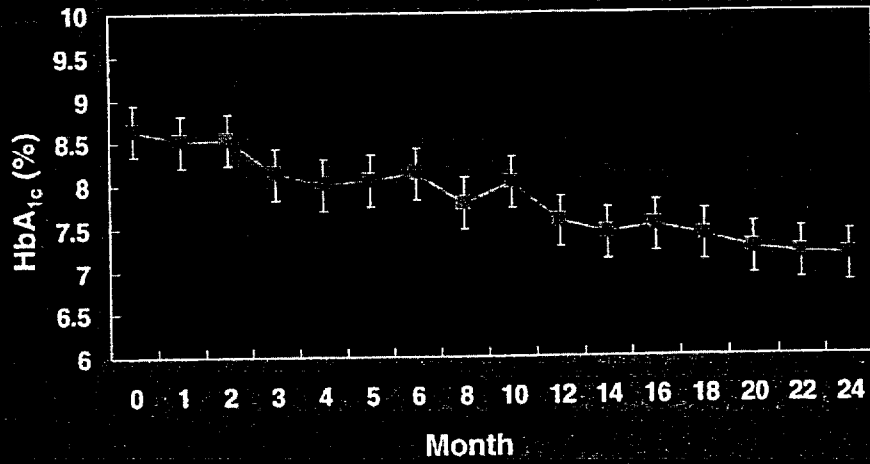
Mean Levels of HbA_{1c}



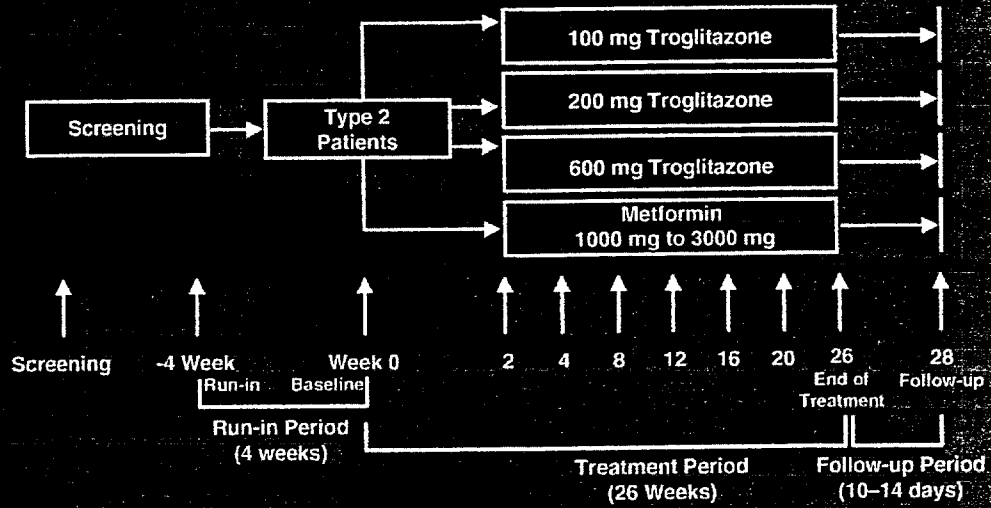
Troglitazone Monotherapy

OL Extension 400 and 600 mg Patients (n=36)

Mean values



TROGLITAZONE VS METFORMIN Study Design



TROGLITAZONE VS METFORMIN

Glycemic Parameters at Week 26

	Troglitazone 200 mg	Troglitazone 600 mg	Metformin 1000-3000 mg
HbA_{1c}			
n†	91	96	92
Week 26 value	7.9	7.3	7.3
% Change from Metformin	8	1	-
P-value	0.002	0.737	-
Fasting Serum Glucose (mmol/L)			
n	91	98	95
Week 26 value	10.0	9.2	9.0
% Change from Metformin	11	2	-
P-value	0.002	0.489	-

TROGLITAZONE COMPARATOR VS METFORMIN

**Proportion of Patients with HbA_{1c} \geq 1%
Decrease from Baseline (Responder)
at Week 26 (ITT)**

	Troglitazone 200 mg	Troglitazone 600 mg	Metformin 1000-3000 mg
Number of Patients	95	103	97
HbA _{1c} Responder	23 (25%)	37 (39%)	32 (35%)
HbA _{1c} Non-Responder	68 (75%)	59 (61%)	60 (65%)

TROGLITAZONE VS METFORMIN

Insulin Parameters at Week 26

	Troglitazone 200 mg	Troglitazone 600 mg	Metformin 1000-3000 mg
Insulin (μ U/mL)			
n	91	96	92
Week 26 value	6.9	6.5	8.5
% Change from Metformin	-20	-23	-
P-value	<0.001	<0.001	-

TROGLITAZONE COMPARATOR VS METFORMIN

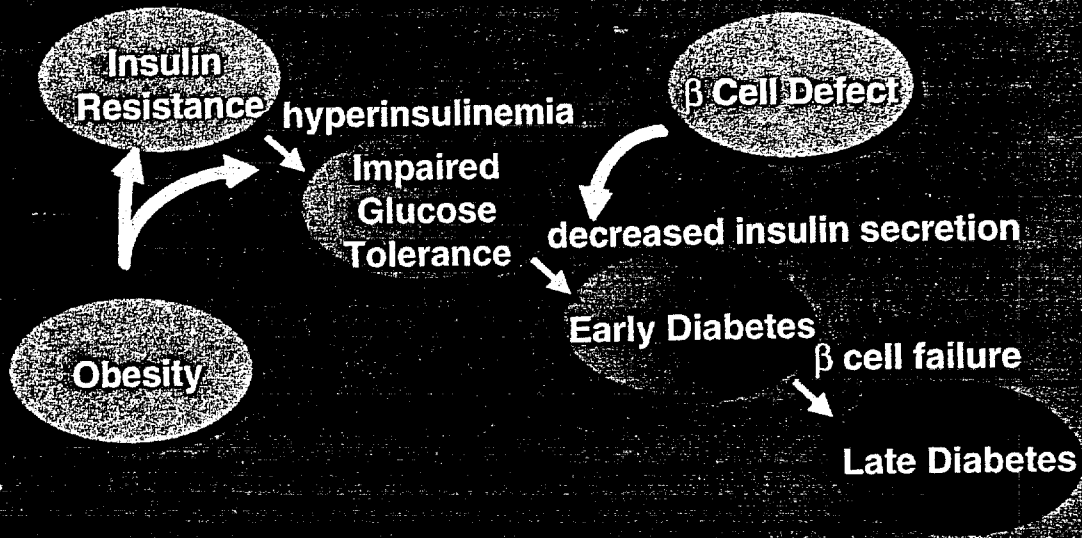
**Change in Body Weight (kg)
at Week 26 (ITT)**

	Troglitazone 200 mg	Troglitazone 600 mg	Metformin 1000-3000 mg
Number of Patients	90	94	95
Mean Baseline	80.8	76.7	82.7
Mean Week 26	80.4	76.9	81.1
Mean Difference	-0.4	0.2	-1.6

Significant Benefits

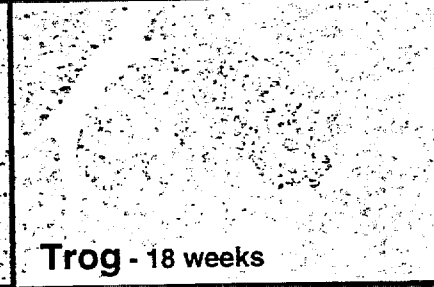
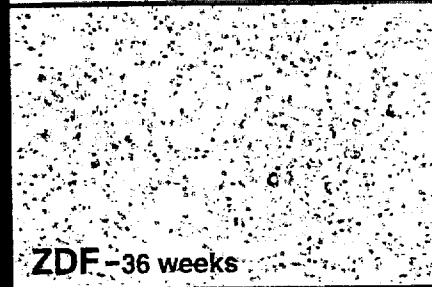
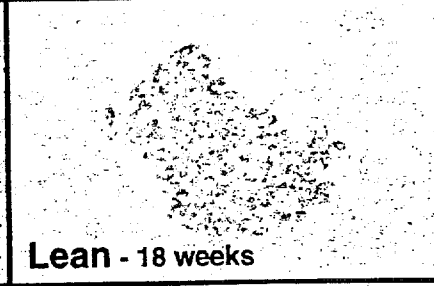
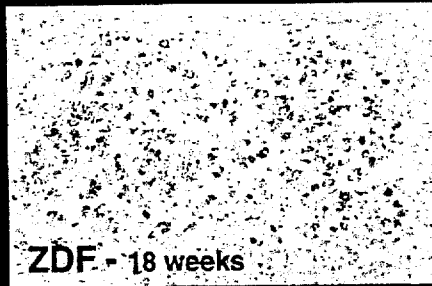
- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination
- Significant and sustained glucose lowering in combination with sulfonylurea
- Effective as monotherapy both short- and long-term

Metabolic Staging of Type 2 Diabetes



Insulin

Rat Pancreas

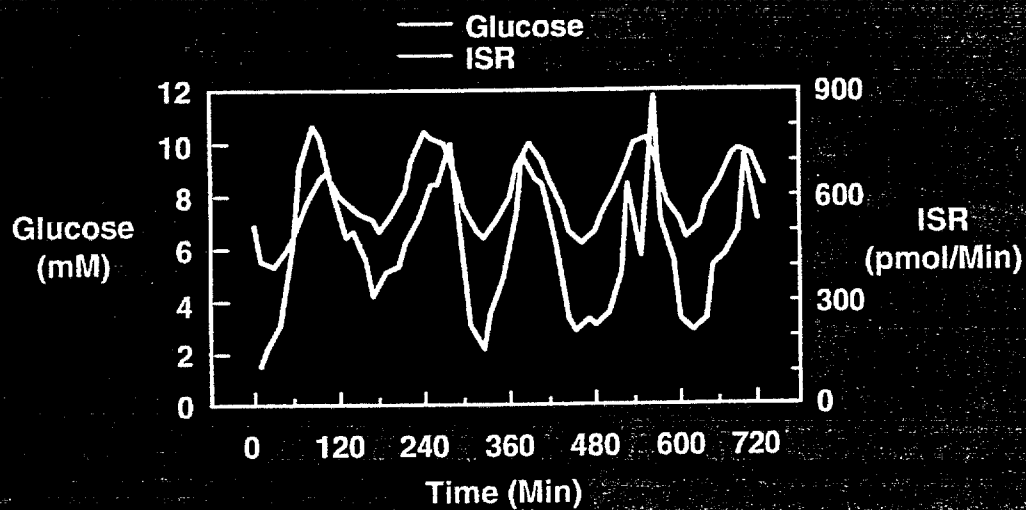


Aims of Study

To determine whether the alterations in insulin secretion and β -cell glucose signaling seen in subjects with impaired glucose tolerance are reversible by treatment with troglitazone

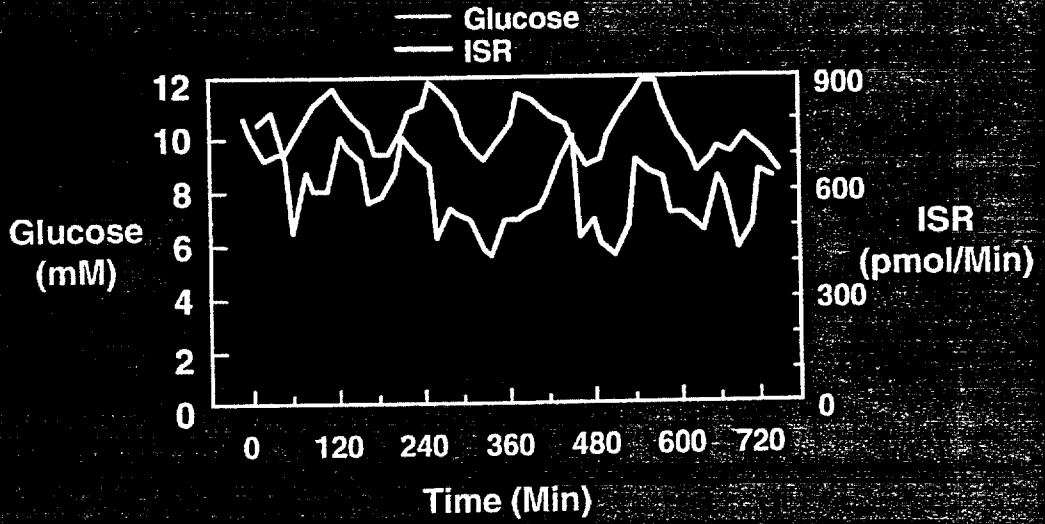
Oscillatory Glucose Infusion

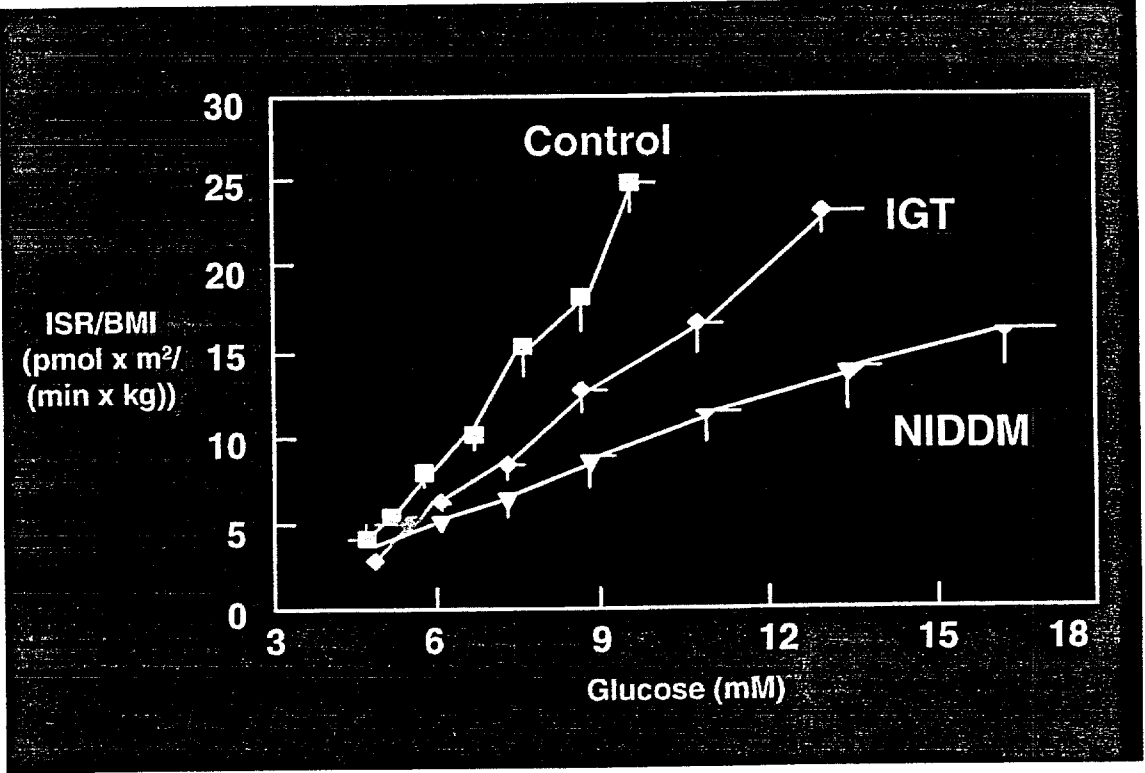
Control Subject



Oscillatory Glucose Infusion

IGT Subject





Study Design

- Randomized double blind placebo controlled trial
- Subjects with IGT (n = 24) were randomly allocated to treatment with placebo or troglitazone (400 mg q d)

Cavaghan MK, et al. *JCI* 110;1997

Clinical Protocols

At baseline and after treatment the following tests were performed

- Frequently sampled IVGTT with tolbutamide
- Entrainment to glucose oscillations
- Insulin secretory response to a graded IV glucose infusion

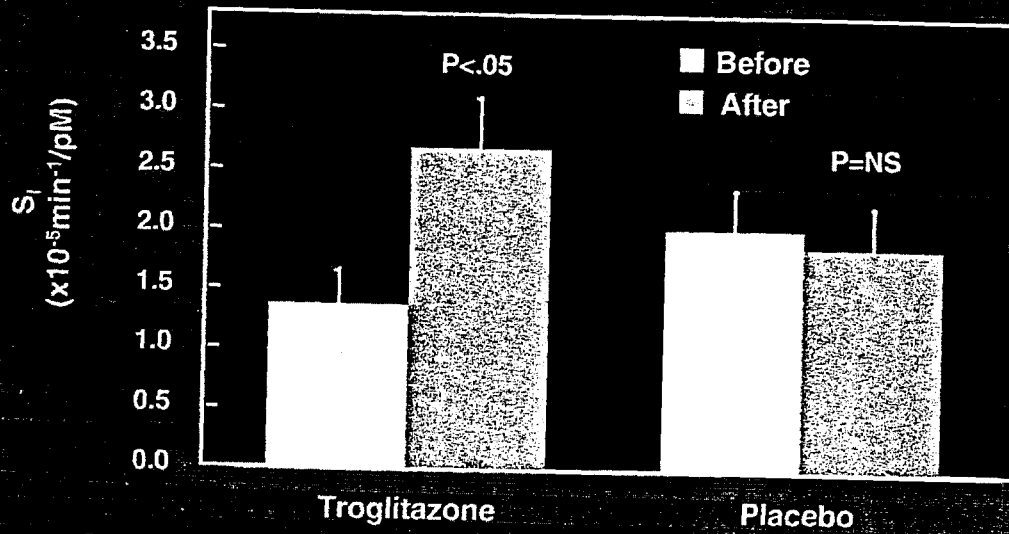
Cavaghan MK, et al. *JCI* 110;1997

Subject Characteristics

• n = 24 (17 female, 7 male)	
• Age (Yr)	43 ± 3.3
• Weight (kg)	102 ± 3.4
• BMI (kg/m ²)	37 ± 1.32
• HbA1c (%)	6.27 ± 0.18
• Fasting BS (mg/dL)	101 ± 2.7
• 2-h glucose (mg/dL)	186 ± 8.2

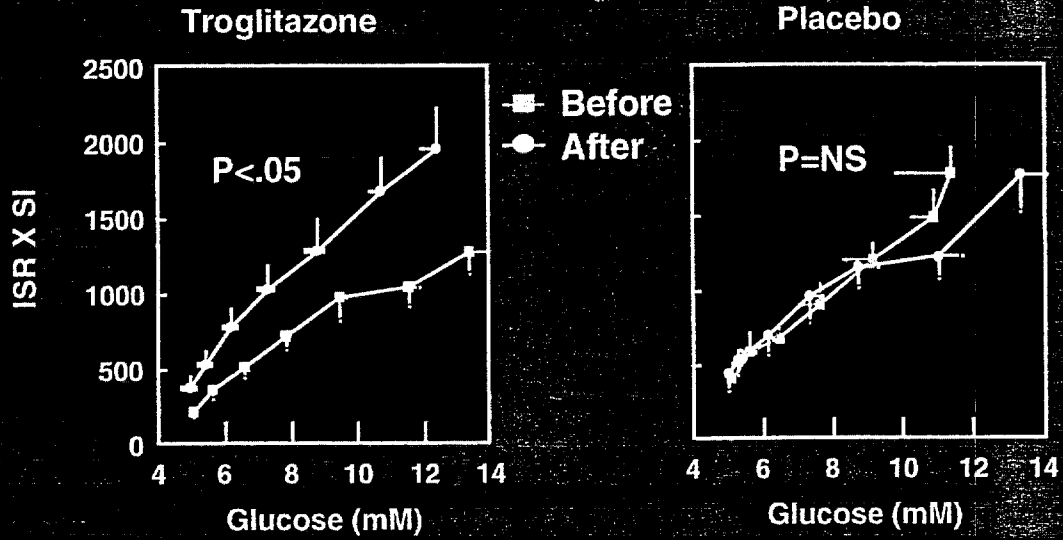
Cavaghan MK, et al. *JCI* 110;1997

Insulin Sensitivity (S_i)



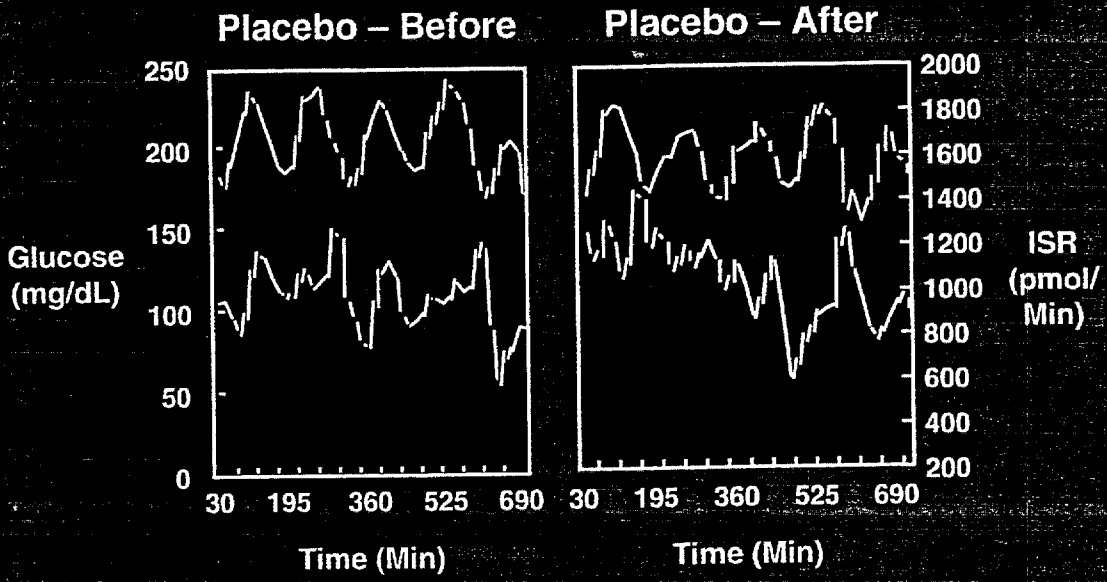
Cavaghan MK, et al. *JCI* 110;1997

Graded Glucose Infusion

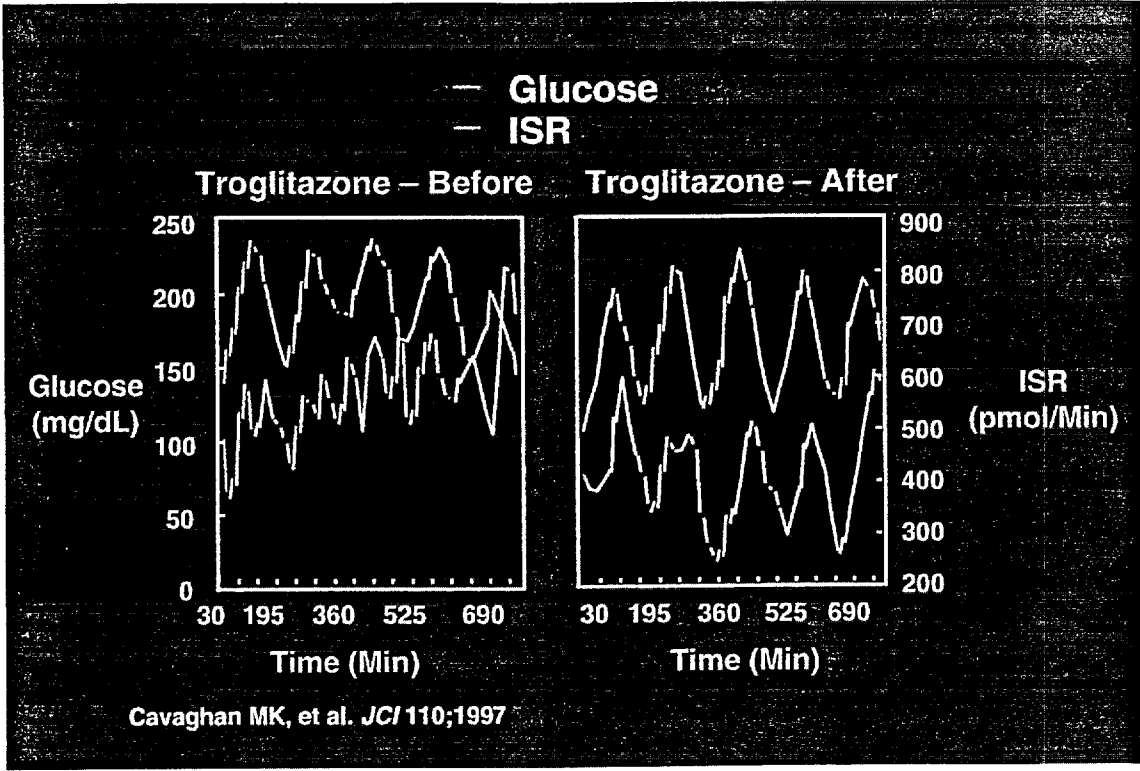


Cavaghan MK, et al. *JCI* 110;1997

— Glucose
— ISR



Cavaghan MK, et al. *JCI* 110;1997



Significant Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination
- Significant and sustained glucose lowering in combination with sulfonylurea
- Effective as monotherapy both short- and long-term
- Positive effects on beta cell function

Troglitazone Has Salutory Effects on Atherosclerotic Risk Factors: Lipids

- Decreases free fatty acids
- Decreases triglycerides
- Increases HDL
- Increases LDL particle size
- Decreases LDL oxidation
- Decreases ApoB levels

Troglitazone Has Salutary Effects on Atherosclerotic Risk Factors: Vascular Function

- Decreases PAI-1 activity
- Decreases platelet activation
- Decreases intimal-medial thickening
- Decreases E-selectin levels
- Decreases vascular reactivity
- Increases flow mediated coronary dilation

Beneficial Effects of Troglitazone in Vasospastic Angina Pectoris With Diabetes Mellitus

- Diabetic patients with angiographically documented coronary vasospasm and residual angina pectoris
- Treatment with troglitazone for 4 mos; n = 8
- Anginal episodes assessed at baseline and 4 mos.
- Flow-mediated vasodilation assessed at baseline and 4 mos.

Murakami et al. ACC 1998 (abstract);1162-131.

Beneficial Effects of Troglitazone in Vasospastic Angina Pectoris With Diabetes Mellitus

	Premedication (%)	Postmedication (%)	P-Value
AP; Minutes Per Month	72 ± 68	14 ± 17	0.04
Flow-mediated Dilation	4.3 ± 1.4	6.6 ± 1.6	0.03
GTN (Endothelium- independent vasodilation)	11.5 ± 4.3	13.3 ± 2.9	NS

Murakami et al. ACC. 1998 (abstract):1162-131.

Significant Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination
- Significant and sustained glucose lowering in combination with sulfonylurea
- Effective as monotherapy both short- and long-term
- Positive effects on beta cell function and atherosclerotic risk factors

Comparison of Reduction in Risk

	Type 2 UKPDS	Type 1 DCCT	Rezulin Model
Microvascular Disease	21%	76%	51%

Significant Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination
- Significant and sustained glucose lowering in combination with sulfonylurea
- Effective as monotherapy both short- and long-term
- Positive effects on beta cell function and atherosclerotic risk factors
- Projected risk reduction for microvascular endpoints