

‘Type 2 Diabetes Prevention: What the trials tell us about pathogenesis’

Nick Oliver

Type 2 Diabetes Prevention

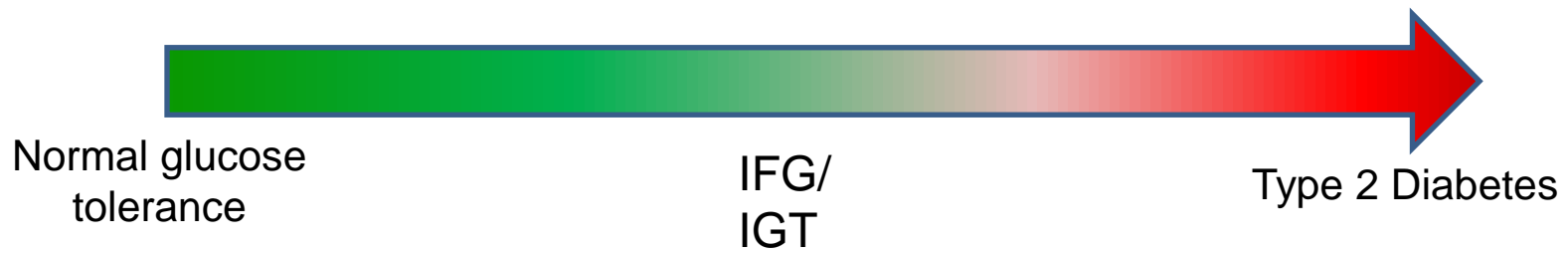
- Abnormal glucose metabolism
- Prevention of progression
 - Lifestyle interventions
 - Diabetes-specific pharmacological intervention
 - Non-specific pharmacological intervention
- Pathophysiology

Abnormal Glucose Metabolism

- Impaired fasting glycaemia
 - Fasting plasma glucose 6.1→7.0mmol/L
- Impaired glucose tolerance
 - Fasting glucose <7.0mmol/L
 - 2 hour glucose on OGTT 7.8→11.0mmol/L
- Diabetes
 - Fasting glucose \geq 7.0mmol/L
 - 2 hour glucose \geq 11.1mmol/L

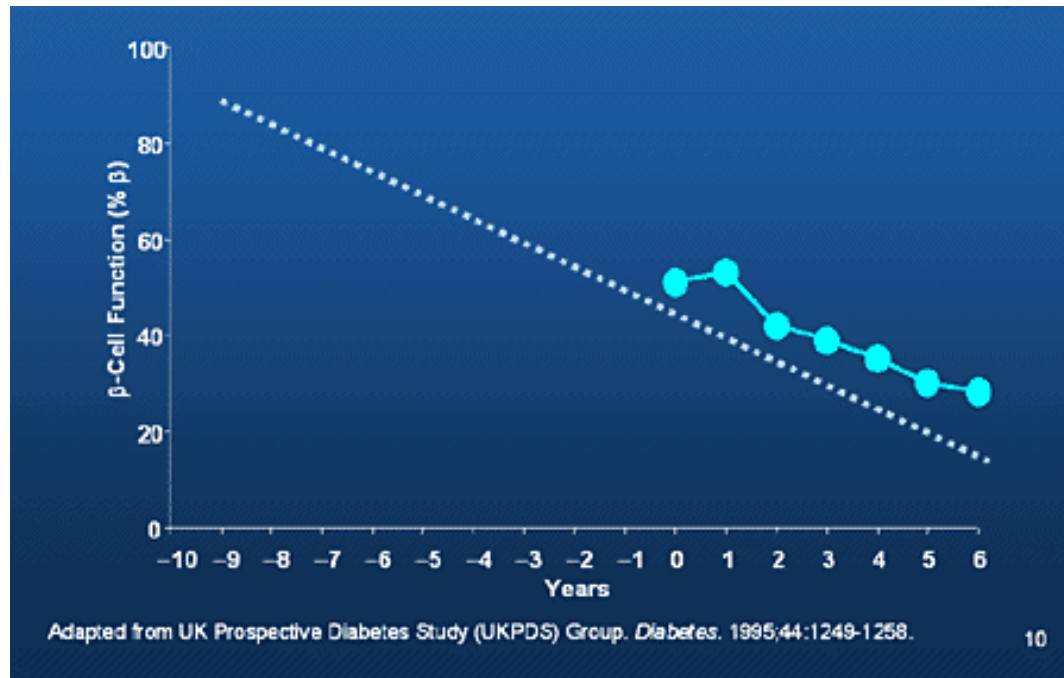
Abnormal Glucose Metabolism

- Spectrum of disease
- Type 1 diabetes is a categorical divide
 - Defined by risk of microvascular disease
- Type 2 diabetes



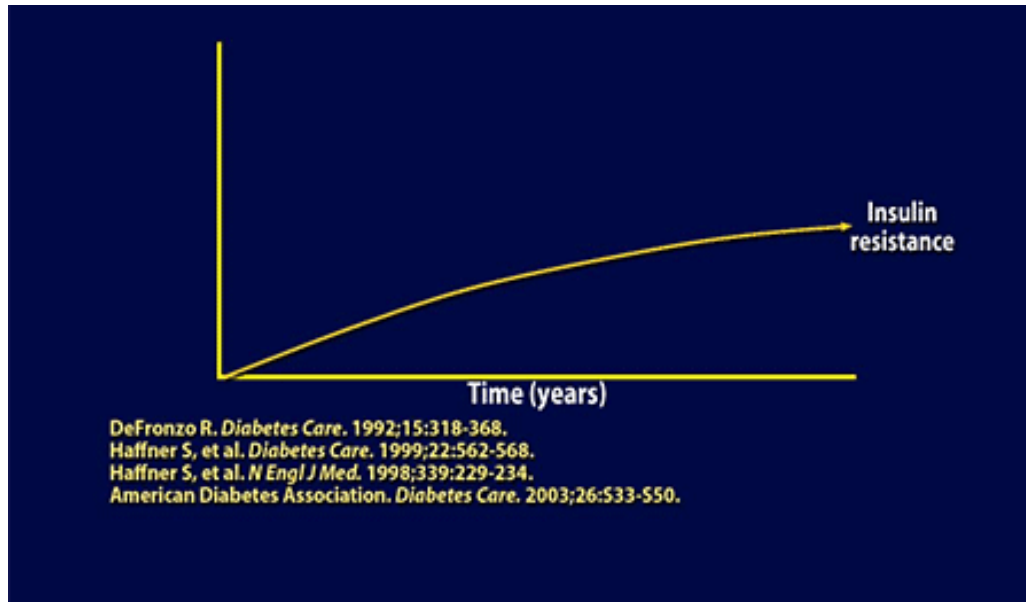
Physiology

- Declining beta cell function

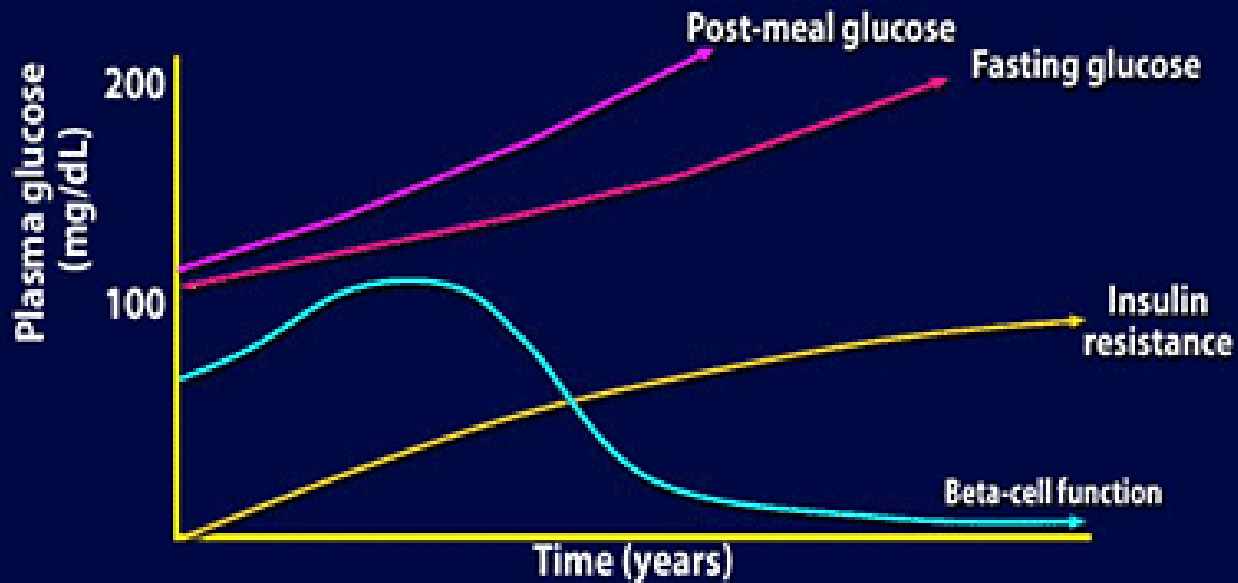


Physiology

- Increasing insulin resistance



Physiology



DeFronzo R. *Diabetes Care*. 1992;15:318-368.

Haffner S, et al. *Diabetes Care*. 1999;22:562-568.

Haffner S, et al. *N Engl J Med*. 1998;339:229-234.

American Diabetes Association. *Diabetes Care*. 2003;26:S33-S50.

Pathogenesis

- Genetic factors
 - Cannot be modified
 - Complex polygenic inheritance of risk for diabetes
- Non-genetic factors
 - Modifiable
 - **Can they be modified to prevent type 2 diabetes?**

Finnish Study

The New England Journal of Medicine

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NUMBER 18



PREVENTION OF TYPE 2 DIABETES MELLITUS BY CHANGES IN LIFESTYLE AMONG SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

JAAKKO TUOMILEHTO, M.D., PH.D., JAANA LINDSTRÖM, M.S., JOHAN G. ERIKSSON, M.D., PH.D., TIMO T. VALLE, M.D.,
HELENA HÄMÄLÄINEN, M.D., PH.D., PIRJO ILANNE-PARIKKA, M.D., SIRKKA KEINÄNEN-KIUKAANNIEMI, M.D., PH.D.,
MAURI LAAKSO, M.D., ANNE LOUHERANTA, M.S., MERJA RASTAS, M.S., VIRPI SALMINEN, M.S.,
AND MATTI UUSITUPA, M.D., PH.D., FOR THE FINNISH DIABETES PREVENTION STUDY GROUP

Finnish Study

- 522 'middle aged' overweight subjects
- All had IGT
- Randomised to
 - Intensive lifestyle intervention
 - Control group

Finnish Study

- Intervention Arm
 - Detailed individualised advice
 - Goals
 - Weight reduction of $\geq 5\%$
 - Fat intake reduction to $\leq 30\%$ of total Kcal intake
 - Increase fibre to $\geq 15\text{g}/1000\text{Kcal}$
 - Moderate exercise ≥ 30 minutes per day
 - Dietary advice
 - 3 day food diaries completed 4 times/year
 - 7 sessions with dietitian in 1st year, 4 per year thereafter
 - Individualised exercise schedule
 - Supervised circuit training

Finnish Study

- Control group
 - Oral and written diet and exercise information annually
- Mean follow up 3.2 years

Finnish Study

VARIABLE	INTERVENTION GROUP (N= 256)		CONTROL GROUP (N= 250)		P VALUE†
	mean ±SD	95% CI	mean ±SD	95% CI	
Change in weight					
In kilograms	-4.2±5.1	-4.8 to -3.6	-0.8±3.7	-1.3 to -0.3	<0.001
Percent change	-4.7±5.4	-5.0 to -4.4	-0.9±4.2	-1.0 to -0.8	<0.001
Change in waist circumference (cm)	-4.4±5.2	-5.1 to -3.9	-1.3±4.8	-1.9 to -0.7	<0.001
Change in plasma glucose (mg/dl)					
Fasting	-4±12	-6 to -2	1±12	0 to 2	<0.001
2 Hr after oral glucose challenge	-15±34	-19 to -11	-5±40	-8 to -2	0.003
Change in serum insulin (μg/ml)					
Fasting	-2±9	-3 to -1	-1±7	-2 to 0	0.14
2 Hr after oral glucose challenge	-29±64	-37 to -21	-11±51	-18 to -4	0.001
Change in serum lipids (mg/dl)‡					
Total cholesterol	-5±28	-8 to -2	-4±28	-7 to -1	0.62
High-density lipoprotein cholesterol	2±7	1 to 3	1±6	0 to 2	0.06
Triglycerides	-18±51	-24 to -12	-1±60	-8 to 6	0.001
Change in blood pressure (mm Hg)§					
Systolic	-5±14	-7 to -3	-1±15	-3 to 1	0.007
Diastolic	-5±9	-6 to -4	-3±9	-4 to -2	0.02

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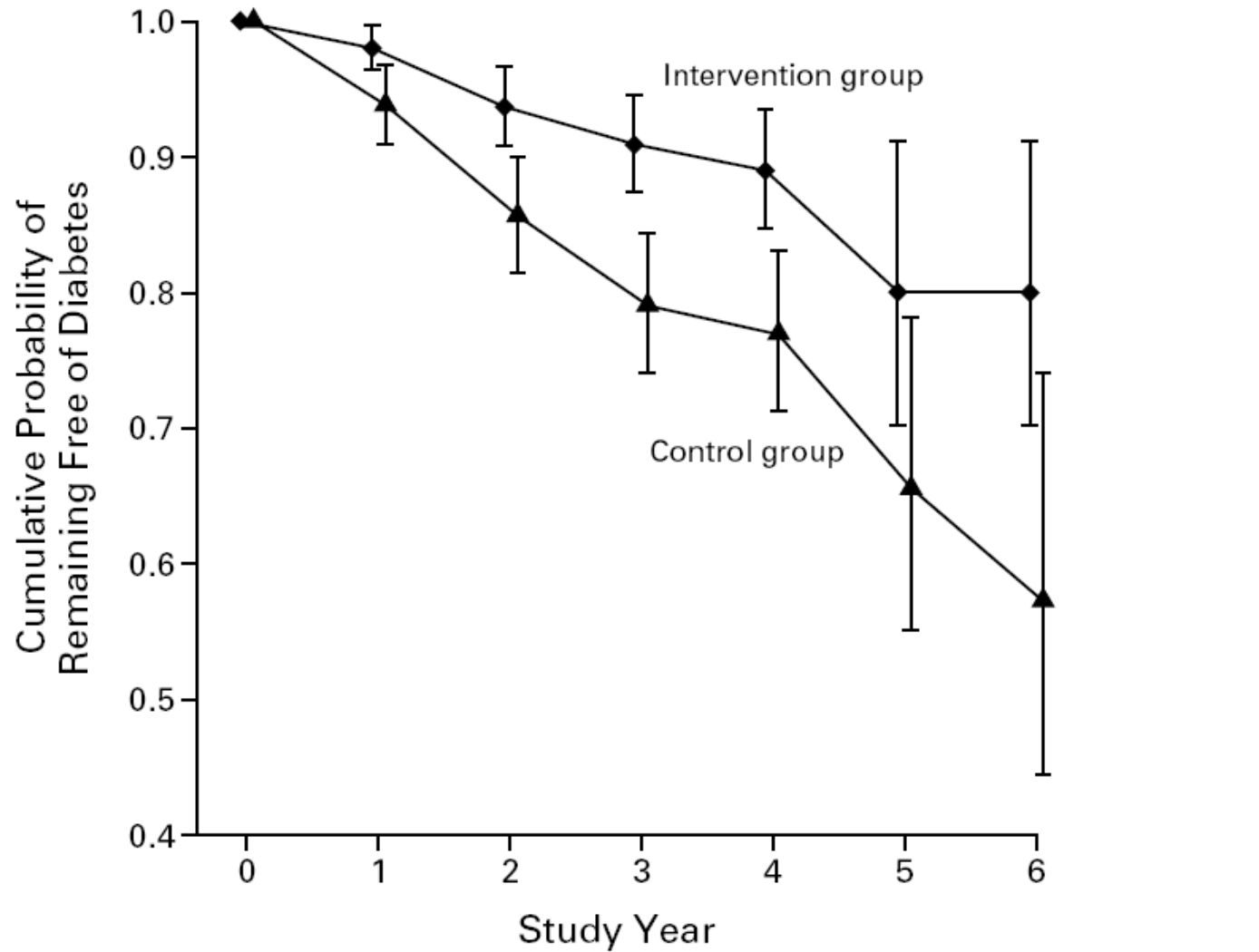
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Finnish Study



Finnish Study

- Intensive lifestyle intervention
 - Reduced progression to type 2 diabetes by **58%**
 - Reduced weight
 - Improved 2hr insulin response
 - Reduced fasting and 2 hour glucose
 - Reduced triglycerides
 - Reduced blood pressure

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All features of insulin resistance

Nurses' Health Study

- Background
 - Nurses' Health Study started in 1976
 - 121,700 nurses answered biennial questionnaire about their health
- Data from those not previously diagnosed with diabetes assessed
- N=89,941 women only

Nurses' Health Study

FACTOR	NO. OF CASES*	PERCENTAGE OF PERSON-YEARS†	RELATIVE RISK (95% CI)‡
Quintile for dietary score§			
1	670	15	1.0
2	1032	27	0.86 (0.78–0.95)
3	561	17	0.77 (0.68–0.86)
4	746	26	0.67 (0.60–0.74)
5	291	15	0.49 (0.42–0.56)
Weekly exercise¶			
<0.5 hr	263	5	1.0
0.5–1.9 hr	1055	29	0.89 (0.77–1.02)
2.0–3.9 hr	734	22	0.87 (0.75–1.00)
4.0–6.9 hr	668	26	0.83 (0.71–0.96)
≥7.0 hr	97	7	0.71 (0.56–0.90)
Body-mass index			
<23.0	121	32	1.0
23.0–24.9	202	18	2.67 (2.13–3.34)
25.0–29.9	884	25	7.59 (6.27–9.19)
30.0–34.9	885	9	20.1 (16.6–24.4)
≥35.0	759	4	38.8 (31.9–47.2)
Smoking status			
Never smoked	1446	43	1.0
Former smoker	1217	35	1.15 (1.07–1.25)
Current smoker			
1–14 cigarettes/day	181	7	1.20 (1.03–1.41)
≥15 cigarettes/day	439	15	1.34 (1.20–1.50)
Daily alcohol consumption			
0 g	1715	34	1.0
0.1–5.0 g	1034	33	0.78 (0.72–0.84)
5.1–10.0 g	189	11	0.56 (0.48–0.65)
>10.0 g	358	21	0.59 (0.52–0.66)



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Nurses' Health Study

- Excess body fat single largest determinant of longitudinal type 2 diabetes risk
- Further evidence that risk of type 2 diabetes is attributable to modifiable risk factors

Diabetes Prevention Program

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NUMBER 6



REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE
INTERVENTION OR METFORMIN

DIABETES PREVENTION PROGRAM RESEARCH GROUP*

DPP

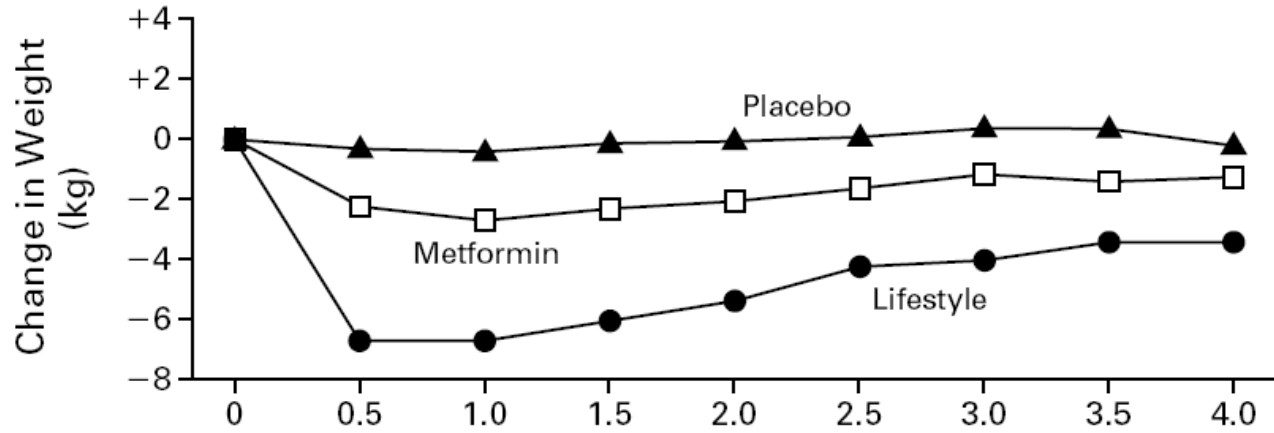
- 3234 Subjects with IFG/ IGT
- Randomised to
 - Metformin and standard lifestyle advice
 - Intensive lifestyle intervention
 - Standard lifestyle advice only
 - (Troglitazone group)

DPP

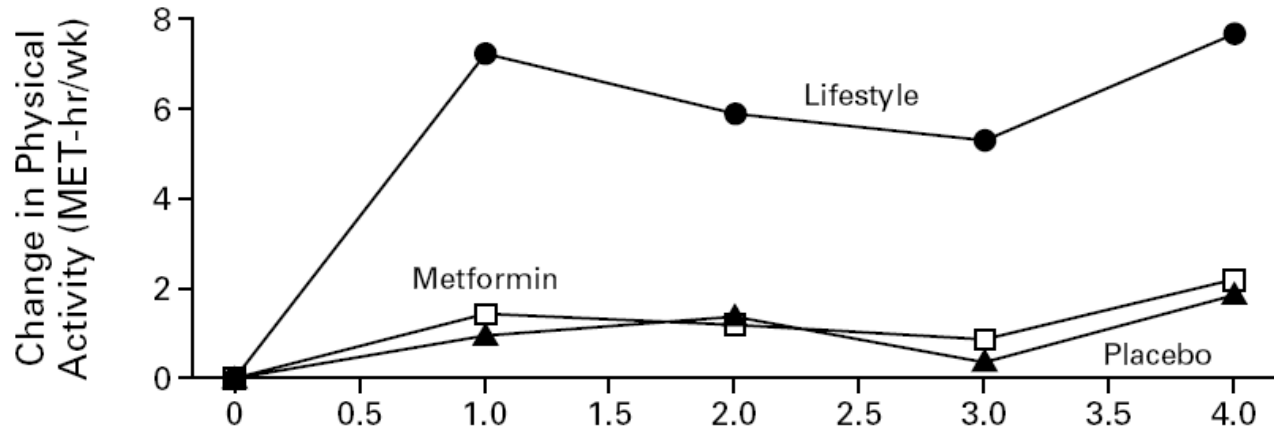
- Intensive lifestyle
 - Target
 - Weight reduction of $\geq 7\%$
 - Moderate exercise for ≥ 150 minutes/ week
 - Low calorie/ low fat diet
 - 16 lesson curriculum taught one to one over 24 weeks with subsequent monthly sessions

DPP

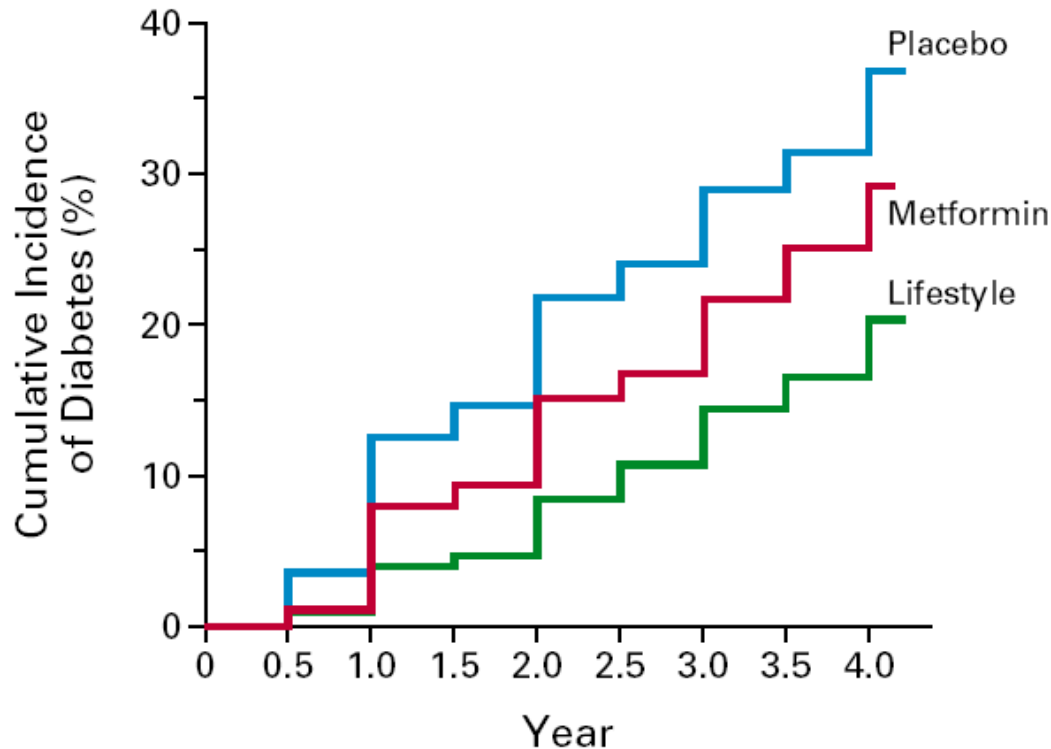
A



B

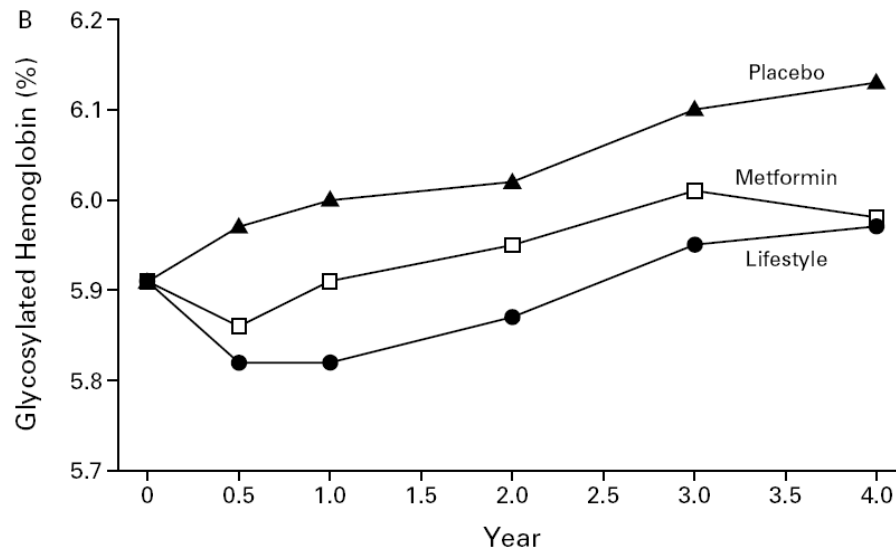
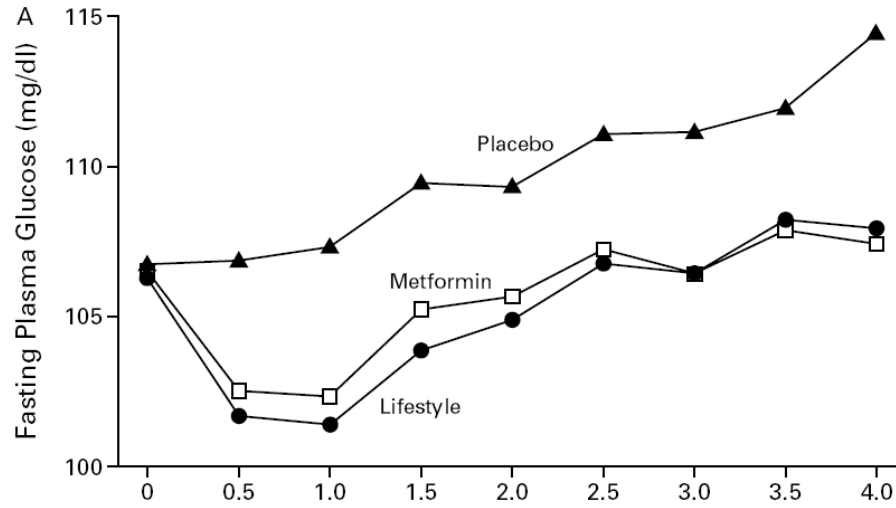


DPP



- 58% reduction in progression to T2DM in lifestyle group
- 31% reduction in metformin group

DPP



DPP

- Intensive lifestyle intervention
 - Reduced risk of progression to T2DM by **58%**
 - Reduced weight
 - Reduces 2 hour glucose on OGTT

DPP

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Cost > \$200m

DPP

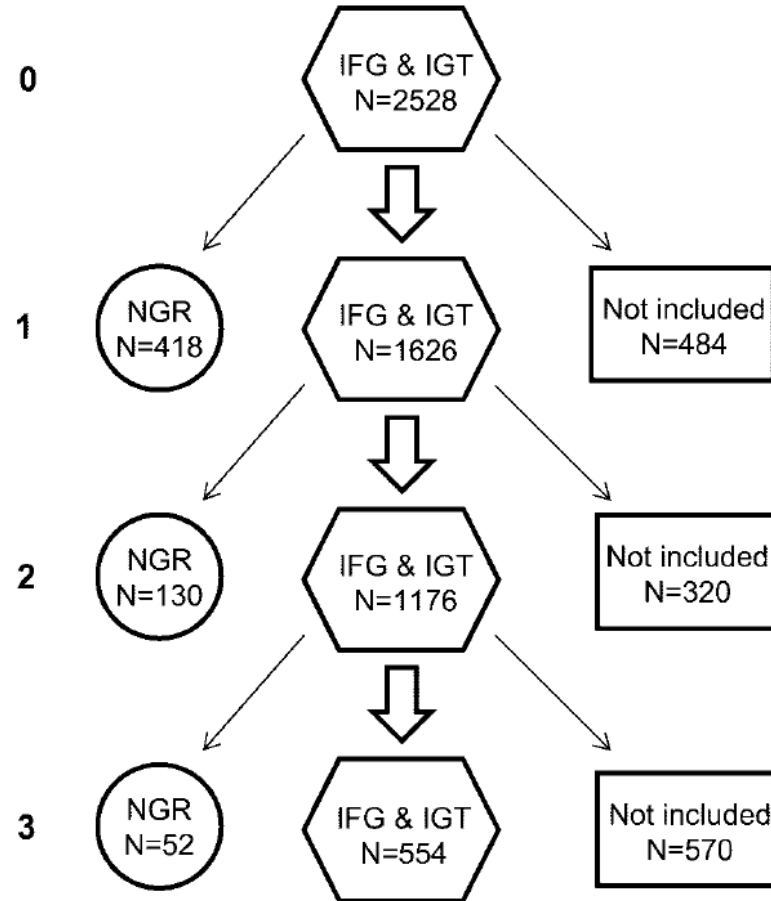
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Who Benefits?

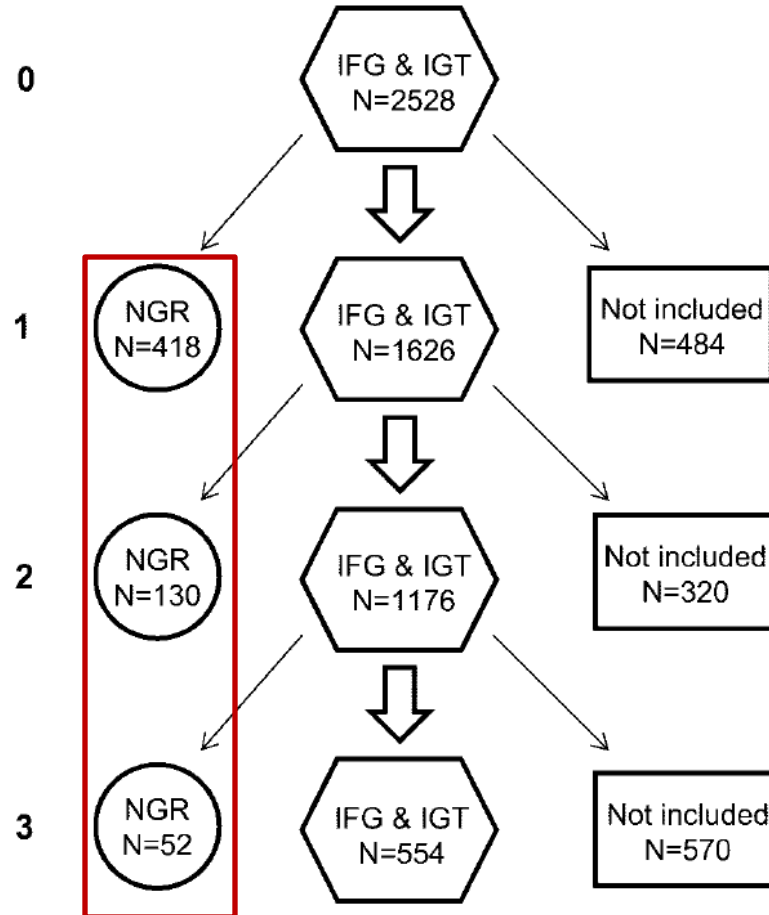
DPP

Year



DPP

Year



DPP

	HR (95% CI)	P
Regression to NGR		
ILS versus placebo	2.05 (1.66–2.53)	<0.0001
Metformin versus placebo	1.25 (0.99–1.58)	0.0601
Younger age	1.07 (1.02–1.11)	0.0031
Male versus female sex	1.17 (0.98–1.40)	0.0784
Caucasian versus non-Caucasian	1.00 (0.84–1.19)	0.9986
Lower fasting plasma glucose	1.52 (1.36–1.68)	<0.0001
Lower 2-h plasma glucose	1.24 (1.13–1.35)	<0.0001
Greater insulin sensitivity (1/fasting insulin)	1.07 (0.99–1.16)	0.0934
Greater insulin secretion (CIR)	1.09 (1.01–1.17)	0.0353
Higher baseline weight	1.01 (0.92–1.11)	0.8229
Greater weight loss	1.34 (1.21–1.49)	<0.0001

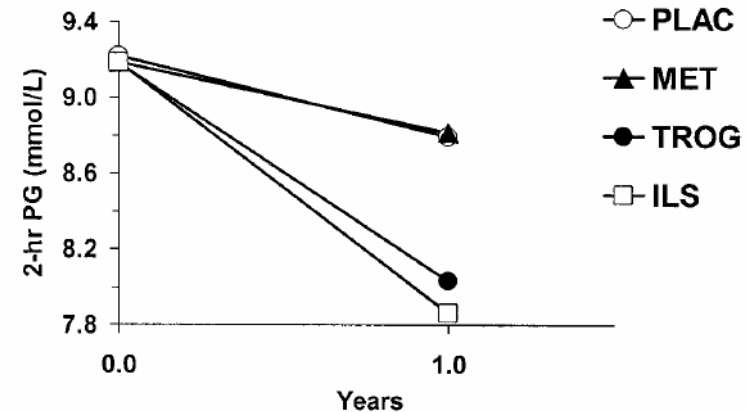
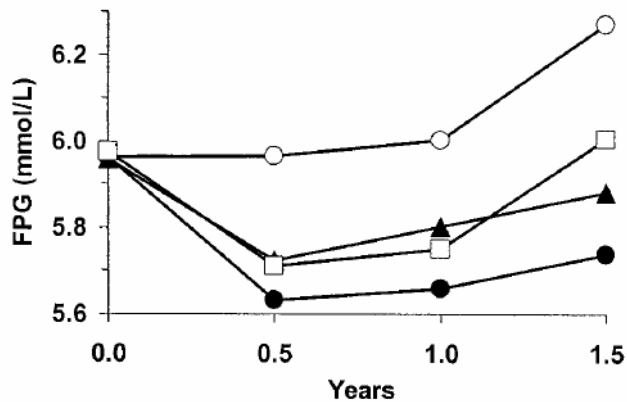
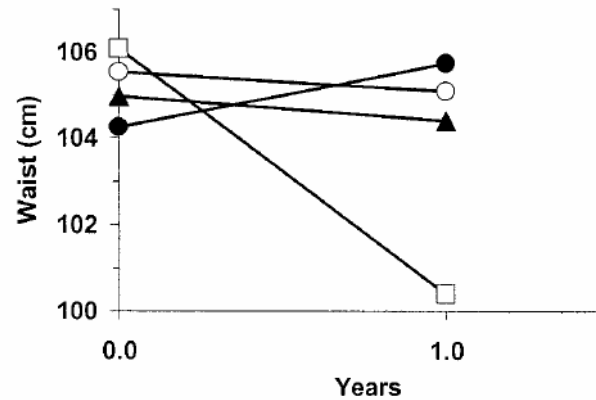
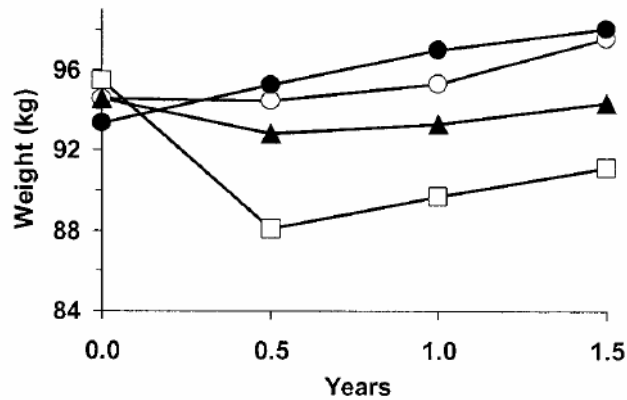
What about Troglitazone?

- Troglitazone
 - Thiazolidenedione class (Rosiglitazone, Pioglitazone)
 - PPAR γ agonist
 - Nuclear receptor, alters gene transcription
 - Glucose lowering
 - Insulin sensitizing

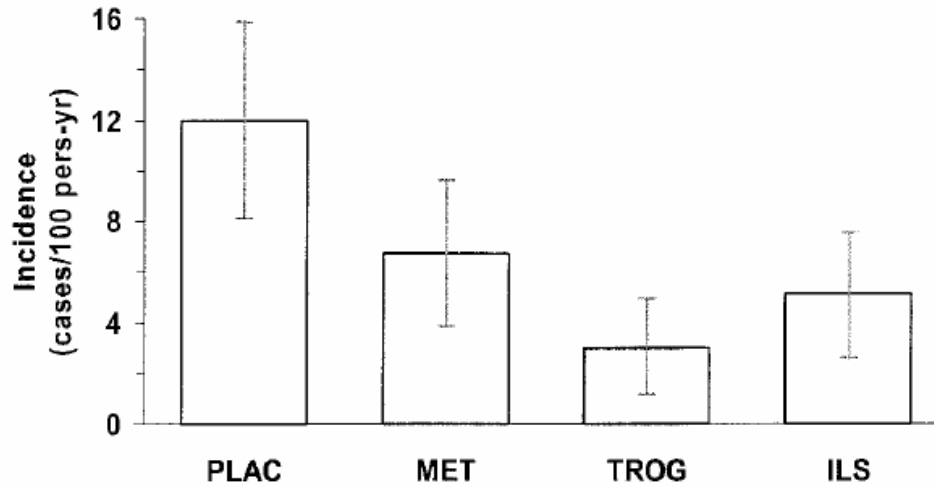
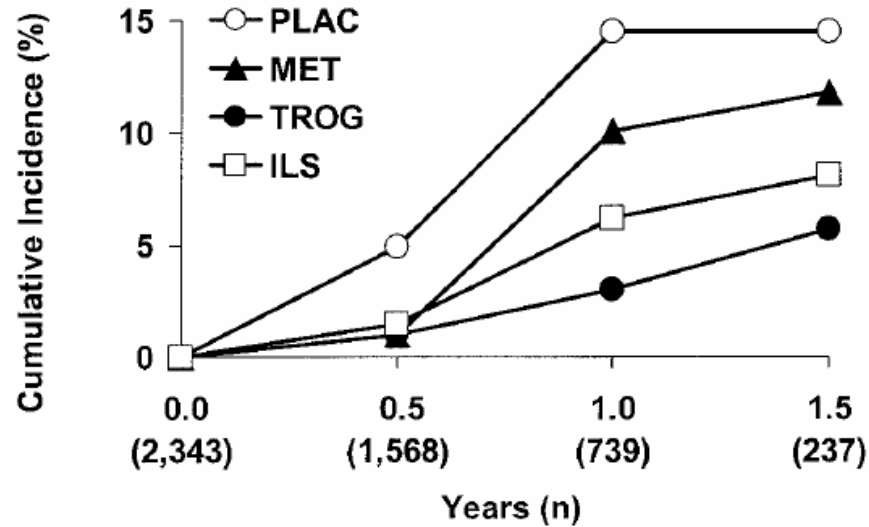
 - Withdrawn soon after release due to liver safety concerns

Troglitazone DPP

- Only 0.9 years mean follow up (cf 2.8 years)



Troglitazone DPP



Troglitazone DPP

Variable	Time (years)	Placebo	Metformin	Troglitazone	ILS	<i>P</i> difference among four treatments (Kruskal-Wallis)
<i>n</i>		172	164	187	183	
Fasting insulin (pmol/l)	0	144	138	132	132	0.58
	1	132	111	90	102	<0.01
	Δ	—	*	*	*	<0.01
30-min insulin (pmol/l)	0	513	498	498	474	0.72
	1	522	447	402	408	<0.01
	Δ	—	*	*	—	<0.01
Sensitivity [1/fasting insulin 1,000/(pmol/l)]	0	6.94	7.25	7.58	7.58	0.58
	1	7.58	9.02	11.11	9.80	<0.01
	Δ	—	*	*	*	<0.01
Sensitivity {ISI 10,000/ [(pmol/l) × (mmol/l)]}	0	11.8	12.0	12.3	12.5	0.64
	1	13.2	15.4	19.9	17.0	<0.01
	Δ	—	*	*	*	<0.01
Secretion {CIR (pmol/l)/ [(mmol/l) ²]}	0	10.1	9.05	9.58	9.06	0.19
	1	10.3	8.47	10.15	8.34	0.05
	Δ	—	—	—	—	0.99
Secretion [IGR (pmol/l)/ (mmol/l)]	0	116.4	102.1	108.1	101.5	0.24
	1	109.1	91.1	103.2	91.4	0.03
	Δ	—	—	—	—	0.43

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Troglitazone DPP

- Troglitazone
 - Reduces incidence of T2DM
 - Improves measures of glycaemia
 - Improves insulin sensitivity
 - ***Despite weight gain***
- Troglitazone study confirms that intensive lifestyle intervention improves insulin sensitivity

Acarbose

ARTICLES

Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial

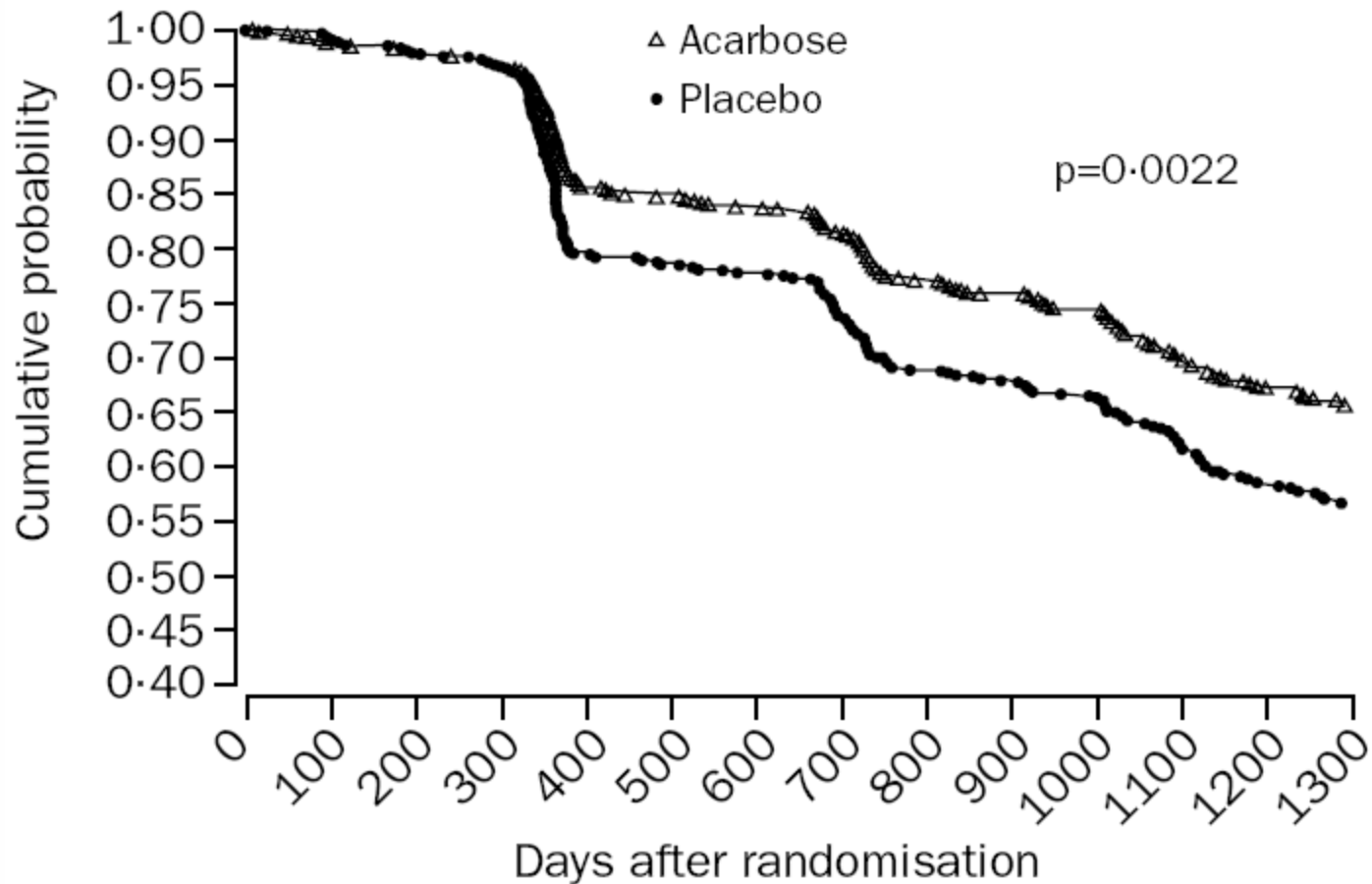
*Jean-Louis Chiasson, Robert G Josse, Ramon Gomis, Markolf Hanefeld, Avraham Karasik, Markku Laakso,
for The STOP-NIDDM Trial Research Group**

STOP-NIDDM

- Acarbose
 - α -glucosidase inhibitor
 - Decreases post-prandial glucose
 - Shown to increase insulin sensitivity
- 1368 subjects with IGT randomised to
 - Acarbose treatment
 - Placebo

STOP-NIDDM

- Mean follow up 3.3 years



STOP-NIDDM

- Risk of progression to T2DM reduced by 25%
- Change in first phase insulin and post-prandial
- Are diabetes drugs *preventing* diabetes or simply masking the diagnosis?
 - Metformin and troglitazone used in treatment with glucose lowering effect and insulin sensitizing
 - Effect of drugs accounted for in statistics
 - Acarbose not absorbed and does not affect monosaccharide absorption

Non-Diabetes Drugs

Emerging Treatments and Technologies

ORIGINAL ARTICLE

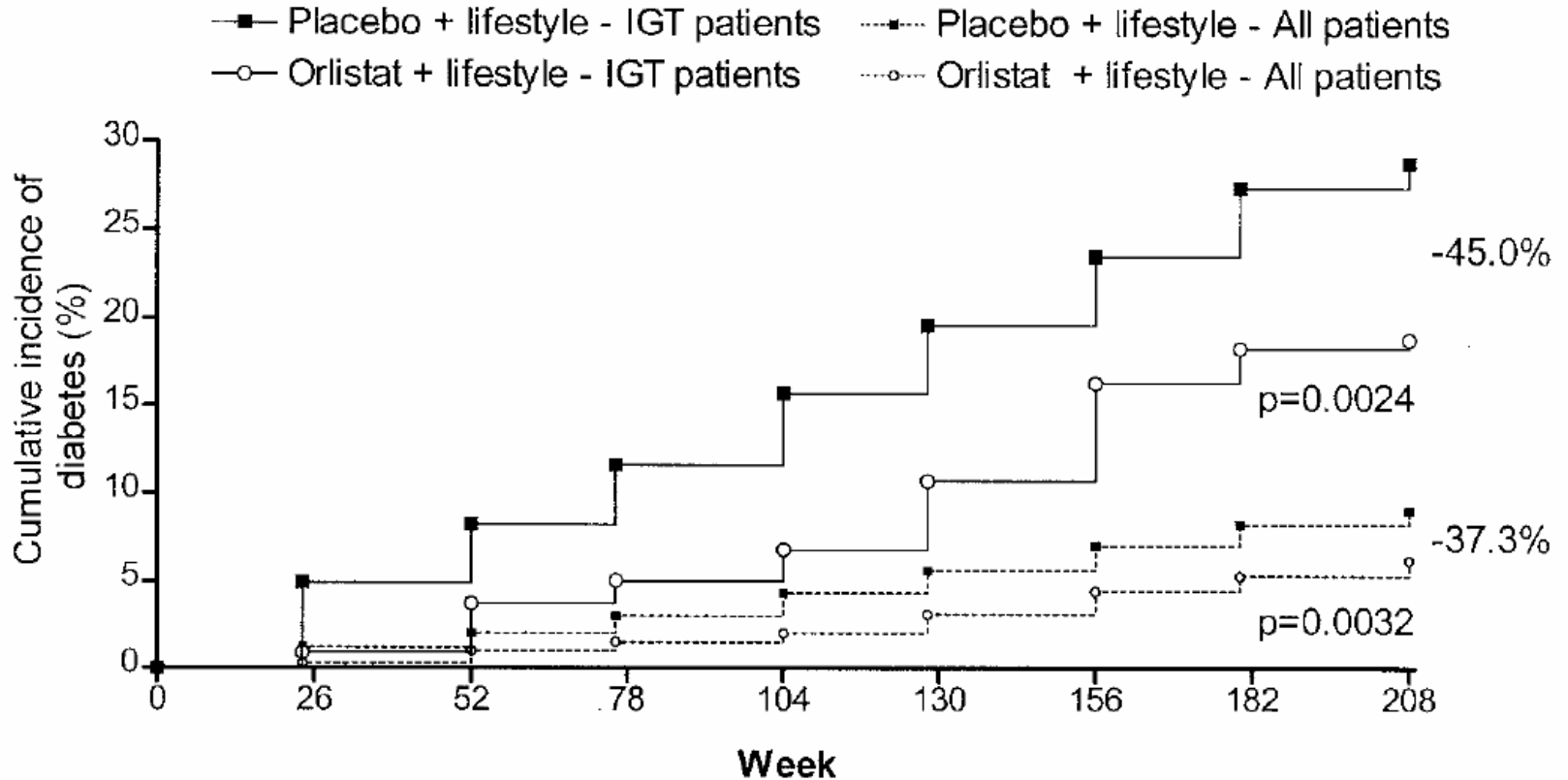
XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study

A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients

XENDOS

- Orlistat
 - GI lipase inhibitor
 - Not absorbed
 - Weight loss agent
- XENDOS
 - 3305 subjects, all obese
 - 21% had IGT
 - Randomised to
 - Lifestyle advice only
 - Lifestyle plus Orlistat

XENDOS



XENDOS

	Year 1			Year 4		
	Placebo + lifestyle	Orlistat + lifestyle	P between treatments*	Placebo + lifestyle	Orlistat + lifestyle	P between treatments*
<i>n</i>	1,295	1,487		567	851	
Diastolic BP (mmHg)	-2.6	-3.6	<0.01	-1.9	-2.6	<0.01
Systolic BP (mmHg)	-5.2	-7.3	<0.01	-3.4	-4.9	<0.01
Total cholesterol (%)	-1.3	-8.8	<0.01	-2.3	-7.9	<0.01
LDL cholesterol (%)	-1.6	-11.4	<0.01	-5.1	-12.8	<0.01
HDL cholesterol (%)	8.5	3.4	<0.01	9.1	6.5	<0.01†
LDL-to-HDL ratio	-0.3	-0.5	<0.01	-0.4	-0.6	<0.01
Triglycerides (%)	-6.3	-6.2	<0.05‡	2.9	2.4	NS
Waist circumference (cm)	-7.0	-9.6	<0.01	-4.4	-6.4	<0.01
Venous whole blood glucose (mmol/l)						
Fasting	0.2	0.1	<0.01§	0.2	0.1	<0.01
2 h	-0.4	-0.6	<0.01	-0.2	-0.4	<0.01¶
AUC (mmol · min ⁻¹ · l ⁻¹)#	-27	-51	<0.01	3	-14	<0.01
Serum insulin (pmol/l)						
Fasting	-17.0	-26.5	<0.01	-20.6	-32.0	<0.01
2 h	-107.5	-157.4	<0.01	-76.7	-115.4	<0.01¶
AUC (nmol · min ⁻¹ · l ⁻¹)#	-11.0	-14.6	<0.01	-8.4	-10.9	<0.01
Fibrinogen (µmol/l)	0.1	0.2	NS	-0.5	-0.4	<0.05
Plasminogen activator inhibitor-1 (U/ml)	-3.0	-7.1	<0.01	0.1	-3.0	<0.01

XENDOS

- Orlistat
 - Reduces risk of developing T2DM in obese subjects with normal and impaired glucose tolerance
 - Improves
 - BP
 - Lipids
 - 2 hour glucose values
 - Glucose AUC
 - Fasting insulin and insulin response

Diabetes Prevention

Lifestyle intervention, diabetes-specific drugs and non-diabetes drug all prevent progression of glucose metabolic abnormality and improve the parameters of insulin resistance

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HOW?

Back to Troglitazone

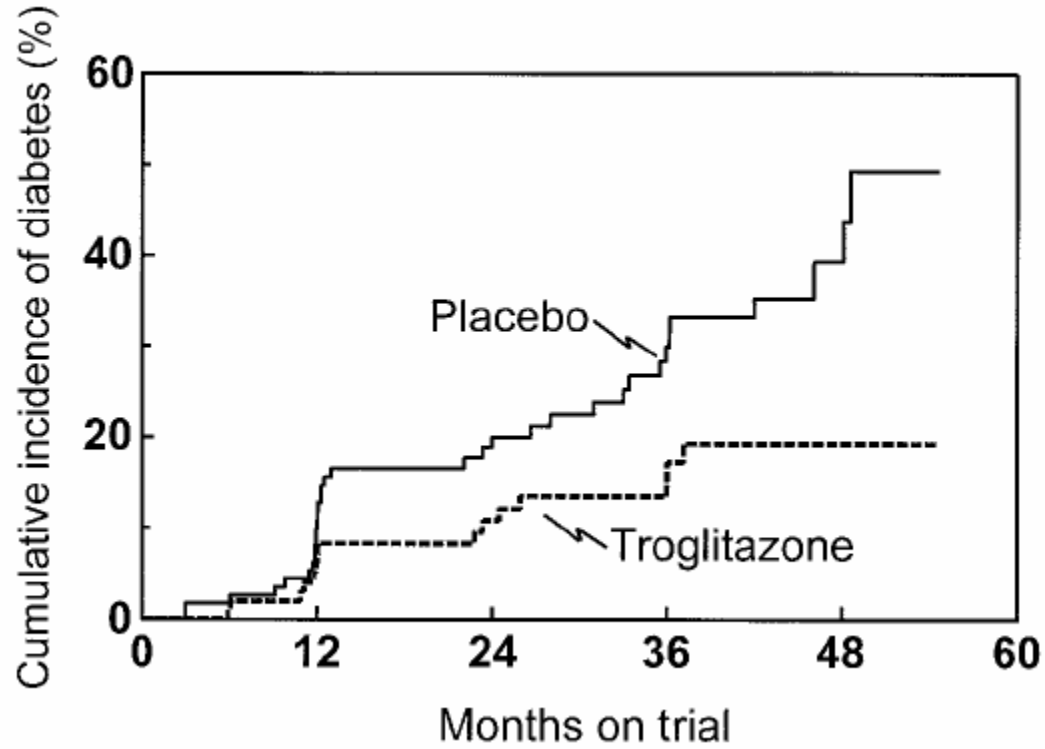
Preservation of Pancreatic β -Cell Function and Prevention of Type 2 Diabetes by Pharmacological Treatment of Insulin Resistance in High-Risk Hispanic Women

Thomas A. Buchanan,^{1,2,3} Anny H. Xiang,^{3,4} Ruth K. Peters,^{3,4} Siri L. Kjos,^{2,3} Aura Marroquin,¹ Jose Goico,¹ Cesar Ochoa,¹ Sylvia Tan,⁴ Kathleen Berkowitz,² Howard N. Hodis,^{1,3,4} and Stanley P. Azen^{3,4}

Troglitazone II

- 266 women with previous GDM randomised to
 - Troglitazone
 - Placebo
- Median follow up 3 years

Troglitazone II



Troglitazone II

	Tertile 1	Tertile 2	Tertile 3	<i>P</i>
Change in S_I				
Median	-0.09	0.99	2.28	
Range	-2.13 to 0.44	0.54 to 1.41	1.43 to 7.67	
Annual diabetes incidence	9.8%	1.1%*	4.8%†	0.04
Change in IVGTT insulin area				
Median	-40	-1,813	-5,315	
Range	4,487 to -1,180	-1,238 to -3,053	-3,160 to -19,364	
Annual diabetes incidence	7.2%	7.8%	0.9%‡	0.05

- Protection from diabetes limited to the 2/3 of women with greatest increase in insulin sensitivity over the first 3 months

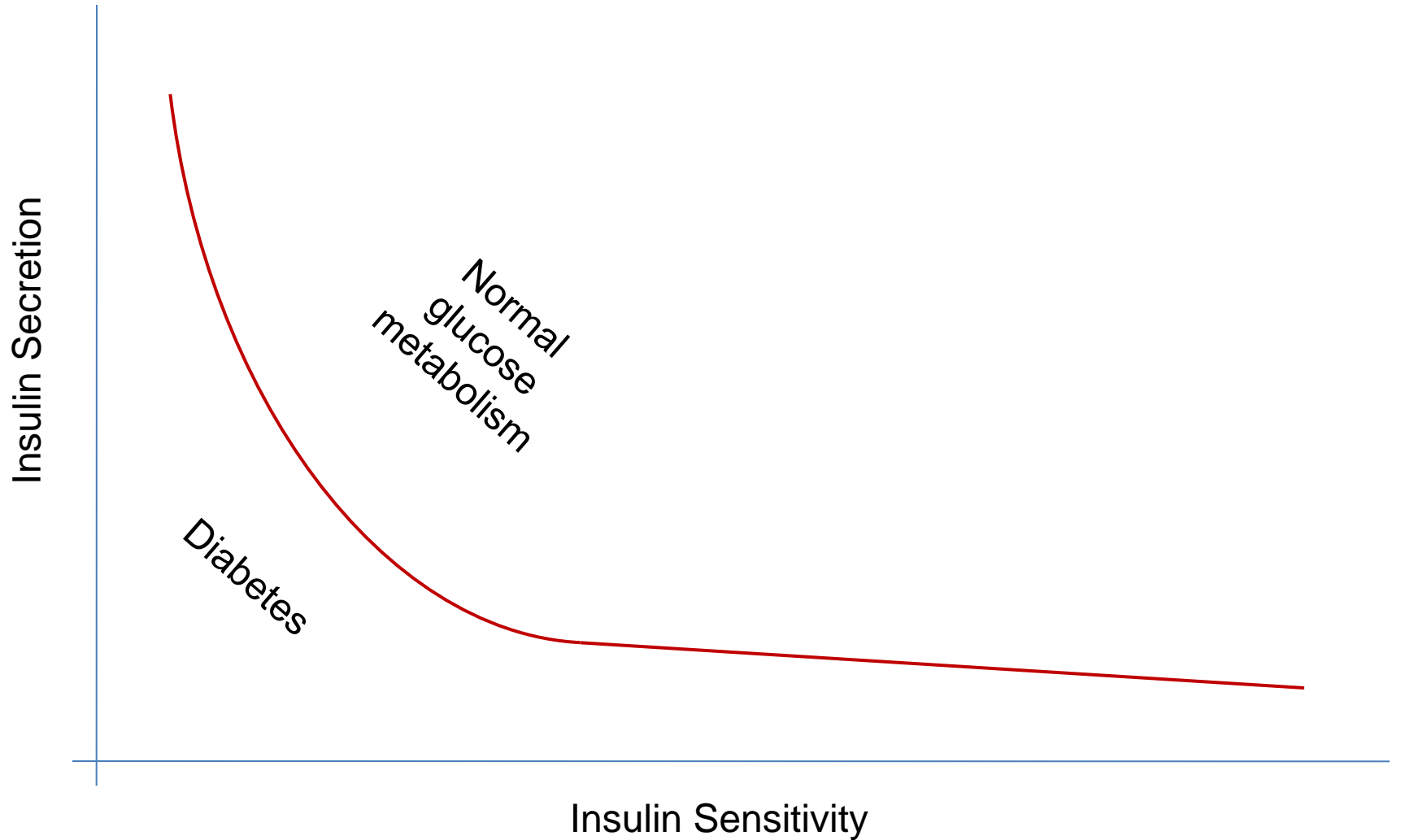
Troglitazone II



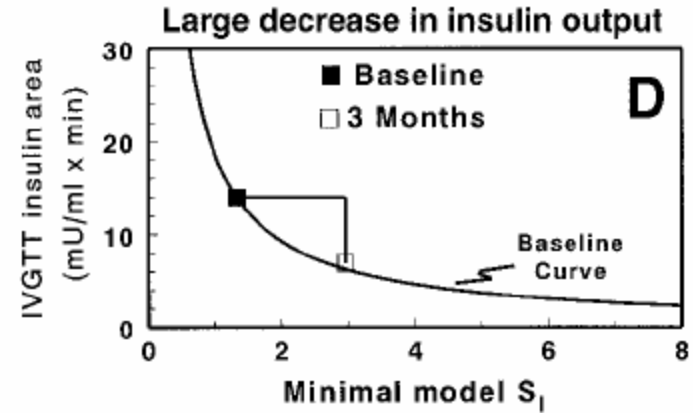
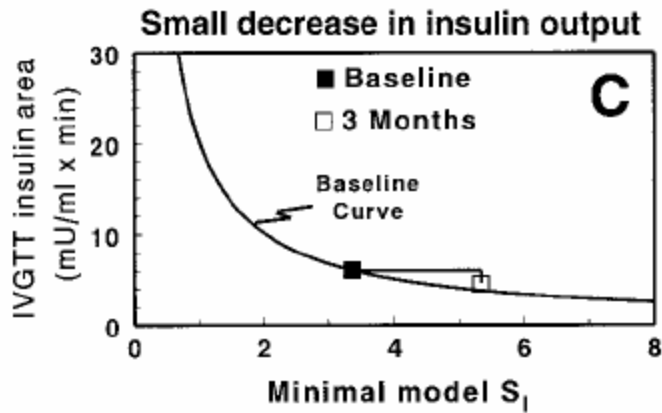
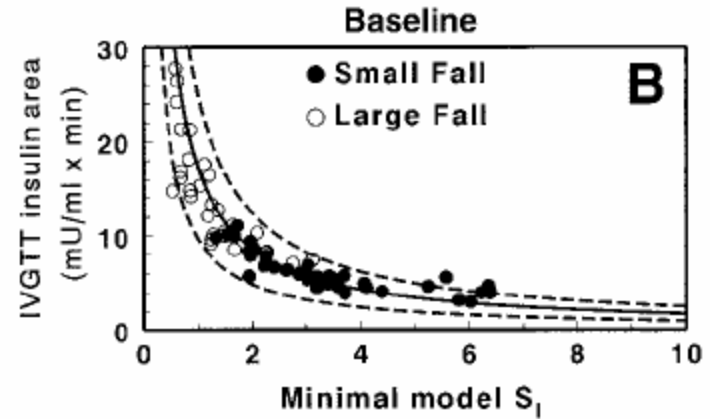
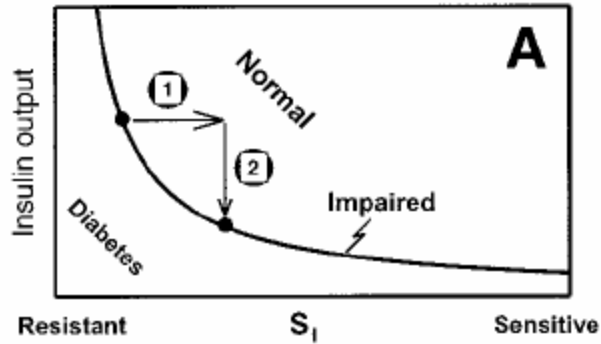
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- For insulin output, protection from diabetes was limited to 1/3 of women who had the greatest reduction from baseline in first 3 months

Troglitazone II



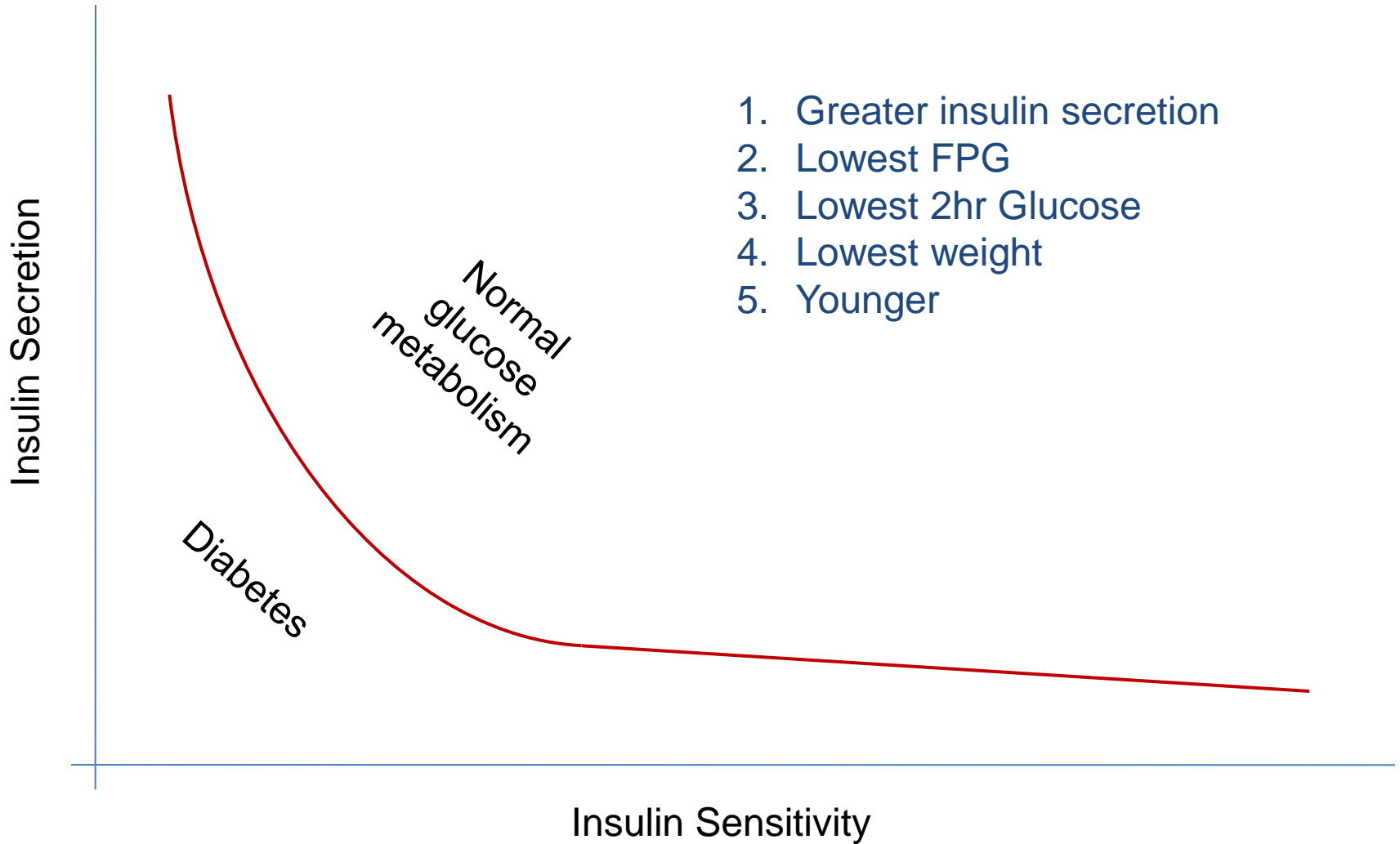
Troglitazone II



Troglitazone II

- Elucidated mechanism of diabetes prevention
 - ‘Responders’ move back along the parabolic relationship between insulin secretion and insulin sensitivity

DPP: Cui Bono?



Summary

- Abnormal glucose metabolism is a spectrum of disease
- Progression to type 2 diabetes may be prevented by lifestyle and pharmacology
- Pharmacology may not be specifically targeted at glucose
- Prevention of progression to type 2 diabetes is dependent on a change in insulin sensitivity