Durability e Protezione β-Cellulare nel DMT2

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Hyperglycemia

y pathogenesis of hyperglycemia

Possibili Strumenti di Intervento per la Prevenzione del Diabete Tipo 2

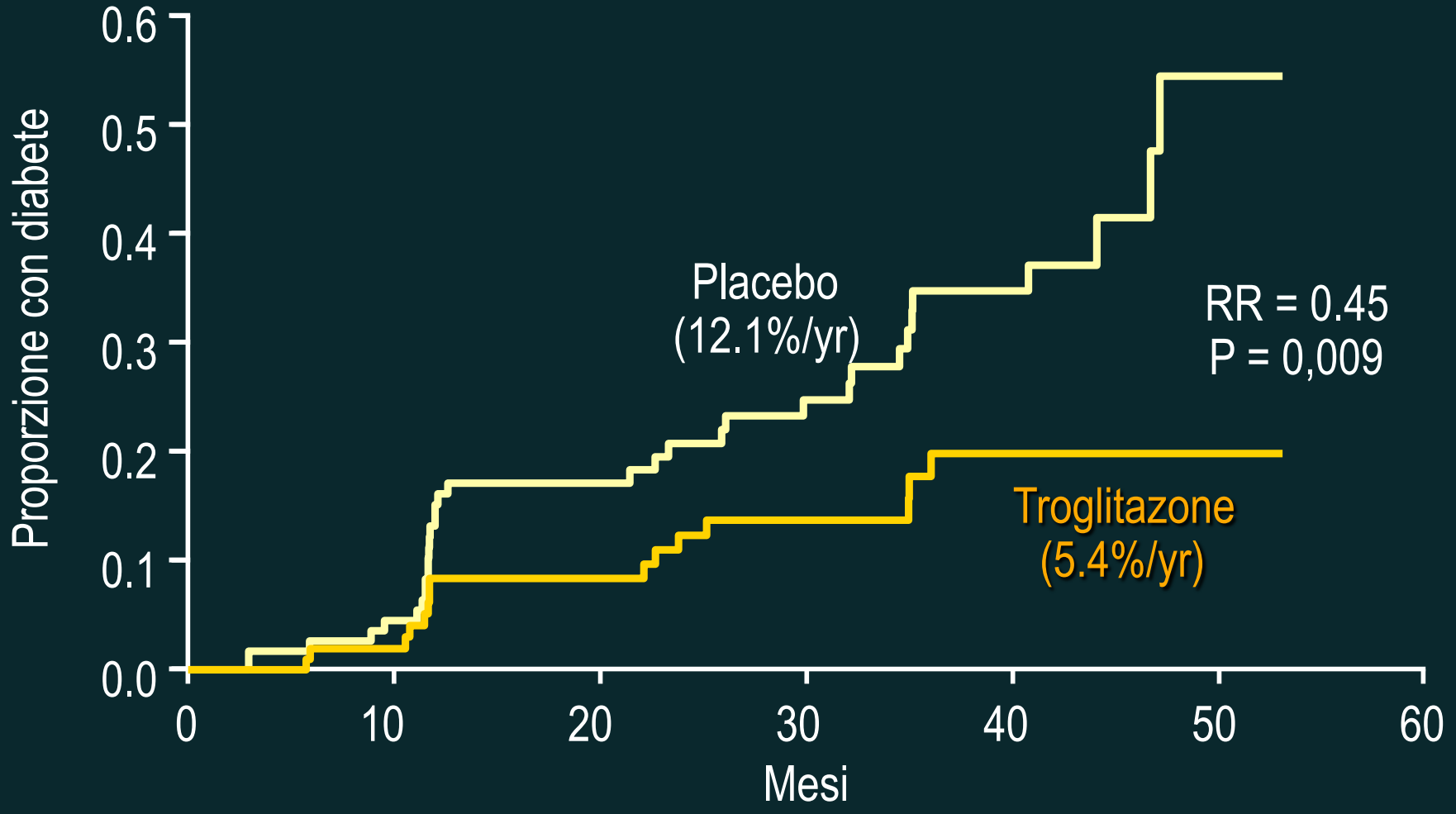
• Modifica stile di vita	dieta, attività fisica
• Farmaci insulino-sensibilizzanti	metformina, glitazoni
• Altri farmaci ipoglicemizzanti	acarbose, SU, glinidi, *insulina,* liraglutide
• Farmaci per l'obesità	orlistat, sibutramina
• Farmaci ipolipemizzanti	statine, fibrati, ω-3
• Farmaci anti-ipertensivi	ACE-I (ramipril), ARB (valsartan)
• Altri farmaci	ERT

Efficacia Farmaci Ipoglicemizzanti

Farmaco	**Riduzione HbA_{1c}** ***Monoterapia*** **(Nathan 2009)**	**Riduzione HbA_{1c}** ***Add-on Metformina*** **(revisione letteratura)**
Metformina	1,0-2,0	-
Insulina	1,5-3,5	1,0-2,0 (insulina basale)
Sulfoniluree	1,0-2,0	1,0-1,5
Glinidi	0,5-1,5	0,8-1,4
Tiazolidinedioni	0,5-1,4	1,0-1,5
Exenatide	0,5-1,0	0,8-1,2
Liraglutide	0,8-1,1	0,9-1,4
Inibitori DPP4	0,6-0,9	0,6-1,2
Acarbosio	0,5-0,8	-

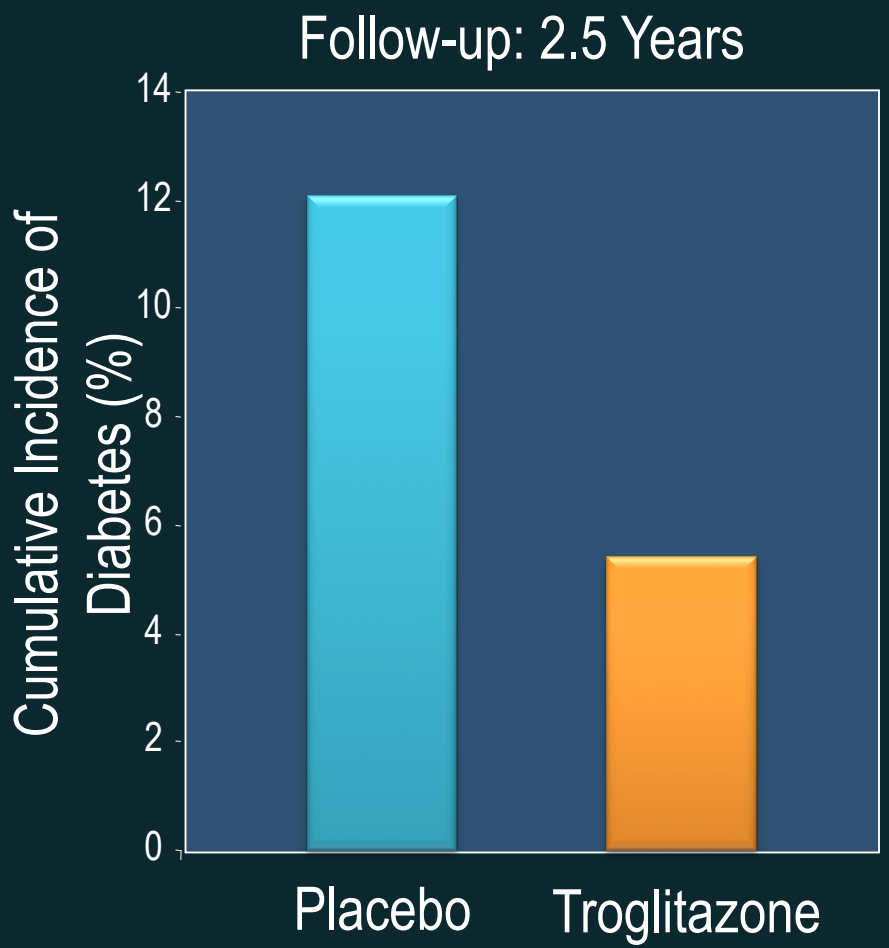
Glitazoni e Prevenzione del Diabete Tipo 2

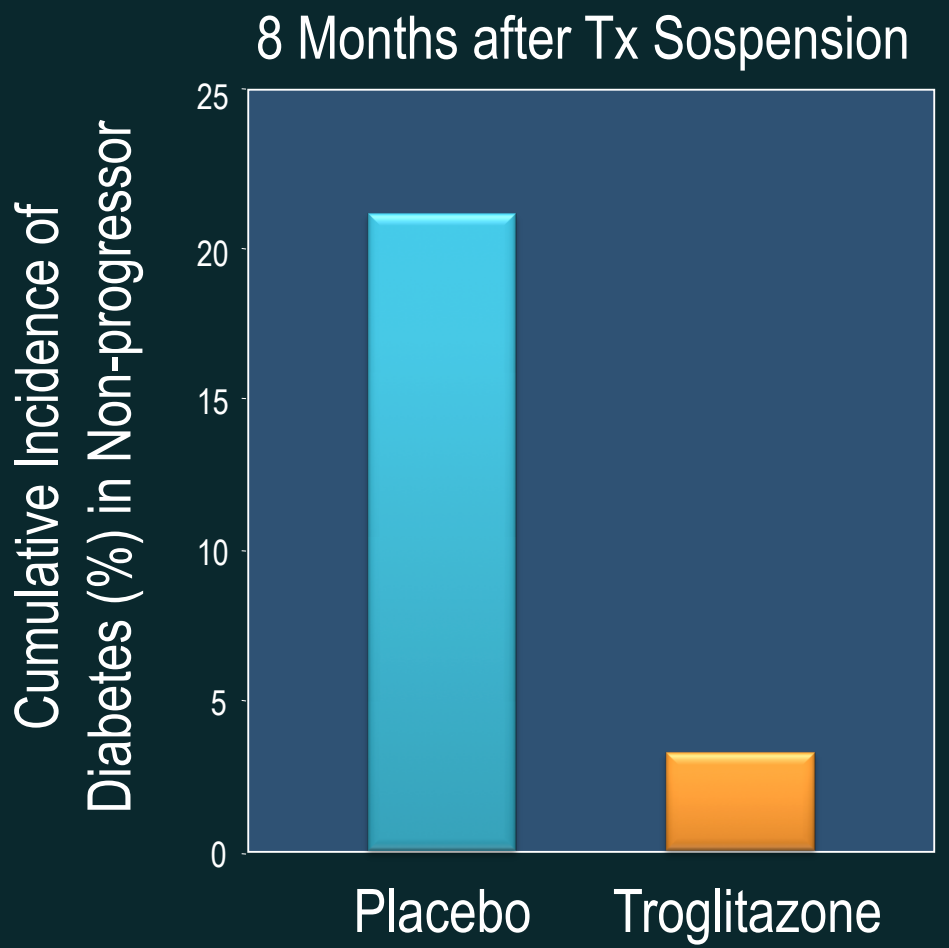
Studio TRIPOD



Buchanan TA, et al. Diabetes, 2002

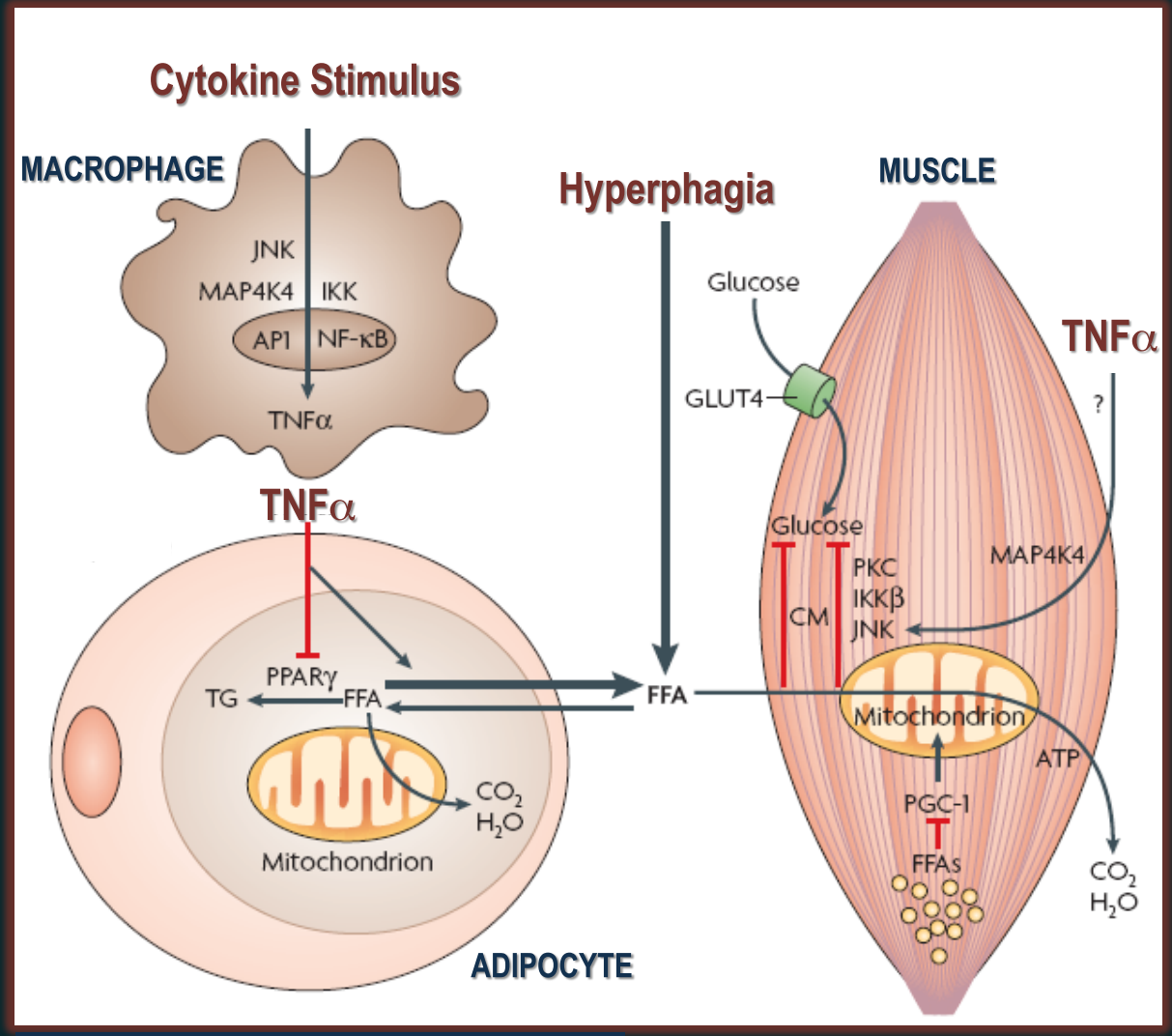
Cumulative Incidence of Diabetes in the TRIPOD Study

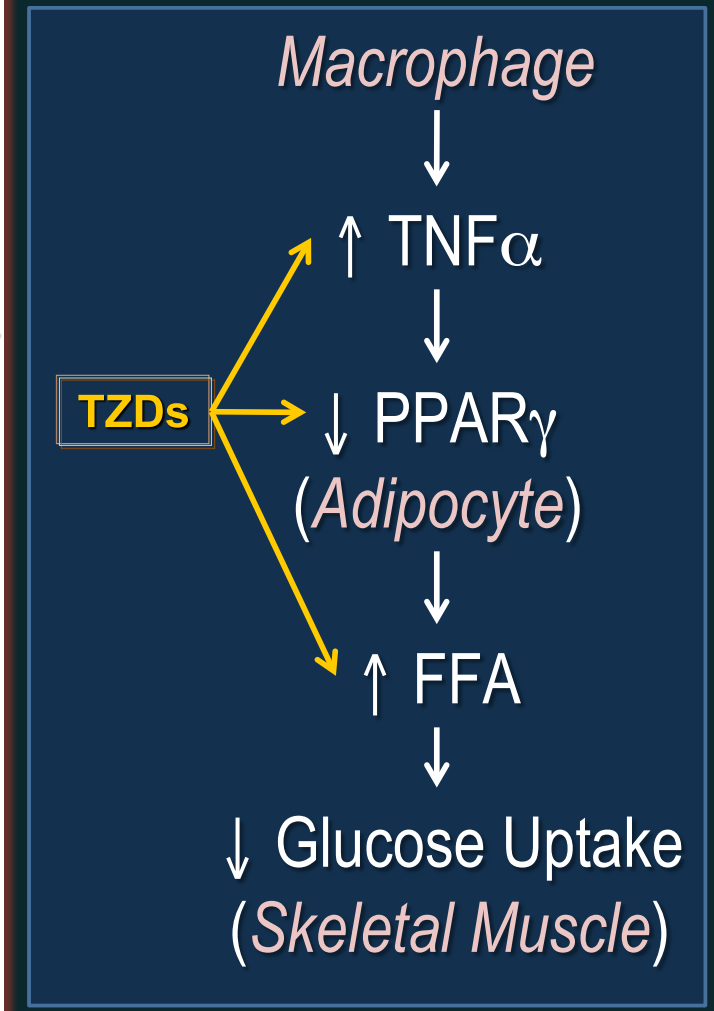




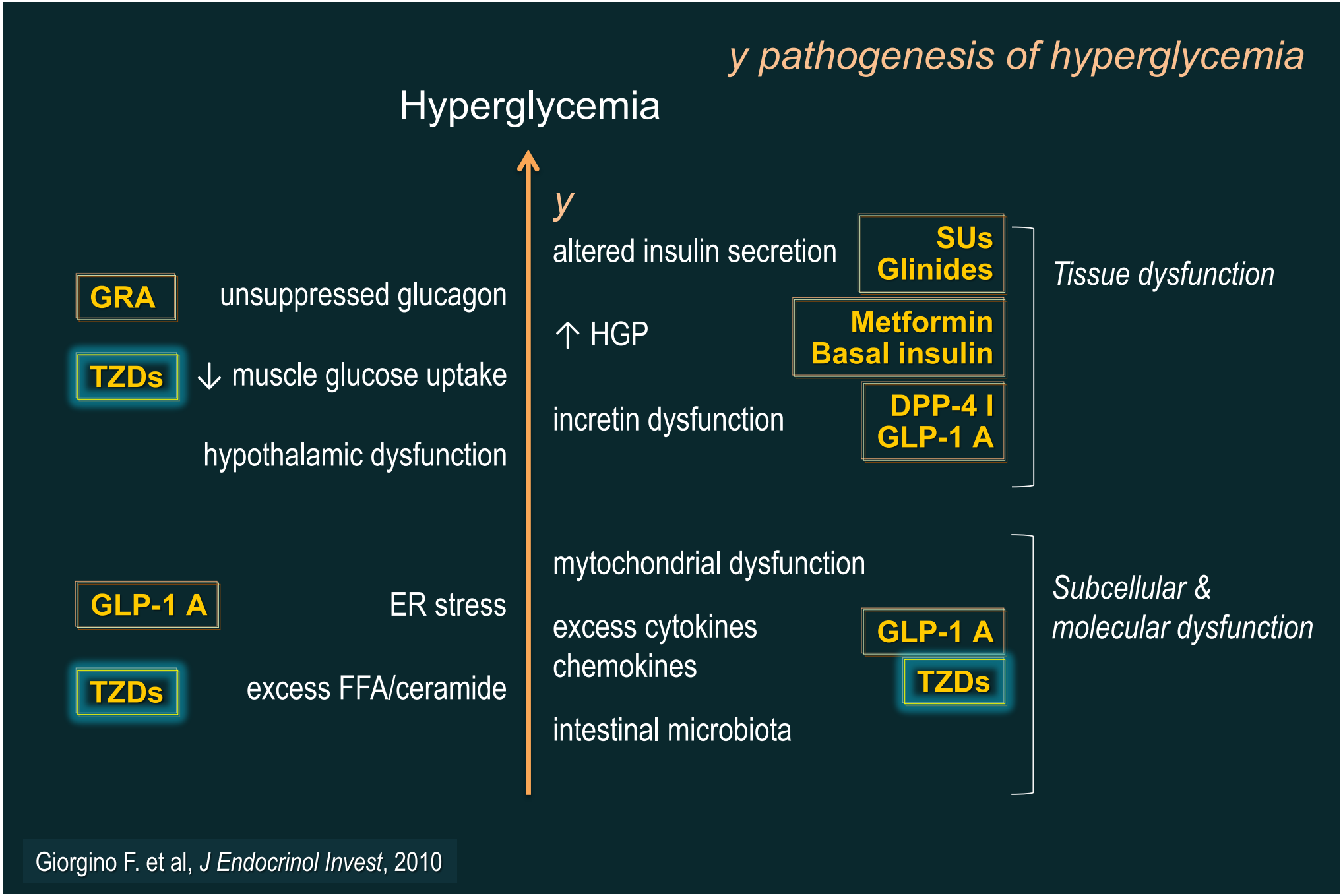
Buchanan TA et al, *Diabetes*, 2002

Adipocyte Dysfunctions Linking Obesity to Insulin Resistance and Type 2 Diabetes



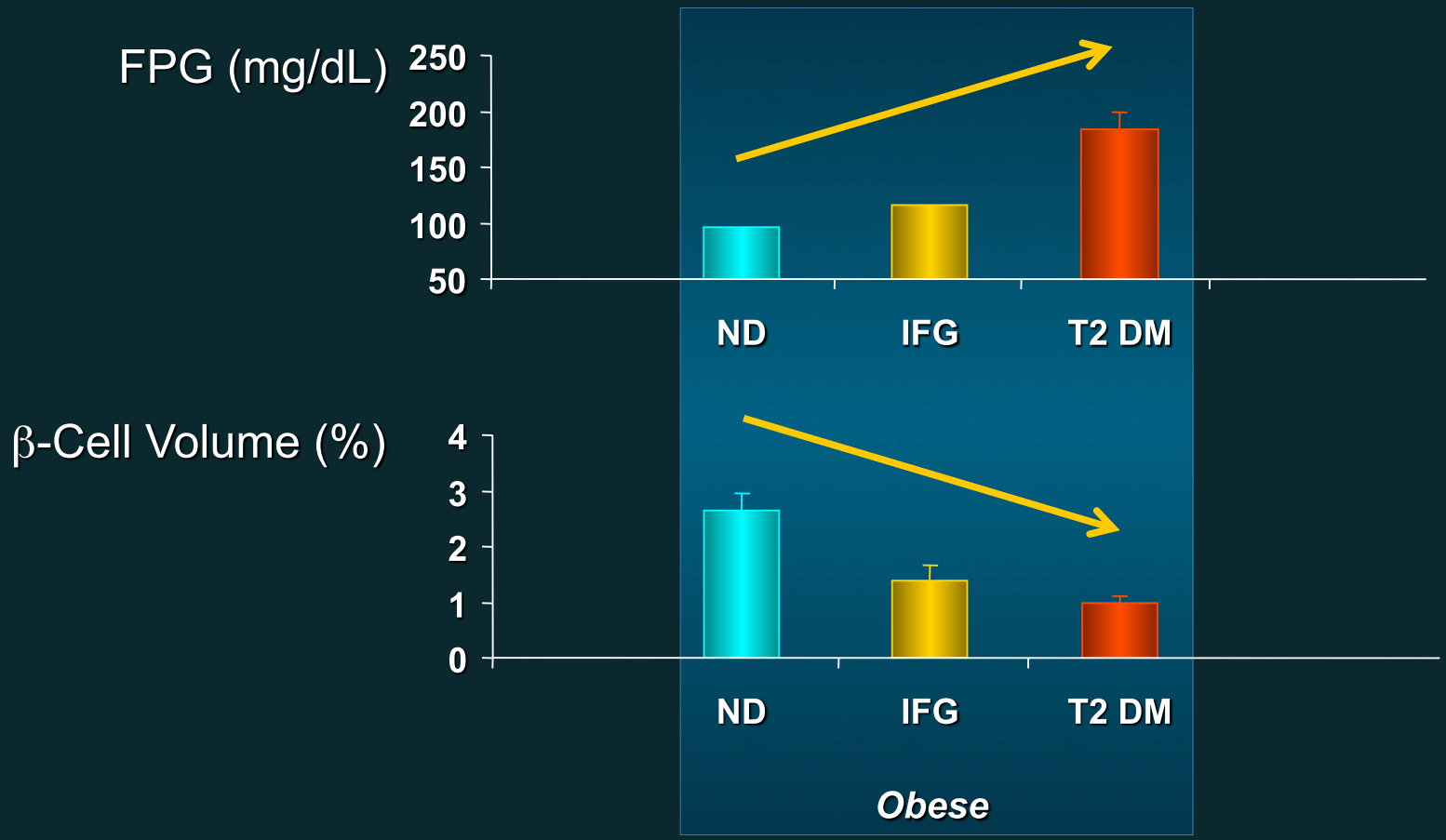


Guilherme A et al, *Nature Rev*, 2008



Giorgino F. et al, *J Endocrinol Invest*, 2010

Decrease in β-Cell Volume in Type 2 DM



ND=nondiabetic; IFG=impaired fasting glucose; FPG=fasting plasma glucose.

Adapted from Butler AE et al. *Diabetes*. 2003;52:102–110.

Caratteristiche Generali dei Pazienti in Studio

Esordio Dopo 5 anni

(M=117/F=116)	media	ES
Età	61.1	0.5
Peso	**77.6**	**0.9**
BMI	**30**	**0.3**
FPG	150.3	3.2
HbA1c	**6.8**	**0.1**
PAS	**134.7**	**1.2**
PAD	**79.8**	**0.6**
Colesterolo totale	**205.8**	**2.8**
TG	**166.1**	**7.8**
HDL	47.8	0.9
LDL	**130.1**	**2.8**
GOT	25.1	1.1
GPT	35.2	1.6
AER	17.2	2.5

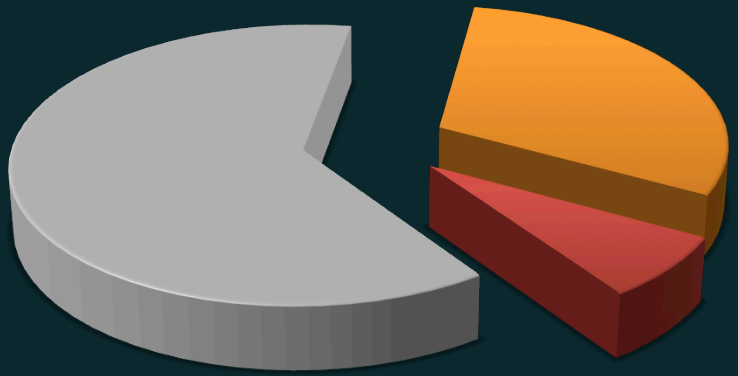
Pazienti a Target alla Diagnosi e Dopo 5 Anni

%	HbA1c	LDL	HDL	TG	PA
Esordio	**48.1**	**25.9**	52.1	**60.6**	**58.7**
Dopo 5 aa.	**36.1**	**42.6**	54.8	**69.7**	**75.4**
	*	*	n.s.	*	*

* p<0.001 Chi-quadrato

Farmacoterapia Ipoglicemizzante alla Diagnosi e dopo 5 Anni

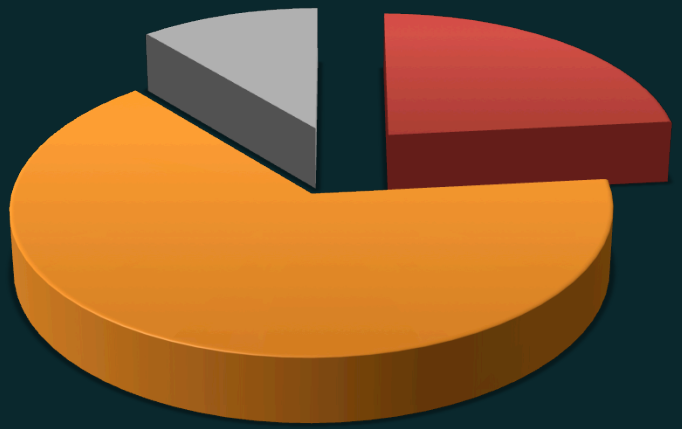
All'esordio



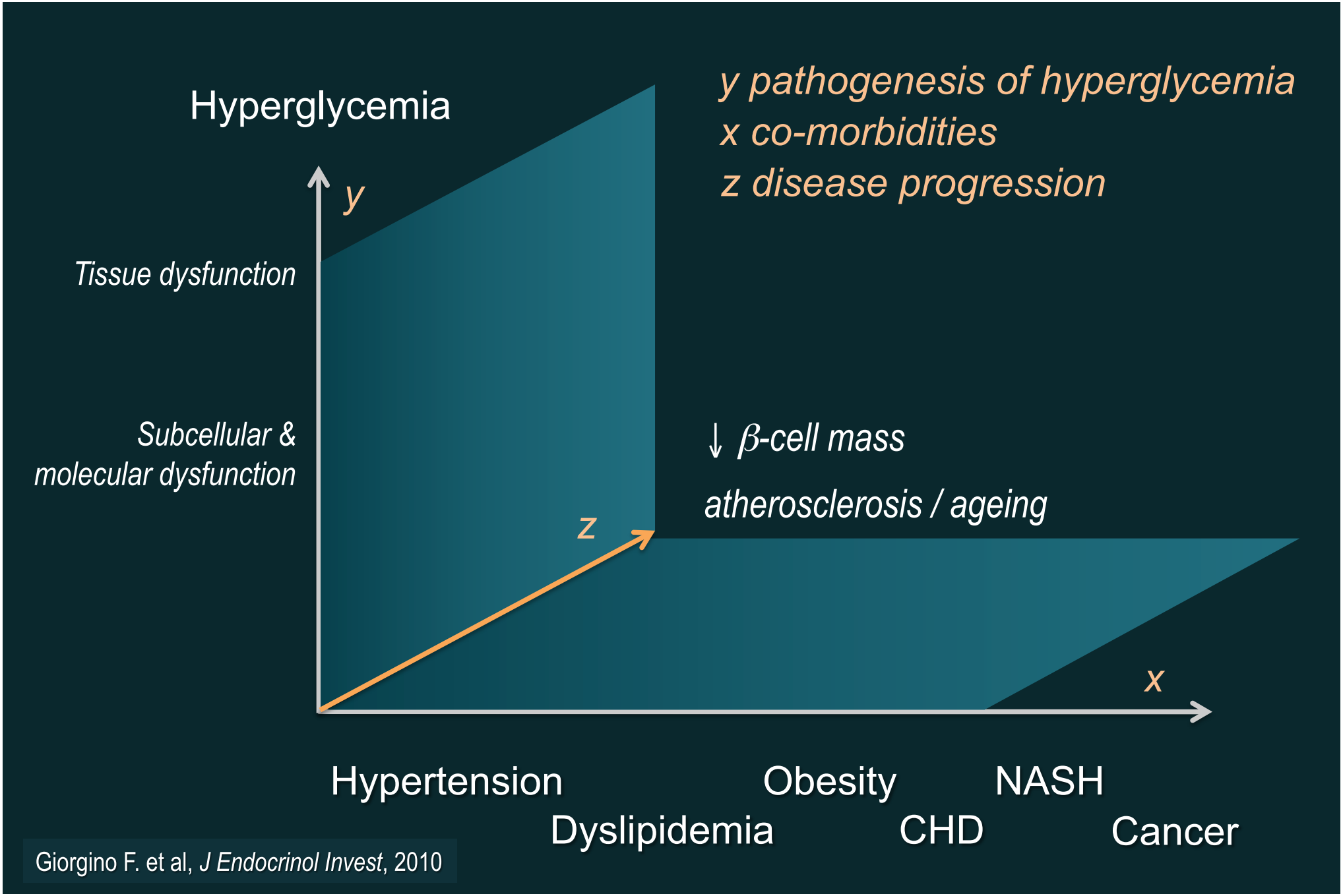
Dieta
Monoterapia
Politerapia

Dopo 5 anni

*

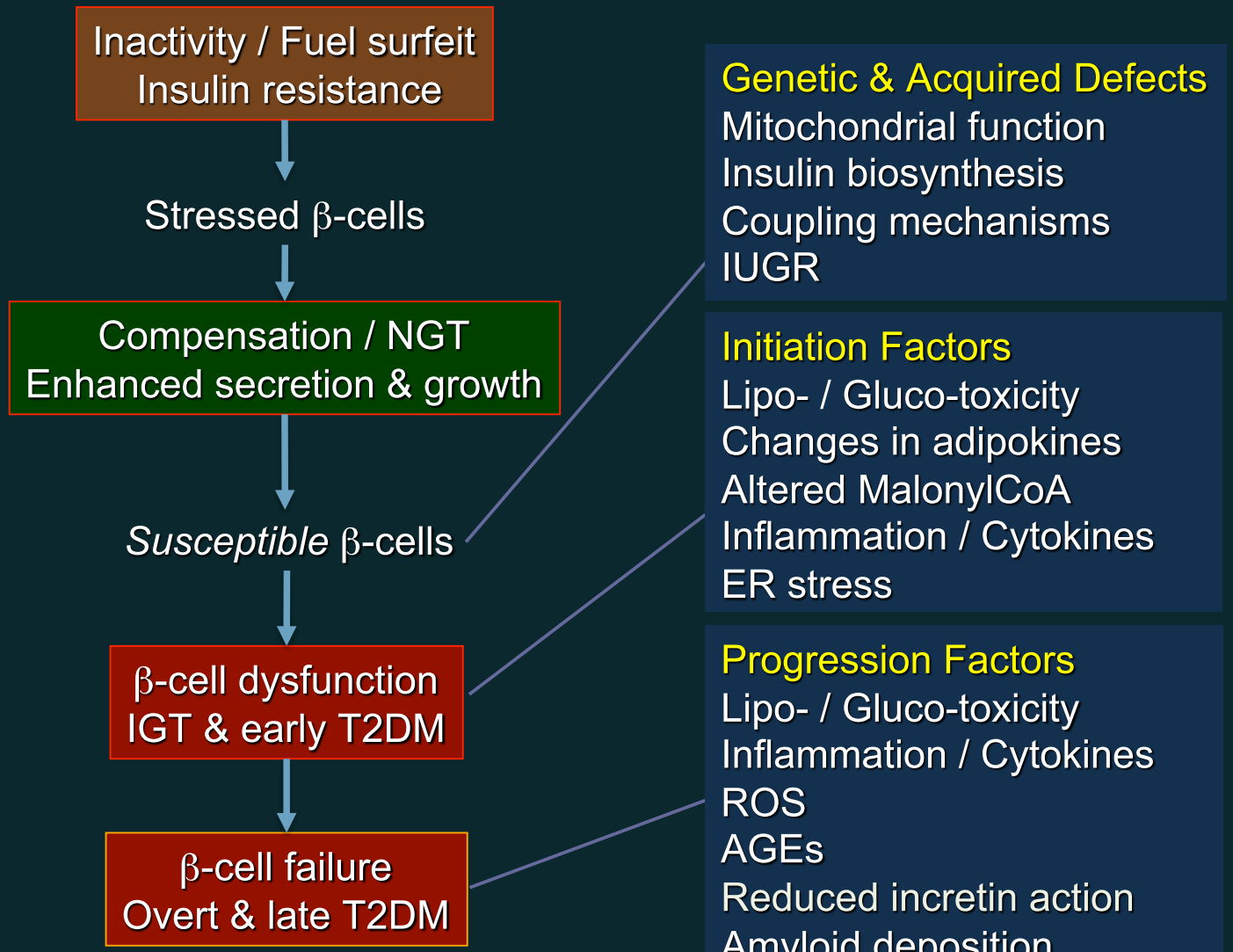


* p<0,001 Chi-quadrato



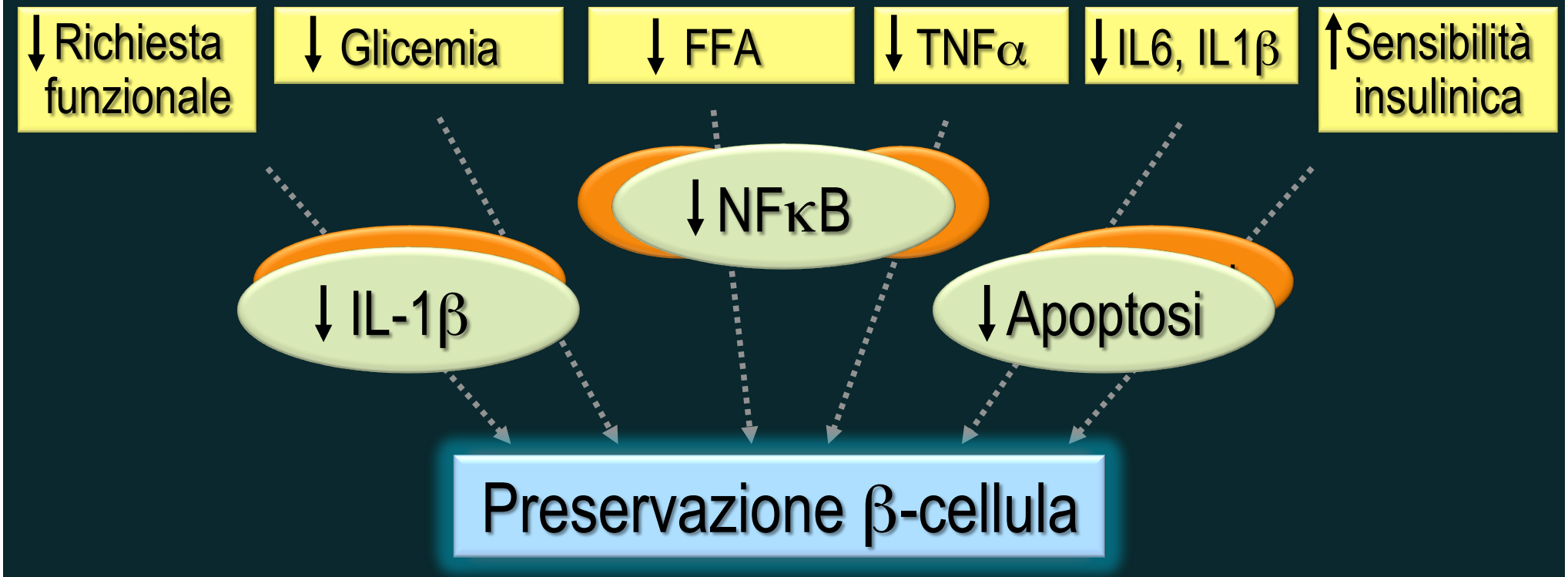
Giorgino F. et al, *J Endocrinol Invest*, 2010

Mechanisms of β-Cell Failure in T2DM



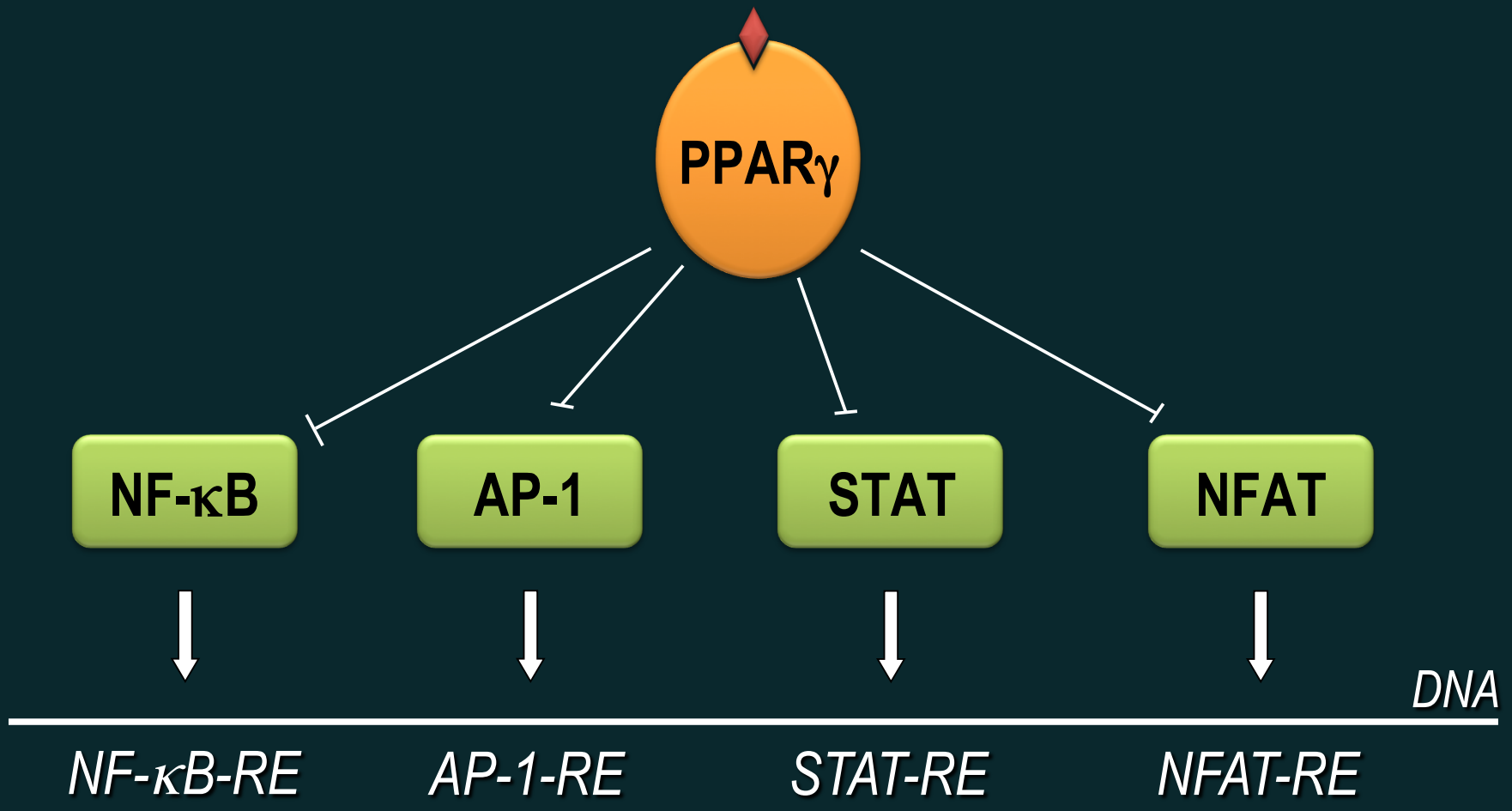
Adapted from Prentki M et al., *J. Clin. Invest.*, 2006

Effetti Protettivi dei Glitazoni sulla β-Cellula

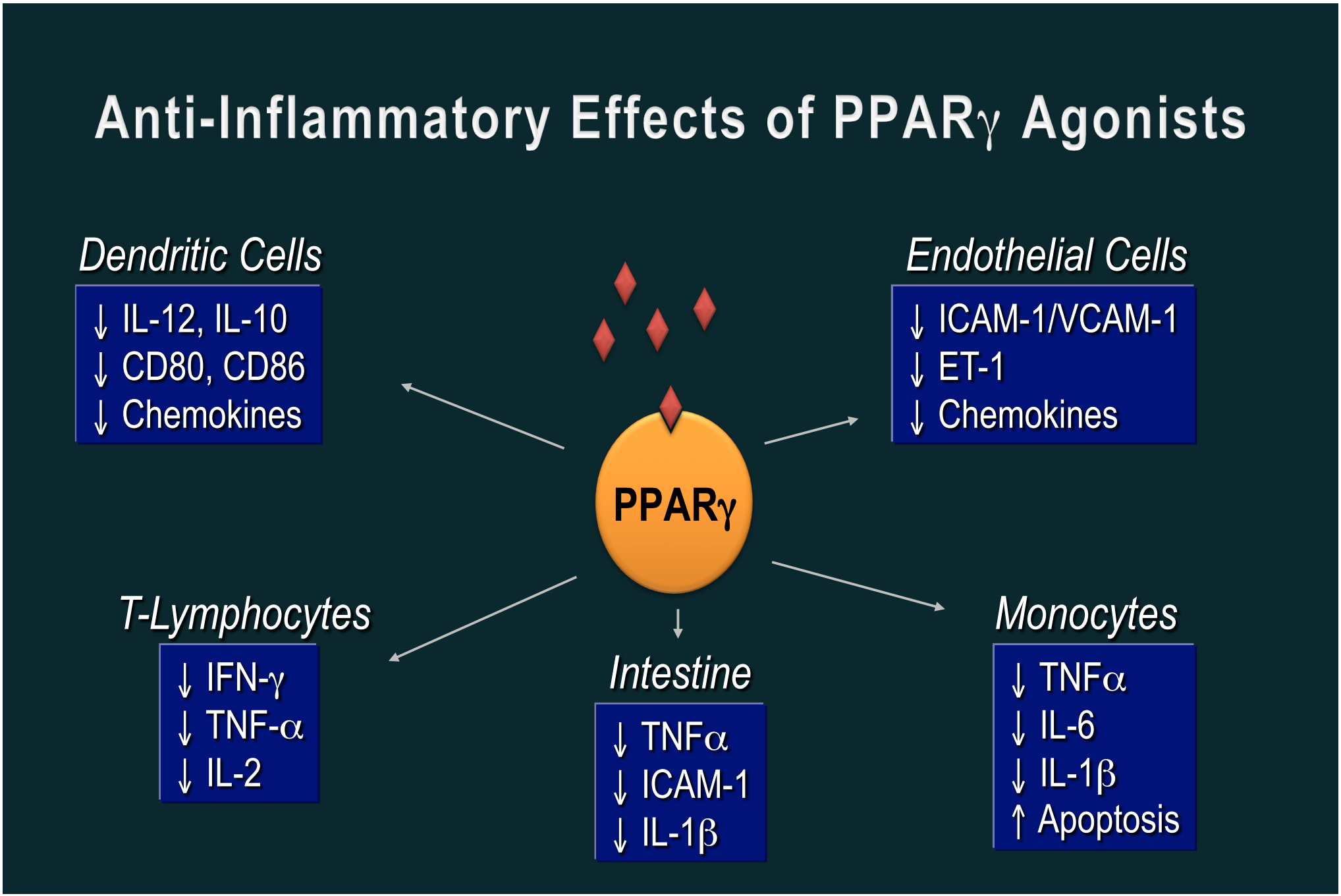


PPARγ – Mechanism of Action

Transcriptional Transrepression

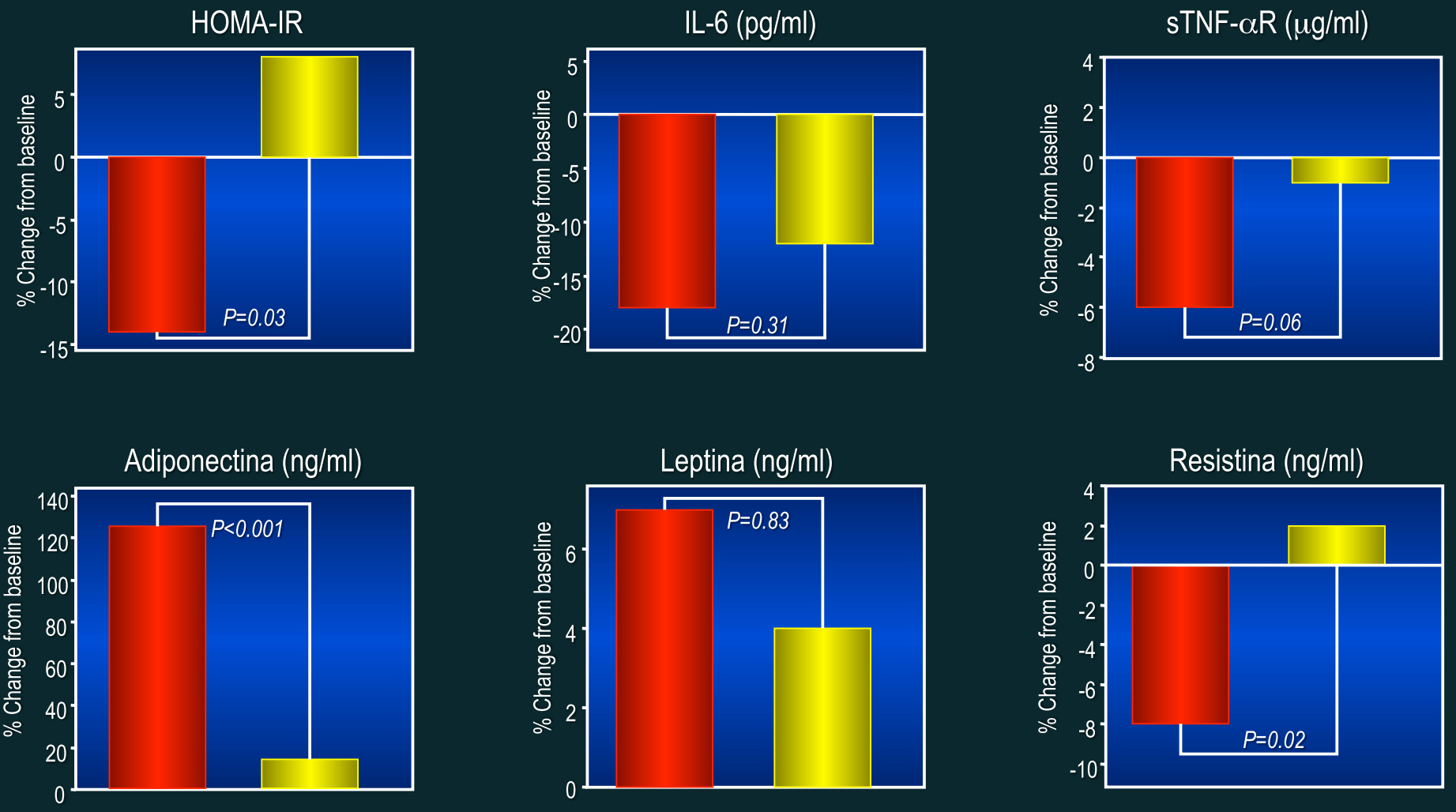


Anti-Inflammatory Effects of PPARγ Agonists



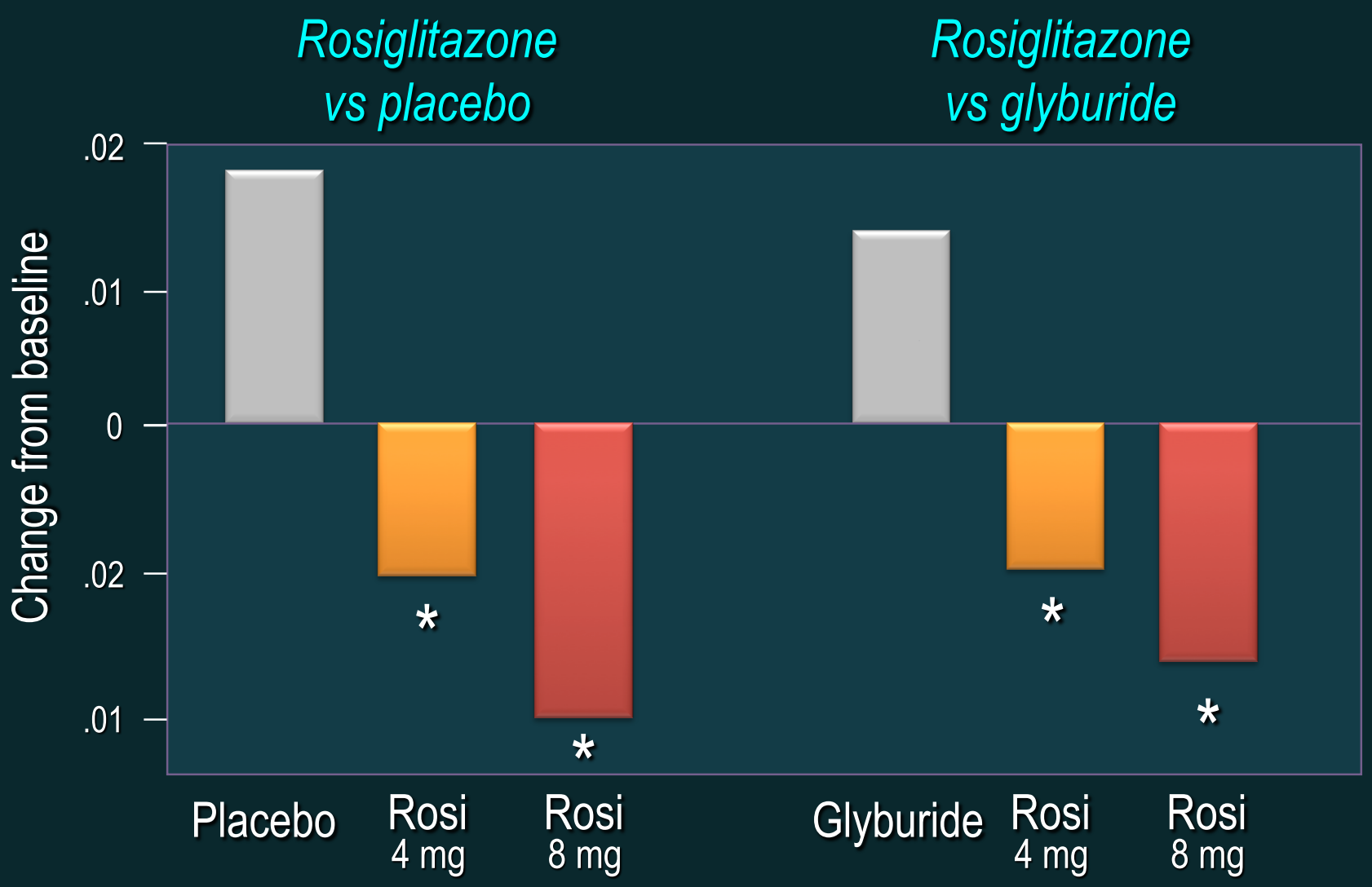
Effetti del Pioglitazone su Insulino-Resistenza, Indici di Infiammazione e Adipochine

60 soggetti con SM – pioglitazone vs placebo per 12 settimane



Szapary PO et al, ATVB, 2006

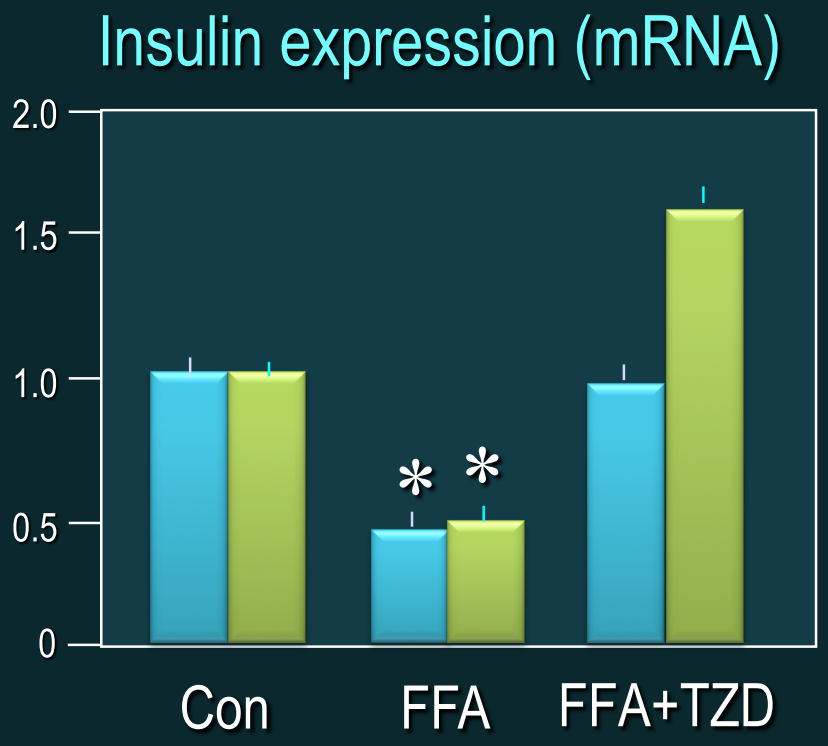
Proinsulin/Insulin Ratio in T2DM Patients

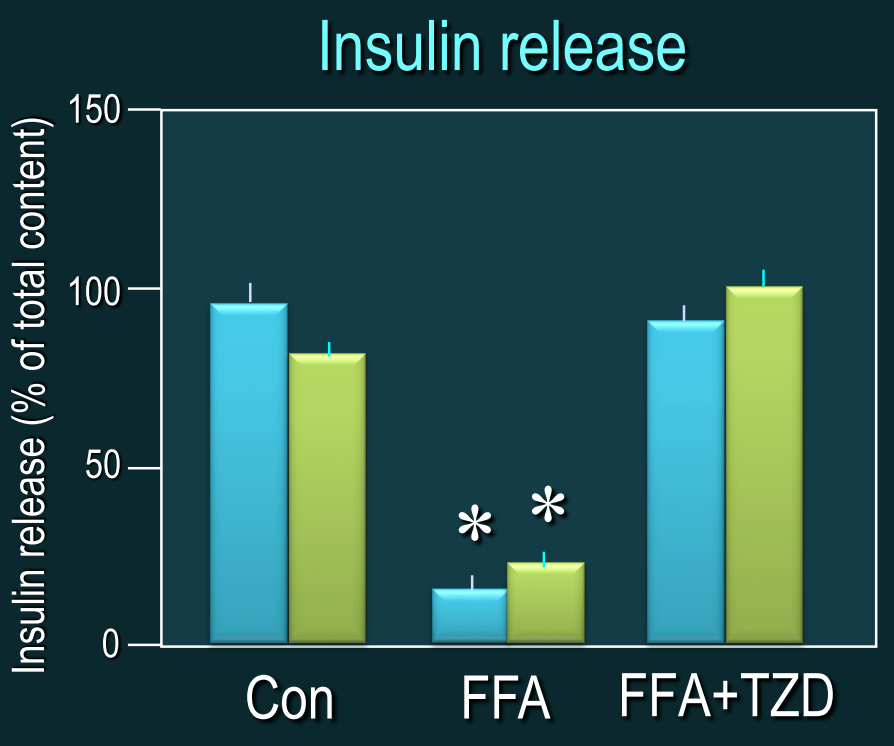


Zinman B, Diabetes Obes Metab, 2001

Protection from FFA-induced β-Cell Damage

Human islets





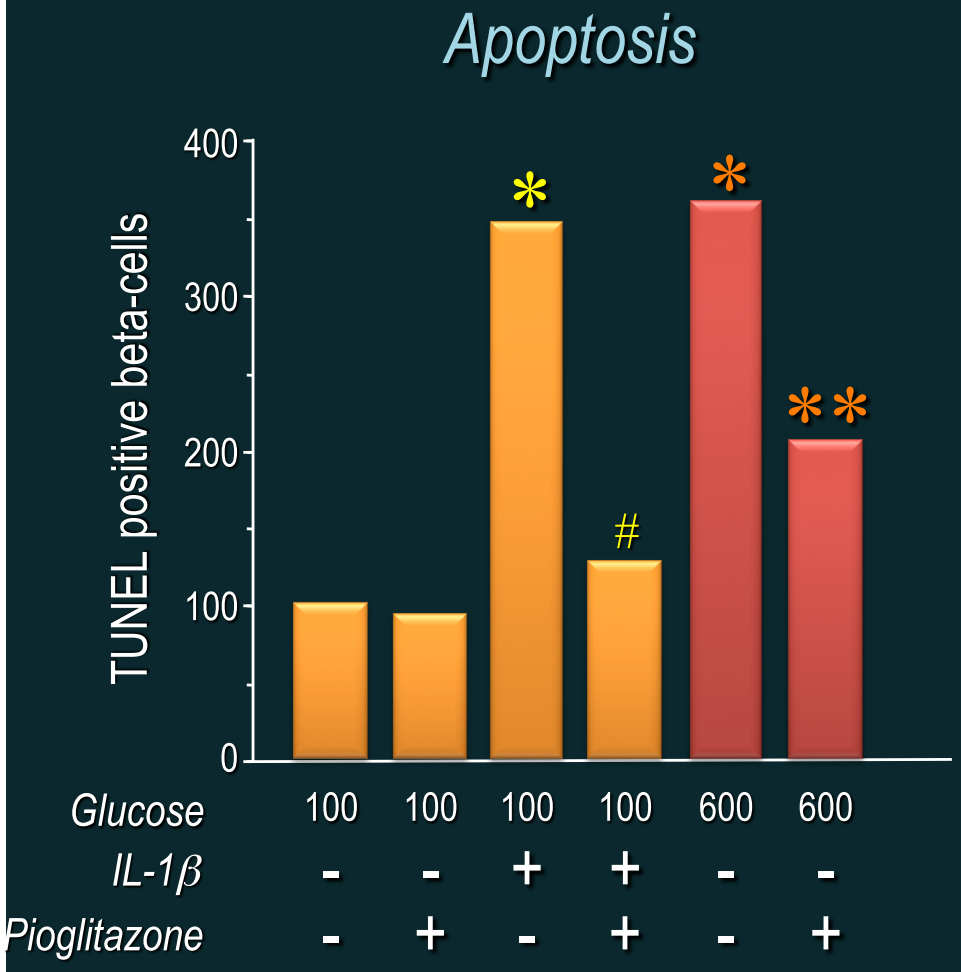
Rosiglitazone

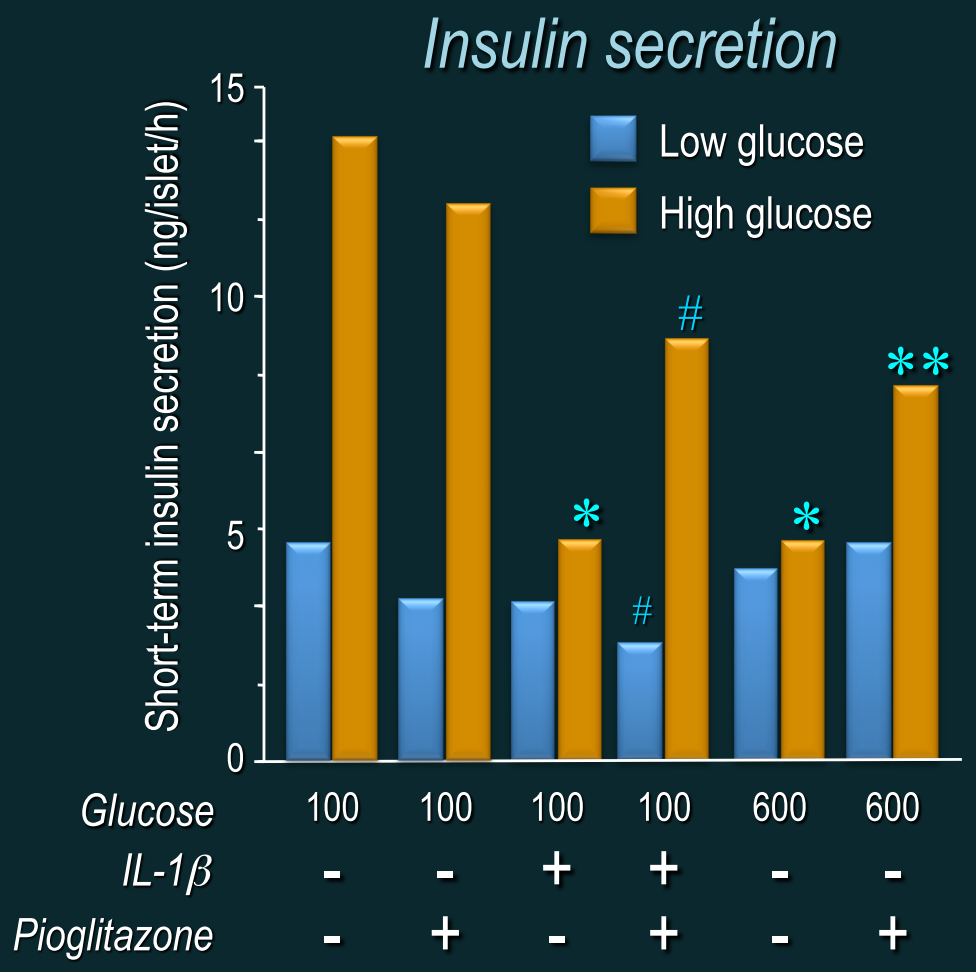
PGJ2

Lupi, R. et al. Am J Physiol Endocrinol Metab, 2004

Protection from Cytokine- or Glucose-induced Dysfunction

Human islets



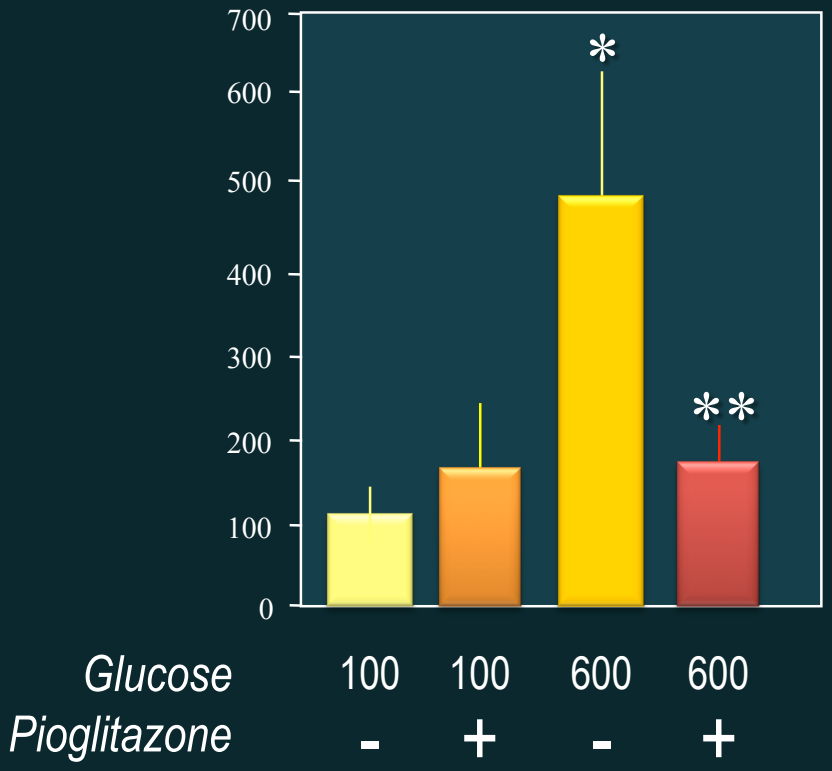


Zeender E et al, J Clin Endocrinol Metab, 2004

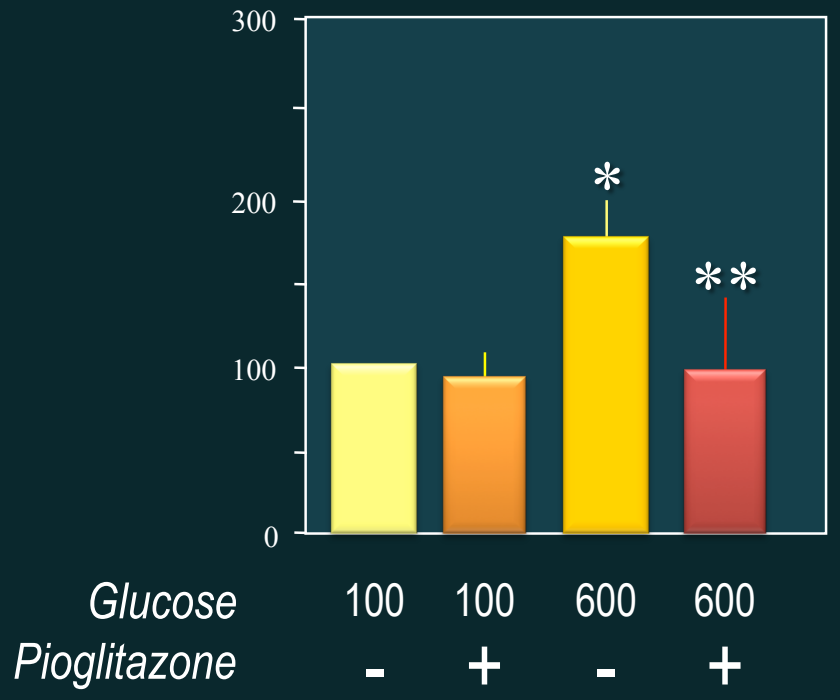
Modulation of Inflammatory Pathways

Human islets

IL-1β secretion

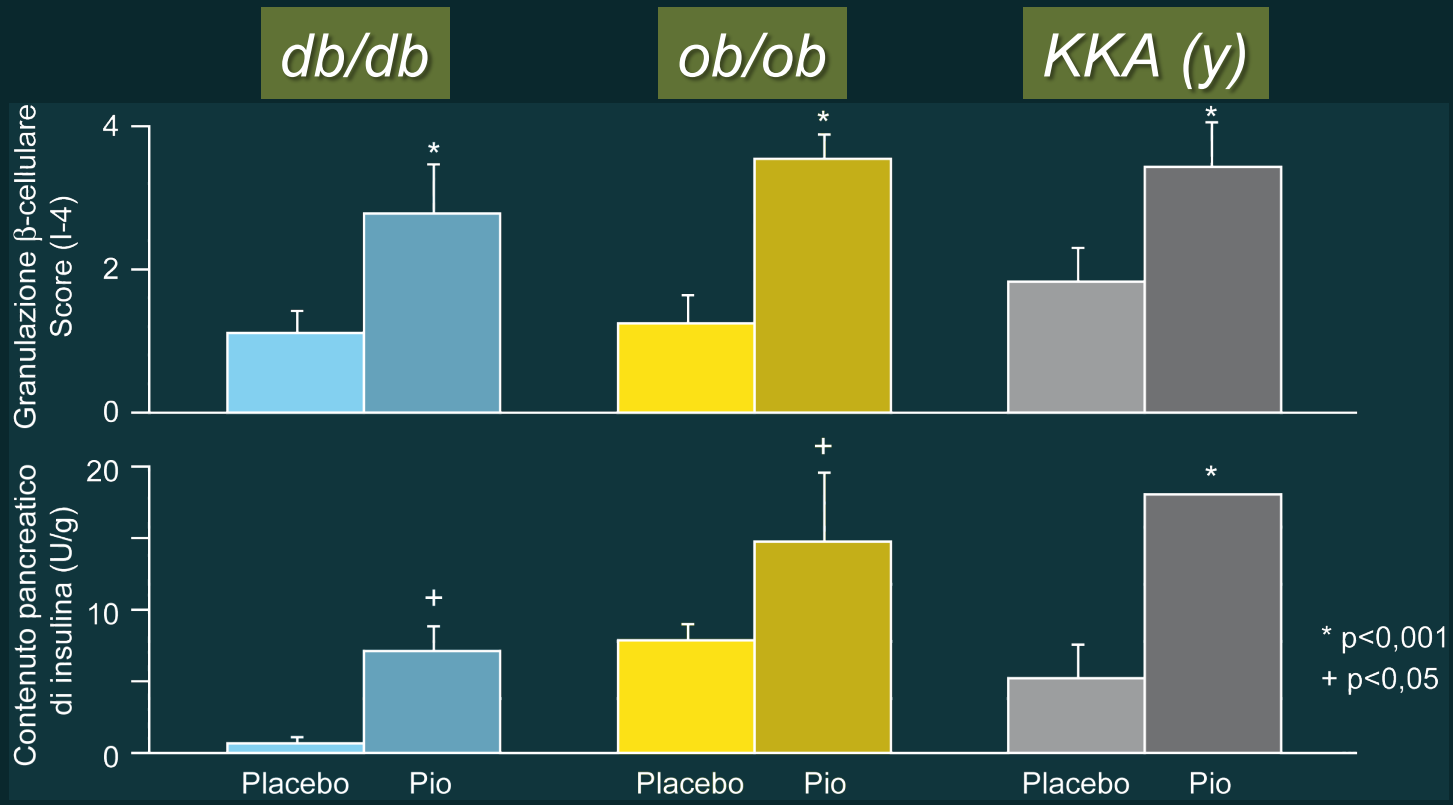


NFκB activity



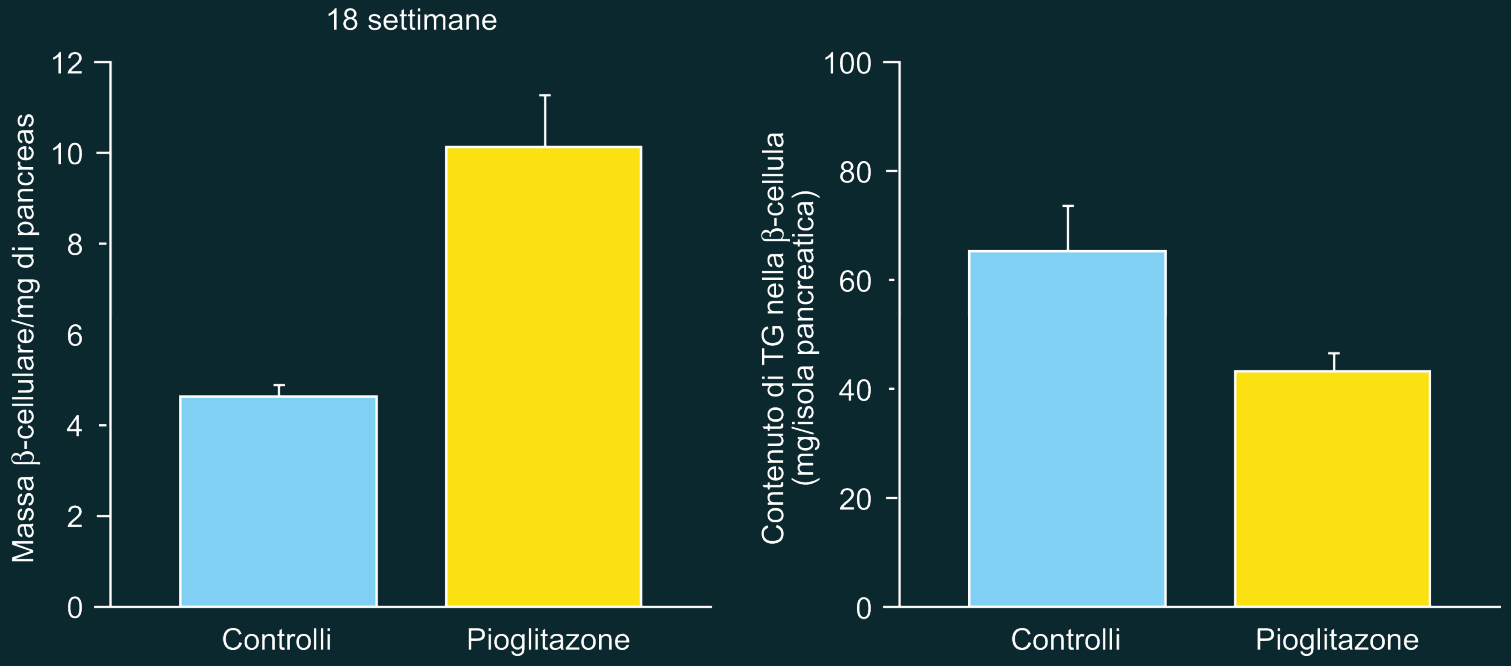
Zeender, E. et al. J Clin Endocrinol Metab 2004

Effetti del Pioglitazone sulla Struttura delle Isole Pancreatiche nel Topo Diabetico



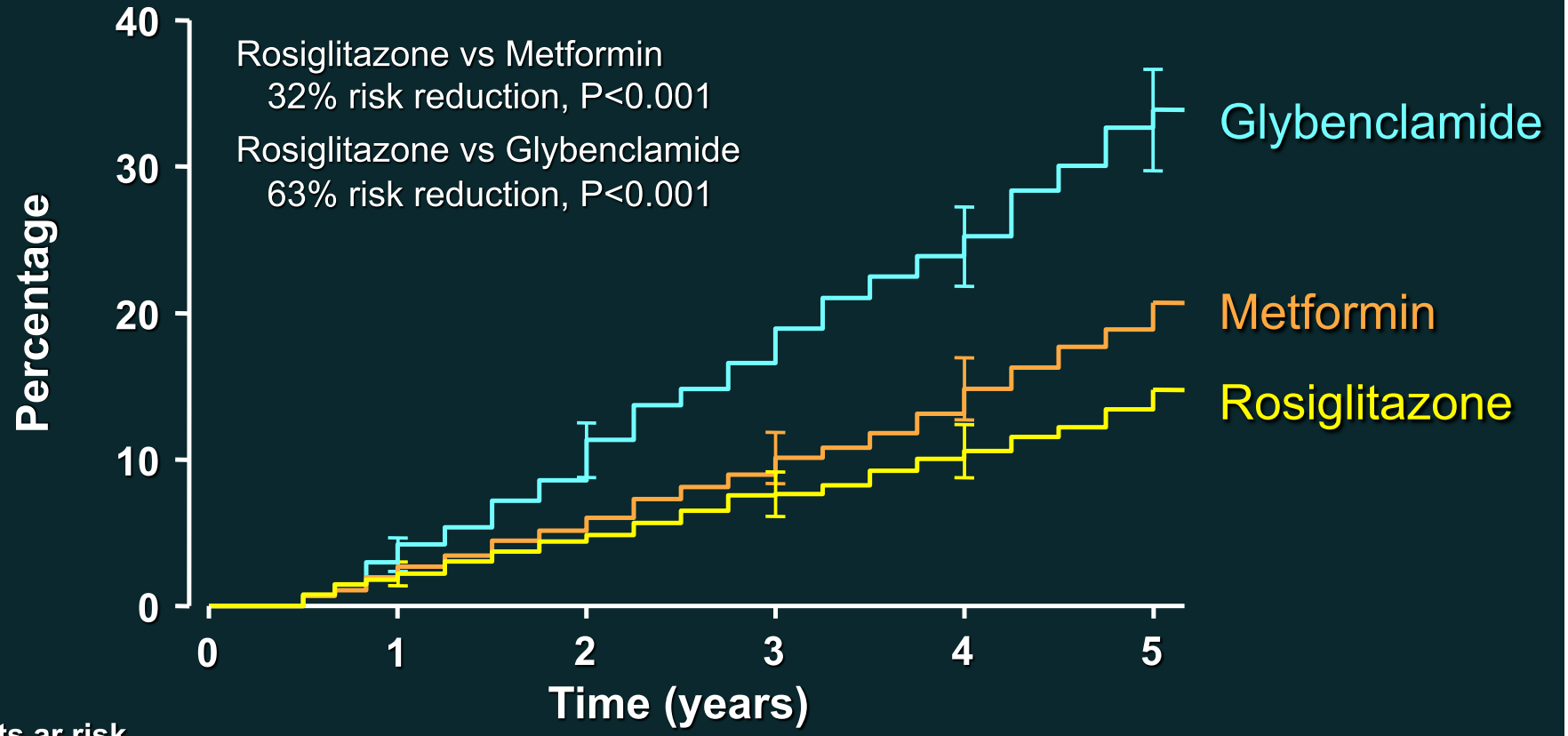
Diani AR et al. Am J Physiol Endocrinol Metab 286:E116-E122, 2004

Effetti di Pioglitazone sulla Massa e sul Grasso Ectopico β-Cellulare nel Topo db/db



Kawasaki F et al. Am J Physiol Endocrinol Metab 288:E510-E518, 2005

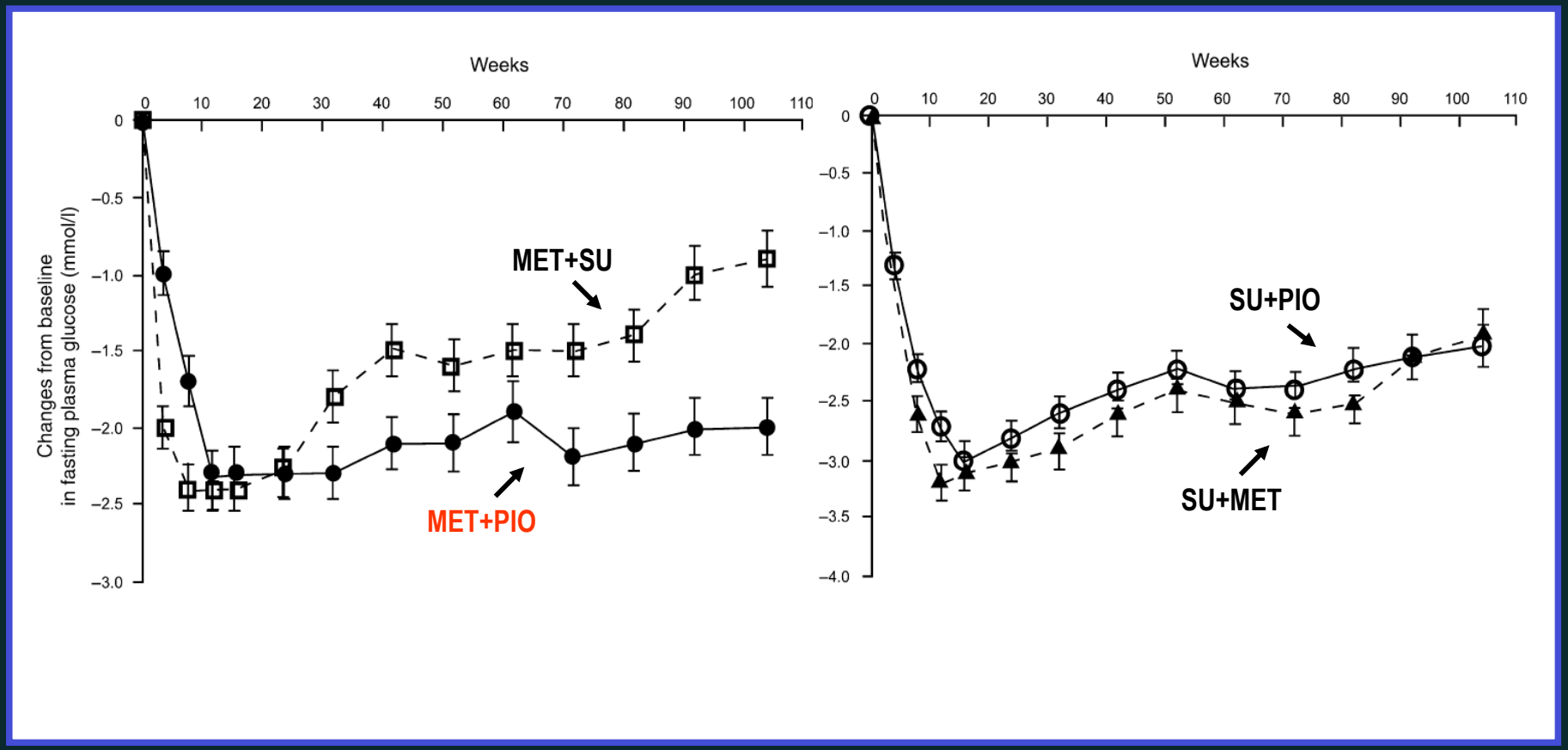
Primary Endpoint: Time to Monotherapy Failure
(Fasting Blood Glucose >180 mg/dl)



Patients ar risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glybenclamide	1337	1114	958	781	617	218

Kahn SE et al. *N Engl J Med*, 2006

Long-term Efficacy of Add-on Pioglitazone Tx to Failing Metformin or SU Monotherapy in T2DM

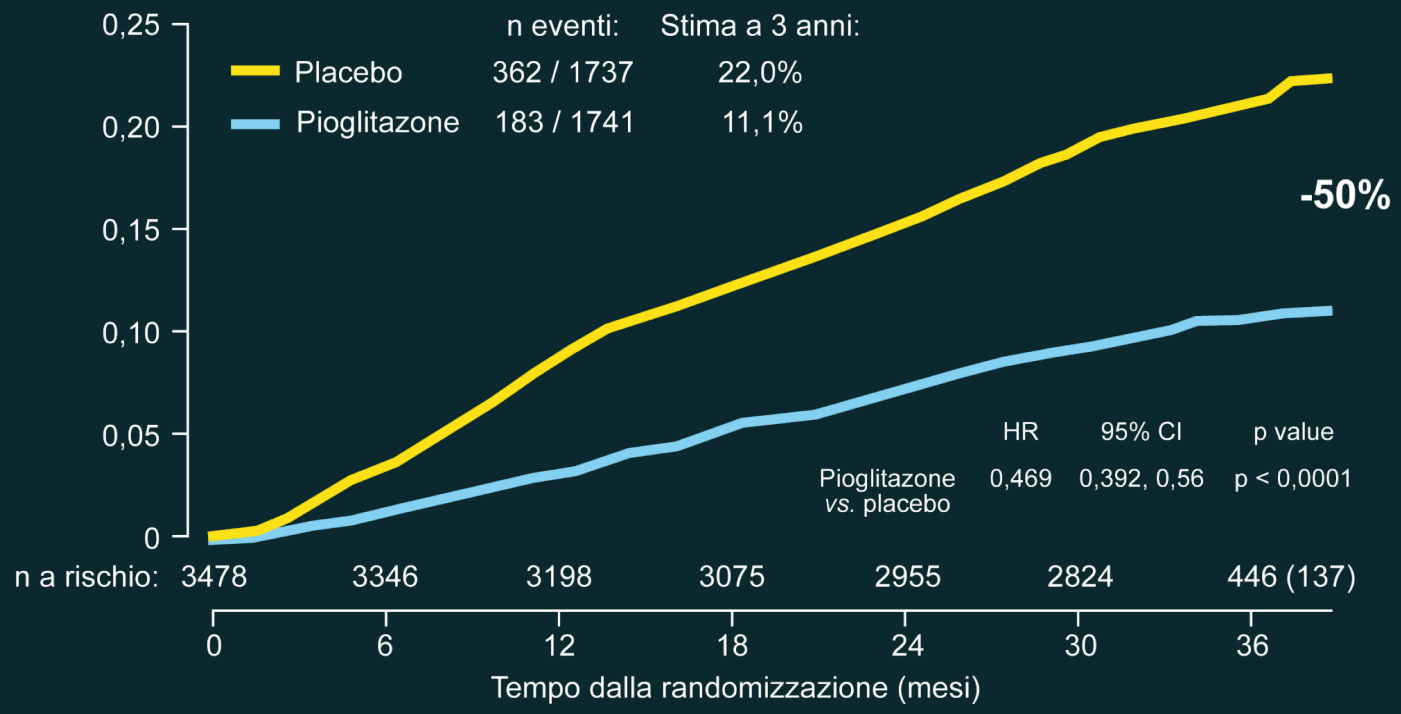


Charbonnel et al. Diabetologia 2005; 48: 1093–1104

Tempo all'Uso Permanente di Insulina

Studio PROactive

Tasso di eventi Kaplan-Meyer di progressione all'uso permanente di Insulina



Dormandy JA et al. Lancet 366:1279–89, 2005

Obiettivi Terapeutici nel Diabete di Tipo 2

- Ridurre i livelli di HbA_1c attraverso la riduzione dei livelli di glicemia a digiuno e post-prandiale
- Controllare i fattori di rischio CV tradizionali (PA, lipidi, fumo) e non tradizionali (PCR, PAI-1, Albuminuria)
- Ridurre gli eventi e la mortalità CV
- Evitare l'aumento di peso
- Preservare la massa β-cellulare
- Ridurre la progressione della malattia
- Evitare le ipoglicemie
- Favorire la *compliance* del paziente

Approccio Terapeutico Multifattoriale

Pioglitazone preserva la struttura delle insule pancreatiche e la funzione secretoria dell'insulina in tre modelli murini di DMT2

- Sono stati studiati sul topo gli effetti di pioglitazone sulla struttura e la funzione β-cellulare
- Coinvolti 3 modelli genetici murini di diabete 2: KKA(y), C57BL/6J ob/ob, C57BL/KsJ db/db
- Il trattamento con pioglitazone ha ridotto in modo significativo i livelli glicemici e di A1c
- Tutti i gruppi trattati con pioglitazone hanno mostrato un maggior livello di granulazione β-cellulare e livelli di insulina pancreatica maggiori da 1,5 a 15 volte

Diani AR et al. Am J Physiol Endocrinol Metab 286:E116-E122, 2004