



**Curs intensiu de diabetes per residents**

**Futur immediat en el camp  
de la diabetes  
Nous tractaments**

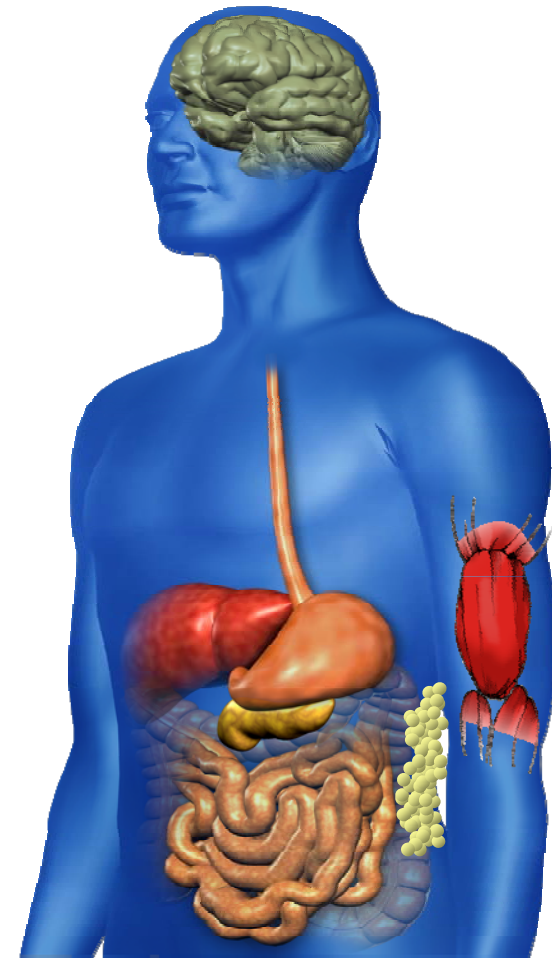
**Manel PuigDomingo**

**Servei d'Endocrinologia  
Hospital Clínic**

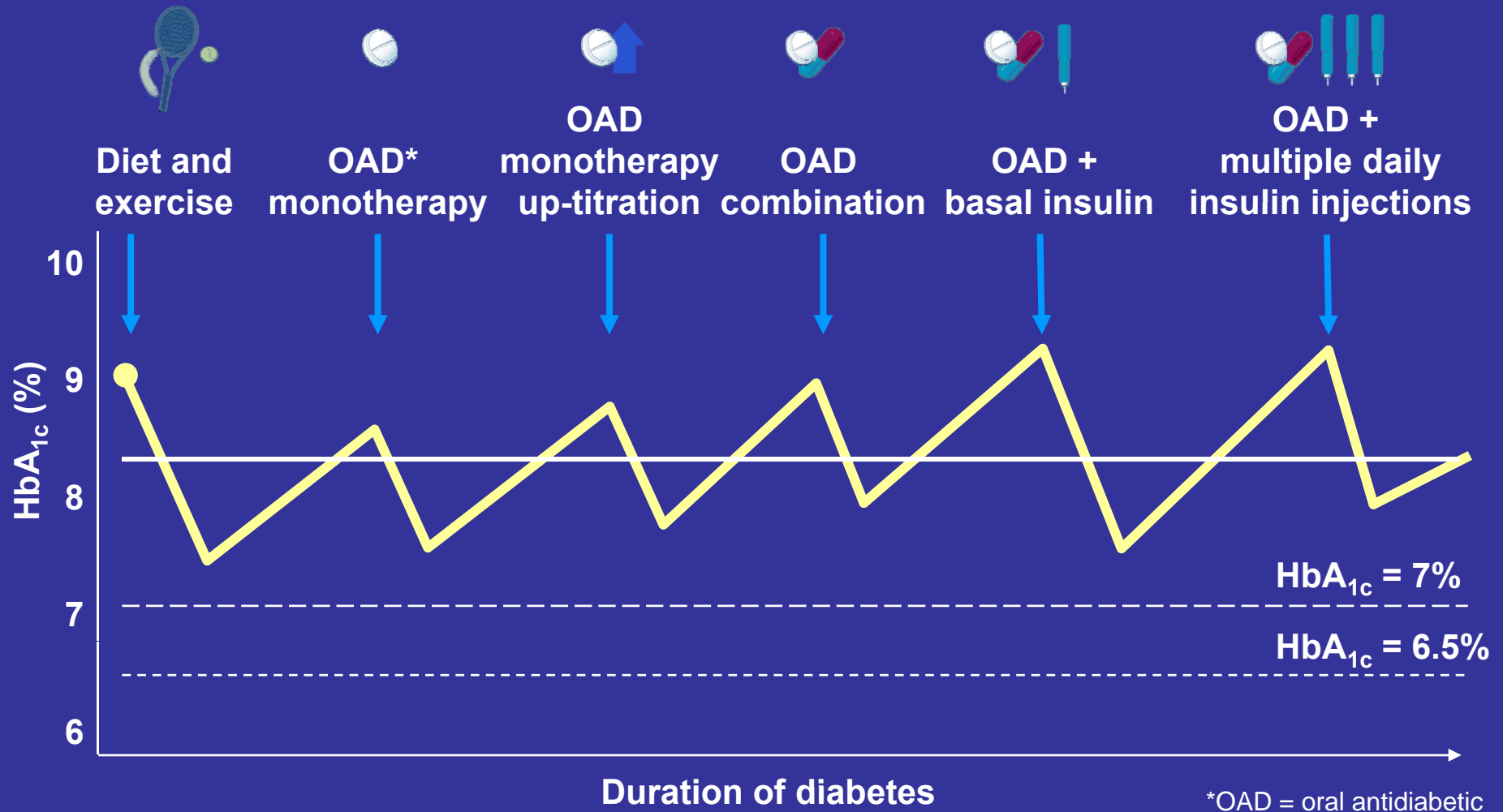
**Barcelona**

# Tratamiento fisiopatológico de la DM2

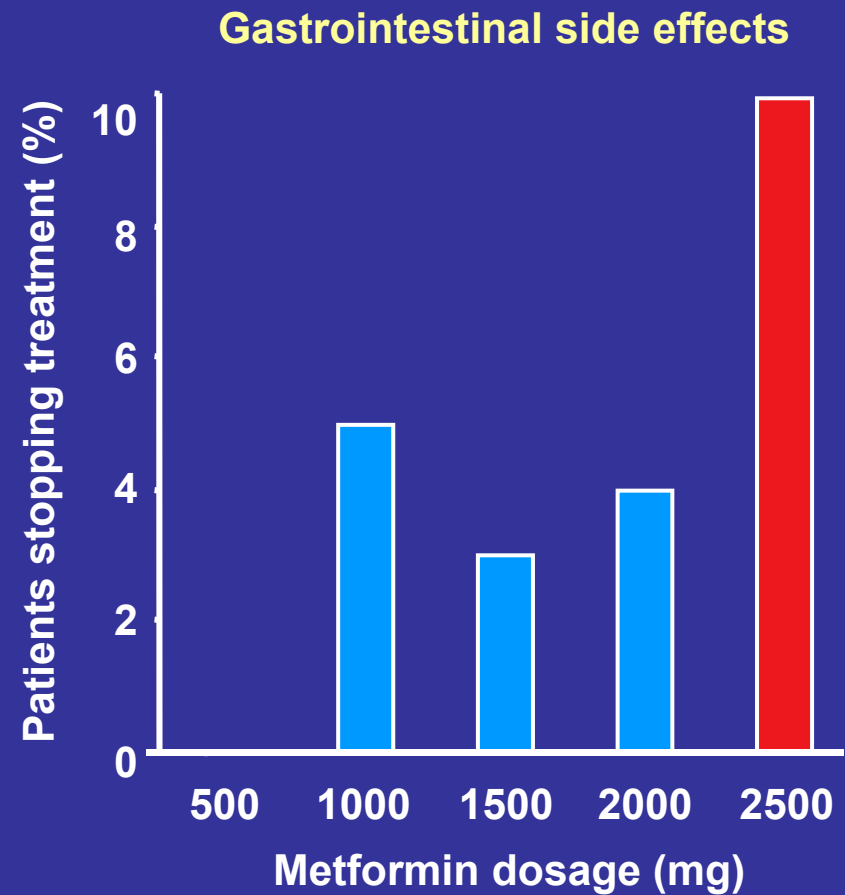
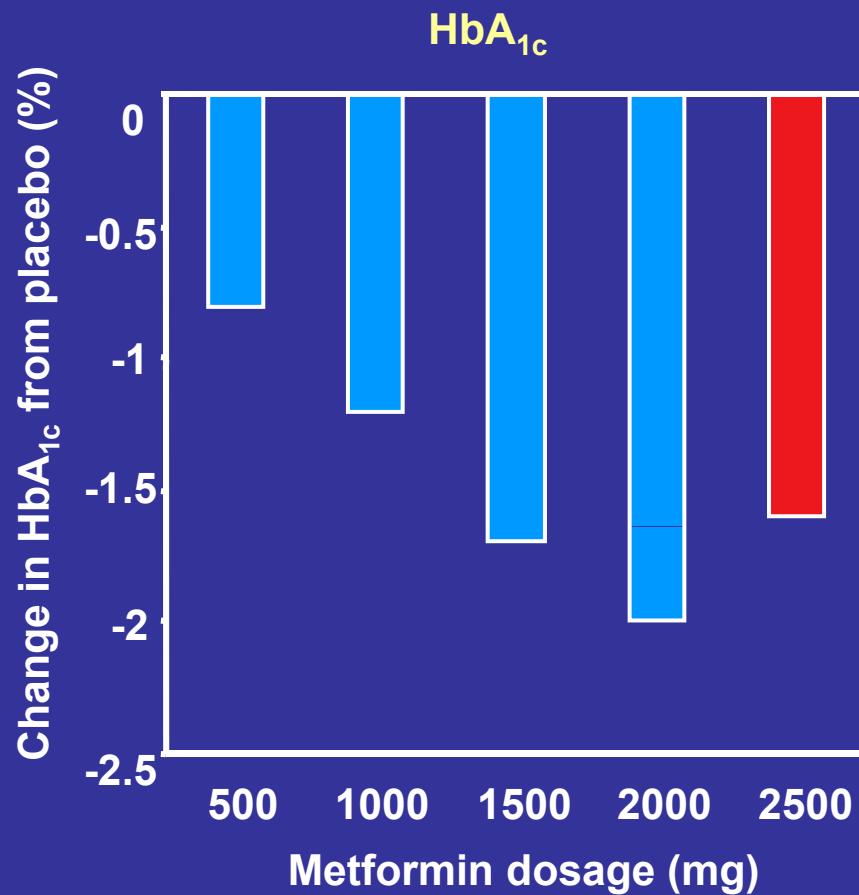
- **Actuar sobre la secreción de insulina secretagogos:** sulfonilureas y meglitinidas
- **Mejorar la respuesta a la insulina endógena:**
  - **Inhibir la producción hepática de glucosa:** Biguanidas
  - **Mejorar la resistencia a la insulina:** Biguanidas y TZD
- **Enlentecer la absorción de carbohidratos:** inhibidores de la  $\alpha$ -Glucosidasa
- **Tratamiento sustitutivo con insulina**



# Conservative management of glycemia: consequences of traditional stepwise approach

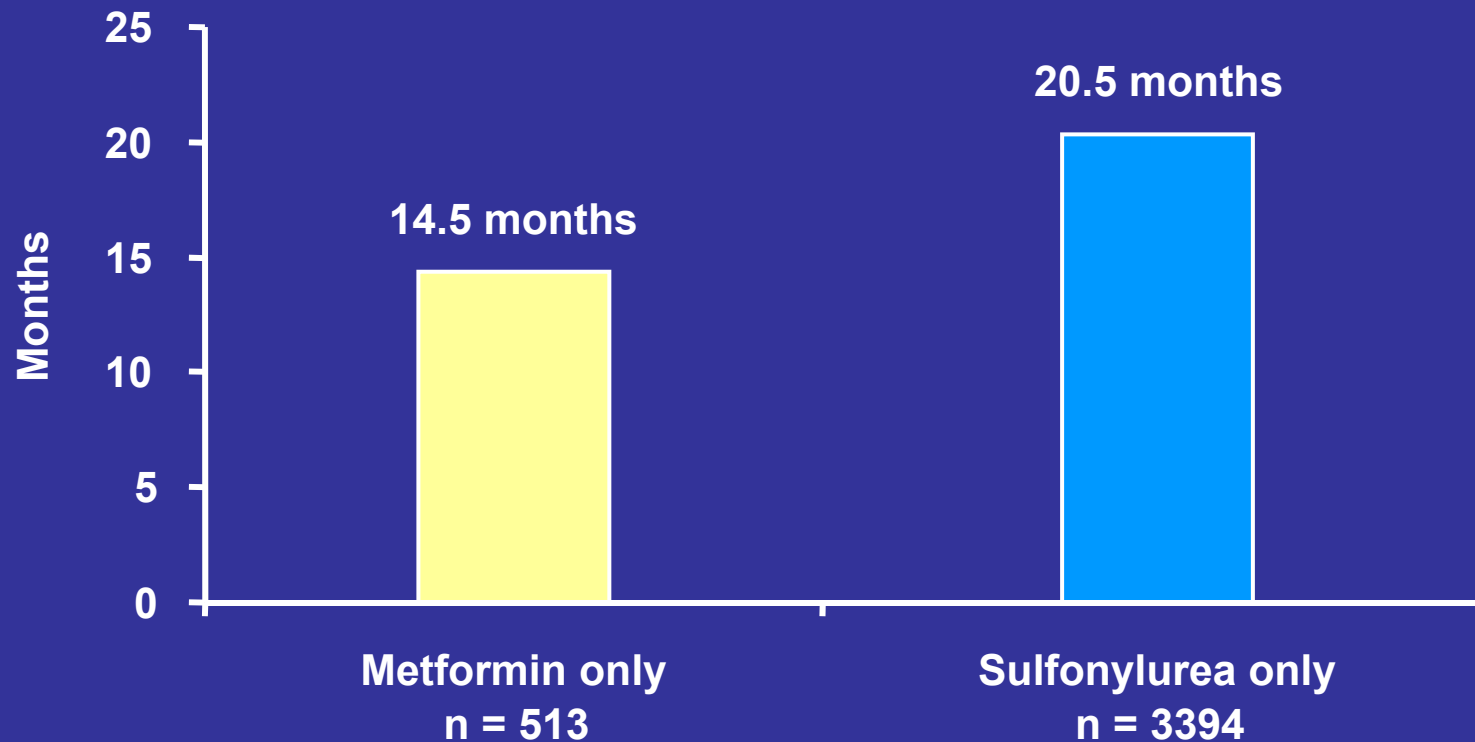


# Up-titrating monotherapy to the maximum recommended dose may not provide benefit

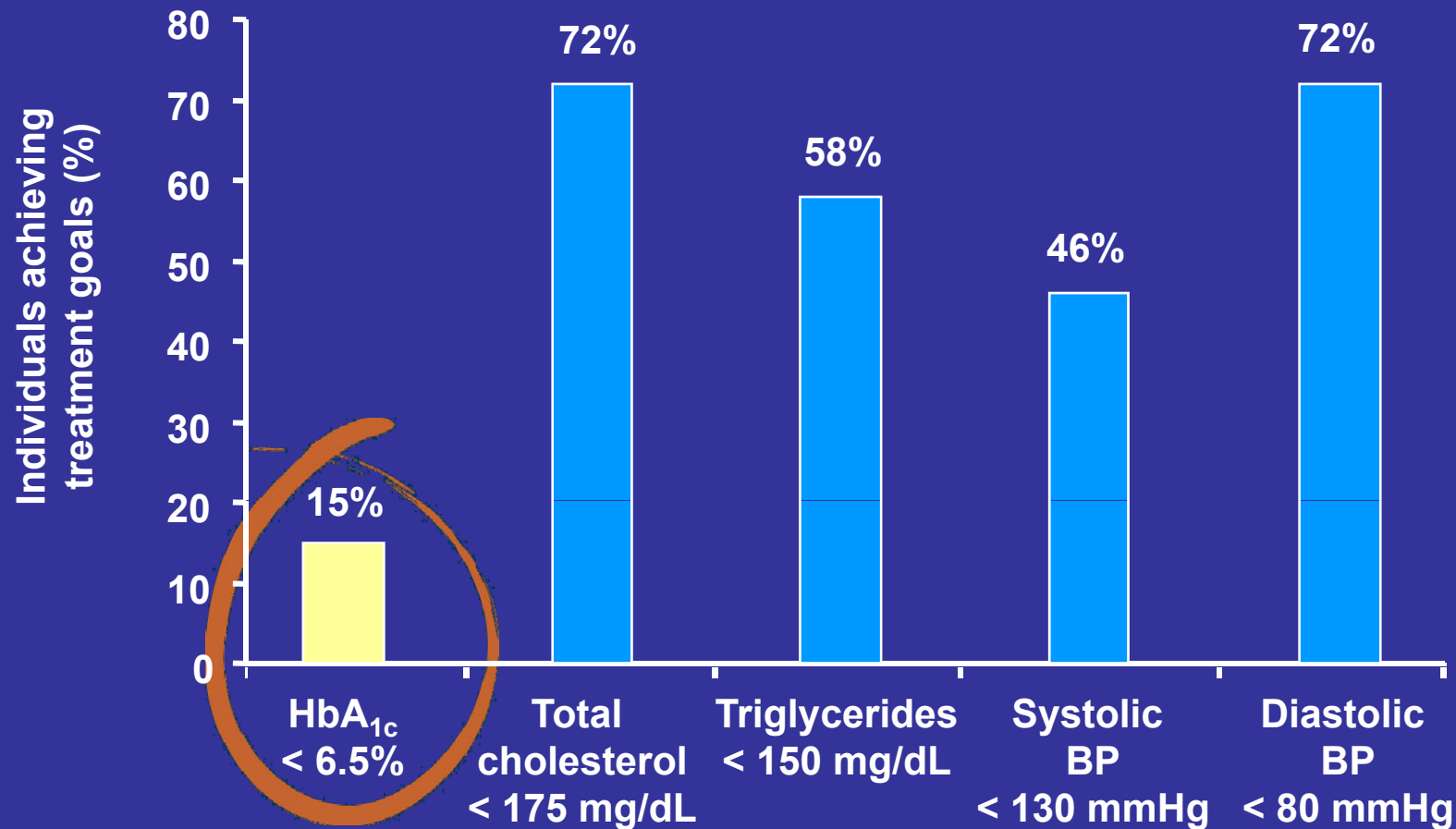


# Delays often occur between stepping up from monotherapy to combination therapy

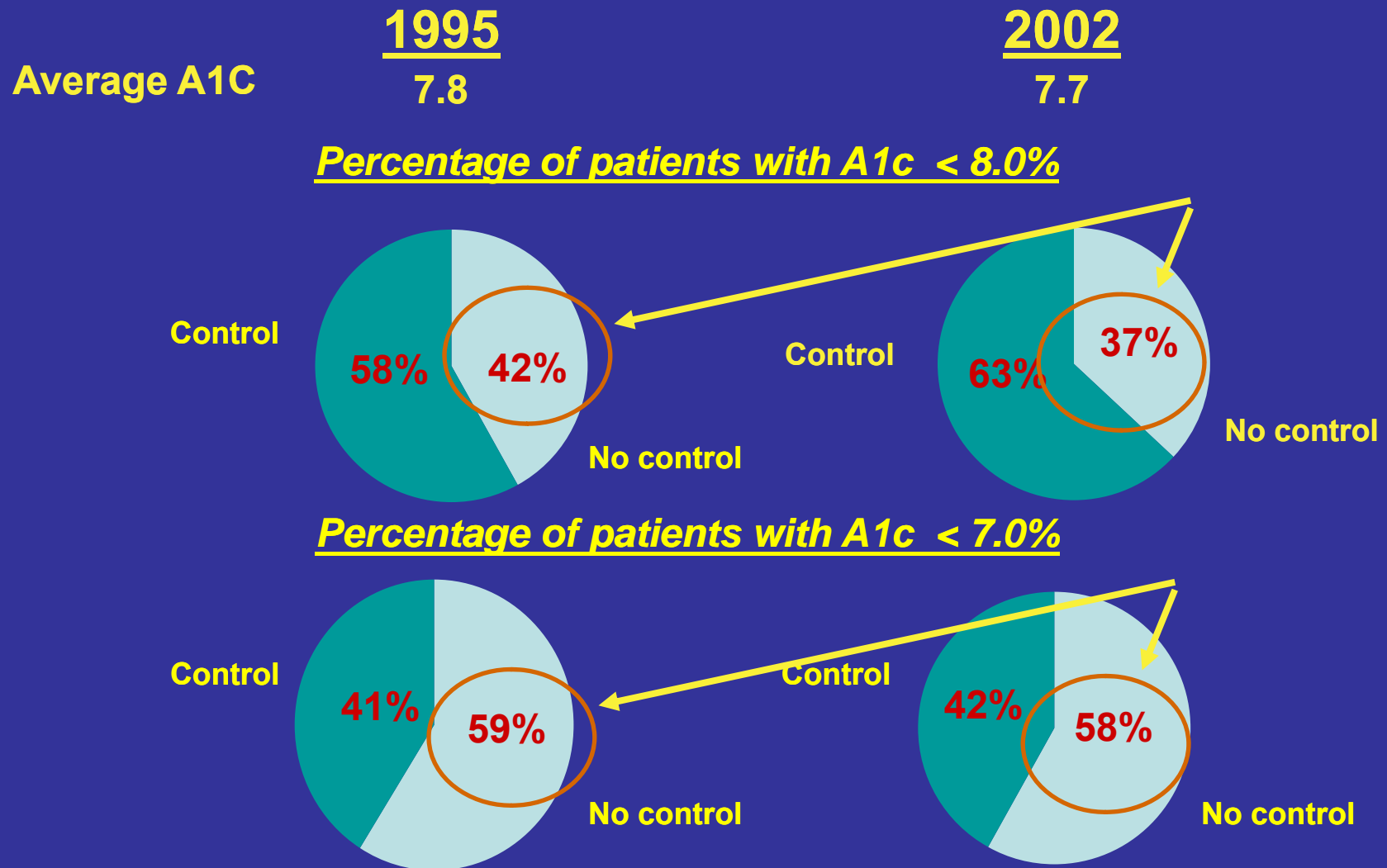
Length of time between first monotherapy HbA<sub>1c</sub> > 8.0% and switch/addition in therapy (months)



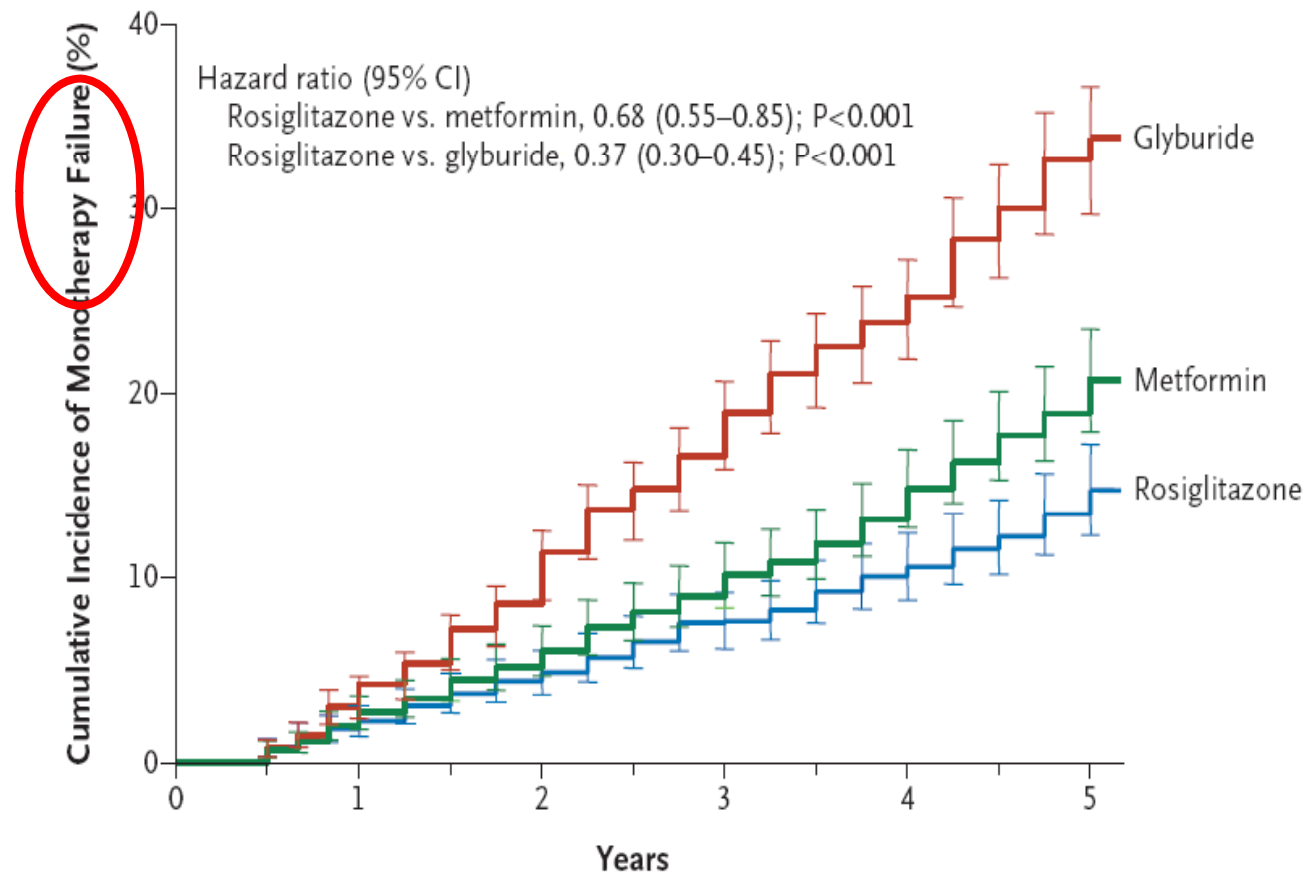
# Fewer individuals achieve goals for HbA<sub>1c</sub> versus lipids and blood pressure



# Treatment of T2DM in the USA: NHANES 1988-2002



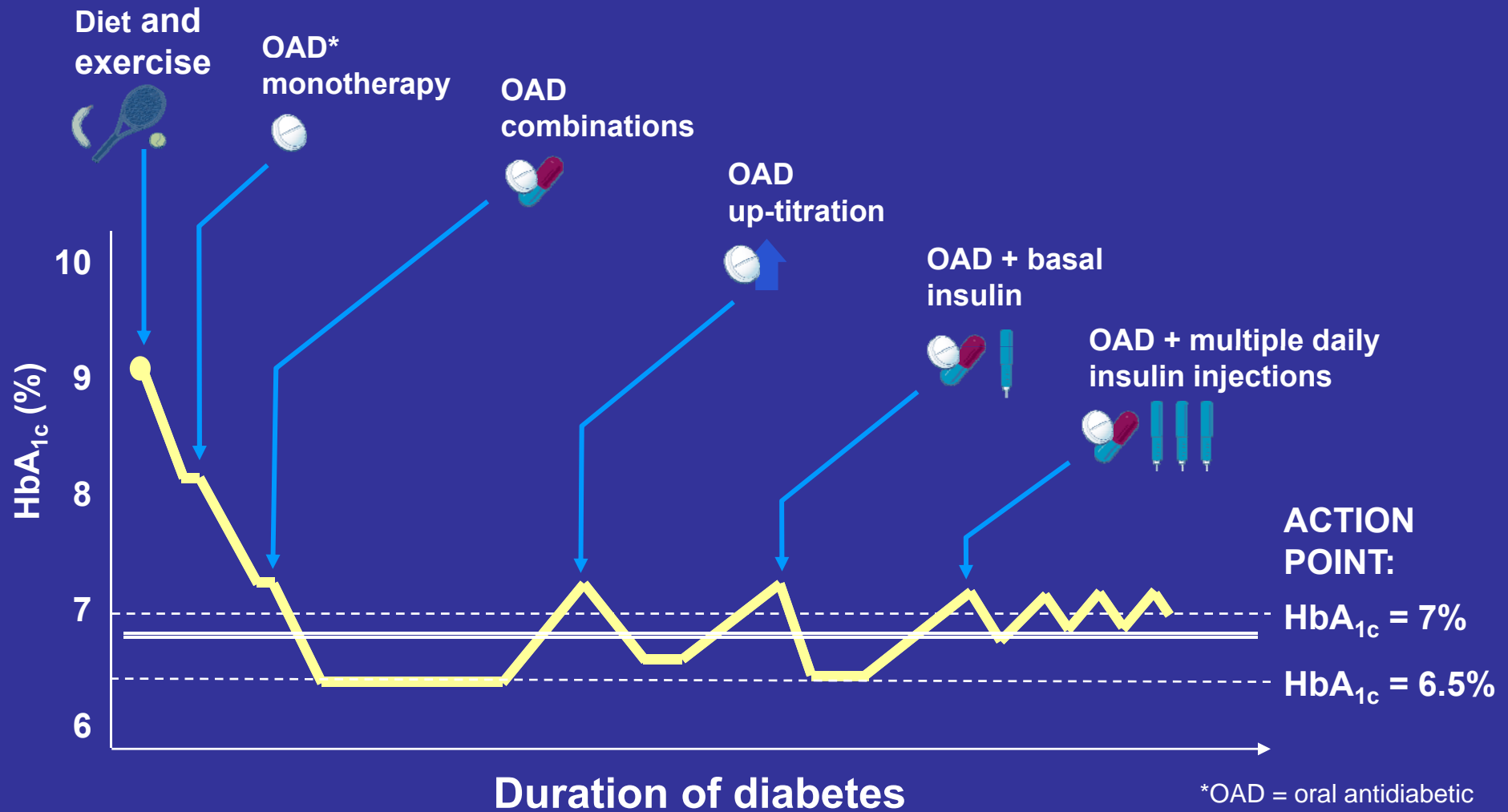
# Treatment failure is a universal phenomenon in T2 DM



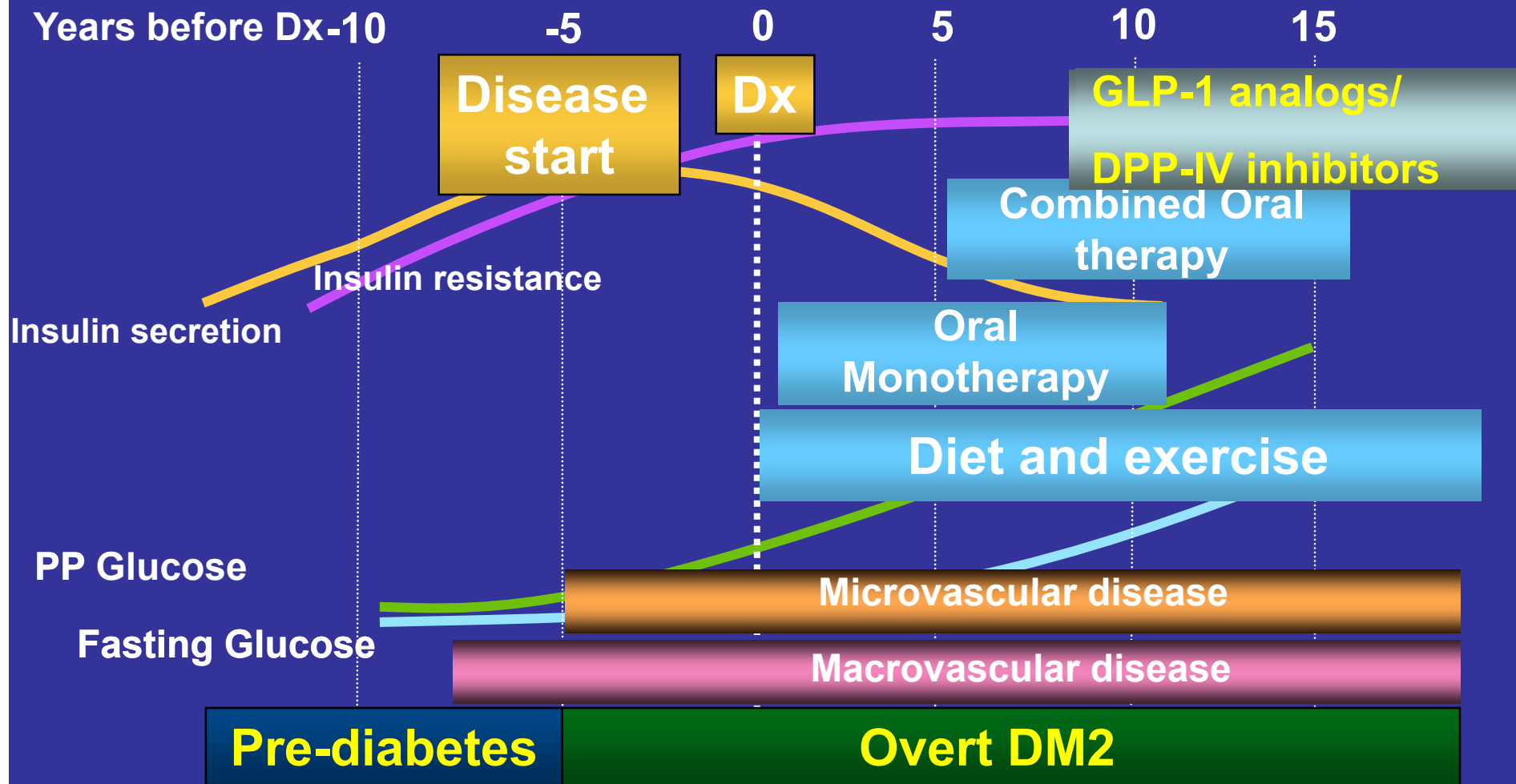
The ADOPT study, NEJM 2007



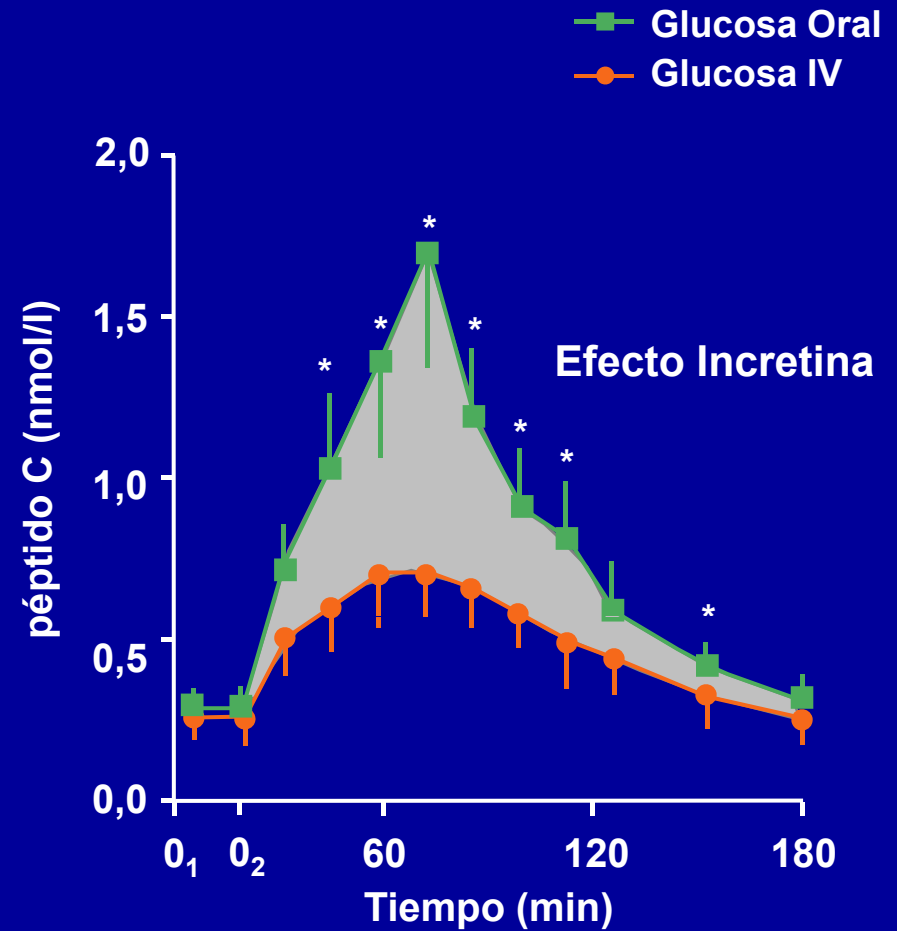
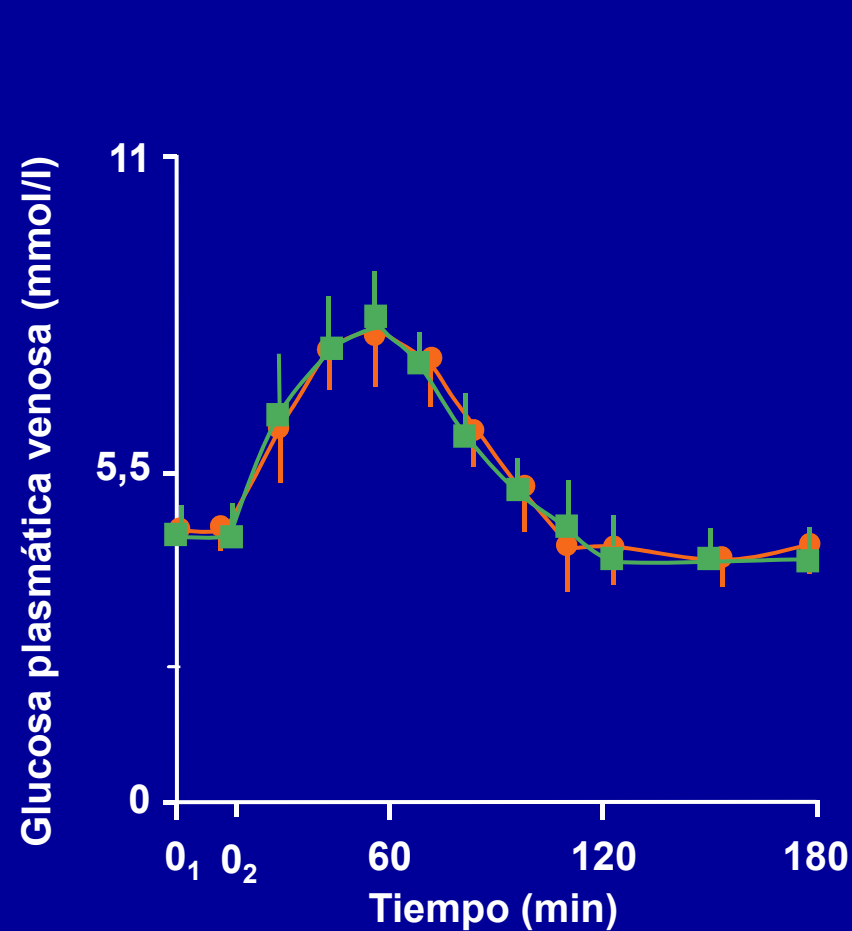
# Proactive management of glycemia: early combination approach



# Natural History (*current practice*) of DM 2 treatment

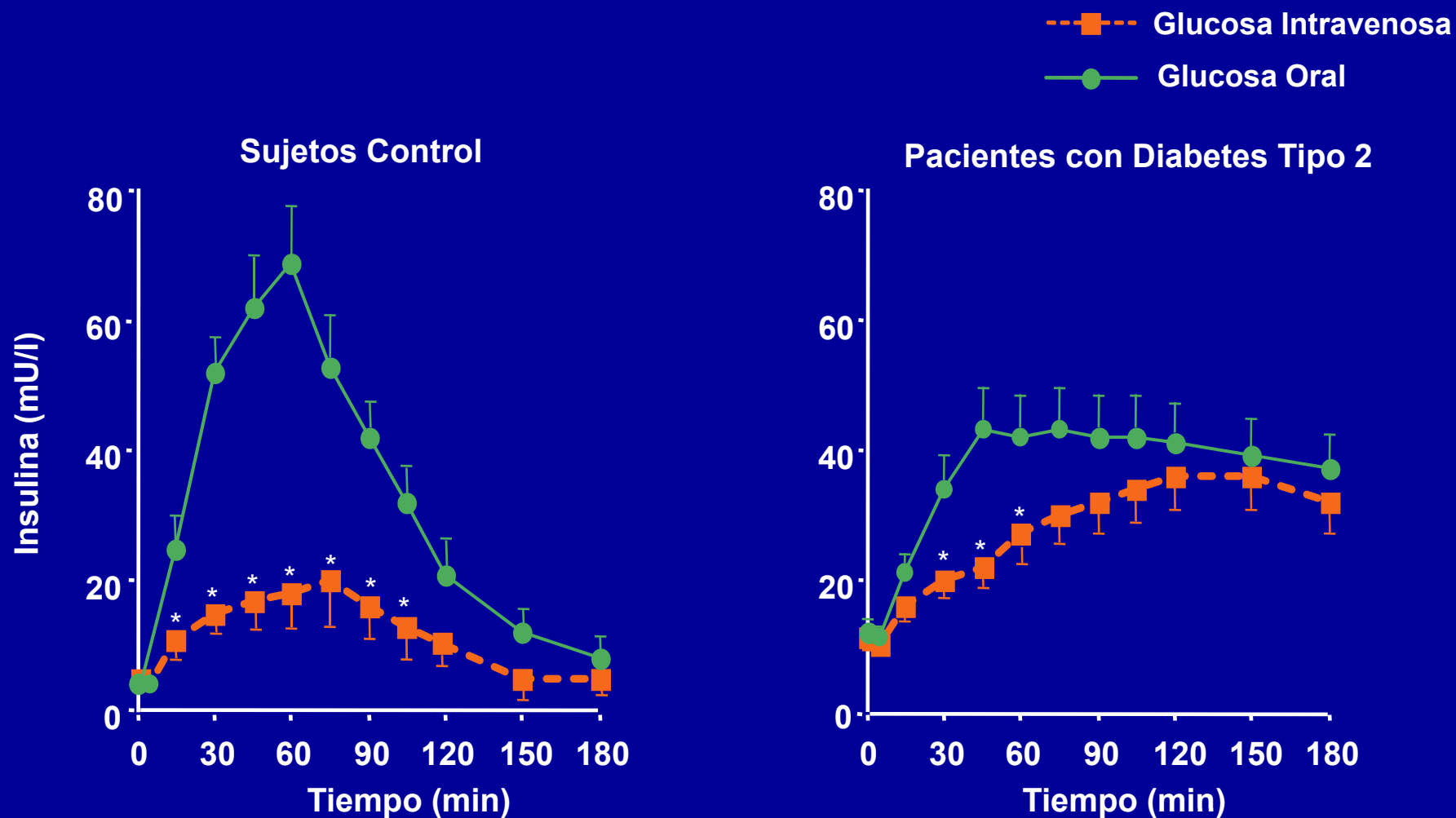


# El Efecto Incretina



Media  $\pm$  EE; N = 6; \* $p \leq 0,05$ ; 0<sub>1</sub>-0<sub>2</sub> = tiempo de infusión de la glucosa.  
Nauck MA, et al. *J Clin Endocrinol Metab.* 1986;63:492-498. Copyright 1986, The Endocrine Society.

# El Efecto Incretina está reducido en pacientes con Diabetes Tipo 2



\* $p \leq 0,05$  comparado con el valor respectivo después de una carga oral.

Nauck MA, et al. *Diabetologia*. 1986;29:46-52. Reimpresa con permiso de Springer-Verlag © 1986.

# Las Incretinas

GLP-1: Glucagon-like Peptide-1



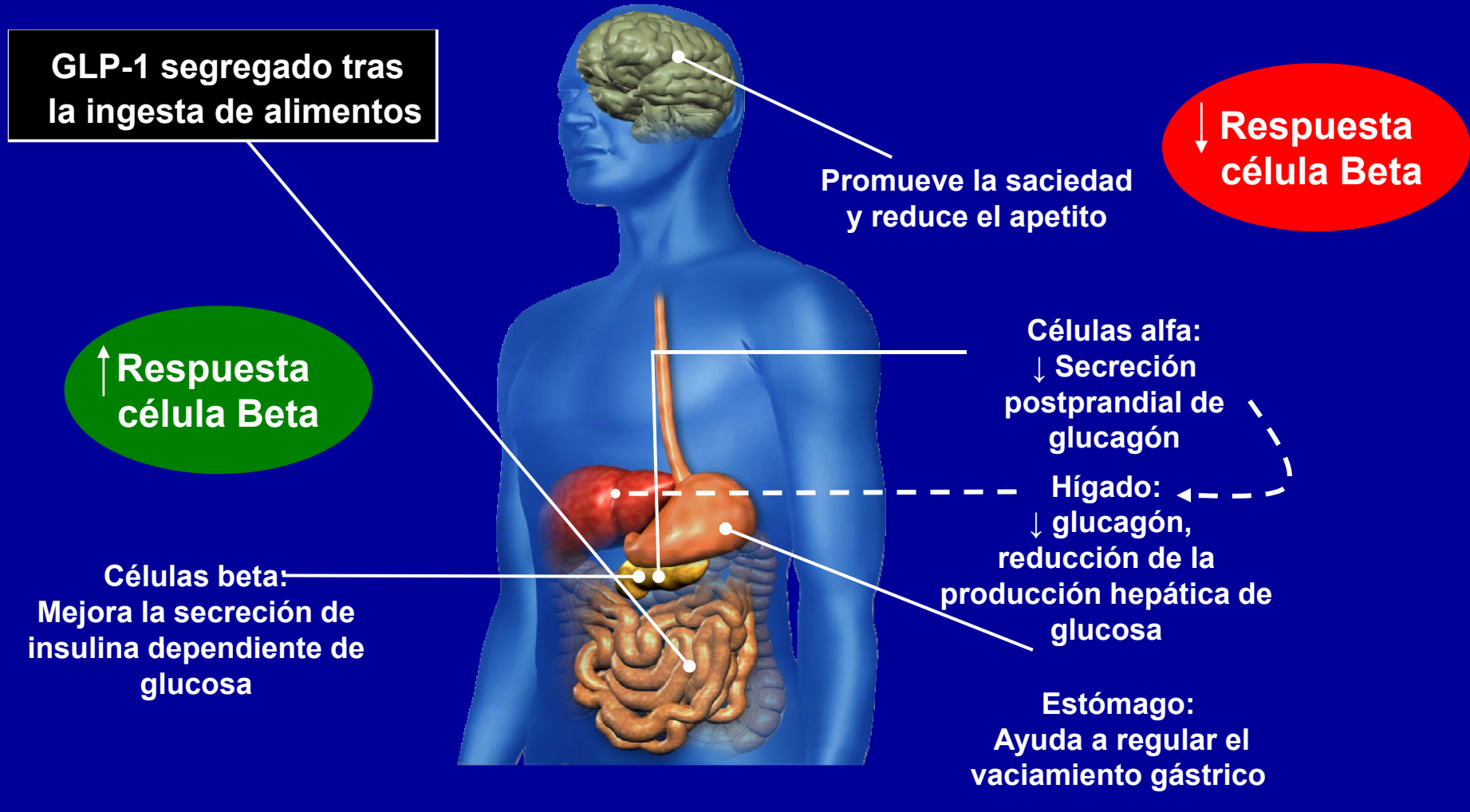
GIP: Glucose-Dependent Insulinotropic Peptide



Amino acids shown in blue are homologous with the structure of glucagon.

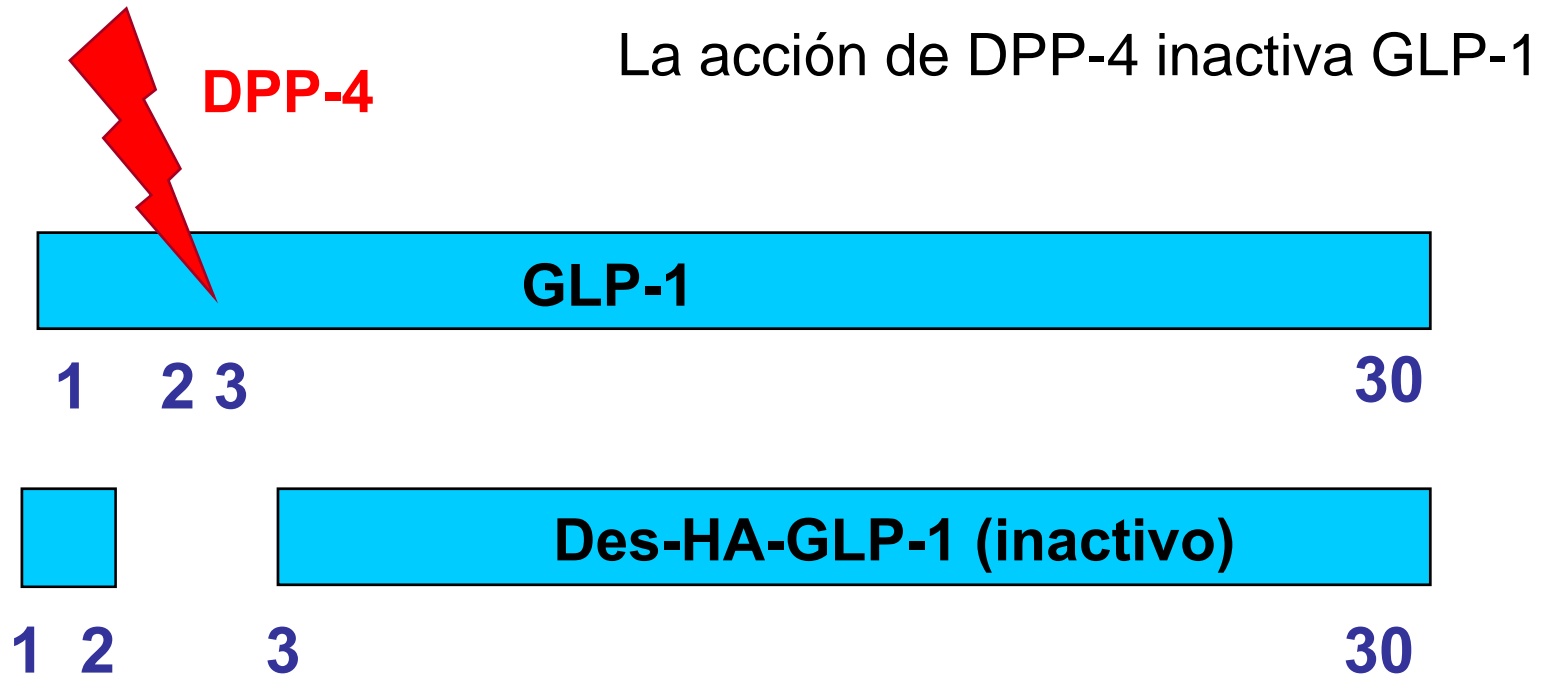
# Efectos del GLP-1 en Humanos:

## papel glucorregulatorio de las Incretinas



Adaptado de Flint A, et al. *J Clin Invest.* 1998;101:515-520.; Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422.; Nauck MA, et al. *Diabetologia.* 1996;39:1546-1553.; Drucker DJ. *Diabetes.* 1998;47:159-169.

# Degradación de GLP-1



2 posibles soluciones para la utilización terapéutica de GLP-1:

1. Análogos LAR de GLP-1 resistentes a DPP-4: **incretín-miméticos**
2. Inhibidores de DPP-4: **incretín-potenciadores**

# Incretín-miméticos

His Ala **Glu** Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg amide



**GLP-1**

**Lugar de acción de DPP-4**

## Liraglutida

His Ala **Glu** Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val **Arg** Gly Arg Gly



**Ácido graso C-16 (unión no covalente a albúmina)**



## Exendina-4, Exenatida

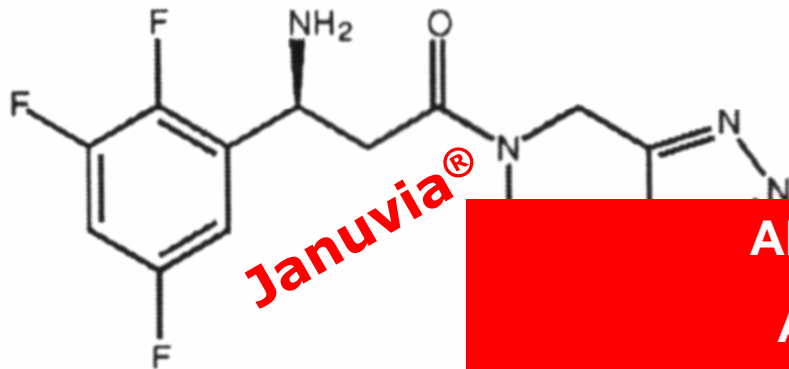
His **Gly** Glu Gly Thr Phe Thr Ser Asp **Leu** Ser **Lys** **Gln** **Me** Glu Glu Glu Ala **Val** **Arg** **Leu** Phe Ile **Glu** Trp Leu **Lys** **Asr** Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser amide



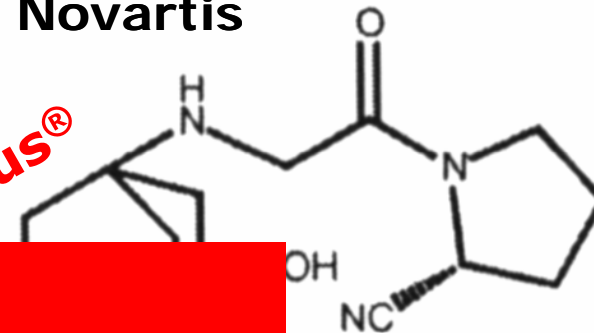


# Inhibidores de DPP-4

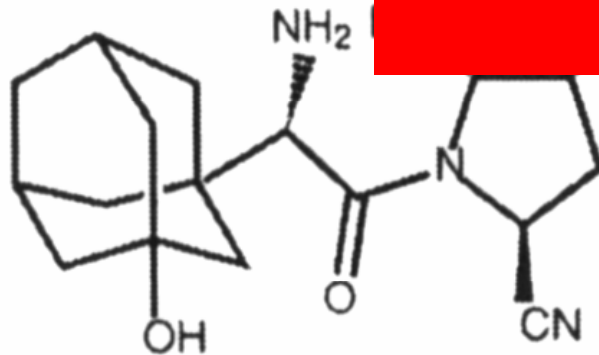
A. MK-0431 (Sitagliptin),  
Merck, Sharp & Dohme



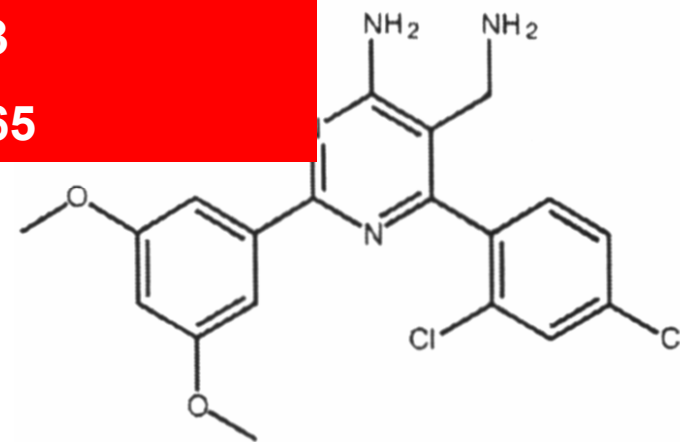
B. NVP-LAF 237 (Vildagliptin),  
Novartis



C. BMS-47718 (Saxagliptin),  
Bristol-Myers Squibb



D. Alogliptin (Tosigliptin),  
Novartis



Januvia®

Galvus®

Alogliptina

ABT-279

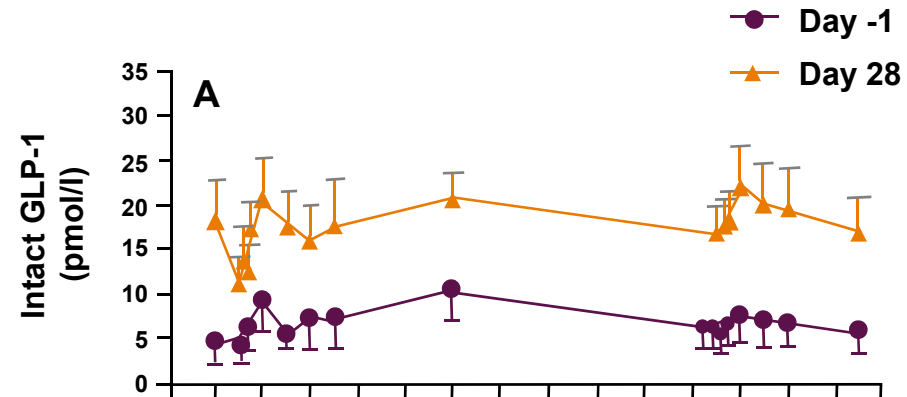
BI 1356

ARI 2243

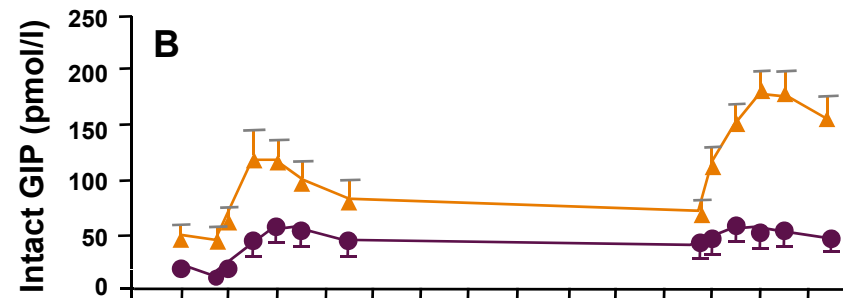
LY 2463665

# Efecto de iDPP-4 en los niveles de incretinas circulantes

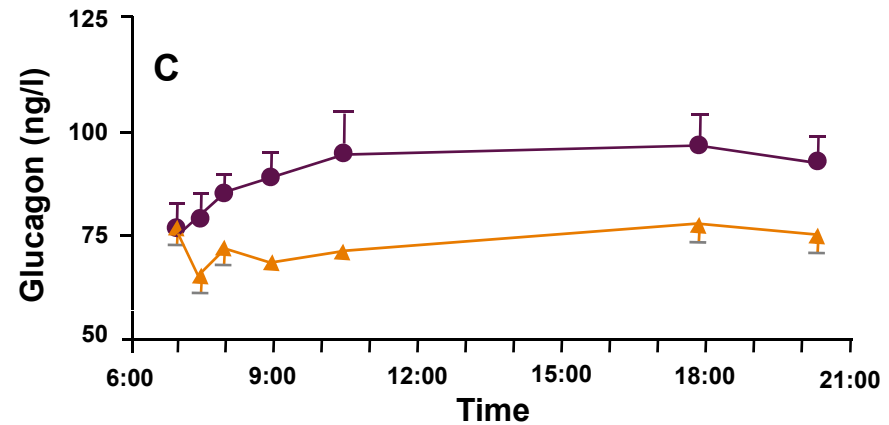
**GLP-1**



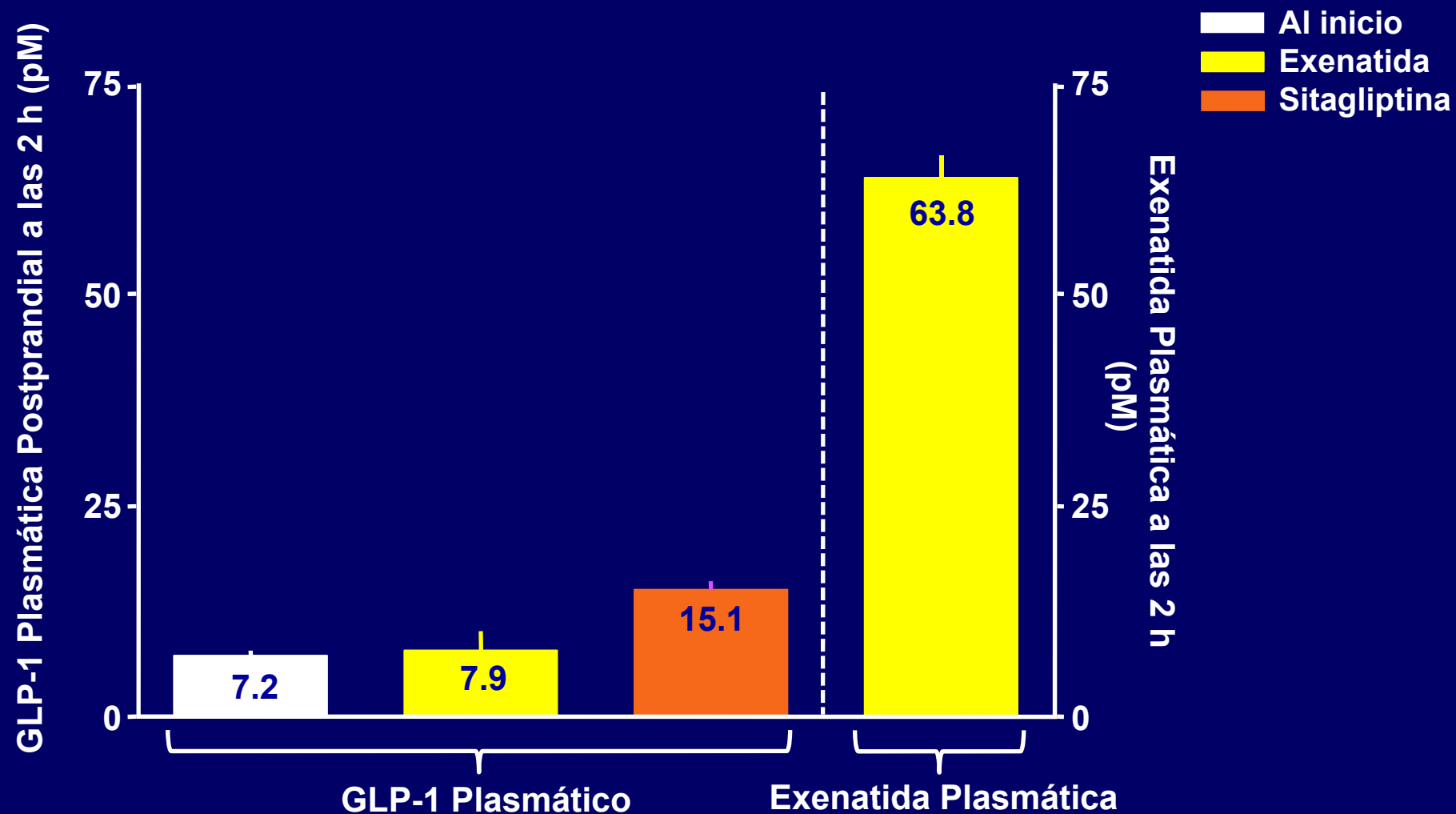
**GIP**



**Glucagon**



# Los Niveles Plasmáticos Postprandiales de Exenatida Exceden los Niveles Fisiológicos de GLP-1

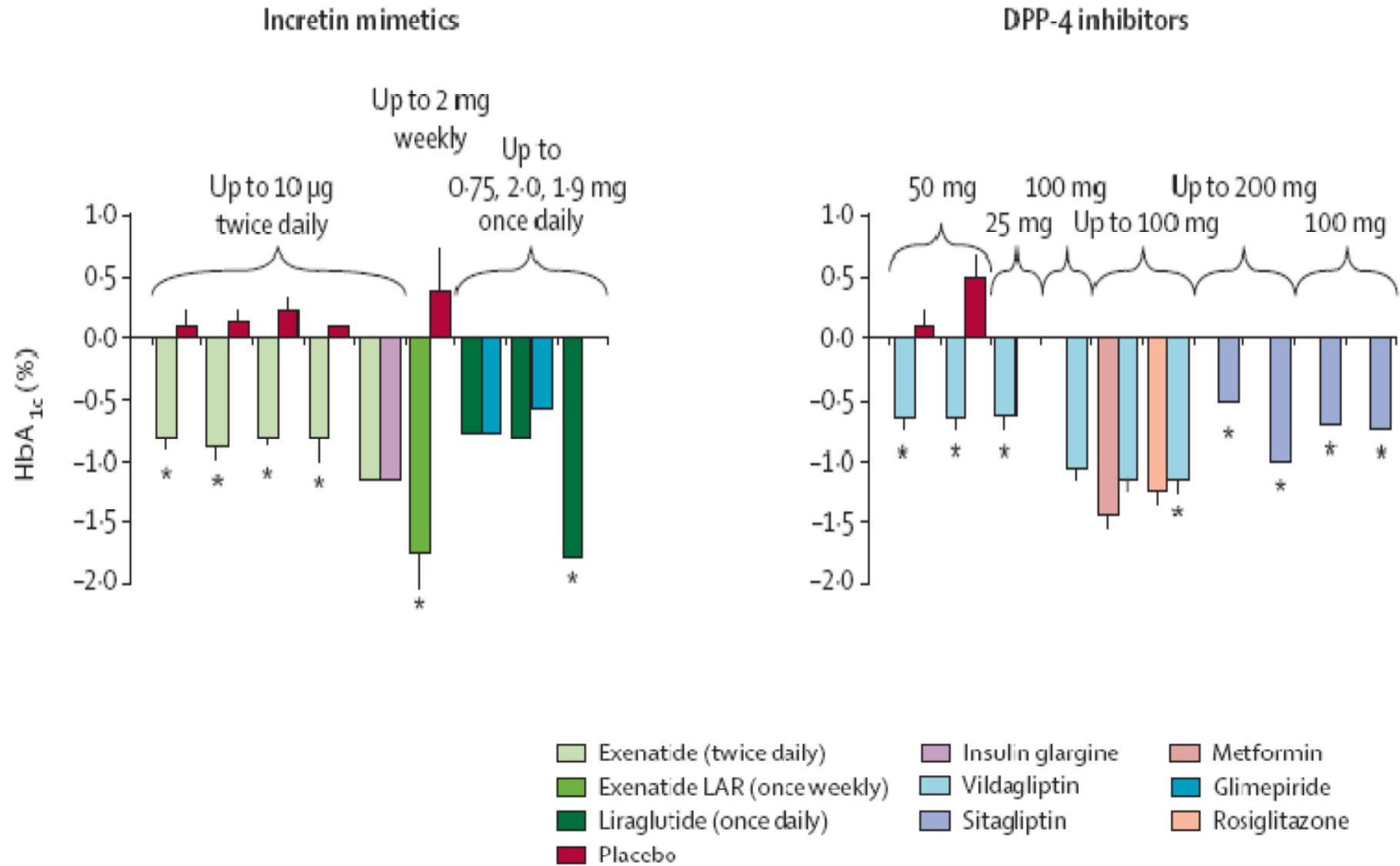


Pacientes con DT2; Población evaluable, n = 61 para todos los grupos de tratamiento; Media  $\pm$  EE; datos de concentraciones posttratamiento a las 2 semanas  
DeFronzo RA, et al. *Curr Med Res Opin.* 2008;24(10)2943-2952.

# Incretín Miméticos vs iDPP-4: Diferencias

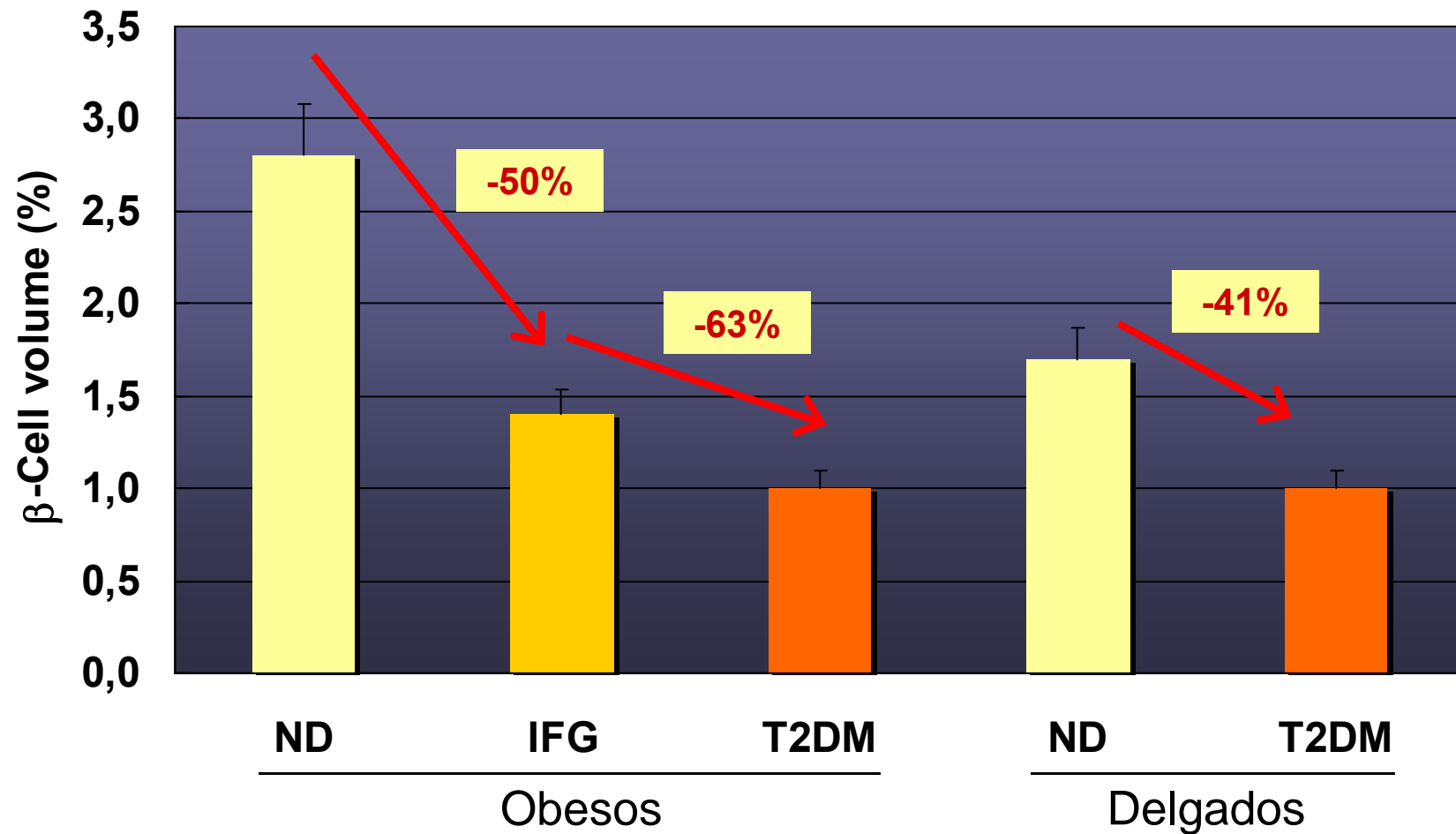
Propiedades/Efectos	Incretín Miméticos	iDPP-4
Estimulación de la secreción de insulina exclusivamente via GLP-1	Sí	Probablemente no exclusivamente vía GLP-1(PACAP? GIP? otras?)
Restitución de secreción fisiológica de insulina (2 fases)	Sí	No probado
Mantenimiento de contrarregulación por glucagon en situación de hipoglicemia	Sí	No probado
Inhibición de la motilidad digestiva	Sí	No
Efecto en el peso corporal	Disminución	No disminución
Efectos adversos	Nausea	No
Formación de anticuerpos	Sí	No
Administración	Inyección Subcutánea	Oral

# Resultados de estudios clínicos con incretinas en DM2: control glicémico



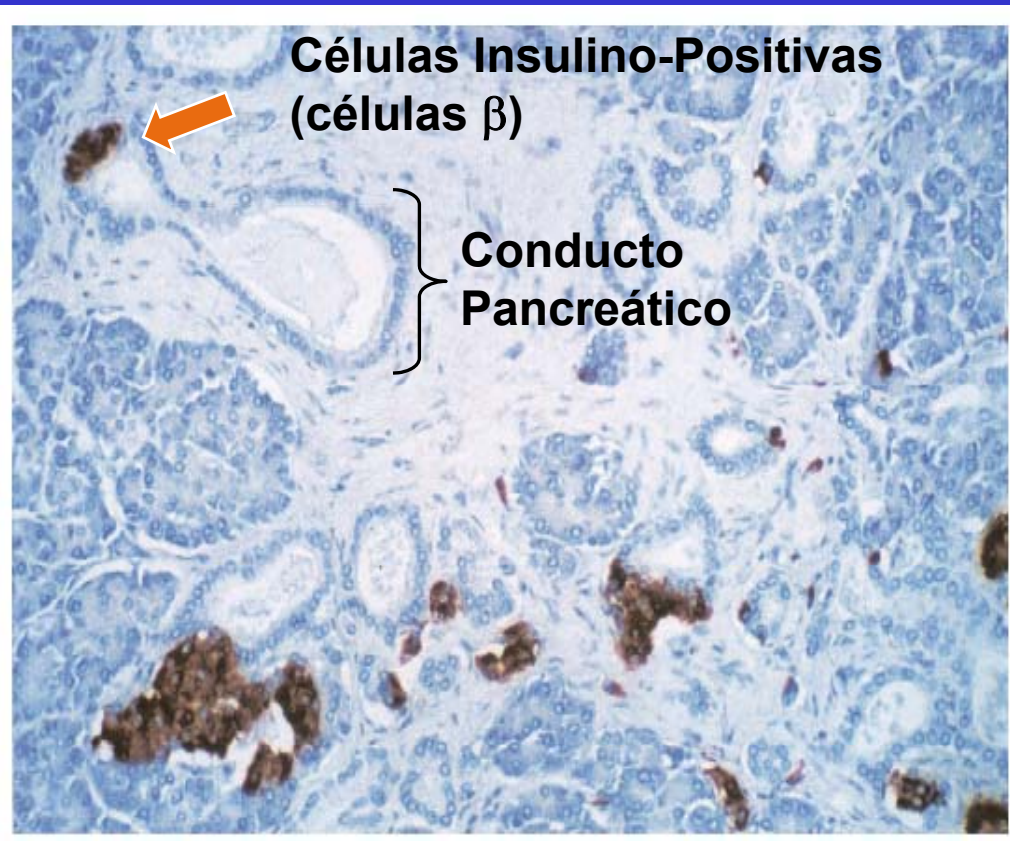
Nos ofrecen algo más la terapia  
basada en incretinas ?

# Masa de células $\beta$ en pacientes con Diabetes tipo 2



ND=non-diabetic; IFG=impaired fasting glucose; T2DM=Type 2 diabetes mellitus  
Butler AE et al. *Diabetes*. 2003;52:102-110.

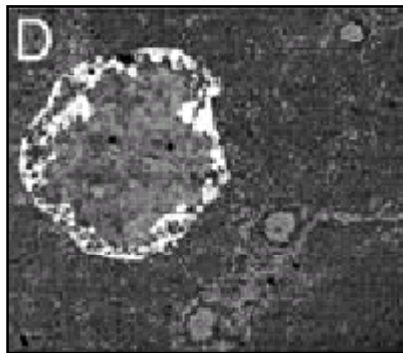
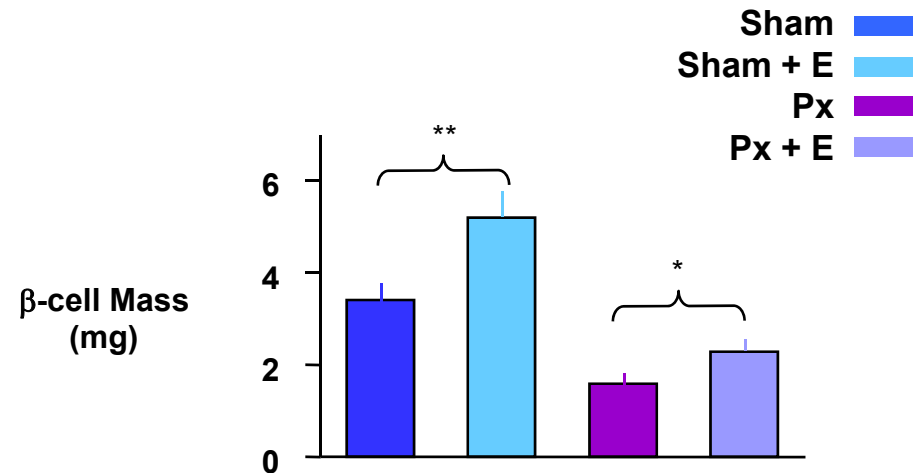
# El mantenimiento de la masa de células $\beta$ es un proceso dinámico



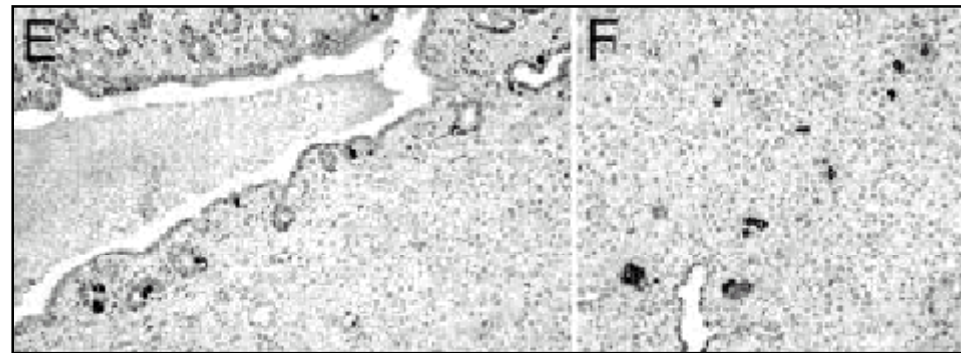
- Equilibrio dinámico de pérdida de células  $\beta$  vs. neogénesis
- Los islotes se reabastecen de nuevas células  $\beta$
- Replicación:
  - Células epiteliales ductales
- Proliferación:
  - Células madre y precursoras



# Neogenesis y replicación Beta-celular incrementadas tras tratamiento con exenatida en ratas parcialmente pancreatectomizadas



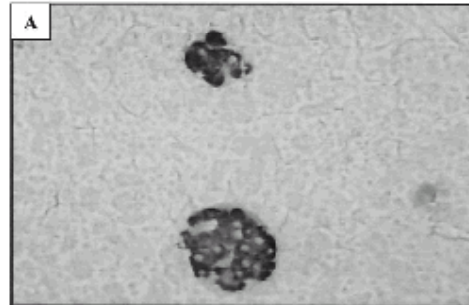
BrdU in islets



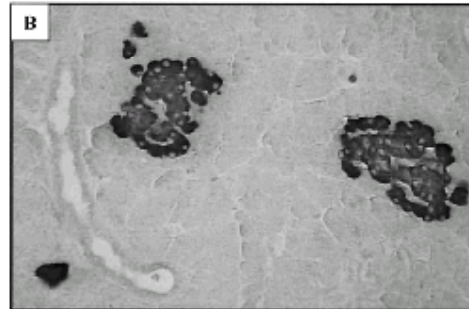
Glucagon-IR in ductal and exocrine tissue

# Incremento de la masa Beta en ratas tratadas con estreptozotocina +incretinas

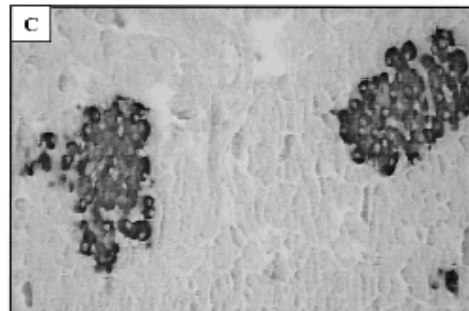
**Control – STZ**  
( $\beta$  cell mass = 2.2mg/pancreas)



**GLP-1 – STZ**  
( $\beta$  cell mass = 3.1mg/pancreas)



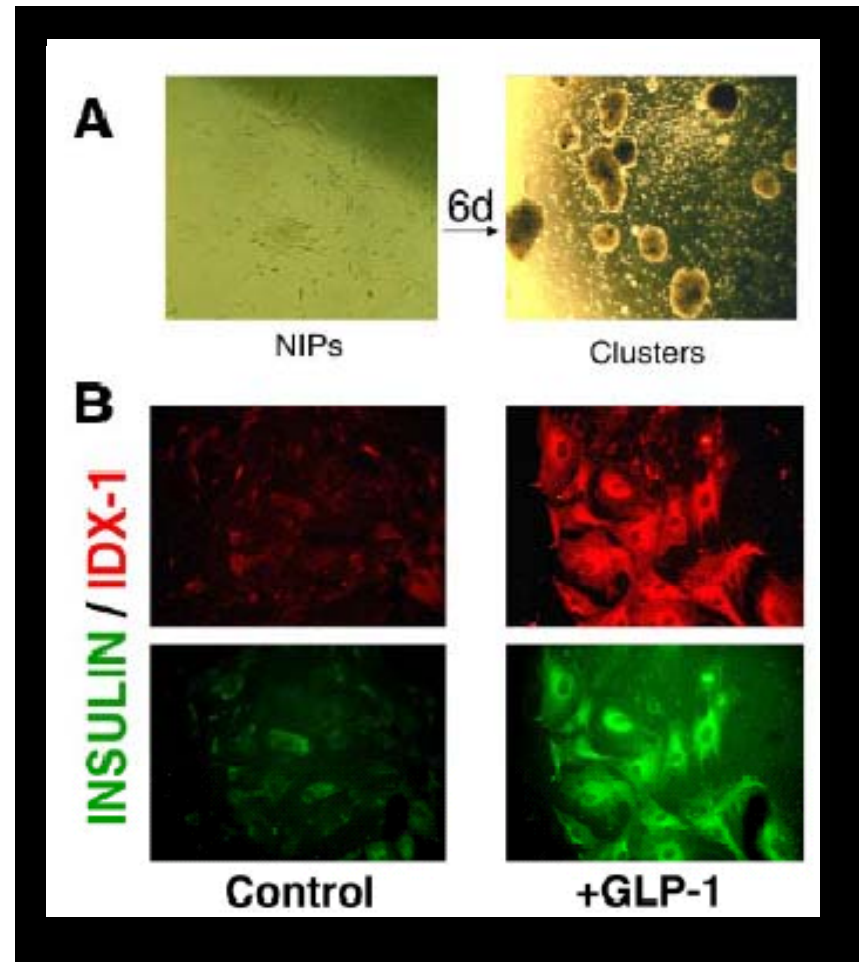
**Exendin-4 – STZ**  
( $\beta$  cell mass = 3.6mg/pancreas)



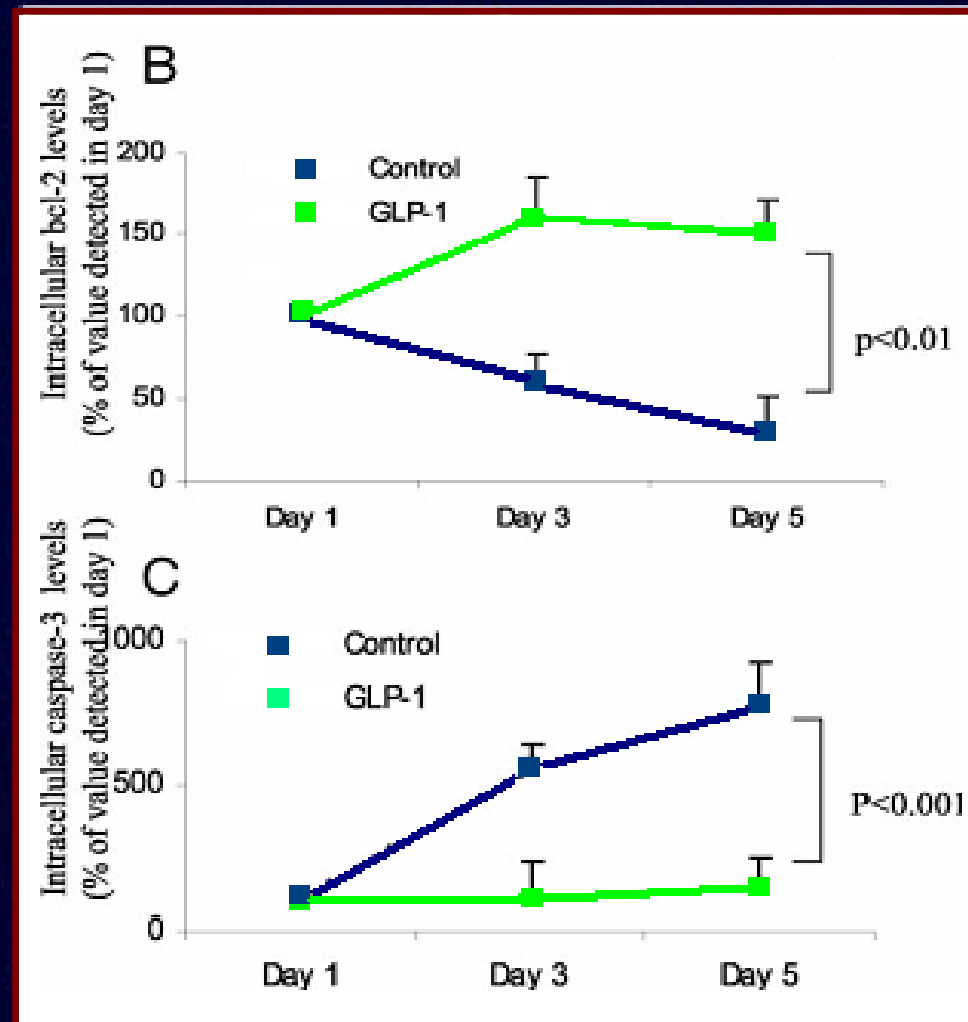
# GLP-1 induce diferenciación de células madre pancreáticas

NIP:

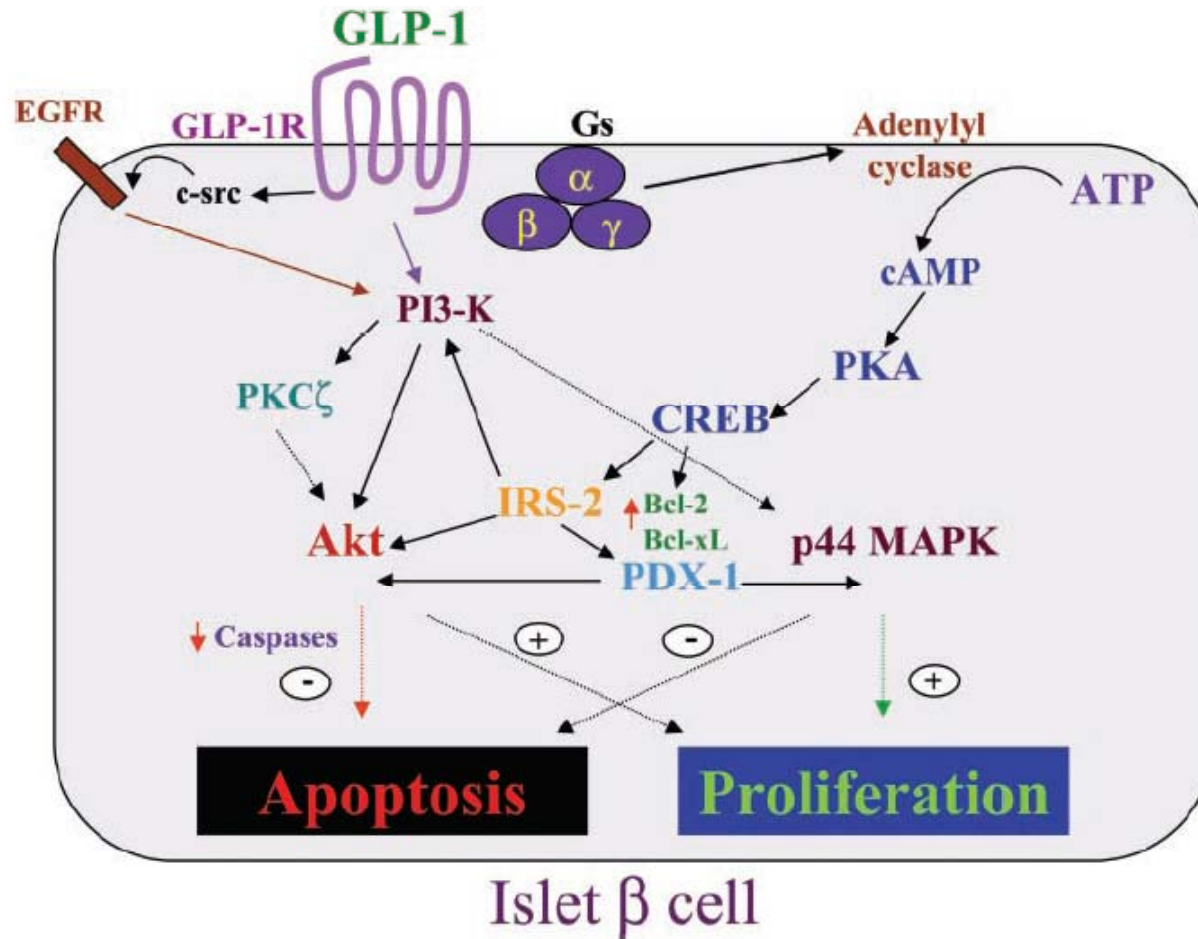
Nestin-positive  
islet progenitor  
cells



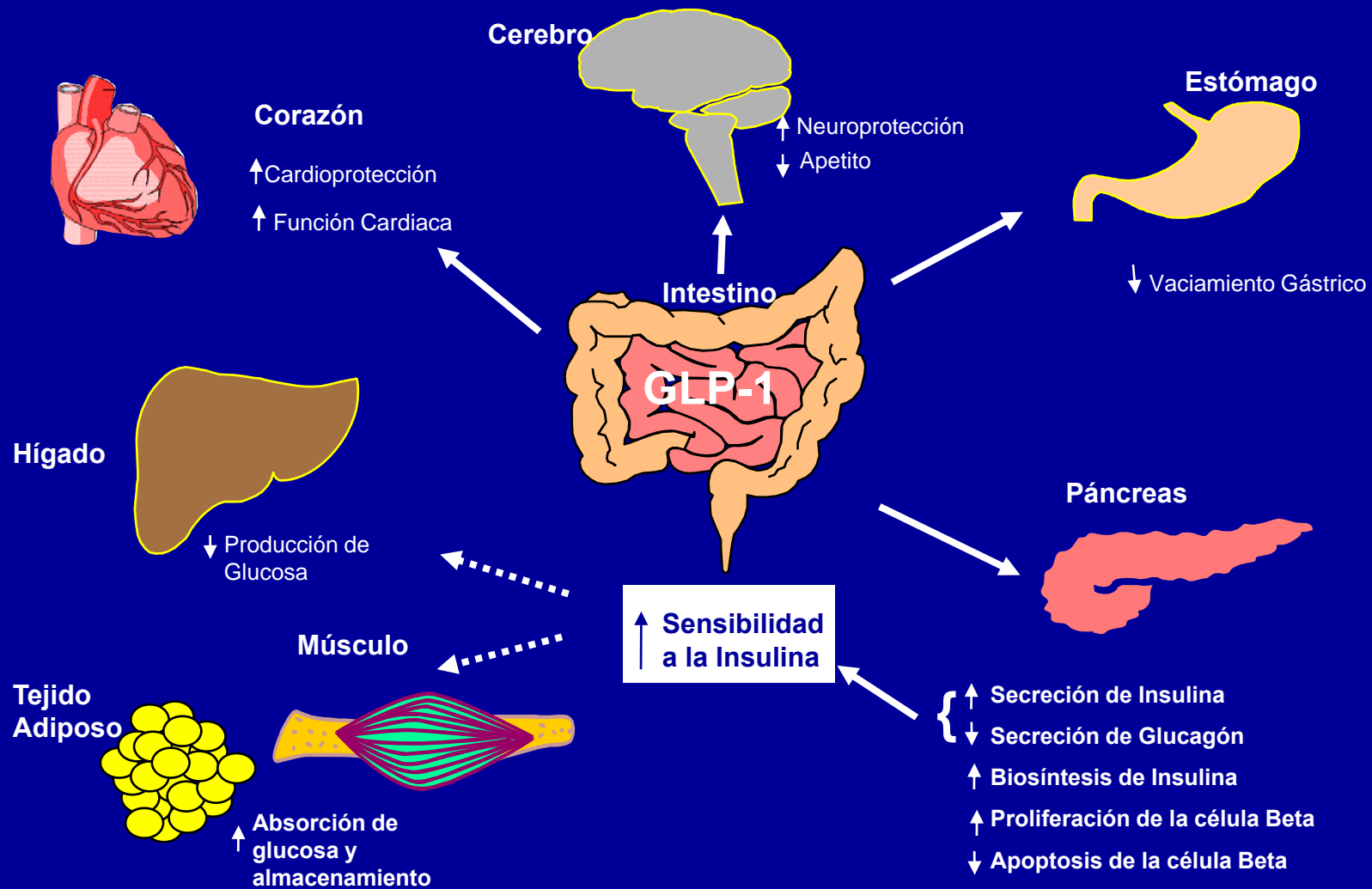
# GLP-1 preserva la integridad de los islotes y reduce la apoptosis en islotes humanos



# GLP-1 y proliferación/apoptosis de las células insulares



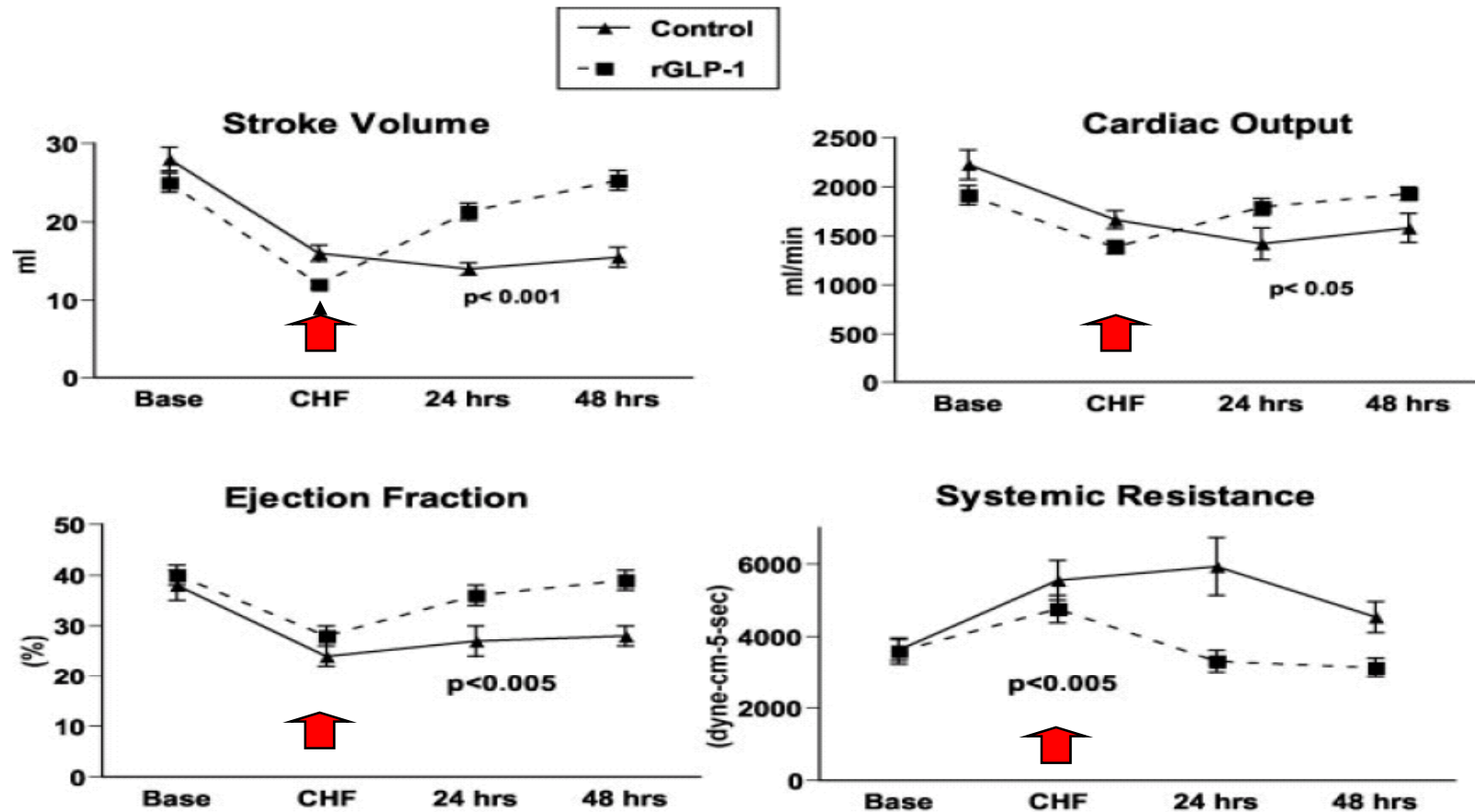
# Acciones clásicas y nuevas de la molécula de supervivencia GLP-1



Baggio LL, Drucker DJ. *Gastroenterology*. 2007;132:2131-2157.

# Recombinant Glucagon-Like Peptide-1 Increases Myocardial Glucose Uptake and Improves Left Ventricular Performance in Conscious Dogs With Pacing-Induced Dilated Cardiomyopathy

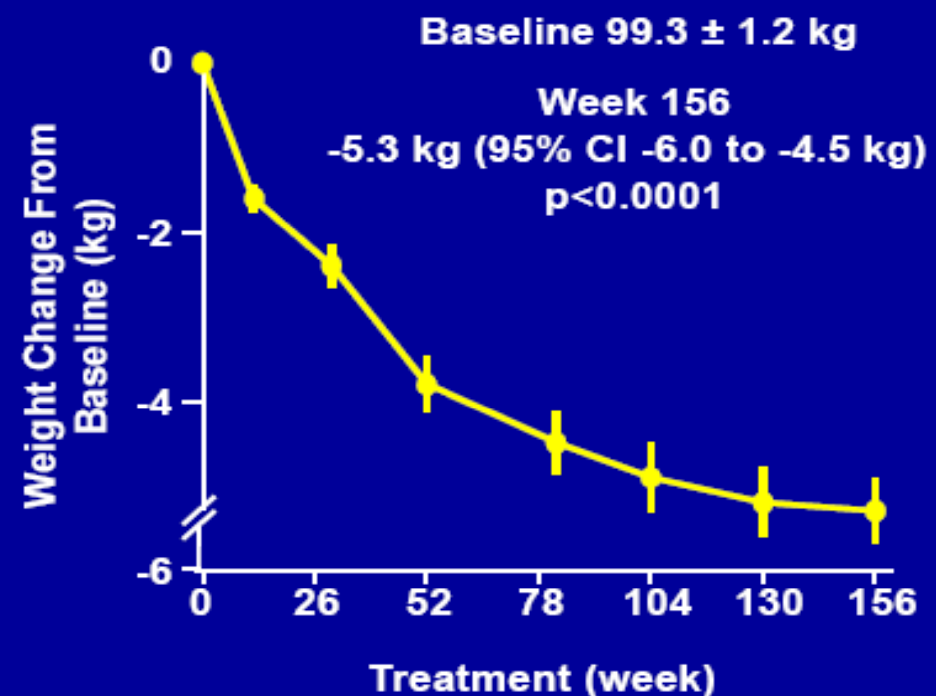
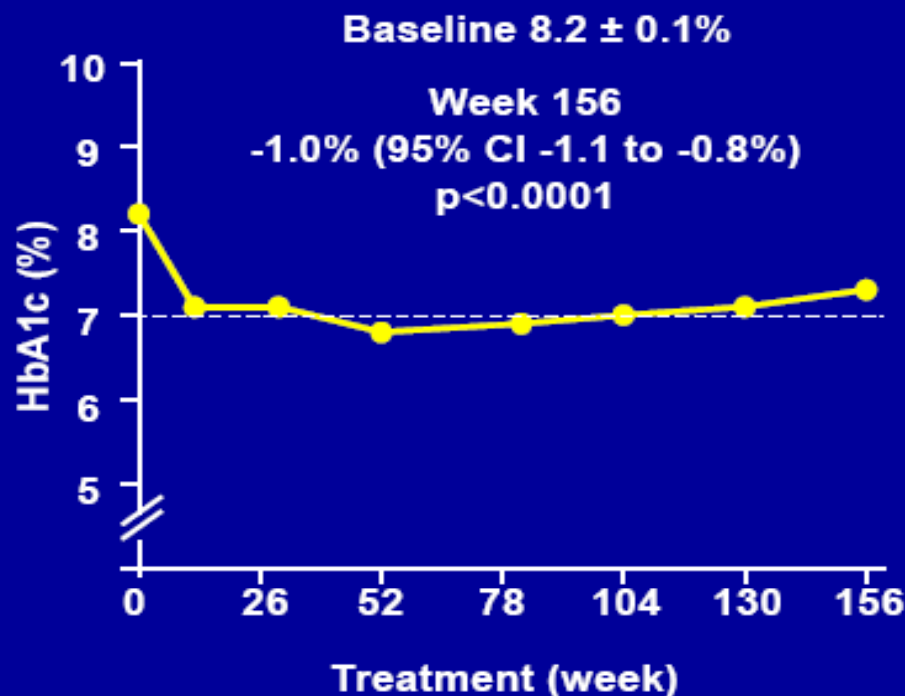
Lazaros A. Nikolaidis, MD; Dariush Elahi, PhD; Teresa Hentosz, BS;  
 Aaron Doverspike, MS; Rhonda Huerbin, LVT; Lee Zourelis, LVT; Carol Stolarski, BS;  
 You-tang Shen, MD; Richard P. Shannon, MD



¿Cuáles son los determinantes de la respuesta a la terapia basada en incretinas?

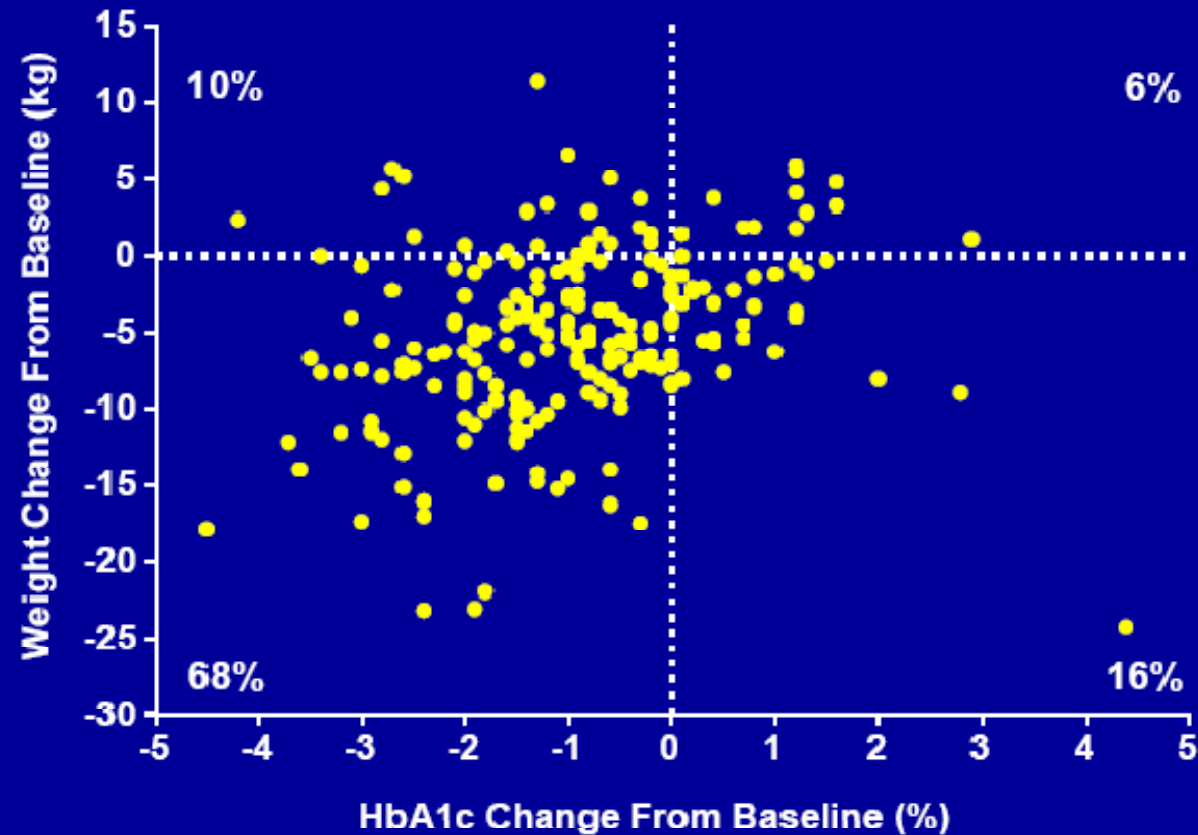


# Cambios en A1c y en el peso tras exenatida durante 3 años



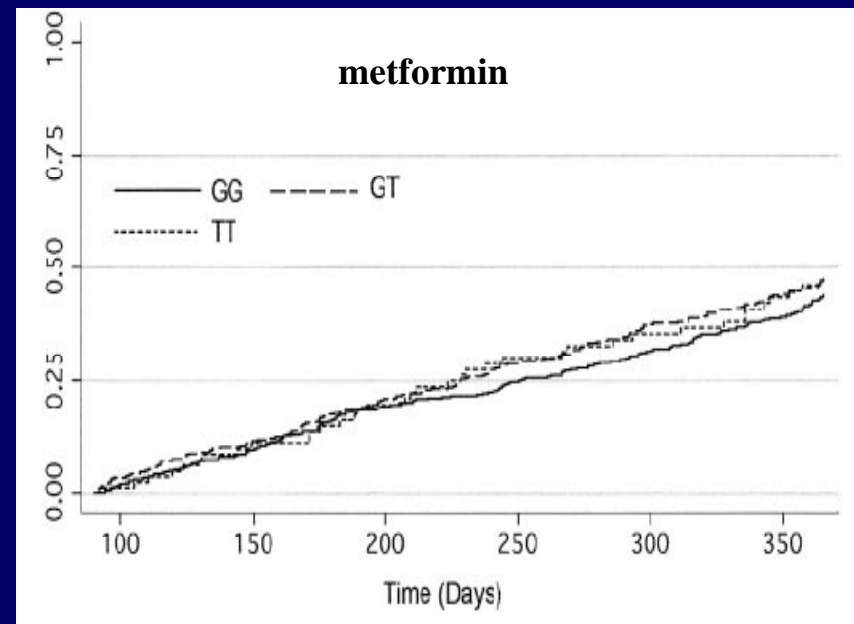
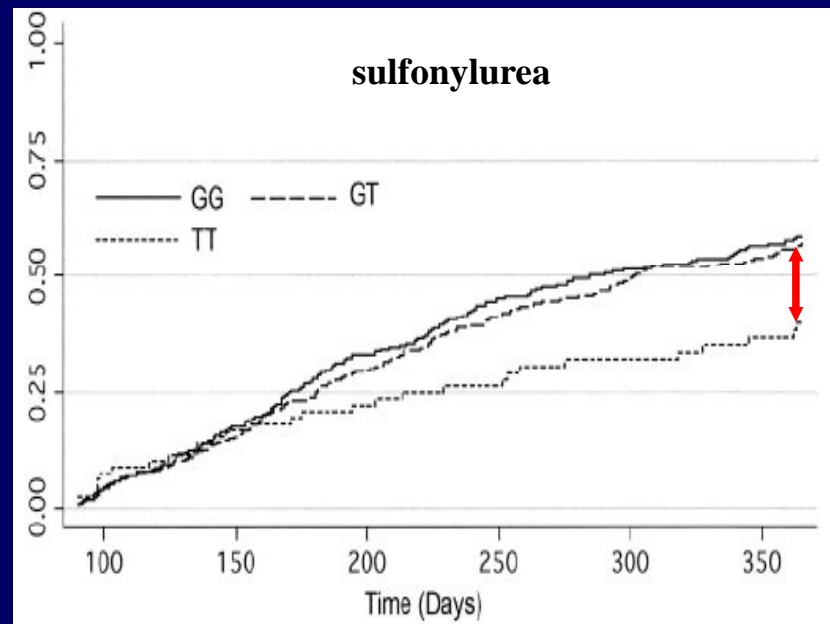
CI: Confidence interval. N=217; Mean  $\pm$  SEM.  
Klonoff DC, et al. *Curr Med Res Opin.* 2008;24:275-286.

# El 68% de los sujetos tratados con exenatida durante 3 años mejoran A1c y pierden peso



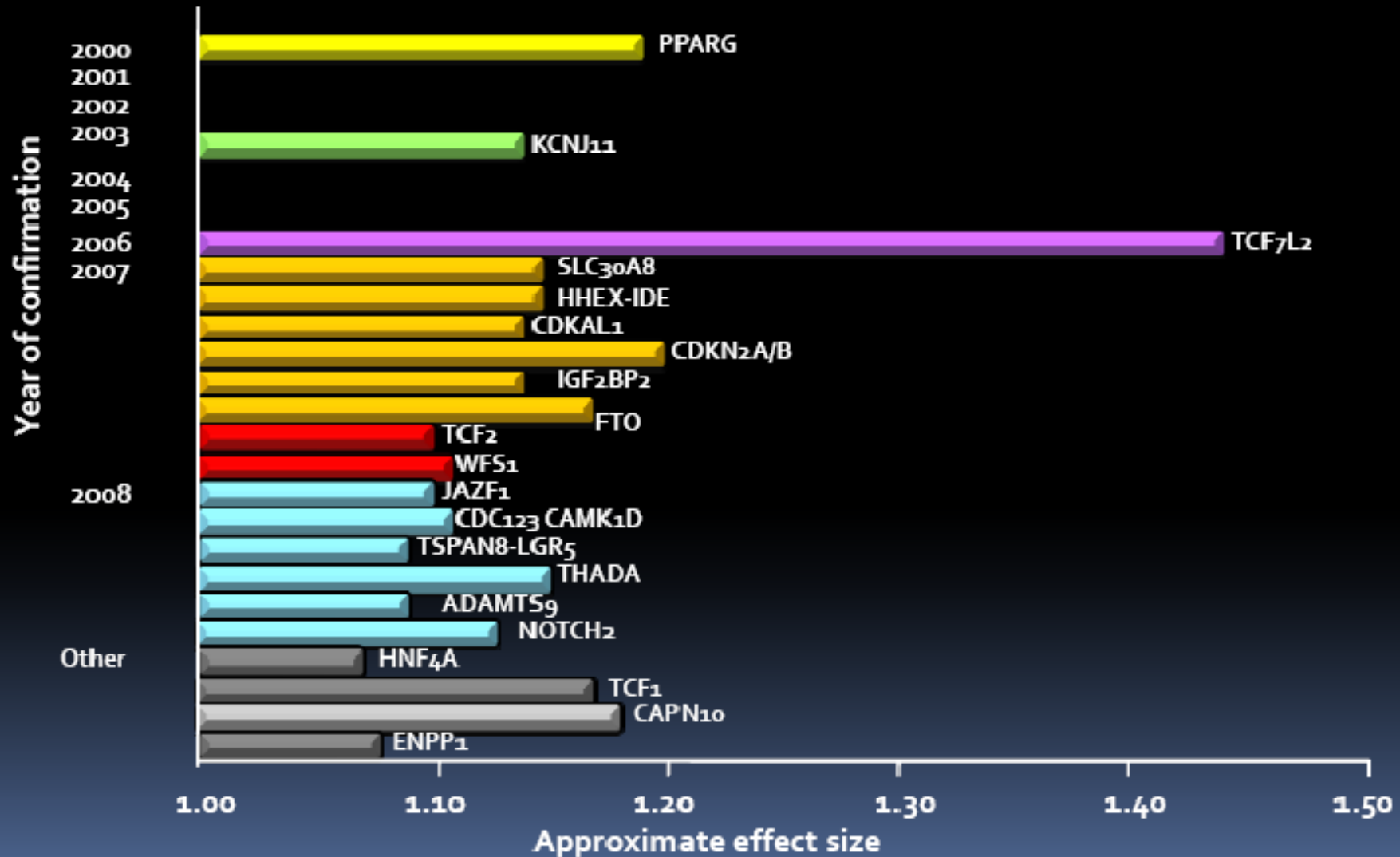
N=217  
Klonoff DC, et al. *Curr Med Res Opin.* 2008;24:275-286.

# TCF7L2 influye en la respuesta a sulfonilureas



Proportion of patients, by genotype rs1225372, who achieve a target A1c <7%

# Genes asociados a DM2

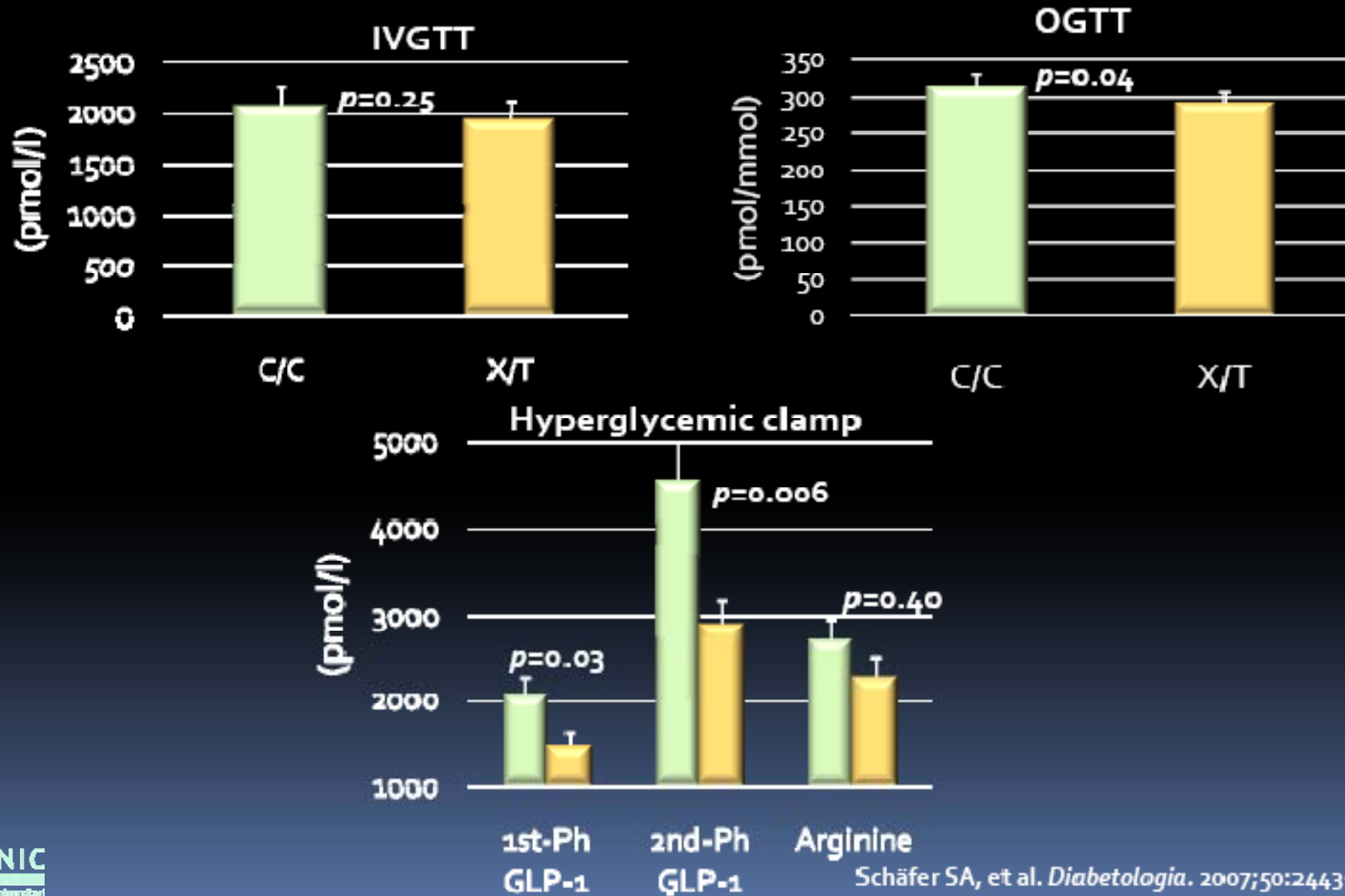


# Polimorfismos de *TCF7L2*

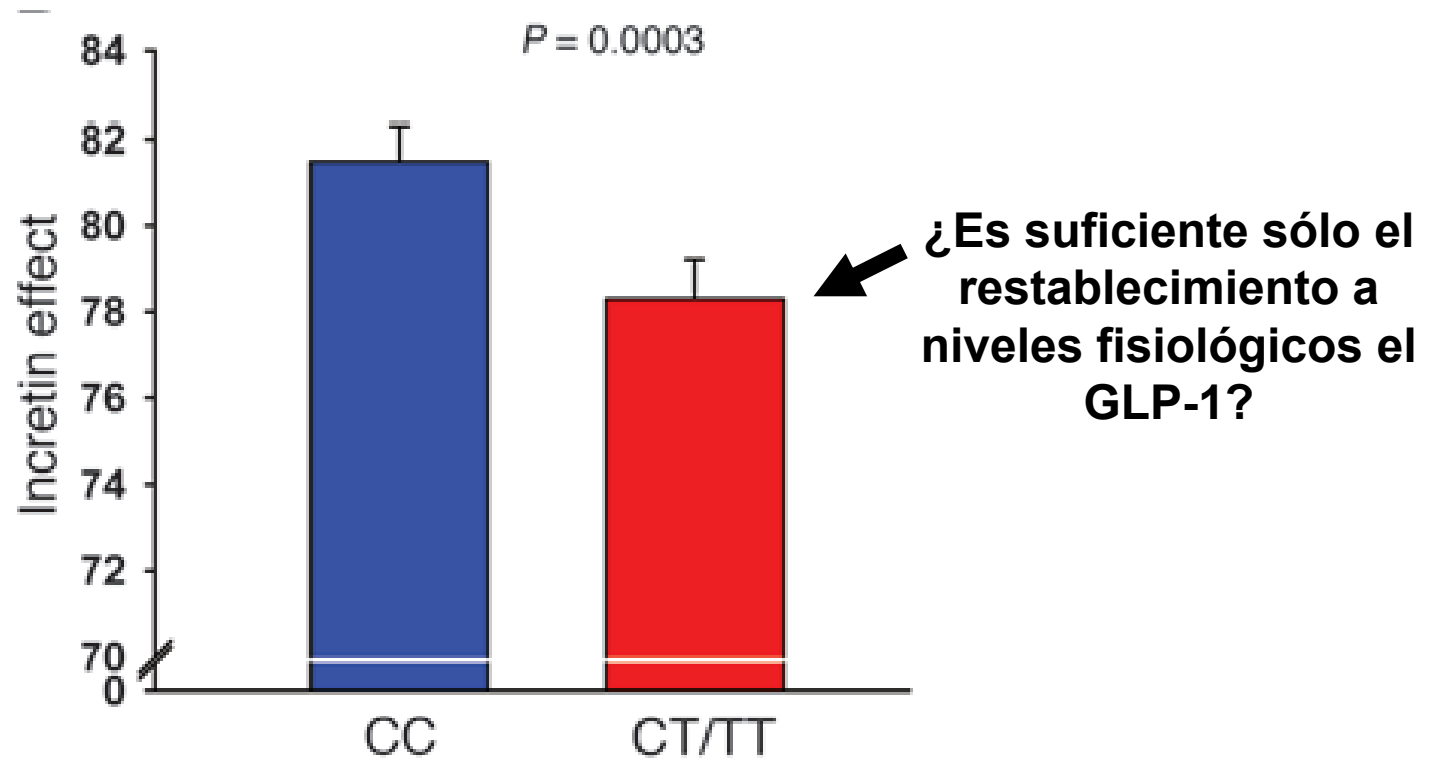
*rs7903146*

- Confieren un elevado riesgo de DM2
- Se asocian IMC bajo y a fallo precoz al tratamiento con hipoglicemiantes orales
- Determinan una menor repuesta insulino-secretora
- No se asocian a niveles inferiores de GLP-1 pero sí a una menor respuesta insulínica mediada por incretinas, todo ello concordante con una situación biológica de **resistencia a las incretinas o de respuesta defectuosa a incretinas**

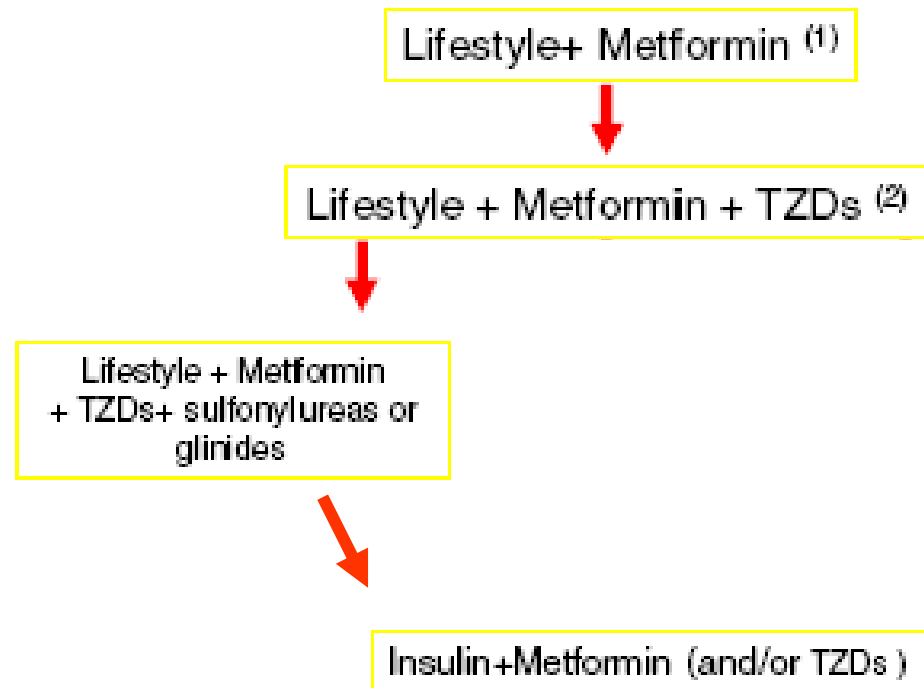
# Secreción de insulina mediada por GLP-1 reducida en portadores de alelos de riesgo de TCF7L2



# El efecto incretina está reducido en portadores de alelos de riesgo de TCF7L2



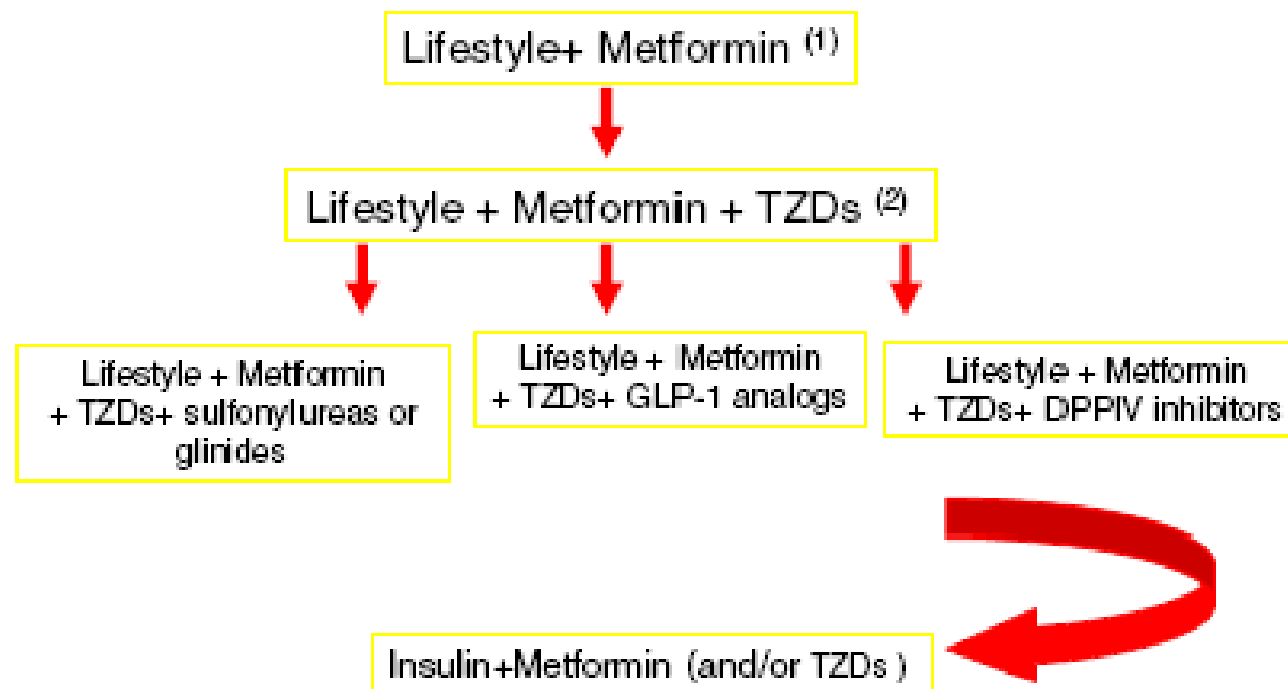
# Dónde colocar estos agentes incretínicos en el algoritmo terapéutico de la DM2?



- (1) TZDs if there are side effects or contraindication for metformin.  
In presence of PPH, +  $\alpha$ -glucosidase inhibitors
- (2) In presence of PPH, +  $\alpha$ -glucosidase inhibitors

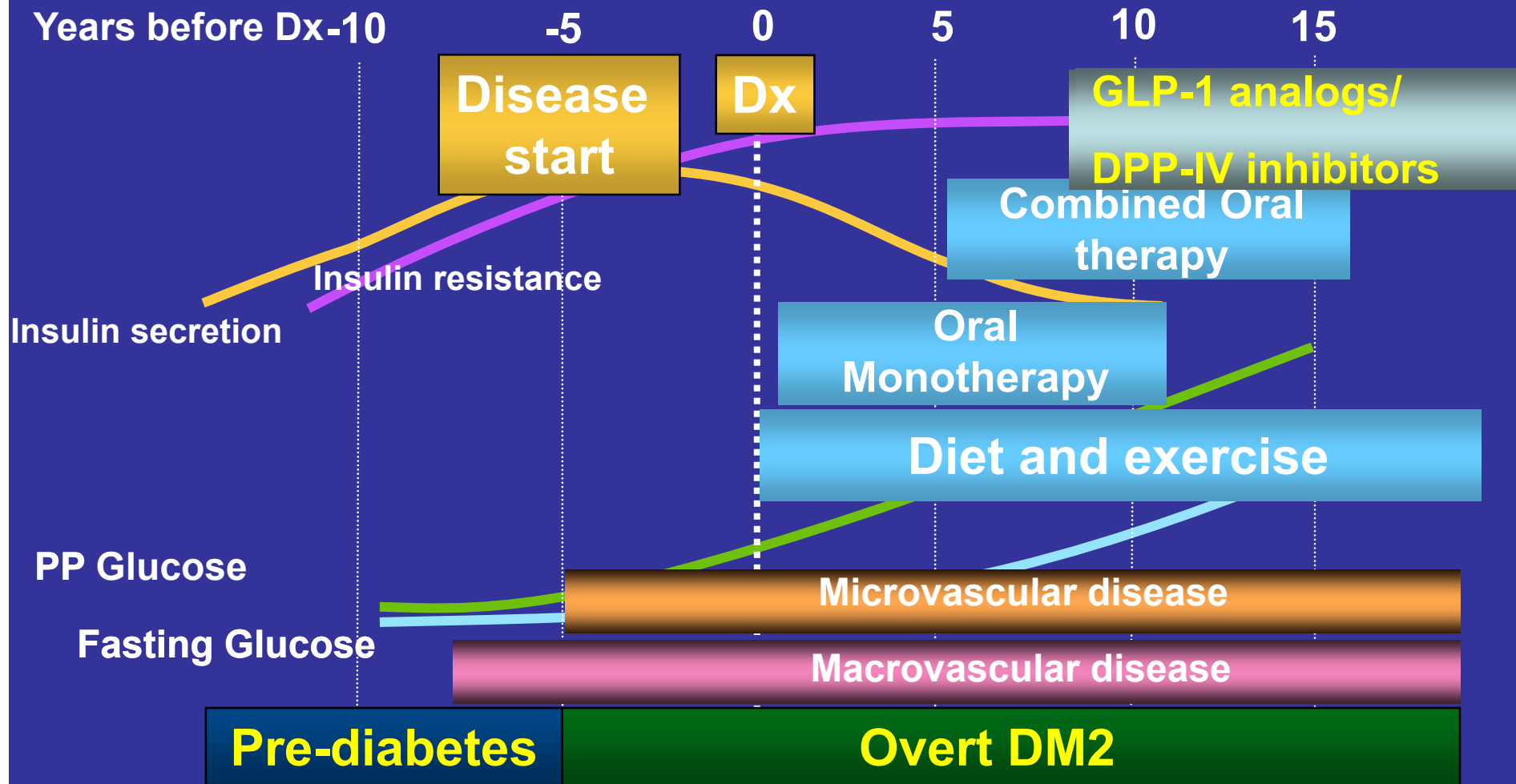


# Dónde colocar estos agentes incretínicos en el algoritmo terapéutico de la DM2?



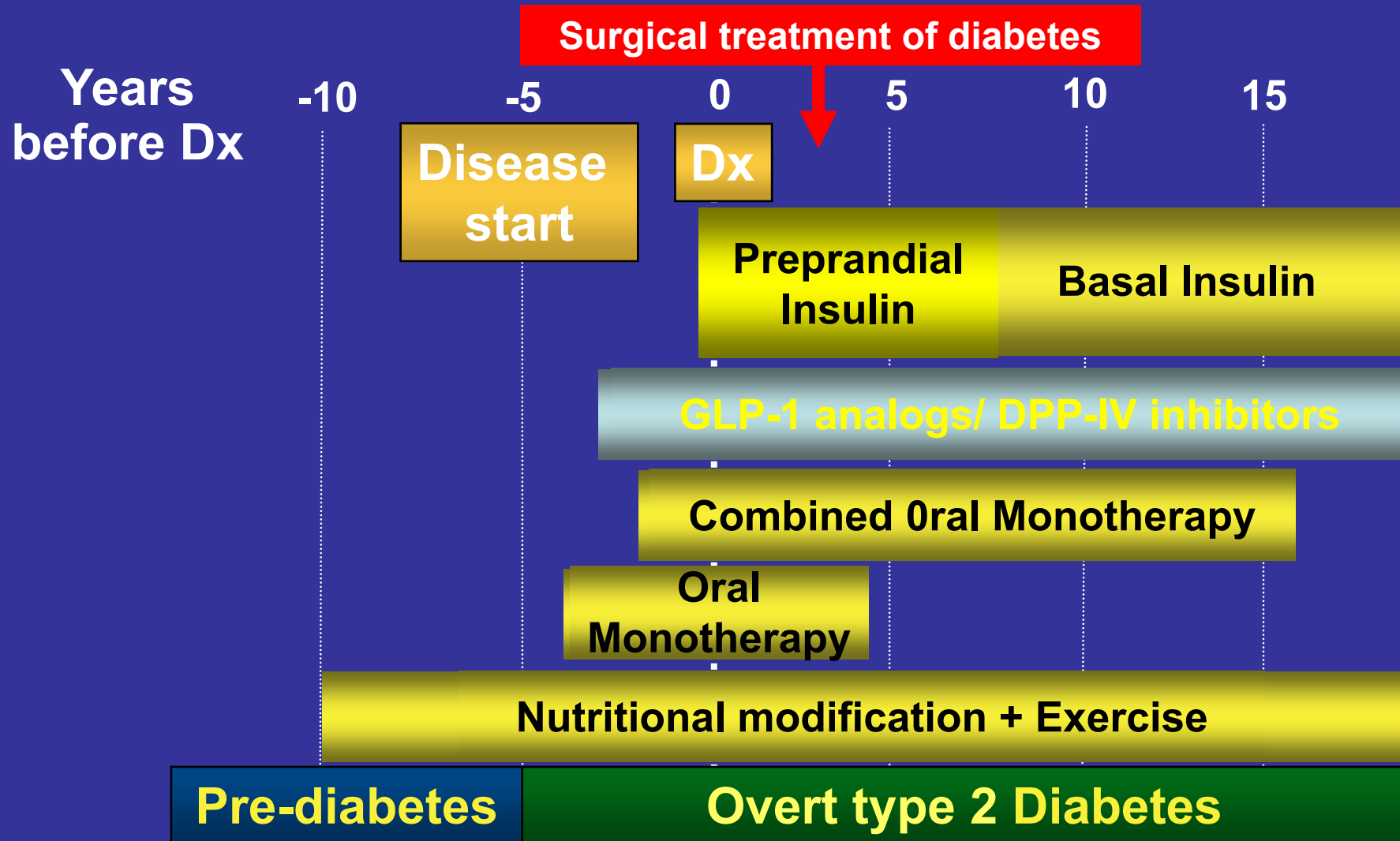
- (1) TZDs if there are side effects or contraindication for metformin.  
In presence of PPH, +  $\alpha$ -glucosidase inhibitors
- (2) In presence of PPH, +  $\alpha$ -glucosidase inhibitors

# Natural History (*current practice*) of DM 2 treatment



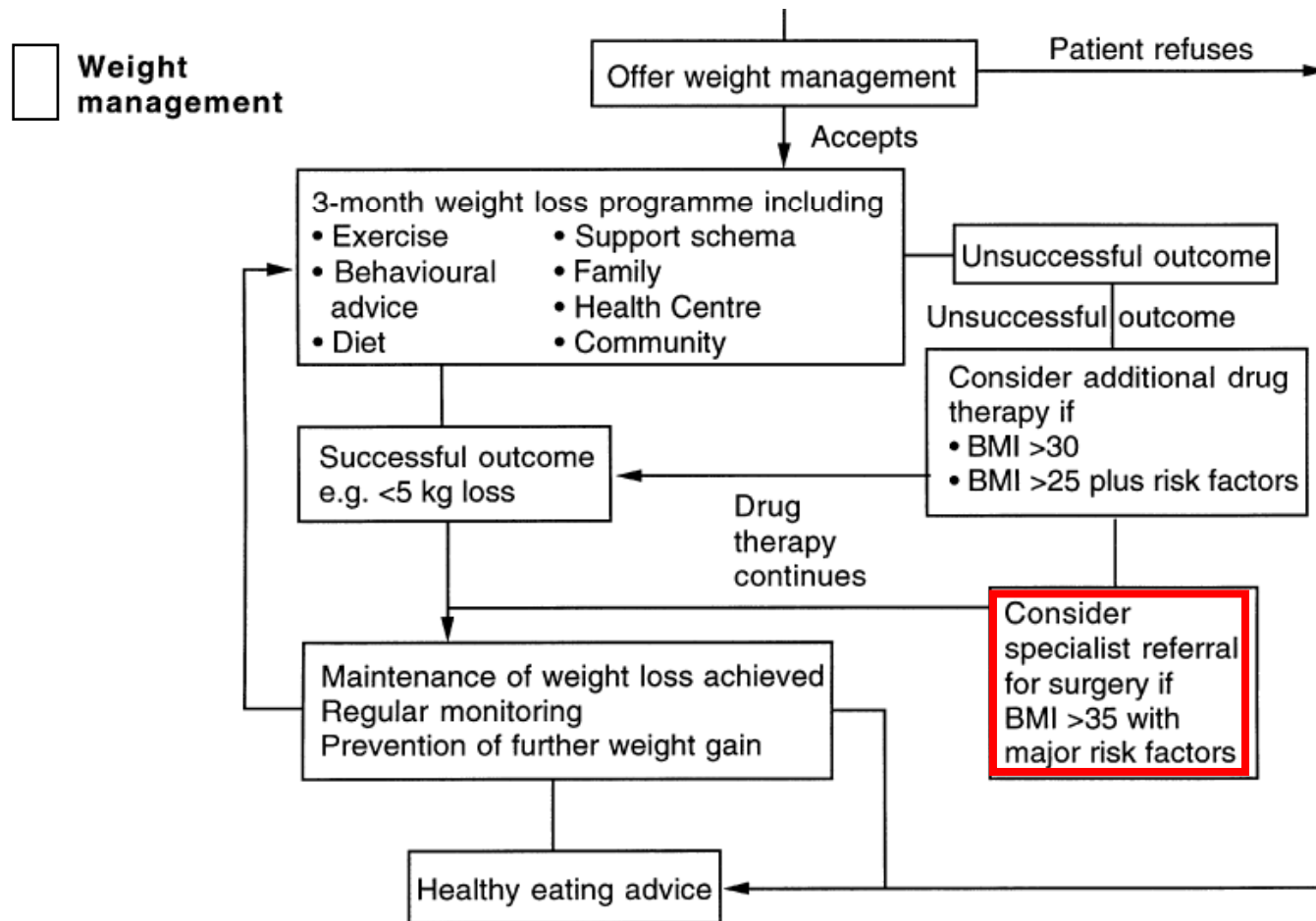
# Modern treatment of T2DM

Towards a new paradigm



# Management of obesity in patients with Type 2 diabetes

L. Campbell and S. Rössner\*



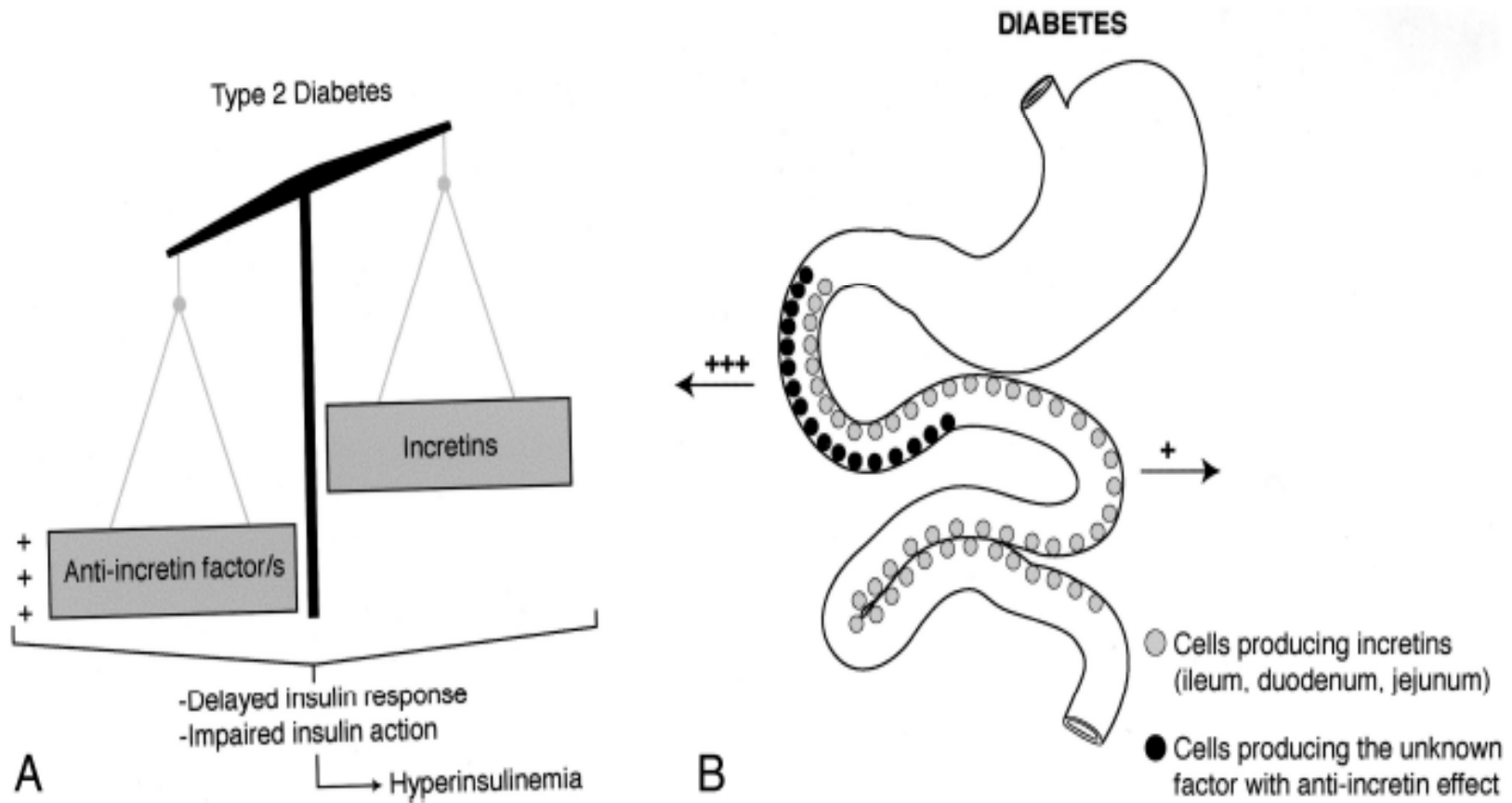
# Resultados de la cirugía metabólica

Metabolic outcomes	Years of follow up	Procedure	Post-surgical weight change	Reference
93% resolution of diabetes	3.5 years	Roux-en-Y	38% decrease in weight	DeMaria [17]
93% resolution of diabetes	1 year	Roux-en-Y	34% decrease in weight	Cowan [45]
71% resolution of diabetes	9 years	Roux-en-Y	33% decrease in weight	MacDonald [29]
64% resolution of diabetes	1 year	Lap-Band	20% decrease in weight	Dixon [7]
83% resolution of diabetes	7.6 years	Roux-en-Y	32% decrease in weight	Poires [5]
99% non-progression				
99% non-progressed	5.8 years	Roux-en-Y	52% excess weight loss	Long [6]
58% reduction in incidence of diabetes	3.2 years	Lifestyle intervention	5% decrease in weight	Tuomilehto [26]
58% reduction in incidence of diabetes	2.8 years	Lifestyle intervention	4.2% decrease in weight	DPP [2]

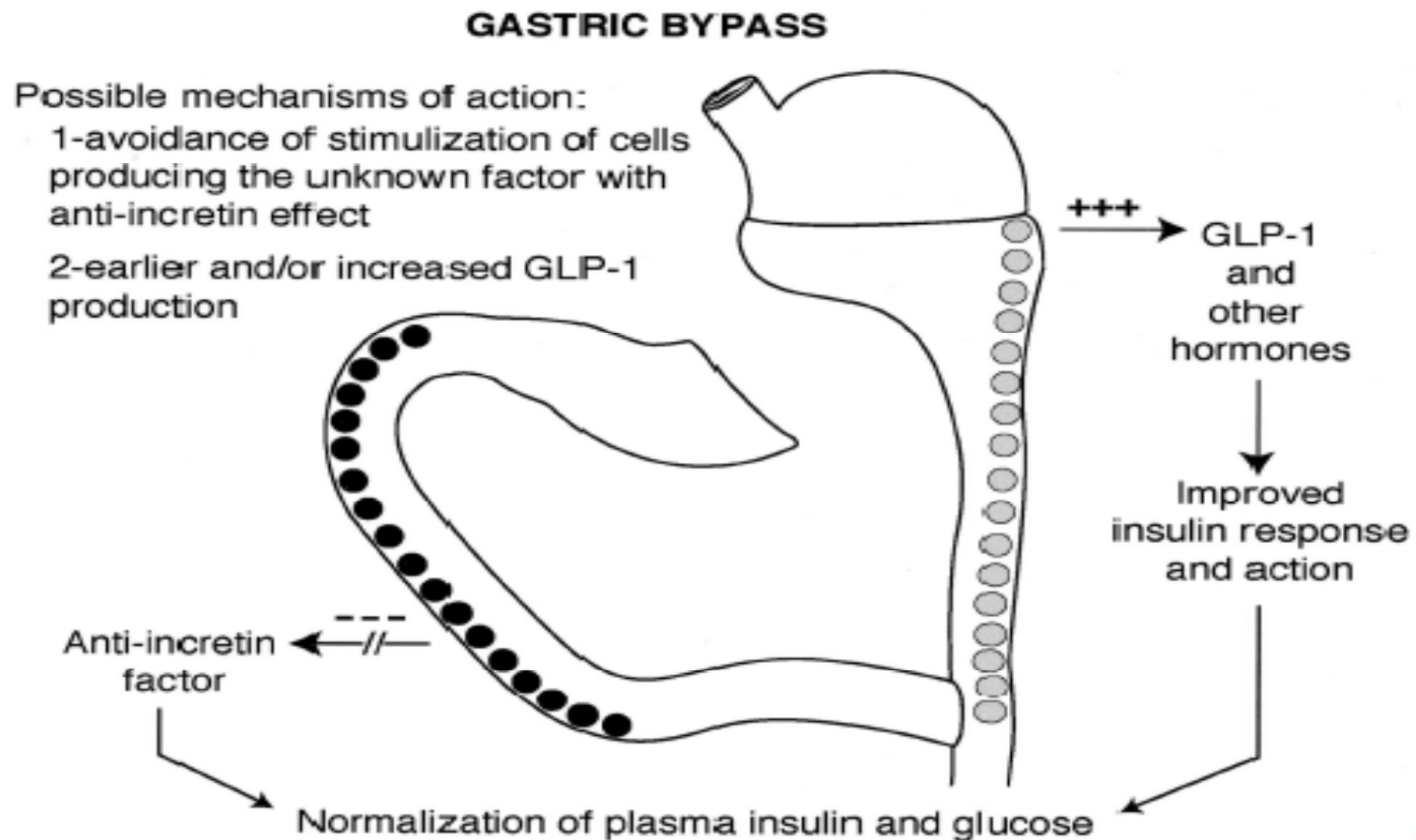
# Potential of Surgery for Curing Type 2 Diabetes Mellitus

Francesco Rubino, MD,\* and Michel Gagner, MD, FACS, FRCSC†

From the \*IRCAD-European Institute of Telesurgery, Strasbourg, France, and the †Division of Laparoscopic Surgery, Mount Sinai Medical Center, New York, New York



# Potential effects of gastric by-pass on the pathophysiology of T2 DM



# Canvis hormonal després de by pass gastic i el seu efecte sobre la insulina

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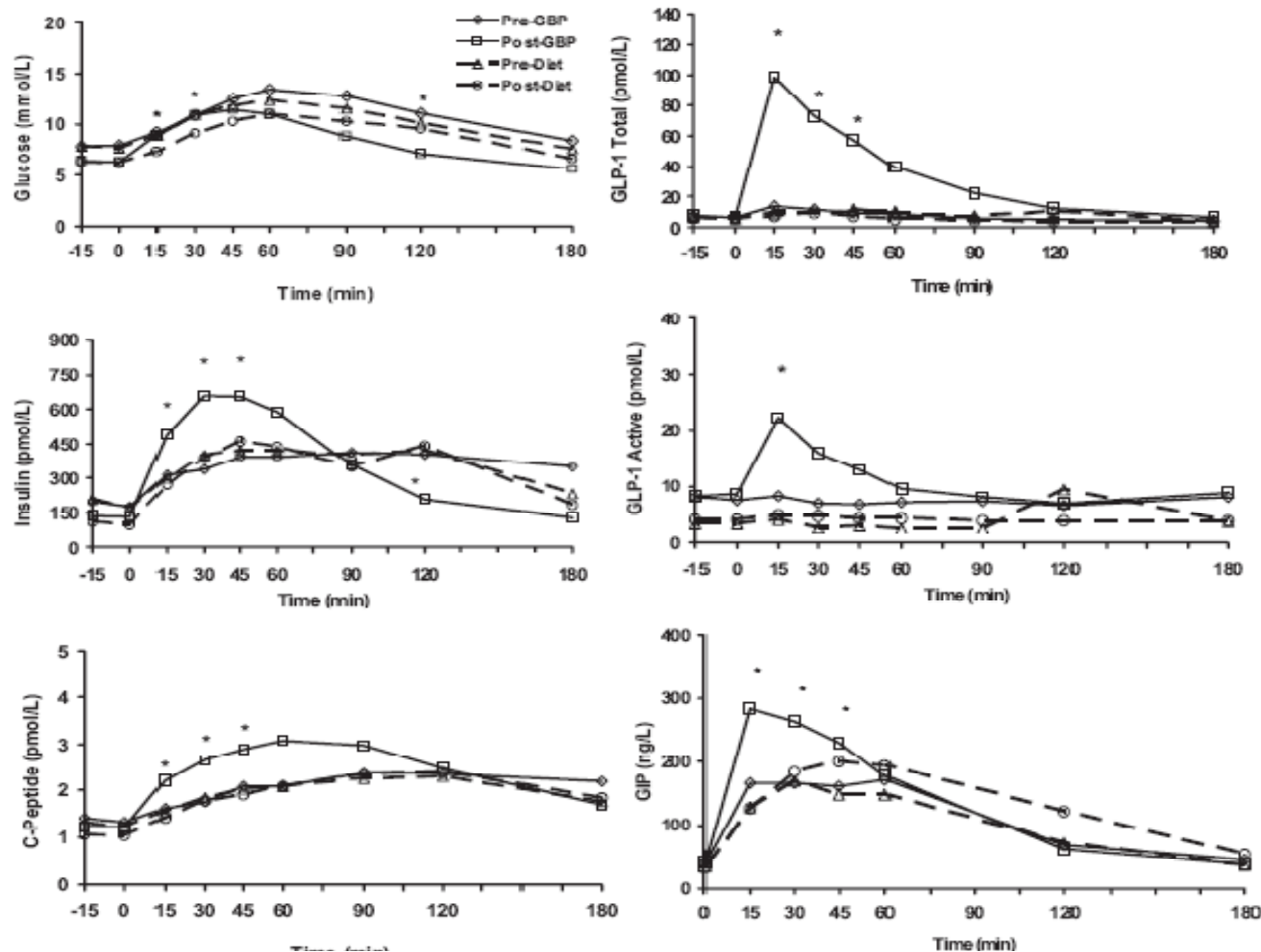
<b>Hormone</b>	<b>Change After Bypass</b>	<b>Effect on Insulin Secretion</b>
Ghrelin	Decrease	Low-level stimulatory
Gastric inhibitory peptide	Increase	High-level stimulatory
Glucagon like peptide	Increase	High-level stimulatory
Leptin	Decrease	Low-level stimulatory



## Effects of bariatric surgery on incretins

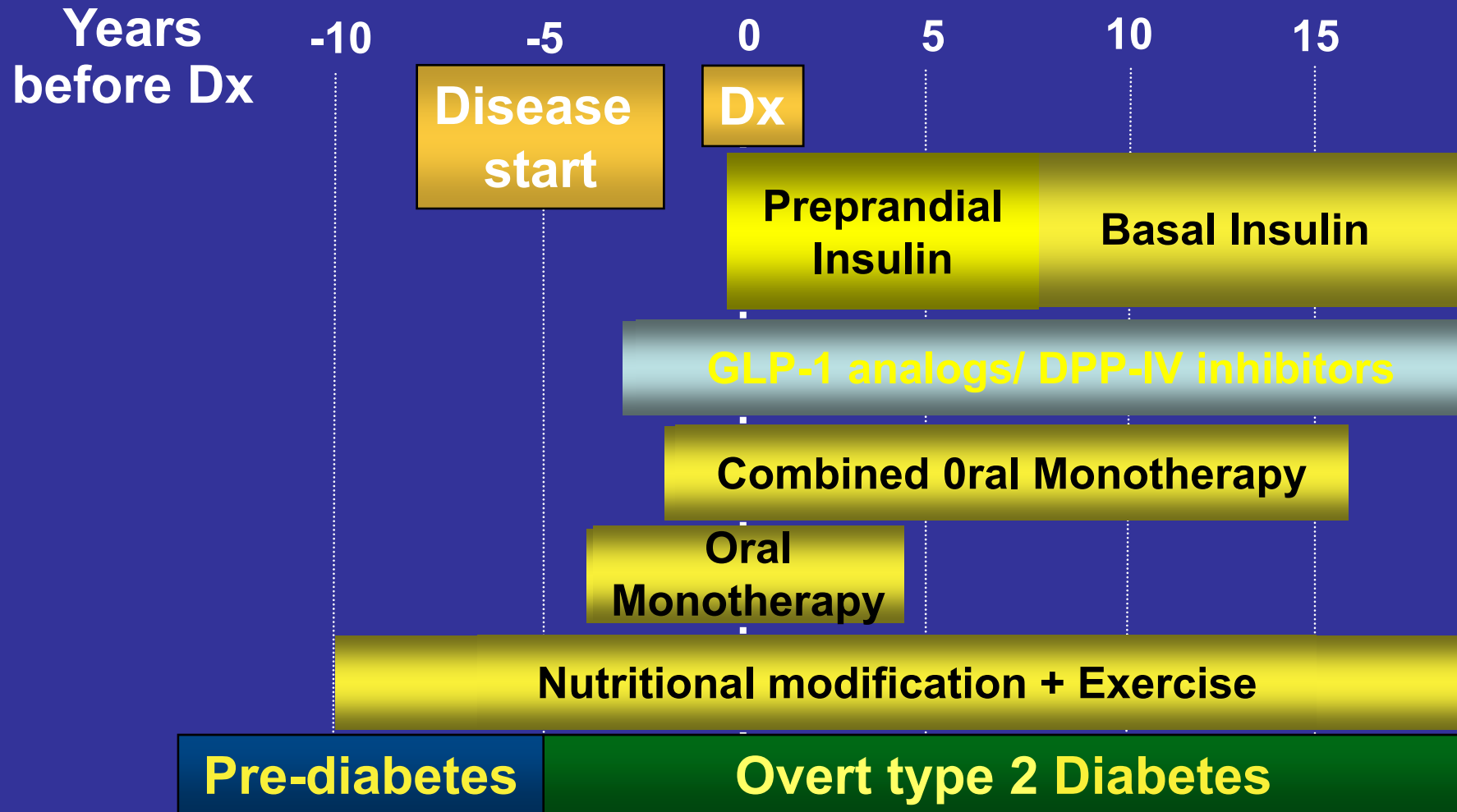
Reference	n	Surgery type	Study type	Control group	GLP-1, EG*	GIP	IE‡
Lauritsen 1980	44	JIB 3/1 (12) JIB 1/3 (5)	C-S	<ul style="list-style-type: none"> <li>• Obese (12)</li> <li>• Nonobese s/p IAS for FHC (5)</li> <li>• Nonobese (10)</li> </ul>	Not measured	↓ GIP after oral glucose vs. obese	<ul style="list-style-type: none"> <li>• JIB 3/1 ↓ IE vs. obese</li> <li>• JIB 1/3 ↑ IE vs. nonobese</li> </ul>
Sarson 1981	87	JIB (20) or BPD (38)	C-S	<ul style="list-style-type: none"> <li>• Lean (13)</li> <li>• Obese (16)</li> </ul>	↑ fasting and postprandial EG	↑ fasting GIP vs. lean, ↓ postprandial GIP vs. lean and obese	Not measured
Sirinek 1986	12	GBP	L	• Before and 3–4 months after GBP	Not measured	↓ fasting and postglucose GIP	Not measured
Naslund 1998	24	20 years after JIB (6)	C-S	<ul style="list-style-type: none"> <li>• Lean (6)</li> <li>• Nonoperated obese (6)</li> <li>• Obese 9 months after JIB (6)</li> </ul>	↑ fasting and meal-stimulated GLP-1	↑ fasting and meal-stimulated GIP	Not measured
Barry 1977	12	JIB	L	Before, 3 weeks and 6 months after JIB	↑ EG 3 weeks and 6 months after oral glucose	Not measured	Not measured
Moninigo 2003	5	GBP	L	Before and 1.5 months after surgery	↑ GLP-1 after test meal	Not measured	Not measured
Jorde 1981	21	JIB	C-S and L	<ul style="list-style-type: none"> <li>• Before, 2 and 6 weeks s/p JIB (5)</li> <li>• Lean (8)</li> <li>• 2 years s/p JIB (8)</li> </ul>	Not measured	↓ GIP after liquid test meal (with less of a decrease 2 years after surgery vs. preoperative and lean)	Not measured
Kellum 1990	16	GBP (9) or VBG (7)	L	• Before and after surgery	↑ EG after glucose meal	Not measured	Not measured
Clements 2004	20	GBP	L	• Before and 2, 6 and 12 weeks after surgery	No change in fasting levels	↓ fasting GIP at 6 and 12 weeks	Not measured
Rubino 2004	10	GBP	L	• Before and 3 weeks after surgery	No change in fasting levels	↓ fasting GIP only in diabetics	Not measured

# Effects of bariatric surgery on incretins



# Modern treatment of T2DM

Towards a new paradigm





Gràcies per la vostra atenció