

Exenatida:

Efectos sobre el control glucémico, la obesidad y los factores de riesgo cardiovascular tras 4 años de experiencia en la práctica clínica con pacientes diabéticos

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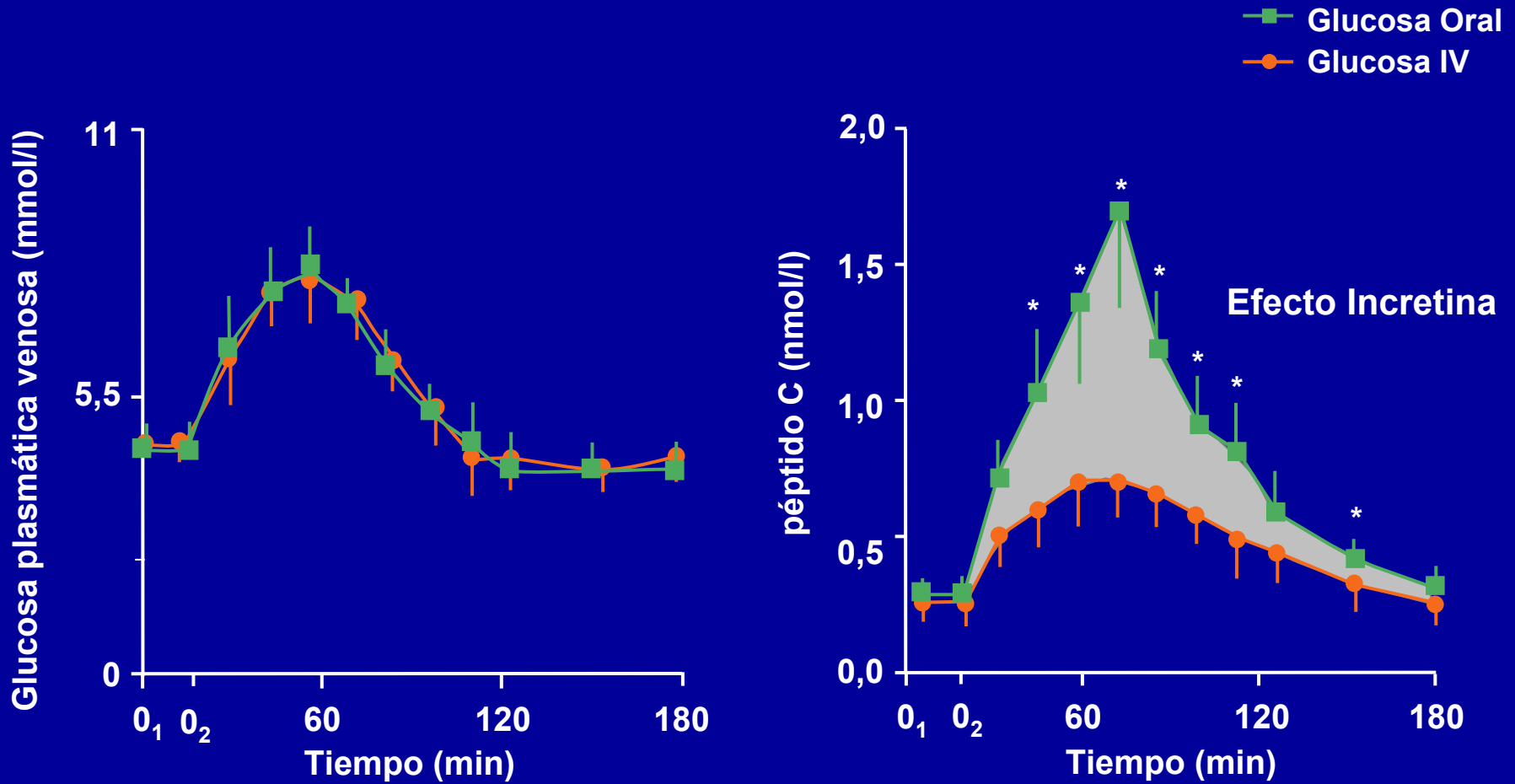
Conflictos de interés

- ◆ Comités de asesoramiento internacional: Novartis, Lilly
- ◆ Comités de asesoramiento nacional: Lilly, Novartis
- ◆ Conferencias: Lilly, Novartis, Novo-Nordisk

Sumario

- ◆ El efecto incretina en la diabetes tipo 2
- ◆ Los análogos de GLP-1 y los incretín-miméticos
- ◆ Efectos de exenatida sobre el control glucémico y la trigliceridemia postprandiales
- ◆ Efectos de exenatida sobre los otros factores de riesgo CV
- ◆ Efectos de exenatida sobre la función beta a largo plazo

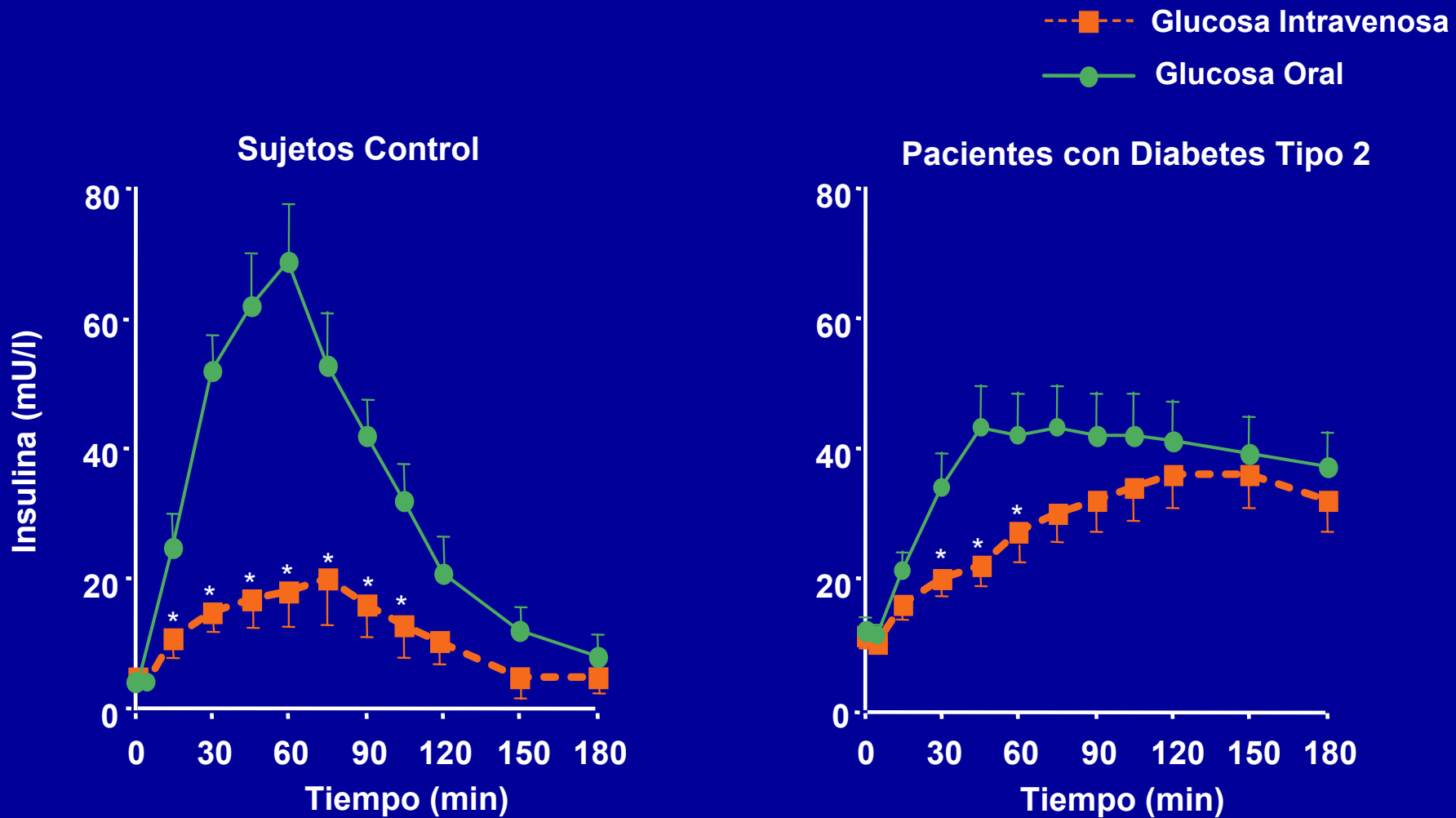
El Efecto Incretina



Media \pm EE; N = 6; * $p \leq 0,05$; 0₁-0₂ = 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



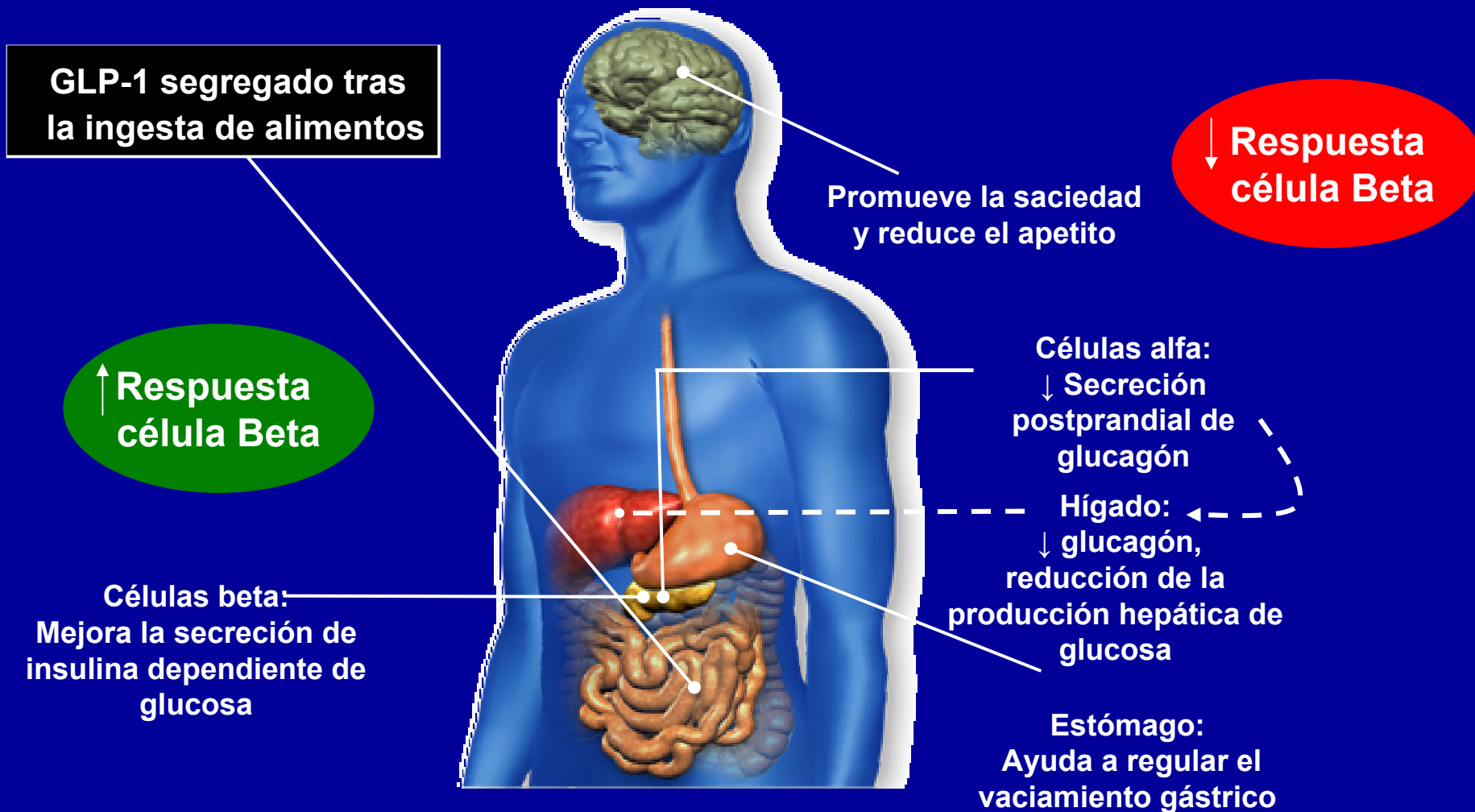
GIP: Glucose-Dependent Insulinotropic Peptide



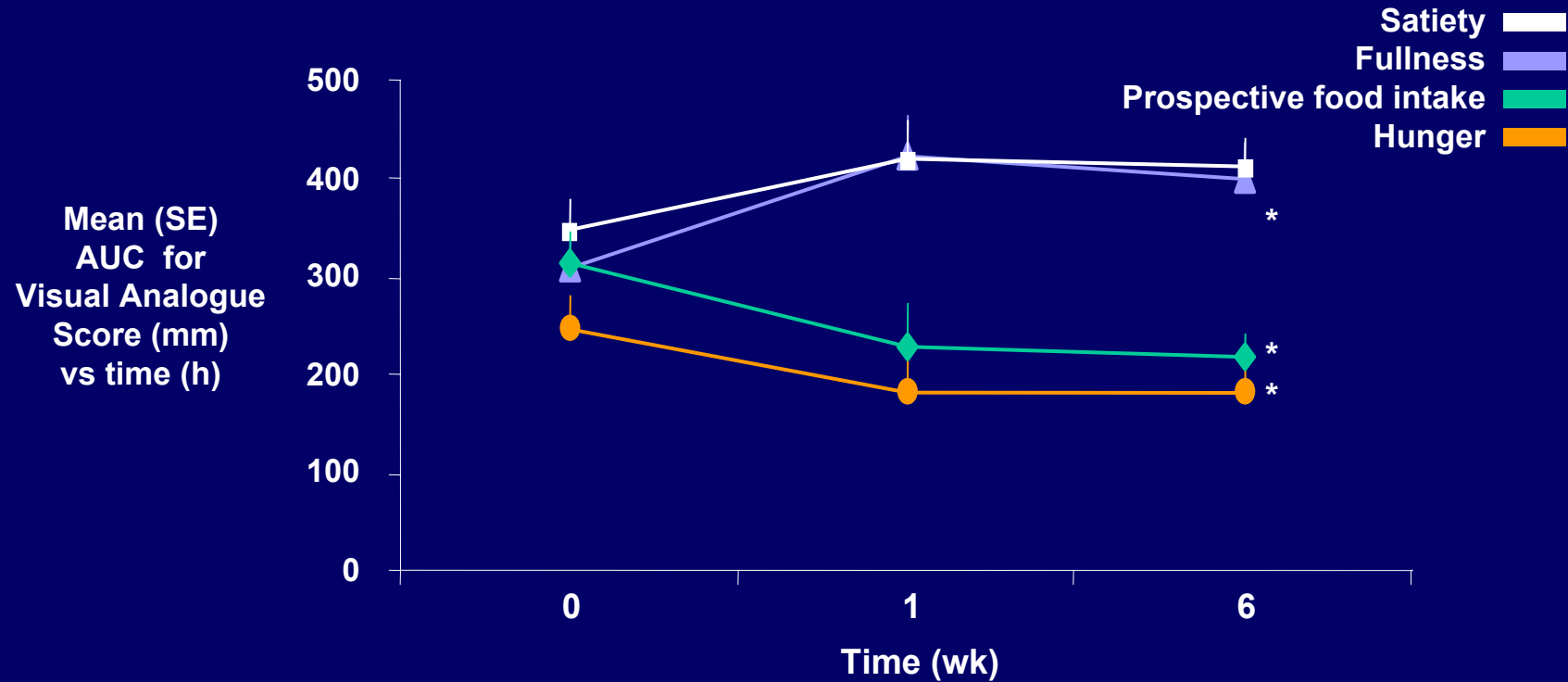
Amino acids shown in blue are homologous with the structure of glucagon.

Efectos del GLP-1 en Humanos:

papel glucorregulatorio de las Incretinas



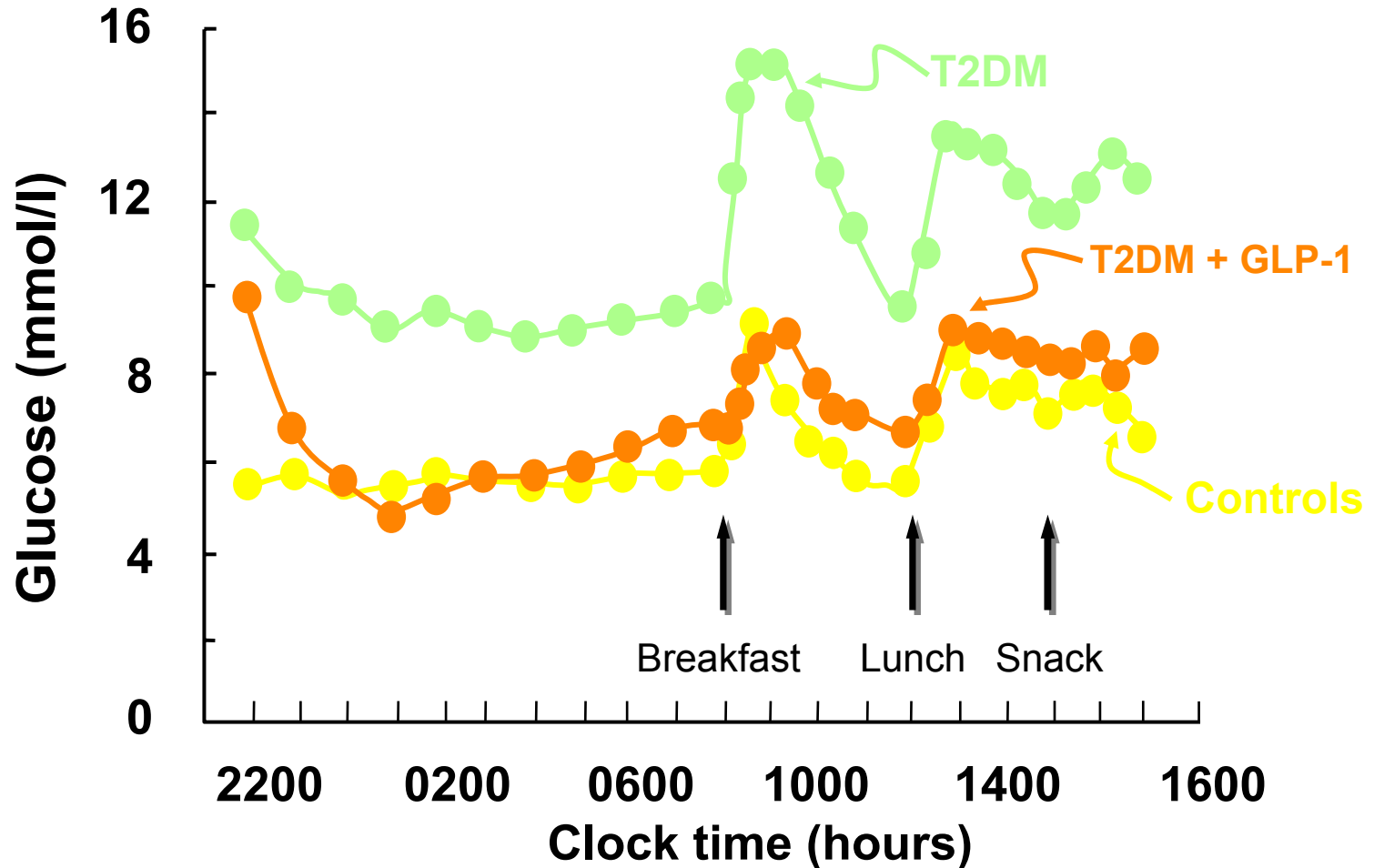
Efecto de la infusión de GLP-1 en las sensaciones asociadas con el apetito



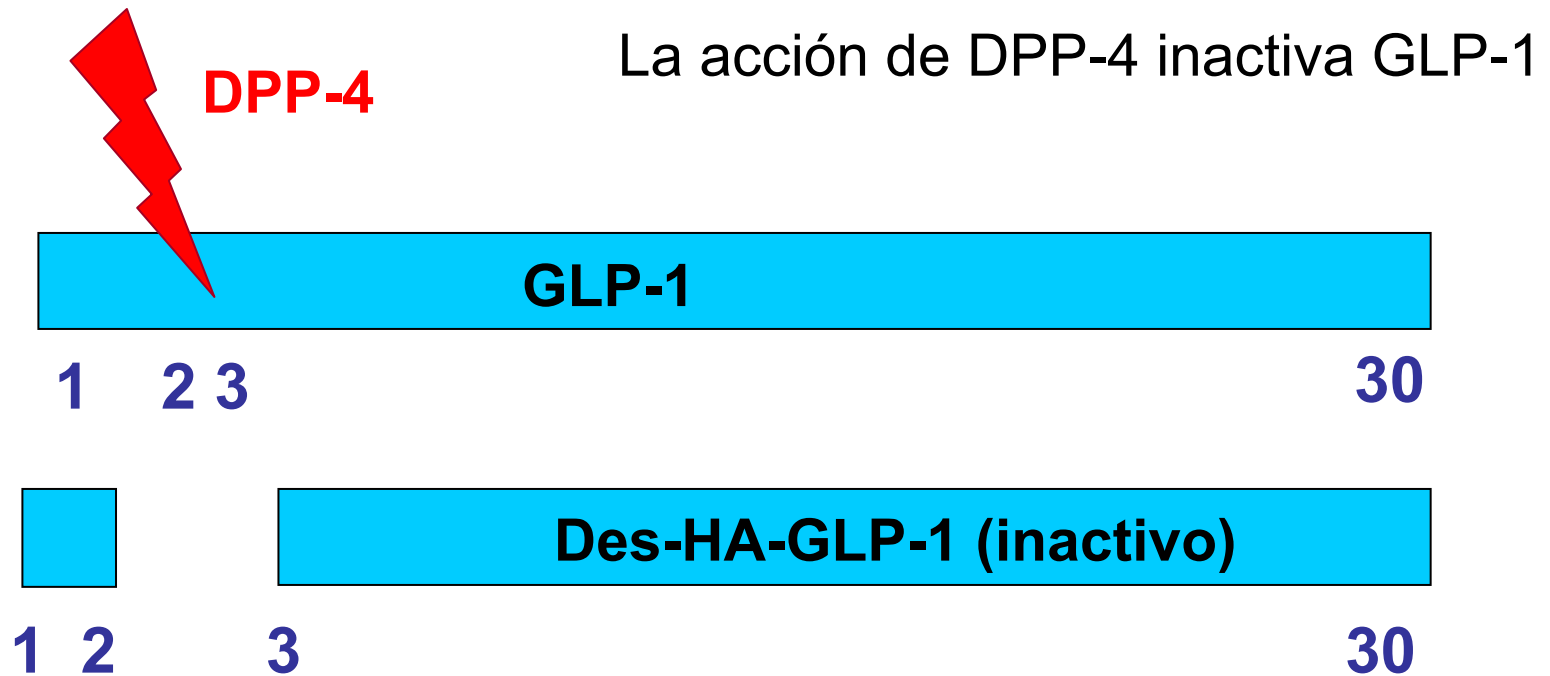
Only data of patients treated with GLP-1 showed
n=10

*P < 0.05 vs saline group

Efecto de la infusión de GLP-1 en el control glicémico de Pacientes diabéticos tipo 2 con fallo de terapia oral



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 y análogos de GLP-1



Lugar de acción de DPP-4

Liraglutida



Albumina

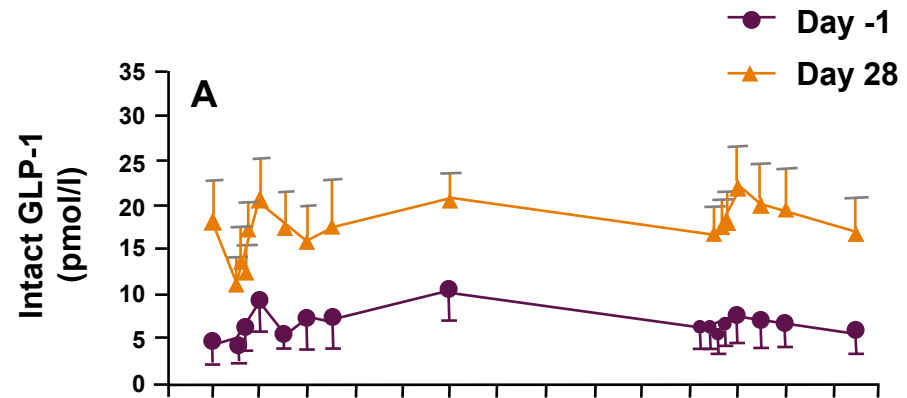
Ácido graso C-16 (unión no covalente a albúmina)

Exendina-4, Exenatida

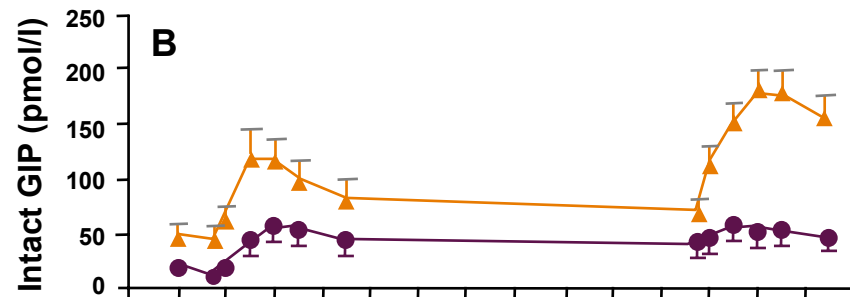


Efecto de iDPP-4 en los niveles de incretinas circulantes

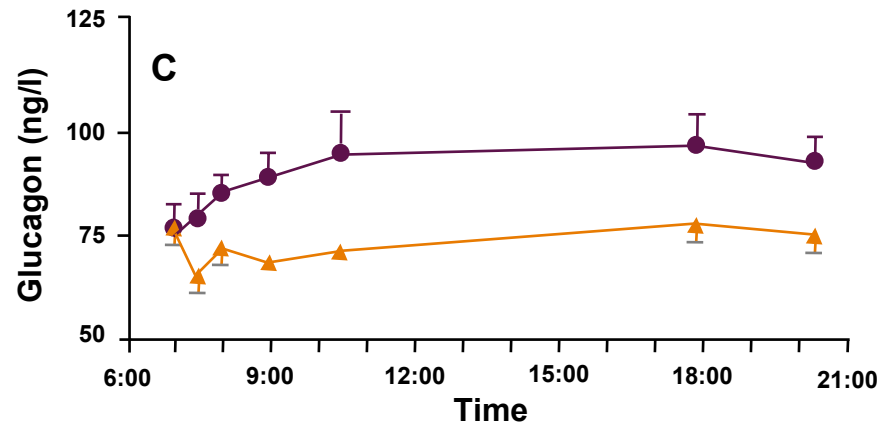
GLP-1



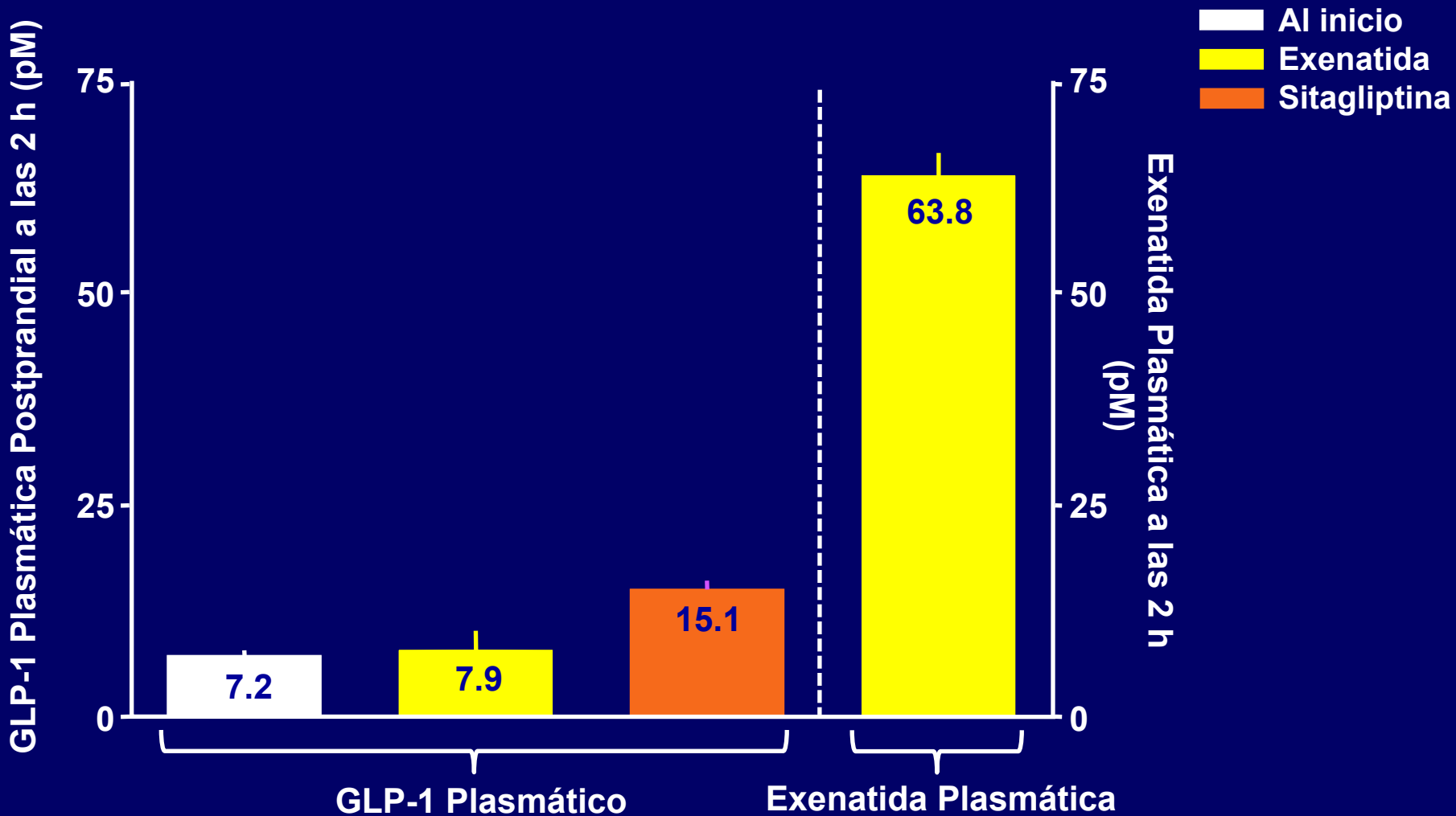
GIP



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 postratamiento a las 2 semanas
DeFronzo RA, et al. *Curr Med Res Opin.* 2008;24(10)2943-2952.

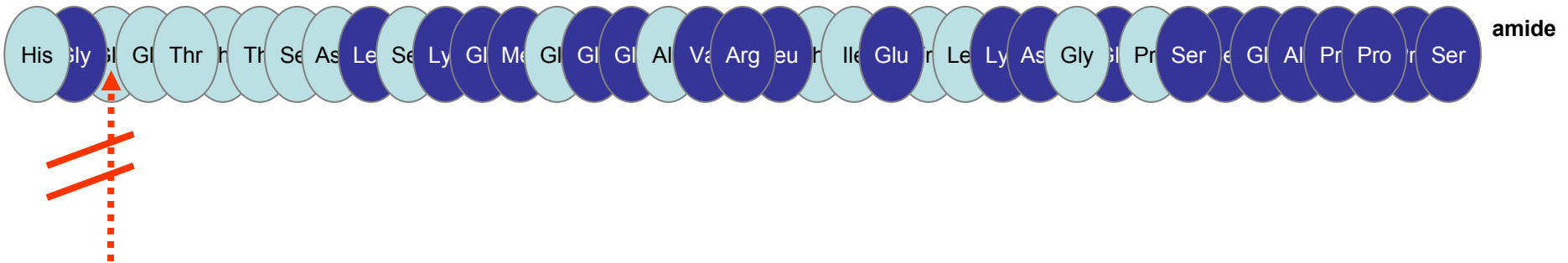
Exenatide es el primer Incretín-mimético utilizado en la práctica clínica



Lugar de acción de DPP-4



Exendina-4, Exenatida



Desarrollo de Exenatida: Un Incretín-Mimético

Exenatida (Exendina-4)

- Versión sintética de una proteína presente en la saliva del monstruo de Gila
- Aproximadamente un 50% de identidad con el GLP-1 humano
 - Se une a los receptores del GLP-1 humano en las células β *in vitro*
 - Resistente a la inactivación de la DPP-IV



Sitio de Inactivación de la DPP-IV

Exenatida (Exendina-4)



Secuencias de Aminoácidos

Exendin-4

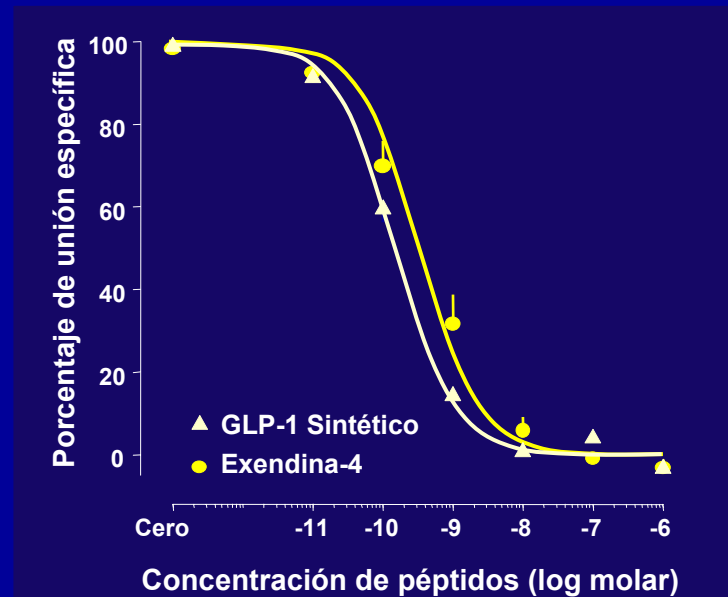
H G E G T F T S D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S

GLP-1
Human

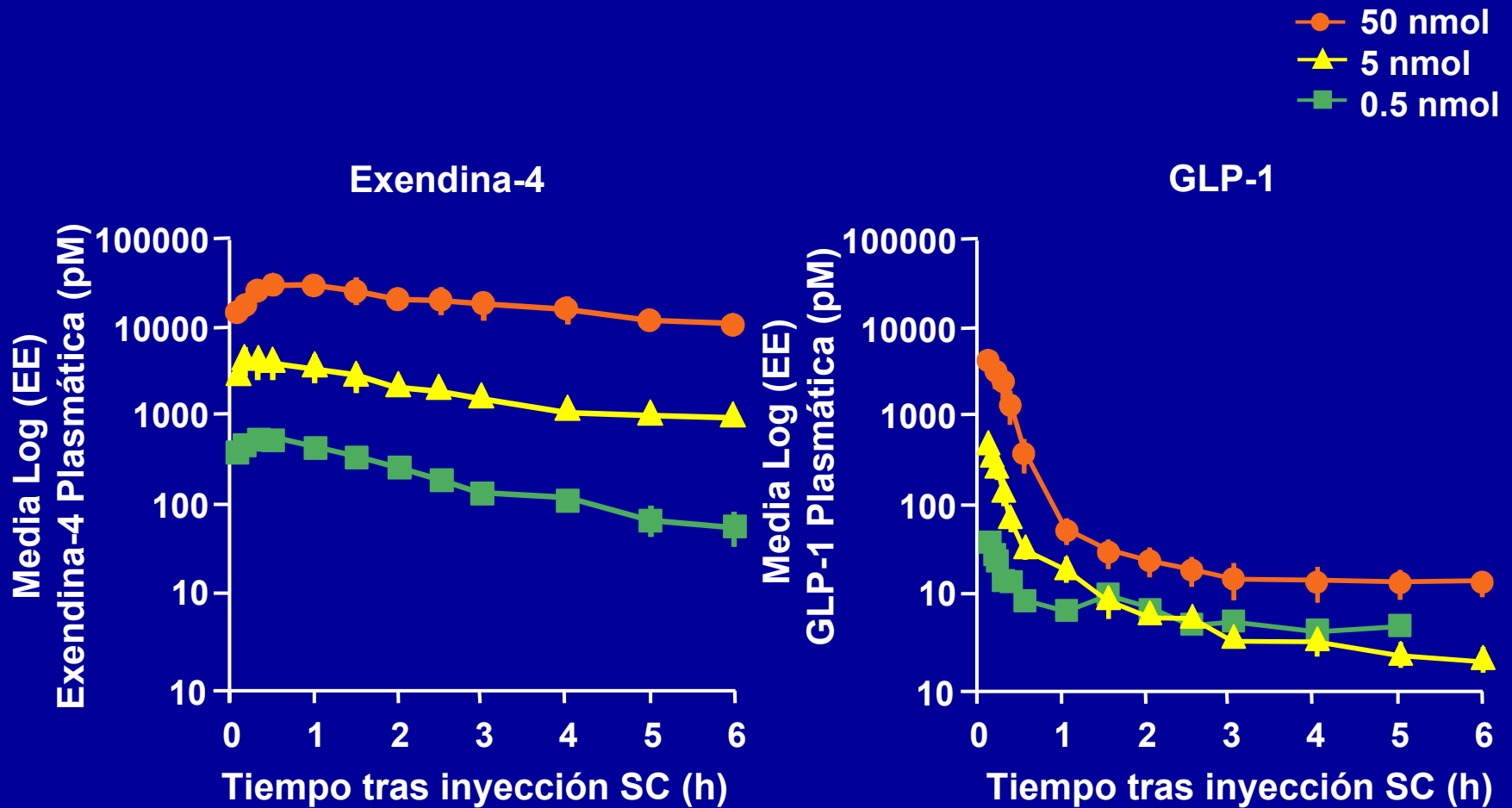
H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R

- ◆ Exendina-4 comparte aproximadamente el 50% de la identidad de los aminoácidos con GLP-1
- ◆ Exendina-4 y GLP-1 tienen una afinidad de unión similar al receptor de GLP-1 *in vitro*

Afinidad por el Receptor de GLP-1 *



Semivida de Exenatida (Exendina-4) vs GLP-1

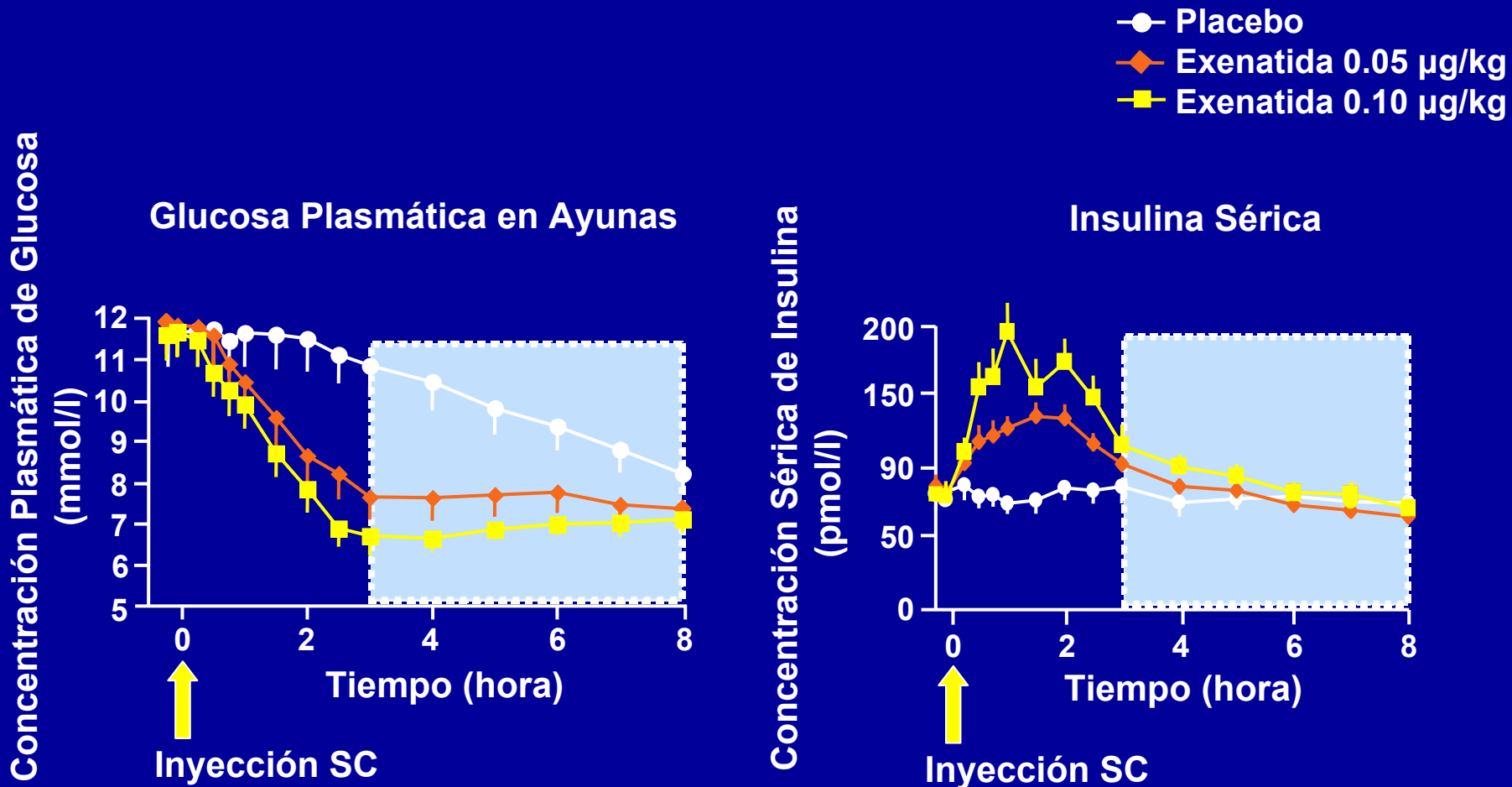


N = 4-7 (ratas); $p < 0,05$.

Adaptado de Parkes D, et al. *Drug Dev Res.* 2001;53:260-267. Reproducido con permiso de John Wiley & Sons, Inc.

Acciones Glucorreguladoras de Exenatida

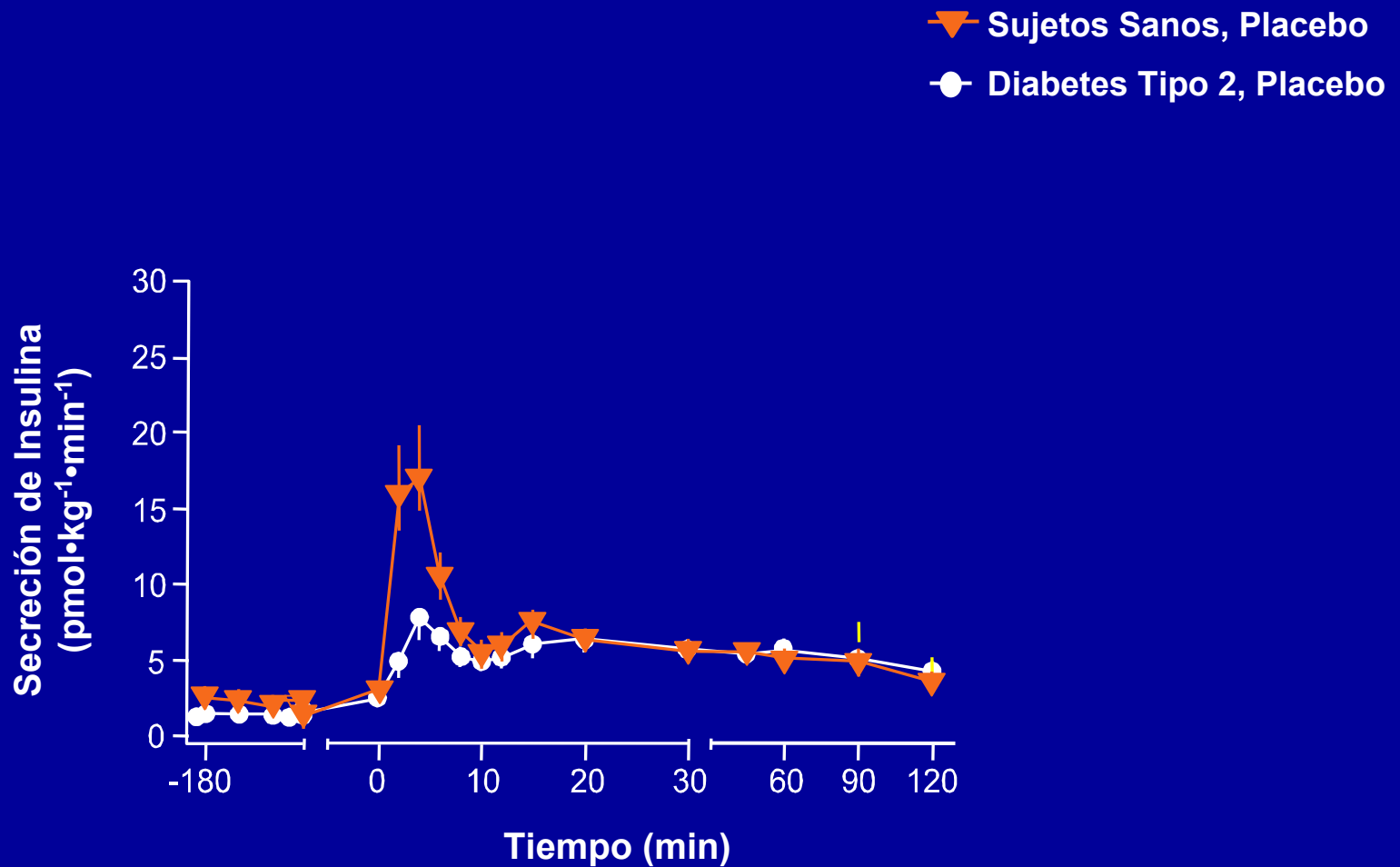
Exenatida reduce la hiperglucemia en ayunas en pacientes con Diabetes Tipo 2



Media (EE); N=12; p<.0001 para glucosa; p<.001 para insulina.

Adaptado de Kolterman OG, et al. *J Clin Endocrinol Metab.* 2003;88:3082-3089. Copyright 2003, The Endocrine Society.

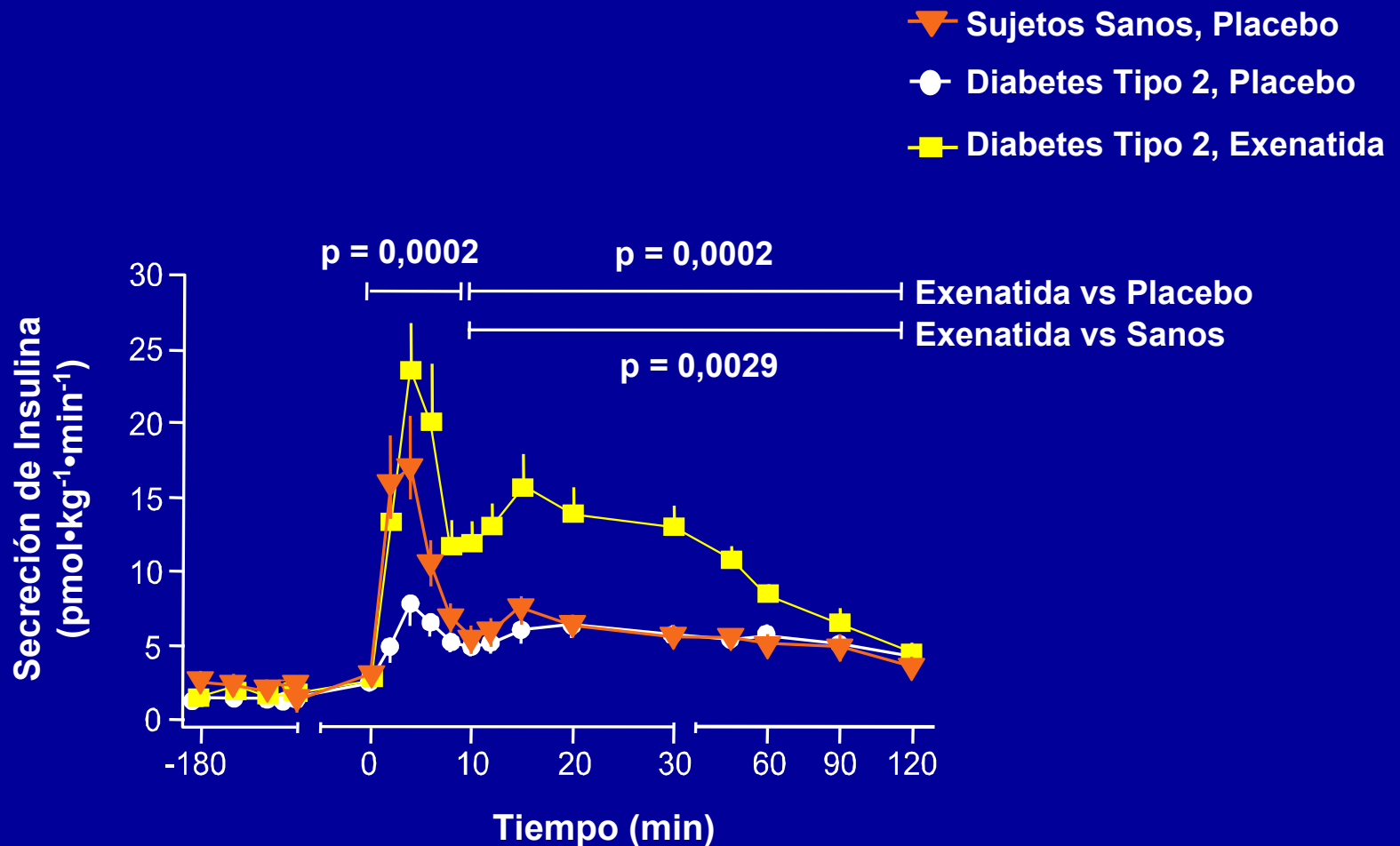
La infusión aguda de Exenatida restaura la primera fase de secreción de insulina en pacientes con DM2



Media (EE); N = 25.

Fehse F, et al. J Clin Endocrinol Metab. 2005 Nov;90(11):5991-7. Copyright 2005, The Endocrine Society.

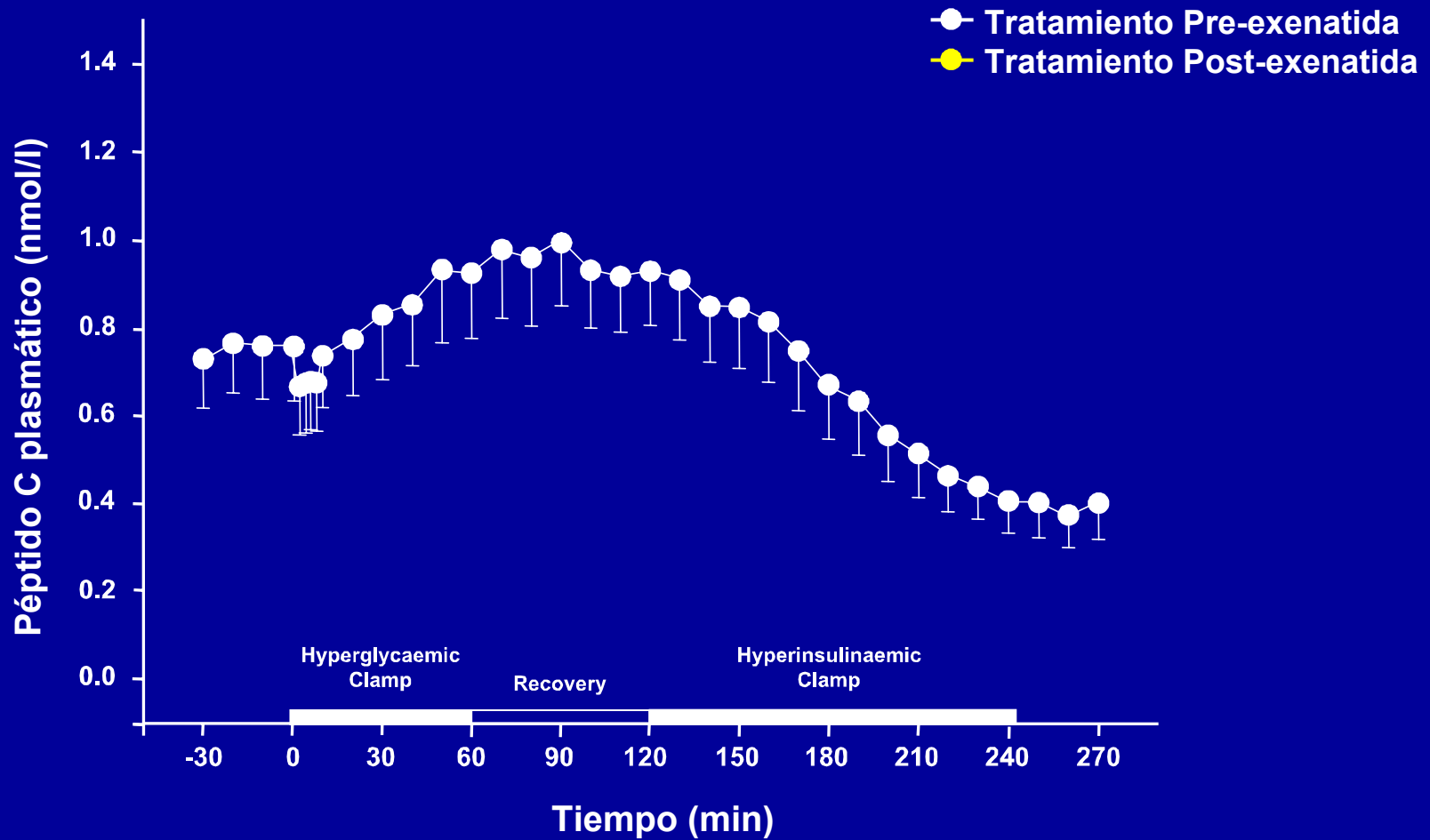
La infusión aguda de Exenatida restaura la primera fase de secreción de insulina en pacientes con DM2



Media (EE); N = 25.

Fehse F, et al. J Clin Endocrinol Metab. 2005 Nov;90(11):5991-7.

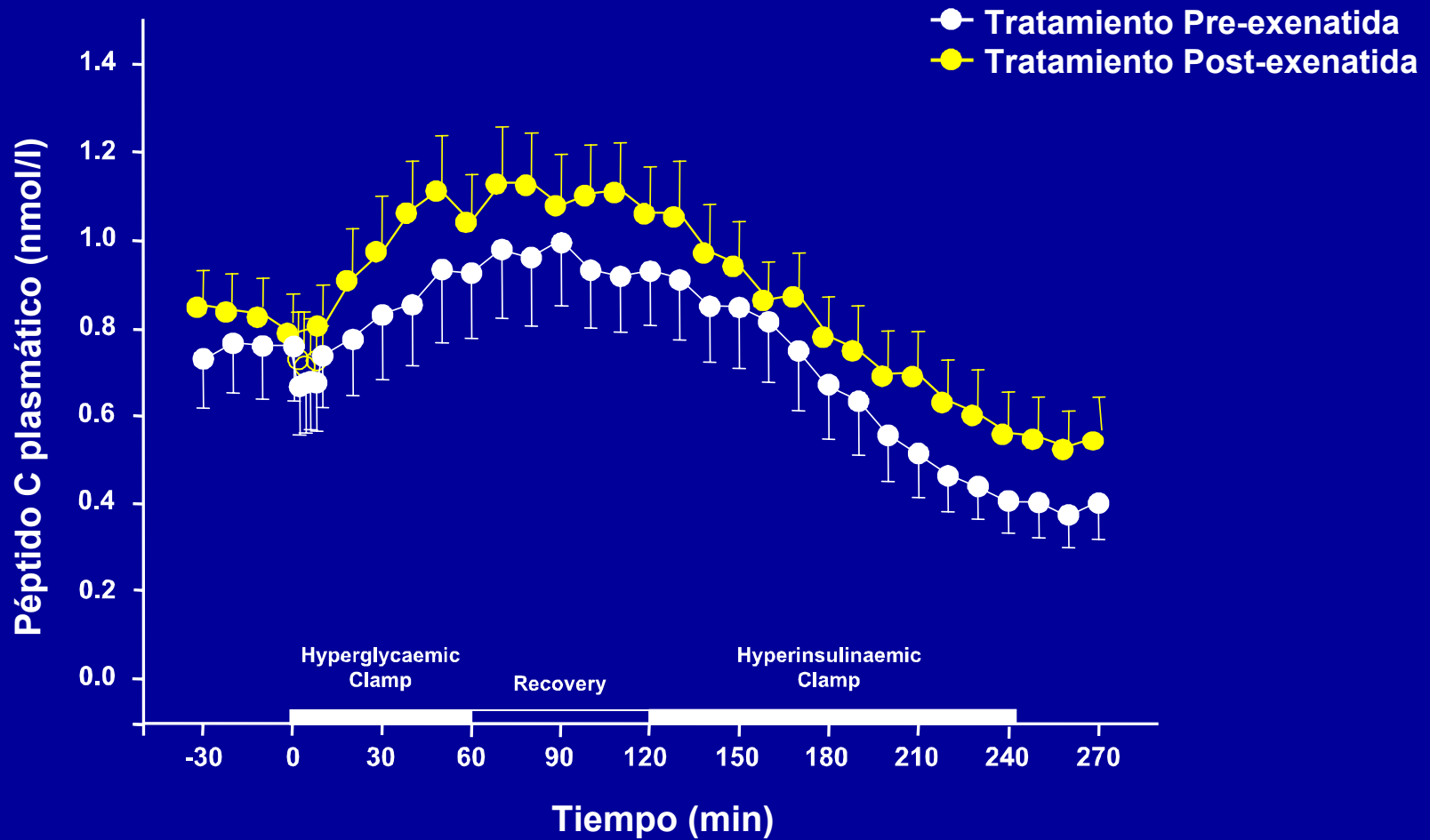
Exenatida mejora la sensibilidad de la célula β en pacientes con diabetes tipo 2



Media (EE); N = 9; p <0,002.

Egan JM, et al. *Am J Physiol Endocrinol Metab.* 2003;284:E1072-E1079.

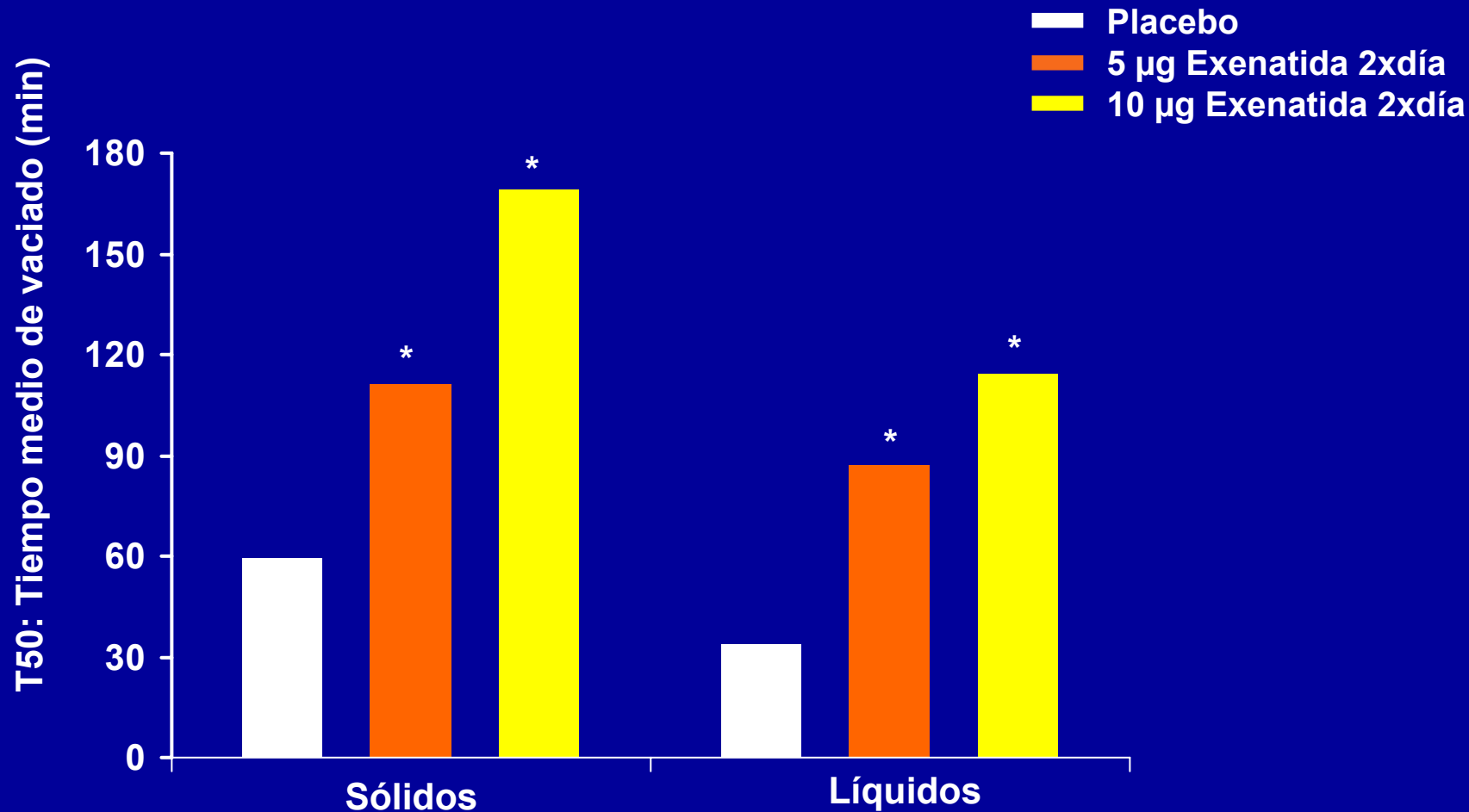
Exenatida mejora la sensibilidad de la célula β en pacientes con diabetes tipo 2



Media (EE); N = 9; p <0,002.

Egan JM, et al. *Am J Physiol Endocrinol Metab.* 2003;284:E1072-E1079.

Exenatida: Enlentecimiento dosis-dependiente del vaciado gástrico

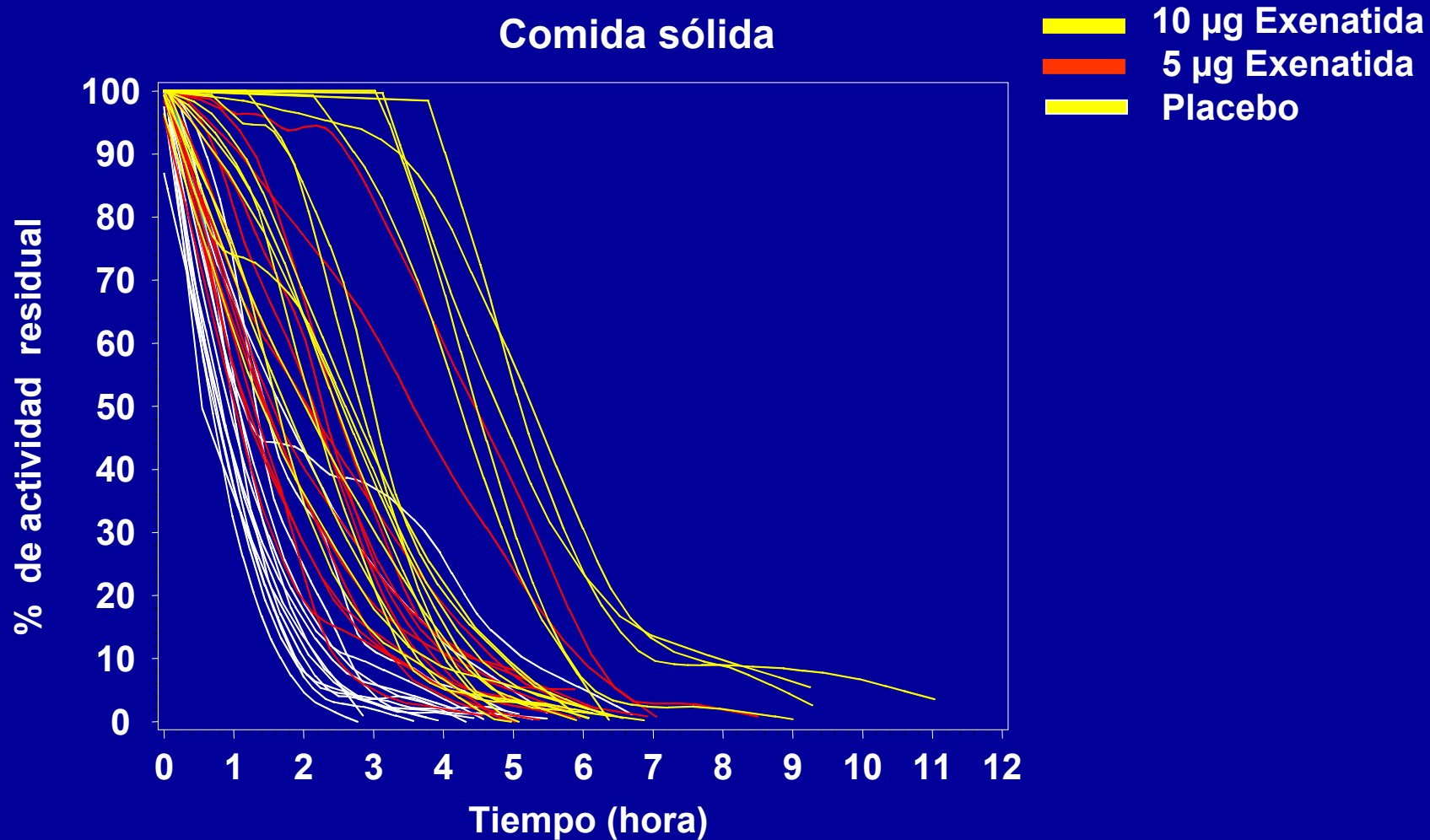


Se muestra la media de mínimos cuadros.

*p < 0,01 vs placebo.

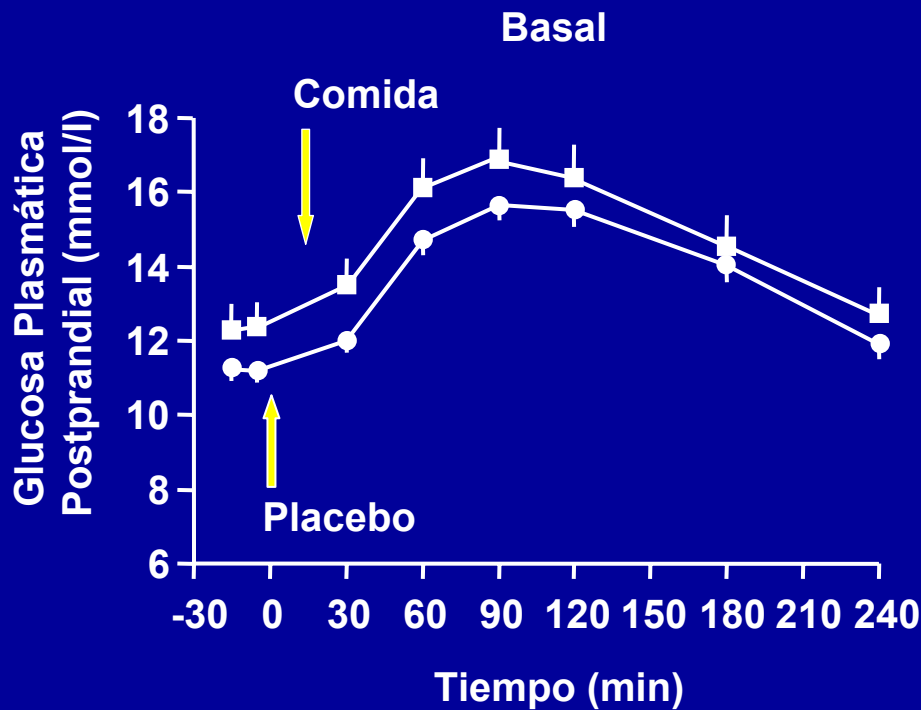
Linnebjerg H, et al. *Diabetes*. 2006;55(Suppl 1): A116-OR.

Exenatida: Enlentecimiento dosis-dependiente del vaciado gástrico



Exenatida reduce la hiperglucemia postprandial en pacientes con Diabetes Tipo 2

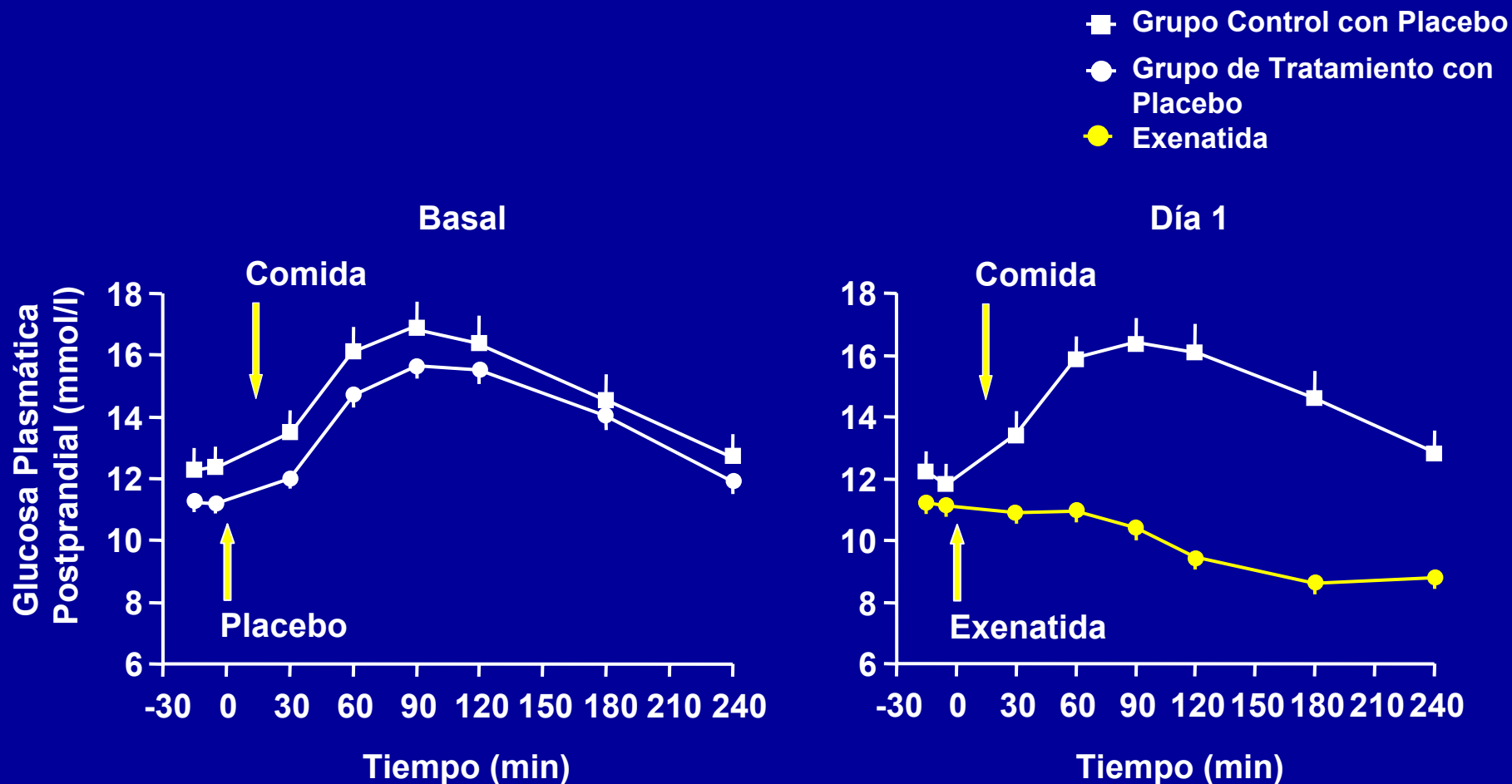
- Grupo Control con Placebo
- Grupo de Tratamiento con Placebo



Media (EE); N = 109; $p \leq 0,004$.

Fineman MS, et al. *Diabetes Care*. 2003;26:2370-2377. Reproducido con permiso de la American Diabetes Association.

Exenatida reduce la hiperglucemia postprandial en pacientes con Diabetes Tipo 2



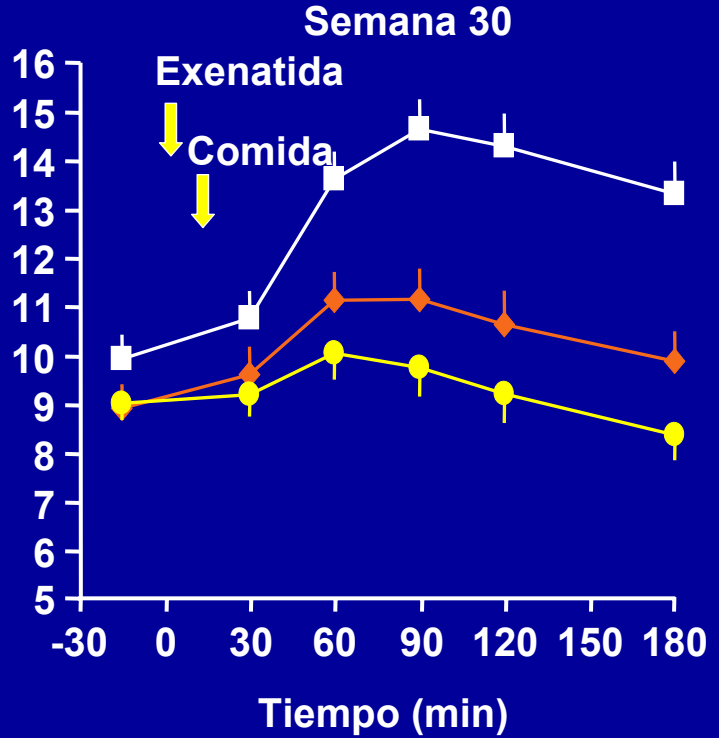
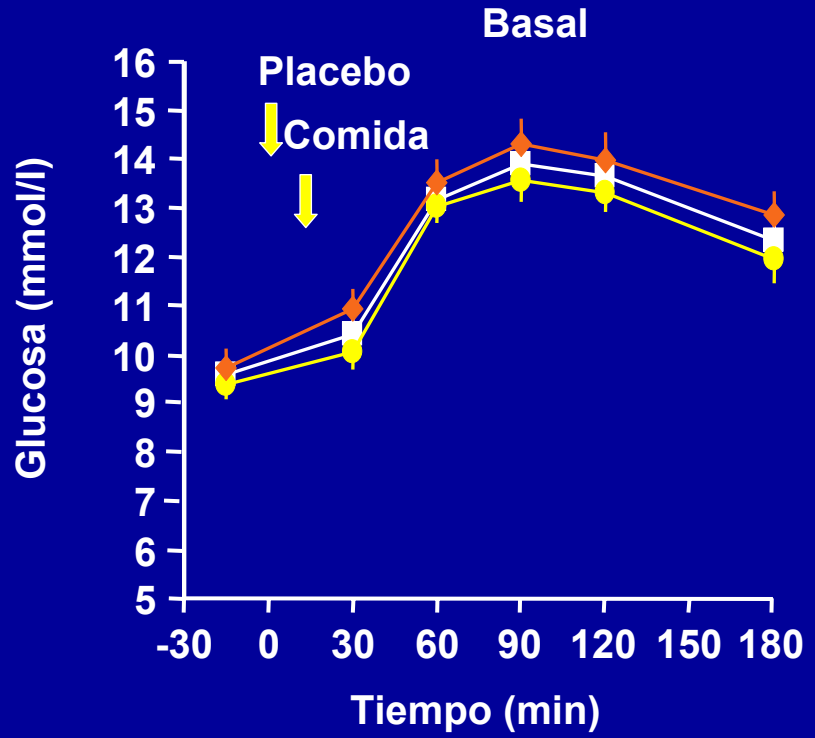
Media (EE); N = 109; $p \leq 0,004$.

Fineman MS, et al. *Diabetes Care*. 2003;26:2370-2377. Reproducido con permiso de la American Diabetes Association.

Efecto de Exenatida en la glucosa postprandial a lo largo de 30 semanas

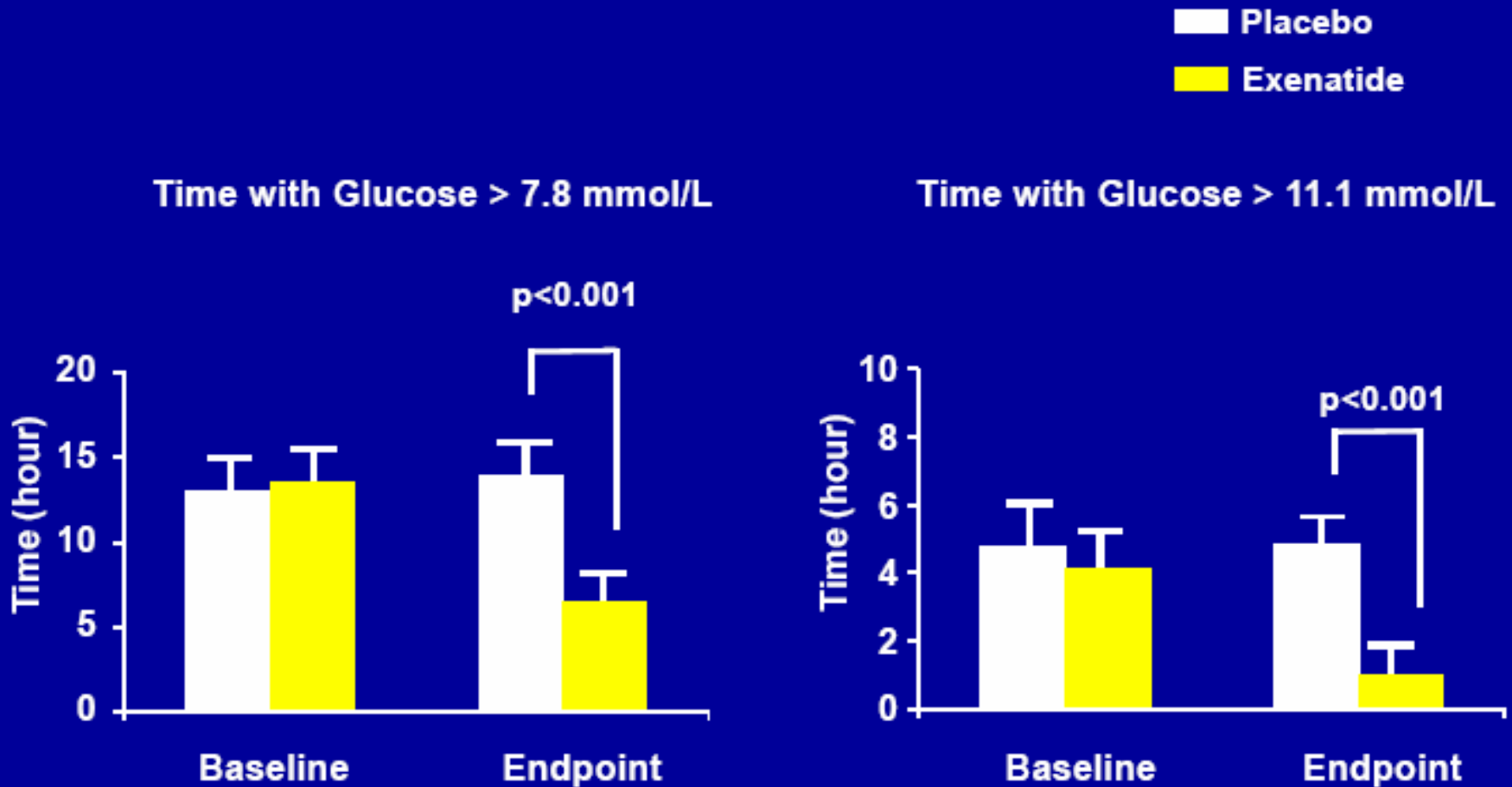
- Placebo 2 x día
- ◆ Exenatida 5 µg 2 x día
- Exenatida 10 µg 2 x día

Resultados Combinados de los Estudios en Fase 3 de Exenatida



Media (EE); N = 138; Cohorte evaluable con tolerancia a las comidas.
 $p < 0,0001$ para el cambio en la PPG desde la línea basal hasta la Semana 30, grupo de exenatida vs placebo.
Datos de archivo, Amylin Pharmaceuticals, Inc.

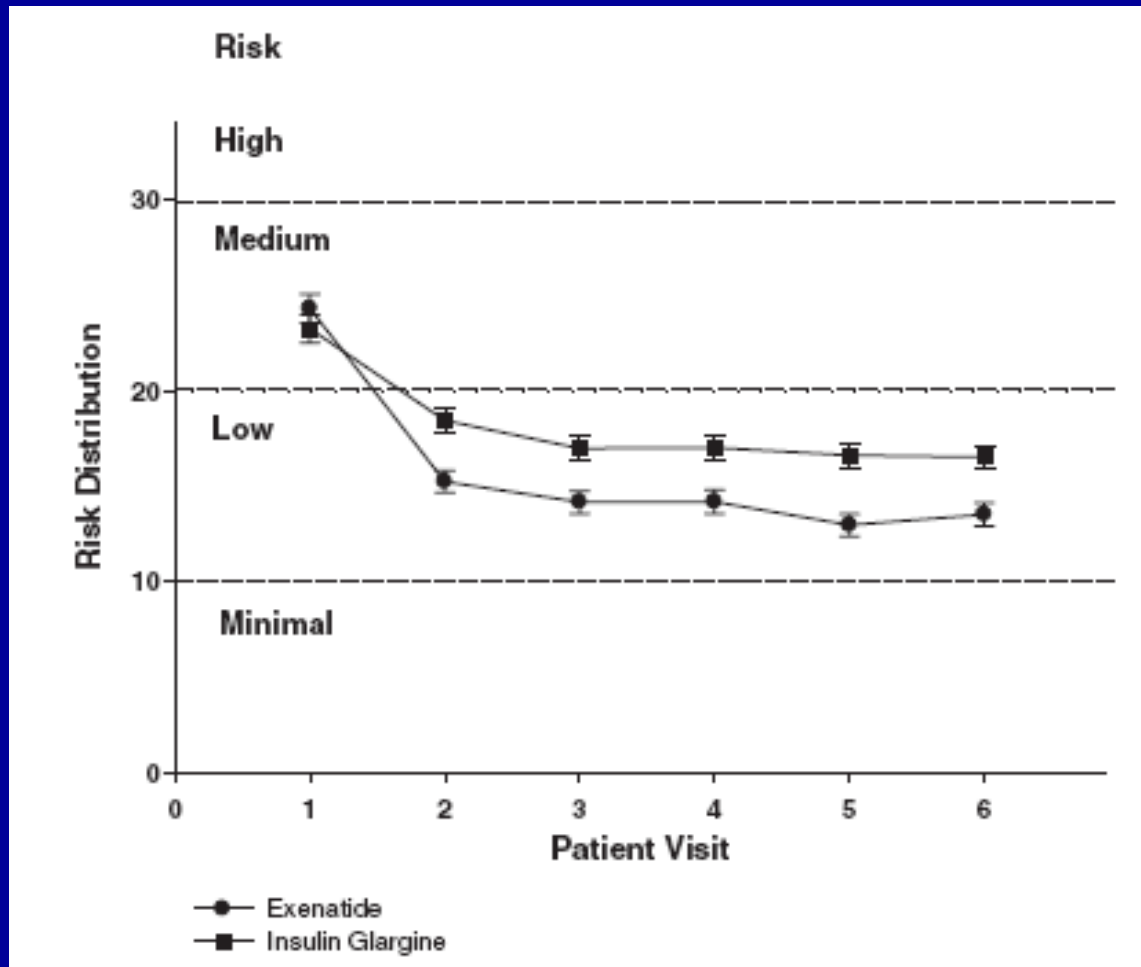
Duración de la exposición a hiperglucemia con Exenatida a lo largo de 30 semanas

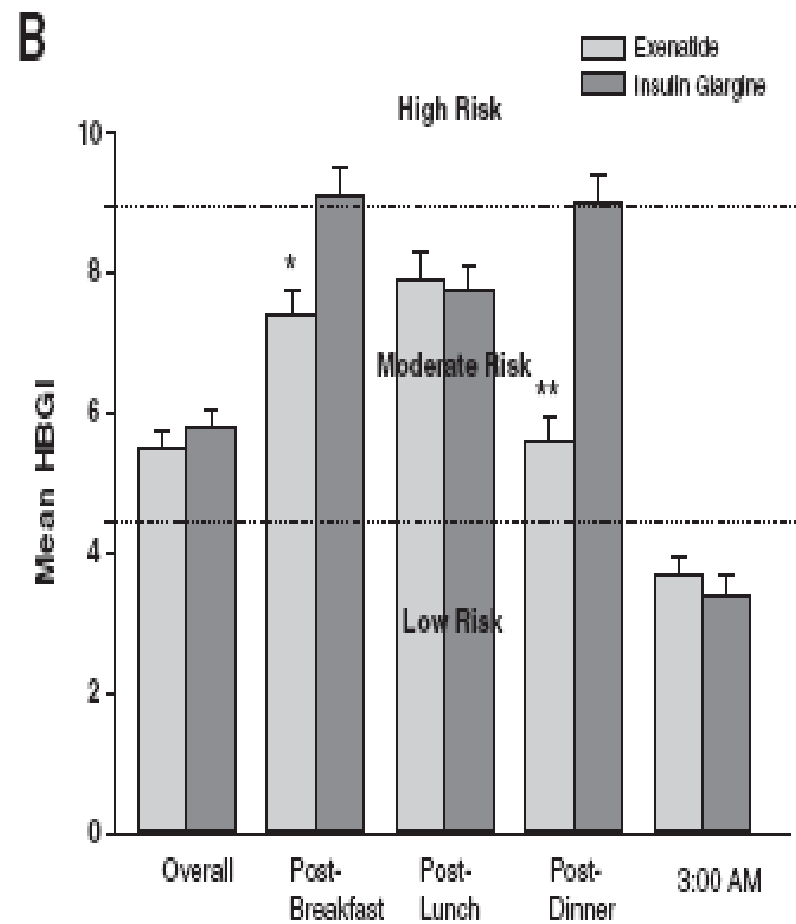
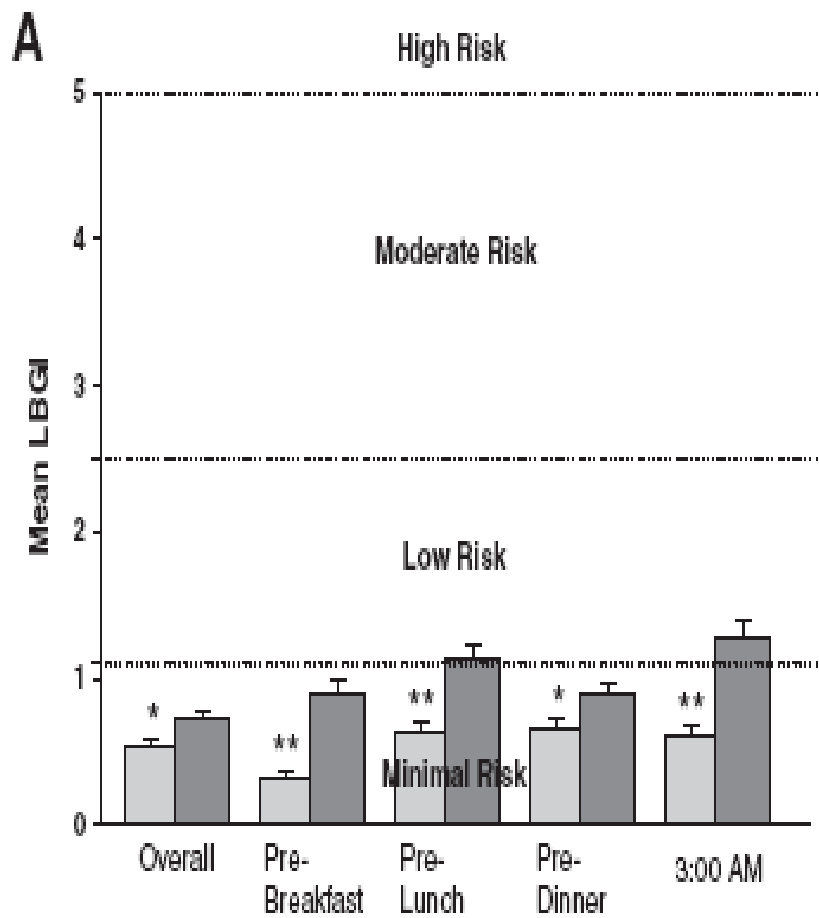


N=30

Schwartz S, et al. *Clin Ther.* 2008;30:858-867;

Reducción del riesgo de variabilidad de la glucemia con Exenatida





La Glicemia postprandial es un factor de riesgo independiente de enf cardiovascular

estudios epidemiológicos

Hoorn Study

2-h glucose better predictor of mortality than HbA_{1c}

Honolulu Heart Program

1-h glucose predicts coronary heart disease

Chicago Heart Study

2-h postchallenge glucose predicts all-cause mortality

DECODE

High 2-h postload blood glucose is associated with increased risk of death, independent of fasting glucose

Coutinho et al.

2-h glucose associated with CHD

Whitehall Study, Paris Prospective Study, and

2-h postchallenge glucose predicts all-cause and CHD mortality

Helsinki Policemen Study

Diabetes Intervention Study

Postmeal but not fasting glucose is associated with CHD

La regresión de la placa se asocia a la Glucemia PostPrandial y no a la Basal

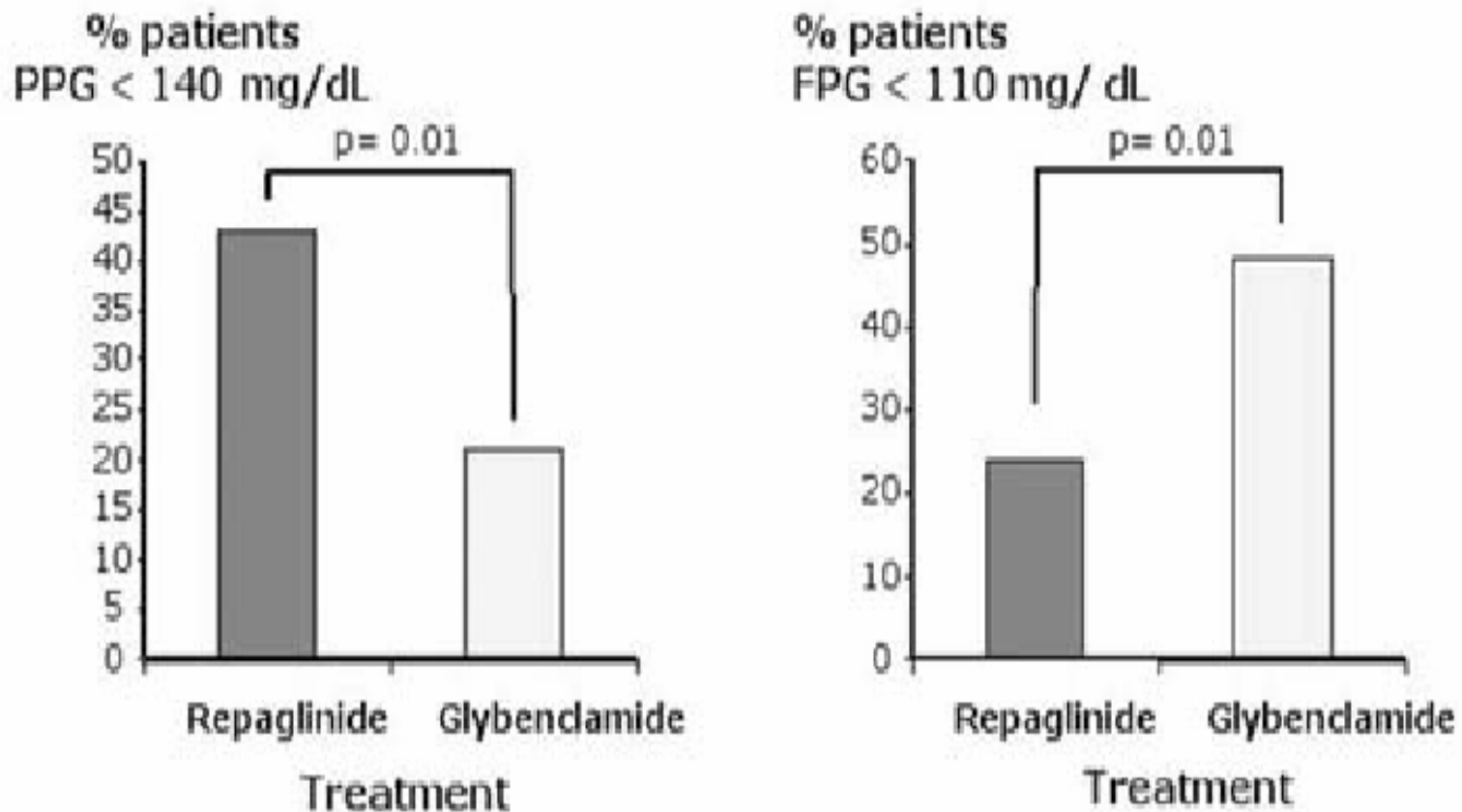


Figure 7. Reduction in CIMT is associated with changes postprandial (PPG) but not with fasting (FPG) glucose. [Esposito K et al. *Circulation* 2004;110:214-9 (ref. 43)].

Regresión de la placa tras control de la glicemia postprandial

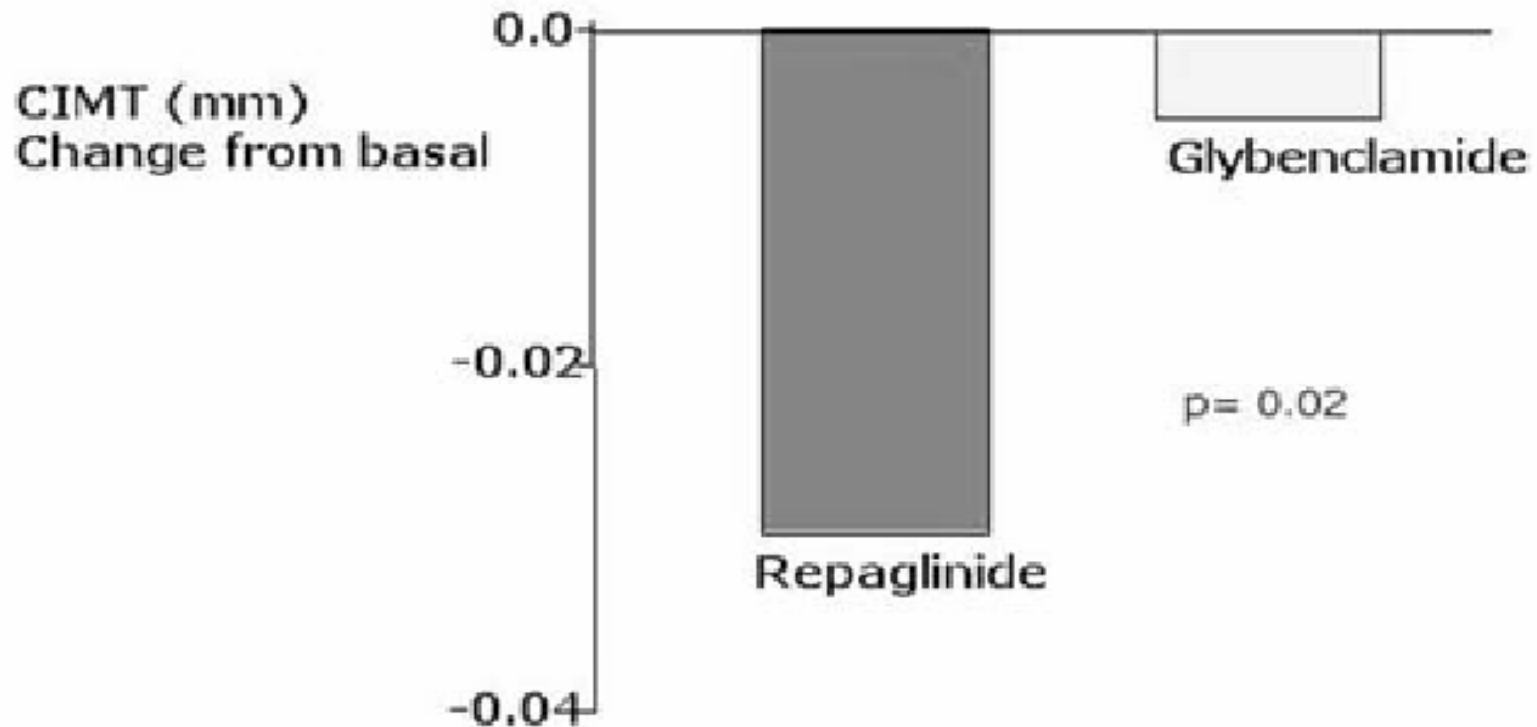
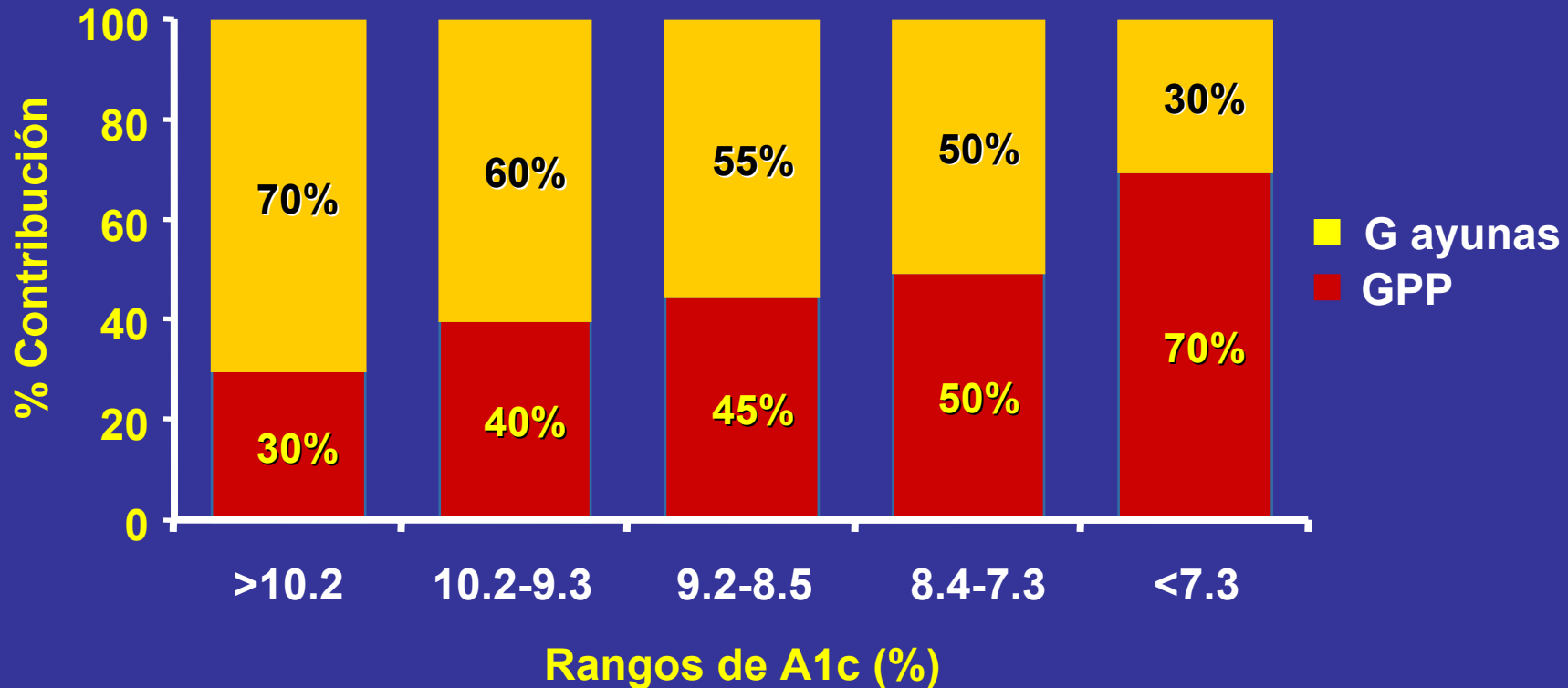
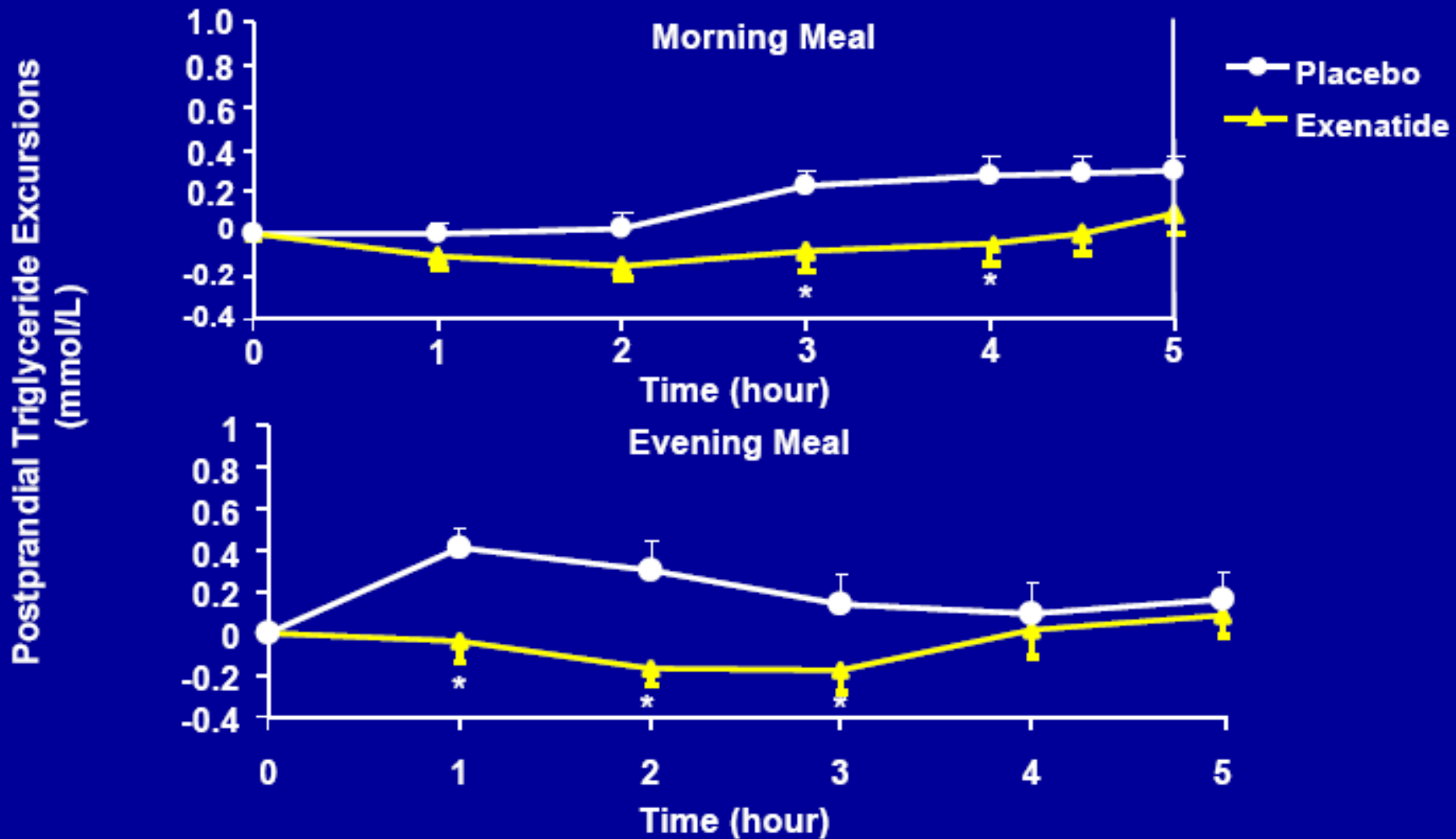


Figure 6. Atherosclerosis regression in the carotid* after post-prandial glucose control in type 2 diabetic patients. [Esposito K et al. *Circulation* 2004;110:214-9 (ref. 43)].

Contribución de la hiperglucemia en ayuno y posprandial a las cifras de A1c



Triglyceridemia postprandial durante tratamiento con Exenatida

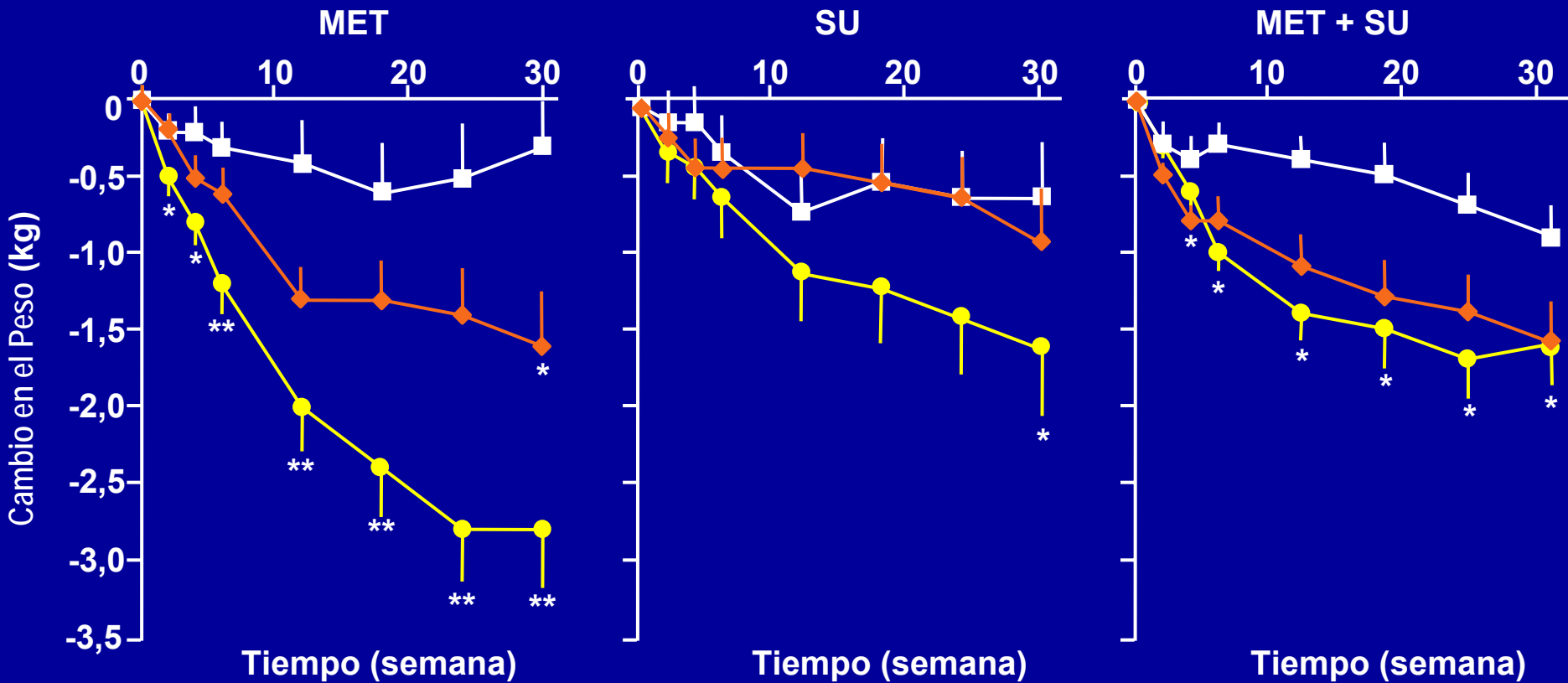


N=30; *p<0.05.

Schwartz S, et al. *Clin Ther.* 2008;30:858-867;

Estudios Clínicos en Fase 3: Efecto sobre el peso corporal a lo largo de 30 semanas

- Placebo 2 x día
- ◆ Exenatida 5 µg 2 x día
- Exenatida 10 µg 2 x día



Población ITT; Media (EE); MET (N = 336), SU (N = 377), MET + SU (N = 733); * $p < 0,05$ vs placebo; ** $p < 0,001$ vs placebo.

El peso basal medio osciló de 95 kg a 101 kg en todas las ramas del estudio.

DeFronzo RA, et al. *Diabetes Care*. 2005;28:1092-1100.; Buse JB, et al. *Diabetes Care*. 2004;27:2628-2635.; Kendall DM, et al.

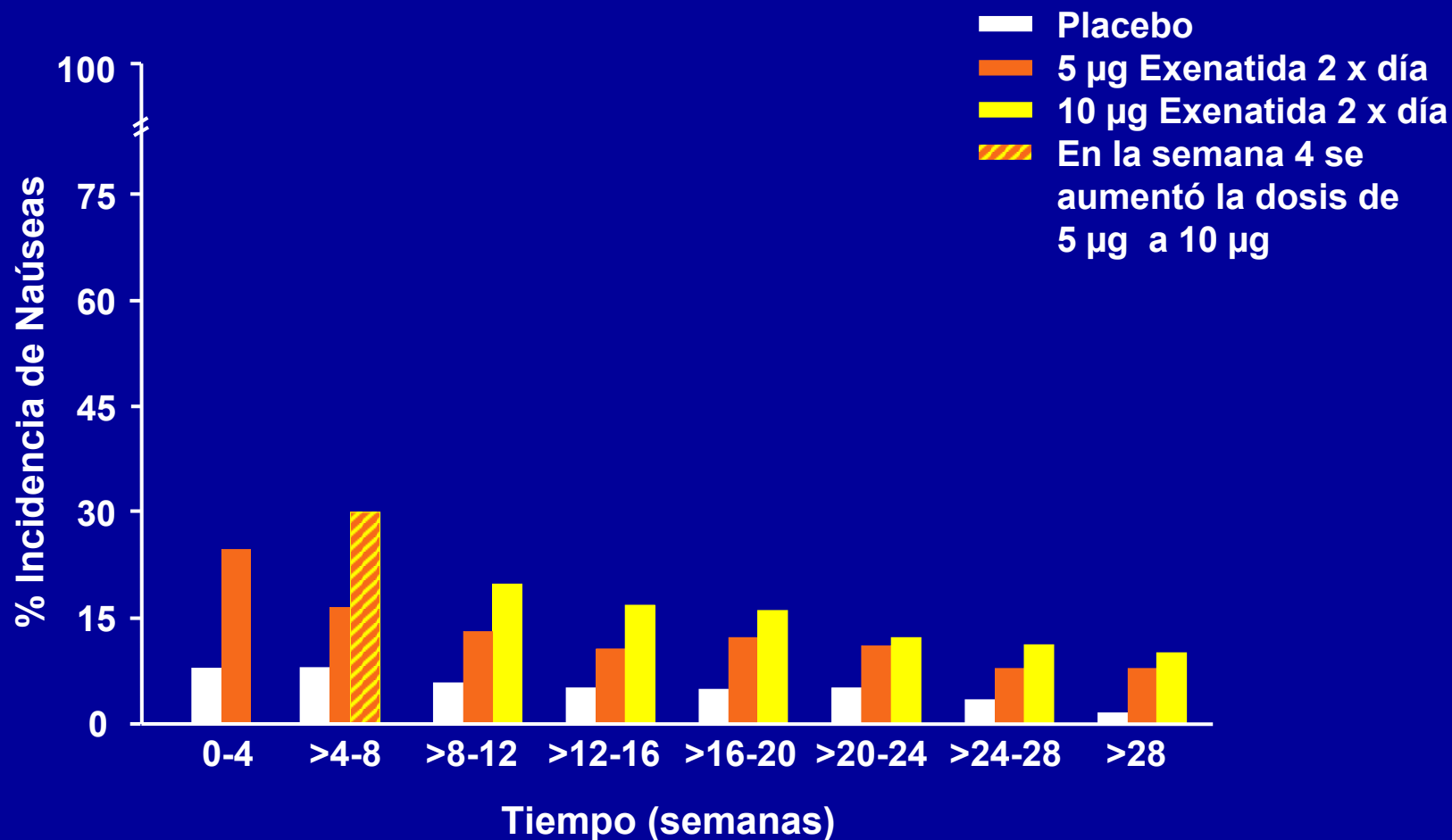
Diabetes Care. 2005;28:1083-1091. Reproducido con permiso de American Diabetes Association.

Estudios Clínicos en Fase 3 (Combinados): Acontecimientos Adversos Comunes

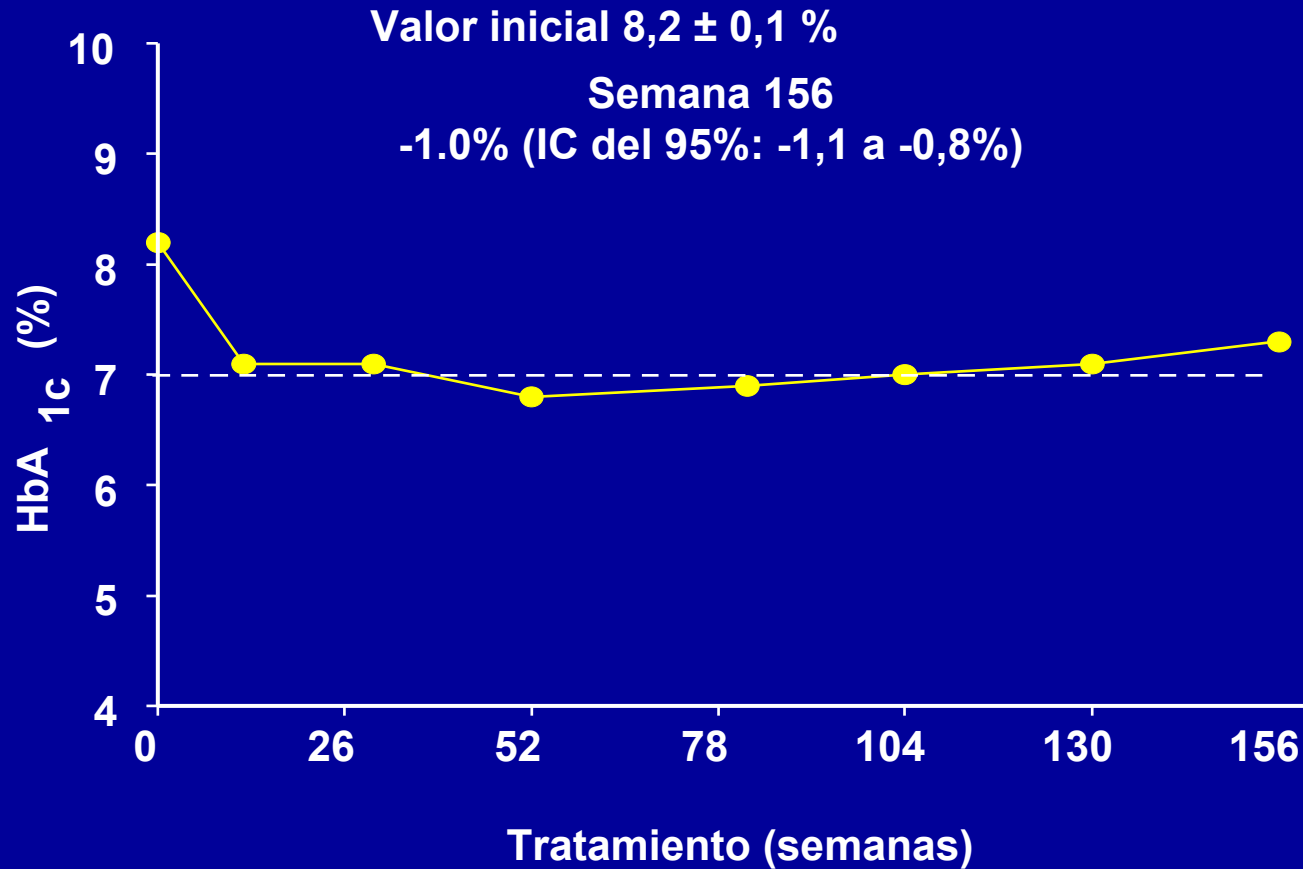
Resultados Combinados de los Estudios en Fase 3 de Exenatida de 30 Semanas

	Placebo (N = 483)	5 µg Exenatida (N = 480)	10 µg Exenatida (N = 483)
Náuseas	18%	39%	48%
Hipoglucemia	8%	15%	25%
Diarrea	6%	11%	15%
Vómitos	4%	13%	13%
Cefalea	6%	10%	7%
Sensación de nerviosismo	4%	9%	10%

Estudios Clínicos en Fase 3 (Combinados): Evolución de las náuseas a lo largo del tiempo



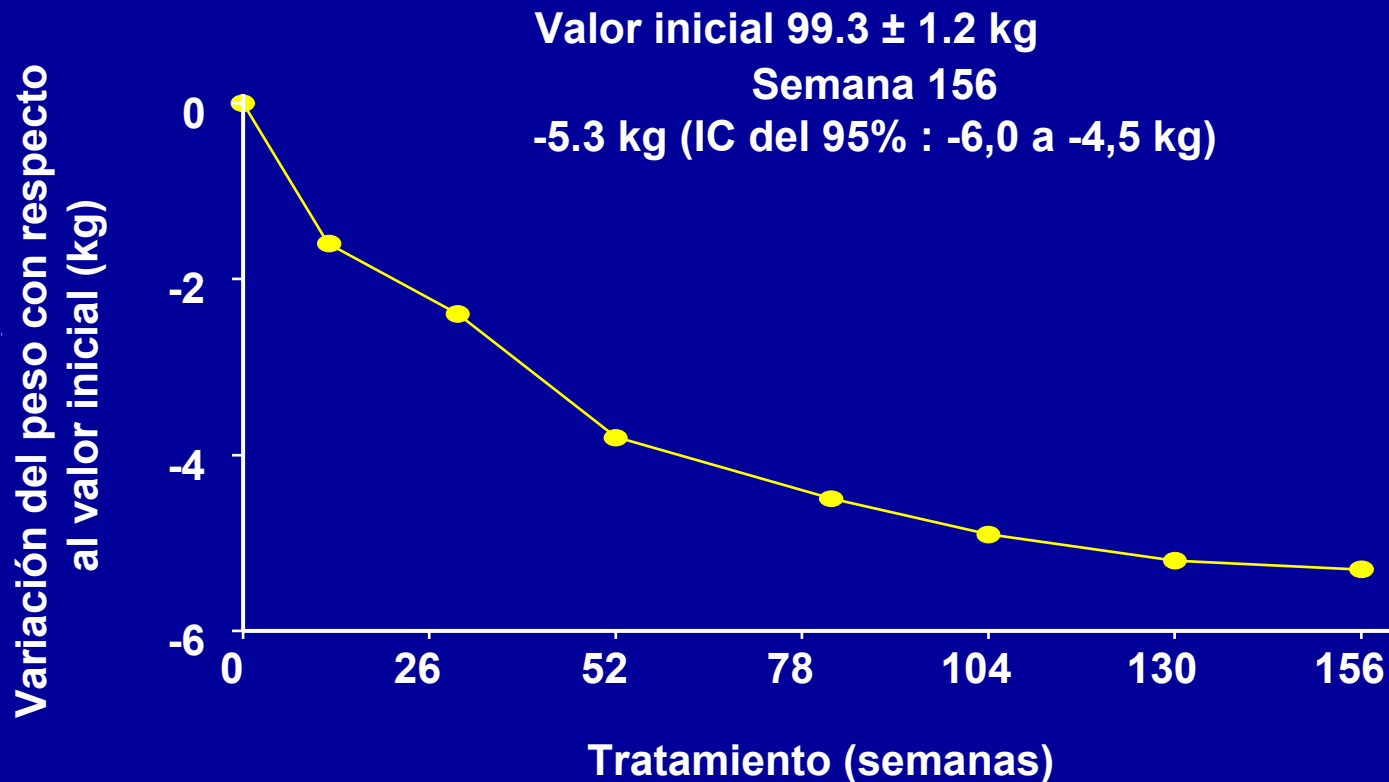
Variación en la HbA_{1c} durante 3 años de tratamiento con Exenatida



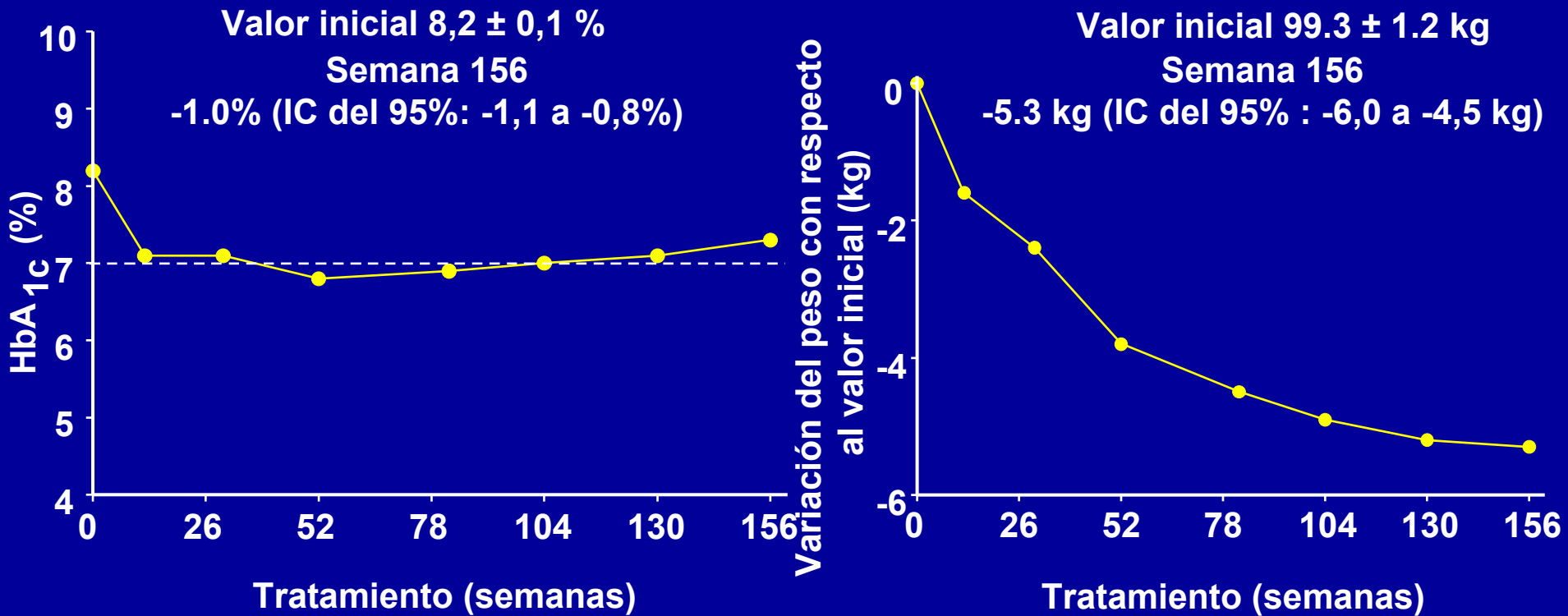
N=217; Media \pm EE.

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

Variación en el Peso a lo largo de 3 años de tratamiento con Exenatida



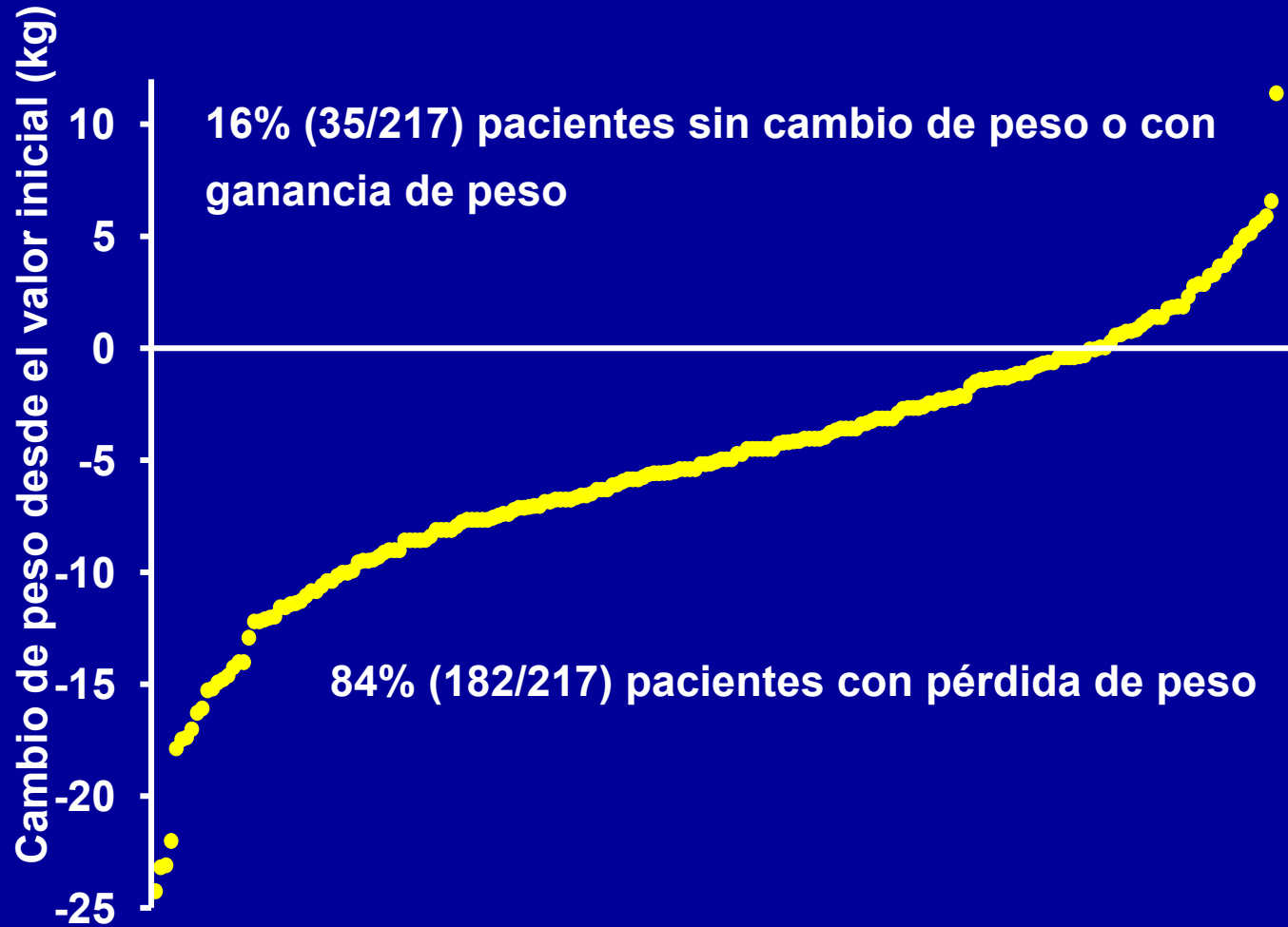
Mejoría combinada en la HbA_{1c} y en el Peso a lo largo de 3 años de tratamiento con Exenatida



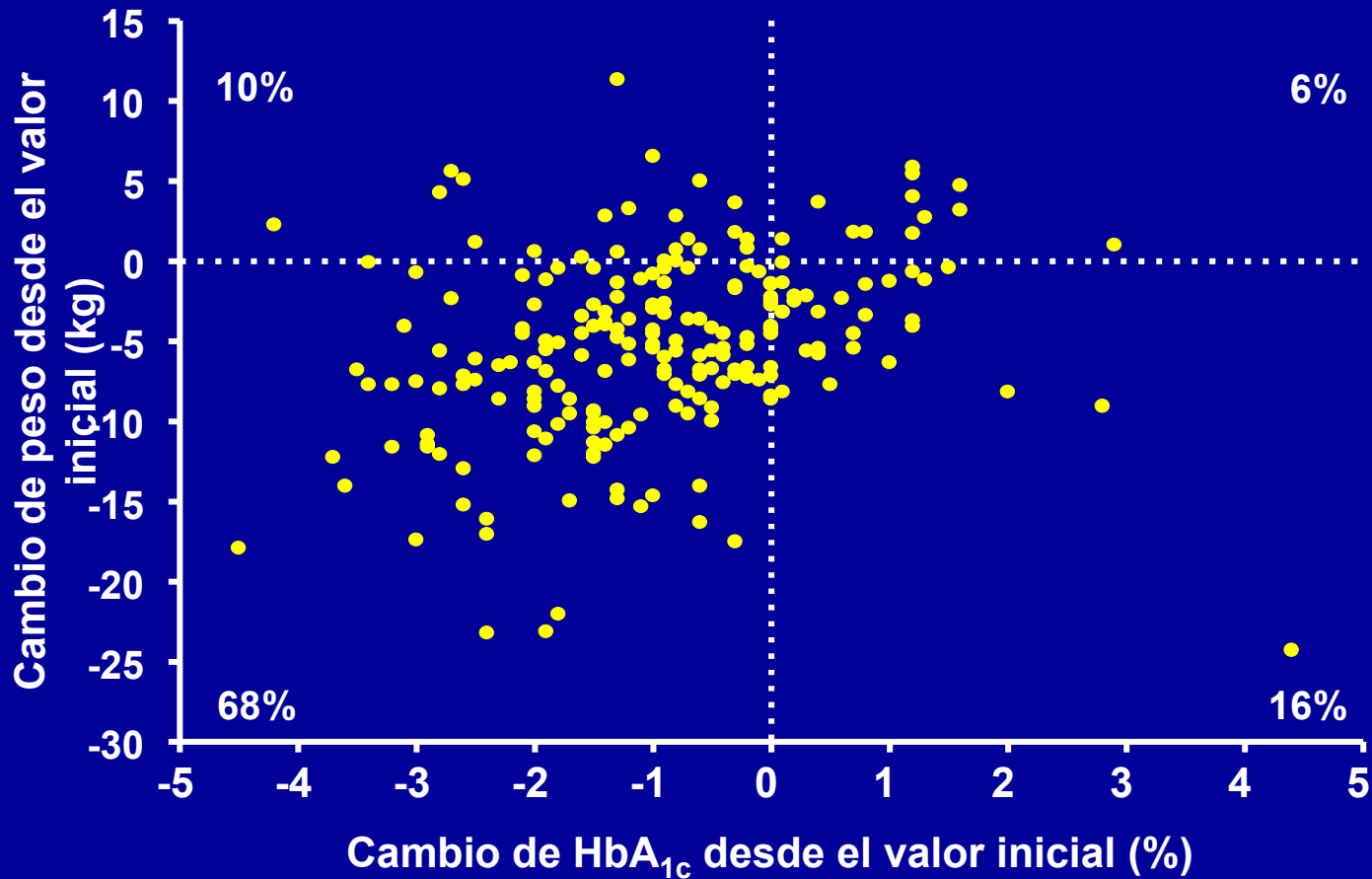
N=217; Media ± EE.

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

Pérdida de peso en los pacientes que completaron 3 años de tratamiento con exenatida



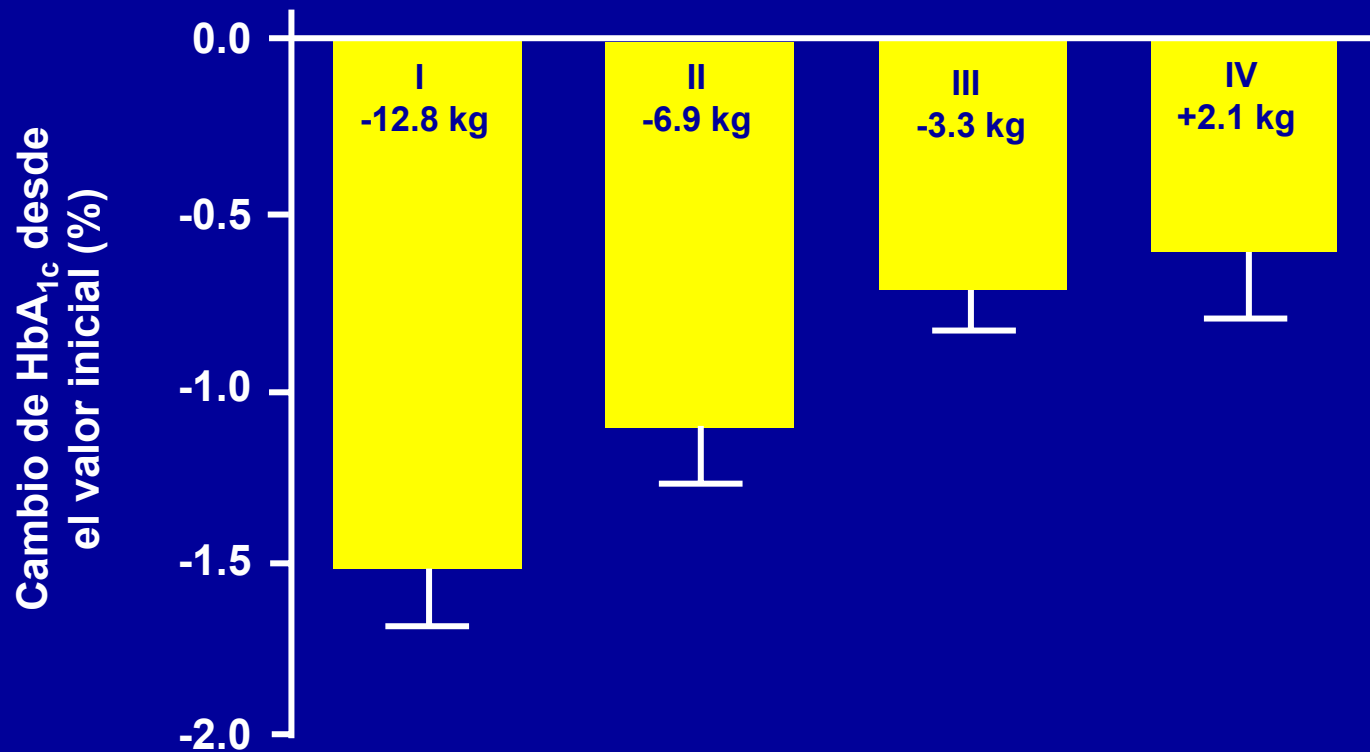
Pérdida de Peso y Reducción de HbA_{1c} en los pacientes que completaron 3 años de tratamiento con exenatida



N=217.

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

Variación de HbA_{1c} estratificada en cuartiles de variación de peso a los 3 años



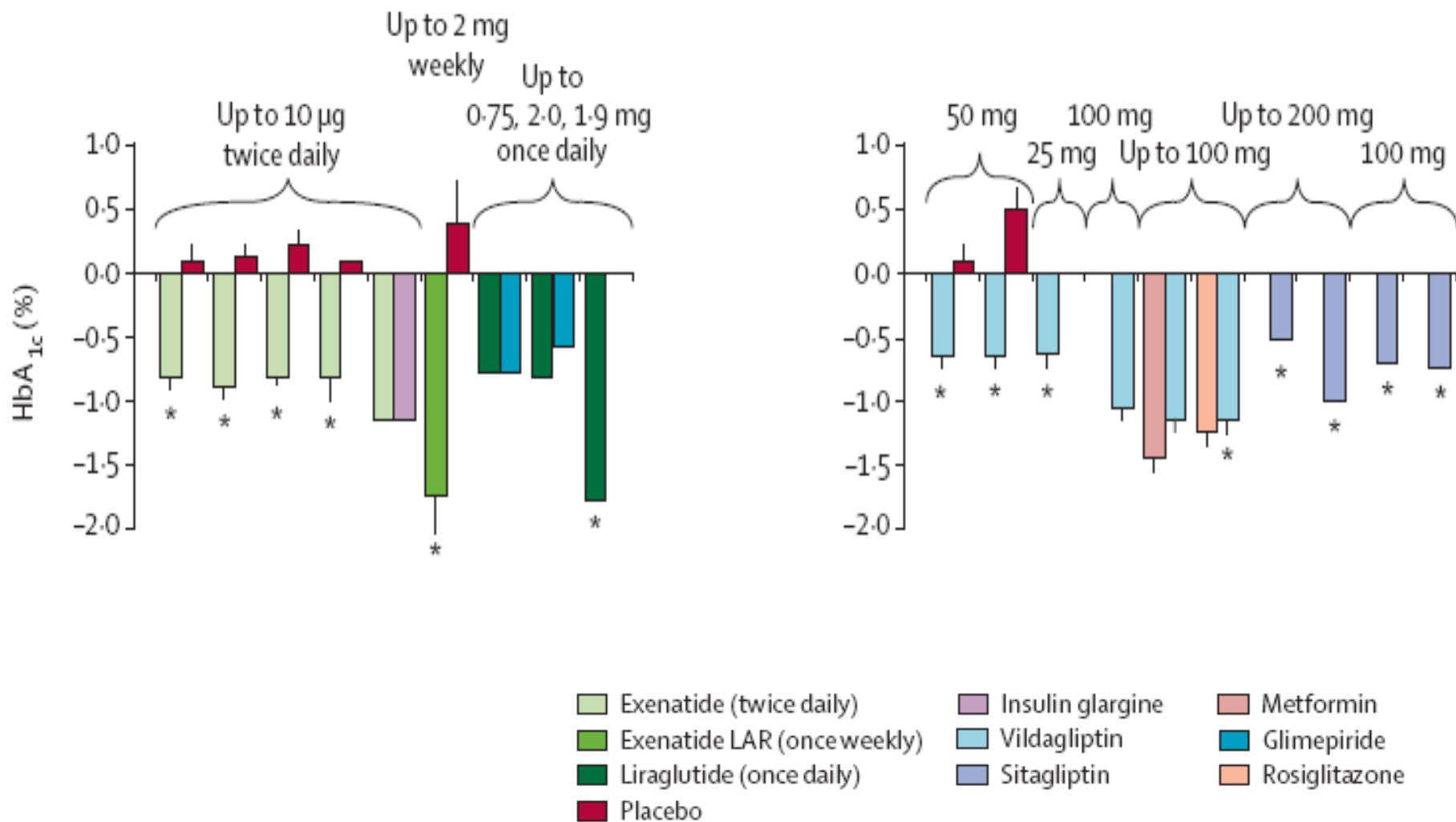
N=217.

Klonoff DC, et al. *Curr Med Res Opin* 2008;24:275-286.; Kendall DM, et al. Presented at: 67th ADA Annual Scientific Sessions; June 22-26, 2007; Chicago, IL.

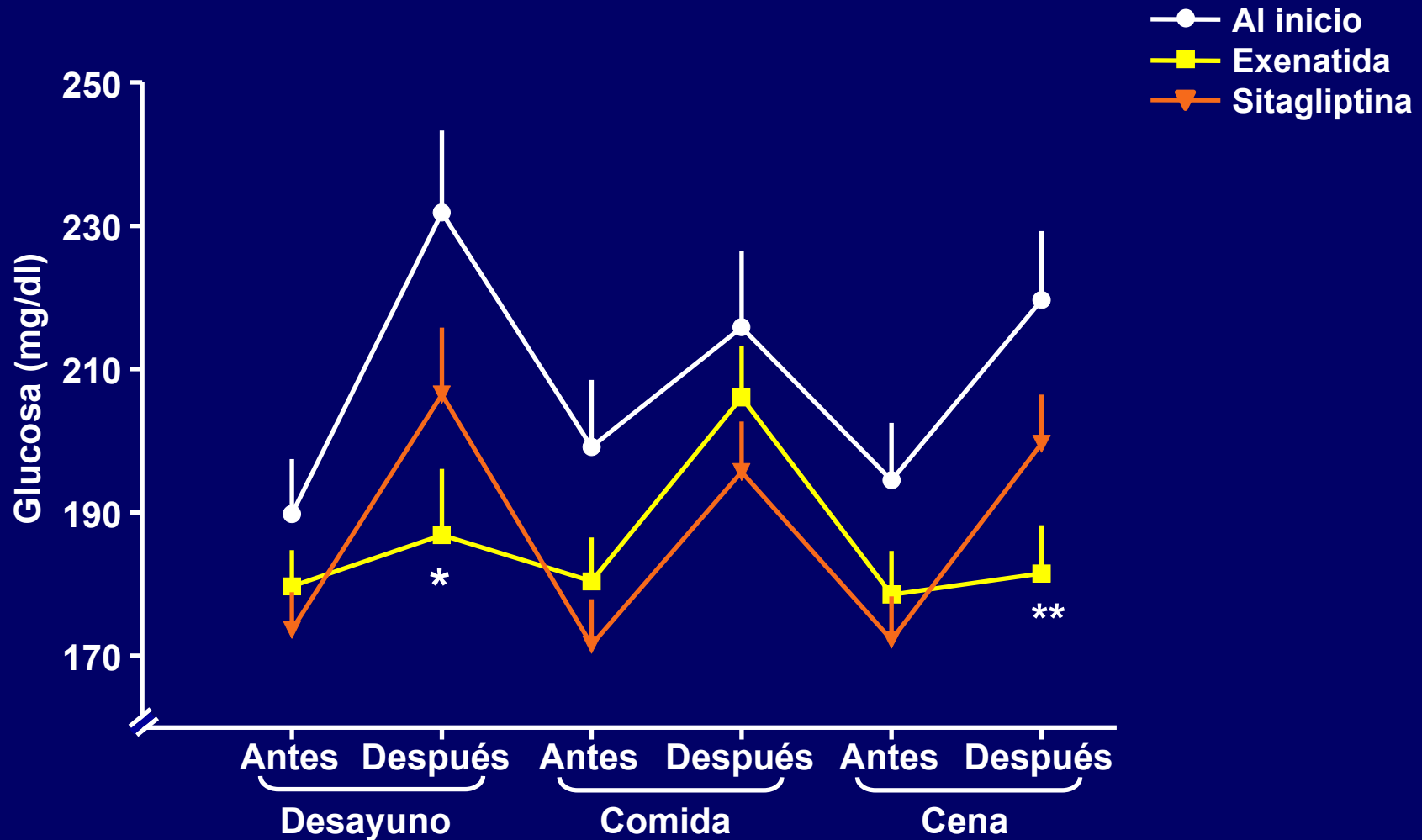
Cambios en A1c con incretín-miméticos e inhibidores DPP4 en DM2

Incretin mimetics

DPP-4 inhibitors



Exenatida vs sitagliptina: comparación de la reducción de glucemia postprandial

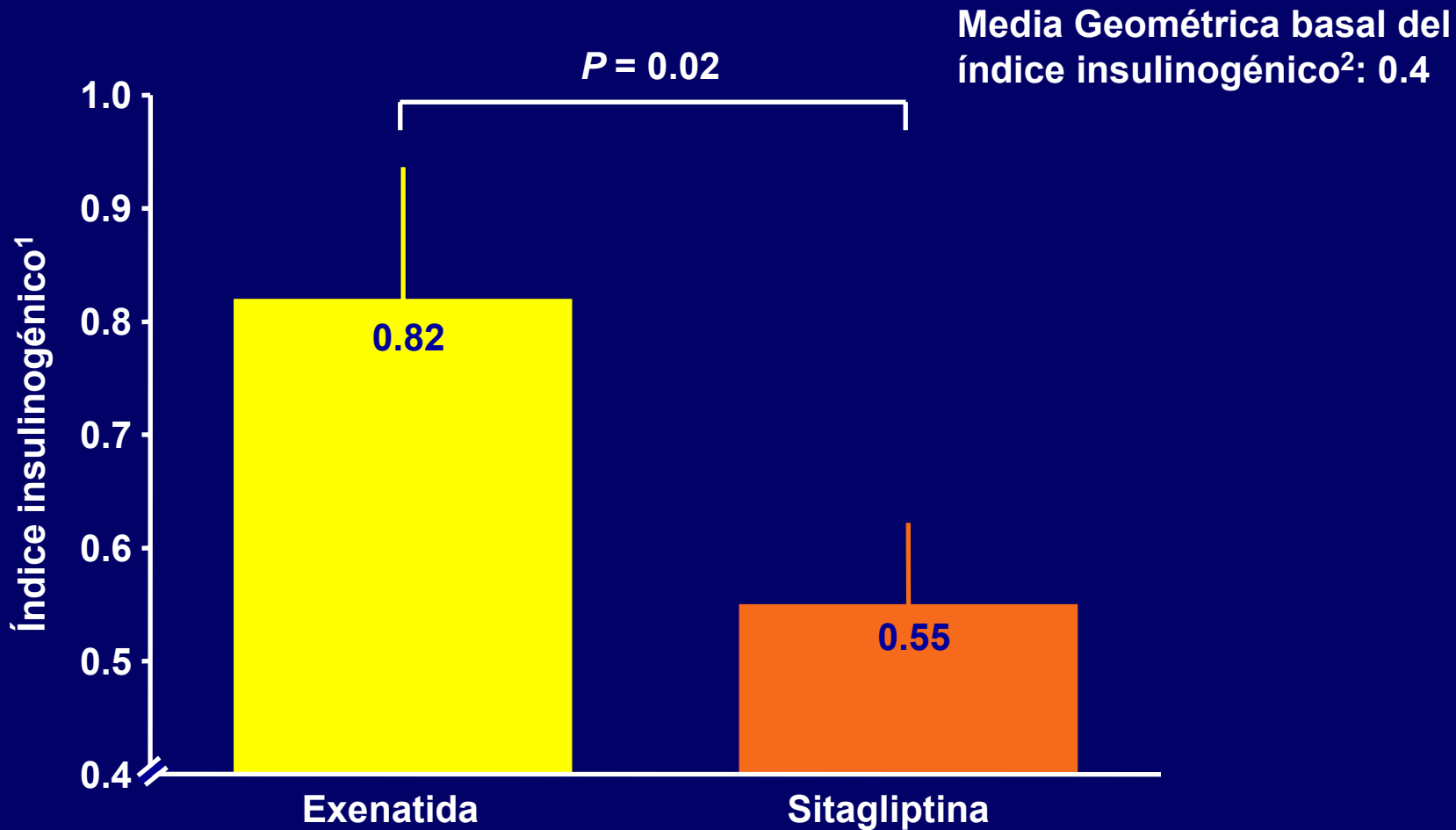


Autoanálisis de concentraciones de glucosa-perfil de 6 puntos

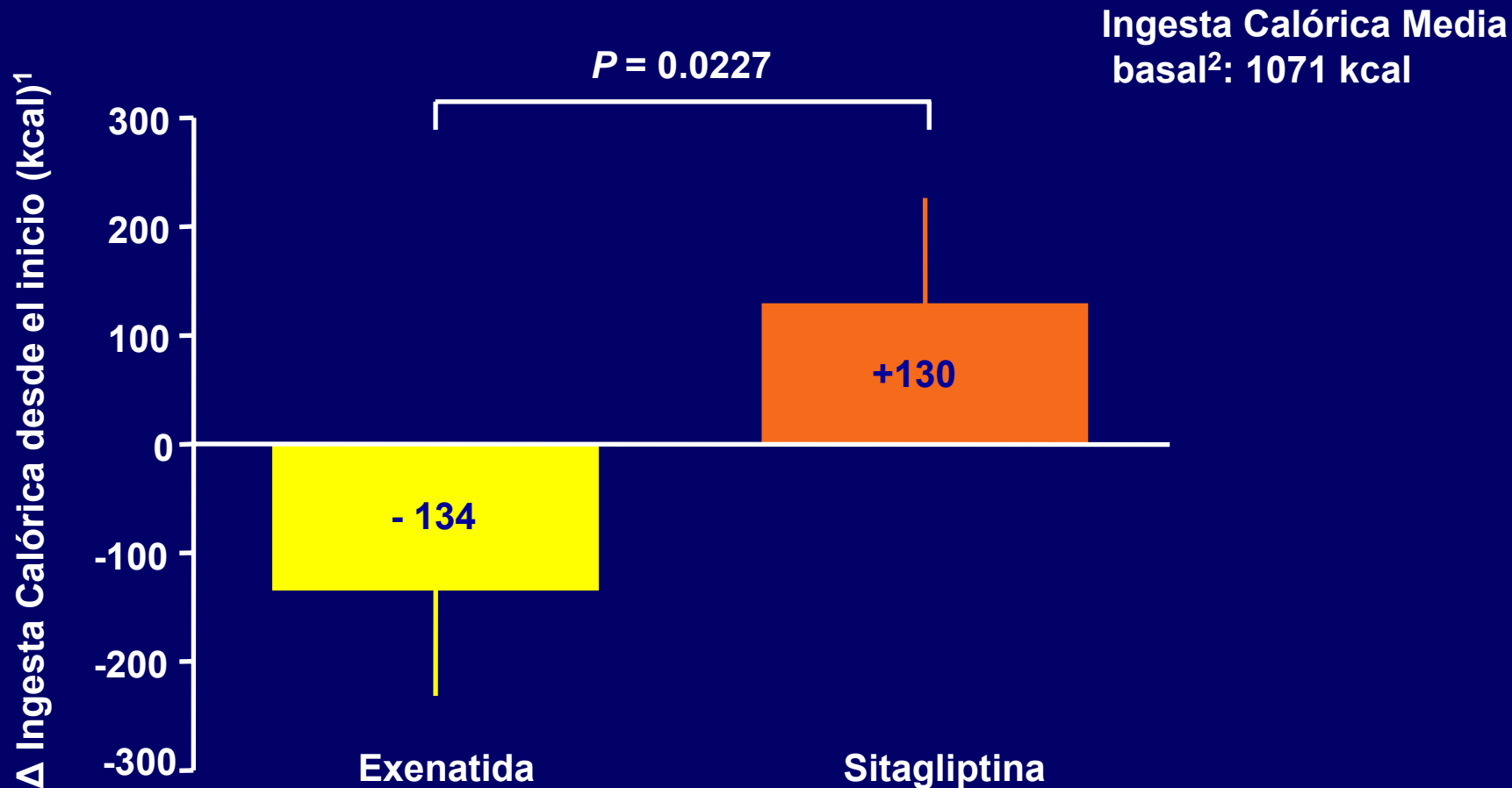
Población evaluable; Al inicio: n = 57, media \pm EE; Exenatida y sitagliptina: n = 61, *P = 0.0016; **P = 0.0383

DeFronzo RA, et al. *Curr Med Res Opin.* 2008;24(10)2943-2952.

Exenatida vs sitagliptina: Mejora en el índice insulínogénico



Exenatida vs sitagliptina: Reducción de la Ingesta Calórica Media

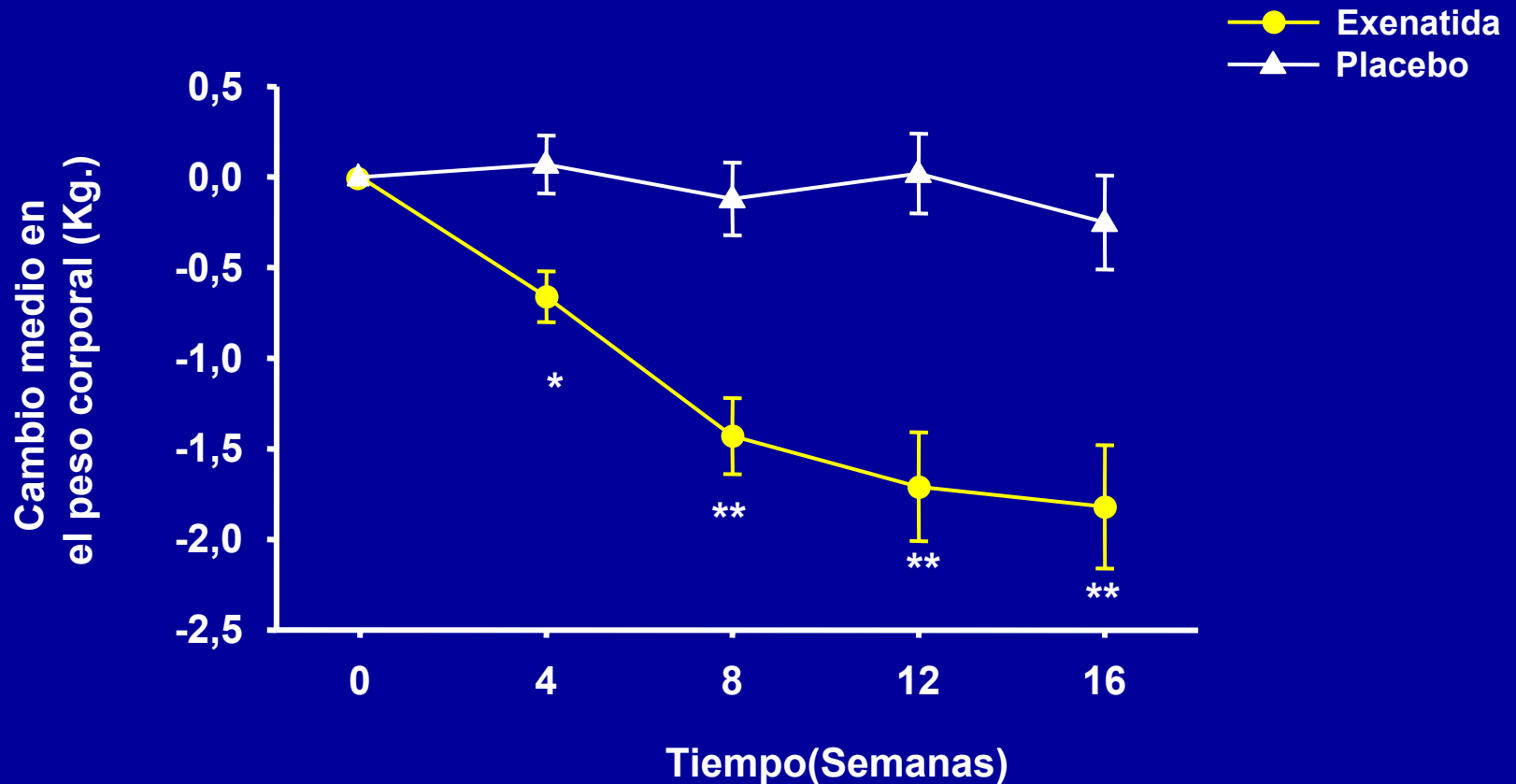


- Cambios en la mediana de ingesta calórica mostraron tendencias similares (exenatida, -138 kcal; sitagliptina, 63 kcal)

Acciones de las Terapias Basadas en las Incretinas para DT2: Agonistas del Receptor de GLP-1 e Inhibidores de DPP-4

Acción		Agonistas receptor GLP-1 ^{1,2}	Inhibidores DPP-4 ^{1,2}
	↑ Producción Insulina	+++	++
	↑ Primera fase respuesta insulínica	+++	++
	↓ Glucagon; Gasto Glucosa	+++	+
	↓ Vaciado gástrico	Retrasado	Sin efecto
	Ingesta	Disminuida	Sin efecto

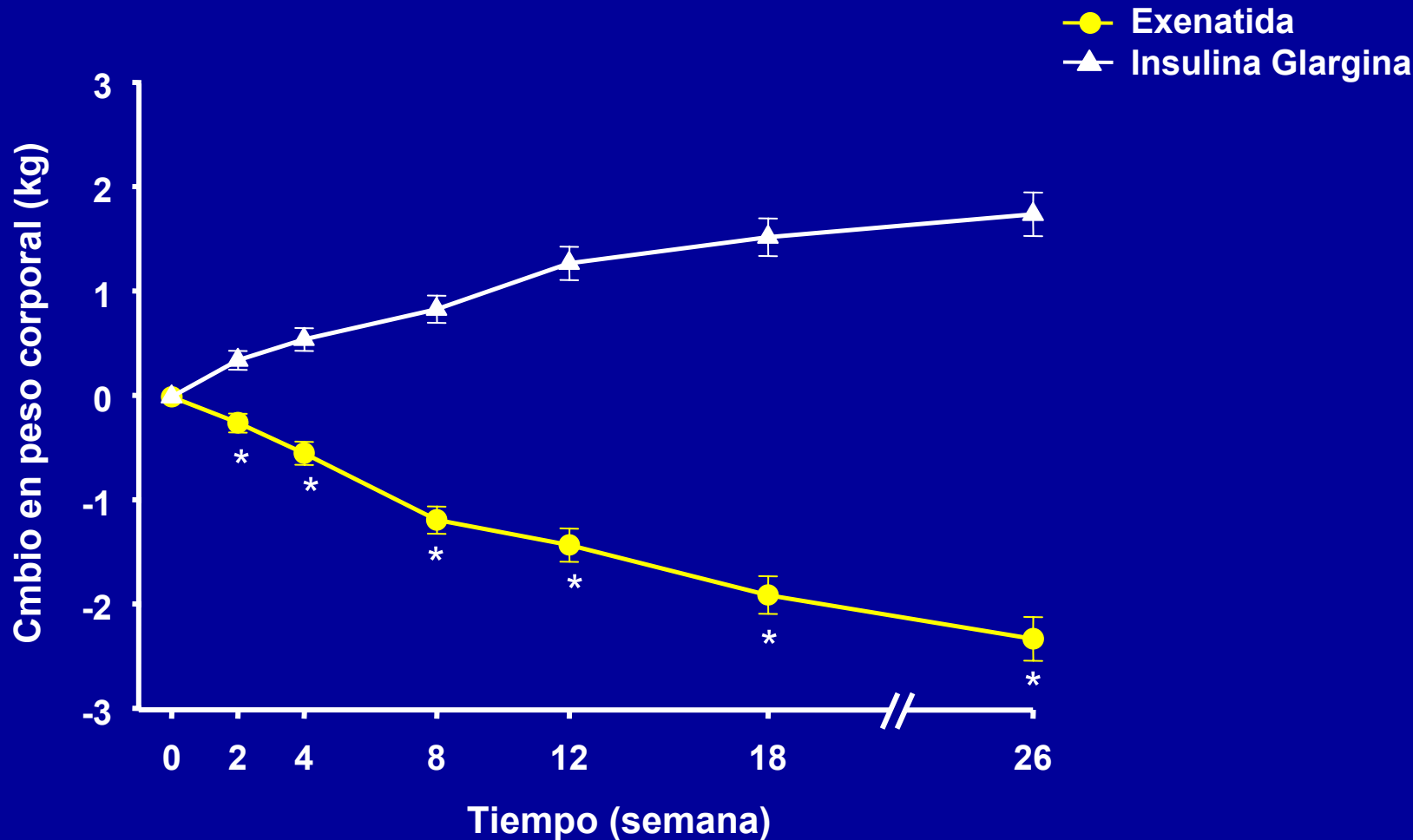
Exenatida en Combinación con TZD: Cambio en el peso corporal



Muestra de pacientes ITT, Gráfico muestra la media \pm EE. * $p < 0.01$, ** $p < 0.001$. Peso en la línea basal para toda la muestra ITT (Media \pm DE), exenatide: 97.5 ± 18.8 kg, placebo: 96.9 ± 19.0 kg.

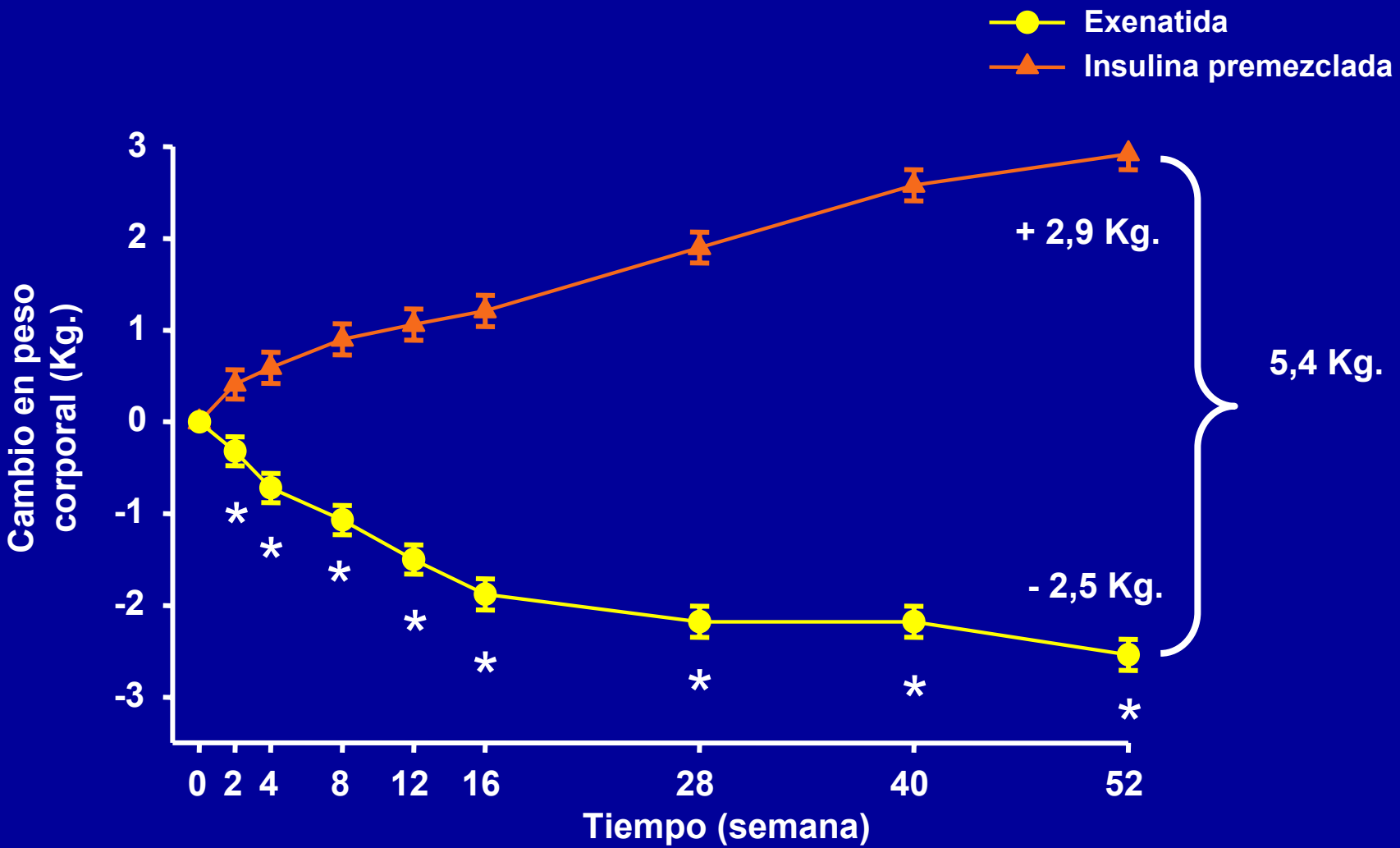
Zinman B. et al. *Ann Intern Med* 2007;146:477-485

Estudio Comparativo de Exenatida/Insulina Glargina: Modificaciones del Peso



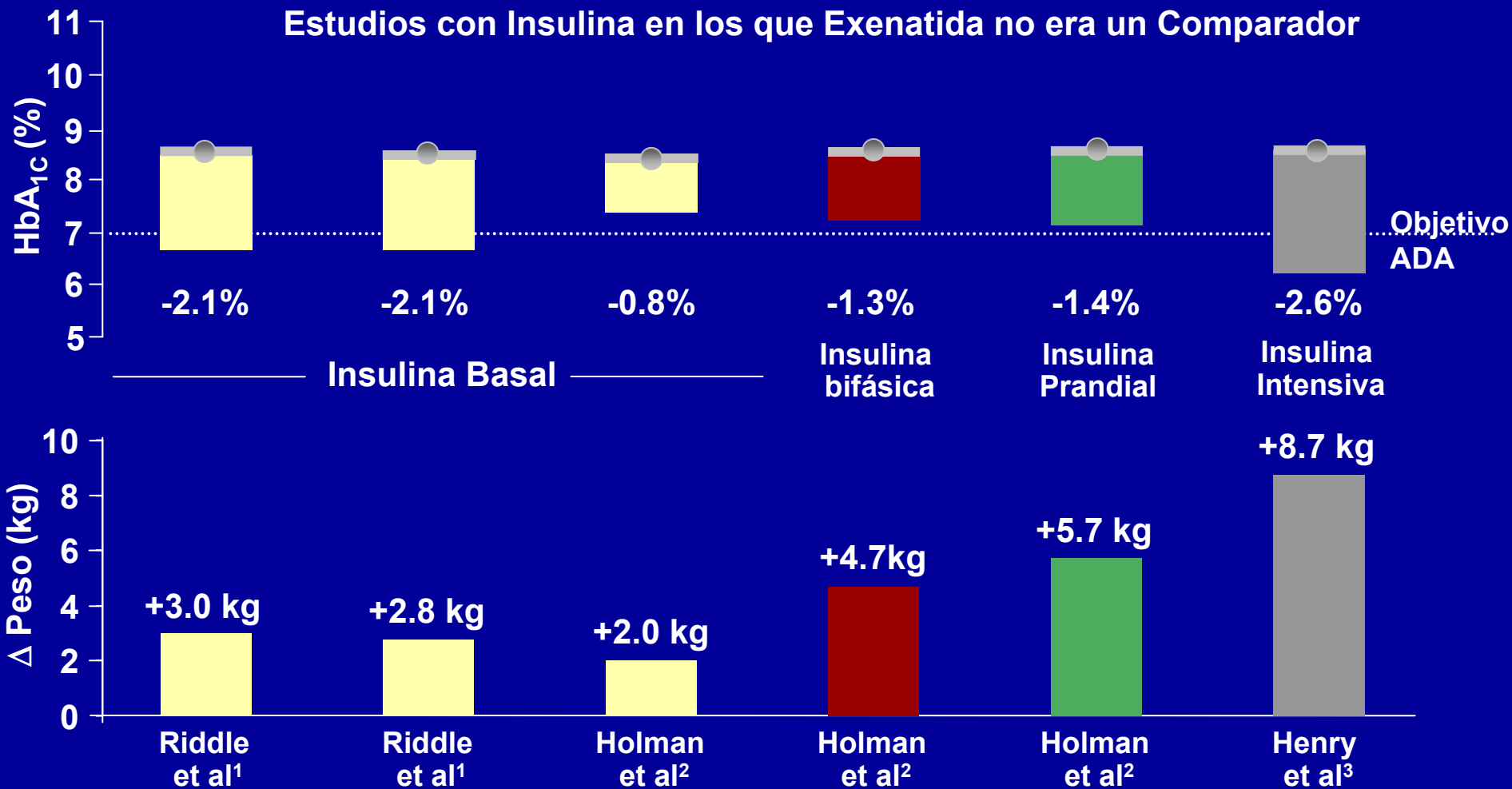
Población ITT; se muestra la media \pm EE; *P < 0,0001, exenatida vs insulina glargina en los mismos puntos temporales. Heine RJ, et al. *Ann Intern Med.* 2005;143:559-569. Reproducido con permiso de The American College of Physicians

Estudio comparativo de exenatida frente a insulina aspart bifásica: Cambios en el peso corporal



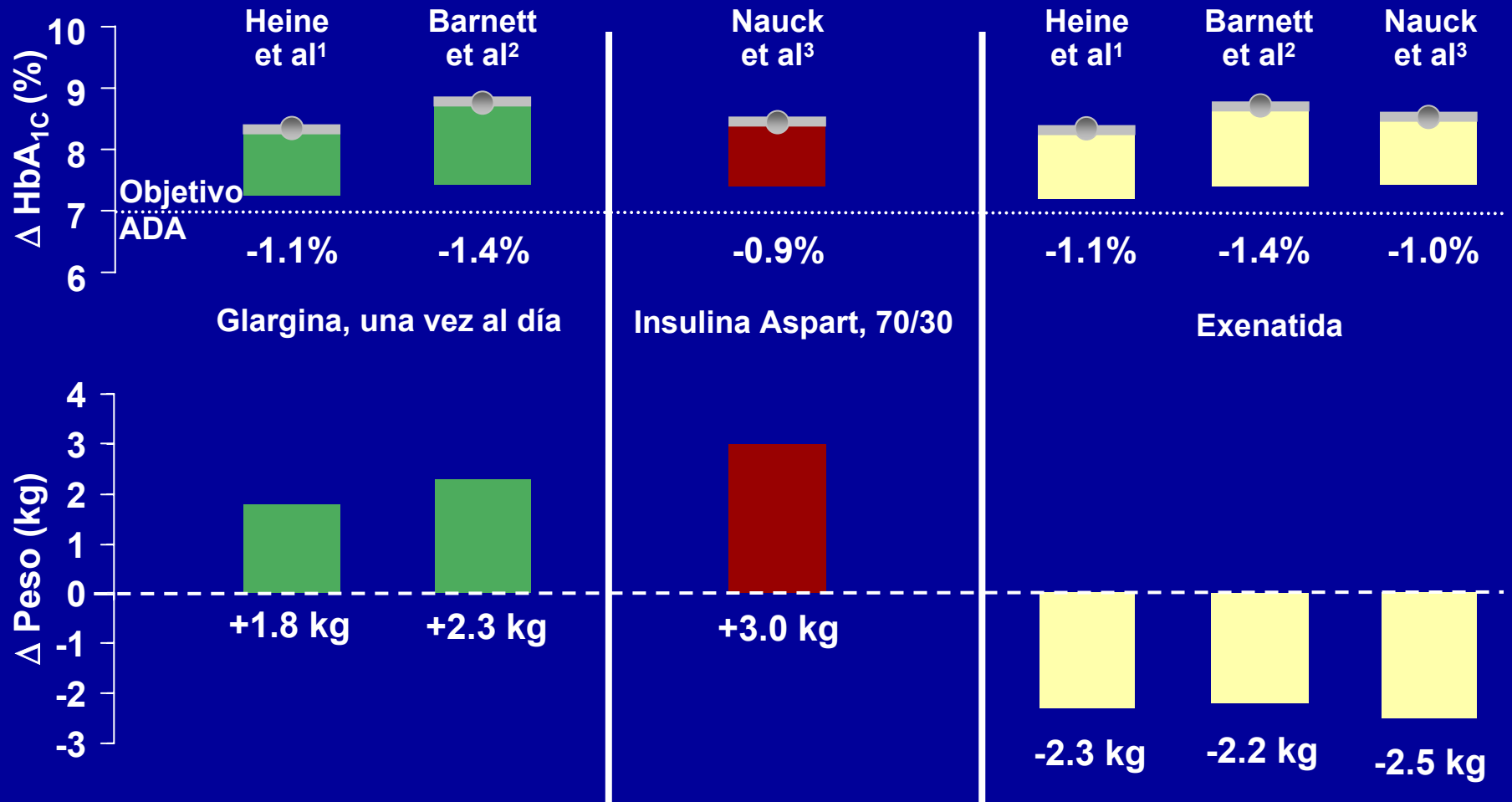
Muestra ITT, se muestra la media (EE) p<0,001, exenatida frente a insulina premezclada en puntos después del inicio. Nauck MA, et al. *Diabetologia*. 2007;50:259-267. Copyright © 2007 Springer-Verlag. Reproducido con permiso de Springer-Verlag.

Tratamiento con Insulina y Ganancia de peso



1. Riddle MC, et al. *Diabetes Care*. 2003;26:3080-3086. 2. Holman RR, et al. *N Engl J Med*. 2007;357:1716-1730. 3. Henry RR, et al. *Diabetes Care*. 1993;16:21-31.

Variaciones en Glucemia y Peso en 3 Estudios comparativos: Exenatida vs Insulina



1. Heine RJ, et al. *Ann Int Med.* 2005;143:559-569.
2. Barnett AH, et al. *Clin Ther.* 2007;29:2333-2348.
3. Nauck M, et al. *Diabetologia.* 2007;50(2):259-267.

The Impact of Weight Gain on Motivation, Compliance, and Metabolic Control in Patients with Type 2 Diabetes Mellitus

F. Xavier Pi-Sunyer, MD

Abstract: Patients with type 2 diabetes, approximately 85% of whom are overweight or obese, often have an increased incidence of cardiovascular disease (CVD) risk factors such as hypertension and dyslipidemia. Both type 2 diabetes and obesity are independent risk factors for CVD. Unfortunately, many therapies aimed at maintaining and improving glucose control are associated with weight gain. Among the older antidiabetes agents, most, including the insulin secretagogues and sensitizers, can lead to weight gain, except for metformin, which is weight-neutral. Among the newer agents, the dipeptidyl peptidase-4 inhibitors generally are weight-neutral in addition to lowering glucose, while the glucagon-like peptide-1 receptor agonists lead to weight reduction. Patients with type 2 diabetes are at an increased risk for both diabetes- and CV-related outcomes, and weight reduction is an important component of diabetes management. **Weight gain in patients with type 2 diabetes can contribute to patient frustration and may negatively impact their compliance to therapeutic regimens.** The selection of antidiabetes agents that not only improve glucose control but reduce or have a neutral effect on weight with beneficial effects on lipids are ideal options for managing patients with type 2 diabetes.

The Impact of Weight Gain on Motivation, Compliance, and Metabolic Control in Patients with Type 2 Diabetes Mellitus

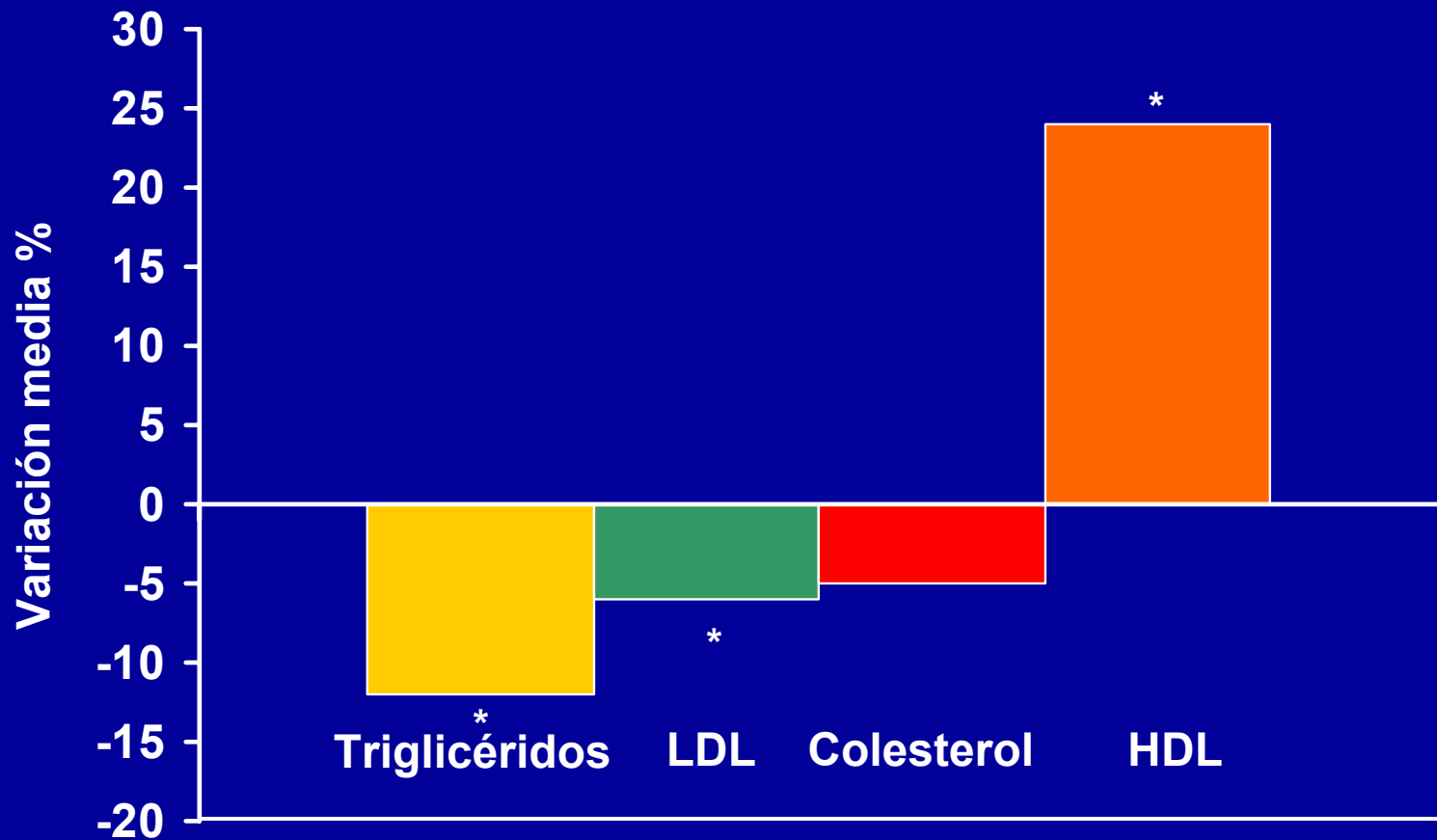
F. Xavier Pi-Sunyer, MD

Abstract: Patients with type 2 diabetes, approximately 85% of whom are overweight or obese, often have an increased incidence of cardiovascular disease (CVD) risk factors such as hypertension and dyslipidemia. Both type 2 diabetes and obesity are independent risk factors for CVD. Unfortunately, many therapies aimed at maintaining and improving glucose control are associated with weight gain. Among the older antidiabetes agents, most, including the insulin secretagogues and sensitizers, can lead to weight gain, except for metformin, which is weight-neutral. Among the newer agents, the dipeptidyl peptidase-4 inhibitors generally are weight-neutral in addition to lowering glucose, while the glucagon-like peptide-1 receptor agonists lead to weight reduction. Patients with type 2 diabetes are at an increased risk for both diabetes- and CV-related outcomes, and weight reduction is an important component of diabetes management. **Weight gain in patients with type 2 diabetes can contribute to patient frustration and may negatively impact their compliance to therapeutic regimens.** The selection of antidiabetes agents that not only improve glucose control but reduce or have a neutral effect on weight with beneficial effects on lipids are ideal options for managing patients with type 2 diabetes.

Modificaciones de los Factores de Riesgo Cardiovascular tras 3,5 años de tratamiento con Exenatida (n=151)

Factor de riesgo cardiovascular	Valor inicial (Media ± EEM)	Variación con respecto al valor inicial (Media ± EEM)	Variación media	Intervalo de confianza del 95%	Valor de p
Triglicéridos (mmol/l)	2.5 ± 0.1	-0.5 ± 0.1	-12%	-0.8 a -0.2	.0003
Colesterol total (mmol/l)	4.8 ± 0.1	-0.3 ± 0.1	-5%	-0.4 a -0.1	.0007
cHDL (mmol/l)	1.0 ± 0.0	0.2 ± 0.0	+24%	0.2 a 0.3	<.0001
cLDL (mmol/l)	2.9 ± 0.1	-0.3 ± 0.1	-6%	-0.5 a -0.2	<.0001
Presión arterial sistólica (mmHg)	129.3 ± 1.0	-3.5 ± 1.2	-2%	-5.9 a -1.0	.0063
Presión arterial diastólica (mmHg)	79.2 ± 0.6	-3.3 ± 0.8	-4%	-4.9 a -1.7	<.0001

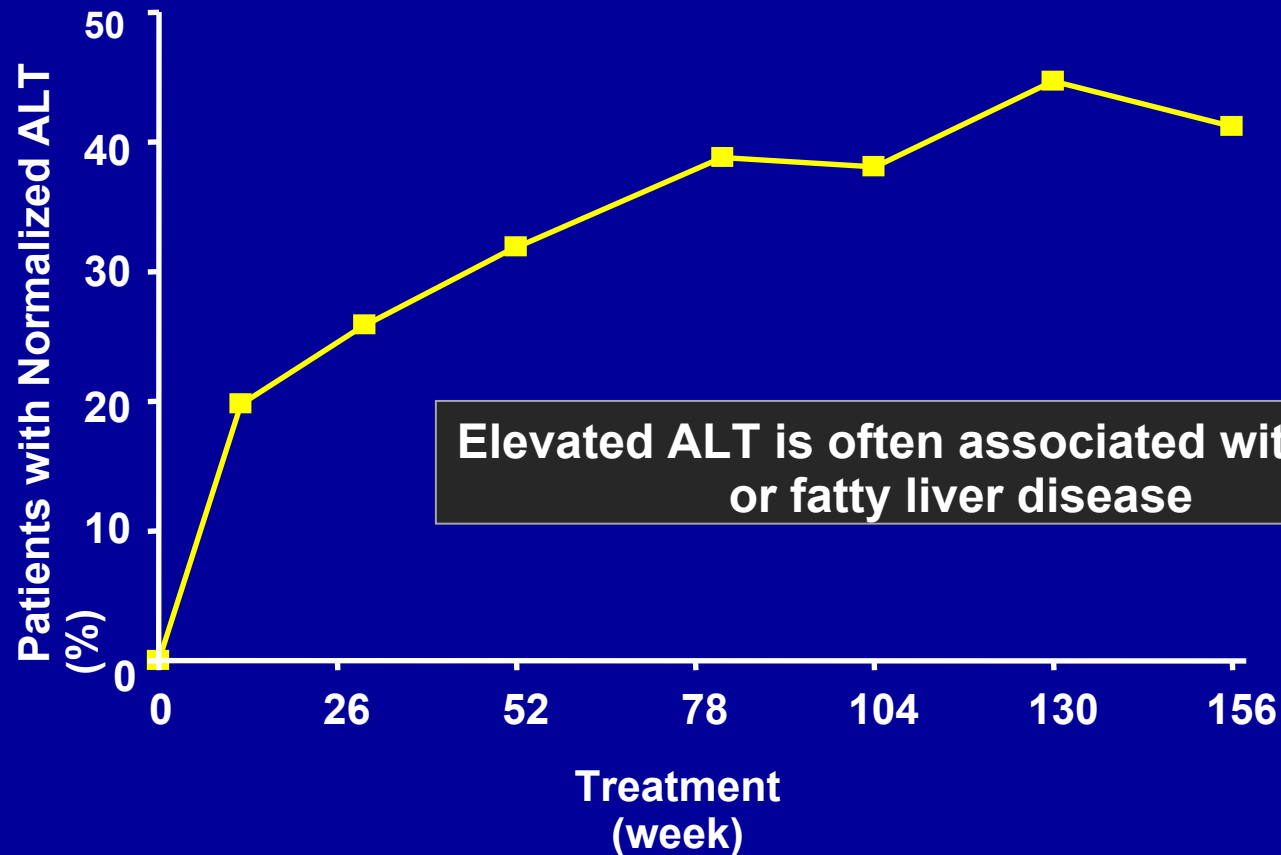
Estudios Controlados con Placebo/Extensión abierta: Perfil de lípidos a los 3,5 años



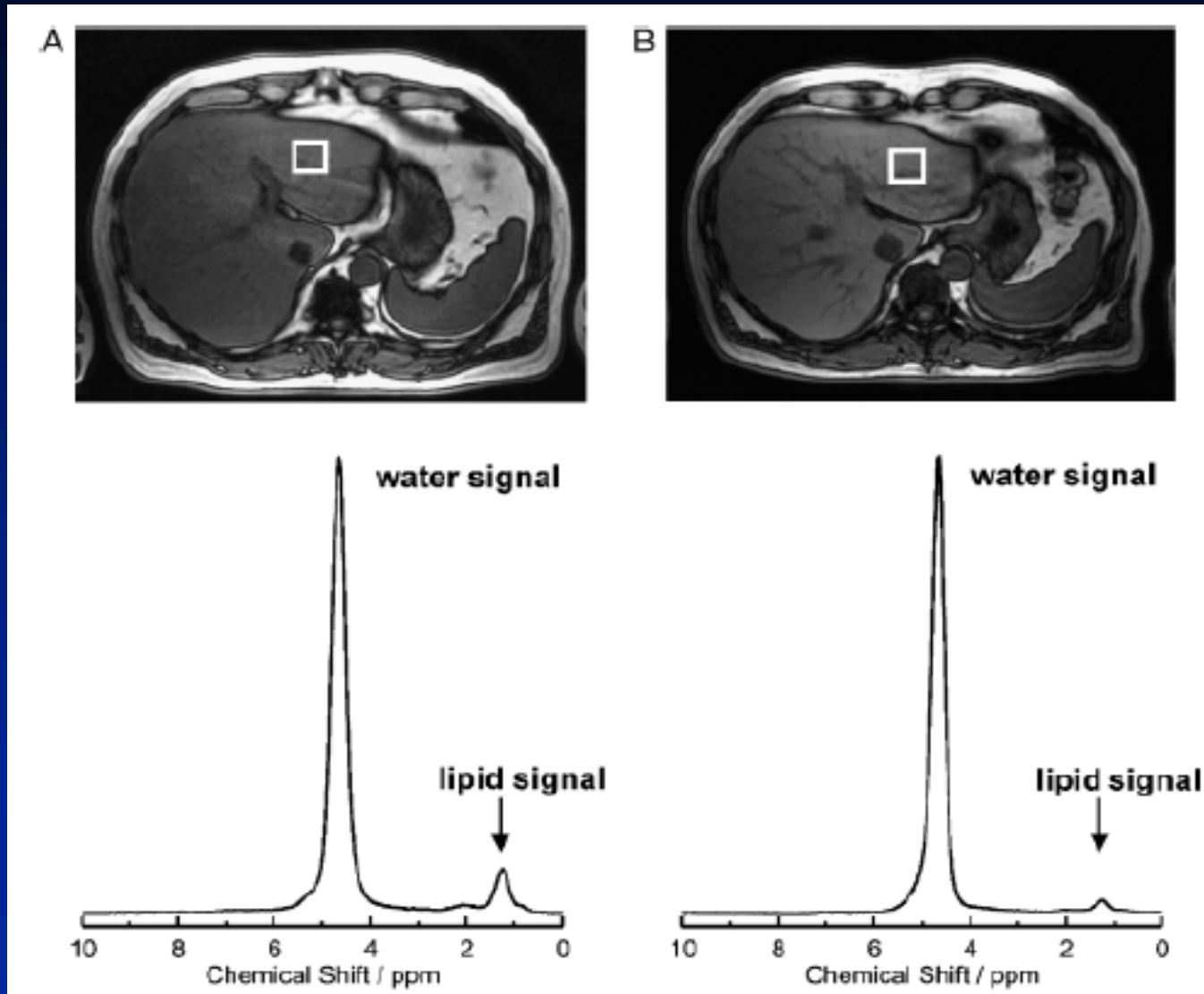
N=151; *p<.05.

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

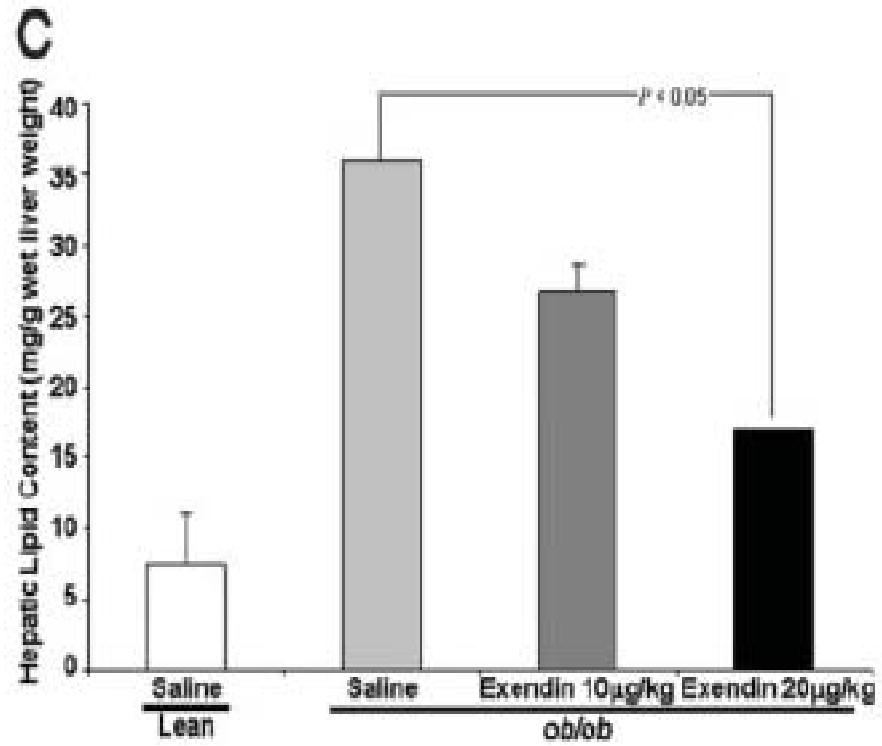
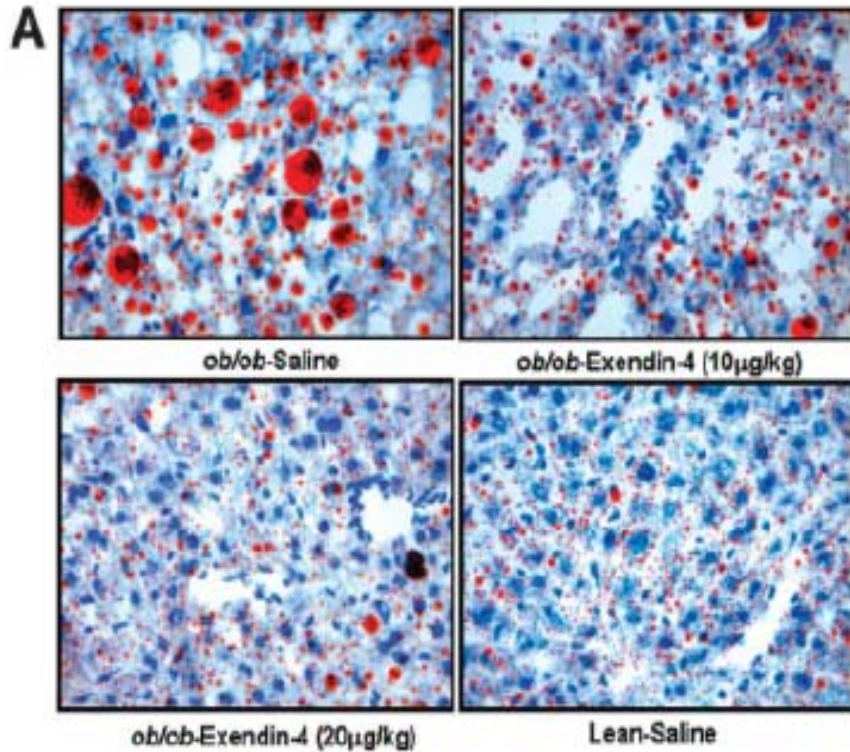
Normalización de ALT en sujetos DM2 tratados con exenatida



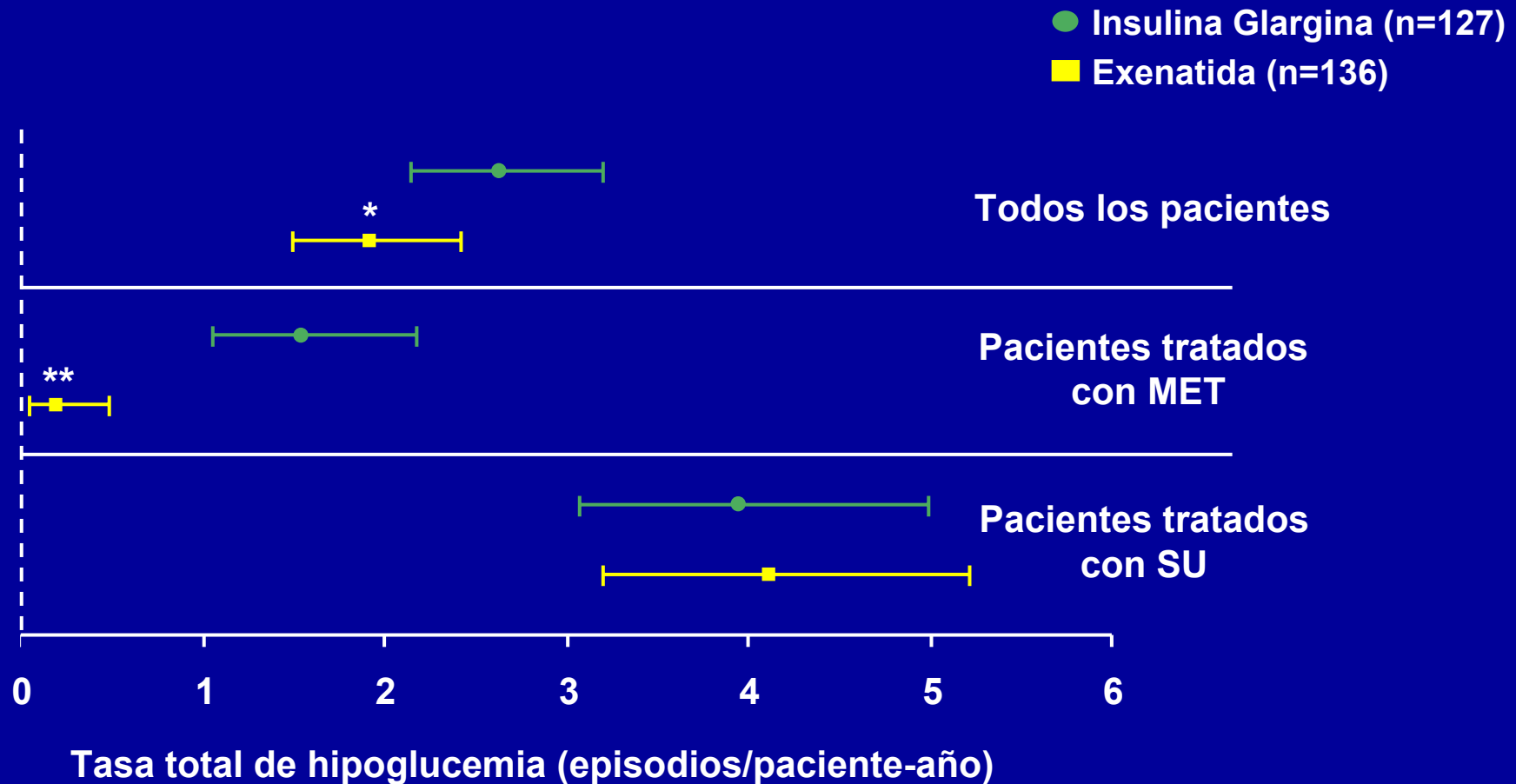
EXENATIDA Y ESTEATOSIS HEPATICA



EXENATIDA Y ESTEATOSIS HEPÁTICA



Estudio Cruzado de no Inferioridad de Exenatida/Insulina Glargina Glargina: Tasa Total de Hipoglucemia

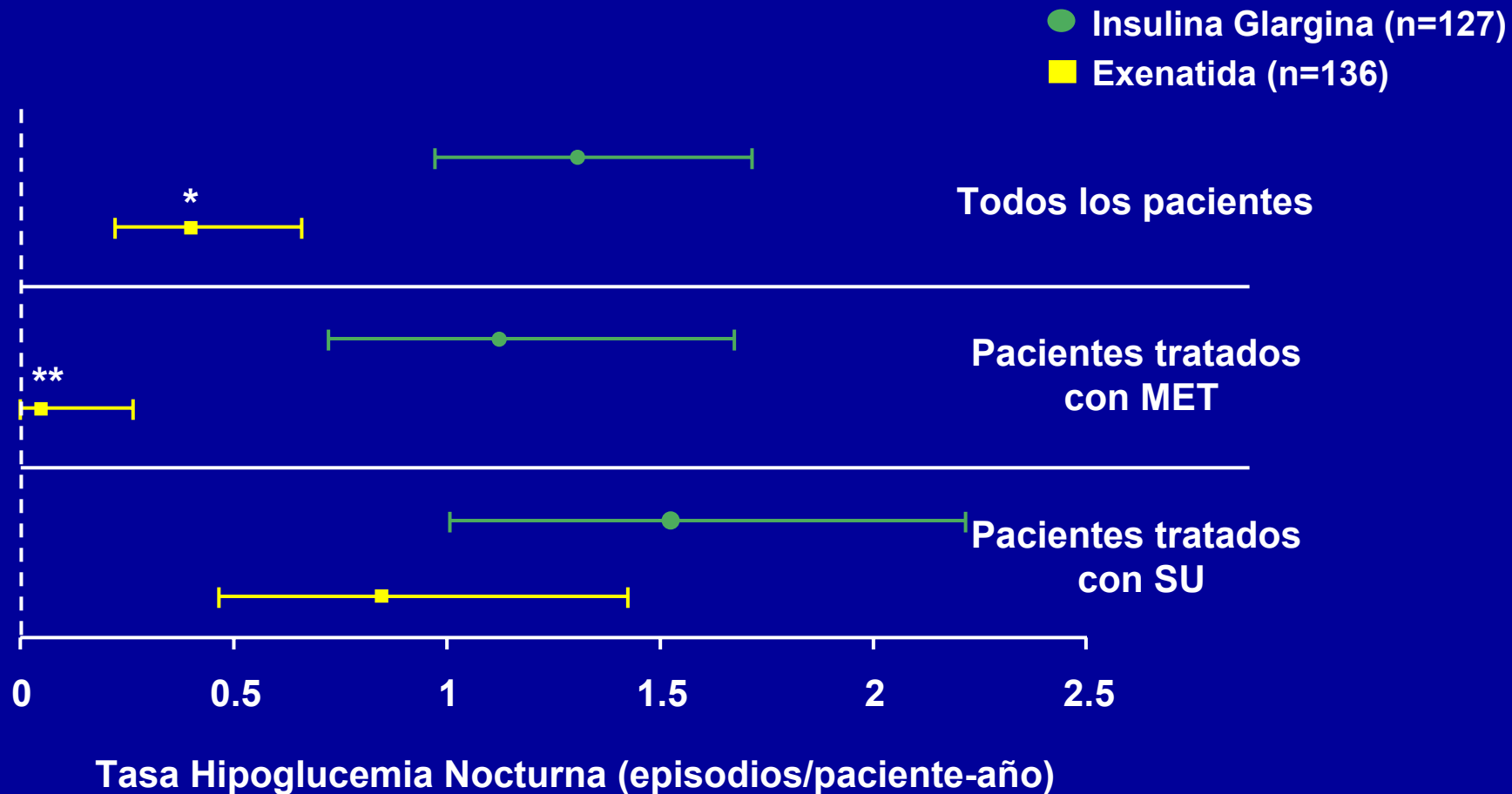


Muestra ITT, N=138; Densidades de incidencia (número de episodios/exposición) \pm IC 95%.

*p=.039, exenatida versus insulina glargina; **p<.001, exenatida + metformina versus insulina glargina + metformina.

Barnett AH, et al. *Clin Ther.* 2007;29:2333-2348.

Estudio Cruzado de no Inferioridad de Exenatida/Insulina Glargina: Tasa nocturna de Hipoglucemia



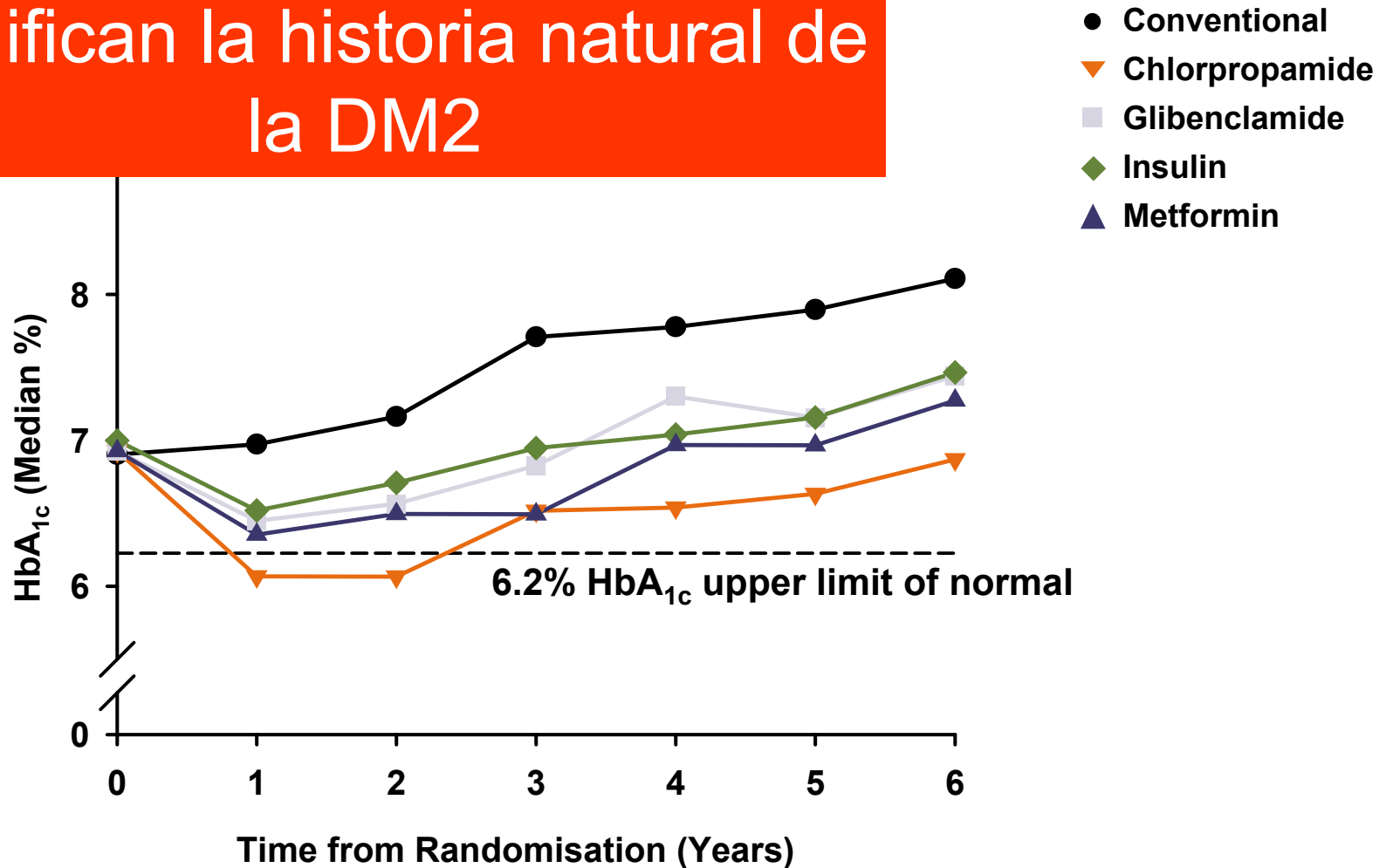
Muestra ITT, N=138; densidades de incidencia (número de episodios/exposición) \pm IC 95%.

* $p < .001$, exenatida versus insulina glargina; ** $p = .002$, exenatida + metformina versus insulina glargina + metformina.

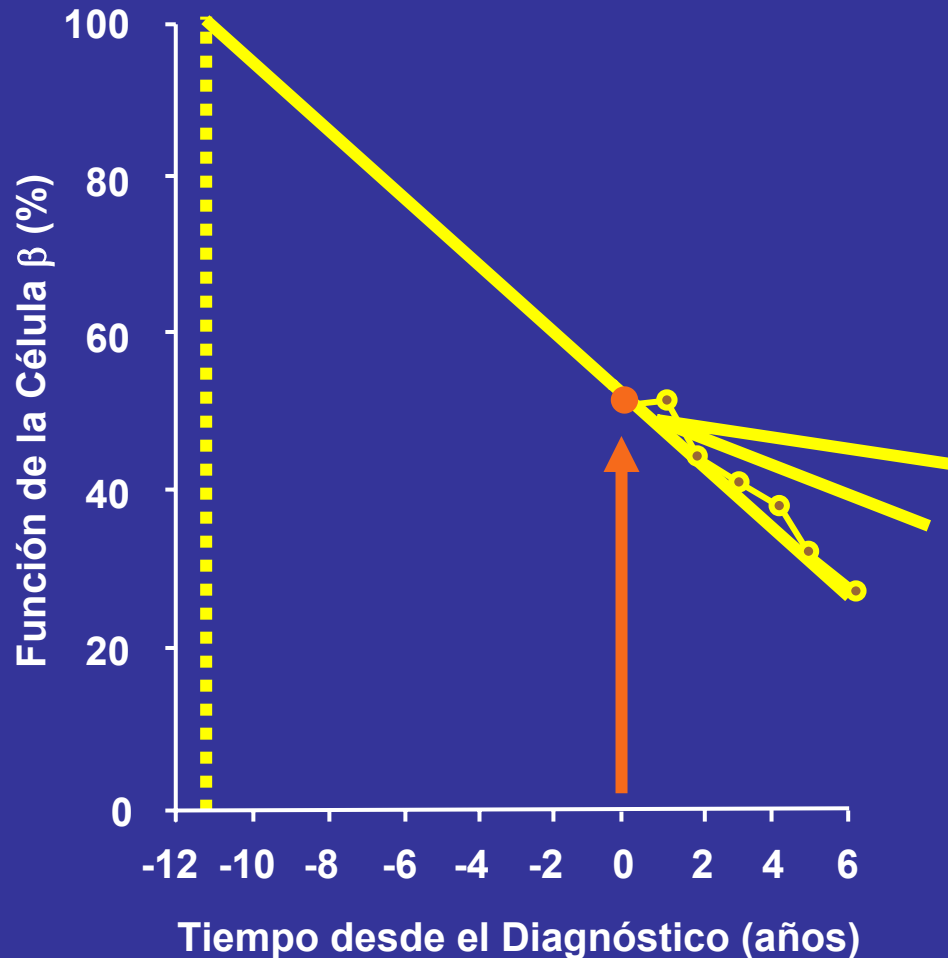
Barnett AH, et al. *Clin Ther.* 2007;29:2333-2348.

La DM2 es una enfermedad progresiva: UKPDS

Los tratamientos clásicos no modifican la historia natural de la DM2



La función de la célula β disminuye a lo largo del tiempo en pacientes con Diabetes Tipo 2



Es posible que la función de la célula β ya haya disminuido en un 50% en el momento del diagnóstico, pero...

Quizás la función de la célula β disminuya de forma distinta con el tiempo dependiendo del tipo de paciente y también del tipo de tratamiento

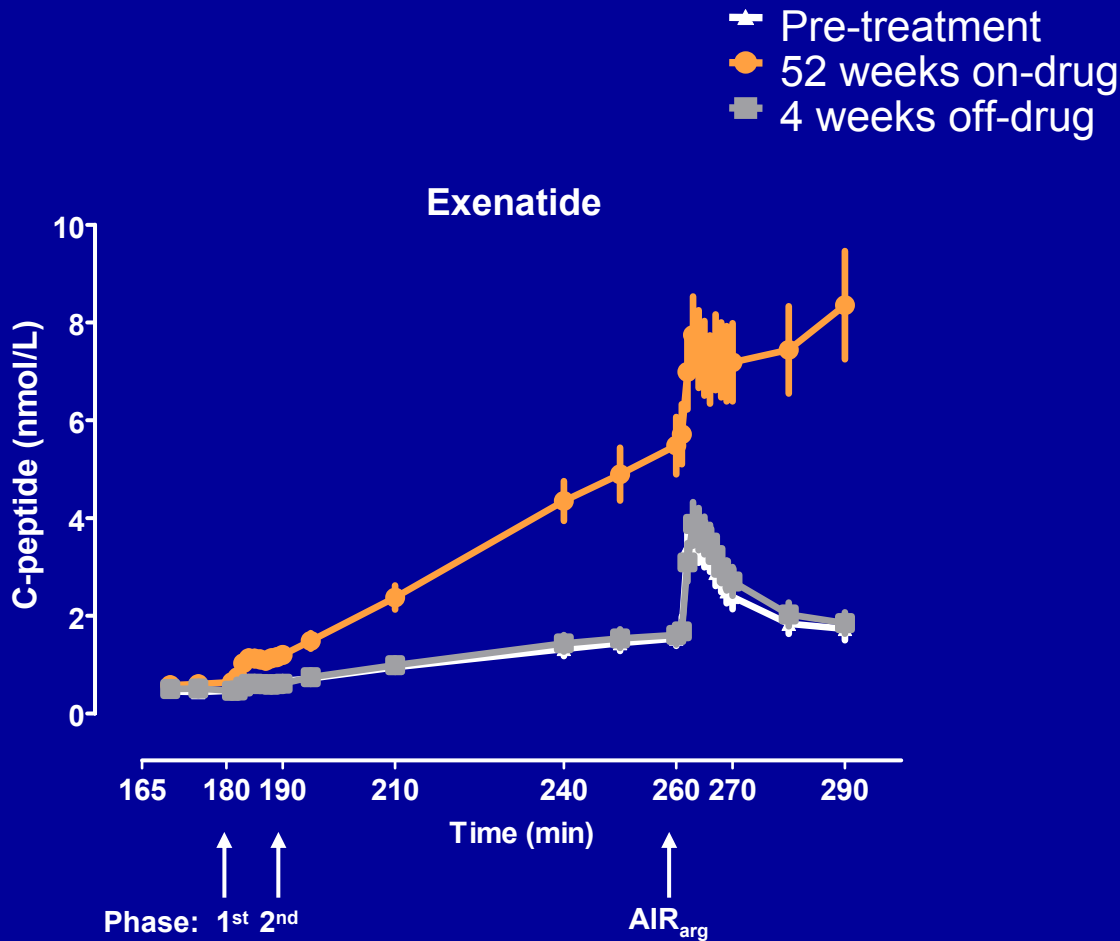
¿Modifica el tratamiento con exenatida la función de la célula beta en la DM2?

Concentraciones de C-péptido durante un clamp hiperglicémico: exenatida vs glargina

- ✚ Pre-treatment
- 52 weeks on-drug
- 4 weeks off-drug

Data represent mean \pm SE

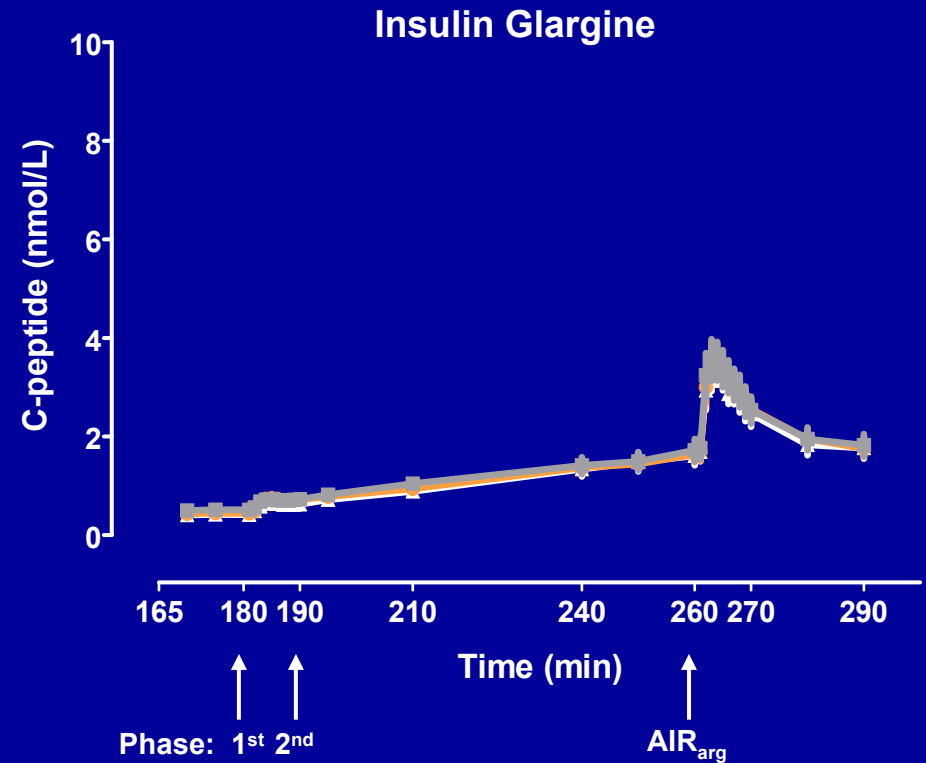
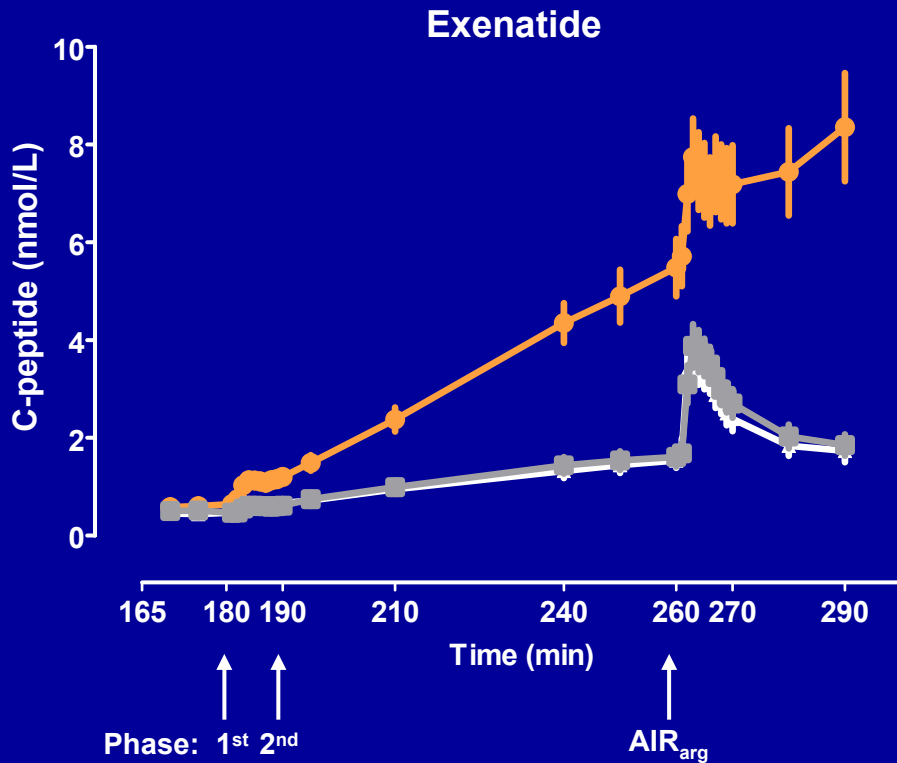
Concentraciones de péptido C durante un clamp hiperglicémico



Data represent mean \pm SE

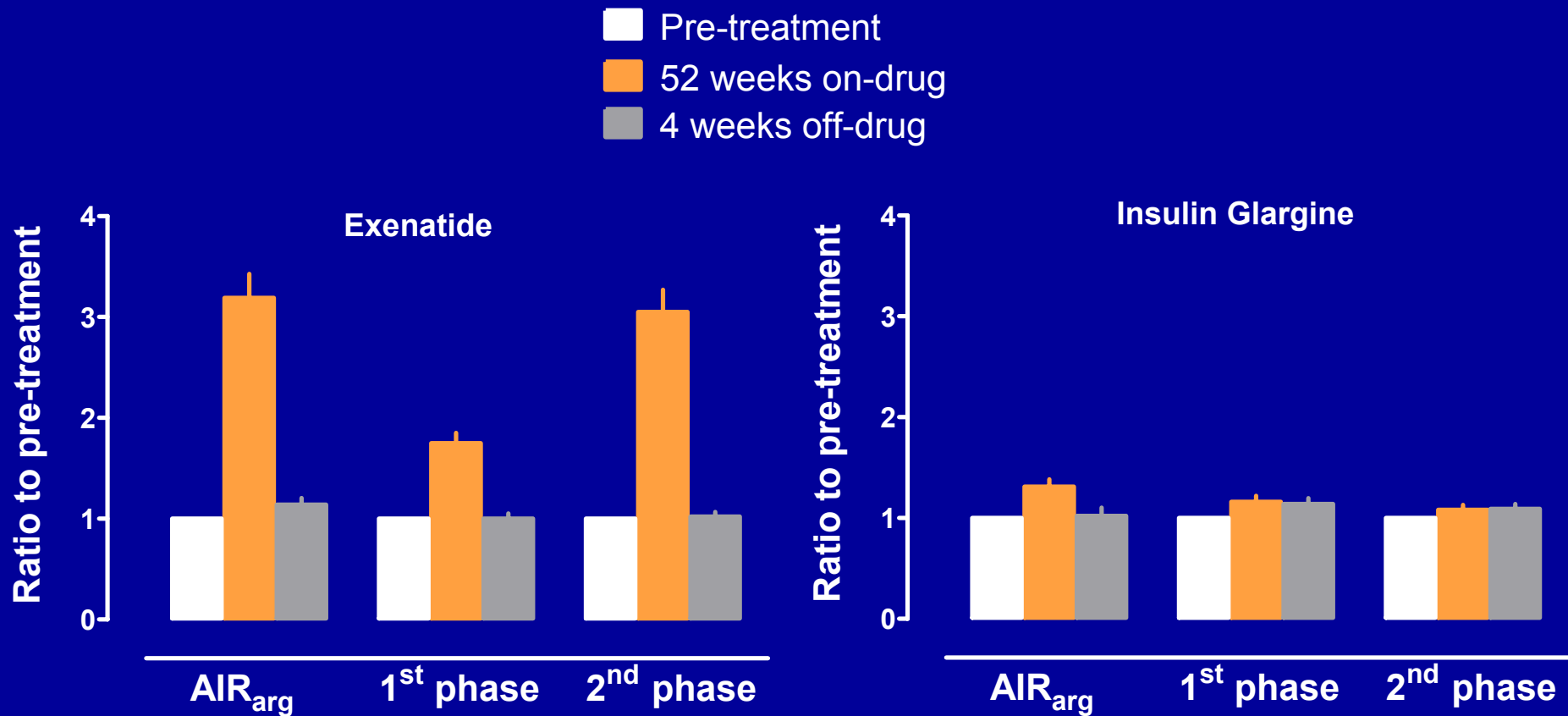
Concentraciones de péptido C durante un clamp hiperglicémico

- Pre-treatment
- 52 weeks on-drug
- 4 weeks off-drug



Data represent mean \pm SE

Evaluación de la función beta pancreática tras 52 semanas: exenatida vs glargina



Data are geometric mean \pm SE

AIR_{arg}, C-peptide response to arginine at 15 mmol/L glucose concentration; 1st phase, first-phase C-peptide response to glucose
2nd phase, second-phase C-peptide response to glucose

Bunck et al. Diabetes Care 2009;32:762-8.



Gracias por vuestra atención

GLP-1 MEJORA DISFUNCIÓN ENDOTELIAL EN DIABETICOS TIPO 2

Table 2. Brachial artery, heart rate, and blood pressure data in healthy subjects

Variable	Saline		GLP-1	
	Onset	Clamp	Onset	Clamp
Baseline diameter FMD, mm	3.8±0.1	4.0±0.2	3.8±0.2	4.0±0.2
Maximal diameter FMD, mm	4.2±0.2	4.4±0.2	4.2±0.2	4.4±0.2
Δ FMD(%)	11.4±1.5	11.9±0.6	10.1±0.7	10.3±1.0
Baseline diameter NTG, mm	3.8±0.2	4.0±0.2	3.9±0.2	4.0±0.2
Maximal diameter NTG, mm	4.6±0.2	4.6±0.2	4.5±0.2	4.7±0.2
Δ NTG(%)	19.6±1.2	16.5±1.3	16.9±1.5	15.2±1.4
Baseline flow FMD, ml/min	31±2	35±2	37±3	36±4
Maximal flow FMD, ml/min	156±18	164±15	167±14	166±23
Baseline flow NTG, ml/min	35±4	40±4	36±3	40±3
Maximal flow NTG, ml/min	45±5	57±8	53±5	56±6
Heart rate, beats/min	52±2	55±3	52±2	56±3
sBP, mmHg	112±2	111±2	107±1	108±1
dBp, mmHg	71±3	69±2	72±1	69±1

Data are means ± SE. Brachial artery, heart rate, and blood pressure data in healthy subjects at onset and at steady-state hyperinsulinemic clamp during glucagon-like peptide-1-(7-36) amide (GLP-1) or saline infusion. Onset, resting state without any procedure or infusions; Clamp, 90- to 120-min interval in hyperinsulinemic clamp; FMD, flow-mediated dilation (endothelial-dependent vasodilation); NTG, nitroglycerin-mediated dilation (endothelial-independent vasodilation); ΔFMD(%), relative increases in FMD; Δ NTG(%), relative increases in NTG; sBP, systolic blood pressure; dBp, diastolic blood pressure

Table 3. Brachial artery, heart rate, and blood pressure data in type 2 diabetes subjects

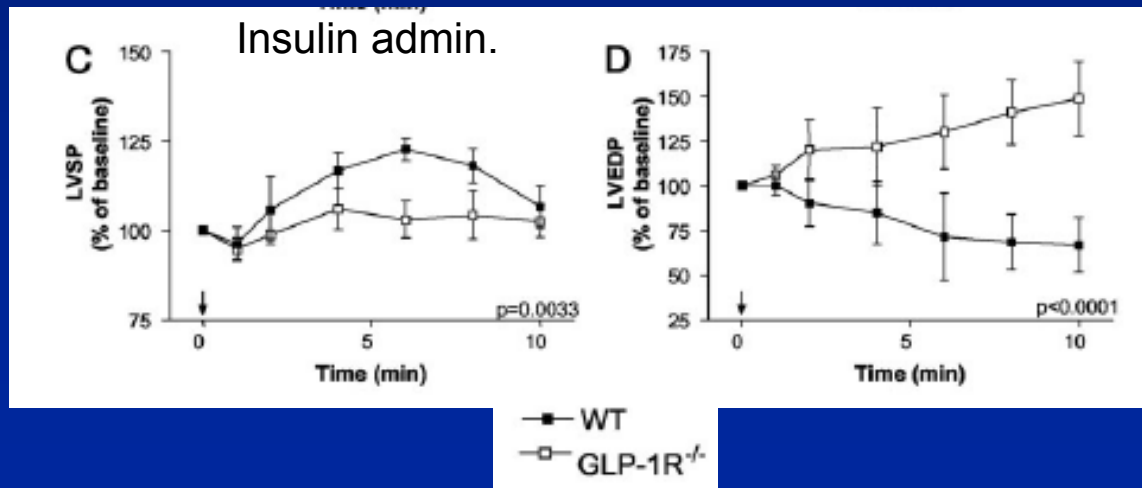
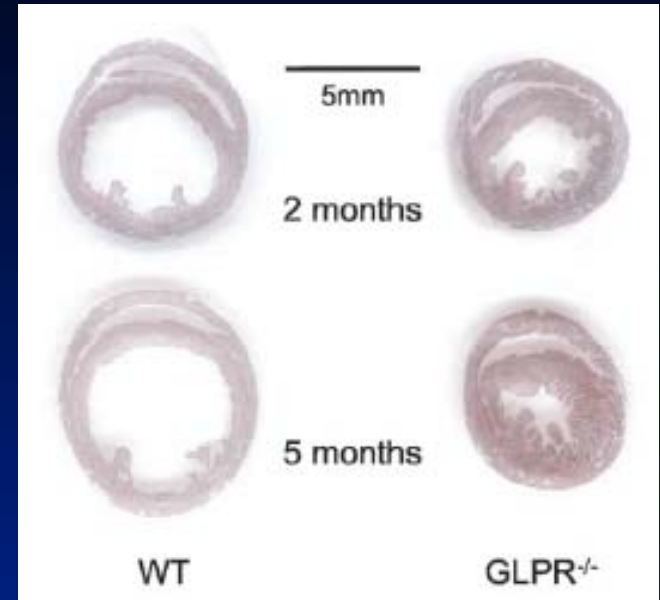
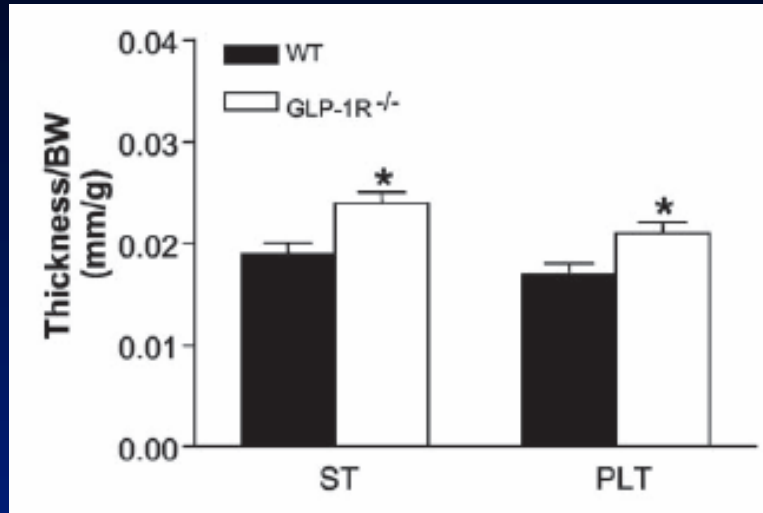
Variable	Saline		GLP-1	
	Onset	Clamp	Onset	Clamp
Baseline diameter FMD, mm	4.2±0.1	4.4±0.2	4.3±0.1	4.4±0.2
Maximal diameter FMD, mm	4.3±0.1	4.6±0.1	4.3±0.1	4.7±0.2
Δ FMD(%)	2.0±0.7	3.1±0.6	2.2±0.5	6.6±1.0*
Baseline diameter NTG, mm	4.3±0.1	4.5±0.2	4.3±0.1	4.5±0.2
Maximal diameter NTG, mm	5.0±0.1	5.1±0.1	5.0±0.1	5.2±0.1
Δ NTG(%)	17.5±2.0	14.5±2.0	16.7±1.5	16.5±2.4
Baseline flow FMD, ml/min	56±4	52±4	60±10	54±5
Maximal flow FMD, ml/min	166±9	161±11	162±12	167±18
Baseline flow NTG, ml/min	58±4	53±4	57±4	58±4
Maximal flow NTG, ml/min	64±4	62±3	67±4	69±4
Heart rate, beats/min	61±3	60±3	60±3	62±3
sBP, mmHg	127±5	125±4	124±4	127±3
dBp, mmHg	78±2	77±2	78±2	78±2

Data are means ± SE. Brachial artery, heart rate, and blood pressure data in type 2 diabetes subjects at onset and at steady-state hyperinsulinemic clamp during GLP-1 or saline infusion. See Table 2 legend for additional information. *P < 0.05 compared with saline (onset and clamp) and with GLP-1 (onset), ANOVA.

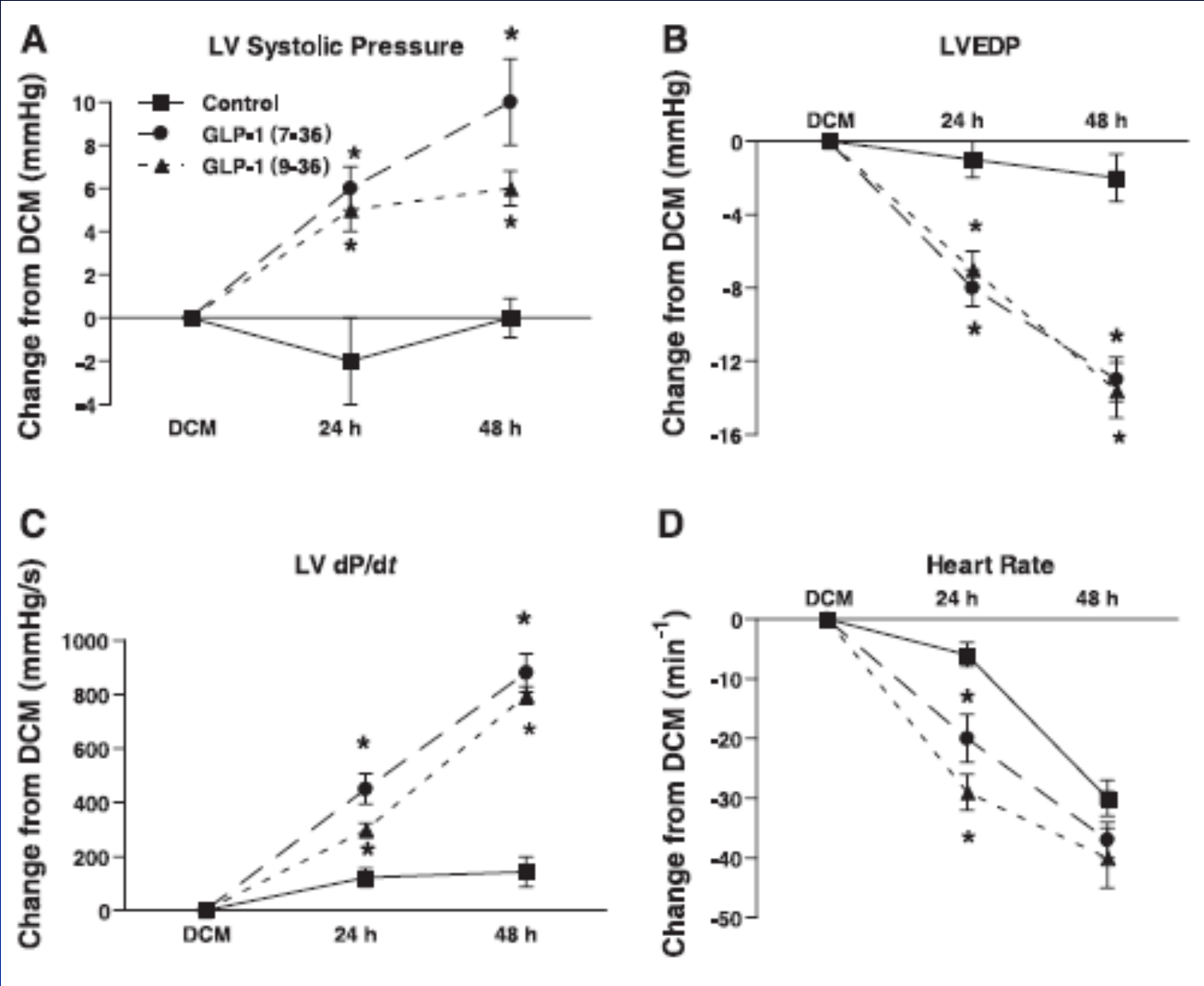
GLP-1 2 pmol/kg/min 120 min

Nystrom et al. Am J Physiol Endocr Metab 2004

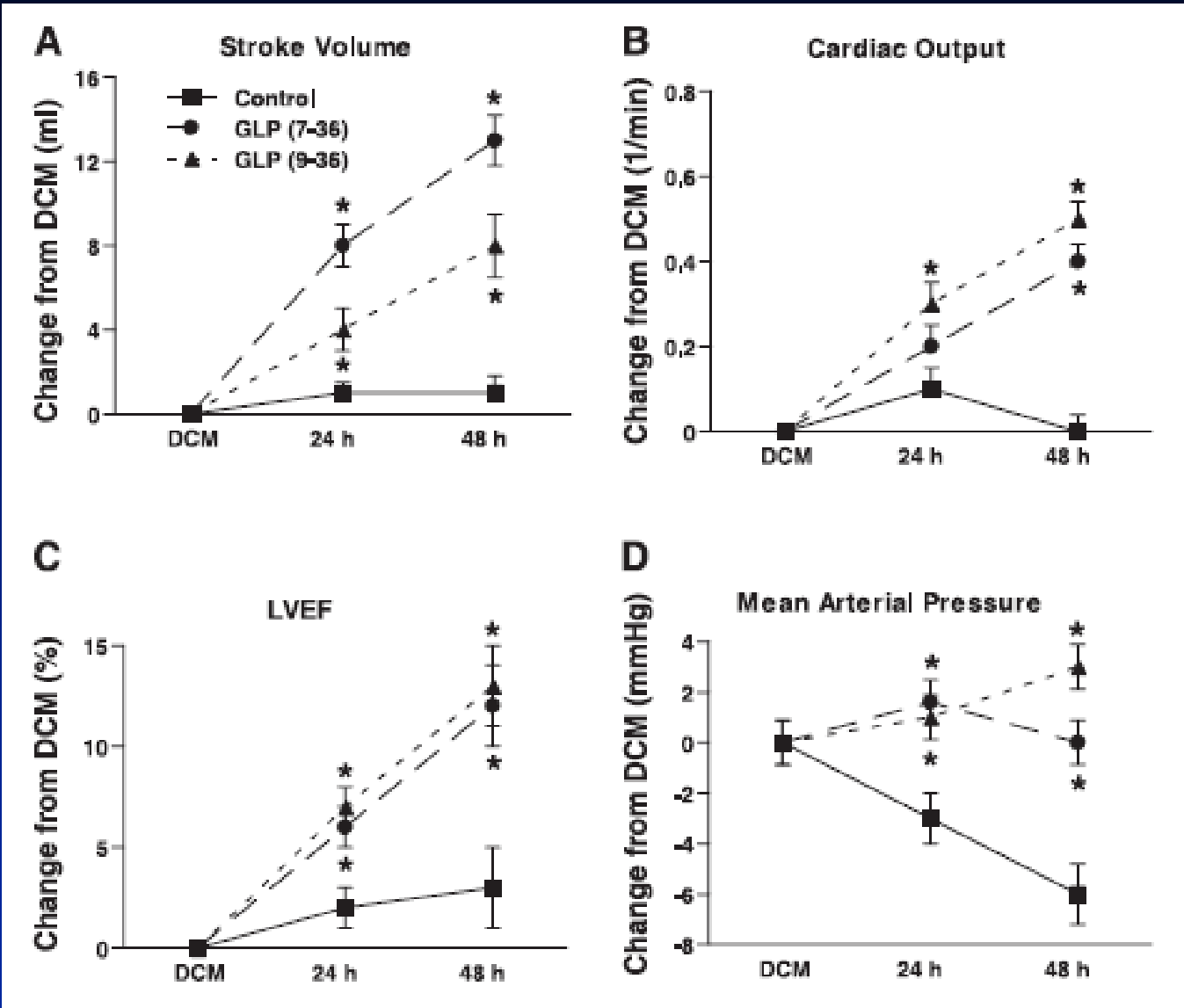
MICE LACKING GLP-1R SHOW CARDIAC DYSFUNCTION



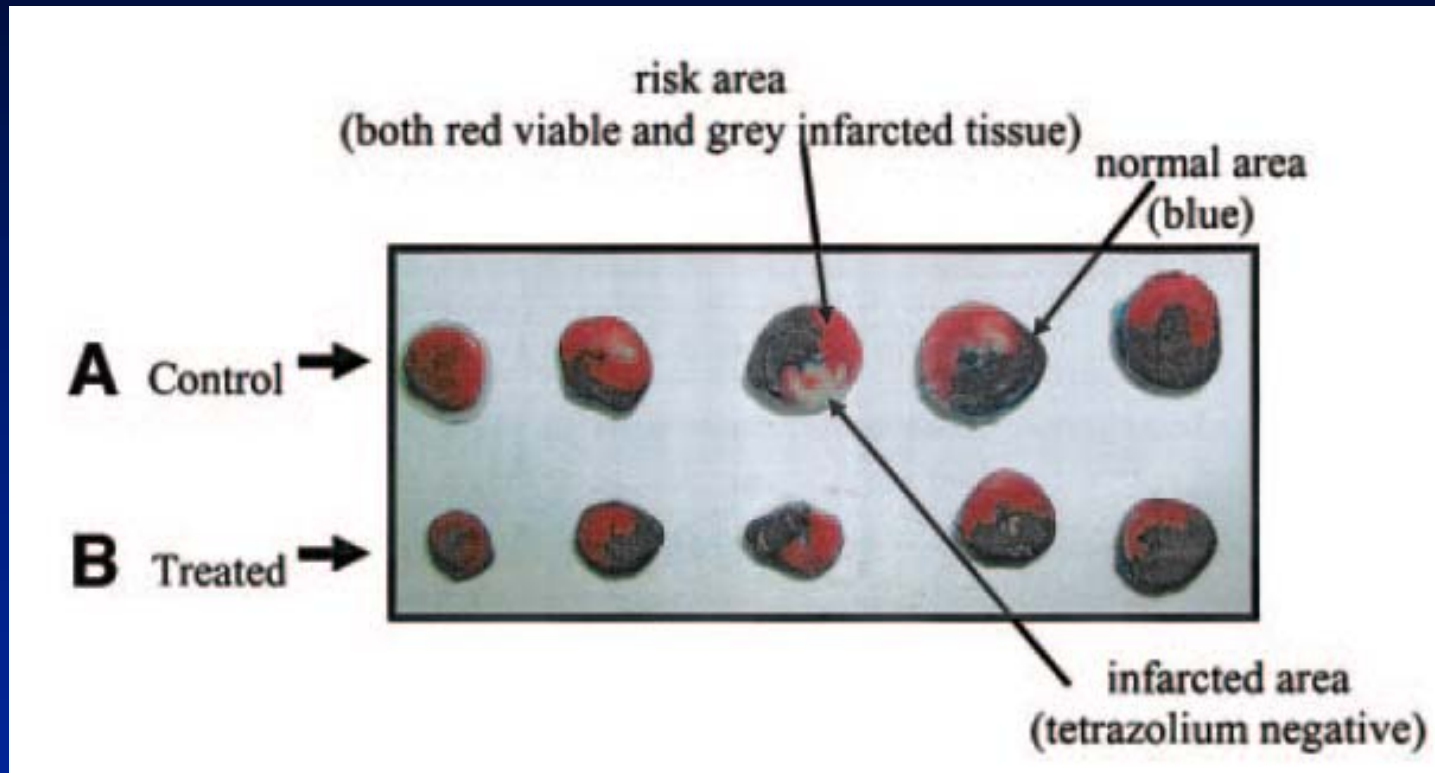
GLP-1 IMPROVES CARDIAC FUNCTION IN DILATED CARDIOMYOPATHY



GLP-1 IMPROVES CARDIAC FUNCTION IN DILATED CARDIOMYOPATHY

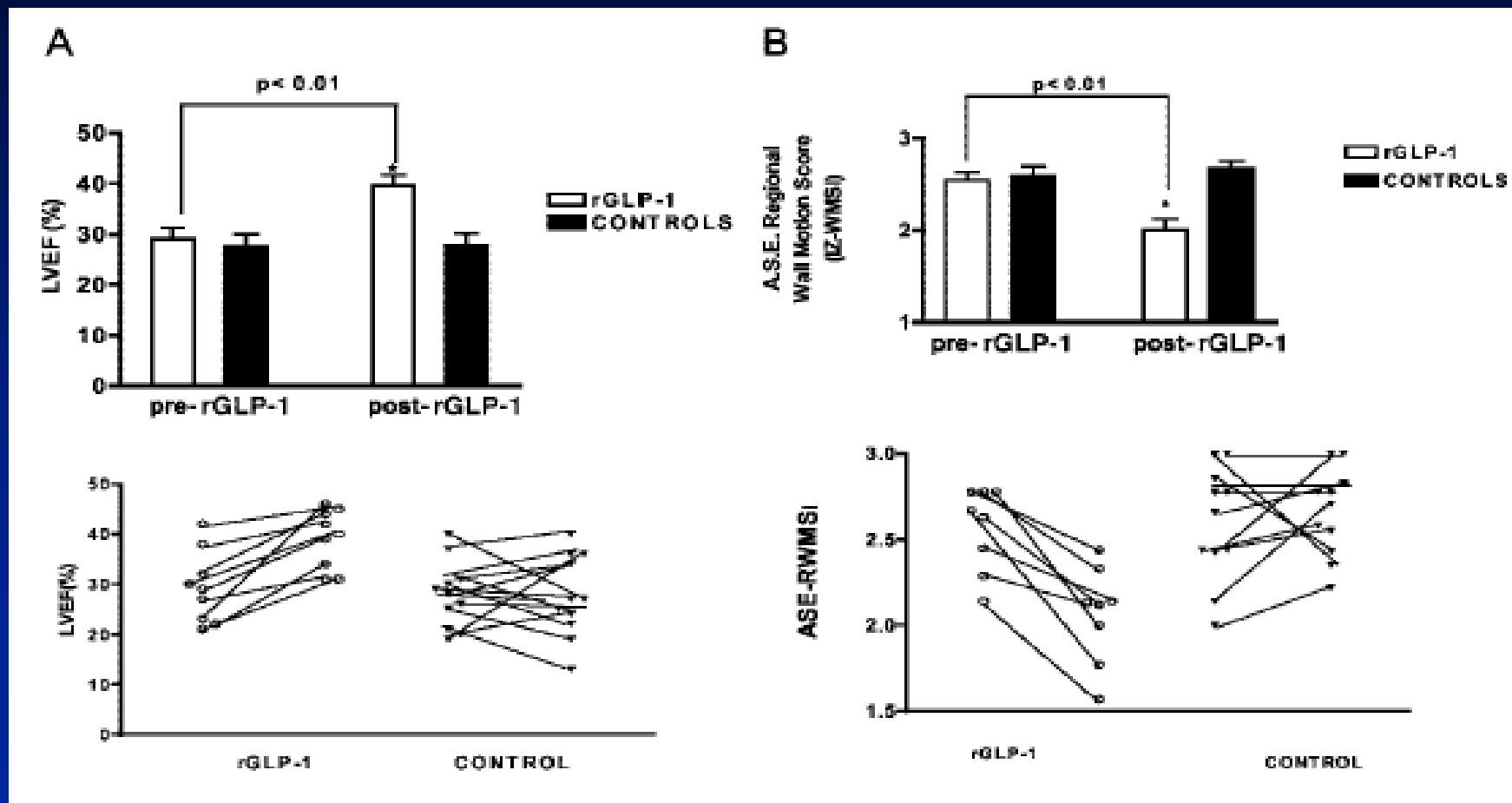


GLP-1 AND MYOCARDIAL INFARCTION SIZE



GLP-1 IMPROVES VENTRICULAR DYSFUNCTION FOLLOWING MI

Patients after MI and angioplasty

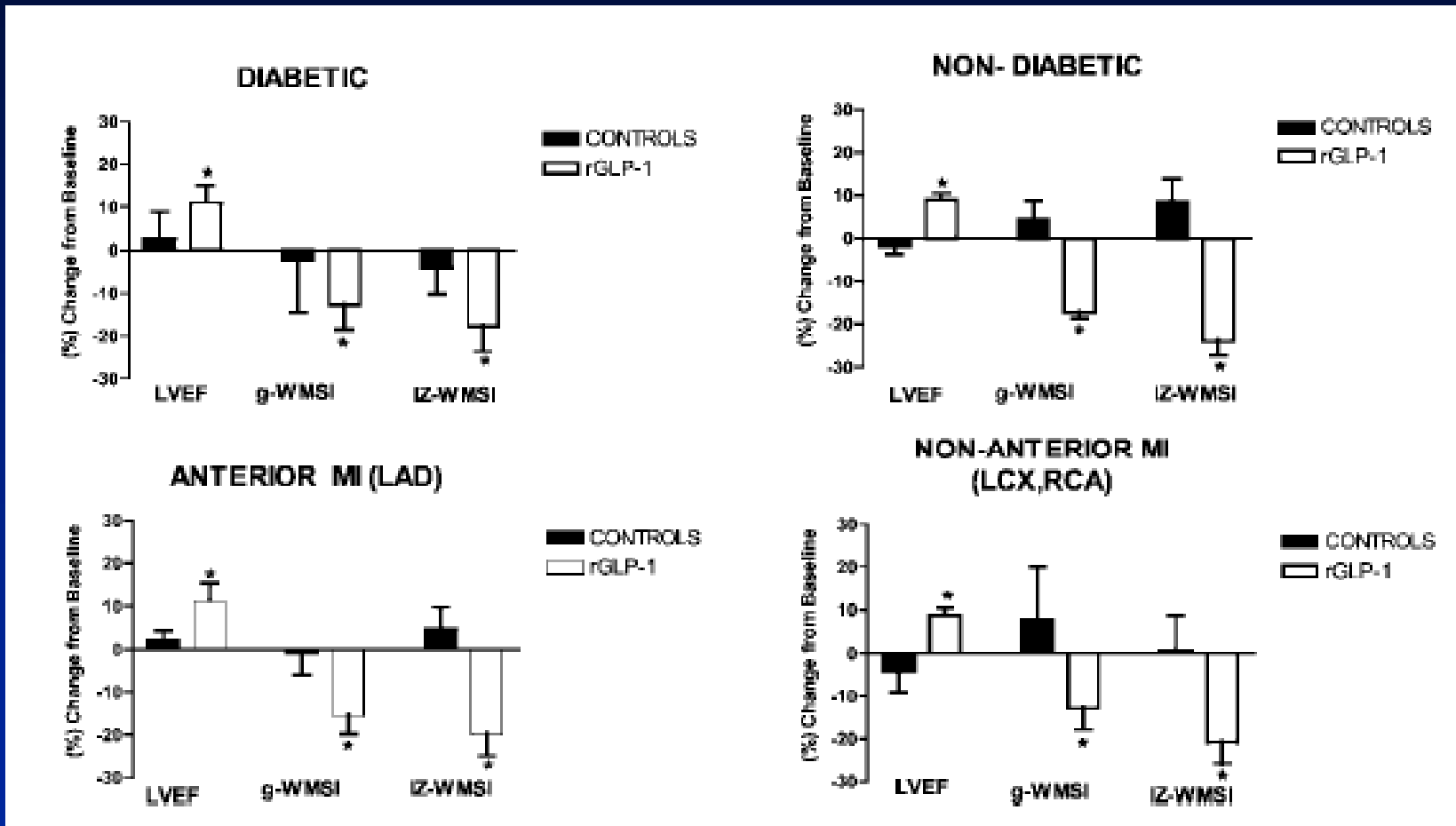


GLP-1

1.5 pmol/kg/min x 72h

GLP-1 IMPROVES VENTRICULAR DYSFUNCTION FOLLOWING MI

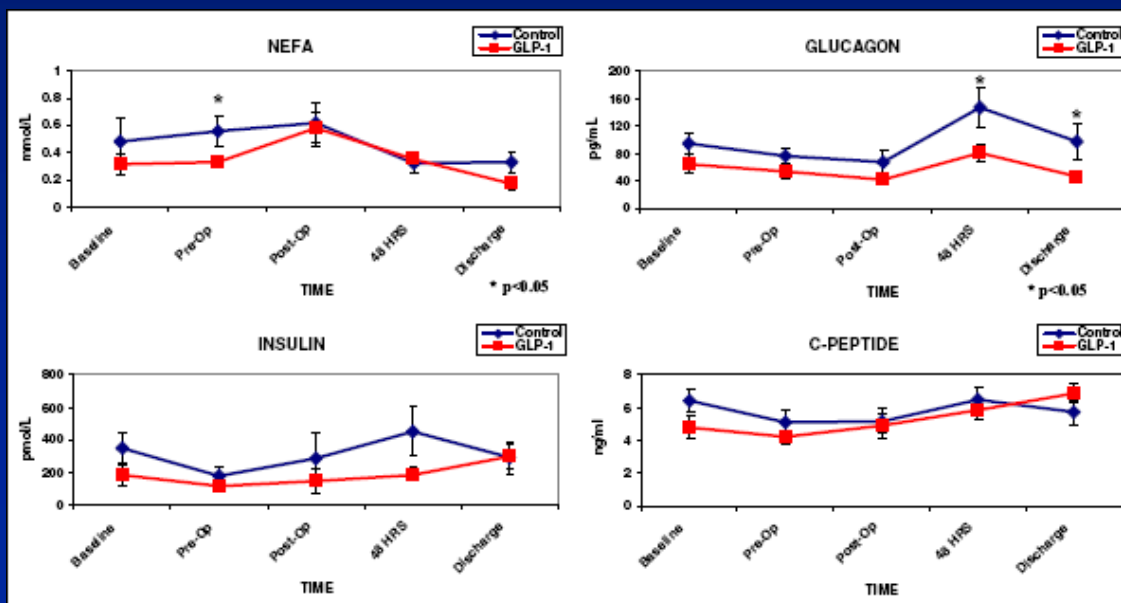
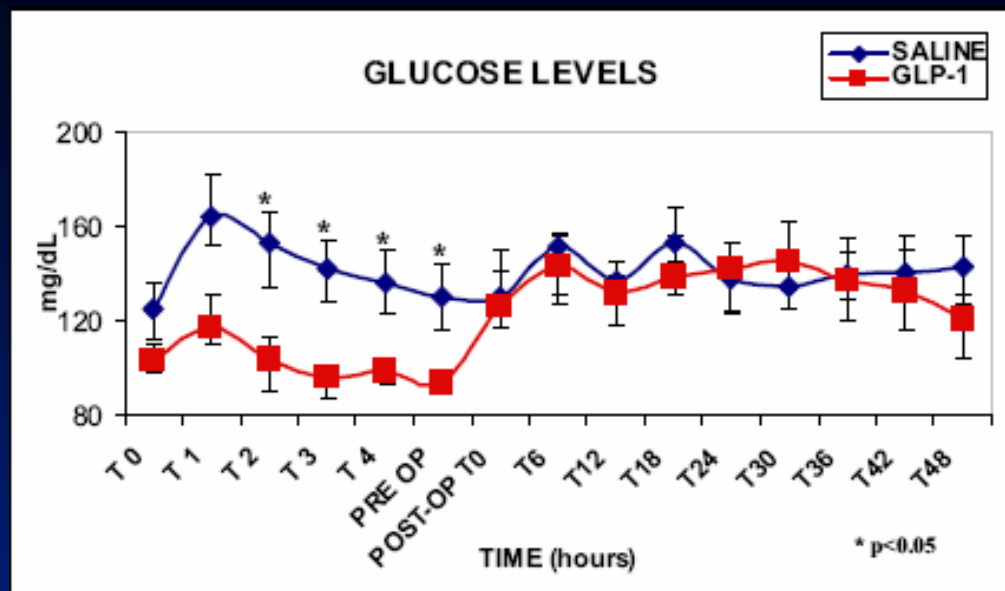
Patients after MI and angioplasty



GLP-1

1.5 pmol/kg/min x 72h

GLP-1 IMPROVES GLUCOSE METABOLISM IN CORONARY BYPASS



GLP-1 EFFECTS ON MYOCARDIAL FUNCTION IN EXPERIMENTAL MODELS

Author	Peptide	Model	Myocardial function	Postischemic	Infarct size	Other effects
Kavianipour 2003	GLP-1	Pig Open-chest	Unchanged MAP,CVP		Unchanged	Reduction PIR, LACT
Nikolaidis 2004	GLP-1 1.5pmol/k/m 48h	Dogs DCM	+ LV dP/dt + Cardiac output Only in DCM			+ Myocard Glucose Uptake -Glucagon & NE
Nikolaidis 2005	GLP-1 (7-36) GLP-1 (9-36) 1.5pmol/k/m 48h	Dogs DCM	+ LV dP/dt + Cardiac output + LVSP - HR			+ Myocard Glucose uptake

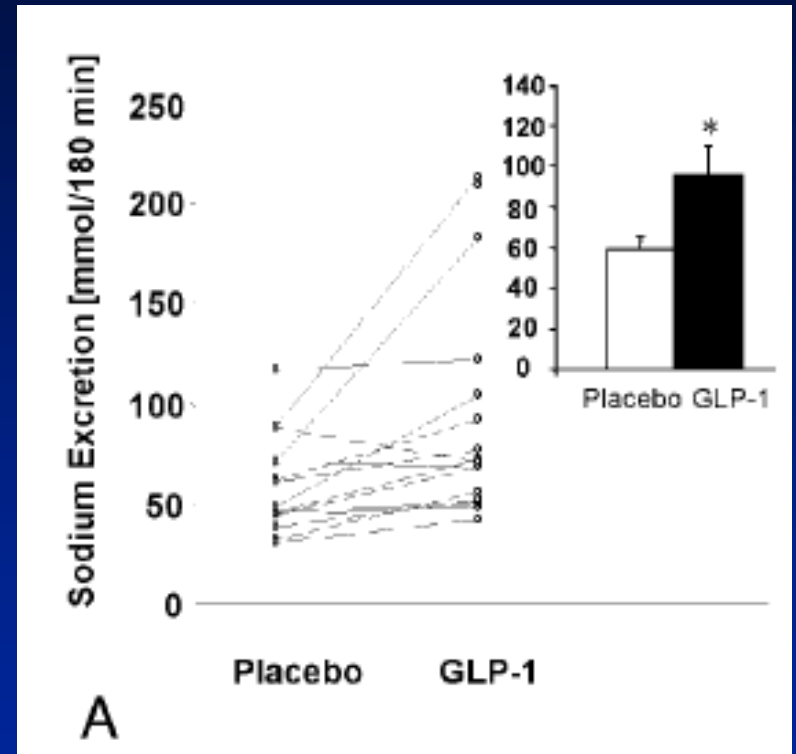
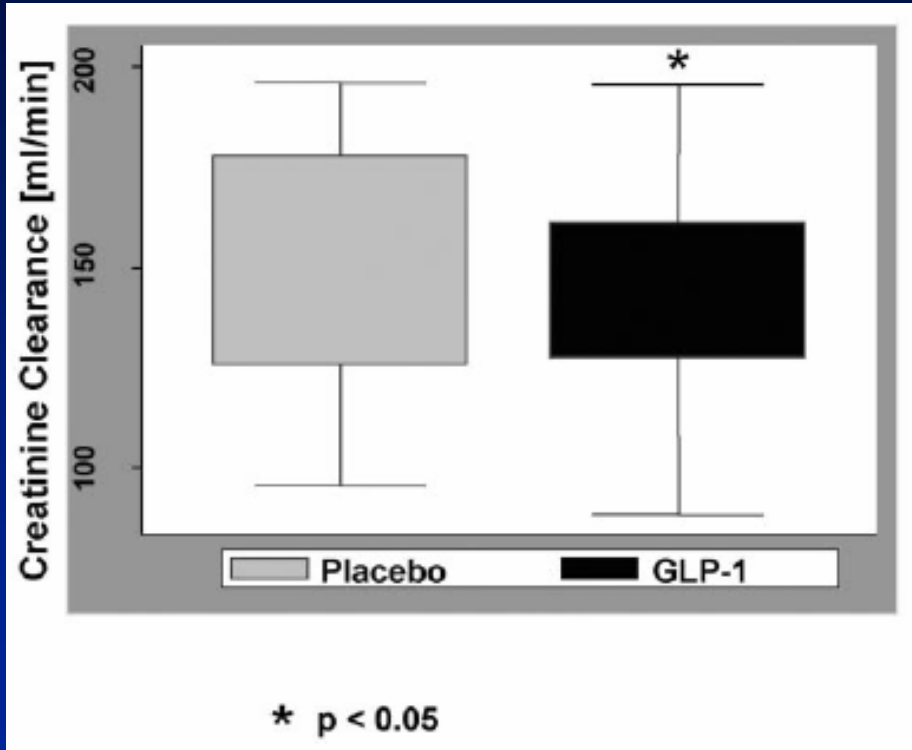
GLP-1 IN ISCHEMIA-REPERFUSION EXPERIMENTS

Author	Peptide	Model	Myocardial function	Postischemic	Infarct size	Other effects
Bose 2005	GLP-1 4.8pmol/k/m	Rats Isch-reperf vivo & vitro			Reduced Abolished by intracel antagonists	
Zhao 2006	GLP-1	Rats Isch-reperf In vivo	- LVDP - dP/dt In normal heart	+ LV function		+ NO + glucose uptake
Sonne 2007	EXEND-4 GLP-1 (9-36)	Rats Isch-reperf Isolated heart		+ LV dP/dt (EXE & GLP-1)	Reduced (EXE) Unchanged (GLP-1)	
Bose 2007	GLP-1	Rats Isch-reperf Isolated heart In vitro			Reduced Abolished by rapamycin (only GLP- 1+VP)	

GLP-1 ON HEART IN HUMANS

Author	Peptide	Model	Myocardial function	Post ischemic	Infarct size	Other effects
Nikolaidis 2004	GLP-1 1.5pmol/k/m 72h	Humans MI & LVEF<40%		+ LVEF + motion scores		Indepdent of diabetes or MI area
Thrainsdottir 2004	GLP-1 3-4 pmol/k/m 3 days	Humans DM2 & CHF	+ myocard function (TDI)			-Glucose -FFA
Sokos 2006	GLP-1 2.5pmol/k/m 5 weeks	Humans CHF	+ LVEF + VO2 max + Walk test + QoL			-Glucose -FFA -DM &noDM
Sokos 2007	GLP-1 1.5pmol/k/m 60h	Humans Coronary Bypass	LVEF unchanged			-Glucose -Insul req -arrhythmias -drug req

GLP-1 AUMENTA LA NATRIURESIS



Pancreatitis is a Rare Adverse Event

◆ Exenatide

- Spontaneous cases of pancreatitis have been reported with use of exenatide
- As of January 31, 2009 the cumulative reporting rate of pancreatitis is 0.57 events per 1000 patient years of exenatide exposure¹

◆ General population*

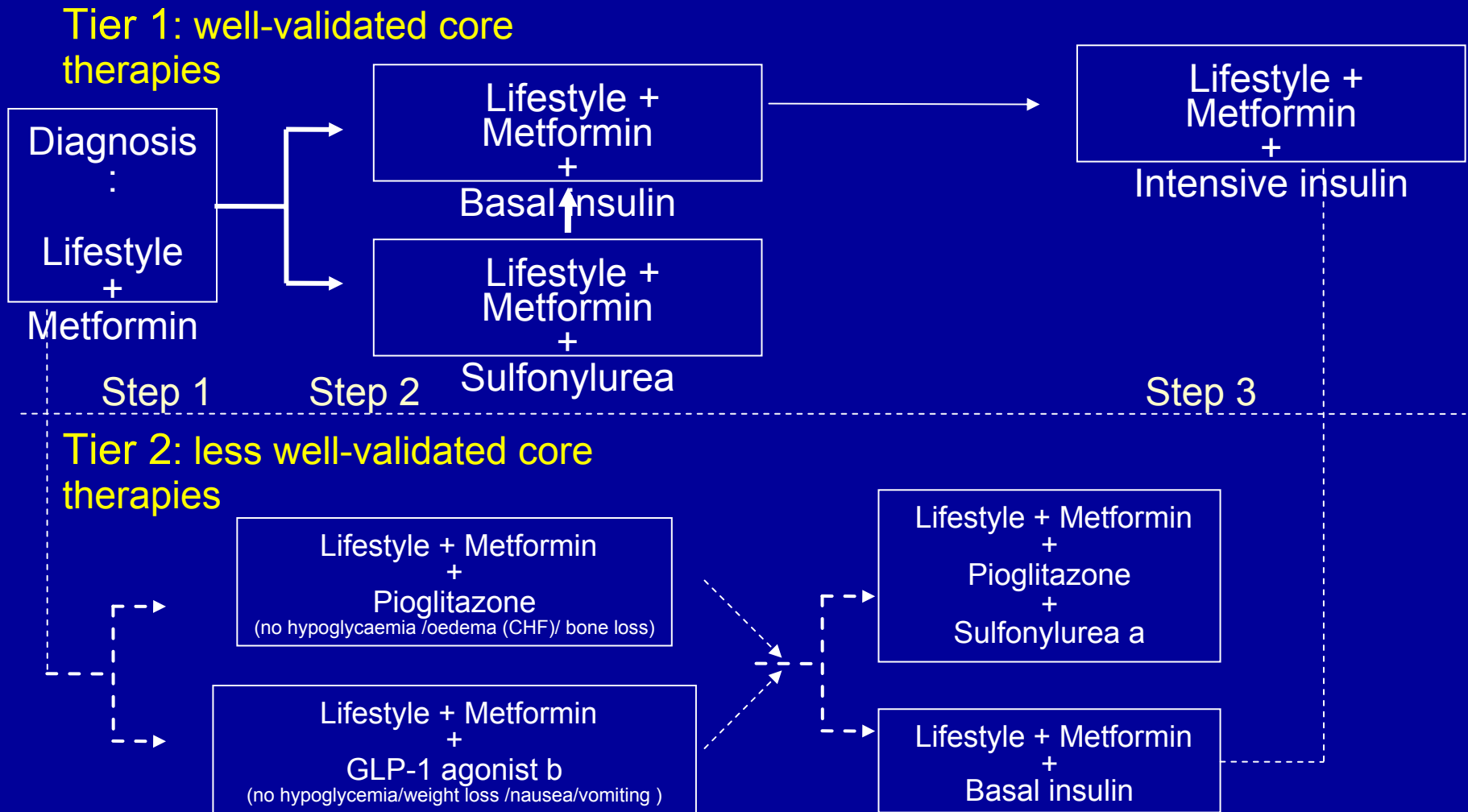
- Recent estimates of the incidence of pancreatitis in the general US population are as follows:
 - 0.7 events per 1000 adults per year^{2,3,4}
 - Severe disease develops in 15-20% of those pancreatitis cases^{5,6}
 - Death occurs in 2-9% of cases^{5,6}
 - Drug-induced pancreatitis is a relatively rare event (1.4-2.0% of all cases)⁶

◆ Patients with T2D

- A recent epidemiological study has reported that patients with T2D are at nearly 3 times the risk of developing pancreatitis than those without diabetes²

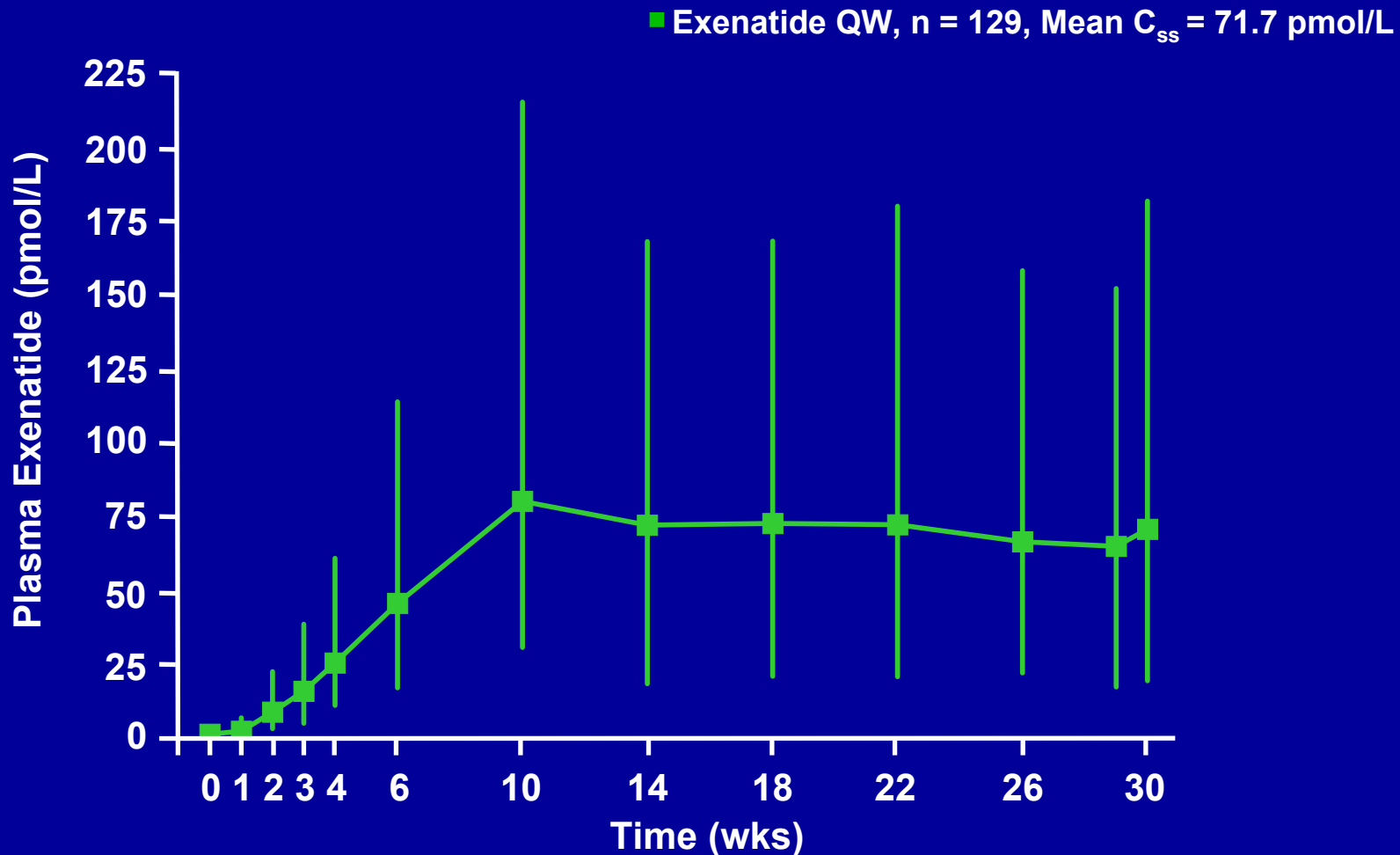
*Note: The pancreatitis rates in the general population should not be directly compared to those rates seen in exenatide-treated patients.

ADA/EASD Consensus Statement for T2D



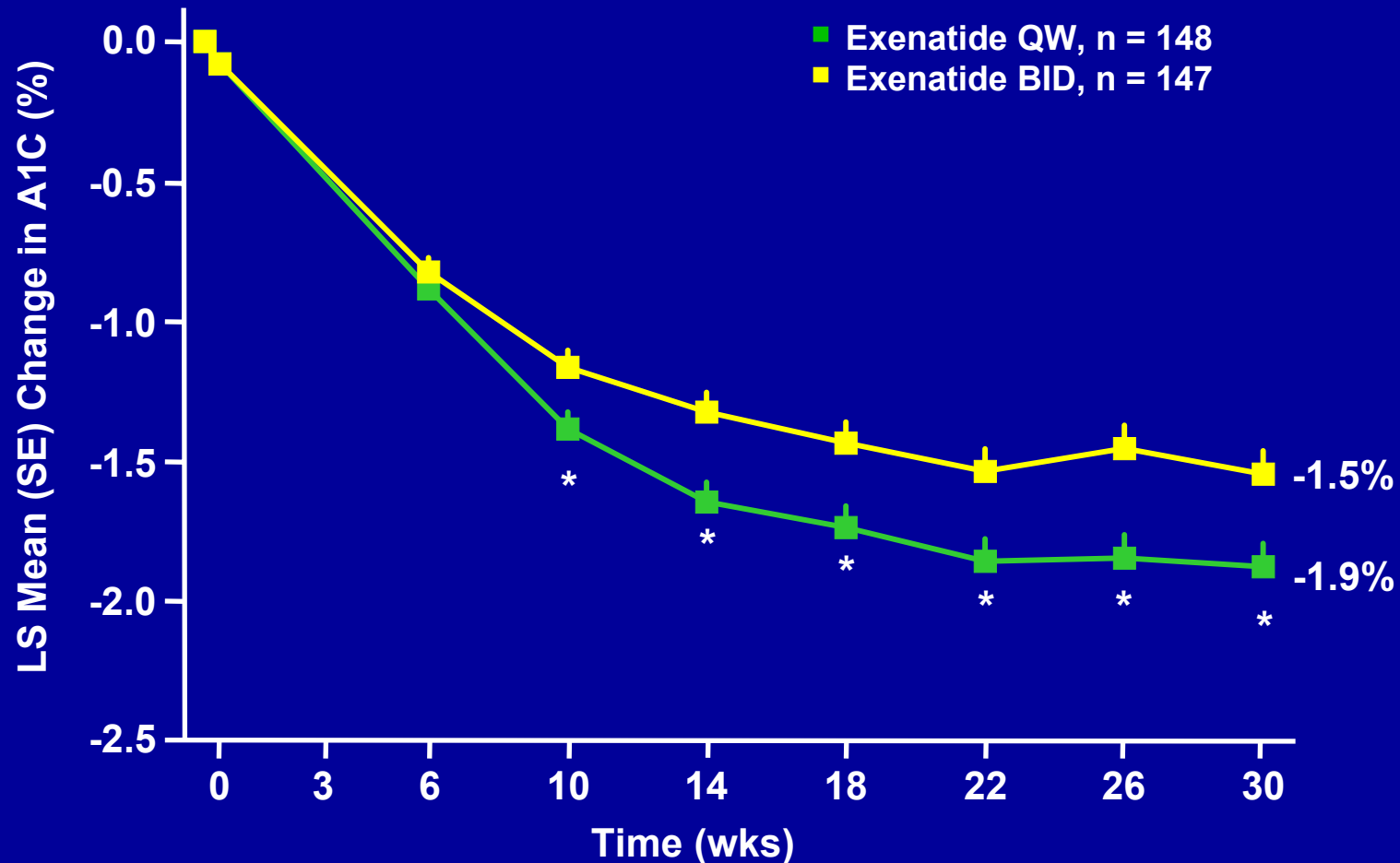
EXENATIDE LAR

Pharmacokinetic Profile of Plasma Exenatide QW



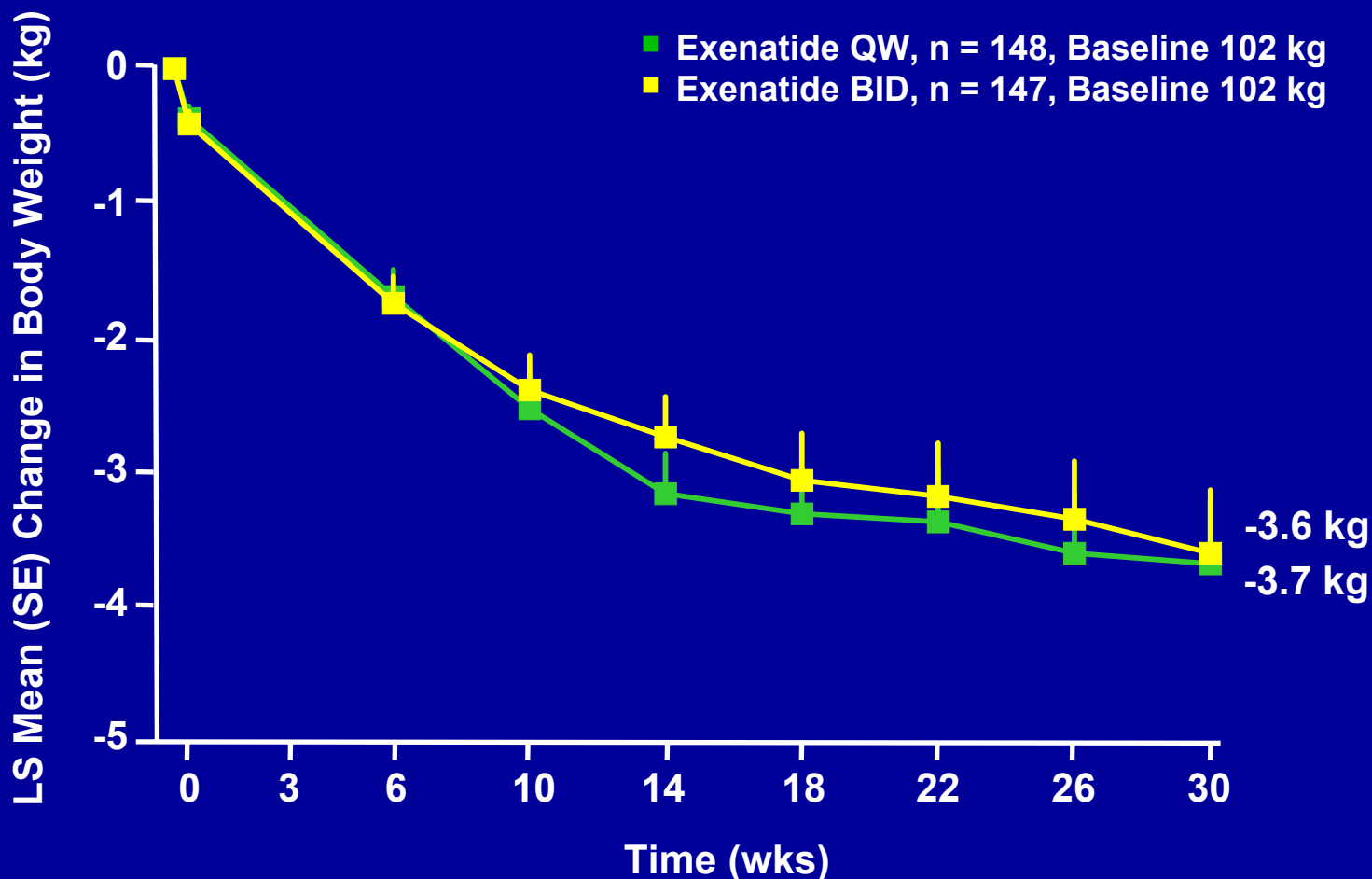
Geometric mean \pm 25-75th percentile range

Efficacy of Exenatide QW versus Exenatide BID: Change in A_{1C} from Baseline Over 30 Weeks



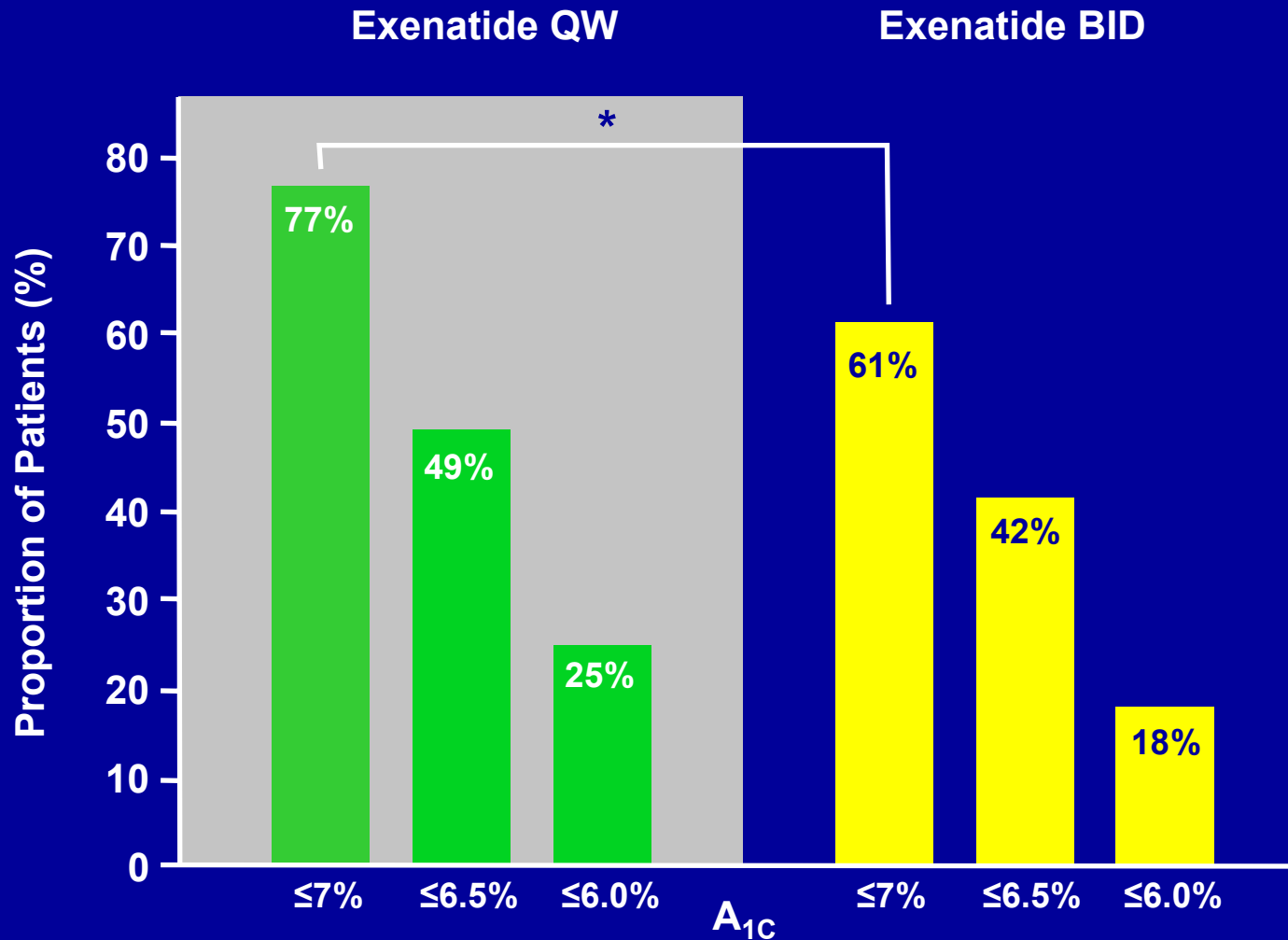
*p = 0.0023, QW vs. BID

Change in Body Weight From Baseline Over 30 Weeks



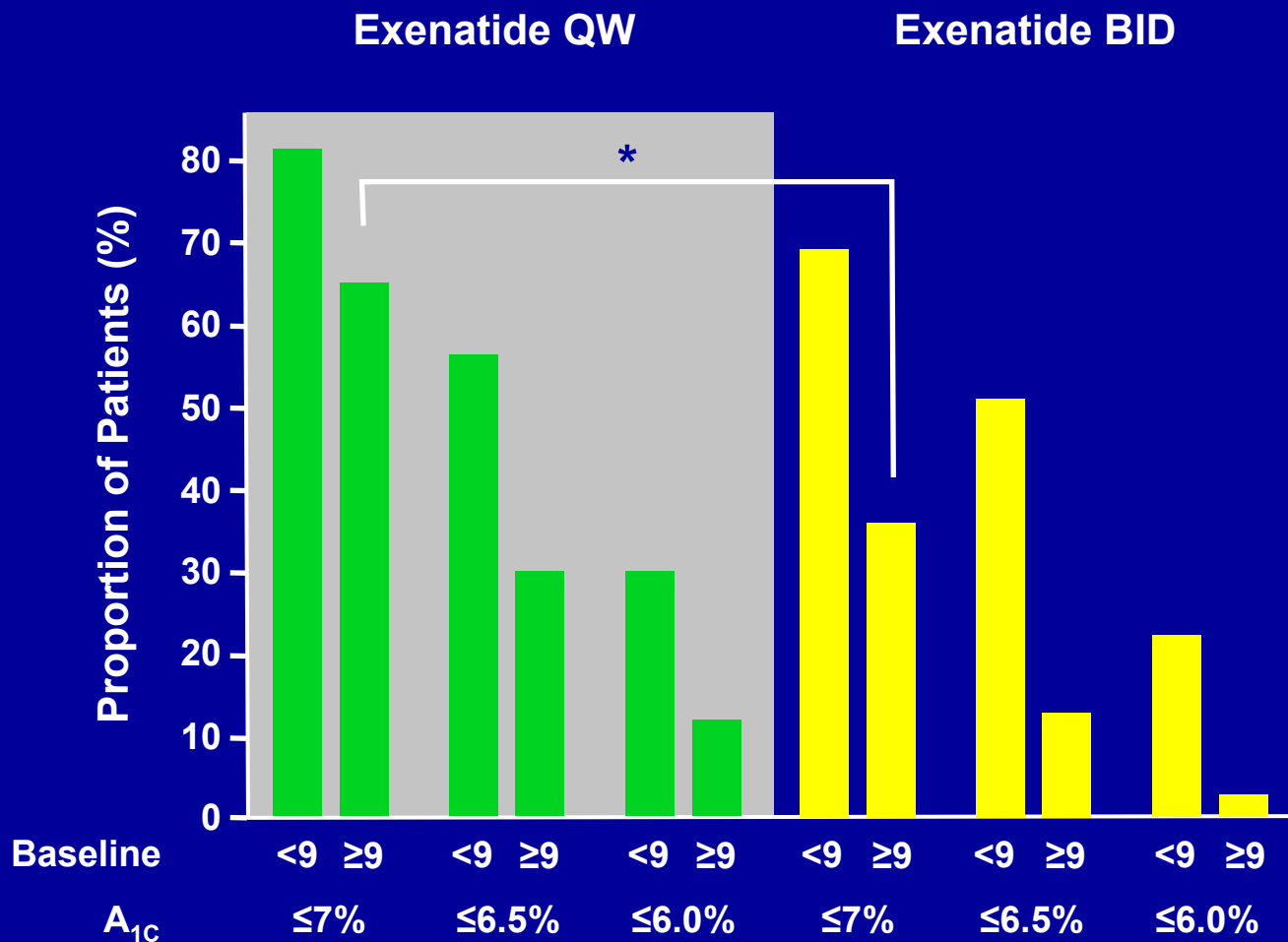
ITT, N=295

Percentage of Evaluable Patients (N = 259) Achieving HbA_{1c} ≤7, ≤6.5, ≤6.0 at Week 30



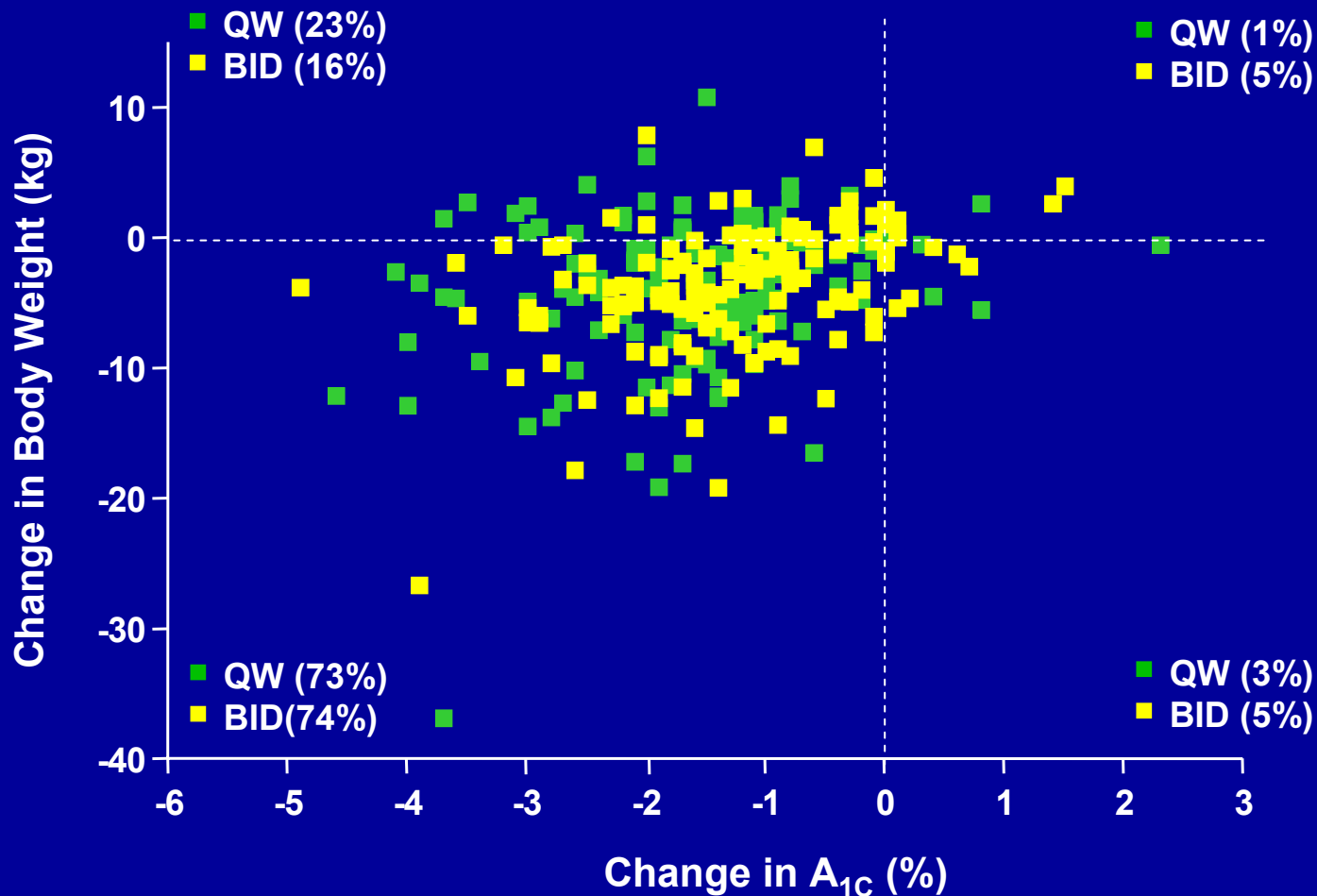
*p = 0.0039, QW vs. BID

Percentage of Evaluable Patients (N = 259) by Baseline HbA_{1c} Strata of <9.0% and ≥9.0% Achieving HbA_{1c} ≤7 at Week 30

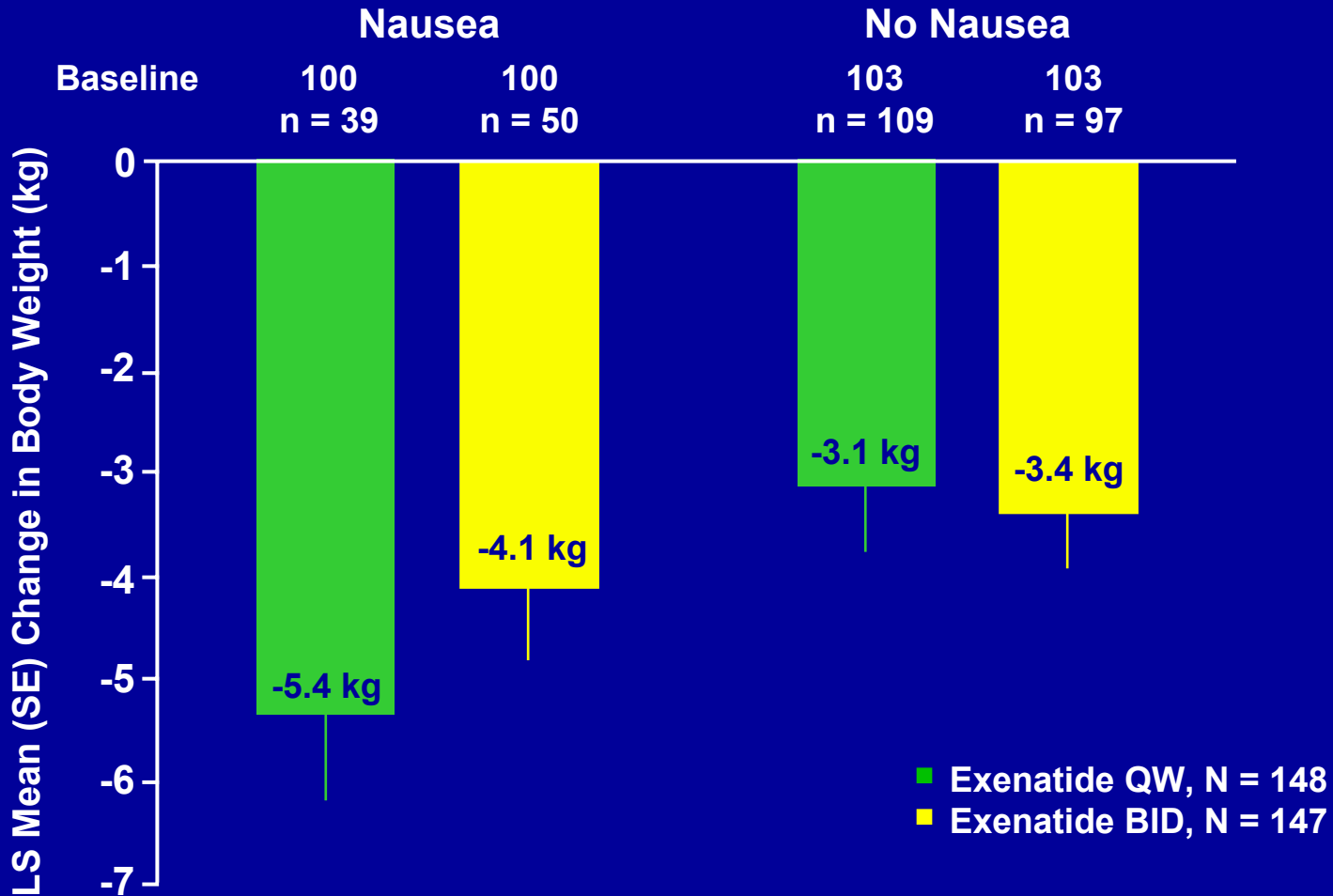


*p = 0.02, QW vs. BID

Individual Patient Data on Treatment Responses for A_{1c} and Body Weight

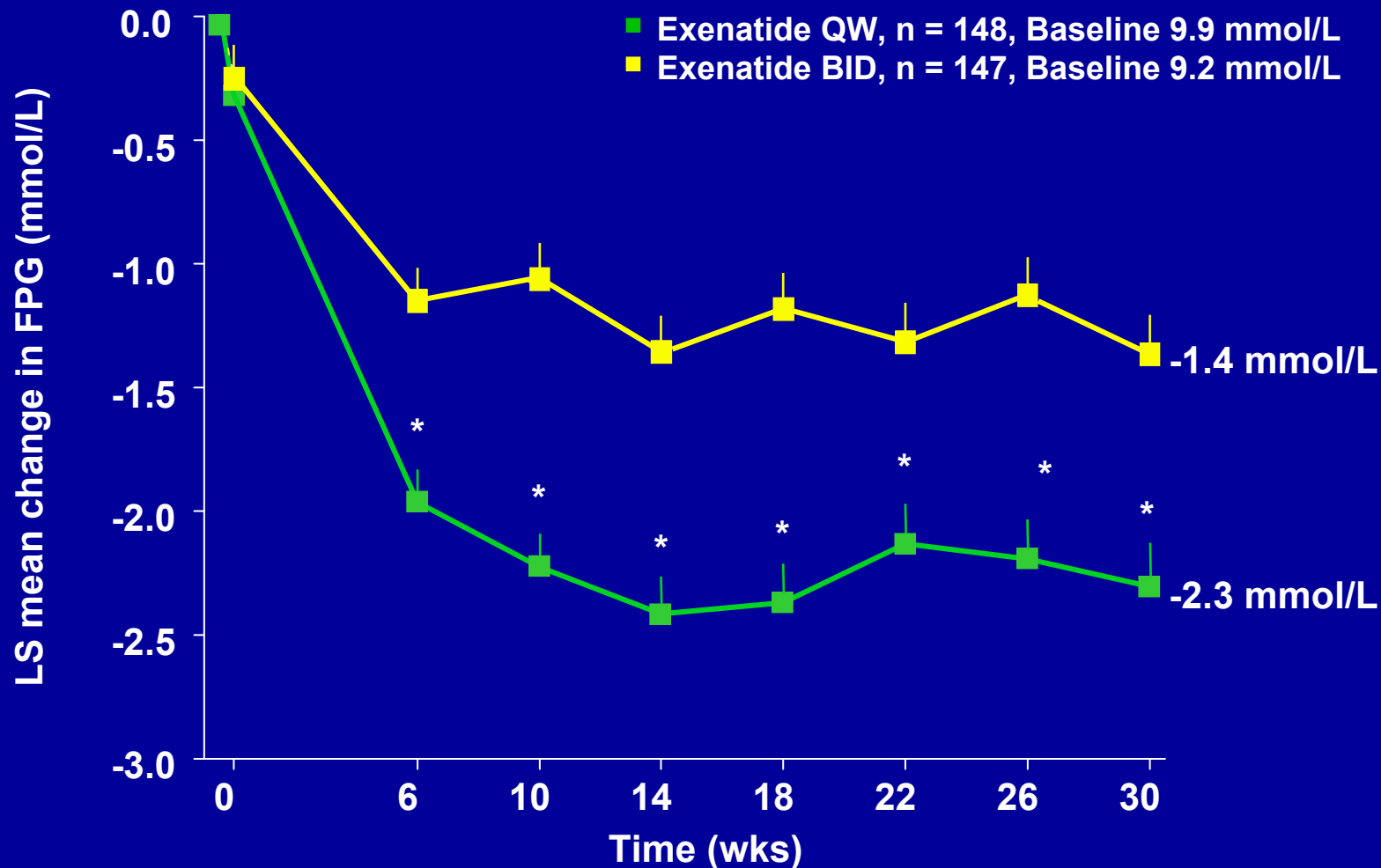


Effects on Body Weight Based on Presence* or Absence of Nausea



*at least one episode

Change in Fasting Plasma Glucose From Baseline Over 30 Weeks



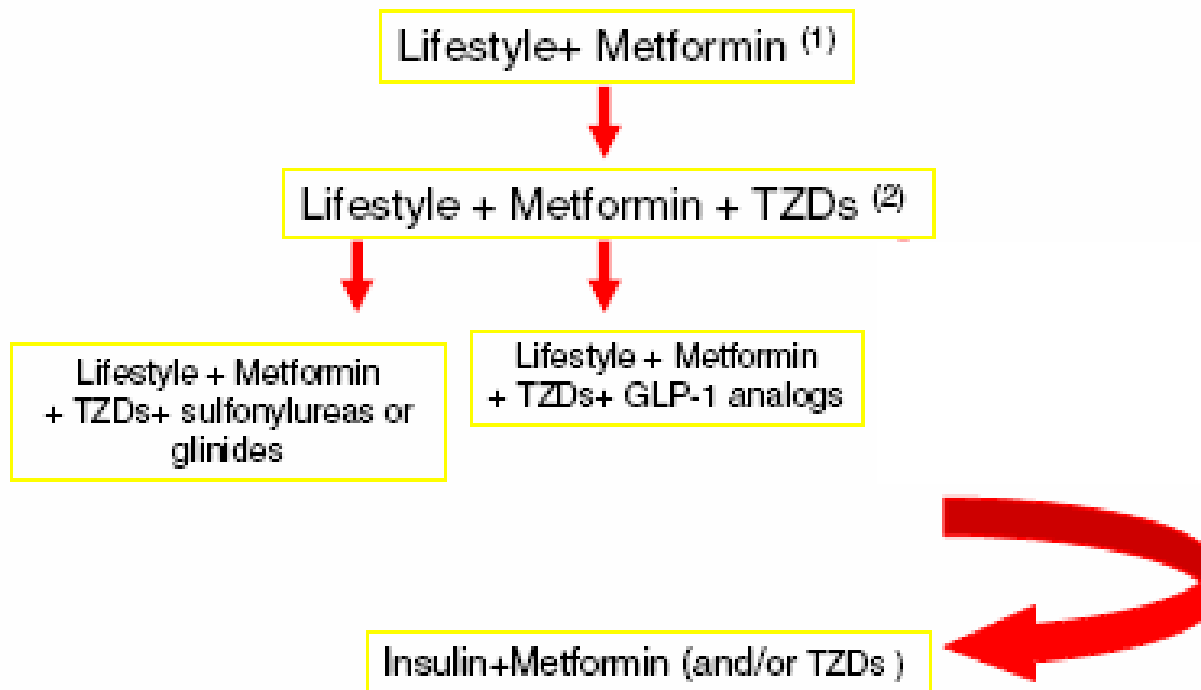
*p<0.0001, QW vs. BID; ITT, N=295

Función secretora de la célula beta durante un clamp hiperglicémico

	Pre-treatment (week 2)	On-drug (week 52)	Off-drug (week 56)	On-drug ratio to pre-treatment (week 52)		Off-drug ratio to pre-treatment (week 56)	
				Geometric mean	Between- group difference	Geometric mean	Between- group difference
1st phase (nmol*min/L)							
Insulin glargine	5.4 ± 0.6	6.1 ± 0.5	6.1 ± 0.6	1.17 ± 0.06	1.53 ± 0.11	1.13 ± 0.05	0.90 ± 0.06
Exenatide	5.4 ± 0.6	9.4 ± 1.0	5.0 ± 0.6	1.78 ± 0.11	P<.0001	1.00 ± 0.05	P=0.1188
2nd phase (nmol*min/L)							
Insulin glargine	77.4 ± 8.8	80.7 ± 6.9	86.2 ± 9.1	1.08 ± 0.05	2.85 ± 0.22	1.10 ± 0.05	0.92 ± 0.06
Exenatide	78.5 ± 8.3	235.6 ± 23.0	79.5 ± 9.1	3.05 ± 0.22	P<.0001	1.01 ± 0.04	P=0.1996
AIR_{arg} (nmol*min/L)							
Insulin glargine	20.0 ± 2.5	24.8 ± 2.2	21.4 ± 2.5	1.31 ± 0.08	2.46 ± 0.20	1.03 ± 0.08	1.08 ± 0.10
Exenatide	19.7 ± 2.1	62.2 ± 7.0	22.0 ± 2.6	3.19 ± 0.24	P<0.0001	1.12 ± 0.06	P=0.4052

Data represent mean ± SE; Ratio from pre-treatment are presented as geometric mean ± SE
 AIR_{arg}, C-peptide response to arginine at 15 mmol/L glucose concentration; 1st phase, first-phase C-peptide response to glucose
 2nd phase, second-phase C-peptide response to glucose

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, + α -glucosidase inhibitors
- (2) In presence of PPH, + α -glucosidase inhibitors