

IV
Reunión
Diabetes y
Obesidad



Palacio de Congresos. Salamanca
28-30 Enero 2010

AGONISTAS DE GLP-1 EN EL TRATAMIENTO DE LA DIABETES TIPO 2

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Clínica Universidad de Navarra

DECLARACION DE INTERESES

Labores de consultoría para Laboratorios Lilly

Conferencias sponsorizadas por Lilly, Novo Nordisk, Sanofi-Aventis, MSD, Abbott, Roche.

AGENDA

- . Fármacos moduladores del efecto incretínico
 - . AGONISTAS GLP-1
 - . Efectos sobre control glucémico
 - . Efectos sobre el peso corporal
 - . Efectos sobre factores de riesgo cardiovascular
 - . Seguridad
 - . Resumen y lugar en el tratamiento de la DM2
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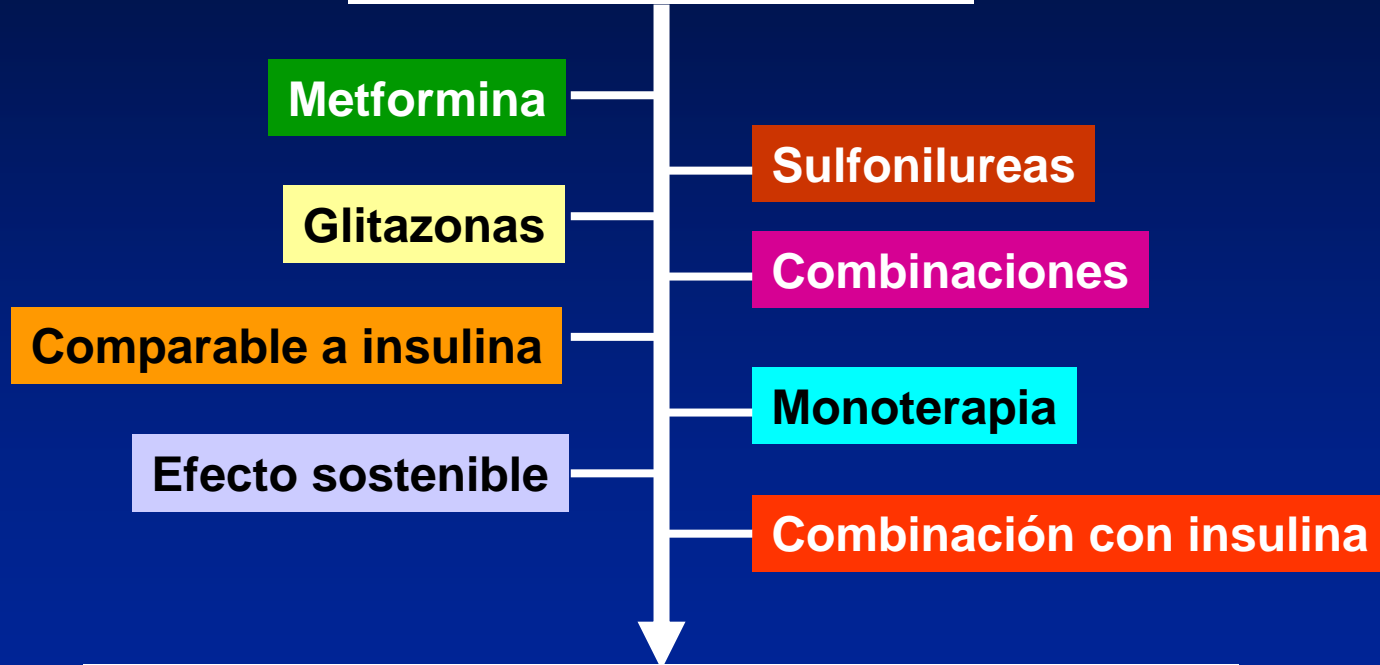


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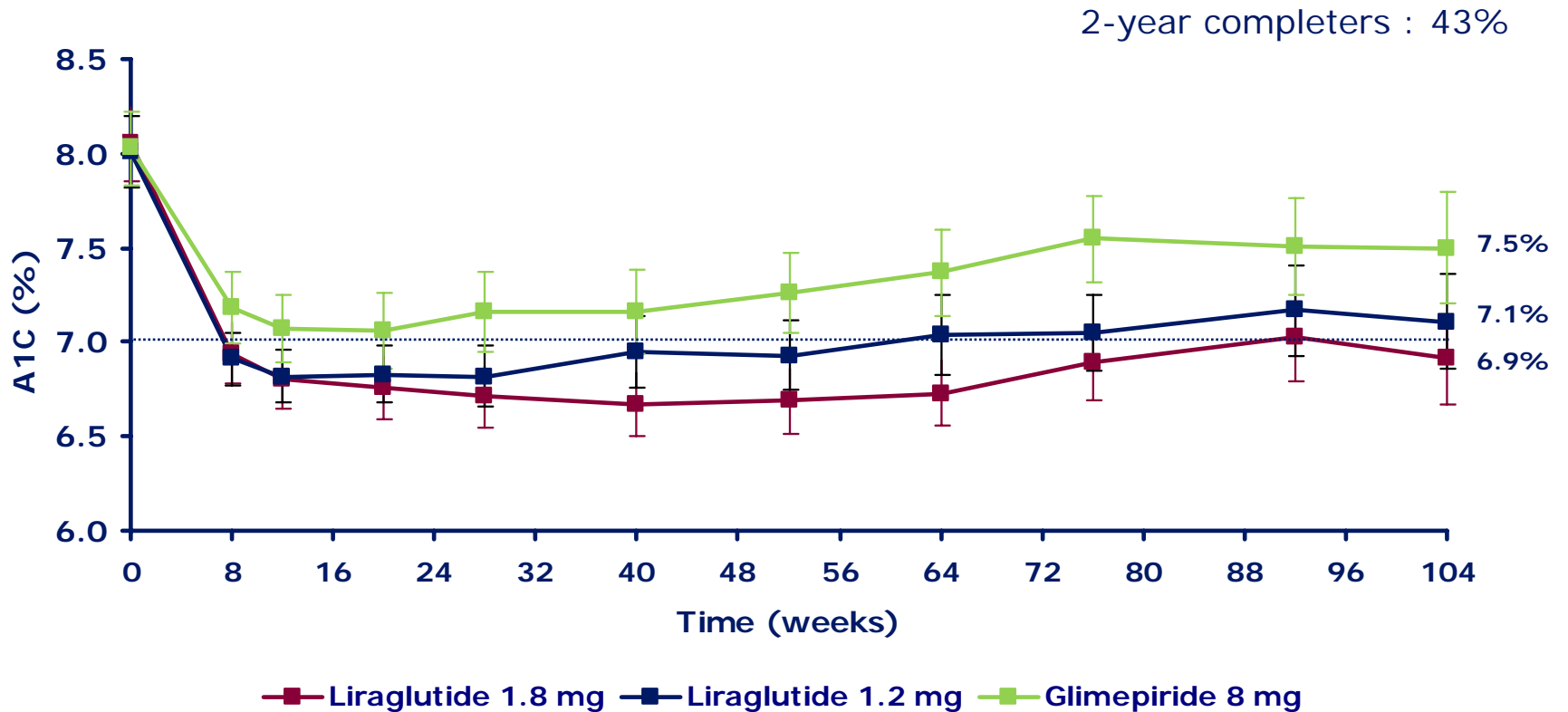
CONTROL METABÓLICO

AGONISTAS GLP-1



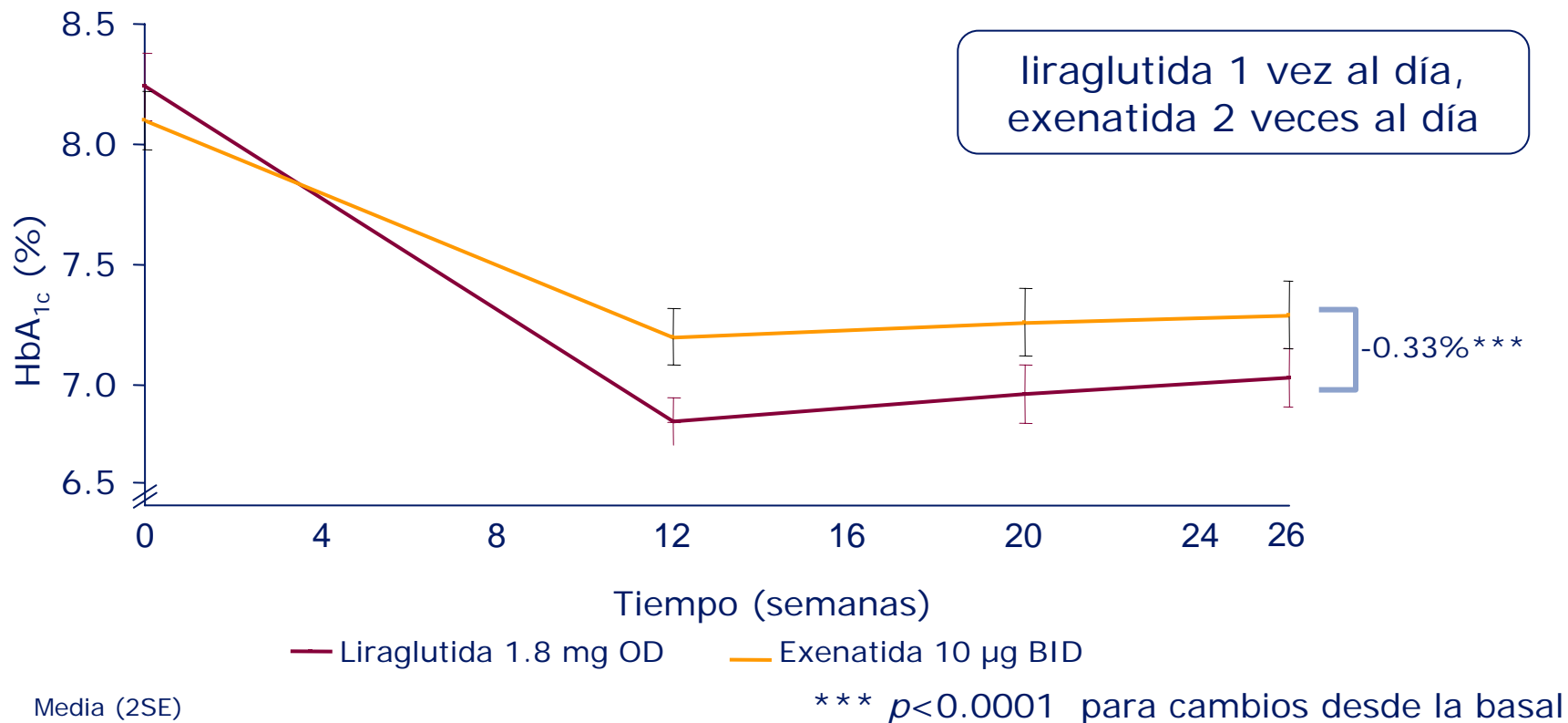
Mejor control metabólico
No hipoglucemias
Reducción de peso y consecuencias

Sustained efficacy over 2 years with liraglutide as monotherapy (LEAD 3 ext)



Observed mean \pm 2SE, no imputation for missing values.

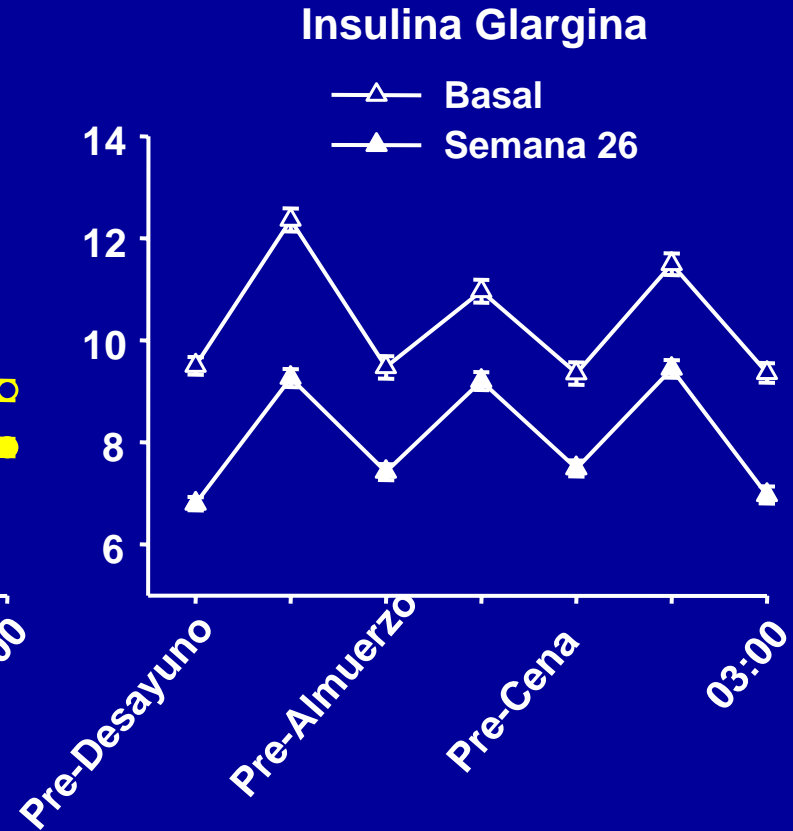
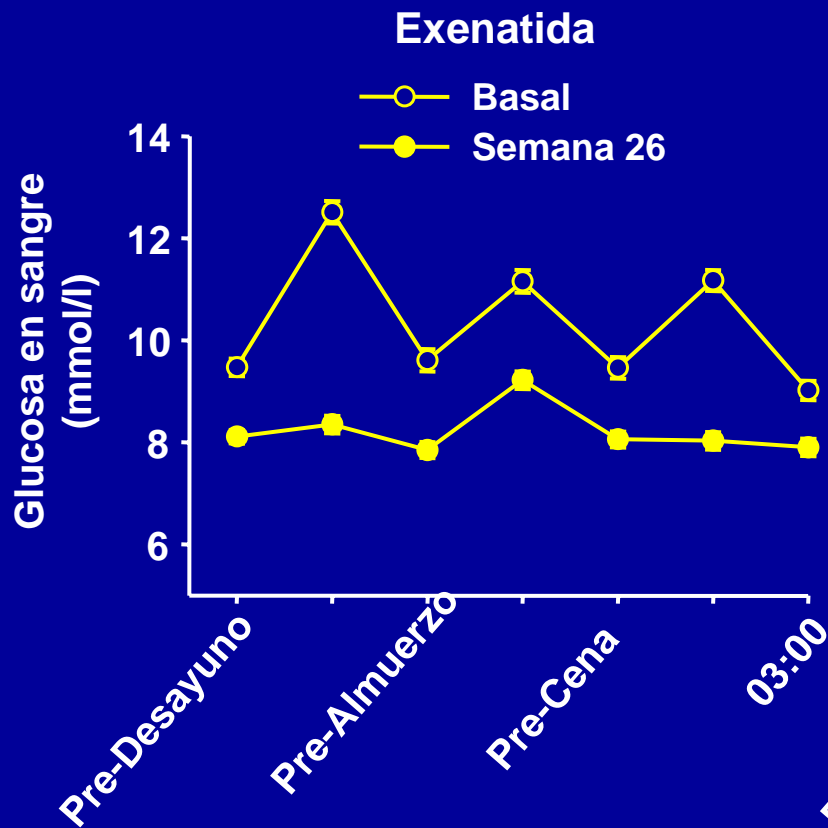
Liraglutida en comparación directa con exenatida: mayor reducción significativa de la HbA_{1c}



- Tanto liraglutida como exenatida se combinaron con metformina y/o una sulfonilurea

Buse *et al. Lancet* 2009

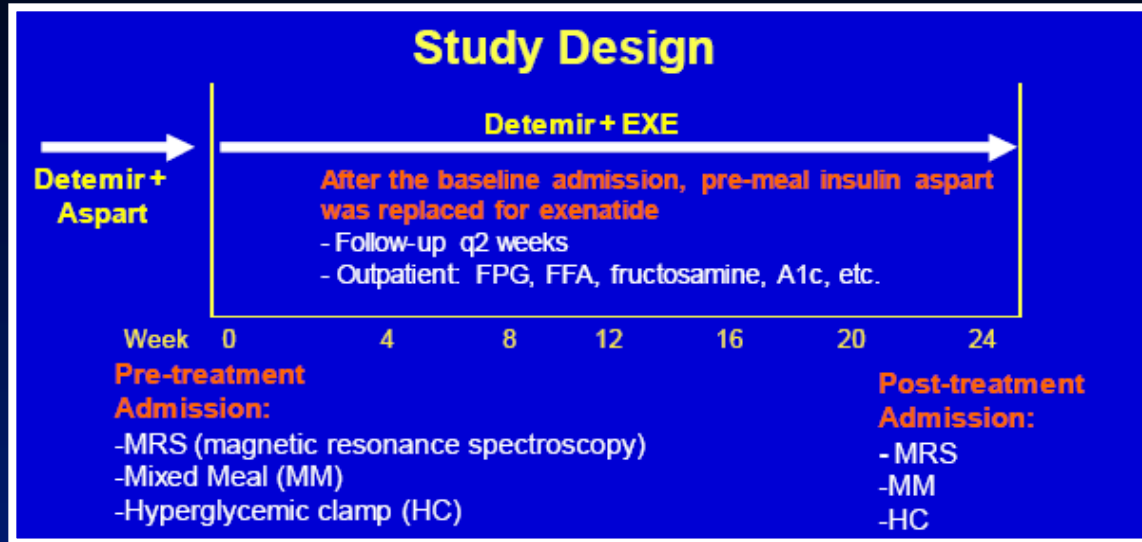
Exenatida reduce más la glucemia postprandial, pero menos la glucemia basal respecto a insulina glargina



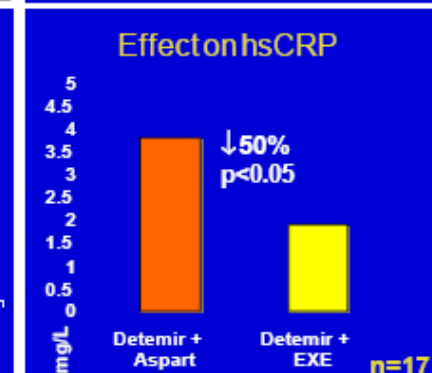
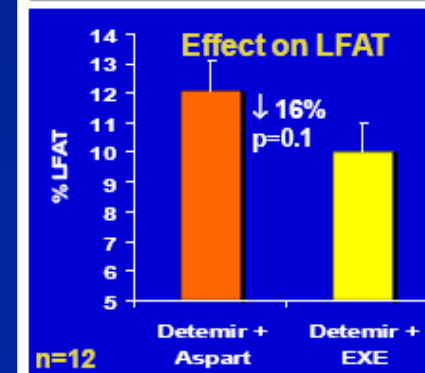
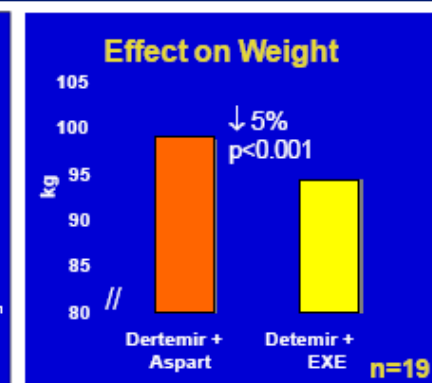
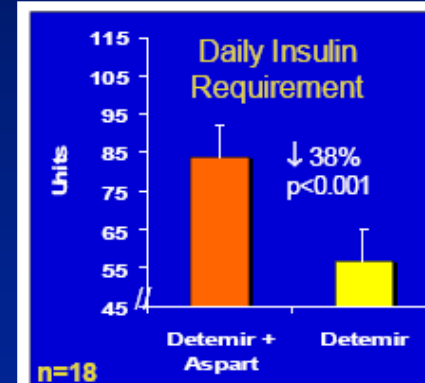
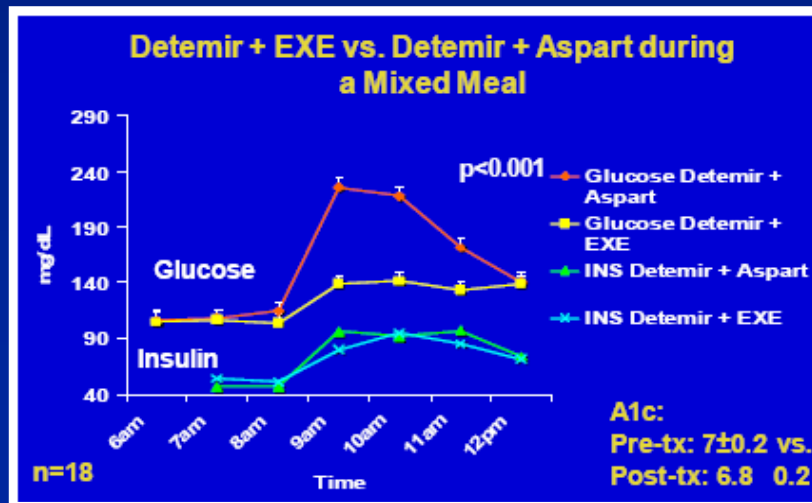
Muestra ITT; se muestra la media \pm EE.

Heine RJ, et al. *Ann Intern Med.* 2005;143:559-569. Reproducido con permiso de The American College of Physicians.

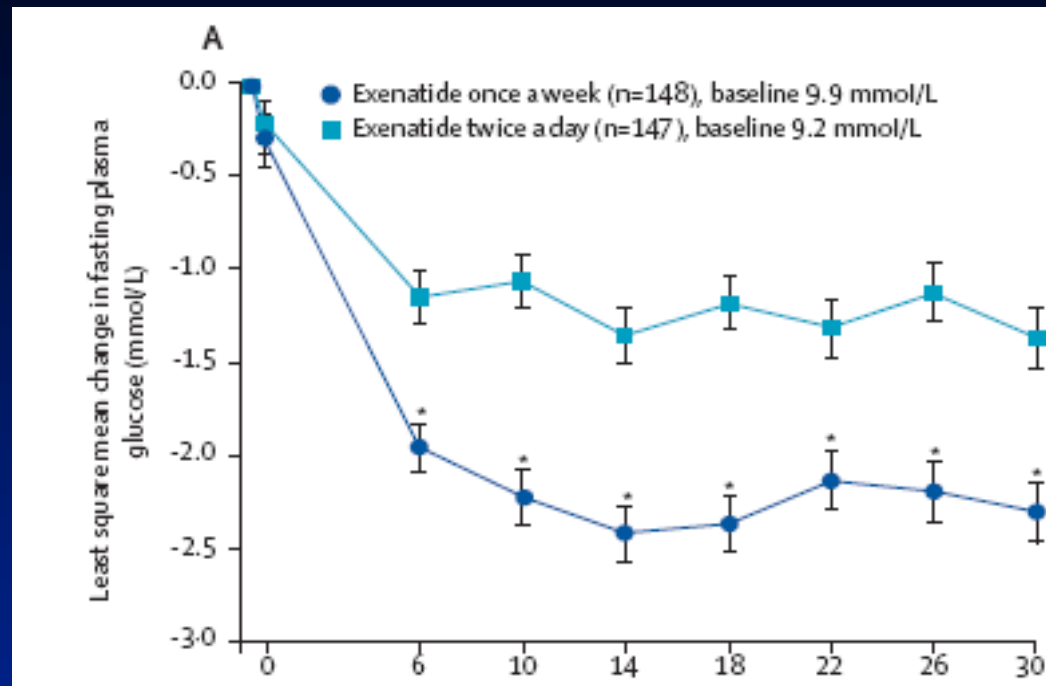
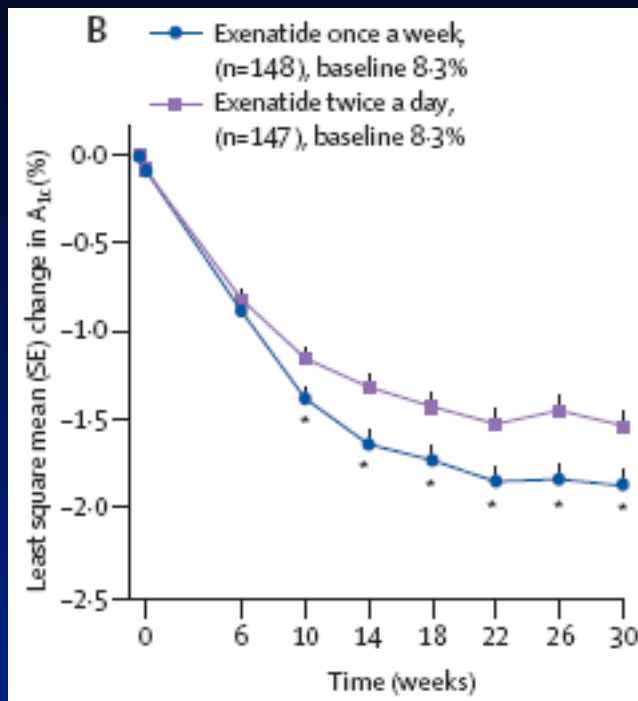
EXENATIDA Y REEMPLAZAMIENTO DE INSULINA PREPRANDIAL



Orsi et al.
ADA, 2009



EXENATIDA LAR ES MÁS POTENTE QUE BYETTA

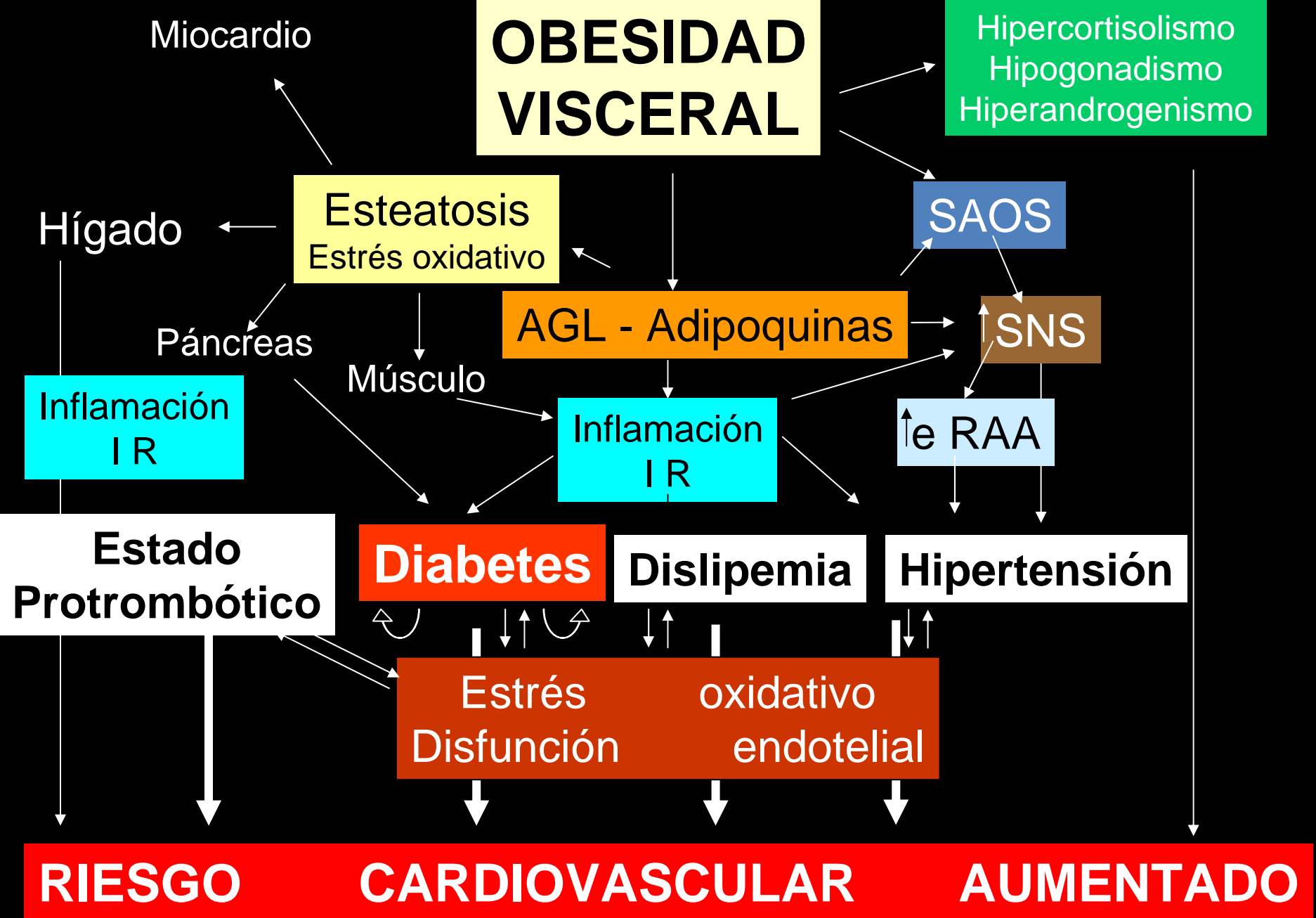


	2.0 mg exenatide once a week (N=148) n (%)	10 µg exenatide twice a day (N=145) n (%)
Nausea	39 (26.4)	50 (34.5)
Vomiting	16 (10.8)	27 (18.6)
Injection site pruritus	26 (17.6)	2 (1.4)
Upper respiratory tract infection	12 (8.1)	25 (17.2)
Diarrhoea	20 (13.5)	19 (13.1)
Constipation	16 (10.8)	9 (6.2)
Injection site bruising	7 (4.7)	15 (10.3)
Urinary tract infection	15 (10.1)	12 (8.3)

Drucker et al
Lancet 2008

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-



LA DIABESIDAD EXISTE

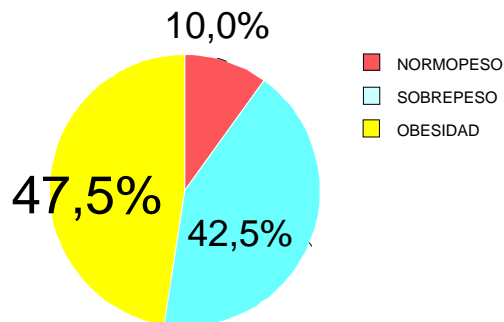
El índice de masa corporal y la circunferencia abdominal infraestiman el diagnóstico de obesidad en pacientes con diabetes mellitus tipo 2

S. Laguna, R. Príncipe, S. Botella, S. Santos, M. Pizarro, G. Frühbeck, J. Escalada, J. Salvador.
Departamento de Endocrinología y Nutrición. Clínica Universidad de Navarra, Pamplona

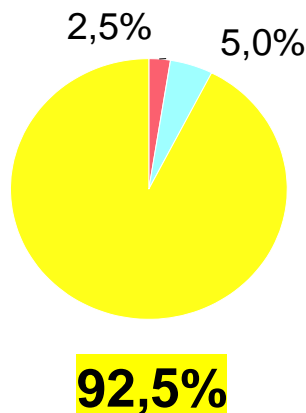
XX Congreso Nacional de la Sociedad Española de Diabetes, Tenerife abril 2009



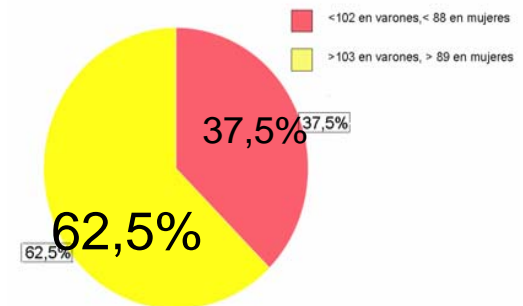
Obesidad por IMC



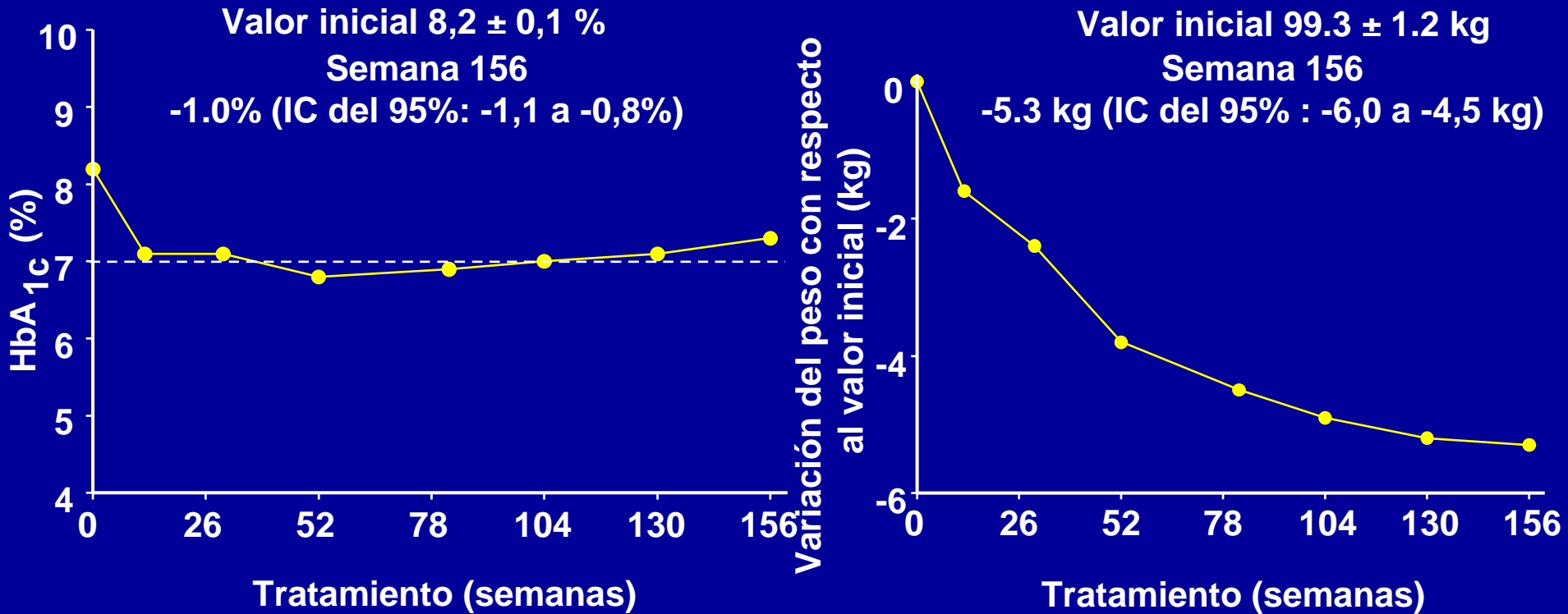
Obesidad por BodPod



Obesidad por CC



Reducción concomitante de HbA_{1c} y peso a lo largo de 3 años de tratamiento con exenatida

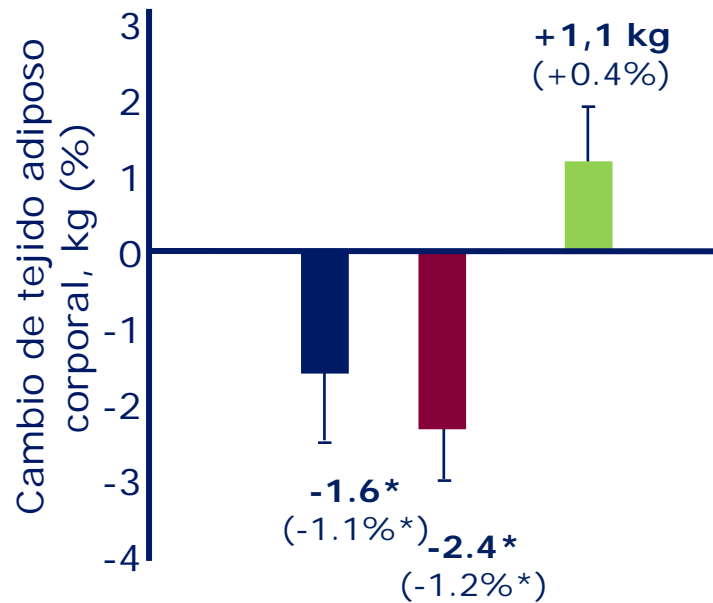


N=217; Media ± EE.

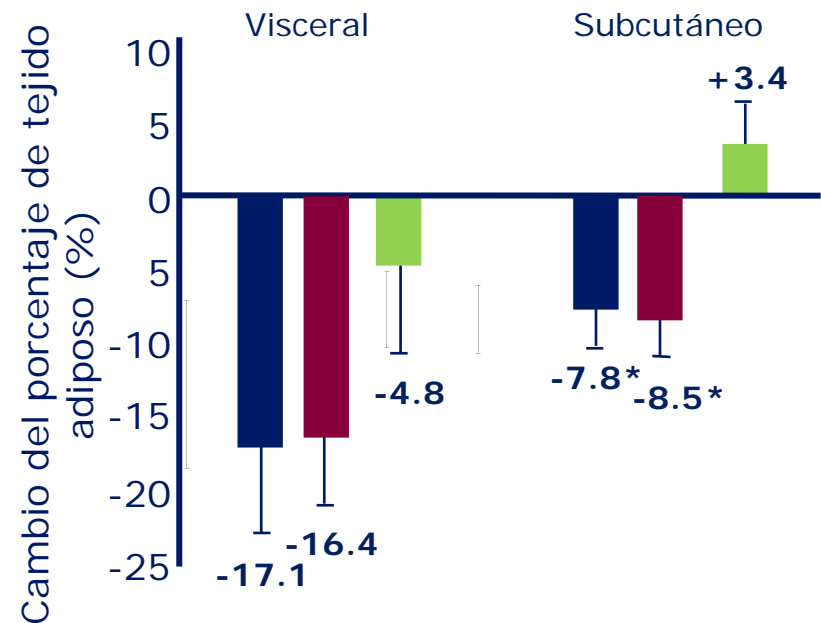
Klonoff DC, et al. *Curr Med Res Opin* 2008;24:275-286.

Liraglutida reduce la grasa visceral

Cambio en el tejido adiposo corporal DEXA scan



Tejido adiposo visceral vs. subcutáneo CT scan



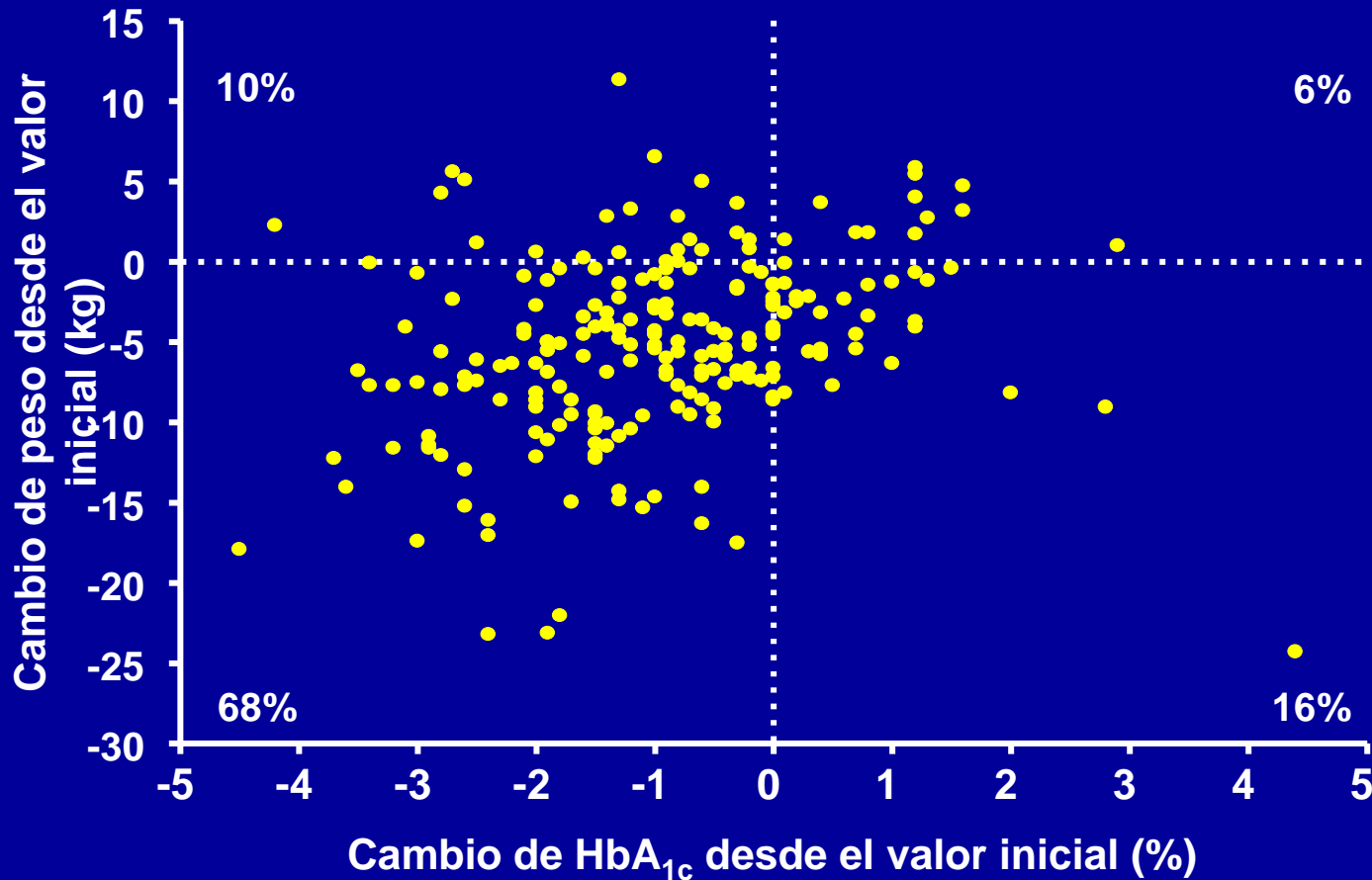
■ Liraglutida 1,2 mg + met

■ Liraglutida 1,8 mg + met

■ Glimepirida + met

- El 86% de la pérdida de peso es tejido adiposo (liraglutida 1,8 mg)

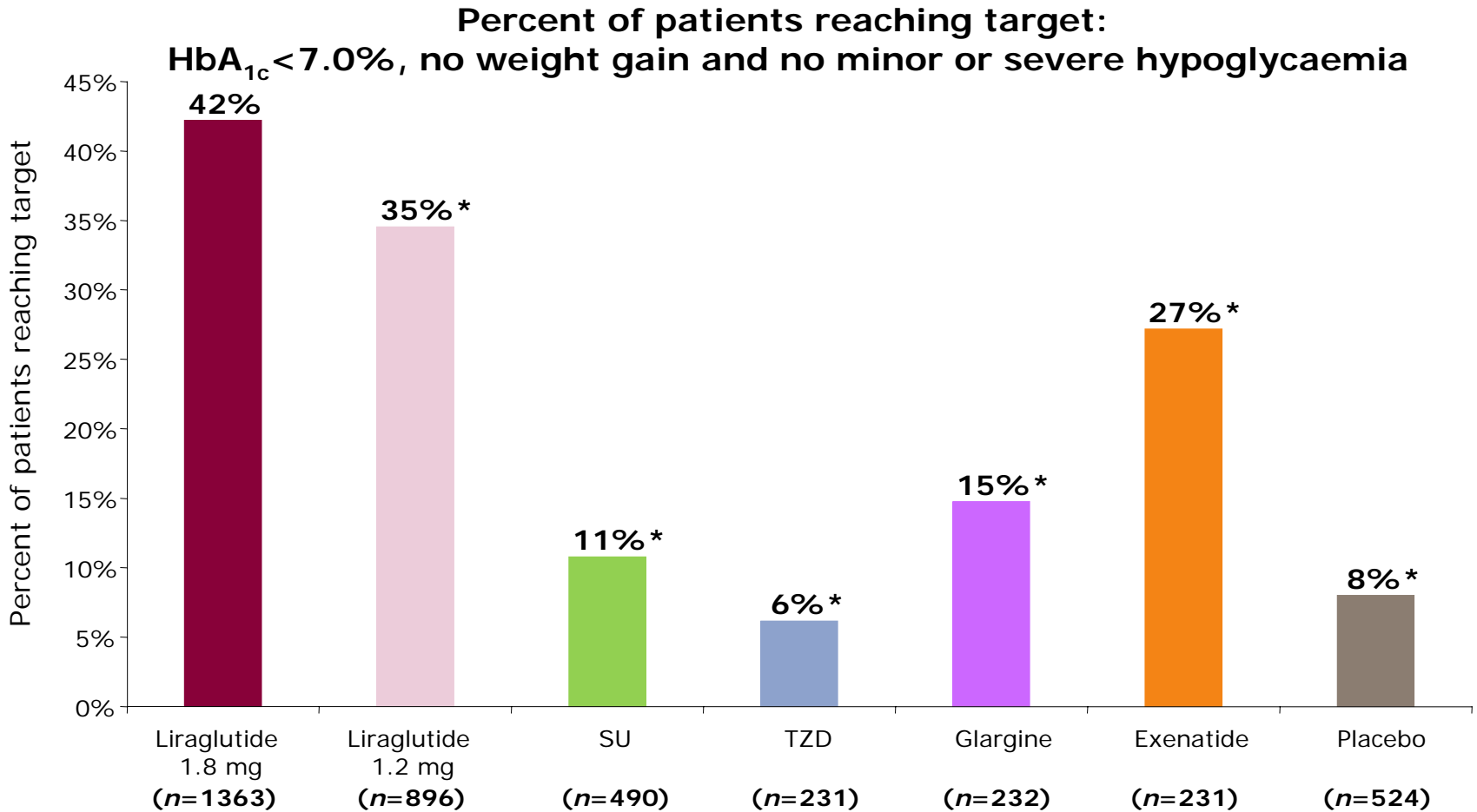
El 68% de los pacientes que completaron 3 años de tratamiento con Exenatida mostraron pérdida de peso y reducción de HbA_{1c}



N=217.

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

Composite endpoint: HbA_{1c} < 7.0%, no weight gain and no hypos



***p < 0.01 vs. liraglutide 1.8 mg**

Based on meta-analysis of LEAD1-6.

Adjusted for previous treatment, baseline values and randomization. LOCF, ITT.

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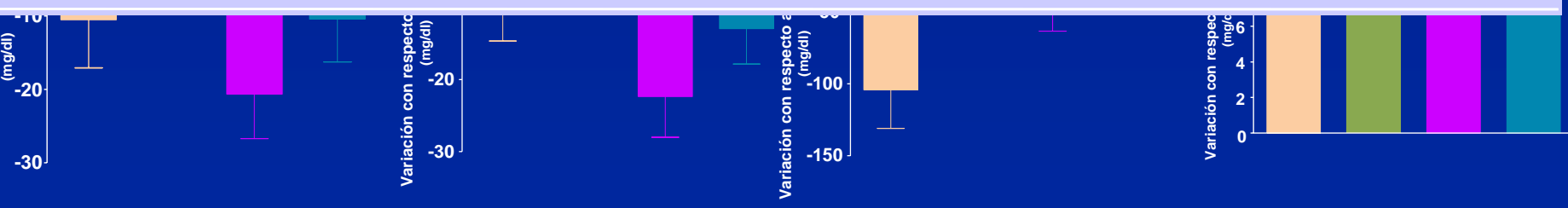
EXENATIDA REDUCE F. DE RIESGO CARDIOVASCULAR

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

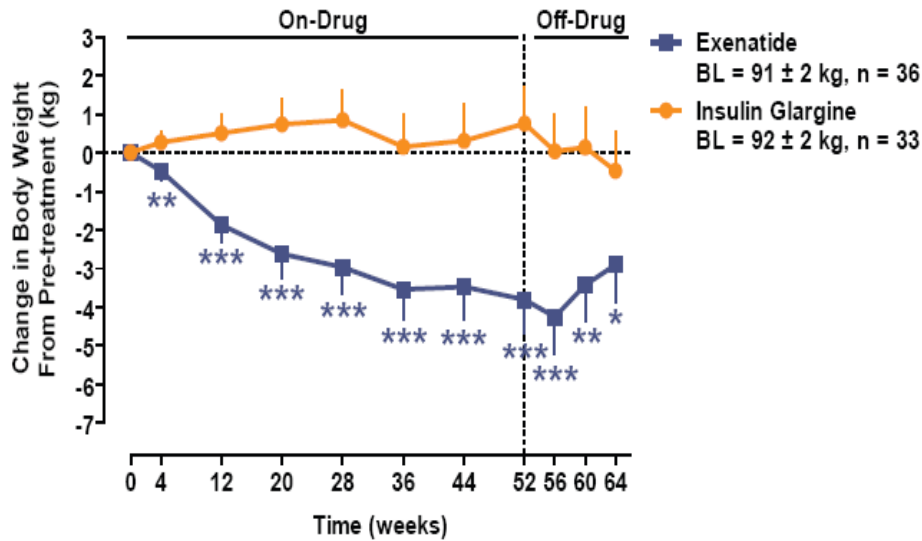
Factor de riesgo cardiovascular	Valor inicial (Media ± EEM)	Variación con respecto al valor inicial (Media ± EEM)	Media variación	Intervalo de confianza del 95%	valor de p
Triglicéridos (mg/dl)	225,1 ± 11,6	-44,4 ± 12,1	-12%	-68,3 a -20,5	0,0003
Colesterol total (mg/dl)	184,4 ± 3,0	-10,8 ± 3,1	-5%	-17,0 a -4,6	0,0007
cHDL (mg/dl)	38,6 ± 0,8	8,5 ± 0,6	+24%	7,2 a 9,7	<0,0001
cLDL (mg/dl)	113,7 ± 2,7	-11,8 ± 2,9	-6%	-17,5 a -6,1	<0,0001
Presión arterial sistólica (mmHg)	129,3 ± 1,0	-3,5 ± 1,2	-2%	-5,9 a -1,0	0,0063
Presión arterial diastólica (mmHg)	79,2 ± 0,6	-3,3 ± 0,8	-4%	-4,9 a -1,7	<0,0001

Variación respecto al valor inicial

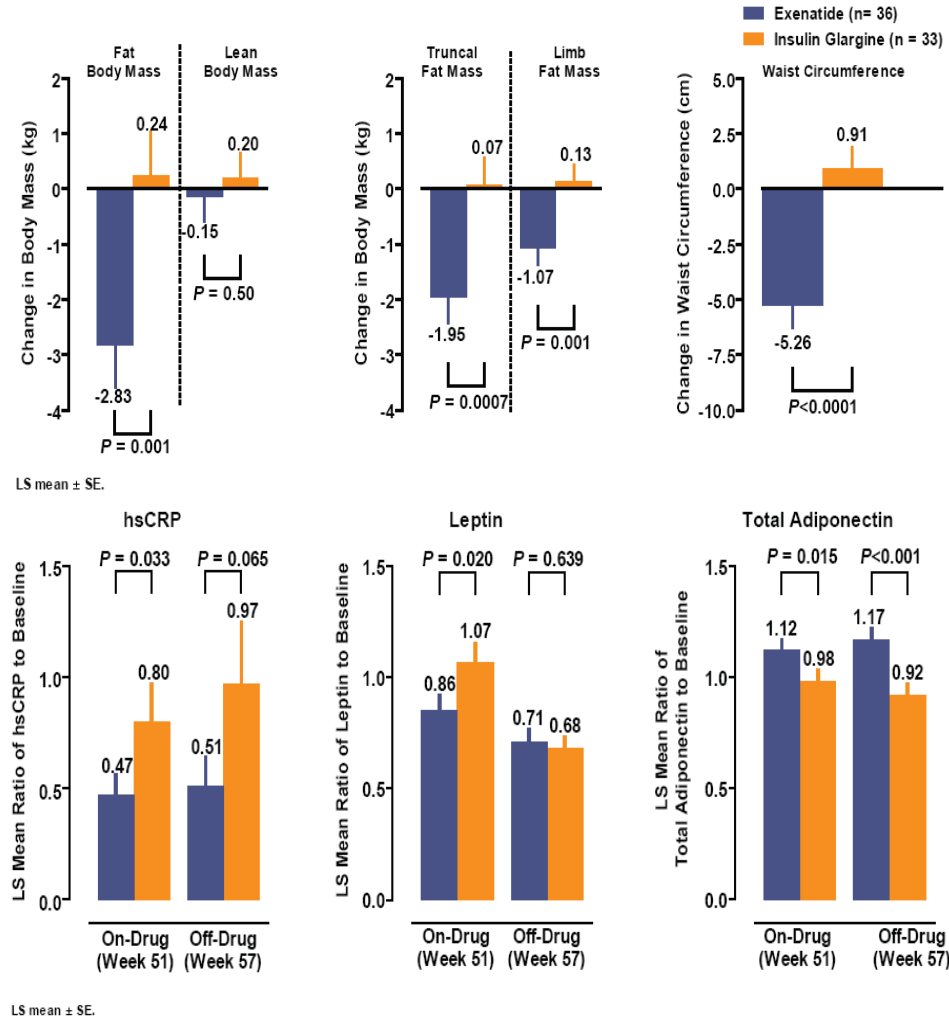
Variación con respecto al valor inicial



Beneficial Changes on Body Composition and Circulating Adiponectin, Leptin, and hsCRP Levels Following One-Year Exenatide Therapy, Compared With Insulin Glargine, in Metformin-Treated Patients With Type 2 Diabetes

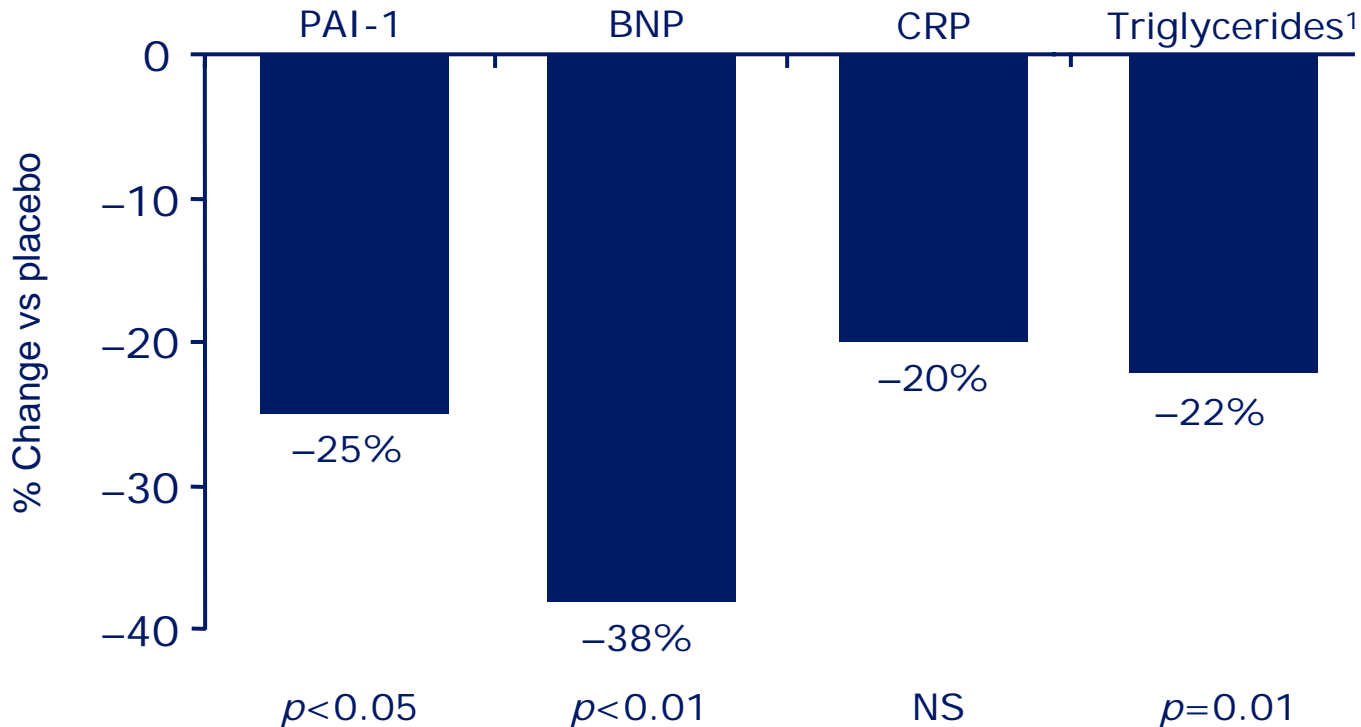


*P<0.05; **P<0.01; ***P<0.001; LS mean ± SE.



Liraglutida mejora marcadores de riesgo cardiovascular

14 weeks' treatment with liraglutide 1.90 mg/day



p values vs. placebo;

PAI-1 = plasminogen activating inhibitor; BNP = B-type natriuretic peptide;

CRP = C-reactive protein

Courrèges *et al.* *Diab Med* 2008;¹Vilsbøll *et al.* *Diab Care* 2007;30:1608-10.

EXENATIDA REDUCE EL TAMAÑO DEL INFARTO DE MIOCARDIO

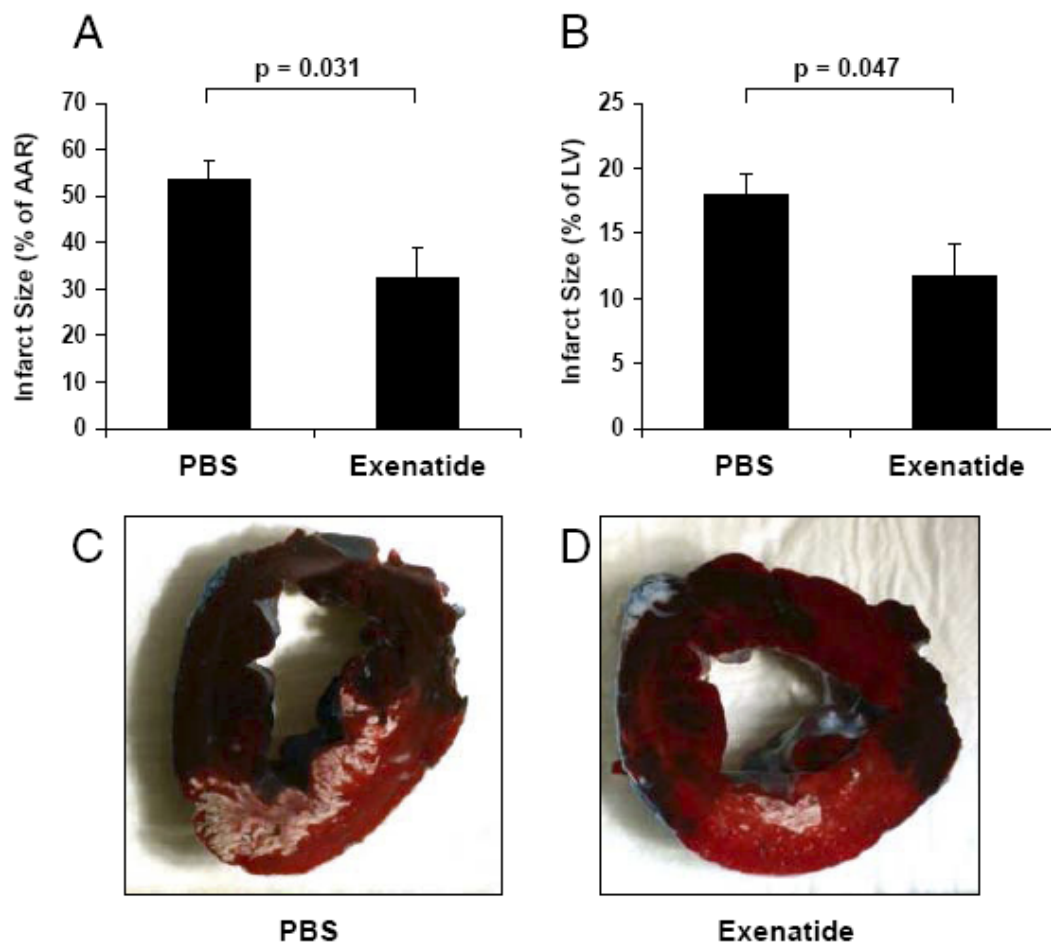


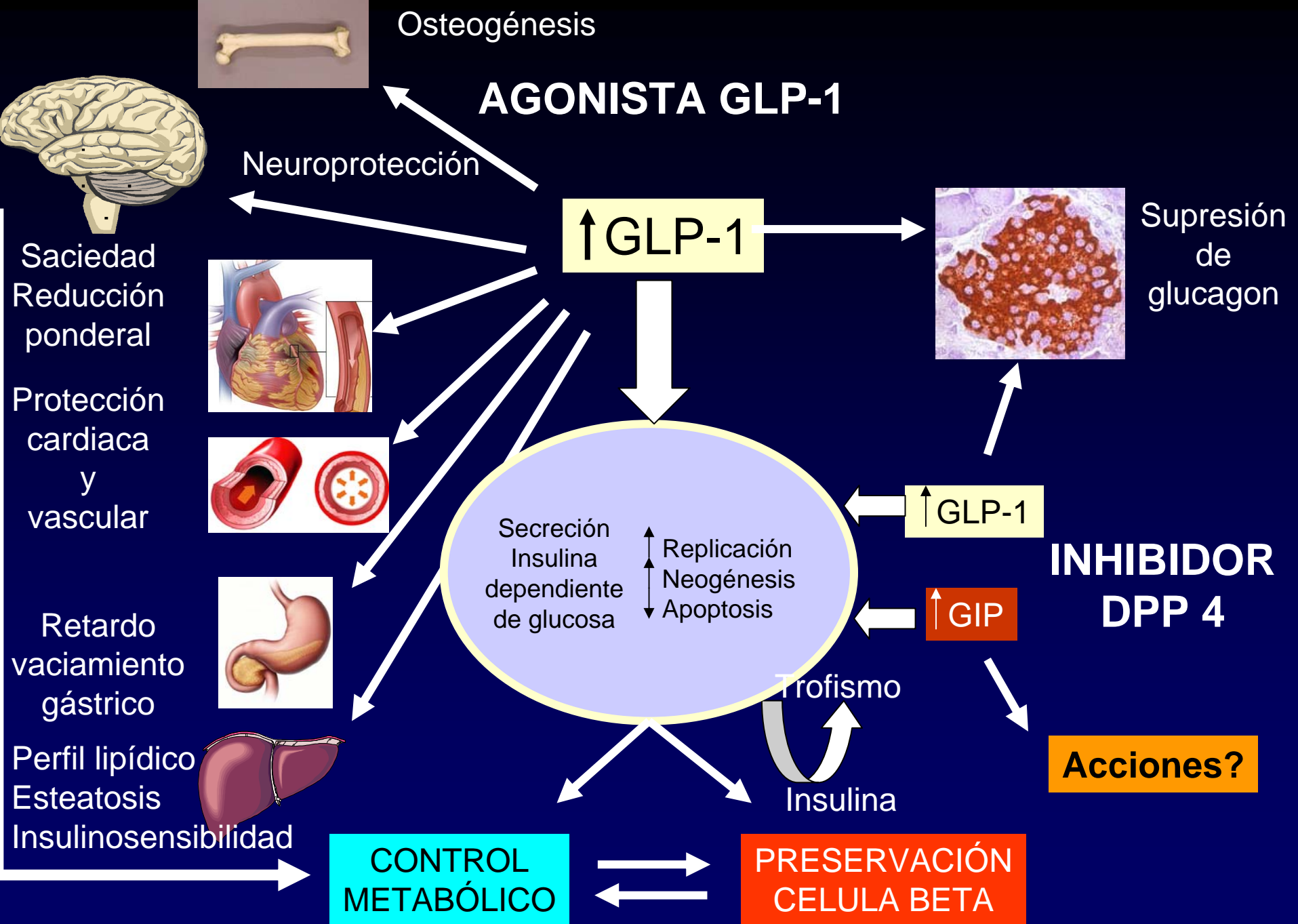
Figure 1 Myocardial Infarct Size

Myocardial infarct size quantification as a percentage of the area at risk (AAR) (A) and as a percentage of the total left ventricle (B). Phosphate-buffered saline (PBS) $n = 9$; exenatide $n = 9$. Representative pictures after Evans Blue (Sigma-Aldrich) and triphenyltetrazolium chloride staining are shown in C and D. Blue indicates non-threatened myocardium, red indicates the noninfarcted area within the area at risk, and white indicates myocardial infarction.

EFECTOS CARDIACOS DE GLP-1 EN HUMANOS

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

PACIENTES

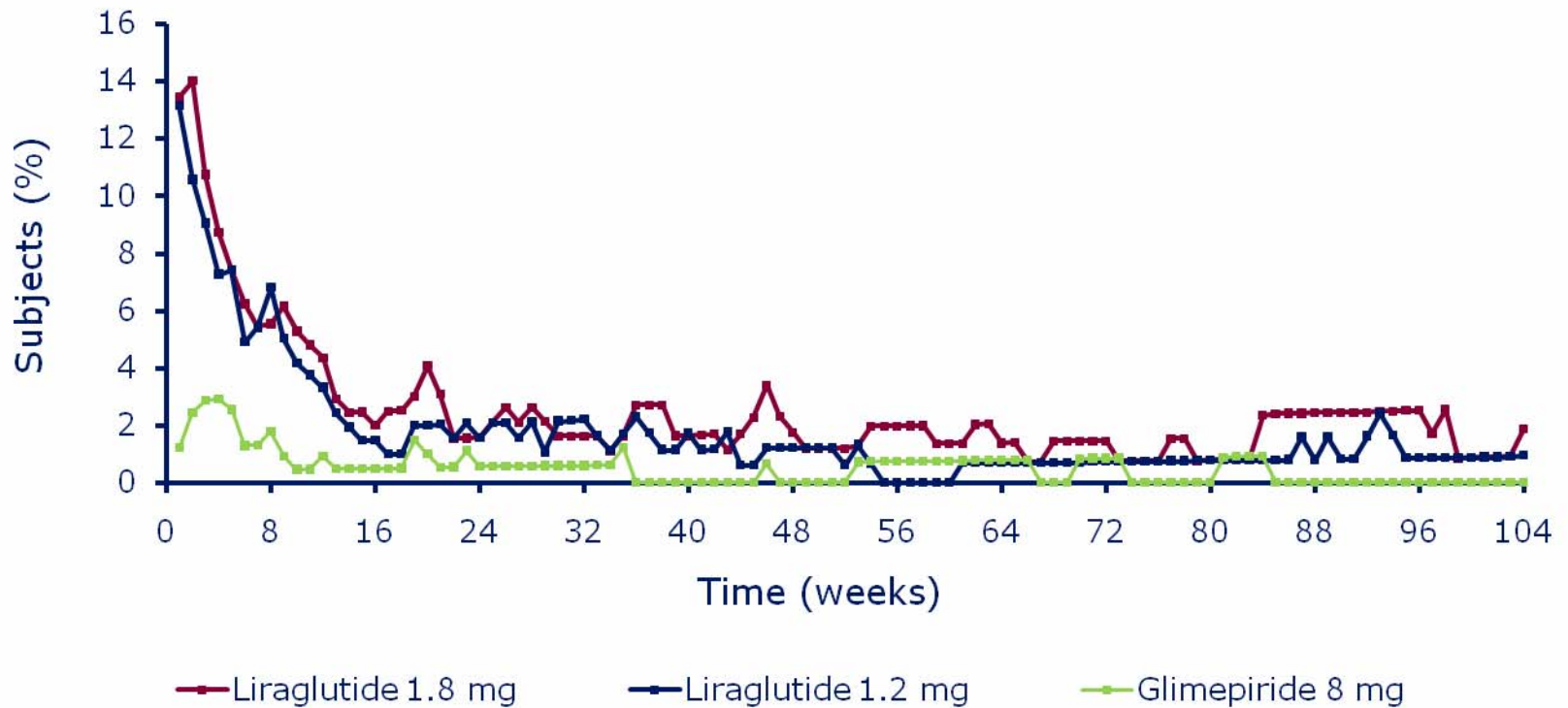


AGENDA

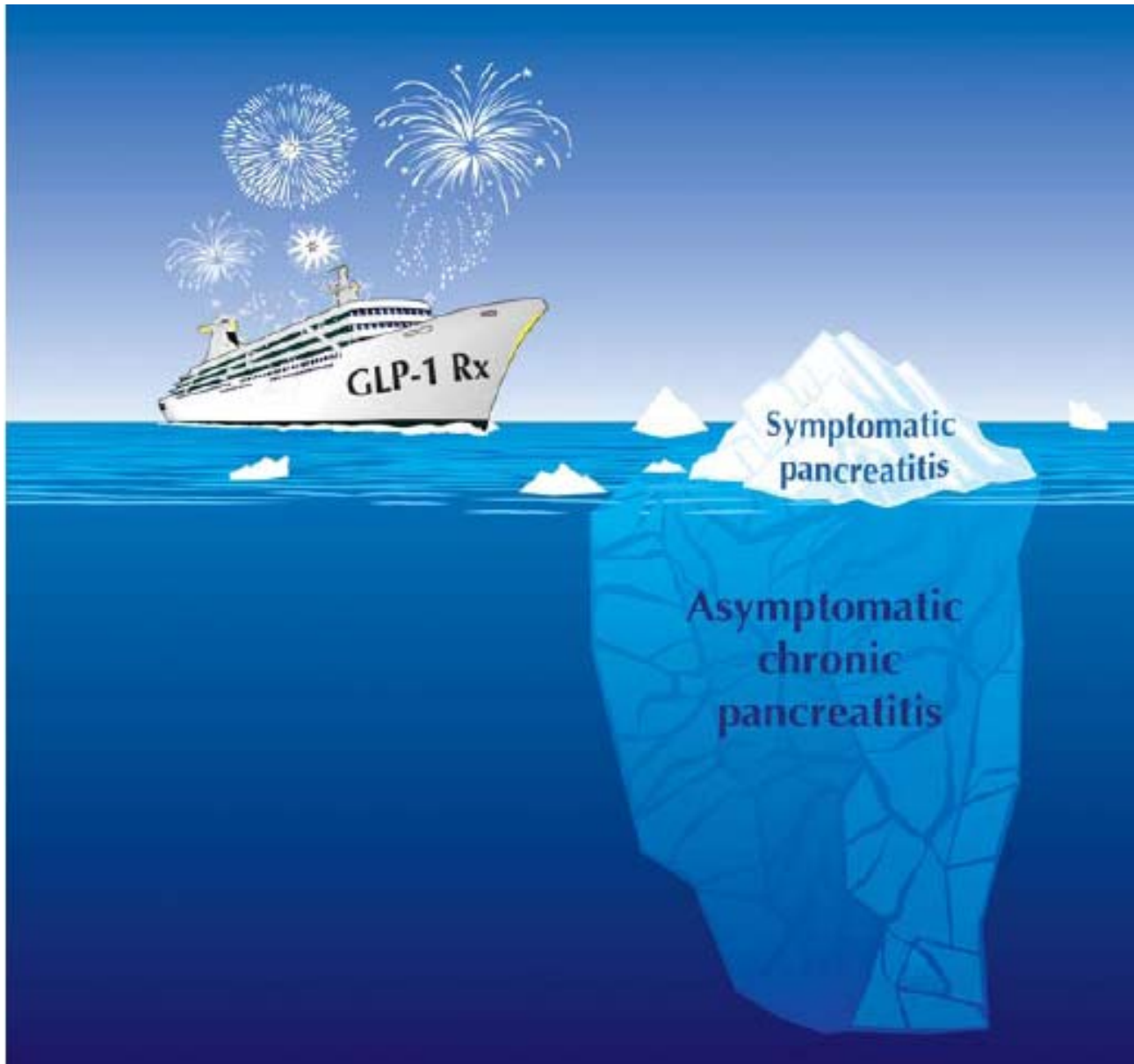
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Frequency of nausea over time – extension subjects

Proportion of subjects with nausea by week and treatment



- No extension subjects withdrew due to nausea.



Butler et al. Diabetologia 2010

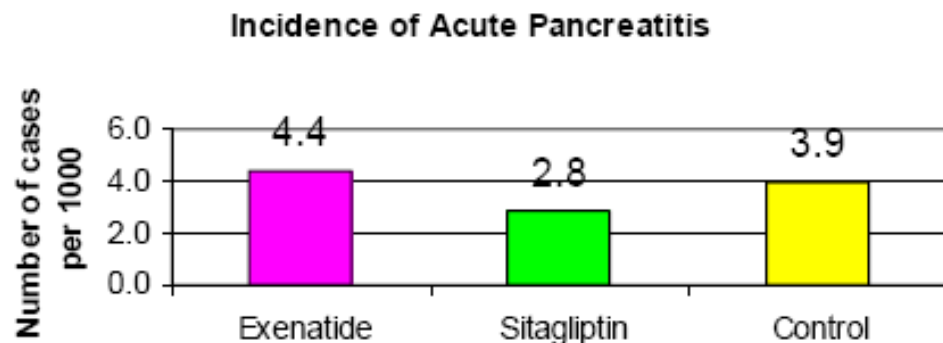
ADA, 2009

DESCRIPTIVE STATISTICS PRIOR TO EXCLUSIONS

	Exenatide	Sitagliptin	Control
ICD-9 claims suggesting pancreatic disease, alcohol abuse, or hepatitis	5%	5%	4%
Fibrate treatment	18%	21%	13%

SUBJECT CHARACTERISTICS AFTER EXCLUSIONS

	Exenatide	Sitagliptin	Control
N	9,160	2,143	112,218
Cases acute pancreatitis (#)	42	6	438
Age (yrs)	53 ± 7	54 ± 7	54 ± 7
Female (%)	59	47	47
Chronic disease score	36 ± 17	29 ± 16	29 ± 16



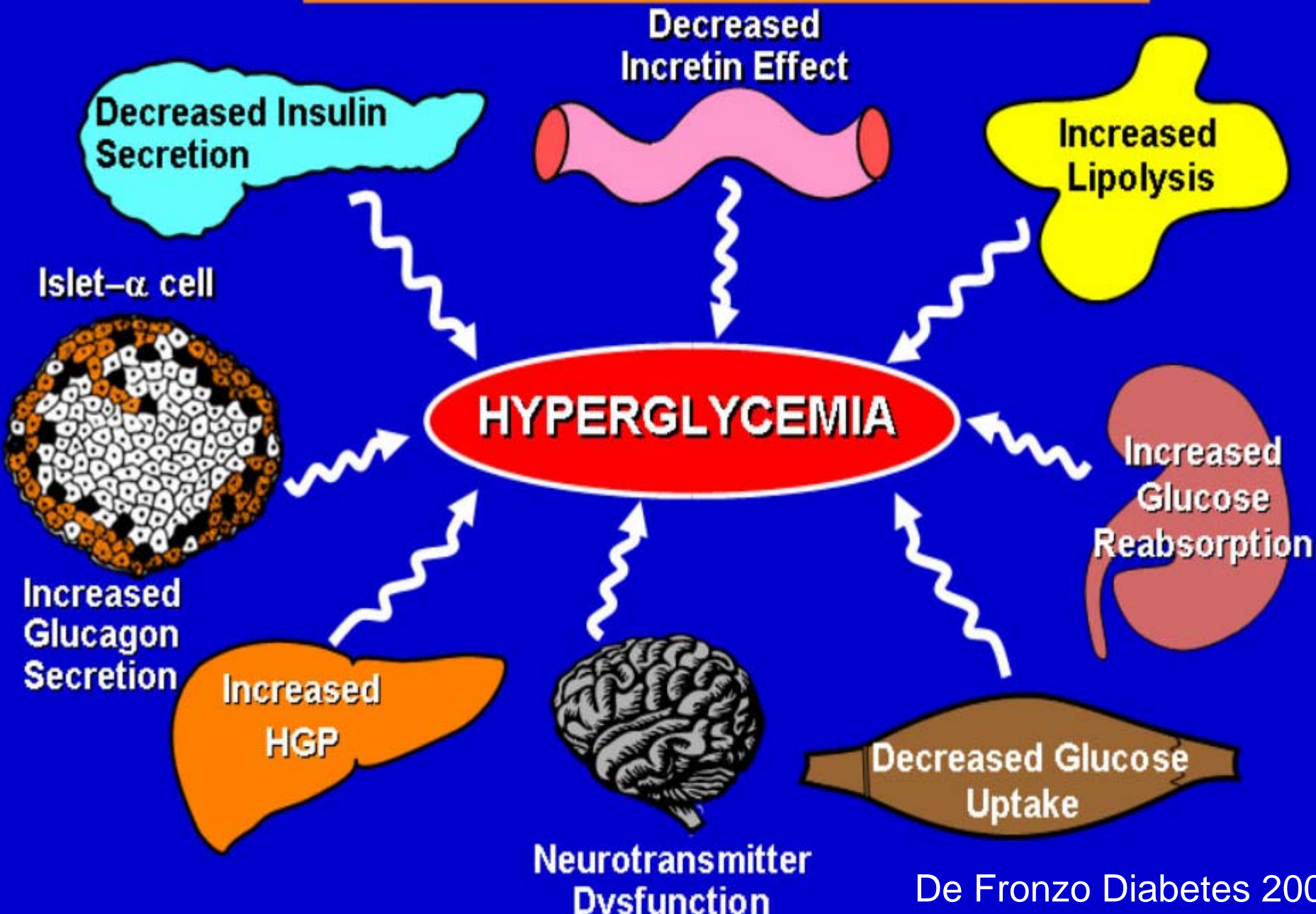
Summary

- Although these data are only descriptive, they suggest the incidence of pancreatitis in patients with type 2 diabetes is rare.
- These data do not suggest the risk of pancreatitis is appreciably increased in patients treated with exenatide or sitagliptin

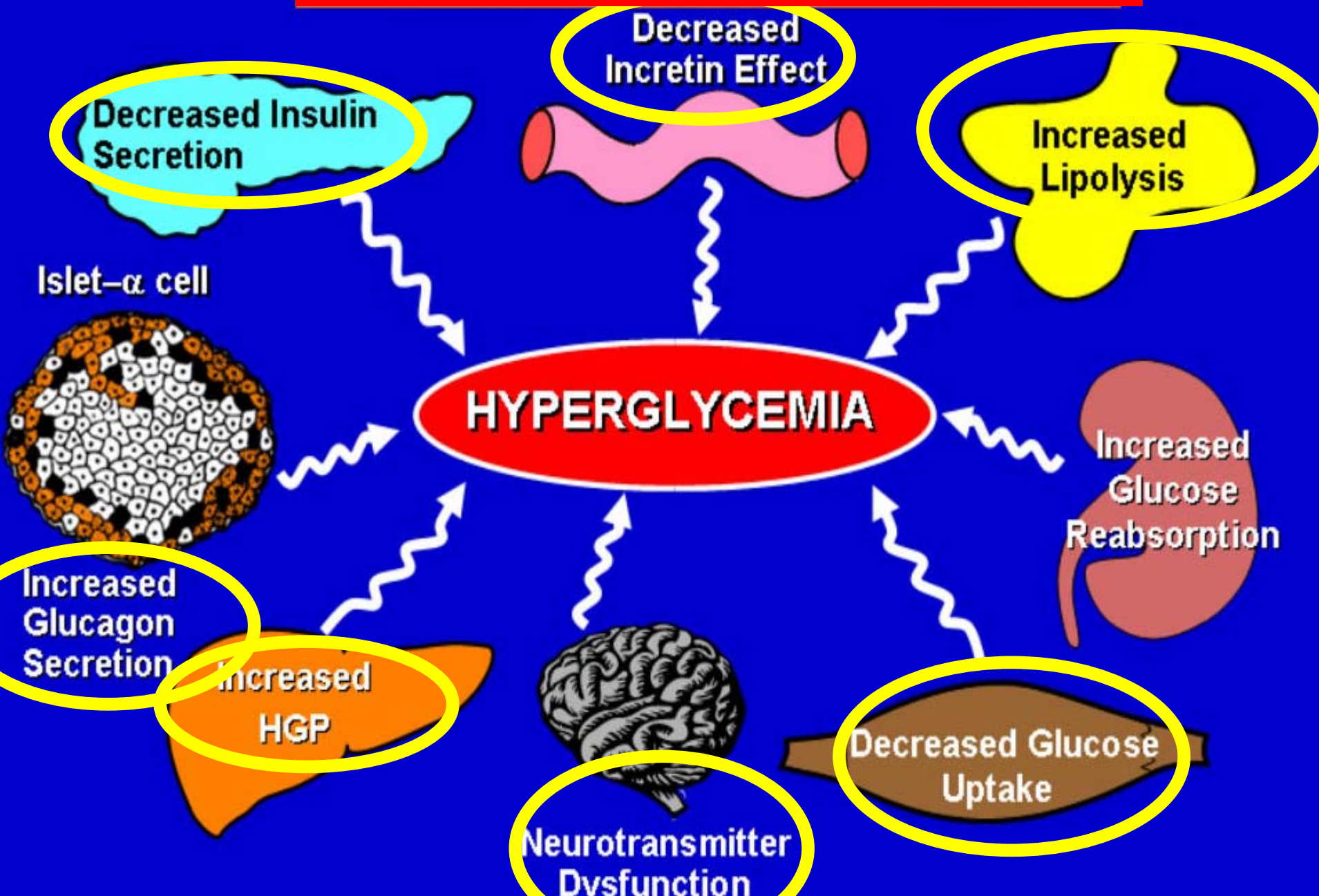
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OMINOUS OCTET



AGONISTAS GLP-1



Control Metabólico
+
Reducción de peso

Control de glucemia postprandial
Sin hipoglucemias
Asociable

AGONISTAS GLP-1

Efectos sobre supervivencia
de la célula beta ?

**Efectos adicionales metabólicos
y cardiovasculares**

Facilidad de
ajuste de dosis

Vía subcutánea

Efectos gastrointestinales

¿LUGAR EN ALGORITMO
TERAPÉUTICO?

NO DATOS DE SEGURIDAD
A LARGO PLAZO



AAACE/ACE DIABETES ALGORITHM *For Glycemic Control*

**A1C Goal
≤ 6.5%**

LIFESTYLE MODIFICATION

A1C 6.5 – 7.5%**

Monotherapy

MET	TZD ²	DPP4 ¹	AGI ³
-----	------------------	-------------------	------------------

↓ 2-3 Mos.***

Dual Therapy

MET	+	GLP-1 or DPP4 ¹	TZD ²
		Glinide or SU ⁵	
TZD	+	GLP-1 or DPP4 ¹	
MET	+	Colesevelam	AGI ³

↓ 2-3 Mos.***

Triple Therapy

MET	+	TZD ²
GLP-1 or DPP4 ¹		Glinide or SU ^{4,7}

↓ 2-3 Mos.***

INSULIN ± Other Agent(s)⁶

A1C 7.6 – 9.0%

Dual Therapy⁸

MET	+	GLP-1 or DPP4 ^{1,10} or TZD ²
		SU or Glinide ^{4,5}

↓ 2-3 Mos.***

Triple Therapy⁹

MET	+	GLP-1 or DPP4 ¹	+ TZD ²
		GLP-1 or DPP4 ¹	+ SU ⁷
		TZD ²	

↓ 2-3 Mos.***

INSULIN ± Other Agent(s)⁶

A1C > 9.0%

Drug Naive | *Under Treatment*

Symptoms | *No Symptoms*

INSULIN ± Other Agent(s)⁶

MET	+	GLP-1 or DPP4 ¹	± SU ⁷
		TZD ²	
MET	+	GLP-1 or DPP4 ¹	± TZD ²

INSULIN ± Other Agent(s)⁶

AAACE/ACE Algorithm for Glycemic Control Subcommittee

Cochairpersons:
 Helena W. Rodbard, MD, FACP, MACE
 Paul S. Jellinger, MD, MACE

Members:
 Zachary T. Bloomgarden, MD, FACE
 Jaime A. Davidson, MD, FACP, MACE
 Daniel Einhorn, MD, FACP, FACE
 Alan J. Garber, MD, PhD, FACP
 James R. Gavin, II, MD, PhD
 George Gunderberger, MD, FACP, FACE
 Yeluda Handelsman, MD, FACP, FACE
 Edward S. Horton, MD, FACE
 Harold Lebovitz, MD, FACE
 Philip Levy, M.D., MACE
 Ella S. Magness, MD, FACP, FACE
 Stanley S. Schwartz, MD, FACE

- * May not be appropriate for all patients
- ** For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered
- *** If A1C goal not achieved safely
- 1 DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG
- 2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
- 3 AGI if ↑ PPG
- 4 Glinide if ↑ PPG or SU if ↑ FPG
- 5 Low-dose secretagogue recommended
- 6 a) Discontinue insulin secretagogue with multidosage insulin
b) Can use pramlintide with prandial insulin
- 7 Decrease secretagogue by 60% when added to GLP-1 or DPP-4
- 8 If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution
- 9 If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered
- 10 GLP-1 not approved for initial combination Rx

¡¡MUCHAS GRACIAS!!



EFFECTOS DE LIRAGLUTIDA SOBRE S. METABÓLICO Y PREDIABETES

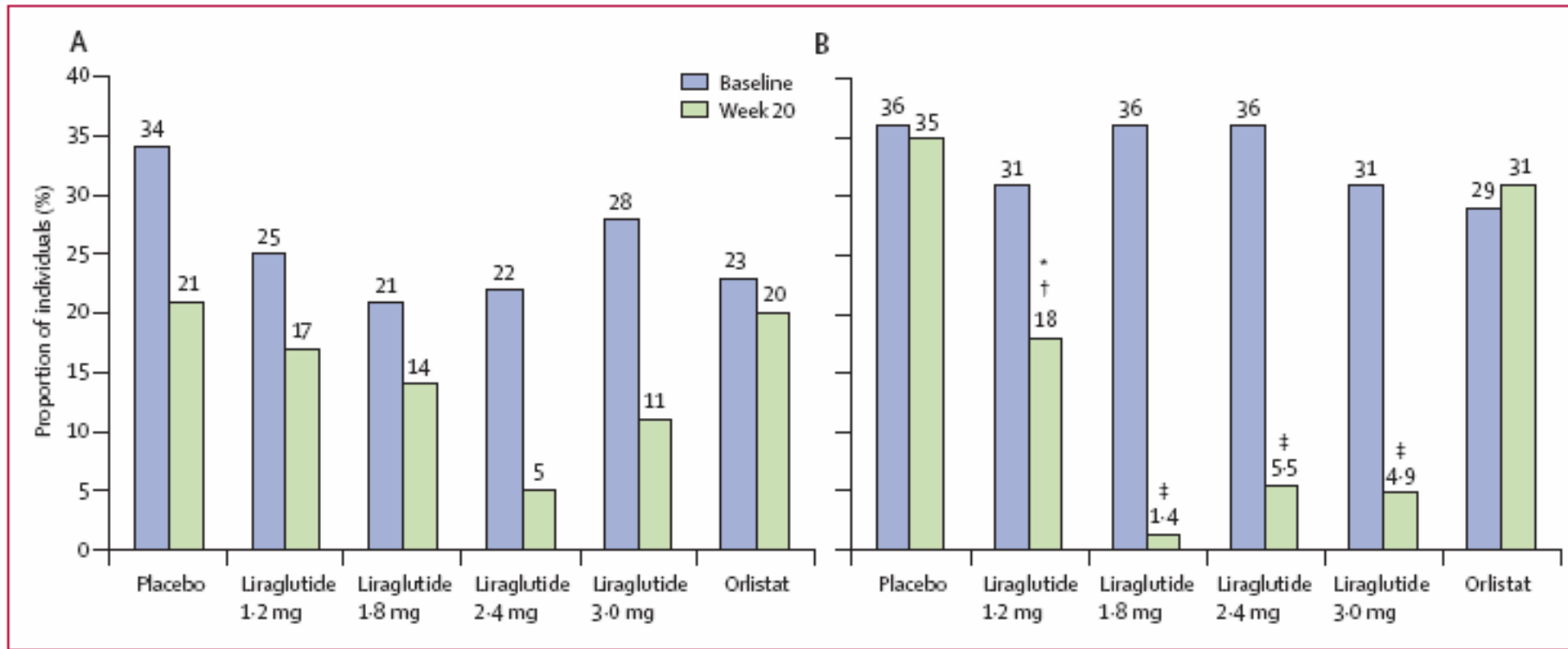


Figure 4: Percentage of individuals with metabolic syndrome (A) and prediabetes (B) at randomisation and after 20 weeks of treatment

Individuals included are those with valid assessment at the start and the end of the 20-week trial period. * $p=0.007$ vs placebo. † $p=0.008$ vs orlistat. ‡ $p\leq 0.0001$ vs placebo or orlistat.

Astrup et al. Lancet 2009

EFECTOS DE LIRAGLUTIDA SOBRE PESO CORPORAL

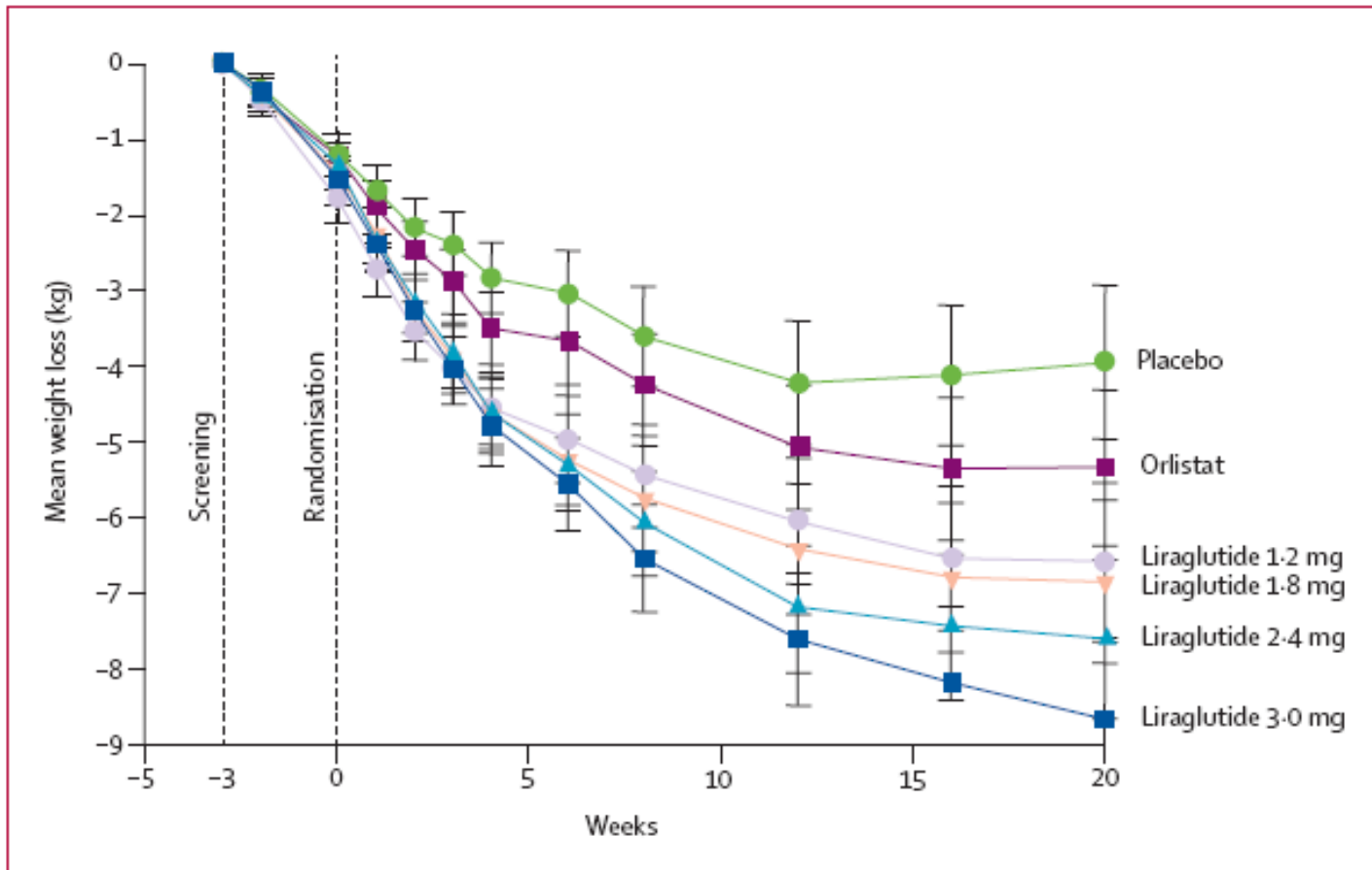
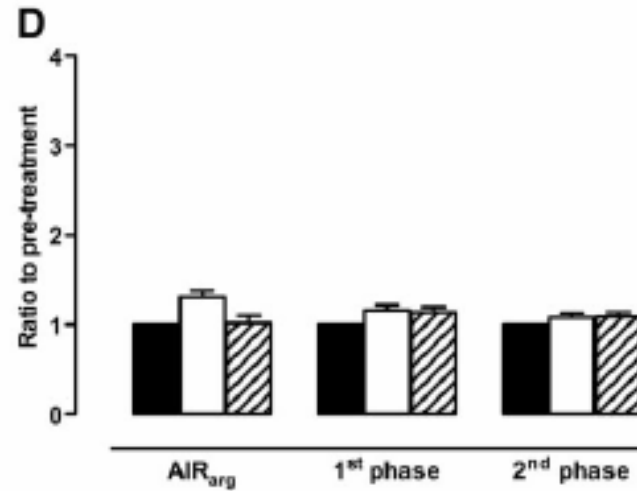
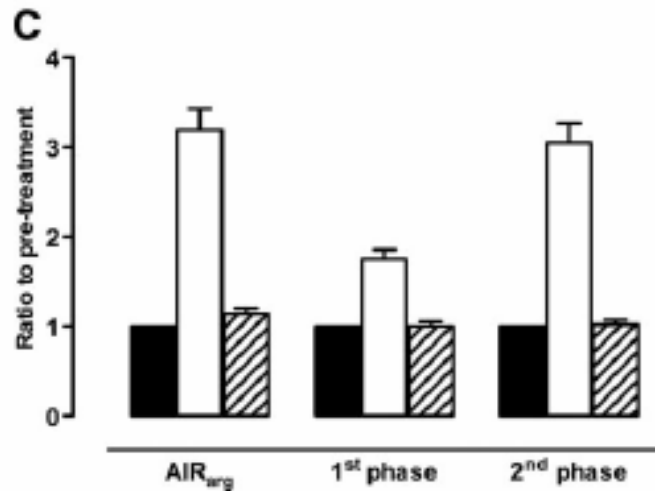
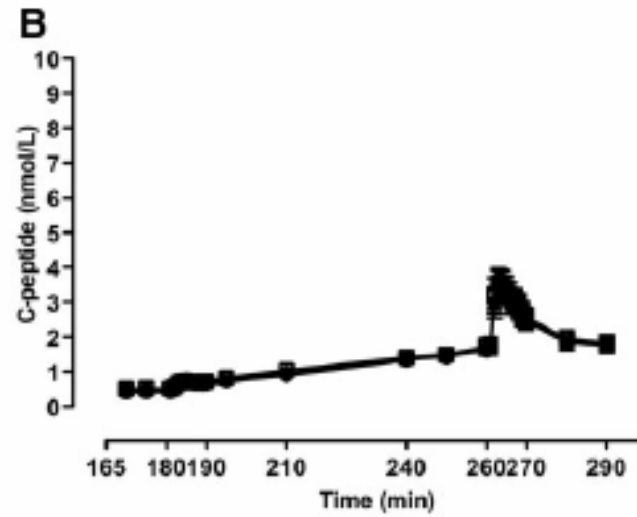
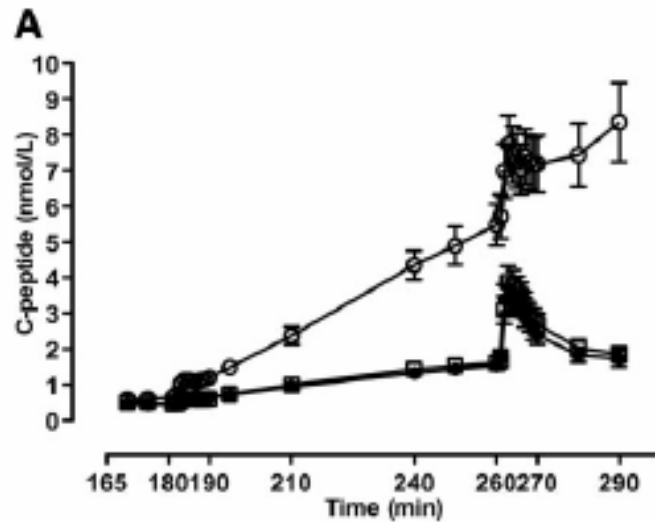


Figure 2: Change in bodyweight

Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward.

EXENATIDE PERFORMS BETTER THAN GLARGINE IN IMPROVING BETA-CELL FUNCTION AFTER 1 YEAR

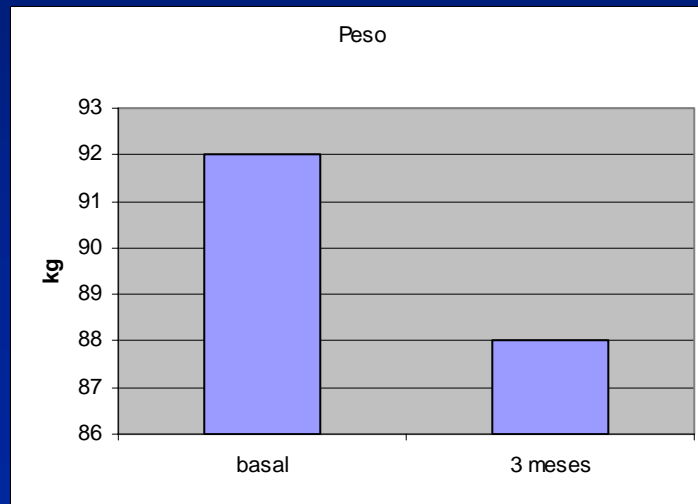
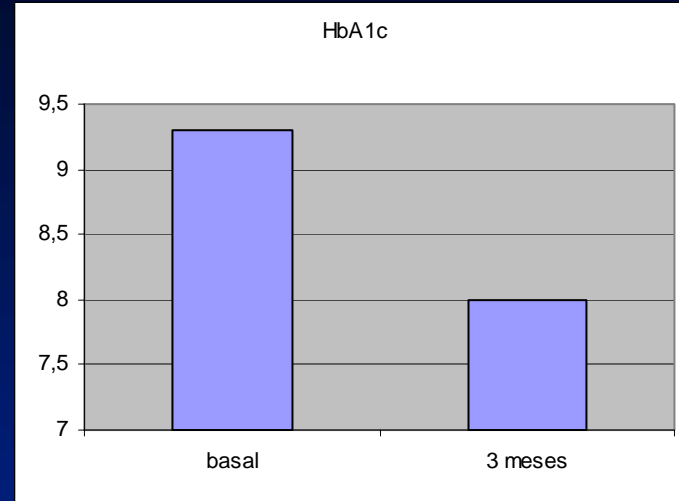
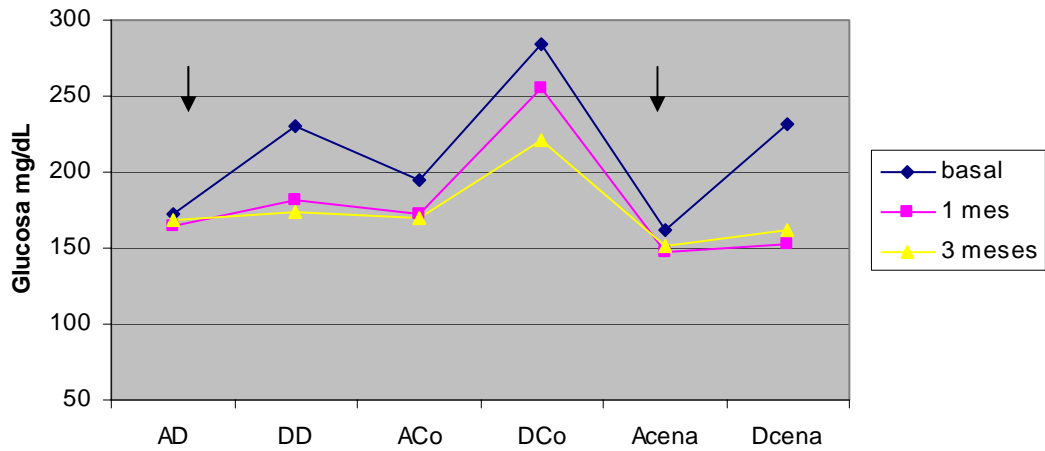


EXENATIDA Y CALIDAD DE VIDA

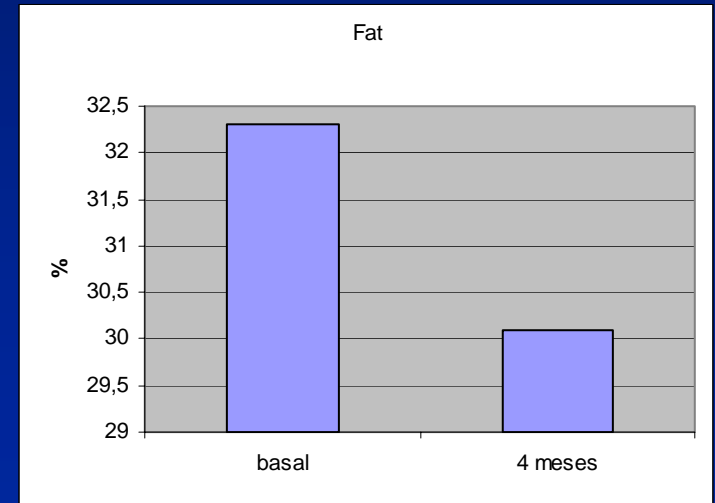
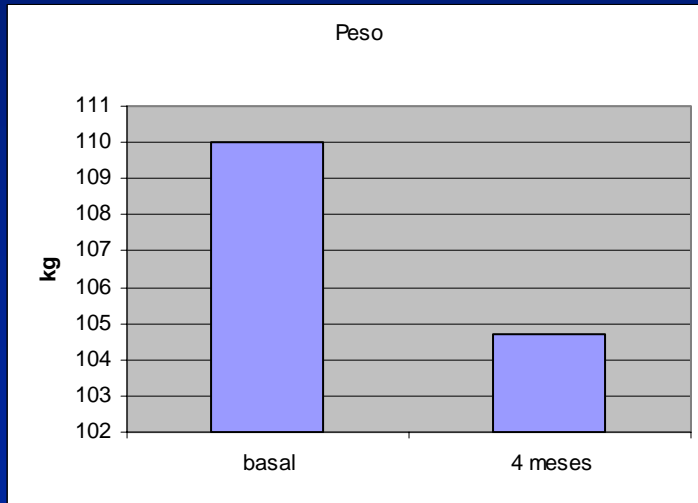
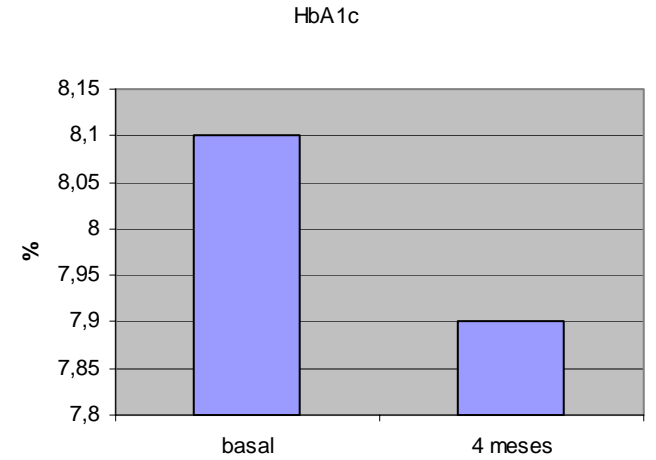
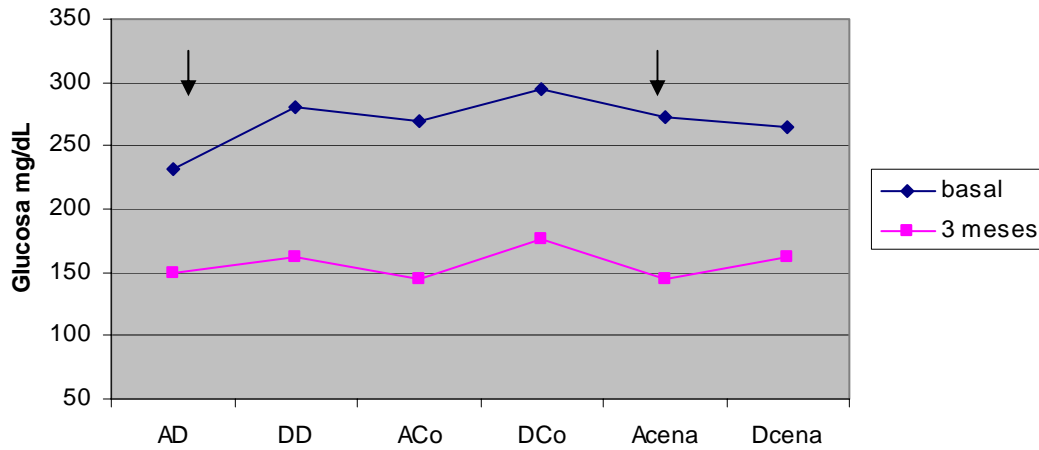
Table 2: Paired t-tests comparing baseline and endpoint scores within each treatment group

Health Outcomes Measure (mean, SD)	Exenatide			Insulin Glargine		
	Baseline	Endpoint	p value	Baseline	Endpoint	p value
DSC-R Overall Score	1.07 (0.83)	0.90 (0.80)	< 0.0001	0.99 (0.78)	0.84 (0.73)	0.0002
EQ-5D Index Score	0.82 (0.22)	0.85 (0.19)	0.08	0.84 (0.22)	0.87 (0.20)	0.049
Diabetes Treatment Flexibility Score	60.37 (22.24)	60.48 (22.33)	0.93	58.85 (22.81)	58.95 (23.37)	0.93
Diabetes Treatment Satisfaction Score	26.41 (7.00)	29.48 (6.12)	< 0.0001	26.31 (6.33)	30.04 (5.21)	< 0.0001
SF-36 Vitality Subscale Score	53.18 (20.87)	56.30 (20.58)	0.005	55.18 (21.35)	57.62 (20.37)	0.04
DSC-R Psychology: Fatigue Score	1.83 (1.26)	1.49 (1.21)	< 0.0001	1.60 (1.29)	1.34 (1.17)	0.0003
DSC-R Psychology: Cognitive Score	1.18 (1.12)	0.99 (1.08)	0.0006	1.14 (1.09)	0.91 (0.99)	0.0001
DSC-R Neurology: Pain Score	0.76 (0.98)	0.70 (0.99)	0.21	0.67 (0.90)	0.63 (0.92)	0.49
DSC-R Neurology: Sensory Score	0.91 (1.07)	0.83 (1.01)	0.10	0.77 (0.94)	0.78 (0.93)	0.83
DSC-R Cardiology Score	0.78 (0.89)	0.71 (0.86)	0.16	0.73 (0.86)	0.61 (0.80)	0.02
DSC-R Ophthalmology Score	0.79 (1.00)	0.62 (0.86)	0.003	0.79 (0.98)	0.64 (0.92)	0.006
DSC-R Hypoglycemia Score	1.09 (1.16)	0.94 (1.09)	0.03	1.10 (1.09)	0.93 (1.00)	0.009
DSC-R Hyperglycemia Score	1.47 (1.31)	1.07 (1.15)	< 0.0001	1.42 (1.25)	1.02 (1.13)	< 0.0001
DTSQ Frequency High Blood Sugar	3.61 (1.76)	2.19 (1.61)	< 0.0001	3.57 (1.67)	2.11 (1.45)	< 0.0001
DTSQ Frequency Low Blood Sugar	1.02 (1.37)	1.36 (1.56)	0.007	0.80 (1.21)	1.50 (1.43)	< 0.0001

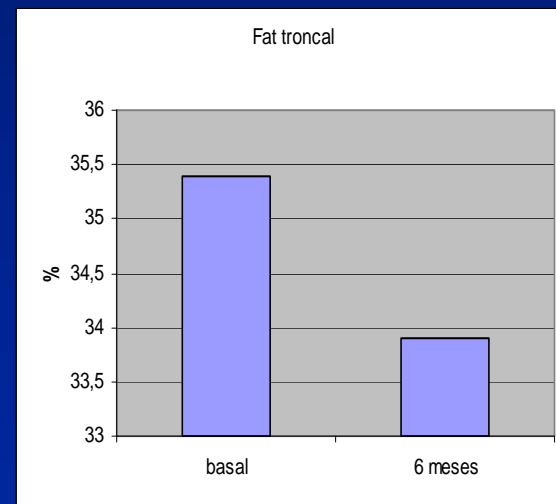
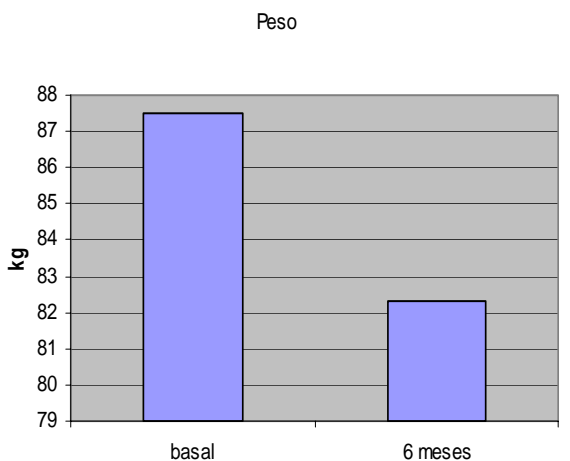
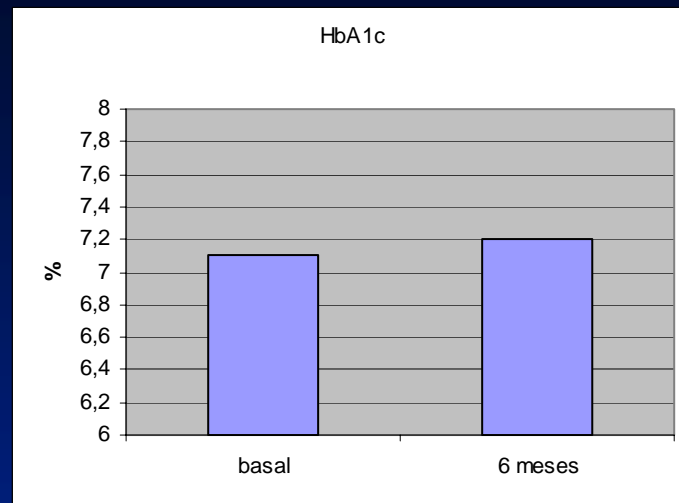
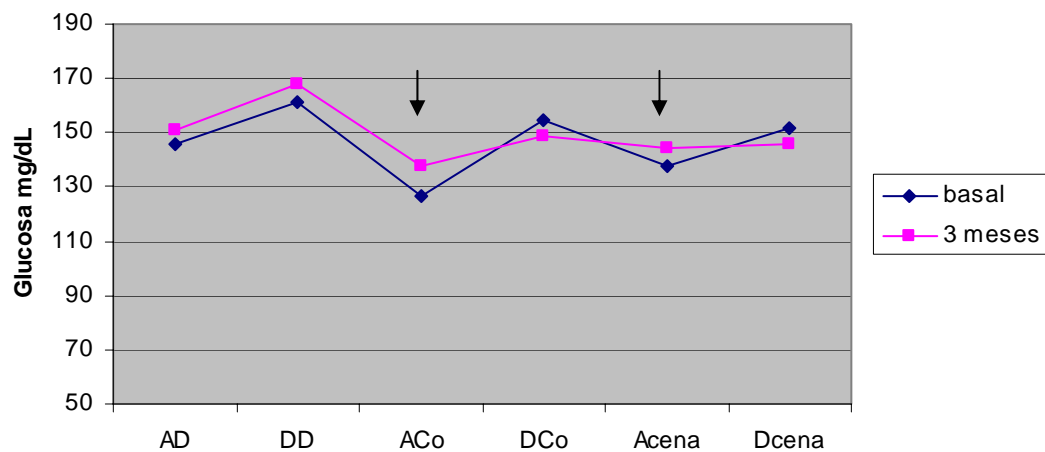
Varón de 54 años. DM2 de 7 años de evolución. En tratamiento con Metformina 1.0.1



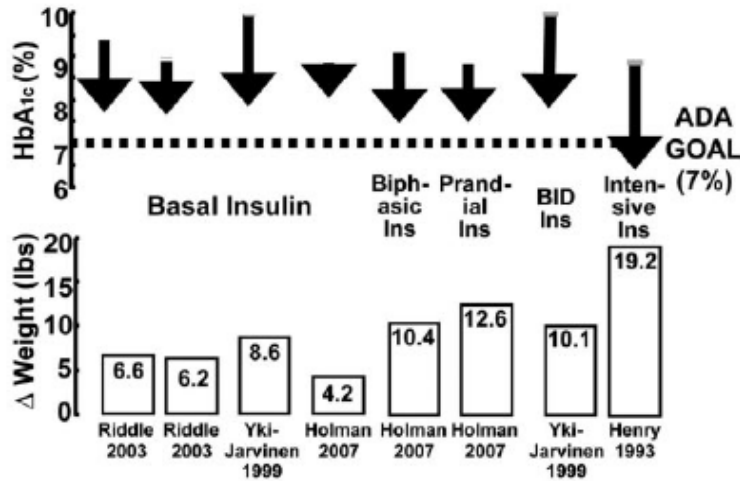
Varón de 61 años con DM2 de 5 años de evolución. En tratamiento con Repaglinida y Metformina



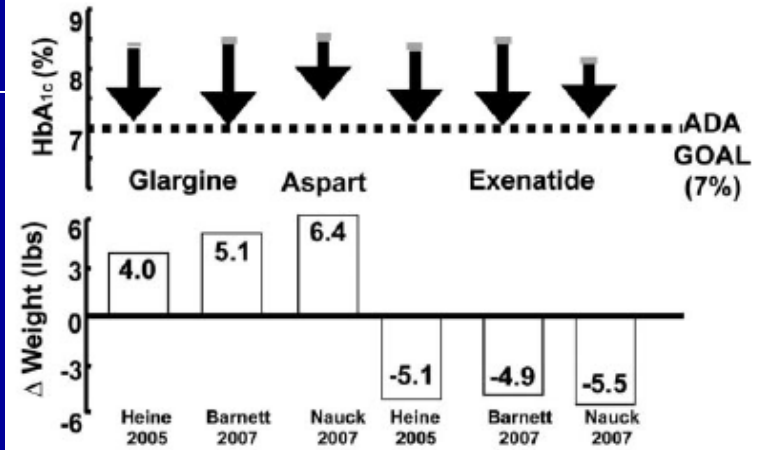
Varón de 64 años de edad con DM2 de 14 años de evolución. En tratamiento con Metformina, y Repaglinida



ALL INSULIN REGIMENS IMPROVE GLYCEMIC CONTROL, BUT WITH WEIGHT GAIN

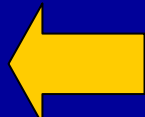


EXENATIDE VERSUS INSULIN: CHANGES IN GLYCEMIA AND WEIGHT



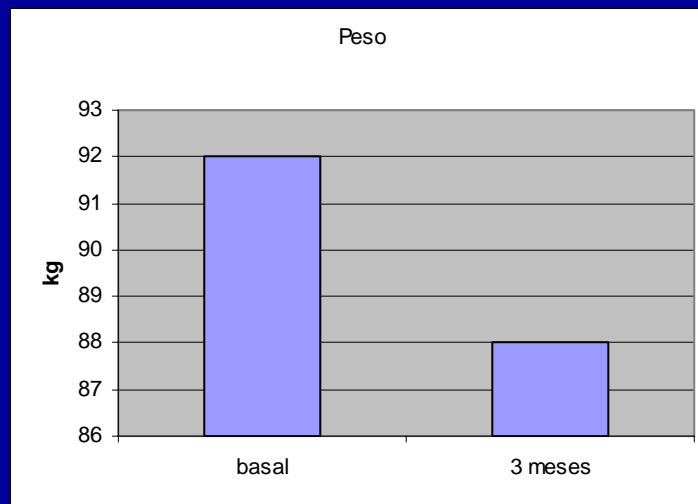
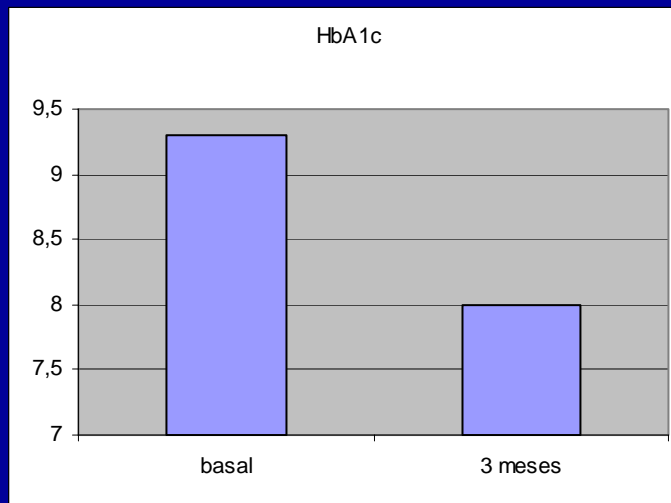
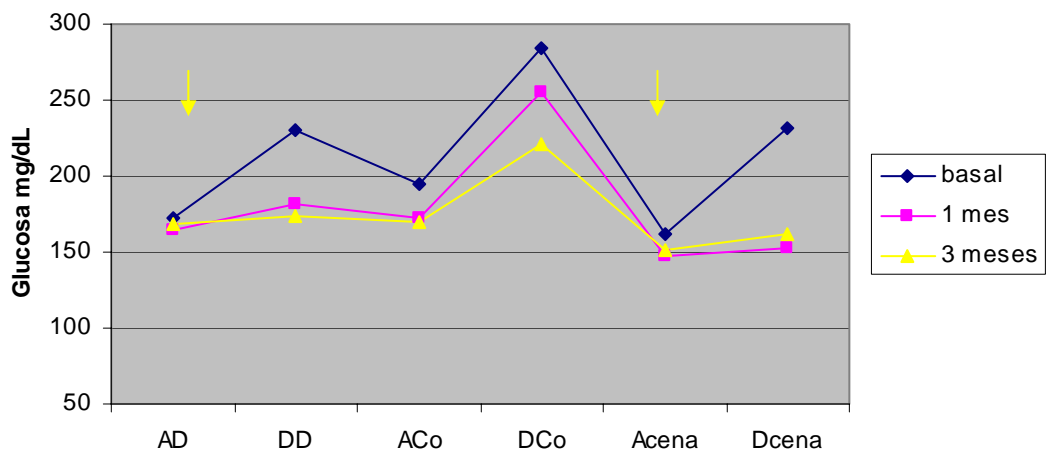
Lifestyle + TRIPLE COMBINATION: TZD + Metformin + Exenatide

HbA_{1c} < 6.0%

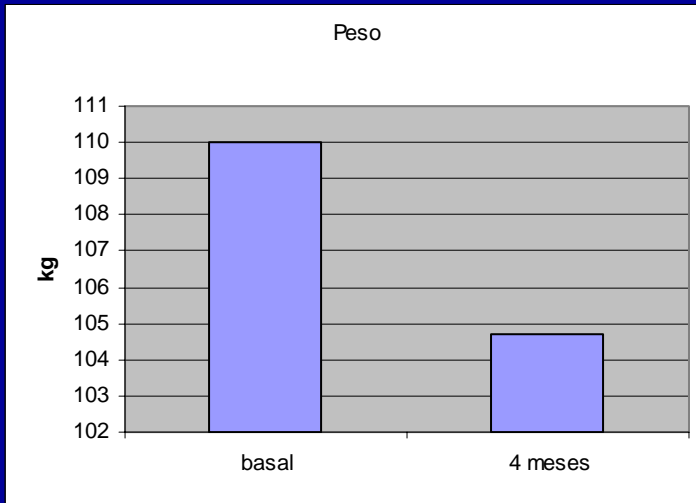
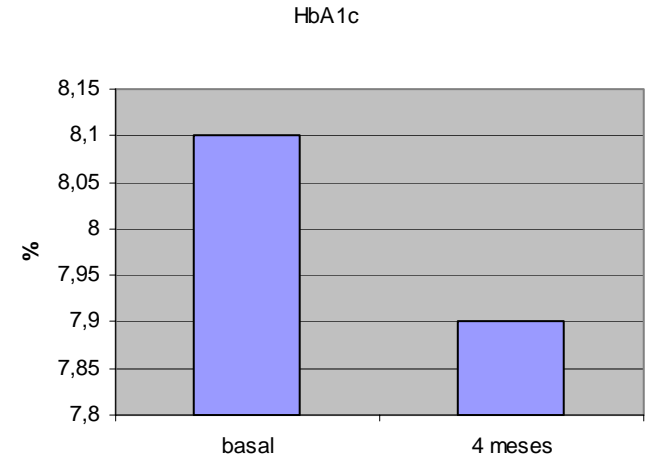
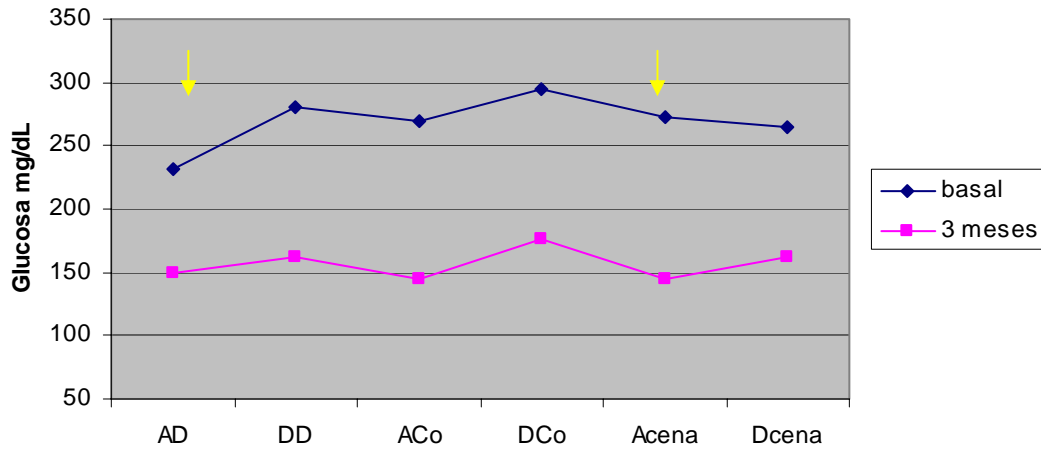


	<u>ADA</u>	<u>PATHOPHYSIOLOGIC-BASED</u>
Durability	No	Yes
β Cell Preservation	No	Yes
Hypoglycemia	Yes	No
Weight Gain	Yes	No

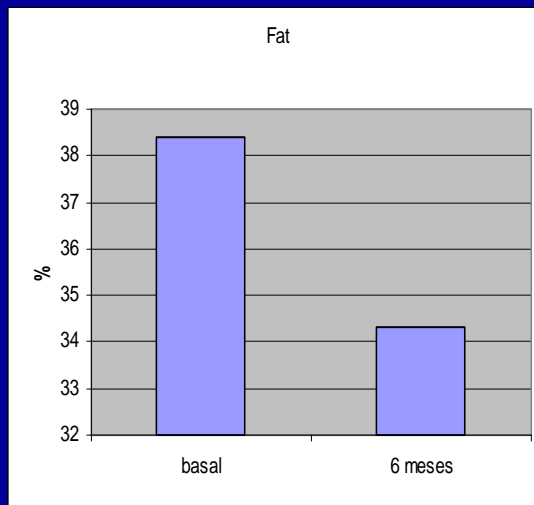
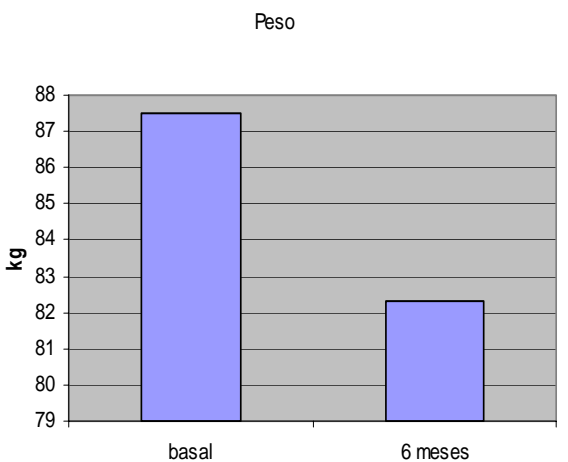
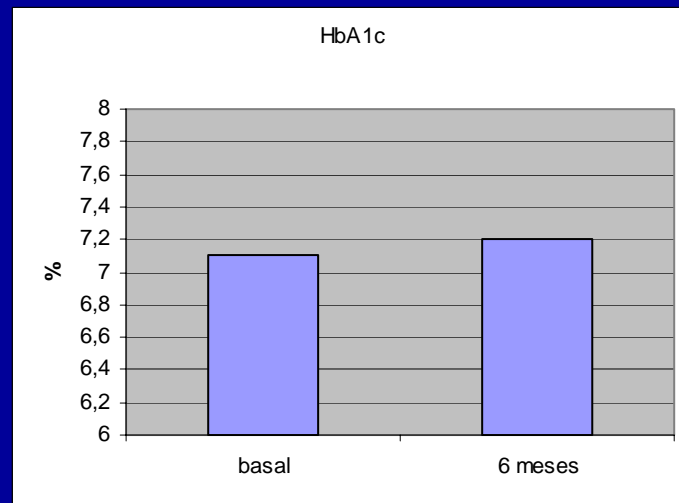
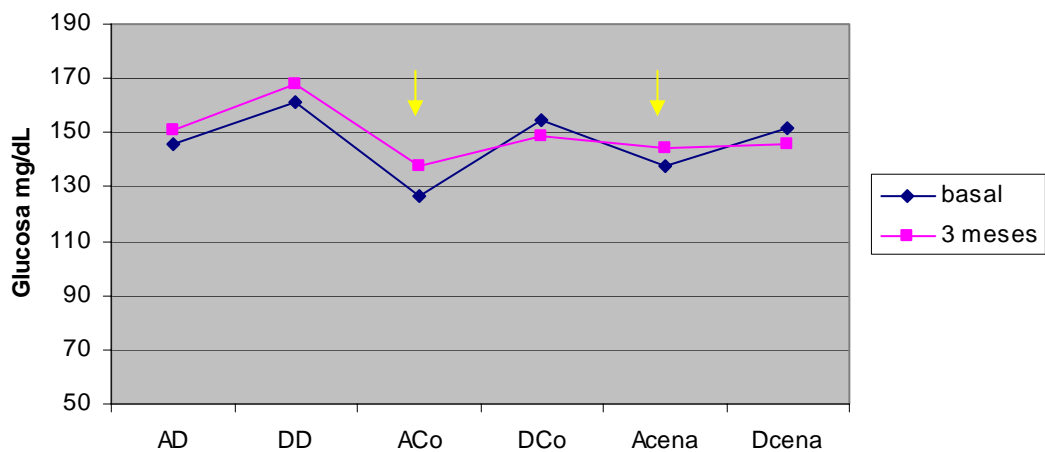
Varón de 54 años. DM2 de 7 años de evolución. En tratamiento con Metformina 1.0.1



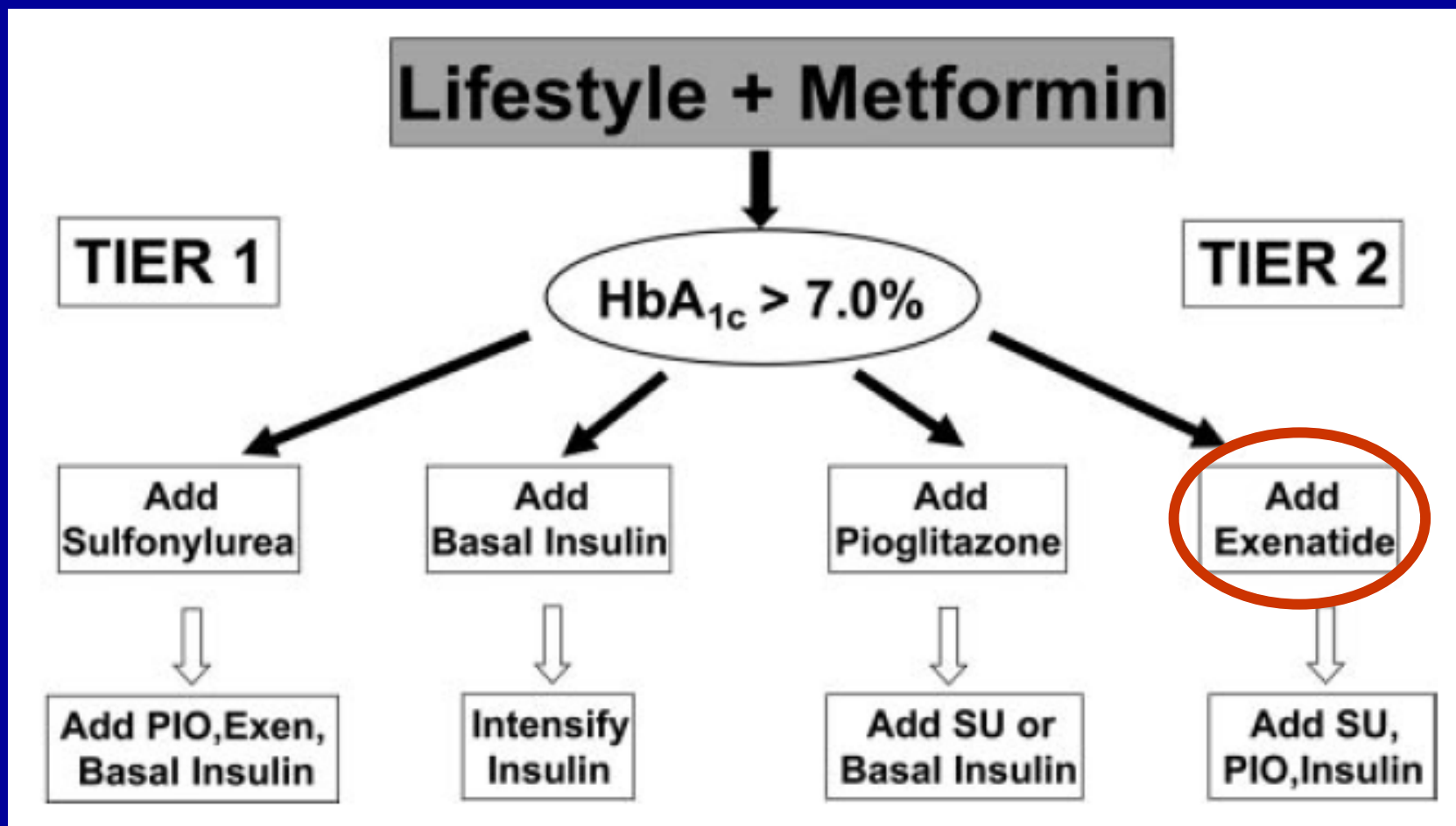
Varón de 61 años con DM2 de 5 años de evolución. En tratamiento con Repaglinida y Metformina



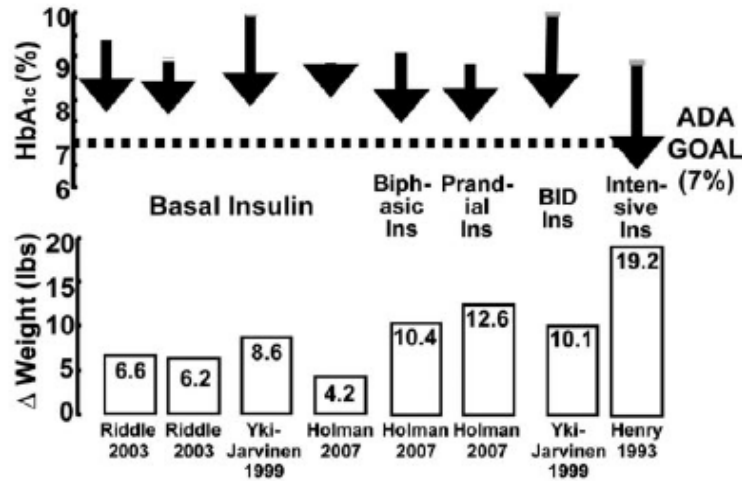
Varón de 64 años de edad con DM2 de 14 años de evolución. En tratamiento con Metformina, y Repaglinida



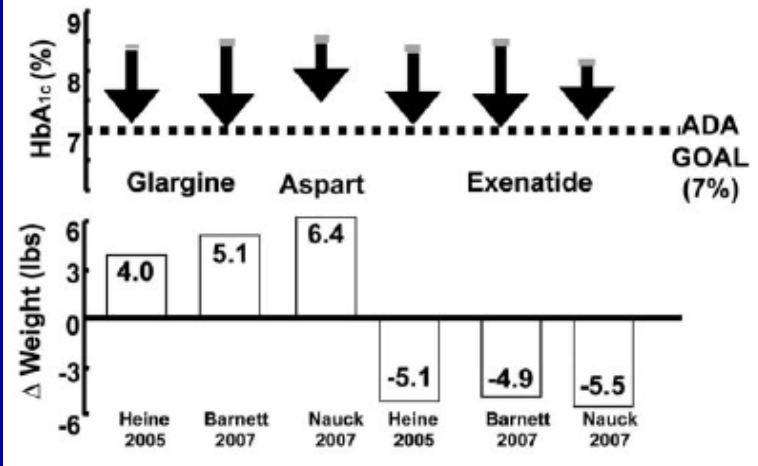
LUGAR DE EXENATIDA EN EL TRATAMIENTO DE LA DIABETES TIPO 2



ALL INSULIN REGIMENS IMPROVE GLYCEMIC CONTROL, BUT WITH WEIGHT GAIN

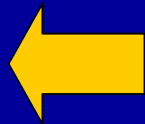


EXENATIDE VERSUS INSULIN: CHANGES IN GLYCEMIA AND WEIGHT



Lifestyle + TRIPLE COMBINATION: TZD + Metformin + Exenatide

HBA1c < 6.0%



	<u>ADA</u>	<u>PATHOPHYSIOLOGIC-BASED</u>
Durability	No	Yes
β Cell Preservation	No	Yes
Hypoglycemia	Yes	No
Weight Gain	Yes	No

MEDICATIONS*

	Metformin (MET)	DPP4 Inhibitor	GLP-1 Agonist (Incretin Mimetic)	Sulfonylurea (SU)	Glinide**	Thiazolidinedione (TZD)	Colesevelam	Alpha-glucosidase inhibitor (AGI)	Insulin	Pramlintide
BENEFITS										
Postprandial Glucose (PPG) - lowering	Mild	Moderate	Moderate to Marked	Moderate	Moderate	Mild	Mild	Moderate	Moderate to Marked	Moderate to Marked
Fasting glucose (FPG) - lowering	Moderate	Mild	Mild	Moderate	Mild	Moderate	Mild	Neutral	Moderate to Marked	Mild
Nonalcoholic fatty liver disease (NAFLD)	Mild	Neutral	Mild	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
RISKS										
Hypoglycemia	Neutral	Neutral	Neutral	Moderate	Mild	Neutral	Neutral	Neutral	Moderate to Severe	Neutral
Gastrointestinal Symptoms	Moderate	Neutral	Moderate	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Moderate
Risk of use with renal insufficiency	Severe	Reduce Dosage	Moderate	Moderate	Neutral	Mild	Neutral	Neutral	Moderate	Unknown
Contraindicated in Liver Failure or Predisposition to Lactic Acidosis	Severe	Neutral	Neutral	Moderate	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral
Heart failure / Edema	Contra-indicated in CHF	Neutral	Neutral	Neutral	Neutral	Mild / Moderate Contraindicated in class 3,4 CHF	Neutral	Neutral	Neutral unless with TZD	Neutral
Weight Gain	Benefit	Neutral	Benefit	Mild	Mild	Moderate	Neutral	Neutral	Mild to Moderate	Benefit
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
Drug-Drug Interactions	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral

* The abbreviations used here correspond to those used on the algorithm (Fig. 1).
 ** The term 'glinide' includes both repaglinide and nateglinide.

GLP-1 has receptor mediated and receptor independent effects

