El reto del internista en el manejo de la diabetes: uso de los agonistas del receptor de GLP-1

“Uso de los agonistas del receptor de GLP-1 en el paciente del internista”

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Hospital Regional Universitario de Málaga

Conflicto de intereses

Asesoramiento: Boehringer-Lilly, Novo Nordisk, Sanofi.

Trabajos remunerados: Astra-Zeneca, Boehringer-Lilly, Novartis, Novo-Nordisk, Sanofi.

Estudios de investigación: Boehringer-Lilly, Novo-Nordisk, Sanofi.

AGENDA

1. ¿Cuál es el perfil del paciente con diabetes atendido por Medicina Interna?

2. Papel de los AR-GLP1 en situaciones especiales

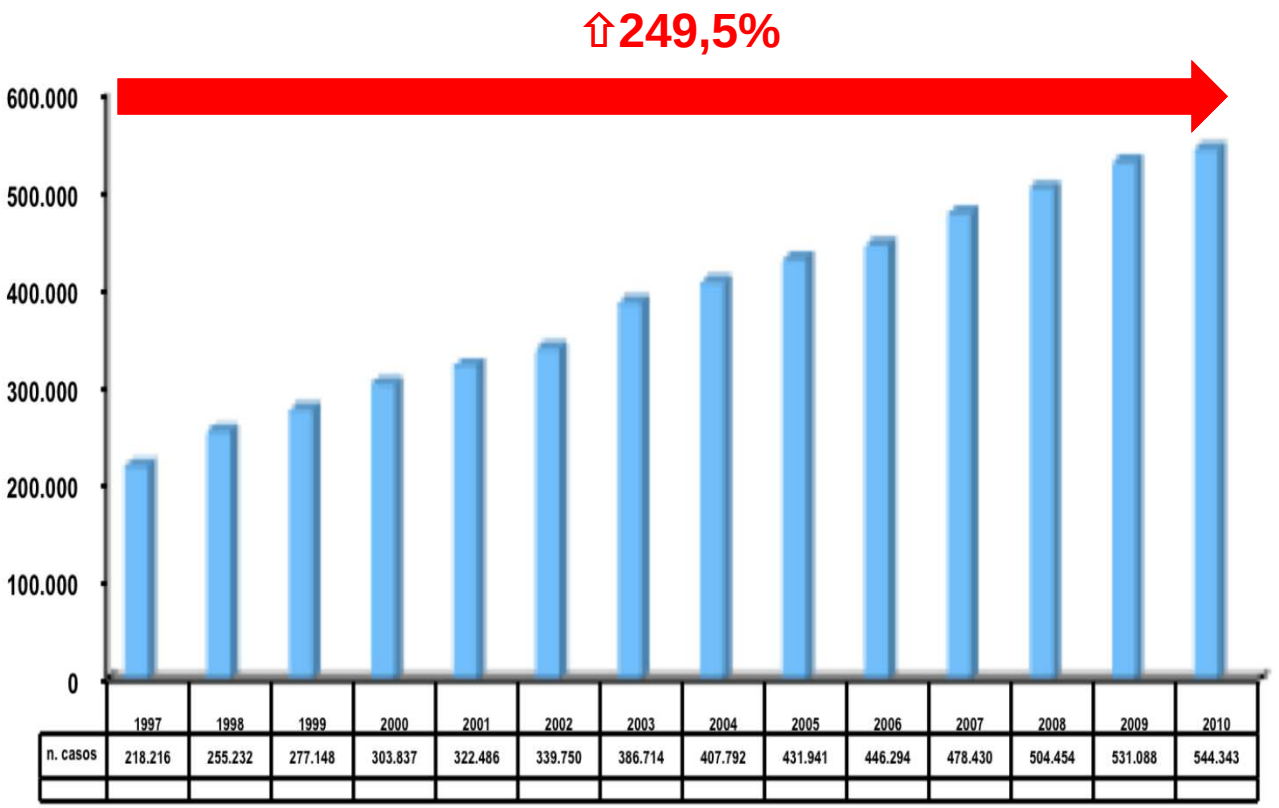
AGENDA

1. ¿Cuál es el perfil del paciente con diabetes atendido por Medicina Interna?

2. Papel de los AR-GLP1 en situaciones especiales

Número de altas hospitalarias en pacientes con diabetes

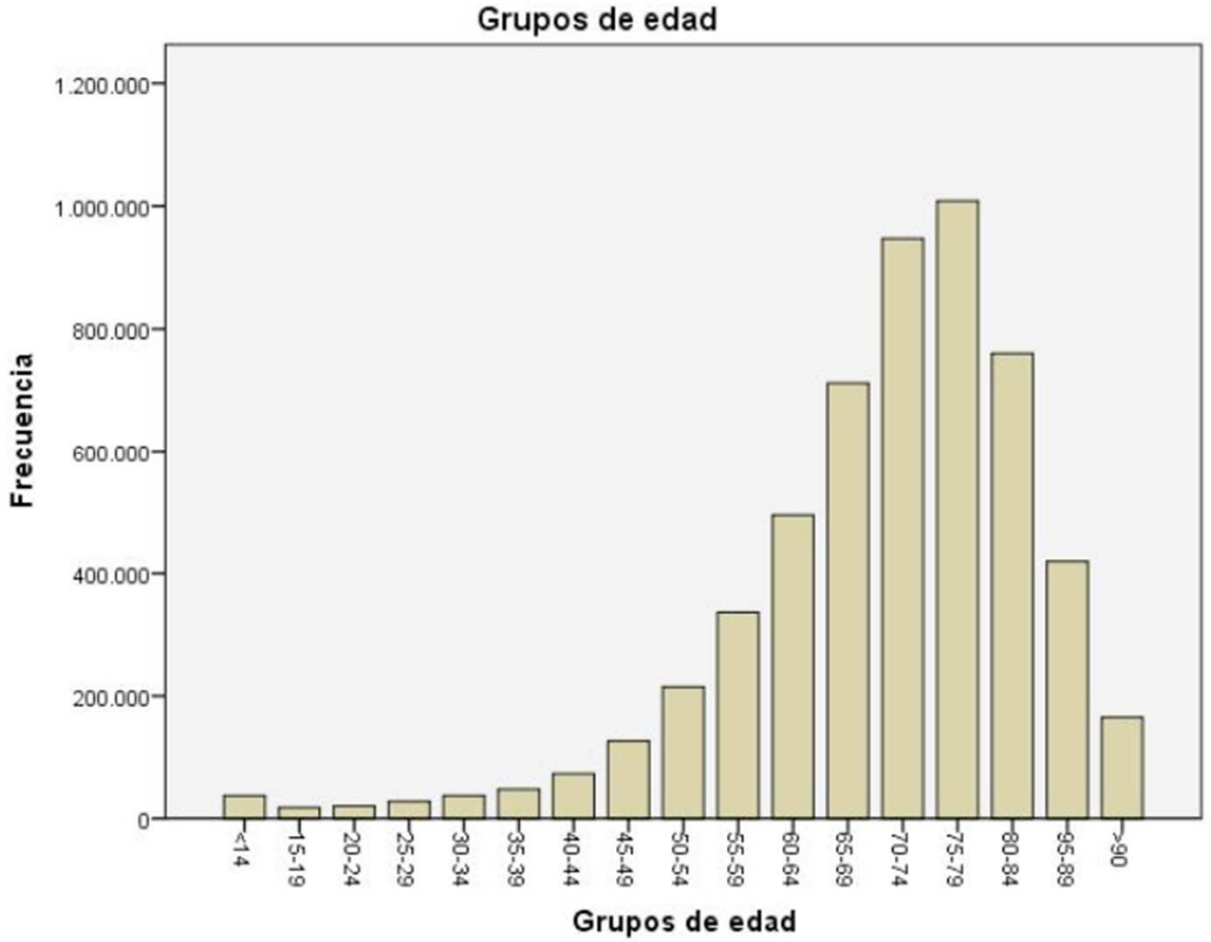
CMBD 1997 - 2010



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
n. casos	218.216	255.232	277.148	303.837	322.486	339.750	386.714	407.792	431.941	446.294	478.430	504.454	531.088	544.343

Gómez-Huelgas R (in press)

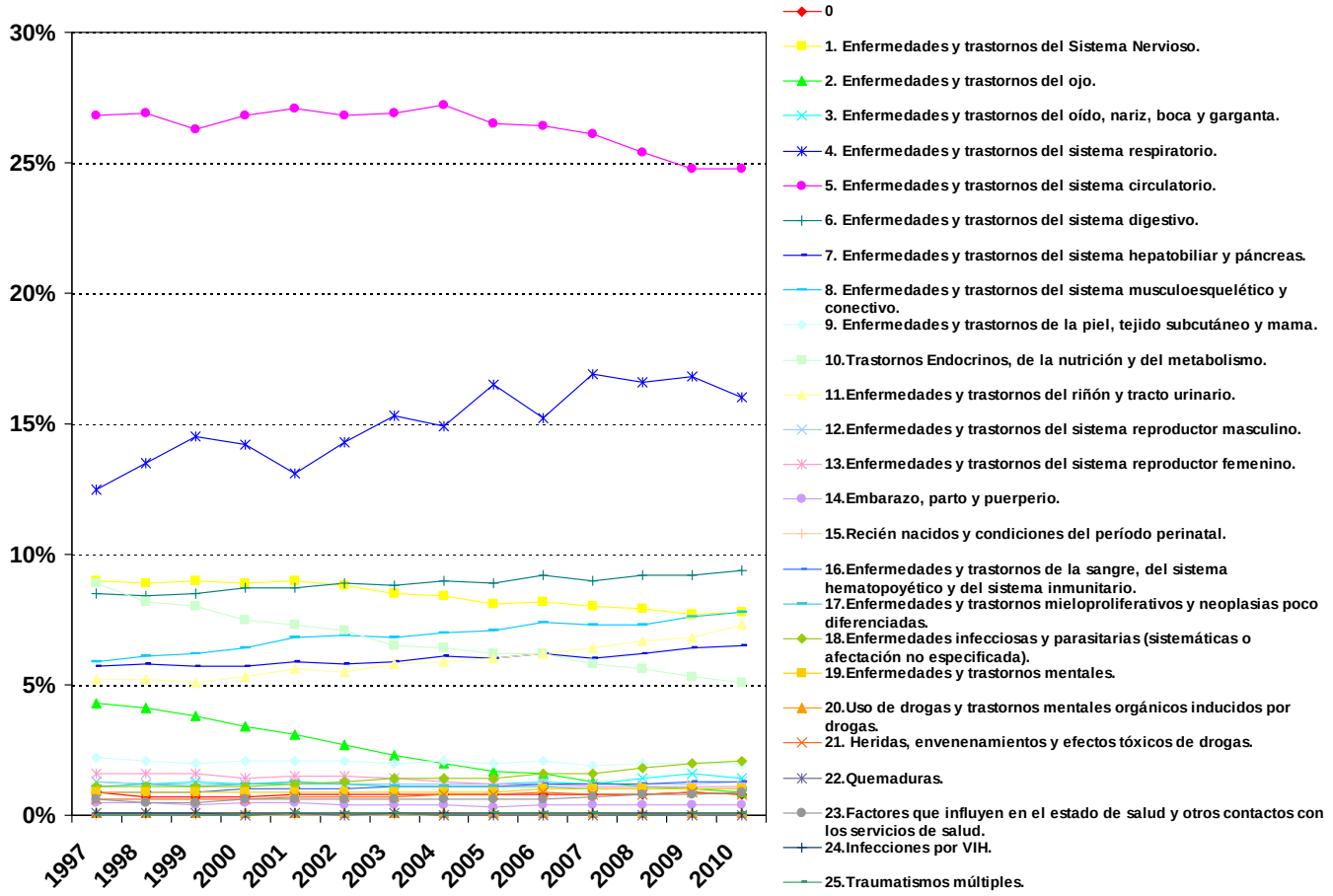
Distribución etaria
de los pacientes con diabetes hospitalizados
CMBD 1997 - 2010



Gómez-Huelgas R (in press)

Causas de ingreso en pacientes con diabetes
CMBD 1997 - 2010

Causas de Ingreso en Diabetes por CDM (% con respecto al total de ingresos de diabéticos). Evolución anual



Gómez-Huelgas R (in press)

Diagnósticos principales más frecuentes en pacientes diabéticos hospitalizados

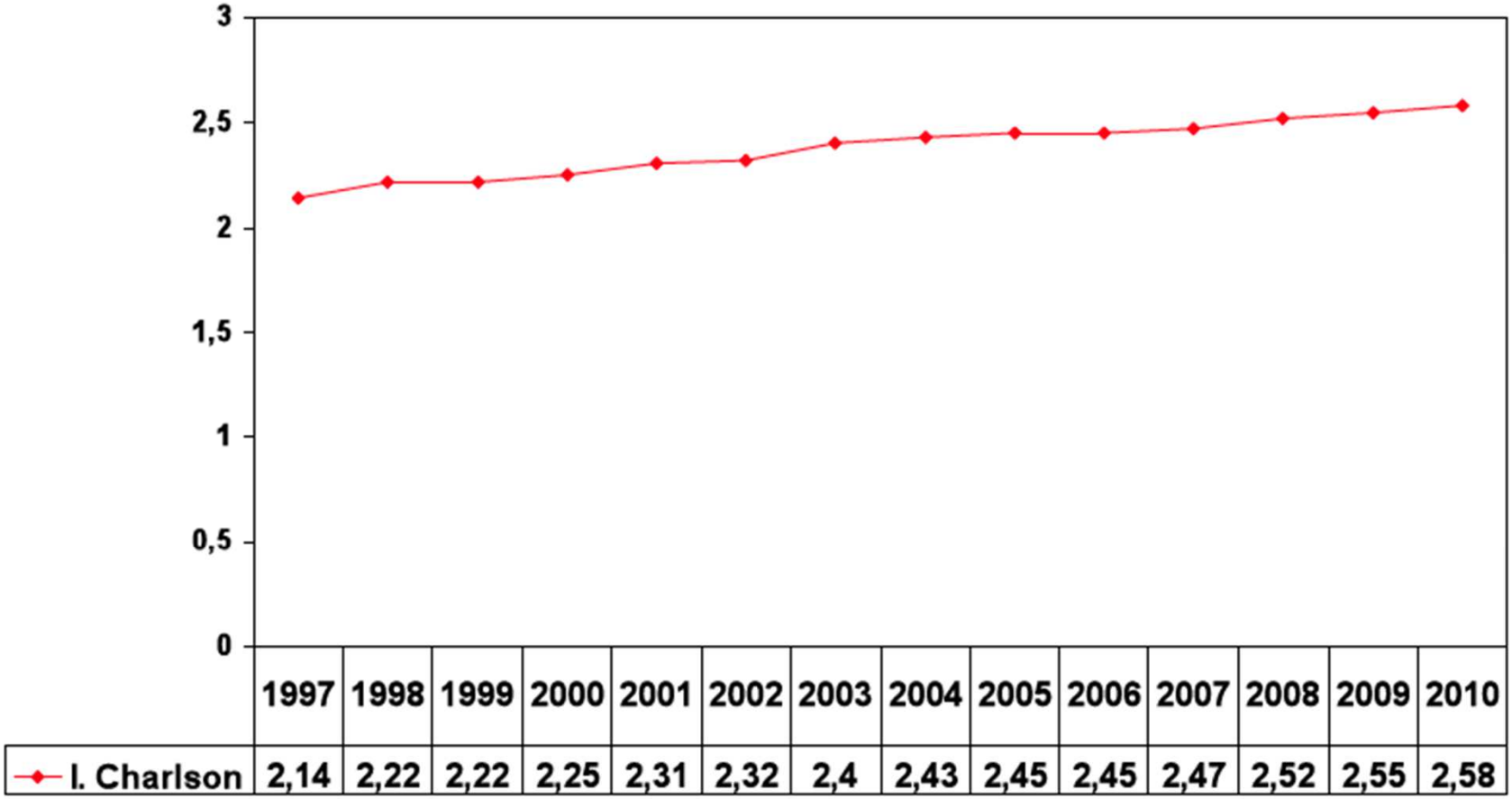
CMBD 1997 - 2010

GDR	Descripción	Recuento	%	% acumulado
127	Insuficiencia cardiaca & shock	267.623,00	4,91	4,91
541	Neumonía simple y otros trast.respiratorios exc. bronquitis & asma con CC mayor	251.175,00	4,61	9,52
294	Diabetes edad>35	163.477,00	3,00	12,52
14	Ictus con infarto	155.419,00	2,85	15,38
544	ICC & arritmia cardiaca con CC mayor	127.003,00	2,33	17,71
140	Angina de pecho	109.258,00	2,01	19,71
88	Enfermedad pulmonar obstructiva crónica	101.683,00	1,87	21,58
295	Diabetes edad<36	78.009,00	1,43	23,01
89	Neumonía simple & pleuritis edad>17 con CC	73.203,00	1,34	24,36
87	Edema pulmonar & insuficiencia respiratoria	69.772,00	1,28	25,64
122	Trast. circulatorios con IAM sin compl. mayores alta con vida	65.979,00	1,21	26,85
15	Accidente cerebrovascular no especifico & oclusión precerebral sin infarto	61.382,00	1,13	27,97

Gómez-Huelgas R (in press)

Evolución del índice de Charlson en la población diabética hospitalizada

CMBD 1997 - 2010

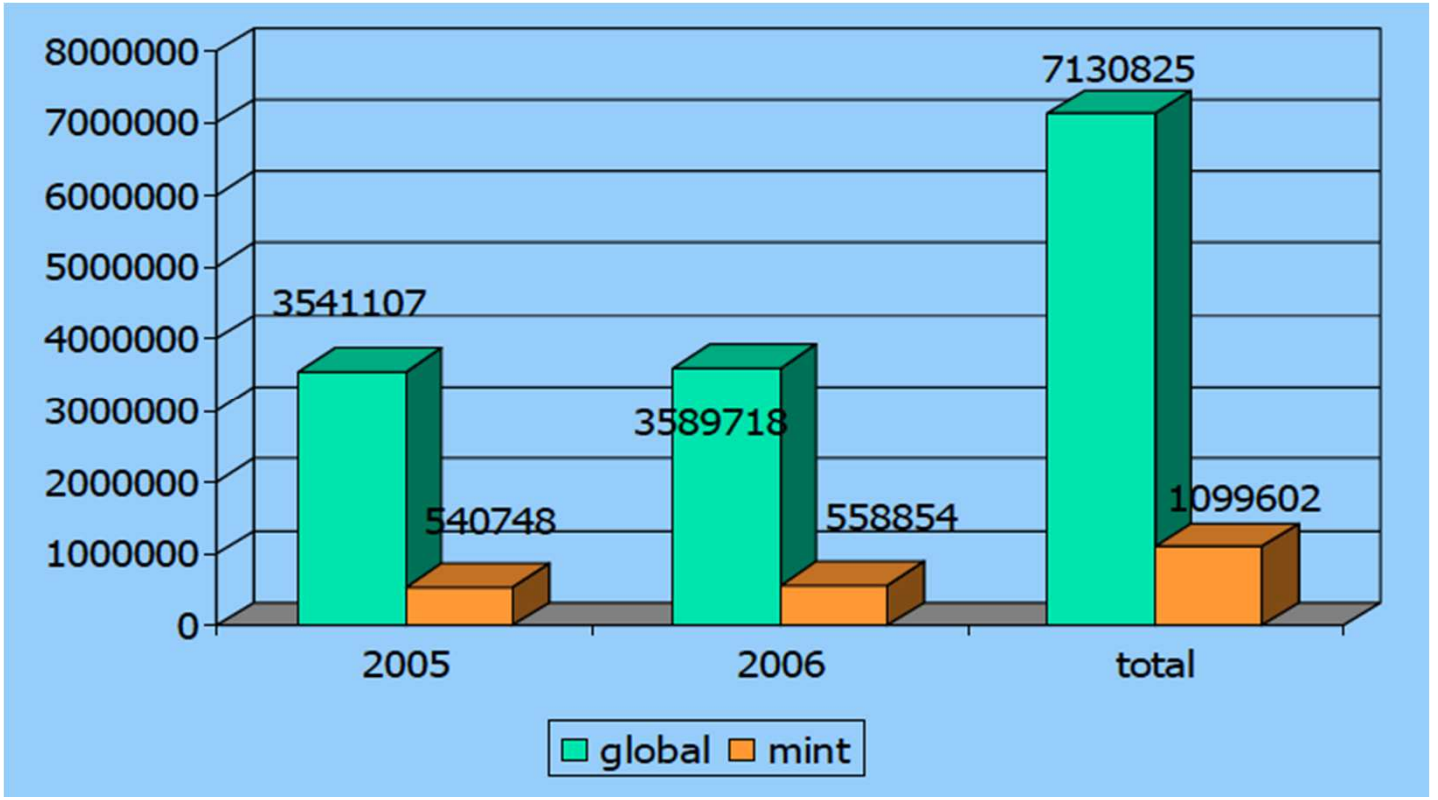


	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
I. Charlson	2,14	2,22	2,22	2,25	2,31	2,32	2,4	2,43	2,45	2,45	2,47	2,52	2,55	2,58

Gómez-Huelgas R (in press)

Los servicios de Medicina Interna son responsables del 15,4% de las altas hospitalarias en España

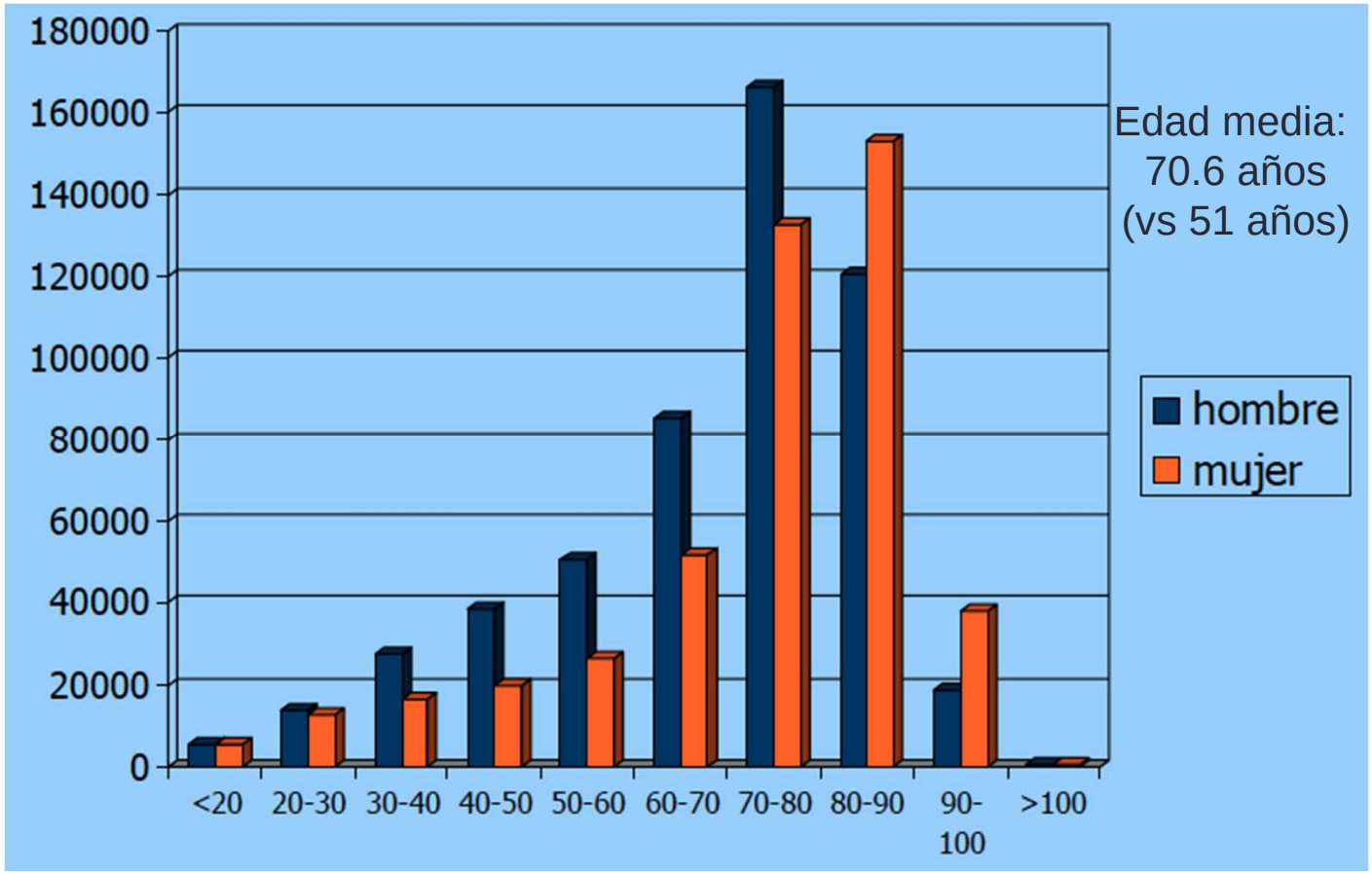
Análisis del CMBD 2005-2006



Barba R. Rev Clin Esp 2009

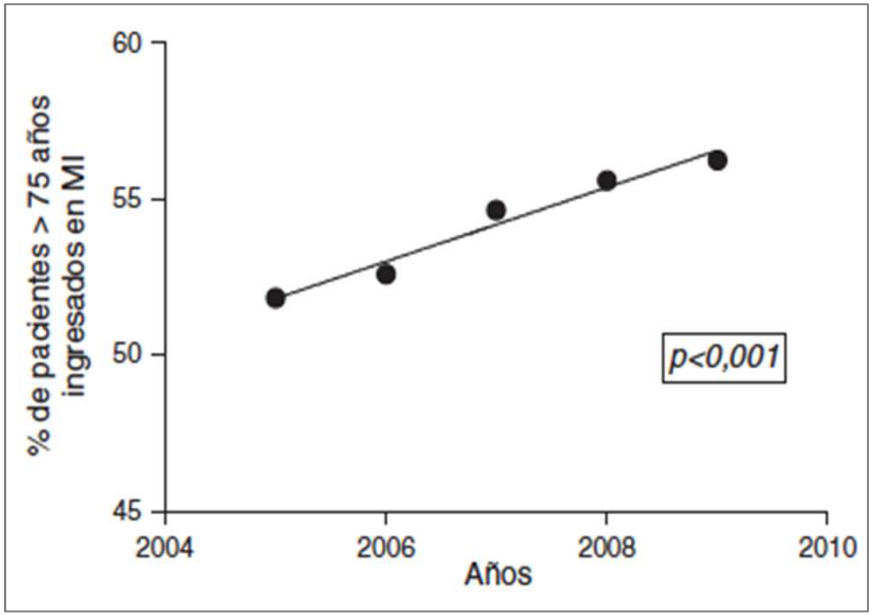
Análisis de 1 millón de altas hospitalarias en Medicina Interna

CMBD 2005-2006

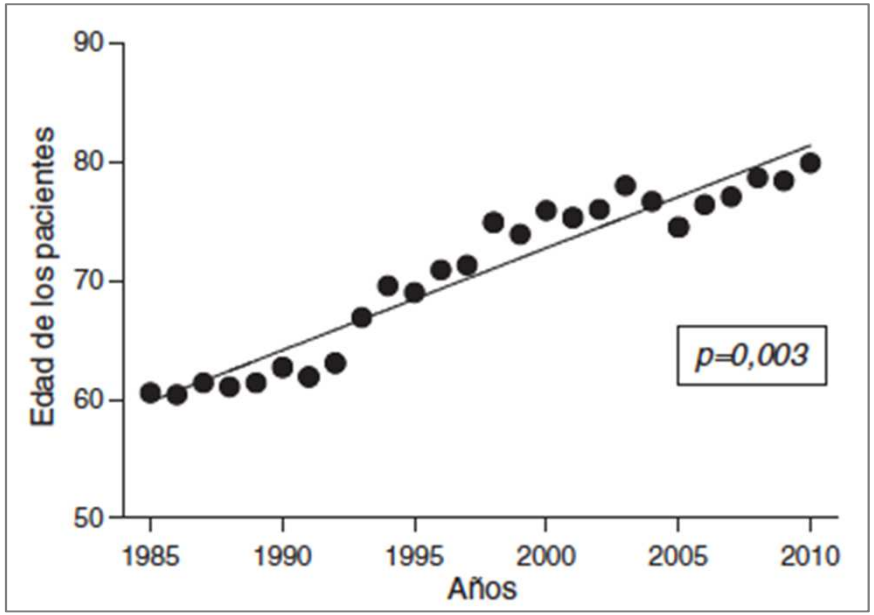


Barba R. Rev Clin Esp 2009

Age of patients hospitalized in Spanish Internal Medicine Departments



Fuente: CMBD

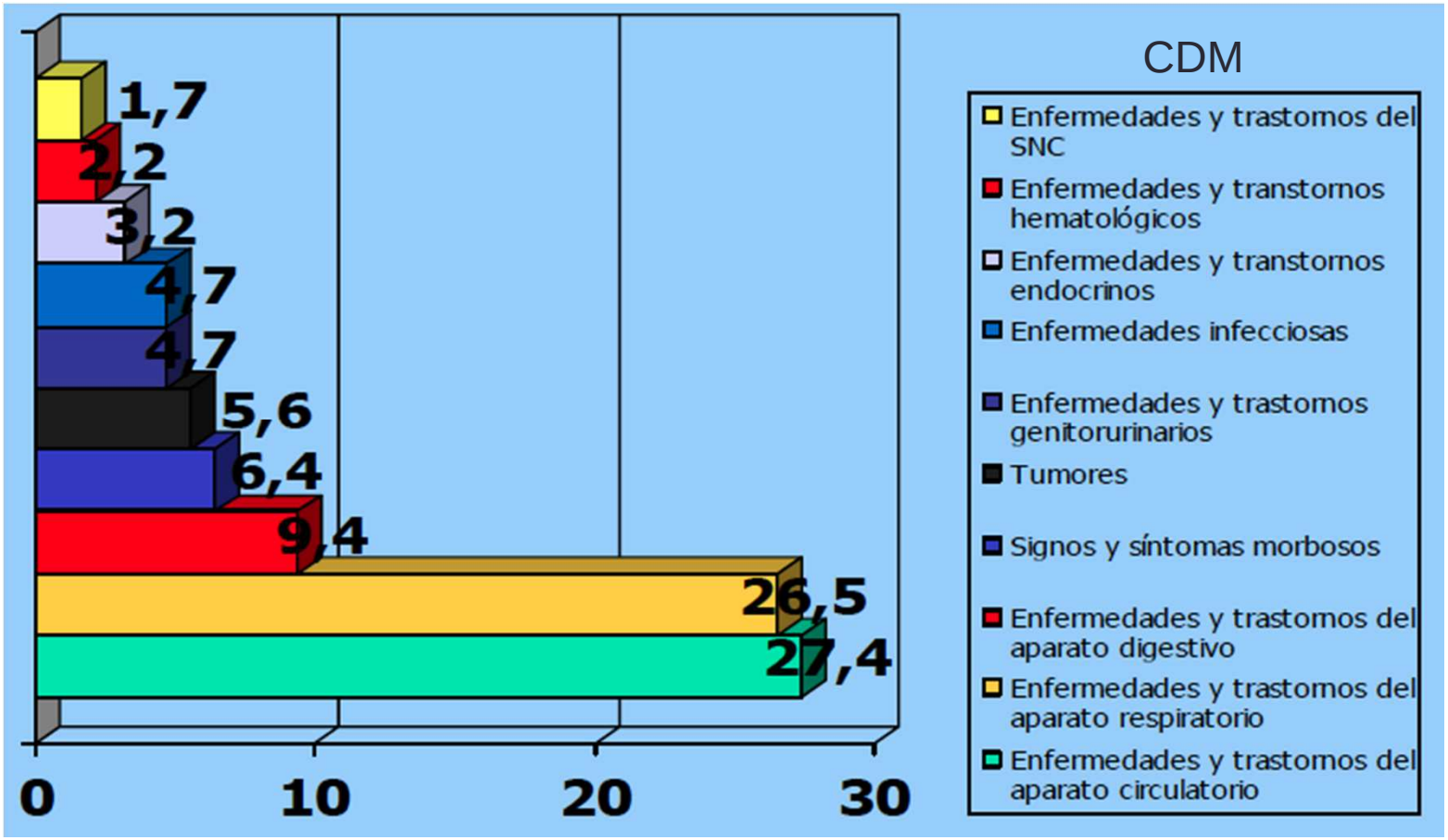


Fuente: Hospital Santa Creu i Sant Pau (Barc)

Casademont J. Med Clin 2012

Análisis de 1 millón de altas hospitalarias en Medicina Interna

CMBD 2005-2006



Barba R. Rev Clin Esp 2009

Diagnósticos principales más frecuentes en Medicina Interna

CMBD 2005-2006

CIE-9	Descripción	N.º (%)
428.0	Insuficiencia cardiaca	54.469 (5,5%)
491.21	Bronquitis crónica con exacerbación	50.865 (5,2%)
486	Neumonía, organismo no especificado	49.411 (5,0%)
519.8	Otras enfermedades del aparato respiratorio no clasificadas	32.186 (3,3%)
599.0	Infección del tracto urinario de sitio no especificado	25.140 (2,6%)
518.81	Fracaso respiratorio agudo	19.238 (2,0%)
434.91	Oclusión arteria cerebral con infarto cerebral	18.268 (1,9%)
481	Neumonía neumocócica	16.145 (1,6%)
428.1	Insuficiencia cardiaca izquierda	14.481 (1,5%)
466.2	Bronquitis y bronquiolitis aguda	13.967 (1,4%)

Barba R. Rev Clin Esp 2009

Diagnósticos secundarios más frecuentes en Medicina Interna

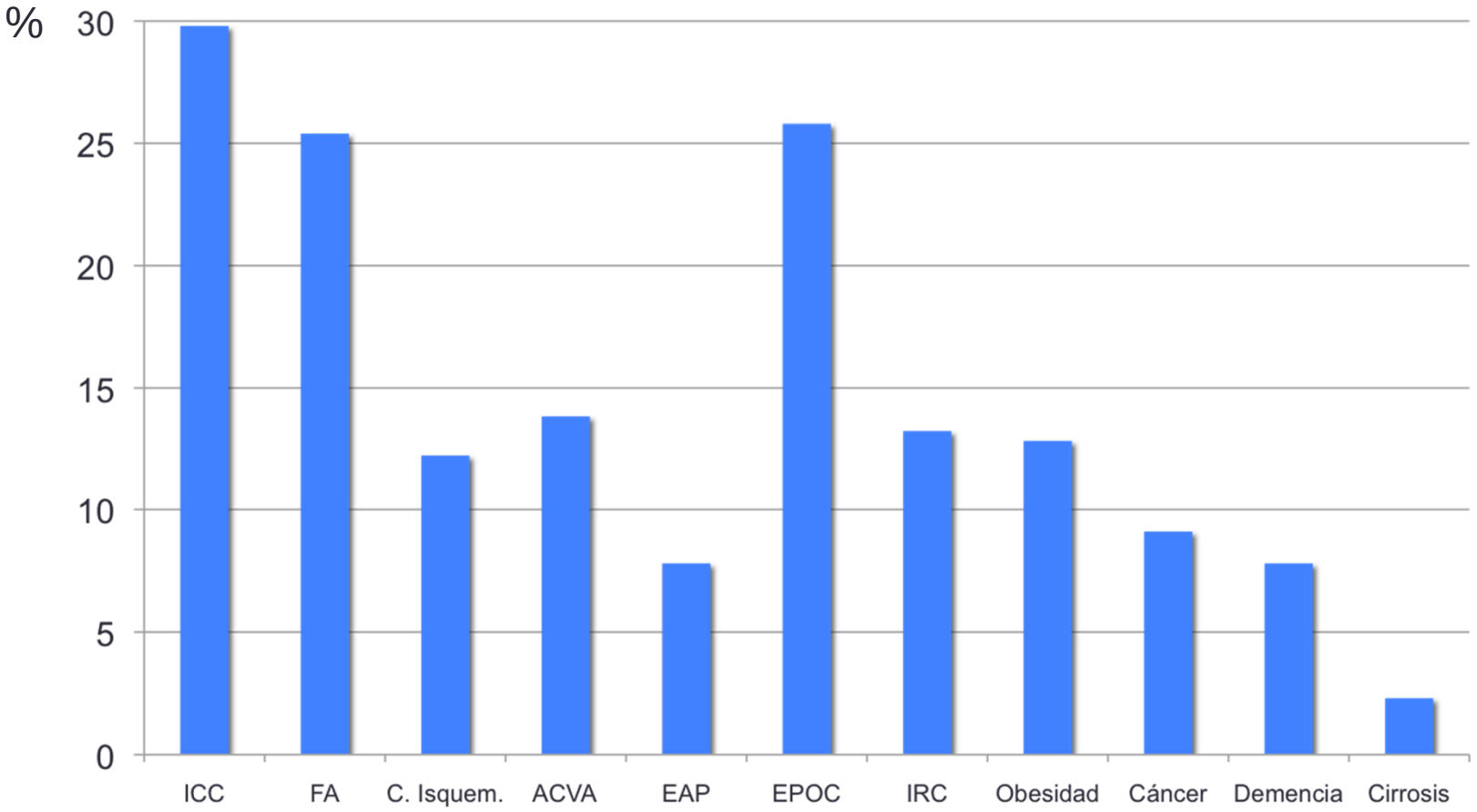
CMBD 2005-2006

CIE-9	Diagnósticos	N.º de pacientes (%)
401.9	Hipertensión arterial	286.495 (29,1%)
250.0	Diabetes mellitus	255.022 (25,9%)
427.3	Fibrilación auricular	199.000 (20,2%)
272.0, 272.4	Hipercolesterolemia	106.738 (10,9%)
305.1		93.477 (9,5%)
278.0		67.124 (6,8%)
290.xx		66.156 (5,7%)
303; 305.0		31.140 (3,2%)
V11.8		

Peso medio GRD: 1.74
Media de dx: 5.84
Mortalidad: 9.9% (vs 3.9%)

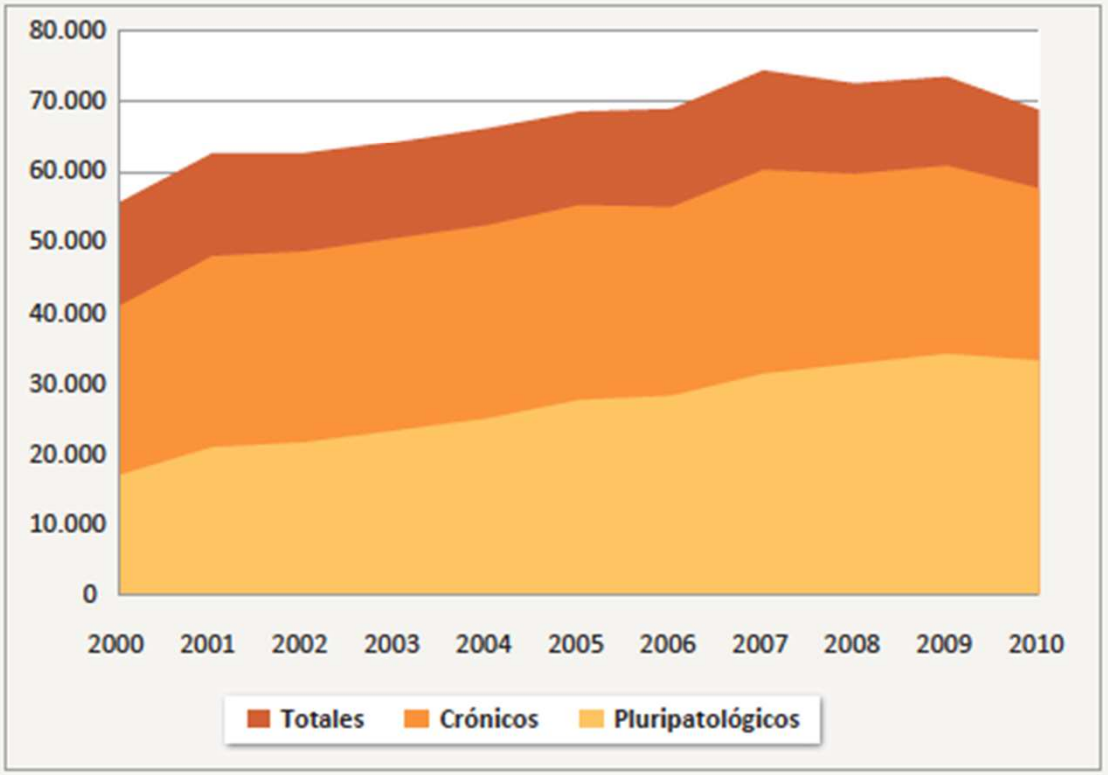
Barba R. Rev Clin Esp 2009

Comorbilidad en la población diabética hospitalizada en MI



Zapatero A. End Pract 2014

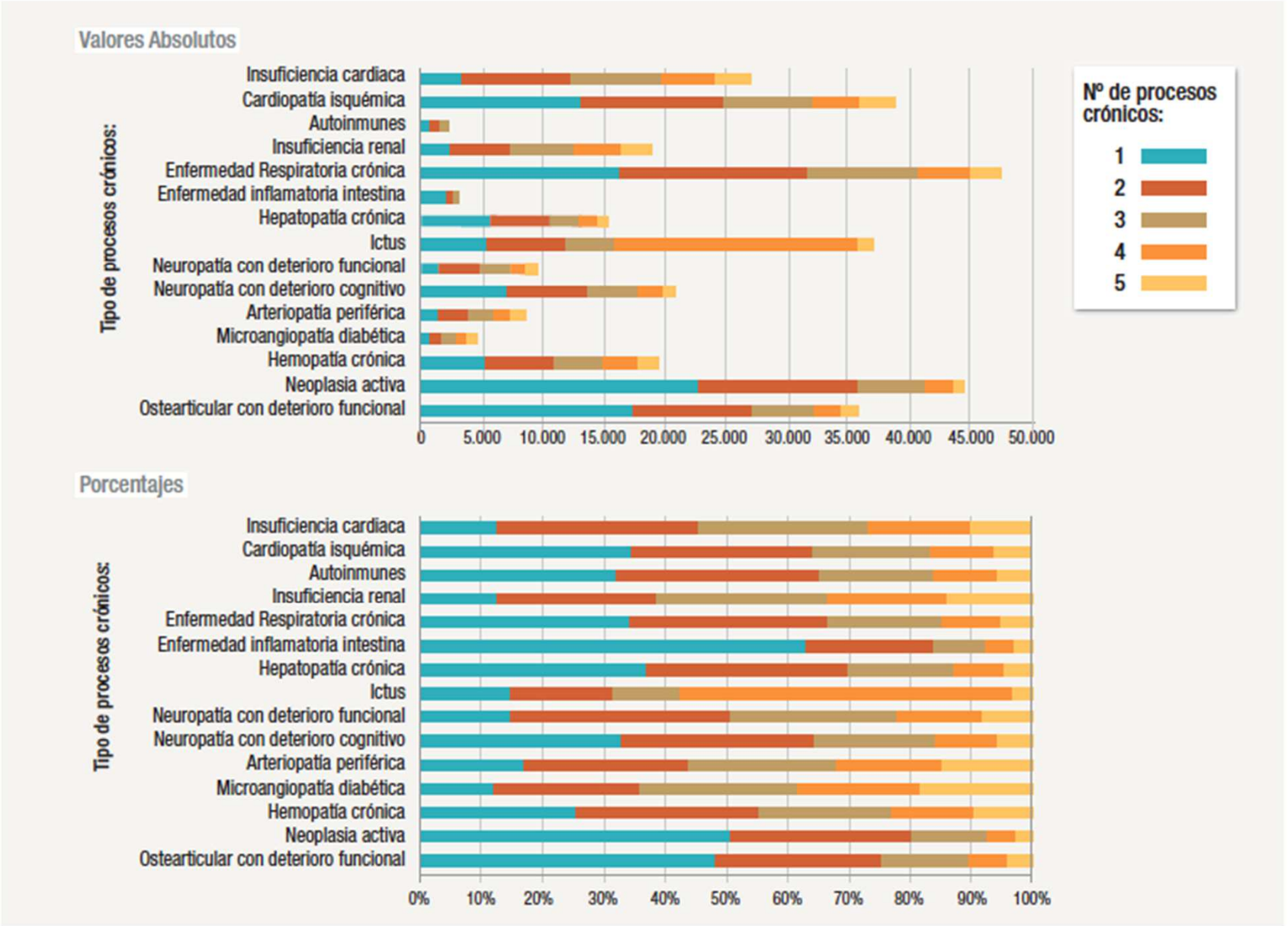
Evolución del número de altas hospitalarias del CMBD del SSPA en el periodo 2000-2010. Servicios de Medicina Interna. Distribución según la presencia de una o más categorías clínicas de la definición de pacientes pluripatológicos. Se considera pluripatología la presencia de dos o más procesos crónicos.



	Año 2000	Año 2010	% Incremento
% sin cronicidad	26,41 %	16,43 %	- 23%
% Cronicidad (≥ 1 enfermedad crónica)*	73,59 %	83,57 %	40,4%
% Pluripatoligía	30,61 %	48,24 %	94,83%
Total Pluripatológico	17.063	33.244	

***Cronicidad:** presencia de una enfermedad crónica invalidante de las incluidas en las categorías del Proceso Atención a Pacientes Pluripatológico. (Ollero y cols 2007)*

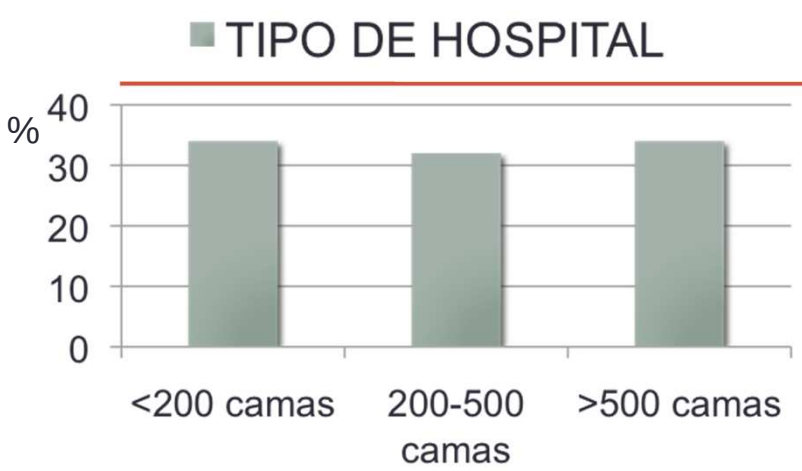
Altas hospitalarias del CMBD del SSPA en el año 2010. Peso de las diferentes categorías clínicas y presencia de pluripatología. Se considera pluripatología la presencia de dos o más procesos crónicos.

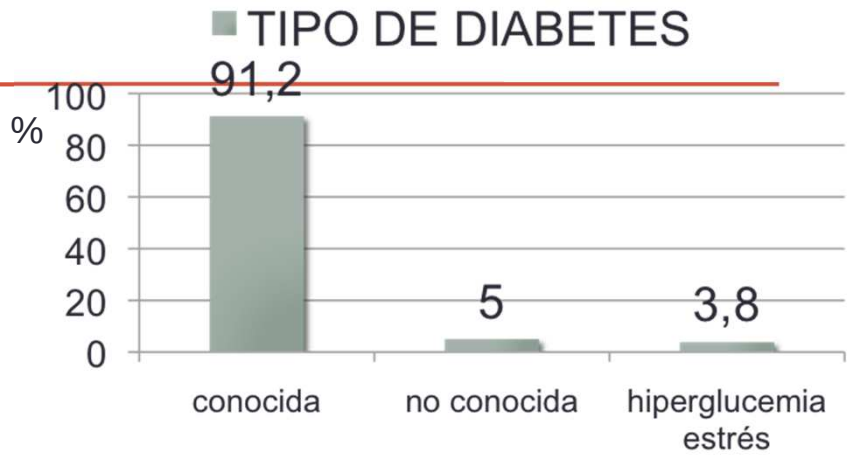


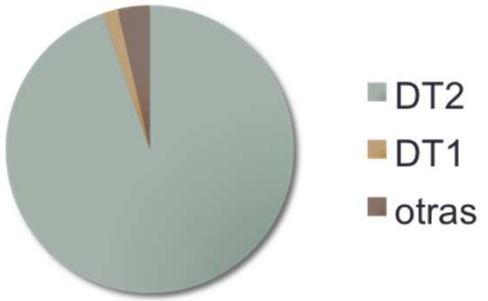
Estudio MIDIA

- Nº pacientes: 5439
- Nº hospitales: 111
- CCAA participantes: 17

- Nª pacientes con hiperglucemia: 1000
- Tasa de hiperglucemia hospitalaria: 18,4%





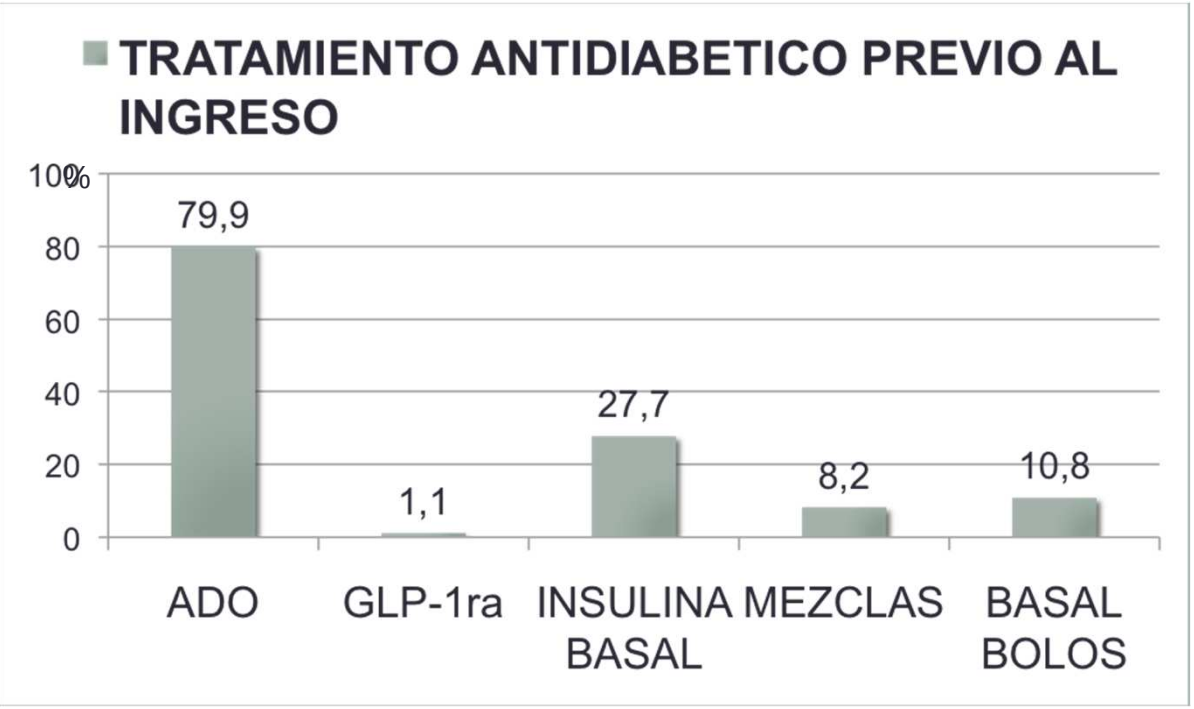


Ena J (in press)

Estudio MIDIA

Características de la población

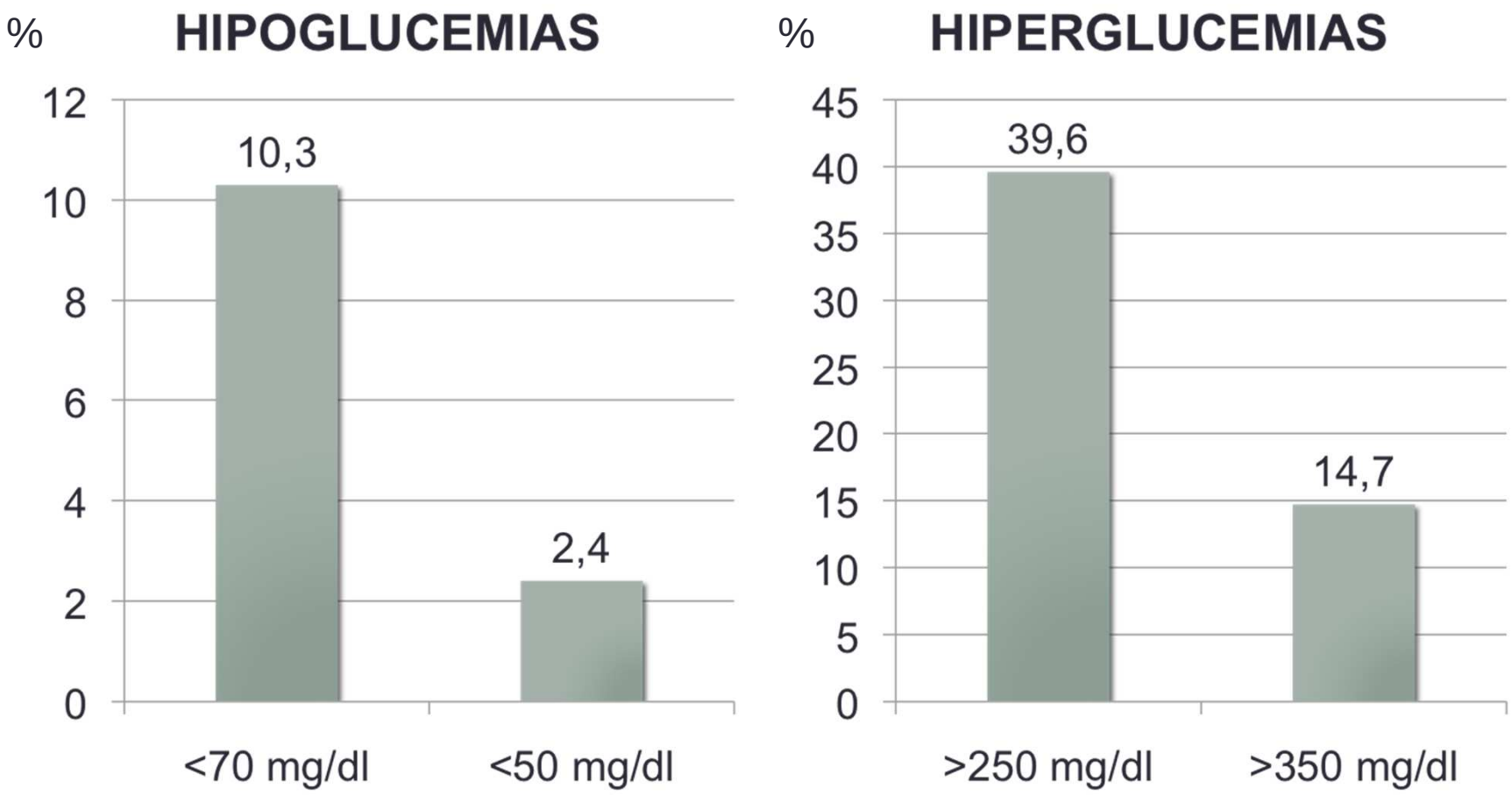
- Hombres: 52%
- Edad: 76,1 ± 10,7
- Duración de la diabetes: 11 ± 8,5 años
- HbA1c media: 7,2 ± 1,7 %
- Nº diagnósticos: 4
- Depencia ABVD: 1/3
- Tto glucocorticoideo: 24,5%
- Nutrición artificial: 7,7%



Ena J (in press)

Estudio MIDIA

Tasa de hipoglucemias y de hiperglucemias en pacientes hospitalizados en Servicios de Medicina Interna en España



Ena J (in press)

AGENDA

1. **¿Cuál es el perfil del paciente con diabetes atendido por Medicina Interna?**

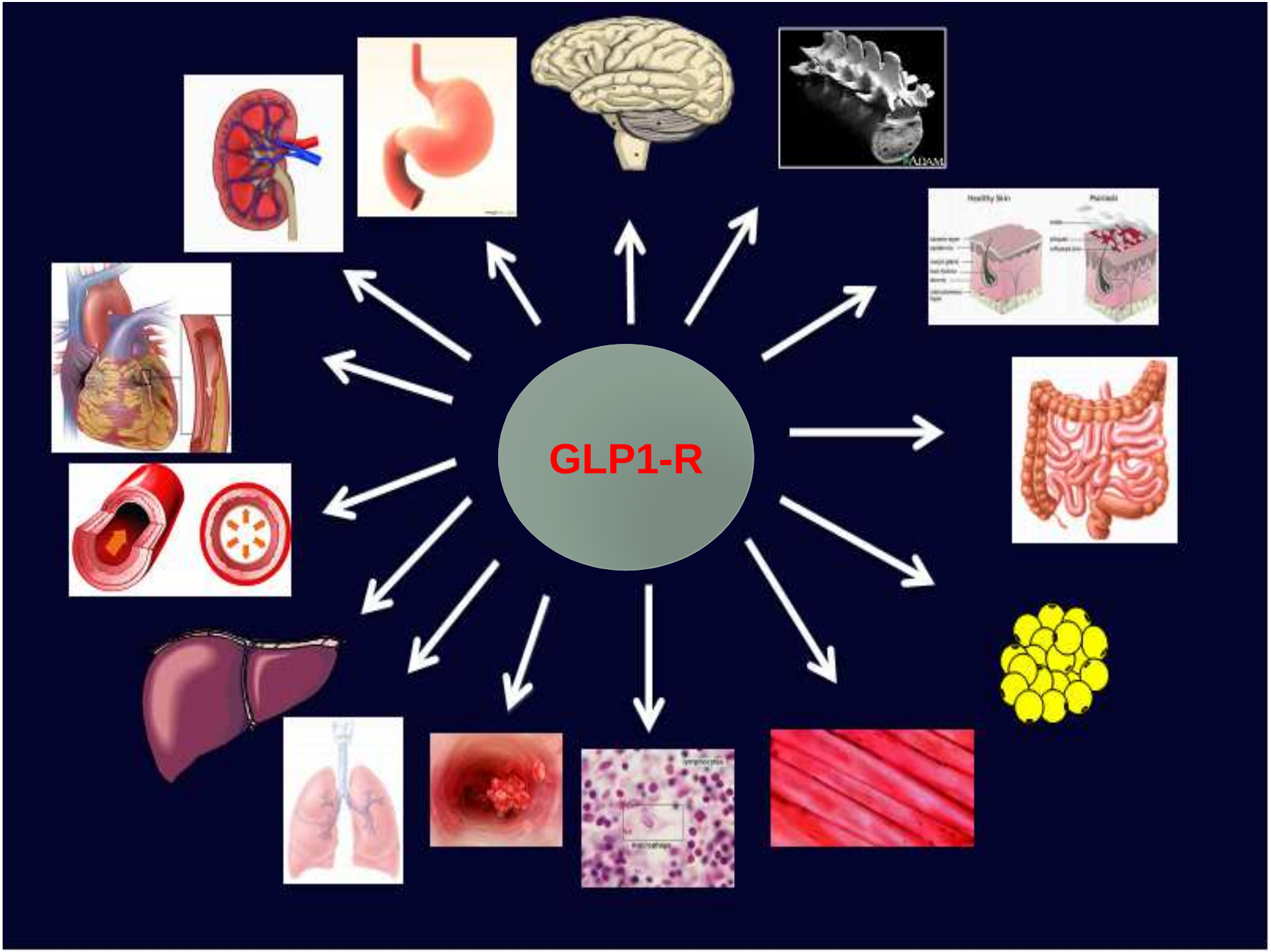
    - Elevada prevalencia de diabetes en pacientes hospitalizados
    - Edad avanzada
    - Multicomorbilidad (cardiorrespiratoria)
    - Alta complejidad
    - Factores diabetógenos: esteroides, nutrición artificial
    - Riesgo de hipoglucemia

AGENDA

1. ¿Cuál es el perfil del paciente con diabetes atendido por Medicina Interna?

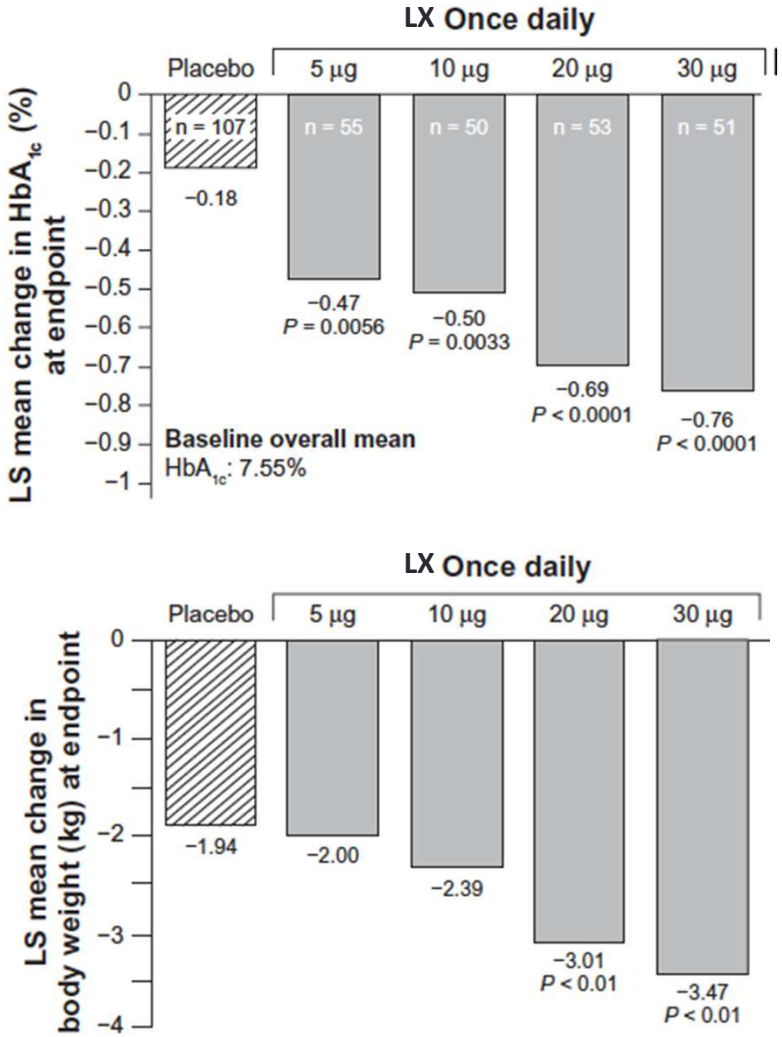
2. Papel de los AR-GLP1 en situaciones especiales

- RIESGO CARDIOVASCULAR
- ANCIANOS
- ALTA HOSPITALARIA
- HIPERGLUCEMIA INDUCIDA POR GLUCOCORTICOIDES
- INSUFICIENCIA RENAL
- INSUFICIENCIA HEPATICA
- COMORBILIDAD ASOCIADA A OBESIDAD
- OTRAS: demencia, osteoporosis, psoriasis


GLP1-R

CONTROL GLUCEMICO SEGURO

Descenso HbA1c + No hipoglucemias + Pérdida de peso



Barnett AH, 2011

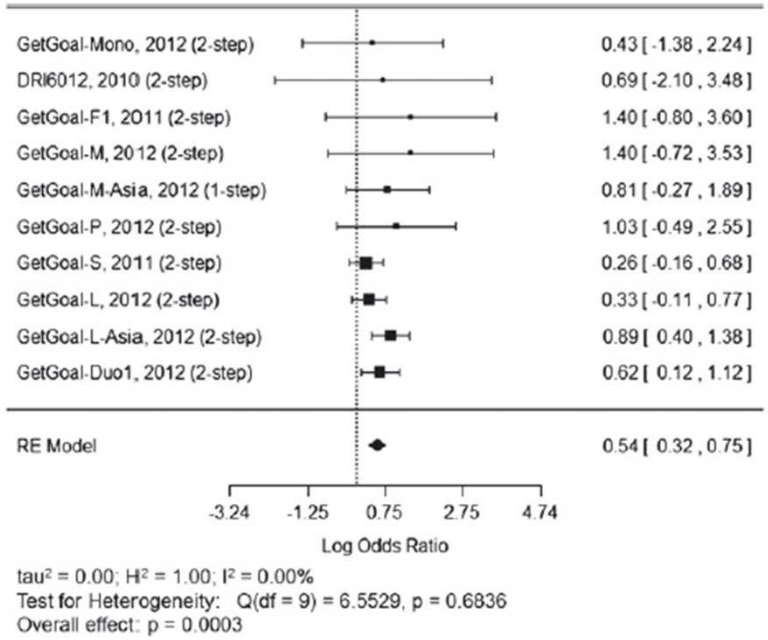


Figure 3. Meta-analysis of symptomatic hypoglycaemic events (lixisenatide vs. placebo).

Schmidt J, 2014

Efficacy of GLP-1RA and DPP-4-I added to Metformin: Meta-Analysis from 80 RCT

GLP-1RA

- higher efficacy
- weight reduction

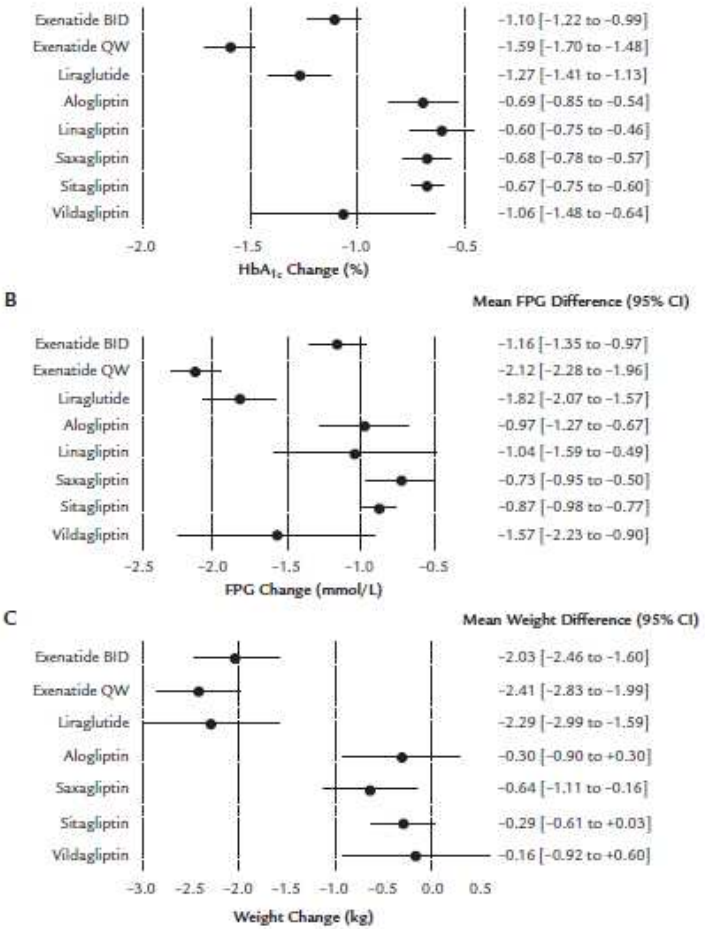


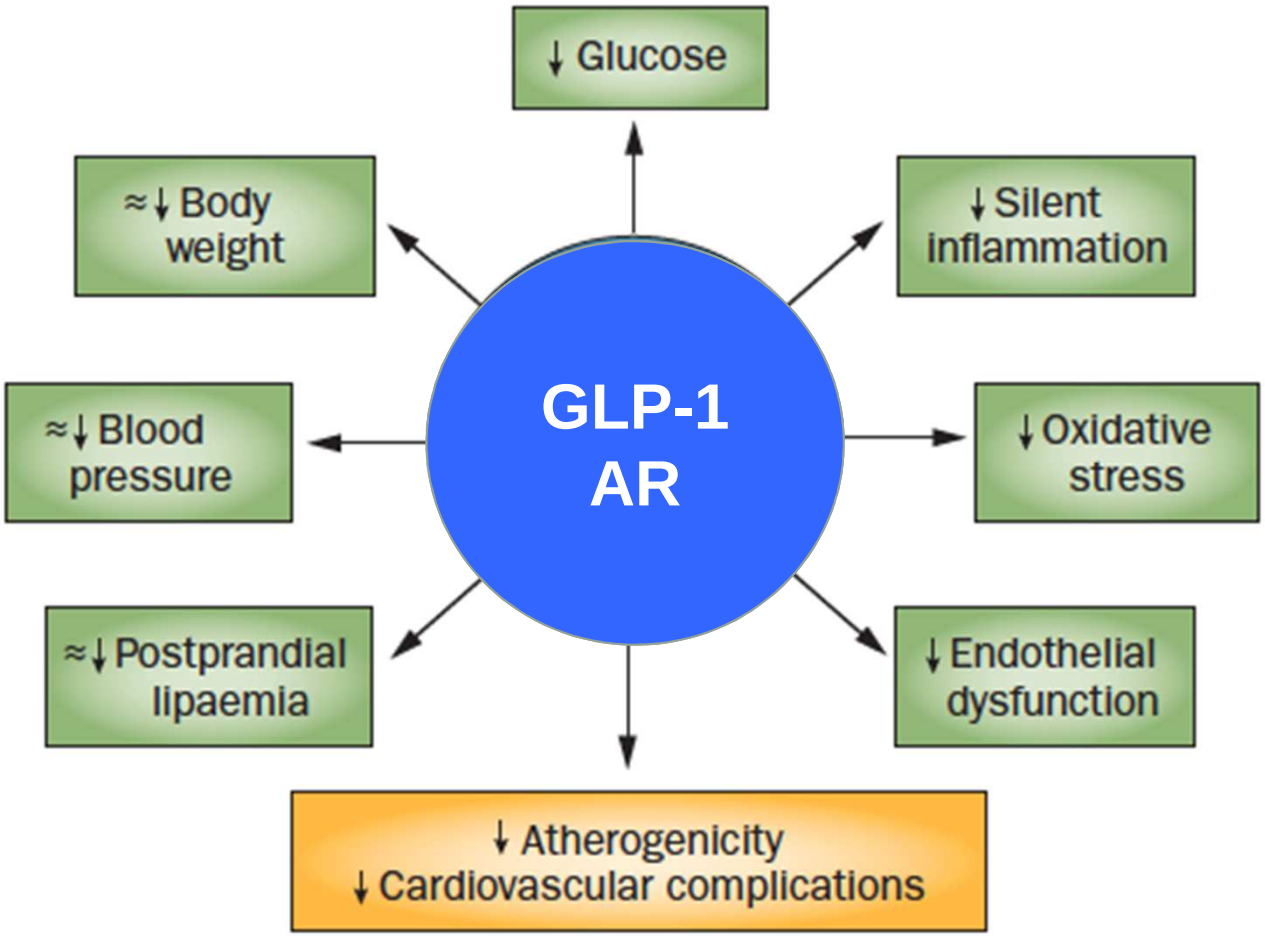
Figure 2. Overall mean changes from baseline in (A) hemoglobin A_{1c} (HbA_{1c}), (B) fasting plasma glucose (FPG), and (C) weight with the use of glucagon-like peptide 1 receptor agonists (GLP-1RAs) or dipeptidyl-peptidase IV (DPP-4) inhibitors at the highest maintenance doses evaluated in this meta-analysis and systemic review of the efficacy of incretin-based therapies in type 2 diabetes mellitus.

DPP-4-I

- lower efficacy
- weight neutral
- better GI tolerance

Aroda VR. Clin Ther 2012

EFECTO DEL GLP-1 EN LOS FACTORES DE RIESGO VASCULAR EN PACIENTES CON DIABETES TIPO 2



(-) platelet aggregation
(+) myocardial glucose uptake
(-) proliferation
(+) plaque stability

2013, 11:84
JOURNAL OF TRANSLATIONAL MEDICINE

Cardioprotective effects of lixisenatide in rat myocardial ischemia-reperfusion injury studies

Paulus Wohlfart[1*], Wolfgang Linz[1], Thomas Hübschle[1], Dominik Linz[2], Jochen Huber[1,3], Sibylle Hess[1], Daniel Crowther[1], Ulrich Werner[1] and Hartmut Ruetten[1]

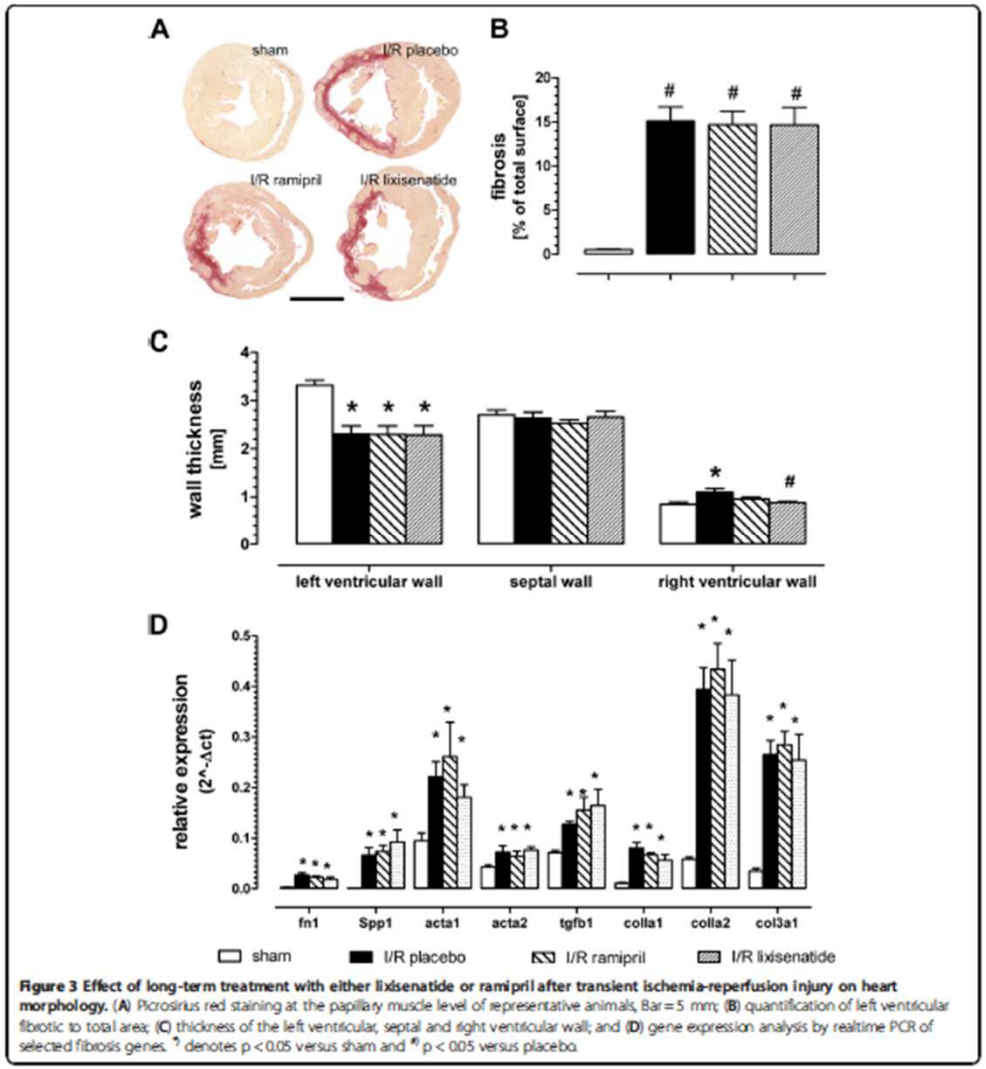


Figure 3 Effect of long-term treatment with either lixisenatide or ramipril after transient ischemia-reperfusion injury on heart morphology. (**A**) Picrosirius red staining at the papillary muscle level of representative animals, Bar = 5 mm; (**B**) quantification of left ventricular fibrotic to total area; (**C**) thickness of the left ventricular, septal and right ventricular wall; and (**D**) gene expression analysis by realtime PCR of selected fibrosis genes. * denotes $p < 0.05$ versus sham and # $p < 0.05$ versus placebo.

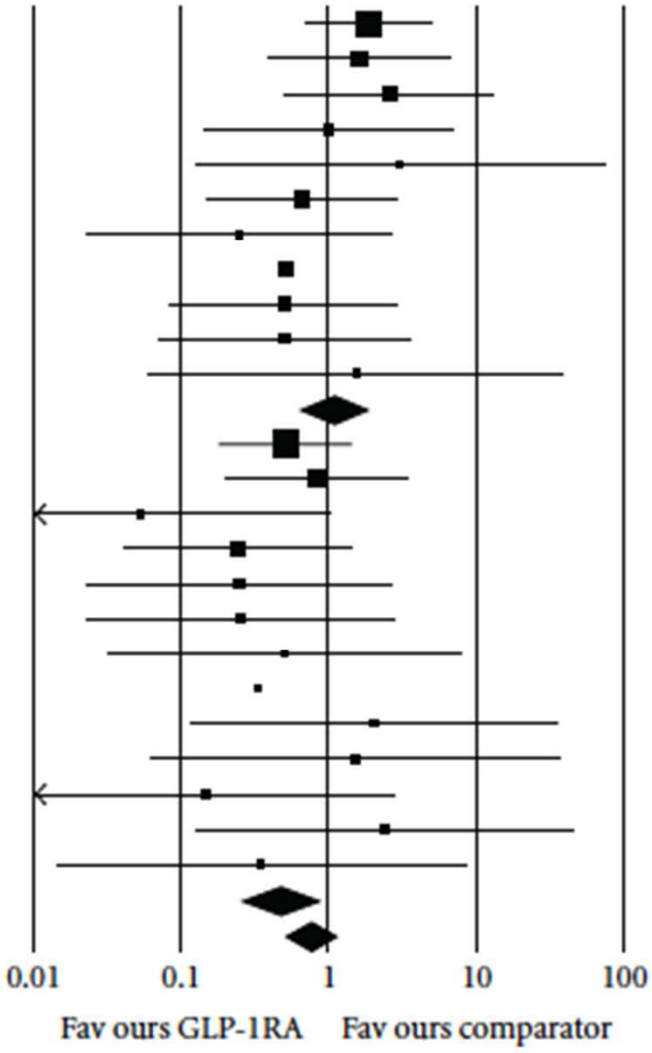
Effect of GLP-1 RA on fatal and nonfatal major CV events

Meta-analysis

Study name	MH odds ratio	Lower limit	Upper limit	*Z* value	*P* value
Nauck et al. [31]	1.833	0.667	5.036	1.176	.24
Heine et al. [34]	1.588	0.376	6.713	0.629	.529
Russell-Jones# et al. [44]	2.555	0.4911	3.304	1.114	.265
NCT00360334 et al. [33]	0.983	0.136	7.096	−0.017	.986
Diamant et al. [36]	3	0.122	74.023	0.672	.502
NCT00393718 et al. [33]	0.652	0.144	2.954	−0.556	.579
Pratley et al. [50]	0.244	0.022	2.704	−1.15	.25
Nauck# et al. [47]	0.497	0.099	2.492	−0.85	.396
NCT00614120 et al. [33]	0.494	0.082	2.976	−0.769	.442
Garber et al. [49]	0.496	0.069	3.542	−0.699	.484
Davis et al. [37]	1.523	0.059	39.477	0.253	.8
Versus active comparators (overall)	1.054	0.633	1.756	0.203	.839
Kendall et al. [28]	0.501	0.174	1.445	−1.279	.201
Russell-Jones et al. [44]	0.822	0.193	3.503	−0.265	.791
Rosenstock et al. [17]	0.053	0.003	1.042	−1.933	.053
Marre et al. [46]	0.243	0.04	1.469	−1.541	.123
Buse et al. [27]	0.245	0.022	2.728	−1.144	.253
DeFronzo et al. [26]	0.25	0.022	2.787	−1.127	.26
Kaku et al. [43]	0.497	0.031	8.043	−0.492	.623
Gao et al. [21]	0.329	0.013	8.119	−0.68	.497
Nauck et al. [47]	2.017	0.113	36.059	0.477	.633
Zinman et al. [45]	1.485	0.06	36.644	0.242	.809
Bergenstal et al. [39]	0.145	0.007	2.823	−1.275	.202
Marre# et al. [46]	2.35	0.121	45.668	0.564	.572
Bergenstal et al. [39]#	0.344	0.014	8.500	−0.652	.514
Versus placebo (overall)	0.459	0.255	0.826	−2.599	.009
Overall	0.737	0.501	1.083	−1.552	.121

Statistics for each study

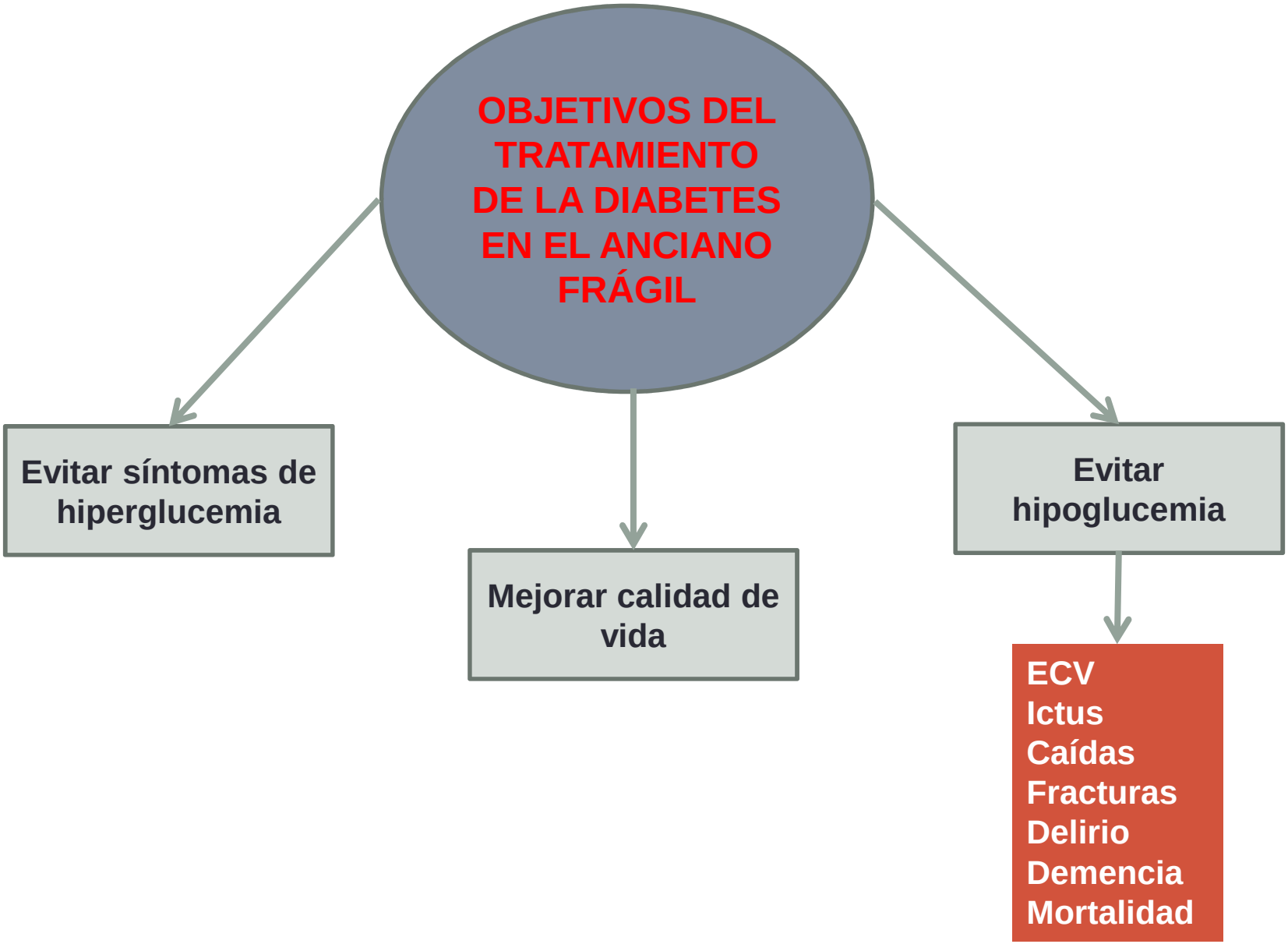
MH odds ratio and 95% CI



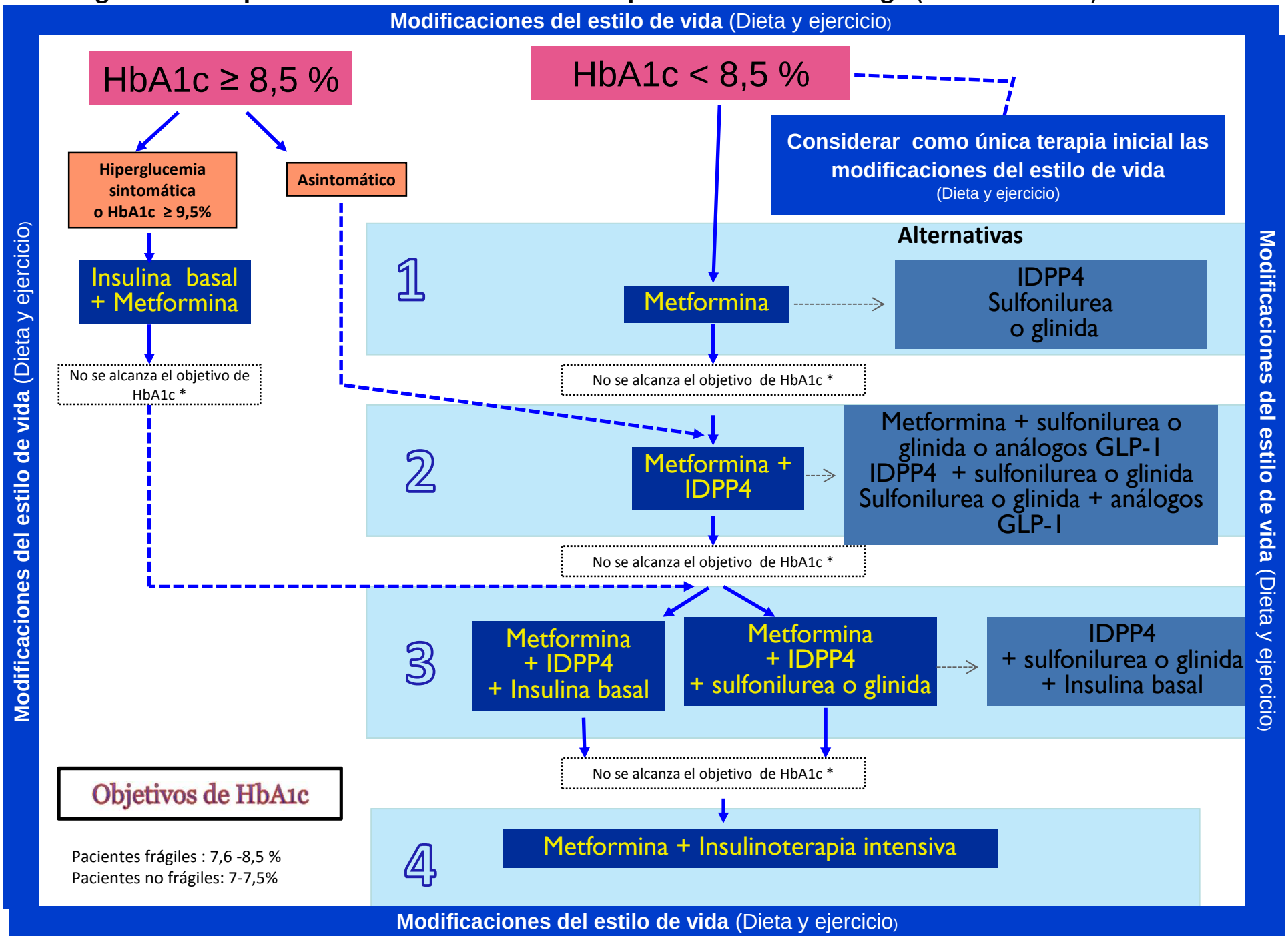
Monami M, 2011

GLP-1RA: CLINICAL TRIALS IN CARDIOVASCULAR SAFETY

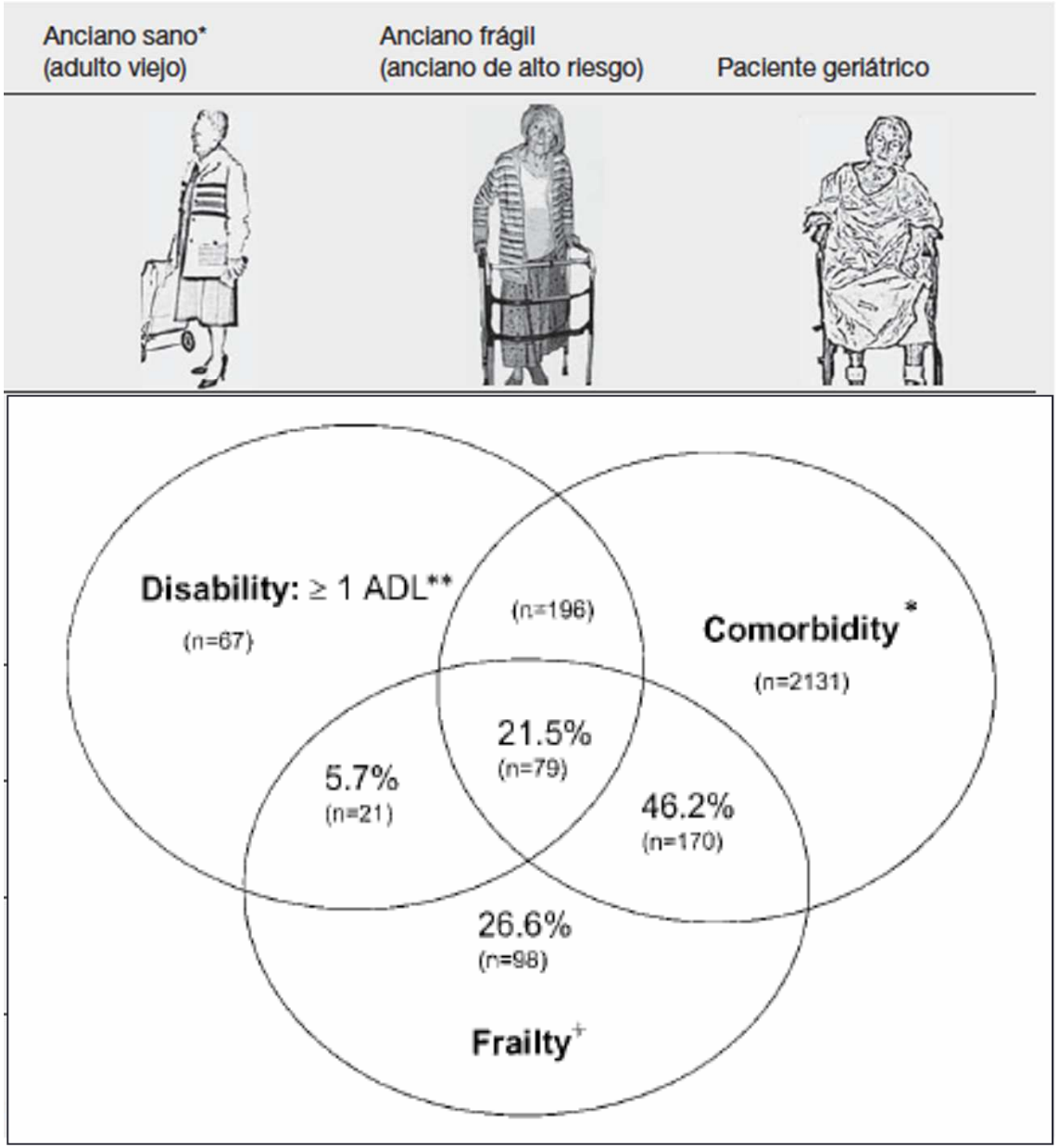
Drug	Study	Start / end	Design	Patients	Main outcome
Exenatide OW	**EXSCEL**	jun 2010 / mar 2017	N: 9500 2 mg OW vs pbo Non-inferiority	HbA1c 6.5-10%	MACE + CF + ACS
Liraglutide	**LEADER**	aug 2010 / jan 2016	N: 9340 1.8 mg vs pbo Non-inferiority and superiority	HbA1c ≥7% ≥50 yr and CVD, CKD or CF; ≥60 yr and high CV risk	MACE
Lixisenatide	**ELIXA**	jun 2010 / may 2014	N: 6000 20 mg/d vs pbo Non-inferiority and superiority	HbA1c 5.5-11% ACS 6 months	MACE + unstable angina
Dulaglutide	**REWIND**	jul 2011 / apr 2019	N: 9600 1.5 mg OW vs pbo Non-inferiority and superiority	HbA1c ≤9.5% ≥50 yr and CVD; ≥55 yr and subc. CVD; ≥60 yr and >2 CVRF	MACE
Albiglutude	**In progress**				


OBJETIVOS DEL TRATAMIENTO DE LA DIABETES EN EL ANCIANO FRÁGIL
Evitar síntomas de hiperglucemia
Mejorar calidad de vida
Evitar hipoglucemia
ECV
Ictus
Caídas
Fracturas
Delirio
Demencia
Mortalidad

Algoritmo terapéutico de la diabetes mellitus tipo 2 en el anciano frágil (Med Clin 2013)



Tipologías de ancianos



GLP-1 AR en ancianos – Fichas técnicas

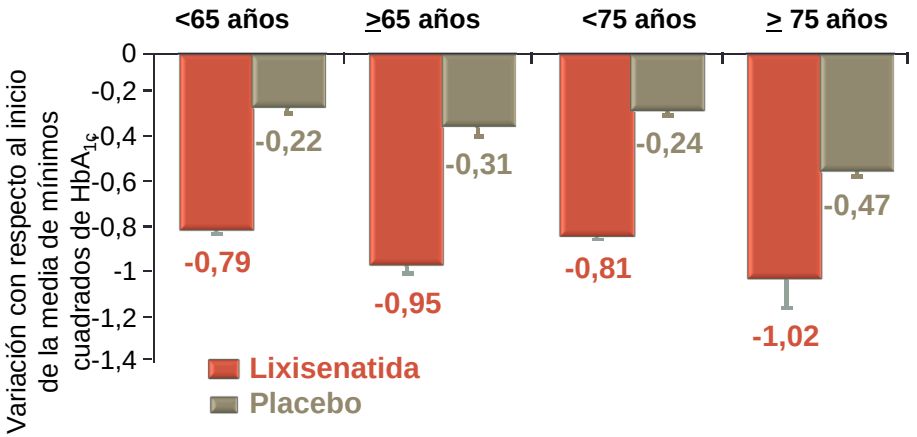
EXENETIDA	Precaución en pacientes > 70 años, escalado cuidadoso de dosis de 5 µg a 10 µg Experiencia clínica en pacientes > 75 años muy limitada
LIRAGLUTIDA	No es necesario ajuste de dosis en pacientes > 65 años Experiencia limitada en ≥ 75 años
EXENATIDA LAR	No es necesario un ajuste de la dosis basado en la edad Experiencia clínica en pacientes > 75 años es muy limitada
LIXISENATIDA	No es necesario ajustar la dosis en función de la edad Experiencia clínica en pacientes ≥ 75 años es limitada

Efecto similar de Lixisenatida sobre la $HbA1_C$ en pacientes ancianos (≥65 años) y muy ancianos (≥75 años) respecto a sujetos más jóvenes

GetGoal meta-análisis

Variación en la media de MC de HbA_{1c}

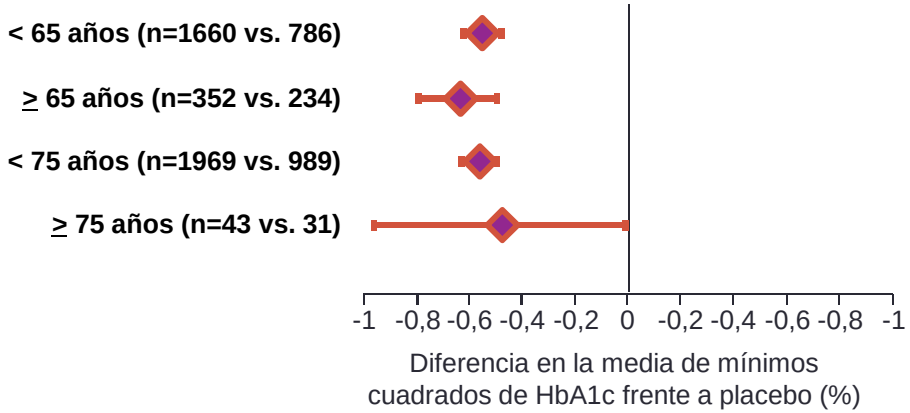
desde el inicio a partir de un metaanálisis
de los datos combinados de seis estudios de fase III



Las barras de error representan los errores estándar; datos del periodo de tratamiento principal de los estudios incluidos (GetGoal-Mono ☯12 semanas❁, GetGoal-M, -F1, -S,
-L, -L-Asia ☯todos 24 semanas❁, - población ITm

Variación en la media de MC de HbA_{1c}

con lixisenatida frente a placebo a partir de un metaanálisis
de los datos combinados de seis estudios de fase III



Las barras de error representan el intervalo de confianza del 95%; Datos del principal periodo de tratamiento de los estudios incluidos (GetGoal-Mono ☯12 weeks❁, GetGoal-M, -F1, -S, -L, -L-Asia ☯todos 24 semanas❁, población ITm

Raccah D., et al. Efficacy and safety of lixisenatide in elderly (≥65 years) and very elderly (≥75 years) patients with type 2 diabetes: an analysis from the GetGoal Phase 3 programme. Poster 815. Presentado en 73th ADA Scientific Sessions. 21-25 Junio 2013 (Chicago). Disponible en: http://www.easdvirtualmeeting.org/resources/1770. Ultimo acceso: junio 2014

Similar ratio de acontecimientos adversos con Lixisenatida en pacientes ancianos (≥65 años) y muy ancianos (≥75 años)

Incidencia de acontecimientos adversos emergentes del tratamiento

	<65 años		≥65 años	<75 años	≥75 años
n (%)	Placebo N=817	LIXI N=1748	LIXI N=379	LIXI N=2079	LIXI N=48
AAET de cualquier índole	516 (63,2%)	1203 (68,8%)	272 (71,8%)	1440 (69,3%)	35 (72,9%)
Trastornos digestivos	170 (20,8%)	715 (40,9%)	164 (43,3%)	857 (41,2%)	22 (45,8%)
Náuseas	47 (5,8%)	446 (25,5%)	110 (29,0%)	540 (26,0%)	16 (33,3%)
Vómitos	13 (1,6%)	170 (9,7%)	54 (14,2%)	218 (10,5%)	6 (12,5%)
Diarrea	53 (6,5%)	141 (8,1%)	35 (9,2%)	173 (8,3%)	3 (6,3%)

Datos del periodo principal de tratamiento de los estudios incluidos (GetGoal-Mono [12 semanas], GetGoal-M, -F1, -S, -L,-L-Asia [todos 24 semanas]) - población de seguridad; AAET = acontecimientos adversos emergentes del tratamiento; LIXI = lixisenatida.

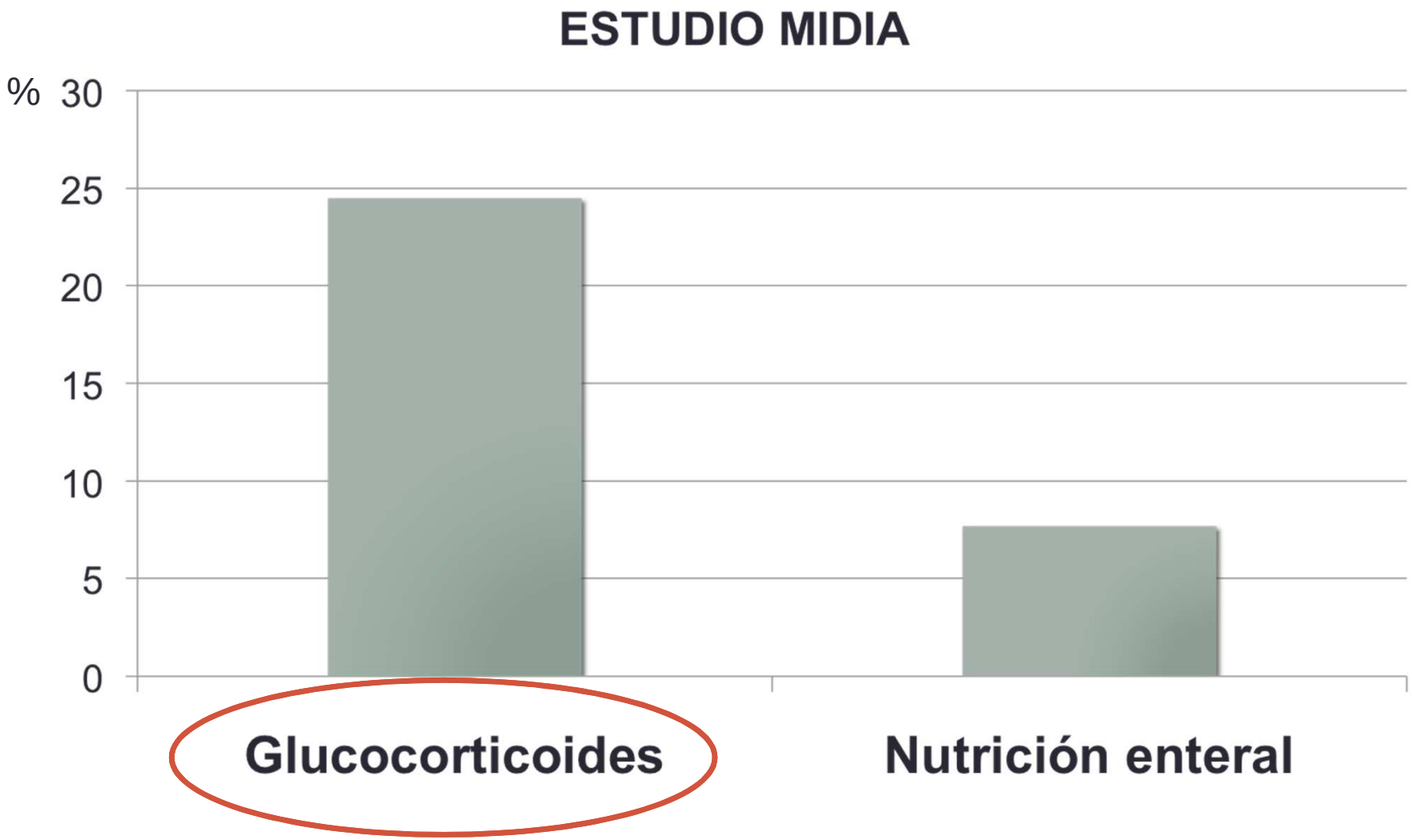
Incidencia de hipoglucemia sintomática con lixisenatida

Tratamiento de base	<65 años		≥65 años	<75 años	≥75 años
n/N (%)	Placebo	LIXI	LIXI	LIXI	LIXI
Monoterapia[a]	1/104 (1,0%)	4/211 (1,9%)	0/28	4/233 (1,7%)	0/6
Metformina[b]	2/258 (0,8%)	21/726 (2,9%)	5/106 (4.7%)	25/822 (3,0%)	1/10 (10,0%)
Insulina basal[c]	9/30 (30,0%)	10/34 (29,4%)	5/12 (41.7%)	15/44 (34,1%)	0/2
Insulina basal ± metformina[d]	29/131 (22,1%)	72/258 (27,9%)	19/70 (27.1%)	89/319 (27,9%)	2/9 (22,2%)

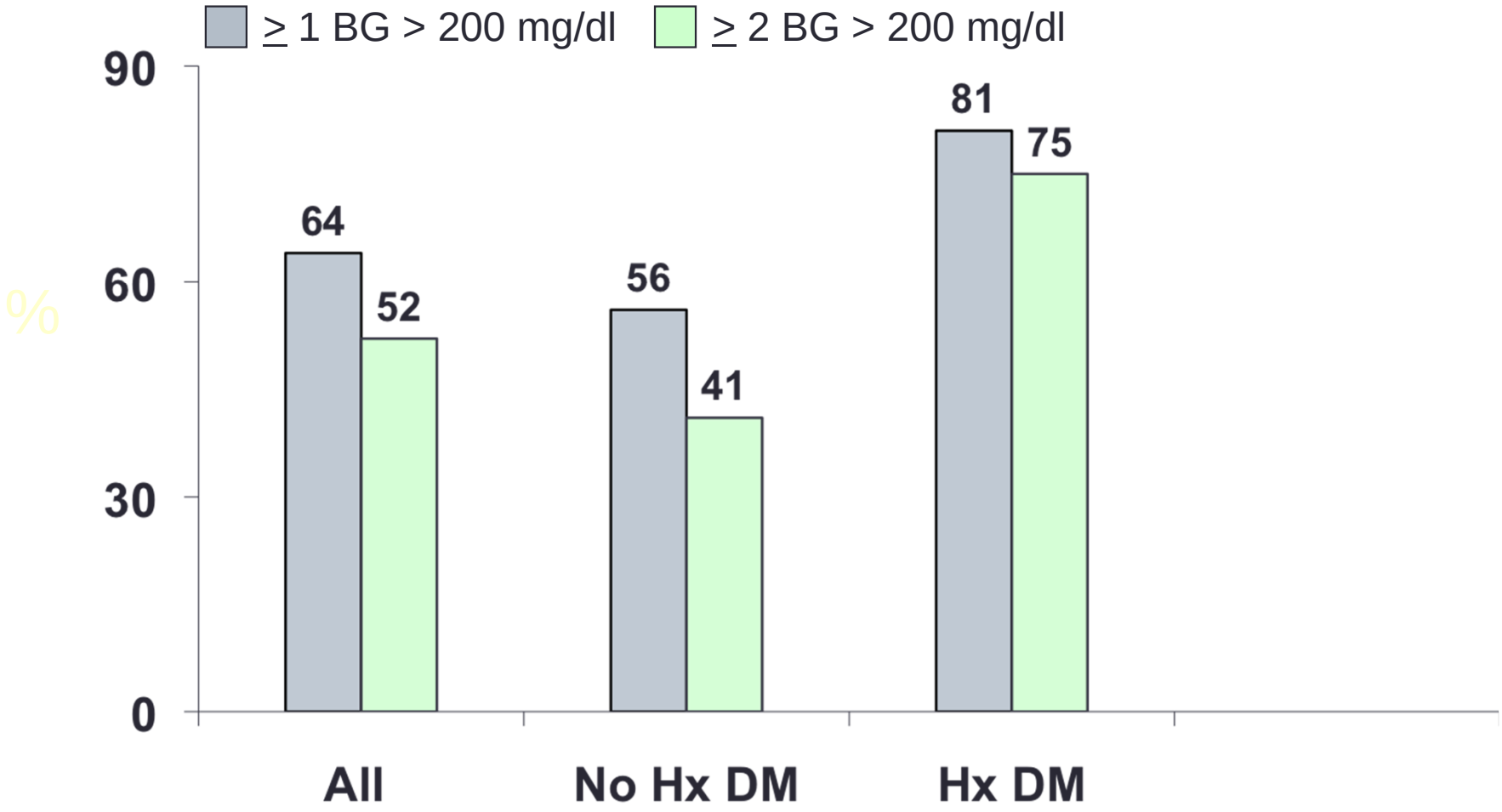
Datos del periodo principal de tratamiento de los estudios incluidos (GetGoal-Monoa [12 semanas], GetGoal-M[b], -F1[b], -L-Asia[c], -Ld, -S[e], [todos 24 semanas]) – población de seguridad; LIXI = lixisenatida; SU=sulfonilurea.

Raccah D., et al. Efficacy and safety of lixisenatide in elderly (≥65 years) and very elderly (≥75 years) patients with type 2 diabetes: an analysis from the GetGoal Phase 3 programme. Poster 815. Presentado en 73th ADA Scientific Sessions. 21-25 Junio 2013 (Chicago). Disponible en: http://www.easdvirtualmeeting.org/resources/1770. Ultimo acceso: junio 2014

Factores hiperglucemiantes en pacientes hospitalizados en Medicina Interna



Prevalencia de hiperglucemia en pacientes tratados con dosis altas de glucocorticoides*

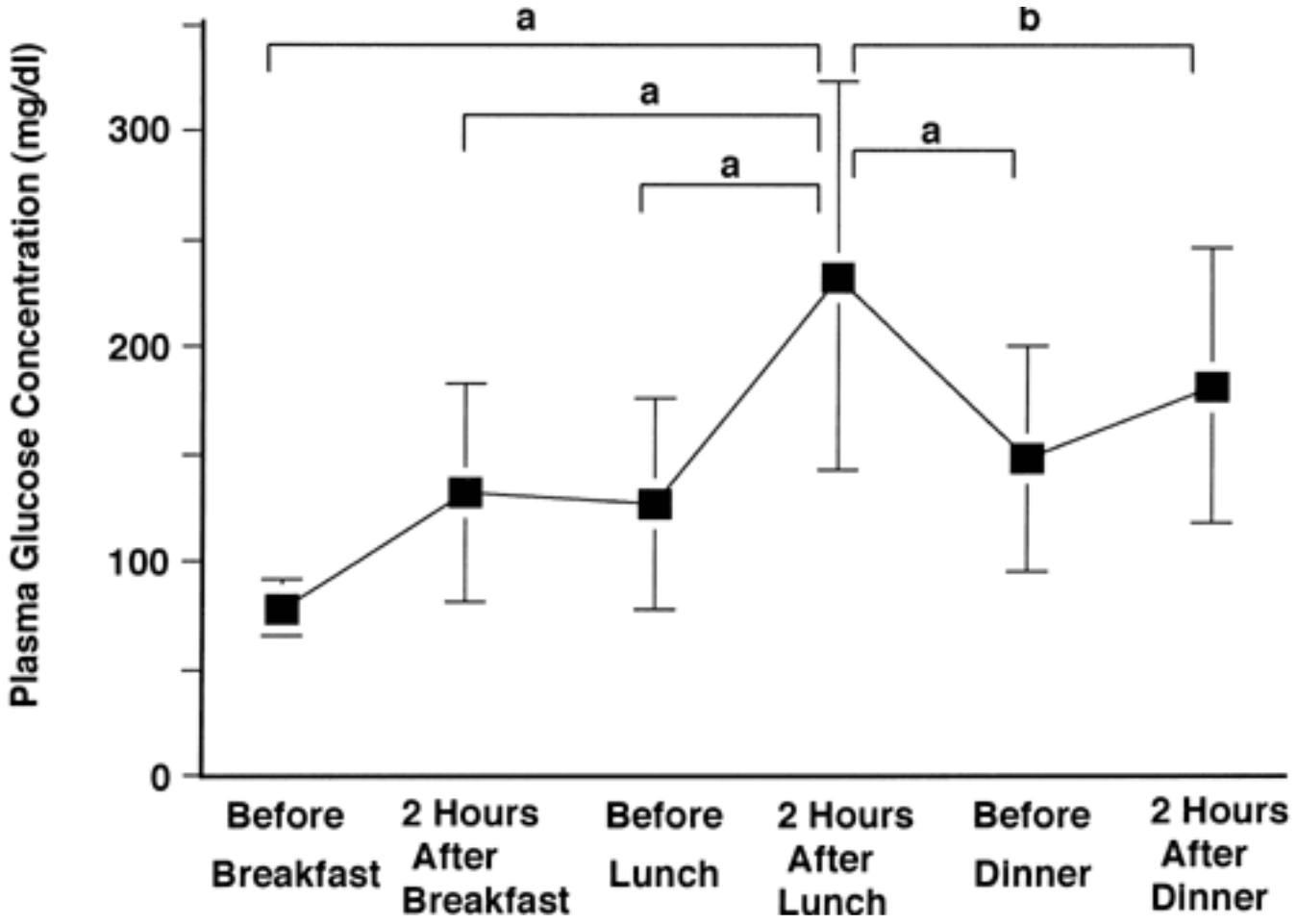


(*≥Prednisone 20 mg or equivalent)

Donihi AD et al. Endocrine Practice 12:358 2006.

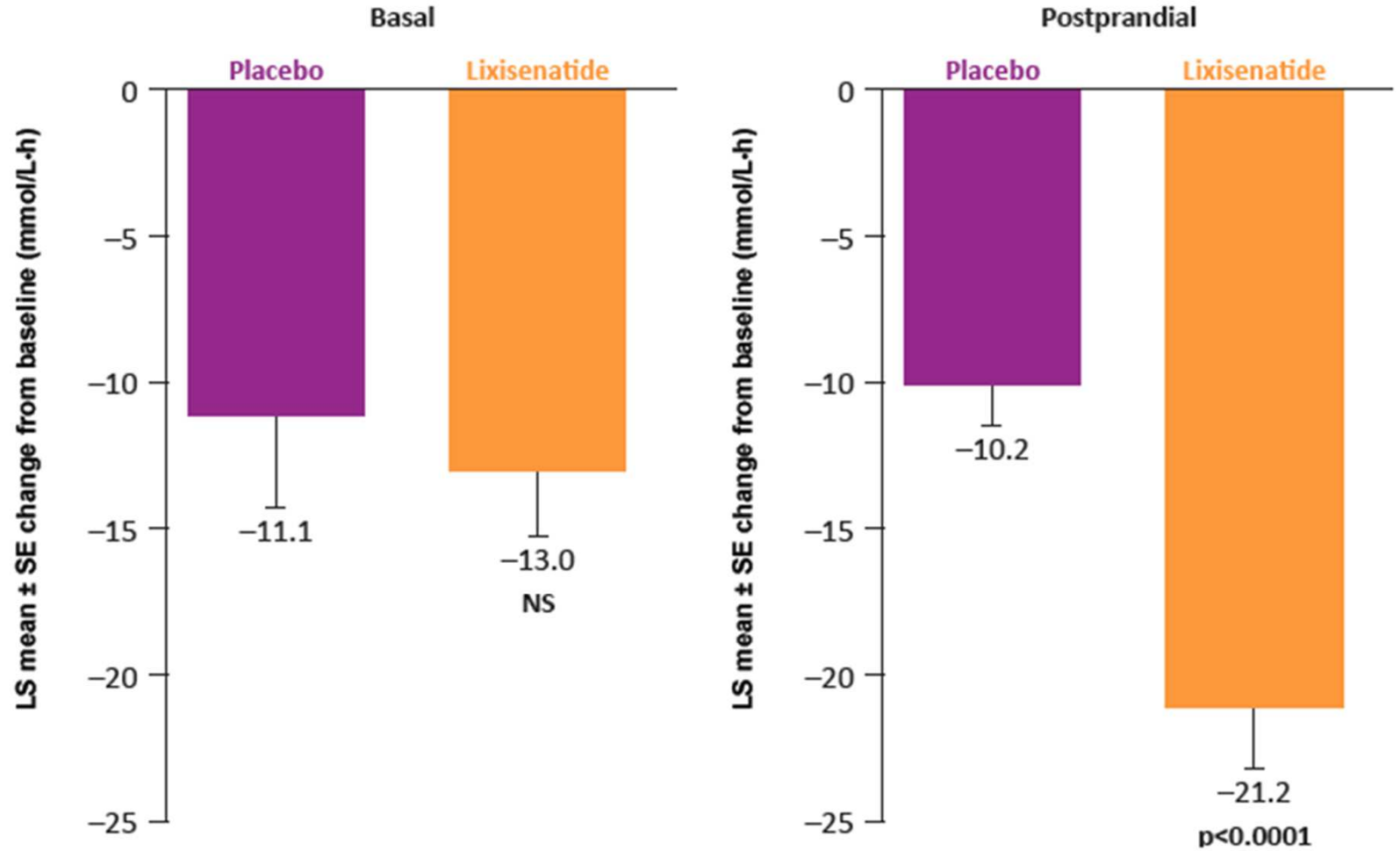
Patrón de la hiperglucemia inducida por glucocorticoides

Monodosis matutina de GC de acción intermedia



Pharmacotherapy 2004

Lixisenatida: GLP-1 AR con marcado efecto postprandial



AUC=area under the curve; LS=least squares; SE=standard error; NS=not significant

Gómez-Huelgas R, EASD 2013

Med Clin (Barc). 2012;xx(x):xxx–xxx

MEDICINA CLINICA

ELSEVIER DOYMA

www.elsevier.es/medicinaclinica

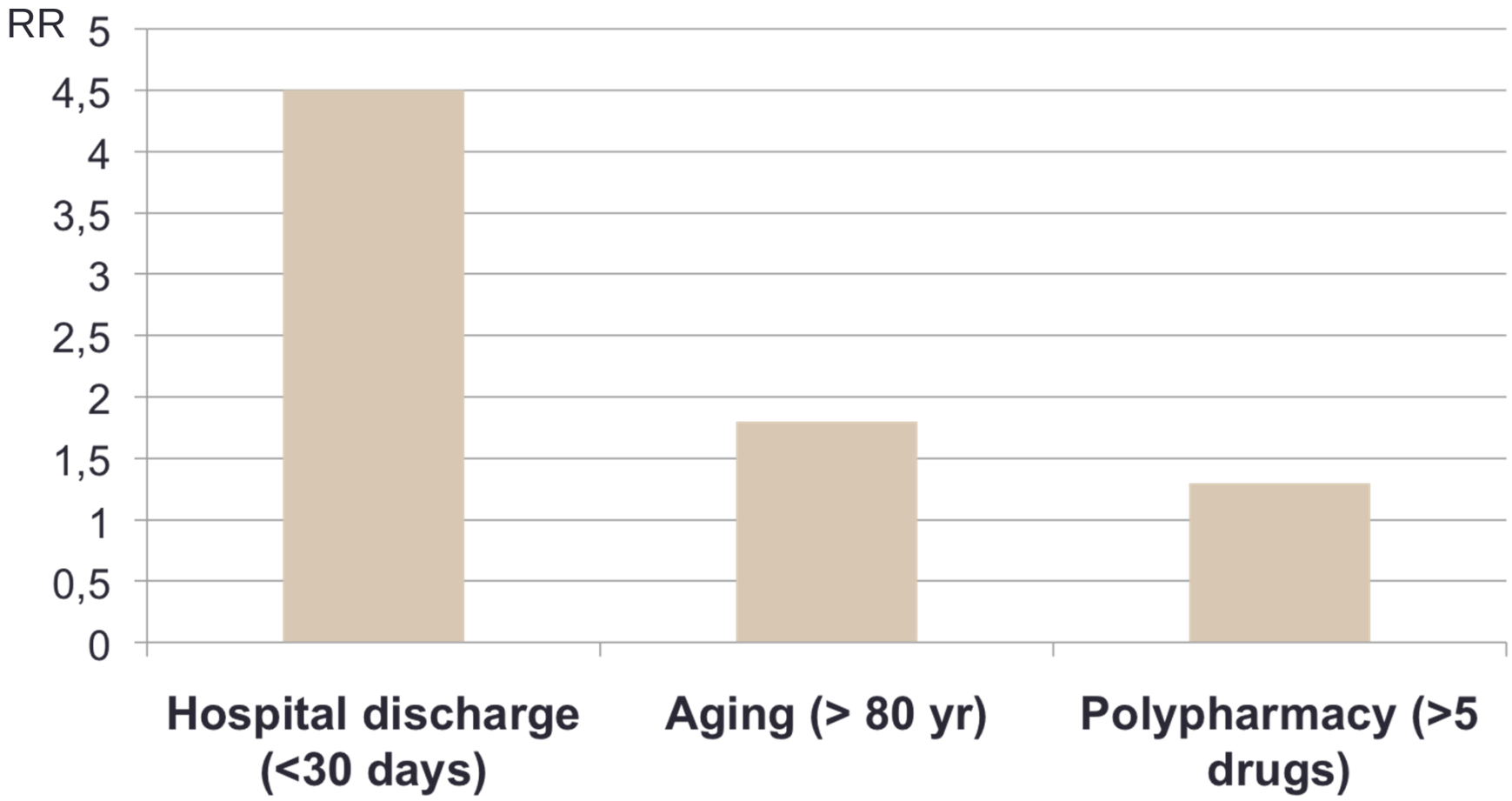
Conferencia de consenso

Documento de consenso sobre el tratamiento al alta hospitalaria del paciente con hiperglucemia

Antonio Pérez Pérez [a,*], Ricardo Gómez Huelgas [b], Fernando Álvarez Guisasola [c], Javier García Alegría [b], José Javier Mediavilla Bravo [d] y Edelmiro Menéndez Torre [a]

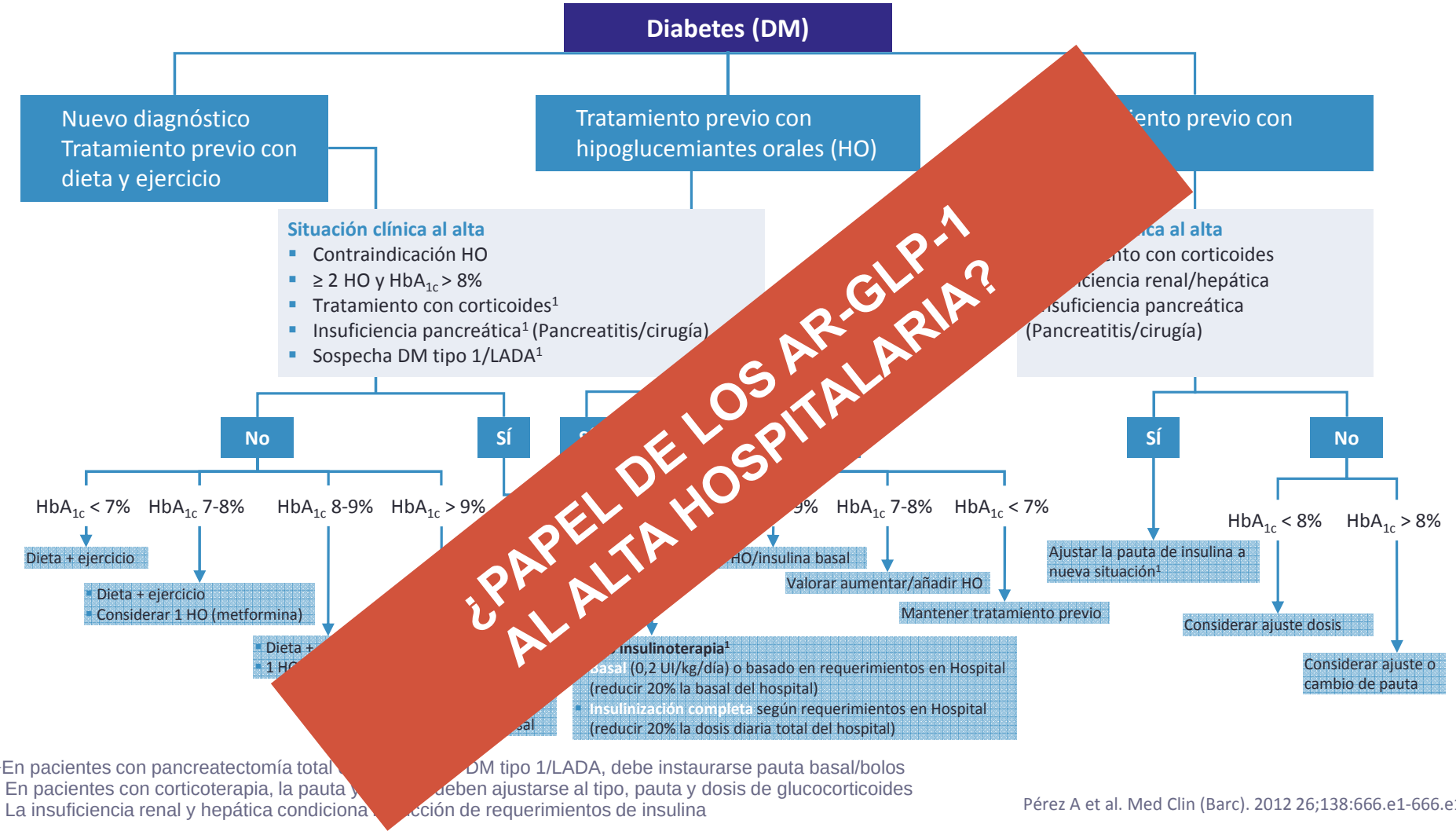
[a] *Sociedad Española de Diabetes*
[b] *Sociedad Española de Medicina Interna*
[c] *Sociedad Española de Medicina de Familia y Comunitaria*
[d] *Sociedad Española de Médicos de Atención Primaria*

Risk factors of hypoglycaemia in elderly with type 2 diabetes treated with insulin or sulphonilureas



Shorr RI. Arch Intern Med 1997;157:1681

Ajustes del tratamiento al alta según tratamiento previo y situación clínica al alta



¿PAPEL DE LOS AR-GLP-1 AL ALTA HOSPITALARIA?

[1]En pacientes con pancreatectomía total … DM tipo 1/LADA, debe instaurarse pauta basal/bolos
En pacientes con corticoterapia, la pauta y … deben ajustarse al tipo, pauta y dosis de glucocorticoides
La insuficiencia renal y hepática condiciona … cción de requerimientos de insulina

Pérez A et al. Med Clin (Barc). 2012 26;138:666.e1-666.e10

Endocrine (2014) 46:406–419
DOI 10.1007/s12020-014-0179-0

REVIEW

Pharmacokinetics, safety, and efficacy of DPP-4 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes mellitus and renal or hepatic impairment. A systematic review of the literature

Carlo B. Giorda · Elisa Nada · Barbara Tartaglino

	Renal impairment	Hepatic impairment
Exenatide	Mean $t_{1/2}$ for healthy subjects, mild RI, moderate RI and ESRD groups was 1.5, 2.1, 3.2, and 6.0 h, respectively. After combining data from multiple studies, least squares geometric means for exenatide clearance in the four categories were 8.14, 5.19, 7.11, and 1.3 l/h, respectively (*Linnebjerg* et al., *2007*).	No studies have been performed with exenatide in patients with HI
Liraglutide	Liraglutide exposure was lowered by 33, 14, 27, and 28 %, respectively, in subjects with mild, moderate and severe RI, and in ESRD requiring dialysis (*Jacobsen* et al., *2009*)	Liraglutide exposure was decreased by 13-23 % in subjects with mild-to-moderate HI, as compared to healthy subjects. Exposure was significantly lower (44 %) in subjects with severe HI (*Flint* et al., *2010*)
Lixisenatide	No relevant differences in mean Cmax and AUC between subjects with normal renal function and subjects with mild impaired renal function (50-80 ml/min). In subjects with eGFR 30-50 ml/min, the AUC was increased by 24 % and by 46 %.in subjects with eGFR 15-30 ml/min	No pharmacokinetic study has been performed in patients with acute or chronic HI

INDICACIÓN DE FÁRMACOS ANTIDIABÉTICOS SEGÚN EL GRADO DE INSUFICIENCIA RENAL

ESTADIOS 1-2 FG >60 mL/min	ESTADIO 3a FG 45-60 mL/min	ESTADIO 3b FG 30-45 mL/min	ESTADIOS 4-5 FG <30 mL/min
	INSULINA		
	REPAGLINIDA		
INHIBIDORES DE LA DPP-4			
METFORMINA			
SULFONILUREAS			
PIOGLITAZONA			
IN. GLUCOSIDASA			
AGONISTAS GLP-1R	Exenatida Lixisenatida		
IN. SGLT-2			

Uso seguro

Usar con precaución

Uso no recomendado

Consenso SEMI - SED - SEN - redGDAPS

GLP-1 AR en insuficiencia renal – Fichas técnicas

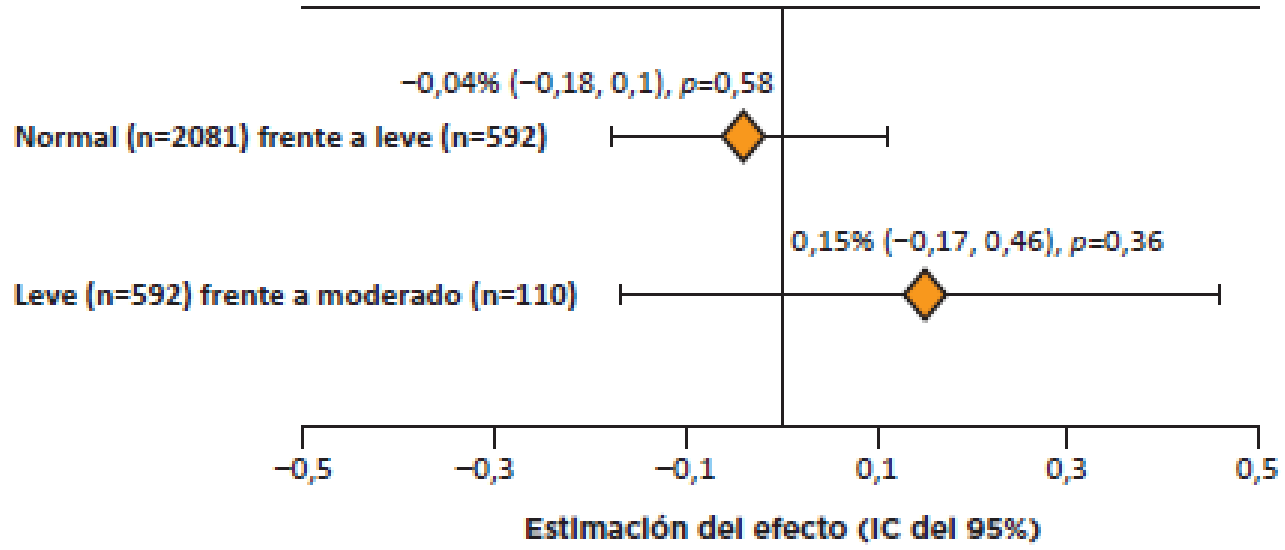
<table>
<tr><th></th><th>IR leve</th><th>IR moderada</th><th>IR avanzada</th></tr>
<tr><td>EXENETIDA</td><td>No requiere ajuste de dosis (FG 60-90 ml/min)</td><td>Proceder cuidadosamente al escalado de dosis de 5 µg a 10 µg (FG 30-50 l/min)</td><td>No recomendado</td></tr>
<tr><td>LIRAGLUTIDA</td><td>No requiere ajuste de dosis (FG 60-90 ml/min)</td><td colspan="2" rowspan="2">No experiencia clínica
Uso no recomendado

No experiencia clínica
Uso no recomendado</td></tr>
<tr><td>EXENATIDA LAR</td><td>No requiere ajuste de dosis (FG 50-80 ml/min)</td></tr>
<tr><td>LIXISENATIDA</td><td>No requiere ajuste de dosis (FG 50-80 ml/min)</td><td>Experiencia clínica limitada. Usar con precaución (FG 30-50 ml/min)</td><td>No experiencia clínica. Uso no recomendado</td></tr>
</table>

Lixisenatida en insuficiencia renal leve-moderada

Análisis post-hoc de 9 estudios GetGoal

Figura 1. Estimación del efecto para la diferencia entre las categorías renales en cuanto a la variación ajustada por placebo de la HbA_{1c} entre el período basal y la semana 24 (semana 12 en el estudio GetGoal-Mono) con lixisenatida



Función renal normal: FGe ≥ 90 ml/min; insuficiencia leve: FGe 60–89 ml/min; insuficiencia moderada: FGe 30–59 ml/min

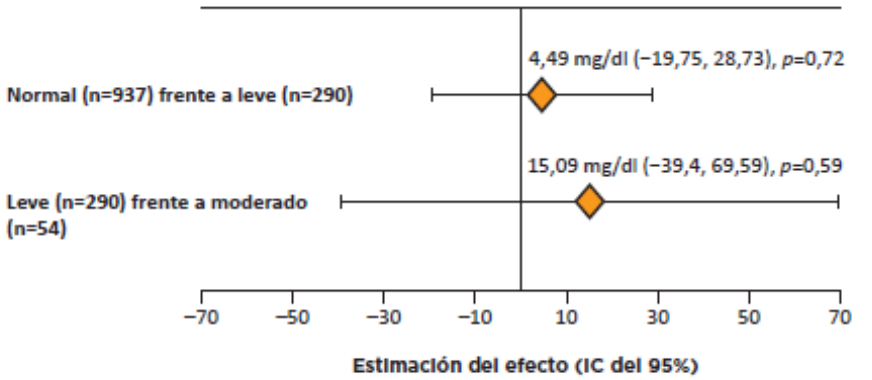
IC=intervalo de confianza; FGe=filtración glomerular estimada; HbA_{1c}=glucohemoglobina.

Gómez-Huelgas R, ADA 2014

Lixisenatida en insuficiencia renal leve-moderada

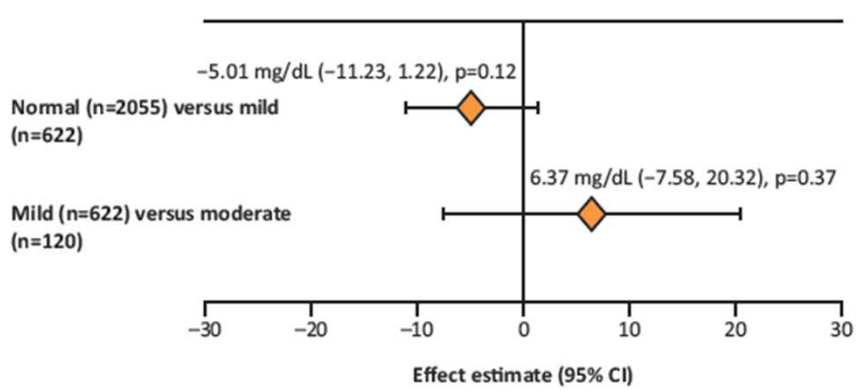
Análisis post-hoc de 9 estudios GetGoal

Figura 2. Estimación del efecto para la diferencia entre las categorías renales en cuanto a la variación ajustada por placebo de la respuesta de GPP al cabo de 2 horas entre el período basal y la semana 24 (semana 12 en el estudio GetGoal-Mono) con lixisenatida



Función renal normal: FGe ≥90 ml/min; insuficiencia leve: FGe 60–89 ml/min; insuficiencia moderada: FGe 30–59 ml/min
IC=intervalo de confianza; FGe=filtración glomerular estimada; GPP=glucemia posprandial.

Figure 3. Effect estimate for the difference between renal categories in placebo-adjusted change in FPG from baseline to Week 24 (Week 12 for GetGoal-Mono) with lixisenatide



Normal renal function, eGFR ≥90 mL/min; mild impairment, eGFR 60–89 mL/min; moderate impairment, eGFR 30–59 mL/min
CI=confidence interval; eGFR=estimated glomrular filtration rate; FPG=fasting plasma glucose

Gómez-Huelgas R, ADA 2014

Lixisenatida en insuficiencia renal leve-moderada

Análisis post-hoc de 9 estudios GetGoal

- Lixisenatida fue generalmente bien tolerada en pacientes con insuficiencia renal leve-moderada
- Mayor incidencia (10%) de nauseas y vómitos en pacientes con insuficiencia renal
- No diferencias de hipoglucemia

Tohoku J Exp Med. 2013;231(1):57-61.

The glucagon-like peptide-1 receptor agonist, liraglutide, attenuates the progression of overt diabetic nephropathy in type 2 diabetic patients.

Imamura S1, Hirai K, Hirai A.

Abstract

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease. Glucagon-like peptide-1 (GLP-1) is one of the incretins, gut hormones released from the intestine in response to food intake. GLP-1 receptor (GLP-1R) agonists have been used to treat type 2 diabetes. Here, we studied the effect of the administration of a GLP-1R agonist, liraglutide, on proteinuria and the progression of overt DN in type 2 diabetic patients. Twenty-three type 2 diabetic patients with overt DN, who had already been treated with blockade of renin-angiotensin system under dietary sodium restriction, were given liraglutide for a period of 12 months. Treatment with liraglutide caused a significant decrease in HbA1c from 7.4 ± 0.2% to 6.9 ± 0.3% ($p = 0.04$), and in body mass index (BMI) from 27.6 ± 0.9 kg/m² to 26.5 ± 0.8 kg/m² after 12 months ($p < 0.001$), while systolic blood pressure did not change. The progression of DN was determined as the rate of decline in estimated glomerular filtration rate (eGFR). The 12-month administration of liraglutide caused a significant decrease in proteinuria from 2.53 ± 0.48 g/g creatinine to 1.47 ± 0.28 g/g creatinine ($p = 0.002$). The administration of liraglutide also substantially diminished the rate of decline in eGFR from 6.6 ± 1.5 mL/min/1.73 m²/year to 0.3 ± 1.9 mL/min/1.73 m²/year ($p = 0.003$). Liraglutide can be used not only for reducing HbA1c and BMI, but also for attenuating the progression of nephropathy in type 2 diabetic patients.

GLP-1 AR en insuficiencia renal

- Escasa experiencia clínica

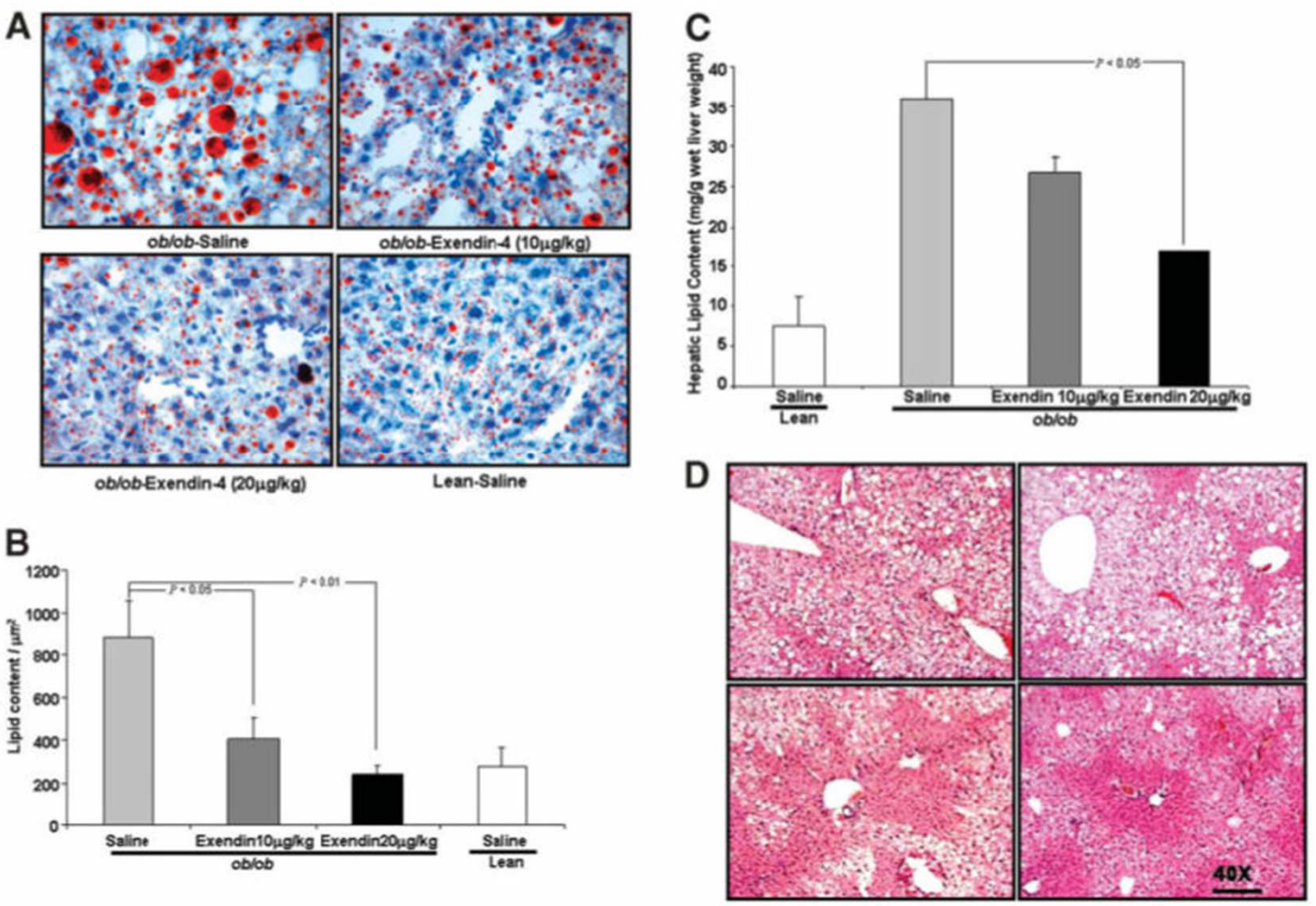
- Similar eficacia antidiabética
- No hipoglucemias
- Más efectos adversos gastrointestinales (gastroparesia)
- Riesgo de agudización (vómitos)

- Nefroprotección (efecto antiproteinúrico)

GLP-1 AR en insuficiencia hepática – Ficha técnica

EXENETIDA	No es necesario un ajuste de la dosis en pacientes con insuficiencia hepática
LIRAGLUTIDA	Experiencia clínica limitada. No se recomienda su uso en insuficiencia hepática leve, moderada o grave
EXENATIDA LAR	No es necesario un ajuste de la dosis en pacientes con insuficiencia hepática
LIXISENATIDA	No es necesario ajustar la dosis en pacientes con insuficiencia hepática

Exendine-4 reverses hepatic steatosis in ob/ob mice



Ding X. Hepatology 2006.

Review
Obesity and Metabolic Syndrome
Diabetes Metab J 2012;36:262-267
http://dx.doi.org/10.4093/dmj.2012.36.4.262
pISSN 2233-6079 · eISSN 2233-6087

GLP-1 Receptor Agonist and Non-Alcoholic Fatty Liver Disease

Jimmi Lee[1], Seok-Woo Hong[2], Eun-Jung Rhee[2], Won-Young Lee[2]

[1]Institute of Medical Research, [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Non-alcoholic fatty liver disease (NAFLD), one of the most common liver diseases, is caused by the disruption of hepatic lipid homeostasis. It is associated with insulin resistance as seen in type 2 diabetes mellitus. Glucagon-like peptide-1 (GLP-1) is an incretin that increases insulin sensitivity and aids glucose metabolism. In recent *in vivo* and *in vitro* studies, GLP-1 presents a novel therapeutic approach against NAFLD by increasing fatty acid oxidation, decreasing lipogenesis, and improving hepatic glucose metabolism. In this report, we provide an overview of the role and mechanism of GLP-1 in relieving NAFLD.

Keywords: Fatty acid oxidation; Glucagon-like peptide 1; Non-alcoholic fatty liver disease

INTRODUCTION

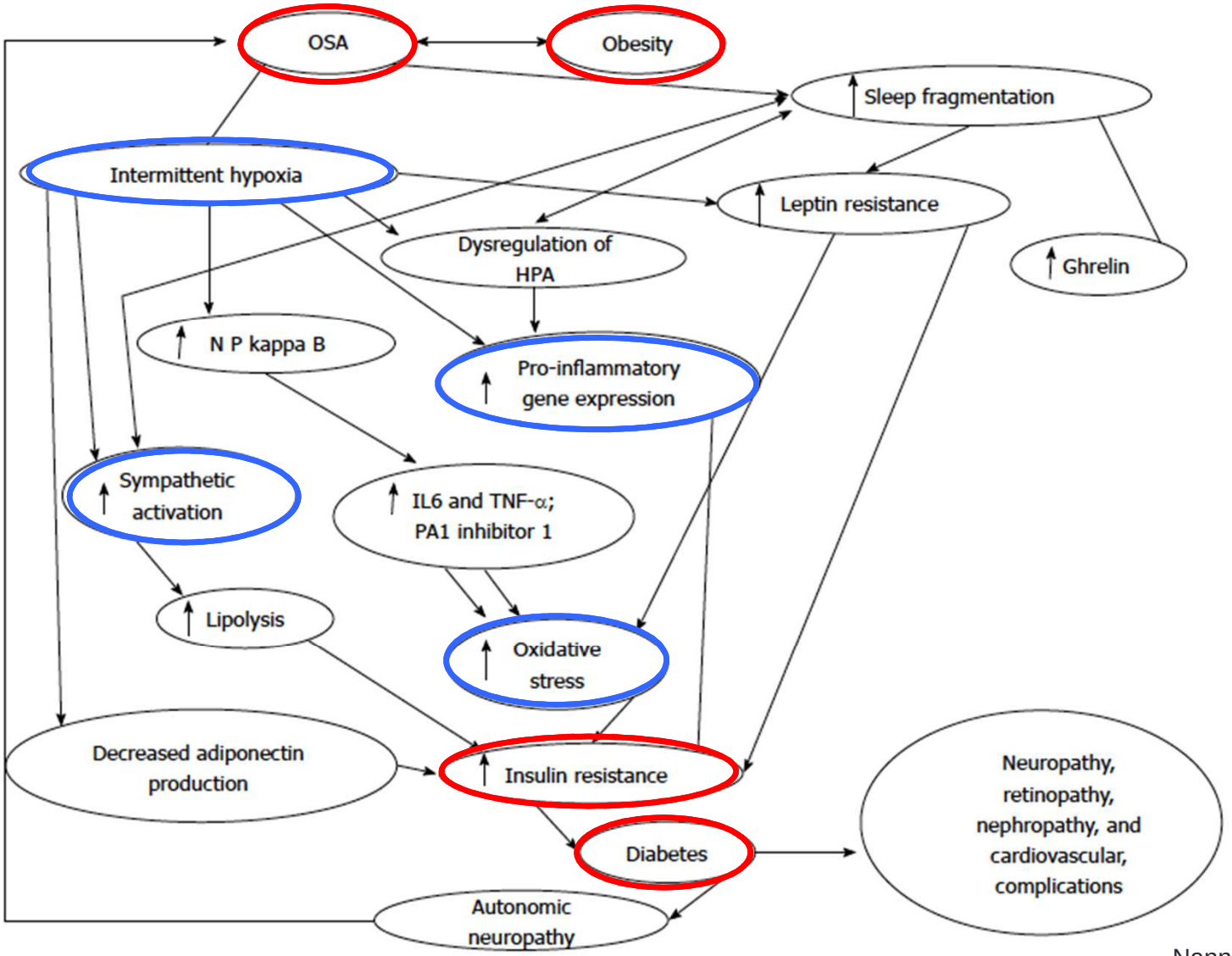
Excess accumulation of fat in the liver is known as fatty liver disease. Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in the Western hemisphere, affecting 20% to 30% of the adult population [1]. Approximately 10% to 25% patients with NAFLD can progress to non-alcoholic steatohepatitis (NASH) and 10% to 15% patients with NASH develop hepatocellular carcinoma [2,3]. In addition, NAFLD is closely associated with metabolic syndrome, type 2 diabetes mellitus (T2DM) and cardiovascular morbidity and mortality. Despite these associated pathologies, there is still no specific treatment for NAFLD.

Glucagon-like peptide-1 (GLP-1) is an incretin secreted by L-cells in the small intestine in response to food intake [4]. The main roles of GLP-1 are stimulation of glucose-dependent insulin secretion, inhibition of postprandial glucagon release, delay of gastric emptying, and induction of pancreatic β-cell proliferation [5].

Once in circulation, GLP-1 has a short half-life (1 to 2 minutes) due to rapid degradation by the ubiquitous endogenous enzyme dipeptidyl peptidase-4 (DPP-4). To overcome this obstacle, GLP-1 receptor agonists that have increased resistance to DPP-4 (such as exenatide and liraglutide) or DPP-4 inhibitors (such as sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin) have been used in animal and human studies [6,7].

Recent studies have shown that exendin-4 could improve hepatic steatosis by modulation of lipid metabolism and hepatic insulin signaling in *ob/ob* mice and in human hepatocyte [8,9]. Additional studies have demonstrated that treatment with exendin-4 and liraglutide could reduce steatosis by enhancing autophagy. Treatment with exendin-4 and liraglutide leads to reduced endoplasmic reticulum (ER) stress-related apoptosis in human hepatocytes treated with fatty acids as well as in mice fed a high fat diet, respectively [10]. In this review, we present the pleiotropic effects of GLP-1 on reducing NAFLD.

SAHOS y DIABETES TIPO 2



Nannapaneni S, 2013

OBSERVATIONS

Liraglutide Treatment in a Patient With HIV and Uncontrolled Insulin-Treated Type 2 Diabetes

Combination antiretroviral therapy has improved survival in human immunodeficiency virus (HIV)-infected patients but has become associated with altered body fat distribution, type 2 diabetes, and increased cardiovascular risk (1). Both the protease inhibitors and nucleotide reverse transcriptase inhibitors have been implicated (1). Management of HIV-associated type 2 diabetes may be challenging because of severe insulin resistance, which—in spite of the initial use of insulin sensitizers—often requires a high dose of insulin, causing additional weight gain (1). The glucagon-like peptide-1 receptor agonists lower glucose, reduce weight, and improve the cardiovascular risk profile in type 2 diabetes (2,3). Recently, exenatide use in an HIV-associated type 2 diabetic case and in atype 1 diabetic HIV patient was reported (4,5). Here, we report the first successful liraglutide use in an HIV patient with type 2 diabetes.

A 57-year-old man regularly visited the outpatient clinic since 2003 because of an HIV infection, which was diagnosed in 1995. Initial treatment consisted of zidovudine, then dual-therapy zidovudine and zalcitabine. From 1997–2003 he received zidovudine and lamivudine, then triple-therapy with efavirenz, didanosine, and lamivudine, which was discontinued because of dizziness, rash, and depression. Then, atazanavir, tenofovir, and lamivudine were given. In 2005, because of a progressive abdominal distention, the protease inhibitor atazanavir was replaced by raltegravir, an integrase inhibitor with a better metabolic profile.

In 2005, at a weight of 105 kg, compatible with a 15-kg weight gain in 2 years, type 2 diabetes was diagnosed. After lifestyle consultation, metformin (1,000 mg b.i.d.) was initiated. Since A1C rose to 8.8%, NPH insulin was started (November 2007). Body weight increased by 5 kg in 6 months with little glycemic improvement. Insulin treatment was replaced by glimepiride (up to 6 mg q.i.d.), but A1C remained 8.3%. He could be persuaded to start insulin glargine (September 2010), titrated to 60 U/day, while glimepiride was discontinued. Unfortunately, weight increased by 7 kg in 6 months without glycemic improvement. In May 2011, at a weight of 116 kg (BMI 35.1 kg/m^2) and A1C 8.1%, off-label liraglutide was initiated at 0.6 mg/day, and uptitrated to 1.8 mg/day. He consulted a dietitian and diabetes educator and was advised to lower daily insulin dose by 10 U when self-monitored blood glucose was <5 mmol/L. After 3 weeks of liraglutide therapy, body weight dropped to 110 kg, insulin dose was reduced to 30 U/day, and discontinued altogether after 6 weeks. Fasting glucose decreased from 12.3 to 7.0 mmol/L. The patient reported no side-effects or hypoglycemia, rather less fatigue and overall improved quality of life. Self-monitored blood glucose varied between 5.6–8.3 mmol/L, HIV-RNA remained undetectable. Four months after liraglutide initiation, A1C decreased to 6.8% and body weight to 102 kg, but body weight rose slightly to 108 kg at 7 months, while A1C remained 6.8%. Previously elevated liver enzymes normalized while his lipid profile improved significantly (total cholesterol from 5.6 to 4.9 mmol/L, HDL cholesterol from 0.79 to 1.0 mmol/L, triglycerides from 6.6 to 3.1 mmol/L). This case illustrates that glucagon-like peptide-1 receptor agonists, possibly by improving weight control, body fat distribution, and cardiovascular markers (3), may be a valuable tool in the treatment of HIV-associated type 2 diabetes, which is characterized by central obesity, lipodystrophy, and insulin resistance.

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M.D. advised regarding the therapy and the clinical data to be collected and wrote the manuscript. M.v.A. is the treating physician of the patient described in this case report, performed the practical collection of the clinical data, edited the manuscript, and contributed to discussion.

The patient described in this case-report has given written informed consent to publish his case anonymously.

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BMJ Open

Does a GLP-1 receptor agonist change glucose tolerance in patients treated with antipsychotic medications? Design of a randomised, double-blinded, placebo-controlled clinical trial

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ABSTRACT

Background: Metabolic disturbances, obesity and life-shortening cardiovascular morbidity are major clinical problems among patients with antipsychotic treatment. Especially two of the most efficacious antipsychotics, clozapine and olanzapine, cause weight gain and metabolic disturbances. Additionally, patients with schizophrenia-spectrum disorders not infrequently consume alcohol. Glucagon-like peptide-1 (GLP-1) has shown to improve glycaemic control and reduce alcohol intake among patients with type 2 diabetes.

Objectives: To investigate whether the beneficial effects of GLP-1 analogues on glycaemic control and alcohol intake, in patients with type 2 diabetes, can be extended to a population of pre-diabetic psychiatric patients receiving antipsychotic treatment.

Methods and analysis: *Trial design, intervention and participants:* The study is a 16-week, double-blinded, randomised, parallel-group, placebo-controlled clinical trial, designed to evaluate the effects of the GLP-1 analogue liraglutide on glycaemic control and alcohol intake compared to placebo in patients who are prediabetic, overweight (body mass index ≥27 kg/m^2), diagnosed with a schizophrenia-spectrum disorder and on stable treatment with either clozapine or olanzapine. *Outcomes: The primary endpoint* is the change in glucose tolerance from baseline (measured by area under the curve for the plasma glucose excursion following a 4 h 75 g oral glucose tolerance test) to follow-up at week 16. *The secondary endpoints* include changes of dysglycaemia, body weight, waist circumference, blood pressure, secretion of incretin hormones, insulin sensitivity and β cell function, dual-energy X-ray absorption scan (body composition), lipid profile, liver function and measures of quality of life, daily functioning, severity of the psychiatric disease and alcohol consumption from baseline to follow-up at week 16. *Status:* Currently recruiting patients.

Ethics and dissemination: Ethical approval has been obtained. Before screening, all patients will be provided oral and written information about the trial. The study will be disseminated by peer-review publications and conference presentations.

Strengths and limitations of this study

- The study is a double-blinded, randomised, parallel-group, placebo-controlled clinical trial, designed to evaluate the effects of the GLP-1 analogue liraglutide on glycemic control (measured by area under the curve for the plasma glucose excursion following a 4 h 75 g oral glucose tolerance test) in patients treated with either clozapine or olanzapine.
- The study duration is only 16 weeks.
- The study has no third treatment arm for comparing liraglutide to one of the two established add-on treatments for antipsychotic induced weight gain and metabolic abnormalities–that is, metformin or topiramate.
- The effect of liraglutide on alcohol consumption is evaluated without requiring a certain weekly minimum amount of alcohol consumption.

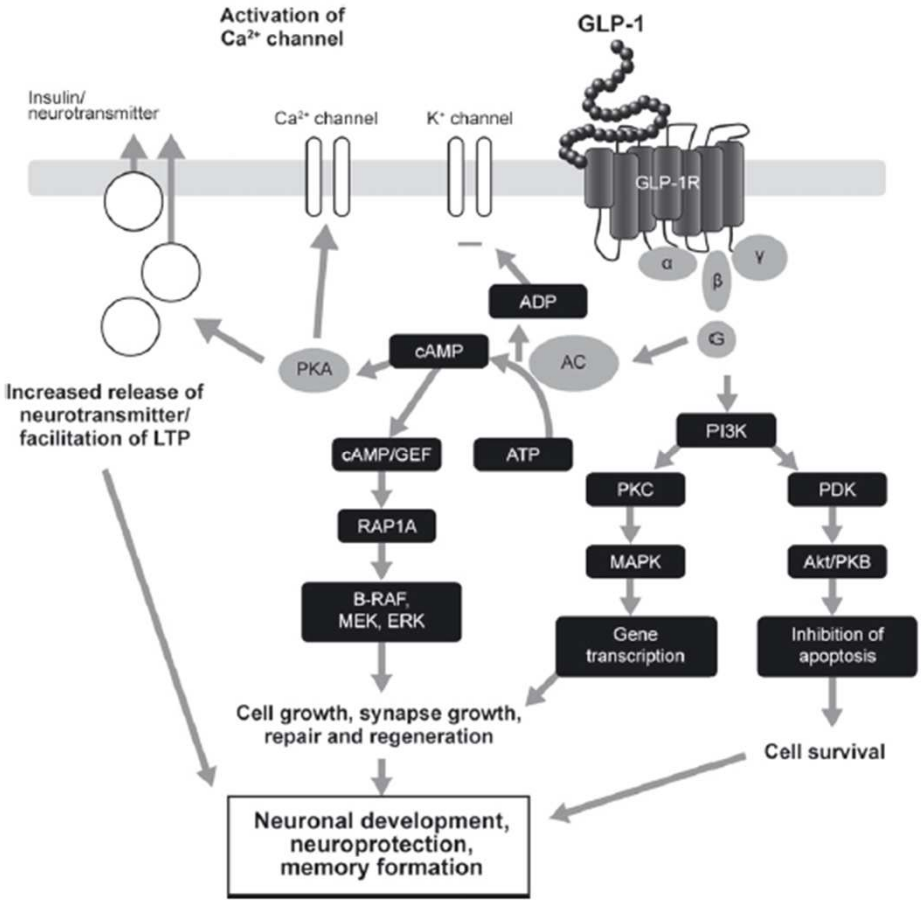
Trial registration number: ClinicalTrials.gov: NCT01845259, EudraCT: 2013-000121-31.

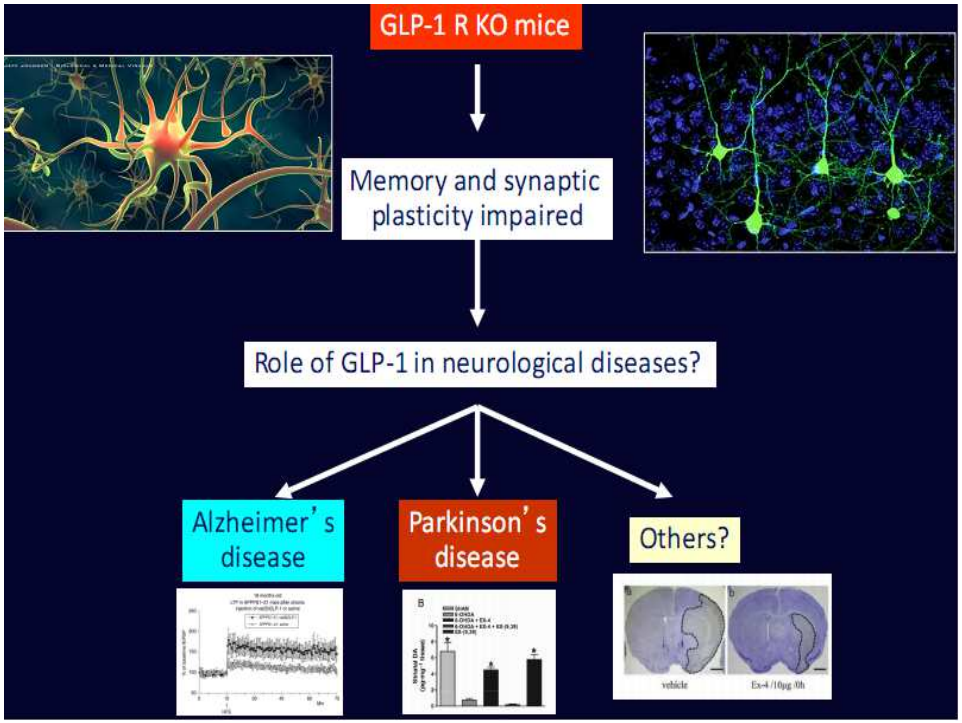
INTRODUCTION

Metabolic disturbances, overweight and obesity among patients with antipsychotic treatment are major clinical problems,[1 2] which most likely result from the interaction of medication, genes and lifestyle factors, such as physical inactivity and high fat diet.[3] However, the mechanisms underlying antipsychotic metabolic adverse effects are incompletely understood.[4]

Glucagon-like peptide-1 (GLP-1)-based therapy was introduced to the market for treatment of type 2 diabetes in 2006.[5] GLP-1 is an incretin hormone, which is secreted from endocrine L-cells of the small intestine

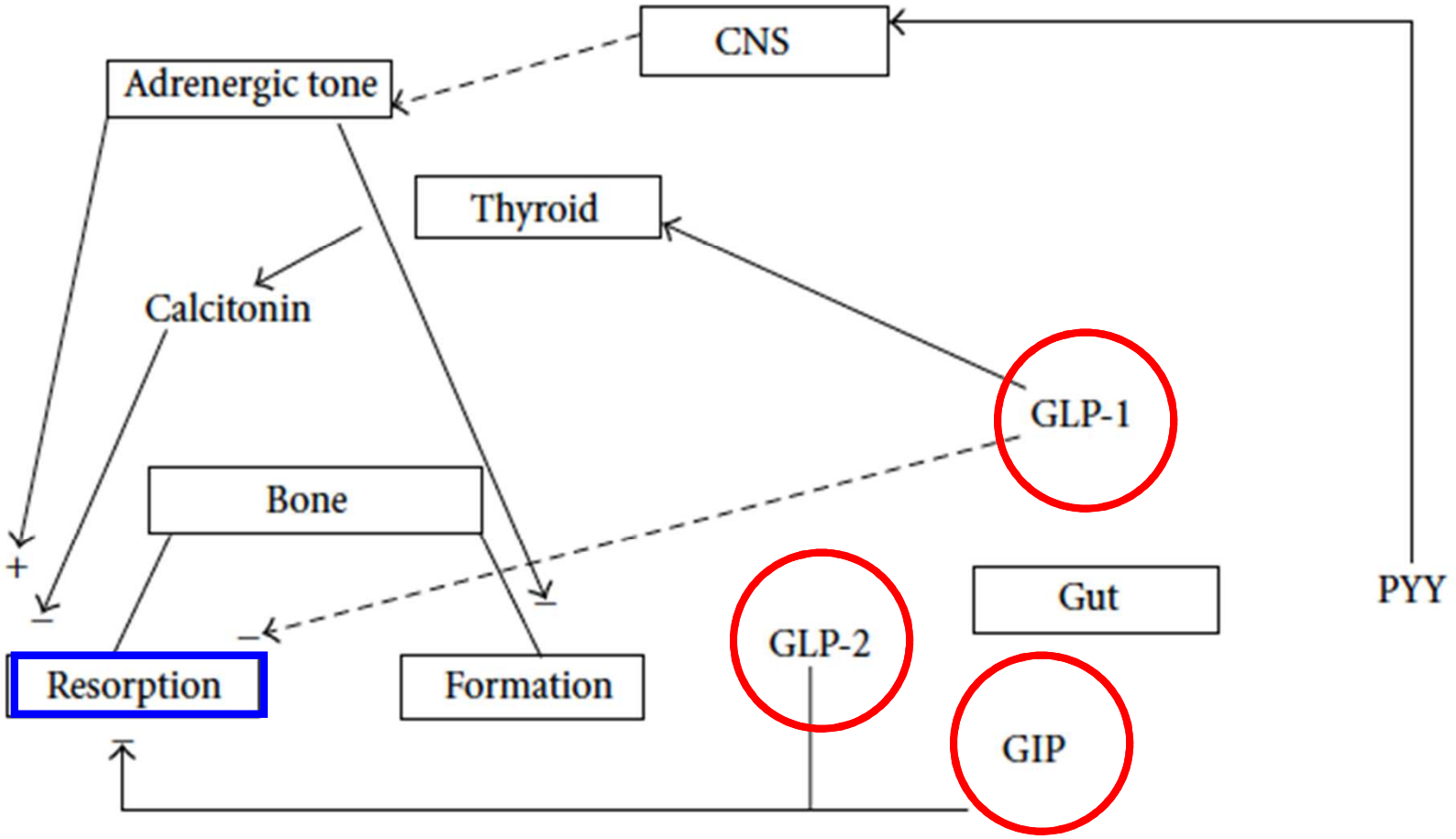
Molecular signalling pathways that may exert neuroprotective effects of GLP-1 in the central nervous system





Seufert J, 2014

TERAPIAS INCRETINAS: EFECTOS ESQUELÉTICOS



GLP-1 and exendin-4 can reverse hyperlipidic-related osteopenia

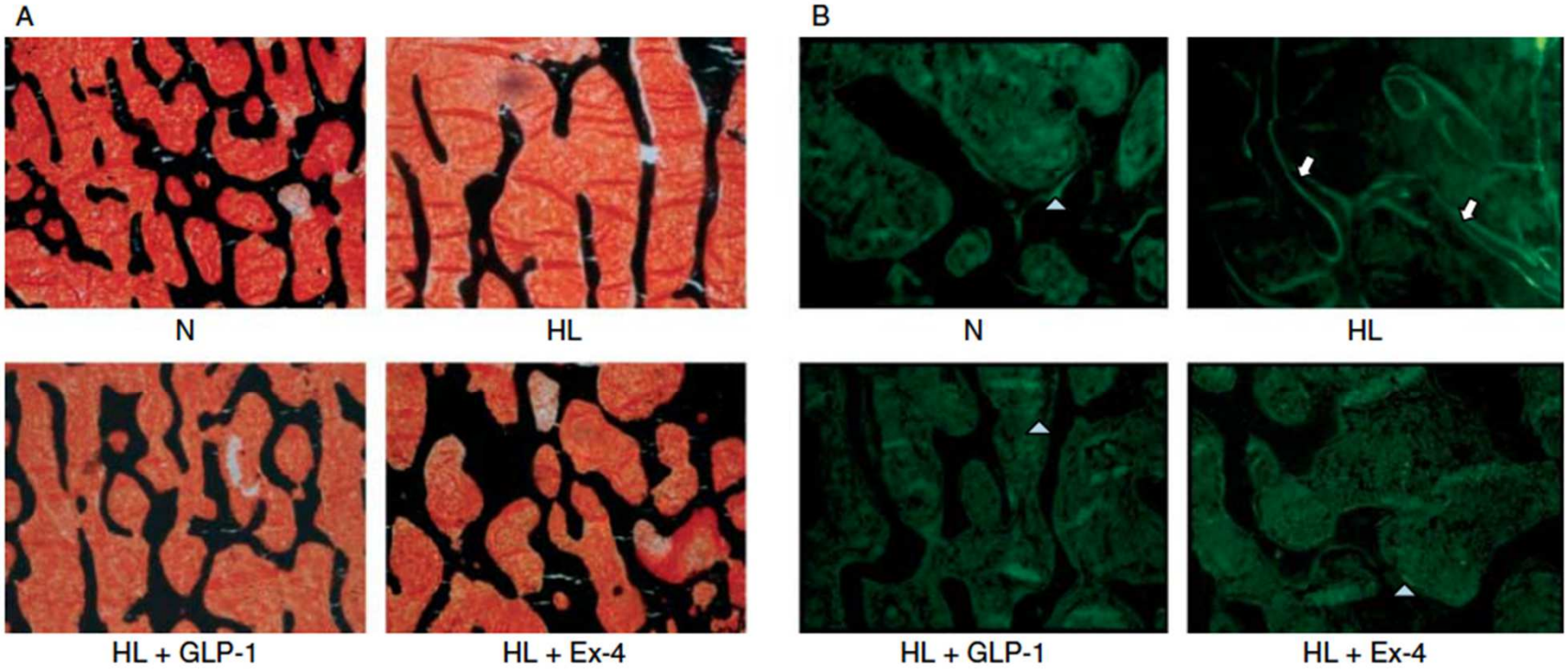


Figure 3 Light microscopy images showing the trabecular structure using von Kossa's staining (A), and single (arrowheads) and double (arrows) demeclocycline labels (B), in the lumbar vertebrae from representative normal (N) and hyperlipidemic (HL) rats, untreated or treated with GLP-1 or Ex-4. Original magnifications, ×400.

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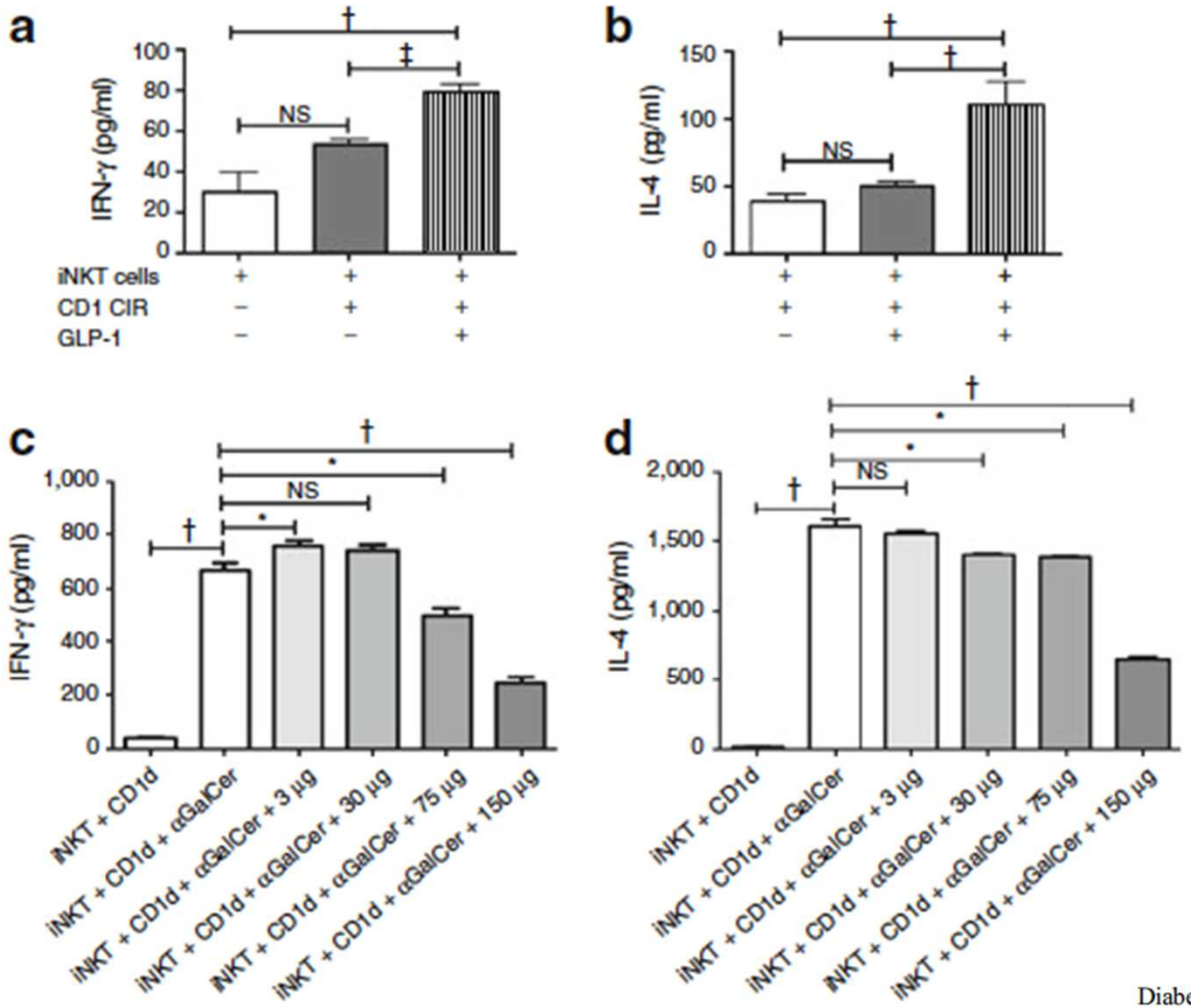
Glucagon-like peptide-1 (GLP-1) and the regulation of human invariant natural killer T cells: lessons from obesity, diabetes and psoriasis

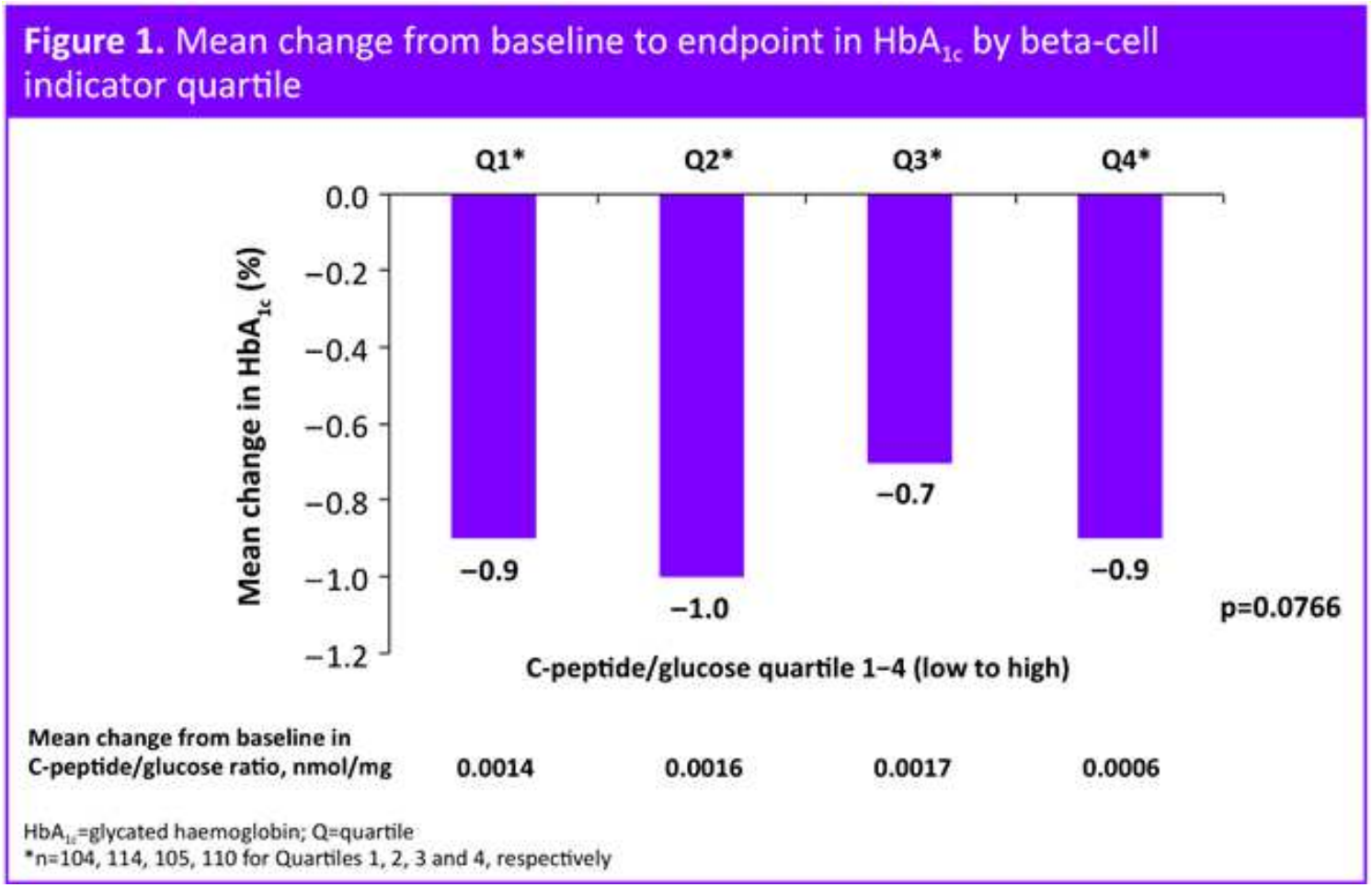
A. E. Hogan · A. M. Tobin · T. Ahern · M. A. Corrigan · G. Gaoatswe · R. Jackson · V. O'Reilly · L. Lynch · D. G. Doherty · P. N. Moynagh · B. Kirby · J. O'Connell · D. O'Shea



Diabetologia (2011) 54:2745–2754

Lixisenatida es eficaz con independencia del grado de función de las células β

Figure 1. Mean change from baseline to endpoint in HbA_{1c} by beta-cell indicator quartile



HbA_{1c}=glycated haemoglobin; Q=quartile
*n=104, 114, 105, 110 for Quartiles 1, 2, 3 and 4, respectively

Meier J. et al. Differential efficacy of lixisenatide in patients with different levels of beta-cell funtion as assessed by C-peptide/glucose ratio. EASD Congres, Spain, Barcelona 2013. Poster 896

Uso de AR GLP-1 en pacientes médicos

Indicaciones potenciales	Evitar en:
Alto riesgo vascular (no hipoglucemias)	**Anciano frágil**
Alta hospitalaria (no hipoglucemias)	**Gastroparesia diabética**
Hiperglucemia inducida por glucocorticoides (efecto postprandial)	**Varices esofágicas**
Obesidad grave	**Enfermedad inflamatoria intestinal**
Complicaciones asociadas a la obesidad: - SAHOS - Esteatohepatosis - Síndrome metabólico (VIH, antipsicóticos) - Gonartrosis	**Insuficiencia renal grave** **Insuficiencia hepática grave**

Muchas gracias