CONTROVERSIA EN EL 2º PASO TERAPEUTICO

INHIBIDORES DPP 4

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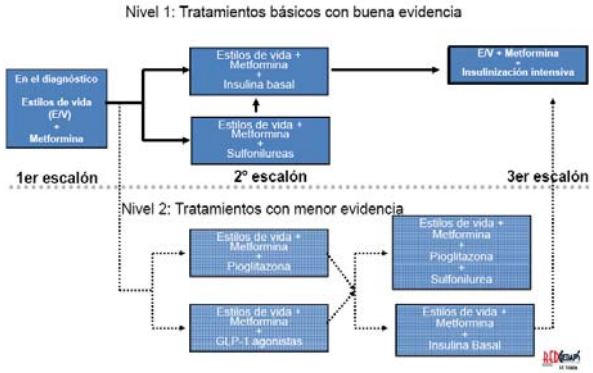
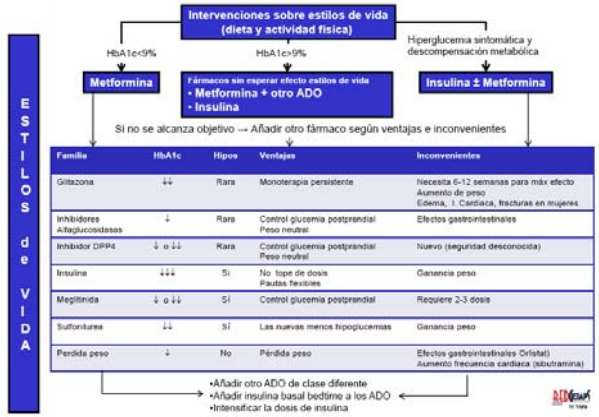
Servicio de Endocrinología y Nutrición
HUNSC (Santa Cruz de Tenerife)

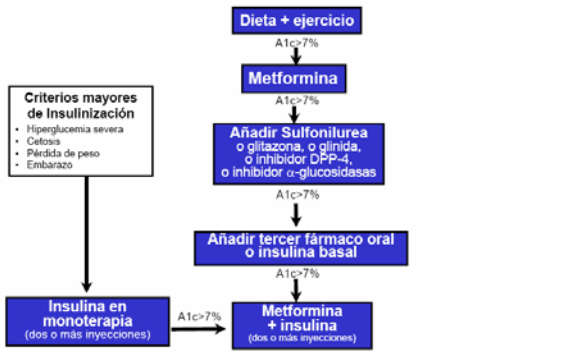
Algoritmo de tratamiento DM2 ADA/EASD 2008



ALGORITMO CANADIAN DIABETES ASSOCIATION 2008



Algoritmo de tratamiento de la DM2. GEDAPS 2008

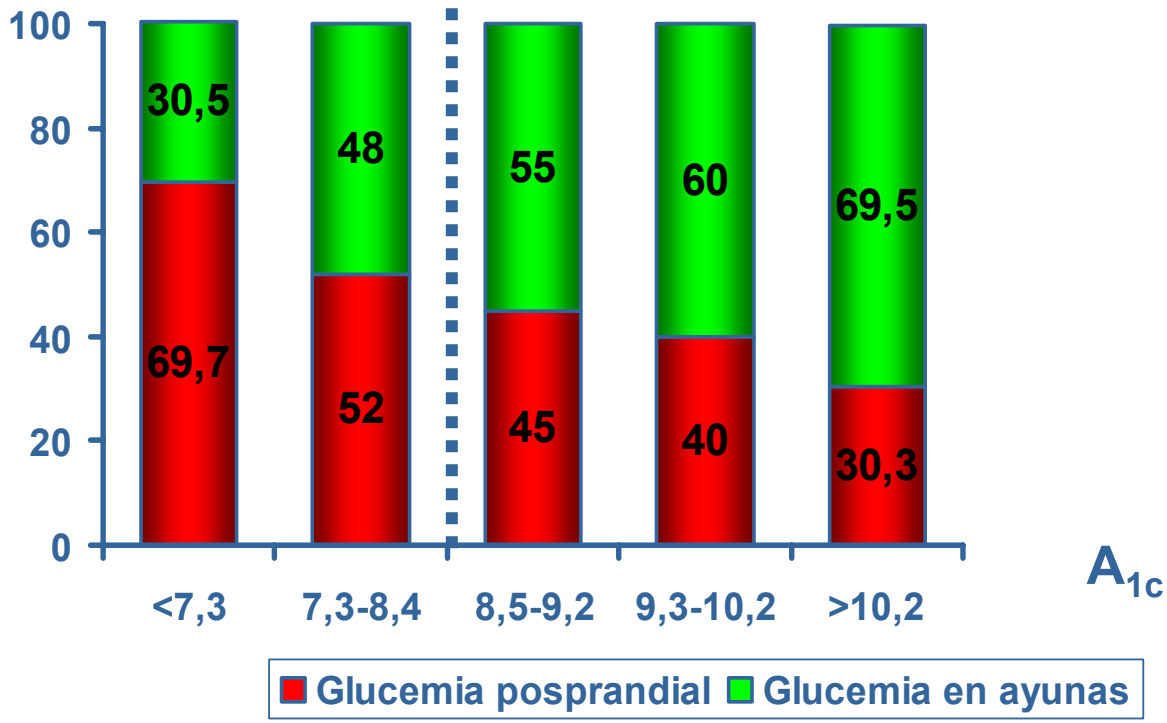


ALGORITMO GUIA MINISTERIO SANIDAD Y CONSUMO 2008

Objetivos en el tratamiento (1)

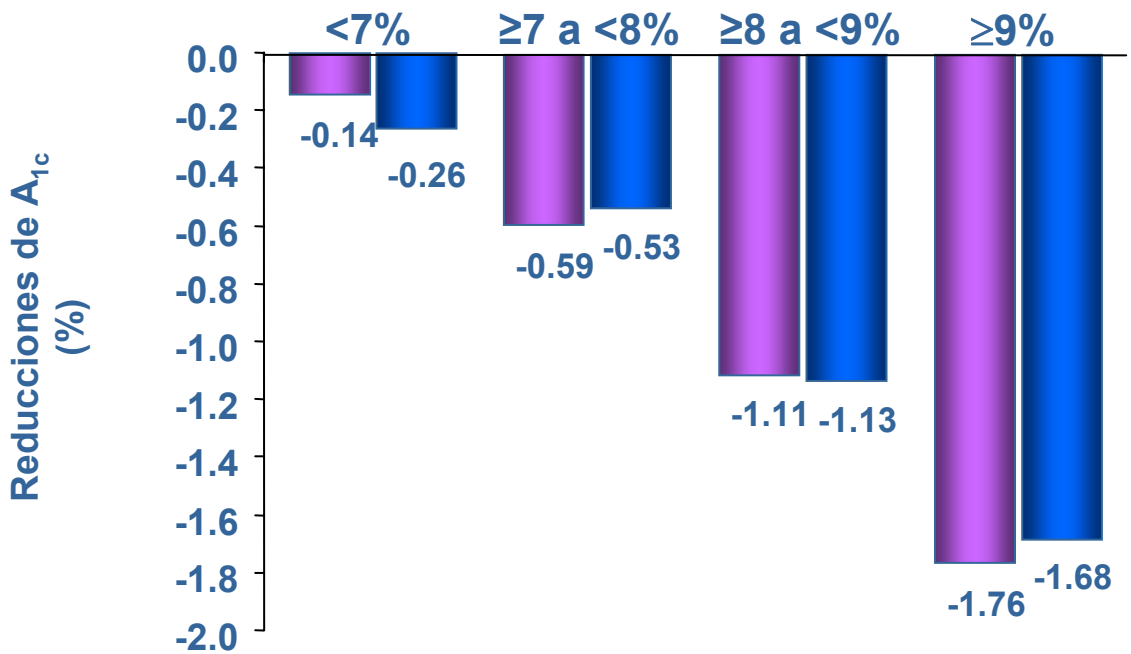
1. Obtener un control glucémico efectivo
2. Minimizar los efectos secundarios
3. Asegurar el cumplimiento terapéutico

Control glucémico efectivo



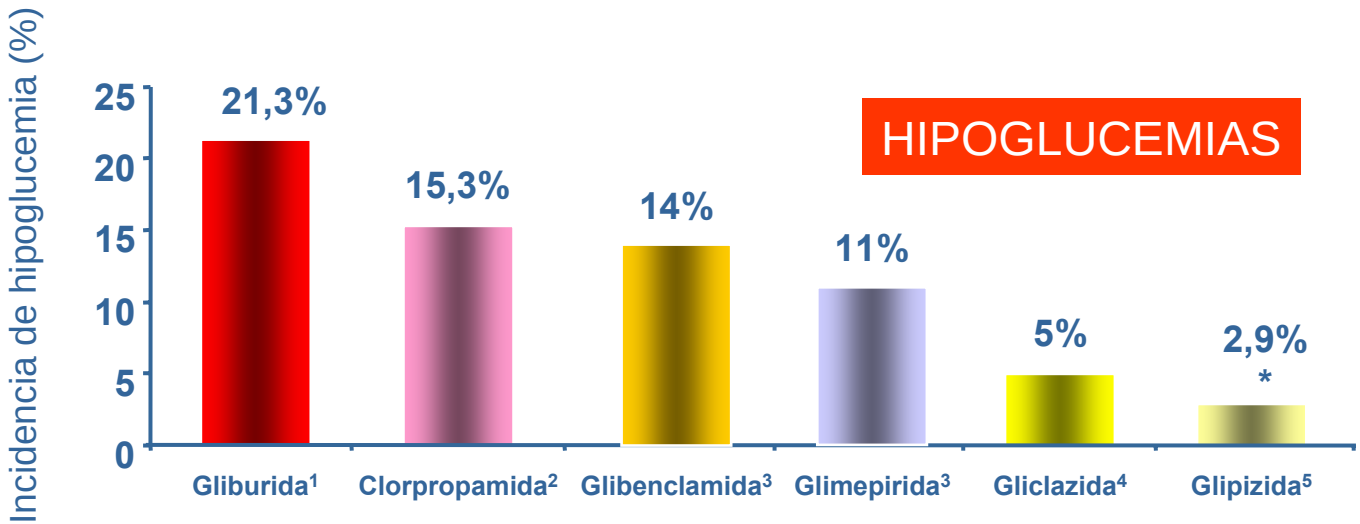
Monnier L et al. *Diabetes Care*. 2003;26:881–885.. From Diabetes Care, 26; 881–885.

Control glucémico efectivo

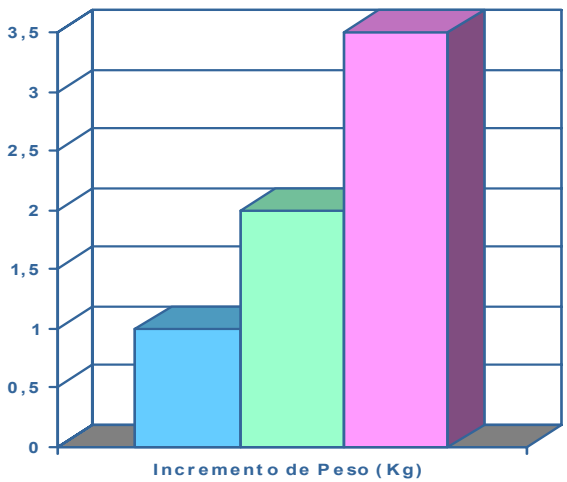


Nauck et al. Diabetes Obes Metab. 2007;9:194–205

Efectos Secundarios



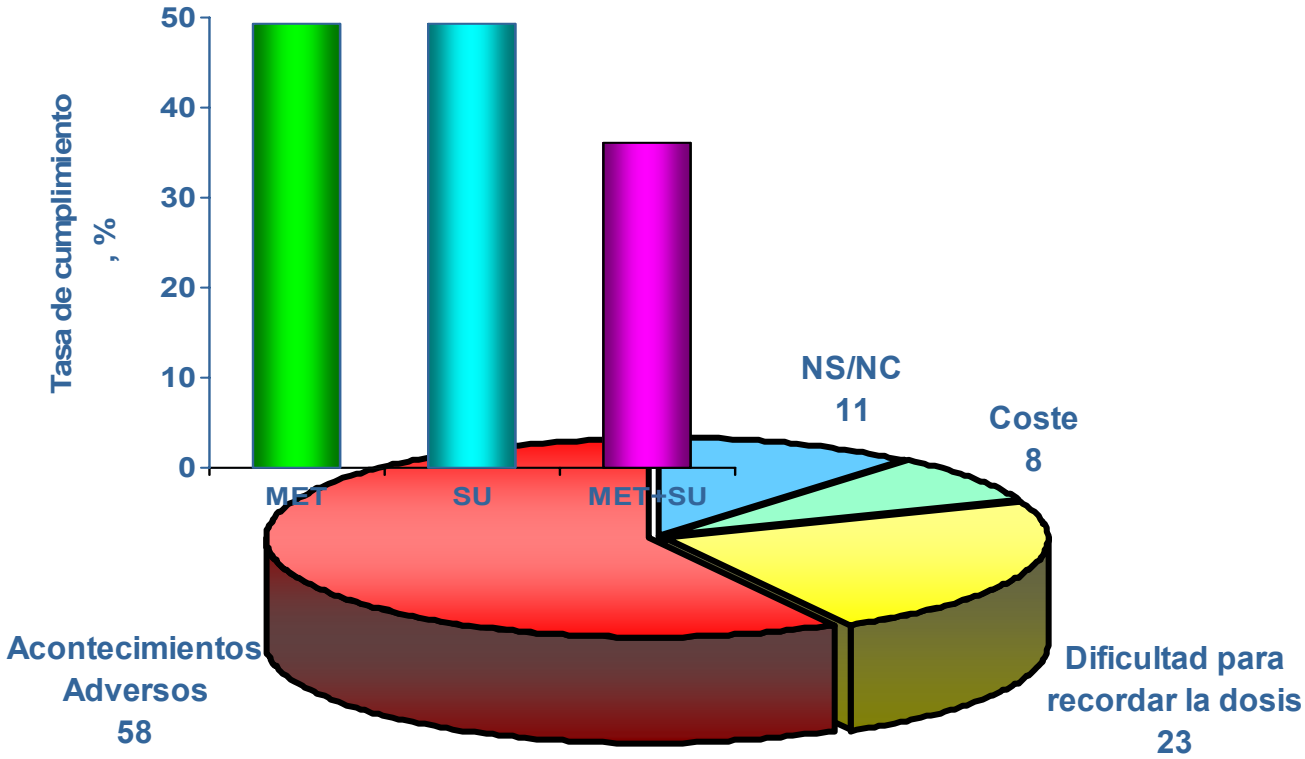
HIPOGLUCEMIAS



INCREMENTO PONDERAL

(UKPDS 34). Lancet 352:854–865

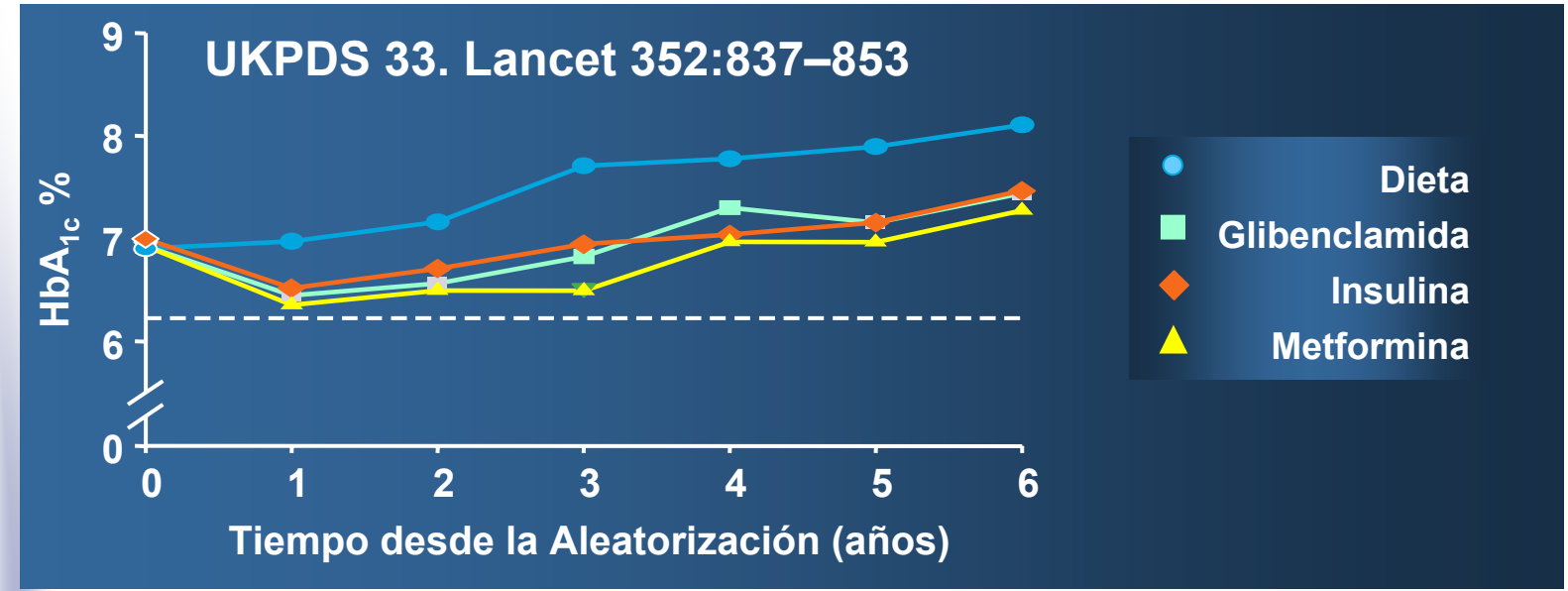
Cumplimiento terapéutico

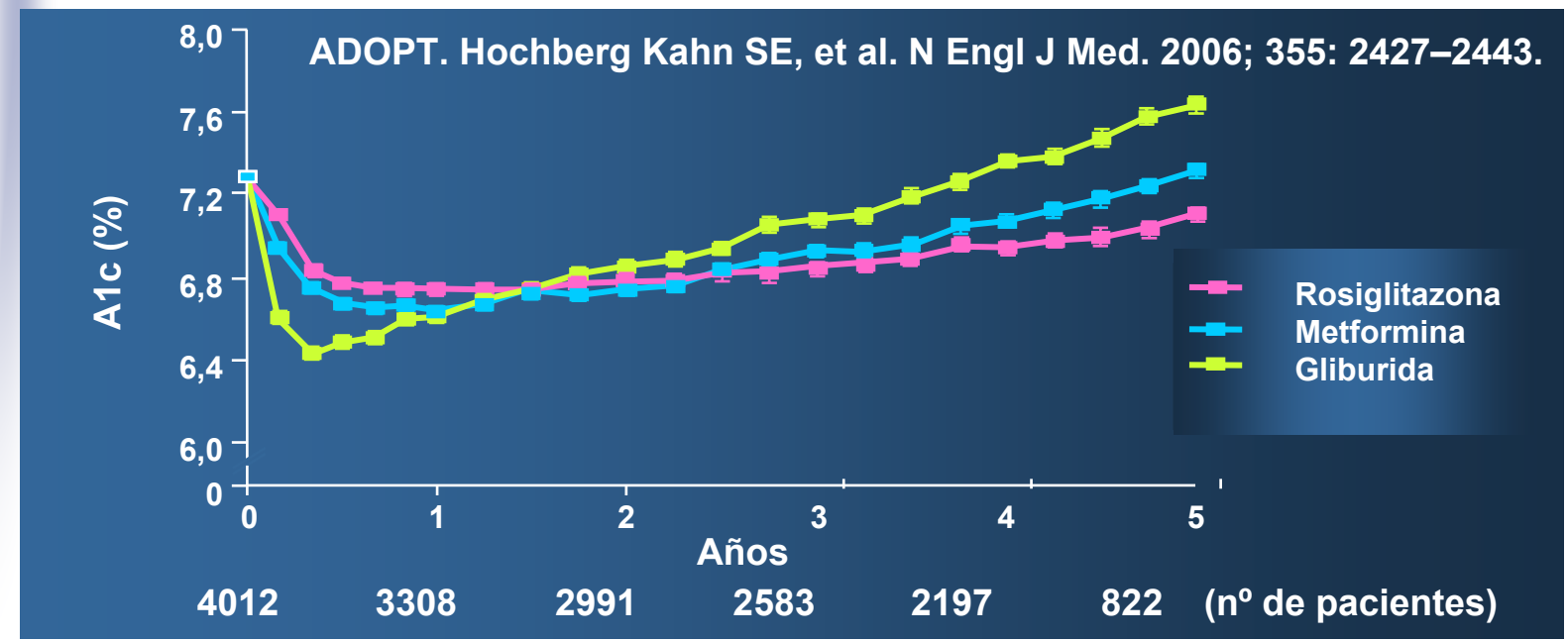


Dailey G et al. Clin Ther. 2001;23:1311–1320.

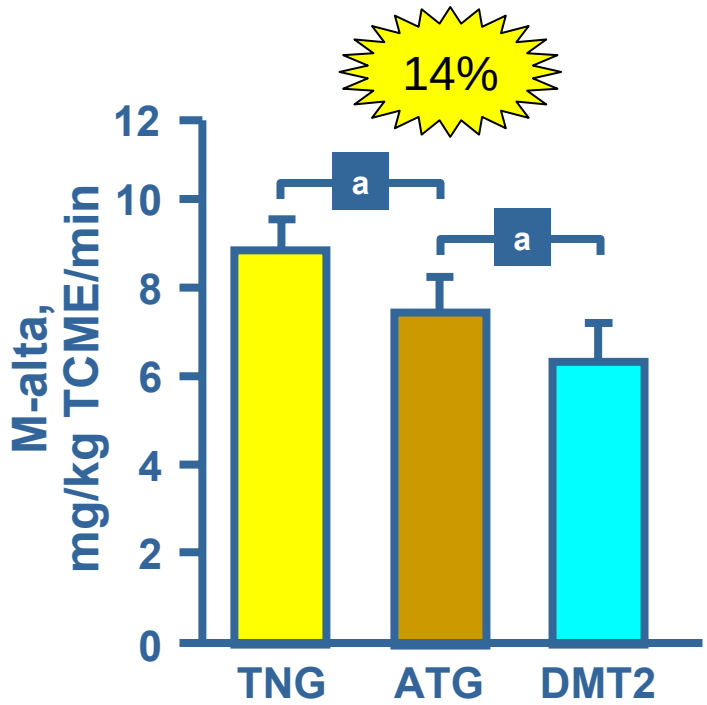
Objetivos en el tratamiento (2)

4. **Abordaje fisiopatológico**
   - Mejorar secreción y resistencia a la Insulina
   - Evitar hiperglucemia en ayunas y postprandial
   - Control glucémico sostenido
5. **Reducir complicaciones**
   - Microvasculares
   - Enfermedad cardiovascular
6. **Mejorar perfil de seguridad**
   - Seguridad Cardiovascular
   - Ausencia de efectos colaterales relevantes

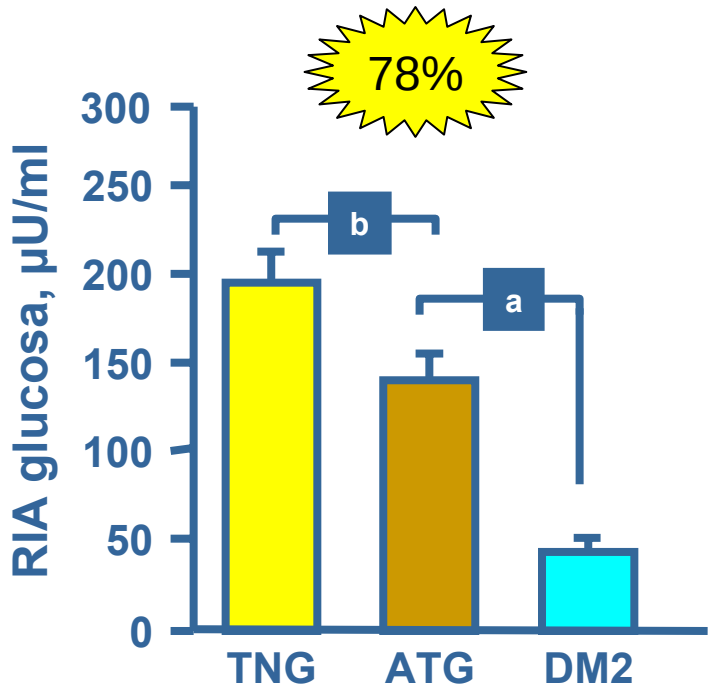

UKPDS 33. Lancet 352:837–853
HbA1c %
9
8
7
6
0
0
1
2
3
4
5
6
Tiempo desde la Aleatorización (años)
Dieta
Glibenclamida
Insulina
Metformina


ADOPT. Hochberg Kahn SE, et al. N Engl J Med. 2006; 355: 2427–2443.
A1c (%)
8,0
7,6
7,2
6,8
6,4
6,0
0
0
1
2
3
4
5
Años
4012
3308
2991
2583
2197
822
(nº de pacientes)
Rosiglitazona
Metformina
Gliburida

Sensibilidad a la insulina



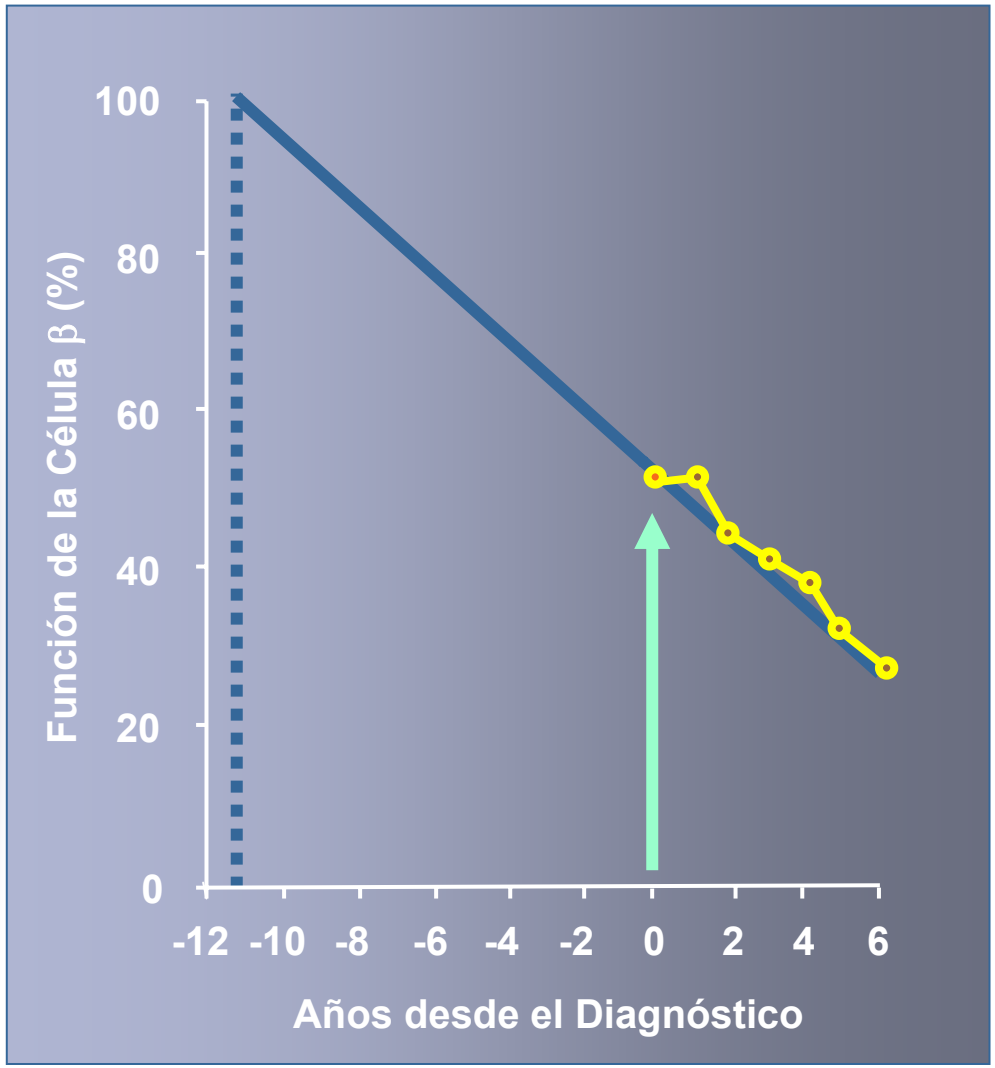
Secreción de insulina



Estudio longitudinal durante 5,1 ± 1,4 años
N= 45 indios Pima (17 con DM2)
Peso (Kg.) inicial: 93,7; Peso final:106,9

Wallace TM, Levy JC, MatthewsDR2004 Use and abuse of HOMA modeling. Diabetes Care 27:1487–1495

Weyer C, Bogardus C, Mott DM, Pratley RE 1999 The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 104:787–794

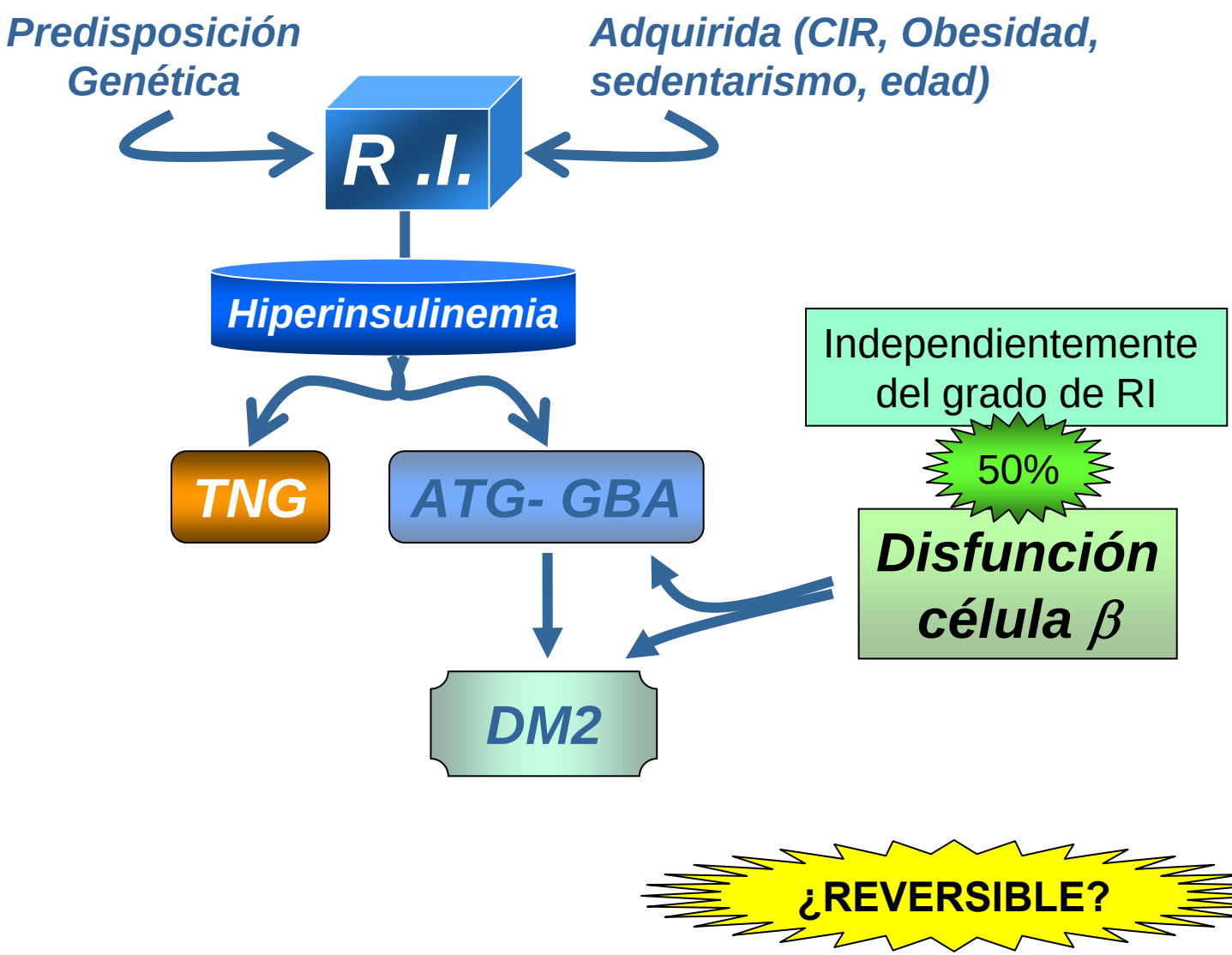


Se estima que la función de la célula β ya haya disminuido en un 50% en el momento del diagnóstico

La función de la célula β disminuye progresivamente con el tiempo a razón de aproximadamente 6% por año

Holman RR 1998 Assessing the potential for α-glycosidase inhibitors in prediabetic states. Diabetes Res Clin Pract 40 (Suppl):S21–S25

Abordaje fisiopatológico

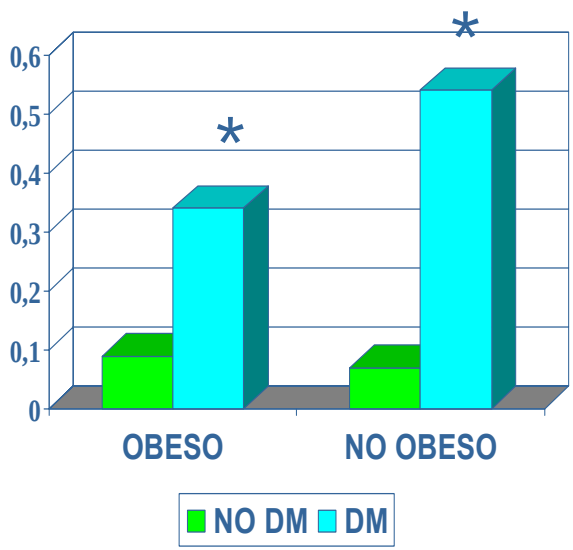


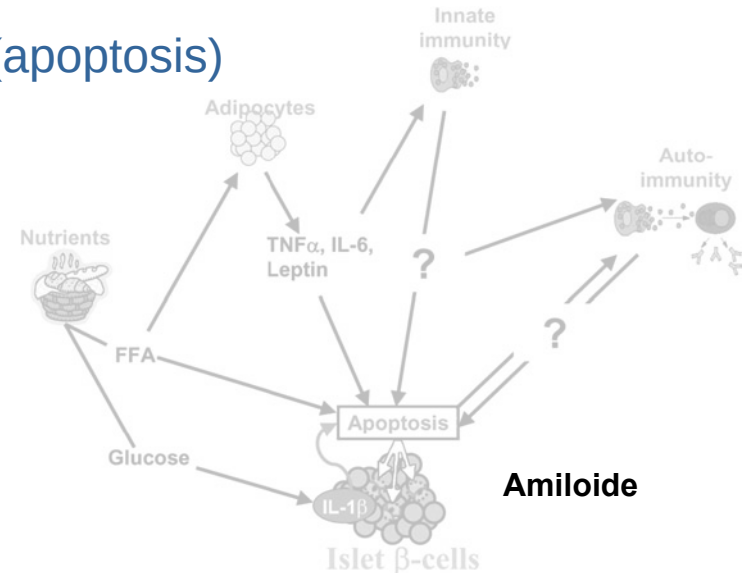
RI: resistencia a la insulina; TNG: tolerancia normal a la glucosa; TAG: tolerancia alterada a la glucosa; GBA: glucemia basal alterada

Abordaje fisiopatológico

Disfunción de la célula β

-Deficiencia insulínica
-Defecto secretor
-Disminución de la masa celular (apoptosis)





Amiloide

Secreción deficiente de insulina

Secreción excesiva de glucagón

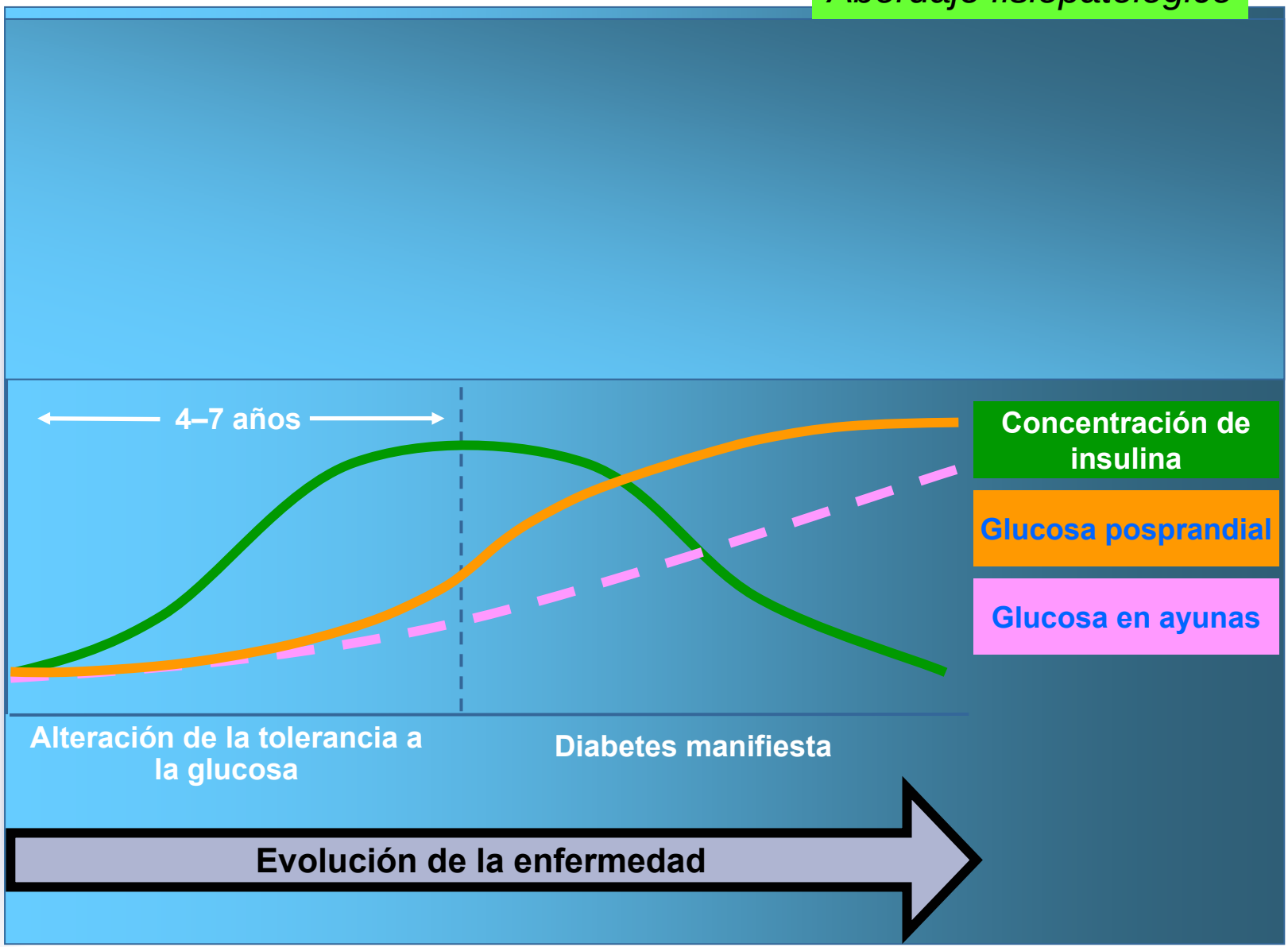
- Alteración de la sensibilidad a la glucosa

Disfunción de la célula α

Butler AE, et al. 2003. Diabetes 52:102–110

Wajchenberg, B. L. Endocr Rev 2007;28:187-218

Abordaje fisiopatológico



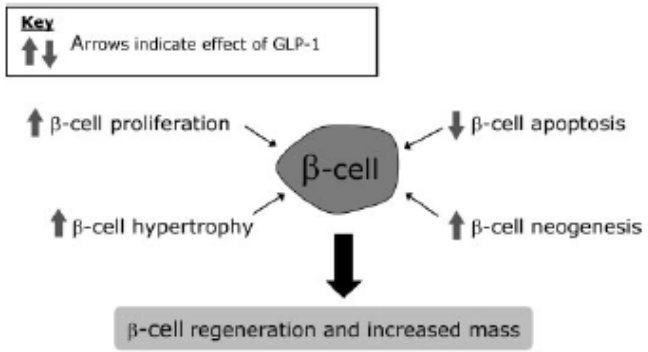
Primary Care, 26, Ramlo-Halsted BA, Edelman SV, The natural history of type 2 diabetes. Implications for clinical practice, 771–789, © 1999, con autorización de Elsevier.

Incretinas

- **Las incretinas son hormonas segregadas por las células endocrinas intestinales en respuesta a la ingesta de nutrientes**

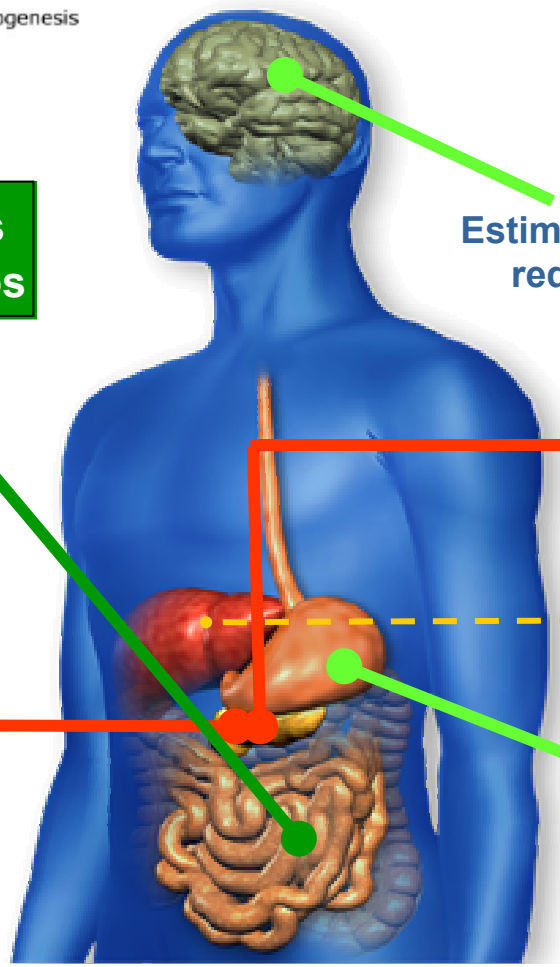
Mayo et al 2003; Wideman and Kieffer 2004

Abordaje fisiopatológico



GLP 1 segregado tras la ingesta de alimentos

↑ **Respuesta célula β**



Estimula la saciedad y reduce el apetito

↓ **Carga de trabajo célula β**

Células alfa:
↓ Secreción posprandial de glucagón dependiente de la glucosa

Hígado:
reducción de la producción hepática de glucosa

Estómago:
Enlentecimiento del vaciado gástrico

Células beta:**
Mejora la secreción de insulina dependiente de glucosa

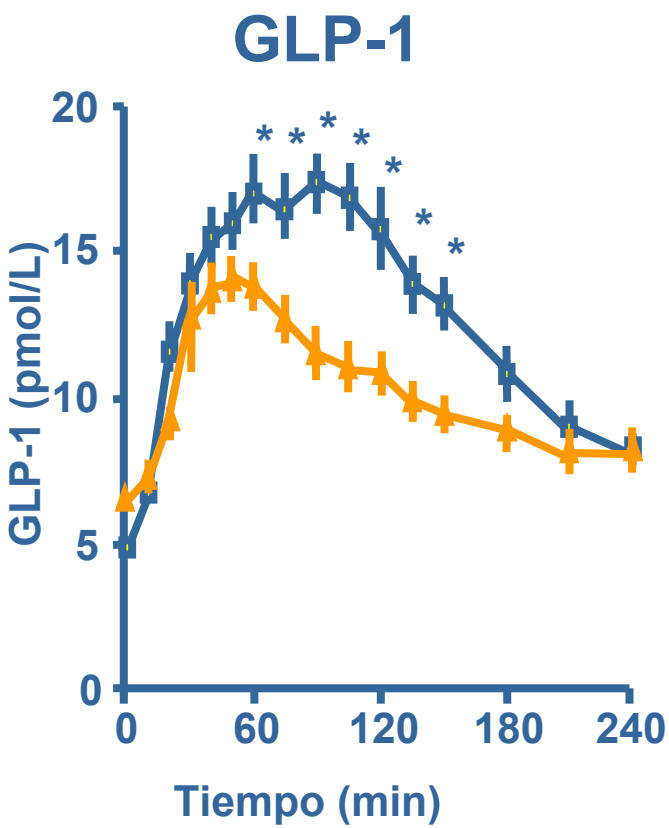
Adaptado de Flint A, et al. J Clin Invest. 1998;101:515-520.; Adaptado de Larsson H, et al. Acta Physiol Scand. 1997;160:413-422.; Adaptado de Nauck MA, et al. Diabetologia. 1996;39:1546-1553.; Adaptado de Drucker DJ. Diabetes. 1998;47:159-169.

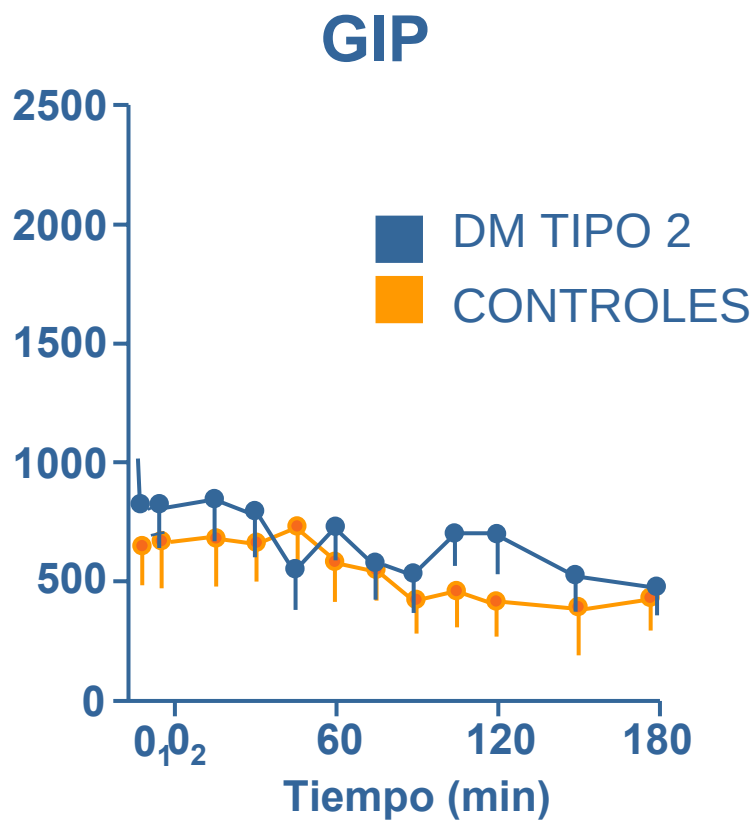
Abordaje fisiopatológico

Incretinas en la DM 2

1. Disminución en la secreción
2. Metabolismo acelerado
3. Alteración en los receptores
4. Interferencia de distintos neuropéptidos

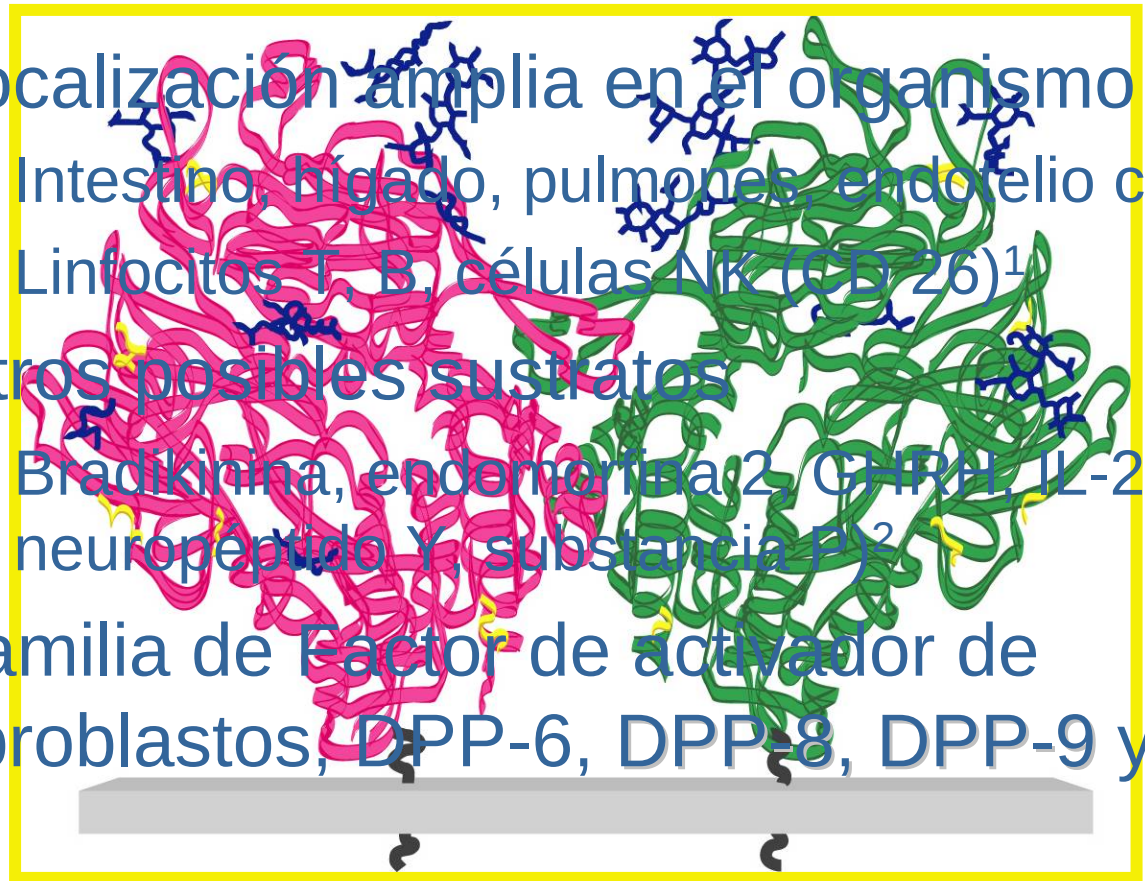
(Mannucci et al 2005, Nauck and El-Ouaghlidi 2005).





Nauck MA, et al. Diabetologia. 1986;29:46-52; Toft-Nielsen M, et al. J Clin Endocrinol Metab. 2001;86:3717-3723.
Toft-Nielsen M, et al. J Clin Endocrinol Metab. 2001;86:3717-3723.

DPP-4



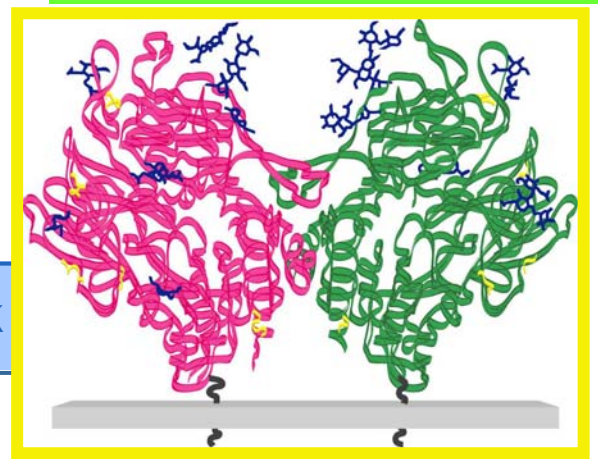
- Localización amplia en el organismo
  - Intestino, hígado, pulmones, endotelio capilar
  - Linfocitos T, B, células NK (CD 26)[1]
- Otros posibles sustratos
  - Bradikinina, endomorfina 2, GHRH, IL-2, IL-1β, neuropéptido Y, substancia P)[2]
- Familia de Factor de activador de fibroblastos, DPP-6, DPP-8, DPP-9 y DPP-4β[3]

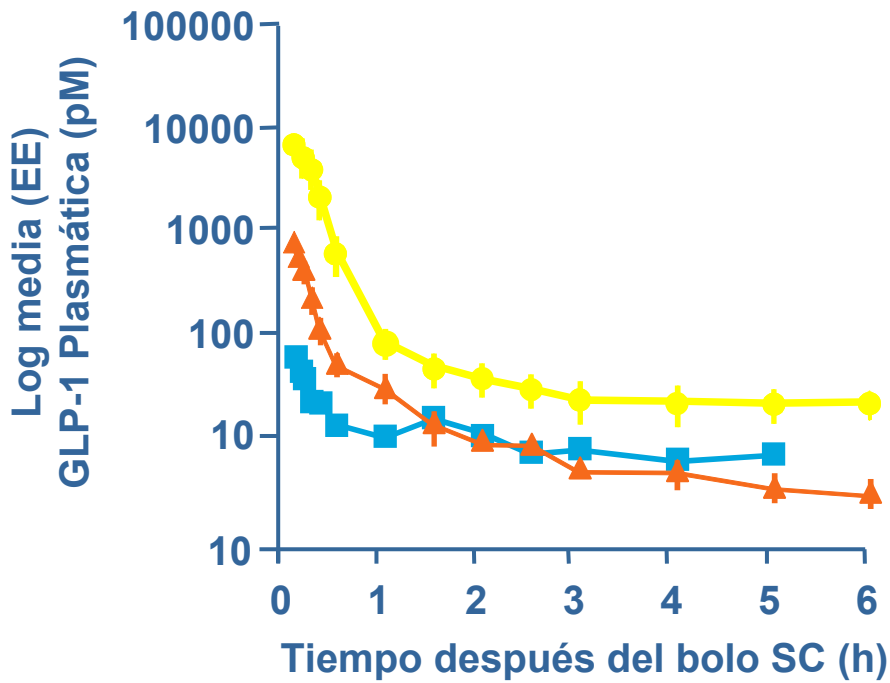
[1] Mentlein 1999;De Meester et al 2000 ; [2] De Meester et al 2003; [3] Busek et al 2004

Abordaje fisiopatológico

La DPP-4 divide GLP-1

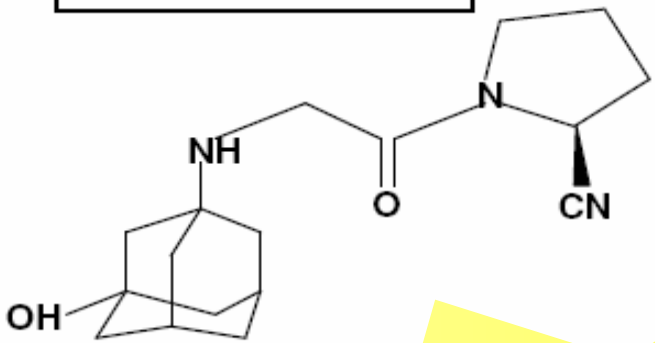
50% en capilares intestinales



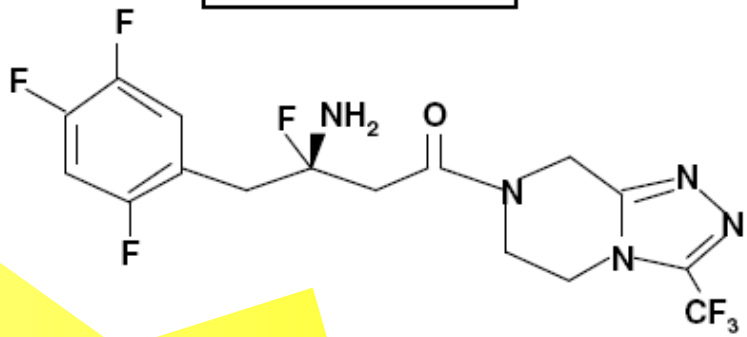


Deacon CF. 2005. What do we know about the secretion and degradation of incretin hormones? *Regul Pept*, 128:117–24.

VILDAGLIPTIN

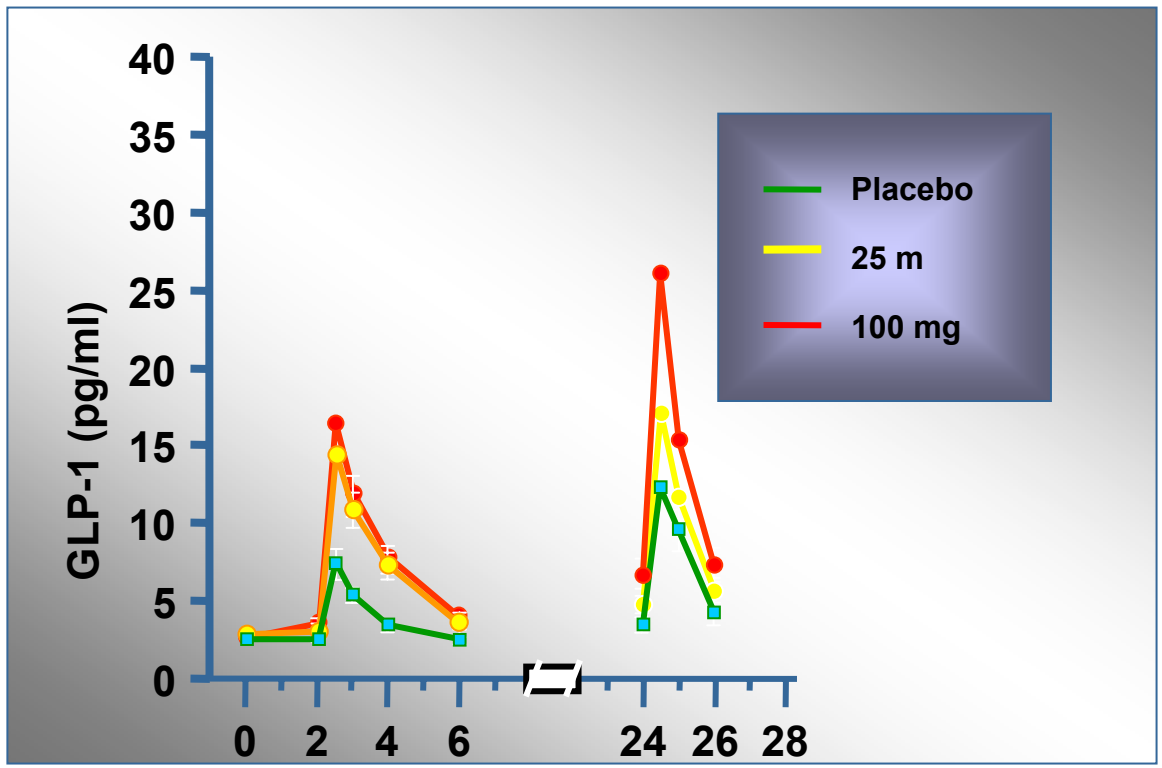


SITAGLIPTIN



Inhibidores de DPP-4

- Estrategia: prevenir la inactivación de las incretinas aumentando y prolongando sus efectos



Holst JJ, Deacon CF. 1998. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. Diabetes, 47:1663–70.
Holst JJ, Deacon CF. 2005. Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. Diabetologia, 48:612–5.

Table 1 Clinically important pharmacokinetic/-dynamic parameters of current DPP-4 inhibitors

	Sitagliptin	Vildagliptin
Selectivity for DPP-4 over DPP-8/9 [-fold]	>2600	32–250
Absolute bioavailability [%]	87	85
Time to reach maximum plasma concentration, T_{max} [hr]	2	1–2
Volume of distribution [L]	198	70.5
Plasma protein binding [%]	38	9
Terminal half life, $T_{1/2}$ [hr]	11.0	1.7[a]
Renal clearance [L/hr]	21	13
Elimination in urine [%]	87	85
Recommended dosage [mg/day]	100	100

Notes: [a]100 mg once daily (2.5 hrs with 100 mg twice daily).
Abbreviations: DPP-4, dipeptidyl peptidase-4.

Farmacocinética no influida por edad, sexo o IMC; No interacciones
Ajuste en IR leve (S); no en IR e IH (S y V)

1. Inhibidores competitivos de DPP-4
2. Activos vía oral, absorbidos rápidamente y eliminados vía renal
3. La actividad DPP-4 es inhibida casi al 100% a los 15-30 minutos, y más del 80% a las 16 horas de la administración (2 fases)

DOSIS RECOMENDADA: 100 mg/día

Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes
Bernd Richter et al. Vascular Health and Risk Management 2008:4(4)

	DPP-IV inhibitors
Administration	Orally available
GLP-1 concentrations	Physiological
Mechanism of actions	GLP-1 + GIP
Activation of portal glucose sensor	Yes
↑ Insulin secretion	+
↓ Glucagon secretion	++
Gastric emptying	+/−
Weight loss	No
Expansion of β-cell mass in preclinical studies	Yes
Nausea and vomiting	No
Potential immunogenicity	No

β-Cell Failure in Diabetes and Preservation by Clinical Treatment

Bernardo L. Wajchenberg Endocrine Reviews, April 2007, 28(2):187–218

Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes

Bernd Richter
Elizabeth Bandeira-Echtler
Karla Bergerhoff
Christian Lerch

Vascular Health and Risk Management 2008:4(4) 753–768

HASTA 2 AÑOS; 6028 (S)/5239 (V)

Table 2 Main baseline characteristics (mean values across all study arms) of randomized controlled trials of DPP-4 inhibitors

	Sitagliptin		Vildagliptin	
	Intervention[a]	Control[b]	Intervention[a]	Control[b]
Female sex [%]	49.2	47.7	45.9	45.2
Age [yrs]	55.0	54.2	54.4	54.2
Ethnic group, white participants [%]	68.8	59.1	67.5	67.2
Duration of disease [yrs]	4.5	4.7	3.3	4.4
Body mass index [kg/m^2]	31.5	31.7	31.4	31.8
Pharmaco-naïve patients[c] [%]	39.9	45.4	[d]	[d]
HbA_{1c} [%]	8.0	8.5	8.2	8.4

Notes: [a]intervention indicates active sitagliptin or vildagliptin treatment; [b]control denotes placebo or hypoglycemic comparator; [c]type 2 diabetic patients on exercise and/or diet only; [d]patients on no antidiabetic drugs was an inclusion criterion in 7/12 studies.
Abbreviations: DPP-4, dipeptidyl peptidase-4; HbA_{1c}, hemoglobin A1c.

Vildagliptina

Ahrén et al 2004b; Ristic, et al 2005; Mimori et al 2006; Pratley et al 2006; Bosi et al 2007; Dejager et al 2007; Fonseca et al 2007; Garber et al 2007; Pi-Sunyer et al 2007; Rosenstock et al 2007a, 2007b; Schweizer et al 2007

Sitagliptina

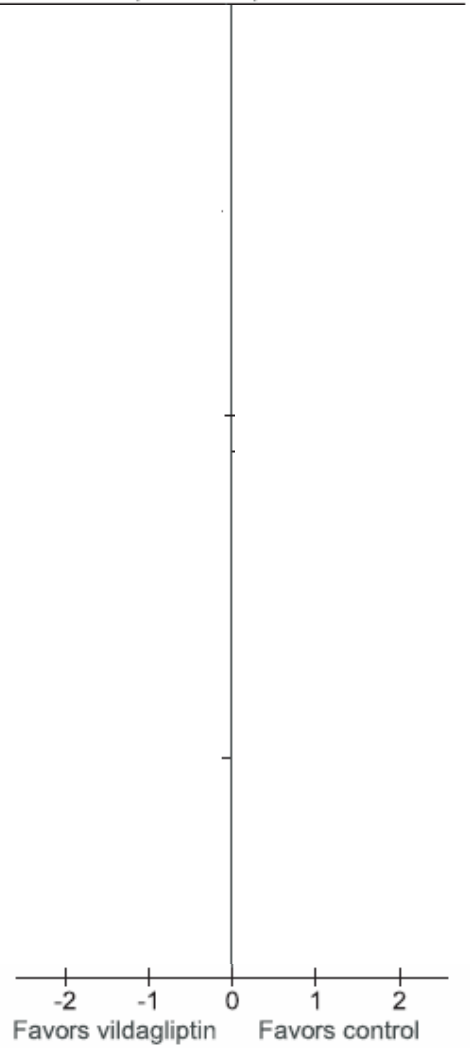
Aschner et al 2006; Charbonnel et al 2006; Nonaka et al 2006; Raz et al 2006; Rosenstock et al 2006; Goldstein et al 2007; Hanefeld et al 2007; Hermansen et al 2007; Nauck et al 2007; Scott et al 2007.

Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes

Bernd Richter Vascular Health and Risk Management 2008:4(4) 753–768

VILDAGLIPTINA: A1c

Study or Subgroup	Vildagliptin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
1.1.2 Vildagliptin vs placebo								
Dejager 2007	-0.9	0.86	150	-0.3	0.86	149	3.4%	-0.60 [-0.79, -0.41]
Mimori 2006	-0.92	0.61	76	0.28	0.59	72	3.4%	-1.20 [-1.39, -1.01]
Pi-Sunyer 2007	-0.8	0.94	89	0	0.94	88	3.2%	-0.80 [-1.08, -0.52]
Pratley 2006	-0.6	0.84	70	0	1.06	28	2.9%	-0.60 [-1.04, -0.16]
Ristic 2005	-0.53	0.77	60	-0.13	0.74	55	3.2%	-0.40 [-0.68, -0.12]
Subtotal (95% CI)			**445**			**392**	**16.1%**	**-0.73 [-1.04, -0.42]**
Test for heterogeneity: Chi² = 29.31, df = 4 (P < 0.00001), I² = 86.4%								
Test for overall effect: Z = 4.64 (P < 0.00001)								
1.1.3 Vildagliptin vs hypoglycemic agent								
Rosenstock 2007a	-1.1	2.14	459	-1.3	1.54	238	3.2%	0.20 [-0.08, 0.48]
Rosenstock 2007b	-1.1	1.22	150	-1.4	1.25	157	3.2%	0.30 [0.02, 0.58]
Schweizer 2007	-1	2.26	511	-1.4	1.58	249	3.2%	0.40 [0.12, 0.68]
Subtotal (95% CI)			**1120**			**644**	**9.7%**	**0.30 [0.14, 0.46]**
Test for heterogeneity: Chi² = 1.00, df = 2 (P = 0.61), I² = 0%								
Test for overall effect: Z = 3.68 (P = 0.0002)								
1.1.4 Vildagliptin combination therapy								
Ahren 2004	-0.6	0.75	56	0.1	0.71	51	3.2%	-0.70 [-0.98, -0.42]
Bosi 2007	-0.9	1.2	143	0.2	1.14	130	3.2%	-1.10 [-1.38, -0.82]
Fonseca 2007	-0.5	1.18	140	-0.2	1.22	149	3.2%	-0.30 [-0.58, -0.02]
Garber 2007	-1	1.17	136	-0.3	1.17	138	3.2%	-0.70 [-0.98, -0.42]
Rosenstock 2007bVILDA+PIO	-1.9	1.21	146	-1.4	1.25	157	3.2%	-0.50 [-0.78, -0.22]
Subtotal (95% CI)			**621**			**625**	**16.2%**	**-0.66 [-0.92, -0.40]**
Test for heterogeneity: Chi² = 17.59, df = 4 (P = 0.001), I² = 77.3%								
Test for overall effect: Z = 4.98 (P < 0.00001)								

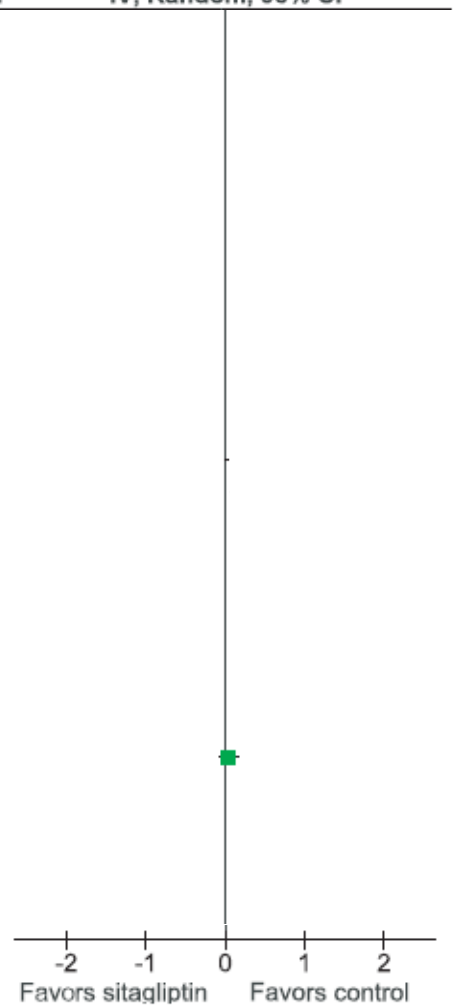


Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes

Bernd Richter Vascular Health and Risk Management 2008:4(4) 753–768

SITAGLIPTINA: A1c

Study or Subgroup	Sitagliptin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
2.1.2 Sitagliptin vs placebo								
Aschner 2006	-0.61	0.97	229	0.18	0.96	244	3.1%	-0.79 [-0.96, -0.62]
Goldstein 2007 PLA	-0.66	1.11	175	0.17	1.08	165	3.0%	-0.83 [-1.06, -0.60]
Hanefeld 2007	-0.44	0.74	106	0.12	0.74	107	3.1%	-0.56 [-0.76, -0.36]
Nonaka 2006	-0.65	1.32	75	0.41	1.32	76	2.6%	-1.06 [-1.48, -0.64]
Raz 2006	-0.48	0.92	193	0.12	0.91	103	3.0%	-0.60 [-0.82, -0.38]
Scott 2007 PLA	-0.54	0.79	121	0.23	0.76	121	3.1%	-0.77 [-0.97, -0.57]
Subtotal (95% CI)			**899**			**816**	**17.9%**	**-0.73 [-0.85, -0.62]**
Test for heterogeneity: Chi² = 7.85, df = 5 (P = 0.16), I² = 36.3%								
Test for overall effect: Z = 12.69 (P < 0.00001)								
2.1.3 Sitagliptin vs hypoglycemic agent								
Goldstein 2007 MET	-0.66	1.11	175	-1.13	1.09	177	3.0%	0.47 [0.24, 0.70]
Scott 2007 GLIP	-0.54	0.79	121	-0.76	0.78	119	3.1%	0.22 [0.02, 0.42]
Subtotal (95% CI)			**296**			**296**	**6.1%**	**0.34 [0.09, 0.58]**
Test for heterogeneity: Chi² = 2.60, df = 1 (P = 0.11), I² = 61.6%								
Test for overall effect: Z = 2.71 (P = 0.007)								
2.1.4 Sitagliptin vs combination therapy								
Charbonnel 2006	-0.67	1.09	453	-0.02	0.95	224	3.2%	-0.65 [-0.81, -0.49]
Goldstein 2007 SITA+MET	-1.9	1.09	178	-1.13	1.09	177	3.0%	-0.77 [-1.00, -0.54]
Hermansen 2007 GLI	-0.3	0.93	103	0.27	0.94	104	3.0%	-0.57 [-0.82, -0.32]
Nauck 2007	-0.51	1.04	576	-0.56	1.02	559	3.2%	0.05 [-0.07, 0.17]
Rosenstock 2006	-0.85	0.85	163	-0.15	0.84	174	3.1%	-0.70 [-0.88, -0.52]
Subtotal (95% CI)			**1473**			**1238**	**15.5%**	**-0.52 [-0.89, -0.16]**
Test for heterogeneity: Chi² = 85.95, df = 4 (P < 0.00001), I² = 95.3%								
Test for overall effect: Z = 2.79 (P = 0.005)								



Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes

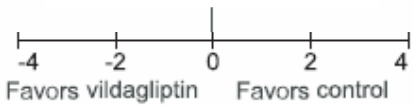
Bernd Richter Vascular Health and Risk Management 2008:4(4) 753–768

VILDAGLIPTINA y SITAGLIPTINA: Peso

	Vildagliptin			Control				Mean difference	Mean difference
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]	IV, Random, 95% CI [kg]
1.3.1 Vildagliptin vs control									
Ahren 2004	-0.4	1.5	56	-0.5	1.4	51	6.0%	0.10 [-0.45, 0.65]	
Bosi 2007	0.2	3.6	143	-1	3.4	130	5.5%	1.20 [0.37, 2.03]	
Dejager 2007	-0.8	3.8	92	-1.4	3.9	94	5.0%	0.60 [-0.51, 1.71]	
Fonseca 2007	1.3	3.5	140	0.6	3.7	149	5.5%	0.70 [-0.13, 1.53]	
Pi-Sunyer 2007	-0.4	2.8	89	-1.4	3.8	88	5.2%	1.00 [0.02, 1.98]	
Ristic 2005	-0.07	2.5	63	-0.73	2.5	58	5.4%	0.66 [-0.23, 1.55]	
Rosenstock 2007b	0.2	3.7	150	1.5	3.8	157	5.5%	-1.30 [-2.14, -0.46]	
Rosenstock 2007bVILDA+PIO	2.1	3.6	146	1.5	3.8	157	5.5%	0.60 [-0.23, 1.43]	
Schweizer 2007	0.3	4.5	511	-1.9	0.3	47	6.2%	2.20 [1.80, 2.60]	
Subtotal (95% CI)			**1390**			**931**	**50.0%**	**0.65 [-0.11, 1.41]**	

Test for heterogeneity: Chi² = 76.50, df = 8 (P < 0.00001), I² = 89.5%

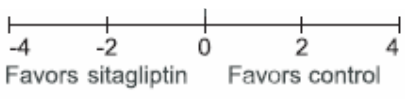
Test for overall effect: Z = 1.68 (P = 0.09)



	Sitagliptin			Control				Mean difference	Mean difference
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]	IV, Random, 95% CI [kg]
2.3.1 Sitagliptin vs control									
Aschner 2006	-0.2	3	229	-1.1	3.1	244	6.7%	0.90 [0.35, 1.45]	
Charbonnel 2006	-0.7	5.9	453	-0.6	5.9	224	6.0%	-0.10 [-1.04, 0.84]	
Goldstein 2007 PLA	0	3.2	175	-0.9	3.2	165	6.5%	0.90 [0.22, 1.58]	
Hermansen 2007 GLI	1.1	3.4	103	0	3.4	104	6.0%	1.10 [0.17, 2.03]	
Hermansen 2007 GLIM+MET	0.4	2.7	115	-0.7	3.4	107	6.2%	1.10 [0.29, 1.91]	
Nauck 2007	-1.5	6.7	576	1.1	6.6	559	6.3%	-2.60 [-3.37, -1.83]	
Raz 2006	-0.6	2.8	193	-0.7	3.1	103	6.4%	0.10 [-0.62, 0.82]	
Rosenstock 2006	1.8	4.2	163	1.5	4.4	174	6.0%	0.30 [-0.62, 1.22]	
Subtotal (95% CI)			**2007**			**1680**	**50.0%**	**0.21 [-0.64, 1.07]**	

Test for heterogeneity: Chi² = 69.09, df = 7 (P < 0.00001), I² = 89.9%

Test for overall effect: Z = 0.49 (P = 0.62)



Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes

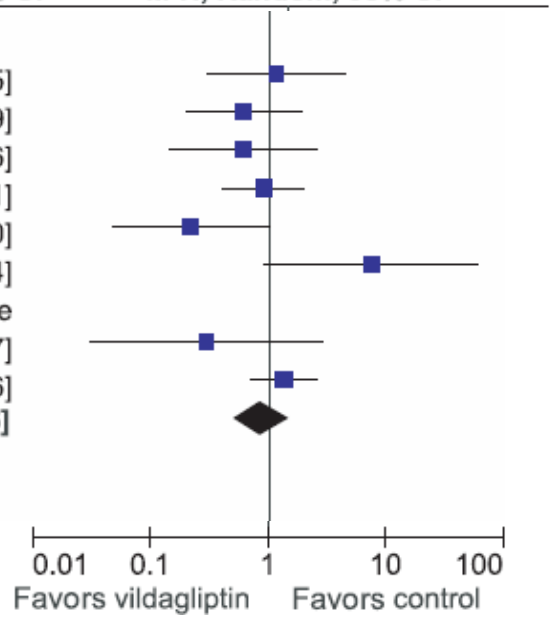
Bernd Richter Vascular Health and Risk Management 2008:4(4) 753–768

VILDAGLIPTINA : Efectos adversos graves

Study or Subgroup	Vildagliptin Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
1.2.2 Serious adverse events						
Ahren 2004	5	56	4	51	2.3%	1.15 [0.29, 4.55]
Bosi 2007	5	183	8	181	3.1%	0.61 [0.19, 1.89]
Dejager 2007	3	155	5	157	2.1%	0.60 [0.14, 2.56]
Fonseca 2007	12	144	14	152	5.0%	0.90 [0.40, 2.01]
Garber 2007	2	158	9	158	1.8%	0.21 [0.05, 1.00]
Pi-Sunyer 2007	7	91	1	92	1.1%	7.58 [0.91, 62.94]
Pratley 2006	0	70	0	28		Not estimable
Ristic 2005	1	62	3	56	0.9%	0.29 [0.03, 2.87]
Schweizer 2007	35	519	13	252	6.3%	1.33 [0.69, 2.56]
Subtotal (95% CI)	**70**	**1438**	**57**	**1127**	**22.5%**	**0.86 [0.51, 1.46]**

Test for heterogeneity: Chi² = 10.41, df = 7 (P = 0.17), I² = 32.7%

Test for overall effect: Z = 0.54 (P = 0.59)



Hipoglucemias

Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes

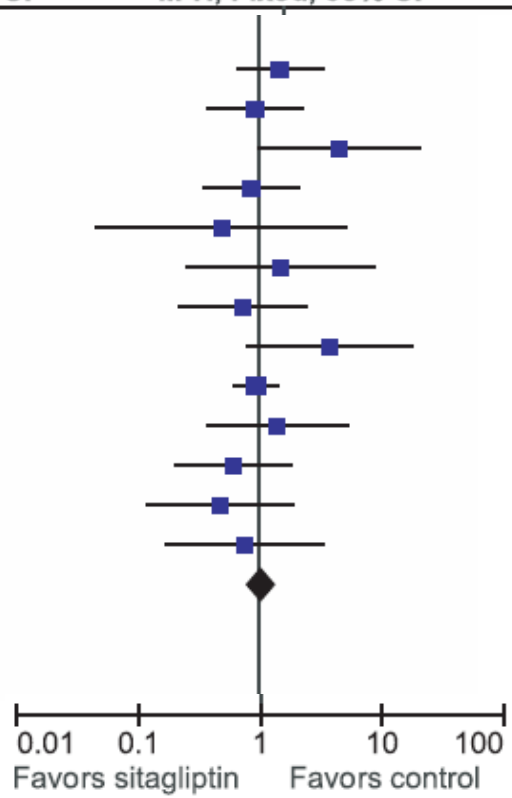
Bernd Richter Vascular Health and Risk Management 2008:4(4) 753–768

SITAGLIPTINA : Efectos adversos graves

Study or Subgroup	Sitagliptin Events	Total	Control Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
2.2.2 Serious adverse events						
Aschner 2006	14	238	10	253	2.5%	1.52 [0.66, 3.49]
Charbonnel 2006	13	464	7	237	2.5%	0.95 [0.37, 2.41]
Goldstein 2007 MET	9	179	2	182	0.5%	4.76 [1.01, 22.37]
Goldstein 2007 PLA	9	179	10	176	2.6%	0.88 [0.35, 2.22]
Goldstein 2007 SITA+MET	1	182	2	182	0.5%	0.50 [0.04, 5.53]
Hanefeld 2007	3	110	2	111	0.5%	1.53 [0.25, 9.33]
Hermansen 2007 GLI	5	116	6	106	1.7%	0.75 [0.22, 2.54]
Hermansen 2007 GLIM+MET	7	106	2	113	0.5%	3.92 [0.80, 19.33]
Nauck 2007	43	588	44	584	11.3%	0.97 [0.63, 1.50]
Raz 2006	8	205	3	110	1.0%	1.45 [0.38, 5.57]
Rosenstock 2006	5	175	8	178	2.1%	0.63 [0.20, 1.95]
Scott 2007 GLIP	3	122	6	123	1.6%	0.49 [0.12, 2.01]
Scott 2007 PLA	3	122	4	125	1.1%	0.76 [0.17, 3.48]
Subtotal (95% CI)	**123**	**2786**	**106**	**2480**	**28.5%**	**1.07 [0.82, 1.40]**

Test for heterogeneity: $Chi^2 = 10.54$, df = 12 (P = 0.57), $I^2 = 0\%$

Test for overall effect: Z = 0.52 (P = 0.60)



Hipoglucemias

Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes

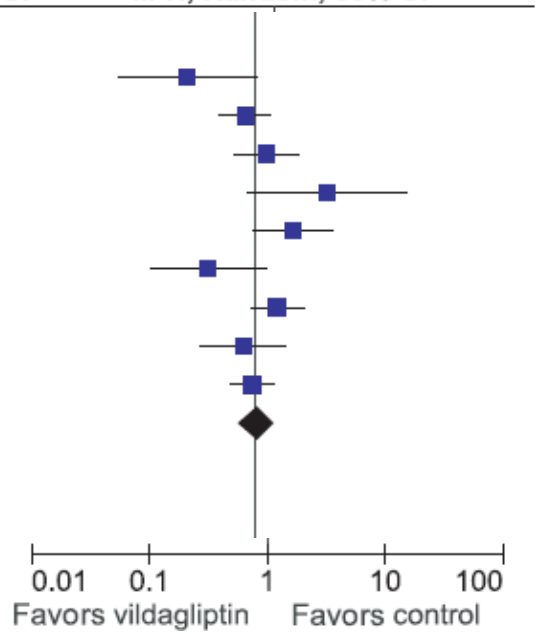
Bernd Richter Vascular Health and Risk Management 2008:4(4) 753–768

VILDAGLIPTINA : Infecciones

Study or Subgroup	Vildagliptin Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
1.2.3 All-cause infections						
Ahren 2004	3	56	9	51	2.3%	0.26 [0.07, 1.04]
Bosi 2007	35	183	40	181	8.0%	0.83 [0.50, 1.39]
Dejager 2007	24	155	20	157	6.5%	1.25 [0.66, 2.38]
Garber 2007	8	158	2	158	1.8%	4.16 [0.87, 19.91]
Pi-Sunyer 2007	22	91	12	92	5.2%	2.13 [0.98, 4.61]
Ristic 2005	5	62	10	56	3.0%	0.40 [0.13, 1.26]
Rosenstock 2007a	58	515	20	267	7.7%	1.57 [0.92, 2.67]
Rosenstock 2007b	10	153	13	161	4.6%	0.80 [0.34, 1.87]
Schweizer 2007	77	519	39	252	9.2%	0.95 [0.63, 1.45]
Subtotal (95% CI)	**242**	**1892**	**165**	**1375**	**48.4%**	**1.05 [0.74, 1.50]**

Test for heterogeneity: $Chi^2 = 16.64$, df = 8 (P = 0.03), $I^2 = 51.9\%$

Test for overall effect: Z = 0.29 (P = 0.77)



Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes

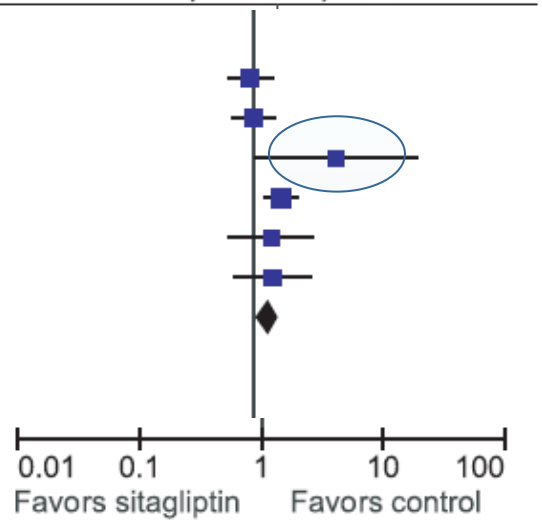
Bernd Richter Vascular Health and Risk Management 2008:4(4) 753–768

SITAGLIPTINA : Infecciones

Study or Subgroup	Vildagliptin Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
2.2.3 All-cause infections						
Aschner 2006	48	238	53	253	11.3%	0.95 [0.62, 1.48]
Charbonnel 2006	77	464	39	237	11.9%	1.01 [0.66, 1.54]
Hanefeld 2007	9	110	2	111	0.5%	4.86 [1.02, 23.02]
Nauck 2007	113	588	71	584	15.9%	1.72 [1.25, 2.37]
Raz 2006	23	205	9	110	2.9%	1.42 [0.63, 3.18]
Rosenstock 2006	18	175	13	178	3.2%	1.46 [0.69, 3.07]
Subtotal (95% CI)	**288**	**1780**	**187**	**1473**	**45.6%**	**1.34 [1.10, 1.64]**

Test for heterogeneity: $Chi^2 = 9.04$, $df = 5$ ($P = 0.11$), $I^2 = 44.7\%$

Test for overall effect: $Z = 2.86$ ($P = 0.004$)



Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes

Bernd Richter Vascular Health and Risk Management 2008:4(4) 753–768

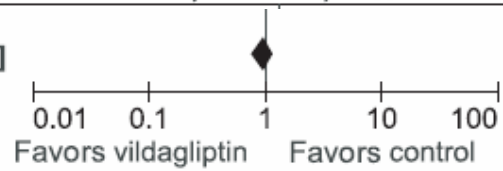
VILDAGLIPTINA y SITAGLIPTINA : Efectos Adversos

Study or Subgroup	Vildagliptin Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Total (95% CI)	389	5584	286	4218	100.0%	0.96 [0.77, 1.21]

Test for heterogeneity: Chi² = 39.28, df = 27 (P = 0.06), I² = 31.3%

Test for overall effect: Z = 0.35 (P = 0.73)

Test for subgroup differences: Not applicable



Study or Subgroup	Vildagliptin Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Total (95% CI)	507	7353	386	6433	100.0%	1.16 [1.01, 1.33]

Test for heterogeneity: Chi² = 44.52, df = 31 (P = 0.06), I² = 30.4%

Test for overall effect: Z = 2.03 (P = 0.04)

Test for subgroup differences: Not applicable

Safety and tolerability of sitagliptin in patients with type 2 diabetes: a pooled analysis

Debora Williams-Herman*, Elizabeth Round, Arlene S Swern, Bret Musser, Michael J Davies, Peter P Stein, Keith D Kaufman and John M Amatruda

BMC Endocrine Disorders 2008, 8:14 doi:10.1186/1472-6823-8-14

Table 6: Clinical adverse experiences occurring at an incidence rate ≥1% in any group

Adverse Experience	Sitagliptin 100 mg n (%) (N = 3415)	Non-Exposed n (%) (N = 2724)	Difference between Sitagliptin and Non-Exposed, % (95% CI)*
Influenza	145 (4.2)	127 (4.7)	-0.4 (-1.5, 0.6)
Nasopharyngitis	244 (7.1)	162 (5.9)	1.2 (-0.1, 2.4)
Pharyngitis	52 (1.5)	35 (1.3)	0.2 (-0.4, 0.8)
Sinusitis	80 (2.3)	60 (2.2)	0.1 (-0.6, 0.9)
Upper Respiratory Tract Infection	265 (7.8)	228 (8.4)	-0.6 (-2.0, 0.8)
Urinary Tract Infection	134 (3.9)	100 (3.7)	0.3 (-0.7, 1.2)
Bronchitis	135 (4.0)	83 (3.0)	0.9 (-0.0, 1.8)
Cellulitis	28 (0.8)	26 (1.0)	-0.1 (-0.6, 0.3)

"There were no meaningful differences observed between treatment groups in the incidence rate, severity, and type of infections".

VILDAGLIPTINA y SITAGLIPTINA : función célula β

TABLE 7. Clinical evidence of incretin enhancer (sitagliptin and vildagliptin) effects on β-cell function in humans with DM2

Peptide	Added medication	Ref.	Findings
Sitagliptin	Monotherapy (24 wk)	230	Postmeal ↑ Insulin and C-peptide AUC ↑ Ratio insulin AUC/glucose AUC ↑ HOMA-β ↓ PI/IRI ratio
	Monotherapy or + metformin (24 wk)	231	Postmeal ↑ Insulin and C-peptide AUC ↑ Ratio insulin AUC/glucose AUC ↑ HOMA-β ↓ PI/IRI ratio
		232	Postprandial β-cell function ↑ β-cell responsiveness to basal glucose ↑ β-cell responsiveness to above-basal glucose after meal ↑ Disposition index[a]
Vildagliptin	Monotherapy (4 wk)	236	Postmeal β-cell function ↑ Insulin secretion at any given glucose level No change in slope of β-cell dose response and other model parameters
	+ Metformin or metformin alone (52 wk)	237	Postmeal β-cell function Vildagliptin + metformin: ↑ postprandial insulin secretion, ↑ insulin sensitivity to meal intake, ↑ adaptation index (insulin secretion × insulin sensitivity) Placebo + metformin: ↓ postprandial insulin secretion and ↓ adaptation index. No change in insulin sensitivity during meal intake
	Monotherapy (12 wk)	243	FSIVGTT ↑ AIR_g, ↑ S_i ↑ Disposition index[a]

[a] $S_i \times AIR_g$.

En asociación con Metformina

¿Sulfonil Ureas o Inhibidores de DPP-4?

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial

1

M. A. Nauck,[1] G. Meininger,[2] D. Sheng,[2] L. Terranella[2] and P. P. Stein[2] for the Sitagliptin Study 024 Group*

N=1172

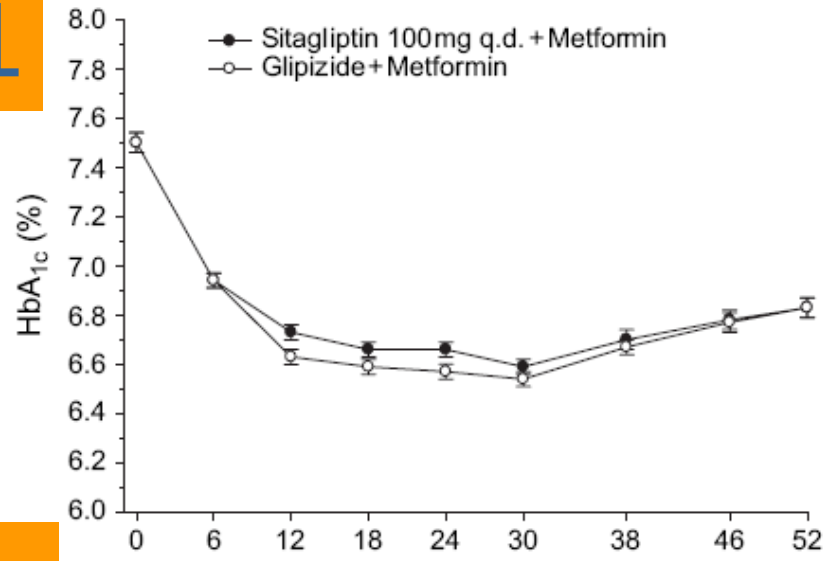
Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy

2

E. Ferrannini,[1] V. Fonseca,[2] B. Zinman,[3] D. Matthews,[4] B. Ahrén,[5] S. Byiers,[6] Q. Shao[7] and S. Dejager[8]

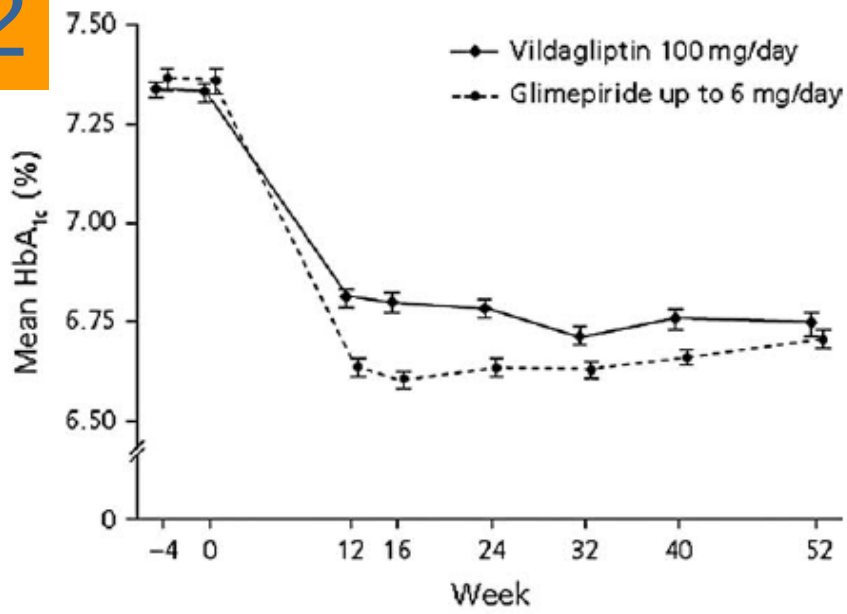
N=2190

1


Sitagliptin 100mg q.d. + Metformin
Glipizide + Metformin
HbA1c (%)
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
0
6
12
18
24
30
38
46
52

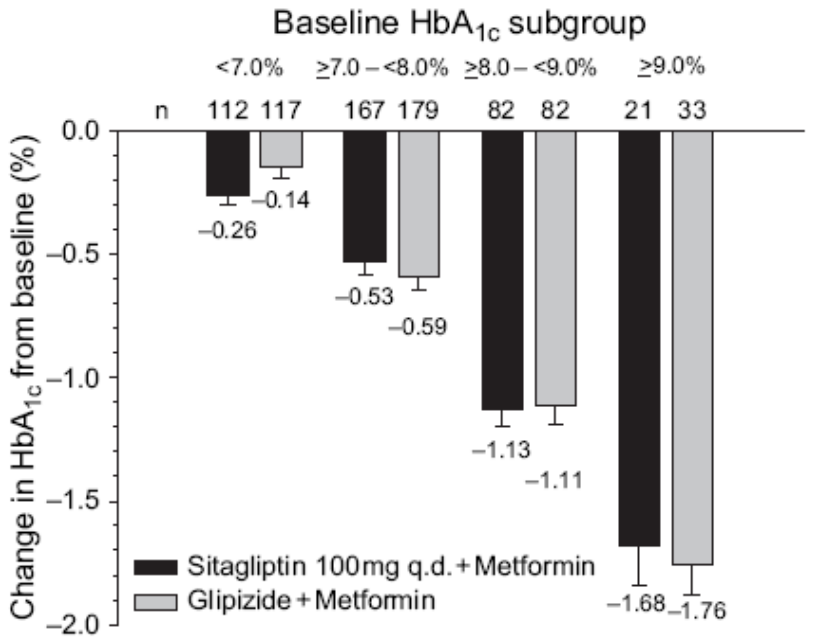
A1c

2

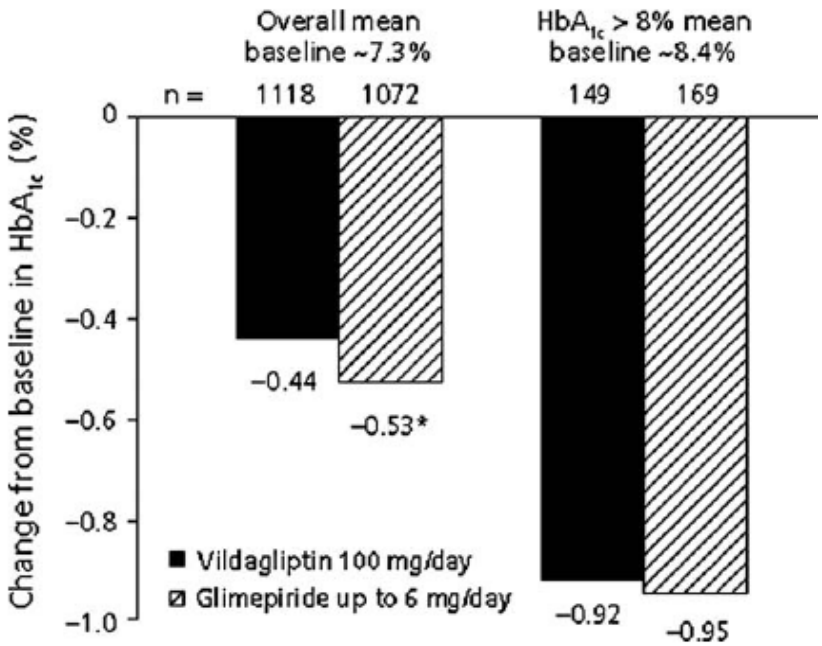

Vildagliptin 100 mg/day
Glimepiride up to 6 mg/day
Mean HbA1c (%)
7.50
7.25
7.00
6.75
6.50
0
−4
0
12
16
24
32
40
52
Week

A1c

1

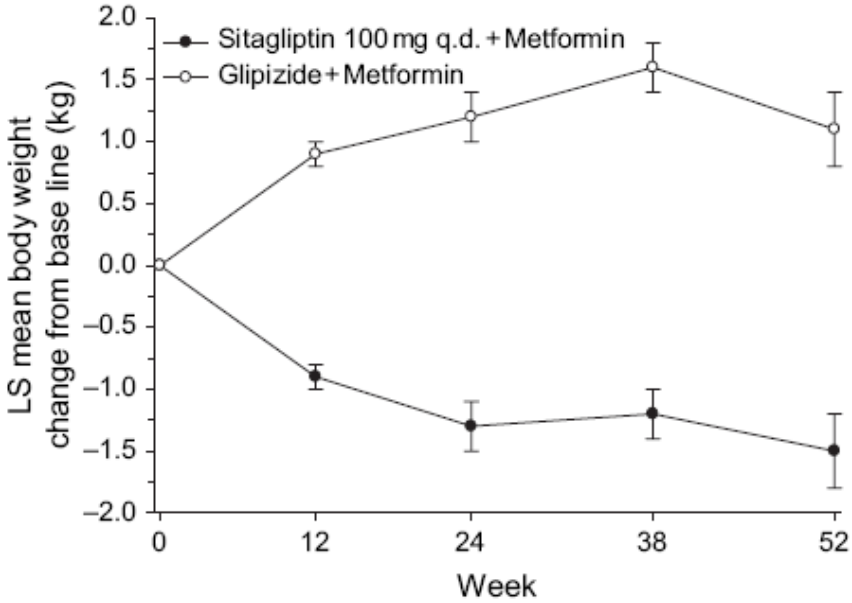

B
Baseline HbA1c subgroup
<7.0%
≥7.0 – <8.0%
≥8.0 – <9.0%
≥9.0%
n
112 117
167 179
82 82
21 33
0.0
–0.5
–1.0
–1.5
–2.0
Change in HbA1c from baseline (%)
–0.26
–0.14
–0.53
–0.59
–1.13
–1.11
–1.68
–1.76
Sitagliptin 100mg q.d. + Metformin
Glipizide + Metformin

2


Overall mean baseline ~7.3%
HbA1c > 8% mean baseline ~8.4%
n =
1118
1072
149
169
0
–0.2
–0.4
–0.6
–0.8
–1.0
Change from baseline in HbA1c (%)
–0.44
–0.53*
–0.92
–0.95
Vildagliptin 100 mg/day
Glimepiride up to 6 mg/day

Peso

1



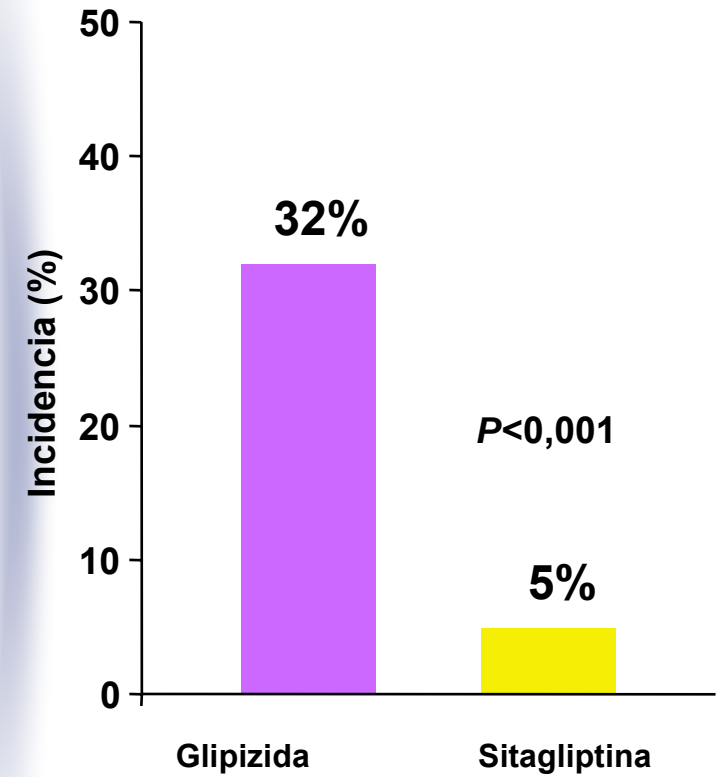
2

	Vildagliptina + Metformina	Glimepirida + Metformina
Peso inicial	89.01	88.62
Peso final	- 0.23	+1.56

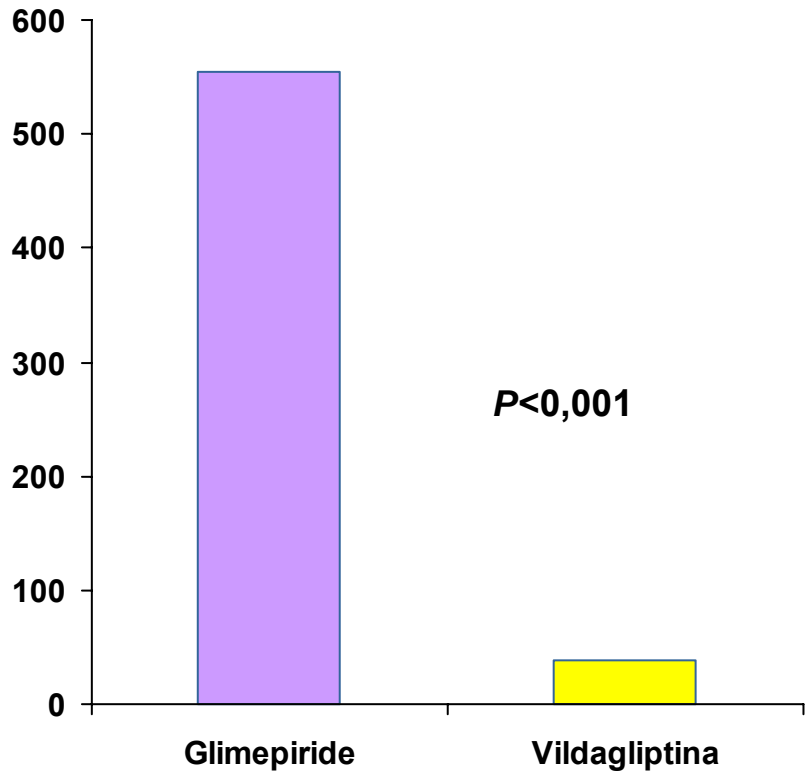
$p<0.001$

Hipoglucemias

1



2



Eventos Adversos

1

	Sitagliptin 100 mg q.d. + metformin (N = 588), n (%)	Glipizide + metformin (N = 584), n (%)
One or more AEs	419 (71.3)	444 (76.0)
Drug-related AEs*	85 (14.5)	177 (30.3)
SAEs	43 (7.3)	44 (7.5)
Drug-related SAEs*	0	2 (0.3)
Deaths	1 (0.2)	2 (0.3)
Discontinuations because of AEs	16 (2.7)	21 (3.6)
Discontinuations because of drug-related AEs	8 (1.4)	8 (1.4)
Discontinuations because of SAEs	6 (1.0)	7 (1.2)
Discontinuations because of drug-related SAEs	0	0
Clinical AEs of special interest		
Hypoglycaemia	29 (4.9)	187 (32.0)
Prespecified selected gastrointestinal AEs		
Abdominal pain	16 (2.7)	12 (2.1)
Nausea	15 (2.6)	16 (2.7)
Vomiting	5 (0.9)	9 (1.5)
Diarrhoea	34 (5.8)	32 (5.5)

2

	Vildagliptin (50 mg twice daily) n = 1389, n (%)	Glimepiride (up to 6 mg/day) n = 1383, n (%)
Overall safety summary		
Any AE	1035 (74.5)	1121 (81.1)
Discontinuation because of AEs	69 (5.0)	111 (8.0)
Drug-related AEs	244 (17.6)	494 (35.7)
Serious AEs	99 (7.1)	132 (9.5)
Adjudicated CCV AEs	12 (0.9)	22 (1.6)
Hypoglycaemia	23 (1.7)	224 (16.2)
Deaths	2 (0.1)	3 (0.2)
Most common AEs		
Nasopharyngitis	131 (9.4)	129 (9.3)
Headache	106 (7.6)	109 (7.9)
Dizziness	91 (6.6)	188 (13.6)
Influenza	79 (5.7)	60 (4.3)
Diarrhoea	76 (5.5)	71 (5.1)
Back pain	75 (5.4)	71 (5.1)
Fatigue	57 (4.1)	90 (6.5)
Nausea	56 (4.0)	71 (5.1)
Asthenia	53 (3.8)	144 (10.4)
Tremor	52 (3.7)	276 (20.0)
Hyperhidrosis	46 (3.3)	240 (17.4)
Hypoglycaemia	23 (1.7)	224 (16.2)
Hunger	10 (0.7)	71 (5.1)

¿Inhibidores de DPP-4?

PREGUNTA	RESPUESTA
Eficacia en control glucémico	
Causa potencial de hipoglucemias	
Efecto sobre el peso	
Abordaje fisiopatológico	
Durabilidad del control glucémico	
Prevención de complicaciones microvasculares	
Prevención de complicaciones macrovasculares	
Seguridad Cardiovascular	
Efectos colaterales relevantes	
Cumplimiento (combinación)	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