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Málaga. Nov 21, 2013

Acciones cardiovasculares de las terapias incretínicas: los inhibidores de la DPP-4

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Desglose de intereses

Alianza Boehringer - Lilly
- patrocinador de esta ponencia
- participante en reuniones de consenso en diabetes
- diseño e I.P. estudio REDIM (SEMI)

sanofi-Aventis
- asistencia a congresos nacionales
- profesor en cursos insulinoterapia

Novartis, Novo-Nordisk
- trabajos de asesoría en diabetes

Outline

- ¿Por qué es importante hablar de efectos cardiovasculares de los antidiabéticos?
- Mecanismos fisiopatológicos y evidencia experimental inhibidores DPP-4
- Evidencia clínica
- Conclusiones

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Keywords: first, launch, usa, sb, avandia, new, data

First launch in the USA for SB's Avandia, new data show combination efficacy

Article | 16 June 1999

SmithKline Beecham says it has introduced its type 2 diabetes drugAvandia (rosiglitazone) into 40,000 pharmacies in the USA. This is the first market for the drug and signals competition to Warner-Lambert's insulin sensitizer Rezulin (troglitazone).

As the Marketletter reported when the US Food and Drug Administration approved Avandia for use as a monotherapy and in combination with metformin last month (Marketletter May 31), the

Related Articles

Lilly/Takeda's Actos: first efficacy data presented at ADA
23 June 1999

Labeling strengthened for Rezulin in wake of Avandia launch
23 June 1999

sNDA filed for Taxol plus Herceptin
24 June 1999

Roberts purchases rights to Agrylin from B-MS
24 June 1999

ClinPhone appointment
24 June 1999

Latest Articles

Rates of Myocardial Infarction and Death from Cardiovascular Causes

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Nissen SE, Wolski K. N Engl J Med. 2007; 356:2457-2471

The NEW ENGLAND JOURNAL of MEDICINE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

>> Metaanálisis de estudios en fases II y III (edad avanzada, DM larga evolución, IR; seguimiento >2 años; adjudicación independiente eventos CV;…)

Fase III: HRs para eventos cardiovasculares:

- 1.2; 95%CI [0.5-1.9]: estudio precomercialización (>1.8)
- 1.5; 95%CI [1.3-1.7]: estudio precomercialización (>1.3)

Precomercialización: HRs para eventos cardiovasculares:

- 1.04; 95%CI [0.70-1.4]: estudio postcomercialización (>1.3)
- 1.01; 95%CI [0.81-1.21]: en principio, prescindibles (<1.3).

Postcomercialización: demostrar HR≈1, 95%CI [y - <1.3]: con diseño de no inferioridad y una tasa de eventos del 2%, se necesitaría hacer un seguimiento de **6,100 pacientes x 5 años**.

Exigencia de la Sociedad

"It is hoped that pharmaceutical companies developing new glucose-lowering agents will focus on providing some added value beyond what is already available by addressing unmet clinical needs such as the effects leading to a reduction in CVD risk factors and meaningful cardiovascular and other outcomes".

Raz I, Riddle MC, Rosenstock J, et al. Personalized Management of Hyperglycemia in Type 2 Diabetes. Reflections from a Diabetes Care Editors' Expert Forum. Diabetes Care. 2013; 36:1779-1788.

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Principal mecanismo de acción DPP-4

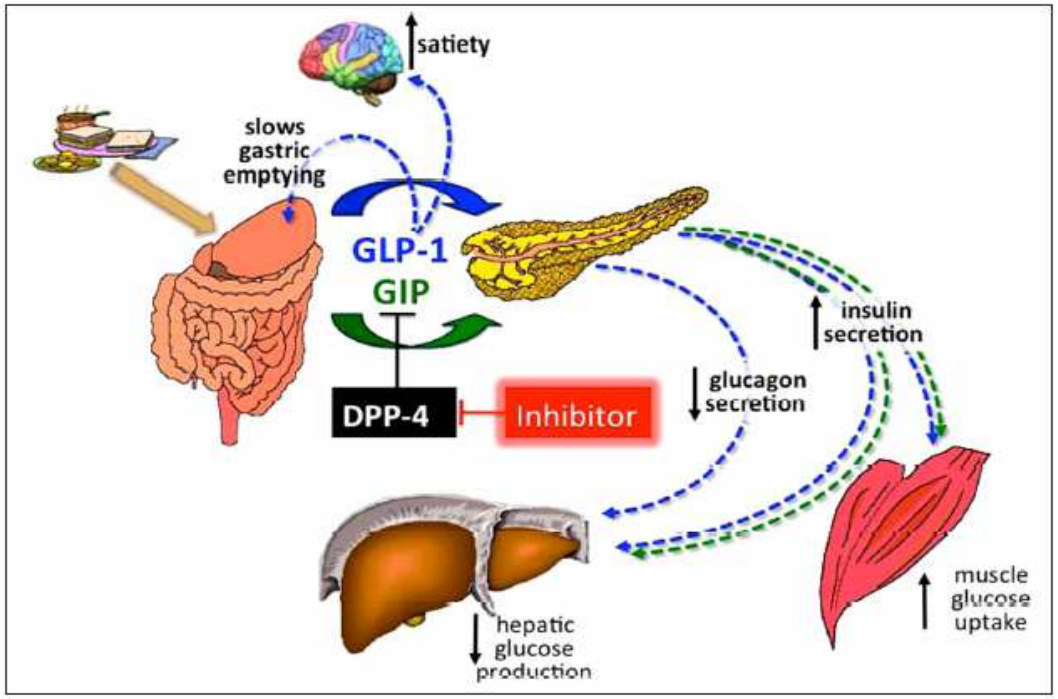


Figure 1. Physiology of the incretin system. After meal ingestion, as blood glucose levels rise, neuroendocrine cells of the intestine secrete the incretin hormones GLP-1 and GIP. Both stimulate insulin secretion by pancreatic beta cells, in a glucose dependent fashion. GLP-1 additionally decreases glucagon secretion from pancreatic alpha-cells, slows gastric emptying and increases satiety, allowing for reduced food intake. Physiologically, the enzyme dipeptidyl peptidase(DPP)-4 rapidly degrades both GLP-1 and GIP to their inactive metabolites. Pharmacological competitive inhibition of DPP-4 increases the half-life and bioavailability of active incretin hormones, enhancing their physiological effect.

Jose T, et al. Diab Vasc Dis Res. 2012.

Acciones adicionales DPP-4

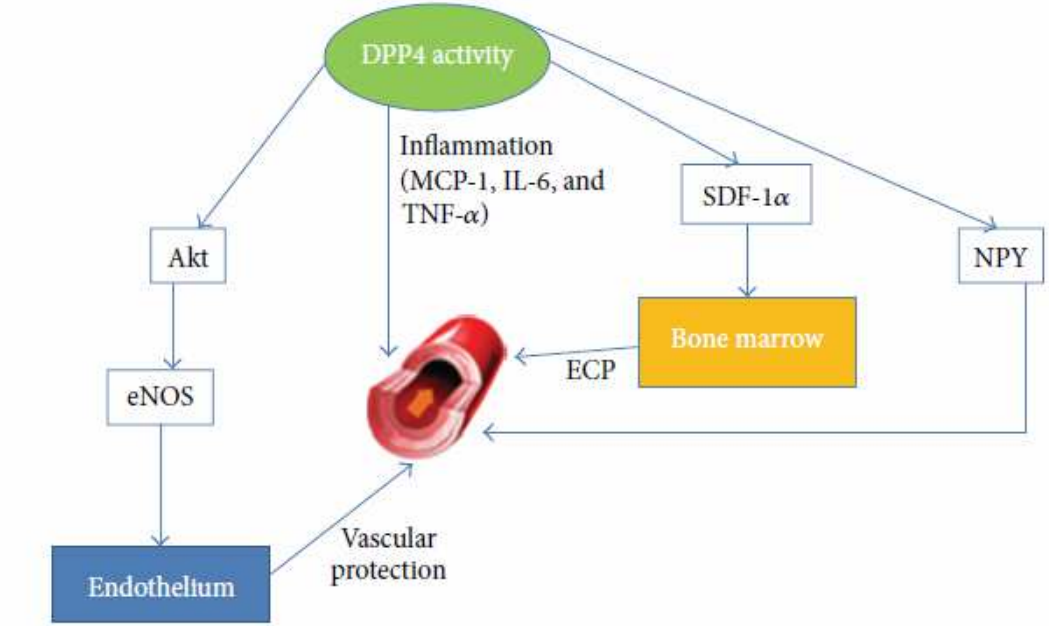


FIGURE 1: Effect of DPP4 on cardiovascular districts.

Pala L, J Diabetes Res. 2013;2013:590456.

Sitagliptina aumenta células progenitoras endoteliales y el factor derivado del estroma (mejoría de angiogénesis).

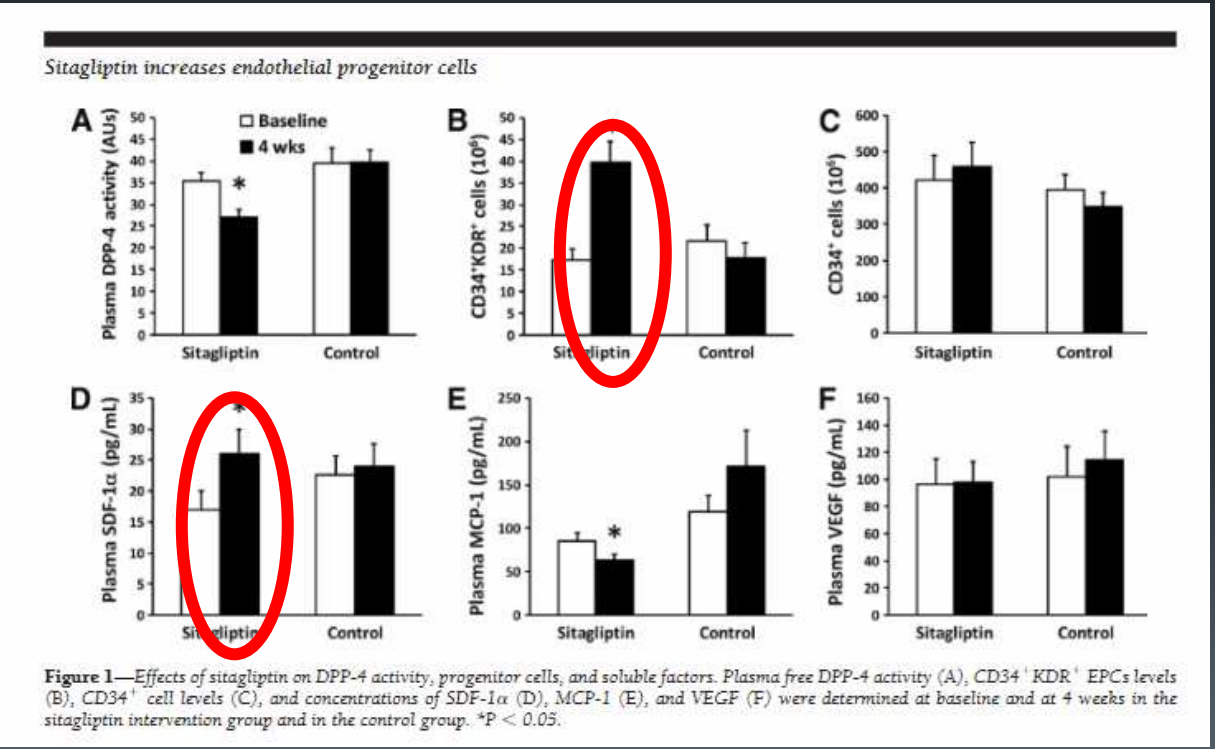


Figure 1—*Effects of sitagliptin on DPP-4 activity, progenitor cells, and soluble factors. Plasma free DPP-4 activity (A), $CD34^+KDR^+$ EPCs levels (B), $CD34^+$ cell levels (C), and concentrations of SDF-1α (D), MCP-1 (E), and VEGF (F) were determined at baseline and at 4 weeks in the sitagliptin intervention group and in the control group. *$P < 0.05$.*

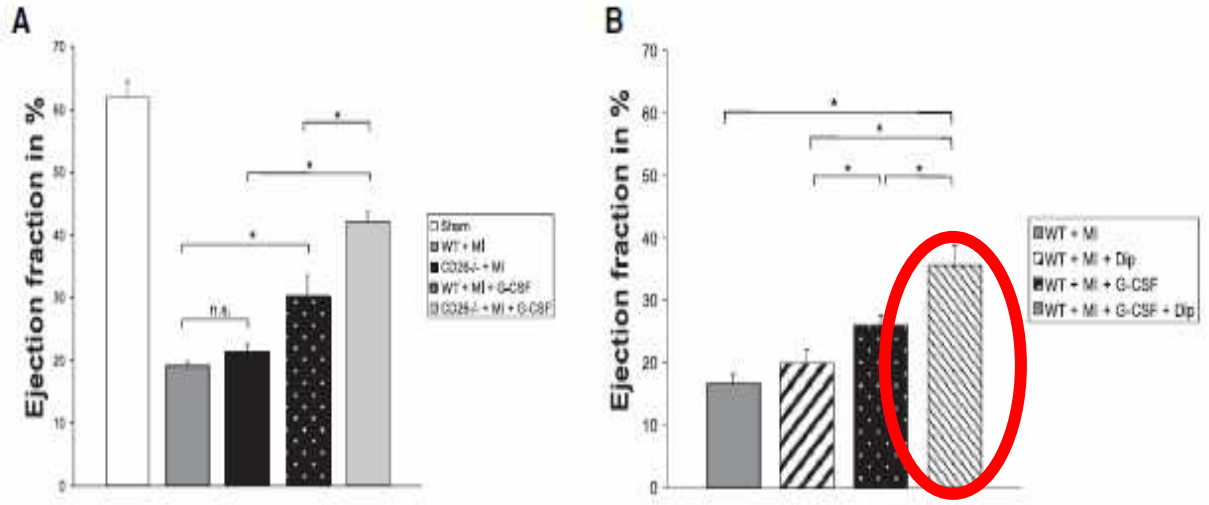
Fadini GP. Diab Care. 2010; 33:1607-2609

Combinados con G-CSF, mejoran FEVI post-IAM

Cell Stem Cell

DPP-IV Inhibition and G-CSF Enhance Stem Cell Homing

Ratones tratados con diprotina A



Zaruba MM, et al. Cell Stem Cell. 2009; 4:313-323

Linagliptina aproxima PA en ratas obesas insulín-resistentes a la de ratas delgadas

doi: 10.1210/en.2013-1096

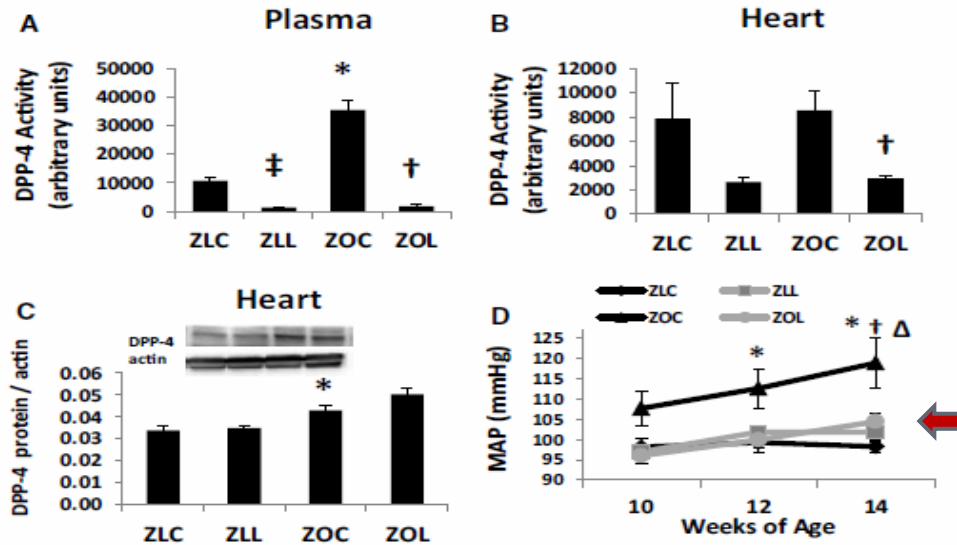


Figure 1. Linagliptin (LGT) reduces DPP-4 activity in the plasma (A) and myocardium (B) of Zucker Lean (ZL) and Obese rats. C, DPP-4 protein expression is elevated in control- and LGT-treated ZO rat hearts compared to lean counterparts. D, Twenty four hour ambulatory mean arterial pressure (MAP) of Zucker rats. Symbols indicate differences in MAP between treatment groups within a single time period. $P < .05$, *, ZLC vs ZOC; ‡, ZLC vs ZLL; †, ZOC vs ZOL; and Δ, ZOC vs ZLL.

ZLC: delgadas control
ZLL: delgadas liraglutide
ZOC: obesas control
ZOL: obesas linagliptina

Aroor AR, et al. Endocrinology. 2013, 154(7):2501–2513

Linagliptina aproxima la función diastólica del VI de ratas obesas insulín-resistentes a la de ratas delgadas

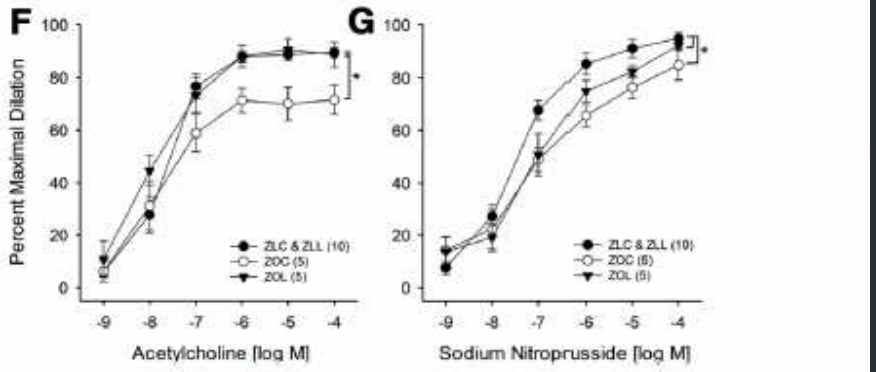


Figure 2. Zucker Obese (ZO) rats exhibit diastolic dysfunction (A–E) and impaired vasomotor reactivity of skeletal muscle arterioles (F and G) which are ameliorated by the DPP-4 inhibitor, linagliptin (LGT). A, Representative tissue doppler images are shown of the early and late (E′ and A′) motion of the septal annulus during diastole and during early systole (S′). Mean group values for E′, A′ and E′/A′ are listed in Table 2. B, Representative pressure-volume loops are shown of ZOC and ZOL during pre-load reduction. C–E, Regression analysis indicates significant relationships between tau (t), the time constant of isovolumic relaxation, generated by PV analysis and echocardiography-derived parameters of early diastolic relaxation. Vp = propagation velocity of mitral inflow; IVRT = isovolumic relaxation time; E′ = velocity of early septal annular wall motion determined by pulse wave echocardiography for the same rats. Data points were plotted from ZOC and ZOL rats that had both cardiac procedures. Lintagliptin treatment improved vasomotor reactivity of skeletal muscle arterioles. Concentration-response curves of gastrocnemius 1A arterioles to acetylcholine (F) and sodium nitroprusside (G). Values are mean ± SE, sample size in parentheses. *, $P < .05$ for ZOC versus all other groups (F) and ZLC & ZLL versus all other groups (G).

Aroor AR, et al. Endocrinology. 2013, 154(7):2501–2513

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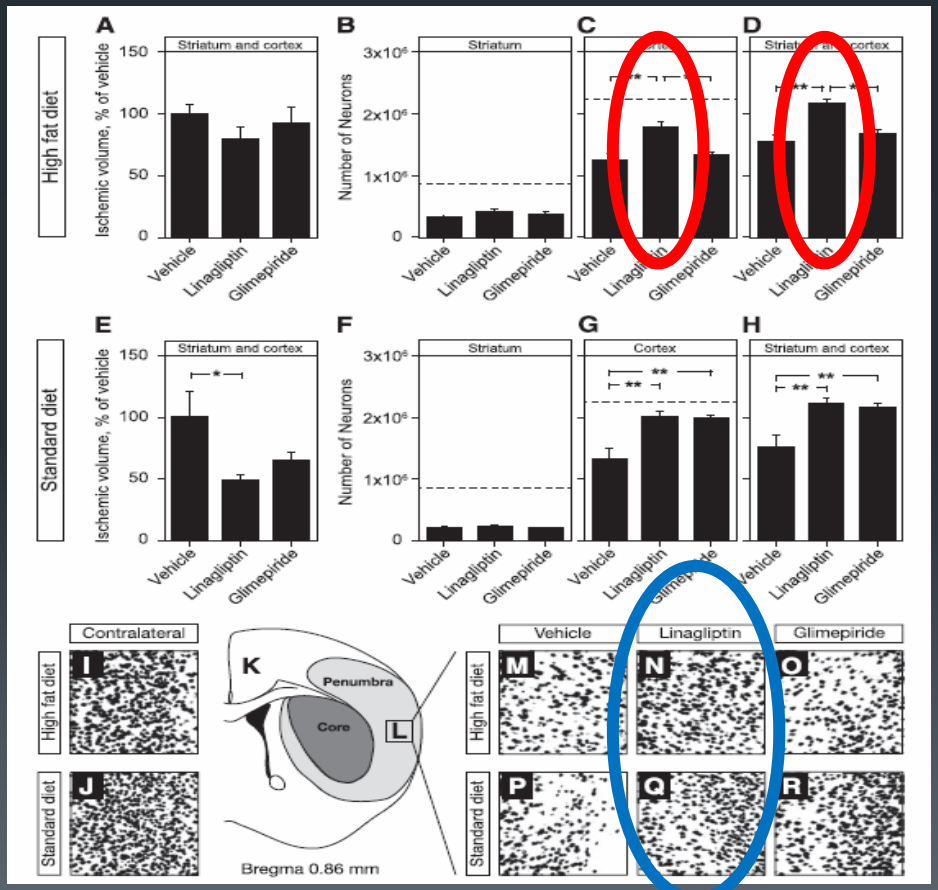
ORIGINAL ARTICLE

The DPP-4 Inhibitor Linagliptin Counteracts Stroke in the Normal and Diabetic Mouse Brain

A Comparison With Glimepiride

Vladimer Darsalia,[1] Henrik Ortsäter,[1] Anna Olverling,[1] Emilia Darlöf,[1] Petra Wolbert,[1] Thomas Nyström,[1] Thomas Klein,[2] Åke Sjöholm,[1] and Cesare Patrone[1]



Dieta rica en grasas

Darsalia V, et al. Diabetes. 2013.

Resumen acción DPP-4

- Enzimática:

>>Inactivación incretinas (GLP1, GIP).

  - Descenso de presión arterial (natriuresis, BNP, vasodilatación, SN Autónomo), incluso sin perder peso
  - Mejora del perfil lipídico
  - Efectos en FRCV “no clásicos”
  - Disminución de necrosis experimental del miocardio en animales (elevación de Ca++ intracelular, activación de vía RISK)

>>Degradación péptidos no incretínicos: SDF (angiogénesis), NPY.

- No enzimática:

>>Acción estimuladora de células T de memoria

>>Interacción con proteínas de membrana: caveolina, etc.

Por tanto, con los inhibidores DPP-4 podemos esperar efectos adicionales independientes de GLP1: anti-inflamatorios, endotelio vascular, aterosclerosis, obesidad visceral.

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Metaanálisis linagliptina fase III

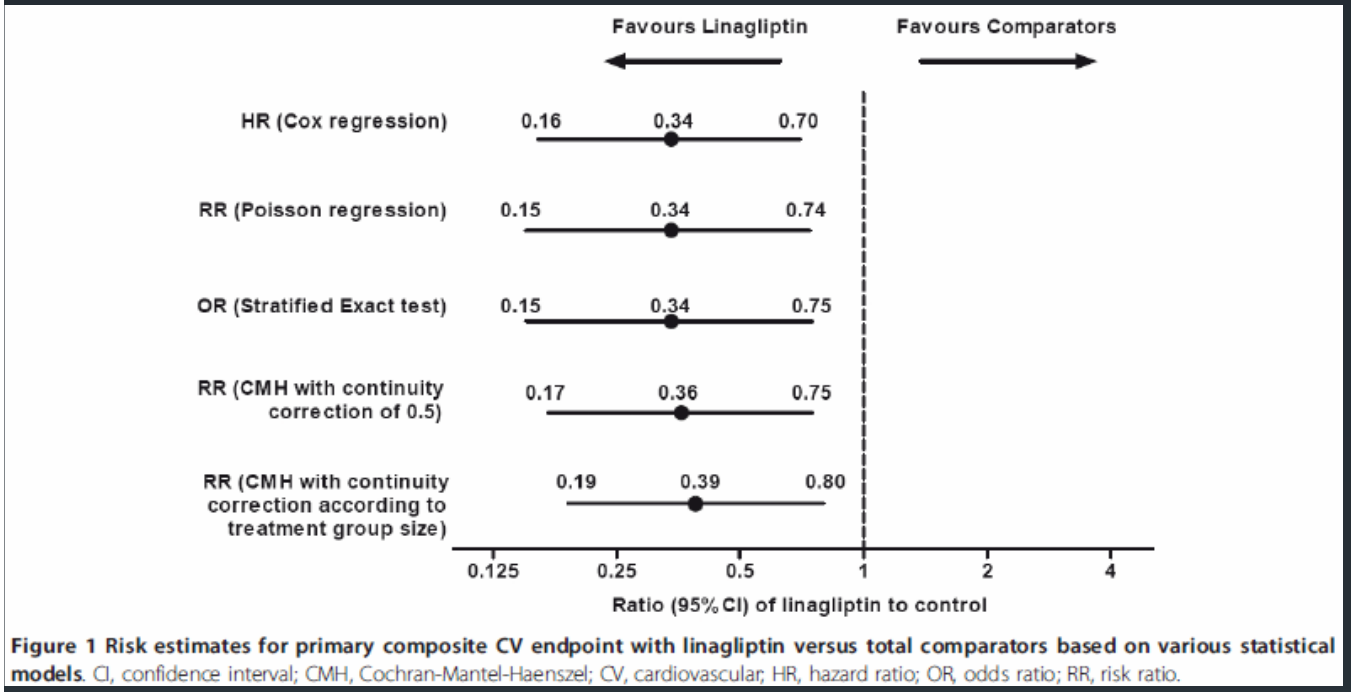
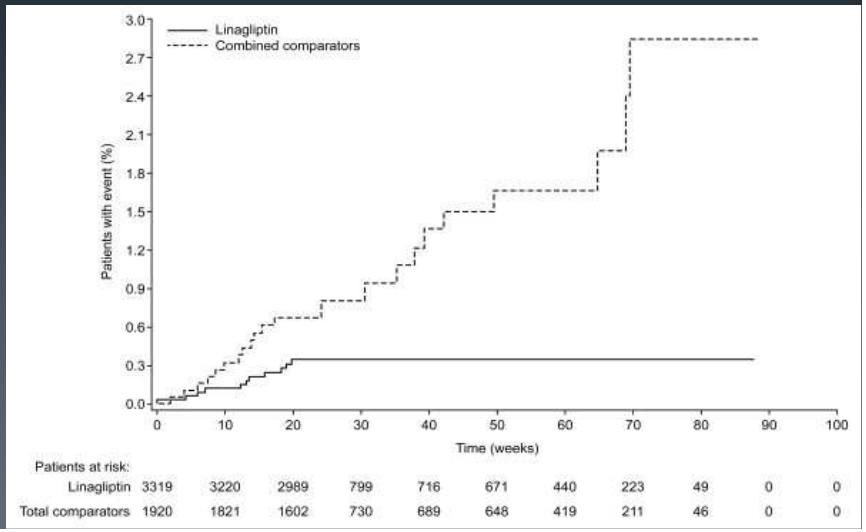


Figure 1 Risk estimates for primary composite CV endpoint with linagliptin versus total comparators based on various statistical models. CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CV, cardiovascular; HR, hazard ratio; OR, odds ratio; RR, risk ratio.

Johansen et al. Cardiovascular Diabetology. 2012

Metaanálisis >5,000 pt.
Media seguimiento 6 meses
Adjudicación ciega prospectiva de eventos CV
Comparador: glimepirida
Endpoint combinado



Linagliptina: RCT vs. glimepirida

- RCT. Doble ciego, no inferioridad.
- 1,552 pacientes tratados con metformina.
- Linagliptina vs. glimepirida.
- Seguimiento de 2 años.
- Desenlace principal: variación en HbA1C.
- Secundarios: hipoglucemias y Δ peso.
- Comité independiente para MACE.

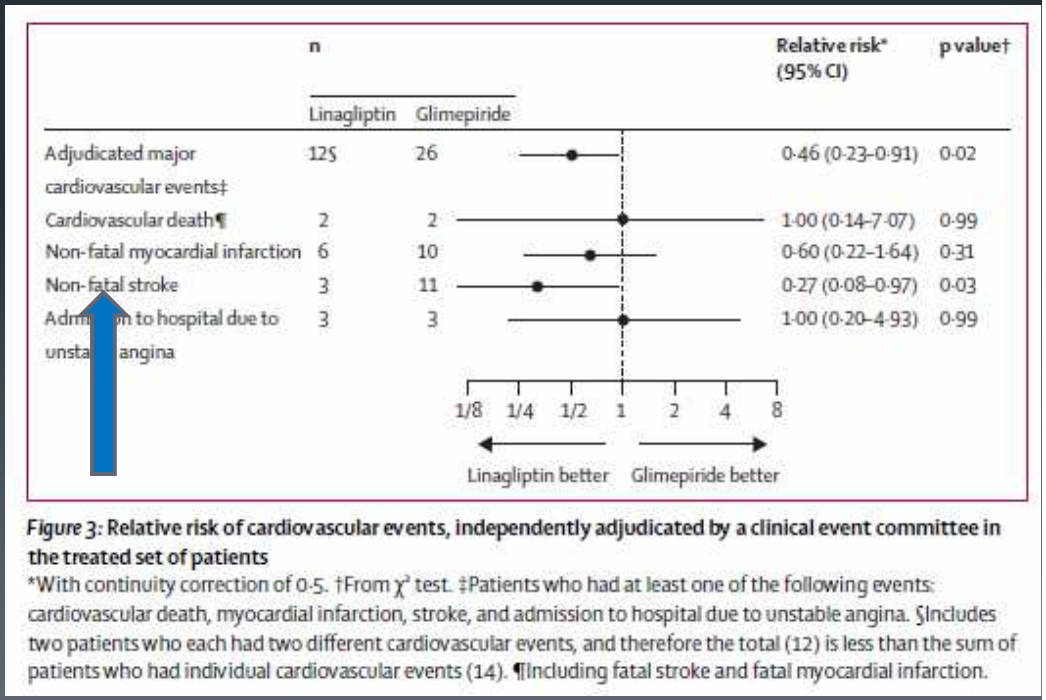


Figure 3: **Relative risk of cardiovascular events, independently adjudicated by a clinical event committee in the treated set of patients**

*With continuity correction of 0·5. †From χ^2 test. ‡Patients who had at least one of the following events: cardiovascular death, myocardial infarction, stroke, and admission to hospital due to unstable angina. §Includes two patients who each had two different cardiovascular events, and therefore the total (12) is less than the sum of patients who had individual cardiovascular events (14). ¶Including fatal stroke and fatal myocardial infarction.

Gallwitz B, et al. Lancet. 2012.

Riesgos relativos < 1 para MACE

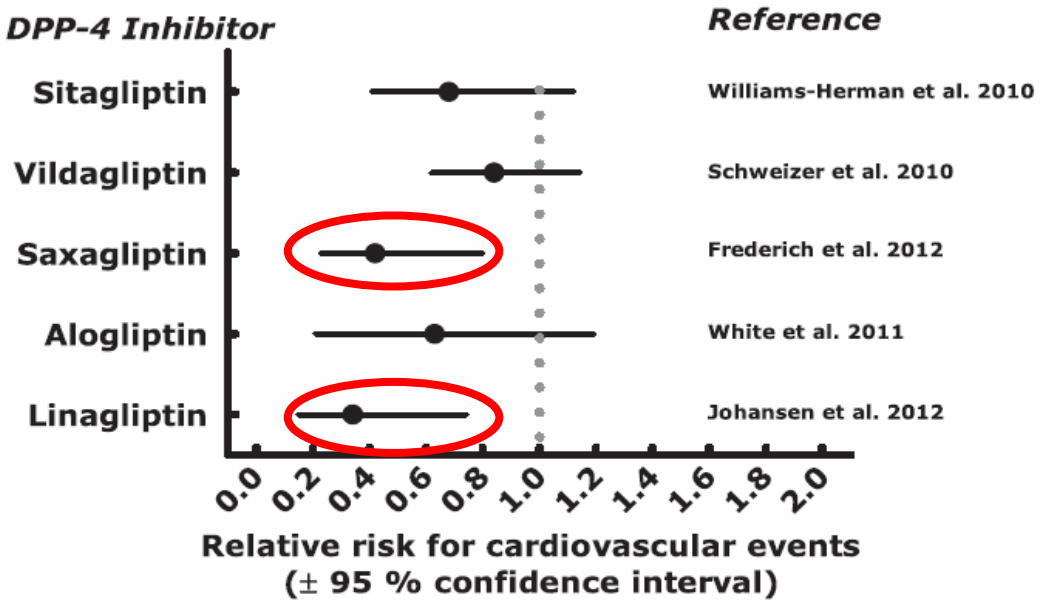
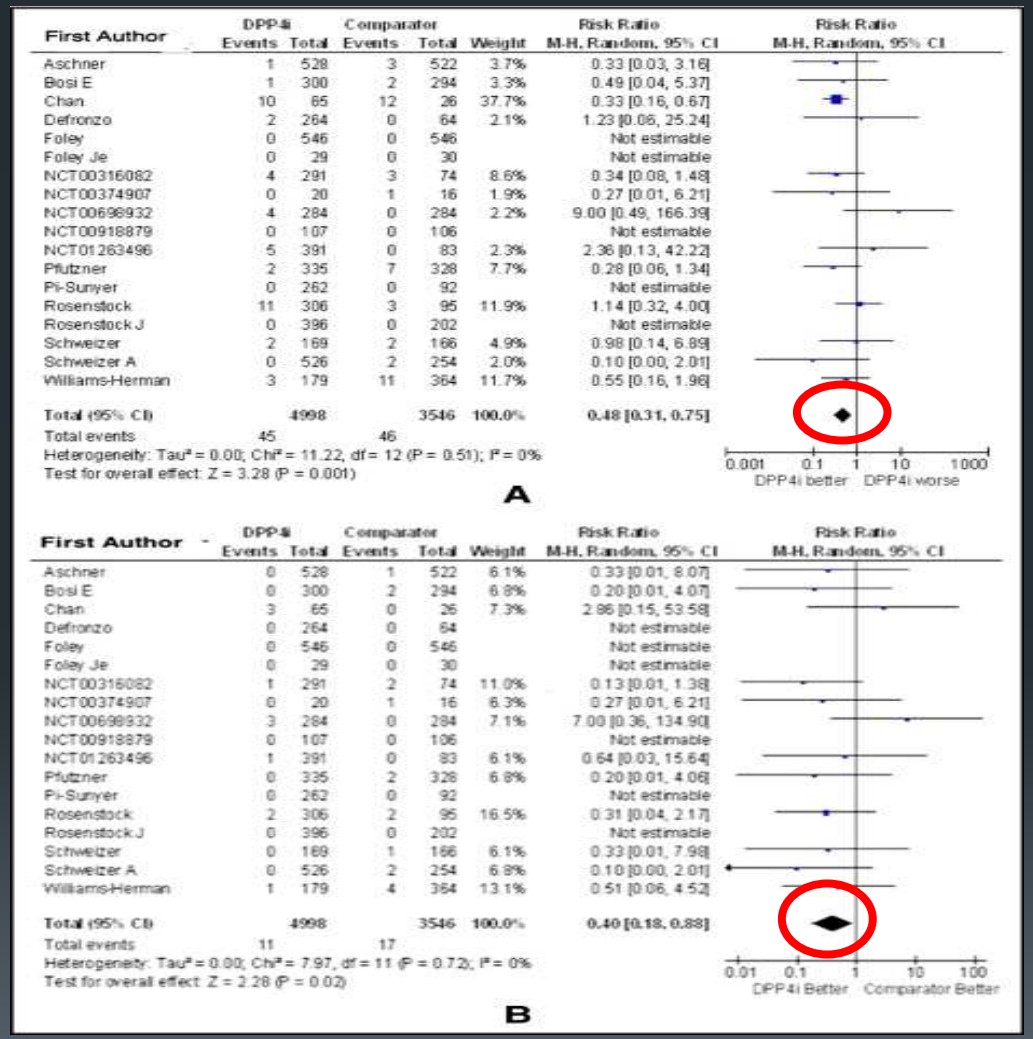


Figure 2—*Relative risk for major cardiovascular events reported as adverse events during phase 3 studies with the GLP-1 receptor agonists exenatide and liraglutide* (upper panel) *and with the DPP-4 inhibitors sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin* (lower panel) *compared with pooled comparators (placebo or active control medications). The relative risk is displayed together with the 95% CIs (bars). Data have been taken from the references quoted in the figure (37–43).*

Nauck MA. Diab Care. 2013; 36:2126-2132.



First Author	DPP4i Events	DPP4i Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Random, 95% CI
Aschner	1	528	3	522	3.7%	0.33 [0.03, 3.16]
Bosi E	1	300	2	294	3.3%	0.49 [0.04, 5.37]
Chan	10	65	12	26	37.7%	0.33 [0.16, 0.67]
Defronzo	2	264	0	64	2.1%	1.23 [0.06, 25.24]
Foley	0	546	0	546		Not estimable
Foley Je	0	29	0	30		Not estimable
NCT00316082	4	291	3	74	8.6%	0.34 [0.08, 1.48]
NCT00374907	0	20	1	16	1.9%	0.27 [0.01, 6.21]
NCT00698932	4	284	0	284	2.2%	9.00 [0.49, 166.39]
NCT00918879	0	107	0	106		Not estimable
NCT01263496	5	391	0	83	2.3%	2.36 [0.13, 42.22]
Pfutzner	2	335	7	328	7.7%	0.28 [0.06, 1.34]
Pi-Sunyer	0	262	0	92		Not estimable
Rosenstock	11	306	3	95	11.9%	1.14 [0.32, 4.00]
Rosenstock J	0	396	0	202		Not estimable
Schweizer	2	169	2	166	4.9%	0.98 [0.14, 6.89]
Schweizer A	0	526	2	254	2.0%	0.10 [0.00, 2.01]
Williams-Herman	3	179	11	364	11.7%	0.55 [0.16, 1.96]
Total (95% CI)		**4998**		**3546**	**100.0%**	**0.48 [0.31, 0.75]**
Total events	45		46			

Heterogeneity: Tau² = 0.00; Chi² = 11.22, df = 12 (P = 0.51); I² = 0%
Test for overall effect: Z = 3.28 (P = 0.001)

0.001 0.1 1 10 1000
DPP4i better DPP4i worse

A

First Author	DPP4i Events	DPP4i Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Random, 95% CI
Aschner	0	528	1	522	6.1%	0.33 [0.01, 8.07]
Bosi E	0	300	2	294	6.8%	0.20 [0.01, 4.07]
Chan	3	65	0	26	7.3%	2.86 [0.15, 53.58]
Defronzo	0	264	0	64		Not estimable
Foley	0	546	0	546		Not estimable
Foley Je	0	29	0	30		Not estimable
NCT00316082	1	291	2	74	11.0%	0.13 [0.01, 1.38]
NCT00374907	0	20	1	16	6.3%	0.27 [0.01, 6.21]
NCT00698932	3	284	0	284	7.1%	7.00 [0.36, 134.90]
NCT00918879	0	107	0	106		Not estimable
NCT01263496	1	391	0	83	6.1%	0.64 [0.03, 15.64]
Pfutzner	0	335	2	328	6.8%	0.20 [0.01, 4.06]
Pi-Sunyer	0	262	0	92		Not estimable
Rosenstock	2	306	2	95	16.5%	0.31 [0.04, 2.17]
Rosenstock J	0	396	0	202		Not estimable
Schweizer	0	169	1	166	6.1%	0.33 [0.01, 7.98]
Schweizer A	0	526	2	254	6.8%	0.10 [0.00, 2.01]
Williams-Herman	1	179	4	364	13.1%	0.51 [0.06, 4.52]
Total (95% CI)		**4998**		**3546**	**100.0%**	**0.40 [0.18, 0.88]**
Total events	11		17			

Heterogeneity: Tau² = 0.00; Chi² = 7.97, df = 11 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.28 (P = 0.02)

0.01 0.1 1 10 100
DPP4i Better Comparator Better

B

Riesgo de eventos cardiovasculares con DPP-4 inh.

Riesgo de SCA con DPP-4 inh.

Harshal R, et al. Am J Cardiol. 2012; 110:826-833.

Estudios de seguridad CV inhibidores DPP-4

Table 2. Key features of ongoing CV safety studies of DPP-4 inhibitors.

Drug/comparator	Study (acronym and official title)	Background therapy	Composite primary end point	Estimated enrolment	Planned duration	NCT number
Linagliptin/glimepiride	CAROLINA: a multicenter, international, randomized, parallel-group, double-blind study to evaluate CV safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high CV risk	Largely metformin and/or SU, glinide or α-glucosidase inhibitor	CV death, non-fatal MI, non-fatal stroke or hospitalized unstable angina	6000	6–7 years	NCT01243424
Sitagliptin/placebo	TECOS: a randomized, placebo-controlled clinical trial to evaluate CV outcomes after treatment with sitagliptin in patients with type 2 diabetes mellitus and inadequate glycaemic control on mono or dual combination oral anti-hyperglycaemic therapy	Mono or dual oral combination (metformin, SU and pioglitazone) or stable dose of insulin	CV death, non-fatal MI, non-fatal stroke or hospitalized unstable angina	14,000	4–5 years	NCT00790205
Saxagliptin/placebo	SAVOR-TIMI-53: a multicenter, randomized, double-blind, placebo-controlled phase IV trial to evaluate the effect of saxagliptin on the incidence of CV death, myocardial infarction or ischaemic stroke in patients with type 2 diabetes	Current standard care	CV death, non-fatal MI or non-fatal ischaemic stroke	16,500	5 years	NCT01107886
Alogliptin/placebo	EXAMINE: a multicenter, randomized, double-blind, placebo-controlled study to evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with type 2 diabetes and acute coronary syndrome	Current standard care	CV death, non-fatal MI or non-fatal stroke	5400	4.75 years	NCT00968708

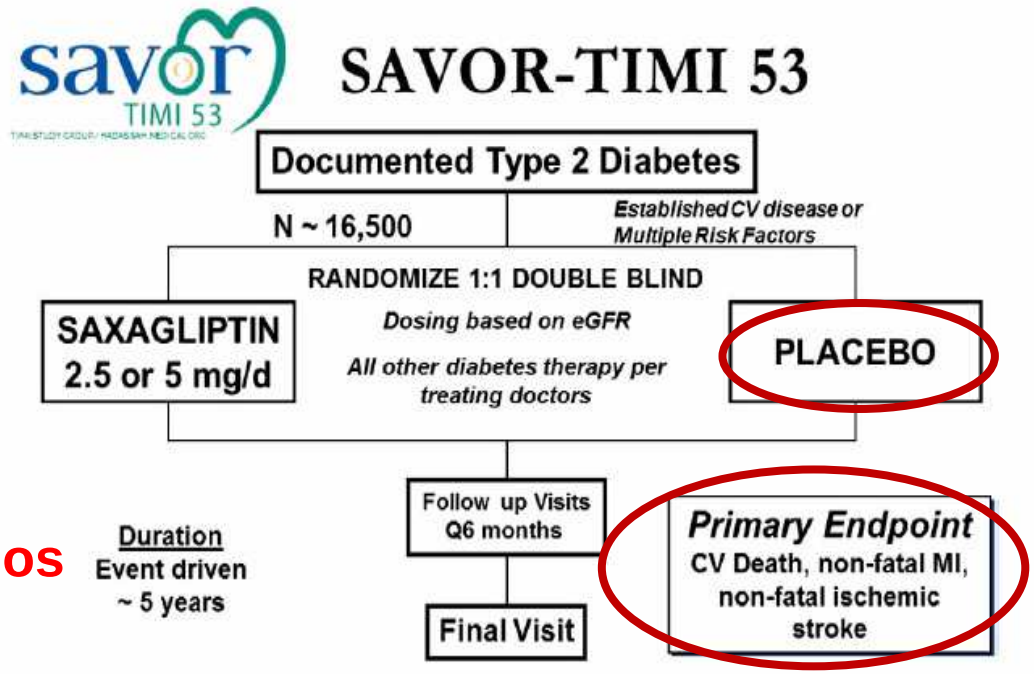
Σ=220,000 pt-years

SU: sulphonylurea; CV: cardiovascular; DPP-4: dipeptidyl peptidase-4; CAROLINA: Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes; MI: myocardial infarction; TECOS: Trial Evaluating Cardiovascular Outcomes with Sitagliptin; SAVOR-TIMI-53: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; EXAMINE: Examination of Cardiovascular Outcomes: Alogliptin versus Standard Care in Patients with Type 2 Diabetes and Acute Coronary Syndrome.
Further details of these trials are available at http://clinicaltrials.gov/

Rosenstock J et al. Diab Vasc Dis Res 2013;10:289-301

Ensayos clínicos aleatorizados de seguridad CV

Figure 2



Trial schema of the SAVOR-TIMI 53 Trial.

Mediana 2,1 años

Scirica BM, et al. Am Heart J. 2011; 162:818-825.

SAVOR-TIMI 53: Clinical End Points

Table 2. Prespecified Clinical End Points.*

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

* Event rates and percentages are 2-year Kaplan–Meier estimates.

Scirica BM et al. N Engl J Med 2013.

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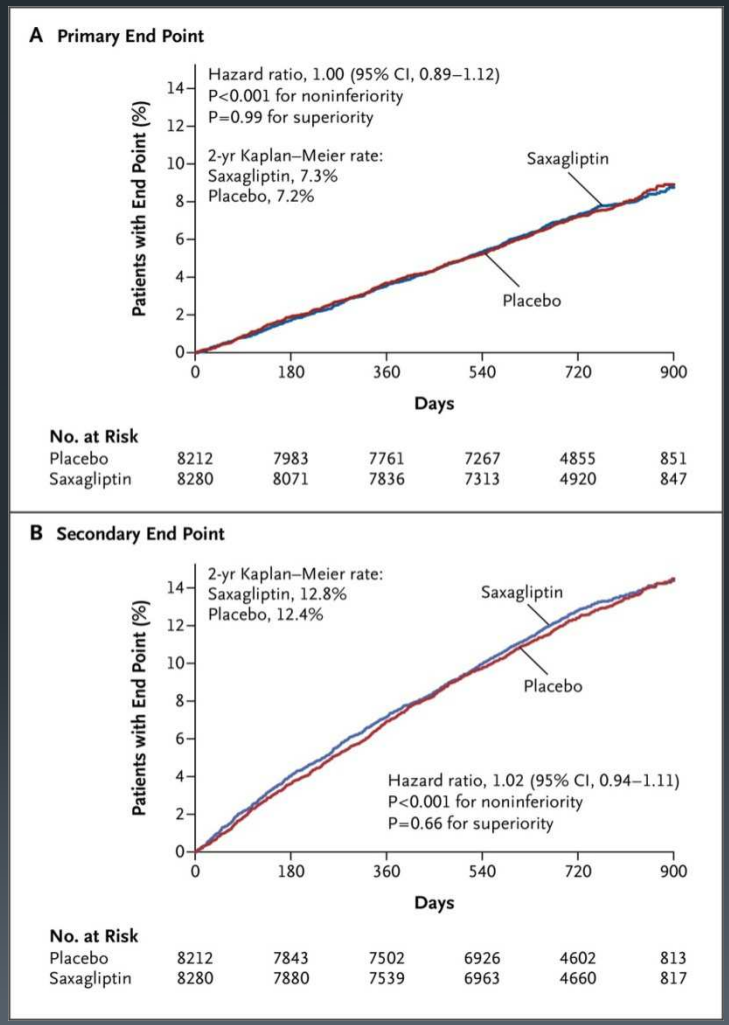
SAVOR-TIMI 53: Kaplan–Meier Rates of the Primary and Secondary End Points



Scirica BM et al. N Engl J Med 2013.

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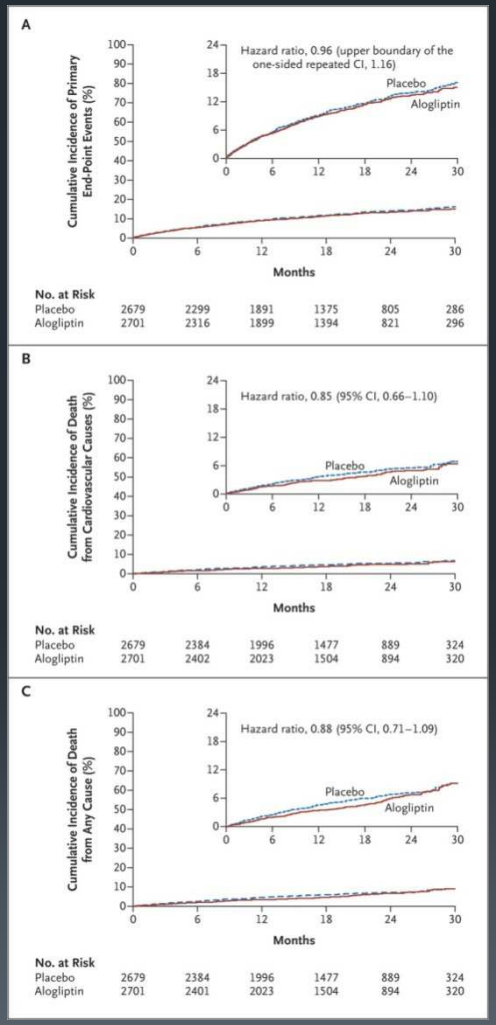
EXAMINE Study: Cumulative Kaplan–Meier Estimates of the Time to the Primary End-Point Event or Other Safety End Point.



- Coronarios (mayor RCV), alogliptina vs. placebo, MACE.
- Stop prematuro tras demostrar no-inferioridad.
- Mediana de exposición de 18 meses.

White WB et al. N Engl J Med 2013; 369:1327-1335.

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EXAMINE STUDY: Major Safety End Points

Table 3. Major Safety End Points.

End Point	Placebo (N = 2679)	Alogliptin (N = 2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
Primary end point†	316 (11.8)	305 (11.3)	0.96 (≤1.16)‡	0.32
Components of primary end point				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Nonfatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Nonfatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end point§	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡	0.26
Other end points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	0.21

* P values for testing the superiority of alogliptin to placebo were calculated with the use of a Cox regression analysis.
† The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
‡ The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01.
§ The secondary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina within 24 hours after hospital admission.
¶ Included are deaths that occurred as primary end-point events and deaths that occurred after a nonfatal primary end-point event.

White WB et al. N Engl J Med 2013;369:1327-1335.

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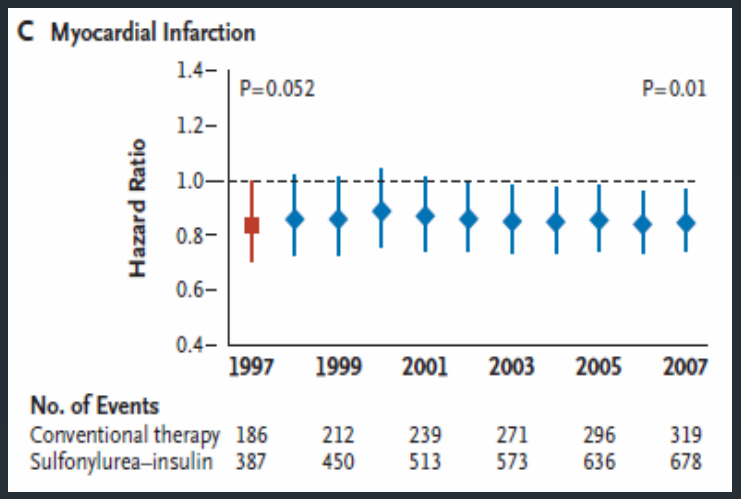
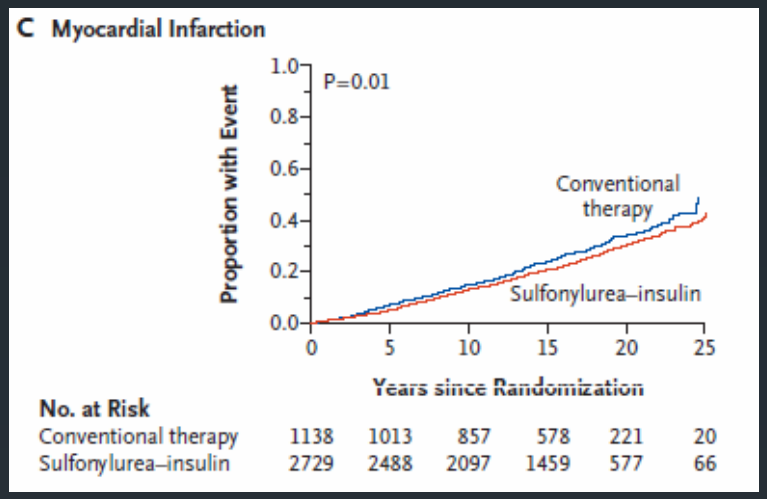
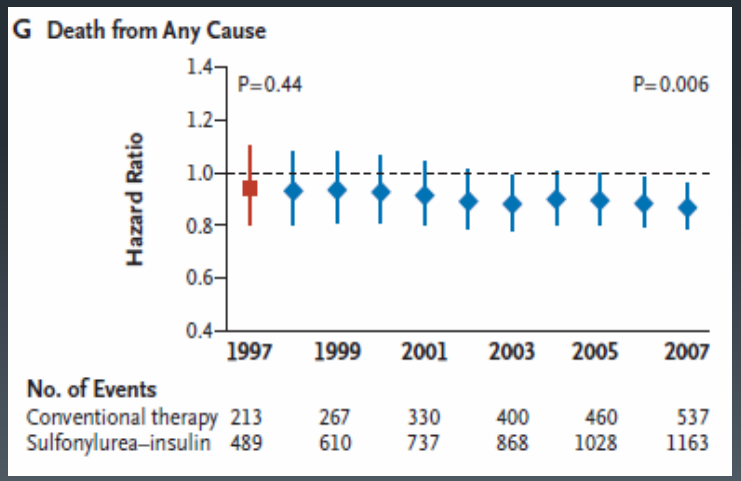
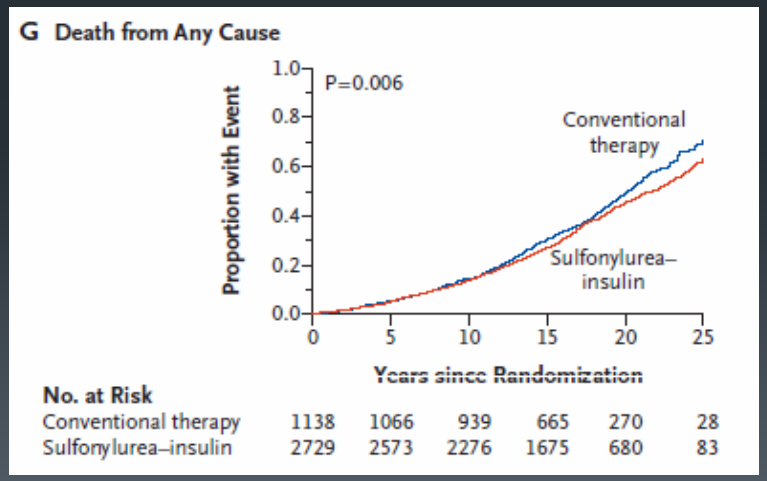
Kaplan-Meier Curves for Four Prespecified Aggregate Clinical Outcomes









Holman RR et al. N Engl J Med 2008;359:1577-1589

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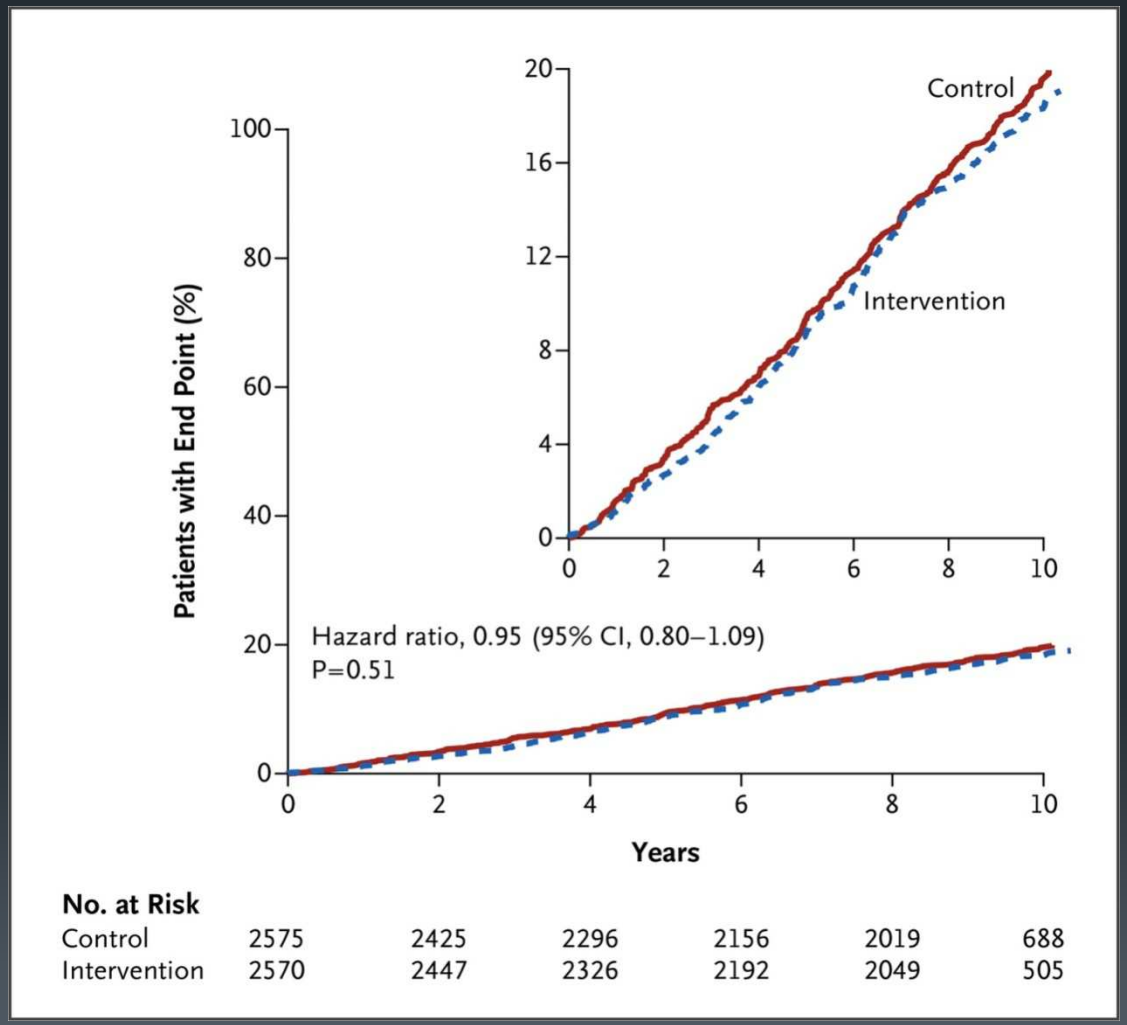
Cumulative Hazard Curves for the Primary Composite End Point



The Look AHEAD Research Group. N Engl J Med 2013;369:145-154

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Outline

- ¿Por qué es importante hablar de efectos cardiovasculares de los antidiabéticos?
- Mecanismos fisiopatológicos y evidencia experimental inhibidores DPP-4
- Evidencia clínica
- Conclusiones

Conclusiones: efectos CV de inhibidores DPP-4

- Los estudios fisiológicos demuestran acciones añadidas no mediadas por efecto incretínico / enzimático.
- Como efecto de clase, la evidencia apunta a que los inhibidores de la DPP-4 son seguros desde el punto de vista de mortalidad y eventos cardiovasculares.
- Puede haber diferencias intraclase en su efecto sobre variables concretas: ictus y linagliptina; ingreso por IC y saxagliptina.
- Será difícil que, en pacientes de riesgo vascular en los que ya se hace un abordaje integral del mismo, demuestren SEPARADAMENTE superioridad frente a comparadores, con seguimientos cortos y pocos eventos

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Gracias por su atención