XI Reunión de Riesgo Vascular SEMI
Madrid, 23-24 Abril 2015

Fármacos antidiabéticos y riesgo cardiovascular

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Hospital General Universitario Gregorio Marañón

Potenciales conflictos de interés

Proyectos de investigación

- IP estudio REDIM (Böehringer-Lilly) (2011-2013)

Asesoría en el área de diabetes

- Novartis, Novo-Nordisk

Charlas esponsorizadas en congresos previos

- Böehringer-Lilly, Novo-Nordisk, Astra-Zeneca

Profesor en cursos de insulinización para médicos residentes

- sanofi-Aventis, Novo-Nordisk

Elaboración de material científico de divulgación en diabetes

- Böehringer-Lilly, Novo-Nordisk, Ferrer

Guión

- La *rabiosa* actualidad del tópico
- Un puñado de *clásicos*
- Los recién llegados
- Algunas reflexiones
- Conclusiones: para llevar a casa

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Incidencia de infarto de miocardio en expuestos a rosiglitazona

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

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

December 2008
Clinical/Medical

Fases 2 y 3 (añosos, ERC, > 2 años, adjudicación indep. MACEs)
Ratios de riesgo para MACEs:
•1,2; 95%CI [0,5-1,9] (>1,8) ► estudio **pre-comercialización**
•1,5 (>1,3); 95%CI [1,3-1,7] ► estudio **pre-comercialización**

Pre-comercialización:
Ratios de riesgo para MACEs:
•1,1; 95%CI [0,7-1,4] (>1,3;<1,8) ► estudio **post-comercialización**
•1,0; 95%CI [0,8-1.2] (<1.3) ► **aprobación**, no más estudios

Post-comercialización:
Para demostrar OR≈1; 95%CI [0,x-<1,3], no inferioridad y una tasa de eventos del 2%, >6.000 pacientes x 5 años

La *rabiosa* actualidad…

ELIXA

Lixisenatide

novo nordisk®

LEADER®

janssen

CANVAS STUDY

EXAMINE

GRADE

Your Text Size: A- A A+

ABOUT GRADE QUESTIONS? IMPORTANT RESOURCES

The GRADE Research Study for People with Type 2 Diabetes

savor

TIMI 53

TIMI STUDY GROUP / HADASSAH MEDICAL ORG

EXSCEL

Exenatide Study of Cardiovascular Event Lowering

TECOS

Lilly

CAROLINA

Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)

Guión

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Metformina

"[…]. 753 were included in a randomised controlled trial, median duration 10·7 years, of conventional policy, primarily with diet alone (n=411) versus intensive blood-glucose control policy with metformin, aiming for FPG below 6 mmol/L (n=342). A secondary analysis compared the 342 patients allocated metformin with 951 overweight patients allocated intensive blood-glucose control with chlorpropamide (n=265), glibenclamide (n=277), or insulin (n=409)".

"Patients allocated metformin, compared with the conventional group, had risk reductions of 32% (95% CI 13–47, p=0·002) for any diabetes-related endpoint, 42% for diabetes-related death (9–63, p=0·017), and 36% for all-cause mortality (9–55, p=0·011)".

"Among patients allocated intensive blood glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for any diabetes-related endpoint (p=0·0034), all-cause mortality (p=0·021), and stroke (p=0·032)".

UKPDS Group. Lancet. 1998;352:854-65

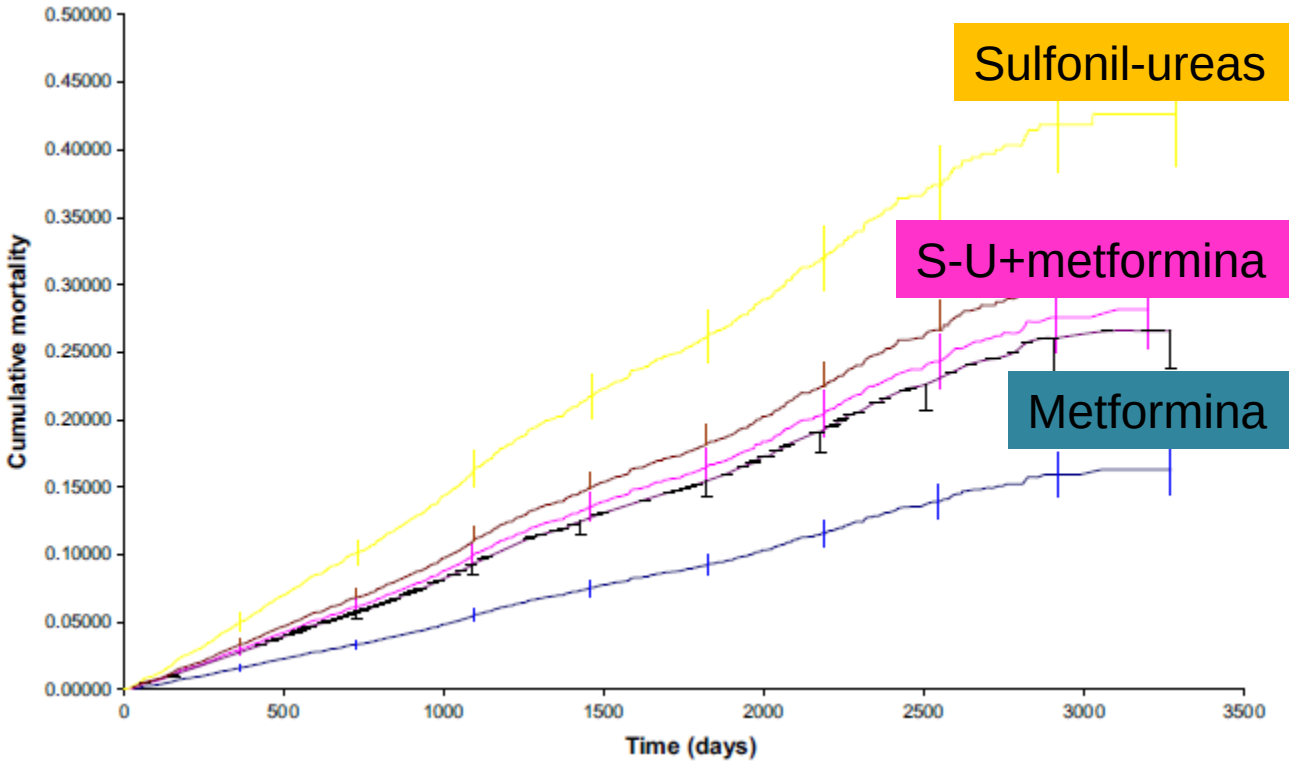
Diabetologia (2006) 49: 930–936
DOI 10.1007/s00125-006-0176-9

ARTICLE

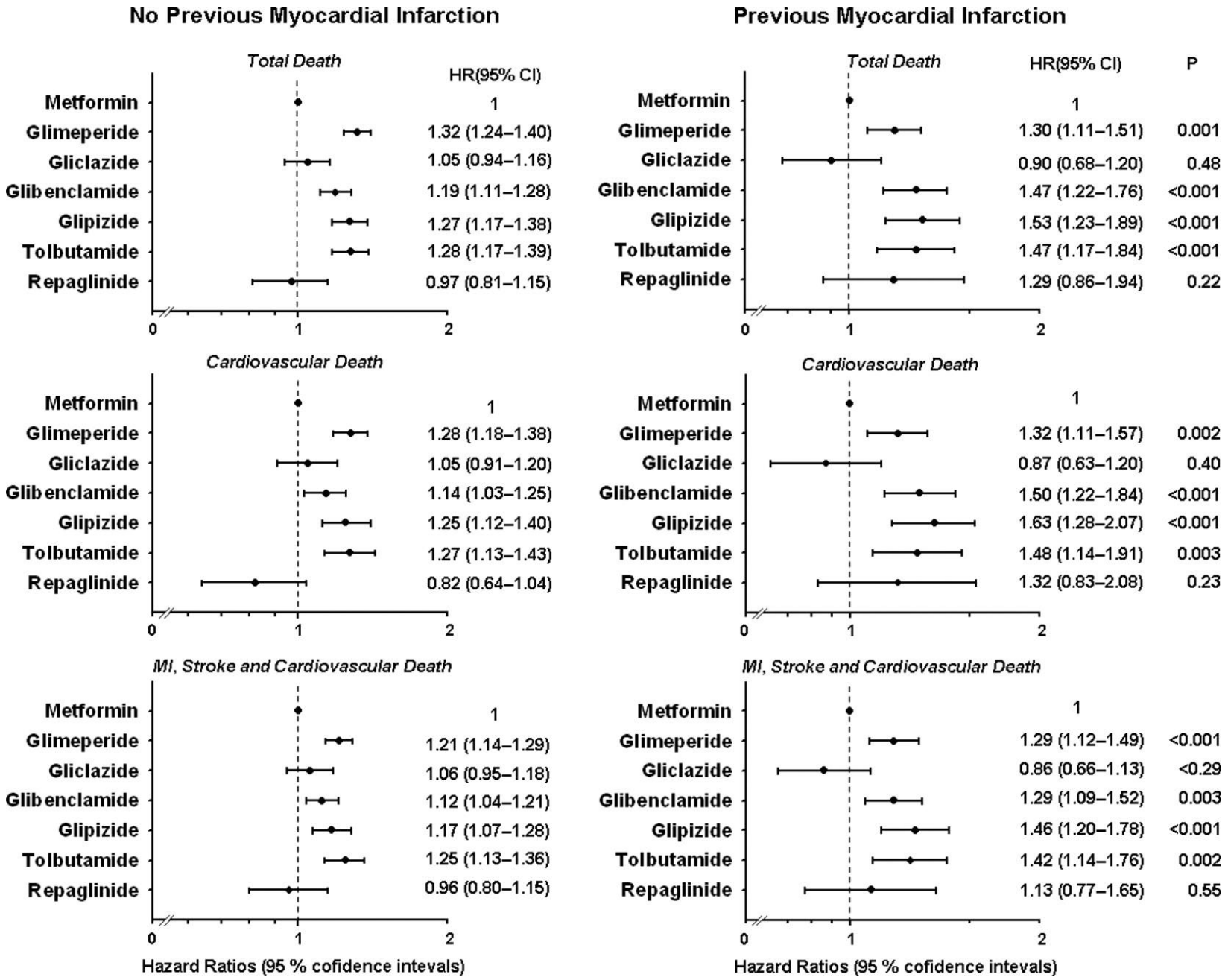
Sulfonil-ureas: penalizaciones

J. M. M. Evans · S. A. Ogston ·
A. Emslie-Smith · A. D. Morris

Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin



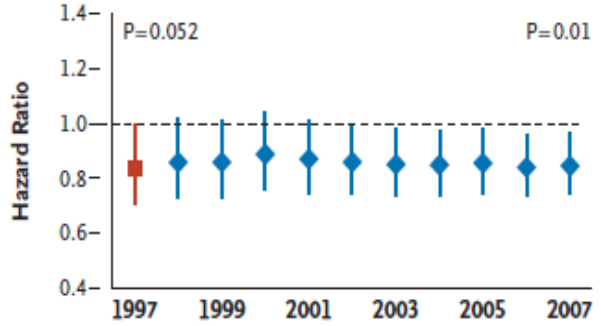
DARTS (N=5.730)



Schramm TK, et al. Eur Heart J. 2011;32:1900-8

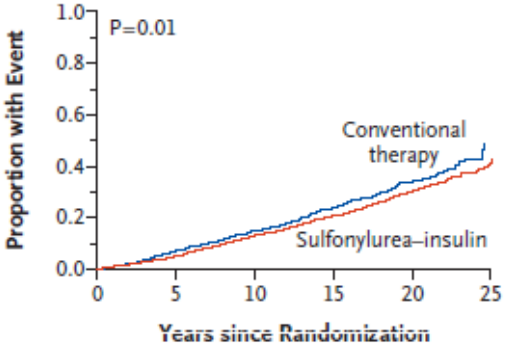
Sulfonil-ureas: UKPDS 80

C Myocardial Infarction



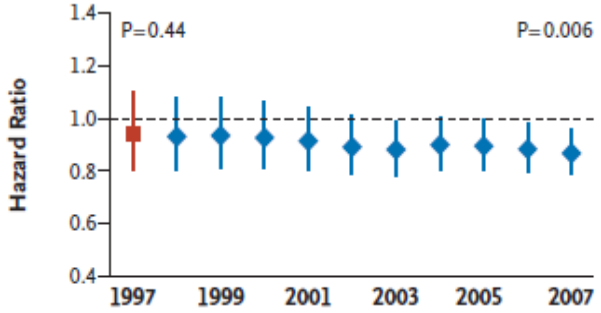
No. of Events						
Conventional therapy	186	212	239	271	296	319
Sulfonylurea–insulin	387	450	513	573	636	678

C Myocardial Infarction



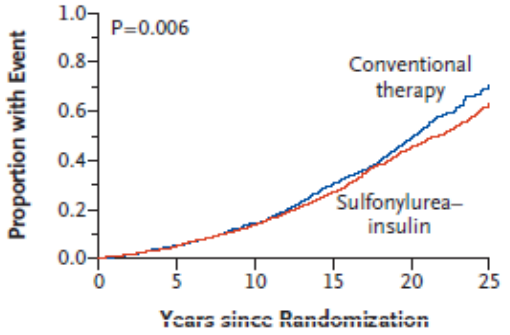
No. at Risk						
Conventional therapy	1138	1013	857	578	221	20
Sulfonylurea–insulin	2729	2488	2097	1459	577	66

G Death from Any Cause



No. of Events						
Conventional therapy	213	267	330	400	460	537
Sulfonylurea–insulin	489	610	737	868	1028	1163

G Death from Any Cause



No. at Risk						
Conventional therapy	1138	1066	939	665	270	28
Sulfonylurea–insulin	2729	2573	2276	1675	680	83

The NEW ENGLAND JOURNAL of MEDICINE

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

RCT S-U (>72 w)	Brazos	N total	Dif. muerte CV	Dif. eventos CV
UKPDS 33	Intensivo insulina/S-U vs. **convencional**	3.041	NS	NS (P=0,052)
UKPDS 80	Intensivo insulina/S-U vs. **convencional**	2.998	Reducción 13%	Reducción 15%
ADOPT	**Rosiglitazona** vs. S-U vs. **metformina**	4.360	NS	NS
CHICAGO	S-U vs. **pioglitazona**	462	NS	NS
PERISCOPE	S-U vs. **pioglitazona**	543	NS	NS
APPROACH	S-U vs. rosiglitazona	672	NS	NS
Matthews et al	Met+**vilda** vs. Met+S-U	3.118	NS	NS
Seck et al	Met+**Sitagliptina** vs. Met+S-U	1.172	8† glipizida, 1† sitaglipt.	NA
Chacra et al	S-U con vs. sin **saxagliptina**	559	NS	NS
BARI 2D	**Metf/rosiglit**. vs. S-U/ins.	2.368	NS	NS
ADVANCE	Intensivo S-U vs. **estándar**	11.140	NS	NS
RECORD	S-U+**rosiglitazona** vs. S-U +**metformina**	4.447	NS	NS
VADT	Intensivo vs **estándar**	1.791	NS	NS
ACCORD	Intensivo vs. **estándar**	10.251	Mayor † tto. intensivo	NS

RCTs comparando metformina y S-U

Supplementary Table 3. Multivariate Proportional Means Regression Analysis

Variable	Hazard Ratio	95% Confidence Interval
Medications		
Glipizide	1.00	
Metformin	0.54	0.30 – 0.90
Age	1.03	1.00 – 1.06
Male	0.73	0.27 – 1.93
Duration of diabetes	0.98	0.86 – 1.08
Duration of CAD	0.98	0.92 – 1.05
Smoking history	1.07	0.81 – 1.40

Hong J, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. **2013**;36:1304-11.

Pioglitazona…

Lancet. 2005 Oct 8;366(9493):1279-89.

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial.

Dormandy JA[1], Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; PROactive investigators.

FINDINGS: Two patients were lost to follow-up, but were included in analyses. The average time of observation was 34.5 months. 514 of 2605 patients in the pioglitazone group and 572 of 2633 patients in the placebo group had at least one event in the primary composite endpoint (HR 0.90, 95% CI 0.80-1.02, p=0.095). The main secondary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, and stroke. 301 patients in the pioglitazone group and 358 in the placebo group reached this endpoint (0.84, 0.72-0.98, p=0.027). Overall safety and tolerability was good with no change in the safety profile of pioglitazone identified. 6% (149 of 2065) and 4% (166 of 2633) of those in the pioglitazone and placebo groups, respectively, were admitted to hospital with heart failure; mortality rates from heart failure did not differ between groups.

American Diabetes Association. Clinical Diabetes

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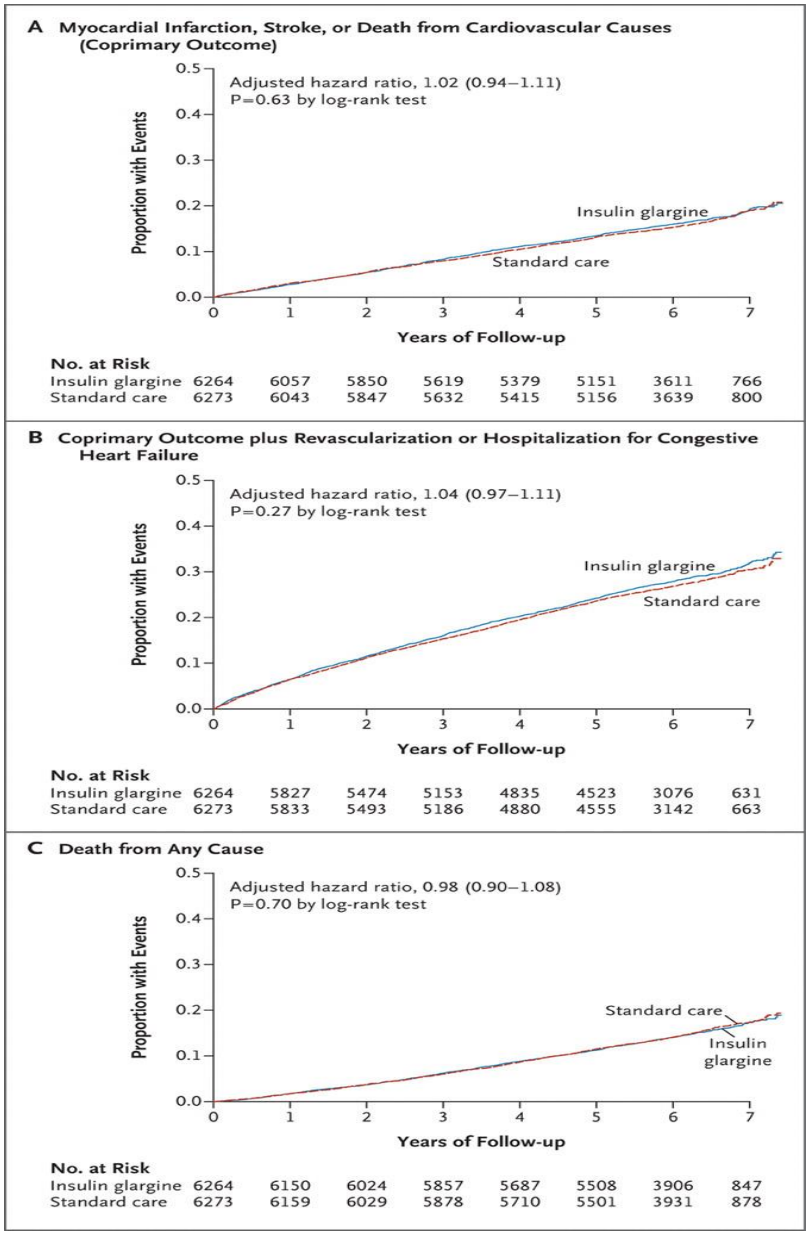
PROactive: A Sad Tale of Inappropriate Analysis and Unjustified Interpretation

Jay S. Skyler, MD, MACP



Insulina glargina

N=12.537
Seguimiento: 6,2 años

The ORIGIN Trial Investigators. N Engl J Med 2012;367:319-328.

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DPP4-inhibidores

	# trials	# trials with events	# events (*DPP4i*)	# events (*Comparator*)	MH-OR [95%, CI]	p	Kendall's tau	p
MACE	**70**	**63**	**263**	**232**	**0.71[0.59;0.86]**	**<0.001**	**0.04**	**0.64**
Sitagliptin	27	24	77	67	0.86[0.60;1.24]	0.430	0.04	0.80
Vildagliptin	16	15	75	74	0.61[0.43;0.86]	0.005	0.03	0.89
Saxagliptin	13	12	62	46	0.67[0.45;0.99]	0.047	0.36	0.10
Linagliptin	9	8	37	41	0.72[0.45;1.16]	0.18	0.00	1.00
Alogliptin	5	4	12	4	0.86[0.25;2.93]	0.81	0.30	0.15
AMI	**62**	**41**	**61**	**59**	**0.64[0.44;0.94]**	**0.023**	**-0.13**	**0.27**
Stroke	**63**	**29**	**41**	**33**	**0.77[0.48;1.24]**	**0.290**	**-0.24**	**0.14**
Mortality	**53**	**30**	**50**	**51**	**0.60[0.41;0.88]**	**0.008**	**0.13**	**0.28**
CV Mortality	**48**	**20**	**26**	**26**	**0.67[0.39;1.14]**	**0.140**	**0.05**	**0.76**

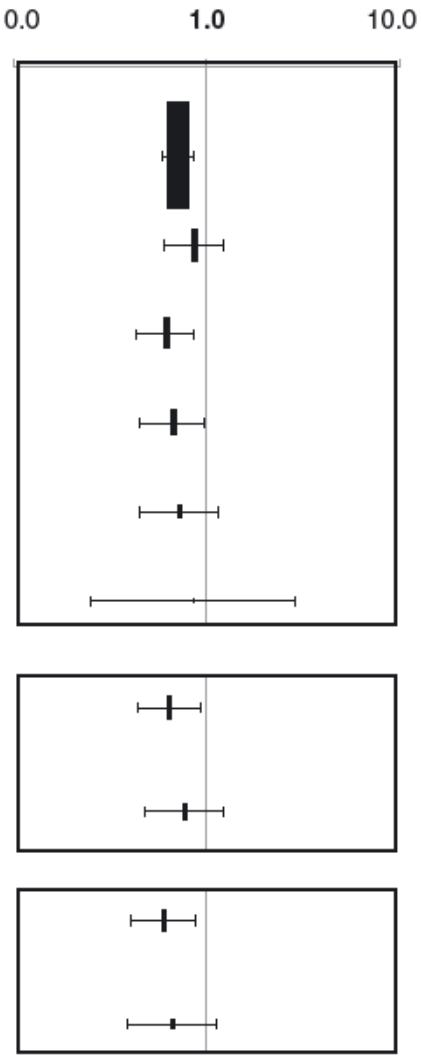
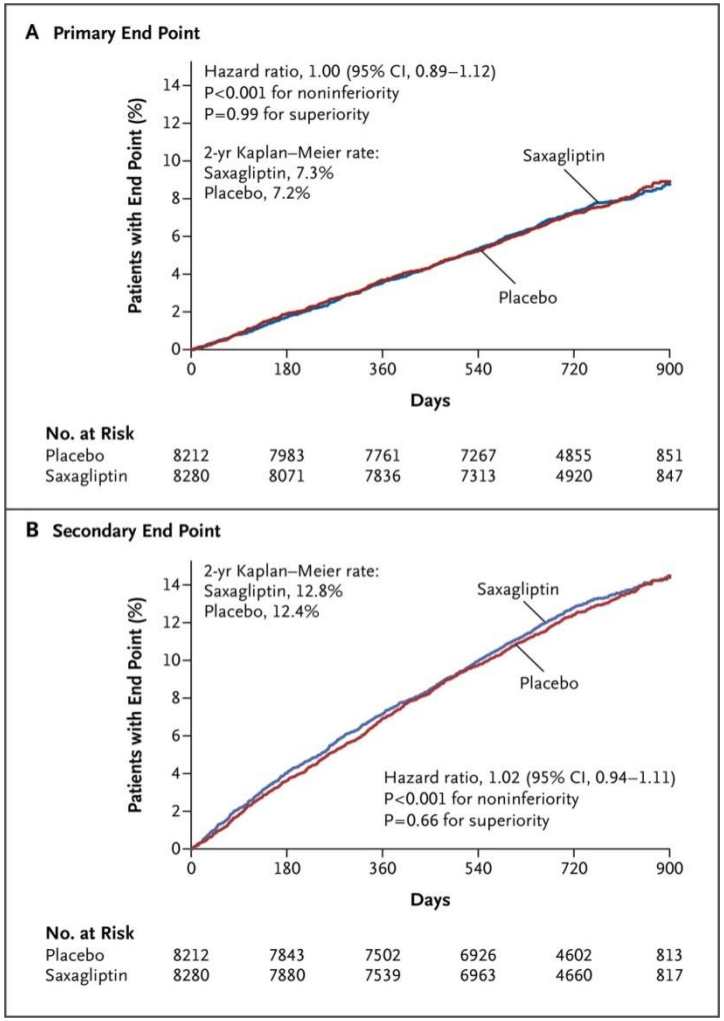


Figure 3. Mantel–Haenzel odds ratio (MH–OR) for major cardiovascular events (MACE), acute myocardial infarction (AMI), stroke, mortality and cardiovascular (CV) mortality with 95% CI. DPP4i, dipeptidyl peptidase-4 inhibitors.

N=41.959

Monami M, et al. Diabetes, Obesity and Metabolism. 2013;15: 112-20

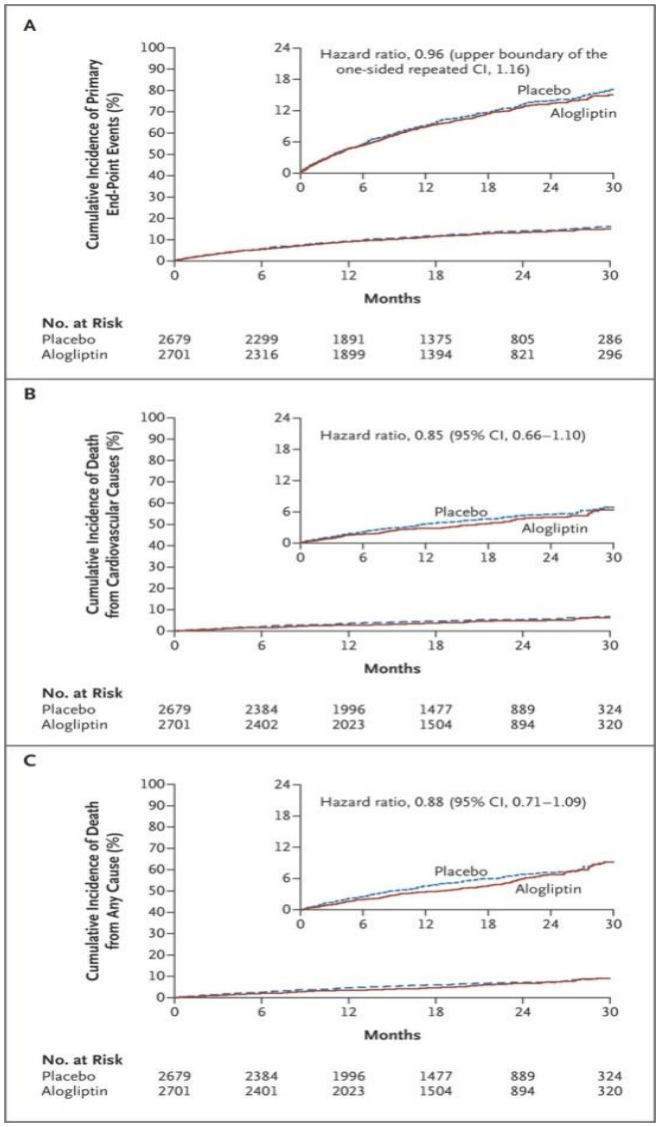
SAVOR-TIMI 53



Mediana seguimiento 2,1 años

Scirica BM et al. N Engl J Med 2013

EXAMINE: Tiempo hasta eventos CV



Cualquier evento CV

Muerte CV

Muerte

Mediana seguimiento 1,5 años

White WB et al. N Engl J Med 2013; 369:1327-35

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La *gran* pregunta…

¿O son dos?

►¿Son seguros los fármacos antidiabéticos desde el punto de vista cardiovascular? (seguridad)

► ¿Son eficaces los fármacos antidiabéticos desde el punto de vista cardiovascular? (eficacia)

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, et al. Personalized management of hyperglycemia in type 2 diabetes. Reflections from a Diabetes Care Editors' Expert Forum. Diabetes Care. 2013;36:1779-88

Análogos del receptor GLP-1

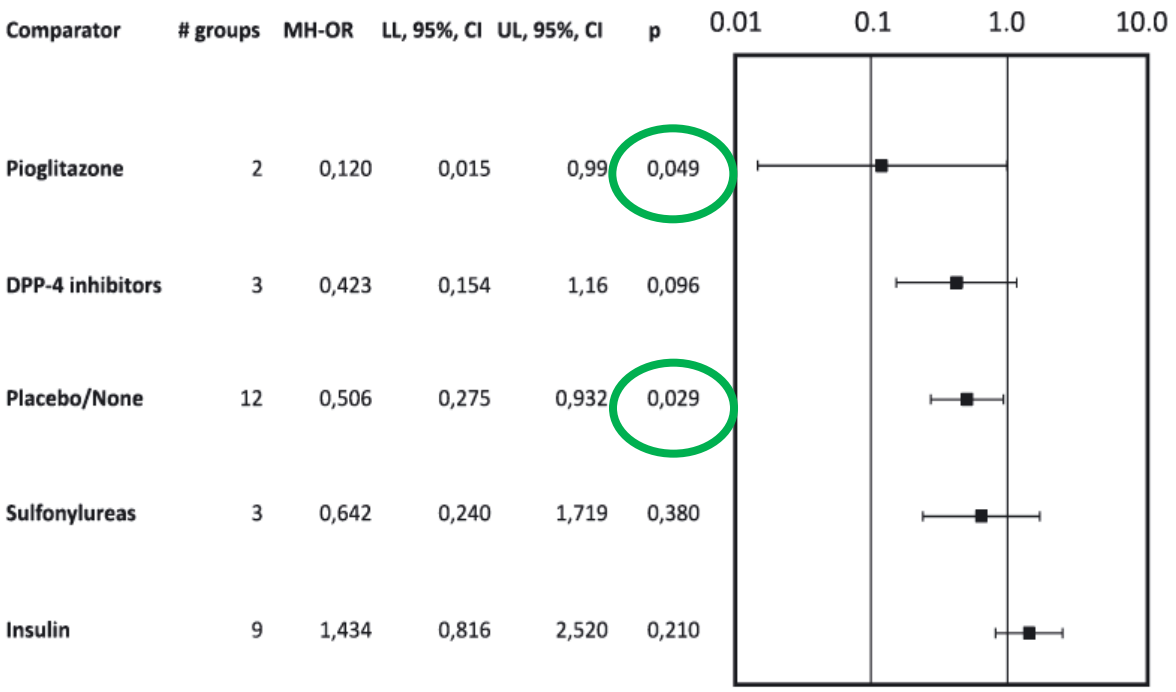


Figure 2. Mantel–Haenszel odds ratio with 95% confidence interval [MH-OR (95%, CI)] for major cardiovascular events. Subgroup analyses for different comparator groups.

Monami M, et al. Diabetes Obes Metab. 2014;16:38-47

Empagliflozina reduce HbA1C y PA

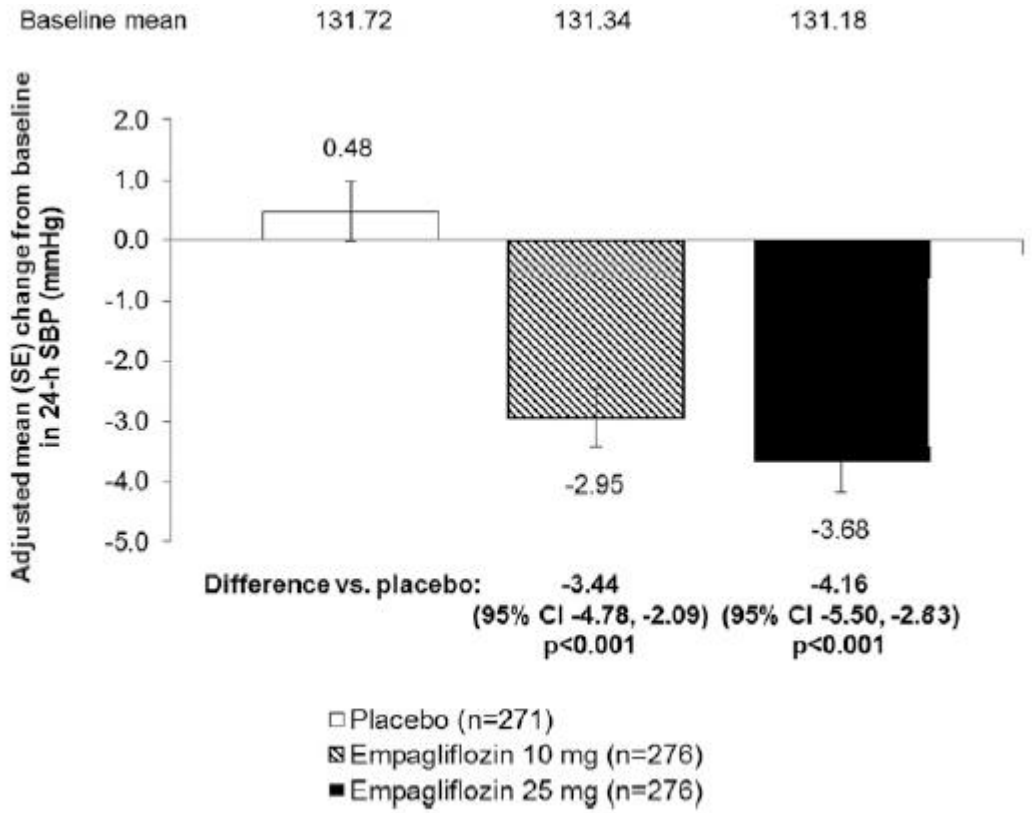
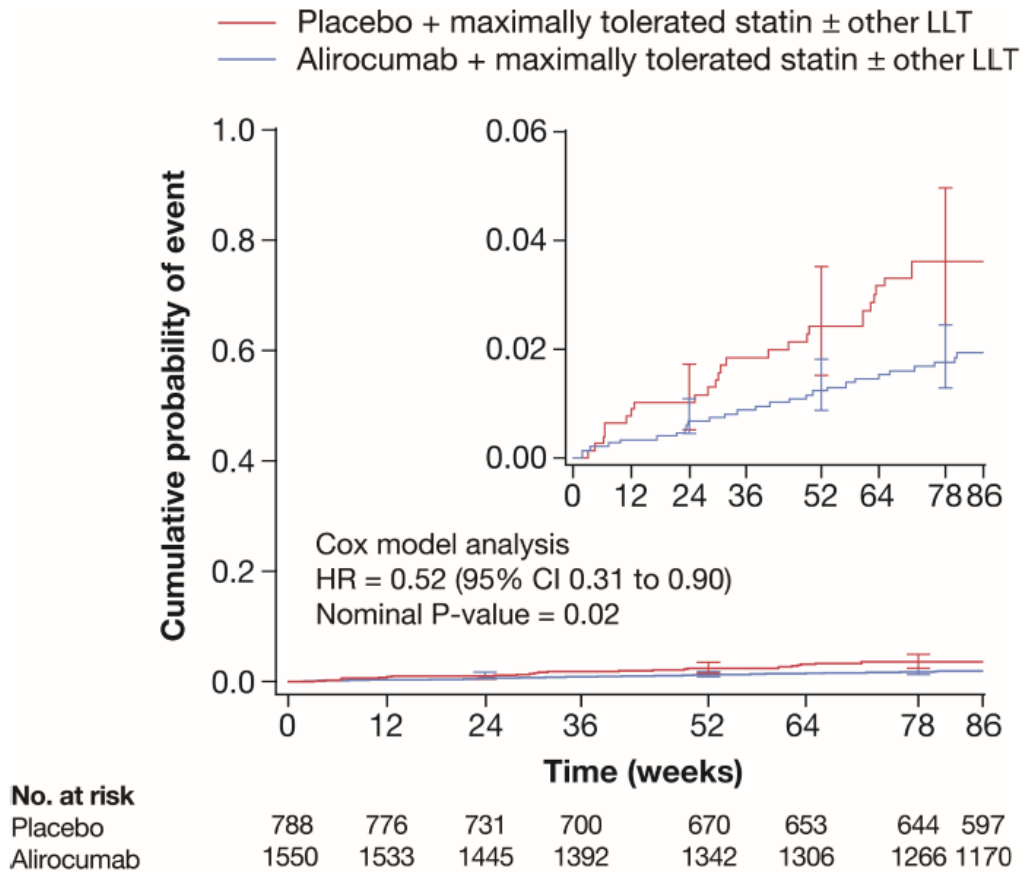


Figure 1—Blood pressure at week 12. *A*: Hourly mean SBP (APBM). *B*: Hourly mean DBP (ABPM).

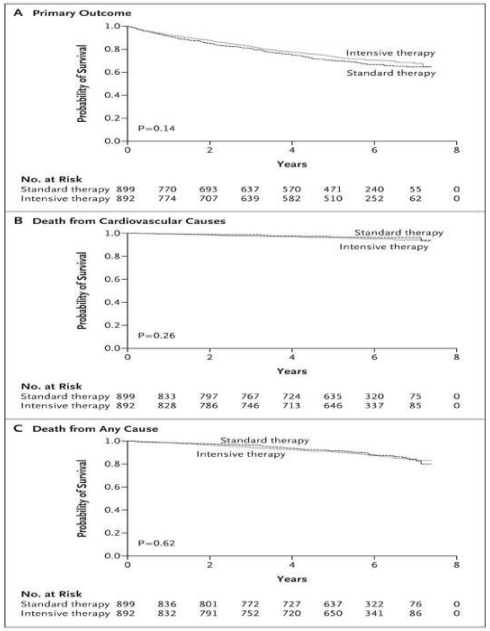
Tikkanen I, et al. Diabetes Care 2015;38:420-28

Estudio ODISSEY LONG TERM

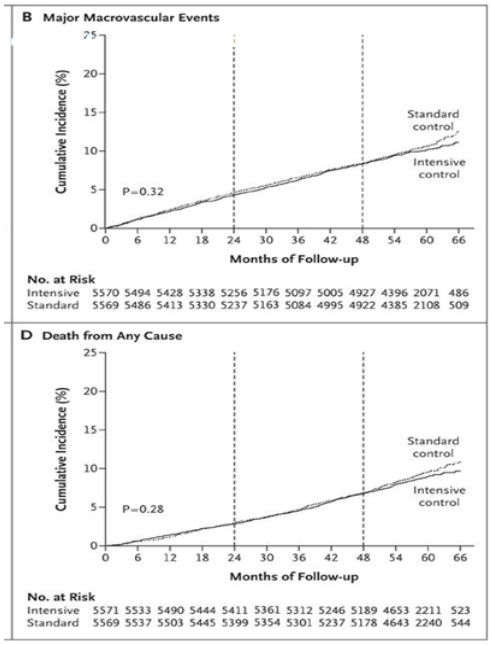


Robinson JG, et al. NEJM. 2015;372:1489-99

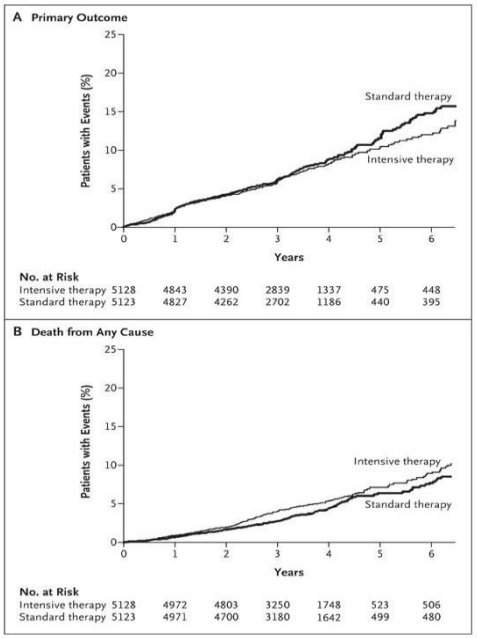
¿ES CUESTIÓN DE SER MÁS AGRESIVOS?



Estudio
ACCORD



Estudio
ADVANCE



Estudio
VADT

Accord Study Group. N Engl J Med. 2008;358:2545-59
The ADVANCE Collaborative Group. N Engl J Med 2008;358:2560-72
Duckworth W et al. N Engl J Med 2009;360:129-39

El mejor *antidiabético*, ¿una estatina?

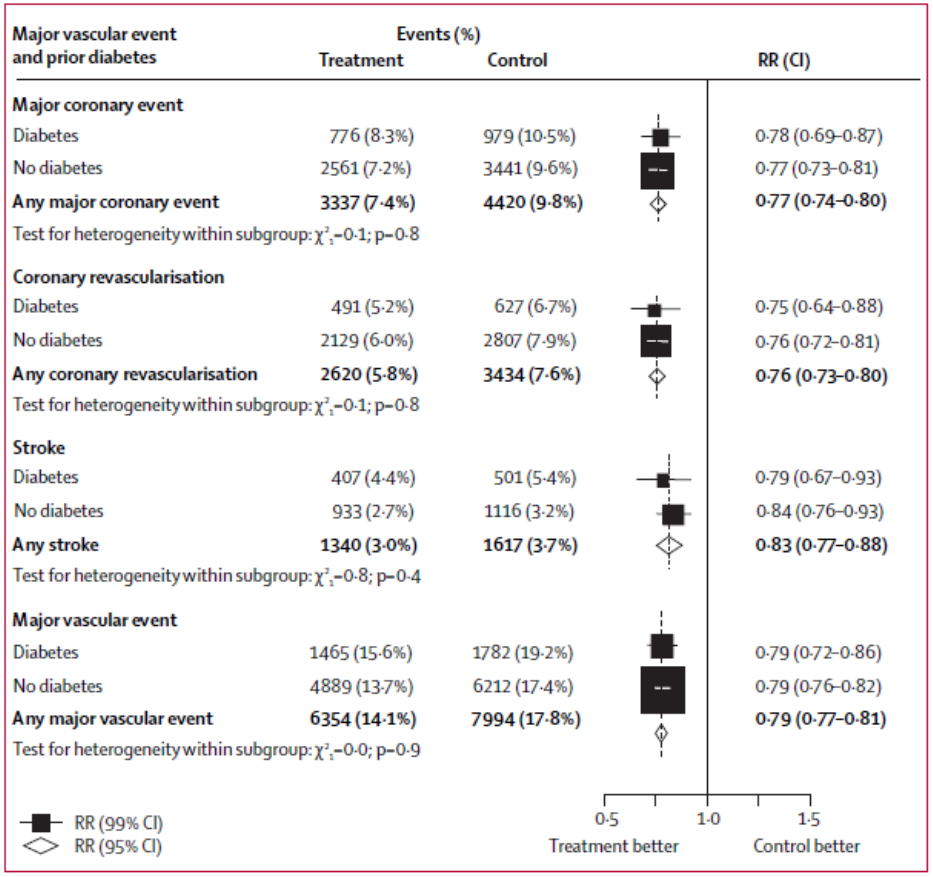
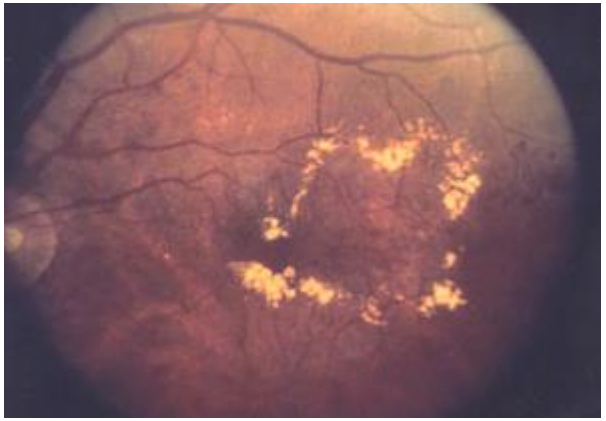


Figure 2: **Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol in participants presenting with or without diabetes**

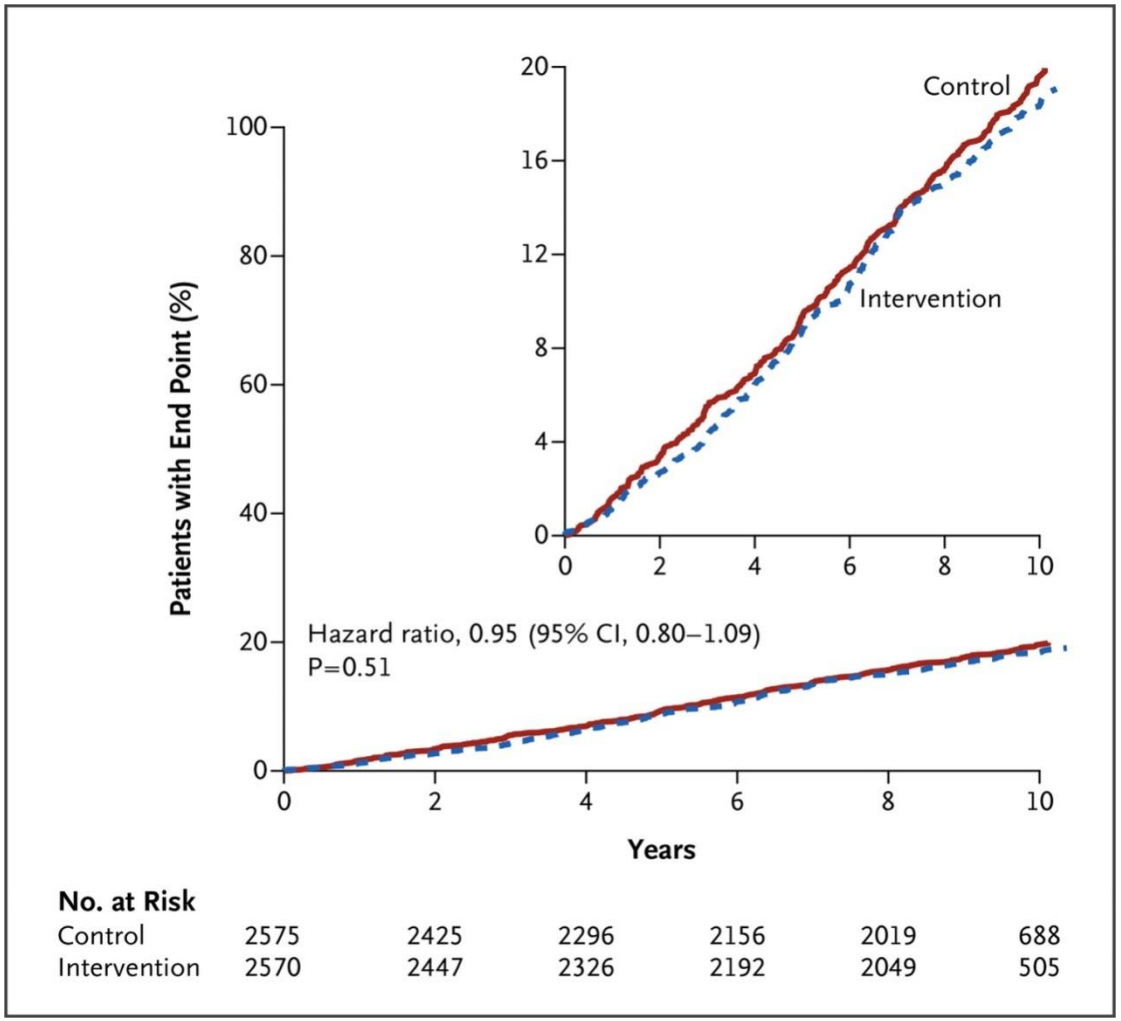
Cholesterol Treatment Trialists' (CTT) Collaborators. The Lancet. 2008;371:117-25

¿Qué buscamos con el tratamiento?

"Me encuentro cansado; he tenido dos infecciones de orina y he perdido 4 kg de peso en 3 meses. Mi médico me ha explicado que se debe a que tengo una glucemia de 288 mg/dl"



Calidad de vida: Estudio LOOK-AHEAD



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

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Conclusiones: fármacos antidiabéticos y riesgo cardiovascular

- La seguridad de los fármacos antidiabéticos se ha de evaluar a corto-medio plazo; la eficacia, muy a la larga.
- Metformina reduce eventos cardiovasculares mayores; sulfonil-ureas e insulina probablemente también.
- Muy probablemente, los fármacos antidiabéticos aparecidos en los últimos años son seguros desde el punto de vista cardiovascular.
- Sería extraordinario que algún nuevo antidiabético mostrara eficacia a medio plazo en cuanto a eventos cardiovasculares.
- Es improbable que los fármacos antidiabéticos que *simplemente* reduzcan la glucemia modifiquen la tasa de aparición de eventos cardiovasculares a medio plazo.
- Con el uso de fármacos antidiabéticos perseguimos objetivos añadidos a la prevención de eventos cardiovasculares: daño microvascular, calidad de vida.

Gracias por su atención