



Seguridad cardiovascular de antidiabéticos orales

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Conflictos de interés

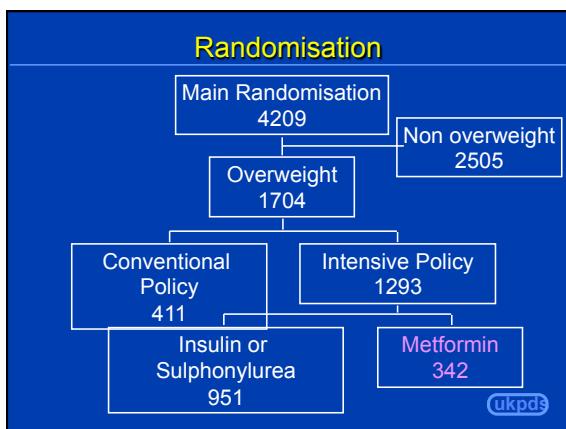
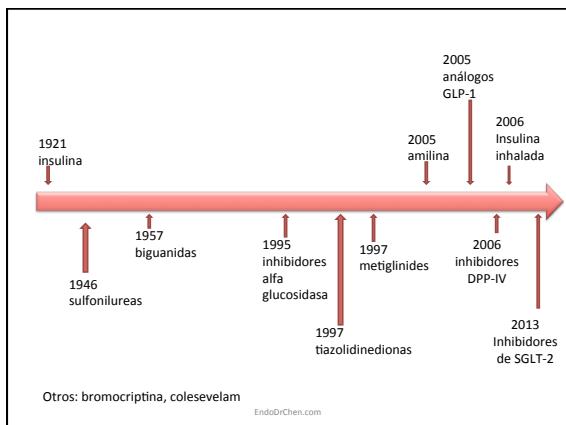
- He recibido honorarios por conferencias, advisory board y/o investigación clínica de:
 - Astra Zeneca
 - Novartis Pharma Logistics Inc
 - Novartis Oncology
 - Novo Nordisk
 - Merck Sharp & Dohme
 - Roche
 - Glaxo SmithKline
 - Sanofi Aventis
 - Boehringer
 - Organon
 - Abbott Nutrición

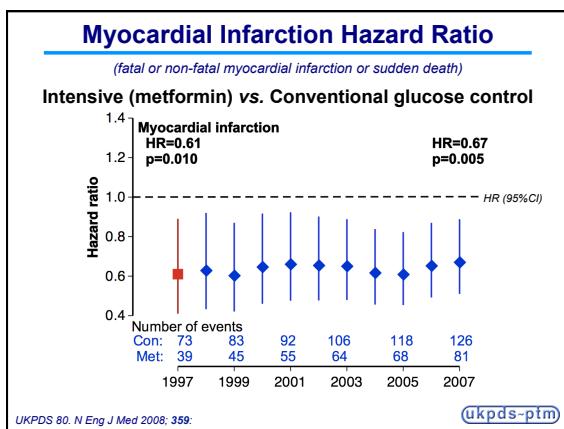
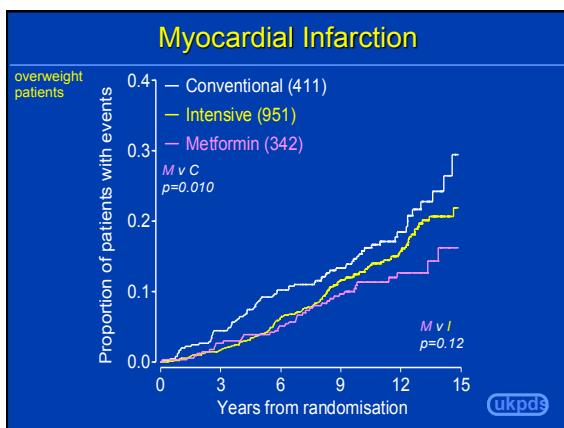
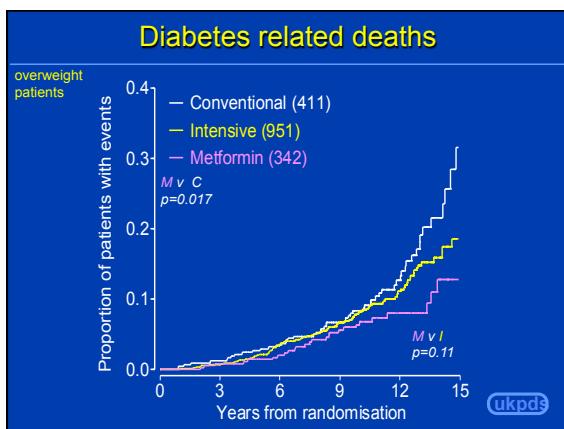
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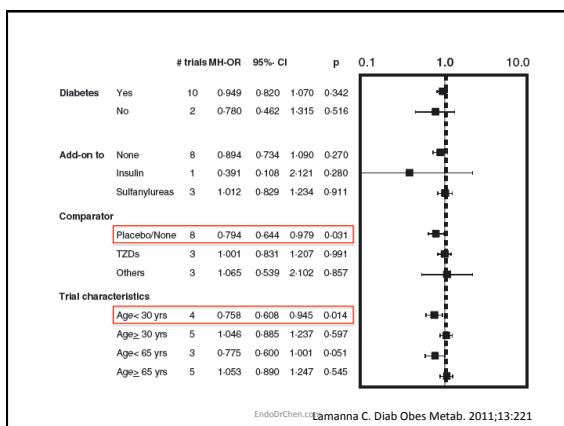
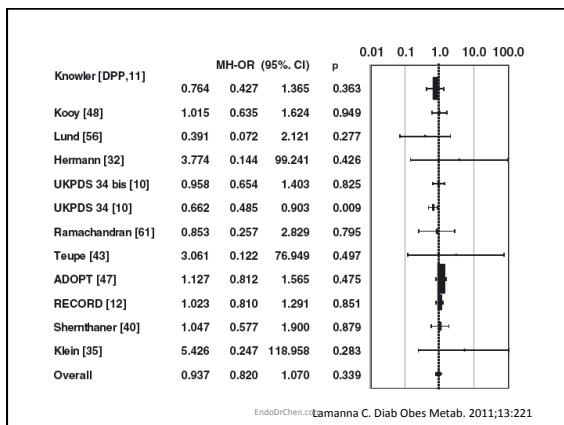
Agenda

- Revisar la evidencia de eficacia o seguridad cardiovascular
 - Metformin
 - Sulfonilureas
 - Tiazolidinedionas
 - Acarbose
- Enfatizar sobre algunos aspectos de los ensayos clínicos que influyen en su interpretación

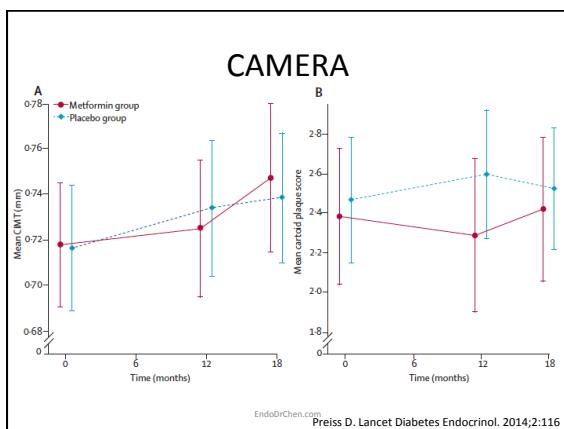
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ESTUDIOS MÁS RECIENTES CON METFORMIN



Por qué estos resultados

- Uso de estatinas:
 - UKPDS: 0%
 - CAMERA: 100%
- Mejor control de hipertensión a través de los años
- Mejor manejo de otros factores de riesgo
- Cada vez es más difícil demostrar beneficios adicionales con fármacos que se agregan a “standard of care”

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SPREAD-DIMCAD

- Aleatorizado doble ciego controlado
- 304 pacientes chinos con enfermedad coronaria
- Seguimiento por 5 años
- Resultados
 - Glipizida: 52 pacientes con eventos (35.1%)
 - Metformin: 39 pacientes con eventos (25%)
- HR 0.54 (95% IC 0.30-0.90; p=0.026)

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Hong J. Diabetes Care. 2013;36:1304

Ensayos nuevos

- **GLINT**
 - 12000 pacientes con hiperglicemia no DM, RCT metformin vs placebo por 5 años para evaluación de eventos cardiovasculares
- **REMOVAL**
 - Metformin vs placebo en DM-1 evaluando IMT
- **GIPS-III**
 - Cambios en FE por 4 meses en pacientes post IAM

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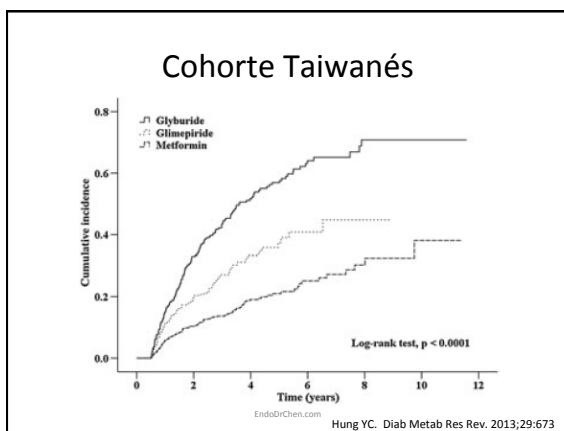
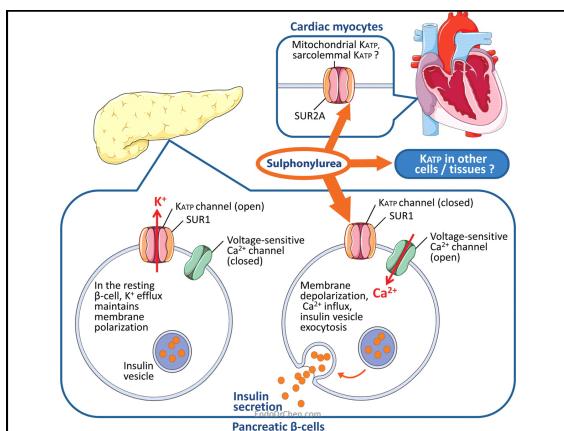
LA HISTORIA ANTES DE LOS ENSAYOS CLÍNICOS CONTROLADOS: LAS SULFONILUREAS

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Introducción

- No todas las sulfonilureas son iguales
- En teoría, efectos extraglicémicos pueden traducirse en diferencias
 - Selectividad y afinidad por receptor SUR
 - Efectos en coagulación: glicazida
 - Riesgo de hipoglicemias: glibenclamida

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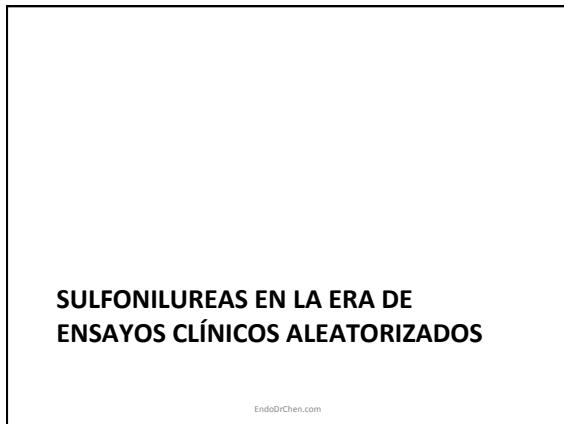
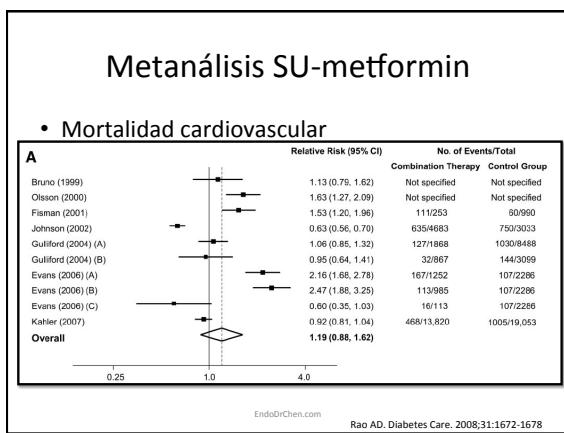
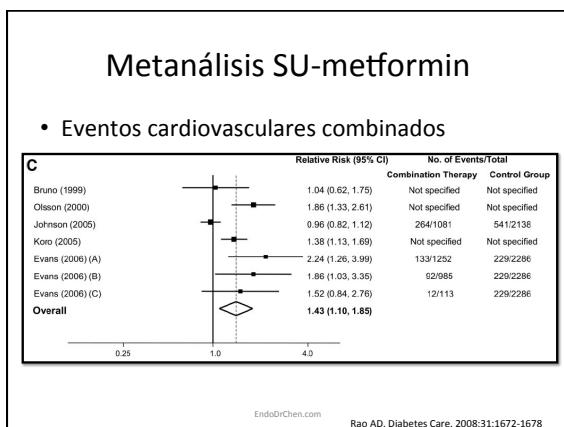


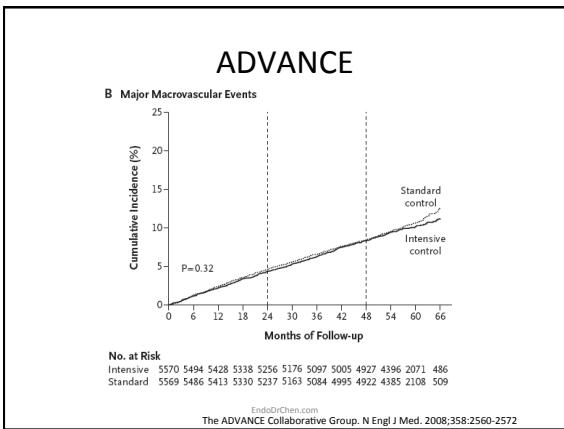
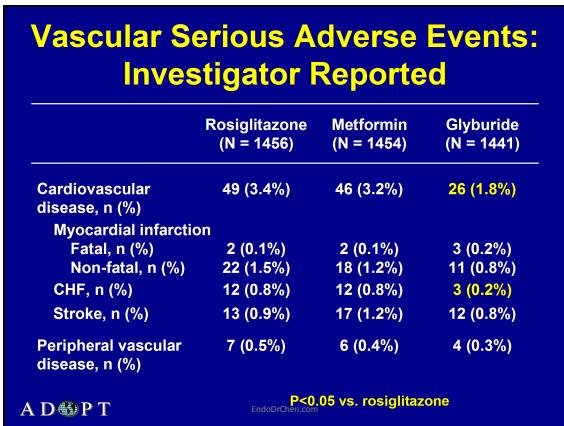
Estudios de cohorte

	Glibenclamide (n=977)	Glicazida (n=141)	Tolbutamida (n=159)
All-cause mortality			
Number of deaths (%)	429 (43.9)	55 (39.0)	72 (45.3)
Crude HR (95% CI) ^a	1	0.89 (0.67–1.17)	1.08 (0.84–1.39)
Adjusted HR (95% CI) ^b	1	0.76 (0.56–1.02)	0.79 (0.60–1.03)
Cancer mortality			
Number of deaths (%)	128 (13.1)	10 (7.1)	20 (12.6)
Crude HR (95% CI) ^a	1	0.52 (0.27–0.99)	0.96 (0.60–1.53)
Adjusted HR (95% CI) ^b	1	0.30 (0.16–0.55)	0.48 (0.29–0.79)
Cardiovascular mortality			
Number of deaths (%)	194 (19.9)	30 (21.3)	38 (23.9)
Crude HR (95% CI) ^a	1	1.10 (0.75–1.62)	1.26 (0.88–1.79)
Adjusted HR (95% CI) ^b	1	1.28 (0.84–1.95)	1.20 (0.79–1.84)
Mortality from other causes			
Number of deaths (%)	107 (11.0)	15 (10.6)	14 (8.8)
Crude HR (95% CI) ^a	1	0.99 (0.57–1.71)	0.80 (0.46–1.41)
Adjusted HR (95% CI) ^b	1	0.81 (0.44–1.51)	0.62 (0.34–1.15)
Adjusted HR (95% CI) ^b	1	0.87 (0.19–4.03)	0.62 (0.29–1.33)

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Bo S. Eur J Endocrinol. 2013;169:117





Uso de antidiabéticos en ADVANCE

Characteristic	Baseline		End of Follow-up	
	Intensive Control (N=557)	Standard Control (N=5569)	Intensive Control (N=4828)	Standard Control (N=4741)
Glucose-lowering drug				
Gliclazide (modified release) — no. (%)	422 (7.6)	443 (8.0)	4209 (90.5)	80 (1.6)
Other sulfonylurea — no. (%)	3578 (64.2)	3513 (63.1)	89 (1.9)	2606 (57.1)
Metformin — no. (%)	3397 (61.0)	3355 (60.2)	3455 (73.8)	3057 (67.0)
Thiazolidinedione — no. (%)	201 (3.6)	206 (3.7)	788 (16.8)	495 (10.9)
Acarbose — no. (%)	512 (9.2)	448 (8.0)	891 (19.1)	576 (12.6)
Glimepiride — no. (%)	103 (1.8)	84 (1.5)	58 (1.2)	127 (2.8)
Any oral hypoglycemic drug — no. (%)	5084 (91.3)	5045 (90.6)	4525 (91.7)	4001 (84.4)
Insulin — no. (%)	82 (1.5)	77 (1.4)	1953 (40.5)	1142 (24.1)
None — no. (%)	487 (8.7)	524 (9.4)	42 (1.5)	220 (6.4)
Other drugs				
Aspirin — no. (%)	2460 (44.2)	2435 (43.7)	2665 (57.0)	2503 (54.9)
Other antiplatelet agent — no. (%)	271 (4.9)	235 (4.2)	333 (7.1)	284 (6.2)
Statins — no. (%)	1554 (27.9)	1592 (28.6)	2131 (45.6)	2174 (47.7)
Other lipid-modifying drug — no. (%)	501 (9.0)	435 (7.8)	326 (7.0)	317 (7.0)
Any blood-pressure-lowering drug — no. (%)	4183 (75.1)	4182 (75.1)	4291 (88.9)	4190 (88.4)

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The ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560-2572

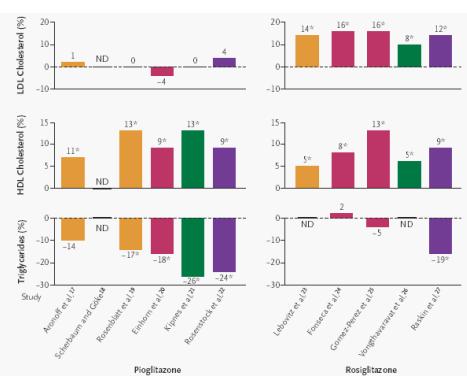
Limitantes

- La interpretación de los datos con sulfonilureas se ha dificultado por:
 - Los agrupa a todos en el mismo grupo terapéutico
 - Pocos estudios comparativos prospectivos entre diferentes sulfonilureas
 - Mayoría son estudios retrospectivos y de cohorte
 - Muchísimos factores confusores para llegar a concluir que es la sulfonilurea
- Es importante aclarar este punto por la cantidad de personas que están expuestas a SU

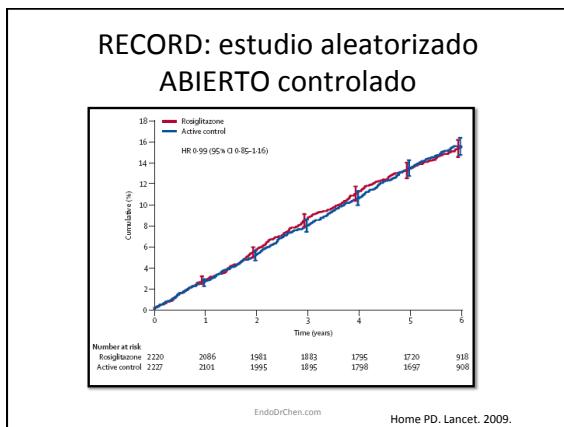
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LLEGAR A CONCLUSIONES PRECIPITADAS: LA HISTORIA DE ROSIGLITAZONA

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EndoDrChen.com Yki-Järvinen H. N Engl J Med. 351:1106



Revaluación de los datos de RECORD

	Rosiglitazone	Metformin/sulfonilurea	HR (95% CI)
DCR CEC results (original definitions)			
CV (or unknown cause) death, MI, or stroke	181 (8.3%)	188 (8.4%)	0.95 (0.78-1.15)
CV (or unknown cause) death	88 (4.0%)	96 (4.3%)	0.90 (0.68-1.21)
MI	68 (3.1%)	60 (2.7%)	1.13 (0.80-1.59)
Stroke	50 (2.3%)	43 (2.8%)	0.79 (0.54-1.14)
All death	139 (6.3%)	160 (7.2%)	0.86 (0.68-1.08)
Original RECORD CEC results (original definitions)			
CV (or unknown cause) death, MI, or stroke	154 (6.9%)	165 (7.4%)	0.93 (0.74-1.15)
CV (or unknown cause) death	60 (2.7%)	71 (3.2%)	0.84 (0.59-1.18)
MI	64 (2.9%)	56 (2.5%)	1.14 (0.80-1.43)
Stroke	46 (2.1%)	63 (2.8%)	0.72 (0.49-1.06)
All death	136 (6.1%)	157 (7.0%)	0.86 (0.68-1.08)

EndoDrChen.com Mahaffey KW. Am Heart J. 2013;166:240

Drugs

Home Drugs Drug Safety and Availability

FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines

[View and print full Drug Safety Communication \(PDF 92KB\)](#)

This update is in follow-up to the FDA Drug Safety Communications issued on November 4, 2011, and May 15, 2012.

Drug Shortages

Postmarket Drug Safety Information for Patients and Healthcare Professionals

Information by Drug Class

Medication Errors

Drug Safety Podcasts

Safe Use Initiative

Drug Recalls

Drug Supply Chain Integrity

Multistate outbreak of fungal meningitis and other infections

Safety Announcement | **Data Summary**

Safety Announcement

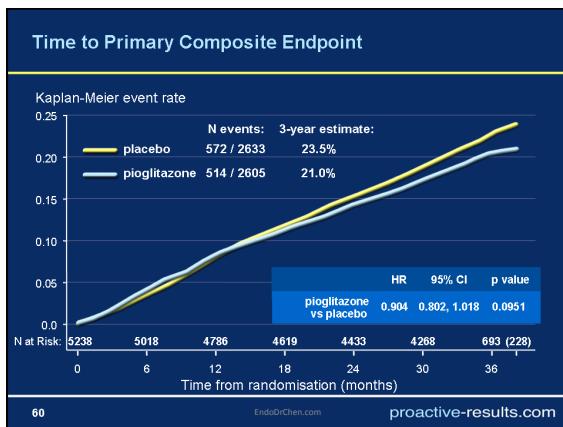
[11-25-2013] The U.S. Food and Drug Administration (FDA) has determined that recent data for rosiglitazone-containing diabetes medicines show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin and sulfonylureas. This decision is based on a review of data from a large, long-term clinical trial and is supported by a comprehensive, outside, expert re-evaluation of the data conducted by Duke University.

Type 2 diabetes is a disease that can lead to serious complications and premature death. Rosiglitazone is a prescription medicine used to treat Type 2 diabetes. People with type 2 diabetes should continue to work closely with their health care professionals to determine treatment options that are most appropriate.

FDA monitors the safety and effectiveness of drugs after they go on the market. In the case of rosiglitazone medicines, previous data from a large, combined analysis of mostly short-term, randomized controlled trials suggested an increased risk of heart attack, so FDA required a Risk Evaluation and Mitigation Strategy (REMS), called the Rosiglitazone REMS program. The Rosiglitazone REMS program restricted the use of rosiglitazone medicines to help ensure that their benefits outweigh their risks.

Although some scientific uncertainty about the cardiovascular safety of rosiglitazone medicines still remains, in light of the new re-evaluation of the Rosiglitazone REMS for Cardiovascular Outcomes and Revascularization Effects (Duke University), our concern is sufficiently reduced that the rosiglitazone REMS program requirements will be modified (see Data Summary). We are also requiring

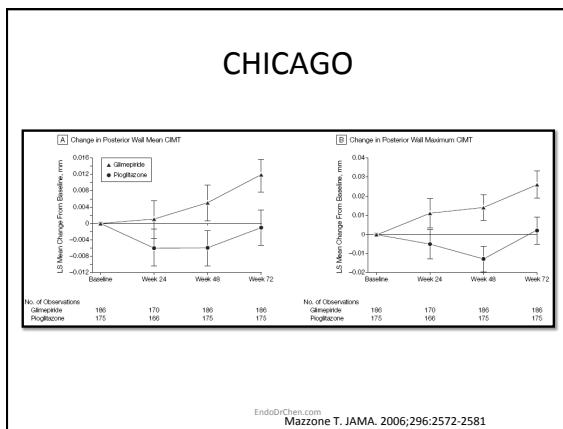
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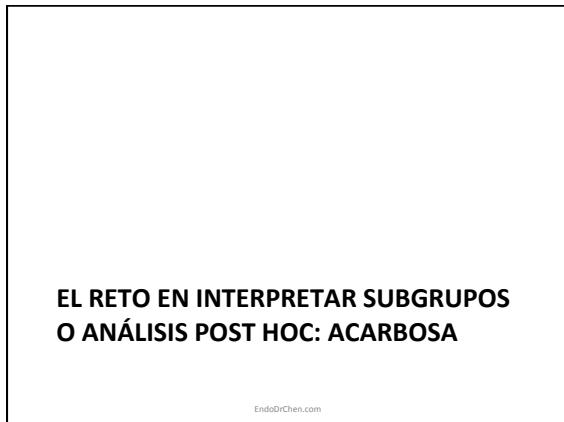


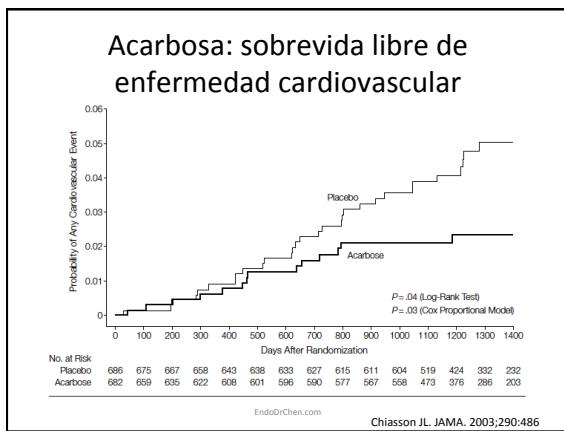
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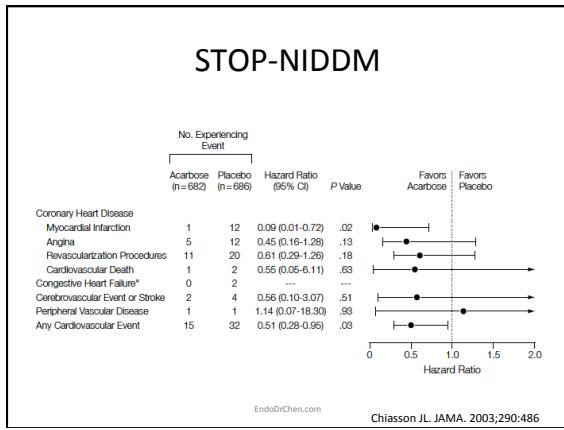
Glimepiride (n = 181)		Pioglitazone (n = 179)		P	
Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Value ^a	
Baseline Examination					
Percent atherosclerosis volume, % ^b	40.3 (8.0)	40.3 (34.7 to 45.0)	40.6 (8.4)	40.3 (34.1 to 46.0)	.54
Maximum atherosclerosis thickness, mm ^c	0.82 (0.26)	0.80 (0.64 to 0.98)	0.81 (0.25)	0.79 (0.61 to 1.00)	.94
Normalized total atherosclerosis volume, ^c mm ³	219.8 (95.2)	197.8 (148.1 to 277.7)	207.5 (83.8)	190.9 (147.6 to 254.5)	.27
Atherosclerosis volume in 10-mm most diseased segment, ^c mm ³	64.7 (31.5)	62.1 (40.0 to 86.6)	62.7 (28.1)	59.4 (45.6 to 78.7)	.50
Follow-up Examination					
Percent atherosclerosis volume, % ^b	41.0 (9.0)	40.5 (35.2 to 46.9)	40.5 (8.5)	40.5 (33.6 to 46.3)	.73
Maximum atherosclerosis thickness, mm ^c	0.83 (0.26)	0.81 (0.64 to 0.98)	0.80 (0.24)	0.76 (0.62 to 0.97)	.39
Normalized total atherosclerosis volume, ^c mm ³	217.7 (95.3)	192.6 (150.0 to 278.3)	200.8 (81.8)	184.5 (144.6 to 248.4)	.13
Atherosclerosis volume in 10-mm most diseased segment, ^c mm ³	62.4 (31.2)	57.8 (30.5 to 83.1)	60.0 (27.5)	57.9 (39.7 to 77.8)	.62
Nominal Change From Baseline					
LS Mean (95% CI)	P Value Change From Baseline	LS Mean (95% CI)	P Value Change From Baseline	P Value ^d	
Percent atherosclerosis volume, % ^b	0.73 (0.33 to 1.12) <.001	-0.16 (-0.57 to 0.25) .44	<.001	.002	
Maximum atherosclerosis thickness, mm ^c	0.011 (-0.002 to 0.022) .054	-0.011 (-0.022 to 0.004) .06	<.001	.006	
Normalized total atherosclerosis volume, ^c mm ³	-1.5 (-4.50 to 1.50) -.34	-5.9 (-8.67 to -2.38) <.001	<.001	.06	
Atherosclerosis volume in 10-mm most diseased segment, ^c mm ³	-2.1 (-3.33 to -0.64) .001	-2.0 (-3.33 to -0.67) .003	<.001	.93	

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Nissen SE. JAMA. 2008;299(13):1561-1573









Predefined endpoints—multiple hypothesis testing. Administration of Acarbose was associated with a combined cardiovascular event risk reduction of 49% [11]. However, the kind and the number of assessed cardiovascular events changed during the course of the study. Prospectively predefined end-points comprised myocardial infarction, cerebrovascular event and heart failure [13]. In the final report angina, revascularisation procedures, cardiovascular death and peripheral vascular disease were also included [11]. The report of the safety population also includes coronary disorder, hypertension and arrhythmia [18]. In total, ten different cardiovascular end-points were assessed. This results in 1023 possible statistical comparisons of different combinations of these endpoints. The reason for choosing a non-predefined combination of events for assessment of the cumulative risk of cardiovascular end-points is not stated. At least, a separate analysis of the prospectively defined combination of end-points is missing.

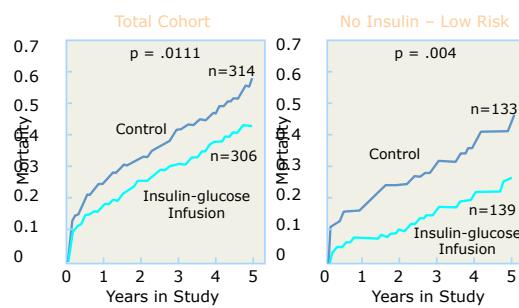
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Kaiser T. Diabetologia. 2004;47:575

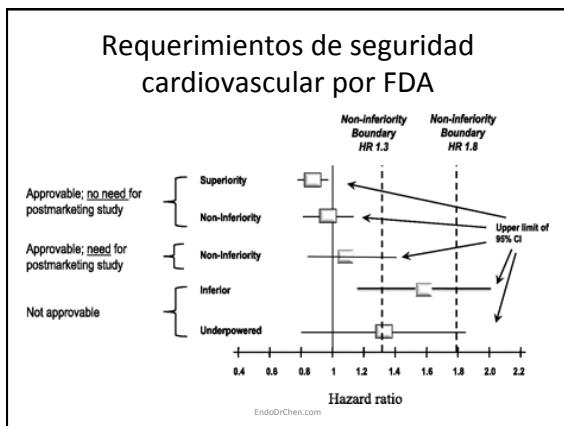
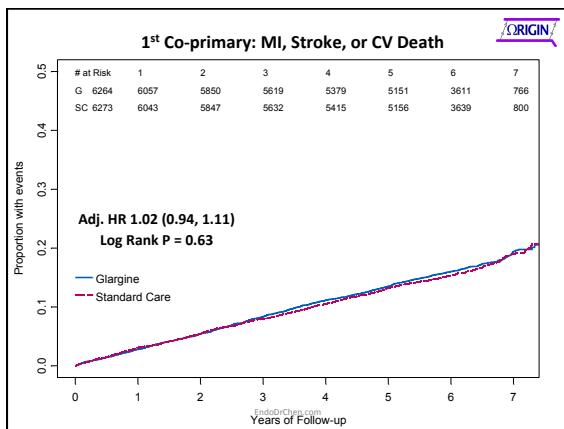
VAMOS MEJORANDO CALIDAD DE ESTUDIOS: INSULINAS

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Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI): Benefit of Tight Glycemic Control in No Insulin – Low Risk Cohort



Malmberg K, et al. BMJ. 1997;314:1512-1515.



**EN EL FUTURO PRÓXIMO:
INHIBIDORES DE SGLT-2**

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En teoría...

- Desde el punto de vista cardiovascular, todo luce bien
 - Reducción de peso
 - Reducción de grasa visceral
 - Reducción de presión arterial
 - Lípidos???

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	PBO	CANA 100 mg	CANA 300 mg
Systolic BP, n	190	192	195
Mean (s.d.) baseline (mmHg)	127.7 (13.7)	126.7 (12.5)	128.5 (12.7)
I.S. mean (s.e.) change	0.4 (0.8)	-3.3 (0.8)	-5.0 (0.8)
Difference versus PBO (95% CI)		-3.7 (-5.8, -1.6)*	-5.4 (-7.8, -3.3)*
Diastolic BP, n	190	192	195
Mean (s.d.) baseline (mmHg)	77.4 (8.4)	77.2 (6.8)	79.1 (8.3)
I.S. mean (s.e.) change	-0.1 (0.5)	-1.7 (0.5)	-2.1 (0.5)
Difference versus PBO (95% CI)		-1.6 (-2.9, -0.2)†	-2.0 (-3.4, -0.7)†
Triglycerides, n	171	183	183
Mean (s.d.) baseline (mmol/l)	2.2 (1.2)	2.0 (1.2)	2.0 (1.1)
I.S. mean (s.e.) change	0.07 (0.07)	-0.16 (0.07)	-0.18 (0.07)
Median (IQR) percent change	0.0 (-16.4, 19.3)	-7.6 (-25.9, 19.5)	-9.7 (-27.8, 17.5)
I.S. mean (s.e.) percent change	7.9 (3.5)	2.5 (3.4)	2.3 (3.4)
Difference versus PBO (95% CI)		-5.4 (-14.9, 4.1)‡	-10.2 (-19.6, -0.7)‡
LDL-C, n	169	180	181
Mean (s.d.) baseline (mmol/l)	3.1 (1.1)	3.1 (1.0)	2.9 (0.9)
I.S. mean (s.e.) change	-0.07 (0.05)	0.00 (0.05)	0.12 (0.05)
Median (IQR) percent change	-2.4 (-16.5, 12.2)	0.4 (-14.4, 13.9)	3.1 (-7.4, 19.5)
I.S. mean (s.e.) percent change	1.0 (1.9)	0.9 (1.8)	1.3 (1.8)
Difference versus PBO (95% CI)		2.0 (-3.2, 7.1)†	6.1 (0.9, 11.3)†
HDL-C, n	170	182	183
Mean (s.d.) baseline (mmol/l)	1.1 (0.3)	1.2 (0.3)	1.2 (0.3)
I.S. mean (s.e.) change	0.04 (0.02)	0.11 (0.02)	0.11 (0.02)
Median (IQR) percent change	3.2 (-6.6, 15.8)	9.2 (-2.3, 19.8)	8.9 (-1.0, 20.3)
I.S. mean (s.e.) percent change	4.5 (1.4)	11.2 (1.4)	10.6 (1.4)
Difference versus PBO (95% CI)		6.8 (12.9, 10.6)†	6.1 (2.3, 9.9)†

EndoDrChen.com Stenlof K. Diab Obes Metab. 2013;15:372

Relexiones finales

- Viene una era promisoria de estudios clínicos
- Debemos dejar de pensar sólo en glucosa y ponerle más énfasis a puntos finales duros como eventos clínicos
 - Mortalidad y eventos cardiovascular
 - Eventos microvascular
- Estudios con puntos finales cardiovasculares con inhibidores DPP-4, análogos GLP-1, inhibidores SGLT-2

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Conclusiones

- La causa principal de muerte en DM es cardiovascular
 - Cualquier impacto en este punto es significativo, tanto en beneficio como empeoramiento
- Los datos de fármacos viejos como metformina y SU no son del todo tan claros, muchos factores confusos
- Seguridad CV de nuevos fármacos está siendo mejor evaluado

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Preguntas...
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