



Rompiendo paradigmas de eficacia y seguridad en DM-2: qué sucede con las sulfonilureas?

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EndoDrChen.com

Conflictos de interés

- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Pfizer, Novartis
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer
- Investigación clínica: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

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Agenda

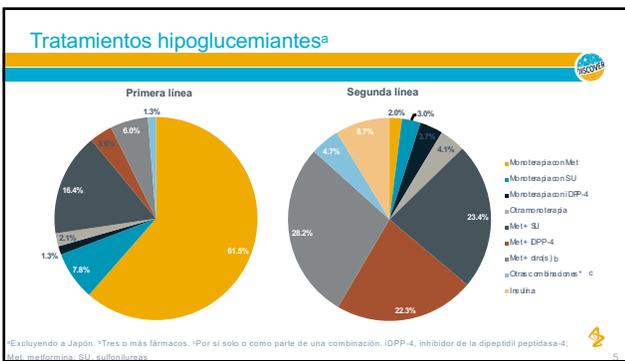
- Efecto en control glicémico
- Riesgo cardiovascular
- Sostenibilidad del control glicémico y agotamiento de células beta
- Eventos adversos: hipoglicemias y aumento de peso
- Costo

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Introducción

- Es el grupo terapéutico oral más viejo que se ha usado para la diabetes
- Introducidos por primera vez en 1956
- Sigue siendo ampliamente utilizado a nivel mundial, incluso en países desarrollados
- Siguen generando controversia:
 - Hipoglucemia
 - Aumento de peso
 - Cardiovascular? Precondicionamiento cardíaco?
 - Agotamiento de células beta?

Tratamientos hipoglucemiantes^a

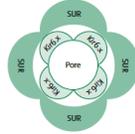


Second line therapy	Central America*	Mexico	Colombia	Argentina	Brazil
Met mono	2.7%	5.2%	4.0%	1.7%	4.3%
SU mono	1.8%	8.5%	11.5%	7.3%	13.7%
DPP4 mono	13.7%	2.8%	9.0%	16.6%	6.1%
SGLT mono	13.7%	1.3%	6.0%	4.6%	3.8%
Met + SU	4.1%	36.7%	7.5%	23.8%	29.1%
Met + DPP4	36.1%	16.2%	22%	22.5%	16.7%
Met + SGLT	7.8%	4.4%	1.0%	1.7%	16.4%
SU + TZD	0.5%	3.1%	7.0%	6.0%	0.5%
Insulin	0.5%	10.9%	19.5%	6.6%	2.0%
Antihypertensive drugs	61.2%	46.7%	53.5%	57%	62.2%
Lipid lowering drugs	47%	45.4%	52%	41.4%	48%
Antiplatelet drugs	15.1%	24.9%	34.5%	23.2%	19.6%

Chen-Ku CH, Gonzalez-Galvez G. Endocrine Practice. Oct 2019

Diferencias

Tejido		
Páncreas	SUR1	Kir 6.2
Cardiomiocitos	SUR2B	Kir 6.2
Músculo liso vascular	SUR2B	Kir 6.1



Khunti K. Lancet Diab Endocrinol. 2015;6:821-32

Diferencias entre agentes

Product	Daily dose (mg)	Peak plasma level (h)	Duration of action (h)	Active metabolites	Excretion	SUR subtype affinity (concentration of half maximal inhibition [K _{1/2}])		Relative affinity SUR1/SUR2A
						SUR 1	SUR 2A	
First generation sulfonylureas								
Flibutamide	500-2000 in 2 or 3 divided doses	3-4	Short	No	Urine ~100%	5.4 µmol/L	1.7 mmol/L	314.8
Chlorpropamide	100-500 single daily dose	2-4	>24	Yes	Urine ~80 to 90%	-	-	-
Second generation sulfonylureas								
Glibenclamide (glyburide) expirone (regular)	2.5-15	2-4	16-24	Yes	Bile > 50%	4.2 nmol/L	27 nmol/L	6.4
	2.5-15 divided into 3-2 doses	1-3	12-24	No	Urine ~70%	-	-	-
Gliclazide (regular)	80-320	4-6	10-24	No	Urine ~65%	50 nmol/L	0.8 mmol/L	16,000
Third generation sulfonylureas								
Glimepiride expirone cr + ligandotomental interspecific system	1-6	2-3	24	Yes	Urine ~60%	5.4 nmol/L	7.3 nmol/L	1.35
			>24	No	Urine ~70%	-	-	-
Gliclazide MR, modified release	30-120	6-12	>24	No	Urine ~65%	50 nmol/L	0.8 mmol/L	16,000

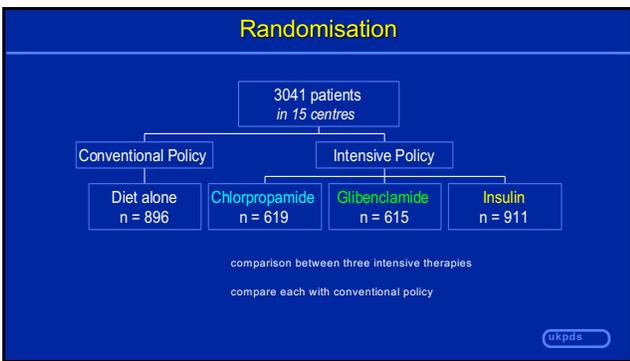
JACC Vol. 31, No. 5 April 1998:950-6

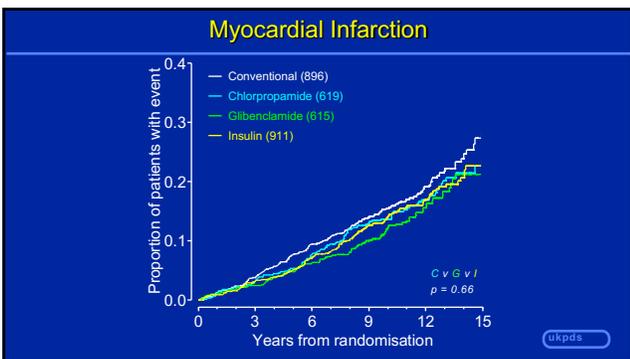
Por qué preocupación cardiovascular?

- Antecedente de estudio del Grupo Universitario
- Efecto directo en músculo liso vascular evitando vasodilatación mediada por isquemia (precondicionamiento cardíaco)
 - En teoría no se presenta con glimepiride ni con gliclazida
- Efecto indirecto
 - Mediado por hipoglicemias
 - Aumento de peso

Khunti K. Lancet Diab Endocrinol. 2015;6:821-32

Seguridad cardiovascular





Sulphonylurea or insulin : Summary 2

Sulphonylurea therapy

- no evidence of deleterious effect on myocardial infarction, sudden death or diabetes related deaths

Insulin therapy

- no evidence for more atheroma-related disease

ukpds

Vascular Serious Adverse Events: Investigator Reported

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Cardiovascular disease, n (%)	49 (3.4%)	46 (3.2%)	26 (1.8%)
Myocardial infarction			
Fatal, n (%)	2 (0.1%)	2 (0.1%)	3 (0.2%)
Non-fatal, n (%)	22 (1.5%)	18 (1.2%)	11 (0.8%)
CHF, n (%)	12 (0.8%)	12 (0.8%)	3 (0.2%)
Stroke, n (%)	13 (0.9%)	17 (1.2%)	12 (0.8%)
Peripheral vascular disease, n (%)	7 (0.5%)	6 (0.4%)	4 (0.3%)

A D 45 P T P<0.05 vs. rosiglitazone

Randomization and Masking

Prospective, randomized, open label, blinded end point design

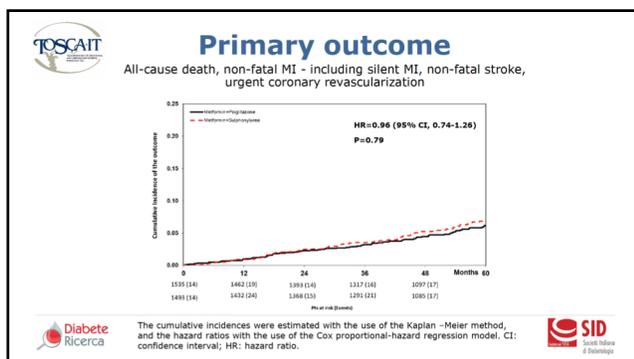
- Participants and investigators were aware of treatment group assignment
- An external Adjudication Committee, blind with regard to treatment, reviewed and adjudicated:
 - Components of the primary end point
 - Safety end points of interest in relation to the study drugs

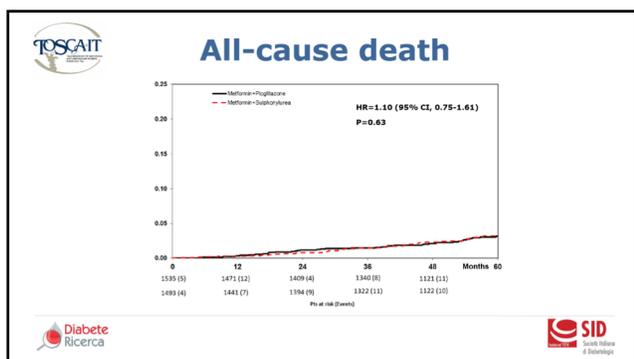
Diabete Ricerca SID

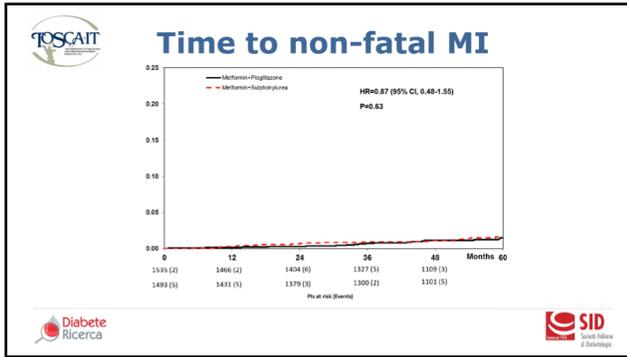
Study Medications

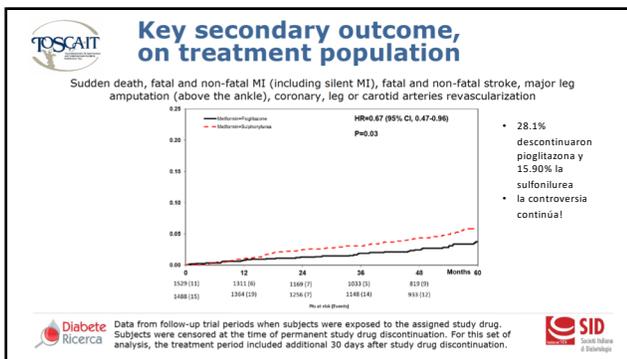
	Metformin + Pioglitazone (average dose, mg)	Metformin + Sulphonylurea (average dose, mg)
Pioglitazone	23.0±8.6	---
Glibenclamide (1.6%)	---	7.6±4.0
Glimepiride (49.9%)	---	2.5±0.9
Gliclazide (48.5%)	---	42.0±18.6

Diabete Ricerca SID







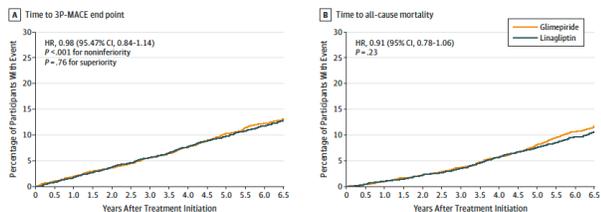


CAROLINA

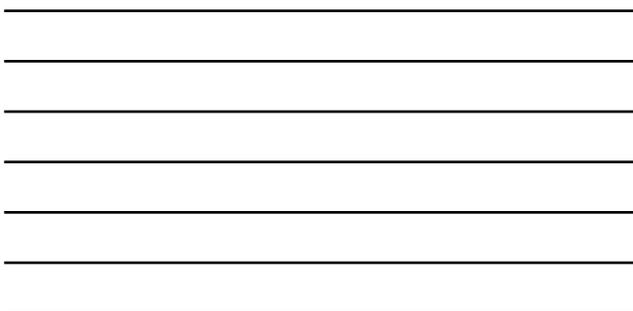
- Criterios de inclusión:
 - HbA1c 6.5-8.5%
 - Alto riesgo cardiovascular:
 - Enfermedad cardiovascular establecida (34.8%)
 - Múltiples factores de riesgo: al menos 2 de los siguientes: (37.4%)
 - Duración de DM mayor a 10 años
 - PAS >140 mm Hg o estar recibiendo al menos un antihipertensivo
 - Tabaquismo activo
 - LDL >135 mg/dl o recibir hipolipemiantes
 - Edad >70 años (18.7%)
 - Evidencia de complicaciones microvasculares (8.5%)
 - AEC 30-59 cc/min
 - Albúmina/creatinina >30 mg/g

Rosenstock J. JAMA. 2019; online Sep 19

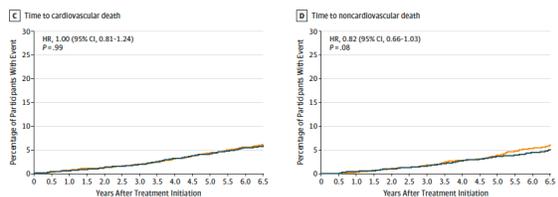
CAROLINA: linagliptina vs glimepiride



Rosenstock J. JAMA. 2019; online Sep 19



CAROLINA: linagliptina vs glimepiride

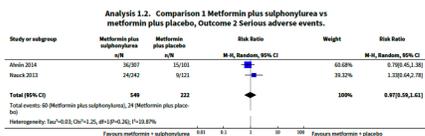
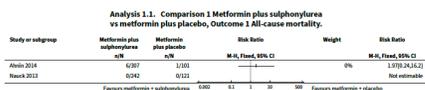


	Glimepiride	2982	2937	2885	2823	2751	2068
No. of participants	3010	2982	2937	2885	2823	2751	2068
Linagliptin	3023	2991	2951	2908	2838	2780	2045

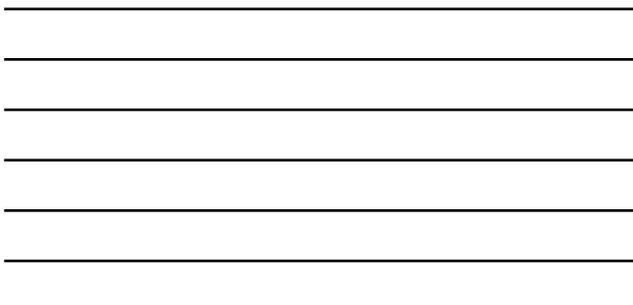
Rosenstock J. JAMA. 2019; online Sep 19



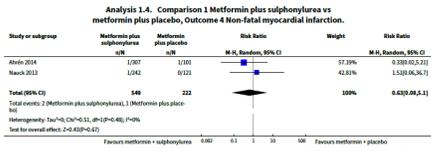
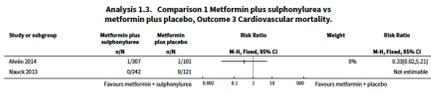
Cochrane: met + SU vs met + placebo



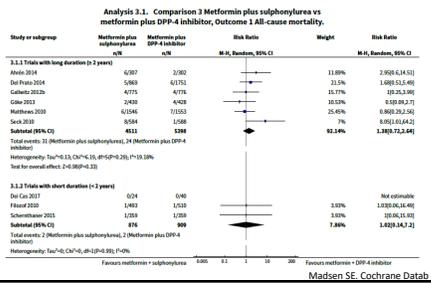
Madsen SE. Cochrane Datab System Rev. 2019;4.



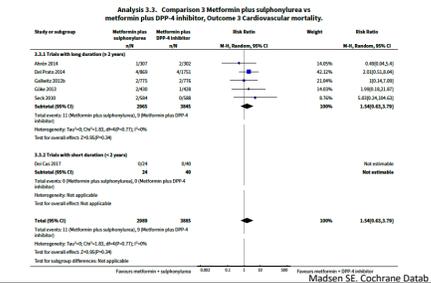
Cochrane: met + SU vs Met + placebo



Cochrane: Met + SU vs Met + iDPP4

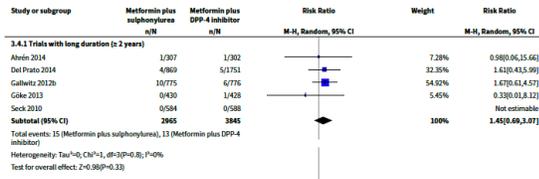


Cochrane: Met + SU vs Met + iDPP4



Cochrane: Met + SU vs Met + iDPP4

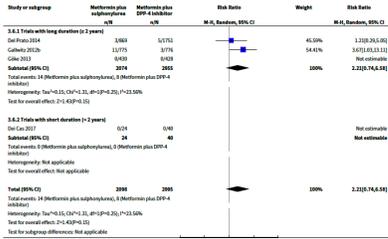
Analysis 3.4. Comparison 3 Metformin plus sulphonylurea vs metformin plus DPP-4 inhibitor, Outcome 4 Non-fatal myocardial infarction.



Madsen SE. Cochrane Datab System Rev. 2019;4.

Cochrane: Met + SU vs Met + iDPP4

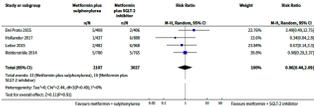
Analysis 3.6. Comparison 3 Metformin plus sulphonylurea vs metformin plus DPP-4 inhibitor, Outcome 6 Non-fatal stroke.



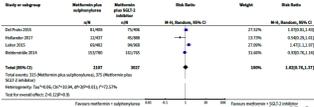
Madsen SE. Cochrane Datab System Rev. 2019;4.

Cochrane: Met + SU vs Met + iSGLT2

Analysis 3.1. Comparison 3 Metformin plus sulphonylurea vs metformin plus SGLT-2 inhibitor, Outcome 1 All-cause mortality.

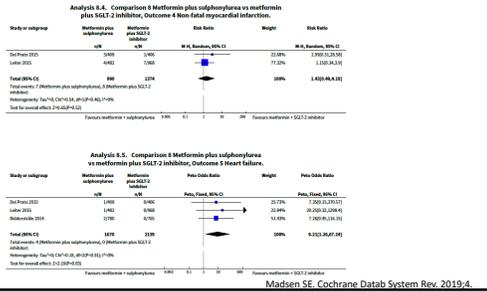


Analysis 3.2. Comparison 3 Metformin plus sulphonylurea vs metformin plus SGLT-2 inhibitor, Outcome 2 Serious adverse events.



Madsen SE. Cochrane Datab System Rev. 2019;4.

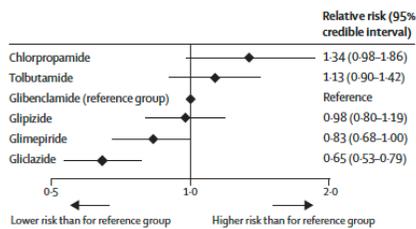
Cochrane: Met + SU vs Met + iSGLT2



Consideraciones

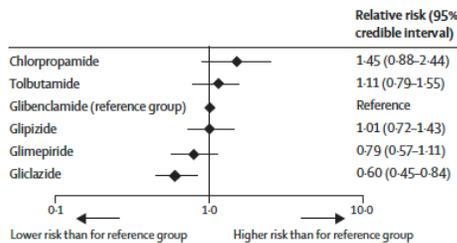
- Esta revisión sistemática de Cochrane está basado en los RCT fase III cuyo objetivos era comparación directa entre agentes para ver control glicémico
- No están diseñados para ver diferencias cardiovasculares
- La mayoría son estudios a corto plazo y con pequeño número de pacientes
- La evidencia de que los iSGLT2 y los arGLP1 reducen MACE es incuestionable
- Hay alguna diferencia cuando se comparan las sulfonilureas entre sí?

Revisión sistemática: diferencias en mortalidad total entre sulfonilureas



Simpson SH. Lancet Diab Endocrinol. 2015;3:43

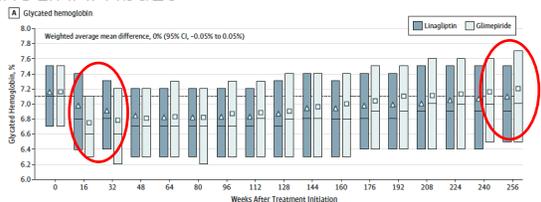
Revisión sistemática: diferencias en mortalidad cardiovascular entre sulfonilureas



Simpson SH. Lancet Diab Endocrinol. 2015;3:43

Diferencias en control glicémico

CAROLINA: Hba1c



No. of participants	3000	2920	2808	2731	2668	2600	2544	2498	2467	2401	2361	2300	2271	2233	2196	2165	2146
Glimepiride	3013	2924	2806	2719	2653	2593	2518	2467	2426	2393	2382	2333	2288	2247	2235	2190	2184
Linagliptin	6033	6021	5995	5979	5953	5929	5901	5879	5856	5826	5787	5752	5702	5662	5629	5592	5551

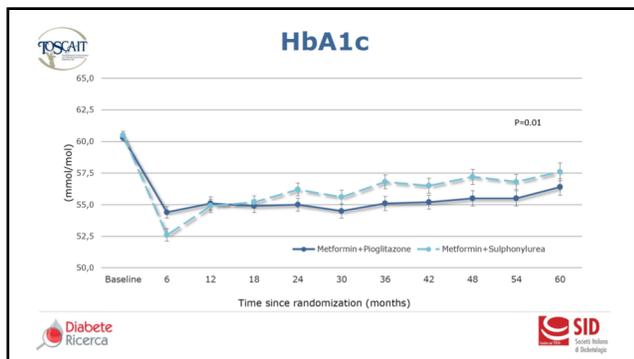
No diferencias en la necesidad de agregar medicamentos de rescate, pero fue más rápido en el grupo de linagliptina comparado con el grupo de glimepiride

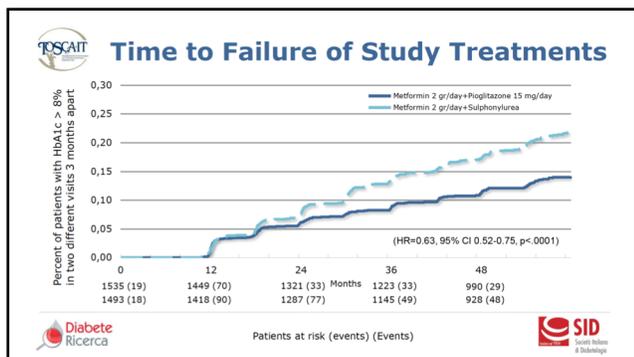
Rosenstock J. JAMA. 2019; online Sep 19

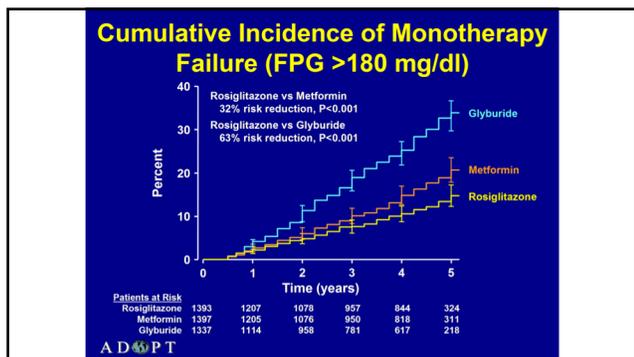
CAROLINA: desenlaces secundarios

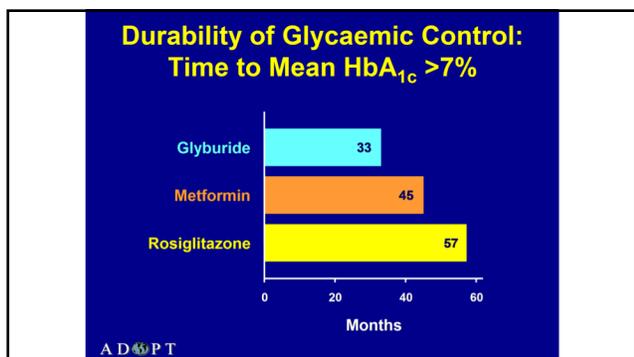
Outcome	Linagliptin (n = 3023)		Glimepiride (n = 3010)		Incidence Rate/ 100 Patient-Years Difference, Linagliptin - Glimepiride (95% CI)	HR ^a /Odds Ratio ^b (95% CI)
	No. (%)	Rate/100 Patient-Years	No. (%)	Rate/100 Patient-Years		
Key Secondary End Points						
Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable-angina pectoris (4F-MACE)	398 (13.2)	2.3	401 (13.3)	2.4	0.0 (-0.4 to 0.3)	0.99 (0.86 to 1.14) ^a
Receiving treatment and maintaining HbA _{1c} ≤7.0% at final visit [onwards from titration] without the need for rescue medication, without any moderate/severe hypoglycemic episodes, and without >2% weight gain ^c	481 (16.0)		305 (10.2)			1.68 (1.44 to 1.96) ^b
Receiving treatment and maintaining HbA _{1c} ≤7.0% at final visit [onwards from titration] without the need for rescue medication and without >2% weight gain ^c	524 (17.4)		422 (14.1)			1.29 (1.12 to 1.48) ^b

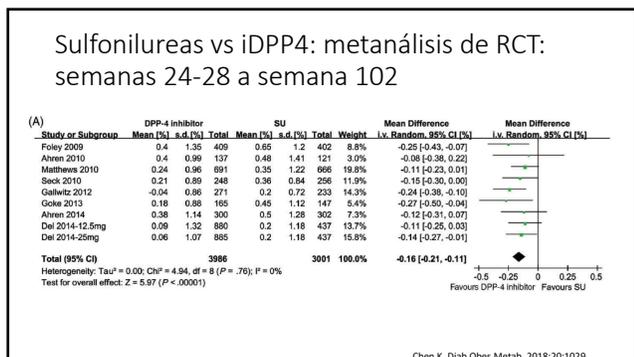
Rosenstock J. JAMA. 2019; online Sep 19



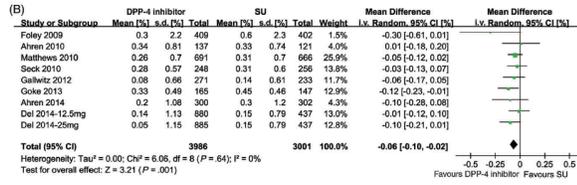








Sulfonilureas vs iDPP4: metanálisis de RCT
semanas 52 a 104



Chen K. Diab Obes Metab. 2018;20:1029

Necesidad de terapia de rescate

Characteristic	Sitagliptin 100 mg o.d. + metformin		Glipizida + metformin (N = 584)
	(N = 588)	(N = 584)	
Age (years)	56.8 (9.3)	56.6 (9.8)	
Sex, n (%)			
Male	336 (57.1)	359 (61.3)	
Female	252 (42.9)	226 (38.7)	
Race, n (%)			
Caucasian	432 (73.5)	434 (74.3)	
Black	41 (7.0)	35 (6.0)	
Hispanic	43 (7.3)	46 (7.9)	
Asian	50 (8.5)	49 (8.4)	
Other	22 (3.7)	20 (3.4)	
Body weight (kg)	89.5 (17.4)	89.7 (17.5)	
Body mass index (kg/m ²)	31.2 (5.0)	31.3 (5.2)	
Duration of diabetes mellitus (years)	6.5 (6.1)	6.2 (5.4)	
Use of OHA at screening, n (%)			
Dual therapy	177 (30.1)	159 (27.2)	
Monotherapy	386 (65.6)	397 (68.0)	
Absence	25 (4.3)	28 (4.8)	
HbA _{1c} % (range)	7.7 (6.9) (6.1-11.0)	7.6 (6.9) (5.8-10.5)	
HbA _{1c} distribution at baseline, n (%)			
HbA _{1c} < 8%	375 (64.0)	381 (65.5)	
HbA _{1c} ≥ 8 to <9%	151 (25.8)	141 (24.2)	
HbA _{1c} ≥ 9%	60 (10.2)	60 (10.3)	
FPG (mmol/l)	9.2 (2.3)	9.1 (2.3)	

Nauck MA. Diab Obes Metab. 2007;9:194

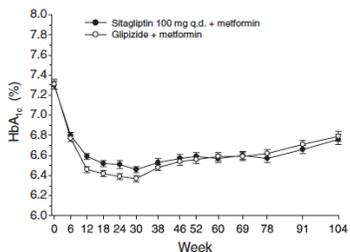
ORIGINAL PAPER

THE INTERNATIONAL JOURNAL OF
CLINICAL PRACTICE

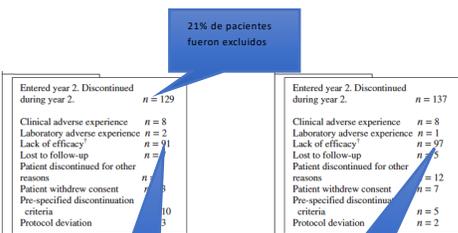
Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study

T. Seck,¹ M. Nauck,² D. Sheng,¹ S. Sunga,¹ M. J. Davies,¹ P. P. Stein,¹ K. D. Kaufman,¹ J. M. Amatruda¹ for the Sitagliptin Study 024 Group*

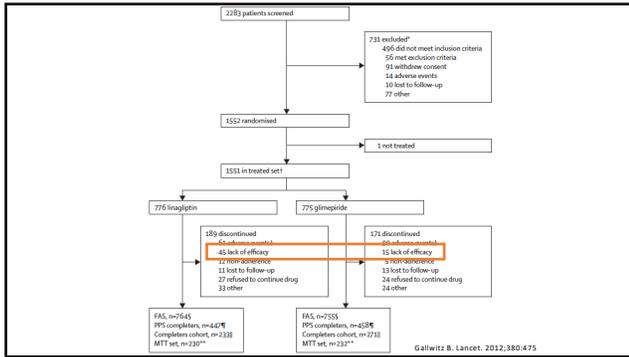
Seck T. In J Clin Pract. 2010;64:562

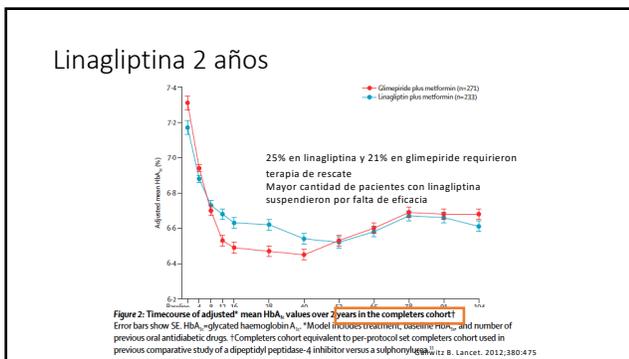


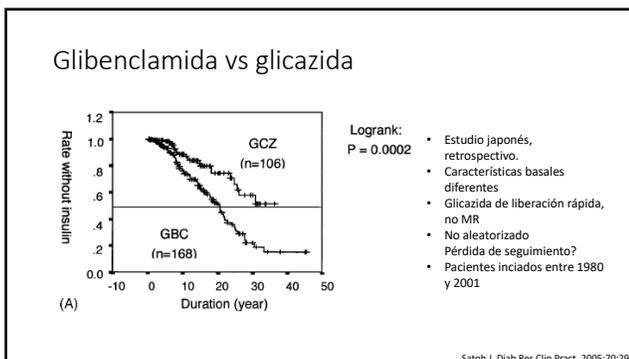
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Seck T. In J Clin Pract. 2010;64:562





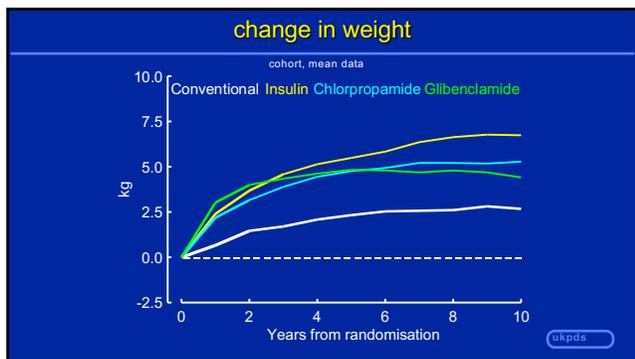


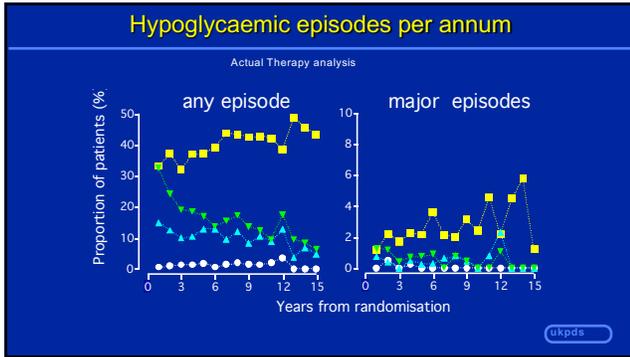
Glibenclamida vs glicazida

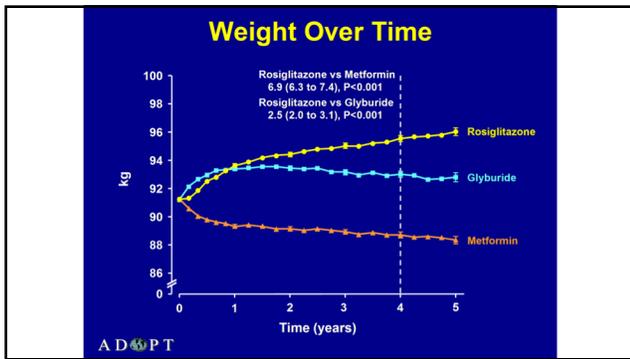
Variables	GCZ (mean ± S.D.)	GBC (mean ± S.D.)	P
Number (male/female)	106 (60/46)	168 (81/87)	NS
Age (years)			
At onset of DM	48.9 ± 12.3	47.5 ± 13.5	NS
At start of any OHAs	56.0 ± 12.0	55.4 ± 14.4	NS
At start of GCZ or GBC	56.2 ± 11.9	56.2 ± 14.5	NS
Duration (years)			
Onset of DM—start of any OHAs	7.1 ± 7.0	7.5 ± 7.7	NS
Onset of DM—start of GCZ or GBC	7.3 ± 7.0	8.7 ± 8.2	NS
BMI (kg/m ²)	23.2 ± 3.4	23.9 ± 3.4	NS
Blood pressure (mmHg)			
Systolic BP	130.7 ± 13.2	131.0 ± 13.0	NS
Diastolic BP	77.0 ± 7.8	75.6 ± 6.9	NS
Fasting plasma glucose (mg/dl)			
At start of any OHAs	158.2 ± 41.7	169.6 ± 47.9	<0.05
At start of GCZ or GBC	163.4 ± 43.2	168.7 ± 45.5	NS
HbA1c (%)			
At start of any OHAs	7.3 ± 1.4	7.8 ± 1.6	<0.05
At start of GCZ or GBC	7.4 ± 1.4	7.7 ± 1.7	NS
Mean until insulin from start of any OHAs	6.8 ± 0.9	7.3 ± 1.2	<0.0001
Mean until insulin from start of GCZ or GBC	6.8 ± 0.9	7.4 ± 1.3	<0.0001

Satoh J. Diab Res Clin Pract. 2005;70:23

Efectos adversos: hipoglicemia y peso







Other Adverse Events

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Gastrointestinal, n (%)	335 (23%)	557 (38%)	316 (22%)
Weight gain, n (%)	100 (7%)	18 (1%)	47 (3%)
Hypoglycaemia, n (%)	142 (10%)	168 (12%)	557 (39%)
Oedema, n (%)	205 (14%)	104 (7%)	123 (9%)

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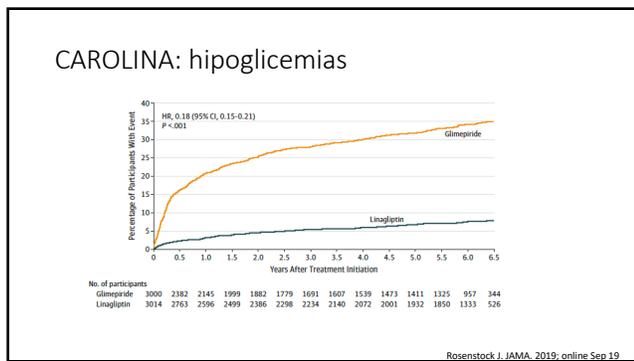
P<0.05 vs. rosiglitazone

Hypoglycemic events

Hypoglycemic events*	Pioglitazone (N=1535)		Sulfonylurea (N=1493)		IRR ** (95%CI)
	N (%)	N events	N (%)	N events	
Severe	1 (0.1)	2	24 (1.6)	33	0.06 (0.01-0.25)
Moderate	147 (9.6)	515	484 (32.4)	1868	0.27 (0.24-0.30)

* defined as a glucose value lower than 60 mg/dl graded as moderate (not requiring assistance) or severe (requiring assistance)
 ** Incidence rate ratio

Diabete Ricerca SID

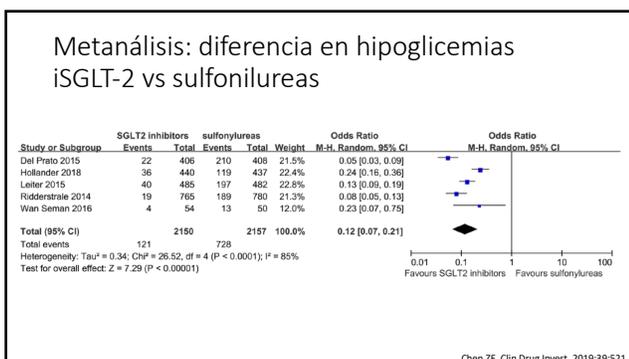
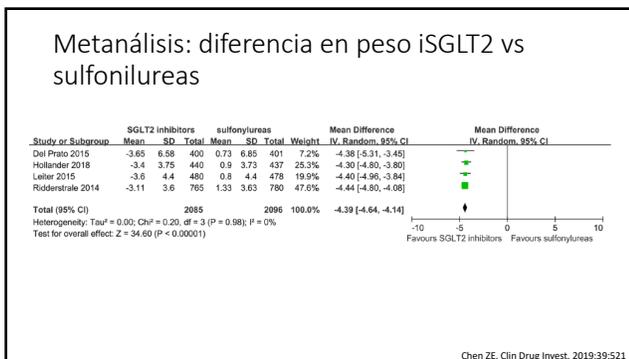
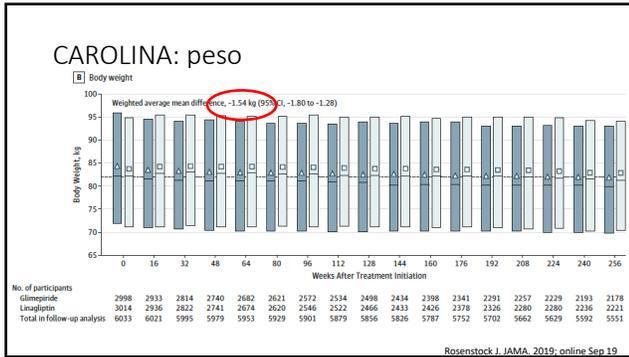


CAROLINA: hipoglicemias

Corresponde a NNH de 3.69 por 6.3 años

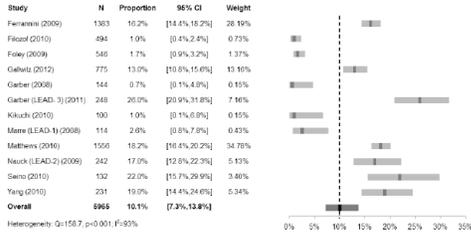
Adverse Events ^a	Linagliptin (n = 3023)			
	No. (%)	Rate/100 Patient-Years	No. of Events	Incident Years
Hypoglycemic adverse events ^b				
≥1 Investigator-reported episode of hypoglycemia	320 (10.6)	2.3	1132 (37.7)	11.1
≥1 Investigator-reported episode of symptomatic hypoglycemia with plasma glucose ≤70 mg/dL or severe hypoglycemia	195 (6.5)	1.4	927 (30.9)	8.4
≥1 Investigator-reported episode of severe hypoglycemia ^c	10 (0.3)	0.1	65 (2.2)	0.5
≥1 Episode of hospitalized hypoglycemia	2 (0.1)	<0.1	27 (0.9)	0.2

Rosenstock J. JAMA. 2019; online Sep 19



Hipoglicemias menores a 55 mg/dl

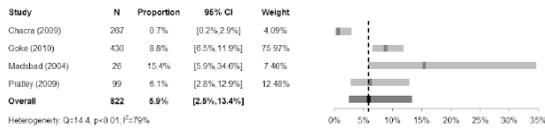
A. Mild hypoglycaemia: ≤ 5.1 mmol/L



Schopman JE. Diab Metab Res Rev. 2014;30:11

Hipoglicemias menores a 50 mg/dl

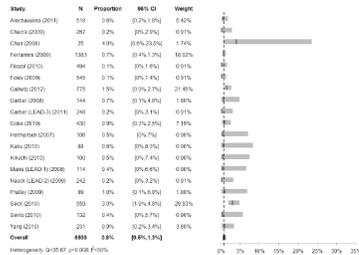
B. Mild hypoglycaemia: ≤ 2.8 mmol/L



Schopman JE. Diab Metab Res Rev. 2014;30:11

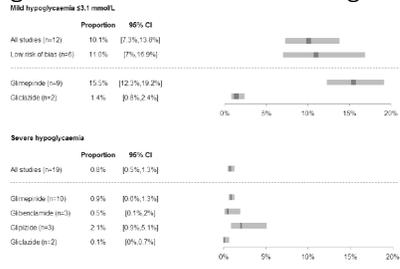
Hipoglicemias severas

C. Severe hypoglycaemia

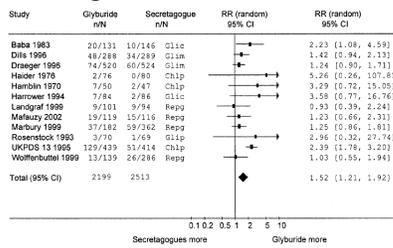


Schopman JE. Diab Metab Res Rev. 2014;30:11

Hipoglicemias: diferencias entre agentes



Hipoglicemias: glibenclamida vs otros secretagogos



Glibenclamide vs otros secretagogos e insulina y riesgo de hipoglicemias y eventos CV

Comparator	Patients with any hypoglycemic episode (n/N) [95% CI]	Patients with a major hypoglycemic episode (n/N) [95% CI]	All hypoglycemic episodes per patient year (rate ratio) [95% CI]	Major hypoglycemic episodes per patient year (rate ratio) [95% CI]	Cardiovascular events (RR) [95% CI]	Death (RR) [95% CI]	Weight gain (kg) (WMD) [95% CI]
All secretagogues	1.32 (1.21-1.43) 42.1%	ND	1.80 (1.06-3.00) 76.8%*	ND	0.84 (0.36-1.20) 12.0%	0.87 (0.70-1.07) 0%	1.09 (-0.41 to 3.60) 31.4%
Insulin	1.81 (1.25-2.60) 41.4%	ND	1.44 (1.13-1.83) 37.0%	4.69 (0.76-28.08) 0%	0.82 (0.71-1.10) 0%	0.79 (0.41-1.23) 31.7%	2.49 (-0.48 to 5.47) 4.9%
Insulin	0.88 (0.25-3.00) 92.3%*	ND	0.89 (0.019-4.40) 83.1%*	ND	0.89 (0.70-1.14) NA*	0.97 (0.79-1.20) NA†	-2.28 (-2.42 to -2.14) 0%

*Heterogeneity: unreliable due to heterogeneity. †No data on cardiovascular outcome clusters but data on myocardial infarction extracted from single study (UKPDS 33). ‡Data from single study (UKPDS 33). NA, not applicable; ND, no data.

Gangji AS. Diabetes Care. 2007;30:389

Análisis de costos

Producto	Original	Genérico
Glimepiride 2 mg	\$14.34	\$6.24
Gliclazida MR 30 mg	\$13.68	
Glibenclamida 5 mg		\$1.44
Sitagliptina 100 mg	\$36.29	
Linagliptina 5 mg	\$37.92	
Vildagliptina 50 mg bid	\$42.11	
Saxagliptina 5 mg	\$57.34	
Dapagliflozina 10 mg	\$40.80	
Empagliflozina 25 mg	\$40.80	

Fybeca.com Accedido el 7 de noviembre 2019.

glicemias

	Linagliptin (n = 3023)		Glimepiride (n = 3010)	
Adverse Events ^a	No. (%)	Rate/100 Patient-Years	No. (%)	Rate/100 Patient-Years
Hypoglycemic adverse events ^b				
≥1 Investigator-reported episode of hypoglycemia	320 (10.6)	2.3	1132 (37.7)	11.1
≥1 Investigator-reported episode of symptomatic hypoglycemia with plasma glucose <20 mg/dL or symptoms	195 (6.5)	1.4	7 (30.9)	8.4
≥1 of symptoms		0.1		
≥1 of symptoms		<0.1	27 (0.9)	0.2

Costo de tratamiento por 6.3 años \$8.666.193 USD

Corresponde a NNH de 3.69 por 6.3 años

Hubo 812 episodios menos de hipoglicemias. Por la diferencia del costo, prevenir cada episodio de hipoglicemia costaría \$4845 sin tomar en cuenta otros factores como peso y adherencia

Dosis media 2.9 mg. Costo tratamiento por 6.3 años \$4.731.571 USD

Rosenstock J. JAMA. 2019; online Sep 19

Conclusiones

- Siguen siendo una terapia eficaz en reducción de glucosa
- Son neutros a nivel cardiovascular: glimepiride y glicazida, al parecer glibenclamida es seguro
- No sostienen el control a largo plazo, es similar en este sentido a los inhibidores de DPP4
- Producen más efectos adversos, sobre todo aumento de peso y riesgo de hipoglicemias
- En Ecuador sí son menos costosos que los nuevos antidiabéticos, no por ello quiera decir que sean costo efectivo (cuánto vale el aumento de peso y las hipoglicemias?)
- Al final de cuentas es un problema farmacoeconómico!

Preguntas...

chenku2409@gmail.com

Puede descargar la presentación en:



www.EndoDrChen.com
