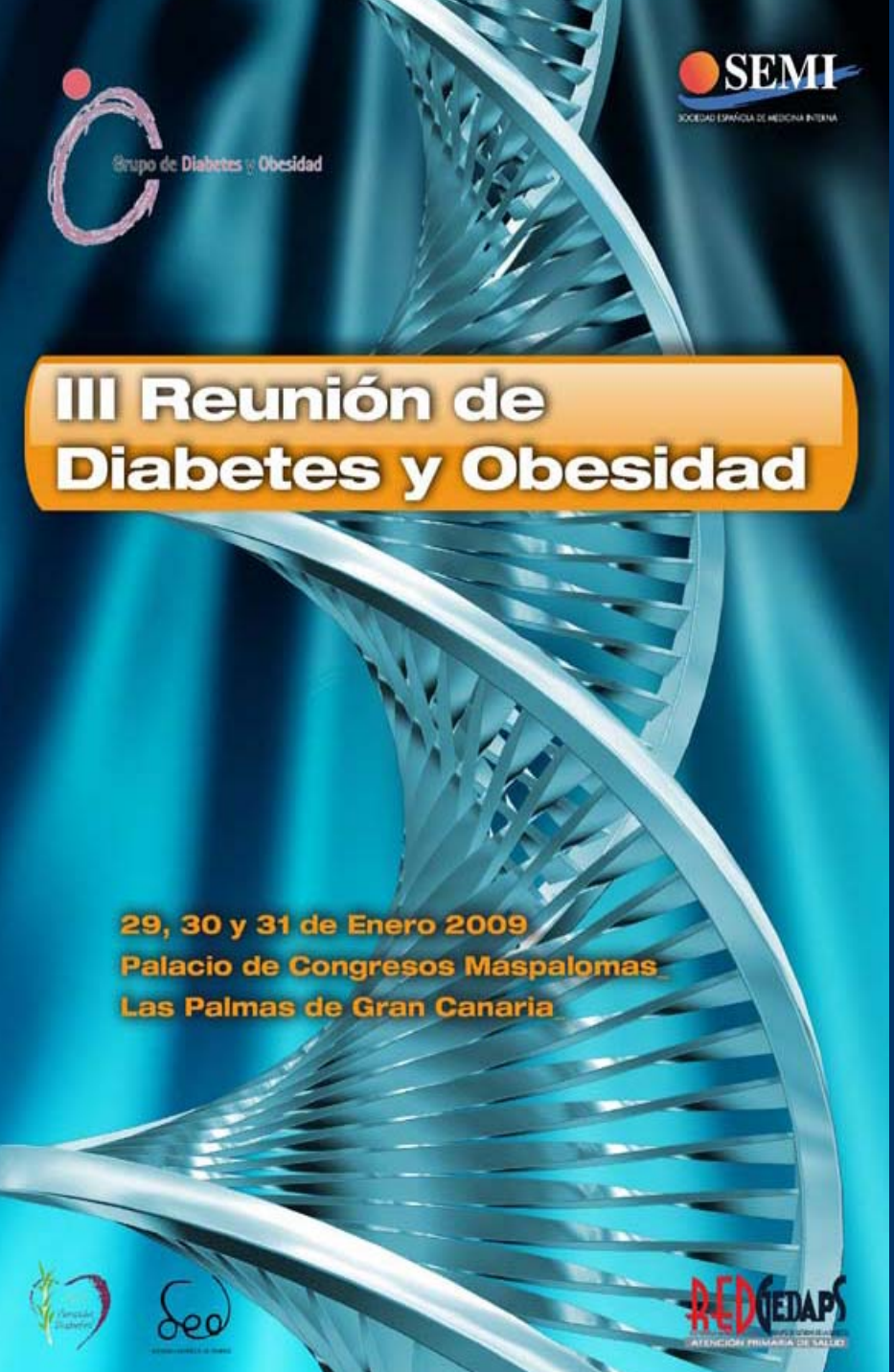


Controversia en el 2º paso terapéutico

SULFONILUREAS

Ricardo Gómez Huelgas
Medicina Interna
Hospital Carlos Haya - Málaga

Conflicto de intereses

Ninguno

SULFONILUREAS

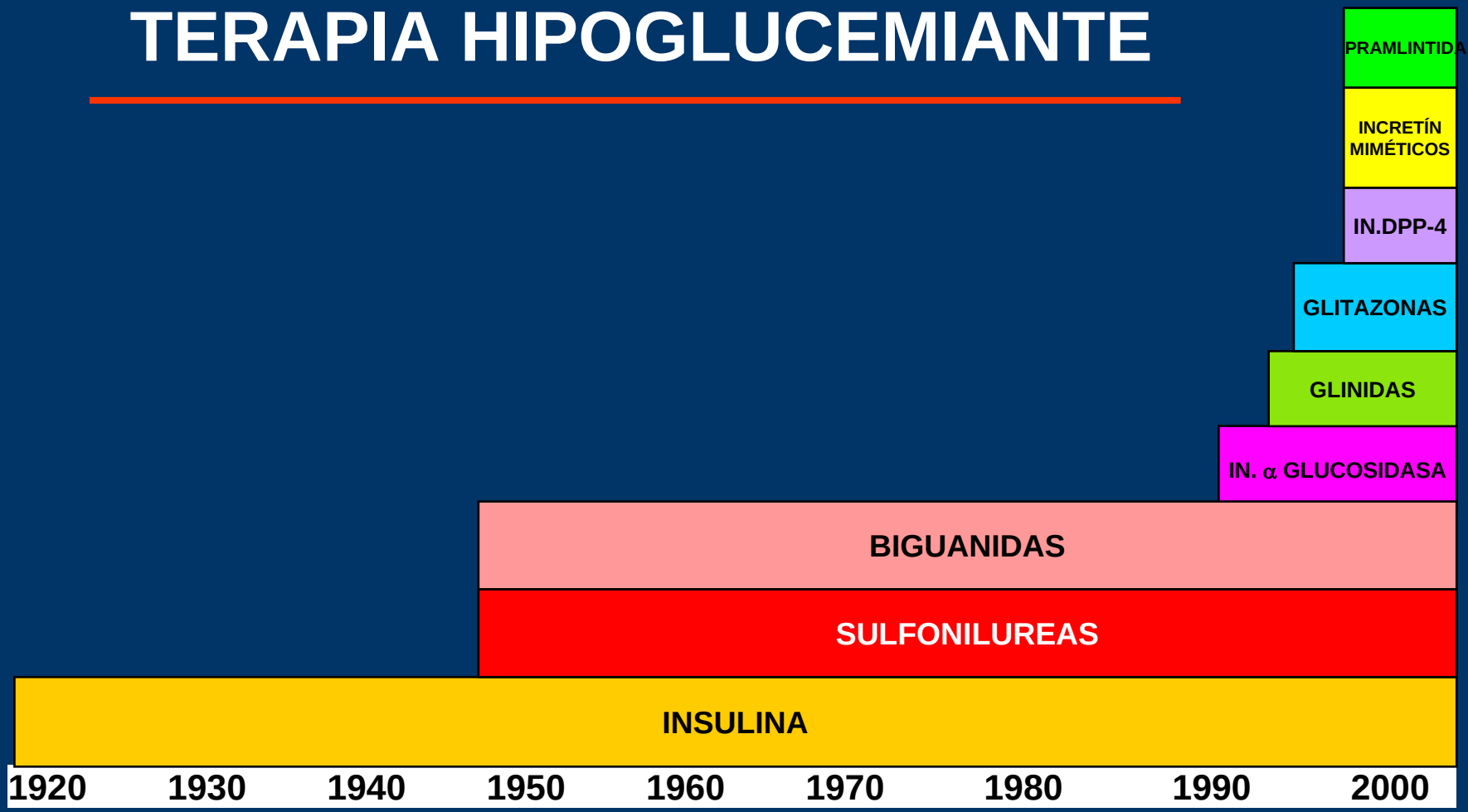
A FAVOR

- Amplia EXPERIENCIA
- Bajo COSTE
- EFICACIA HIPOGLUCEMIANTE
- REDUCE MICROANGIOPATÍA

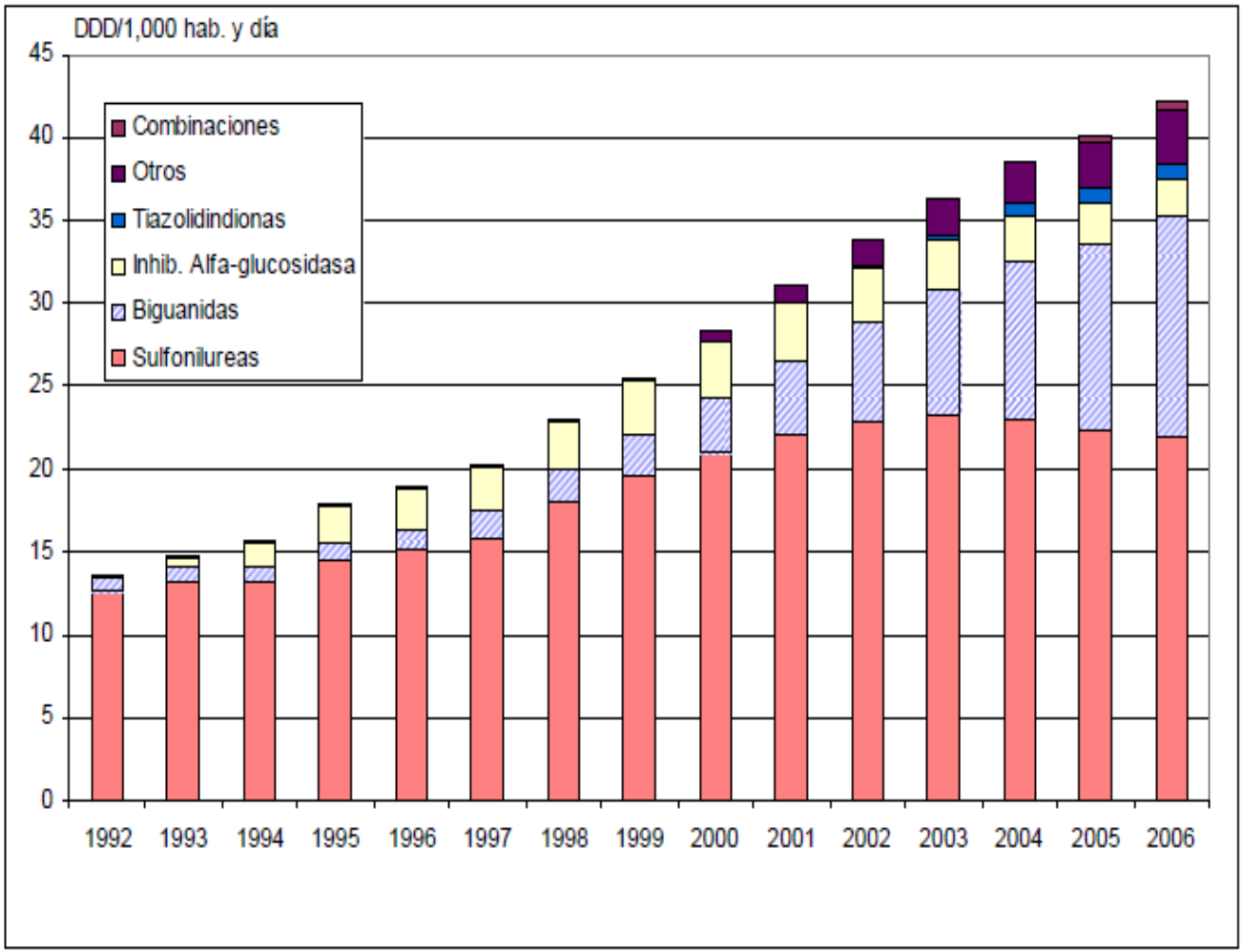
EN CONTRA

- HIPOGLUCEMIAS
- GANANCIA DE PESO
- AGOTAMIENTO CÉLULA β
- RIESGO CARDIOVASCULAR

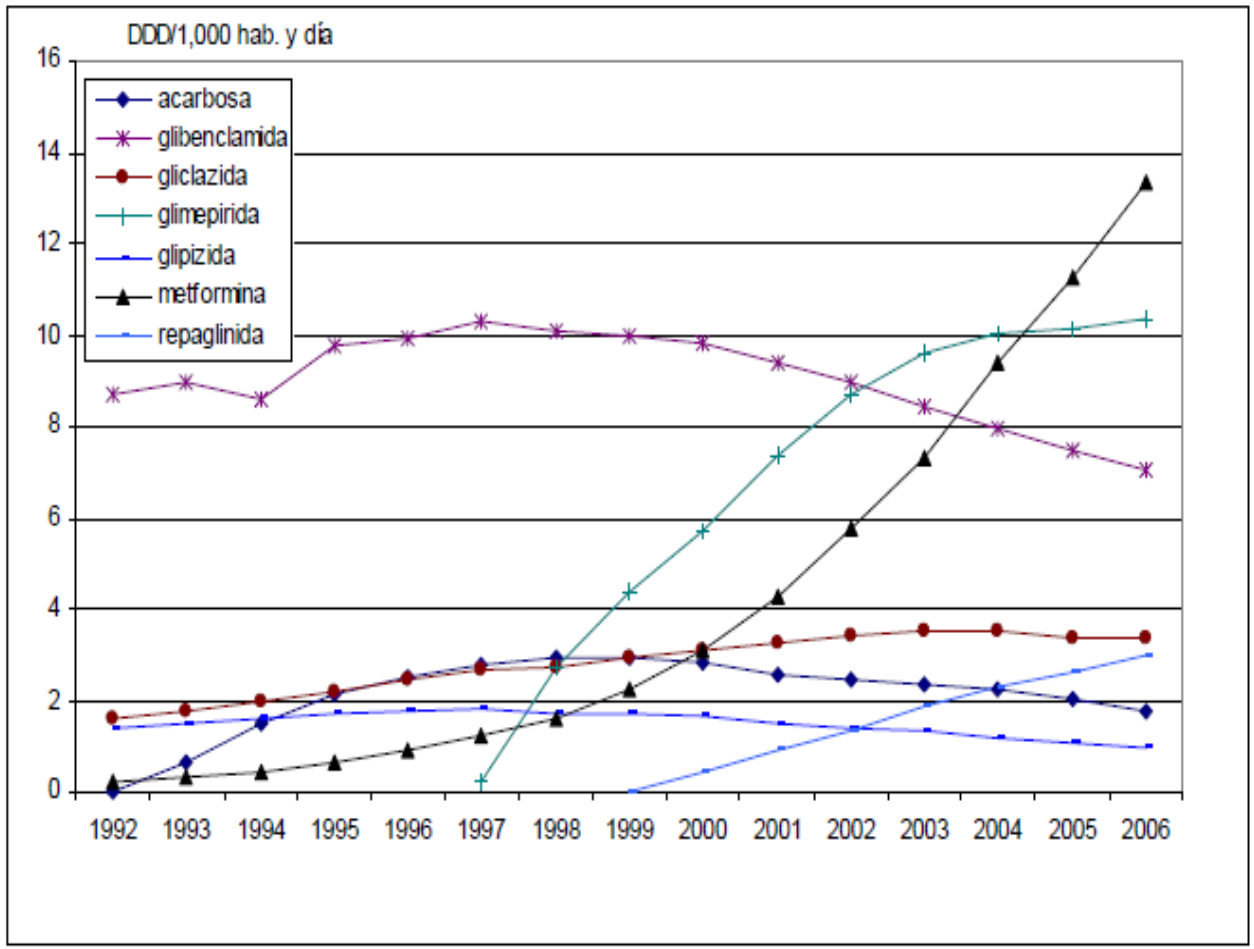
CRONOLOGÍA DE LA TERAPIA HIPOGLUCEMIANTE



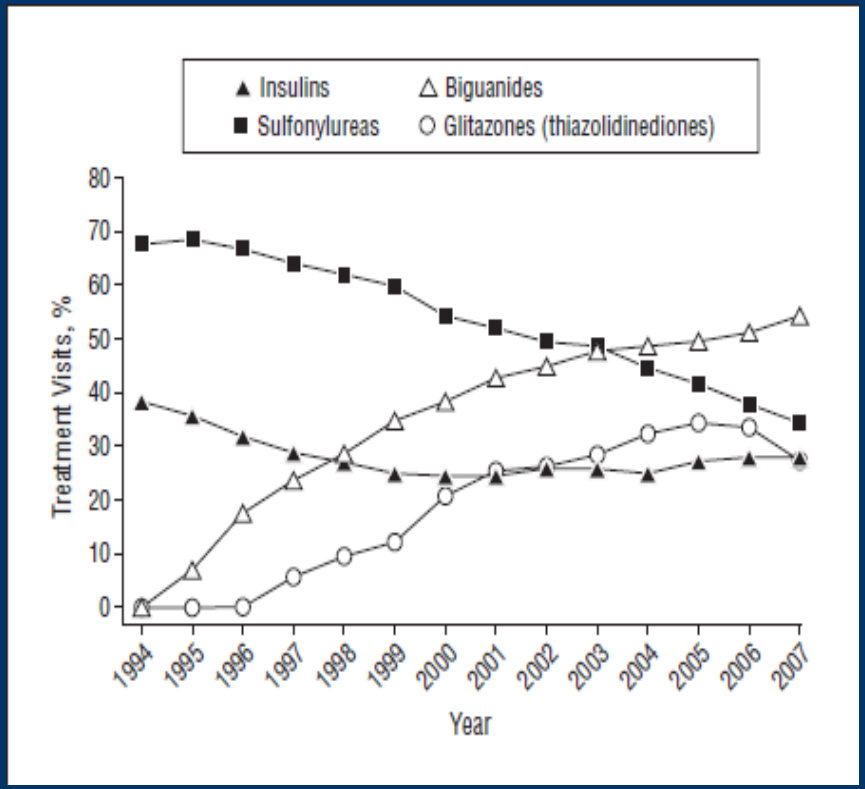
Evolución de la utilización de antidiabéticos orales en España. Datos del Sistema Nacional de Salud para el periodo 1992-2006.

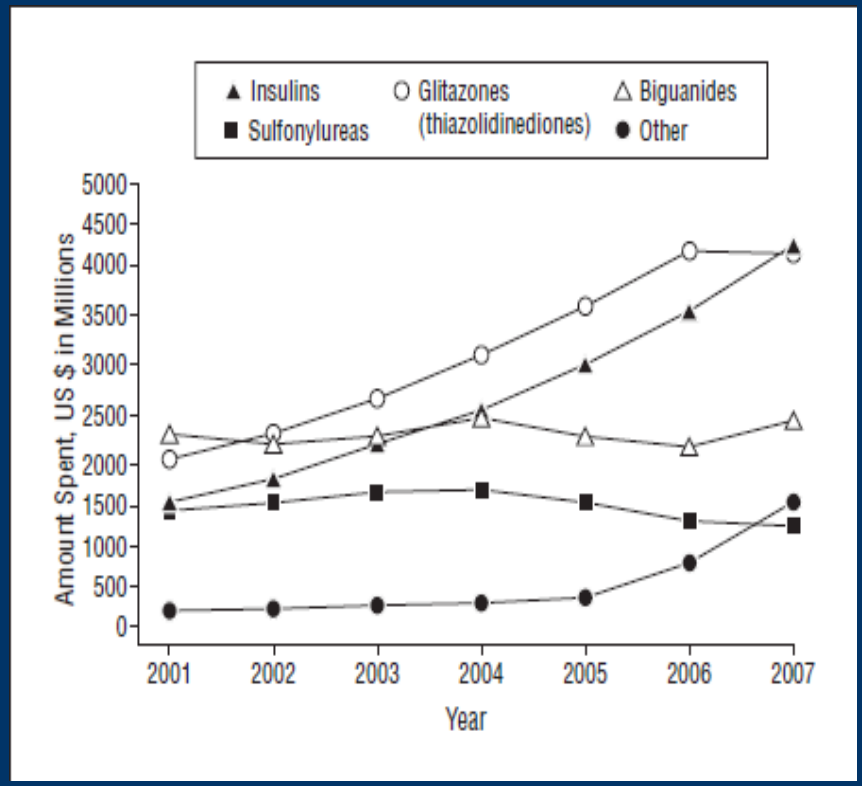


Evolución de la utilización de algunos antidiabéticos orales en España. Datos del Sistema Nacional de Salud para el periodo 1992-2006.



Tendencias en el consumo de medicación antidiabética USA 1994-2007



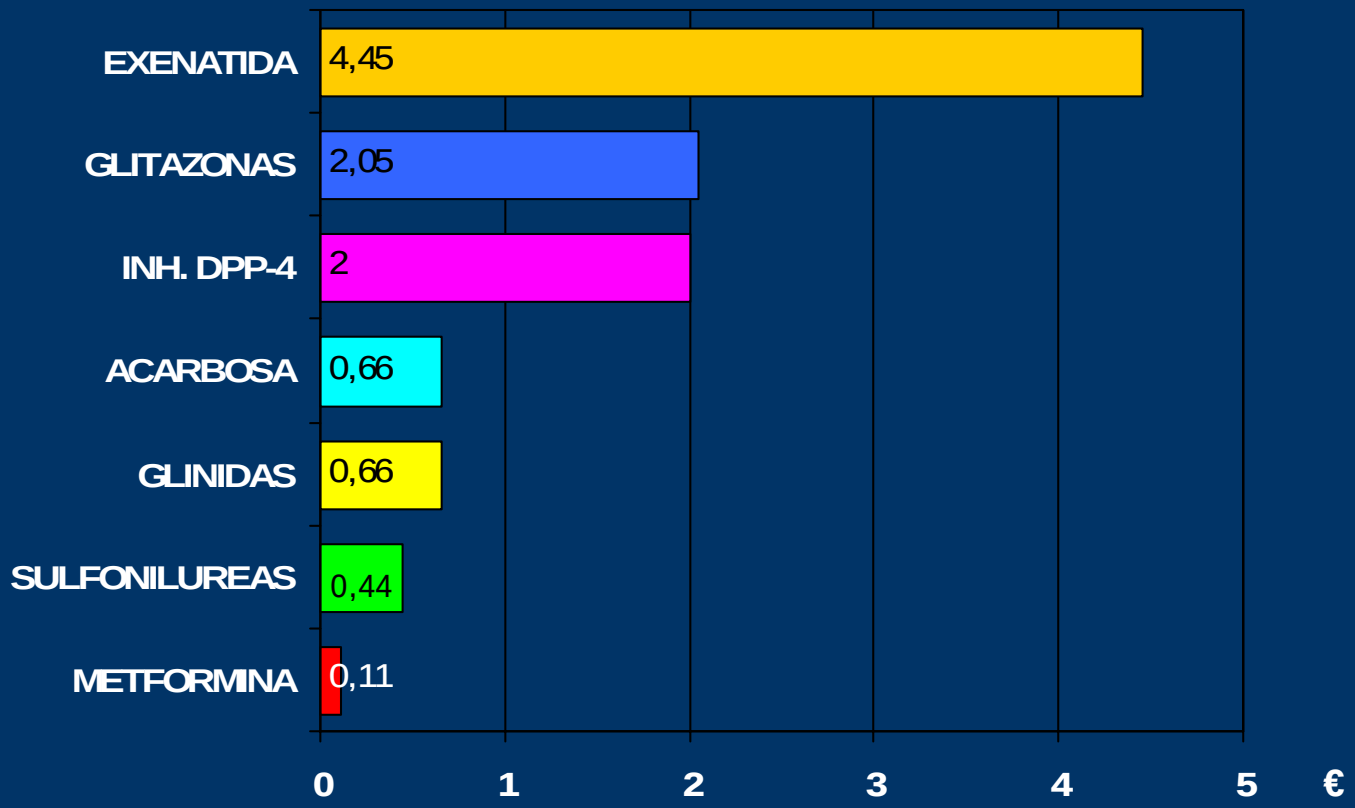


Other: glinides, α-glucosidase inhibitors, DPP-4 inhibitors, incretins

Alexander GB. Arch Intern Med 2008;168:2088-94.

2. BAJO COSTE

Fármacos antidiabéticos
Coste diario (DDD)



PVP (2008)
Gliclazida-SR: 90 mg/d
Repaglinida: 6 mg/d
Metformina: 1700 mg(d
L-Acarbosa: 300 mg/d
Rosi 8 mg/d o Pio 30 mg/d
Sitagliptina 100 mg/d
Exenatida 20 mcg/d

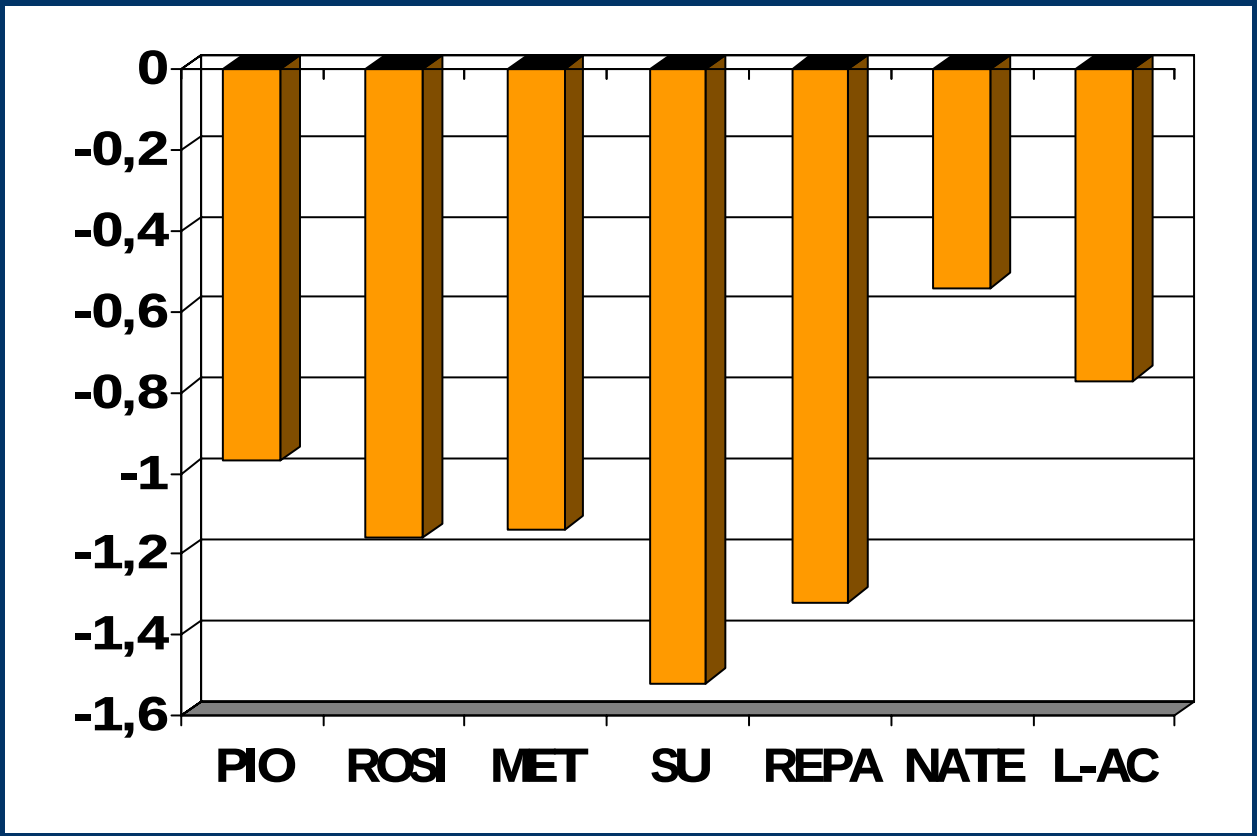
3. EFICACIA HIPOGLUCEMIANTE

REVIEW | Annals of Internal Medicine
Ann Intern Med. 2007;147:386-399.

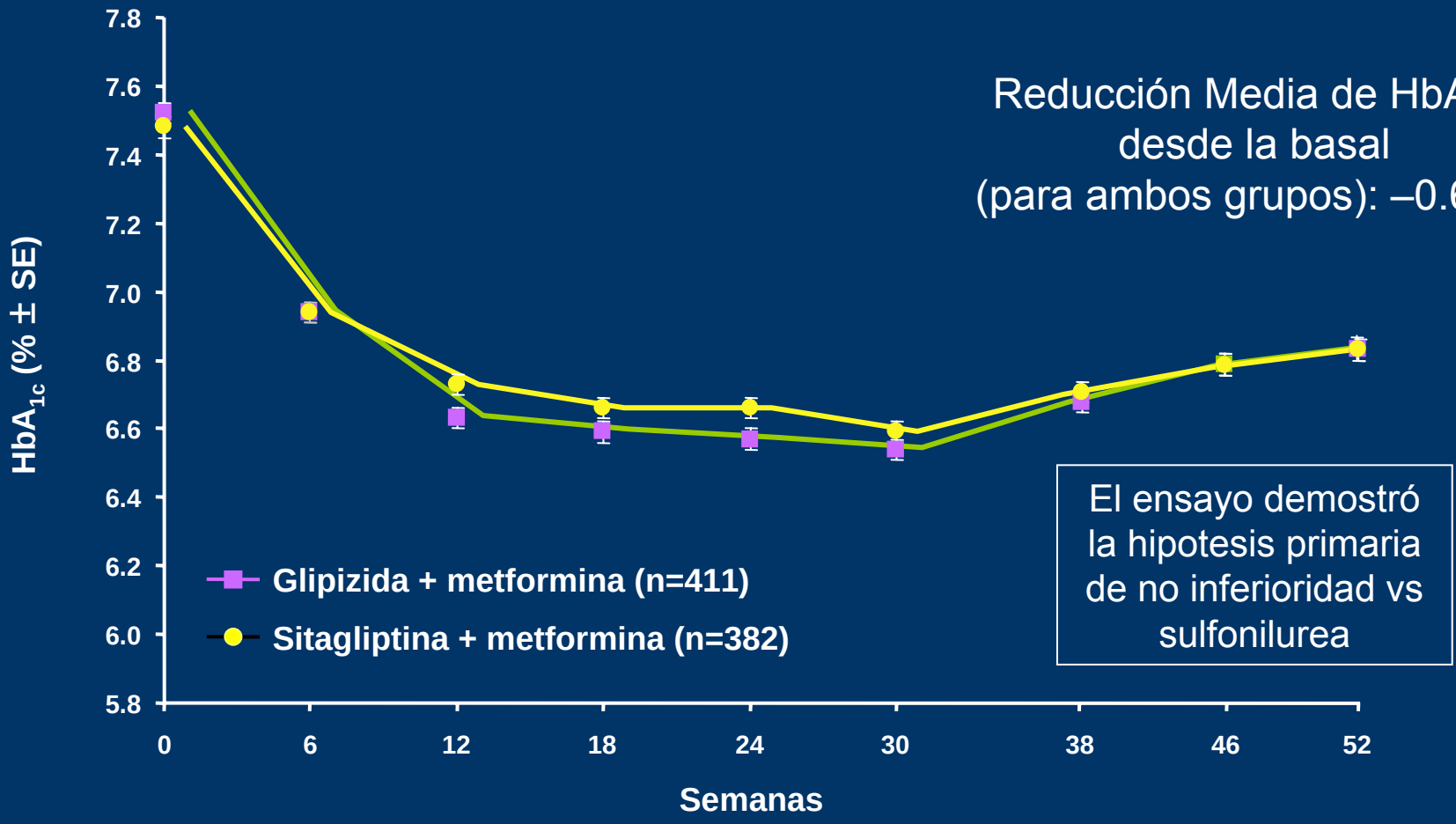
Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus

Shari Bolen, MD, MPH; Leonard Feldman, MD; Jason Vassy, MD, MPH; Lisa Wilson, BS, ScM; Hsin-Chieh Yeh, PhD; Spyridon Marinopoulos, MD, MBA; Crystal Wiley, MD, MPH; Elizabeth Selvin, PhD; Renee Wilson, MS; Eric B. Bass, MD, MPH; and Frederick L. Brancati, MD, MHS

Eficacia hipoglucemiante (% HbA1c)



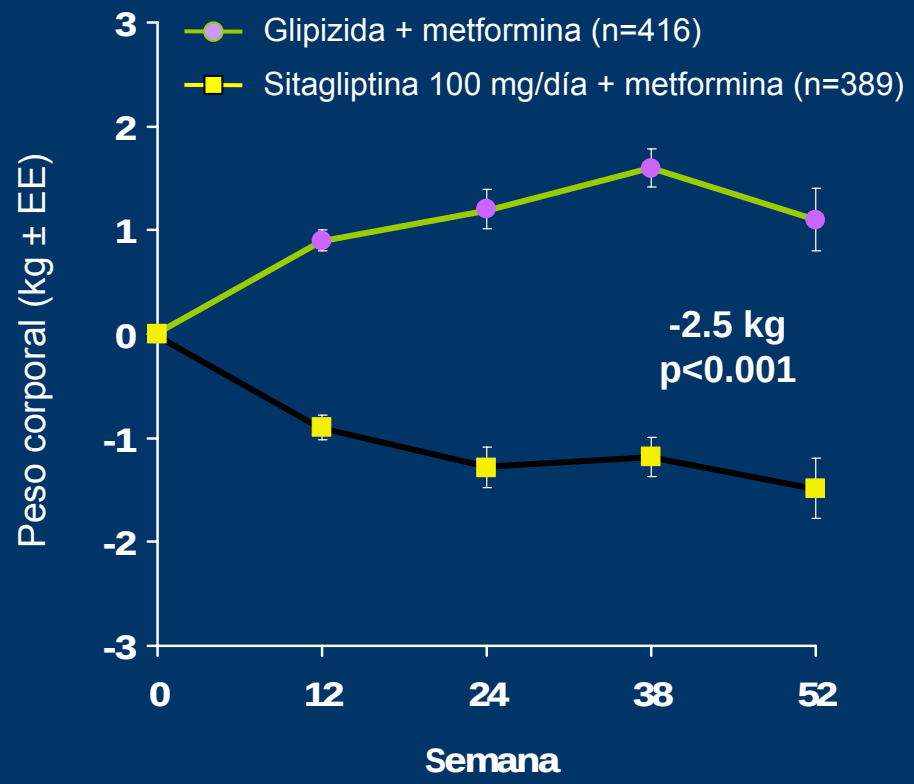
Eficacia comparable de Sitagliptina y Glipizida añadidas ambas a Metformina (52 Semanas)



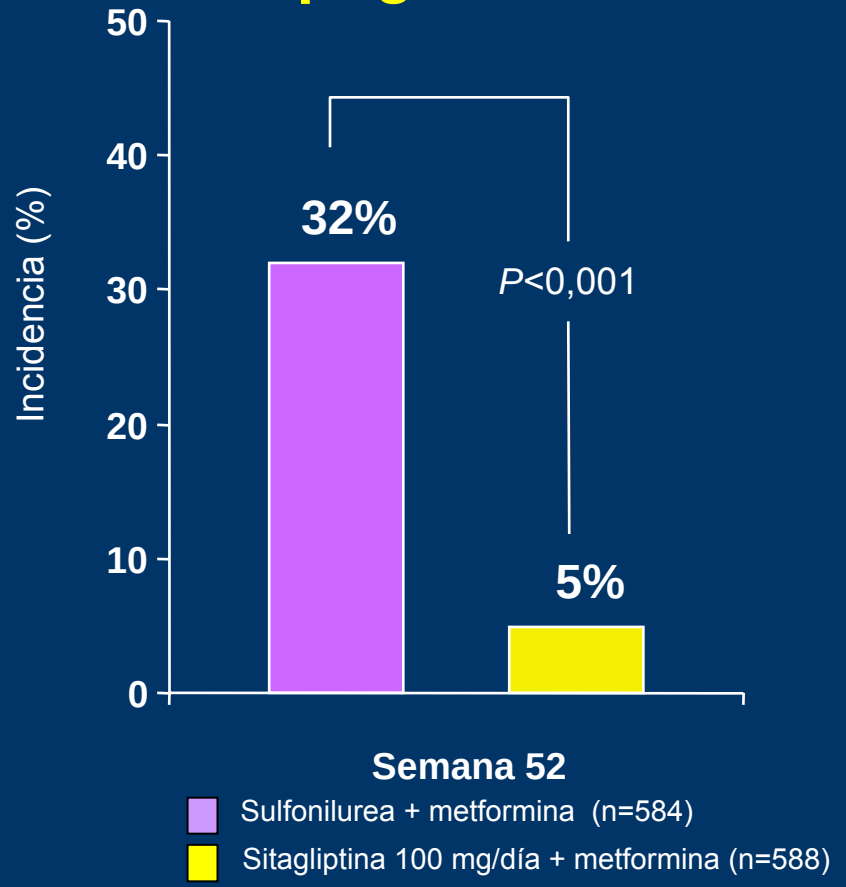
Nauck et al. *Diabetes Obes Metab* 2007;9:194–205.

Estudio de 52 semanas de sitagliptina frente a glipizida añadidas a metformina

Variación media del peso corporal



Hipoglucemia

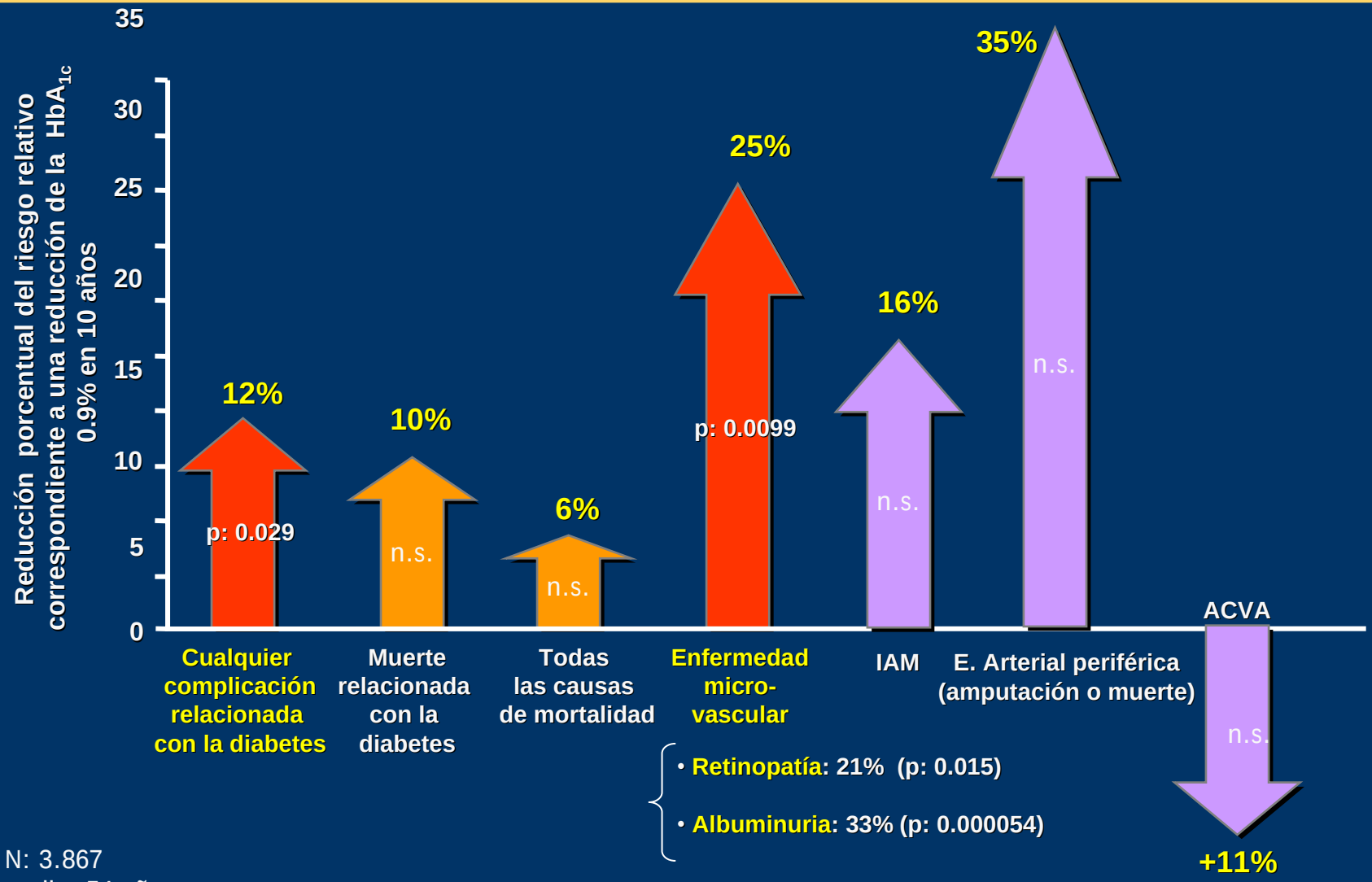


Δ del peso corporal = –2,5 kg [–3,1, –2,0] (*P*<0,001); variación de MMC desde el momento basal hasta la semana 52: glipizida: +1,1 kg; sitagliptina: –1,5 kg (*P* < 0,001)

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

4. REDUCEN COMPLICACONES MICROVASCULARES

UKPDS. Terapia intensiva con INSULINA o SULFONILUREAS



N: 3.867
Edad media: 54 años
Seguimiento: 10 años
HbA1c: 7% vs 7.9%

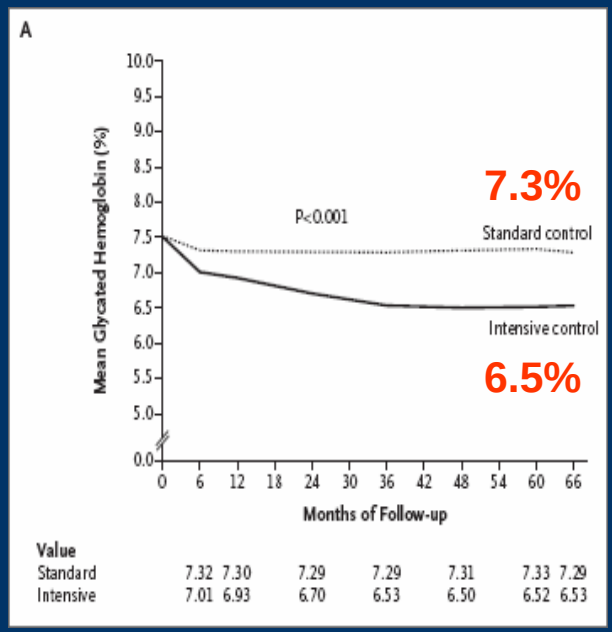
UKPDS 33. BMJ 1998; 352:837–53.

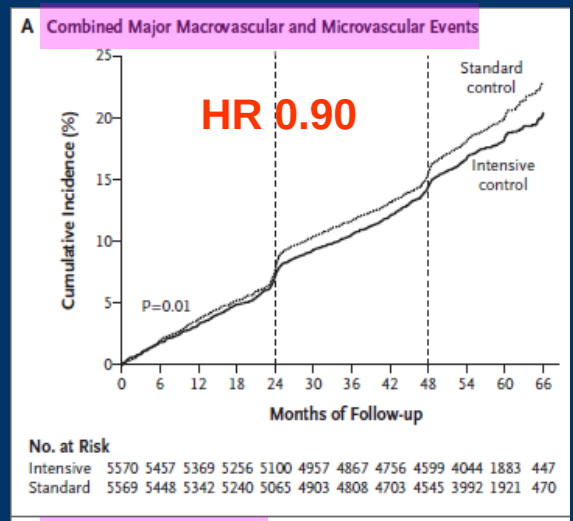
ADVANCE

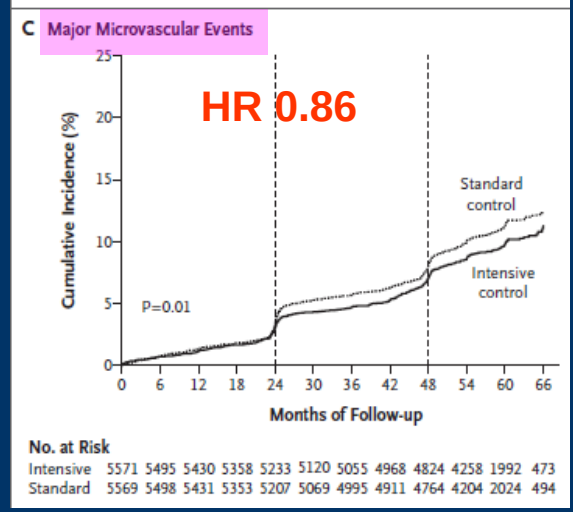
Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

- gliclazida SR (30-120 mg)
- metformina
- glitazona
- L-acarbosa
- insulina basal
- insulina prandial





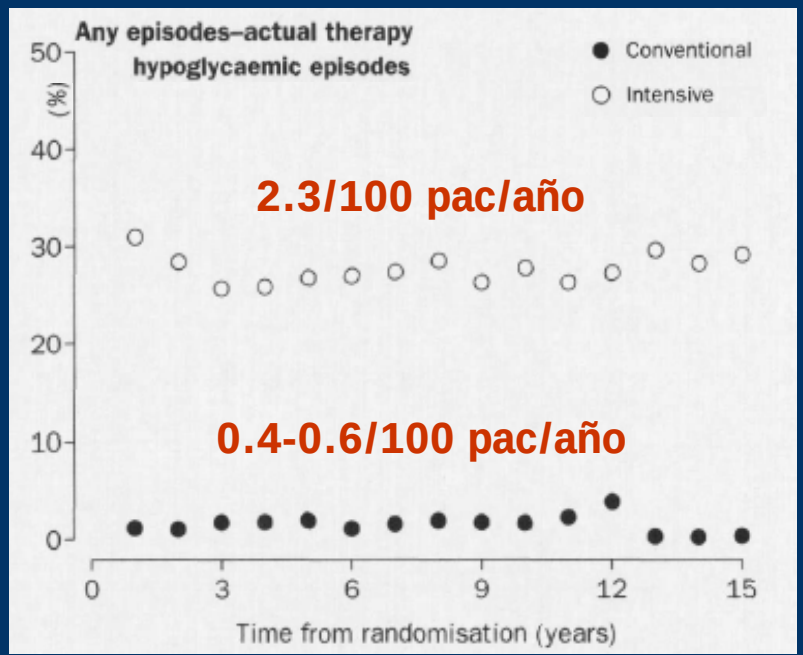


n: 11.140, t: 5 años
DM2 alto riesgo: ≥55 años, ECV o microvascular, o >1 FRCV
no insulinizados

UKPDS 33

BMJ 1998; 352:837–53

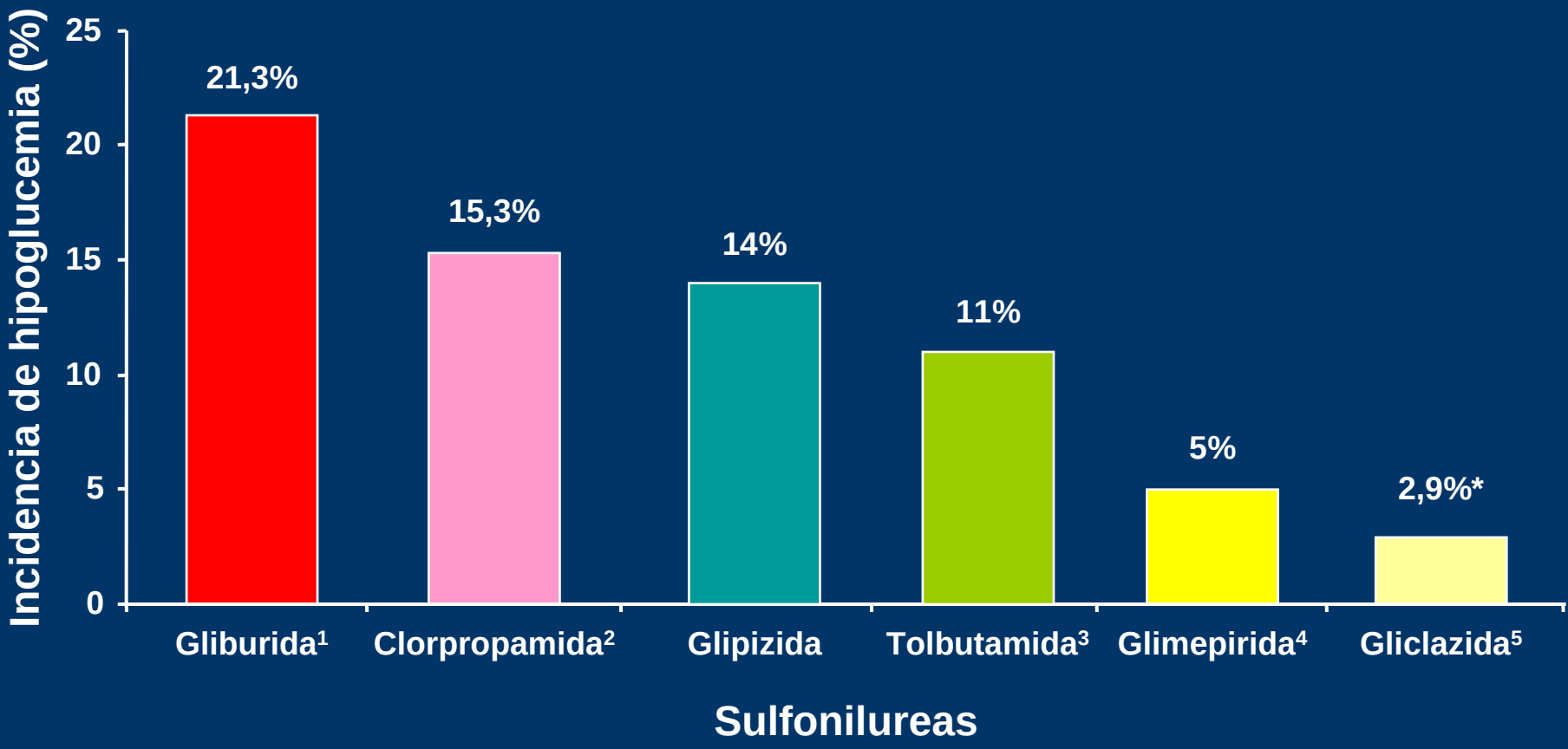
El tratamiento intensivo con sulfonilureas se asocia a mayor riesgo de hipoglucemia



Mayor riesgo de hipoglucemia con gliburida que con clorpropamida:

0.6 vs 0.4 por 100 pacientes-año
17.7% vs 11% episodios

Hipoglucemia por Sulfonilureas

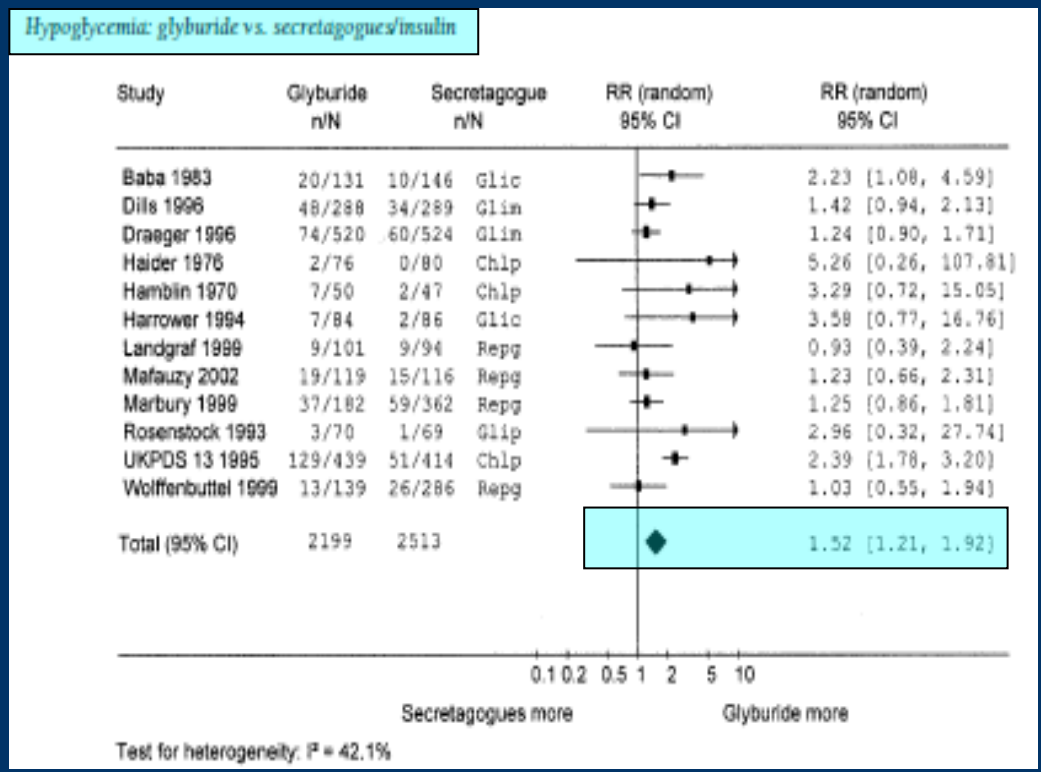


•*Hipoglucemia: punción capilar para la medición de la glucosa en sangre ≤ 50 mg/dL (2,75 mmol/L)

•**1. Glucovance [prospecto]. Princeton, NJ: Bristol-Myers Squibb Company; 2004. 2. UKPDS Group. *Lancet* 1998; 352: 837–853. 3. Draeger KE, et al. *Horm Metab Res*. 1996; 28: 419–425. 4. McGavin JK, et al. *Drugs* 2002; 62; 1357–1364. 5. Metaglip [prospecto]. Princeton, NJ: Bristol-Myers Squibb Company; 2002 . 6. JAGS 1996;44(7):751**

Riesgo de hipoglucemia de glibenclamida frente a otras sulfonilureas o insulina

Metanálisis



Gangji AS. Diabetes Care 2007;30:389-94.

Diabetes Care, Vol 17, Issue 2 142-145, Copyright © 1994 by American Diabetes Association

Slow elimination of glyburide in NIDDM subjects

A Jonsson, T Rydberg, G Ekberg, B Hallengren and A Melander
Department of Endocrinology, Lund University, Malmo General Hospital, Sweden.

- La VM de glibenclamida (cromatografía de gases) es de 15±6.7 horas
- Glibenclamida es una SU de VM larga
- Puede administrase 1 vez al día

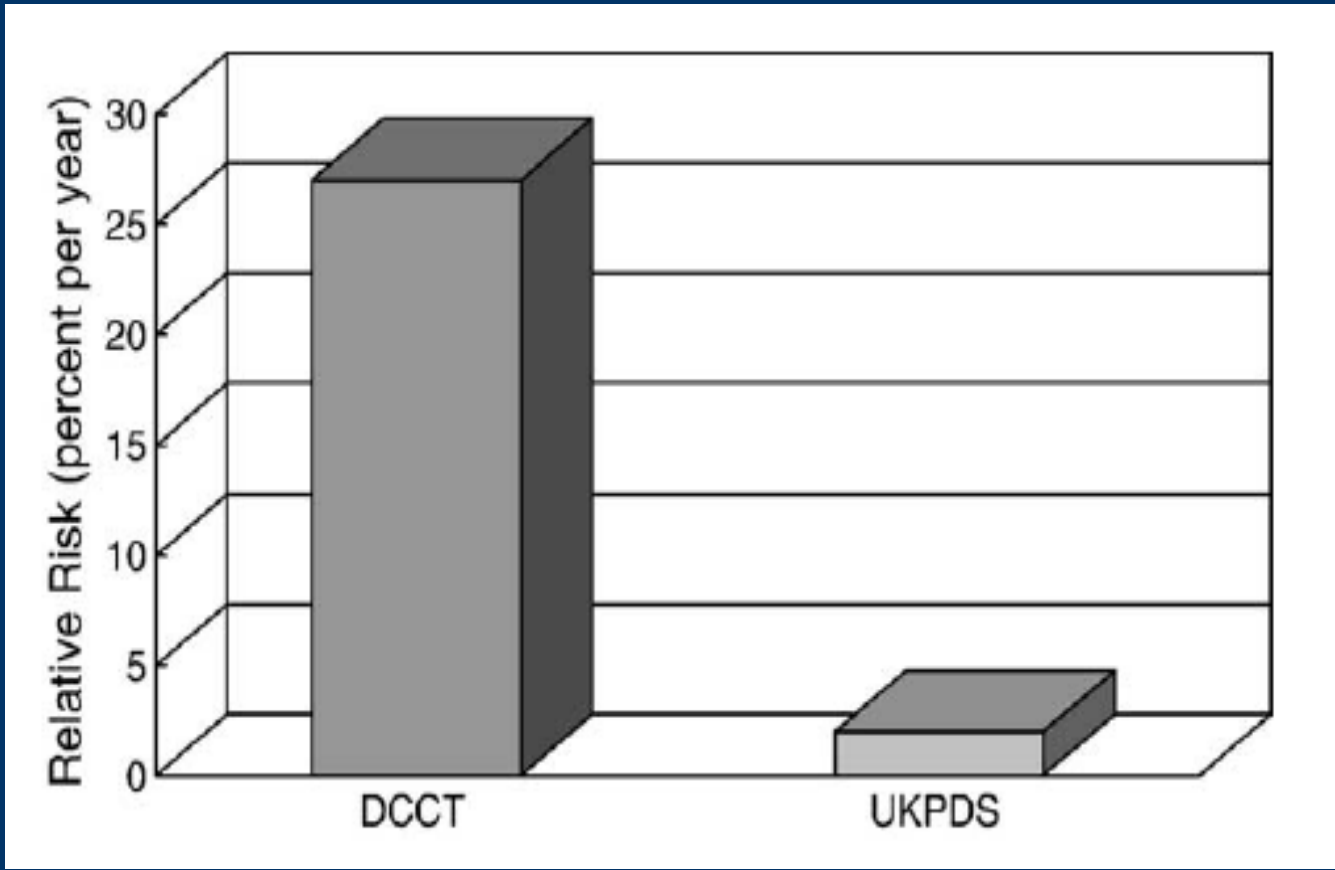
Diabetes Care, Vol 17, Issue 9 1026-1030, Copyright © 1994 by American Diabetes Association

Hypoglycemic activity of glyburide (glibenclamide) metabolites in humans

T Rydberg, A Jonsson, M Roder and A Melander
Hospital Pharmacy, Kristianstad County Central Hospital, Sweden.

- Los 2 principales metabolitos de la glibenclamida
  M1 (4 trans-hidroxi-glibenclamida)
  M2 (3 cis-hidroxi-glibenclamida)
  tienen efecto hipoglucemiante en humanos

Riesgo relativo de hipoglucemia grave en diabetes tipo 1 y diabetes tipo 2



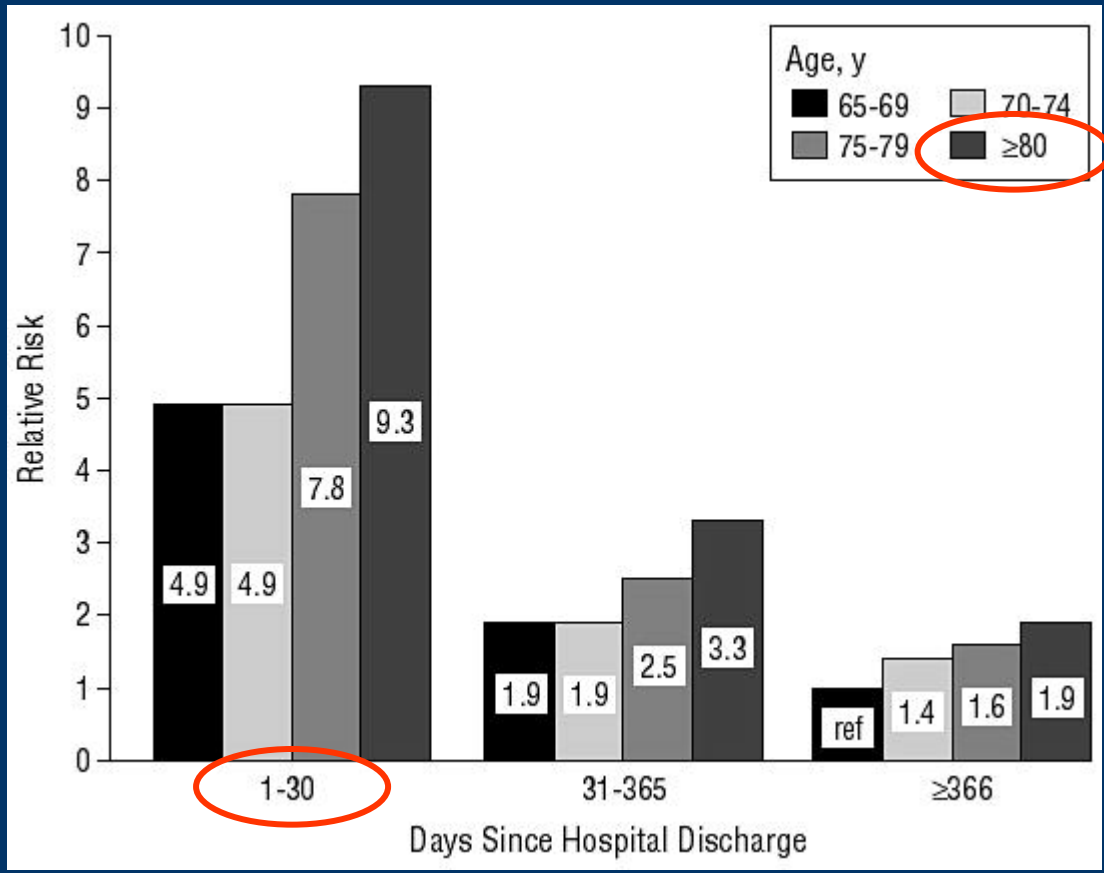
Del Prato S. Metab Clin Exp 2006;55 (suppl 1):S20-S27.

HIPOGLUCEMIAS por SULFONILUREAS
Factores de riesgo

- Edad avanzada
- Ayuno
- Ejercicio
- Alcohol
- Interacciones medicamentosas (polimedicación)
- Comorbilidad. Insuficiencia renal o hepática.
- Inicio del tratamiento
- Empleo de dosis máximas
- Terapia antidiabética combinada

Riesgo de hipoglucemia grave en diabéticos tipo 2 mayores de 65 años tratados al alta hospitalaria con sulfonilureas o insulina

(Tennessee Medicaid, 1984-1989)



Shorr RI. Arch Intern Med 1997;157:1681

Fármacos que interaccionan con las sulfonilureas

Potencian	*Inhiben*
Salicilatos	**Tiazidas**
Dicumarínicos	**Furosemida**
Sulfonamidas	**Propanolol**
Clofibrato	**Corticoides**
Alopurinol	Cloranfenicol
Alcohol	Rifampicina
Metotrexate	Diazóxido
Sulfinpirazona	Contraceptivos
Fenilbutazona	Barbitúricos
Esteroides anabolizantes	
Guanetidina	
IMAO	

Aloe vera
Gymnema sylvestre

REVIEW | Annals of Internal Medicine
Ann Intern Med. 2007;147:386-399.

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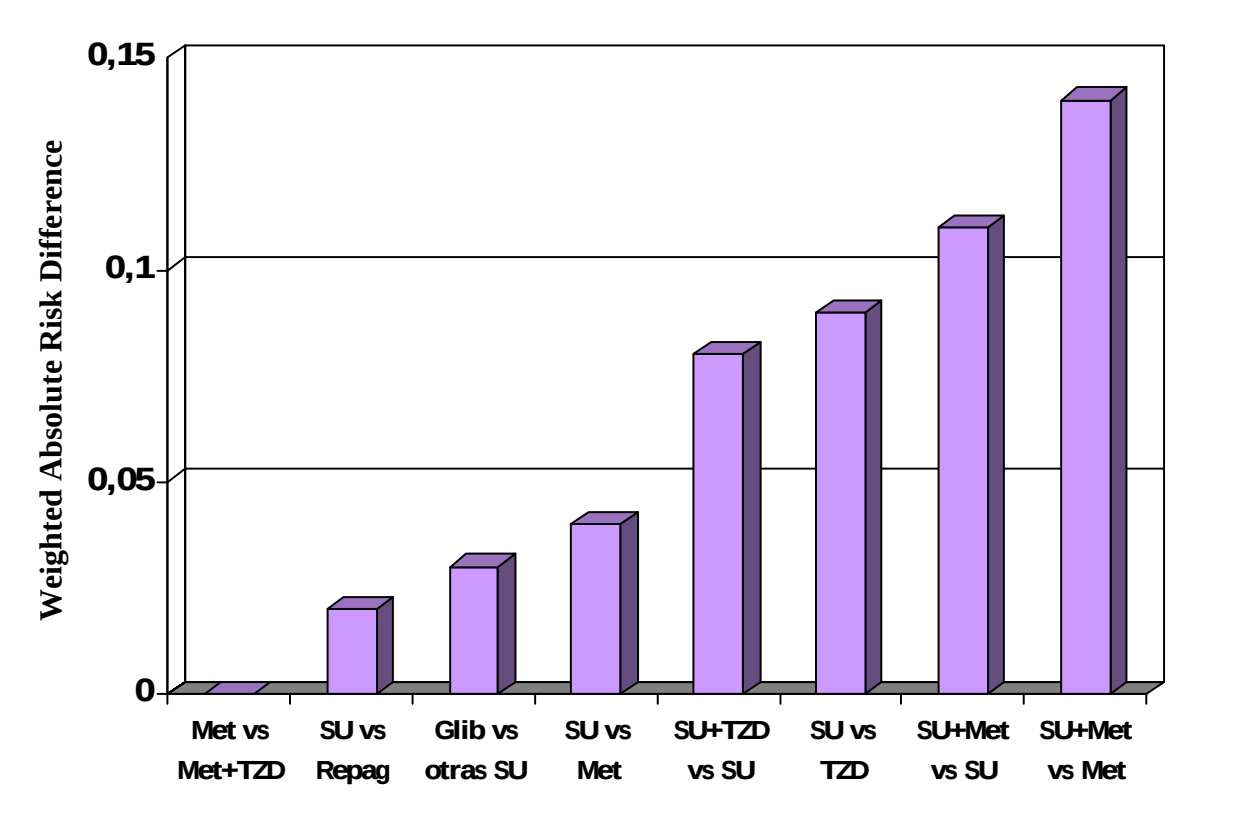
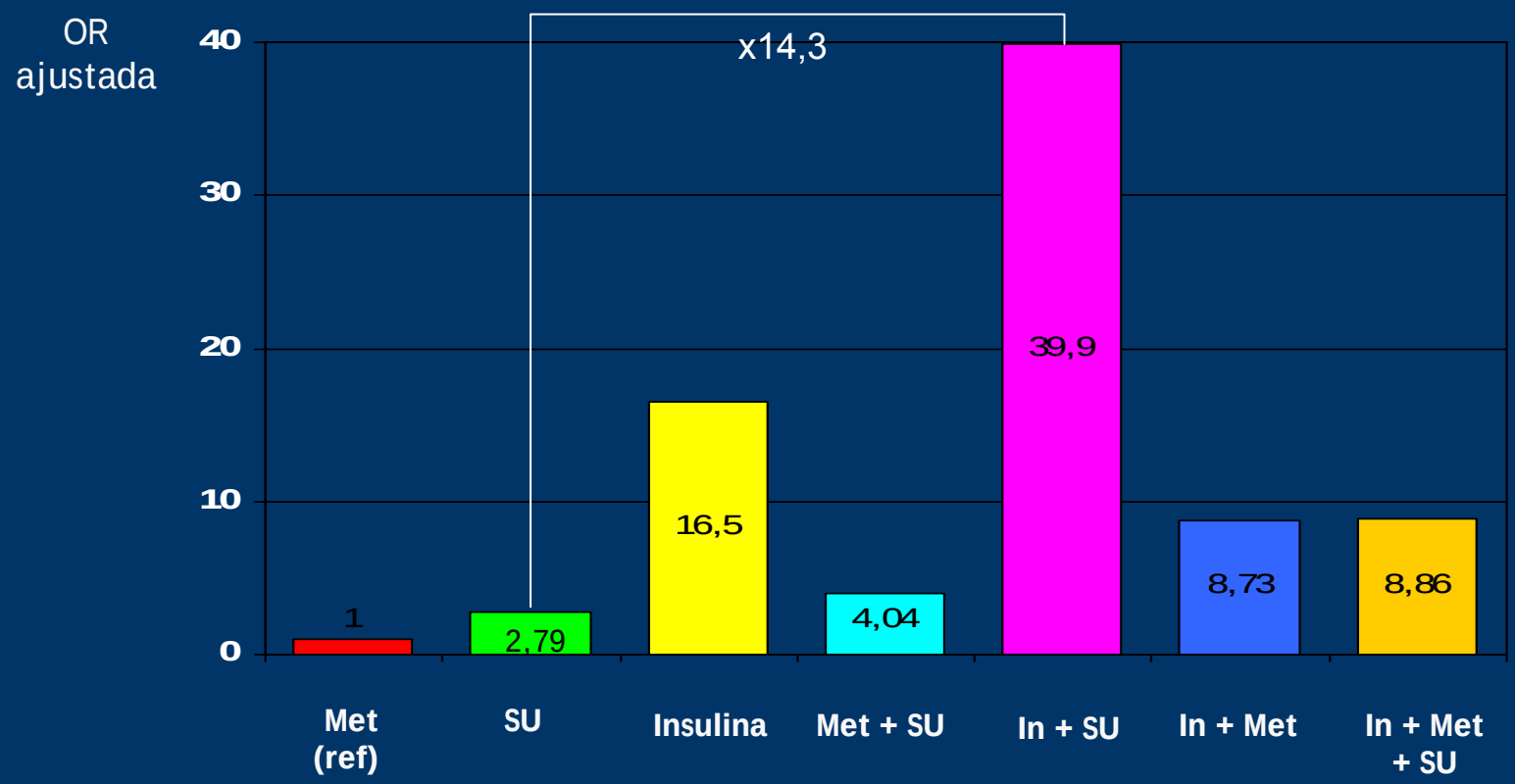
Riesgo de hipoglucemia



Riesgo de hipoglucemia grave en diabetes tipo 2



Bodner M. Diabetes Care 2008;31:2086-91.

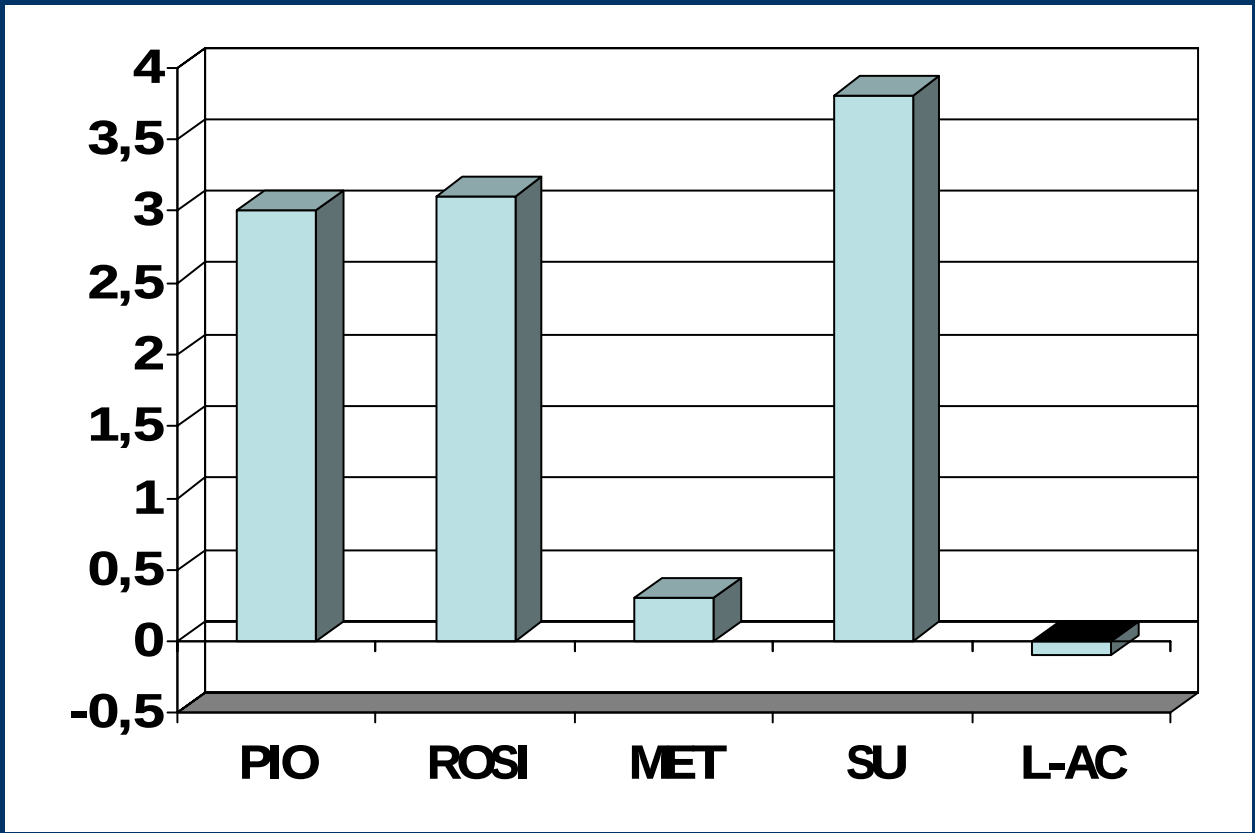
2. GANANCIA DE PESO

REVIEW | Annals of Internal Medicine
Ann Intern Med. 2007;147:386-399.

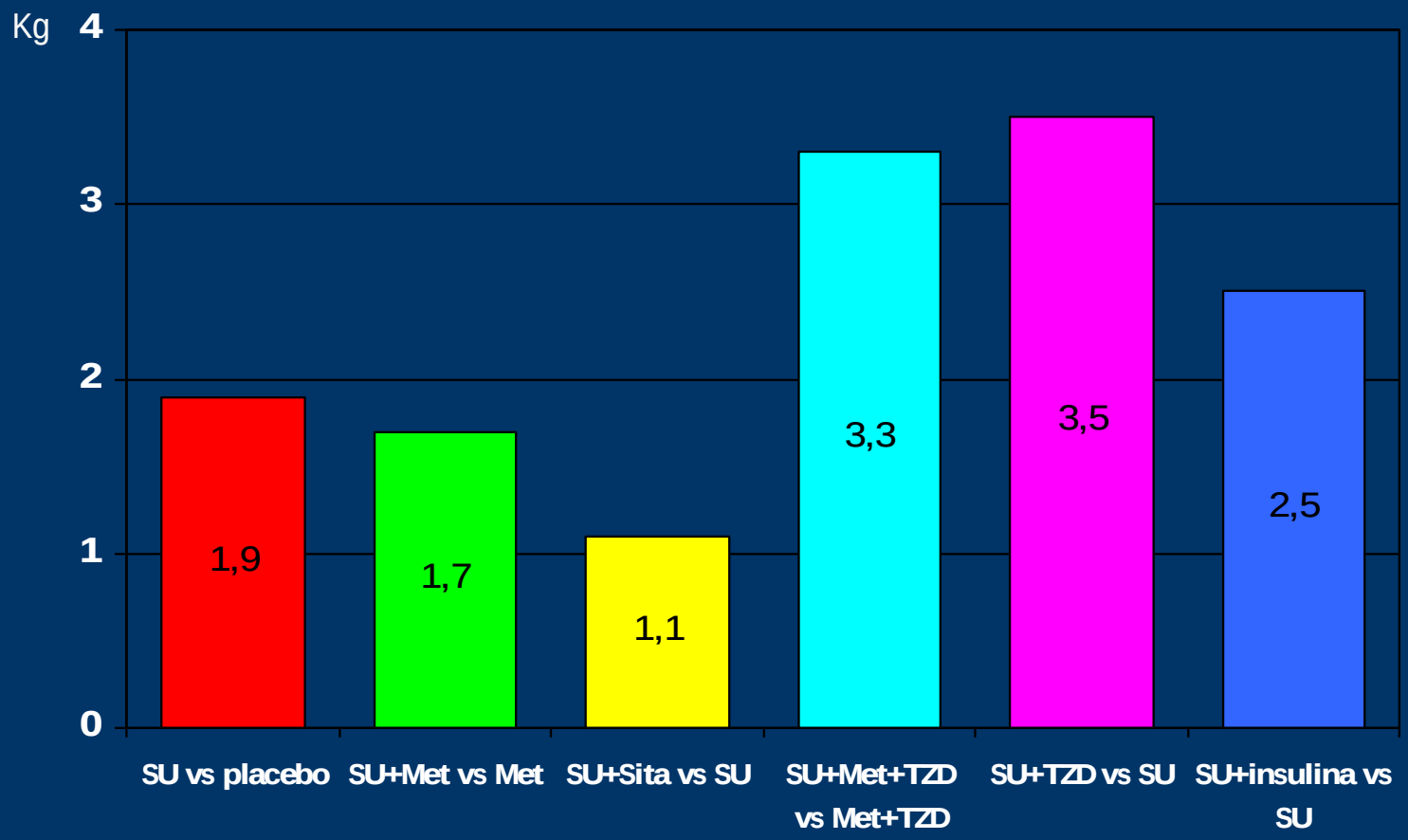
Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus

Shari Bolen, MD, MPH; Leonard Feldman, MD; Jason Vassy, MD, MPH; Lisa Wilson, BS, ScM; Hsin-Chieh Yeh, PhD; Spyridon Marinopoulos, MD, MBA; Crystal Wiley, MD, MPH; Elizabeth Selvin, PhD; Renee Wilson, MS; Eric B. Bass, MD, MPH; and Frederick L. Brancati, MD, MHS

Cambios en el peso corporal (kg) frente a placebo



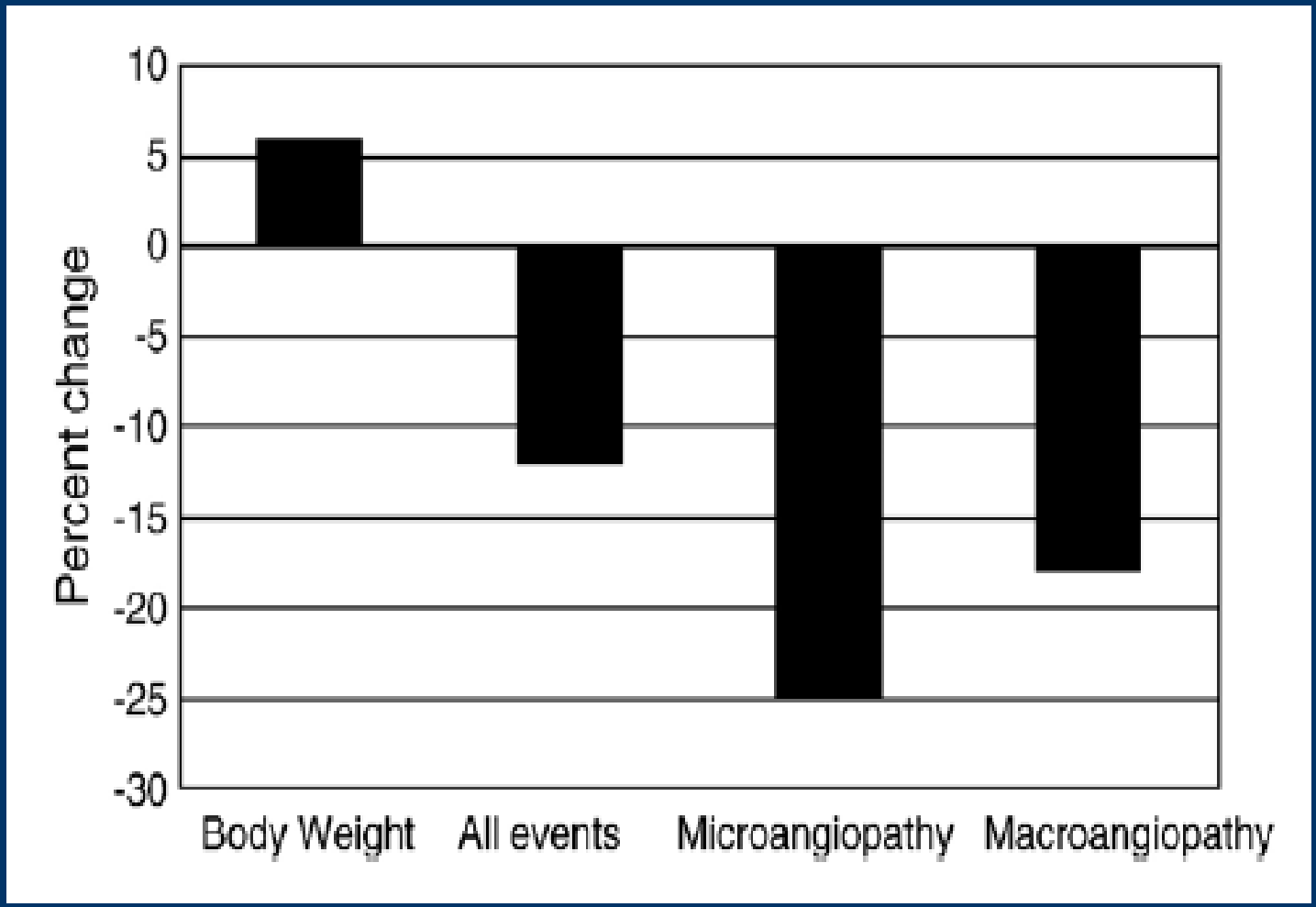
Ganancia de peso en terapia combinada de sulfonilureas con otros fármacos



Estudios a 24-26 semanas

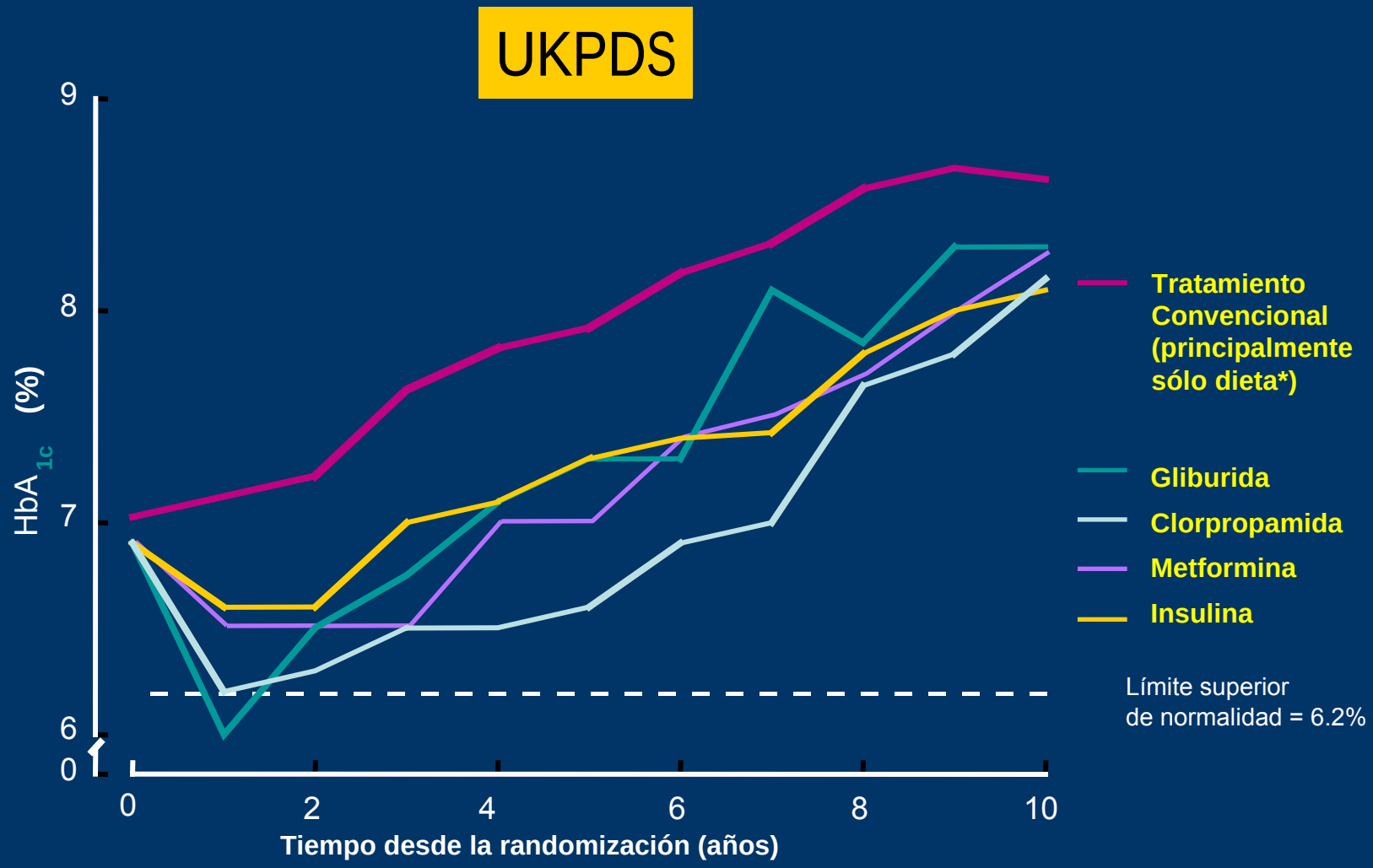
Diabetes Obes Metab.2006;8:156-63.. Curr Med Res Opin 2006;22:751-9. Clin Ther. 2005;27:1535-47. Diabetes Obes Metab 2007;9: 733–745. Diabetes Care 2001;24:758-67.

UKPDS



Del Prato S. Metab Clin Exp 2006;55 (suppl 1):S20-S27.

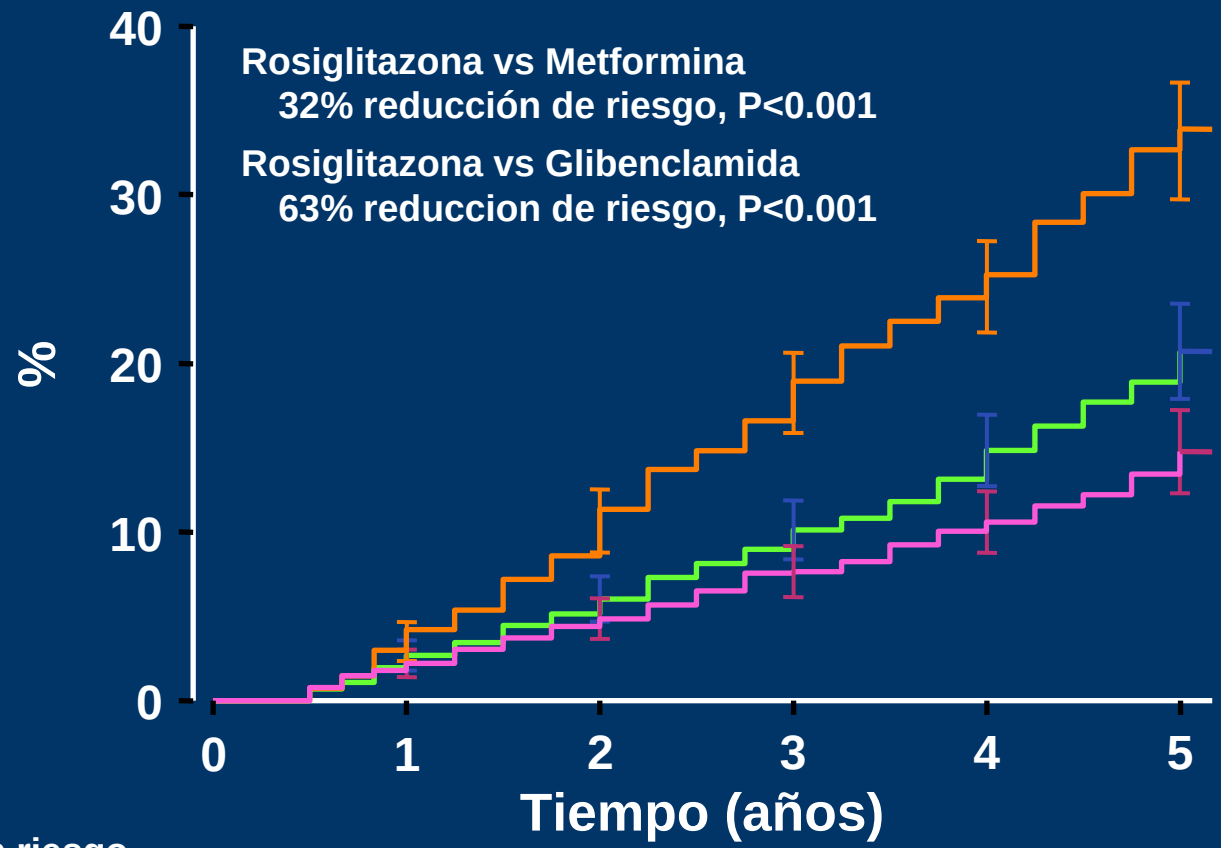
3. AGOTAMIENTO FUNCIONAL BETA



*Iniciado tratamiento farmacológico si FPG > 270 mg/dl o síntomas de hiperglucemia
Pacientes obesos
Cohorte, valores medios

UKPDS 34. Lancet 1998; 352:854–865.

Incidencia acumulada de fallo de monoterapia (GBA >180 mg/dl)



Pacientes en riesgo						
Rosiglitazona	1393	1207	1078	957	844	324
Metformina	1397	1205	1076	950	818	311
Glibenclamida	1337	1114	958	781	617	218

A los 5 años

- 15% con RSG
- 21% con MTF
- 34% con GliB

ADOPT

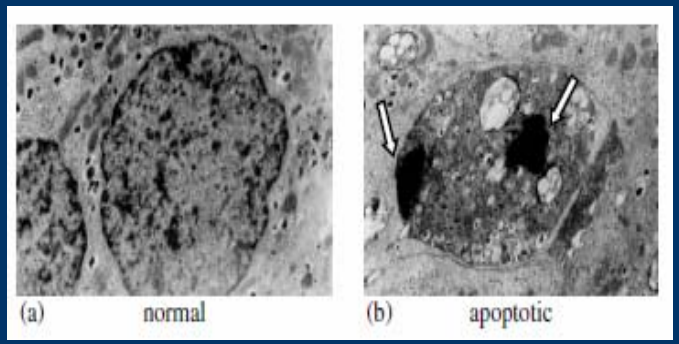
Kahn SE. NEJM 2006;355:2427-43.;

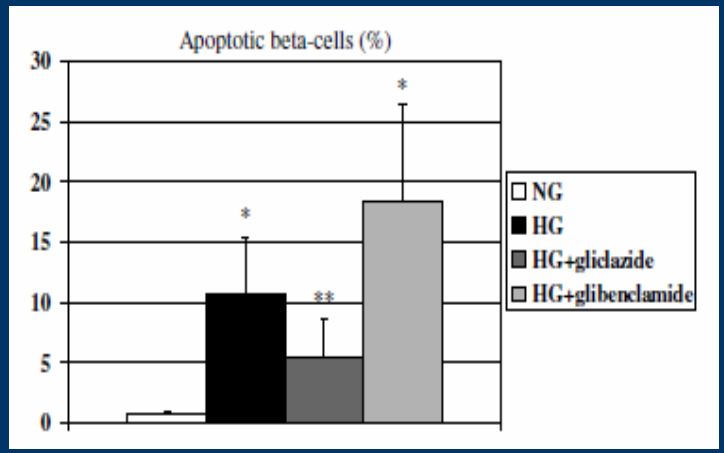
DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2007; **23**: 234–238.
Published online 4 September 2006 in Wiley InterScience (www.interscience.wiley.com) **DOI:** 10.1002/dmrr.680

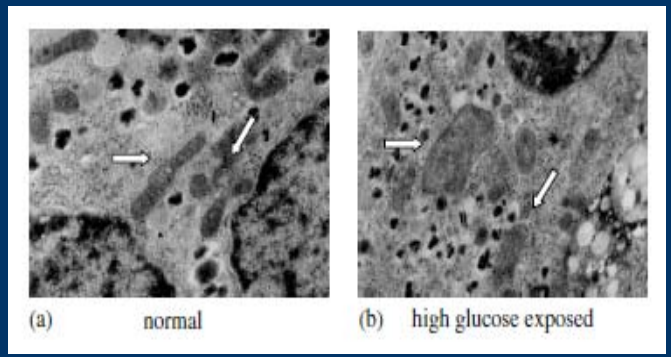
RESEARCH ARTICLE

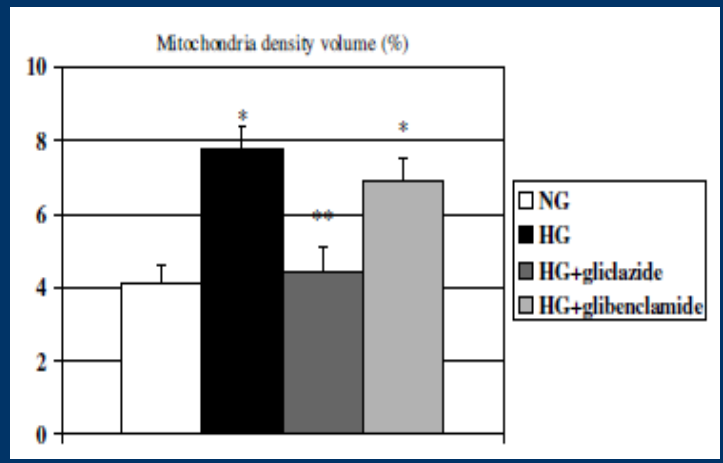
S Del Guerra

Gliclazide protects human islet beta-cells from apoptosis induced by intermittent high glucose

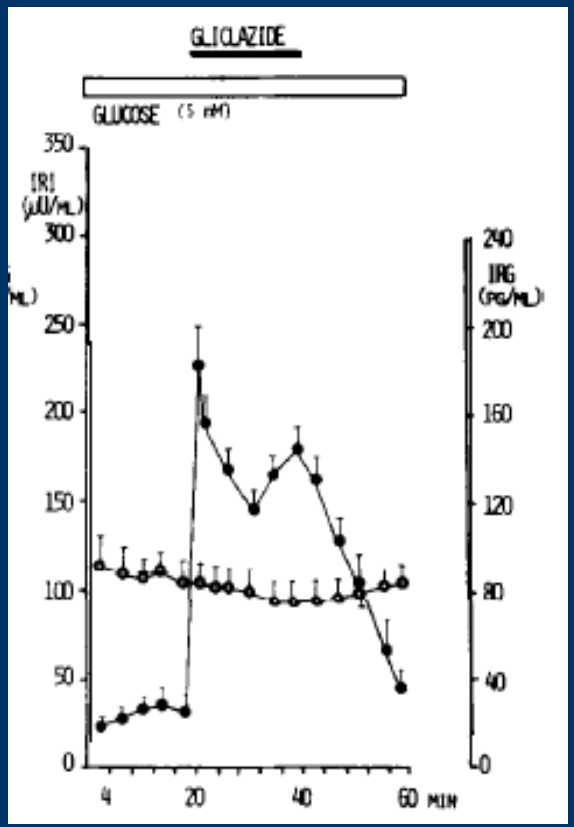


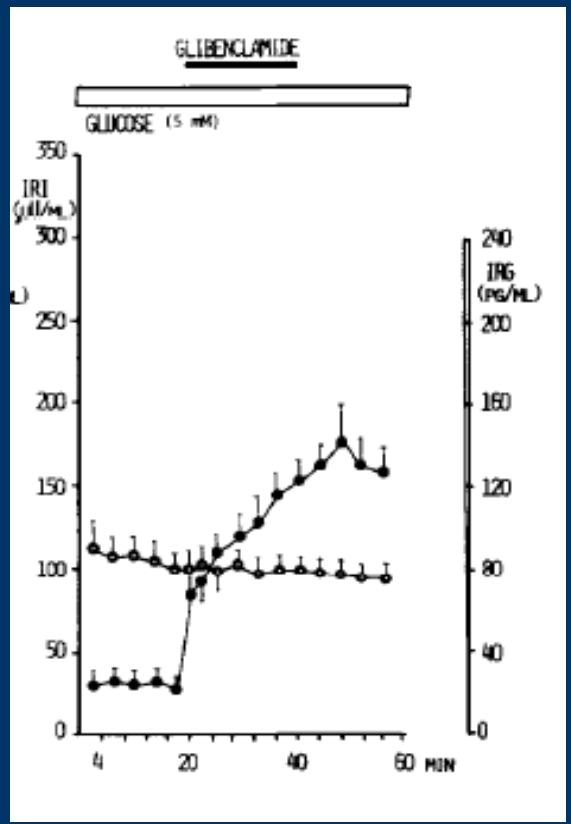






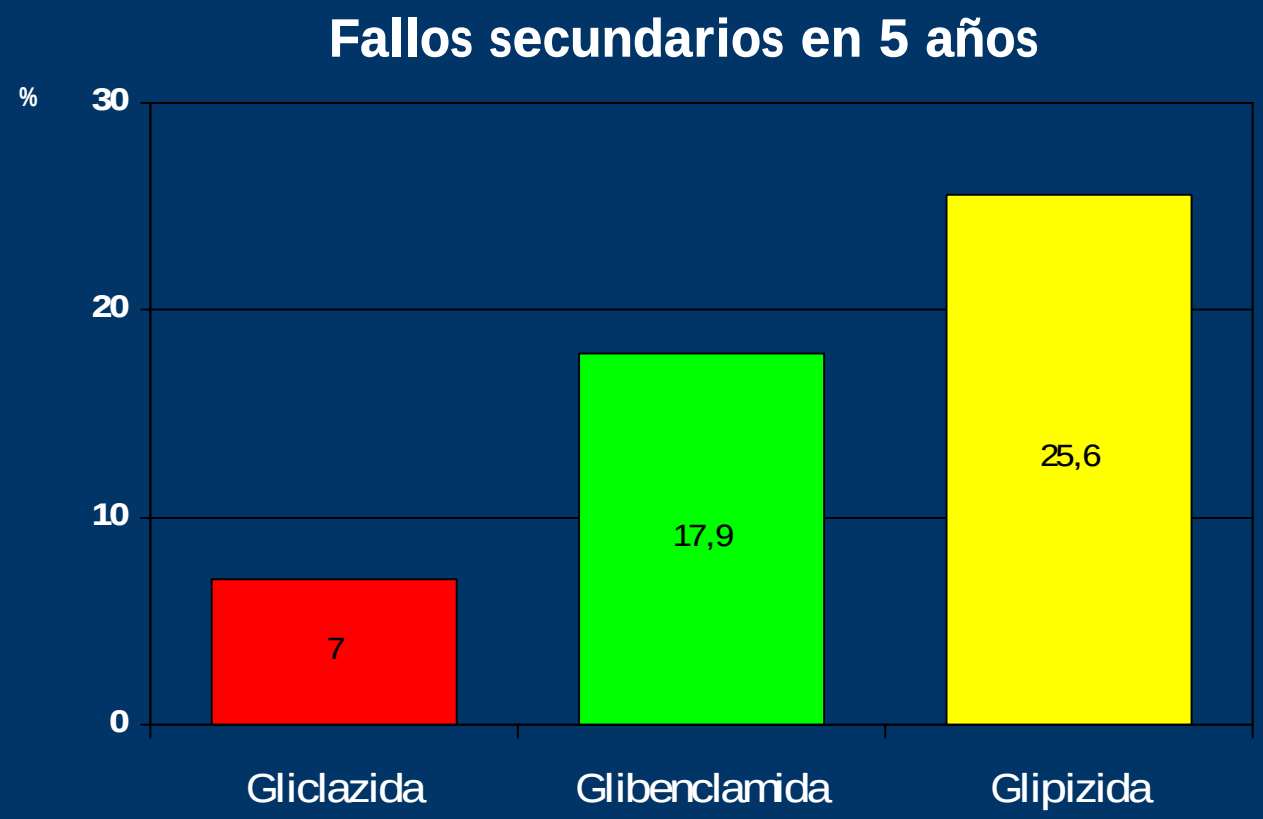
Gliclazida restaura el perfil bifásico fisiológico de secreción de insulina que se pierde en la DMT2, a diferencia de la respuesta monofásica tardía de la glibenclamida





Gregorio F. Diabetes Res Clin Pract 1992;18:197-206.

Gliclazida puede ser más eficaz que otras SU en el control glucémico



J Diabetes Complications 1994;8(4):201.

Estudio UGDP

Meinert CL. Diabetes 1970;19:Supp:789-830.

- ensayo clínico aleatorizado (1961-1966)
- n: 1.027
- DM2 diagnosticados ≤1 año
- seguimiento: 5,5 años

- No evidencia que el tratamiento intensivo reduzca el riesgo cardiovacular
- Mayor mortalidad cardiovascular con tolbutamida vs placebo
  12,7% vs 4,9% (p= 0.005, NNH 12)

Limitaciones metodológicas

1) Pérdidas 17%
2) Población asignada a tolbutamida con mayor riesgo basal: mayor edad, colesterol y arteriosclerosis asintomática

UKPDS

¿El tratamiento combinado de metformina y sulfonilureas aumenta la mortalidad?

AGGREGATE ENDPOINT	Patients with aggregate endpoint/total		Absolute risk (events per 1000 patient-years)		Log-rank 2p	RR (95%CI) for conventional/ metformin
	Added metformin	Conventional/ sulphonylurea	Added metformin	Conventional/ sulphonylurea		
Any diabetes-related endpoint						
Metformin	98/342	160/411	29·8	43·3	0·0023	0·68 (0·53–0·87)
Sulphonylurea plus metformin	81/268	82/269	60·5	58·4	0·78	1·04 (0·77–1·42)
Combined groups	179/610	242/680	38·7	47·5	0·033	0·81 (0·67–0·98)
Diabetes-related death						
Metformin	28/342	55/411	7·5	12·7	0·017	0·58 (0·37–0·91)
Sulphonylurea plus metformin	26/268	14/269	16·8	8·6	0·039	1·96 (1·02–3·75)
Combined groups	54/610	69/680	10·3	11·6	0·47	0·88 (0·61–1·25)
All-cause mortality						
Metformin	50/342	89/411	13·5	20·6	0·011	0·64 (0·45–0·91)
Sulphonylurea plus metformin	47/268	31/269	30·3	19·1	0·041	1·60 (1·02–2·52)
Combined groups	97/610	120/680	18·4	20·2	0·49	0·91 (0·70–1·19)
Myocardial infarction						
Metformin	39/342	73/411	11·0	18·0	0·010	0·61 (0·41–0·89)
Sulphonylurea plus metformin	33/268	31/269	22·0	20·2	0·73	1·09 (0·67–1·78)
Combined groups	72/610	104/680	14·2	18·6	0·077	0·76 (0·56–1·03)
Stroke						
Metformin	12/342	23/411	3·3	5·5	0·13	0·59 (0·29–1·18)
Sulphonylurea plus metformin	15/268	13/269	9·9	8·2	0·61	1·21 (0·58–2·55)
Combined groups	27/610	36/680	5·2	6·2	0·49	0·84 (0·51–1·38)
Peripheral vascular disease						
Metformin	6/342	9/411	1·6	2·1	0·57	0·74 (0·26–2·09)
Sulphonylurea plus metformin	2/268	1/269	1·3	0·6	0·53	2·12 (0·19–23·3)
Combined groups	8/610	10/680	1·7	1·7	0·82	0·90 (0·35–2·27)
Microvascular disease						
Metformin	24/342	38/411	6·7	9·2	0·19	0·71 (0·43–1·19)
Sulphonylurea plus metformin	15/268	19/269	10·1	12·1	0·62	0·84 (0·43–1·66)
Combined groups	39/610	57/680	7·7	10·0	0·20	0·77 (0·51–1·15)

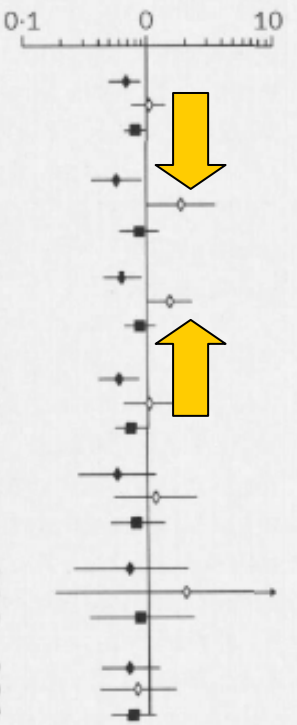


Figure 10: **Incidence of clinical endpoints in sulphonylurea *vs* metformin study and diet *vs* metformin study**

Relative risk (RR) is for comparison with conventional or sulphonylurea alone. Results of a combined analysis of these two studies shown also.

UKPDS 34. Lancet 1998:352:854-65

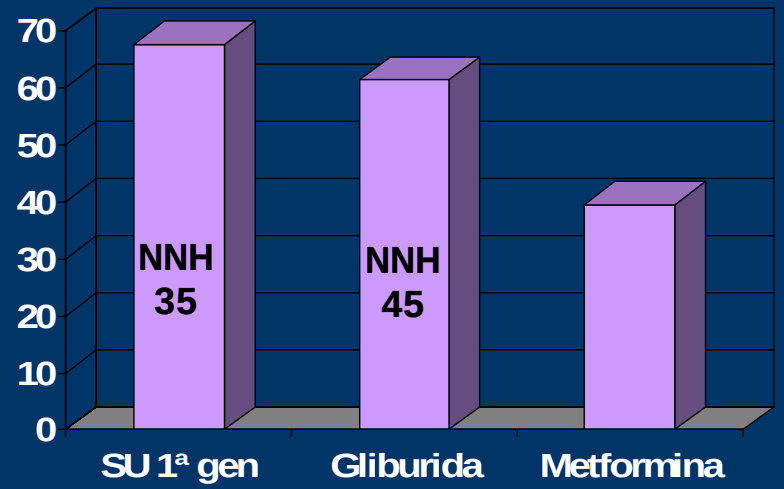
Dose–response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study

CMAJ 2006;174(2):169-74

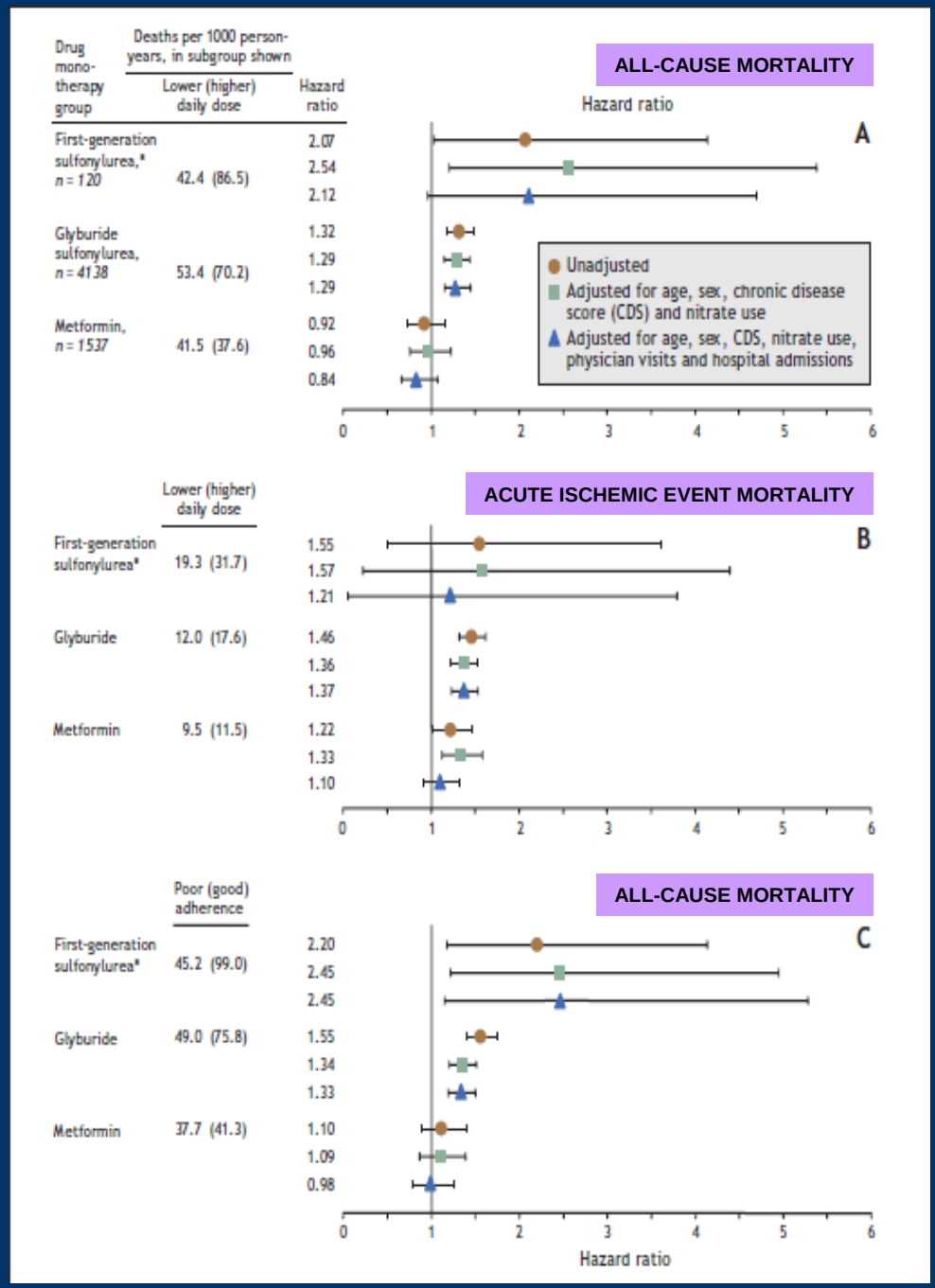
Scot H. Simpson, Sumit R. Majumdar, Ross T. Tsuyuki, Dean T. Eurich, Jeffrey A. Johnson

Relación dosis-respuesta entre sulfonilureas y mortalidad

Saskatchewan Health

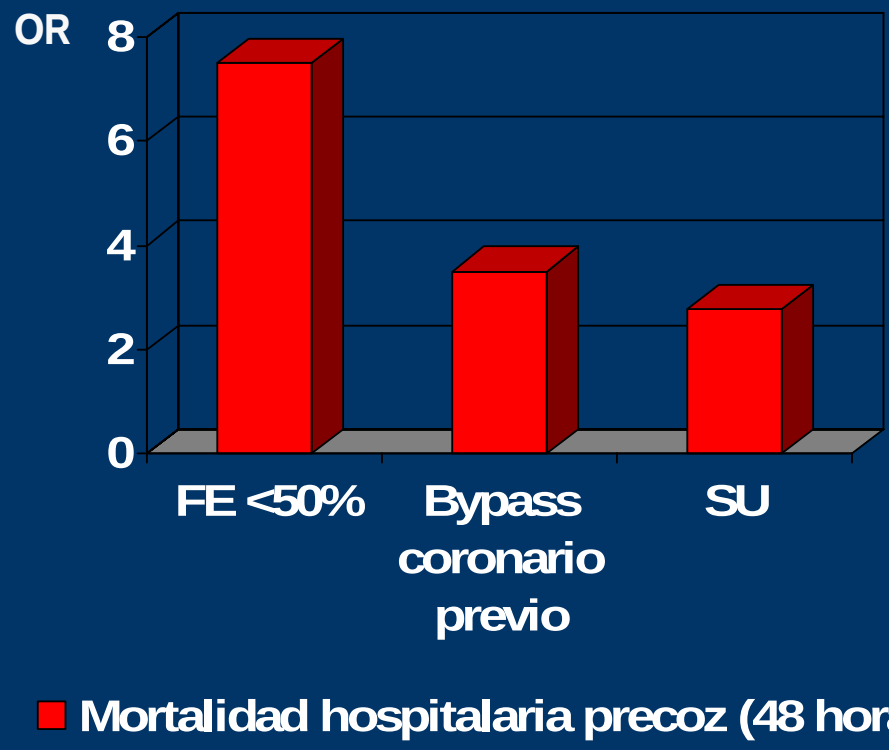


Tasa de mortalidad por 1000 pacientes - año



Las sulfonilureas pueden aumentar la mortalidad en pacientes con síndrome coronario agudo

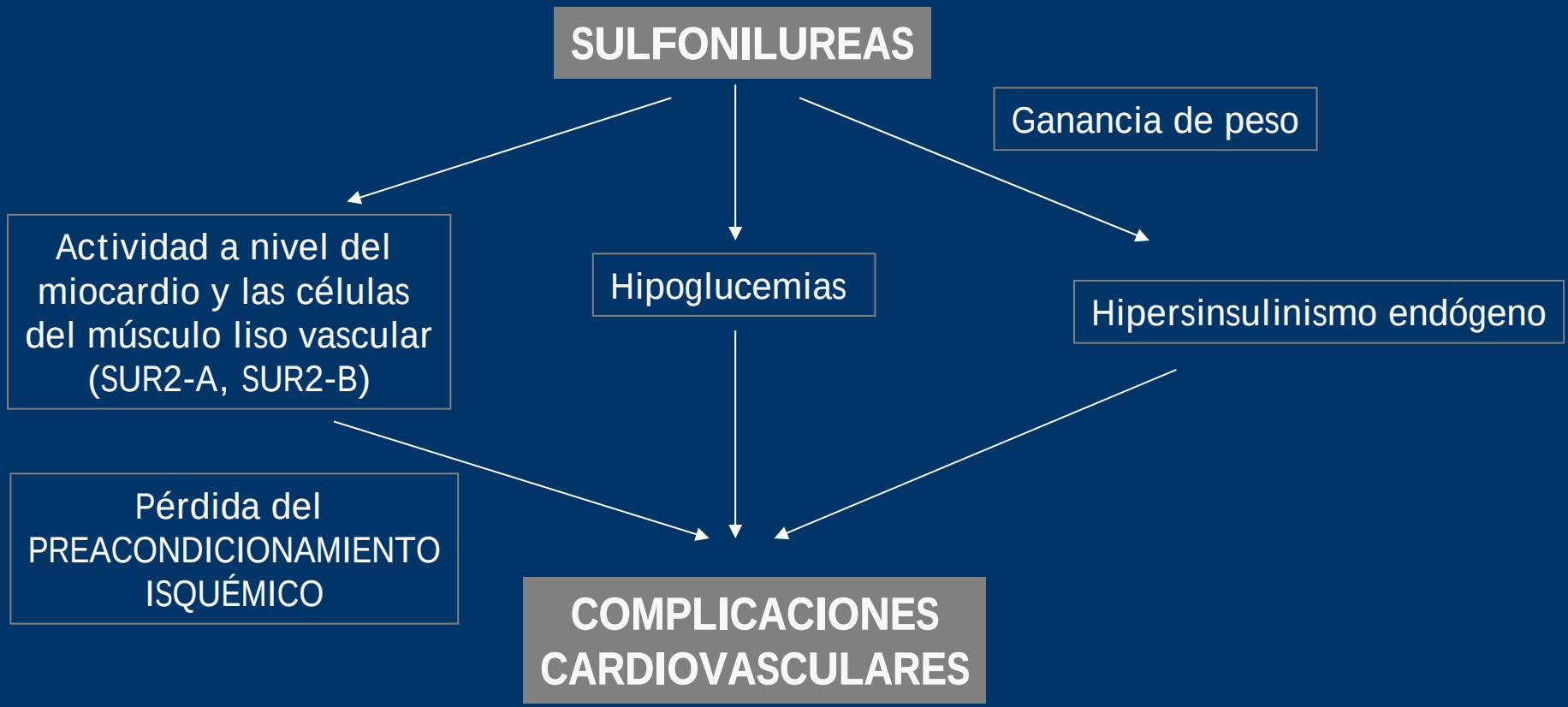
- estudio observacional, caso-control
- 185 diabéticos tipo 2 sometidos a ACTP con balón por IAM
- 67 tomaban SU
- los pacientes con SU tenían más edad, menor FEVI y menos ACTP exitosas (75% vs 81%)



Tasa de mortalidad (48 h):
Sulfonilureas: 24%
Insulina o dieta: 11%
p= 0.017

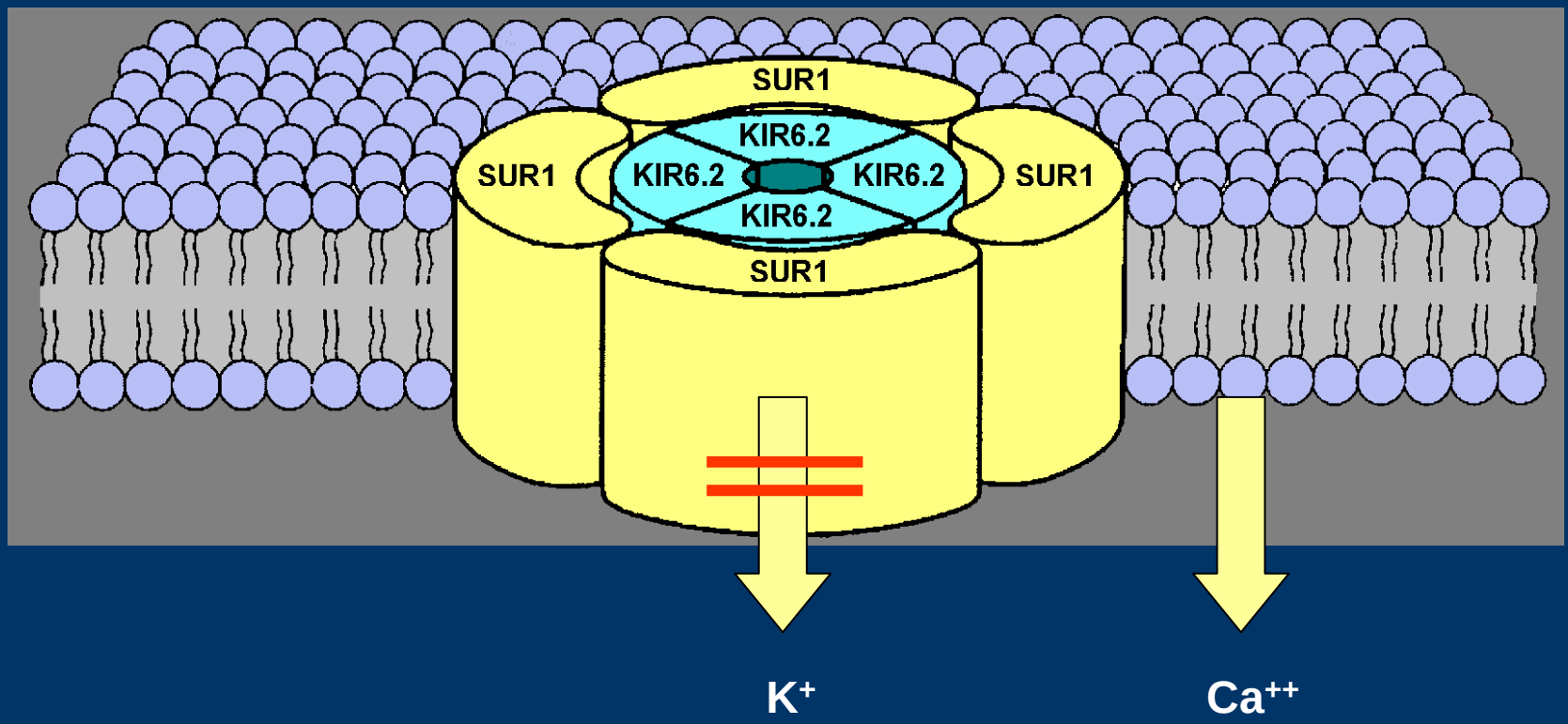
Garratt KN. J Am Coll Cardiol 1999;33:119-24.

MORTALIDAD CARDIOVASCULAR Y SULFONILUREAS

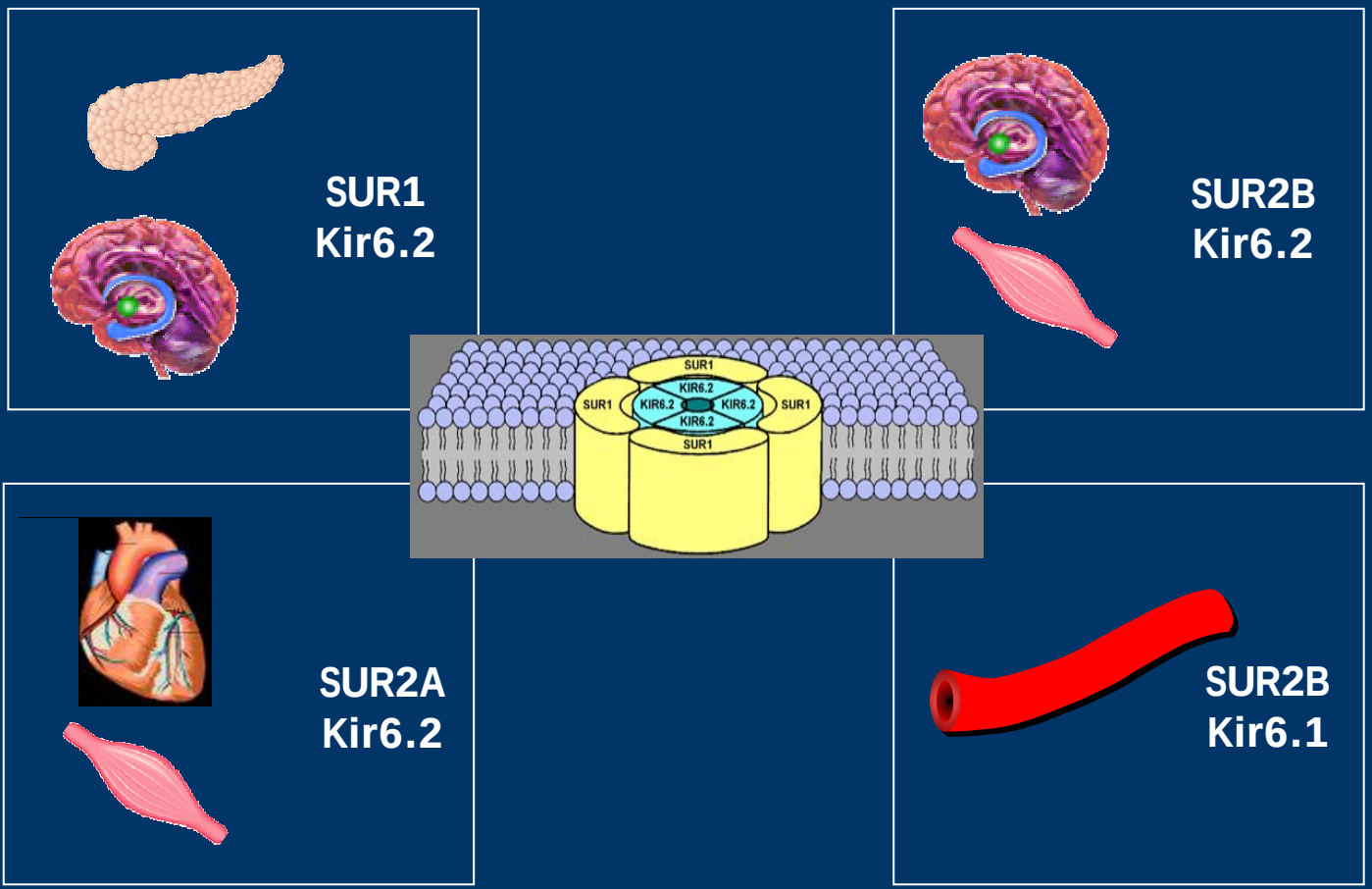


SULFONILUREAS
Modo de acción

DIANA FARMACOLÓGICA DE LAS SULFONILUREAS: CANAL K_{ATP} EN LA CÉLULA ß



Isoformas de los canales de K_{ATP}



Una nueva propuesta de clasificación: Sulfonilureas SUR1-selectivas y SUR1-no selectivas

Comparison of the IC_{50} for K_{ATP} channel inhibition by various sulfonylureas with the K_d for drug binding

	SUR1		SUR2A		SUR2B	
	IC_{50} (current)	K_d (binding)	IC_{50} (current)	K_d (binding)	IC_{50} (current)	K_d (binding)
Glibenclamide (nmol/l)	0.13 †[22] 4.2 †[21]	≈0.7 *,†[22] 7.1 *[32] 1.5 ‡, 1.8*[41] 0.2 {†}[55]	45 †[22] 27 †[21]	≈300 (*,†)[22] 1,200 *,¶[14]	42 †[22] 43 ‡[23] 166 †[36]	≈350 *,(†,‡)[22] 6.3 ‡, 32 *[23]
Glipizide (nmol/l)	3.8 †[22]	≈17 *,†[22]		≈6,000 (*,†)[22]	1,200 †[22]	≈6,000 *,(†,‡)[22]
Glimepiride (nmol/l)	3.0 †[34]	—	5.4 †[34]		7.3 †[34]	
Tolbutamide (µmol/l)	4.9 †[22] 5.4 †[21] 10.5 † [52]	≈29 *,†[22] 140 *[32] 9 {†}[55]	85 †[22] ≥ nmol/l †[21,54] >1 mmol/l [55]	≈270 (*,†)[22]	88 †[22]	≈280 *,(†,‡)[22]
Gliclazide (nmol/l)	50 †[21]	—	>100 µmol/l †[21]			
Meglitinide (µmol/l)	1.2 †[22] 0.26 †[21]	≈7 *[22]	0.53 †[21]	≈7 (*)[22]	1.6 †[22]	≈8 (*)[22]
Mitiglinide (nmol/l)	≈60 †[32]	280 *[32]	> 100 µmol/l †[32]		>100 µmol/l †[32]	
Repaglinide (nmol/l)	3.8 †[33] 5.6 †[53] 21 †[55]	1,600 *[32] 0.6 {†}[55]	3200 †[33] 2.2 †[53]		4,600 †[33] 2.0 †[53]	
Nateglinide (µmol/l)	— 0.8 †[55]	8 *[32] 0.2 {†}[55]				

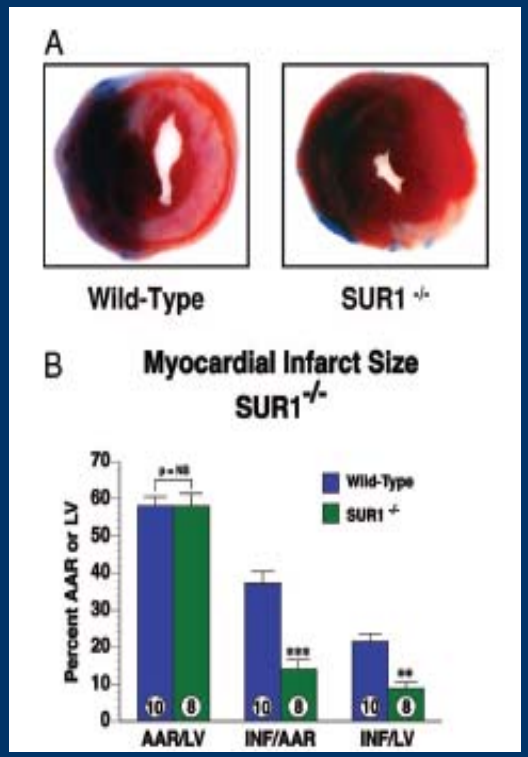
Proks P. Diabetes 2002;51(Supl.3):S368-76.

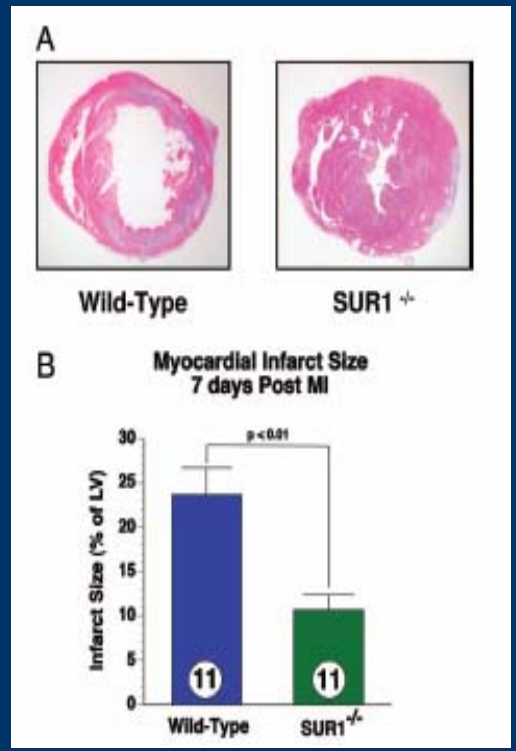
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.

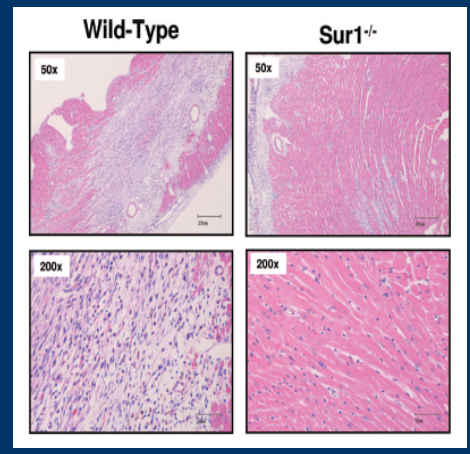
Molecular Cardiology

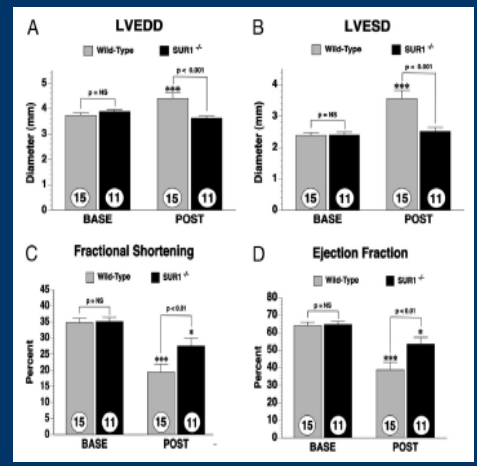
Role of Sulfonylurea Receptor Type 1 Subunits of ATP-Sensitive Potassium Channels in Myocardial Ischemia/Reperfusion Injury

John W. Elrod, PhD; Maddison Harrell, BS; Thomas P. Flagg, PhD; Susheel Gundewar, MD; Mark A. Magnuson, MD; Colin G. Nichols, PhD; William A. Coetzee, PhD; David J. Lefer, PhD









Circulation. 2008;117:1405-1413.

Stroke
Journal of the American Heart Association
American Stroke Association
A Division of American Heart Association

Sulfonylureas Improve Outcome in Patients With Type 2 Diabetes and Acute Ischemic Stroke

Hagen Kunte, MD; Sein Schmidt, MD; Michael Eliasziw, PhD; Gregory J. del Zoppo, MD; J. Marc Simard, MD, PhD; Florian Masuhr, MD; Markus Weih, MD; Ulrich Dirnagl, MD

Background and Purpose—The sulfonylurea receptor 1-regulated $NC_{Ca\text{-}ATP}$ channel is upregulated in rodent models of stroke with block of the channel by the sulfonylurea, glibenclamide (glyburide), significantly reducing mortality, cerebral edema, and infarct volume. We hypothesized that patients with type 2 diabetes mellitus taking sulfonylurea agents both at the time of stroke and during hospitalization would have superior outcomes.

Methods—We reviewed medical records of patients with diabetes mellitus hospitalized within 24 hours of onset of acute ischemic stroke in the Neurology Clinic, Charité Hospital, Berlin, Germany, during 1994 to 2000. After exclusions, the cohort comprised 33 patients taking a sulfonylurea at admission through discharge (treatment group) and 28 patients not on a sulfonylurea (control group). The primary outcome was a decrease in National Institutes of Health Stroke Scale of 4 points or more from admission to discharge or a discharge National Institutes of Health Stroke Scale score of 0. The secondary outcome was a discharge modified Rankin Scale score ≤ 2.

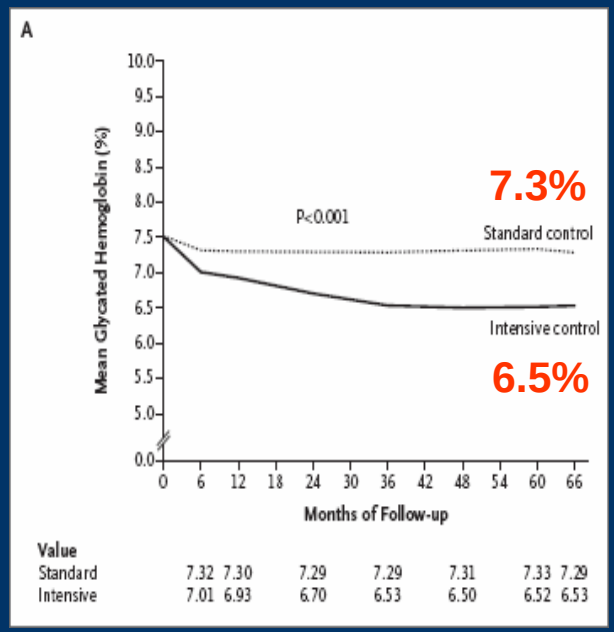
Results—No significant differences, other than stroke subtype, were observed among baseline variables between control and treatment groups. The primary outcome was reached by 36.4% of patients in the treatment group and 7.1% in the control group ($P=0.007$). The secondary outcome was reached by 81.8% versus 57.1% ($P=0.035$). Subgroup analyses showed that improvements occurred only in patients with nonlacunar strokes and were independent of gender, previous transient ischemic attack, and blood glucose levels.

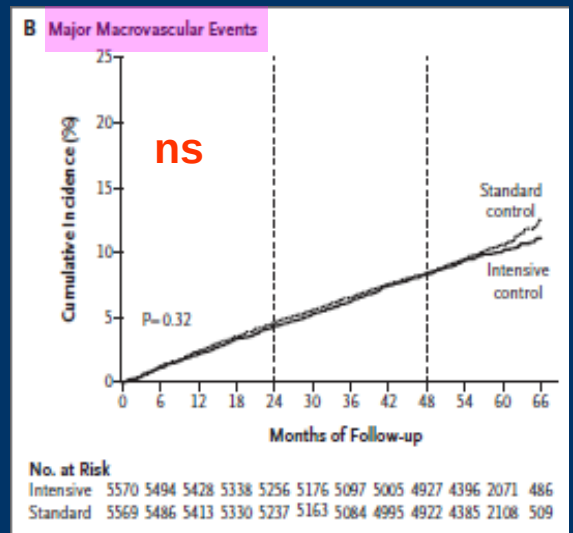
Conclusion—Sulfonylureas may be beneficial for patients with diabetes mellitus with acute ischemic stroke. Further investigation of similar cohorts and a prospective randomized trial are recommended to confirm the present observations. (***Stroke*. 2007;38:2526-2530.**)

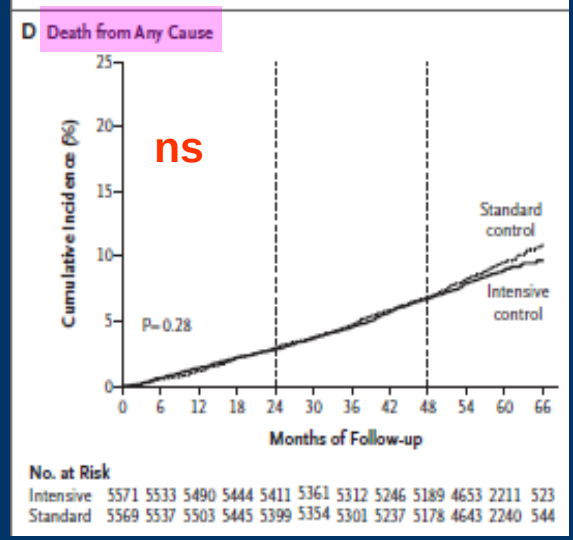
ADVANCE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

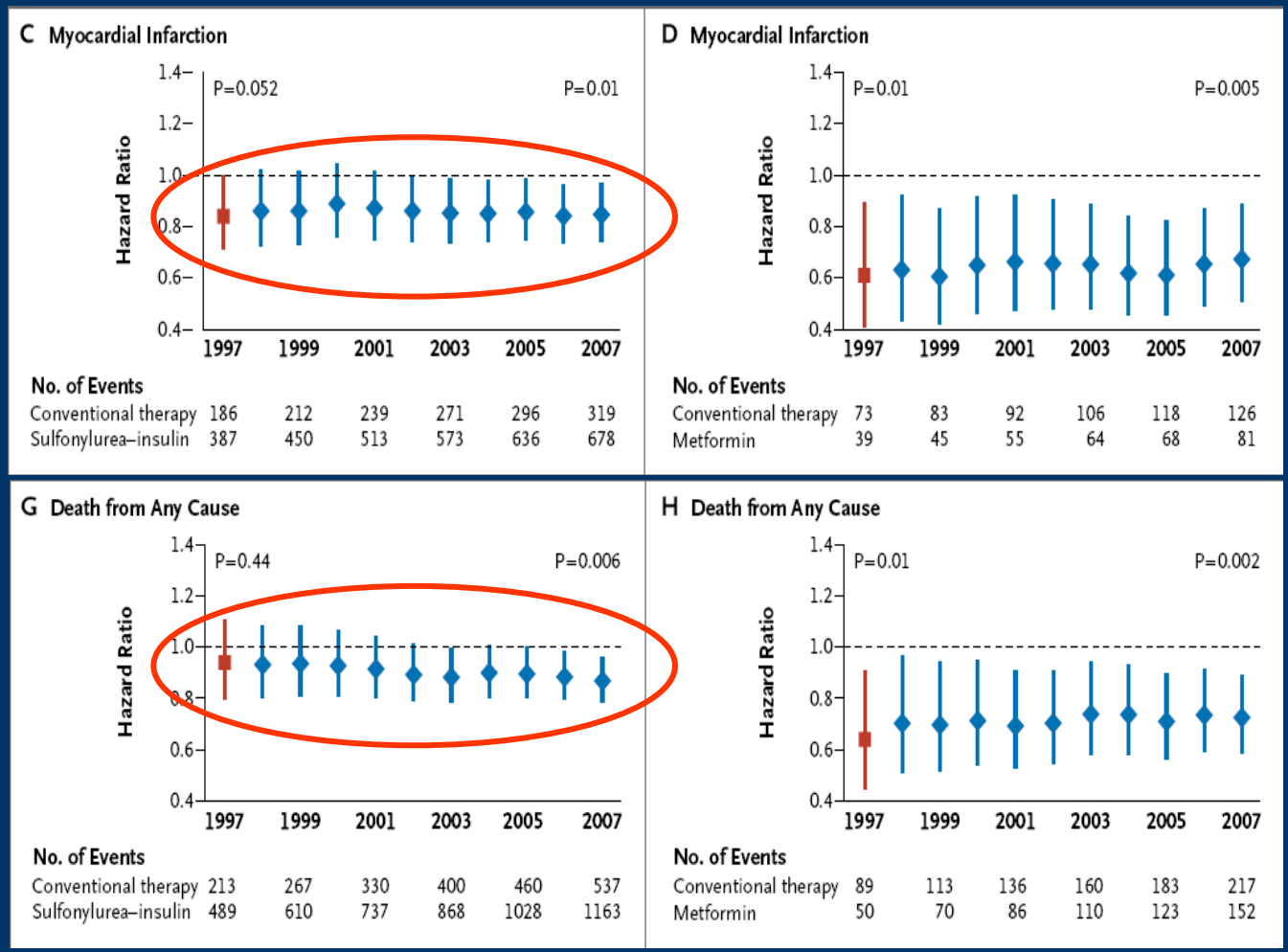






Efectos del control glucémico intensivo a largo plazo

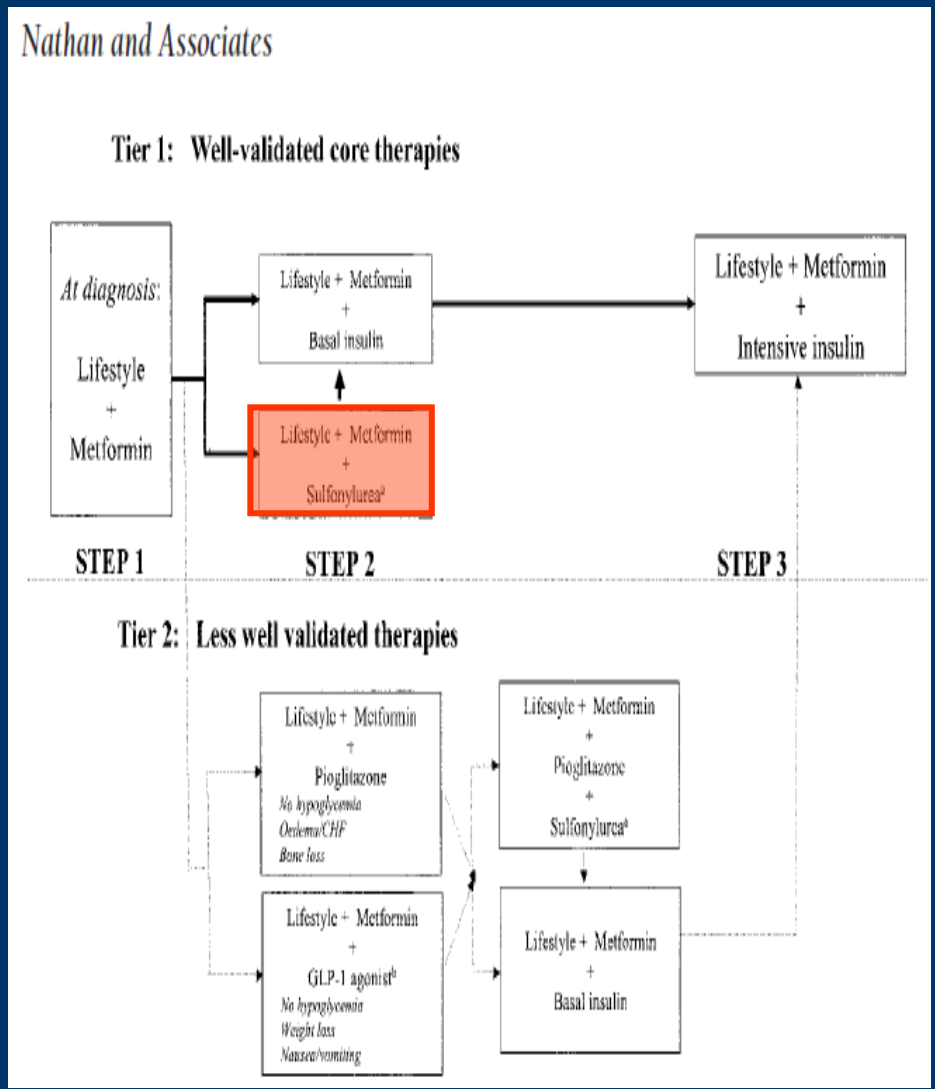
UKPDS: seguimiento a 10 años

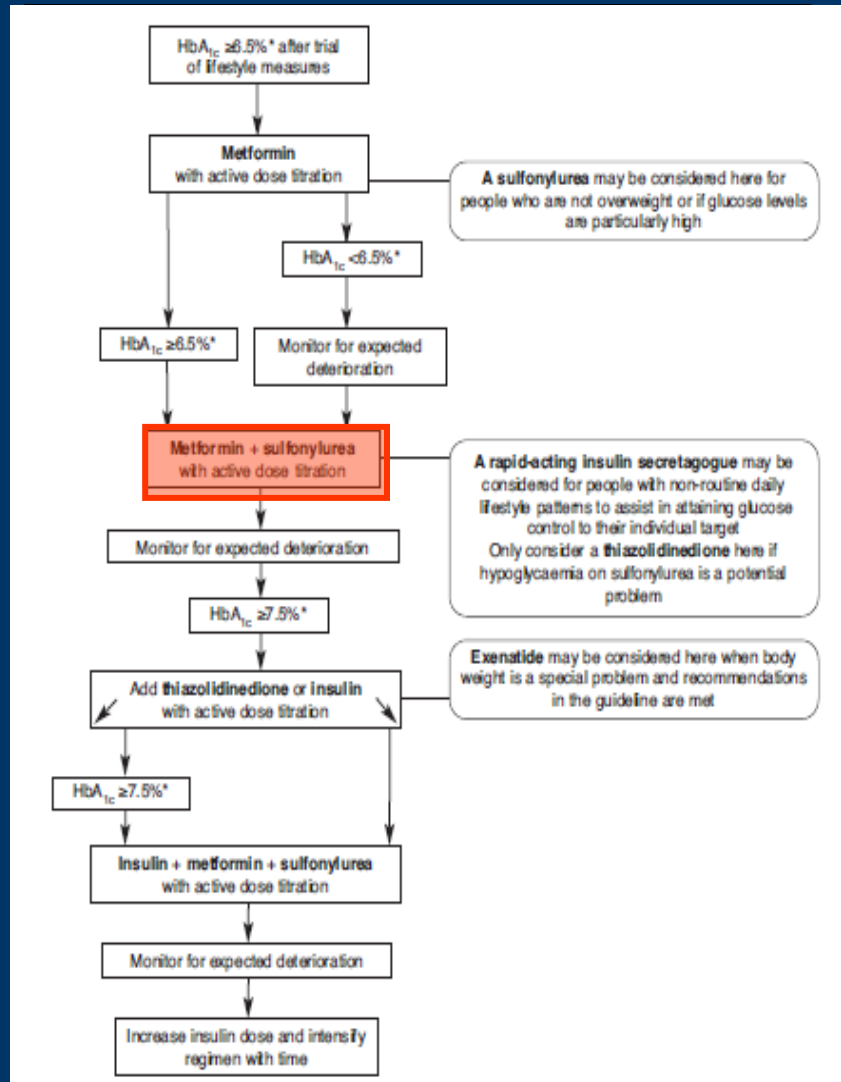


Holman RR. NEJM 2008;359

¡A veces lo viejo funciona bien!

SULFONILUREAS
¿Qué dicen los consensos?





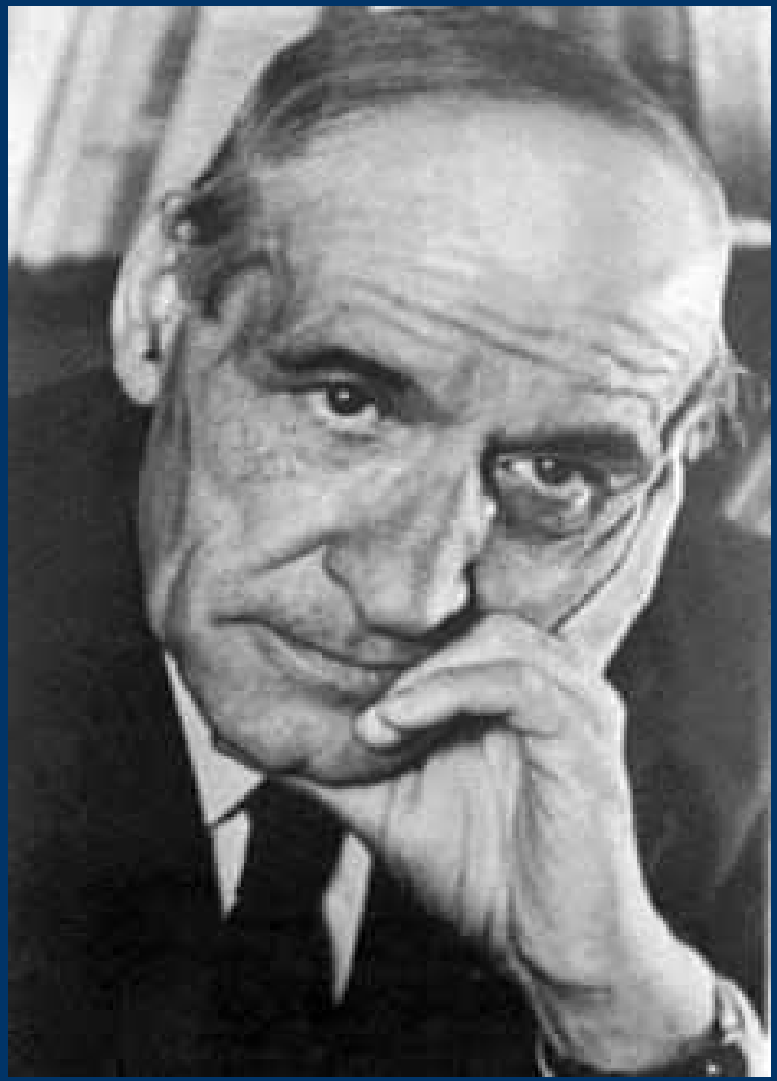
SULFONILUREAS
Conclusiones

- Efecto rápido y potente a corto plazo: reducción HbA1c 1-1.5%
- Menos eficaz a largo plazo que metformina y rosiglitazona (ADOPT)

- Previenen complicaciones microvasculares (UKPDS, ADVANCE)
- No evidencias firmes de cardiotoxicidad
  - No usar glibenclamida
  - Evitar en SCA y ACTP

- Ganancia de peso (3 kg)
- Hipoglucemias
  - No usar glibenclamida. Usar gliclazida, glimepirida, glipizida.
  - Titulación progresiva. Evitar dosis máximas
  - Vigilar interacciones medicamentosas y alcohol
  - Precaución en ancianos: alta hospitalaria, comorbilidad, polimedicación
  - Evitar en profesiones de riesgo

- Gliclazida: mejor perfil de seguridad (hipoglucemias, cardiovascular? betaprotección?)



José Ortega y Gasset (1983-1955)

Siempre que enseñes,
enseña a la vez
a dudar de lo que enseñas