

Inhibidores SGTL-2 2014



¿de qué se habla?

Dapaglifozina

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Madrid



- ✓ Oportunidad renal para el control de Glucosa
- ✓ Eficacia y Seguridad a corto y largo plazo del bloqueo SGTL-2
- ✓ Experiencia clínica en práctica real

Retos actuales en el tratamiento de la DM 2

Controlar la hiperglucemia

Mejorar el pronóstico cardiovascular

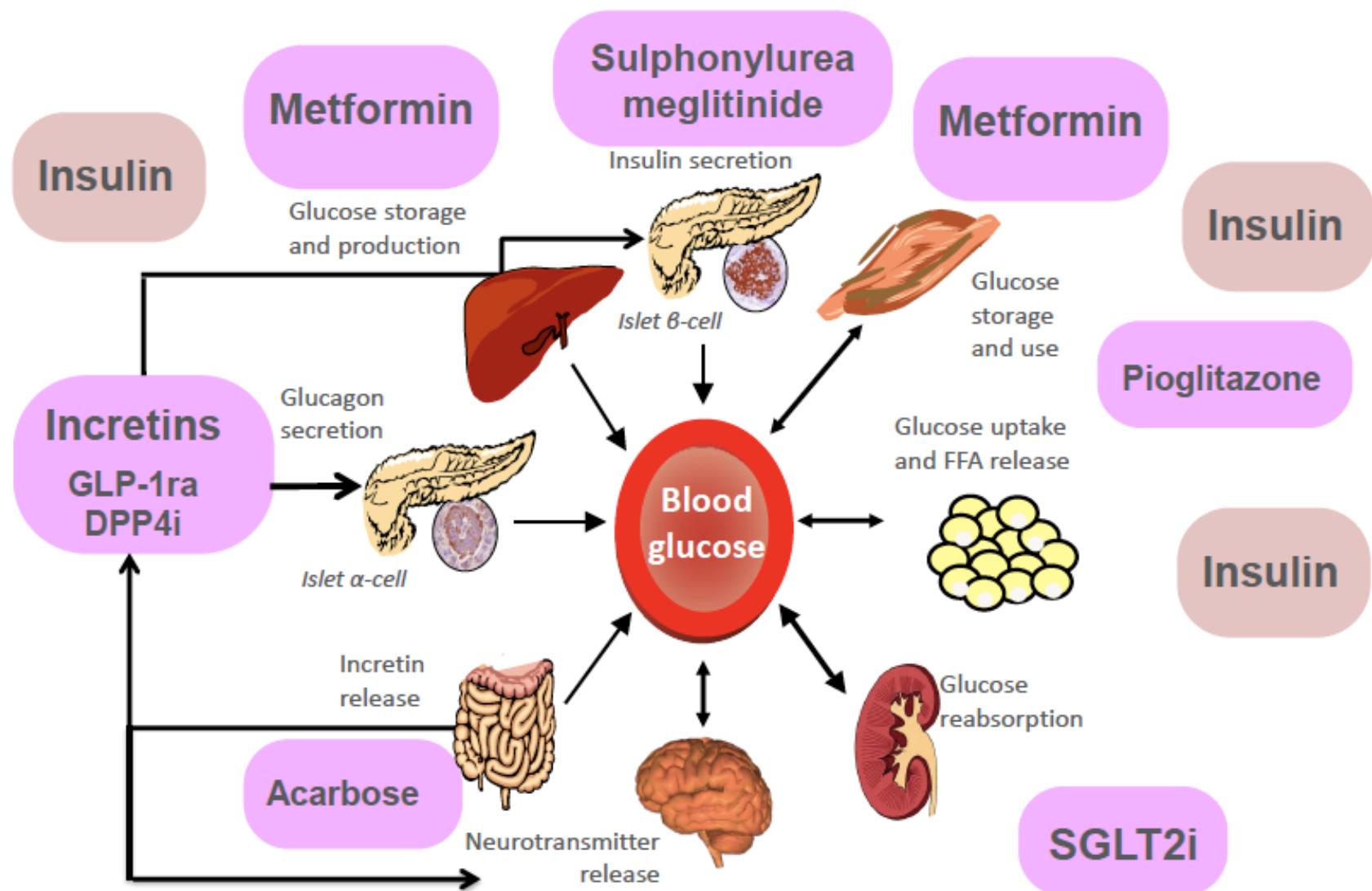
Abordar el control de peso

Minimizar efectos adversos

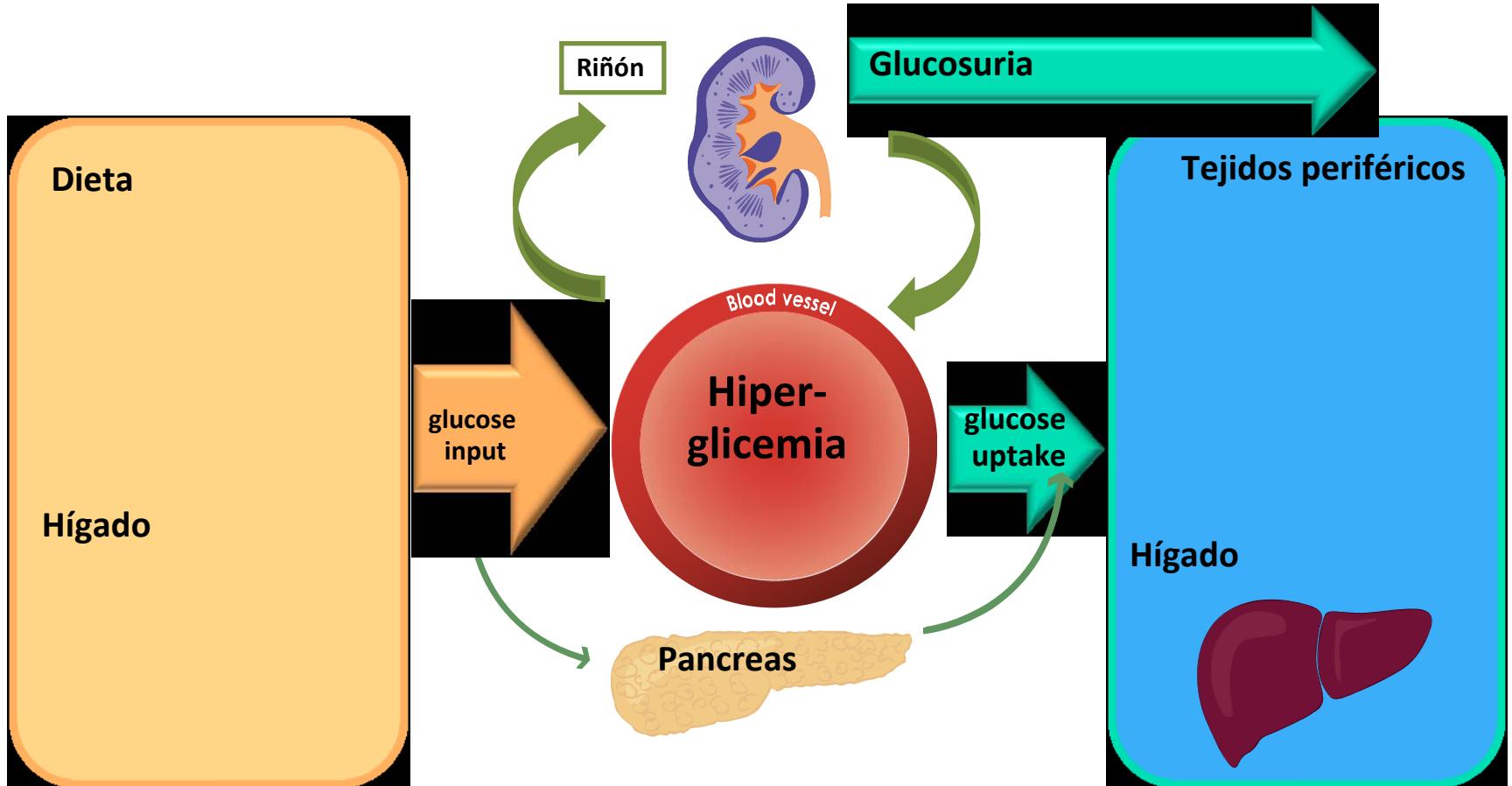
Aceptación del tratamiento

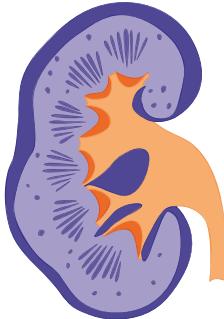


Órganos alterados en DM 2 y fármacos reguladores de la glucosa



La oportunidad “renal”



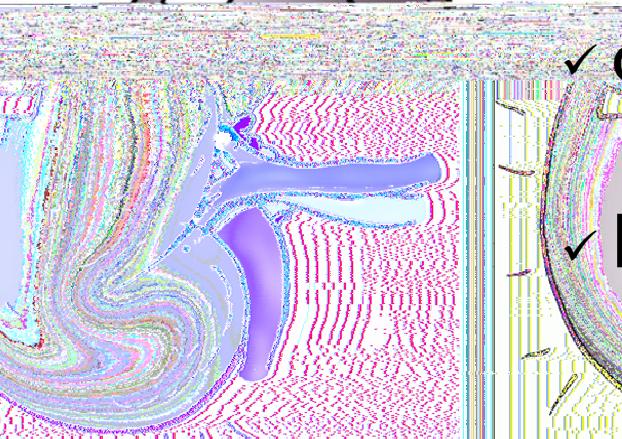


Agent	Company	
Dapagliflozin ^a	BMS and AZ— Astra	EU /3/13
Canagliflozin ^b	Johnson & Johnson	USA /3/13
Empagliflozin ^a	Boehringer Ingelheim	6/2014?
Ipragliflozin ^a	Astellas	Japón /1/14
Luseogliflozin ^a	Taisho	?
Tofogliflozin ^a	Chugai	?
LX4211 ^c	Lexicon	?

- a) Dapagliflozina aprobado Europa, Australia, Argentina, Brasil, Nueva Zelanda y USA

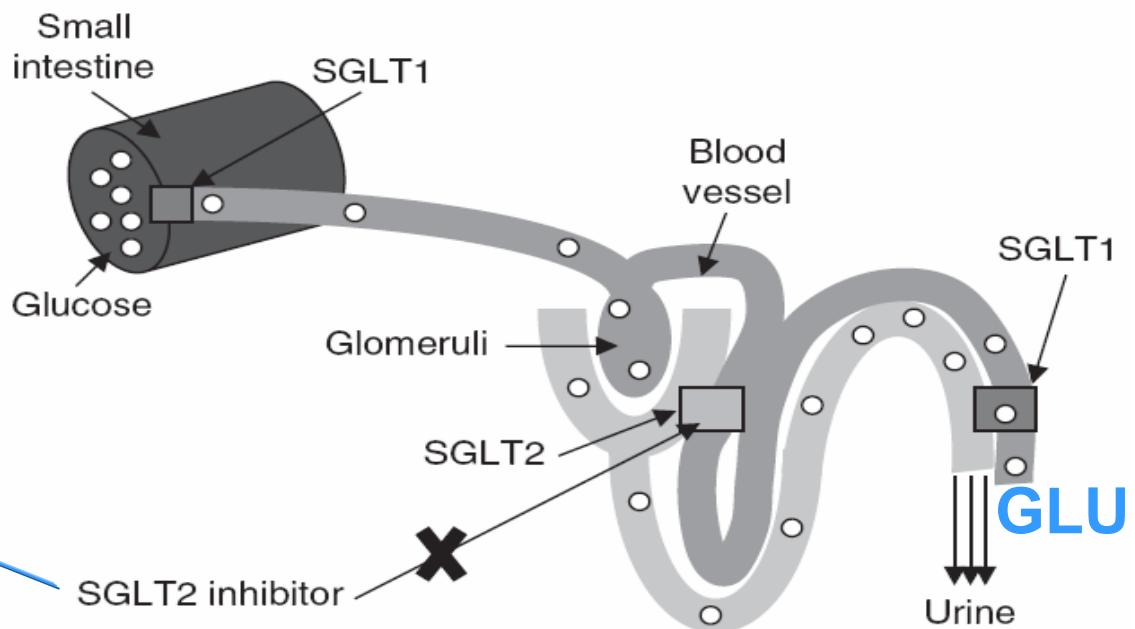


Papel del Riñón en homeostasis de Glucosa



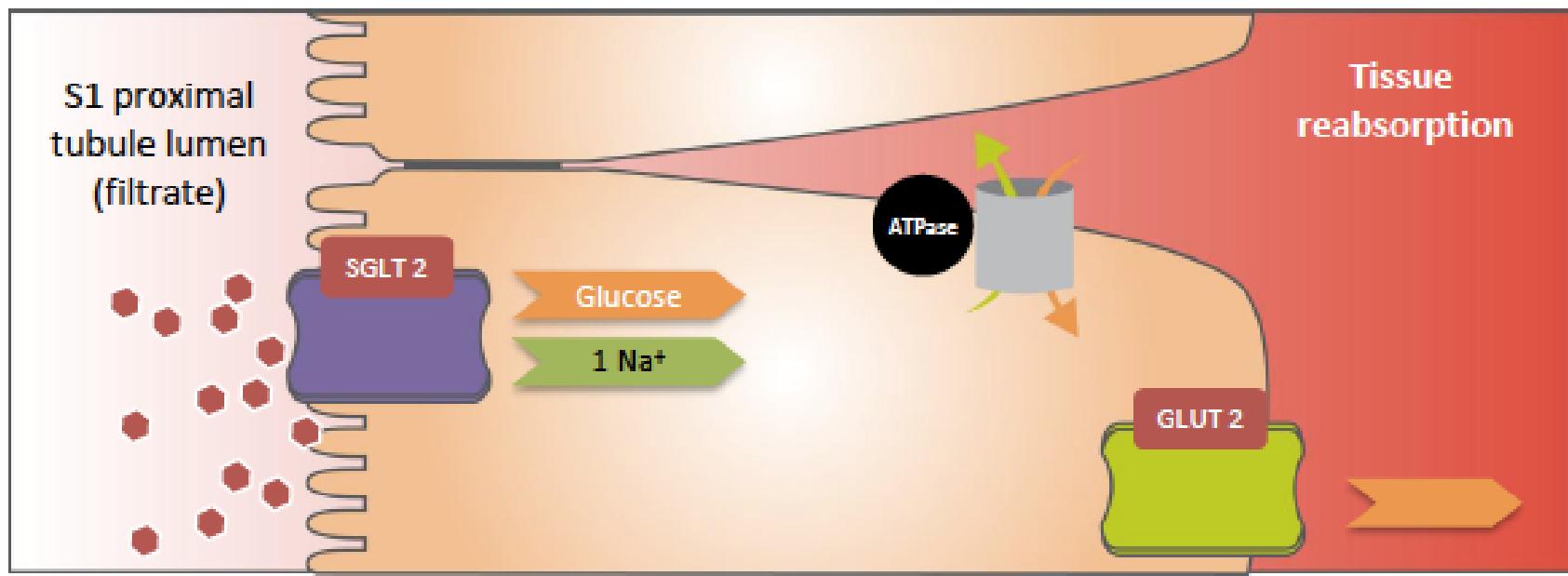
✓ Gluconeogénesis y Consumo de glucosa

✓ Reabsorción de glucosa (180 gr/d)



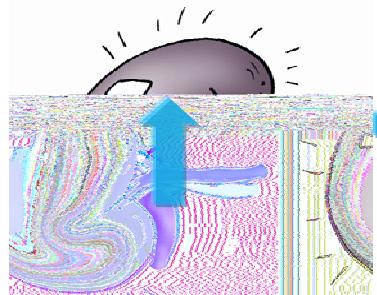
Sodio-glucosa co-transportadores (SGLTs)

Transporter	Major site of action	Function
SGLT1	Small intestine, heart, trachea and kidneys	Co-transports sodium, glucose and galactose across the brush border of the intestine and proximal tubule of the kidneys

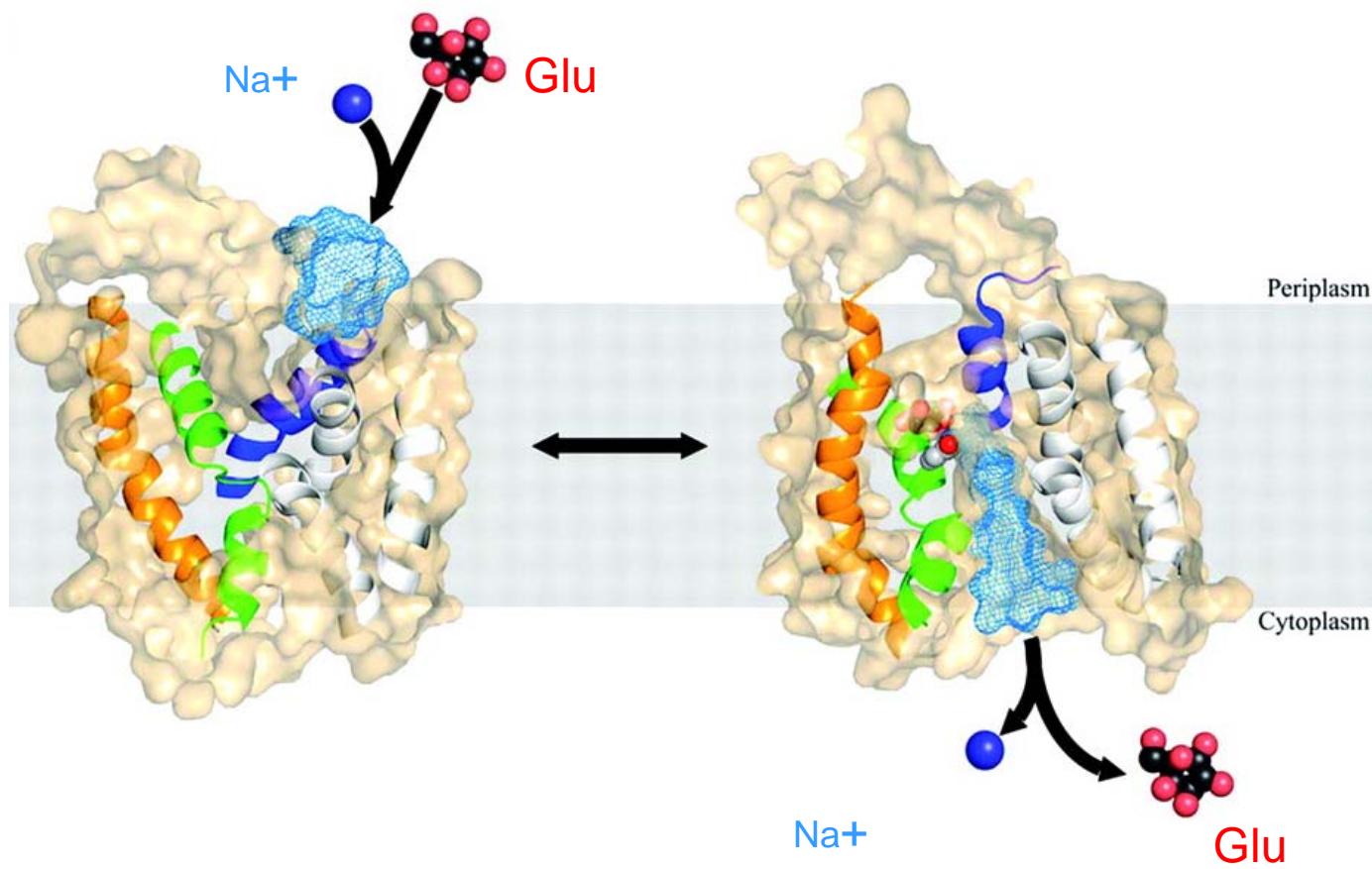


En la DM el aumento de la reabsorción de Glucosa contribuye a mantener la hiperglucemia

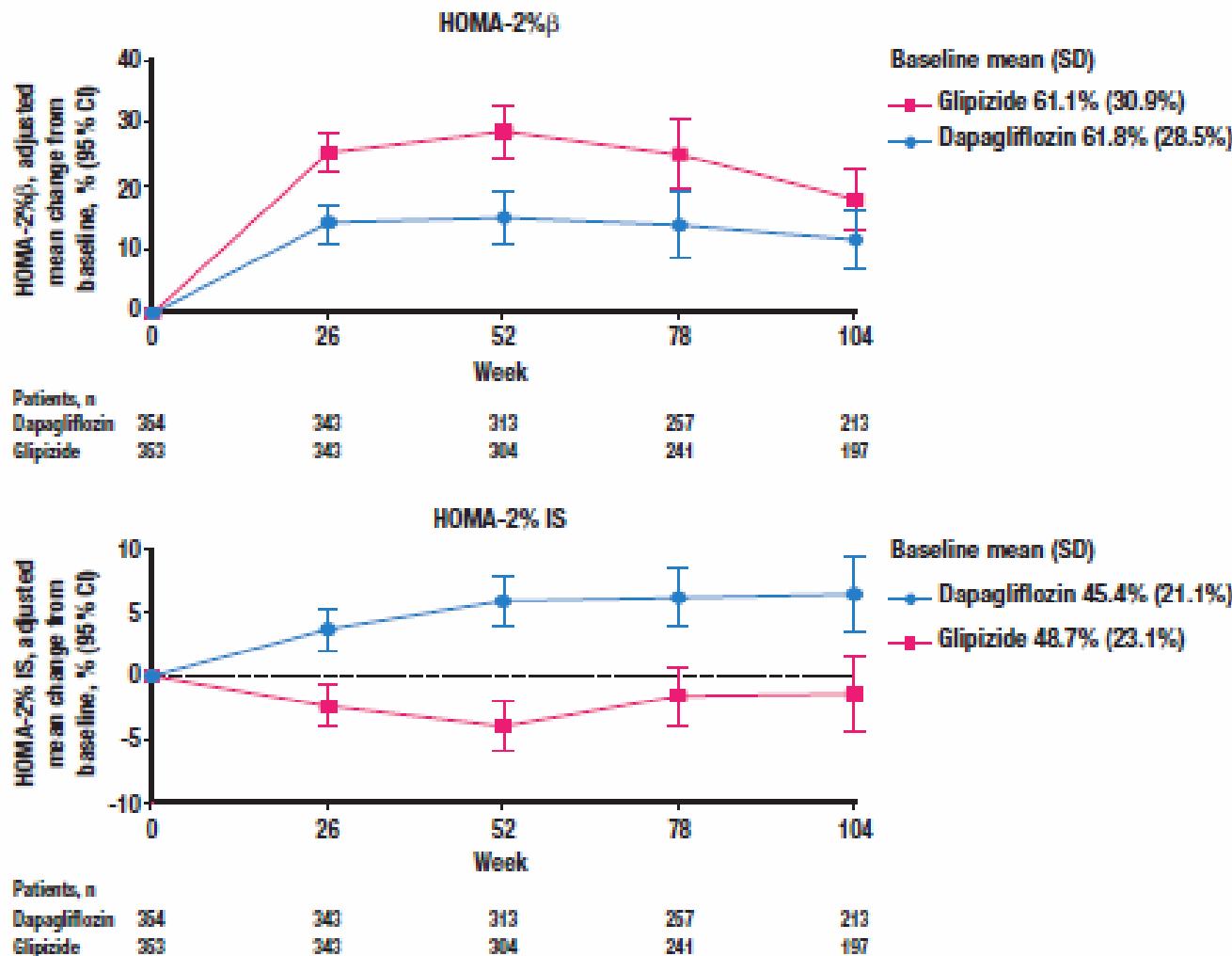
Hiperfiltración renal
propia de la DM



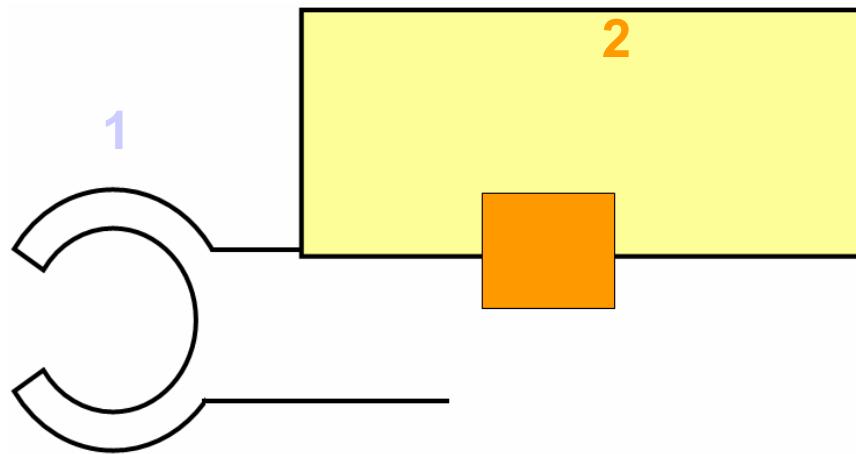
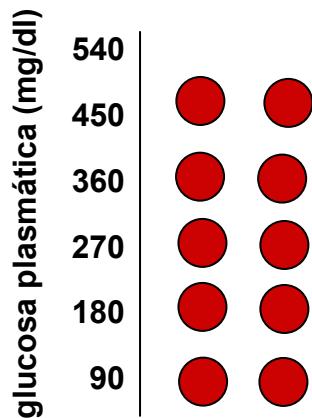
Glucotoxicidad
Deterioro Célula Beta

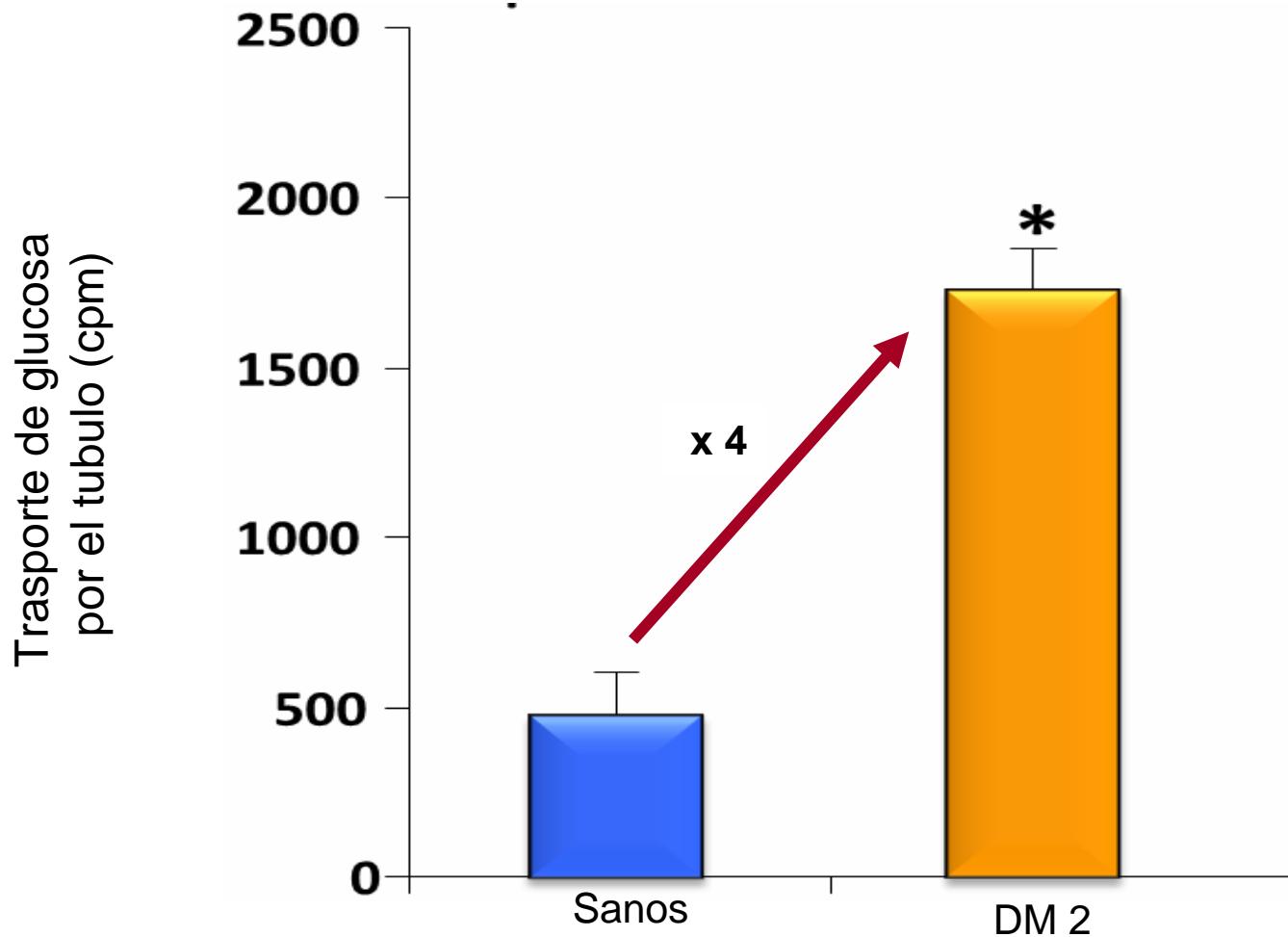


Dapagliflozina, Sensibilidad a la insulina y función de la Célula Beta



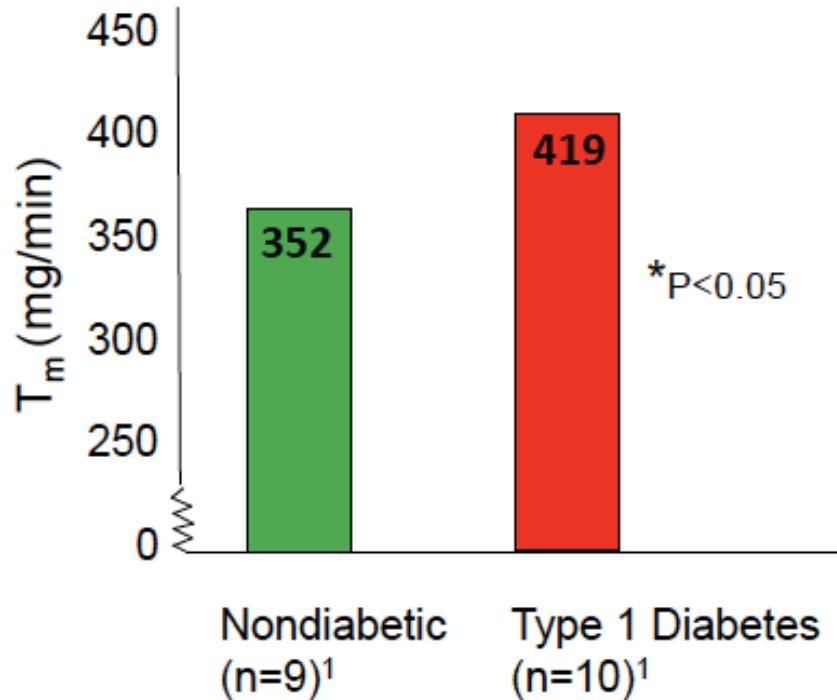
TUBULO PROXIMAL EN LA DM: AUMENTO REABSORCION DE GLUCOSA



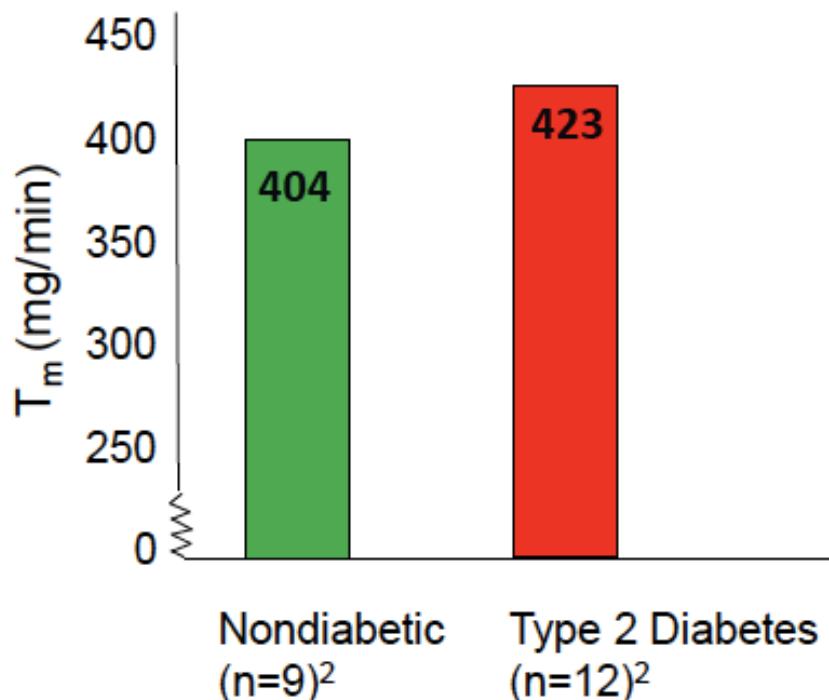


Aumento de reabsorción de Glucosa en pacientes con DM1 y DM 2

T_mG increased in Type 1 Diabetes

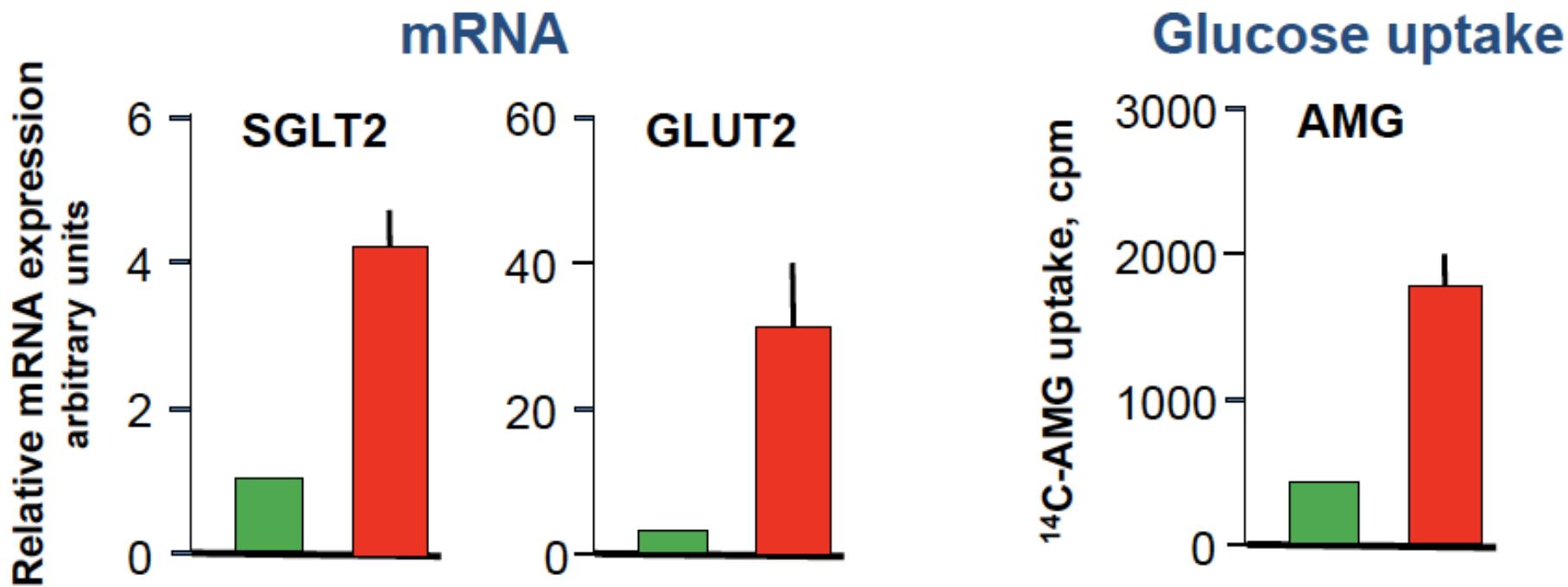


T_mG increased in Type 2 Diabetes



Renal threshold for glucose appears to be slightly raised in diabetic states

Expresión de STGTL-2, GLUT y Uptake de Glucosa en tubulo proximal renal en DM



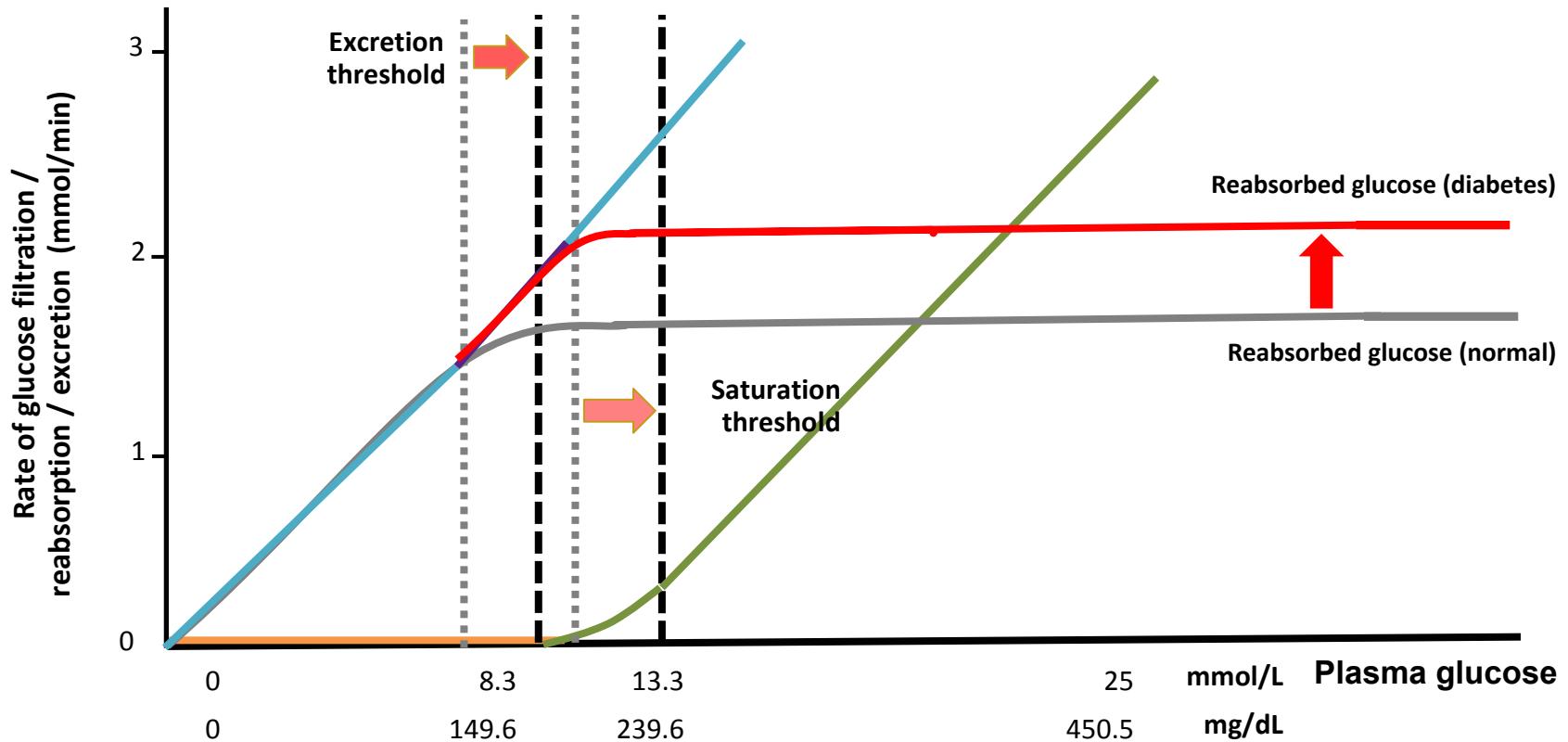
Renal proximal cells (HEPTECs) isolated from urine of healthy and T2DM subjects

mRNA expression of SGLT2 (n=4) and GLUT2 (n=5) in HEPTECs

Analyzed by real-time RT-PCR and normalized to GAPDH. Values are means ± SE (*P < 0.05).

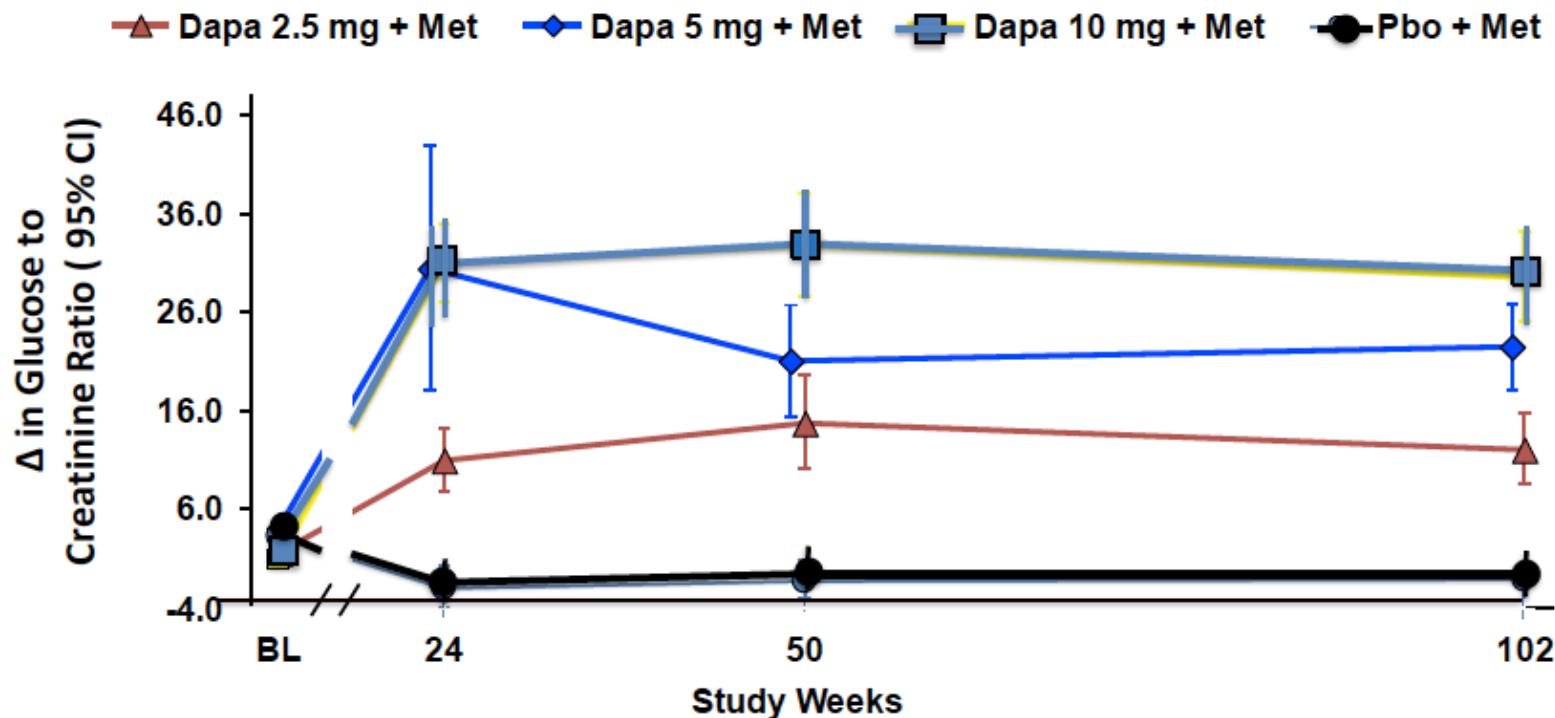
El aumento de reabsorción de glucosa en la DM contribuye a la hiperglucemia mantenida

Paradoxically, SGLT2 reabsorbs glucose through an insulin-independent pathway, even in the presence of hyperglycaemia



Adapted from Chao EC, et al. *Nat Rev Drug Discov* 2010;9:551-559; Marsenic O. *Am J Kidney Dis* 2009;53:875-883; Nairs S, et al. *J Clin Endocrinol Metab* 2010;95:34-42.

Mantenimiento de Glucosuria a lo largo de 2 años mediante bloqueo de SGTL-2 con Dapagliflozina



Number of Patients

Dapa 2.5 mg	127	111	113	75
Dapa 5 mg	127	116	109	81
Dapa 10 mg	125	115	111	84
Pbo + Met	124	114	102	67

Unadjusted mean change from baseline based on t-distribution, including data after rescue (observed values)

Bailey et al, Lancet 2010, 375, 2223-33; Bailey et al BMC Med 2013, 11, 43

El “experimento de la Naturaleza”

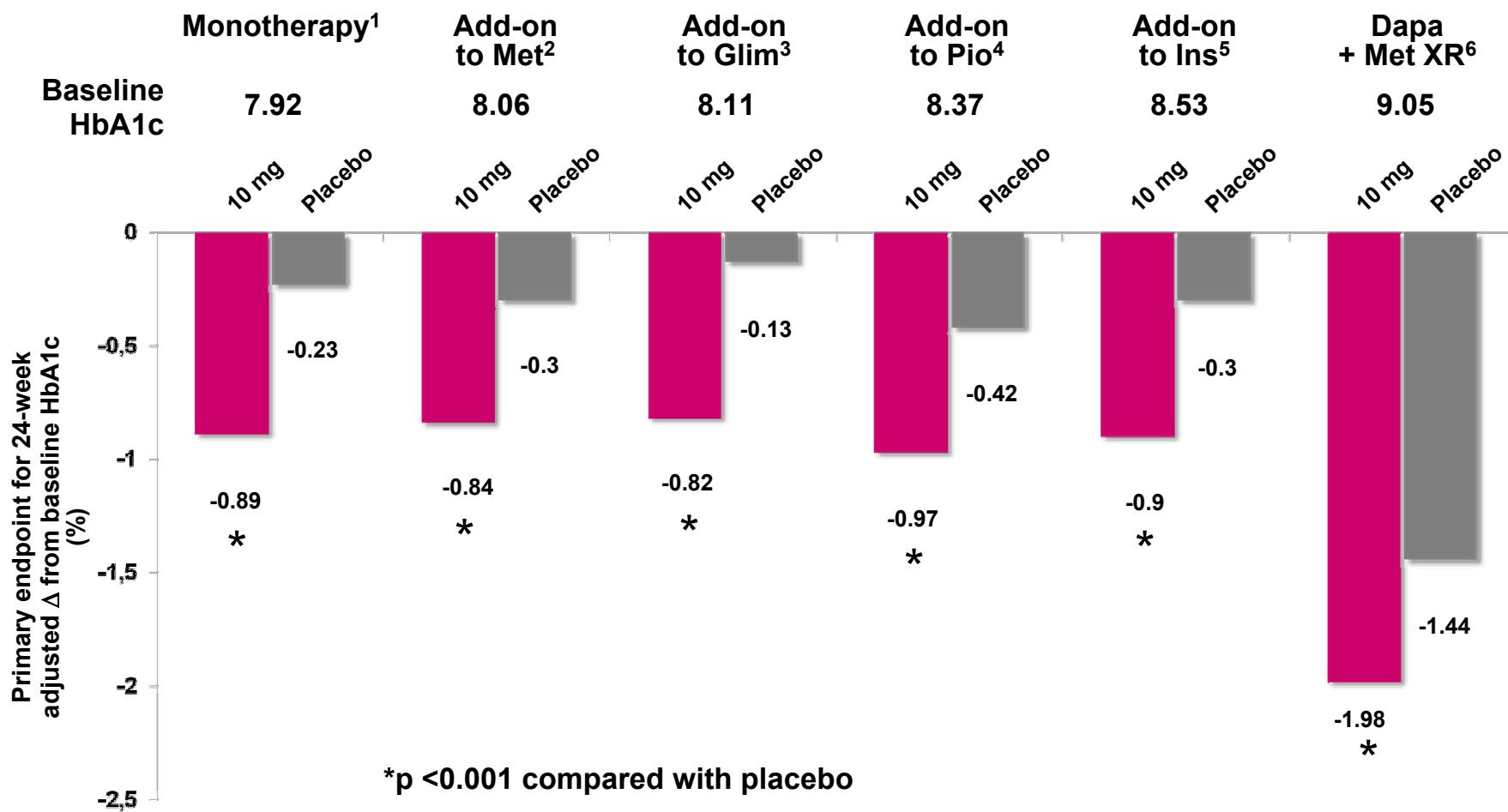
TRASPORTADO CON MUTACION	Condición con transporte alterado de GLUCOSA	SINTOMAS / PROBLEMAS
GLUT2	Fanconi–Bickel syndrome	Numerous symptoms, including enlarged liver, abdominal bloating and vitamin D-resistant rickets
SGLT1	Glucose–galactose malabsorption syndrome	Severe diarrhoea
GLUT1	De Vito disease	Numerous symptoms, including microcephaly and delayed mental and motor development

Adapted from Bays H. *Curr Med Res Opin* 2009;25:671–681.

Inh. SGTL-2: ¿de qué se habla?

- ✓ Oportunidad renal control de Glucosa
- ✓ Eficacia y Seguridad a corto y largo plazo del bloqueo SGTL-2
- ✓ Experiencia clínica en práctica real

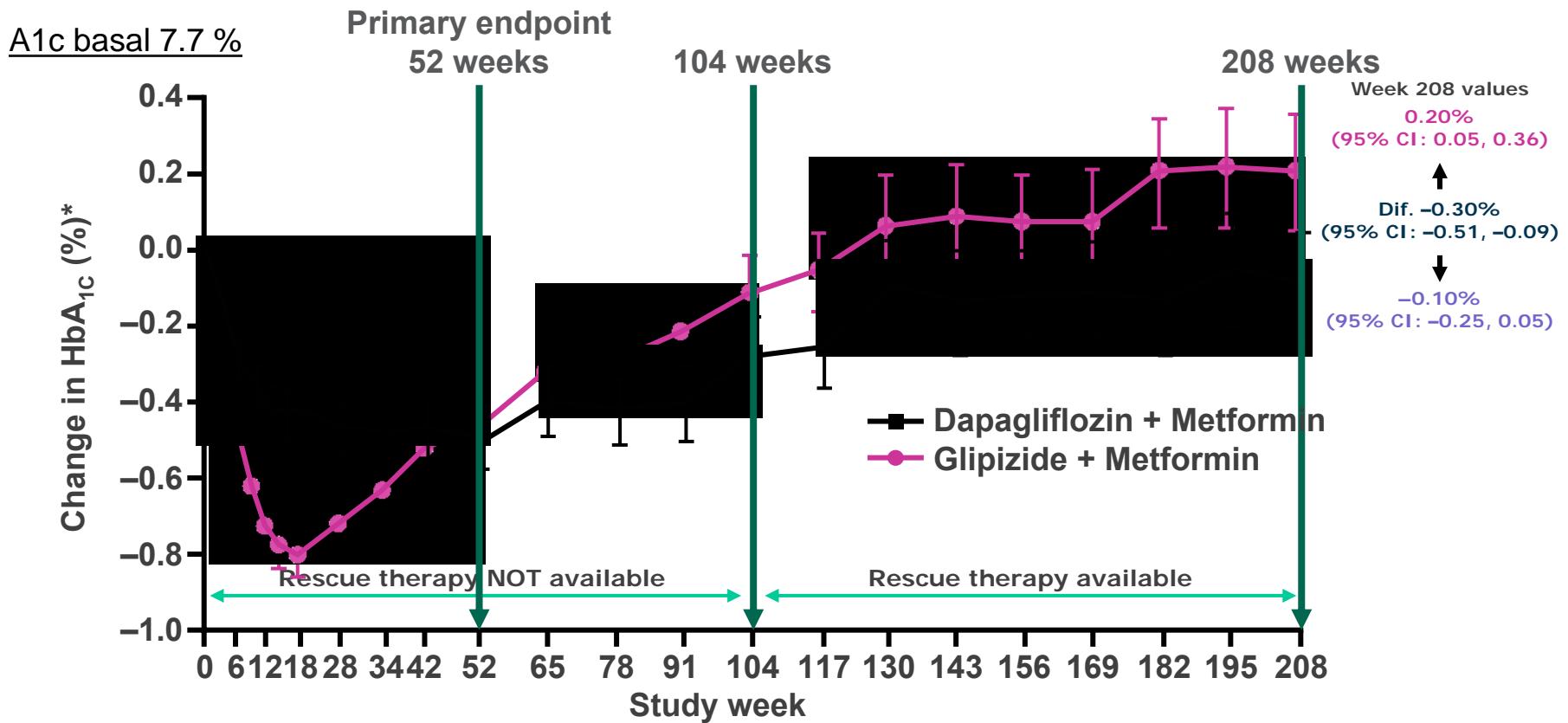
Descensos de HbA1c con dapagliflozina (24 semanas)



¹Ferrannini E, et al. *Diabetes Care* 2010;33:2217-24. ²Bailey CJ, et al. *Lancet* 2010;375:2223-33. ³Strojek K, et al. *Diabetes Obes Metab* 2011;13:928-38.

⁴Rosenstock J, et al. 71st ADA Scientific Sessions, San Diego, 24-28 June, 2011 Abstract 0986-P. ⁵Wilding J, et al. *Diabetes*. 2010;59 (Suppl 1):A21-A22. Abstract 0078-OR. ⁶Henry R, et al. 71st ADA Scientific Sessions, San Diego, 24-28 June, 2011 Abstract 307-OR.

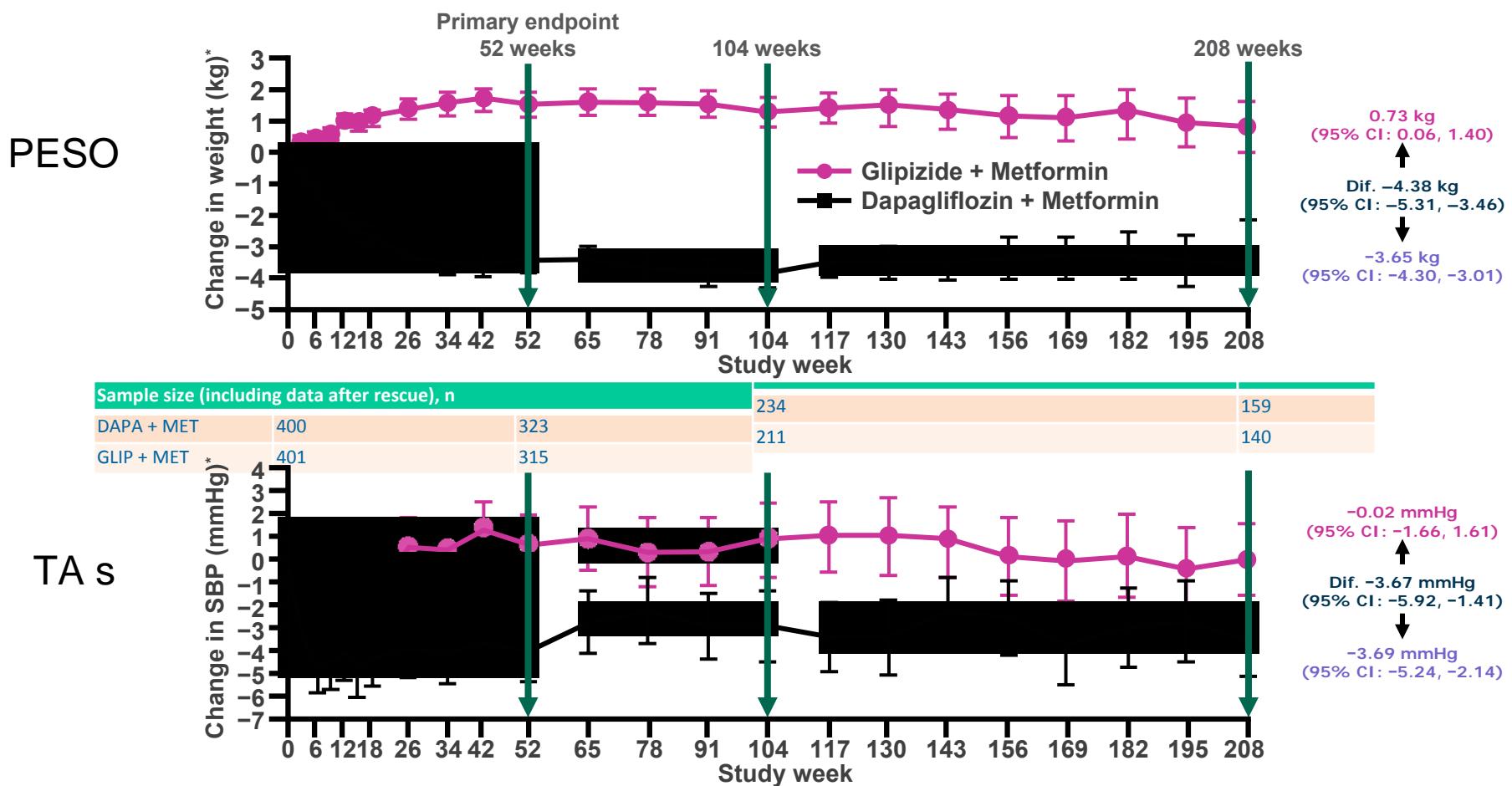
Estudio vs Glipizida: Control de la Glicada sostenido a 4 años



DAPA, dapagliflozin; GLIP, glipizide; MET, metformin.

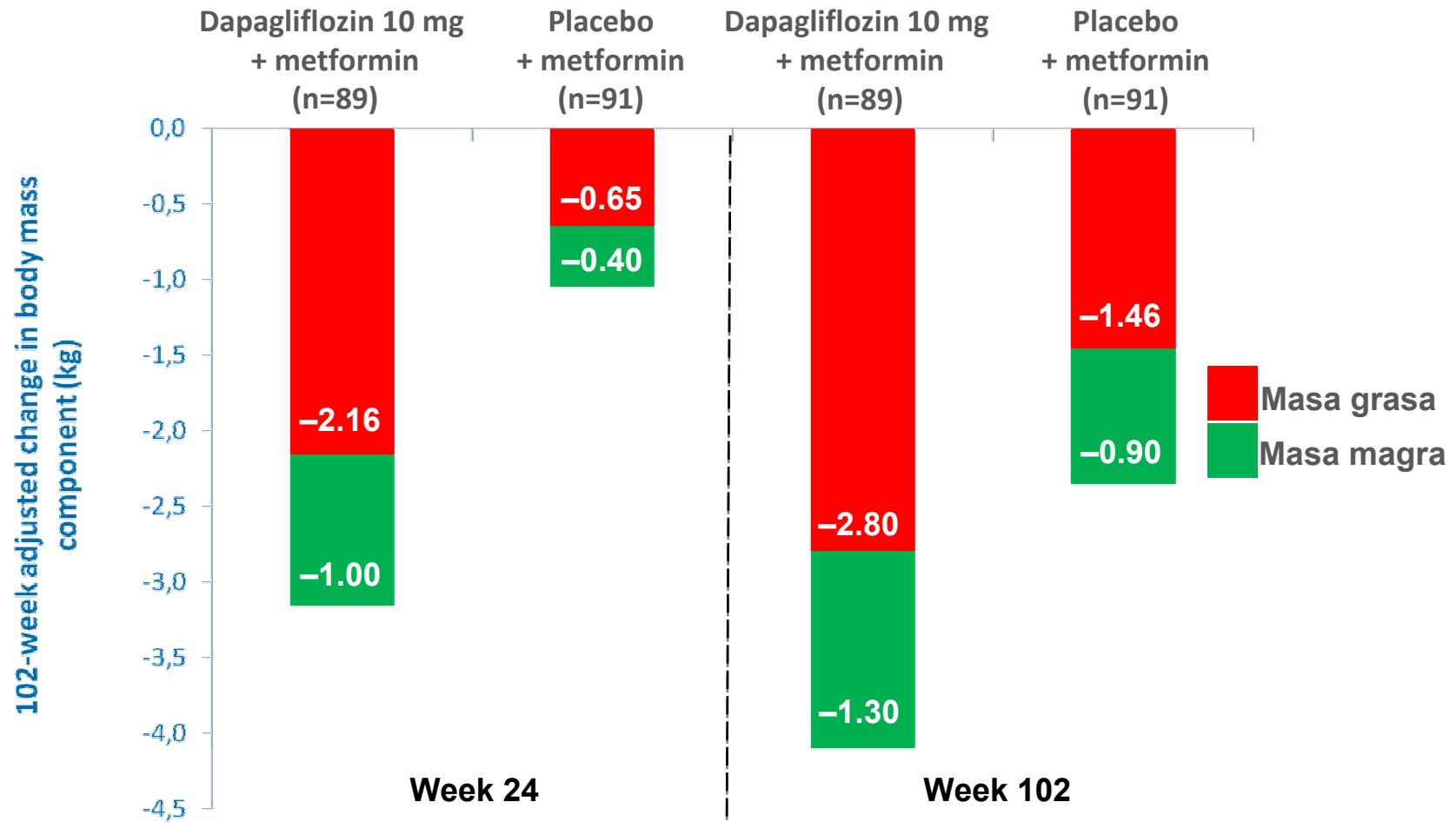
Del Prato S, et al. Presented at the 73rd American Diabetes Association Scientific Sessions, Chicago, USA; 21–25 June 2013: Abstract 62-LB.

Estudio vs Glipizida: Perdida de peso y descenso de PAS sostenidos en estudio a 4 años



Data are adjusted mean change from baseline; 95% CIs derived from a repeated-measures mixed model.
Del Prato S, et al. Presented at the 73rd ADA Scientific Sessions, Chicago, USA; 21–25 June 2013: Abstract 62-LB.

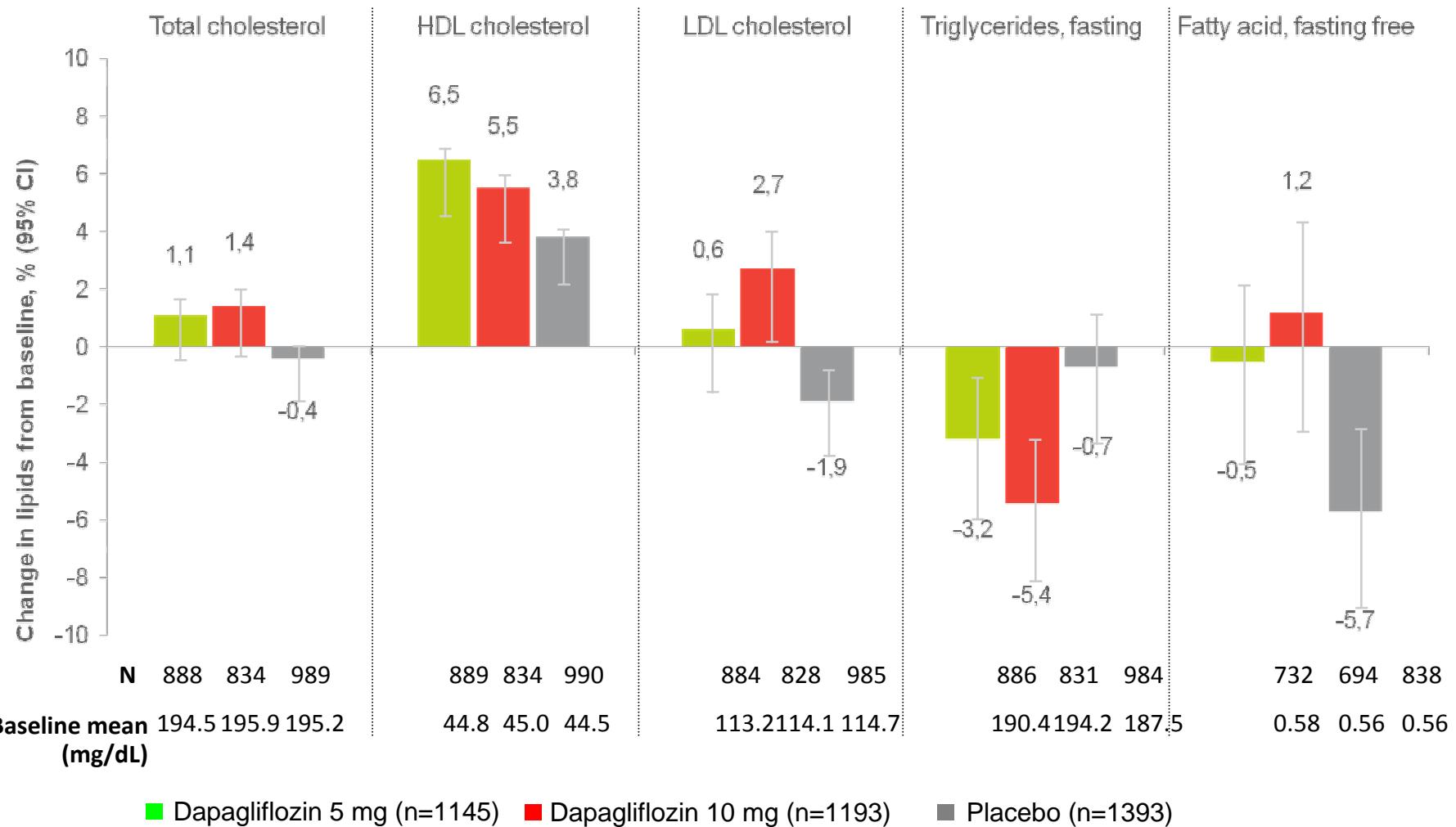
Cambios de masa grasa y de masa magra (medido por DXA)



*Data are adjusted mean change from baseline derived from a mixed model and include data after rescue therapy.

Bolinder J, et al. Diabetes, Obesity and Metabolism 16: 159-169, 2014.

Cambio en Lípidos con Dapagliflozina (%)



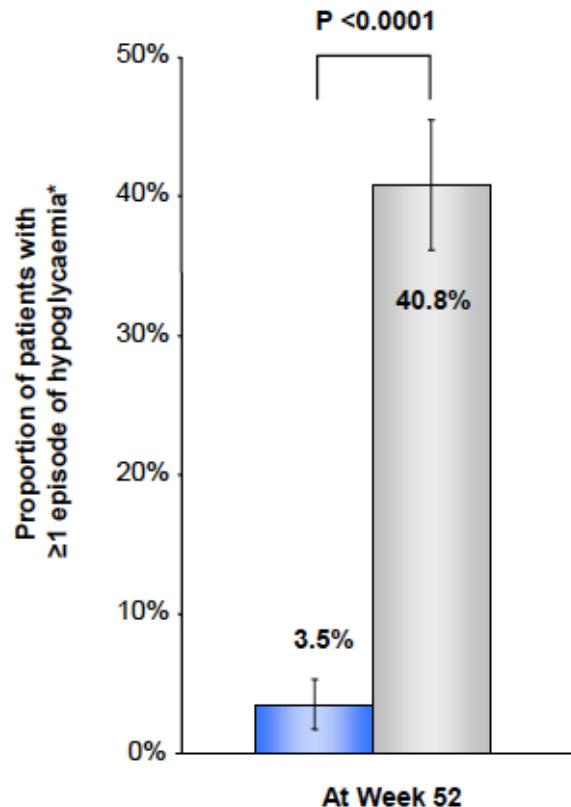
Placebo-controlled pool – short-term double-blind treatment period, including rescue. Data set: Treated patients.

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Hardy E. Dapagliflozin Effects on the Lipid Profile of Patients with Type 2 Diabetes Mellitus 1188-P ADA 2013.

Hipoglucemias

Dapagliflozin + metformin
(n = 400) Glipizide + metformin
(n = 401)

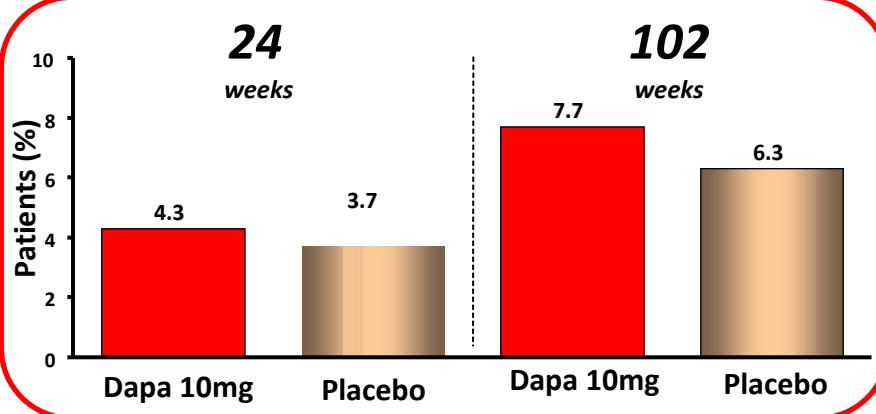


	Dapagliflozin + metformin (n=406)	Glipizide + metformin (n=408)
Total hypoglycaemic events [†] , n (%)	14 (3.4) [‡]	162 (39.7) [‡]
Major episode	0	3 (0.7)
Minor episode	7 (1.7)	147 (36.0)
Other episode	7 (1.7)	40 (9.8)

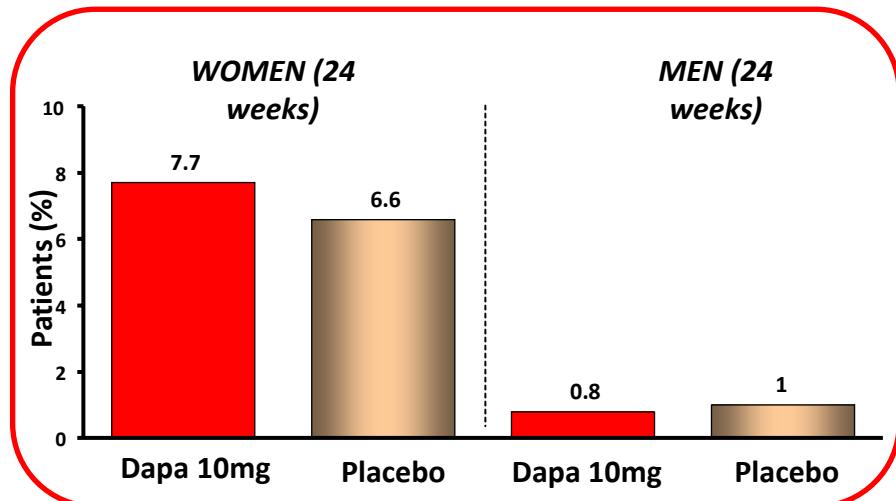
*Dapagliflozin difference from glipizide -37.2% (95% CI -42.3 to -21.2, p<0.0001)

[†] Major hypoglycaemia was defined as a symptomatic episode requiring external assistance, glucose <3.0 mmol/L; minor defined as symptomatic or asymptomatic.

Efectos Adversos: Infecciones del tracto urinario:

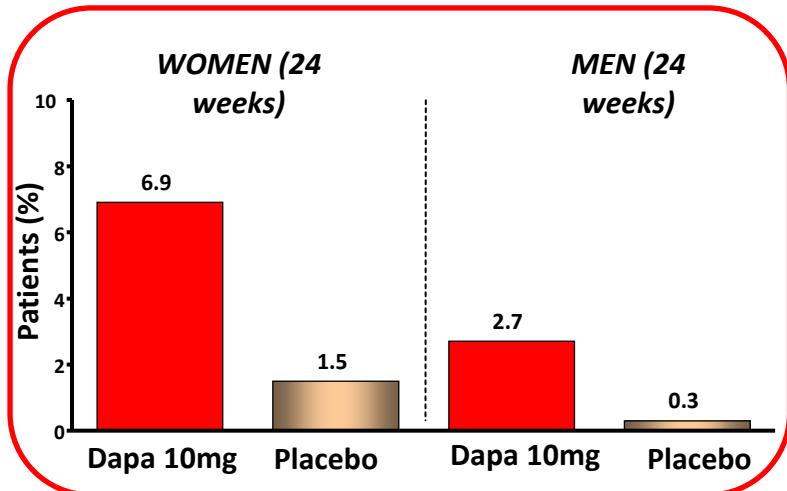
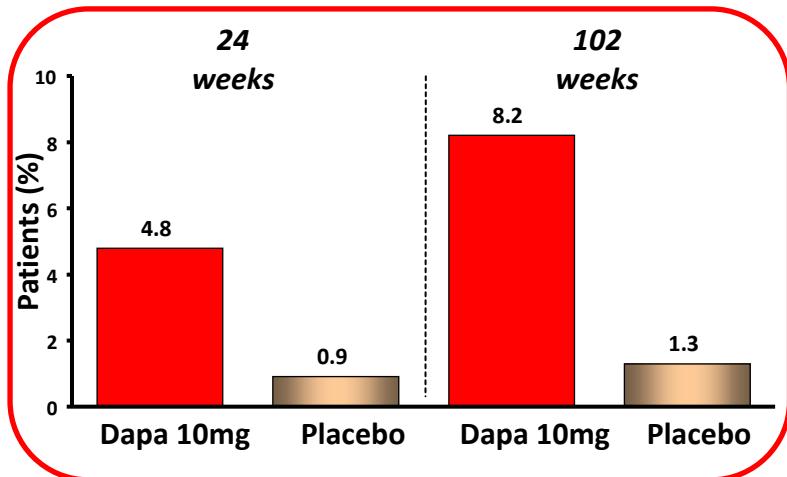


Resumen de los datos acumulados



- Todas de Intensidad leve/moderada
- La mayoría respondieron a un ciclo de tratamiento estándar
- Raramente llevaron a discontinuación (0.3%)
- La mayoría de pacientes solo 1 episodio a las 102 semanas (74.6% de dapa vs 86.4% placebo)
- Infecciones urinarias de tracto superior muy raras y balanceadas entre ambos grupos

Infecciones genitales: Resumen de los datos acumulados



- Todas de Intensidad leve/moderada
- La mayoría respondieron a un ciclo de tratamiento estándar
- Raramente llevaron a discontinuación (0.2%)
- La mayoría de pacientes solo 1 episodio a las 102 semanas (74.6% dapa vs 77.8% placebo)

Metabolismo fosfocálcico y alteraciones de laboratorio

Placebo-controlled pool – Short-term period

	N	Dapagliflozin	Dapagliflozin 10 mg	
			Change at week 24 (SE)	Baseline
Urinary-Calcium*	47	No effect		
Serum-Calcium	935	No effect		
Serum-Magnesium (mEq/L)	936	↑	0.07 (0.01)	1.71
Serum-Phosphorous (mg/dL)	935	↑	0.17 (0.02)	3.58
Serum-parathyroid hormone (pg/mL)	914	↑	1.8 (0.58)	37.7
Serum-25-OH Vitamin D	812	No effect		
Serum-1,25-OH Vitamin D*	47	No effect		

N = range 812–936 for dapagliflozin 10 mg dose

*From 12 week Phase 2b study (dapagliflozin 10 mg, n = 47)

Metanálisis de efectos Adversos

Frequency of reactions related to volume depletion*	All events
Dapagliflozin 10 mg	0.8%
Control	0.4%

*Including dehydration, hypovolaemia, or hypotension.

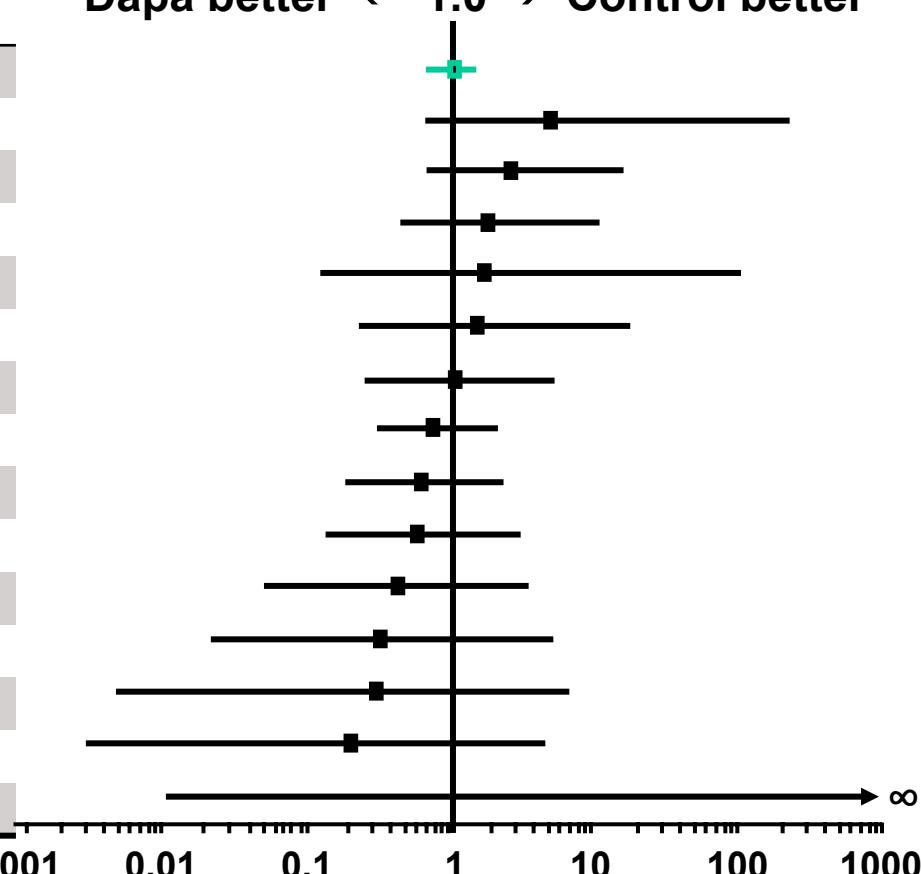
- Serious events relating to volume depletion occurred in <0.2% of patients and were comparable between groups

Incidencia de tumores

Tumour Origin	N =	Events	
		All dapagliflozin 5501	Control 3184
Subjects with Tumour Events*		81	43
Bladder		9	1
Prostate (male only)		10	3
Breast (female only)		10	3
Hepatobiliary		3	1
Pancreatic		5	2
Thyroid and Endocrine		7	4
Skin		15	10
Respiratory and Mediastinal		8	6
Gastrointestinal		6	4
Blood and Lymphatic		3	3
Metastases and Site unspecified		2	2
Female Reproductive		1	2
Renal Tract		1	2
Musculoskeletal and Soft Tissue		1	0

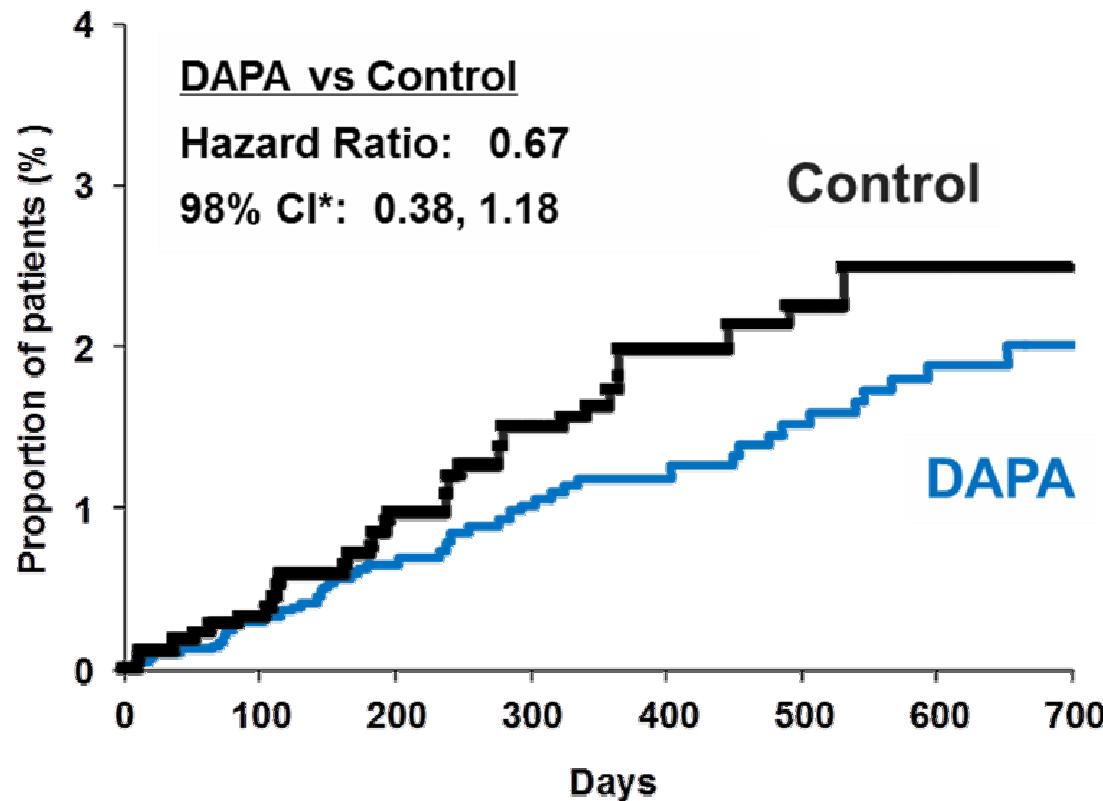
Dapagliflozin:control exposure ratio ~ 1.8

Incidence Rate Ratio with 95% CI
Dapa better ← 1.0 → Control better



*Incidence Rate Ratio = 1.047, 95% CI: (0.702 - 1.579)

Metaanalisis de seguridad Cardiovascular (pool de estudios)



Number of patients

DAPA	4097	3826	2767	2350	1532	1368	1062	585
Control	1850	1696	1197	1004	622	538	415	233

Inh. SGTL-2: ¿de qué se habla?

- ✓ Oportunidad renal control de Glucosa
- ✓ Eficacia y Seguridad a corto y largo plazo del bloqueo SGTL-2
- ✓ Experiencia clínica en práctica real

Dapagliflozin: indications and exclusions

- **Indication. Type 2 diabetes**
 - monotherapy (if diet and exercise inadequate and metformin inappropriate)
 - combination with other glucose-lowering products including insulin
- **Exclusions**
 - type 1 diabetes mellitus or for treatment of diabetic ketoacidosis
 - concomitantly treated with pioglitazone
 - moderate to severe renal impairment (<60 ml/min).
 - monitoring of renal function recommended before and at least annually
 - more frequent renal monitoring if adding medicines that may reduce renal function and for patients approaching moderate renal impairment.
 - not recommended aged \geq 75 years due to limited experience
 - not recommended if volume depleted, eg. acute GI illness
 - not recommended to initiate if receiving a loop diuretic
- **Cautions**
 - in mild or moderate hepatic impairment start with 5 mg
 - haematocrit may increase: caution if haematocrit already elevated.

Benefits

- Insulin independent action
- Sustained reductions in HbA_{1c}
- Secondary benefit of weight loss
- Low risk of hypoglycaemia
- Oral, once daily dosing
- Can assist blood pressure control
- Compatible with other diabetes therapies
- Few drug interactions
- CV events well inside FDA requirements

Risks

- Mycotic genital infection
- Urinary tract infection
- Increased haematocrit
- Polyuria - dehydration
- Hypotension
- Bladder cancer ??
- Hypersensitivity reactions
- Unknown long-term AEs

Limitations

- Renal function >60 ml/min (monitor as appropriate)
- No experience in elderly (>75 yrs)
- Not in acute GI or other potentially hypovolemic states
- Not with loop diuretic
- Not with pioglitazone

Initial use in UK

- **UK**
 - Approved EMA Dec 2012, available Jan 2013
 - Reviewed by Scottish Medicines Consortium Mar 2013
recommended as add-on to metformin
 - Nominal use in rest of UK until re-reviewed by NICE in May 2013
 - NICE recommended use similarly to DPP4i
- **Germany**
 - Initial high rate of new prescriptions
~30,000 in first 3 months, similar to sitagliptin
 - Use by primary care mostly as add-on to metformin
 - Use by secondary care mainly as either triple therapy (not in Australia) to defer insulin or as add-on to insulin
 - Nearly all obese/overweight patients who are only modestly above target



Issue date: June 2013

Information for the public

Dapagliflozin given with other drugs for type 2 diabetes

Why has NICE said this?

NICE looks at how well treatments work, and also at how well they work in relation to how much they cost the NHS.

NICE recommended dapagliflozin taken with metformin or insulin because these treatments work as well as or better than other treatments available on the NHS, and are good value for money.

NICE did not recommend dapagliflozin taken with metformin and a sulfonylurea except as part of a clinical trial because there is not enough evidence to decide whether this treatment works as well as other treatments available on the NHS.

Dapagliflozin compared with other oral anti-diabetes treatments when added to metformin monotherapy: A systematic review and network meta-analysis

Diabetes Obes Metab. 2013 Nov 14. doi: 10.1111/dom.12239. [Epub ahead of print]

Goring SM, Hawkins N, Wygant G, Roudaut M, Townsend R, Wood I, Barnett A

METODOLOGÍA

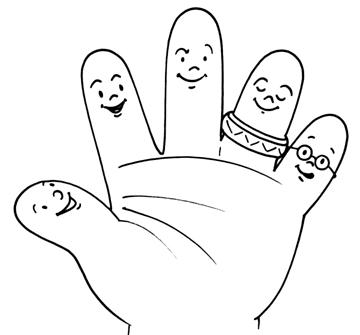
A systematic literature review and Bayesian network meta-analysis (NMA) of RCTs involving anti-diabetes treatments added to metformin were conducted. RCTs enrolling subjects with type 2 diabetes inadequately controlled on metformin monotherapy were included. Comparators included dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones (TZDs), glucagon-like peptide-1 (GLP-1) analogues, and dapagliflozin. Outcomes of interest were: mean change from baseline HbA_{1c}, weight and systolic blood pressure, and incidence of hypoglycaemia.

CONCLUSIÓN

Compared with existing licensed anti-diabetes therapies added to metformin, after one year, dapagliflozin offers similar HbA_{1c} control with either similar or reduced risk of hypoglycaemia and the additional benefit of weight loss. This analysis provides an important perspective on the clinical utility of dapagliflozin compared with existing anti-diabetes treatments.

Inh. SGTL-2: ¿hay un perfil preferente?

- ✓ Un paciente con A1c alcanzado > deseable, con metformina
- ✓ Reticente a terapia parenteral y especialmente indeseable hipoglucemias
- ✓ Motivado para perder peso, y control de otros Factores de Riesgo Cv
- ✓ Sin A.P. de inf genitorurinarias, hematurias ni Ins. Renal ($FG < 60 \text{ ml/m}$)
- ✓ Entendiendo mecanismo (¡ojo! Adherencia Terapeútica)



Muchas gracias