Nuevos hipoglicemiantes orales

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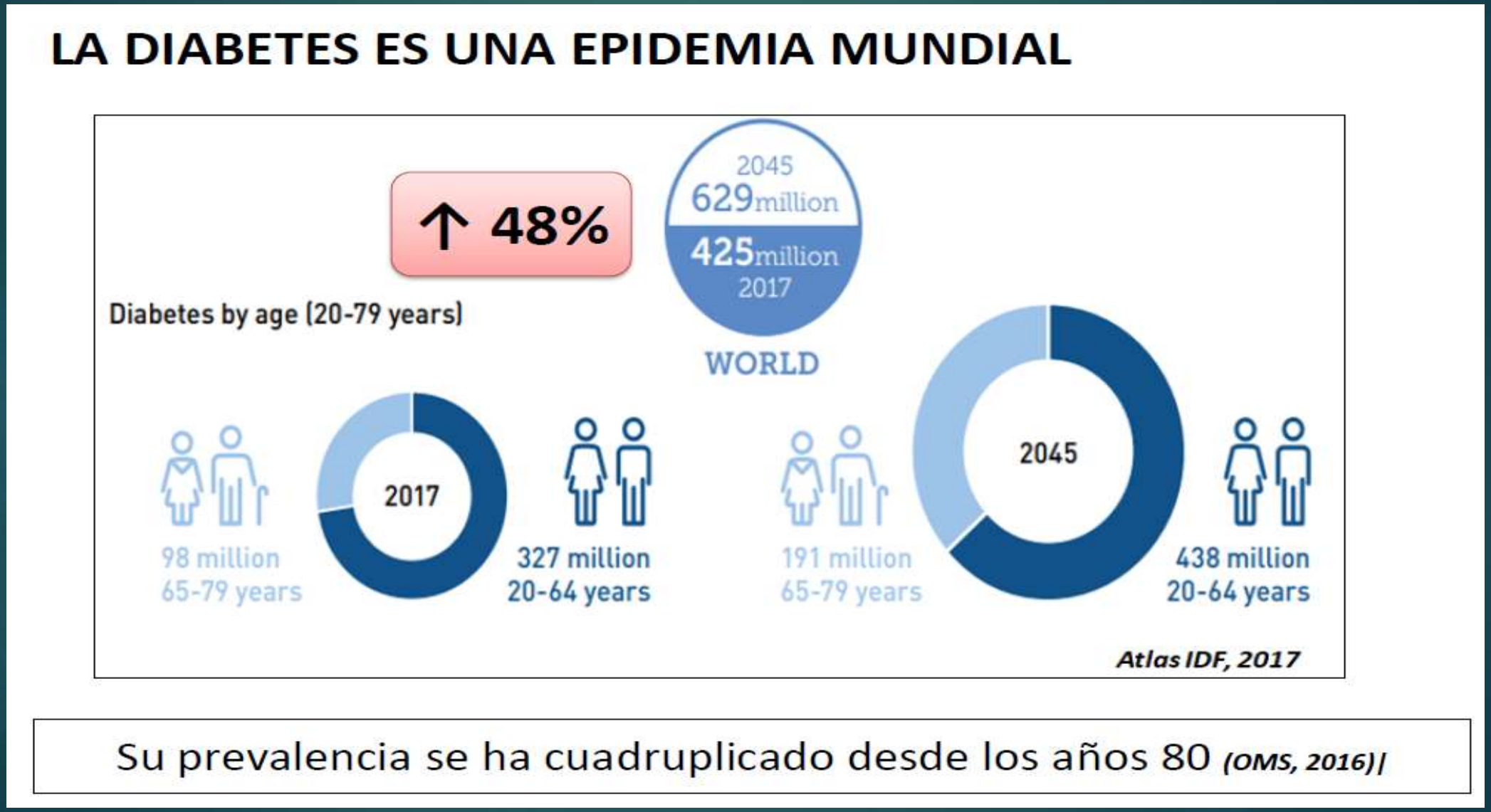
04 DE SEPTIEMBRE 2019

Lo que aprenderemos hoy

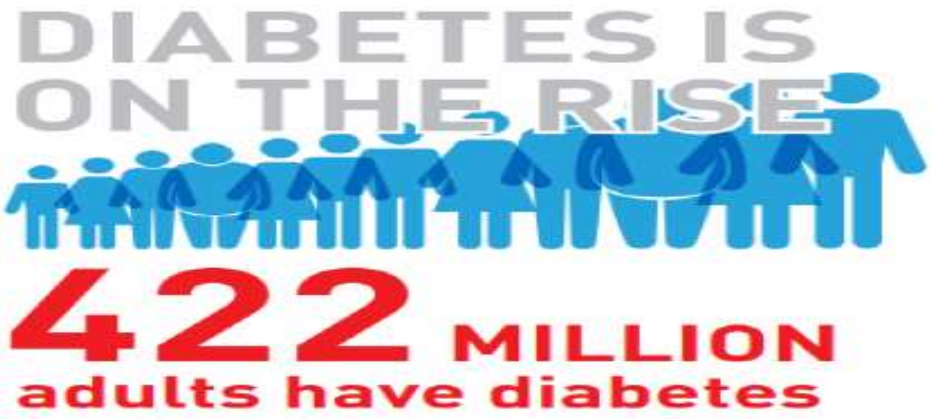
- ¿Qué es el efecto incretina y cuáles son los mecanismos fisiopatológicos involucrados?
- ¿Cuáles son los fármacos incretinomiméticos y sus características farmacológicas?
- ¿Cuáles son las principales indicaciones, contraindicaciones y efectos adversos?
- Efectos farmacológicos de la inhibición SGLT-2
  - Efectos glicémicos
  - Efectos extraglicémicos
- Protección renal
- Efectos adversos

INTRODUCCIÓN



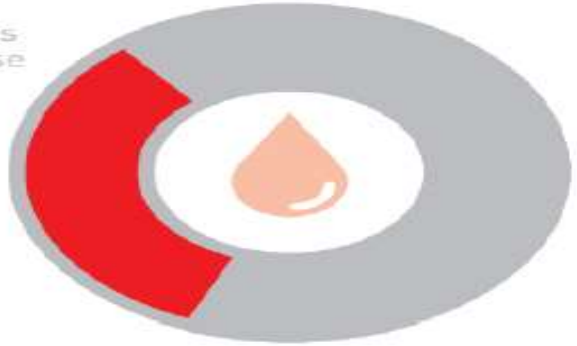
Su prevalencia se ha cuadruplicado desde los años 80 *(OMS, 2016)*

INTRODUCCIÓN



3.7 MILLION
deaths due to diabetes
and high blood glucose

1.5 MILLION
deaths caused
by diabetes



OMS, 2016

Encuesta Nacional de Salud 2016 -2017

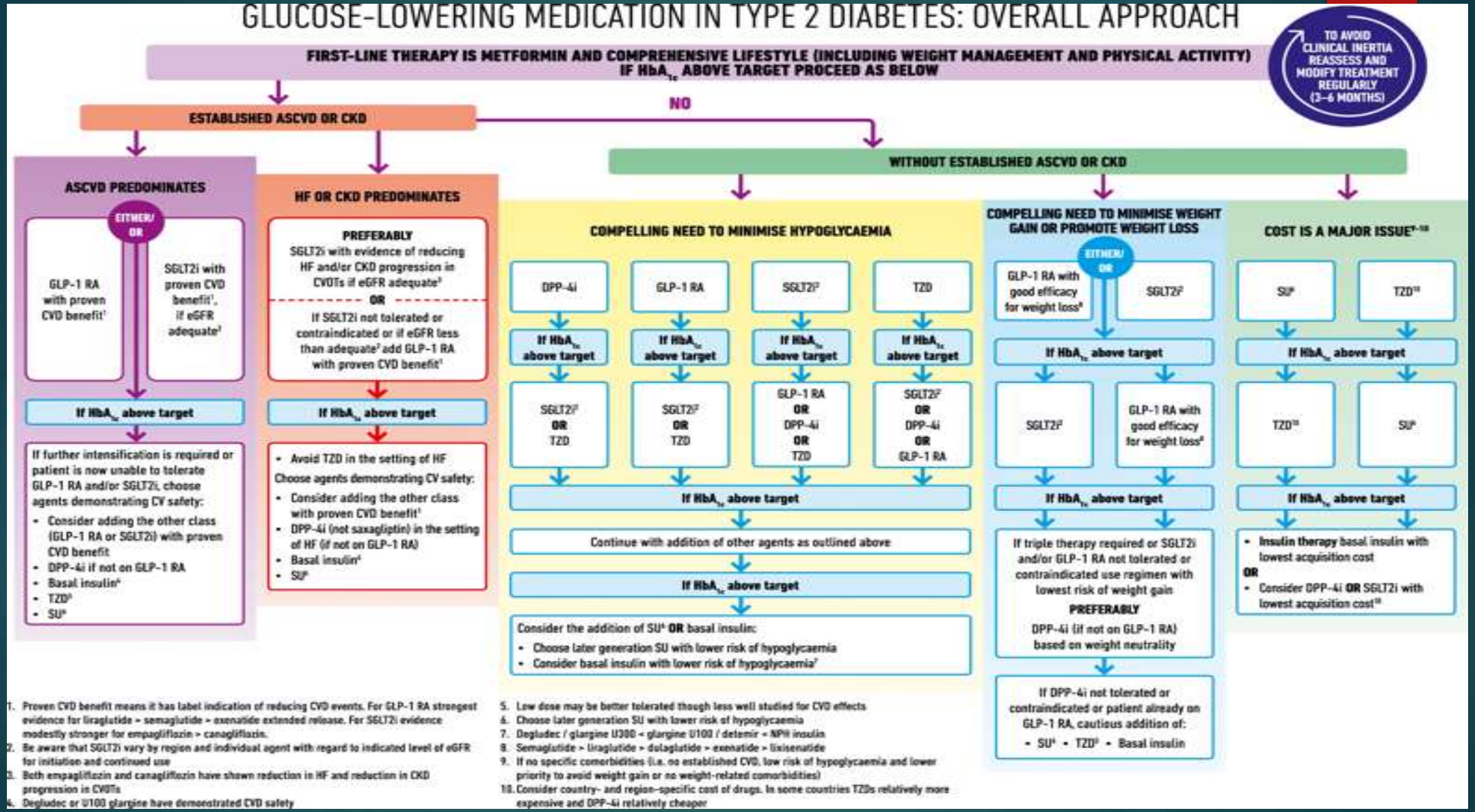
SOSPECHA DE DIABETES MELLITUS

12,3% nacional

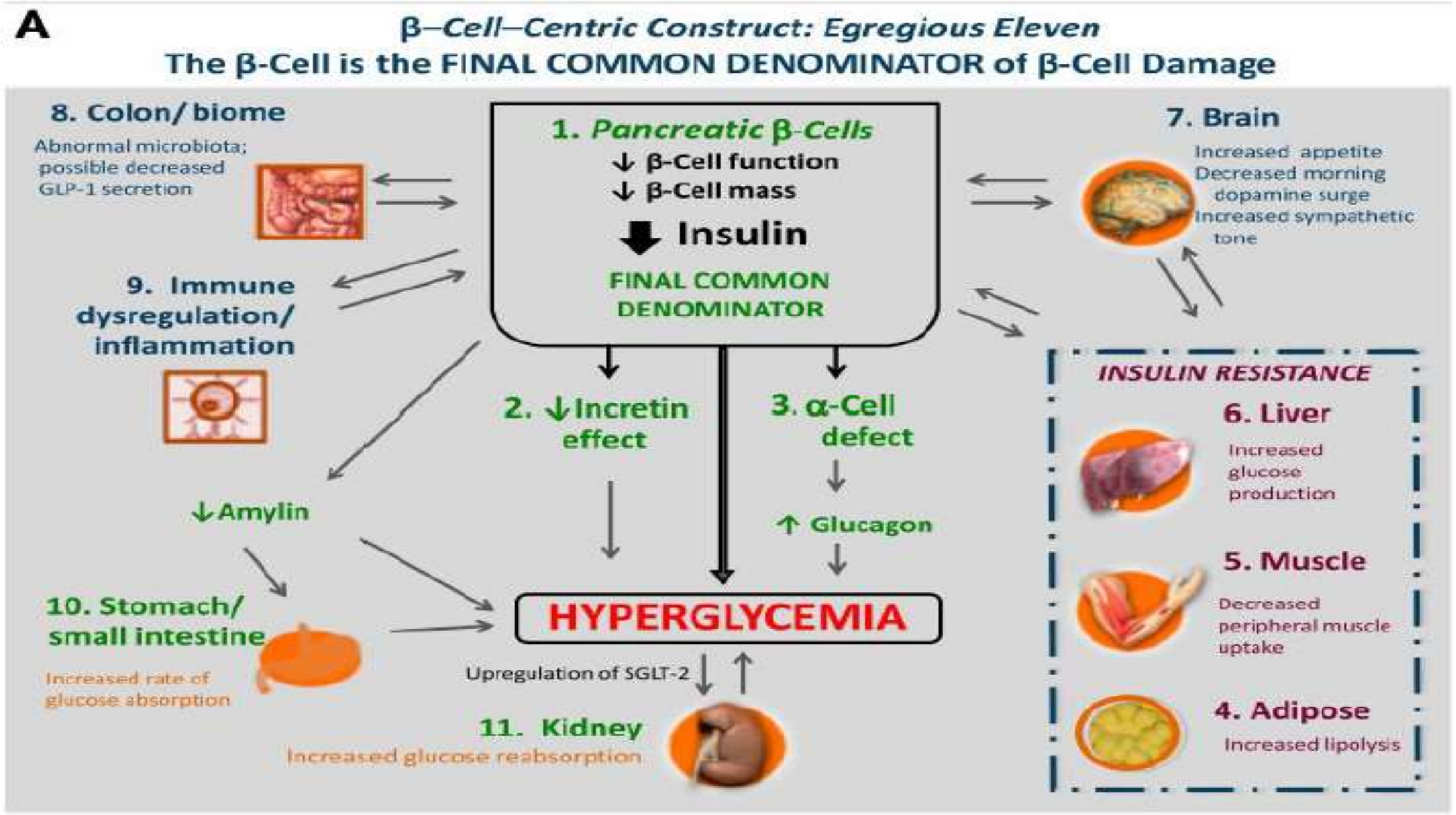
INE PROYECTA AL AÑO 2018…

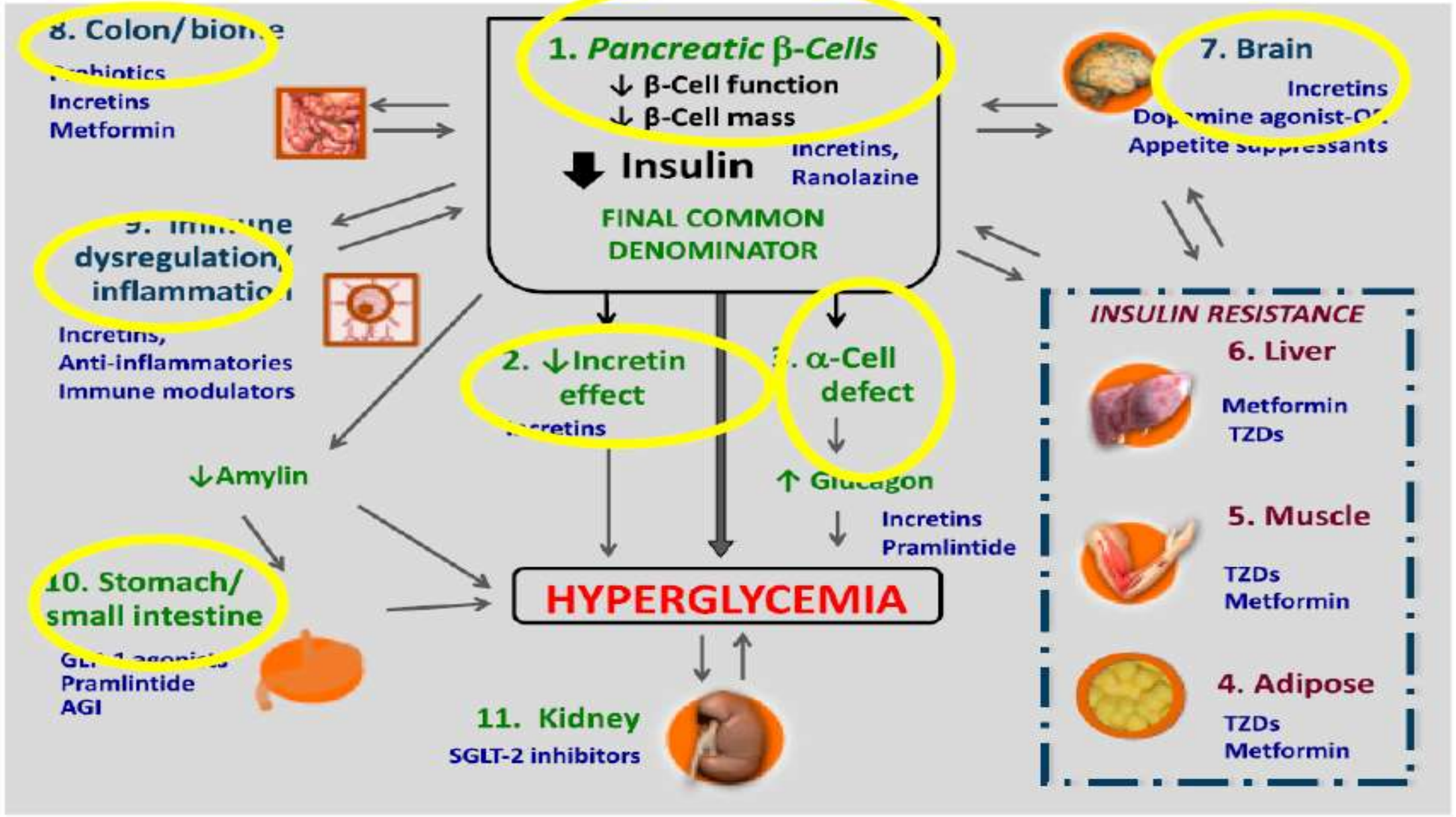
18.751.405 PERSONAS

Más de 2.300.000



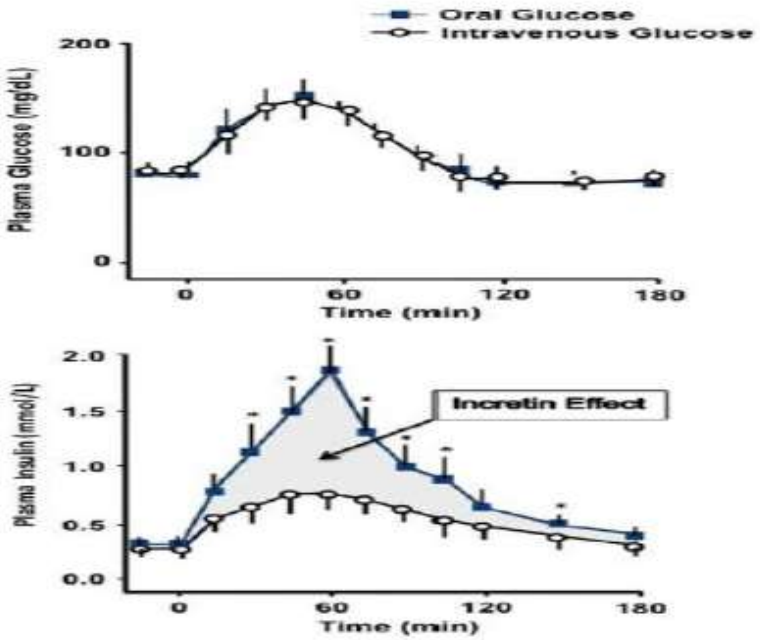
https://www.ncbi.nlm.nih.gov/pubmed/?term=Management+of+hyperglycaemia+in+type+2+diabetes%2C+2018.+A+consensus+report+by+the+American+Diabetes+Association+(ADA)+and+the+European+Association+for+the+Study+of+Diabetes+(EASD)


A
β–Cell–Centric Construct: Egregious Eleven
The β-Cell is the FINAL COMMON DENOMINATOR of β-Cell Damage
8. Colon/ biome
Abnormal microbiota; possible decreased GLP-1 secretion
1. Pancreatic β-Cells
↓ β-Cell function
↓ β-Cell mass
Insulin
FINAL COMMON DENOMINATOR
7. Brain
Increased appetite
Decreased morning dopamine surge
Increased sympathetic tone
9. Immune dysregulation/ inflammation
2. ↓Incretin effect
3. α-Cell defect
↓Amylin
↑ Glucagon
INSULIN RESISTANCE
6. Liver
Increased glucose production
5. Muscle
Decreased peripheral muscle uptake
4. Adipose
Increased lipolysis
10. Stomach/ small intestine
Increased rate of glucose absorption
HYPERGLYCEMIA
Upregulation of SGLT-2
11. Kidney
Increased glucose reabsorption


8. Colon/biome
Incretins
Metformin
1. Pancreatic β-Cells
↓ β-Cell function
↓ β-Cell mass
Insulin
Incretins,
Ranolazine
FINAL COMMON DENOMINATOR
7. Brain
Incretins
Appetite suppressants
dysregulation/
inflammation
Incretins,
Anti-inflammatories
Immune modulators
2. ↓Incretin effect
α-Cell defect
↓Amylin
↑ Glucagon
Incretins
Pramlintide
INSULIN RESISTANCE
6. Liver
Metformin
TZDs
5. Muscle
TZDs
Metformin
4. Adipose
TZDs
Metformin
10. Stomach/
small intestine
Pramlintide
AGI
HYPERGLYCEMIA
11. Kidney
SGLT-2 inhibitors

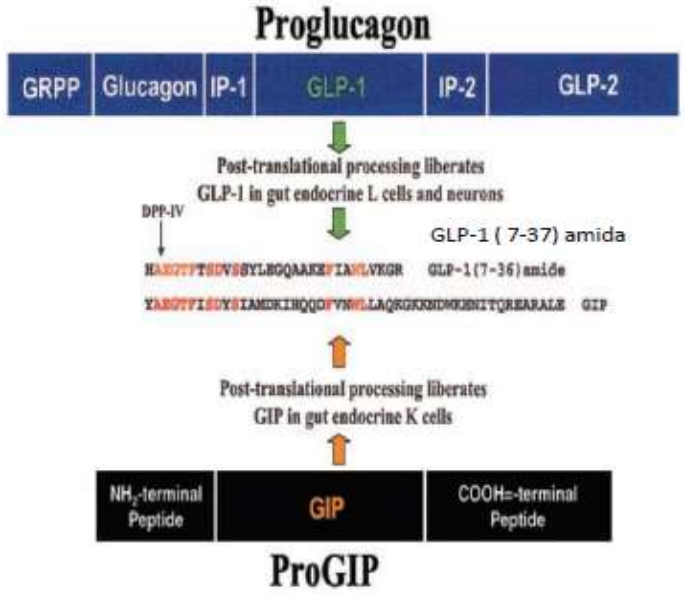
EFECTO INCRETINA

- Fenómeno fisiológico: mayor liberación de insulina secundario a la ingesta de glucosa vía oral en relación a la endovenosa.



- 70% secreción insulina postprandial.
- Fundamental en la homeostasis de la glucosa postprandial.

HORMONAS INCRETINAS



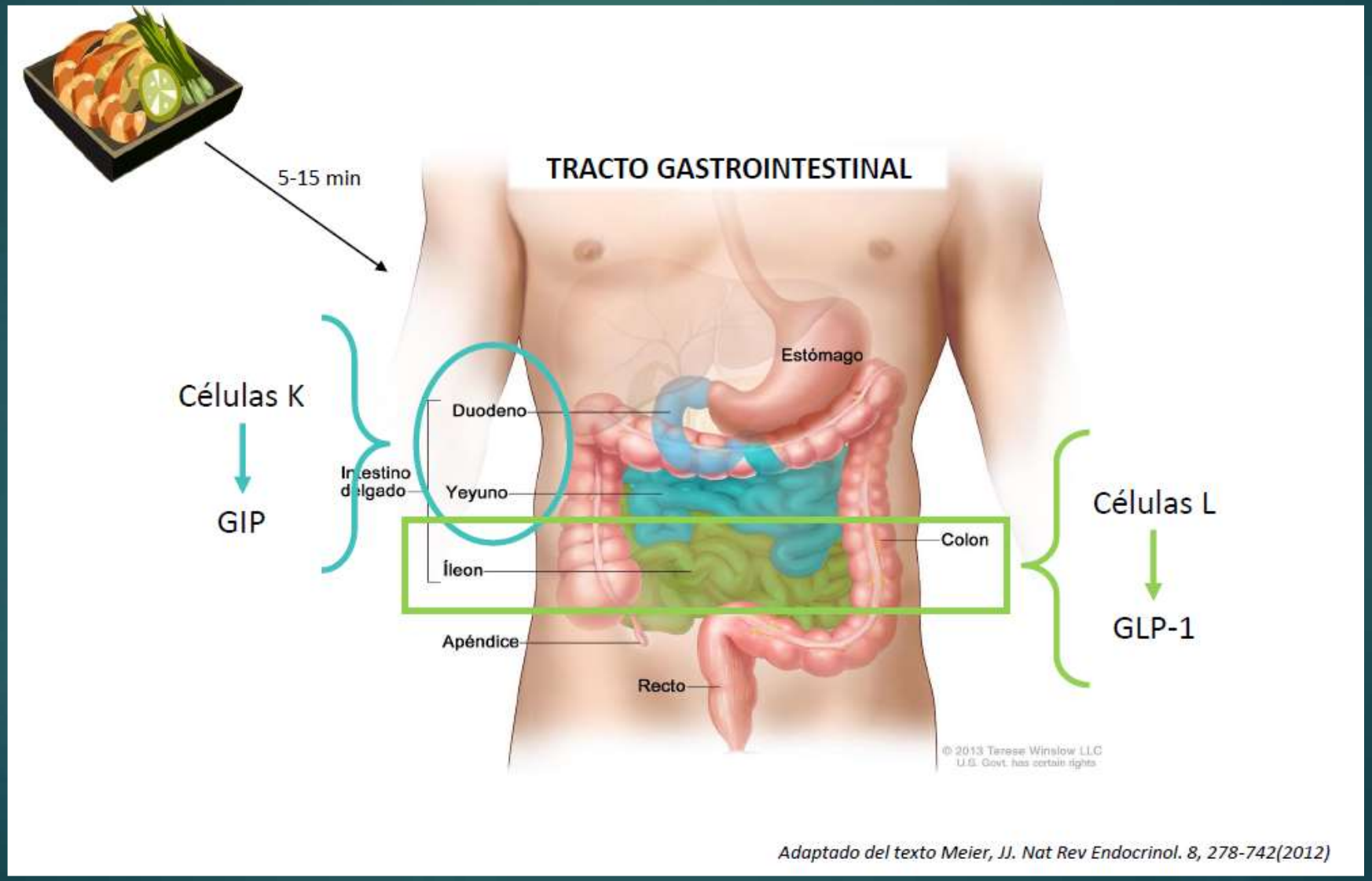
GLP-1

- Hormonas peptídicas secretadas a nivel intestinal.
- Miembros de la superfamilia de péptido glucagón.
- GIP: gastric inhibitory polypeptide.
- GLP-1: glucagón like peptide 1.

Meier, JJ. Nat Rev Endocrinol. 8, 278-742(2012)

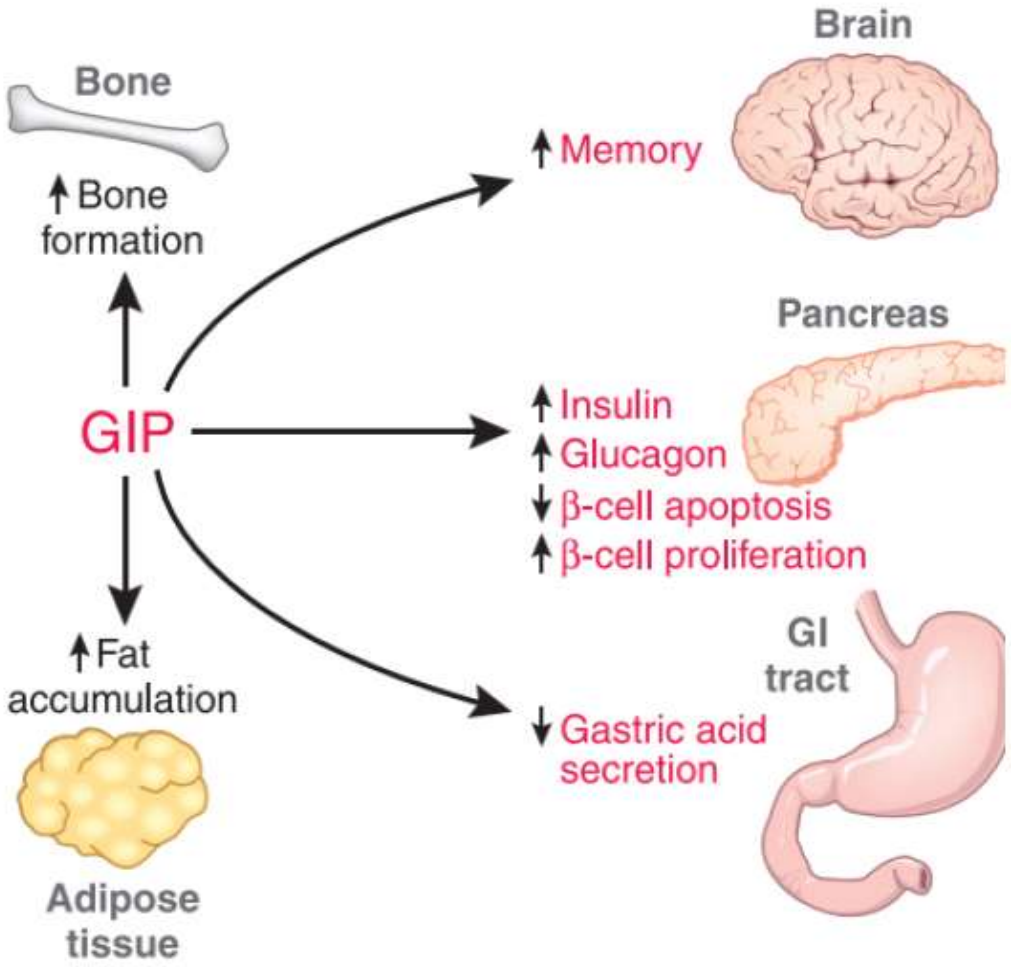
Drucker DJ. Diabetes Care 26:2929–2940, 2003

HORMONAS INCRETINAS



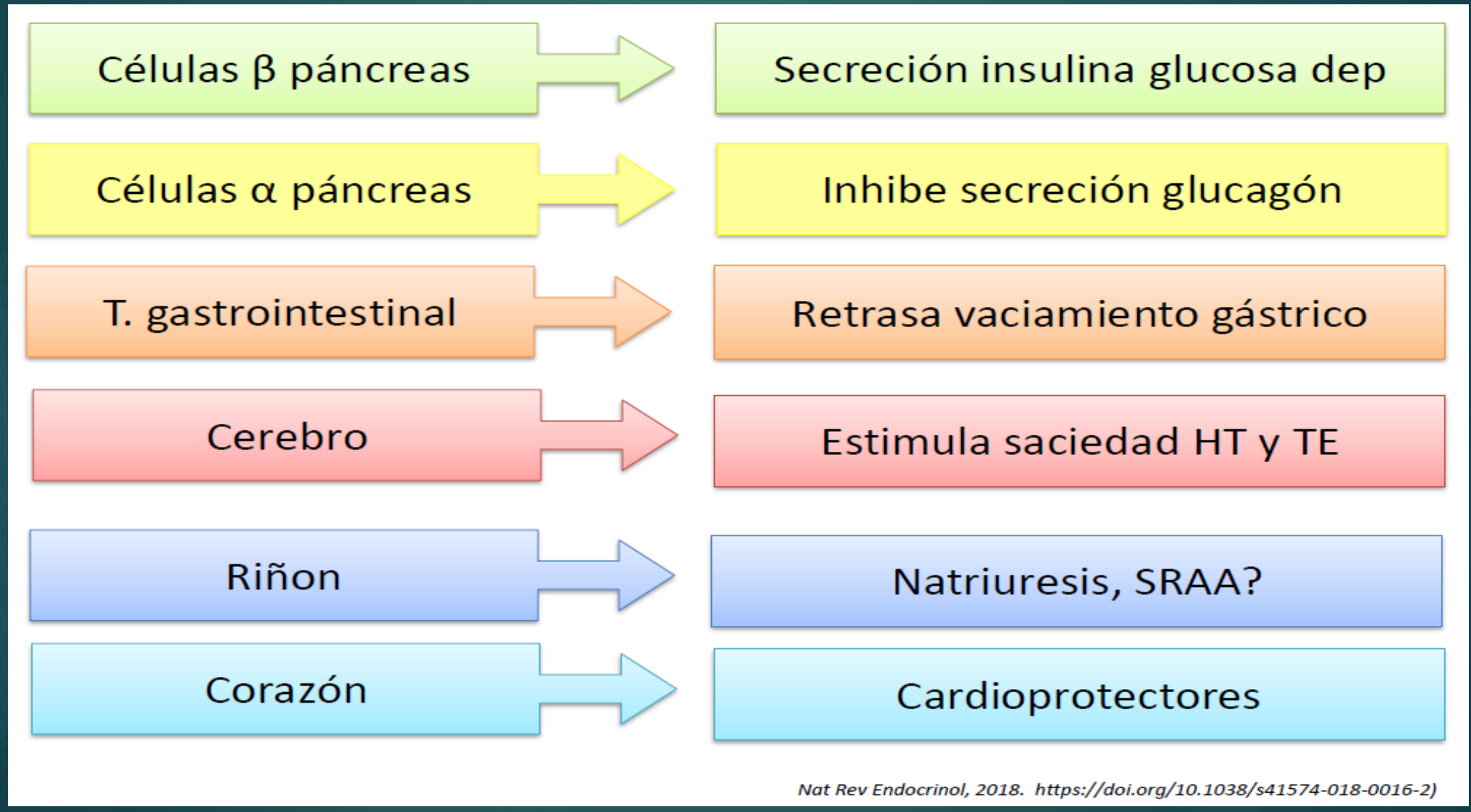
Adaptado del texto Meier, JJ. Nat Rev Endocrinol. 8, 278-742(2012)

HORMONAS INCRETINAS



Journal of Diabetes Investigation, 2010; 1: 8-23

GLP-1



Nat Rev Endocrinol, 2018. https://doi.org/10.1038/s41574-018-0016-2)

INHIBIDORES DPP-4

FARMACODINAMIA

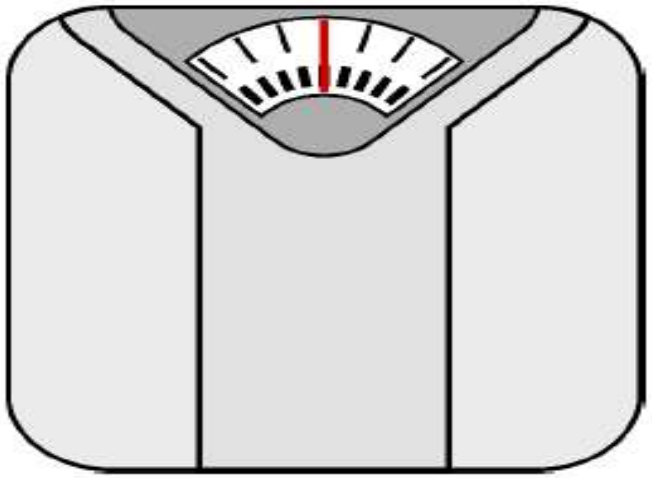
Fármaco	Selectividad DPP-4	Inhibición DPP-4	↑ GLP-1 activo	Vía eliminación
Alogliptina	> 14.000	> 75	2-3 veces	Renal
Linagliptina	> 10.000	≥ 70	2-3 veces	Entero-hepática

Linagliptina

sitagliptina, vildagliptina, saxagliptina.

Golightly et al. Clin Pharmacokinet 2012; 51 (8)

NEUTROS



VÍA ORAL

SIN RIESGO

MODERADA

ALTO

EFICACIA GLICÉMICA

- Eficacia similar → modesto
- No hay estudio a largo plazo (hasta 2-3 años)
- Meta-análisis versus placebo:
  - Sitagliptina: A1c (%) -0,74 (95% CI -0,84 a – 0,53)
  - Vildagliptina: A1c (%) -y -0,73 (95% CI - 0,92 a – 0,52)
- Eficacia similar como monoterapia o adicionado a otro
- No inferioridad: sitagliptina vs glipizide y vildagliptina vs tiazolidinedionas
- No inferioridad no demostrada para vildagliptina vs metformina.
- Efectos glicemia:
  - Ayuno – 18 mg/dl (- 14 a – 22 mg/dl)
  - Efectos significativos en reducción glicemia post prandial.

REACCIONES ADVERSAS

Hipoglicemia

RR 0.97 (95% CI) 0,5-1.86

Nasofaringitis

RR 1,17 (95% CI) 0,98-1,4

ITU

RR 1.52 (95% CI) 1.04-2.21

Cefalea

RR 1.38 (95% CI) 1.10-1.72

Pancreatitis

JAMA, 2007; 298 (2): 194-206

ANÁLOGOS RECEPTOR GLP-1

GLP-1

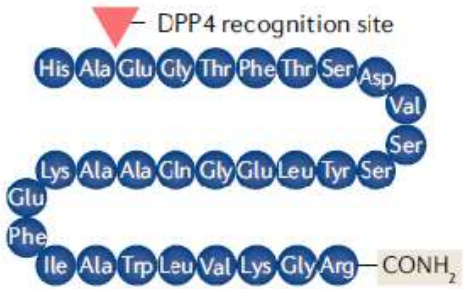
- Estimulado por ingesta de glucosa o comida mixta.
- Vida media muy corta 2-3 min (degradación por DPP-4).
- Forma nativa no es alternativa para tratamiento DM2.
- 2 formas circulantes: **GLP-1 (7-36)-amida,** GLP-1 (7-37) amida.

Exendina-4

50% aa GLP-1 mamíferos

Activa GLP-1 misma potencia

Native human GLP1 (3.3 kDa)



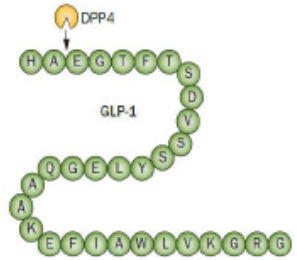
Alteración secuencia aminoácidos GLP-1 nativo para evitar degradación DPP4.

Pharm & Theraputics, 2017; 170: 116-147

Nat Rev Endocrinol, 2018. https://doi.org/10.1038/s41574-018-0016-2)

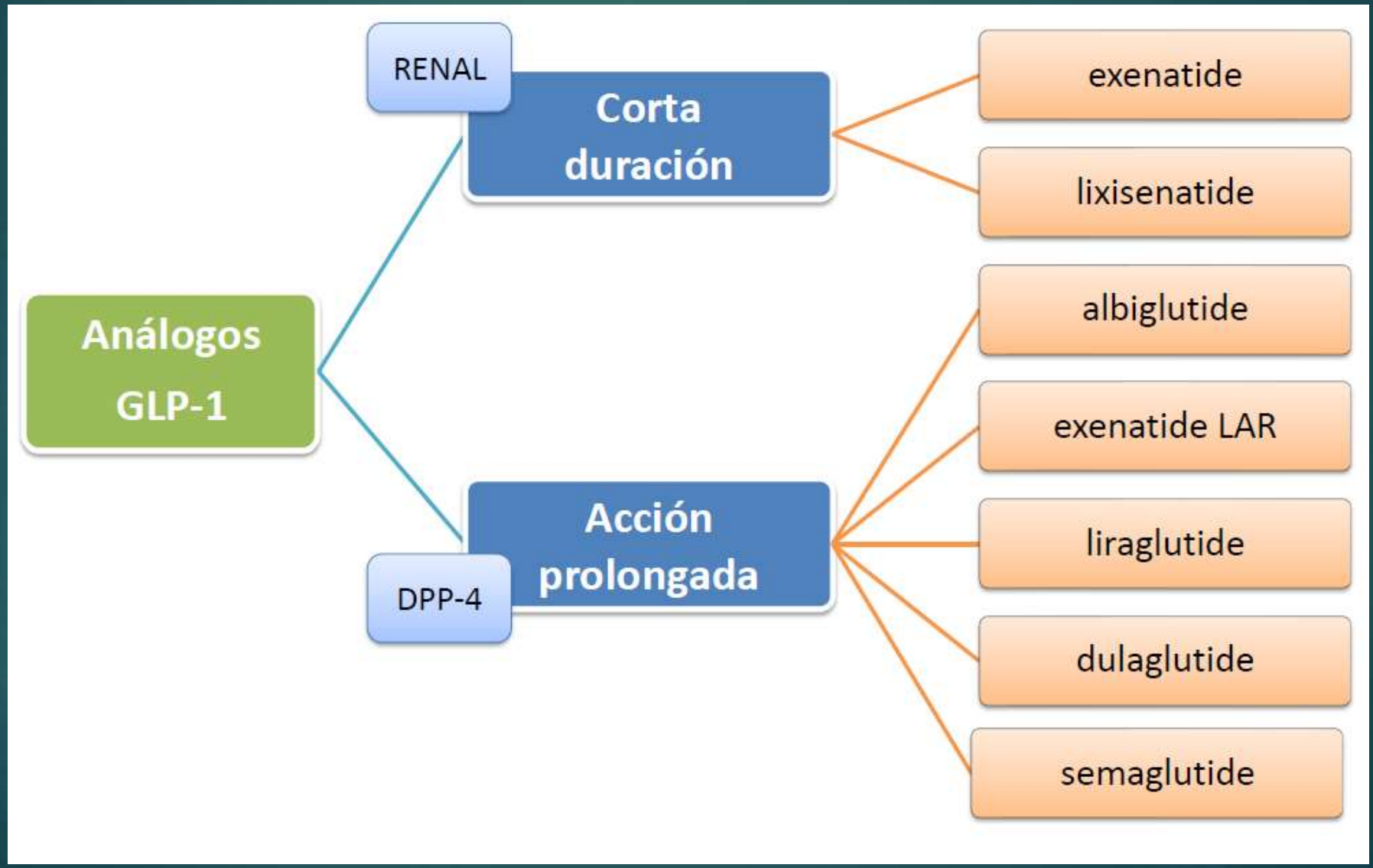
ALTERACIONES EN DM2

- Menor secreción de insulina en respuesta a glucosa oral
- Pérdida de la respuesta bifásica insulina.
- Menor velocidad respuesta insulínica post comidas.
- Hiperglucagonemia
- Pérdida de la respuesta contrarregulación ante hipoglicemia.
- Menor contenido de insulina en células β pancreáticas.
- Incremento apoptosis células β.
- Mayor ingesta/obesidad
- Alteraciones vaciamiento gástrico?

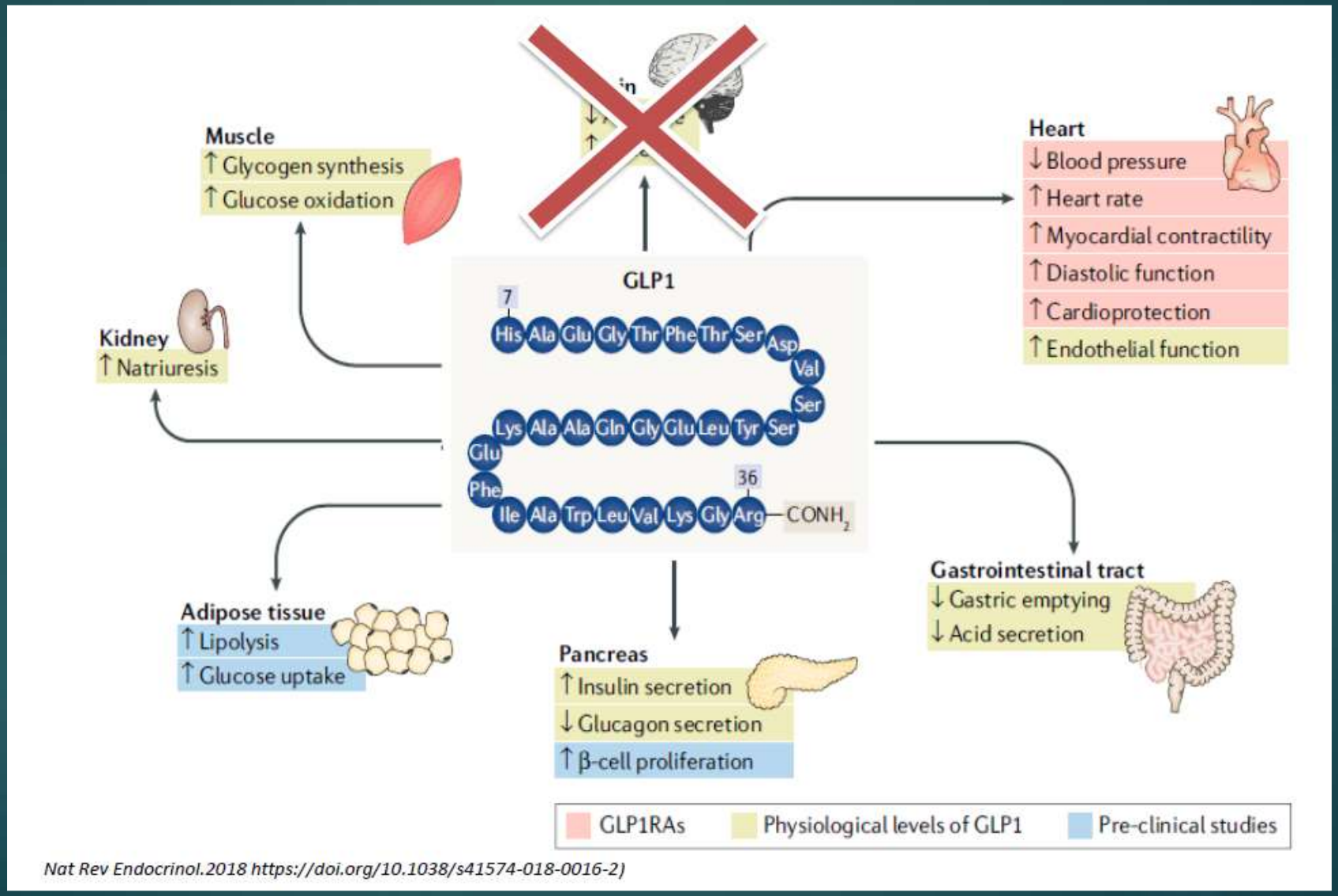


Meier, JJ. Nat Rev Endocrinol. 8, 278-742(2012)

CLASIFICACIÓN DE AGONISTA GLP-1



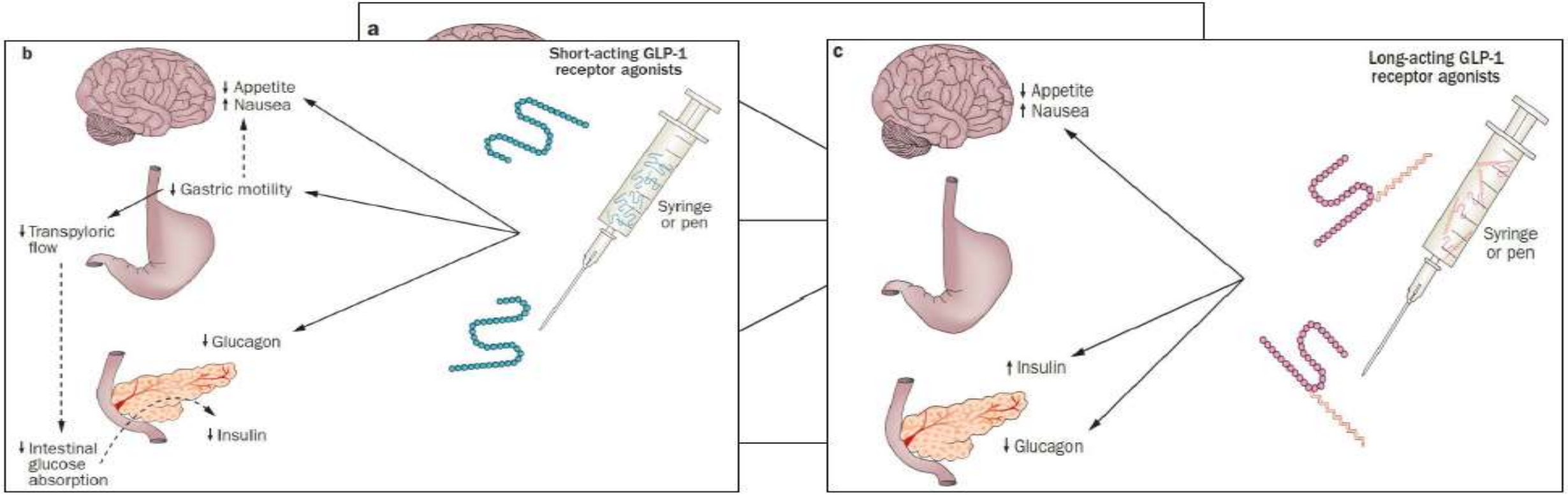
EFECTOS PLEIOTRÓPICOS AGONISTAS GLP-1



Nat Rev Endocrinol.2018 https://doi.org/10.1038/s41574-018-0016-2)

EFECTOS INSULINOTRÓPICOS AGONISTAS GLP-1

- Reducción glicemia ayuno
  - Inhibición de las células α (hipoglucagonemia)
  - Estimulación de las β pancréaticas (insulinotrópico)
- Reducción glicemia postprandial
  - Disminución velocidad vaciamiento gástrico
  - Retraso entradas de glucosa en el torrente sanguíneo
  - Efecto insulinotrópico (menor)



Los mecanismos de acción son diferentes

Meier, JJ. Nat Rev Endocrinol. 8, 278-742(2012)

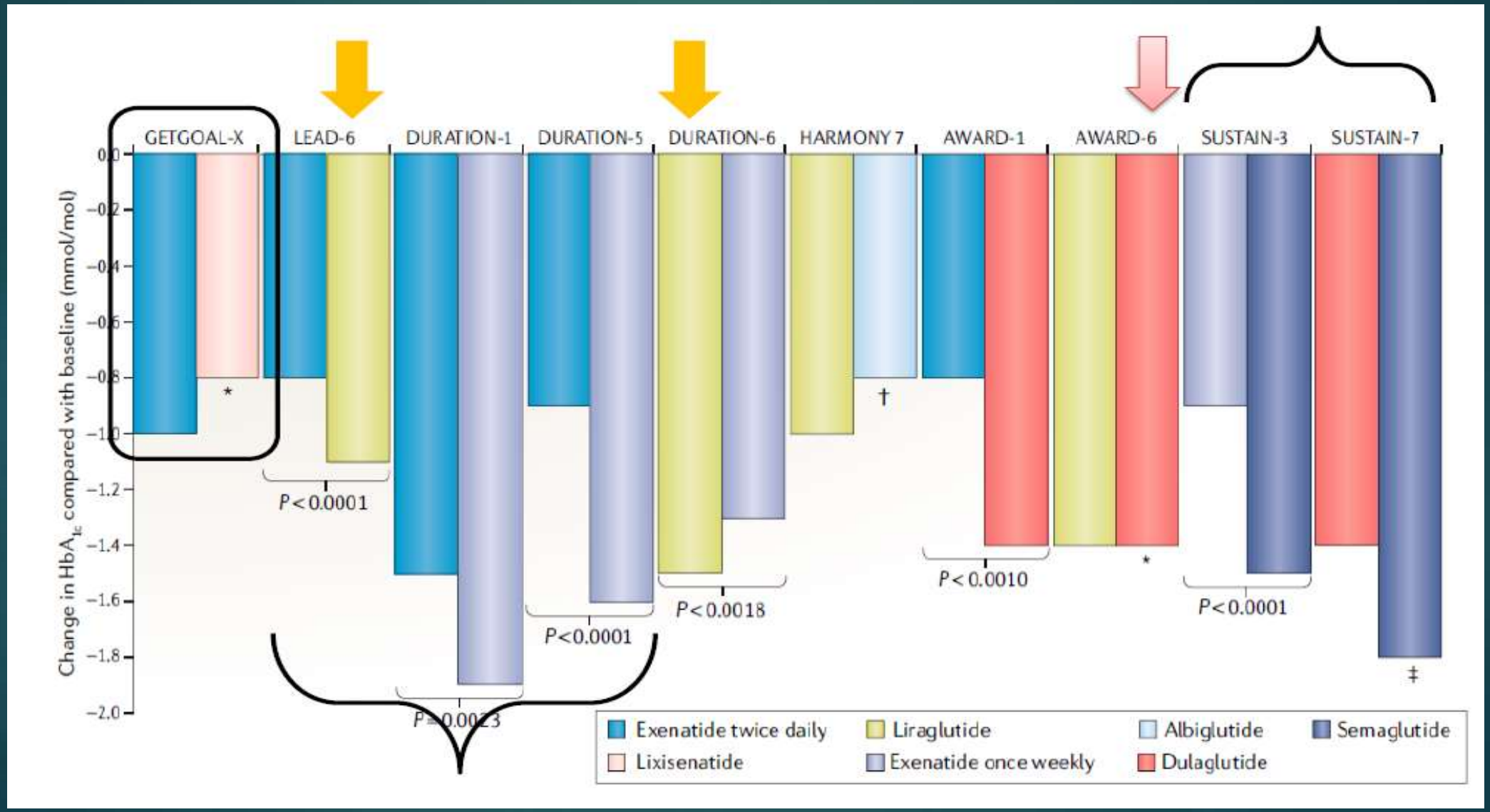
EFECTOS FARMACOLÓGICOS

Table 1 | Comparison of short-acting versus long-acting GLP-1 receptor agonists

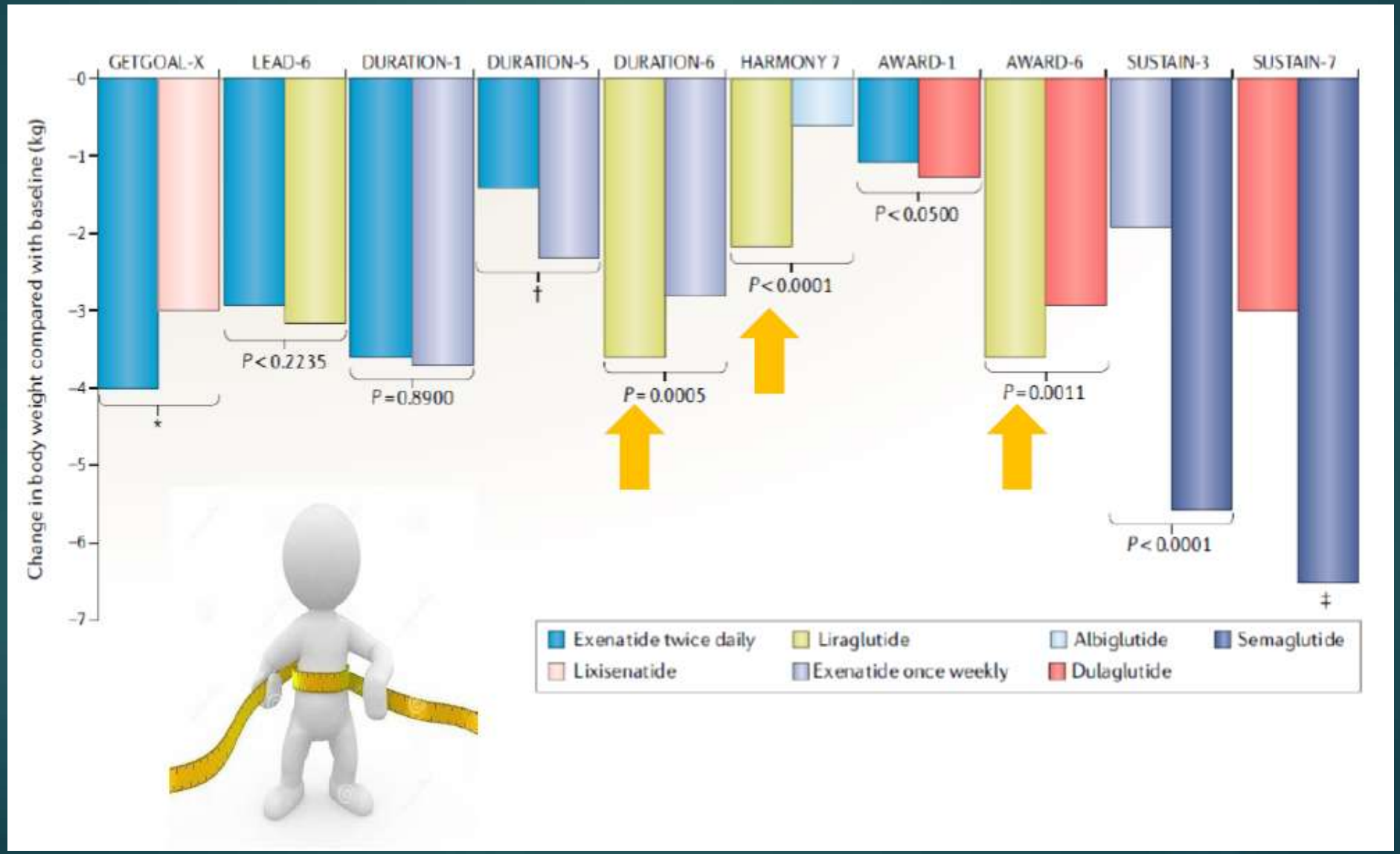
Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide-LAR Liraglutide
Half-life	2–5 h	12 h–several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Induction of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly (~4–8 weeks)

Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.

EFICACIA CONTROL GLICÉMICO



PÉRDIDA DE PESO



Efectos adversos descritos seguimiento estudio LEADER

Event	Liraglutide (N=4668)	Placebo (N=4672)	P Value
	no. of patients (%)		
Adverse event			
Any adverse event	2909 (62.3)	2839 (60.8)	0.12
Serious adverse event	2320 (49.7)	2354 (50.4)	0.51
Confirmed hypoglycemia†	2039 (43.7)	2130 (45.6)	0.06
Severe adverse event	1502 (32.2)	1533 (32.8)	0.51
Severe hypoglycemia†	114 (2.4)	153 (3.3)	0.02
Acute gallstone disease	145 (3.1)	90 (1.9)	<0.001
Cholelithiasis	68 (1.5)	50 (1.1)	0.09
Acute cholecystitis	36 (0.8)	21 (0.4)	0.046
Hypothyroidism	44 (0.9)	33 (0.7)	0.21
Hyperthyroidism	13 (0.3)	8 (0.2)	0.27
Diabetic foot ulcer	181 (3.9)	198 (4.2)	0.38
Allergic reaction	59 (1.3)	44 (0.9)	0.14
Injection-site reaction	32 (0.7)	12 (0.3)	0.002
Adverse event leading to permanent discontinuation of trial regimen			
Any adverse event	444 (9.5)	339 (7.3)	<0.001
Serious adverse event	192 (4.1)	245 (5.2)	0.01
Severe adverse event	164 (3.5)	188 (4.0)	0.30
Nausea	77 (1.6)	18 (0.4)	<0.001
Vomiting	31 (0.7)	2 (<0.1)	<0.001
Diarrhea	27 (0.6)	5 (0.1)	<0.001
Increased lipase level‡	15 (0.3)	11 (0.2)	0.43
Abdominal pain	11 (0.2)	3 (0.1)	0.03
Decreased appetite	11 (0.2)	2 (<0.1)	0.01
Abdominal discomfort	10 (0.2)	0	0.002
Pancreatitis or neoplasm§			
Acute pancreatitis	18 (0.4)	23 (0.5)	0.44
Chronic pancreatitis	0	2 (<0.1)	0.16
Any benign neoplasm	168 (3.6)	145 (3.1)	0.18
Any malignant neoplasm	296 (6.3)	279 (6.0)	0.46
Pancreatic carcinoma	13 (0.3)	5 (0.1)	0.06
Medullary thyroid carcinoma	0	1 (<0.1)	0.32

SEGURIDAD CARVIOVASCULAR

Compound	Trial name	Month and year of completion	n	Median follow-up (months)	Exposure to trial drug during follow-up period	Risk factors at baseline			Effect on primary composite cardiovascular end point (HR; 95% CI)]
						Age	HbA_{1c}	CVD (% of patients)	
Lixisenatide	ELIXA[83]	Feb 2015	6,068	25	• Lixisenatide: 690 days • Placebo: 712 days	• Lixisenatide: 59.9 • Placebo: 60.6	7.7	100	1.02; 0.89–1.17
Liraglutide	LEADER[84]	Dec 2015	9,340	46	• Liraglutide: 84% • Placebo: 83%	• Liraglutide: 64.2 • Placebo: 64.4	8.7	81.3	0.89; 0.78–0.97
Semaglutide	SUSTAIN-6[85]	Mar 2016	3,297	25	• Semaglutide 1.0 mg: 88% • Semaglutide 0.5 mg: 85% • Placebo 1.0 mg: 90% • Placebo 0.5 mg: 90%	• Semaglutide 1.0 mg: 64.7 • Semaglutide 0.5 mg: 64.6 • Placebo 1.0 mg: 64.4 • Placebo 0.5 mg: 64.8	8.7	83.0	0.74; 0.58–0.95
ITCA 650	FREEDOM-CVO[89]	May 2016	4,000	NA	NA	NA	NA	NA	Noninferiority compared with placebo
Exenatide once weekly	EXSCEL[90]	May 2017	14,752	38	• Exenatide once weekly: 76% • Placebo: 75%	• Exenatide once weekly: 62.0 • Placebo: 62.0	8.0	73.1	0.91; 0.83–1.00

CONTRAINDICACIONES

- Cáncer células C tiroides
- Cáncer neuroendocrinos
- Patología gastro-intestinales severas
- Gastroparesia
- ERC etapa IV-V (acción corta).
- Pancreatitis
- Patología biliar litiásica

Diabetes Care. https://doi.org/10.2337/dci18-0033

NIVEL SATISFACCIÓN PACIENTES

Medical

DTSQ

means

Diabetes Treatment Satisfaction Questionnaire

by acronymsandslang.com

Exenatide qw vs bid

Liraglutide vs Exe bid

No lira vs dula

Menor frec. inyecciones

conveniencia

Flexibilidad


$ 32.000
Lyxumia 10
Lyxumia 20


Bydureon
10

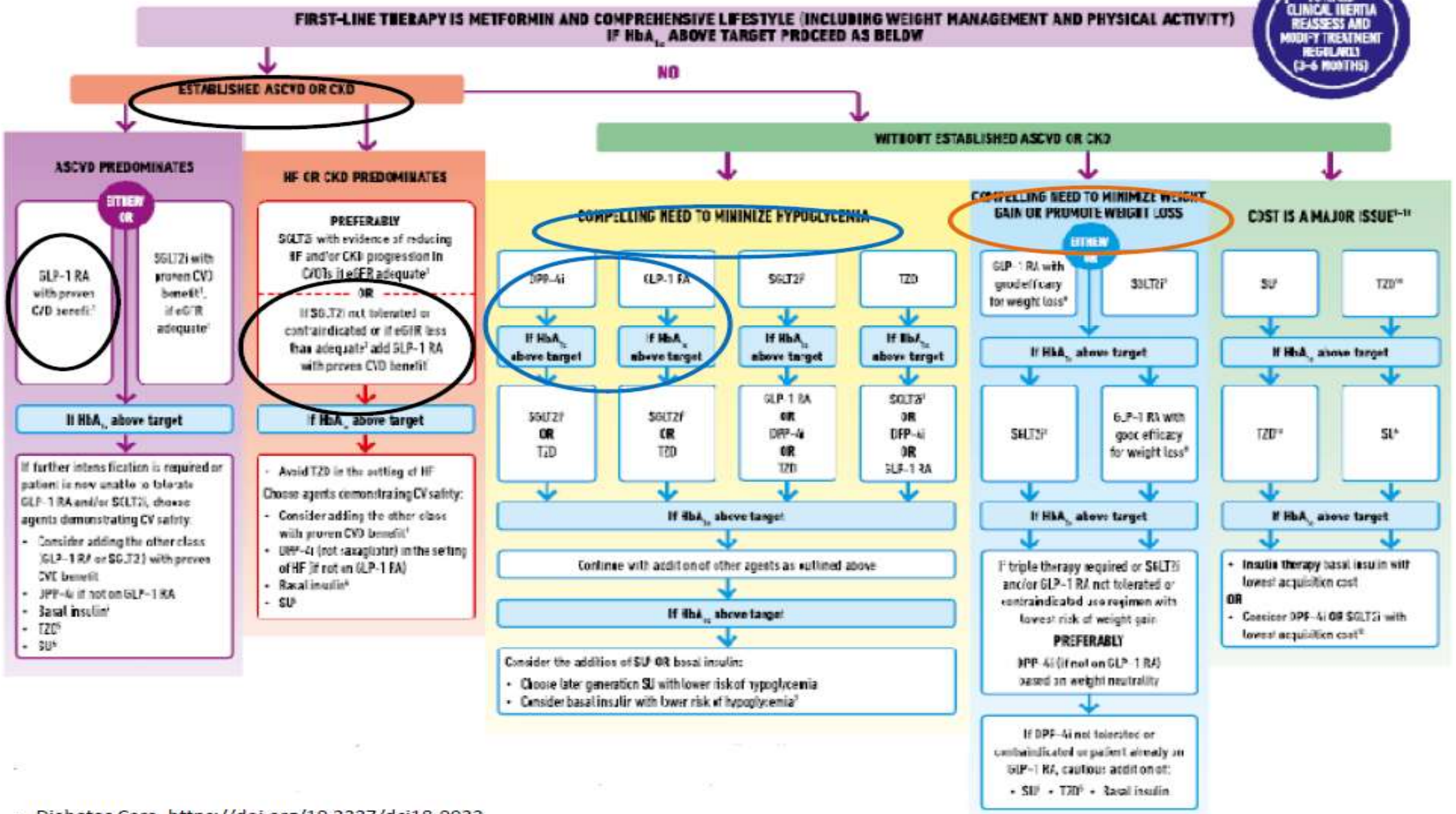

$ 55.000 a 80.000
VICTOZA


$ 75.000
trulicity
dulaglutide injection once weekly
0.75 mg/0.5 mL, 1.5 mg/0.5 mL


NEW
ONCE-WEEKLY
OZEMPIC
semaglutide injection
OZEMPIC 0.25 mg
solution for injection in pre-filled pen
semaglutide
subcutaneous use
once weekly

Entonces…
¿Cuándo los indicamos?

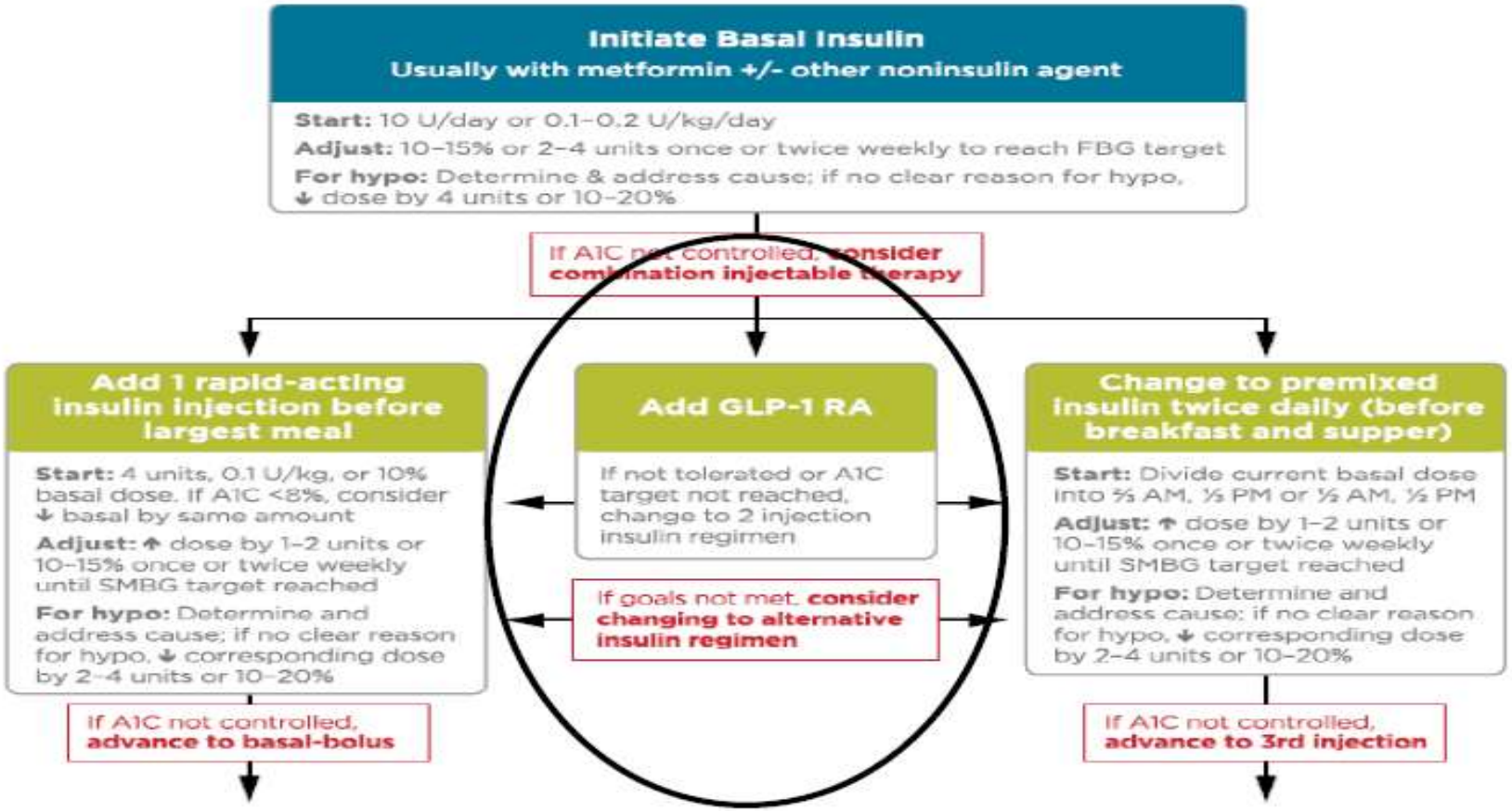
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



Diabetes Care. https://doi.org/10.2337/dci18-0033

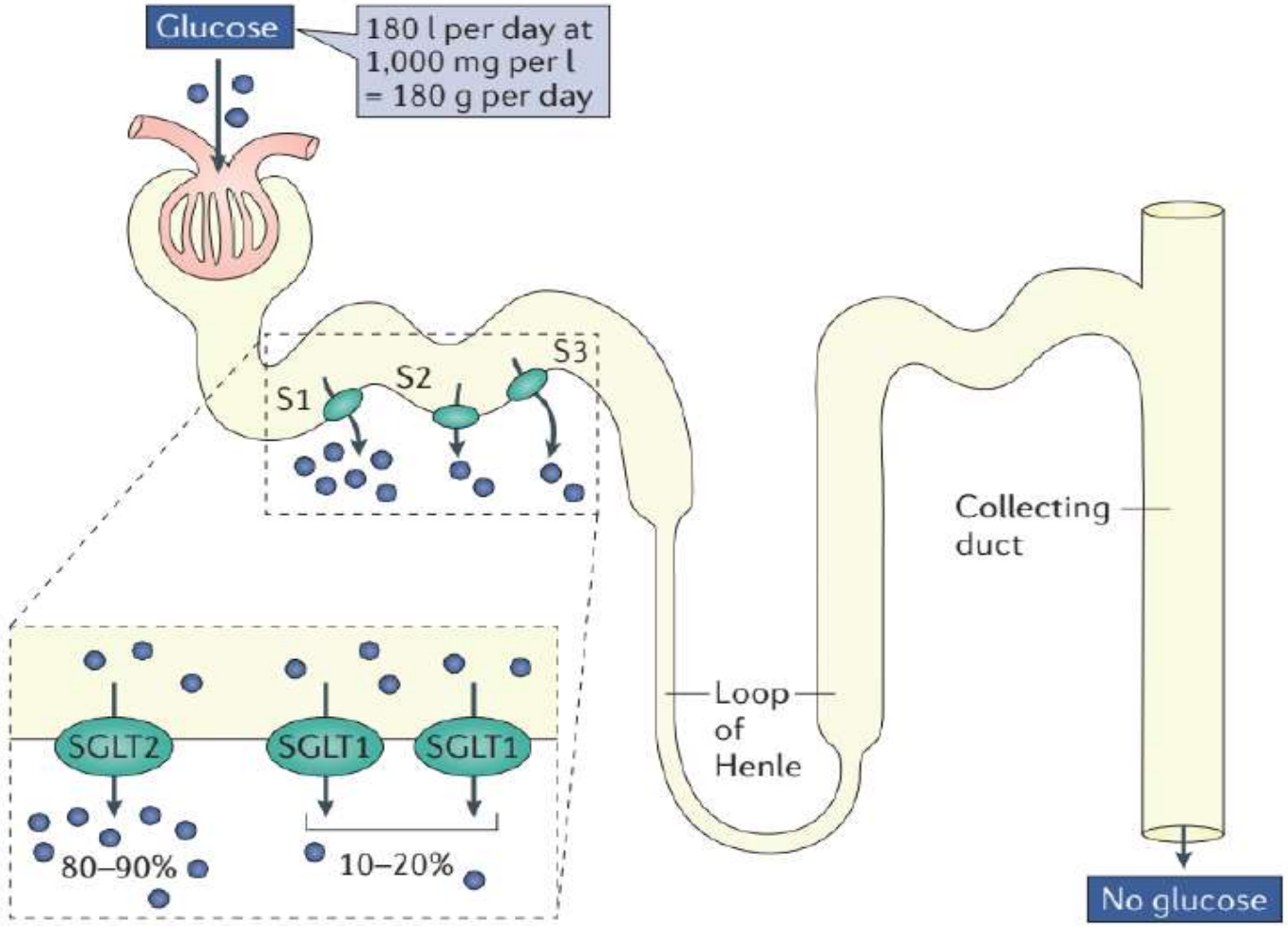
A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Combination Injectable Therapy



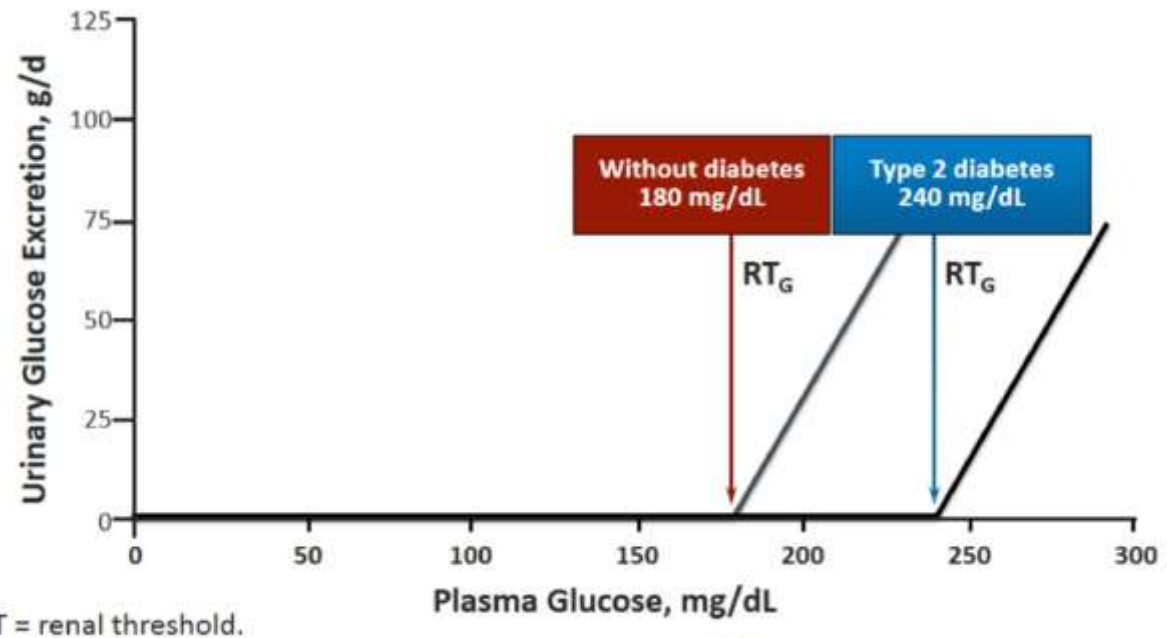
INHIBIDORES DE SGLT-2

SGLT-2



Nature Reviews Nephrology 13, 11–26

SGLT-2: DIABÉTICOS V/S NO DIABÉTICOS



RT = renal threshold.

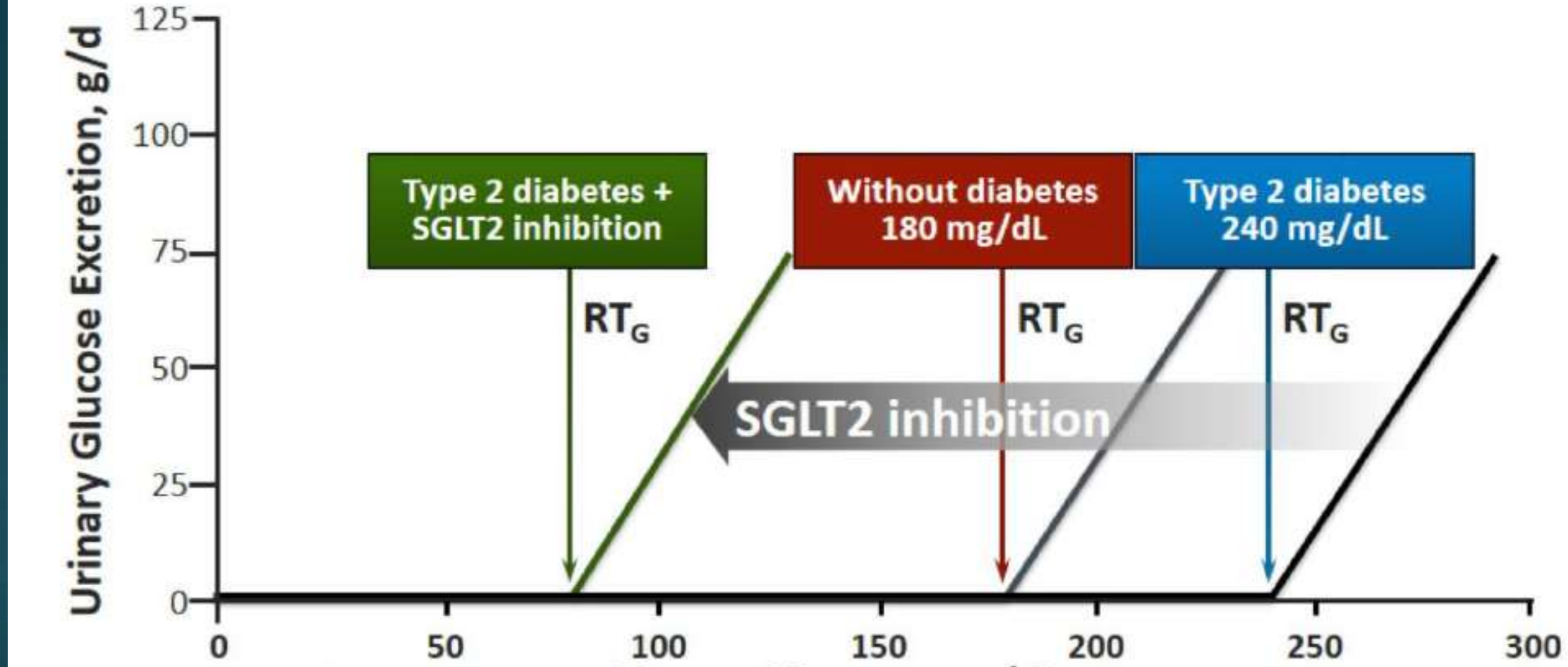
Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42[6]; Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14:782-790.[10]

La capacidad máxima de reabsorción tubular de glucosa está incrementada en paciente diabéticos

El nivel de glicemia umbral para aparición de glucosuria está aumentado en pacientes diabéticos

INHIBIDOR DE SGLT-2

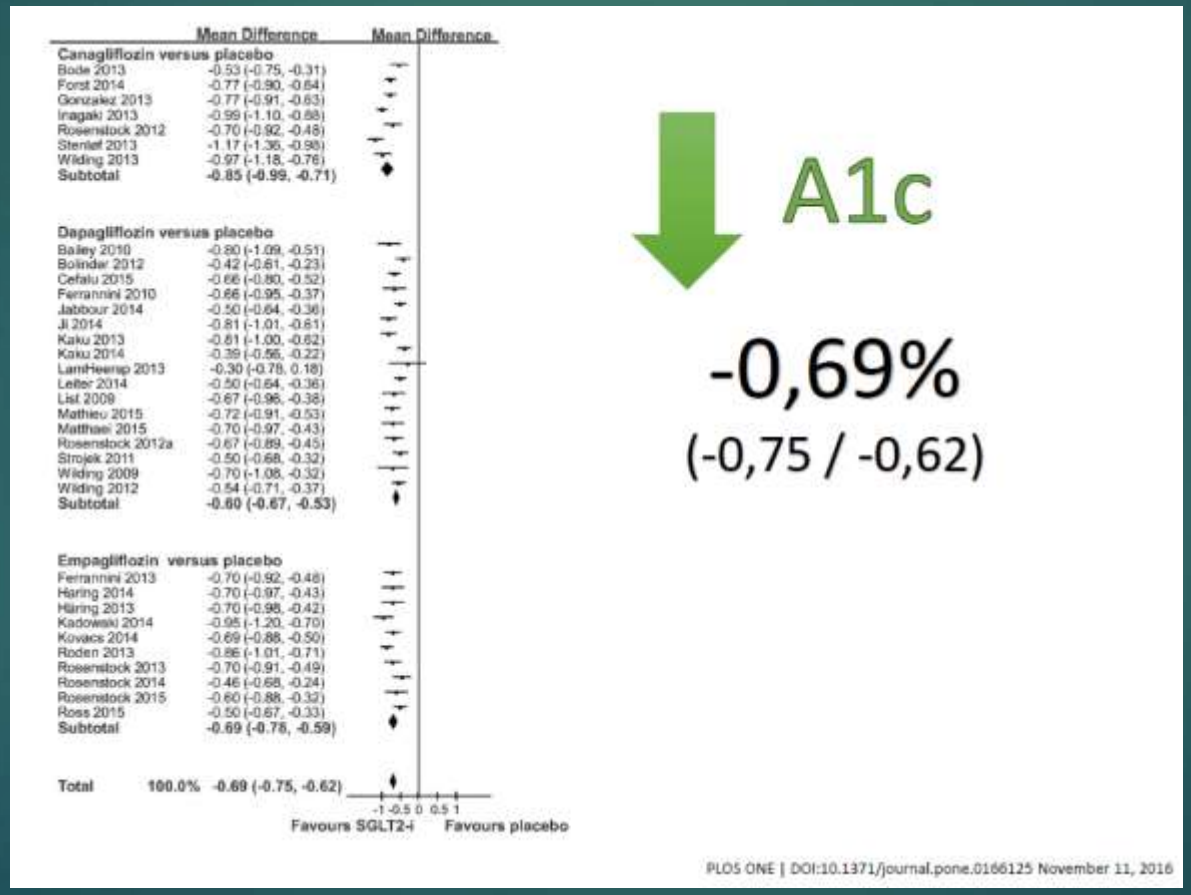
- Disminución de la capacidad máxima de reabsorción tubular de glucosa
- Disminución del umbral de glucosuria
- Aumento de natriuresis
- Aumento de actividad de SGLT1 distal (30-35%)
- Efecto independiente del nivel de glicemia
- **Efecto insulino-independiente**
- Pérdida de glucosa equivalente a 250 – 450 kcal/d



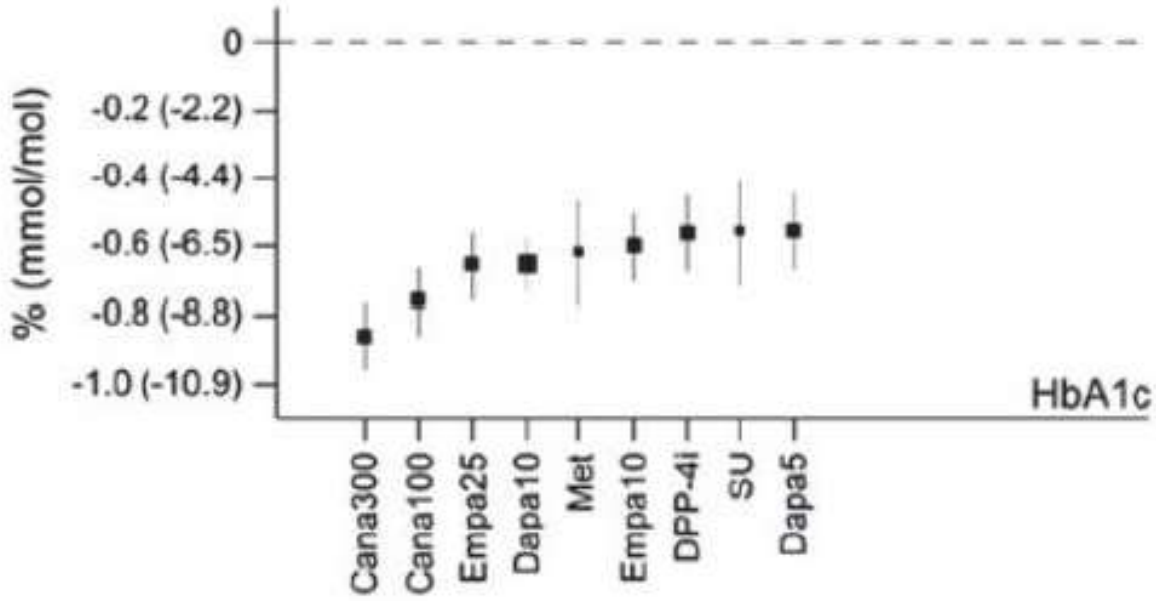
RT = renal threshold.

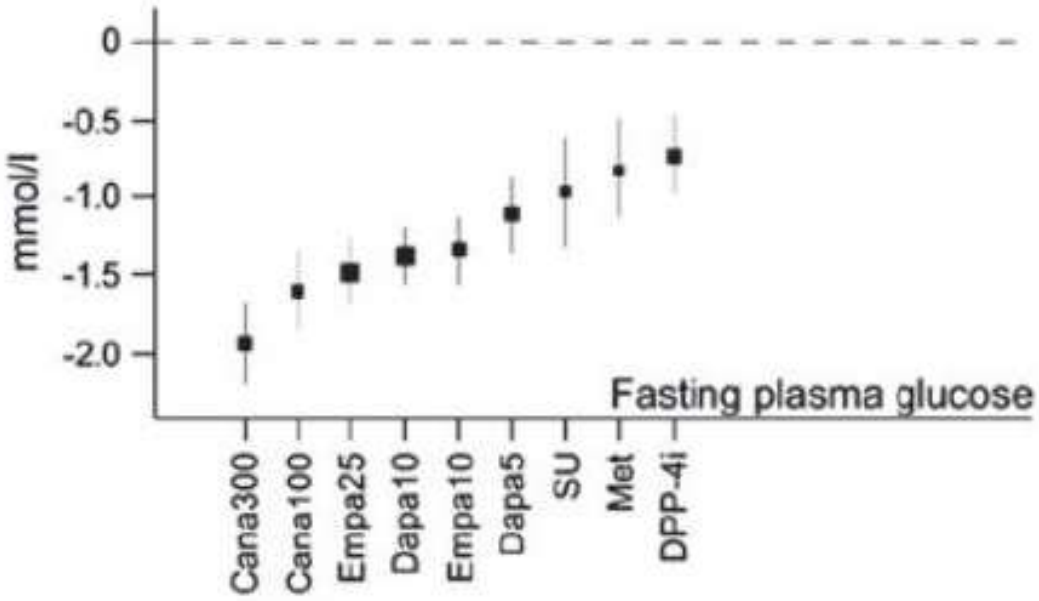
Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42[6]; Abdul-Ghani MA, et al. *Endocr Pract*. 2008;14:782-790[10]; Chao EC, et al. *Nat Rev Drug Discov*. 2010;9:551-559.[11]

POTENCIA HIPOGLICEMIANTE



EFECTO HIPOGLICEMIANTE





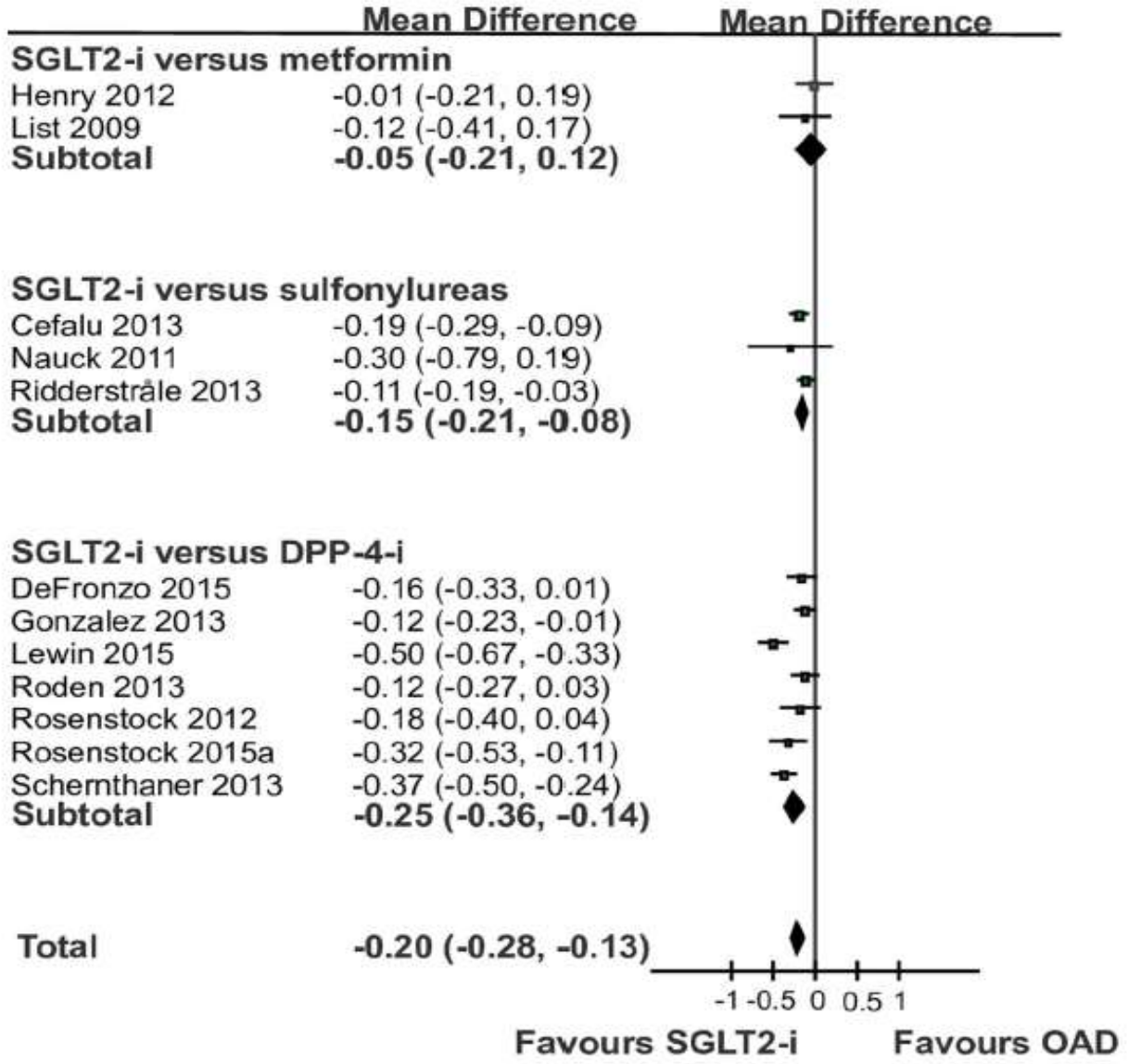
INHIBIDOR DE SGLT-2

Efecto en glicemia de ayuno y postprandial

Efecto Independiente de:

- Glicemia previa (A1c)
- Peso
- Secreción de insulina
- Resistencia a la insulina
- Presencia de otros HGO

Dependiente de GFR



PLOS ONE | DOI:10.1371/journal.pone.0166125 November 11, 2016

INHIBIDORES DE SGLT-2

Equivalente a Metformina como monoterapia

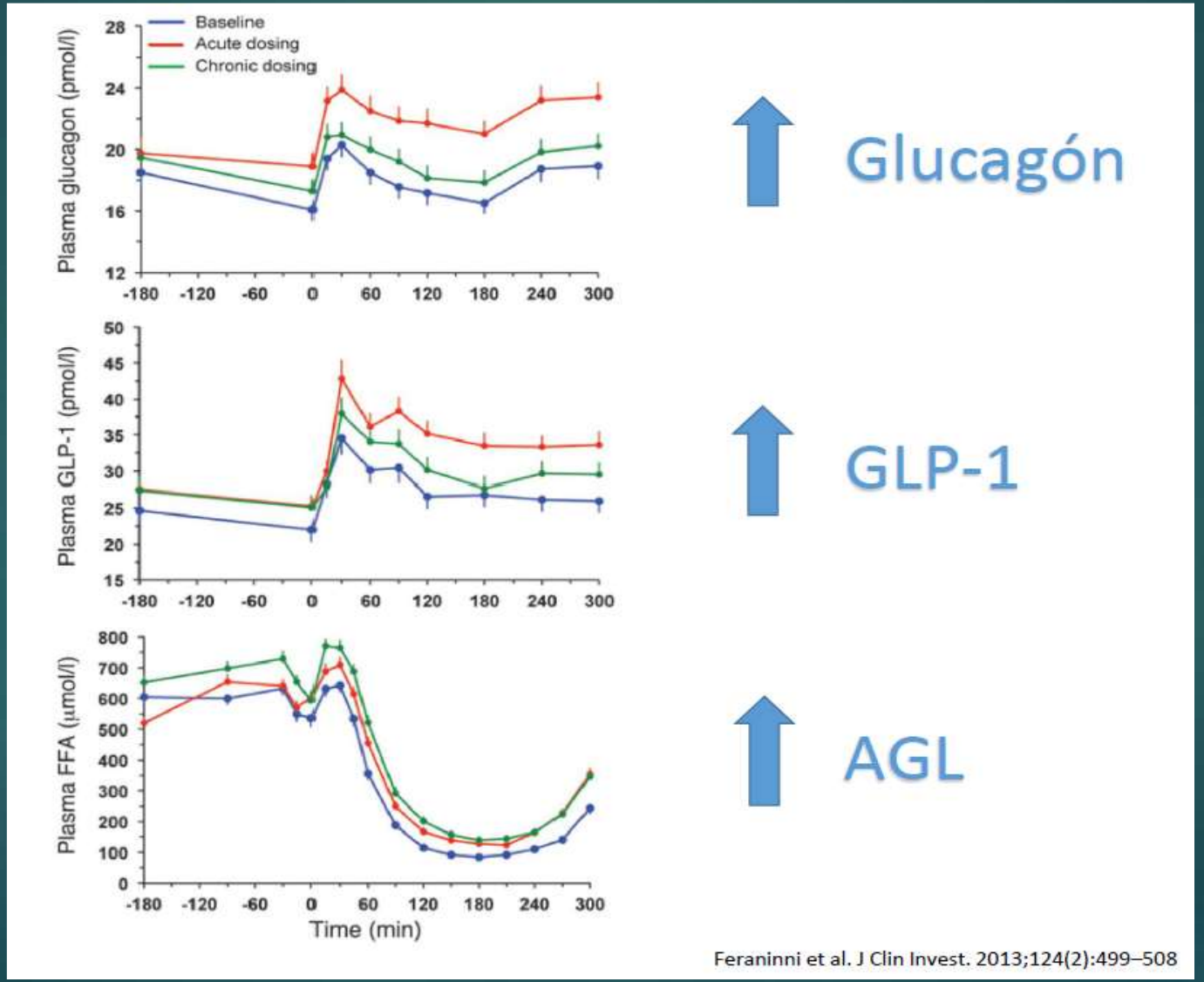
Superior a iDPP4 y SU

Eficacia demostrada como biterapia asociado a metformina

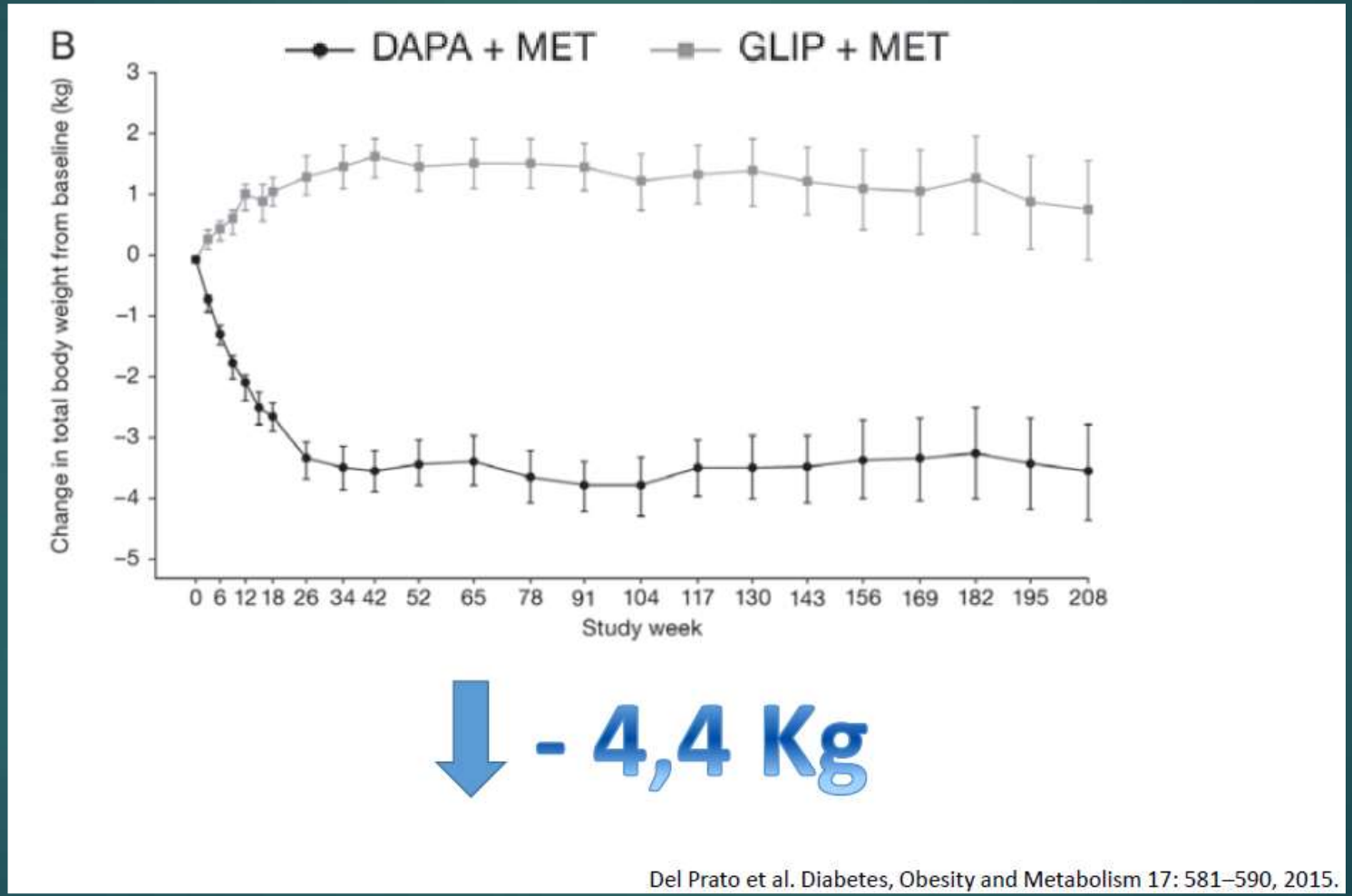
Eficacia demostrada como triterapia asociado a iDPP4/SU + MTF

Eficacia demostrada asociado a insulina

EFECTOS METABÓLICOS

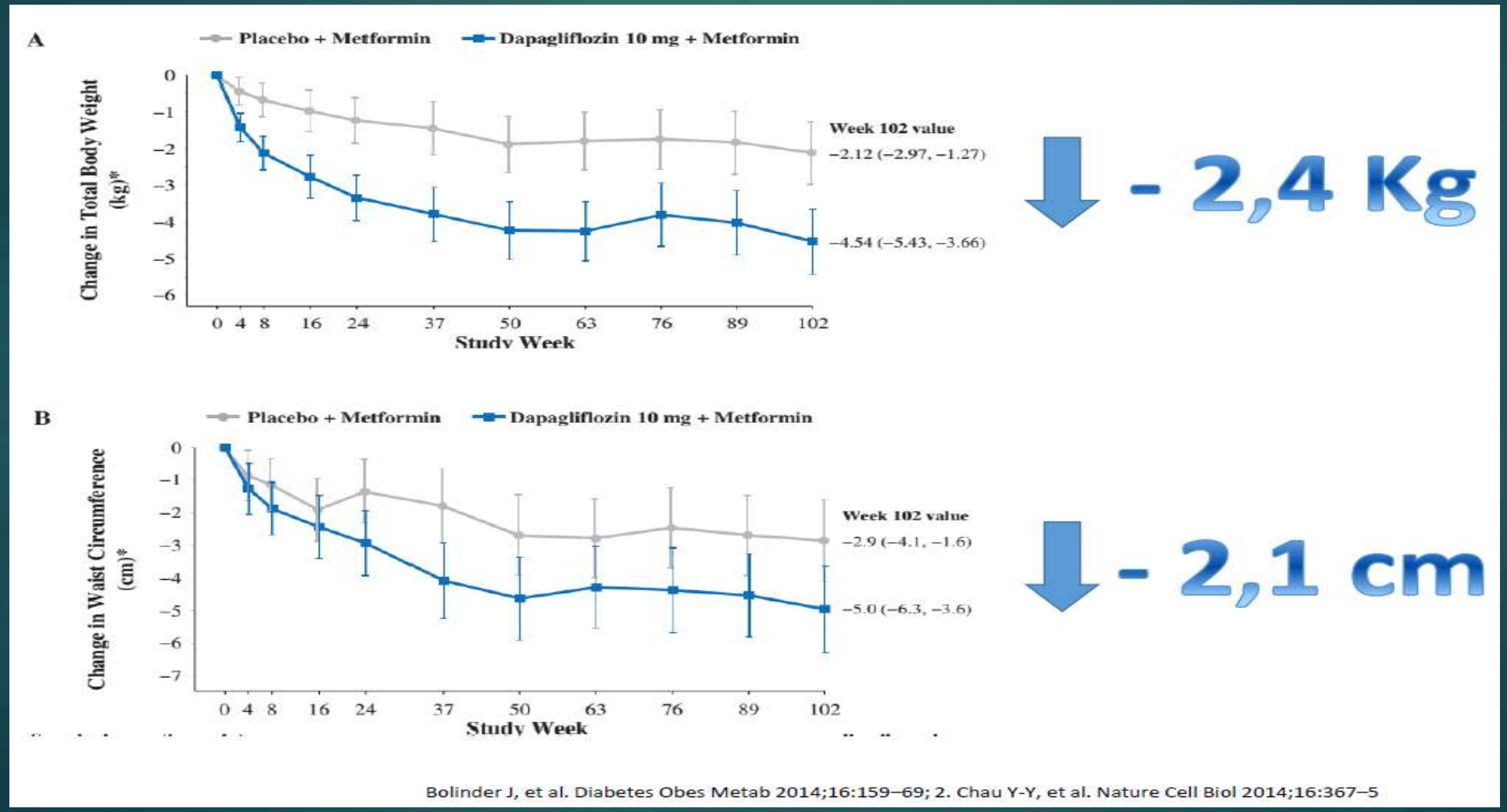


CAMBIOS EN PESO



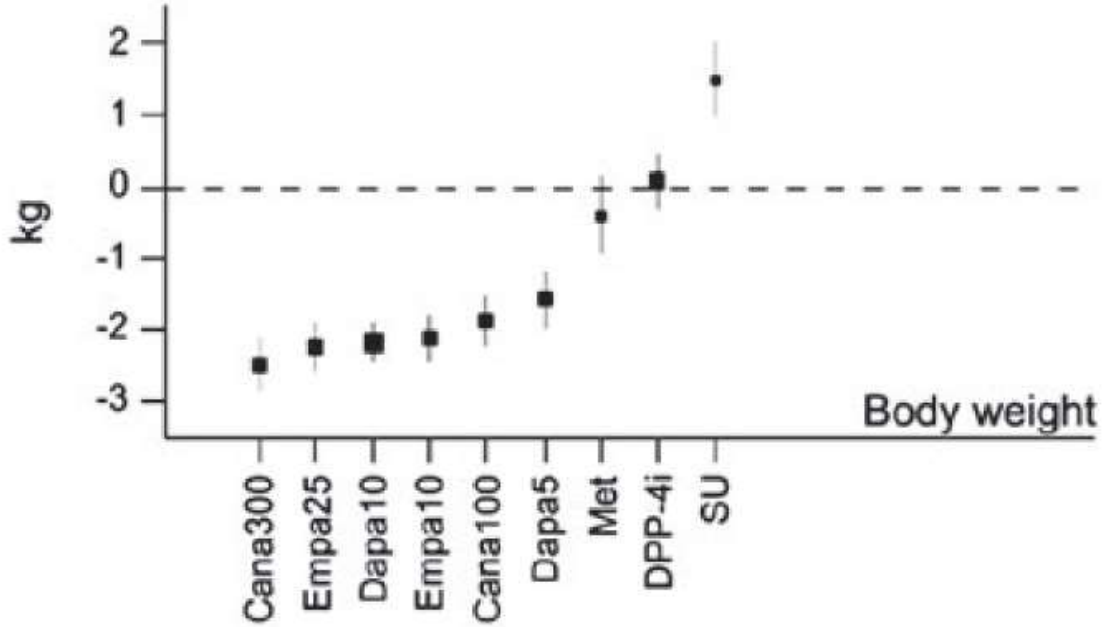
Del Prato et al. Diabetes, Obesity and Metabolism 17: 581–590, 2015.

CAMBIOS EN PESO

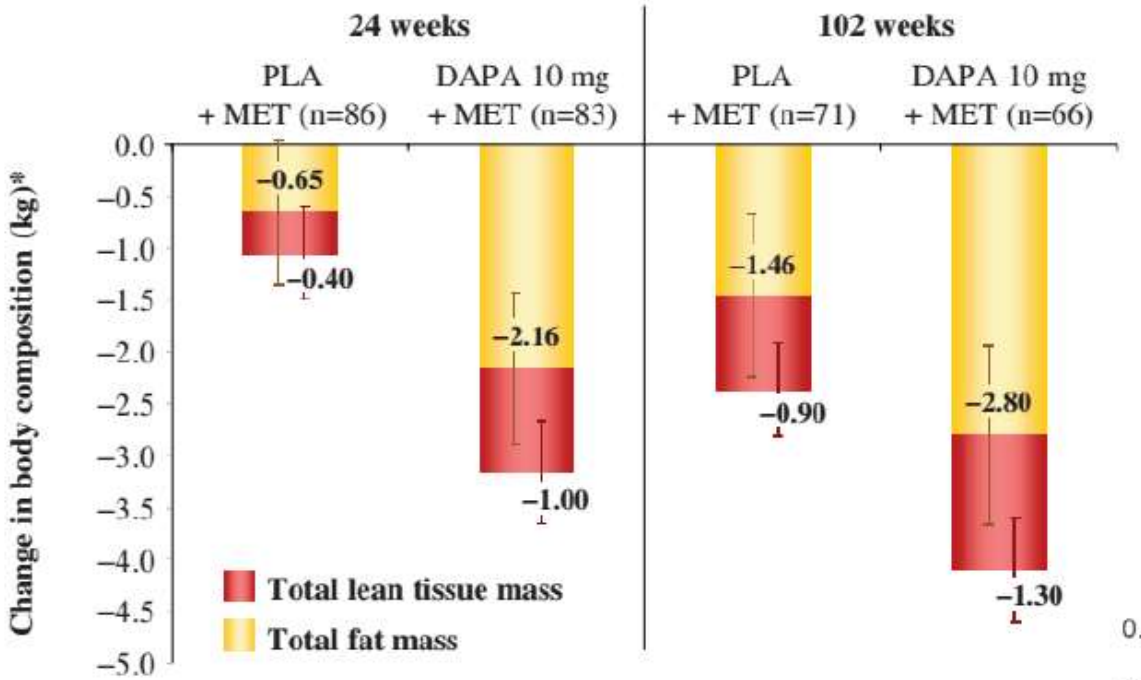


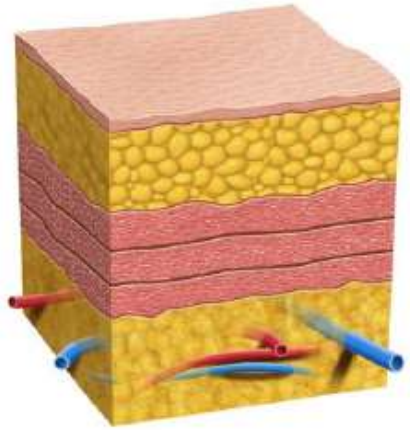
Bolinder J, et al. Diabetes Obes Metab 2014;16:159–69; 2. Chau Y-Y, et al. Nature Cell Biol 2014;16:367–5

CAMBIOS EN PESO

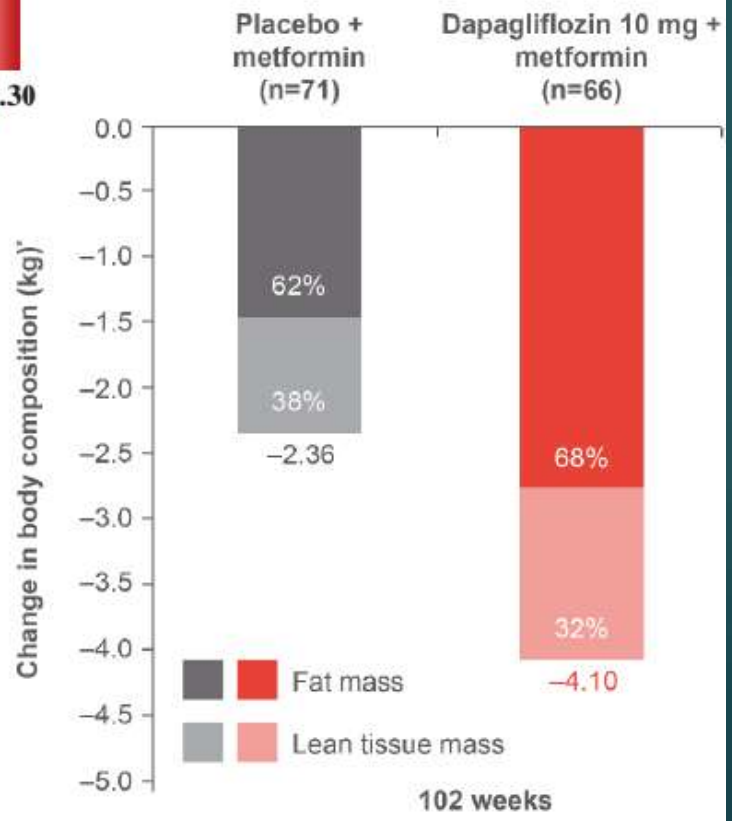


Zaccardi F et al. Diabetes, Obesity and Metabolism 18: 783–794, 2016



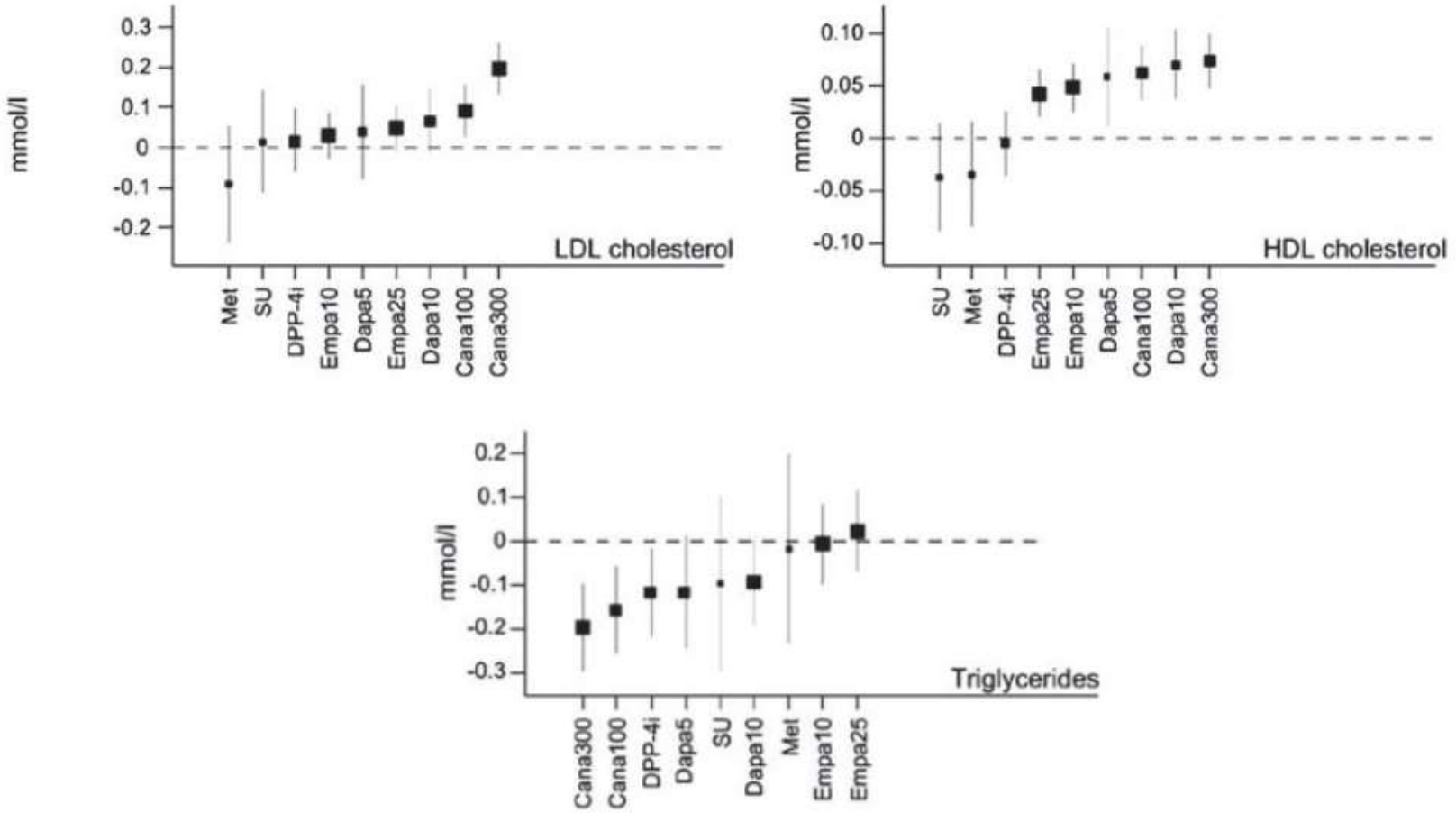


Pérdida de peso:
2/3 masa grasa
1/3 masa magra



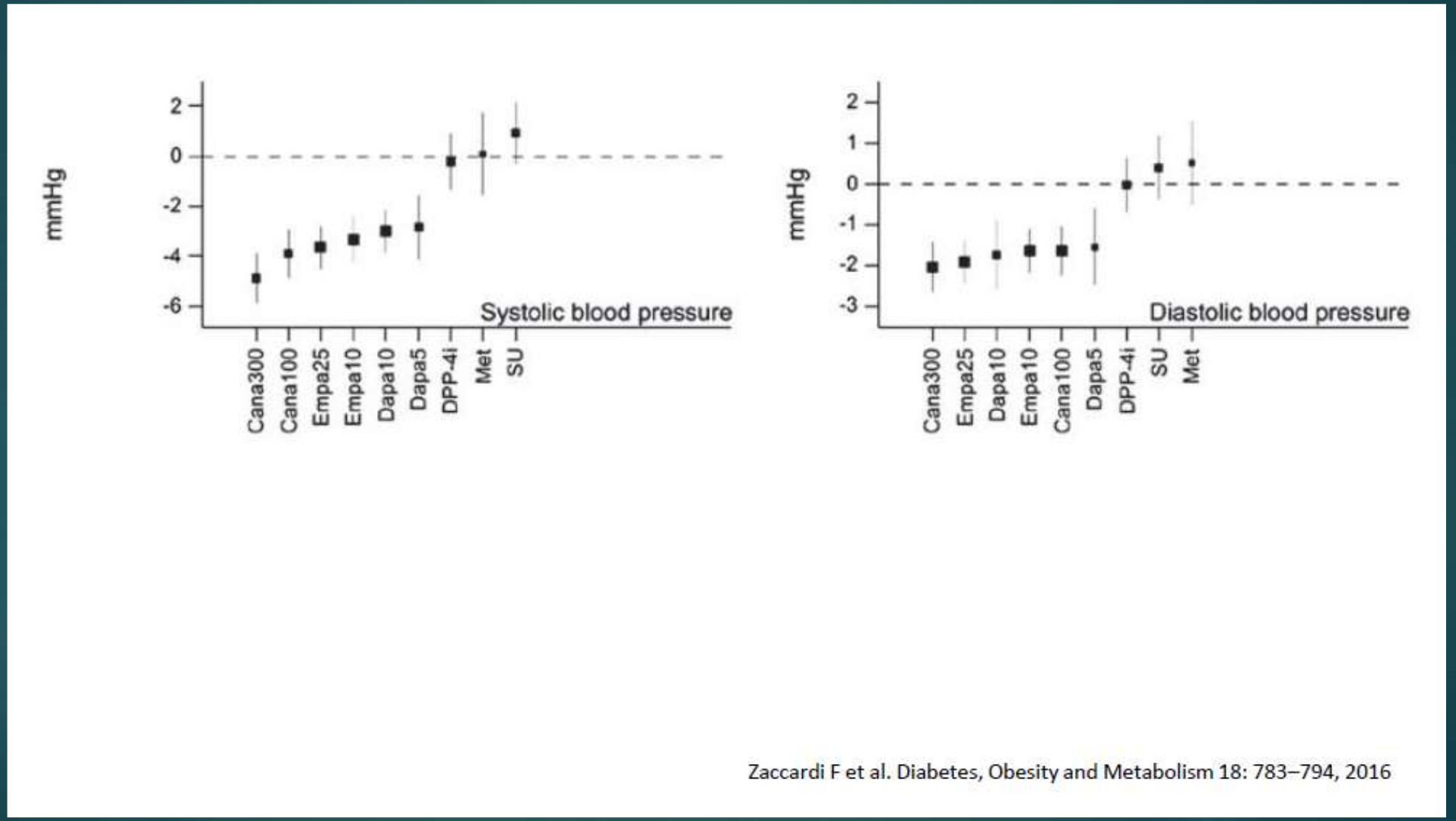
Bolinder J, et al. Diabetes Obes Metab 2014;16:159–69; 2. Chau Y-Y, et al. Nature Cell Biol 2014;16:367–5

PERFIL LIPÍDICO



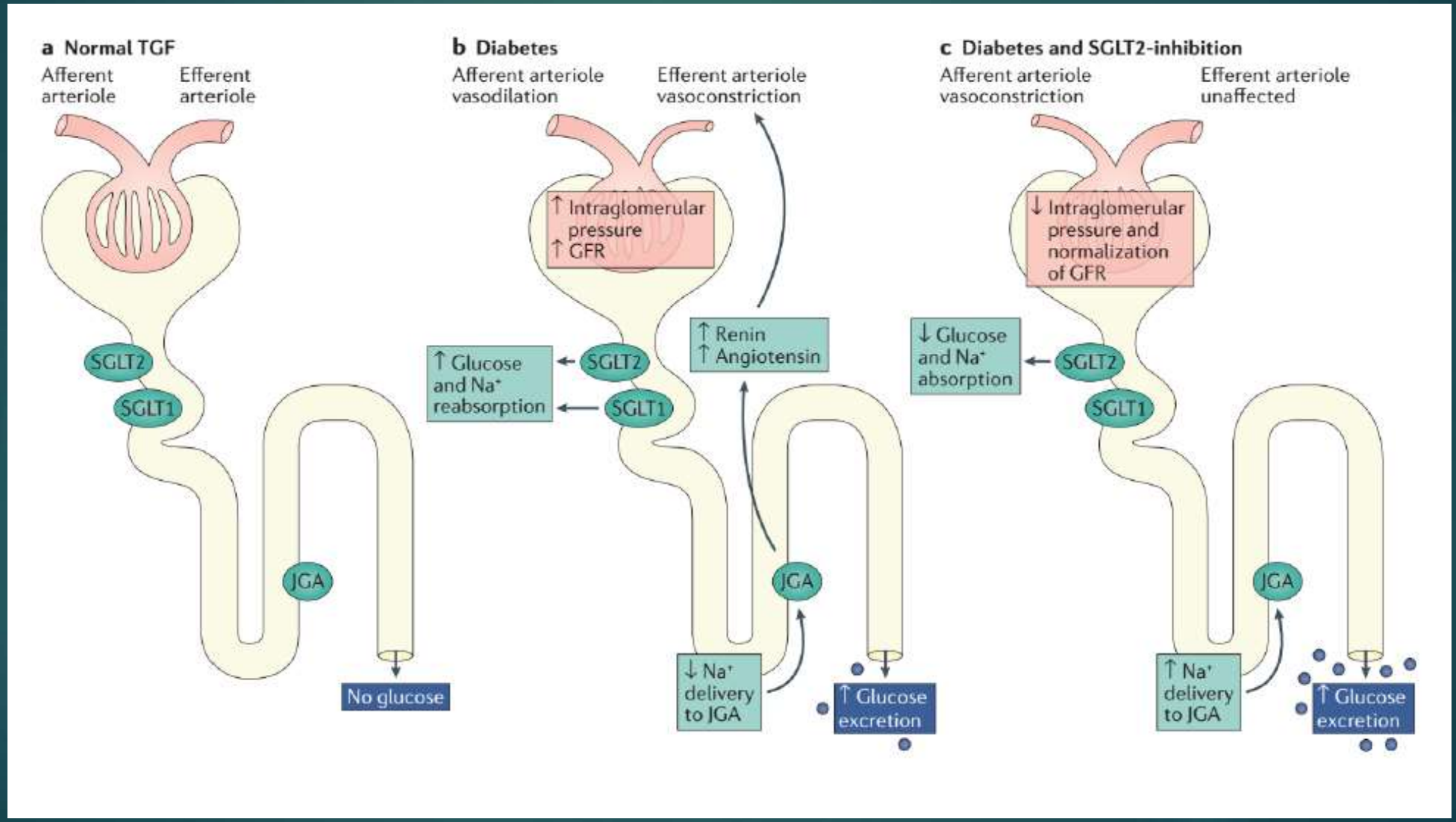
Zaccardi F et al. Diabetes, Obesity and Metabolism 18: 783–794, 2016

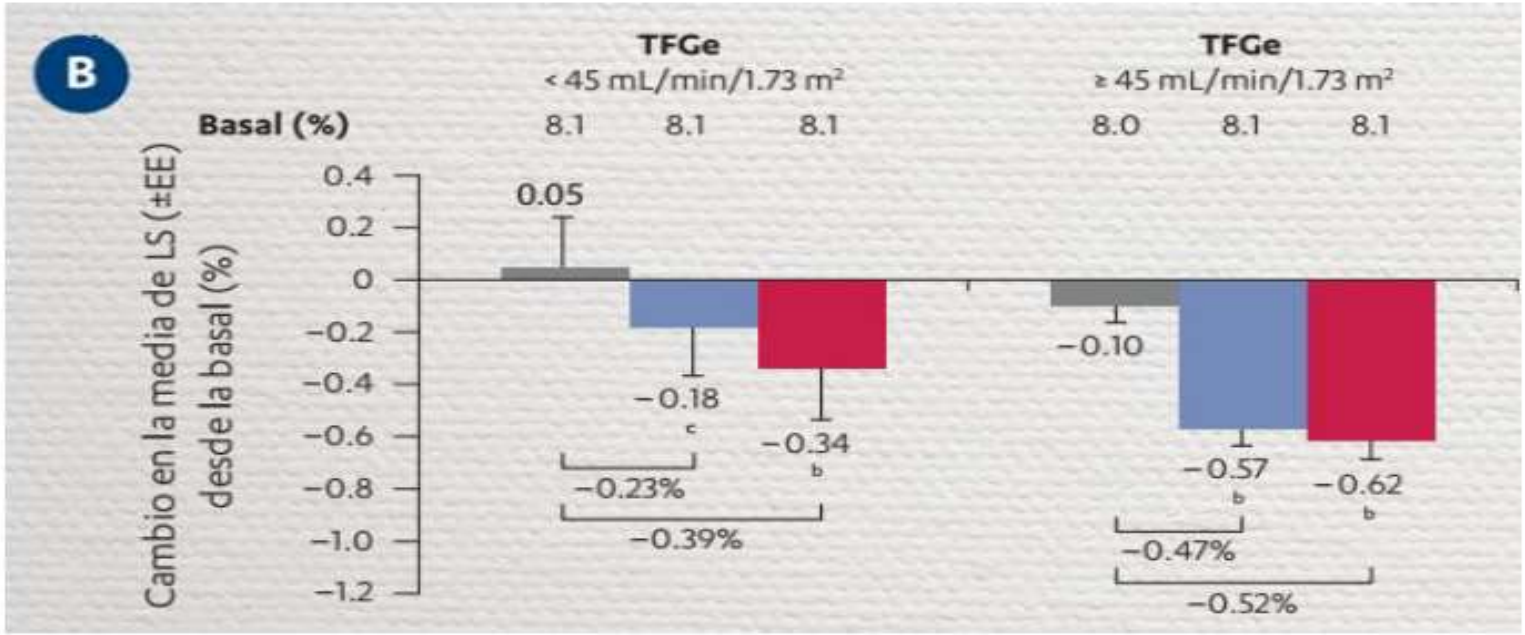
PRESIÓN ARTERIAL



Zaccardi F et al. Diabetes, Obesity and Metabolism 18: 783–794, 2016

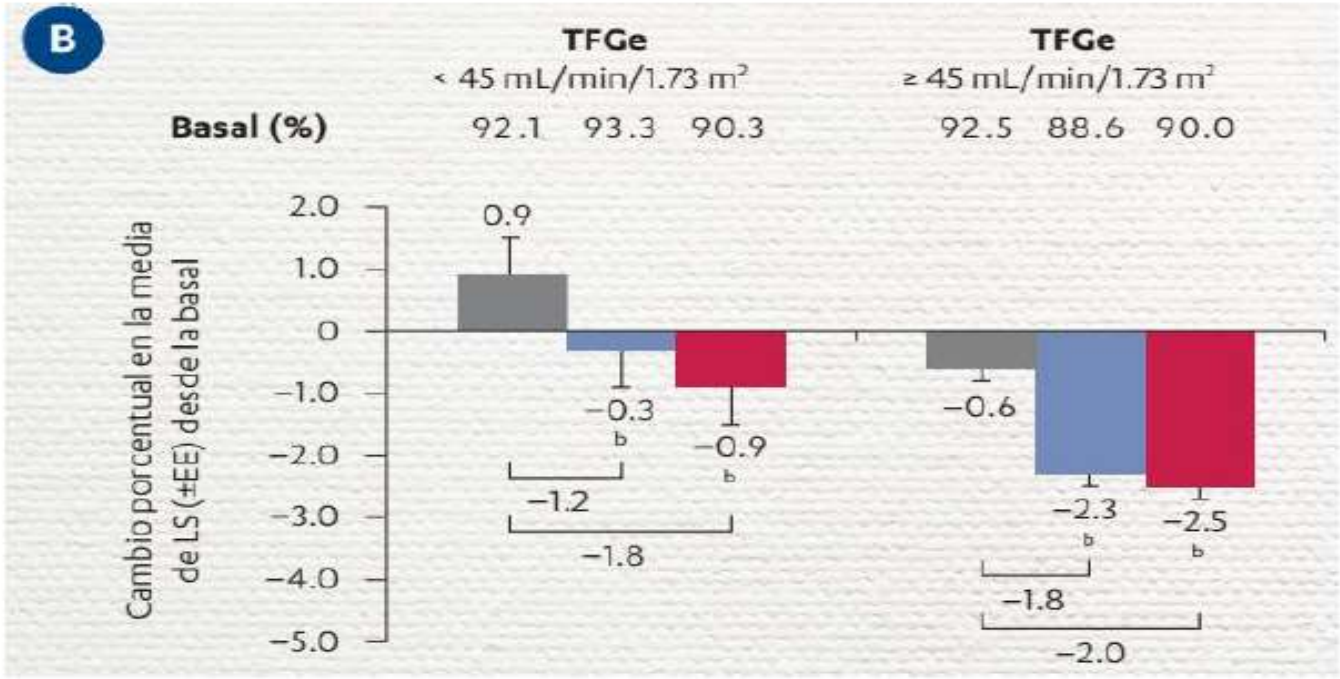
EFECTOS RENALES



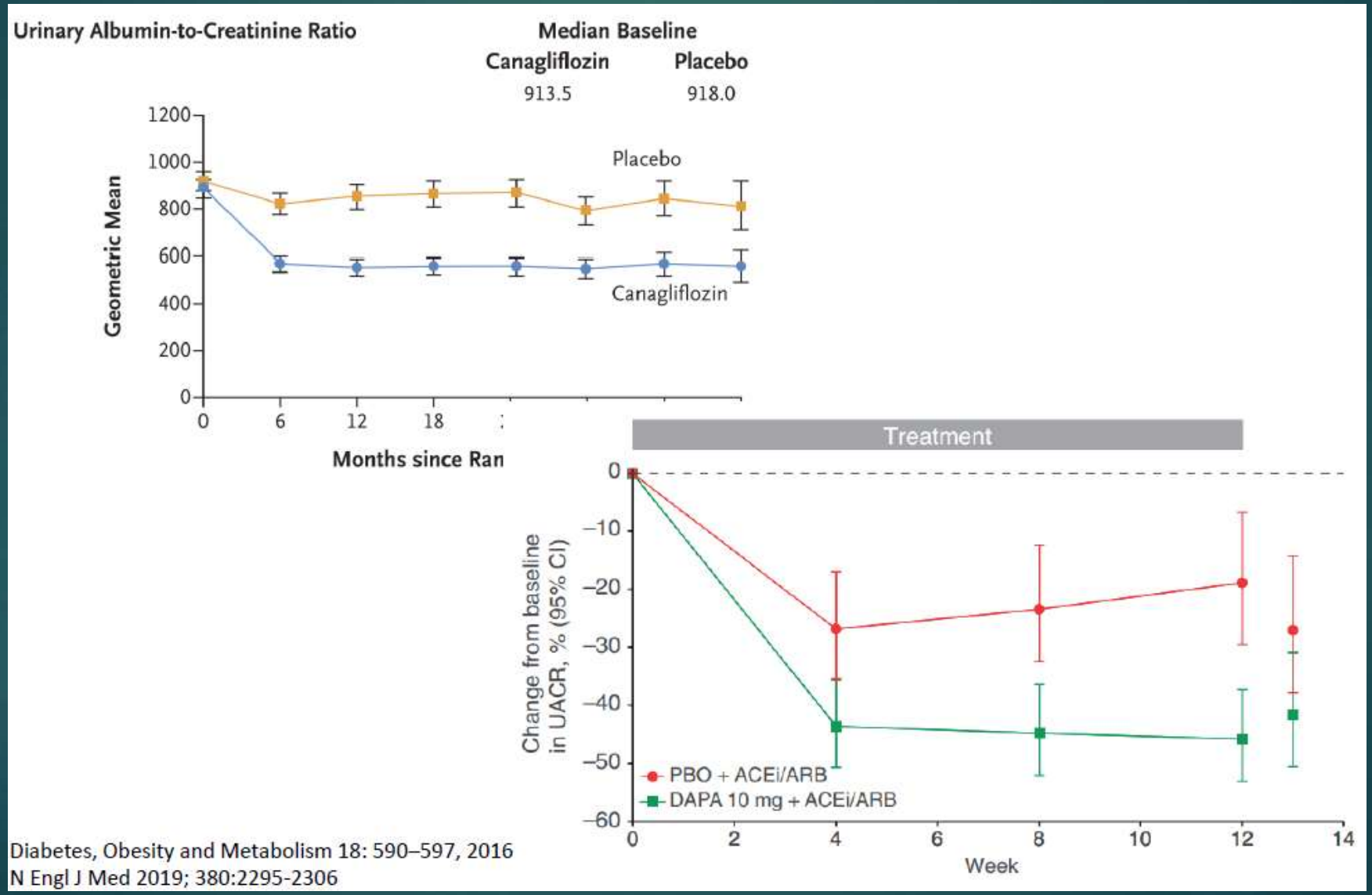

B
TFGe
< 45 mL/min/1.73 m²
TFGe
≥ 45 mL/min/1.73 m²
Basal (%)
8.1 8.1 8.1
8.0 8.1 8.1
Cambio en la media de LS (±EE) desde la basal (%)
0.4
0.2
0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
0.05
−0.18 c
−0.34 b
−0.23%
−0.39%
−0.10
−0.57 b
−0.62 b
−0.47%
−0.52%

A1c

Peso

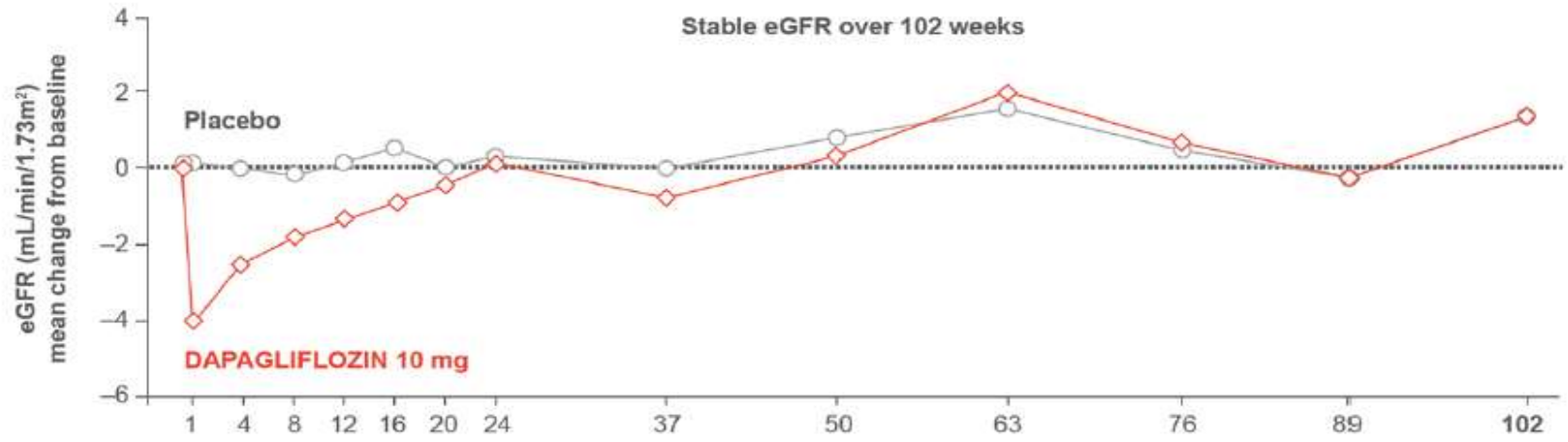

B
TFGe
< 45 mL/min/1.73 m²
TFGe
≥ 45 mL/min/1.73 m²
Basal (%)
92.1 93.3 90.3
92.5 88.6 90.0
Cambio porcentual en la media de LS (±EE) desde la basal
2.0
1.0
0
−1.0
−2.0
−3.0
−4.0
−5.0
0.9
−0.3 b
−0.9 b
−1.2
−1.8
−0.6
−2.3 b
−2.5 b
−1.8
−2.0

INHIBIDORES SGLT-2 Y ALBUMINURIA



Diabetes, Obesity and Metabolism 18: 590–597, 2016
N Engl J Med 2019; 380:2295-2306

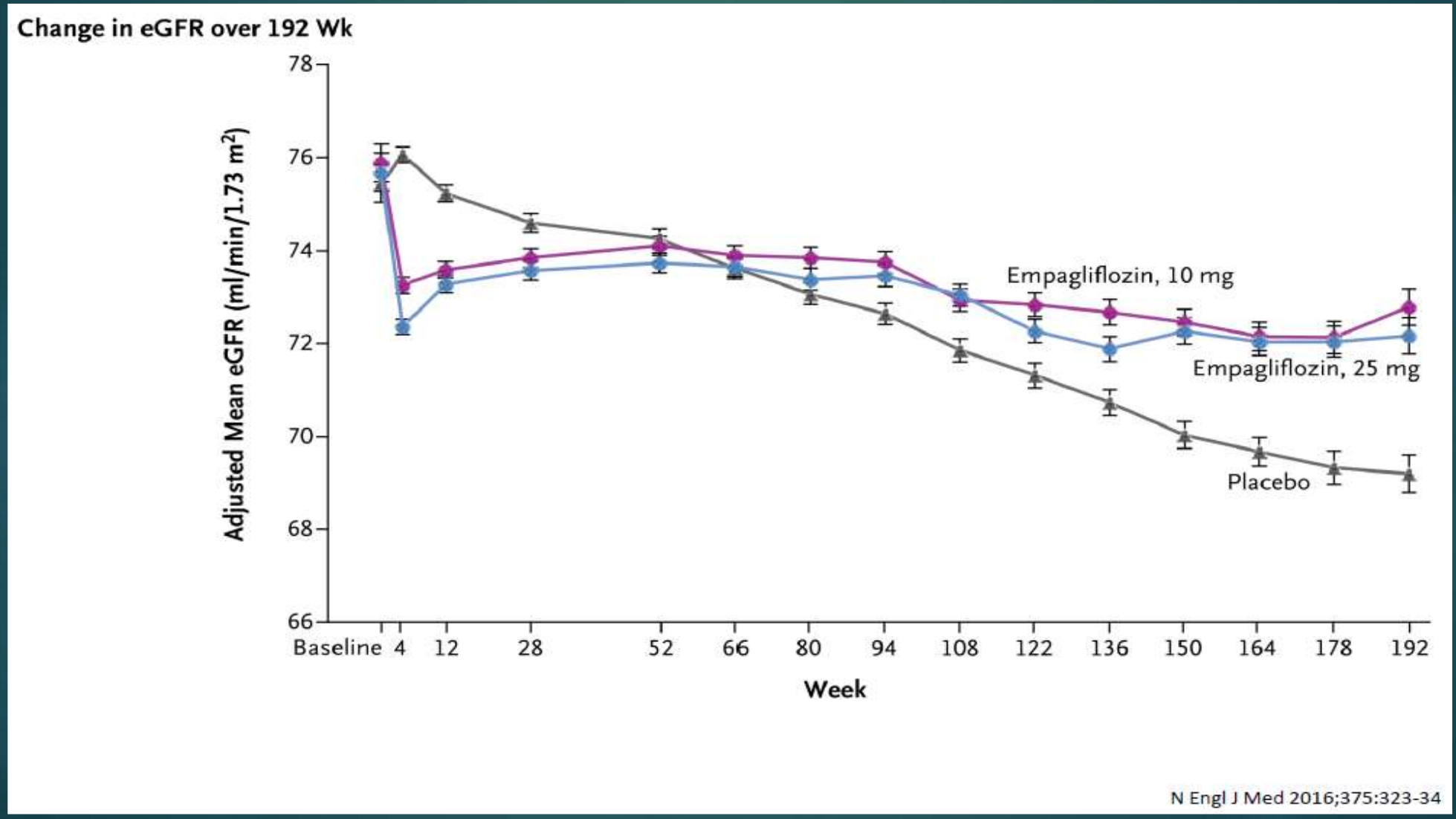
INHIBIDOR DE SGLT-2 Y EFECTO EN VFG



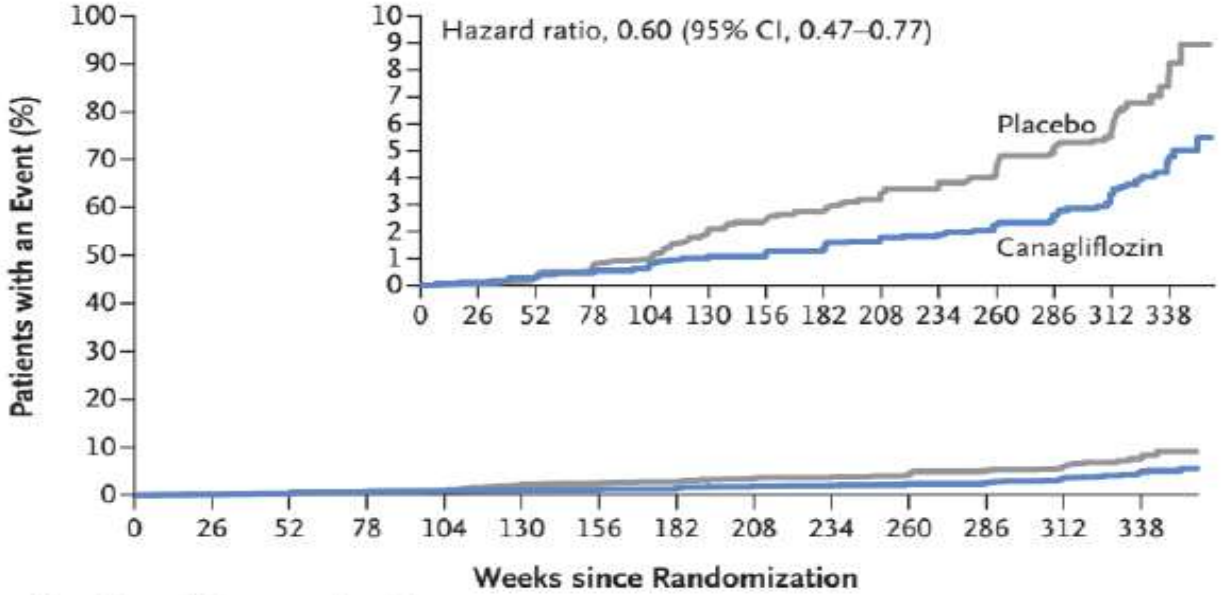
Number of patients													
DAPAGLIFLOZIN 10 mg	744	740	728	717	706	681	676	670	646	367	310	220	166
Placebo	683	666	649	626	616	598	598	578	546	266	219	148	107

Kohan DE, et al. J Nephrol 2016;29:391–400

INHIBIDOR DE SGLT-2 Y EFECTO EN VFG

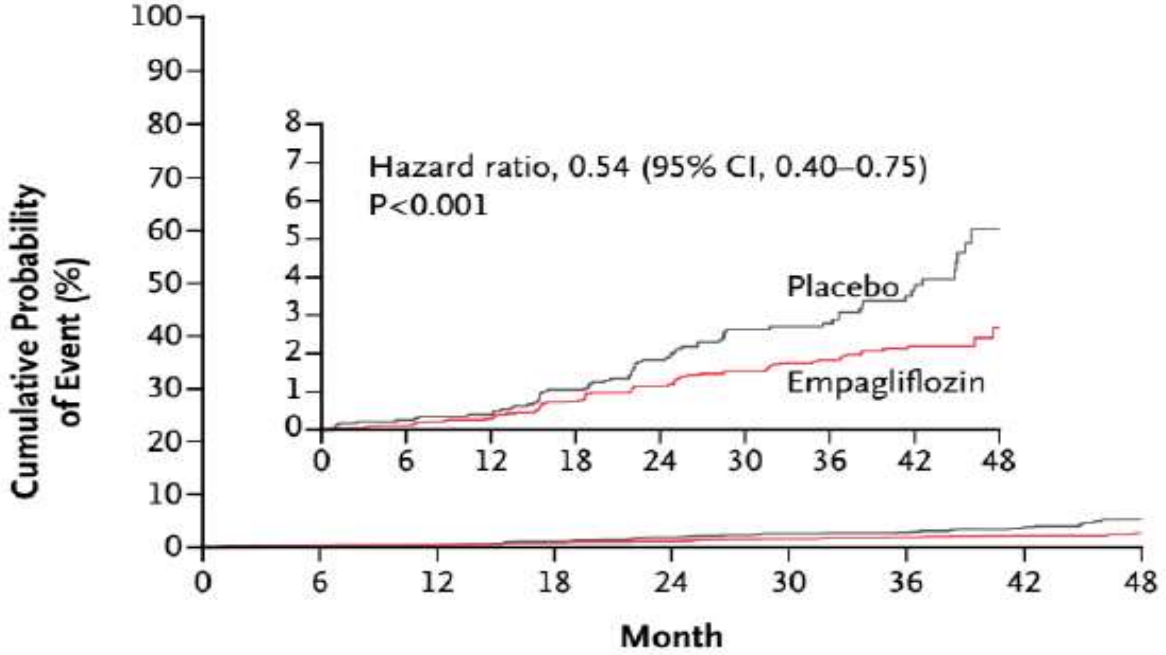


D Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy, or Death from Renal Causes



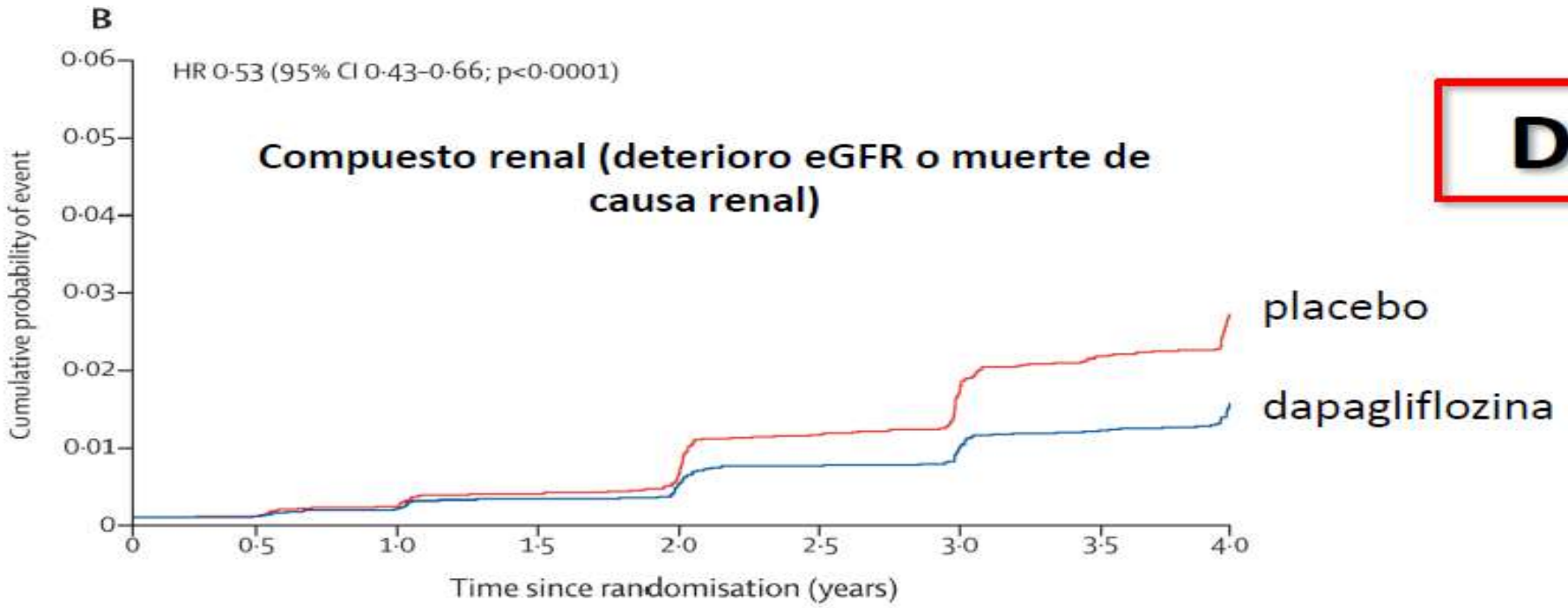
CANVAS

B Post Hoc Renal Composite Outcome

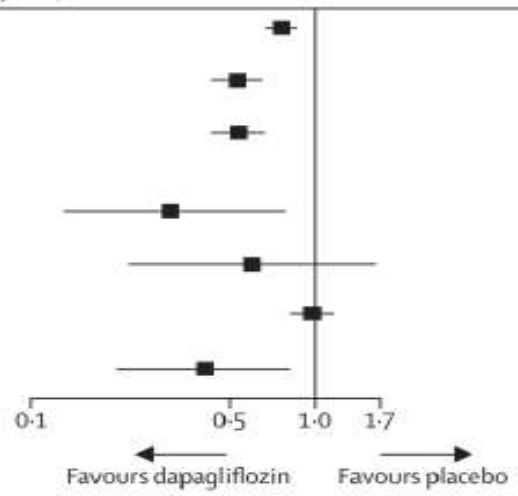


EMPA-REG

DECLARE



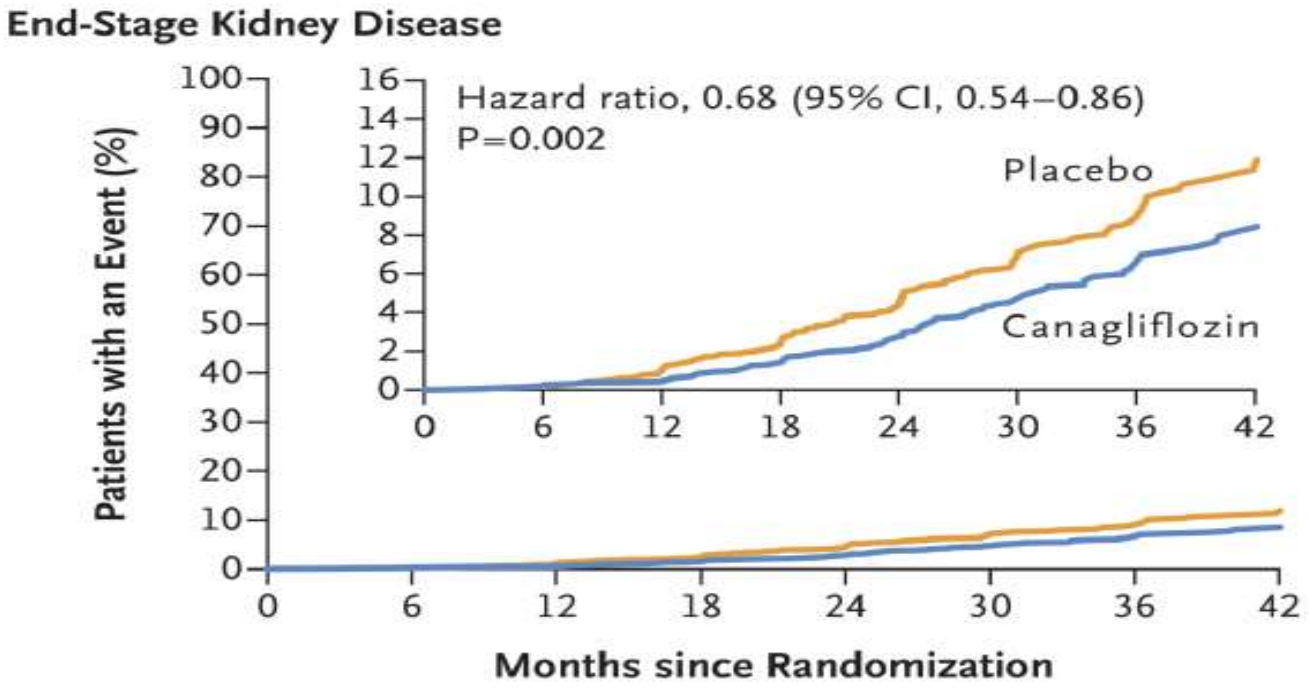
	Dapagliflozin group		Placebo group		Hazard ratio (95% CI)	p value
	n/N (%)	Kaplan-Meier event rate (4 years)	n/N (%)	Kaplan-Meier event rate (4 years)		
Composite cardiorenal outcome	370/8582 (4·3%)	4·2%	480/8578 (5·6%)	5·3%	0·76 (0·67–0·87)	<0·0001
Composite renal-specific outcome	127/8582 (1·5%)	1·5%	238/8578 (2·8%)	2·6%	0·53 (0·43–0·66)	<0·0001
Sustained eGFR decrease ≥40% to eGFR <60mL/ min per 1·73m²	120/8582 (1·4%)	1·4%	221/8578 (2·6%)	2·5%	0·54 (0·43–0·67)	<0·0001
End-stage renal disease	6/8582 (0·1%)	0·1%	19/8578 (0·2%)	0·2%	0·31 (0·13–0·79)	0·013
Renal death	6/8582 (0·1%)	0·1%	10/8578 (0·1%)	0·1%	0·60 (0·22–1·65)	0·32
Cardiovascular death	245/8582 (2·9%)	2·7%	249/8578 (2·9%)	2·7%	0·98 (0·82–1·17)	0·83
End-stage renal disease or renal death	11/8582 (0·1%)	0·1%	27/8578 (0·3%)	0·3%	0·41 (0·20–0·82)	0·012



Estudio CREDENCE

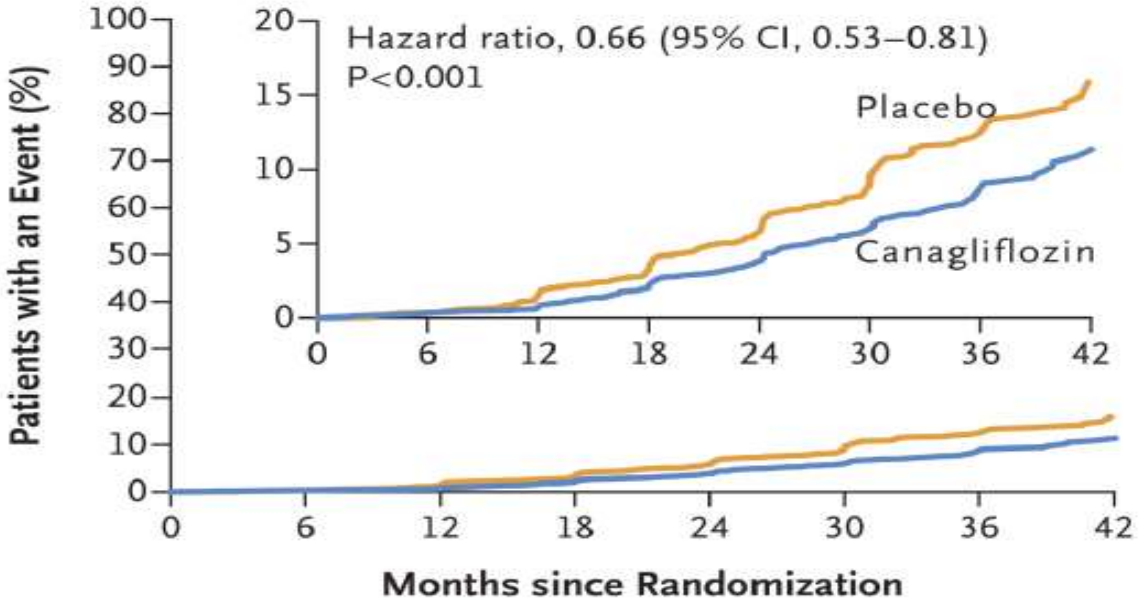
- Primer y único estudio publicado a la fecha, con diseño para búsqueda de efectos renales con iSGLT-2 (canagliflozina)

- 4401 pacientes DM2
- 96% HTA, eGFR promedio 56 ml/min y albuminuria promedio de 927 mg/gr creatinina

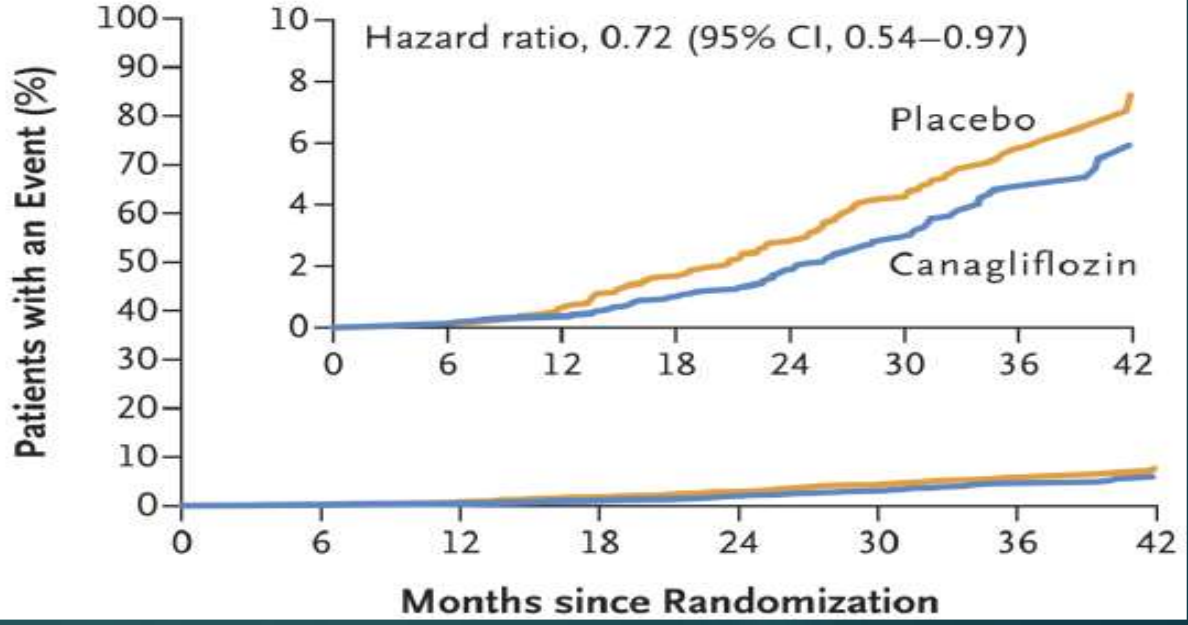


N Engl J Med 2019; 380:2295-2306

Renal-Specific Composite Outcome

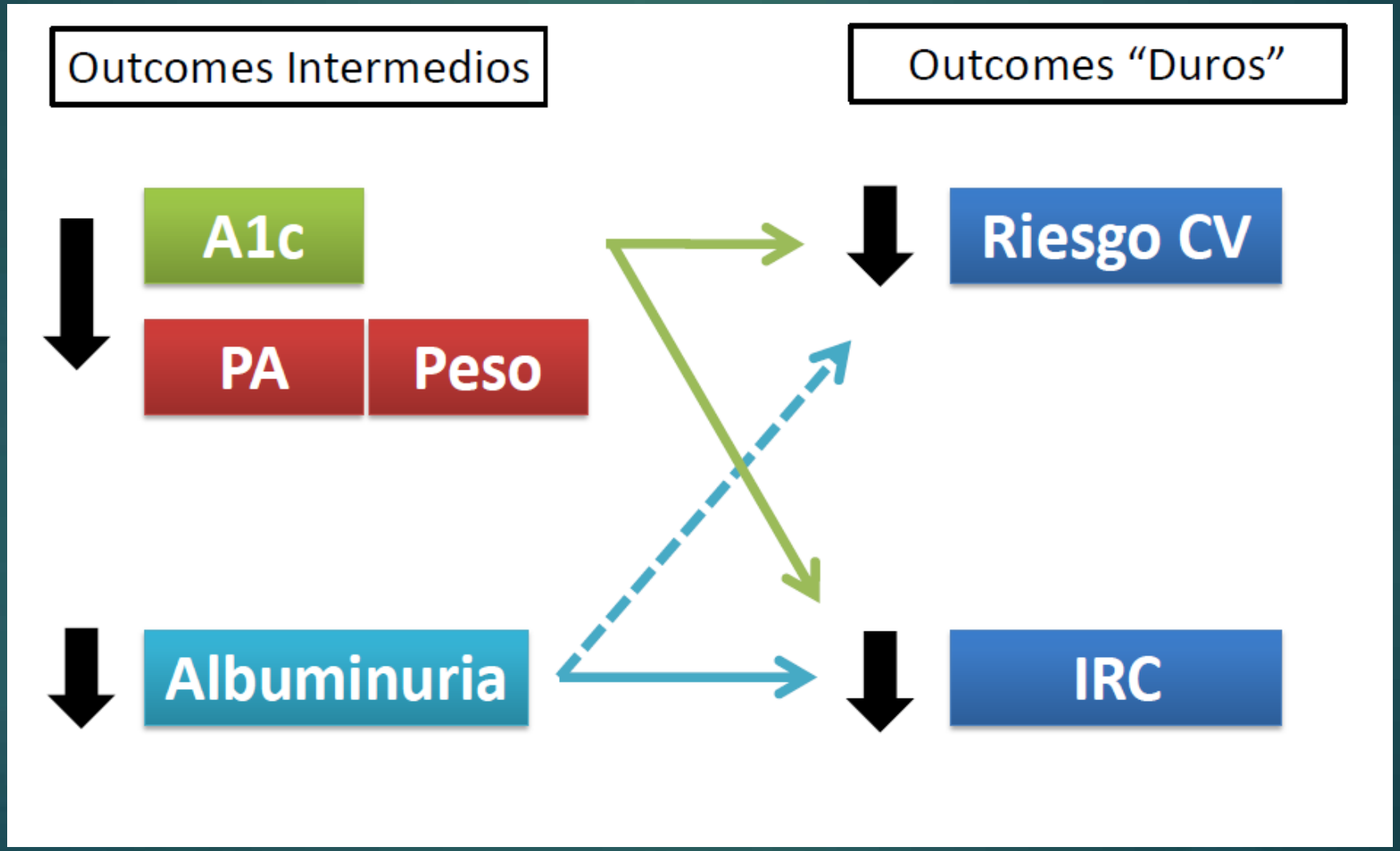


Dialysis, Kidney Transplantation, or Renal Death



N Engl J Med 2019; 380:2295-2306

INHIBIDORES SGLT-2: RESUMEN



EFECTOS ADVERSOS ISGLT-2

- Infección urinaria
- Infección genital micótica
- Depleción de volumen –Hipotensión
- Hipoglicemia
- CAD
- Amputaciones / Fracturas?
- Litiasis