Mesures farmacològiques en el maneig de la Diabetes tipus 2

II JORNADA d'Actualització en Risc Cardiovascular

de la VOCALIA DE TARRAGONA de la CAMFiC

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RedGDPS
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PCDE primary care diabetes europe

redGDPS Red de Grupos de Estudio de la Diabetes EN ATENCIÓN PRIMARIA DE LA SALUD

UAB Universitat Autònoma de Barcelona

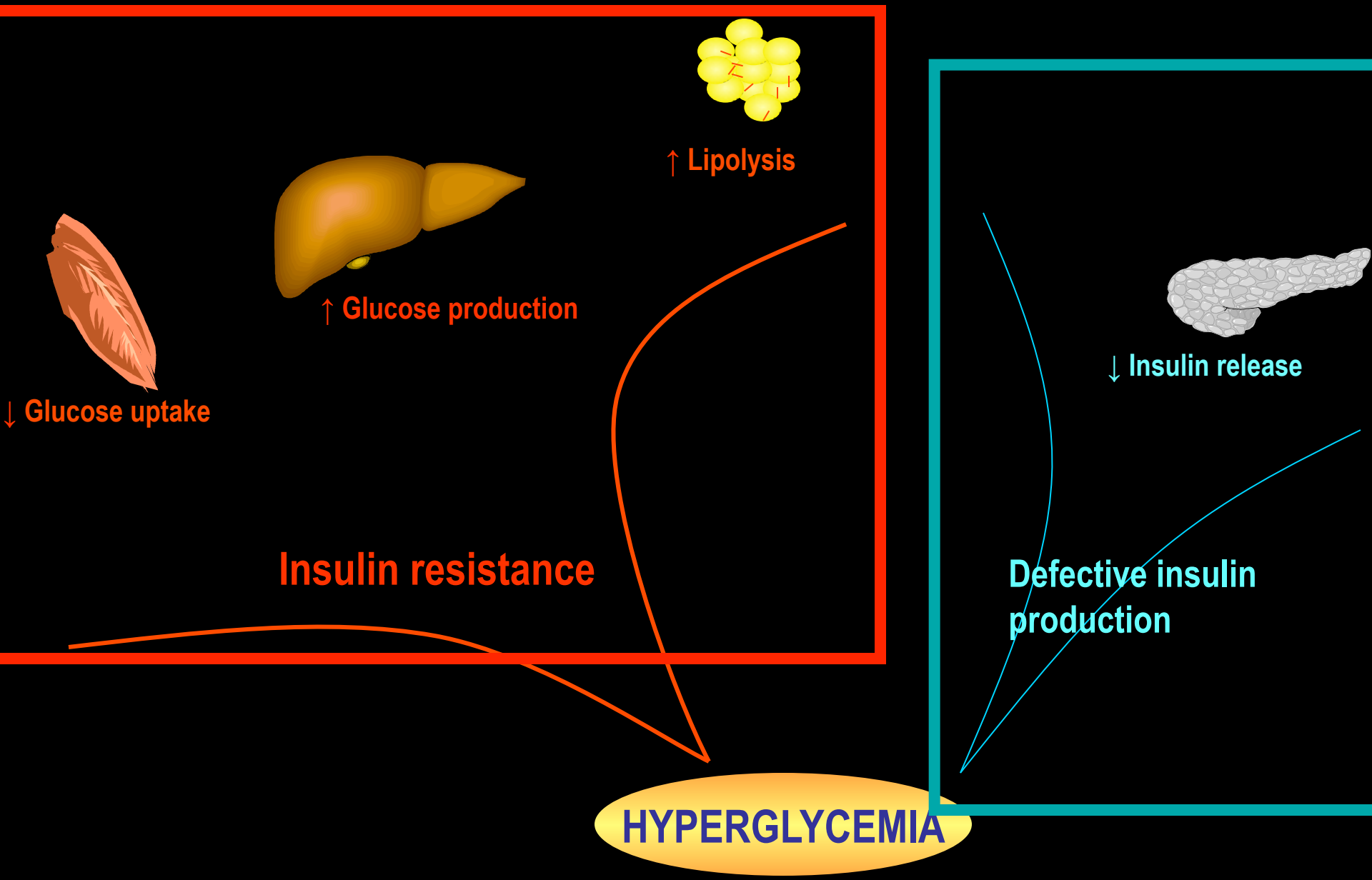
IDIAP Jordi Gol

Conflicte interès

XC: Ha rebut honoraris assaitjos clínics, consultant i advisory board per Boehringer Ingelheim, Lilly, MSD, Abbott, Novartis, Novo Nordisk, Sanofi-Aventis, Janssen y Astra-Zeneca.

Sumari

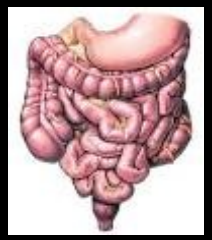
- La fisipatologia de la DM i el tractament
- Guies/Algoritmes/Recomanacions
- Tractament no insulinic (Inh DPP IV,AR GLP1,Inh.SGLT2)
- Individualització



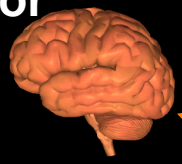
Inzucchi SE. Oral antihyperglycemic therapy for type 2 Diabetes. Scientific review. JAMA 2002; 287:360-376

Currently Approved Non-Insulin Diabetes Medications

α–Glucosidase Inhibitor
Acarbose Miglitol



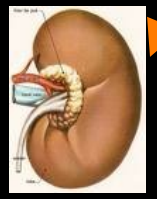
GI Tract



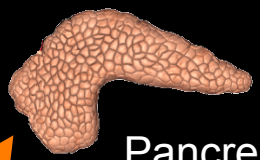
Brain

GLP-1 Receptor Agonists
Exenatide
Exenatide XR
Liraglutide
Lixisenatide

Sodium-Glucose Cotransporter 2 Inhibitor
Dapagliflozina
Canaglifozina
Empaglifozina



Kidney

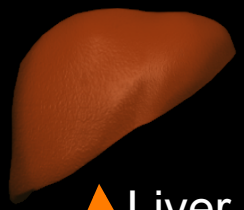


Pancreas

Sulfonilureas
Glimepiride
Glipizide
Glibenclamide
+ Others

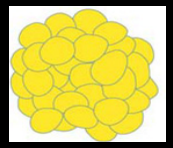
Meglitinides
Nateglinide
Repaglinide

DPP-4 Inhibitors
Sitagliptin
Saxagliptin
Linagliptin
Vildagliptin

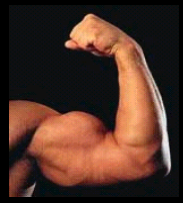


Liver

Metformin



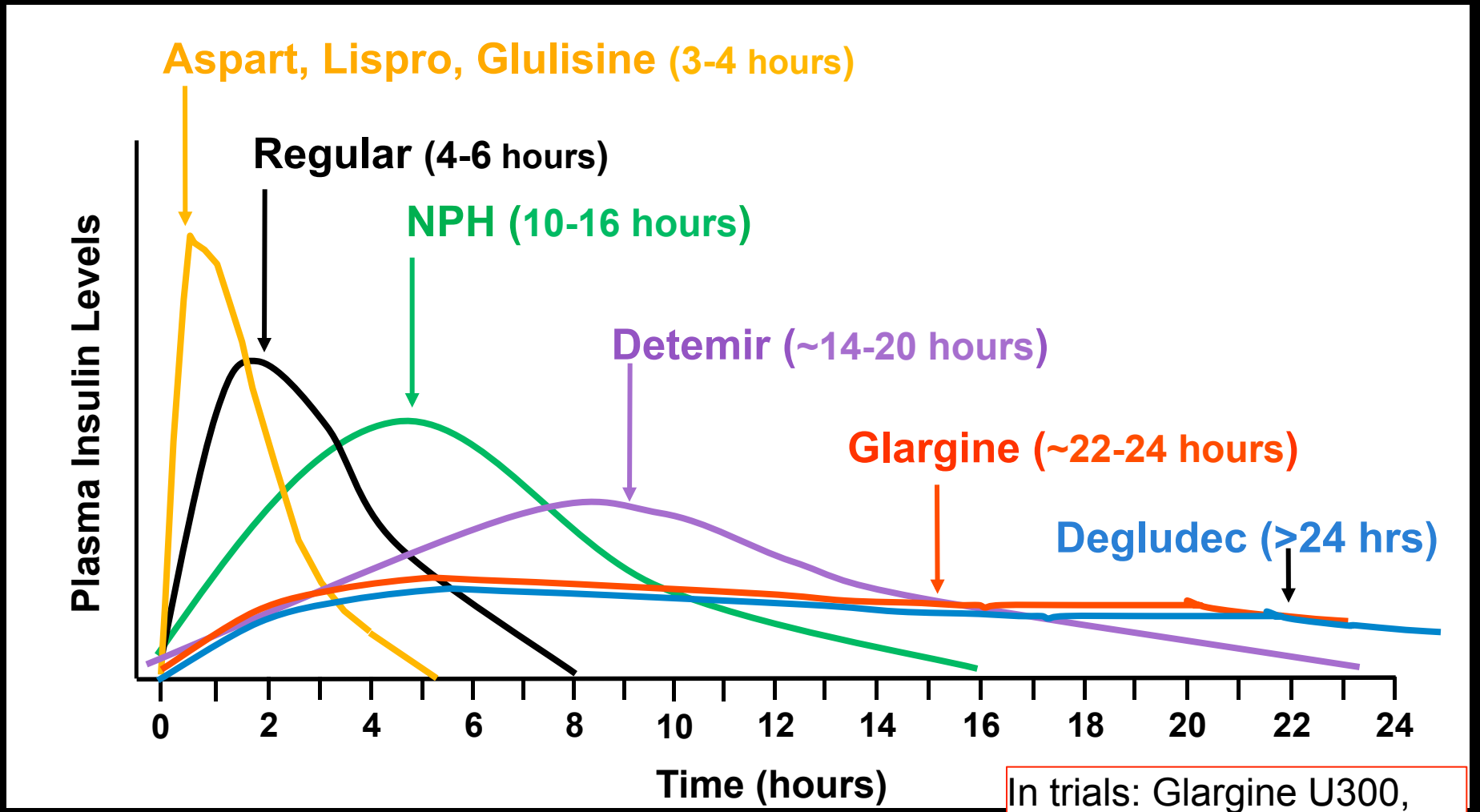
Adipose



Muscle

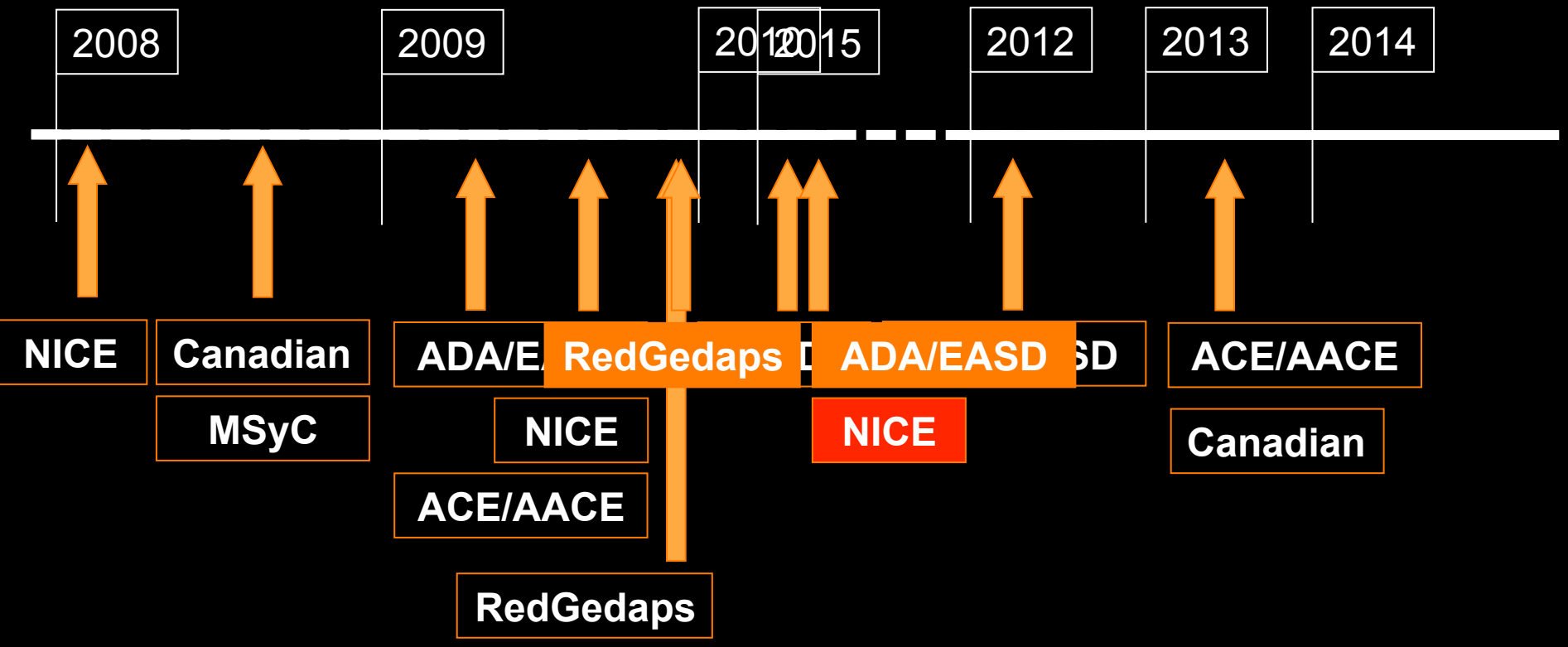
Thiazolidinediones
Pioglitazone

Insulines

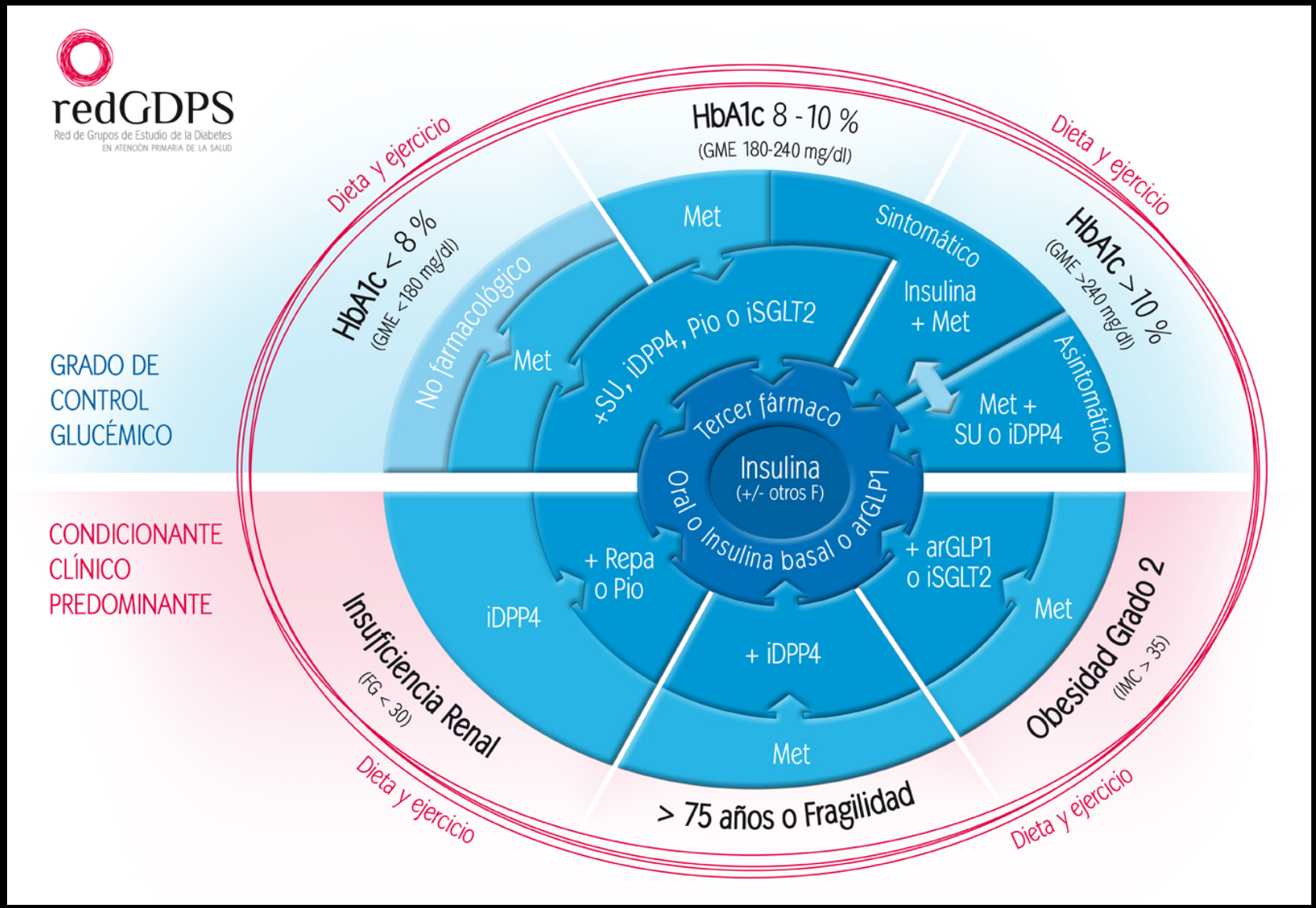


In trials: Glargine U300, Lilly Biosimilar glargina

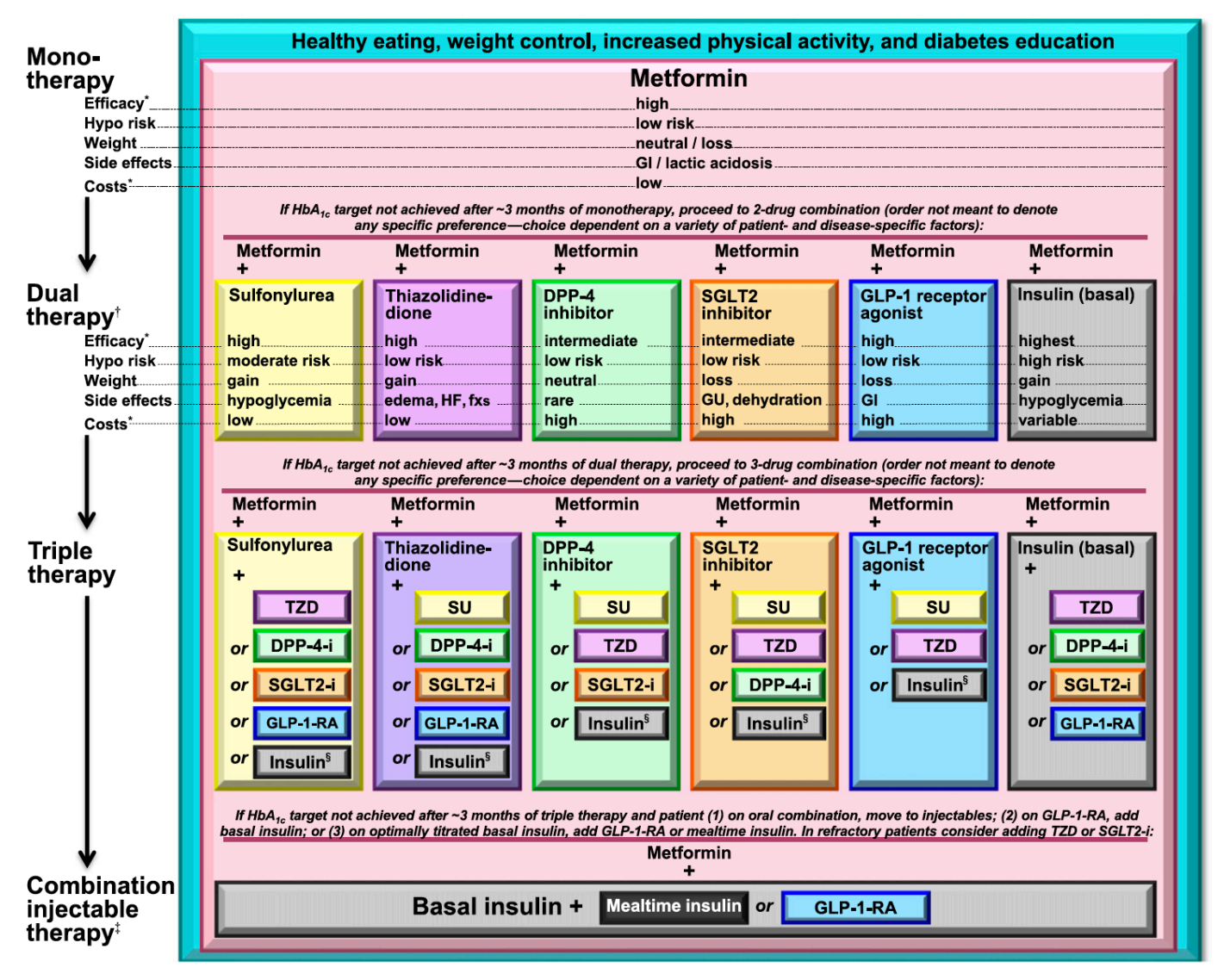
Guies · Recomenacions



Guies · Recomenacions

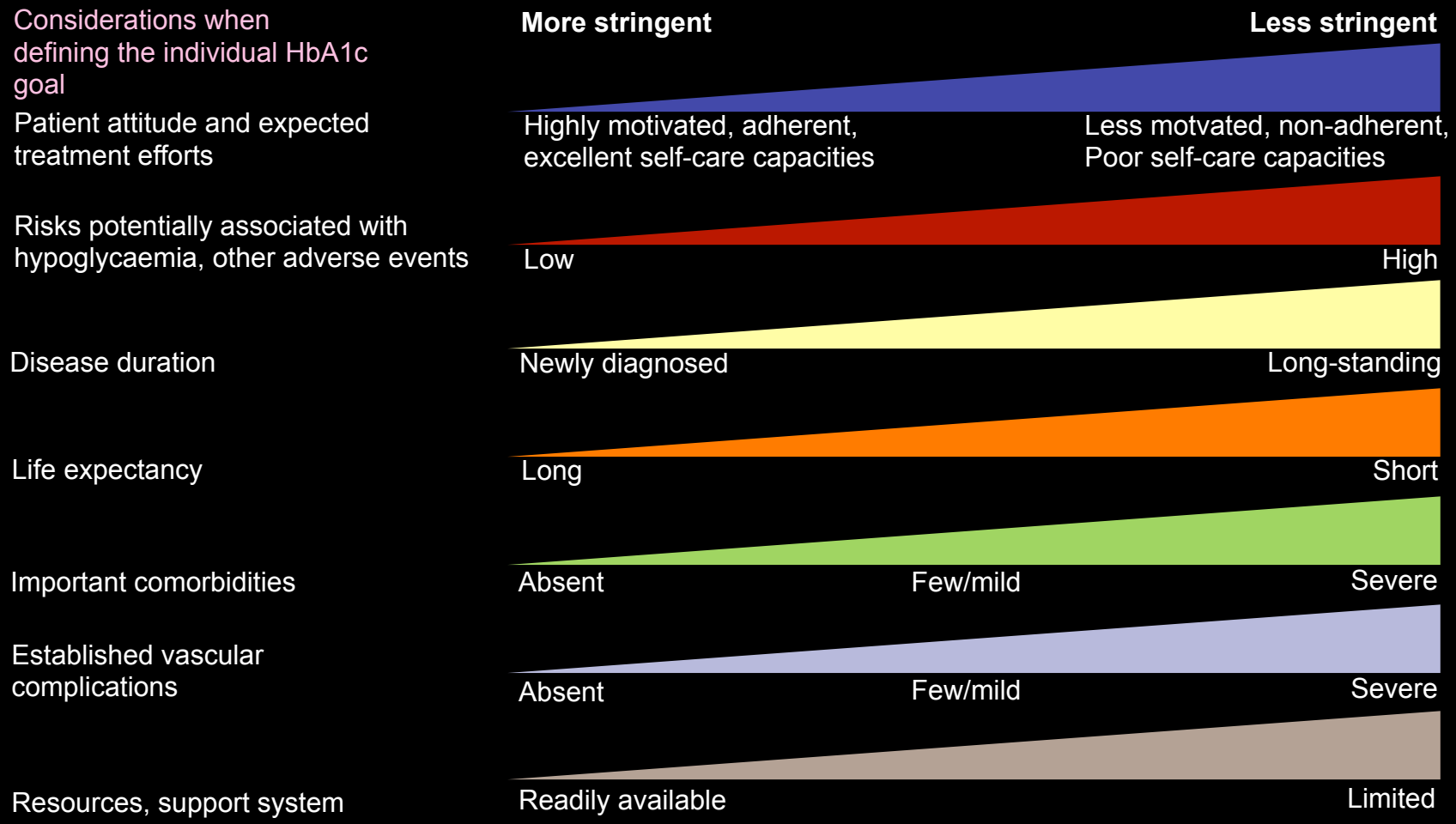


Guies · Recomenacions



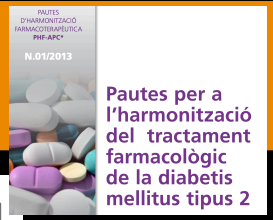
Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015 Jan;38(1):140-149.

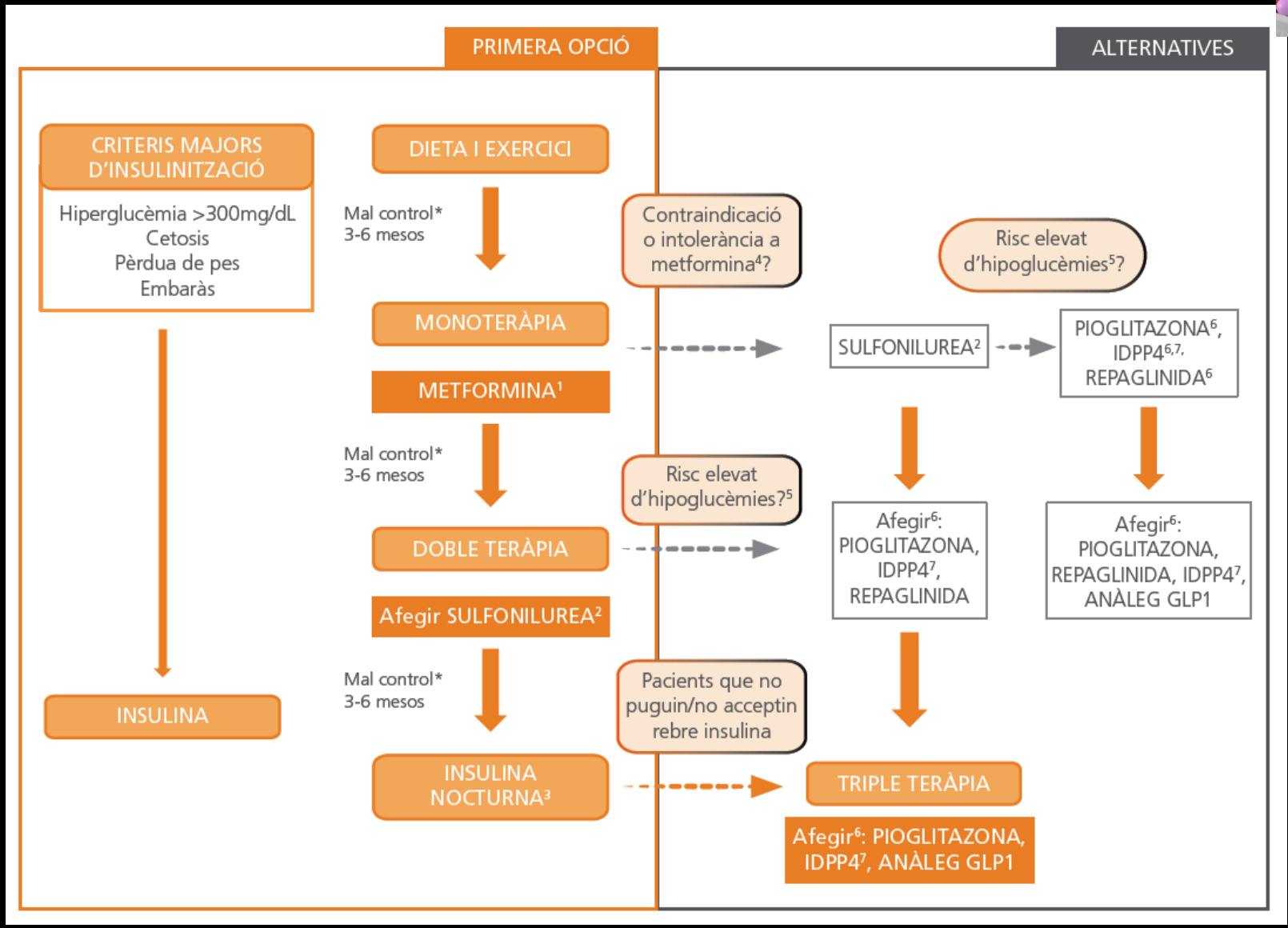
ADA/EASD position statement: A patient-centered approach...



Adapted from ADA/EASD position statement; Inzucchi et al. Diabetologia /Diab. Care (2012)

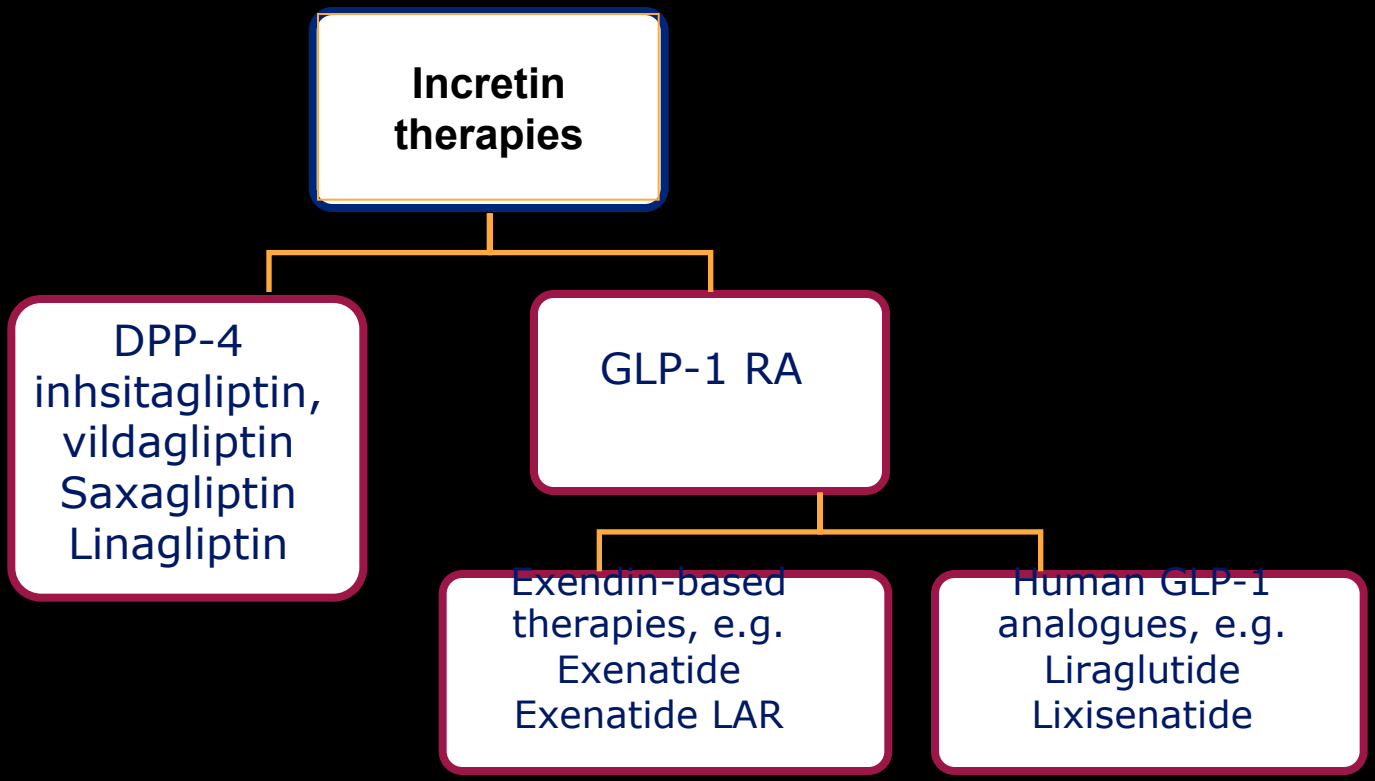
Guies · Recomenacions

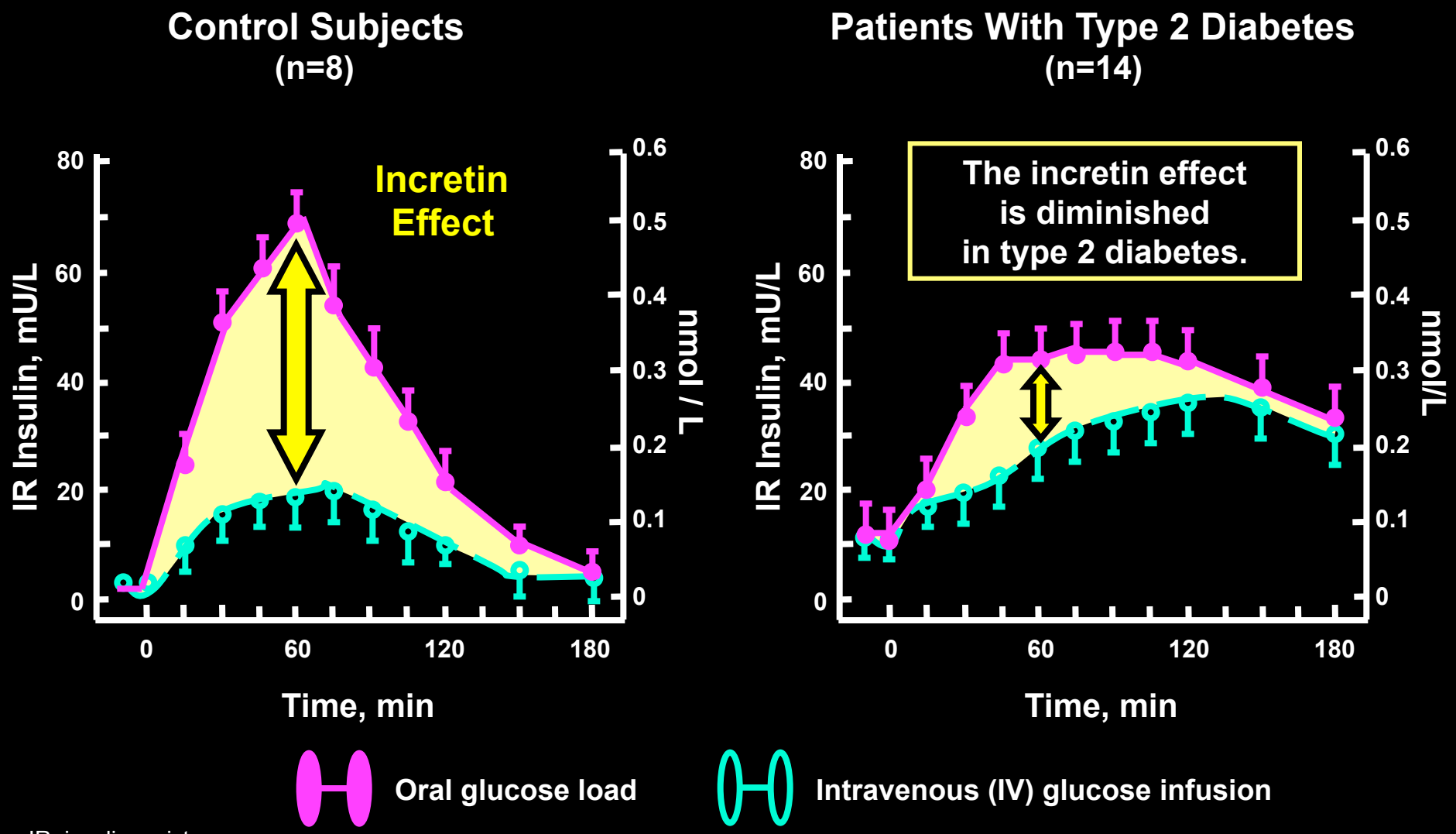




Pautes per al tractament farmacològic de la diabetis mellitus tipus 2. Barcelona: Agència de Qualitat i Avaluació Sanitàries de Catalunya.Departament de Salut. Generalitat de Catalunya; 2013. (Programa d'Harmonització Farmacoterapèutica de Medicaments en l'Àmbit de l'Atenció Primària i Comunitària del Servei Català de la Salut; 1/2013).

Tractament

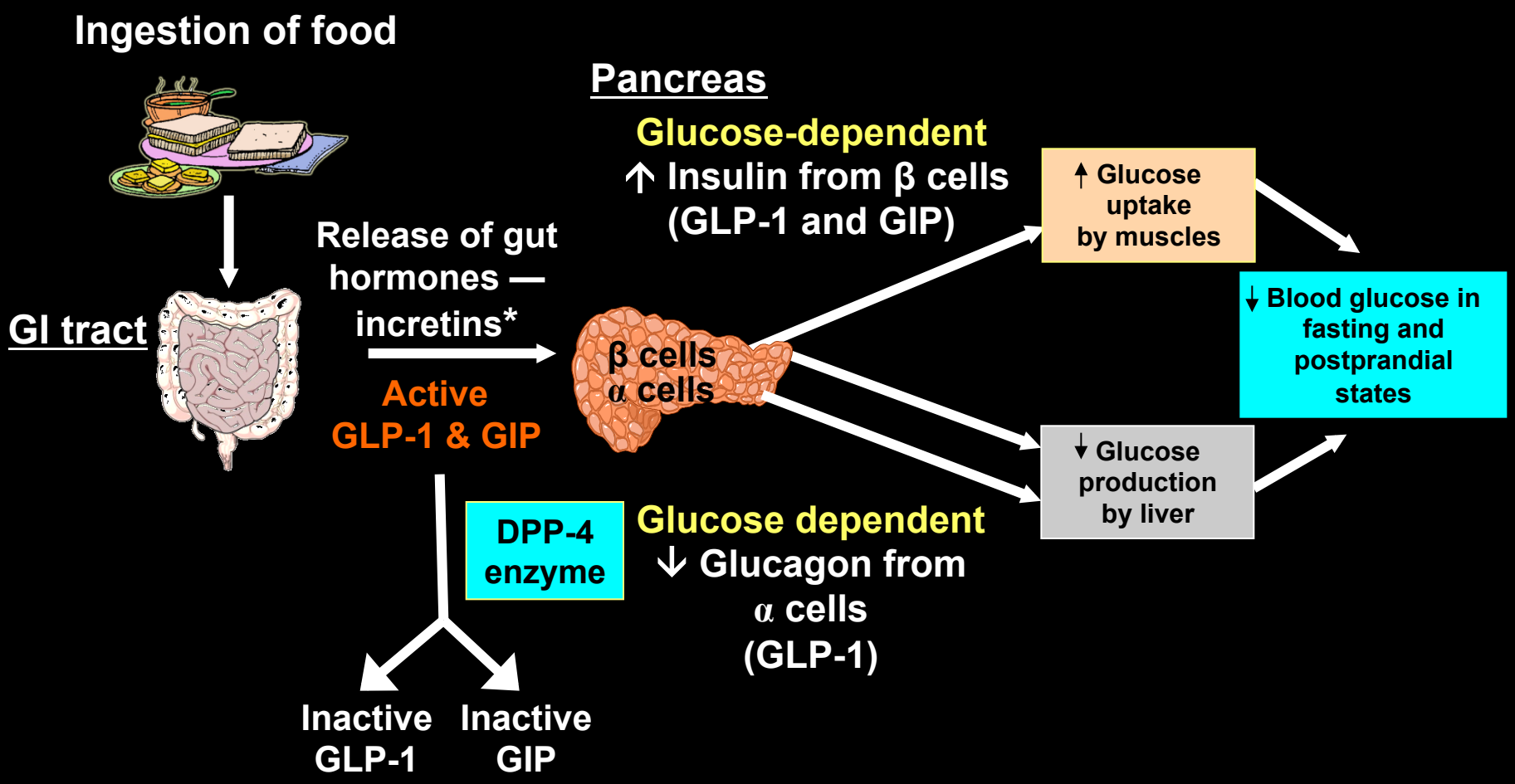

Incretin therapies
DPP-4 inhsitagliptin, vildagliptin Saxagliptin Linagliptin
GLP-1 RA
Exendin-based therapies, e.g. Exenatide Exenatide LAR
Human GLP-1 analogues, e.g. Liraglutide Lixisenatide



IR=insulin resistance.

Adapted from Nauck M et al. *Diabetologia*. 1986;29:46–52. Copyright © 1986 Springer-Verlag.

Role of Incretins in Glucose Homeostasis



*Incretins are also released throughout the day at basal levels.

Adapted from Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876–913; Ahrén B. *Curr Diab Rep*. 2003;2:365–372; Drucker DJ. *Diabetes Care*. 2003;26:2929–2940; Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430–441.

Incretins

Ingestion of food

GI tract

GLP1-analogue

GLP-1 and GIP

DPP-4 inhibitor

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

Pancreas

β cells

α cells

Glucose dependent

↑ Insulin (GLP-1and GIP)

↑ Glucose uptake by peripheral tissues

Glucose-dependent

↓ Glucagon (GLP-1)

↓ Hepatic glucose production

↓ Blood glucose in fasting and postprandial states

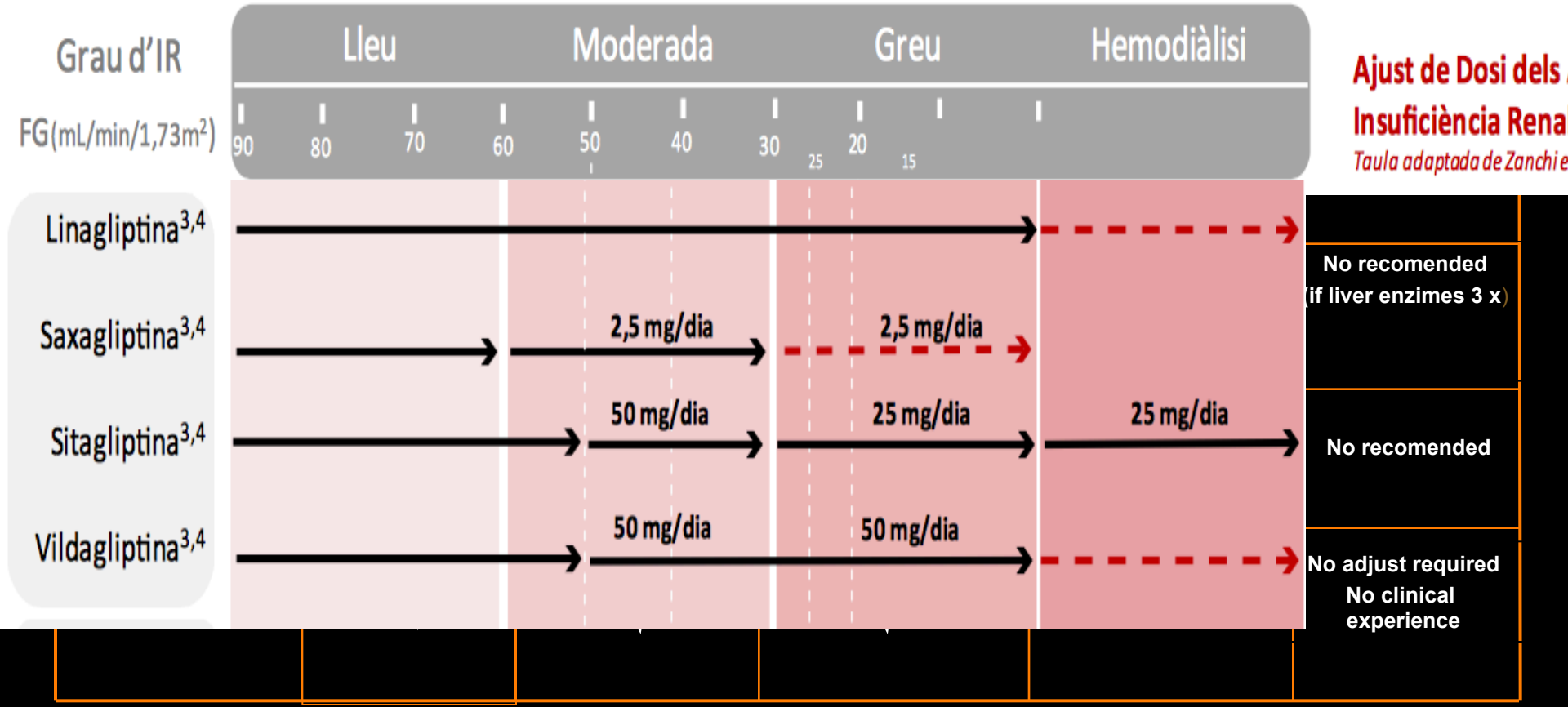
Authorized clinical use of DPP IV Inh. (EMA-AGEMED)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

	Sitagliptina[1]	Vildagliptina[2]	Saxagliptina[3]	Linagliptina[4]
Therapeutic use	Once daily	Twice daily Once daily (add on SU lower dose)	Once daily	Once daily
Monotherapy:	Yes*	Yes*	Yes*	Yes**
Add on metformin				
Add on SU				
Add on Pioglitazon				
Triple therapy add on MET + SU				
Triple therapyadd on Met + Pio				
Add on insulin				

1. Ficha Técnica JANUVIA® / MSD; 2. Ficha Técnica Galvus® / Novartis. 3. Ficha Técnica Onglyza® / BMS/AstraZeneca; 4. Ficha Técnica Trajenta® / Boehringer Ingelheim/Lilly

Ajust de dosi dels antidiabètics en insuficiència renal (recomanacions Cedi



1. Ficha Técnica JANUVIA® / MSD. 2. Ficha Técnica Galvus® / Novartis. 3. Ficha Técnica Onglyza® / BMS/AstraZeneca. 4. FichaTécnica Trajenta® / Boehringer Ingelheim

Treatment

GLP1 RA

EXENATIDE:
Pen 5 / 10 mcg:
Start 5mcg/12
Titrated to 10 mcg

Exenatide LAR
Pen 2 mg
One weekly

LIRAGLUTIDE:
Pen 6 mg/ml:
Starting doses 0,6 (0,1 ml).
Top dose 1,8 mg (0,3ml)

LIxisenatide:
Pen 10 /20 mcg:
Starting doses 10
Top dose 20 mcg /daily

Characterizing GLP-1 Agonists Short-Acting vs. Long-acting

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.

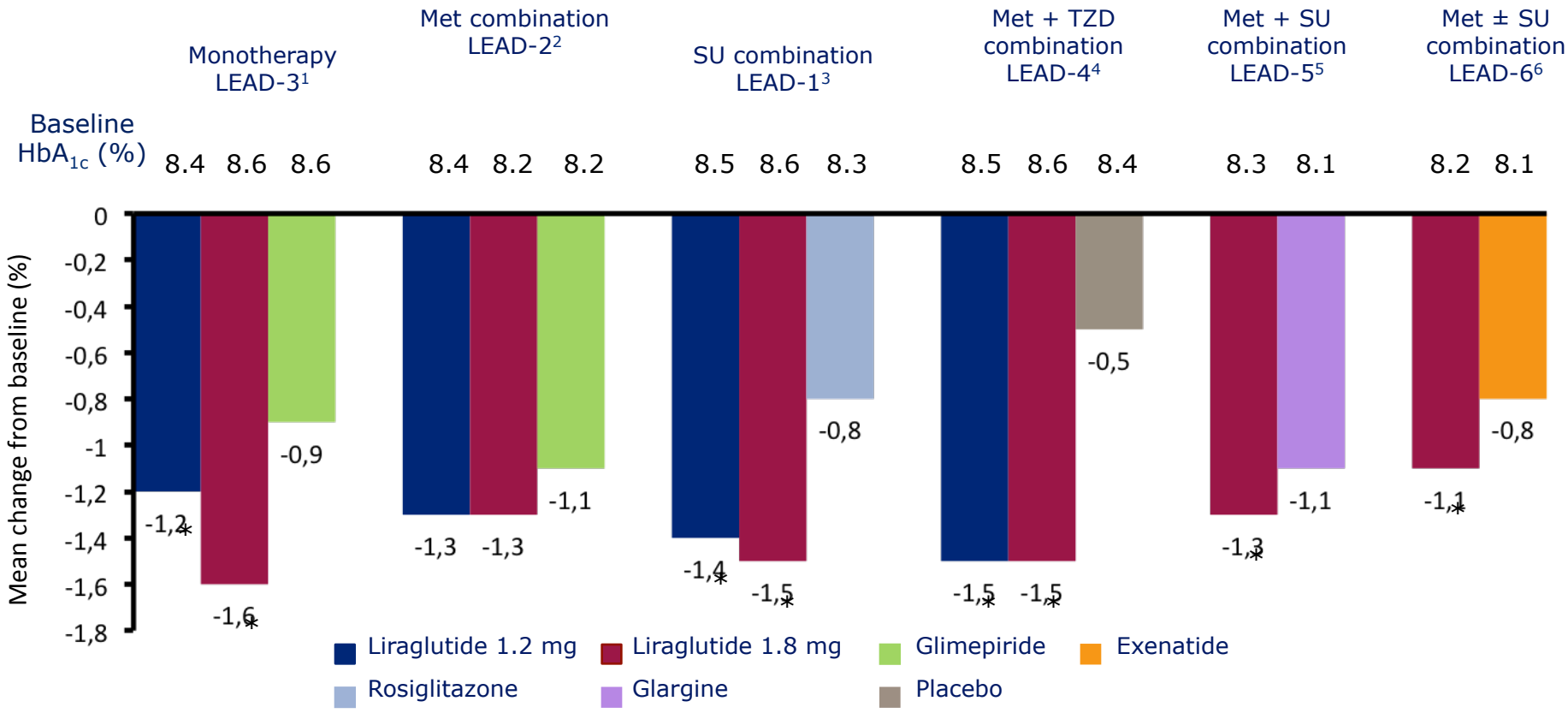
Meier J, Nat. Rev. Endocrinol; 2012;8:728-742

DDP 4 Inh vs GLP-1 agonist

DPP4 Inh	GLP 1 agonist
•GLP1 and GIP effect • Post prandial impact • Weight neutral • Urticaria • Beta cell protection?? • Oral	• GLP1 effect • Fasting and Postprandial • weight reduction • Nausea, vomiting •Beta cell protection?? • subcutaneous

Dr.J. Buse / Dr. R. Prately/ Dr. R Alejandro/Dr. D. Andersen

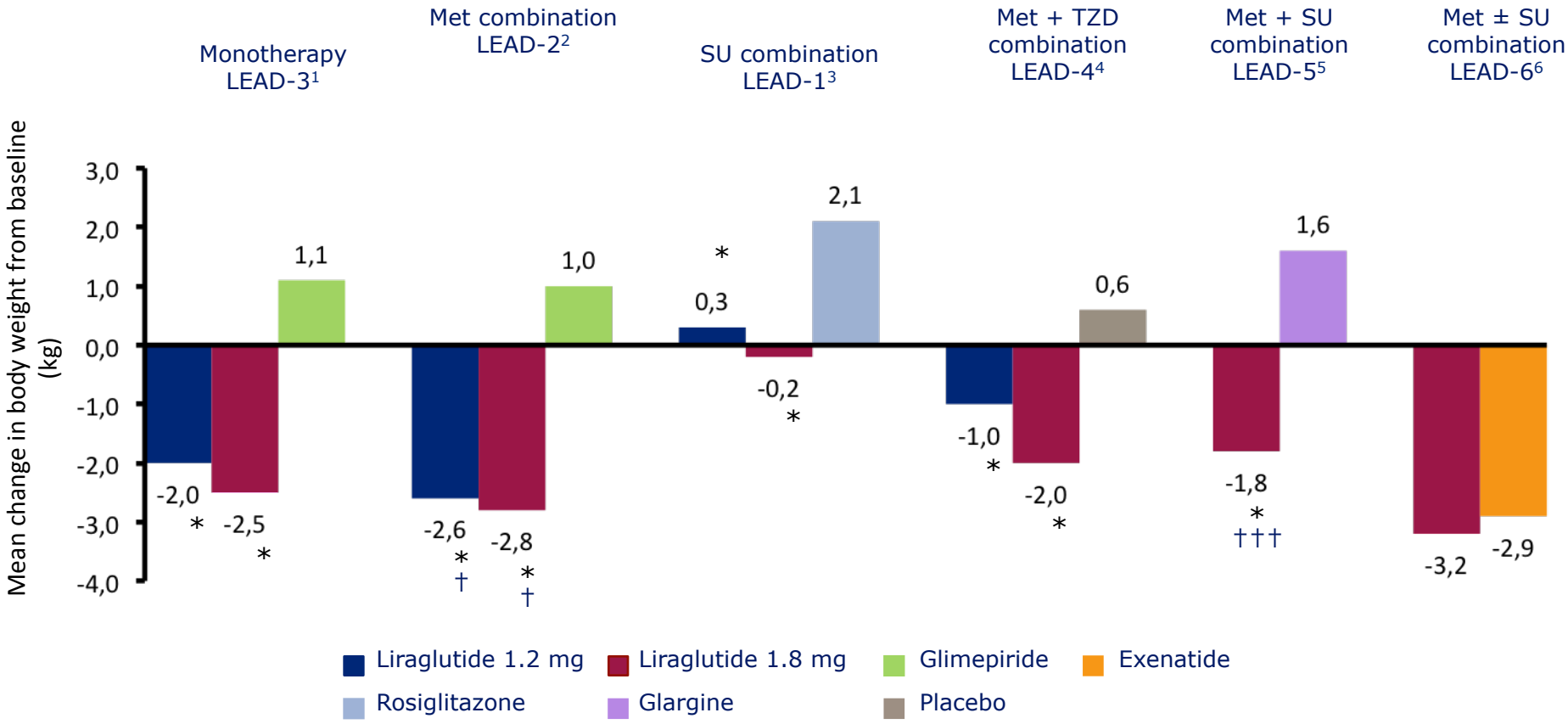
HbA_{1c} effects across LEAD trials



Significant *vs. comparator; change in HbA_{1c} from baseline for overall population (LEAD-4,-5); add-on to diet and exercise failure (LEAD-3); or add-on to previous OAD monotherapy (LEAD-2,-1).
HbA_{1c}, glycosylated haemoglobin; DPP-4, dipeptidyl petidase-4; Met, metformin; OAD, oral anti-diabetic drug; SU, sulphonylurea; TZD, thiazoladinedione.

1. Garber et al. Lancet 2009;373:473–481; 2. Nauck et al. Diabetes Care 2009;32;84–90; 3. Marre et al. Diabet Med 2009;26;268–278; 4. Zinman et al. Diabetes Care 2009;32:1224–1230; 5. Russell-Jones et al. Diabetologia 2009;52:2046–2055; 6. Buse et al. Lancet 2009;374:39–47.

Weight effects across LEAD trials

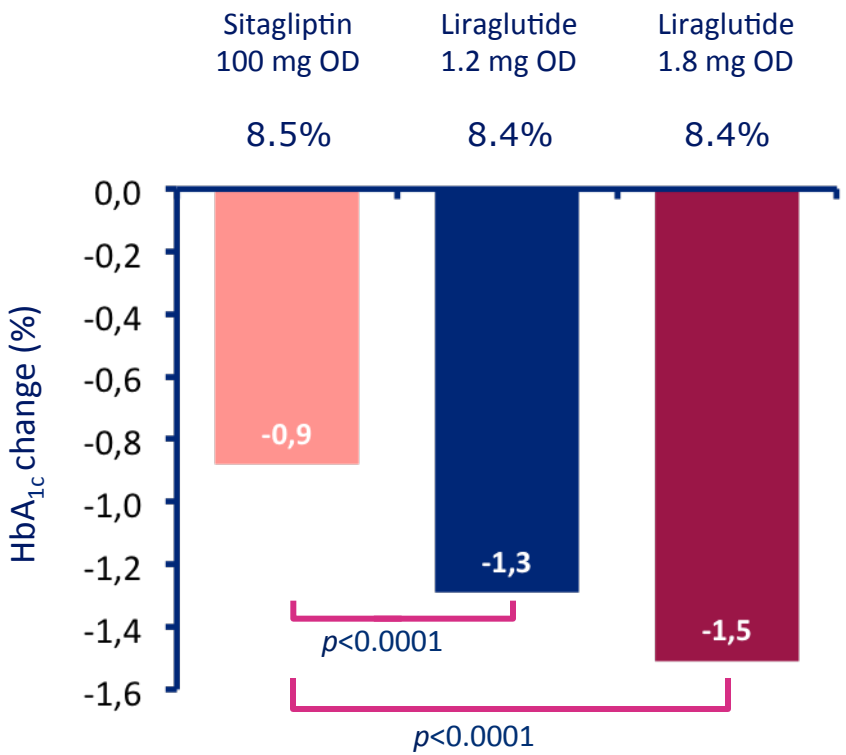


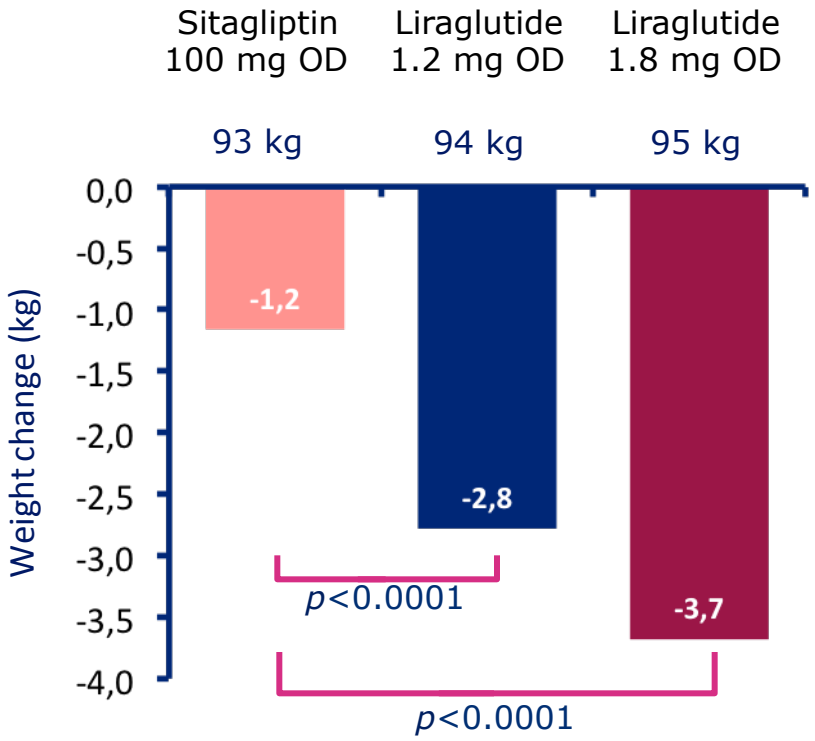
*$p \leq 0.0001$ vs active comparator; †$p \leq 0.01$, †††$p \leq 0.0001$ vs placebo (active comparators vs placebo not shown)
Data from core trials
Met, metformin; SU, sulphonylurea; TZD, thiazoladinedione.

1. Garber et al. Lancet 2009;373:473–481; 2. Nauck et al. Diabetes Care 2009;32;84–90; 3. Marre et al. Diabet Med 2009;26;268–278; 4. Zinman et al. Diabetes Care 2009;32:1224–1230; 5. Russell-Jones et al. Diabetologia 2009;52:2046–2055; 6. Buse et al. Lancet 2009;374:39–47.

Liraglutide vs. sitagliptin: 52-week data

LIRA-DPP-4 (n=665)



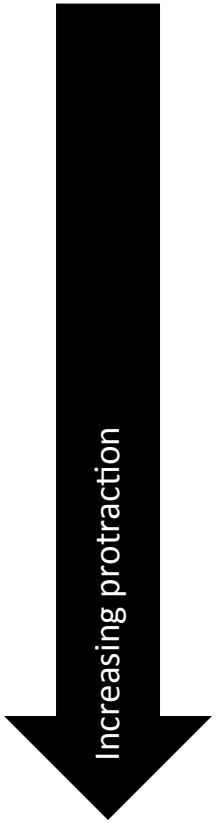


ADA target (<7.0%): **27%** **50%*** **63%*†**

ADA, American Diabetes Association; DPP-4, dipeptidyl peptidase-4; HbA_{1c}, glycosylated haemoglobin; OD, once daily.
Data are least squares means. **p*<0.0001 vs. sitagliptin; †*p*=0.01 vs. liraglutide 1.2 mg.

Pratley et al. Int J Clin Pract 2011;65:397–407.

Pharmacokinetic properties: Short vs long-acting GLP-1RAs

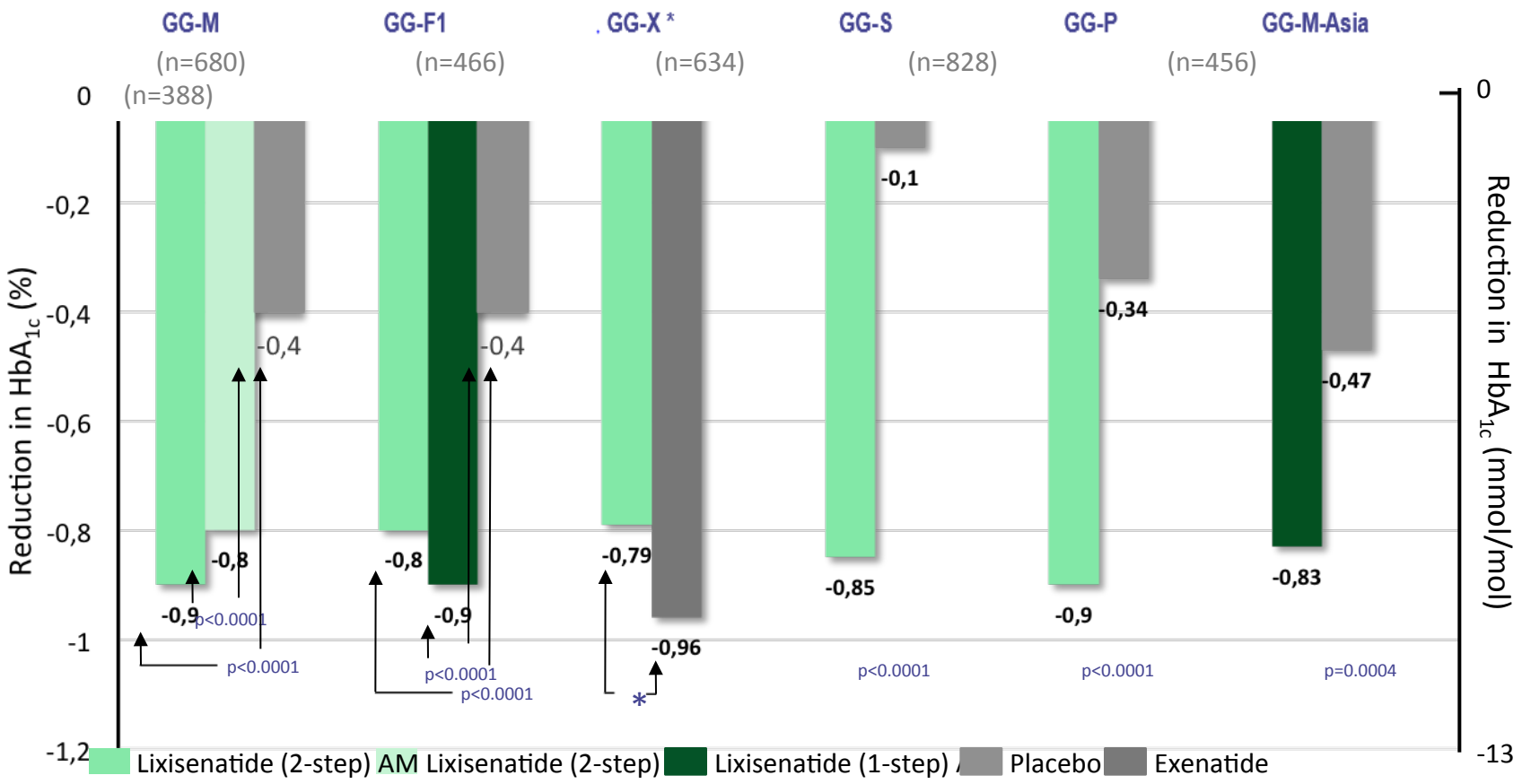


Agent	Half-life	T_{max}
Exenatide BID[1]	2.4 hours	2 hours
Lixisenatide OD[2]	2.7–4.3 hours	1.25–2.25 hours
Liraglutide OD[3]	13 hours	8–12 hours
Semaglutide OW[4]	6.5–7 days	24–36 hours
Dulaglutide OW[5]	90 hours	24–48 hours
Albiglutide OW[6,7]	6–7 days	3–5 days
Exenatide OW[8]	7–14 days	6–7 weeks

BID, twice daily; T_{max}, time to reach maximum concentration; GLP-1RA, glucagon-like peptide-1 receptor agonist; OD, once a day; OW, once weekly

1. Byetta. Summary of Product Characteristics; 2. Lyxumia. Summary of Product Characteristics; 3. Victoza. Summary of Product Characteristics; 4. Novo Nordisk Data on file; 5. Barrington et al. *Diabetes Obes Metab* 2011;13:434–438; 6. Bush et al. *Diabetes Obes Metab* 2009;11:498–505; 7. Matthews et al. *J Clin Endo Metab* 2008;93:4810–4817; 8. Fineman et al. *Clin Pharmacokinet* 2011;50:65–74

Lixisenatide (20 mcg once daily) add-on to OAD
Primary endpoint of HbA_{1c} reduction

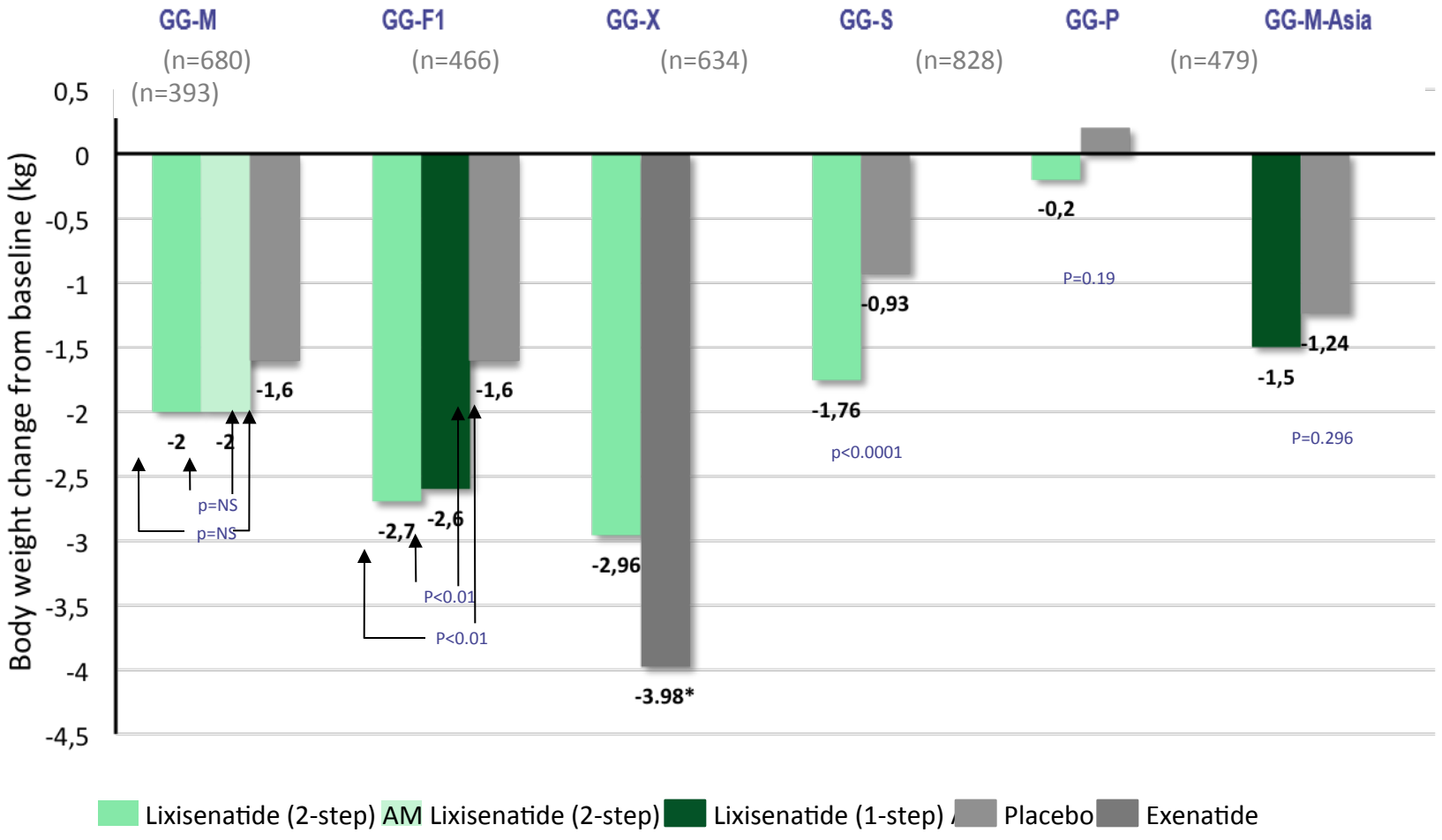


* Lixisenatide 20 mcg OD vs exenatide 10 mcg BD achieved the pre-specified non-inferiority criterion of <0.4% for upper limit of 95% CI; applying the more recent regulatory guideline setting (upper bound of 95% CI at <0.3%), this requirement was met only by the mITT population

MET, metformin; OAD, oral antidiabetic drug; SU, sulfonylurea; TZD, thiazolidinedione; GG, GetGoal

Ahren B et al. *Diabetes Care* 2013;36:2543-50; Bolli GB et al. *Diabetic Medicine* 2013;31:176-84; Rosenstock J et al. *Diabetes Care* 2013;36:2945-51. Rosenstock J et al. *J Diabetes Complications* 2014; doi: 10.1016/j.jdiacomp.2014.01.012; Pinget M et al. *Diabetes Obes Metab* 2013;15:1000-7; Yu Pan C et al. *Diabetes Metab Res Rev* 2014; doi: 10.1002/dmrr.2541.

Lixisenatide (20 mcg once daily) add-on to OAD
Secondary endpoint of body weight change



NS = non-significant; *(95% CI, 0.456 to 1.581)

Lixisenatide is not licensed for weigh

SANOFI DIABETES

Ahren B et al. *Diabetes Care* 2013;36:2543-50; Bolli GB et al. *Diabetic Medicine* 2013;31:176-84; Rosenstock J et al. *Diabetes Care* 2013;36:2945-51. Rosenstock J et al. *J Diabetes Complications* 2014; doi: 10.1016/j.jdiacomp.2014.01.012; Pinget M et al. *Diabetes Obes Metab* 2013;15:1000-7; Yu Pan C et al. *Diabetes Metab Res Rev* 2014; doi: 10.1002/dmrr.2541.

Inhibición de SGLT2: mecanismo de acción

Reabsorción de glucosa renal en condiciones de salud[1,2]

Carga de glucosa filtrada > 180 g/día

Los inhibidores de SGLT2 reducen la reabsorción de glucosa en el túbulo proximal, y provocan la eliminación de glucosa por la orina* y diuresis osmótica

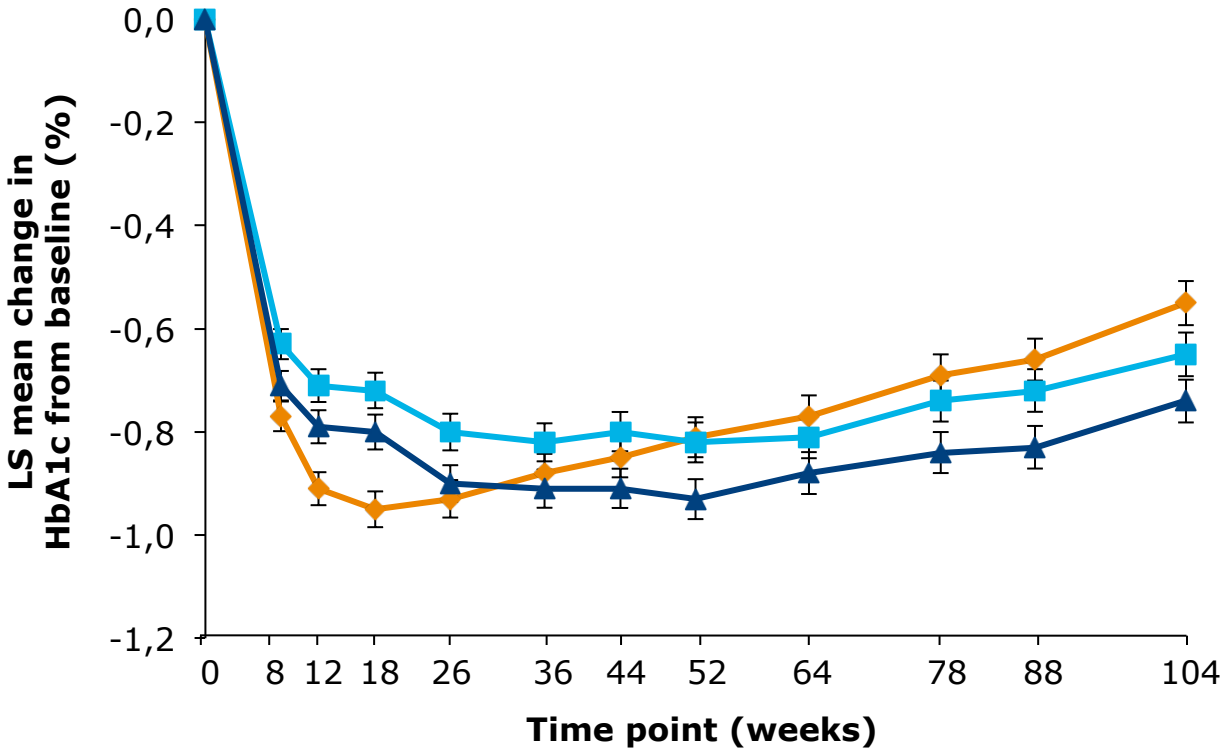
SGLT, cotransportador de sodio y glucosa. *Pérdida de ~ 78 g de glucosa diarios = 312 calorías/día.

1. Gerich JE. Diabet Med. 2010;27:136–142; 2. Bakris GL, et al. Kidney Int. 2009;75;1272–1277;
3. Ferrannini E et al *Nat Rev Endocrinol* 2012; 8: 495. Figura reimpresa con permiso de McMillan Publishers Ltd *Nat Rev Endocrin* 2012

	Canaglifoxin	Dapaglifoxin	Empaglifoxin
Indications	*Monotherapy; combination with metformin, SU, pioglitazone and/or insulin*	*Monotherapy, combination with metformin, SU, and/or insulin*	*Monotherapy; combination with metformin, SU, pioglitazone and/or insulin*
Action	*Modest reduction in FPG and PPG; modest weight loss (2-3%); no additional hypo*	*Modest reduction in FPG and PPG; modest weight loss (~2-3kg); no additional hypo*	*Modest reduction in FPG and PPG; modest weight loss (~2-3kg); no additional hypo*
Dose	*100-300 mg/day*	*10 mg daily*	*10-25 mg /day*
eGFR dose adjustments			

Canagliflozin: sustained reduction in HbA1c (LOCF) vs glimepiride

as add-on to metformin over 104 weeks



Mean difference from baseline HbA1c at 104 weeks

GLIM	−0.55%
CANA 100 mg	−0.65%
CANA 300 mg	−0.74%

Difference vs GLIM

CANA 100mg −0.09%
95% CI −0.20, 0.01

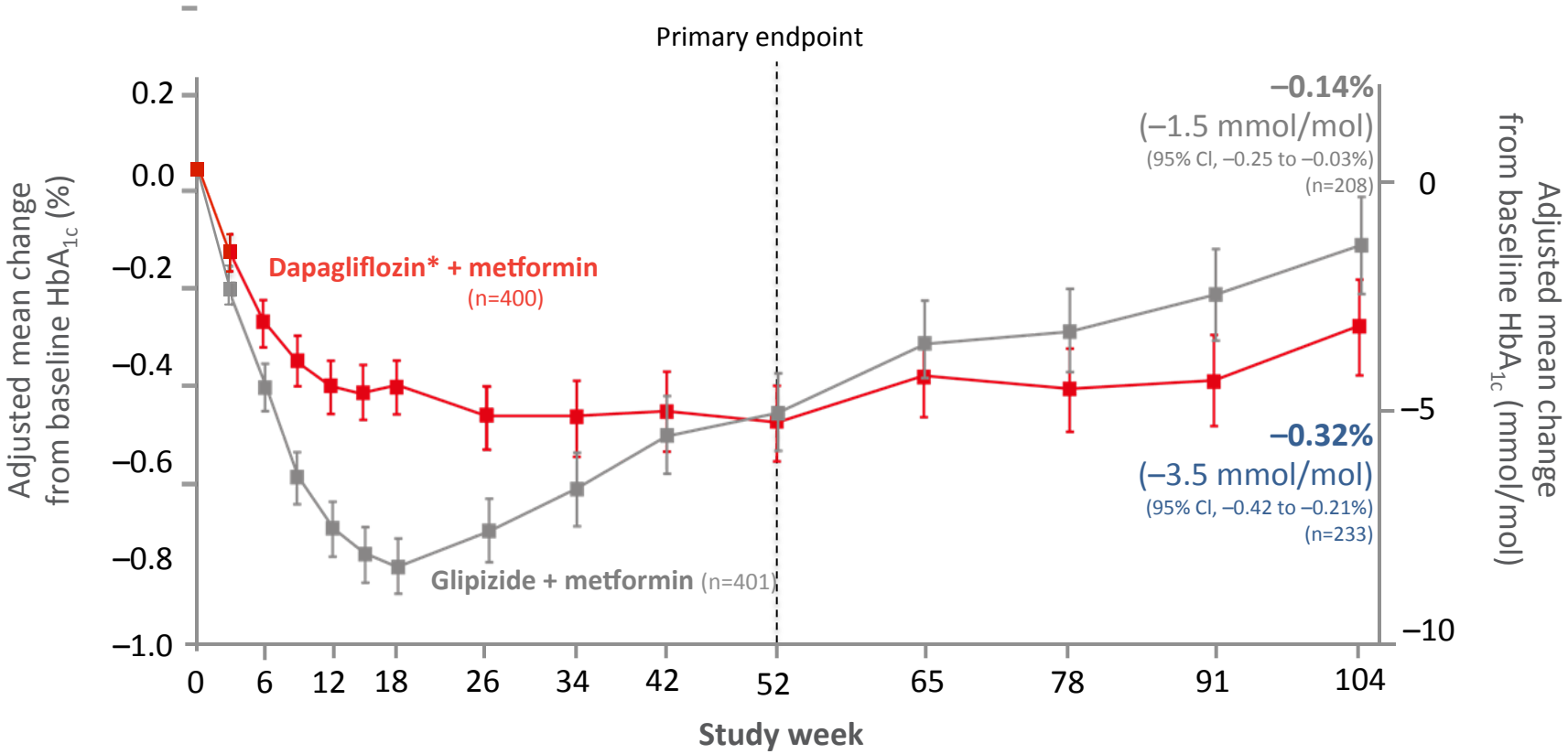
CANA 300mg −0.18%
95% CI −0.29, −0.08

- Reduction in HbA1c at 104 weeks was numerically greater for canagliflozin 100 mg vs glimepiride and reached statistical significance for canagliflozin 300 mg[a,b]

Vertical bars represent standard error.
CANA, canagliflozin; CI, confidence interval; GLIM, glimepiride; LOCF, last observation carried forward; LS, least squares.

Cefalu WT, et al. Poster presented at the 73rd scientific sessions of the American Diabetes Association (ADA), 2013; abstract 65-LB.

Dapagliflozin: Reductions in HbA_{1c} at 52 weeks were sustained over 104 weeks relative to baseline



Adapted from Nauck MA, *et al.* 2011. Short term plus long term treatment period full analysis set. Non-inferiority was met at 52 weeks. p value was not available at 104 weeks. Data are adjusted mean change from baseline and 95% CI derived from a repeated measures mixed model.

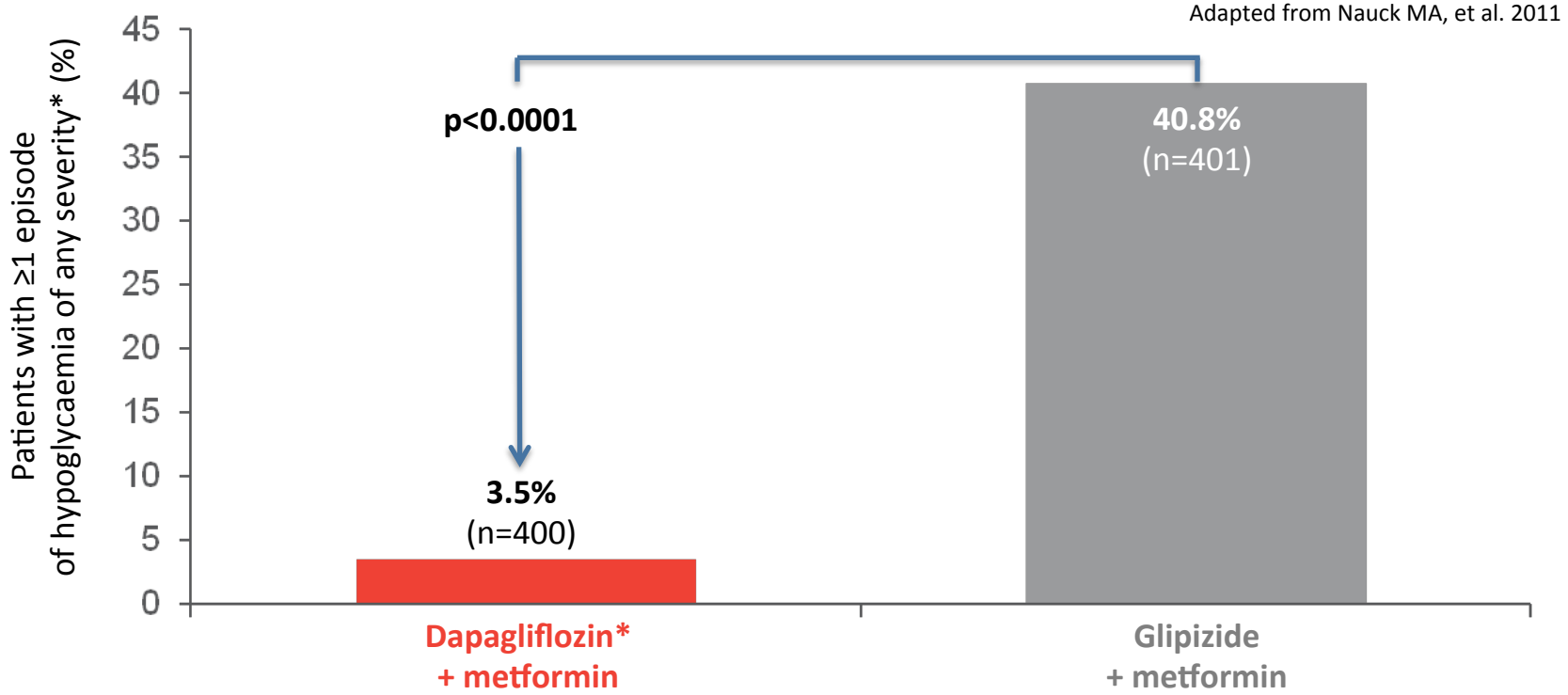
A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week clinical study, plus a 52-week extension period, glipizide-controlled non-inferiority study to evaluate the efficacy and safety of dapagliflozin 10 mg + metformin (≥1500 mg/day) versus glipizide + metformin (≥1500 mg/day) in patients with inadequate glycaemic control (HbA_{1c} >6.5% and ≤10%) on oral antidiabetic medication including metformin. Primary endpoint: HbA_{1c} change at 52 weeks. *Dapagliflozin dose was up-titrated to a maximum of 10 mg (achieved by 87% of patients) over an 18-week period based on glycaemic response and tolerability.

1. Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22; 2. Nauck M, *et al.* Poster 40-LB. Poster presented at 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June, 2011.

Lower incidence of hypoglycaemia with dapagliflozin compared with a sulphonylurea

Number of patients who experienced ≥1 hypoglycaemic episode over 52 weeks[1]

Adapted from Nauck MA, et al. 2011



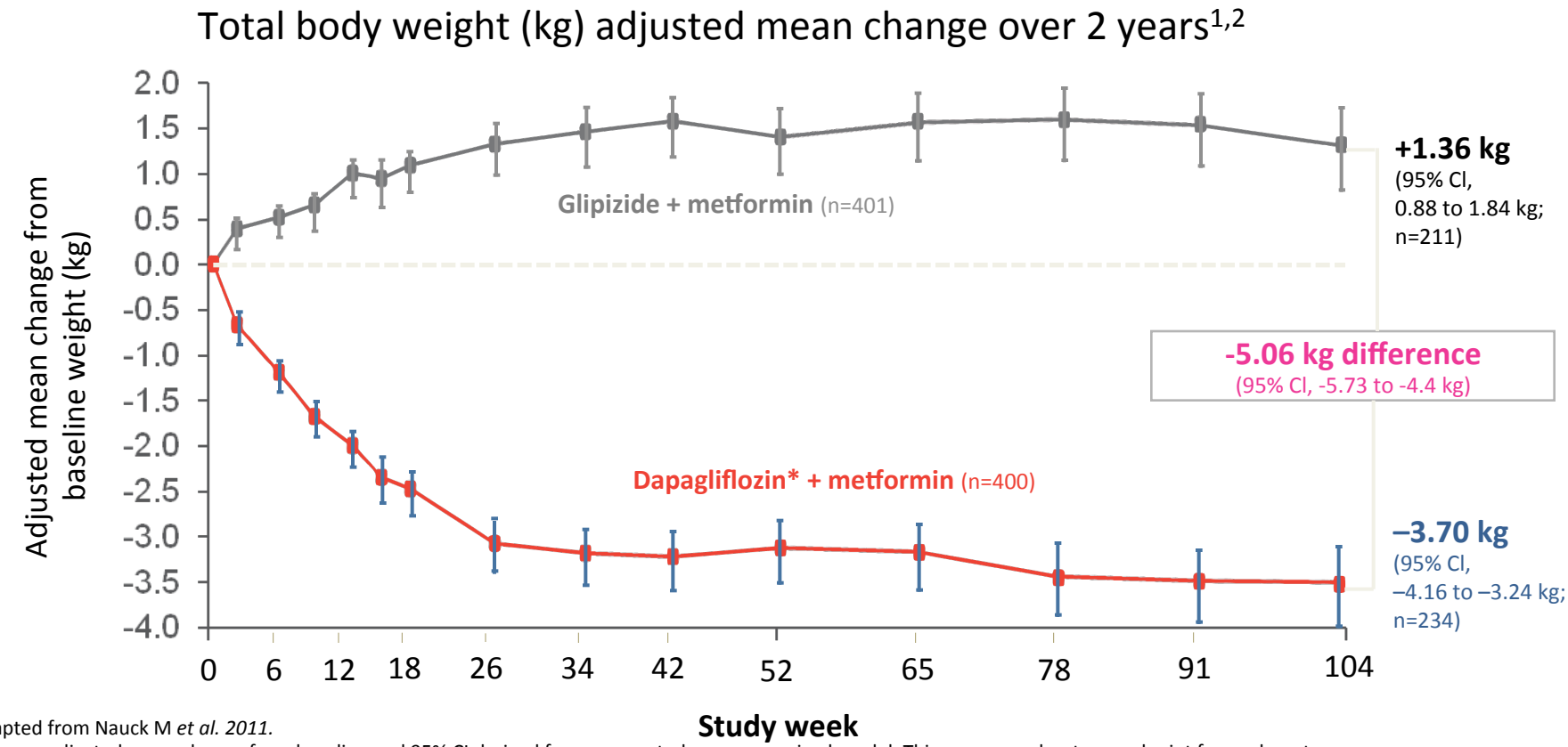
The descriptive statistics for hypoglycaemic episodes are adjusted proportions derived from a logistic regression using the full analysis set

Dapagliflozin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin[2]

*Major hypoglycaemia was defined as a symptomatic episode requiring external assistance due to severely impaired consciousness or behaviour, with capillary or plasma glucose levels of 54 mg/dL(3.0 mmol/L) and recovery alter glucose or glucagon administration. Minor hypoglycaemia was defined as a symptomatic episode with capillary or plasma glucose levels of 63 mg/dL (3.5 mmol/L), irrespective of the need for external assistance, or an asymptomatic episode with capillary or plasma glucose levels of 63 mg/dL (3.5 mmol/L) that did not qualify as a major episode. Other hypoglycaemia was defined as an episode with symptoms suggestive of hypoglycaemia but without measurement confirmation. *Dapagliflozin dose was up-titrated to a maximum of 10 mg (achieved by 87% of patients) over an 18-week period based on glycaemic response and tolerability.

1. Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22 2. FORXIGA Summary of Product Characteristics

Dapagliflozin: secondary benefit of weight loss versus a sulphonylurea



Adapted from Nauck M *et al. 2011.*

Data are adjusted mean change from baseline and 95% CI derived from a repeated measures mixed model. This was an exploratory endpoint from a long-term follow-up study. Weight loss in the initial 52 week study was a key secondary endpoint and was measured using LOCF analysis. Results at 52 weeks were –3.22 kg in the dapagliflozin arm (baseline weight 88.4 kg) and +1.44 kg in the SU arm (baseline weight 87.6 kg) p<0.0001.

1. Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22;
2. Nauck M, *et al.* Poster 40-LB. Poster presented 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June, 2011.

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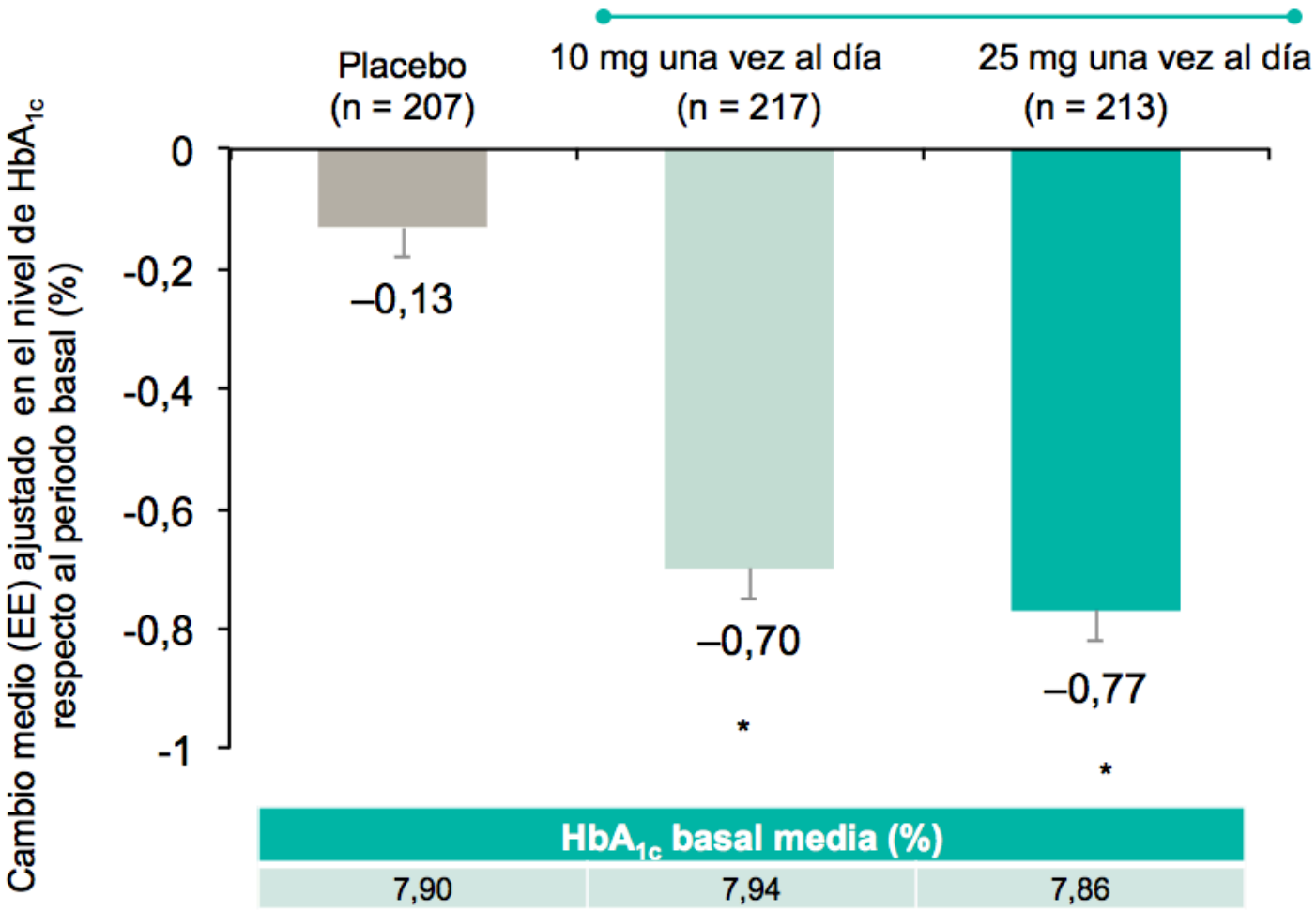
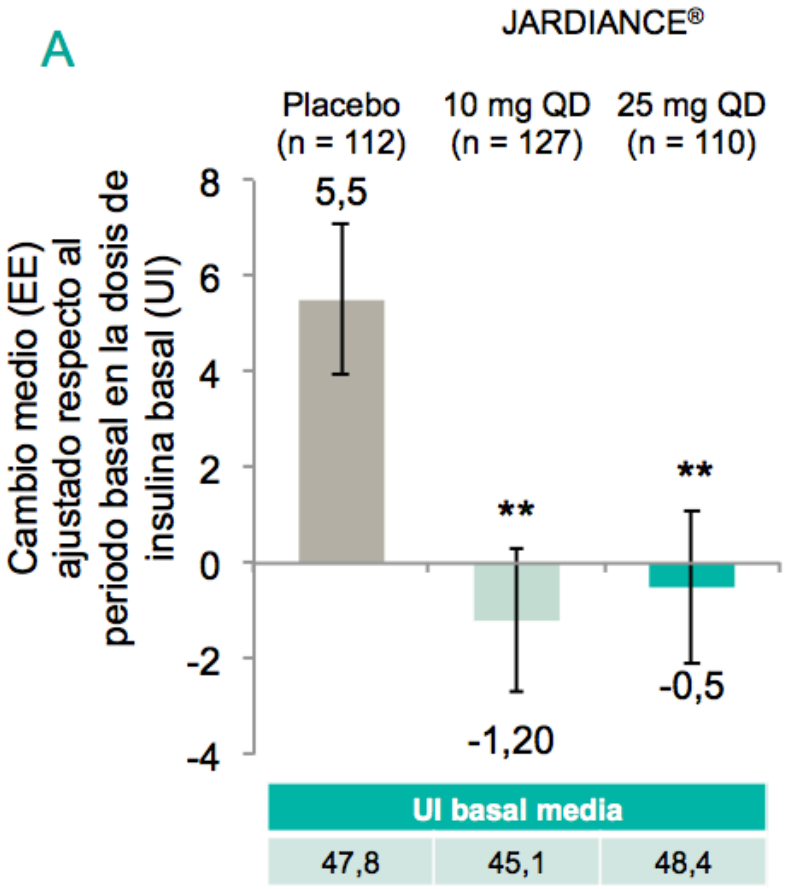
Nauck M, *et al*. Presented at: American Diabetes Association (ADA); June 24-28, 2011; San Diego, CA.

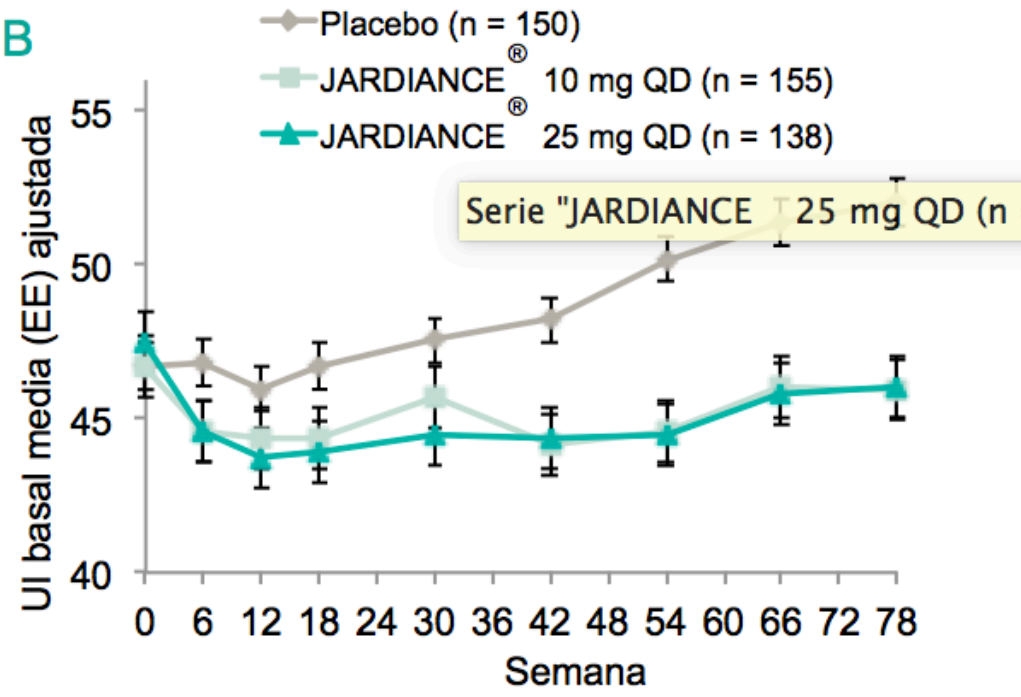
Estudio EMPA-REG MET™: Empaglifozina añadido a metformina

Cambio en el nivel de HbA_{1c} en la semana 24



EMPA-REG BASAL™: Cambio en la dosis de insulina (A) entre el periodo basal y la semana 78; (B) en el tiempo





Genital infections and urinary tract infections*

•Most genital infections† and UTIs were mild to moderate, responded to initial course of standard therapy, and rarely led to discontinuation of dapagliflozin

•Events of genital infection (vulvovaginitis, balanitis and related genital infections) and UTIs with dapagliflozin 10 mg versus placebo:

Frequency at 24 weeks	Genital infections	UTIs
Dapagliflozin 10mg	4.8%	4.3%
Placebo	0.9%	3.7%

•Pyelonephritis was uncommon and occurred at a similar frequency to control

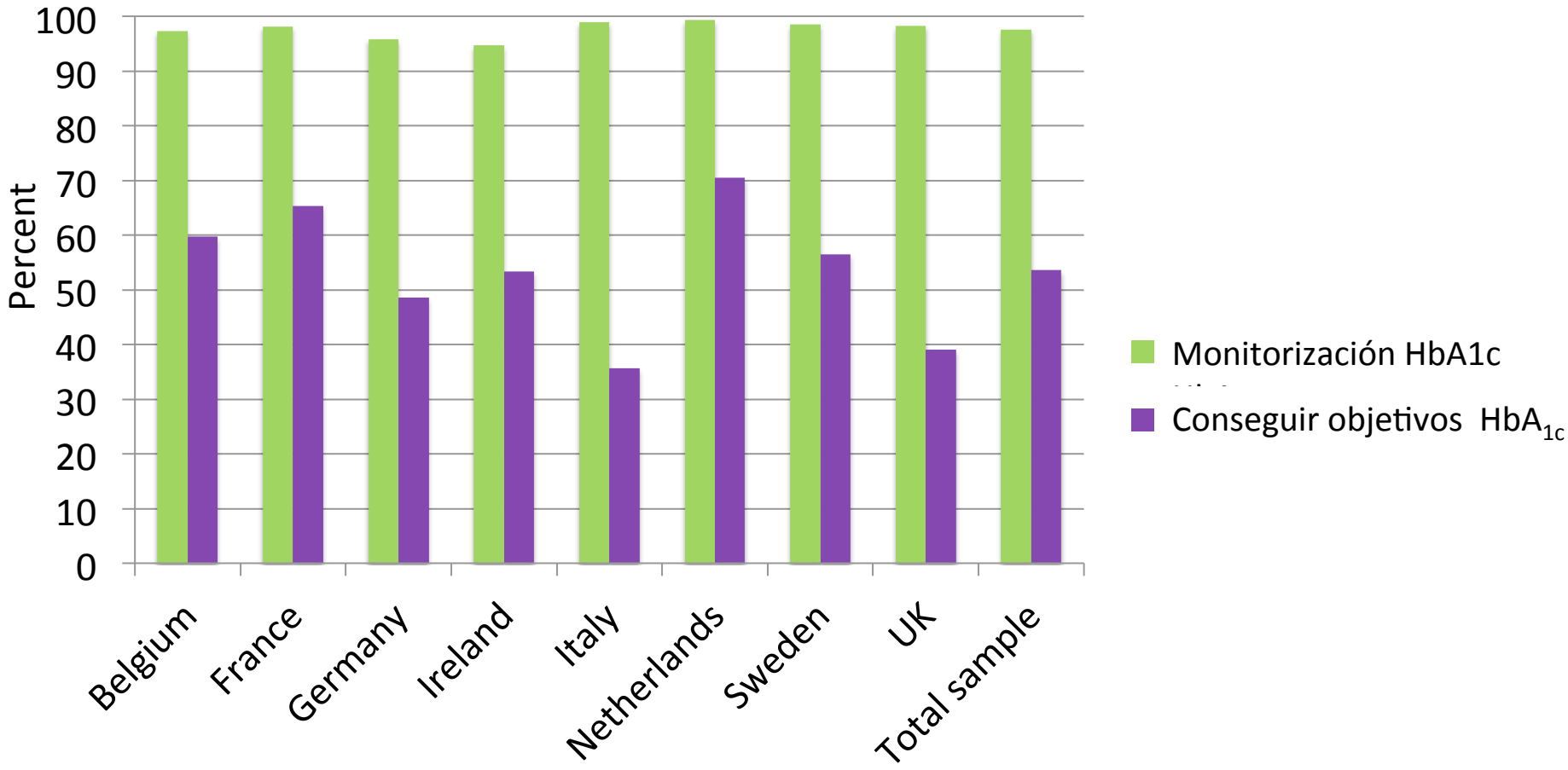
*In a prespecified pooled analysis of 12 placebo-controlled studies;
†Genital infection includes the preferred terms, listed in order of frequency reported: Vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, and vulval abscess.

FORXIGA Summary of product characteristics.

A pesar de los avances terapéuticos, una proporción significativa de pacientes DM2 no alcazan los objetivos de A1c

GUIDANCE Study 7,597 pacientes con T2DM

Existe un vacio entre monitorizacion y control de la HbA_{1c} <7%



T2DM, type 2 diabetes mellitus.

Stone MA et al. *Diabetes Care*. 2013 April 23.

Control of Glycemia and Cardiovascular Risk Factors in Patients With Type 2 Diabetes in Primary Care in Catalonia (Spain)

Irene Vinagre, MD[1]
Manel Mata-Cases, MD[2,3]
Eduard Hermosilla, BSC[3]
Rosa Morros, MD[3,4]
Francesc Fina, MD[3,5]
Magdalena Rosell, MD[3]
Conxa Castell, MD, PHD[6]
Josep Franch-Nadal, MD, PHD[3,7]
Bonaventura Bolíbar, MD, MPH[3,4]
Didac Mauricio, MD, PHD[8,9]

Many studies have shown that the occurrence of these complications depends largely on the degree of glycemic control and intensive control of cardiovascular risk factors (CVRFs) (3–5).

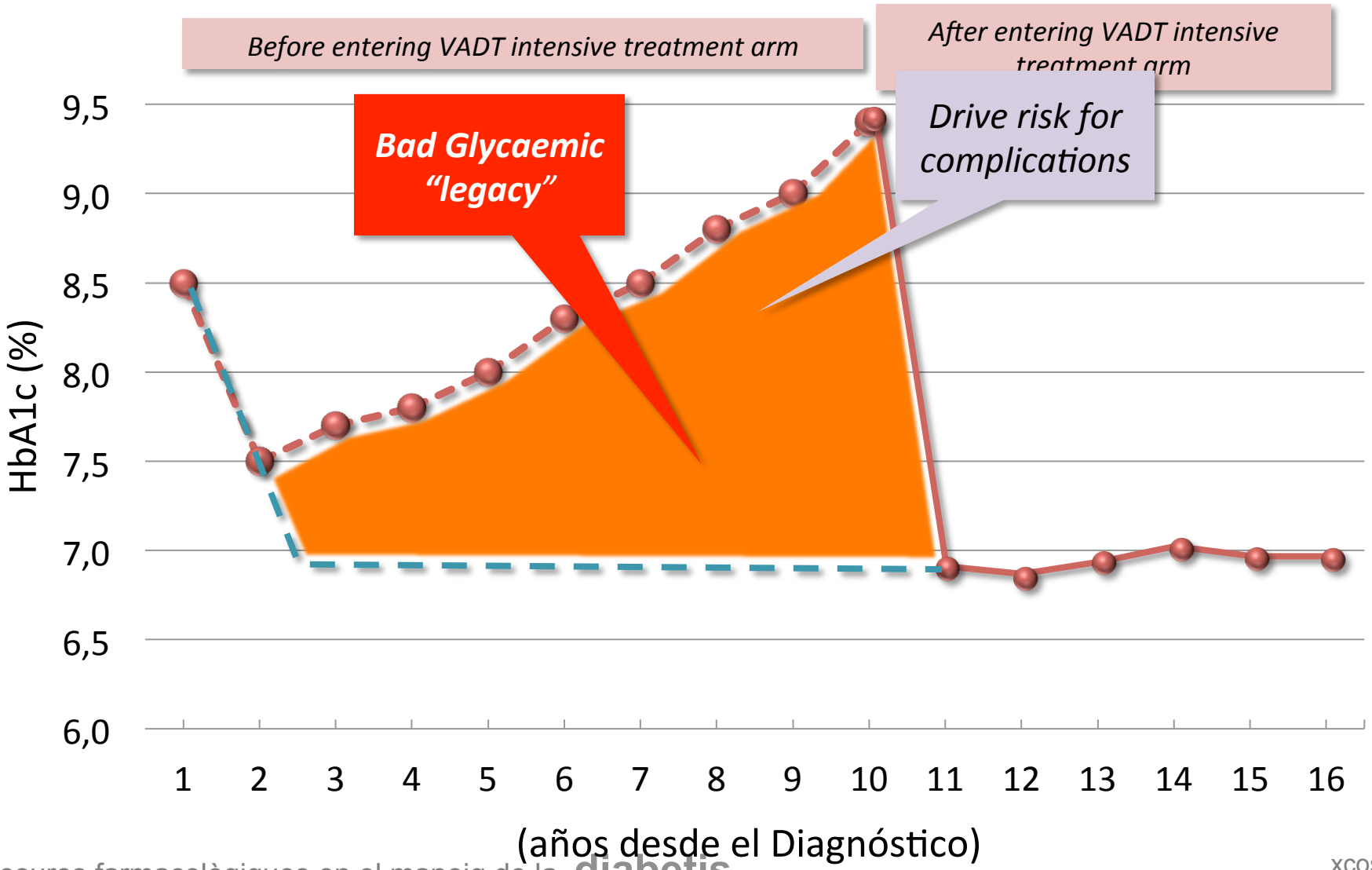
In the last few decades, a consensus

	Age <65 years	Age ≥65 years	Age <65 years	Age ≥65 years
A	women = 102,063; ≥65 years = 139,161)			58.5
A				82.5
A				3.3
B	A1C ≤7% (242,842; women = 114,493; ≥65 years = 159,838	51.8	58.5	30.9
B				61.9
T	A1C ≤8% ,623; women = 91,627; ≥65 years = 126,014)	74.2	82.5	63.4
L	A1C >10% 199,586; women = 95,426; ≥65 years = 130,529)	8	3.3	40.6
L				75.2
T				35.4
B	Secondary prevention: A1C ≤7%, BP ≤130/80 mmHg, and LDL-C <100 mg/dL (*n* = 34,310; women = 12,200; ≥65 years = 27,386)	11.9	12.1	42.1
N				73.7
Primary prevention: A1C ≤7%, BP ≤130/80 mmHg, and LDL-C <130 mg/dL (*n* = 145,605; women = 71,246; ≥65 years = 91,689)	12.9	13.3	12.7	12.2	13.3
Secondary prevention: A1C ≤7%, BP ≤130/80 mmHg, and LDL-C <100 mg/dL (*n* = 34,310; women = 12,200; ≥65 years = 27,386)	12.1	13.3	9.9	11.9	12.1

Dara are percentages. The primary and secondary prevention treatment goals were defined according to the local guidelines. The percentages are from the study subjects with available data for each variable. All variables showed significant differences between sex ($P < 0.005$) and age groups ($P < 0.001$).

Vinagre et al. Diabetes Care 2012;35.

Consecuencias de la demora de la intervención
Interpretación de VADT

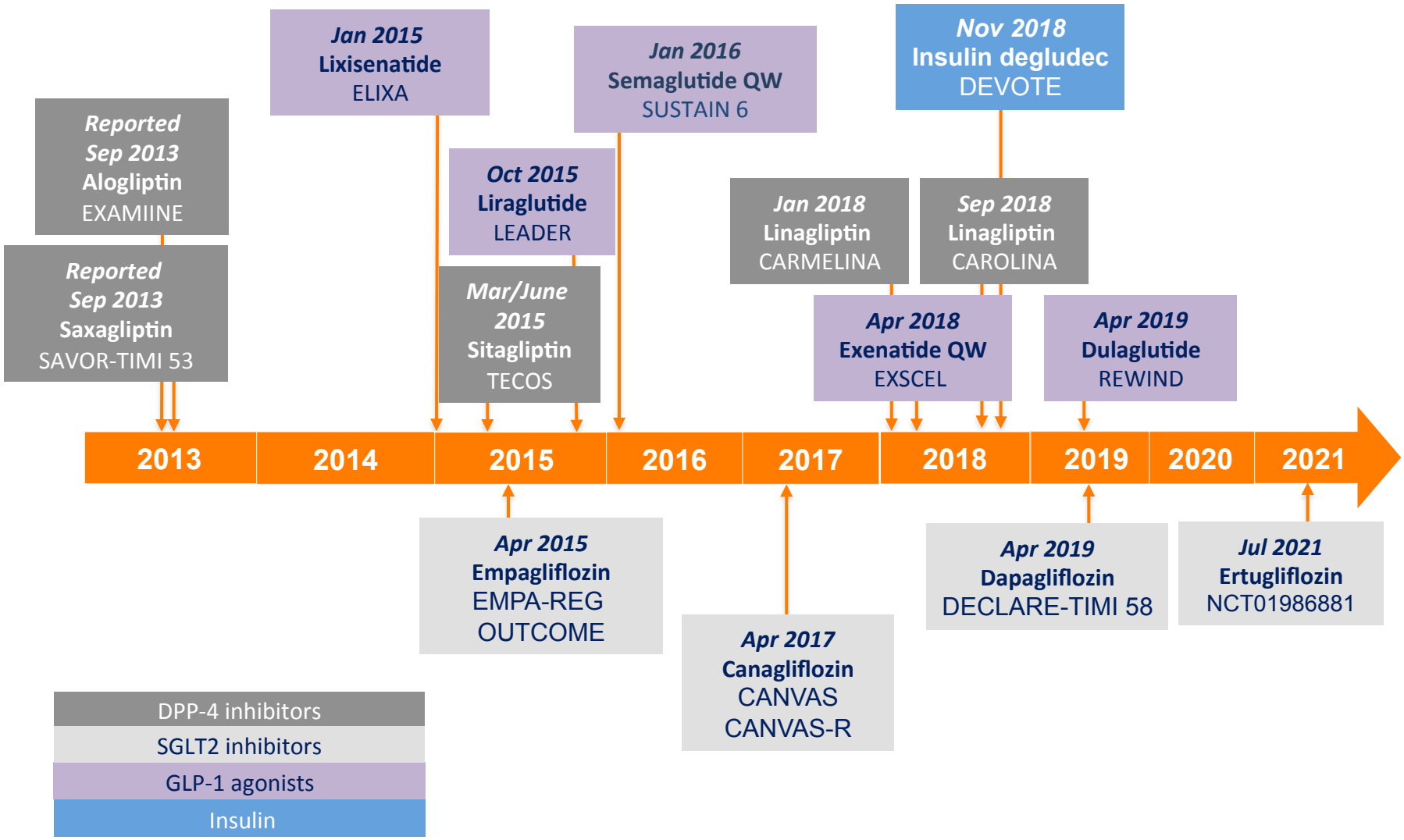


Del Prato S Diabetologia 2009;52:1219

Complejidad progresiva del manejo de la DM2

1,2. Adapted from National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 diabetes – newer agents (a partial update of CG66): quick reference guide. NICE clinical guideline 66: Type 2 Diabetes Management. Available at: http://www.nice.org.uk/nicemedia/pdf/CG66NICEGuideline.pdf (accessed November 2012).
3. Go AS, et al. *N Engl J Med.* 2004;351:1296–1305; 4. Morley JE. *Diabet Med.* 1998;15 (Suppl. 4): S41–6.

Timelines for outcomes studies



Aleglitazar studies: AleCardio and AlePrevent were stopped July 2013