SAC 27 y 28 mayo 2022

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

Congreso de la Sociedad Asturiana de Cardiología

Sede: Parador de Corias

Cangas de Narcea

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

HOSPITAL UNIVERSITARIO CENTRAL de ASTURIAS

Análogos del receptor de GLP1 oral en Diabetes Mellitus.

Congreso de la Sociedad Asturiana de Cardiología.
Cangas de Narcea, 27 de Mayo de 2022.

José Rozado Castaño
Adjunto de Cardiología Clínica
Hospital Universitario Central de Asturias

Conflicto de intereses:

Colaborador en sesiones científicas con las siguientes empresas farmacéuticas:

- Novonordisk./Brystol-Myers./Pfizer./Bayer./Menarini./Esteve.
- Astrazeneca./Amgen./Novartis./Rovi.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

HOSPITAL UNIVERSITARIO CENTRAL de ASTURIAS

¿Por qué hablar de DM en un congreso de Cardiología?

Importancia de DM en Cardiología:

¿Cuántos de nuestros pacientes tiene DM 2?

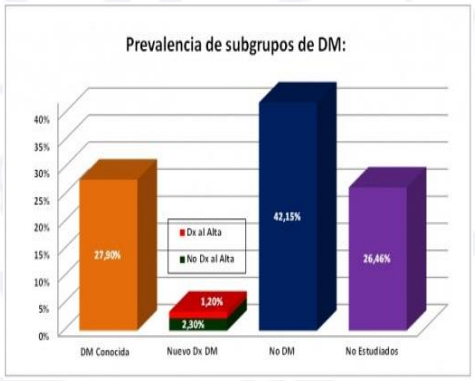
¿Nuestros pacientes DM visitan a otros médicos que controlen su DM y su riesgo CV?

¿Qué impacto tiene la ECV en la DM?

¿Tratar la DM tiene Beneficio CV?

Importancia de DM en Cardiología:

¡1 de cada 3 de nuestros pacientes son DM!



Rozado et al. DIABETES MELLITUS EN HOSPITALIZACIÓN DE CARDIOLOGÍA: PREVALENCIA, HERRAMIENTAS DIAGNÓSTICAS Y BÚSQUEDA ACTIVA POR PARTE DEL CARDIÓLOGO. Rev Esp Cardiol. 2014;67 Supl 1:964

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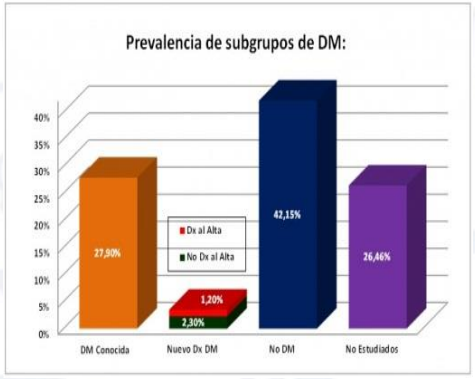

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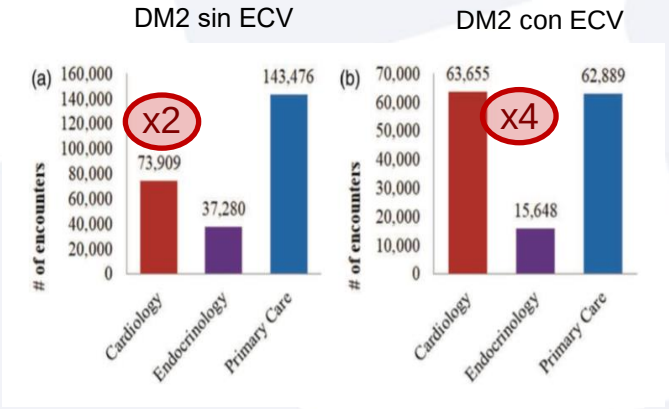

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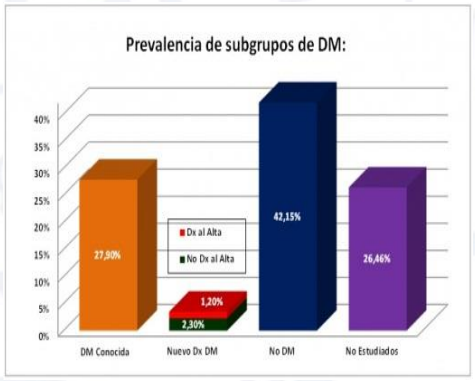

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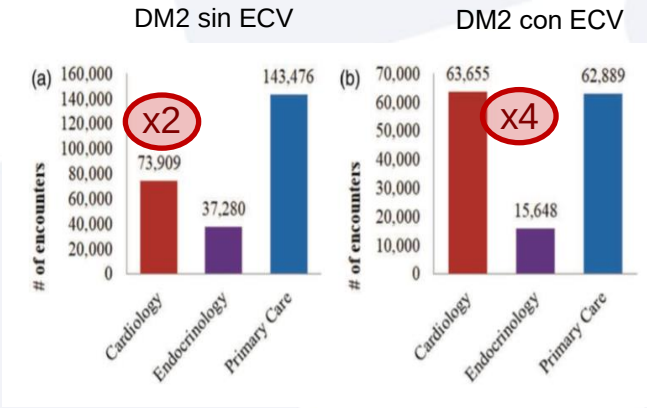

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1. Ortega E, et al. *Med Clin.* 2015;233-8; 2. Vinagre I, et al. *Diabetes Care.* 2012;35:774-9; 3. Franch-Nadal J, et al. *Int J Endocrinol.* 2014;2014:131709; 4. Garzón G, et al. *Gac Sanit.* 2015;29(6):425-30;
5. Mata-Cases M, et al. *Eur J Health Econ.* 2016;17:1001–10; 6. Sicras-Mainar A, et al. *Rev Clin Esp (Barc).* 2014;21:121-30; 7. Baena-Díez JM, et al. *Diabetes Care.* 2016; 8. Low Wang CC, et al. *Circulation.* 2016;133:2459–502; 9. International Diabetes Federation. Diabetes and cardiovascular disease. 2016.

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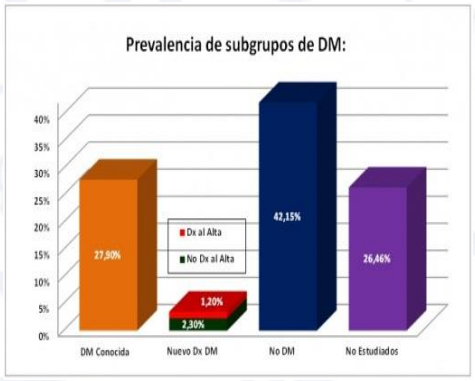

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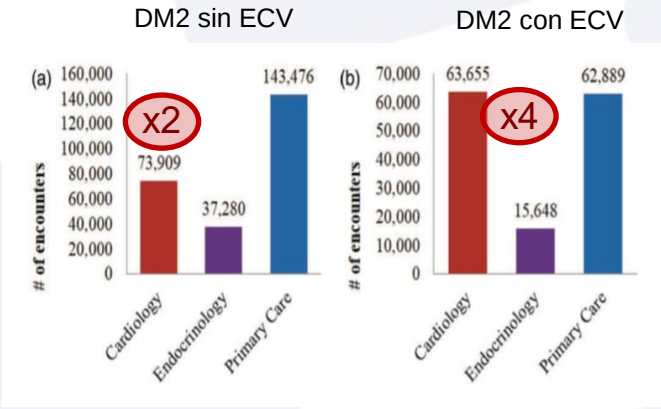

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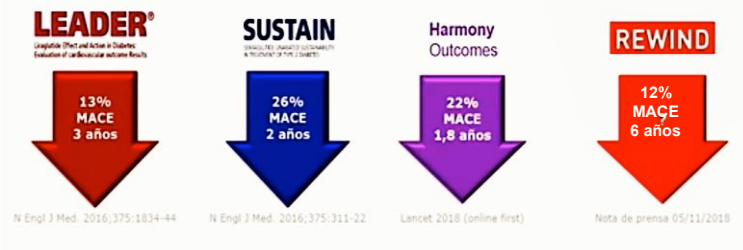
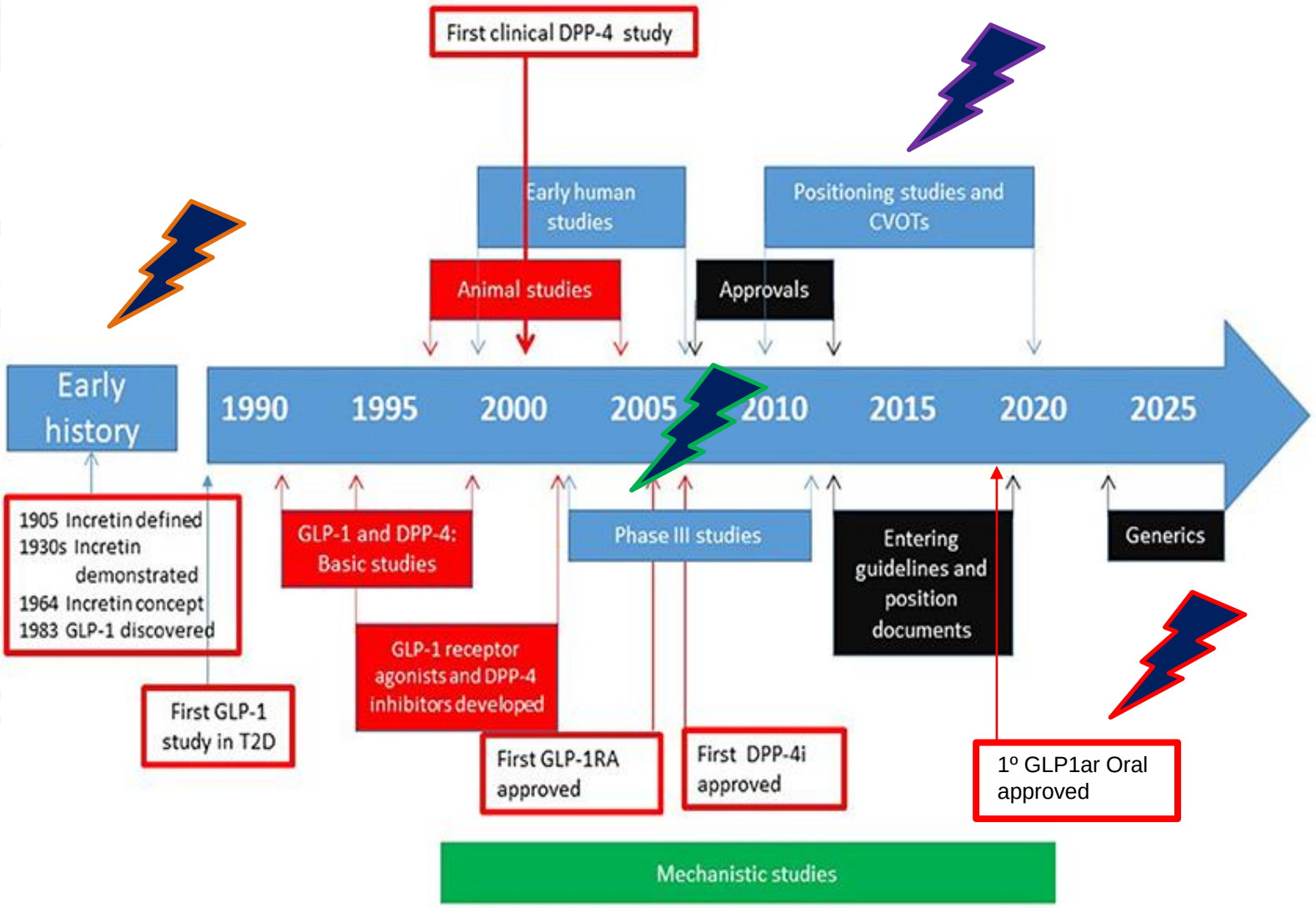
¡Evidencias de Farmacos con Beneficio CV!

iSGLT2

aGLP1



Historia de los arGLP1:



Modificado de Gobble, Reimann. Metabolic Messengers: glucagon-like peptide 1. Nature metabol.2021; 3: 142-148.

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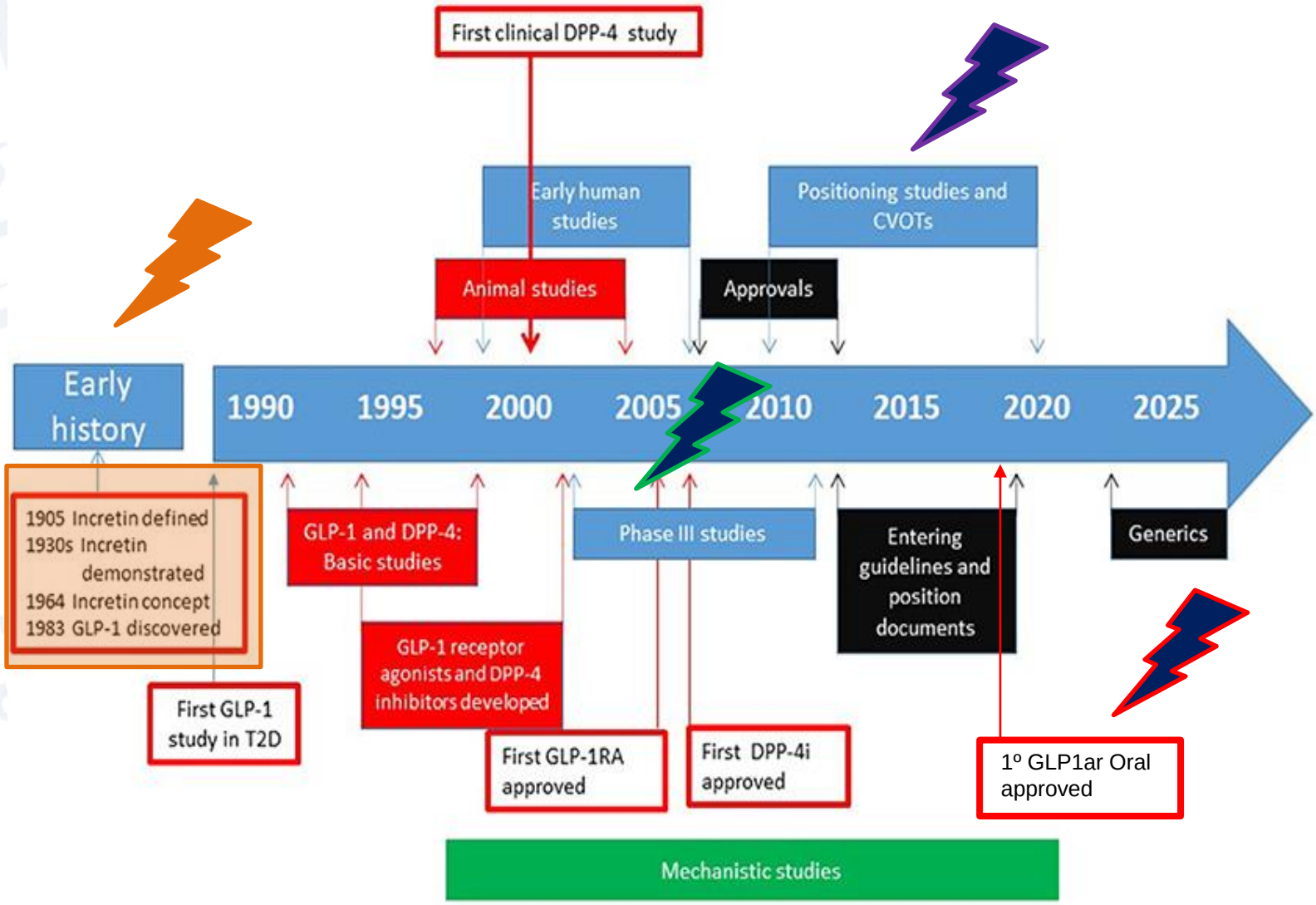

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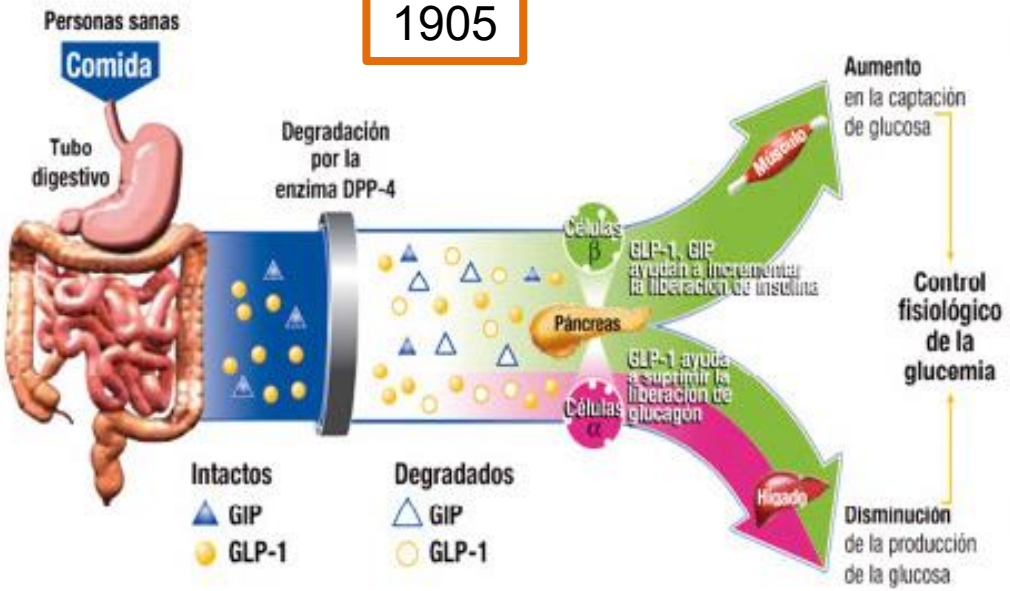
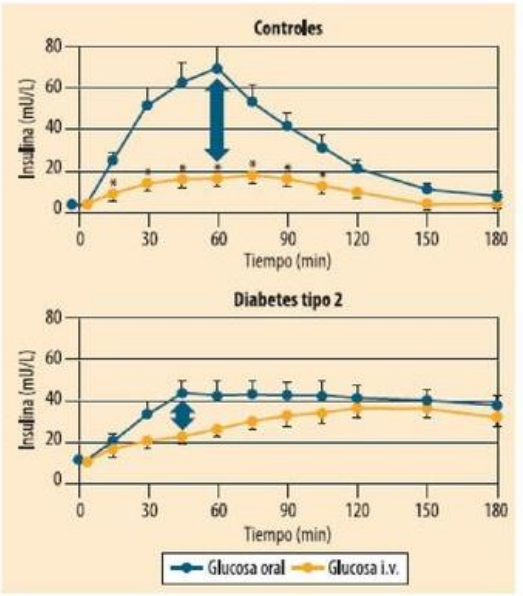
Las Incretinas: INtestine seCRETion of Insulin:

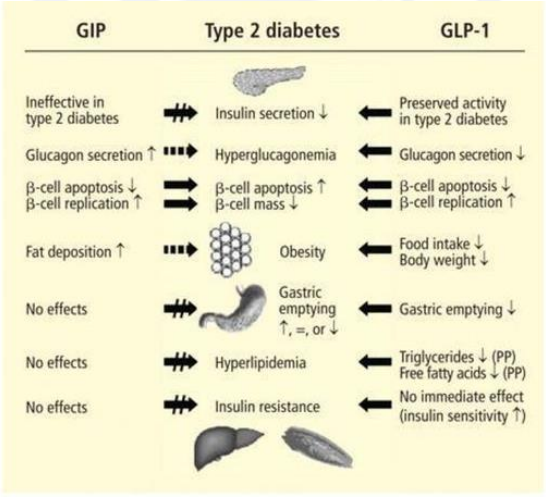
1905



1964



1987



1993

Rico-Fontalvo et al. Glp-1 Receptor Agonists: From their Physiological Effect on the Incretine System to their Role in Diabetic Kidney Disease. doi: 10.3823/1463.

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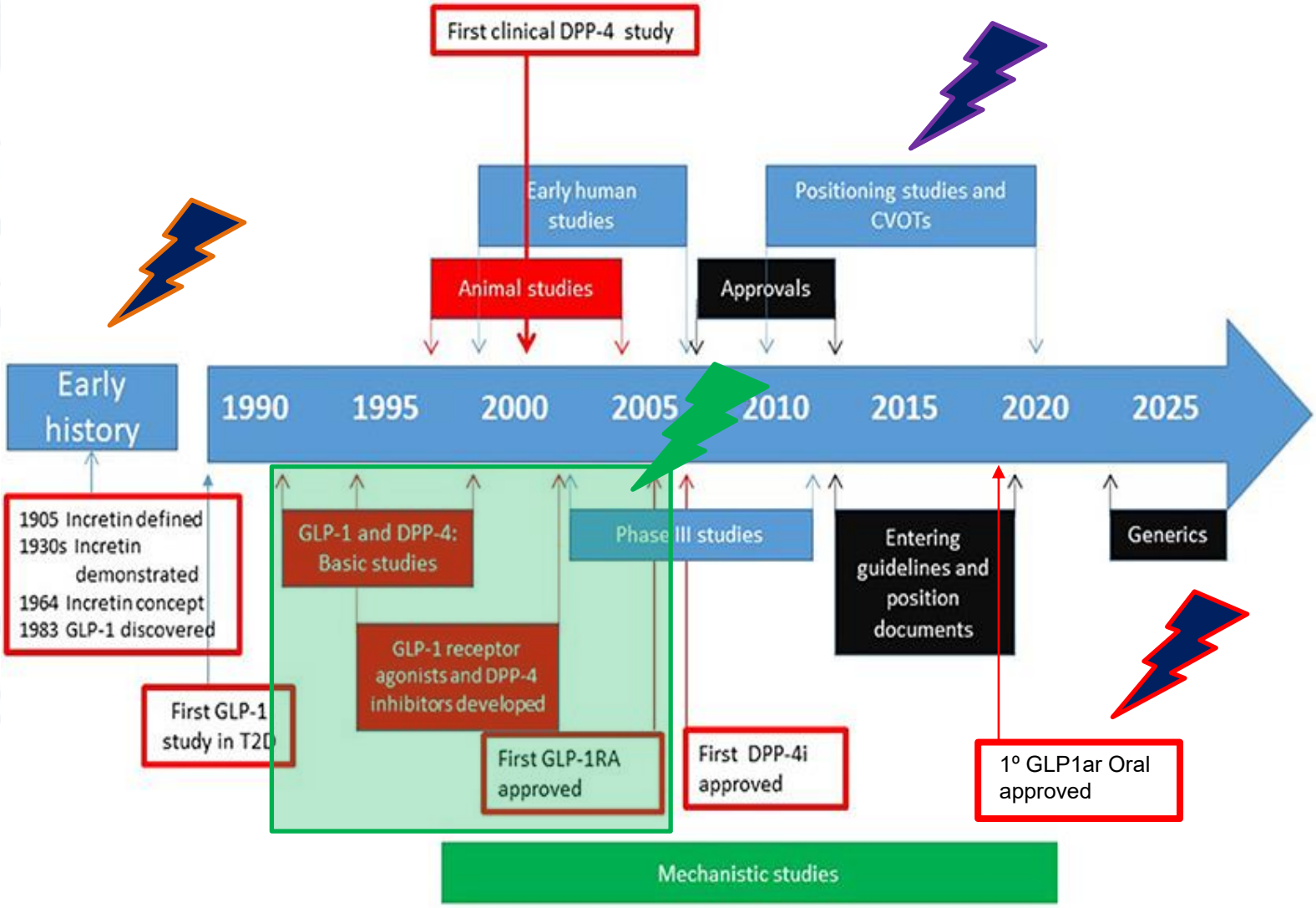

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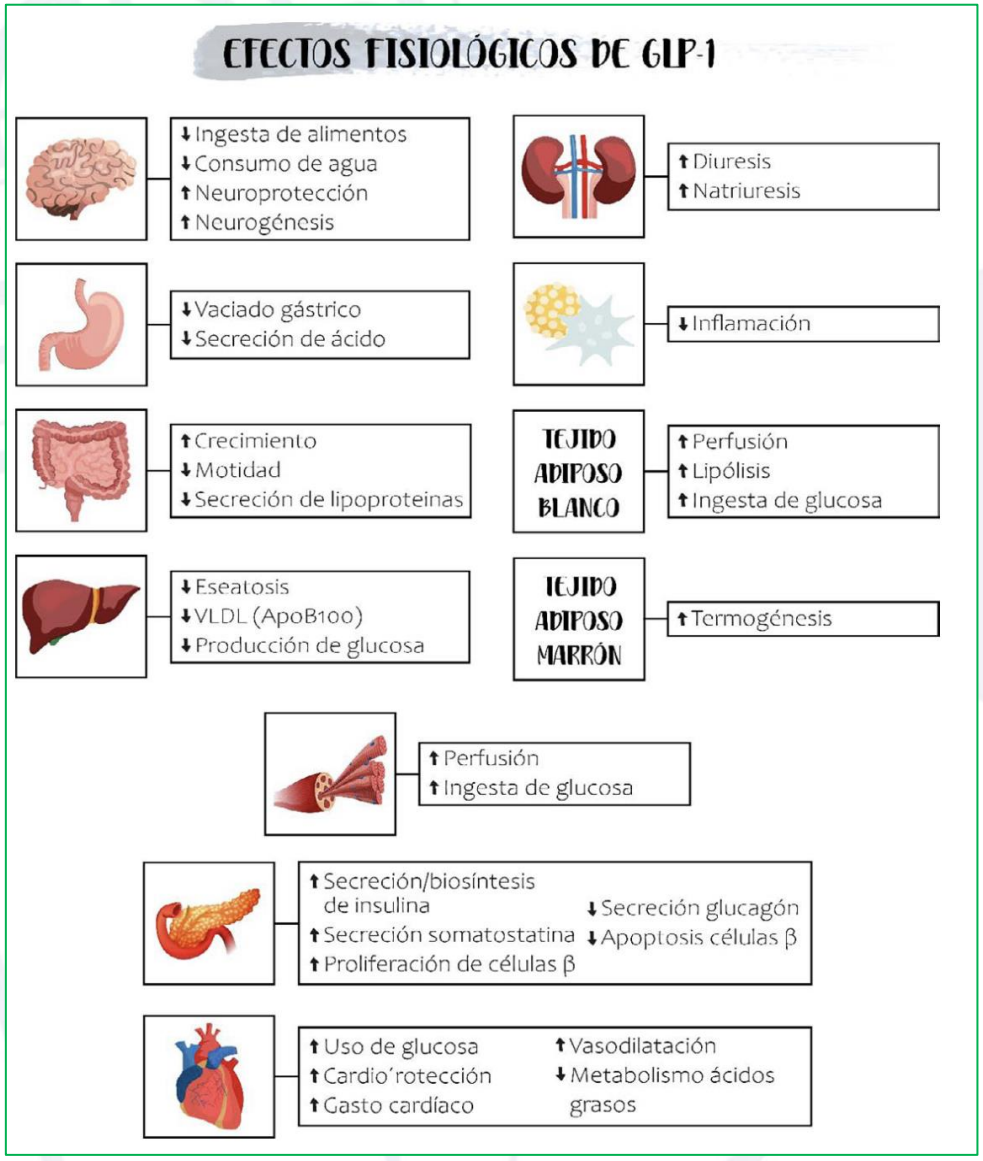
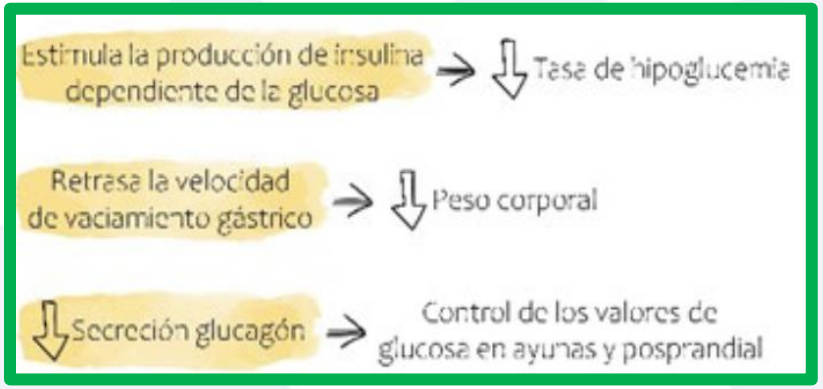
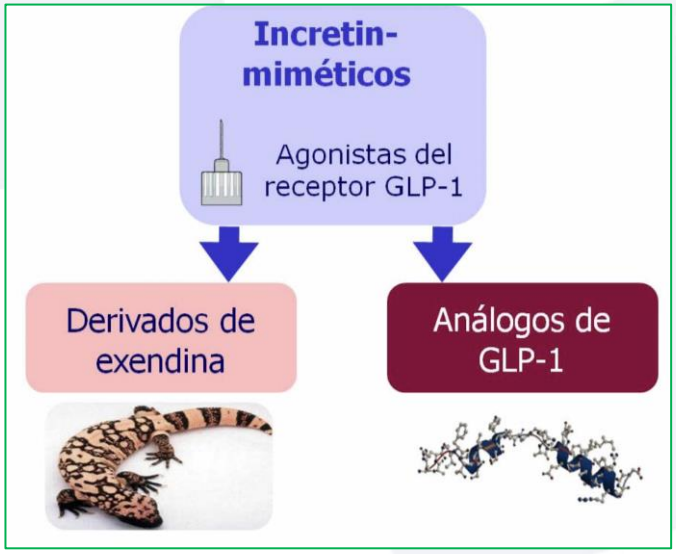
Fisiología de los arGLP1:







EXENATIDE
LIXISENATIDE
EPFIXENATIDE

LIRAGLUTIDE
DULAGLUTIDE
ALBIGLUTIDE
SEMAGLUTIDE

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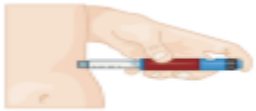
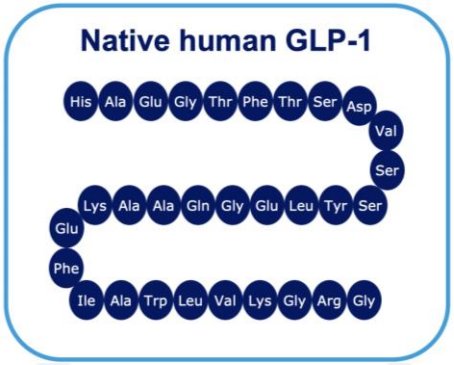
arGLP1: Tipos

Compound	Native GLP-1	Short-acting GLP-1 RAs	Long-acting GLP-1 RAs
Clinical milestone	Nauck et al. 1993	Fineman et al. 2003	Nauck et al. 2006
Approval for clinical use	NA	2005	2009
$t_{1/2}$	~ 2 min	~ 3 h	1 week
Administration	i.v. or s.c. (continuous)	s.c. BD–QD	s.c. QD–QW
Molecular weight (Da)	~ 3,298	~4,187–4,860	~4,114–73,000
Clinical features	Requires continuous infusion	Predominant effect on postprandial plasma glucose	Predominant effect on fasting plasma glucose





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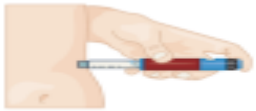
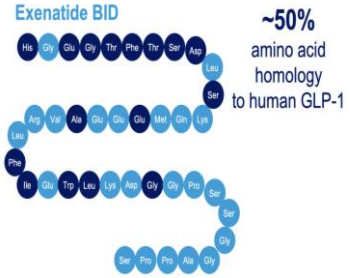


EXENATIDE
LIXISENATIDE



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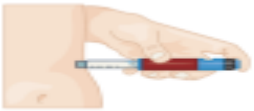
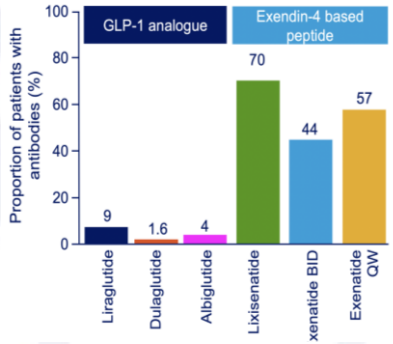
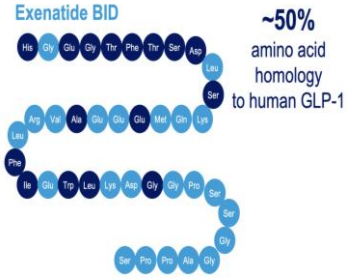


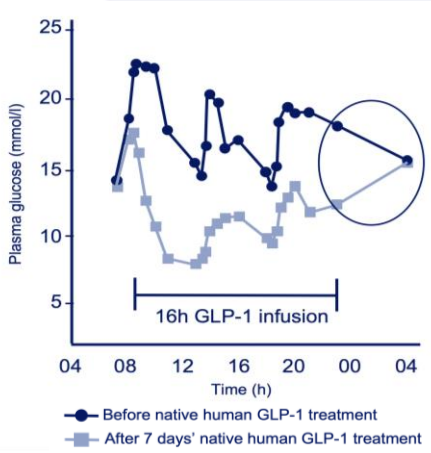
Elevada Inmunogenicidad

EXENATIDE
LIXISENATIDE





arGLP1 Acción corta:
↓↓ **Glc Postprandial**
↓ Glc Ayunas
↓ HbA1c



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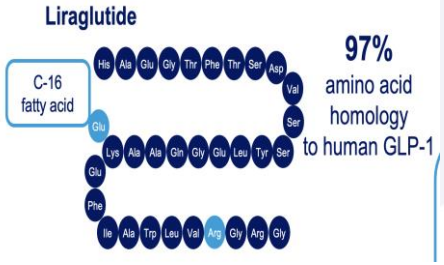

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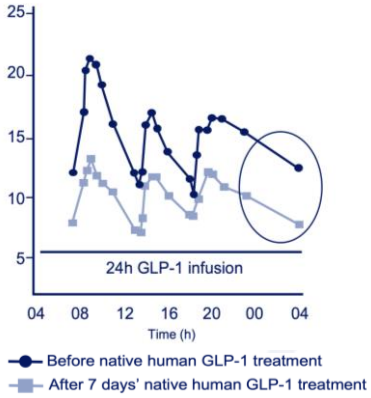
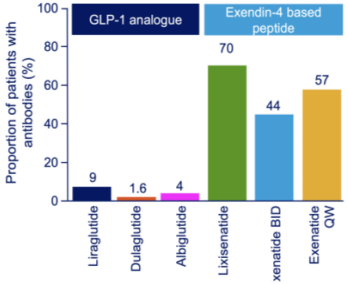
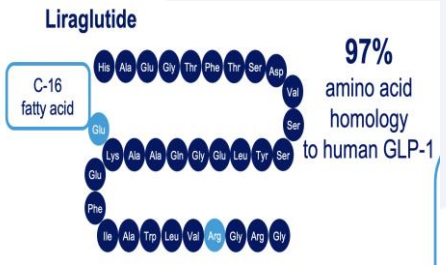
arGLP1 Acción larga:
↓ Glc Postprandial
↓↓ **Glc en Ayunas**
↓↓ **HbA1c**

Menos Inmunógenos

LIRAGLUTIDE
DULAGLUTIDE
ALBIGLUTIDE
SEMAGLUTIDE







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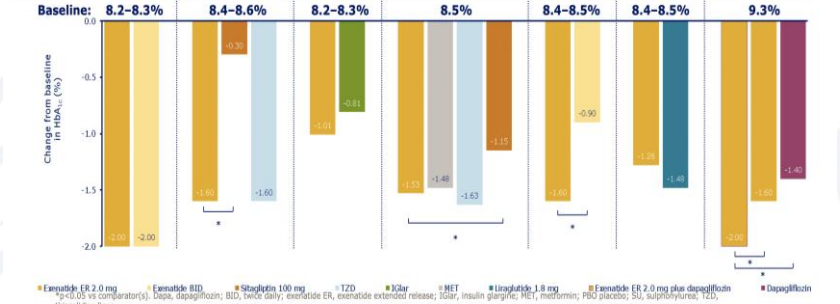
arGLP1: Evidencias en DM2

Change in HbA_{1c} with exenatide ER

CHANGE FROM BASELINE AT END OF TREATMENT (%)

	DURATION-1[1]	DURATION-2[2]	DURATION-3[3]	DURATION-4[4]	DURATION-5[5]	DURATION-6[6]	DURATION-8[7]
Comparator:	Exenatide BID	Sitagliptin/TZD	IGlar	Sitagliptin/TZD/MET	Exenatide BID	Liraglutide	Dapagliflozin
Background:	N/A	MET	MET ± SU	N/A	MET/SU/TZD	MET/SU/TZD	MET ± Dapa
Trial duration:	52 weeks	52 weeks	156 weeks	26 weeks	24 weeks	26 weeks	28 weeks
Baseline:	8.2–8.3%	8.4–8.6%	8.2–8.3%	8.5%	8.4–8.5%	8.4–8.5%	9.3%



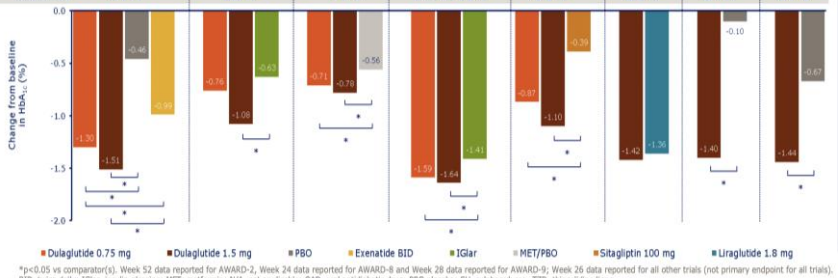
*p<0.05 vs comparator(s). Dapa, dapagliflozin; BID, twice daily; exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; PBO placebo; SU, sulphonylurea; TZD, thiazolidinedione.

1. Buse JB et al. *Diabetes Care* 2010; 33(6):1255–61; 2. Wysham C et al. *Diabet Med* 2011; 28(6):705–14; 3. Diamant M et al. *Lancet Diabetes Endocrinol* 2014; 2(6):464–73; 4. Russell-Jones D et al. *Diabetes Care* 2012;35(2):252–8; 5. Blevins T et al. *J Clin Endocrinol Metab* 2011; 96(5):1301–10; 6. Buse JB et al. *Lancet* 2013; 381(9861):117–2; 7. Frias JP, et al. Lancet Diab Endocrinol 2016; 4(12):1004–16.

Change in HbA_{1c} with dulaglutide

CHANGE FROM BASELINE AT WEEK 26 (%)

	AWARD-1[1]	AWARD-2[2]	AWARD-3[3]	AWARD-4[4]	AWARD-5[5]	AWARD-6[6]	AWARD-8[7]	AWARD-9[8]
Comparator:	Exenatide BID/PBO	IGlar	MET/PBO	IGlar	Sitagliptin	Liraglutide	PBO	PBO
Background:	MET+TZD	MET+SU	N/A	Insulin lispro±OADs	MET	MET	SU	IGlar±MET
Trial duration:	52 weeks	78 weeks	52 weeks	52 weeks	52 weeks	26 weeks	24 weeks	28 weeks
Endpoint:	26 weeks	52 weeks	26 weeks	26 weeks	52 weeks	26 weeks	24 weeks	28 weeks
Baseline:	8.1%	8.1%	7.6%	8.40–8.53%	8.1%	8.1%	8.4%	8.4%



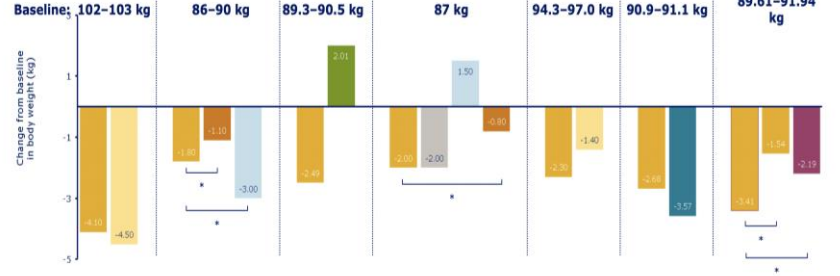
*p<0.05 vs comparator(s). Week 52 data reported for AWARD-2, Week 24 data reported for AWARD-8 and Week 28 data reported for AWARD-9; Week 26 data reported for all other trials (not primary endpoint for all trials). BID, twice daily; IGlar, insulin glargine; MET, metformin; N/A, not applicable; OAD, oral antidiabetic drug; PBO placebo; SU, sulphonylurea; TZD, thiazolidinedione.

1. Wysham C et al. *Diabetes Care* 2015; 38:1393–1394; 2. Giorgino F et al. *Diabetes Care* 2015; 38:2241–2249; 3. Umpierrez G et al. *Diabetes Care* 2014; 37:2168-2176; 4. Blonde L et al. *Lancet* 2015; 385:2057–2066; 5. Nauck M et al. *Diabetes Care* 2014; 37:2149–2158; 6. Dungan KM et al. *Lancet* 2014; 384:1349–1357; 7. Dungan KM et al. *Diabetes Obes Metab* 2016; 18:475–482; 8. Pozzilli P et al. *Diabetes* 2016; 65(Supplement 1):A62.

Change in body weight with exenatide ER

CHANGE FROM BASELINE AT END OF TREATMENT (kg)

	DURATION-1[1]	DURATION-2[2]	DURATION-3[3]	DURATION-4[4]	DURATION-5[5]	DURATION-6[6]	DURATION-8[7]
Comparator:	Exenatide BID	Sitagliptin/TZD	IGlar	Sitagliptin/TZD/MET	Exenatide BID	Liraglutide	Dapagliflozin
Background:	N/A	MET	MET ± SU	N/A	MET/SU/TZD	MET/SU/TZD	MET ± Dapa
Trial duration:	52 weeks	52 weeks	156 weeks	26 weeks	24 weeks	26 weeks	28 weeks
Baseline:	102–103 kg	86–90 kg	89.3–90.5 kg	87 kg	94.3–97.0 kg	90.9–91.1 kg	89.61–91.94 kg



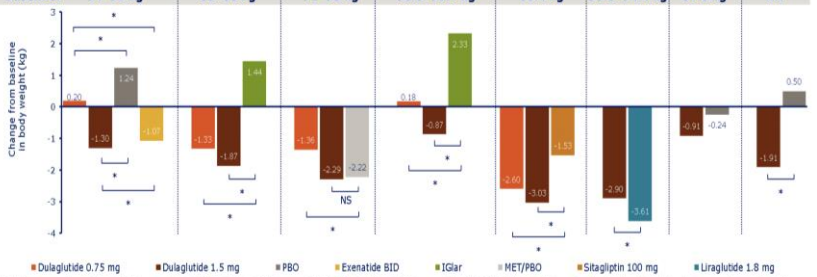
*p<0.05 vs comparator(s). BID, twice daily; Dapa, dapagliflozin; exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; PBO placebo; SU, sulphonylurea; TZD, thiazolidinedione.

1. Buse JB et al. *Diabetes Care* 2010; 33(6):1255–61; 2. Wysham C et al. *Diabet Med* 2011; 28(6):705–14; 3. Diamant M et al. *Lancet Diabetes Endocrinol* 2014; 2(6):464–73; 4. Russell-Jones D et al. *Diabetes Care* 2012;35(2):252–8; 5. Blevins T et al. *J Clin Endocrinol Metab* 2011; 96(5):1301–10; 6. Buse JB et al. *Lancet* 2013; 381(9861):117–2; 7. Frias JP, et al. Lancet Diab Endocrinol 2016; 4(12):1004–16.

Change in body weight with dulaglutide

CHANGE FROM BASELINE AT WEEK 26 (kg)

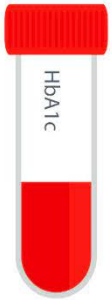
	AWARD-1[1]	AWARD-2[2]	AWARD-3[3]	AWARD-4[4]	AWARD-5[5]	AWARD-6[6]	AWARD-8[7]	AWARD-9[8]
Comparator:	Exenatide BID/PBO	IGlar	MET/PBO	IGlar	Sitagliptin	Liraglutide	PBO	PBO
Background:	MET+TZD	MET+SU	N/A	Insulin lispro±OADs	MET	MET	SU	IGlar±MET
Trial duration:	52 weeks	78 weeks	52 weeks	52 weeks	52 weeks	26 weeks	24 weeks	28 weeks
Endpoint:	26 weeks	52 weeks	26 weeks	26 weeks	52 weeks	26 weeks	24 weeks	28 weeks
Baseline:	94–97 kg	85–88 kg	92–93 kg	90.8–91.7 kg	86.4 kg	93.8–94.4 kg	87.0 kg	NR

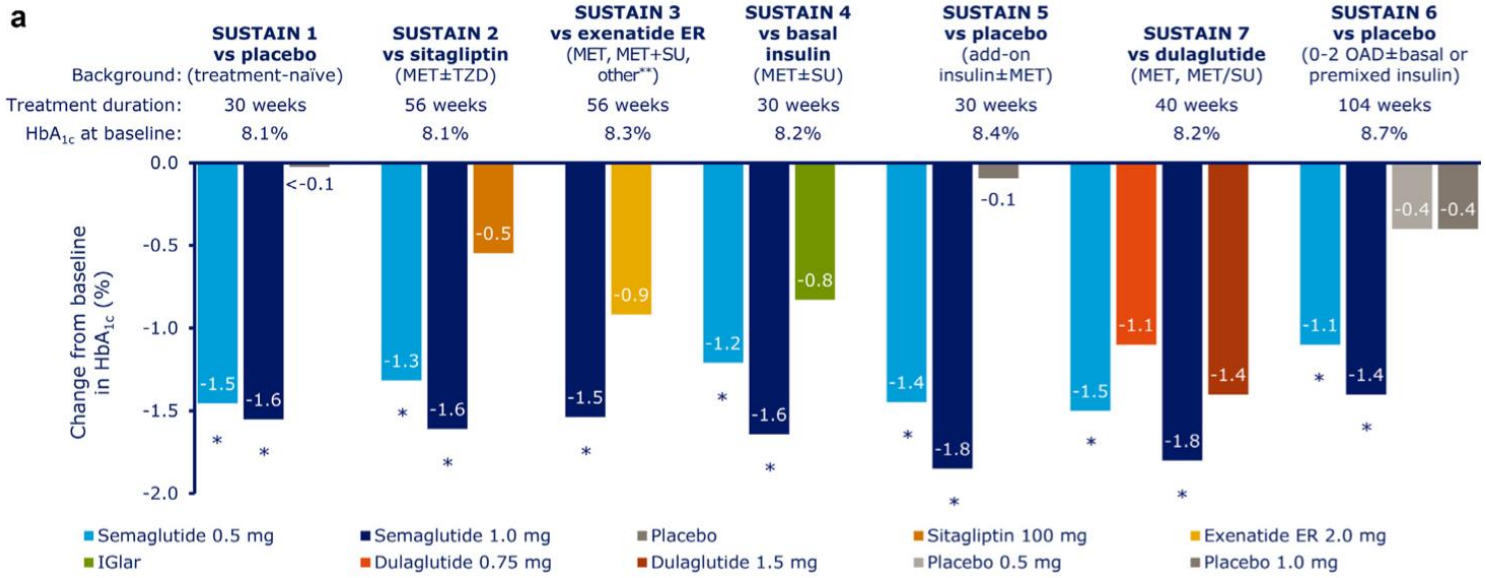


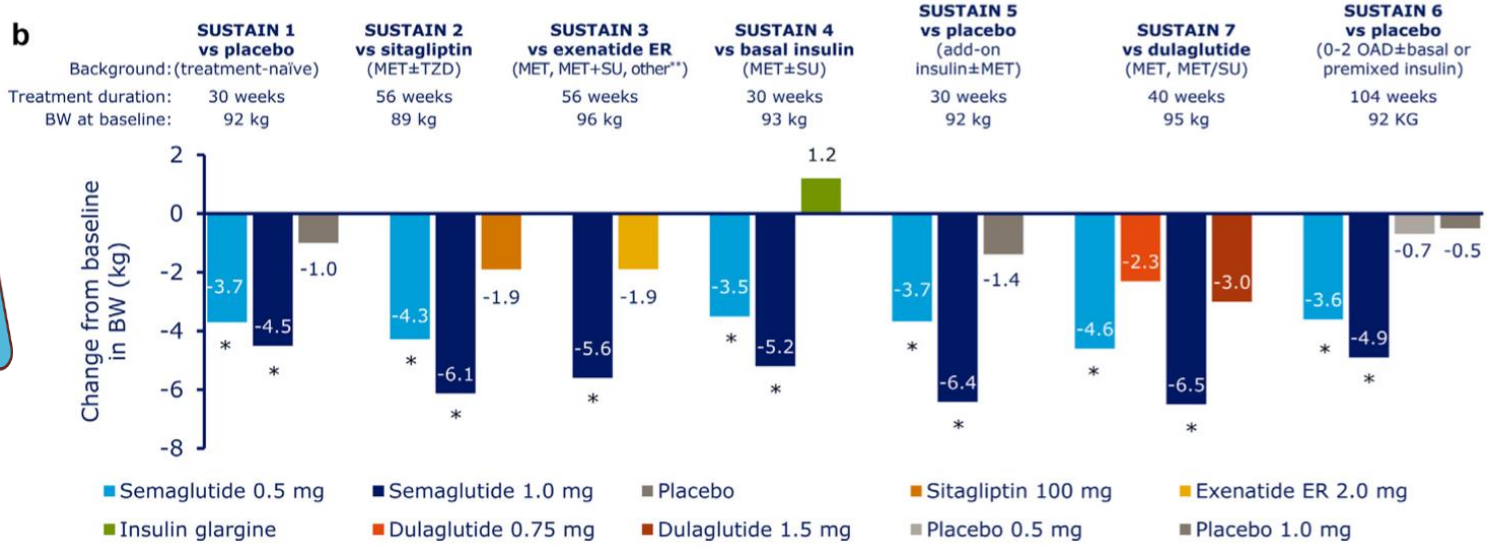
*p<0.05 vs comparator(s). Week 52 data reported for AWARD-2, Week 24 data reported for AWARD-8; Week 28 data reported for AWARD-9. Week 26 data reported for all other trials (not primary endpoint for all trials). BID, twice daily; MET, metformin; N/A, not applicable; PBO placebo; NR, not reported; NS, not significant.

Wysham C et al. *Diabetes Care* 2015; 38:1393–1394; 2. Giorgino F et al. *Diabetes Care* 2015; 38:2241–2249; 3. Umpierrez G et al. *Diabetes Care* 2014; 37:2168-2176; 4. Blonde L et al. *Lancet* 2015; 385:2057–2066; Nauck M et al. *Diabetes Care* 2014; 37:2149–2158; 6. Dungan KM et al. *Lancet* 2014; 384:1349–1357; 7. Dungan KM et al. *Diabetes Obes Metab* 2016; 18:475–482; Pozzilli P et al. *Diabetes* 2016; 65(Supplement 1):A62.

arGLP1: Evidencias en DM2

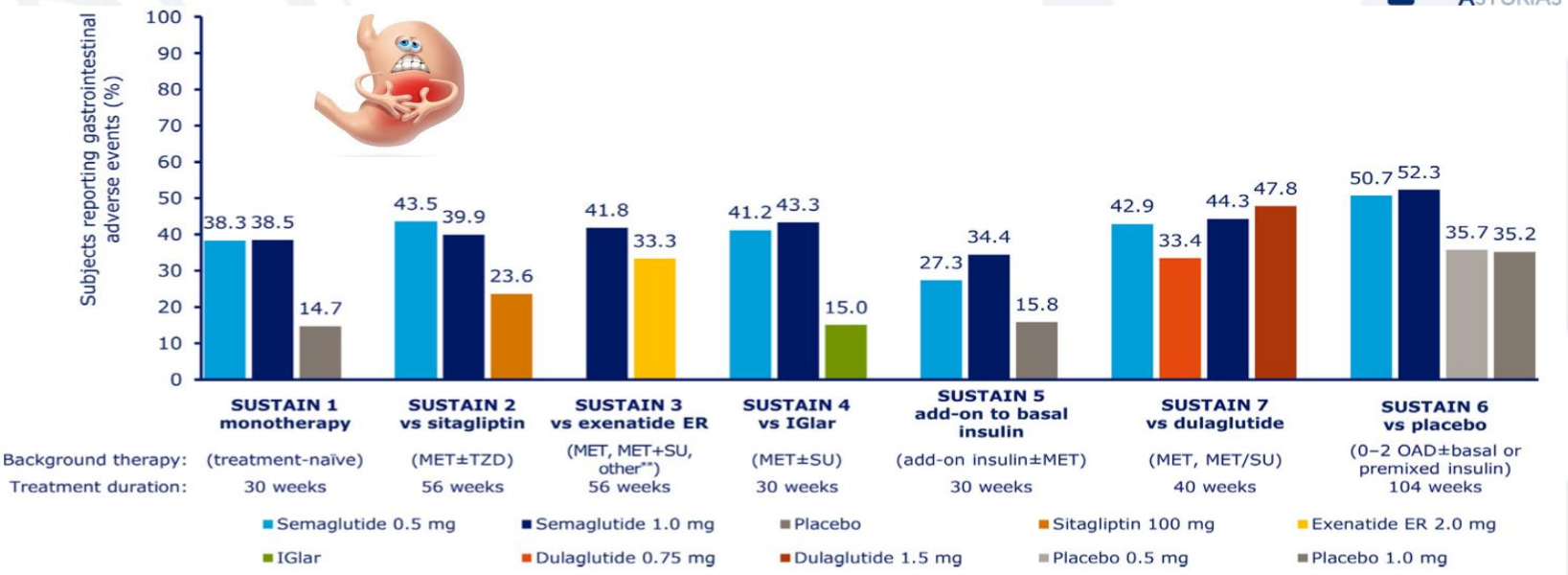


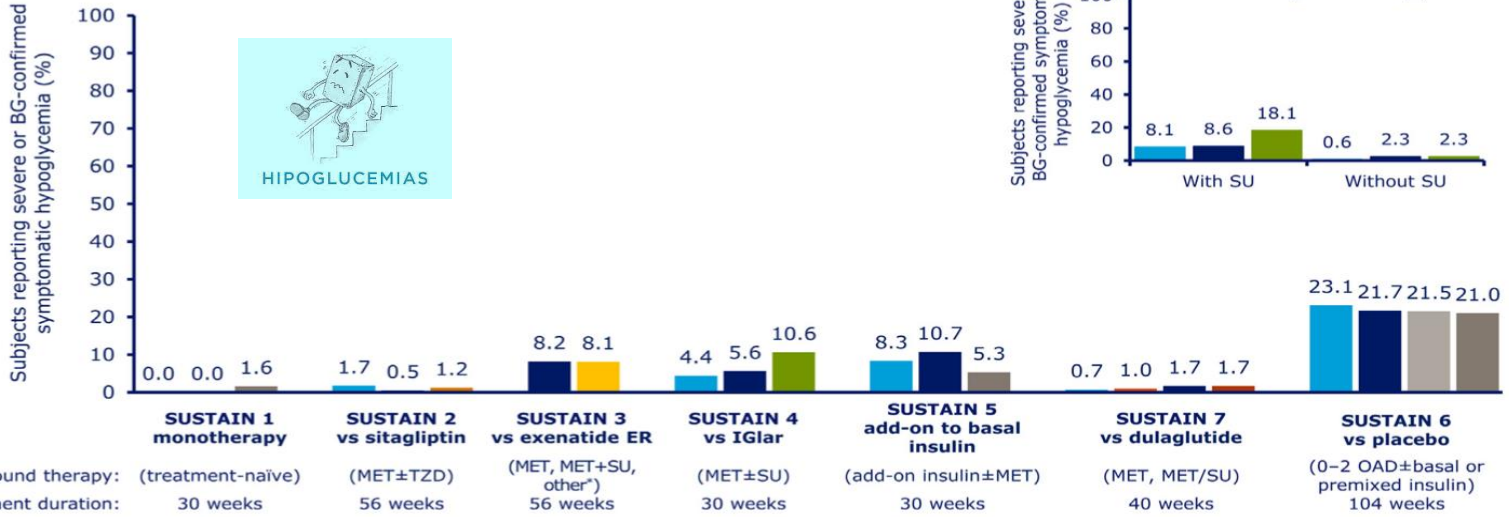




V.R. Aroda et al./Diabetes & Metabolism 45 (2019) 409–418

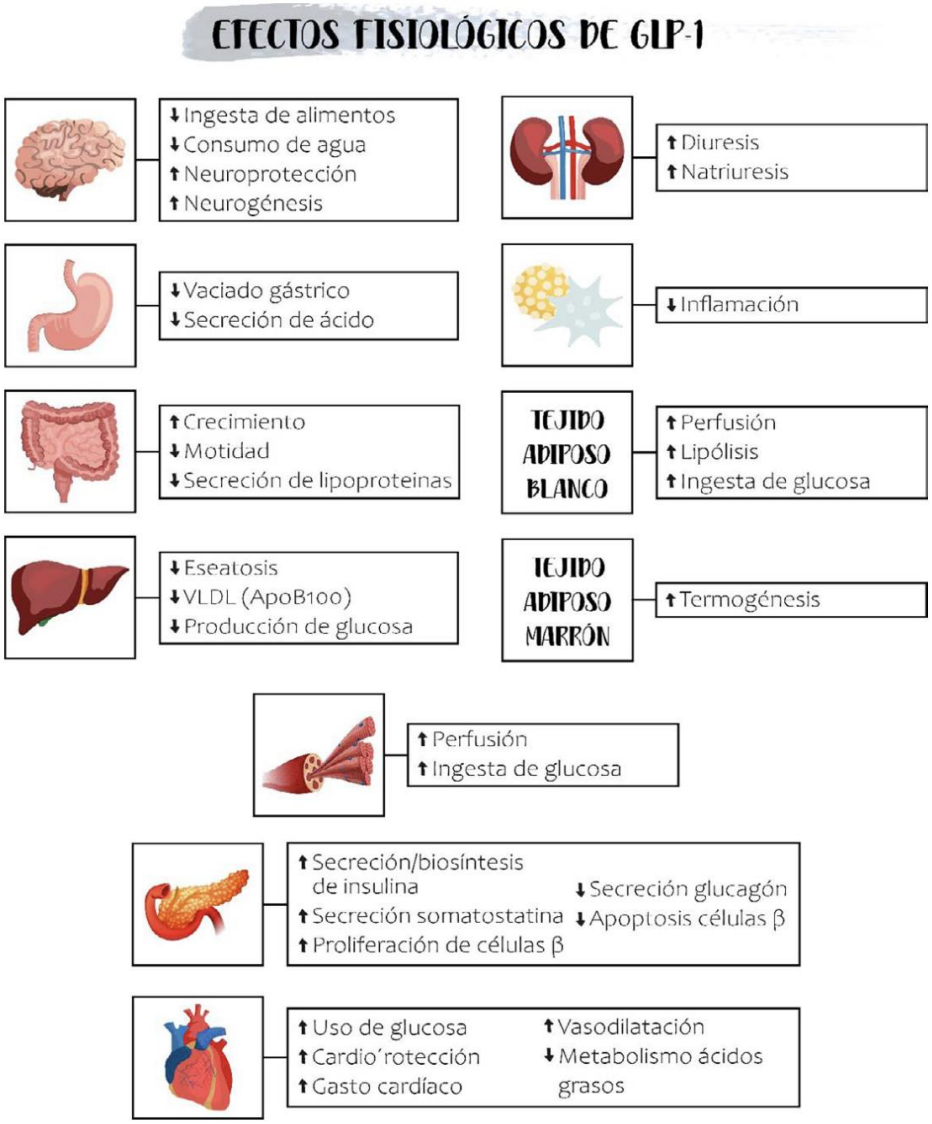
arGLP1: Evidencias en DM2





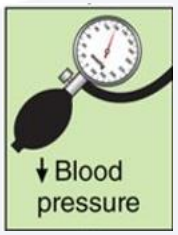
V.R. Aroda et al./Diabetes & Metabolism 45 (2019) 409–418

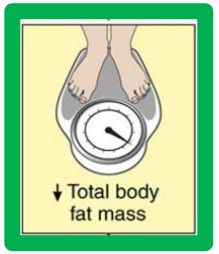
arGLP1: Evidencias en DM2



↓ 1-1,6 HbA1c

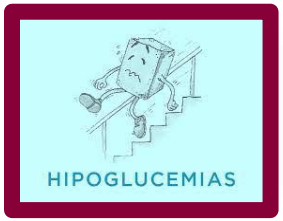
SIN HIPOGLUCEMIAS





↓ 2-6 Kg

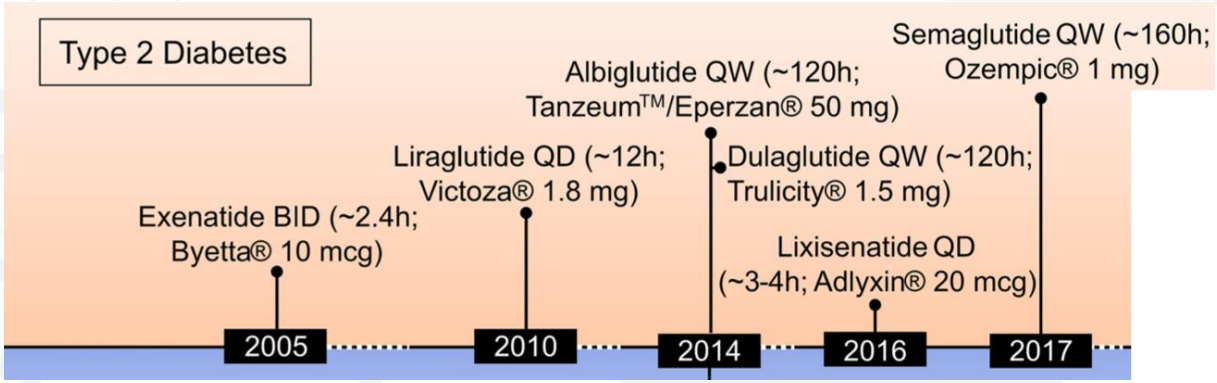
Educación
Titulación



Insulina
Sulfonilureas

Rico-Fontalvo et al. Glp-1 Receptor Agonists: From their Physiological Effect on the Incretine System to their Role in Diabetic Kidney Disease. doi: 10.3823/1463.

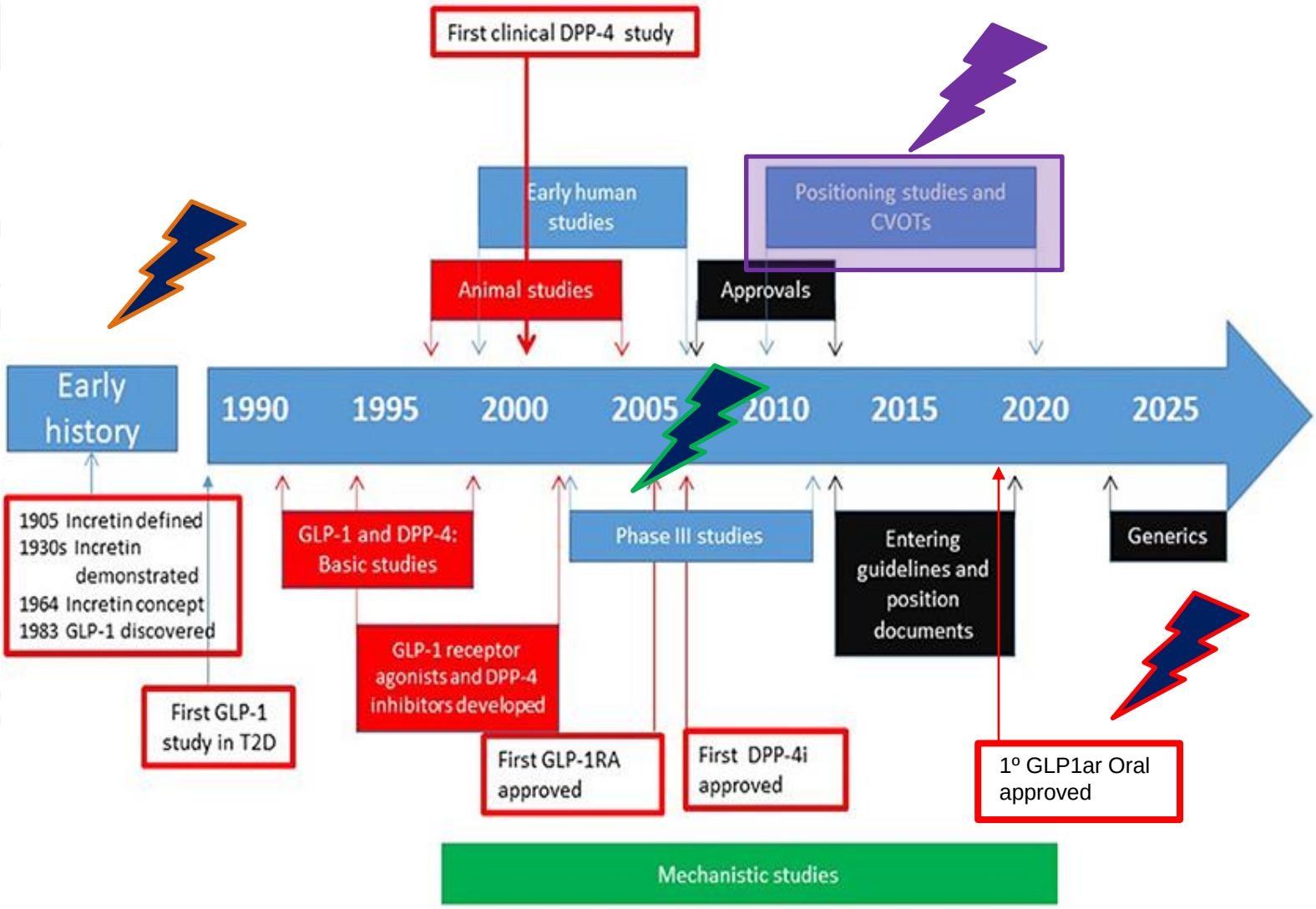
arGLP1: Aprobación en DM2



U.S Food and Drug Administration

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Historia de los arGLP1:



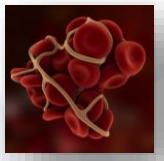
arGLP1: Seguridad Cardiovascular

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.



IAM: OR 1,43 (1,03-1,98), **p=0,03**.

Mort CV: OR 1,64 (0,98-2,74), p=0,06.

arGLP1: Seguridad Cardiovascular

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

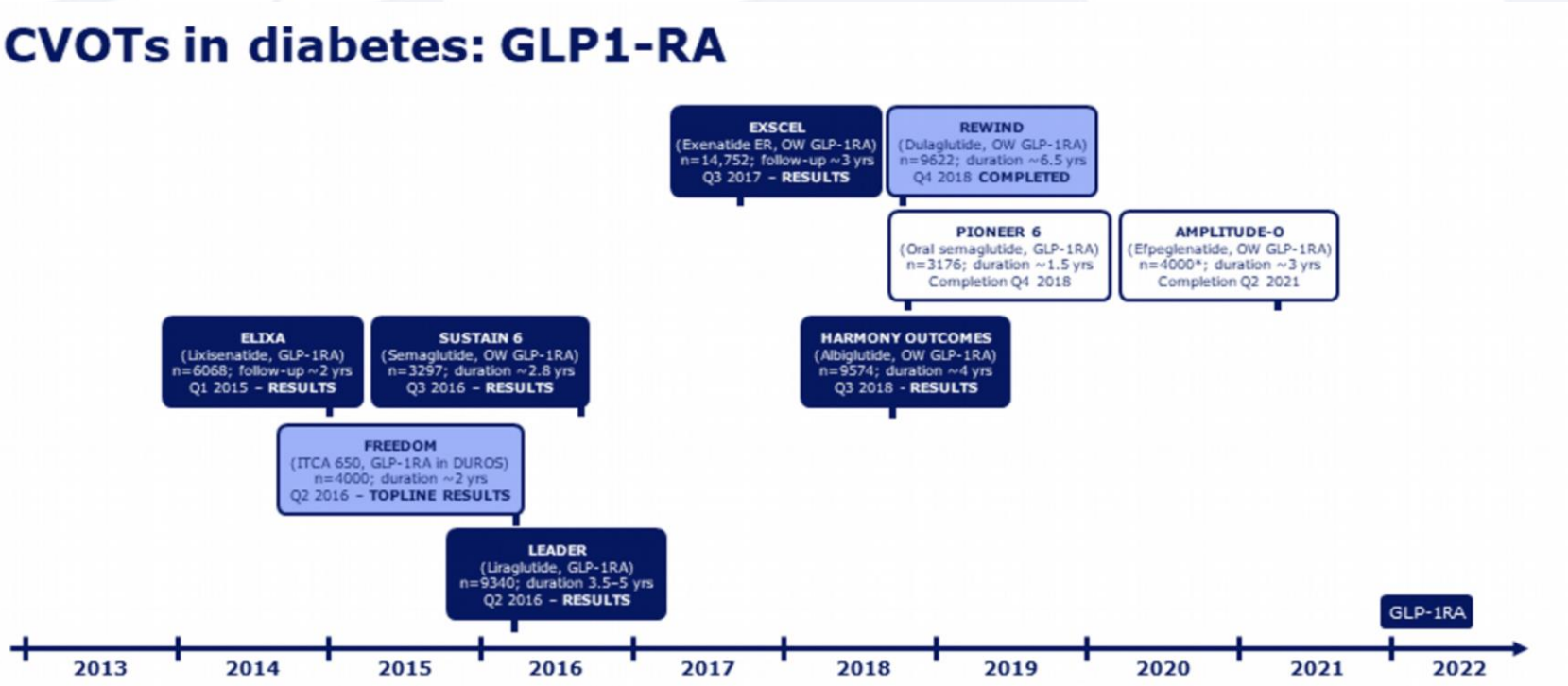
ENSAYOS DE SEGURIDAD CV

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

arGLP1: Seguridad Cardiovascular

ENSAYOS DE SEGURIDAD CV



arGLP1: Seguridad Cardiovascular

ENSAYOS DE SEGURIDAD CV

GLP-1RA CVOTs. Patient population

	REWIND[1] (N=9901)	ELIXA[2] (N=6068)	EXSCEL[3] (N=14,752)	SUSTAIN 6[4] (N=3297)	LEADER[5] (N=9340)	HARMONY[6] (N=9463)
Drug tested	**Dulaglutide**	**Lixisenatide**	**Exenatide**	**Semaglutide**	**Liraglutide**	**Albiglutide**
Dosage	1.5 mg /week	20 µg* /day	2.0 mg /week	0.5 or 1 mg /week	1.2 or 1.8 mg /day	30 mg† /week
Mean age, years	66	60	63	65	64	64
Gender, % female	46	31	38	39	36	30
Diabetes duration, years	10.0	9.3	12	13.9	12.8	14
Prior CVD, %	31	100	73	59	72	100
Mean BMI, kg/m²	32	30	32	33	33	32
Mean HbA_{1c}, %	7.3	7.7	8.0	8.7	8.7	8.7

PACIENTES CON EVENTO CARDIOVASCULAR
<60 AÑOS + HTA-HTF/ALBUMINURIA/DISF. SIST/DIAST

arGLP1: Seguridad Cardiovascular

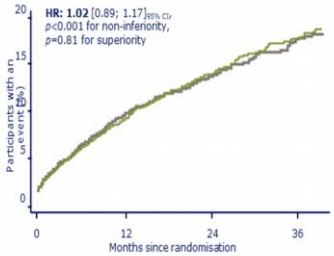
Derivados de exendina

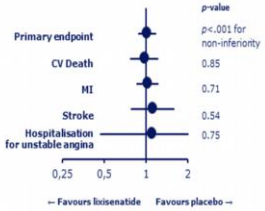
ENSAYOS DE SEGURIDAD CV

Análogos de GLP-1

Lixisenatide: ELIXA results

Neutral



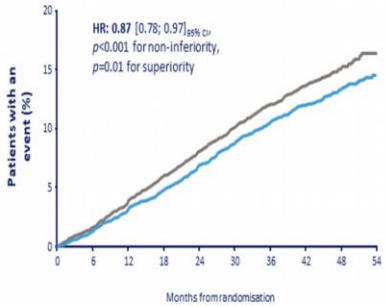


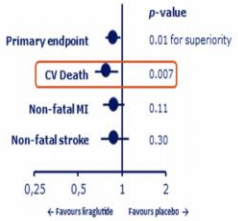
The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, or hospitalisation for unstable angina

1. Pfeffer et al. *N Engl J Med* 2015;373:2247–57.

Liraglutide: LEADER results

BENEFICIAL

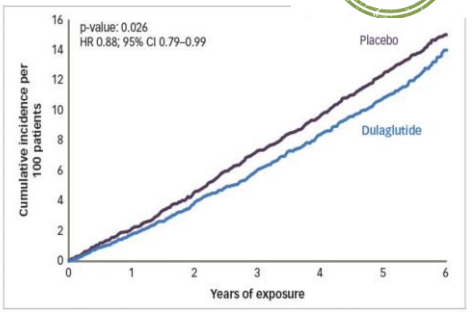




N Engl J Med. 2016; 375:1834-33.

Dulaglutide: REWIND

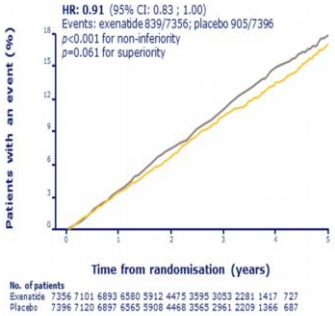
BENEFICIAL

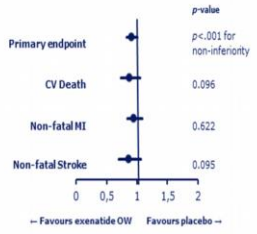


Gerstein et al. Lancet. 2019 Jul 13;394(10193):121-130.-3.

Exenatide once weekly: EXSCEL results

Neutral

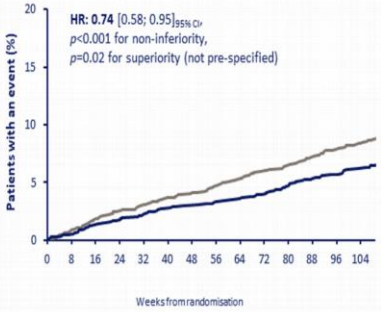


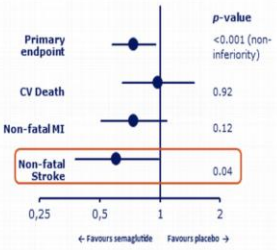


Holman RR et al. *N Engl J Med* 2017;377:1228–1239

Semaglutide: SUSTAIN-6 result

BENEFICIAL

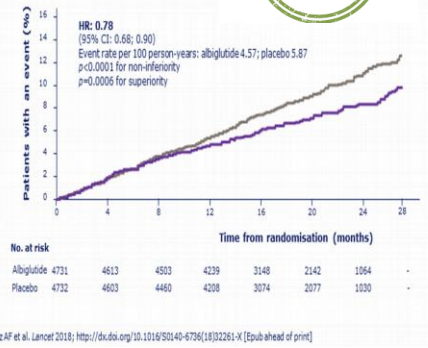




Marso et al. *New Engl J Med* 2016;375:1834–44.

Albiglutide: HARMONY outcom

BENEFICIAL



Hernandez AF et al. Lancet 2018; http://dx.doi.org/10.1016/S0140-6736(18)32261-X [Epub ahead of print]

arGLP1: Seguridad Cardiovascular

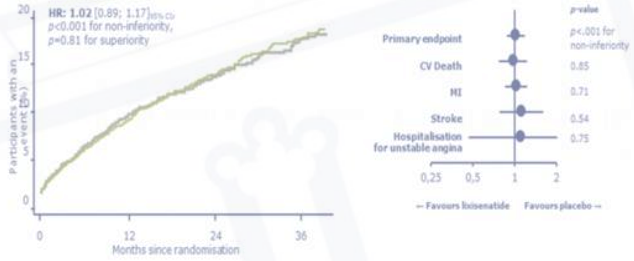
ENSAYOS DE SEGURIDAD CV

Derivados de exendina

Análogos de GLP-1

Lixisenatide: ELIXA results

Neutral



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1. Pfeffer et al. *N Engl J Med* 2015;373:2247–57.

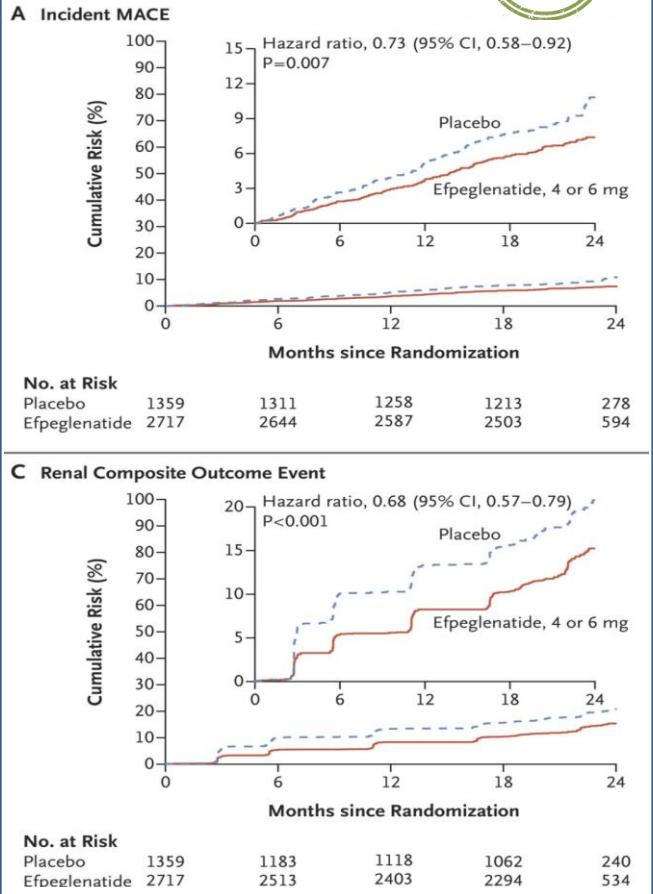
Exenatide once weekly: EXSCEL results

Neutral

Holman RR et al. *N Engl J Med* 2017;377:1228–1239

Efpeglenatide: AMPLITUD-O

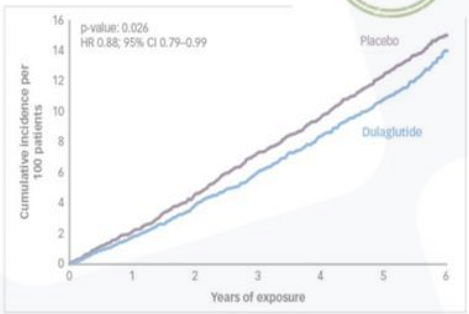
BENEFICIAL



Gerstein et al. Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes. NEJM 2021; 385:896-907.

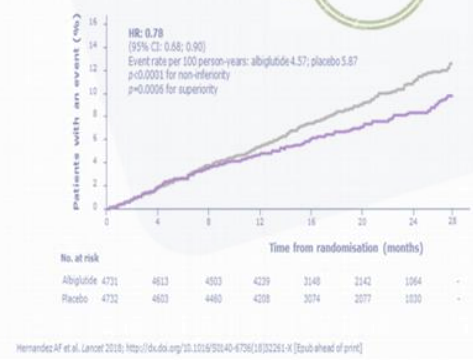
Dulaglutide: REWIND

BENEFICIAL



Albiglutide: HARMONY outcom

BENEFICIAL



Hernandez AF et al. *Lancet* 2018; http://dx.doi.org/10.1016/S0140-6736(18)32261-X [Epub ahead of print]

arGLP1: Seguridad Cardiovascular

ENSAYOS DE SEGURIDAD CV

LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

13% MACE 3 años

SUSTAIN

26% MACE 2 años

Harmony Outcomes

22% MACE 1,8 años

REWIND

12% MACE 6 años

AMPLITUDE-O
Efpeglenatide Cardiovascular Outcomes

17% MACE 2 años

LONG ACTING

arGLP1: Seguridad Cardiovascular

LONG ACTING

ENSAYOS DE SEGURIDAD CV

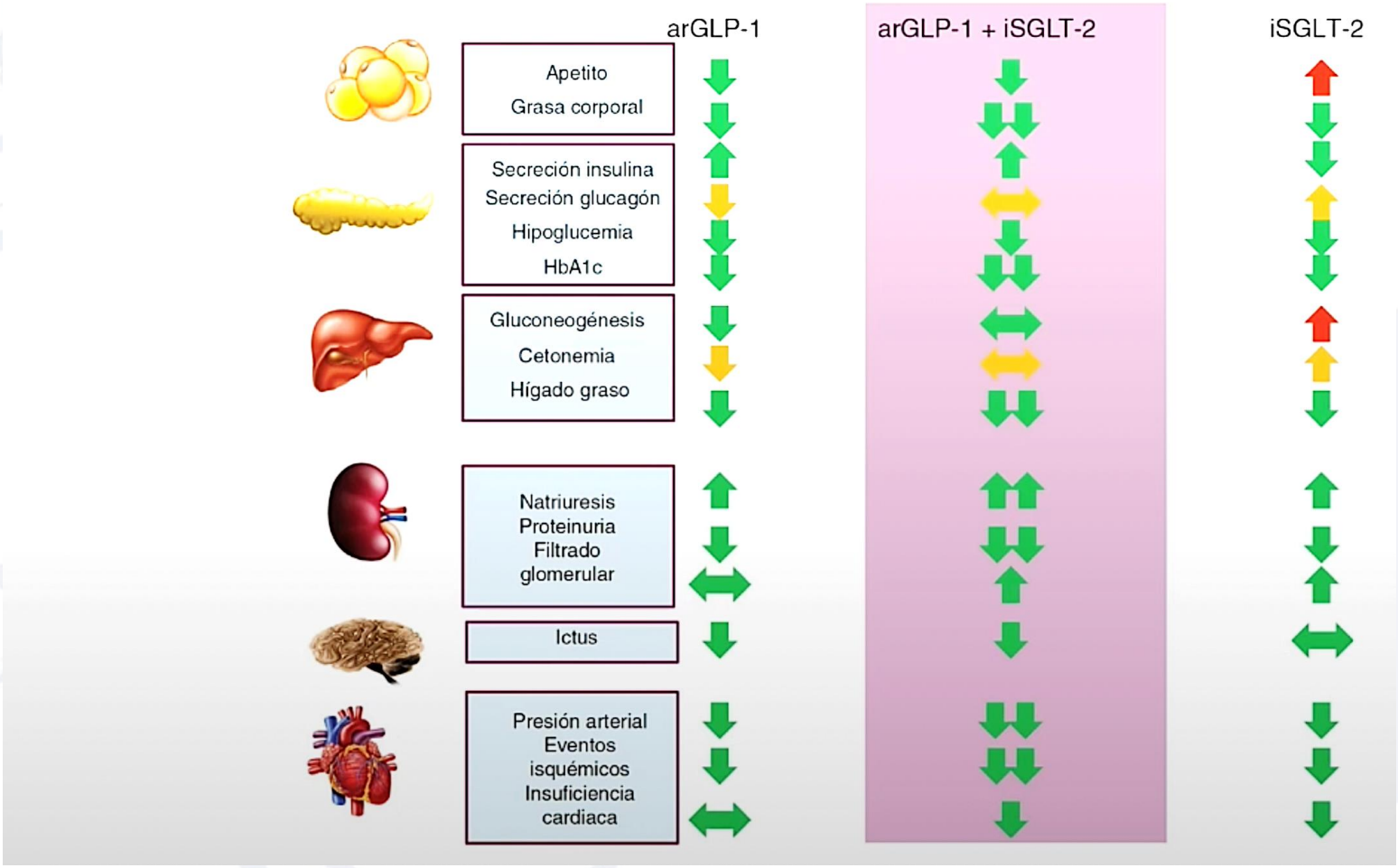
	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER-6	overall
	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide o	
3-MACE	1.02 0.89-1.17	0.87 0.78-0.97	0.74 0.58-0.95	0.91 0.83-1.00	0.78 0.68-0.90	0.88 0.79-0.99	0.79 0.57-1.11	0.88 0.82-0.94
CV death	0.98 0.78-1.22	0.78 0.66-0.93	0.98 0.65-1.48	0.88 0.76-1.02	0.93 0.73-1.19	0.91 0.78-1.06	0.49 0.27-0.92	0.88 0.81-0.96
fatal or no fatal MI	1.03 0.87-1.22	0.86 0.73-1.00	0.81 0.57-1.16	0.97 0.85-1.10	0.75 0.61-0.90	0.96 0.79-1.15	1.18 0.73-1.90	0.91 0.84-1.00
fatal or no fatal Stroke	1.12 0.79-1.58	0.86 0.71-1.06	0.65 0.41-1.03	0.85 0.70-1.03	0.86 0.66-1.14	0.76 0.62-0.94	0.74 0.35-1.57	0.84 0.76-0.93
All cause mortality	0.94 0.78-1.13	0.85 0.74-0.97	1.05 0.74-1.50	0.86 0.77-0.97	0.95 0.79-1.16	0.90 0.80-1.01	0.51 0.31-0.84	0.88 0.83-0.95
Hospital for Heart failure	0.96 0.75-1.23	0.87 0.73-1.05	1.11 0.77-1.61	0.94 0.78-1.13	0.71 0.53-0.94	0.93 0.77-1.12	0.86 0.48-1.44	0.91 0.83-0.99
composite kidney outcome	0.84 0.68-1.02	0.78 0.67-0.92	0.64 0.46-0.88	0.88 0.76-1.01		0.85 0.77-0.93		0.83 0.78-0.89
worsening of Kidney function	1.16 0.74-1.83	0.89 0.67-1.19	1.28 0.64-2.58	0.88 0.74-1.05		0.70 0.57-0.85		0.87 0.73-1.03

Kristensen. Lancet Diab Endoc 2019

J.Barrot (personal contribution)

arGLP1: Seguridad Cardiovascular

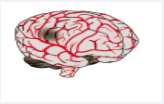
Efectos combinados de arGLP-1 e iSGLT2

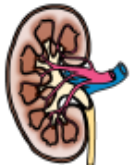


Gorgojo Martinez et al. Hipertensión y riesgo Vascular 2019:36; 145-161.

arGLP1: Seguridad Cardiovascular

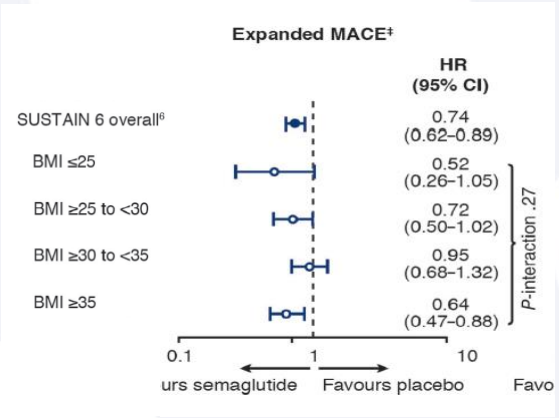
Efectos CV y Renales INDEPENDIENTES de HbA1c e IMC:

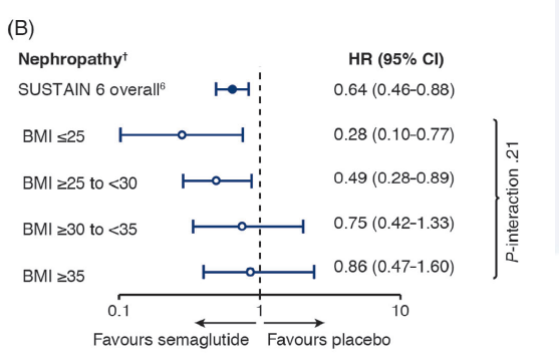




	HbA1c	p Interacción
SUSTAIN (N Engl J Med 2016;375:1834-44)	≤ 8,5% / > 8,5%	0.94
LEADER® (N Engl J Med 2016; 375:311-322)	≤ 8,3% / > 8,3%	0.58
Harmony Outcomes (The Lancet. October 2, 2018 S0140-6736(18)32261-X)	< 8 % / ≤ 8 % - < 9% / ≥ 9%	0.187

A favor de aGLP1 A favor de Placebo

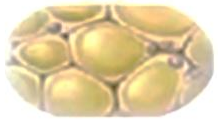




Verma et al. Diabetes Obes Metab. 2020;22:2487–2492.

arGLP1: Seguridad Cardiovascular

CAMBIO DEL PARADIGMA EN DM2:



ESTRATEGIA GLUCOCÉNTRICA (MICROVASCULAR)
UKPDS, ACCORD, ADVANCE, VADT, CARMELINA, ORIGIN, DEVOTE

ESTRATEGIA ADIPOCÉNTRICA (MACROVASCULAR)
PREDIMED, LOOK-AHEAD, SOS, EMPA-REG, CANVAS, DECLARE, CREDENCE, DAPA-HF, EMPEROR-R, EMPEROR-P, DAPA-CKD, LEADER, SUSTAIN6, HARMONY OUTCOMES, REWIND, AMPLITUDE-O

aumentan peso
SU, glitazonas, glinidas,insulina

neutros peso
MET, iDPP4, i. αglucosidasas, colesevelam, bromocriptina

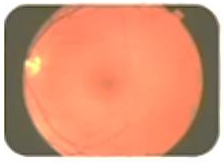
switch

dieta mediterránea,ejercicio, iSGLT2, arGLP1, fármacos para obesidad, cirugía metabólica

pérdida de peso ≥10% a expensas de perímetro abdominal (grasa visceral)

- hipoglucemias
- ganancia de peso
- deterioro comorbilidades obesidad

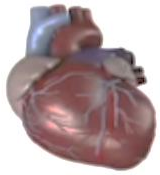
- no hipoglucemias
- mejoría de otros FRCV
- mejoría comorbilidades obesidad



Reducción complicaciones microvasculares

Disminución de HbA1c

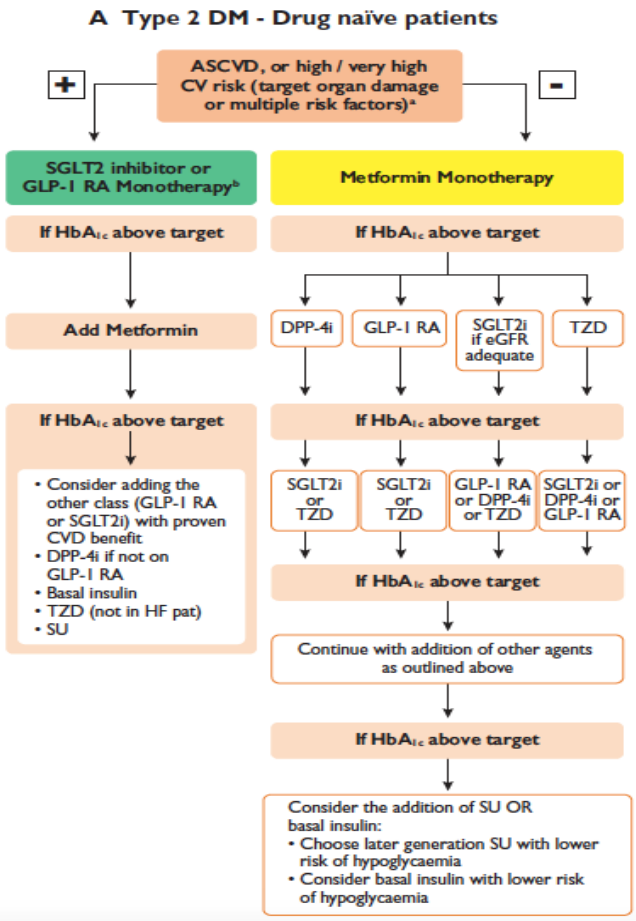
Reducción complicaciones macrovasculares

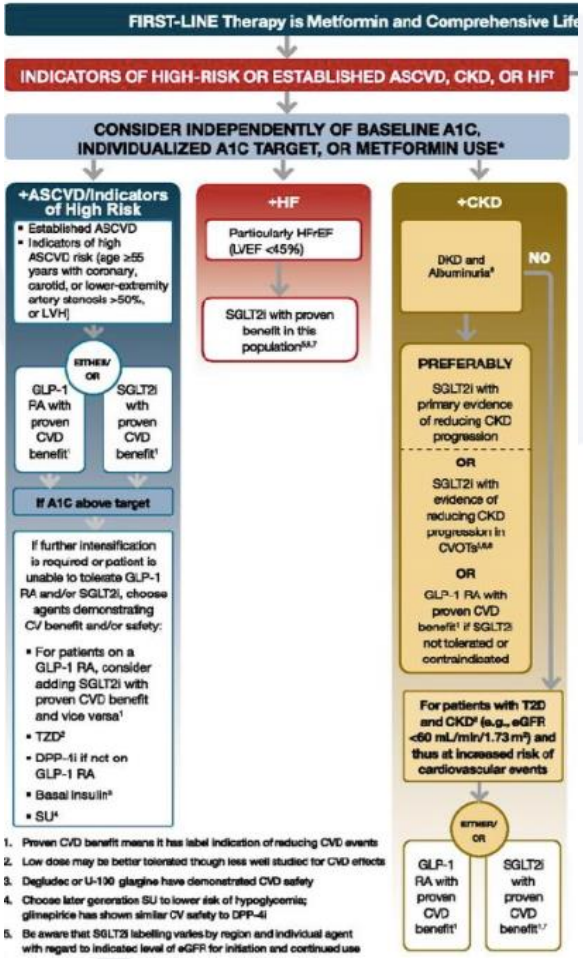


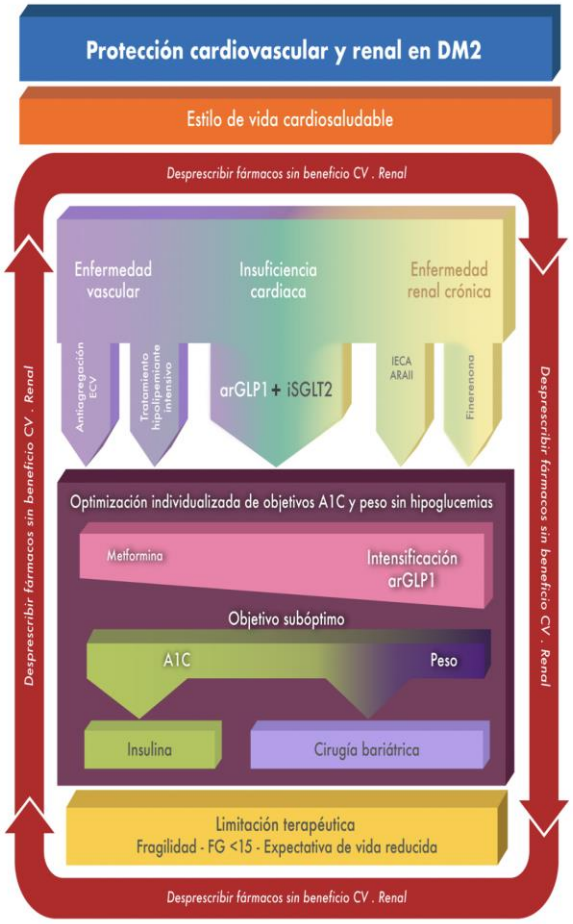
Modificado de JJ Gorgojo . Med Clin (Barc). 2016;147(Supl 1):8-16

arGLP1: Seguridad Cardiovascular

CAMBIO DE GPC EN DM2:







Guía ESC 2019. DM y ECV. EHJ 2019: 00. 1-69.

Diabetes Care 2022. ADA

Documento de consenso Grupo de DM. SEC. 2022.

arGLP1: Seguridad Cardiovascular

¿Cuánto arGLP1 se prescribe?

2019 ESC/EASD Guidelines CV risk categories *Cosentino F et al. Eur Heart J 2020;41:255–323*		Total N = 373.185	Women N = 168,478	Men N = 204,707
Very high risk (10-year risk of CV death >10%)	Established CVD *(%)	99,52[illegible] (26.7)	37,635 (22.3)	61,892 (30.2)
	Target organ damage ** or ≥3 CV risk factors (%)	99,57[illegible] (26.7)	47,702 (28.3)	51,873 (25.3)
High risk (%) (10-year risk of CV death 5-10%)		147,779 (39.6)	71,879 (42.7)	73,577 (35.9)
Moderate Risk (%) (10-year risk of CV death <5%)		26,304 (7.0)	11,262 (6.7)	17,365 (8.5)

* *Coronary Heart Disease, Stroke, Peripheral arteriopathy or Heart Failure*

** *Diabetic Retinopathy, Macroalbuminuria, eGFR<30 ml/min)*

Cebrian-Cuenca A, Mata-Cases M, et al. Eur J prev cardiolo 2020.

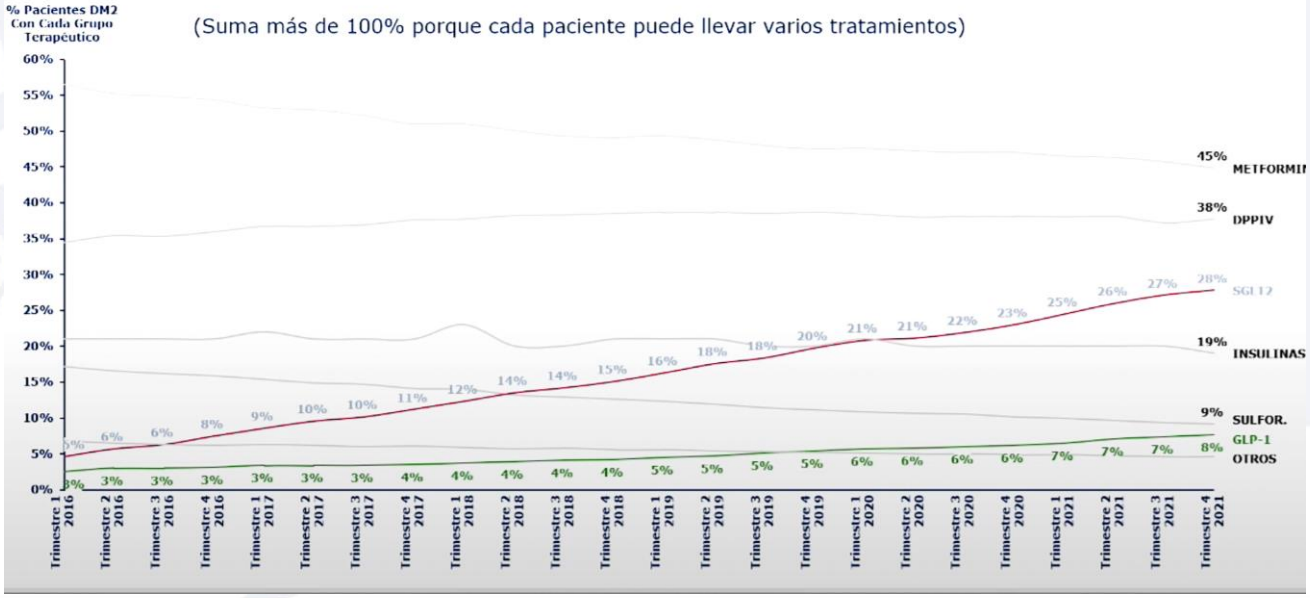
Obesidad: 40-50%

Leitner DR et al. Obes Facts. 2017;10(5):483-92.

WARNING

La realidad

% Pacientes DM2 en cada grupo terapéutico



arGLP1: 8%

Prescripción en España de antidiabéticos. Fuente de datos: IQVIA 2021.

arGLP1: Seguridad Cardiovascular

WARNING

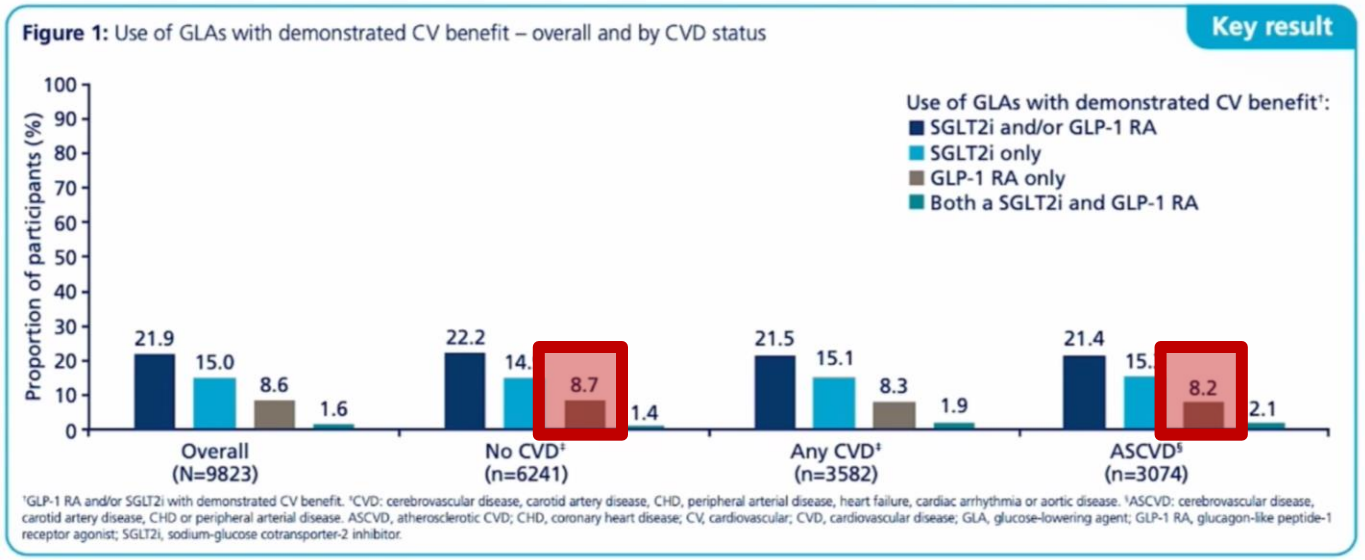
¿A quien se prescribe arGLP1?

HbA1c 8-8,5

IMC 35

Fadini GP et al. Diabetol 2020; 57: 367-375.

Sin diferencias en DM2 con y sin ECV

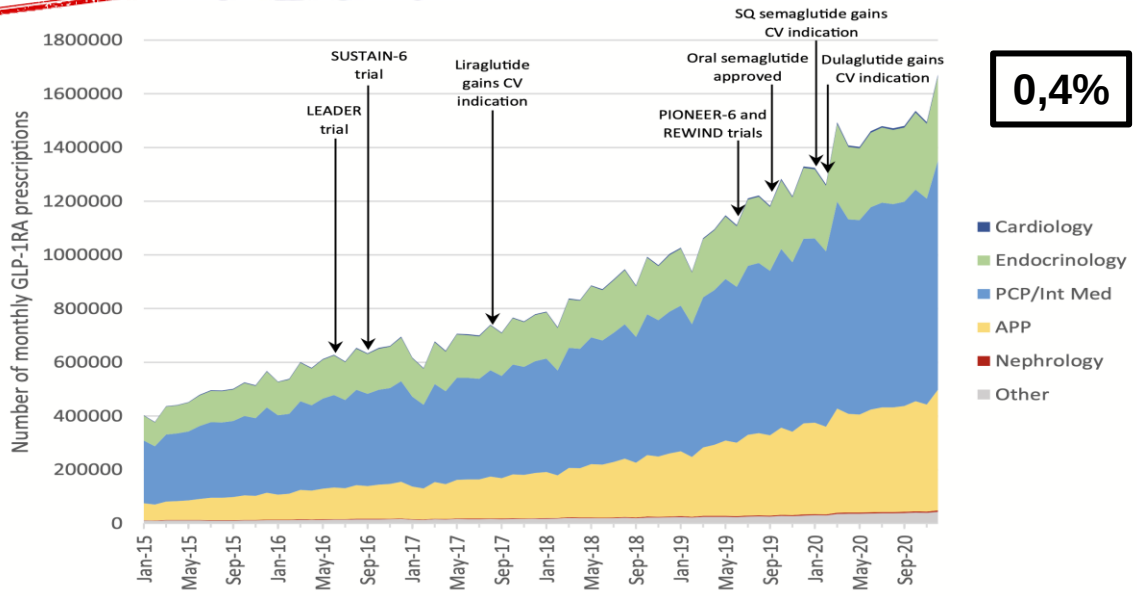


Vencio et al. EASD 2022.

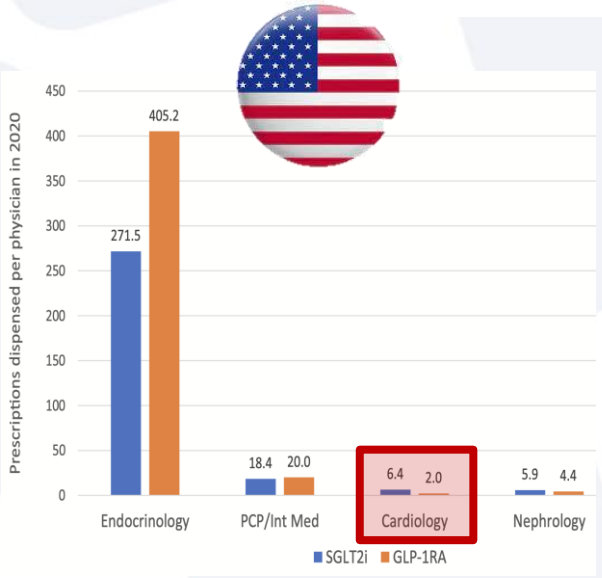
arGLP1: Seguridad Cardiovascular

WARNING

¿Quién prescribe arGLP1?



0,4%

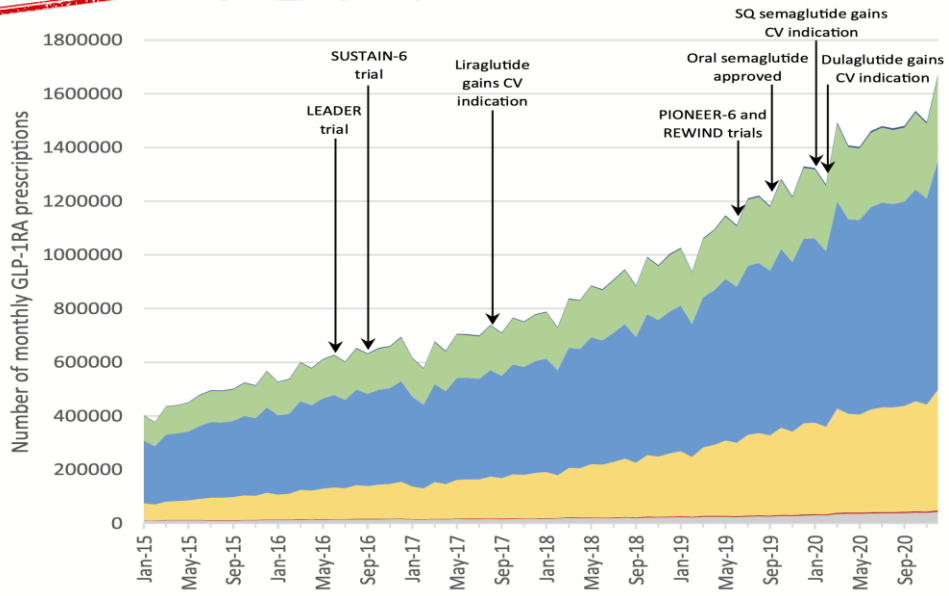


Adhikari et al. *J Am Heart Assoc.* 2022;11:e023811.

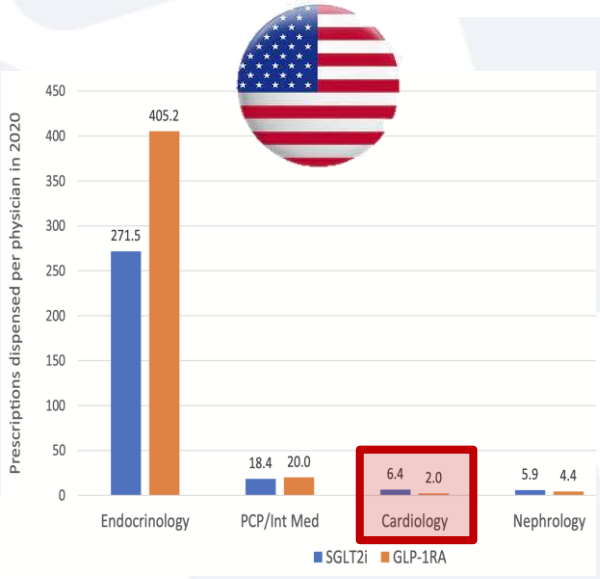
arGLP1: Seguridad Cardiovascular

WARNING

¿Quién prescribe arGLP1?



0,4%



Adhikari et al. *J Am Heart Assoc.* 2022;11:e023811.

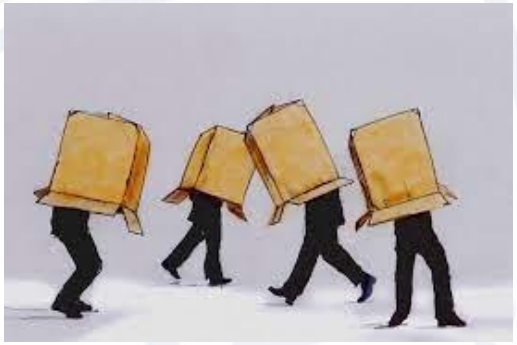
Prescripción en España de arGLP1 a lo largo del año 2020:

# of patients	Endo	Cardio	Nefro	MI	AP
No patients	3.1%	95.4%	85.1%	89.1%	91.4%
Total	1,621 physicians	3,799 physicians	1,645 physicians	7,216 physicians	33,486 physicians

Prescripción en España de antidiabéticos. Marzo 2021. Fuente de datos: IQVIA 2021.

arGLP1: Seguridad Cardiovascular

LOS CARDIÓLOGOS casi NO PRESCRIBIMOS arGLP1:

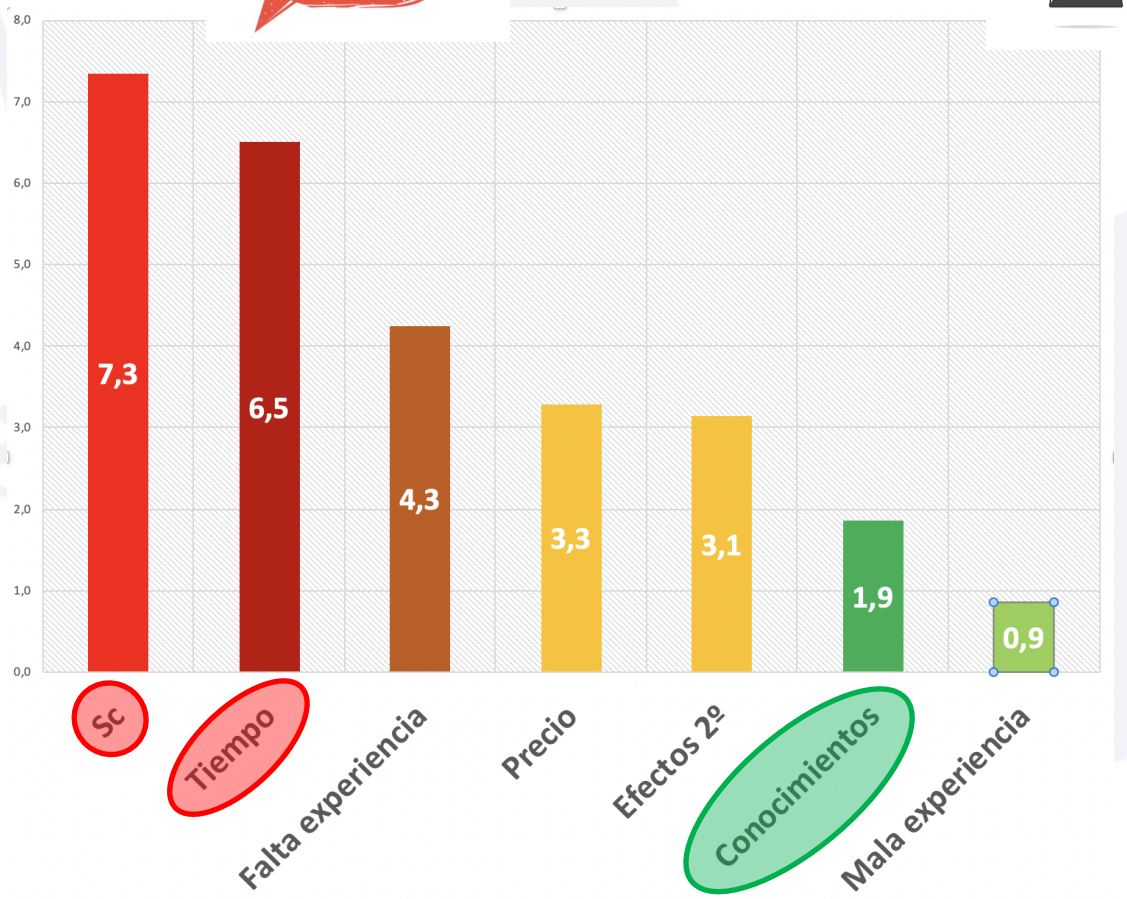


Datos propios del HUCA. Pendientes de publicación. Mayo de 2022.

arGLP1: Seguridad Cardiovascular

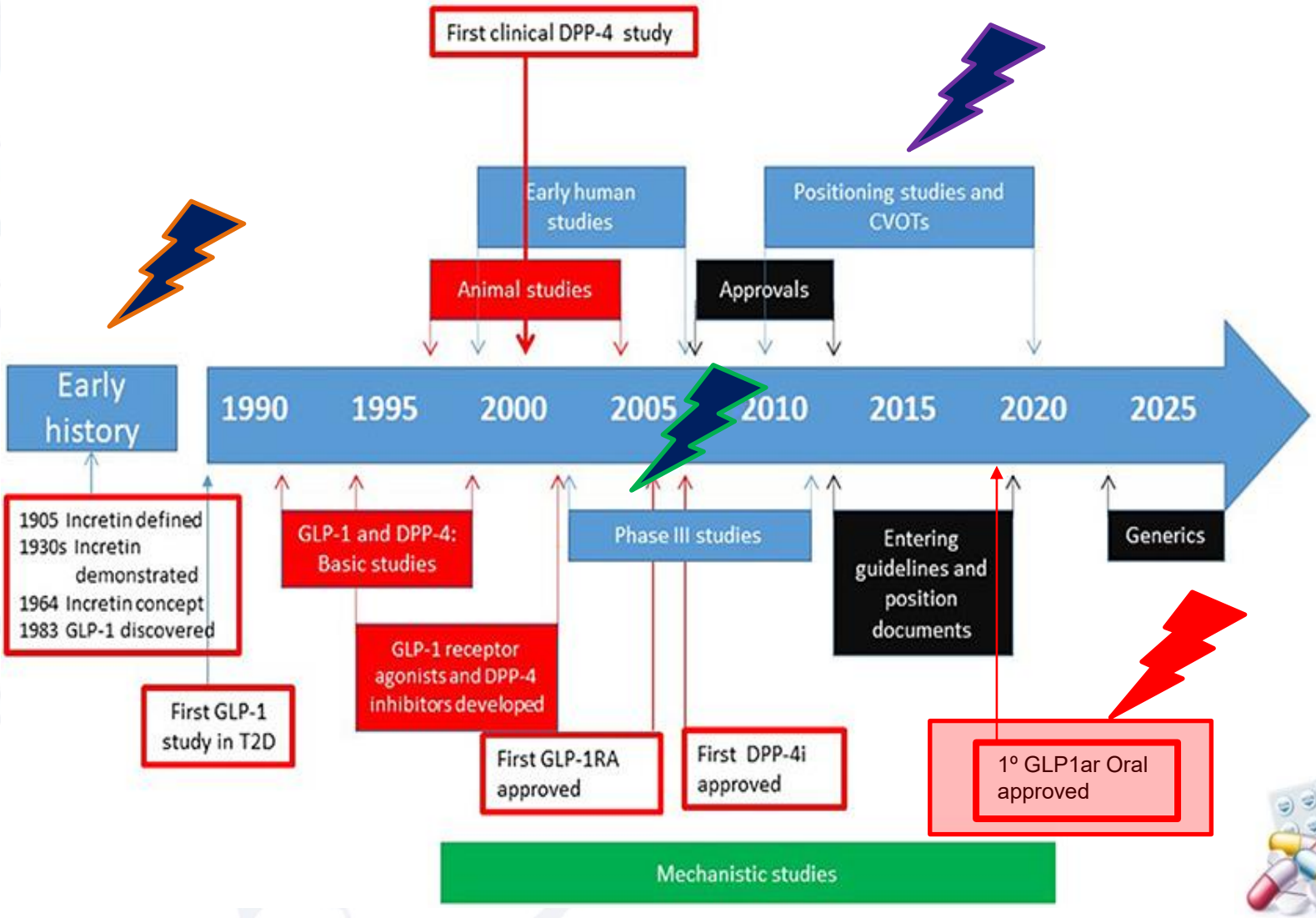
LOS CARDIÓLOGOS casi NO PRESCRIBIMOS arGLP1:

92% Cardiologos reconocia barreras para prescribir arGLP1 en su practica clinica



Datos propios del HUCA. Pendientes de publicación. Mayo de 2022.

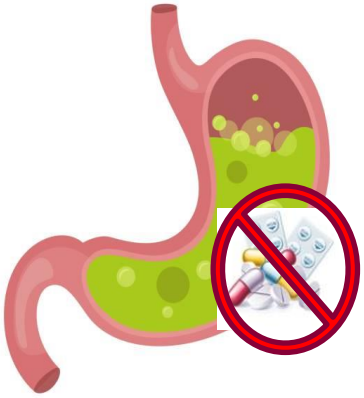
Historia de los arGLP1:

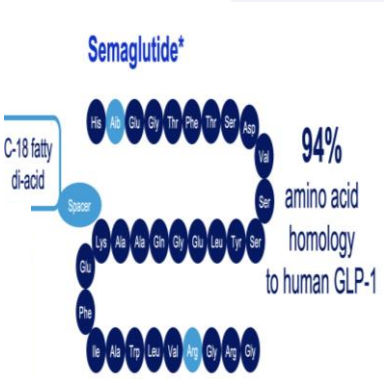


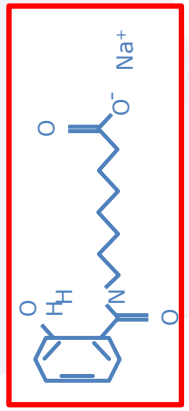
arGLP1 oral: Semaglutida oral

Compound	Native GLP-1	Short-acting GLP-1 RAs	Long-acting GLP-1 RAs	Oral peptide GLP-1 RAs
Clinical milestone	Nauck et al. 1993	Fineman et al. 2003	Nauck et al. 2006	Davies et al. 2017
Approval for clinical use	NA	2005	2009	2019
$t_{1/2}$	~ 2 min	~ 3 h	1 week	1 week
Administration	i.v. or s.c. (continuous)	s.c. BD–QD	s.c. QD–QW	p.o. QD
Molecular weight (Da)	~ 3,298	~4,187–4,860	~4,114–73,000	~4,114
Clinical features	Requires continuous infusion	Predominant effect on postprandial plasma glucose	Predominant effect on fasting plasma glucose	Minimum interval of 30 min between drug intake and subsequent meal

SEMAGLUTIDE



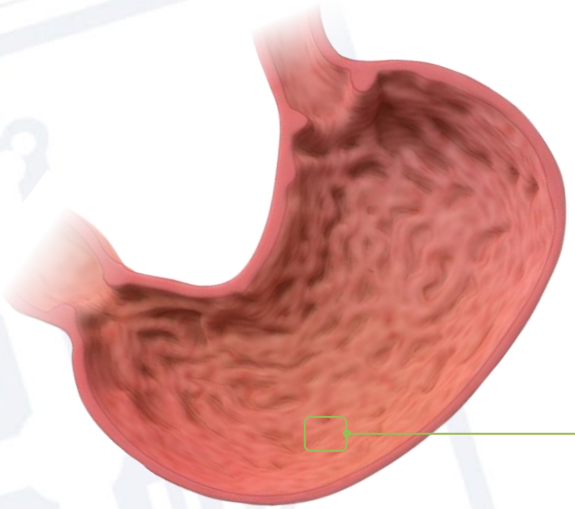




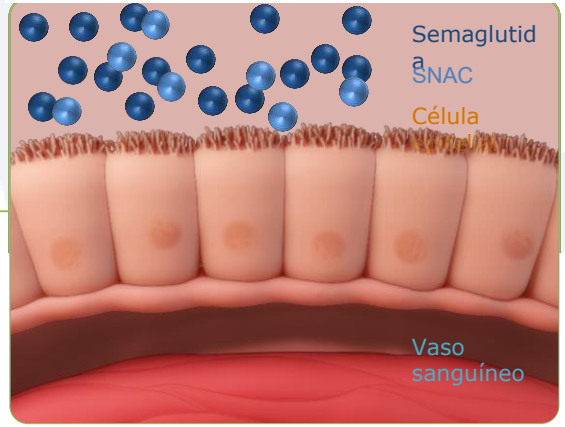
Potenciador de absorción SNAC

Lau J, et al. *J Med Chem.* 2015;58:7370-80; Kapitza C, et al. *J Clin Pharmacol.* 2015;55:497-504; Marbury TC, et al. *Diabetologia.* 2014;57:S358; Buckley ST, et al. *Sci Transl Med.* 2018;10(467).

arGLP1 oral: Semaglutida oral



El resultado es un **aumento del pH** que ayuda a proteger semaglutida de la degradación



SNAC, N-(8-(2-hidroxibenzoil) amino) caprilato sódico

1. Buckley ST, et al. *Sci Transl Med.* 2018;10(467).

arGLP1 oral: Semaglutida oral

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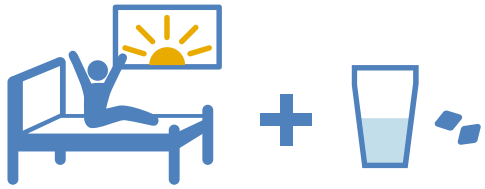
INICIO → **3 mg** 1 mes

MANTENIMIENTO → **7 mg** Al menos 1 mes → **14 mg**



1

Tómese el comprimido de semaglutida con el **estómago vacío** a cualquier hora del día. Se debe **ingerir entero con un sorbo de agua** (hasta medio vaso de agua equivalente a 120 ml)†.[1]

En los ensayos clínicos se recomendó la administración de semaglutida oral por la mañana en ayunas.[2]

2

Espere al menos 30 minutos antes de comer, beber o tomar cualquier otra medicación oral.[1]

3

Tome la primera comida y bebida del día y cualquier otro medicamento que necesite.

Factores que disminuyen la exposición a semaglutida

Disminución del tiempo de ayuno tras la administración§[3]

Consumo de alimentos antes de la administración[3]

Aumento del volumen de agua‡[3,4]

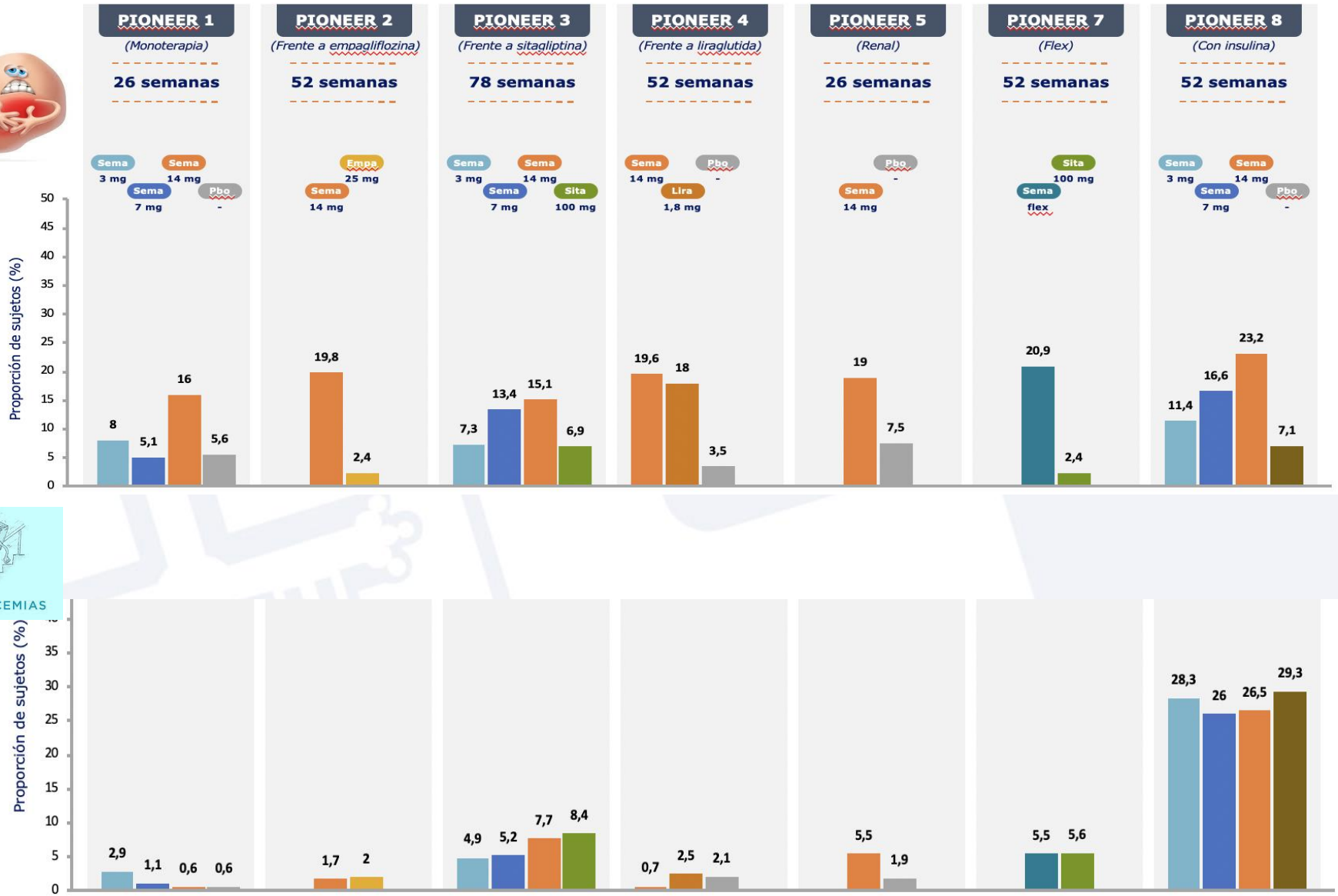
Utilizado en el programa de fase 2 y fase 3a (PIONEER). †Los comprimidos no se deben partir, triturar ni masticar, ya que no se conoce si esto afecta a la absorción de semaglutida. ‡Más de 120 ml. §Menos de 30 minutos.
PIONEER, *Peptide innovation for early diabetes treatment* (innovación peptídica para el tratamiento precoz de la diabetes).

1. Ficha técnica semaglutida oral; 2. Thethi TK et al. Diabetes Obes Metab. 2020;1–15; 3. Buckley ST, et al. *Sci Transl Med.* 2018:10:467; 4. Connor et al. Poster 1179–P. ADA 77th Scientific Sessions. 9–13 de junio, 2017.

arGLP1 oral: Semaglutida oral

*1. Aroda VR, et al. *Diabetes Care.* 2019;42:1724–32; 2. Rodbard HW, et al. *Diabetes Care.* 2019;42:2272–2281; 3. Rosenstock J, et al. *JAMA.* 2019;321:1466–80; 4. Pratley R, et al. *Lancet.* 2019;394:39–50; 5. Mosenzon O, et al. *Lancet Diabetes Endocrinol.* 2019;7:515–27; 6. Pieber TR, et al. *Lancet Diabetes Endocrinol.* 2019;7:528–39; 7. Zinman B, et al. *Diabetes Care.* 2019;42:2262–2271.

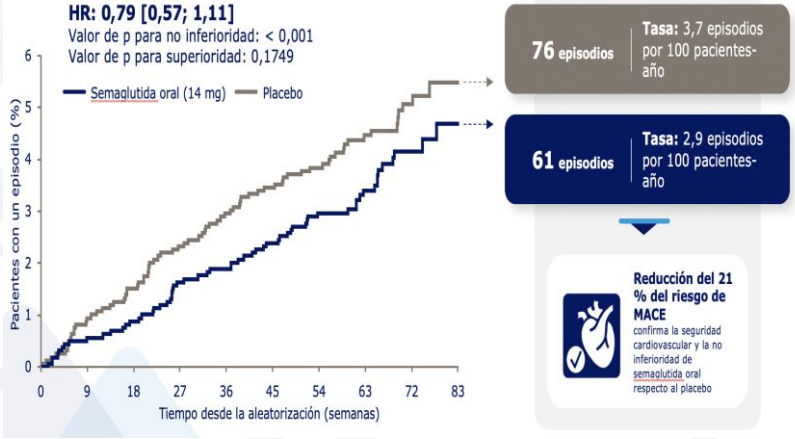
arGLP1 oral: Semaglutida oral



Flex, flexible; Empa, empagliflozina; Lira, liraglutida; Pbo, placebo; Sema, semaglutida; Sita, sitagliptina. Aroda VR, et al. *Diabetes Care* 2019;42:1724–32; Rodbard HW, et al. *Diabetes Care* 2019;42:2272–2281; Rosenstock J, et al. *JAMA* 2019;321:1466–80; Pratley R, et al. *Lancet* 2019;394:39–50; Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:515–27; Pieber TR, et al. *Lancet Diabetes Endocrinol* 2019;7:528–39; Zinman B et al. Diabetes Care 2019;42:2262–2271.

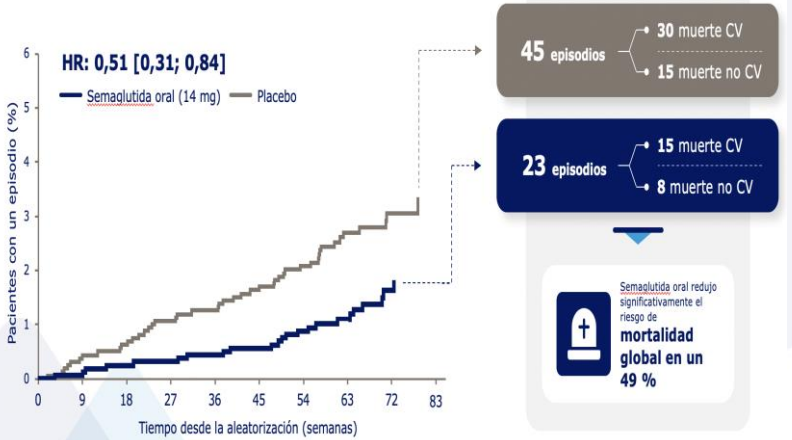
arGLP1 oral: Semaglutida oral

ENSAYO DE SEGURIDAD CV



PIONEER 6

Husain M, et al. *N Engl J Med.* 2019;381:841–51.



Eficacia y seguridad de semaglutida oral

HbA_{1c} y peso

- ✓ Semaglutida oral fue eficaz en todo el espectro de la DM2 y más eficaz que los fármacos comparadores en el control de la glucemia y la pérdida de peso.
- ✓ Se observaron reducciones clínicamente significativas de la HbA_{1c} y del peso corporal con semaglutida con independencia de la vía de administración.

Seguridad cardiovascular

- ✓ En PIONEER 6, semaglutida oral mostró una reducción no significativa del 21 % de MACE en comparación con placebo, lo que confirma la seguridad cardiovascular.
- ✓ Se observó una reducción significativa del 51 % del riesgo de muerte cardiovascular y una reducción significativa del 49 % de la mortalidad global.

Seguridad global

- ✓ Semaglutida oral se toleró bien, con un perfil de seguridad consistente con el grupo de arGLP-1.

Reflexión final:

1980s

1990s

2002

2007

2022

Reflexión final:

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HbA1c

Riesgo CV

INSULINA

SULFONILUREAS

TIAZOLIDINDIONAS

1980s

METFORMINA

iDPP4

iGLUCOSIDASAα

1990s

aGLP1 sc

2002

iSGLT2

aGLP1 vo

2007

iSGLT2

aGLP1 vo

aGLP1-GIP

2022

Reflexión final:

↓ HbA1c

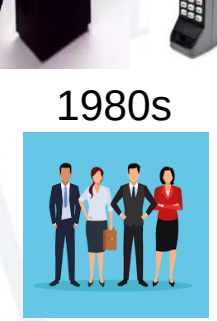
↓ Riesgo CV

INSULINA

SULFONILUREAS

TIAZOLIDINDIONAS

1980s



METFORMINA

iDPP4

iGLUCOSIDASAα

1990s

aGLP1 sc

2002

iSGLT2

aGLP1 vo

2007

iSGLT2

aGLP1 vo

aGLP1-GIP

2022

Muchas Gracias.....

Faro de San Juan. Avilés. Asturias.