XXXIII Congreso Sociedad Andaluza de Medicina Interna (SADEMI)
IV Encuentro de Enfermería de Medicina Interna de Andalucía
8, 9 y 10 de Junio de 2017
Hospital Universitario Reina Sofía. Córdoba

NUEVOS ABORDAJES EN EL TRATAMIENTO DE LA DIABETES MELLITUS TIPO 2 CON ENFERMEDAD CARDIOVASCULAR

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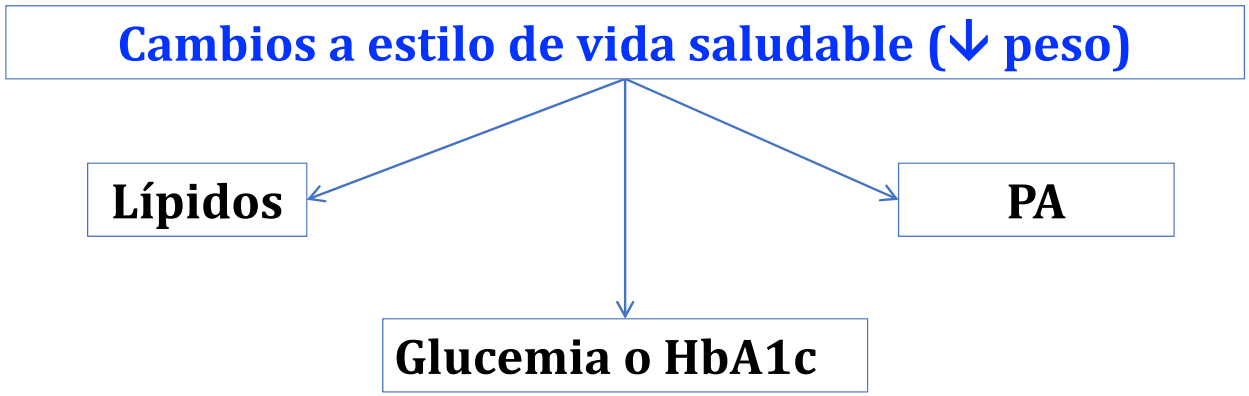
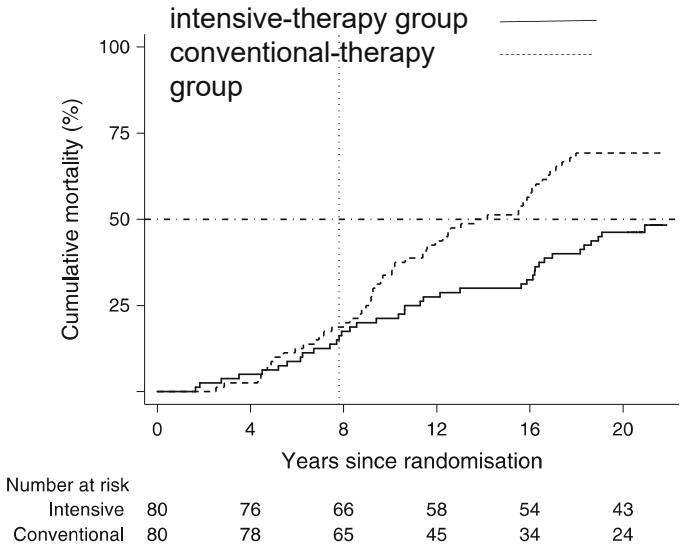
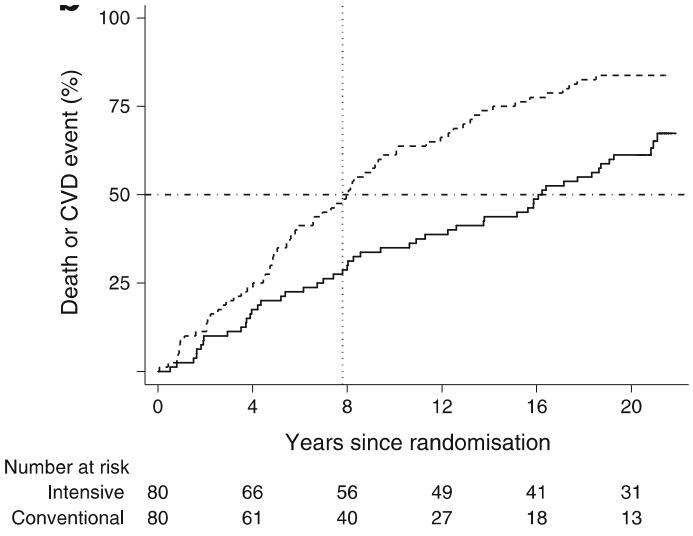
Tratamiento de la diabetes con enfermedad CV



Cumulative mortality and incidence of the composite cardiovascular or death endpoint





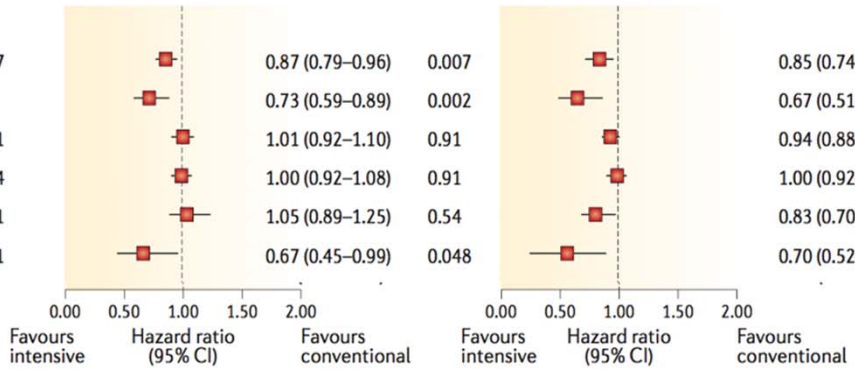
21 years follow-up on the Steno-2 randomised trial

Diabetologia 2016; 59:2298–2307

Control glucémico o de la HbA1c

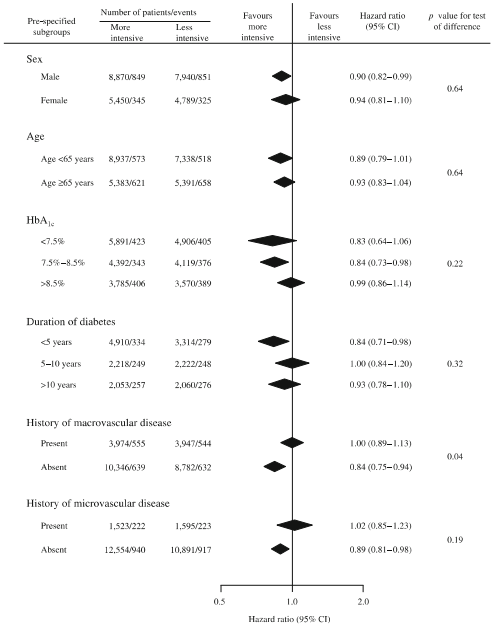
Glycemic Control: Mortality & CV Events in T2DM

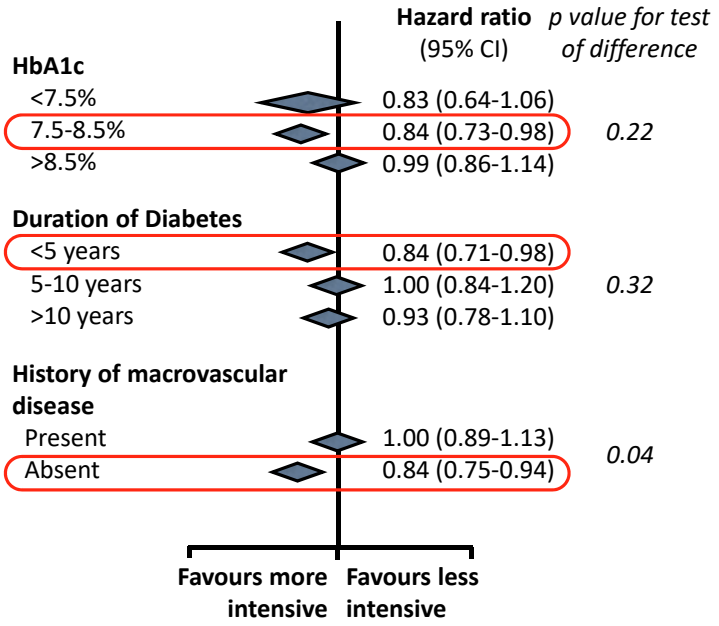
Trial	Years	n (at start)	All cause mortality	HR (95% CI)	P	Incident cardiovascular events	HR (95% CI)	P
Glucose lowering intervention trials								
UKPDS (SU-insulin group)[3]	10	3,867		0.87 (0.79–0.96)	0.007		0.85 (0.74–0.97)	0.01
UKPDS (metform group)[3]	10	753		0.73 (0.59–0.89)	0.002		0.67 (0.51–0.89)	0.005
ACCORDION[5]	9	8,601		1.01 (0.92–1.10)	0.91		0.94 (0.88–1.00)	0.05
ADVANCE-ON[6]	10	8,494		1.00 (0.92–1.08)	0.91		1.00 (0.92–1.08)	0.93
VADT[7]	11.8	1,791		1.05 (0.89–1.25)	0.54		0.83 (0.70–0.99)	0.04
DCCT/EDIC[2]	30	1,441		0.67 (0.45–0.99)	0.048		0.70 (0.52–0.93)	0.016



Diabetologia 2016. doi.org/10.1007/ s00125-016-4065-6

Intensive glucose control and macrovascular outcomes





Turnbull et al. Diabetologia 2009; 52:2288-98

Hipoglucemiante ideal en la diabetes tipo 2

- ✓ *Normaliza la glucemia (HbA1c) sin efectos secundarios:*
  - *No hipoglucemias (GD <70 mg/dL → Aumentan el riesgo CV coronario y cerebral).*
  - *No aumento de peso → empeora la diabetes y otras alteraciones metabólicas.*
- ✓ *Disminuye la morbi-mortalidad cardiovascular.*
- ✓ *Disminuye complicaciones crónicas.*
- ✓ *Mantiene la integridad de las células del islote.*

Hipoglucemiantes

	Eficacia	Peso	HG	Efectos 2º y ECV	Precio
Metformina	alta	=/↓	+/-	Digestivos, rara acidosis láctica. No IRC FG <45 ↓ moderada episodios ECV (UKPDS)	+
Sulfonilureas/ Glinidas	alta	↑	↑	Hipoglucemias + Precondicionamiento de isquemia miocárdica	+
Pioglitazona	alta	↑	+/-	Edema e insuficiencia cardíaca ↓ episodios ECV (PROactive)	++
Inh DPP4	media	=	+/-	Bien tolerados Acciones cardioprotectoras?	++
Análogos RGLP1	alta	↓	+/-	Náuseas. ↓ episodios ECV (LEADER) Protección masa de células beta?	++
Inh SGLT2	media/alta	↓	+/-	Infecciones urinarias y vaginales ↓ episodios ECV e Insuf cardíaca (EMPAREG)	++
Insulina B	Muy alta	↑	↑	Hipoglucemias	++

HG = hipoglucemia

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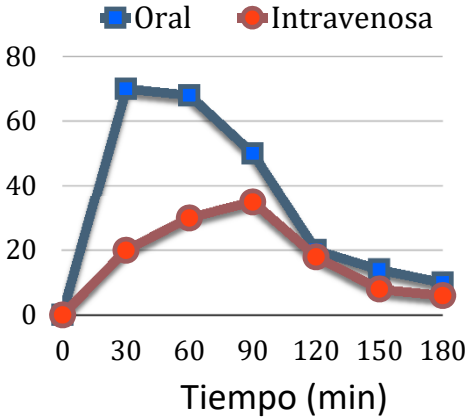
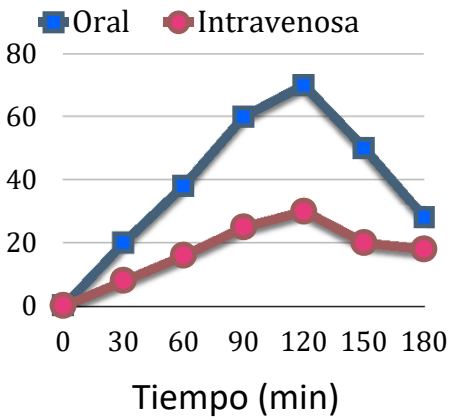
Fármacos con efecto incretina

Respuesta insulina después de la administración de glucosa oral e intravenosa

No diabéticos con peso normal



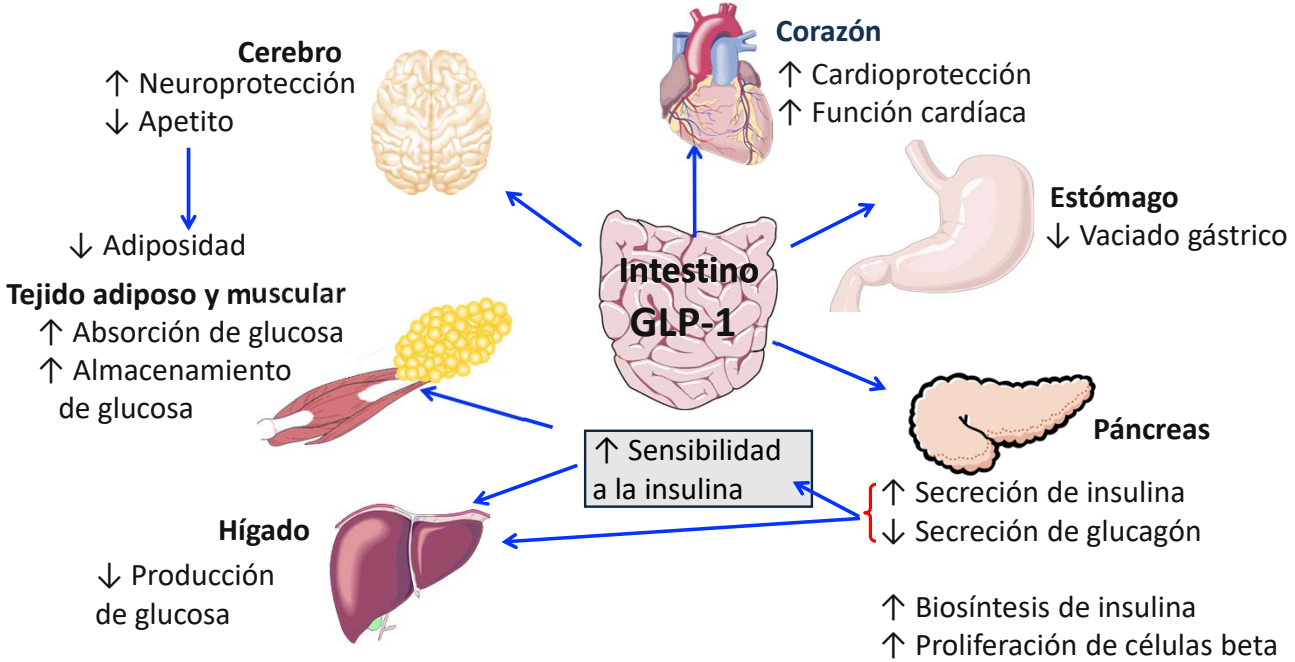
Diabéticos con peso normal



Perley M, et al. J Clin Invest 1967; 46:1954-62

Efecto mediado por las hormonas gastrointestinales: GLP-1 y GIP

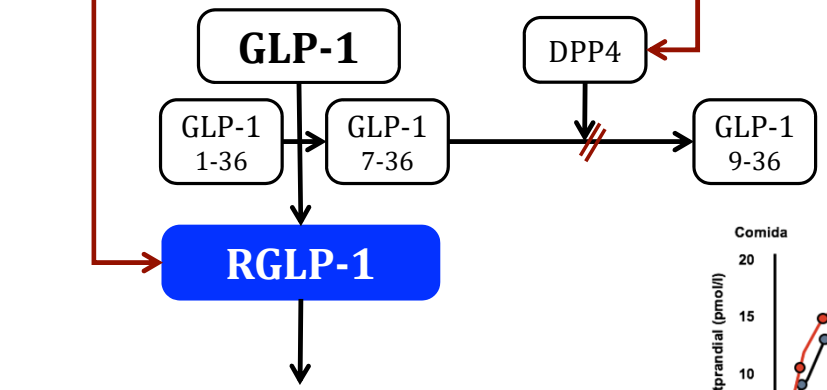
Actividad biológica de GLP-1



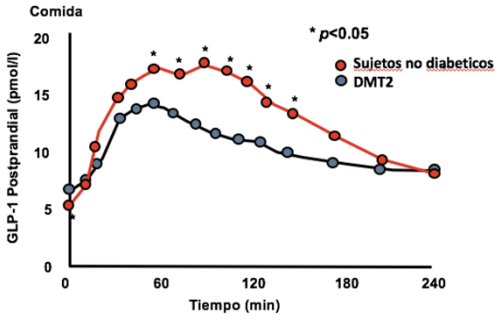
Baggio LL, Drucker DJ. Gastroenterology. 2007;132:2131-57.

Agonistas RGLP1

Inhibidores DPP4



Actividad biológica o tisular



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Hipoglucemiantes no insulinicos

IDPP-4

Cambio HbA1c %	Cambio en peso (Kg)	Hipoglucemias RR (IC95%)
-0,78	**-0,14**	**0,63** (0,26-1,71)

Julio 2008. Comité Asesor de la FDA elaboró una guía para determinar la seguridad CV de los nuevos fármacos para el tratamiento de la DM2

Los ensayos con iDPP4 se diseñaron para demostrar no inferioridad con el comparador. NO PARA EVALUAR BENEFICIOS CARDIOVASCULARES

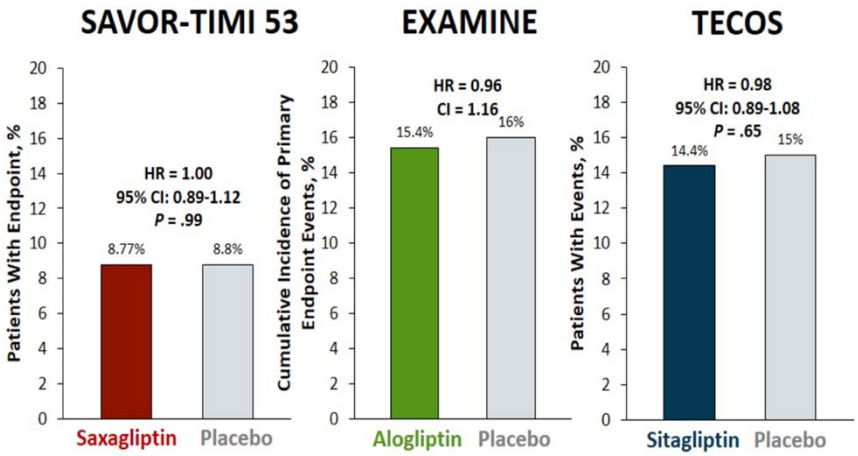
Estudios con Inhibidores de DPP-4 (IDPP-4)

Saxagliptina	**Savor-TIMI 53** vs placebo	completado
Alogliptina	**Examine** vs placebo	completado
Sitagliptina	**Tecos** vs placebo	completado
Linagliptina	**Carolina** vs glimepiride	2018
	Carmelina vs placebo	2018
Omarigliptina	**Omneon** vs placebo	2020
Anagliptina		
Vildagliptina		
Teneligliptina		

DPP-4 Inhibitor CV Outcomes Trials

	SAVOR-TIMI 53	EXAMINE	TECOS
Active comparator	Saxagliptin	Alogliptin	Sitagliptin
Patients	T2DM	T2DM	T2DM
CV risk at baseline	History of or at risk for CV events	Recent ACS event (MI or UA requiring hospitalization)	Pre-existing CVD
N	16,492	5380	14,671
Median follow-up	2.1 years	1.5 years	3 years

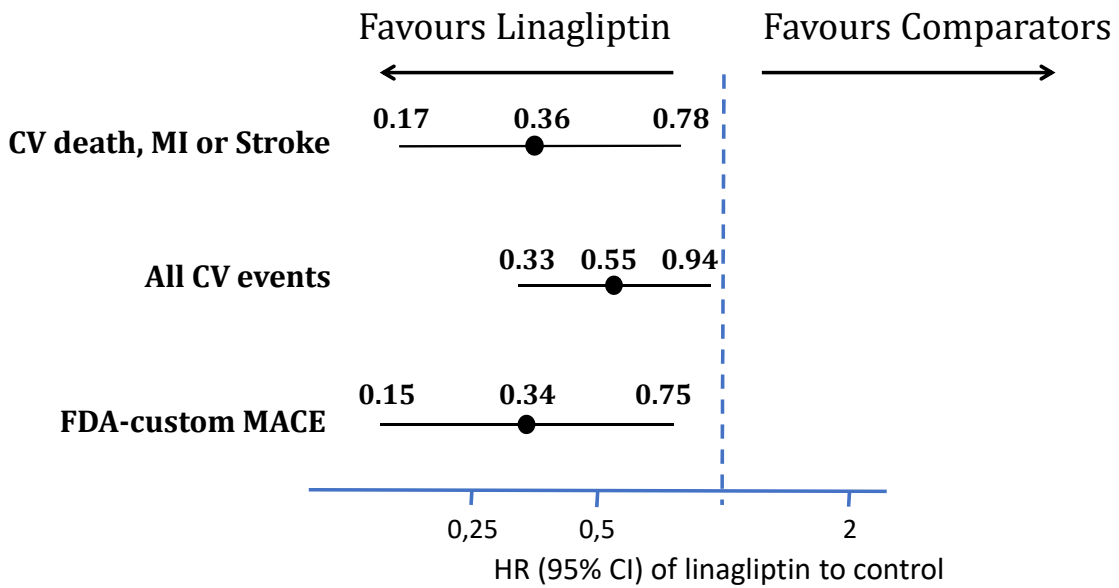
Primary End-Point. CV Death, MI, Stroke



Saxa +27% RR
Hospitalización por IC

Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.
White WB, et al. *N Engl J Med*. 2013;369:1327-1335.
Green JB, et al. *Am Heart J*. 2013;166:983-989.

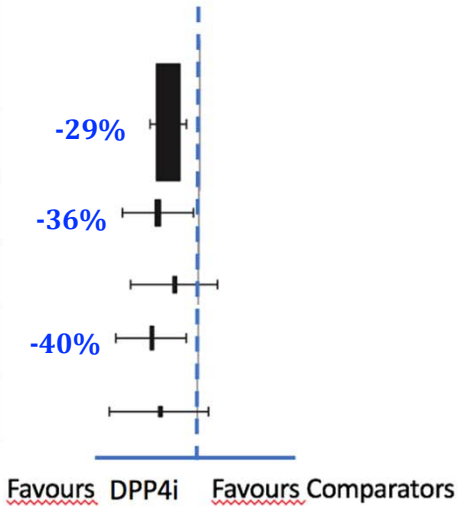
HR estimates for secondary composite CV endpoints with Linagliptin versus total comparators



Johansen et al. Cardiovascular Diabetology 2012, 11:3

Inhibidores de DPP4 y riesgo CV. Meta-análisis de estudios clínicos randomizados

	Trials	Trials with events	OR (95%CI)	p
MACE	70	63	0.71 (0.59-0.86)	<0.001
AMI	62	41	0.64 (0.44-0.94)	0.023
Stroke	63	29	0.77 (0.48-1.24)	0.290
Mortality	53	30	0.60 (0.41-0-88)	0.008
CV Mortality	48	20	0.67 (0.39-1.14)	0-140



Modified. Monami M. et al. Diabetes Obes Metab. 2013; 15(2):112-20

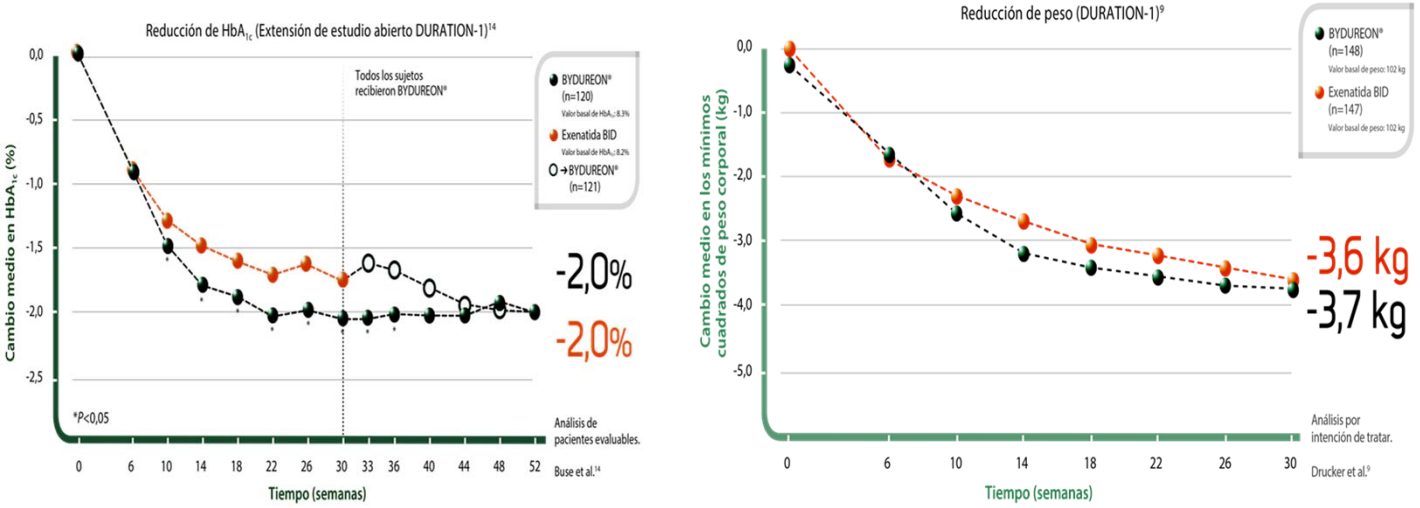
Resumen de iDPP4

- ✓ *Disminución moderada de la HbA1c*
- ✓ *No modifican desfavorablemente el peso.*
- ✓ *Bajo riesgo de hipoglucemia.*
- ✓ *Son seguros, especialmente en **ancianos y en sujetos con IRC**.*
- ✓ *Meta-análisis:*
  - *Indican beneficios cardiovasculares.*
  - *Pendiente de confirmar en ensayos de larga evolución diseñados con la variable principal ECV.*

Hipoglucemiantes no insulinicos

ARGLP1

DURATION-1. Exenatida larga acción



Drucker DJ et al. Lancet. 2008;372:1240-1250.

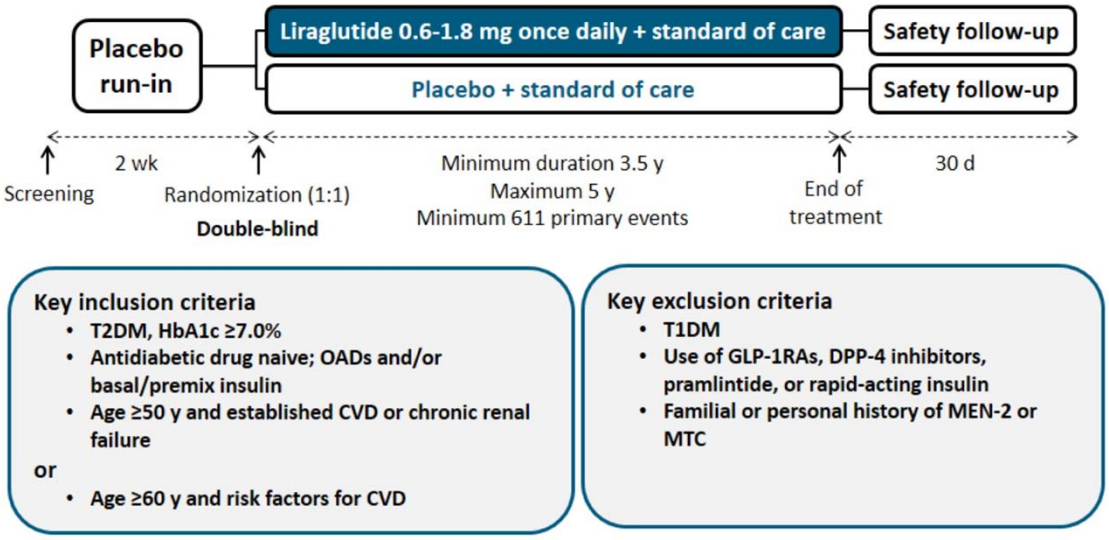
Estudios con ARGLP-1 y episodios CV

Lixisenatida	**ELIXA** vs placebo	2105
Liraglutida	**LEADER** vs placebo	2016
Semaglutida	**SUSTAIN-6** vs placebo	2016
Exenatida sem	**EXSCEL** vs placebo	2018
Exenatida	**FREEDOM-CVO** vs placebo	2018
Dulaglutida	**REWIND** vs placebo	2019
Albiglutida	**HARMONY Outcomes** vs placebo	2019

LEADER (Liraglutida)

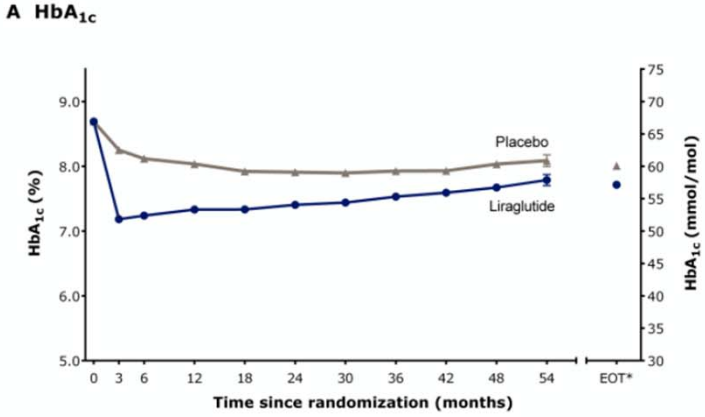
DMT2 12 años de evolución e IMC 32
N 9340
Seguimiento 4 años

Basal
Hypertension 90.7%
Hyperlipemia 80.8%
LDL-C 89.5 mg/dL, estatin
ACEI o ARAII,
HbA1c 8.7%



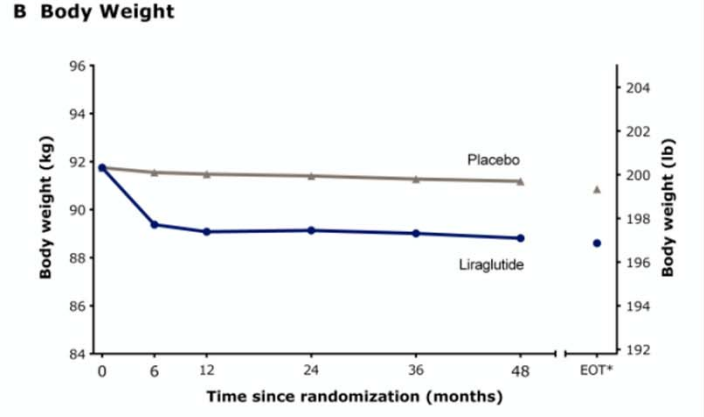
Marso SP et al. Am Heart J 2013;166:823--30

LEADER (Liraglutida)



Number of patients at each visit

Liraglutide	4668	4402	4355	4295	4135	4034	3877	3810	2349	809	101	3705
Placebo	4672	4413	4355	4235	4030	3905	3742	3640	2303	756	87	3561



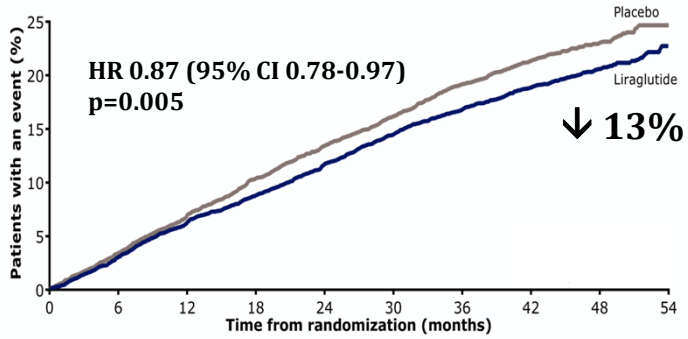
Number of patients at each visit

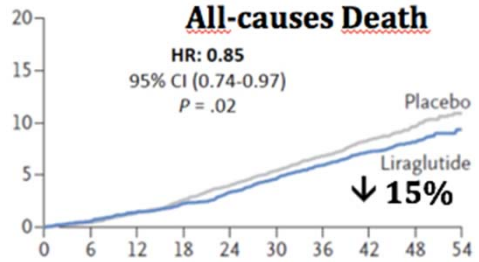
Liraglutide	4667	4434	4324	4088	3835	824	3708
Placebo	4671	4423	4285	3970	3680	766	3555

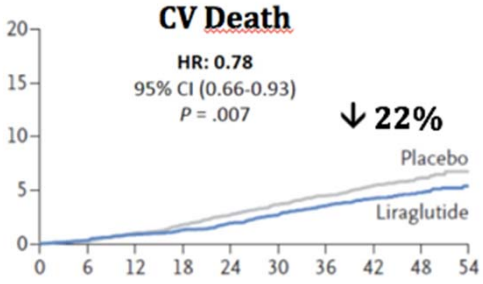
Marso SP et al. NEJM 2016

LEADER (Liraglutida)

Primary Outcome: 3-point MACE: CV death, nonfatal MI or nonfatal stroke







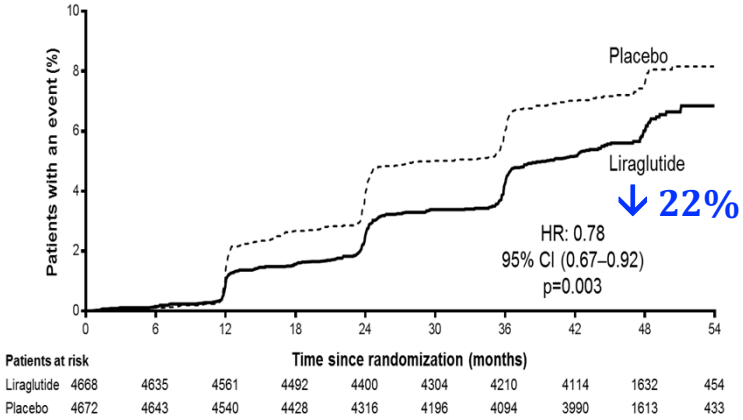
Nonfatal MI	HR 0.88 (95%CI 0.75-1.03)	p 0.11
Nonfatal Stroke	HR 0.89 (95%CI 0.72-1.11)	p 0.30
Hospitalization HF	HR 0.87 (95%CI 0.73-1.15)	p 0.14

Marso SP et al. NEJM 2016

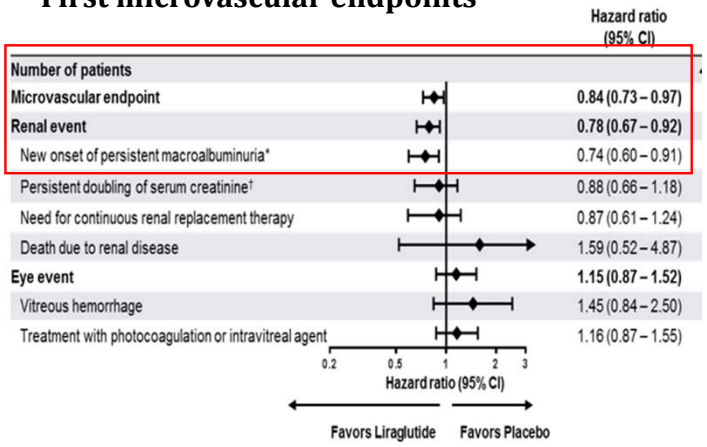
LEADER (Liraglutida)

Time to first renal event

Macroalbuminuria, doubling of serum *creatinine*, ESRD, renal death



First microvascular endpoints



The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio.

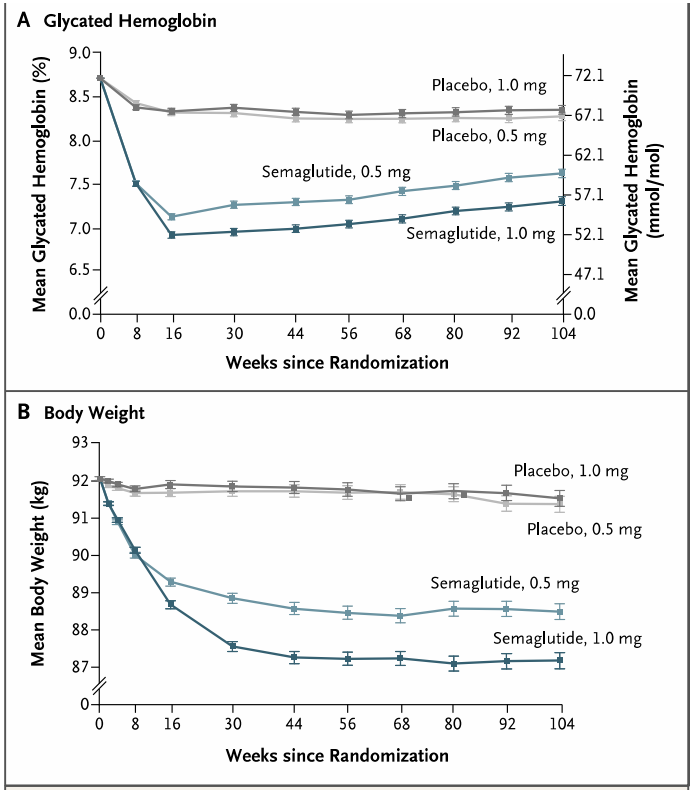
Marso SP. NEJM 2016

SUSTAIN-6 Semaglutida

(once-weekly) Glycated Hemoglobin and Body Weight.

Basal

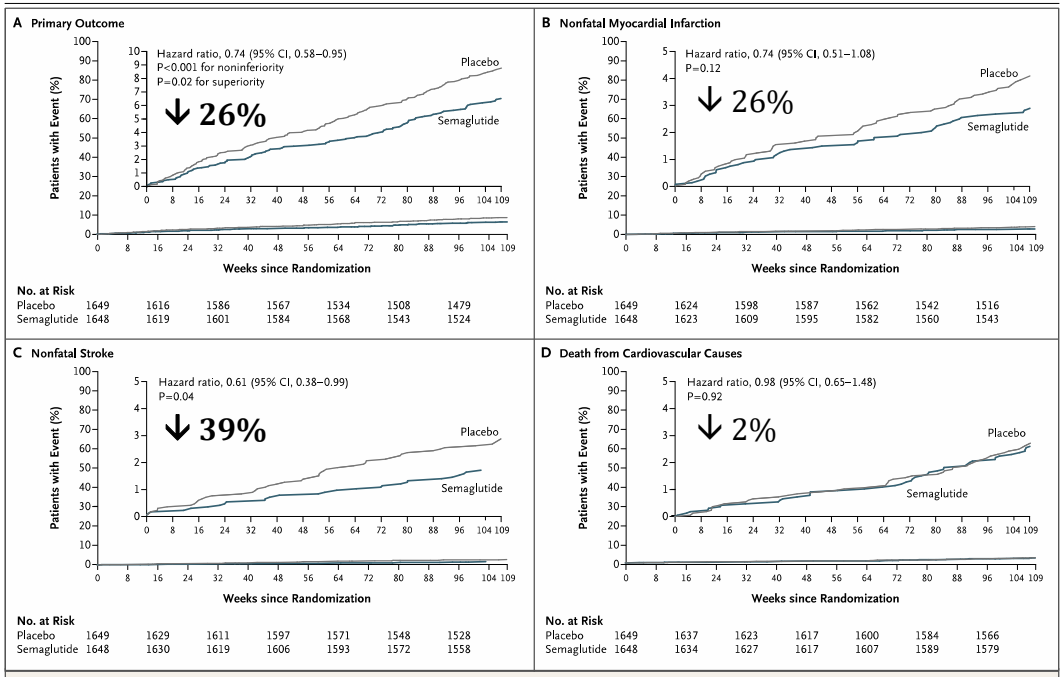
2735 of the patients (83.0%) had established CVD, CKD, or both
Body weight 92 Kg
SBP 135.6 mmHg
LDL-C 83.5 mg/dL, estatin
HbA1c 8.7%
Duration DM 14 yr



SUSTAIN-6 *ClinicalTrials. NEJM 2016; 375;1935*

Cardiovascular Outcomes.

- ✓ **Primary outcome** (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel A)
- ✓ **Nonfatal myocardial infarction** (Panel B)
- ✓ **Nonfatal stroke** (Panel C)
- ✓ **Death from cardiovascular causes** (Panel D).



SUSTAIN-6 ClinicalTrials. NEJM 2016; 375;1935

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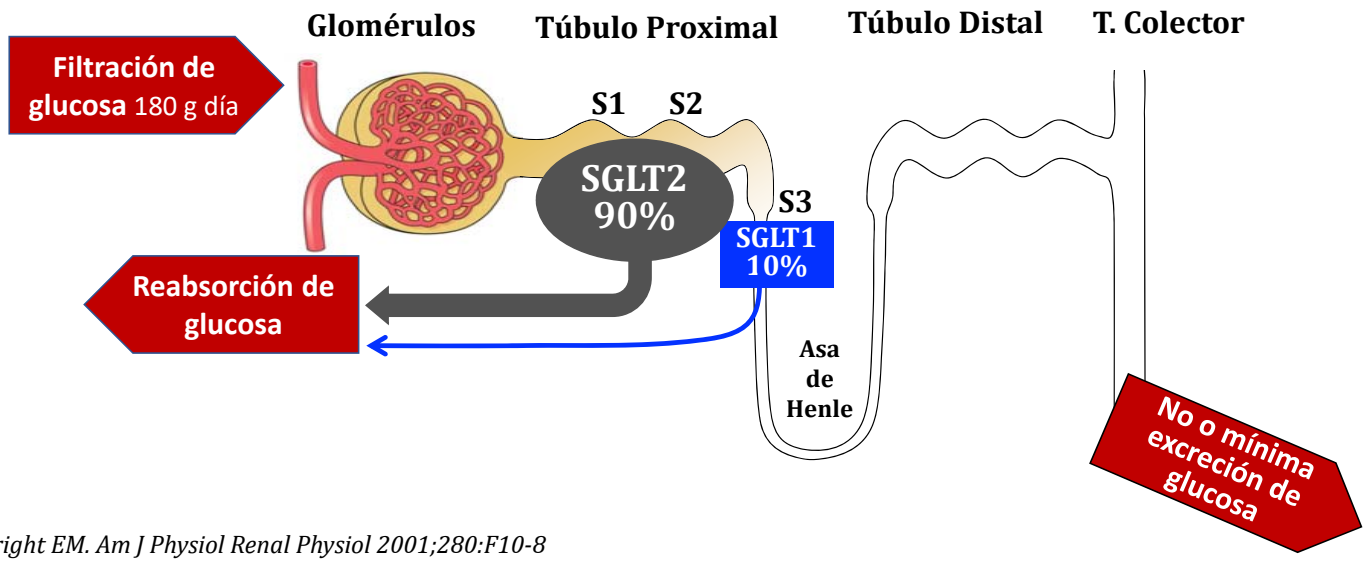
GLP-1 receptor agonists on primary and secondary CV outcomes in the LEADER trial and SUSTAIN-6

	LEADER	SUSTAIN-6
Study duration (y)	4	2
GLP-1RA	Liraglutide / day	Semaglutide / week
Patients (n)	9340	3297
Major CV events	↓**13%** (p 0.01)	↓**26%** (p 0.02)
Myocardial infarction	↓**14%** (p 0.04)	↓1% (p 0.38) NS
Non-fatal Stroke	↓11% (p 0.30)	↓**39%** (p 0.04)
CV Death	↓**22%** (p 0.007)	NS
Total mortality	↓**15%** (p 0.02)	NS

Modified. Verges & Charbonnell. Diabetes & Metabolism 2017;43: S3-S12

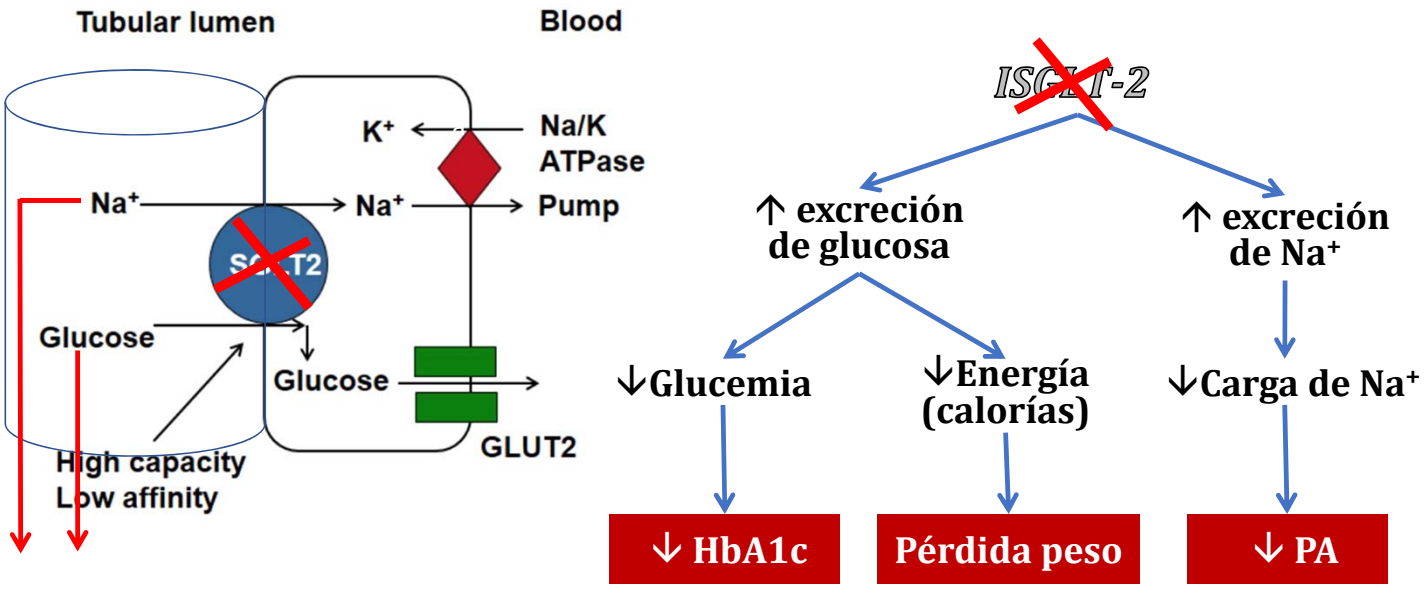
Hipoglucemiantes no insulinicos

ISGLT2



Wright EM. Am J Physiol Renal Physiol 2001;280:F10-8
Lee YJ, et al. Kidney Int Suppl 2007;106:S27-35
Brown GK. J Inherit Metab Dis 2000;23:237-46

Inhibition of Glucose Reabsortion via the SGLT2 Pathway



Nair S, et al. J Clin Endocrinol Metab 2010; 95:34-42

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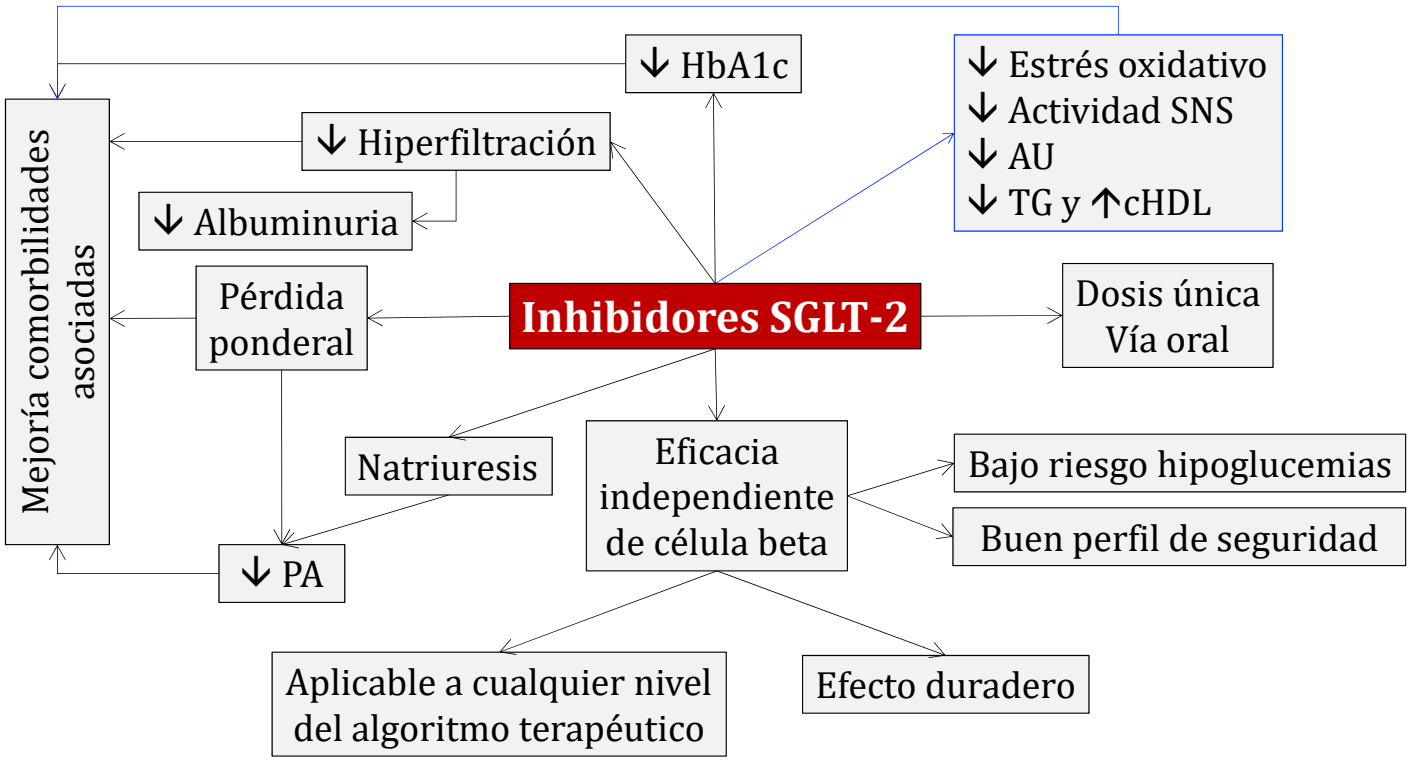

Inzucchi et al. Diab Vasc Dis Res 2015;12:90–100.

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SGLT2 inhibitors CV Events and Mortality

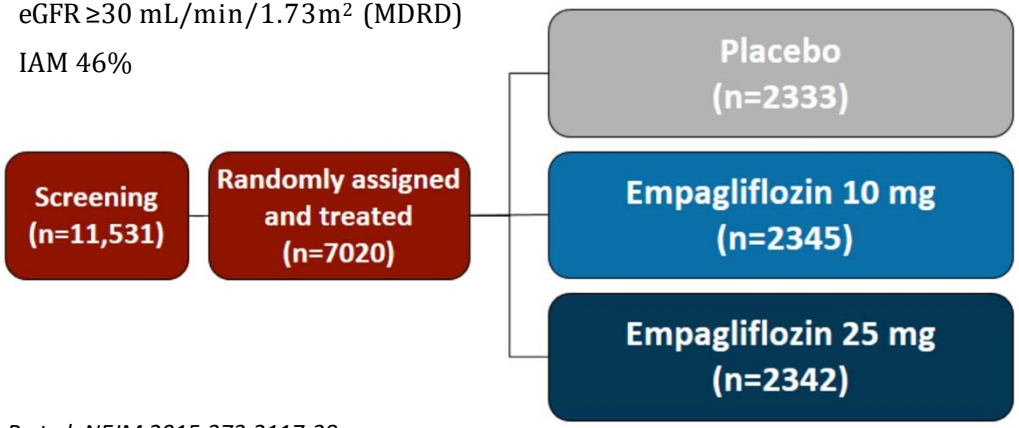
Empagliflocina	**EMPA-REG OUTCOMES** vs placebo	2015
Canagliflocina	**CANVAS** vs placebo	2017
	CANVAS-R	2017
	CREDENCE vs placebo	2020
Dapagliflocina	**DECLARE-TIMI 58** vs placebo	2019
Estugliflocina	**NCT0198681**	2021
Ipragliflocina		
Tofogliflocina		

EMPA-REG Outcome (Empagliflocina)

- ✓ DMT2 con ECV (IAM, ictus, angor inestable, EAP).
- ✓ Objetivo primario: ECVM (muerte cardiovascular, IAM no mortal, ictus no mortal).

Key inclusion criteria:

- Age 63 yr, BMI ≤ 45 kg/m²; HbA1c 8%;
- eGFR ≥30 mL/min/1.73m² (MDRD)
- IAM 46%

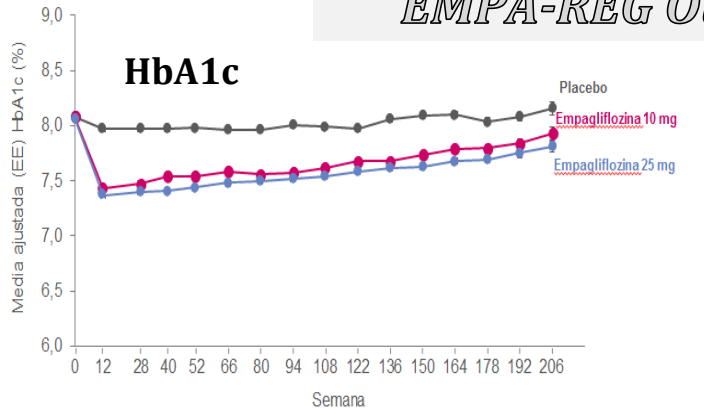


No diferencias entre grupos:
Control
Tiempo de evolución
Medicación

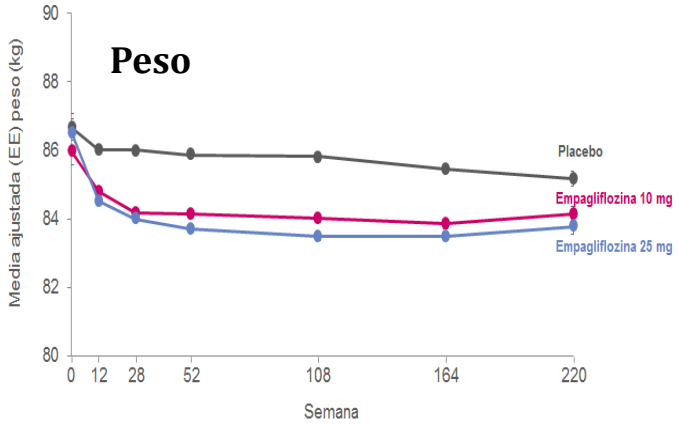
Zinman B et al. NEJM 2015;373:2117-28

EMPA-REG Outcome (Empagliflocina)

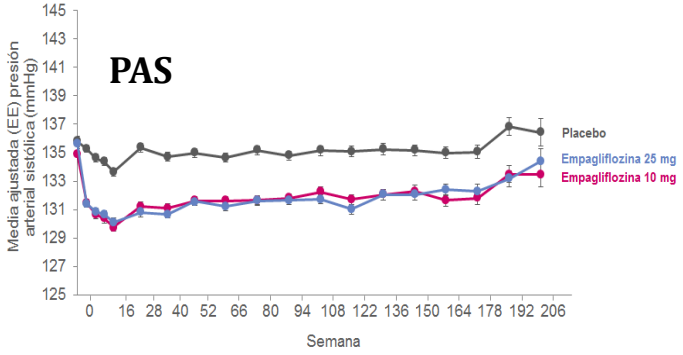
HbA1c



Peso



PAS



↓ Peso y PA
No son dosis dependiente

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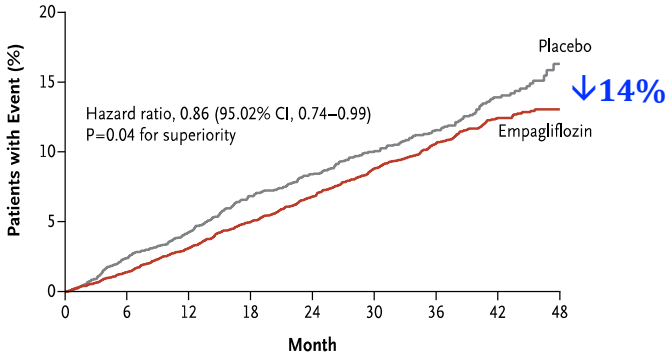
EMPA-REG Outcome (Empagliflocina)

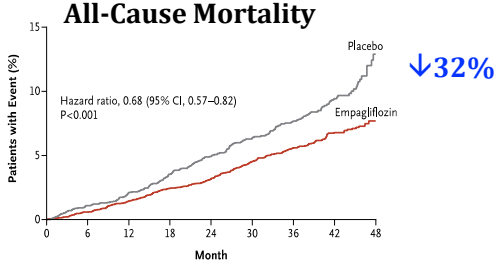
Primary Outcome

CV Death, Nonfatal MI or Nonfatal Stroke



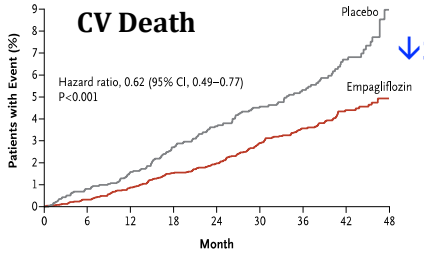
No. at Risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

All-Cause Mortality



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

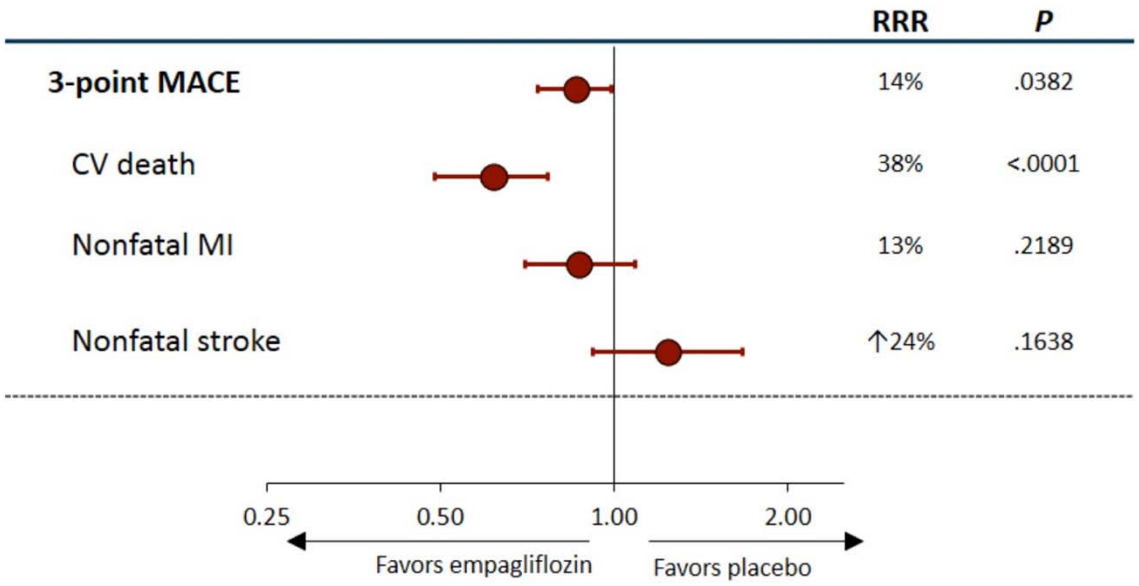
CV Death



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

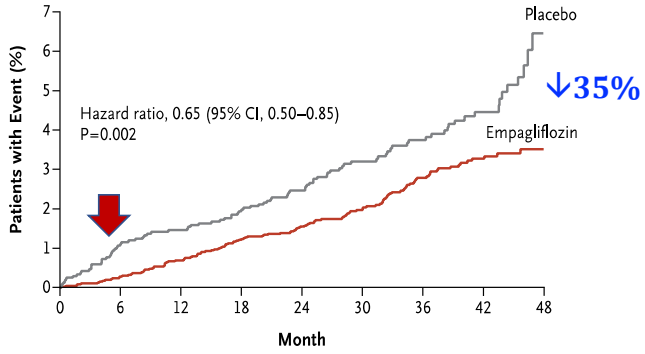
Zinman B et al. NEJM 2015;373:2117-28

EMPA-REG Outcome

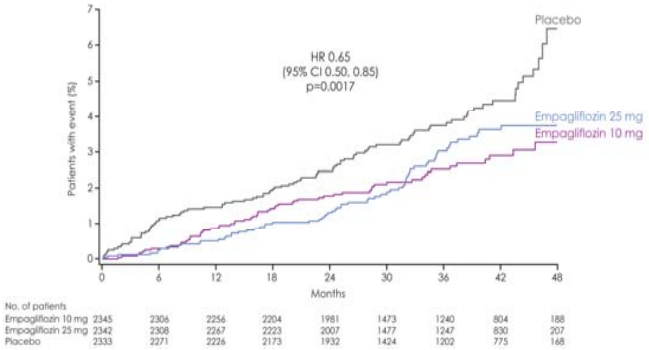


EMPA-REG Outcome (Empagliflocina)

Hospitalization for Heart Failure



No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168



Zinman B et al. NEJM 2015;373:2117-28

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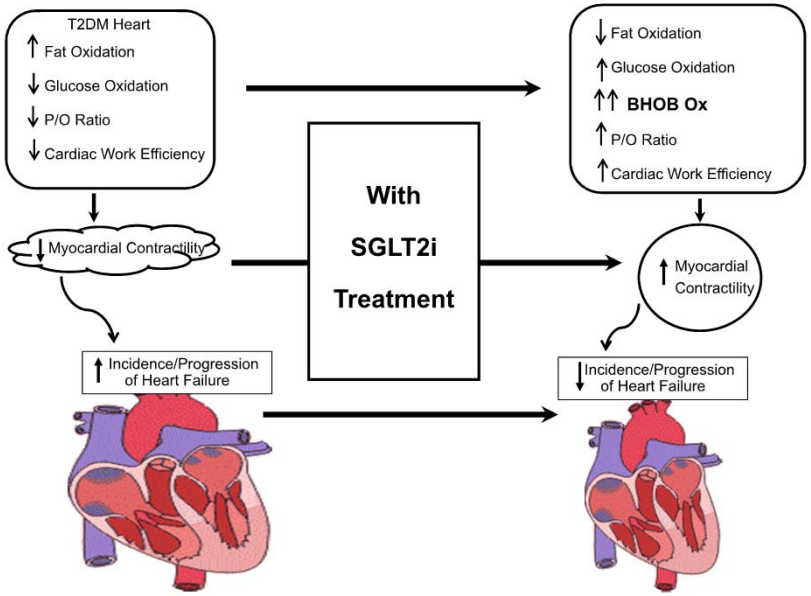
Postulated changes in myocardium fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy

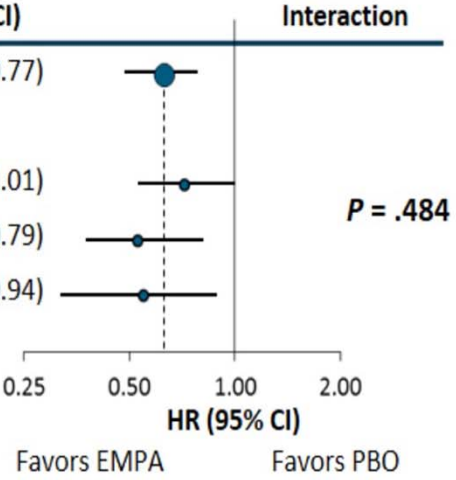
P/O ratio reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain.



Diabetes Care 2016;39:1115-22

EMPA-REG. Effect on CV Death in Subgroups by Age

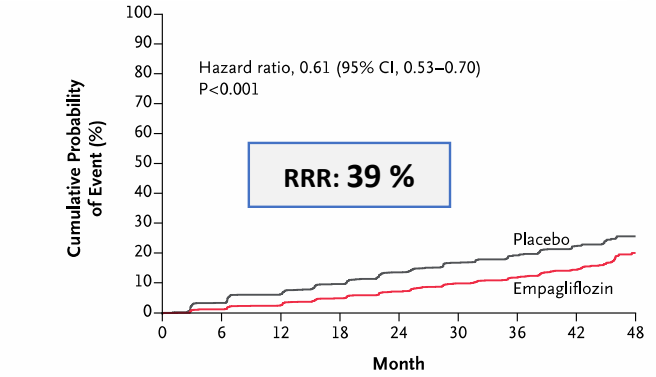
CV Death	EMPA n With Events/N	%	PBO n With Events/N	%	HR (95% CI)
All patients	172/4687	3.7	137/2333	5.9	0.62 (0.49-0.77)
Age at baseline (y)					
<65	85/2596	3.3	59/1297	4.5	0.72 (0.52-1.01)
65 to <75	59/1667	3.5	51/808	6.3	0.54 (0.37-0.79)
≥75	28/424	6.6	27/228	11.8	0.55 (0.32-0.94)



ADA 2016

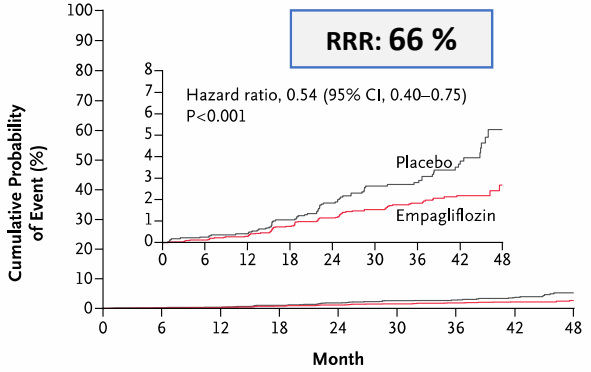
Kaplan–Meier Analysis of Two Key Renal Outcomes.

Incident or Worsening Nephropathy



No. at Risk									
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

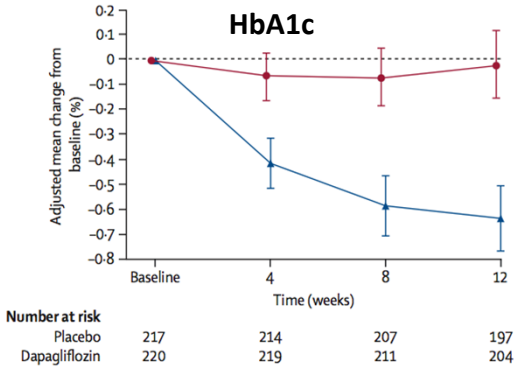
Post Hoc Renal Composite Outcome

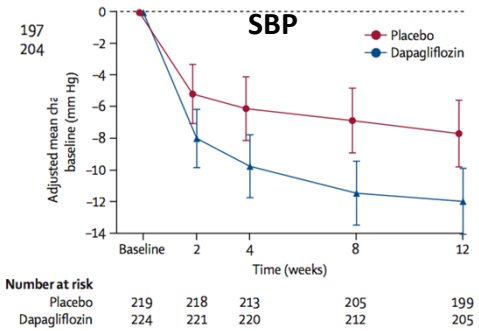


No. at Risk									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

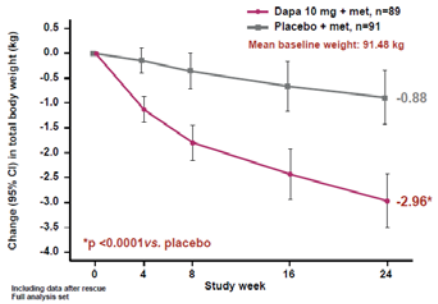
Wanner C, et al. N Engl J Med 2016;375:323-34.

Dapagliflozin. Randomised, double-blind, placebo-controlled, phase 3 study





Body weight Mean change in total body weight at week 24 (primary efficacy endpoint)

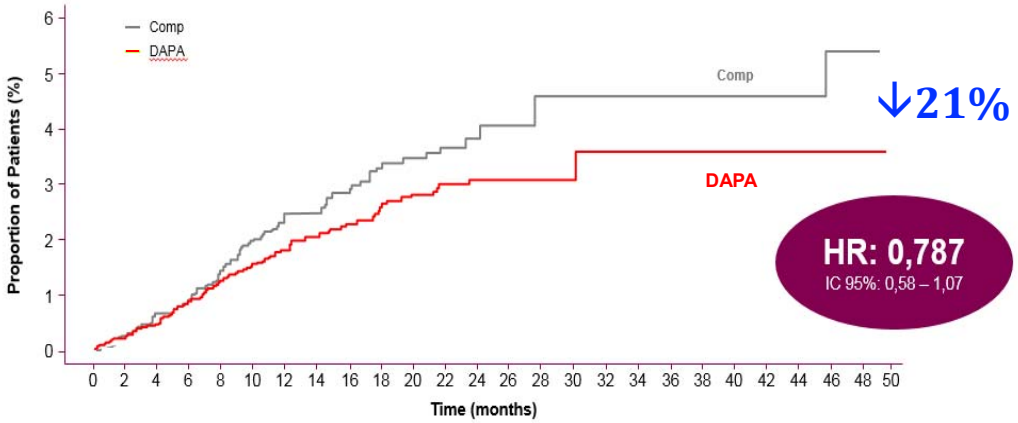


↓ PAS y Peso no son dosis dependiente

Weber MA et al. Lancet Diabetes Endocrinol 2015. http://dx.doi.org/10.1016/S2213-8587(15)00417-9

Resultados meta-análisis CV de dapagliflocina

Eventos: **muerte cardiovascular, infarto de miocardio, ictus y hospitalización por angina inestable**

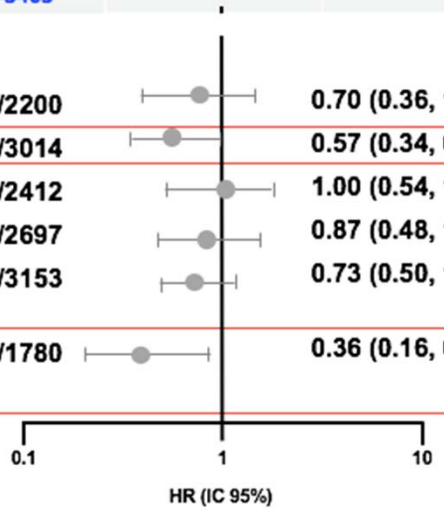


Primary end point: CV death, myocardial infarction, stroke, and hospitalization for unstable angina.
Cumulative probability of primary CV composite end point over time (Kaplan-Meier estimate).
PBO=placebo; ST=short term; LT=long term; 30-MU=30-month update; Comp=comparator; DAPA=dapagliflozin; CV=cardiovascular.

EMDAC Briefing Document. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugs AdvisoryCommittee/UCM378079.pdf.

Meta-análisis resultados con Dapagliflocina

Evento	Pacientes con eventos DAPA N=5936	Pacientes con eventos CTRL N=3403	Hazard ratio (IC 95%)
Muerte CV	20/3825	18/2200	0.70 (0.36, 1.36)
Infarto de miocardio	30/5244	33/3014	0.57 (0.34, 0.95)
Ictus	25/4227	18/2412	1.00 (0.54, 1.86)
Angina inestable	26/4592	20/2697	0.87 (0.48, 1.59)
Revascularisation coronaria no planificada	58/5525	55/3153	0.73 (0.50, 1.07)
Hospitalización por fallo cardiaco	10/2576	16/1780	0.36 (0.16, 0.84)



1. FDA Endocrinologic & Metabolic Advisory Committee DAPAGLIFLOZIN BMS-512148 NDA 202293 2. Última visita: 8 jul 2014. Disponible en: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf..2. List J, et al. AHA 2014, Abstract 2339

Data sources

Kosiborod M et al. CVD-REAL Investigators and Study Group. Circulation. 2017 May 18. pii: CIRCULATIONAHA.117.029190.

CVDREAL

Cohort 1
HHF

US
- Truven Health MarketScan Claims and Encounters and linked Medicare Supplemental and Coordination of Benefits (Medicare Supplemental) databases

Norway
- Linked Prescribed Drug, National Patient and Cause of Death Registries

Sweden
- Linked Prescribed Drug, National Patient and Cause of Death Registries

Denmark
- Linked Prescribed Drug, National Patient and Cause of Death Registries

UK
- Clinical Practice Research Datalink (CPRD) dataset
- The Health Improvement Network (THIN) dataset

Germany
- Diabetes-Patienten-Verlaufsdokumentation (Diabetes Prospective Follow-Up; DPV)

Cohort 2
All-cause death and composite HHF/all-cause death

J.F. Ascaso. HC-UV

Inclusion/exclusion criteria

Inclusion criteria

- New users receiving SGLT2 inhibitors or other glucose-lowering drugs
  - Established T2DM on or prior to the index date
  - ≥18 years old
  - >1 year* historical data available prior to the index date

NO ECV
Menor riesgo CV

Exclusion criteria

- Patients with type 1 diabetes
- Patients with gestational diabetes

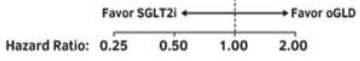
*In Germany, >6 months

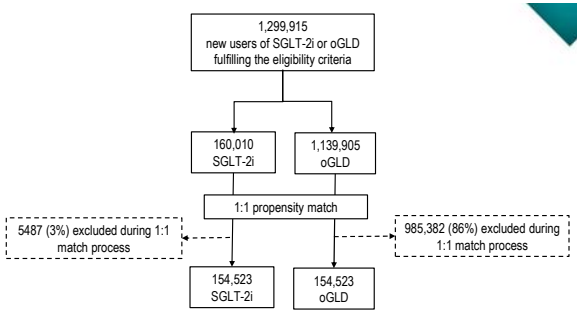
iSGLT-2 en clínica habitual

N 309.046

HF

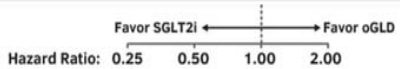
Outcome	N	# of events	HR (95% CI)
On treatment, adjusted*	309,056	961	0.61 (0.53, 0.69)
ITT, unadjusted	309,056	1379	0.67 (0.60, 0.75)
On treatment, adjusted*, excluding TZD, insulin and SU	196,802	423	0.57 (0.42, 0.76)





All-Cause Death

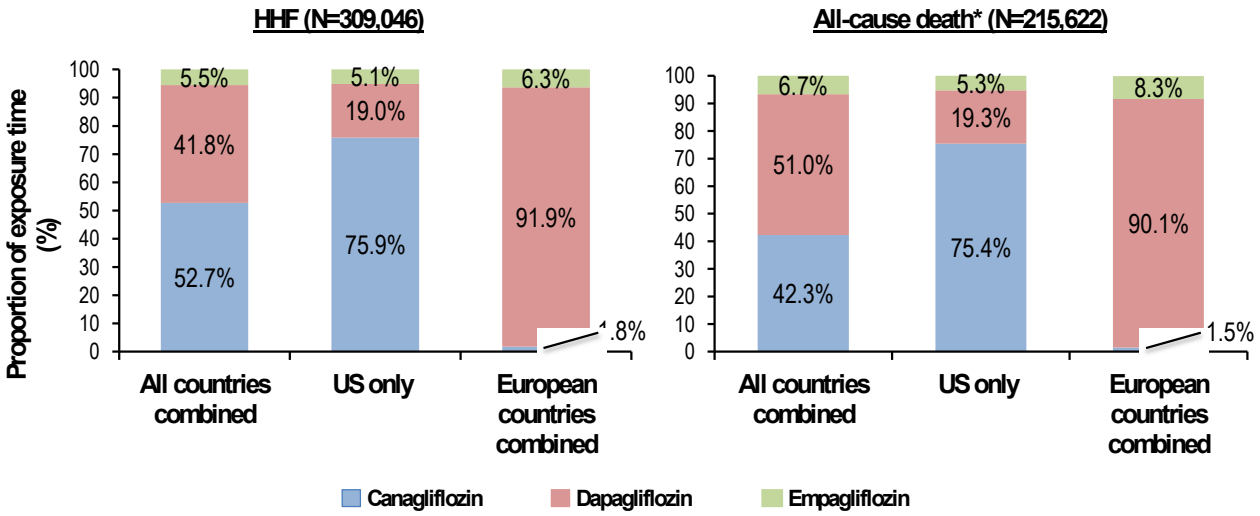
Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)



CVD-REAL Investigators and Study Group. ACC 2017

J.F. Ascaso. HC-UV

Contribution of SGLT-2i compounds



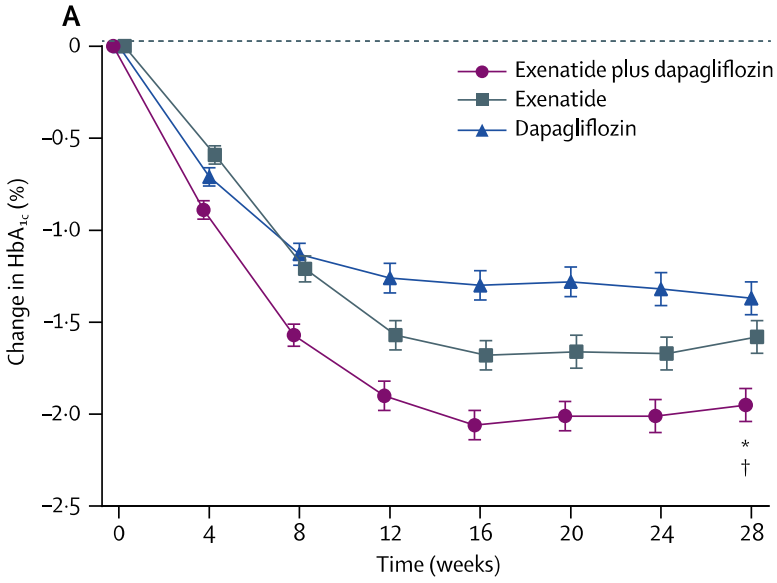
Kosiborod M et al on behalf of the CVD-REAL Investigators and Study Group. ACC 2017
Kosiborod M, et al. ***CVD-REAL*** *Investigators and Study Group.Circulation. 2017 May 18. pii: CIRCULATIONAHA.117.029190.*

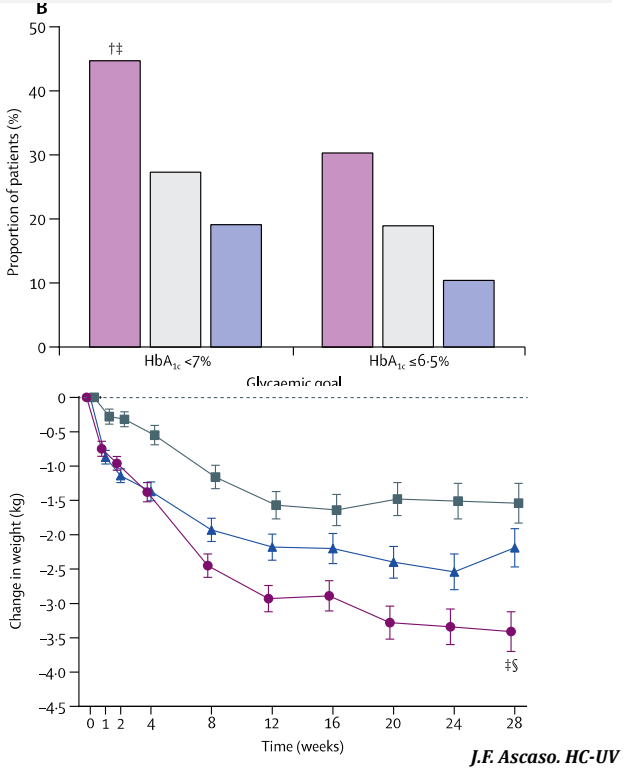
Comparación entre los grupos ARGLP-1 y ISGLT2

Objetivo	ARGLP-1	ISGLT2
Reducción HbA1c (%)	0,7-1,7	0,3-1,2
Reducción de la glucemia	Acción corta principalmente PP Acción larga ayuno y PP	Ayuno y postprandial
Riesgo de hipoglucemia	Bajo	Bajo
Perdida de peso (kg)	2-5	1,5-3
Reducción PAS mm Hg	2-5	3-5
Episodios CV	Beneficio no claro en prevención 1ª y 2ª	Reducción muerte CV en pacientes con ECVA, no claro en prevención 1ª
Efectos adversos	Gastrointestinales. A largo plazo no establecidos.	Infecciones genito-urinarias, fracturas óseas. Deshidratación. A largo plazo no establecidos.
Administración	Subcutánea, 2xd, 1xd, 1xs	Oral 1xd
Precio	Caro	Caro

Gurgle HE, et al. Vasc Health Risk Manag 2016:12 239–249

DURATION-8: a 28 week, multicentre, double-blind, phase 3, randomised controlled trial





Lancet Diabetes Endocrinol 2016

J.F. Ascaso. HC-UV

Pauta del tratamiento de hiperglucémia en la DMT2

Establecer objetivos + **CEV** (dieta hipocalórica si sobrepeso u obesidad) +

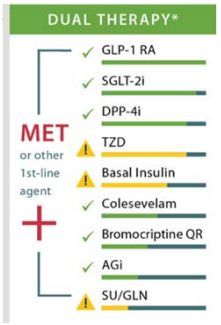
Monoterapia:
Metformina, si intolerancia o contraindicación otro hipoglucemiante no insulínico

No objetivos en cada escalón, después 3-6 m, con buena cumplimentación

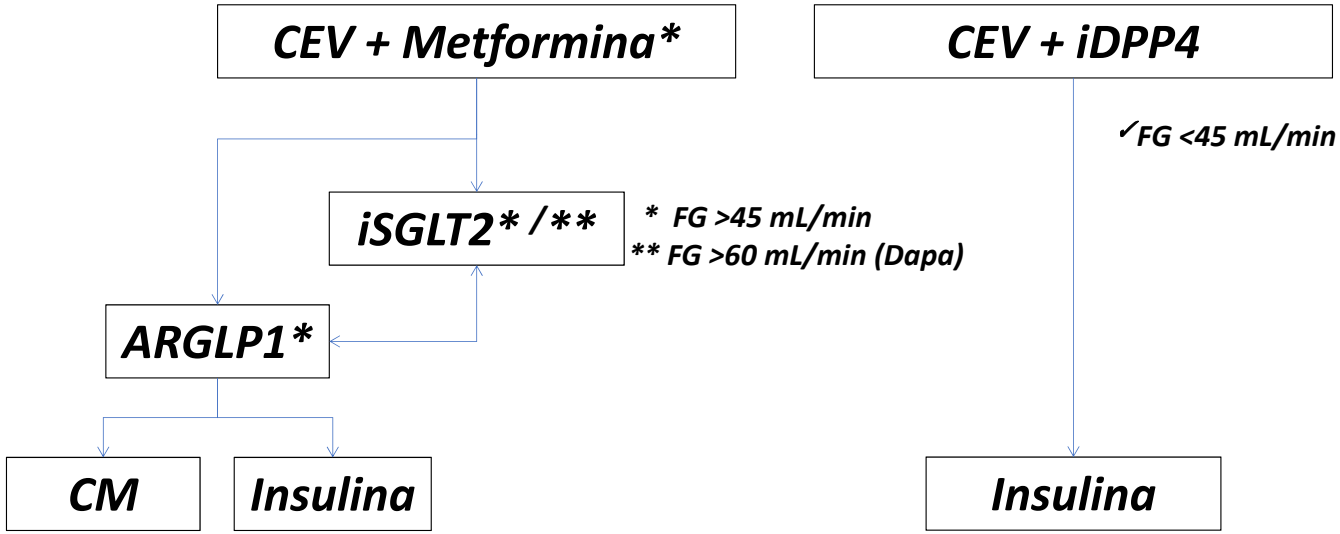
Doble terapia

ADA
La elección del **segundo fármaco** se basará en: eficacia, costes, efectos secundarios, efectos sobre el peso, comorbilidades (ECV, IRC, etc), riesgo hipoglucemia i preferencias del paciente.
TODOS EN EL MISMO ESCALÓN

AACE
- ✓ GLP1-RA
- ✓ GSLT2i
- ✓ DPP4i
- ✓ Pioglitazona
- ✓ Basal insulin
- ✓ SU/Glinides

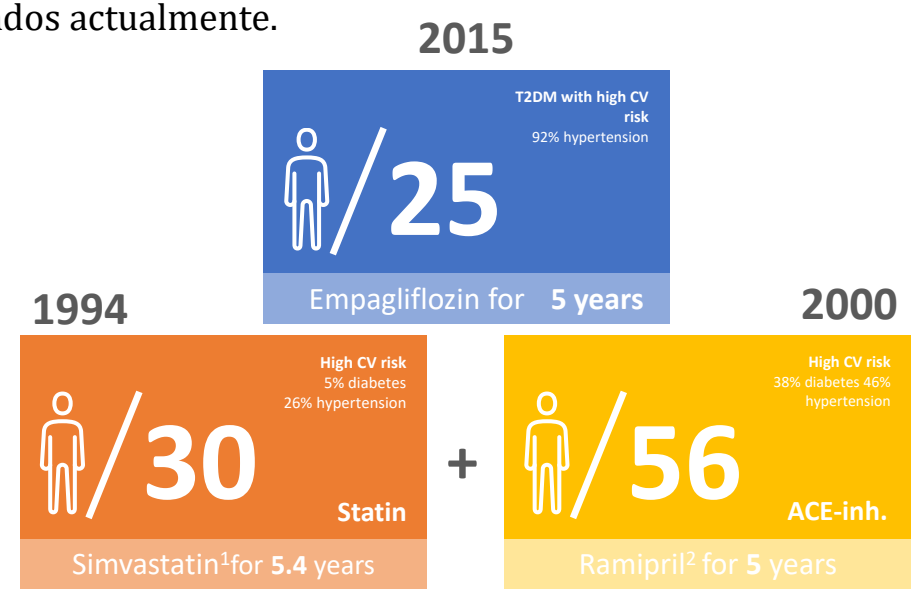


Tratamiento DMT2 con ECV



NNT para prevenir una muerte en pacientes con alto riesgo CV

Ensayos realizados actualmente.



1:4S investigator. Lancet 1994; 344: 1383-89
2: HOPE investigator N Engl J Med 2000;342:145-53,
EBM2000;5 :47 http://www.trialresultscenter.org/study2606-HOPE.htm

Conclusiones

- ✓ Metformina disminuye la IR y es neutra respecto a ECV.
- ✓ Los iDPP4, son seguros y los meta-análisis indican posibles beneficios CV.
- ✓ Los aRGLP-1 disminuyen el peso, la ECV y mortalidad
- ✓ Los iSGLT2 reducen la ECV, IC y mortalidad (EMPA-REG).
  - Son necesarios más estudios.
  - Es necesario conocer mejor los mecanismos por los que se producen los beneficios y determinar potenciales efectos de clase.