

XXXIV Congreso Sociedad Andaluza
de Medicina Interna (SADEMI)

V Encuentro de Enfermería de
Medicina Interna de Andalucía

14, 15 y 16 de
Junio 2018
CAMPUS DE
LA SALUD
- GRANADA -

10.00-11.30 h. PARANINFO
MESA REDONDA 1
ACTUALIZACIÓN TERAPÉUTICA EN

Moderador: Dr. Ismael Aomar Millán
Servicio de Medicina Interna
Hospital Universitario San Cecilio. Granada

Insuficiencia cardíaca: Sacubitrilo/valsartán
Dr. Manuel Beltrán Robles
Servicio de Medicina Interna
Hospital Virgen del Camino
Sanlúcar de Barrameda, Cádiz

Diabetes mellitus: Empagliflozina/Metformina
Dr. Cristobal Morales
Servicio de Endocrinología
Hospital Universitario Virgen Macarena. Sevilla

Dislipemias
Dr. Miguel Quesada Charneco
Servicio de Endocrinología
Hospital Universitario San Cecilio. Granada





INVESTIGACION:

Novonordisk. Lilly, Sanofi Aventis, Merck, Hammi, Boehringer, Astra Zeneca, Pfizer, Roche, Takeda, Mankind, Novartis, Theracos, Lexicon, Fundación Progreso y Salud

iDPP4: Sitagliptina, Vildagliptina, Linagliptina, Alogliptina, Omarigliptina

SGLT2: Dapagliflozina, Canagliflozina, Empagliflozina, Sotagliflozina, Bexagliflozina

GLP1: Liraglutide, Dulaglutide, Lisixenatide, ITCA, Albiglutide, Dulaglutide, HM203

INSULINAS: Levemir, Degludec, Toujeo, MK1293, Afrezza

HIBRIDOS: IdegLira, Lixilan, OxintomodulinaS

LIPIDOS: Anacetrapid, Bocazizumab, Alirocumab

OTROS: ILE21-LIRA, Terapia celular

ASESORIAS/FORMACION:

Novonordisk. Lilly, Sanofi Aventis, Astra Zeneca, Pfizer, Roche, Novartis, Boeringer, BMS, MSD, Janssen.



Editar perfil

Cristobal Morales

@Cristob_Morales

Padre y en mis ratos libres Endocrino. Hospital de Día de Diabetes & Unidad de Investigación del Hospital Universitario Virgen Macarena. Sevilla.

📍 Sevilla, Andalucía [🌐 insulinator.com](https://insulinator.com)

ACTUALIZACION TERAPEUTICA EMPAGLIFLOZINA

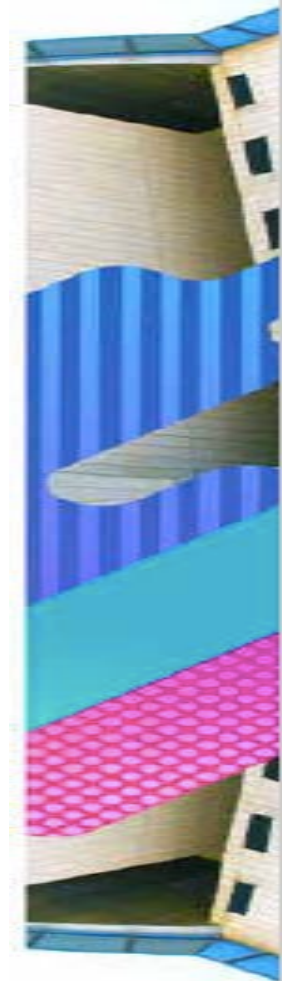
@Cristob_morales

INTRO: DM2 Y ECV

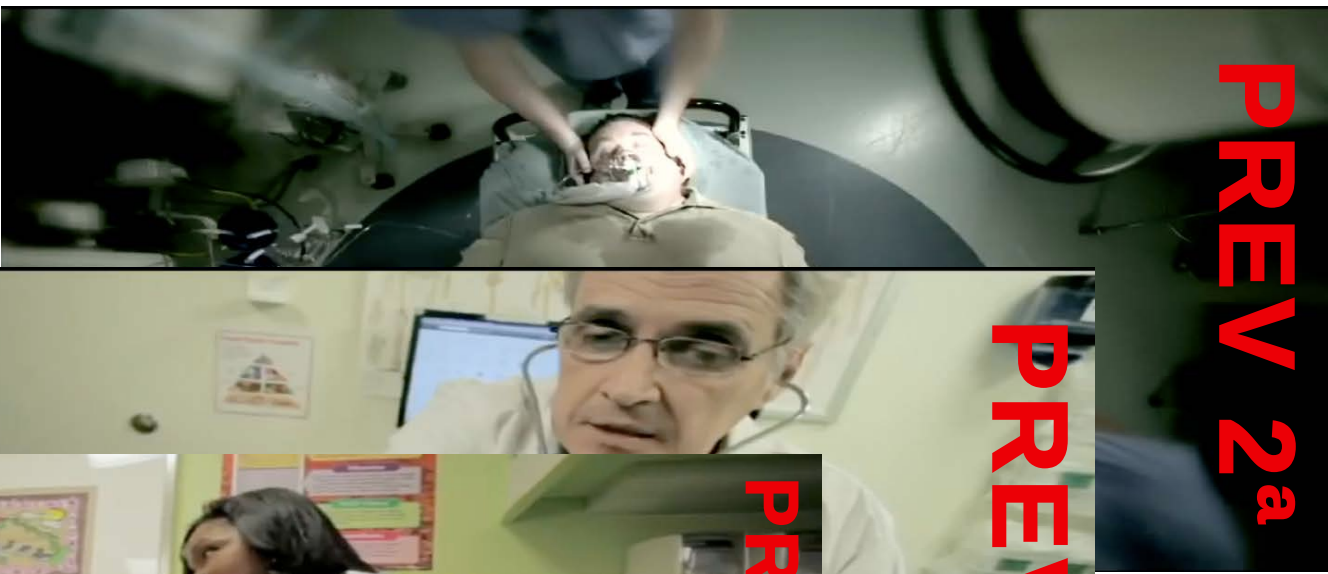
**EECC DE SEGURIDAD CV EN
DIABETES: BEFORE-EMPAREG**

**CAMBIO DE ERA: AFTER
EMPAREG**

GUIAS CLINICAS



**EECC
SEGURIDAD
CARDIOVASCULAR**
(PREV 2ª)



PREV 2^a

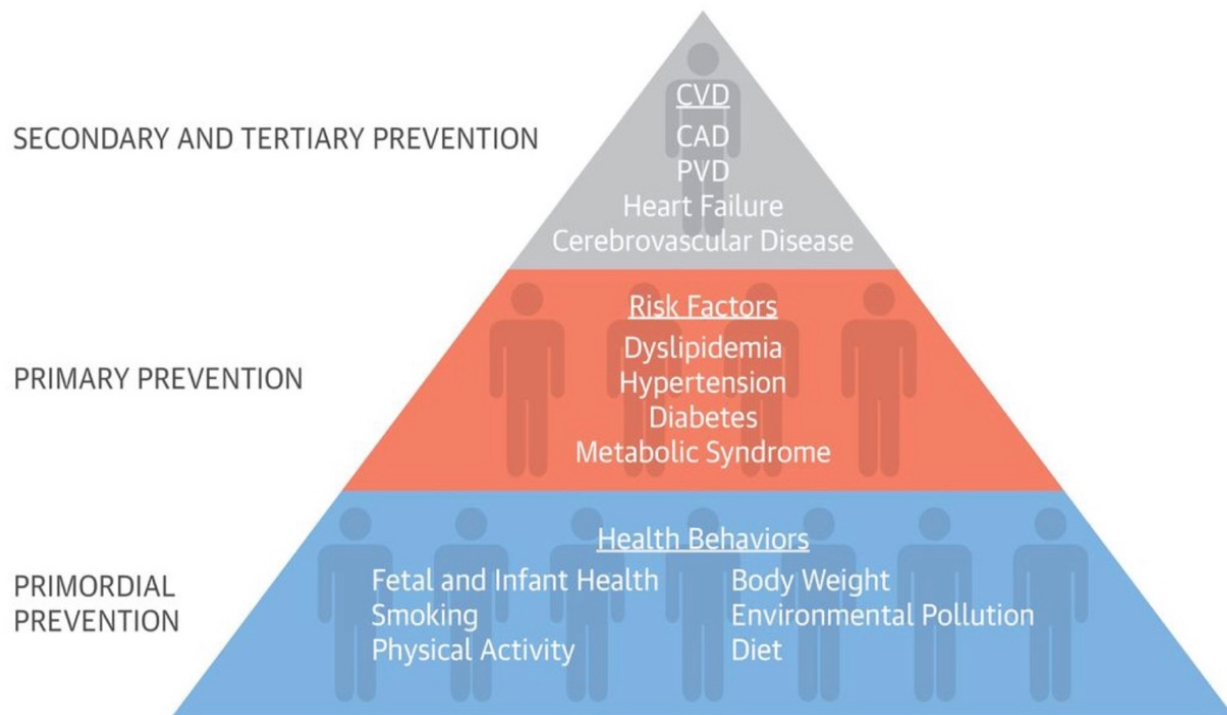


PREV 1^a



**PRIMORDIAL
PREV**

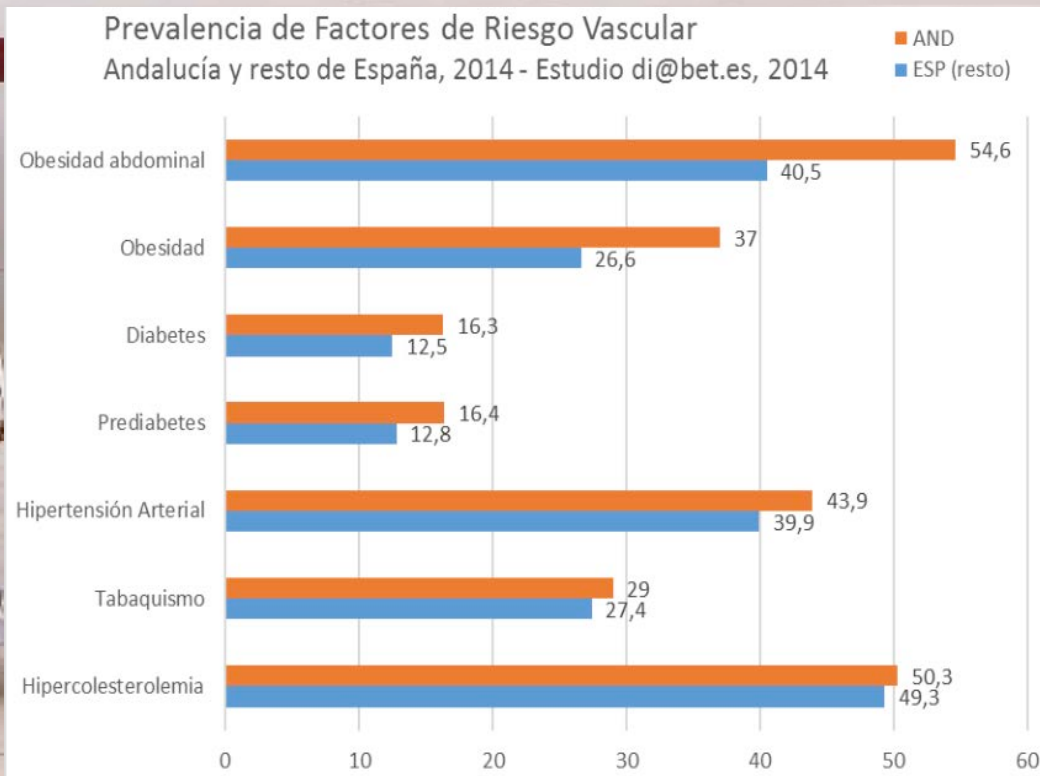
CENTRAL ILLUSTRATION: Cardiovascular Disease Prevention and Health Promotion

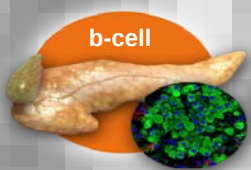


Hong, K.N. et al. J Am Coll Cardiol. 2017;70(17):2171-85.



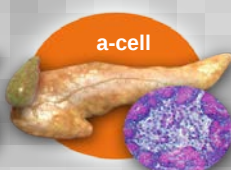
Prevalencia de Factores de Riesgo Vascular
Andalucía y resto de España, 2014 - Estudio di@bet.es, 2014





b-cell

Secreción
alterada de
insulina

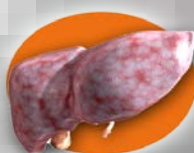


a-cell

Aumento
secreción
Glucagón



Aumento
reabsorción
glucosa



Aumento
producción glucosa



Lipólisis
aumentada



Captación
glucosa
disminuida



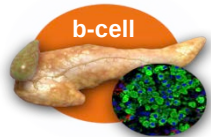
Efecto
disminuidos
incretinas



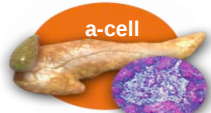
Disfunción Neuro-
transmisores



Adaptado de R.Fronzo



Secreción alterada de insulina



(+) secreción Glucagón



(-) Efecto incretinas



(+) producción glucosa



(+) Lipólisis



(-) Captación glucosa



(+) reabsorción glucosa



Microbiota anormal



Disregulación Inmune /Inflamación



(+) ratio absorción glucosa



Disfunción Neuro-transmisores

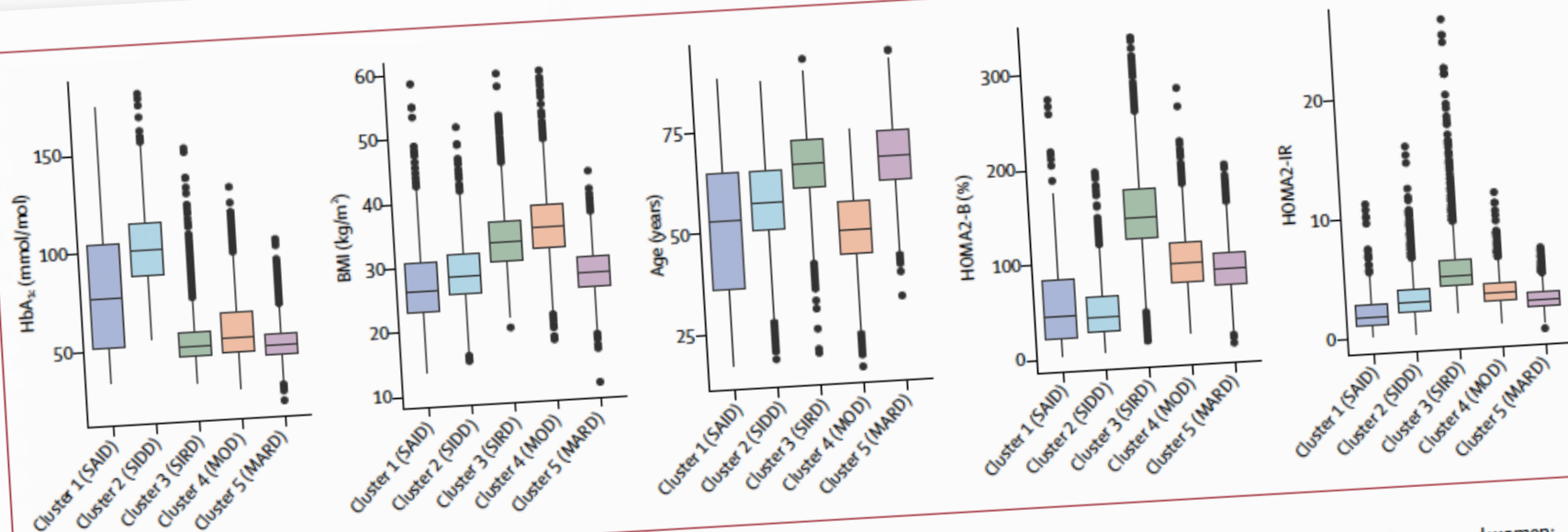


Figure 2: Cluster characteristics in the ANDIS cohort

Distributions of HbA_{1c} and age at diagnosis, and BMI, HOMA2-B, and HOMA2-IR at registration, in the ANDIS cohort for each cluster. k-means clustering was done separately for men and women; pooled data are shown here for clusters 2–5. SAID—severe autoimmune diabetes. SIDD—severe insulin-deficient diabetes. MOD—mild obesity-related diabetes. MARD—mild age-related diabetes. HOMA2-B—homoeostatic model assessment 2 estimates of β -cell function. HOMA2-IR—homoeostatic model assessment 2 estimates of insulin resistance. ANDIS—All New Diabetics in Scania.

Articles

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, PhD, Petter Storm, PhD, Annetamari Käräjämäki, MD¹, Mats Martinell, MD², Moshgan Dorkhan, PhD, Annelie Carlsson, PhD, Petter Vikman, PhD, Razmi B Prasad, PhD, Dinā Mansour Aly, MSc, Peter Almgren, MSc, Ylva Wessman, MSc, Nael Shaat, PhD, Peter Spiegel, PhD, Prof Hindrik Mulder, PhD, Eero Lindholm, PhD, Prof Olla Melander, PhD, Ola Hansson, PhD, Ulf Malmqvist, PhD, Prof Åke Lernmark, PhD, Kaj Lahti, MD, Tom Forsén, PhD, Tiinamajja Tuomi, PhD, Anders H Rosengren, PhD, Prof Leif Groop, PhD^{3,4,5}

¹ Contributed equally

Published: 01 March 2018

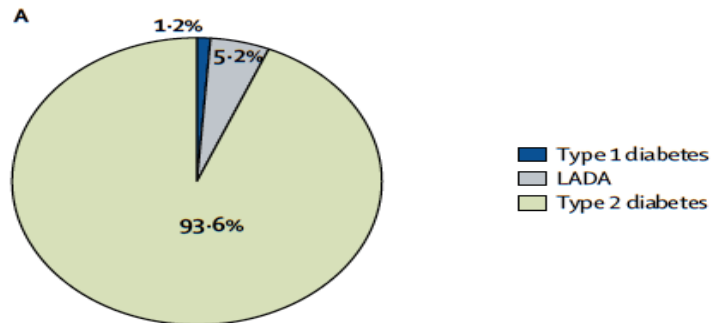
PlumX Metrics

DOI: [https://doi.org/10.1016/S2213-8587\(18\)30051-2](https://doi.org/10.1016/S2213-8587(18)30051-2) | CrossMark



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DIABETES AUTOINMUNE GRAVE

6-15%

Desarrollo en la infancia (mayoritariamente)
Deficiencia de insulina
Presencia de auto - anticuerpos

9-20%

DIABETES GRAVE CON DEFICIENCIA DE INSULINA

Individuos jóvenes
Secreción insulina alterada
Control metabólico bajo

HbA1C alta
Retinopatías

DIABETES GRAVE CON RESISTENCIA A LA INSULINA

11-17%

OBESIDAD
Daño renal

Resistencia insulina severa

18-23%

DIABETES LEVE RELACIONADA CON LA OBESIDAD

OBESIDAD desde edad temprana

DIABETES LEVE RELACIONADA CON LA EDAD

39-43%

Pacientes con edad avanzada
Forma más moderada de diabetes

DE LA **DIABESIDAD** AL ...**OBESIBETICO**

“TENGO UN POCO DE AZUCAR”

“Pero de la buena”

FUMO LO NORMAL

**NO SOY HIPERTENSO, TOMO
2 PASTILLAS PA LA
TENSION**

**NO PUEDO TENER
COLESTEROL ME TOMO
DANACOL DIARIO**

ME ENCANTA COMER



ACTUALIZACION TERAPEUTICA EMPAGLIFLOZINA

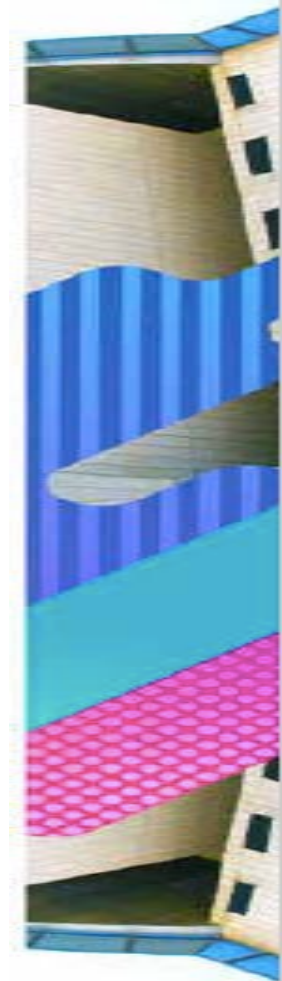
@Cristob_morales

INTRO: DM2 Y ECV

**EECC DE SEGURIDAD CV EN
DIABETES: BEFORE-EMPAREG**

**CAMBIO DE ERA: AFTER
EMPAREG**

GUIAS CLINICAS



Sept 2015



Pues mi padre es
Cirujano y salva
vidas

Y mi madre es
Cardióloga pone
Stent y también,
ea!!!

The NEW ENGLAND JOURNAL of MEDICINE

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

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

NEJM 2007

2007

An increased risk of myocardial infarction (MI) and CV death was observed in a meta-analysis of rosiglitazone trials¹

Myocardial infarction
1.43 (95% CI: 1.03, 1.98), $p=0.03$
Cardiovascular death
1.64 (95% CI: 0.98, 2.74), $p=0.06$



GRACIAS STEVEN NISSEN, CONTIGO EMPEZO TODO...



CardioDM THINGS

98% de coincidencia 2017 16+ 2 temporadas

A raíz del metanálisis de S.Nissen en 2007 las agencias reguladoras exigen un estudio de seguridad cardiovascular en los nuevos fármacos para la diabetes

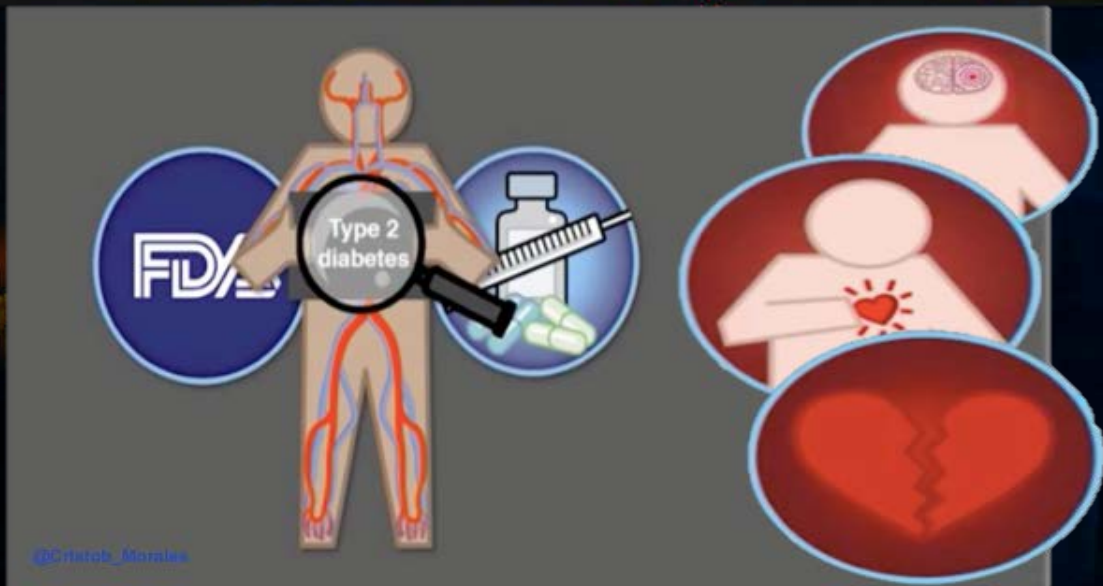
▶ REPRODUCIR

✓ MI LISTA



Protagonizada por : Alogliptina, Saxagliptina, Sitagliptina, Lixisenatide, Empagliflozina, Liraglutide, Canagliflozina, Exenatide LAR

Pertenece a: De miedo, Inquietantes



INFORMACIÓN GENERAL

EPISODIOS

TRÁILERS Y MÁS

SIMILARES

DETALLES

Series TV

NETFLIX

POR
TRECE
RAZONES ▶

NUEVOS EPISODIOS



CardioDM

THINGS



2ªTEMPORADA: DESPUES DEL EMPAREG



3ªTEMPORADA: WAITING DECLARE





EMPA-REG
OUTCOME®

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,
David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D.,
Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H.,
Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D.,
and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

NEJM, 17Sep15

EMPA-REG OUTCOME® trial design

Patients with T2D and established
CV disease

42 countries
7020
patients

CV disease was defined as
≥1 of the following:

- CAD
- PAD
- History of MI
- History of stroke

Empagliflozin or
placebo given on top
of standard of care



3.1 years median
observation time

Primary endpoint:
3P-MACE



Pre-specified primary endpoint
components:

- CV death
- Non-fatal MI
- Non-fatal stroke

Other pre-specified outcomes:

- All-cause mortality
- Hospitalisation for heart failure
- Incident or worsening nephropathy

To examine the long-term effects of empagliflozin versus placebo, on top of standard of care,
on CV morbidity and mortality in patients with T2D and established CV disease.

EMPA-REG OUTCOME: The Patient



~63 años

IMC 31

HbA1c ~8%

~57 % > 10 años del diagnóstico

Metformina (74%)
Insulina (48 %)
Sulfonilurea (42%)

Enfermedad CV establecida:

~75% con enfermedad coronaria
~46% antecedentes de infarto de miocardio
~10% Insuficiencia Cardíaca

~ 52% IR leve
~ 26% IR moderada

Bien controlado

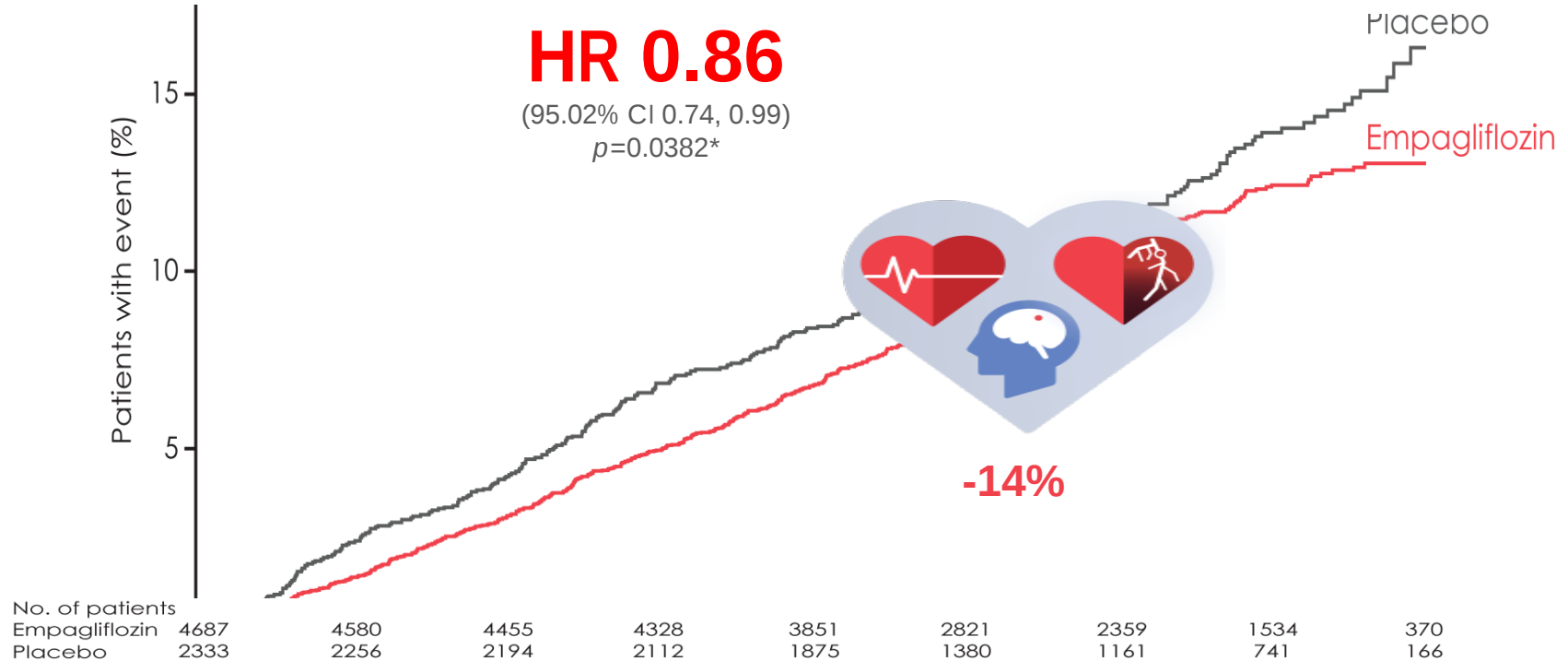
- Lípidos (C-LDL ~ 85 mg/dl)
- Presión arterial ~ 135/77 mmHg

Antihipertensivos: 95%

Hipolipemiantes: 80%

Anticoagulantes/Antiplaquetarios: 89%

PRIMARY OUTCOME: MACE-3



Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.

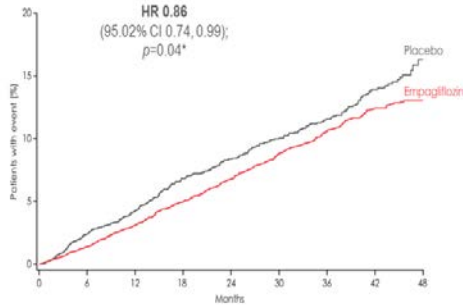
* Two-sided tests for superiority were conducted (statistical significance was indicated if $p \leq 0.0498$)

Cardiovascular Events in EMPA-REG Outcome

14%



↓ 3P-
MACE

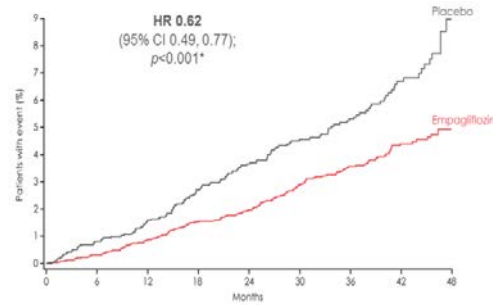


No. of patients	4887	4580	4455	4328	3851	2821	2309	1334	370
Empagliflozin	4887	4580	4455	4328	3851	2821	2309	1334	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

38%



↓ CV death

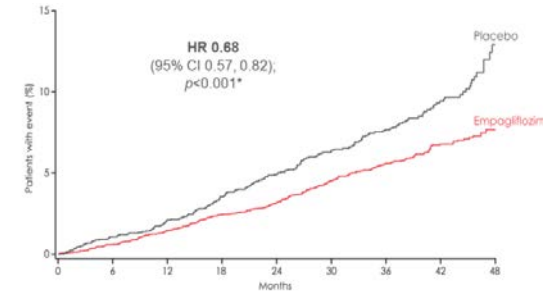


No. of patients	4887	4651	4606	4556	4128	3079	2617	1722	414
Empagliflozin	4887	4651	4606	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

32%



↓ All-cause
mortality



No. of patients	4887	4651	4606	4556	4128	3079	2617	1722	414
Empagliflozin	4887	4651	4606	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177



EMPA-REG
OUTCOME®

EMPA-REG OUTCOME: **una nueva era**

14%



↓ 3P-MACE¹

38%



↓ CV death¹

32%



↓ All-cause mortality¹

35%



↓ HF hospitalisations¹

39%



↓ New or
worsening
nephropathy^{*,2}

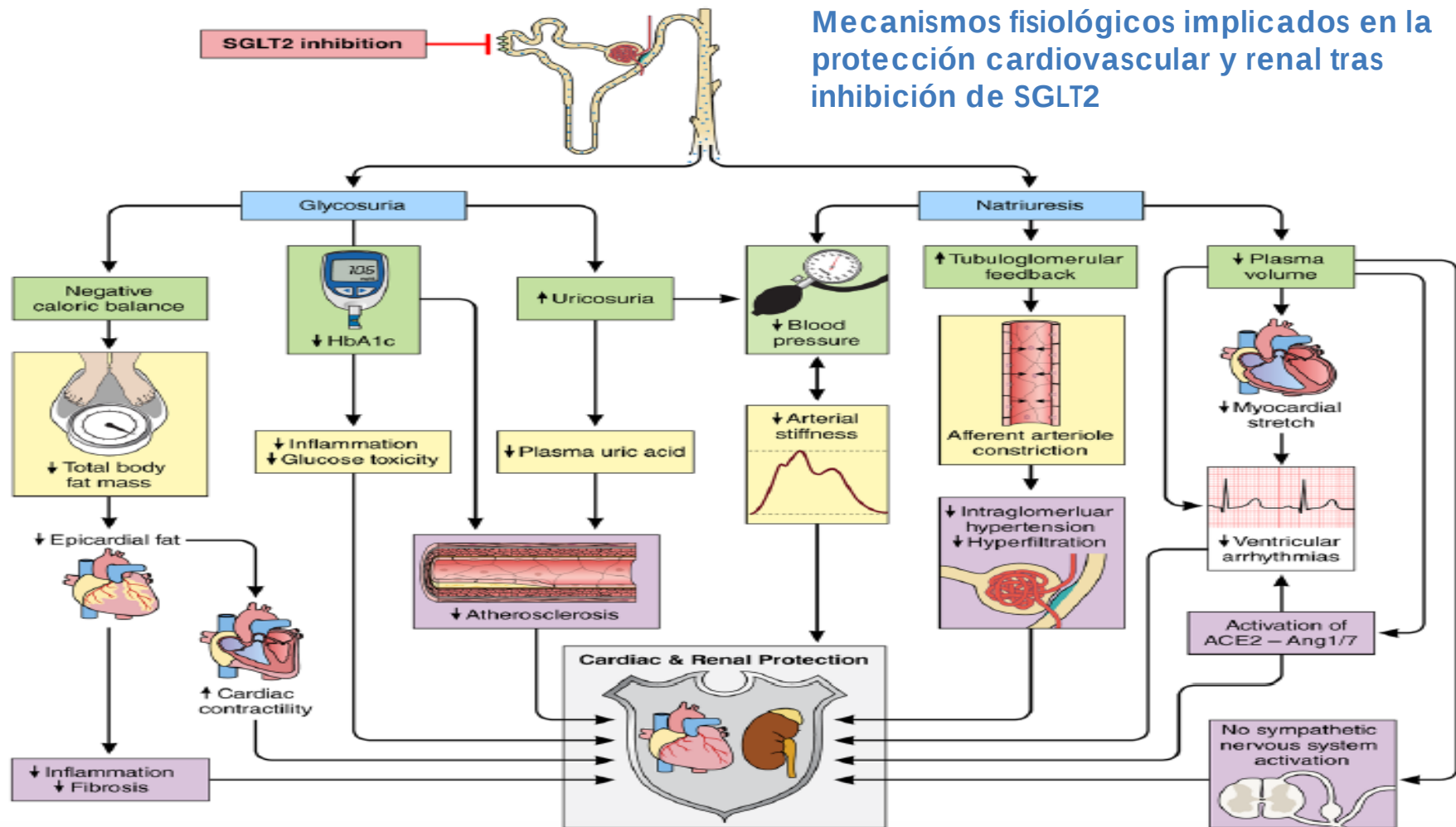
*Defined as new onset of macroalbuminuria, doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73m²), initiation of renal replacement therapy or death due to renal disease; 3P-MACE, 3-point major adverse cardiovascular events

1. Zinman B et al. *N Engl J Med* 2015;373:2117; 2. Wanner C et al. *N Engl J Med* 2016 (submitted)

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SGLT2 inhibition

Mecanismos fisiológicos implicados en la protección cardiovascular y renal tras inhibición de SGLT2





iSGLT2 HAN SUBIDO A LOS ALTARES



CardioDM

THINGS



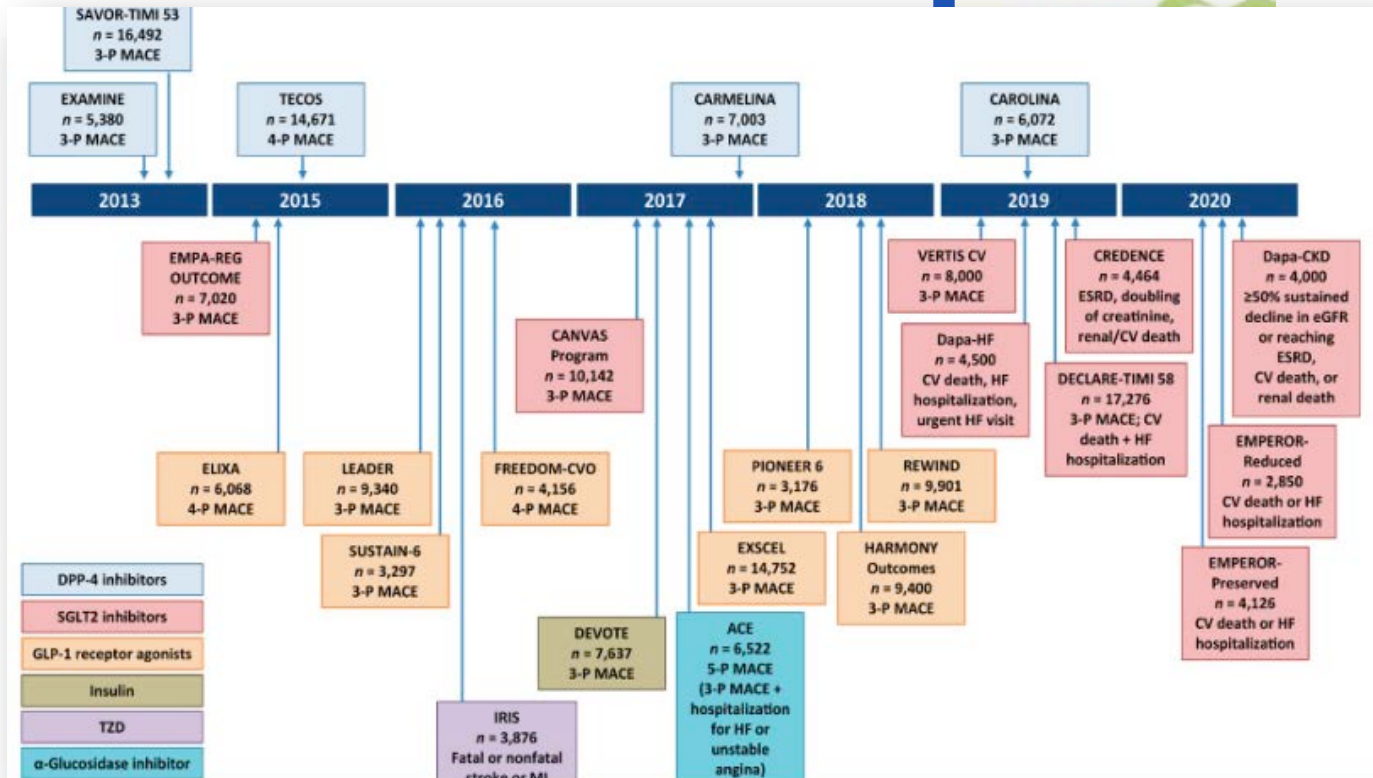
2ªTEMPORADA: DESPUES DEL EMPAREG



3ªTEMPORADA: WAITING DECLARE



LA DECADA DE LOS ESTUDIOS DE SEGURIDAD CARDIOVASCULAR EN DM2



¿EXISTE EFECTO CLASE CV?

ELIXA

EXSCEL

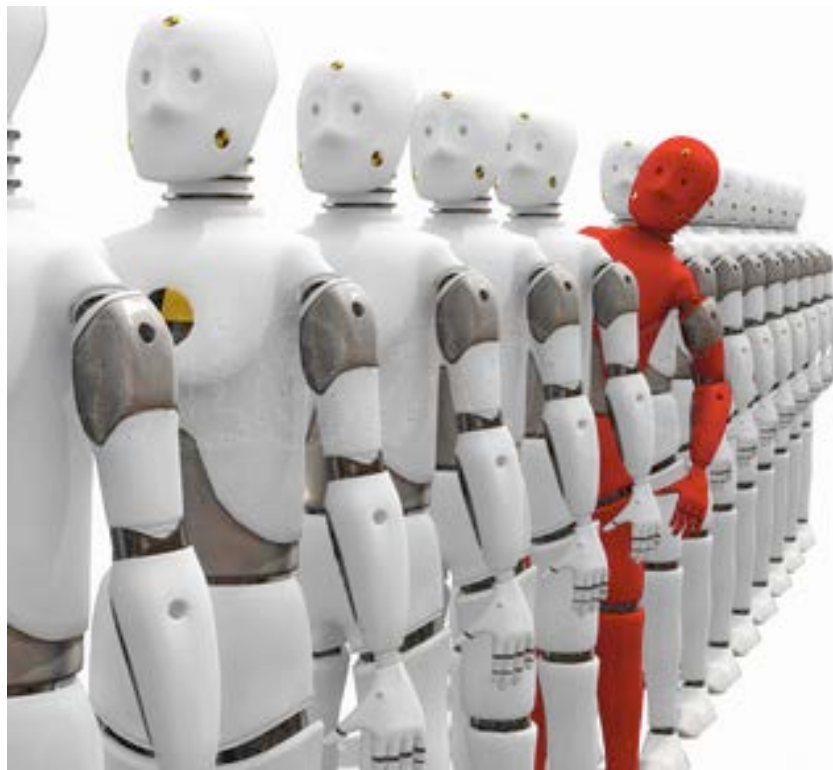
Exenatide Study of Cardiovascular Event Lowering

FREEDOM

TECOS

EXAMINE

savor
TIMI 53



REWIND Trial

DECLARE
TIMI-58
TIMI STUDY GROUP/NADASSAN MEDICAL ORG

¿Son todos
iguales o hay
diferencias entre
ellos?



EMPA-REG
OUTCOME®

LEADER®

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

SUSTAIN™

SEMAGLUTIDE UNABATED SUSTAINABILITY
IN TREATMENT OF TYPE 2 DIABETES



CANVAS Program

@Cristob_Morales

TABLE 2. NHANES-Weighted Variables Analyzed For Adult Patients With Type 2 Diabetes Identified From NHANES Data for 2009-2010 and 2011-2012 (N = 23,941,512)

Weighted Variable	
Mean age (years $\pm$ SD)	59.6 $\pm$ 13.5
Mean body mass index (kg/m ² $\pm$ SD)	33.3 $\pm$ 7.6
Percentage of this population	
Sex	
Men	52.2
Women	47.8
Race	
Non-Hispanic white	57.2

REPORT

Eligibility Varies Among the 4 Sodium-Glucose Cotransporter-2 Inhibitor Cardiovascular Outcomes Trials: Implications for the General Type 2 Diabetes US Population

Eric T. Wittbrodt, PharmD, MPH; James M. Eudicone, MS, MBA;
Kelly F. Bell, PharmD, MSPH; Devin M. Enhoffer, PharmD; Keith Latham, PharmD;
and Jennifer B. Green, MD

TABLE 3. Baseline Characteristics of Patients Included in the CANVAS Program, DECLARE-TIMI 58, EMPA-REG OUTCOME, and VERTIS-CV Trials³⁷

	CANVAS Program	DECLARE-TIMI 58	EMPA-REG OUTCOME	VERTIS-CV
Number randomized	10,142	17,160	7020	8237
Age (mean, yrs)	63	65	63	64
A1C level (mean, %)	8.2	8.3	8.1	8.3
CV status	• 34% primary prevention • 66% secondary prevention • 41% established CVD • 59% multiple risk factors • >99% established CVD • >99% established CVD			

A1C indicates glycated hemoglobin; CANVAS, CANagliflozin cardioVascular Assessment Study; CVD, cardiovascular disease.

ACTUALIZACION TERAPEUTICA EMPAGLIFLOZINA

@Cristob_morales

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