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REVISTA DIABETES PRÁCTICA



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**Dr. Francisco
Mera Cordero**

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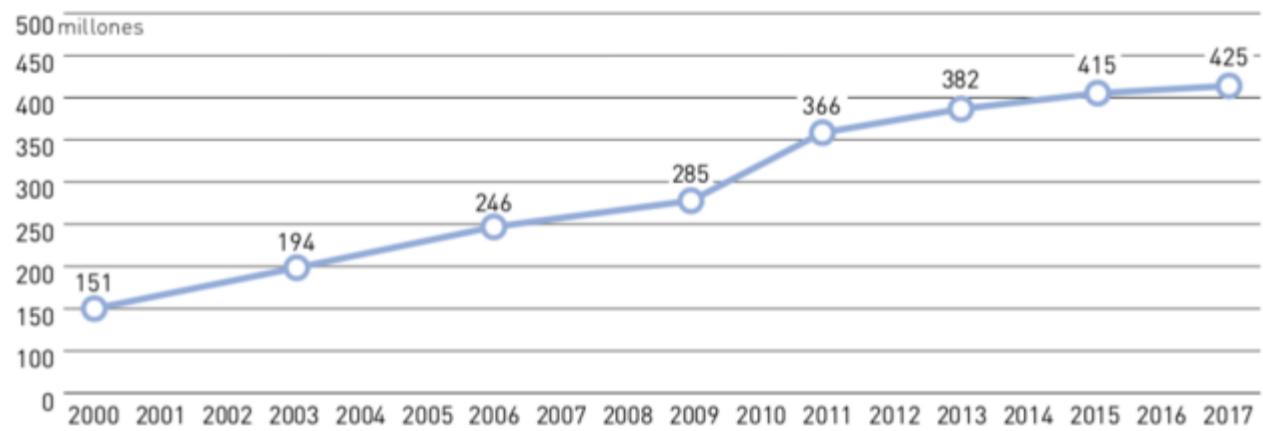
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Diabetes alrededor del mundo

número de DM x 3 en últimas 2 décadas.

Figura 3.2 Número total de adultos con diabetes (20-79 años)



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Historia natural de IOG/prediabetes



TIPO DE PREDIABETES	HR	IC 95%
HbA1c 5,7-6,4 %	1,00	-
Glucemia 100-125 mg/dl	1,41	(0,78-2,55)
Glucemia 100-125 mg/dl y HbA1c 5,7-6,4 %	4,78	(3,04-7,54)

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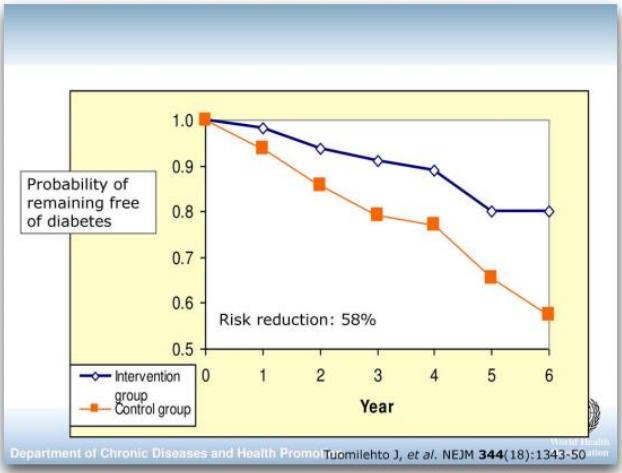


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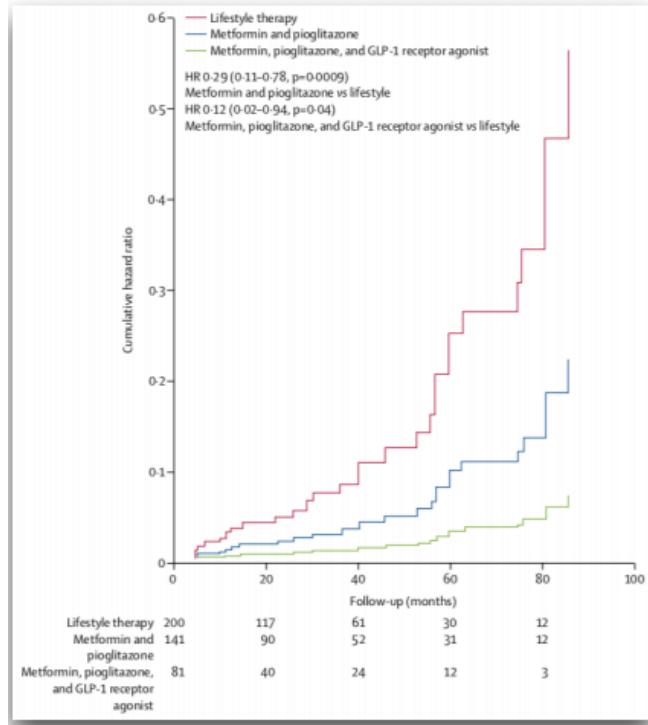
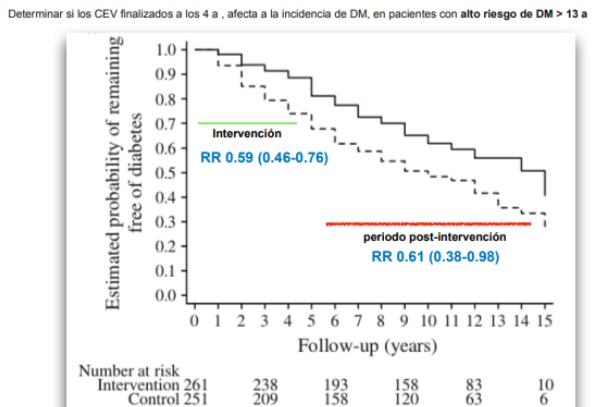
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Comprometidos con la DIABETES

Reducción de la incidencia de DM con CEV - Finnish Diabetes Prevention Study (DPS)



Improved lifestyle and decreased DM risk over 13 years:long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS)



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HARMONY-OUTCOMES

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

Adrian E Wenzel, Jennifer B Green, Sallie Jameson, Ralph B D'Agostino Sr, Christopher R Granger, Alfred P Jones, Lawrence A Leiter, Anne L Rosenberg, Kristina P Sagnier, Matthew C Somerville, Karl M Thorpe, John V McMurray, Stefano Del Prato, for the Harmony Outcomes Committee and Investigators*

Summary

Background Glucagon-like peptide 1 receptor agonists differ in chemical structure, duration of action, and in their effects on clinical outcomes. The cardiovascular effects of once-weekly albiglutide in type 2 diabetes are unknown. We aimed to determine the safety and efficacy of albiglutide in preventing cardiovascular death, myocardial infarction, or stroke.

Methods We did a double-blind, randomised, placebo-controlled trial in 610 sites across 28 countries. We randomly assigned patients aged 40 years and older with type 2 diabetes and cardiovascular disease (at a 1:1 ratio) to groups that either received a subcutaneous injection of albiglutide (30–50 mg, based on glycaemic response and tolerability) or of a matched volume of placebo once a week, in addition to their standard care. Investigators used an interactive voice or web response system to obtain treatment assignment, and patients and all study investigators were masked to their treatment allocation. We hypothesised that albiglutide would be non-inferior to placebo for the primary outcome of the first occurrence of cardiovascular death, myocardial infarction, or stroke, which was assessed in the intention-to-treat population; if non-inferiority was confirmed by an upper limit of the 95% CI for a hazard ratio of less than 1.30,



Así comentan, que los derivados de la estructura original del GLP-1 (liraglutide y semaglutide) tendrían efectos preventivos CV, no así los asociados a la estructura del exendin-4, como el lixisenatide y el exenatide.

Summary of CV outcomes trials with GLP1 ra

Inclusion criteria	A1c, %	Median follow-up (y)	Nº patients	Primary endpoint	RR
 ACS within 180d, > 30y	5.5-11.0	2.1	6068	MACE-4 (non-inferiority)	1.02 (0.89-1.17)
 >50y, CVD/renal dysfunction/HF, or > 60y With CV RFs	>7	3.8	9340	MACE-3 (non-inferiority)	0.87 (0.78-0.97)
 >50y with CVD, or > 60y with subclinical CVD	>7	2.1	3297	MACE-3 (non-inferiority)	0.74 (0.58-0.95)
 CVD as well as primary prevention(70/30 split) , > 18y	6.5-10.0	3.2	14.000	MACE-3 (non-inferiority)	0.91 (0.83-1.00)
 established CVD	>7	1.6	9.400	MACE-3 (non-inferiority)	

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>7

1.6

9.400

MACE-3
(non-inferiority)

Albiglutide and cardiovascular outcomes in patients T2DM and CV disease

(Harmony Outcomes): a double-blind, randomised placebo-controlled trial

- standard blood glucose lowering therapies, non-inferior

Primary outcome

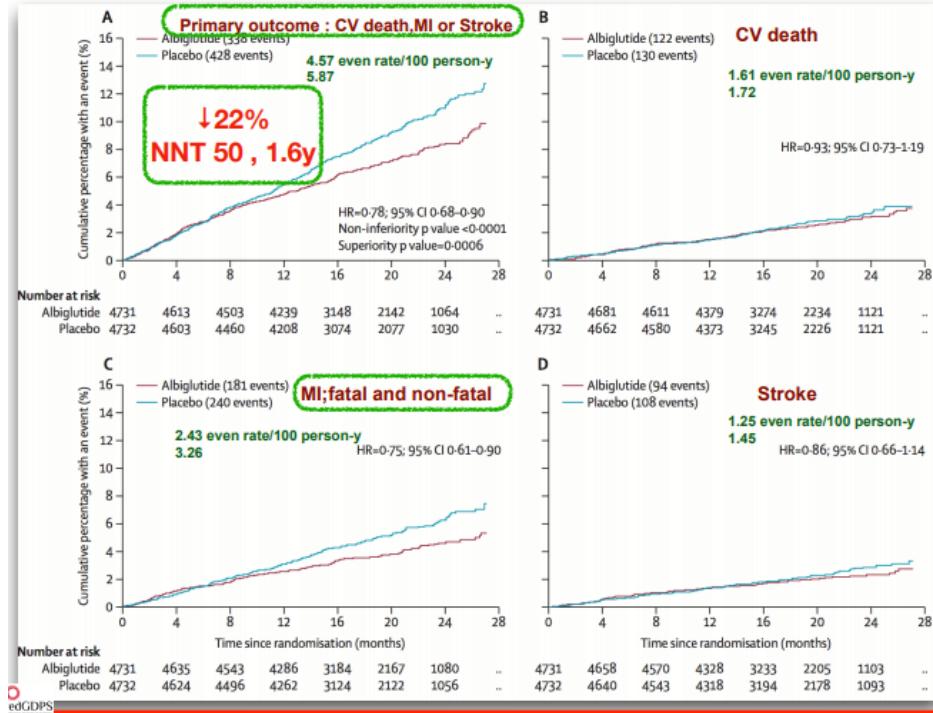
- MACE: CV death, MI, AVC
- MACE+ urgent revascularisation for unstable angina
- CV death + hospitalisation for HF

Microvascular

- Necesidad de Tx renal o dialysis o
- Nuevo ceguera-DM o
- PFcoagulación, tratamiento antiVEGF o vitrectomía

Seguridad /Metabólicos -outcomes

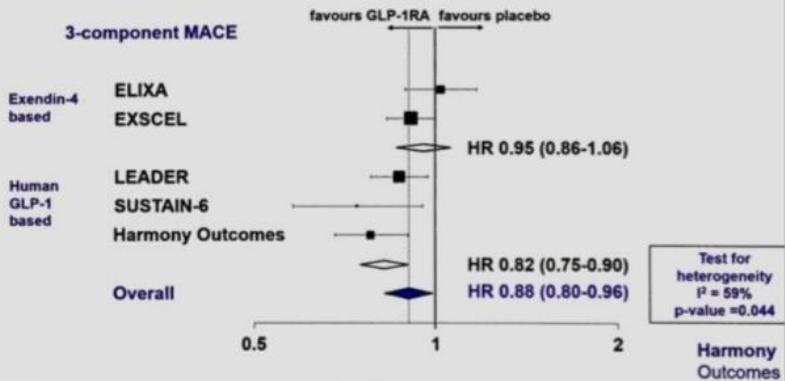
	n 9.400	Albiglutide (n=4731)	Placebo (n=4712)	Hazard ratio (95% CI)	p value*
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)	
Primary composite outcome†	338 (7%)	4.57	428 (9%)	5.87	0.78 [0.68-0.90]
Secondary outcomes					<0.001, 0.006
Expanded composite outcome‡	373 (8%)	5.06	468 (10%)	6.45	0.78 [0.69-0.90]
Death from cardiovascular causes	122 (3%)	2.61	139 (3%)	1.72	0.83 [0.73-1.19]
Fatal or non-fatal myocardial infarction	183 (4%)	2.43	240 (5%)	3.26	0.75 [0.61-0.90]
Fatal or non-fatal stroke	94 (2%)	1.25	108 (2%)	1.45	0.86 [0.66-1.14]
Composite of death from cardiovascular causes or hospital admission for heart failure	188 (4%)	2.49	238 (5%)	2.92	0.85 [0.70-1.04]
Death from any cause	196 (4%)	2.44	205 (4%)	2.56	0.85 [0.73-1.16]



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Findings in Context with Other GLP-1R Agonist CV Outcome Trials



Resumen:

Albiglutida añadido al tratamiento hipoglucemiante se asocia con:

- Mejor control glucémico ($\downarrow \text{A1c } 0.6\%$)
- Modesta pérdida de peso ($\downarrow 1.5 \text{ Kg}$)
- Modesta reducción PAS ($\downarrow 0.6 \text{ mmHg}$)
- Reduce la necesidad de iniciar insulina. **RR 0.42 (0.33-0.53)**
- Bajo riesgo de hipoglucemia severa. **RR 0.56 (0.36-0.87)**
- No exceso de eventos microvasculares importantes
 - *Tiempo al primer evento RR 0.66 (0.43-1.01)*

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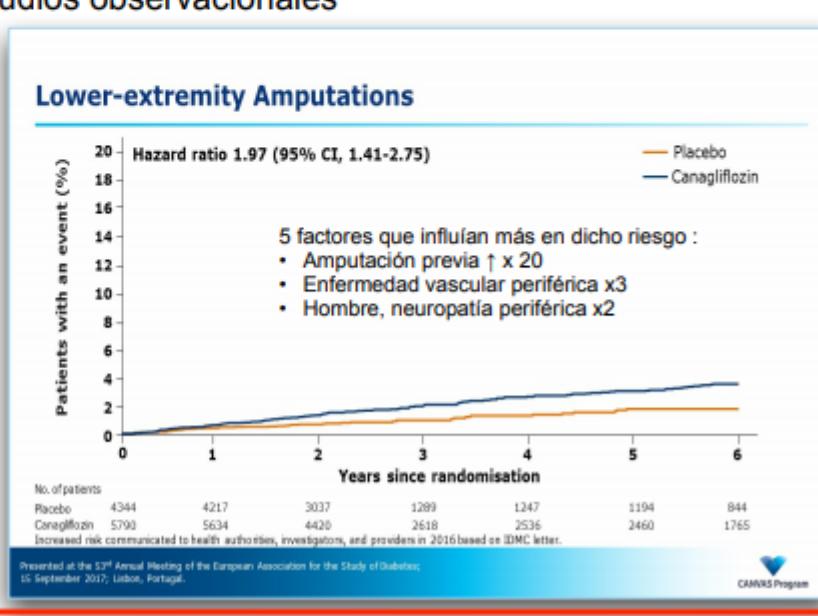


Foot prints:

- Association of diuretics use and amputations in T2DM:
A hypothesis driven from CANVAS warning?



- La DM es la principal causa de amputaciones de EEII
- **Factores implicados:** arteriopatía periférica, neuropatía periférica, susceptibilidad de infecciones, curación de heridas tórpida.....
- ↑ riesgo de amputaciones con **Canagliflozina (CANVAS trial)**
- Resultados confusos de estudios observacionales
 - Udell, Circulation 2018
 - Fadini, Lancet Diab Endocrinol 2018
 - Khouri, Diab Ob Metab 2018
 - Adimadyqm, Diab Obes Metab 2018
 - Yuan, Diab bes metab 2018
- **Mecanismo no conocido**



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Antihypertensive drug therapy and the risk of lower extremity amputations in pharmacologically treated T2DM patients

Efecto del ajuste en la asociación del uso de tiazida y el riesgo de LEA en pacientes con DM2 vs. otros medicamentos antihipertensivos

No adjustment	3.33 [1.00–11.06]
Duration of T2DM (1)	6.70 [1.21–37.08]
Congestive heart failure (2)	3.53 [1.00–12.45]
Other vascular diseases (3)	2.53 [0.64–10.08]
Cardiovascular disease (4)	3.36 [0.95–11.84]
Combination of antihypertensives (5)	3.36 [1.00–11.30]
Chronic Disease Score > 5 (6)	3.83 [1.10–13.29]
Use of insulin (7)	4.87 [1.19–20.01]
Use of lipid lowering drugs (8)	3.62 [1.06–12.35]
Use of antithrombotics (9)	3.72 [1.03–13.47]
Use of antibiotics (10)	3.58 [0.99–13.02]
1, 4 and 7	7.04 [1.10–45.30]

- Entre los DM2 que usaron fármacos antihipertensivos, los **diuréticos tiazídicos**, solos o en combinación, tuvieron un mayor riesgo de LEA vs. la monoterapia con IECA, **RR 6.11(1.32-28.27)**.
- Los diuréticos tiazídicos se asoció con un mayor riesgo de LEA vs. de cualquier fármaco antihipertensivo no tiazídico , **RR 7.04 (1.10-45.30)**.
- El mayor riesgo de LEA asociado con el uso de tiazidas vs. no tiazidas depende de la **duración del uso RR 4.82 (0.61-38.34) ≤ 365 d y RR 26.16 (1.02-674.02) > 365 d**, $p=0.01$.

Erkens. Pharmacoepidemiology Drug 2004; 13: 139–146
Gary.Medicine (Baltimore) 2015

Cohorte de pacientes del estudio SURDIAGENE

n 1.468 DM2 con seguimiento de 7,2 años (hasta diciembre 2015).

El objetivo primario : la primera amputación de EEl y revascularización (compuesto)

Análisis de supervivencia

Propensity score : 1.074 sujetos de la muestra inicial, 80% **diuréticos** vs 68% **no diuréticos**

Al realizar el análisis de Cox y ajustando por HTA y uso de IECA/ARA II, betabloqueantes y estatinas :

- ↑ tasa de amputaciones y revascularización **RR 1,6 (1,06-2,42)**
- ↑ tasa de amputaciones en miembros inferiores **RR 2,13 (1,17-3,87)**
- ↑ revascularización de miembros inferiores **RR 1,12 (0,7 -1,79)**

Potier. Diabetes 2018 Jul; 67(Supplement 1):

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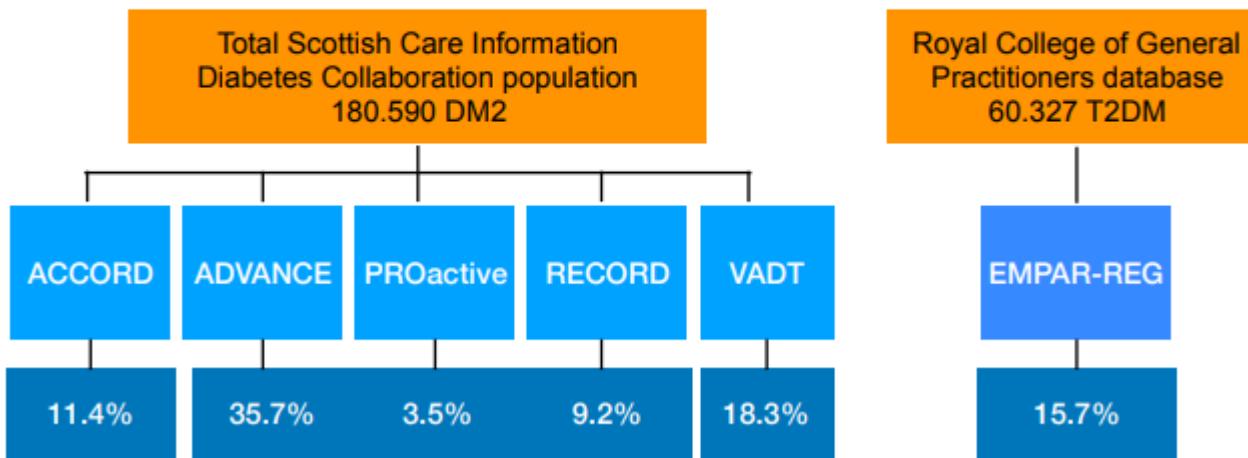
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Comparative effectiveness of CV outcomes in new users of SGLT2 inhibitors (CVD-REAL)



La mayoría de los pacientes no están representados en los CTs





Intentando integrar los CVOTs con RWE

RCTs (vs placebo)

- Randomizados/monitorización
- Alta validez interna
- Escasa validez externa
- Control factores de confusión
- Eficacia y seguridad
- Gold standard

RWE (vs standard care)

- Alta validez externa
- Baja validez interna
- Sesgos: "missing data", *immortalidad*, etc..
- efectividad

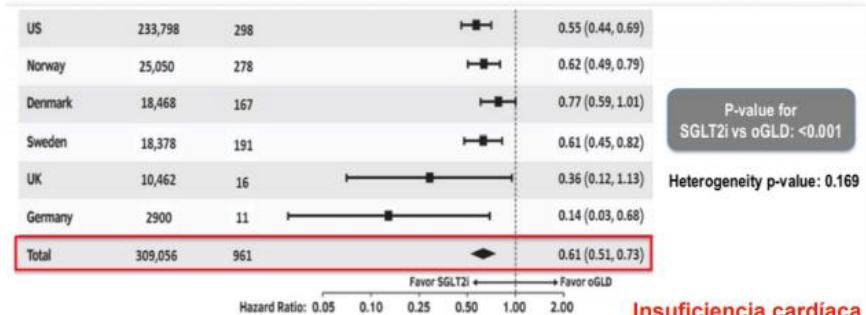
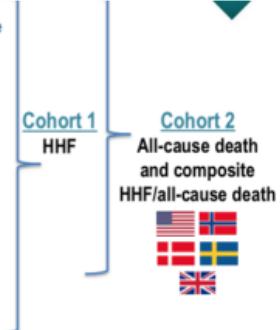
Aceptado por agencias regulatorias



Lower Rates of Hospitalization for Heart Failure and All-Cause Death in New Users of SGLT-2 Inhibitors: The CVD-REAL Study

- Los pacientes DM2 tienen un alto riesgo de desarrollar complicaciones de enfermedad cardiovascular, incluida la insuficiencia cardíaca.
- EMPA-REG OUTCOME demostró una reducción en la hospitalización por IC y muerte por todas las causas con empagliflozina, en DM2 y enfermedad CV.

Truven MarketScan Claims & Encounters and linked Medicare
National full-population registries
National full-population registries
National full-population registries
Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN)
Diabetes Patienten Verlaufsdocumentation (DPV) initiative





Study Objectives

- To evaluate the relationship between the initiation of SGLT-2i vs. other glucose-lowering drugs (oGLD) and a broad range of CV outcomes (all-cause death, HF, MI and stroke) in patients with T2D from three major world regions: Asia-Pacific, Middle East, and North America

Countries and Data Sources



Australia – National Diabetes Services Scheme (NDSS)*



Canada – Manitoba Population Health Research Data Repository



Israel – The Maccabi Health Management Organization



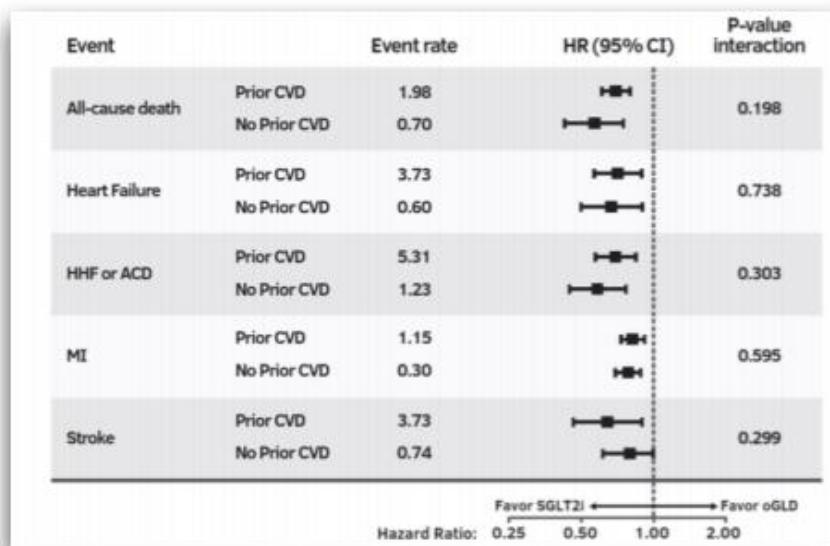
Japan – Medical Data Vision



Singapore – SingHealth Diabetes Registry



South Korea – National Health Insurance Service (NHIS)

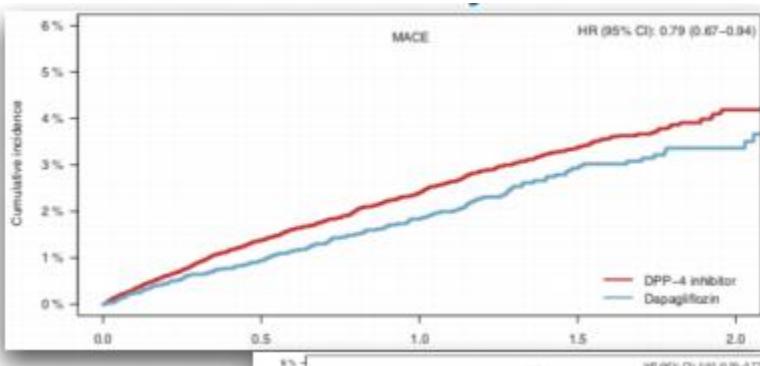
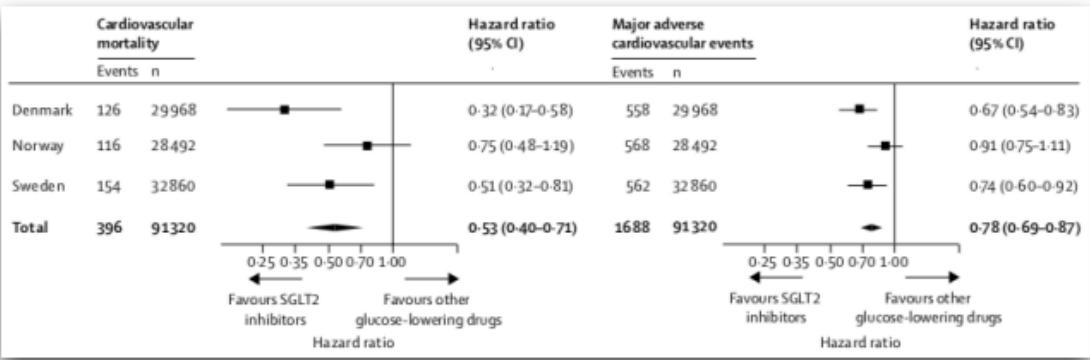


All-cause death	RR 0.51 (0.37-0.70)
Hospitalization HF	RR 0.64 (0.50-0.82)
HF + ACD	RR 0.60 (0.47-0.76)
MI	RR 0.81 (0.74-0.88)
Stroke	RR 0.68 (0.55-0.85)

n 400.000



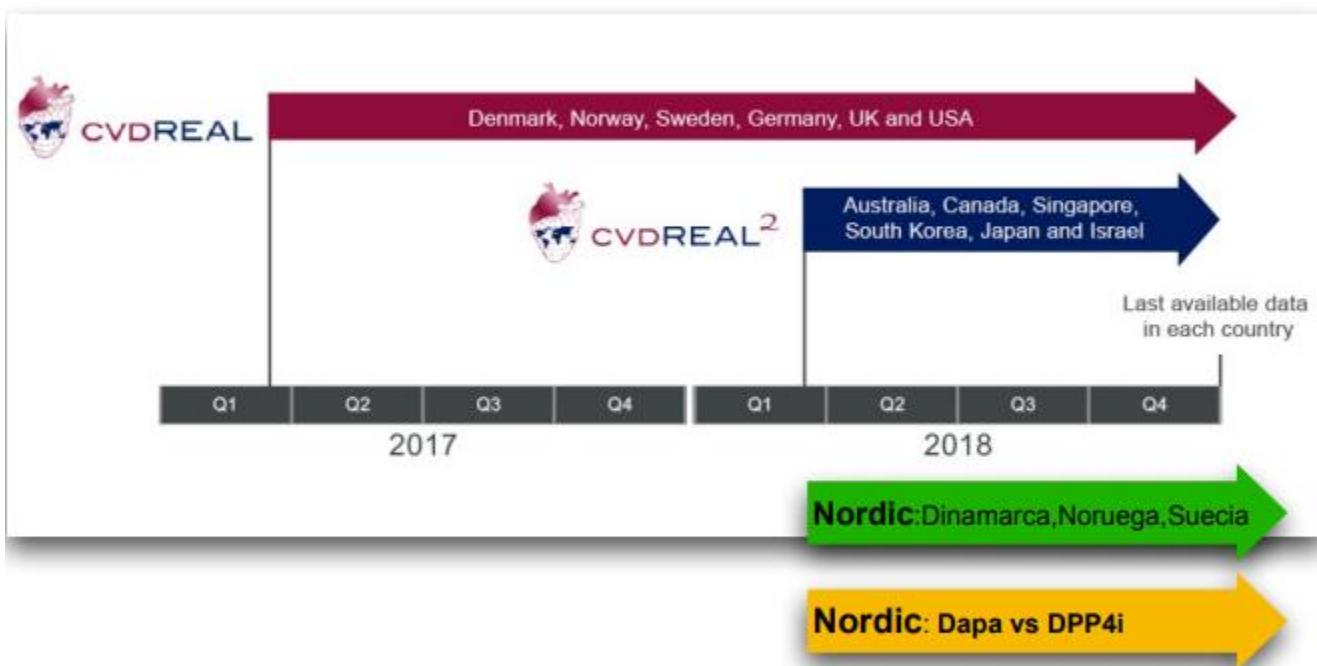
CV mortality and morbidity in T2DM following initiation of SGLT2i vs. oGLD (CVD-REAL Nordic): a multinational observational analysis



- Dapagliflozina se asoció con menor riesgo de eventos CV, hospitalización por IC y mortalidad por todas las causas vs iDPP-4 en un entorno clínico real y en una amplia población T2D.
- No se observaron asociaciones con FA e hipoglucemias severas.



CVD-REAL: future Direction



- Continuing expansion.
- New countries being added: Finland, Taiwan, **Spain**, Portugal , others

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Comparación de outcomes SGLT2i en CVOTs vs CVD-REAL

Data source	Death	heart failure hospitalization	Myocardial infarction	Stroke
RCT meta-analysis	0.79 (0.70-0.88)	0.67 (0.55-0.80)	0.84 (0.73-0.98)	1.03 (0.86-1.24)
Observational data	0.51 (0.37-0.70)	0.64 (0.50-0.82)	0.81 (0.74-0.88)	0.28 (0.55-0.84)

La evidencia total, requiere estudios que se complementen.



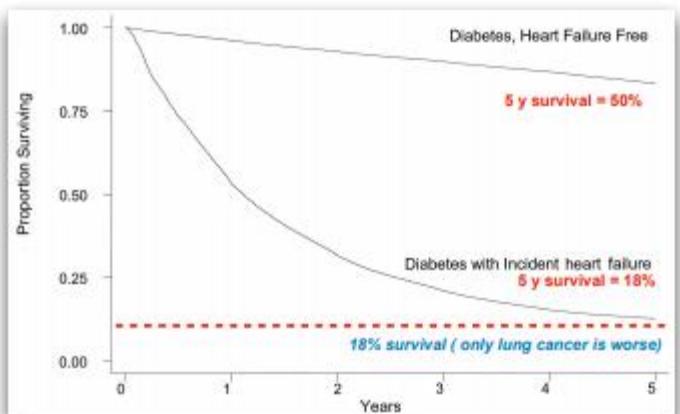
E. Ferrarini. Commentator

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Prevalencia, incidencia y mortalidad de la insuficiencia cardíaca en el anciano con DM



Diabetes Care 2004 Mar; 27(3): 699-703

Risk of heart failure in a population with T2DM vs a population without diabetes with and without coronary heart disease

T2DM	1.47 (1.40-1.54) Both sexes, < 45 y 2.54 (1.62-3.98) M , 4.12 (2.35-7.23) W
T2DM no CHD	1.54 (1.41-1.68) M, 1.56 (1.43-1.71) W
no DM + CHD	1.60 M, 1.55 W

Coronary revascularization procedures and CHDs (percutaneous transluminal coronary angiography, coronary artery bypass surgery and acute MI), were found to greatly increase risk of HF in T2DM

Chen. Diab Obes Metab. 08 August 2018

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	EMPA-REG OUTCOME	CANVAS	DECLARE- TIMI 58	ERTUGLIFLOZIN CVOT
Interventions	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Main inclusion criteria	Est. vascular complications	Est. vascular complications or > 2 CV risk factors	High risk for CV events	Est. vascular complications
No. of patients	7034	4339	17.150	3900
Primary outcome	3P-MACE	3P-MACE	3P-MACE death or HHF	3P-MACE
Key secondary outcome	4P-MACE	insulin secretion, albuminuria	4P-MACE+ HHF+ revascularisation	4P-MACE
No. of events	691	> 420	1390	TBD
Median FU	3 y	6-7 y	4-5 y	5-7 y
Estimated completion	2015	Apr 2017	2018	2019



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FARXIGA Achieved a Positive Result in the Phase III DECLARE-TIMI 58 Trial, a Large Cardiovascular Outcomes Trial in 17,000 Patients with Type 2 Diabetes

FARXIGA met the primary composite endpoint of a statistically-significant reduction in hospitalization for heart failure or CV death in a broad patient population.

Results confirmed the well-established safety profile of FARXIGA.

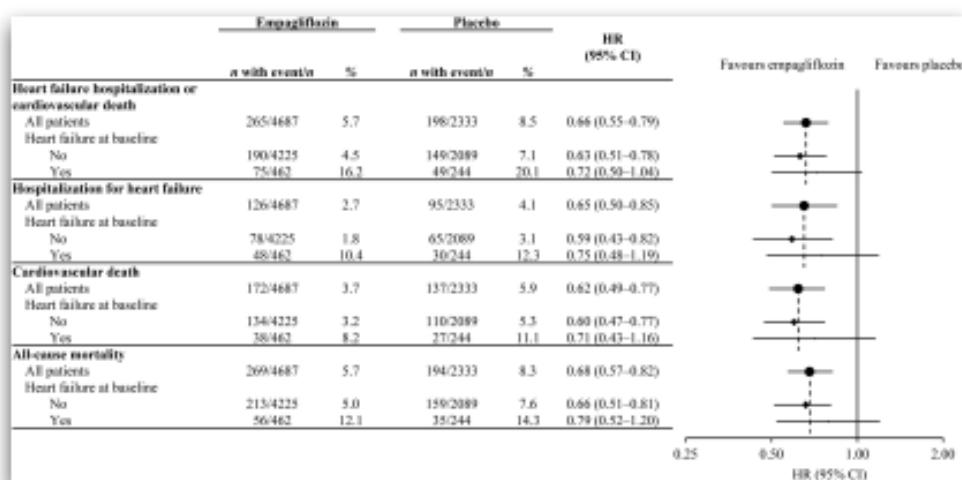
September 9, 2016 07:00 AM Eastern Daylight Time

WILMINGTON, Del.—(BUSINESS WIRE)—AstraZeneca today announced positive results from the Phase III DECLARE-TIMI 58 cardiovascular outcomes trial (CVOT) for FARXIGA® (dapagliflozin), the first SGLT-2 inhibitor CVOT conducted to date. The trial evaluated the CV outcomes of FARXIGA vs. placebo over a period of up to five years, across 30 countries and in more than 17,000 adults with type 2 diabetes (T2D) who have multiple CV risk factors or established CV disease.

The DECLARE-TIMI 58 results offer compelling evidence that dapagliflozin helps to address an important medical need among a diverse group of patients with type 2 diabetes by reducing the composite of hospitalization for heart failure or CV death, with a safety

In the DECLARE (Dapagliflozin Effect on Cardiovascular Events) TIMI 58 trial, FARXIGA met its primary safety endpoint of non-inferiority for major adverse cardiovascular events (MACE). FARXIGA achieved a statistically-significant reduction in the composite endpoint of hospitalization for heart failure (HF) or CV death, one of the two primary efficacy endpoints. Additionally, fewer MACE events were observed with FARXIGA for the other primary efficacy endpoint; however, this did not reach statistical significance. FARXIGA is not indicated to

Heart failure outcomes with empagliflozin in patients with T2DM at high CV risk: results of the EMPA-REG OUTCOME trial



Eur Heart J. 2016;37(19):1526-1534

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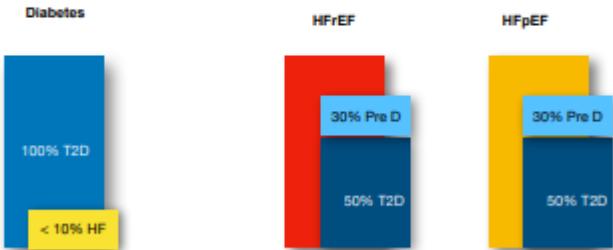
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Comprometidos con la DIABETES

From EMPAREG to EMPEROR

EMPAREG

EMPEROR- reduced
EMPEROR-Preserved



Therapies successful in HFrEF: ACEi/ARB, MRA, Ivabradine, Hydralazine ,exercise
 Therapies successful in HFpEF: ACEi/ARB, Digoxin, mineralocorticoid ra , Hydralazine

Randomised controlled (outcome) trials of SGLT2i in HF

	EMPEROR-preserved	EMPEROR-reduced	Dapa-HF / Dapa-HFpEF (Diver)	SOLOIST-WHF (Sotagliflozin)
Sample size	4126	2850	4500	4000
Key inclusion criteria	<ul style="list-style-type: none"> • Chronic HF • Elevated NT- pro BNP • eGFR > 20 30 ml/min/1,73m² 	<ul style="list-style-type: none"> • Chronic HF • Elevated NT- pro BNP • eGFR > 20 30 ml/min/1,73m² 	<ul style="list-style-type: none"> • Symptomatic HFpEF • Elevated NT-proBNP • eGFR > 30 ml/min/1,73m² 	<ul style="list-style-type: none"> • T2DM • Chronic HF • Elevated NT-proBNP • Hospital admission for worsening HF and hemodynamically stable
HFpEF (LVEF > 40%)			HFpEF (LVEF < 40%)	
Primary endpoint	Time to first of adjudicated CV death or adjudicated HF	Time to first of adjudicated CV death or adjudicated HF	HFpEF (LVEF < 40%) HFpEF (LVEF > 40%)	Time to first event of CV death or HF
Key secondary endpoints	<ul style="list-style-type: none"> • Individual components of primary endpoint • All-cause mortality • All-cause hospitalisation • Time to first occurrence or sustained reductions of eGFR • Change from baseline in KCCQ 	<ul style="list-style-type: none"> • Individual components of primary endpoint • All-cause mortality • All-cause hospitalisation • Time to first occurrence or sustained reductions of eGFR • Change from baseline in KCCQ 	<ul style="list-style-type: none"> • Total number of CV death or HF • All-cause mortality • Composite of > 50% sustained eGFR decline, ESRD or renal death • Change from baseline in KCCQ 	<ul style="list-style-type: none"> • Total number of CV death, HF or urgent HF visit • Composite of > 50% sustained eGFR decline, chronic dialysis, renal transplant or sustained eGFR < 15 ml/min/1,73m²
Start date Expected completion date	March 2017 June 2020	March 2017 June 2020	February 2017 December 2019	May 2017 January 2021

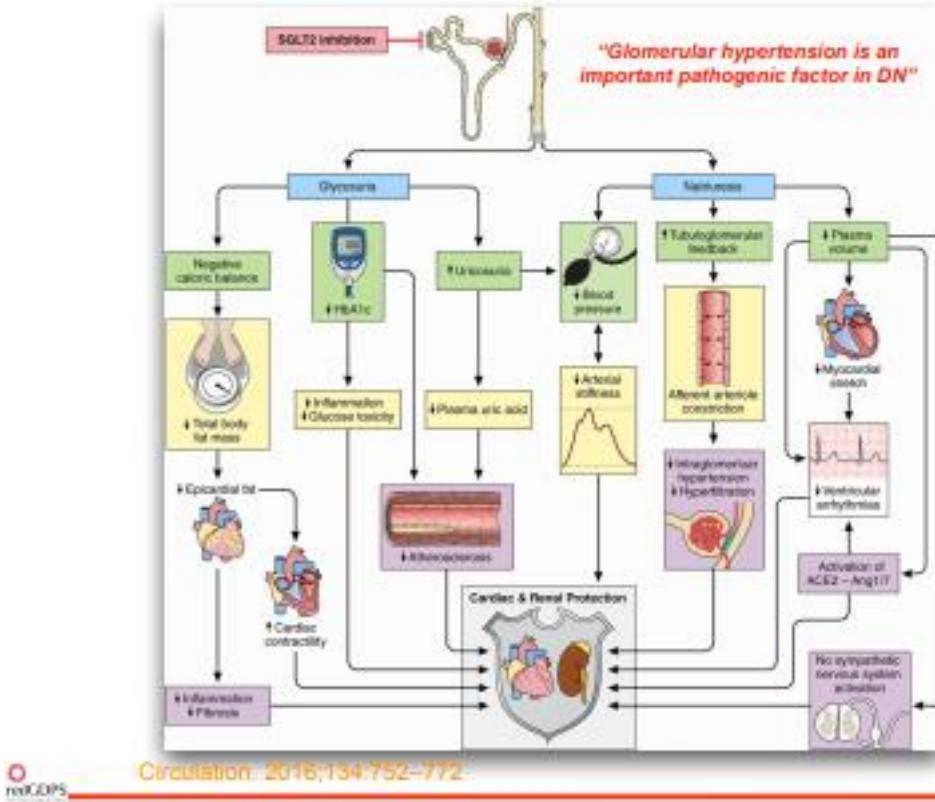
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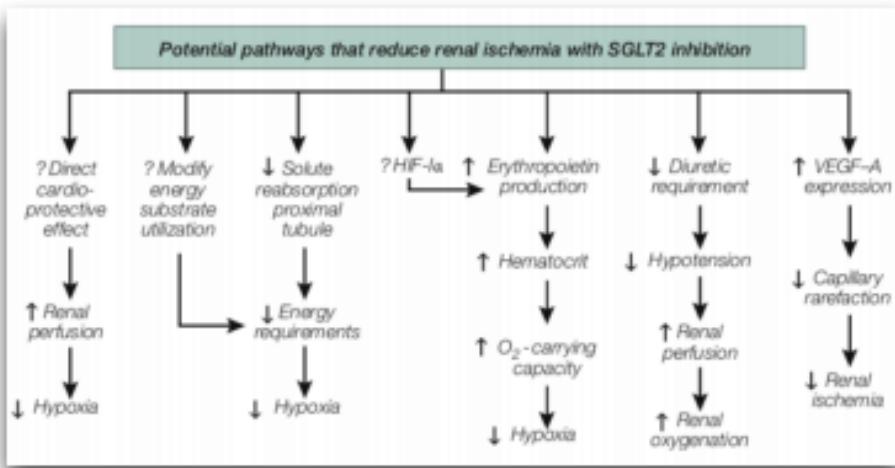
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Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications





ISGLT2 e isquemia renal: implicaciones para futuros ensayos clínicos



T2DM: Epitelio tubular proximal (fibroblastos transformados, fibrosis intersticial y disminución de la EPO).

SGLT2i : Atenua la lesión renal por isquemia-reperfusión.

SGLT2i : Conservando la estructura de los podocitos.

J Am Soc Nephrol. 2017 Apr; 28(4): 1023–1039.

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Take home messages

- CV RCT han demostrado la reducción de los endpoints con **SGLT2i en DM2**

CREDENCE Renal Outcomes Trial of Canagliflozin . Detenido temprano por eficacia positivos

Vías posibles de la **nefroprotección**:

- Inducen natriuresis/diuresis
- Restaura el feedback túbulo-glomerular
- Reduce la tensión renal de oxígeno y la hipoxia
- Preserva las estructuras de los podocitos

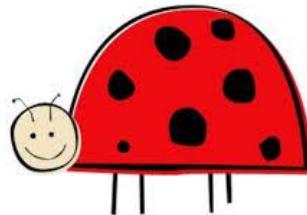
Estudios (práctica clínica) en pacientes (**DM y sin DM**)

EMPA KIDNEY: efectos de Empagliflozin en la progresión de la muerte por ERC y CV en ERC establecida con y sin DM.

DAPA-CKD: Efecto de la dapagliflozina en los resultados renales y la mortalidad por CV en ERC

Diabetes Tipo 2

11º JORNADA
DE ACTUALIZACIÓN TERAPÉUTICA
DE LA redGDPS



MOITAS GRAZAS



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**muchas,
gracias!**
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