Perspectivas para el futuro del paciente con DM: implicaciones de los CVOT en la práctica

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Conflictos de interés

- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Pfizer, Novartis
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer
- Investigación clínica: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

Agenda

- Resultados de los últimos CVOT
- DECLARE
- Qué impacto ha tenido estos estudios en las últimas guías
- Interpretación personal de los resultados
- Actualización en seguridad

DECLARE

Trial Design

17,160 with Type 2 DM
Established CV Disease (6974) or
Multiple Risk Factors (10186)

RANDOMIZE 1:1
DOUBLE BLIND
All other DM Rx per treating MD

DAPAGLIFLOZIN *10 mg DAILY*

PLACEBO

Follow-up visits
In Person Q 6 mo/ telephone Q 3 mo

DURATION
EVENT DRIVEN
≥1390 MACE

Primary EPs
Safety: MACE (CVD/MI/Ischemic Stroke)
Dual Efficacy: CVD/HHF, MACE

Median follow up
4.2 years

Wiviott SD, Raz I, Sabatine MA. *AHJ* 2018

Enrollment Criteria

Diagnosis of T2DM, HbA1c 6.5-12%, CrCl ≥60 ml/min

AND

Established ASCVD (Secondary prevention)
- Ischemic heart disease
- Cerebrovascular disease
- Peripheral Artery Disease

Or

Multiple risk factors for ASCVD (Primary prevention)
Men ≥ 55 yrs and women ≥ 60 yrs with at least one additional risk factor:
- Dyslipidemia
- Hypertension
- Current Tobacco use

Wiviott SD, Raz I, Sabatine MA. *AHJ* 2018

Analytic Plan

MACE
Non-inferiority (Upper Bound CI <1.3): 1-sided α = 0.023

If non-inferior …

Superiority for Dual Primary Efficacy Endpoints (MACE & CVD/HHF)
test each simultaneously with 2-sided α = 0.0231
if either significant, may recycle α to test other at 0.0462

If both significant …

Renal composite
40%↓ eGFR, ESRD, Renal or CV death
$\alpha = 0.0462$

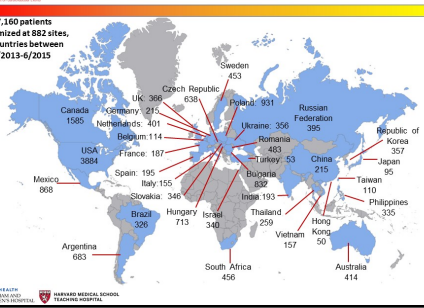
If significant …

All-cause mortality
$\alpha = 0.0462$

Wiviott SD, Raz I, Sabatine MA, *AHJ* 2018

Global Enrollment

17,160 patients randomized at 882 sites, 33 countries between 5/2013-6/2015



Follow-up

Randomized 17,160 patients
Established ASCVD (6,974), MRF (10,186)

Dapagliflozin (N=8582) | **Placebo (N=8578)**

Follow-up median 4.2 yr (IQR 3.9-4.4)

1559 patients experienced MACE
913 experienced CVD/HHF

Premature perm. drug discontinuation	**5.2%/yr**	**6.2%/yr**
Withdrew consent	**0.28%/yr**	**0.37%/yr**
Lost to follow-up	**12 patients**	**18 patients**

Baseline Characteristics

	Full Trial Cohort N = 17160
Age, yrs, Mean (SD)	64 (7)
Female Sex (%)	37
BMI, Mean (SD)	32 (6)
Duration of T2DM, yrs, Median (IQR)	11 (6, 16)
HbA1c (%), Mean (SD)	8.3 (1.2)
eGFR (CKD-EPI), Mean (SD)	85 (16)
Region (%): North America	32
Europe	44
Latin America	11
Asia Pacific	13
Established CV Disease (%)	41
History of Heart Failure (%)	10

P=NS for all between treatment arm comparisons

Baseline Characteristics: Medication Use

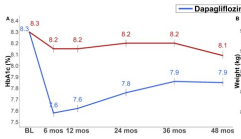
	Full Trial Cohort N = 17160
Glucose lowering therapies (%)	
Metformin	82
Insulin	41
Sulfonylurea	43
DPP4i	17
GLP-1 RA	4
Cardiovascular therapies (%)	
Antiplatelet	61
ACEI/ARB	81
Beta-blocker	53
Statin or Ezetimibe	75

P=NS for all between treatment arm comparisons

Cardiovascular Risk Factors

HbA1c

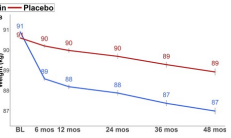
LSM Difference 0.42% (95% CI 0.40-0.45)



All P-values (except BL) <0.001

Weight

LSM Difference 1.8 kg (95% CI 1.7-2.0)



All P-values (except BL) <0.001

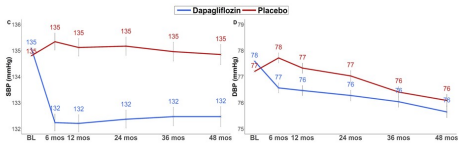
Cardiovascular Risk Factors

SBP

LSM Difference 2.7 mmHg (95% CI 2.4-3.0)

DBP

LSM Difference 0.7mmHg (95% CI 0.6-0.9)



All P-values (except BL) <0.001

All P-values (except BL) <0.001

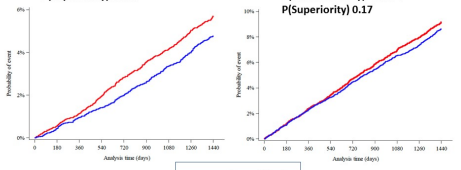
Primary Endpoints

CVD/HHF

4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005

MACE

8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17



Dapagliflozin
Placebo

Secondary Endpoints

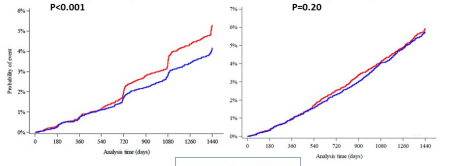
Renal Composite EP

40%↓ eGFR, ESRD, Renal or CV death

4.3% vs. 5.6%
HR 0.76 (0.67-0.87)
P<0.001

All-Cause Mortality

6.2% vs 6.6%
HR 0.93 (0.82-1.04)
P=0.20



Dapagliflozin
Placebo

Endpoints and Components

	Dapagliflozin rate/1000 patient-yr	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P value
CV death/HHF	12.2	14.7	0.83 (0.73-0.95)	0.005*
MACE	22.6	24.2	0.93 (0.84-1.03)	<0.001** 0.17*
40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal or CV death	10.8	14.1	0.76 (0.67-0.87)	
All-cause death	15.1	16.4	0.93 (0.82-1.04)	
HHF	6.2	8.5	0.73 (0.61-0.88)	
Myocardial infarction	11.7	13.2	0.89 (0.77-1.01)	
Ischemic Stroke	6.9	6.8	1.01 (0.84-1.21)	
CV death	7.0	7.1	0.98 (0.82-1.17)	
Non-CV death	6.0	6.8	0.88 (0.73-1.06)	
40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal death	3.7	7.0	0.53 (0.43-0.66)	

0.40 0.50 1.0 1.5
Favors Dapagliflozin ← → Favors Placebo

*P for superiority, **P for non-inferiority

Primary Efficacy Endpoints by Presence of ASCVD vs MRF

Outcomes	Dapagliflozin Events per 1000 pt years	Placebo Events per 1000 pt years	Hazard Ratio (95% CI)	P value for interaction
CV death/HHF	**12.2**	**14.7**	**0.83 (0.73-0.95)**	**0.99**
ASCVD	19.9	23.9	0.83 (0.71-0.98)	
MRF	7.0	8.4	0.84 (0.67-1.04)	
MACE	**22.6**	**24.2**	**0.93 (0.84-1.03)**	**0.25**
ASCVD	36.8	41.0	0.90 (0.79-1.02)	
MRF	13.4	13.3	1.01 (0.86-1.20)	

0.50 1.0 1.5
Favors Dapagliflozin ← → Favors Placebo

Effect on CVD/HHF in Key Subgroups

	CVD/HHF Dapagliflozin n/N	Placebo n/N	Hazard Ratio (95% CI)	HR (95%-CI)	P Value for Interaction
Total Cohort	**417/8582**	**496/8578**		**0.83 (0.73-0.95)**	
Risk Group					**0.99**
ASCVD	272/3474	325/3500		0.83 (0.71-0.98)	
MRF	145/5108	171/5078		0.84 (0.67-1.04)	
History of HF					**0.60**
Yes	142/852	172/872		0.79 (0.63-0.99)	
No	275/7730	324/7706		0.84 (0.72-0.99)	
eGFR					**0.37**
>=90 mL/min/1.73m2	163/4137	163/4025		0.96 (0.77-1.19)	
60 - <90 mL/min/1.73m2	199/3838	252/3894		0.79 (0.66-0.95)	
<60 mL/min/1.73m2	55/606	81/659		0.78 (0.55-1.09)	

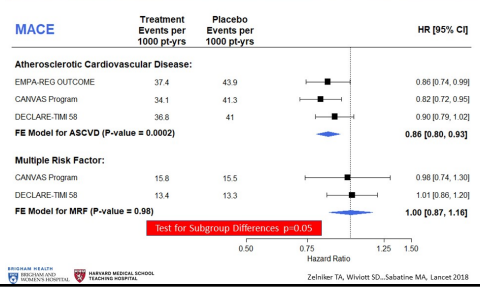
0.50 1.0 1.5
Favors Dapagliflozin ← → Favors Placebo

Summary

In DECLARE – TIMI 58, the largest SGLT2i trial, which included a broad representation of 1° and 2° prevention patients:

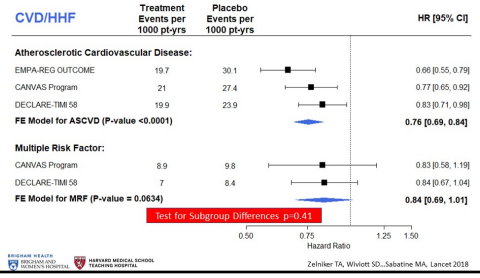
- **Dapagliflozin reduced CVD/HHF, was safe with regard to MACE and appeared to reduce renal events**
  - **↓ CVD/HHF was consistent regardless of baseline ASCVD or HF**
- **Dapagliflozin was safe and generally well-tolerated**
  - **↑ Genital infections & DKA**
  - **No difference in: amputation, fracture, or stroke**
  - **↓ Hypoglycemia, AKI, bladder Ca**

Meta-Analysis of CVOTs: MACE by Presence of ASCVD



Zelniker TA, Wiviott SD...Sabatine MA, Lancet 2018

Meta-Analysis of CVOTs: CVD/HHF by Presence of ASCVD

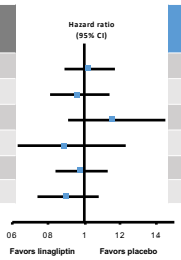


Zelniker TA, Wiviott SD...Sabatine MA, Lancet 2018

Cómo se compara con los otros estudios?

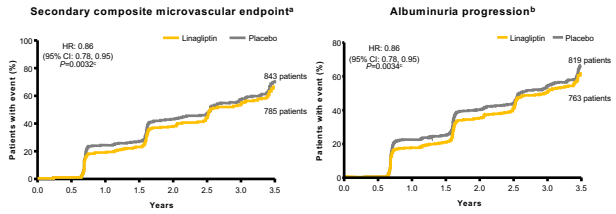
CARMELINA: Primary CV endpoints

Endpoint	Linagliptin group (n=3494)	Placebo group (n=3485)	Hazard ratio (95% CI)	*P* value
3P-MACE[a]	434 (12.4%)	420 (12.1%)	1.02 (0.89, 1.17)	0.74
CV death	255 (7.3%)	264 (7.6%)	0.96 (0.81, 1.14)	0.63
Nonfatal MI	156 (4.5%)	135 (3.9%)	1.15 (0.91, 1.45)	0.23
Nonfatal stroke	65 (1.9%)	73 (2.1%)	0.88 (0.63, 1.23)	0.45
All-cause mortality	367 (10.5%)	373 (10.8%)	0.98 (0.84, 1.13)	0.74
hHF	209 (6.0%)	226 (6.5%)	0.90 (0.74, 1.08)	0.26



[a]Composite of CV death, nonfatal MI, and nonfatal stroke.
3P-MACE, 3-point major adverse cardiovascular events; CI, confidence interval; CV, cardiovascular; hHF, hospitalized heart failure; MI, myocardial infarction

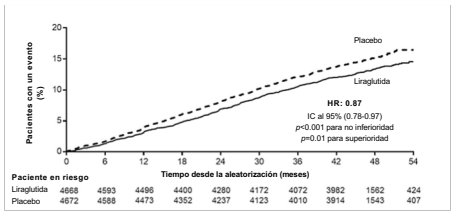
CARMELINA: Secondary microvascular endpoints



[a]Defined as a composite of albuminuria progression, sustained decrease of ≥50% in eGFR, sustained ESRD, death due to kidney disease, retinal photocoagulation, intravitreal injection of an anti-VEGF therapy for diabetic retinopathy, vitreous hemorrhage, or diabetes-related blindness in the right eye.
[b]Defined as a composite of albuminuria progression, doubling of serum creatinine, or transition to ESRD, in patients with baseline albuminuria. Time-to-first event.
[c]Stratified by eGFR (<60 versus ≥60 mL/min/1.73 m2), baseline use of ACE inhibitor (ACEI), ARB, and sulfonylurea, and baseline HbA1c (<8.0% versus ≥8.0%).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; VEGF, vascular endothelial growth factor

LEADER: Desenlaces primarios

muerte por enfermedad CV, infarto de miocardio no fatal o accidente cerebrovascular no fatal

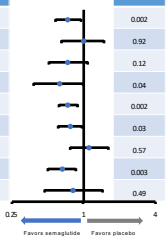


Las incidencias acumuladas se estimaron con el uso del método de Kaplan-Meier y las razones de riesgo con el uso del modelo de regresión de riesgos proporcionales de Cox. El análisis de los datos se detiene a los 54 meses, ya que menos del 10% de los pacientes tenían un tiempo de observación más allá de 54 meses.
IC: intervalo de confianza; CV: cardiovascular; HR: hazard ratio

Marso SP et al. *N Engl J Med* 2016;375:311–322

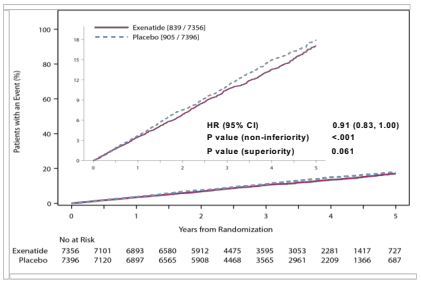
SUSTAIN-6: Primary and secondary endpoint results

Endpoints	Patients with event (%)		HR (95% CI)	*P* value
	Semaglutide (N=1648)	Placebo (N=1649)		
Primary composite outcome (3P-MACE)	108 (6.6)	146 (8.9)	0.74 (0.58, 0.95)	0.002
CV death	44 (2.7)	46 (2.8)	0.98 (0.65, 1.48)	0.92
Nonfatal MI	47 (2.9)	64 (3.9)	0.74 (0.51, 1.08)	0.12
Nonfatal stroke	27 (1.6)	44 (2.7)	0.61 (0.38, 0.99)	0.04
Expanded composite outcome[a]	199 (12.1)	264 (16.0)	0.74 (0.62, 0.89)	0.002
All-cause mortality, nonfatal MI, nonfatal stroke	122 (7.4)	158 (9.6)	0.77 (0.61, 0.97)	0.03
Hospitalization for heart failure	59 (3.6)	54 (3.3)	1.11 (0.77, 1.61)	0.57
Revascularization	83 (5.0)	126 (7.6)	0.65 (0.50, 0.86)	0.003
Hospitalization for unstable angina	22 (1.3)	27 (1.6)	0.82 (0.47, 1.44)	0.49



CV death, nonfatal MI, nonfatal stroke, revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure
3P-MACE, 3-point major adverse cardiovascular events; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction

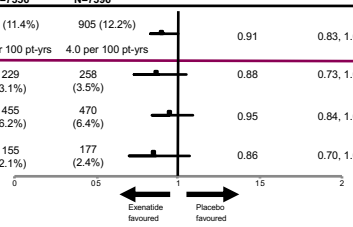
Primary Composite Cardiovascular Outcome
Intention-to-Treat Analysis for Non-inferiority & Superiority



EXSCEL

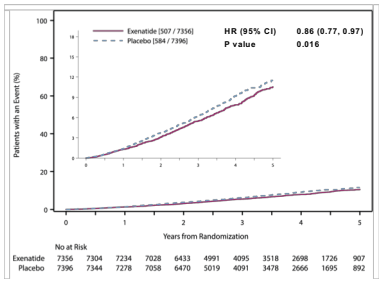
Primary Composite Cardiovascular Outcome
Intention-to-Treat Analysis

	Exenatide N=7356	Placebo N=7396	Hazard Ratio	95% CI	P value
MACE	839 (11.4%) 3.7 per 100 pt-yrs	905 (12.2%) 4.0 per 100 pt-yrs	0.91	0.83, 1.00	<.001 (non-inferiority) 0.061 (superiority)
CV-death	229 (3.1%)	258 (3.5%)	0.88	0.73, 1.05	0.628 (homogeneity among components)
Non-fatal MI	455 (6.2%)	470 (6.4%)	0.95	0.84, 1.09	
Non-fatal stroke	155 (2.1%)	177 (2.4%)	0.86	0.70, 1.07	



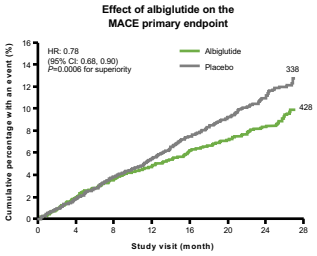
EXSCEL

All-Cause Mortality
Intention-to-Treat Analysis



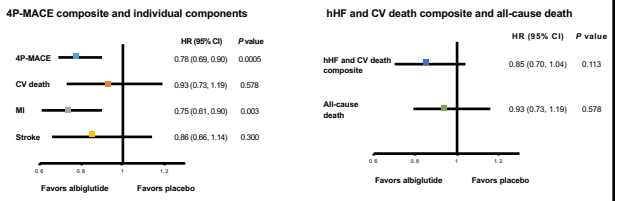
EXSCEL

HARMONY: Primary endpoint results



CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events

HARMONY: Secondary endpoint results



4P-MACE defined as a composite of CV death, nonfatal MI, nonfatal stroke, and revascularization for unstable angina
4P-MACE, 4-point major adverse cardiovascular events; CI, confidence interval; CV, cardiovascular; hHF, hospitalized heart failure; HR, hazard ratio; MI, myocardial infarction
Reproduced with permission from Saseen J et al. Presented at the American Diabetes Association 77th Scientific Sessions, June 9–13, 2017, San Diego, California.

Estudio	MACE	IAM no fatal	Ictus no fatal	Mortalidad CV	Mortalidad total	Hospitalización por falla cardíaca
Inhibidores de SGLT2						
EMPAREG (empaglifozina)	0.86 (0.74-0.99)	0.87 (0.70-1.09)	1.24 (0.92-1.67)	0.62 (0.49-0.77)	0.68 (0.57-0.82)	0.65 (0.5-0.85)
CANVAS (canagliflozina)	0.86 (0.75-0.97)	0.85 (0.69-1.05)	0.90 (0.71-1.15)	0.87 (0.72-1.06)	0.87 (0.74-1.01)	0.67 (0.52-0.87)
DECLARE (dapagliflozina)	0.93 (0.84-1.03)	0.89 (0.77-1.01)	1.01 (0.84-1.21)	0.98 (0.82-1.17)	0.93 (0.82-1.04)	0.73 (0.61-0.88)
Análogos de GLP1						
ELIXA (lixisenatide)	1.02 (0.89-1.17) &	1.03 (0.87-1.22)	1.12 (0.79-1.58)	0.98 (0.78-1.22)	0.94 (0.78-1.13)	0.96 (0.75-1.23)
LEADER (liraglutide)	0.87 (0.76-0.97)	0.88 (0.75-1.03)	0.89 (0.72-1.11)	0.78 (0.66-0.93)	0.85 (0.74-0.97)	0.87 (0.73-1.05)
SUSTAIN (semaglutide)	0.74 (0.58-0.95)	0.74 (0.51-1.08)	0.61 (0.38-0.99)	0.98 (0.65-1.48)	1.05 (0.74-1.50)	1.11 (0.77-1.61)
EXSCEL (exenatide)	0.91 (0.83-1.00)	0.95 (0.84-1.09)	0.86 (0.70-1.07)	0.88 (0.73-1.05)	0.86 (0.77-0.97)	0.94 (0.78-1.13)
HARMONY (albiglutide)	0.78 (0.68-0.90)	0.75 (0.61-0.90)	0.86 (0.66-1.14)	0.93 (0.73-1.19)	0.93 (0.73-1.19)	0.95 (0.79-1.16)

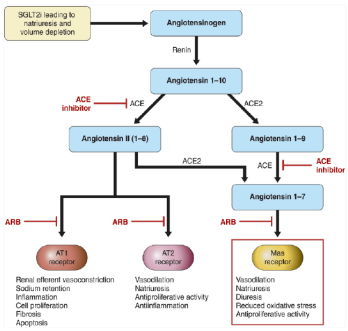
Estudio	MACE	IAM no fatal	Ictus no fatal	Mortalidad CV	Mortalidad total	Hospitalización por falla cardíaca
Inhibidores de DPP4						
SAVOR (saxagliptina)	1.00 (0.89-1.12)	0.95 (0.80-1.12)	1.11 (0.88-1.39)	1.03 (0.87-1.22)	1.11 (0.96-1.27)	1.27 (1.07-1.51)
EXAMINE (alogliptina)	0.96 (<1.16)	1.08 (0.88-1.33)	0.91 (<1.14)	0.85 (0.66-1.10)	0.88 (0.71-1.09)	1.07 (0.79-1.46)
TECOS (sitagliptina)	0.99 (0.89-1.11)	0.95 (0.81-1.11) *	0.97 (0.79-1.19) *	1.03 (0.89-1.19)	1.01 (0.90-1.14)	1.00 (0.83-1.20)
CARMELINA (linagliptina)	1.02 (0.89-1.17)	1.15 (0.91-1.45)	0.88 (0.63-1.23)	0.96 (0.81-1.14)	0.98 (0.84-1.13)	0.90 (0.74-1.08)
Otros						
PROACTIVE (pioglitazone)	0.84 (0.72-0.98) $	0.83 (0.65-1.06)	0.81 (0.61-1.07)	NS	0.96 (0.78-1.18)	1.23 #
TOSCA-IT @ (sulfonilureas)	0.96 (0.74-1.26) ¡	0.87 (0.48-1.55)	0.79 (0.41-1.53)	NA	1.10 (0.75-1.61)	NS
ORIGIN (insulina glargine)	1.02 (0.94-1.11)	1.02 (0.88-1.19)*	1.03 (0.89-1.21)*	1.00 (0.89-1.13)	0.98 (0.90-1.08)	0.90 (0.77-1.05)
DEVOTE (insulina degludec)*	0.91 (0.78-1.06)	0.85 (0.68-1.06)	0.90 (0.65-1.23)	0.96 (0.76-1.21)	0.91 (0.76-1.11)	NA

	Desenlace compuesto microvascular	Desenlace compuesto renal	Nueva aparición microalbuminuria	Doblamiento creatinina	Terapia reemplazo renal	Muerte renal
Inhibidores de SGLT2						
EMPAREG (empagliflozina)	0.62 (0.54-0.70)	0.61 (0.53-0.70)	0.62 (0.54-0.72)	0.56 (0.39-0.79)	0.45 (0.21-0.97)	NA
CANVAS (canagliflozina)	0.86 (0.75-0.97)	0.60 (0.47-0.77)	0.80 (0.79-0.88)	0.50 (0.30-0.84)	0.77 (0.30-1.97)	NA
DECLARE (dapagliflozina)	NA	0.53 (0.43-0.66)	NA	NA	NA	NA
Inhibidores de DPP4						
SAVOR (saxagliptina) [31]	NA	1.08 (0.88-1.32)	NA	1.1 (0.89-1.36)	0.90 (0.61-1.32)	NA
EXAMINE (alogliptina)	NA	NA	NA	NA	NA	NA
TECOS (sitagliptina)	NA	NA	NA	NA	NA	NA
CARMELINA (linagliptina)	0.86 (0.78-0.95)	0.98 (0.82-1.18)	NA	NA	0.87 (0.69-1.10)	NS
Análogos de GLP1						
ELIXA (lixisenatide) [32]	NA	NA	NA	1.16 (0.74-1.82)	NS	NS
LEADER (liraglutide)	0.84 (0.79-0.97)	0.78 (0.67-0.92)	0.74 (0.60-0.91)	0.88 (0.66-1.18)	0.87 (0.6-1.24)	1.59 (0.52-4.87)
SUSTAIN-6 (semaglutide)	NA	0.64 (0.46-0.88)	0.54 (0.37-0.77)	1.28 (0.64-2.58)	0.91 (0.40-2.07)	NA
HARMONY (albiglutide)	NA	NA	NA	NA	NA	NA

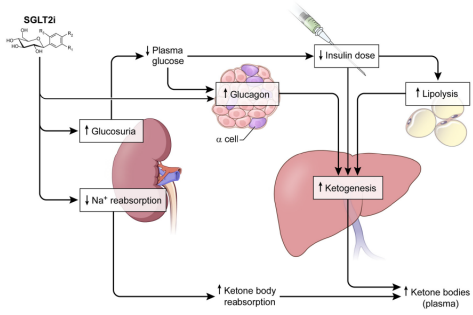
Nuevos mecanismos de protección

Consumo de O2

- Disminuye el consumo cortical de O2
- Aumenta el consumo medular de O2
- Bajo algunas circunstancias, el efecto final puede ser diferente:
  - En agudo, con depleción de volumen y otros factores tóxicos como AINEs y uso de medios de contraste puede predisponer a lesion renal aguda
  - En el crónico, el aumento de Hb podría explicar el efecto nefroprotector



De Albuquerque Rocha N. Diab Vasc Dis Res. https://doi.org/10.1177/1479164118783753

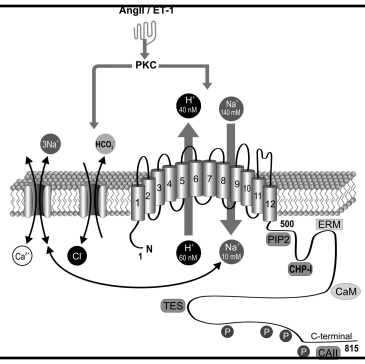


Taylor SI. J Clin Endocrinol. Metab. 2015; epub junio.

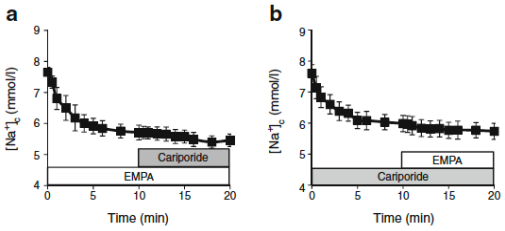
Glucagon y efectos vasculares

- Niveles altos de glucagon:
  - Vasodilatación
  - Aumento de flujo plasmático renal
  - Aumento de TFG
  - Aumento de natriuresis en estados de ayuno

Wanner C. Am J Med. 2017;130:S63

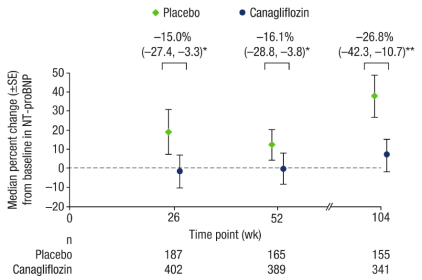


Efecto en Na^+-H^+



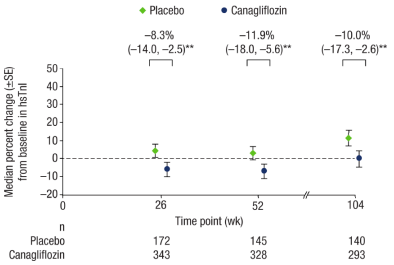
Baartscheer A. Diabetologia. 2016; online oct 16.

BNP



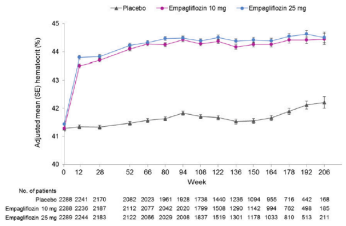
Januzzi JL. JACC. 2017. Online June 8.

Troponina



Januzzi JL. JACC. 2017. Online June 8.

EMPAREG: efecto en hematocrito



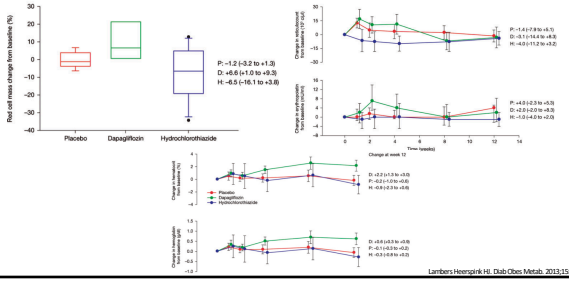
Inzucchi SE. Diabetes Care. 2018;41:356

Regulación de secreción de eritropoyetina

- Caída de perfusión renal
- Hipoxia
- Sales de cobalto
- Andrógenos
- Alcalosis
- catecolaminas

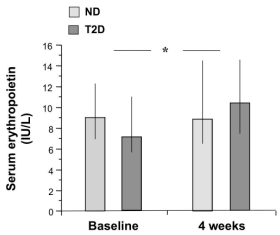
Ganong Physiology 2018. Chapter 38

Masa de glóbulos rojos

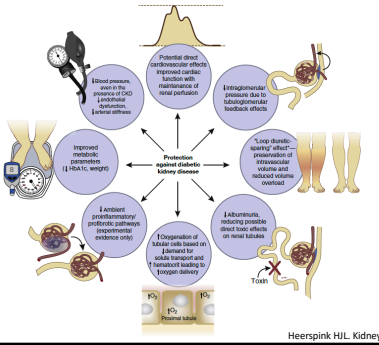


Lambers Heerspink HJ. Diab Obes Metab. 2013;15:853

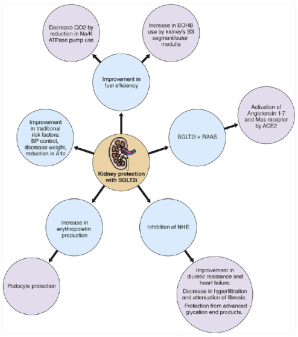
Niveles de EPO con empagliflozina



Ferrannini E. Diabetes Care. 2017;40:771



Heerspink HJL. Kidney Intl. 2018. early online.



De Albuquerque Rocha N, Diab Vasc Dis Res. https://doi.org/10.1177/1479164118783753

Que hay nuevo en eventos adversos?

ITU

EMPAREG: Adverse events consistent with urinary tract infection

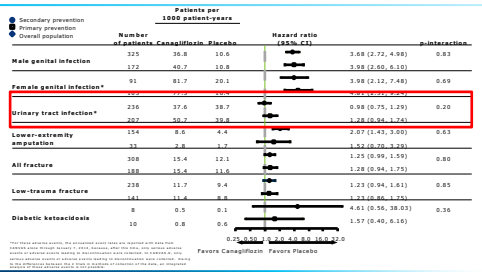
	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Events consistent with UTI	423 (18.1%)	8.21	426 (18.2%)	8.02	416 (17.8%)	7.75
Events leading to discontinuation	10 (0.4%)	0.17	22 (0.9%)	0.37	19 (0.8%)	0.31
By sex						
Male	158 (9.4%)	3.96	180 (10.9%)	4.49	170 (10.1%)	4.09
Female	265 (40.6%)	22.81	246 (35.5%)	18.83	246 (37.3%)	20.38

Rate = per100 patient-years

Patients treated with ≥1 dose of study drug
Based on 79 MedDRA preferred terms

52

Effects of Canagliflozin Versus Placebo on Safety Outcomes



*For these adverse events, the presented event rates are reported with data that ended some through January 7, 2016. Analyses, after the fact, only serious adverse events or adverse events leading to discontinuation were collected. In CANVAS-R, only serious adverse events or adverse events leading to discontinuation were collected. During the initial phase of the study, adverse events were collected at interims. At the time, we recognized that some adverse events were not being reported.

Mahaffey KW, et al. *Circulation*. 2017. doi:10.1161/CIRCULATIONAHA.117.032038.

CANVAS Program

Key Safety Events

	Dapagliflozin (%)	Placebo (%)	Between Group Comparison
Treatment emergent SAE	34.1	36.2	P<0.001
Treatment emergent AE leading to drug D/C	8.1	6.9	P=0.01
Major Hypoglycemia	0.7	1.0	P=0.02
Diabetic Ketoacidosis* (DKA)	0.3	0.1	P=0.02
Amputation	1.4	1.3	NS
Fracture	5.3	5.1	NS
Acute Kidney Injury	1.5	2.0	P=0.002
Symptoms of volume depletion	2.5	2.4	NS
Genital infection (SAE, DAE)	0.9	0.1	P<0.001
Urinary tract infection (SAE, DAE)	1.5	1.6	NS
Fournier's Gangrene	0.01	0.08	NS
Cancer of Bladder*	0.3	0.5	P=0.02

*CEC Adjudicated

Lesión renal aguda

FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)

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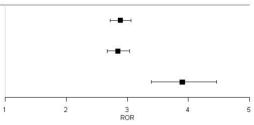
[06-14-2016]

Lesión renal aguda y FAERS

Reporting Odds Ratio of ARF with SGLT2-i and FDA Warning

Subgroup	SGLT2-i	Non-Sglt2-i
Whole Observation Period	1224 / 18915	85512 / 3813100
Before FDA Warning	991 / 15405	76142 / 3368833
After FDA Warning	232 / 2277	9266 / 364420

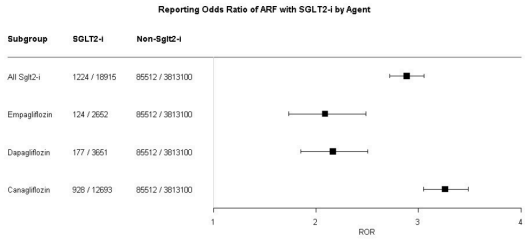


Consideraciones:

- El denominador no es número de pacientes, es número de eventos adversos reportados!
- Los pacientes con iSGLT2 usaron más diuréticos

Perlman A. Nutr Metab Cardiovasc Dis. 2017; doi: 10.1016/j.numecd.2017.10.011

Lesión renal aguda y FAERS



Perlman A. Nutr Metab Cardiovasc Dis. 2017; doi: 10.1016/j.numecd.2017.10.011

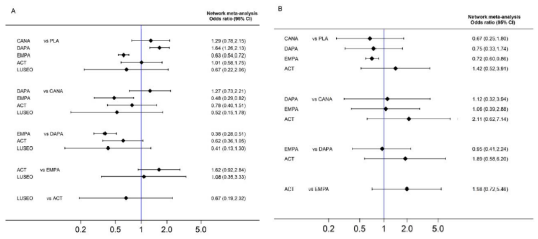
Network metanálisis

Eventos renales compuestos		
Producto	Efecto	IC 95%
Canagliflozina	1.29	0.78-2.15
Dapagliflozina	1.64	1.26-2.13
Empagliflozina	0.38	0.28-0.51
Tratamiento acdtivo	1.01	0.58-1.75

Eventos de falla renal aguda		
Producto	Efecto	IC 95%
Canagliflozina	0.67	0.26-1.73
Dapagliflozina	0.75	0.33-1.74
Empagliflozina	0.72	0.60-0.86
Tratamiento active	1.42	0.52-3.89

Tang H. Diab Obes Metab. 2017;19:1106

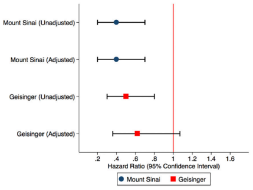
Network metanalisis: eventos renales



Tang H. Diab Obes Metab. 2017;19:1106

	Mount Sinai cohort			Geisinger cohort		
	User (n = 372)	Nonuser (n = 372)	P1	User (n = 1,207)	Nonuser (n = 1,207)	P2
AKI_{KDIGO}–inpatient	14 (3.8)	36 (9.7)	0.002	26 (2.2)	55 (4.6)	0.001
AKI_{ICD}	22 (5.9)	40 (10.8)	0.02	15 (1.2)	36 (3.0)	0.003
Peak creatinine in AKI_{KDIGO} events	1.6 (1.4–1.8)	1.9 (1.6–2.4)	0.02	1.7 (1.4–2.6)	1.6 (1.3–2.4)	0.91
Change in serum creatinine during AKI_{KDIGO} events	0.5 (0.4–0.7)	0.9 (0.8–1.3)	0.004	0.6 (0.5–1.0)	0.6 (0.4–1.2)	0.80
Need for acute dialysis	1 (0.3)	1 (0.3)	1.00	0 (0.0)	1 (0.1)	0.317

P1 and P2 are P values for primary and secondary analyses, respectively.



Nadkarkin GN. Diabetes Care. 2017;40:1479

Consideraciones de este metanálisis

- Los resultados de empagliflozina fueron mayormente derivados de EMPAREG
  - Cuando se excluyó se pierde el efecto protector observado en el metanálisis
  - Contribuyó el 95% de todo el efecto de empagliflozina
- No se incluyó (por el tiempo de publicación) los datos de CANVAS ni DECLARE
- Estos incluyen mayor número de pacientes que los estudios de fase III

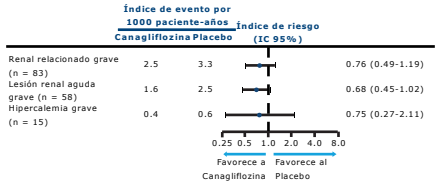
Other adverse events (1)

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Diabetic ketoacidosis*	1 (<0.1%)	0.02	3 (0.1%)	0.05	1 (<0.1%)	0.02
Acute kidney injury†	155 (6.6%)	2.77	121 (5.2%)	2.07	125 (5.3%)	2.12
Events consistent with volume depletion§	115 (4.9%)	2.04	115 (4.9%)	1.97	124 (5.3%)	2.11
Serious events	24 (1.0%)	0.42	19 (0.8%)	0.32	26 (1.1%)	0.43
Events leading to discontinuation	7 (0.3%)	0.12	1 (<0.1%)	0.02	4 (0.2%)	0.07
Venous thrombotic events**	20 (0.9%)	0.35	9 (0.4%)	0.15	21 (0.9%)	0.35

Rate = per100 patient-years
Patients treated with ≥1 dose of study drug
*Based on 4 MedDRA preferred terms. †Based on 1 standardised MedDRA query
§Based on 8 MedDRA preferred terms. **Based on 1 standardised MedDRA query

EMPA-REG OUTCOME®

Seguridad Renal



Mahaffey KW, et al. Circulation. 2017. doi:10.1161/CIRCULATIONAHA.117.032038.

CANVAS Program

Key Safety Events

	Dapagliflozin (%)	Placebo (%)	Between Group Comparison
Treatment emergent SAE	34.1	36.2	P<0.001
Treatment emergent AE leading to drug D/C	8.1	6.9	P=0.01
Major Hypoglycemia	0.7	1.0	P=0.02
Diabetic Ketoacidosis* (DKA)	0.3	0.1	P=0.02
Amputation	1.4	1.3	NS
Fracture	5.3	5.1	NS
Acute Kidney Injury	1.5	2.0	P=0.002
Symptoms of volume depletion	2.5	2.4	NS
Genital infection (SAE, DAE)	0.9	0.1	P<0.001
Urinary tract infection (SAE, DAE)	1.5	1.6	NS
Fournier's Gangrene	0.01	0.08	NS
Cancer of Bladder*	0.3	0.5	P=0.02

*CEC Adjudicated

Otros eventos adversos

Key Safety Events

	Dapagliflozin (%)	Placebo (%)	Between Group Comparison
Treatment emergent SAE	34.1	36.2	P<0.001
Treatment emergent AE leading to drug D/C	8.1	6.9	P=0.01
Major Hypoglycemia	0.7	1.0	P=0.02
Diabetic Ketoacidosis* (DKA)	0.3	0.1	P=0.02
Amputation	1.4	1.3	NS
Fracture	5.3	5.1	NS
Acute Kidney Injury	1.5	2.0	P=0.002
Symptoms of volume depletion	2.5	2.4	NS
Genital infection (SAE, DAE)	0.9	0.1	P<0.001
Urinary tract infection (SAE, DAE)	1.5	1.6	NS
Fournier's Gangrene	0.01	0.08	NS
Cancer of Bladder*	0.3	0.5	P=0.02

*CEC Adjudicated

Resultados comparativos de Amputaciones de la Extremidad Inferior en: Empa Reg Outcome y Canvas.

	EMPA-REG OUTCOME[1,1*]			CANVAS[2]			CANVAS-R[2]	
	Placebo (N=2333)	EMPA 10 (N=2345)	EMPA 25 (N=2342)	Placebo (N=1441)	CANA 100 (N=1445)	CANA 300 (N=1441)	Placebo (N=2903)	CANA (N=2904)
Patients with lower limb amputation n (%)	43 (1.8)	42 (1.8)	46 (2.0)	22 (1.5)	50 (3.5)	45 (3.1)	25 (0.9)	45 (1.5)
Lower limb amputation incidence rate (per 1,000 patient-years)	6.5	6.2	6.8	2.8	6.2	5.5	4.2	7.5
Hazard ratio (95% CI)	-	0.96 (0.63, 1.47)	1.04 (0.69, 1.58)	-	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	-	1.80 (1.10, 2.93)

*In empagliflozin clinical trials, procedures such as amputations have been classified as therapeutic procedures, and are not routinely captured as adverse events. Post-hoc analyses of amputations in the empagliflozin clinical trial database were performed searching concomitant therapies, comment fields for adverse event listings and case narratives (fields that may contain information regarding amputations). The analysis of the cases of LLA from empagliflozin clinical trials should be interpreted with caution considering the limitations inherited from this strategy of case retrieval. For 19 patients with an event but without an event date the event date was estimated; results are comparable when these patients were excluded from the analyses.

Hazard ratio for pooled doses of empagliflozin: HR 1.00 (95% CI 0.70, 1.44)

Direct comparisons of trials cannot be made due to differences in study design, populations and methodology

1. Kohler et al. Adv Ther. 2017;34(7):1-32 and data on file. 2. https://www.fda.gov/Drugs/DrugSafety/ucm587601.htm (accessed 6-Jan-2017)

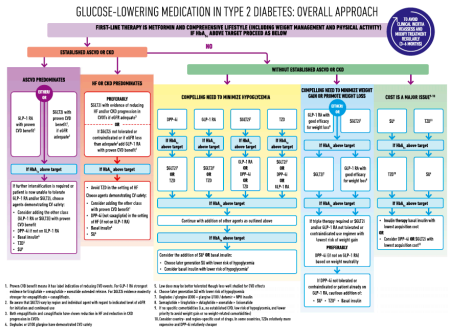
CANVAS Program

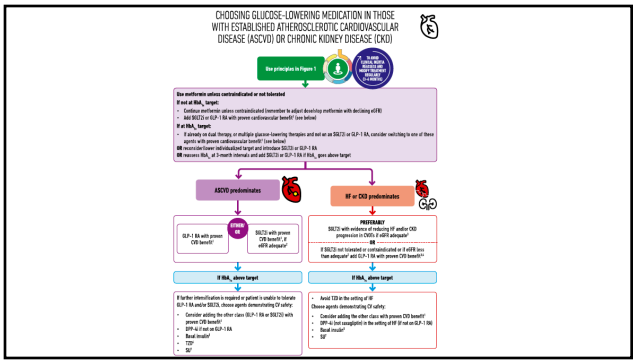
Cómo implementamos esto?

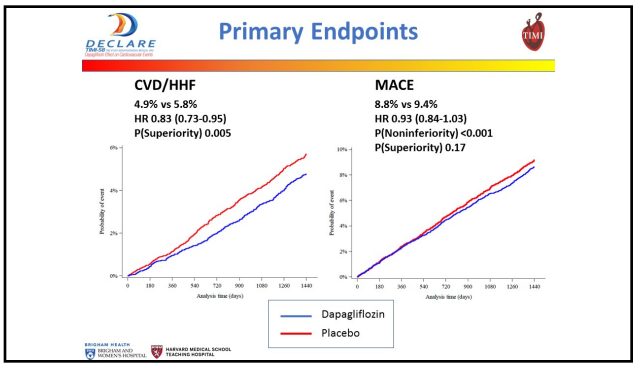
Reflexiones sobre puntos relevantes

- Parece que los iSGLT-2 reducen MACE en el contexto de prevención secundaria
- La reducción de hospitalización por falla cardíaca se produce independientemente de la historia previa de falla cardíaca
- Nefroprotección!

Analizando las guías…




CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)
Use principles in Figure 1
Use metformin unless contraindicated or not tolerated
If not at HbA1c target:
Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (see below)
If at HbA1c target:
If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (see below)
OR reconsider lower individualized target and intensify SGLT2i or GLP-1 RA
OR reassess HbA1c at 3-month intervals and add SGLT2i or GLP-1 RA if HbA1c goes above target
ASCVD predominates
HF or CKD predominates
ASCVD OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1], if eGFR adequate[2]
PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs, if eGFR adequate[2]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]
If HbA1c above target
If HbA1c above target
If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit[1]
DPP-4i if not on GLP-1 RA
Basal insulin[3]
TZD[3]
SU[3]
Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
Consider adding the other class with proven CVD benefit[1]
DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
Basal insulin[3]
SU[3]


DECLARE
TIMI 58
Dapagliflozin Effect on Cardiovascular Events
Primary Endpoints
TIMI
CVD/HHF
4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005
MACE
8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17
Probability of event
Analysis time (days)
Dapagliflozin
Placebo
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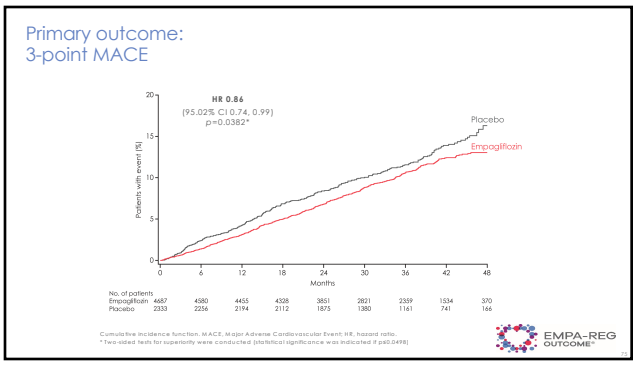
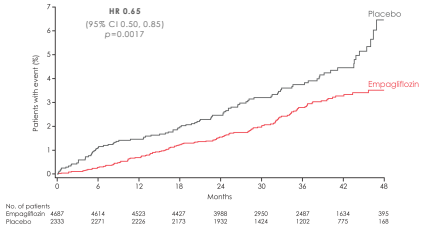

Primary outcome:
3-point MACE
HR 0.86
(95.02% CI 0.74, 0.99)
p=0.0382*
Placebo
Empagliflozin
Patients with event (%)
Months
No. of patients
Empagliflozin 4687 4580 4455 4328 3851 2821 2359 1534 370
Placebo 2333 2256 2194 2112 1875 1380 1161 741 166
Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
*Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)
EMPA-REG OUTCOME

Hospitalisation for heart failure

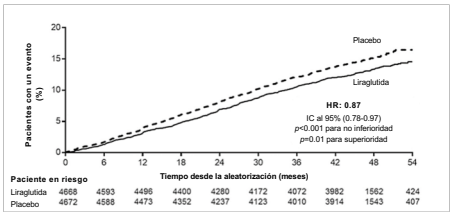


Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

LEADER: Desenlaces primarios

muerte por enfermedad CV, infarto de miocardio no fatal o accidente cerebrovascular no fatal

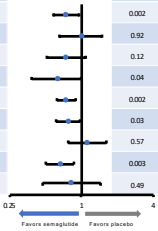


Las incidencias acumuladas se estimaron con el uso del método de Kaplan-Meier y las razones de riesgo con el uso del modelo de regresión de riesgos proporcionales de Cox. El análisis de los datos se detiene a los 54 meses, ya que menos del 10% de los pacientes tenían un tiempo de observación más allá de 54 meses.
IC: intervalo de confianza; CV: cardiovascular; HR: hazard ratio

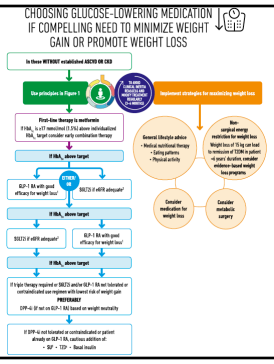
Marso SP et al. *N Engl J Med* 2016;375:311–322

SUSTAIN-6: Primary and secondary endpoint results

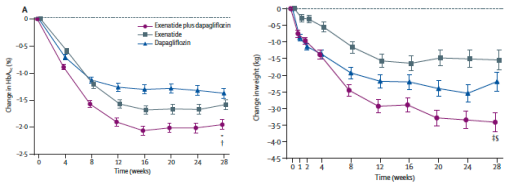
Endpoints	Patients with event (%)		HR (95% CI)	P value
	Semaglutide (N=1648)	Placebo (N=1649)		
Primary composite outcome (3P-MACE)	108 (6.6)	146 (8.9)	0.74 (0.58, 0.95)	0.002
CV death	44 (2.7)	46 (2.8)	0.98 (0.65, 1.48)	0.92
Nonfatal MI	47 (2.9)	64 (3.9)	0.74 (0.51, 1.08)	0.12
Nonfatal stroke	27 (1.6)	44 (2.7)	0.61 (0.38, 0.99)	0.04
Expanded composite outcome[a]	199 (12.1)	264 (16.0)	0.74 (0.62, 0.89)	0.002
All-cause mortality, nonfatal MI, nonfatal stroke	122 (7.4)	158 (9.6)	0.77 (0.61, 0.97)	0.03
Hospitalization for heart failure	59 (3.6)	54 (3.3)	1.11 (0.77, 1.61)	0.57
Revascularization	83 (5.0)	126 (7.6)	0.65 (0.50, 0.86)	0.003
Hospitalization for unstable angina	22 (1.3)	27 (1.6)	0.82 (0.47, 1.44)	0.49



CV death, nonfatal MI, nonfatal stroke, revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure
[a]MACE, 3-point major adverse cardiovascular events; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction

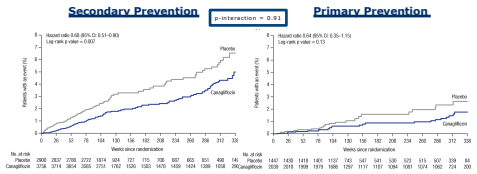


DURATION-8: dapagliflozina vs exenatide semanal



Frias JP. Lancet Diab Endocrinol. 2016. Online Sep 15.

Hospitalization for Heart Failure

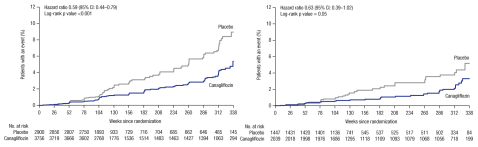


Mahaffey KW, et al. Circulation. 2018 Jan 23;137(4):323-334. doi: 10.1161/CIRCULATIONAHA.117.032038. Epub 2017 Nov 13.

CANVAS Program

Renal Composite*

Secondary Prevention | p-interaction = 0.73 | **Primary Prevention**



*Renal Composite: composite renal outcome comprising a 40% reduction in estimated glomerular filtration rate, requirement for renal replacement therapy, or renal death.

Mahaffey KW, et al. Circulation. 2018 Jan 23;137(4):323-334. doi: 10.1161/CIRCULATIONAHA.117.032038. Epub 2017 Nov 13.

CANVAS Program

Effect on CVD/HHF in Key Subgroups

	CVD/HHF				
	Dapagliflozin n/N	Placebo n/N	Hazard Ratio (95% CI)	HR (95%-CI)	P Value for Interaction
Total Cohort	**417/8582**	**496/8578**		**0.83 (0.73-0.95)**	
Risk Group					**0.99**
ASCVD	272/3474	325/3500		0.83 (0.71-0.98)	
MRF	145/5108	171/5078		0.84 (0.67-1.04)	
History of HF					**0.60**
Yes	142/852	172/872		0.79 (0.63-0.99)	
No	275/7730	324/7706		0.84 (0.72-0.99)	
eGFR					**0.37**
>=90 mL/min/1.73m2	163/4137	163/4025		0.96 (0.77-1.19)	
60 - <90 mL/min/1.73m2	199/3838	252/3894		0.79 (0.66-0.95)	
<60 mL/min/1.73m2	55/606	81/659		0.78 (0.55-1.09)	

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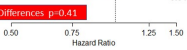
Meta-Analysis of CVOTs: CVD/HHF by Presence of ASCVD

CVD/HHF	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	HR [95% CI]
Atherosclerotic Cardiovascular Disease:			
EMPA-REG OUTCOME	19.7	30.1	0.66 [0.55, 0.79]
CANVAS Program	21	27.4	0.77 [0.65, 0.92]
DECLARE-TIMI 58	19.9	23.9	0.83 [0.71, 0.98]
FE Model for ASCVD (P-value <0.0001)			**0.76 [0.69, 0.84]**
Multiple Risk Factor:			
CANVAS Program	8.9	9.8	0.83 [0.58, 1.19]
DECLARE-TIMI 58	7	8.4	0.84 [0.67, 1.04]
FE Model for MRF (P-value = 0.0634)			**0.84 [0.69, 1.01]**

Test for Subgroup Differences p=0.41



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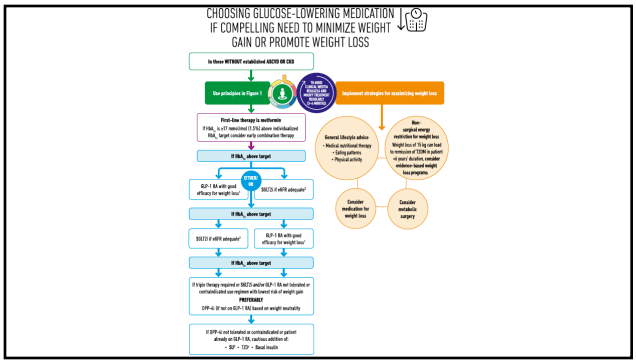
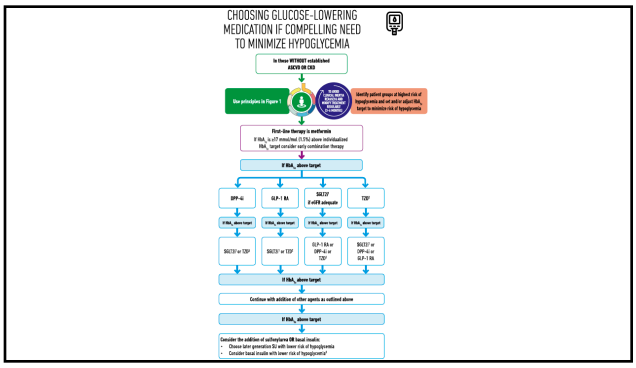
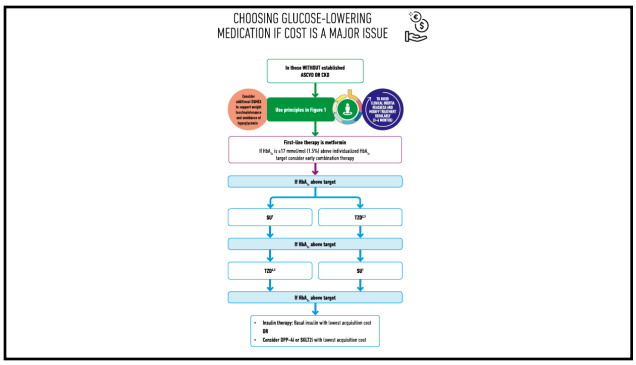
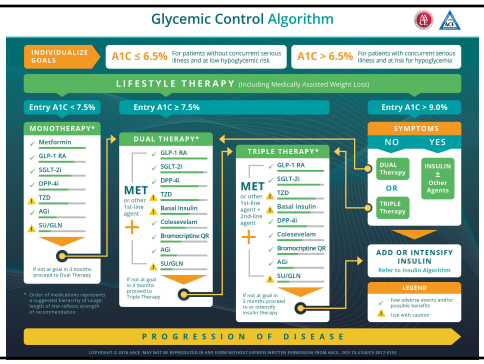
Zelniker TA, Wiviott SD...Sabatine MA. Lancet 2018


CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
In those WITHOUT established ASCVD OR CKD
Use principles in Figure 1
Implement strategies for maximizing weight loss
First-line therapy is metformin
If HbA1c is ≥1.5 mmol/mol (1.5%) above individualized HbA1c target consider early combination therapy
If HbA1c above target
OR
GLP-1 RA with good efficacy for weight loss[1]
SGLT2i if eGFR adequate[2]
If HbA1c above target
SGLT2i if eGFR adequate[2]
GLP-1 RA with good efficacy for weight loss[1]
If HbA1c above target
If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality
If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
• SU[3] + T2D[4] + Basal insulin
General lifestyle advice
• Medical nutritional therapy
• Eating patterns
• Physical activity
Non-surgical energy restriction for weight loss
Weight loss of 15 kg can lead to remission of T2DM in patient <6 years' duration; consider evidence-based weight loss programs
Consider medication for weight loss
Consider metabolic surgery


CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
In those WITHOUT established ASCVD OR CKD
Use principles in Figure 1
Identify patient groups at highest risk of hypoglycemia and set and/or adjust HbA1c target to minimize risk of hypoglycemia
First-line therapy is metformin
If HbA1c is ≥1.5 mmol/mol (1.5%) above individualized HbA1c target consider early combination therapy
If HbA1c above target
DPP-4i
GLP-1 RA
SGLT2i
If eGFR adequate
T2D[4]
If HbA1c above target
If HbA1c above target
If HbA1c above target
If HbA1c above target
SGLT2i[2] or T2D[4]
SGLT2i[2] or T2D[4]
GLP-1 RA or DPP-4i or T2D[4]
SGLT2i[2] or DPP-4i or GLP-1 RA
If HbA1c above target
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of sulfonylurea OR basal insulin:
• Choose later generation SU with lower risk of hypoglycemia
• Consider basal insulin with lower risk of hypoglycemia[5]


CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE
In those WITHOUT established ASCVD OR CKD
Consider additional CDM3 for renal protection and/or cardiovascular and mortality benefit
Use principles in Figure 1
First-line therapy is metformin
If HbA1c is ≥1.5 mmol/mol (1.5%) above individualized HbA1c target consider early combination therapy
If HbA1c above target
SU[7]
T2D[4,7]
If HbA1c above target
T2D[4,7]
SU[7]
If HbA1c above target
• Insulin therapy: Basal insulin with lowest acquisition cost
OR
• Consider DPP-4i or SGLT2i with lowest acquisition cost



Cuál agente para quién?

	iSGLT2	GLP1RA (basado en estructura GLP1)	iDPP4
Enfermedad aterosclerótica			
Insuficiencia cardíaca			
Nefropatía diabética			
Peso			
Propenso a cetosis			
Fragilidad/fractura previa/caídas			
Amputación previa			
Insuficiencia renal crónica (estadio 4-5)			
Infección genital a repetición			

Conclusiones

- Cada vez hay mayor justificación para pasar a los inhibidores de SGLT2 como primera opción en segunda línea de tratamiento
- Tenemos opciones terapéuticas que nos reducen desenlaces duros más allá del beneficio del control glicémico
- Nos hemos olvidado del impacto que tiene falla cardíaca e insuficiencia renal
- Parece no aumentar riesgo de ITU y lesión renal aguda, no tenemos claro aún sobre amputaciones

Preguntas…

chenku2409@gmail.com

Puede descargar la presentación en:

www.EndoDrChen.com