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 y sus subestudios
- 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 $\alpha = 0.023$

If non-inferior …

Superiority for Dual Primary Efficacy Endpoints (MACE & CVD/HHF)
test each simultaneously with 2-sided $\alpha = 0.0231$
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

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

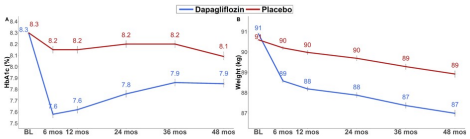
Cardiovascular Risk Factors

HbA1c

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

Weight

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



All P-values (except BL) <0.001

All P-values (except BL) <0.001

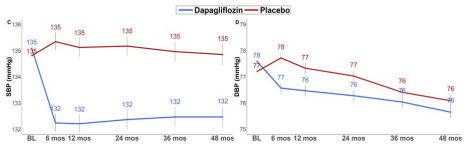
Cardiovascular Risk Factors

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

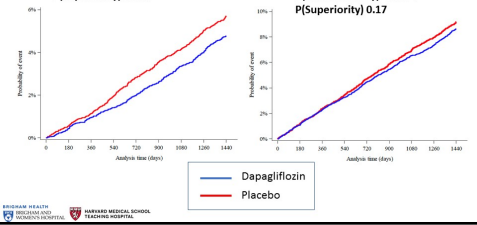
Primary Endpoints

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



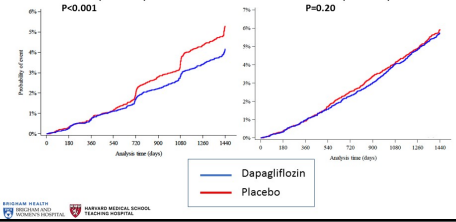
Secondary Endpoints

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



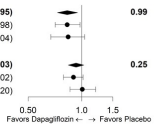
Endpoints and Components

	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)	

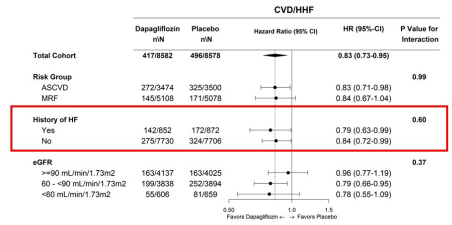
*P for superiority, **P for non-inferiority

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)	



Effect on CVD/HHF in Key Subgroups

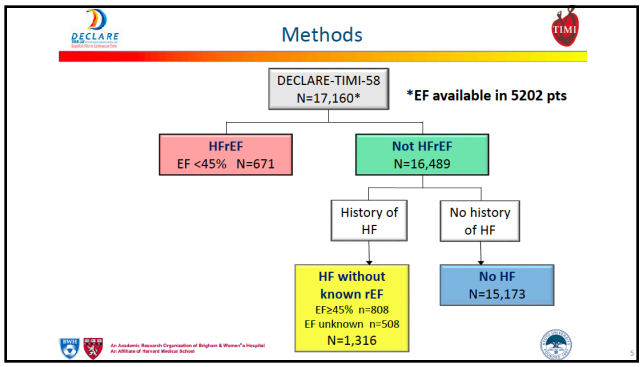


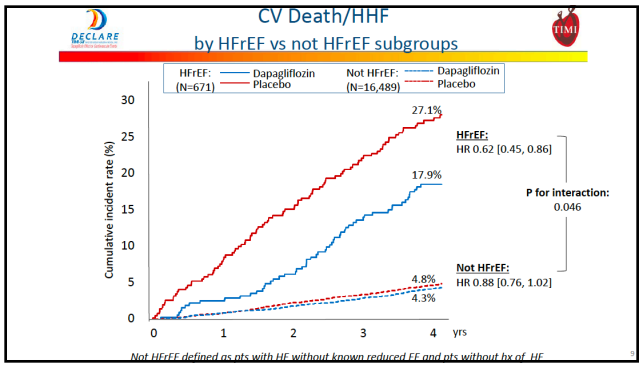
Summary

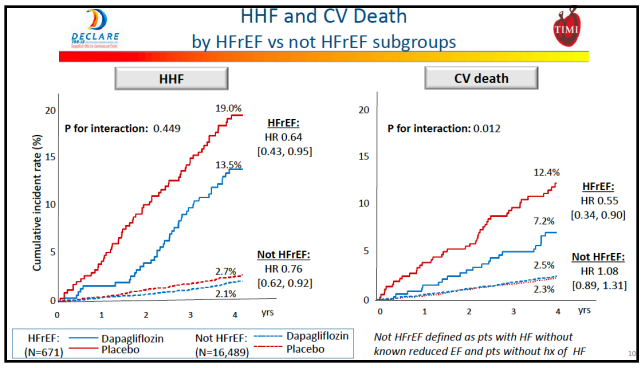
In DECLARE – TIMI 58, the largest SGLT2i trial, which included a broad representation of 1° and 2° prevention patients:

- **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**

Subgrupos por falla cardíaca


Methods
DECLARE-TIMI-58
N=17,160*
*EF available in 5202 pts
HFrEF
EF <45% N=671
Not HFrEF
N=16,489
History of HF
No history of HF
HF without known rEF
EF≥45% n=808
EF unknown n=508
N=1,316
No HF
N=15,173


CV Death/HHF
by HFrEF vs not HFrEF subgroups
HFrEF: (N=671) Dapagliflozin Placebo
Not HFrEF: (N=16,489) Dapagliflozin Placebo
Cumulative incident rate (%)
27.1%
17.9%
4.8%
4.3%
HFrEF:
HR 0.62 [0.45, 0.86]
P for interaction:
0.046
Not HFrEF:
HR 0.88 [0.76, 1.02]
yrs
Not HFrEF defined as pts with HF without known reduced EF and pts without hx of HF


HHF and CV Death
by HFrEF vs not HFrEF subgroups
HHF
CV death
Cumulative incident rate (%)
P for interaction: 0.449
19.0%
13.5%
2.7%
2.1%
HFrEF:
HR 0.64
[0.43, 0.95]
Not HFrEF:
HR 0.76
[0.62, 0.92]
P for interaction: 0.012
12.4%
7.2%
2.5%
2.3%
HFrEF:
HR 0.55
[0.34, 0.90]
Not HFrEF:
HR 1.08
[0.89, 1.31]
yrs
HFrEF: (N=671) Dapagliflozin Placebo
Not HFrEF: (N=16,489) Dapagliflozin Placebo
Not HFrEF defined as pts with HF without known reduced EF and pts without hx of HF

Outcomes by Different EF

		KM rate (%) Dapa	KM rate (%) Placebo	HR (95% CI)	P trend for interaction
CV death / HHF	EF <30%	22.1	44.7	0.45 (0.23-0.87)	0.039
	EF 30-<45	17.0	23.2	0.68 (0.47-1.00)	
	EF 45-<55	10.2	12.0	0.83 (0.58-1.20)	
	EF ≥55	5.8	6.4	0.89 (0.68-1.16)	
HHF	EF <30%	19.3	40.4	0.41 (0.19-0.85)	0.084
	EF 30-<45	12.1	14.2	0.76 (0.47-1.23)	
	EF 45-<55	6.7	8.8	0.76 (0.48-1.19)	
	EF ≥55	3.9	4.1	0.89 (0.64-1.24)	
CV death	EF <30%	5.0	10.9	0.39 (0.12-1.29)	0.049
	EF 30-<45	7.7	12.8	0.60 (0.35-1.02)	
	EF 45-<55	5.4	4.3	1.18 (0.69-2.01)	
	EF ≥55	2.5	2.6	1.05 (0.70-1.57)	
All-cause death	EF <30%	9.8	17.1	0.52 (0.21-1.33)	0.026
	EF 30-<45	11.7	17.9	0.64 (0.41-0.99)	
	EF 45-<55	8.6	8.6	0.98 (0.66-1.46)	
	EF ≥55	5.7	5.4	1.02 (0.78-1.32)	

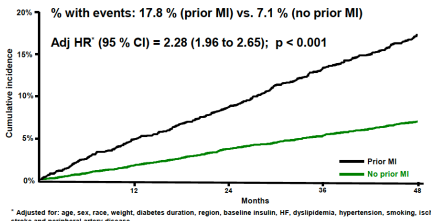
0.1 Favors dapa 1 Favors placebo 10

13

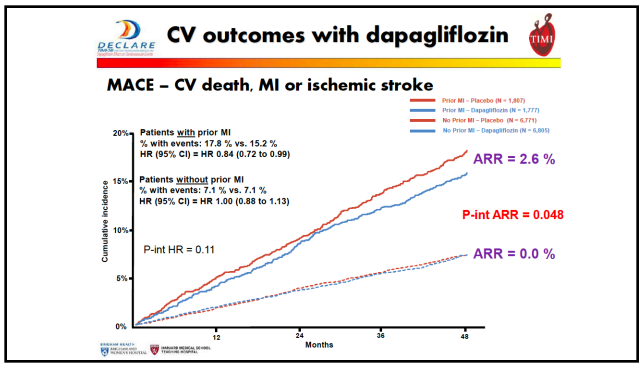
Subestudio con IAM previo

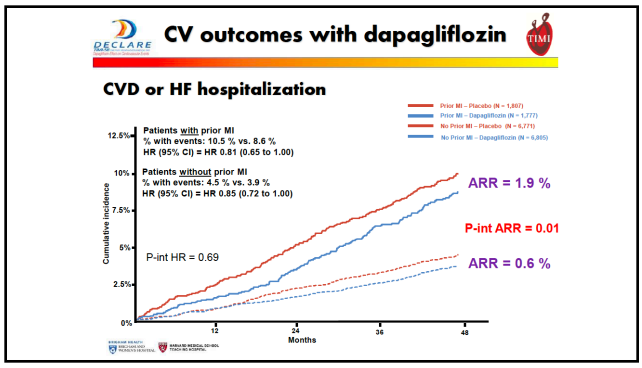
Event rates in placebo arm

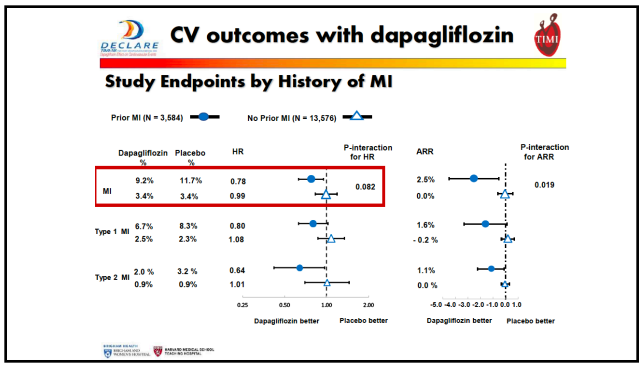
MACE – CV death, MI or ischemic stroke

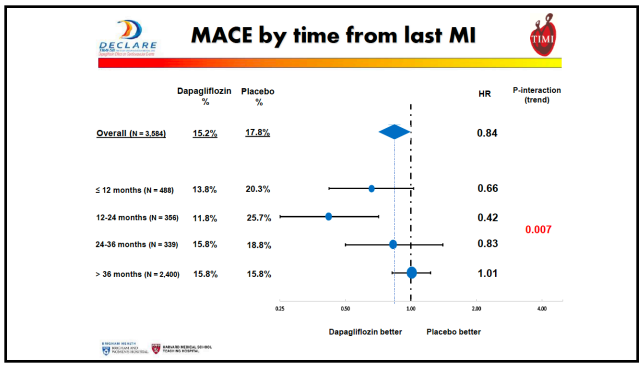


* Adjusted for: age, sex, race, weight, diabetes duration, region, baseline insulin, HF, dyslipidemia, hypertension, smoking, ischemic stroke and peripheral artery disease.

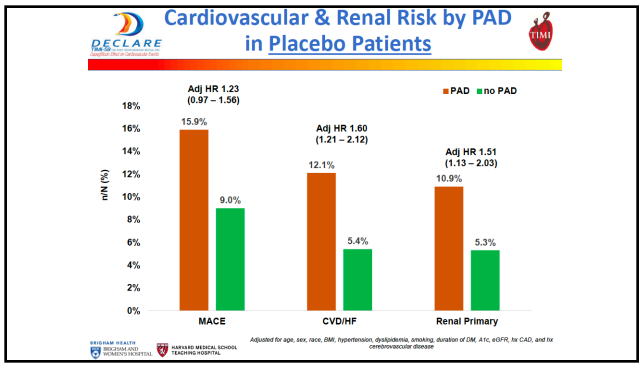

CV outcomes with dapagliflozin
MACE – CV death, MI or ischemic stroke
Prior MI – Placebo (N = 1,867)
Prior MI – Dapagliflozin (N = 1,777)
No Prior MI – Placebo (N = 6,771)
No Prior MI – Dapagliflozin (N = 6,805)
Patients with prior MI
% with events: 17.8 % vs. 15.2 %
HR (95% CI) = HR 0.84 (0.72 to 0.99)
Patients without prior MI
% with events: 7.1 % vs. 7.1 %
HR (95% CI) = HR 1.00 (0.88 to 1.13)
P-int HR = 0.11
ARR = 2.6 %
P-int ARR = 0.048
ARR = 0.0 %
Cumulative incidence
20%
15%
10%
5%
0%
12
24
36
48
Months

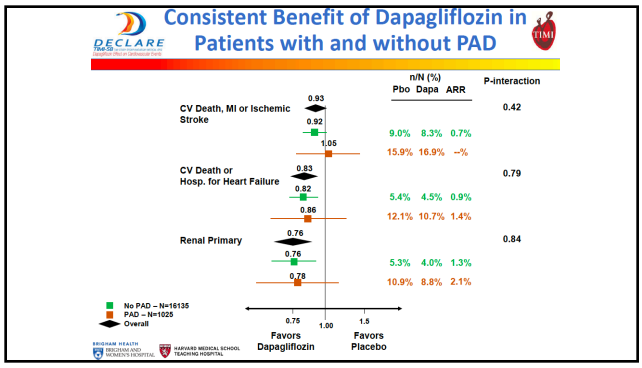

CV outcomes with dapagliflozin
CVD or HF hospitalization
Prior MI – Placebo (N = 1,867)
Prior MI – Dapagliflozin (N = 1,777)
No Prior MI – Placebo (N = 6,771)
No Prior MI – Dapagliflozin (N = 6,805)
Patients with prior MI
% with events: 10.5 % vs. 8.6 %
HR (95% CI) = HR 0.81 (0.65 to 1.00)
Patients without prior MI
% with events: 4.5 % vs. 3.9 %
HR (95% CI) = HR 0.85 (0.72 to 1.00)
P-int HR = 0.69
ARR = 1.9 %
P-int ARR = 0.01
ARR = 0.6 %
Cumulative incidence
12.5%
10%
7.5%
5%
2.5%
0%
12
24
36
48
Months

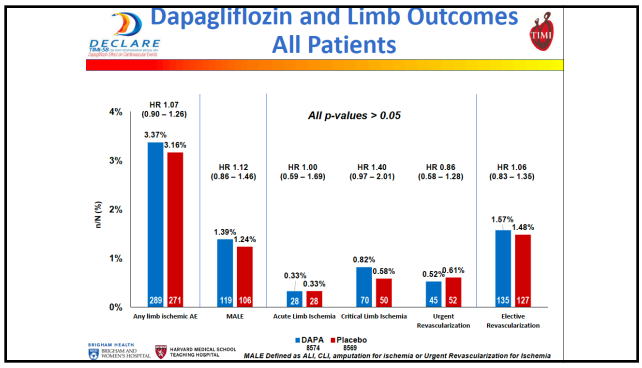

CV outcomes with dapagliflozin
Study Endpoints by History of MI
Prior MI (N = 3,584)
No Prior MI (N = 13,576)
Dapagliflozin %
Placebo %
HR
P-interaction for HR
ARR
P-interaction for ARR
MI 9.2% 11.7% 0.78
3.4% 3.4% 0.99
0.082
2.5%
0.0%
0.019
Type 1 MI 6.7% 8.3% 0.80
2.5% 2.3% 1.08
1.6%
- 0.2 %
Type 2 MI 2.0 % 3.2 % 0.64
0.9% 0.9% 1.01
1.1%
0.0 %
0.25
0.50
1.00
2.00
Dapagliflozin better
Placebo better
-5.0 -4.0 -3.0 -2.0 -1.0 0.0 1.0
Dapagliflozin better
Placebo better

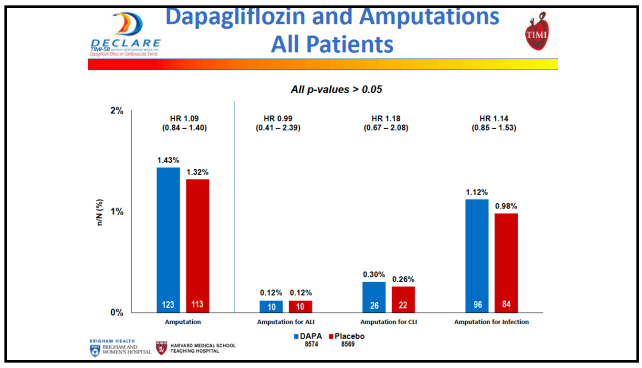


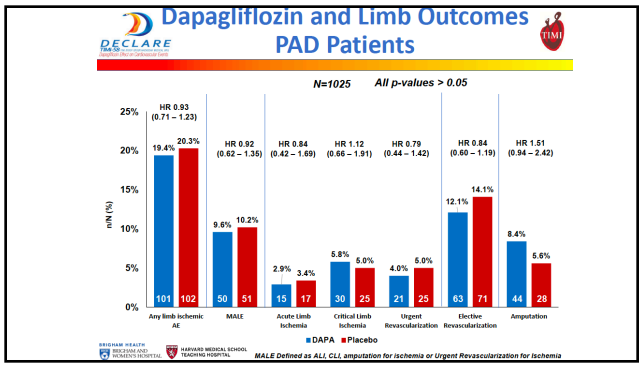
Subestudio con enfermedad arterial periférica

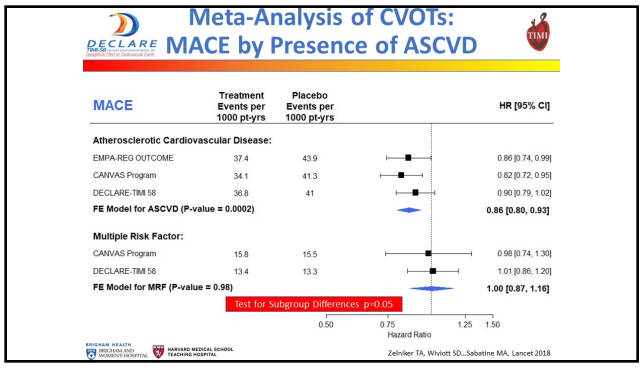


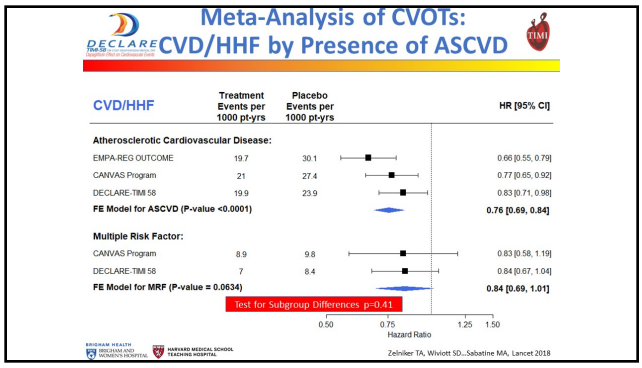

Consistent Benefit of Dapagliflozin in Patients with and without PAD
n/N (%)
Pbo Dapa ARR
P-interaction
CV Death, MI or Ischemic Stroke
0.93
0.92
1.05
9.0% 8.3% 0.7%
15.9% 16.9% –%
0.42
CV Death or Hosp. for Heart Failure
0.83
0.82
0.86
5.4% 4.5% 0.9%
12.1% 10.7% 1.4%
0.79
Renal Primary
0.76
0.76
0.78
5.3% 4.0% 1.3%
10.9% 8.8% 2.1%
0.84
No PAD – N=16135
PAD – N=1025
Overall
0.75
1.00
1.5
Favors Dapagliflozin
Favors Placebo


Dapagliflozin and Limb Outcomes All Patients
All p-values > 0.05
n/N (%)
4%
3%
2%
1%
0%
HR 1.07 (0.90 – 1.26)
3.37%
3.16%
289
271
Any limb ischemic AE
HR 1.12 (0.86 – 1.46)
1.39%
1.24%
119
106
MALE
HR 1.00 (0.59 – 1.69)
0.33%
0.33%
28
28
Acute Limb Ischemia
HR 1.40 (0.97 – 2.01)
0.82%
0.58%
70
50
Critical Limb Ischemia
HR 0.86 (0.58 – 1.28)
0.52%
0.61%
45
52
Urgent Revascularization
HR 1.06 (0.83 – 1.35)
1.57%
1.48%
135
127
Elective Revascularization
DAPA 8574
Placebo 8569
MALE Defined as ALI, CLI amputation for ischemia or Urgent Revascularization for Ischemia


Dapagliflozin and Amputations All Patients
All p-values > 0.05
n/N (%)
2%
1%
0%
HR 1.09 (0.84 – 1.40)
1.43%
1.32%
123
113
Amputation
HR 0.99 (0.41 – 2.39)
0.12%
0.12%
10
10
Amputation for ALI
HR 1.18 (0.67 – 2.08)
0.30%
0.26%
26
22
Amputation for CLI
HR 1.14 (0.85 – 1.53)
1.12%
0.98%
96
84
Amputation for Infection
DAPA 8574
Placebo 8569


Dapagliflozin and Limb Outcomes
PAD Patients
N=1025
All p-values > 0.05
n/N (%)
25%
20%
15%
10%
5%
0%
HR 0.93 (0.71 – 1.23)
19.4%
20.3%
101
102
Any limb ischemic AE
HR 0.92 (0.62 – 1.35)
9.6%
10.2%
50
51
MALE
HR 0.84 (0.42 – 1.69)
2.9%
3.4%
15
17
Acute Limb Ischemia
HR 1.12 (0.66 – 1.91)
5.8%
5.0%
30
25
Critical Limb Ischemia
HR 0.79 (0.44 – 1.42)
4.0%
5.0%
21
25
Urgent Revascularization
HR 0.84 (0.60 – 1.19)
12.1%
14.1%
63
71
Elective Revascularization
HR 1.51 (0.94 – 2.42)
8.4%
5.6%
44
28
Amputation
DAPA
Placebo
MALE Defined as ALI, CLI, amputation for ischemia or Urgent Revascularization for Ischemia

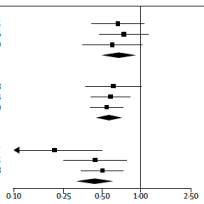

Meta-Analysis of CVOTs:
MACE by Presence of ASCVD
MACE
Treatment Events per 1000 pt-yrs
Placebo Events per 1000 pt-yrs
HR [95% CI]
Atherosclerotic Cardiovascular Disease:
EMPA-REG OUTCOME 37.4 43.9 0.86 [0.74, 0.99]
CANVAS Program 34.1 41.3 0.82 [0.72, 0.95]
DECLARE-TIMI 58 36.8 41 0.90 [0.79, 1.02]
FE Model for ASCVD (P-value = 0.0002) 0.86 [0.80, 0.93]
Multiple Risk Factor:
CANVAS Program 15.8 15.5 0.98 [0.74, 1.30]
DECLARE-TIMI 58 13.4 13.3 1.01 [0.86, 1.20]
FE Model for MRF (P-value = 0.98) 1.00 [0.87, 1.16]
Test for Subgroup Differences p=0.05
0.50
0.75
1.25
1.50
Hazard Ratio
Zelniker TA, Wiviott SD...Sabatine MA, Lancet 2018


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
0.50
0.75
1.25
1.50
Hazard Ratio
Zelniker TA, Wiviott SD...Sabatine MA, Lancet 2018

Desenlace renal compuesto

A

	Patients: Treatment (n/N)	Patients: Placebo (n/N)	Events	Events per 1000 patient-years: Treatment	Events per 1000 patient-years: Placebo	Weight (%)	HR (95% CI)
eGFR <60 mL/min per m²							
EMPA-REG OUTCOME	1196/1801	605/1801	NA	NA	NA	33·5	0·66 (0·41-1·07)
CANVAS Program	NA/2039	NA/2039	83	11·4	15·1	39·6	0·74 (0·48-1·15)
DECLARE-TIMI 58	606/1265	659/1265	59	8·9	15·2	27·0	0·60 (0·35-1·02)
Fixed effects model for eGFR <60 (p=0·0054)							**0·67 (0·51-0·89)**
eGFR 60 to <90 mL/min per m²							
EMPA-REG OUTCOME	2406/3638	1232/3638	NA	NA	NA	16·8	0·61 (0·37-1·03)
CANVAS Program	NA/5625	NA/5625	118	4·6	7·4	34·4	0·58 (0·41-0·84)
DECLARE-TIMI 58	3838/7732	3894/7732	186	4·2	7·8	48·9	0·54 (0·40-0·73)
Fixed effects model for eGFR 60 to <90 (p<0·0001)							**0·56 (0·46-0·70)**
eGFR ≥90 mL/min per m²							
EMPA-REG OUTCOME	1043/1529	486/1529	NA	NA	NA	11·7	0·21 (0·09-0·53)
CANVAS Program	NA/2476	NA/2476	48	3·8	8·1	27·5	0·44 (0·25-0·78)
DECLARE-TIMI 58	4137/8162	4025/8162	120	2·5	4·9	60·8	0·50 (0·34-0·73)
Fixed effects model for eGFR ≥90 (p<0·0001)							**0·44 (0·32-0·59)**

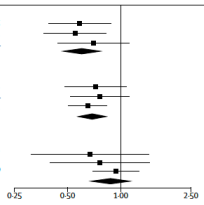


Zelniker TA. Lancet. Online Nov 10 2018

Hospitalización por falla cardíaca

B

	Patients: Treatment (n/N)	Patients: Placebo (n/N)	Events	Events per 1000 patient-years: Treatment	Events per 1000 patient-years: Placebo	Weight (%)	HR (95% CI)
eGFR <60 mL/min per m²							
EMPA-REG OUTCOME	1212/1819	607/1819	94	14·9	25·8	36·5	0·59 (0·39-0·88)
CANVAS Program	NA/2039	NA/2039	98	11·6	21·3	36·1	0·55 (0·37-0·83)
DECLARE-TIMI 58	606/1265	659/1265	77	12·3	19·3	27·4	0·70 (0·44-1·12)
Fixed effects model for eGFR <60 (p<0·0001)							**0·60 (0·47-0·77)**
eGFR 60 to <90 mL/min per m²							
EMPA-REG OUTCOME	2423/3661	1238/3661	100	8·4	11·7	21·3	0·72 (0·48-1·07)
CANVAS Program	NA/5625	NA/5625	108	4·6	6·1	23·4	0·76 (0·52-1·12)
DECLARE-TIMI 58	3838/7732	3894/7732	251	6·5	9·9	55·2	0·65 (0·51-0·84)
Fixed effects model for eGFR 60 to <90 (p<0·0001)							**0·69 (0·57-0·83)**
eGFR ≥90 mL/min per m²							
EMPA-REG OUTCOME	1050/1538	488/1538	27	5·4	7·9	11·3	0·67 (0·31-1·44)
CANVAS Program	NA/2476	NA/2476	37	3·7	5·1	15·7	0·76 (0·40-1·47)
DECLARE-TIMI 58	4137/8162	4025/8162	170	5·1	5·4	73·0	0·94 (0·69-1·26)
Fixed effects model for eGFR ≥90 (p=0·31)							**0·88 (0·68-1·13)**

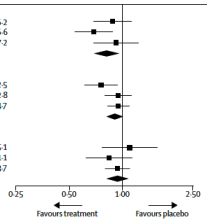


Zelniker TA. Lancet. Online Nov 10 2018

MACE

C

	Patients: Treatment (n/N)	Patients: Placebo (n/N)	Events	Events per 1000 patient-years: Treatment	Events per 1000 patient-years: Placebo	Weight (%)	HR (95% CI)
eGFR <60 mL/min per m²							
EMPA-REG OUTCOME	1212/1819	607/1819	275	52·7	60·5	36·2	0·88 (0·69-1·13)
CANVAS Program	NA/2039	NA/2039	261	36·3	49·5	36·6	0·69 (0·54-0·89)
DECLARE-TIMI 58	606/1265	659/1265	189	37·3	43·1	27·2	0·92 (0·69-1·23)
Fixed effects model for eGFR <60 (p=0·0077)							**0·82 (0·70-0·95)**
eGFR 60 to <90 mL/min per m²							
EMPA-REG OUTCOME	2423/3661	1238/3661	351	30·8	40·6	22·5	0·76 (0·61-0·94)
CANVAS Program	NA/5625	NA/5625	563	26·8	29·0	32·8	0·95 (0·80-1·13)
DECLARE-TIMI 58	3838/7732	3894/7732	757	24·5	25·8	44·7	0·95 (0·82-1·09)
Fixed effects model for eGFR 60 to <90 (p=0·0520)							**0·91 (0·82-1·00)**
eGFR ≥90 mL/min per m²							
EMPA-REG OUTCOME	1050/1538	488/1538	146	35·4	32·2	15·1	1·10 (0·77-1·57)
CANVAS Program	NA/2476	NA/2476	187	20·8	23·6	21·1	0·84 (0·62-1·13)
DECLARE-TIMI 58	4137/8162	4025/8162	613	18·8	19·7	63·7	0·94 (0·80-1·10)
Fixed effects model for eGFR ≥90 (p=0·35)							**0·94 (0·82-1·07)**

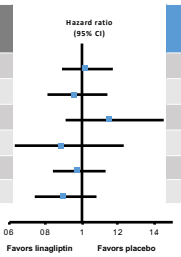


Zelniker TA. Lancet. Online Nov 10 2018

Cómo se compara con los otros estudios?

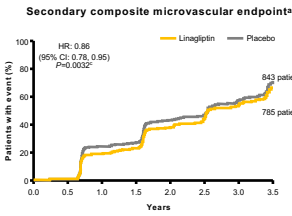
CARMELINA: Primary CV endpoints

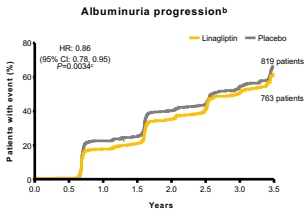
Endpoint	Linagliptin group (n=3494)	Placebo group (n=3485)	Hazard ratio (95% CI)	*P* value
3P-MACE[a]	434 (12.4%)	420 (12.1%)	1.02 (0.89, 1.17)	0.74
CV death	255 (7.3%)	264 (7.6%)	0.96 (0.81, 1.14)	0.63
Nonfatal MI	156 (4.5%)	135 (3.9%)	1.15 (0.91, 1.45)	0.23
Nonfatal stroke	65 (1.9%)	73 (2.1%)	0.88 (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
Rosenstock J, et al. JAMA 2018 [Epub ahead of print]

CARMELINA: Secondary microvascular endpoints

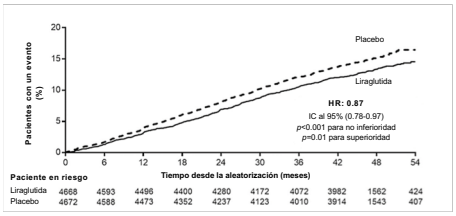




[a]Defined as a composite of albuminuria progression, sustained decrease of ≥50% in eGFR, sustained ESRD, death due to kidney disease, retinal photocoagulation, intravitreal injection of an anti-VEGF therapy for diabetic retinopathy, vitreous hemorrhage, or diabetes-related blindness. [b]Change from normo- to micro- or macroalbuminuria, or from micro- to macroalbuminuria. [c]two-sided
CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; VEGF, vascular endothelial growth factor
Rosenstock J, et al. JAMA 2018 [Epub ahead of print]

LEADER: Desenlaces primarios

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



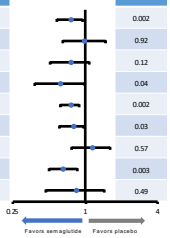
Las incidencias acumuladas se estimaron con el uso del método de Kaplan-Meier y las razones de riesgo con el uso del modelo de regresión de riesgos proporcionales de Cox. El análisis de los datos se detiene a los 54 meses, ya que menos del 10% de los pacientes tenían un tiempo de observación más allá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

IC: intervalo de confianza; CV: cardiovascular; HR: hazard ratio

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

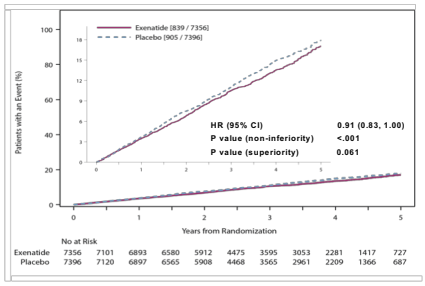
SUSTAIN-6: Primary and secondary endpoint results

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



[a]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
Marso SP et al. *N Engl J Med* 2016;375:1834–44

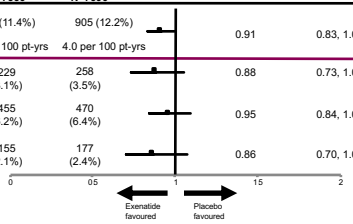
Primary Composite Cardiovascular Outcome
Intention-to-Treat Analysis for Non-inferiority & Superiority



EXSCEL

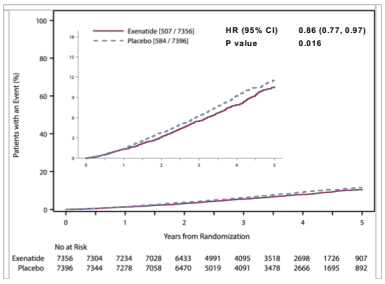
Primary Composite Cardiovascular Outcome
Intention-to-Treat Analysis

	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	
Non-fatal MI	455 (6.2%)	470 (6.4%)	0.95	0.84, 1.09	0.628 (homogeneity among components)
Non-fatal stroke	155 (2.1%)	177 (2.4%)	0.86	0.70, 1.07	



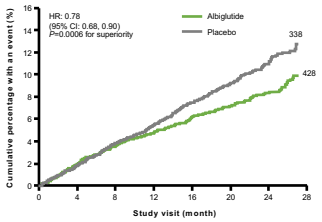
EXSCEL

All-Cause Mortality
Intention-to-Treat Analysis



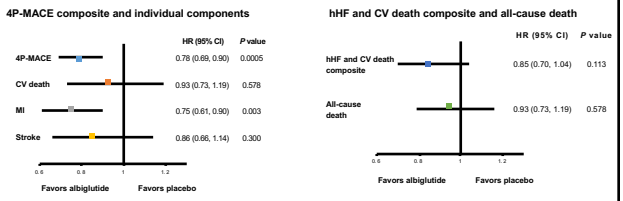
EXSCEL

HARMONY: Primary endpoint results



CI, Confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events.
Hernandez A.F. et al. Lancet 2018 [Epub Aug 27 2018]

HARMONY: Secondary endpoint results



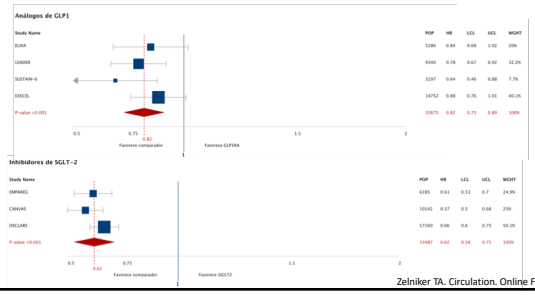
4P-MACE defined as a composite of CV death, nonfatal MI, nonfatal stroke, and revascularization for unstable angina
4P-MACE, 4-point major adverse cardiovascular events; CI, confidence interval; CV, cardiovascular; hHF, hospitalized heart failure; HR, hazard ratio; MI, myocardial infarction
Hernandez AF, et al. Lancet 2018 (Supplemental prior)

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

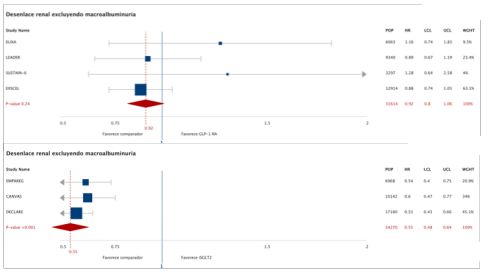
	Desenlace compuesto microvascular	Desenlace compuesto renal	Nueva aparición microalbuminuria	Doblamiento creatinina	Terapia reemplazo renal	Muerte renal
Inhibidores de SGLT2						
EMPAREG (empagliflozina)	0.62 (0.54-0.70)	0.61 (0.53-0.70)	0.62 (0.54-0.72)	0.56 (0.39-0.79)	0.45 (0.21-0.97)	NA
CANVAS (canagliflozina)	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) [E1]	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) [E2]	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

Desenlace renal compuesto incluyendo macroalbuminuria



Zelniker TA. Circulation. Online Feb 21 2019

Desenlace renal excluyendo macroalbuminuria



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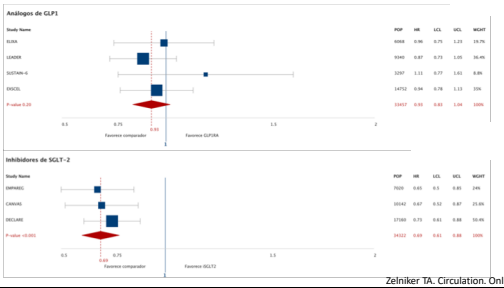
Hospitalización por falla cardíaca



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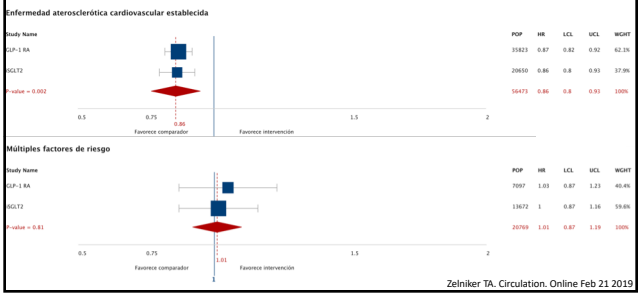
MACE



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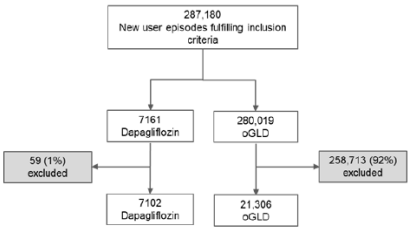
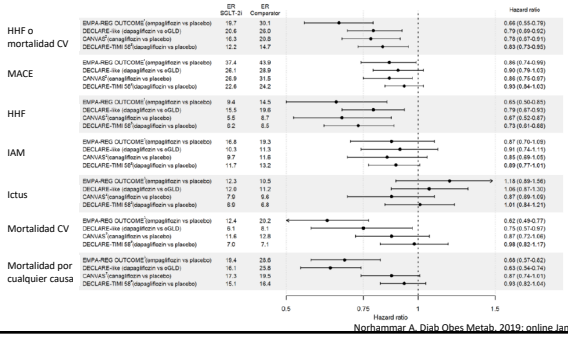
Estudios de la vida real

Población sueca tipo DECLARE

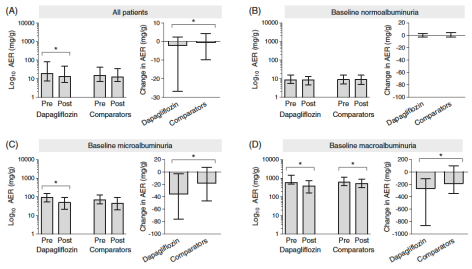


Norhammar A. Diab Obes Metab. 2019; online Jan 4



Norhammar A. Diab Obes Metab. 2019; online Jan 4

DARWIN-T2D



Fadini GP. Diab Obes Metab. 2019;21:252

Que hay nuevo en eventos adversos?

ITU

EMPAREG: Adverse events consistent with urinary tract infection

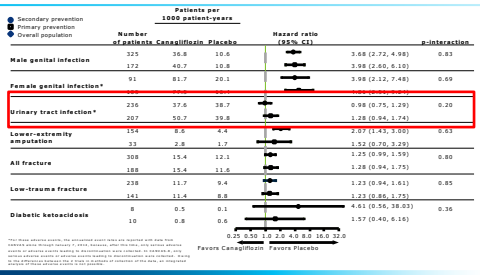
	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Events consistent with UTI	423 (18.1%)	8.21	426 (18.2%)	8.02	416 (17.8%)	7.75
Events leading to discontinuation	10 (0.4%)	0.17	22 (0.9%)	0.37	19 (0.8%)	0.31
By sex						
Male	158 (9.4%)	3.96	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

78

Effects of Canagliflozin Versus Placebo on Safety Outcomes



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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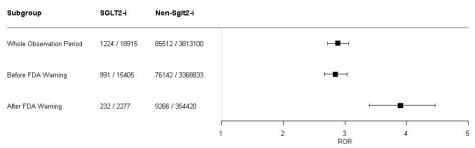
[06-14-2016]

Lesión renal aguda y FAERS

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

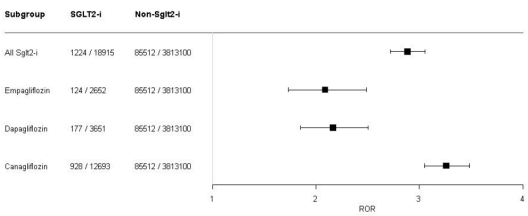


Consideraciones:
- El denominador no es número de pacientes, es número de eventos adversos reportados!
- Los pacientes con iSGLT2 usaron más diuréticos

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

Lesión renal aguda y FAERS

Reporting Odds Ratio of ARF with SGLT2-i by Agent



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

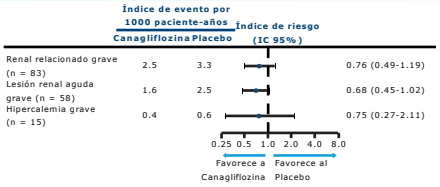
Other adverse events (1)

	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[1]	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 comparison of trials is not advisable due to differences in study design, populations and methodology

1. Kohler et al, Adv Ther. 2017;34(7):1-22 and data on file. 2. https://www.fda.gov/Drugs/DrugSafety/ucm467927.htm (accessed 6-Jun-2017)

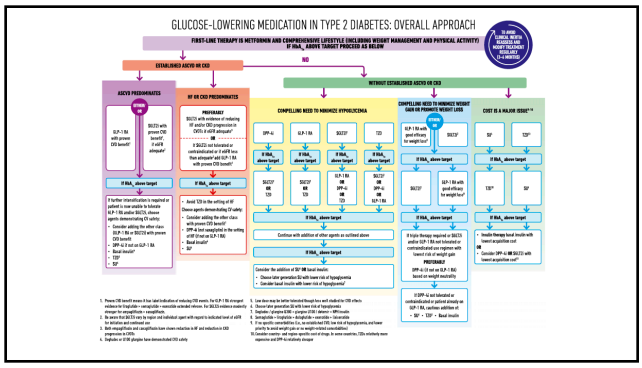
CANVAS Program

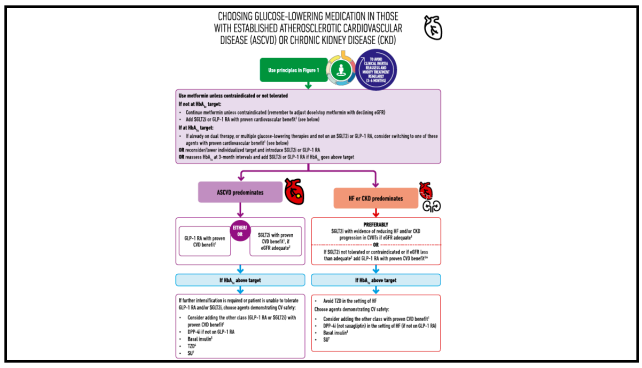
Cómo implementamos esto?

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…

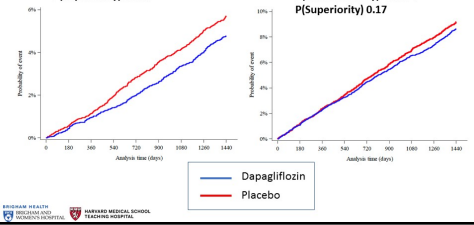




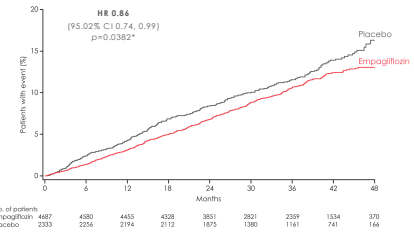
Primary Endpoints

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



Primary outcome: 3-point MACE

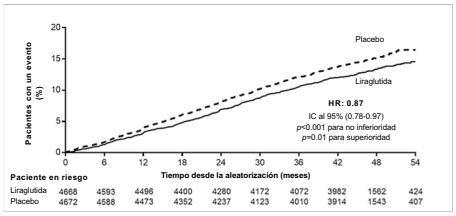


Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

EMPA-REG OUTCOME®

LEADER: Desenlaces primarios

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

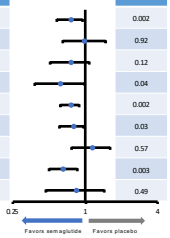


Las incidencias acumuladas se estimaron con el uso del método de Kaplan-Meier y las razones de riesgo con el uso del modelo de regresión de riesgos proporcionales de Cox. El análisis de los datos se detiene a los 54 meses, ya que menos del 10% de los pacientes tenían un tiempo de observación más alto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

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

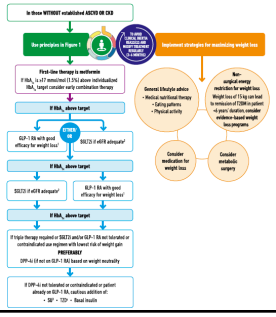
SUSTAIN-6: Primary and secondary endpoint results

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

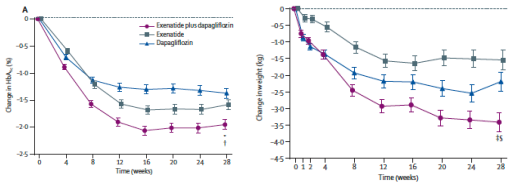


[a]CV death, nonfatal MI, nonfatal stroke, revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure
3P-MACE, 3-point major adverse cardiovascular events; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction
Marso SP et al. N Engl J Med 2016;375:1834–44.

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



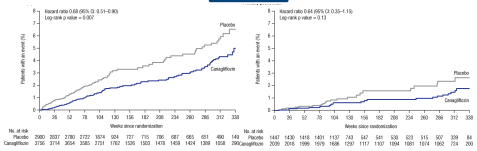
DURATION-8: dapagliflozina vs exenatide semanal



Frias JP. Lancet Diab Endocrinol. 2016. Online Sep 16

Hospitalization for Heart Failure

Secondary Prevention | p-interaction = 0.91 | **Primary Prevention**

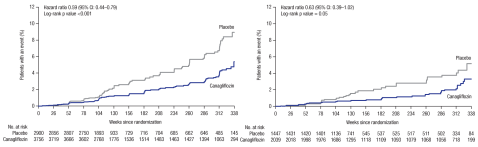


Mahaffey KW, et al. *Circulation*. 2018 Jan 23;137(4):323-334. doi: 10.1161/CIRCULATIONAHA.117.032038. Epub 2017 Nov 13.

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.

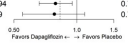
Mahaffey KW, et al. *Circulation*. 2018 Jan 23;137(4):323-334. doi: 10.1161/CIRCULATIONAHA.117.032038. Epub 2017 Nov 13.

CANVAS Program

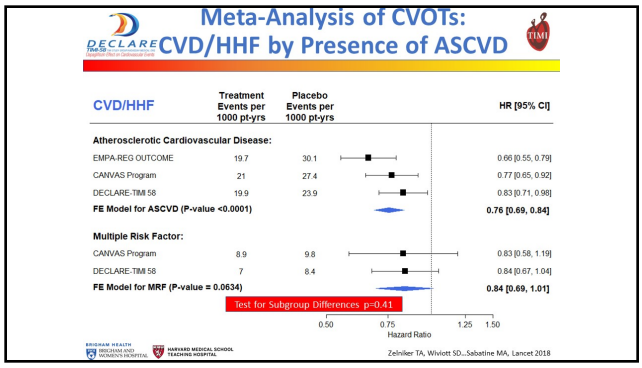
Effect on CVD/HHF in Key Subgroups

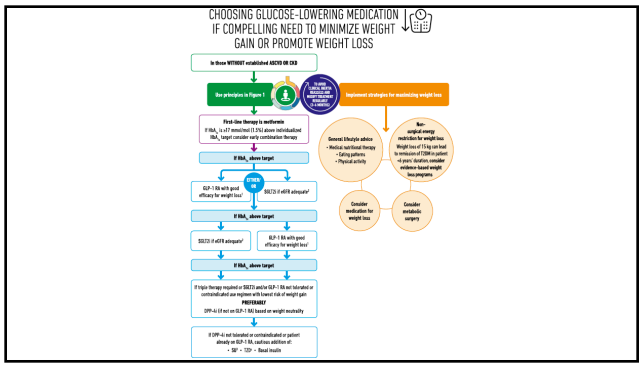
DECLARE TIMI 58 Dapagliflozin Effect on Cardiovascular Events

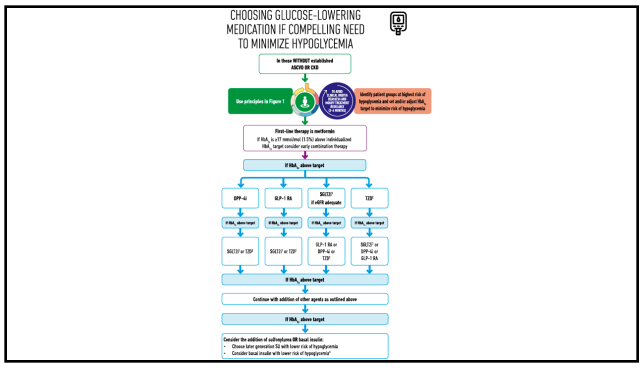
	CVD/HHF				
	Dapagliflozin n/N	Placebo n/N	Hazard Ratio (95% CI)	HR (95%-CI)	P Value for Interaction
Total Cohort	**417/8582**	**496/8578**		**0.83 (0.73-0.95)**	
Risk Group					**0.99**
ASCVD	272/3474	325/3500		0.83 (0.71-0.98)	
MRF	145/5108	171/5078		0.84 (0.67-1.04)	
History of HF					**0.60**
Yes	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)	

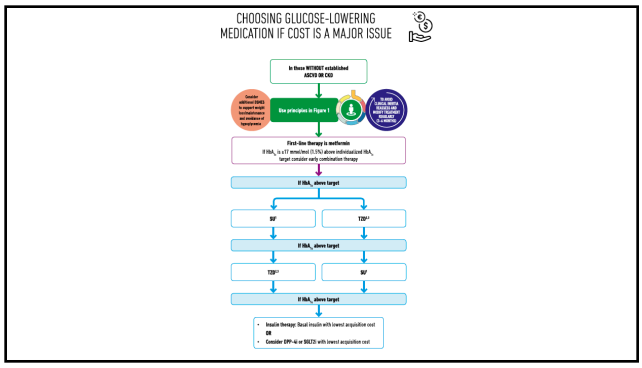


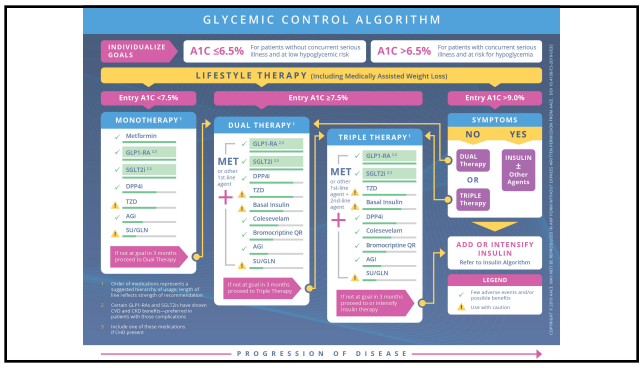
BRIGHAM HEALTH BRIGHAM AND WOMEN'S HOSPITAL | HARVARD MEDICAL SCHOOL TEACHING HOSPITAL


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
0.50 0.75 1.25 1.50
Hazard Ratio
Zelniker TA, Wiviott SD...Sabatine MA, Lancet 2018


CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
Use principles in Figure 1
Implement strategies for maximizing weight loss
General lifestyle advice
Non-surgical energy restriction for weight loss
Consider medication for weight loss
Consider metabolic surgery


CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
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
DPP-4i
GLP-1 RA
SGLT2i
TZD
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





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			


THE LANCET

"Sabatine and colleagues' meta-analysis...provides compelling evidence that SGLT2i should now be considered as first-line therapy after metformin in most people with type 2 diabetes..."

See Comment page 2

Qué viene en los siguientes meses?

- CREDENCE: abril 2019
  - Canagliflozina vs placebo
  - Nefropatía diabética: AEC 30-66 cc/min más proteinuria
  - Endpoint: muerte CV, reducción 40% filtración glomerular, enfermedad renal terminal, muerte renal
- DAPA-HF: noviembre 2019
  - Dapagliflozina vs placebo
  - Endpoint primario: muerte CV + hospitalización por falla cardíaca
  - Diagnóstico establecido de HFrEF
  - Pacientes con o sin DM

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…

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Puede descargar la presentación en:

www.EndoDrChen.com