



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

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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

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DECLARE



Trial Design



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

RANDOMIZE 1:1
DOUBLE BLIND

PLACEBO

All other DM Rx per treating MD

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

BRIGHAM & WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Wilmott SD, Raz I, Sabatine MS. 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

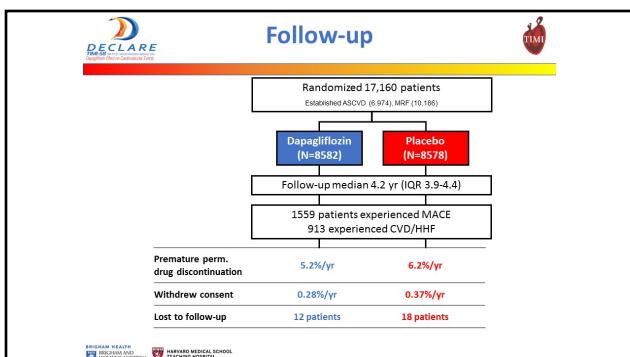
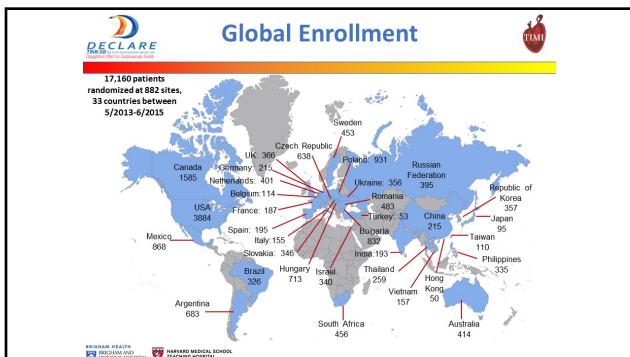
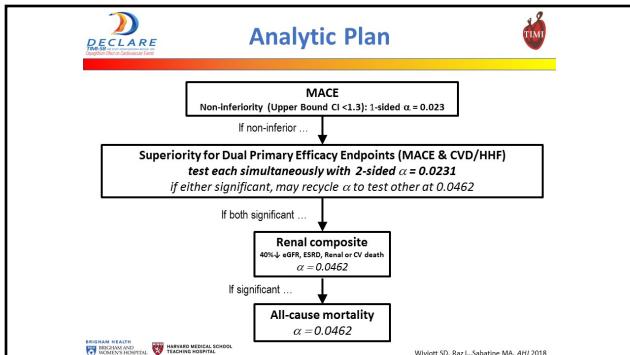
Or

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

BRIGHAM & WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Wilmott SD, Raz I, Sabatine MS. AHJ 2018

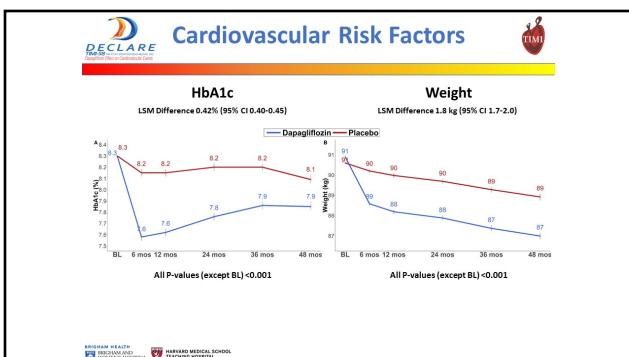


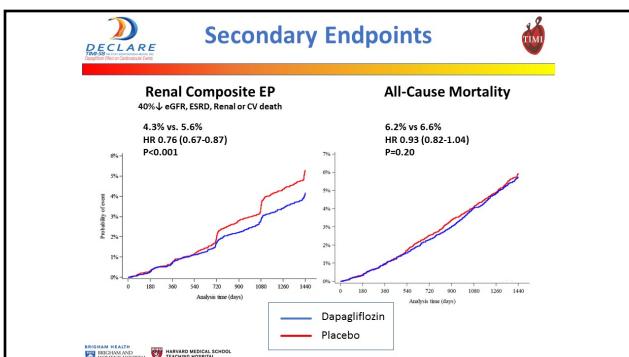
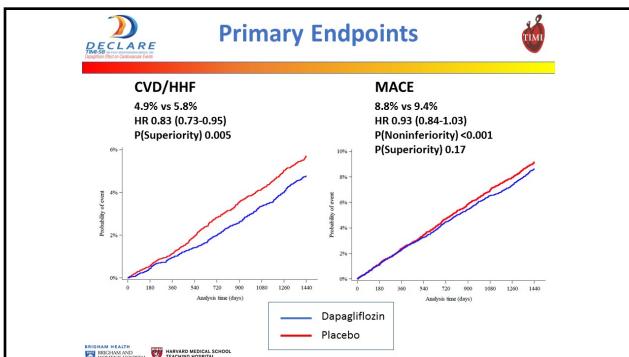
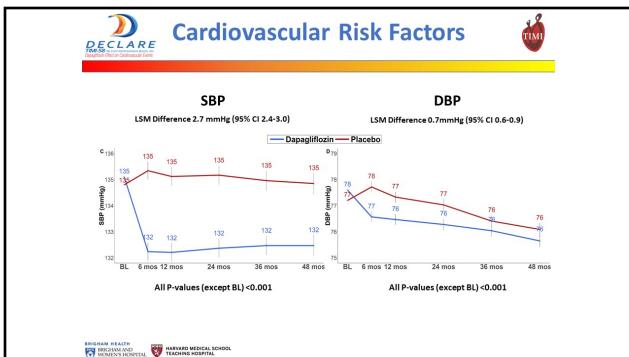
Baseline Characteristics	
	Full Trial Cohort N = 17160
Age, yrs, Mean (SD)	64 (7)
Female Sex (%)	37
BMI, Mean (SD)	32 (6)
Duration of T2DM, yrs, Median (IQR)	11 (6, 16)
HbA1c (%), Mean (SD)	8.3 (1.2)
eGFR (CKD-EPI), Mean (SD)	85 (16)
Region (%): North America	32
Europe	44
Latin America	11
Asia Pacific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

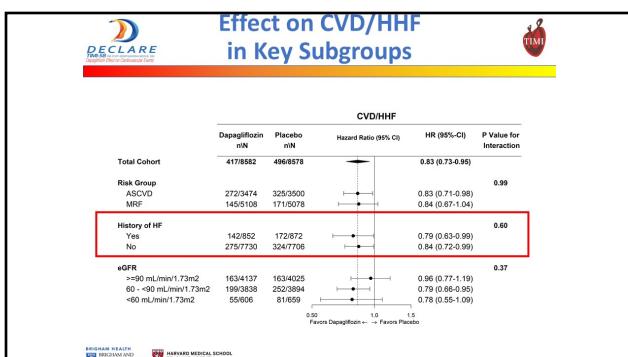
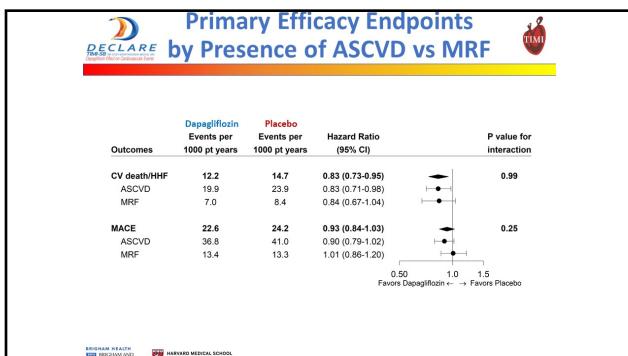
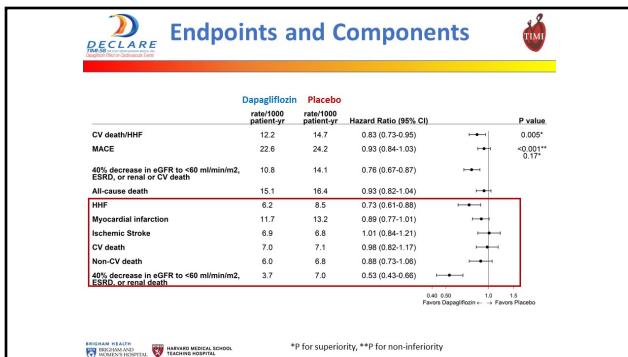
P=NS for all between treatment arm comparisons

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

P=NS for all between treatment arm comparisons





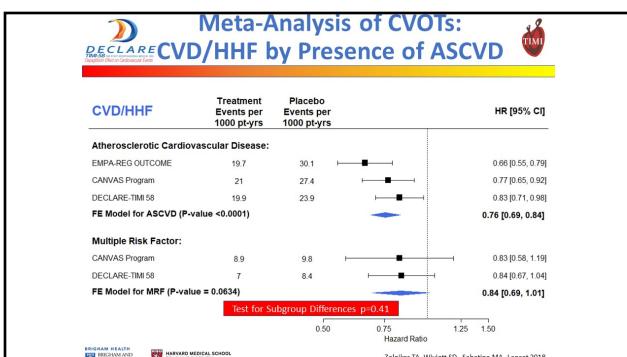
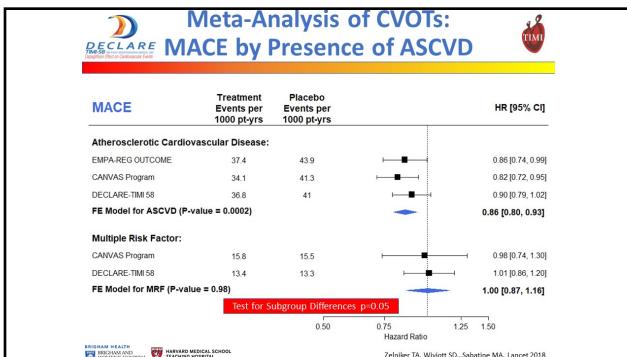


DECLARE
Dapagliflozin in Cardiovascular Disease
Summary

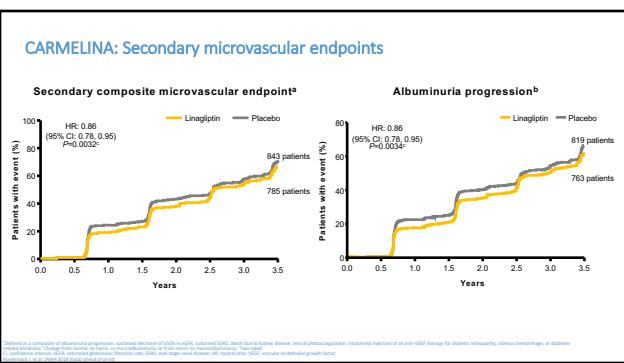
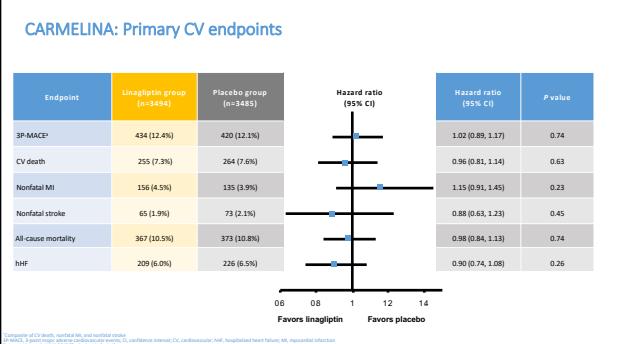
In DECLARE – TIMI 58, the largest SGLT2i trial, which included a broad representation of 1^o and 2^o prevention patients:

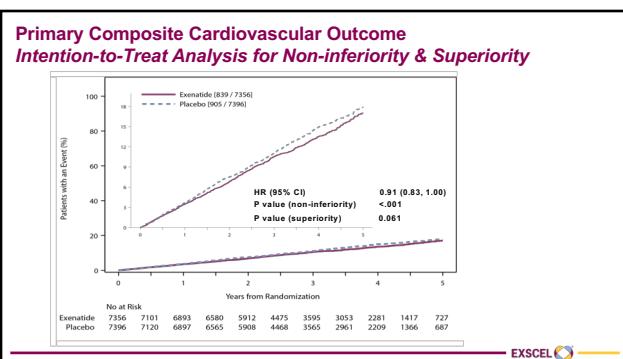
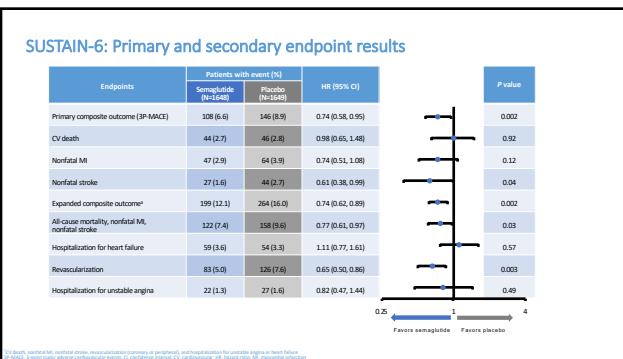
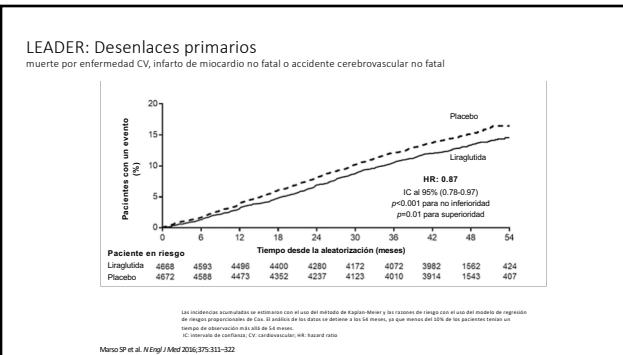
- Dapagliflozin reduced CVD/HHF, was safe with regard to MACE and appeared to reduce renal events
 - ↓ CVD/HHF was consistent regardless of baseline ASCVD or HF
- Dapagliflozin was safe and generally well-tolerated
 - ↑ Genital infections & DKA
 - No difference in: amputation, fracture, or stroke
 -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

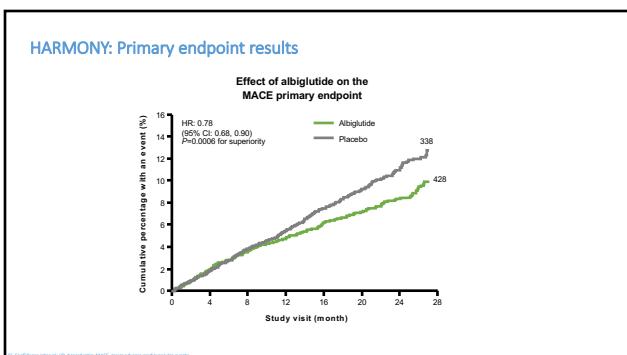
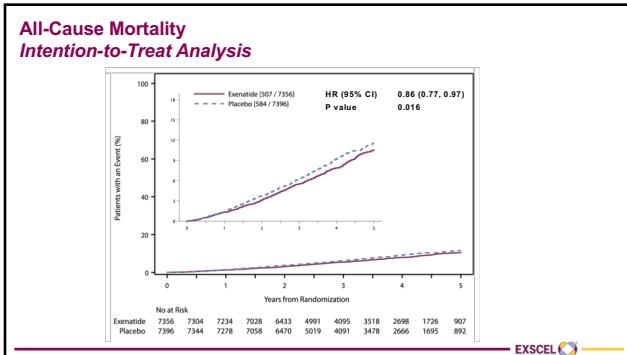
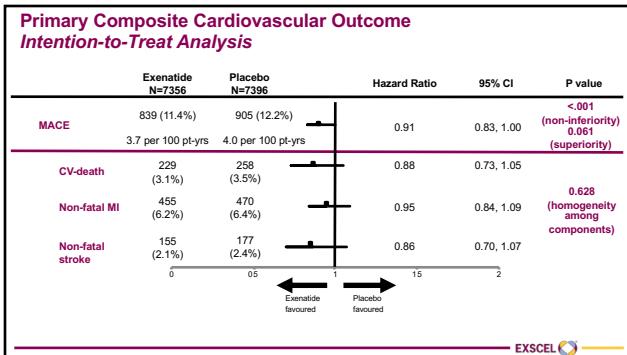
BRIEFING HEALTH
CANVAS AND
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

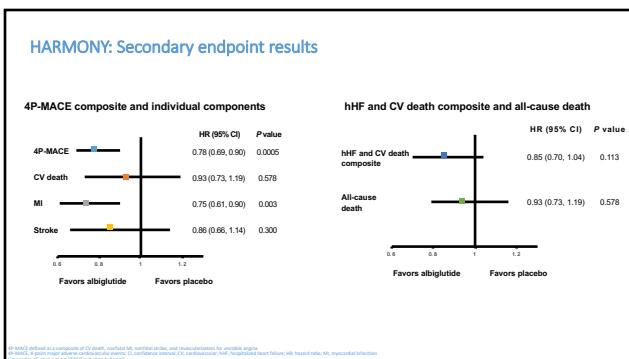


Cómo se compara con los otros estudios?









Estudio	MACE	IAM no fatal	Ictus no fatal	Mortalidad CV	Mortalidad total	Hospitalización por falla cardíaca
EMPAREG	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 (0.50-0.85)
CANVAS	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	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)
CARMELINA	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)
LEADER	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	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	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	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)

Complicaciones renales

	Compuesto microvascular	Compuesto renal	Nueva aparición microalbuminuria	Doblamiento creatinina	Terapia reemplazo renal	Muerte renal
EMPAREG HR(95% IC)	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 HR(95% IC)	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 HR(95% IC)	NA	0.53 (0.43-0.66)	NA	NA	NA	NA
LEADER HR(95% IC)	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 (0.61-1.24)	1.59 (0.52-4.87)
SUSTAIN-6 HR(95% IC)	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
CARMELINA	0.86 (0.78- HR(95% IC))	0.98 (0.82-1.18)	NA	NA	0.87 (0.69-1.10)	

Que hay nuevo en eventos adversos?

ITU

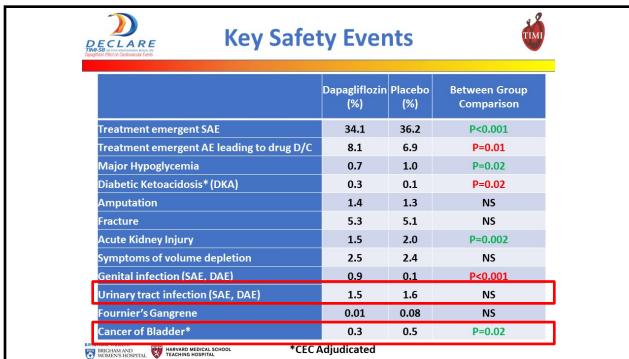
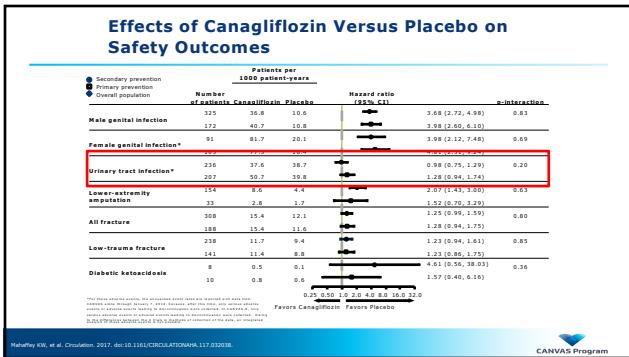
EMPAREG: Adverse events consistent with urinary tract infection

	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 = per 100 patient-years

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

36



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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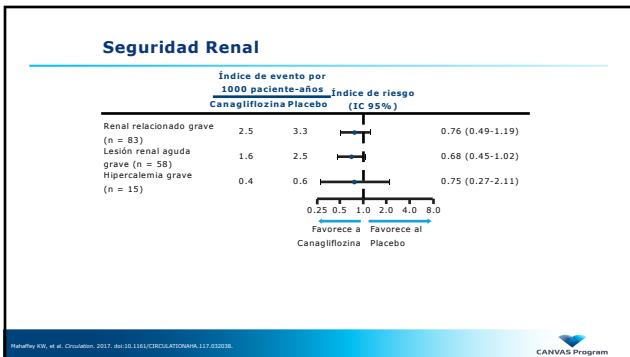
[06-14-2016]

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 ⁱ	155 (6.4%)	2.77	121 (5.2%)	2.07	125 (5.3%)	2.12
Events consistent with volume depletion ^j	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	<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 = per 100 patient-years
Patients treated with at least one dose of study drug.
*Based on 4 MedDRA preferred terms. ⁱBased on 1 standardized MedDRA query.
^jBased on 8 MedDRA preferred terms. **Based on 1 standardized MedDRA query.





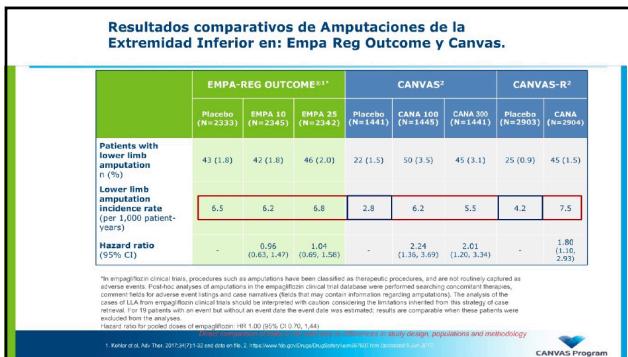
Key Safety Events			
	Dapagliflozin (%)	Placebo (%)	Between Group Comparison
Treatment emergent SAE	34.1	36.2	P<0.001
Treatment emergent AE leading to drug D/C	8.1	6.9	P=0.01
Major Hypoglycemia	0.7	1.0	P=0.02
Diabetic Ketoacidosis* (DKA)	0.3	0.1	P=0.02
Amputation	1.4	1.3	NS
Fracture	5.3	5.1	NS
Acute 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
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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

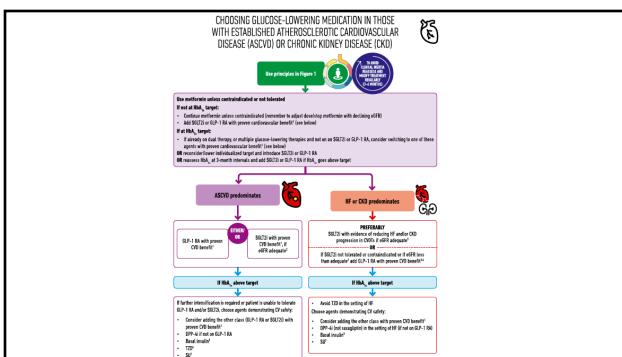
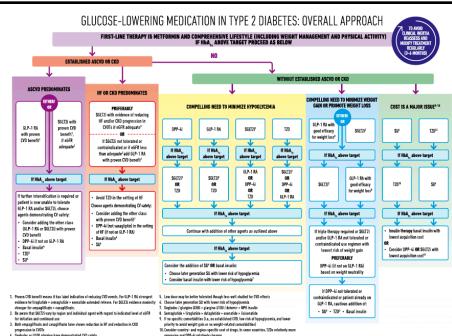


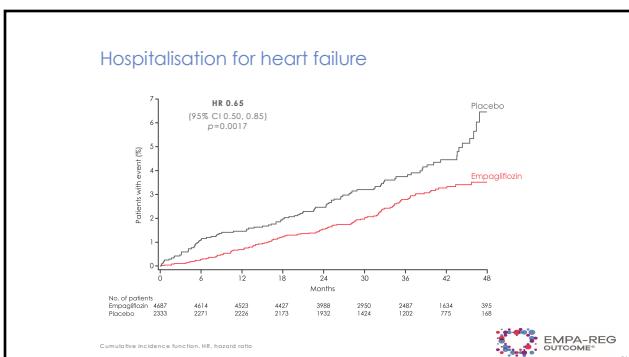
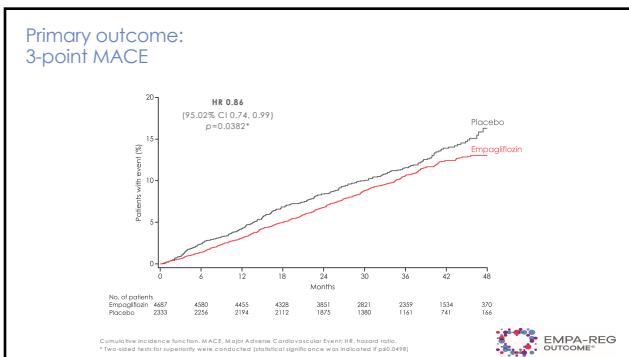
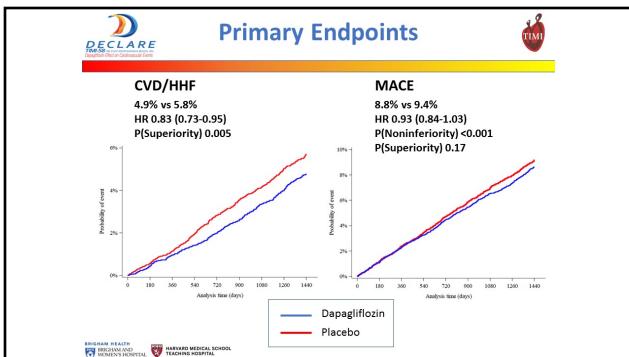
Cómo implementamos esto?

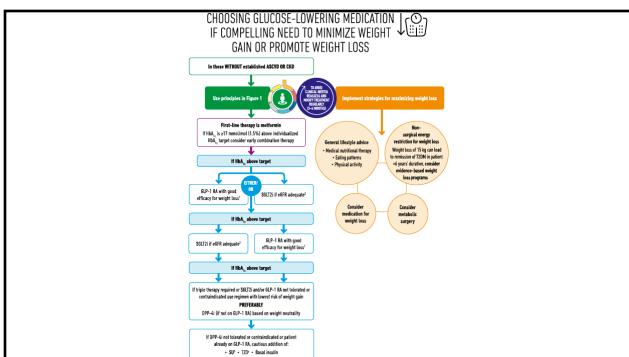
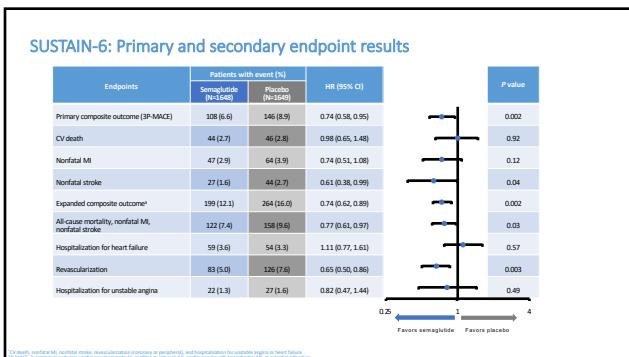
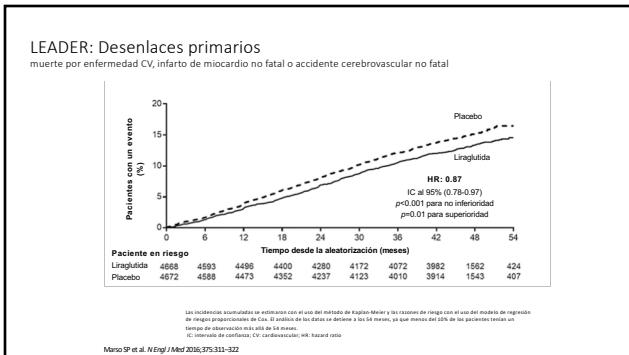
Reflexiones sobre puntos relevantes

- Parece que los iSGT-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!

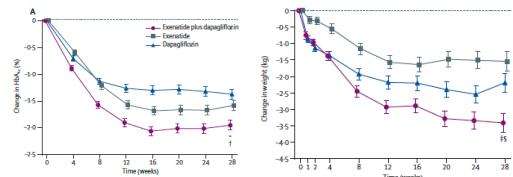
Analizando las guías...





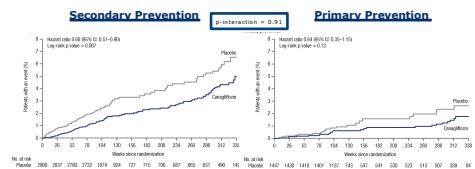


DURATION-8: dapagliflozina vs exenatide semanal



Friis JP. Lancet Diab Endocrinol. 2016; Online Sep 16

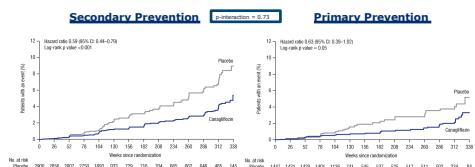
Hospitalization for Heart Failure



Mahaffey KW, et al. Circulation. 2018 Jan 23;137(4):322-334. doi: 10.1161/CIRCULATIONAHA.117.020208.

CANVAS Program

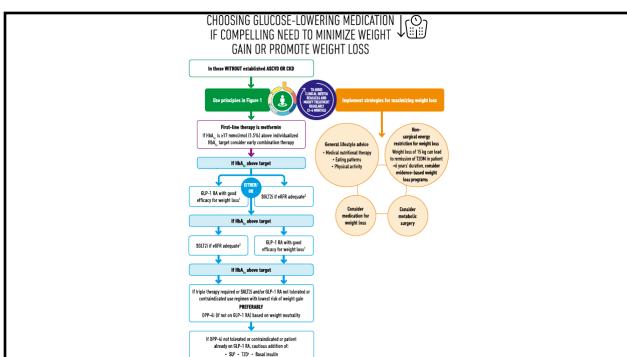
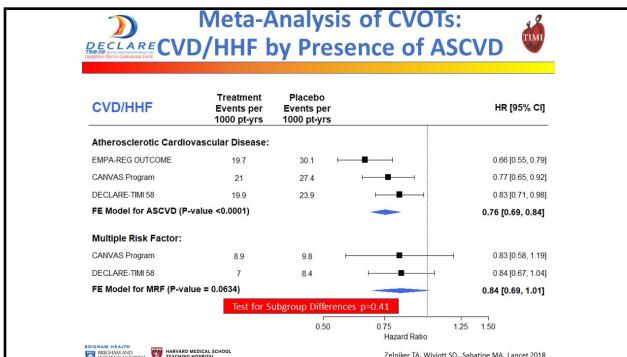
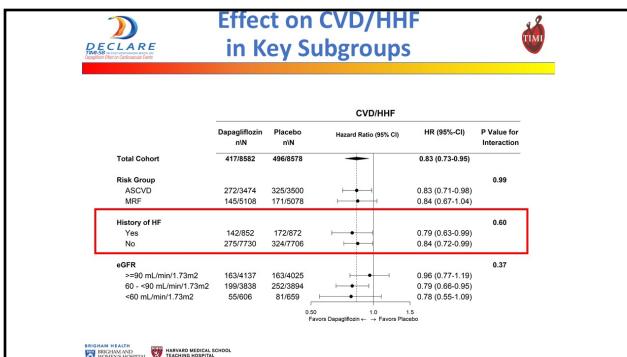
Renal Composite*

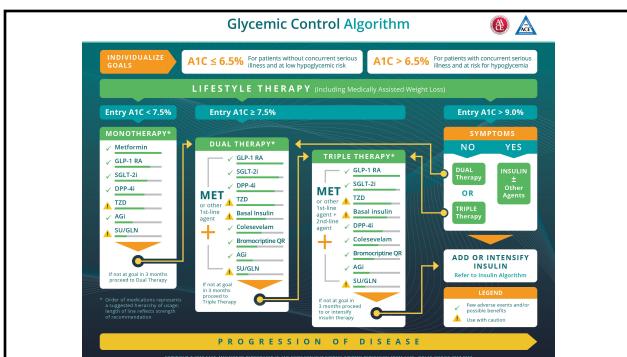
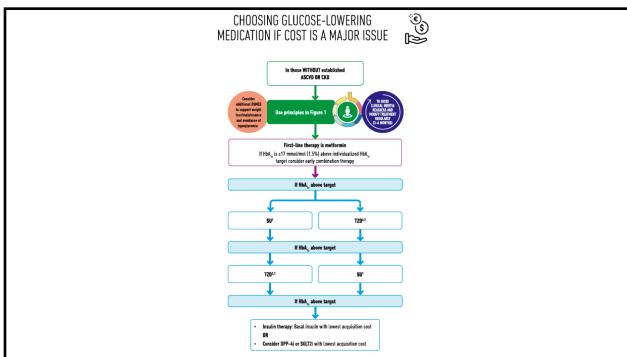
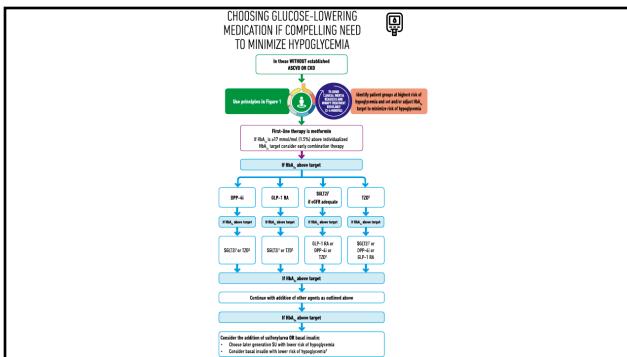


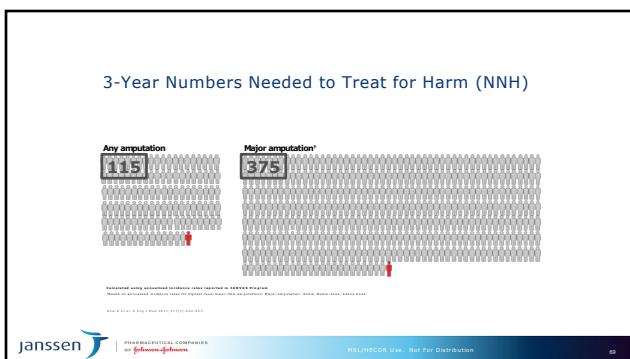
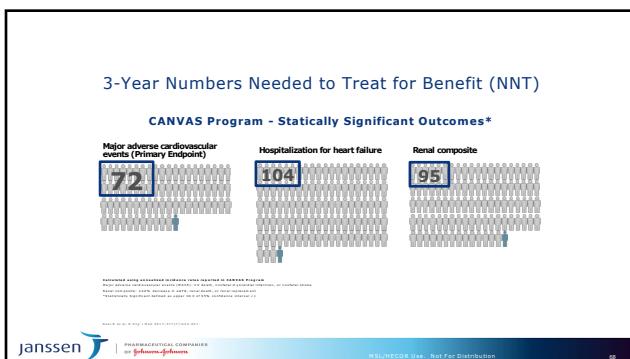
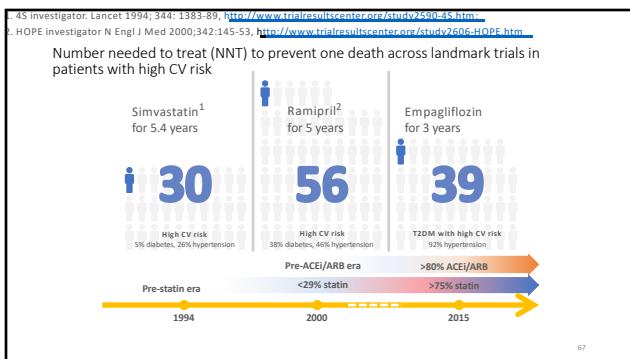
*Renal Composite: composite renal outcome comprising a 40% reduction in estimated glomerular filtration rate.

Requirement for renal replacement therapy, or renal death.

Mahaffey KW, et al. Circulation. 2018 Jan 23;137(4):322-334. doi: 10.1161/CIRCULATIONAHA.117.020208. Epub 2017 Nov 13.







Cuál agente para quién?

	ISGLT2	GLP1RA (basado en estructura GLP1)	iDPP4
Enfermedad aterosclerótica			
Insuficiencia cardíaca	Verde		Ambar
Nefropatía diabética	Verde		
Peso			
Propenso a cetosis	Rojo	Verde	Verde
Fragilidad/fractura previa/caídas	Rojo	Verde	Verde
Amputación previa	Ambar		
Insuficiencia renal crónica (estadio 4-5)	Rojo	Ambar	Verde
Infección genital a repetición	Ambar		

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
