Gli SGT2 inibitori nel trattamento del diabete (e non solo...): come i dati che continuiamo ad acquisire contribuiscono a definire meglio il panorama

GLORIA FORMOSO

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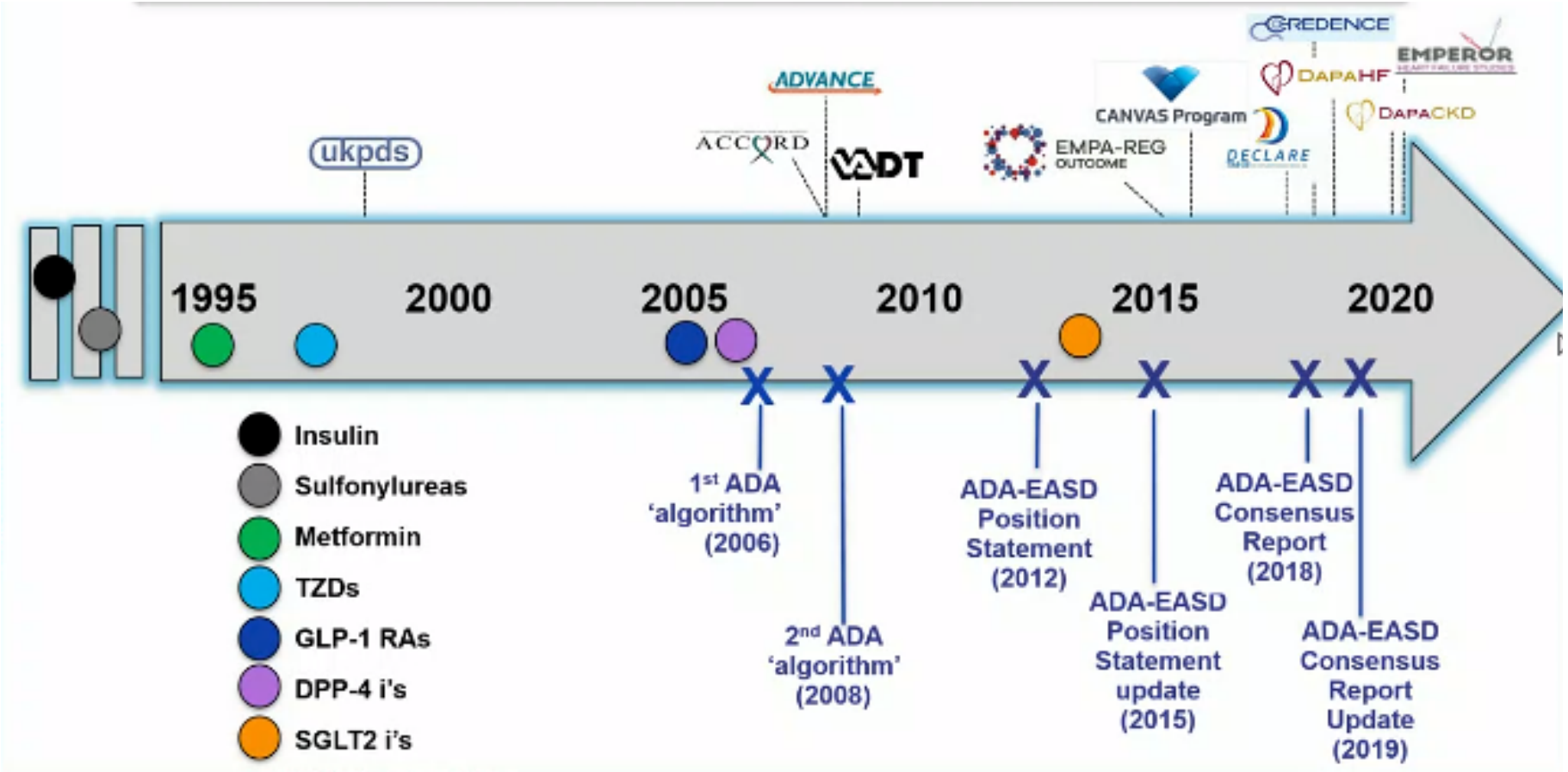
DISCLOSURES

Astra Zeneca, Novo-Nordisk, Servier.
(Speaker)

Astra Zeneca, Novo-Nordisk, Mundipharma.
(Advisory Board)

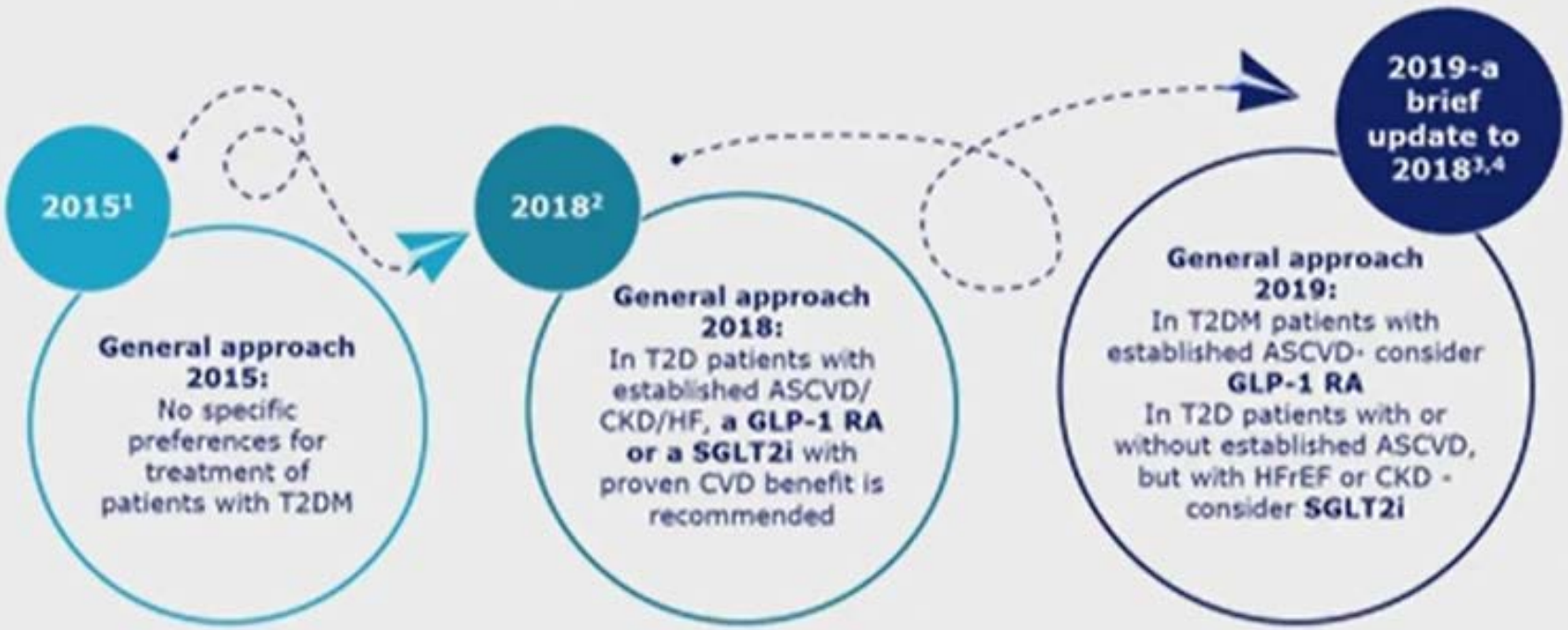
Novo-Nordisk, Boehringer Ingelheim
(Grants)

TRATTAMENTO DEL DM2 NEGLI ULTIMI 25 ANNI



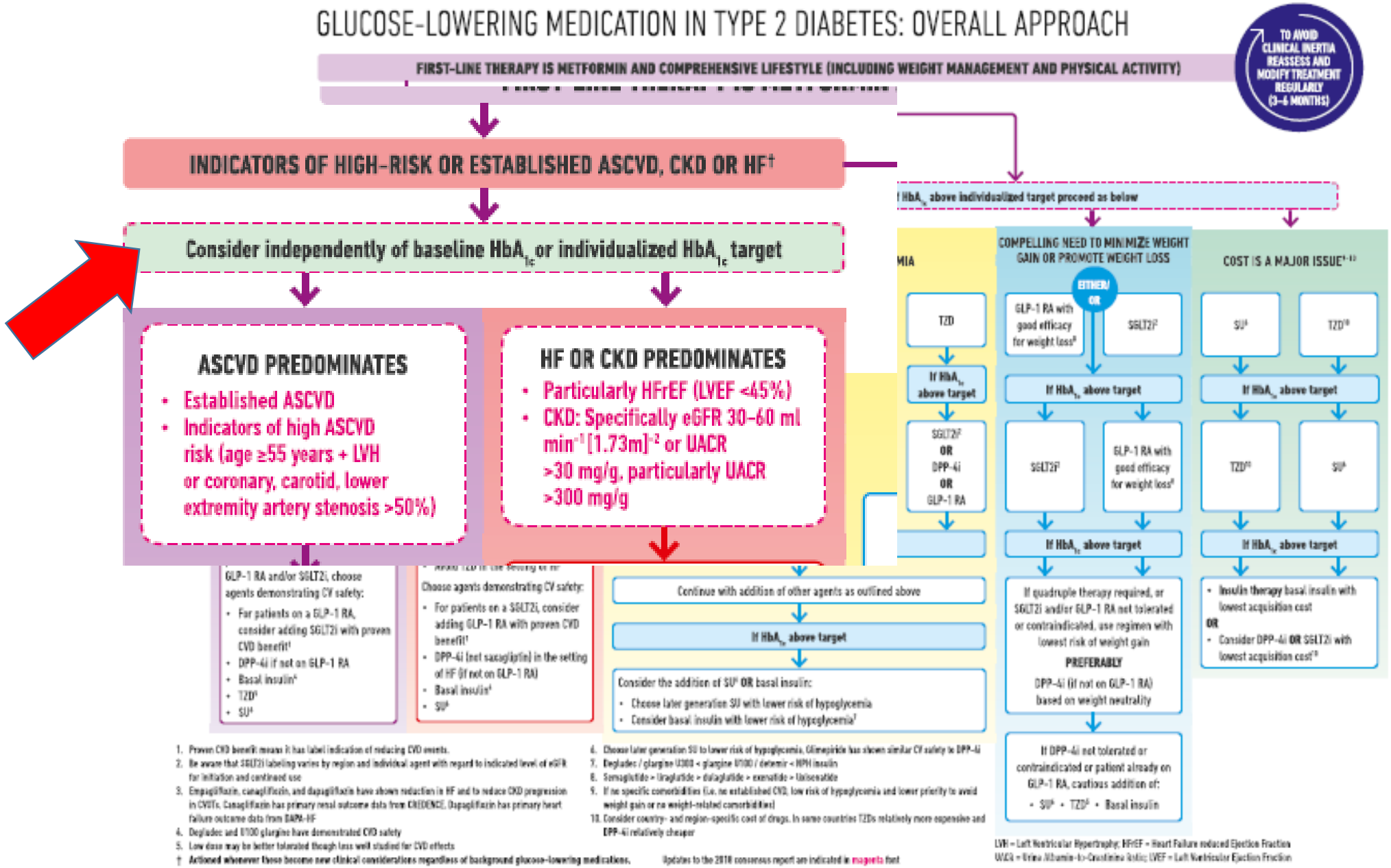
INZUCCHI S. EASD 2020

Evolution of ADA/EASD guidelines for T2DM



ADA, American Diabetes Association; EASD, European Society of Cardiology; T2DM, type 2 diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure; GLP-1 RA, glucagon like peptide 1 receptor agonist, SGLT-2i, sodium glucose cotransporter 2 inhibitor; HFrEF, heart failure with reduced ejection fraction

1. Inzucchi SE et al. Diabetologia 2015;58:429–442 ; 2. Davies MJ et al. Diabetologia 2018;61:2461-2498; 3 Buse JB et al. Diabetologia 2019;doi:10.1007/s00125-019-05039-w; 4. Diabetes Care; 2019 doi190066


GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH
FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD OR HF†
Consider independently of baseline HbA1c or individualized HbA1c target
ASCVD PREDOMINATES
Established ASCVD
Indicators of high ASCVD risk (age ≥55 years + LVH or coronary, carotid, lower extremity artery stenosis >50%)
HF OR CKD PREDOMINATES
Particularly HFrEF (LVEF <45%)
CKD: Specifically eGFR 30–60 ml min⁻¹ [1.73m]⁻² or UACR >30 mg/g, particularly UACR >300 mg/g
If HbA1c above individualized target proceed as below
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
COST IS A MAJOR ISSUE
TZD
If HbA1c above target
SGLT2i OR DPP-4i OR GLP-1 RA
GLP-1 RA with good efficacy for weight loss
SGLT2i
EITHER/ OR
If HbA1c above target
SGLT2i
GLP-1 RA with good efficacy for weight loss
If HbA1c above target
If quadruple 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 • TZD • Basal insulin
SU
TZD
If HbA1c above target
TZD
SU
If HbA1c above target
Insulin therapy basal insulin with lowest acquisition cost
OR
Consider DPP-4i OR SGLT2i with lowest acquisition cost
GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit
DPP-4i if not on GLP-1 RA
Basal insulin
TZD
SU
Choose agents demonstrating CV safety:
For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit
DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
Basal insulin
SU
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of SU OR basal insulin:
Choose later generation SU with lower risk of hypoglycemia
Consider basal insulin with lower risk of hypoglycemia
1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labeling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF
4. Degludec and U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 > glargine U100 / detemir > NPH insulin
8. Semaglutide > Dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries T2Ds relatively more expensive and DPP-4i relatively cheaper
† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
Updates to the 2018 consensus report are indicated in magenta font
LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Dalla corteccia del melo una molecola con effetto antidiabetico: la florizina

Isolata dal tronco del melo (1835)

Scoperto l'effetto ipoglicemizzante (1899)

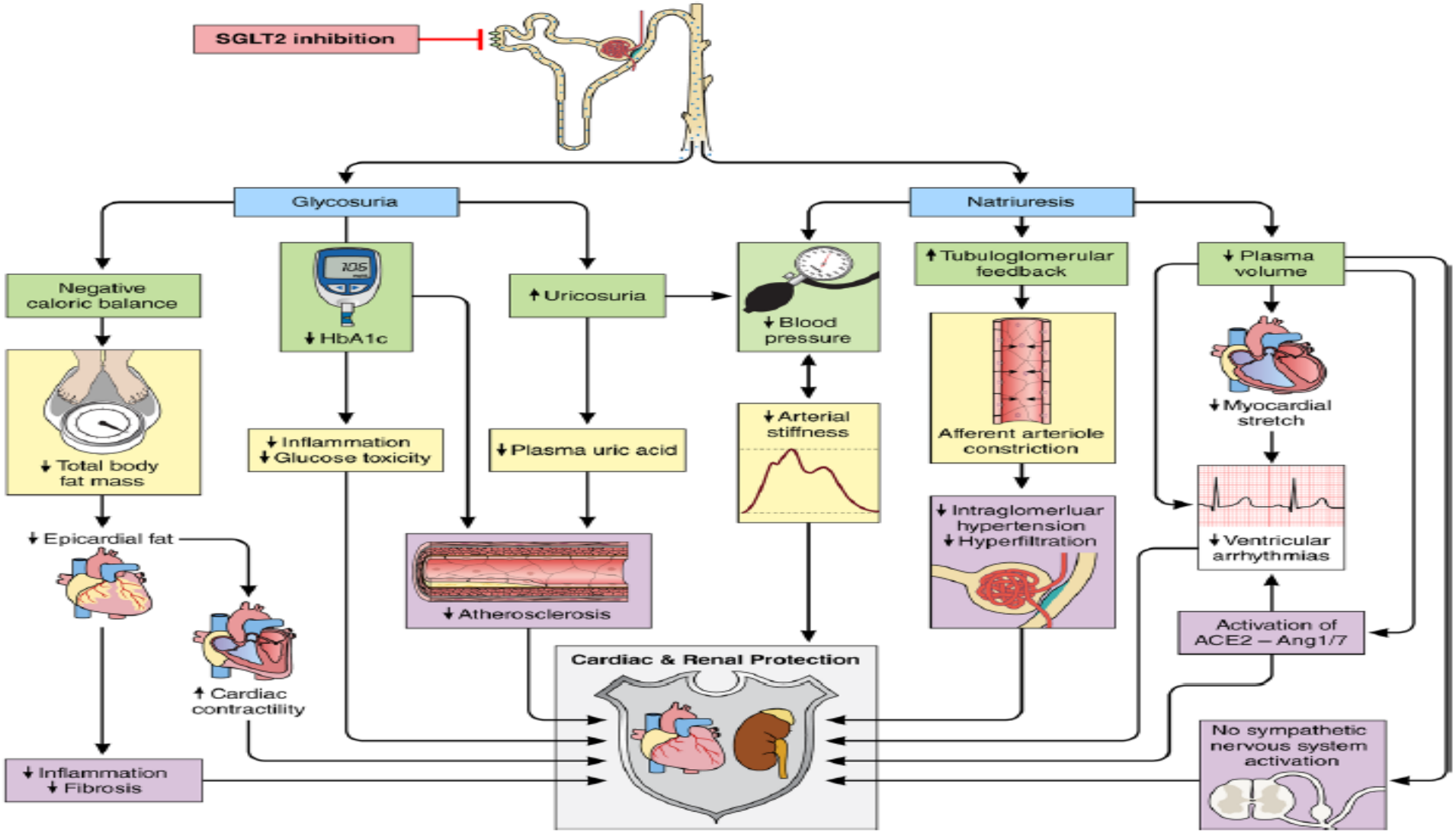
Identificato il meccanismo d'azione renale (1933)

Scoperto l'effetto antidiabetico (1987)

Inibitori SGLT2

https://www.acef.it/glucoflozin-s-tit-mela-50-florizina/

L’inibizione di SGLT2 ha un effetto pleiotropico di protezione cardiorenale



Circulation. 2016;134:752–772. DOI: 10.1161/CIRCULATIONAHA.116.021887

Efficacia degli SGLT2i su glicata, peso, PA

Figure 4: HbA1c lowering (%) with highest approved doses of SGLT-2 inhibitors:

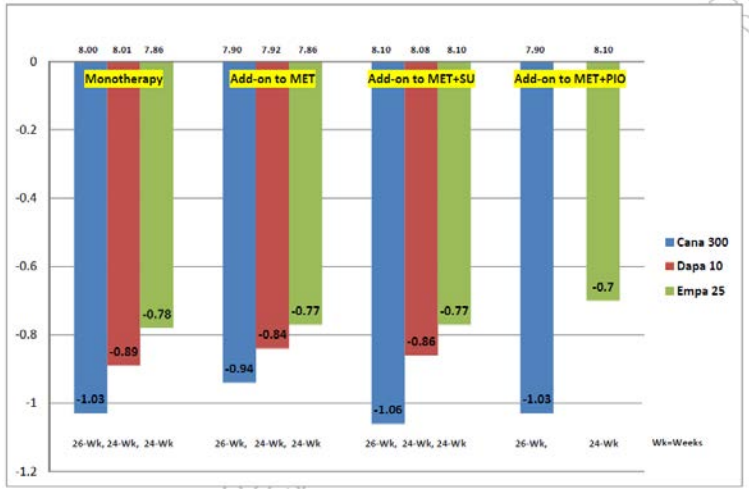


Figure 5: Body weight lowering (Kg) with highest approved doses of SGLT-2 inhibitors:

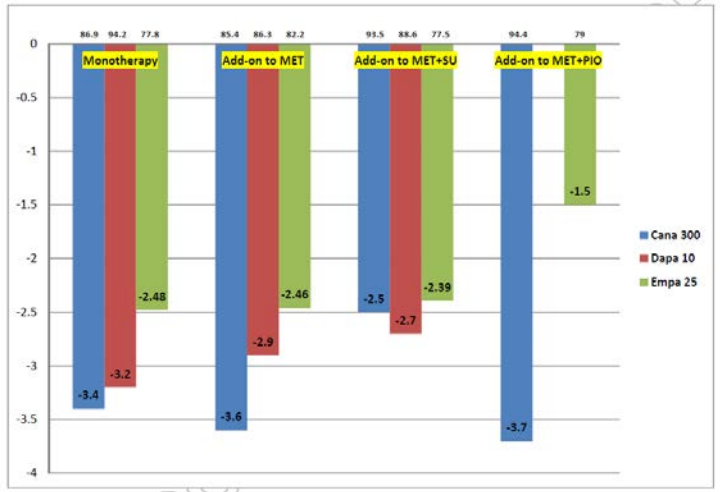
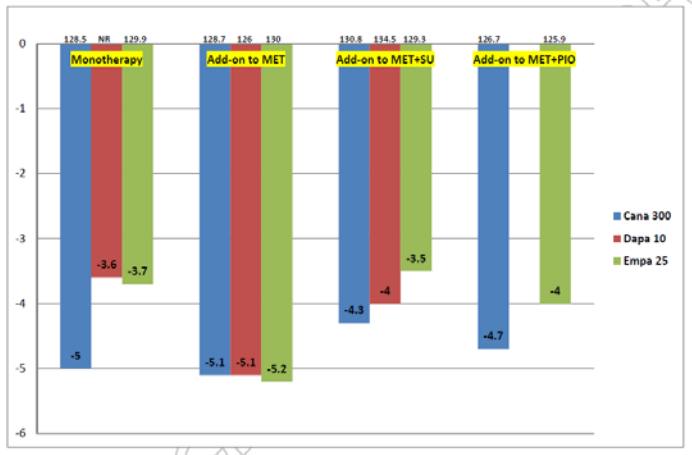
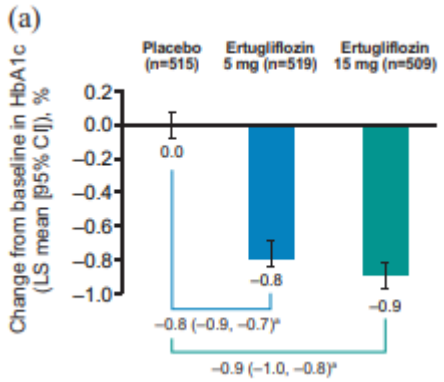
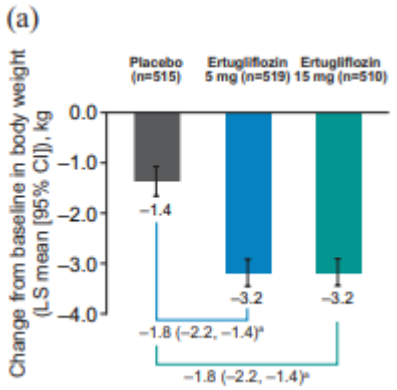
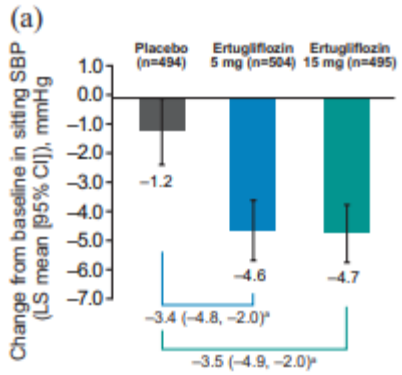


Figure 6: Systolic blood pressure lowering (mm of Hg) with highest approved doses of SGLT-2 inhibitors:









Awadhesh Kumar Singh & Ritu Singh Expert Review of Clinical Pharmacology 2017

Liu J et al Diabetes & Vascular Disease Research 2019

SGLT2i - STUDI DISPONIBILI:

- **EMPA-REG OUTCOME**
- **CANVAS Trials Program**
  - CANVAS
  - CANVAS-R
- **DECLARE-TIMI 58**
- **CREDENCE**
- **VERTIS CV**
- **DAPA CKD, DAPA HF, EMPEROR Reduced**
- (popolazioni speciali con e senza diabete)

SGLT-2i: CVOT nel diabete tipo 2

pazienti con e senza diabete

	EMPA-REG	CANVAS	DECLARE	VERTIS	CREDENCE	DAPA-HF	EMPEROR-R
	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Canagliflozin renal	Dapagliflozin HFrEF	Empagliflozin HFrEF
Type 2 diabetes %	100	100	100	100	100	45	50
Prior CV disease %	100	65	41	100	50	**LVEF %** 31	27
Prior heart failure %	10	14	10	23	14	100	100
3pt MACE	**0.86*** 0,74, 0.99	**0.86*** 0,75, 0.97	**0.93** 0,84, 1.03	**0.97** 0,85, 1.11	**0.80*** 0.67, 0.95	**wHF/CV death** **0.74*** 0.64, 0.85	**0.75*** 0.65, 0.86
CV death	**0.62*** 0.49, 0.77	**0.87** 0,72, 1.06	**0.98** 0.82, 1.17	**0.92** 0.77, 1.11	**0.78** 0.61, 1.00	**0.82*** 0.69, 0.98	**0.92** 0.75, 1.12
Non-fatal MI	**0.87** 0.70, 1.09	**0.85** 0,69, 1.05	**0.89** 0.77, 1.01	**1.00** 0.86, 1.27	**0.81** 0.59, 1.10		
Non-fatal stroke	**1.24** 0.92, 1.67	**0.90** 0,71, 1.15	**1.01** 0.84, 1.21	**1.00** 0.76, 1.32	**0.80** 0.56, 1.15		
Hospitalised HF	**0.65*** 0.50, 0.85	**0.67*** 0,52, 0.87	**0.73*** 0.61, 0.88	**0.70*** 0.54, 0.90	**0.61*** 0.47, 0.80	**Hospitalised HF** **0.70*** 0.59, 0.83	**0.69*** 0.59, 0.81
All cause death	**0.68*** 0.57, 0.82	**0.87** 0,74, 1.01	**0.93** 0,82, 1.04		**0.83** 0.68, 1.02	**All cause death** **0.83*** 0.71, 0.97	**0.92** 0.77, 1.10

CV, cardiovascular; MACE, major adverse cardiovascular event, MI, myocardial infarction; HF, heart failure; wHF, worsening heart failure.

* Statistically significant or nominally statistically significant. Declare may include fatalities in MI and stroke figures

Adapted from Bailey & Day, Diab Res Clin Pract 2019, 155, 107785. and from Zannad et al, Lancet Dbl 2020, 396, 819-829

Bailey C.J. EASD 2020

Figure 1. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Major Adverse Cardiovascular Events—Composite of Myocardial Infarction, Stroke, or Cardiovascular Death

A Overall MACEs

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model ($Q = 5.22$; $df = 4$; $P = .27$; $I^2 = 23.4\%$)					0.90 (0.85-0.95)

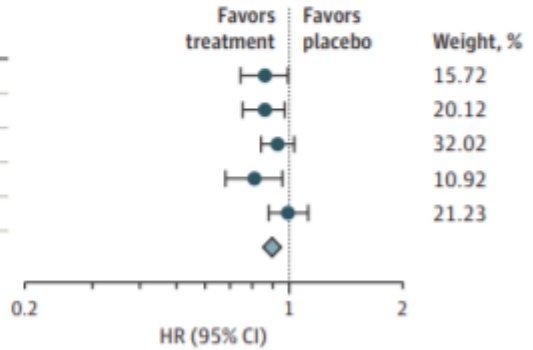
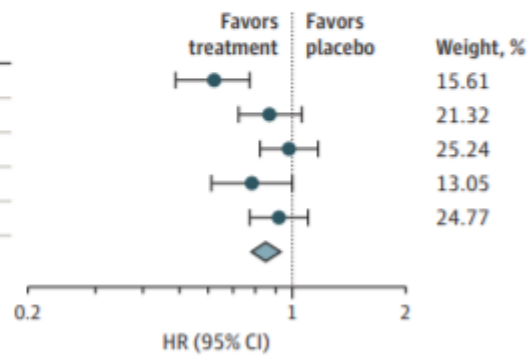


Figure 2. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Cardiovascular Death

A Overall CV death

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)
CANVAS program	NA/5795	11.6	NA/4347	12.8	0.87 (0.72-1.06)
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	0.98 (0.82-1.17)
CREDENCE	110/2202	19.0	140/2199	24.4	0.78 (0.61-1.00)
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)
Fixed-effects model ($Q = 11.22$; $df = 4$; $P = .02$; $I^2 = 64.3\%$)					0.85 (0.78-0.93)

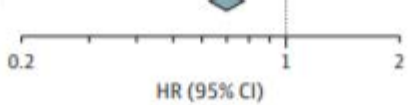


McGuire DK, JAMA 2020

Figure 3. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hospitalization for Heart Failure

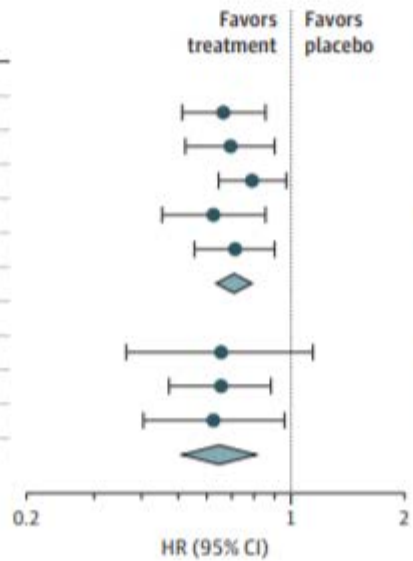
A Overall HHF

	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			16.09
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)			17.10
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)			33.72
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)			16.01
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			17.08
Fixed-effects model (Q = 1.39; *df* = 4; *P* = .85; I^2 = 0.0%)					0.68 (0.61-0.76)			



B HHF by ASCVD status

	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
Patients with ASCVD								
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			19.62
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)			17.13
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)			29.66
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)			12.74
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			20.84
Fixed-effects model (Q = 1.97; *df* = 4; *P* = .74; I^2 = 0.0%)					0.70 (0.62-0.78)			
Patients without ASCVD								
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)			16.38
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)			55.07
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)			28.56
Fixed-effects model (Q = 0.03; *df* = 2; *P* = .99; I^2 = 0.0%)					0.63 (0.50-0.80)			



McGuire DK, JAMA 2020

EMPEROR-Reduced and DAPA-HF trials

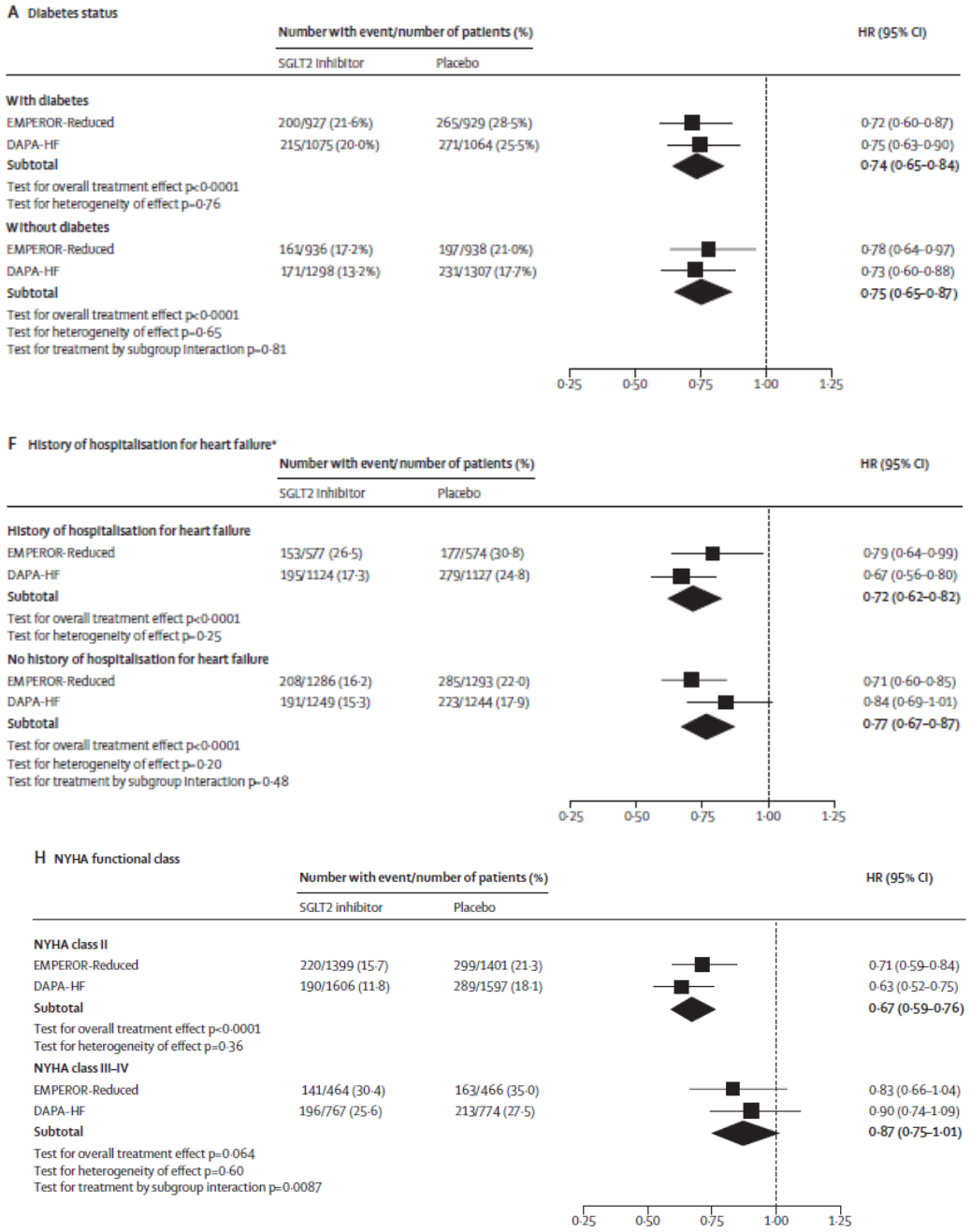
	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Number of participants	1863	1867	2373	2371
Age, years	67·2 (10·8)	66·5 (11·2)	66·2 (11·0)	66·5 (10·8)
Sex				
Men	1426 (76.5%)	1411 (75·6%)	1809 (76·2%)	1826 (77·0%)
Women	437 (23·5%)	456 (24·4%)	564 (23·8%)	545 (23·0%)
NYHA functional classification				
II	1399 (75·1%)	1401 (75·0%)	1606 (67·7%)	1597 (67·4%)
III	455 (24·4%)	455 (24·4%)	747 (31·5%)	751 (31·7%)
IV	9 (0·5%)	11 (0·6%)	20 (0·8%)	23 (1·0%)
Mean LVEF, %	27·7 (6·0)	27·2 (6·1)	31·2 (6·7)	30·9 (6·9)
NT-pro BNP, pg/mL	1887 (1077–3429)	1926 (1153–3525)	1428 (857–2655)	1446 (857–2641)
Medical history				
Hospitalisation for heart failure*	577 (31·0%)	574 (30·7%)	1124 (47·4%)	1127 (47·5%)
Diabetes†	927 (49·8%)	929 (49·8%)	1075 (45·3%)	1064 (44·9%)
eGFR, mL/min per 1·73 m²‡	61·8 (21·7)	62·2 (21·5)	66·0 (19·6)	65·5 (19·3)
Heart failure medications				
ACE inhibitor	867 (46·5%)	836 (44·8%)	1332 (56·1%)	1329 (56·1%)
ARB	451 (24·2%)	457 (24·5%)	675 (28·4%)	632 (26·7%)
Mineralocorticoid receptor antagonist	1306 (70·1%)	1355 (72·6%)	1696 (71·5%)	1674 (70·6%)
ARNI	340 (18·3%)	387 (20·7%)	250 (10·5%)	258 (10·9%)
Device therapy				
ICD or CRT-D	578 (31·0%)	593 (31·8%)	622 (26·2%)	620 (26·1%)
CRT-D or CRT-P	220 (11·8%)	222 (11·9%)	190 (8·0%)	164 (6·9%)

Data are n (%), mean (SD), or median (IQR). ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor neprilysin inhibitor. CRT-D=cardiac resynchronisation therapy defibrillator. CRT-P=cardiac resynchronisation therapy pacemaker. eGFR=estimated glomerular filtration rate. ICD=implantable cardiac defibrillator. LVEF=left ventricular ejection fraction. NT-pro BNP=N-terminal pro B-type natriuretic peptide. NYHA=New York Heart Association. *For EMPEROR-Reduced: preceding 12 months. †Determined by a combination of medical history and pre-treatment glycated haemoglobin. ‡Chronic Kidney Disease Epidemiology Collaboration formula.

Table 1: **Overview of main characteristics of the two trial populations at baseline**

Zannad F. ***Lancet*** **2020; 396: 819–29**

EMPEROR-Reduced and DAPA-HF trials



Zannad F. Lancet 2020; 396: 819–29

SGLT-2i: Outcome renali nel diabete tipo 2

pazienti con e senza diabete

	EMPA-REG	CANVAS	DECLARE	VERTIS	CREDENCE	DAPA-HF	EMPEROR-R
	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Canagliflozin renal	Dapagliflozin HFrEF	Empagliflozin HFrEF
n	7,020	10,142	17,160	8,246	4,401	4,744	3,730
eGFR ml/min/1.73m²	74	76	85	76	56	66	61
Microalbuminuria (%)	29	22.7	23.4				
Macroalbuminuria (%)	11	7.6	6.8		77.3		
Reduce decline in eGFR	Yes	Yes	Yes	Yes	Yes	Yes	Yes
New or worse nephropathy	**0.61*** 0.53, 0.70	**0.73** 0.67, 0.79					
Progression to macroalbuminuria	**0.62*** 0.54, 0.72						
Renal composite* Components vary between studies	**0.54** 0.40, 0.75	**0.60** 0.47, 0.77	**0.53** 0.43, 0.66	**0.81** 0.63, 1.04	**0.70** 0.59, 0.82	**0.71** 0.44, 1.16	**0.50** 0.32, 0.77
Regression of albuminuria		Yes			Yes 31%		
Follow-up (median yr)	3.1	2.4	4.2	3.0	2.6	1.5	1.3

eGFR, estimated glomerular filtration rate by MDRD (EPI for Empa- and Cana-gliflozin studies). Microalbuminuria UACR 30-300 mg/g; macroalbuminuria >300 mg/g
CV, cardiovascular; MACE, major adverse cardiovascular event, MI, myocardial infarction; HF, heart failure; wHF, worsening heart faiture.
* Renal composite varies between studies: mostly 40% ↓ eGFR, end stage / dialysis / transplant, renal death. In EMPA-REG, doubling serum creatinine, decrease eGFR<45, renal replacement, renal death (± CV death).

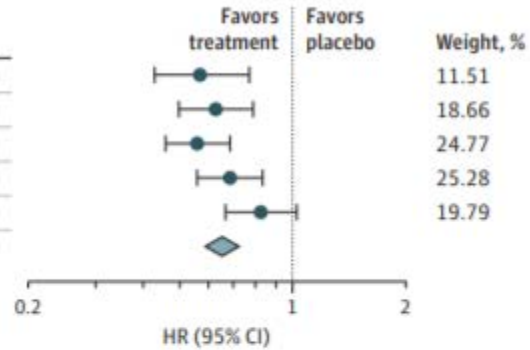
Adapted from Bailey & Day, Diab Res Clin Pract 2019, 155, 107785. and from Zannad et al, Lancet DEI 2020, 396, 819-829

Bailey C.J EASD 2020.

Figure 4. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Kidney-Related Outcomes

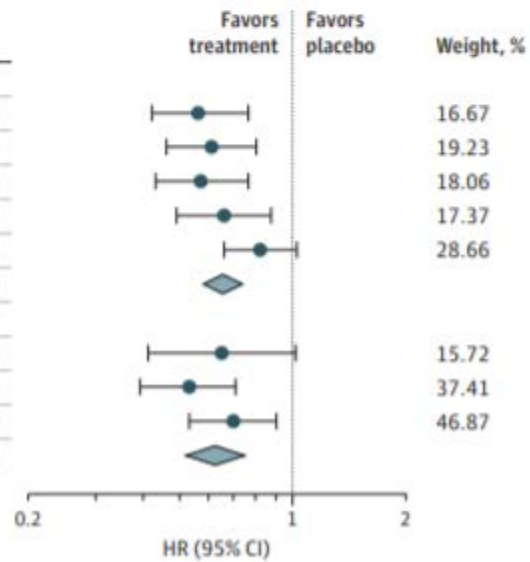
A Overall kidney outcomes

	Treatment		Placebo		Hazard ratio (95% CI)	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years		
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)	11.51
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)	18.66
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)	24.77
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)	25.28
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)	19.79
Fixed-effects model (Q = 7.96; *df* = 4; *P* = .09; I^2 = 49.7%)					0.62 (0.56-0.70)	



B Kidney outcomes by ASCVD status

	Treatment		Placebo		Hazard ratio (95% CI)	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years		
Patients with ASCVD						
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)	16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)	19.23
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)	18.06
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)	17.37
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)	28.66
Fixed-effects model (Q = 6.09; *df* = 4; *P* = .19; I^2 = 34.4%)					0.64 (0.56-0.72)	
Patients without ASCVD						
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)	15.72
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)	37.41
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)	46.87
Fixed-effects model (Q = 1.86; *df* = 2; *P* = .40; I^2 = 0.0%)					0.60 (0.50-0.73)	



McGuire DK, JAMA 2020

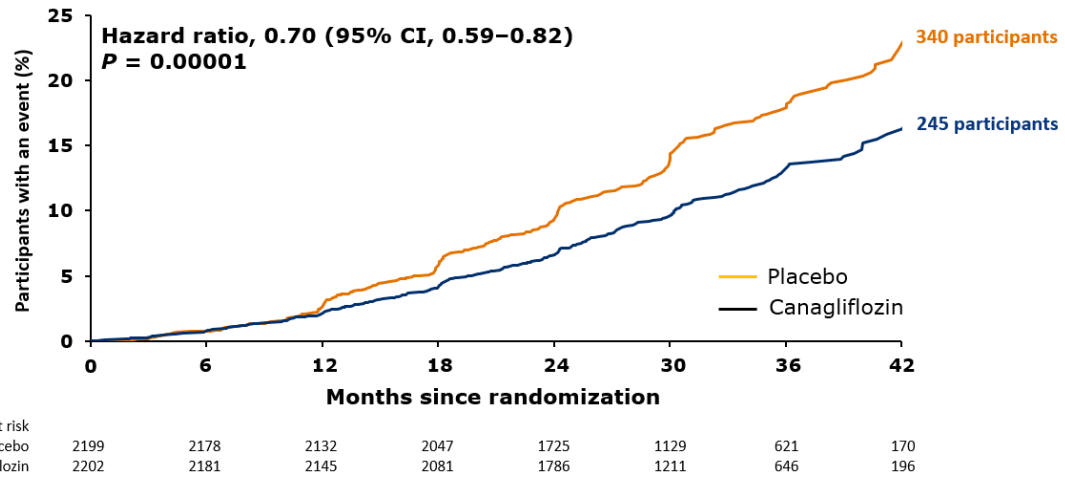
Credence: valutare gli effetti di canagliflozin, sugli outcome renali clinicamente rilevanti nelle persone con DM2 e CKD accertata

Baseline Renal Characteristics

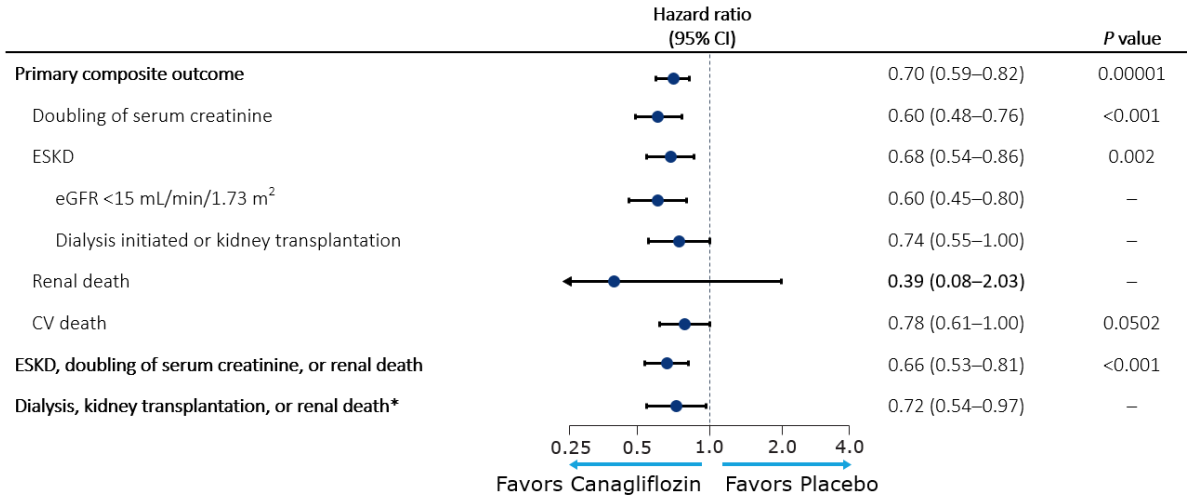
	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Mean eGFR, mL/min/1.73 m²	**56**	**56**	**56**
eGFR ≥90, %	5	5	5
eGFR ≥60 to <90, %	36	35	35
eGFR ≥45 to <60, %	29	29	29
eGFR ≥30 to <45, %	27	27	27
eGFR <30, %	4	4	4
Median UACR (IQR), mg/g	**923 (459-1794)**	**931 (473-1868)**	**927 (463-1833)**
UACR <30, %	<1	<1	<1
UACR 30-300, %	11	11	11
UACR >300-≤3000, %	77	76	77
UACR >3000, %	11	12	11

Età media 63 anni; donne 33,9%, HbA1c media 8,3%; durata del DM2 15,8 anni.

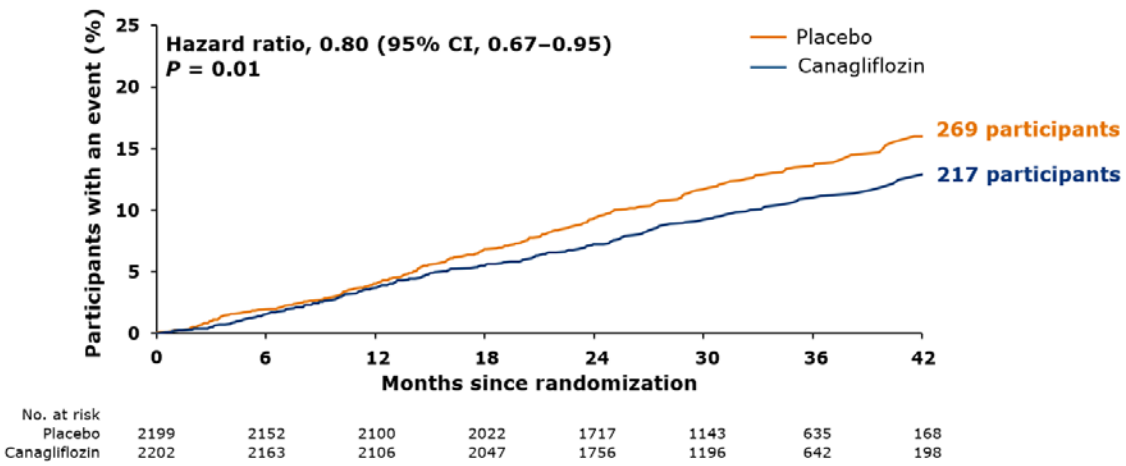
Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death



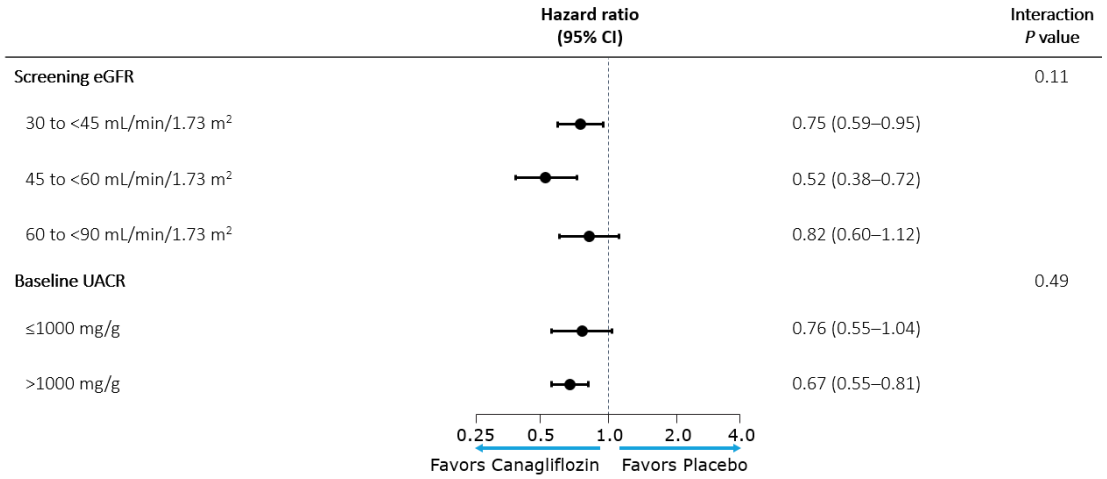
Summary Forest Plot



Major Cardiovascular Events: Cv Death, MI or Stroke



Primary Outcome by Screening eGFR and Albuminuria



DAPA-CKD: valutare se il trattamento con dapagliflozin, rispetto al placebo, riduce il rischio di eventi renali e cardiovascolari in pazienti con CKD con o senza T2D, in trattamento con terapia standard inclusa la dose massima tollerata di un ACEi o ARB

Demographic Characteristics Were Well-Balanced Between Treatment Groups

	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)
Age, years, mean	62	62
Gender, female, %	33	33
Race, %		
White	52	54
Black or African-American	5	4
Asian	35	33
Other	8	8
Type 2 diabetes, %	68	67
Systolic blood pressure, mmHg, mean	137	137
eGFR, mL/min/1.73m^2, mean	43	43
UACR, mg/g, median	965	934
ACEi or ARB, %	97	97

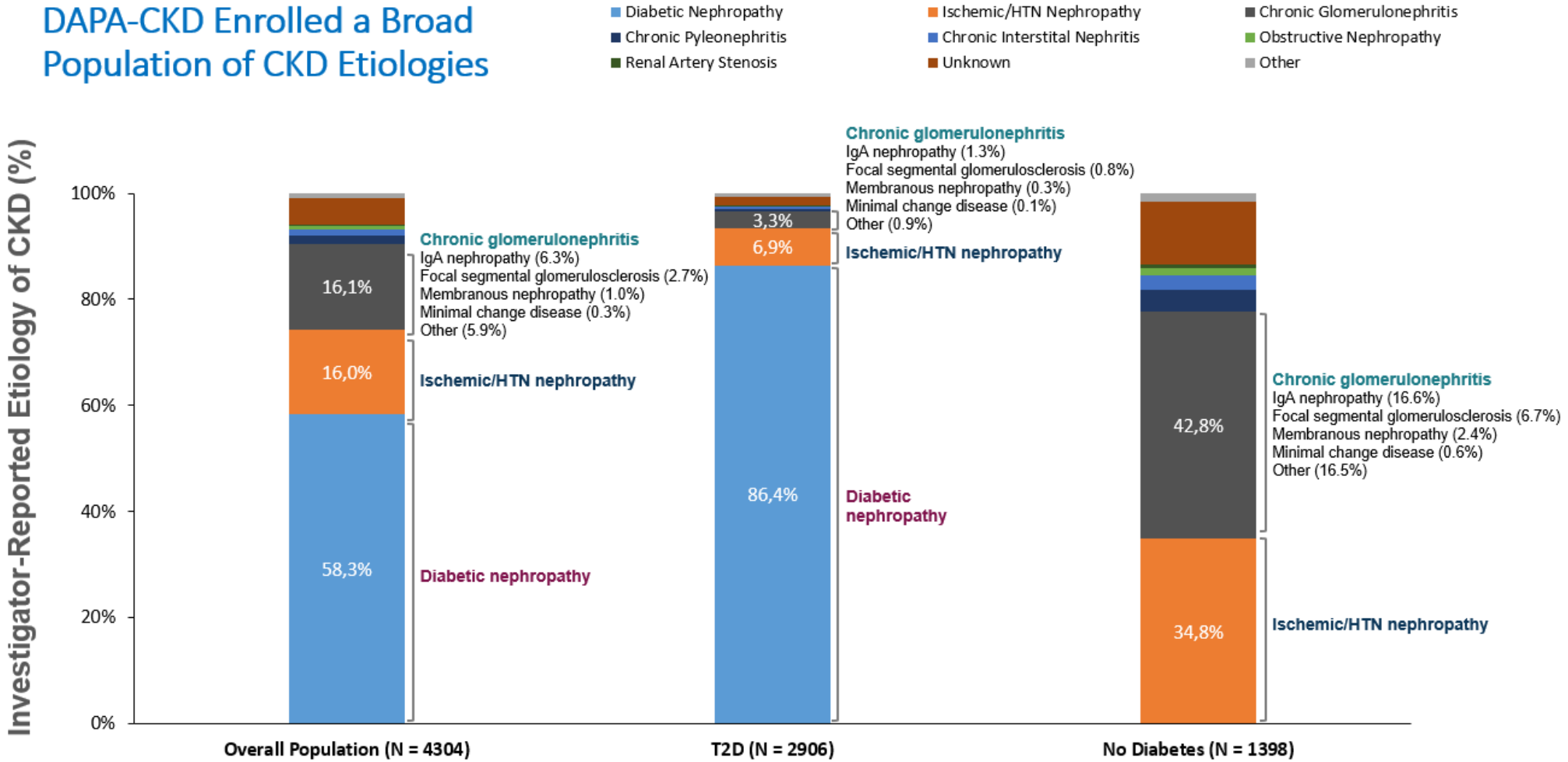
CKD Etiologies in DAPA-CKD

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BL = baseline; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio.

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

DAPA-CKD

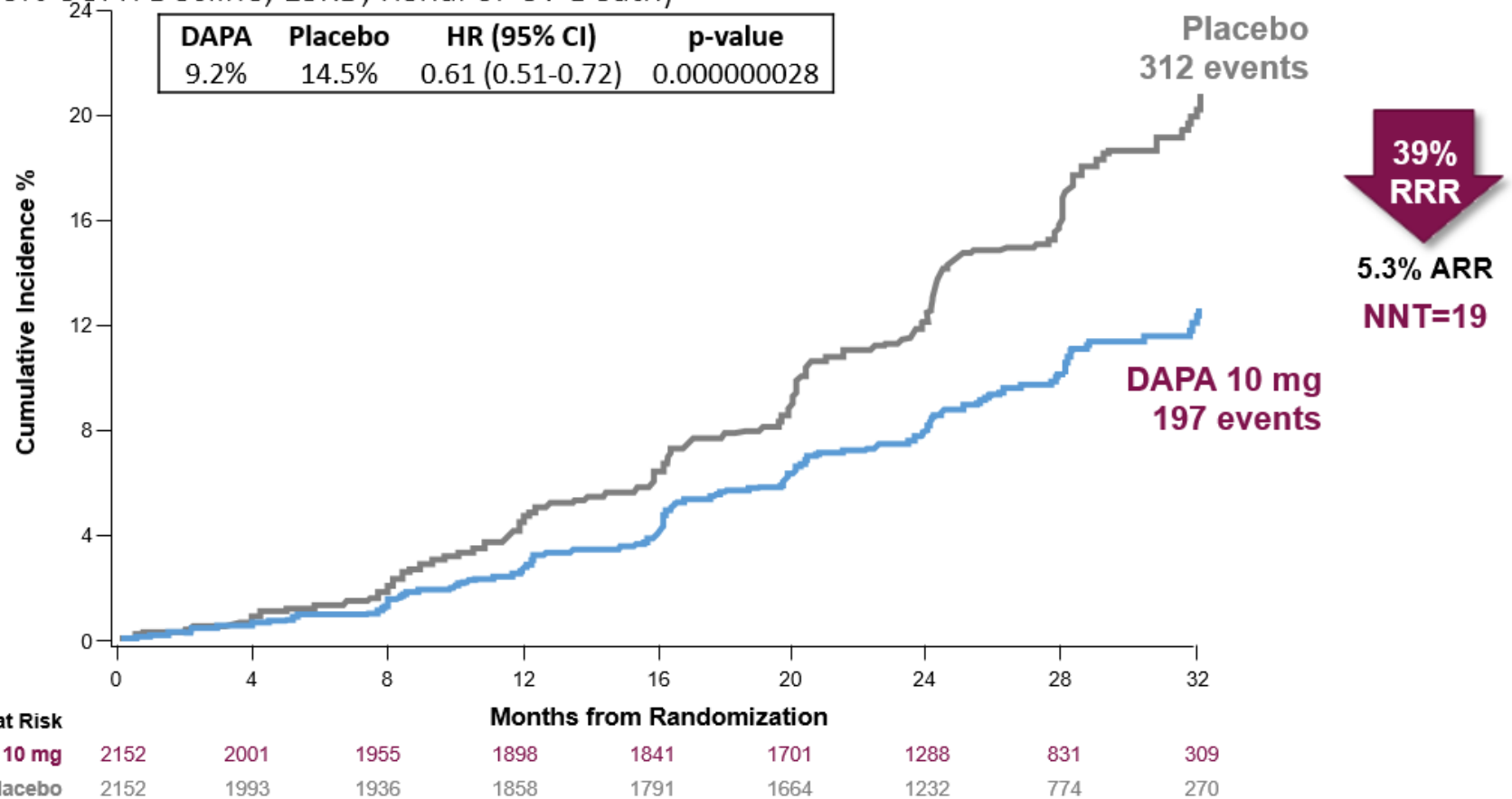
DAPA-CKD Enrolled a Broad Population of CKD Etiologies



HTN = hypertensive; IgA = immunoglobulin A; T2D = type 2 diabetes.

Wheeler DC et.al. Online ahead of print. *Nephrol Dial Transplant*. 2020.

Dapagliflozin Significantly Slowed Progression of Kidney Disease and Reduced the Risk of Adverse Outcomes (Sustained ≥ 50% eGFR Decline, ESKD, Renal or CV Death)[a]



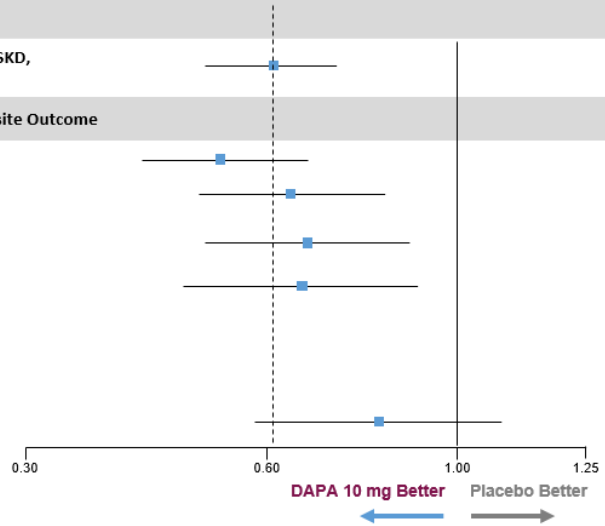
[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m² for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2] ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; RRR = relative risk reduction.

1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020. 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

DAPA-CKD

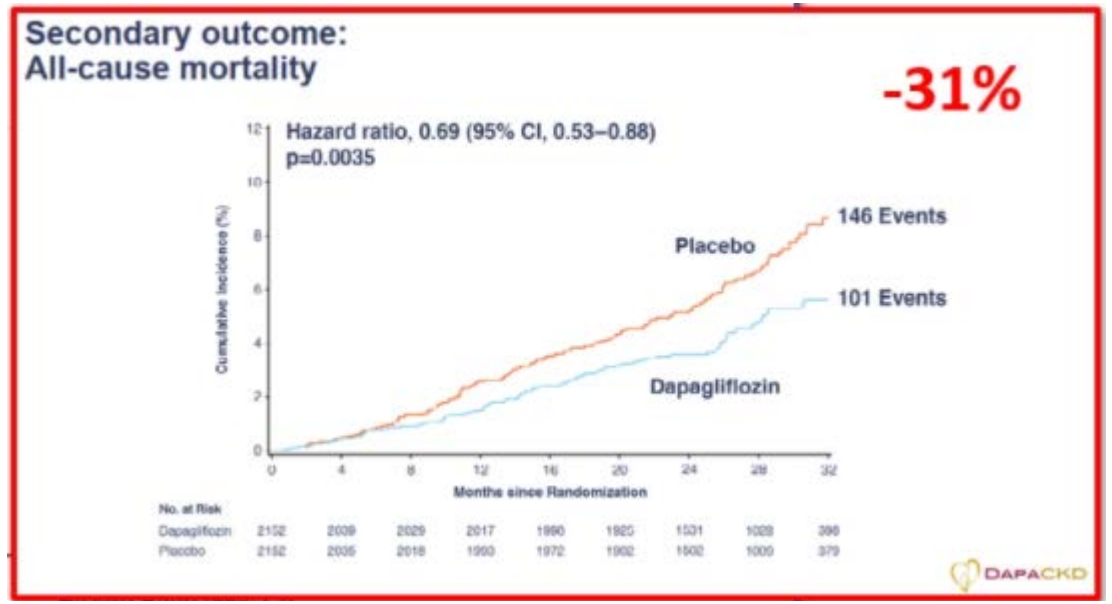
All Individual Components Contributed to the Significant Primary Outcome Treatment Effect

	Number of Events				
HR (95% CI)	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value
Primary Composite Outcome					
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death	197	312	0.61	(0.51, 0.72)	0.000000028
Components of the Primary Composite Outcome					
≥50% eGFR Decline	112	201	0.53	(0.42, 0.67)	<0.0001
ESKD	109	161	0.64	(0.50, 0.82)	0.0004
eGFR <15mL/min/1.73m²	84	120	0.67	(0.51, 0.88)	0.0045
Chronic Dialysis	68	99	0.66	(0.48, 0.90)	0.0080
Transplantation	3	8	NC		
Renal Death	2	6	NC		
CV Death	65	80	0.81	(0.58, 1.12)	0.2029



CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NC = not calculable

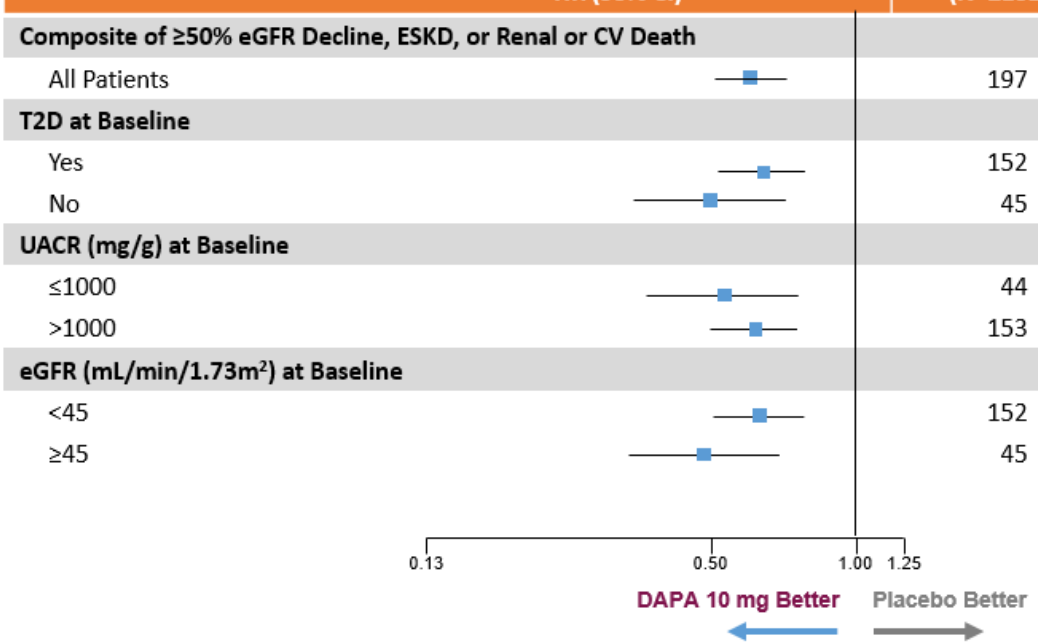
Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.



DAPA-CKD

Treatment Benefit Was Consistent Across Key Pre-Specified Subgroups

	Number of Events				
	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline					0.52
≤1000	44	84	0.54	(0.37, 0.77)	
>1000	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m²) at Baseline					0.22
<45	152	217	0.63	(0.51, 0.78)	
≥45	45	95	0.49	(0.34, 0.69)	



Additional Subgroups

CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

SGLT2i nel DM2 e nella gestione del rischio cario-renale
effetto di classe?

Gli effetti degli SGLT2i sugli outcome cardiovascolari e renali sono ampiamente coerenti tra tutte le molecole e suggeriscono un effetto di classe

E' stato osservato un beneficio maggiore sulla riduzione del rischio di ospedalizzazione per scompenso (30%) e progressione della malattia renale (40%). Tali effetti sono indipendenti dalla pregressa ASCVD o malattia renale e coerenti in popolazioni con scompenso o malattia renale a prescindere dal presenza di diabete

Le stime dell'effetto sul rischio di ospedalizzazione per scompenso erano le più coerenti in tutti gli studi

Effetti più modesti sulla riduzione dei MACE, (circa il 10%), con eterogeneità tra gli studi, EMPAREG, CANVAS, CREDENCE, che mostrano effetti benefici e minore efficacia in pazienti con ASCVD.

Riduzione della morte CV solo in EMPAREG e DAPA HF

Ongoing Large HF & CKD Trials with SGLT2 Inhibitors

Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved)

- Chronic HF (NYHA II-IV)
- LVEF >40%
- ↑ NT-proBNP
- eGFR >20
- N=5988
- 1°: HHF / CV death
- Est. completion: 2021

Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction HF (DELIVER)

- Chronic HF (NYHA II-IV)
- LVEF >40%
- ↑ NT-proBNP
- eGFR ≥25
- N=6100
- 1°: Worsening HF/CV death
- Completion: 2021

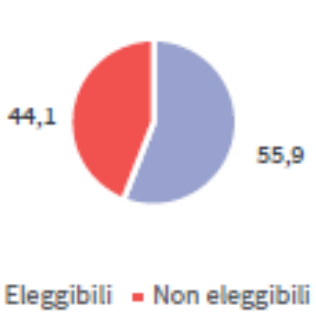
EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin)

- eGFR 20-45 or 45-90 + UACR >500
- N=6000
- Outcome: ESKD, renal or CV death or 40% ↓ in eGFR
- Completion: 2022

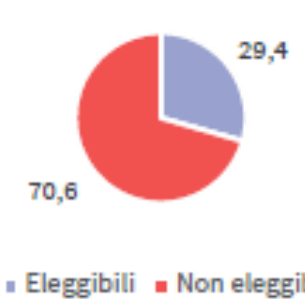
www.clinicaltrials.gov (accessed 9/19/20)

Soggetti complessivamente eleggibili per lo studio EMPAREG OUTCOME
e trattati con SGLT2i tra i soggetti eleggibili

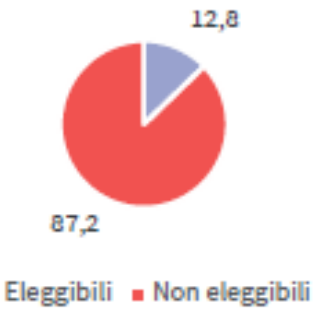
Soggetti complessivamente eleggibili per lo studio DECLARE–TIMI 58
e trattati con SGLT2i tra gli eleggibili



Soggetti complessivamente eleggibili per lo studio CANVAS e
trattati con SGLT2i tra gli eleggibili



Soggetti complessivamente eleggibili per lo studio VERTIS-CV
e trattati con SGLT2i tra gli eleggibili



HbA1c

Rischio e
Outcome cardiorenali