SGLT2i e rene

Perché è importante la prevenzione primaria

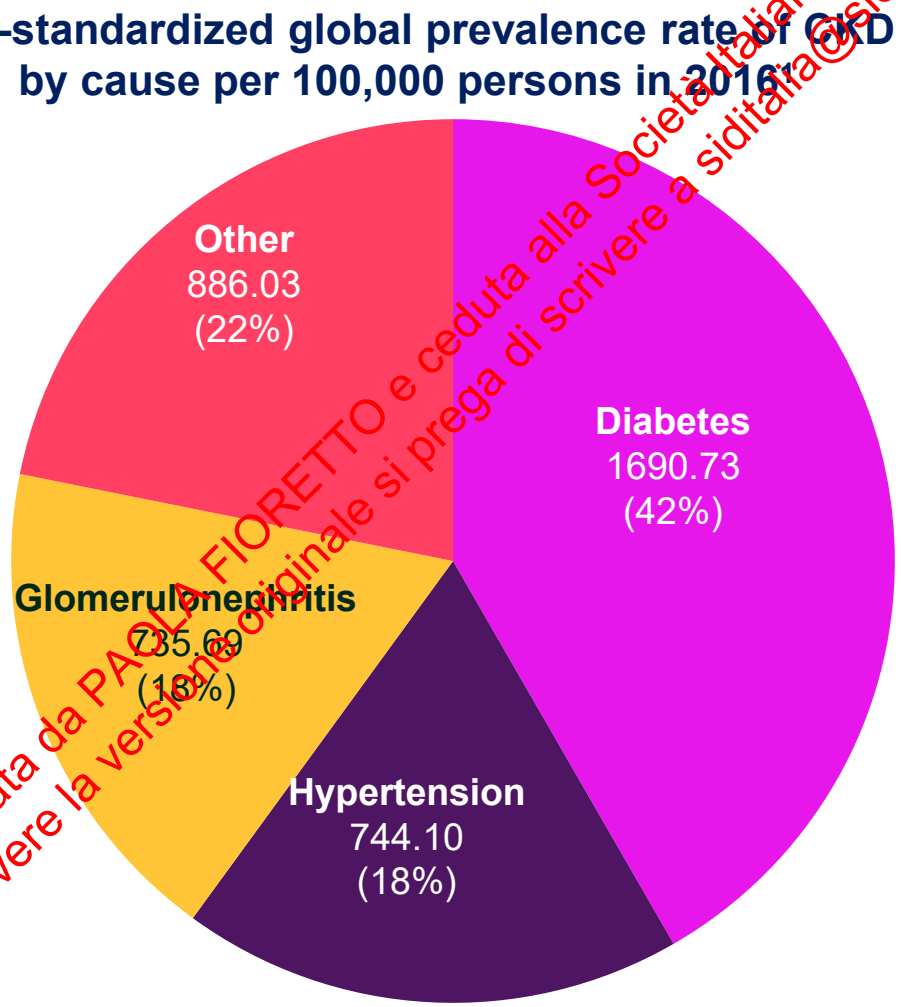
Paola Fioretto
Dipartimento di Medicina
Università di Padova

Disclosures

Professor Paola Fioretto has served as an Advisory Board member and received speaker fees from:

AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Mundipharma, Novo

DIABETES IS THE SINGLE MOST SIGNIFICANT CAUSE OF CKD



Xie Y, et al, Kidney Int, 2018

Cardio-renal disease is the most frequent first comorbidity in T2D

Retrospective analysis of data from > 1.1 million patients with T2D

- **England** Population data
- **Germany** Claims data
- **Japan** Claims data
- **The Netherlands** Population data
- **Norway** Full population data
- **Sweden** Full population data

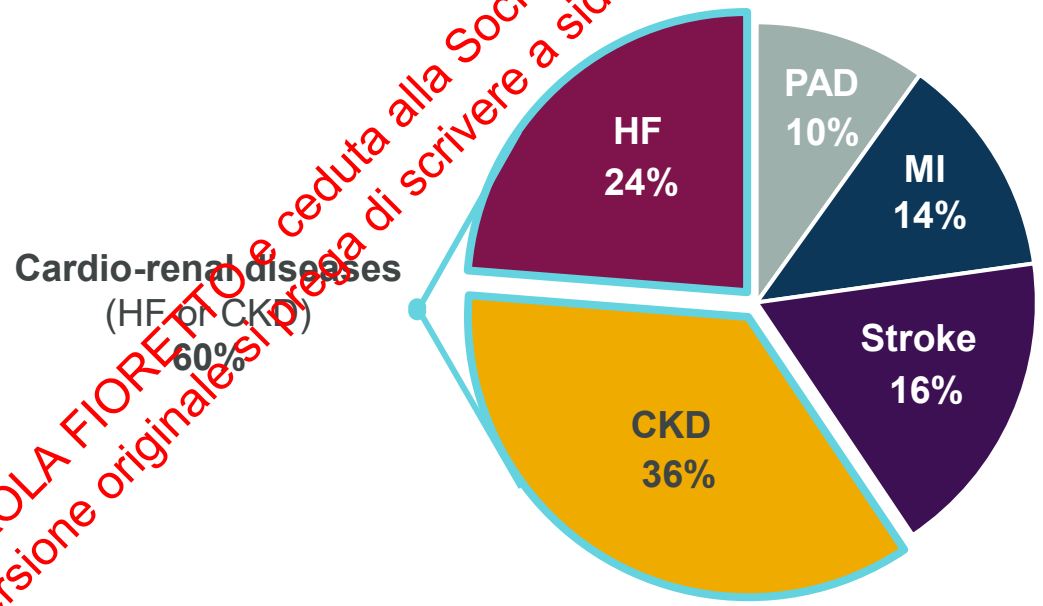
Initially, the majority (66%) of patients were free from CV disease or CKD (CV-free)

Birkeland KI et al. Diabetes Obes Metab, 2020

First comorbidity identified in CV-free patients with T2D

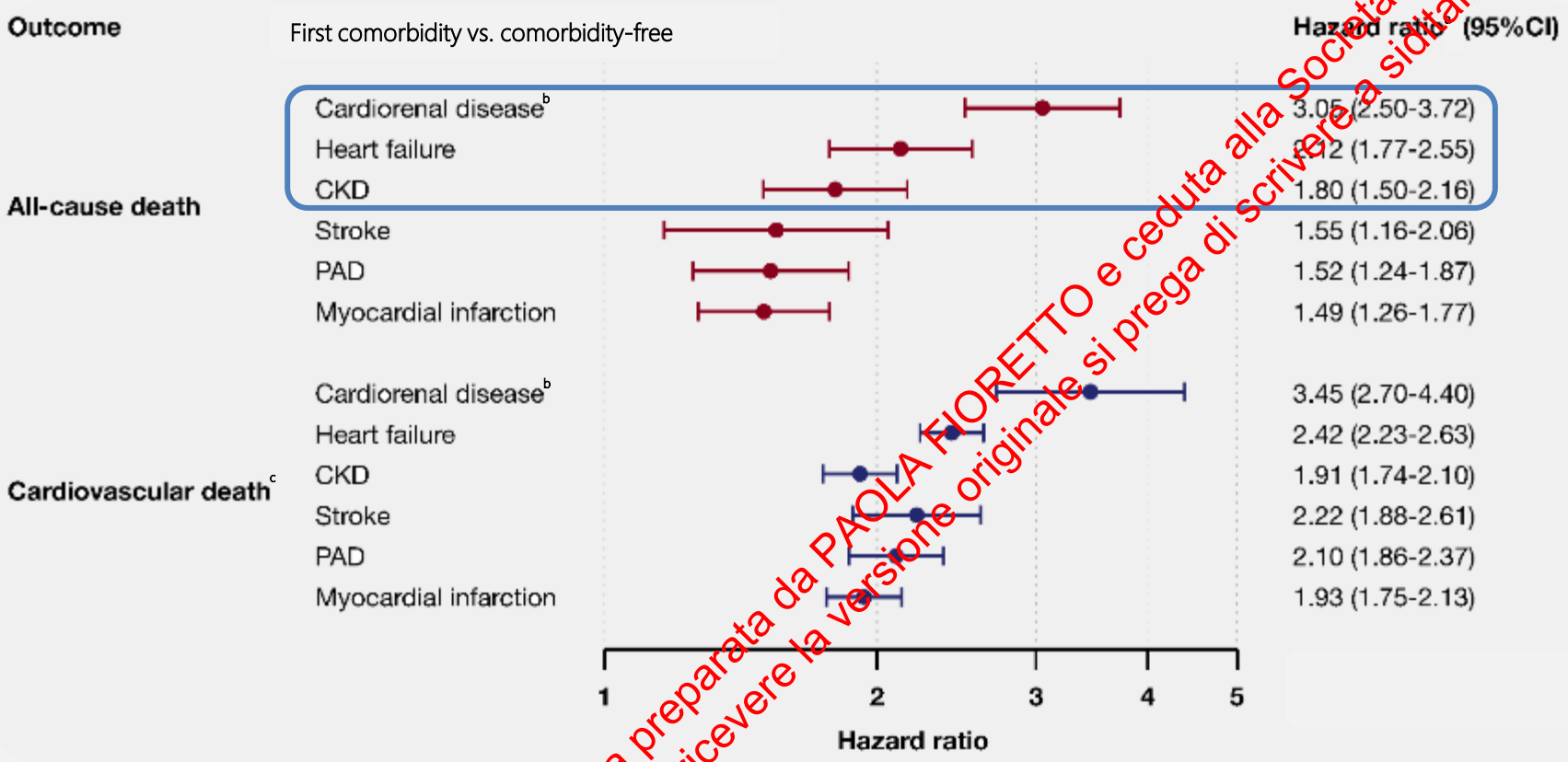
137,081 patients (18% of total CV-free patient population)

Mean follow-up: 4.5 years



Compared with comorbidity-free patients with T2D, **cardio-renal disease was associated with a greater risk of mortality** than stroke, PAD and MI

Mortality Risks Associated With First Comorbidity



Compared with comorbidity-free T2D patients,

- Cardiorenal disease was associated with highest risks of all-cause and CV mortality.

Bidirectional Risk Associations[d]

Compared with comorbidity-free T2D patients,

- HF was associated with >2-fold increased risk of CKD;
- CKD was associated with >2-fold increased risk of HF.

Birkeland KI, et al. Diabetes Obes Metab, 2020

Annali AMD 2019
343.369 patients

Risk of progression

- Low risk (if no other markers of kidney disease, no CKD)
- Moderately increased risk
- High risk
- Very high risk

Declining kidney function (eGFR)

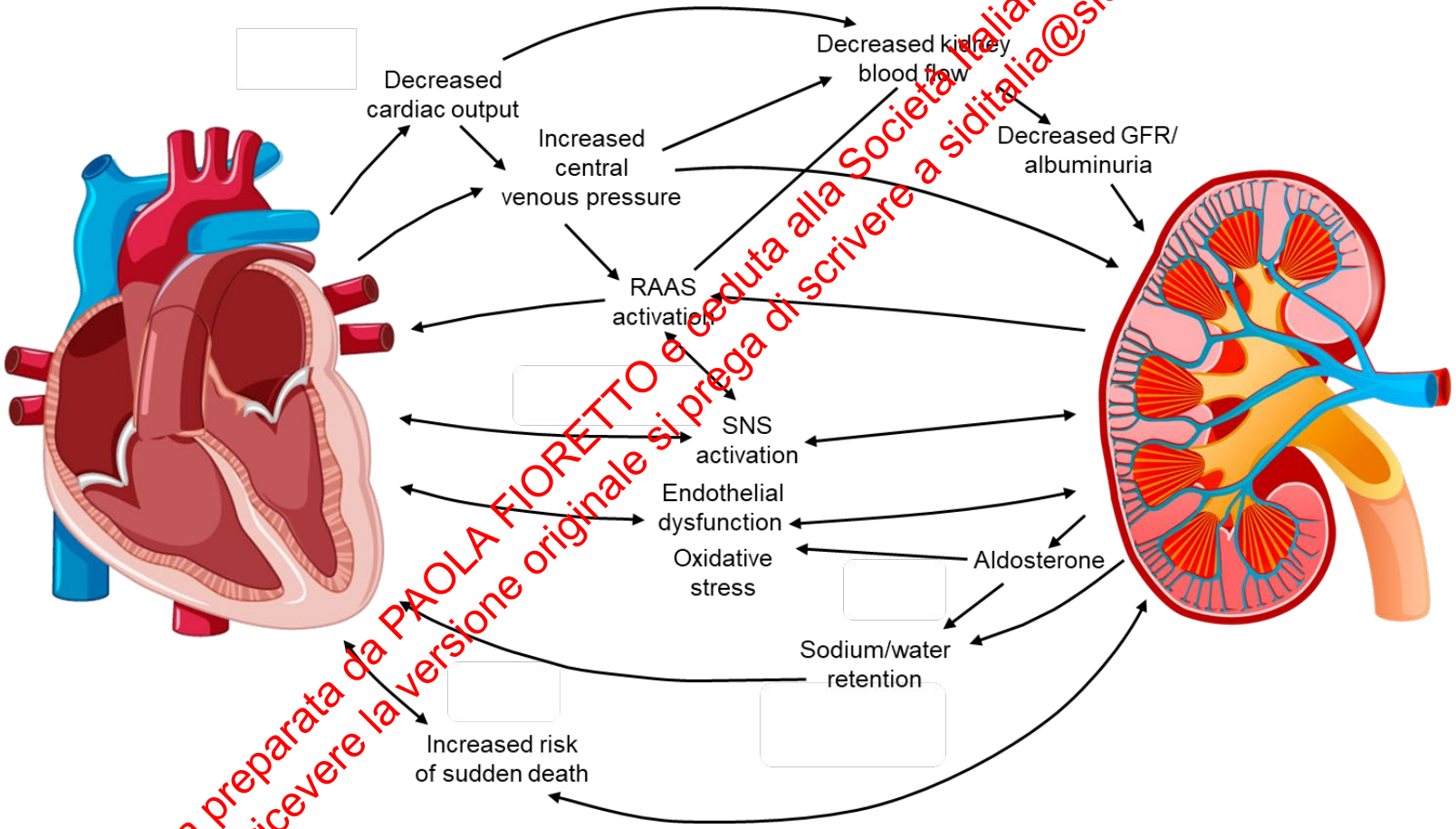
Progressing kidney damage (UACR)

Prognosis of CKD by GFR and albuminuria categories

GFR categories (mL/min/1.73 m²)			Persistent albuminuria categories[a] A1 Normal to mildly increased <30 mg/g	A2 Moderately increased 30–300 mg/g	A3 Severely increased >300 mg/g
			223.687 (65.4 %)	90.551 (26.1 %)	29.131 (8.5 %)
G1	Normal or high	≥90	29,6	36 %	
G2	Mildly decreased	60–89	46,8		
G3a G3b	Mildly to moderately and moderately to severely decreased	30-59	29 %		
G4	Severely decreased	15–29			
G5	Kidney failure	<15			

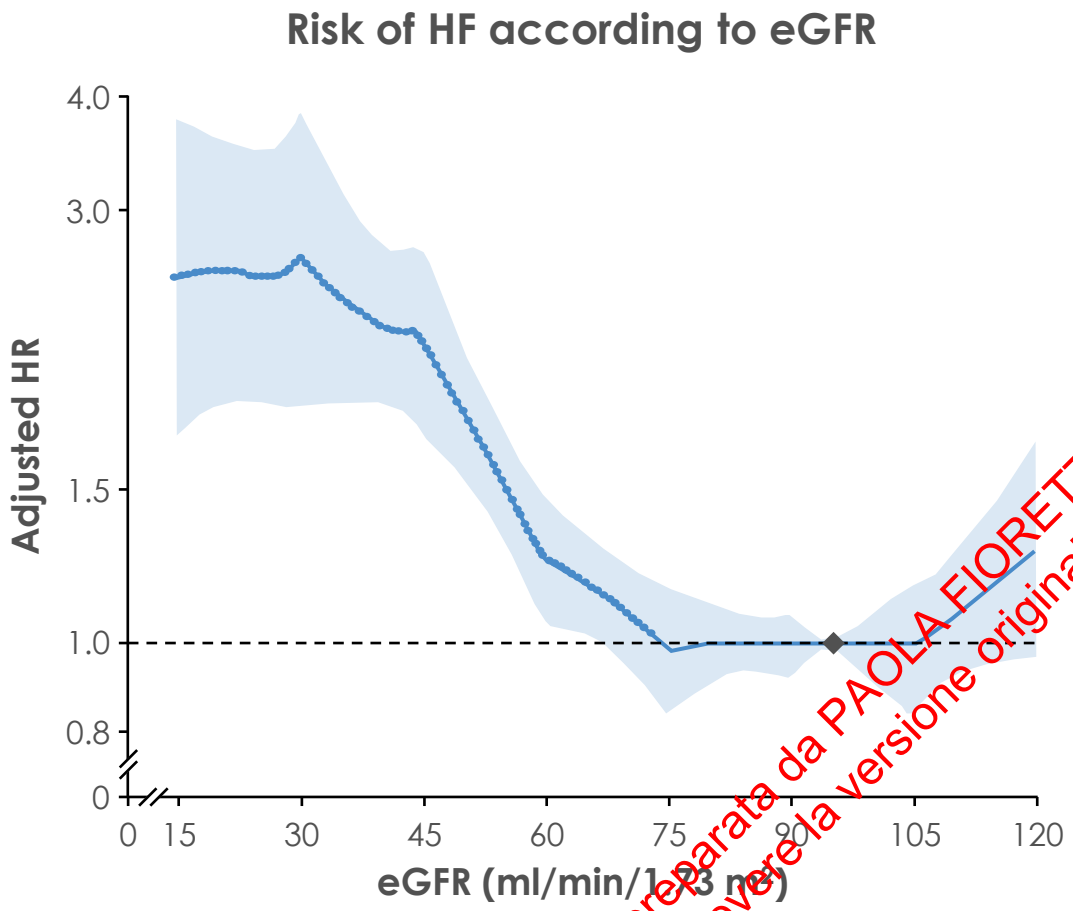
Di Bartolo P, Unpublished Data

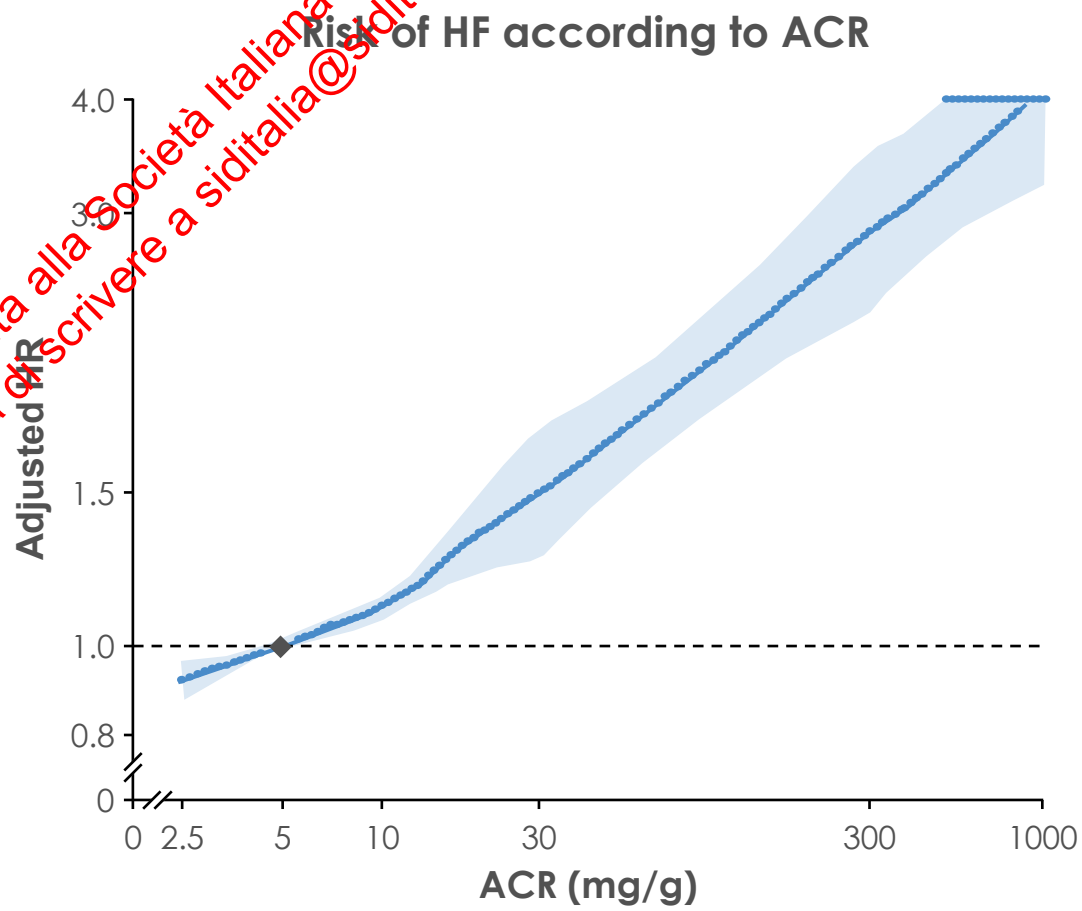
There is a close and specific association between HF and CKD pathophysiology



Damman K et al. J Am Coll Cardiol 2014;63:853

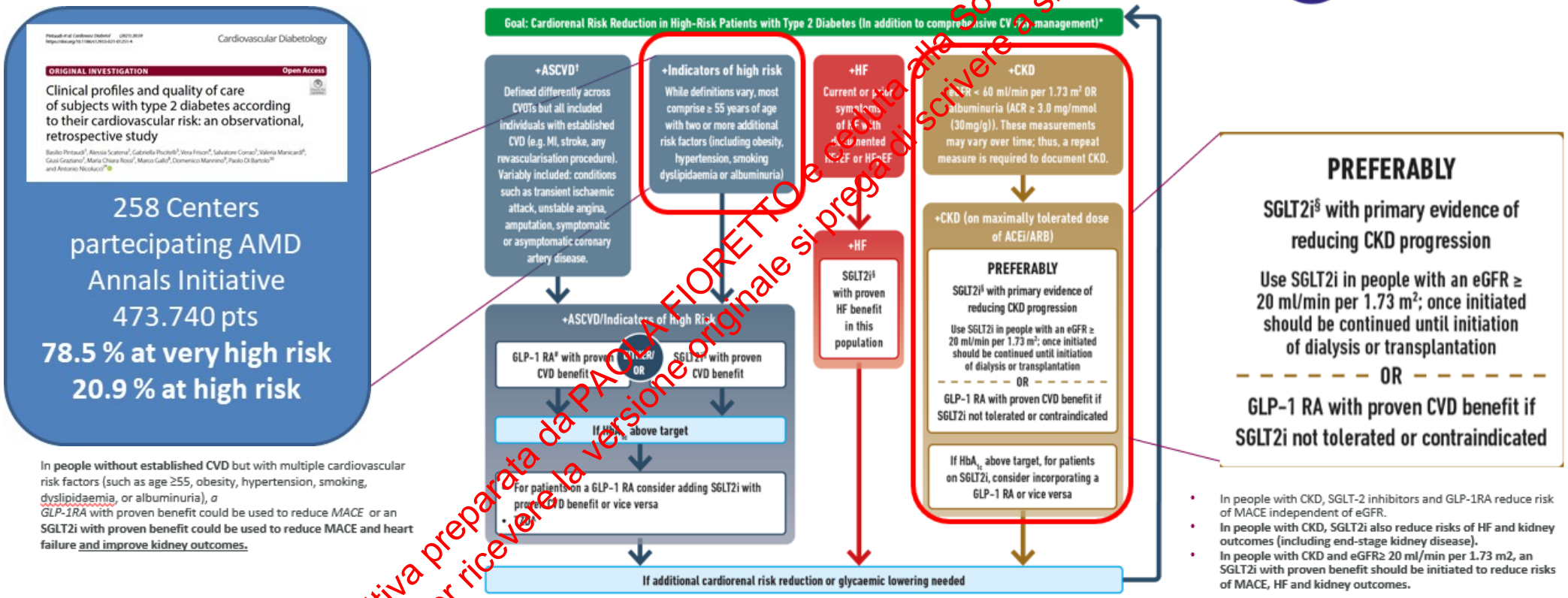
Patients are at an increased risk of HF, with risk increasing with declining eGFR and worsening albuminuria





Matsushita K *et al. Lancet Diabetes Endocrinol* 2015;3:514

ADA Standards of Care 2024



- American Diabetes Association. *Diabetes Care*. 2024;47(Suppl 1):S1-S321.

SUMMARY OF THE 2024 ADA STANDARDS OF CARE IN DIABETES

- The choice of pharmacologic agents should be guided by a person-centered approach including CV and renal comorbidities, effectiveness, risk for adverse reactions and tolerability, and individual preferences.
- In adults with T2D and **HF, CKD, and/or established/high risk of ASCVD**, the treatment plan should **include agent(s) that reduce CV and kidney disease risk** independent of metformin use or HbA1c.

Recommended Therapy	T2D Population	Rationale
SGLT2 inhibitor[a]	**HF** Established HF with reduced or preserved EF	Reduce the risk of worsening HF and CV death, improve symptoms, physical limitations, and QOL
	CKD[b] eGFR <60 mL/min/1.73 m^2 OR UACR ≥30 mg/g	Reduce CKD progression and CV events
	Established ASCVD or multiple ASCVD risk factors	Reduce the risk of MACE, hHF, kidney disease
GLP-1 RA	**CKD** (if SGLT2 inhibitor not tolerated or contraindicated) eGFR <60 mL/min/1.73 m^2 OR UACR ≥30 mg/g	Reduce the risk of CV events
	Established ASCVD or multiple ASCVD risk factors[c]	Reduce the risk of MACE

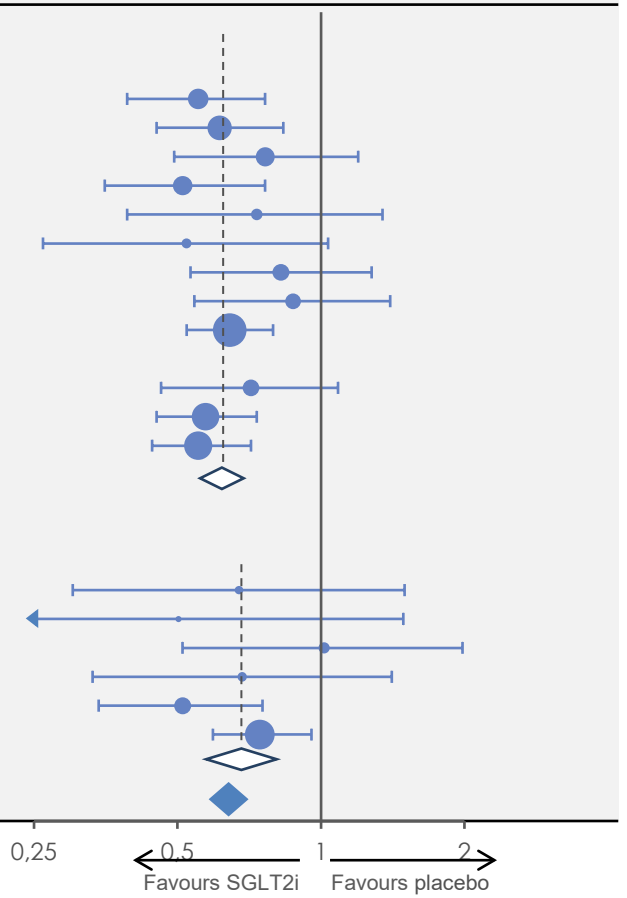
2022 ADA-KDIGO Consensus: Risk of CKD Progression, Visit Frequency, and Nephrology Referral

2022 KDIGO Approach for Improving Outcomes in Patients with CKD

American Diabetes Association. *Diabetes Care*. 2024;47(suppl 1):S1-S321.

Effects of SGLT2 i on kidney outcomes

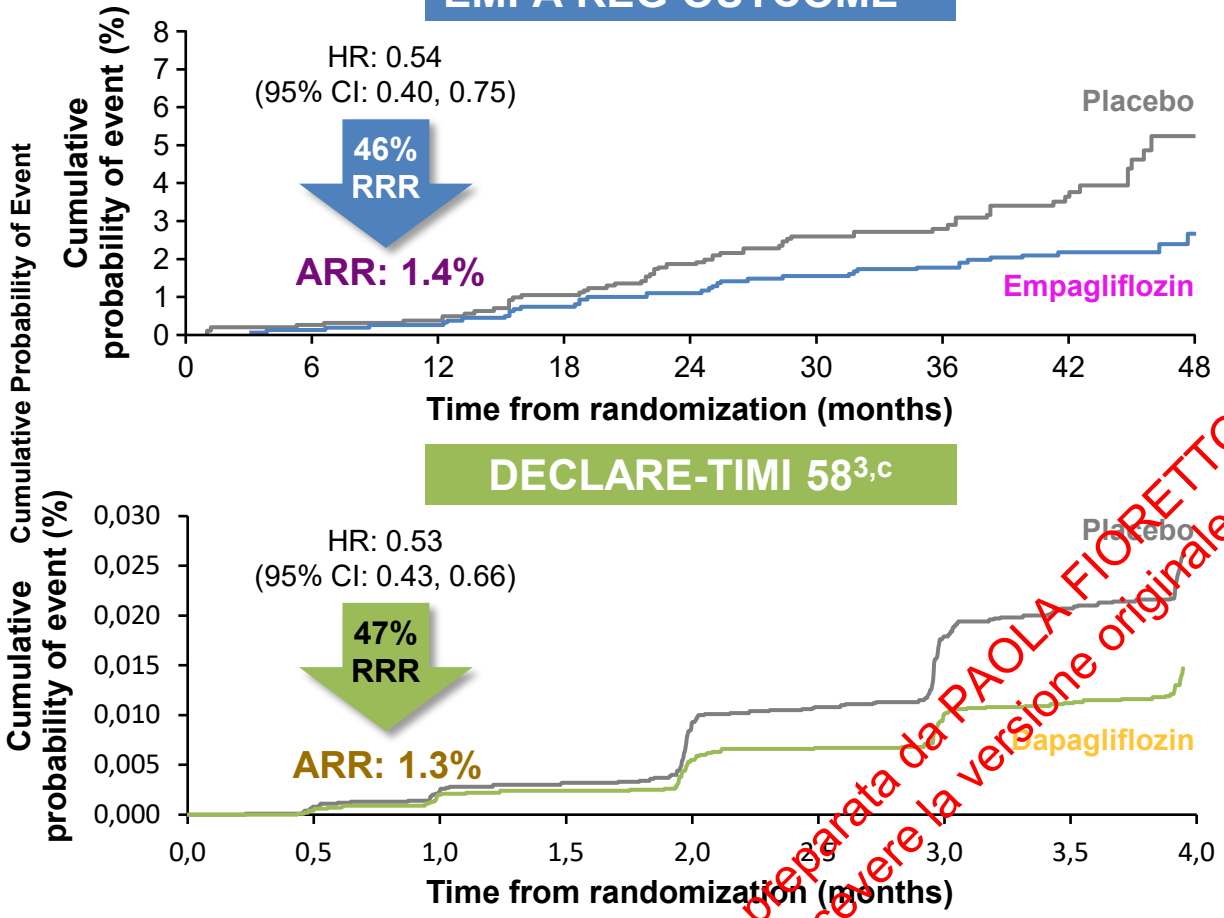
	Mean baseline eGFR (ml/min/1.73 m²)	SGLT2i Events/participants	Placebo Events/participants	Relative risk (95% CI)
Diabetes				
DECLARE-TIMI 58	85	56/8582	102/8578	0.55 (0.39, 0.76)
CANVAS Program	77	80/5795	81/4347	0.61 (0.45, 0.83)
VERTIS CV	76	49/5499	32/2747	0.76 (0.49, 1.19)
EMPA-REG OUTCOME	74	51/4645	47/2323	0.54 (0.35, 0.78)
DAPA-HF	63	18/1075	24/1064	0.73 (0.39, 1.34)
EMPORER-REDUCED	61	13/927	23/929	0.52 (0.26, 1.03)
EMPORER-PRESERVD	60	38/1466	44/1472	0.82 (0.53, 1.27)
DELIVER	60	33/1578	37/1572	0.87 (0.54, 1.39)
CREDENCE	56	153/2202	230/2199	0.64 (0.52, 0.79)
SOLOIST-WHF	51	NA/NA	NA/NA	-
SCORED	44	37/5292	52/5292	0.71 (0.46, 1.08)
DAPA-CKD	44	103/1455	173/1451	0.57 (0.45, 0.73)
EMPA-KIDNEY	42	108/1525	175/1515	0.55 (0.44, 0.71)
Subtotal diabetes	**67**	**739/40041**	**1020/33489**	**0.62 (0.56,0.68)**
No diabetes				
DAPA-HF	68	10/1298	15/1307	0.67 (0.30, 1.49)
EMPORER-REDUCED	63	5/936	10/938	0.50 (0.17, 1.48)
DELIVER	63	17/1551	17/1557	1.01 (0.51, 1.97)
EMPORER-PRESERVED	62	12/1531	18/1519	0.68 (0.33, 1.40)
DAPA-CKD	42	39/697	70/701	0.51 (0.34, 0.75)
EMPA-KIDNEY	39	119/1779	157/1790	0.74 (0.59, 0.95)
Subtotal no diabetes	56	202/7792	287/7812	0.69 (0.57, 0.82)
Total overall	65	941/47833	1307/41301	0.63 (0.58, 0.69)



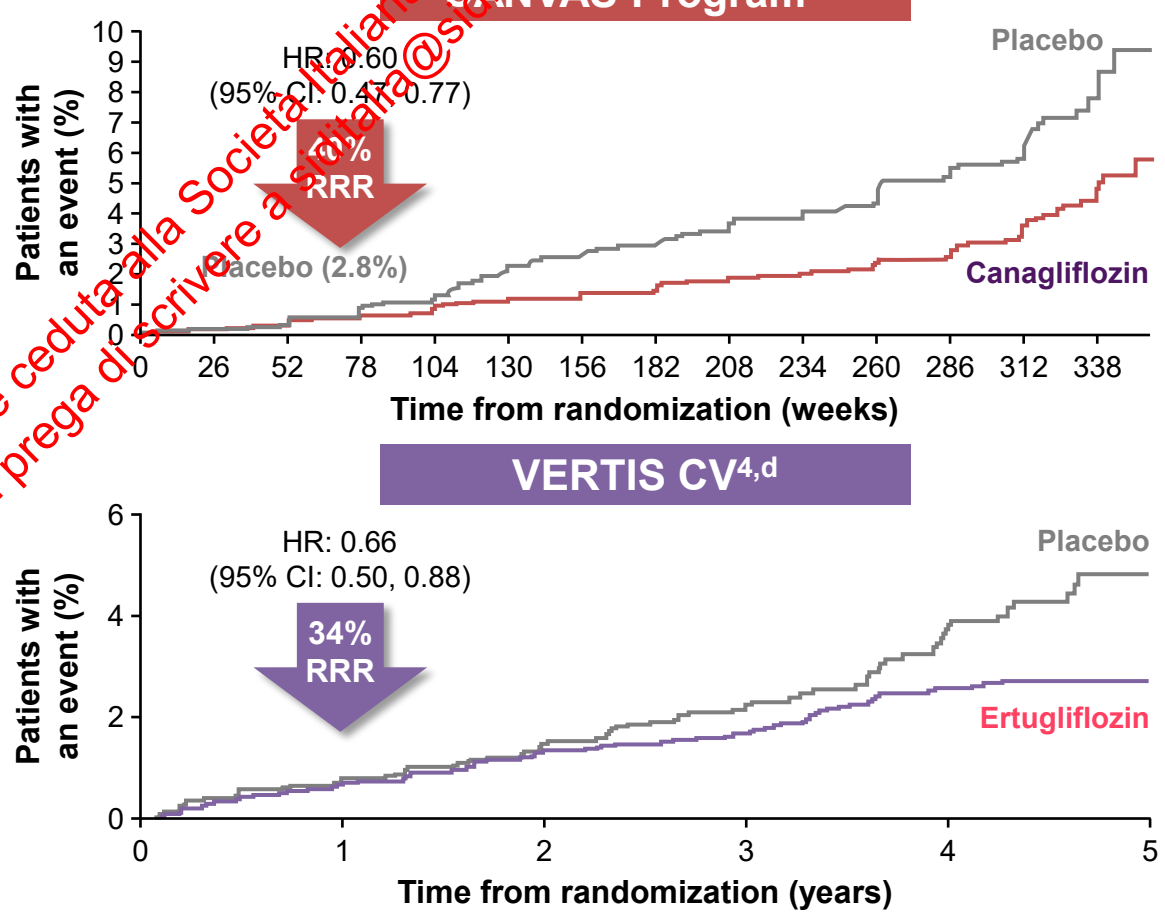
The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. *Lancet* 2022;400:1788

SGLT2 INHIBITORS IN CVOTS CONSISTENTLY REDUCED THE RISK OF KIDNEY ENDPOINTS

EMPA-REG OUTCOME[1,a]



CANVAS Program[2,b]



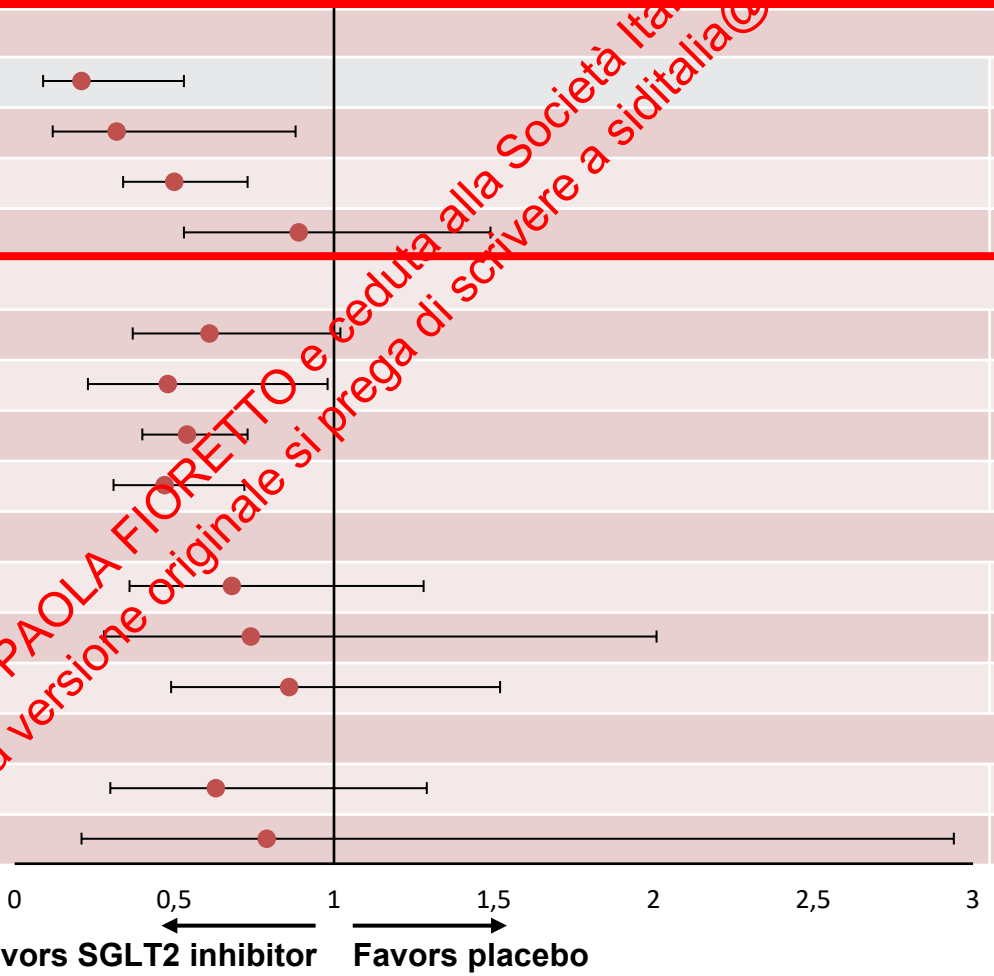
DECLARE-TIMI 58[3,c]

VERTIS CV[4,d]

1. Wanner C, et al. N Engl J Med 2016; 2. Neal B, et al. N Engl J Med 2017; 3. Mosenzon O, et al. Lancet Diabetes Endocrinol 2019; 4. Cherney DZI, et al. Diabetologia 2021

THE KIDNEY BENEFITS OF SGLT2i WERE CONSISTENT OVER A WIDE RANGE OF EGFR

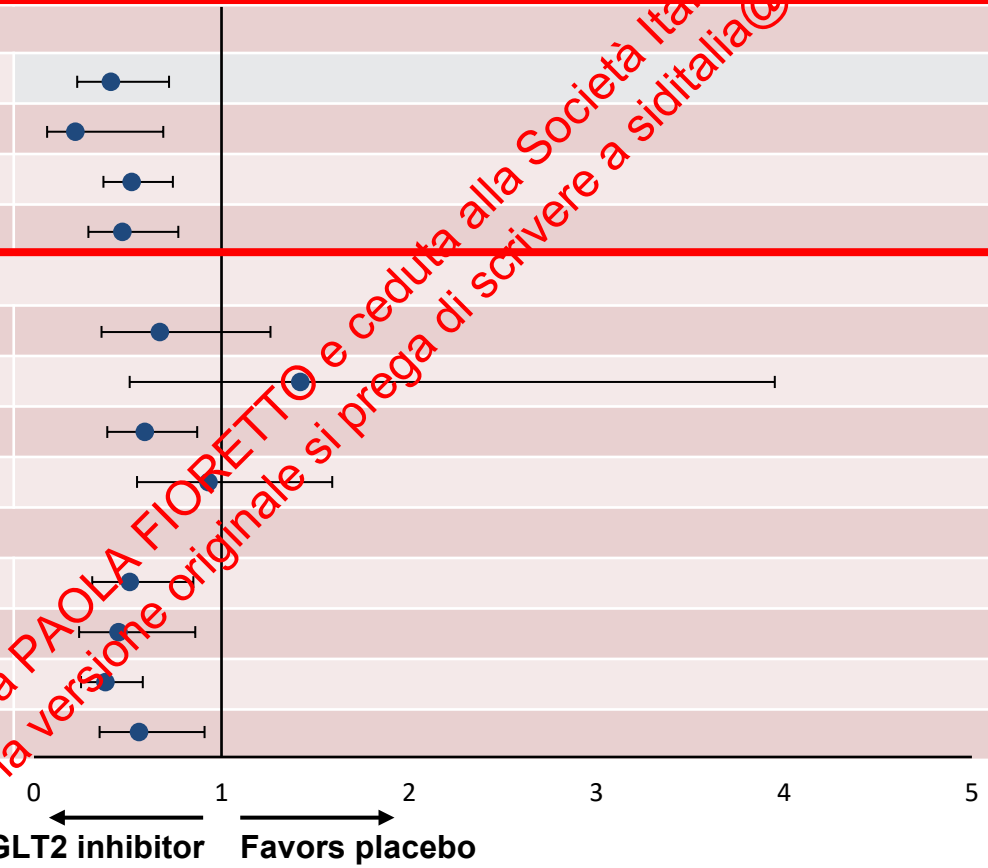
	Events	Patients	RR (95% CI)
eGFR ≥90 mL/min/1.73 m²			
EMPA-REG OUTCOME	22	1529	0.21 (0.09, 0.53)
CANVAS Program	17	2476	0.32 (0.12, 0.88)
DECLARE-TIMI 58	120	8162	0.50 (0.34, 0.73)
VERTIS CV[a]	61	2048	0.89 (0.53, 1.49)
eGFR 60–<90 mL/min/1.73 m²			
EMPA-REG OUTCOME	61	3638	0.61 (0.37, 1.02)
CANVAS Program	30	5625	0.48 (0.23, 0.98)
DECLARE-TIMI 58	186	7732	0.54 (0.40, 0.73)
VERTIS CV[a]	86	4390	0.47 (0.31, 0.72)
eGFR 45–<60 mL/min/1.73 m²			
EMPA-REG OUTCOME	39	1238	0.68 (0.36, 1.28)
CANVAS Program	16	1485	0.74 (0.28, 2.01)
VERTIS CV[a]	51	1807	0.86 (0.49, 1.52)
eGFR <45 mL/min/1.73 m²			
EMPA-REG OUTCOME	30	563	0.63 (0.30, 1.29)
CANVAS Program	10	554	0.79 (0.21, 2.94)



1. Neuen BL, et al. Lancet Diabetes Endocrinol 2019; 2. Cherney DZI, et al. Diabetologia 2021

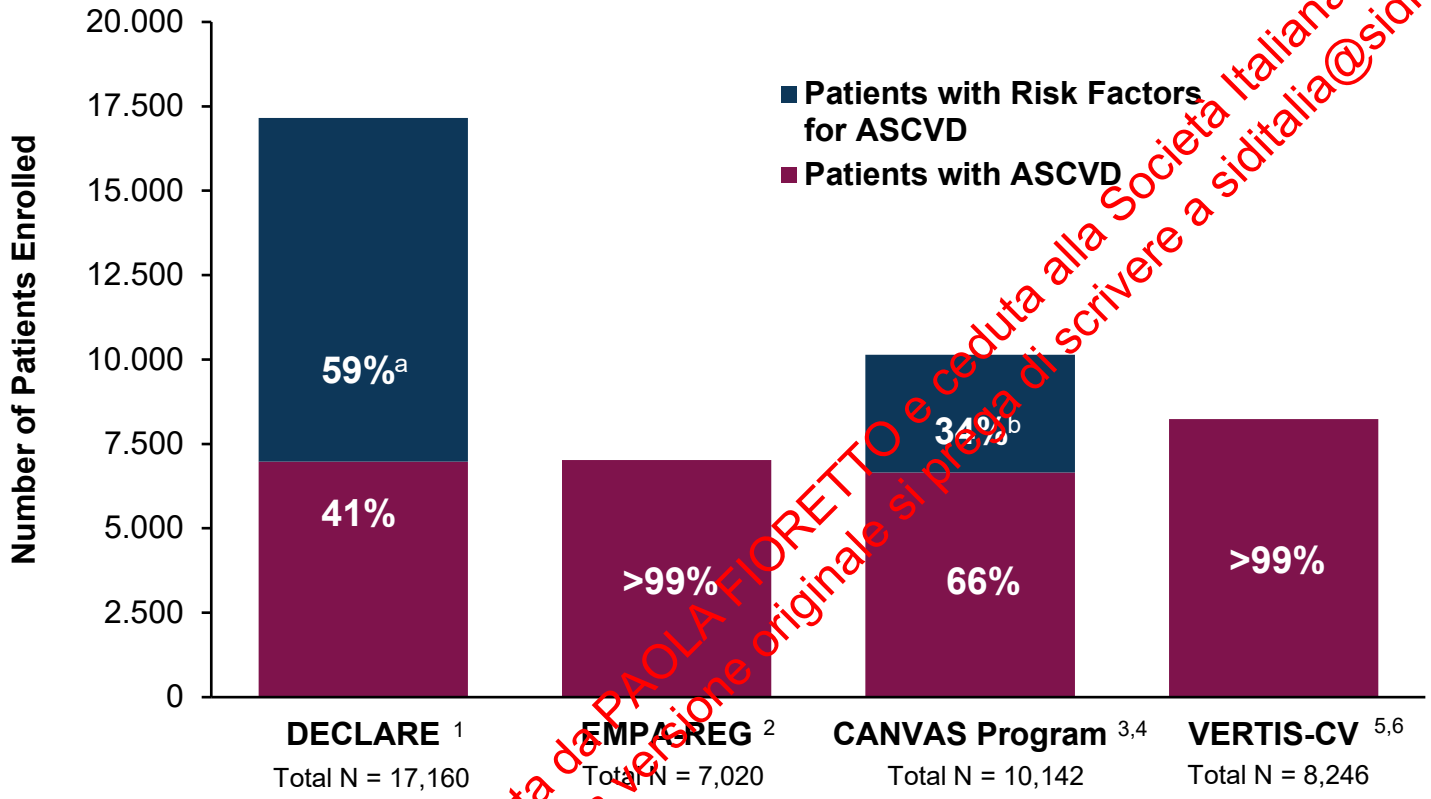
…AS WELL AS OVER A RANGE OF UACR

	Events	Patients	RR (95% CI)
UACR <30 mg/g			
EMPA-REG OUTCOME	48	4142	0.41 (0.23, 0.72)
CANVAS Program	15	7007	0.22 (0.07, 0.69)
DECLARE-TIMI 58	145	11644	0.52 (0.37, 0.74)
VERTIS CV	66	4783	0.47 (0.29, 0.77)
UACR 30–300 mg/g			
EMPA-REG OUTCOME	40	1996	0.67 (0.36, 1.26)
CANVAS Program	19	2266	1.42 (0.51, 3.95)
DECLARE-TIMI 58	105	4030	0.59 (0.39, 0.87)
VERTIS CV	60	2492	0.93 (0.55, 1.59)
UACR >300 mg/g			
EMPA-REG OUTCOME	61	764	0.51 (0.31, 0.85)
CANVAS Program	39	760	0.45 (0.24, 0.86)
DECLARE-TIMI 58	106	1169	0.38 (0.25, 0.58)
VERTIS CV	66	755	0.56 (0.35, 0.91)



1. Neuen BL, et al. Lancet Diabetes Endocrinol 2019; 2. Cherney DZI, et al/ Diabetologica 2021

DECLARE ENROLLED PATIENTS EARLY IN THE DISEASE CONTINUUM, INCLUDING THOSE WITHOUT ASCVD[1]



Placebo MACE rate per 1000 patient years[1-6]

DECLARE: 24.2
CANVAS: 31.5
VERTIS-CV: 40.0
EMPA-REG: 43.9

In the general T2D population, only 20% of patients have established CVD[7]

1. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; 2. Zinman B et al. *N Engl J Med*. 2015;373:2117-2128; 3. Neal B et al. *N Engl J Med*. 2017;377:644-657; 4. Neal B et al. *Diabetes Obes Metab*. 2017;19:387-393; 5. Cannon CP et al. *Am Heart J*. 2018;206:11-23; 6. Cannon CP et al. *N Engl J Med*. 2020;383:1425-1435; 7. Iglay K et al. *Curr Med Res Opin*. 2016;7:1243-1252.

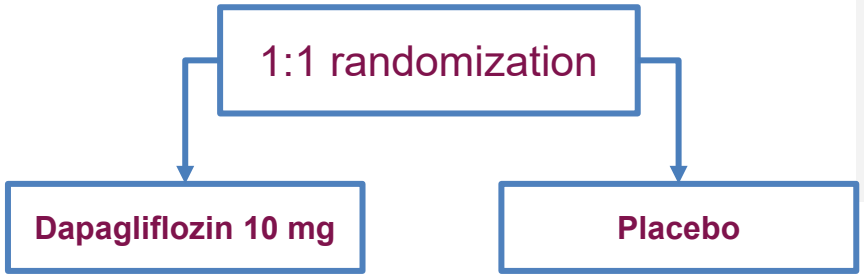
DECLARE ENROLLED PATIENTS EARLY IN THE DISEASE CONTINUUM WITH PREDOMINANTLY PRESERVED RENAL FUNCTION

	eGFR[a], mean (mL/min/1.73 m^2)	Micro-/macro-albuminuria (%)	Renal composite (Placebo rate per 1000 pt-yrs)	Renal composite definition
DECLARE[1,2]	85.2	30.9[b]	7.0	≥40% decrease in eGFR to <60 mL/min/1.73 m^2, ESKD, or renal death
CANVAS[3]	76.5	30.2	9.0	40% reduction in eGFR, renal-replacement therapy, or renal death
EMPA-REG[4,5]	74[c]	39.6	11.5	Doubling SCr accompanied by eGFR of ≤45 mL/min/1.73 m^2, renal-replacement therapy, or renal death
VERTIS-CV[6]	76	39.4	12.0	Doubling SCr, renal-replacement therapy, or renal death

1. Wiviott SD et al. N Engl J Med. 2019; 2. Mosenzon O et al. Lancet Diabetes Endocrinol. 2019; 3. Neal B et al. N Engl J Med. 2017; 4. Zinman B et al. N Engl J Med. 2015;
2. 5. Wanner C et al. N Engl J Med. 2016; 6. Cannon CP et al. N Engl J Med. 2020

DECLARE-TIMI 58: PATIENT CHARACTERISTICS

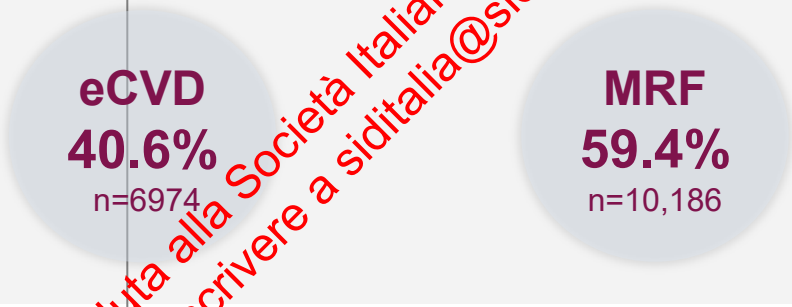
N=17.160 pazients with DMT2

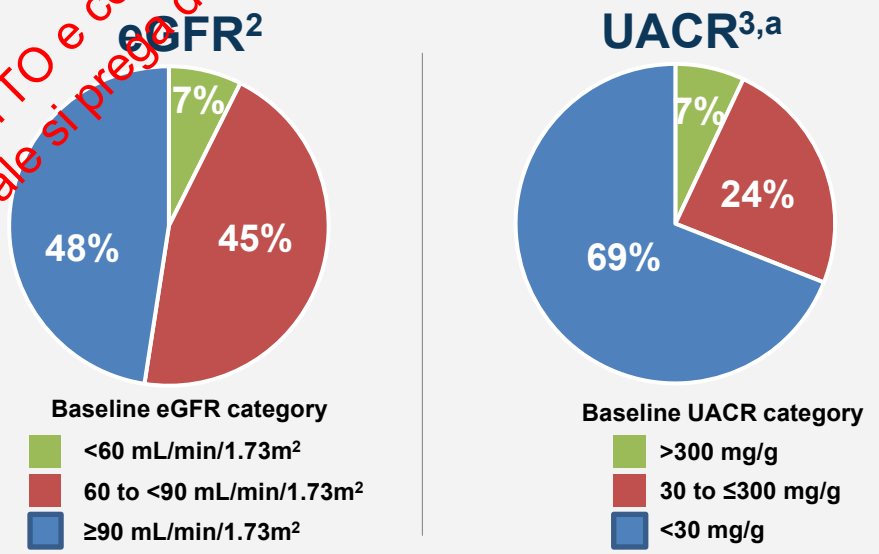


Follow up: 4.2 anni

Key inclusion criteria

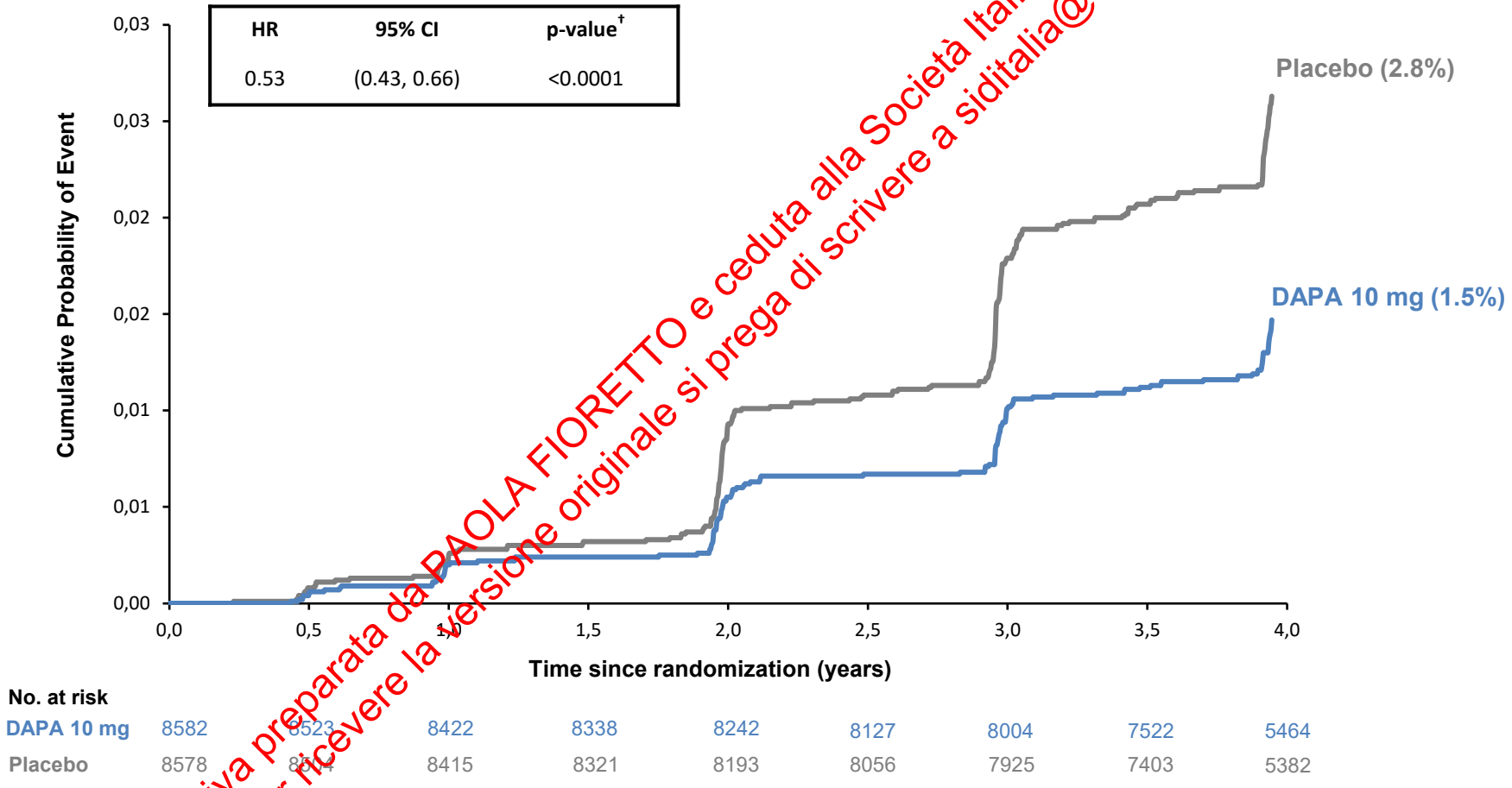
- T2D
- Age ≥40 yrs
- CVD or multiple CVR risk factors
- HbA_{1c} ≥6.5% and <12.0%
- CrCl ≥60 mL/min





1. Wiviott SD et al. N Engl J Med, 2019; 2. Mosenzon O et al. Lancet Diabetes Endocrinol, 2019; 3. Mosenzon O et al. Diabetes Care, 2021

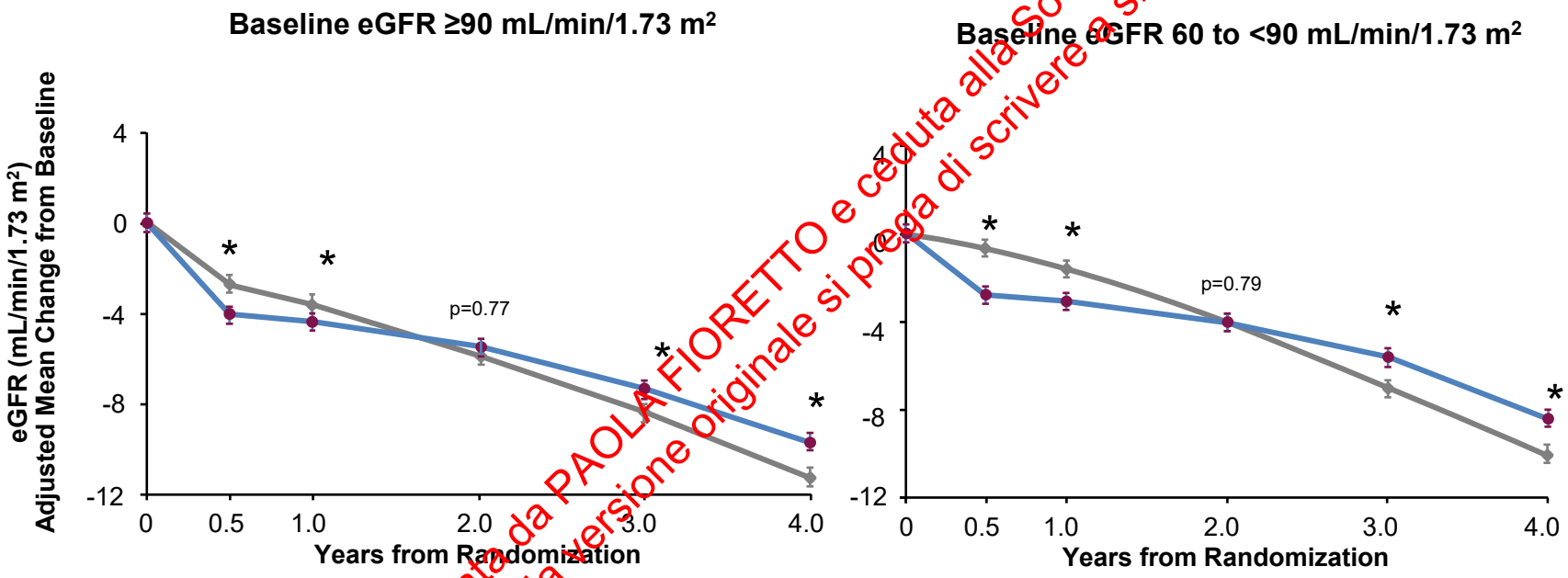
DECLARE-TIMI 58: RENAL-SPECIFIC OUTCOME DECREASE EGFR ≥40%, ESRD OR RENAL DEATH



47% RRR

Mosenzon O et al, Lancet Diabetes Endocrinol, 2019

CHANGE IN eGFR OVER TIME BY BASELINE eGFR SUBGROUPS

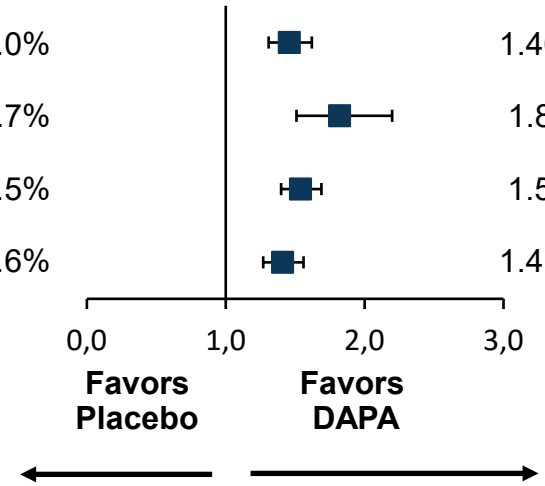


.

Mosenzon O et al. Lancet Diabetes Endocrinol, 2019

IMPROVEMENT OF ALBUMINURIA CATEGORY FROM BASELINE

	Dapagliflozin		Placebo			
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate	Hazard Ratio (95% CI)	Cox p-value
Endpoints						
Improvement from baseline						
Micro to Normo	774/2017 (38.4)	38.90%	576/2013 (28.6)	29.0%	1.46 (1.31, 1.62)	<0.0001
Macro to Normo/Micro	282/594 (47.5)	48.10%	175/575 (30.4)	31.7%	1.82 (1.51, 2.2)	<0.0001
Macro to Normo/Micro or Micro to Normo	1056/2611 (40.4)	41.00%	751/2588 (29.0)	29.5%	1.54 (1.4, 1.69)	<0.0001
Micro/Macro to Normo	809/2611 (31.0)	31.50%	604/2588 (23.3)	23.6%	1.41 (1.27, 1.56)	<0.0001

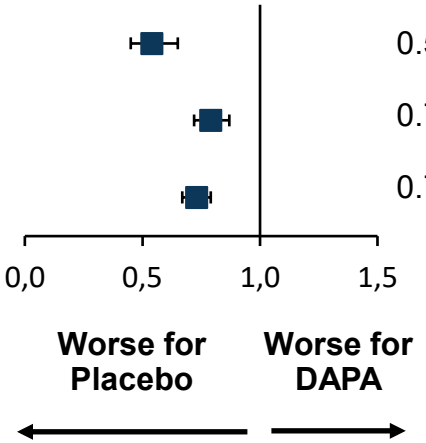


Definitions of Albuminuria Categories	
Macroalbuminuria	UACR ≥300 mg/g
Microalbuminuria	UACR ≥30 to <300 mg/g
Normoalbuminuria	UACR <30 mg/g

Mosenzon O et al, Diabetes Care, 2021

DETERIORATION OF ALBUMINURIA CATEGORY FROM BASELINE

	Dapagliflozin		Placebo			
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate	Hazard Ratio (95% CI)	Cox p-value
Endpoints						
Deterioration from baseline						
Normo/Micro to Macro	181/7836 (2..3)	2.30%	330/7838 (4.2)	4.2%	0.54 (0.45, 0.65)	<0.0001
Normo to Micro/Macro	772/5819 (13.3)	13.30%	959/5825 (16.5)	16.3%	0.79 (0.72, 0.87)	<0.0001
Normo to Micro/Macro or Micro to Macro	928/7836 (11.8)	11.90%	1243/7838 (15.9)	15.8%	0.73 (0.67, 0.79)	<0.0001

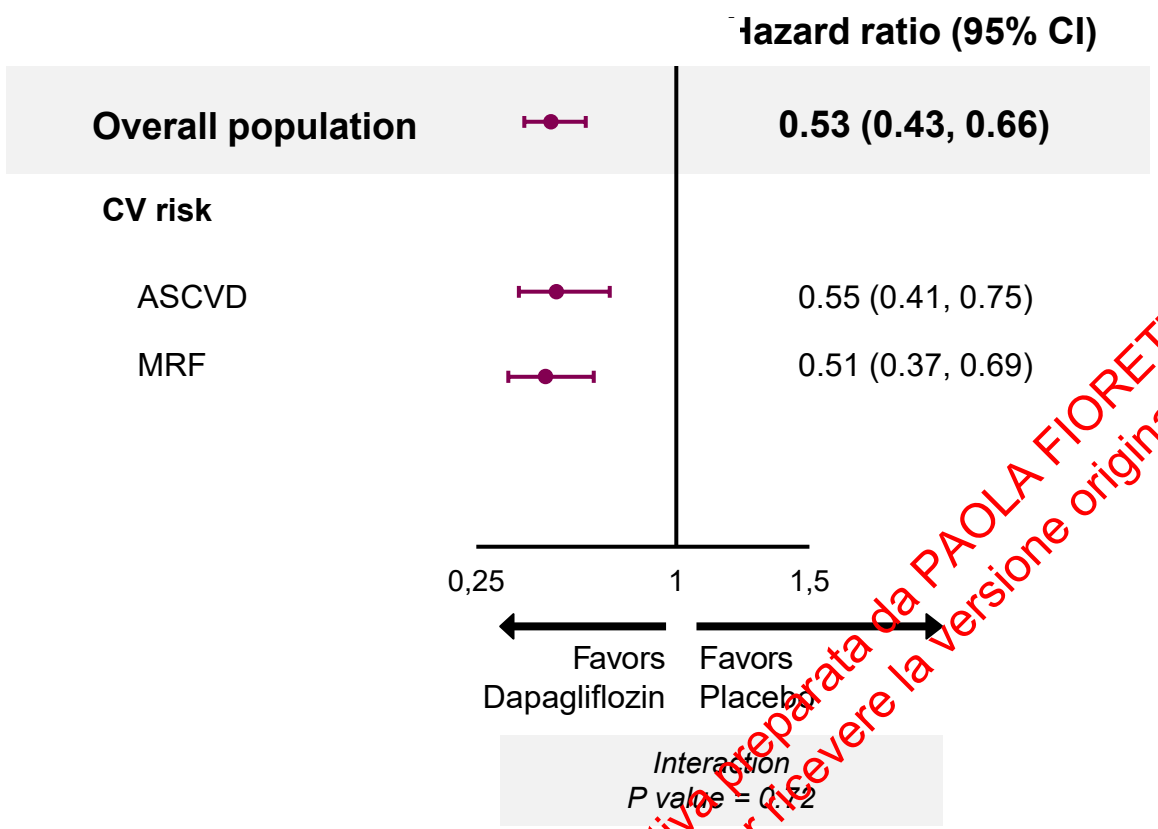


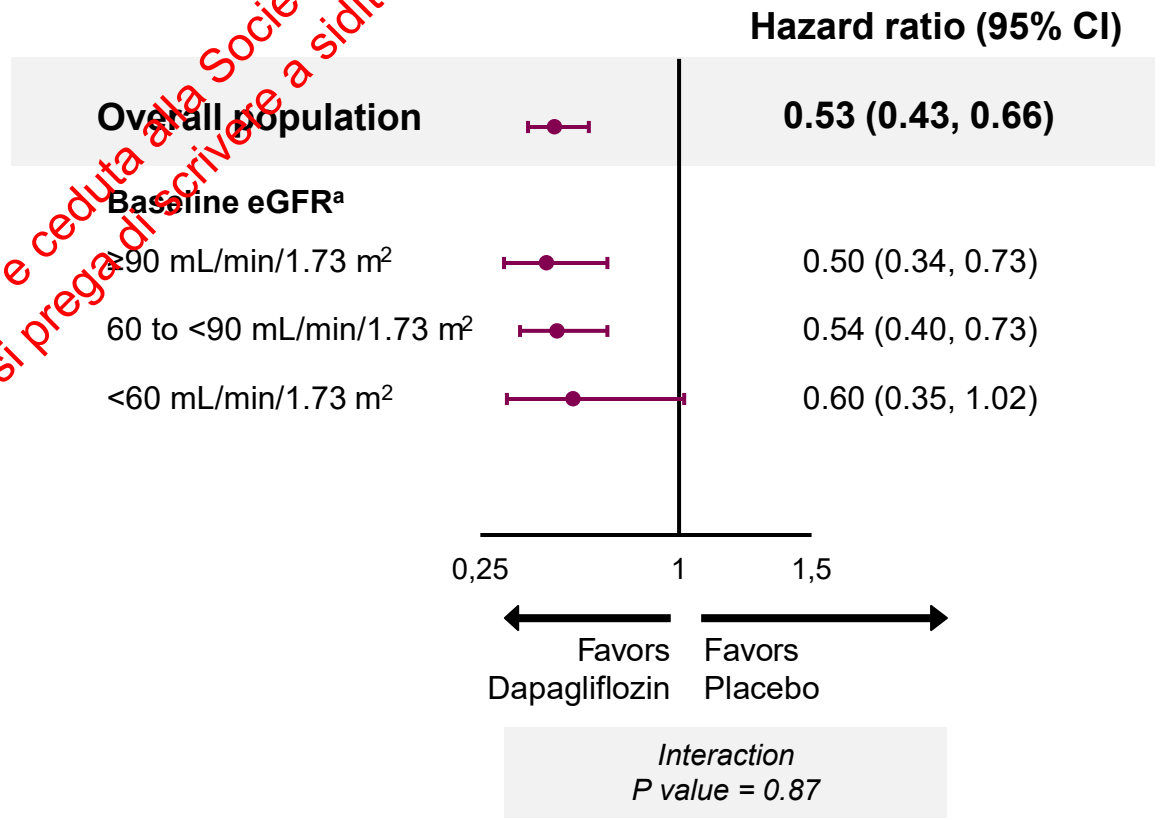
Definitions of Albuminuria Categories	
Macroalbuminuria	UACR ≥300 mg/g
Microalbuminuria	UACR ≥30 to <300 mg/g
Normoalbuminuria	UACR <30 mg/g

Mosenzon O et al, Diabetes Care, 2021

THE RENAL PROTECTIVE EFFECTS OF DAPAGLIFLOZIN WERE SIMILAR ACROSS BASELINE CV RISK AND EGFR SUBGROUPS

Renal Composite: ≥40% decrease in eGFR[a] to <60 mL/min/1.73 m², ESRD, or renal death

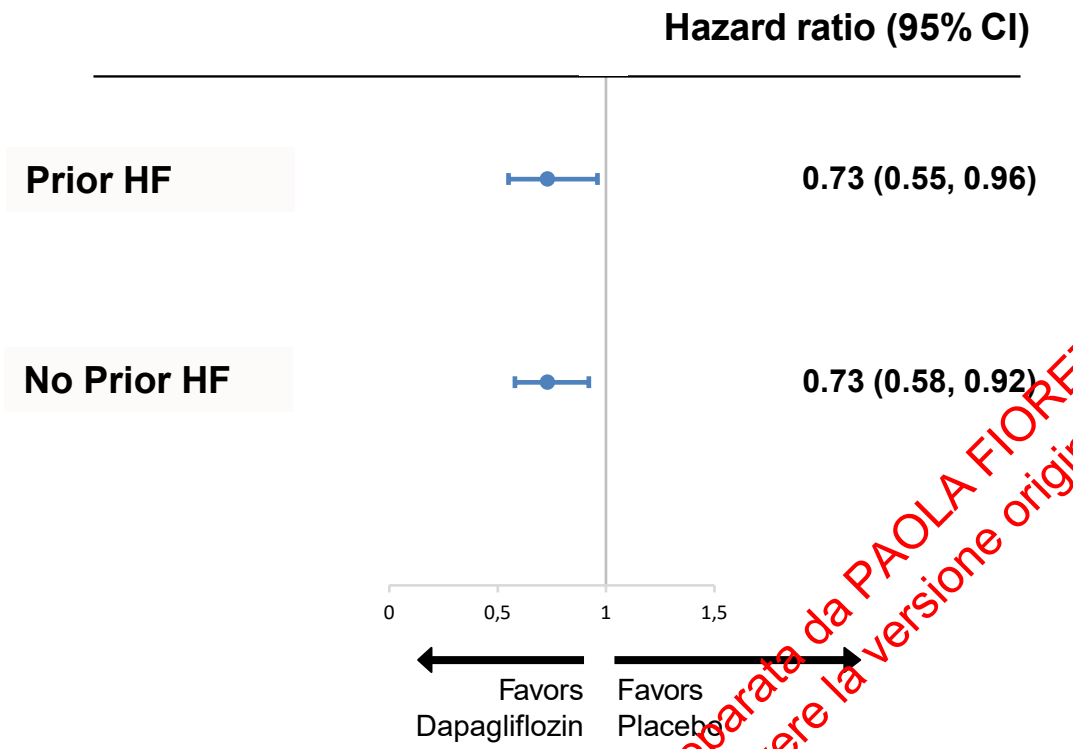




Wiviott SD et al, N Engl J Med. 2019

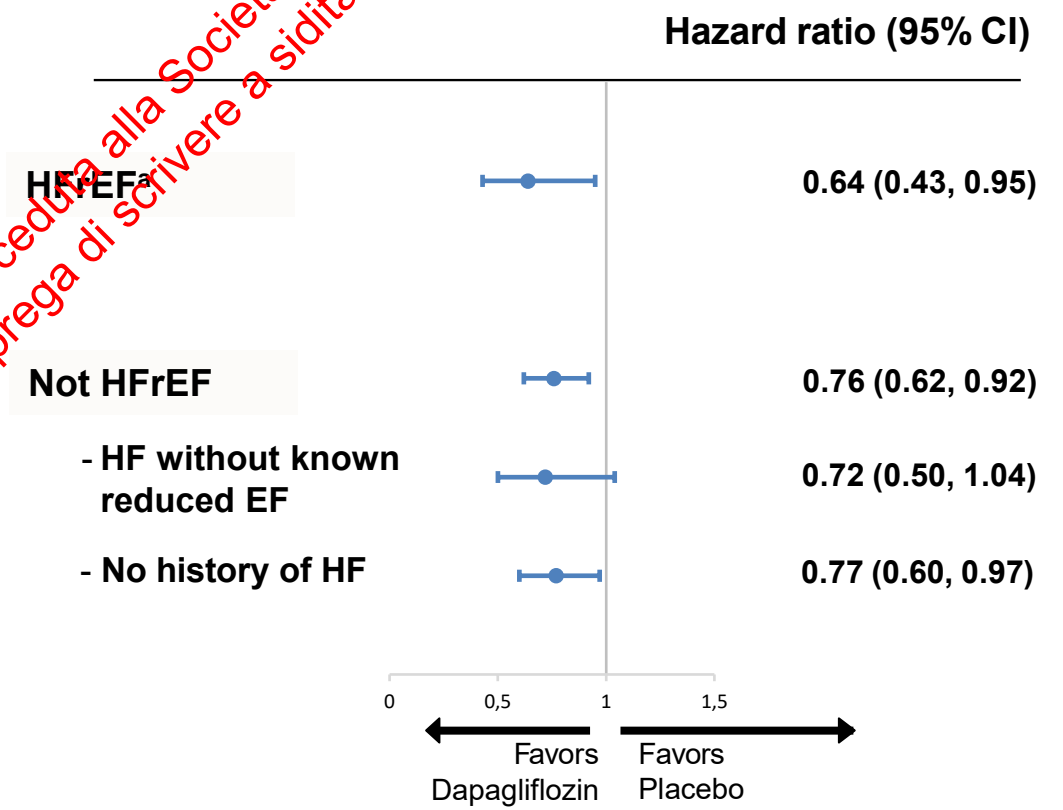
Dapagliflozin prevents hHF regardless of history of HF or EF in patients with T2D

hHF: history of HF[1]



10% of patients in DECLARE had prior HF

hHF: ejection fraction[2]

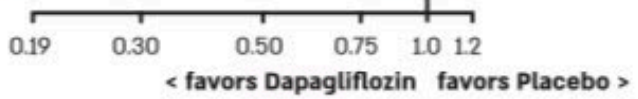


3.9% of patients in DECLARE had HFrEF[a]

1. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; 2. Kato ET et al, *Circulation*. 2019.

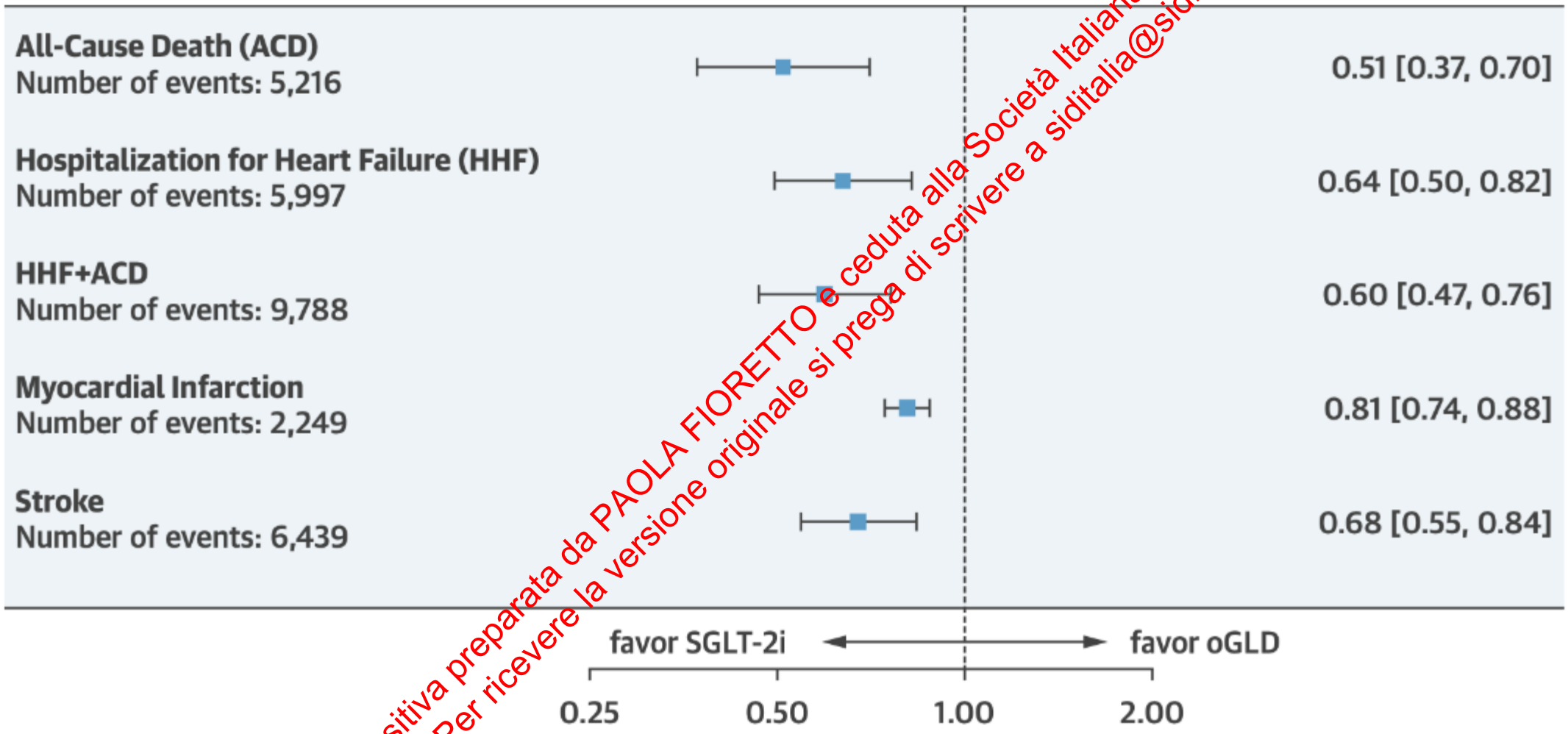
DAPAGLIFLOZIN REDUCED THE KIDNEY COMPOSITE OUTCOME IN LOW KDIGO RISK POPULATION

KDIGO Category	Dapagliflozin n/N(%)	Dapagliflozin KM	Placebo n/N(%)	Placebo KM	Hazard Ratio (95% CI)	p-value	p-interaction	NNT
Cardiorenal Composite Outcome								
Overall	370/8582 (4.3%)	4.2%	480/8578 (5.6%)	5.3%	0.76 (0.67, 0.87)	<0.0001		89
Low Risk	165/5485 (3.0%)	2.9%	187/5473 (3.4%)	3.2%	0.88 (0.71, 1.08)	0.2132	0.1510	289
Moderate Risk	117/2124 (5.5%)	5.3%	156/2119 (7.4%)	7.0%	0.73 (0.58, 0.93)	0.0112		60
High Risk	69/706 (9.8%)	9.5%	96/697 (13.8%)	13.3%	0.70 (0.51, 0.95)	0.0225		27
Very High Risk	12/114 (10.5%)	11.8%	32/124 (25.8%)	25.4%	0.36 (0.19, 0.71)	0.0033		8
Kidney Specific Composite Outcome								
Overall	127/8582 (1.5%)	1.5%	238/8578 (2.8%)	2.8%	0.53 (0.43, 0.66)	<0.0001		87
Low Risk	46/5485 (0.8%)	0.8%	85/5473 (1.6%)	1.4%	0.54 (0.38, 0.77)	0.0007	0.9681	177
Moderate Risk	34/2124 (1.6%)	1.6%	69/2119 (3.3%)	3.3%	0.48 (0.32, 0.73)	0.0005		62
High Risk	30/706 (4.2%)	3.9%	60/697 (8.6%)	8.5%	0.48 (0.31, 0.75)	0.0011		23
Very High Risk	10/114 (8.8%)	8.8%	22/124 (17.7%)	18.1%	0.41 (0.19, 0.88)	0.0228		13



Diabetes Care 2022; 45:2350-2359

CVD REAL 2: SGLT2i vs other glucose lowering drugs



Kosiborod, M et al, JACC, 2018

CVD-REAL 3 – renal outcomes

CVD-REAL 3

- Mean age: 61 years
- CVD: 23%
- ACE inhibitor / ARB use: 69%
- Mean eGFR: 91 mL/min/1.73 m^2
- eGFR <60 mL/min/1.73 m^2: 8.3%
- Albuminuria???

SGLT2 inhibitors
35,561

Mean follow-up
14.9 months

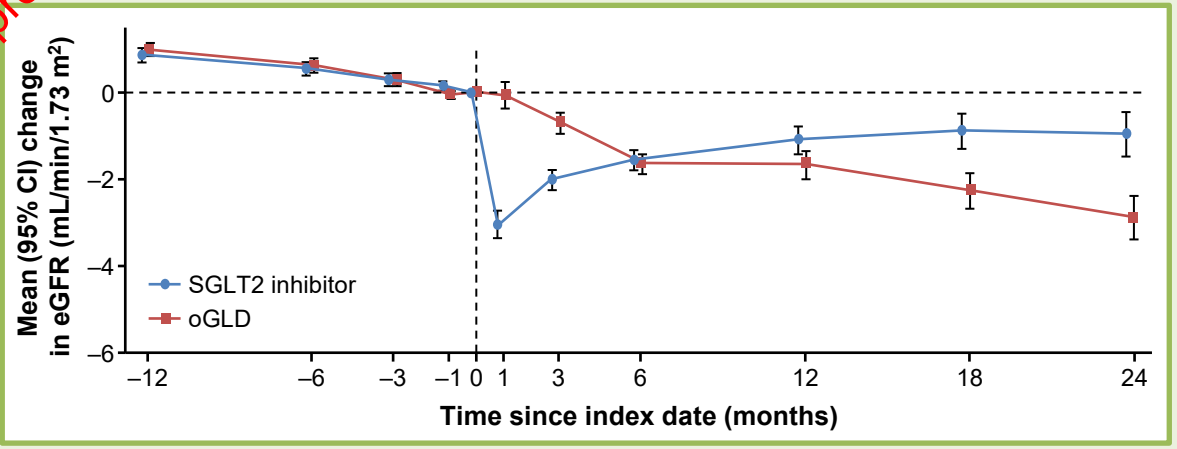
oGLDs
35,561

50% eGFR decline or ESRD

HR: 0.49; *P*<0.0001

SGLT2 inhibitors: 3.0/1000 patient-years
oGLDs: 6.3/1000 patient-years

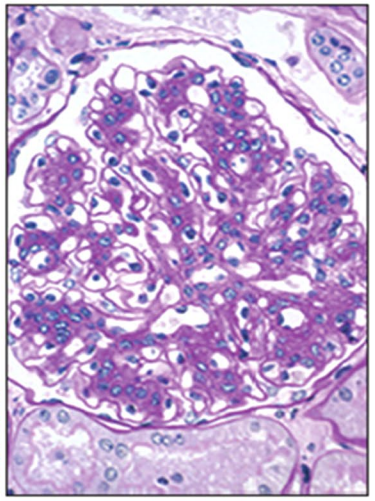
Changes in eGFR decline



Heerspink HJL, et al. Lancet Diabetes Endocrinol, 2020

THE LANCET
Diabetes & Endocrinology

SGLT2 inhibitors to prevent diabetic kidney disease


Paola Fioretto

See Articles page 27

Up to 40% of patients with type 2 diabetes develop the risk of developing new-onset microalbuminuria diabetic kidney disease presenting with increased was documented in the CANVAS Program[2] and

But this important study does have some limitations. The main finding is the significant difference in eGFR slopes in the two treatment groups. However, because of the well known biphasic trend of GFR trajectories over time due to haemodynamic changes occurring after initiation of SGLT2 inhibitor therapy—a model assuming linearity was used in the study[7]—and because of the relatively short duration of the follow-up, some caution is needed in translating the observed difference into a clinically relevant benefit for patients using SGLT2 inhibitors. Notably, when these data are compared with those from the DECLARE–TIMI 58

could be considered for most, if not all, patients with type 2 diabetes.

Paola Fioretto, Roberto Vettor, Roberto Pontremoli
Department of Medicine, University of Padua, 35128 Padua, Italy (PF, RV); and Department of Internal Medicine, University of Genoa and IRCCS Ospedale Policlinico San Martino, Genoa, Italy (RP)
paola.fioretto@unipd.it

PF has received personal fees from AstraZeneca, Boehringer Ingelheim, Mundipharma, Eli Lilly, and Novartis. RV has received grants from AstraZeneca and personal fees from AstraZeneca, Novo Nordisk, Eli Lilly, Novartis, and Gilead. RP has received personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Menarini, Merck Sharp & Dohme, Novartis, and Alfa Sigma.

(ESKD) worldwide.

However, this scenario might be about to change over the coming years if the promise of renal protection by sodium–glucose co-transporter-2 (SGLT2) inhibitors holds true in real-world clinical settings. All three large

substantially from the tightly controlled setting of randomised clinical trials, a circumstance that has led the US Food and Drug Administration to include real-world evidence in their decision making. With respect to SGLT2 inhibitors, several real-world studies have been

Summary

- The global prevalence of CKD in T2D is increasing and these patients have an increased risk of renal failure, HF, CV and of all-cause mortality.
- The CV outcome trials have demonstrated a reduction in renal endpoints with SGLT2 inhibitors in patients with T2D.
- The DECLARE-TIMI 58 trial, along with the CVD-REAL 3 study, demonstrated the efficacy of dapagliflozin for the primary prevention of renal outcomes.
- Current guidelines recommend the use of SGLT2i not only in patients with ASCVD, HF and CKD but also in those at high CV risk.