II SESSIONE

Basta con la DKD!

Moderatori: Paola Fioretto, Anna Solini

……basta con MRC nel DMT2

SGLT2i

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CSL Vifor
Bayer

T2D and CKD have a significant global disease burden

Global prevalence of diabetes in adults aged 20–79 years[1]

2021

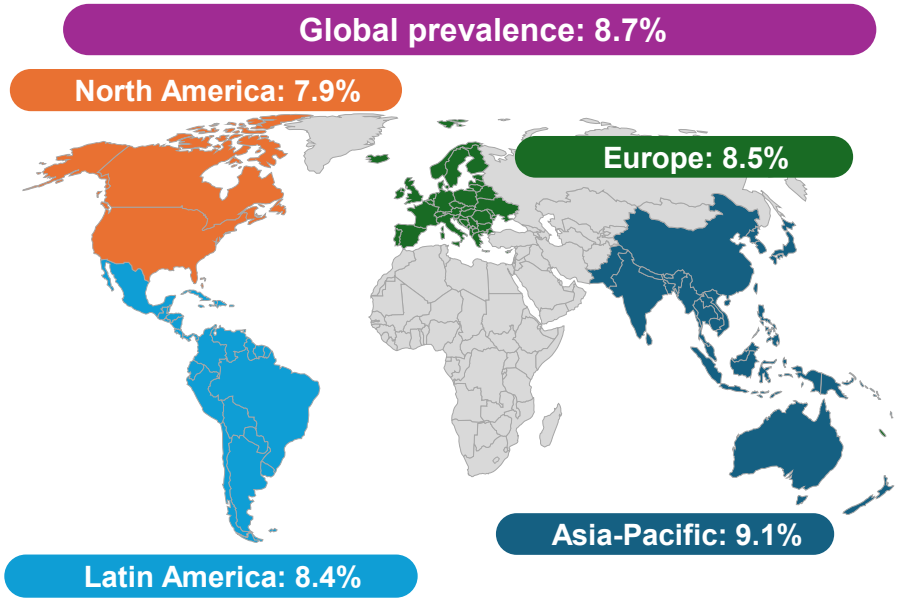
537 MILLION
adults with diabetes
10.5% of global population*

by 2045, **783 MILLION**
adults are projected to be living with diabetes

T2D accounts for approximately **90%**[2] of diabetes and at least **2** in every **5** people with T2D have CKD[3]

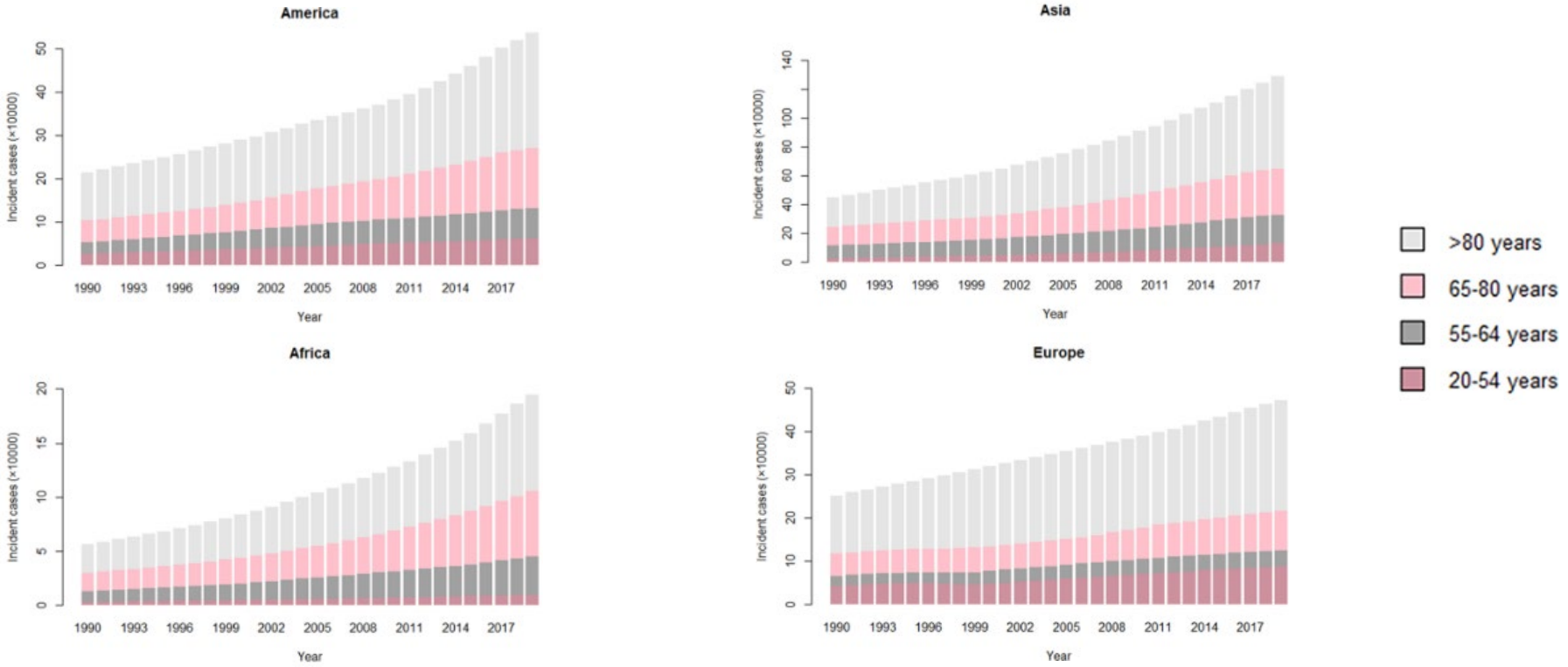
An estimated
190 MILLION#
adults had CKD in T2D in 2021

Age-standardised prevalence of CKD globally and in Europe, 2017[4]



1. International Diabetes Federation. 2021. 10th Edition. https://diabetesatlas.org/en/ [accessed 11 May 2022]; 2. International Diabetes Federation. 2019. 9th Edition. https://diabetesatlas.org/atlas/ninth-edition/ [accessed 21 Jan 2022]; 3. Wu B, *et al. BMJ Open Diabetes Res Care* 2016;4:e000154; 4. GBD Chronic Kidney Disease Collaboration. *Lancet* 2020;395:709–733

CKD in T2D.....THE NEXT PANDEMIA?



Deng Y (GBD 2019), Front Endocrinol July 2021

Renal Center for Precision Medicine

Rence

What is the residual risk in DKD patients treated with RAASi?

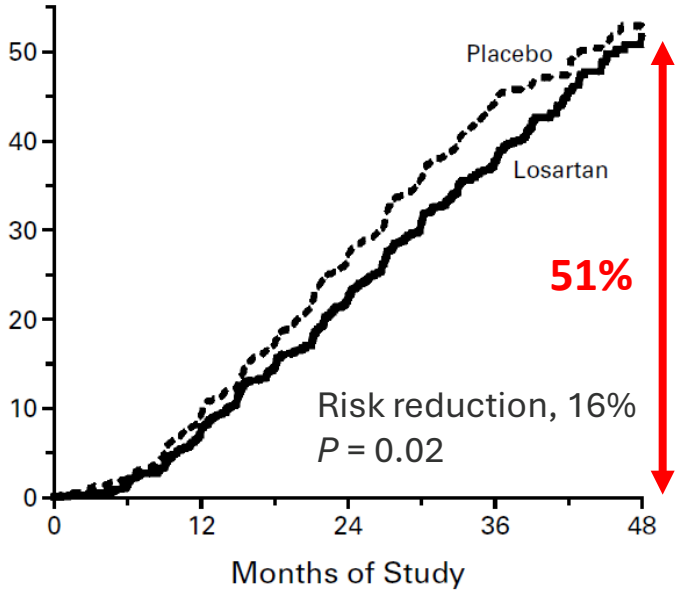
Doubling of serum creatinine, ESKD, or death

1. 25-30%
2. 30-35%
3. 35-40%
4. >40%

The residual risk in RAASi treated DKD patients: RENAAL & IDNT

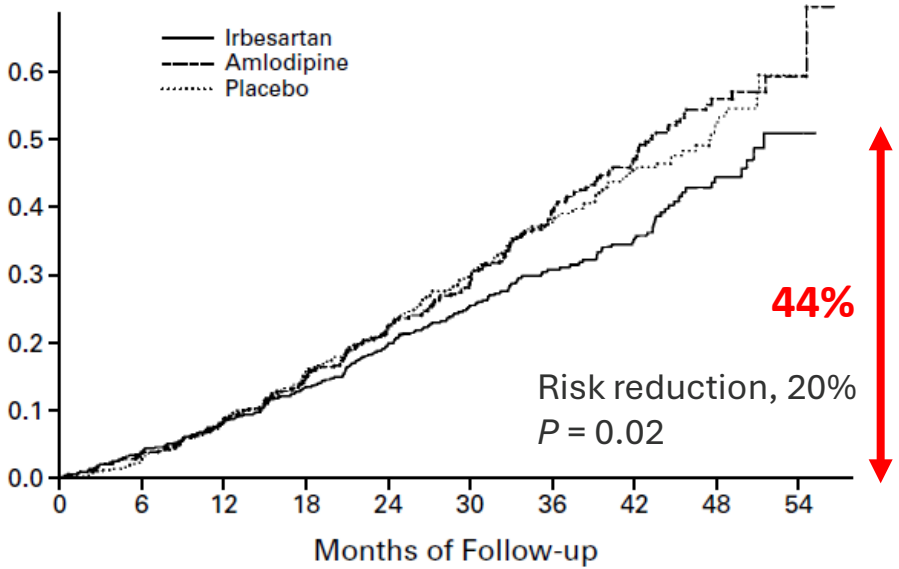
Doubling of serum creatinine, ESKD, or death

RENAAL



T2DM; CKD (UACR ≥300; SCr 1,3-3mg/dL)

IDNT



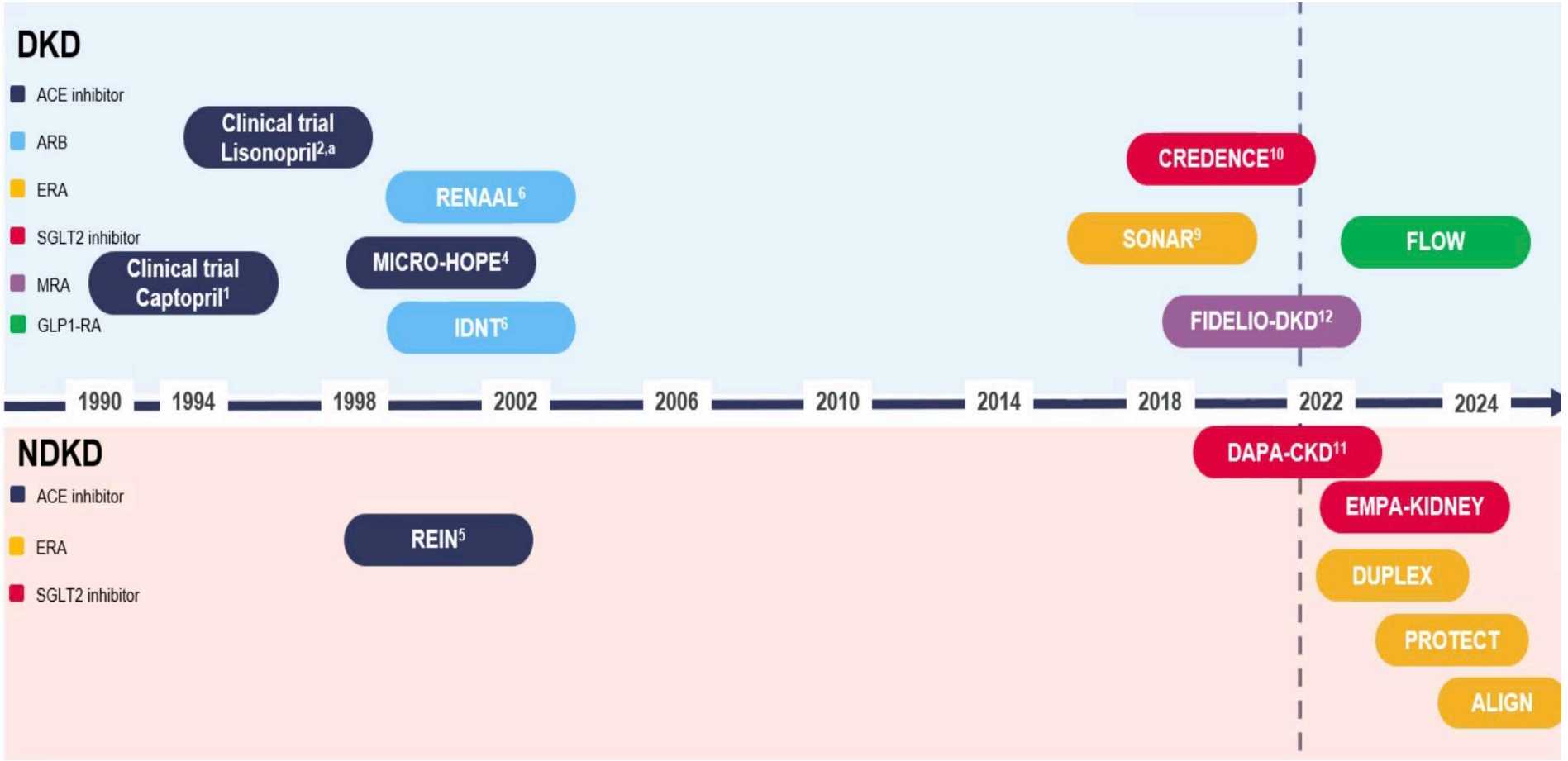
T2DM; CKD (UPE ≥900mg/24h; SCr 1-3 mg/dL)

RENAAL Brenner BM et al. N Engl J Med 2001

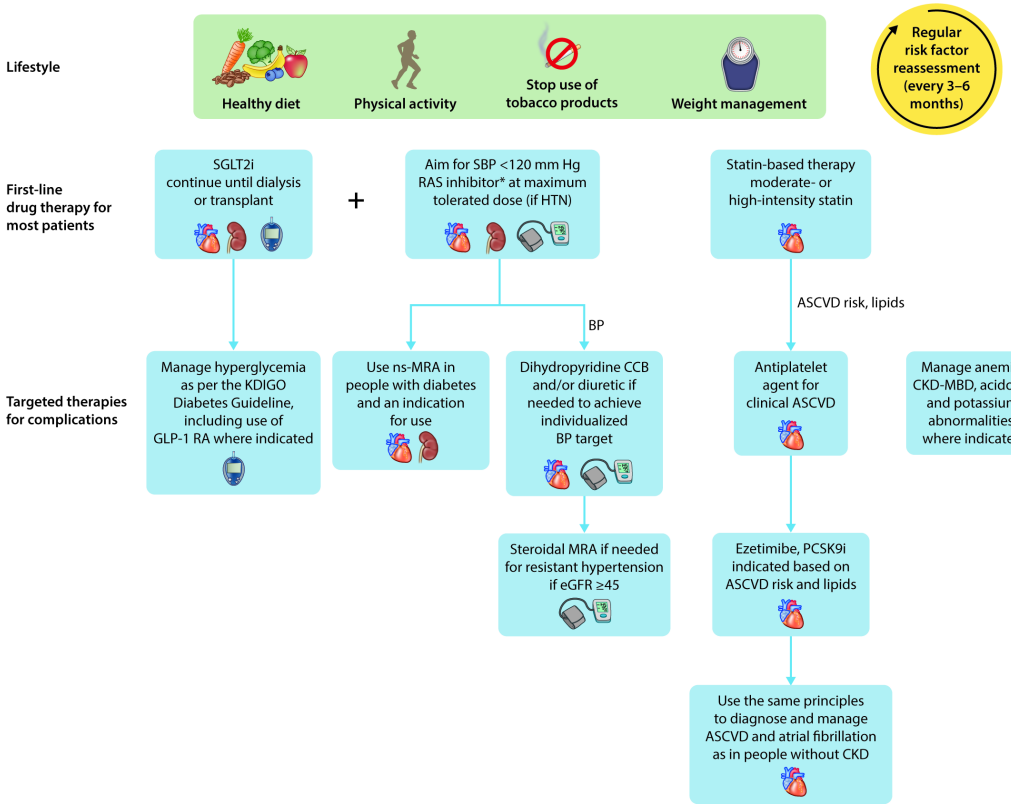
IDNT Lewis EJ et al. N Engl J Med 2001

PERCHE’

SGLT2i…….. filling the gap



2024: MANAGEMENT OF CKD

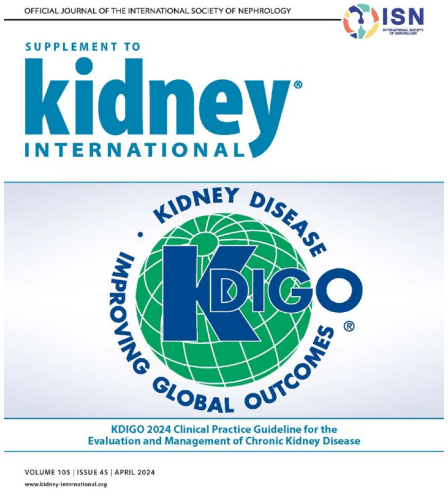


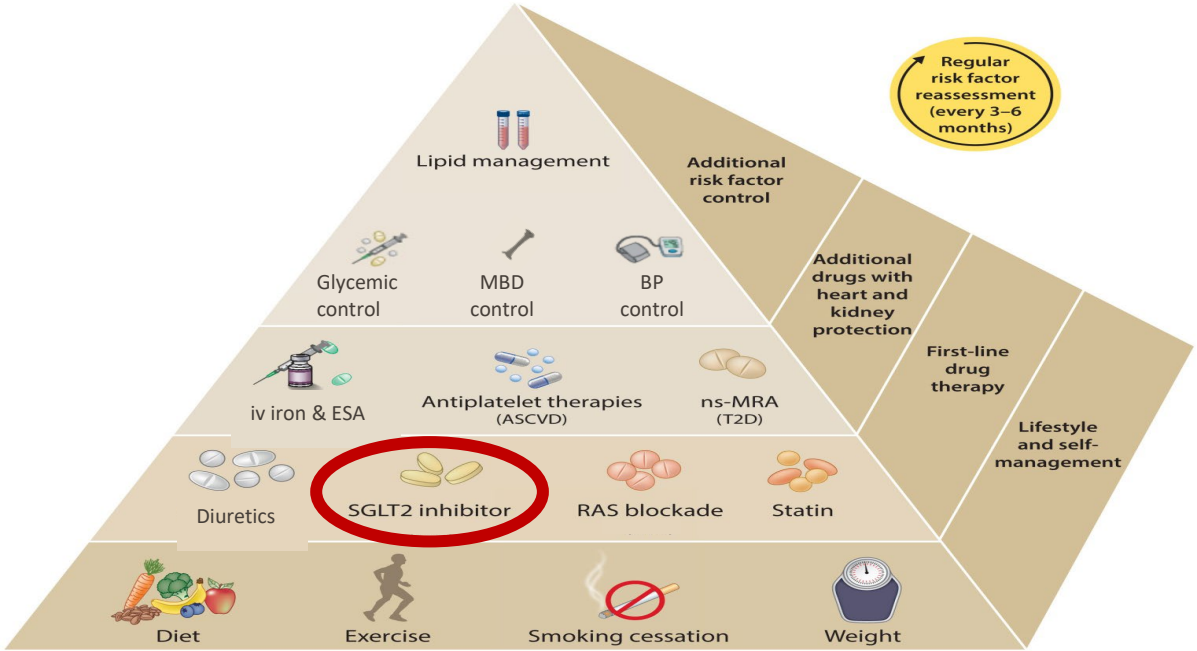
Recommendation 3.7.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min with an SGLT2i (1A)

Recommendation 3.7.2: We recommend treating adults with CKD with an SGLT2i for the following (1A):

- **eGFR ≥ 20 ml/min per 1.73 m^2 with urine ACR ≥ 200 mg/g, or**
- **heart failure, irrespective of level of albuminuria.**

Recommendation 3.7.3: We suggest treating adults with eGFR 20 to 45 ml/min with urine ACR<200 mg/g with an SGLT2i (2B).





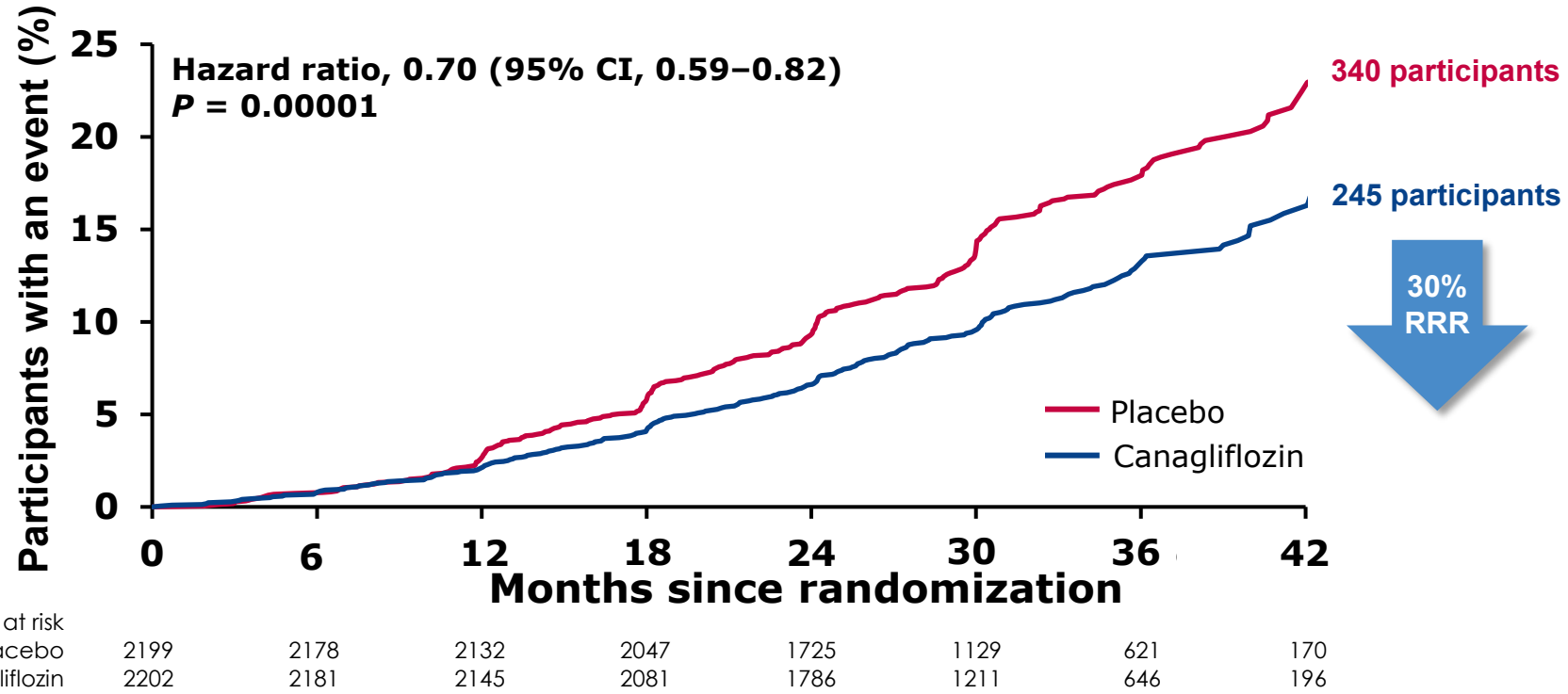
Modified from Kidney Int. April, 2024

What is the residual risk in DKD patients treated with SGLT2i?

Doubling of serum creatinine, ESKD, or death

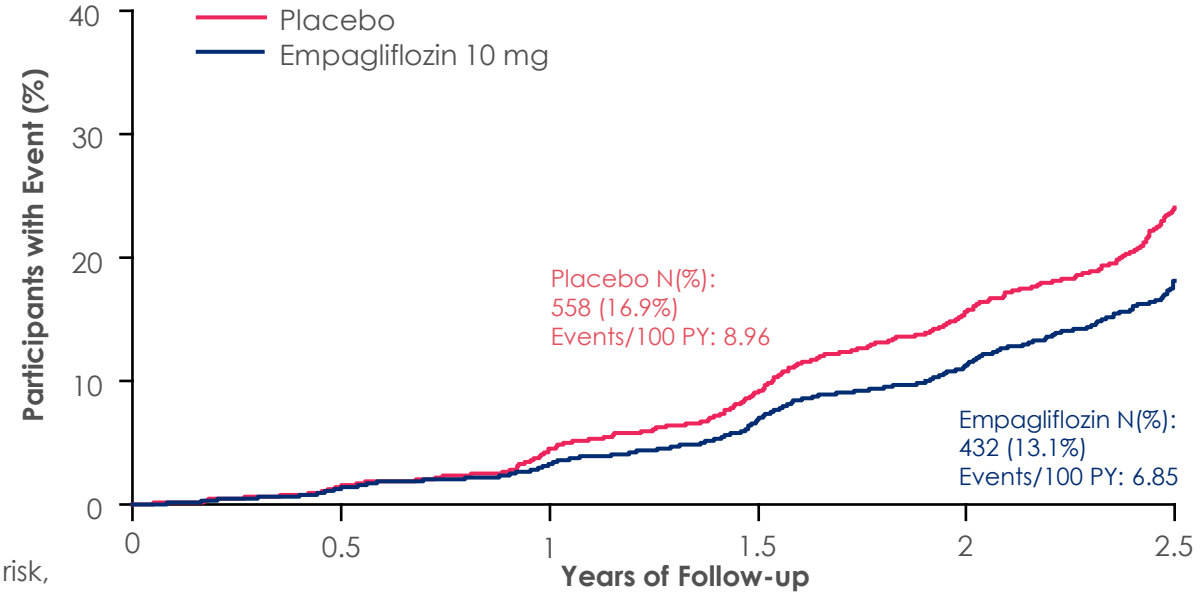
1. 25-30%
2. 30-35%
3. 35-40%
4. >40%

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



Perkovic V, et al. N Engl J Med 2019

EMPA-KIDNEY: Primary composite outcome
Kidney disease progression or CV death



Patients at risk, n

Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

HR 0.72
(95% CI 0.64, 0.82)
P < 0.001

RRR 28%

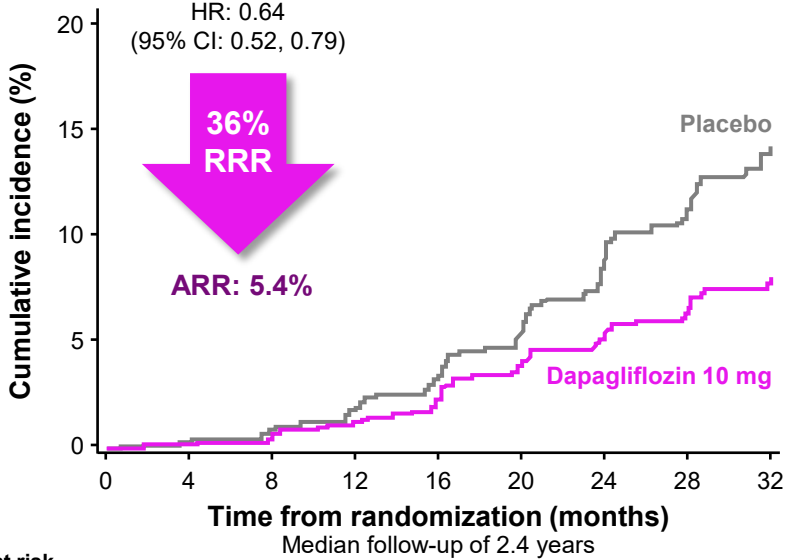
NNT=28*

The EMPA-KIDNEY Collaborative Group. N Engl J Med, 2023

DAPA-CKD: the effect of dapagliflozin on the risk of the primary endpoint is consistent in patients with and without T2D

The effect of dapagliflozin on the primary composite outcome[a] compared with placebo, stratified by diabetes status

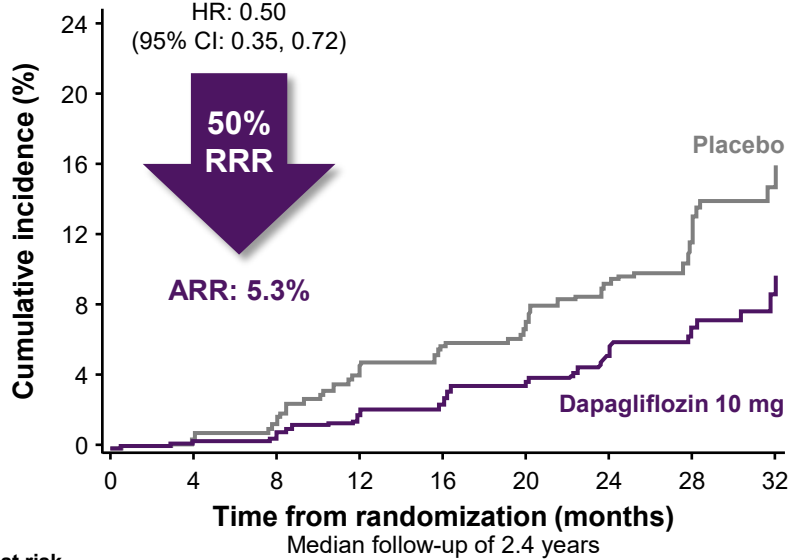
Patients with T2D



Median follow-up of 2.4 years

No. at risk									
Dapagliflozin	1455	1383	1349	1307	1262	1155	910	580	215
Placebo	1451	1360	1321	1275	1224	1130	868	545	190

Patients without T2D



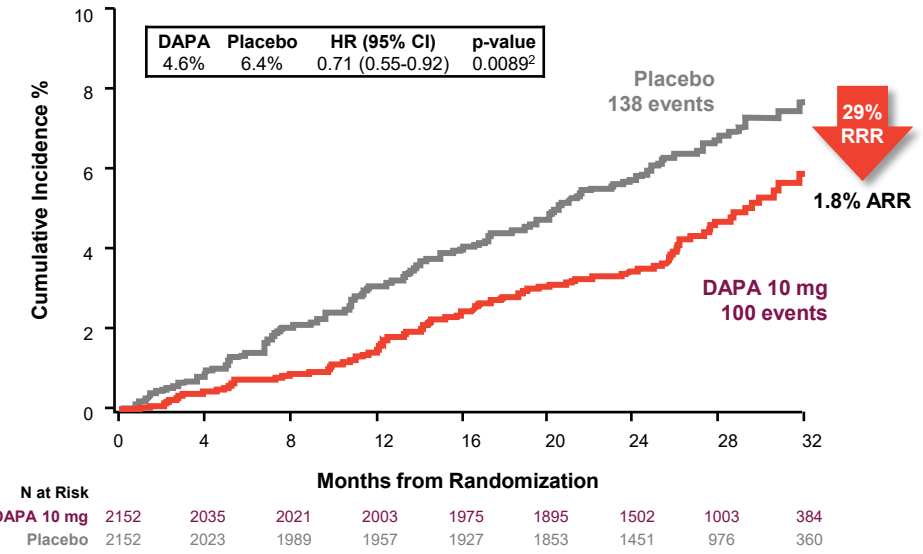
Median follow-up of 2.4 years

No. at risk									
Dapagliflozin	697	618	606	591	579	546	378	251	94
Placebo	701	633	615	583	567	534	364	229	80

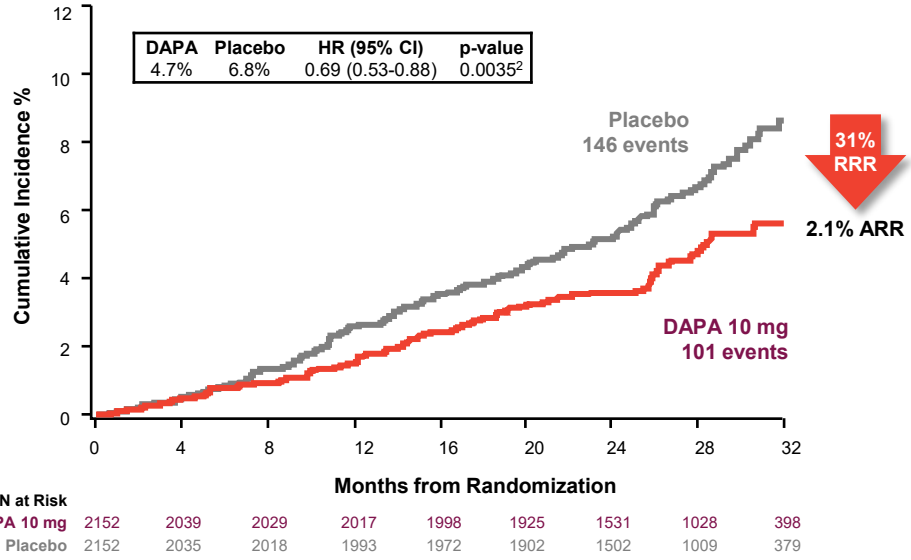
Wheeler DC, et al. Lancet Diabetes Endocrinol 2021;

DAPA-CKD: significant reductions in the composite endpoint of CV death or hospitalization for HF and in all-cause mortality

hHF/CV death



All-cause mortality

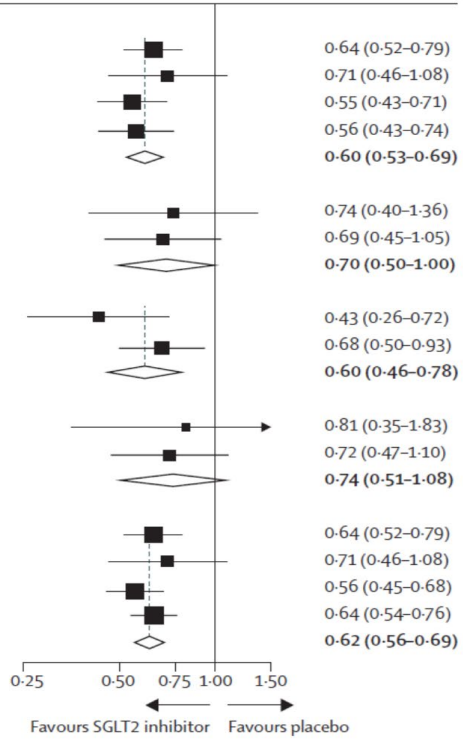


Heerspink HJL et al. N Engl J Med. 2020:

EFFECT OF SGLT2-I ON CKD PROGRESSION BY PRIMARY KIDNEY DISEASE

	Mean baseline eGFR, mL/min per 1·73m²	Events/participants		Event rate per 1000 patient-years		RR (95% CI)
		SGLT2 inhibitor	Placebo	SGLT2inhibitor	Placebo	
Diabetic kidney disease or nephropathy*						
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA–CKD	43	93/1271	157/1239	36	64	0·55 (0·43–0·71)
EMPA–KIDNEY	36	85/1032	133/1025	42	67	0·56 (0·43–0·74)
Subtotal	**46**	**368/9797**	**572/9755**	..	..	**0·60 (0·53–0·69)**
Ischaemic and hypertensive kidney disease						
DAPA–CKD	43	18/324	26/363	28	37	0·74 (0·40–1·36)
EMPA–KIDNEY	35	37/706	52/739	27	37	0·69 (0·45–1·05)
Subtotal	**38**	**55/1030**	**78/1102**	..	..	**0·70 (0·50–1·00)**
Glomerular disease						
DAPA–CKD	43	21/343	46/352	33	70	0·43 (0·26–0·72)
EMPA–KIDNEY	42	69/853	95/816	44	64	0·68 (0·50–0·93)
Subtotal	**42**	**90/1196**	**141/1168**	..	..	**0·60 (0·46–0·78)**
Other kidney disease or unknown						
DAPA–CKD	43	10/214	14/198	25	37	0·81 (0·35–1·83)
EMPA–KIDNEY	36	36/713	52/725	26	36	0·72 (0·47–1·10)
Subtotal	**38**	**46/927**	**66/923**	..	..	**0·74 (0·51–1·08)**
Any diagnosis						
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA–CKD	43	142/2152	243/2152	33	58	0·56 (0·45–0·68)
EMPA–KIDNEY	37	227/3304	332/3305	36	52	0·64 (0·54–0·76)
Total	**44**	**559/12950**	**857/12948**	..	..	**0·62 (0·56–0·69)**

Heterogeneity across groups of primary kidney disease: p=0·67
Trend across trials sorted by eGFR for any diagnosis: p=0·88



DKD: risk reduction 40%

HTN: risk reduction 30%

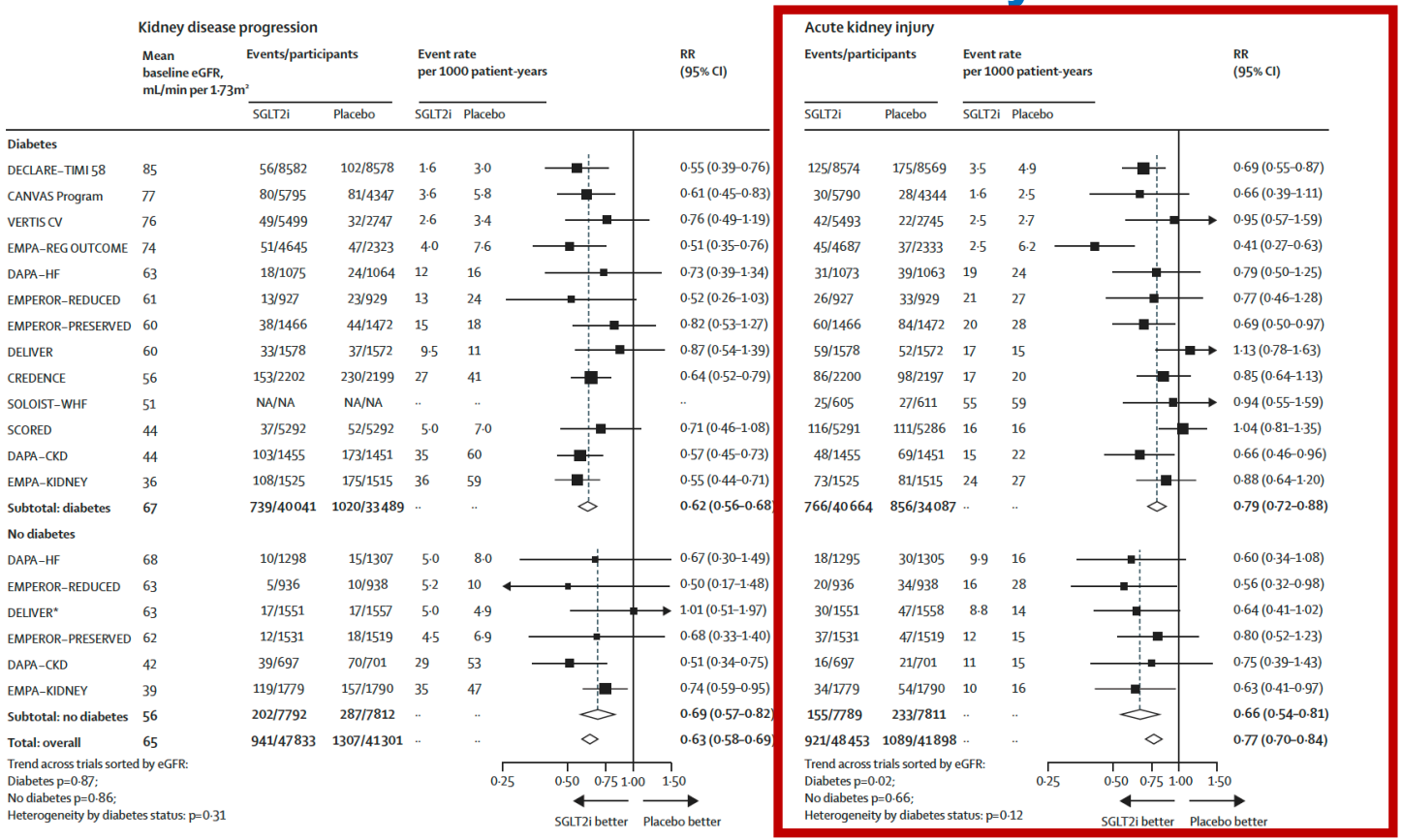
GN: risk reduction 40%

Other/UNK: risk reduction 26%

Overall: risk reduction 38%

Lancet 2022; 400: 1788–801

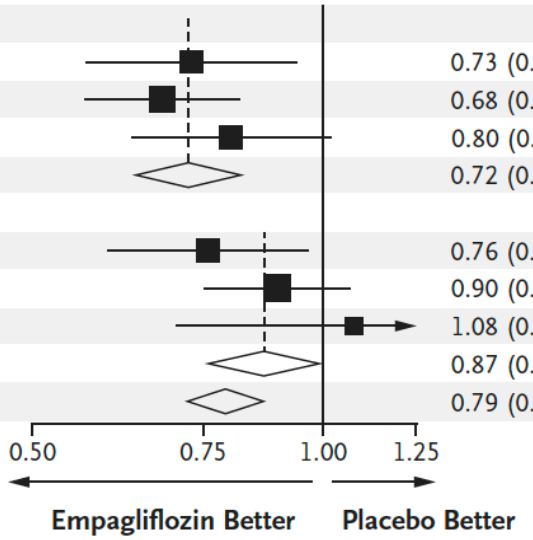
Effects of SGLT2i on kidney outcomes



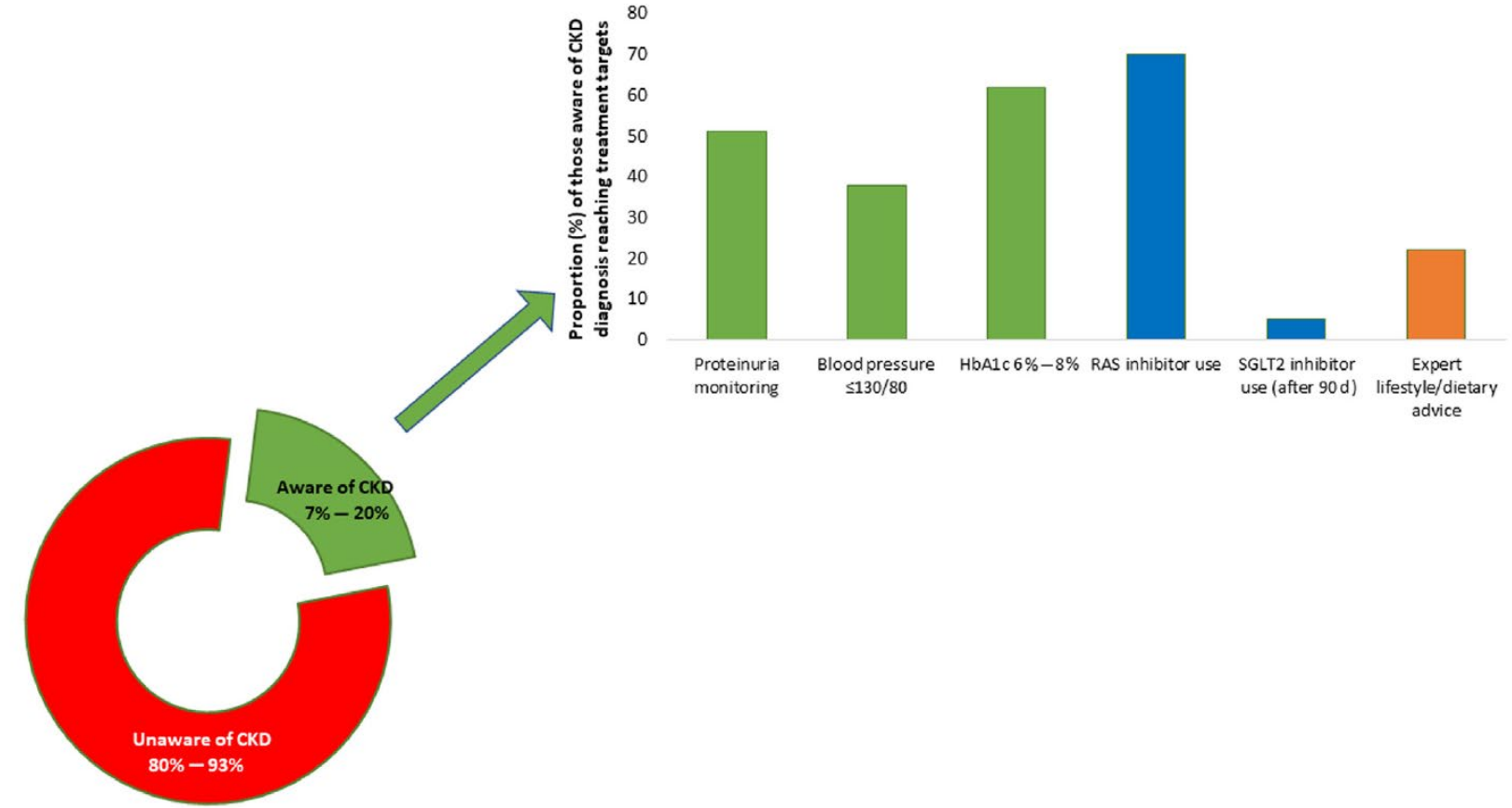
The Nuffield Department of Population Health Renal Studies Group* and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium, Lancet 2023

Long-term effects of Empagliflozin in patients with CKD

Subgroup	Use of SGLT2 Inhibitor (percent) Empagliflozin	Placebo	Primary Outcome (no. of events/total no. (%)) Empagliflozin	Placebo	Hazard Ratio (95% CI)
Active trial					
Yr 1	92	1	105/3304 (3.2)	144/3305 (4.4)	0.73 (0.57–0.94)
Yr 2	88	2	194/3163 (6.1)	271/3129 (8.7)	0.68 (0.57–0.82)
Yr ≥3	83	4	133/1543 (8.6)	143/1501 (9.5)	0.80 (0.63–1.02)
All active-trial period	90	2	432/3304 (13.1)	558/3305 (16.9)	0.72 (0.64–0.82)
Post trial					
Yr 1	40	37	125/2184 (5.7)	148/2073 (7.1)	0.76 (0.60–0.96)
Yr 2	45	42	258/2029 (12.7)	258/1899 (13.6)	0.90 (0.75–1.07)
Yr 3 (median, 0.8 mo)	45	42	50/1032 (4.8)	37/912 (4.1)	1.08 (0.70–1.65)
All post-trial period	43	40	433/2184 (19.8)	443/2073 (21.4)	0.87 (0.76–0.99)
All active- and post-trial period	71	16	865/3304 (26.2)	1001/3305 (30.3)	0.79 (0.72–0.87)



EMPA-Kidney Collaborative Group, N Engl J Med, 2025



Proportion of people with CKD aware of their diagnosis

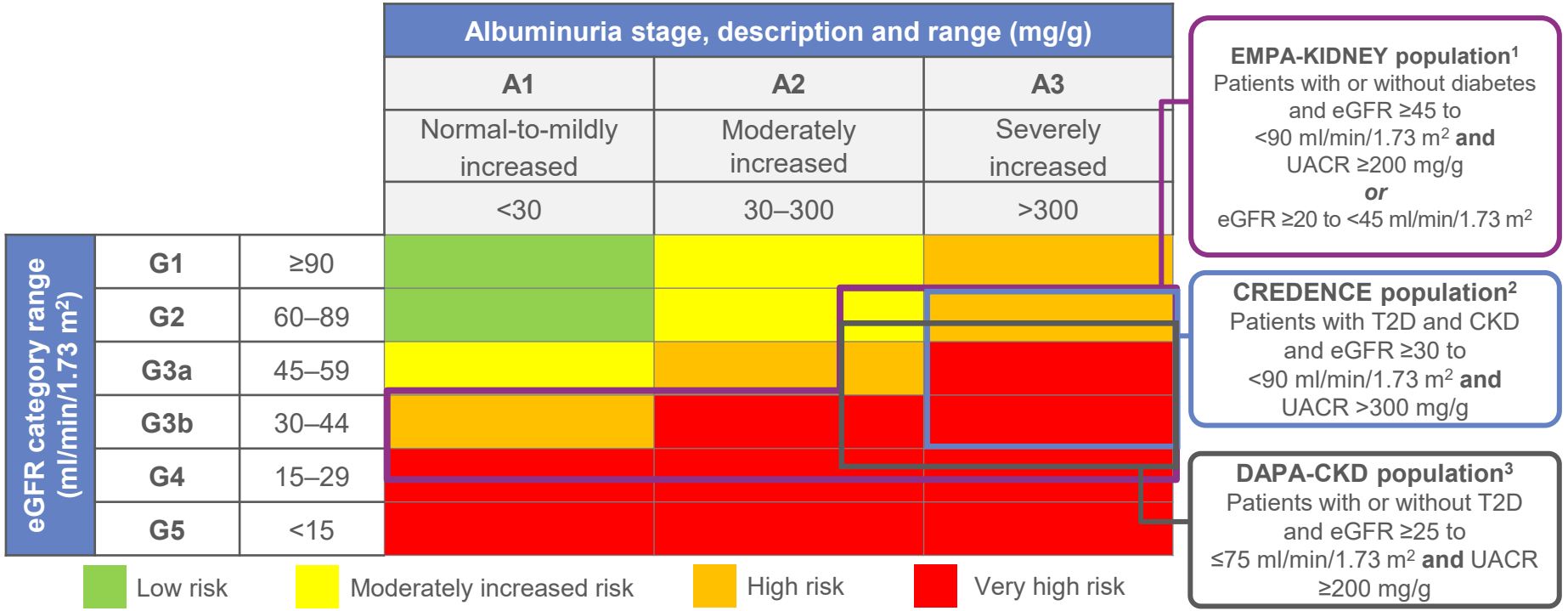
Kidney International Reports (2024) 9, 1541–1552

QUALI?

Randomised controlled trials of SGLT2is in DKD/CKD

	CREDENCE	DAPA-CKD	EMPA-KIDNEY
SGLT2 inhibitor	Canagliflozin vs placebo	Dapagliflozin vs placebo	Empagliflozin vs placebo
Population	**DKD incl.** ✓ T2DM x Without DM x Non-albuminuria	**CKD** ✓ T2DMDM ✓ Without DM~30% x Non-albuminuria	**CKD** ✓ T2DM ✓ Without DM~50% ✓ Non-albuminuria~20%
No. of patients	4401	4304	6609
Key inclusion criteria†	eGFR ≥30 to <90 mL/min/1.73m^2 **and** UACR >300 mg/g	eGFR ≥25 to ≤75 mL/min/1.73m^2 **and** UACR ≥200 mg/g	eGFR ≥45 to <90 mL/min/1.73m^2 and UACR ≥200 mg/g **or** eGFR ≥20 to <45 mL/min/1.73m^2
Primary outcome	Composite of doubling of serum creatinine, ESKD, or renal or CV death	Composite of ≥50% sustained decline in eGFR or ESKD, or renal or CV death	Composite of ≥40% sustained decline in eGFR or ESKD, or renal or CV death
RASi	**100%** Maximally tolerated RAS blockade, unless documented intolerance	**97%** Maximally tolerated RAS blockade, unless documented intolerance	**86%** Clinically appropriate RAS blockade, unless not indicated or not tolerated
Study start date **Study stop date**	February 2014 Reported April 2019	February 2017 Reported September 2020	January 2019 November 2022

Study populations in the key SGLT2 inhibitor trials have populations that cover the eGFR and UACR spectra



1. The EMPA-KIDNEY Collaborative Group. N Engl J Med 2023; Perkovic V et al. N Engl J Med 2019; 3. Wheeler DC et al. Nephrol Dial Transplant 2020

QUANDO?

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

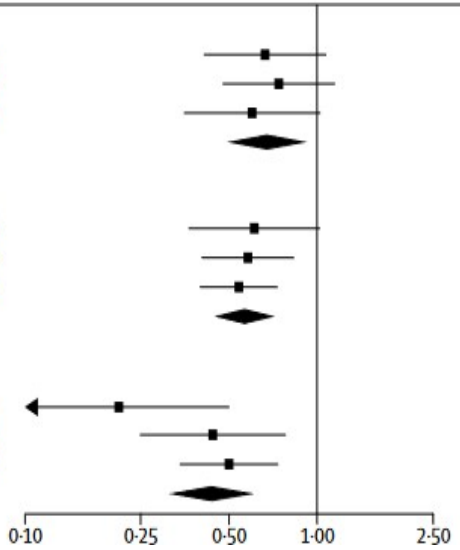
THE LANCET

Zelniker TA, 2019

Meta-analysis of SGLT2i trials on the composite of worsening of renal function, ESKD, or renal death

A

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1196	605	NA	NA	NA	33·5		0·66 (0·41–1·07)
CANVAS Program	NA	NA	83	11·4	15·1	39·6		0·74 (0·48–1·15)
DECLARE-TIMI 58	606	659	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	1232	NA	NA	NA	16·8		0·61 (0·37–1·03)
CANVAS Program	NA	NA	118	4·6	7·4	34·4		0·58 (0·41–0·84)
DECLARE-TIMI 58	3838	3894	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	486	NA	NA	NA	11·7		0·21 (0·09–0·53)
CANVAS Program	NA	NA	48	3·8	8·1	27·5		0·44 (0·25–0·78)
DECLARE-TIMI 58	4137	4025	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)**

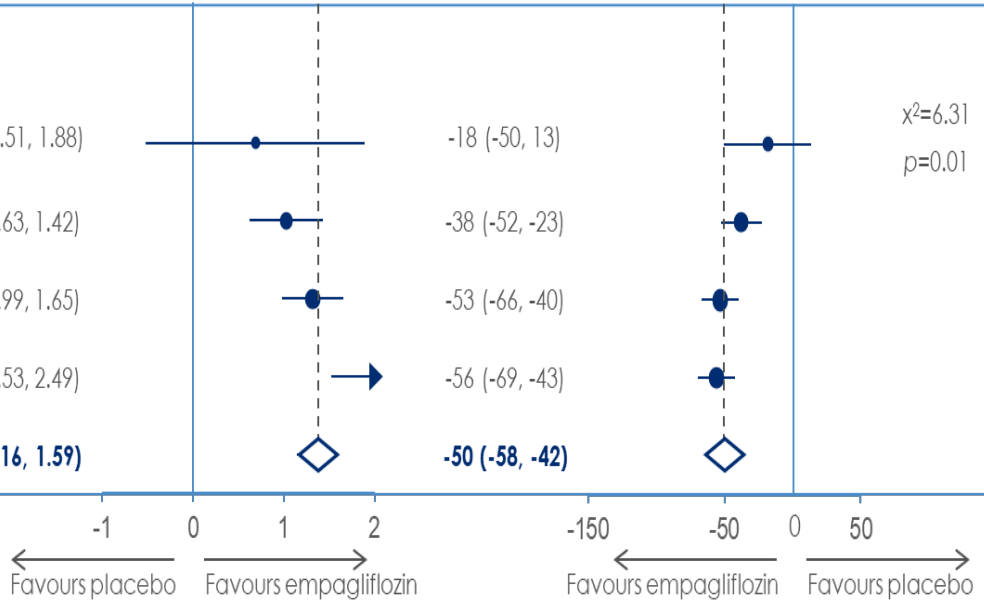


The earlier the better

Lesser reductions in progression of renal disease was observed in patients with more severe kidney disease at baseline

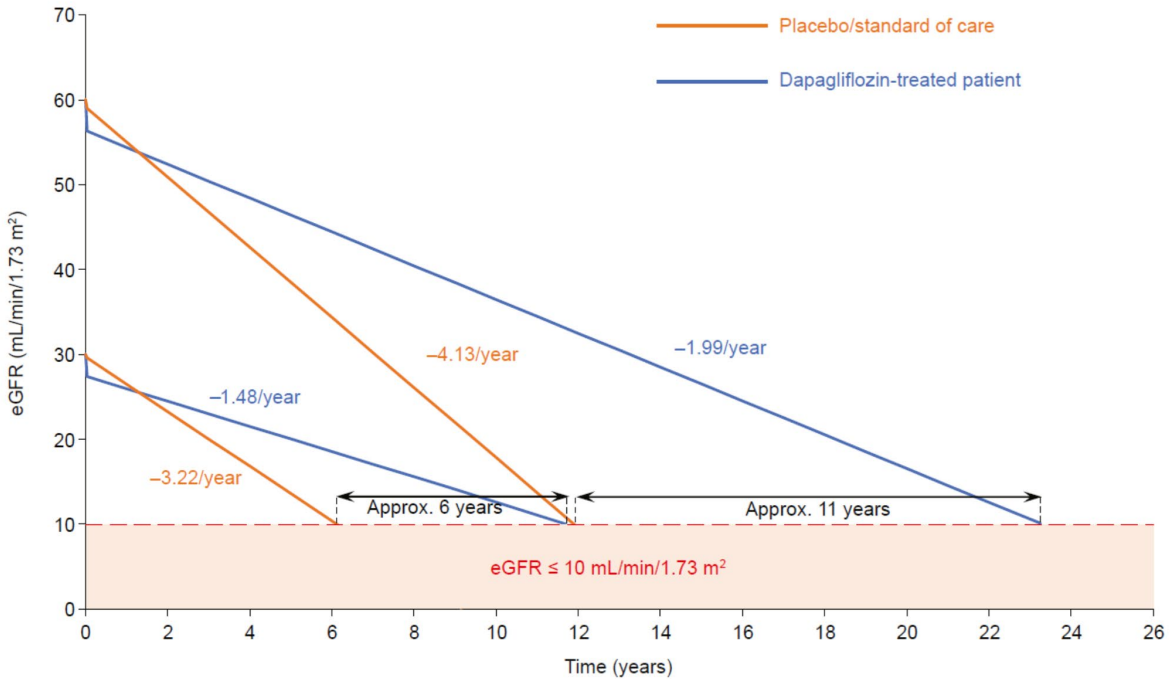
Absolute and relative effects on chronic slopes by expanded analysis of eGFR subgroup

Subgroup	Study average reduction in UACR (%)	Empagliflozin	Placebo	Absolute difference (95% CI)	Relative difference (95% CI)	Het/trend test
		Annual rate of change in eGFR, ml/min/1.73 m^2, mean (SE)				
eGFR, ml/min/1.73 m^2						
<20	5	-3.08 (0.44)	-3.77 (0.43)	0.69 (-0.51, 1.88)	-18 (-50, 13)	x^2=6.31
≥20 to <30	-27	-1.70 (0.14)	-2.73 (0.14)	1.03 (0.63, 1.42)	-38 (-52, -23)	*p*=0.01
≥30 to <45	-17	-1.18 (0.12)	-2.50 (0.12)	1.32 (0.99, 1.65)	-53 (-66, -40)	
≥45	-15	-1.58 (0.17)	-3.59 (0.17)	2.01 (1.53, 2.49)	-56 (-69, -43)	
All participants	-19	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37 (1.16, 1.59)**	**-50 (-58, -42)**	



DAPA CKD: time to kidney replacement therapy

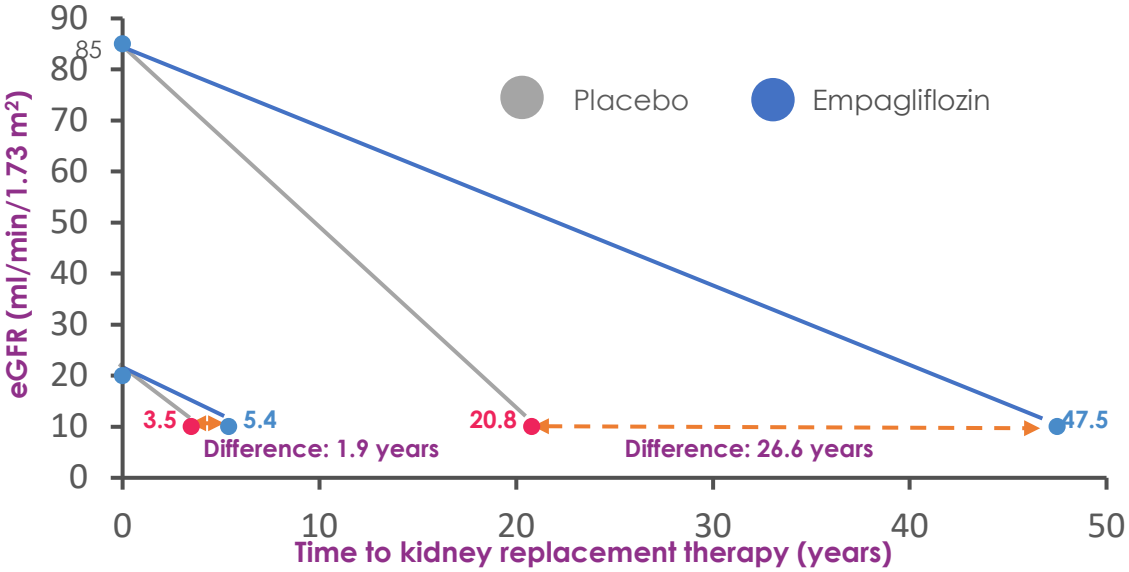
Extrapolation of data from the DAPA-CKD trial to estimate the delay of kidney failure



Madero M et al, Kidney Med 2024

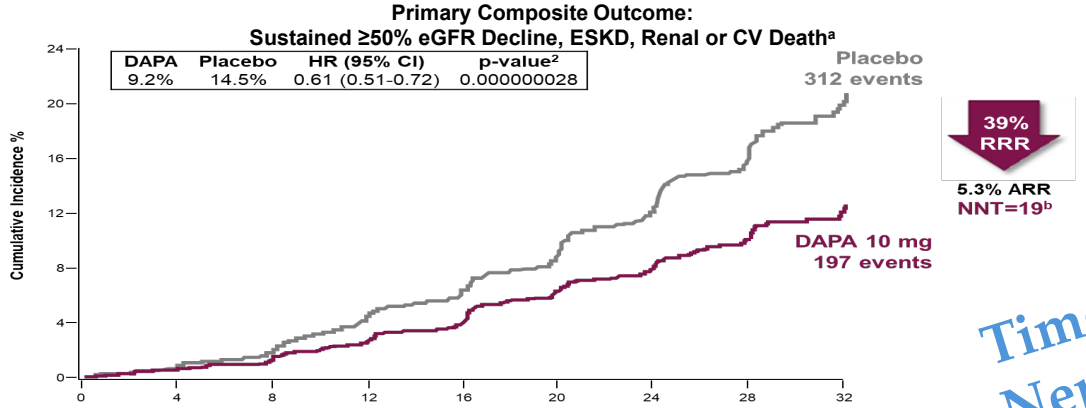
EMPA-KIDNEY: time to kidney replacement therapy

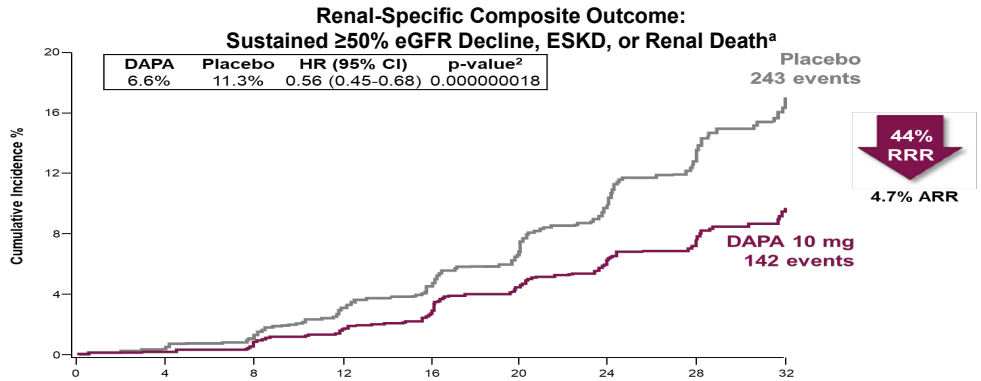
Hypothetical transformation of chronic eGFR slopes into time to kidney replacement therapy



Fernández-Fernandez B *et al. Clin Kidney J* 2023

Secondary Renal-Specific Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, or Renal Death[a,1]





Time needed…..
Nephrologist be patient

1. Heerspink HJL et al. Online ahead of print. *N Engl J Med*. 2020; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

Time needed….be patient and keep going

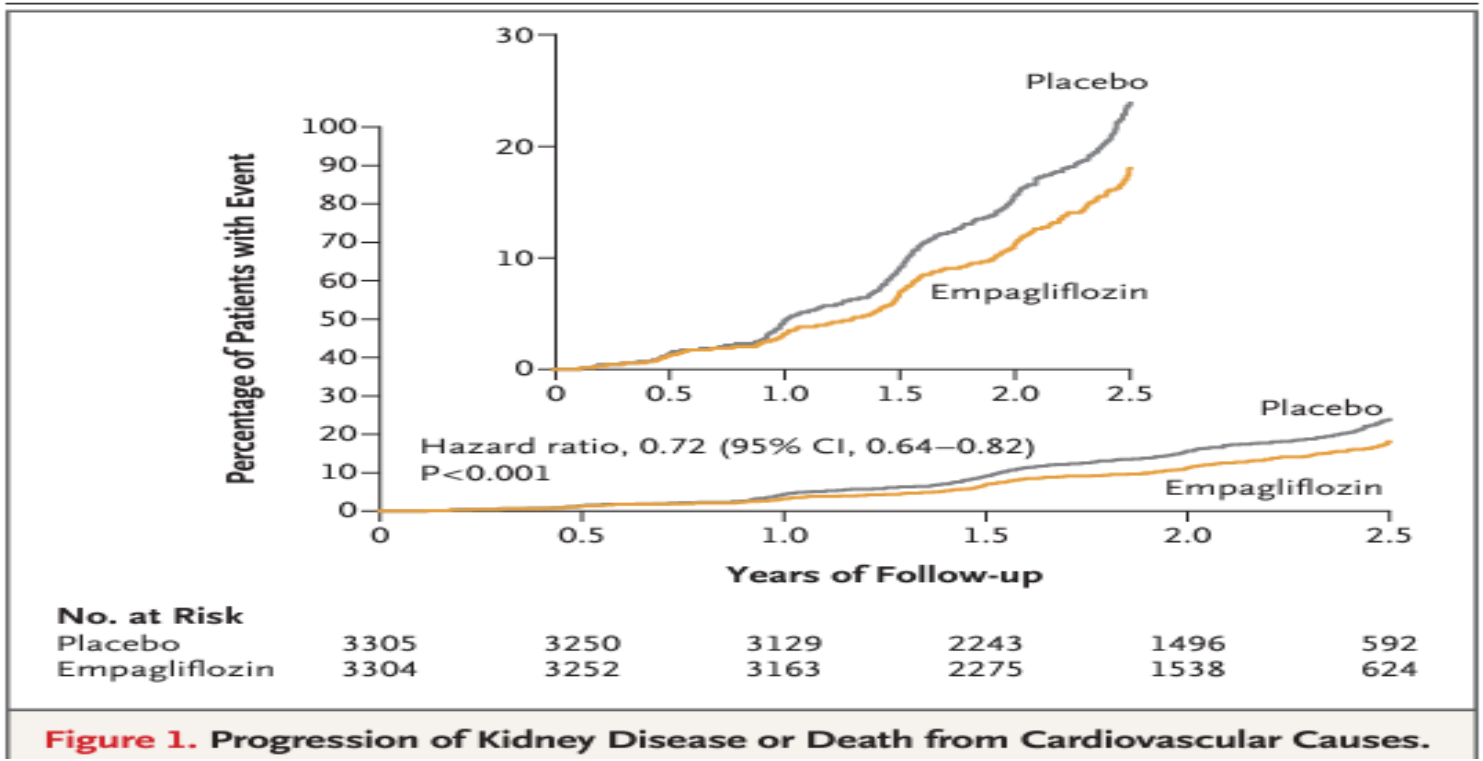
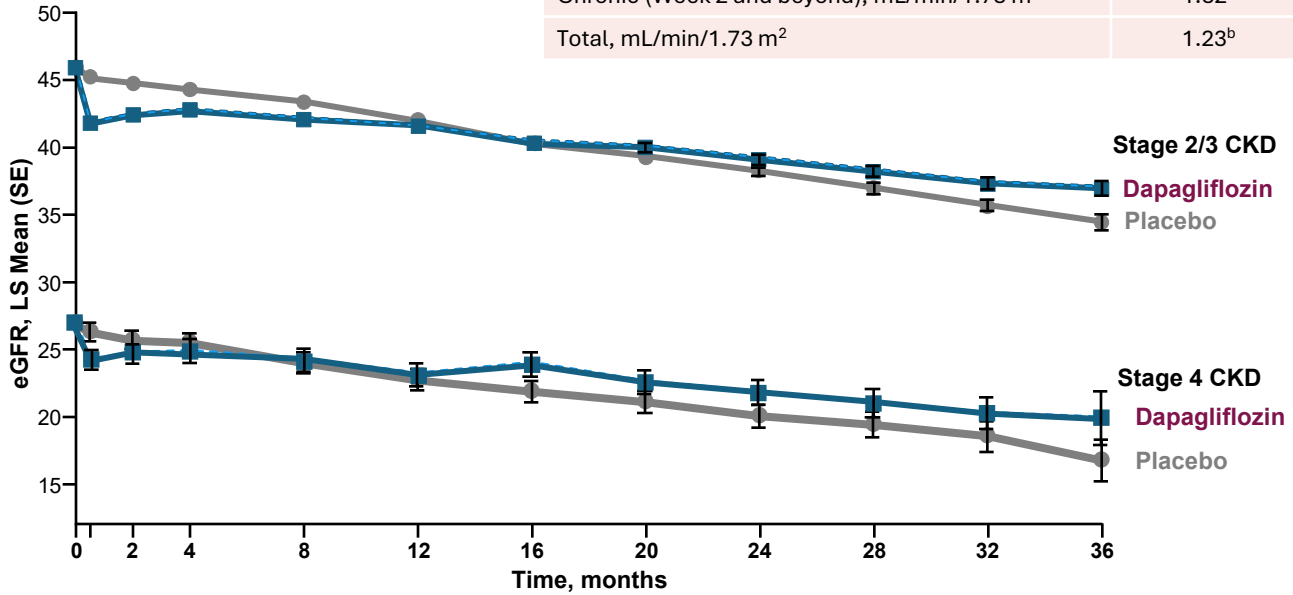


Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.

Empagliflozin in Patients with Chronic Kidney Disease *N Engl J Med 2023;388:117-27*

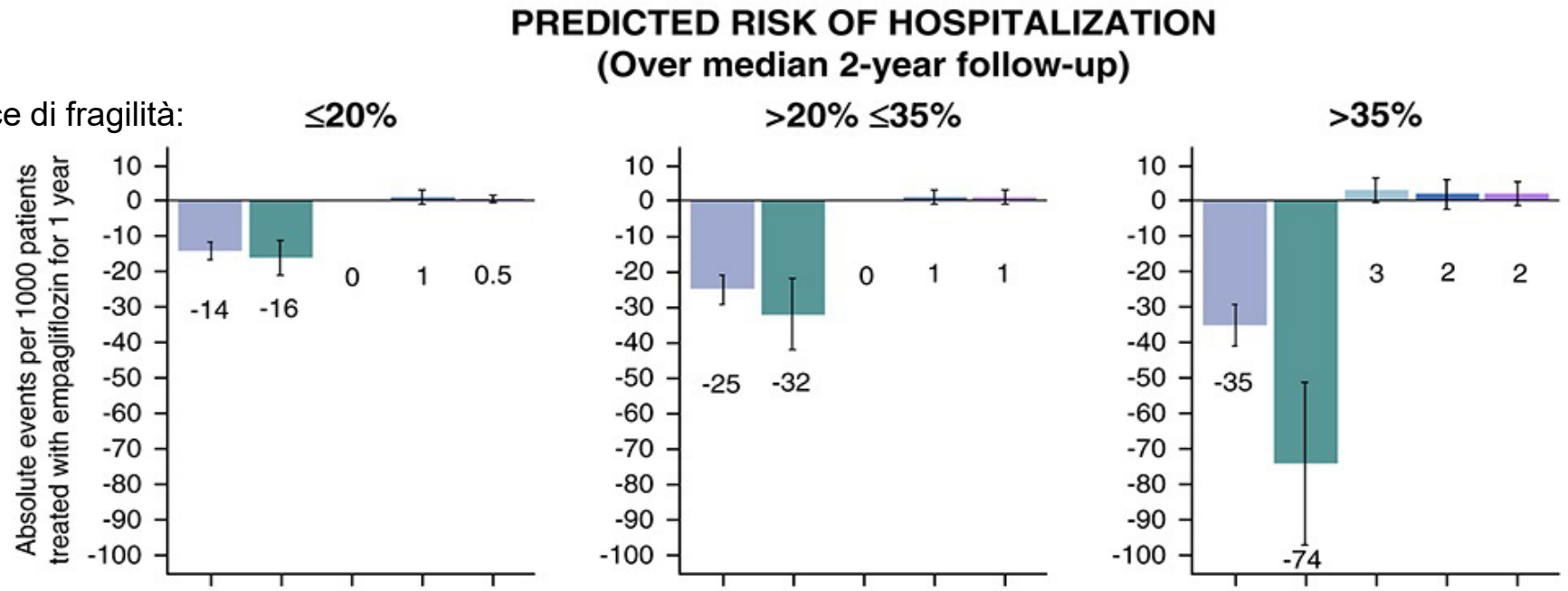
eGFR Decline Over the Study by Baseline CKD Stage

Between-group slope difference[a]	Stage 4 CKD	Stage 2/3 CKD
Acute (2 weeks), mL/min/1.73 m^2	-1.42[b]	-2.56
Chronic (Week 2 and beyond), mL/min/1.73 m^2	1.82[c]	1.95
Total, mL/min/1.73 m^2	1.23[b]	0.89



NOTE: Stage 4 CKD = eGFR <30 mL/min/1.73m^2; Stage 2/3 CKD = eGFR ≥30 mL/min/1.73m^2.
[a]Dapagliflozin vs placebo; [b]p=0.005 vs PBO; [c]p<0.0001 vs PBO.
CKD = chronic kidney disease; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; NA = not available; PBO = placebo.
Chertow GM et al. *J Am Soc Nephrol*. 2021;32:2352-2361.

EMPA-KIDNEY: ACROSS THE SPECTRUM OF FRAILTY



CJASN19(9):1119-1129,2024

What is the residual risk in DKD patients treated with SGLT2i?

Doubling of serum creatinine, ESKD, or death

1. 25-30%
2. 30-35%
3. 35-40%
4. >40%

2015-2024: Standard-of-Care and Cardio-Renal Protection

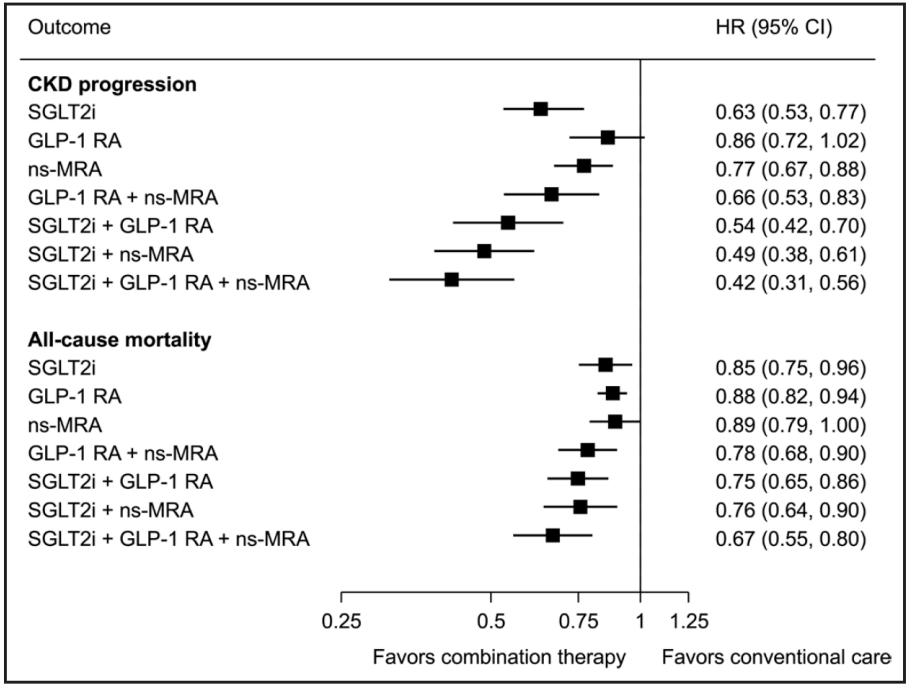
ORIGINAL RESEARCH ARTICLE

Estimated Lifetime Cardiovascular, Kidney, and Mortality Benefits of Combination Treatment With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Nonsteroidal MRA Compared With Conventional Care in Patients With Type 2 Diabetes and Albuminuria

Brendon L. Neuen, MBBS, MSc, PhD; Hiddo J.L. Heerspink, PhD; Priya Vart, PhD; Brian L. Claggett, PhD; Robert A. Fletcher, MSc; Clare Arnott, MBBS, PhD; Julianna de Oliveira Costa, PhD; Michael O. Falster, PhD; Sallie-Anne Pearson, PhD; Kenneth W. Mahaffey, MD; Bruce Neal, MB ChB, PhD; Rajiv Agarwal, MD; George Bakris, MD; Vlado Perkovic, MBBS, PhD; Scott D. Solomon, MD; Muthiah Vaduganathan, MD, MPH

Circulation. 2024;149:450–462

Effects of combination therapy on CKD progression and all-cause mortality



BARI BEAT-DKD COHORT

CKD

in T2D

99 Pts

Phenotype

Subtype

Endotype

37.1%

Metabolic 37

Pure Metabolic 8

Metabolic and Vascular 29

DKD

36.1%

Vascular 35

NDKD

20.6%

Immunologic 21

Pure Immunologic 4

Immunologic and Vascular 17

6.2%

Mixed Forms 6

1 AL Amyloidosis

8 FSGS

5 IgAN

NDKD

2 Membranous Nephropathy

2 Chronic Interstitial Nephritis

1 Podocytopathy

1 MPO Anca-Positive

1 FSGS + Membranous Nephropathy

1 DN + Chronic Intertitial Nephritidis

1 DN + IgAN

1 DN + Light Chain Cast Nephropathy

1 DN + K-LCDD

1 DN + Minimal Change Disease

1 DN + FSGS

DKD+ NDKD

HERD OF ZEBRAS

the coat looks the same among them, but each of them has its own coat

Ex uno, Plures

Preserving Kidney Function Instead of Replacing It

*Alan S. Kliger,[1] and Frank C. Brosius,[2] on behalf of the Diabetic Kidney Disease Task Force of the American Society of Nephrology**

It is time for nephrology to embrace a change in paradigm: returning to our traditional focus on pathophysiology and kidney preservation.

CJASN 15: 129–131, 2020.

ASN
American Society of Nephrology

KIDNEY WEEK 2022
Annual Meeting | November 3 - 6

Joint ASN-National Academy of Medicine Opening Plenary:
ASN President's Address, Expert Panel "Preventing the Next Pandemic"

"I am asking each of you ... to join the movement — the revolution — until a world without kidney diseases is no longer seen as impossible but becomes inevitable."

Susan E. Quaggin, MD, FASN

Thanks for your attention

Loreto Gesualdo, MD, FERA
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IN NEFROLOGIA