A new era in Management of CKD and the role of Dapagliflozin

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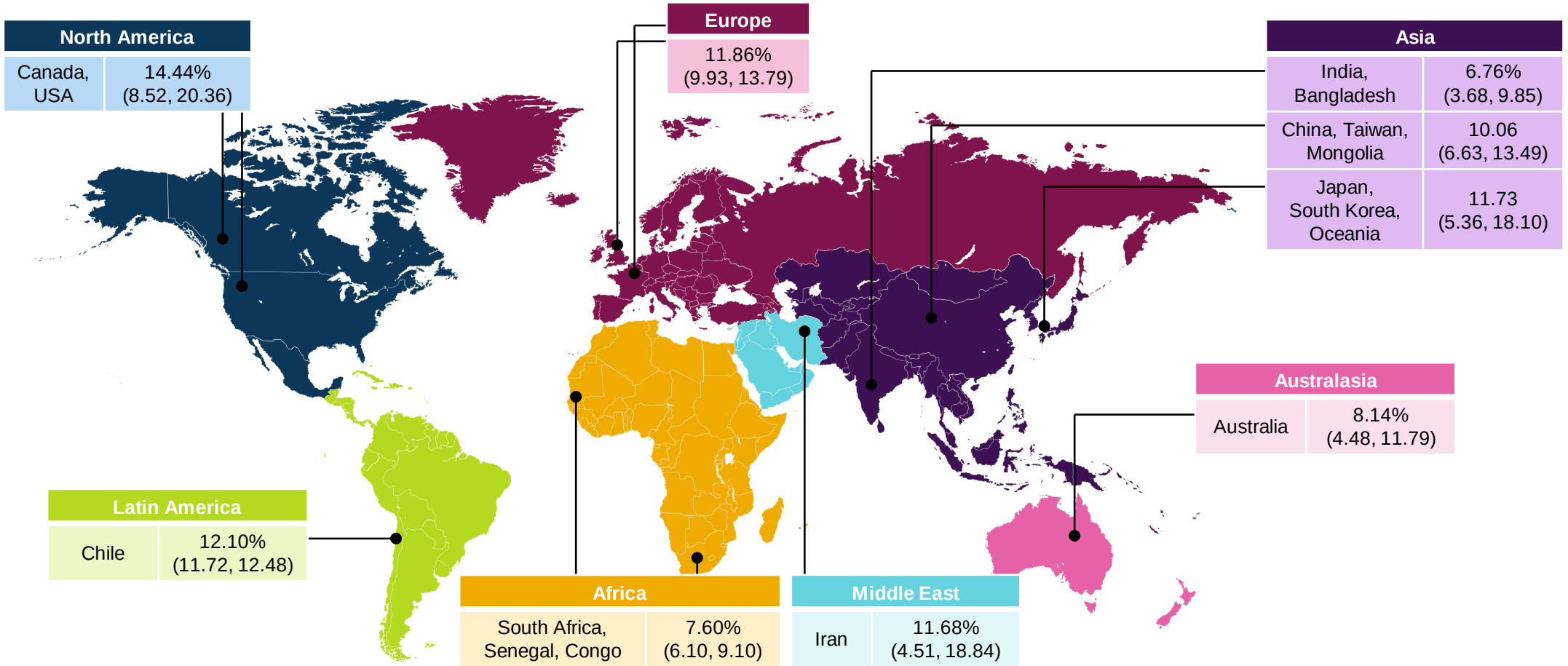
Over 840 million people suffer from CKD worldwide[1]

Meta-analysis estimating the global prevalence of CKD (stages 3–5)[2,a]



[a]Global prevalence reported as percentage with 95% confidence intervals.
CKD = chronic kidney disease.

1. Jager KJ et al. *Nephrol Dial Transplant.* 2019;34:1803-1805; 2. Hill NR et al. *PLoS One.* 2016;11:e0158765.

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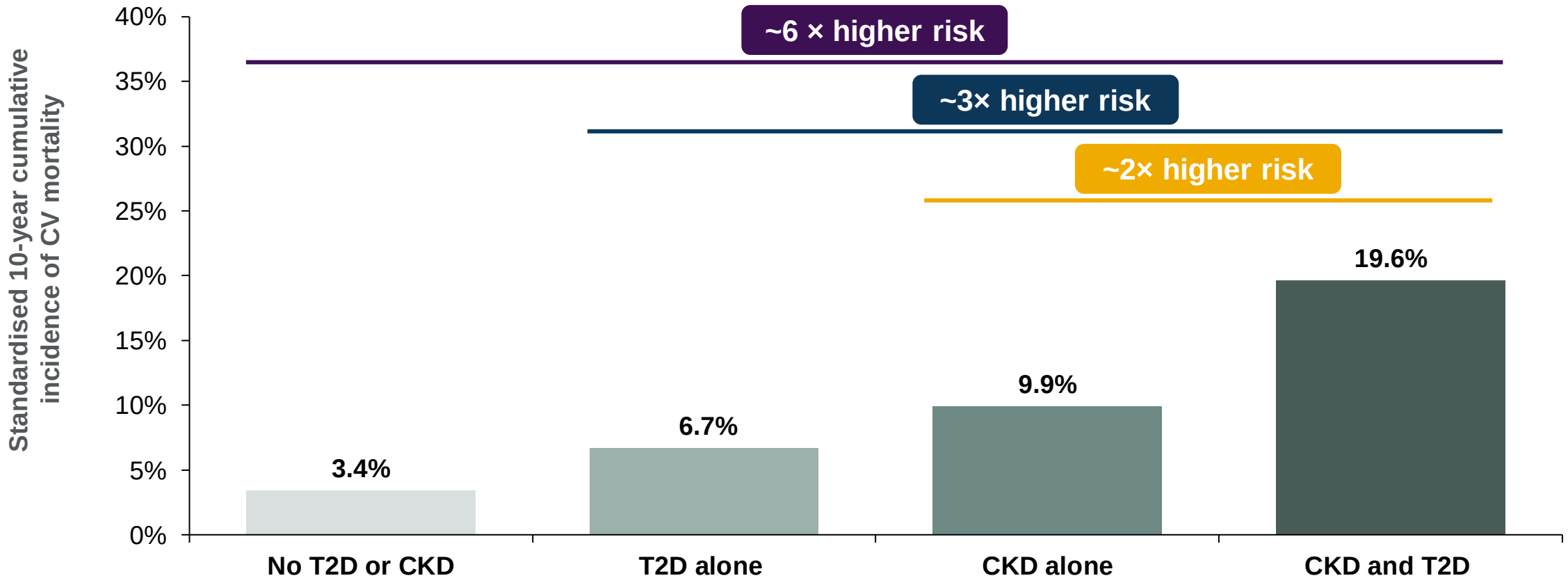
Compared with T2D alone, comorbid CKD increases CV mortality

Standardised 10-year cumulative incidence of CV mortality by diabetes and kidney disease status



Afkarian M, *et al*. *J Am Soc Nephrol* 2013;24:302–308

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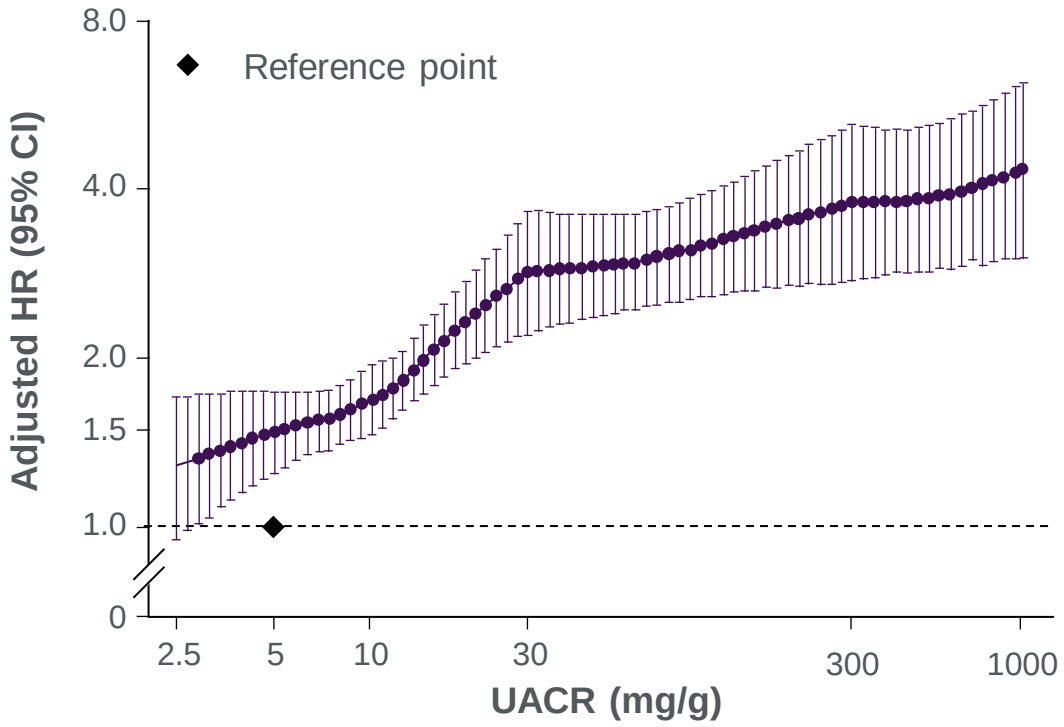
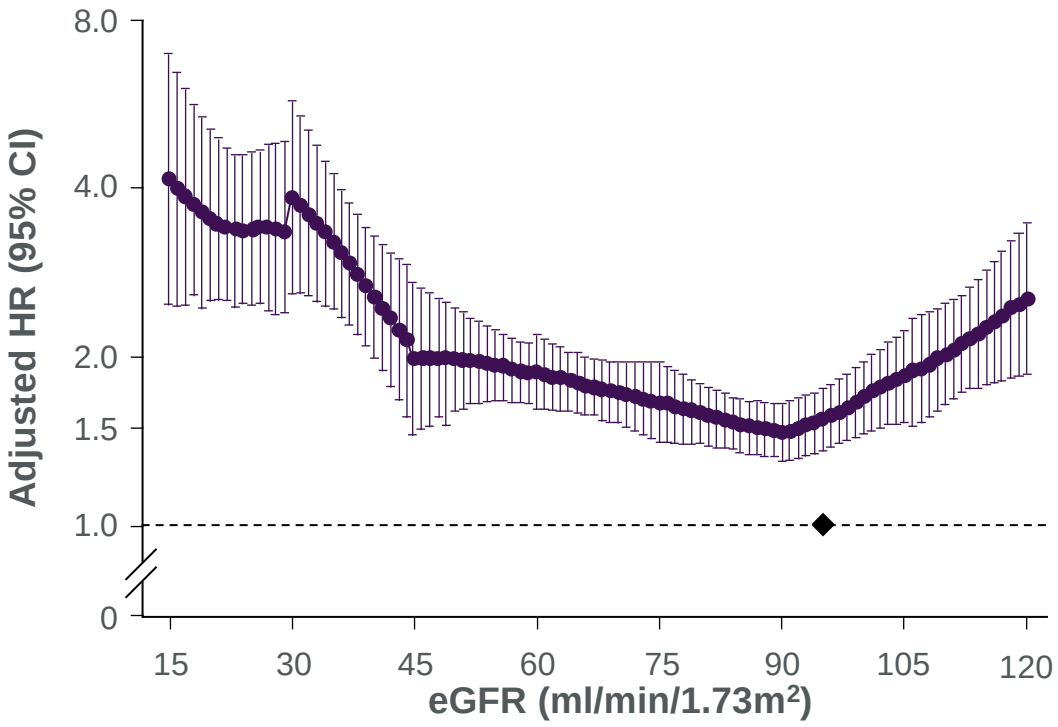
Risk of CV events in patients with diabetes increases as albuminuria progresses and eGFR declines

CV mortality according to UACR



Risk of CV death is significantly increased as UACR rises above 10 mg/g

CV mortality according to eGFR



Risk of CV death is significantly increased as eGFR falls below 75 ml/min/1.73 m²

Fox CS, *et al. Lancet* 2012;380:1662–1673

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Diagnosis of CKD relies on assessment of kidney damage and/or function[1]

Early-stage kidney disease is usually **asymptomatic, requiring laboratory tests for detection[1]**

Guideline-recommended laboratory tests to evaluate and stage kidney disease include

eGFR	**Albuminuria (UACR)**
Index of kidney function	**Marker of kidney damage**

Clinical diagnosis of CKD is defined **eGFR <60 mL/min/1.73m^2** or as **UACR >30 mg/g** which persists for > 3 months

UACR and eGFR should be assessed annually in all patients with T2D regardless of treatment, and twice annually in patients with UACR>30mg/g and/or eGFR<60 mL/min/1.73m^2 [2]

1. Levey AS, *et al. JAMA* 2015;313:837–846; 2. American Diabetes Association. *Diabetes Care* 2020;43(suppl 1):S135–S151; 3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl* 2013;3:1–150

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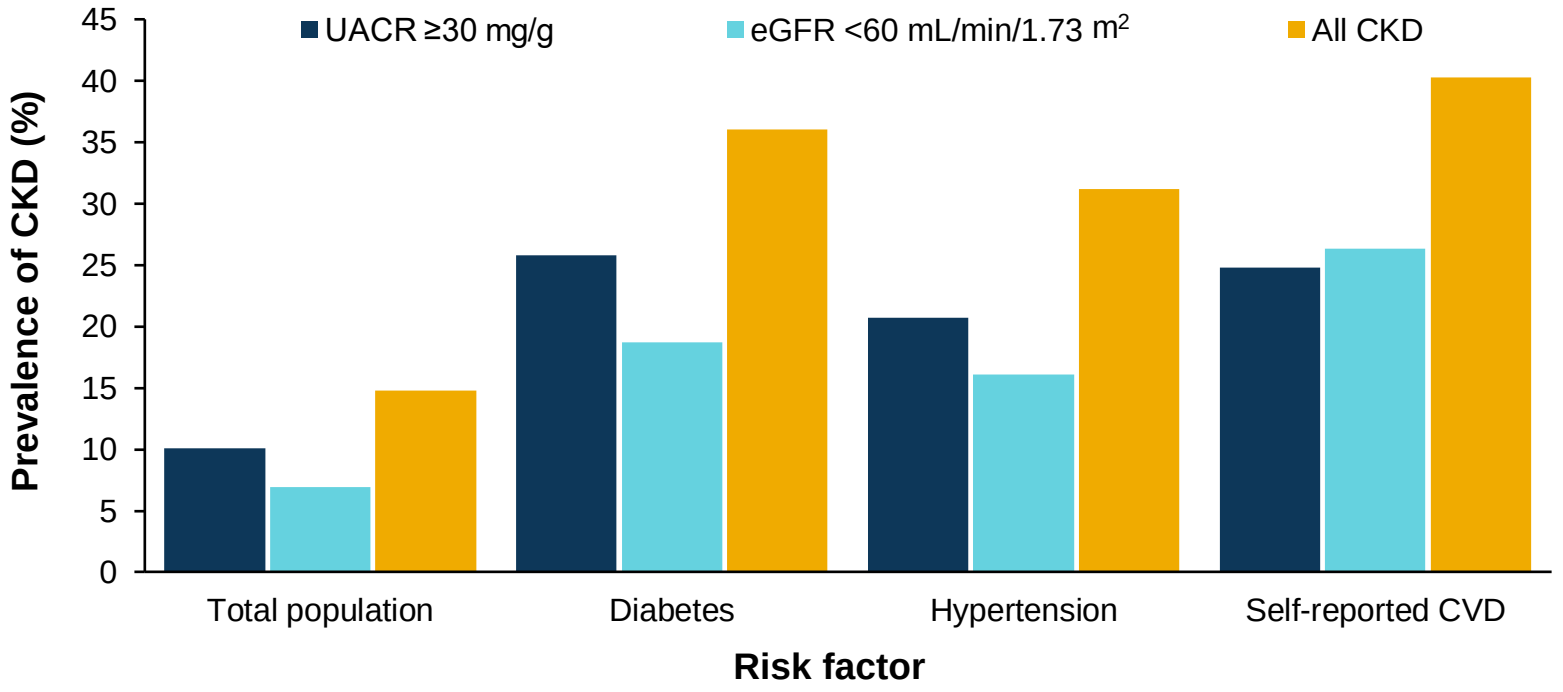
KDIGO recommends screening for CKD in high-risk individuals such as those with hypertension, diabetes, or CVD[1]

Prevalence of CKD in NHANES population by risk factor[2]
NHANES 2013–2016



This CKD screening strategy:[1]

Prioritizes identification of persons at high risk for CKD progression and CV events, with established treatment strategies

Detects individuals with CKD at a lower cost per case identified than population-wide screening programs

Hypertension, diabetes, and CVD are established CKD risk factors[2]
Therefore, CKD prevalence is expected to be higher among these individuals[1]

CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; NHANES = National Health and Nutrition Examination Survey; UACR = urine albumin:creatinine ratio.

1. Shlipak MG et al. *Kidney Int.* 2021;99:34-47; 2. United States Renal Data System. 2018 Annual Data Report. Chronic kidney disease: CKD in the general population. https://www.usrds.org/media/1723/v1_c01_genpop_18_usrds.pdf.

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Assessment of both eGFR and UACR is critical for diagnosing CKD and predicting prognosis[1]

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			Persistent albuminuria categories[a]		
			A1	A2	A3
			Normal to mildly increased <30 mg/g	Moderately increased 30–299 mg/g	Severely increased ≥300 mg/g
G1	Normal or high	≥90	**Monitor**	**Treat**	**Treat and consult**
G2	Mildly decreased	60–89	**Monitor**	**Treat**	**Treat and consult**
G3a	Mildly to moderately decreased	45–59	**Treat**	**Treat**	**Treat and consult**
G3b	Moderately to severely decreased	30–44	**Treat**	**Treat and consult**	**Treat and consult**
G4	Severely decreased	15–29	**Treat and consult**	**Treat and consult**	**Treat and consult**
G5	Kidney failure	<15	**Treat and consult**	**Treat and consult**	**Treat and consult**

GFR categories (mL/min/1.73 m²)

Figure from KDIGO 2020[2]; hypothetical patient profile
[a]Alternative units for these three UACR categories include: <3 mg/mmol, 3–30 mg/mmol, and >30 mg/mmol[2]
See slide notes for abbreviations and references

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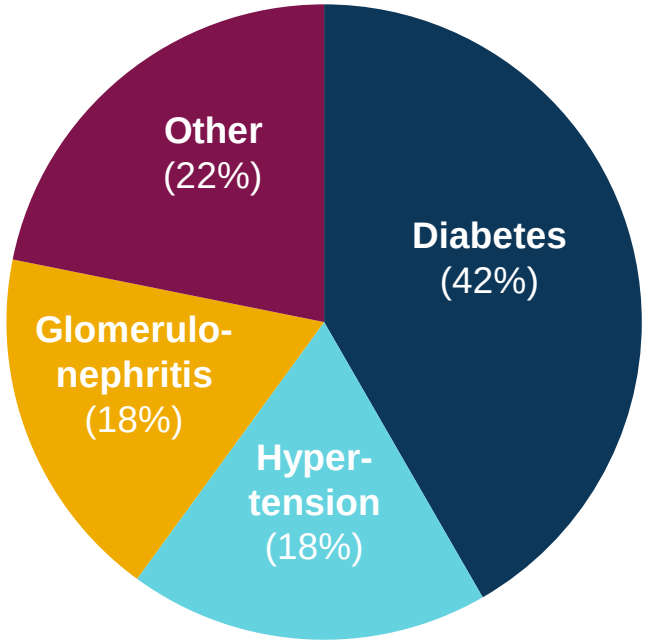
The causes of CKD are diverse, with hypertension and diabetes responsible for more than half of all CKD cases

Age-standardized global prevalence rate of CKD by cause per 100,000 persons in 2016[1]



~50% **of patients with CKD have CVD or diabetes[2,a]**

[a]Self-reported CVD.
CKD = chronic kidney disease; CVD = cardiovascular disease; UI = uncertainty interval.
1. Xie Y et al. *Kidney Int.* 2018;94:567-581; 2. National Institute of Diabetes and Digestive and Kidney Diseases. Kidney disease statistics for the United States. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease; 3. Jager KJ et al. *Nephrol Dial Transplant.* 2017;32:ii121-ii128.

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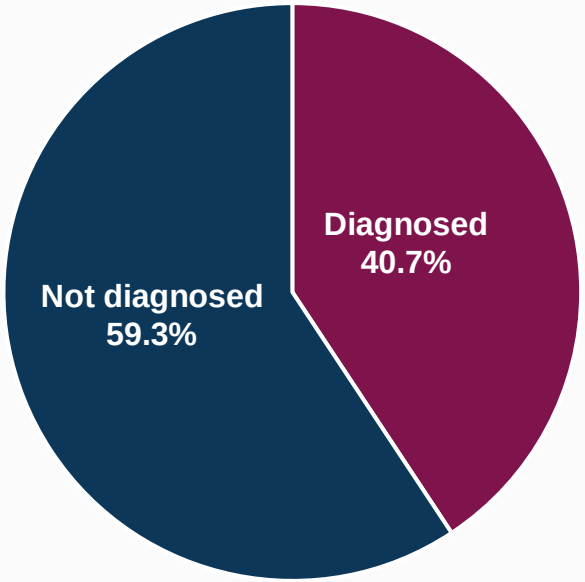
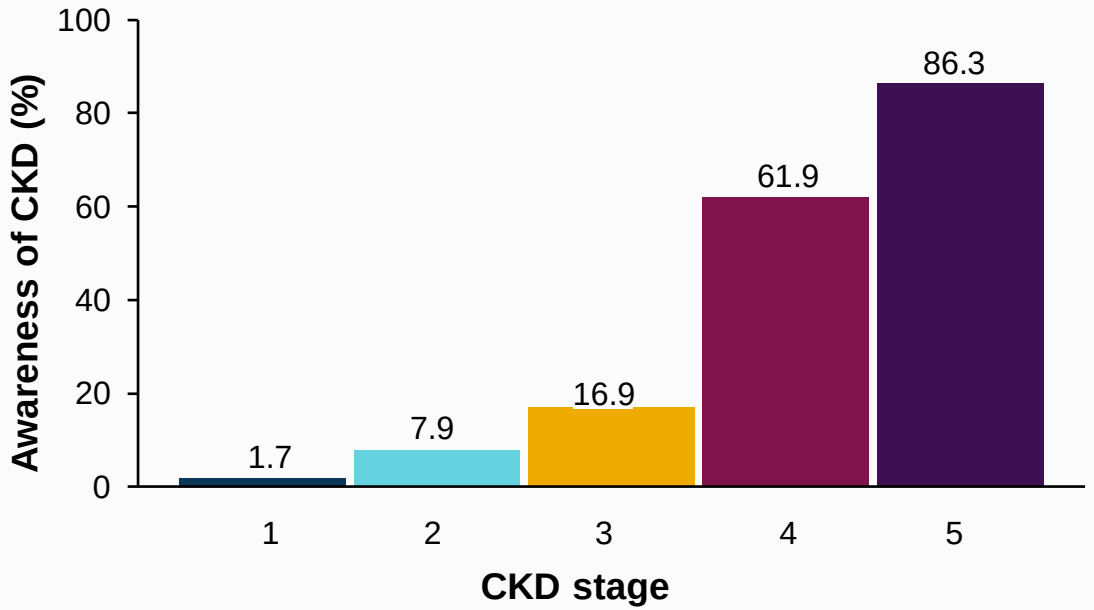
Data suggest a high rate of underdiagnosis and extremely low patient awareness of early-stage CKD

Prevalence of diagnosed CKD cases in CKD patients in CURE-CKD registry[1,a–c]



Data collected:
January 2006 – December 2017

CKD awareness by CKD stage in the NHANES population (2015–2018)[2,d,e]



Additional analyses of population-based survey data in England indicate only 7.4% of patients with Stage 3 CKD were aware of having CKD[3,f]

[a]Excluding end-stage kidney disease treated with dialysis or kidney transplant; [b]EHR-based registry jointly curated and sponsored by PSJH and UCLA using Epic EHRs (Epic Systems); [c]Patients who met the initial CURE-CKD registry criteria were diagnosed with CKD using the CKD-epidemiology equation from the mean of at least two serum creatinine measurements ≥90 days apart; [d]NHANES data are representative of the non-institutionalized U.S. population, with oversampling of certain subgroups to increase reliability and precision of health indicator estimates; [e]Awareness was assessed as those who reported being told that they had kidney disease; [f]Pooled data of 1164 patients with evidence of CKD from the 2009, 2010 and, 2016 Health Survey for England, an annual, population-based cross-sectional survey of adults and children living in private households in England.

CKD = chronic kidney disease; CURE-CKD = Center for Kidney Disease Research, Education, and Hope; EHR = electronic health record; NHANES = National Health and Nutrition Examination Survey; PSJH = Providence St. Joseph Health; UCLA = University of California, Los Angeles.

1. Tuttle KR et al. *JAMA Netw Open.* 2019;2:e1918169; 2. United States Renal Data System. 2020 Annual Data Report. Chronic kidney disease: CKD in the general population. https://adr.usrds.org/2020/chronic-kidney-disease/1-ckd-in-the-general-population; 3. Sultan AA et al. Presented at: WCN; April 16-19, 2021; Virtual.

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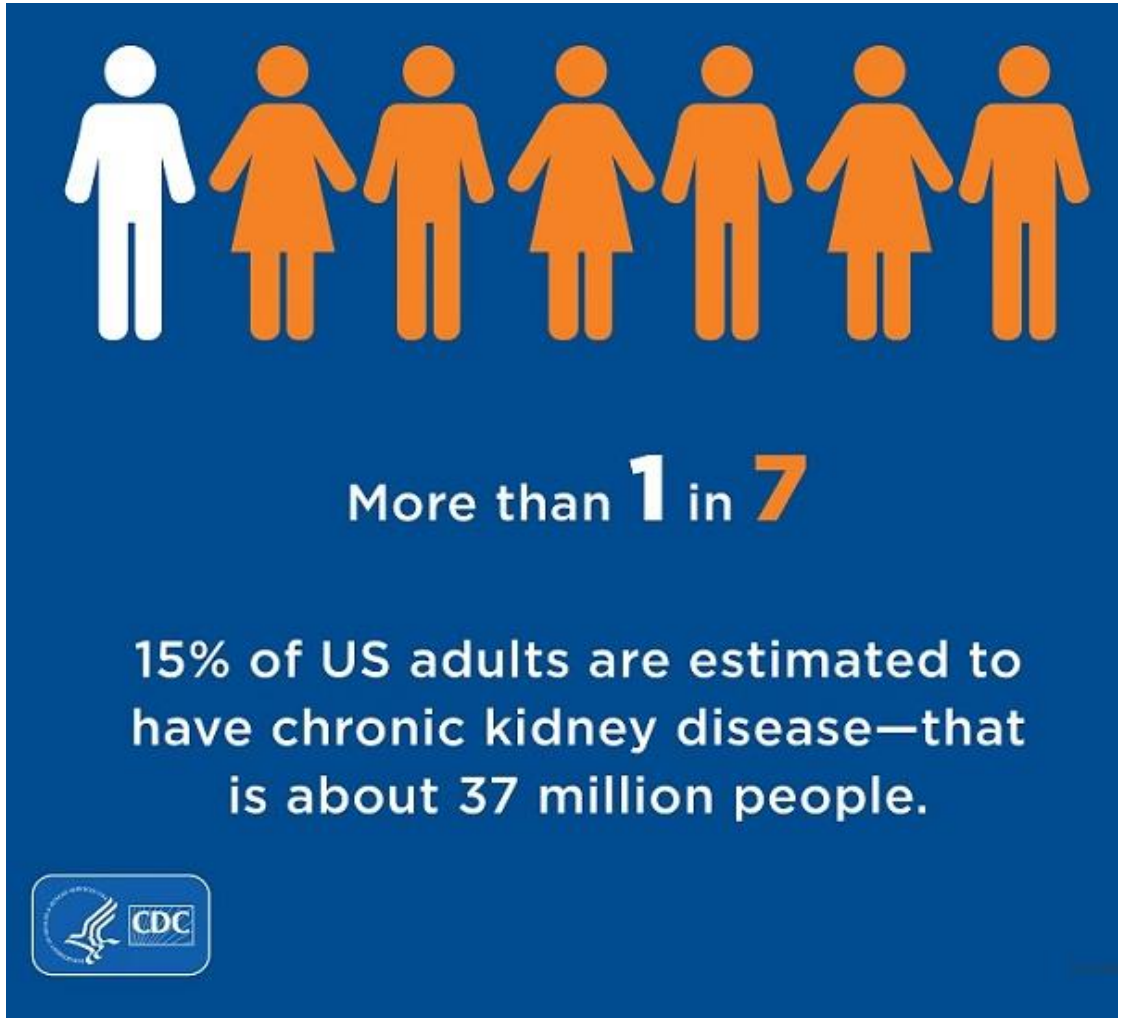
Prevalence of Chronic Kidney Disease

- More than **1 in 7, that is 15%** of US adults or 37 million people, are estimated to have CKD.*
- As many as 9 in 10 adults with CKD **do not know** they have CKD.
- About 2 in 5 adults with **severe** CKD **do not know** they have CKD.



- * These estimates were based on a single measure of albuminuria or serum creatinine; they do not account for the persistence of albuminuria or levels of creatinine that are higher than normal as indicated by the KDIQO recommendations.

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Highlights of the UAE population Statistics 2022

- UAE Population as of March 2022 is **10.08 Million**.
- The Total Expat Population of UAE in 2022 is **8.92 Million**.

- Courtesy : Prof. S. Holt , Dr. Ayman Al Madani

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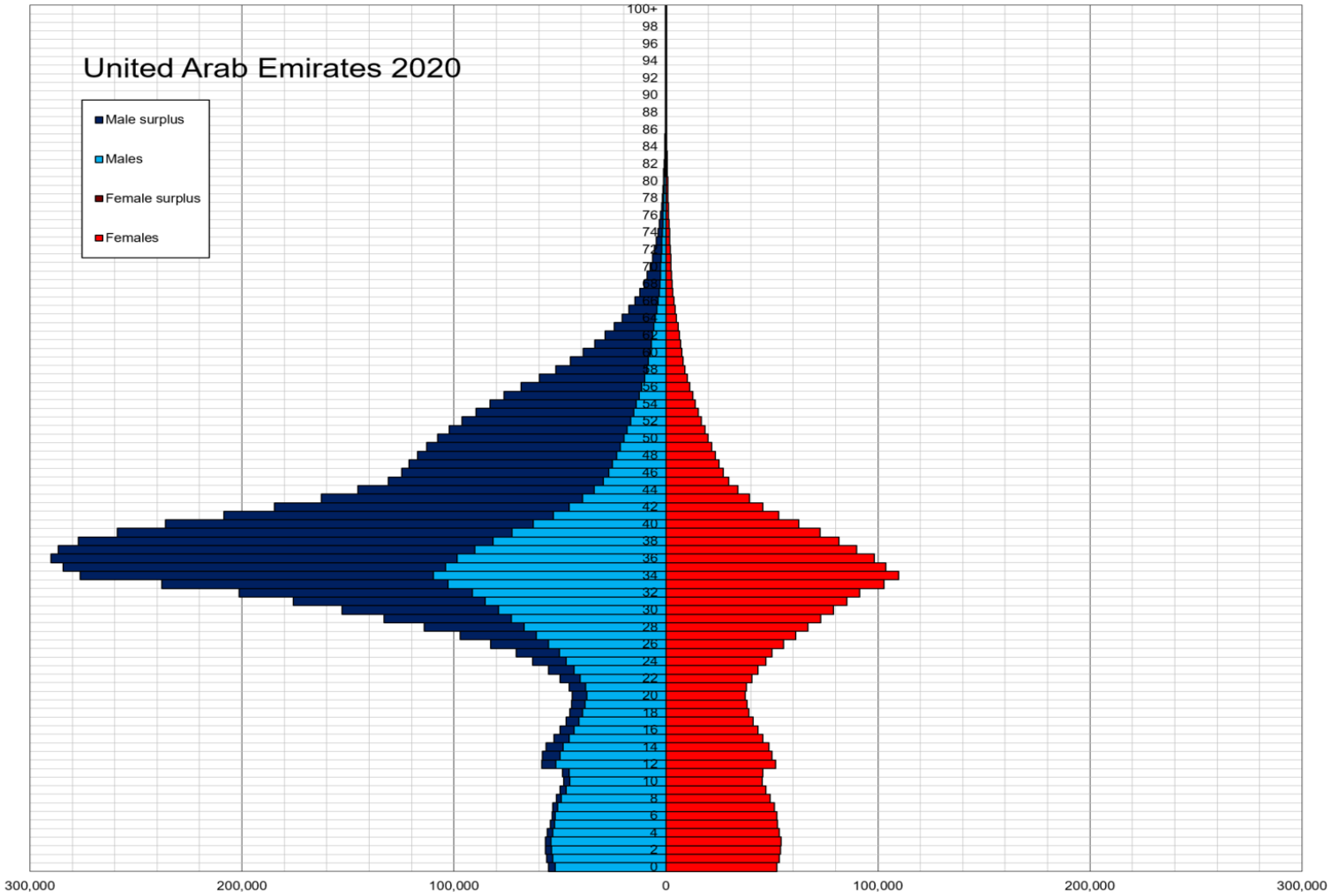
Population pyramid in UAE



Generated from US Census Bureau International Data Base using Excel 2019

- Courtesy : Prof. S. Holt , Dr. Ayman Al Madani

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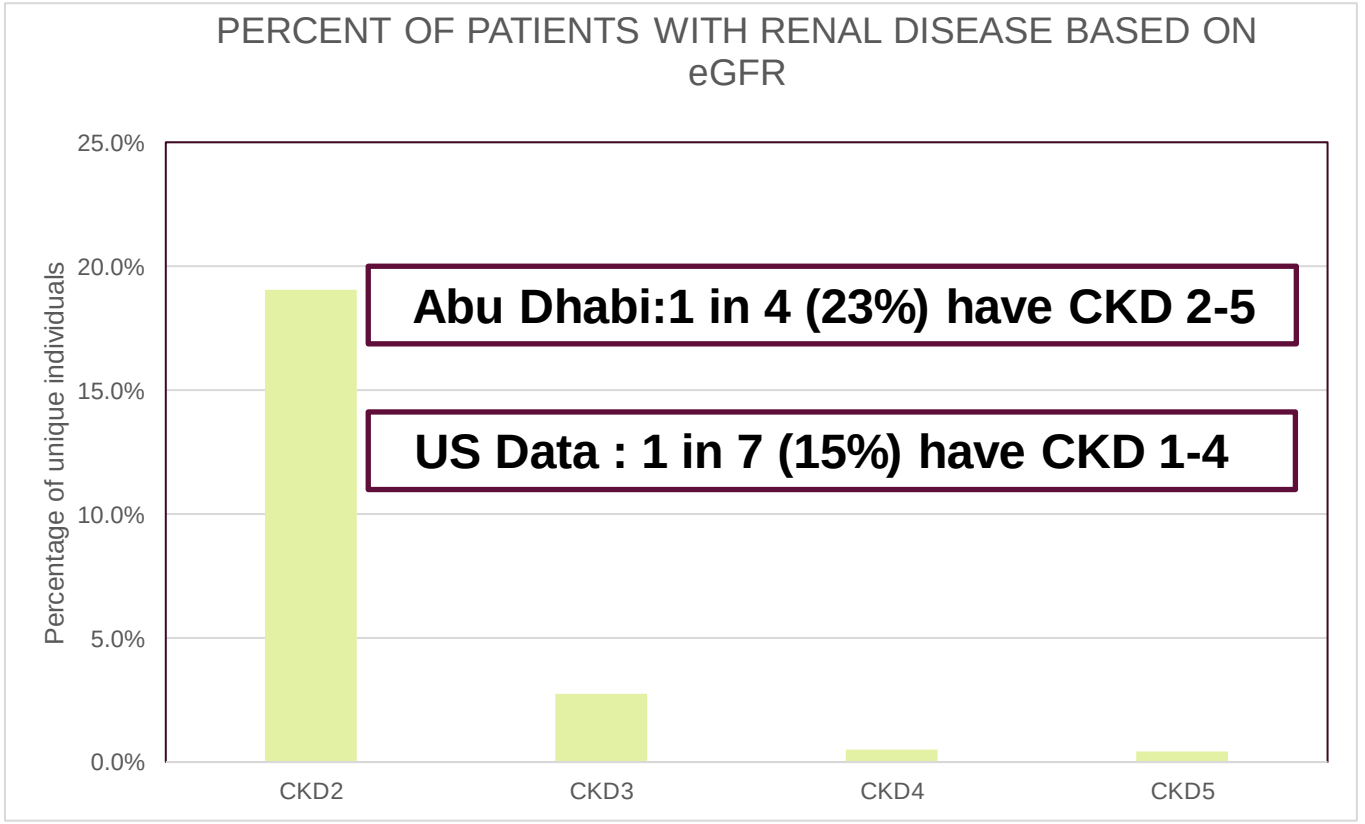
Percent of Patients with Renal Disease Based on eGFR

Total blood tests	1,467,982
Total individuals	400,710
have eGFR	400,710

Stage	Number	%	Mean Age
CKD 2	76444	19.1%	51.1
CKD 3	11072	2.8%	63.1
CKD 4	2031	0.5%	60.2
CKD 5	1709	0.4%	54.7



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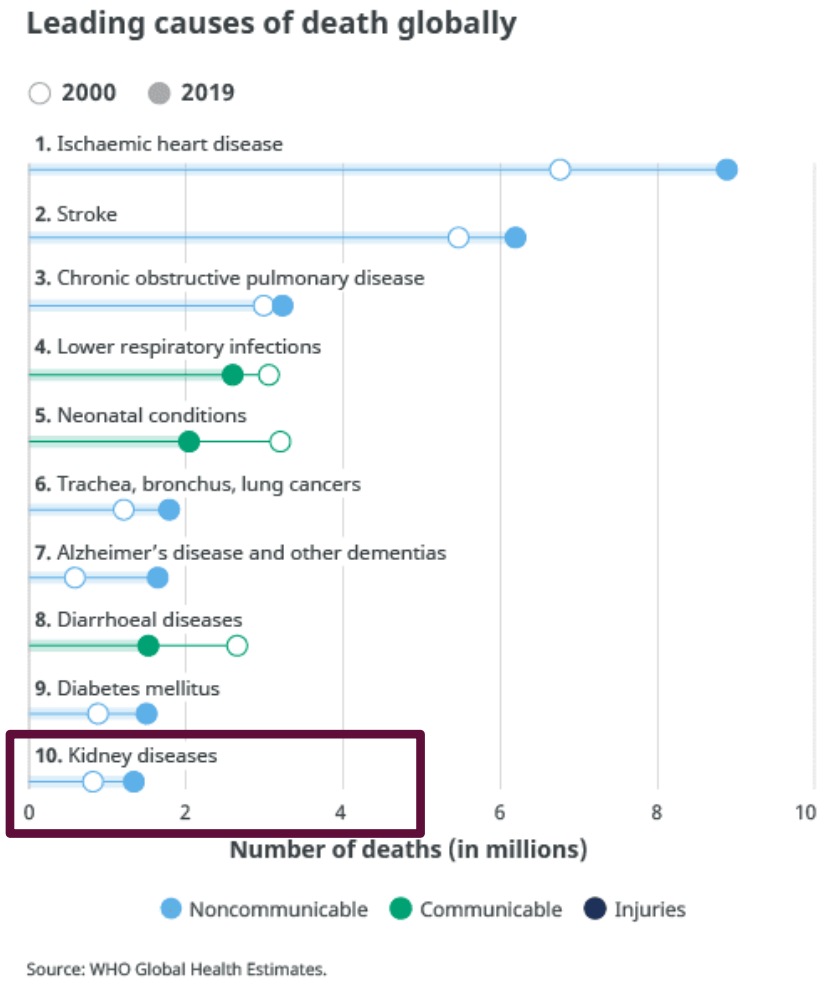
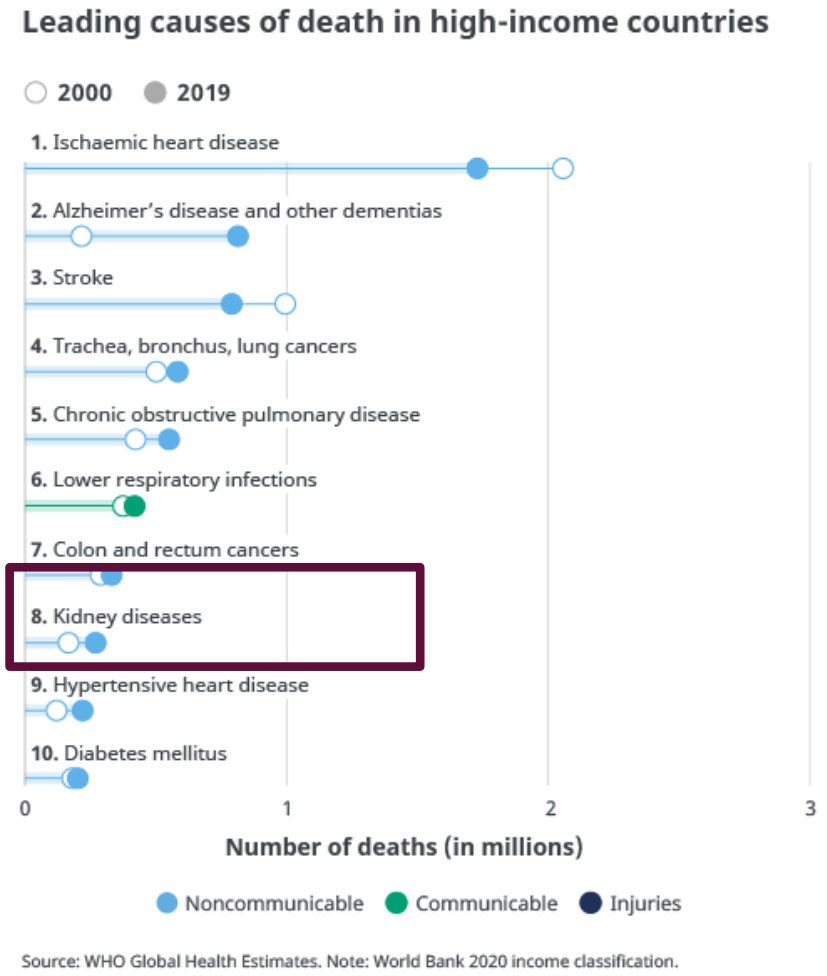
Kidney Disease is a Global Crisis





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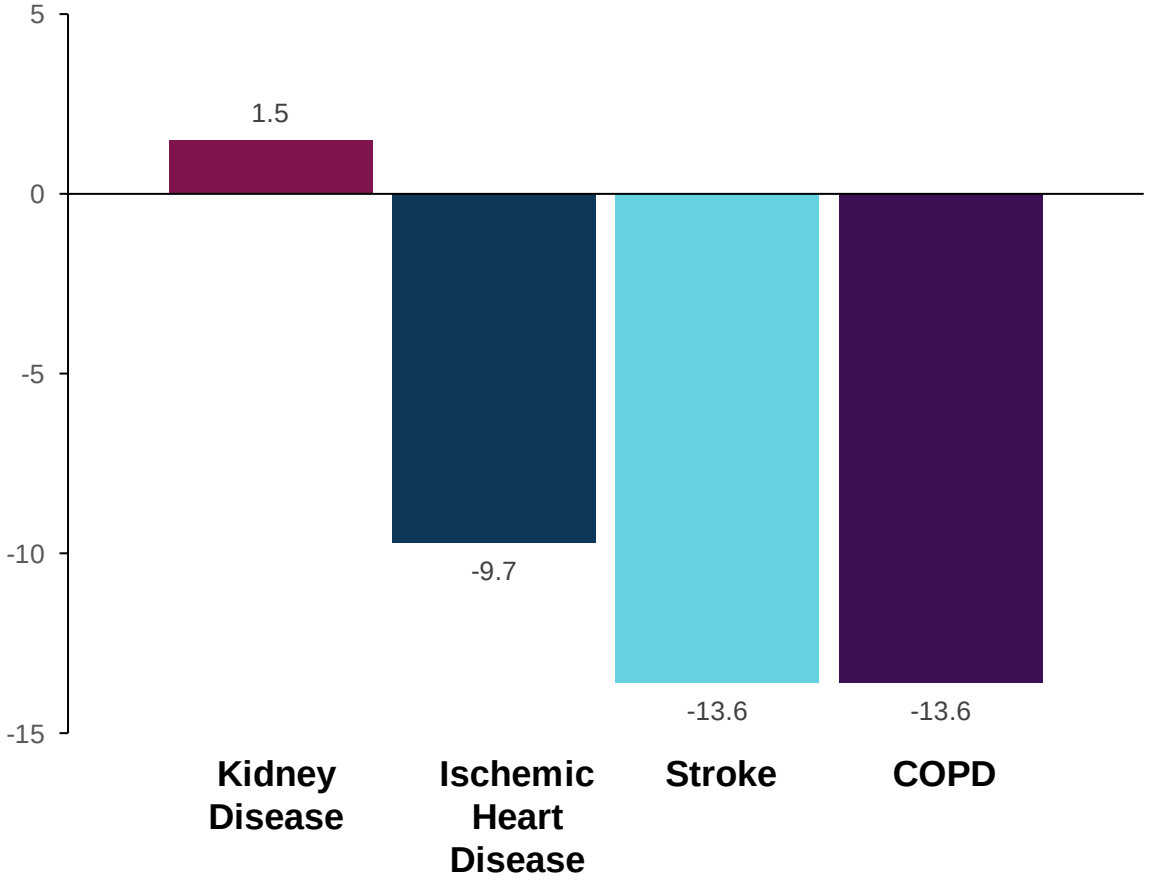
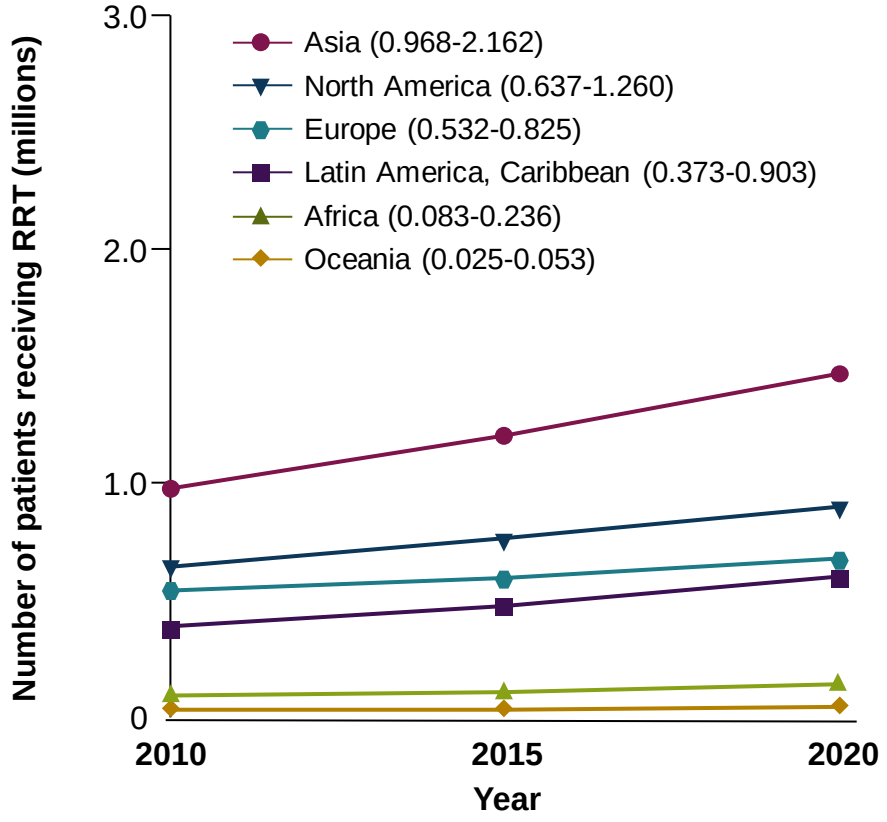
Improvement in CKD Mortality Has Been Limited, While the RRT Burden Has Continued to Rise

Global Age-standardized Mortality Rate (per 100,000) Percent Change, 2007-2017[1]



Number of Patients Receiving RRT, 2010-2020[2]



CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disorder; RRT = renal replacement therapy.

1. GBD 2017 Causes of Death Collaborators. *Lancet*. 2018;392:1736-1788; 2. Liyanage T, et al. *Lancet.* 2015;385:1975-1982.

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Costs in 2019

- Overall Medicare costs for people with **CKD** were **$87.2 billion in 2019**
  - $24,453 per Medicare beneficiary > 65 years.
- Total Medicare fee-for-service spending (including prescription drugs) for patients with **ESRD or kidney failure reached $37.3 billion.**
  - **$86,400 per person ~ AED 328,624**
  - 7% of the Medicare paid claims costs.

- CKD impacts 1 in 9 (~850 million) people globally[1]
  - **~2.6 million receiving RRT**
  - **~1.2 million deaths annually**
- The number receiving RRT is estimated to increase to more than **5 million by 2030**
- Many developed nations spend over **2-3% of their annual healthcare budget on ESKD** treatment alone

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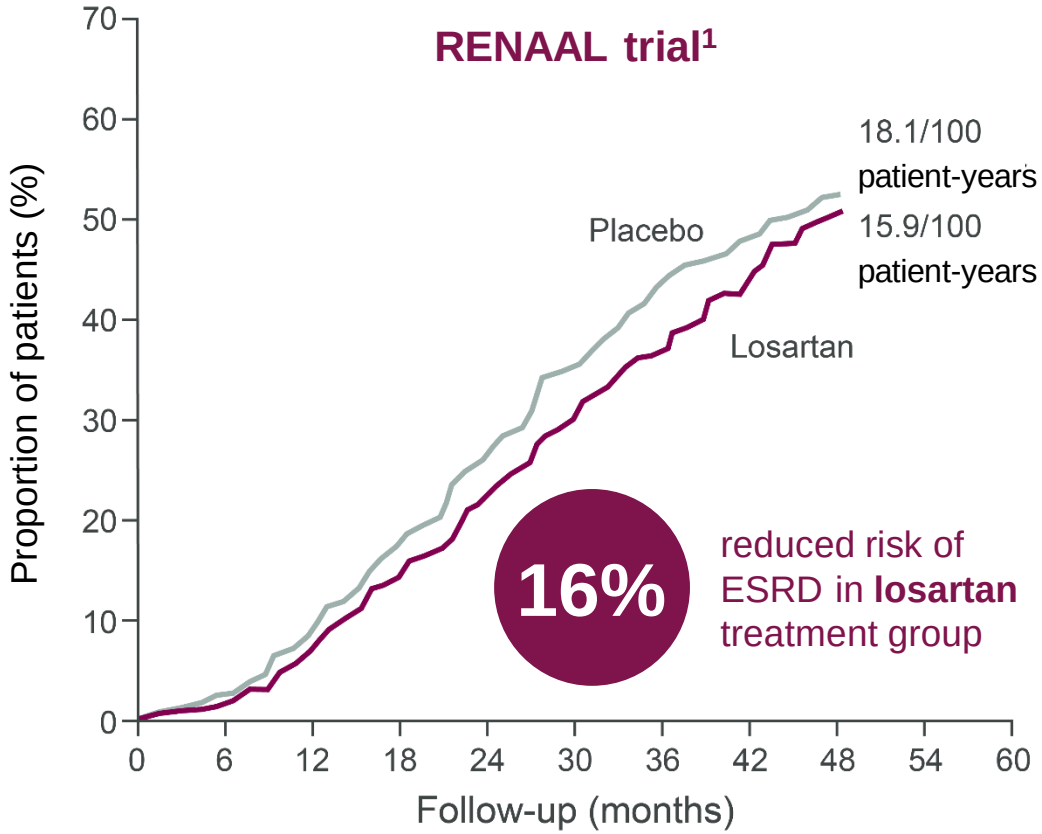
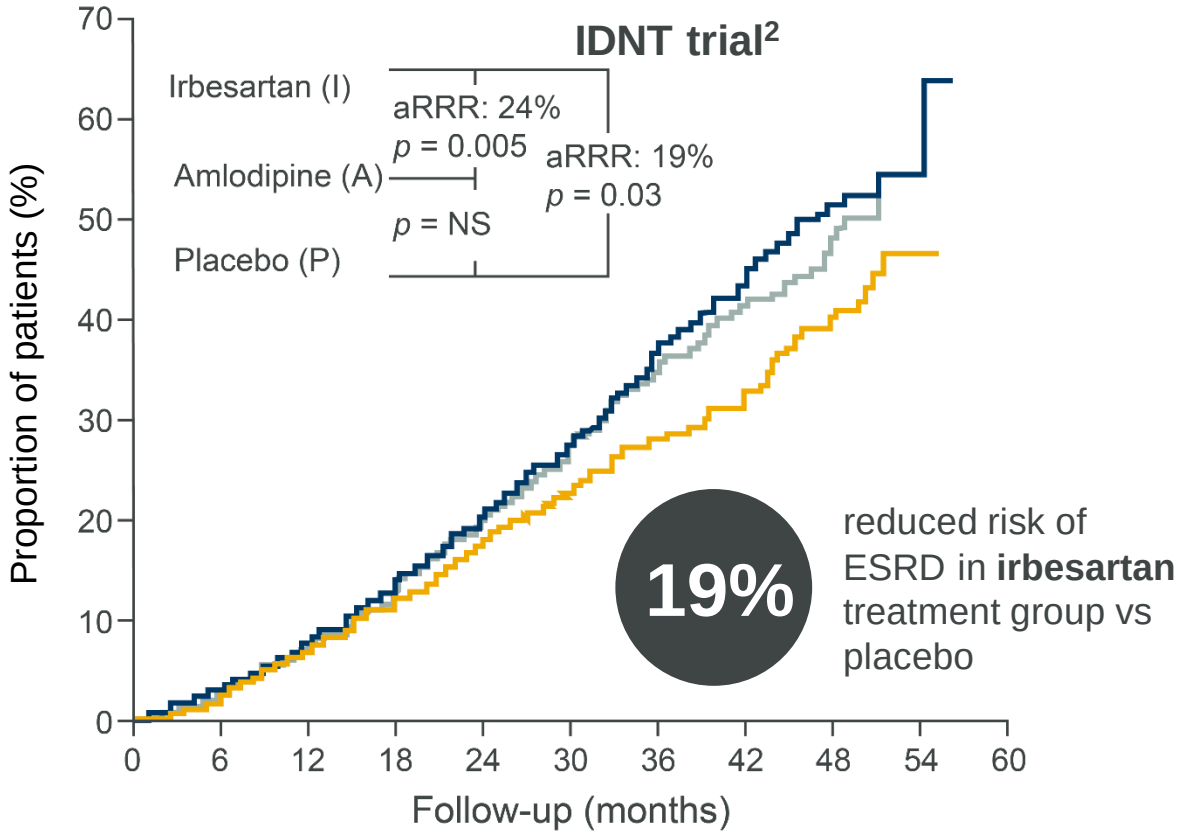
Treatment Strategies in Chronic Kidney Disease

RAASi has been the standard of care for CKD for past 20 years to delay CKD progression

Time to primary composite endpoint
(doubling of serum creatinine, ESRD or death)





aThe relative risks were adjusted for the mean arterial blood pressure during follow-up

aRRR, absolute relative risk reduction; ESRD, end-stage renal disease; IDNT, Irbesartan Diabetic Nephropathy Trial; RAASi, renin-angiotensin-aldosterone system inhibitors; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; T2D, type 2 diabetes

1. Brenner BM et al. N Engl J Med. 2001;345:861–9; 2. Lewis EJ et al. N Engl J Med. 2001;345:851–60

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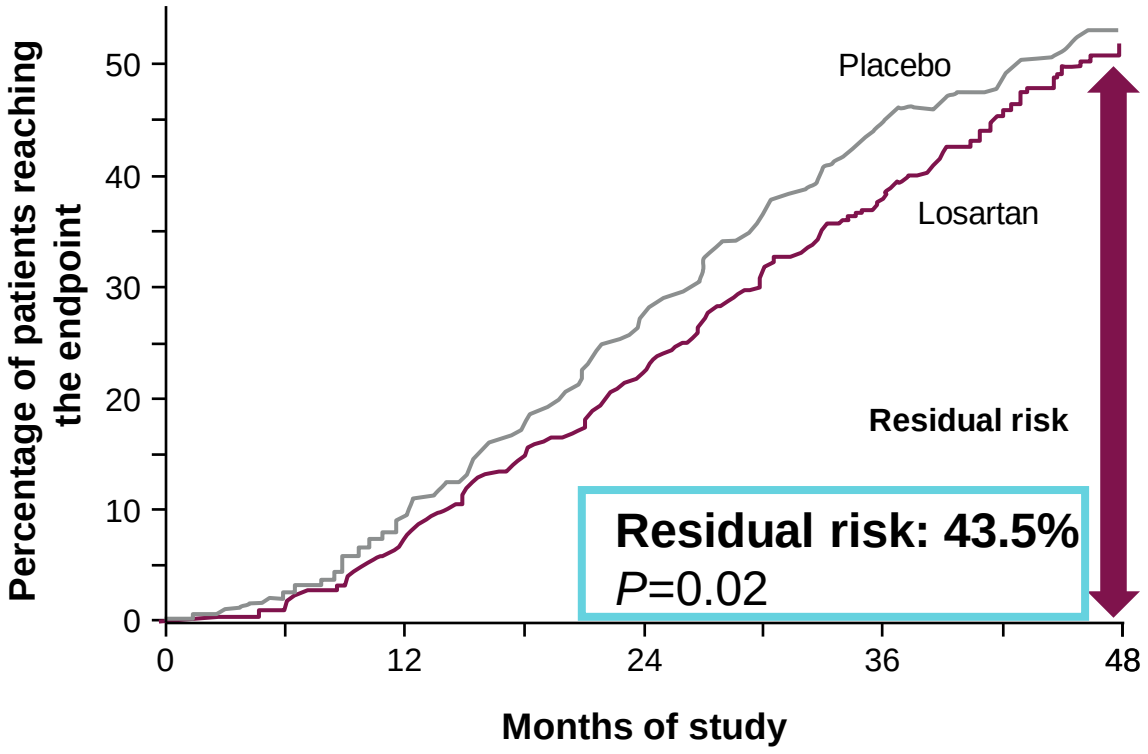
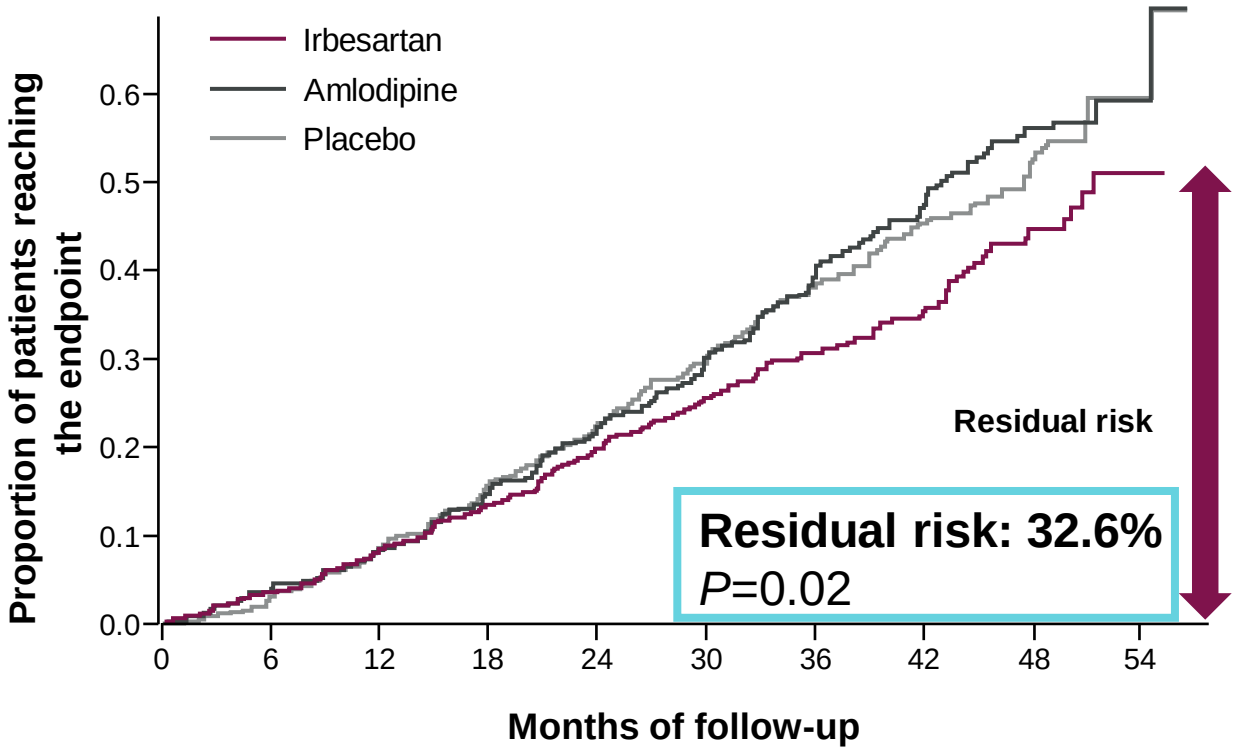
However, RAASi still possesses substantial residual risk of CKD progression

RENAAL[1]



IDNT[2]:



DKD, diabetic kidney disease; ESRD, end-stage renal disease; SoC, standard of care

1. Brenner B, et al. *N Engl J Med* 2001;345:861–869; 2. Lewis EJ, et al. *N Eng J Med* 2001;345:851–860

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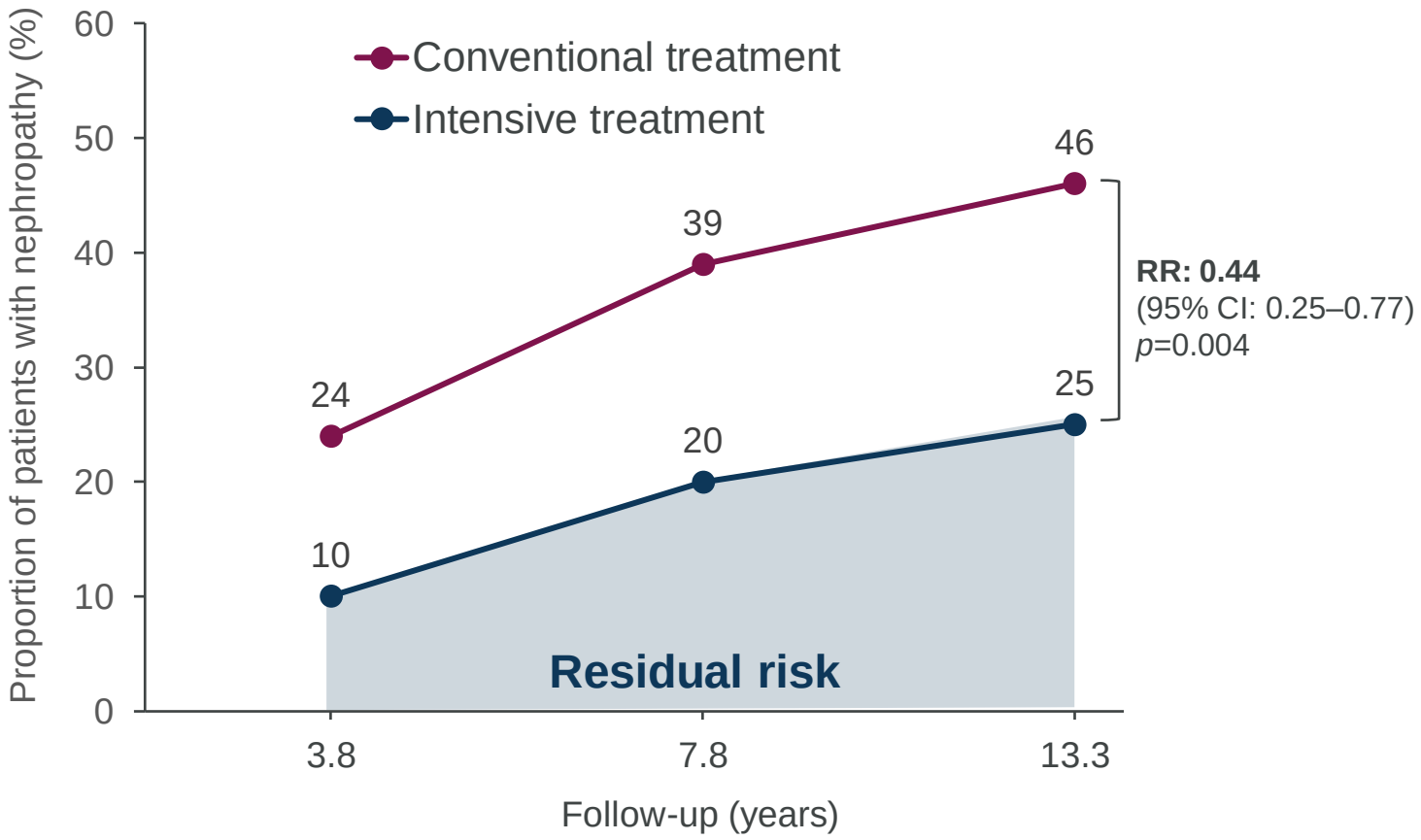
In T2DM optimal risk factor management does not eliminate risk of diabetic nephropathy[a]

Treatment goals for standard and intensive treatment groups[1]

	Conventional	Intensive
Systolic BP (mm Hg)	<160	<140[b]
Diastolic BP (mm Hg)	<95	<85
HbA1c (%)	<7.5	<6.5[c]
Triglycerides (mmol/L)	<2.2	<1.7[d]
Total cholesterol (mmol/L)	<6.5	<5.0[e]
HDL cholesterol (mmol/L)	>0.9	>1.1
ACE inhibitor irrespective of BP	No	Yes
Aspirin in patients with known ischemia	Yes	Yes
Aspirin in patients with peripheral vascular disease	No	Yes
Vitamin C and E supplement	No	Yes

Residual nephropathy risk in patients randomized to multifactorial intensive medical therapy[2]



[a]Diabetic nephropathy was defined as a urinary albumin excretion of more than 300 mg/24 hours in two of three consecutive sterile urine specimens[2]; [b]Hypertension was treated with ACE inhibitors as initial treatment with angiotensin-II receptor antagonist used if adverse events. Thiazides, calcium-channel blockers, and beta-blockers added as needed; [c]Antidiabetic therapy with metformin, gliclazide, and/or insulin; [d]Hypertriglyceridemia treatment with fibrate; [e]Dyslipidemia treatment with statin.

1. Gaede P *et al*. *Lancet.* 1999;353:617–622; 2. Fioretto P *et al*. *Nat Rev Endocrinol.* 2010;6:19–25.

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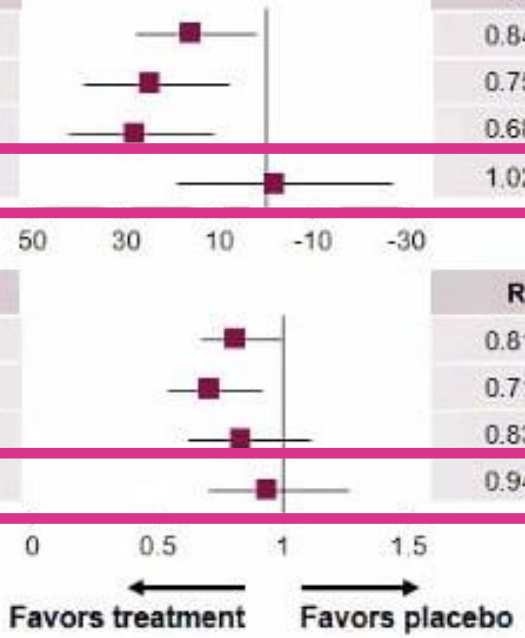
RAASi did not reduce risk of death in CKD patients

Effect of losartan and irbesartan, compared to placebo, on the risk of renal composite[1,2]

Renal outcome	Treatment group Number (%)	Treatment group Events per 100 P-Y	Placebo group Number (%)	Placebo group Events per 100 P-Y	Risk value	*P* value
RENAAL[1]					**HR (95% CI)**	
Primary composite end point	327 (43.5)	15.9	359 (47.1)	18.1	0.84 (0.72, 0.98)	0.02
dSCr	162 (21.6)	7.9	198 (26.0)	10.0	0.75 (0.61, 0.92)	0.006
ESRD	147 (19.6)	6.8	194 (25.5)	9.1	0.68 (0.58, 0.89)	0.002
All-cause mortality	158 (21.0)	6.8	155 (20.3)	6.6	1.02 (0.81, 1.27)	0.88
IDNT[2]					**RR (95% CI)**	
Primary composite end point	189 (32.6)	–	222 (39.0)	–	0.81 (0.67–0.99)	0.03
dSCr	98 (16.9)	–	135 (23.7)	–	0.71 (0.54–0.92)	0.009
ESRD	82 (14.2)	–	101 (17.8)	–	0.83 (0.62–1.11)	0.19
All-cause mortality	87 (15.0)	–	93 (16.3)	–	0.94 (0.70–1.27)	0.69



1. Brenner BM, et al. N Emgl J Med 2001; 345:861-869; 2 2. Lewis EJ et al. *N Engl J Med* 2001; 345:851-860
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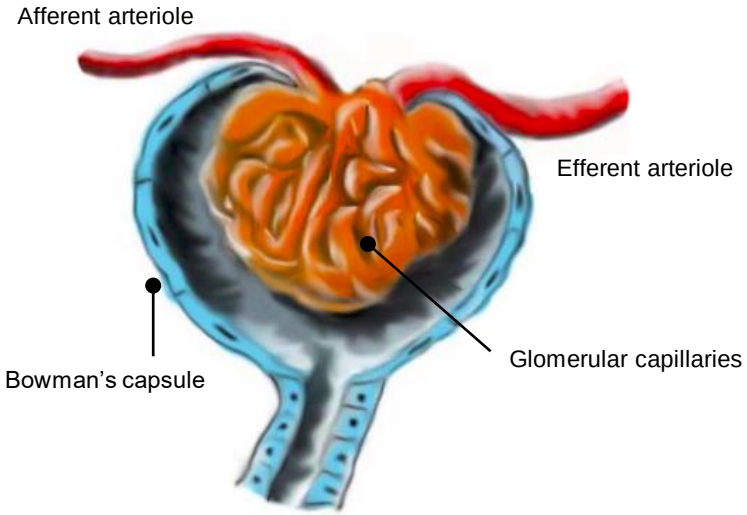
SGLT2i – Explaining its Role in Prevention and Progression of Chronic Kidney Disease

SGLT2 inhibition and RAAS blockade both reduce glomerular pressure and hyperfiltration by complementary mechanisms[1–3]

SGLT2 inhibitors

Afferent constriction[1–3]

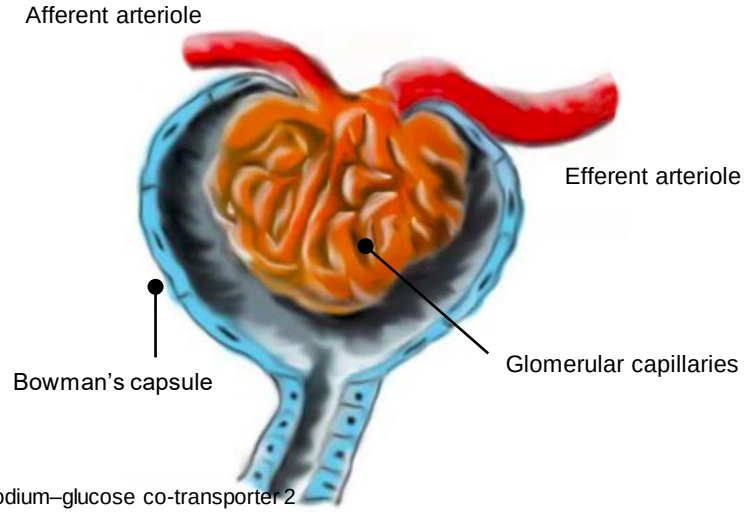
Due to increased Na^+ delivery to the macula densa[1-3]



- **Decreased glomerular pressure[1,3]**
- **Reduction in albuminuria[1,2]**

RAAS blockade

Efferent vasodilation[1]



- **Decreased glomerular pressure[1,3]**
- **Reduction in albuminuria[4]**

- RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2

- 1. Van Bommel EJ, et al. *Clin J Am Soc Nephrol* 2017;12:700–710; 2. Seidu S, et al. *Prim Care Diabetes* 2018;12:265–283; 3. Cherney DZ, et al. *Circulation* 2014;129:587–597; 4. Heerspink HJL, et al. *Diabetes Care* 2011;34(Suppl. 2):S325–S329

forxiga®

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DAPA-CKD was a landmark trial assessing forxiga in over 4,000 patients with CKD, with and without T2D [1,2]

Objective

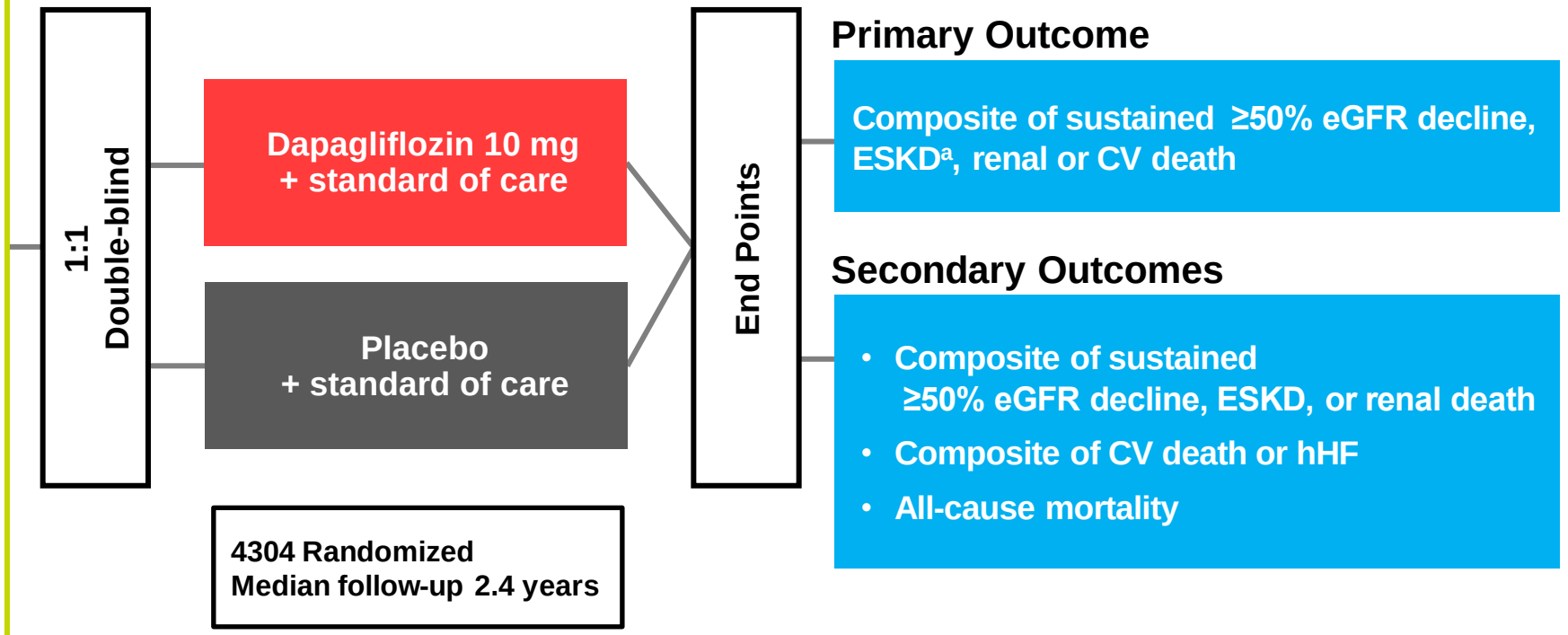
To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a maximum tolerated dose of an ACEi or ARB

Key Inclusion Criteria

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m^2
- UACR ≥200 to ≤5000 mg/g
- Stable max tolerated dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria

- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment



- [a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for more than 28 days, renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days.
- ACEi = angiotensin-converting enzyme inhibitor; ANCA = anti-neutrophil cytoplasmic antibody; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; T1D = type 1 diabetes; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.
- 1. Heerspink HJL, et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL, et al. *N Engl J Med*. 2020; 383:1436-1446.

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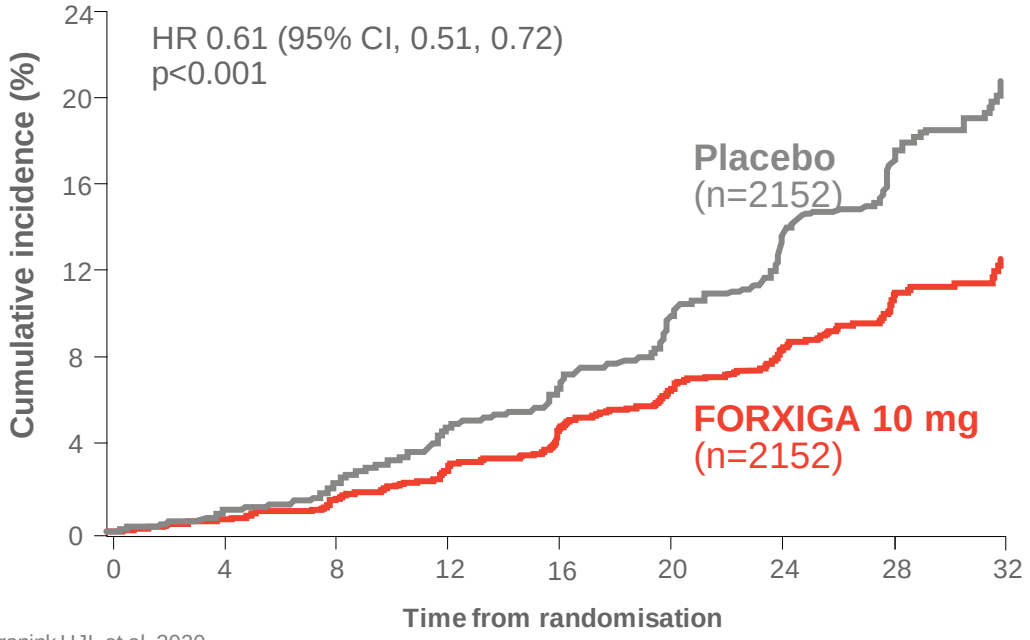
Treatment with forxiga has shown to reduce the risk of the composite of declining kidney function, ESKD, and renal or CV death[1,2]

DAPA-CKD PRIMARY COMPOSITE ENDPOINT: DECLINING KIDNEY FUNCTION, ESKD, AND RENAL OR CV DEATH[1*]



Median follow-up of 2.4 years

Adapted from Heerspink HJL et al. 2020.

39% RRR

5.3% ARR

NNT=19 PATIENTS

Consistent efficacy in patients with or without T2D[2†]

*Primary composite endpoint of ≥50% sustained decline in eGFR, reaching ESKD, and renal or CV death[1]. ESKD defined as the need for maintenance dialysis (peritoneal or haemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15 mL/min/1.73m^2 for at least 28 days[1]; †There was no significant interaction of the effect on the primary composite endpoint by diabetes status (p for interaction = 0.24).[2]

ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; DAPA-CKD = Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction; T2D = Type 2 diabetes.

Reference: 1.Heerspink HJL et al. N Engl J Med. 2020;383(15):1436–1446.2. Wheeler DC et al. Lancet Diabetes Endocrinol. 2021;9(1):22–31

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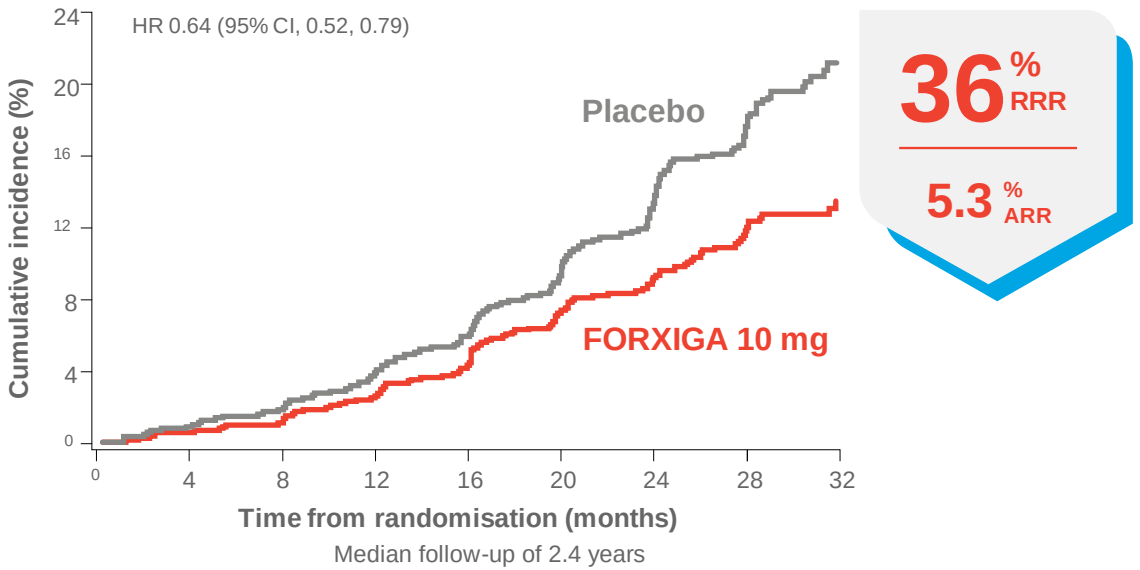
Offered consistent protection by reducing the risk of the primary composite endpoint in patients with or without T2D[1]*

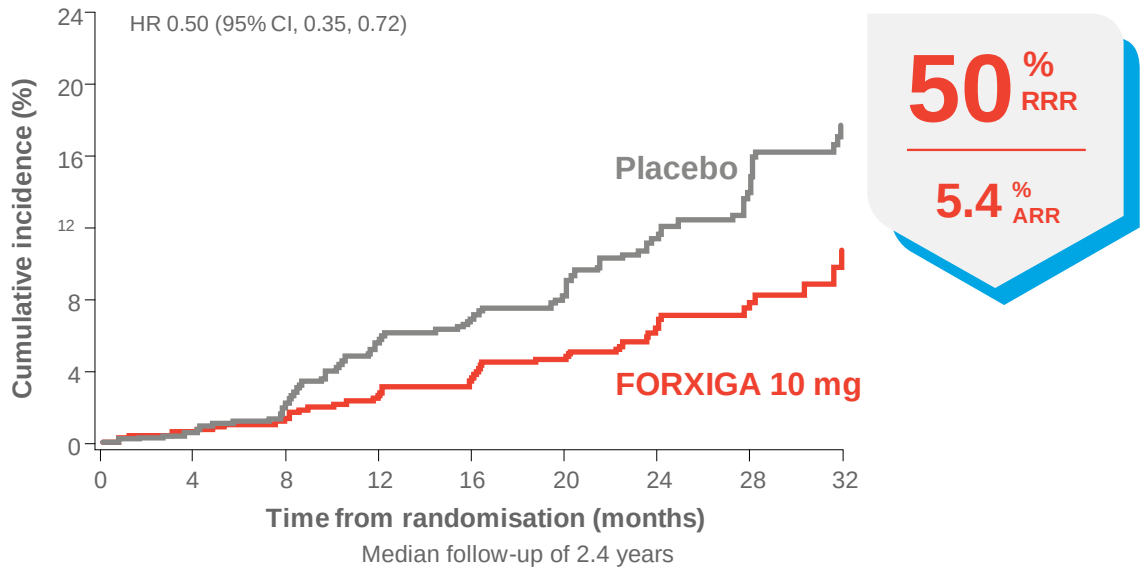
DAPA-CKD EXPLORATORY SUBGROUP ANALYSIS: DECLINING KIDNEY FUNCTION, ESKD, AND RENAL OR CV DEATH[2]*

Patients with T2D[1]



Number at risk									
FORXIGA	1455	1383	1349	1307	1262	1155	910	580	215
Placebo	1451	1360	1321	1275	1224	1130	868	545	190

Patients without T2D[1]



Number at risk									
FORXIGA	697	618	606	591	579	546	378	251	94
Placebo	701	633	615	583	567	534	364	229	80

*Primary composite endpoint of ≥50% sustained decline in eGFR, reaching ESKD, and renal or CV death. ESKD defined as the need for maintenance dialysis (peritoneal or haemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15 mL/min/1.73m2 for at least 28 days.[1]

ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; DAPA-CKD = Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease; HR = hazard ratio; RRR = relative risk reduction; T2D = Type 2 diabetes.

Reference: 1. Wheeler DC et al. Lancet Diabetes Endocrinol. 2021;9(1):22–31. 2.Heerspink HJL et al. N Engl J Med. 2020;383(15):1436–1446.

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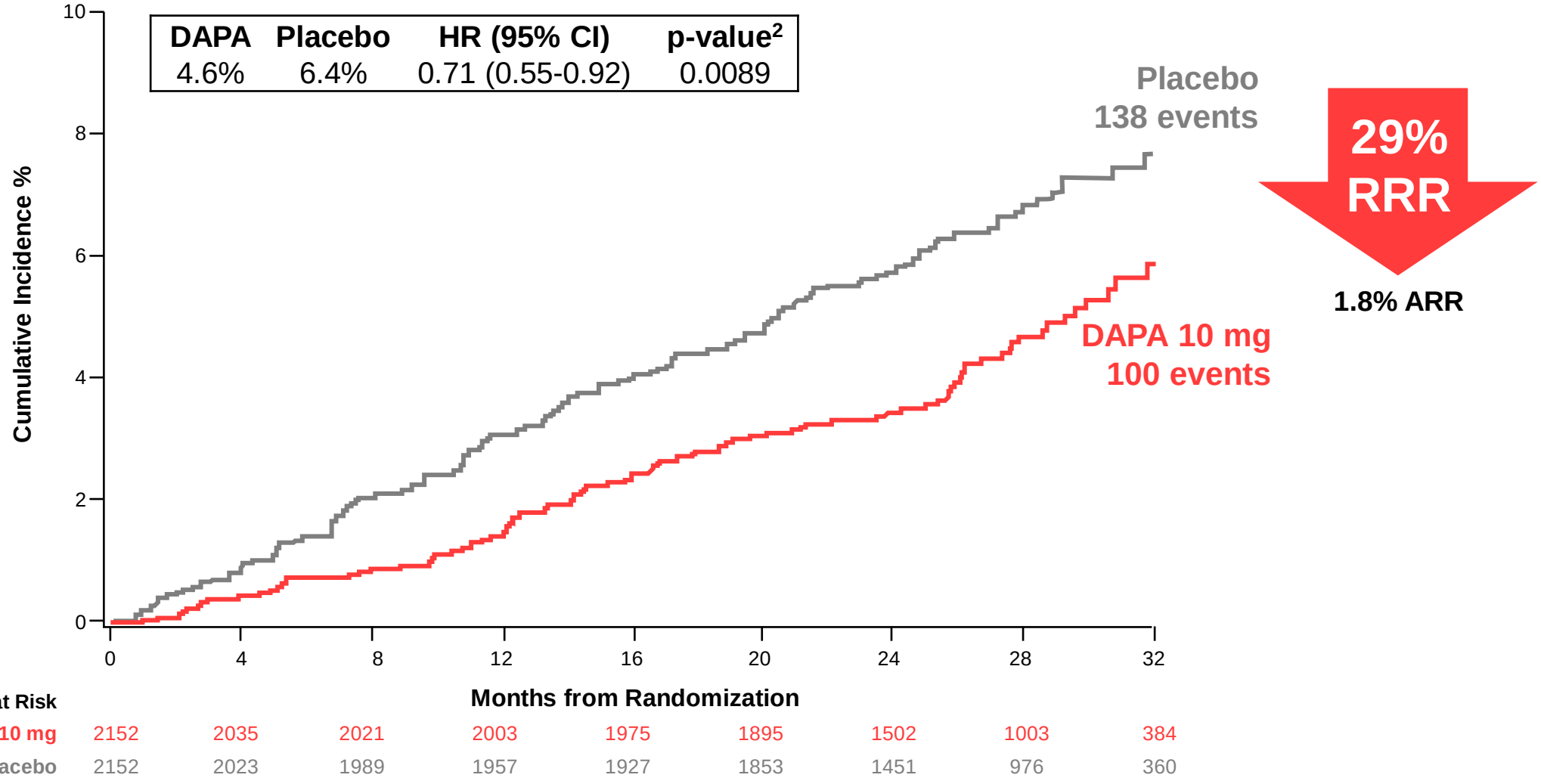
The significant effect on the composite endpoint of CV death or hospitalization for heart failure was consistent with previous Forxiga trials[1]



- ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.
- 1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

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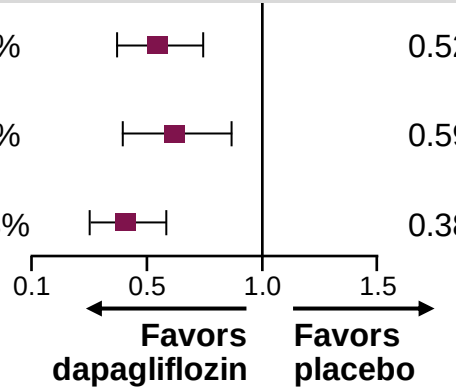
forxiga decreased the risk of progression to the renal composite endpoint[a] across the spectrum of renal function

	Dapagliflozin		Placebo		Hazard ratio (95% CI)	*P* value
	n/N (%)	KM event rate (4 years)	n/N (%)	KM event rate (4 years)		
Baseline eGFR						
≥90 mL/min/1.73 m^2	41/4137 (1.0)	1.0%	79/4025 (2.0)	2.0%	0.50 (0.34, 0.73)	0.87
60–<90 mL/min/1.73 m^2	65/3838 (1.7)	1.6%	121/3894 (3.1)	2.8%	0.54 (0.40, 0.73)	
<60 mL/min/1.73 m^2	21/606 (3.5)	3.8%	38/659 (5.8)	5.8%	0.60 (0.35, 1.02)	
Baseline UACR						
<30 mg/g	50/5819 (0.9)	0.9%	95/5825 (1.6)	1.5%	0.52 (0.37, 0.74)	0.30
30–300 mg/g	39/2017 (1.9)	2.0%	66/2013 (3.3)	3.3%	0.59 (0.39, 0.87)	
>300 mg/g	31/594 (5.2)	4.8%	75/575 (13.0)	12.8%	0.38 (0.25, 0.58)	



- [a]This was a prespecified exploratory endpoint, defined as sustained eGFR decrease ≥40% to <60 mL/min/1.73 m^2, ESRD, or renal death. Due to the trial meeting only one of its primary efficacy endpoints for superiority (CV death or hHF), all other analyses of additional outcomes should be considered hypothesis-generating only
- CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; hHF, hospitalization for heart failure; KM, Kaplan–Meier; UACR, urine albumin:creatinine ratio
- Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617

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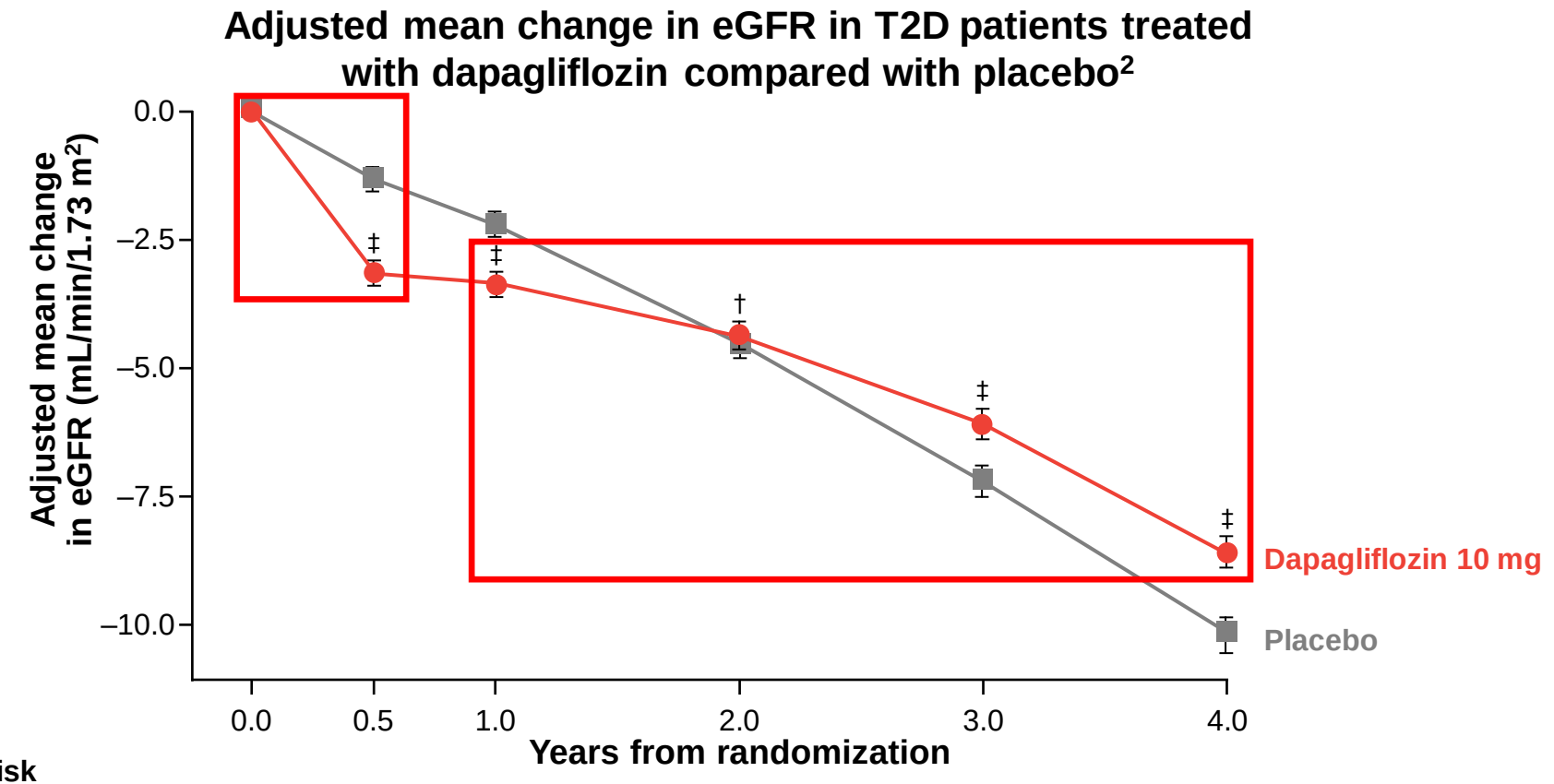
The effects of SGLT2 inhibition on glomerular pressure drive an initial decline in eGFR, which subsequently stabilizes

The initial reduction in eGFR induced by SGLT2 inhibitors is intrinsic to the SGLT2 inhibitor mechanism of action[1]



No. at risk						
Dapagliflozin 10 mg	8581	8273	7978	7513	7098	6050
Placebo	8578	8223	7884	7316	6800	5770

†*P*<0.079; ‡*P*<0.0001, eGFR, estimated glomerular filtration rate; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes 1. Konishi H, et al. *J Endocrinol Metab* 2018;8:106–112; 2. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617

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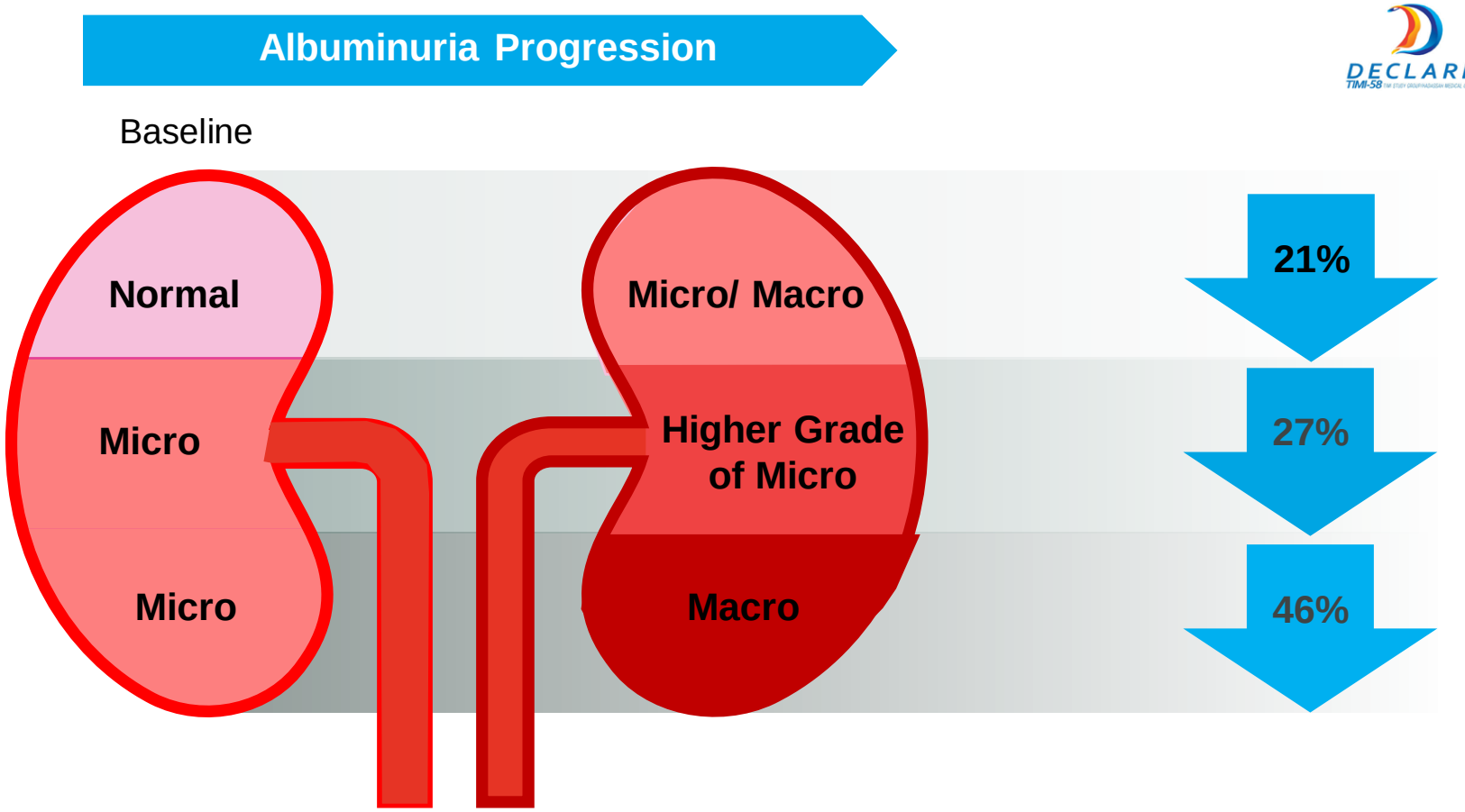
forxiga consistently reduced the risk of microalbuminuria progression in T2D Patients



References:. 1. Wiviott SD et al. *N Engl J Med.* 2019;380(4):347-357; 2. Raz I et al. *Diabetes Obes Metab.* 2018;20(5):1102-1110; 3. Mosenzon O, et al. *Lancet Diabetes Endocrinol.* 2019;7(8):606-617; 4. Zelniker TA et al. Article and supplementary appendix. *JAMA Cardiol.* 2021;6(7):801-810.

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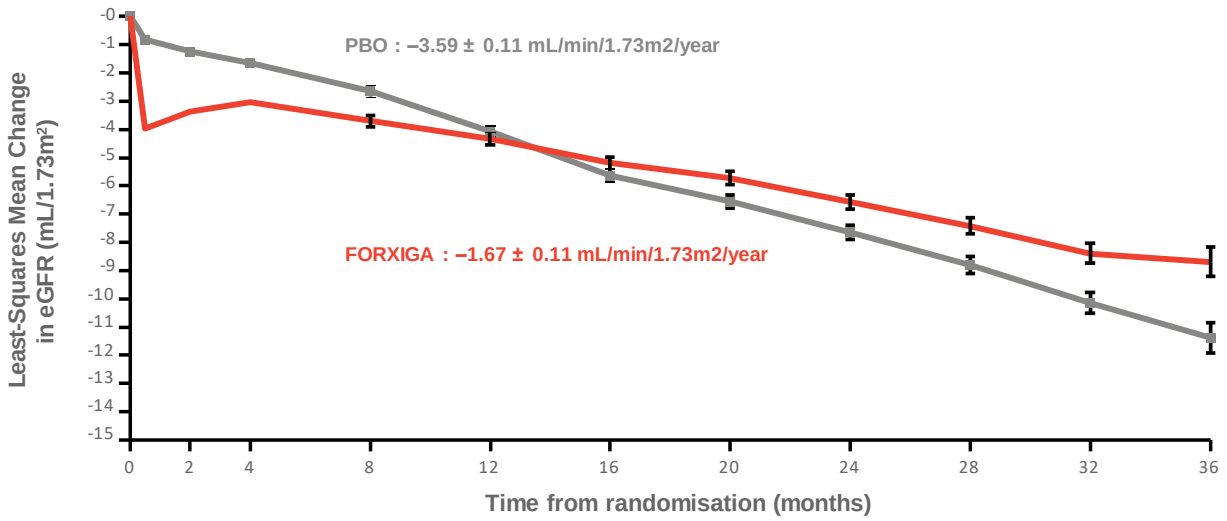
forxiga gives your patient the chance for Dialysis Free Years![1-3]

forxiga Delays Dialysis[2*] by **6.6 Years**



*Delaying mean time to end stage renal disease[2]

eGFR, estimated glomerular filtration rate; PBO, placebo.

1. Wheeler DC et al. Lancet Diabetes Endocrinol. 2021;9(1):22–31. 2. Jongs N et al. Presented at: ERA-EDTA Congress; June 5-8, 2021 3. N Engl J Med. 2020 Oct 8;383(15):1436-1446. 2. Diabetes Ther. 2021 Feb;12(2):499-508. 3.

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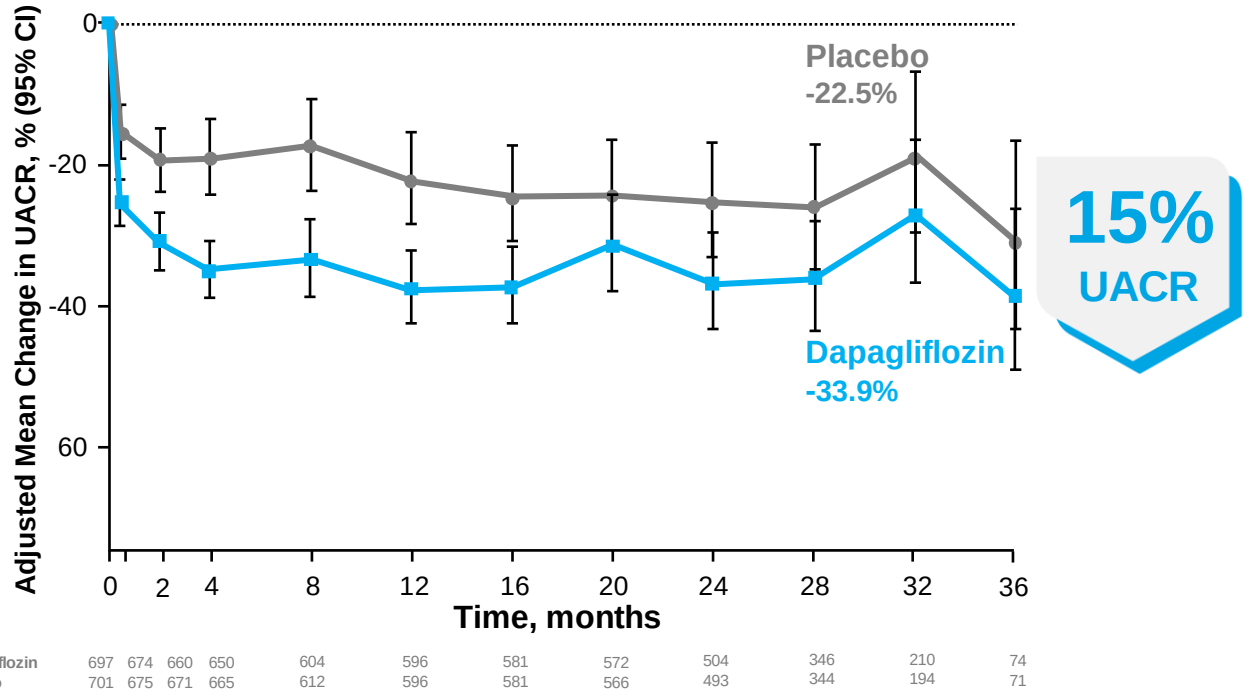
forxiga reduces UACR, an independent risk factor for CV death[1]

Patients without T2D
-14.8% mean reduction in UACR (dapagliflozin vs. placebo)
(95% CI 5.9, 22.9; p=0.001)



CI = confidence interval; IQR = interquartile range; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio
Jongs N et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

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forxiga showed consistent safety profile in CKD patients with or without T2D[1,2]

Prespecified selected safety outcomes by diabetes status[2]

	Patients with T2D		Patients without T2D	
Select AEs	**FORXIGA 10 mg** (n=1453)	**Placebo** (n=1450)	**FORXIGA 10 mg** (n=696)	**Placebo** (n=699)
Diabetic ketoacidosis	0	2	-	-
Major hypoglycaemia*	14	28	-	-
Volume depletion	92	71	35	19
Amputation	35	38	0	1
Fracture	65	51	20	18
Renal AE (e.g acute kidney injury)	121	148	34	40

- In patients with or without T2D, incidence of hyperkalaemia was 0.3% in patients on FORXIGA vs 0.6% in patients receiving placebo[3]
- In DAPA-CKD, rates of overall SAEs were lower with FORXIGA vs. placebo (633/2149 [30%] vs. 729/2149[34%], p=0.002)[1]

No occurrences of severe hypoglycaemic events, or diabetic ketoacidosis, or DKA were observed in patients without T2D in DAPA-CKD.[2]

*All cases of diabetic ketoacidosis occurred in patients with diabetes at baseline[2]; **Adverse event with the following criteria, confirmed by the investigator: symptoms of severe impairment in consciousness or behaviour, need for external assistance, use of an intervention to treat hypoglycaemia, and prompt recovery of acute symptoms following the intervention[2].

AE=adverse event; CKD=chronic kidney disease; DAPA-CKD=Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease; DKA=diabetic ketoacidosis; SAE=serious adverse event; T2D=Type 2 diabetes.

References: 1.Heerspink HJL et al. N Engl J Med. 2020;383(15):1436–1446.2. Wheeler DC et al. Lancet Diabetes Endocrinol. 2021;9(1):22–31 3.Supplement to: Heerspink HJL et al. N Engl J Med. 2020;383(15):1436–1446.

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forxiga has demonstrated a consistent safety profile in >32,000 patients across DECLARE-TIMI 58, DAPA-HF, DAPA-CKD, and DELIVER[1–4]

Prespecified selected safety outcomes across dapagliflozin clinical trials

Select AEs	DECLARE-TIMI 58 (CVOT in T2D)[1]		DAPA-HF (HFrEF)[2]		DAPA-CKD[3]		DELIVER[4]	
	Dapagliflozin 10mg (n=8574)	Placebo (n=8569)	Dapagliflozin 10mg (n=2368)	Placebo (n=2368)	Dapagliflozin 10 mg (n=2149)	Placebo (n=2149)	Dapagliflozin 10mg (N=3131)	Placebo (n=3127)
Diabetic ketoacidosis	0.3%	0.1%	0.1%	0.0%	0.0%	<0.1%	0.1%	0.0%
Severe hypoglycemia[a]	0.7%	1.0%	0.2%	0.2%	0.7%	1.3%	0.2%	0.2%
Volume depletion	2.5%	2.4%	7.5%	6.8%	5.9%	4.2%	1.3%	1.0%
Amputation	1.4%	1.3%	0.5%	0.5%	1.6%	1.8%	0.6%	0.8%
Fracture	5.3%	5.1%	2.1%	2.1%	4.0%	3.2%	TBD	TBD
Hyperkalemia	No hyperkalemia (not listed in SmPC)				No increase in either mild or moderate/severe hypokalemia observed		TBD	TBD
Renal AE	1.5%[b]	2.0%[b]	6.5%	7.2%	7.2%	8.7%	2.3%	2.5%
Serious UTI	0.9%	1.3%	0.5%	0.7%	0.9%	0.7%	TBD	TBD

It is estimated that >23 million patients were treated with FORXIGA and XIGDUO across indications throughout 2023[6]

[a]Severe hypoglycemia was defined in DAPA-CKD and DELIVER as hypoglycemia with the following criteria, confirmed by the investigator: symptoms of severe impairment in consciousness or behavior, need for external assistance, use of an intervention to treat hypoglycemia, and prompt recovery of acute symptoms following the intervention.[2,4,5] Severe hypoglycemia was defined in DECLARE and DAPA-HF as hypoglycemia requiring the assistance of another person to actively administer carbohydrates or glucagon or to take other corrective action.[1,2] All cases of major hypoglycemia in DAPA-CKD and DAPA-HF occurred in patients with diabetes at baseline[2,3]; [b]Acute kidney injury[1]
AE, adverse event; CVOT, cardiovascular outcomes trial; HFrEF, heart failure with reduced ejection fraction; SmPC, Summary of Product Characteristics; T2D, Type 2 diabetes; TBD, to be determined; UTI, urinary tract infection

1. Wiviott SD, et al. *N Engl J Med* 2019;380:347–357; 2. McMurray J, et al. *N Engl J Med* 2019;381:1995–2008; 3. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446; 4. Solomon S, et al. *N Engl J Med* 2022;387:1089–1098; 5. AstraZeneca UK Limited. FORXIGA Summary of Product Characteristics [YEAR]. Available at: [Placeholder for link subject to final approval by the European Medical Agency]; 6. AstraZeneca Pharmaceuticals LP. Data on File

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FORXIGA is the ONLY SGLT2i to demonstrate a significant reduction in all-cause mortality & CV death/hHF in CKD Patients with or without T2D

	DAPA-CKD[1,a] (N=4304)	EMPA-KIDNEY[2,b] (N=6609)
Primary endpoints		
DAPA-CKD: Composite of **≥50%** sustained eGFR decline, ESKD (dialysis/transplantation/ sustained eGFR decline to **<15 mL/min/ 1.73 m²**), or renal or CV death	✓ 39% RRR NNT=19	
EMPA-KIDNEY: Composite of **≥40%** sustained eGFR decline, ESKD (dialysis/transplantation/ sustained eGFR decline to **<10 mL/min/ 1.73 m²**), or renal or CV death		✓ 28% RRR NNT=27
Key secondary endpoints		
All-cause mortality	✓ 31% RRR	NS 13% RRR
Composite of CV death or hHF	✓ 29% RRR	NS 16% RRR

- **Study results not to be directly compared due to differences in design, patient populations, and treatment groups**
- Note: green check indicates the endpoint met statistical significance

- [a]Median follow-up of 2.4 years; [b]Median follow-up of 2.0 years
- CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; hHF, hospitalization for heart failure; NNT, number needed to treat;
  NS, non-significant; RRR, relative risk reduction; SGLT2, sodium–glucose co-transporter 2
- 1. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446; 2. The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117–127

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2023 KDIGO CKD Guideline: SGLT2 Inhibitors in CKD

Preview Presented at 2023 ERA Congress[1,a]

- **Recommendation 3.6.1:**
- **We recommend treating adults with CKD and Heart failure or eGFR ≥20 mL/min/1.73 m^2 with UACR ≥200 mg/g with an SGLT2 inhibitor (1A)**
- **Recommendation 3.6.2:**
- **We suggest treating adults with eGFR ≥20-45 mL/min/1.73 m^2 with UACR <200 mg/g with an SGLT2 inhibitor (2B)**

- [a]Presentation includes draft guideline statements that are subject to change. Note: Level 1 = "We recommend" and Grade A = High quality of evidence; Level 2 = "We suggest" and Grade B = Moderate quality of evidence.[2.] CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ERA = European Renal Association; KDIGO = Kidney Disease: Improving Global Outcomes;
SGLT2 = sodium-glucose cotransporter 2; UACR = urine albumin-to-creatinine ratio.. 1. Madero M. Presented at: 60th ERA Congress; June 15-18, 2023; Milan, Italy and Virtual. https://kdigo.org/conferences/era-2023-ckd-guideline-draft-preview; 2. KDIGO. KDIGO methods manual for guideline development. As

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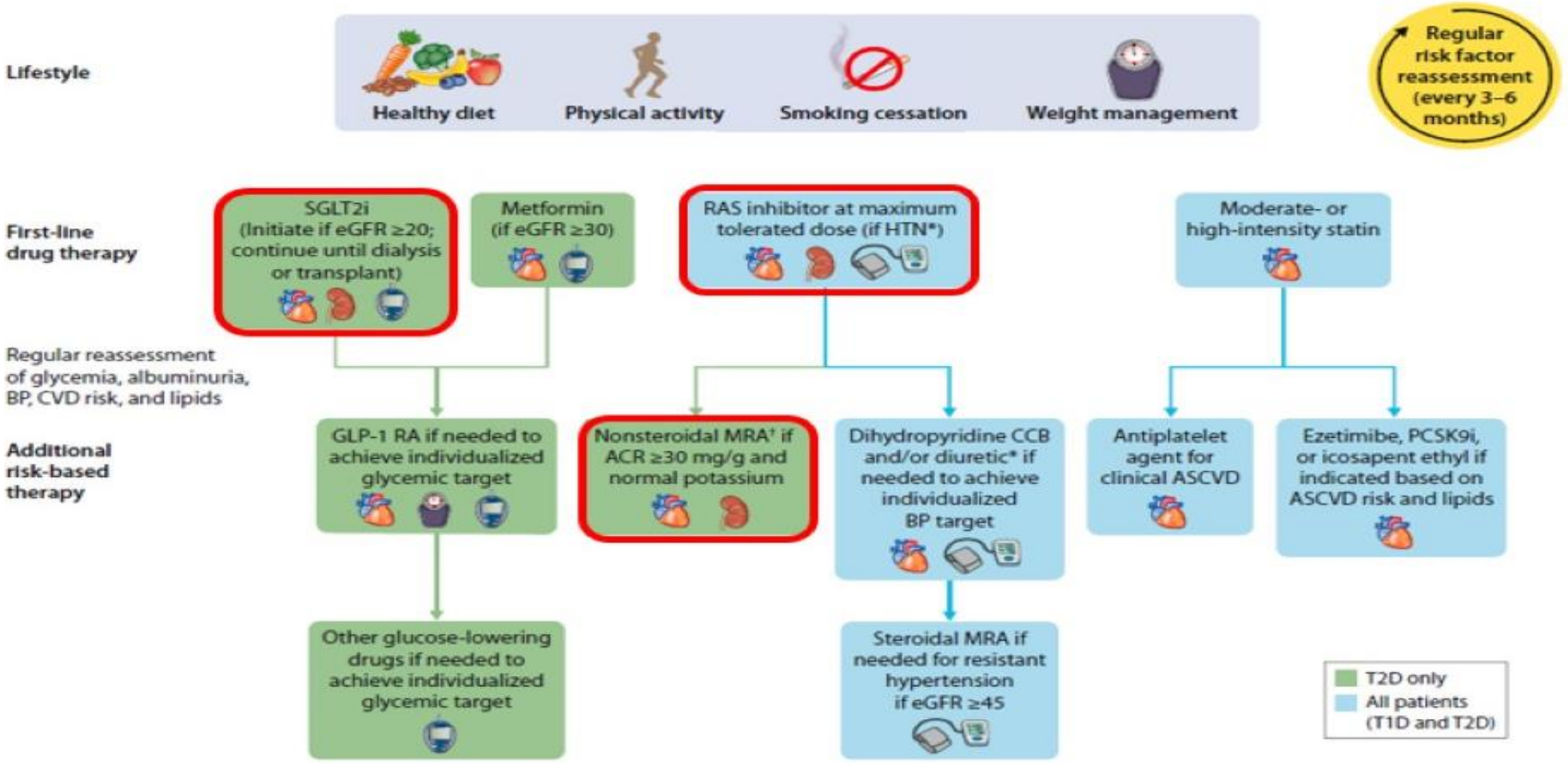
2023 KDIGO Holistic approach to chronic kidney disease (CKD) treatment and risk modification.



KDIGO-2023-CKD-Guideline-Public-Review-Draft_5-July-2023

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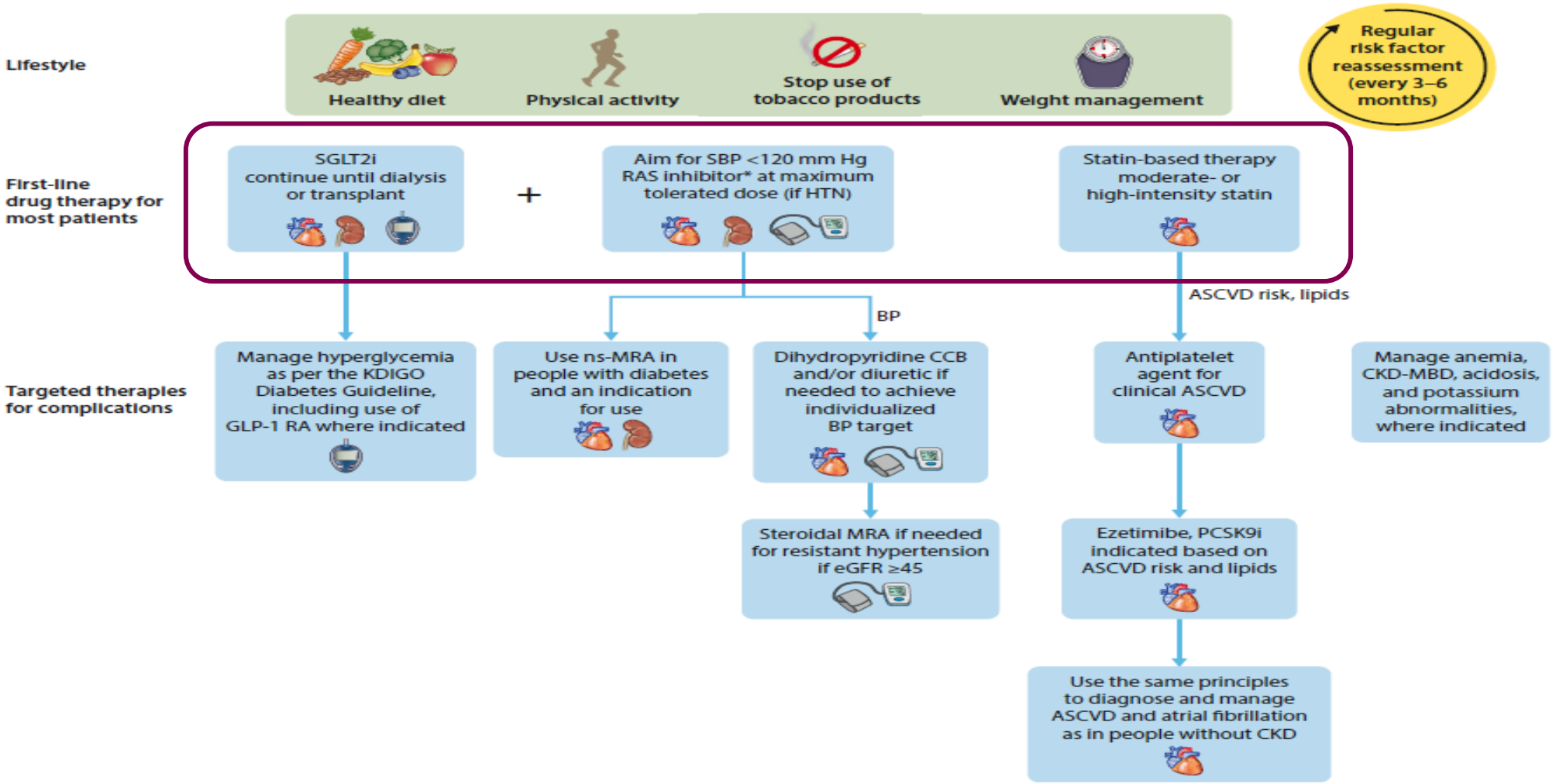
KDIGO Update 2024.



KDIGO-2023-CKD-Guideline-Public-Review-Draft_5-July-2023

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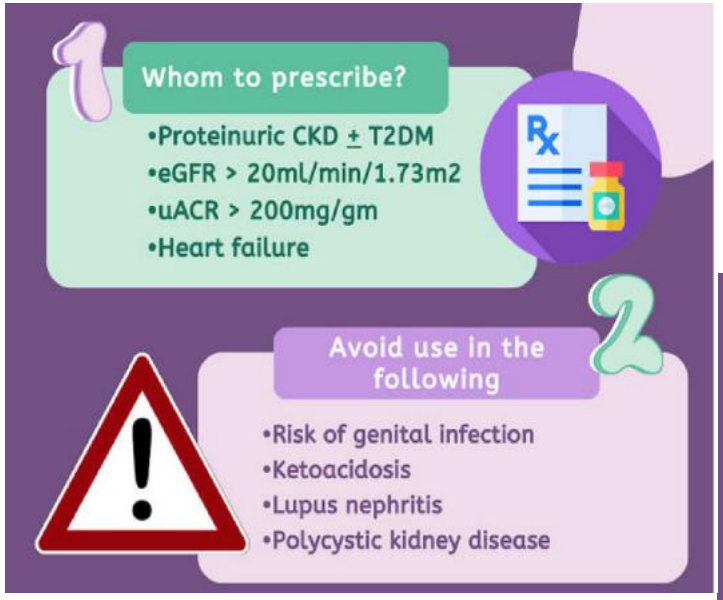
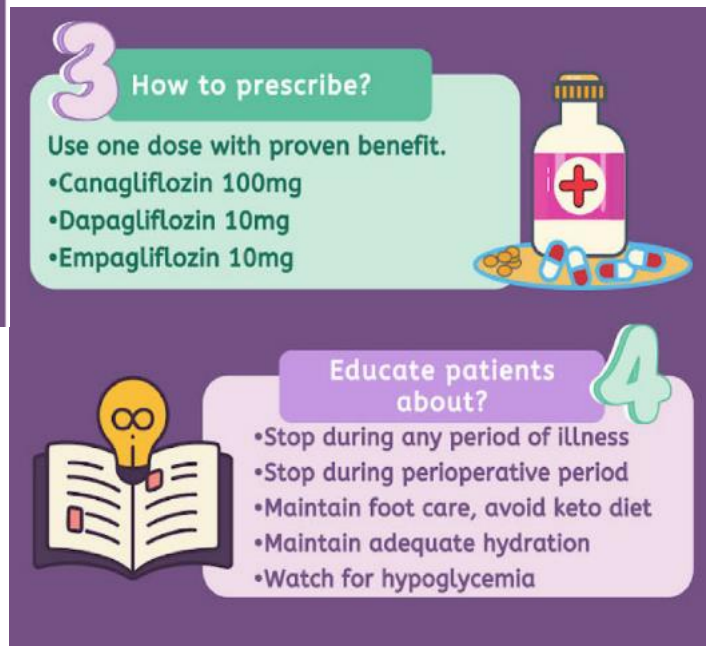
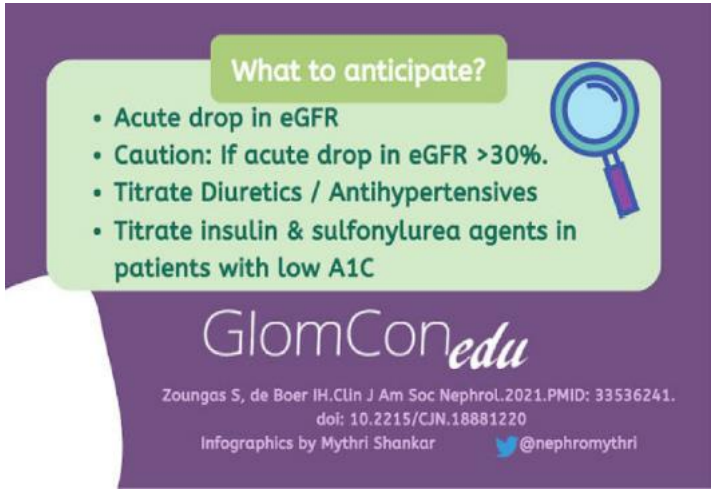
Practical Approach to Prescribing SGLT2i







- Zoungas S, de Boer IH. SGLT2i in diabetic kidney disease . Clin J Am Soc Nephrol . 2021;16(4): 631-633

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Cost-Effectiveness of Dapagliflozin as a Treatment for Chronic Kidney Disease

Health- Economic Analysis of DAPA-CKD

Outcome	Dapagliflozin plus Standard Therapy	Standard Therapy	Incremental
United Kingdom			
Total costs (95% CrI), $	109,596 (77,765 to 133,287)	102,774 (74,017 to 126,749)	6822 (–3293 to 17,138)
Drug acquisition	6034	700	5334
CKD management (not on KRT)	36,815	34,920	1895
KRT	63,357	63,826	–469
Adverse events, hospitalization for heart failure, and acute decline in kidney function	3391	3328	63
Total QALYs gained (95% CrI)	8.68 (6.79 to 9.72)	7.86 (6.21 to 9.00)	0.82 (0.34 to 1.17)
ICER, $/QALY	—	—	8280
Germany			
Total costs (95% CrI), $	254,579 (186,892 to 304,520)	236,908 (174,288 to 286,922)	17,671 (–3328 to 35,900)
Drug acquisition	7428	417	7011
CKD management (not on KRT)	128,095	117,133	10,962
KRT	114,735	115,391	–656
Adverse events, hospitalization for heart failure, and acute decline in kidney function	4321	3967	354
Total QALYs gained (95% CrI)	10.32 (7.96 to 11.49)	9.32 (7.28 to 10.65)	1.00 (0.43 to 1.40)
ICER, $/QALY	—	—	17,623
Spain			
Total costs (95% CrI), $	164,048 (118,905 to 202,510)	152,862 (112,237 to 191,511)	11,186 (–2903 to 24,614)
Drug acquisition	4447	596	3851
CKD management (not on KRT)	74,305	67,320	6985
KRT	81,490	81,660	–170
Adverse events, hospitalization for heart failure, and acute decline in kidney function	3807	3286	521
Total QALYs gained (95% CrI)	9.79 (7.56 to 11.20)	8.83 (6.89 to 10.28)	0.96 (0.43 to 1.41)
ICER, $/QALY	—	—	11,687

ICER= Incremental Increase in Cost / Incremental Increase in QALY

ICER for Dapagliflozin (Germany) = $17,671/1= $17,671

This is below the Willingness to Pay / 1 QALY gained threshold , of $40,000 for Germany - Hence DRUG APPROVED .

- Cost-Effectiveness of Dapagliflozin as a treatment for Chronic Kidney Disease . McEwan et al ; CJASN 17: 1730-1741 , 2022

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Case :

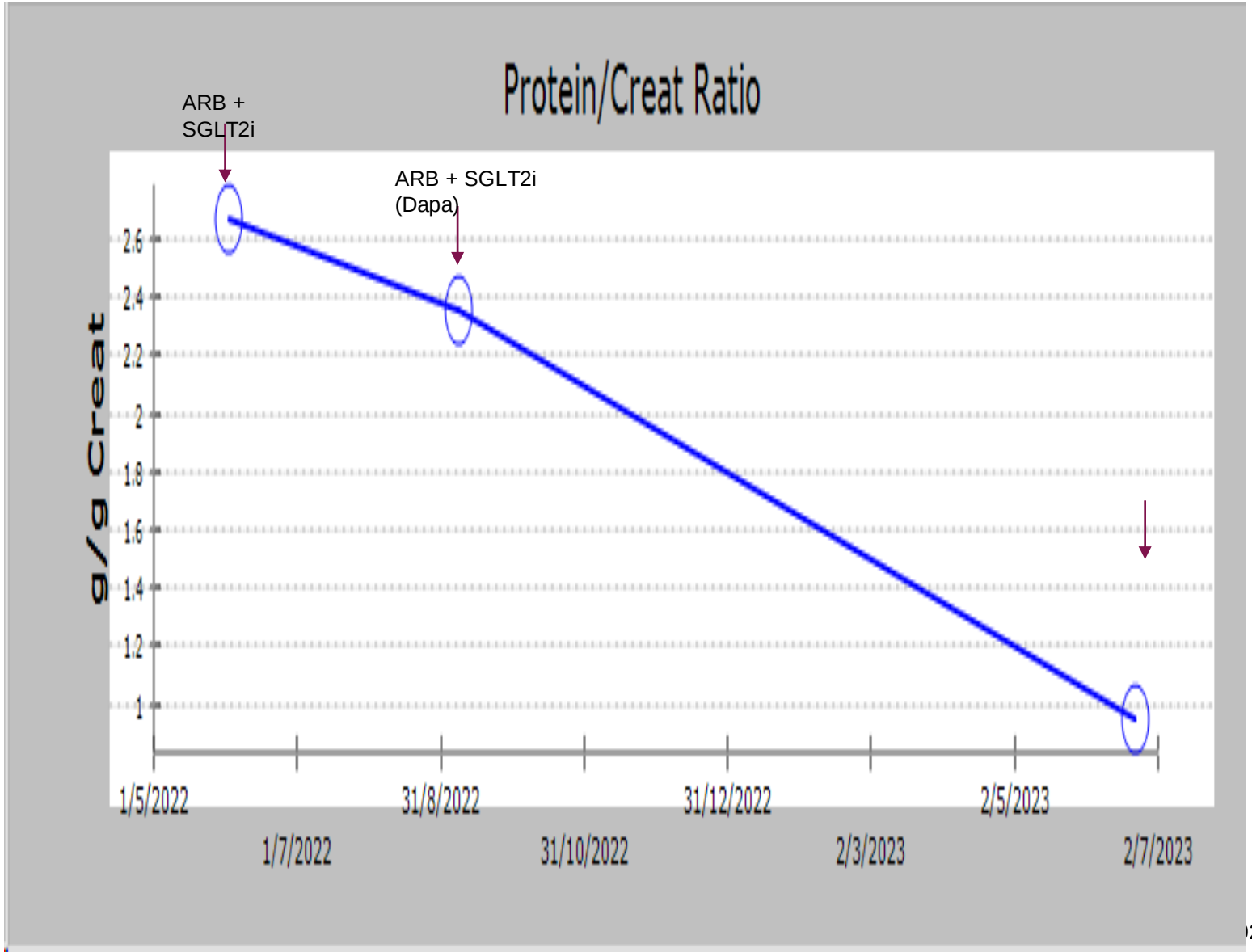
43-year-old Male
DM x 14 years
Weight : 168 kg
BMI : 48

Labs:
eGFR = 65 ml/min
uPCR= 2.4- 3.2 g/g Cr

Meds:
Patient on ARB

Assessment :
Uncontrolled Proteinuria with DM and CKD
Progressive Decline in eGFR > 5ml/min/year

Plan :
What New Treatment Options Available

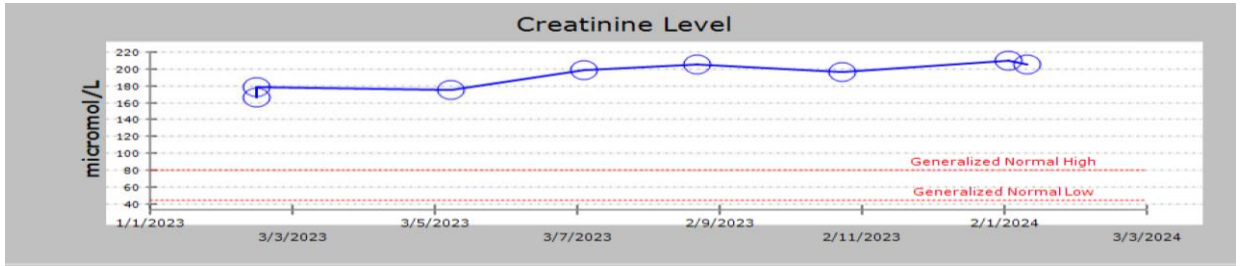


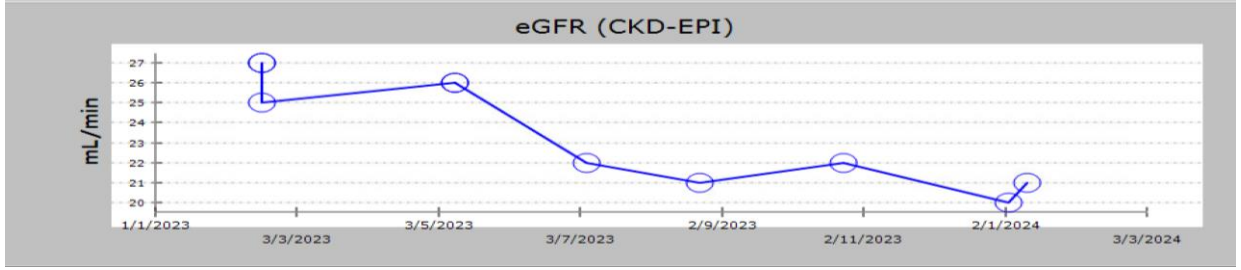
Case:

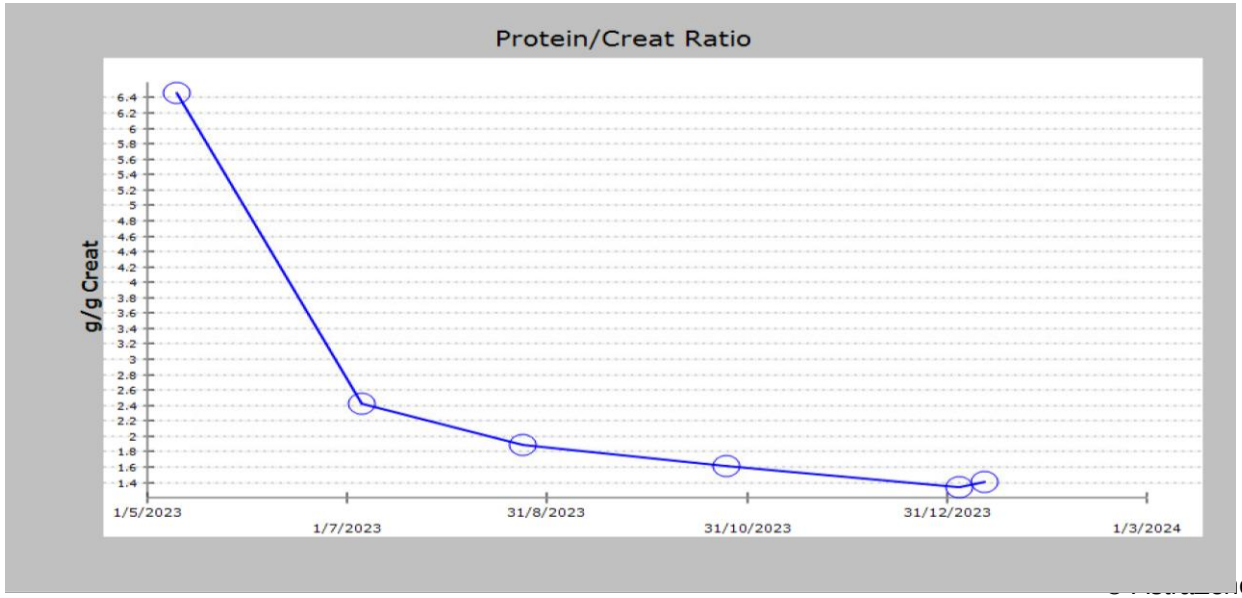
68 year old female , CKD 4 , T2DM x 20 years
uPCR = 6 g/g Creatinine
S.Cr = 180 umol/l
eGFR = 25 ml/min
Meds : Valsartan 160 mg /day

Started on Combination of Dapagliflozin 10 mg/day and Fineronone 10 mg /day

After 6 months uPCR is 1.5 g/g and eGFR 21 ml/min







AstraZeneca 2021

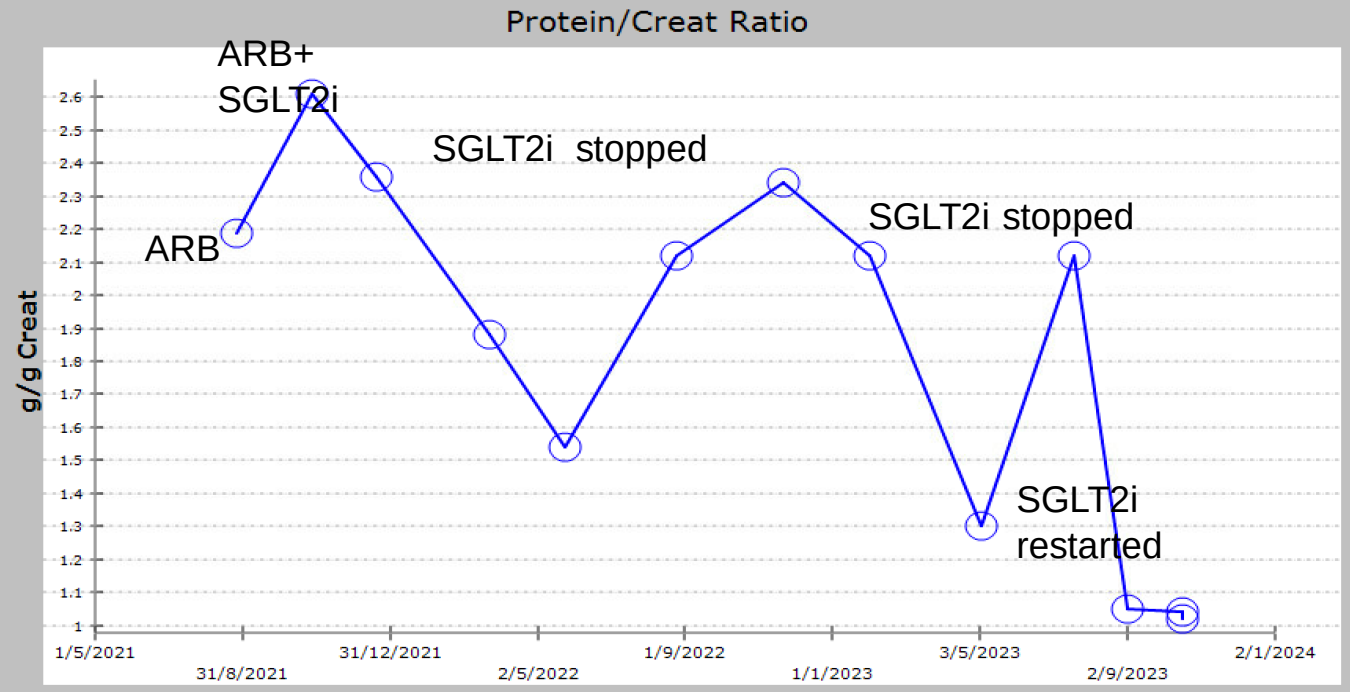
Case :

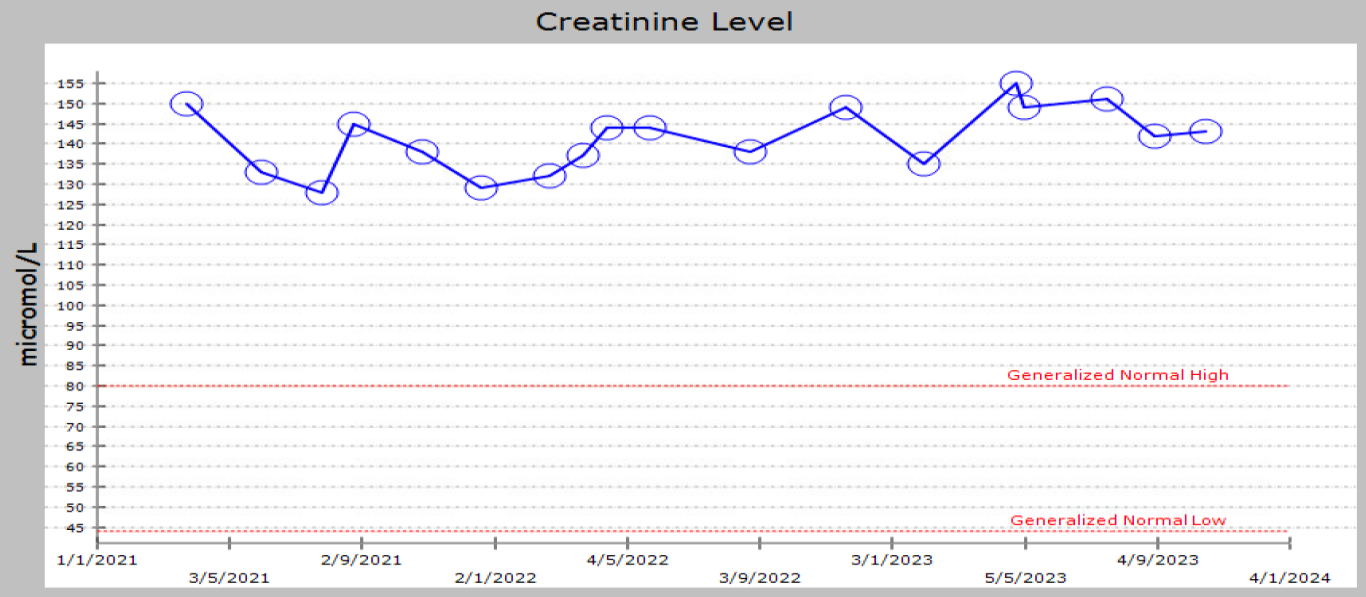
26 year old female with IgA Nephropathy

On ARB

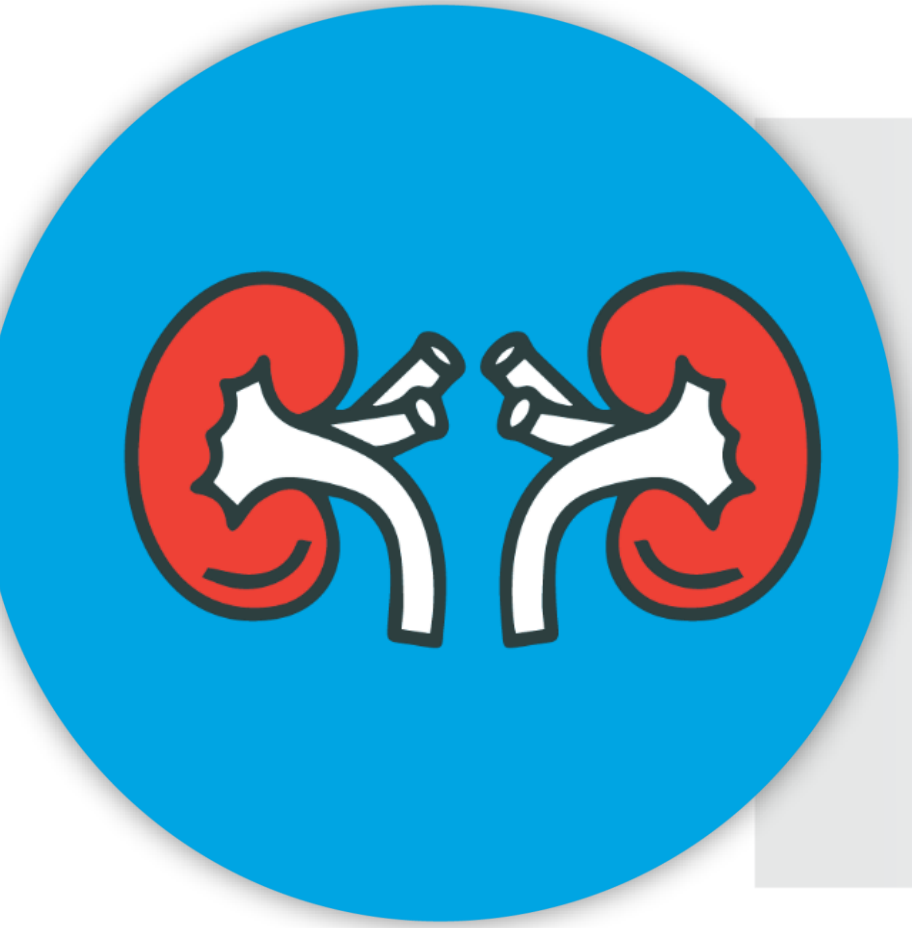
Started on Dapagliflozin with improvement in uPCR

eGFR stable over last 36 months





Summary & Conclusions



DAPA-CKD[1], the first dedicated renal outcomes trial to assess the efficacy and safety of an SGLT-2 inhibitor in patients with CKD with and without T2D, demonstrated:

39% RRR
for the primary composite endpoint (≥50% sustained decline in eGFR, ESKD, renal or CV death)

44% RRR
for the renal composite (≥50% sustained decline in eGFR, ESKD, or renal death)

29% RRR
for the composite of CV death or hospitalization for heart failure

31% RRR
all-cause mortality

- Consistent clinical benefits in patients with CKD across major subgroups including in patients **with and without T2D,** and by baseline eGFR and UACR categories
- Dapagliflozin was well-tolerated for the treatment of CKD (in patients with and without T2D) and data **confirm the known safety profile**
- **DAPA-CKD** builds upon the evidence for dapagliflozin in the prevention of hHF and worsening of kidney disease in **DECLARE[2]** and reduction in the risk of worsening HF and CV death in **DAPA-HF[3]**

CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; hHF = hospitalization for heart failure; RRR = relative risk reduction; SGLT-2 = sodium glucose co-transporter 2; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446. 2. Wiviott SD. et al. *N Engl J Med.* 2019;380:347-357. 3. McMurray JJV et al. *N Engl J Med.* 2019;381:1995-2008.

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Thank You