Diabetic Kidney Disease (DKD)

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I have no relevant financial relationships to disclose.

OBJECTIVES

- ➔ Identify the physiological and structural changes in DKD
- ➔ Define DKD and its clinical courses
- ➔ Describe the main goals of management of DKD
- ➔ Recognize the main pillars of medical management of DKD to improve renal and cardiovascular outcomes.

OVERVIEW

- Introduction & epidemiology
- Physiopathology of DKD
- Clinical course of DKD
- Screening & diagnosis of DKD
- Management of DKD
  - Pillars of treatment
  - 2022 KDIGO Guideline Recommendations
- Conclusions

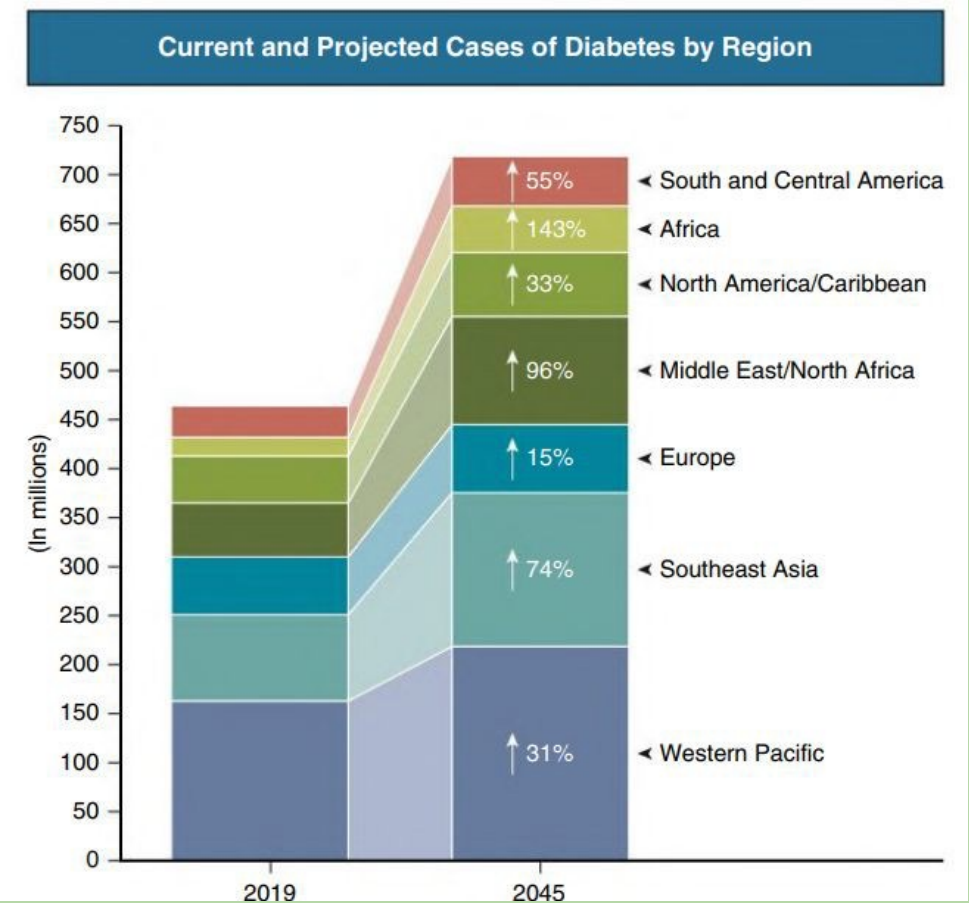
Introduction

- Diabetic Kidney Disease (DKD) is a chronic kidney disease attributable to diabetes, and it is **increasing world wide**, largely in response to a global epidemic of diabetes.
- **1 in 3** patients with diabetes develop DKD.
- DKD is characterized by **albuminuria, decreased estimated glomerular filtration rate (eGFR), or both** in patients with diabetes.
- In DKD, all cause and cardiovascular mortality is **20 to 30 times higher** compared to mortality in the general population.

Brown R.S. Chapter 10. Kidney disorders in other diseases. Clinical Handbook of Nephrology. 2024

Predicted increase in diabetes prevalence.

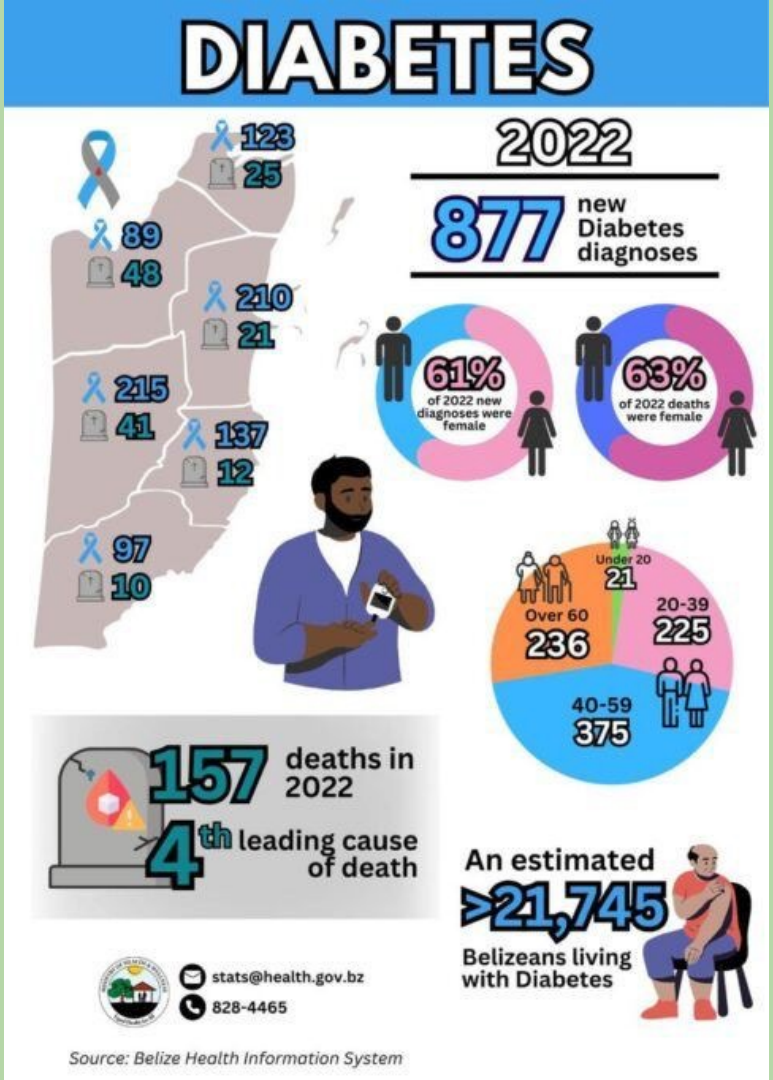
Globally, more than 400 million people have DM and almost 600 million may be affected by 2035.



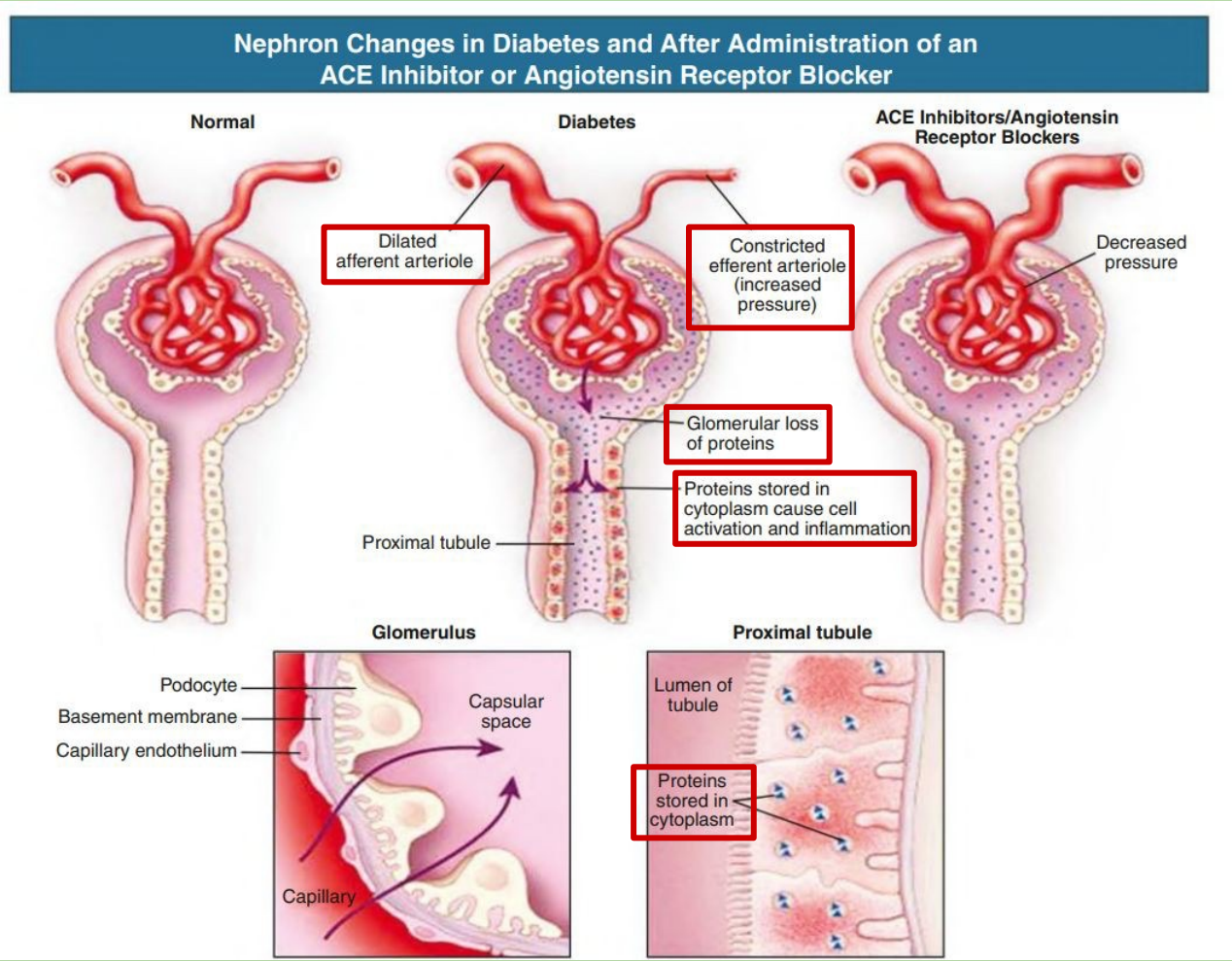
Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract. 2014;103(2):137-149
Tang, S. Sharma K. Chapter 31,Pathogenesis, Clinical Manifestations, and Natural History of Diabetic Kidney Disease. p363-379. Comprehensive Clinical Nephrology, 7th Ed.

Epidemiology in Belize of DM

MOHW has reported that diabetes was the **fourth leading cause** of death in Belize in 2022.



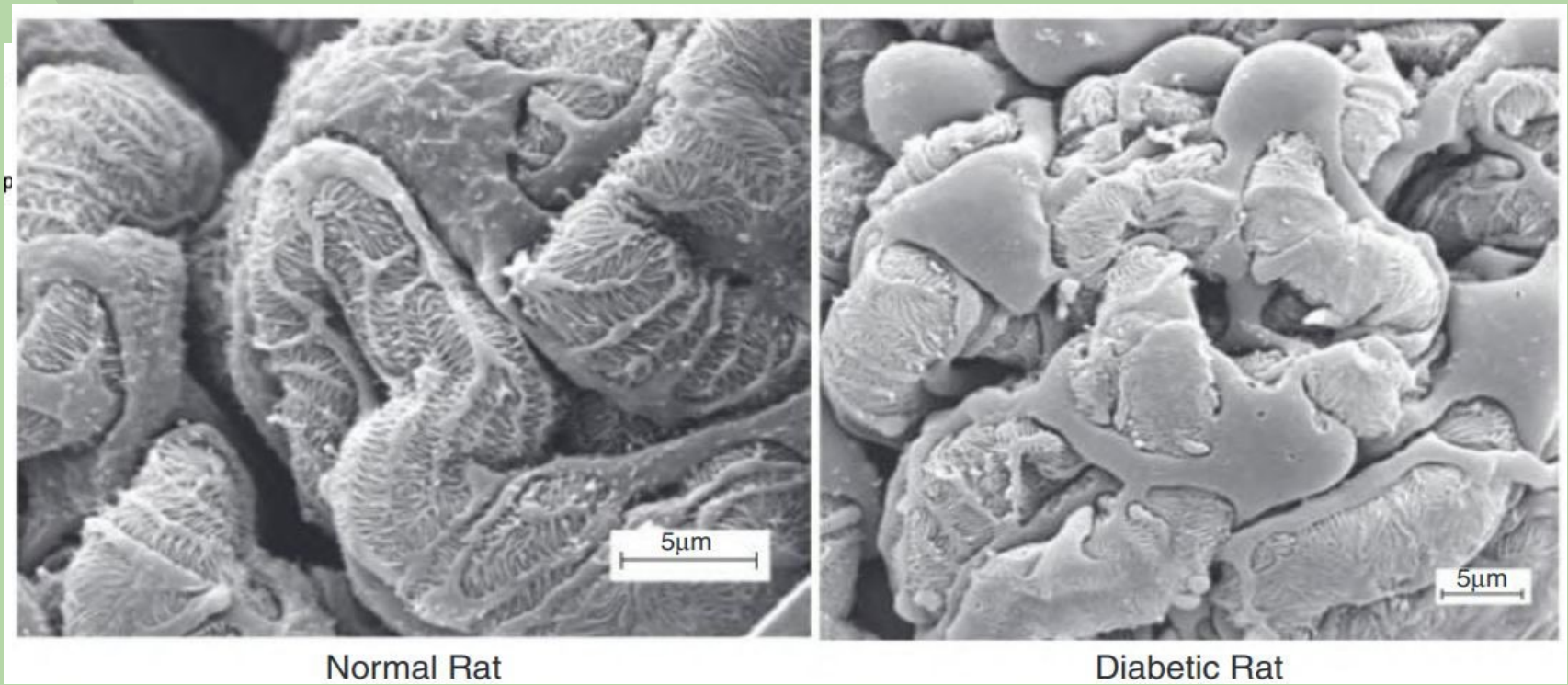
Physiopathology of DKD



Inflammatory reaction that promotes interstitial FIBROSIS

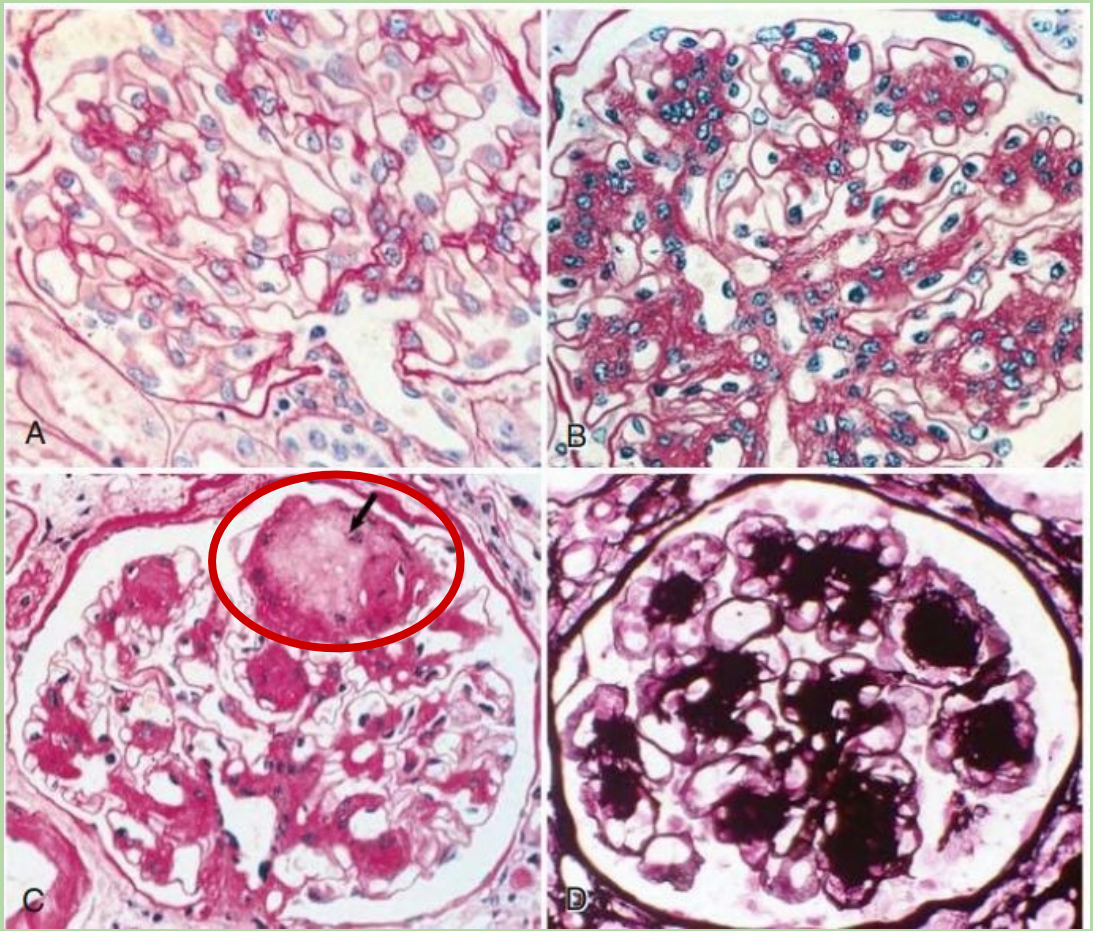
Tang, S. Sharma K. Chapter 31,Pathogenesis, Clinical Manifestations, and Natural History of Diabetic Kidney Disease. p363-379. Comprehensive Clinical Nephrology, 7th Ed.

Structural changes in DKD



Alicic, Radica & Rooney, Michele & Tuttle, Katherine. (2017). Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clinical journal of the American Society of Nephrology : CJASN. 12. 10.2215/CJN.11491116.
Marshall SM. The podocyte: a major player in the development of diabetic nephropathy? Horm Metab Res. 2005;37[suppl 1]:9–16.

Light microscopy of glomerular changes in DKD



A. Normal (PAS)
B. Diffuse glomerular lesion + mesangial expansion (PAS)
C. Nodular lesion + mesangial expansion. Kimmelstiel - Wilson nodule. (PAS)
D. Nodular expansion of mesangial matrix in methenamine silver staining

Tang, S. Sharma K. Chapter 31,Pathogenesis, Clinical Manifestations, and Natural History of Diabetic Kidney Disease. p363-379. Comprehensive Clinical Nephrology, 7th Ed.

Clinical Course of DKD

Clinical course of DKD

01 Classic course of DKD

- Albumin or protein excretion increases & GFR rises then falls, culminating in uremia and ESKD.

02 Non proteinuric DKD

- Loss of GFR in the absence of proteinuria in both T1D and T2D.
- Women with T2D, obesity, dyslipidemia, hypertension and/or hyperfiltration.
- About half of individuals with a decline of kidney function did not have preceding proteinuria or never progressed to proteinuria in T2D.
- Weaker association with diabetic retinopathy.

Lee K. et al. Diabetic Kidney Disease: Challenges, Advances, and Opportunities. Kidney Dis 2020;6:215–225

Fornoni A. et al. Chapter 39. Epidemiology of diabetes kidney disease. P 1327-1378. Brenner & Rector's The Kidney, 11 Ed. 2020

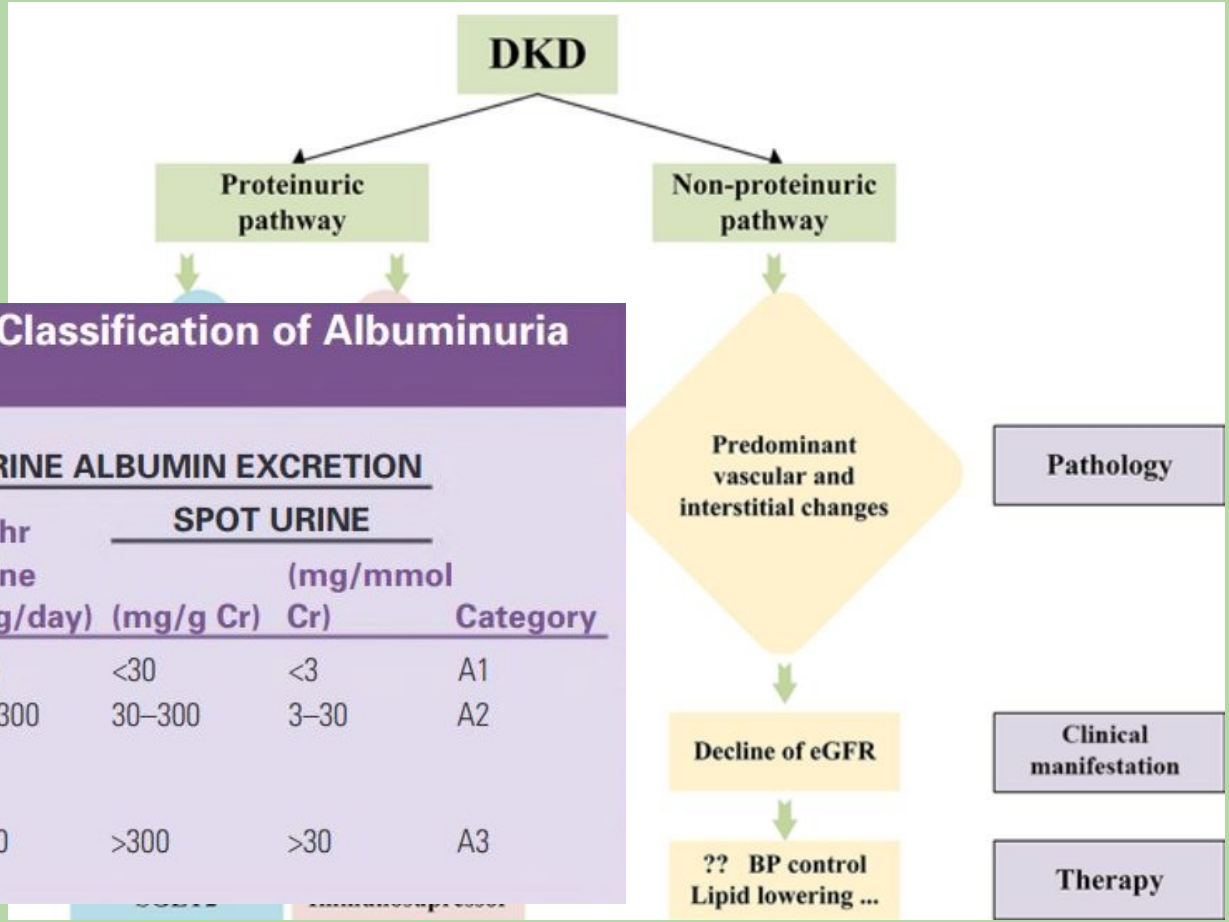
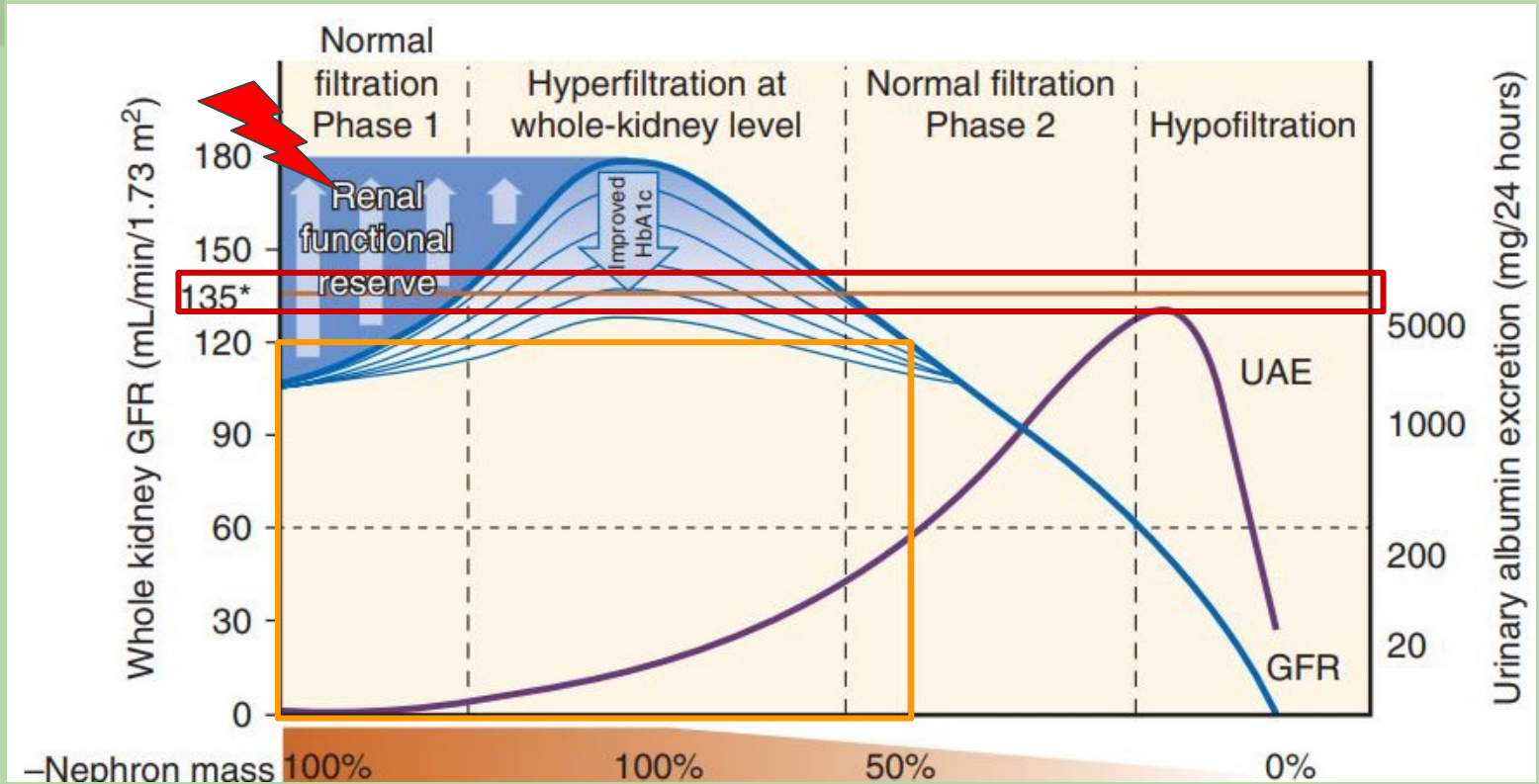


TABLE 31.1 Classification of Albuminuria Categories

	URINE ALBUMIN EXCRETION			
	24-hr Urine	SPOT URINE		
Condition	(mg/day)	(mg/g Cr)	(mg/mmol Cr)	Category
Normoalbuminuria	<30	<30	<3	A1
Moderately increased albuminuria	30–300	30–300	3–30	A2
Severely increased albuminuria	>300	>300	>30	A3

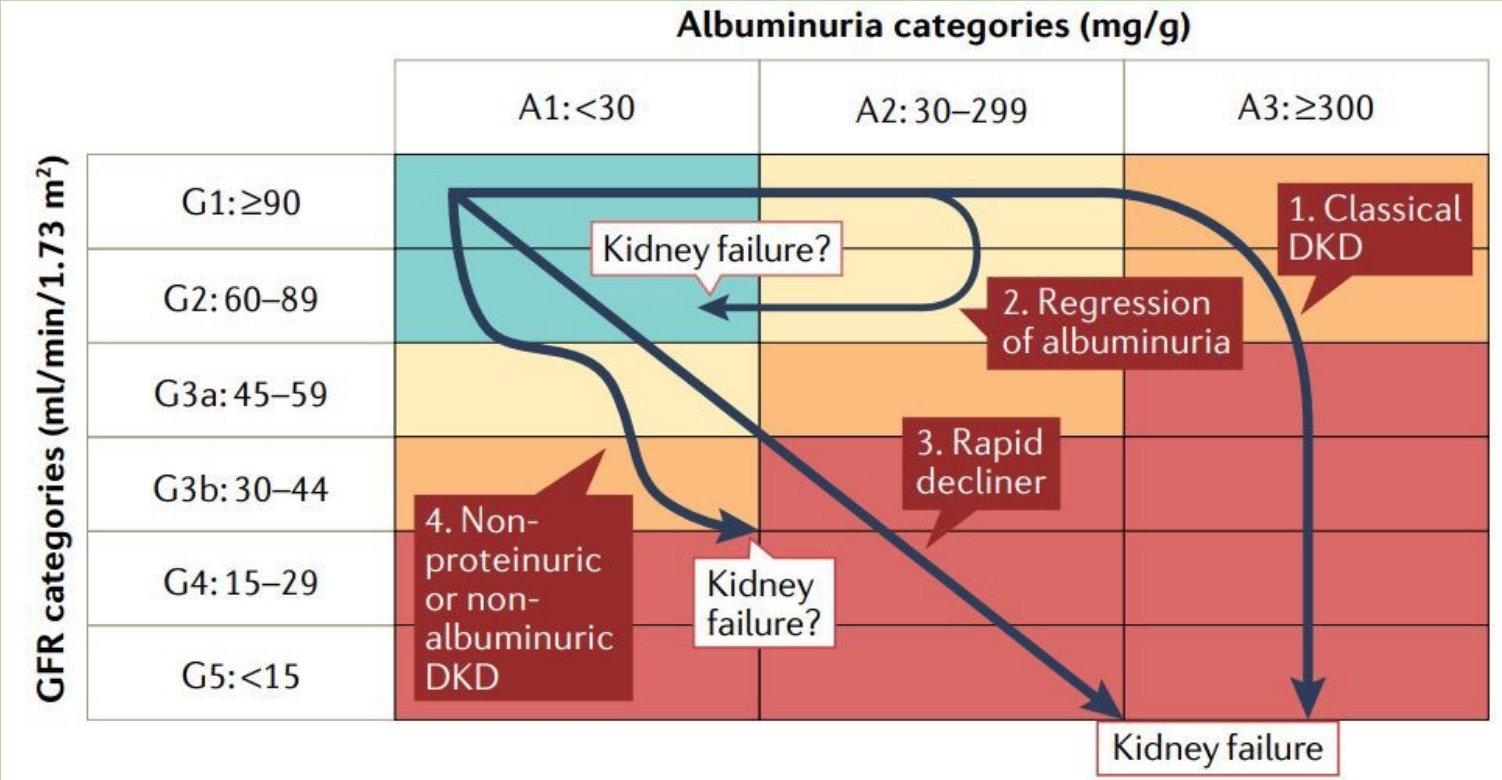
Lee K. et al. Diabetic Kidney Disease: Challenges, Advances, and Opportunities. Kidney Dis 2020;6:215–225
Tang, S. Sharma K. Chapter 31,Pathogenesis, Clinical Manifestations, and Natural History of Diabetic Kidney Disease. p363-379. Comprehensive Clinical Nephrology, 7th Ed.

Classic course of DKD

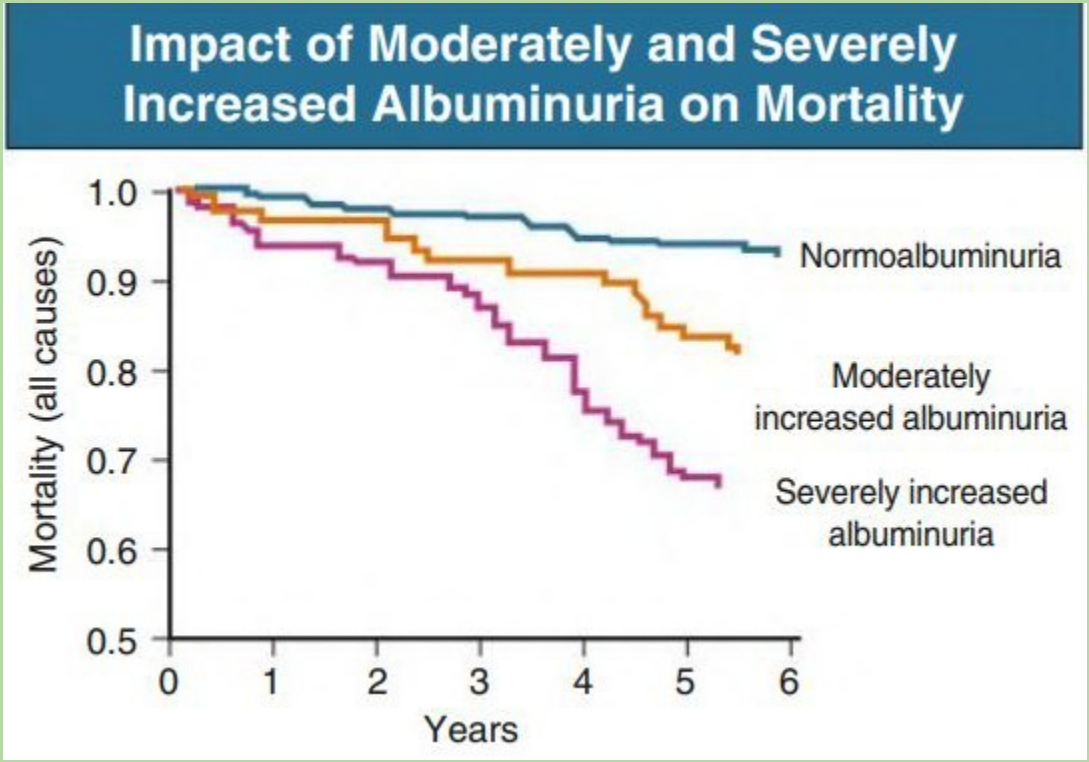


Fornoni A. et al. Chapter 39. Epidemiology of diabetes kidney disease. P 1327-1378. Brenner & Rector's The Kidney, 11 Ed. 2020

Trajectories of kidney function in DKD



Oshima M. et al Trajectories of kidney function in diabetes: a clinicopathological update. Nature Reviews. https://doi.org/10.1038/ s41581-021-00462-y



- UAE is a good predictor of cardiovascular events.
- Generalized endothelial cell dysfunction with increased risk of atherosclerosis and other cardiovascular risk factors.

Tang, S. Sharma K. Chapter 31,Pathogenesis, Clinical Manifestations, and Natural History of Diabetic Kidney Disease. p363-379. Comprehensive Clinical Nephrology, 7th Ed.

Screening & Diagnosis

CKD Screening & Diagnosis in people with DM

Who and when to screen?

- **T1D** Yearly starting 5 years after diagnosis
- **T2D** Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

- Confirmatory urine sample within **3–6 months** is recommended.
- 2021 Chronic Kidney Disease Epidemiology Collaboration **(CKD-EPI) equation**

What to do with a positive result?

Repeat and confirm:
- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

Persistent eGFR <60 mL/min/1.73 m²

and/or

Other evidence of kidney damage

> 3 months
Hematuria
Structural abnormalities

Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022;45:3075–3090 |

KDIGO Heat Map

Stratify & treat

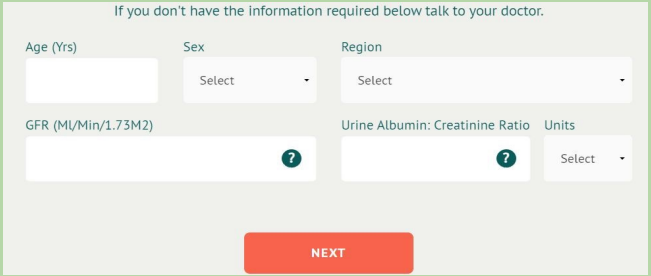
CKD is classified based on: *Cause (C) *GFR (G) *Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min per 1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60-89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15-29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

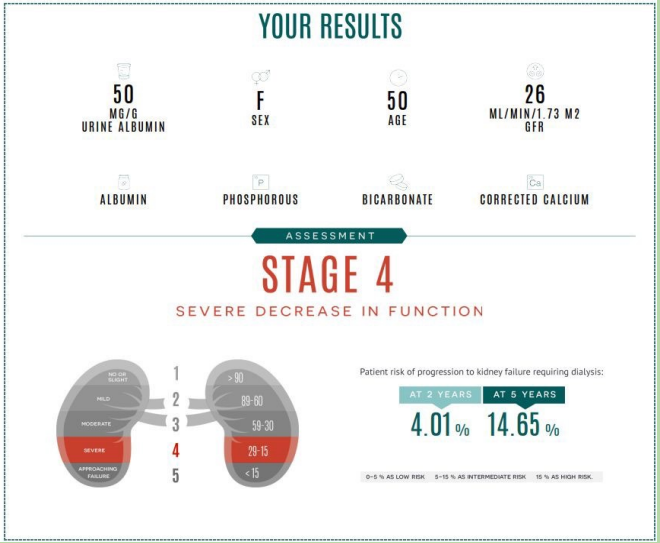
Low Risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022;45:3075–3090 |

The Kidney Failure Risk Equation (KFRE)

- Risk of progression of kidney failure requiring dialysis at **2 and 5 years.**
- Validated in more than **30 countries worldwide**.
- Determining the probability of kidney failure may be useful for **patient and provider communication, triage and management of nephrology referrals.**





- Low risk: 0-5%
- Intermediate risk: 5-15%
- High risk: >15%

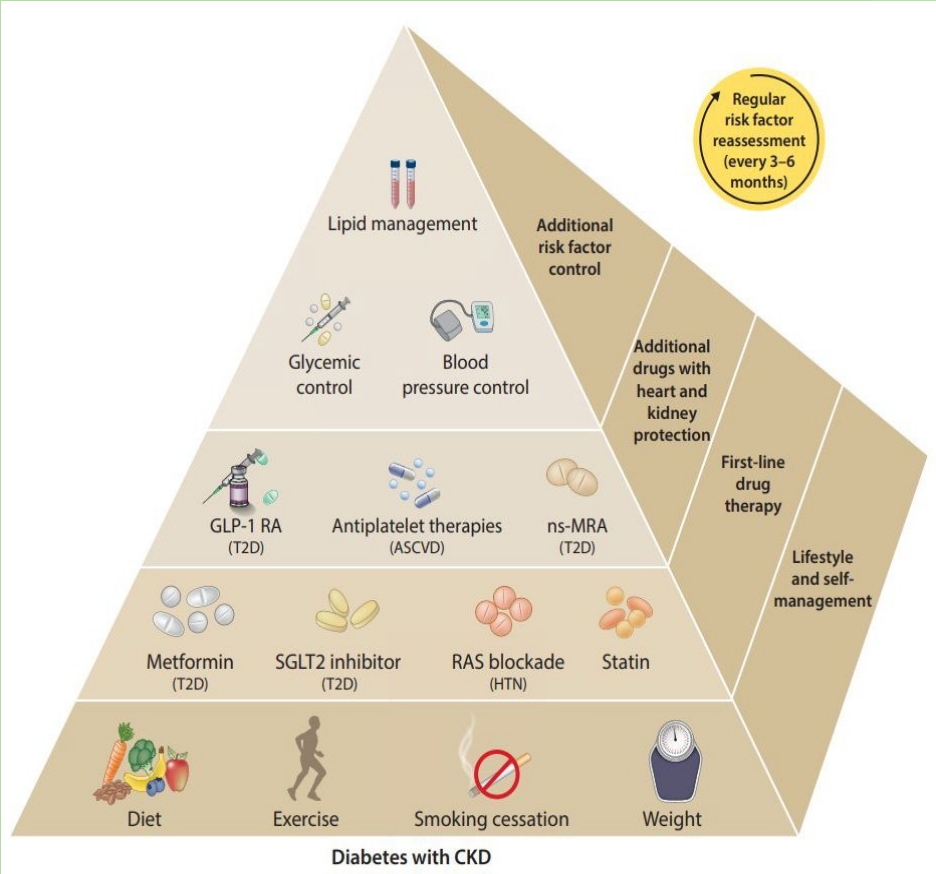
https://kidneyfailurerisk.com/

Management of DKD

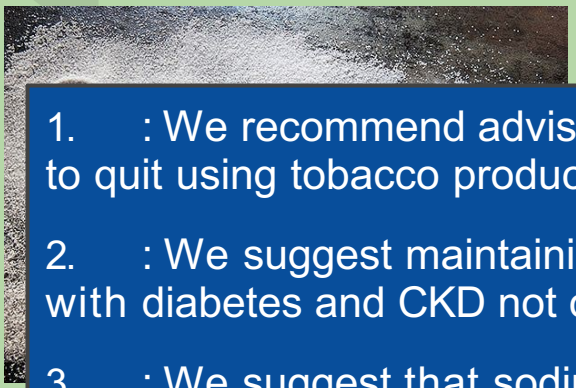
Goals of management of DKD

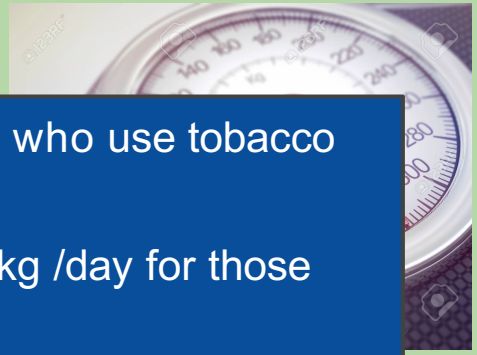
- ★ Albuminuria regression
- ★ Preservation of kidney function
- ★ Prevention of cardiovascular events
- ★ Addressing modifiable risk factors
- ★ Adequate glycemic control
- ★ Proper blood pressure control

Kidney–heart risk factor management.



Lifestyle modifications





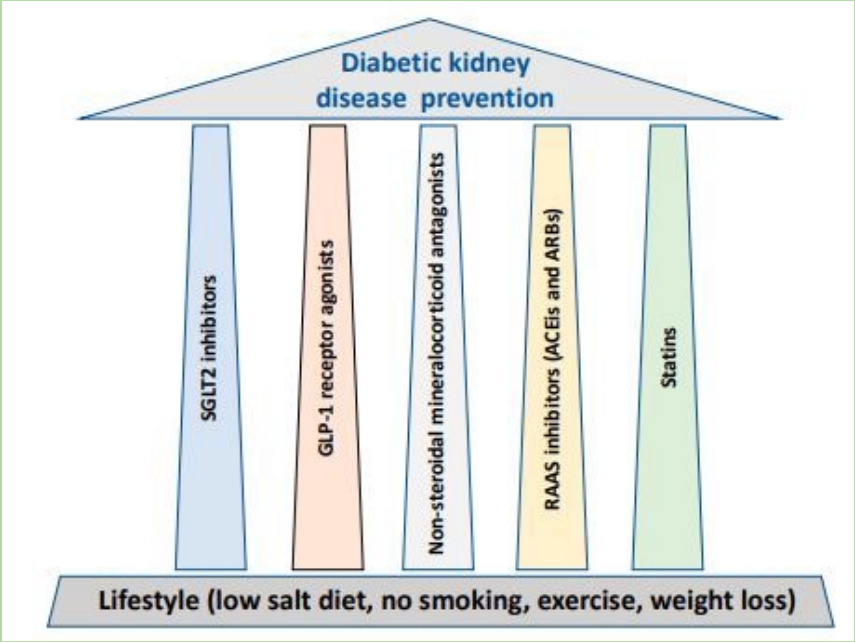
1. : We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products (1D).

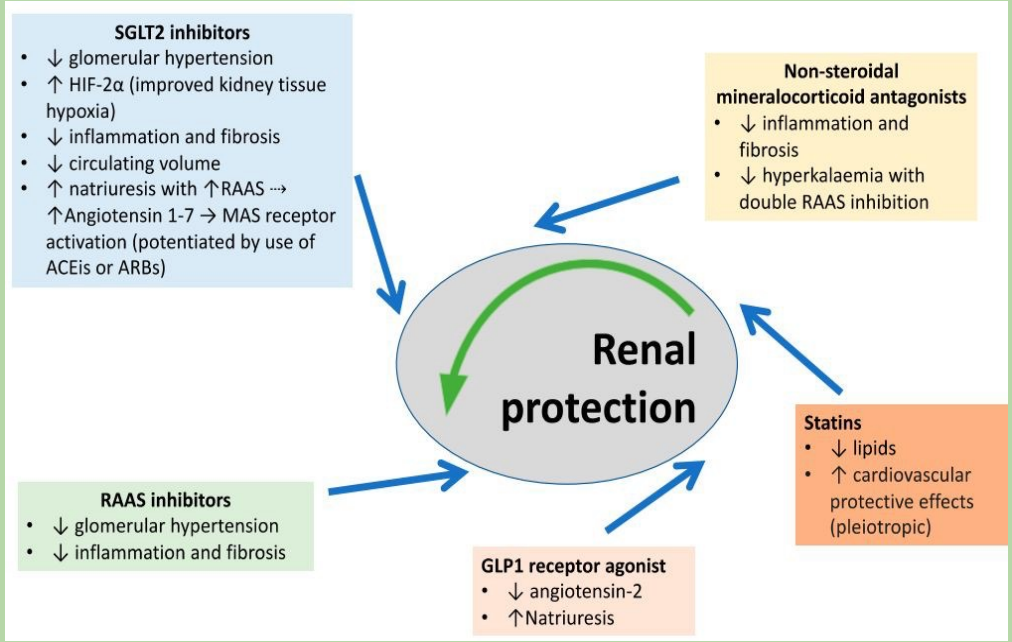
2. : We suggest maintaining a protein intake of 0.8 g protein/kg /day for those with diabetes and CKD not on dialysis (2C)

3. : We suggest that sodium intake be < 2 g of sodium per day (<90mmol of sodium per day, or <5g of sodium chloride per day) (2C)

4. : We recommend patients undertake moderate intensity physical activity for a cumulative duration of at least 150 minutes per week or to a level compatible with the cardiovascular and physical tolerance (1D)

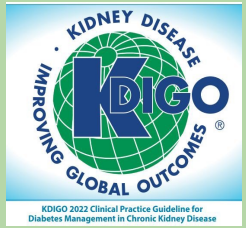
Pillars for renal disease treatment in DKD





Jessica Kearney 1 and Luigi Gnudi 1. The Pillars for Renal Disease Treatment in Patients with Type 2 Diabetes. Pharmaceutics 2023, 15(5), 1343

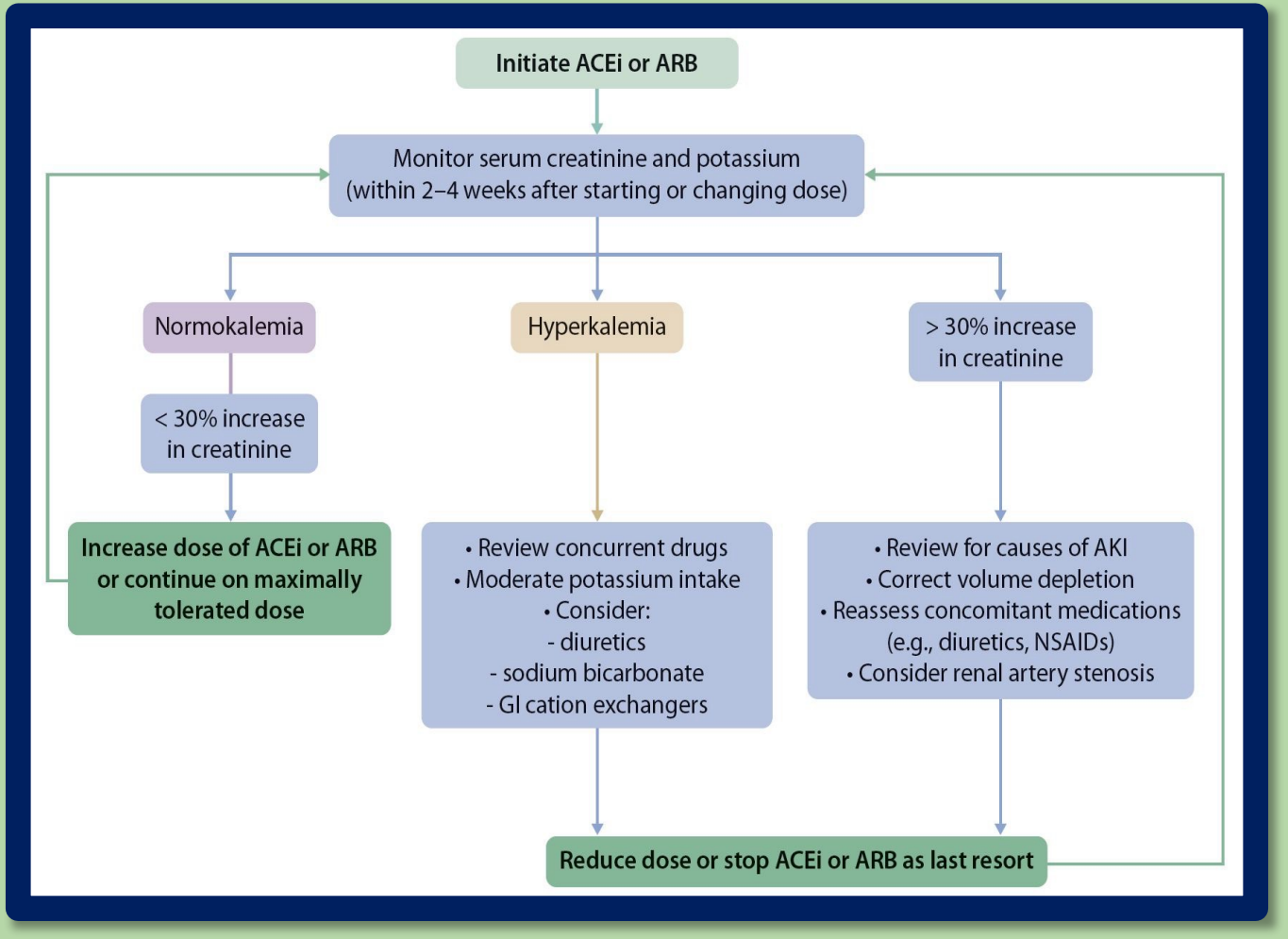
Renin-angiotensin system (RAS) blockade



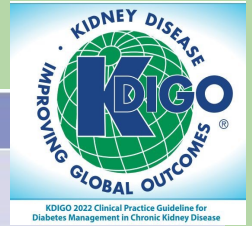
1.2.1. We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated (1B).

IRMA-2	INNOVATION	IDNT	RENAAL
Irbesartan 150 vs 300 mg vs placebo 590 patients 2 years	Telmisartan 40 vs 80 mg vs placebo 527 patients 1 year	Irbesartan 75-300 mg vs Amlodipine 2.5-10mg vs placebo 1,715 patients 2.6 years	Losartan 50-100 mg vs placebo + conventional Tx 1,513 patients 3.4 years

RAS Blockade



KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease



Drug		Starting dose	Maximum daily dose	Kidney impairment
ACE inhibitors	Benazepril	10 mg once daily	80 mg	CrCl ≥ 30 ml/min: No dosage adjustment needed. CrCl < 30 ml/min: Reduce initial dose to 5 mg PO once daily for adults. Parent compound not removed by hemodialysis
	Captopril	12.5 mg to 25 mg 2 to 3 times daily	Usually 50 mg 3 times daily (may go up to 450 mg/day)	Half-life is increased in patients with kidney impairment CrCl 10–50 ml/min: administer 75% of normal dose every 12–18 hours. CrCl <10 ml/min: administer 50% of normal dose every 24 hours. Hemodialysis: administer after dialysis. About 40% of drug is removed by hemodialysis
	Enalapril	5 mg once daily	40 mg	CrCl ≤ 30 ml/min: In adult patients, reduce initial dose to 2.5 mg PO once daily 2.5 mg PO after hemodialysis on dialysis days; dosage on nondialysis days should be adjusted based on clinical response.
	Fosinopril	10 mg once daily	80 mg	No dosage adjustment necessary Poorly removed by hemodialysis
	Lisinopril	10 mg once daily	40 mg	CrCl 10–30 ml/min: Reduce initial recommended dose by 50% for adults. Max: 40 mg/d CrCl < 10 ml/min: Reduce initial dosage to 2.5 mg PO once daily. Max: 40 mg/d
	Perindopril	2 mg once daily	8 mg	Use is not recommended when CrCl <30 ml/min Perindopril and its metabolites are removed by hemodialysis
	Quinapril	10 mg once daily	80 mg	CrCl 61–89 ml/min: start at 10 mg once daily CrCl 30–60 ml/min: start at 5 mg once daily CrCl 10–29 ml/min: start at 2.5 mg once daily CrCl <10 ml/min: insufficient data for dosage recommendation About 12% of parent compound removed by hemodialysis
	Ramipril	2.5 mg once daily	20 mg	Administer 25% of normal dose when CrCl <40 ml/min Minimally removed by hemodialysis
	Trandolapril	1 mg once daily	4 mg	CrCl <30 ml/min: reduce initial dose to 0.5 mg/d

Drug		Starting dose	Maximum daily dose	Kidney impairment
Angiotensin receptor blockers	Azilsartan	20–80 mg once daily	80 mg	Dose adjustment is not required in patients with mild-to-severe kidney impairment or kidney failure
	Candesartan	16 mg once daily	32 mg	In patients with CrCl <30 ml/min, AUC and Cmax were approximately doubled with repeated dosing. Not removed by hemodialysis
	Irbesartan	150 mg once daily	300 mg	No dosage adjustment necessary. Not removed by hemodialysis
	Losartan	50 mg once daily	100 mg	No dosage adjustment necessary. Not removed by hemodialysis
	Olmesartan	20 mg once daily	40 mg	AUC is increased 3-fold in patients with CrCl <20 ml/min. No initial dosage adjustment is recommended for patients with moderate to marked kidney impairment (CrCl <40 ml/min). Has not been studied in dialysis patients
	Telmisartan	40 mg once daily	80 mg	No dosage adjustment necessary. Not removed by hemodialysis
	Valsartan	80 mg once daily	320 mg	No dosage adjustment available for CrCl <30 ml/min—to use with caution. Not removed significantly by hemodialysis

Non steroidal MRA in T2D and CKD

1.4.1: We suggest a **nonsteroidal mineralocorticoid receptor antagonist (NSMRA)**with proven kidney or cardiovascular benefit for patients with T2D, an eGFR >=25 ml/min per 1.73 m2, normal serum potassium concentration, and albuminuria (>=30 mg/g [>=3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) (2A).

FIDELIO-DKD (Oct 2020)	FIGARO-DKD (Aug 2021)
5,734 participants	7,437 participants
2.6 years	3.4 years
Kidney failure, sustained decrease >=40% in GFR, renal death	**Death from CV causes, nonfatal MI, non fatal stroke, or hospitalization for HF**

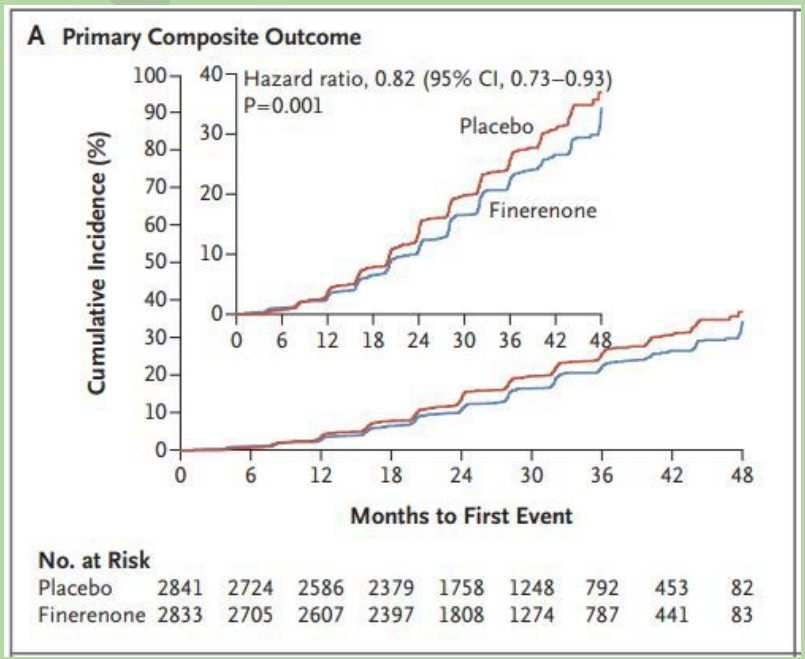
FIDELIO-DKD

- UACR 30 to < 300 mg/g and eGFR ≥ 25 to < 60 mL/min/1.73 m²
- **Or** UACR ≥ 300 mg/g and eGFR ≥ 25 to < 75 mL/min/1.73 m²

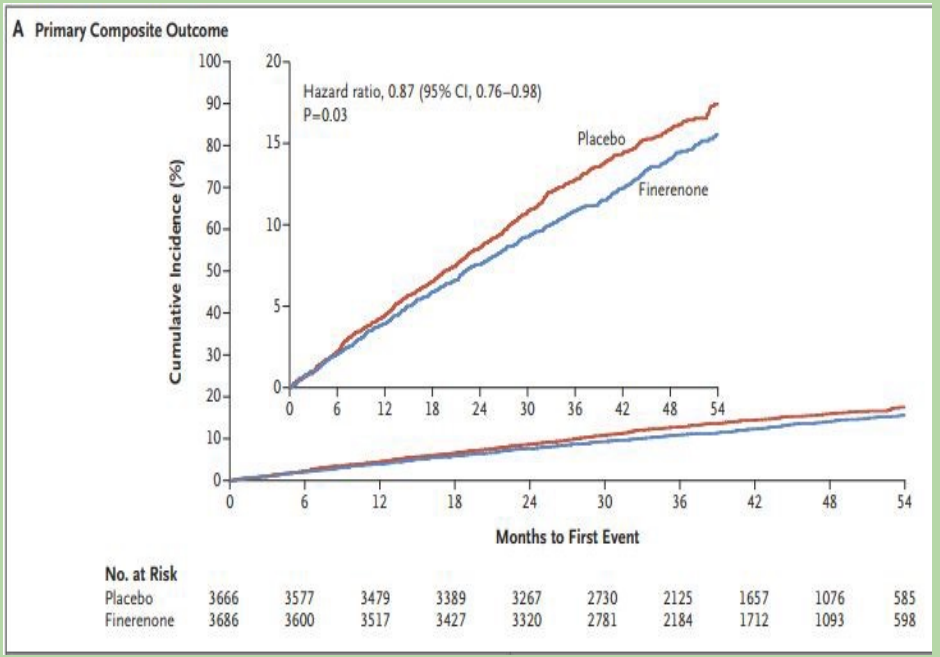
FIGARO-DKD

- UACR 30 to < 300 mg/g and eGFR 25 to ≤ 90 mL/min/1.73 m²
- **Or** UACR ≥ 300 mg/g and eGFR ≥ 60 mL/min/1.73 m²

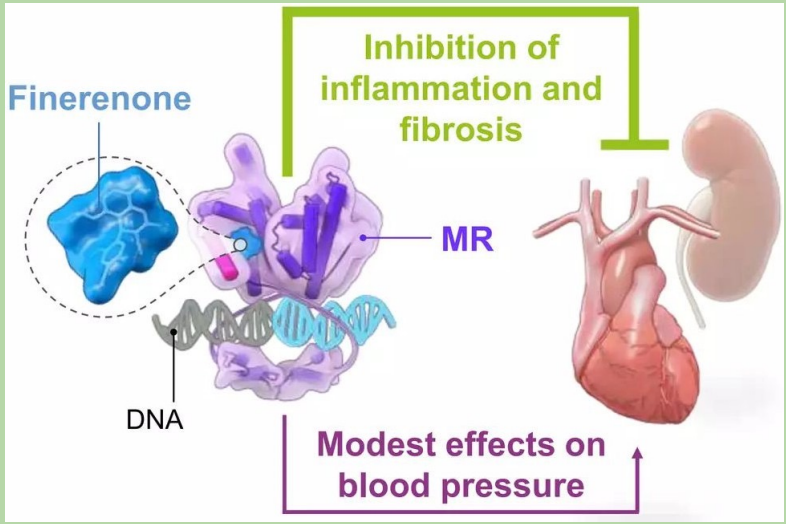
FIDELIO -DKD



FIGARO - DKD



Finerenone lowers risk of progression of kidney disease and improves cardiovascular outcomes compared to placebo in patients with type 2 diabetes and chronic kidney disease



Finerenone blocks mineralocorticoid receptor (MR) overactivation, which contributes to inflammation and fibrosis, leading to kidney and cardiovascular damage.

K^+ ≤4.8 mmol/l

- Initiate finerenone
  - 10 mg daily if eGFR 25–59 ml/min per 1.73 m^2
  - 20 mg daily if eGFR ≥60 ml/min per 1.73 m^2
- Monitor K^+ at 1 month after initiation and then every 4 months
- Increase dose to 20 mg daily, if on 10 mg daily
- Restart 10 mg daily if previously held for hyperkalemia and K^+ now ≤5.0 mmol/l

K^+ 4.9–5.5 mmol/l

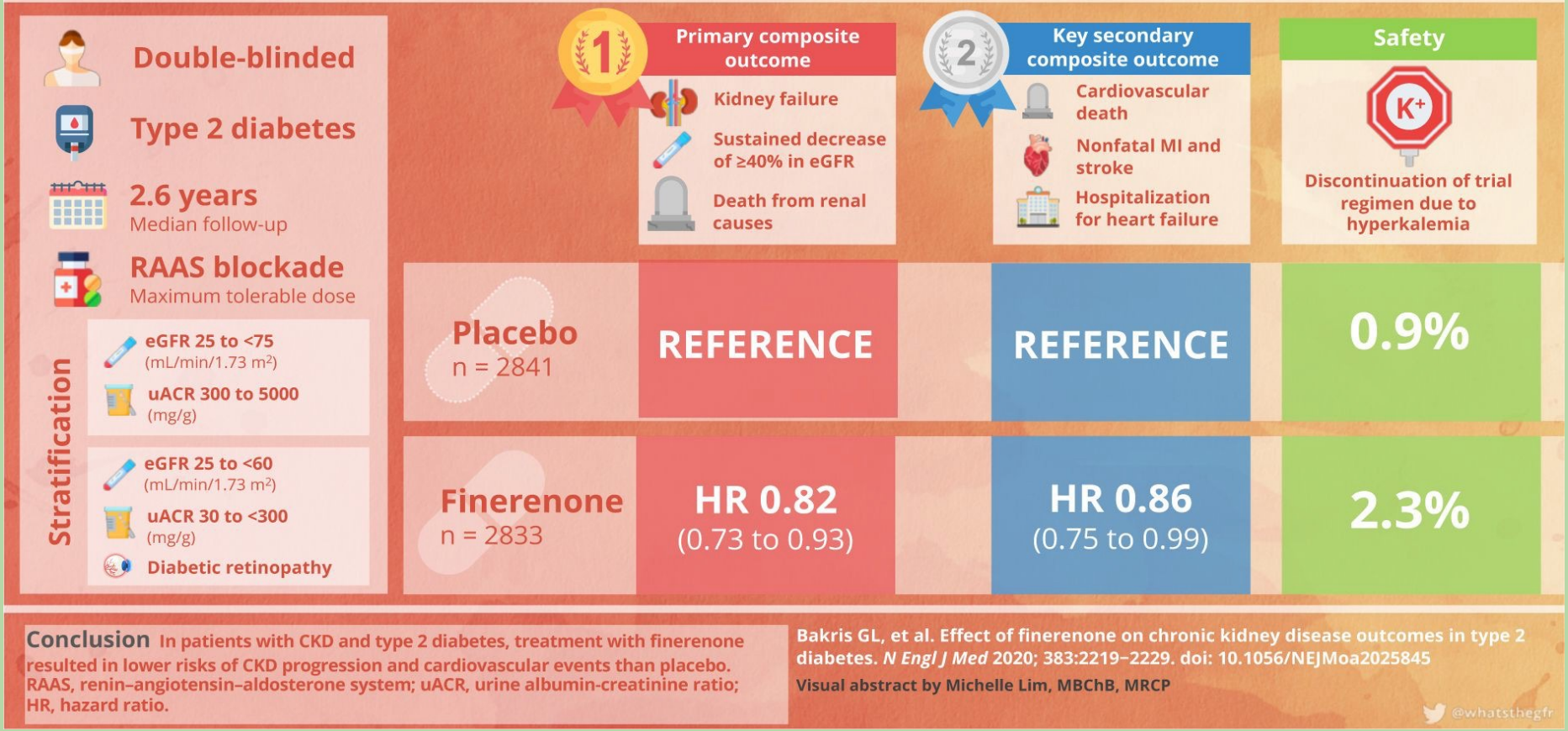
- Continue finerenone 10 mg or 20 mg
- Monitor K^+ every 4 months

K^+ >5.5 mmol/l

- Hold finerenone
- Consider adjustments to diet or concomitant medications to mitigate hyperkalemia
- Recheck K^+
- Consider reinitiation if/when K^+ ≤5.0 mmol/l

Figure 1. FIDELIO-DKD

Does finerenone improve outcomes in CKD with type 2 diabetes?



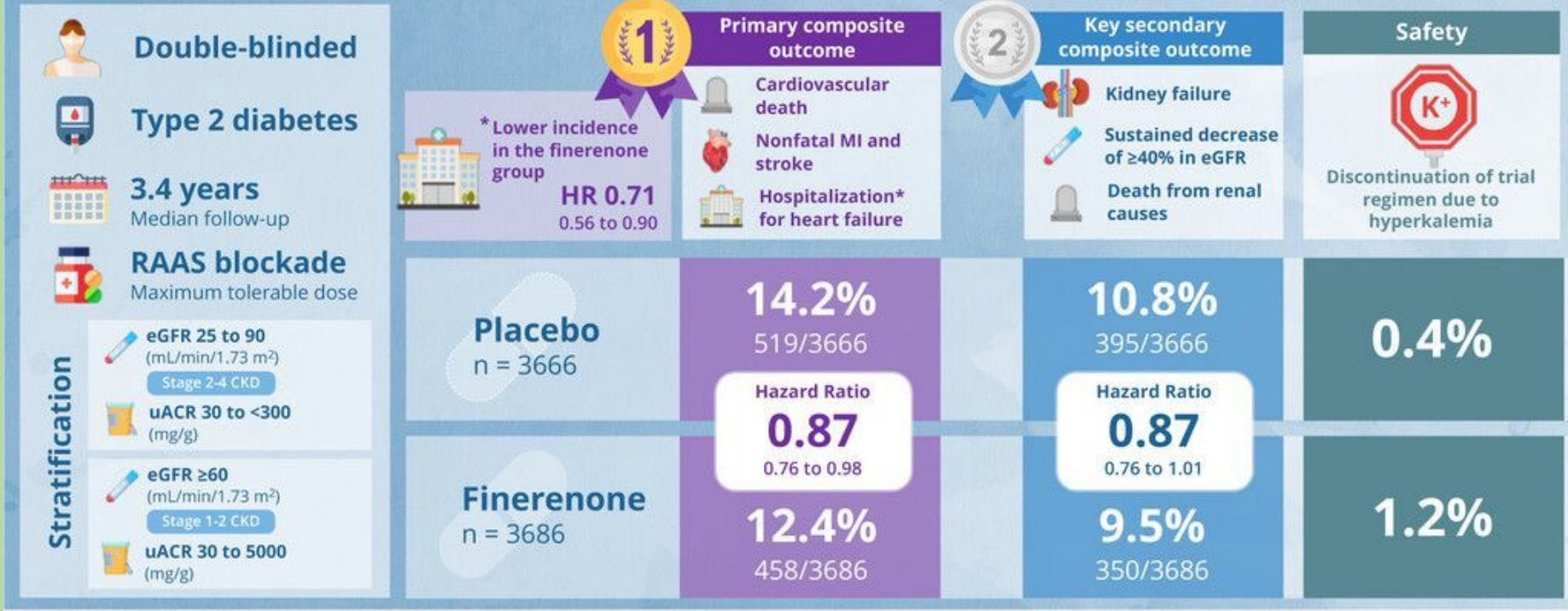
Conclusion In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo.
RAAS, renin–angiotensin–aldosterone system; uACR, urine albumin-creatinine ratio; HR, hazard ratio.

Bakris GL, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020; 383:2219–2229. doi: 10.1056/NEJMoa2025845

Visual abstract by Michelle Lim, MBChB, MRCP

Figure 2. FIGARO-DKD

Does finerenone improve cardiovascular outcomes in type 2 diabetes and CKD?



Conclusion Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone therapy improved cardiovascular outcomes as compared with placebo.

Pitt B, et al.; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* [published online ahead of print August 28, 2021]. doi: 10.1056/NEJMoa2110956

Visual abstract by Michelle Lim, MBChB, MRCP

Glycemic monitoring

2.1.1: We recommend using hemoglobin A1c (HbA1c) to monitor glycemic control (1C)

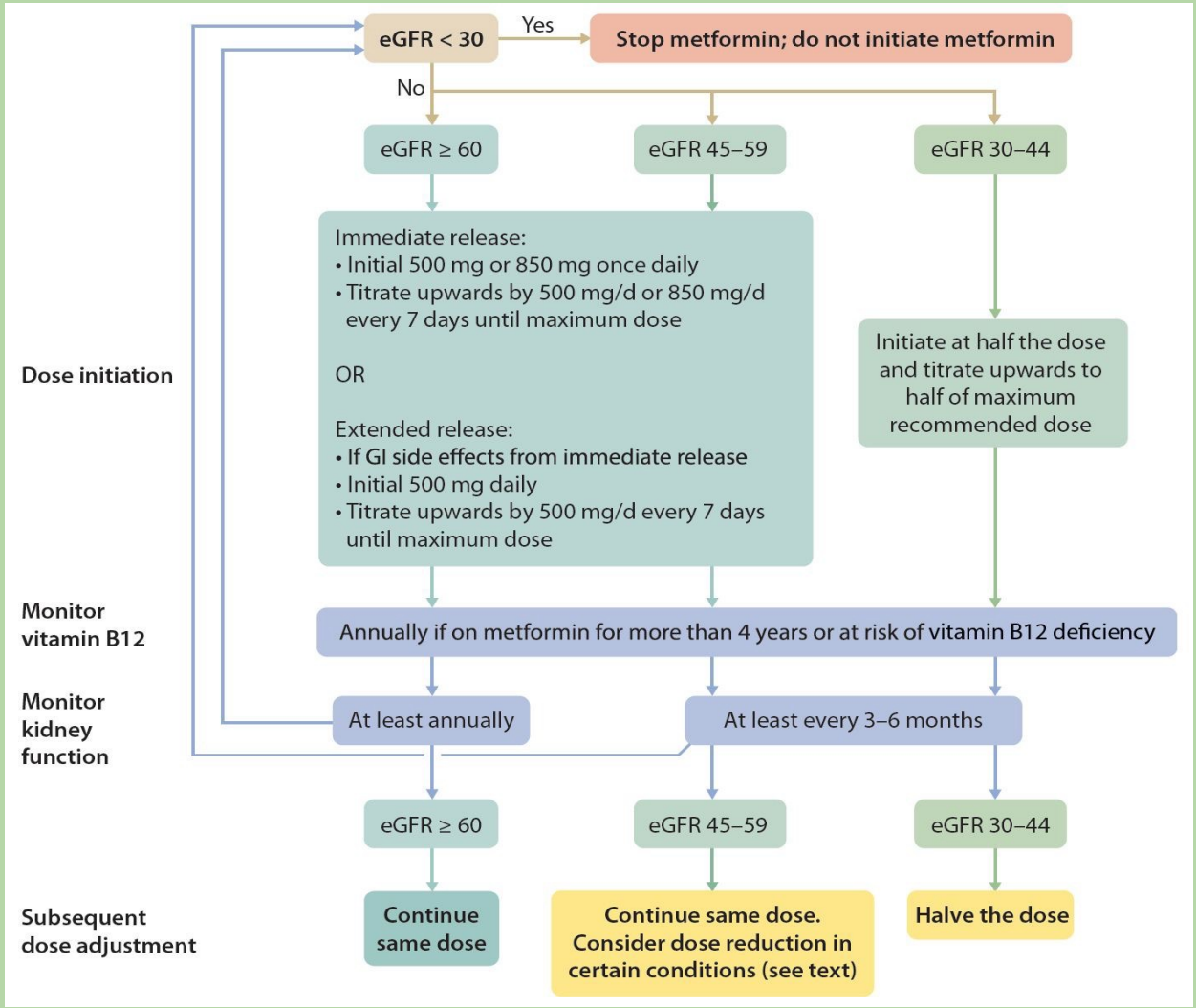
2.2.1: Target ranging from <6.5% to < 8.0% in patient with diabetes and CKD not on dialysis (1C)

< 6.5%	HbA1c	< 8.0%
CKD G1	Severity of CKD	CKD G5
Absent/minor	Macrovascular complications	Present/severe
Few	Comorbidities	Many
Long	Life expectancy	Short
Present	Hypoglycemia awareness	Impaired
Available	Resources for hypoglycemia management	Scarce
Low	Propensity of treatment to cause hypoglycemia	High

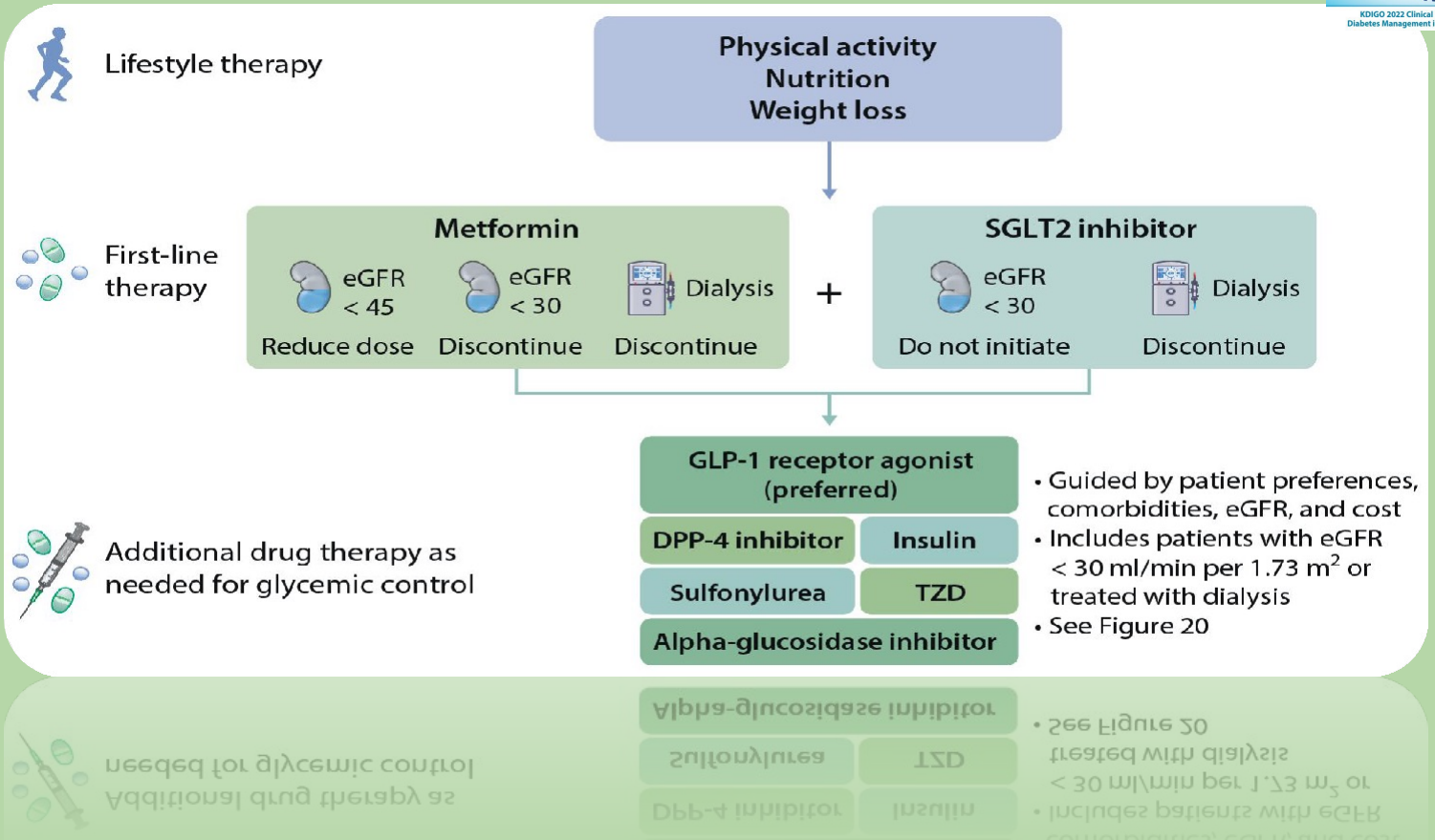
Glucose lowering therapies in T2D and CKD

4.1.1: We recommend treating patients with T2D, CKD, and an **eGFR >=30 ml/min per 1.73 m2 with metformin (1B)**

Formulation	Dosage forms	Starting dose	Maximum dose
Metformin, immediate release	Tablet, oral: 500 mg, 850 mg, 1000 mg	500 mg once or twice daily OR 850 mg once daily	Usual maintenance dose: 1 g twice daily OR 850 mg twice daily Maximum: 2.55 g/d
Metformin, extended release	Tablet, oral: 500 mg, 750 mg, 1000 mg	500 mg once daily OR 1 g once daily	2 g/d


eGFR < 30
Yes
Stop metformin; do not initiate metformin
No
eGFR ≥ 60
eGFR 45–59
eGFR 30–44
Dose initiation
Immediate release:
• Initial 500 mg or 850 mg once daily
• Titrate upwards by 500 mg/d or 850 mg/d every 7 days until maximum dose
OR
Extended release:
• If GI side effects from immediate release
• Initial 500 mg daily
• Titrate upwards by 500 mg/d every 7 days until maximum dose
Initiate at half the dose and titrate upwards to half of maximum recommended dose
Monitor vitamin B12
Annually if on metformin for more than 4 years or at risk of vitamin B12 deficiency
Monitor kidney function
At least annually
At least every 3–6 months
eGFR ≥ 60
eGFR 45–59
eGFR 30–44
Subsequent dose adjustment
Continue same dose
Continue same dose. Consider dose reduction in certain conditions (see text)
Halve the dose

Glucose Control in T2D & CKD

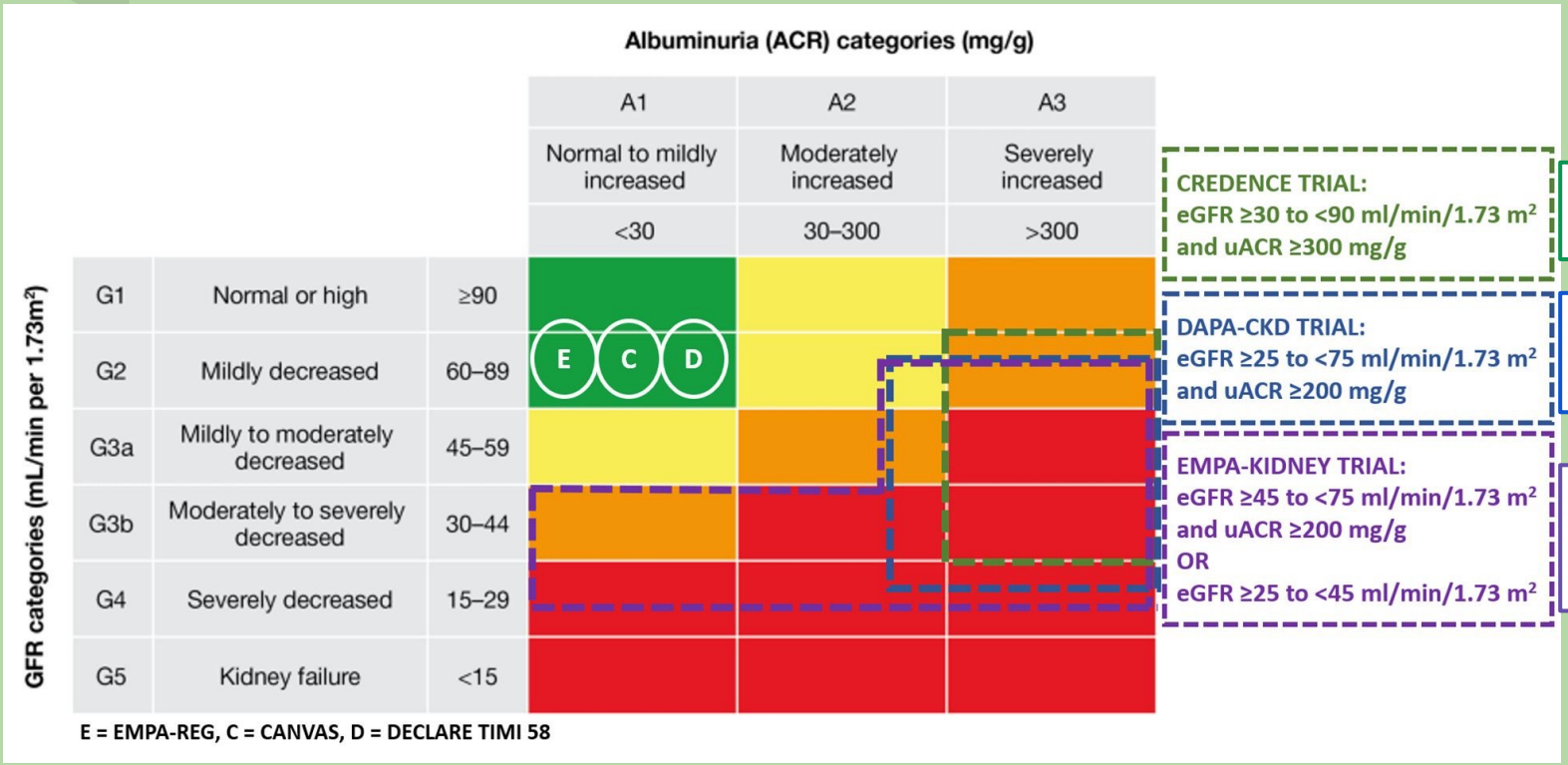


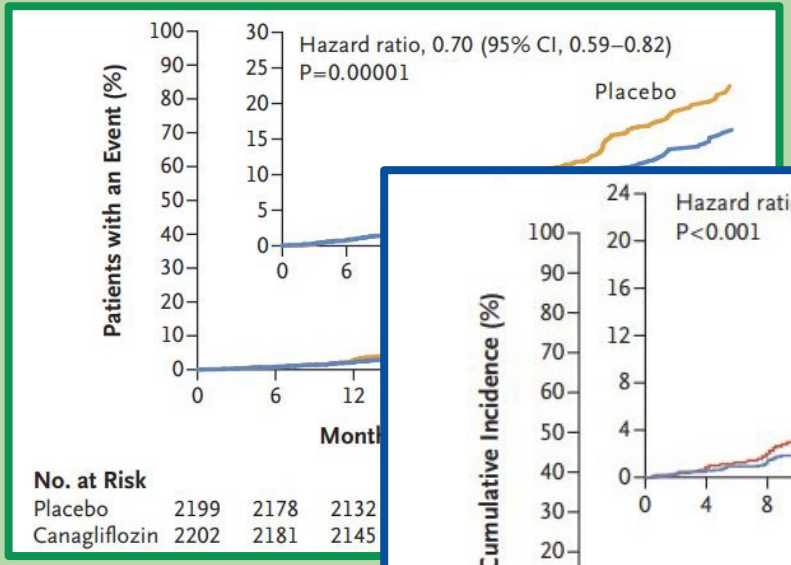
Glucose lowering therapies in T2D and CKD

1.3.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an **eGFR >= 20 ml/min per 1.73 m2 with an SGLT2 inhibitor (1A)**

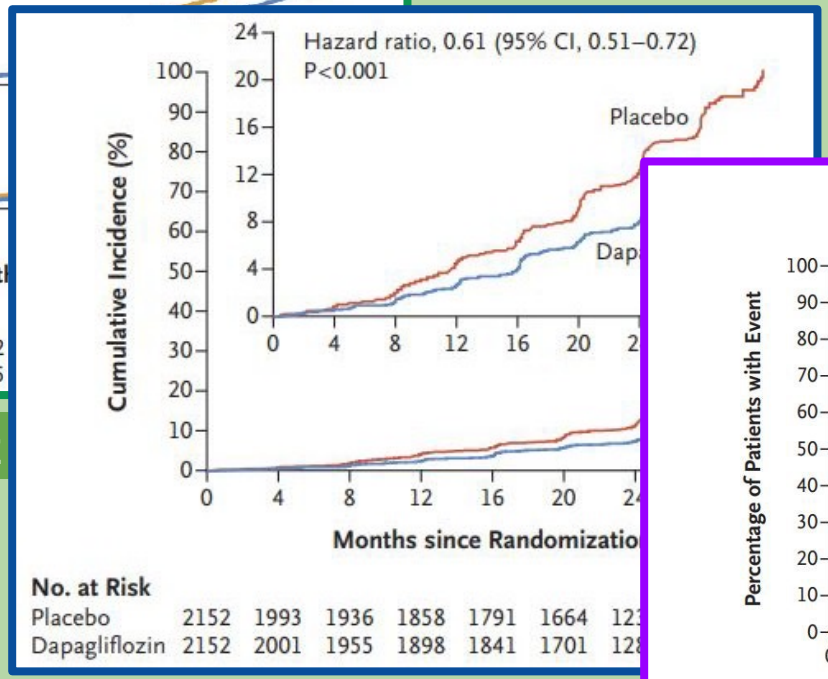
CREDENCE (Apr 2019)	DAPA-CKD* (Sept 2020)	EMPA-KIDNEY* (Nov 2022)
Canaglifozin 100mg QD	Dapaglifozin 10mg QD	Empaglifozin 10mg QD
4,401 participants, 2.6 years	4,304 participants, 2.4 years	6,609 participants, 2.0 years
End stage kidney disease, doubling of SCr, or death from kidney or CV causes	**Sustained decline in eGFR >=50%, end stage kidney disease, or death from kidney or CV causes**	**Kidney disease progression (ESKD, sustained decline in eGFR <10 ml/min, sustained decline eGFR >=40% or renal death) or CV death**

Landmark RCT with SGLT2 inhibitors

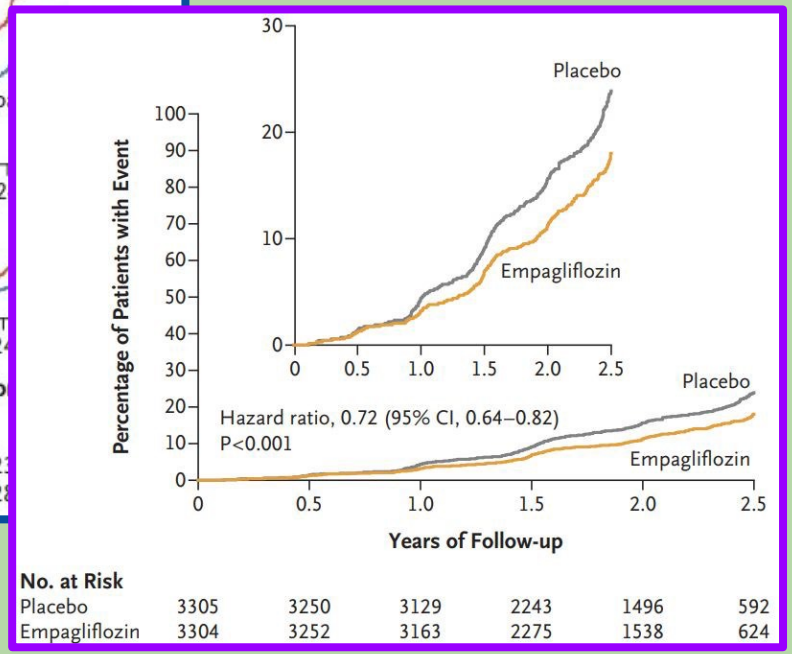




CREDENCE



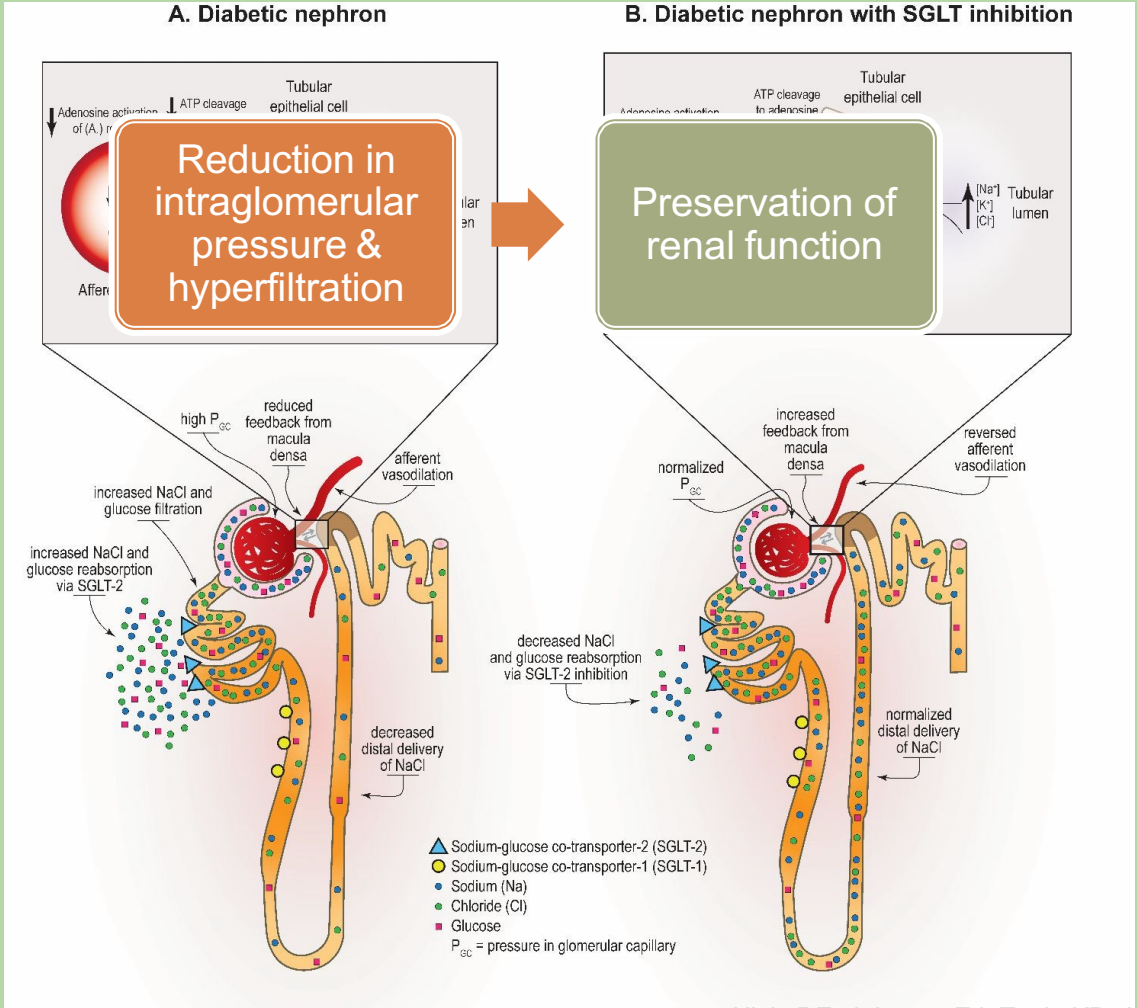
DAPA -CKD



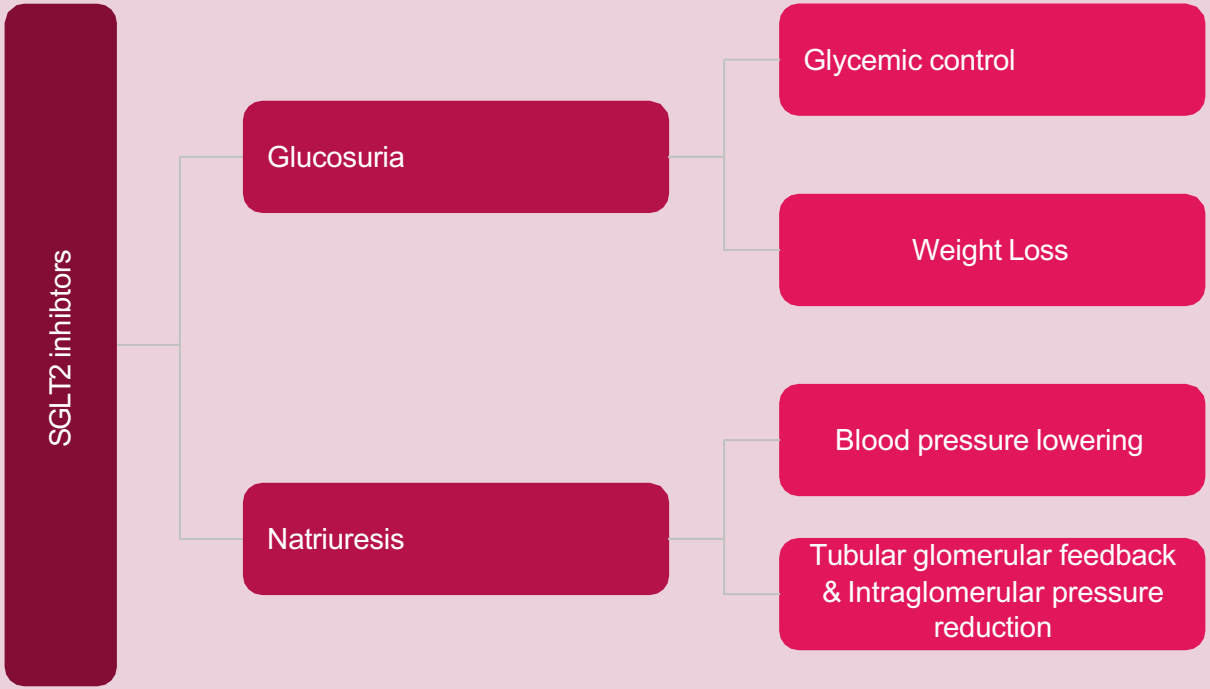
EMPA-KIDNEY

Risk of primary composite outcomes was lower in the canaglifozin (30%), dapaglifozin (39%) and empaglifozin (28%) groups compared to placebo groups.

SGLT2 Inhibitors



Alicic RZ, Johnson EJ, Tuttle KR. Am J Kidney Dis 2018;72:267-277



Alicic RZ, Johnson EJ, Tuttle KR. Am J Kidney Dis 2018;72:267-277

Do SGLT-2 inhibitors slow the progression of CKD in patients with diabetic nephropathy?

CREDENCE

34 Countries
690 Sites

Mean Age: 63 years, 33% Women

Type 2 DM
Mean Hba1c: 8.3%

eGFR 30 to 90 mL/min
Mean eGFR 56.2 mL/min

UACR
300 - 5000 mg/g
Median UACR 927 mg/g

Max tolerated dose of ACEi or ARB

100 mg
CANAGLIFLOZIN
+ Standard of care
n=2201

N=4401

P
PLACEBO
+ Standard of care
n=2219

	ESRD, Doubling of Crea, Renal & CV Death	Renal Composite Outcome	ESRD	Doubling of Creatinine	CV Death
Canagliflozin	11.3%	7.0%	5.4%	5.3%	5.0%
Placebo	15.5%	10%	8.5%	7.5%	6.4%
HR (95% CI)	0.70 (0.59-0.82)	0.66 (0.53-0.81)	0.68 (0.54-0.86)	0.60 (0.48-0.76)	0.78 (0.61-1.00)
p-value	p=0.0001	p<0.001	p<0.001	p=0.002	p=0.05

CONCLUSION: In adult patients with Type 2 DM and kidney disease, Canagliflozin reduced kidney failure, cardiovascular events as well as mortality compared to those in placebo.

Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306. doi: 10.1056/NEJMoa1811744. Epub 2019 Apr 14. PMID: 30990260.

Visual Abstract by: Ana Naidas, MD ananaidas@gmail.com

DIVISION OF NEPHROLOGY
Philippine General Hospital

Does Dapagliflozin compared to placebo reduce the risk of kidney failure and CV events in CKD patients with and without T2DM?

DAPA-CKD

21 Countries
286 Centers

≥ 18 yo

eGFR ≥ 25 to ≤ 75ml/min

UACR ≥ 200 to ≤ 5000mg/g

Max tolerated dose of ACEi/ARB

With and without T2DM

Mean Age 62y, 67% ♂
eGFR 43ml/min
UACR 949mg/g
ACEi/ARB 97%
With T2DM 67.5%

MEAN FOLLOW-UP: 2.4 YEARS

DAPAGLIFLOZIN
+STANDARD CARE
N=2152

N=4304

PLACEBO
+STANDARD CARE
N=2152

Sustained ≥ 50% decline in GFR, ESKD, Renal or CV Death	Sustained ≥ 50% decline in GFR, ESKD, Renal Death	CV Death or hHF	All-cause Mortality
9.2%	6.6%	4.6%	4.7%
HR 0.61 (95% CI 0.51-0.72) p<0.001 NNT=19	HR 0.56 (0.45-0.68) p<0.001	HR 0.71 (0.55-0.92) p=0.009	HR 0.69 (0.53-0.88) p=0.004
14.5%	11.3%	6.4%	6.8%

Benefit of Dapagliflozin on primary end-point was consistent in patients with and without T2DM
% of patients who discontinued the drug or who experienced SAE was similar in both groups
DKA, 2 in placebo group vs none in Dapagliflozin group
No DKA or severe hypoglycemia in patients without T2DM

CONCLUSION: Dapagliflozin compared to placebo significantly reduced the risk of kidney failure, CV death or hospitalization for HF and all-cause mortality in patients with CKD with and without T2DM. Dapagliflozin was well-tolerated, in keeping with its established safety profile.

DAPA-CKD
Heerspink et al (2020). Dapagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine.* September 24,2020
DOI: 10.1056/NEJMoa2024816
Visual Abstract by: Ana Naidas, MD

Empagliflozin in Patients with Chronic Kidney Disease (EMPA-KIDNEY)

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Multicenter
- 241 centers
- 8 countries

Double-blind

6,609 patients

- eGFR 20 – 45 ml/min/1.73m2 Regardless of the level of albuminuria
- eGFR 45 – 90 ml/min/1.73m2 UACR >200

Feb 2019 – Apr 2021

Pre-randomization phase 15wks of placebo

Empagliflozin 10mg/day

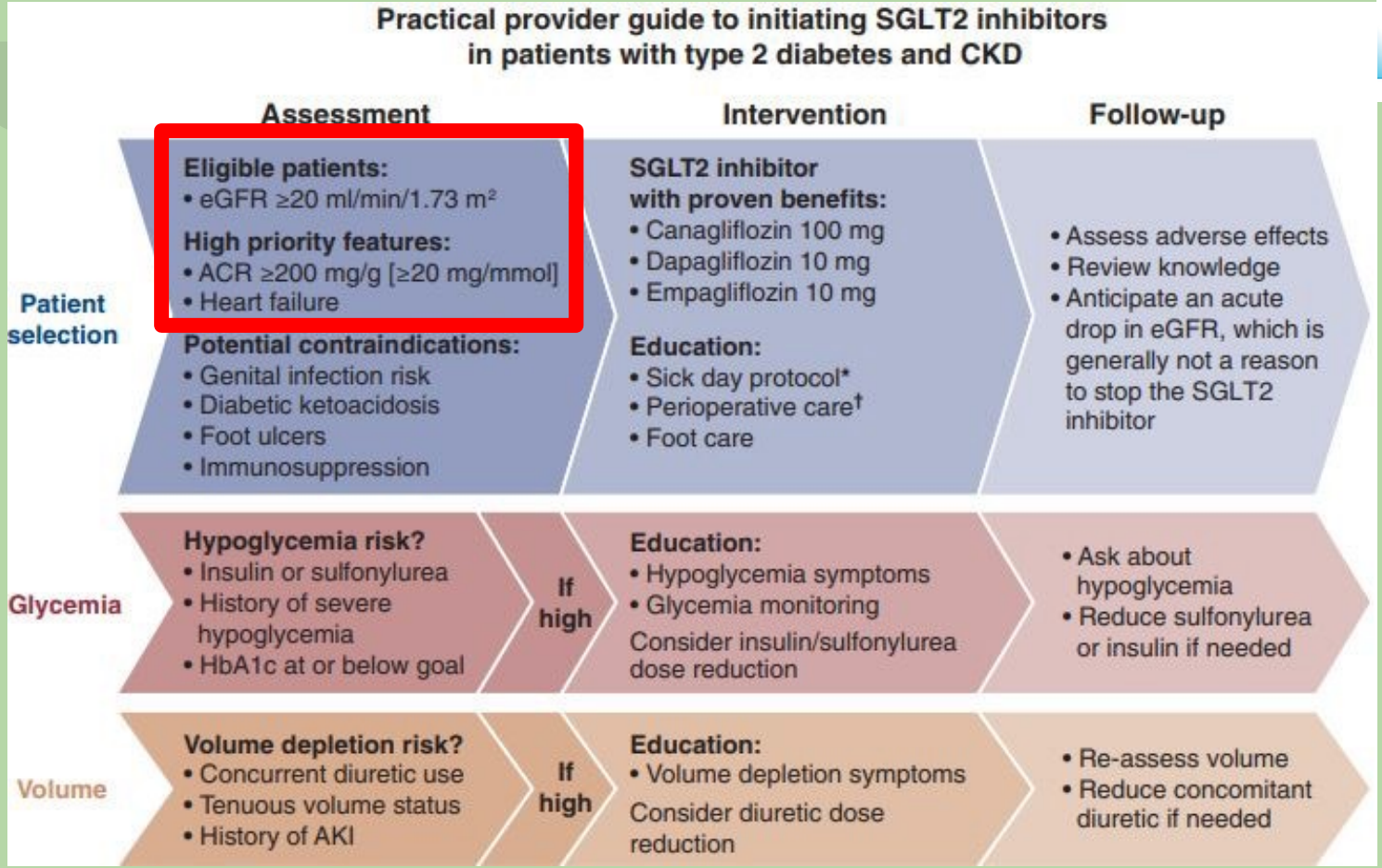
Placebo

CKD progression & death from CV causes	Hospitalizations from any cause	Hospitalization for HF or death from CV causes	Death from any cause
13.1%	24.8% per 100 patients/year	4.0%	4.5%
0.72 (0.64 – 0.82, P<0.001)	0.86 (0.78 – 0.95, P = 0.003)	0.84 (0.67 – 1.07, P = 0.15)	0.87 (0.70 – 1.08, P = 0.21)
16.9%	29.2% per 100 patients/year	4.6%	5.1%

Conclusion: among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo.

Reference: EMPA-KIDNEY Collaborative Group. (2022). Empagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*.

VA by Denisse Arellano, MD @deniise_am


Practical provider guide to initiating SGLT2 inhibitors in patients with type 2 diabetes and CKD
Assessment
Intervention
Follow-up
Patient selection
Eligible patients:
• eGFR ≥20 ml/min/1.73 m²
High priority features:
• ACR ≥200 mg/g [≥20 mg/mmol]
• Heart failure
Potential contraindications:
• Genital infection risk
• Diabetic ketoacidosis
• Foot ulcers
• Immunosuppression
SGLT2 inhibitor with proven benefits:
• Canagliflozin 100 mg
• Dapagliflozin 10 mg
• Empagliflozin 10 mg
Education:
• Sick day protocol*
• Perioperative care†
• Foot care
• Assess adverse effects
• Review knowledge
• Anticipate an acute drop in eGFR, which is generally not a reason to stop the SGLT2 inhibitor
Glycemia
Hypoglycemia risk?
• Insulin or sulfonylurea
• History of severe hypoglycemia
• HbA1c at or below goal
If high
Education:
• Hypoglycemia symptoms
• Glycemia monitoring
Consider insulin/sulfonylurea dose reduction
• Ask about hypoglycemia
• Reduce sulfonylurea or insulin if needed
Volume
Volume depletion risk?
• Concurrent diuretic use
• Tenuous volume status
• History of AKI
If high
Education:
• Volume depletion symptoms
Consider diuretic dose reduction
• Re-assess volume
• Reduce concomitant diuretic if needed

Glucose lowering therapies in T2D and CKD

KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

4.2.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a **long-acting GLP-1 receptor agonists(1B)**

Mechanism of action of GLP-1 RA

- Stimulate insulin release from beta cells
- Suppresses glucagon release from alpha cells
- Slows gastric emptying
- Decreases appetite stimulation in the brain.

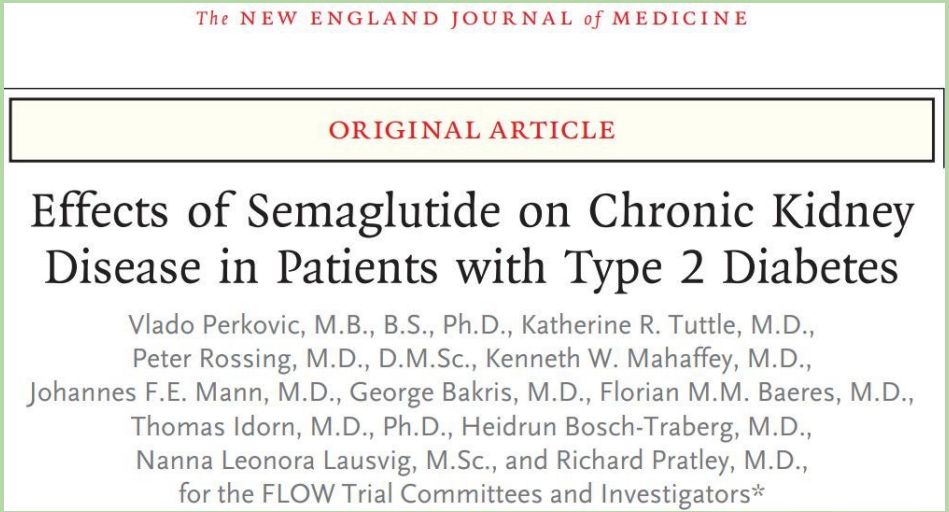
GLP-1 receptor agonists

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with eGFR >45 ml/min per 1.73 m^2
Liraglutide	1.2 mg and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD Not recommended with eGFR <15 ml/min per 1.73 m^2
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

- Improve glycemic control and confer weight loss
- Reduces major adverse cardiovascular events (MACE)
- Kidney benefits by reducing albuminuria and slowing the rate of eGFR decline.

What's new?

FLOW TRIAL



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D.,
Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D.,
Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D.,
Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D.,
Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D.,
for the FLOW Trial Committees and Investigators*

FLOW Trial

Stopped early for clear positive efficacy!

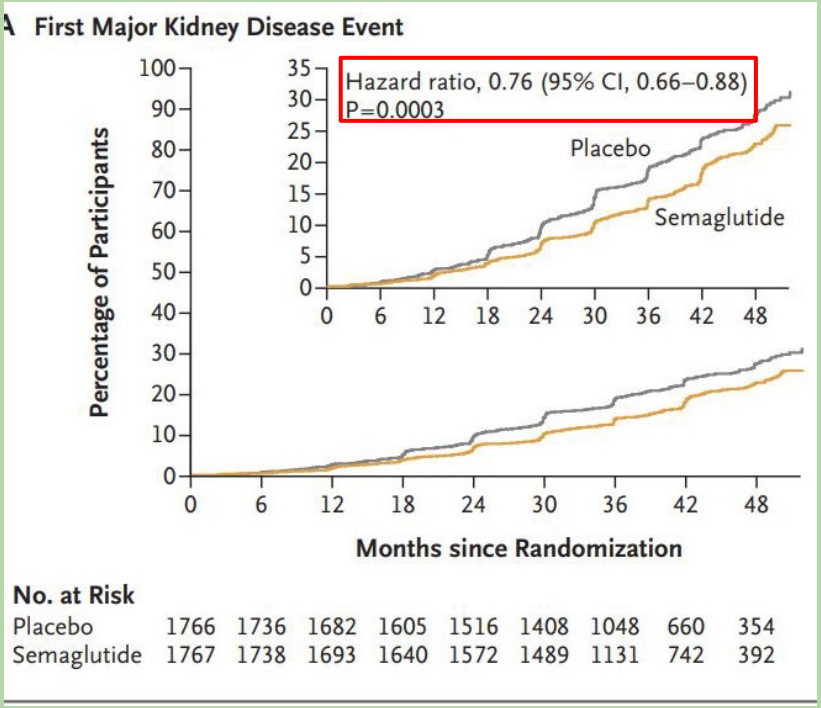
3160 patients

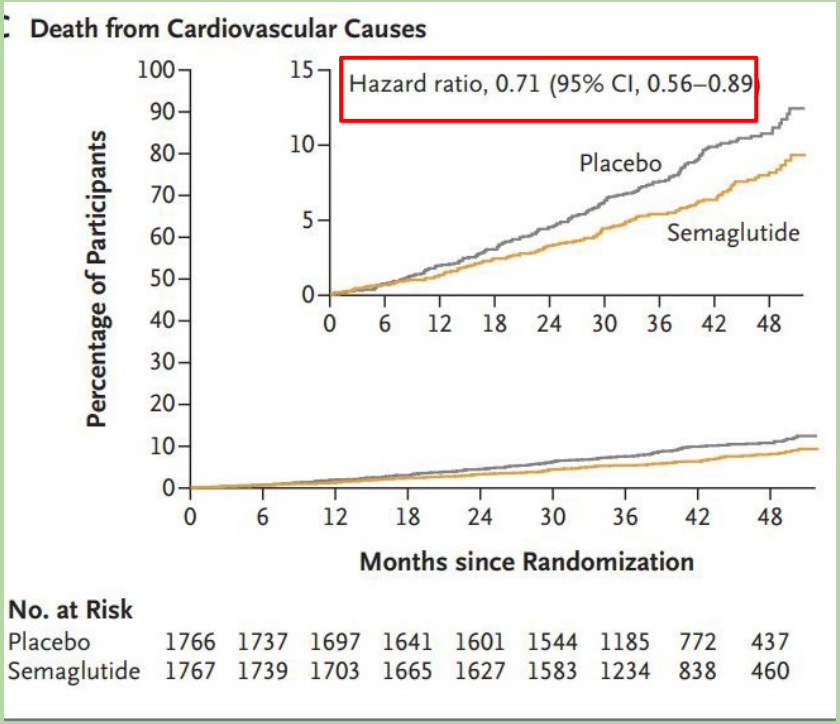
- T2D, HbA_{1c} ≤10%
- eGFR ≤75 to ≥50* and UACR >300 to <5000 mg/g *OR*
  eGFR <50 to ≥25* and UACR >100 to <5000 mg/g
- RAAS blocker

Primary endpoint

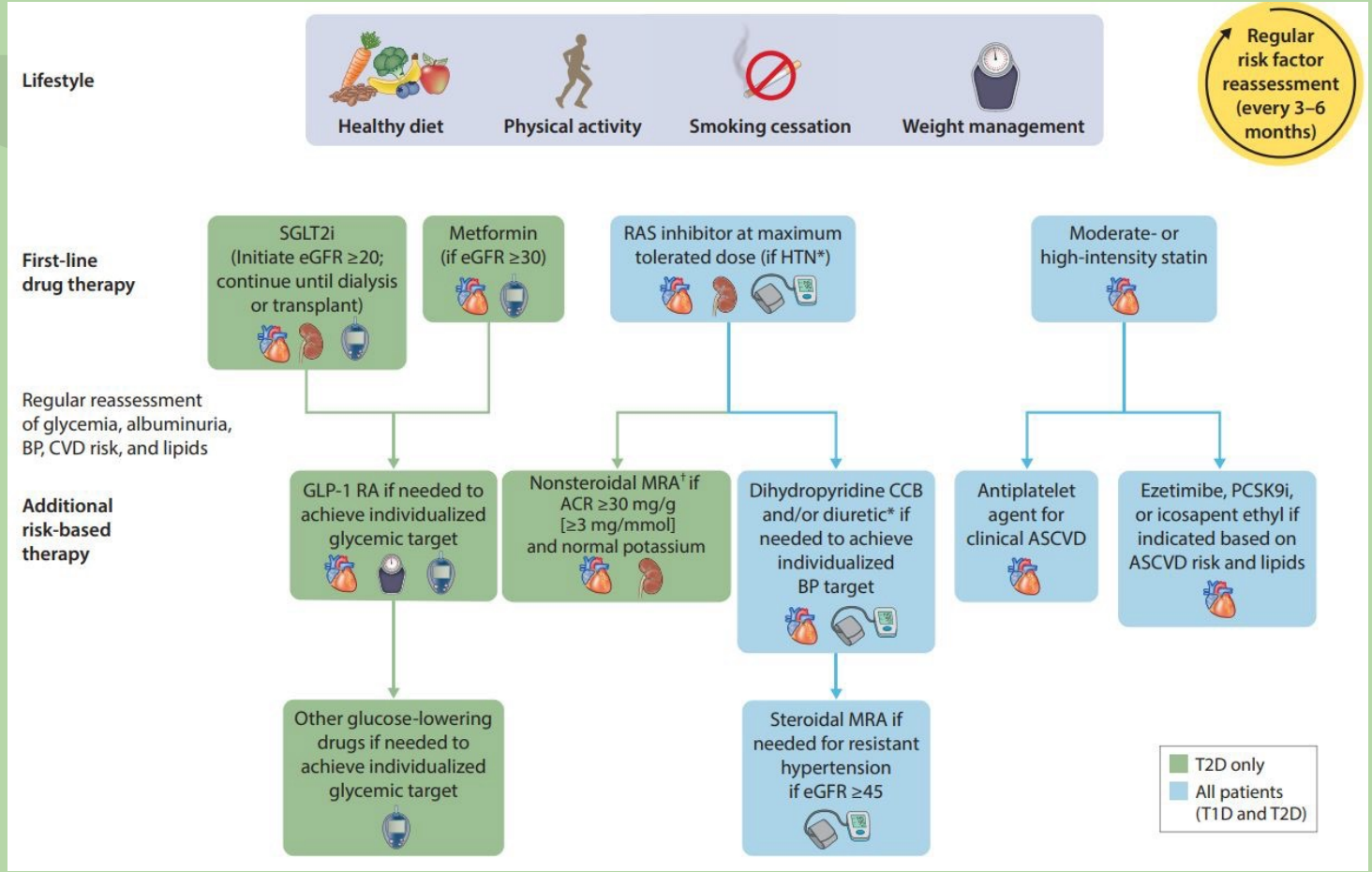
Time to first occurrence of a composite endpoint consisting of

- Onset of persistent ≥50% reduction in eGFR
- Onset of persistent eGFR <15 mL/min/1.73 m^2
- Initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
- Renal death
- CV death





Semaglutide reduced the risk of clinically important kidney outcomes (24%) and death from cardiovascular causes (29%) in patients with type 2 diabetes and CKD.



KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

Considerations for selecting glucose-lowering agents

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022;45:3075–3090 |

Dose adjustments for eGFR <45 mL/min/1.73 m2

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
DPP-4 inhibitors			
Alogliptin	Maximum 12.5 mg daily	Maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Maximum 2.5 mg daily		
Sitagliptin	Maximum 50 mg daily	Maximum 25 mg once daily	
Sulfonylureas (2nd generation)			
Glimepiride	Initiate conservatively at 1 mg daily and titrate slowly to avoid hypoglycemia		
Glipizide	Initiate conservatively (e.g., 2.5 mg once daily) and titrate slowly to avoid hypoglycemia		
Glyburide	Use not recommended		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Use not recommended	
Miglitol	No dose adjustment required	Use not recommended	
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		

Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022;45:3075–3090 |

Conclusions

- DKD is the major cause of end stage kidney disease in the world and the number of patients is expected to rise in the coming years.
- Early detection and management of DKD is essential for improving cardiovascular outcomes.
- A comprehensive care in the management of DKD is needed and must include pharmacotherapy and healthy lifestyle approaches.
- There is a critical need for patients to be treated in accord with the most up-to-date recommendations.

Thankyou!

World Kidney Day
14 MARCH 2024