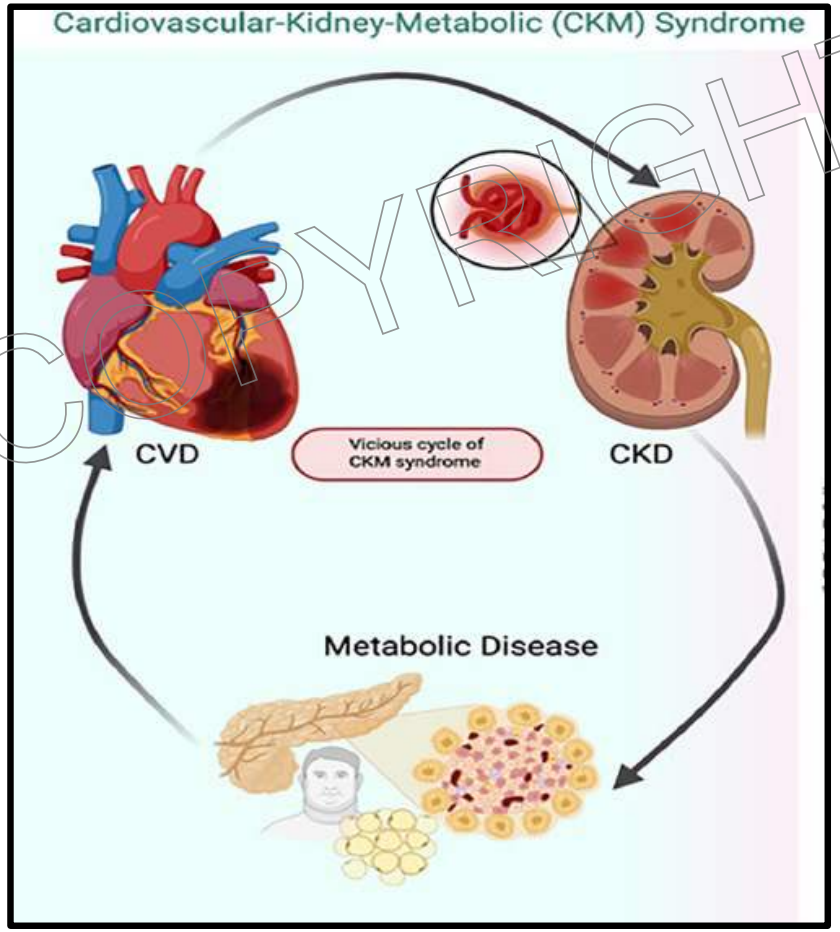
Optimizing Renal Protection in People with Diabetes

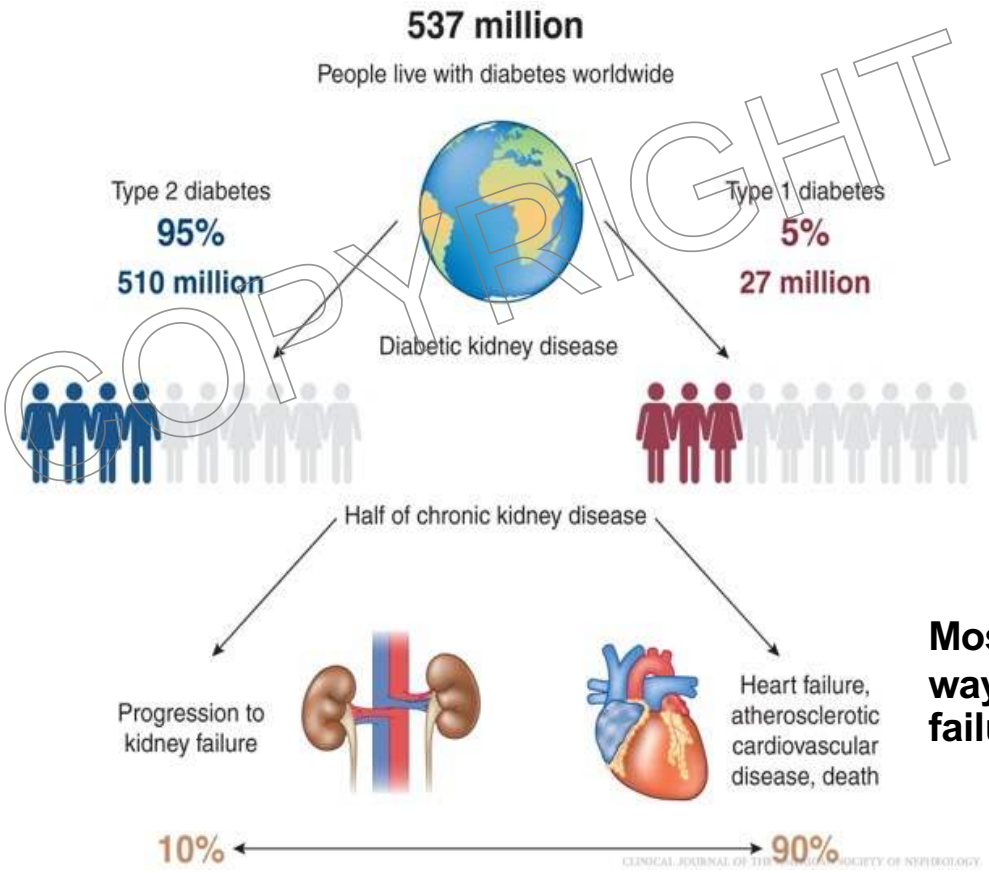
Regional training centre



A/professor Nicci Wearne
Groote Schuur Hospital
Cape Town
South Africa

Sebastian, S.A., et al (CKM): A state-of-the-art review. Current problems in cardiology, 2024

Prevalence of diabetes (2021)



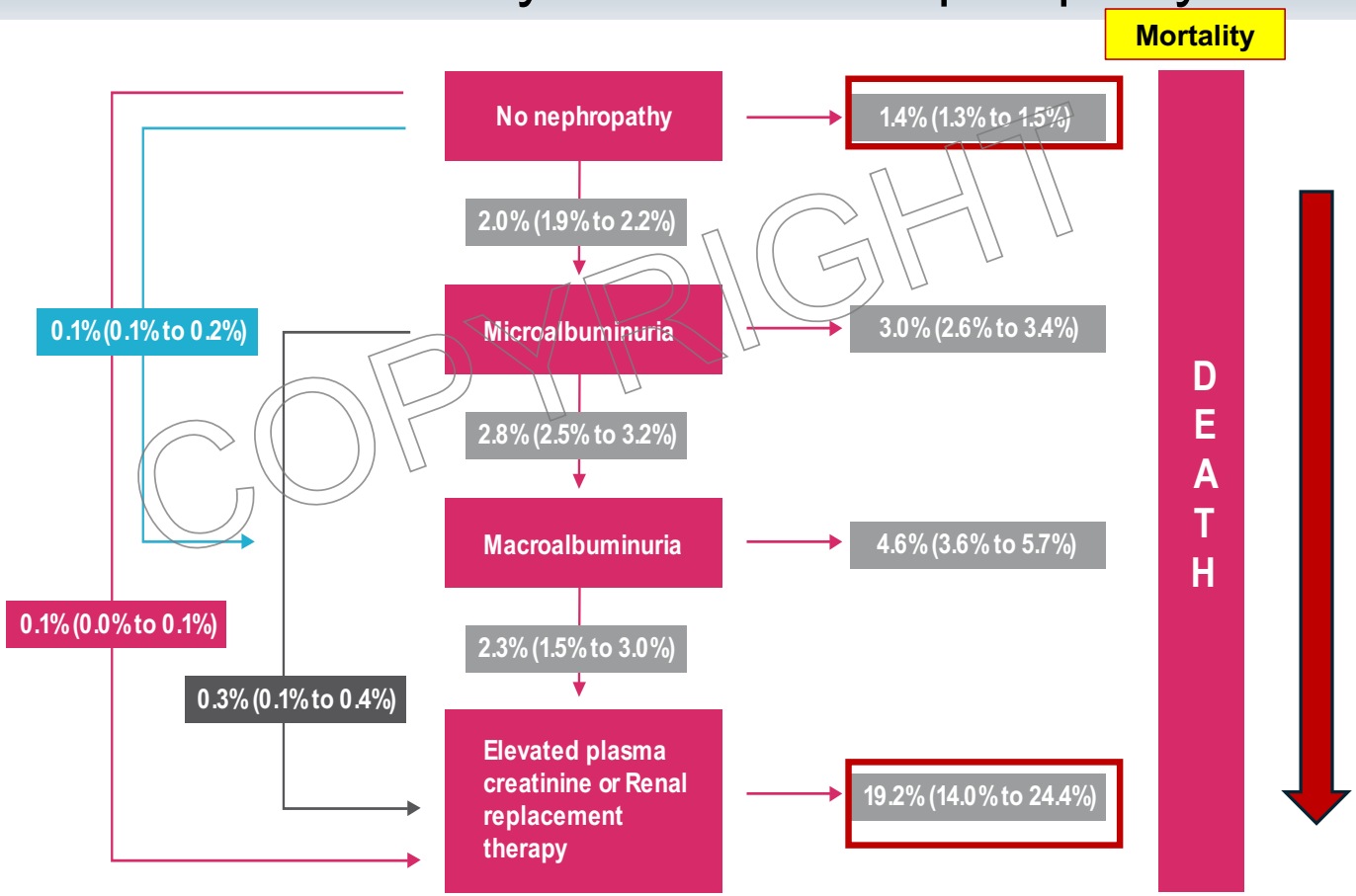
<u>40% of T2DM</u> develop DKD: Most common cause of CKD globally

<u>30%</u> <u>of type 1</u> diabetics develop DKD

Most die on the way to kidney failure from CVD

Tuttle, K, et al behalf of the Diabetic Kidney Disease Collaborative Task Force Clinical Journal of the American Society of Nephrology17(7):1092-1103, July 2022

Natural History of Diabetic Nephropathy

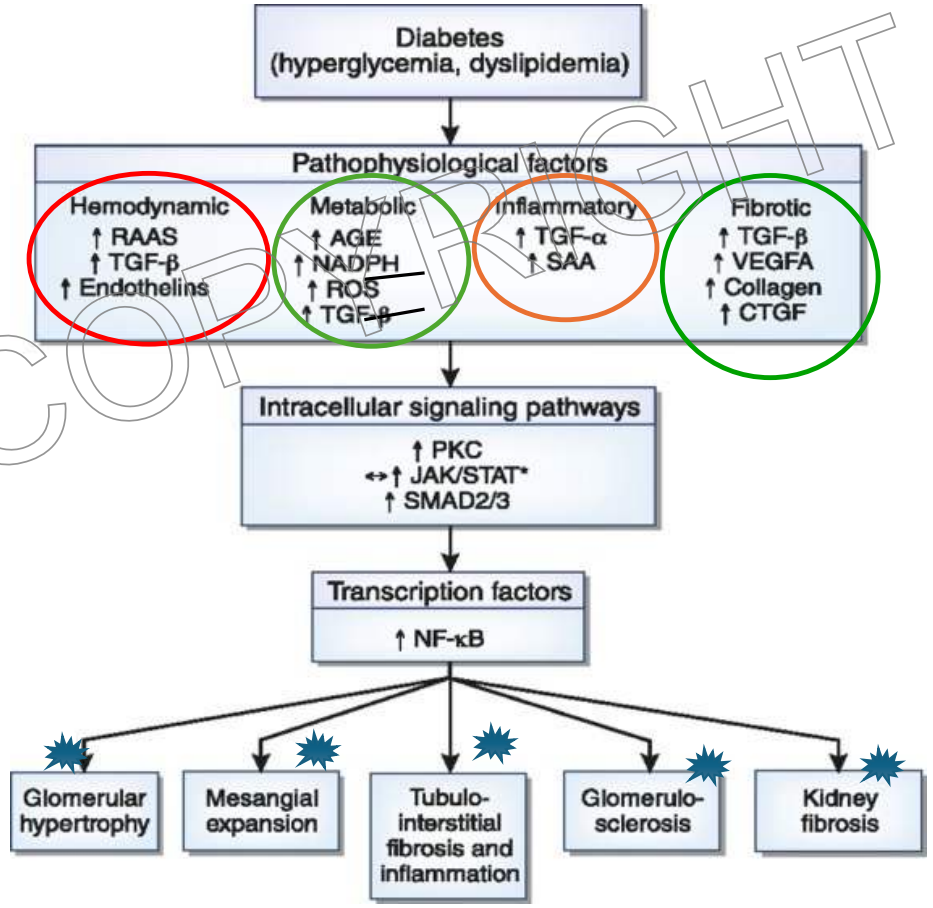


Annual transition rates (with 95% confidence intervals) through stages of diabetic nephropathy (UKPDS) with mortality.

Adapted from: 2. Adler AI et al. Kid Int. 2003;63:225-232. UKPDS 64.

DM Nephropathy Pathophysiology

Hemodynamic effects are central to the maintenance of nephron homeostasis & center around RAAS.



Radica Z. Alicic et al. CJASN 2017

Measurement of Albuminuria

- Normal albuminuria < 30 mg/24 hours
- Micro albuminuria **30-299** mg/24 hours
- Macroalbuminuria ≥ 300mg /24 hours

Levels exceeding **30 mg/day** predict adverse CV outcomes

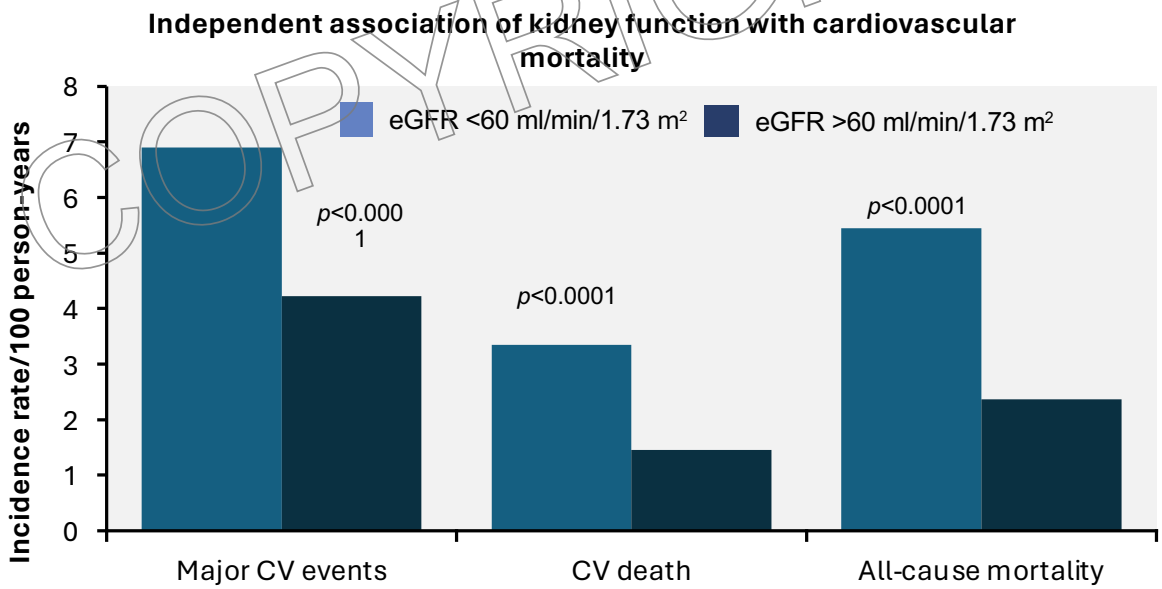
Levels exceeding **300mg/day** are typically diagnostic of underlying DKD and are associated with an accelerated decline in kidney function. (1,2)

Once there is proteinuria on the dipstix – there is macroalbuminura

1. Bakris GL et al. Diabetes Care 2014
2. Patel RB, et al. JAMA Cardiol 2020

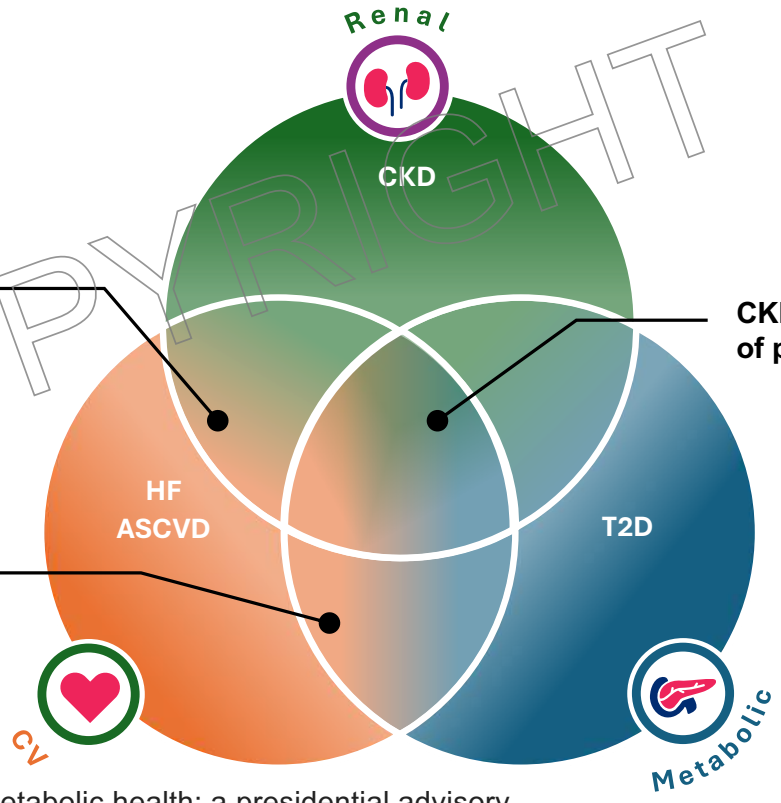
CKD increases the risk of heart attacks, strokes, and early death.

CV death causes 40–50% of deaths in advanced CKD/ESKD vs 26% with normal kidney function.



Jankowski J *et al. Circulation* 2021;143:1157

New terminology :Cardiovascular-Kidney and Metabolic Syndrome (CKM)[1]



T2D and hypertension are the leading causes of ESKD worldwide (>80%)[2]

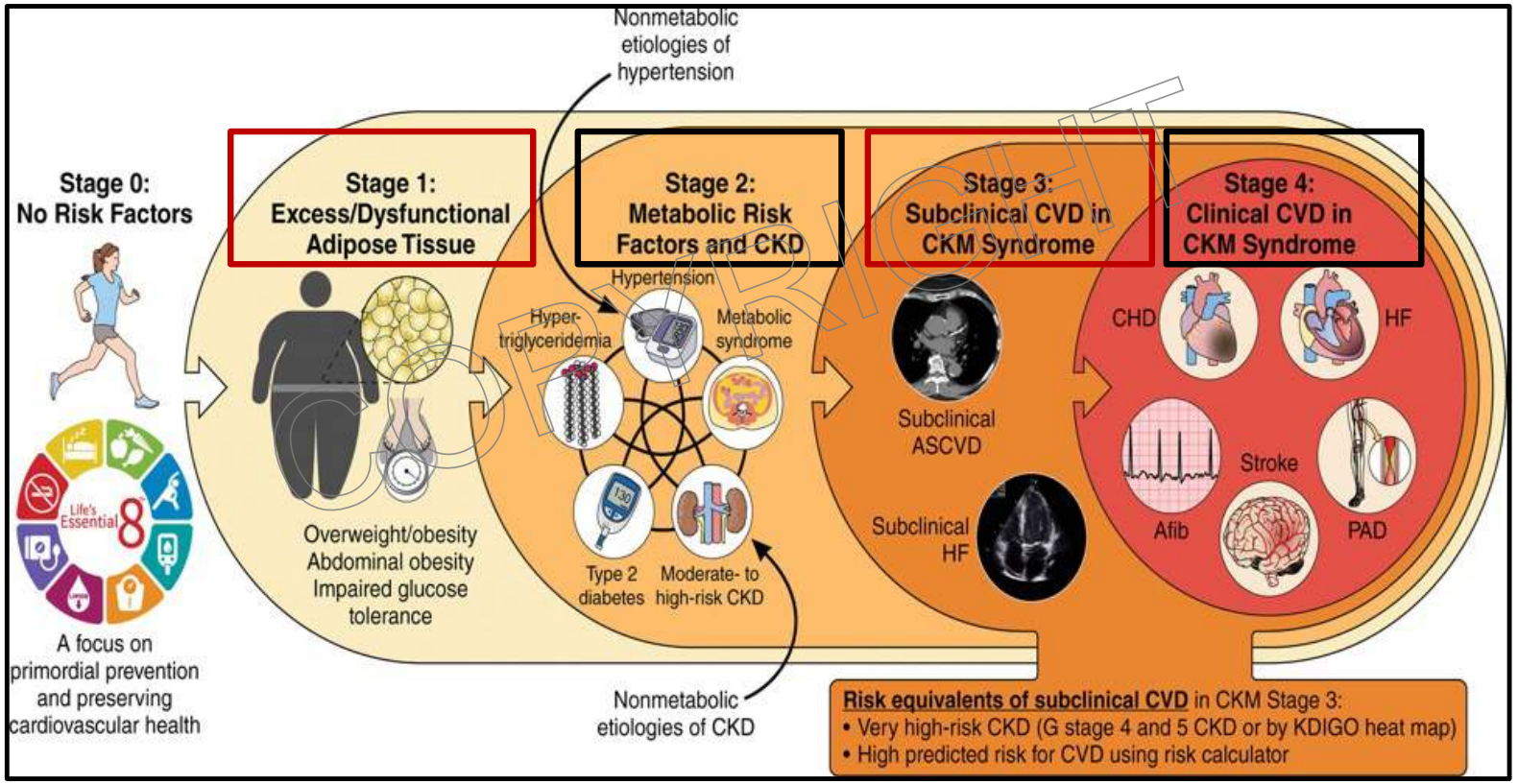
CKD affects up to 40% of people with T2D[2,3]

At least **30% of people with T2D** have CV disease[4]

ASCVD, atherosclerotic cardiovascular disease;

1. Ndumele, C.E.et al, Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*, 2023
2. IDF Diabetes Atlas. 9th edn. 2022.
3. Centres for Disease Control and Prevention. National Diabetes Statistics report
4. Einarson TR *et al. Cardiovasc Diabetol* 2018

Stages of CKM syndrome



Ndumele, C.E.et al, Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*, 2023.

Transforming Diabetes Care: A Paradigm Shift in Outcomes

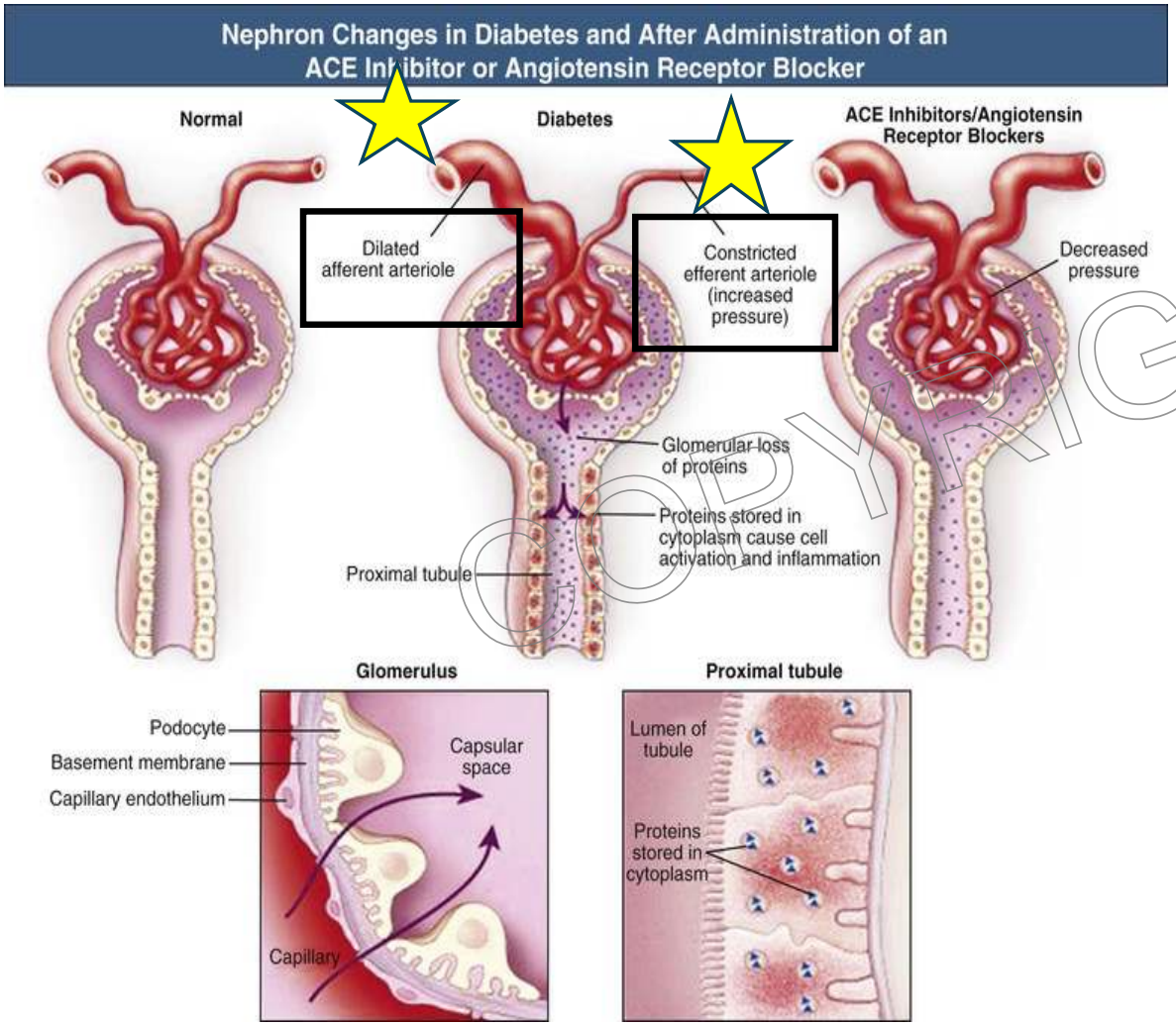
- Diabetes management has evolved, offering new hope for patients.
- Emerging therapies now demonstrate **cardiovascular protection** and effectively slow the **progression of diabetic kidney disease (DKD)**.
- These innovations not only improve survival but also enhance quality of life

RAAS blockade

Since its initial discovery, RAAS blockade has remained a cornerstone of DKD management – *The first trials were performed with captropril on type 1 diabetes*

Many studies now showing that inhibition of RAAS decreases progression of diabetic nephropathy

- ACE inhibitors
- ARBs



RAAS blockade has remained a cornerstone of DKD management

However: despite RAAS blockade there still remains a large component of residual risk.

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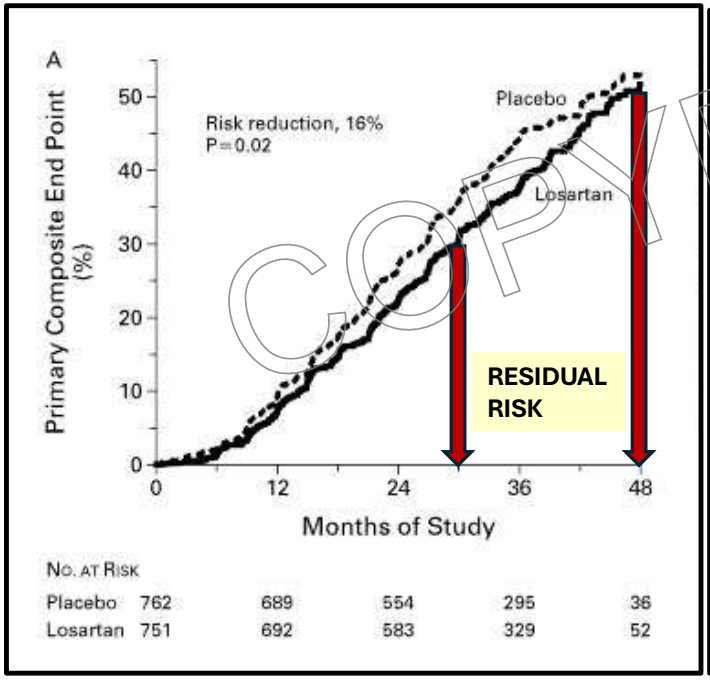
[1] Feehally et al. Comprehensive Clinical nephrology, 2000

Angiotensin receptor blockade in type 2 diabetes and CKD; composite endpoint of doubling of serum creatinine, ESKD or death

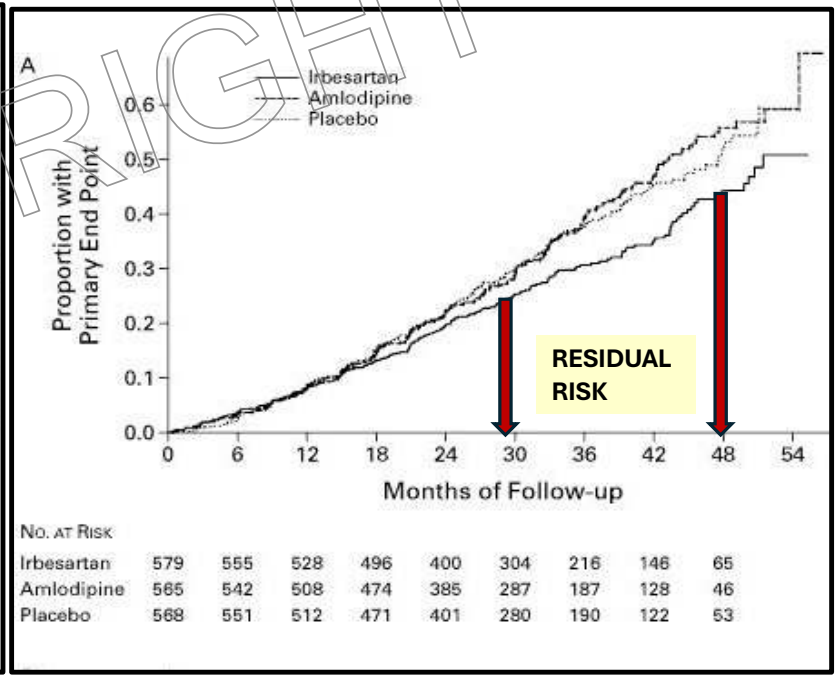
RENAAL- Losartan



2.5 & 4 year absolute residual risk:
~30 % - ~45%

Brenner et al. NEJM 2001;345 (861-869)

IDNT- Irbesartan

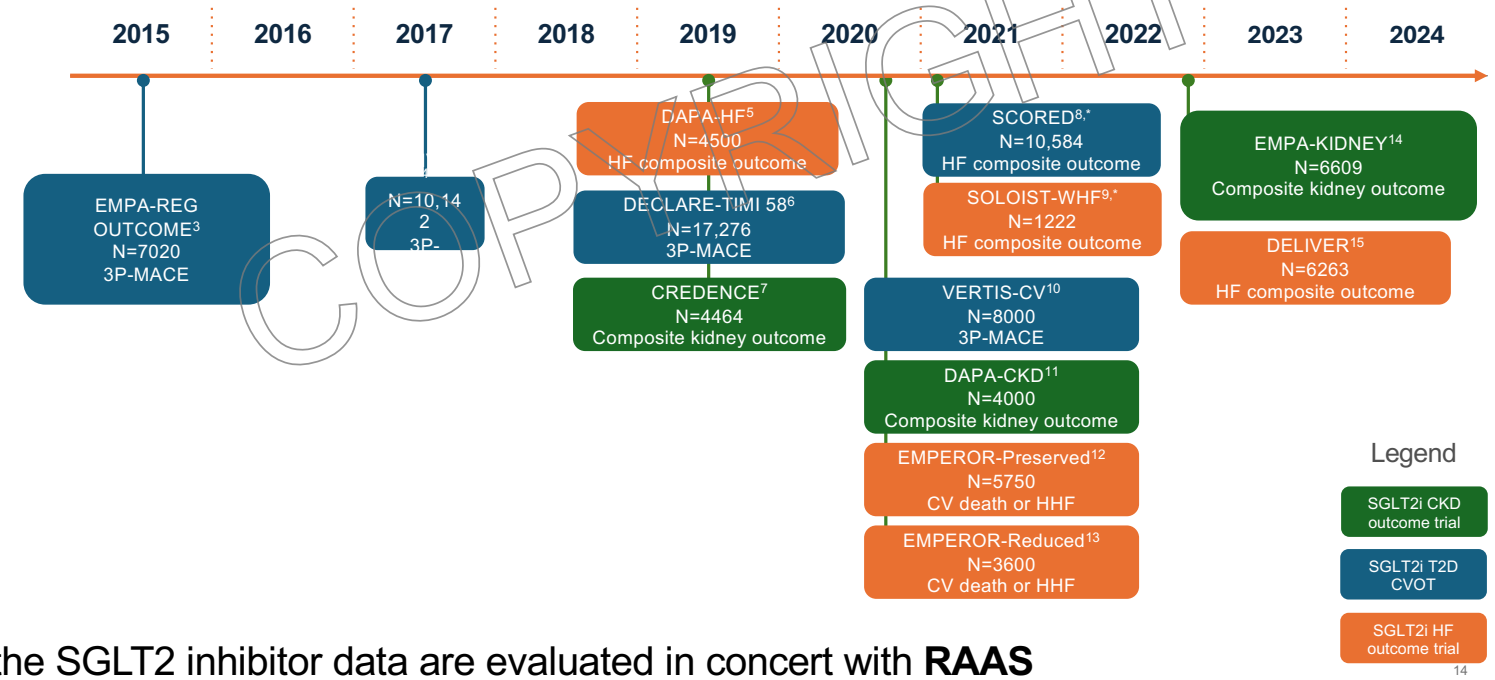


2.5 and 4 year absolute residual risk:
~25 % - ~40%

Lewis et al. NEJM 2001;345 (851-860)

- SGLT inhibitors the gift that keeps giving

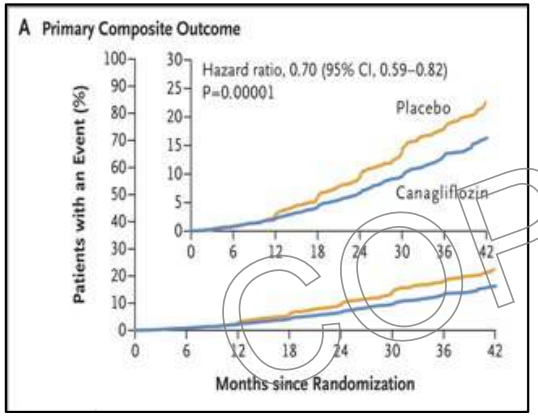
Since 2015, SGLT2 inhibitor trials have enrolled over 90,000 participants and have demonstrated both CV protection and, slowing of DKD progression.

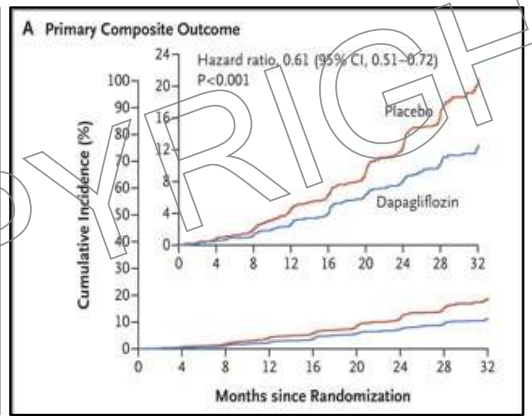


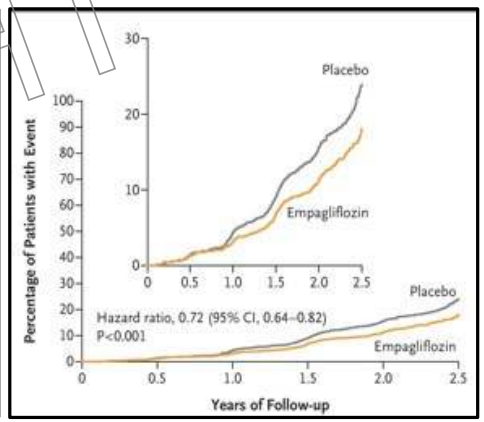
When all the SGLT2 inhibitor data are evaluated in concert with **RAAS inhibition**, kidney function decline is diminished by **~30–40%** above those of ACEI/ARB use alone.

The trilogy of SGLT2 inhibitors: <u>all trials stopped early due to benefit</u>

Primary outcomes: substantial eGFR decline (40%,50% or 57%), kidney failure or death due to kidney or cardiovascular causes;







Credence: Adults with **T2DM** eGFR≥ 30mls/min/1.73m^2 UACR>300mg/g N=4401

DAPA-CKD: Adults **with and without** T2DM; eGFR≥**<u>25</u>** mls/min/1.73m^2 UACR>200mg/g N=2906

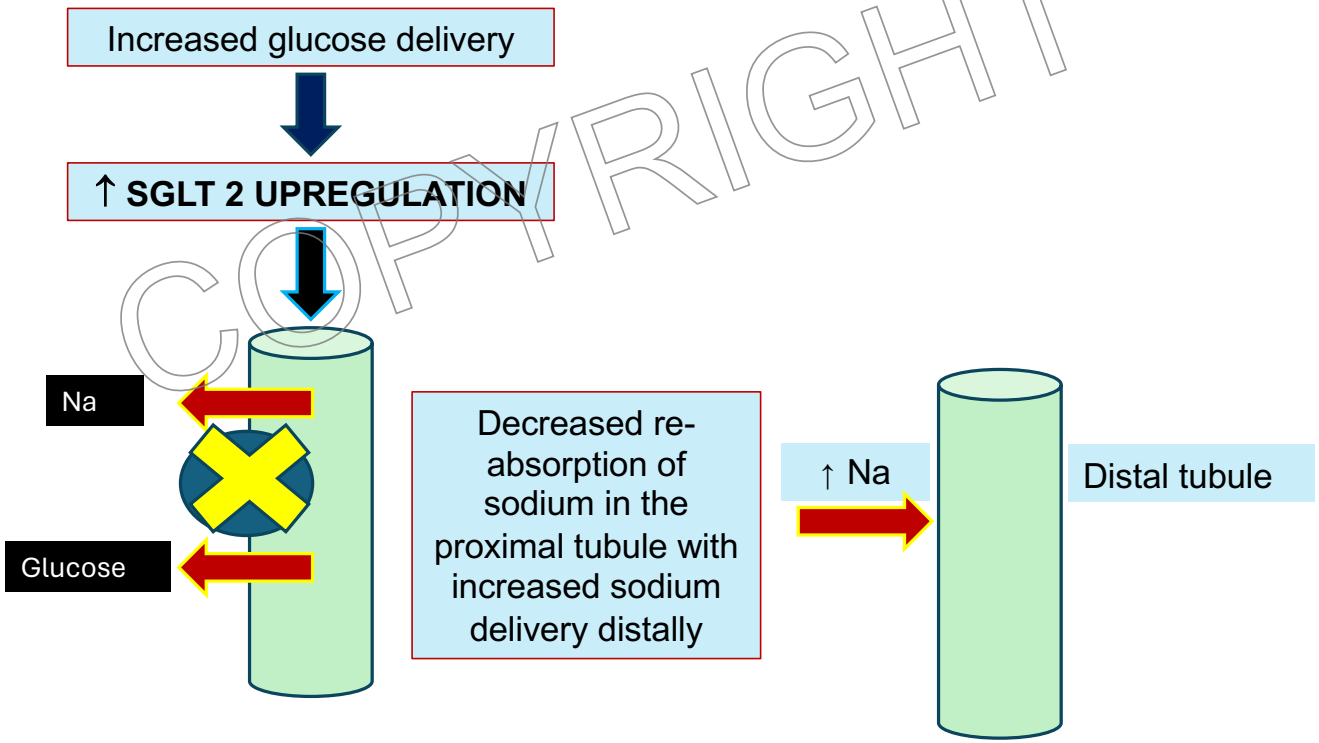
EMPA-KIDNEY: Adults with and without T2DM; eGFR≥**<u>45 TO <90</u>** mls/min/1.73m^2 UACR>200mg/g **or** ≥ to 20 to <45 mls/min/1.73m^2 **irrespective of albuminuria** N= 6609

Perkovic, et al 2019. **Canagliflozin** and renal outcomes in type 2 diabetes and nephropathy. *NEJM 2019*,

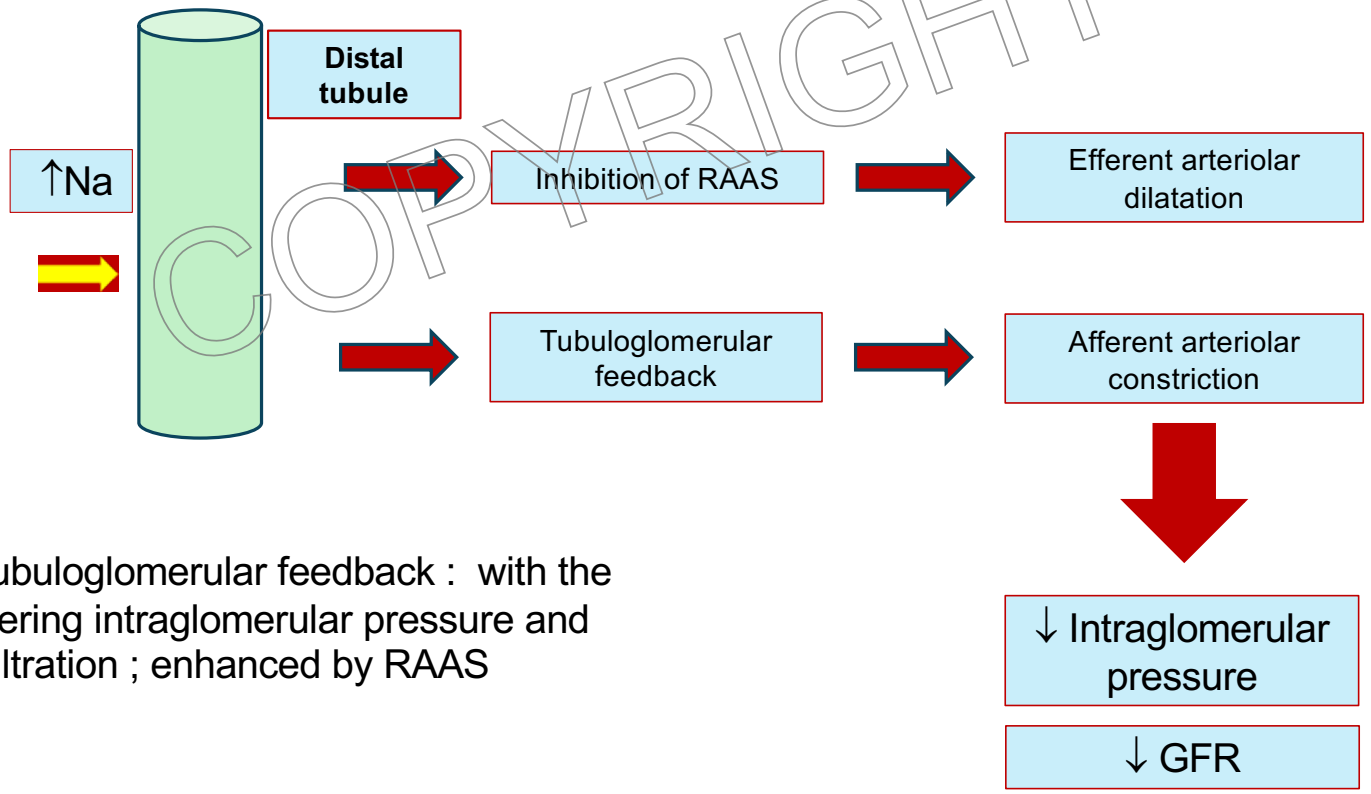
Heerspink, et al 2020. **Dapagliflozi**n in patients with chronic kidney disease. *NEJM 2020*

Herrington, et al 2022. **Empagliflozin** in patients with chronic kidney disease. *NEJM 2022*

How SGLT2 inhibitors protect the kidney



SGLT2 inhibitors protect the kidney



Restoration of tubuloglomerular feedback : with the net effect of lowering intraglomerular pressure and reducing hyperfiltration ; enhanced by RAAS inhibition

Other Hypotheses

- Blood Pressure Lowering
- Reduction in body weight and uric acid levels
- Improved Kidney Oxygenation
- Diuretic Effect

- Anti-inflammatory effect: Hyperglycemia, insulin resistance, and dyslipidemia result in oxidative stress and inflammation creating a vicious cycle of metabolic dysfunction

Meta-analysis of SGLT2 inhibitors

13 large placebo-controlled trials including CREDENCE, DAPA-CKD, EMPA-KIDNEY and SCORED

Design

- **90,413** participants, of which **(17%) did not** have diabetes
- Trial populations included: patients with T2D and high CV risk, patients with HF and patients with CKD

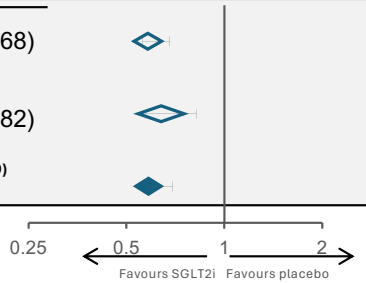
Objectives

- To examine the effects of SGLT2 inhibitors on kidney disease progression, as well as effects on AKI, mortality, HF and key safety outcomes in patients **with and without diabetes**
- **Standardised kidney disease progression composite outcome definition:**
  - Sustained ≥50% eGFR decline from randomisation
  - End-stage kidney disease (i.e. start of dialysis or kidney transplant)
  - Sustained low eGFR (usually <15 ml/min)
  - Kidney death

Meta-Analysis Cardio-Renal Trialists' Consortium. *Lancet* 2022;400:1788

SGLT2 inhibitors helped slow kidney disease progression in people both with and without diabetes.

	Mean baseline eGFR (ml/min/1.73 m²)	SGLT2i	Placebo	Relative risk (95% CI)
		n with event / N analysed		
Diabetes	67	739/40,041	1020/33,489	0.62 (0.56, 0.68)
No diabetes	56	202/7792	287/7812	0.69 (0.57, 0.82)
Total: Overall	**65**	**941/47,833**	**1307/41,301**	**0.63 (0.58, 0.69)**



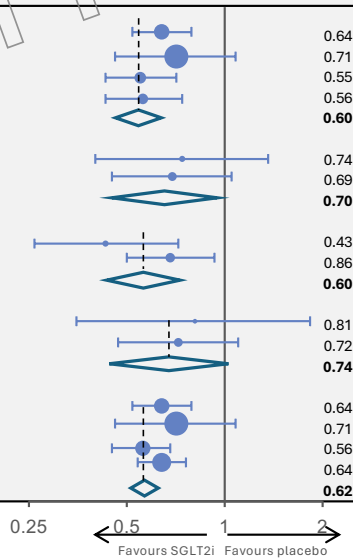
Heterogeneity by diabetes status: *p*=0.31

SGLT2i, sodium glucose co-transporter-2 inhibitor.

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

SGLT2 inhibitors had beneficial effects on the kidney disease progression even when analyses were separated by primary kidney diagnosis[1]

	Mean baseline eGFR (ml/min/1.73 m²)	SGLT2i Events/participants	Placebo Events/participants	SGLT2i Event rate/1000 PY	Placebo Event rate/1000 PY	Relative risk (95% CI)
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	0.86 (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)**



CREDENCE, DAPA-CKD and EMPA-KIDNEY trials were stopped early due to positive efficacy after prespecified conditions were met[2-4]

Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

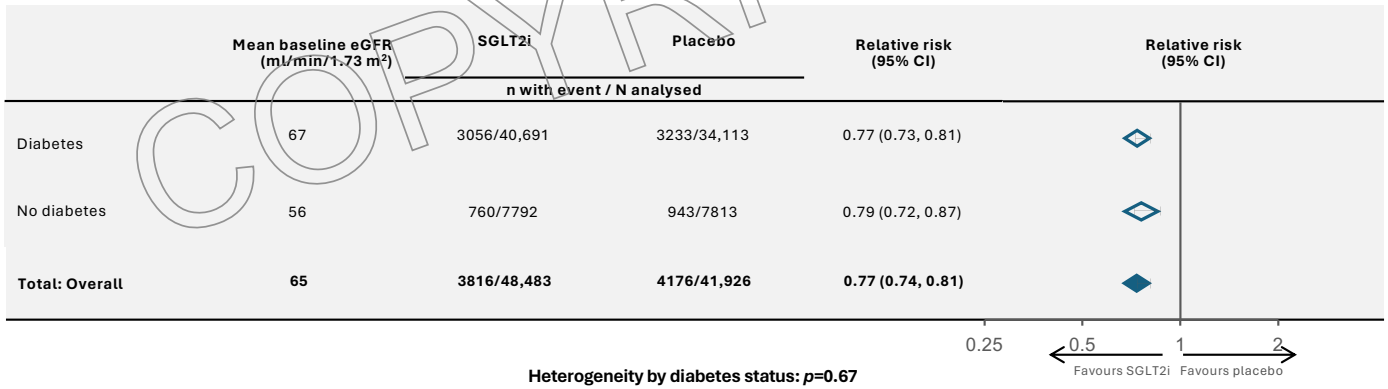
Rate values are not presented for the combined subtotal and total populations due to the heterogeneity in rates across the individual trials[1]

Although the SCORED population consisted of people with T2D and CKD, the primary outcome was composite of CV death, HHF, and urgent visits for HF; the composite of a sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or a sustained eGFR of <15 ml/min/1.73 m² was a secondary endpoint.[5] Sotagliflozin has been withdrawn in the European Union[6]

*Relative risk in the diabetic kidney disease or nephropathy subgroup excluding SCORED (which did not formally assess primary kidney disease) is 0.59 (95% CI 0.52, 0.68)[1]

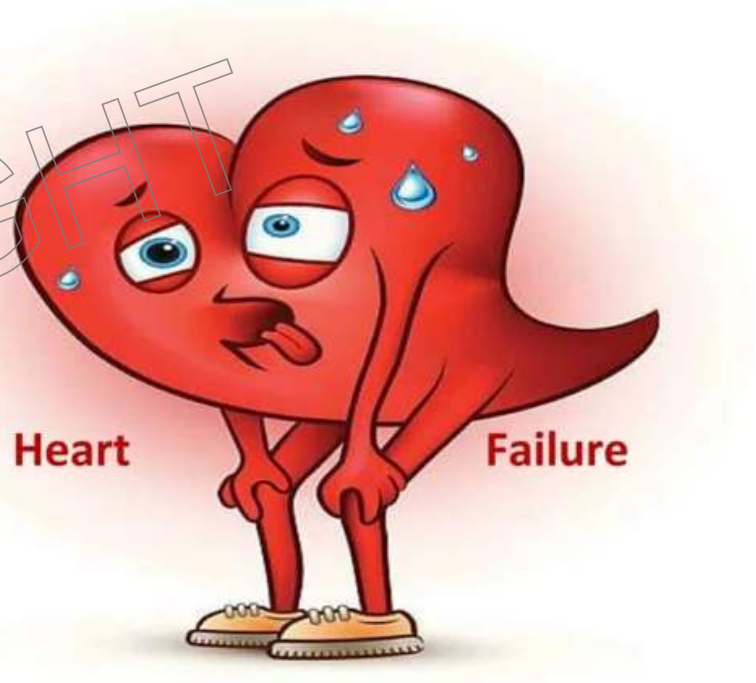
Please see slide notes for abbreviations and references

SGLT2 inhibitors had beneficial effects on CV death or HHF [1]



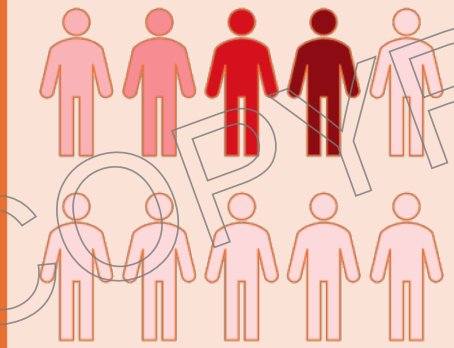
HHF, hospitalisation for heart failure; SGLT2i, sodium glucose co-transporter-2 inhibitor.

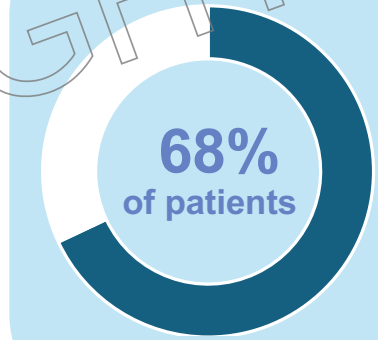
The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. *Lancet* 2022;400:1788



HF is an early, highly prevalent and often undiagnosed complication in patients with T2D[1,2]

Between **25% and 40%** of patients with diabetes have HF[1]





who had T2D for 5 years* (N=386) showed signs of asymptomatic LV dysfunction†[2]

Previously unknown HF was detected in **28% of patients with T2D** aged ≥60 years (N=581) during cardiac screening, which included **23% with HFpEF** and **5% with HFrEF**‡[3]

*

1. Rosano G *et al*. *Cardiac Failure Rev* 2017;3:52;
2. Faden G *et al*. *Diabetes Res Clin Pract* 2013;101:309;
3. Boonman-de Winter LJ *et al*. *Diabetologia* 2012;55:2154

Early trials demonstrate modest CV benefits with intensive glycaemic control in patients with T2D

Meta-analysis of the ACCORD, ADVANCE, UKPDS and VADT trials (Veterans affair diabetes trial)*

Objective: to generate precise estimates of the effects of glucose-lowering therapy on major CV events

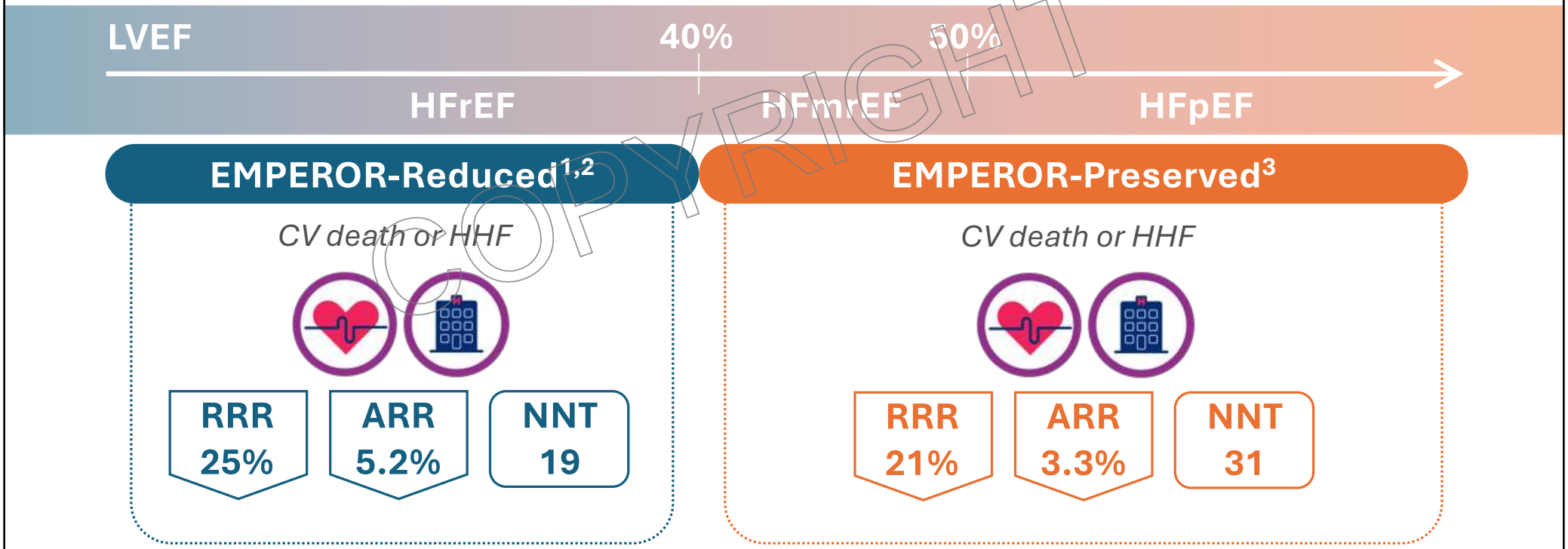
Patients with T2D (N=27,049) allocated to 'more intensive' or 'less intensive' glycaemic control

Major CV events (CV death or non-fatal stroke or non-fatal MI)	MI (fatal or non-fatal)	All-cause mortality
		
Modest benefit HR 0.91 (0.84, 0.99) *p*=0.72	**Modest benefit** HR 0.85 (0.76, 0.94) *p*=0.52	**No effect** HR 1.04 (0.90, 1.20) *p*=0.13

*The trials differed in glucose-lowering and cardioprotective therapies at follow-up. The trials used metformin, insuli sulphonylurea, acarbose, glinide and thiazolidinedione as glucose-lowering agents

Turnbull FM *et al. Diabetologia* 2009;52:2288

Empagliflozin was the **first HF drug** to significantly reduce the risk of CV death or HHF across the entire spectrum of ejection fractions

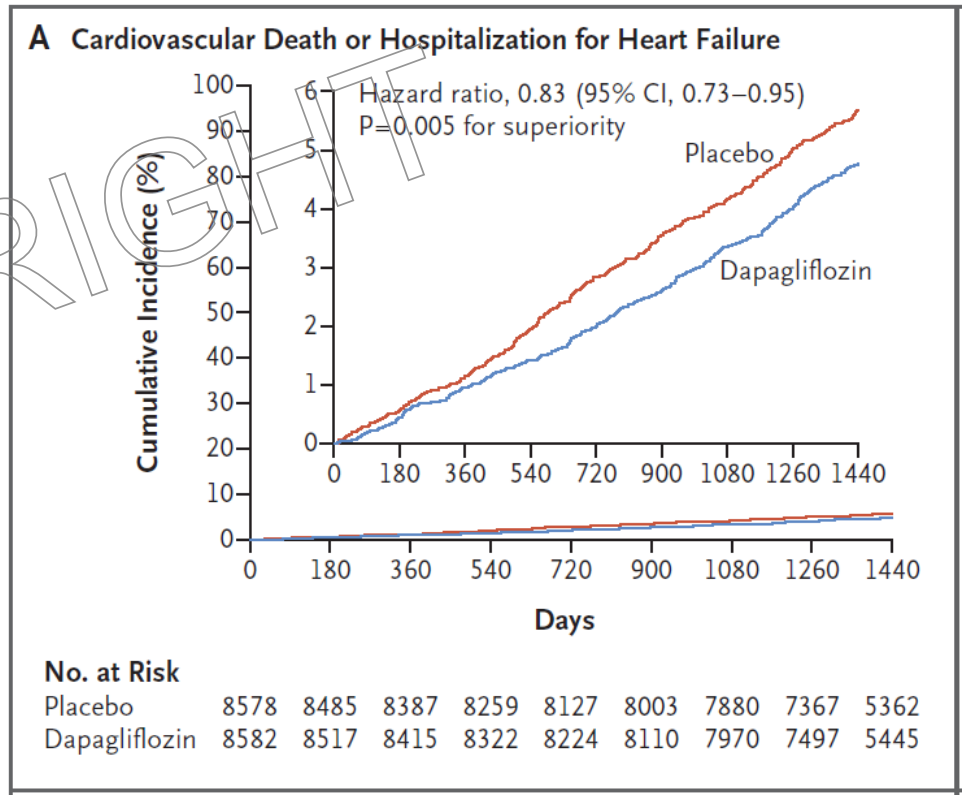


1. Packer M *et al. N Engl J Med*. 2020;383:1413;
2. Butler J *et al. Eur J Heart Fail.* 2020;22:1991;
3. 3Anker SD *et al. N Engl J Med.* 2021;385:1451.

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

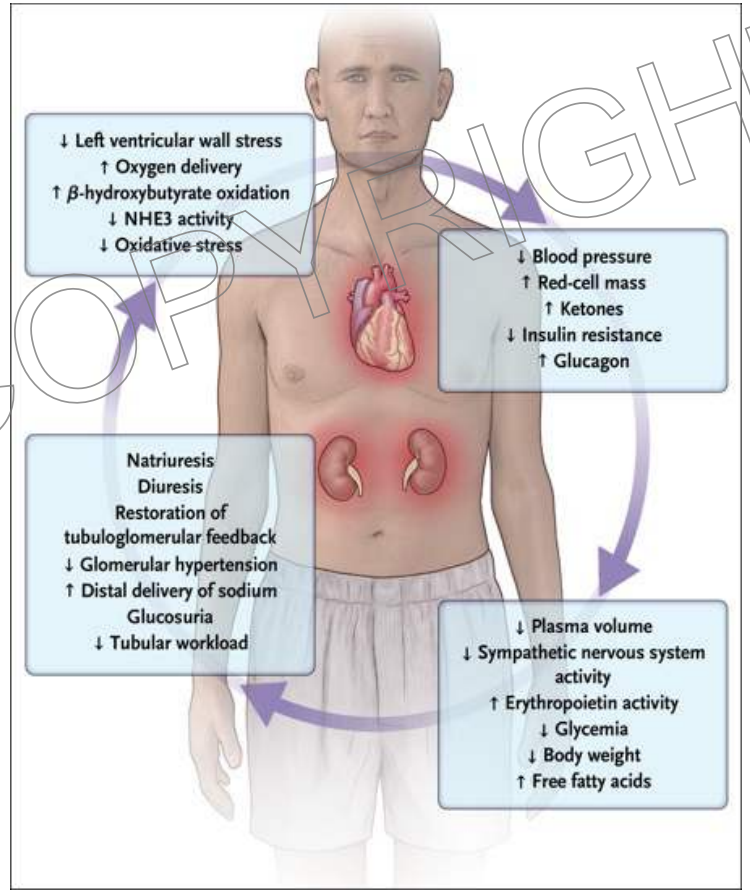
S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*



N Engl J Med 2019; 380: 347 - 57

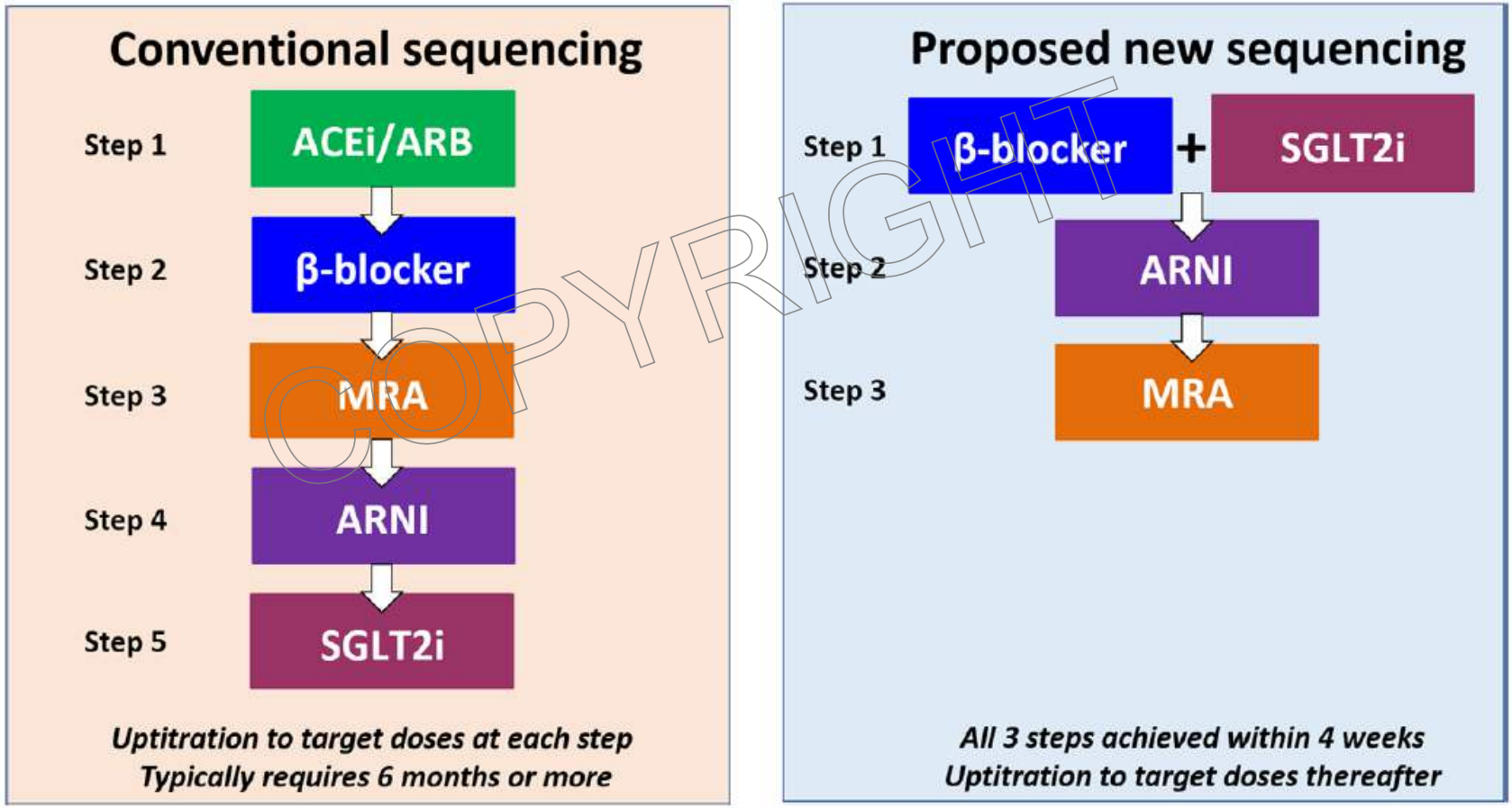
Connecting both the kidney and the Heart

The Kidney–Heart Connection for **Organ Protection** by SGLT2 Inhibitors



Braunwald, E., 2022. *NEJM 386*(21), pp.2024-2034.

Heart Failure treatment



Circulation 2021;143:875–877

The KDIGO 2024 CKD guideline recommends the use of SGLT2 inhibitors in people with CKD across the cardio, kidney and metabolic spectrum

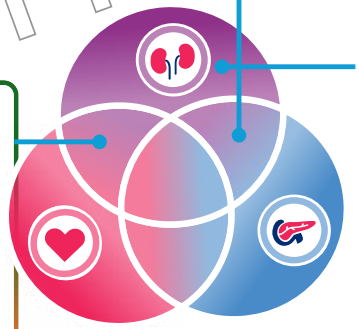
Recommendations indicate SGLT2 inhibitors* to treat:

CKD and T2D

Patients with **T2D, CKD and an eGFR ≥20 ml/min/1.73 m²** (1A)

CKD and HF

Adults with **CKD with an eGFR ≥20 ml/min/1.73 m² with** HF **irrespective** of level of **albuminuria** (1A)



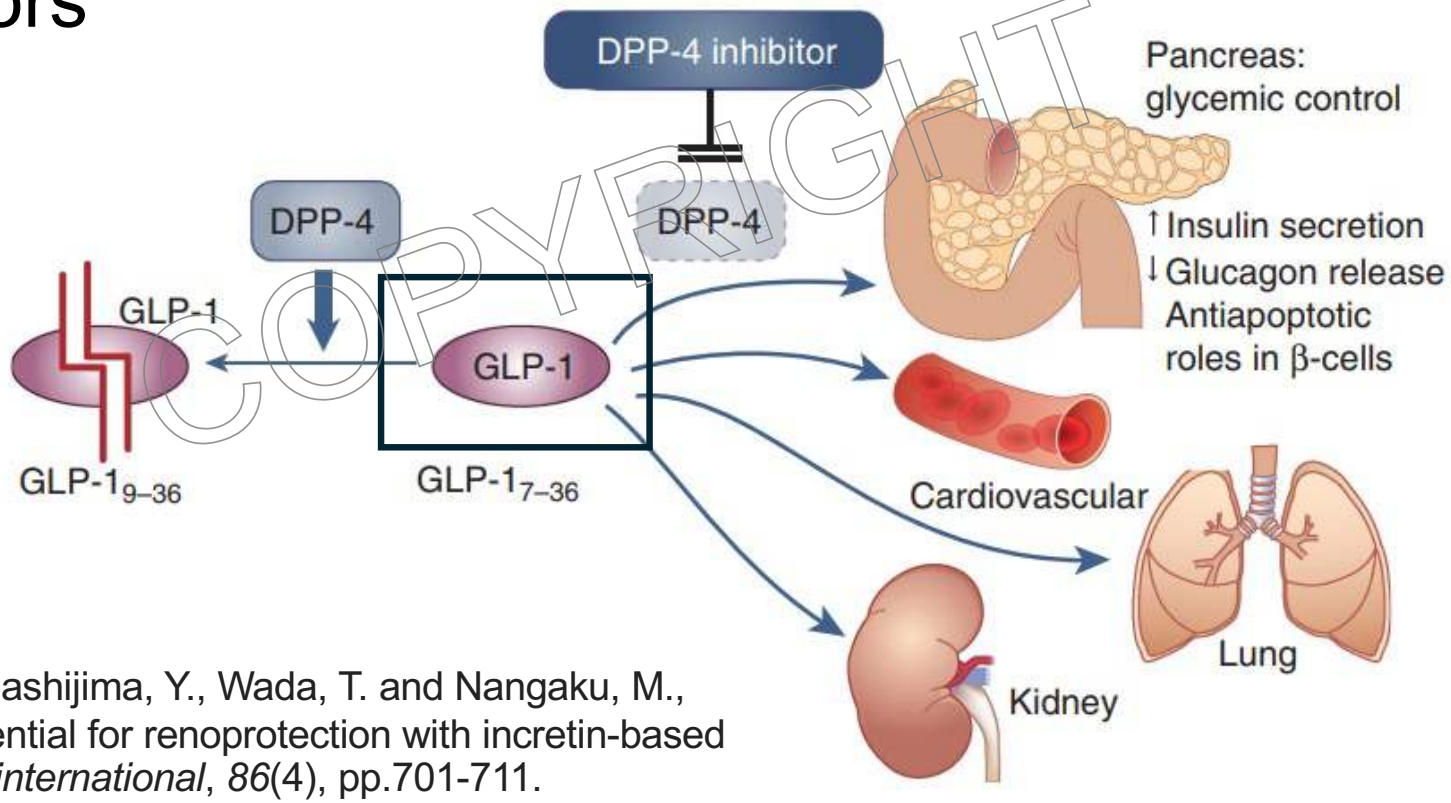
CKD

Adults with **CKD with an eGFR ≥20 ml/min/1.73 m² with UACR ≥200 mg/g (≥20 mg/mmol)** (1A)

Adults with **eGFR 20 to 45 ml/min/1.73 m² with UACR <200 mg/g (<20 mg/mmol)** (2B)

Levin, A. et al. Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD: Kidney International

The Incretin Pathway: GLP1 Agonists and DPP4 Inhibitors



Tanaka, T., Higashijima, Y., Wada, T. and Nangaku, M., 2014. The potential for renoprotection with incretin-based drugs. *Kidney international*, *86*(4), pp.701-711.

Glucagon- like peptide 1 receptor Agonists

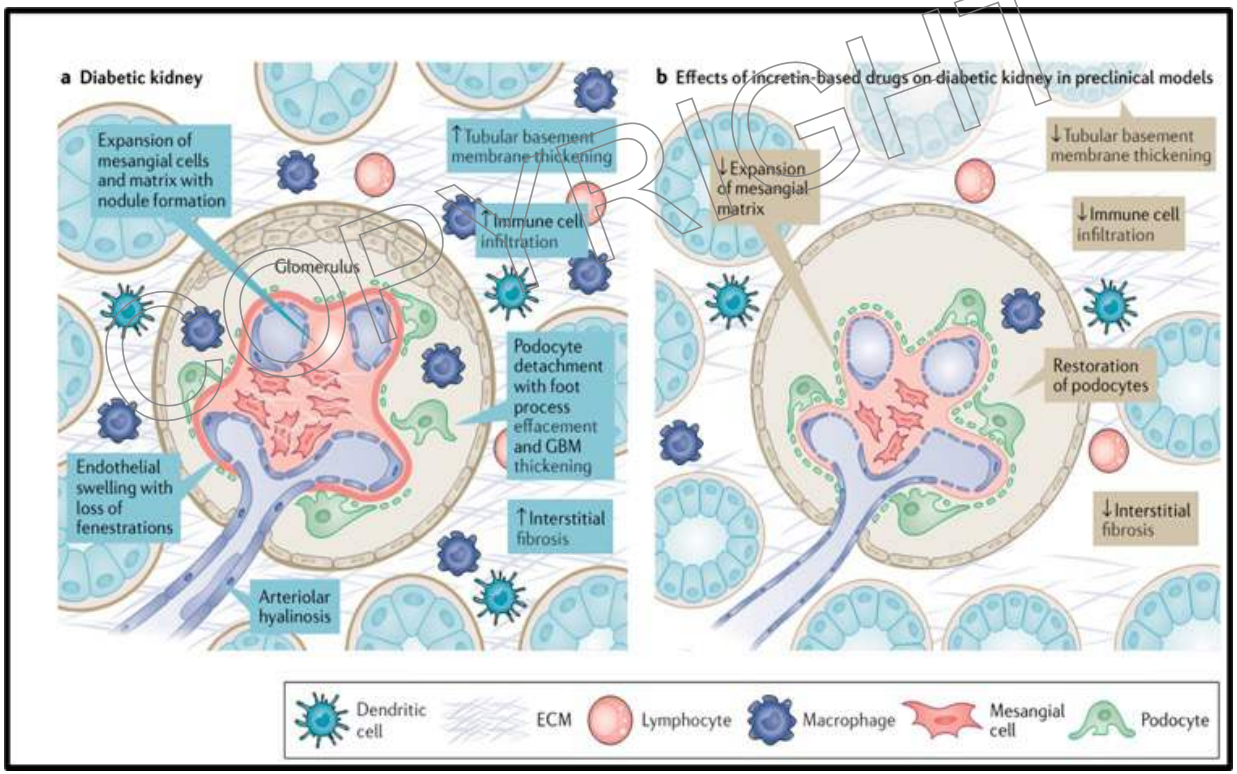
- **GLP1RA** are analogs of the incretin hormone GLP-1

- They **increase insulin and reduce glucagon secretion** in a glucose-dependent manner, lowering HbA1c by 0.6–1.6%, regardless of eGFR.

- GLP1RA also promote **weight loss** through appetite suppression (central hypothalamic effects) and delayed gastric emptying

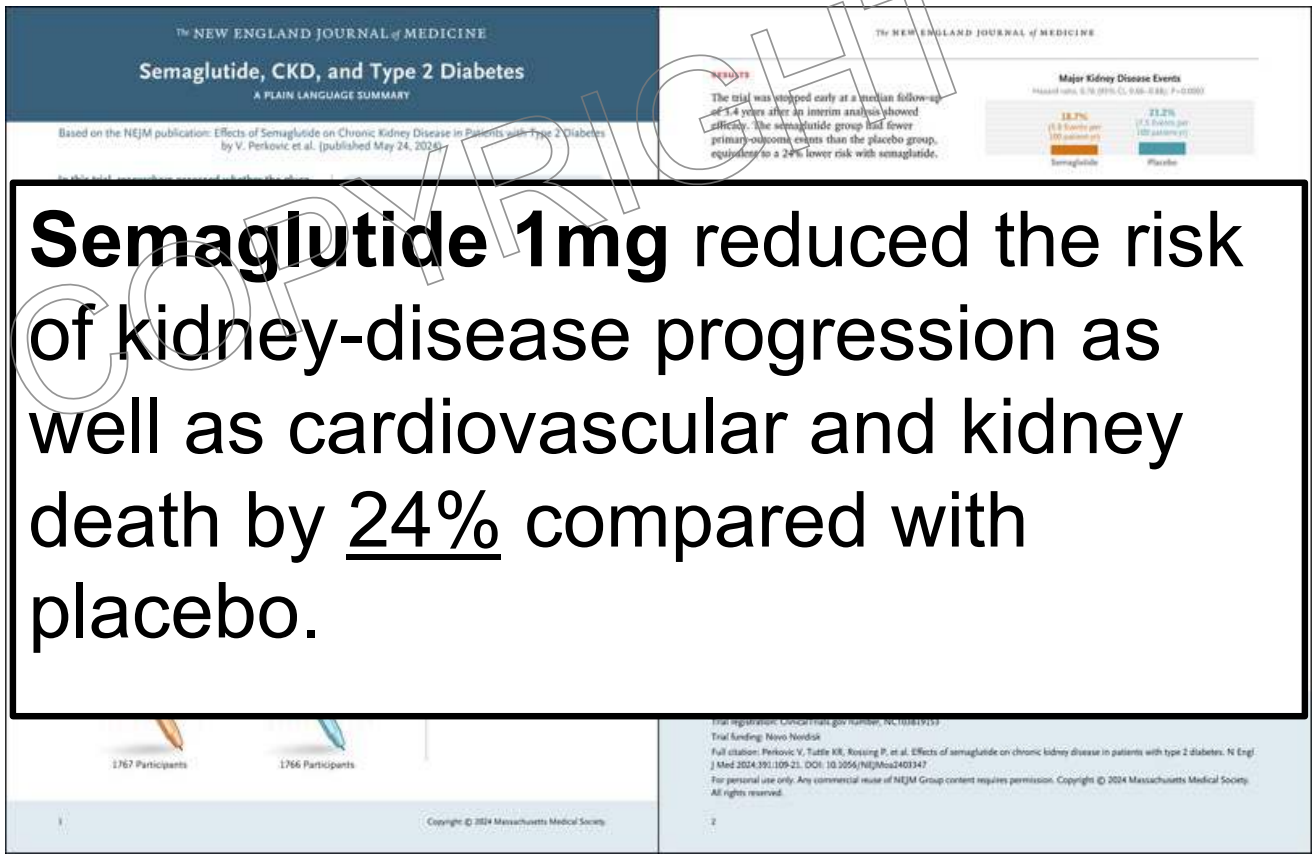
- They are **metabolized by target tissues** and do not require dose adjustment in patients with chronic kidney disease (CKD)

Glucagon Like Peptide-1 receptor Agonists (GLP-1 agonists): cardiovascular trials in T2DM



Radica, Z et al: Incretin drugs in DKD: Biological mechanisms and clinical evidence

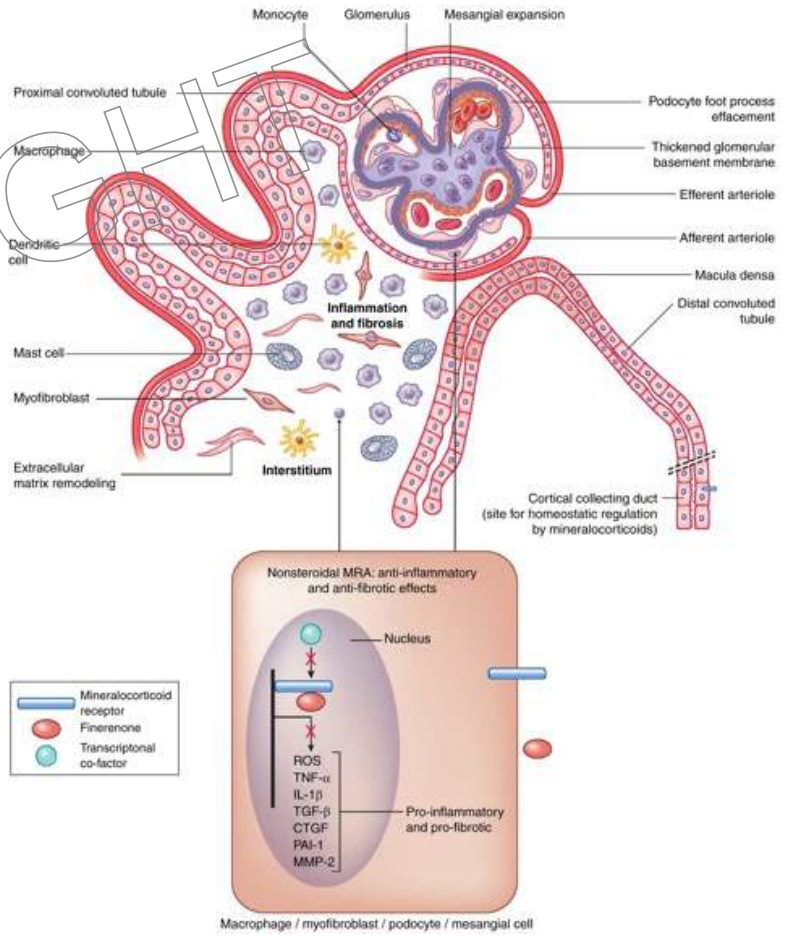
The Flow study: The first study designed to demonstrate primary kidney end points – using Semaglutide cohort :CKD and T2D, as well assessing CVD mortality**.**



Semaglutide 1mg reduced the risk of kidney-disease progression as well as cardiovascular and kidney death by <u>24%</u> compared with placebo.

NS Mineralocorticoid receptors in diabetic kidney disease

- Mineralocorticoid receptors upregulate inflammatory and fibrotic pathways
- Finerenone demonstrates superior anti-inflammatory outcomes compared with is steroidal counterparts in preclinical studies

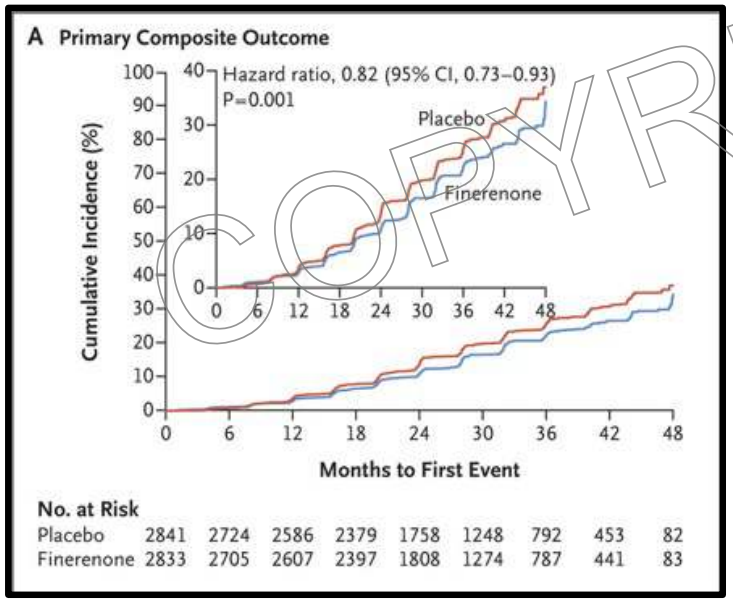


Ghuman, J.K. and Tuttle, K.R., 2022
Kidney360, *3*(4), pp.744-748.

FIDELIO-DKD vs FIGARO-DKD

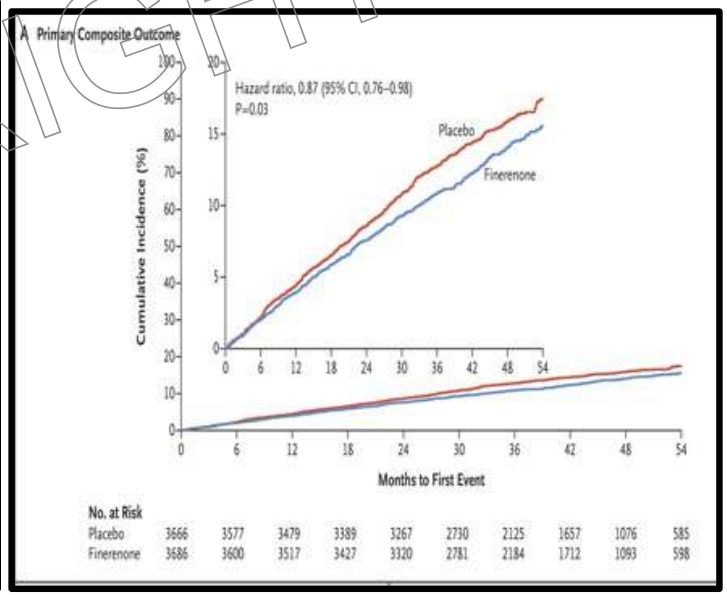
Feature	FIDELIO-DKD (Bakris 2020 NEJM)	FIGARO-DKD (Pitt 2021-NEJM)
Primary Focus	Kidney outcomes	Cardiovascular outcomes
CKD Severity	More advanced CKD	Earlier-stage CKD
Primary Endpoint	Kidney failure, sustained ≥40% ↓ in eGFR, or renal death	CV death, MI, stroke, or hospitalization for HF
Baseline eGFR Range	25–75 mL/min/1.73 m²	≥25 mL/min/1.73 m²
Albuminuria (UACR)	30–5000 mg/g (mostly higher albuminuria)	30–3000 mg/g (moderate to high albuminuria)
Key Outcome	18% ↓ in kidney outcome (HR 0.82)	13% ↓ in CV outcome (HR 0.87)

Fineronone in CKD and T2DM NS- MR antagonists



FIDELIO

Bakris, et al Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *NEJM 2020*



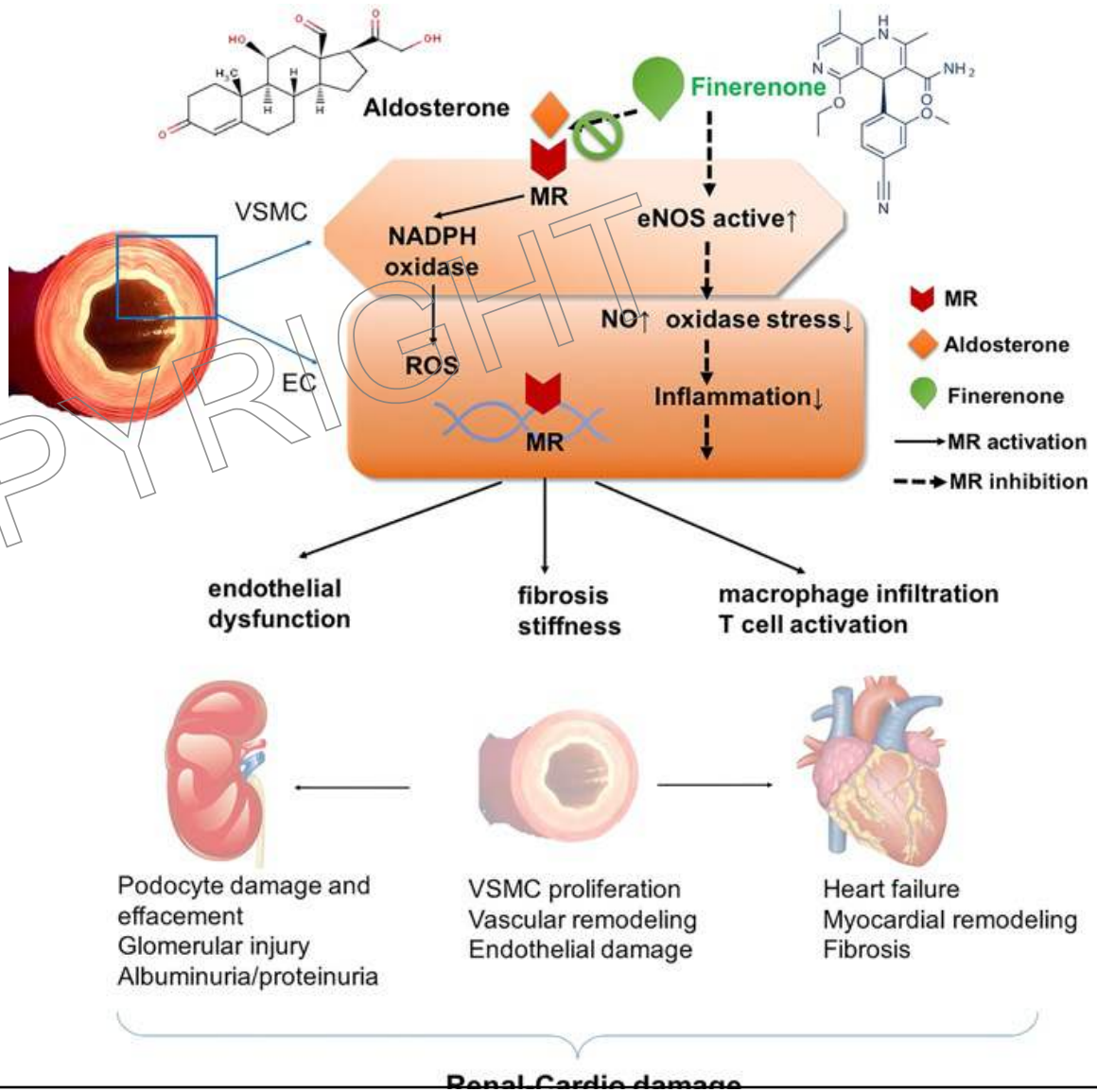
FIGARO - DKD

Pitt, B., et al Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *NEJM 2022*

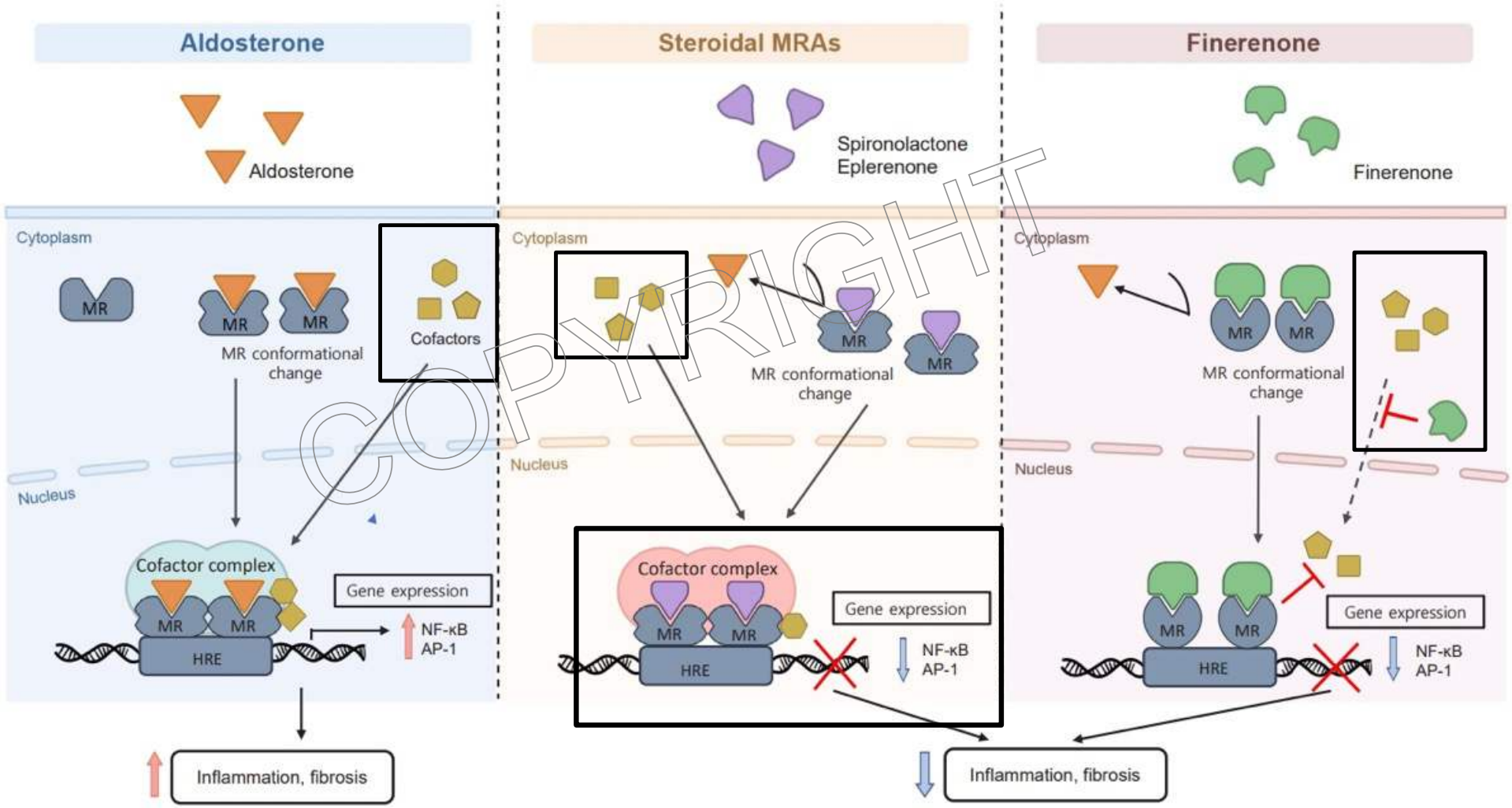
MOA of finerenone vs spironolactone/eplerenone

Feature	Finerenone	Spironolactone/Eplerenone
Drug type	**Non-steroidal MR antagonist**	**Steroidal MR antagonist**
Selectivity	More selective for MR, fewer side effects	Less selective, affects other hormone receptors (e.g., androgen)
Tissue penetration	Better balance in heart and kidney	Tends to accumulate more in kidney
Anti-inflammatory & anti-fibrotic	Stronger anti-inflammatory and anti-fibrotic effects	Effective but more side effects (e.g., gynecomastia)
Tolerability	Better tolerated, especially with less risk of hyperkalemia	Higher risk of hormonal side effects and hyperkalemia

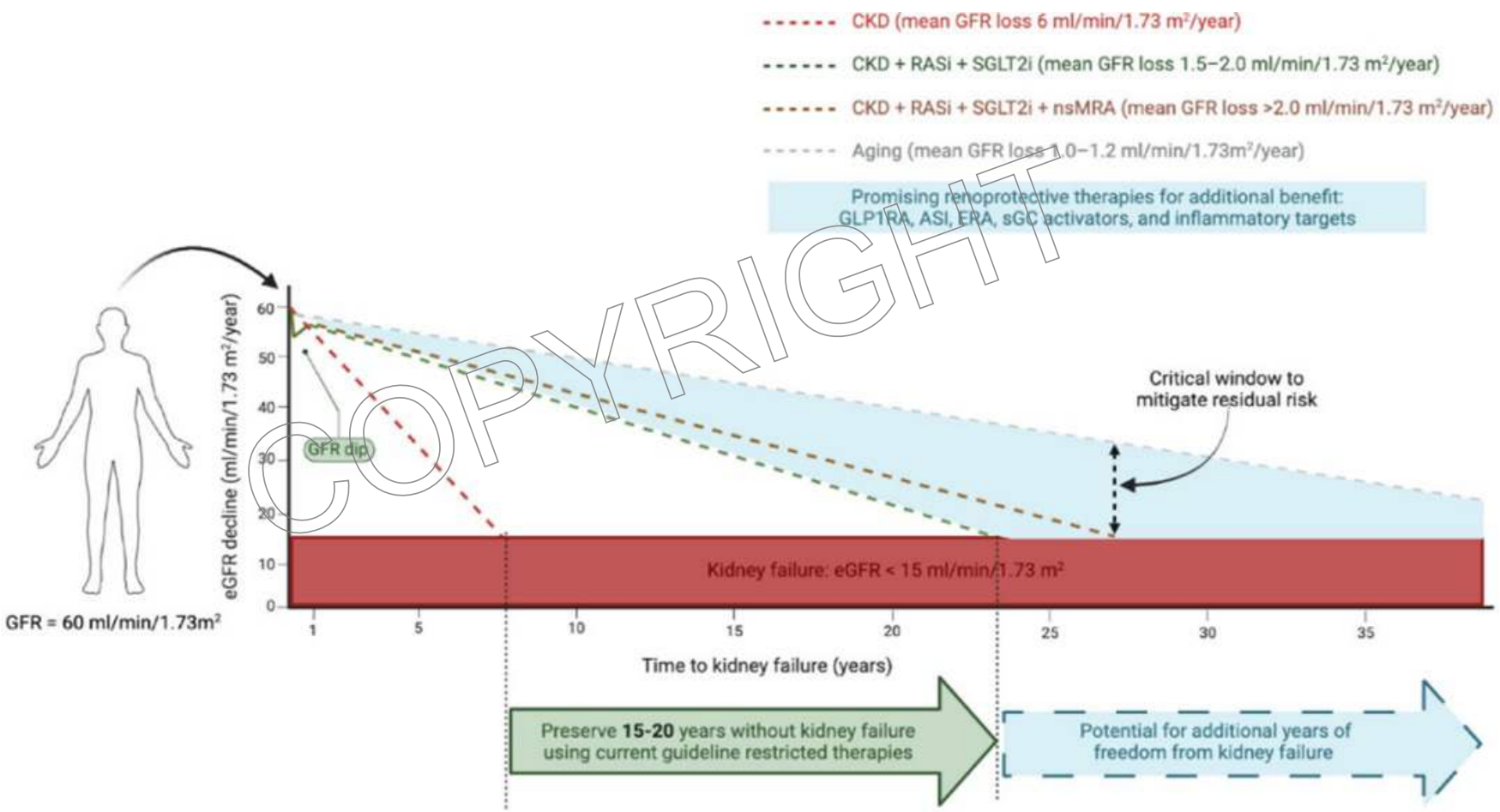
Mineralocorticoid receptor (MR) overactivation causes kidney and CV damage through dysregulation of homeostasis, inflammation and fibrosis



These effects can be ameliorated by fineronone

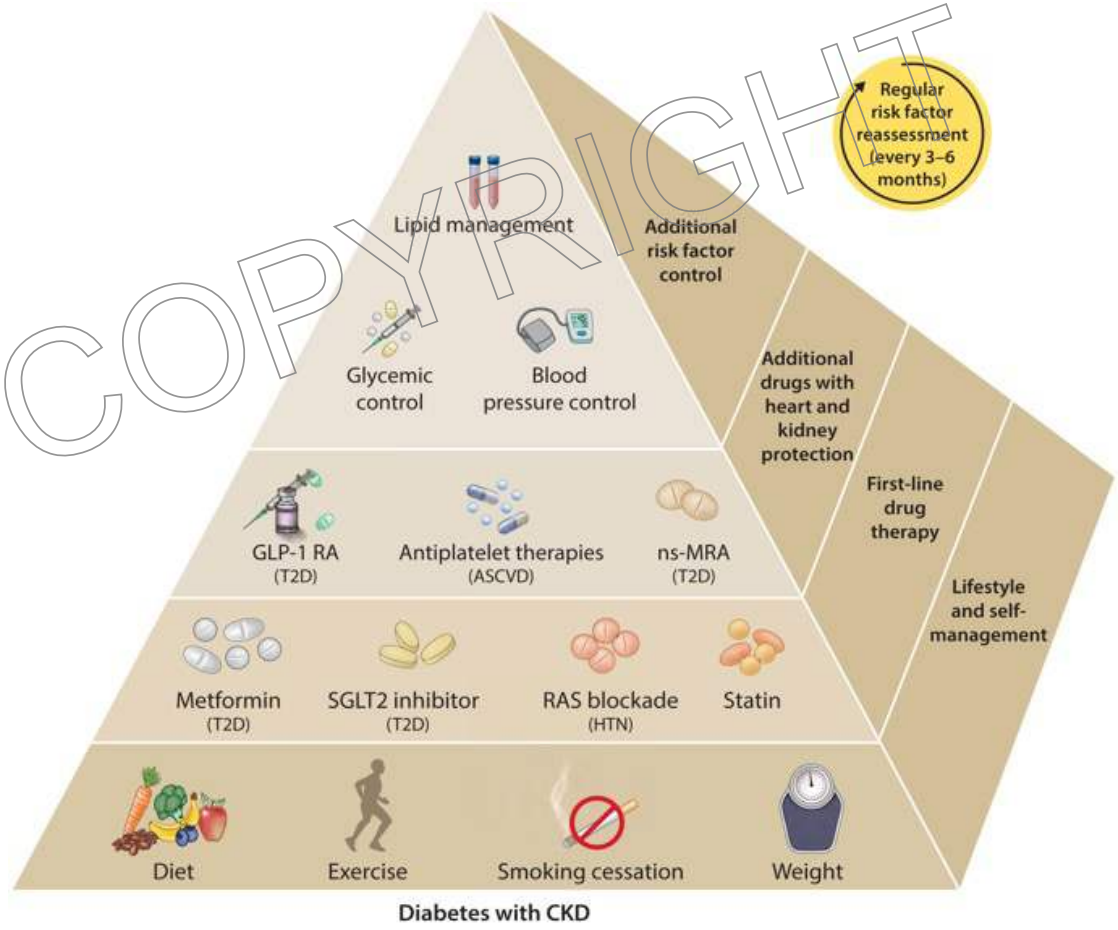


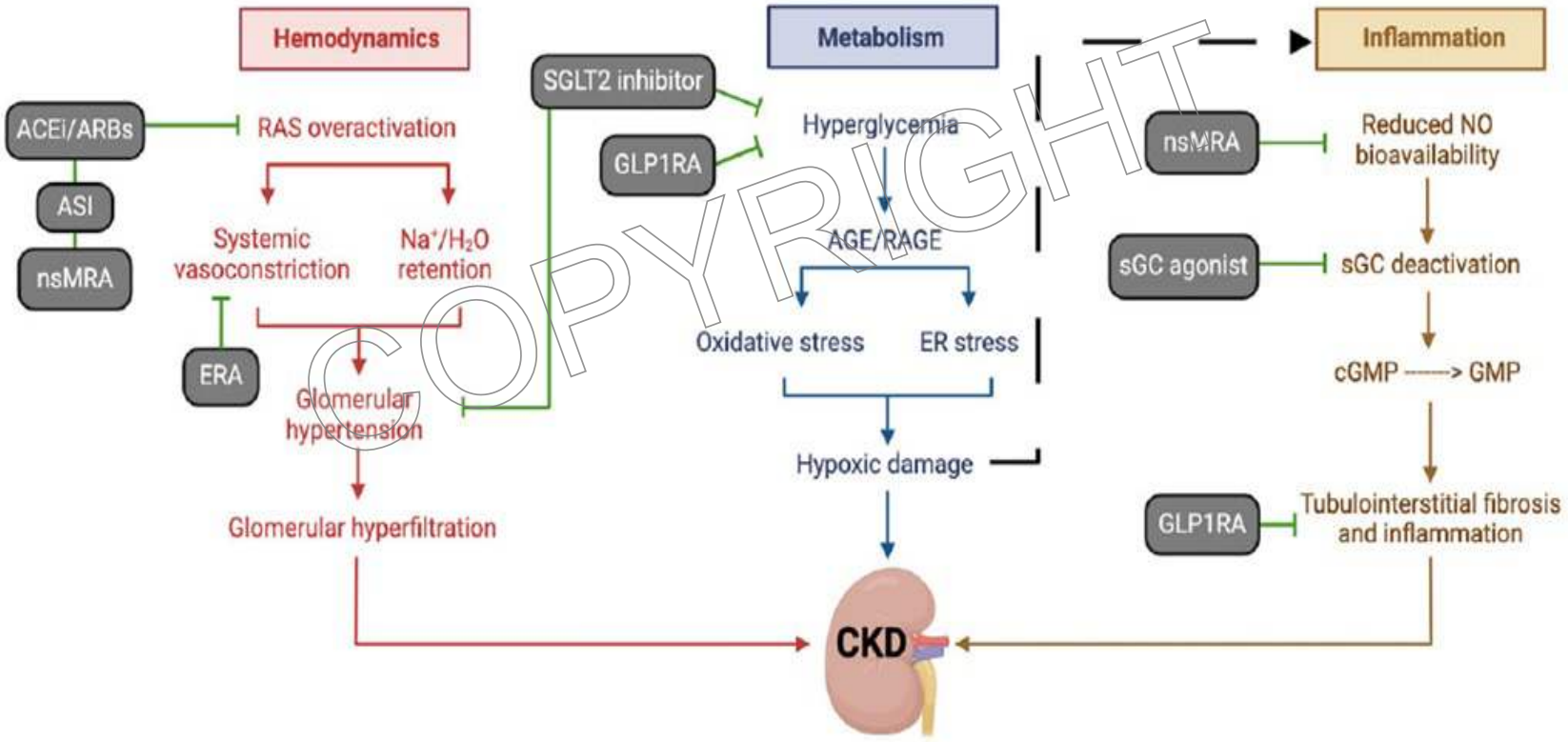
Kim, D.L Renal protection of MC receptor antagonist, finerenone, in DKD *Endo & Metabolism*, *2023*



Nardone, M., et al 2025. Upcoming drug targets for kidney protective effects in chronic kidney disease. *NDT 2025*

KDIGO: Shift towards a pillared "combination of drugs" approach: focuses on the reduction of cardiovascular risk and/or mortality and progression of CKD .





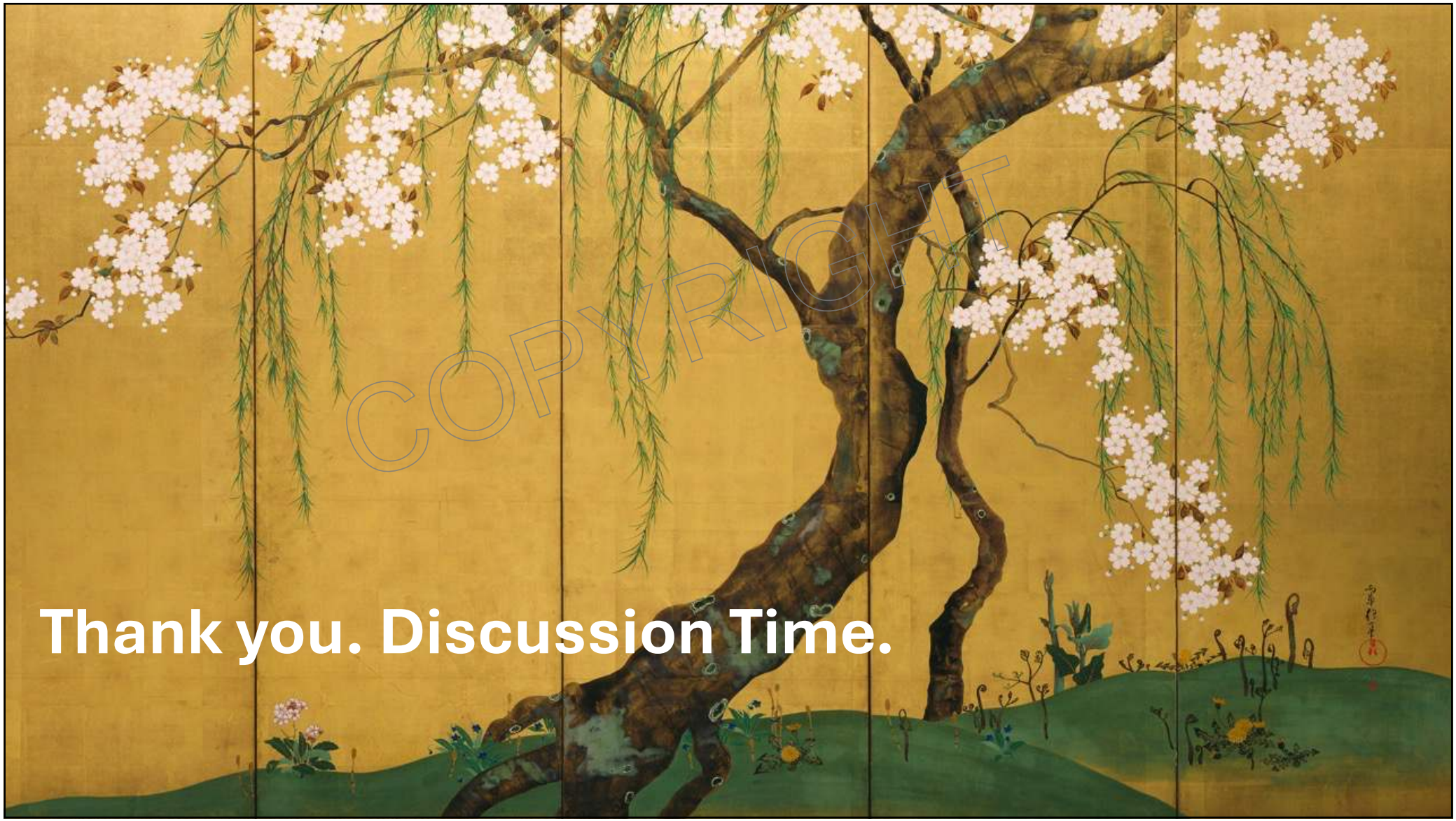
Nardone, M., et al 2025. Upcoming drug targets for kidney protective effects in chronic kidney disease. *NDT 2025*

There must be a holistic approach

Health Promotion | Primary Prevention | Secondary Prevention | Tertiary Prevention

Diabetic Kidney Disease (DKD): Key Messages

- **Common and deadly**: DKD is highly prevalent and linked to **high mortality**.
- **Early warning**: **Microalbuminuria** is often the first sign.
- **Lifestyle matters**: Diet, exercise, and weight control are **foundational**.
- **Multifactorial treatment is essential**:
  - Control **glucose**, **blood pressure**, and **lipids**
  - Use **RAAS inhibitors**
- **New therapies with broad impact**:
  - **SGLT2 inhibitors, GLP-1 receptor agonists, and nsMR antagonists** → Protect the **kidney** and the **heart**
- **Care approach**: Treat both **CKD** and **cardiovascular risk**—they go hand-in-hand.



Thank you. Discussion Time.