“FOUR PILLARS “ IN THE TREATMENT OF DIABETIC NEPHROPATHY[DN]

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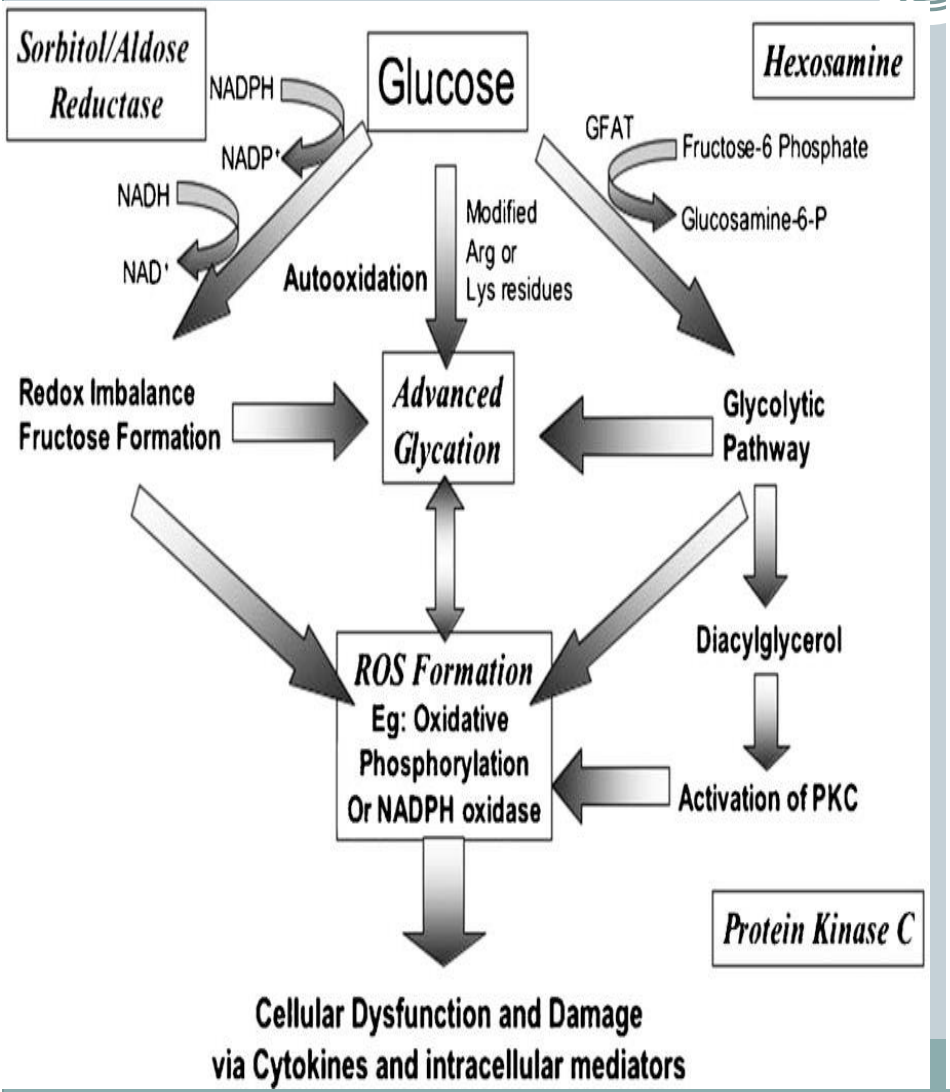
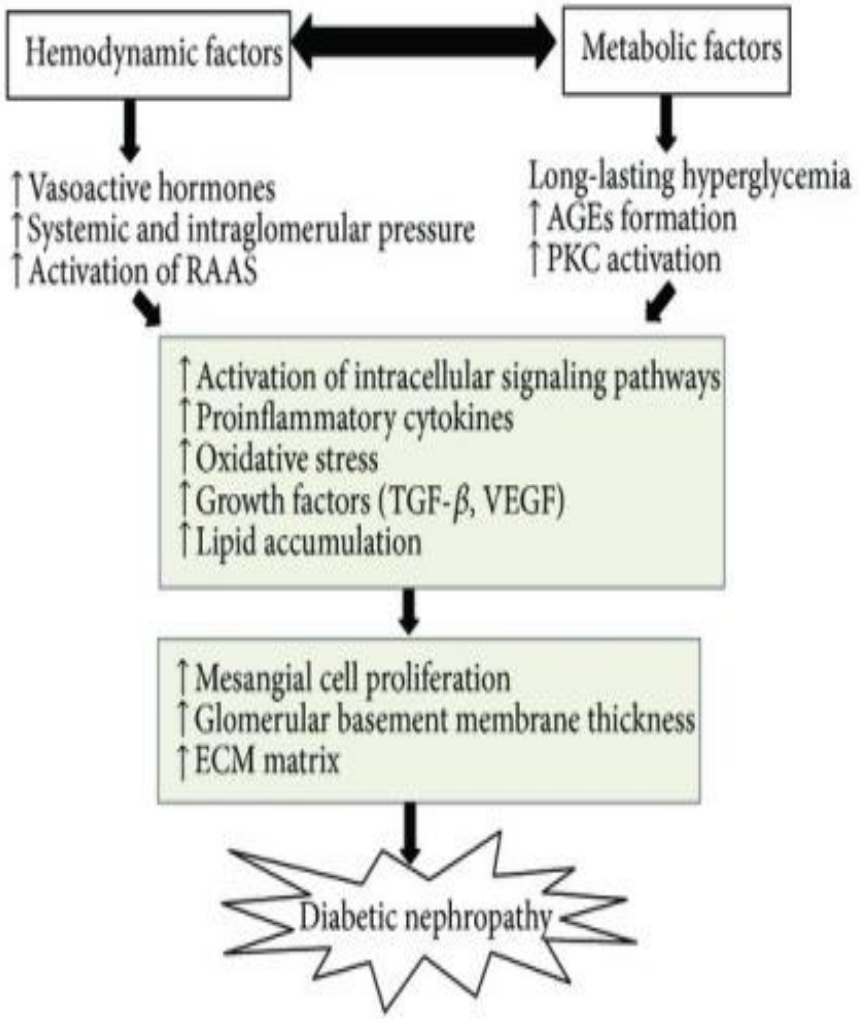
INTRODUCTION

The "four pillars" of treatment for diabetic nephropathy are:

- Renin-angiotensin system (RAS) inhibitors,
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors,
- Glucagon-like peptide-1 (GLP-1) receptor agonists,
- Non-steroidal mineralocorticoid receptor antagonists (nsMRA).
- In combinations they retard progression of diabetic nephropathy.
- Medications are individualized as per patient needs.

MECHANISM OF DN

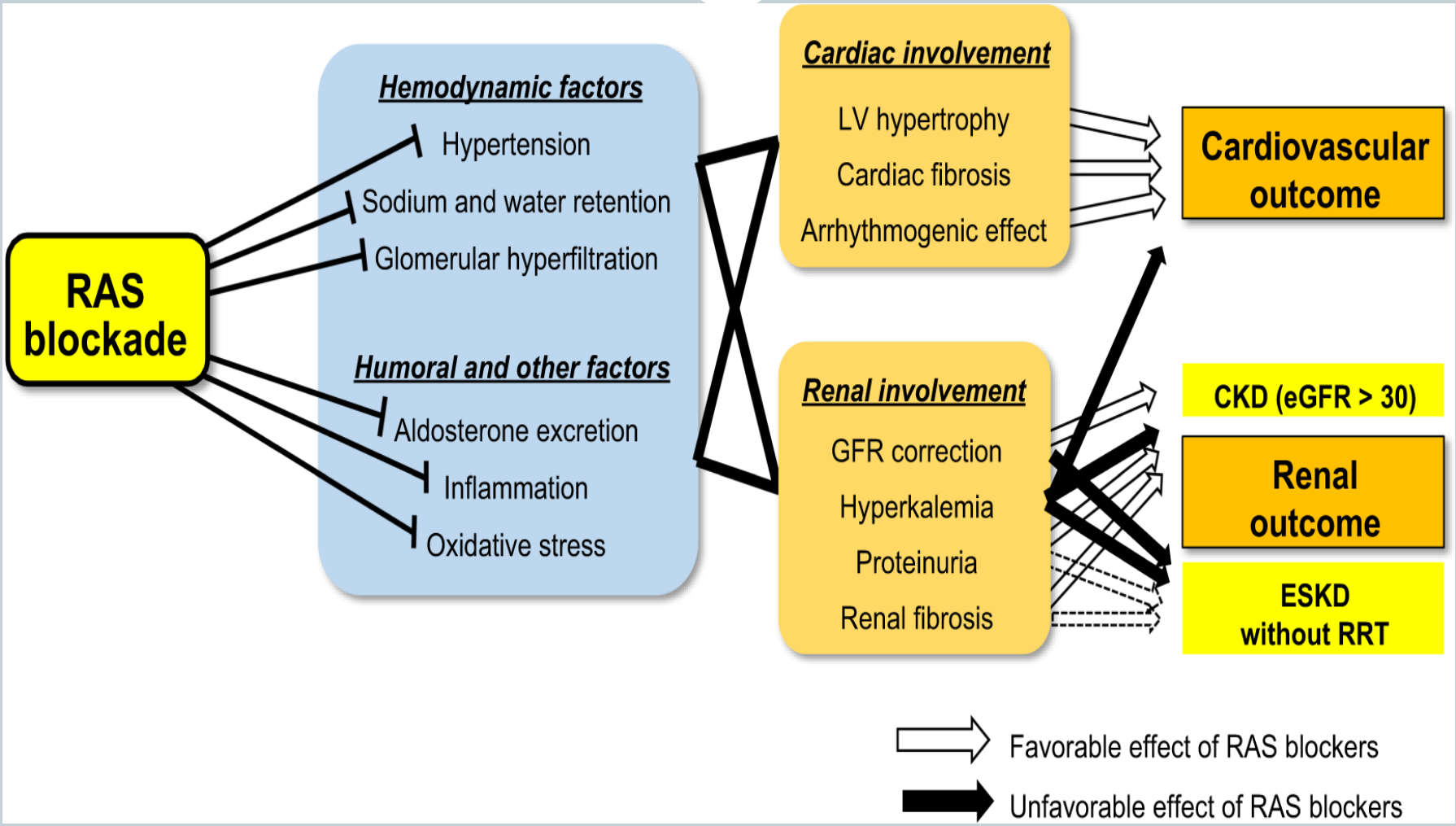




RAAS INHIBHITORS

- Angiotensin II and other components of the renin-angiotensin-aldosterone system (RAAS) have a central role in pathogenesis.
- ACE inhibitors decrease the production of Ang II, which is a potent vasoconstrictor, leading to lower intraglomerular pressure and reduced glomerular hypertension.
- They also decrease the glomerular permeability to urinary albumin leading to decreased proteinuria.
- ARBs act by blocking Ang II type 1 receptors (AT_1 receptors).
- This AT_1 blockade may lead to further increase in synthesis of Ang II which binds to intrarenal AT_2 receptors, resulting in decreased blood pressure and reduced renal interstitial fibrosis.

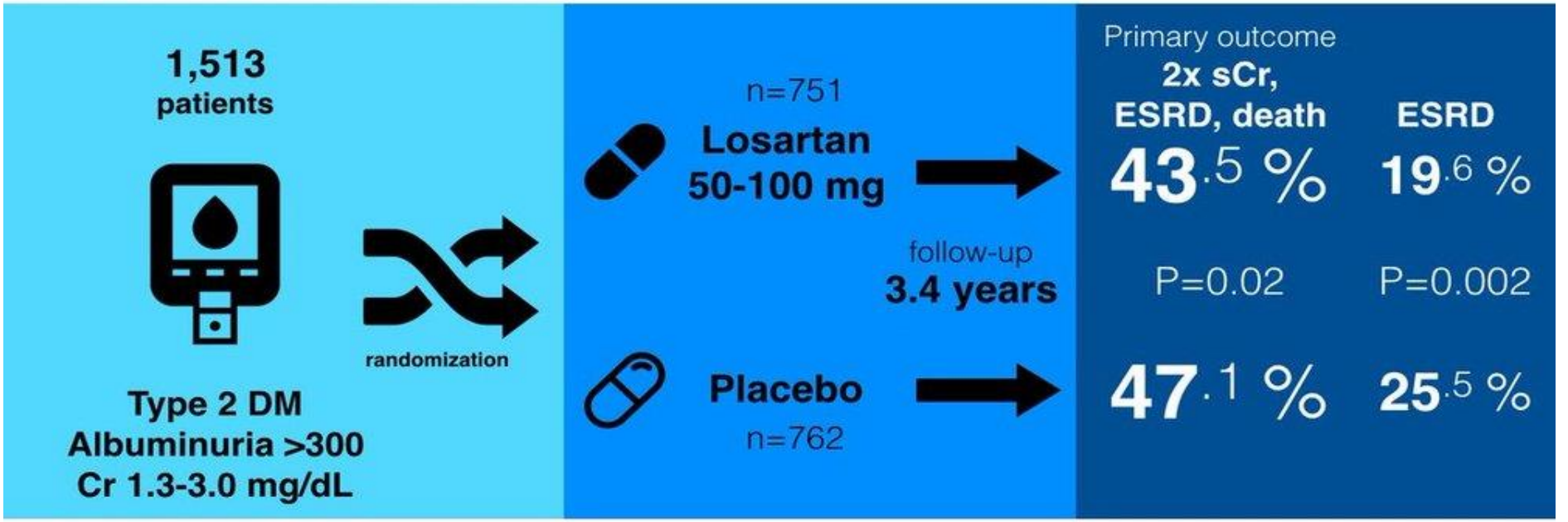
RAAS BLOCKERS



RAAS INHIBITORS

LOSARTAN LED TO DECREMENT OF PROTEINURIA BY 35% AND REDUCTION OF DOUBLING OF CR AND ESKD BY 25%

Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy (RENAAL)



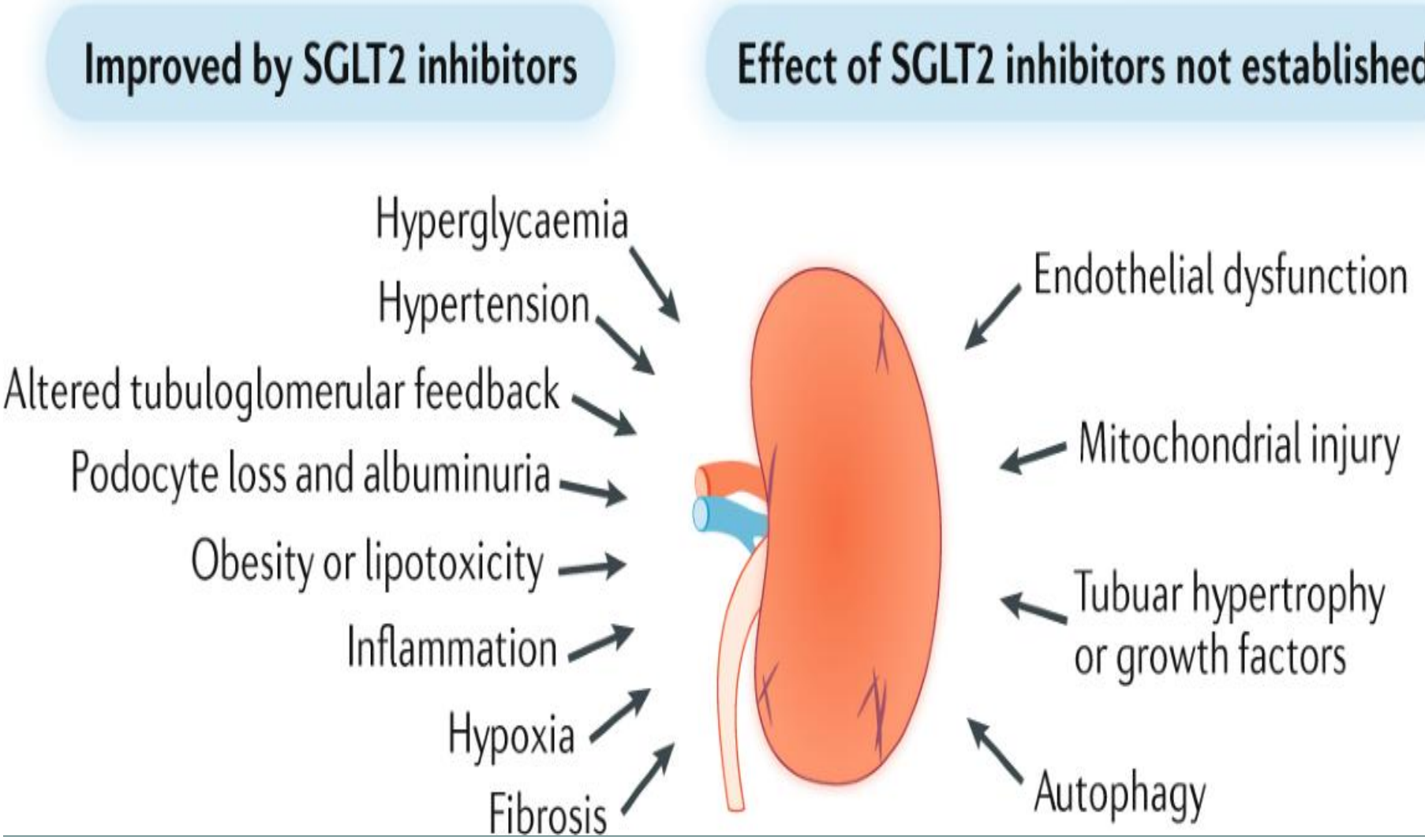
N Engl J Med, Vol. 345, No. 12 · September 20, 2001
The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Main results of major RCTs of various therapeutic approaches in diabetic kidney disease

Trial	*n*	Design	FU	Renal outcome
DCCT [5]	1441 T1DM	Intensive versus standard glycemic control	6.5 years	Intensive glycemic control versus standard control (HbA_{1c} 7.3 versus 9.1%) reduced incident micro- and macro-albuminuria by 39 and 54%.
EDIC/DCCT [6]	1441 T1DM	Intensive versus standard glycemic control	18 years	Renoprotective efficacy of intensive glycemic control persisted and resulted in 45% risk reduction of micro-albuminuria at 18 years
UKPDS 33 [7]	3867 T2DM	Intensive versus standard glycemic control	10 years	Intensive glycemic control versus standard control (HbA_{1c} 7.0 versus 7.9%) led to 33% risk reduction for micro-albuminuria.
ADVANCE [8]	11 140 T2DM	Intensive versus standard glycemic control	5 years	Intensive glycemic control versus standard control (HbA_{1c} 6.5 versus 7.3%) reduced risk of micro-, macro-albuminuria and ESRD by 9, 30 and 65%. For those with macro-albuminuria, number needed to treat to prevent one ESRD = 41.
ACCORD [9]	10 251 T2DM	Intensive versus standard glycemic control	Terminated at 3.5 years	Targeting HbA_{1c} 6.0 versus 7.0–7.9% resulted in excess mortality (HR 1.22; 95% CI 1.01–1.46; P = 0.04).
RENAAL [10, 11]	1513 T2DM	Losartan versus placebo	3.4 years	Multivariate analysis: every 10 mmHg SBP rise increased risk of ESRD or death by 6.7%. Losartan led to decrement of proteinuria (35%; P < 0.001), risk reduction of serum creatinine doubling (25%; P = 0.006) and ESRD (28%; P = 0.002).
MARVAL [12]	332 T2DM	Valsartan versus amlodipine	24 weeks	Reduction of micro-albuminuria with valsartan (44%) greater than amlodipine (8%).
IRMA-2 [13]	590 T2DM	Irbesartan versus placebo	2 years	Irbesartan demonstrated renoprotective efficacy with reduction in disease progression compared with placebo (HR 0.3; 95% CI 0.14–0.61; P < 0.001 for 300 mg irbesartan).
IDNT [14]	1715 T2DM	Irbesartan versus amlodipine versus placebo	2.6 years	Irbesartan was renoprotective with lower risk of serum creatinine doubling (33%; P = 0.003) and ESRD (23%; P = 0.07) compared with placebo.
DETAIL [15]	250 T2DM	Telmisartan versus enalapril	5 years	Telmisartan and enalapril fared equally. No significant differences in level of albuminuria, rate of GFR decline and ESRD.
ROADMAP [16]	4447 T2DM	Olmesartan versus placebo	3.2 years	Olmesartan resulted in a reduction in time to micro-albuminuria onset by 23% (HR 0.77; 95% CI 0.63–0.94; P = 0.01). Blood pressure was similarly controlled in both study arms.
CALM [17]	199 T2DM	Candesartan/lisinopril combo versus candesartan versus lisinopril	12 weeks	Combination therapy more effective with greater reduction in urinary albumin: creatinine ratio (50%) compared with candesartan (24%) or lisinopril (39%) alone.
ONTARGET [18]	25 620 T1&2DM	Telmisartan/ramipril combo versus telmisartan versus ramipril	55 months	Combination therapy was associated with increased composite outcome of dialysis, serum creatinine doubling and death (HR 1.09; 95% CI 1.01–1.18; P ≤ 0.037).
VA NEPHRON-D [19]	1448 T2DM	Losartan/lisinopril combo versus losartan	Terminated at 2.2 years	Combination therapy offered no renal benefit but resulted in excessive risk of hyperkalemia (6.3 versus 2.6 events per 100 person years; P < 0.001) and acute kidney injury (12.2 versus 6.7 events per 100 person years; P < 0.001).
AVOID [20]	599 T2DM	Losartan versus aliskiren/ losartan combo	6 months	Aliskiren (direct renin inhibitor)/losartan combo led to reduction of urinary albumin: creatinine ratio by 20% (95% CI 9–30; P < 0.001) independent of blood pressure control.
ALTITUDE [21]	8561 T2DM	RAS blockade plus aliskiren versus placebo	Terminated at 2.7 years	Addition of aliskiren to maximal ARB offered no additional benefit. Hyperkalemia and hypotension were significantly increased in the aliskiren arm.
BEAM [22]	227 T2DM	Bardoxolone methyl versus placebo	52 weeks	Bardoxolone methyl at 25, 75 and 150 mg resulted in a higher GFR (5.8 ± 1.8, 10.5 ± 1.8 and 9.3 ± 1.9 mL/min/1.73 m^2) compared with placebo at 52 weeks.
BEACON [23]	2185 T2DM	Bardoxolone methyl versus placebo	Terminated at 9 months	Bardoxolone methyl led to a significant increase in cardiovascular morbidity (HR 1.83; 95% CI 1.32–2.55; P < 0.001).
Di.N.A.S. [24]	223 T1&2DM	Sulodexide versus placebo	8 months	4 months of sulodexide (200 mg/day) significantly reduced albuminuria. Effect persisted after 8 months with 62% reduction compared with placebo (P = 0.0001).
Sun-MACRO [25]	1248 T2DM	Maximum ARB plus sulodexide versus placebo	Terminated	No significant benefit observed in end points of serum creatinine doubling and ESRD.
VITAL [26]	281 T2DM	RAS inhibition plus paricalcitol versus placebo	24 weeks	Paricalcitol at 2 μg/day reduced albuminuria (20% compared with placebo). However, 2 μg/day was poorly tolerated and patients often reduced the dosage.
CANTATA-SU [27]	1450 T2DM	Canagliflozin versus glimepiride	52 weeks	Canagliflozin caused initial decrease in GFR but subsequently stabilized while individuals in the glimepiride arm had progressive GFR decline (−1.7 versus −5.1 mL/min/1.73 m^2 after 52 weeks).
ASCEND [28]	1392 T2DM	Avosentan versus placebo	Terminated at 4 months	Avosentan reduced proteinuria compared with placebo, but, had excess adverse cardiovascular events; especially fluid overload (4.6%; P = 0.225), congestive heart failure (3.6%; P = 0.194) and death (2.6%).

ARB, angiotensin receptor blocker; RAS, renin–angiotensin system; T1DM, type 1 diabetes mellitus.

SGLT2 INHIBHITORS



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
Empagliflozin	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
Placebo	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 @denilse_am

Could dapagliflozin improve kidney and cardiovascular outcomes in patients with CKD?

#NephJC

Randomized
Double-blind
Placebo-controlled
Multicenter

386 sites in 21 countries

N= 4304

GFR 25-75 ml/min

67.5% diabetes type 2

ACR 200-5000mg/g

Outcomes

Kidney
- Decline in GFR at least 50%
- ESKD
- Death from renal causes

Cardiovascular
- Hospitalization for heart failure
- Death from cardiovascular causes

Placebo

N= 2152

Dapagliflozin 10mg/d

N= 2152

	Primary composite outcome	Composite kidney outcome	Composite cardio-vascular outcome	Death from any cause
Placebo	14.5%	11.3%	6.4%	6.8%
Dapagliflozin 10mg/d	9.2%	6.6%	4.6%	4.7%
	P<0.001	P<0.001	P=0.009	P=0.004

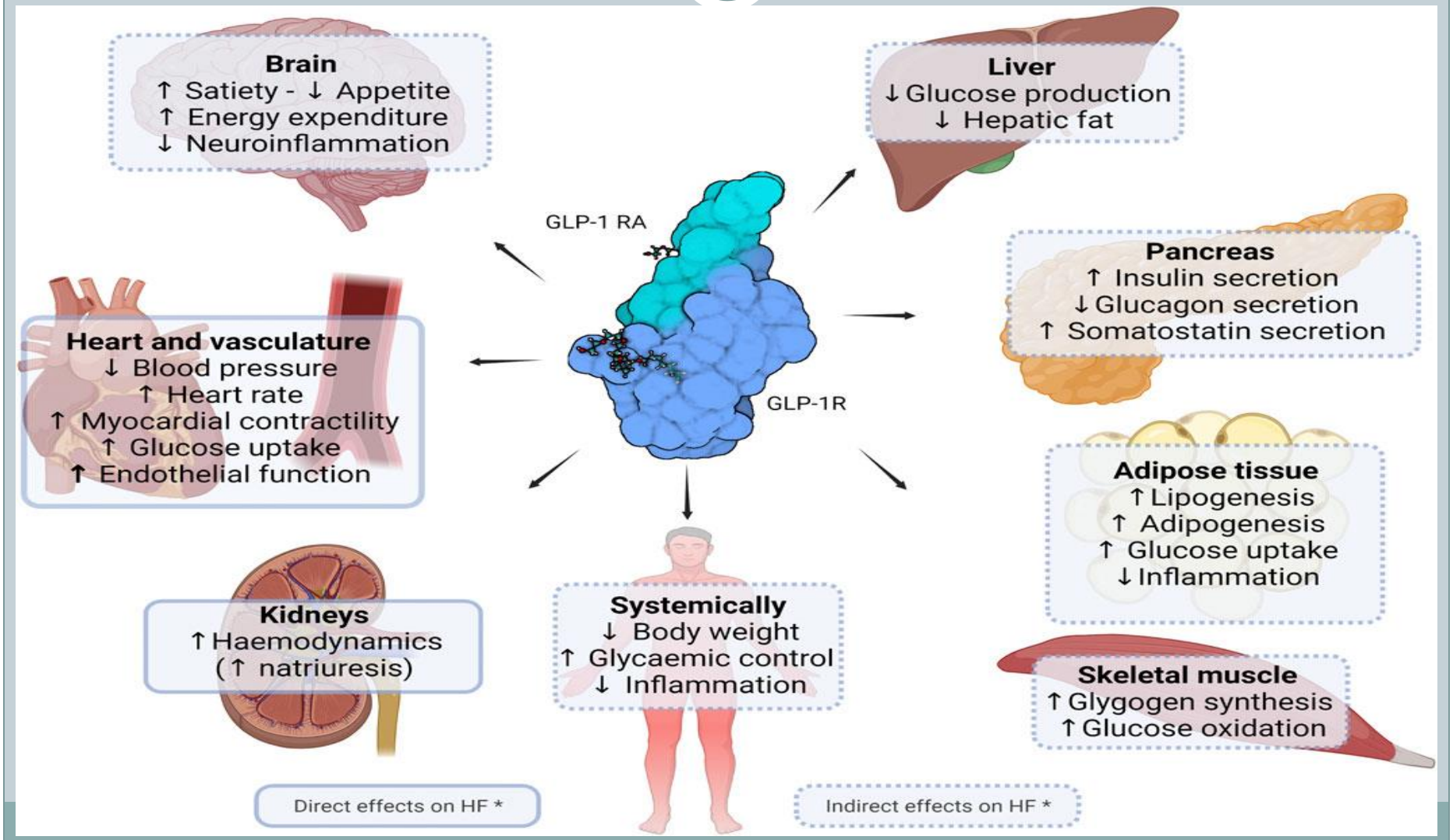
Conclusion: Among patients with chronic kidney disease, the risk of any composite kidney or cardiovascular outcomes or death was significantly lower with dapagliflozin than with placebo.

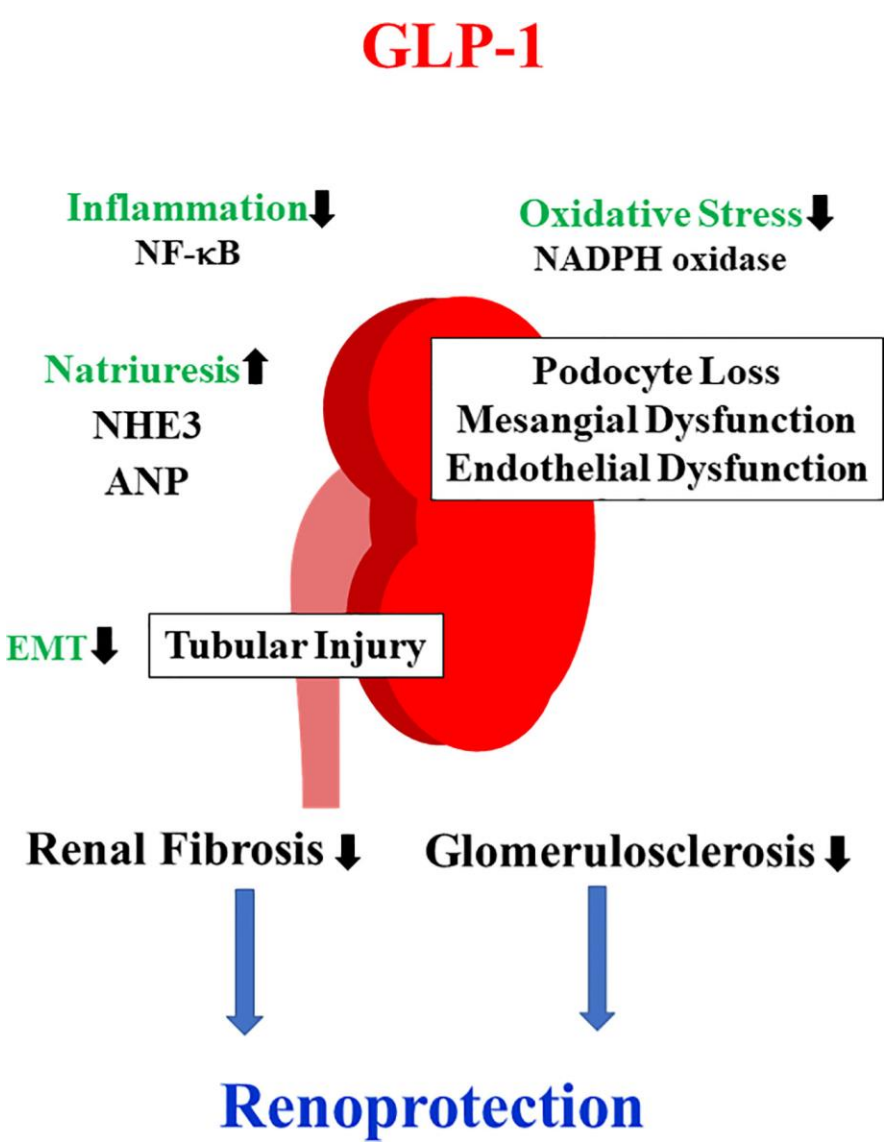
Reference: Heerspink HJL *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Sep 24. DOI: 10.1056/NEJMoa2024816.

Visual abstract: Denisse Arellano, MD @deniise_am

NEPHROLOGY SOCIAL MEDIA COLLECTIVE

EFFECTS OF GLP1A

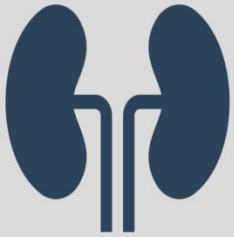




- GLP-1RAs have been shown to activate PKA and increase the production of cyclic adenosine monophosphate (cAMP).
- NADPH oxidase and NF-κB activity are inhibited, resulting in the attenuation of oxidative stress and inflammation.
- Prevent podocyte loss as well as mesangial and endothelial dysfunction.
- GLP-1RAs inactivate NHE3 and promote atrial natriuretic peptide (ANP) secretion, thereby inducing natriuresis.
- GLP-1RAs inhibit tubular injury and subsequent tubulointerstitial fibrosis.

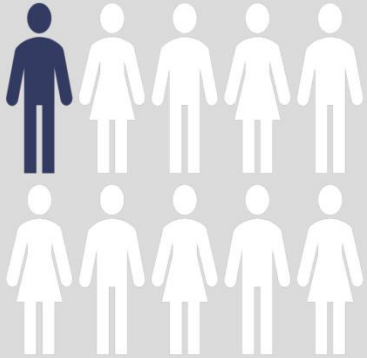
FLOW: the first dedicated kidney outcomes trial with a GLP-1RA

CKD is a common complication of T1D and T2D



46%

536 million affected in 2021, predicted to rise to 783 million by 2045



$39 million in the US alone

85,000 deaths every year

1 in 10 in the general population

A global kidney outcomes trial

Randomized controlled clinical trial

QW SC semaglutide 1 mg + SOC (n=1767)	baseline eGFR: 46.9
Placebo + SOC (n=1766)	baseline eGFR: 47.1

- **3.4**-year follow-up
- **28** countries
- **387** sites
- **3,533** participants
- **Primary outcome:** time to first occurrence of major kidney outcomes

Key findings for semaglutide

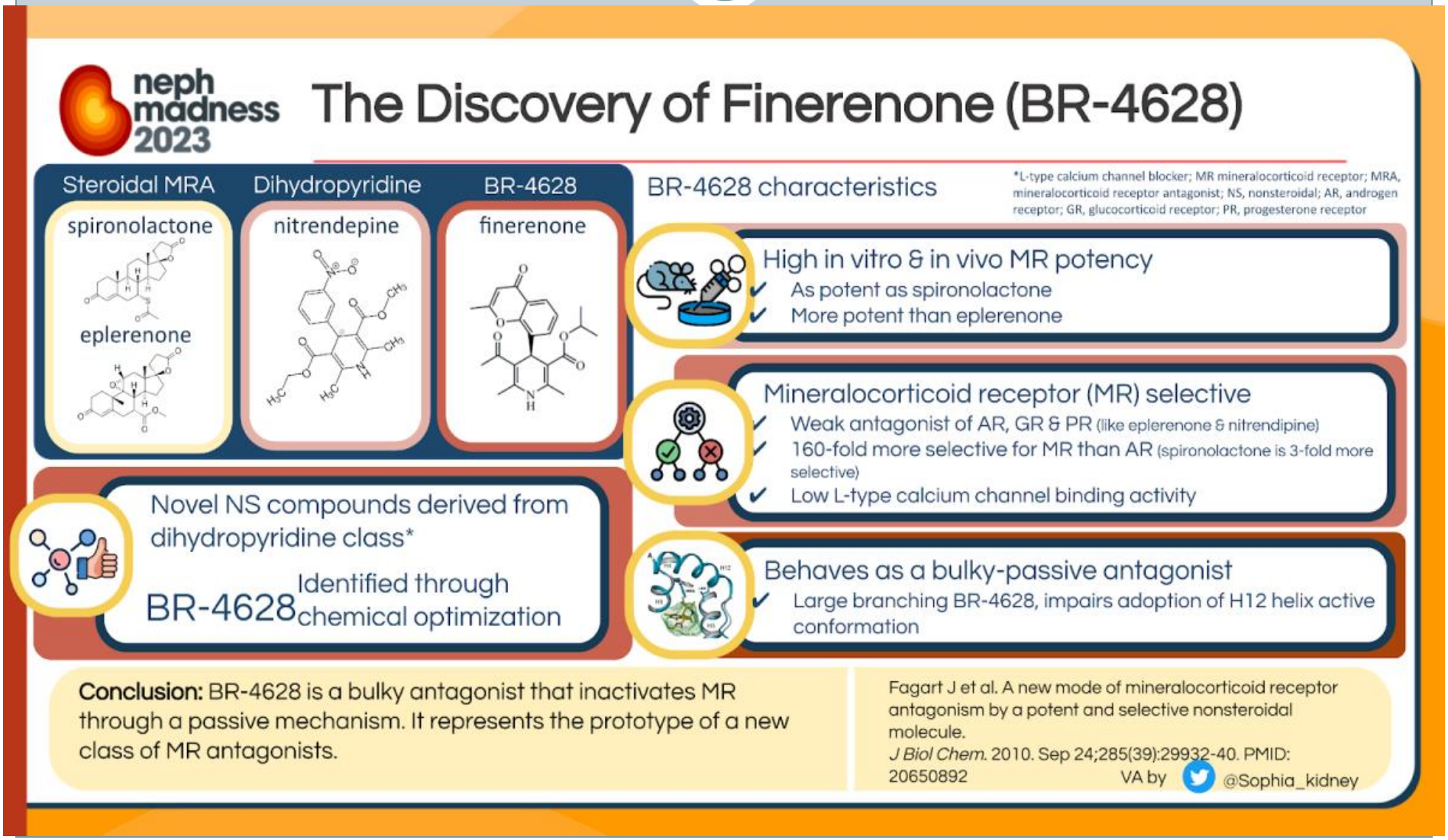
24% lower risk of composite primary outcome

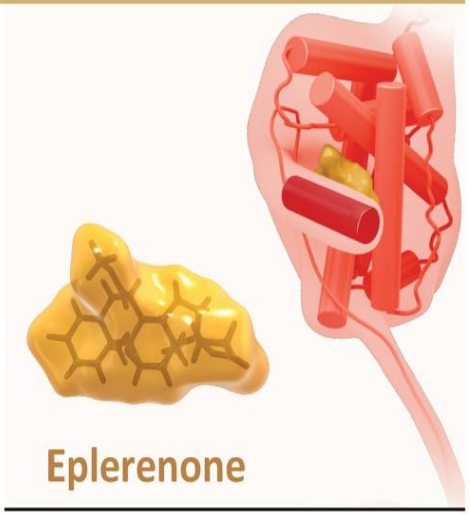
Consistent reductions for kidney disease components

1.16 mL/min/1.73m² per year Slower reduction in mean eGFR

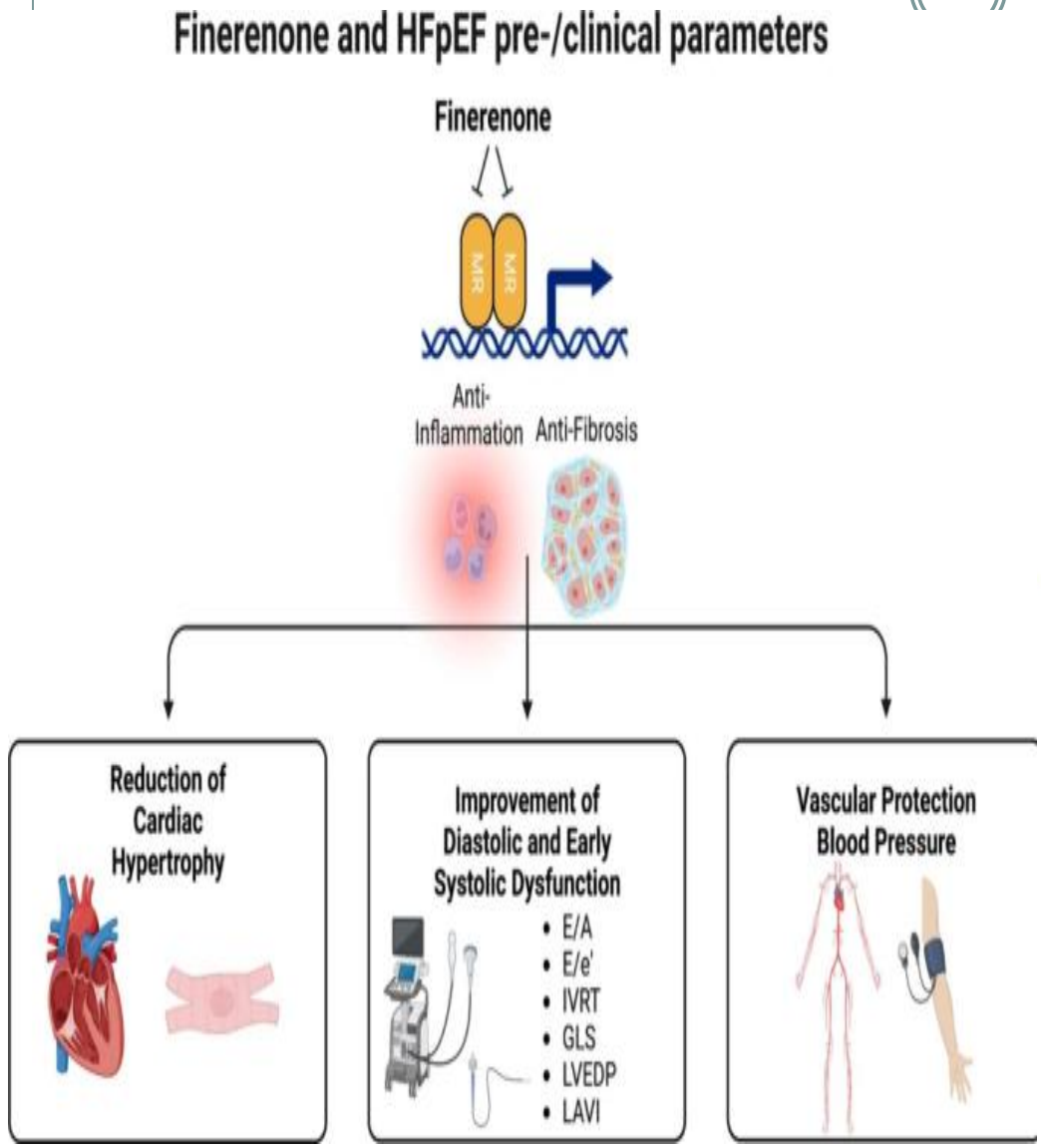
Rossing P, Pratley R, Perkovic V, et al. The First Dedicated Kidney Outcome Trial with a GLP-1 Receptor Agonist—Once-Weekly Semaglutide and the FLOW Trial Results. Presented at ADA 2024.

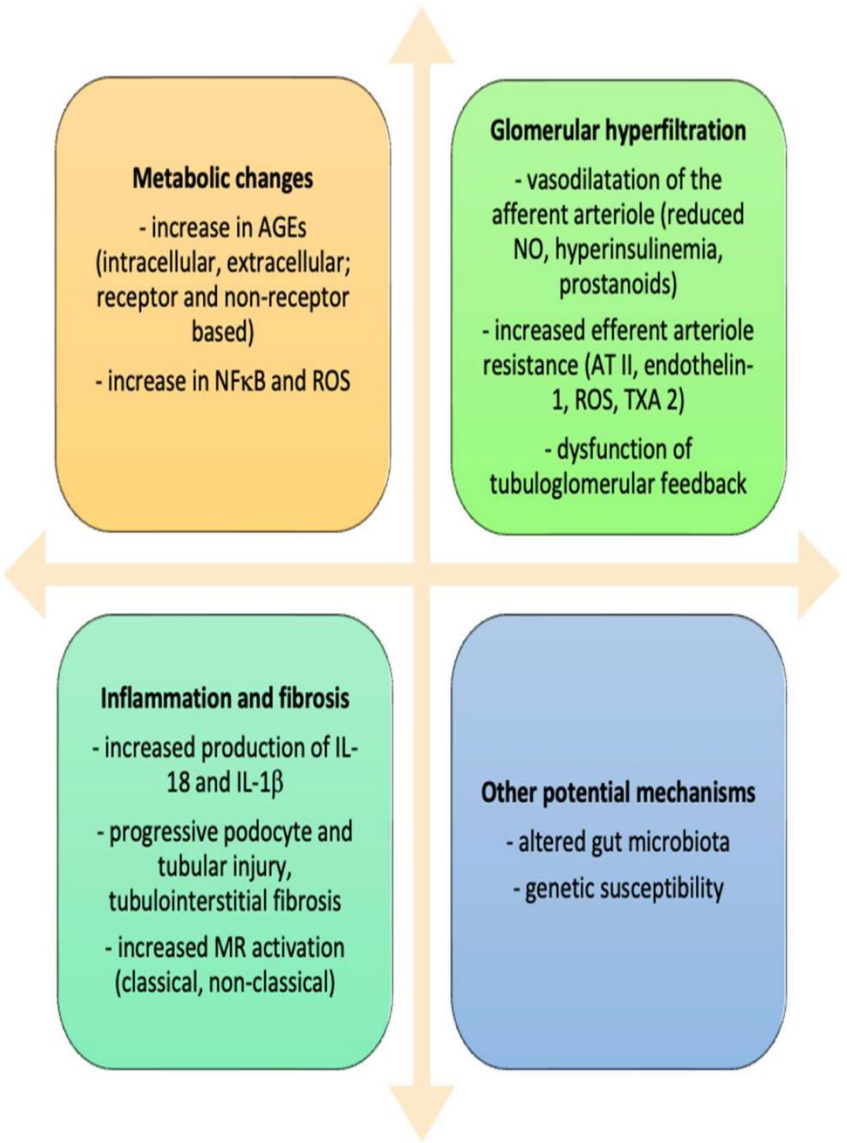
Non-steroidal mineralocorticoid receptor antagonists (nsMRA)



	Steroidal MRAs		Finerenone
	 Spironolactone	 Eplerenone	 Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (non-steroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	–
Sexual side effects	++	(+)	–
Half-life	>20 h**	4–6 h**	2–3 h*
Active metabolites	++	–	–
Effect on BP	+++	++	+

MECHANISM OF FINERENONE





What are the Long-term Effects of Spironolactone on Proteinuria and Kidney Function in Patients with Chronic Kidney Disease?

neph madness 2023

Cohort

- Prospective randomized open-label
- Chronic kidney Disease* (N=165)
- eGFR = 34 to 116 ml/min/1.73m^2
- Proteinuria 1000 – 3900 mg/g

(1:1)

	eGFR (ml/min/1.73m^2)		Proteinuria (mg/g)		Adverse effects
	Baseline	1 year	Baseline	1 year	K^+ (mEq/L) at 1 year
Conventional Rx	62.2 ± 2.1	56.4 ± 2.3	2000 ± 70	2110 ± 80	4.3 ± 0.05
	P<0.01		Not significant		Not significant
Spironolactone + Conventional Rx	62.4 ± 2.4	58.6 ± 2.6	2100 ± 80	890 ± 60	5 ± 0.05
	P<0.001		P<0.001		P<0.001

*Before inclusion, all patients had been followed in the outpatient clinic for at least 1 year and treated with ACEIs and/or ARBs.

Conclusion: This study has shown that spironolactone may reduce proteinuria and decrease progression of chronic kidney disease.

Citation: Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. *Kidney Int.* 2006 Dec;70(12):2116-23.

VA by @nephromythri

Is Finerenone Effective in Improving Outcomes in CKD Patients with Diabetes?

neph madness 2023

Cohort

- CKD and type 2 DM
- RAS blockade
- Categories
  - UACR: 30-<300, eGFR: 25-<60 Or UACR: 300--5000, eGFR: 25-<75

Primary Composite outcome

Kidney failure, sustained ≥40% decrease in eGFR from baseline, or death from renal causes.

Secondary Composite outcome

CV death, nonfatal MI or stroke, or HF hospitalization

Hyperkalaemia-related discontinuation rates

	Placebo n=2841	Finerenone n=2833
Primary Composite outcome	21.1%	17.8%
	HR: 0.82, 95% CI, 0.73 - 0.93	
Secondary Composite outcome	14.8%	13.0%
	HR: 0.86, 95% CI, 0.75 - 0.99	
Adverse events	0.9%	2.3%
	Similar in both groups	

effectiveness

Median follow-up: 2.6 Yr

UACR: urinary albumin-to-creatinine ratio lin mg/g, CKD: Chronic kidney diseases, eGFR: estimated glomerular filtration rate

Conclusion: In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo

Citation : Bakris GL, et al . Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med. 2020 Dec 3;383(23):2219-2229. doi: 10.1056/NEJMoa2025845.

VA by @Priti899

	FIDELIO-DKD	FIGARO-DKD
	Finerenone in reducing kiDney faiLure and disease prOgression in DKD	Finerenone in reducinG cArdiovascular moRtality and mOrbidity in DKD
Patients	Mainly Stage 3-4 CKD	Mainly Stage 1-2 CKD
1 Primary outcome	↓ 18% decrease in CKD progression (HR 0.82; 95% CI 0.73–0.93)	↓ 13% decrease in CV mortality and morbidity (HR 0.87; %95 CI 0.76–0.98)
2 Secondary outcome	↓ %14 decrease in CV mortality and morbidity (HR 0.86; 95% CI 0.75–0.99)	↓ %13 decrease in CKD progression (HR 0.87; %95 CI 0.76–1.01) (not significant)
Safety	Favorable safety profile: small and manageable hyperkalemia risk with minimal clinical effect	

FIDELITY

FIDELIO-DKD plus FIGARO-DKD T2D patients with

- Stage 1-4 CKD
- moderate-to-severe albuminuria
- good glycemic and blood pressure control
- on maximum tolerated labeled doses of ACEi or ARB

Finerenon enabled

14% reduction in the CV morbidity and mortality risk (HR 0.86; %95 CI 0.78-0.95)

23% reduction in CKD progression (HR 0.77; %95 CI 0.67-0.88)

Finerenone is an effective treatment option in T2D patients with stage 1-4 CKD for renal and CV protection

PREVENTION OF PROGRESSION OF DN