Nuovi farmaci per la nefroprotezione: $SGLT_2$ inibitori, agonisti recettoriali GLP1, antagonisti recettoriali aldosterone (MRA)

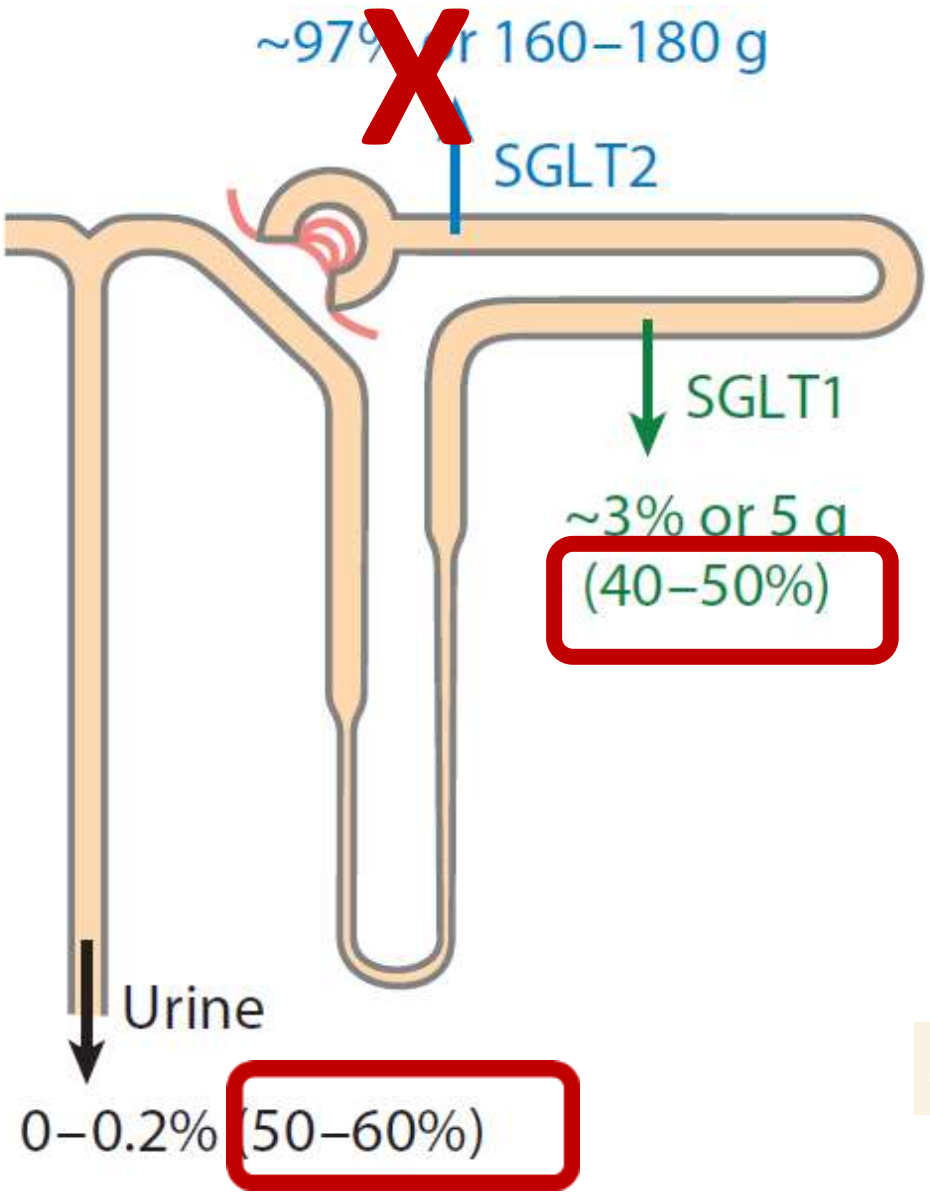
Enrico Fiaccadori

Università di Parma

Agenda

- SGLT2 inhibitors: mechanisms of action in the kidney and clinical trials on renal protection
- Mineralcorticoid receptor antagonists (MRA): mechanisms of action in the kidney and clinical trials on renal protection
- GLP1 receptor agonists: mechanisms of action in the kidney and clinical trials on renal protection
- Association between the new drugs for renal protection and recent guidelines

SGLT2 and SGLT1 mediate glucose reabsorption in the kidney: the effects of SGLT2 inhibition on urinary glucose excretion

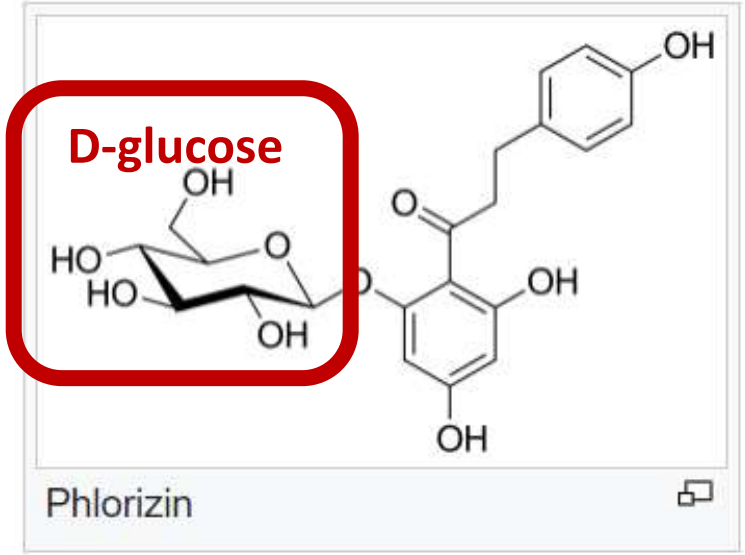


SGLT: sodium-glucose transporter

SGLT2 inhibition induces a condition of acquired euglycemic glycosuria associated with increased urinary sodium in the proximal tubule

Annu. Rev. Med. 2015. 66:255–70

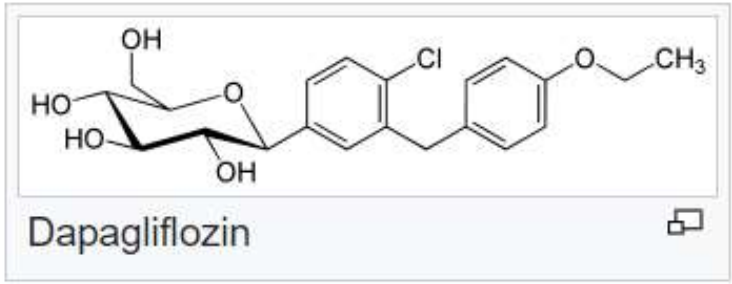
Glifozines

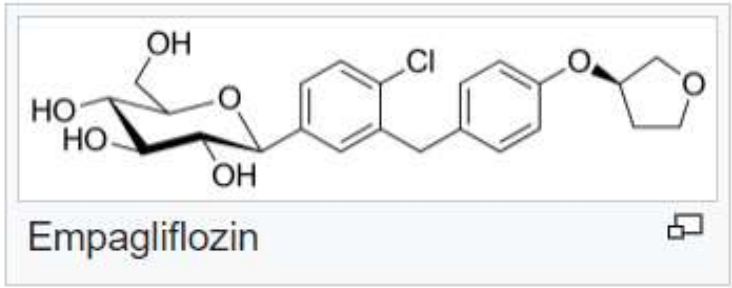


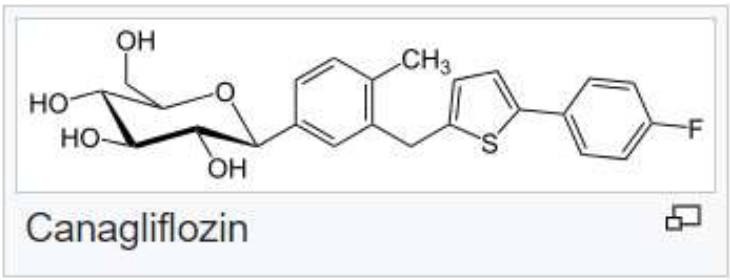
Glicoside O-arilic formed by d-glucose and an aromatic ketone

Natural competitive inhibitor of the glucose transporters SGLT1 and SGLT2

Synthetic selective inhibitors of glucose transporters



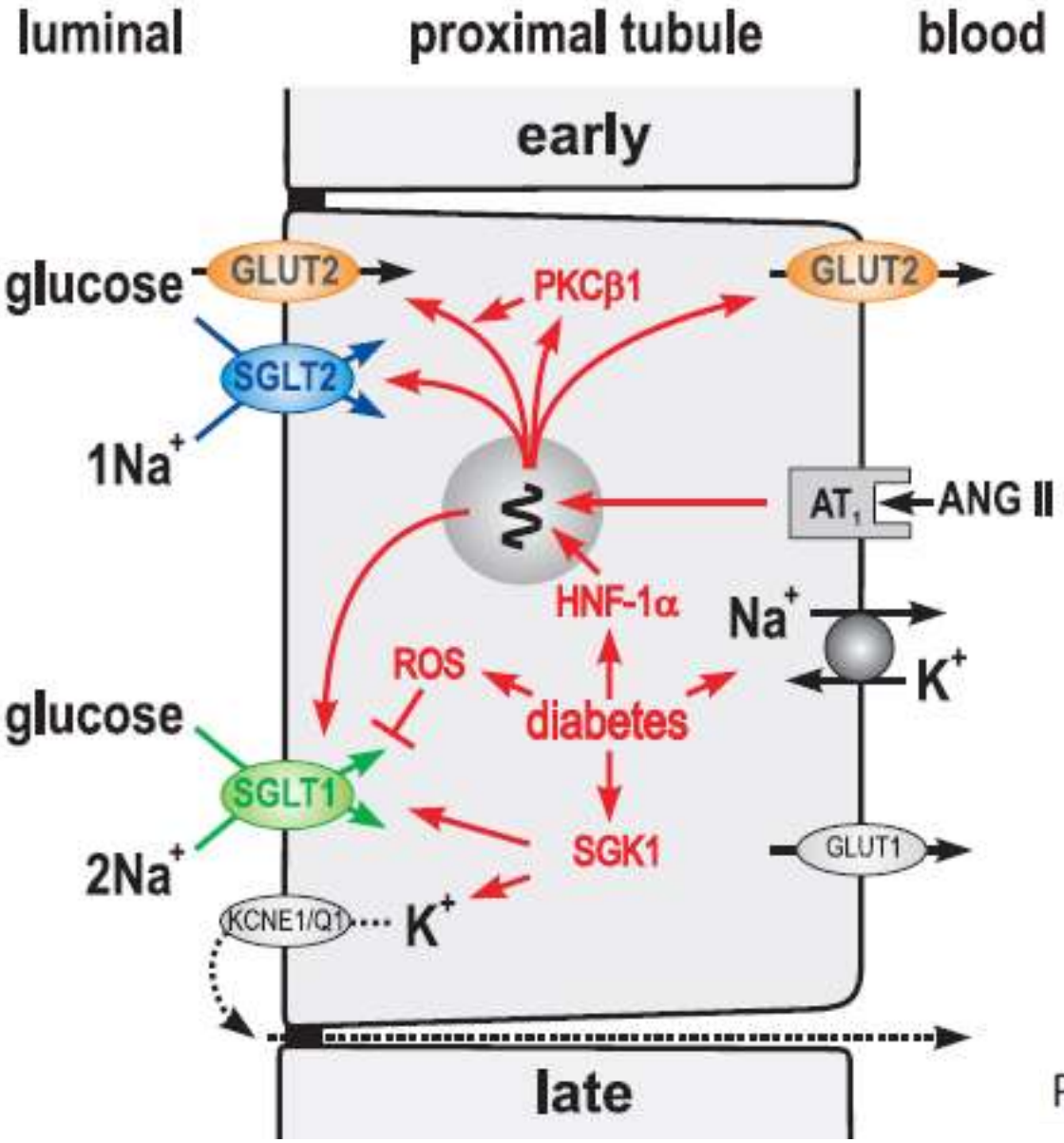




Currently available SGLT inhibitors are selective for the SGLT2 transporter

Generic name (trade name)	Company	SGLT2:SGLT1 selectivity
Dapagliflozin (Forxiga®/Farxiga®)	Bristol-Myers Squibb, AstraZeneca	1242
Canagliflozin (Invokana®)	Janssen	155
Empagliflozin (Jardiance®)	Boehringer Ingelheim	2680
Ipragliflozin (Suglat®)	Astellas Pharma, Kotobuki	254
Luseogliflozin (Lusefi®)	Taisho Pharmaceutical	1770
Tofogliflozin (Apleway®, Deberza®)	Kowa Company, Sanofi, Chugai	2912
Sotagliflozin	Lexicon Pharmaceuticals	20

Factors stimulating glucose reabsorption in the PT



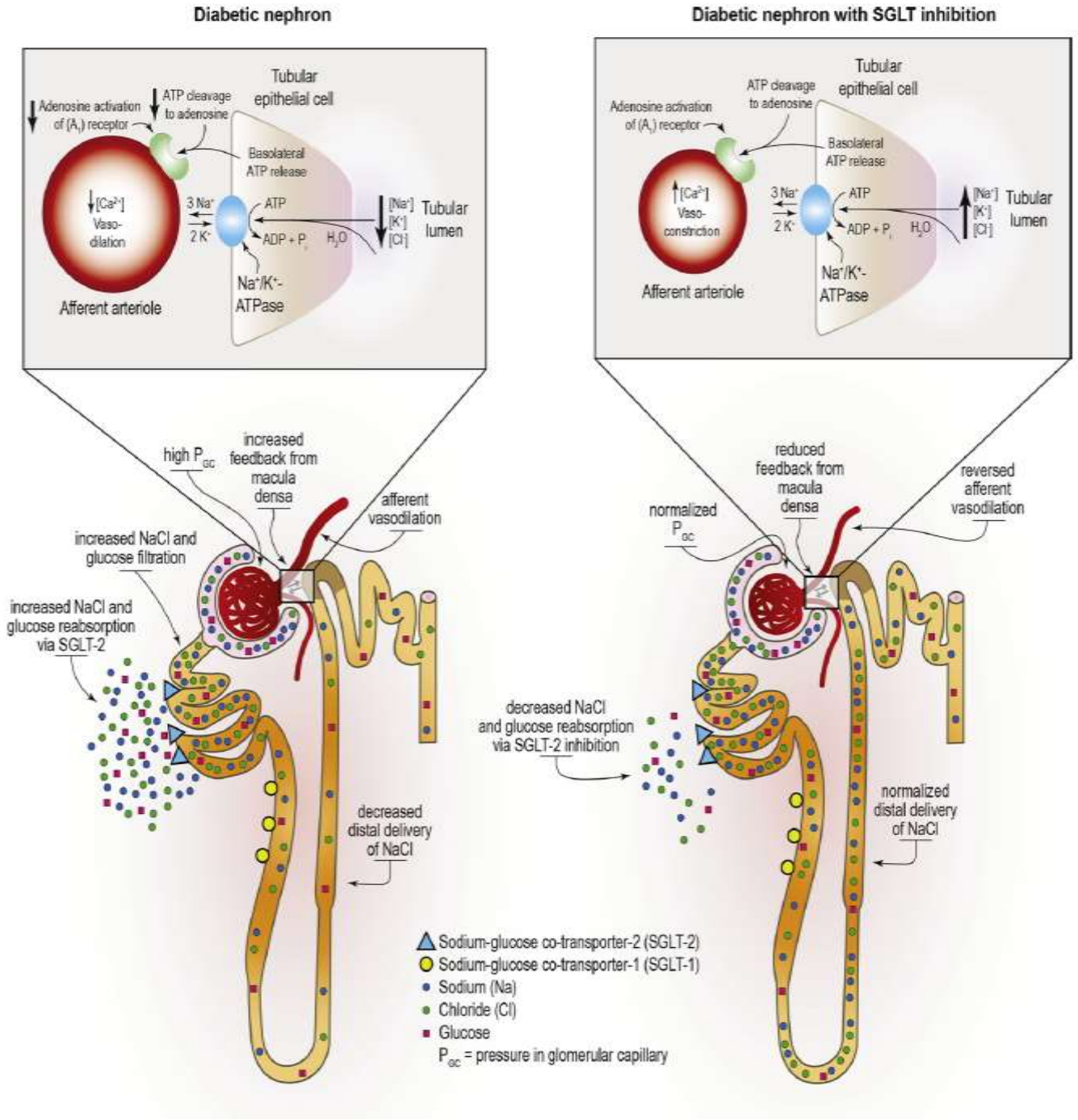
Glucose transporters GLUT2 and GLUT1 mediate glucose transport across the basolateral membrane, but GLUT2 may also translocate to the apical membrane in diabetes.

ANG II, serum and glucocorticoid inducible kinase SGK1, hepatocyte nuclear factor HNF-1, and protein kinase C PKC1 promote glucose reabsorption in the diabetic kidney, whereas the induction of oxidative stress (ROS) can inhibit.

Na-glucose cotransport is electrogenic and luminal K channels serve to stabilize the membrane potential (e.g., KCNE1/KCNQ1 in late proximal tubule).

Pflügers Archiv - European Journal of Physiology (2020) 472:1207–1248

Effects of diabetes and SGLT2 inhibition on nephron hemodynamics



In the diabetic nephron, overexpression and compensatory upregulation of the activity of SGLT2 and SGLT1 in glucose and Na reabsorption in the proximal convoluted tubule results in decreased delivery of solutes to the macula densa. The resulting reduction in solute and water transport into the tubular epithelial cells reduces adenosine triphosphate (ATP) release from the basolateral membrane of tubular epithelial cells, which in turn reduces adenosine production and activation of the A1 receptor expressed in the afferent arteriole with a net effect of vasodilation. In the diabetic nephron with SGLT inhibition, lessening SGLT2-driven sodium-coupled glucose transport in the proximal convoluted tubule normalizes solute delivery to the macula densa, increasing solute and water reabsorption and increasing basolateral release of ATP from the tubular epithelium. The resulting increase in adenosine activation of the A1 adenosine receptor reverses afferent arteriole vasodilation associated with diabetic kidney disease

Alicic RZ et al. Am J Kidney Dis 2018; 72:267-277

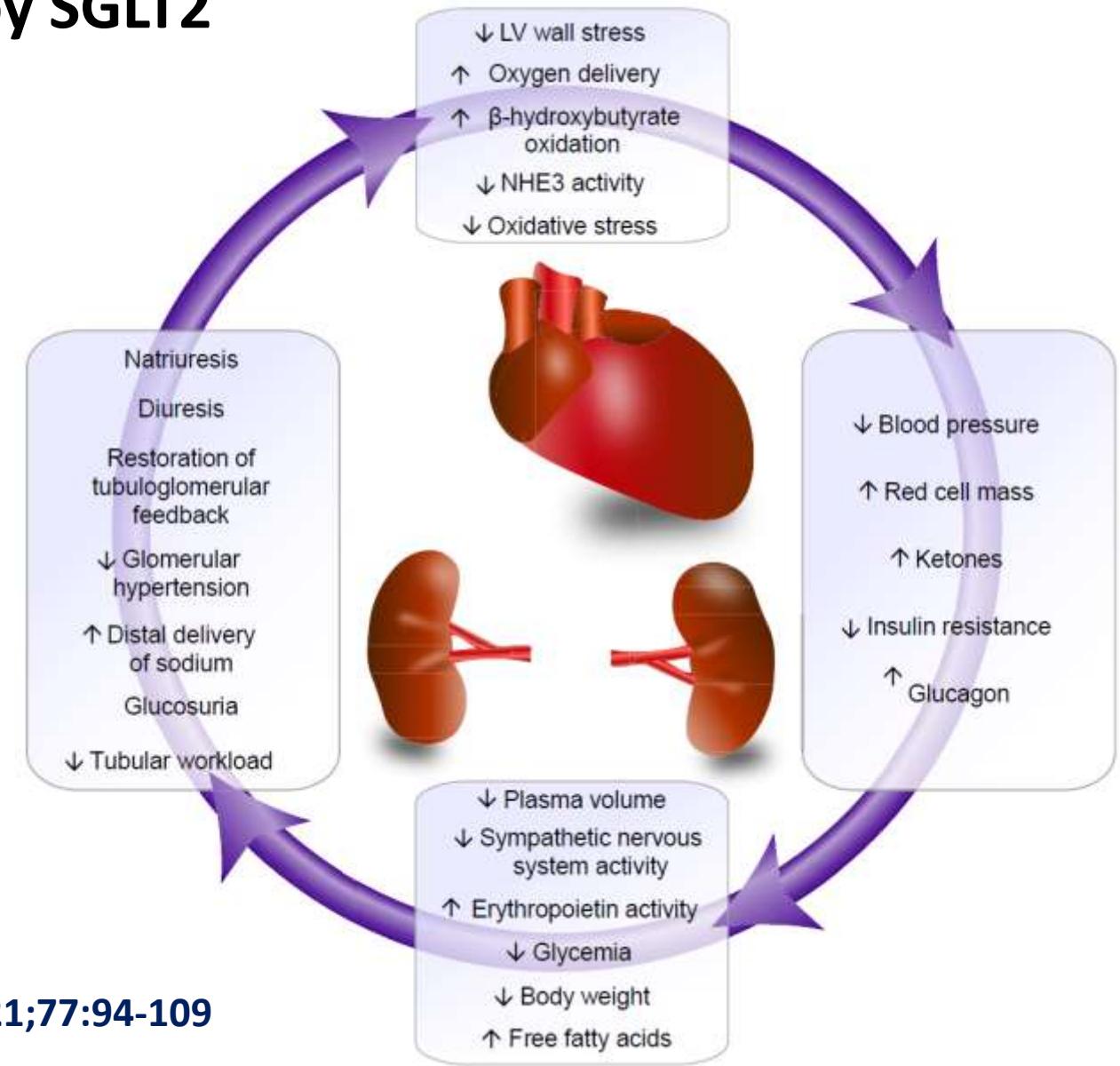
Summary of renal effects of SGLT2 inhibition in the kidney

SGLT2i reduces GFR (reduced hyperfiltration per single nephron) initially, to preserve kidney function in the long term

SGLT2i reduces the hyperactivation of SGLT2 transporters → reduced O_2 consumption by the kidney in parallel to more homogeneous distribution of renal transport work and O_2 consumption → less hypoxia in the parenchima → reduced risk of AKI, reduced fibrotic stimulus → reduced risk of CKD progression

SGLT2i activates kidney metabolic counterregulation, similar to fasting (ketogenesis) and salt loss conditions, that extend their protective effects to the heart

The kidney-heart connection for organ protection by SGLT2



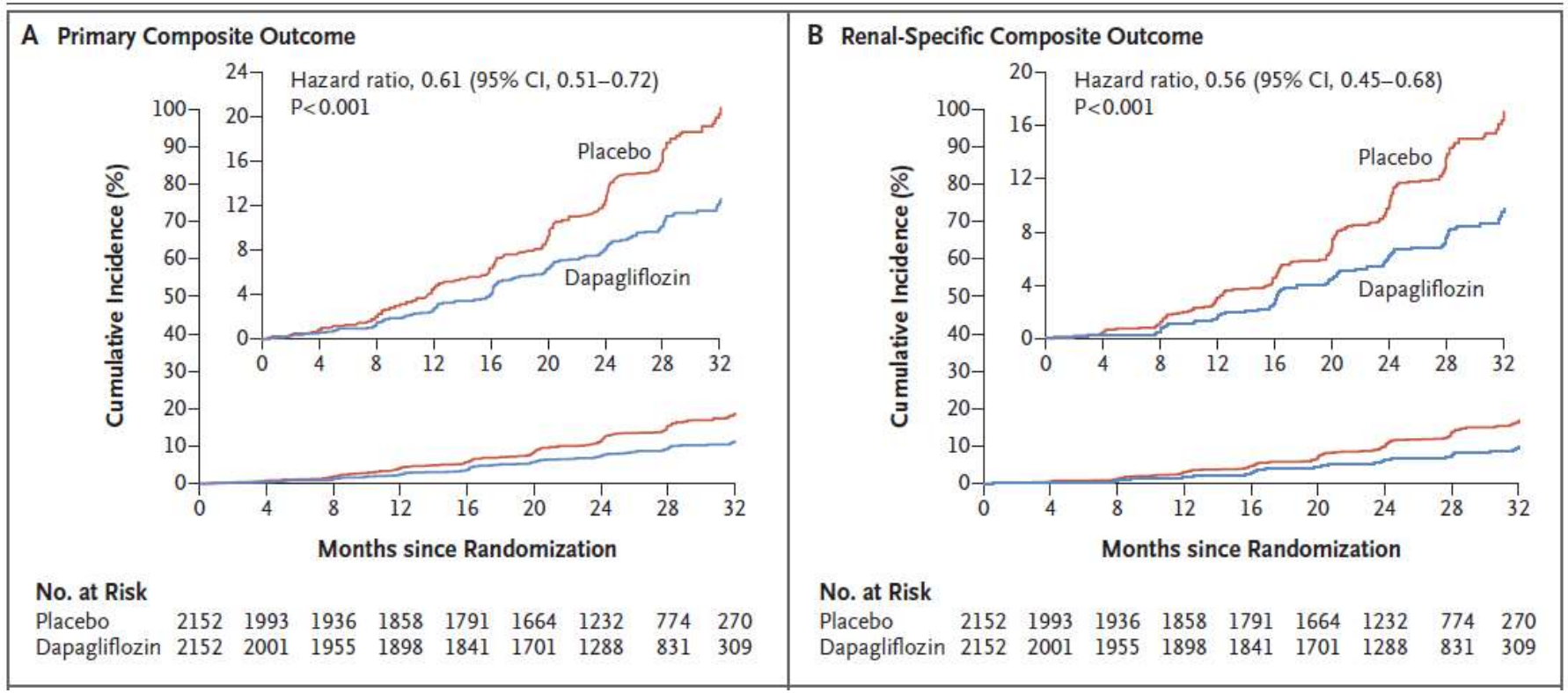
Tuttle KR et al., Am J Kidney Dis 2021;77:94-109

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

METHODS

We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m² of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.



DM-CKD
67.5%

N Engl J Med 2020;383:1436-46.

Dapagliflozin in Patients with Chronic Kidney Disease

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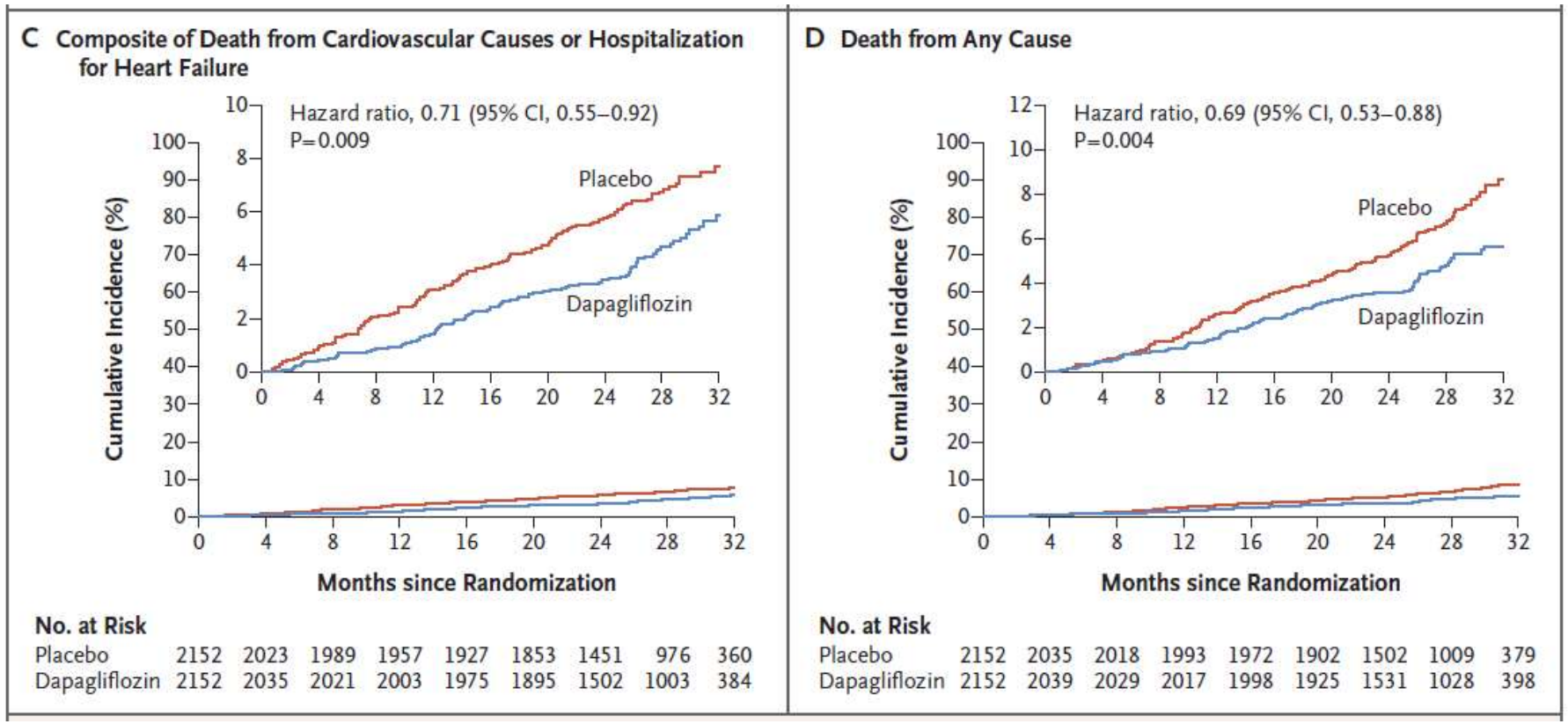

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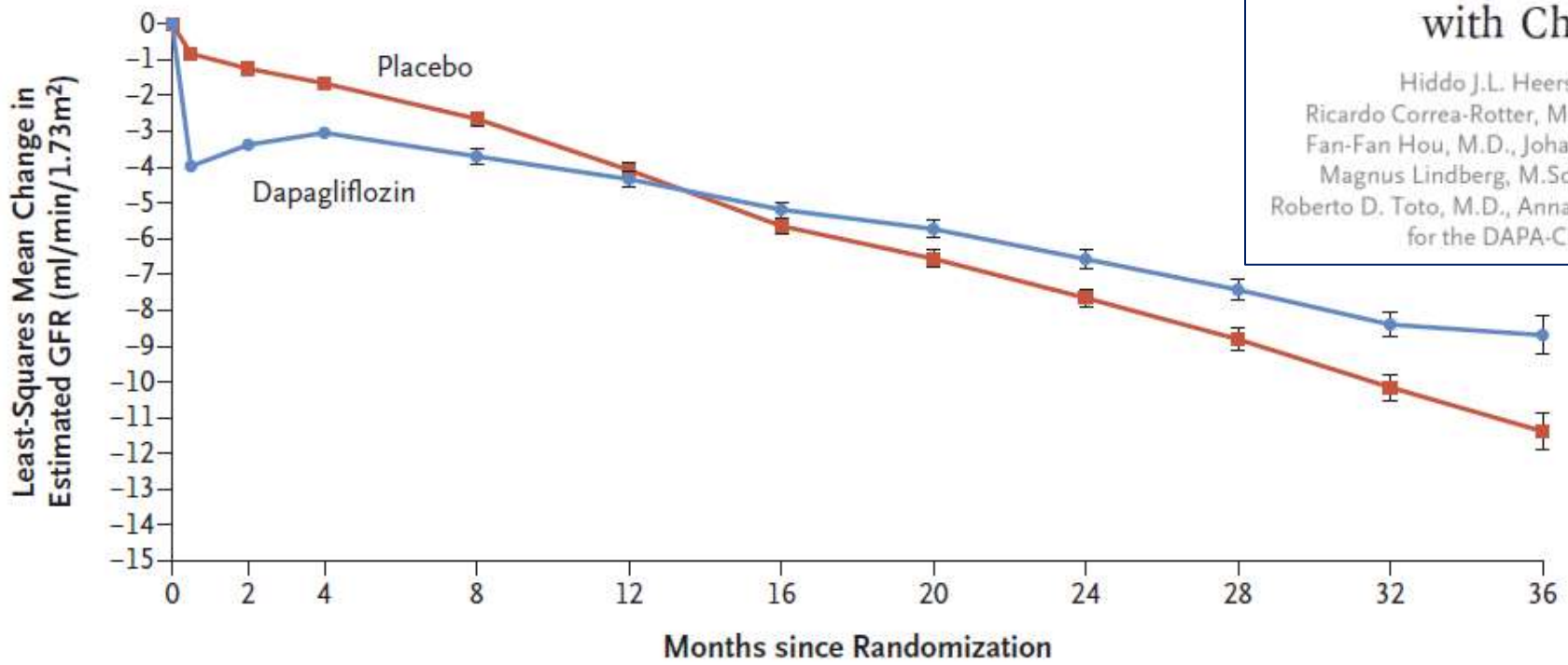


No. of Participants

Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157

Figure 3. Change from Baseline in Estimated GFR.

Shown is the least-squares mean change from baseline in the estimated GFR, calculated with the use of a repeated-measures analysis including terms for trial group, baseline measurement, visit, and interaction between visit and trial group. The I bars indicate standard errors. The mean estimated GFR at baseline was 43.2 ml per minute per 1.73 m^2 of body-surface area in the dapagliflozin group and 43.0 ml per minute per 1.73 m^2 in the placebo group.

N Engl J Med 2020;383:1436-46.

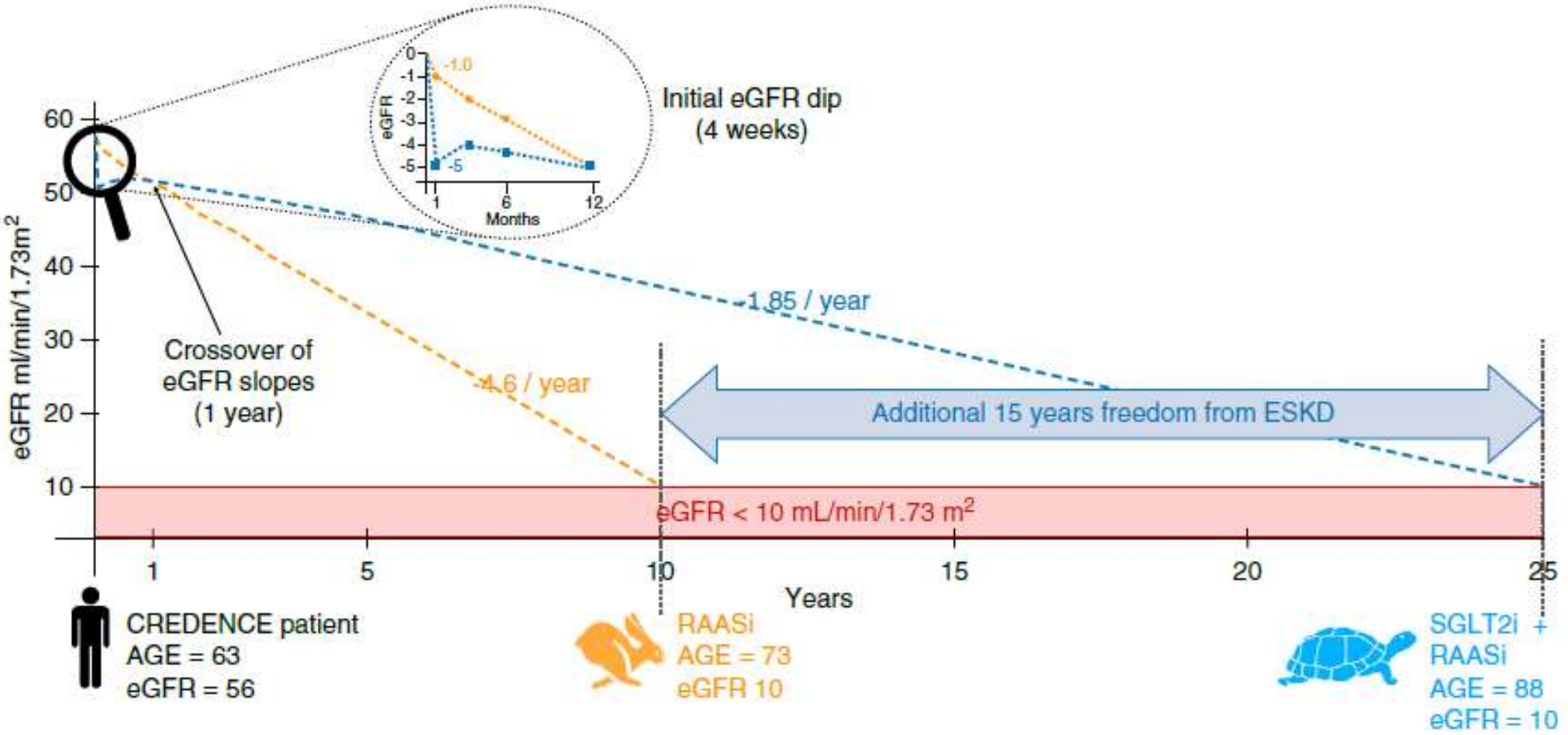


Figure 1. | SGLT2is may delay ESKD by 15 years. A typical patient included in CREDENCE would lose 4.6 ml/min per year of eGFR if treated with RAASi only, reaching ESKD in 10 years. However, if canagliflozin is added to his treatment, he would only lose 1.85 ml/min per year of eGFR, delaying ESKD by 15 years. RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

KIDNEY360 2: 1042–1047, 2021.

SCHEDA DI VALUTAZIONE E PRESCRIZIONE
DI INIBITORI DEL SGLT2, AGONISTI RECETTORIALI DEL GLP1 E INIBITORI DEL DPP4
NEL TRATTAMENTO DEL DIABETE MELLITO TIPO 2

Da compilare a cura del prescrittore che seguirà il paziente nella gestione del trattamento e del follow-up periodico (Specialista SSN, Medico di Medicina Generale).

Scheda di prima prescrizione

Medico prescrittore _____ Tel _____
Specificare se: ☐ Medico di Medicina Generale ☐ Specialista in _____
U.O. _____ Az. Sanitaria _____

Paziente (nome e cognome) _____
Sesso: ☐ M ☐ F Data di Nascita_____ Codice Fiscale _____
Residenza _____

Valutazione

Paziente in trattamento con metformina: ☐ Si ☐ No, per controindicazione o intolleranza

Farmaco

Strategia terapeutica (selezionare farmaco e posologia)

Categoria	Farmaco	Posologia
SGLT2i	☐ canagliflozin	☐ 100 mg una volta/die ☐ 300 mg una volta/die
	☐ dapagliflozin	☐ 10 mg una volta/die ☐ 5 mg una volta/die
	☐ empagliflozin	☐ 10 mg una volta/die ☐ 25 mg una volta/die
	☐ ertugliflozin	☐ 5 mg una volta/die ☐ 15 mg una volta/die
DPP4i	☐ alogliptin	☐ 6,25 mg una volta/die ☐ 12,5 mg una volta/die ☐ 25 mg una volta/die
	☐ linagliptin	☐ 5 mg una volta/die
	☐ saxagliptin	☐ 2,5 mg una volta/die ☐ 5 mg una volta/die
	☐ sitagliptin	☐ 25 mg una volta/die ☐ 50 mg una volta/die ☐ 100 mg una volta/die
	☐ vildagliptin	☐ 50 mg per 2 vv/die ☐ 50 mg una volta/die
GLP1-RA	☐ dulaglutide	☐ 0,75 mg una volta/sett ☐ 1,5 mg una volta/sett ☐ 3,0 mg una volta/sett ☐ 4,5 mg una volta/sett
	☐ exenatide	☐ 5 mcg per 2 vv/die ☐ 10 mcg per 2 vv/die
	☐ exenatide LAR	☐ 2 mg una volta/sett
	☐ liraglutide	☐ 0,6 mg una volta/die ☐ 1,2 mg una volta/die ☐ 1,8 mg una volta/die
	☐ lixisenatide	☐ 10 mcg una volta/die ☐ 20 mcg una volta/die
	☐ semaglutide orale	☐ 3 mg una volta/die ☐ 7 mg una volta/die ☐ 14 mg una volta/die
	☐ semaglutide s.c.	☐ 0,25 mg una volta/sett ☐ 0,50 mg una volta/sett ☐ 1,0 mg una volta/sett

Categoria	Farmaco	Posologia
SGLT2i/MF	☐ canagliflozin/metformina	☐ 50/850 mg per 2 vv/die ☐ 50/1000 mg per 2 vv/die ☐ 150/850 mg per 2 vv/die ☐ 150/1000 mg per 2 vv/die
	☐ dapagliflozin/metformina	☐ 5/850 mg per 2 vv/die ☐ 5/1000 mg per 2 vv/die
	☐ empagliflozin/metformina	☐ 5/850 mg per 2 vv/die ☐ 5/1000 mg per 2 vv/die ☐ 12,5/850 mg per 2 vv/die ☐ 12,5/1000 mg per 2 vv/die
	☐ ertugliflozin/metformina	☐ 2,5/1000 mg per 2 vv/die ☐ 7,5/1000 mg per 2 vv/die
DPP4i/MF	☐ alogliptin/metformina	☐ 12,5/850 mg per 2 vv/die ☐ 12,5/1000 mg per 2 vv/die
	☐ linagliptin/metformina	☐ 2,5/850 mg per 2 vv/die ☐ 2,5/1000 mg per 2 vv/die
	☐ saxagliptin/metformina	☐ 2,5/850 mg per 2 vv/die ☐ 2,5/1000 mg per 2 vv/die
	☐ sitagliptin/metformina	☐ 50/850 mg per 2 vv/die ☐ 50/1000 mg per 2 vv/die^ ☐ 100/1000 mg una volta/die* ☐ 100/1500 mg una volta/die* ☐ 100/2000 mg una volta/die*
	☐ vildagliptin/metformina	☐ 50/850 mg per 2 vv/die ☐ 50/1000 mg per 2 vv/die
DPP4i/TZD	☐ alogliptin/pioglitazone	☐ 12,5/30 mg una volta/die ☐ 12,5/45 mg una volta/diie ☐ 25/30 mg una volta/die ☐ 25/45 mg una volta/die
SGLT2i/ DPP4i	☐ empagliflozin/linagliptin	☐ 10/5 mg una volta/die ☐ 25/5 mg una volta/die
	☐ saxagliptin/dapagliflozin	☐ 5/10 mg una volta/die
	☐ ertugliflozin/sitagliptin	☐ 5/100 mg una volta/die ☐ 15/100 mg una volta/die
GLP1-RA/ insulina	☐ insulina degludec/liraglutide penna	dosi unitarie una volta/die (da 10 a 50U di degludec e da 0,36 a 1,8 mg di liraglutide)
	☐ insulina glargine/lixisenatide penna 10-40	dosi unitarie una volta/die (da 10 a 40U di glargine e da 5 a 20 mcg di lixisenatide)
	☐ insulina glargine/lixisenatide penna 30-60	dosi unitarie una volta/die (da 30 a 60U di glargine e da 10 a 20 mcg di lixisenatide)

La prescrizione dell'associazione SGLT2i+DPP4i o SGLT2i+GLP1-RA può avvenire esclusivamente da parte di specialisti di strutture diabetologiche individuate dalle Regioni.
La prescrizione delle associazioni estemporanee SGLT2i+DPP4i o SGLT2i+GLP1-RA deve avvenire utilizzando esclusivamente le associazioni tra molecole autorizzate in RCP.
^posologia riferita anche all'associazione con metformina a rilascio modificato; *posologia riferita solo all'associazione con metformina a rilascio modificato.

Agenzia Italiana del Farmaco

25.05.23

RegioneEmilia-Romagna

Direzione Generale Cura della persona, Salute e Welfare

ALLEGATO A
DECISIONI ADOTTATE NELLA RIUNIONE DELLA COMMISSIONE REGIONALE DEL FARMACO DEL GIORNO 23 MARZO 2023 AI FINI DELL'AGGIORNAMENTO DEL PTR

A10BK01 DAPAGLIFLOZIN – os, A RRL (prescrizione di Centri ospedalieri o specialisti: cardiologo, internista, endocrinologo, geriatra e nefrologo), PIANO TERAPEUTICO AIFA WEB BASED (MRC), PHT.

NUOVA INDICAZIONE TERAPEUTICA: "negli adulti per il trattamento della malattia renale cronica".

DECISIONE DELLA CRF

La CRF, dopo aver valutato le prove di efficacia e sicurezza disponibili per dapagliflozin nell'estensione delle indicazioni al trattamento della malattia renale cronica negli adulti, ha espresso parere favorevole all'inserimento dell'indicazione in PTR. Dapagliflozin è classificato in classe A RRL (prescrizione di Centri ospedalieri o specialisti: cardiologo, internista, endocrinologo, geriatra e nefrologo), PHT. È previsto che la prescrizione avvenga attraverso un Piano terapeutico AIFA web based ad hoc per la MRC, che definisce i criteri di eleggibilità al trattamento.

nefrologo

-MRC di stadio da 2 a 4 (15 ≤eGFR ≤89 L/min/1,73m^2) ;
-valore al basale 25 ≤eGFR ≤ 75 mL/min/1,73 m^2;
-valore al basale di albuminuria (ACR) 200 ≤ACRe ≤ 5000 mg/g;

Table 1: Summary: of SGLT2 inhibitor kidney outcome trials [52–54].

Trial	CREDENCE ($n = 4401$)	DAPA-CKD ($n = 4304$)	EMPA-KIDNEY ($n = 6609$)
Treatment	Canagliflozin vs. placebo	Dapagliflozin vs. placebo	Empagliflozin vs. placebo
Mean participant age (years)	63	62	64
Key inclusion criteria	• T2D • eGFR 30 to <90 mL/min/1.73 m^2 • UACR >300 to 5000 mg/g • Treated with RAS inhibitor for ≥4 weeks prior to randomization	• eGFR 25 to 75 mL/min/1.73 m^2 • UACR of 200 to 5000 mg/g • Treated with RAS inhibitor for ≥4 weeks prior to screening	• eGFR 20 to <45 mL/min/1.73 m^2 regardless of albuminuria, or • eGFR 45 to <90 mL/min/1.73 m^2 with UACR ≥200 mg/g • Treated with RAS inhibitor unless deemed inappropriate by the investigator
Baseline diagnosis of T2D (%)	100	67	46
Median follow-up (years)	2.6	2.4	2.0
Primary outcome			
HR (95% CI)	ESKD, doubling of SCr, or renal or CV death	≥50% decline in eGFR, ESKD, or renal or CV death	ESKD, ≥40% decline in eGFR, sustained eGFR of <10 mL/min/1.73 m^2, or renal or CV death
	0.70 (0.59–0.82)	0.61 (0.51–0.72)	0.72 (0.64–0.82)
Key secondary outcomes			
Progression to ESKD; HR (95% CI)	0.68 (0.54–0.86)	0.64 (0.50–0.82)	N/R
CV death; HR (95% CI)	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.84 (0.60–1.19)
All-cause mortality; HR (95% CI)	0.83 (0.68–1.02)	0.69 (0.53–0.88)	0.87 (0.70–1.08)

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; HR, hazard ratio; N/R, data not reported; RAS, renin-angiotensin system; SCr, serum creatinine; T2D, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

Neumiller JJ et al., Clinical Kidney Journal 2024; 17:1–16

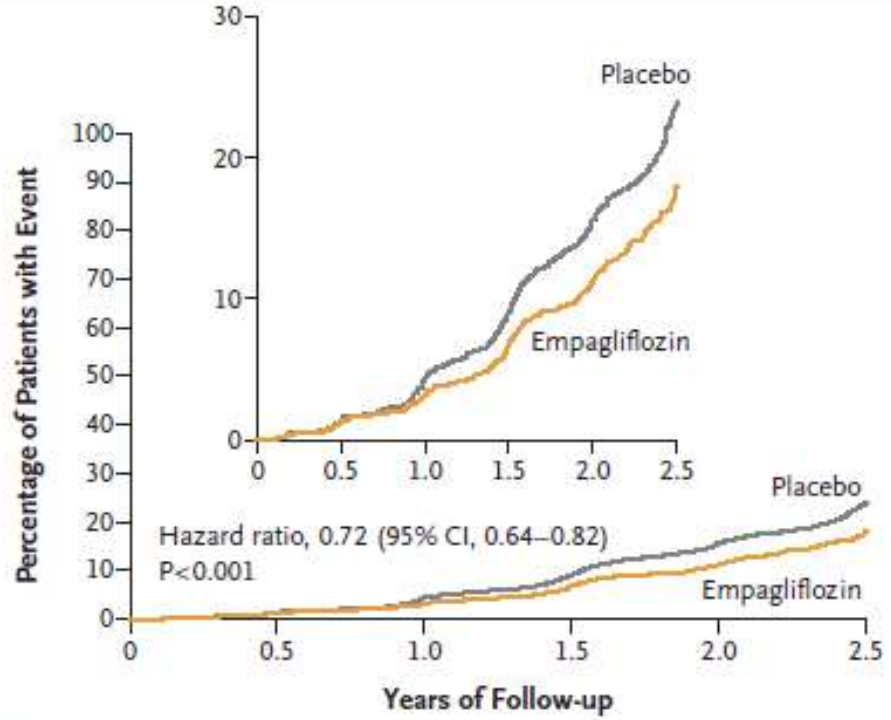


Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.
Shown are the results of the primary composite outcome of progression of kidney disease or death from cardiovascular causes. Over a median of 2 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 patients (13.1%) in the empagliflozin group and in 558 patients (16.9%) in the placebo group, representing 42 fewer primary-outcome events per 1000 patients in the empagliflozin group than in the placebo group over 2 years. The inset shows the same data on an enlarged y axis.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

54% CKD without DM2

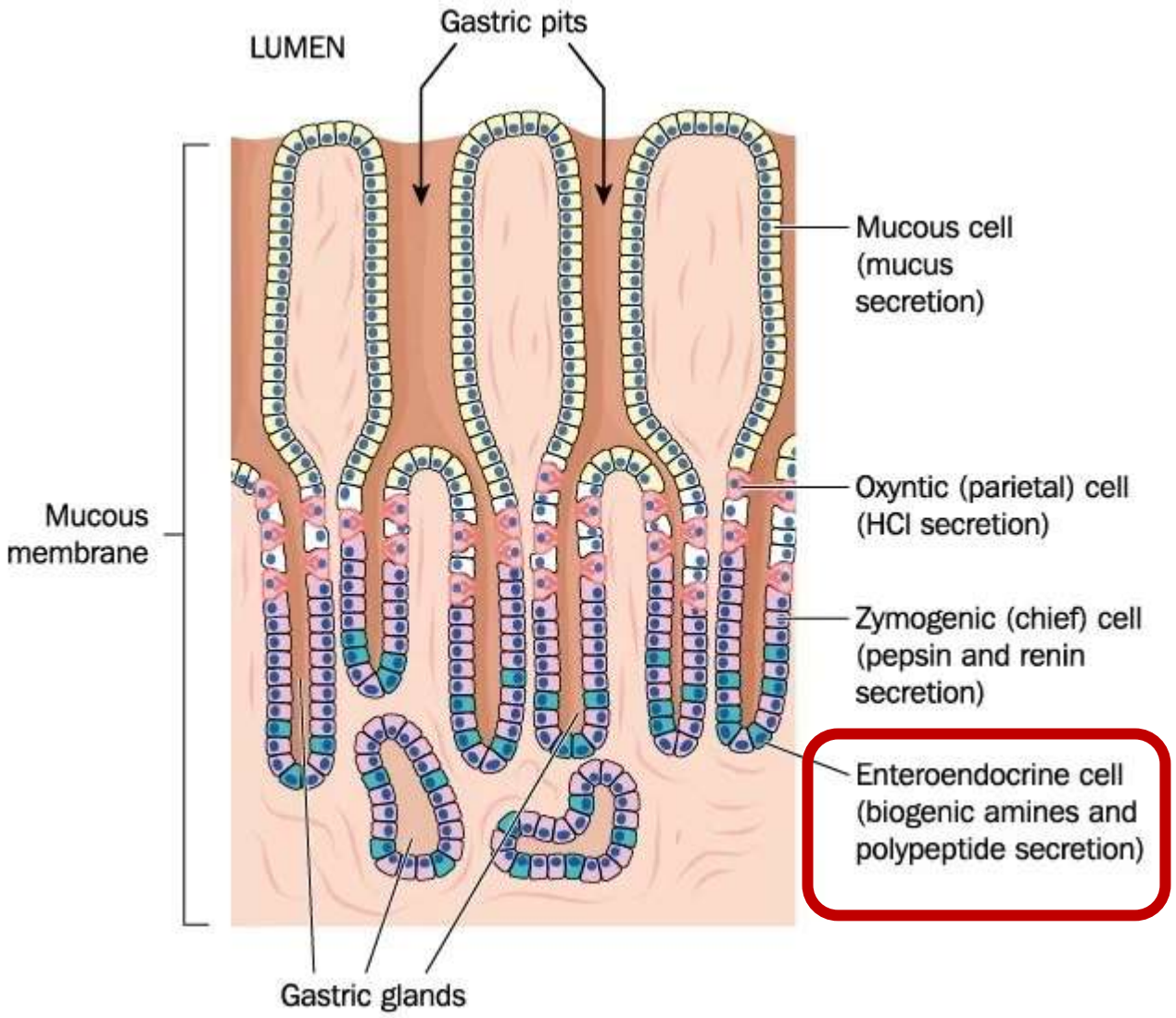
- eGFR 20 to <45 mL/min/1.73 m^2 regardless of albuminuria, or
- eGFR 45 to <90 mL/min/1.73 m^2 with UACR ≥200 mg/g
- Treated with RAS inhibitor unless deemed inappropriate by the investigator

N Engl J Med 2023;388:117-27.

Agenda

- SGLT2 inhibitors: mechanisms of action in the kidney and clinical trials on renal protection
- GLP1 receptor agonists: mechanisms of action in the kidney and clinical trials on renal protection
- Mineralcorticoid receptor antagonists: mechanisms of action in the kidney and clinical trials on renal protection
- Association between the new drugs for renal protection and recent guidelines

Enteroendocrine cells in the gut mucosa



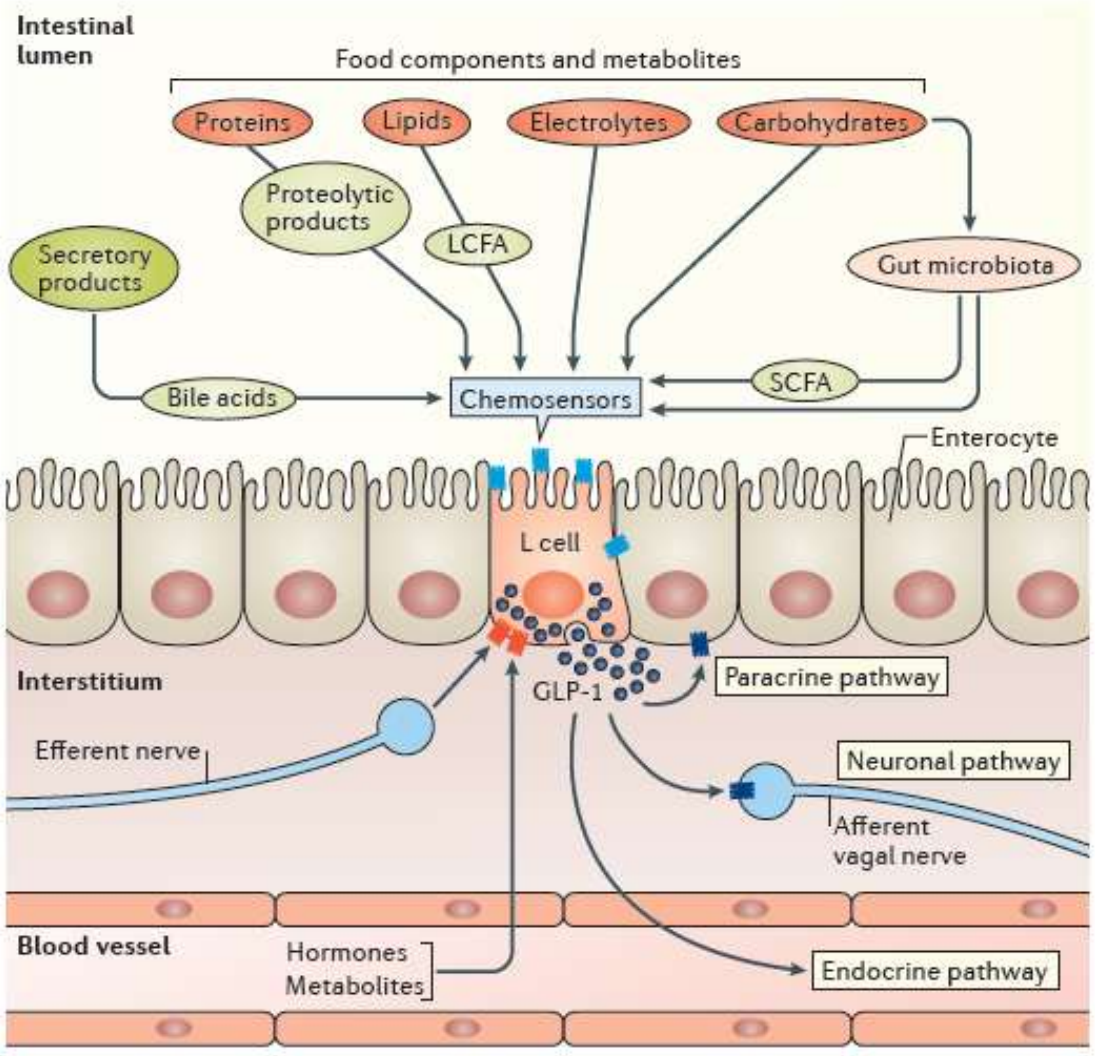
Enteroendocrine cells are specialized cells found within the gastrointestinal tract, stomach and pancreas.

They produce and release hormones (incretins such as glucagon-like peptide 1, GLP-1; gastric inhibitory peptide, GIP) in response to a number of stimuli.

The hormones may be released into the bloodstream to generate systemic effects or may be distributed as local messengers.

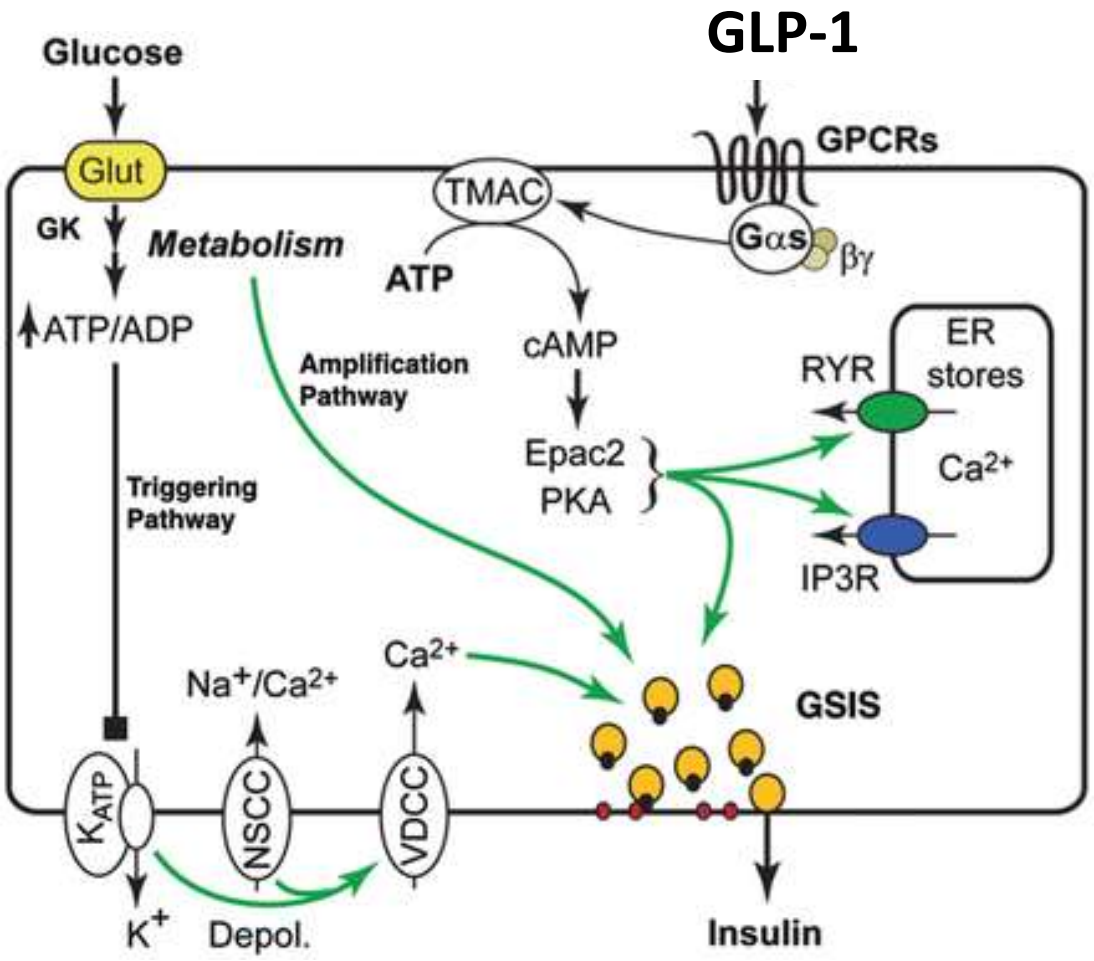
They may also stimulate a nervous response.

The sensory and secretory function of the enteroendocrine L cell producing GLP-1



Release of glucagon-like peptide 1 (GLP-1) from L cells in the ileus-colon is regulated by nutritional, hormonal and neural signals.

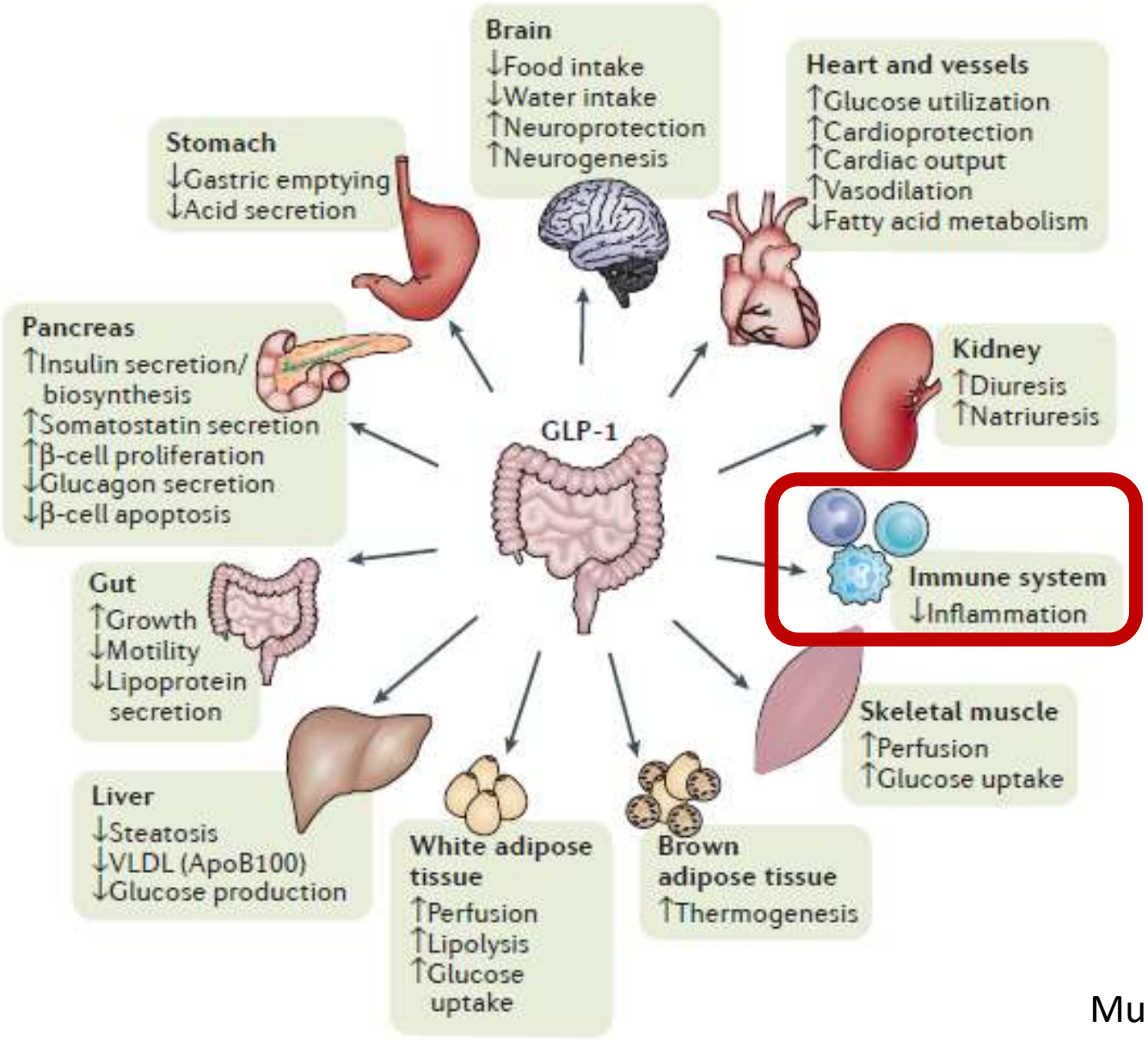
Food components and metabolites at the luminal side of the L cell are directly sensed by various G protein-coupled receptors that function as chemosensors and trigger exocytosis of GLP-1-containing granules at the basolateral side of the cell. GLP-1 can act through endocrine, paracrine and neuronal pathways to regulate physiological responses in local and/or remote tissues and cell types. These effects are consistent with the widespread and abundant expression of the GLP-1 receptor. LCFA, long-chain fatty acid; SCFA, short-chain fatty acid.



GLP-1 stimulates insulin secretion in pancreatic ß cells

Holz GG, Molecular Basis of cAMP Signaling in Pancreatic Beta Cells. In: Islam, M. (eds) Islets of Langerhans, 2014, 2. ed.. Springer, Dordrecht. https://doi.org/10.1007/978-94-007-6884-0_25-4

Putative actions of glucagon-like peptide 1 (GLP-1)

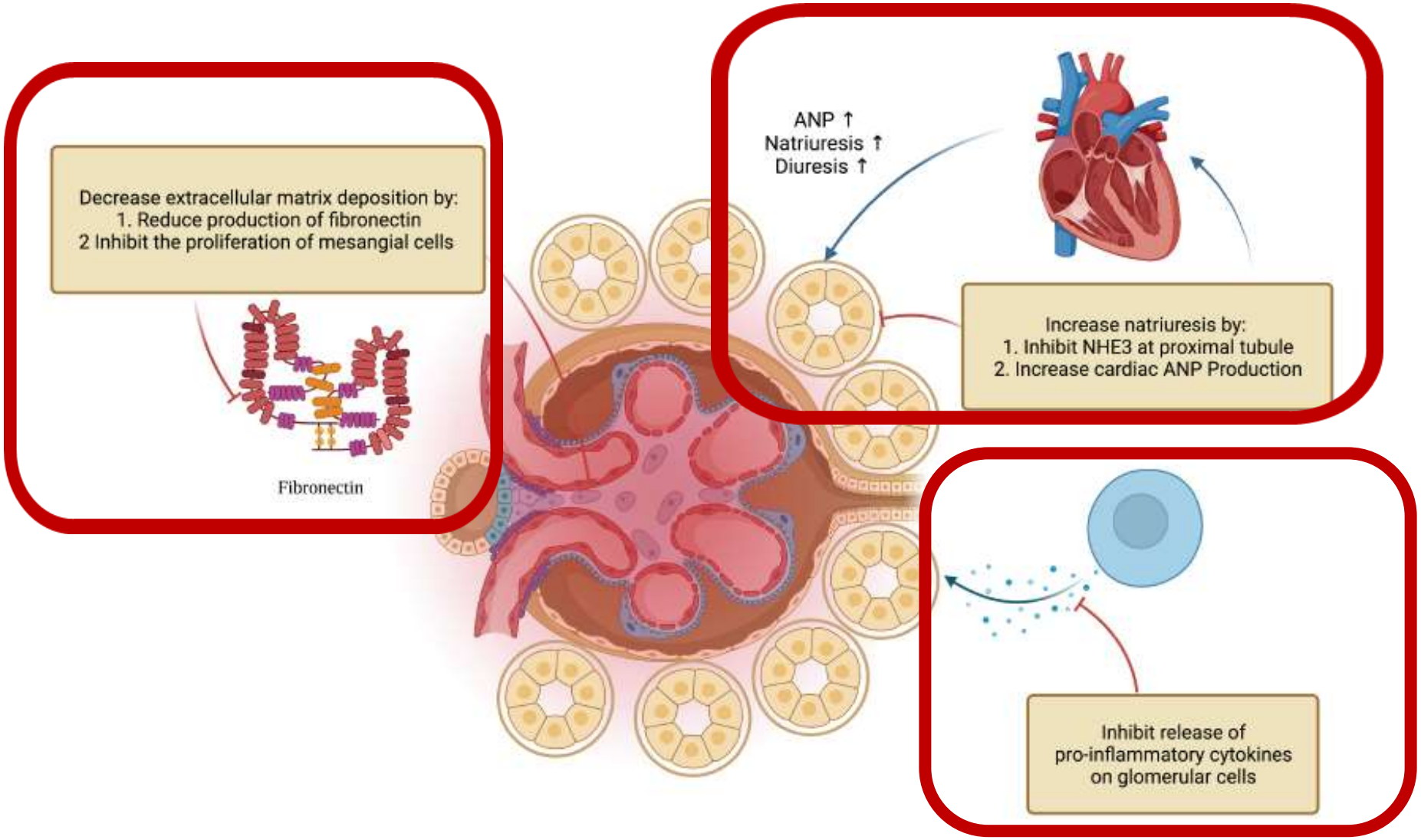


The best elucidated physiological roles of GLP-1 are those related to pancreatic islet cell function

However, GLP-1 and GLP-1 receptor agonists also have pleiotropic effects on various other tissues and organs, with various potential physiological, pathophysiological and pharmacological implications

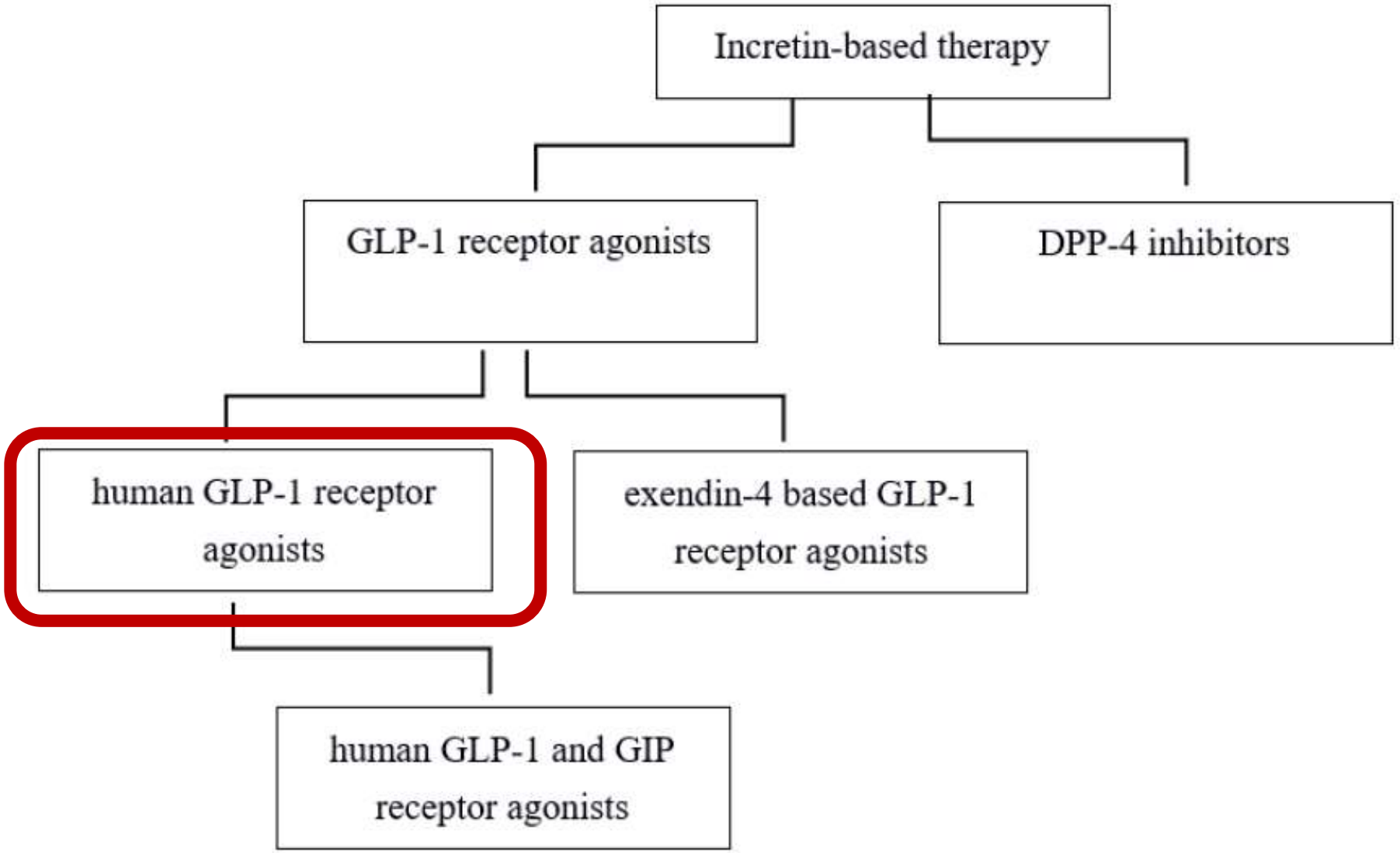
Muskiet MHA et al., Nat Rev Nephrol 2017; 13:605

The biological mechanisms of the GLP1 receptor agonists in the kidney



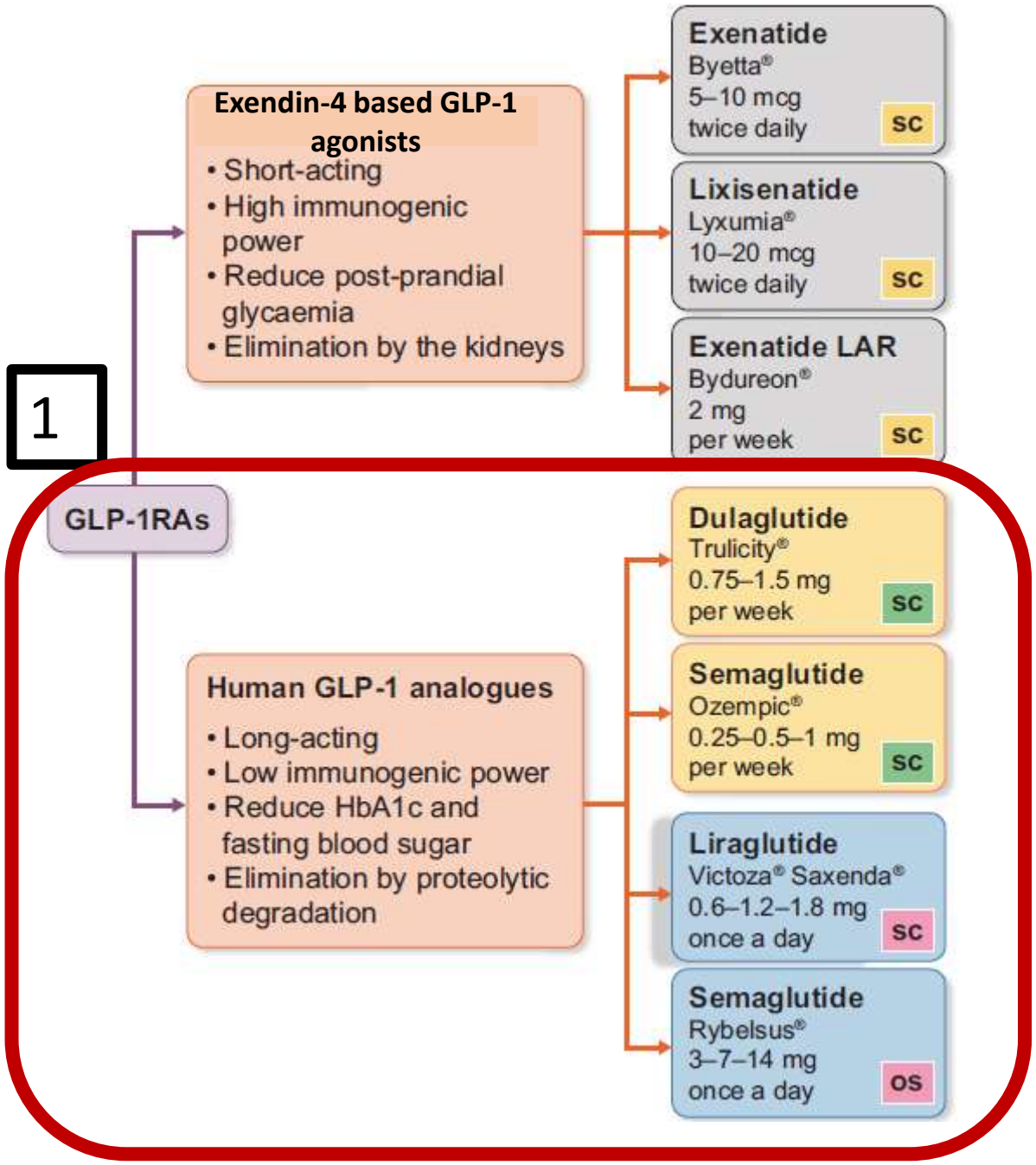
Chan ATP et al., Kidney Res Clin Pract 2022; 41:682-698

Incretin-based therapy (Incretin-mimetic drugs)



Bulum T., Biomedicines 2022; 10:2586

Incretin-based therapies (Incretin mimetic drugs)



2 **DPP4 inhibitors**

3 **Unimolecular GIP-RA:GLP-1RA co-agonists** → **Tirzepatide**

Key CV outcomes for selected GLP-1 receptor agonists in heart failure

GLP-1 RA (class, regimen)	CVOT (years of follow-up)	Population		Outcomes, hazard ratio (95%CI)	
		N	History of heart failure (established CVD[b])	Hospitalisation for heart failure	3-point MACE[c]
Efpeglenatide (exendin-4, s.c. OW[a])	AMPLITUDE-O (31) (1.8 years)	4,076	18% (90%)	0.61 (0.38–0.98)	0.73 (0.58–0.92)
Lixisenatide (hGLP-1, s.c. OD[a])	ELIXA (32) (2.1 years)	6,068	22% (100%)	0.96 (0.75–1.23)	1.02 (0.89–1.17)
Exenatide ER (exendin-4, s.c. OW)	EXSCEL (33) (3.2 years)	14,752	16% (73%)	0.94 (0.78–1.13)	0.91 (0.83–1.00)
Albiglutide (hGLP-1, s.c. OD[a])	HARMONY(34) (1.5 years)	9,463	20% (100%)	0.71 (0.53–0.94)	0.78 (0.68–0.90)
Liraglutide (hGLP-1, s.c. OD)	LEADER (18) (3.8 years)	9,340	18% (81%)	0.87 (0.73–1.05)	0.87 (0.78–0.97)
Semaglutide, oral (hGLP-1, p.o. OD)	PIONEER 6 (35) (1.3 years)[d]	3,183	12% (85%)	0.86 (0.48–1.55)	0.79 (0.57–1.11)
Dulaglutide (hGLP-1, s.c. OW)	REWIND(17) (5.4 years)	9,901	9% (31%)	0.93 (0.77–1.12)	0.88 (0.79–0.99)
Semaglutide, s.c. (hGLP-1, s.c. OW)	SUSTAIN 6 (19) (2.1 years)	3,297	24% (83%)	1.11 (0.77–1.61)	0.74 (0.58–0.95)
Meta-analysis				**0.89 (0.82 to 0.98)** (Sattar et al., 2021)	**0.86 (0.80–0.93)** (Sattar et al., 2021)

Kreiner FF et al., Front Physiol 2022; 20;13:983961

Effect of glucagon-like peptide 1 receptor agonists on the renal protection in patients with type 2 diabetes: A systematic review and meta-analysis

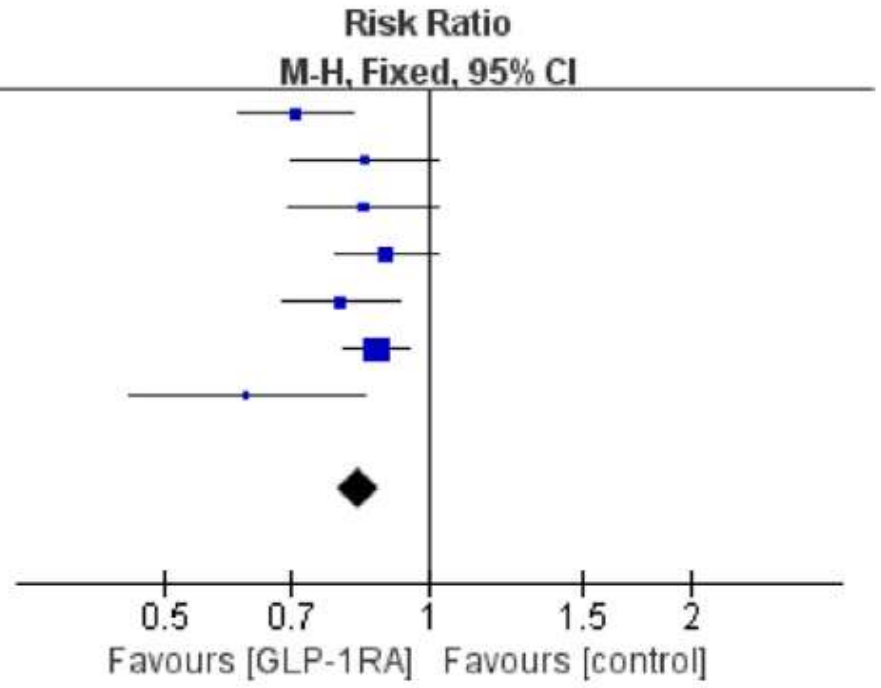
Xiang Li[a], Yujie Song[a], Tao Guo[a], Guiying Xiao[a], Qiumei Li[a,*]

Meta-analysis of the composite renal outcome for GLP-1 receptor agonists users vs. non-users

Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AMPLITUDE-O 2021	353	2717	250	1359	13.5%	0.71 [0.61, 0.82]
AWARD-7 2018	152	382	91	194	4.9%	0.85 [0.70, 1.03]
ELIXA 2015	172	2647	203	2639	8.2%	0.84 [0.69, 1.03]
EXSCEL 2017	366	6259	407	6230	16.5%	0.90 [0.78, 1.03]
LEADER 2017	268	4668	337	4672	13.6%	0.80 [0.68, 0.93]
REWIND 2019	848	4949	970	4952	39.2%	0.87 [0.80, 0.95]
SUSTAIN-6 2016	62	1648	100	1649	4.0%	0.62 [0.46, 0.85]
Total (95% CI)		**23270**		**21695**	**100.0%**	**0.83 [0.79, 0.88]**
Total events	2221		2358			

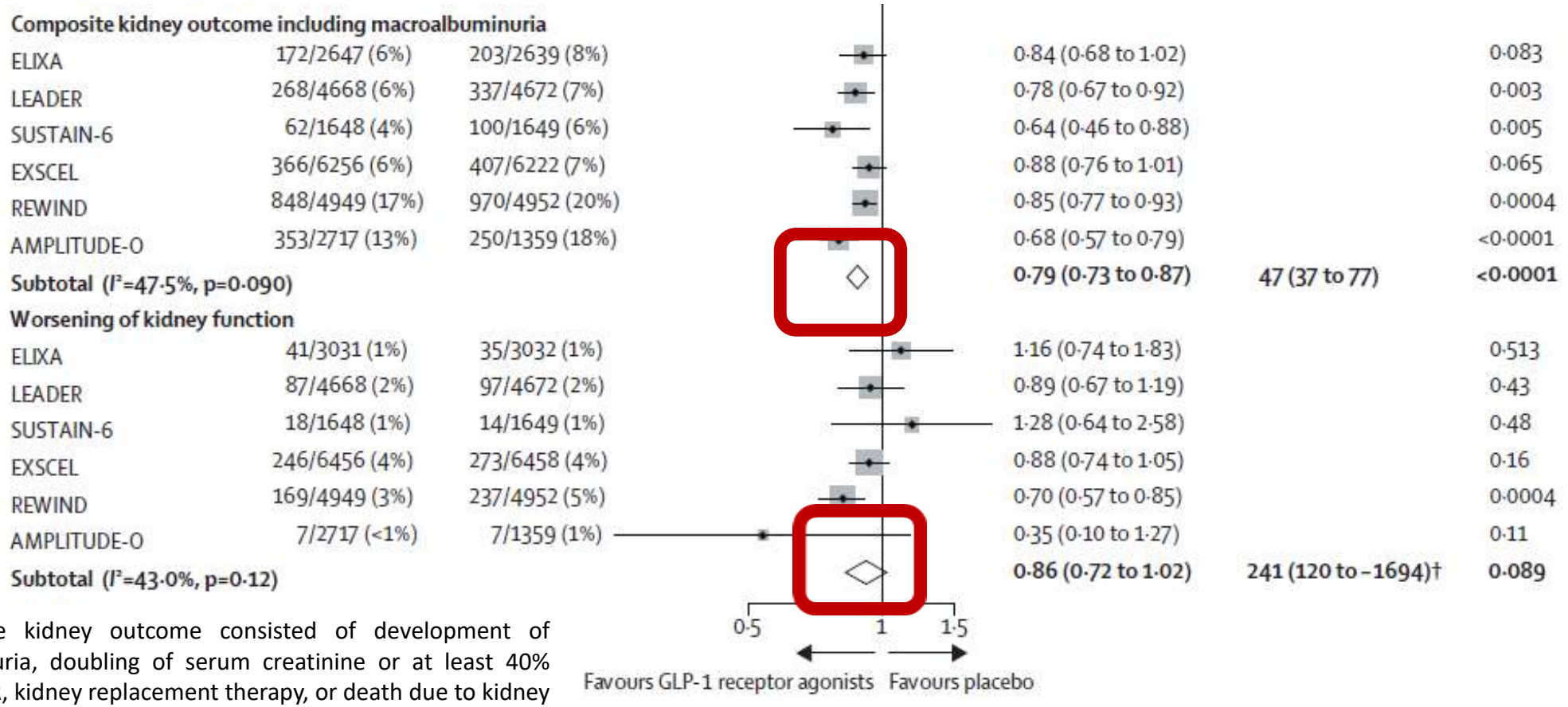
Heterogeneity: $Chi^2 = 11.01$, $df = 6$ ($P = 0.09$); $I^2 = 45\%$

Test for overall effect: $Z = 6.74$ ($P < 0.00001$)



Diabetes & Metabolism 48 (2022) 101366

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials



The composite kidney outcome consisted of development of macroalbuminuria, doubling of serum creatinine or at least 40% decline in eGFR, kidney replacement therapy, or death due to kidney disease; for ELIXA, data are for new-onset macroalbuminuria alone. The worsening of kidney function outcome was defined as either doubling of serum creatinine or at least 40% decline in eGFR; for EXSCEL, the worsening of kidney function outcome included kidney replacement therapy, or death due to kidney disease

Sattar N et al., Lancet Diabetes Endocrinol 2021; 9: 653–62

The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease

Background

Evidence has emerged of potential kidney-protective effects of GLP-1 RAs in people with T2D. FLOW is a dedicated kidney outcomes trial to assess semaglutide in a population with CKD and T2D at high risk of kidney disease progression.

Methods

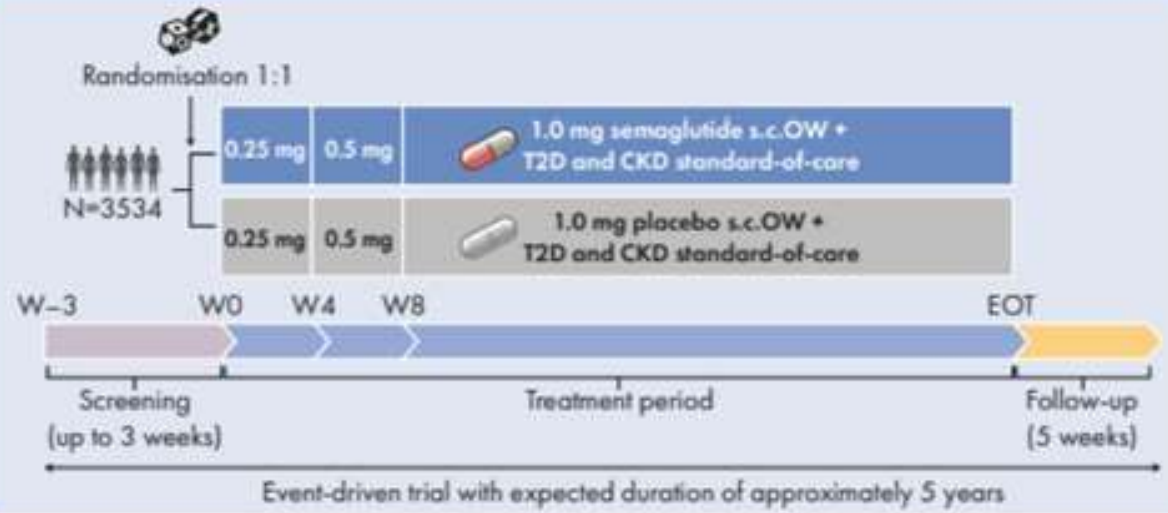
Participants:

- Adults with T2D
- eGFR ≥ 50 to ≤ 75 mL/min/1.73 m² and UACR > 300 to < 5000 mg/g OR
- eGFR ≥ 25 to < 50 mL/min/1.73 m² and UACR > 100 to < 5000 mg/g

Composite primary endpoint:

Time to first occurrence of:

- Kidney failure (persistent eGFR < 15 mL/min/1.73 m² or initiation of CKRT);
- Persistent ≥ 50% reduction in eGFR; or
- Death from kidney or CV causes



Baseline characteristics

68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) mL/min/1.73 m² ; median UACR of 568 (range: 2–11 852) mg/g

Advanced type 2 diabetes:
Mean age 66.6 years
Mean diabetes duration 17.4 years
Mean HbA_{1c} 7.8%

15.5% receiving SGLT-2is

CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; OW, once weekly; s.c., subcutaneous; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; W, week.

Conclusion

FLOW will evaluate the effect of semaglutide on kidney outcomes in participants with CKD and T2D, and is expected to complete in late 2024.

Rossing P et al., Nephrol Dial Transpl 2023; 38:2041-2051

Company announcement

10:37 10 October 2023

Announcement.pdf

Novo Nordisk will stop the once-weekly injectable semaglutide kidney outcomes trial, FLOW, based on interim analysis

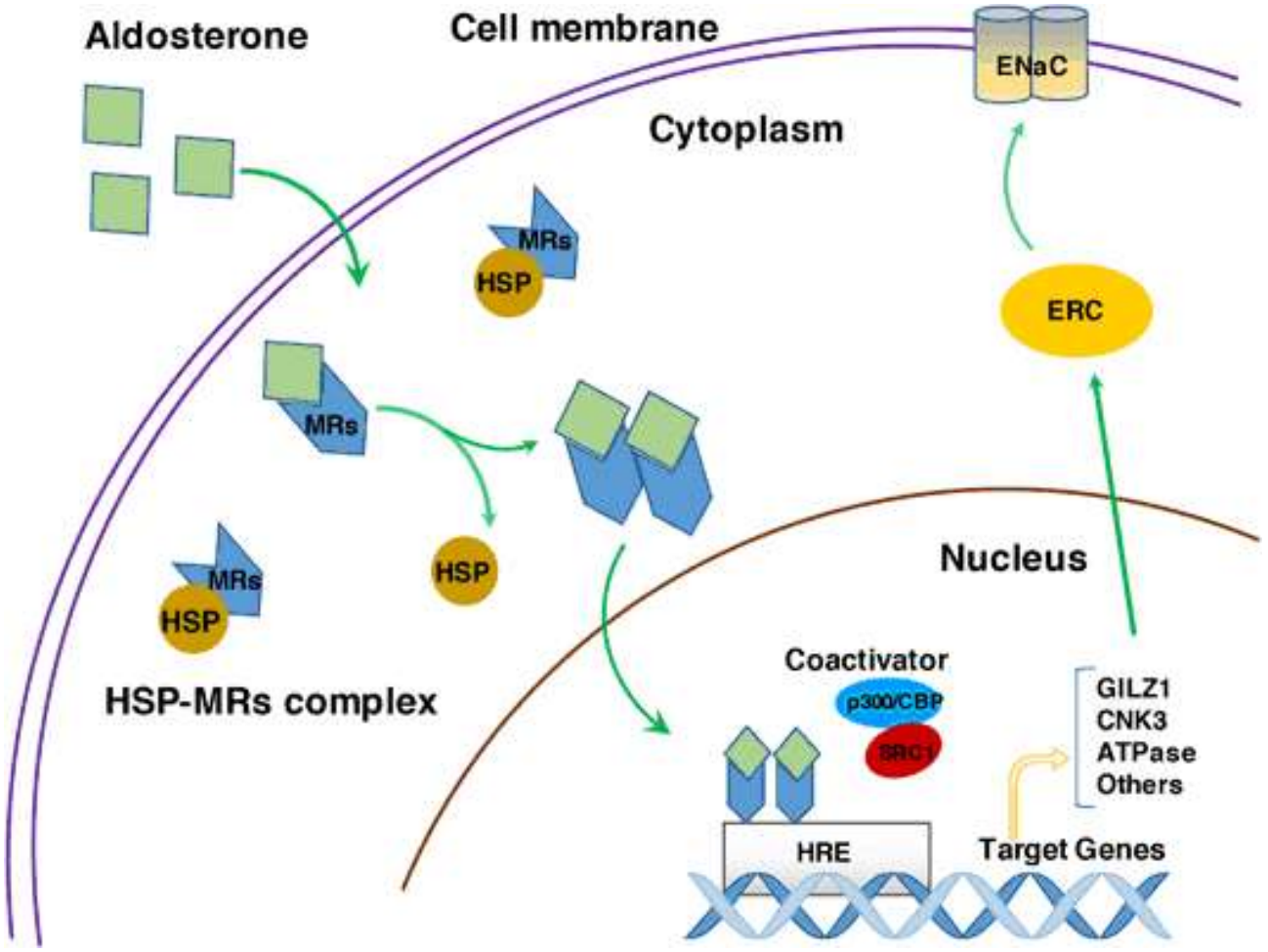
Novo Nordisk will stop the once-weekly injectable semaglutide kidney outcomes trial, FLOW, based on interim analysis

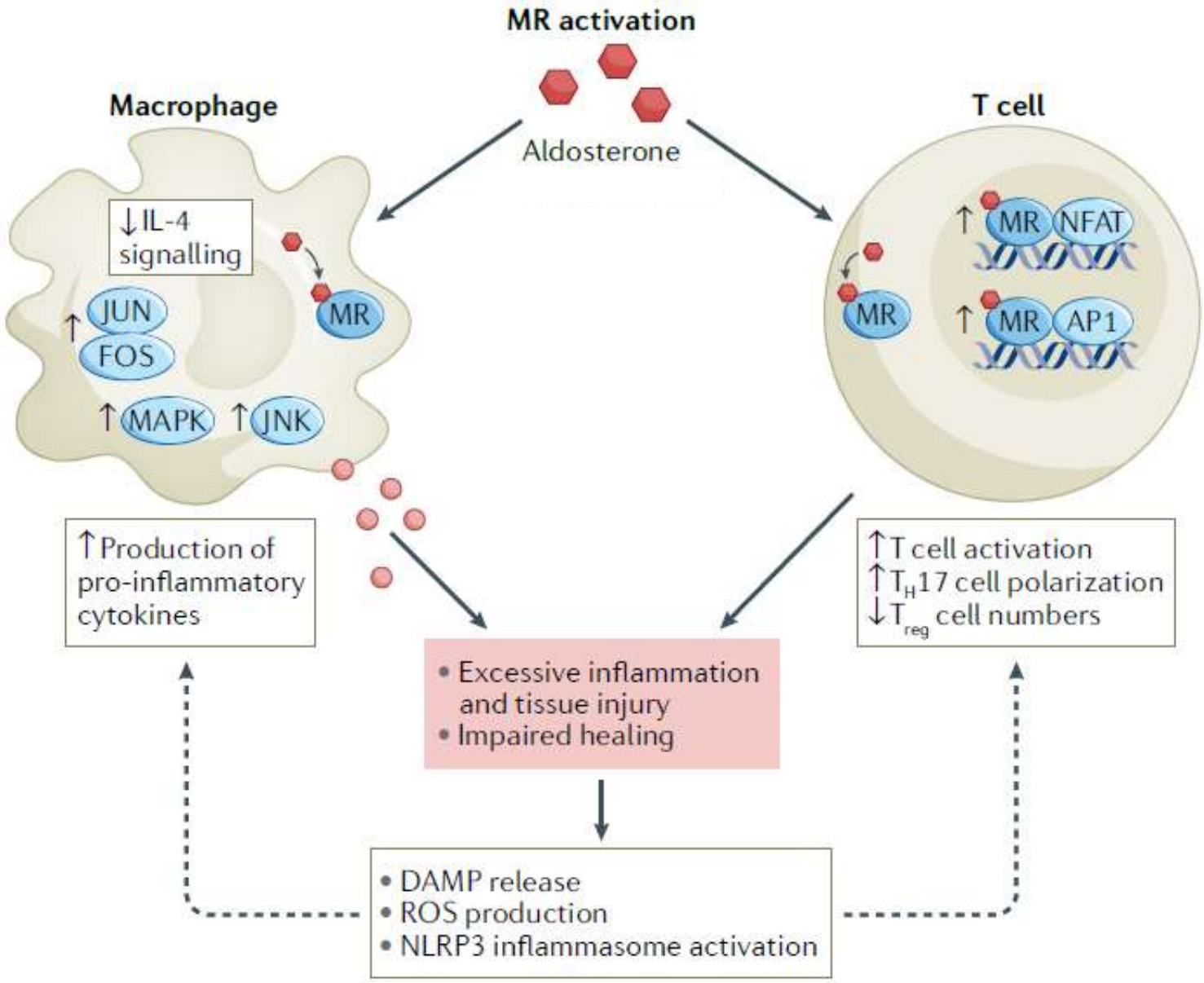
Bagsværd, Denmark, 10 October 2023 – Novo Nordisk today announced the decision to stop the kidney outcomes trial FLOW (Effect of semaglutide versus placebo on the progression of renal impairment in people with type 2 diabetes and chronic kidney disease).

Agenda

- SGLT2 inhibitors: mechanisms of action in the kidney and clinical trial on renal protection
- GLP1 receptor agonists: mechanisms of action in the kidney and clinical trials on renal protection
- Mineralcorticoid receptor antagonists: mechanisms of action in the kidney and clinical trials on renal protection
- Association between the new drugs for renal protection and recent guidelines

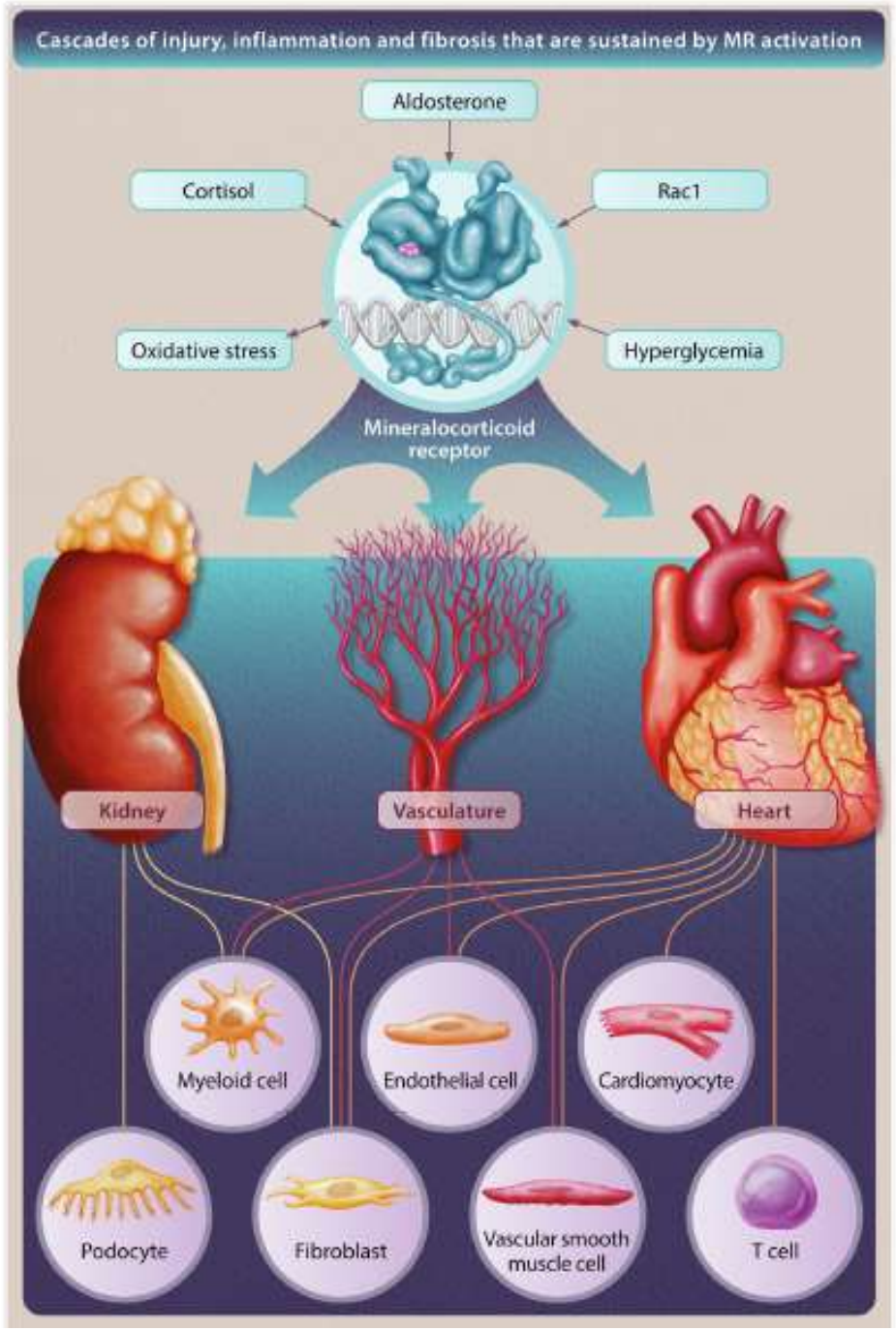
The mineralcorticoid receptor (MR) and mechanism of action of aldosterone





Aldosterone-mediated pro-inflammatory effects in macrophages and T cells

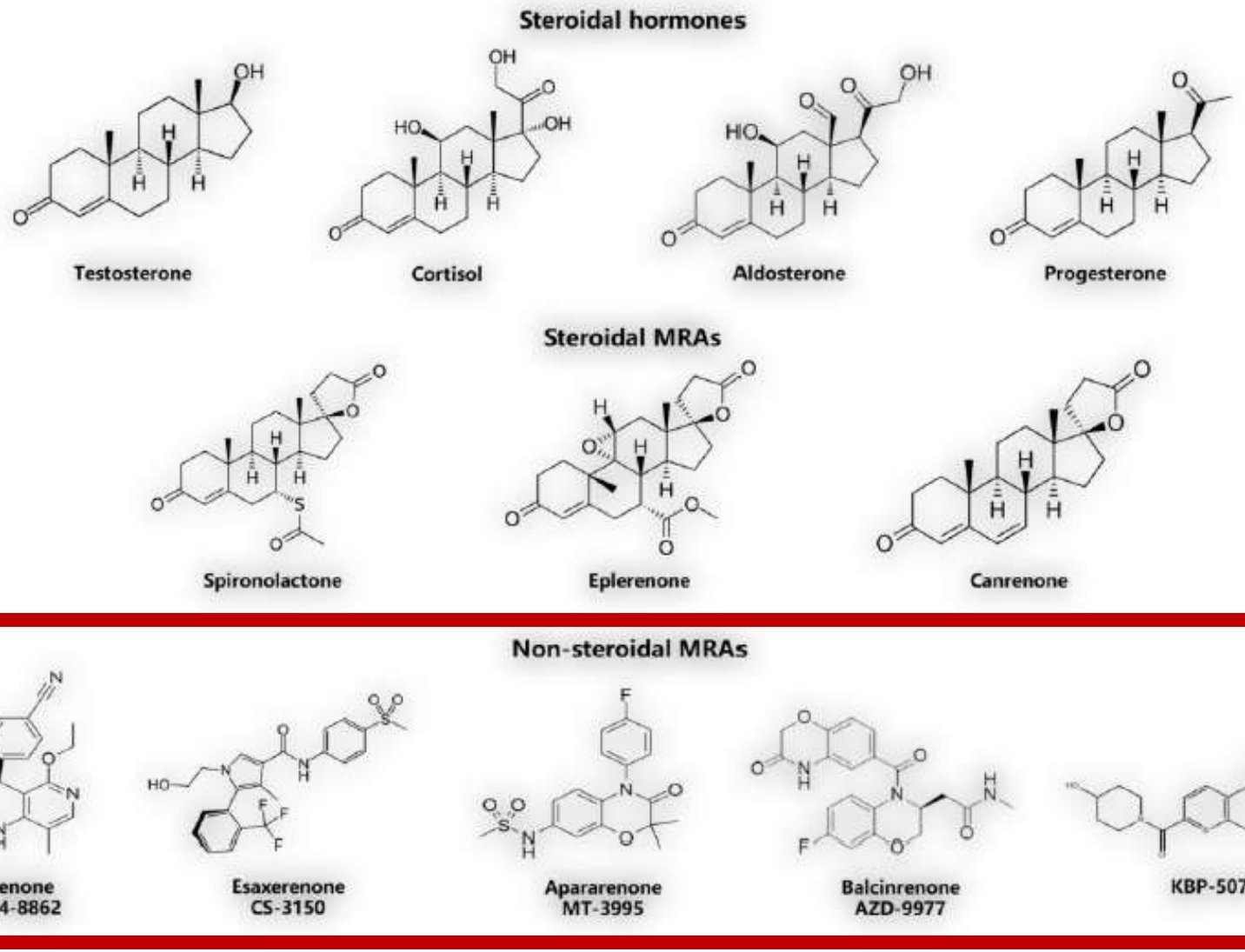
Barrera-Chimal J et al., Nat Rev Nephrol 2022; 18:57-70



Complementary interplay of cascades of injury, inflammation, and fibrosis that are initiated and sustained by MR activation

Epstein M et a., Am J Kidney Dis 2022; 80:658-666

Chemical structure of main steroidal hormones and non-steroidal and steroidal MRAs

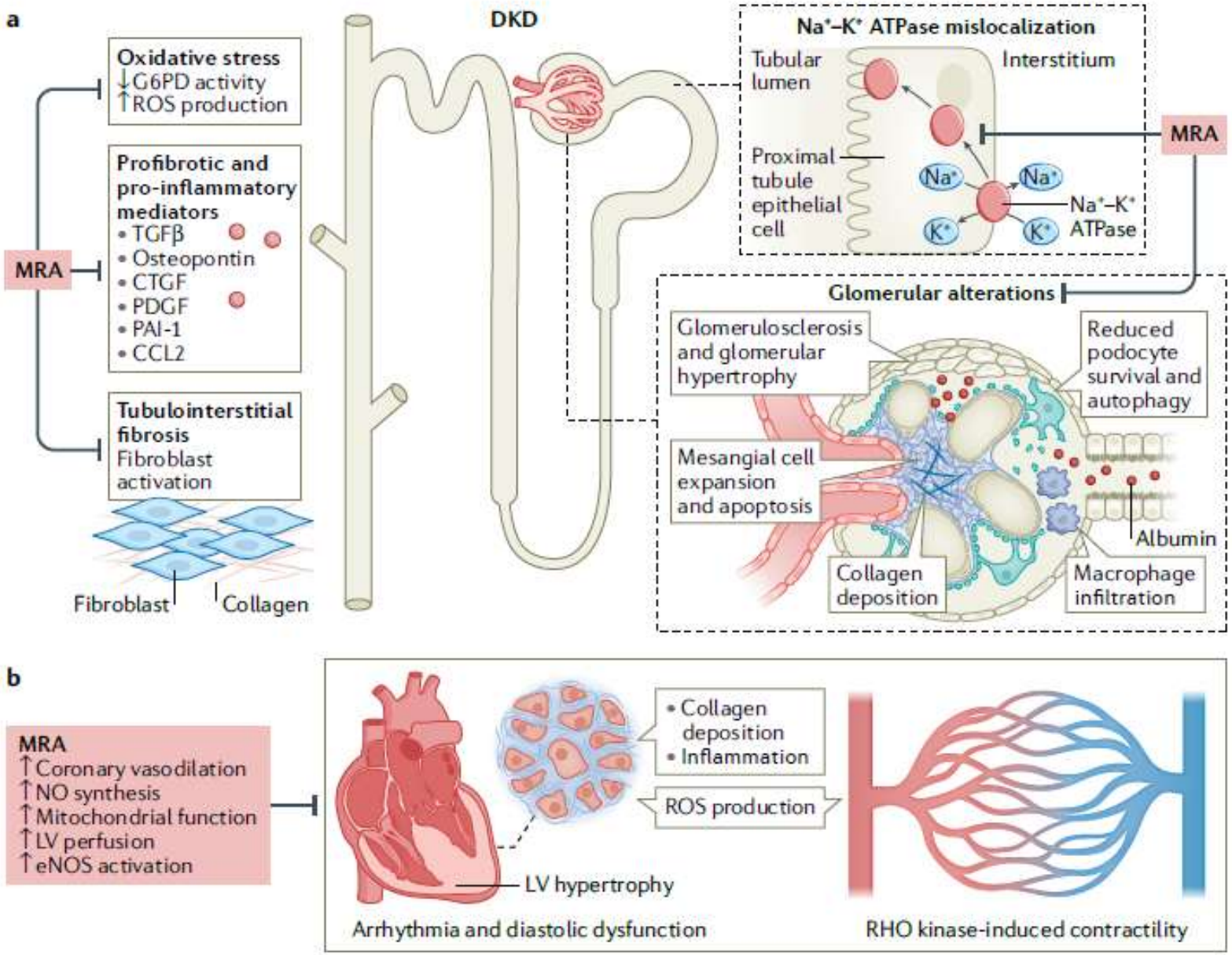


Sarafidis P et al., Clinical Kidney Journal 2023; 16:1885–1907

Schematic of spironolactone, eplerenone, and finerenone binding with proposed/hypothesized conformational change of helix 12 and summary of respective key pharmacodynamic and pharmacokinetic characteristics

	Steroidal MRAs		Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
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	+++	++	+

Epstein M et a., Am J Kidney Dis 2022; 80:658-666



The beneficial effects of MRAs in the kidney, heart and vasculature in preclinical studies of DKD

Barrera-Chimal J et al., Nat Rev Nephrol 2022; 18:57-70

Table 2: Summary of finerenone outcome trials [94, 95].

Trial	FIDELIO-DKD ($n = 5734$)	FIGARO-DKD ($n = 7437$)
Treatment	Finerenone vs. placebo	Finerenone vs. placebo
Mean participant age (years)	66	64
Key inclusion criteria	• T2D • eGFR 25 to <60 mL/min/1.73 m^2 and UACR 30 to <300 mg/g, or • eGFR 25 to <75 mL/min/1.73 m^2 and UACR 300 to 5000 mg/g • Treated with RAS inhibitor at maximum tolerated dose	• T2D • eGFR 25 to 90 mL/min/1.73 m^2 and UACR 30 to <300 mg/g, or • eGFR >60 mL/min/1.73 m^2 and UACR 300 to 5000 mg/g • Treated with RAS inhibitor at maximum tolerated dose
Mean baseline A1C (%)	7.7	7.7
Median follow-up (years)	2.6	3.4
Primary outcome		
HR (95% CI)	Kidney failure, ≥40% decline in eGFR, or renal death 0.82 (0.73–0.93)	CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF 0.87 (0.76–0.98)
Key secondary outcomes		
Key secondary composite; HR (95% CI)	CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF 0.86	Kidney failure, ≥40% decline in eGFR, or renal death 0.87
Progression to ESKD; HR (95% CI)	0.86 (0.67–1.10)	0.64 (0.41–0.995)
[illegible]	[illegible]	[illegible]
	(0.68–1.08)	(0.74–1.09)
All-cause mortality; HR (95% CI)	0.90 (0.75–1.07)	0.89 (0.77–1.04)

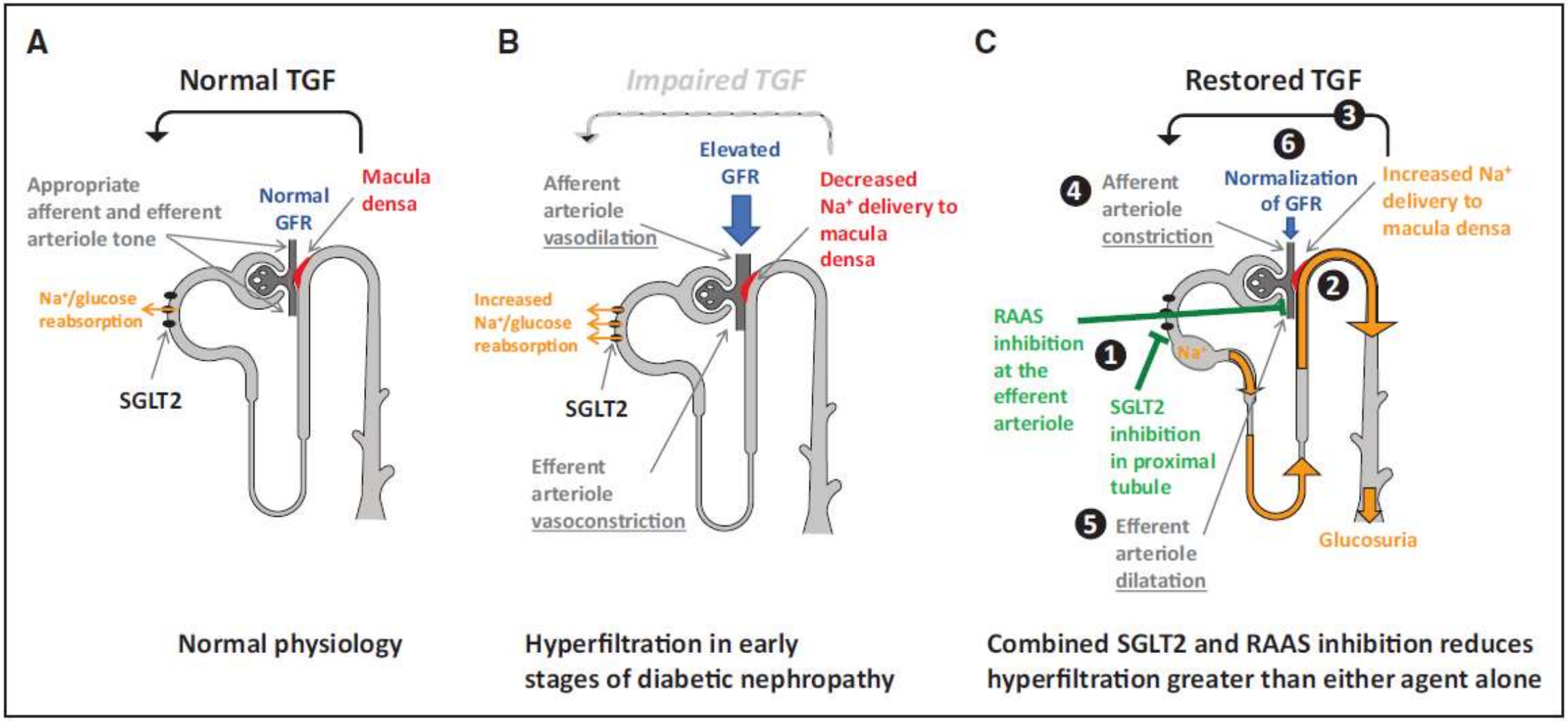
A1C, glycated hemoglobin A1c; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; RAS, renin-angiotensin system; T2D, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

Neumiller JJ et al., Clinical Kidney Journal 2024; 17:1–16

Agenda

- SGLT2 inhibitors: mechanisms of action in the kidney and clinical trial on renal protection
- GLP1 antagonists: mechanisms of action in the kidney and clinical trials on renal protection
- Mineralcorticoid receptor antagonists: mechanisms of action in the kidney and clinical trials on renal protection
- Association between the new drugs for renal protection and recent guidelines

Postulated mechanisms in normal physiology and hyperfiltration in early stages of nephropathy and after combined inhibition of SGLT2 and RAAS



Circulation. 2022;146:450–462.

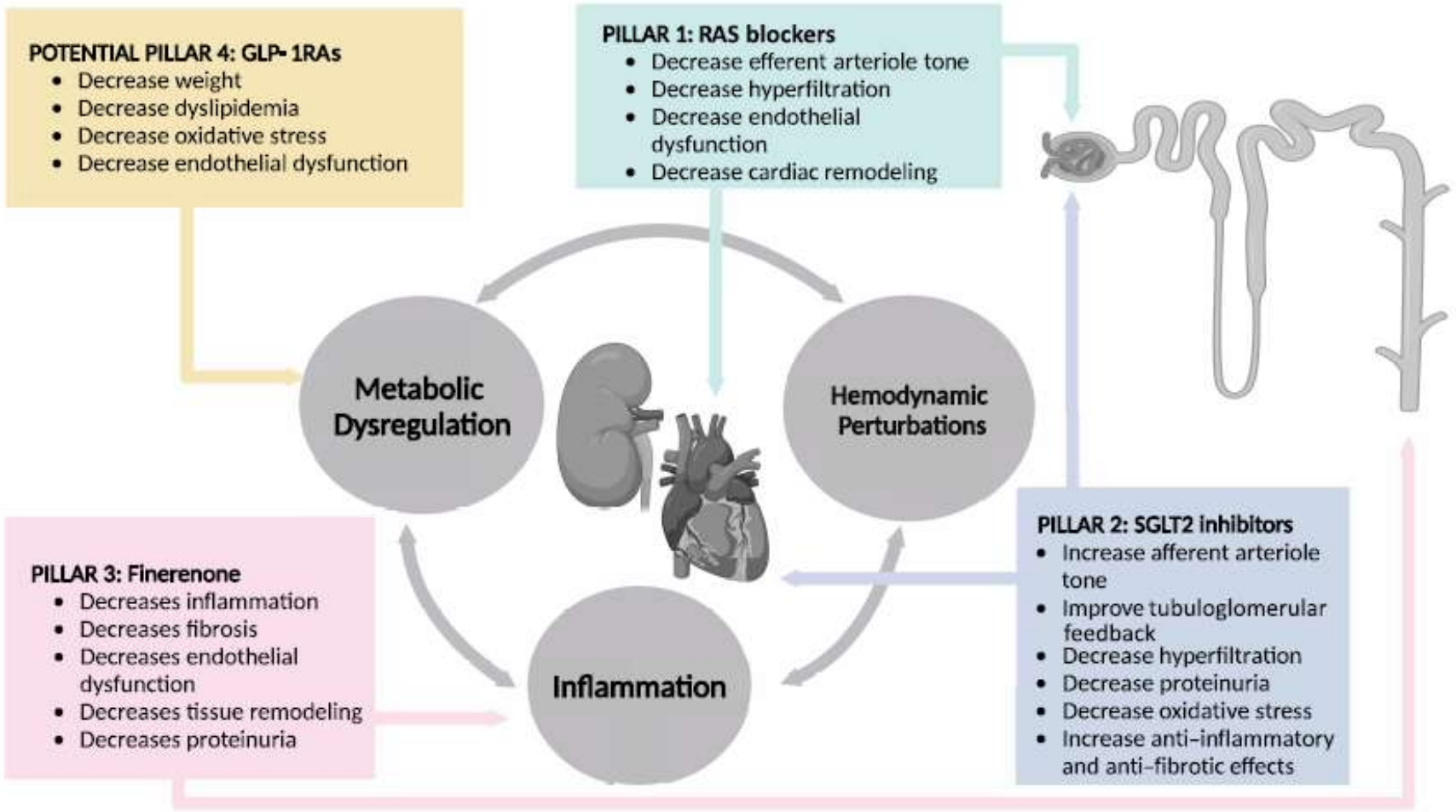
SGLT2 inhibitors and finerenone: one or the other or both?

Table 1. Potential benefits and considerations regarding combination therapy with SGLT2i and finerenone

Rationale	Evidence	Limitations and other considerations
Complementary mechanisms of action	SGLT2i reduces glomerular hyperfiltration along with other direct effects on cellular and metabolic functions Finerenone inhibits mineralocorticoid receptor pathway–dependent inflammation and fibrosis	Based largely on experimental/preclinical models, with few small, randomized trials Shared mechanisms may result in less than additive effects Potential benefits are theoretical and require evaluation in randomized trials
Independent and additive benefits	Benefits of SGLT2i are consistent irrespective of MRA use in people with CKD (DAPA-CKD) and heart failure with reduced ejection fraction (EMPEROR-Reduced and DAPA-HF) Benefits of finerenone appear consistent irrespective of SGLT2i use (FIDELIO and FIGARO)	SGLT2i use was uncommon in FIDELIO and FIGARO, thus limiting the power to assess treatment effects by baseline use of SGLT2i Use of MRAs was uncommon in DAPA-CKD, thus limiting the power to assess consistency of treatment effects across this subgroup
Improved tolerability	SGLT2i reduces the risk of serious hyperkalaemia in people with type 2 diabetes and CKD (CREDENCE), which may enable greater use of MRAs SGLT2i reduces the likelihood of MRA discontinuation in people with heart failure with reduced ejection fraction (EMPEROR-Reduced)	No completed randomized trials evaluating safety and tolerability of combination SGLT2i and finerenone in CKD

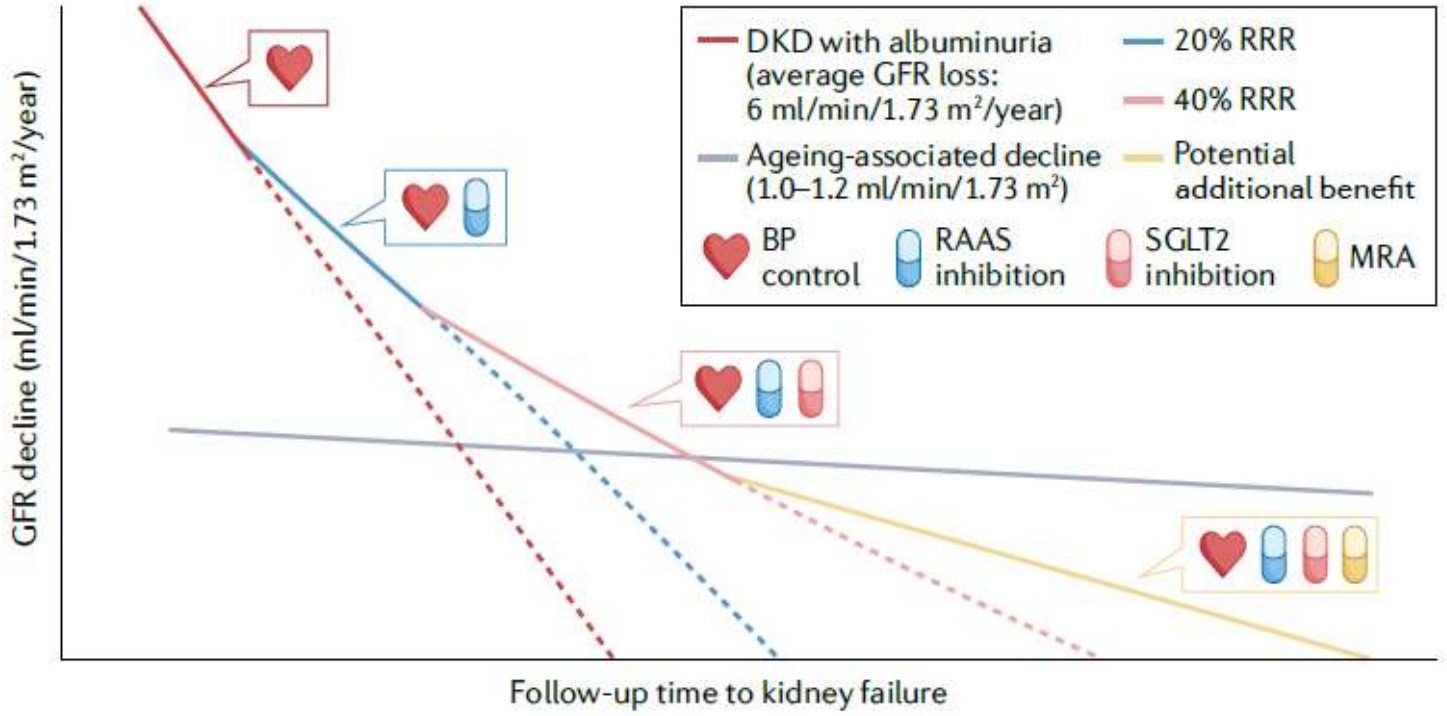
Neuen BL, Jardine M. NDT 2022; 37:1209-1211

The manifold pathophysiological mechanisms involved in end-organ damage argue for a pillared approach with targeted therapies that have distinct pharmacodynamic actions



Naaman SC. Diabetes Care 2023;46:1574–1586

The incremental benefit of multifactorial intervention on GFR decline in DKD

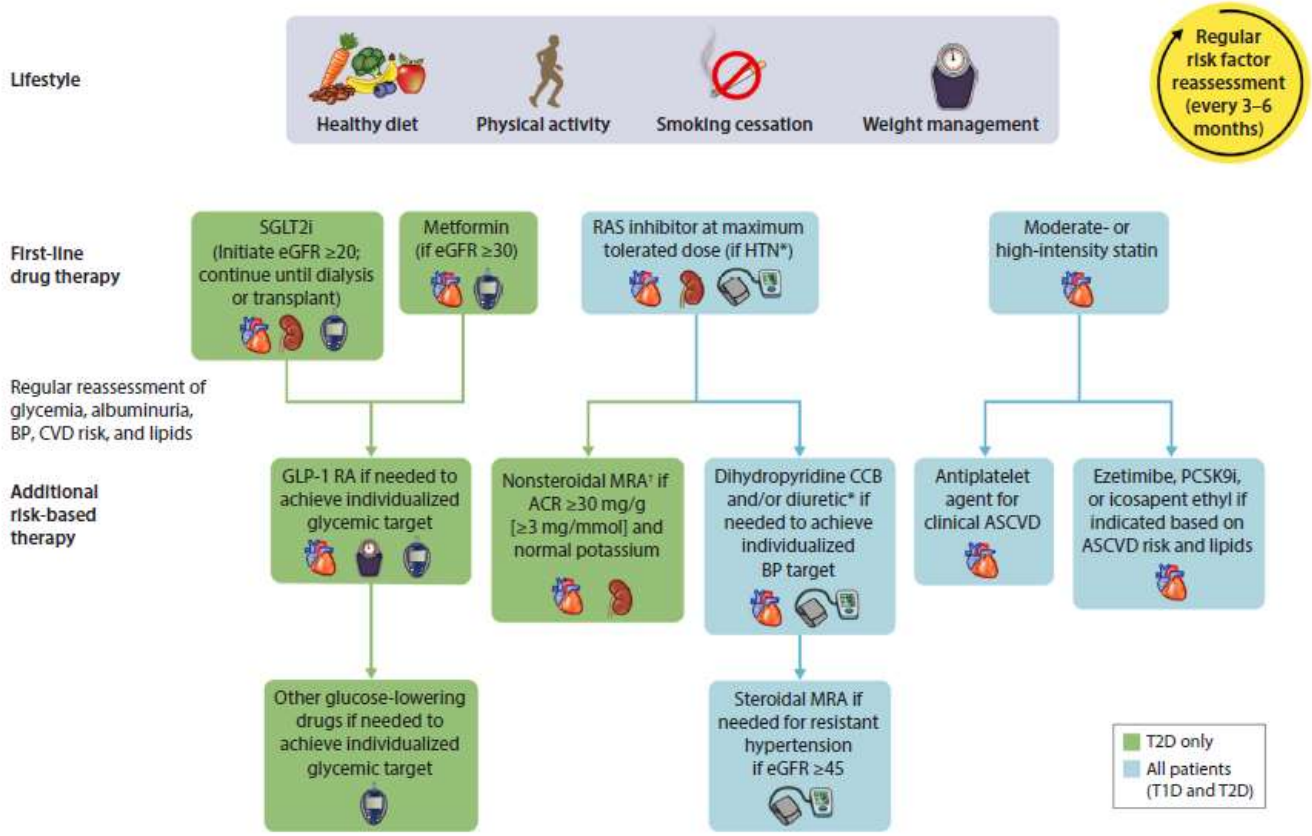


Recent clinical trials suggest that, in patients with diabetic kidney disease (DKD), treatment with SGLT2)i or the MRA finerenone, in addition to standard of care (including blood pressure (BP) control and the use of RAAS inhibitors, might slow the rate of GFR decline towards that typically observed in healthy ageing individuals. The relative risk reduction (RRR) and yearly GFR decline were estimated on the basis of results from the RENAAL and IDNT trials for RAAS inhibition, and the CREDENCE and DAPA-CKD trials for SGLT2 inhibition. The potential benefit of combining SGLT2 inhibitors with MRAs is based on preliminary data from a pooled analysis of the FIGARO-DKD and FIDELIO-DKD clinical trials, which indicates that finerenone has kidney benefits in patients, irrespective of SGLT2 inhibitor use at baseline. Ageing-associated decline is based on data from healthy individuals > 60 years of age.

Fioretto P. Nat Rev Nephrol 2022; 17:78

Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence

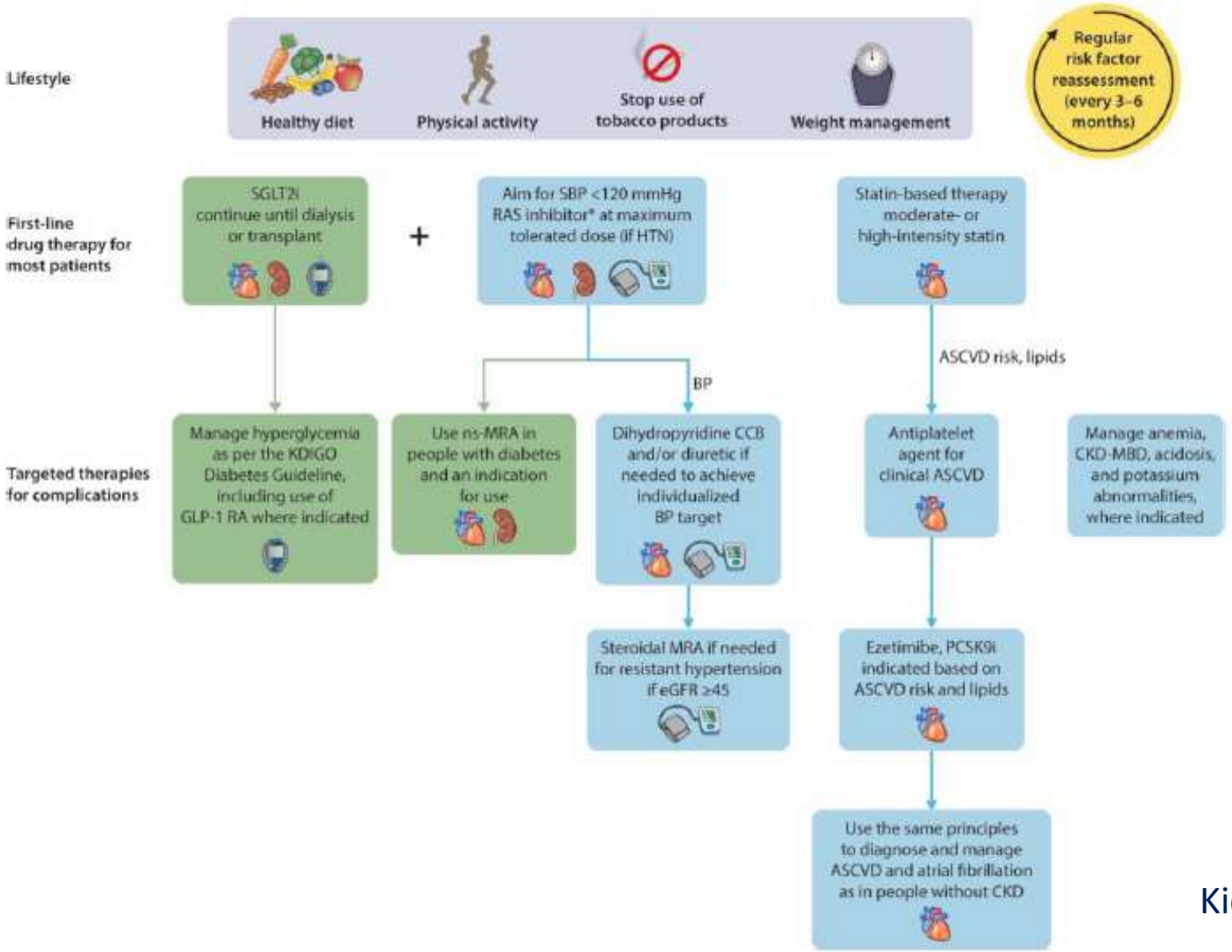
Peter Rossing[1,2], M. Luiza Caramori[3], Juliana C.N. Chan[4,5], Hiddo J.L. Heerspink[6], Clint Hurst[7], Kamlesh Khunti[8], Adrian Liew[9], Erin D. Michos[10], Sankar D. Navaneethan[11,12], Wasiu A. Olowu[13], Tami Sadusky[14], Nikhil Tandon[15], Katherine R. Tuttle[16], Christoph Wanner[17], Katy G. Wilkens[18], Sophia Zoungas[19], Jonathan C. Craig[20,21], David J. Tunnicliffe[21,22], Marcello A. Tonelli[23], Michael Cheung[24], Amy Earley[24] and Ian H. de Boer[25]



Holistic approach for improving outcomes in patients with diabetes and chronic kidney disease

Kidney International (2022) **102,** 990–999;

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



Kidney Int 2024, in press

Take home messages

- Since the institution of the RAS blockade in the 1990s, we have witnessed significant strides in addressing the unmitigated risk associated with CKD progression in patients with or without diabetes mellitus

- We now have two additional drug classes to add to the RAS blockers, SGLT2 inhibitors and NS-MRAs (limited evidence), bolstered by a robust body of outcome data, and a possible third class, since the efficacy of GLP-1 RAs is supported by retrospective analyses and has recently been proven in the FLOW randomized clinical trial in patients with T2DM

- The safety and tolerability of these new drug classes, when given together against a backdrop of maximal RAS blockade, are very encouraging and reflect the complexity of the underlying pathophysiology that drives CKD progression, even independently from the coexistence of diabetes mellitus