UNIVERSITÀ DEL PIEMONTE ORIENTALE

SGLT2-I: soli o ben accompagnati?

Il rene piange…

Prof. Marco Quaglia

29 Nov 2025

AOU AL Azienda Ospedaliero Universitaria di ALESSANDRIA
Santi Antonio e Biagio e Cesare Arrigo

DISCLOSURE

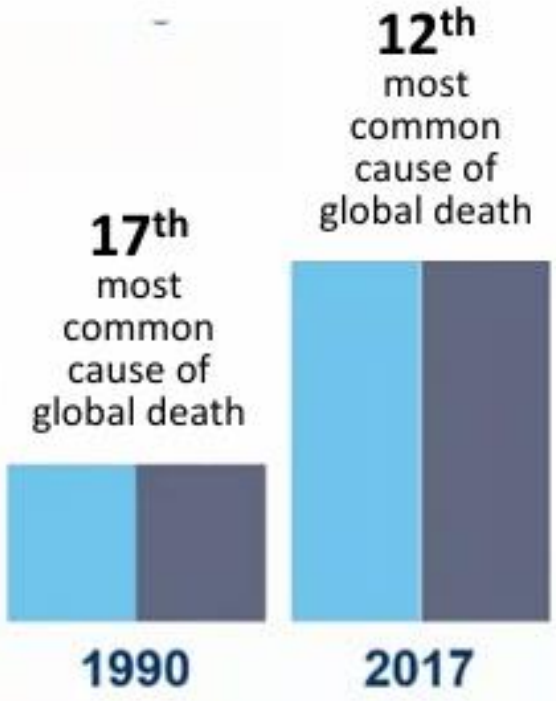
Il Prof M Quaglia dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche

1. Alexion
2. AstraZeneca
3. Boehringer Ingelheim

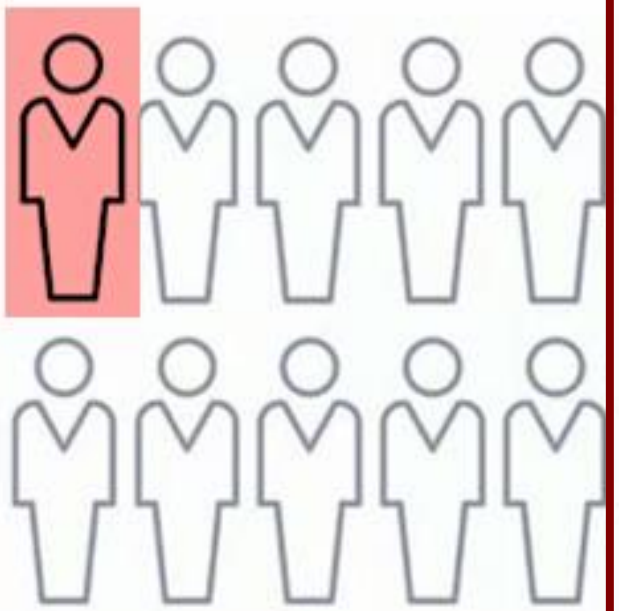
INTRODUZIONE

Global burden of CKD and DKD

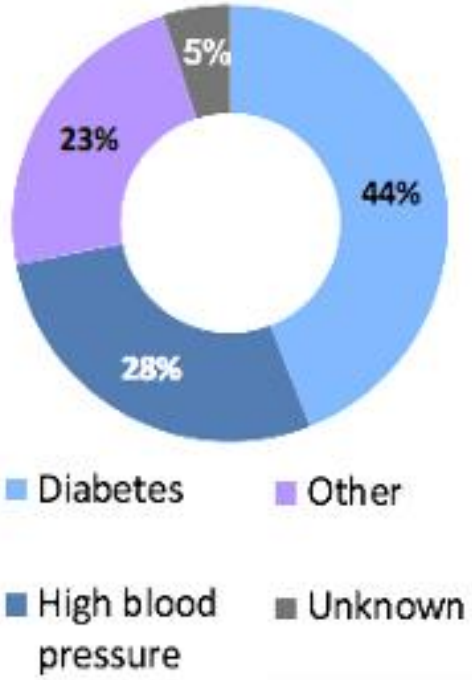
Chronic kidney disease ranks 12 among most common cause of global mortality [1]



In 2017, the prevalence of global CKD was estimated as **9.1%**[1]



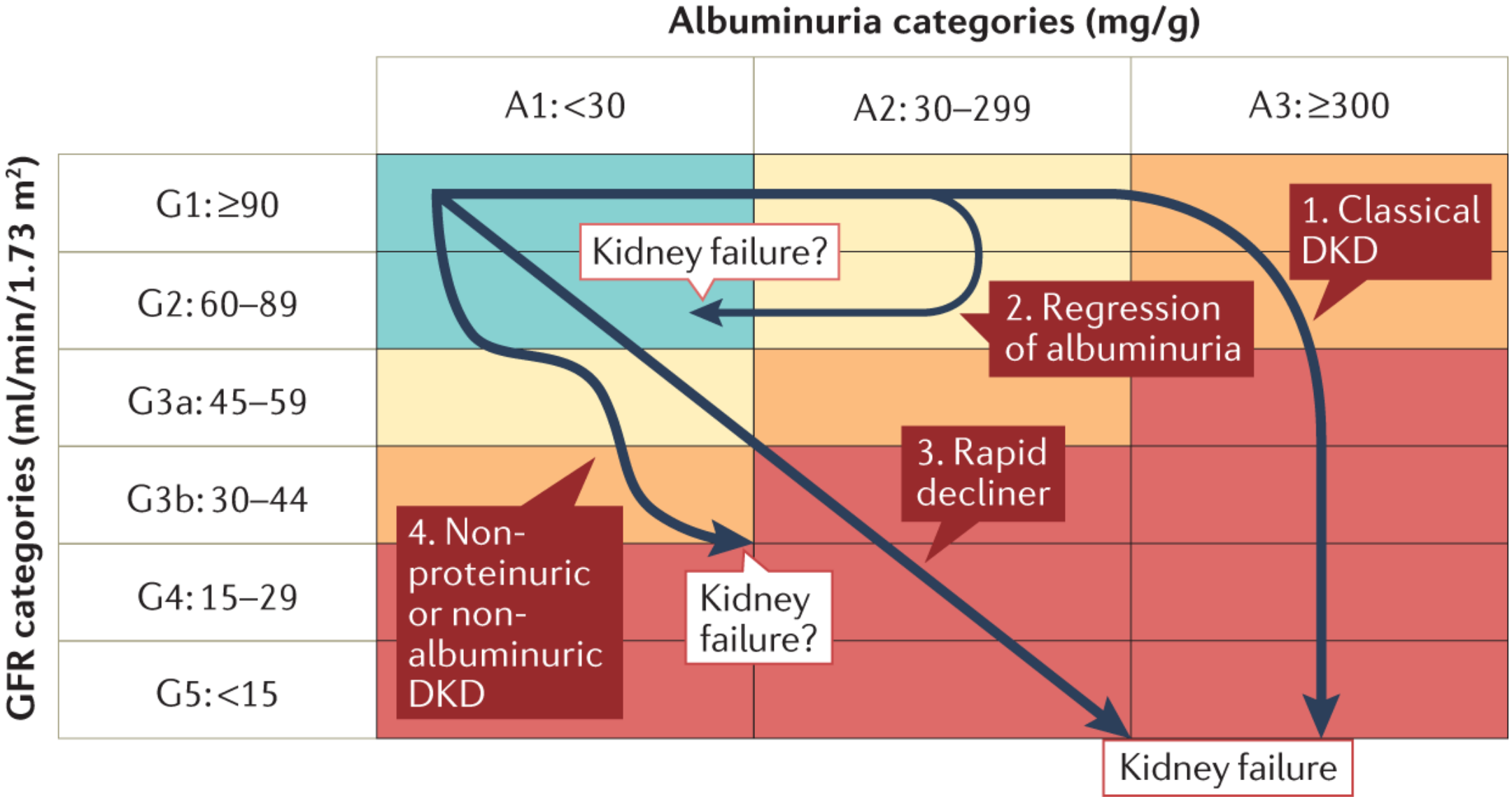
Diabetes is among the leading cause of CKD **(up to 40%)**



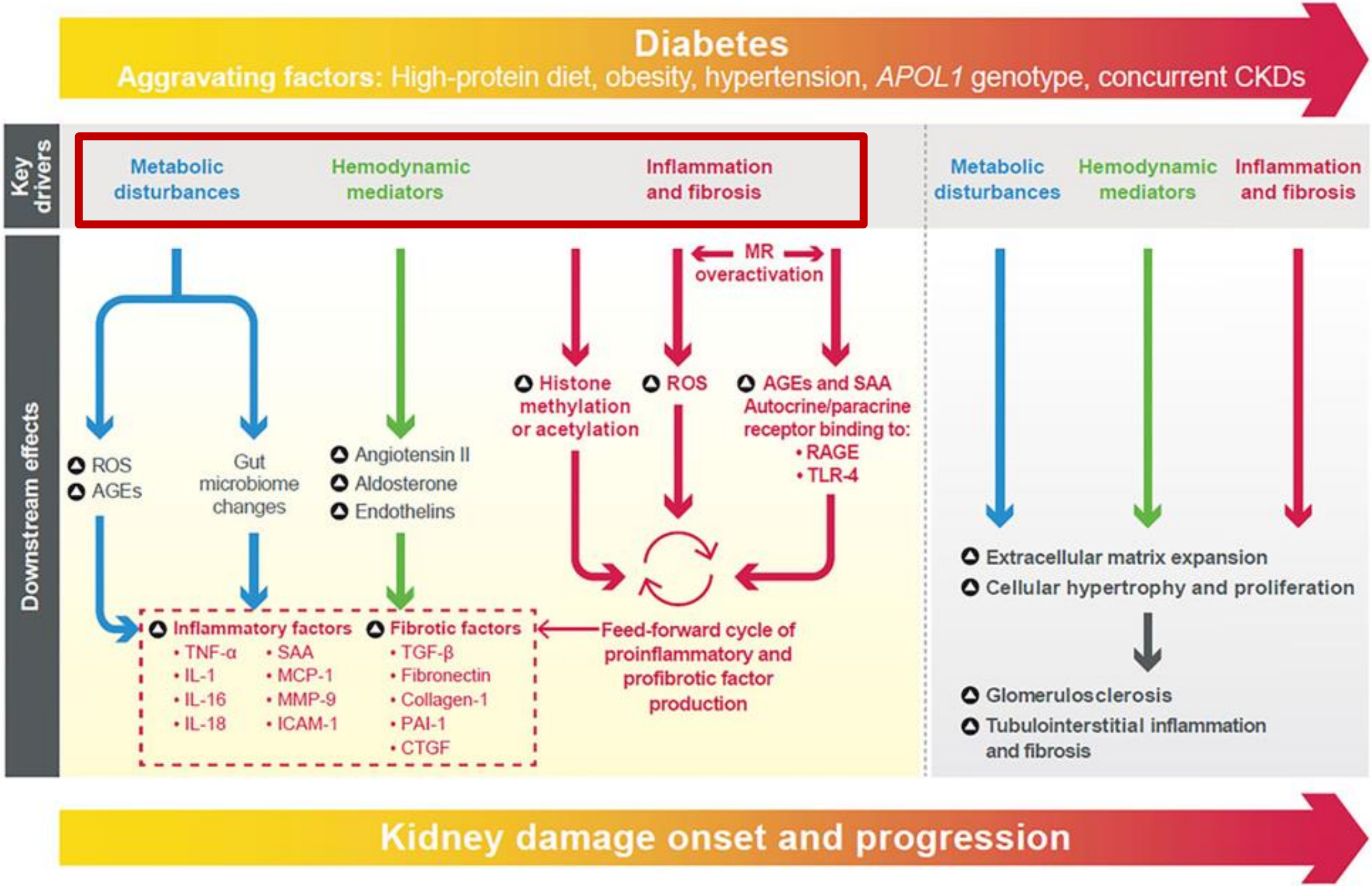
DKD develops in **30-40%** of subjects with diabetes [2,3]

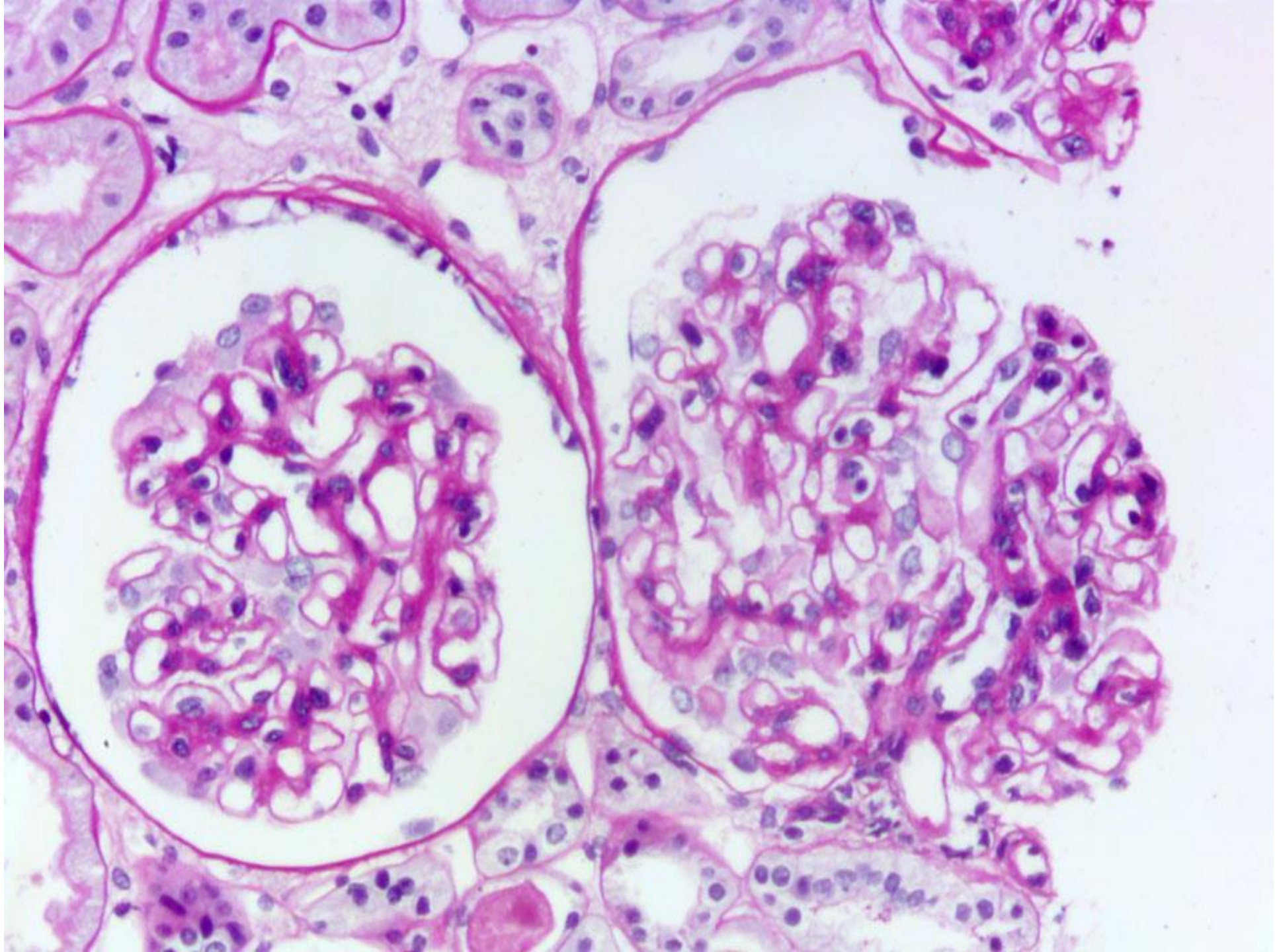
ESRD is a main event, but the majority dies from CVD [4]

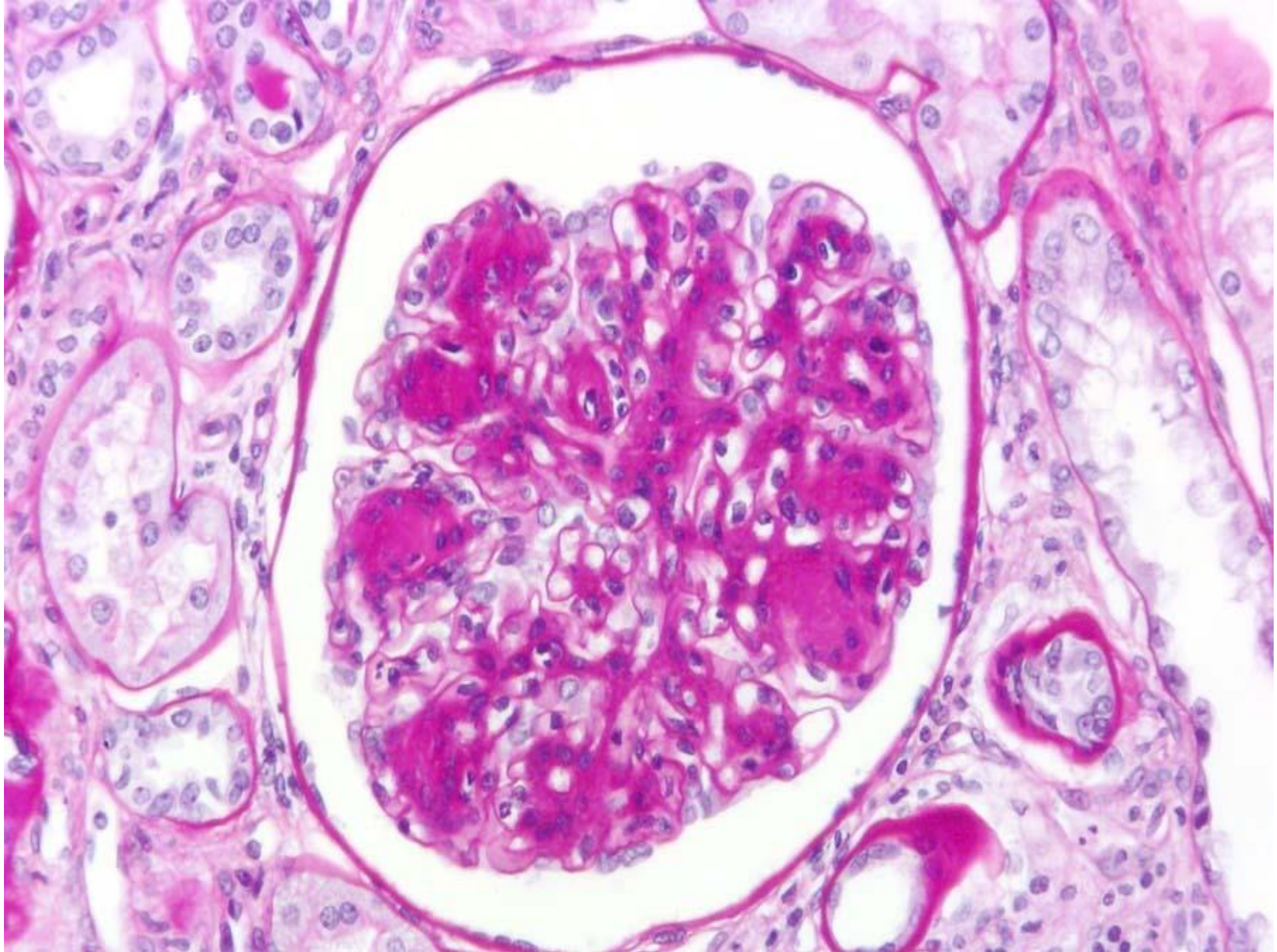
Traiettorie della DKD



MECCANISMI FISIOPATOLOGICI


Diabetes
Aggravating factors: High-protein diet, obesity, hypertension, APOL1 genotype, concurrent CKDs
Key drivers
Metabolic disturbances
Hemodynamic mediators
Inflammation and fibrosis
Metabolic disturbances
Hemodynamic mediators
Inflammation and fibrosis
Downstream effects
MR overactivation
ROS
AGEs
Gut microbiome changes
Angiotensin II
Aldosterone
Endothelins
Histone methylation or acetylation
ROS
AGEs and SAA
Autocrine/paracrine receptor binding to:
• RAGE
• TLR-4
Inflammatory factors
• TNF-α
• IL-1
• IL-16
• IL-18
• SAA
• MCP-1
• MMP-9
• ICAM-1
Fibrotic factors
• TGF-β
• Fibronectin
• Collagen-1
• PAI-1
• CTGF
Feed-forward cycle of proinflammatory and profibrotic factor production
Extracellular matrix expansion
Cellular hypertrophy and proliferation
Glomerulosclerosis
Tubulointerstitial inflammation and fibrosis
Kidney damage onset and progression





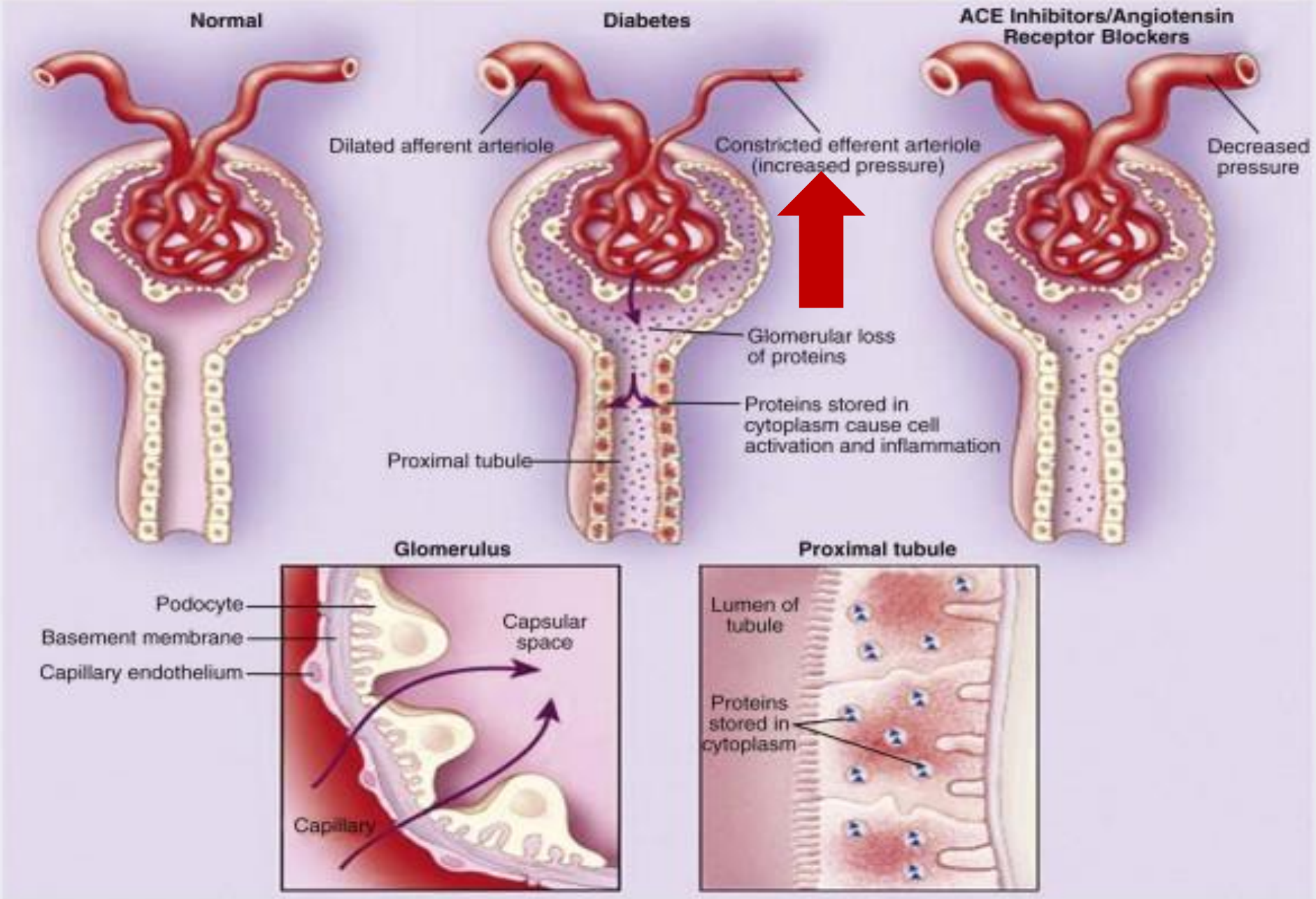
MECCANISMI FISIOPATOLOGICI

- Emodinamici
- Metabolici
- Infiammatori-profibrotici

MECCANISMI FISIOPATOLOGICI

- **Emodinamici**
- Metabolici
- Infiammatori-profibrotici

Nephron Changes in Diabetes and After Administration of an ACE Inhibitor or Angiotensin Receptor Blocker



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- **Metabolici**
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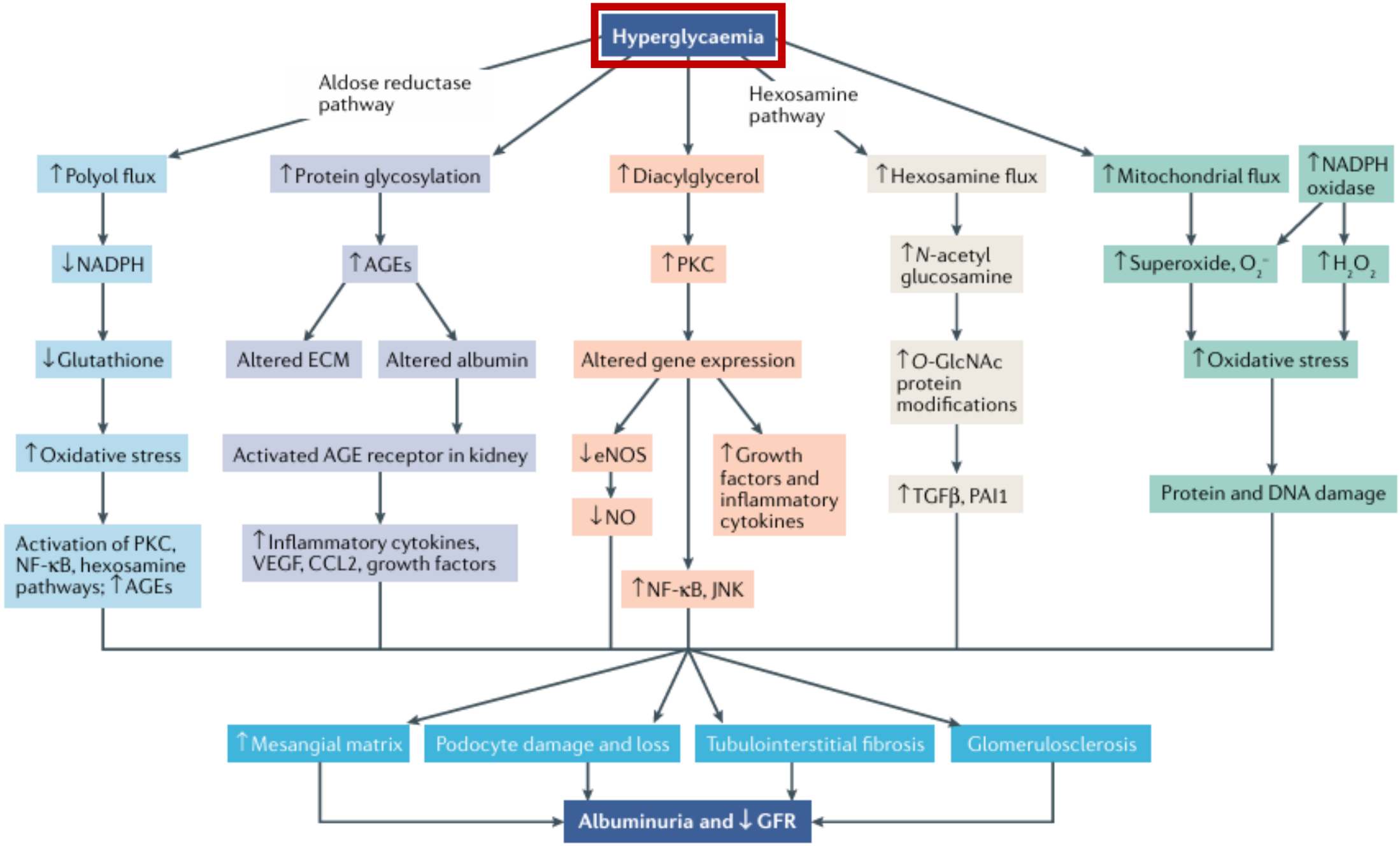
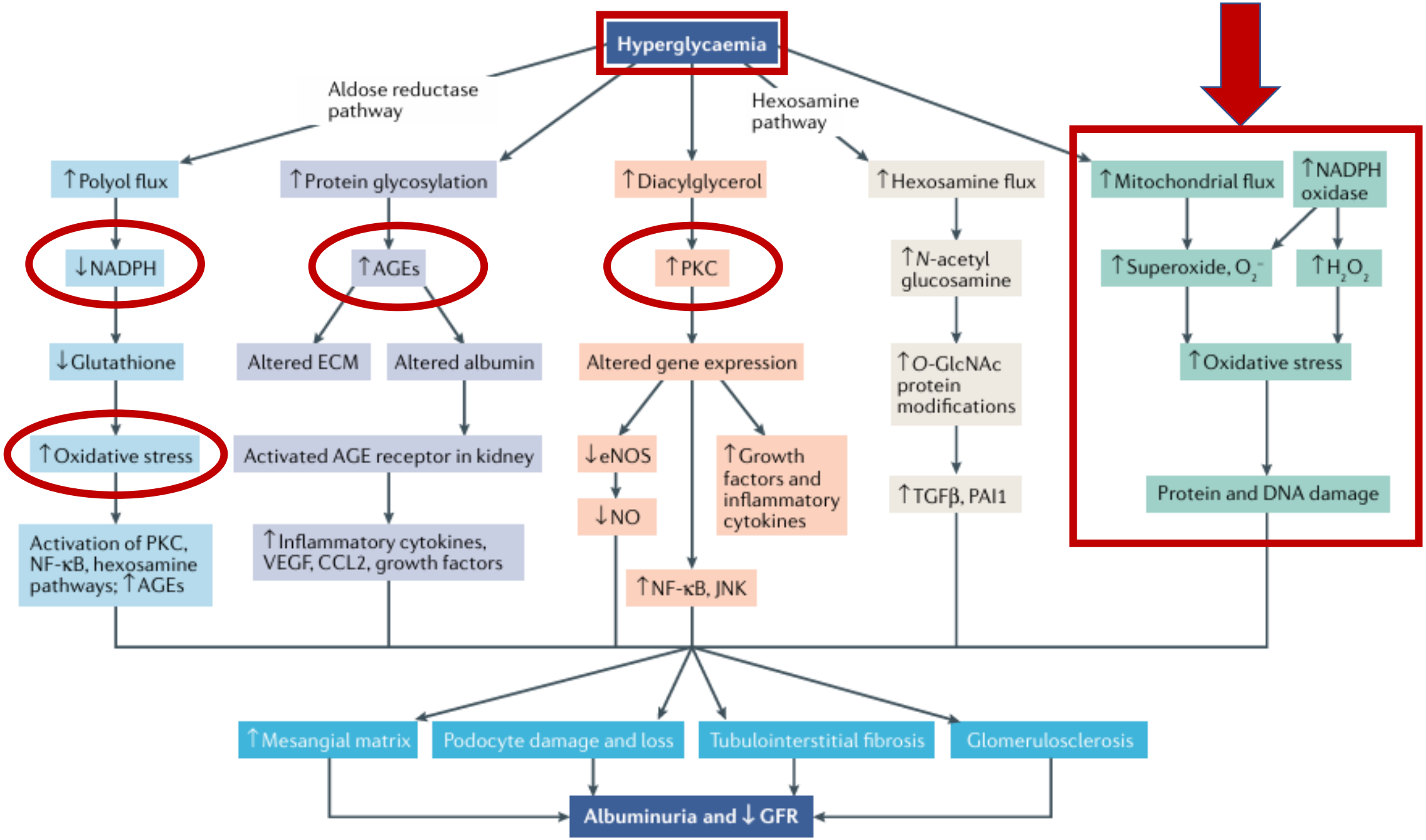

Hyperglycaemia
Aldose reductase pathway
Hexosamine pathway
↑Polyol flux
↓NADPH
↓Glutathione
↑Oxidative stress
Activation of PKC, NF-κB, hexosamine pathways; ↑AGEs
↑Protein glycosylation
↑AGEs
Altered ECM
Altered albumin
Activated AGE receptor in kidney
↑Inflammatory cytokines, VEGF, CCL2, growth factors
↑Diacylglycerol
↑PKC
Altered gene expression
↓eNOS
↓NO
↑Growth factors and inflammatory cytokines
↑NF-κB, JNK
↑Hexosamine flux
↑N-acetyl glucosamine
↑O-GlcNAc protein modifications
↑TGFβ, PAI1
↑Mitochondrial flux
↑NADPH oxidase
↑Superoxide, O_2^-
↑H_2O_2
↑Oxidative stress
Protein and DNA damage
↑Mesangial matrix
Podocyte damage and loss
Tubulointerstitial fibrosis
Glomerulosclerosis
Albuminuria and ↓GFR


Hyperglycaemia
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↑Hexosamine flux
↑Mitochondrial flux
↑NADPH oxidase
↓NADPH
↑AGEs
↑PKC
↑N-acetyl glucosamine
↑Superoxide, O_2^-
↑H_2O_2
↓Glutathione
Altered ECM
Altered albumin
Altered gene expression
↑O-GlcNAc protein modifications
↑Oxidative stress
↑Oxidative stress
Activated AGE receptor in kidney
↓eNOS
↑Growth factors and inflammatory cytokines
↑TGFβ, PAI1
Protein and DNA damage
↓NO
Activation of PKC, NF-κB, hexosamine pathways; ↑AGEs
↑Inflammatory cytokines, VEGF, CCL2, growth factors
↑NF-κB, JNK
↑Mesangial matrix
Podocyte damage and loss
Tubulointerstitial fibrosis
Glomerulosclerosis
Albuminuria and ↓GFR

MECCANISMI FISIOPATOLOGICI

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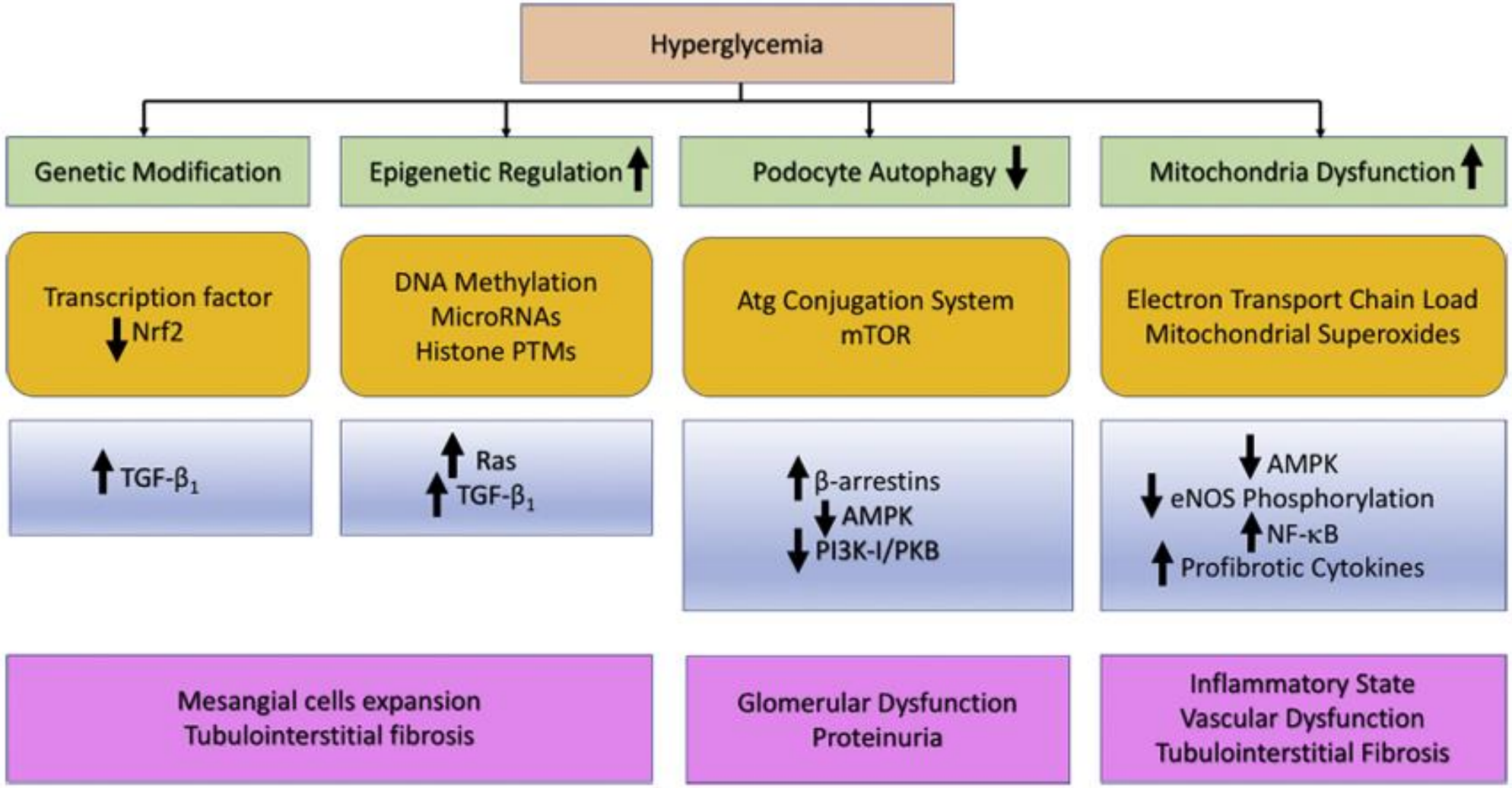
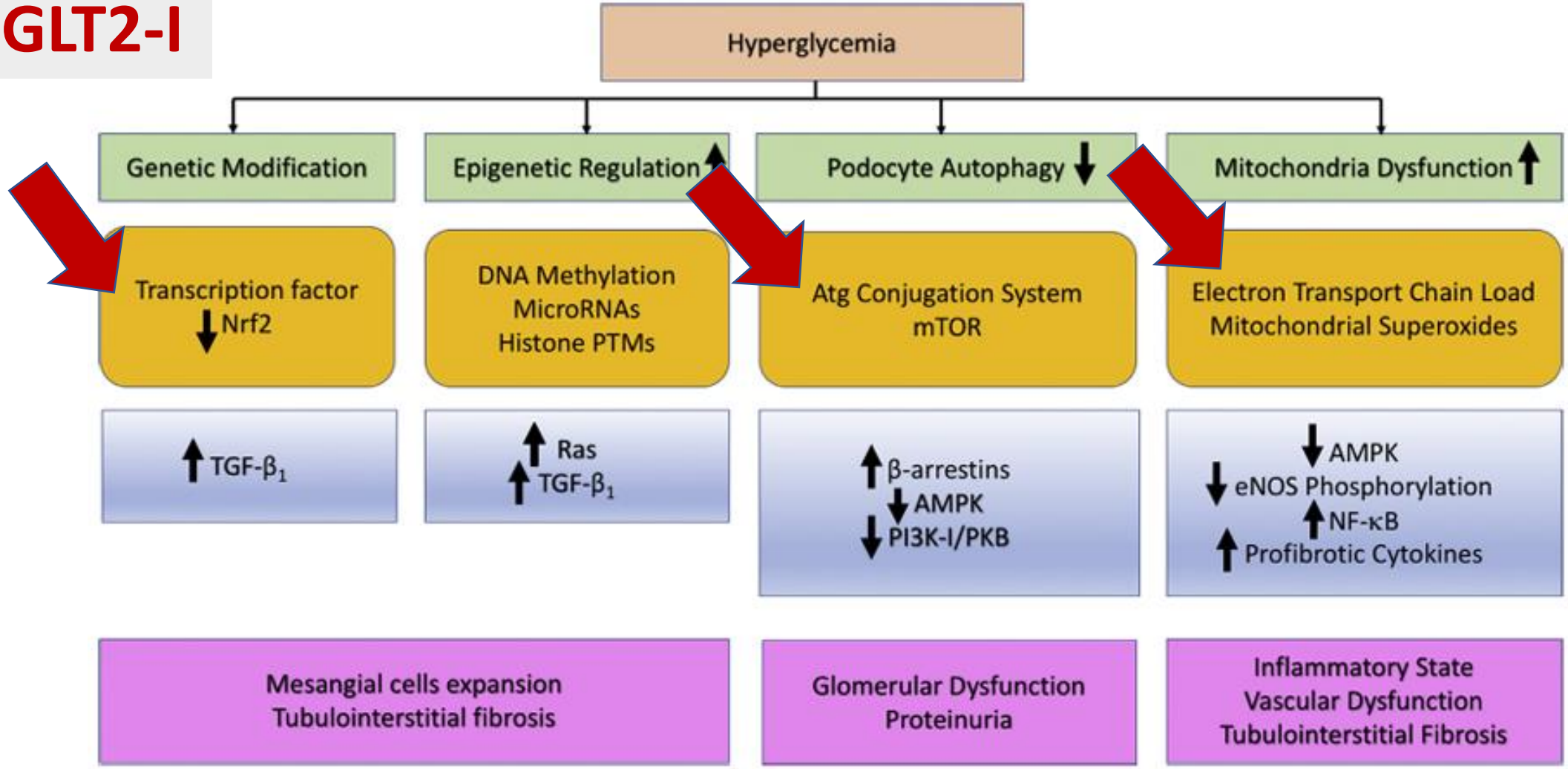
Meccanismi infiammatori e pro-fibrotici

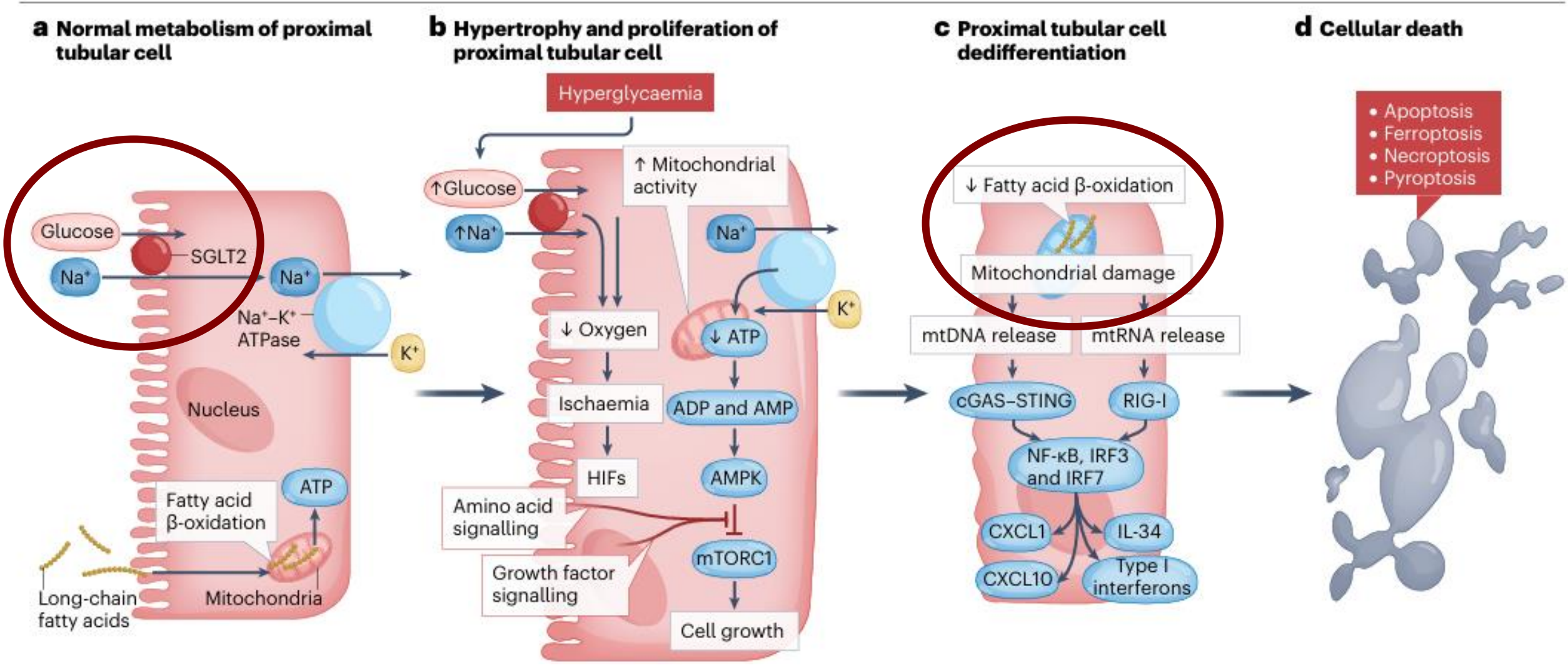


Meccanismi infiammatori e pro-fibrotici

SGLT2-I



Cellula tubulare normale → **Ipertrofia e proliferazione** → **De-differenziazione** → **Morte**



Cellula tubulare prossimale

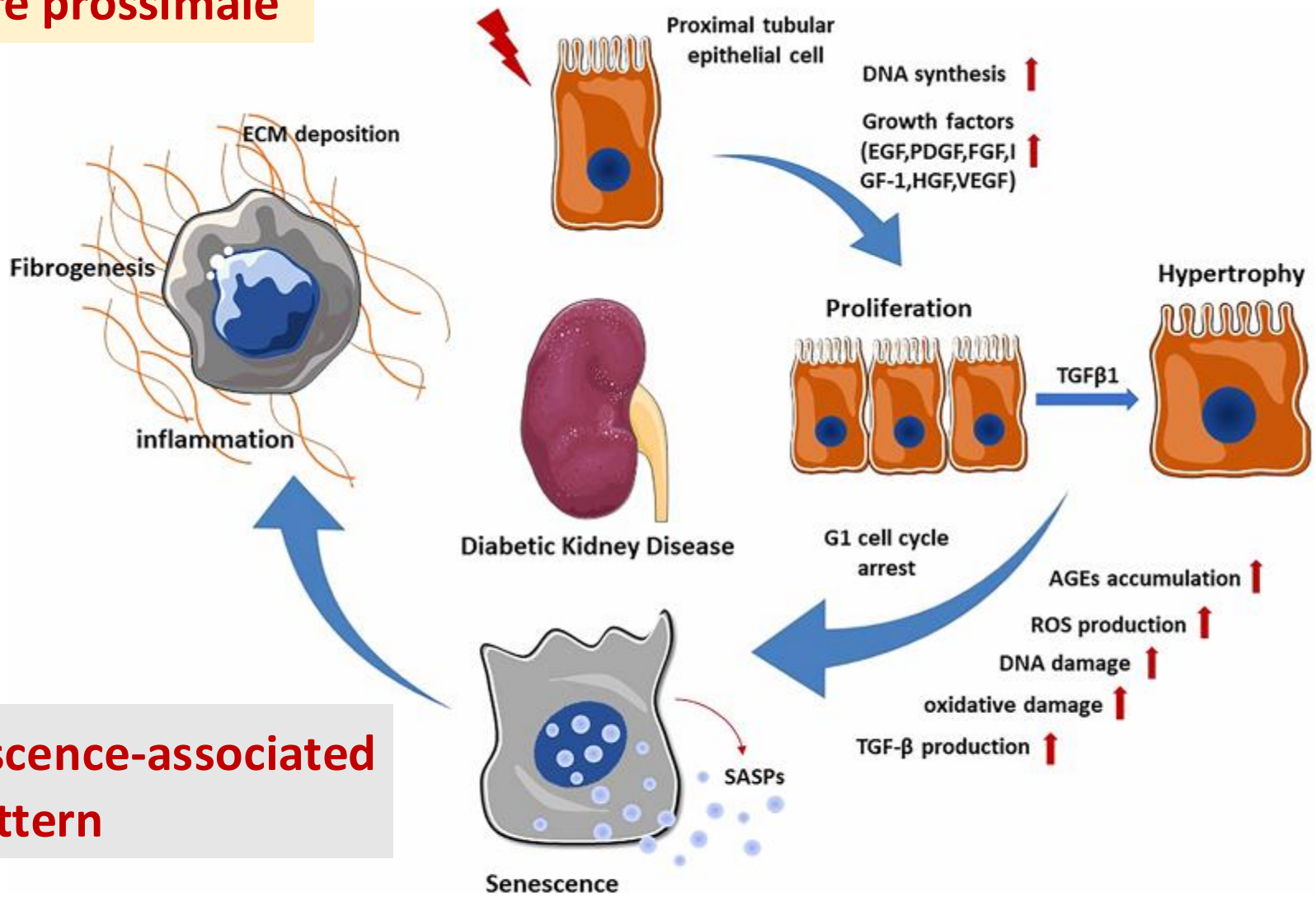
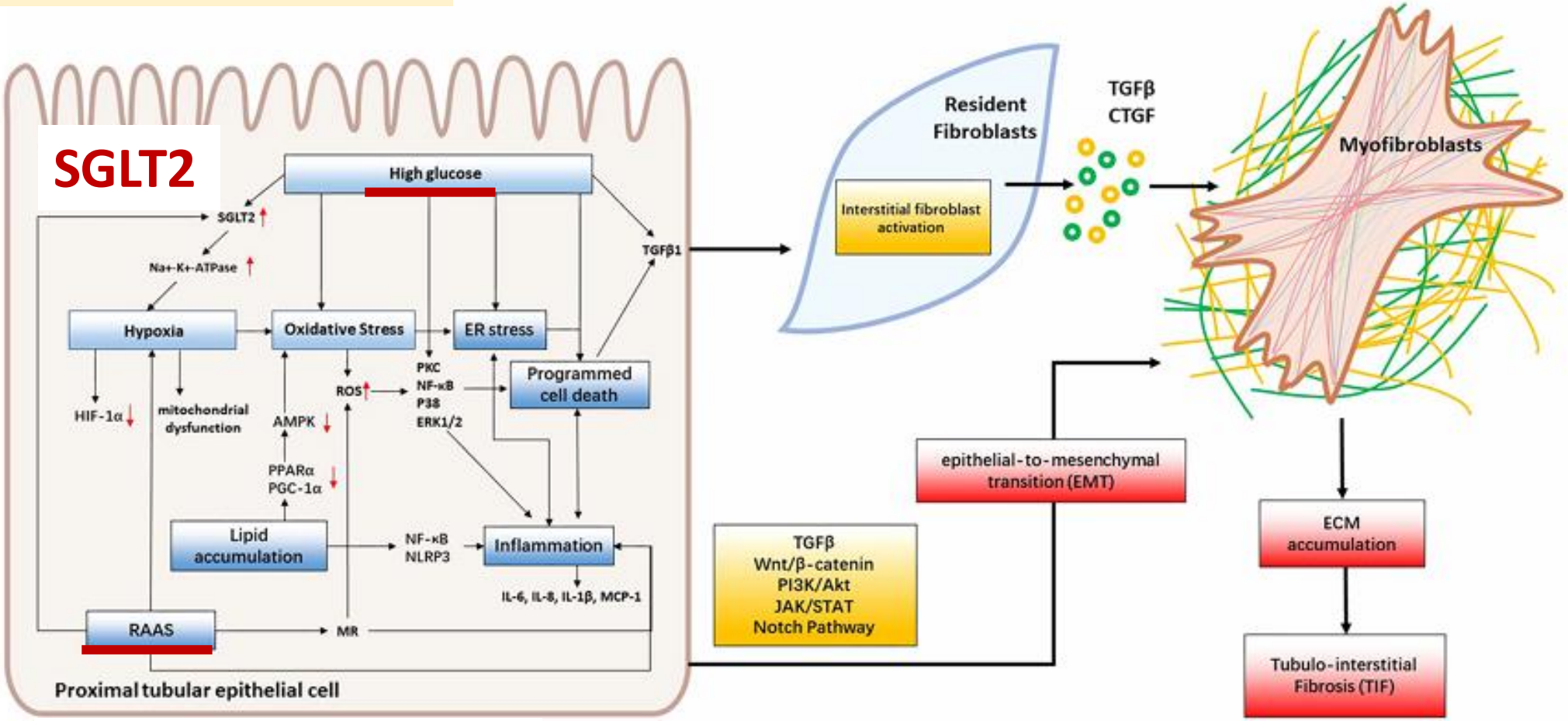


FIGURE 1
Renal tubular epithelial cell changes in DKD. When exposed to various stimuli, PTECs express and secrete multiple growth factors, which promote the proliferation of PTECs. Subsequently, TGF-β1 stimulates the transformation of PTECs from proliferation to hypertrophy through ERK and P38 pathway. In order to prevent excessive proliferation, PTECs undergo G1 cell cycle arrest and transition to senescence. Senescent PTECs can secrete SASPs, promoting renal inflammation and fibrosis.

SASP: senescence-associated secretory pattern

Cellula tubulare prossimale

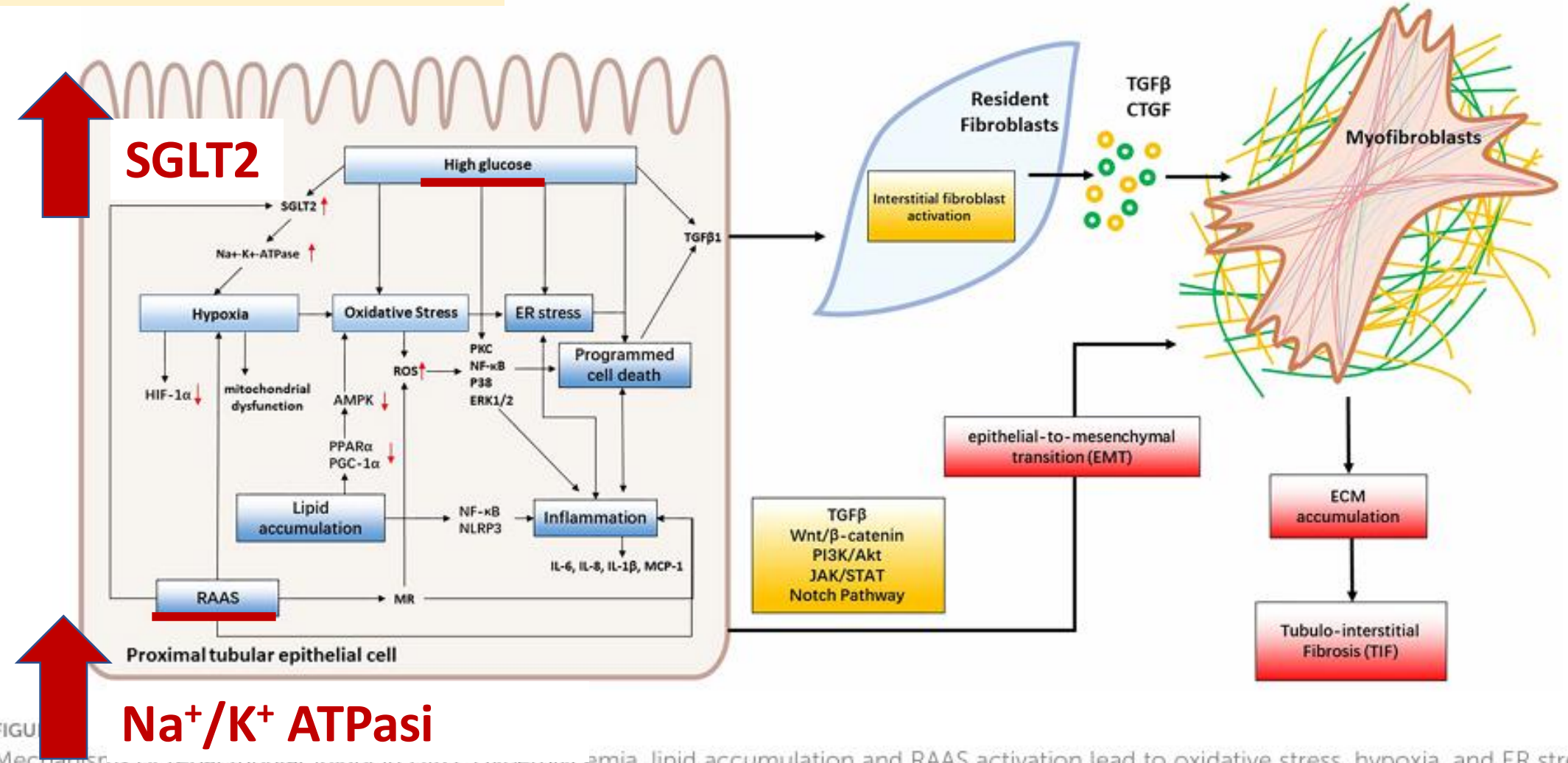


Na^+/K^+ ATPasi

FIGURE 2

Mechanisms of renal tubular injury in DKD. Hyperglycemia, lipid accumulation and RAAS activation lead to oxidative stress, hypoxia, and ER stress, consequently triggering inflammation, programmed cell death and EMT. These cascading effects contribute to renal tubular cell injury and interstitial fibroblast activation. When intrinsic renal cells become activated, they secrete cytokines like TGF-β and CTGF that facilitate the formation of myofibroblasts which contribute to fibrosis by producing collagen I, collagen III, collagen IV, fibronectin, and laminin. This leads to the accumulation of extracellular matrix (ECM) and, ultimately, the development of tubulointerstitial fibrosis and DKD.

Cellula tubulare prossimale



Na^+/K^+ ATPasi

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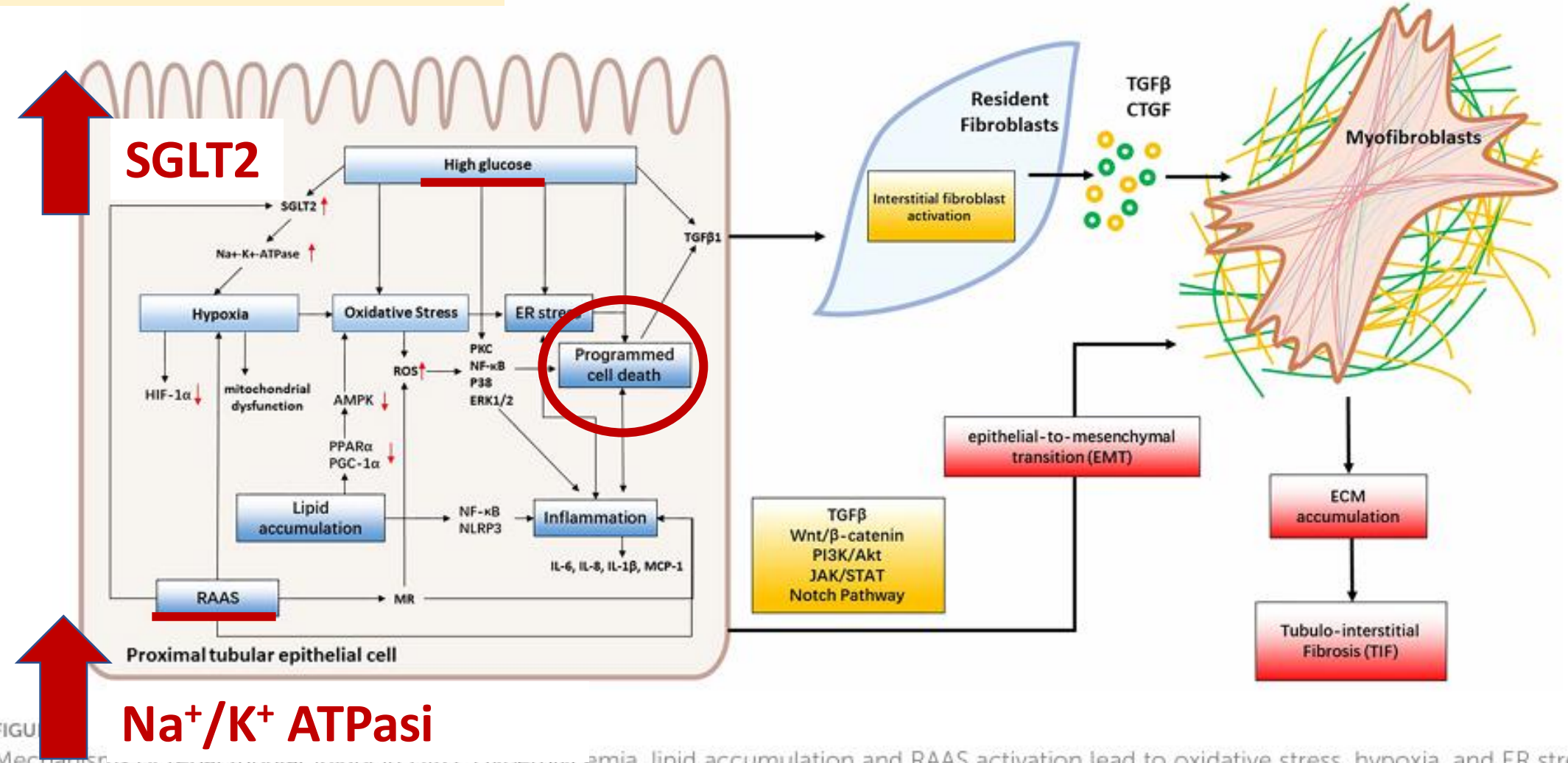

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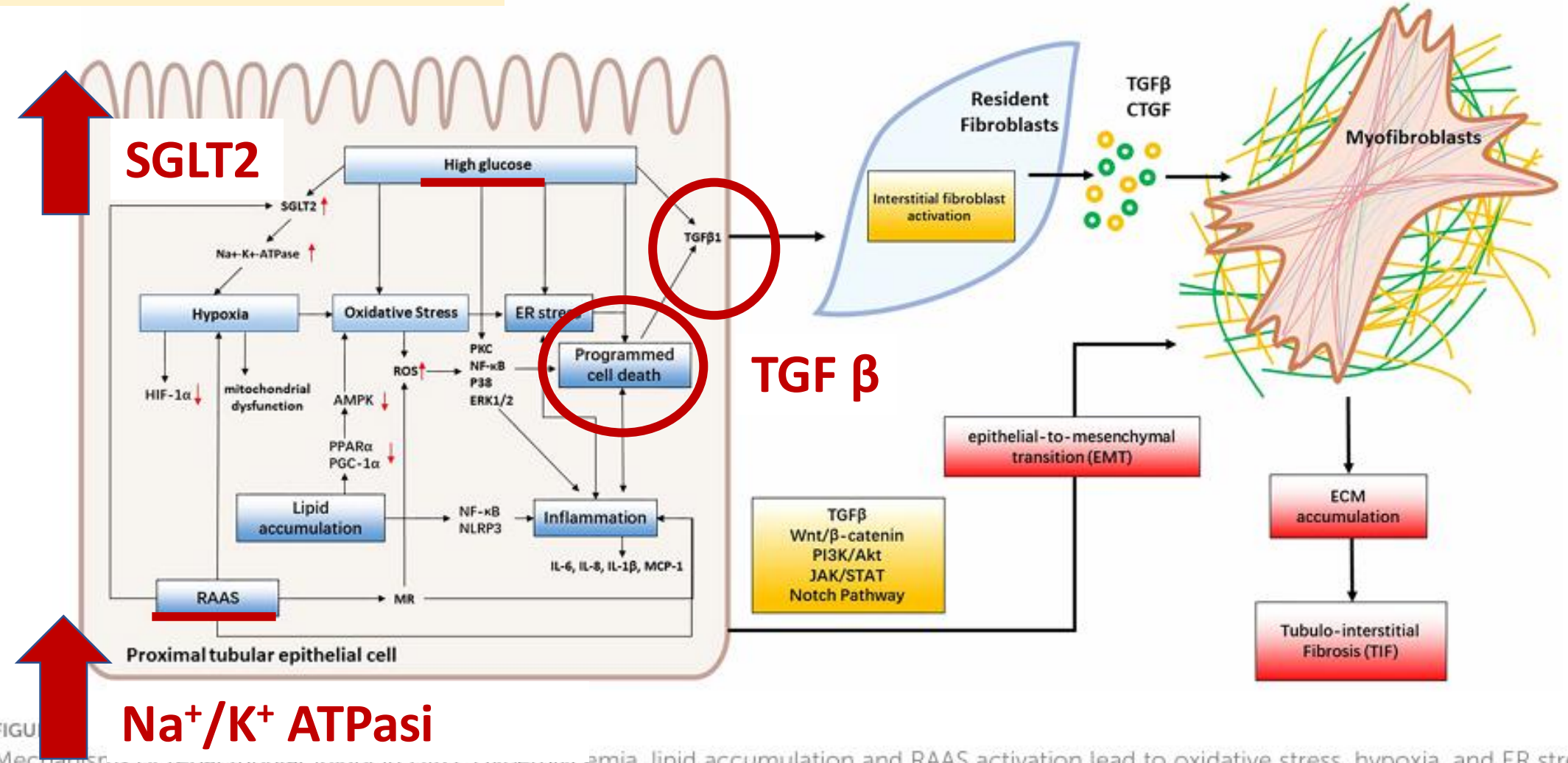

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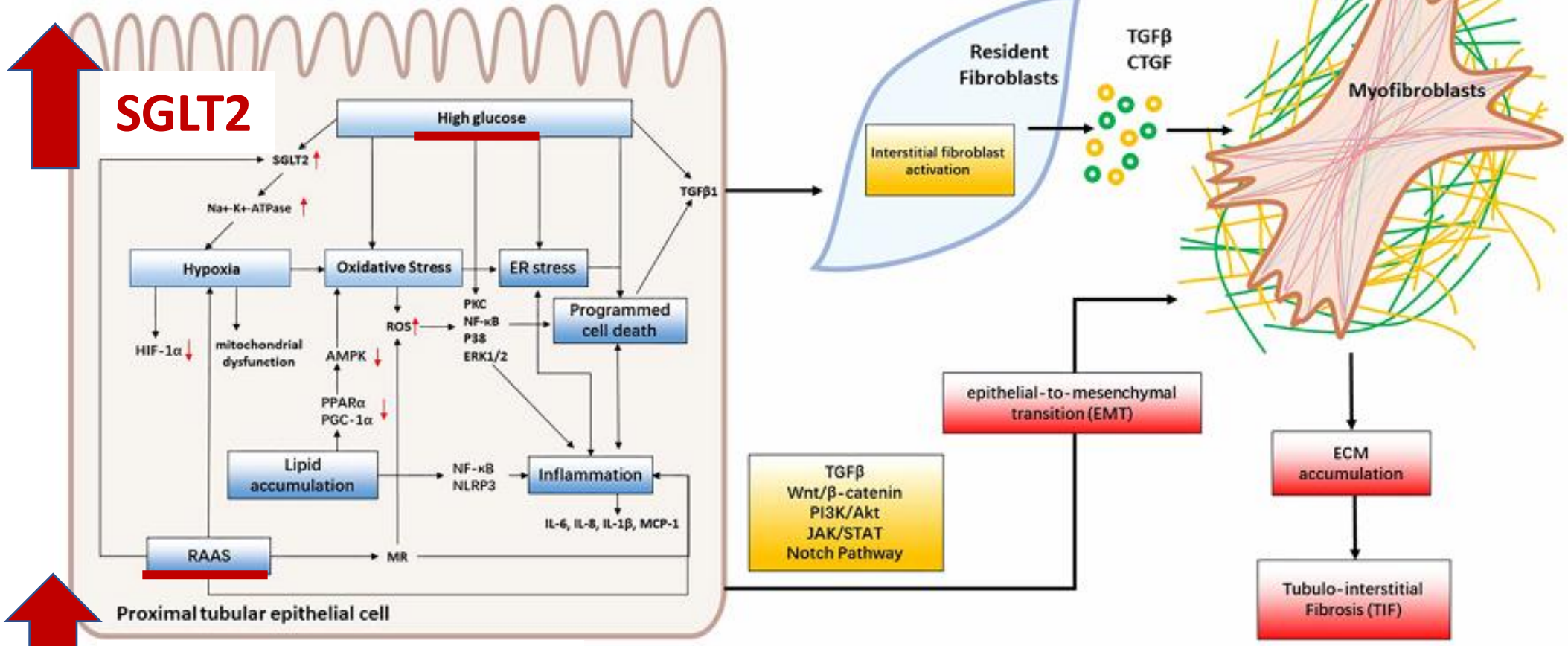
Cellula tubulare prossimale

Attivazione FIBROBLASTI



Na^+/K^+ ATPasi

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Cellula tubulare prossimale

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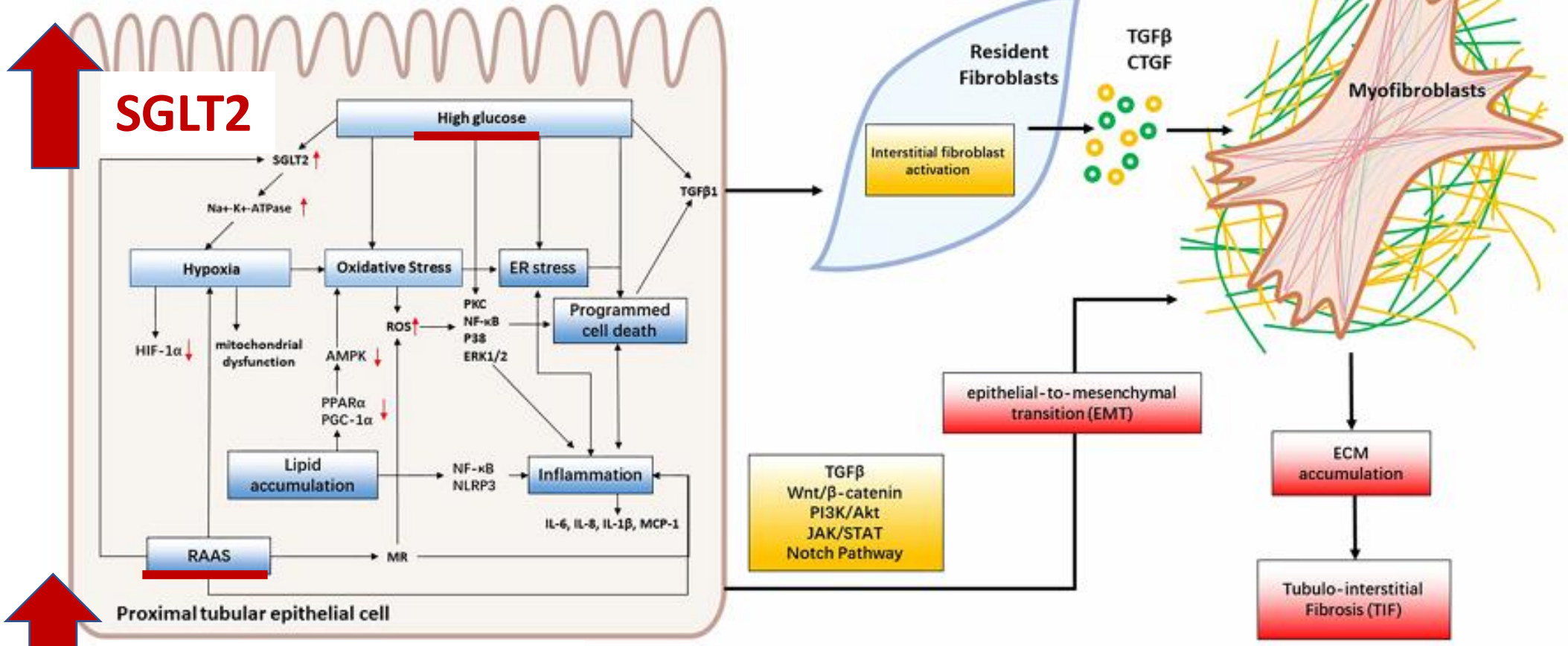

Na^+/K^+ ATPasi

Fibrosi tubulo-interstiziale

FIGU

Mechanisms of renal tubular injury in DKD. Hyperglycemia, lipid accumulation and RAAS activa

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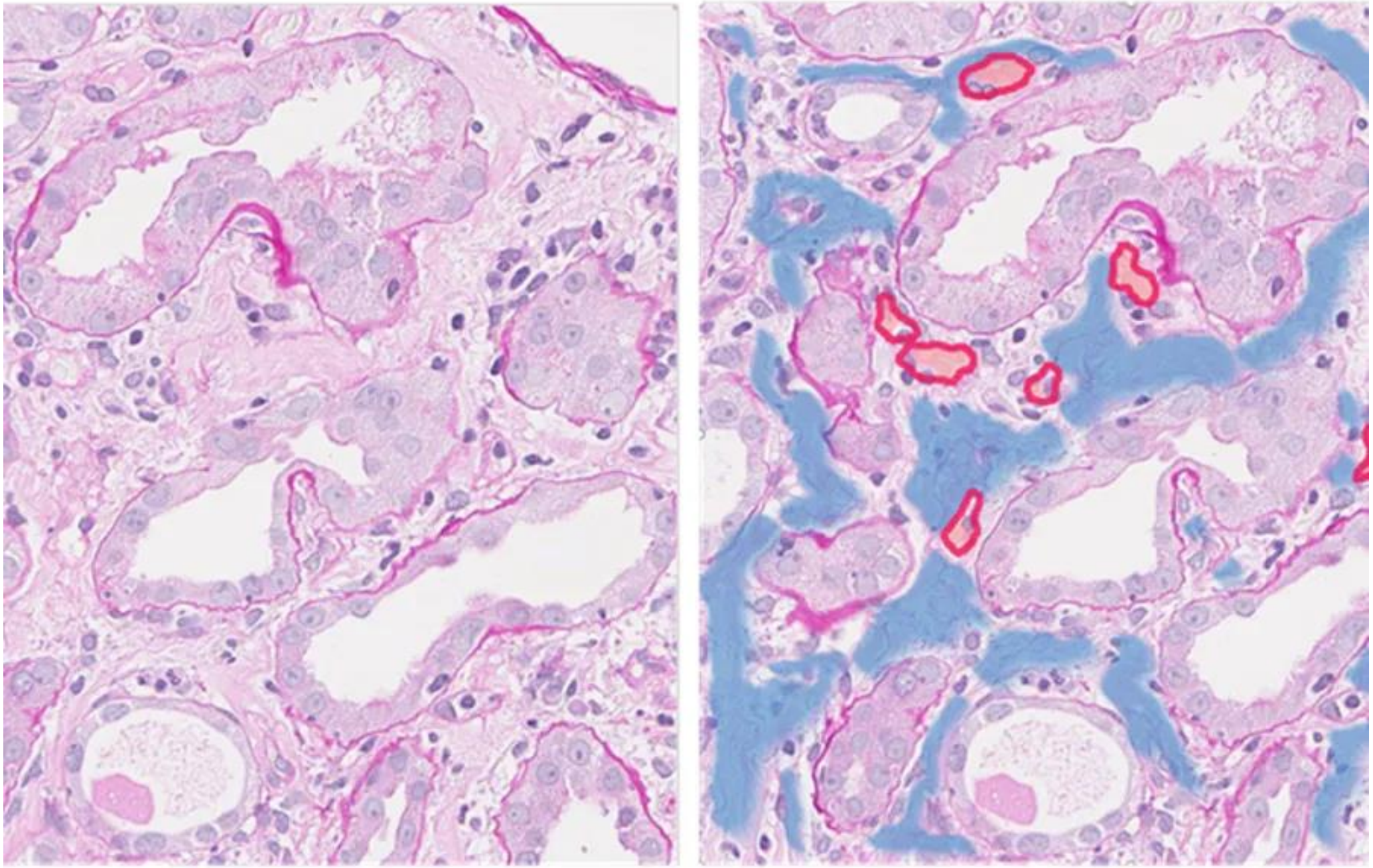
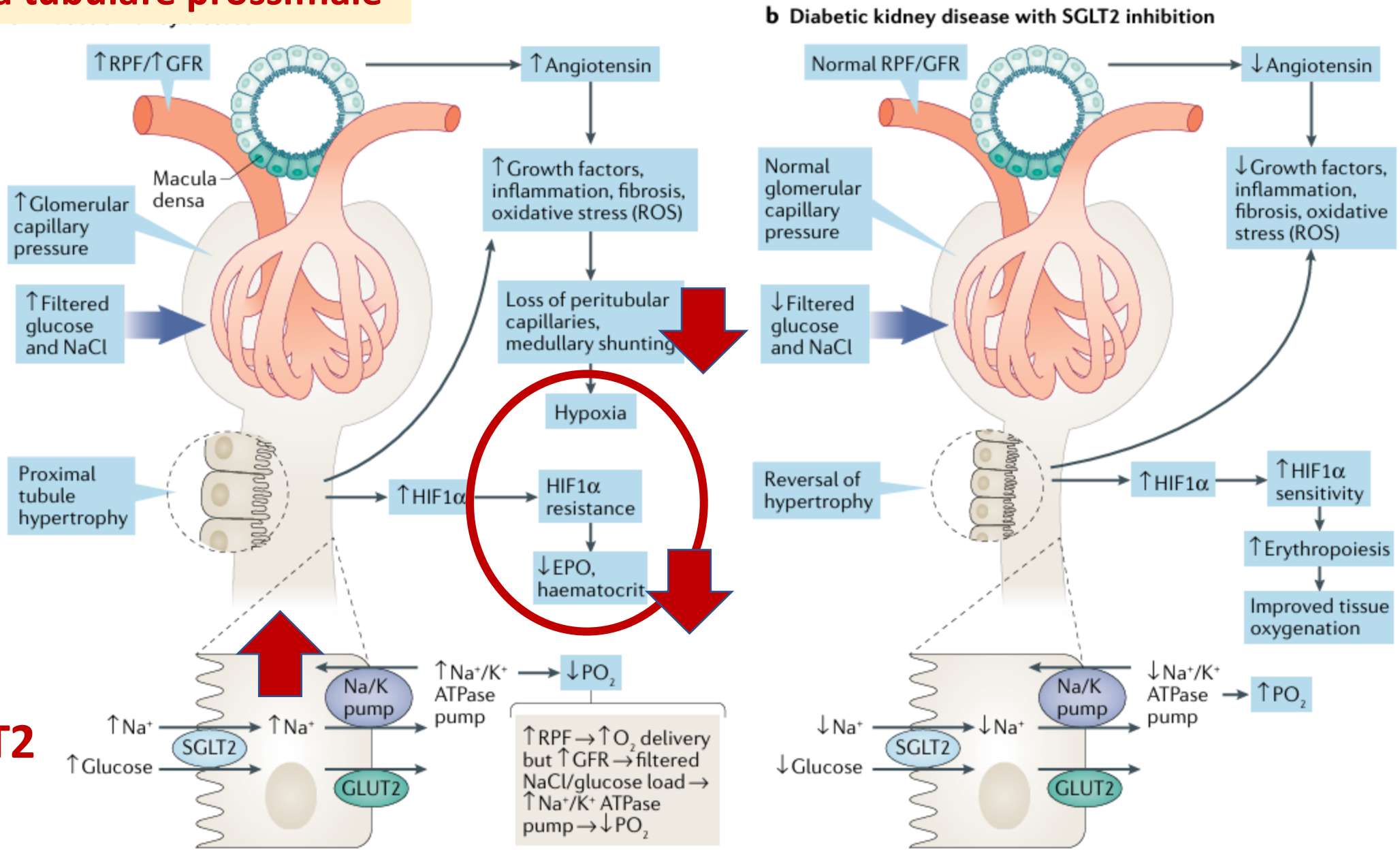


Cellula tubulare prossimale



SGLT2

TERAPIA DELLA DKD

- SGLT2-I
- MRA
- GLP1 RA

TERAPIA DELLA DKD

- **SGLT2-I**
- MRA
- GLP1 RA

Kidney outcomes trials

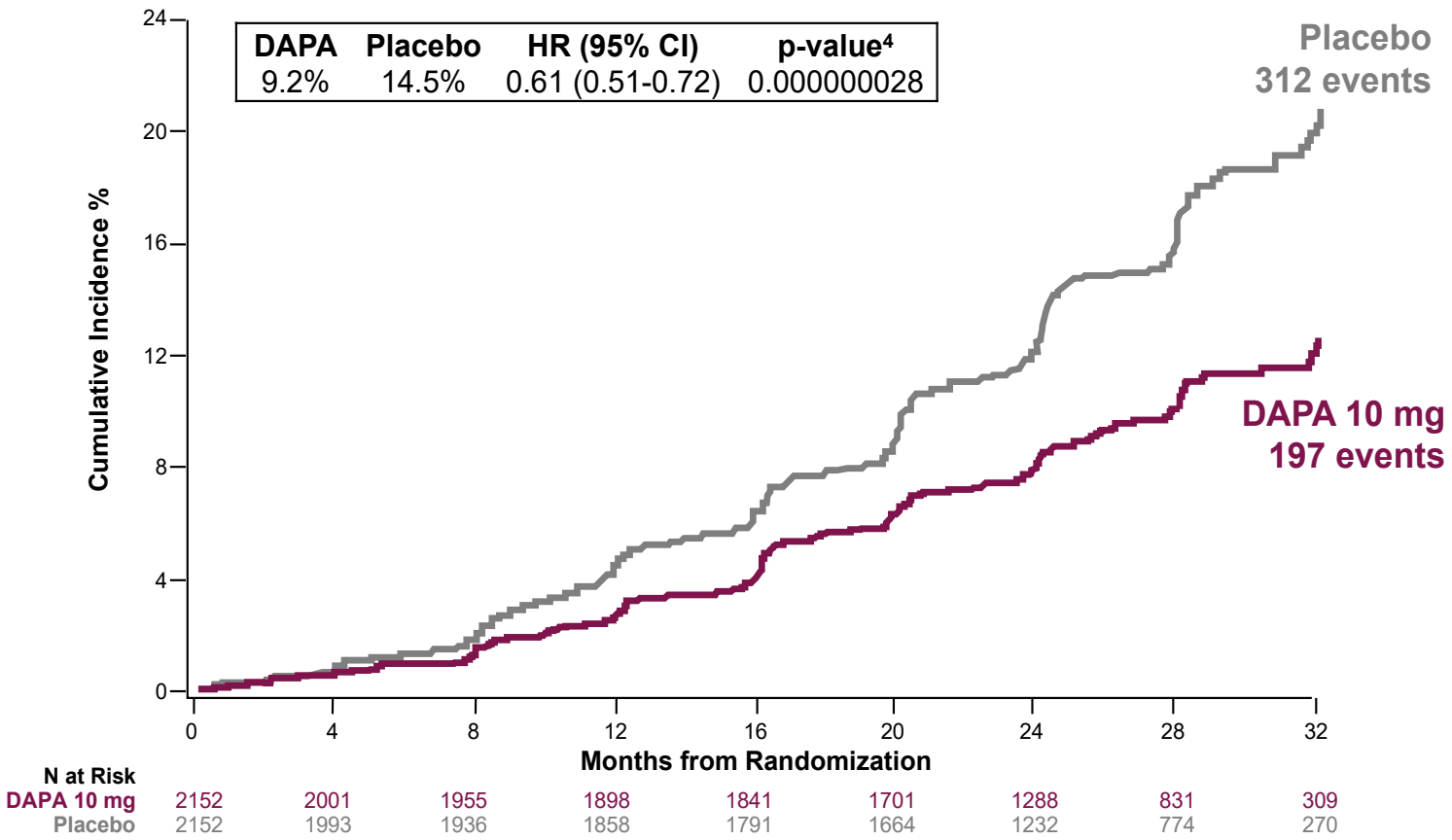
	2018	2020	2023	2021
Study and SGLT2 inhibitor	CREDENCE (canagliflozin)	DAPA-CKD (dapagliflozin)	EMPA-KIDNEY (empagliflozin)	SCORED (sotagliflozin)*
Patients (key inclusion criteria)	*N*=4401 • CKD with T2D • eGFR 30 to <90 mL/min/1.73 m² • UACR >300 to 5000 mg/g	*N*=4304 • CKD with or without T2D • eGFR 25 to 75 mL/min/1.73 m² • UACR >200 to 5000 mg/g	*N*=6609 • CKD with or without T2D • Either eGFR 20 to <45 mL/min/1.73 m² with any UACR, or eGFR ≥45 mL/min/1.73 m² with UACR ≥200 mg/g	*N*=10,584 • CKD with T2D, with or without albuminuria • eGFR 25 to 60 mL/min/1.73 m²
Cardiorenal outcome definition†	ESKD (dialysis, transplant, or sustained eGFR <15 mL/min/1.73 m²), serum creatinine doubled, renal or CV death	ESKD, sustained eGFR decrease by ≥50%, renal or CV death	ESKD (dialysis, transplant), sustained eGFR decrease to <10 mL/min/1.73 m² or by ≥40%, renal or CV death	First occurrence of a sustained decrease of ≥50% in eGFR, kidney failure, renal or CV death
Cardiorenal outcome hazard ratio (95% CI)	0.70 (0.59–0.82) *p*=0.00001	0.61 (0.51–0.72) *p*<0.001	0.72 (0.64–0.82) *p*<0.001	0.77 (0.65–0.91) *p*<0.002

RRR: 30-40%

Nephro-cardioprotective effects of Dapaglifozin

DAPACKD

First trial with SGLT2-I to demonstrate improvement in cardiorenal outcomes and mortality in CKD with or without T2D

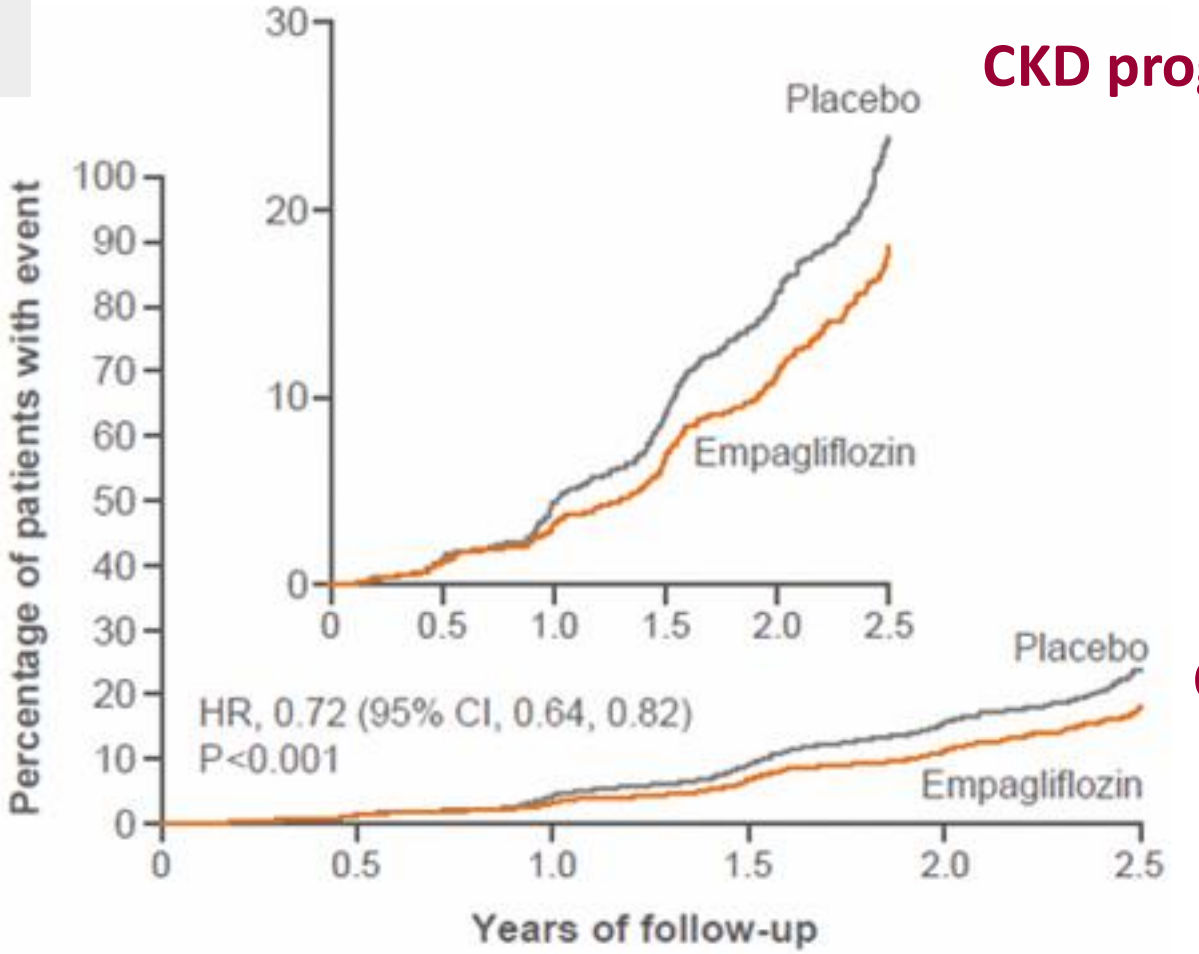


HR 0.61 (0.51- 0.72)

HL Heerspink et al NEJM 2020

Nephro-cardioprotective effects of Empaglifozin

EMPA-KIDNEY

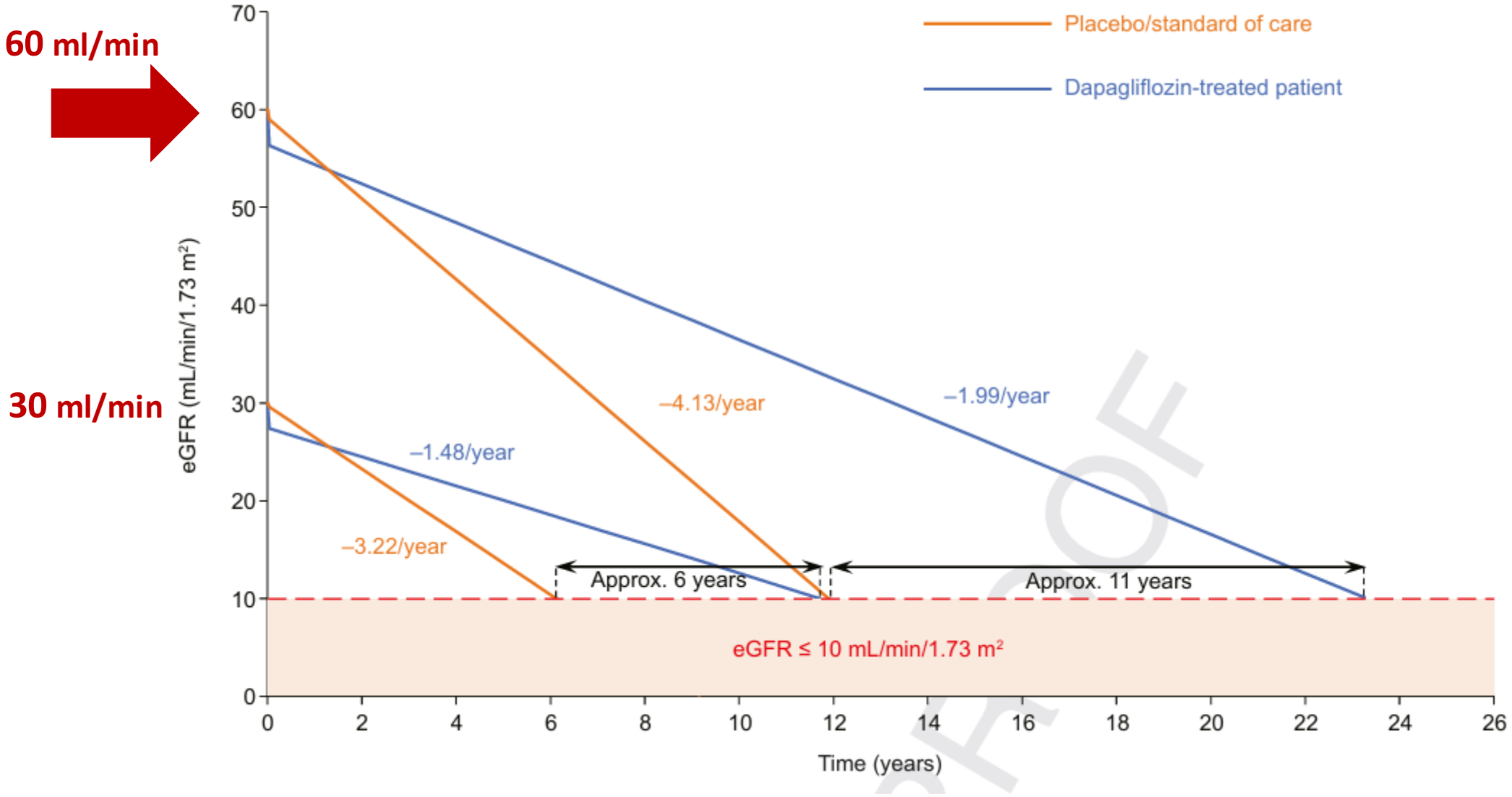


HR 0.72 (0.64-0.82)

No. at risk						
Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

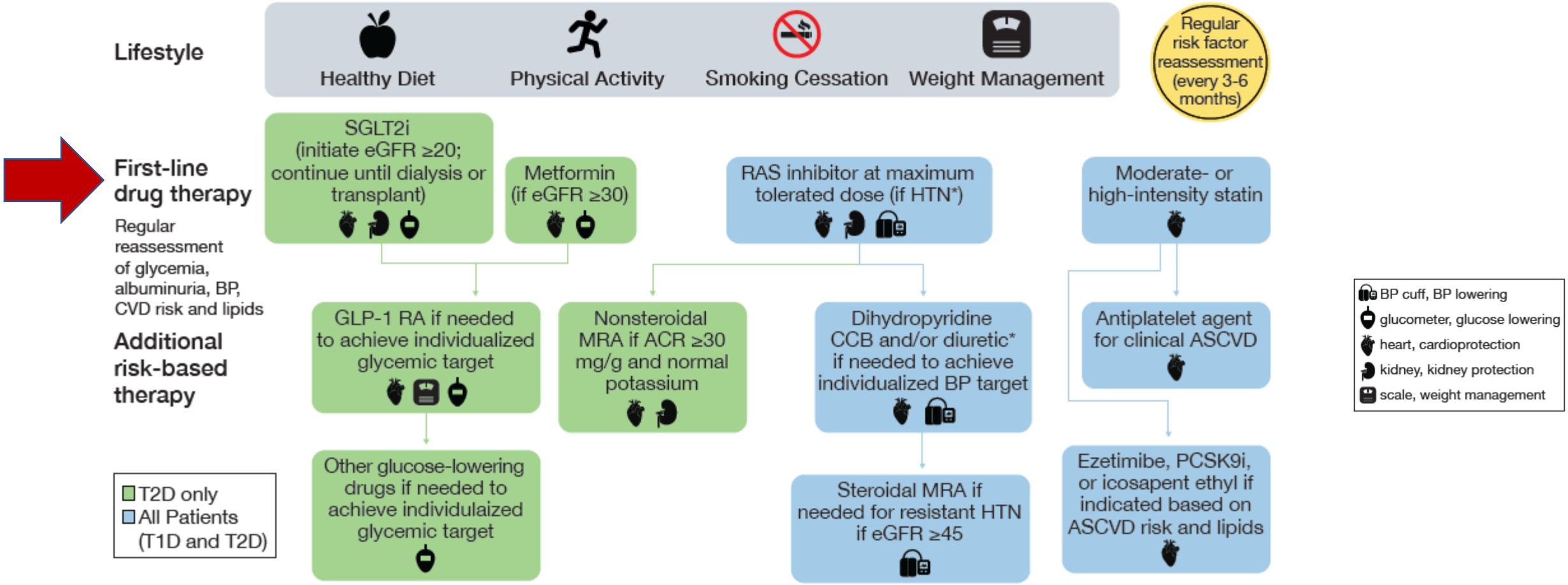
WJ Herrington et al. NEJM 2023

Estrapolazione da DAPA-CKD trial (GFR 25-75 ml/min)



M Madero et al. Kidney Med 2024

2022 KDIGO Approach for People With Diabetes and CKD



Note: eGFR is presented in units of mL/min/1.73 m^2.

*Maximum tolerated ACEi or ARB should be first-line therapy for HTN when albuminuria is present. Otherwise, dihydropyridine CCB or diuretic can also be considered; all three classes are often needed to attain BP targets.

ACEi = angiotensin-converting enzyme inhibitor; ACR = albumin-creatinine ratio; ARB = angiotensin II receptor blocker; ADA = American Diabetes Association: ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HTN = hypertension; KDIGO = Kidney Disease: Improving Global Outcomes; MRA = mineralocorticoid-receptor antagonist; PCSK9i= proprotein convertase subtilisin/kexin type 9 inhibitor; RAS = renin-angiotensin system; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T1D = type 1 diabetes; T2D = type 2 diabetes.

Rossing P et al. *Kidney Int.* 2022;102(5):990-999.

2024 KDIGO recommend SGLT2i as standard of care for CKD, regardless of etiology

1st line

2024 KDIGO Guideline (CKD without T2D)[2,a]

- Patients with CKD across UACR levels:
  - HF, irrespective of level of albuminuria (1A)
  - eGFR ≥20 mL/min/1.73 m^2 with UACR ≥200 mg/g (1A)
  - eGFR ≥20 to 45 mL/min/1.73 m^2 with UACR <200 mg/g (2B)

2023 ERA Consensus[1]

- Foundational therapy for both glomerular disease and cardiometabolic CKD

2022 KDIGO Guideline (CKD and T2D)[3,a]

- Patients with T2D, CKD, eGFR ≥20 mL/min/1.73 m^2 (1A)

2023 ESH Guideline[4,b]

- Patients with CKD and hypertension (1A)[c]

[a]Level 1 = "We recommend" and Grade A = High quality of evidence; Level 2 = "We suggest" and Grade B = Moderate quality of evidence; [b]Class 1 = evidence/general agreement treatment is beneficial/useful/effective and potential benefits clearly outweigh potential risk; Level A = RCT/meta-analysis of RCTs with CV disease outcomes. A single trial is enough if sufficient power and without important limitations; [c]If eGFR ≥20 or 25 mL/min/1.73 m^2. Additional eGFR and albuminuria criteria apply for initiation of different SGLT2i according to their respective approval.

1. Mark PB et al. *Nephrology Dial Transplant*. 2023;38(11):2444-2455; 2. KDIGO CKD Work Group. *Kidney Int*. 2024;105(4S):S117–S314; 3. KDIGO Diabetes Work Group. *Kidney Int*. 2022;102(5S):S1-S127; 4. Mancia G et al. *J Hypertens*. 2023;41(12):1874-2071.

Perchè SGLT2-I è nefroprotettivo ?

Quali effetti esercita
sui meccanismi infiammatori e pro-fibrotici della DKD?

SGLT2-I modula 5 meccanismi-chiave della DKD

1. Riassorbimento di glucosio nel TCP
2. Riassorbimento di sodio nel TCP
3. Attività neuro-ormonale (RAS/Simpatico)
4. Chetogenesi
5. Ossigenazione renale

L Sloan et al Post Grad Med 2024

SGLT2-I modula 5 meccanismi-chiave della DKD

1. Riassorbimento di **glucosio** nel TCP
2. Riassorbimento di **sodio** nel TCP
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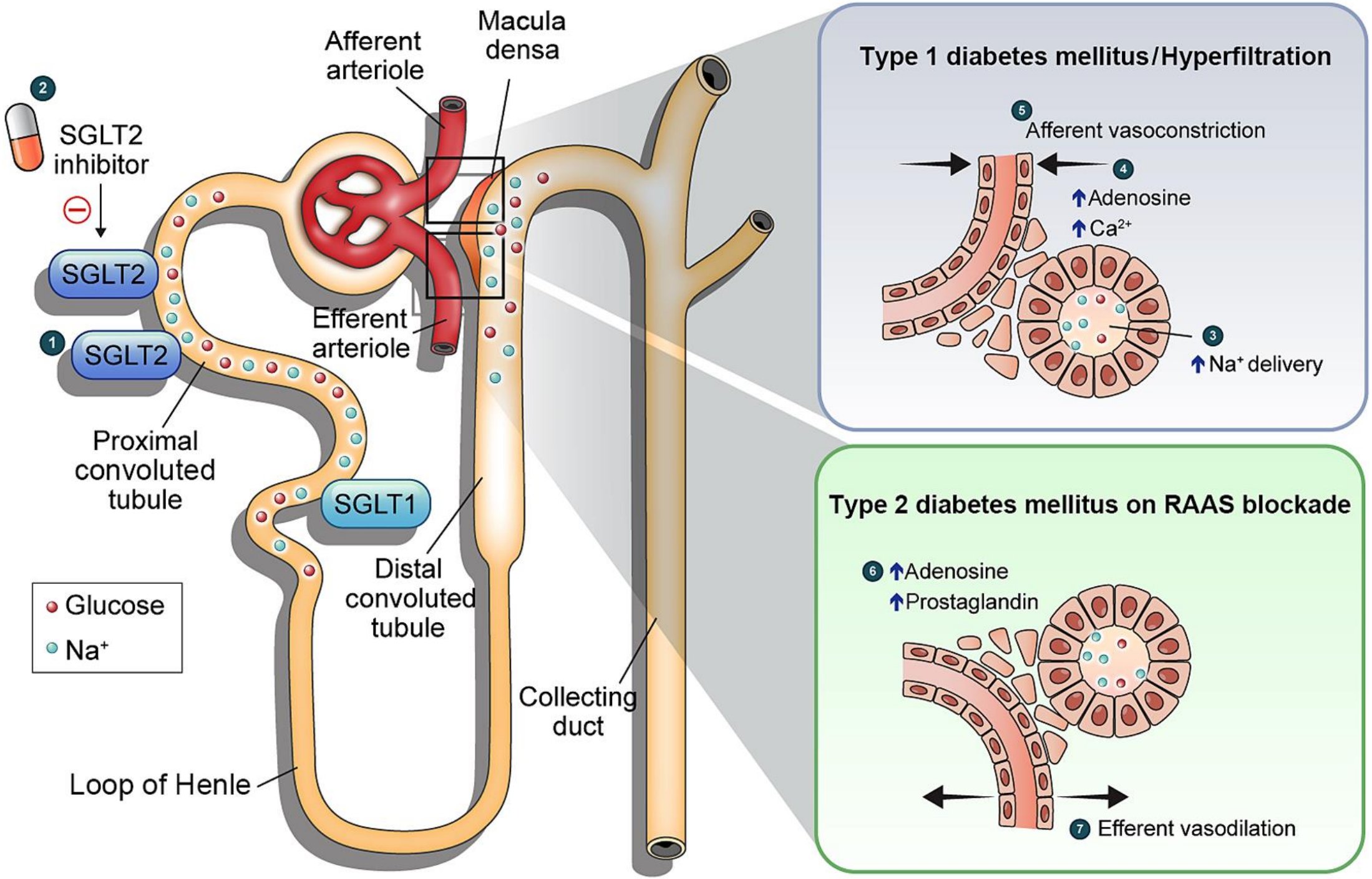
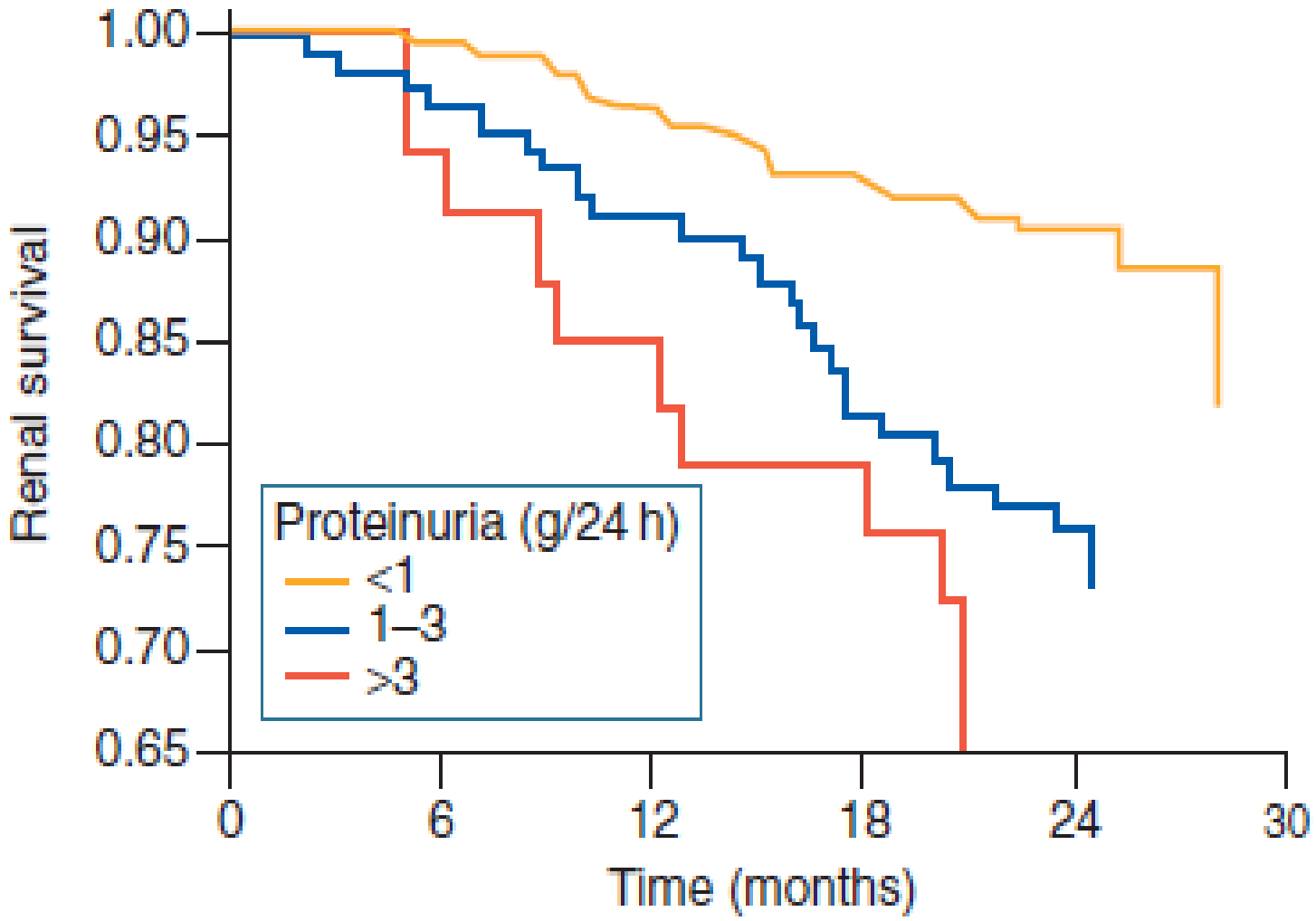
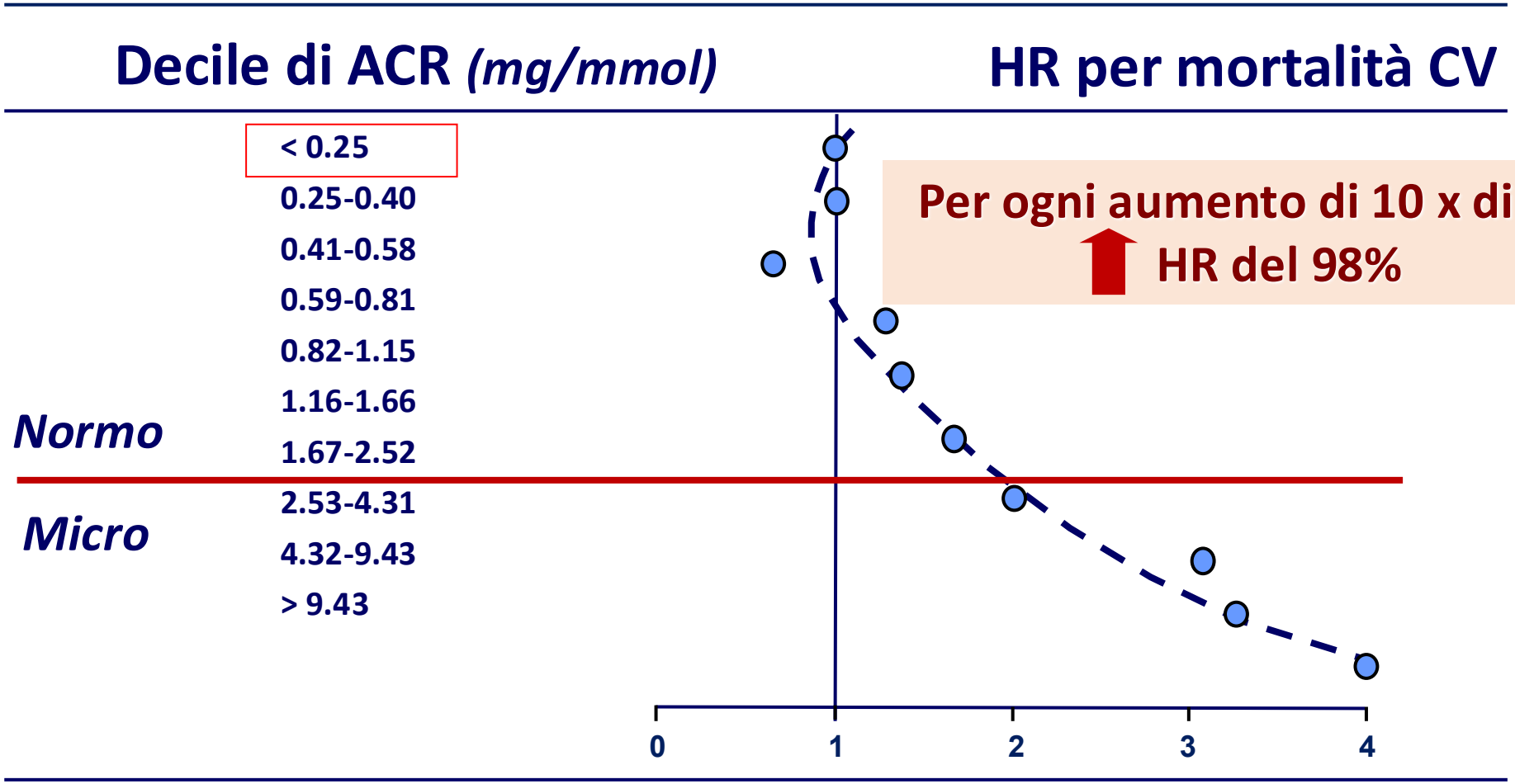

Afferent arteriole
Macula densa
2
SGLT2 inhibitor
SGLT2
1
SGLT2
Efferent arteriole
Proximal convoluted tubule
SGLT1
Distal convoluted tubule
Glucose
Na+
Collecting duct
Loop of Henle
Type 1 diabetes mellitus/Hyperfiltration
5
Afferent vasoconstriction
4
Adenosine
Ca2+
3
Na+ delivery
Type 2 diabetes mellitus on RAAS blockade
6
Adenosine
Prostaglandin
7
Efferent vasodilation

Sopravvivenza renale e proteinuria



La mortalità CV aumenta all'aumentare dell'albuminuria, già nel range della normoalbuminuria



Per ogni aumento di 10 x di ACR, ↑ HR del 98%

Wachtell K et al., Ann Intern Med, 2003

SGLT2-I modula 5 meccanismi-chiave della DKD

1. Riassorbimento di glucosio nel TCP (diabete)
2. Riassorbimento di sodio nel TCP
3. **Attività neuro-ormonale (RAS/Simpatico)**
4. Chetogenesi
5. Ossigenazione renale

L Sloan et al Post Grad Med 2024

Cross-talk tra SGLT2 e sistema simpatico

B Palmer et al cJASN 2023

Cross-talk tra SGLT2 e sistema simpatico

B Palmer et al cJASN 2023

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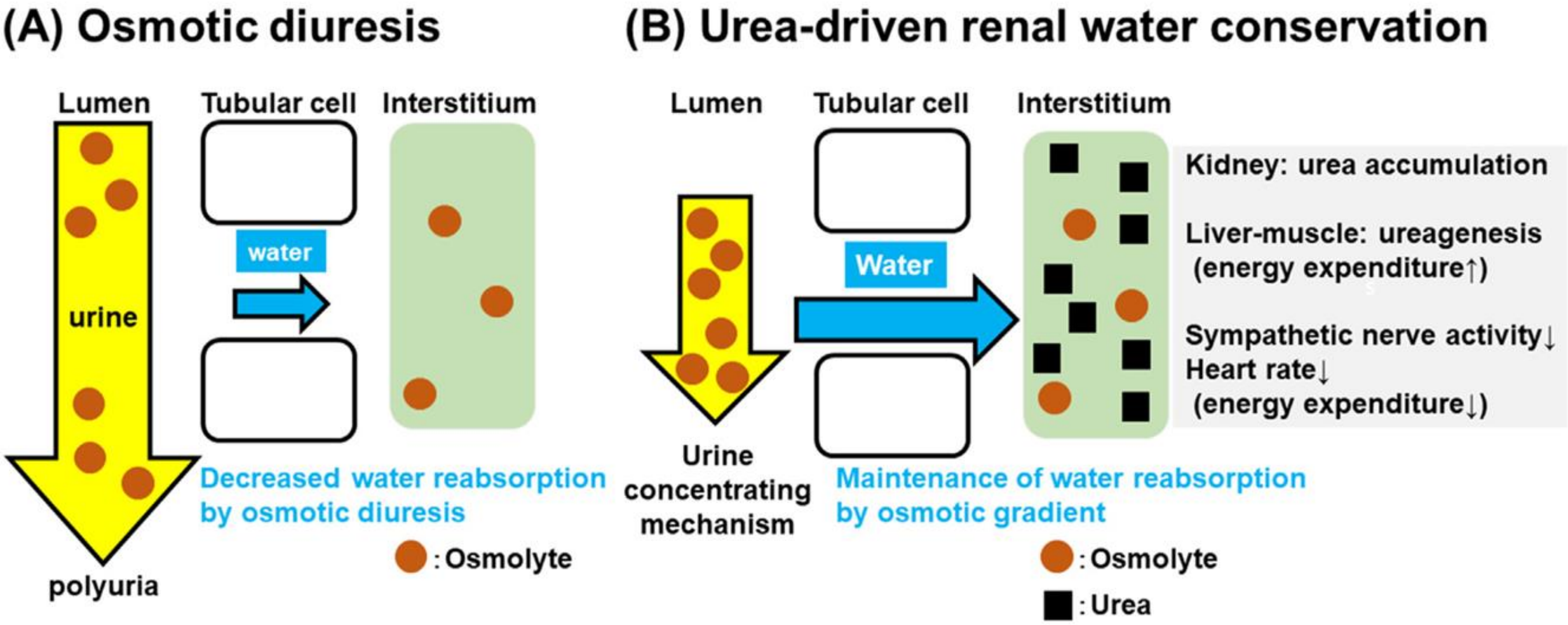
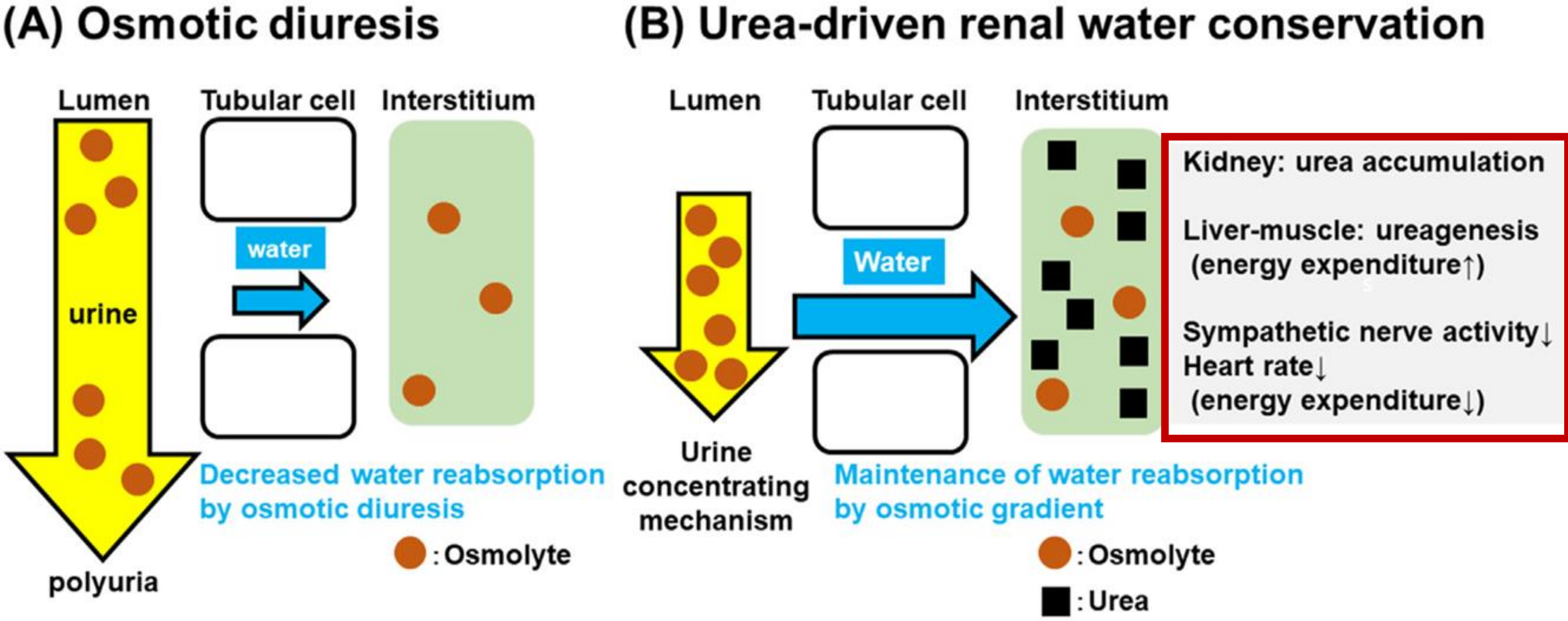


K Kitada et al J Pharmacol Sci 2021

Cross-talk tra SGLT2 e sistema simpatico



K Kitada et al J Pharmacol Sci 2021

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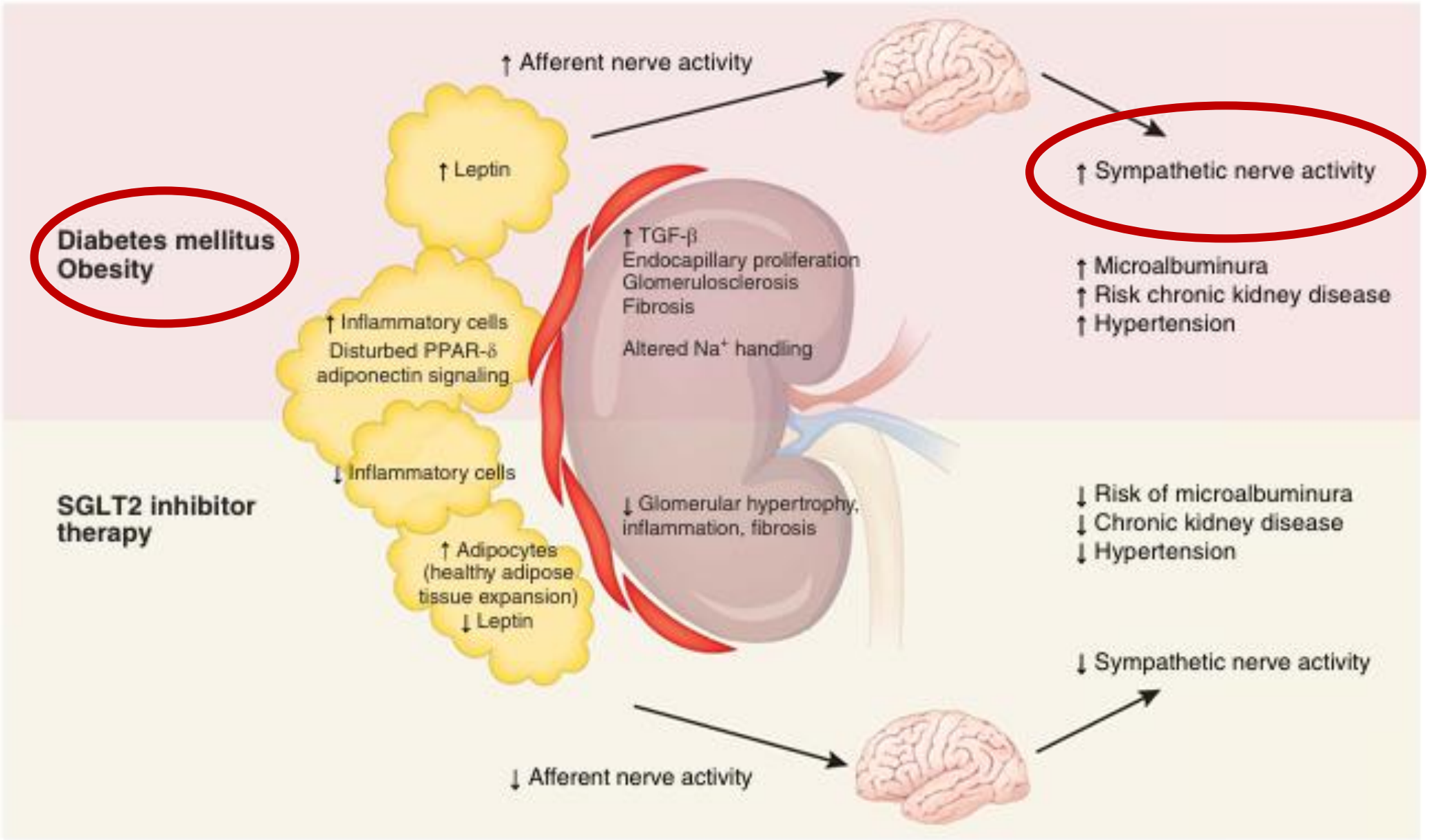

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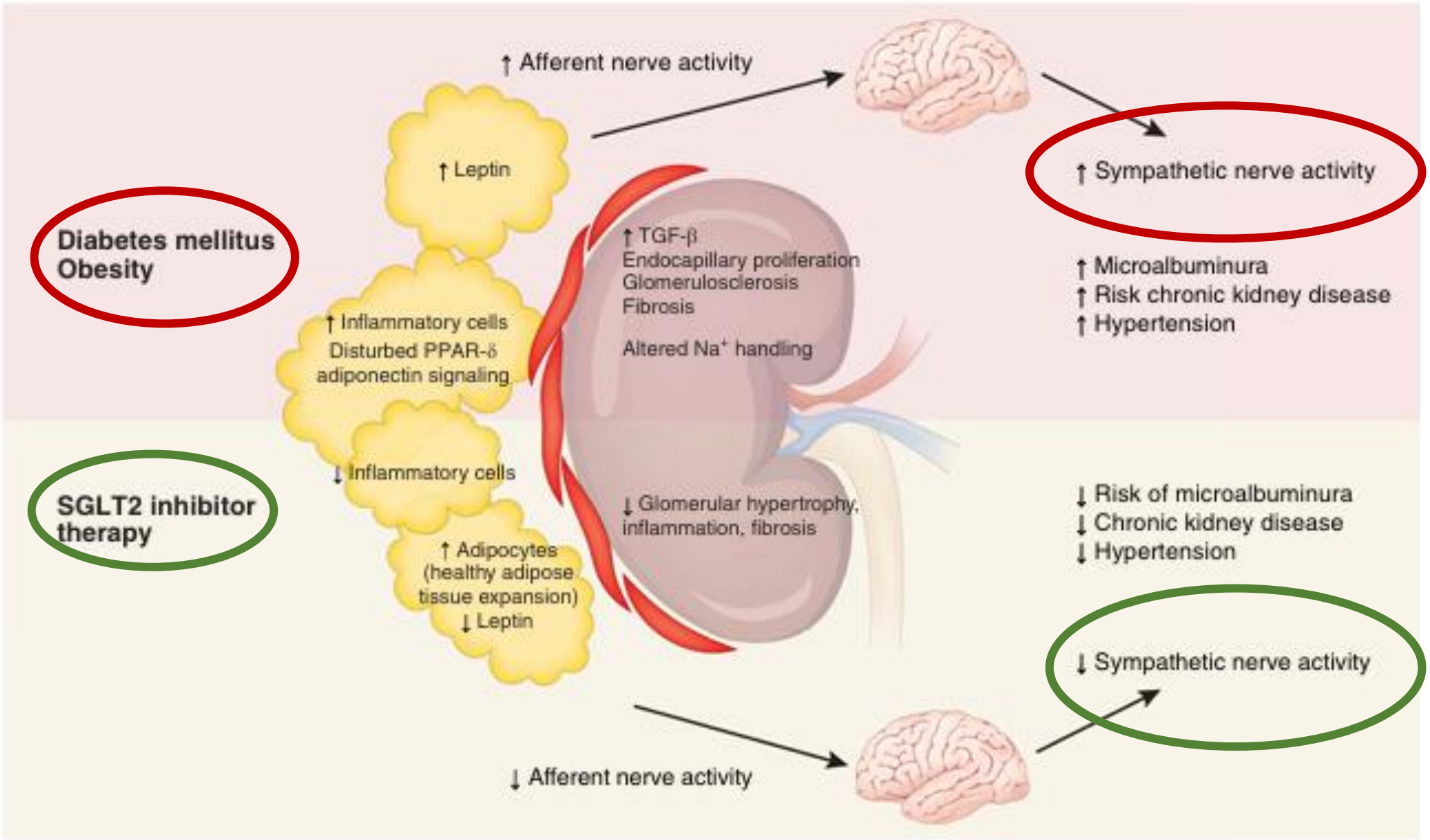

SGLT2-I modula 5 meccanismi-chiave della DKD

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3. Attività neuro-ormonale (RAS/Simpatico)
4. **Chetogenesi**
5. Ossigenazione renale

L Sloan et al Post Grad Med 2024

1. SENESCENZA

β-OX AG

NRF 2 activation

SGLT2 inhibitor

Facilitates metabolic flexibility

↓ Insulin
↑ Glucagon

Energy shift from glucose to fat oxidation

↑ Ketone bodies

↑ Energy expenditure
Nonshivering thermogenesis

↓ Delivery of NADH, FADH

↑ ADP availability

↑ AMP / ATP

↑ NAD+ / NADH

↑ AMPK

↑ SIRT1

↓ mTORC1

↑ Autophagy, mitophagy

Mitochondrial biogenesis

Cellular breakdown(catabolic metabolism) coupled to cellular biogenesis (anabolic metabolism)

Disease resistance

Autophagosome

Lysosome

Amino acids
Fatty acids
Sterols
Sugars

H+ Intermembrane space H+ H+ H+

Complex I 2 e−

CoQ 2 e−

Complex II

Complex III 2 e−

Complex IV 2 e−

ATP synthase

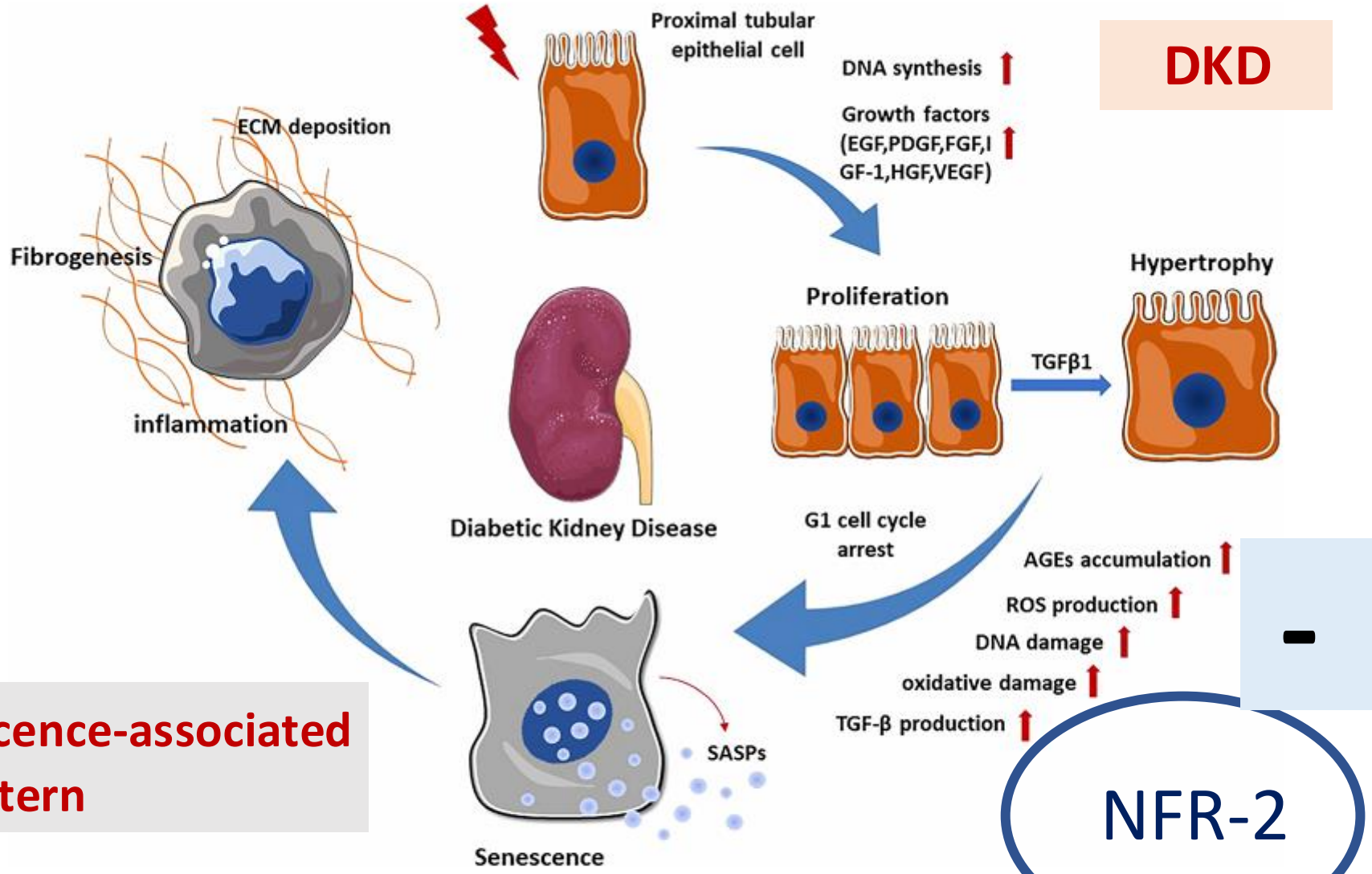
ADP ATP

Electron transport chain

↓ Mitochondrial membrane potential

↓ Mitochondrial accumulation of H_2O_2 and reactive oxygen species

B Palmer et al cJASN 2023



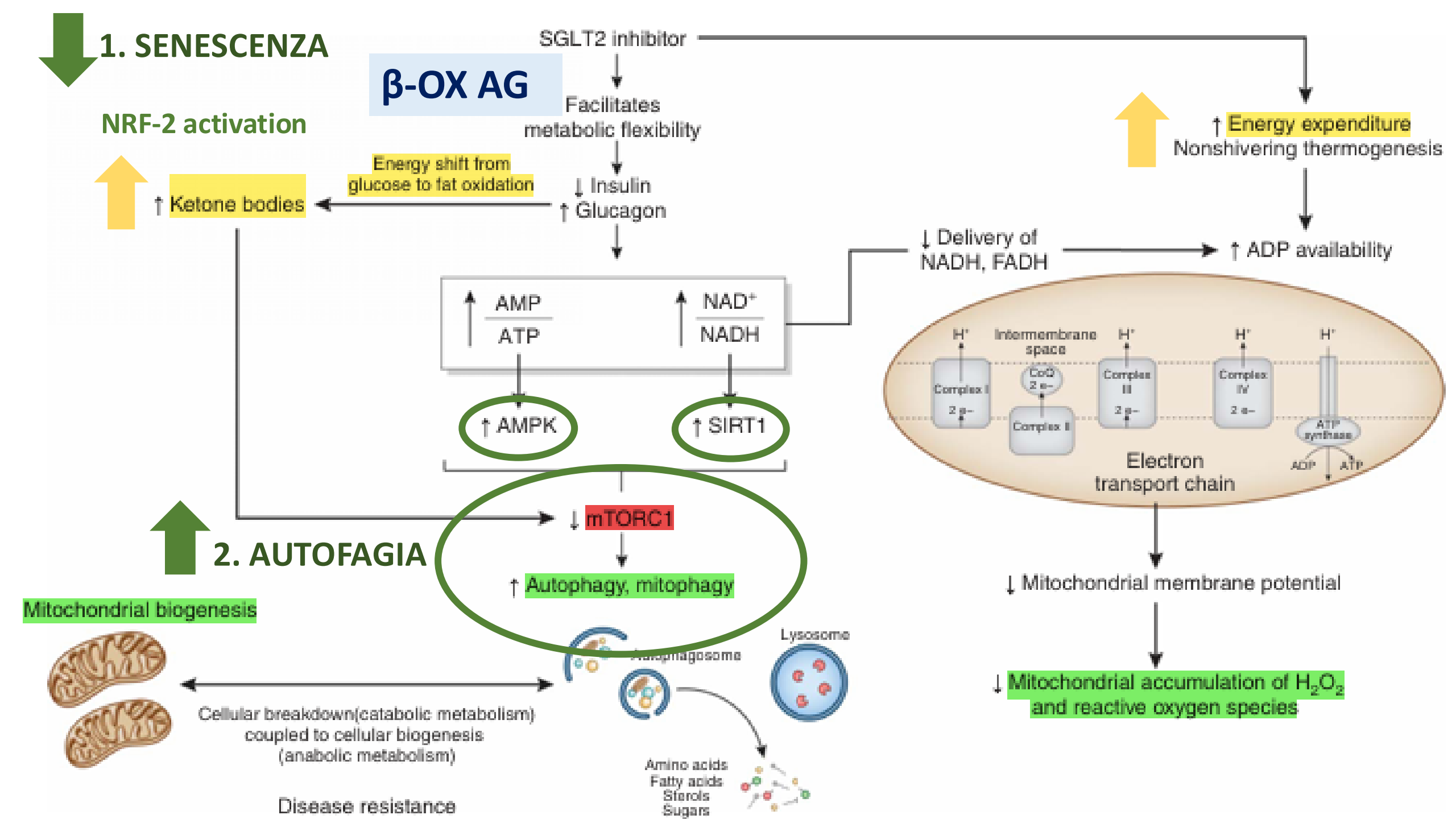
DKD

-

NFR-2

SASP: senescence-associated secretory pattern

FIGURE 1
Renal tubular epithelial cell changes in DKD. When exposed to various stimuli, PTECs express and secrete multiple growth factors which promote the proliferation of PTECs. Subsequently, TGF-β1 stimulates the transformation of PTECs from proliferation to hypertrophy through ERK and P38 pathway. In order to prevent excessive proliferation, PTECs undergo G1 cell cycle arrest and transition to senescence. Senescent PTECs can secrete SASPs, promoting renal inflammation and fibrosis.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Mitochondrial biogenesis
Cellular breakdown(catabolic metabolism) coupled to cellular biogenesis (anabolic metabolism)
Disease resistance
Lysosome
Amino acids
Fatty acids
Sterols
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H+
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Complex I
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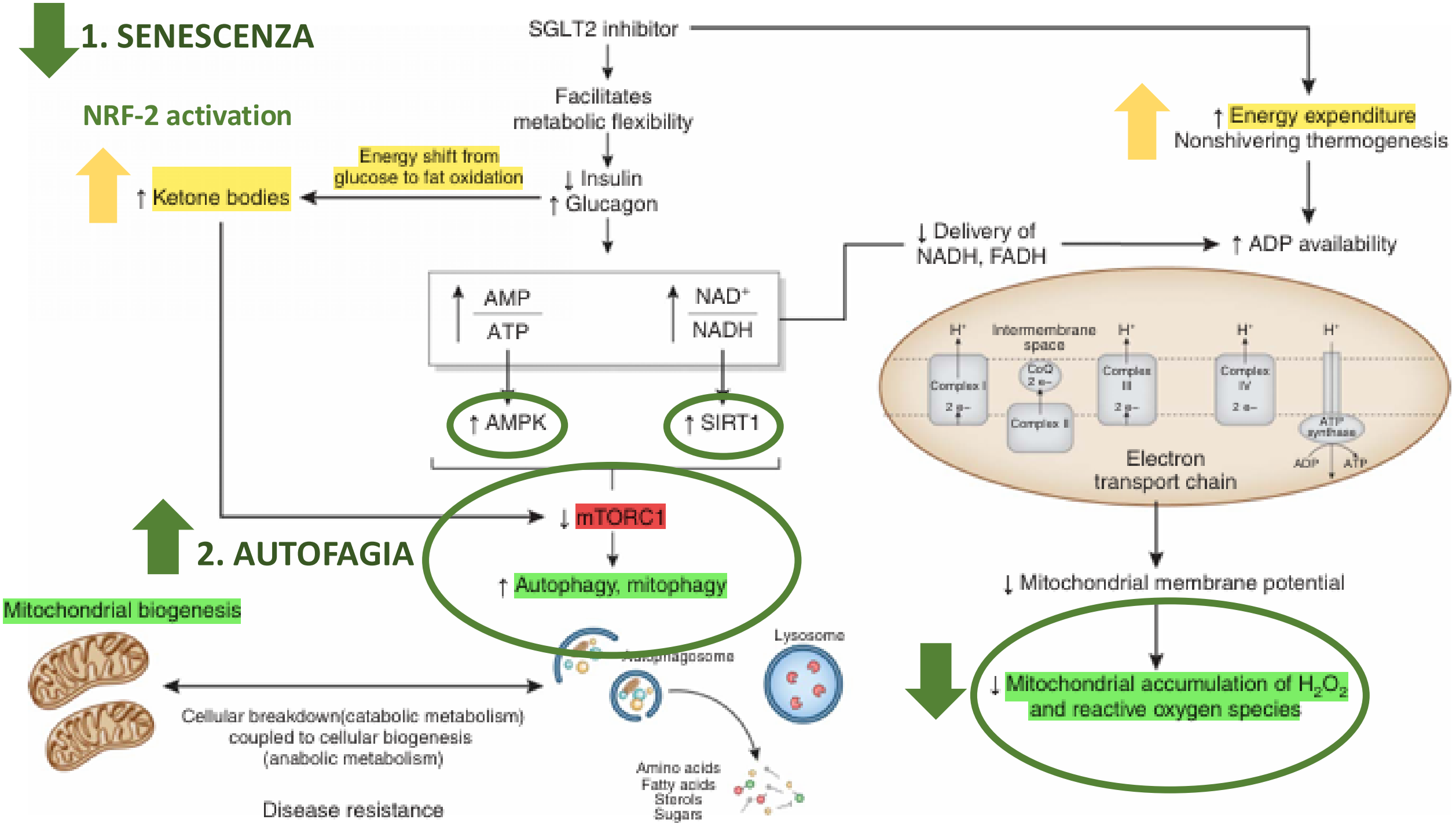
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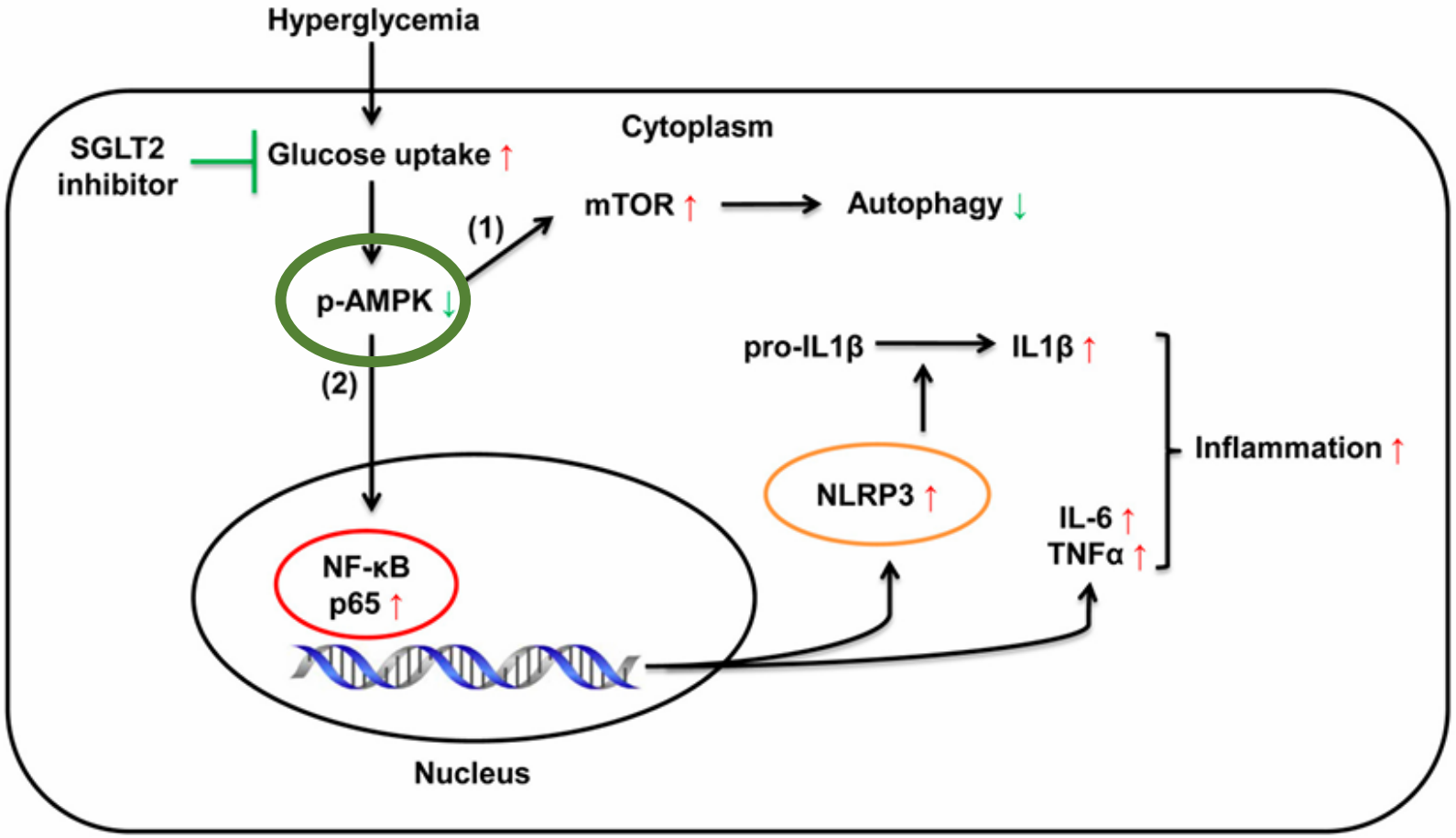
cells

MDPI

Article

Dapagliflozin Restores Impaired Autophagy and Suppresses Inflammation in High Glucose-Treated HK-2 Cells



Human kidney proximal tubular cell

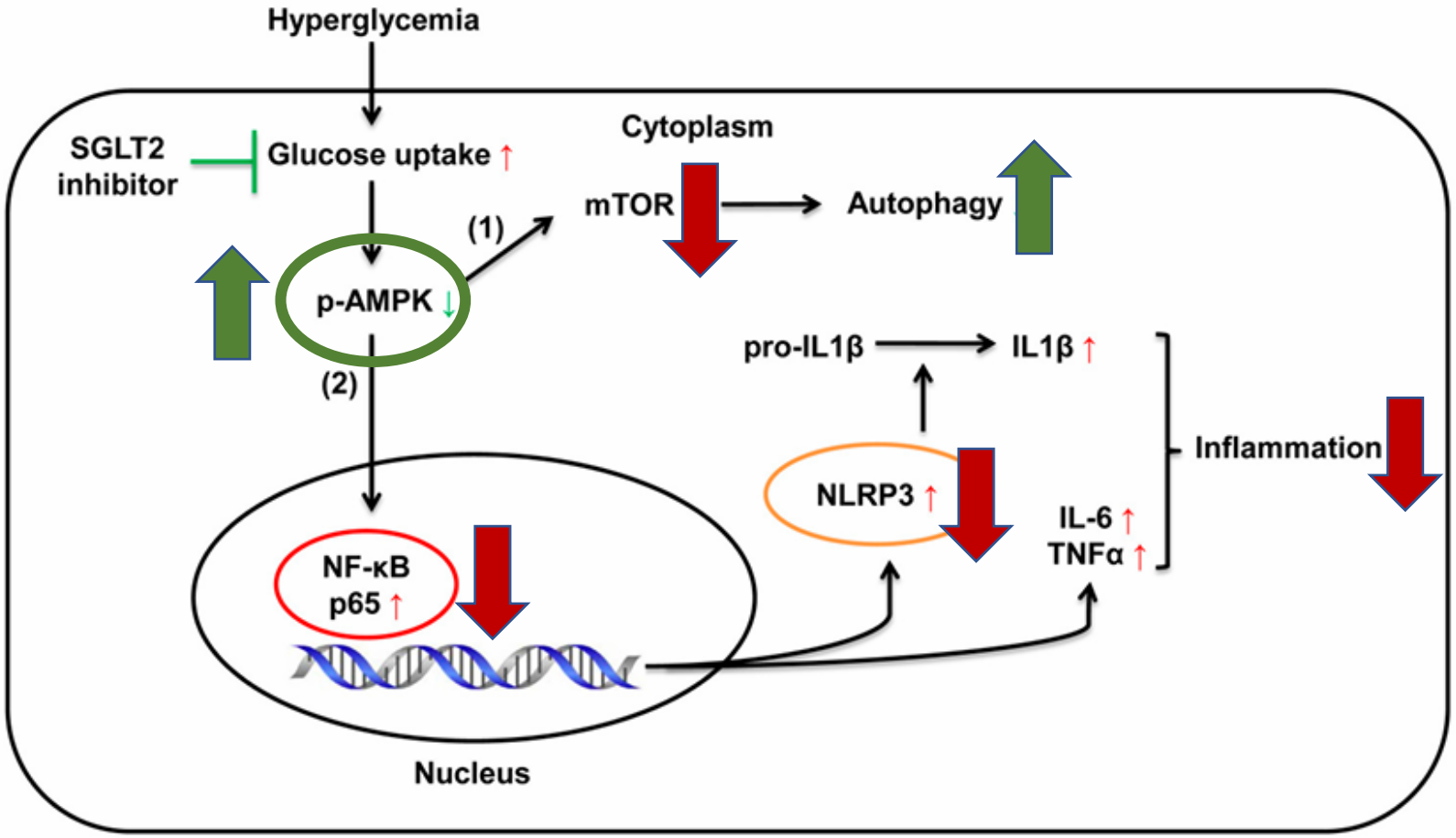
J Xu et al Cells 2021

cells

MDPI

Article

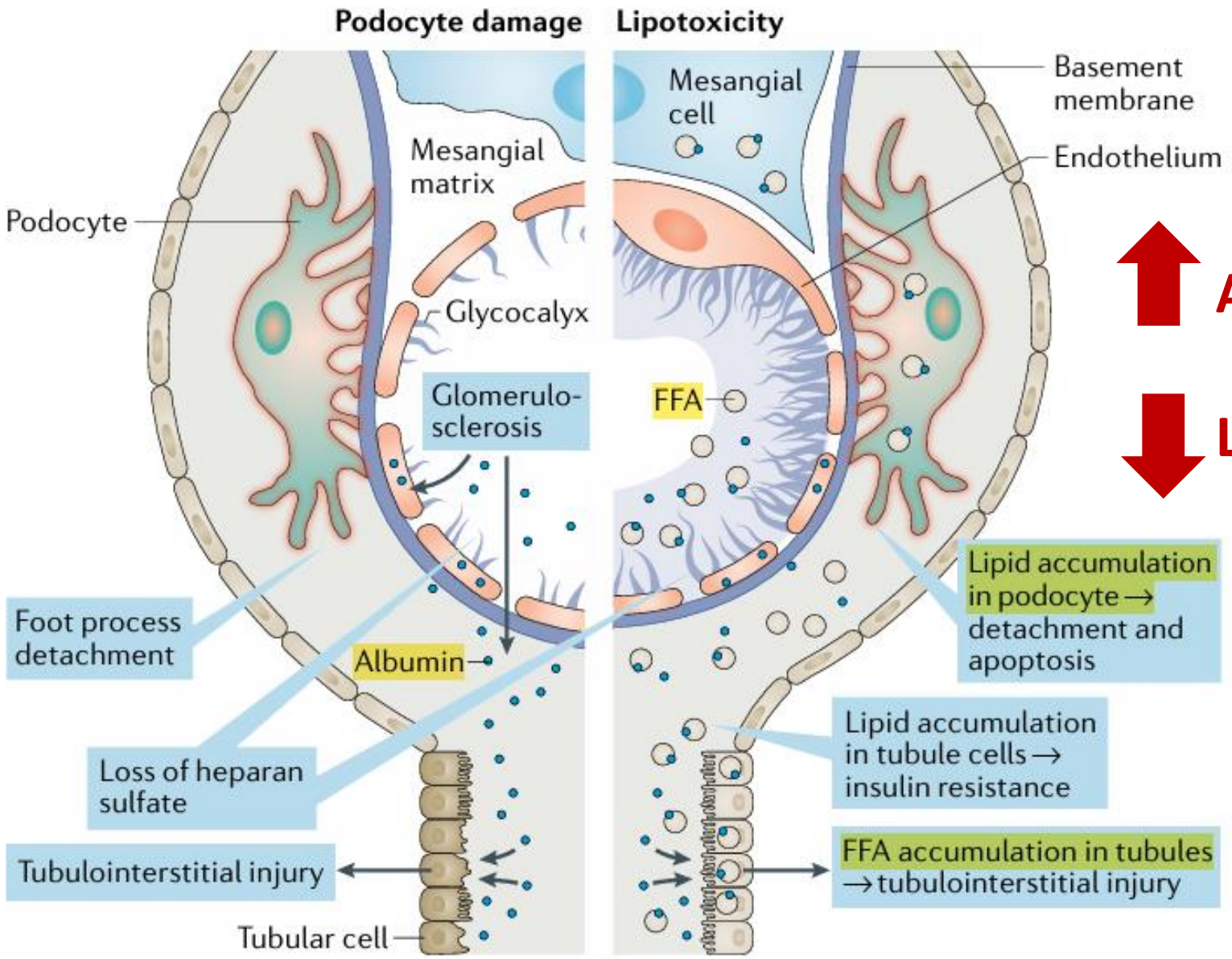
Dapagliflozin Restores Impaired Autophagy and Suppresses Inflammation in High Glucose-Treated HK-2 Cells



Human kidney proximal tubular cell

J Xu et al Cells 2021

Podocita



SGLT2i

↑ **AUTOFAGIA**

↓ **LIPOTOSSICITA'**

SGLT2-I modula 5 meccanismi-chiave della DKD

1. Riassorbimento di glucosio nel TCP (diabete)
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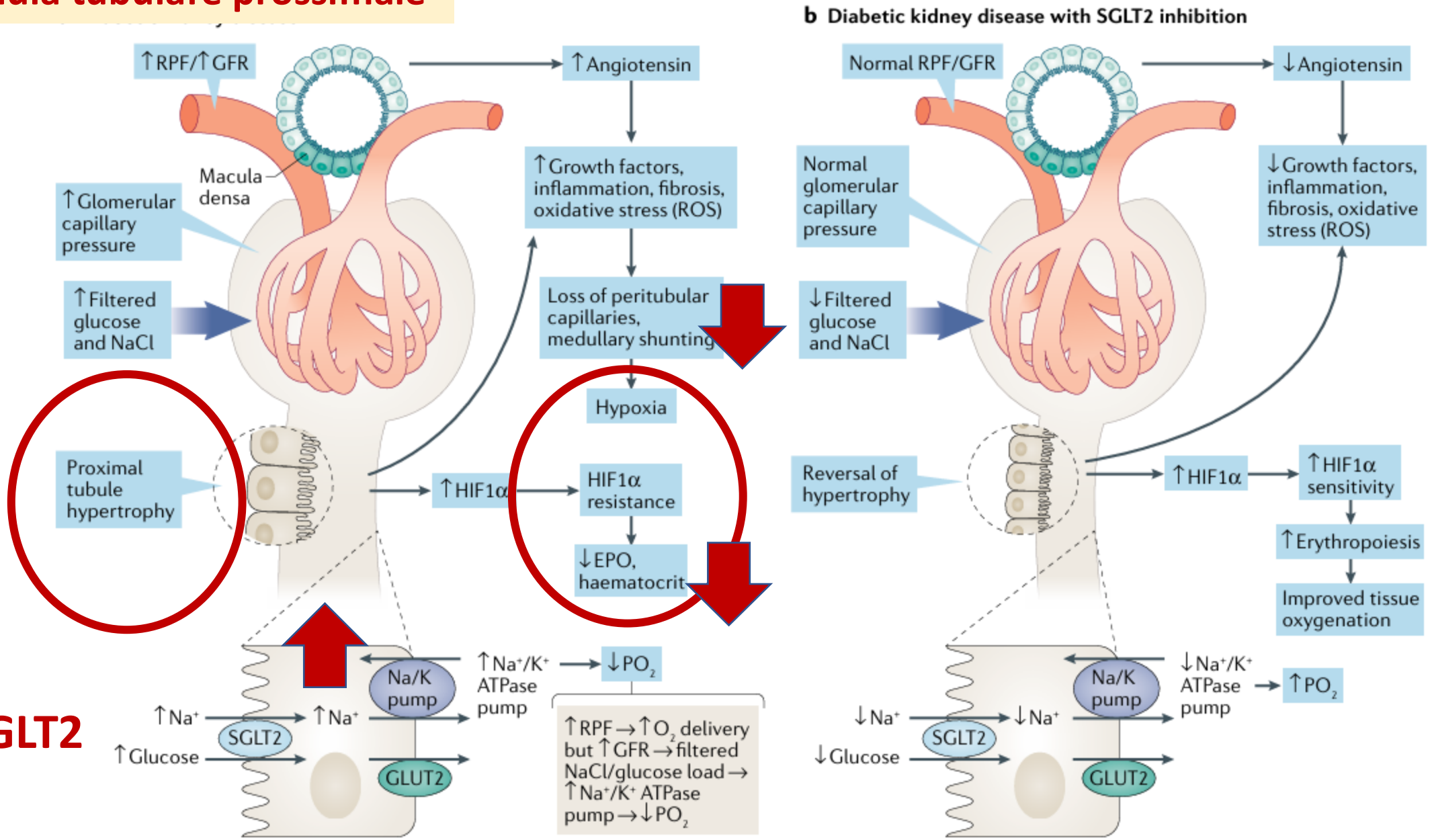
5. **Ossigenazione renale**

L Sloan et al Post Grad Med 2024

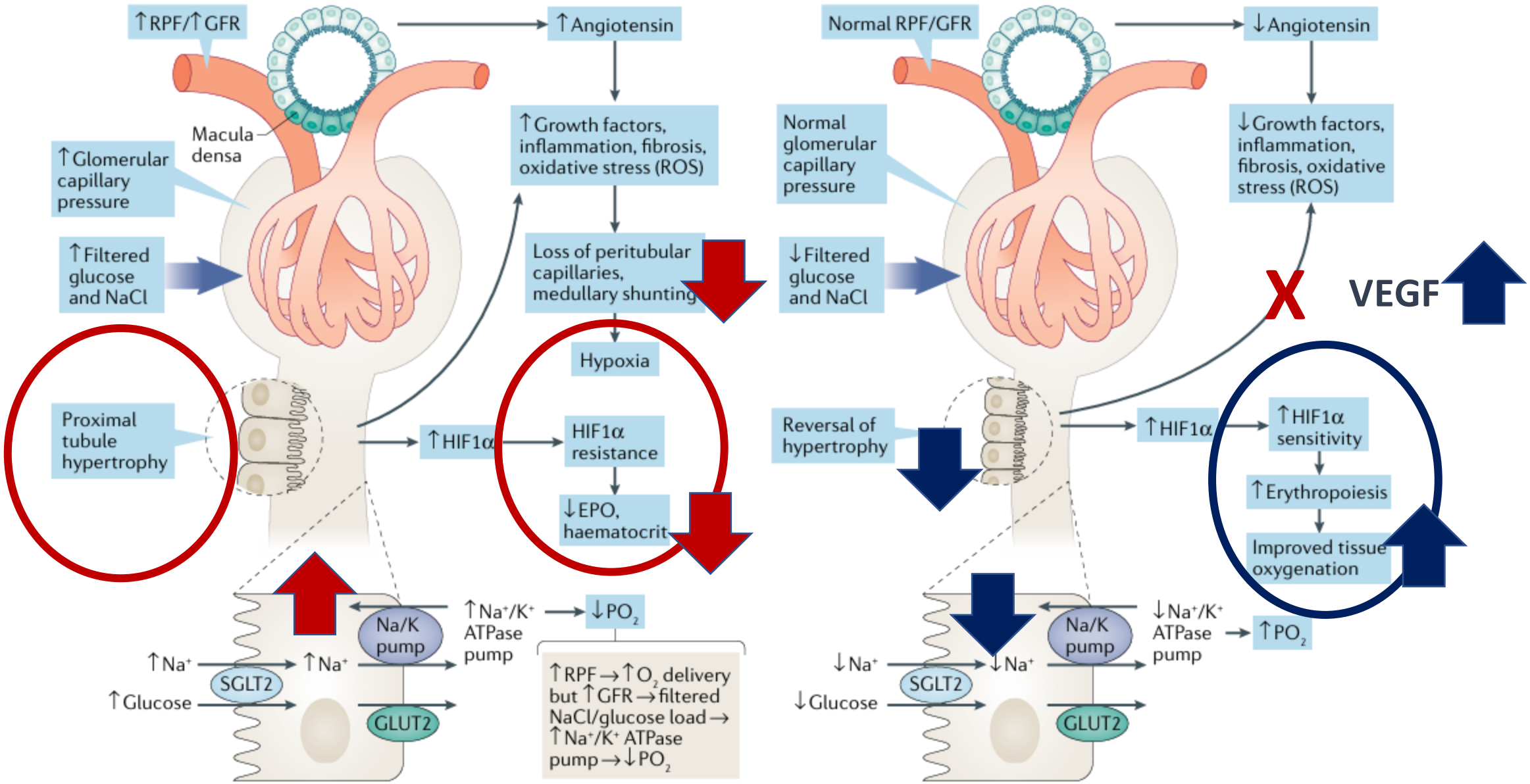
Cellula tubulare prossimale



SGLT2

Cellula tubulare prossimale

SGLT2-i

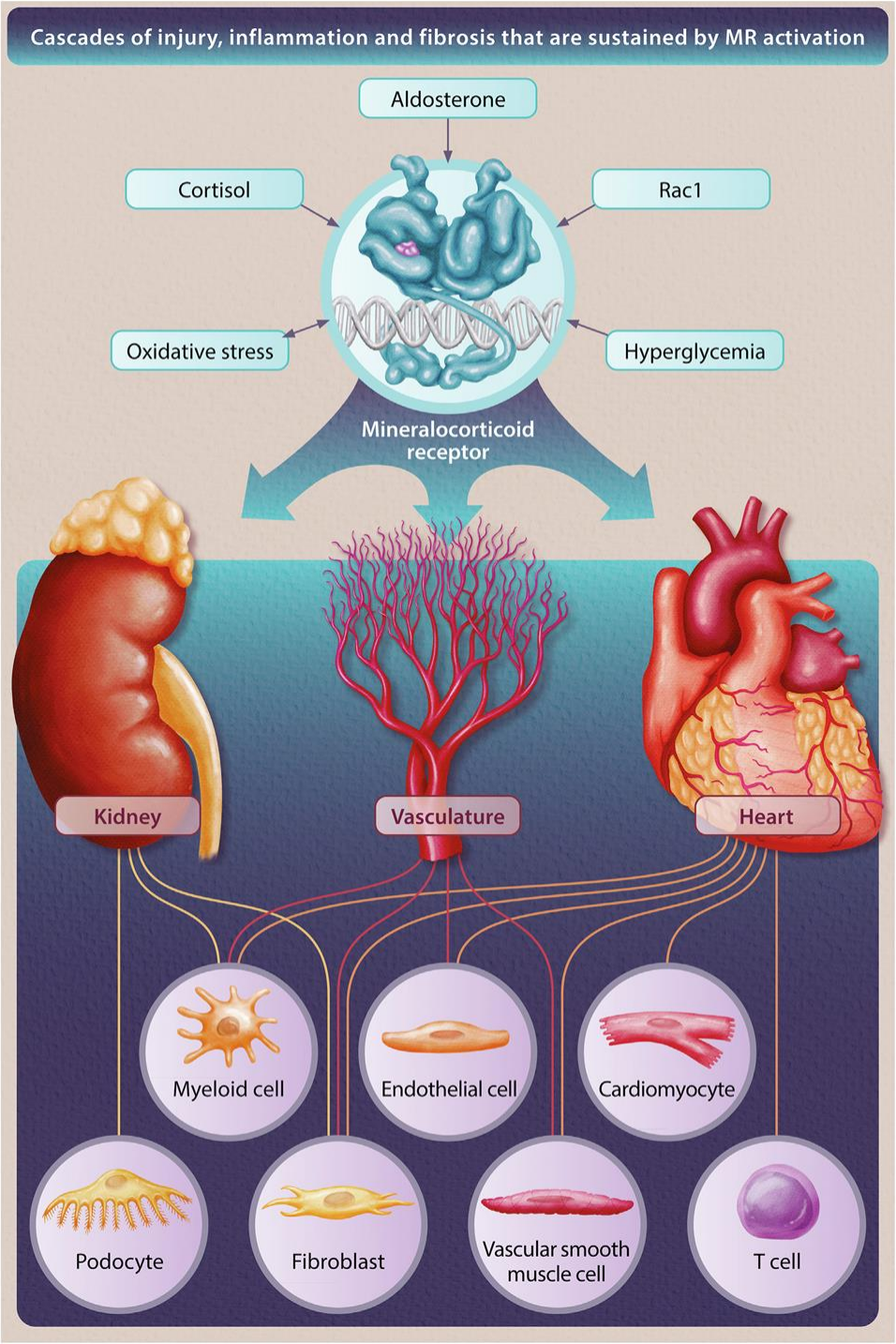


TERAPIA DELLA DKD

- SGLT2-I
- **MRA**
- GLP1 RA

MR hyperactivity

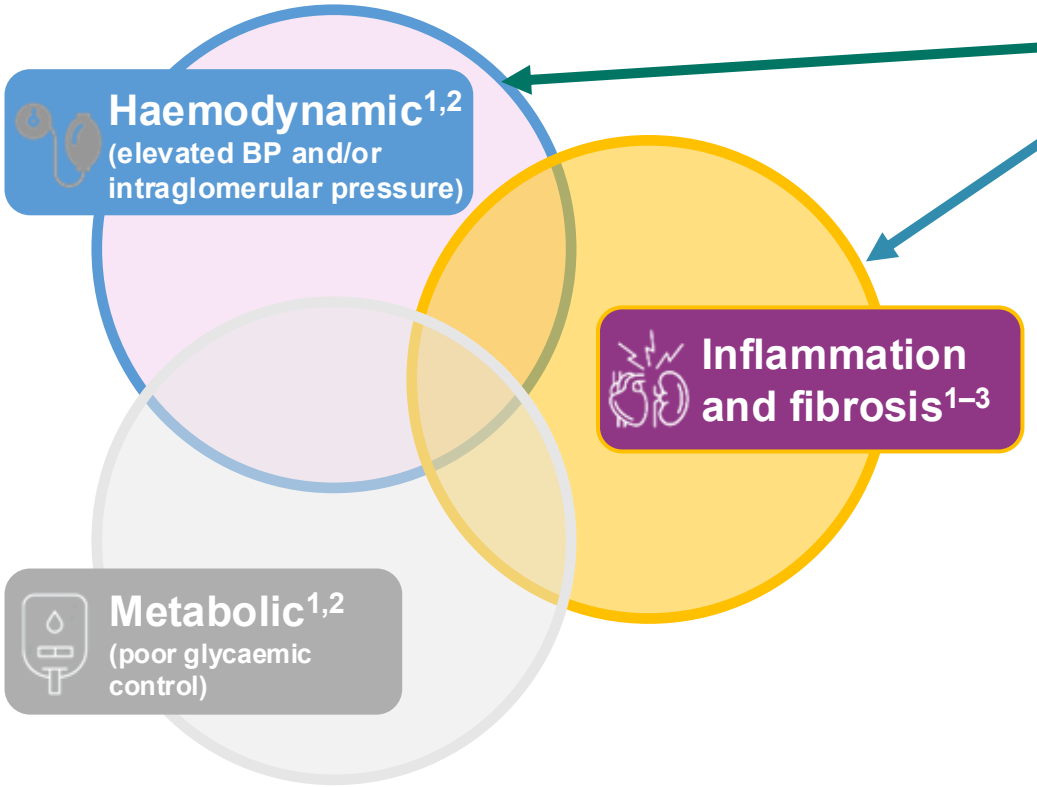
Inflammation and fibrosis



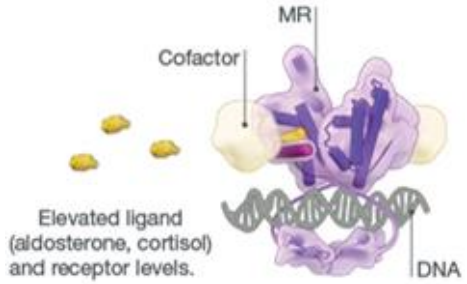
M Epstein et al. AJKD 2022

Finerenone blocca iperattività del MR in CKD e diabete

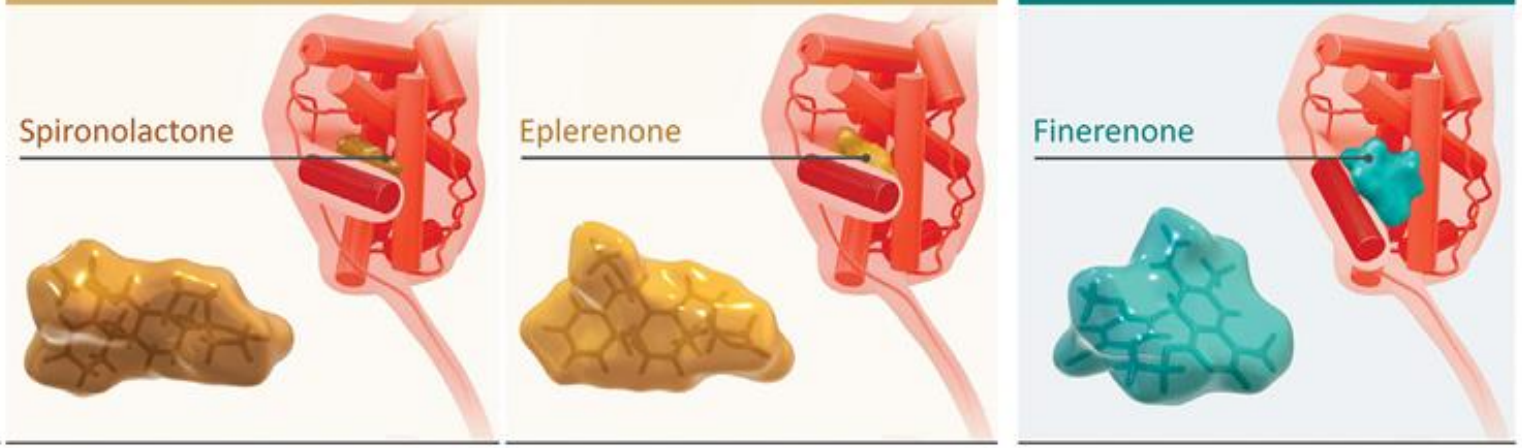
Drivers of CKD in T2D progression[1–3]



MR overactivation

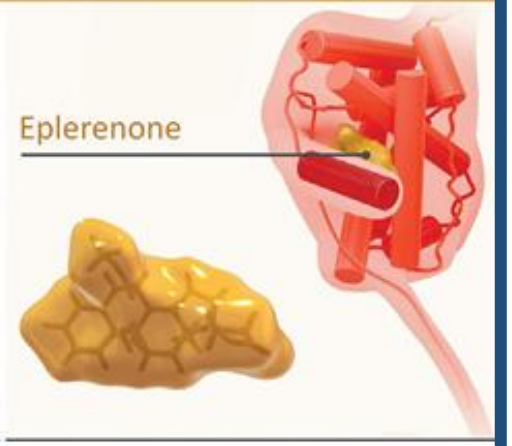
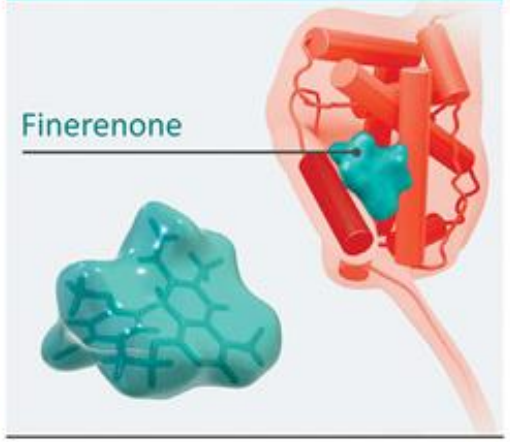


In T2D, MR overactivation may contribute to CKD progression[11,12]



	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	+++	++	+

M Epstein et al. AJKD 2022

	Steroidal MRAs		Finerenone
			
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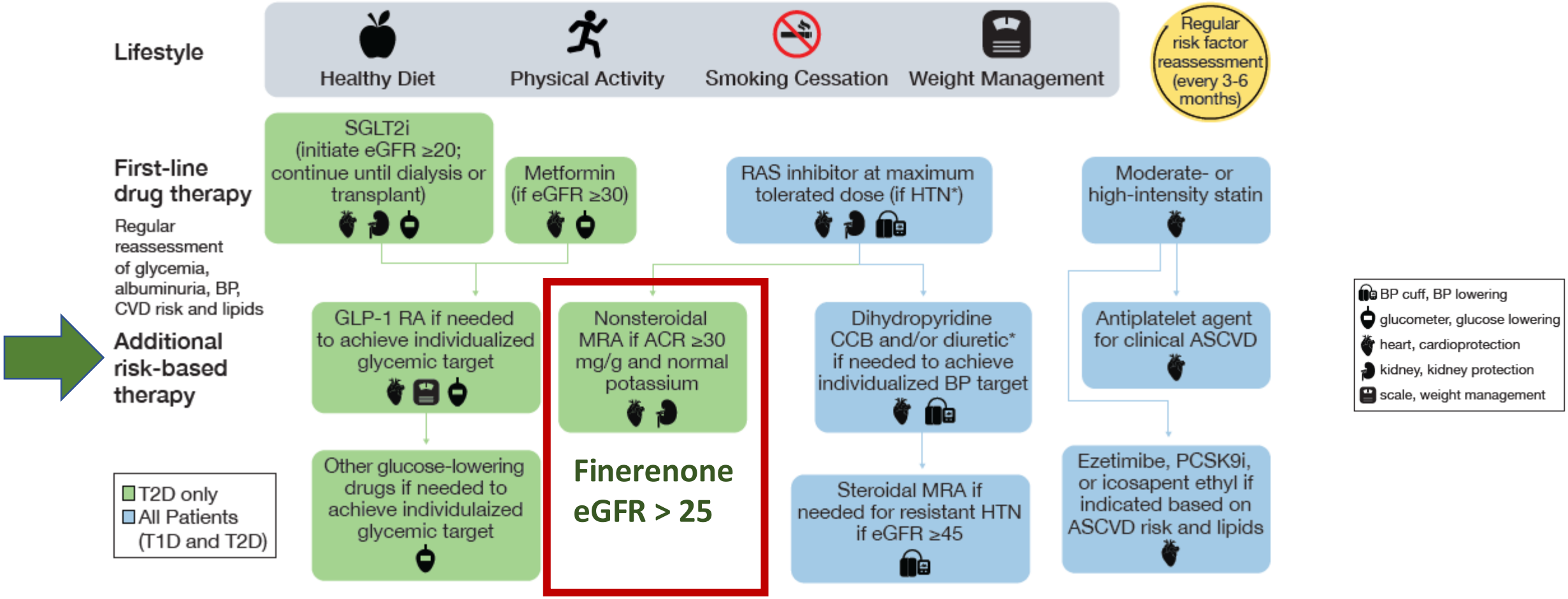
M Epstein et al. AJKD 2022

2022 KDIGO Approach for People With Diabetes and CKD



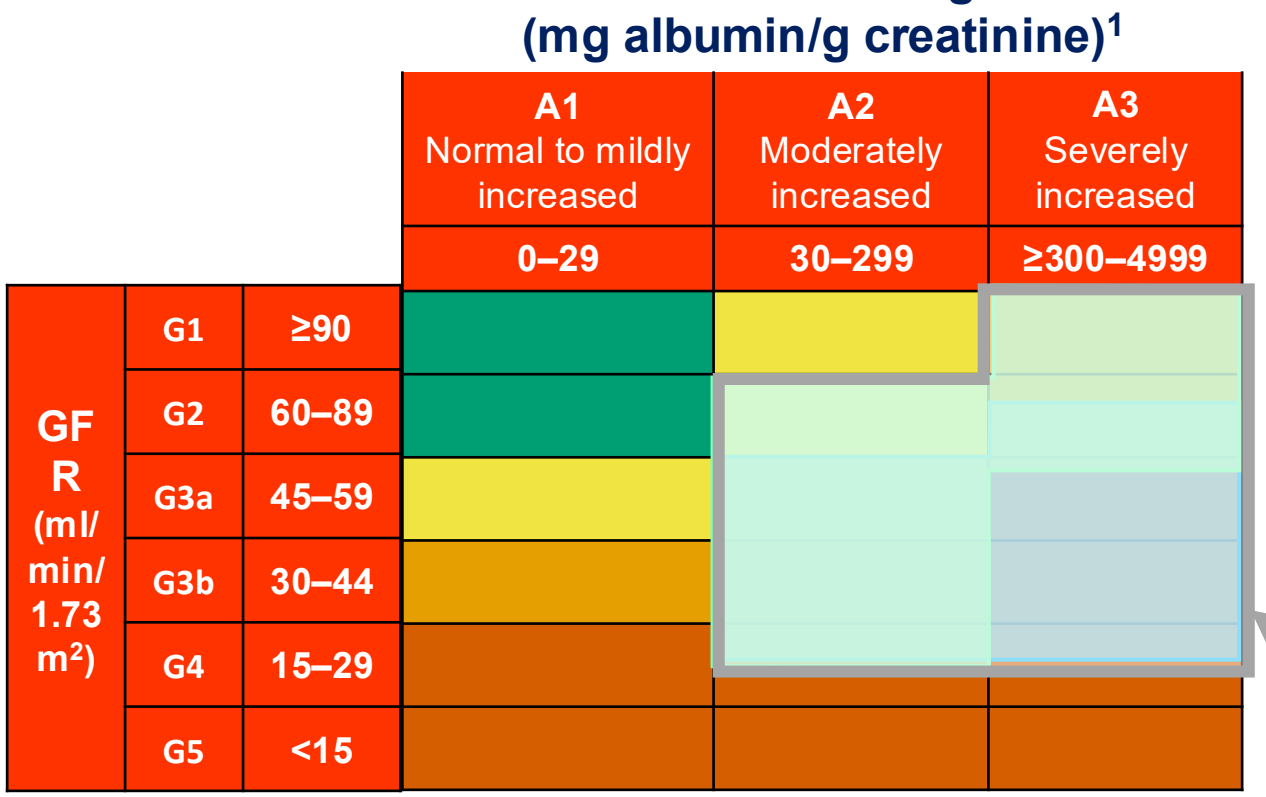
Note: eGFR is presented in units of mL/min/1.73 m^2.

*Maximum tolerated ACEi or ARB should be first-line therapy for HTN when albuminuria is present. Otherwise, dihydropyridine CCB or diuretic can also be considered; all three classes are often needed to attain BP targets.

ACEi = angiotensin-converting enzyme inhibitor; ACR = albumin-creatinine ratio; ARB = angiotensin II receptor blocker; ADA = American Diabetes Association: ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HTN = hypertension; KDIGO = Kidney Disease: Improving Global Outcomes; MRA = mineralocorticoid-receptor antagonist; PCSK9i= proprotein convertase subtilisin/kexin type 9 inhibitor; RAS = renin-angiotensin system; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T1D = type 1 diabetes; T2D = type 2 diabetes.

Rossing P et al. *Kidney Int.* 2022;102(5):990-999.

FIDELITY ha incluso patienti con un ampio spettro di severità della CKD



UACR 30-5000 mg/g

GFR 25-90 ml/min

FIDELIO-DKD (N=5734)[3]

CKD eligibility criteria

- UACR 30–<300 mg/g and eGFR ≥25–<60 ml/min/1.73 m2 and a history of diabetic retinopathy
- Or UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m2

FIGARO-DKD (N=7437)[2]

CKD eligibility criteria

- UACR 30–<300 mg/g and eGFR 25–≤90 ml/min/1.73 m2
- Or UACR ≥300–≤5000 mg/g and eGFR ≥60 ml/min/1.73 m2

FIDELITY (N=13,171)[4]

Prespecified pooled analysis

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; UACR, urine albumin-to-creatinine ratio

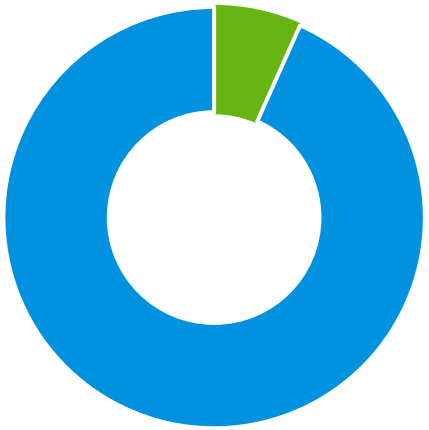
1. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2020;98:S1–S115; 2. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356; 3. Bakris GL, *et* Agarwal G, et al. *Eur Heart J* 2022;43:474–484

Agarwal G et al. Eur Heart J 2022

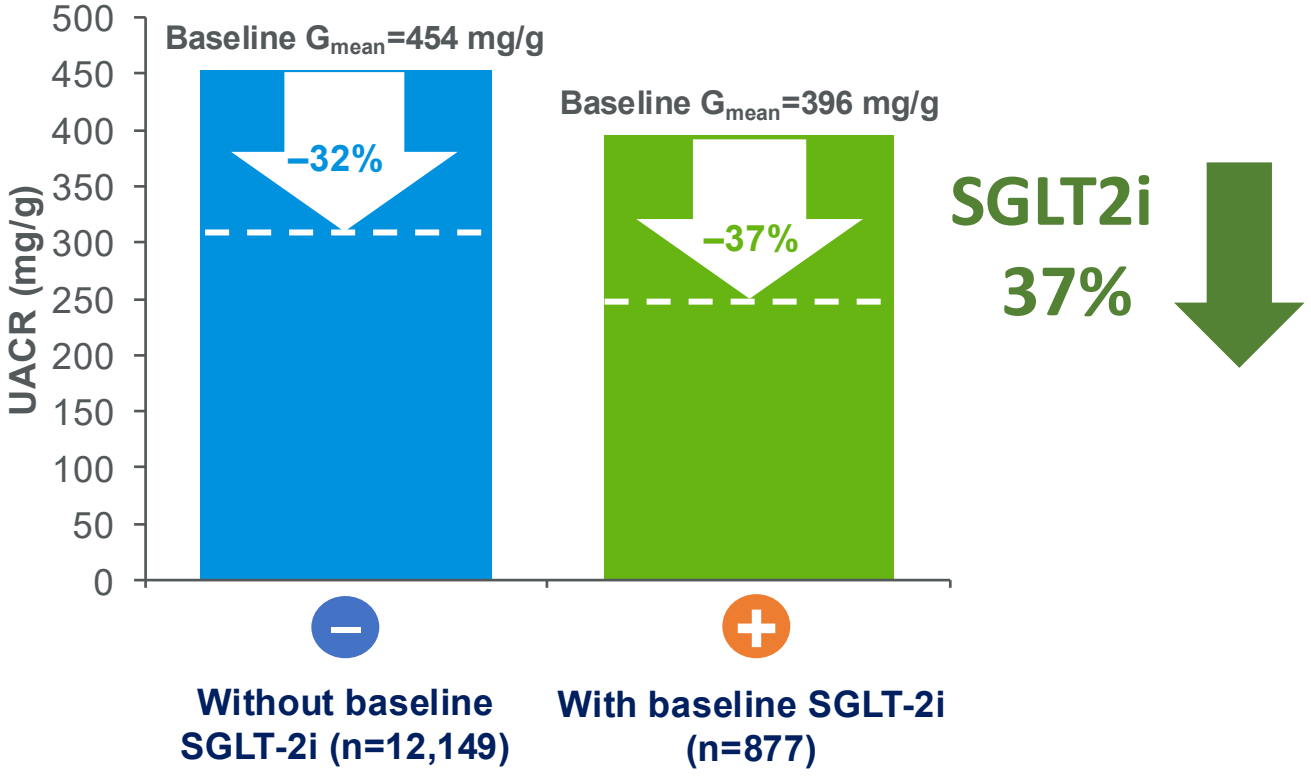
Finerenone treatment alone reduced UACR > 30% and those already treated with an SGLT-2i experienced an even greater reduction

SGLT-2i use at baseline

877 (6.7%) patients on an SGLT-2i



Reduction in UACR (%) with finerenone vs placebo



Full analysis set. Mixed model with factors for treatment group, region, eGFR category at screening, type of albuminuria at screening, CV disease history; time, treatment*time, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value*time as covariates

G_{mean}, geometric mean

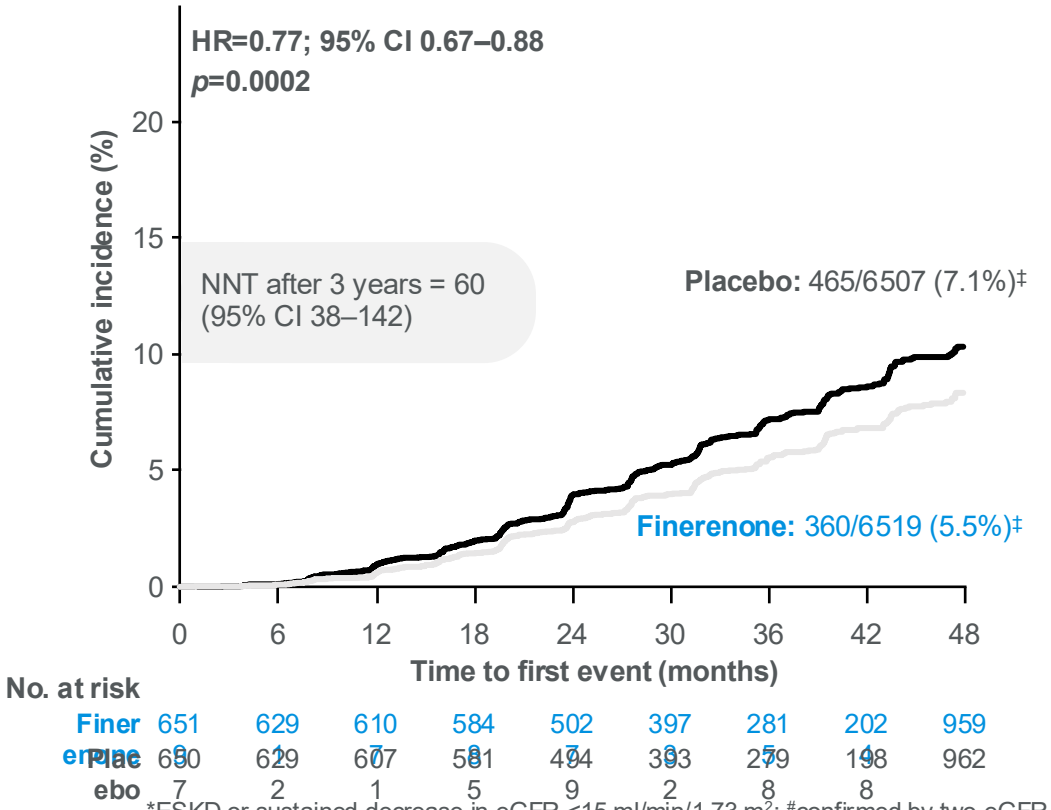
Agarwal R, et al. Eur Heart J 2021; doi:10.1093/eurheartj/ehab777

FIDELITY

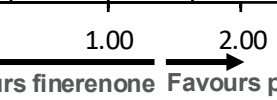
MA-M_FIN-IT-0087-1

Finerenone significantly reduced the risk of the eGFR kidney composite outcome by 23%

Time to kidney failure, sustained ≥57% decrease in eGFR or renal death



Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	p-value
≥57% eGFR kidney composite outcome	**360 (5.5)**	**465 (7.1)**	**0.77 (0.67–0.88)**	**0.0002**
Kidney failure*	254 (3.9)	297 (4.6)	0.84 (0.71–0.99)	0.039
ESRD	151 (2.3)	188 (2.9)	0.80 (0.64–0.99)	0.040¶
Sustained# decrease in eGFR to <15 ml/min/1.73 m²	195 (3.0)	237 (3.6)	0.81 (0.67–0.98)	0.026¶
Sustained# ≥57% decrease in eGFR from baseline	257 (3.9)	361 (5.5)	0.70 (0.60–0.83)	<0.0001
Renal death‡	2 (<0.1)	4 (<0.1)	0.53 (0.10–2.91)	0.459



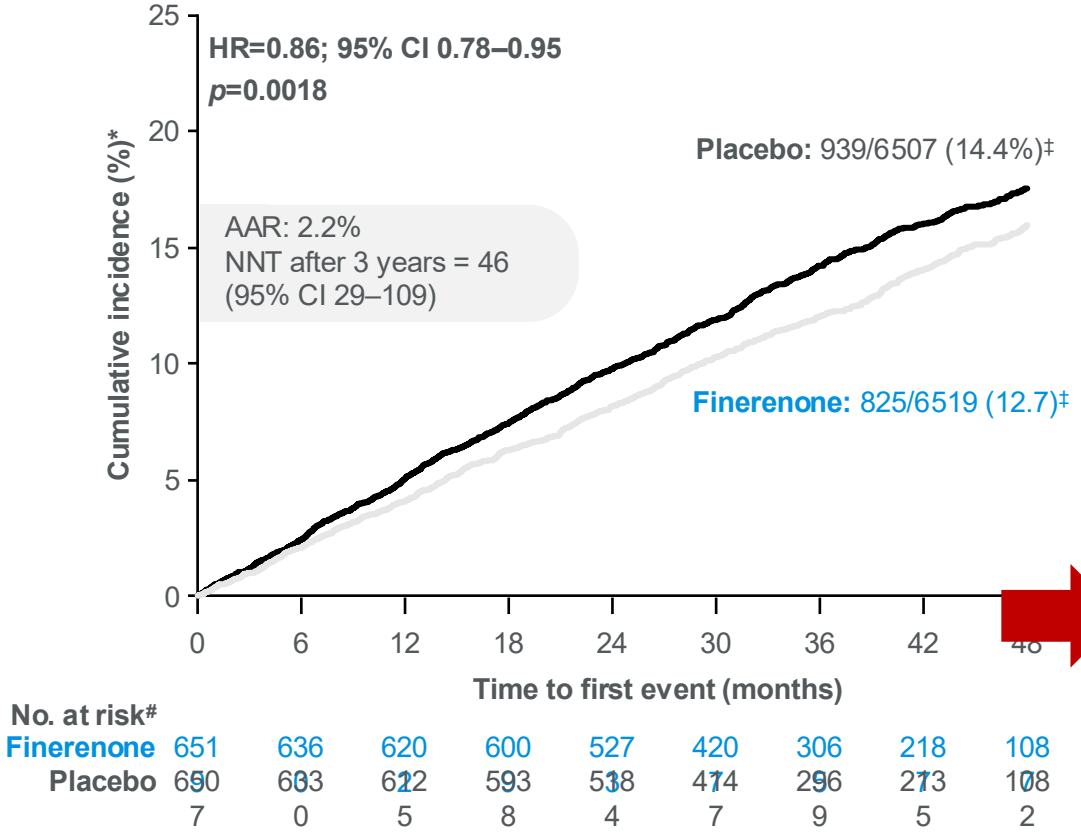
*ESKD or sustained decrease in eGFR <15 ml/min/1.73 m²; #confirmed by two eGFR measurements ≥4 weeks apart; ‡events were classified as renal death if: (1) the patient died; (2) KRT had not been initiated despite being clinically indicated; and (3) there was no other lkely cause of death; §number of patients with an event over a median of 3.0 years of follow-up; ¶analyses for *p*-values not prespecified

Agarwal R et al. *Eur Heart J* 2021. DOI: 10.1093/eurheartj/ehab777/6433104

FIDELITY

Finerenone reduced risk of CV composite outcome by 14% - CV death, MI, stroke and hospitalisation for HF

Time to CV death, non-fatal MI, non-fatal stroke or hospitalisation for HF



Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	Hazard ratio (95% CI)		*p*-value
Composite CV outcome§	**825 (12.7)**	**939 (14.4)**		**0.86 (0.78–0.95)**	**0.0018**
CV death	322 (4.9)	364 (5.6)		0.88 (0.76–1.02)	0.0922
Non-fatal MI	173 (2.7)	189 (2.8)		0.91 (0.74–1.12)	0.3601
Non-fatal stroke	198 (3.0)	198 (3.0)		0.99 (0.82–1.21)	0.9460
Hospitalisation for HF	256 (3.9)	325 (5.0)		0.78 (0.66–0.92)	0.0030

0.5 1 2

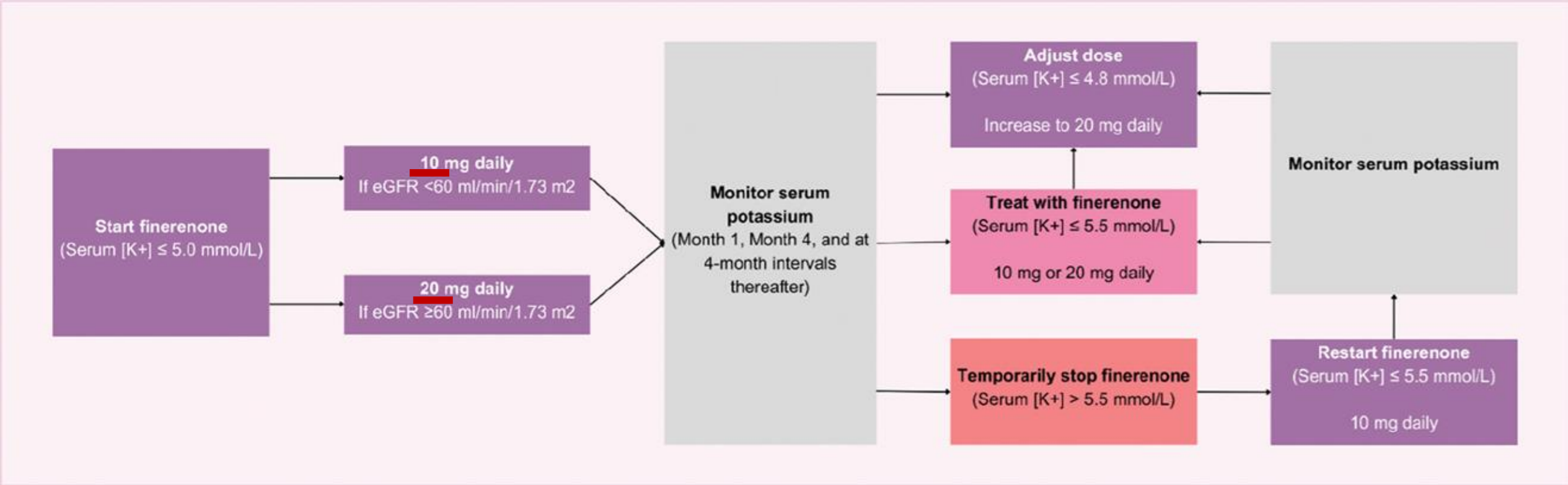
Favours finerenone Favours placebo

*Cumulative incidence calculated by Aalen-Johansen estimator using deaths due to other causes as competing risk; #at-risk subjects were calculated at start of time point; ‡number of patients with an event over a median of 3.0 years of follow-up; § composite of time to first onset of CV death, non-fatal MI, non-fatal stroke or hospitalisation for HF

Agarwal R et al. *Eur Heart J* 2021. DOI: 10.1093/eurheartj/ehab777/6433104

FIDELITY

Potassium management algorithm of the FIDELIO-DKD study protocol



Few hyperkalemia-related discontinuations occurred

Morales J et al. Postgrad Med 2024

Clinical Kidney Journal

Dosing, treatment patterns and safety of finerenone use in routine care: an interim analysis of the prospective, real-world and observational FINE-REAL study

Finerenone improves outcomes in T2D and CKD.
This study aims to better understand finerenone user characteristics and drug utilization in the real world.

Methods

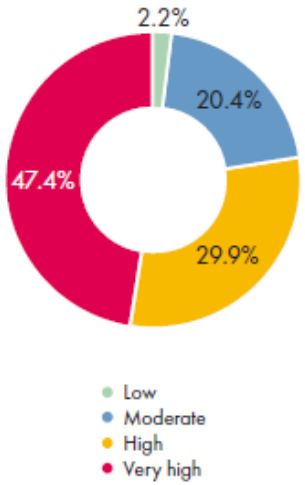
Global, prospective, single-arm, non-interventional study
(N = 1916; T2D/CKD 100%)

Median follow-up: 260 days

Assessments:
- Treatment patterns
- Concomitant medication
- Safety including hyperkalaemia (assessed by the investigator at baseline and follow-up)

Results

Most at high/very high KDIGO risk (N = 1410)



Initial finerenone dose

eGFR < 60mL/min/1.73 m²

94%, 10 mg

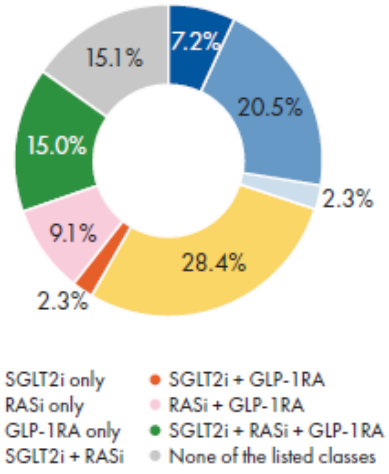
6%, 20 mg

eGFR ≥ 60mL/min/1.73 m²

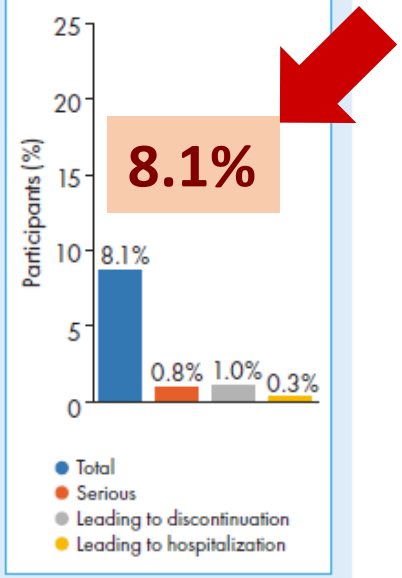
55%, 10 mg

45%, 20 mg

RASi/SGLT2i/GLP-1 RA at initiation



Hyperkalaemia

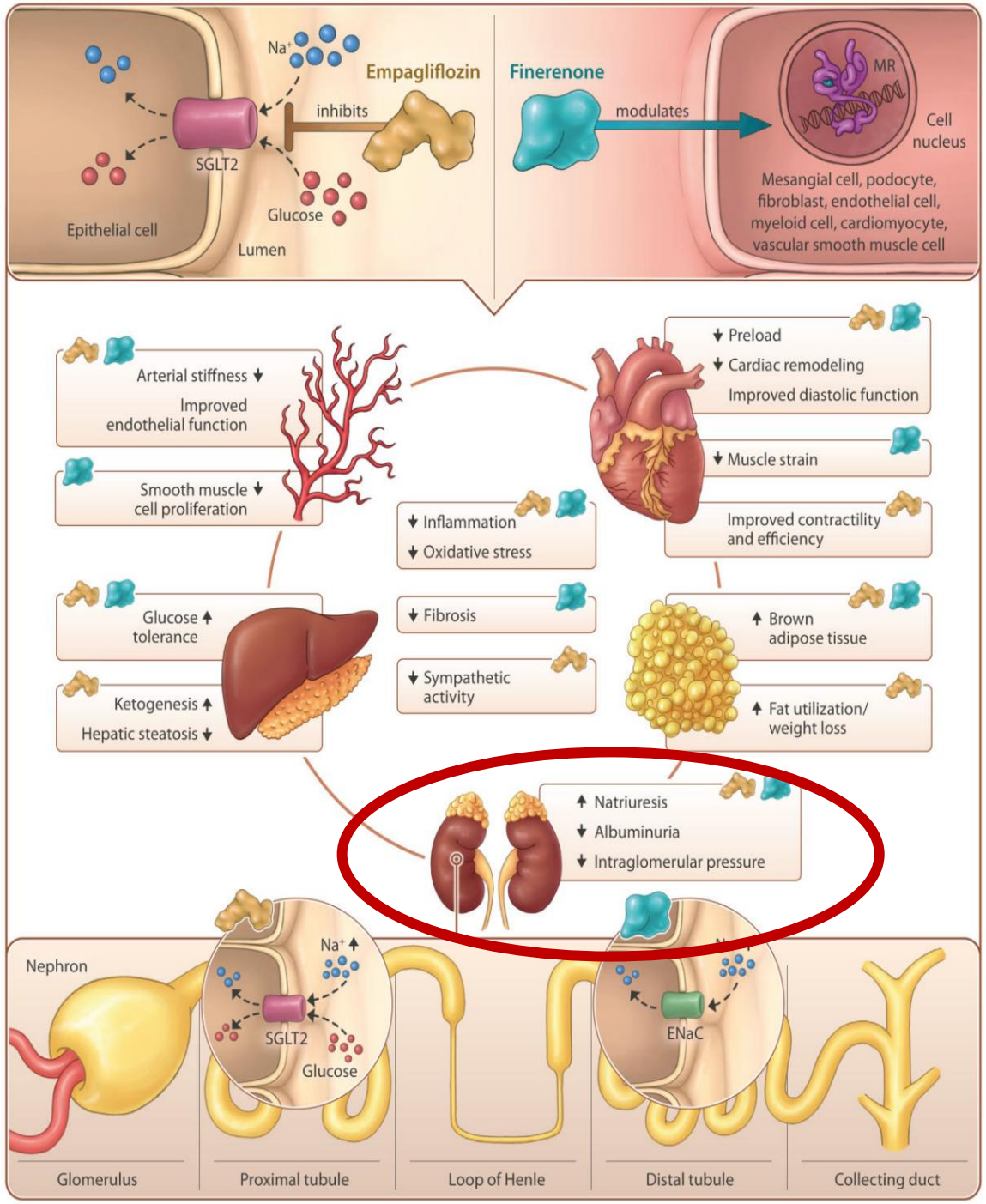


Conclusion: Most participants received 10 mg finerenone and ≥1 guideline-recommended T2D/CKD medication at initiation. Less than 50% with eGFR ≥60 mL/min/1.73 m² received 20 mg finerenone at initiation. Finerenone was well tolerated. These results may aid decision-making in finerenone use in T2D/CKD.

Wheeler, D.C., et al.
Clinical Kidney Journal (2025)
d.wheeler@ucl.ac.uk
@CKJsocial

Associazione SGLT2i + MRA

Empaglifozin (SGLT2 I)



Finerenone (MRA)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 7, 2025 VOL. 393 NO. 6

Finerenone with Empagliflozin in Chronic Kidney Disease and Type 2 Diabetes

Rajiv Agarwal, M.D.,[1,2] Jennifer B. Green, M.D.,[3] Hiddo J.L. Heerspink, Ph.D.,[4] Johannes F.E. Mann, M.D.,[5,6] Janet B. McGill, M.D.,[7] Amy K. Mottl, M.D.,[8] Julio Rosenstock, M.D.,[9] Peter Rossing, M.D.,[10,11] Muthiah Vaduganathan, M.D., M.P.H.,[12] Meike Brinker, M.D.,[13] Robert Edfors, M.D., Ph.D.,[14] Na Li, M.D., Ph.D.,[15] Markus F. Scheerer, Ph.D.,[16] Charlie Scott, M.Sc.,[17] and Masaomi Nangaku, M.D., Ph.D.,[18] for the CONFIDENCE Investigators*

CONFIDENCE study

R Agarwal et al NEJM 2025

Design of the COmbinatioN effect of FInerenone anD EmpagliflozinN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint study (CONFIDENCE)

Background

Both finerenone (nonsteroidal MRA) and empagliflozin (SGLT2i) can reduce kidney and cardiovascular events in people with CKD and T2D.

CONFIDENCE (NCT05254002) investigates whether dual therapy with finerenone and empagliflozin is superior to either agent alone in reducing albuminuria.

Participants

- 807 participants
- 125 centres
- 13 countries

- ≥ 18 years
- T2D, CKD stage 2–3
- UACR ≥ 300 to < 5000 mg/g

- T1D
- Serum K^+ > 4.8 mmol/L
- Treatment with SGLT1/2i or MRA

Treatment arms

R 1:1:1

269	Finerenone (10 or 20 mg od)	+	Empagliflozin (10 mg od)
269	Finerenone (10 or 20 mg od)	+	Placebo
269	Empagliflozin (10 mg od)	+	Placebo

0 — Treatment period (days) — 180

Primary outcomes

Relative change in UACR from baseline to 180 days in:

- Dual therapy vs. Finerenone
- Dual therapy vs. Empagliflozin

Conclusion

Should an additive effect be shown, early and efficient intervention with dual finerenone and SGLT2i therapy could slow disease progression and provide long-term benefits for people with CKD and T2D.

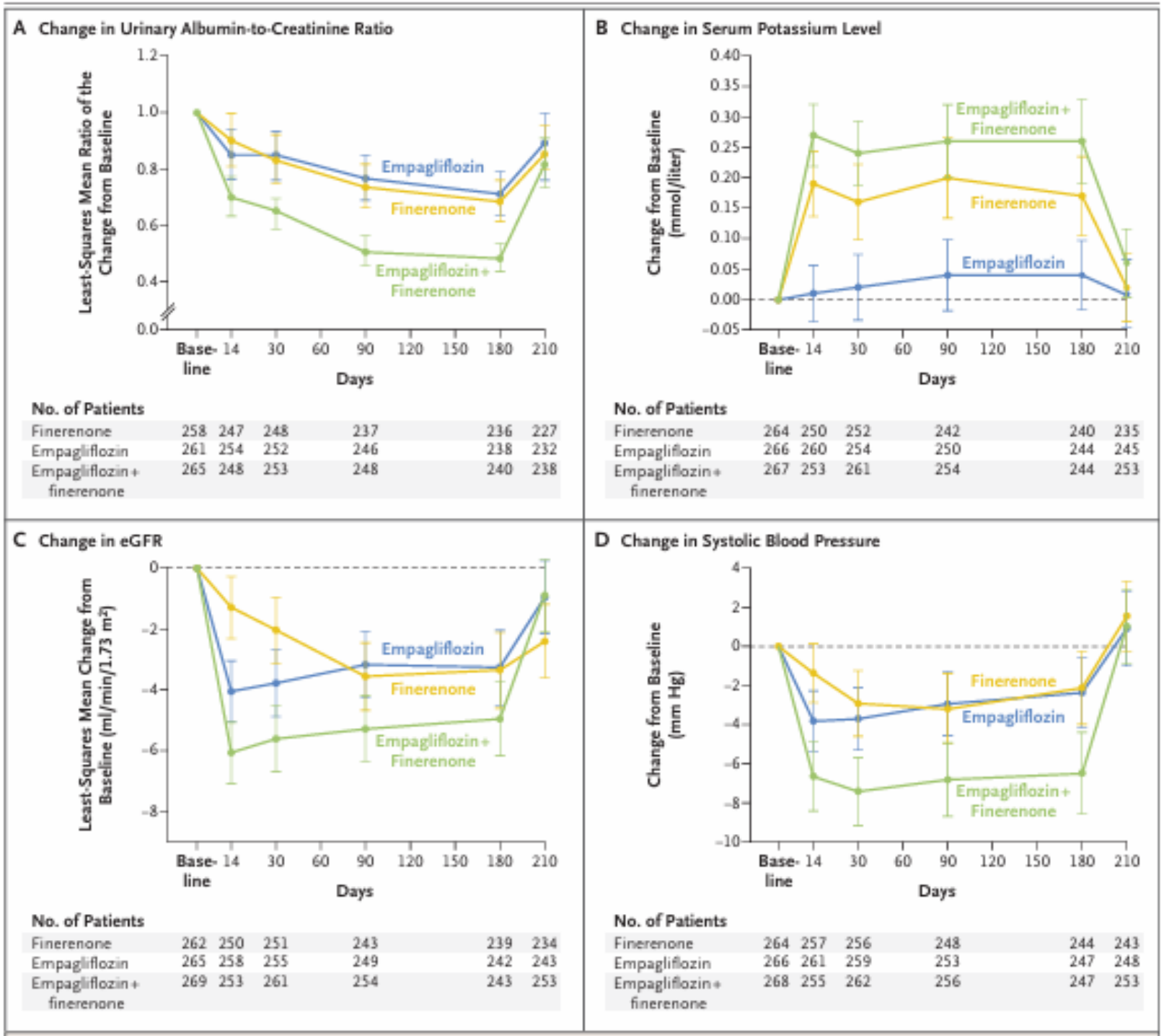
ACR

- 30%

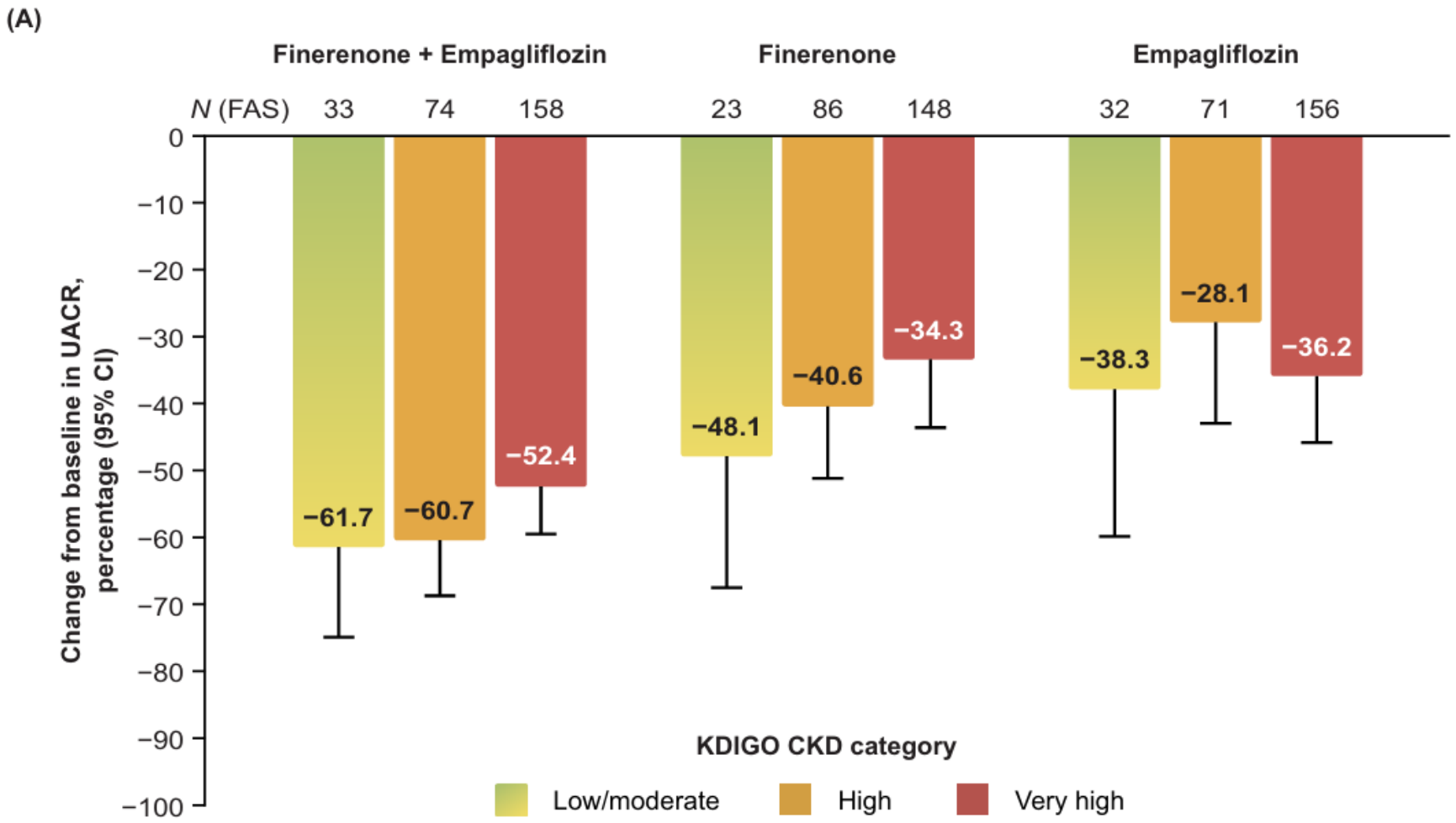
K+

eGFR

Systolic blood pressure

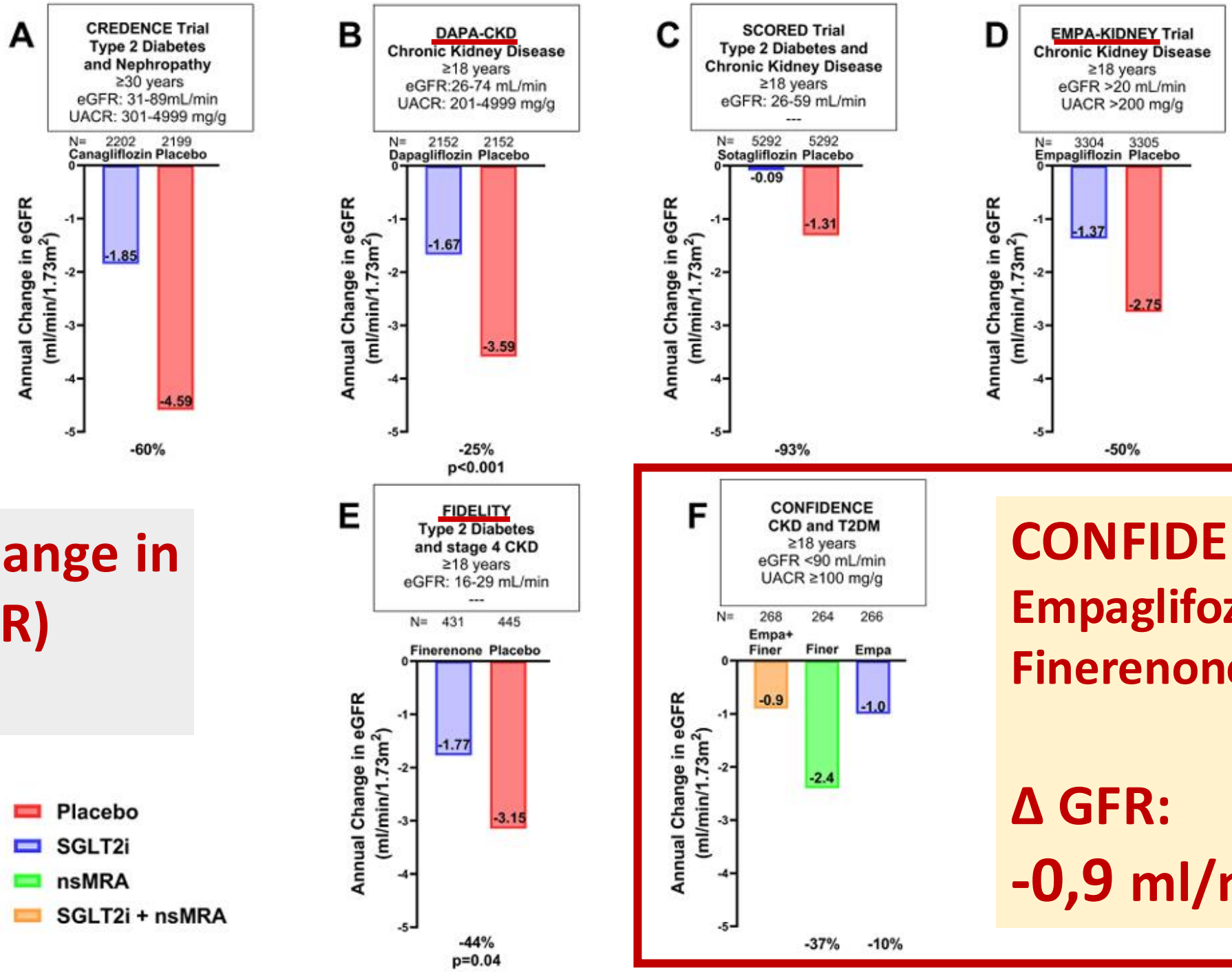


Simultaneous initiation of finerenone and empagliflozin across the spectrum of kidney risk in the CONFIDENCE trial



M Vaduganathan et al NDT 2025

Annual change in GFR (Δ GFR)



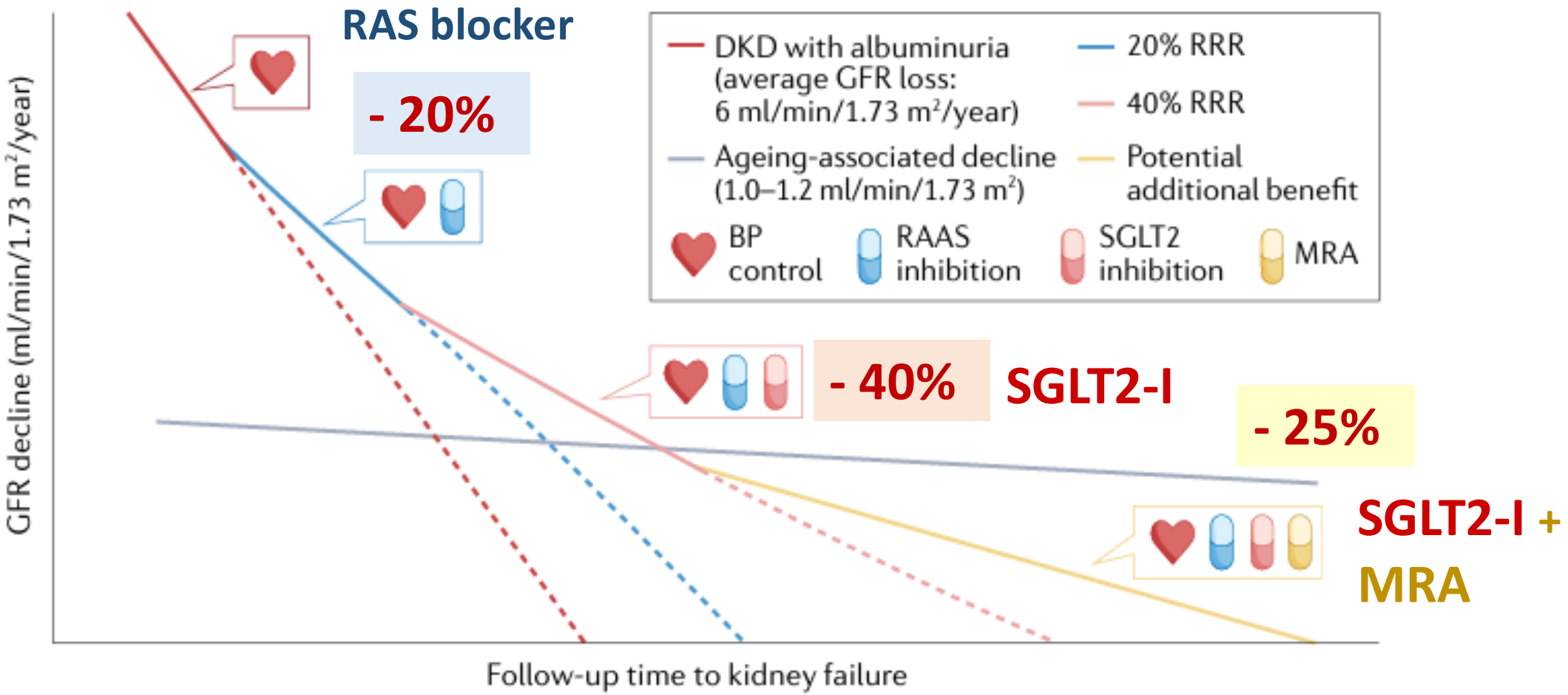
CONFIDENCE

Empaglifozin + Finerenone

Δ GFR:

-0,9 ml/min/aa

Incremental benefit of multifactorial intervention on GFR decline in DKD

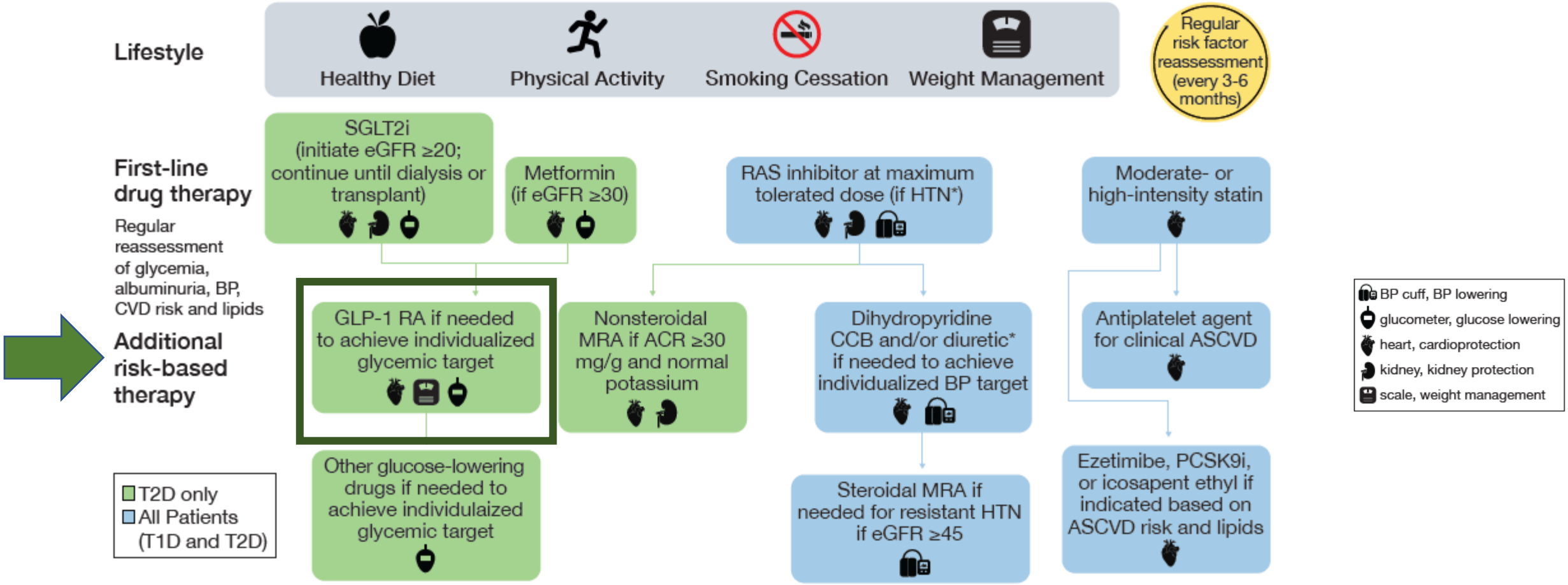


P Fioretto et al Nature 2022

AGENDA

- SGLT2-I
- MRA
- **GLP-1 RA**

2022 KDIGO Approach for People With Diabetes and CKD



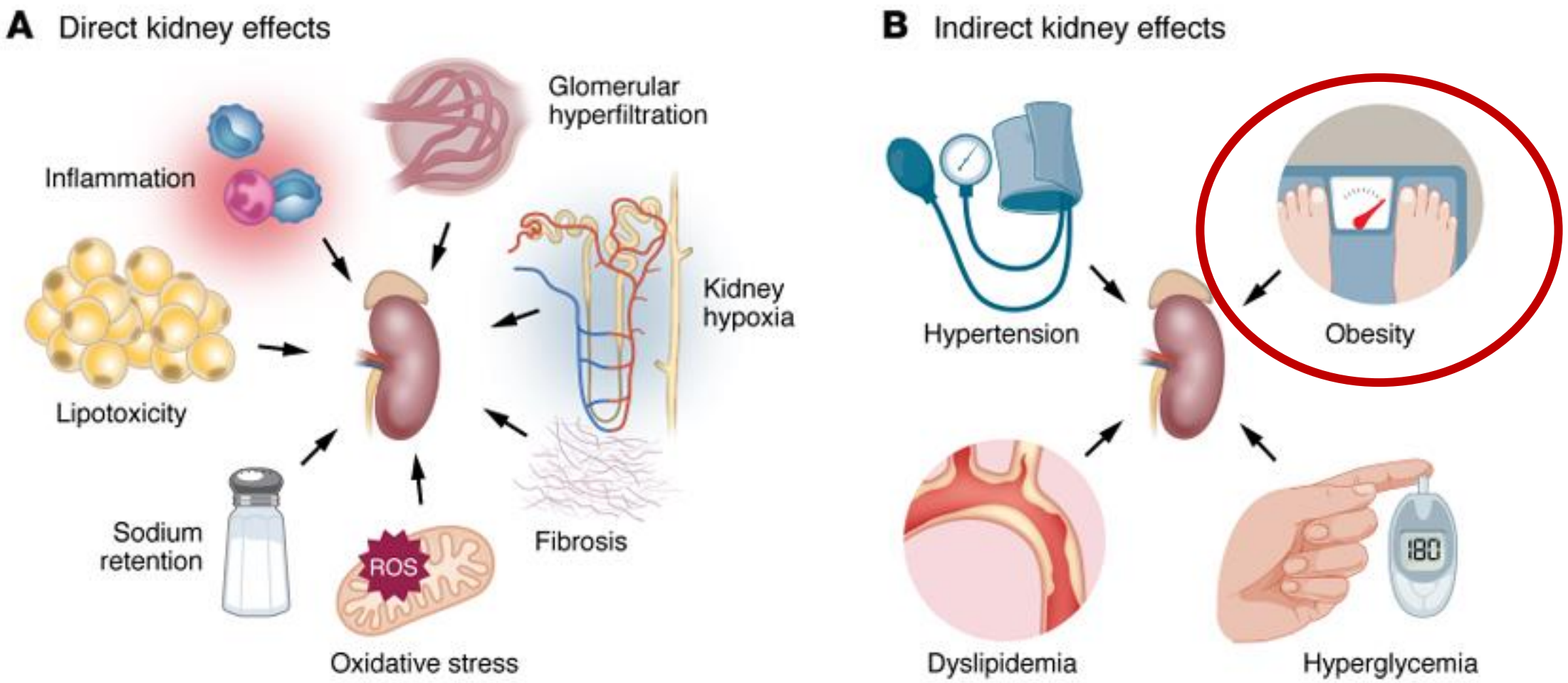
Note: eGFR is presented in units of mL/min/1.73 m^2.

*Maximum tolerated ACEi or ARB should be first-line therapy for HTN when albuminuria is present. Otherwise, dihydropyridine CCB or diuretic can also be considered; all three classes are often needed to attain BP targets.

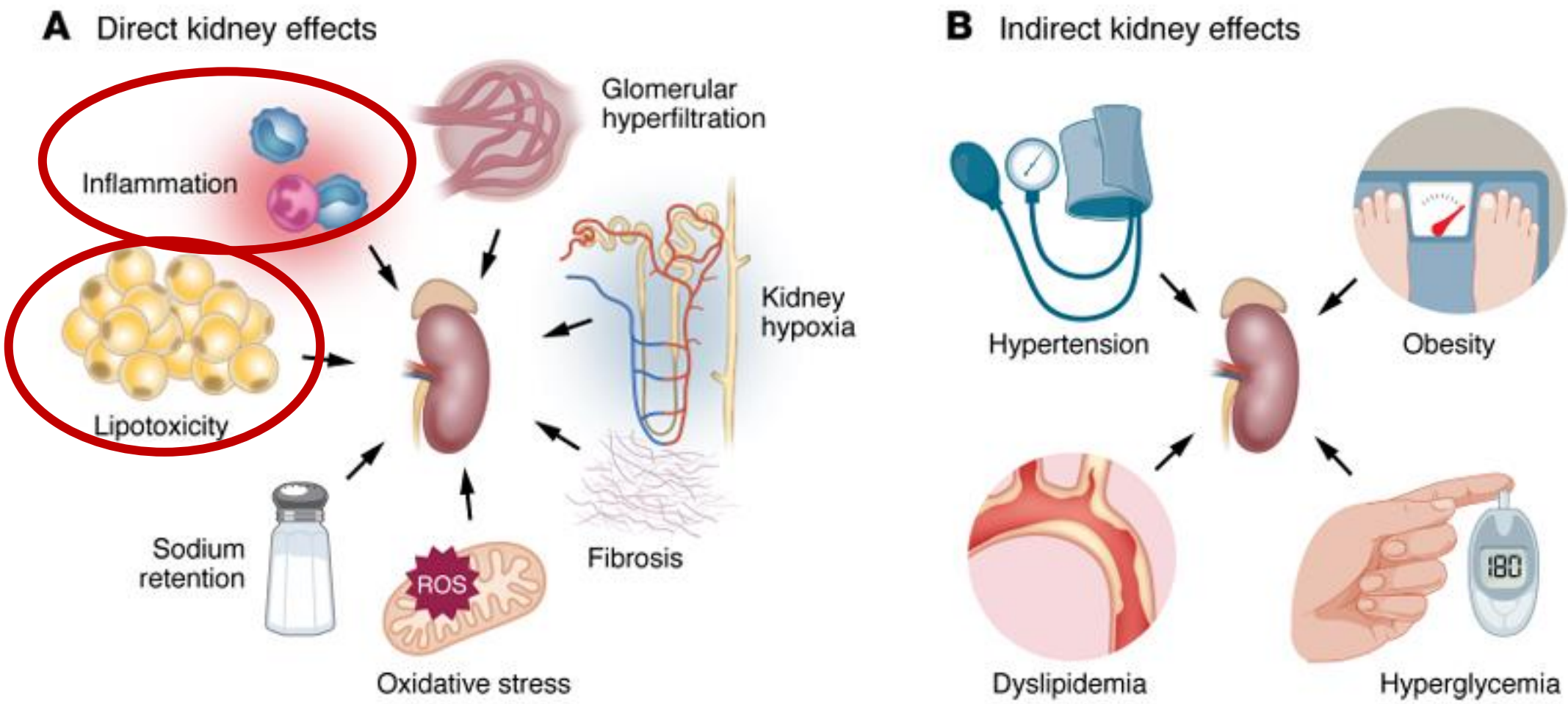
ACEi = angiotensin-converting enzyme inhibitor; ACR = albumin-creatinine ratio; ARB = angiotensin II receptor blocker; ADA = American Diabetes Association: ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HTN = hypertension; KDIGO = Kidney Disease: Improving Global Outcomes; MRA = mineralocorticoid-receptor antagonist; PCSK9i= proprotein convertase subtilisin/kexin type 9 inhibitor; RAS = renin-angiotensin system; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T1D = type 1 diabetes; T2D = type 2 diabetes.

Rossing P et al. *Kidney Int.* 2022;102(5):990-999.

GLP-1 RA effects



GLP-1 RA effects



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 11, 2024 VOL. 391 NO. 2

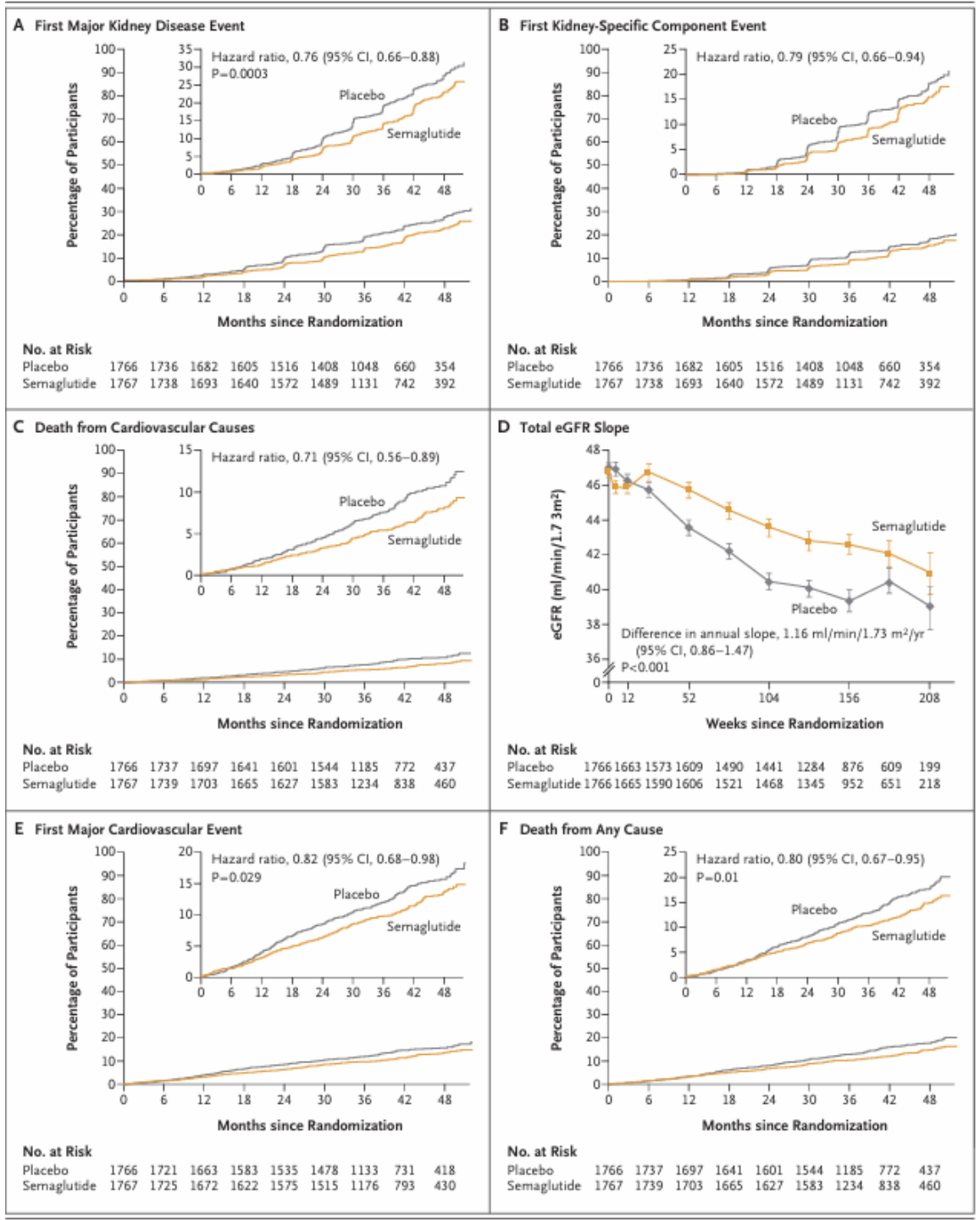
Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

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 study

Semaglutide +ACE-I/ARB + SGLT2i vs ACE-I/ARB + SGLT2i

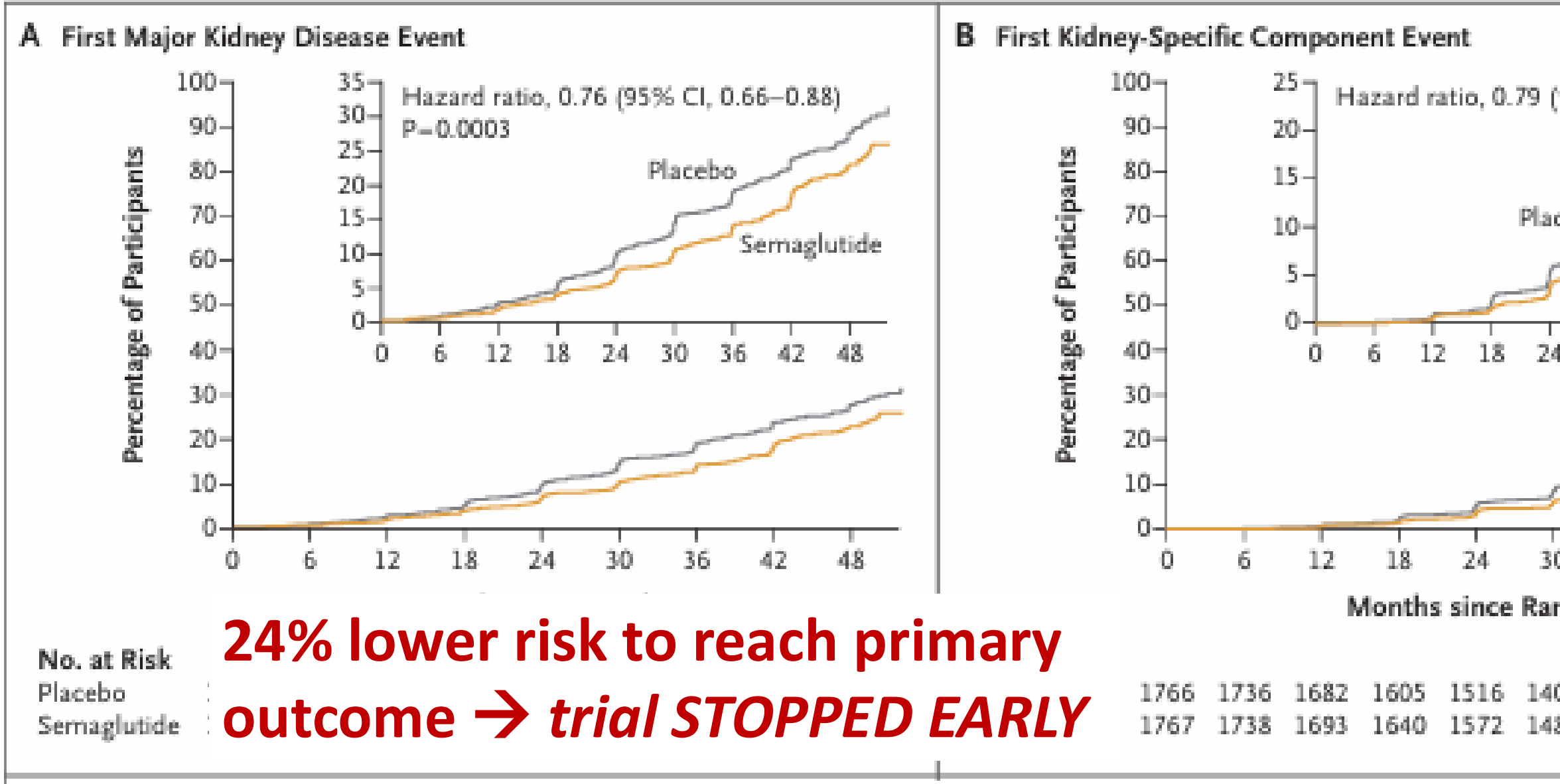
V Perkovitc et al NEJM 2024



Semaglutide 1 mg s.c./sett riduce UACR del 32%

(15% paz con ACE-I/ARB + SGLT2i)

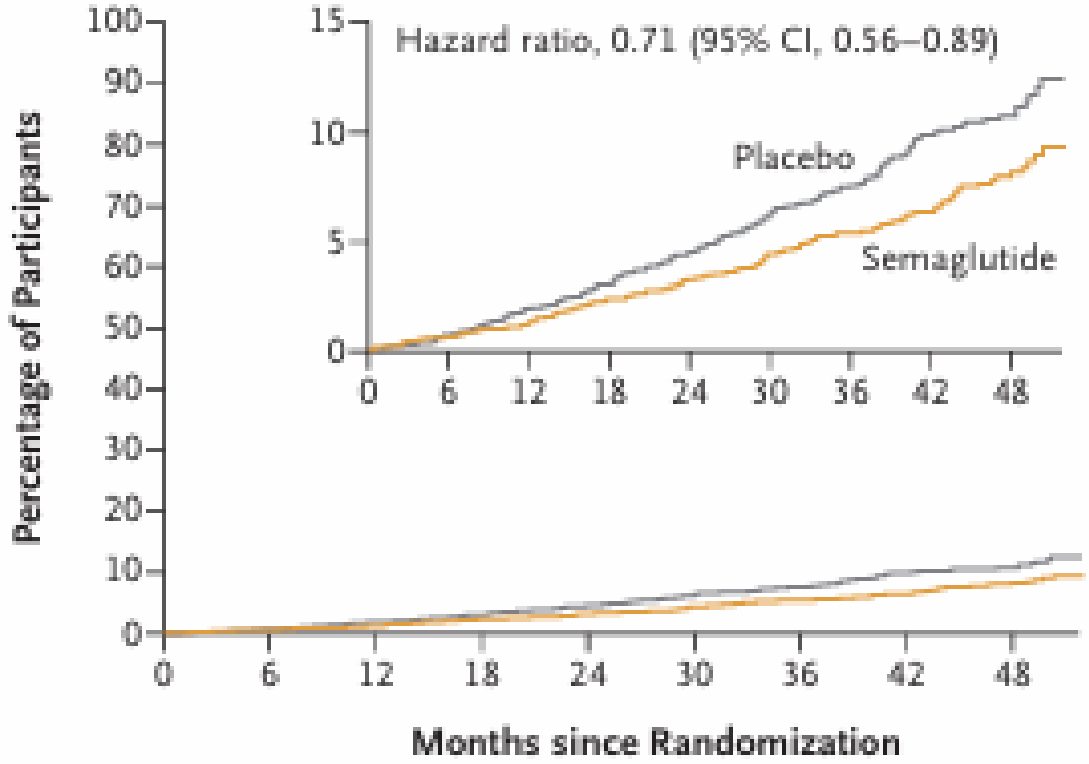
V Perkovitc et al NEJM 2024



24% lower risk to reach primary outcome → *trial STOPPED EARLY*

V Perkovitc et al NEJM 2024

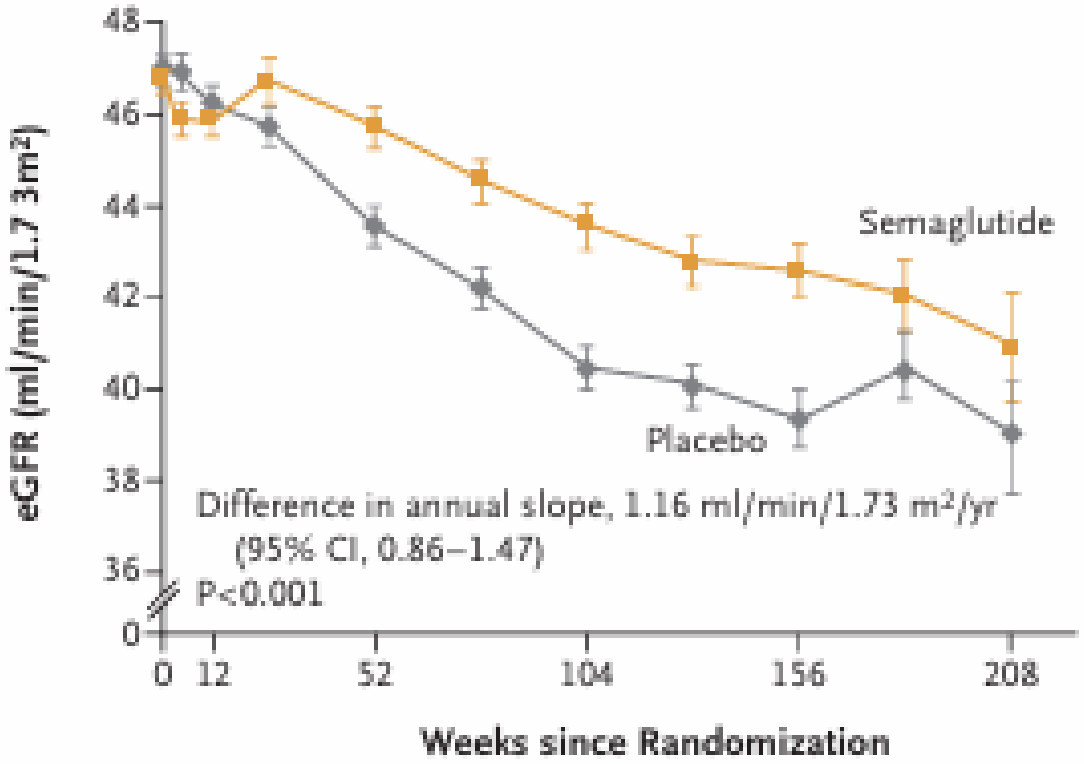
C Death from Cardiovascular Causes



No. at Risk

Placebo	1766	1737	1697	1641	1601	1544	1185	772	437
Semaglutide	1767	1739	1703	1665	1627	1583	1234	838	460

D Total eGFR Slope



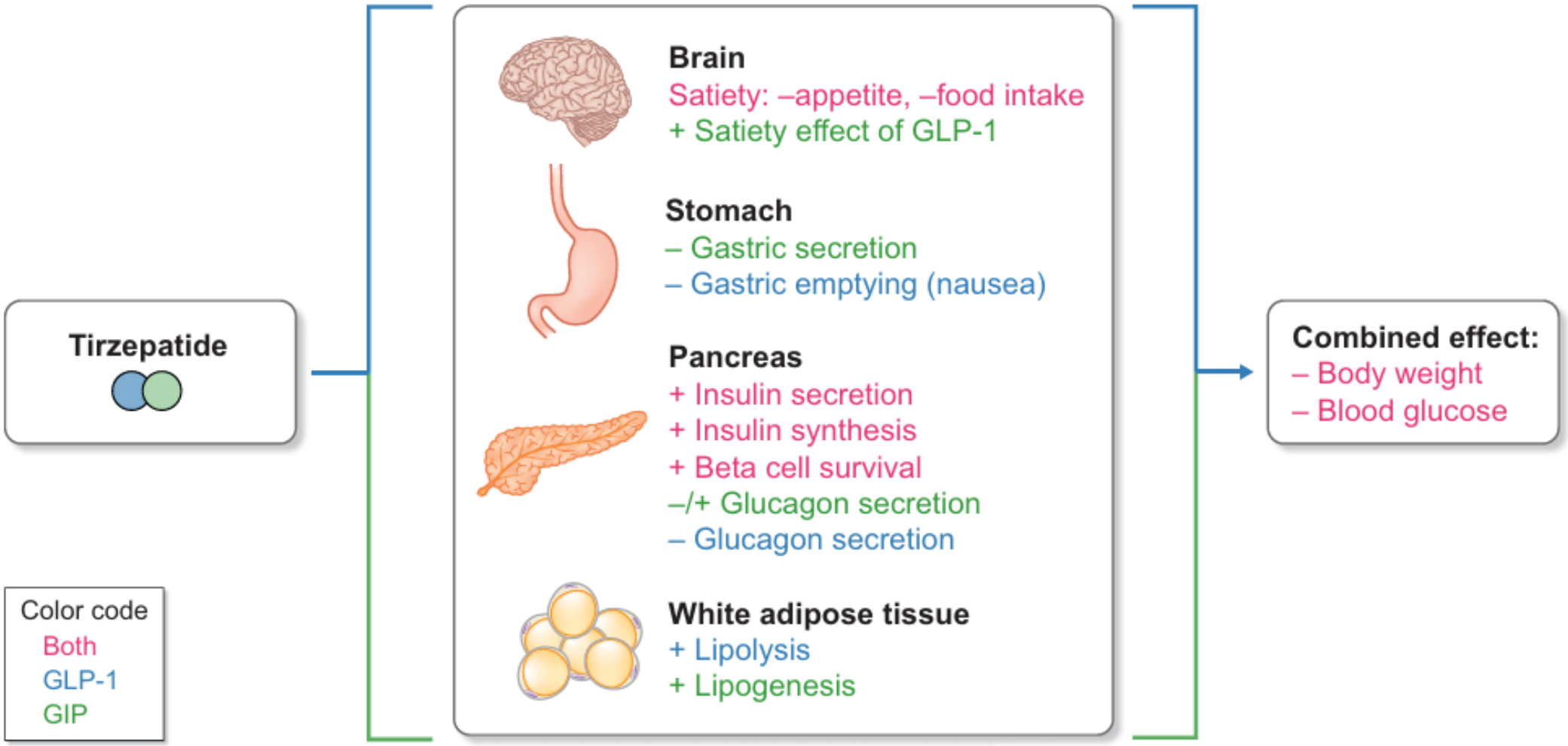
No. at Risk

Placebo	1766	1663	1573	1609	1490	1441	1284	876	609	199
Semaglutide	1766	1665	1590	1606	1521	1468	1345	952	651	218

E First Major Cardiovascular Event

ΔGFR - 1.16 mL/min vs placebo

Dual GLP-1 and GIP receptor agonists



SURPASS-4 post-hoc analysis

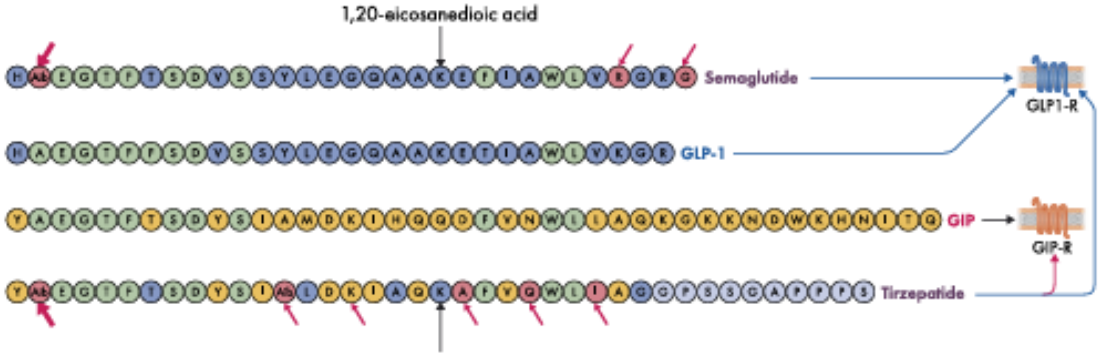
Effetto anche con **eGFR 60-90** e **ACR < 30 mg/g**

Clinical Kidney Journal

Tirzepatide and prevention of chronic kidney disease

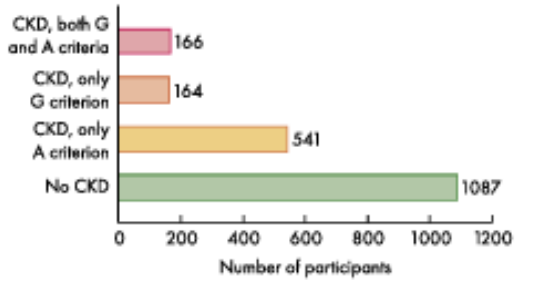
The twincretin tirzepatide was recently approved to improve glycemic control in type 2 diabetes mellitus (T2DM) and has been fast-tracked for approval for obesity or for overweight and SBP ≥ 130 mmHg or DBP ≥ 80 mmHg.

Structure of tirzepatide and semaglutide

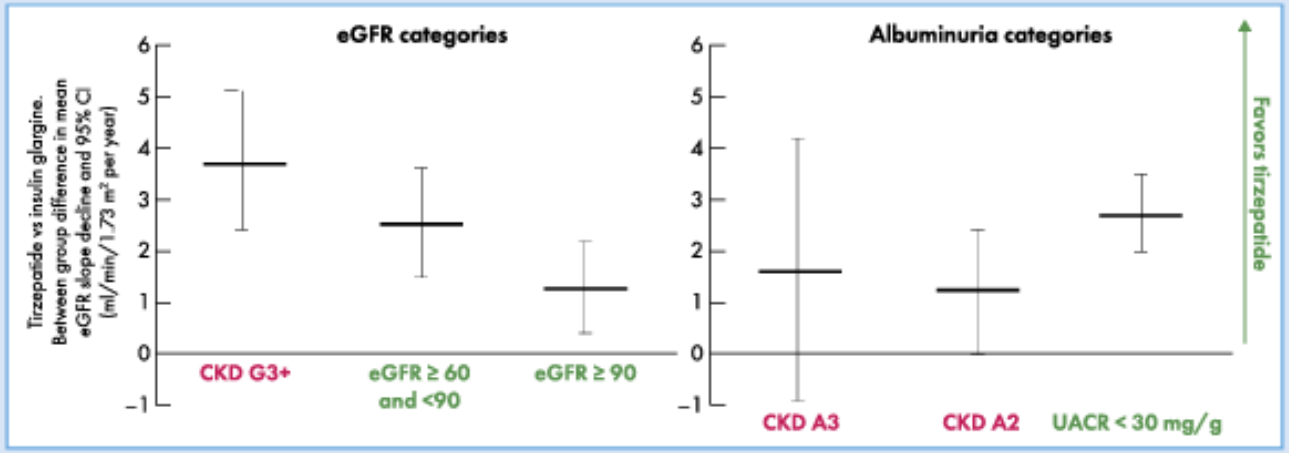


Most SURPASS-4 T2DM participants did not have CKD

Participant distribution according to eGFR/UACR



In SURPASS-4 post-hoc analyses, tirzepatide offered kidney protection as compared with insulin glargine for T2DM participants with CKD and also for participants with eGFR G1–G2 or with albuminuria A1



Conclusion: The potential kidney protective effects of twincretins should be characterized in detail from the points of view of both CKD prevention and CKD treatment.

Bosch, C.
Clinical Kidney Journal (2022)
@CKJsocial

Table 1. Ongoing trials with incretin-based therapies that investigate potential renoprotective mechanisms

Trial (NCT number)	Intervention	Population	*N*	Primary endpoint	(Other) kidney endpoints
GLP-1 receptor agonist					
REMODEL (52) NCT04865770	Semaglutide 1.0 mg vs. placebo	CKD, T2D	105	Multiparametric MRI parameters, including oxygenation, perfusion, and T1 mapping	eGFR and UACR; gene expression by single-cell nucleus RNA sequencing; sodium excretion
ASCEND PLUS NCT05441267	Semaglutide 14 mg vs. placebo	T2D	20,000	5-Point MACE	Risk for CKD
PRECIDENTD (54) NCT05390892	Open-label GLP-1 therapy vs. SGLT-2 inhibition	T2D	6,000	4-Point MACE	Development of end-stage kidney disease/ kidney transplantation
ACHIEVE-4 (90) NCT05803421	Orforglipron vs. insulin glargine	T2D + CV disease	2,620	4-Point MACE	Not specified
GLP-1/GIP receptor agonist					
SURPASS-CVOT (92) NCT04255433	Tirzepatide vs. dulaglutide	T2D + CV disease	13,299	3-Point MACE	Change in UACR; new or worsening nephropathy
SURMOUNT-MMO (93) NCT05556512	Tirzepatide vs. placebo	Overweight or obesity	15,374	4-Point MACE	eGFR slope; composite endpoint ≥40% eGFR decline, kidney failure, or renal death
TREASURE-CKD (53) NCT05536804	Tirzepatide vs. placebo	Obesity with/without T2D + CKD	140	Kidney oxygenation (BOLD-MRI)	Kidney sinus fat and kidney fat content (MRI); kidney blood flow (MRI); kidney apparent diffusion coefficient (MRI); iohexol-measured GFR; 24-hour UAE and UACR
GLP-1/GIP/glucagon agonist					
TRIUMPH-Outcomes (54) NCT06383390	Retatrutide vs. placebo	Overweight or obesity ASCVD and/or CKD	10,000	4-Point MACE; 4-point kidney composite ESRD, ≥40% eGFR decline, CV/renal death	Composite ≥40% decline eGFR, ESRD, or renal death; UACR
J1I-MC-GZBU (54) NCT05936151	Retatrutide vs. placebo	Obesity with/without T2D + CKD		Iohexol-measured GFR	Kidney blood flow (MRI); kidney volume (MRI); T1 map (MRI); kidney oxygenation (BOLD-MRI); 24-hour UAE and UACR
GLP-1/amylin agonist					
REDEFINE-3 NCT05669755	CagriSema vs. placebo	BMI ≥25 + CVD (T2D)	7,000	3-Point MACE	≥40% reduction eGFRcr; persistent eGFRcr <15; initiation of dialysis; kidney death and CV death
NN9388-7700 NCT06131372	CagriSema vs. Sema vs. Cagri vs. placebo	CKD and T2D and overweight or obesity	618	UACR	Creatinine- and cystatin C–based eGFR

CONCLUSIONI

SGLT2-i sono un pilastro della terapia della DKD/CKD

SGLT2-i

Effetti emodinamici

Inibizione simpatico

Chetogenesi

Ossigenazione renale

SGLT2-i sono un pilastro della terapia della DKD/CKD

SGLT2-i

Effetti emodinamici

Inibizione simpatico

Chetogenesi

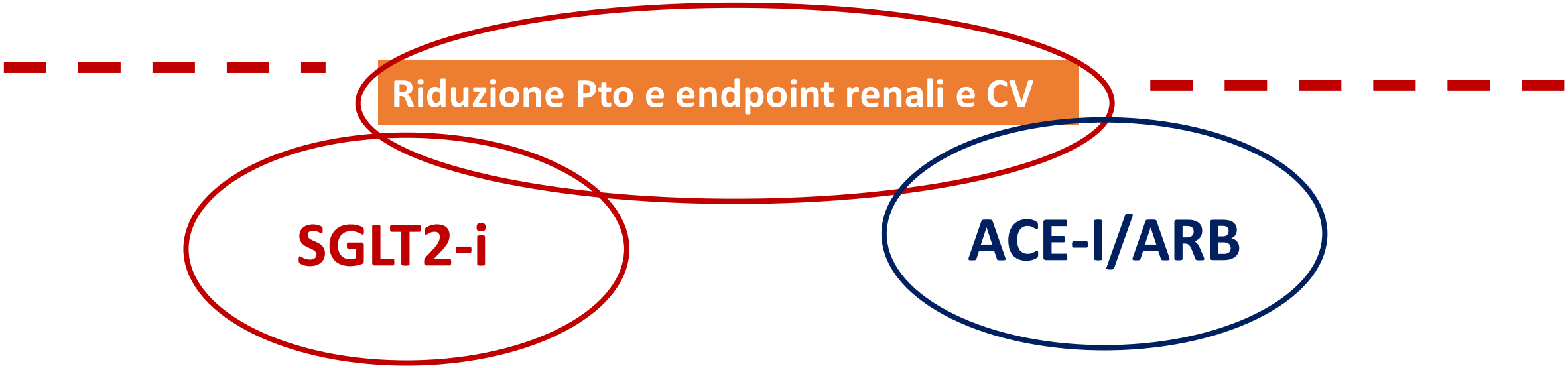
Ossigenazione renale

Senescenza

Autofagia

Disfunzione mitocondriale

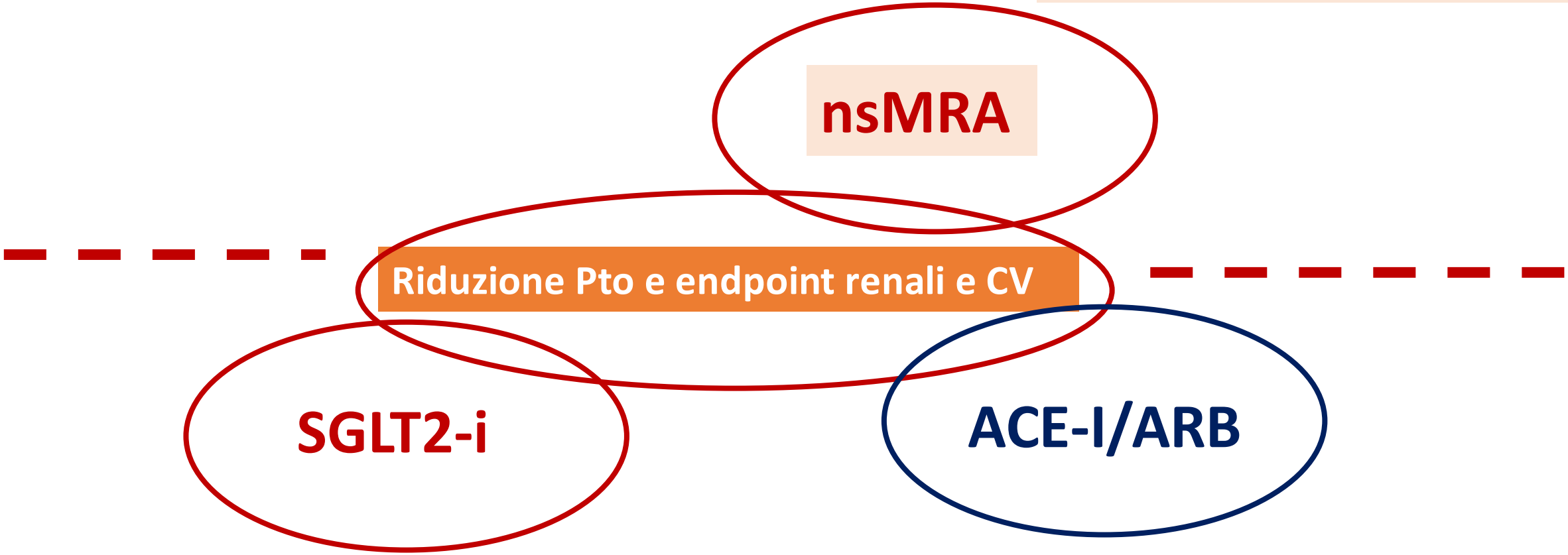
SGLT2-i devono essere *«ben accompagnati»*



Arterial and glomerular hypertension, hyperfiltration

SGLT2-i devono essere «*ben accompagnati*»

Inflammatory and profibrotic factors, cardiac remodeling

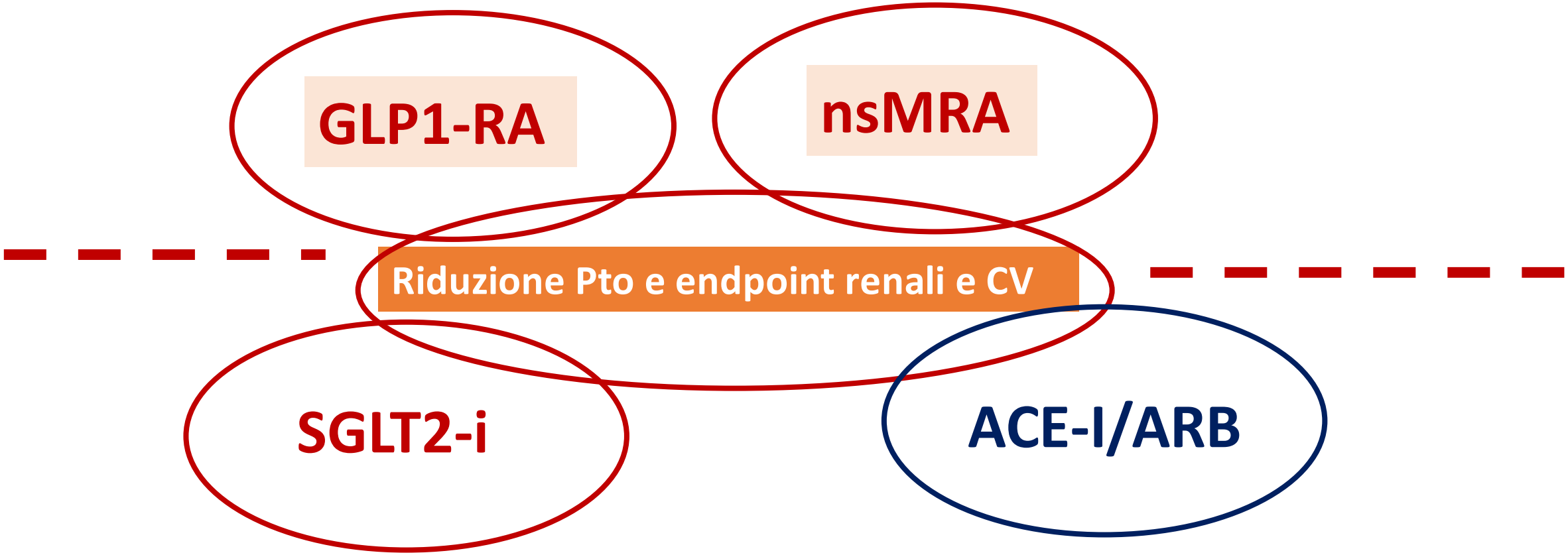


Arterial and glomerular hypertension, hyperfiltration

SGLT2-i devono essere «*ben accompagnati*»

Metabolic factors: poor glycemic control

Inflammatory and profibrotic factors, cardiac remodeling

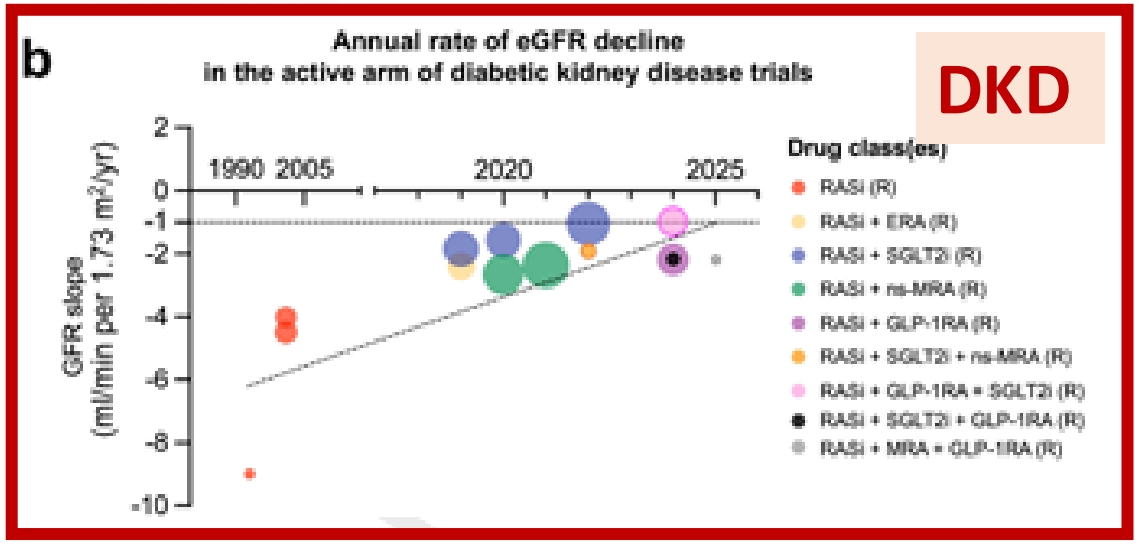


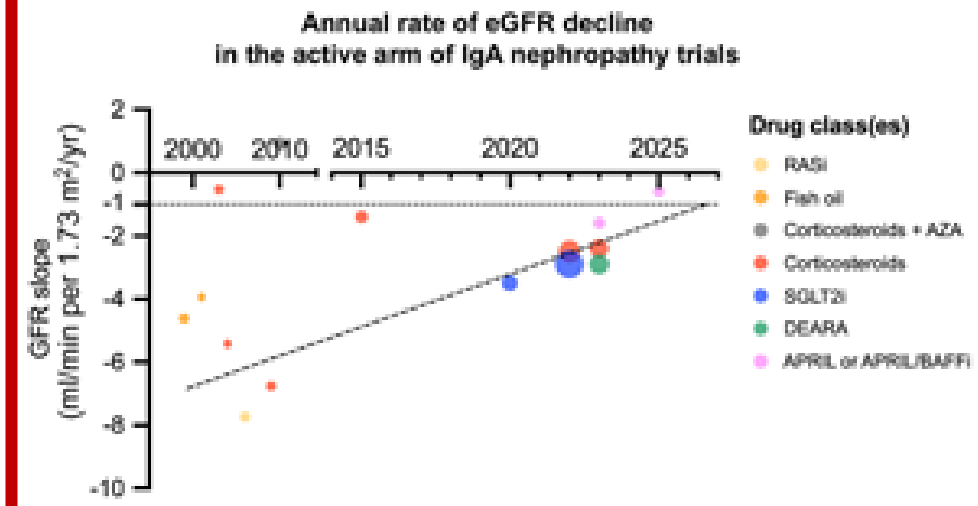
Arterial and glomerular hypertension, hyperfiltration

a

	Historical paradigm: slow CKD progression	New paradigm: aim to achieve CKD remission
Goal	• Delay the inevitable loss of kidney function	• Halt decline in kidney function to normal healthy aging (<1 ml/min per 1.73 m²/yr) OR achieve normalization of GFR and albuminuria
Therapeutic context	• Few effective therapies to prevent loss of kidney function	• Combination therapy with highly effective and safe agents (RASi, SGLT2i, ns-MRA, GLP-1RA, disease-specific therapies [e.g. B-cell–targeted therapies])
Workforce and policy focus	• Major focus on the provision of dialysis and kidney transplantation services	• Early detection, population-based screening, risk-based implementation of guideline-directed therapies

b



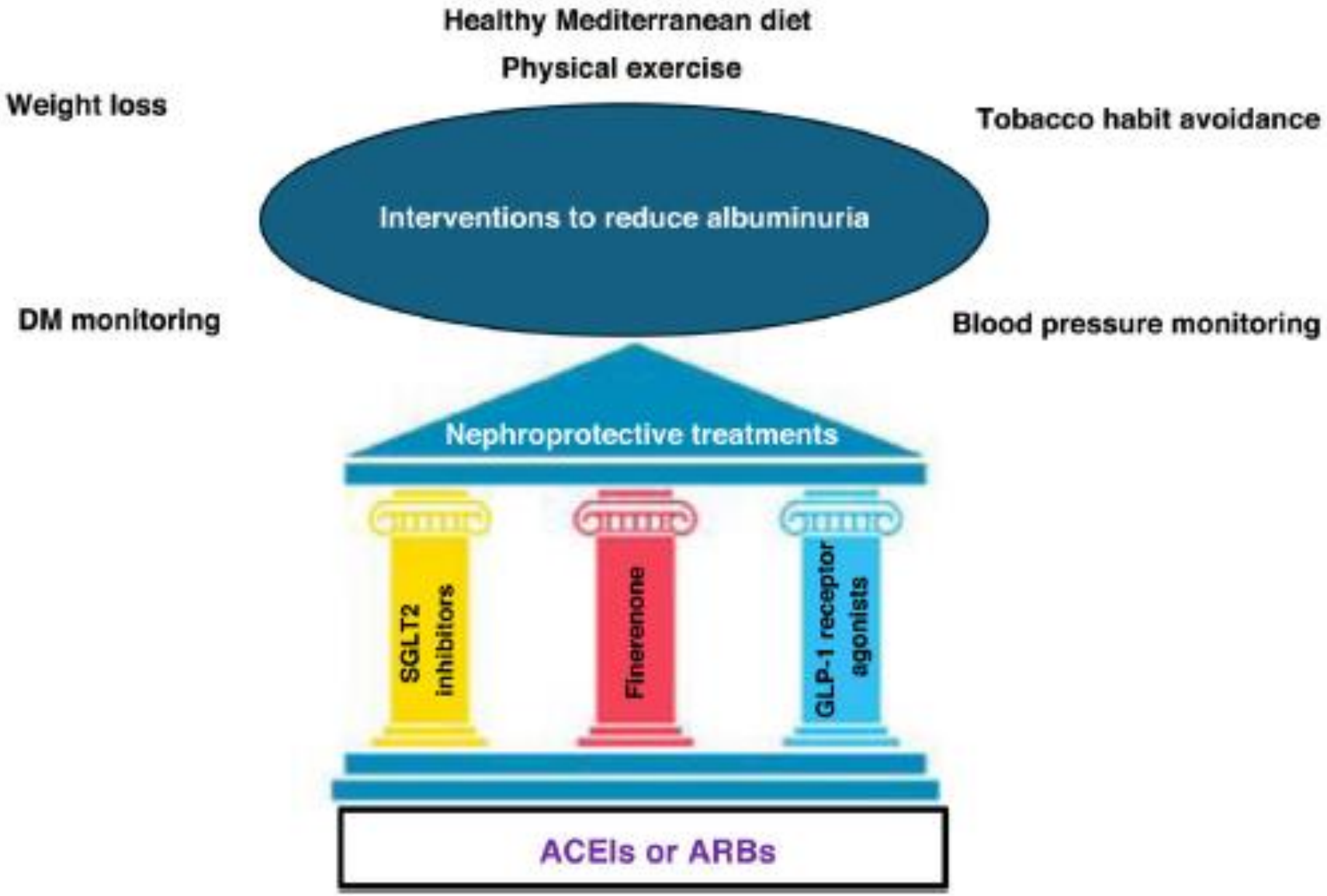


Δ GFR - 1 ml/min/year with RAS-I + SGLT2i + nsMRA/GLP1-RA

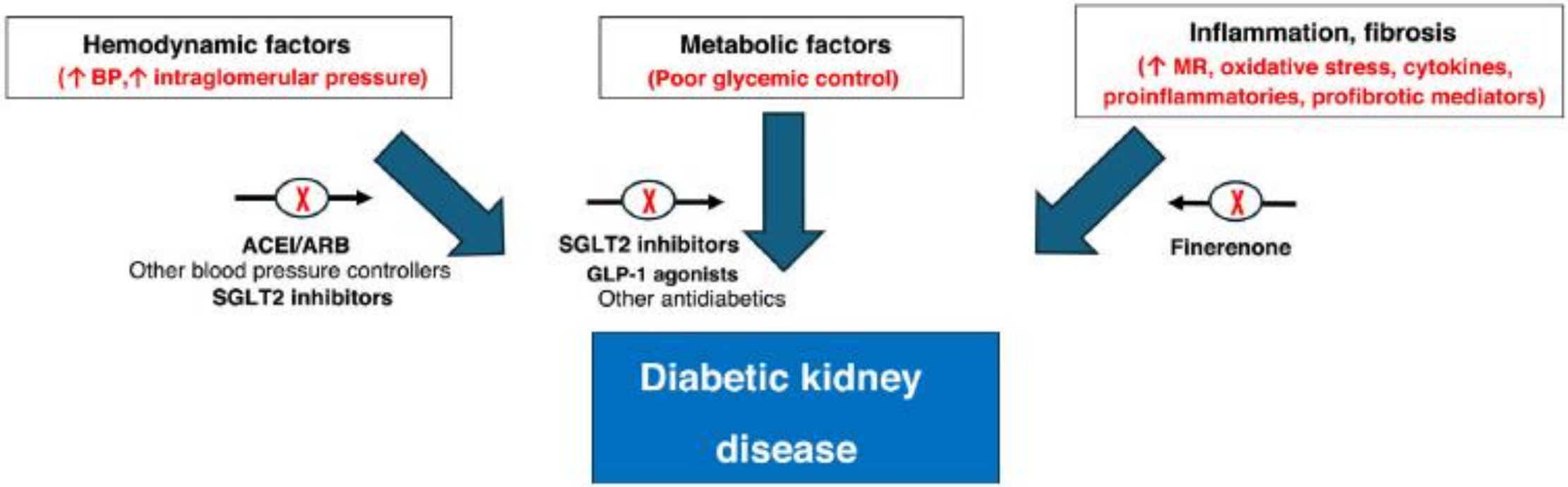
N Tangri et al Kid Int 2025

Grazie!

Altre diapo



JP Lopez et al. Nephrologia 2025



JP Lopez et al. Nephrologia 2025