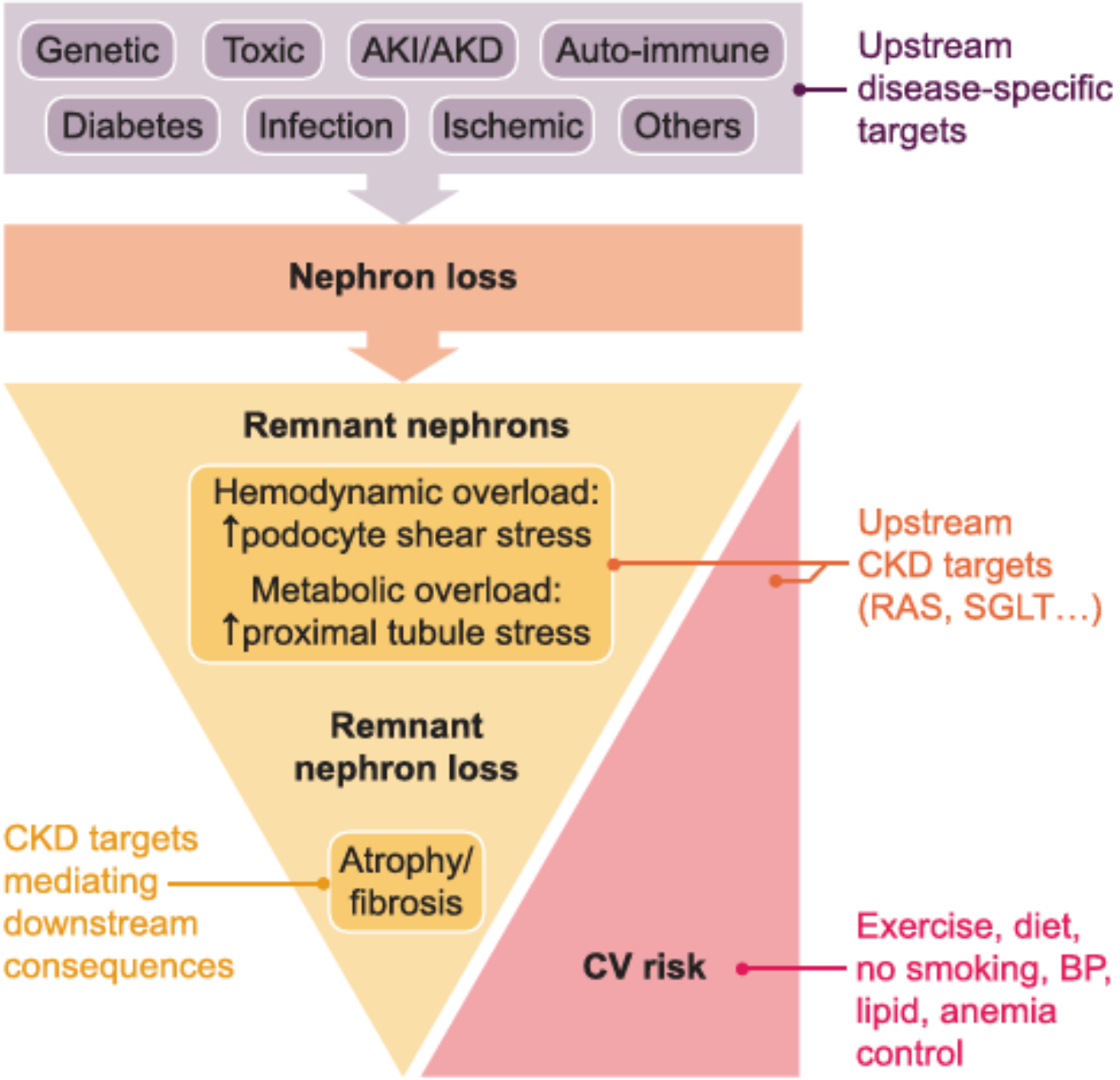
Sodium-glucose cotransporter 2 inhibition in glomerulonephritis

Esmat Abdollahpour, MD, nephrologist, academic member, Shariati Hospital, TUMS

Updated concept of CKD progression



Nephrol Dial Transplant (2020) 1–7 doi: 10.1093/ndt/gfaa329

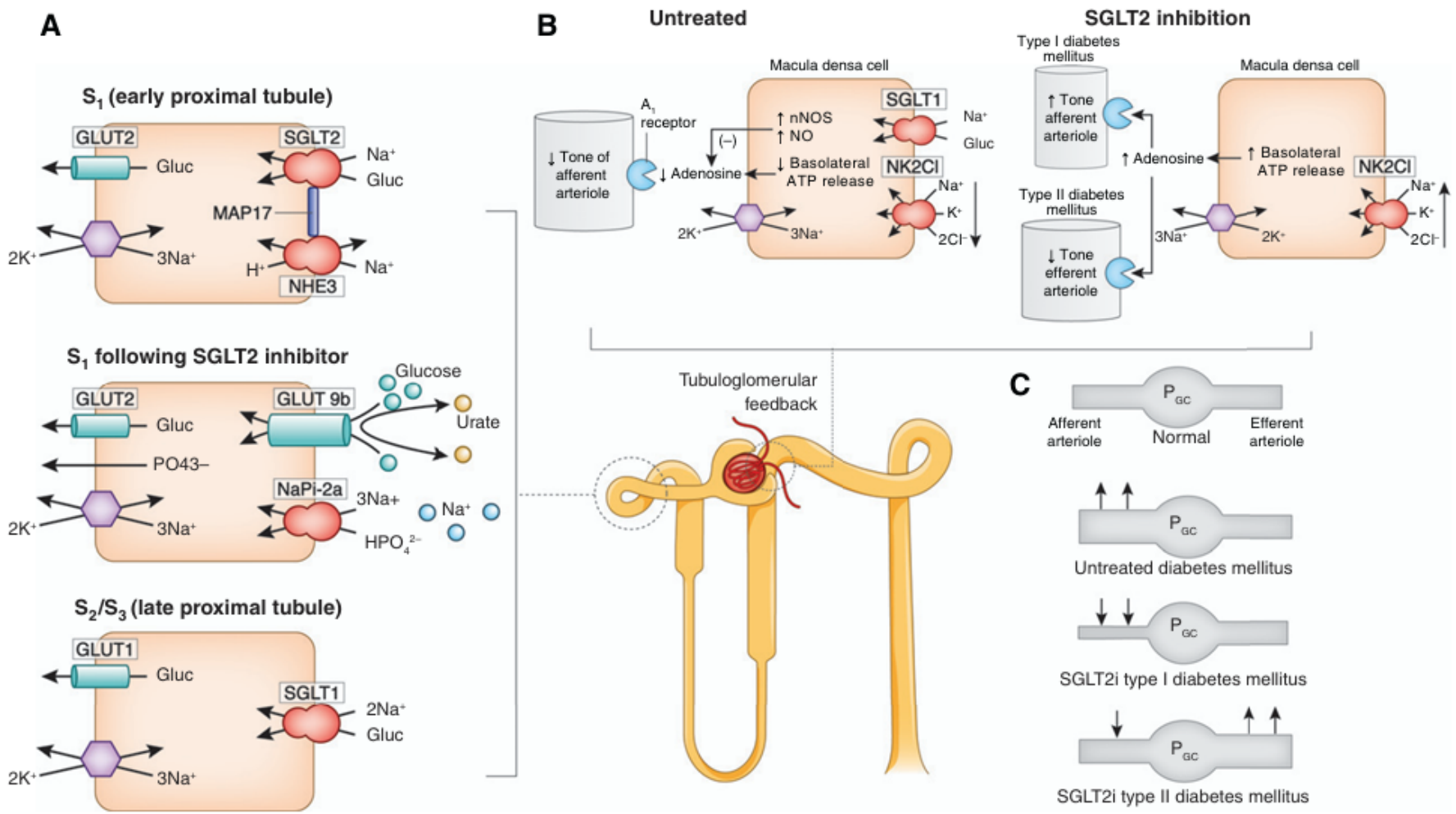
How do SGLT2 inhibitors work?

S-GL-T2

↓ **S**odium reabsorption in S1-PT

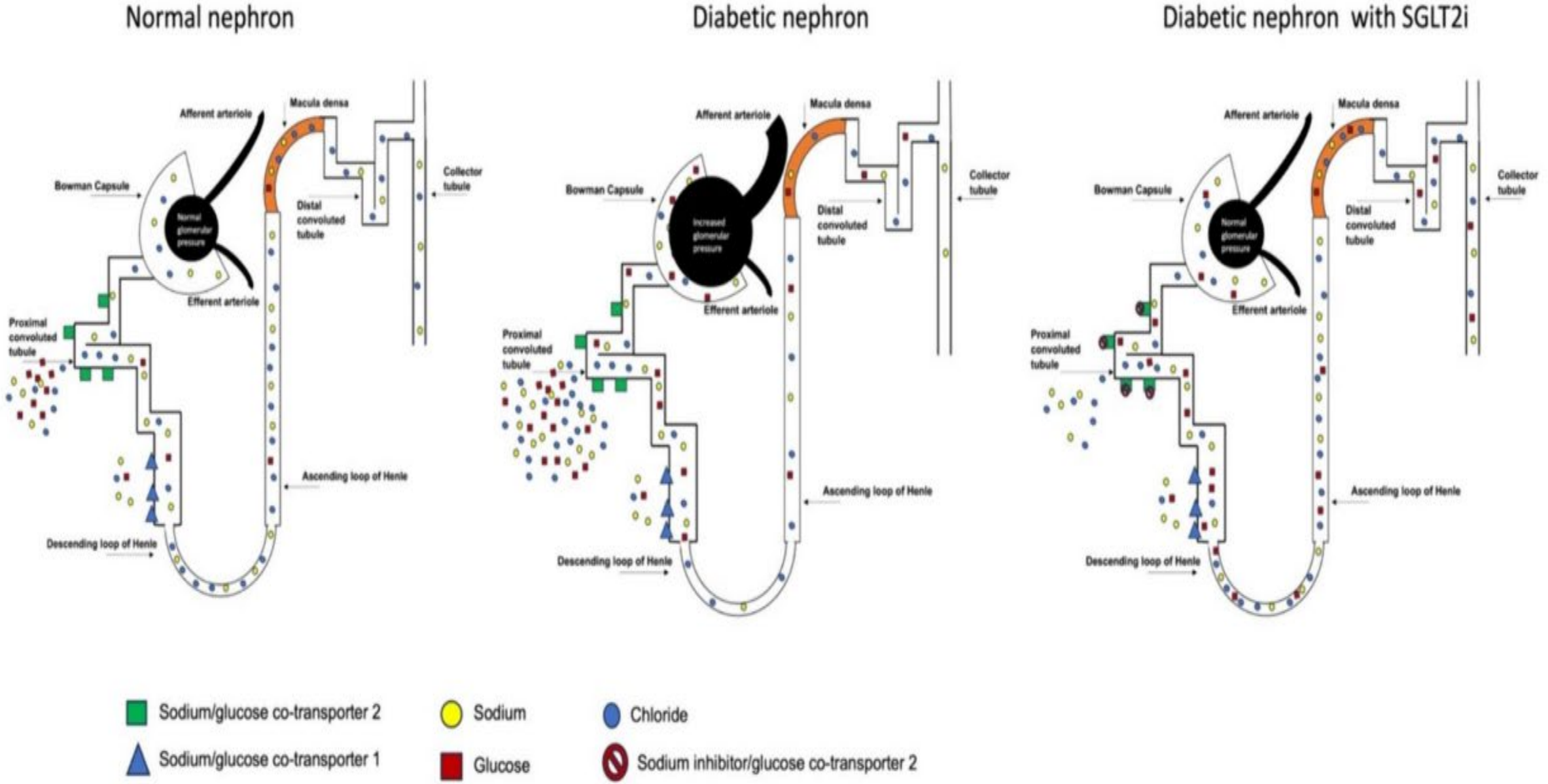
↓ **Gl**ucose reabsorption in S1-PT

↓ Energy-dependent **T**ransport in S1-PT



Mechanism of glucose transport in the proximal tubule and effects of sodium-glucose cotransporter 2 (SGLT2) inhibition on the tubuloglomerular feedback mechanism and transport of uric acid and phosphate.

www.cjasn.org Vol 18 February, 2022



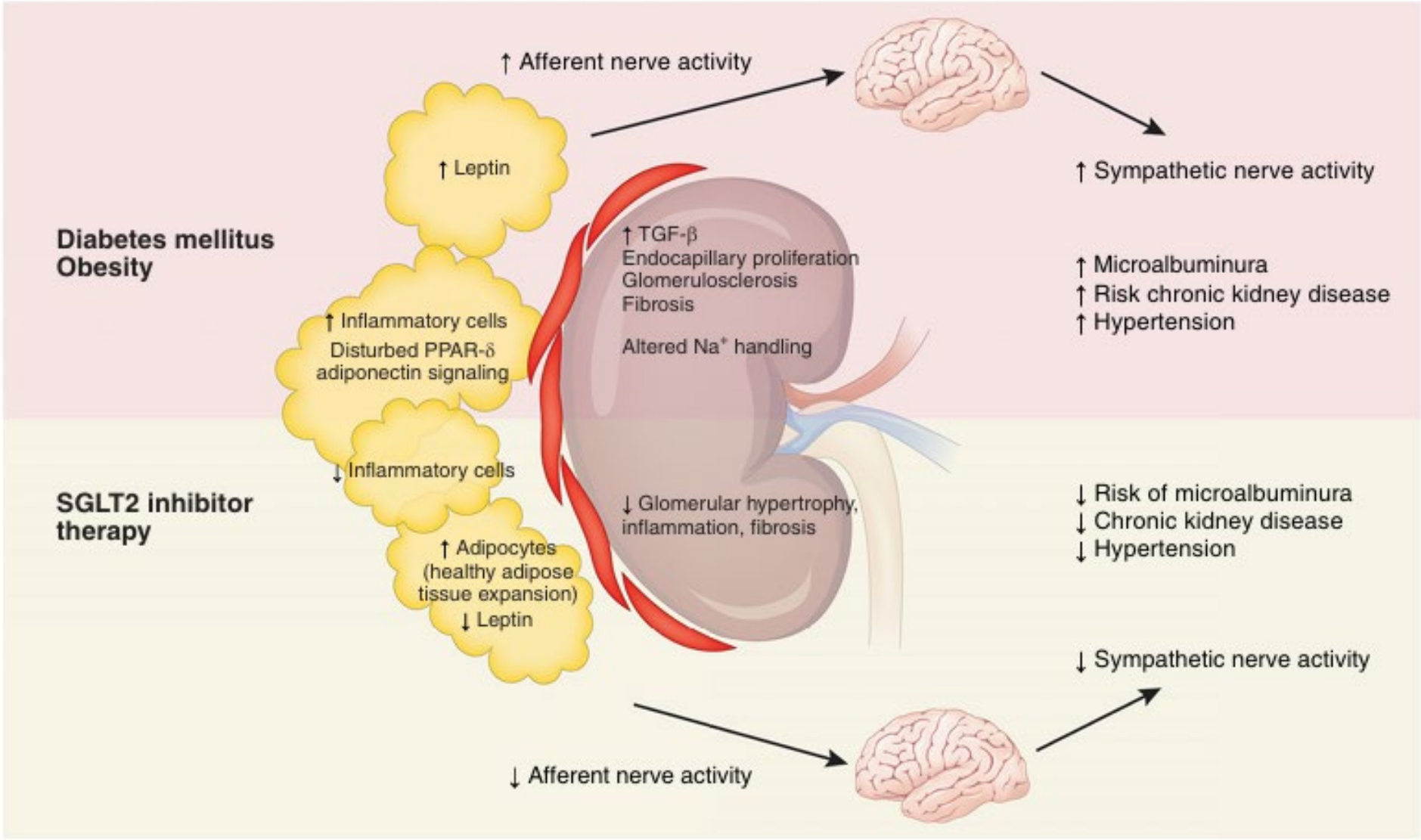
American Journal of Cardiovascular Drugs
https://doi.org/10.1007/s40256-024-00673-1

SGLT2 inhibitors

- Adipocyte effect
- Modulatory effect
- Nephro effect
- POND effect
- Reverse metabolism effect

Reduction of the BMI and Effect on Adipose Tissue ("adipocyte effect")

- Urinary energy loss of 200–250 kcal daily.
- Mean weight reduction of approximately 2 kg (range 1.7–2.9 kg) at least 12 weeks of treatment.
- Decrease in adipose tissue mass
- Reductions in hepatic, perivisceral, pericardial, and perivascular fat accumulation
- Decreased leptin production and enhanced insulin sensitivity, increased adiponectin levels
- Attenuating obesity-related inflammation



SGLT2 inhibition has favorable effects on perirenal fat

www.cjasn.org Vol 18 February, 2022

Reduction of Blood Pressure, Heart Rate, and Circulating Volume, with an Increase in Natriuresis ("modulatory effect")

- Consistent blood pressure reduction: 4 mmHg systolic and 2 mmHg diastolic
- Decreased circulating volume
- weight loss, modulation of the RAAS, and uric acid reduction
- An average urinary volume increase of 300 ml, enhanced natriuresis
- Reduction in plasma volume of approximately 7%
- The use of SGLT2i with loop diuretics increases urine volume (stronger effect at higher doses and in older adults)

- No increase in heart rate, a slight decrease in sympathetic tone.
- Regulate blood pressure through inhibition of the central sympathetic nervous system.
- SGLT2 is expressed in brain regions associated with autonomic control.
- Modulating catecholaminergic neurons within the nucleus tractus solitarii (NTS).
- Both SGLT2 and SGLT1 inhibitors might contribute to this antihypertensive effect by attenuating SNS activity

Vasoconstriction of the Afferent Glomerular Arteriole, Reduction of Albuminuria, and Increase in hematocrit (“nephro effect”)

Renal disease progression involves three primary axes:

- Hemodynamic
- Metabolic
- inflammatory

Hemodynamic axis

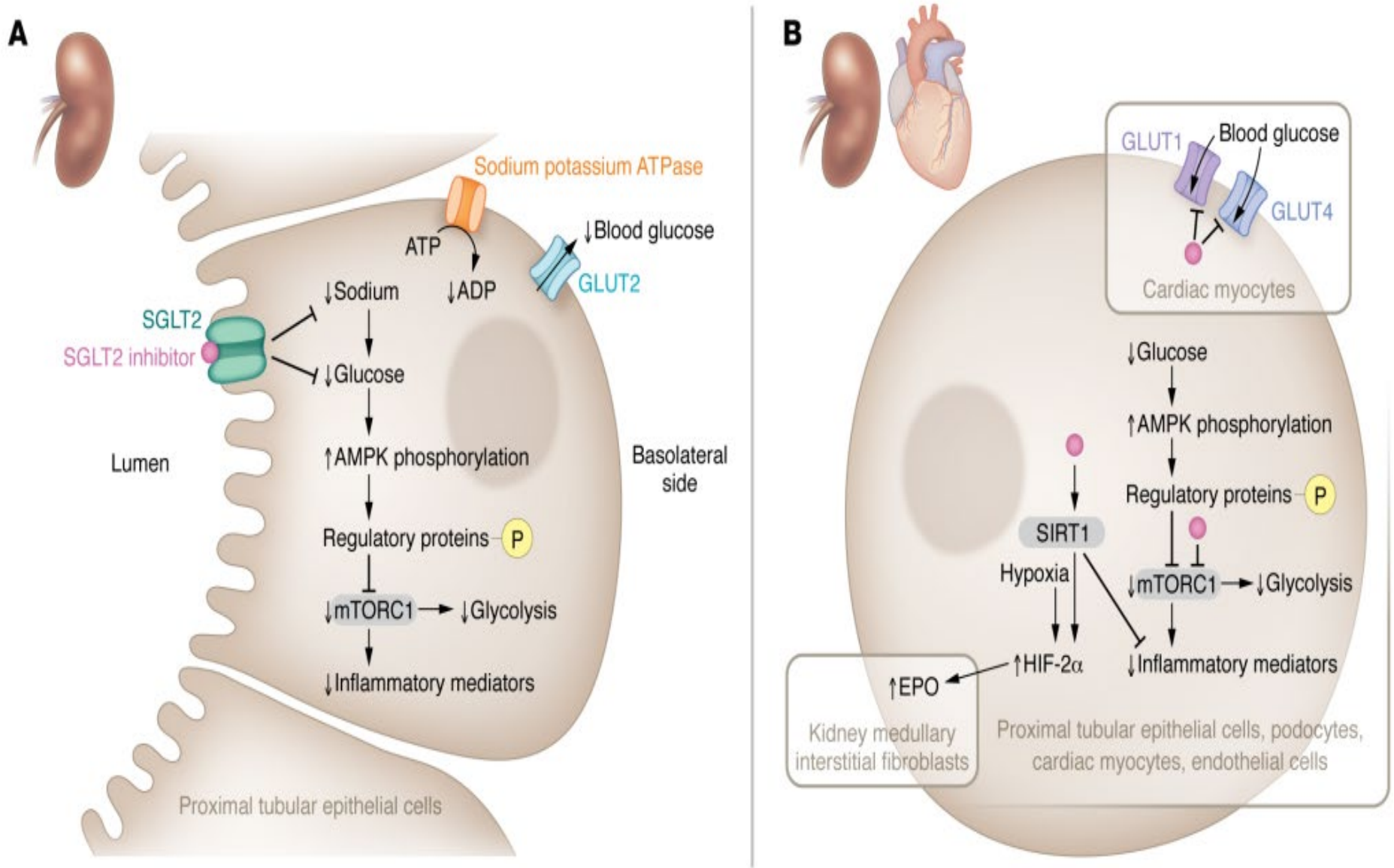
- Transient decline in GFR of approximately 5 ml/min/1.73 m2 (not reflect true renal dysfunction)
- It is reversible within 2-4 weeks
- long-term nephroprotective benefits
- SGLT2-inhibitor-induced diuresis can transiently elevate hematocrit
- protect against renal congestion
- Reduction in albuminuria, an effect more pronounced in patients with higher baseline albuminuria levels

Inflammatory axis

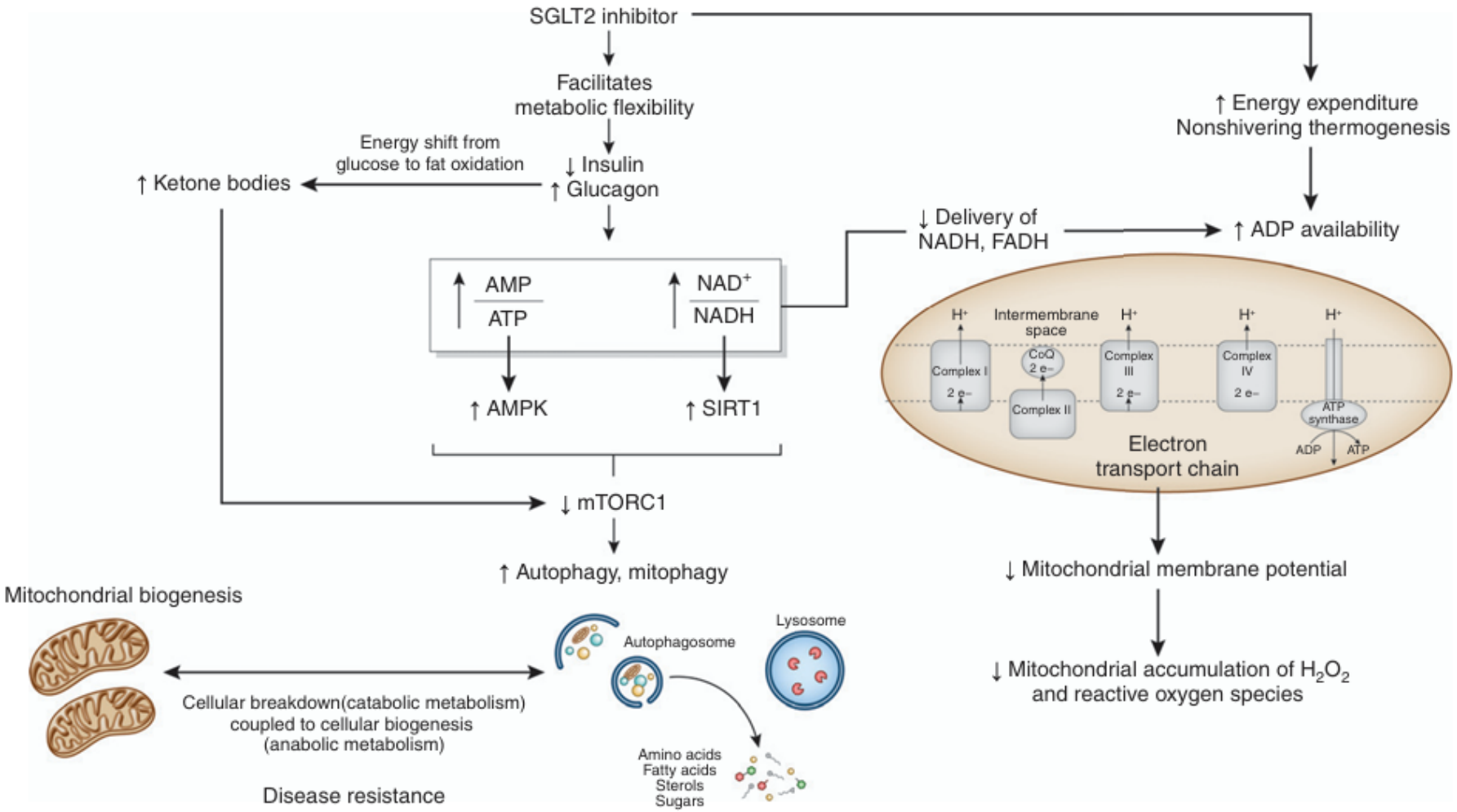
- Anti-inflammatory effects in the kidney.
- Suppresses the production of inflammatory mediators, such as cytokines and chemokines, and reduces local glycolysis.
- Contribute to the overall cardiorenal protective effects of SGLT2 inhibitor

Receptor-mediated pathways

Non- Receptor-mediated pathways



SGLT2 inhibitors mediate kidney-protective effects via receptor- and non-receptor-mediated pathways.



SGLT2is improve metabolic flexibility

www.cjasn.org Vol 18 February, 2022

Reduction of inflammation, Blood Uric Acid Levels, and Vascular Aging ("POND effect")

Inflammation:

- Reduce levels of interleukin-6, TNF, NF-kB, and C-reactive protein (NF-kB lead to increased inflammatory mediators and macrophage accumulation in fatty tissues)
- Reduction of inflammatory markers in the mitochondria

Uric acid:

- Induce a state of starvation mimicry, characterized by a molecular, cellular, and physiological response resembling nutrient deprivation.
- marked by glycosuria, ketogenesis, and upregulation of nutrient deprivation signaling (SIRT1) while downregulating nutrient surplus signaling (mTOR and HIF-1α)

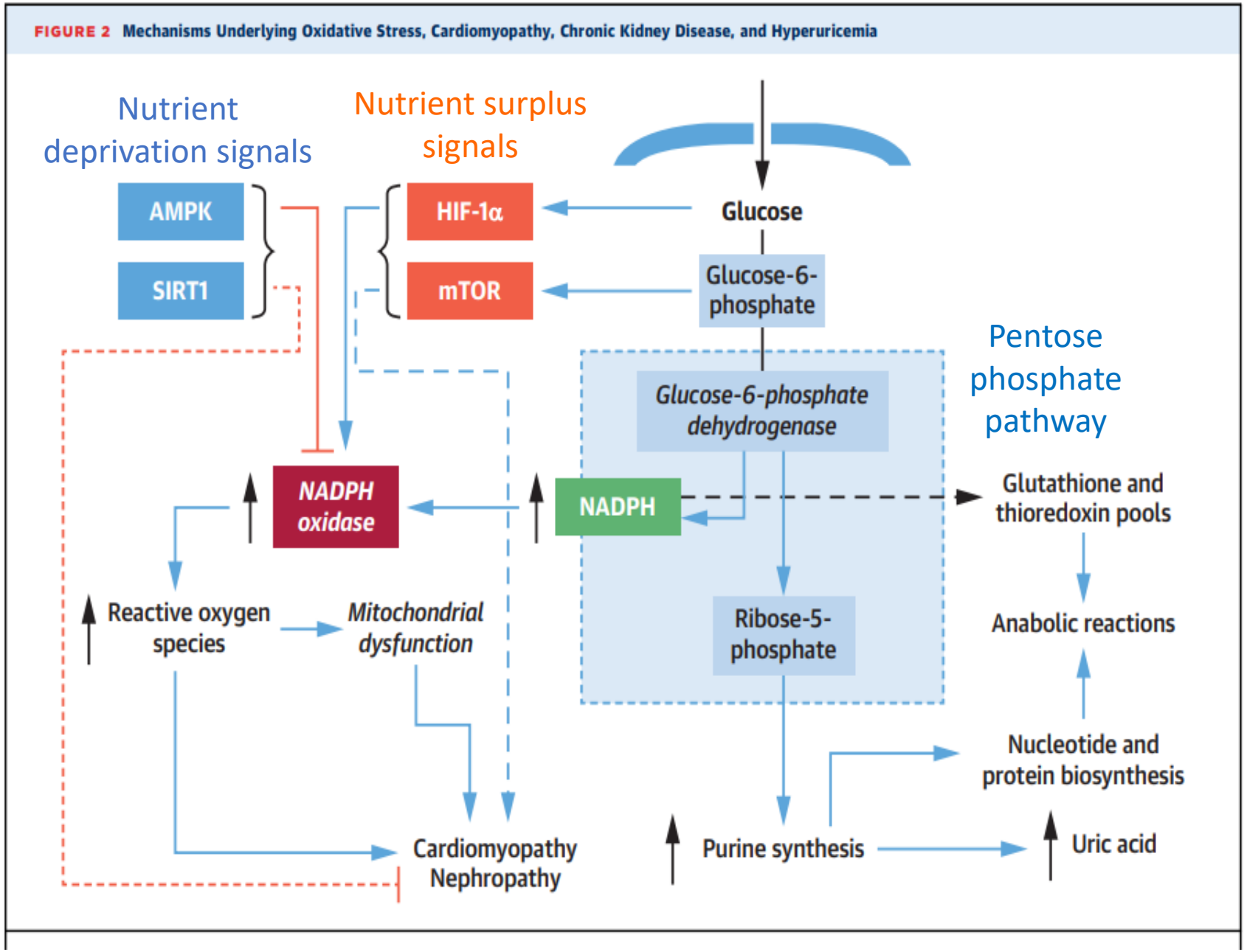
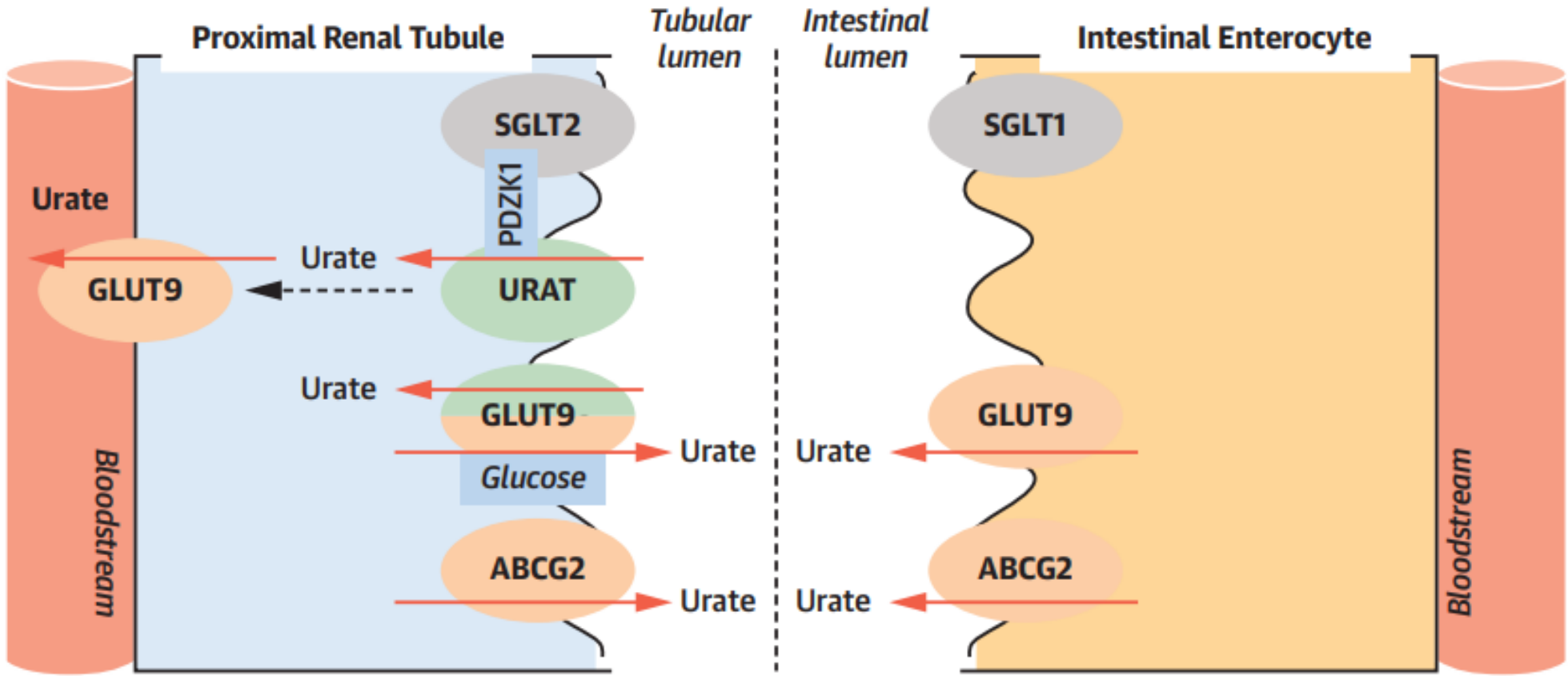


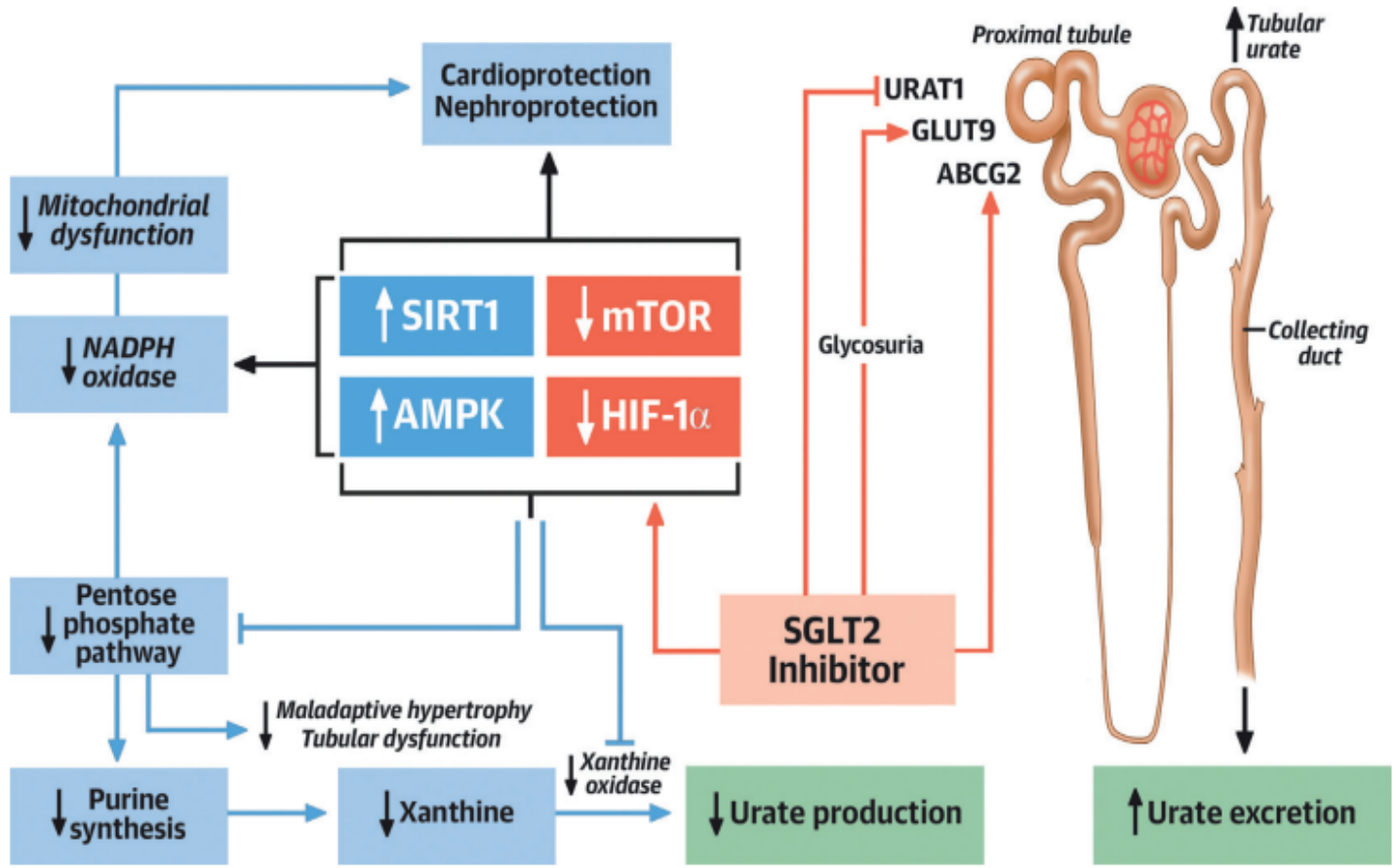
FIGURE 2 Mechanisms Underlying Oxidative Stress, Cardiomyopathy, Chronic Kidney Disease, and Hyperuricemia
Nutrient deprivation signals
Nutrient surplus signals
AMPK
SIRT1
HIF-1α
mTOR
Glucose
Glucose-6-phosphate
Pentose phosphate pathway
Glucose-6-phosphate dehydrogenase
NADPH oxidase
NADPH
Glutathione and thioredoxin pools
Reactive oxygen species
Mitochondrial dysfunction
Ribose-5-phosphate
Anabolic reactions
Nucleotide and protein biosynthesis
Cardiomyopathy
Nephropathy
Purine synthesis
Uric acid

FIGURE 4 Urate Transporters in the Proximal Renal Tubule and Intestinal Enterocyte



Proximal renal tubule and intestinal enterocyte are depicted in blue and dark yellow, respectively. Wavy lines indicate luminal surface. ABCG = adenosine triphosphate-binding cassette subfamily G member; GLUT = glucose transporter; SGLT = sodium-glucose cotransporter; URAT = urate transporter.

CENTRAL ILLUSTRATION **Mechanisms by Which Sodium-Glucose Cotransporter-2 Inhibitors Influence Urate Production and Excretion**



Packer M, J Am Coll Cardiol. 2024;83(2):371-381.

Nutrient surplus signals and nutrient deprivation signals are shown in orange and blue hexagons, respectively. ABCG = adenosine triphosphate–binding cassette subfamily G member; AMPK = adenosine monophosphate protein-activated protein kinase; GLUT = glucose transporter; HIF-1α = hypoxia-inducible factor 1 subunit alpha; mTOR = mammalian target of rapamycin; NADPH = nicotinamide adenine dinucleotide phosphate; SGLT = sodium-glucose cotransporter; SIRT1 = sirtuin-1; URAT = urate transporter.

- uric acid levels decreased by 0.6–1.5 mg/dl
- Uric acid is recognized as a factor that increases oxidative stress, promotes activation of the RAAS axis, and increases smooth muscle tone, leading to endothelial cell apoptosis with a consequent decrease in nitric oxide levels
- The reduced production and increased excretion of uric acid linked to their cardio-, and nephroprotective effects

Vascular aging:

- T2DM: decrease in circulating bone-marrow-derived progenitors, such as endothelial progenitor cells (EPCs), linked to the development and progression of micro- and macrovascular complications
- SGLT2 inhibitors: a direct influence on EPCs, leading to increased EPC concentrations
- Improved progenitor cell-mediated repair
- May reverse alterations in angiogenesis contribute to cardiac remodeling, mitigating cardiac microvascular damage

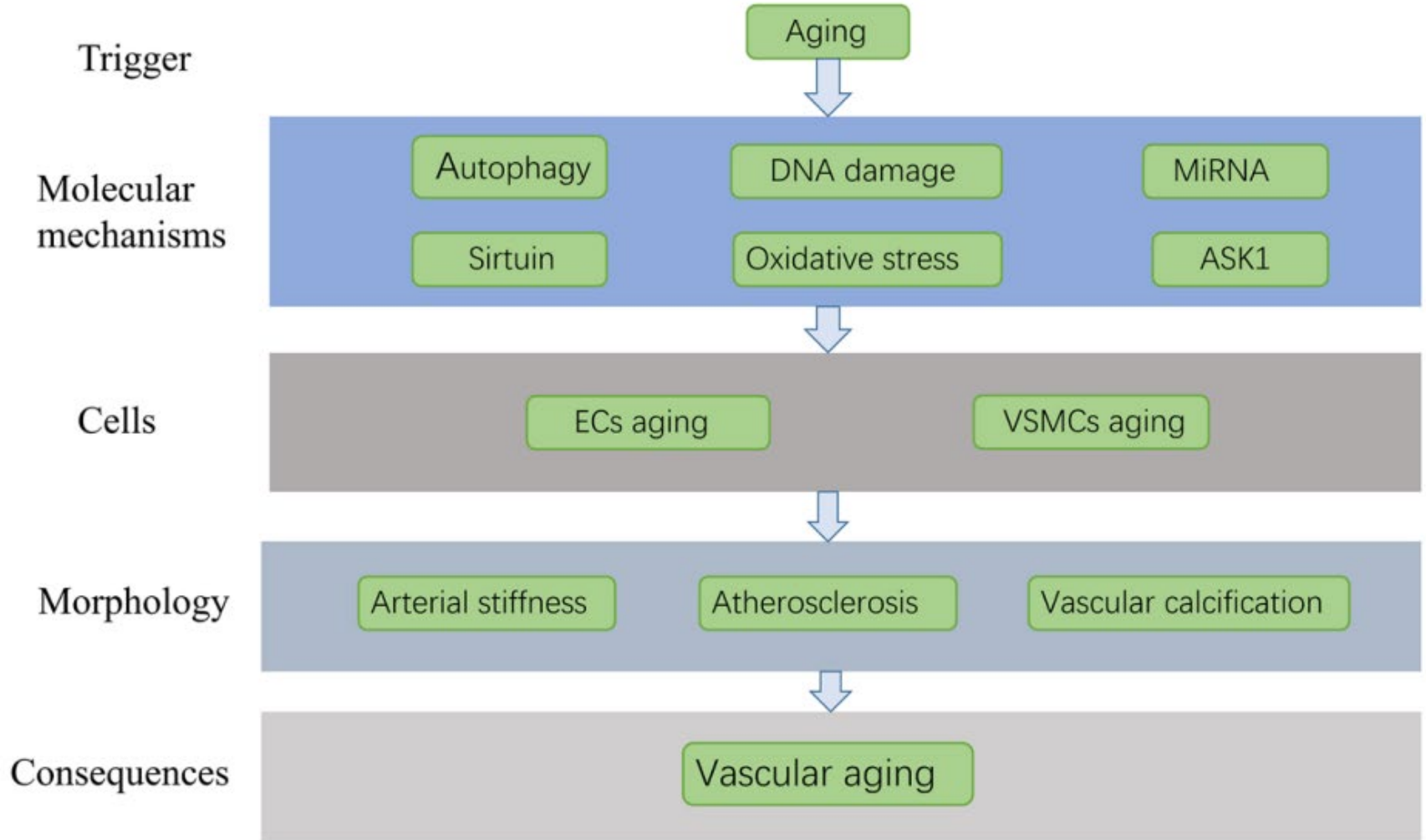


Figure 1. The mechanism of vascular aging.

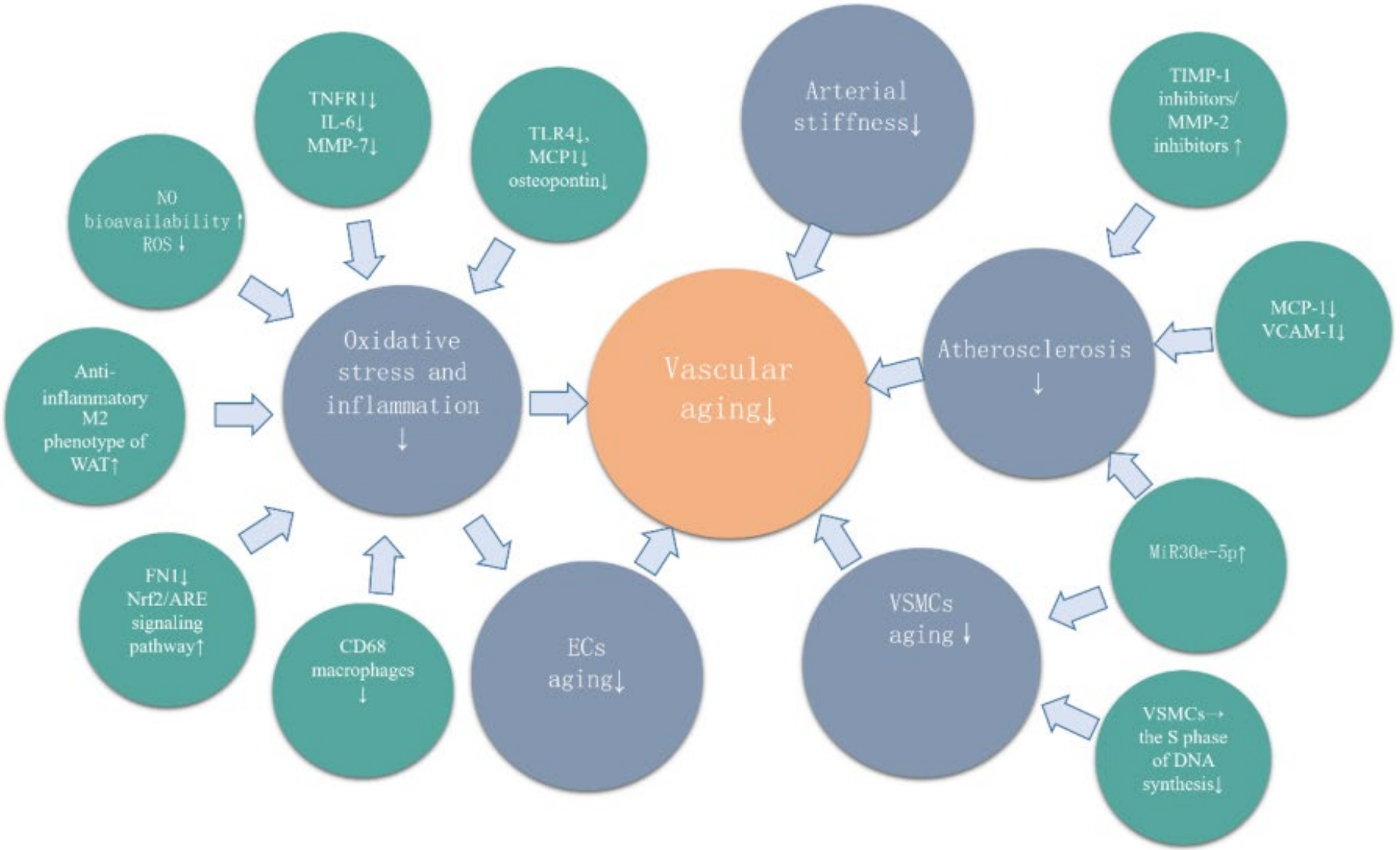


Figure 2. The effect of SGLT2 inhibitor on vascular aging.

Ketone Production, Decreased Na+/H+ Exchange in the Myocardium, Normalization of Nutrient Transport, and Iron Metabolism ("reverse metabolism effect")

Increased Ketone Production and Lipid Oxidation:

- Relative hypoglycemia
- lower insulin/glucagon ratio
- promotes ketogenesis Through Increased lipid oxidation
- Reduced intracellular lipid metabolites (Reversing lipotoxicity)

Increased ketone body supply induced by SGLT2 inhibitors, coupled with their potential to modulate local proinflammatory pathways and lipid autophagy: optimize cardiomyocyte function

Na+/H+ Exchange:

NHE1

- Heart

elevated NHE activity: oxidative stress and arrhythmogenic mechanisms

NHE3

- Kidney (with SGLT2 in early prox tubule)

SGLT2 inhibition affecting NHE3 activity

Cardioprotective and Reno protective effects

SGLT2 Inhibitors, Iron, and Hematopoiesis:

Iron metabolism

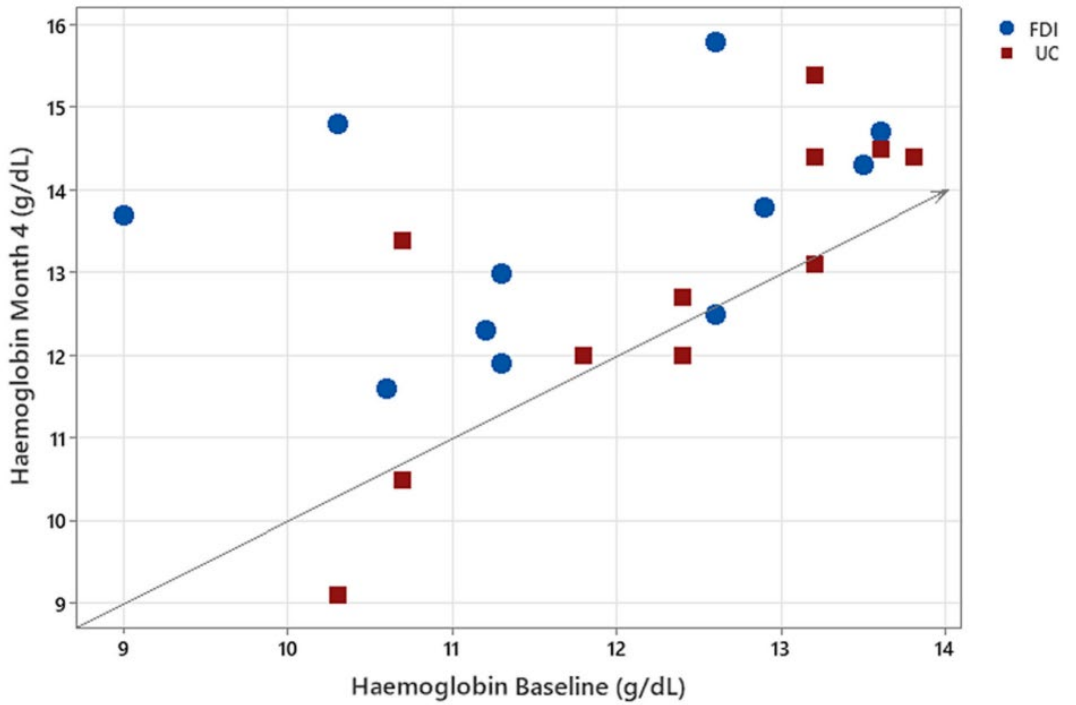
- Enhance iron utilization
- DAPA-HF study: reducing hepcidin and ferritin levels while increasing transferrin receptors in HF patients
- Empire HF trial, IRONMAN trial: greater increase in hemoglobin using SGLT2 inhibitors

Intravenous iron and SGLT2 inhibitors in iron-deficient patients with heart failure and reduced ejection fraction

Kieran F. Docherty[1], John J.V. McMurray[1], Paul R. Kalra[2,3], John G.F. Cleland[1], Ninian N. Lang[1], Mark C. Petrie[1], Michele Robertson[4] and Ian Ford[4]*

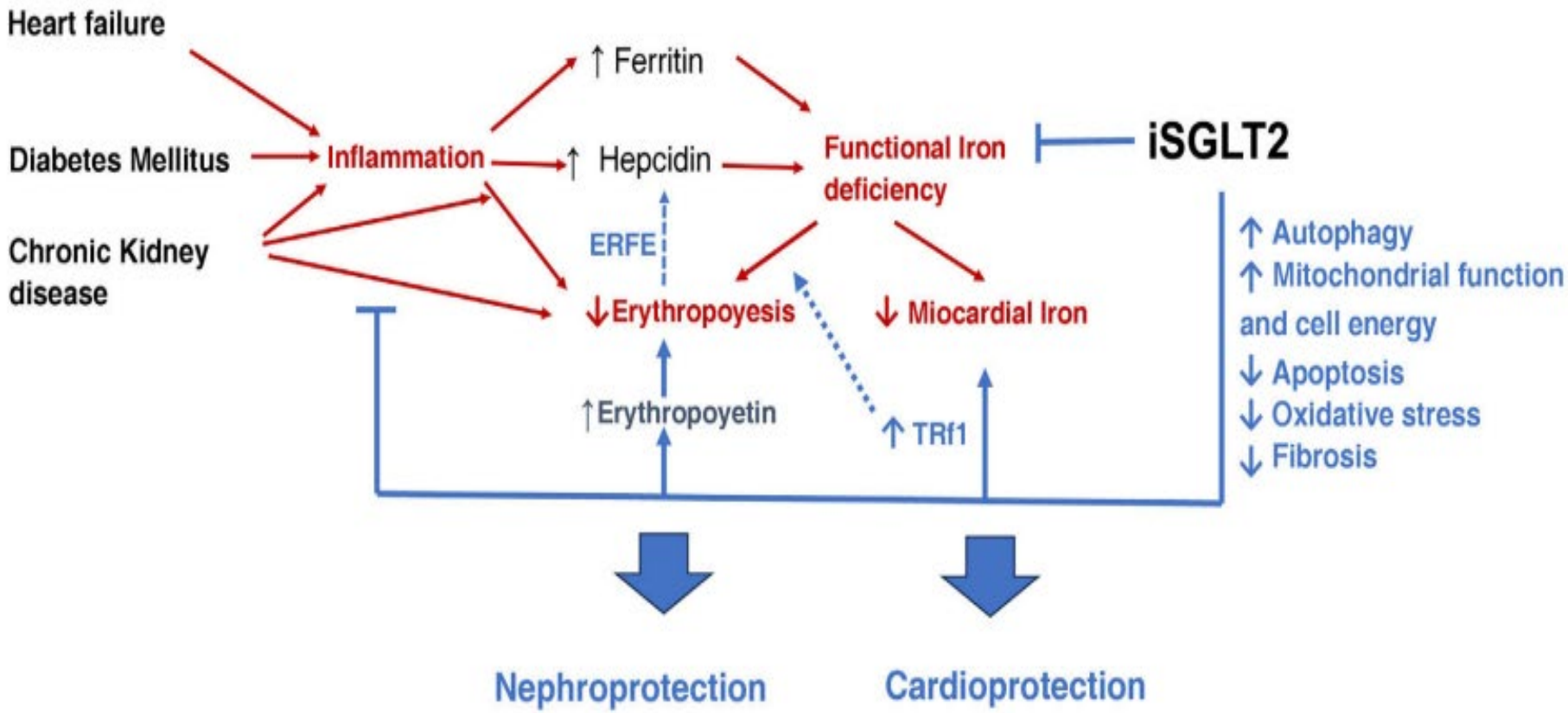
Conclusions In the IRONMAN trial, there was a trend to a greater increase in haemoglobin with ferric derisomaltose in iron-deficient patients taking an SGLT2 inhibitor at baseline, as compared with those not taking one.

Figure 1 Individual patient changes in haemoglobin at 4 months according to randomized treatment group in patients taking an SGLT2 inhibitor at baseline. FDI, ferric derisomaltose; UC, usual care.



Indirectly influence erythropoiesis

- Reducing ATP consumption via the Na+/ K+ pump
- Diminishing hypoxia in the microenvironment
- Facilitate the reversion of myofibroblasts back into erythropoietin-producing fibroblasts, leading to enhanced hematopoiesis and elevated hematocrit



Beneficial effects of SGLT2i beyond the increase in erythropoiesis. Indirect effects on kidney and heart

ne f rologia. 2 0 2 4;44(2):165–172

Reverse metabolism effect

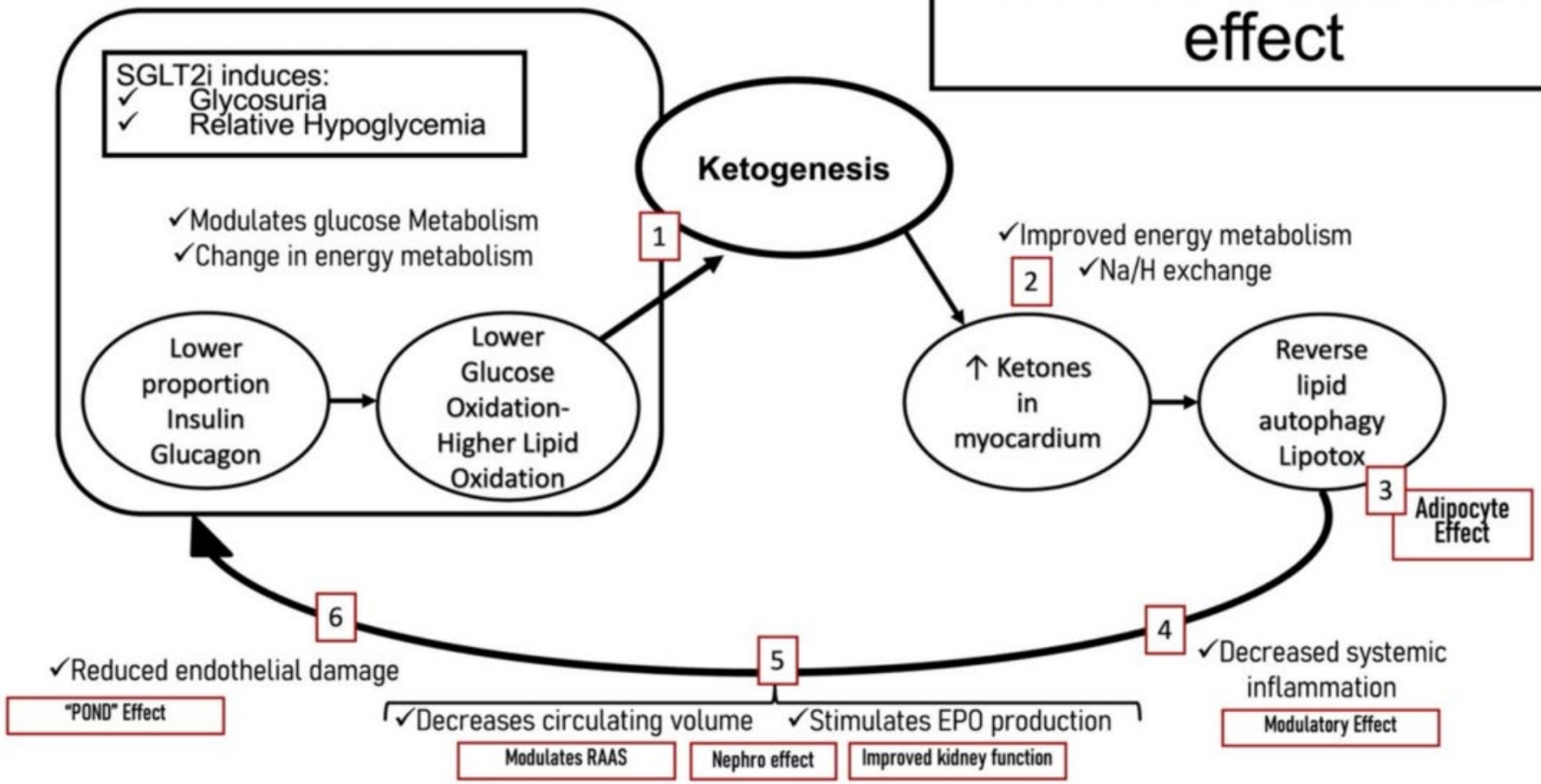


Table 1. Kidney-protective effects of sodium-glucose cotransporter 2 inhibitors

Protective Effect	Mechanism	Comment
Hemodynamic benefits	Increased tubuloglomerular feedback; increased delivery of NaCl to macula densa causes adenosine-mediated vasoconstriction of the afferent arteriole and lowers intraglomerular pressure; efferent vasodilation may predominate in type 2 diabetes mellitus in the setting of renin-angiotensin blockade	A 3- to 6-ml/min reduction in GFR is common in first 2–3 wks of therapy caused by reduction in intraglomerular pressure; increased pressure in Bowman's space may also contribute to the early eGFR decline
Improved glycemic control	Reduction in TM leads to glycosuria, the glucose-lowering effect diminishes as plasma glucose level declines and/or GFR falls due to diminished filtered load	In clinical trials, HgA_{1c} decreases by 0.6%–1.0% versus placebo; the glycosuric effect is no longer evident as eGFR approaches 30–40 ml/min
Decreased glucose flux across cell	Decreased proximal tubular cell glucose entry limits abnormally high rates of glycolysis, potentially limiting kidney fibrosis	Increased glycolysis linked to the activation of HIF1α and the suppression of Sirt3 and increased epithelial-mesenchymal transition, activation of NLRP3 inflammasome
Natriuresis	Inhibition of SGLT2 is accompanied by reduced NHE3 activity, plasma volume is reduced	Contributes to the 4/2–mm Hg reduction in BP, tissue-bound Na^+ is also reduced, despite reduced BP and plasma volume heart rate is not increased consistent with decreased sympathetic outflow
Perirenal fat	Decreased paracrine release of adipokines and proinflammatory cytokines	Decreased leptin release decreases central afferent input and lowers sympathetic outflow, albuminuria and glomerular injury are decreased
Weight loss	Urinary glucose loss corresponding to 200–400 kcal/d, increased energy expenditure associated with beiging of adipocytes	Visceral and subcutaneous fat mass is reduced likely to include perirenal fat, increases in fibroblast growth factor 21 contributes to reduction in fat mass
Improved metabolic flexibility	Loss of glucose in urine leads to a fasting-like state with a decreased insulin-glucagon ratio and increased ketogenesis	Decreased respiratory exchange ratio reflects increased fat oxidation, mTORC1 is suppressed and autophagy is restored in tubular cells and podocytes
Decreased tubular workload	Decrease Na^+ entry into proximal tubular cell reduces ATP and O_2 consumption	SGLT2is are associated with less risk of AKI
Increase hemoglobin concentration (3%)	Increased O_2 consumption to reabsorb Na^+ in downstream segments result in ↑ erythropoietin production	Hypoxia stimulates HIF2α, causing ↑ autophagy and ↓ inflammation
Increase plasma magnesium (Mg^{2+})	↑ glucagon and PTH stimulate Mg^{2+} reabsorption in thick limb, upregulation of TRPM6/7 in DCT	SGLT2is may be useful in Mg^{2+} wasting disorders, decreased risk of arrhythmias and risk of diabetes mellitus
Decrease plasma uric acid	Increased tubular glucose competes with uric acid for reabsorption *via* GLUT9	Reduction in risk of gout flares, decreased risk of CKD due to hyperuricemia
Decrease risk of hyperkalemia from RAASi	Increased flow and Na^+ delivery augment K^+ secretion in the distal nephron	SGLT2is alone have minimal effects on plasma K^+ concentration

www.cjasn.org Vol 18 February, 2022

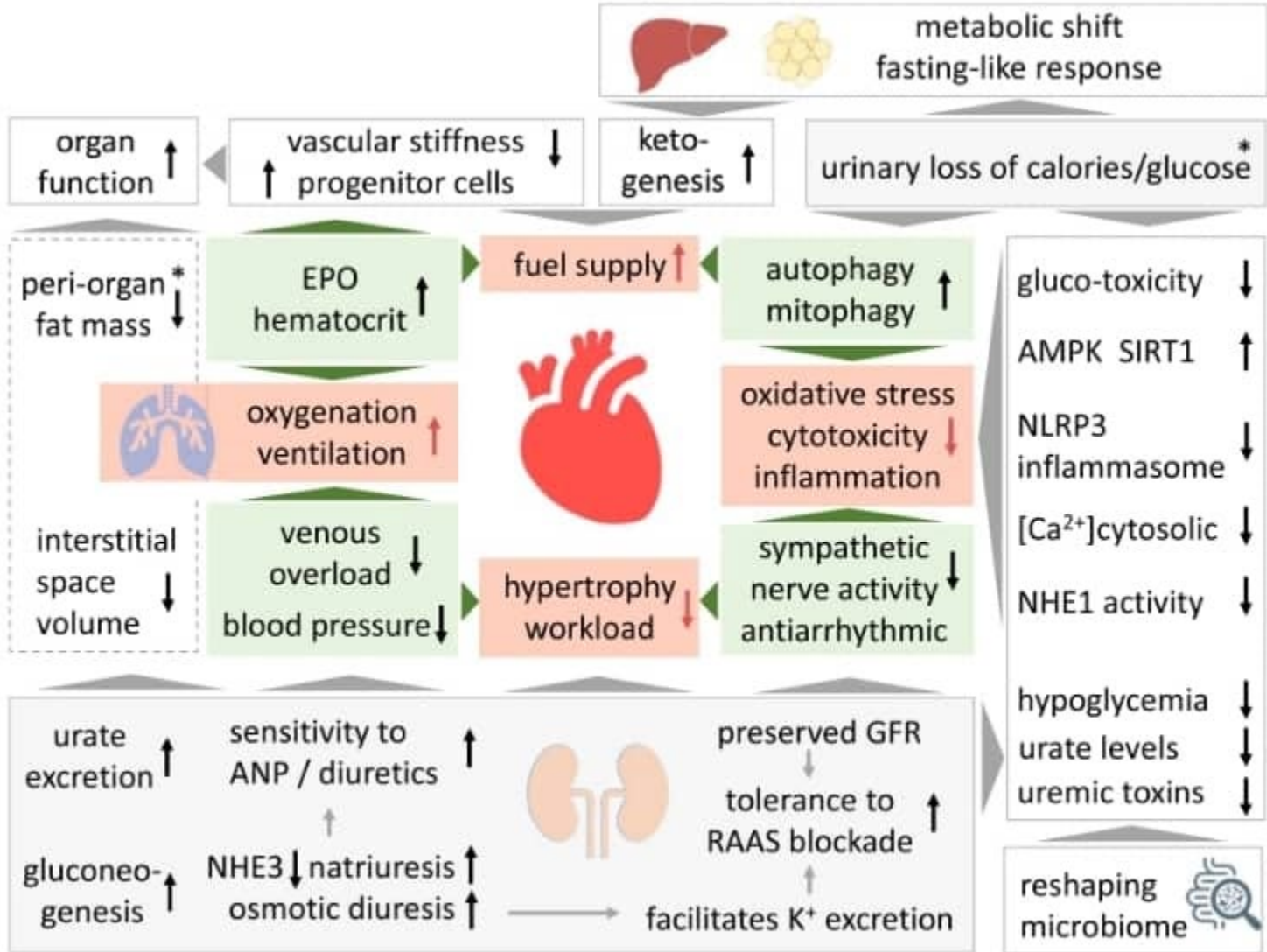


Figure 3: Potential cardioprotective effects of SGLT2i. SGLT2i enhance the cardiac oxygen and fuel supply while simultaneously reducing cardiac workload and cytotoxic and proinflammatory influences. The involved mechanisms are illustrated. Recent data link SGLT2i to less formation of microbiome-derived uremic toxins like p-cresol, which is cardiotoxic. Asterisks (*) denote urinary loss of calories and glucose enhances lipolysis and thereby reduces peri-organ fat mass. AMPK, AMP-activated protein kinase; ANP, atrial natriuretic peptide; SIRT1, Sirtuin 1. Adapted with permission from [7].

Table 2. Practical considerations in prescribing sodium-glucose cotransporter 2 inhibitors

An acute and transient decline in eGFR is common in the first several weeks of therapy[a]

- A decline of <30% does not warrant discontinuation
- A decline of >30% should prompt the following
  - *Assess volume status and consider a decreased dose of diuretics*
  - *Discontinue prescribed or over-the-counter nonsteroidal anti-inflammatory drugs*
  - *A reversible tubular toxicity due to osmotic injury (osmotic nephrosis) can rarely occur* (31)

Hold SGLT2i in the setting of acute illness causing depletion of extracellular fluid volume (decreased intake, vomiting, and/or diarrhea)

Symptomatic drop in BP

- Consider a decrease in dose of diuretics
- Avoid down titration of renin-angiotensin-aldosterone blockers

Hypoglycemia

- More likely to occur with eGFR >60 ml/min
- Consider a 10%–20% decrease in insulin dose or decrease in the dose of sulfonylurea in collaboration with the endocrinologist
- Risk attenuates as eGFR declines and is nonexistent at eGFR <30 ml/min

Given the long-term benefits, every effort should be made to maintain patients on SGLT2i therapy

SGLT2i, sodium-glucose cotransporter 2 inhibitor.

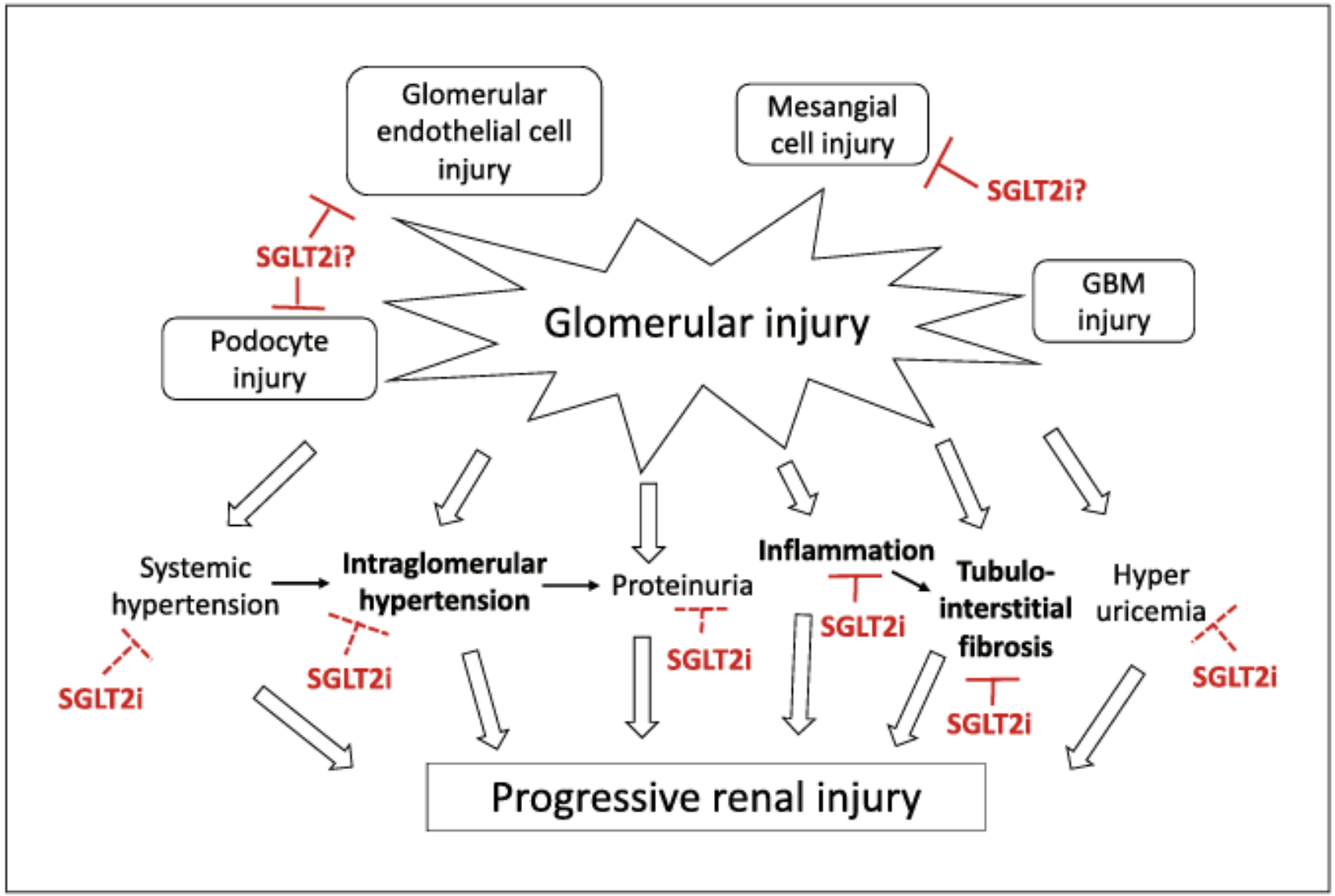
[a]The approach is similar to changes in eGFR following initiation of renin-angiotensin blockers (32).

SGLT2 inhibitors in autoimmune disease

- Patients with autoimmune diseases, a population known to be at high risk for cardiovascular and renal-related morbidity and mortality, could also benefit from SGLT2 inhibitors.
- Interested in the rheumatology community
- Large-scale studies have repeatedly identified the renoprotective benefits of SGLT2 inhibitors when added to RAAS blockade, the current standard of care, in chronic kidney disease with proteinuria.

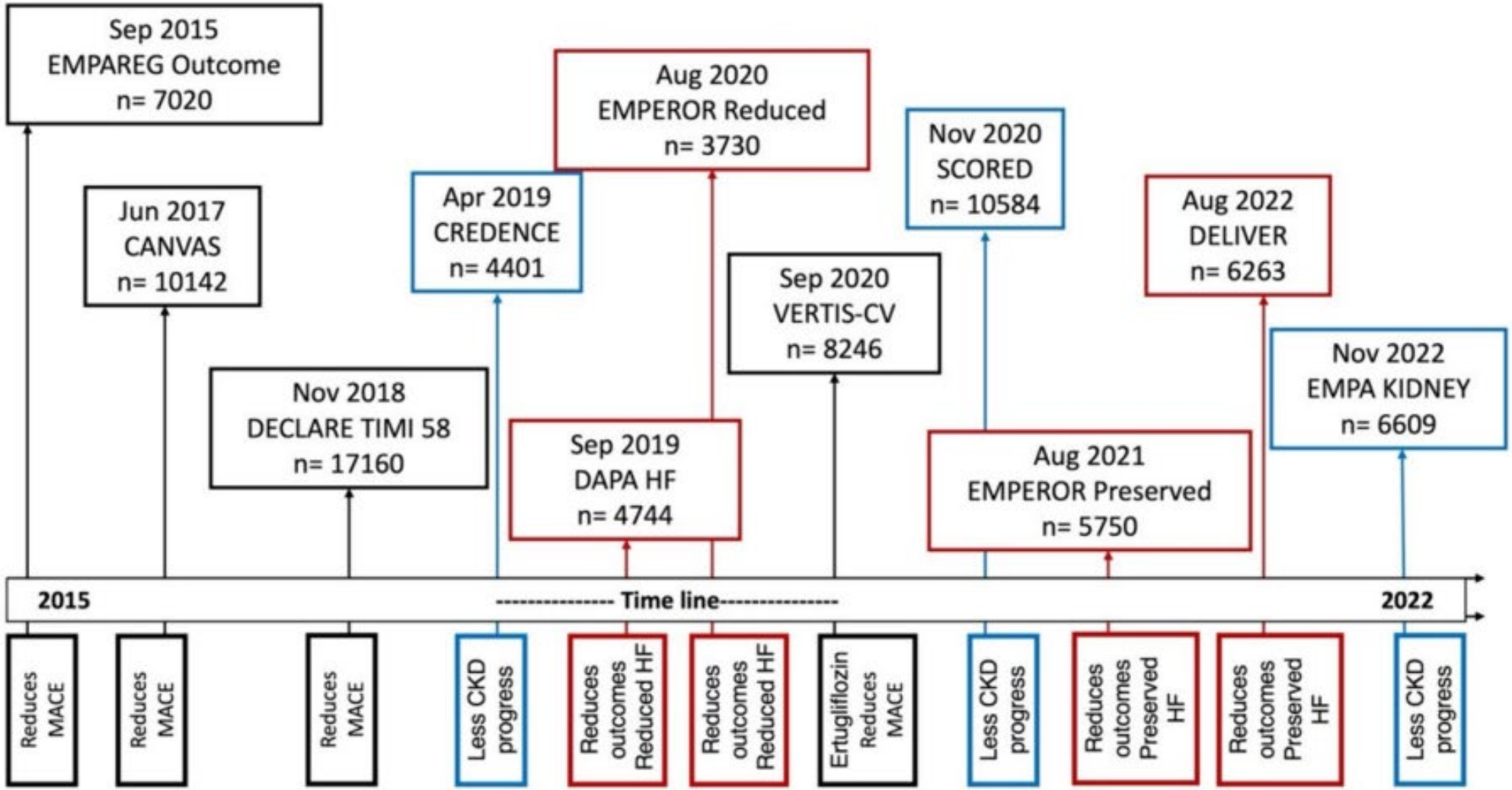
SGLT2 inhibitors decrease inflammation

- Decrease polarization of macrophages and decrease infiltration
- Decrease NLRP3 inflammasome activation
- Reduce oxidative stress and adipose tissue-mediated inflammation
- Suppress secretion of pro-inflammatory cytokines from endothelial cells (IL-17, IFNg)
- Altering T cell-mediated processes (inhibit T cell activation and T cell proliferation via downregulation of mTORC1)
- Decreased podocyte damage in experimental models of lupus nephritis (less foot process effacement, less inflammasome activation and increased autophagy)



Potential Renoprotective mechanisms of SGLT2i in nondiabetic glomerular disease.

Glomerular Dis 2021;1:21–33 DOI: 10.1159/000513659



Timeline of the main clinical trials of the SGLT2i. In black the clinical trials of cardiovascular safety, in blue those of renal outcomes, and in red those of cardiac outcomes. MACE major adverse cardiac events, CKD chronic kidney disease, HF heart failure

American Journal of Cardiovascular Drugs
https://doi.org/10.1007/s40256-024-00673-1

CREDENCE trial in diabetic kidney disease

EMPA-KIDNEY in both diabetic and non-diabetic kidney disease

DAPA-KIDNEY in both diabetic and non-diabetic kidney disease

slows CKD progression and reduces cardiovascular mortality

Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial

David Z I Cherney, Claire C J Dekkers*, Sean J Barbour, Daniel Cattran, Abdul Halim Abdul Gafor, Peter J Greasley, Gozewijn D Laverman, Soo Kun Lim, Gian Luca Di Tanna, Heather N Reich, Marc G Vervloet, Muh Geot Wong, Ron T Gansevoort, Hiddo J L Heerspink, for the DIAMOND investigators*

Summary

Background SGLT2 inhibition decreases albuminuria and reduces the risk of kidney disease progression in patients with type 2 diabetes. These benefits are unlikely to be mediated by improvements in glycaemic control alone. Therefore, we aimed to examine the kidney effects of the SGLT2 inhibitor dapagliflozin in patients with proteinuric kidney disease without diabetes.

Methods DIAMOND was a randomised, double-blind, placebo-controlled crossover trial done at six hospitals in Canada, Malaysia, and the Netherlands. Eligible participants were adult patients (aged 18–75 years) with chronic kidney disease, without a diagnosis of diabetes, with a 24-h urinary protein excretion greater than 500 mg and less than or equal to 3500 mg and an estimated glomerular filtration rate (eGFR) of at least 25 mL/min per 1·73 m², and who were on stable renin–angiotensin system blockade. Participants were randomly assigned (1:1) to receive placebo and then dapagliflozin 10 mg per day or vice versa. Each treatment period lasted 6 weeks with a 6-week washout period in between. Participants, investigators, and study personnel were masked to assignment throughout the trial and analysis. The primary outcome was percentage change from baseline in 24-h proteinuria during dapagliflozin treatment relative to placebo. Secondary outcomes were changes in measured GFR (mGFR; via iohexol clearance), bodyweight, blood pressure, and concentrations of neurohormonal biomarkers. Analyses were done in accordance with the intention-to-treat principle. This study is registered with ClinicalTrials.gov, NCT03190694.

Interpretation 6-week treatment with dapagliflozin did not affect proteinuria in patients with chronic kidney disease without diabetes, but did induce an acute and reversible decline in mGFR and a reduction in bodyweight. Long-term clinical trials are underway to determine whether SGLT2 inhibitors can safely reduce the rate of major clinical kidney outcomes in patients with chronic kidney disease with and without diabetes.

Nephrol Dial Transplant, 2024, 39, 328–340
https://doi.org/10.1093/ndt/gfad175
Advance access publication date: 7 August 2023

Sodium-glucose cotransporter 2 inhibition in primary and secondary glomerulonephritis

ABSTRACT

Background. The role of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in the management glomerular/systemic autoimmune diseases with proteinuria in real-world clinical settings is unclear.

Methods. This is a retrospective, observational, international cohort study. Adult patients with biopsy-proven glomerular diseases were included. The main outcome was the percentage reduction in 24-h proteinuria from SGLT2i initiation to 3, 6, 9 and 12 months. Secondary outcomes included percentage change in estimated glomerular filtration rate (eGFR), proteinuria reduction by type of disease and reduction of proteinuria ≥30% from SGLT2i initiation.

Results. Four-hundred and ninety-three patients with a median age of 55 years and background therapy with renin–angiotensin system blockers were included. Proteinuria from baseline changed by –35%, –41%, –45% and –48% at 3, 6, 9 and 12 months after SGLT2i initiation, while eGFR changed by –6%, –3%, –8% and –10.5% at 3, 6, 9 and 12 months, respectively. Results were similar irrespective of the underlying disease. A correlation was found between body mass index (BMI) and percentage proteinuria reduction at last follow-up. By mixed-effects logistic regression model, serum albumin at SGLT2i initiation emerged as a predictor of ≥30% proteinuria reduction (odds ratio for albumin <3.5 g/dL, 0.53; 95% CI 0.30–0.91; $P = .02$). A slower eGFR decline was observed in patients achieving a ≥30% proteinuria reduction: –3.7 versus –5.3 mL/min/1.73 m^2/year ($P = .001$). The overall tolerance to SGLT2i was good.

Conclusions. The use of SGLT2i was associated with a significant reduction of proteinuria. This percentage change is greater in patients with higher BMI. Higher serum albumin at SGLT2i onset is associated with higher probability of achieving a ≥30% proteinuria reduction.

KEY LEARNING POINTS

What was known:

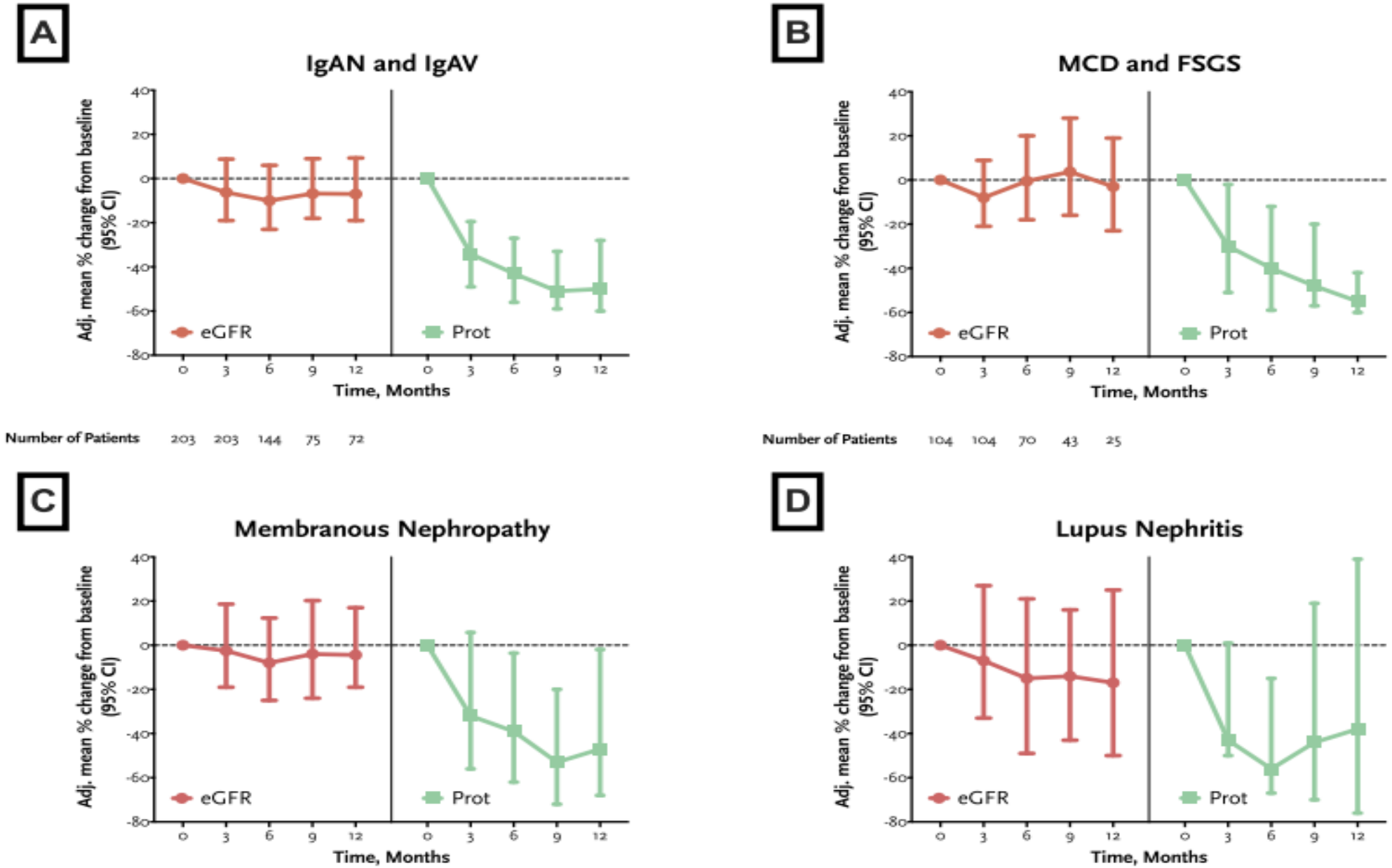
- Recent sub-analyses of some of the large trials performed with sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with diabetes have shown that the association between reduction in albuminuria and long-term nephroprotection is also applicable to SGLT2i.
- SGLT2i started to be used in glomerular and systemic autoimmune diseases with glomerular involvement for the treatment of persistent residual proteinuria, in combination with conventional renin–angiotensin system blockade.
- Information on the antiproteinuric efficacy of SGLT2i in real-world clinical practice is scarce, particularly in several non-diabetic glomerular and systemic autoimmune diseases.

This study adds:

- Proteinuria from baseline changed by −35%, −41%, −45% and −48% at 3, 6, 9 and 12 months after SGLT2i initiation, irrespective of underlying glomerular disease.
- A large number of patients (69%) achieved a ≥30% proteinuria reduction, and an association was found between serum albumin at SGLT2i initiation, and the likelihood of achieving this outcome.
- A significant trend for a slower eGFR decline over time was observed in those patients who achieved a ≥30% proteinuria reduction.

Potential impact:

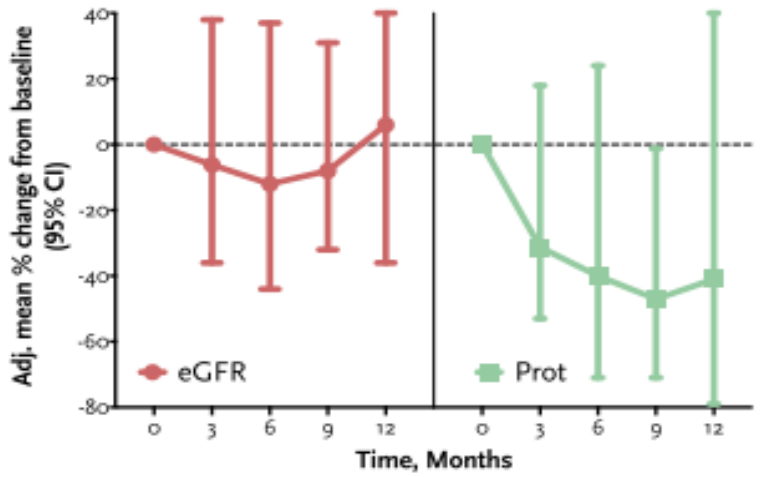
- Our data suggest that the clinical profile of patients with glomerular or systemic autoimmune diseases with persistent residual proteinuria who might benefit most from SGLT2i would be those with serum albumin ≥3.5 g/dL and those with higher body mass index.
- Those patients who achieved a ≥30% proteinuria reduction have a slower eGFR decline over time.
- Patients with a serum albumin <3.5 g/dL at the time of SGLT2i initiation are less likely to achieve an antiproteinuric response ≥30% during follow-up.



Adjusted mean percentage change of eGFR and proteinuria (Prot) from baseline according to underlying glomerular/systemic disease:

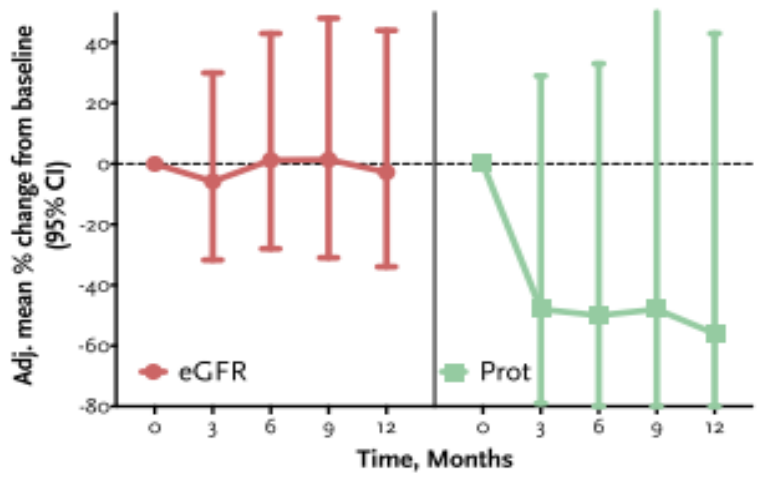
Nephrol Dial Transplant, 2024, 39, 328–340

E



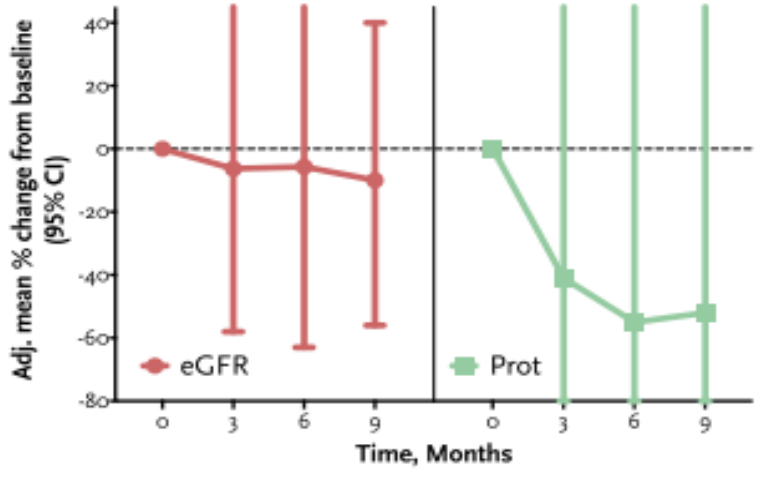
Number of Patients	23	23	13	9	5

F



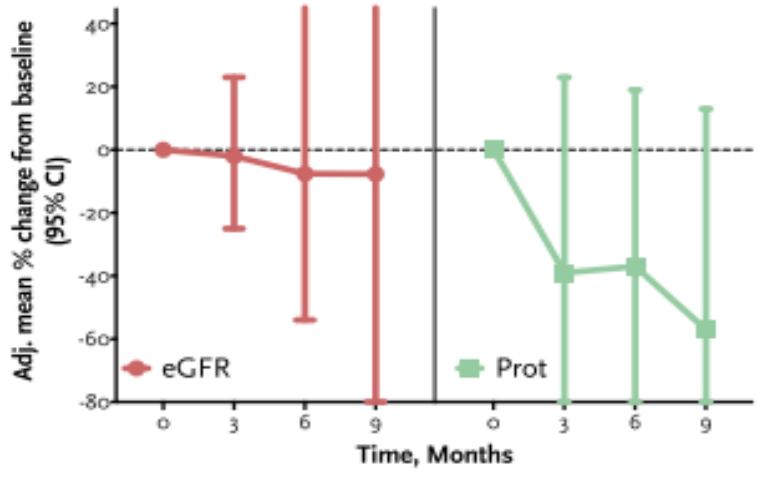
Number of Patients	22	22	17	10	8

G

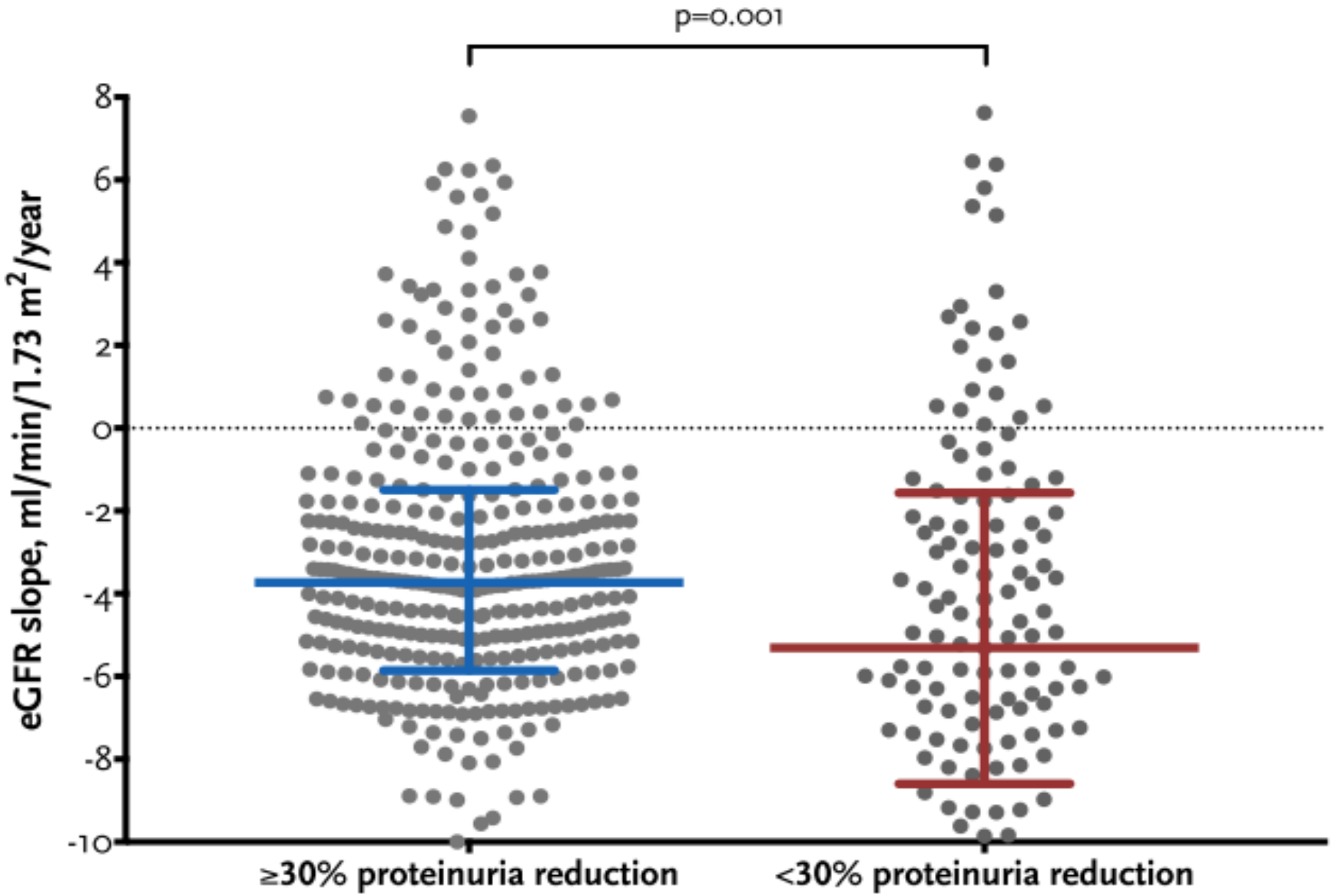


Number of Patients	8	8	5	5

H



Number of Patients	6	6	6	4



eGFR slopes according to the achievement of a proteinuria reduction ≥30% or <30% overtime

Nephrol Dial Transplant, 2024, 39, 328–340

serum albumin would help discriminate between patients with residual proteinuria preferentially due to hyperfiltration (who would respond better to RAS blockade or SGLT2i) from those with greater impairment of glomerular perm selectivity in the setting of other pathogenic mechanisms (who would have a more limited response to RAS blockade or SGLT2i).

Lupus nephritis

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Safety and efficacy of the SGLT2 inhibitor dapagliflozin in patients with systemic lupus erythematosus: a phase I/II trial

Methods We conducted a single-arm, open-label, investigator-initiated phase I/II trial of dapagliflozin in Chinese patients with SLE with/without lupus nephritis (LN). Patients received oral dapagliflozin at a daily dose of 10 mg added to the standard of care for 6 months. The primary end point was the safety profile. The secondary efficacy end points were composite assessments of disease activity.

Results A total of 38 eligible patients were enrolled. Overall, 19 (50%) adverse events (AEs) were recorded, including 8 (21%) AEs leading to drug discontinuation, of which 4 (10.5%) were attributed to dapagliflozin. Two serious AEs (one of major lupus flare and one of fungal pneumonia) were recorded. Lower urinary tract infection was observed in one (2.63%) patient. The secondary end points revealed no improvement of SLE Disease Activity Index scores or proteinuria (among 17 patients with LN); the cumulative lupus flare rate was 18%, and a reduction of ~30% in the prednisone dose was captured. Net changes in body mass index (−0.50 kg/m^2), systolic blood pressure (−3.94 mm Hg) and haemoglobin levels (+8.26 g/L) were detected. The overall estimated glomerular filtration rate (eGFR) was stable, and there was an improvement in the eGFR slope among patients with LN with a baseline eGFR <90 mL/min/1.73 m^2.

Conclusion Dapagliflozin had an acceptable safety profile in adult patients with SLE. Its possible renal/cardiac protective effects and long-term safety issues in patients with SLE, patients with LN in particular, call for further exploration.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Increased glucose metabolism in immune cells has been reported in patients with systemic lupus erythematosus (SLE), and metabolic modulation approaches have become a hot spot in the management of SLE.

⇒ Sodium-glucose cotransporter-2 inhibitors (SGLT2is) exert profound renal and cardiac protective effects in different human diseases.

WHAT THIS STUDY ADD

⇒ This phase I/II trial showed an acceptable safety profile of dapagliflozin add-on therapy in adult patients with SLE.

⇒ No effects in terms of reduced disease activity or proteinuria among patients with LN were detected.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ SGLT2is, as a possible adjunct treatment for renal/cardiac protection in patients with SLE, patients with LN in particular, warrant further properly designed larger-scale, placebo-controlled trials.

Table 1. Studies of SGLT2 inhibitors in patients with lupus and lupus nephritis

Study	Patient population	SGLT2 inhibitor	Follow up	Conclusions
Wang *et al.* RMD Open 2022 [23▪▪]	38 patients with lupus Included 17 patients with active lupus nephritis defined as proteinuria >0.5 g/24 h at entry	Dapagliflozin 10 mg daily	6 months	12/38 patients (31.58%) had adverse events attributed to dapagliflozin, although only two adverse events were severe. No significant change in SLEDAI scores. Proteinuria in patients with lupus nephritis remained unchanged. GFR remained stable. Mean prednisone dose was decreased by approximately 30%.
Morales and Galindo, *Ann Rheum Dis* 2022 [24]	Five patients with biopsy-proven lupus nephritis	Empagliflozin 10 mg daily	2 months	Mean proteinuria decreased from 2.2 g/day to 1.2 g/day No significant changes in GFR.
Zhao *et al.*, *Ann Rheum Dis* 2023 [25▪▪]	Nine patients with biopsy-proven lupus nephritis	Various SGLT2 inhibitors including dapagliflozin 10 mg daily, canagliflozin 100 mg daily, ertugliflozin 5 mg daily	2 months	Proteinuria decreased by 29.6–96.3% GFR was stable over treatment period.

Starting SGLT2 inhibitors at the same time as immunosuppression can lead to clinical confusion	The expectant drop in eGFR with initiation of SGLT2 inhibition may lead the clinician to erroneously believe that initial immunosuppression is not effective
	The initiation of multiple medications, all with a myriad of side effects, can lead to confusion in teasing out any adverse events
	The clinician must be conscious of the pill burden and difficulties with medication compliance

- Metabolism of SGLT- 2i is via simple hepatic glucuronidation and no interference occurs with P450 enzymes or P- glycoprotein pathways via which most immunosuppressive agents are metabolized
- Potential effects of SGLT2 inhibitors on complications of SLE: pulmonary hypertension, metabolic syndrome, and increased BP

patients with mild to moderate decreases in eGFR, particularly those with high levels of proteinuria

patients have completed initial intensive immunosuppressive treatment, are receiving maintenance doses of immunosuppression

SGLT2 inhibitors should be started after the standard of care therapy with ACE inhibitors

Delayed until it can be done safely with the lowest risk for side effects to ensure they can be utilized in the long term (more benefits in long term use)

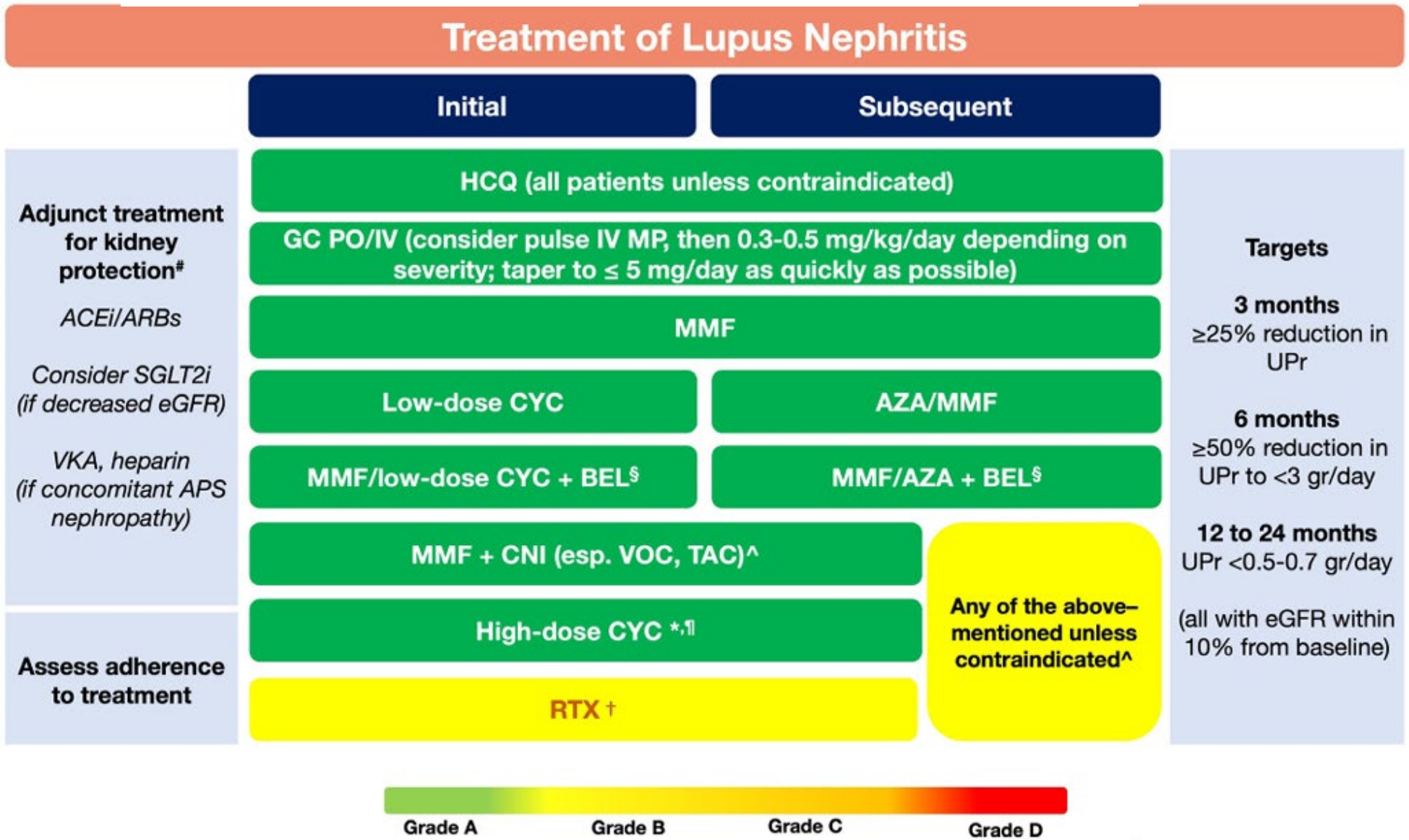
Table 2. Potential side effects of SGLT2 inhibitors

Side effect	High-risk population
Genitourinary infections, including urinary tract infection, candida infections and rare cases of Fournier's gangrene	Patients with known risk factors for genitourinary infections including concomitant immunosuppression
Diabetic ketoacidosis	Any history of diabetic ketoacidosis
Hypotension/volume depletion	Concomitant use of blood pressure medications and/or diuretics Population at risk for being unable to drink sufficient fluids
Fragility fractures	Any other risk factors for osteoporosis including high dose steroid use
Lower limb amputation	Avoid use in patients with severe neuropathy, peripheral vascular disease or foot ulcerations which carry higher risks for amputation

EULAR recommendations for the management of systemic lupus erythematosus: 2023 update

- Novel classes of agents, mainly sodium-glucose transport 2 (SGLT- 2) inhibitors (‘flozins’), have gained attention as kidney protective drugs for any case of CKD
- SGLT-2 is expressed in kidney biopsies of patients with LN and its targeting seems reasonable.
- SGLT-2 inhibitors may be considered in patients with LN with reduced GFR below 60–90 mL/min or proteinuria more than 0.5–1 g/day, on top of ACE/ARBi during the maintenance phase. The final recommendation received 92.8% agreement and the mean (SD) LoA was 9.85 (0.36).

EULAR recommendations for the management of systemic lupus erythematosus: 2023 update

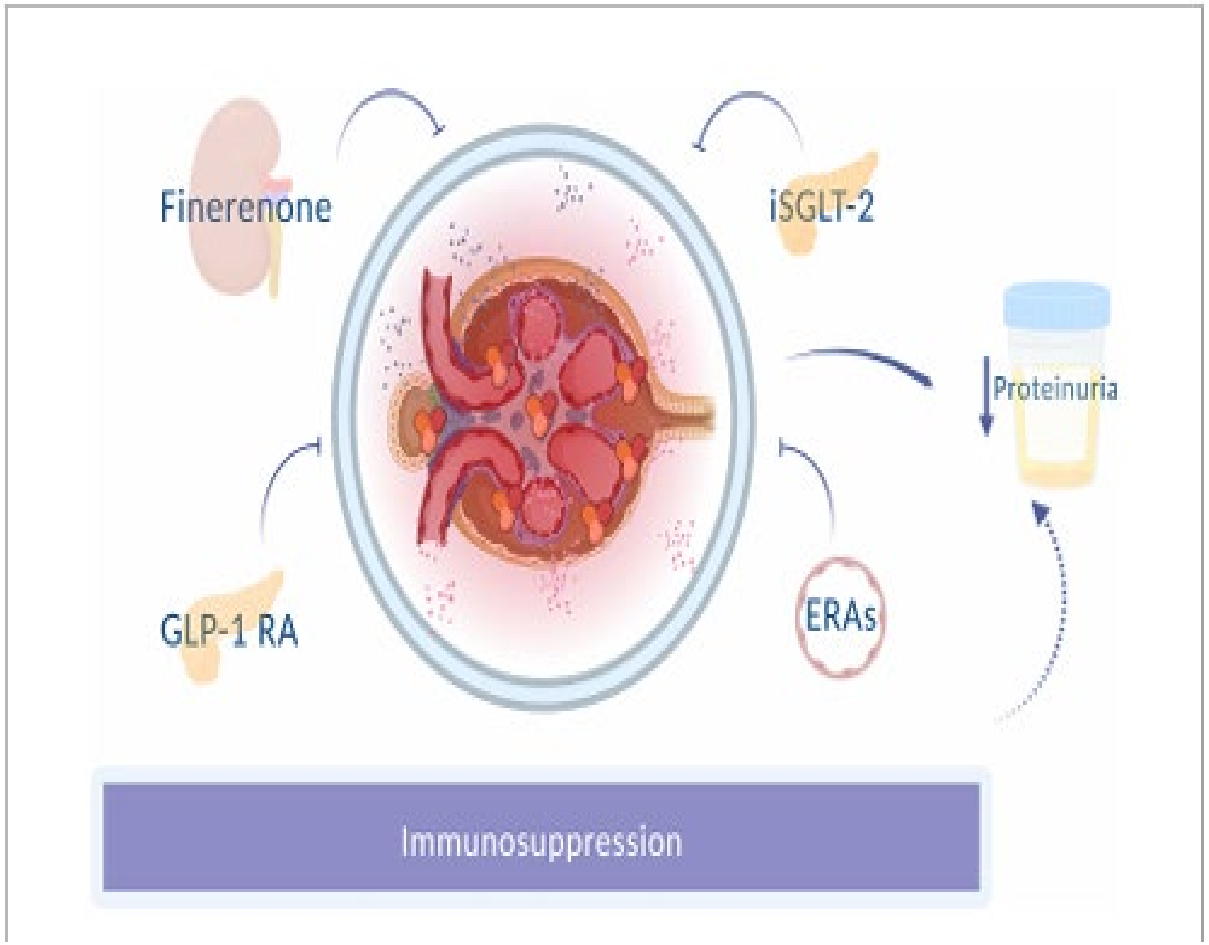


Fanouriakis A, et al. Ann Rheum Dis 2023;0:1–15. doi:10.1136/ard-2023-224762

Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis

OPEN

- Management of patients with LN must include not only immunosuppression for acute treatment of active LN, but also measures to slow or stop CKD progression.
- Blood pressure control, renin-angiotensin-aldosterone system blockade, flare prevention, and nephrotoxin avoidance, it is likely to expand in the future as data on LN and sodium-glucose cotransporter-2 inhibitors or other new agents such as endothelin-A receptor blockers become available.



Novel nephron-protective strategies in lupus nephritis.

Frontiers in nephrology, 2023,
10.3389/fneph.2023.1105676

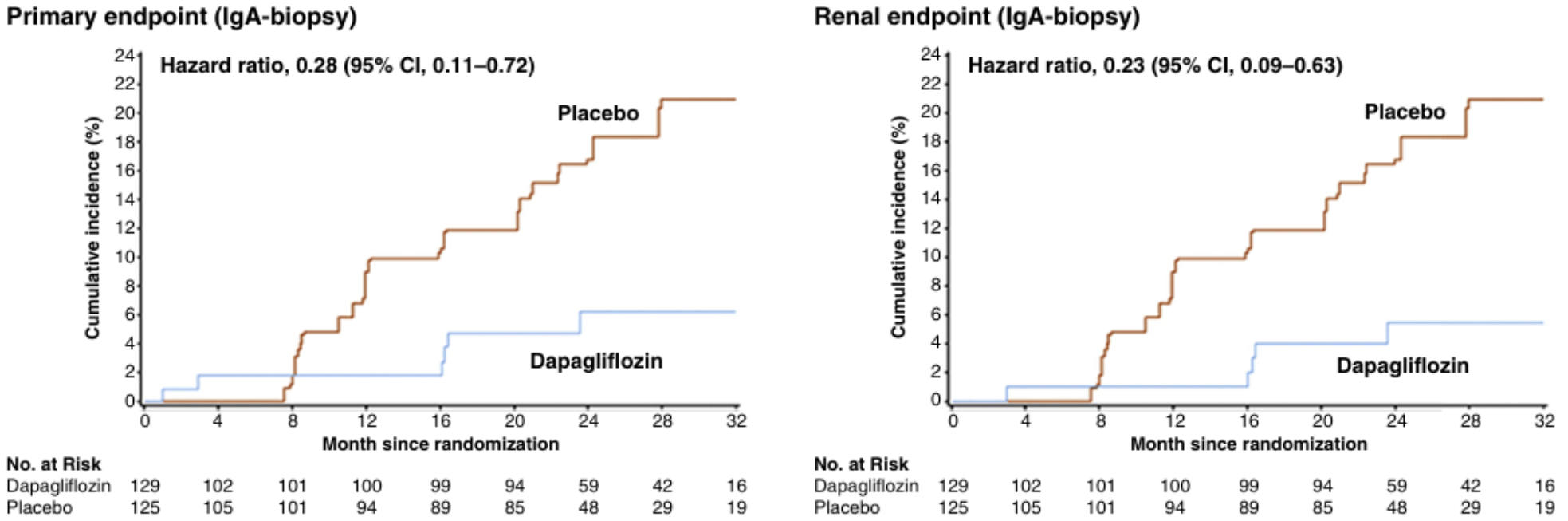
IgA nephropathy

A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy

see commentary on page 24

OPEN

270 participants with IgA nephropathy with significant disease chronicity



a sustained decline in eGFR of 50% or more, end-stage kidney disease, or death from a kidney disease-related or cardiovascular cause

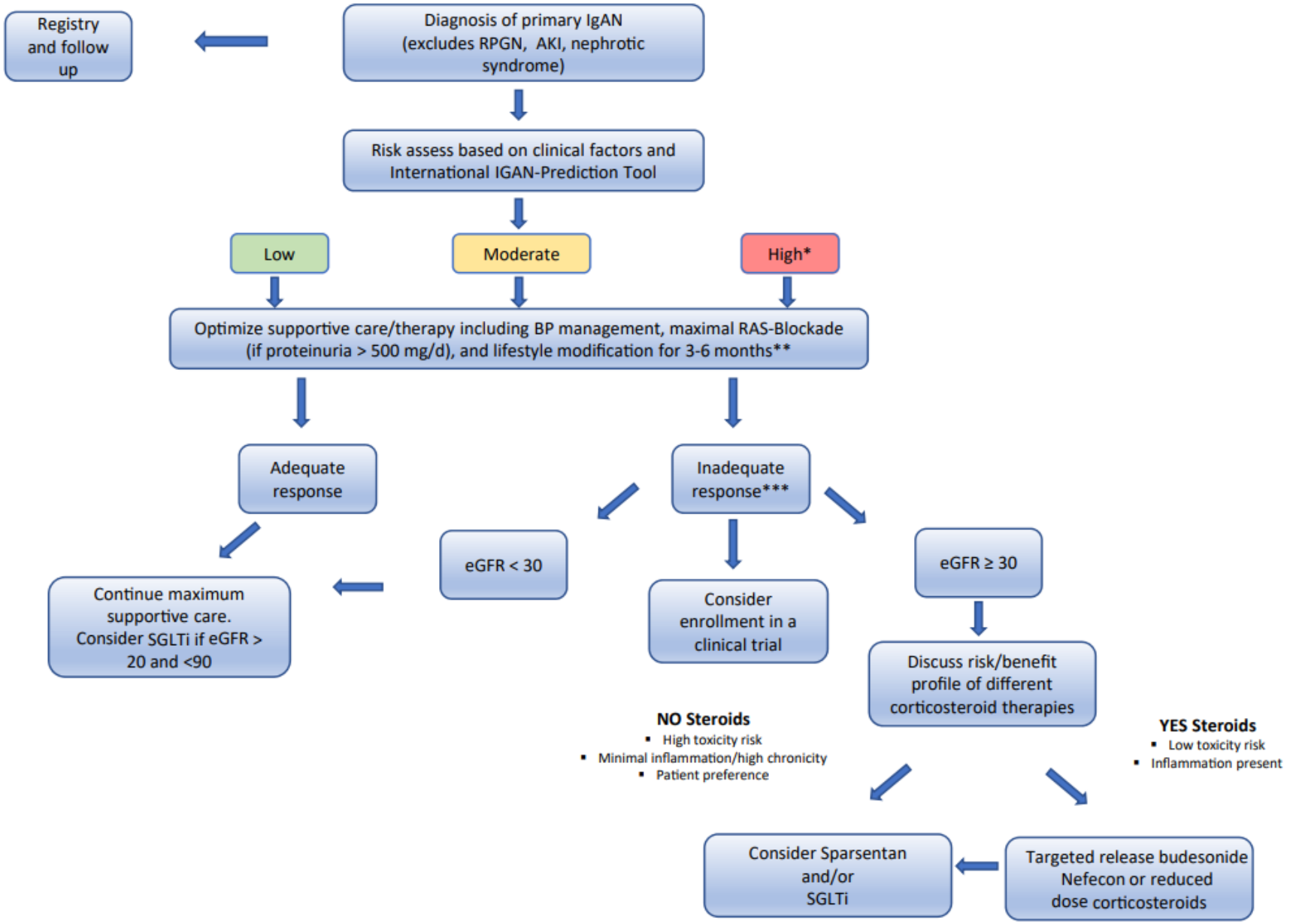
primary composite outcome in patients with IgA nephropathy confirmed by a biopsy, and (d) kidney-specific secondary composite outcome in the patients with IgA nephropathy confirmed by a biopsy

Kidney International (2021) 100, 215–224

The Treatment of Primary IgA Nephropathy: Change, Change, Change

Dawn J. Caster and Richard A. Lafayette

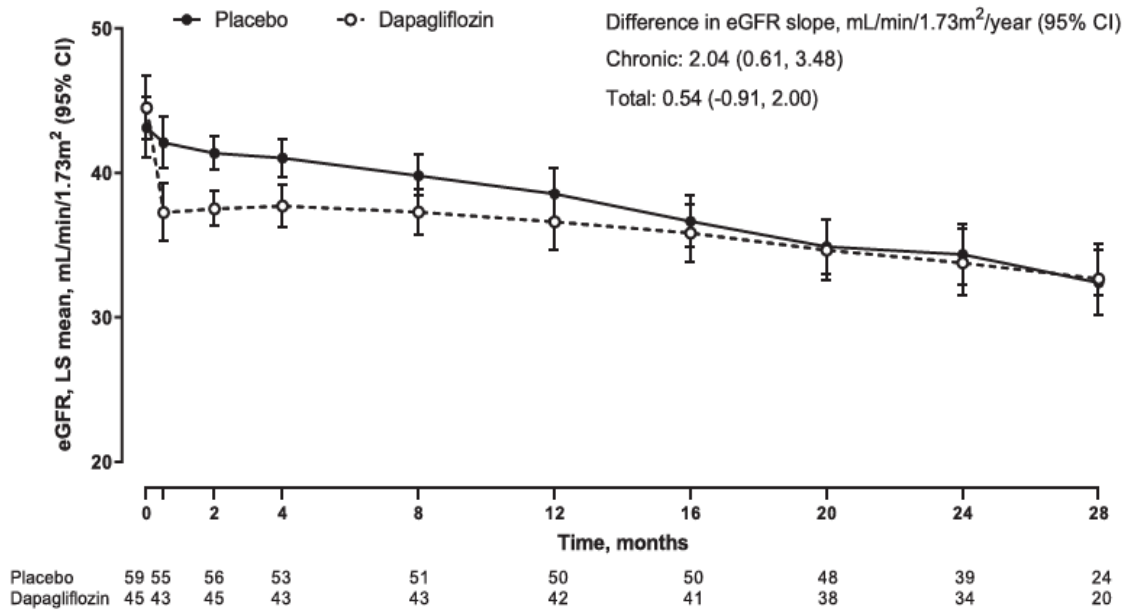
- concern regarding concomitant use of SGLT-2 inhibitor with immunosuppressants (especially corticosteroids) due to the increased risk of urogenital infections
- There was no increased risk of urogenital infection in the DAPA-CKD or EMPA-KIDNEY trials, patients receiving immunosuppressive therapy were excluded in the DAPA-CKD and limited in EMPA-KIDNEY trial.
- Given the relatively short duration of immunosuppressive therapy regimens in IgAN (6-9 months), one approach may be to wait and add SGLT-2 inhibitor after completion of immunosuppression


Registry and follow up
Diagnosis of primary IgAN (excludes RPGN, AKI, nephrotic syndrome)
Risk assess based on clinical factors and International IGAN-Prediction Tool
Low
Moderate
High*
Optimize supportive care/therapy including BP management, maximal RAS-Blockade (if proteinuria > 500 mg/d), and lifestyle modification for 3-6 months**
Adequate response
Inadequate response***
Continue maximum supportive care. Consider SGLTi if eGFR > 20 and <90
eGFR < 30
Consider enrollment in a clinical trial
eGFR ≥ 30
Discuss risk/benefit profile of different corticosteroid therapies
NO Steroids
High toxicity risk
Minimal inflammation/high chronicity
Patient preference
YES Steroids
Low toxicity risk
Inflammation present
Consider Sparsentan and/or SGLTi
Targeted release budesonide Nefecon or reduced dose corticosteroids

FSGS & AAV

Nephrol Dial Transplant (2022) 37: 1647–1656
https://doi.org/10.1093/ndt/gfab335
Advance Access publication date 25 November 2021

Safety and efficacy of dapagliflozin in patients with focal segmental glomerulosclerosis: a prespecified analysis of the dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial



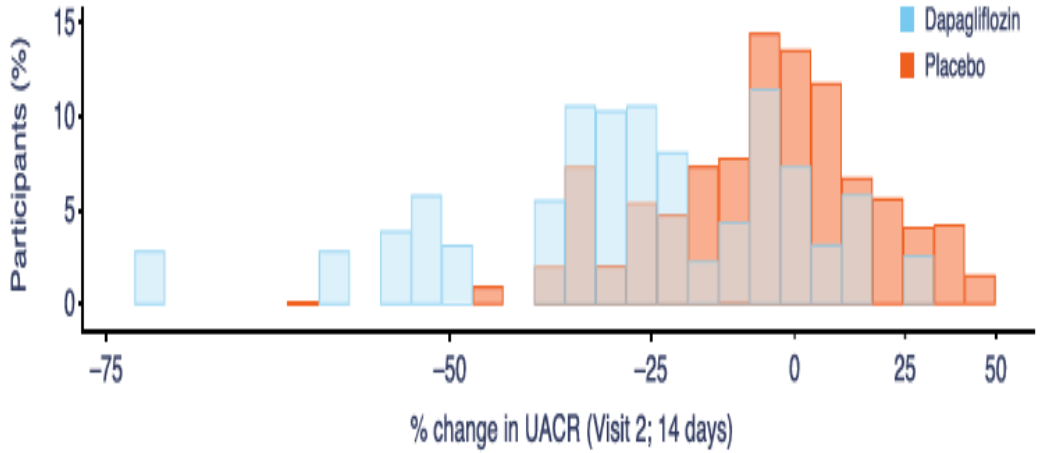


FIGURE 2: eGFR trajectory over time in patients with focal segmental glomerulosclerosis.

Viewpoint

Call for action in ANCA-associated vasculitis and lupus nephritis: promises and challenges of SGLT-2 inhibitors

Marcus Säemann [1,2] Andreas Kronbichler [3]

- CKD remains one of the strongest predictors of a poor prognosis.
- Significantly increased risk of CV morbidity and mortality
- features affecting the cardiorenal axis occur more frequently in patients with AAV such as diastolic dysfunction and pulmonary hypertension along with reduced systolic function
- Benefit from the cardio and nephroprotective properties of SGLT- 2i, once the initial phase of induction immunosuppression is completed
- Currently, trials are in the set- up phase to test dapagliflozin in AAV, such as DAPA- vasculitis.

Säemann M, Kronbichler A. Ann Rheum Dis 2022;81:614–617.
doi:10.1136/annrheumdis-2021-221474

Key Information

SGLT2i are drugs that have been shown to have the following effects:

- They impact obesity and promote the reduction of key fatty deposits such as fatty liver and epicardial deposits.
- They have a systemic-blood-pressure-lowering effect without generating a reflex chronotropic response.
- They mitigate inflammation induced by fatty deposits, uric acid, fatty liver, glucotoxicity, and lipotoxicity through restoration of various metabolic pathways.
- They limit the progression of renal disease and albuminuria.
- They allow a return to energy metabolism from ketone bodies and lipid consumption, optimizing energy efficiency in the myocardium.
- Their potential adverse effects, include an increased risk of urogenital tract infections and euglycemic diabetic ketoacidosis.

Conclusions

SGLT2i represent a novel class of medications with pleiotropic effects extending beyond glycemic control.

SGLT2i have emerged as a cornerstone therapy for patients with comorbidities such as heart disease, renal dysfunction, metabolic disorders, and glomerular diseases.