Sodium-glucose cotransporter 2 inhibition in electrolyte and metabolic disturbances

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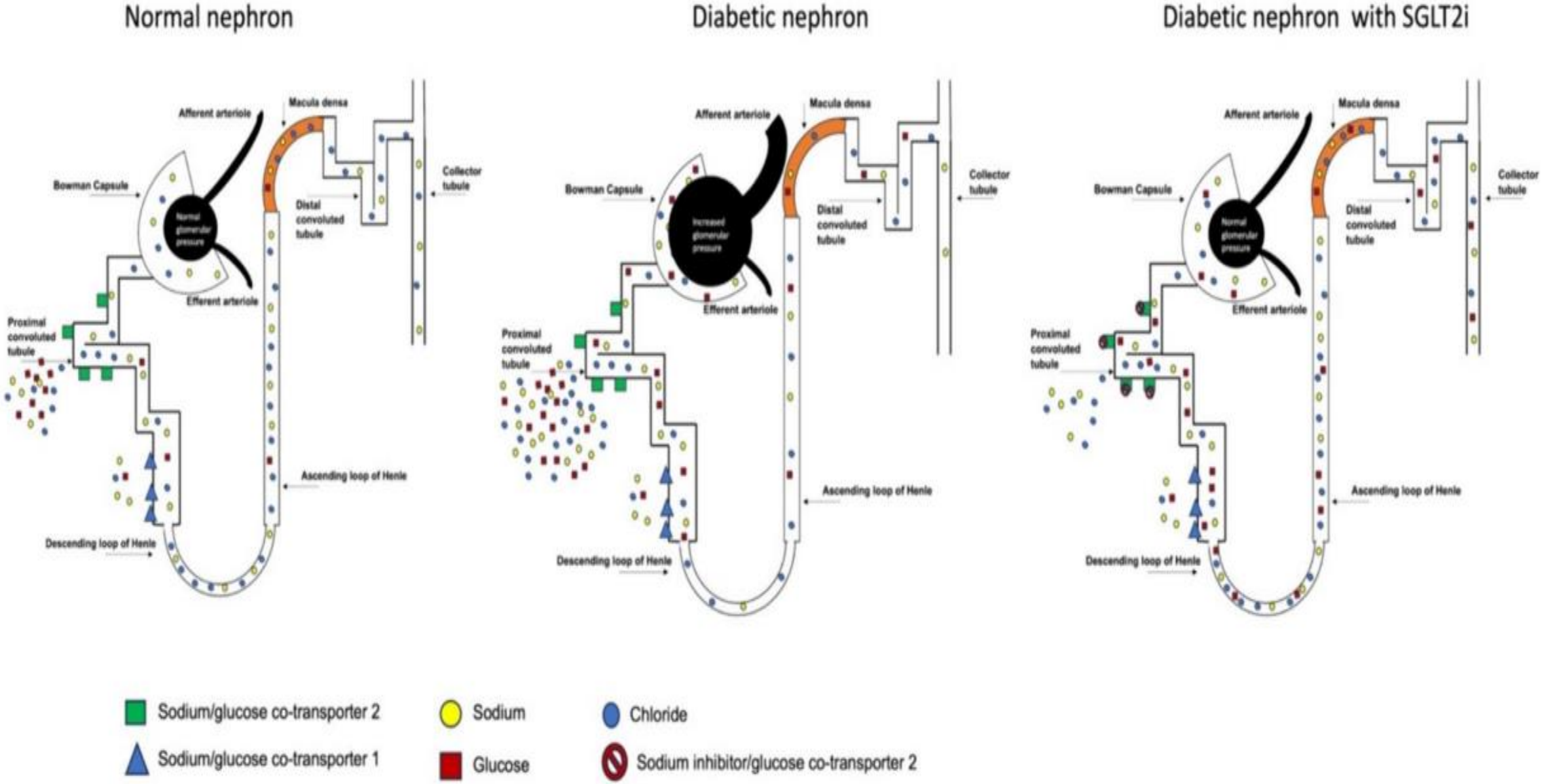
How do SGLT2 inhibitors work?

S-GL-T2

↓ **S**odium reabsorption in S1-PT

↓ **Gl**ucose reabsorption in S1-PT

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



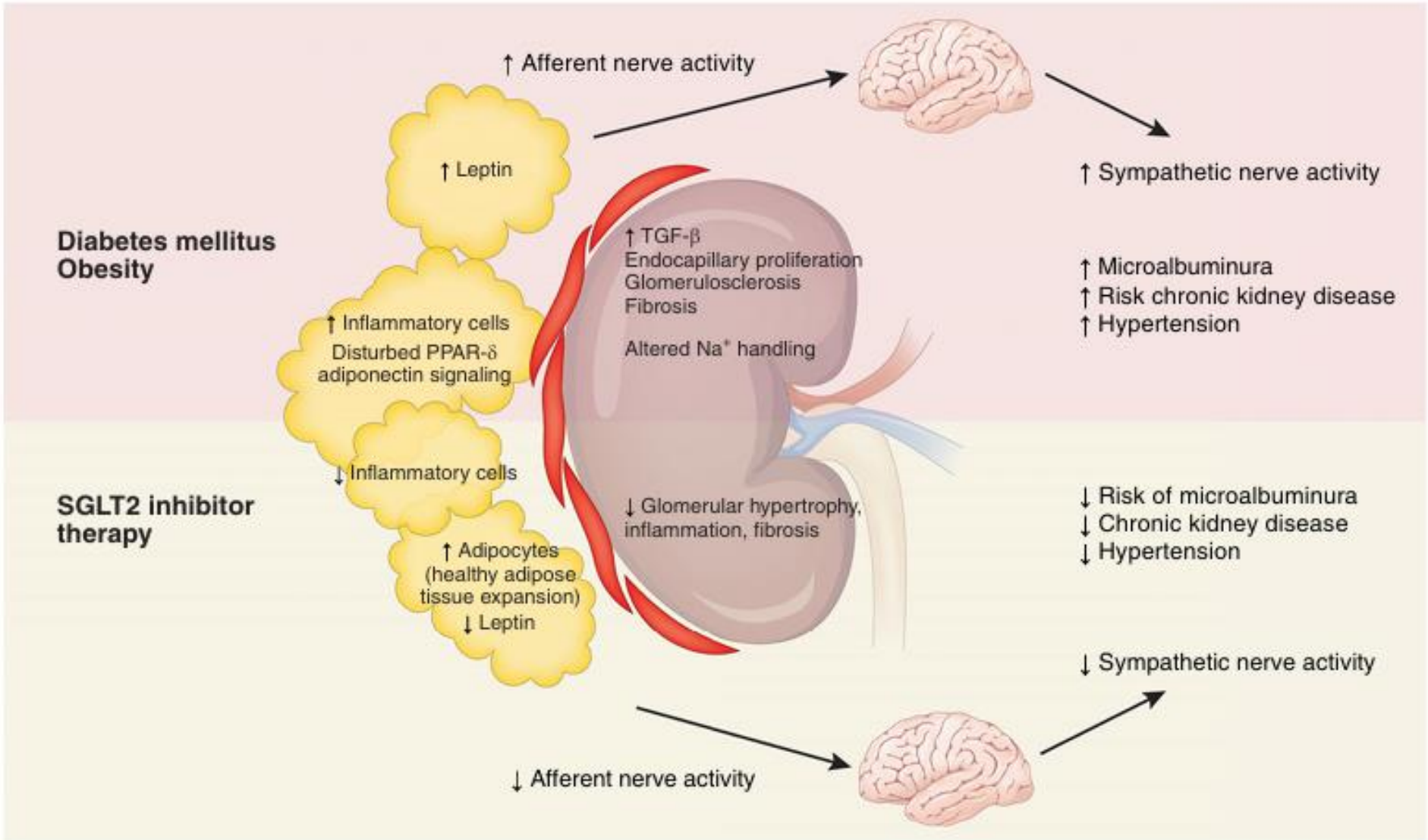
American Journal of Cardiovascular Drugs
https://doi.org/10.1007/s40256-024-00673-1

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

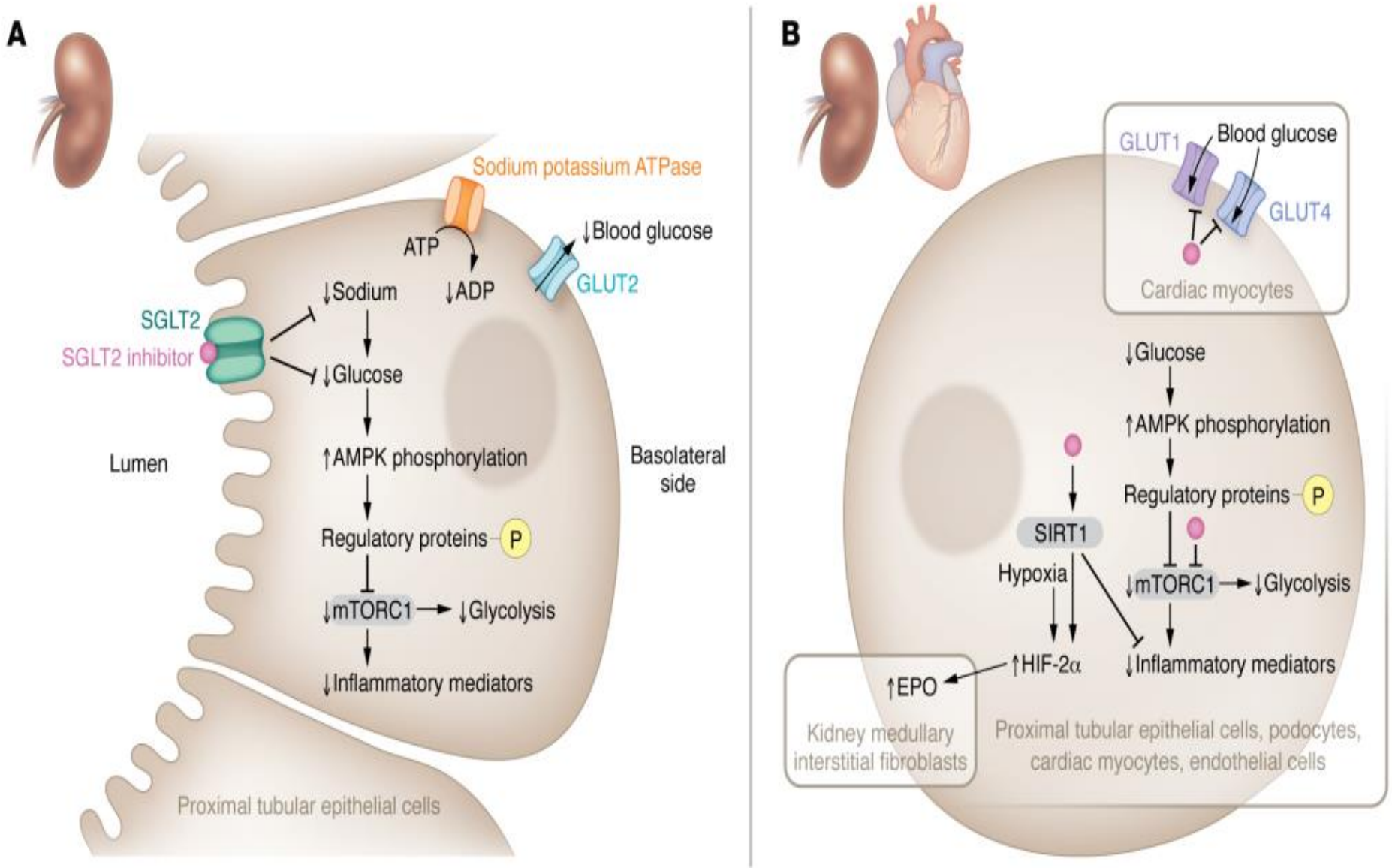
- Transient decline in GFR of approximately 5 ml/min/1.73 m2 (not reflect true renal dysfunction)
- It is reversible within 2-4 weeks
- long-term nephroprotective benefits
- SGLT2-inhibitor-induced diuresis can transiently elevate hematocrit
- Protect against renal congestion
- Reduction in albuminuria, 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.

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

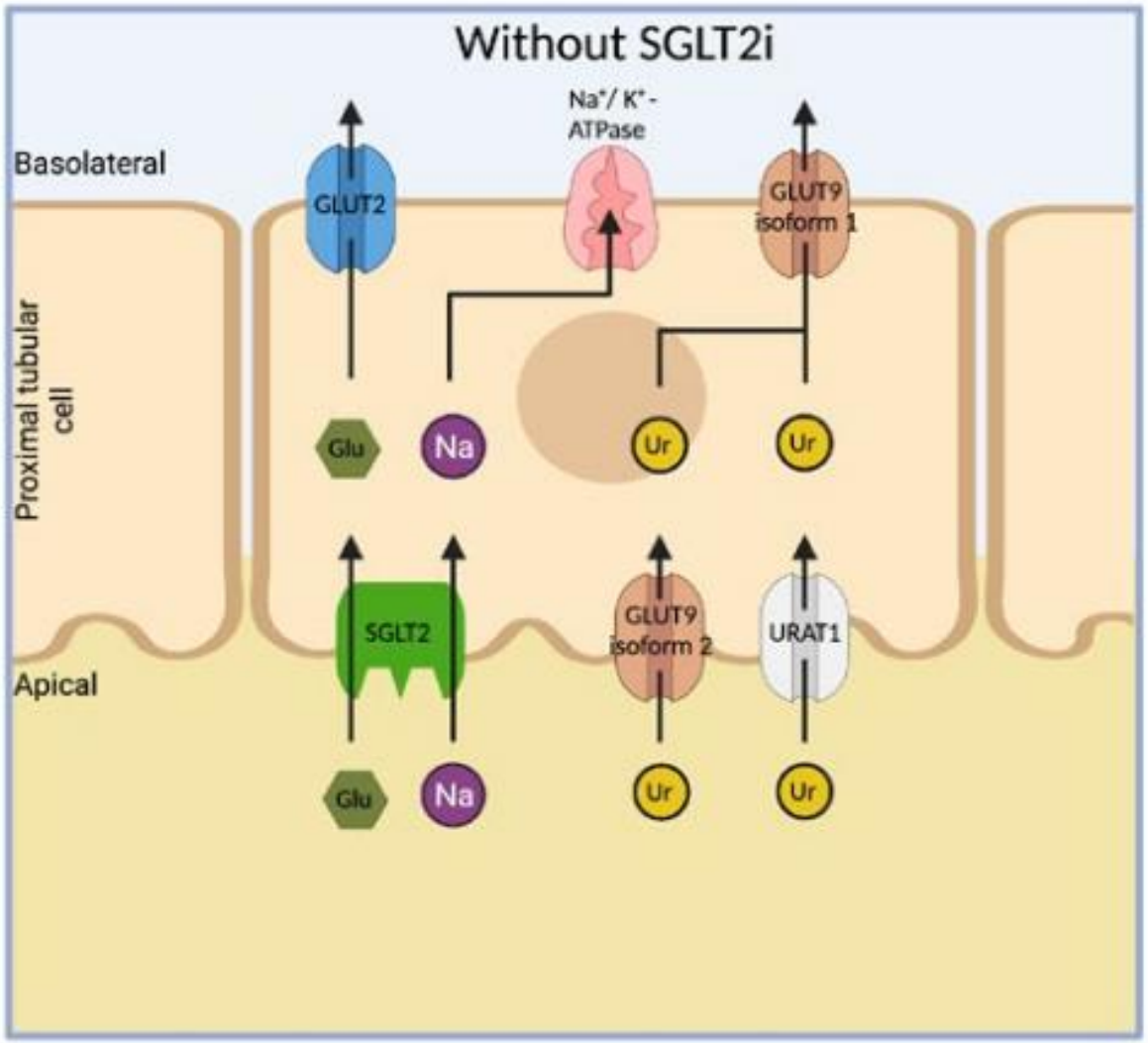
Inflammation:

- 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

Patients with T2D tend to have elevated uric acid levels
An increased risk of cardiovascular and kidney disease
Faster CKD progression
SGLT2i: increased tubular secretion of uric acid
Increased urinary glucose availability with SGLT2 blockade leads to activation GLUT9 isoform 2 for glucose reabsorption as opposed to urate reabsorption, ultimately leading to a uricosuric effect
GLUT9 isoform 2 activation may also facilitate urate secretion.
URAT1: to reabsorb urate under physiological conditions.
SGLT2i downregulates URAT1, leading to more uricosuria

Visual representation of sodium–glucose co-transporters 2 inhibitor effects on urate.



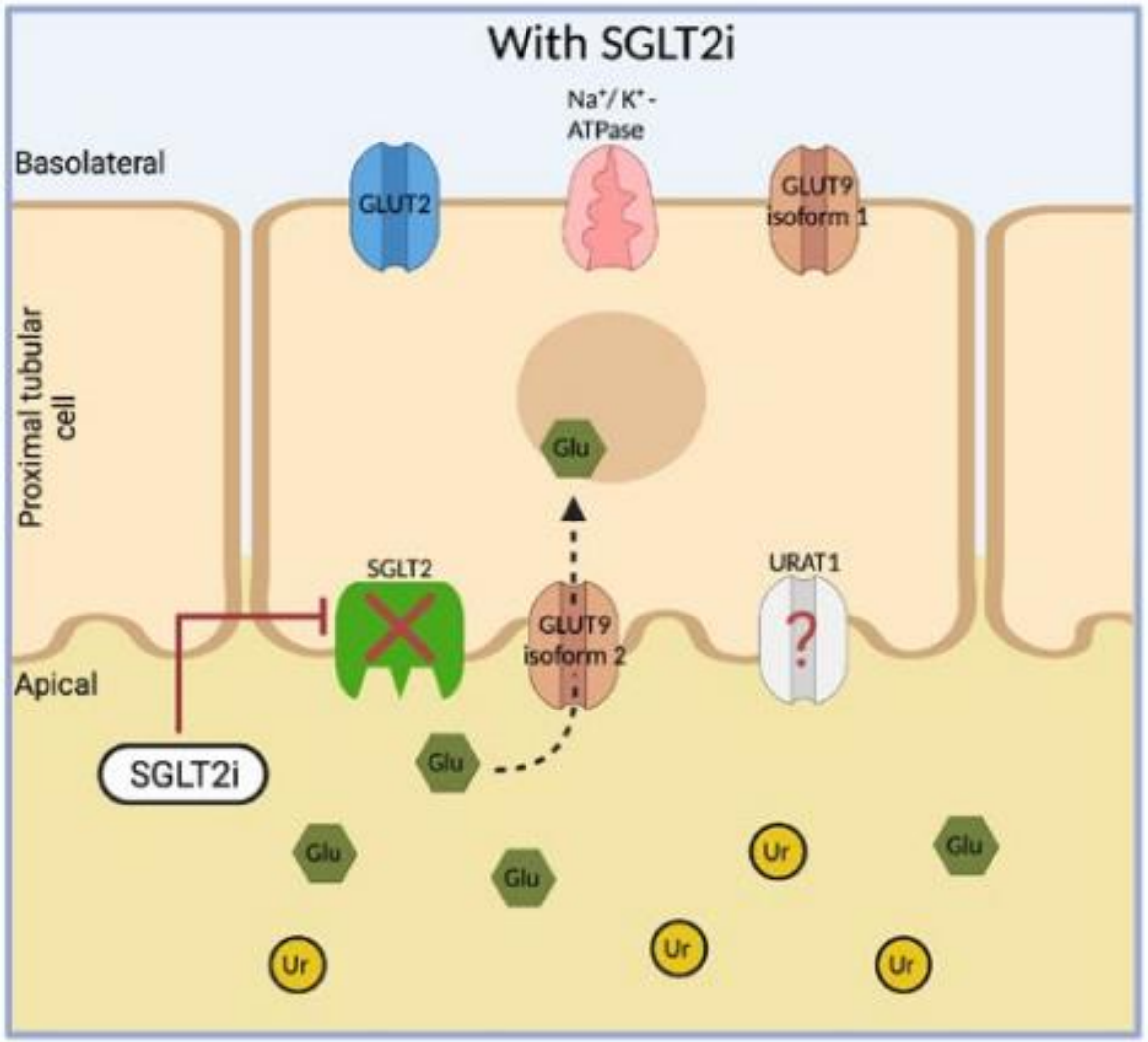
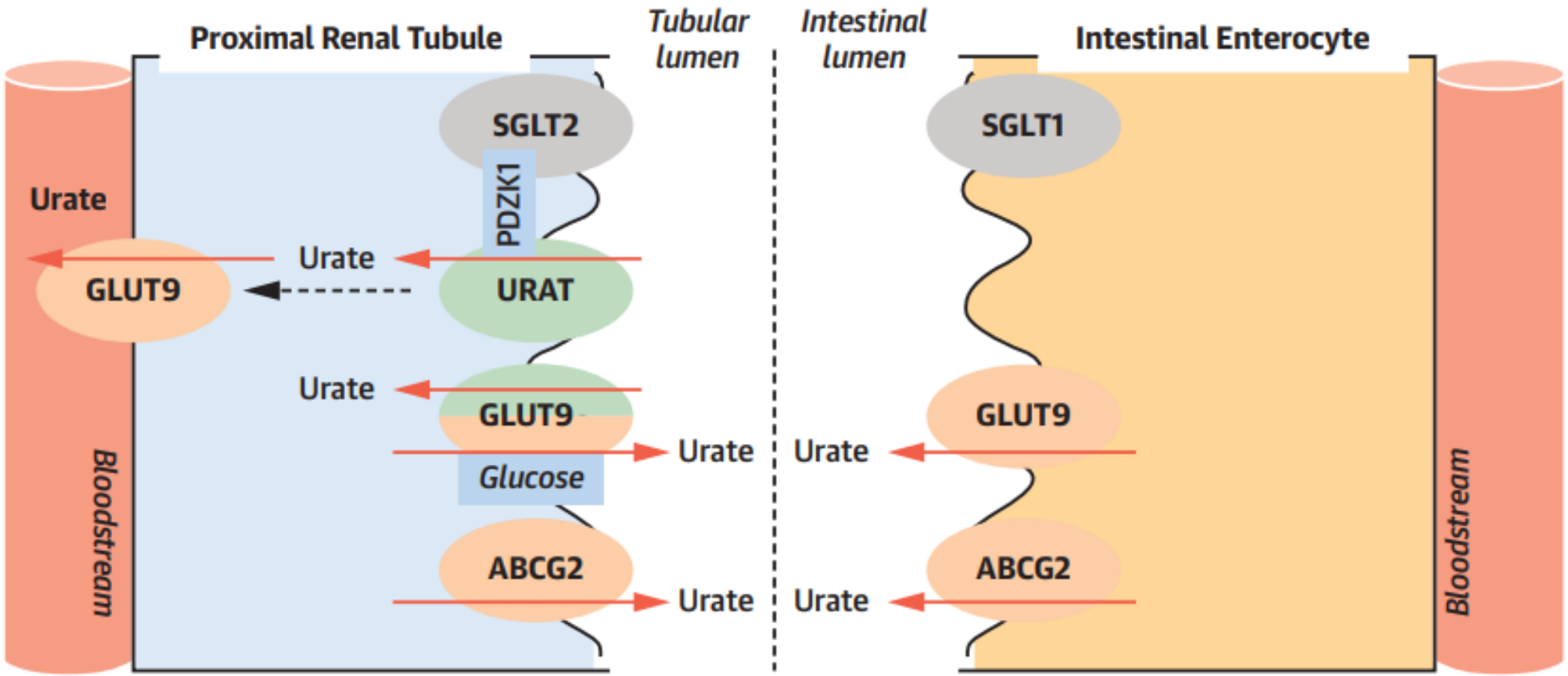


FIGURE 4 Urate Transporters in the Proximal Renal Tubule and Intestinal Enterocyte



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.

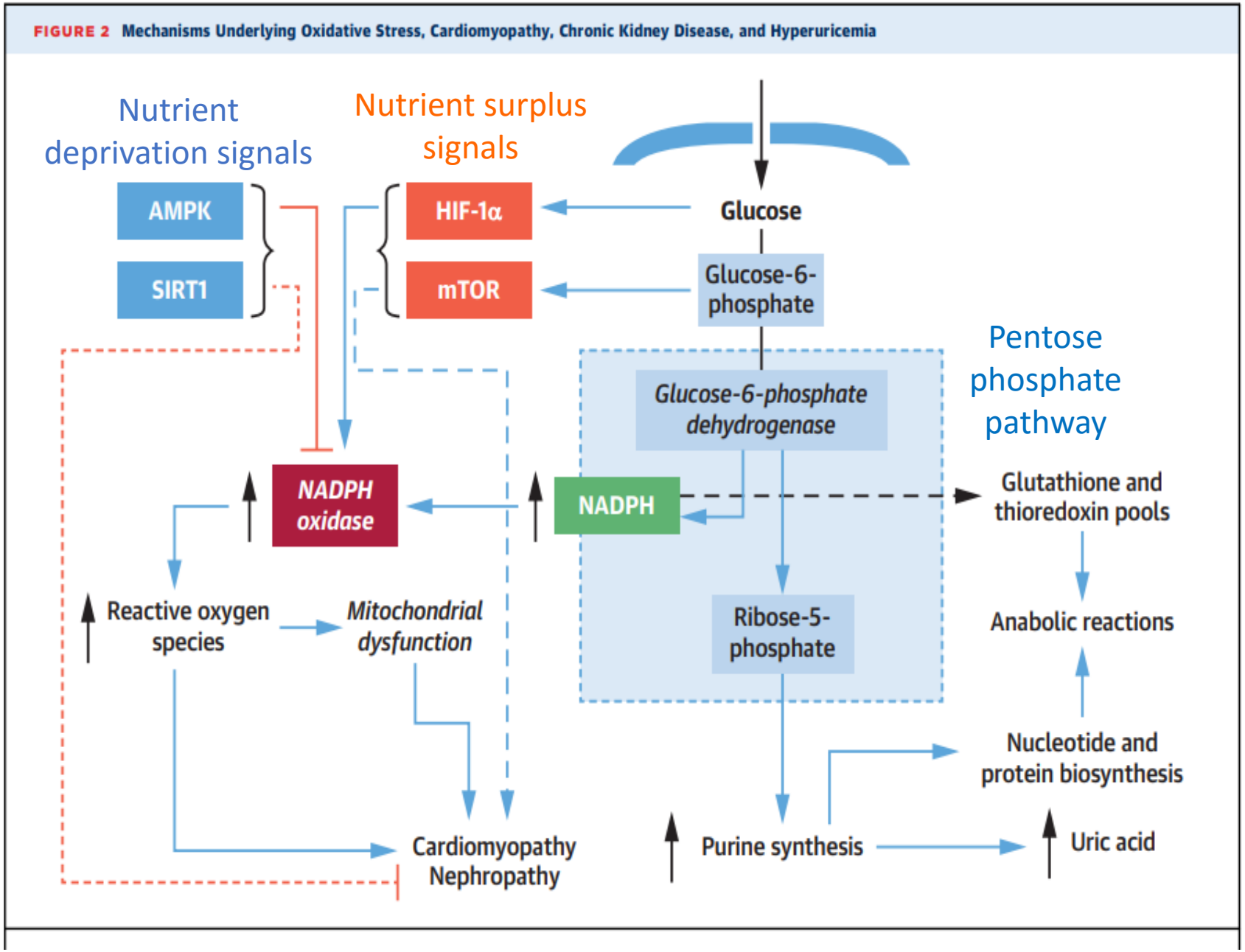
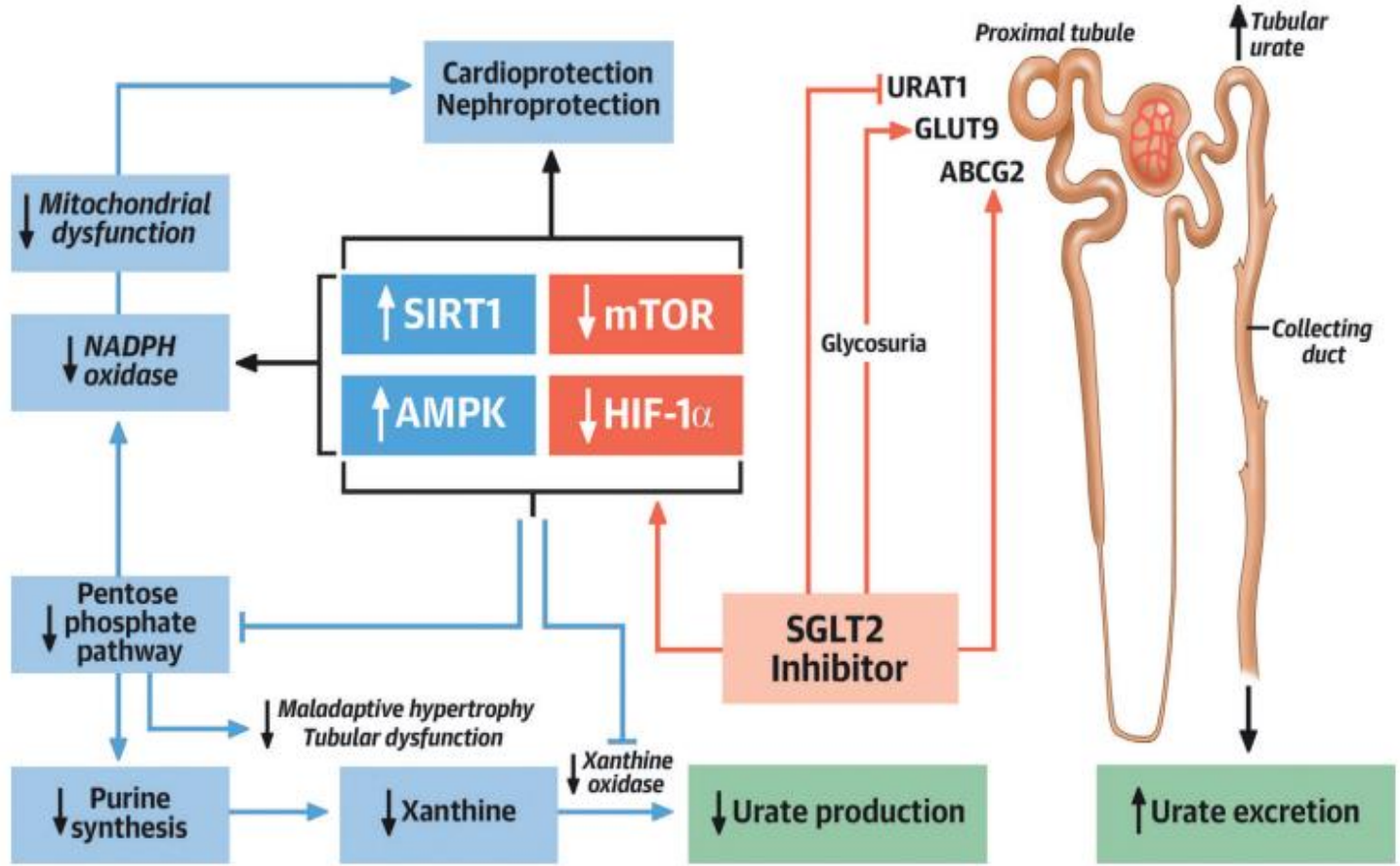


FIGURE 2 Mechanisms Underlying Oxidative Stress, Cardiomyopathy, Chronic Kidney Disease, and Hyperuricemia
Nutrient deprivation signals
Nutrient surplus signals
AMPK
SIRT1
HIF-1α
mTOR
Glucose
Glucose-6-phosphate
Pentose phosphate pathway
Glucose-6-phosphate dehydrogenase
NADPH oxidase
NADPH
Glutathione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

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
- Potential protection against the incidence of gout
- 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

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

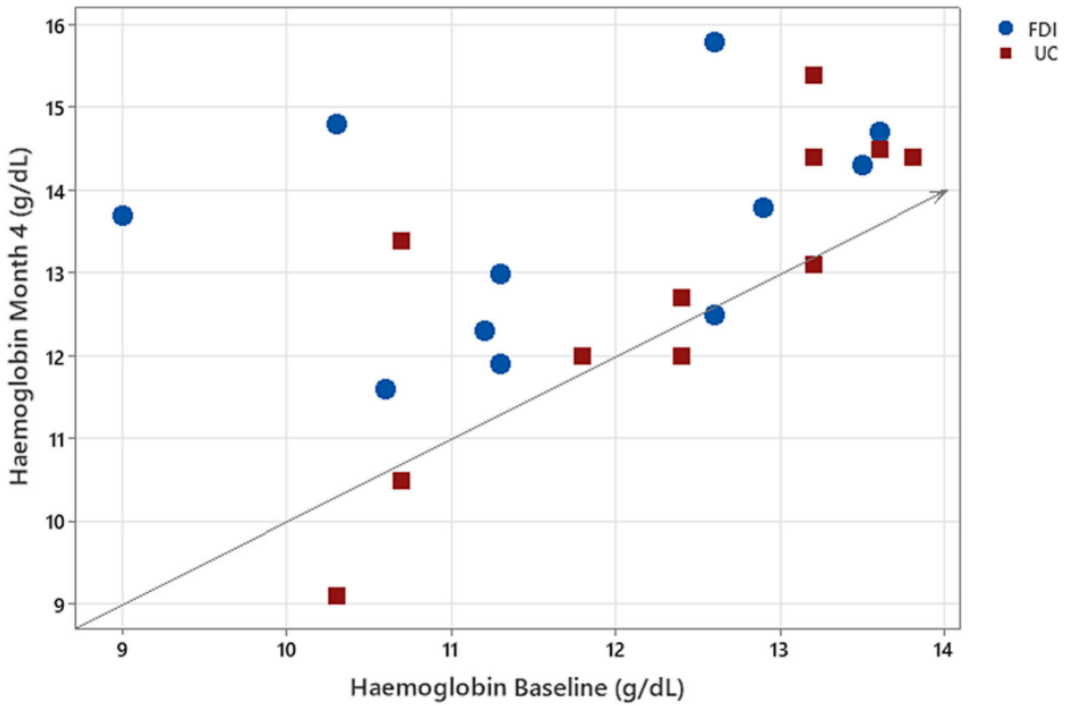
- Enhance iron utilization
- DAPA-HF study: reducing hepcidin and ferritin levels while increasing transferrin receptors in HF patients
- Empire HF trial, IRONMAN trial: greater increase in hemoglobin using SGLT2 inhibitors

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]*

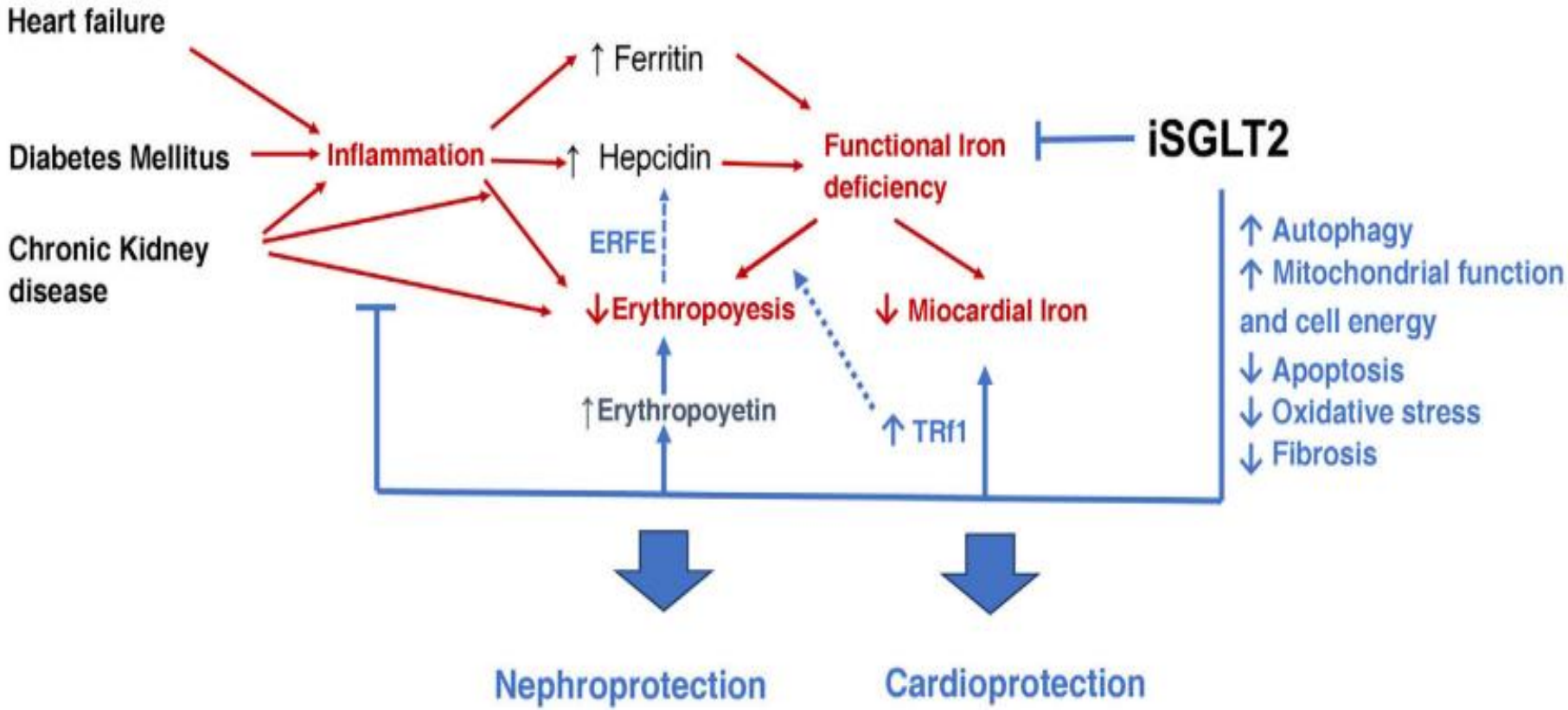
Conclusions In the IRONMAN trial, there was a trend to a greater increase in haemoglobin with ferric derisomaltose in iron-deficient patients taking an SGLT2 inhibitor at baseline, as compared with those not taking one.

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

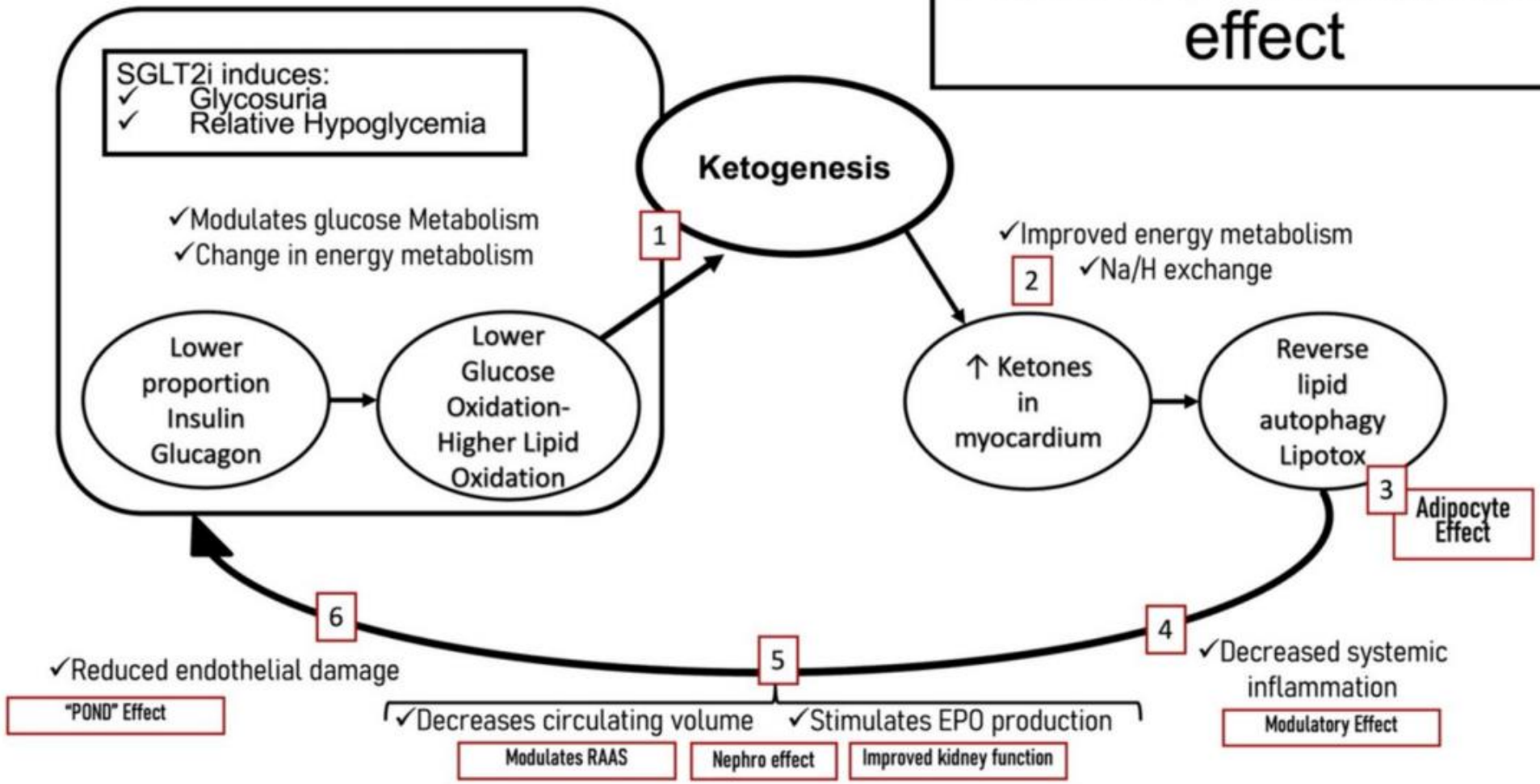
- Reducing ATP consumption via the Na+/ K+ pump
- Diminishing hypoxia in the microenvironment
- Facilitate the reversion of myofibroblasts back into erythropoietin-producing fibroblasts, leading to enhanced hematopoiesis and elevated hematocrit



Beneficial effects of SGLT2i beyond the increase in erythropoiesis. Indirect effects on kidney and heart, ERFE: erythroferrone; TRf1: transferrin receptor type 1

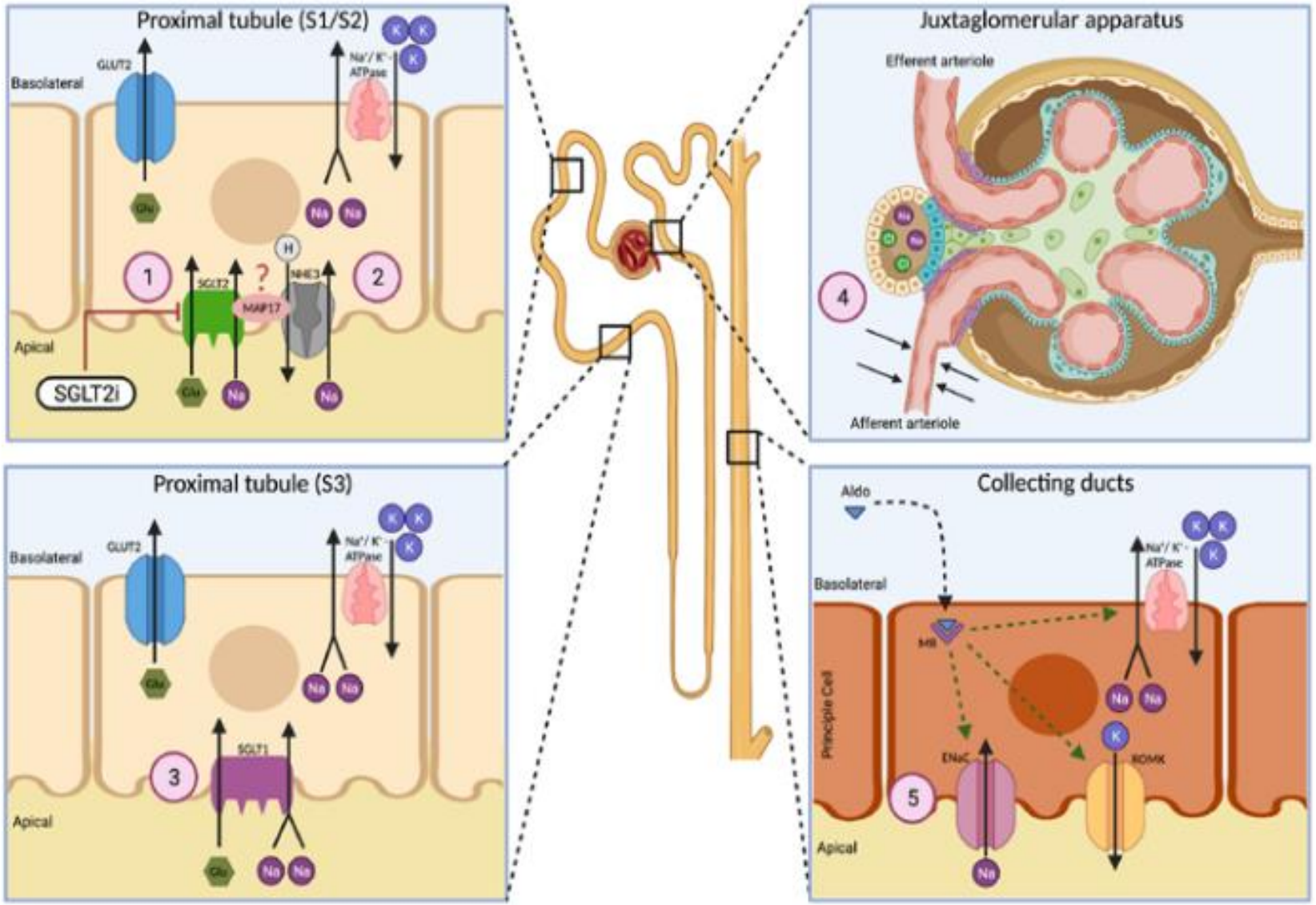
ne f rologia. 2 0 2 4;44(2):165–172

Reverse metabolism effect



Sodium and Water

Summary of sodium–glucose co-transporter 2 inhibitor effects on sodium balance.



1. Inhibition of SLGT2 results in the loss of glucose as well as sodium
2. Inhibition of SGLT2 results in downregulation of NHE3 through MAP17 which results in sodium loss
3. Increased glucose delivery to the S3 segment of the proximal convoluted tubule will result in increased action of SGLT1 which reabsorbs 2 sodium ions per glucose
4. Increased distal tubular sodium and chloride will cause afferent artiolar vasoconstriction through the tubulo glomerular feedback mechanism. This decreases glomerular filtration and results in less sodium loss
5. Decreased renal purfusion will result in an increase in aldosterone due to activation of RAAS. This results in more sodium reabsorption through ENaC

MAP17: membrane associated protein 17

EMJ Nephrol. 2022;10[1]:76-83. DOI/10.33590/emjnephrol/22-00080.

Hypernatremia

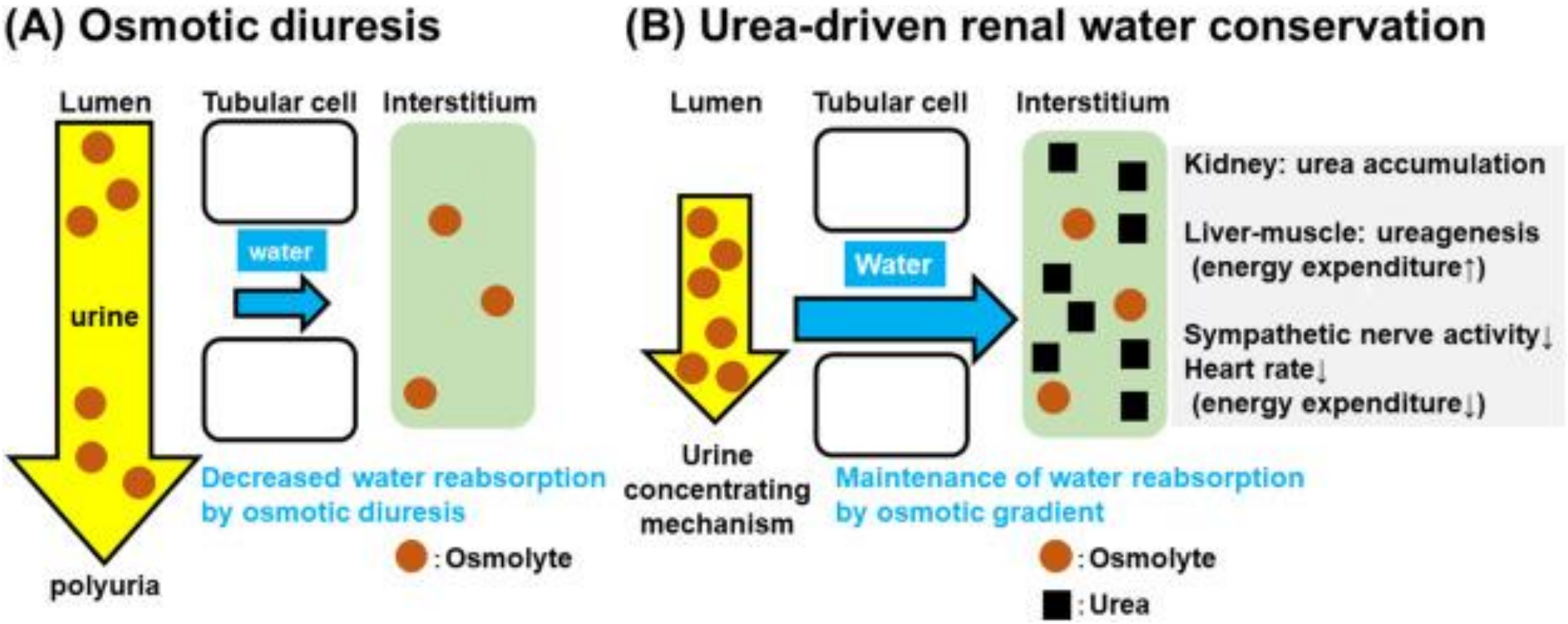
SGLT2i have an interesting effect on water balance, may be associated with hypernatremia

Overall free water loss, as a result of osmotic diuresis

Hypernatremia is rarely observed in patients who can drink water freely or respond to thirst

Discontinuing SGLT2 inhibitors when patients are hospitalized, ill, or undergoing surgery

Preventable electrolyte abnormality, particularly in patients on “Sick Day” or those unable to drink water freely.



Journal of Pharmacological Sciences
Volume 147, Issue 3, November 2021, Pages 245-250

Treatment option for hyponatremia

CLINICAL RESEARCH www.jasn.org

A Randomized Trial of Empagliflozin to Increase Plasma Sodium Levels in Patients with the Syndrome of Inappropriate Antidiuresis

Julie Refardt,[1,2] Cornelia Imber,[1,2] Clara O. Sailer,[1,2] Nica Jeanloz,[1,2] Laura Potasso,[1,2] Alexander Kutz,[1,2] Andrea Widmer,[1,2] Sandrine A. Urwyler,[1,2] Fahim Ebrahimi,[1,2] Deborah R. Vogt,[3] Bettina Winzeler,[1,2] and Mirjam Christ-Crain[1,2]

[1]Department of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Basel, Switzerland; [2]Department of Clinical Research, University of Basel, Basel, Switzerland; and [3]Clinical Trial Unit, Department of Clinical Research, University of Basel and University Hospital Basel, Basel, Switzerland

- 87 patients who completed the trial, 43 treated
- Patients treated with empagliflozin had a significantly higher increase of median plasma sodium concentration in 4 days compared with those receiving placebo (10 versus 7 mmol/L, respectively; P 0.04).
- Conclusions Among hospitalized patients with SIAD treated with fluid restriction, those who received empagliflozin had a larger increase in plasma sodium levels compared with those who received placebo.

JASN 31(3):p 615-624, March 2020.

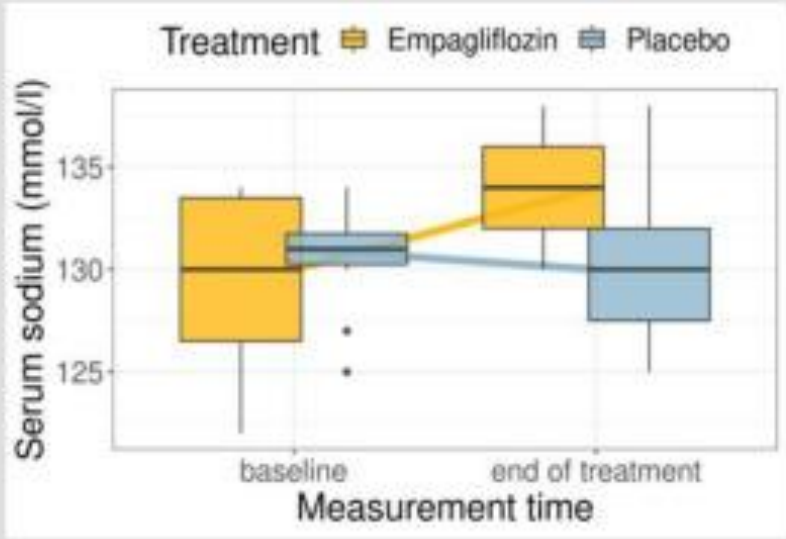
Treatment Effect of the SGLT2-Inhibitor Empagliflozin on Chronic SIAD

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

- Double-blind, randomized, crossover, placebo-controlled trial
- 14 outpatients with chronic SIAD
- Comparison 4-week treatment with empagliflozin 25mg/day to placebo
- Secondary outcome: Neurocognition

OUTCOME: Improvement of serum sodium levels and neurocognition according to exploratory analyses



Conclusion: The SGLT-2 inhibitor empagliflozin is a promising new treatment option for chronic SIAD-induced hyponatremia, possibly improving neurocognitive function

doi: 10.1681/ASN.2022050623

- Empagliflozin reduces expression of Na+ -K+ -2Cl cotransporter and epithelial Na+ channels (ENaC)
- Decreases mRNA and protein levels of aquaporin 2
- May partially contribute to polyuria via its direct effect on sodium and water channels
- Significantly increased urine volume in association with glycosuria, but without a significant difference in total natriuresis, demonstrating a strong aquaretic action
- In patients with SIAD, empagliflozin had no effect on plasma apelin concentration, but led to a significant increase of 25% in median serum levels of copeptin, an equimolar surrogate marker of AVP
- Efficacy of empagliflozin in SIAD is neither mediated through apelin nor blunted by the adaptive stimulation of AVP release
- the effect of empagliflozin on blood sodium levels was largely dependent on the severity of baseline hyponatremia (<125 meq)

Empagliflozin-induced increase of serum sodium in patients with SIAD cannot be extrapolated to patients without SIAD

Long-term therapy with SGLT2 inhibitors does not alter the prevalence of hyponatremia on hospital admission

SGLT2 inhibitors do not prevent the development of hyponatremia and should not be used as prophylaxis for hyponatremia in at-risk individuals

Data about the effect of empagliflozin on hypervolemic hyponatremia due to heart failure or cirrhosis is lacking

Pros and cons of empagliflozin for SIAD

Advantages:

(i) rapid onset of action since difference in serum sodium compared to placebo was already noted after 12 hours

(ii) efficacy in increasing serum sodium concentration compared to placebo in both hospitalized patients and outpatients with SIAD as well as in combination with both standard fluid restriction < 1000 ml/day and limitation of fluid intake to 1500-1600 ml/day

(iii) being well tolerated with no events of hypoglycemia or hypotension in SIAD studies

(iv) favorable safety profile in general

(v) cardiovascular benefits in individuals with type 2 DM and established cardiovascular disease, cardioprotective properties in those with heart failure and nephroprotective effects in those with type 2 DM or CKD (

(vi) widespread availability and relatively low cost

Disadvantages

(i) modest efficacy, as suggested by a mean placebo subtracted serum sodium increase of 3 mmol/l after 4 days and 4.1 mmol/l after 4 weeks

(ii) limited evidence base supporting its efficacy, based on its use in 43 patients over 4 days and 14 individuals over 4 weeks

(iii) lack of data evaluating its efficacy and safety in combination with tight fluid restriction, such as below 500 ml/day

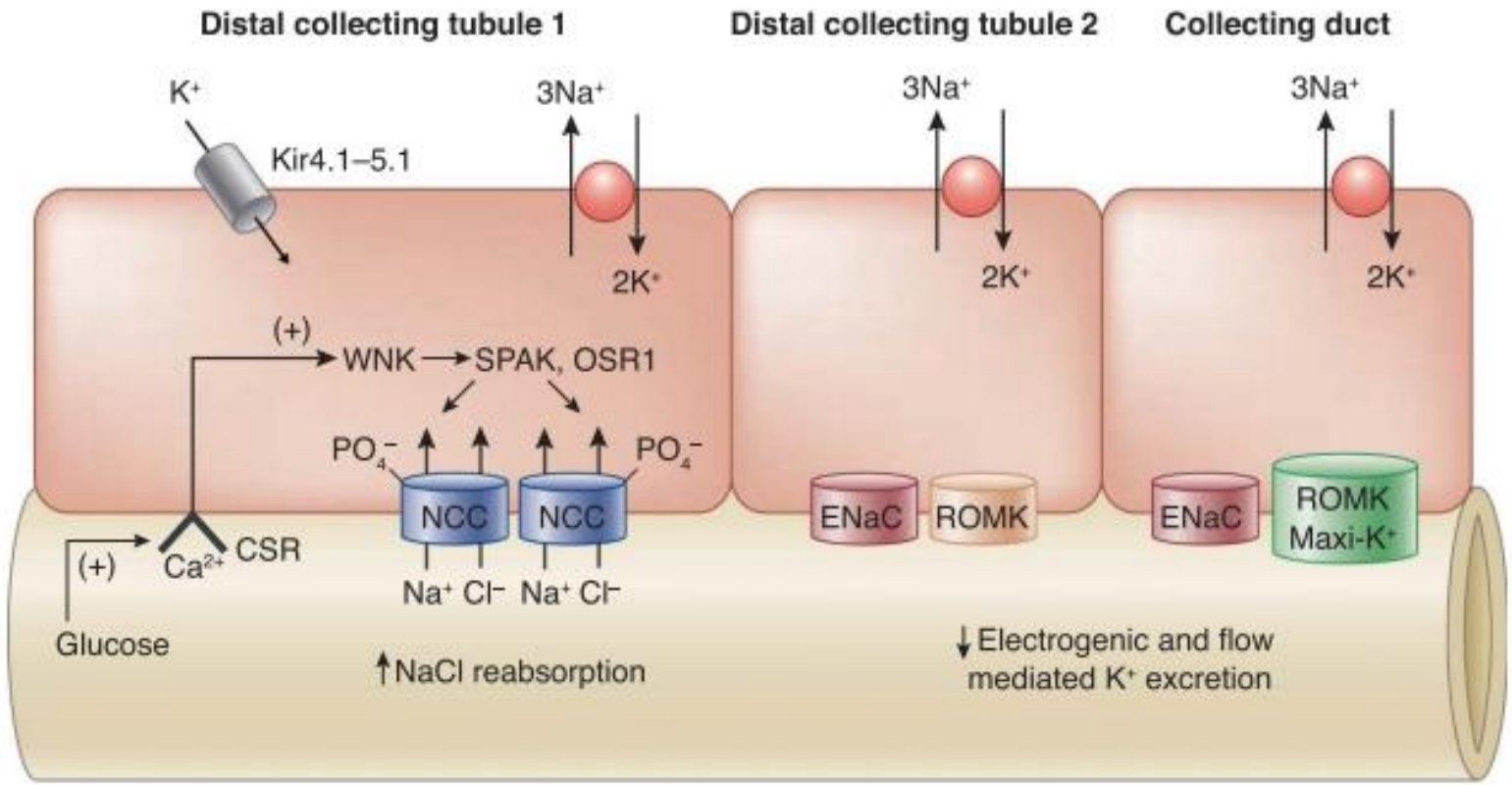
(iv) potential risk of excessive hyponatremia correction and renal deterioration

POTASSIUM

- Initially, concerns on hyperkalemia emerged with the introduction of SGLT2 inhibitors
- Patients with DM are more susceptible to hyperkalemia, specifically in the presence of renal dysfunction.
- The initial decrease in GFR, namely “initial dip or initial drop,”

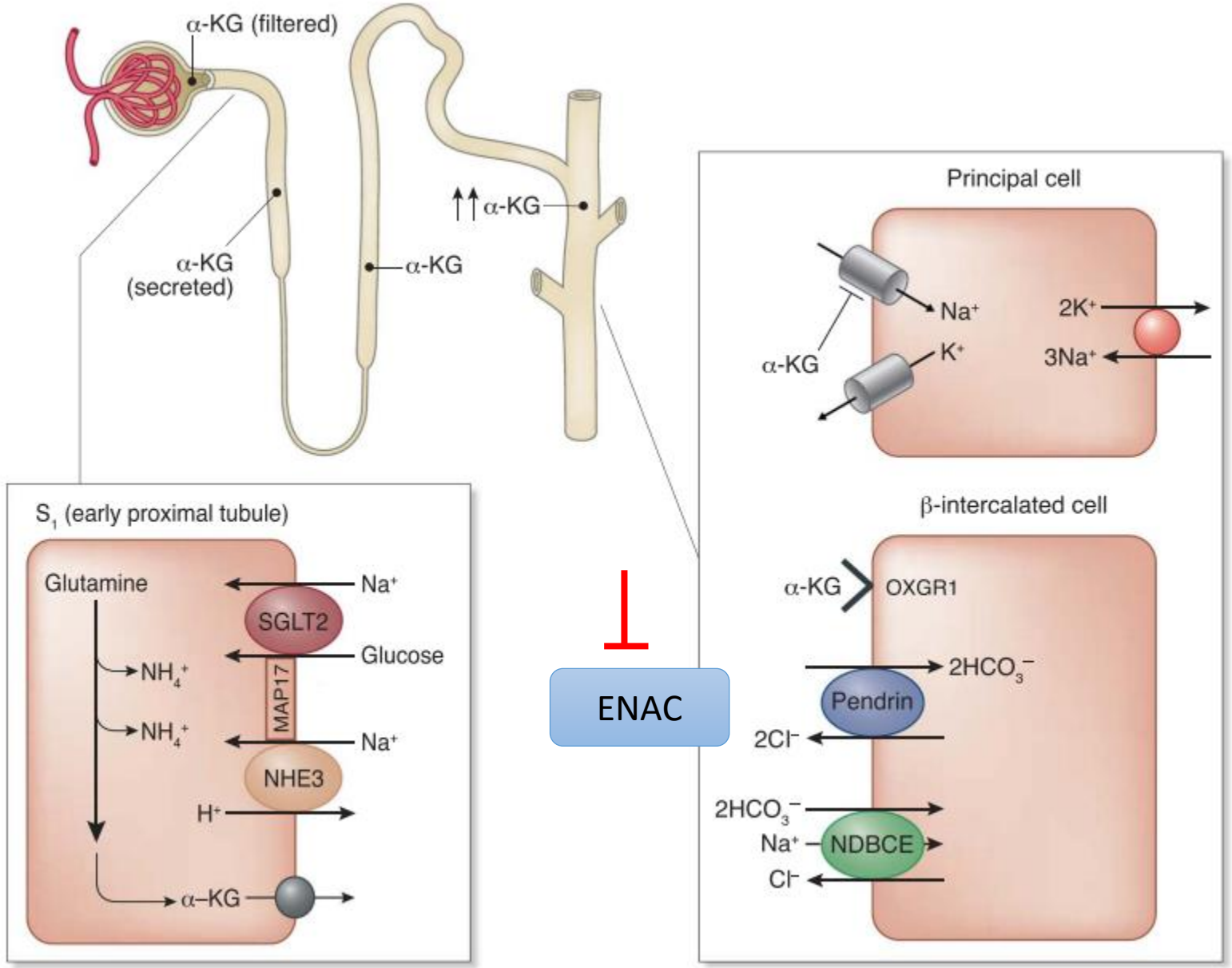
- First, SGLT2 inhibitors promote distal sodium delivery by inhibiting sodium reabsorption in the proximal tubules, both SGLT2 and NHE3 (more important).
- Second, increased urinary pH in the distal tubules arises from the inhibition of sodium–hydrogen exchanger 3 (NHE3)
- Third, SGLT2 inhibitors may transiently increase aldosterone levels shortly after initiation, may be limited because increased sodium delivery to the macula densa, can inhibit the release of renin, followed by aldosterone release.
- Fourth, SGLT2 inhibition increases glucosuria, which raises osmolality in the tubular lumen, resulting in osmotic diuresis and a high urine flow rate.
- Fifth, increased glucagon levels may also play a role in maintaining lower serum potassium levels. (limited effect)

SGLT2i is unlikely to cause hypokalemia



Glucose delivery to DCT1 activates NCC activity via the Ca21-sensing receptor.

CJASN 19: 399–405, 2024



SGLT2i inhibition limits K1 secretion through paracrine signaling between the proximal and distal nephron mediated by a-KG. a-KG, a-ketoglutarate; NDCBE, Na1-dependent Cl2/HCO3 2 exchanger; OXGR1, oxoglutarate receptor 1

▸ Clin J Am Soc Nephrol. 2023 May 31;18(8):1019–1030. doi: 10.2215/CJN.0000000000000205

Influence of SGLT2i and RAASi and Their Combination on Risk of Hyperkalemia in DKD

A Network Meta-Analysis

Xiaoling Luo [1], Jing Xu [1,2], Shoulian Zhou [3], Cheng Xue [1], Zewei Chen [1], Zhiguo Mao [1,✉]

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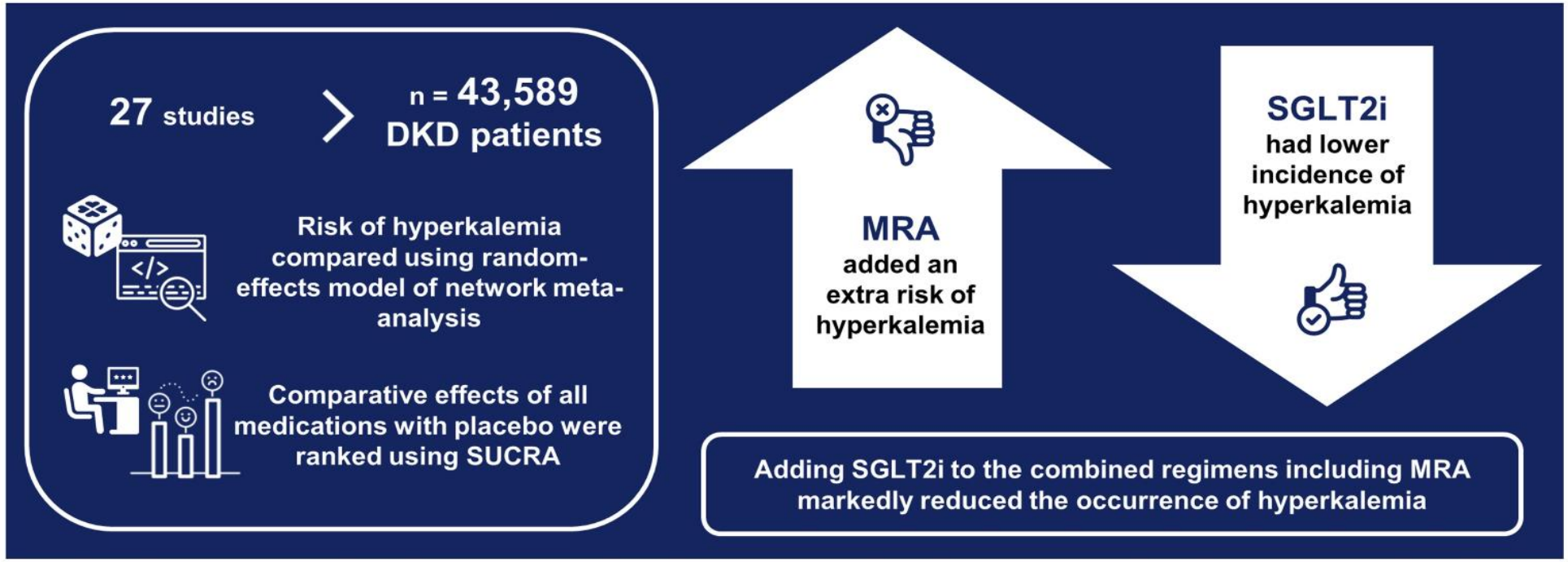
PMCID: PMC10564376 PMID: 37256921

Influence of SGLT2i and RAASi and Their Combination on Risk of Hyperkalemia in DKD: A Network Meta-Analysis

Influence of SGLT2i and RAASi and their combination on risk of hyperkalemia in DKD: A network meta-analysis

CJASN
Clinical Journal of the American Society of Nephrology



Conclusions: MRA added extra risk of hyperkalemia, while SGLT2i had the opposite effect, even in presence of MRA.

Xiaoling Luo, Jing Xu, Shoulian Zhou, et al. ***Influence of SGLT2i and RAASi and Their Combination on Risk of Hyperkalemia in DKD***. CJASN doi: 10.2215/CJN.0000000000000205. **Visual Abstract by José A. Moura-Neto, MD, FASN, FRCP**

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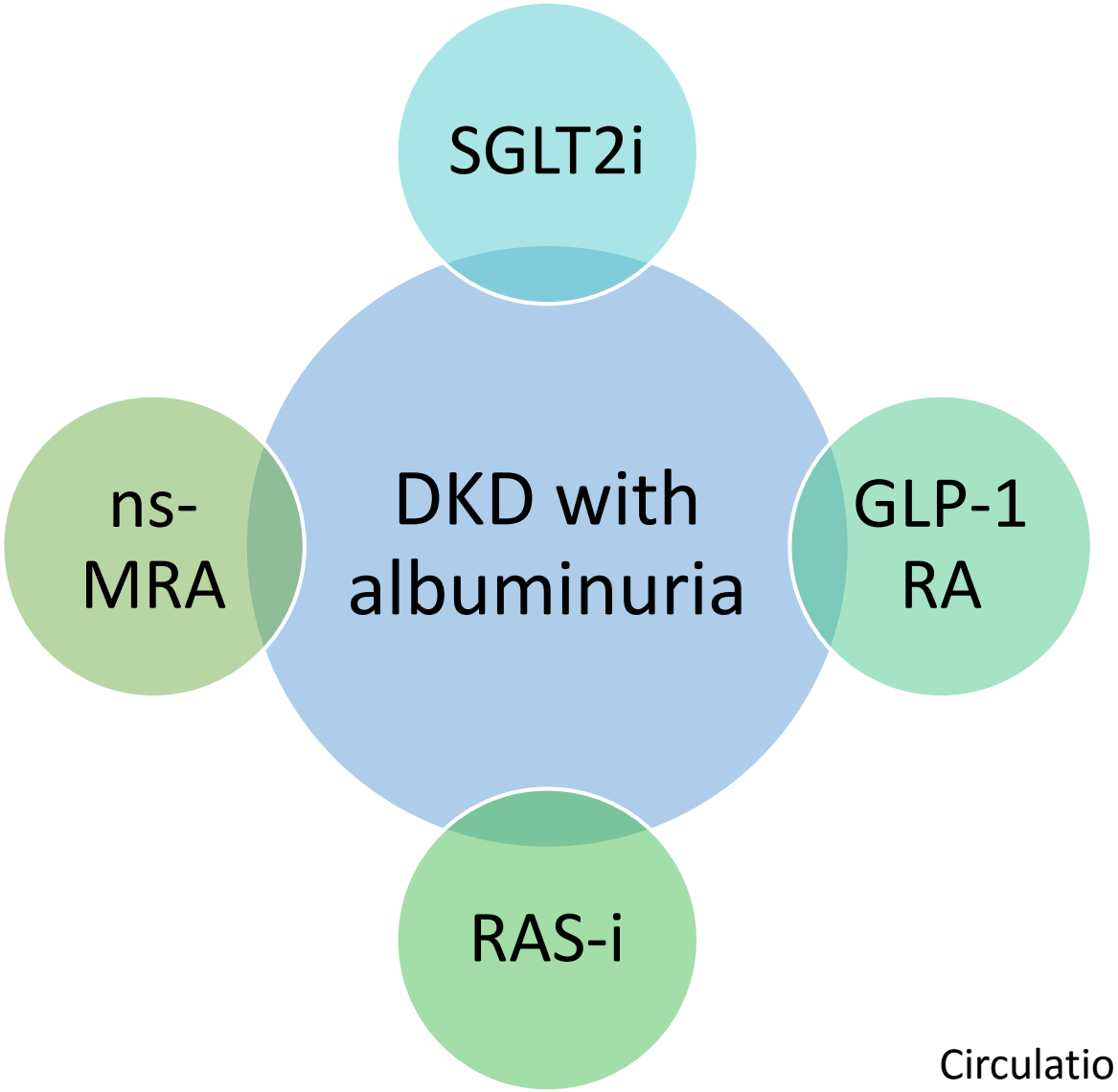
Wolters Kluwer

“Four Pillars” for DKD with albuminuria



Circulation. 2024;149:450–462. DOI: 10.1161/CIRCULATIONAHA.123.067584

“Fantastic Four” for heart failure and reduced ejection fraction (HFrEF)

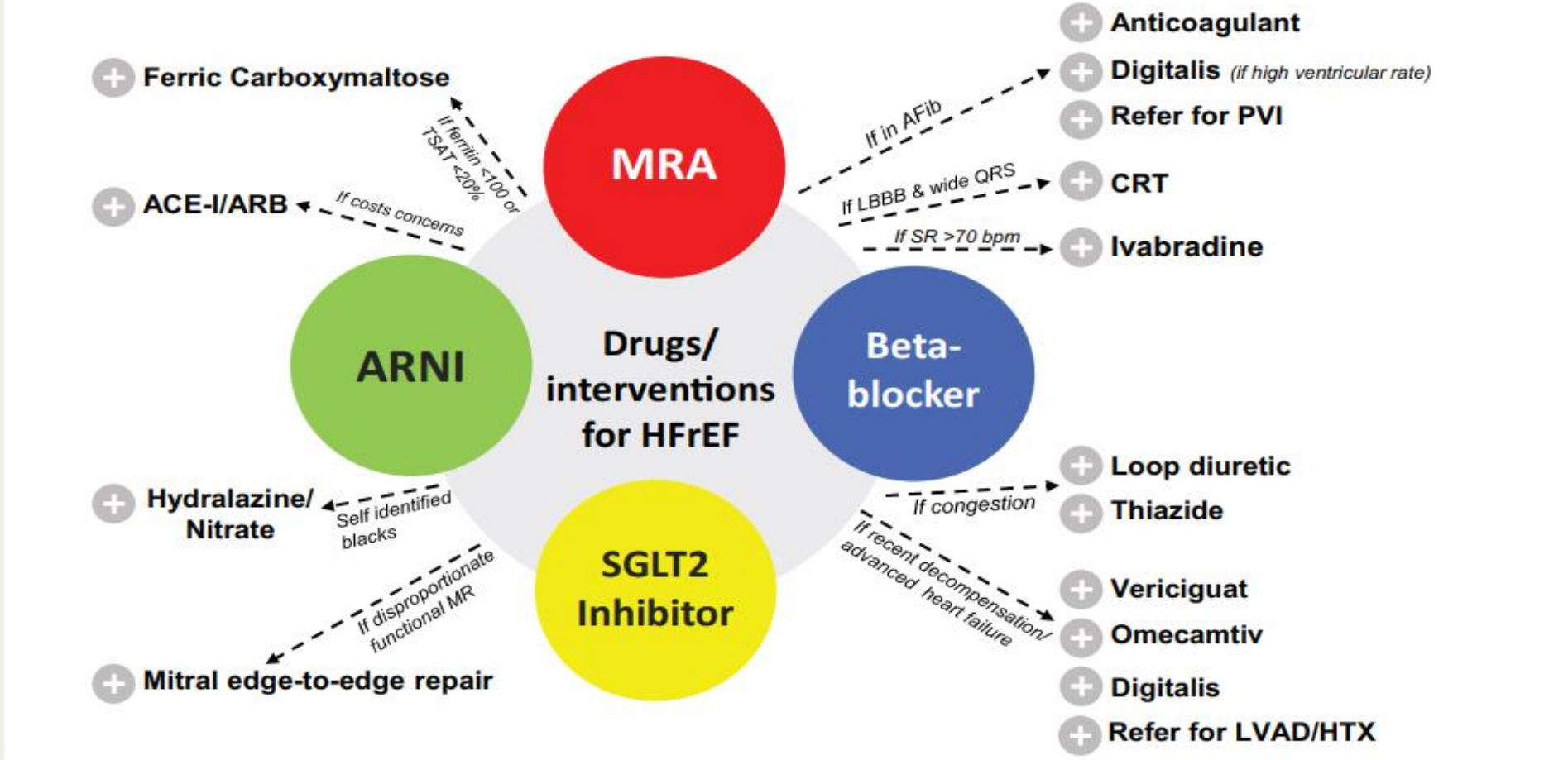


Figure 1 Drug, interventional, and device treatment for heart failure with reduced ejection fraction (HFrEF). ACE-I, angiotensin-converting enzyme inhibitor; Afib, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CRT, cardiac resynchronization therapy; HTX, heart transplantation; LBBB, left bundle branch block; LVAD, left ventricular assist device; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; PVI, pulmonary vein isolation; SGLT2, sodium–glucose co-transporter 2; SR, sinus rhythm; TSAT, transferrin saturation.

European Heart Journal (2021) 42, 681–683

Amani-Beni *et al.*
BMC Cardiovascular Disorders (2025) 25:252
https://doi.org/10.1186/s12872-025-04704-w

BMC Cardiovascular Disorders

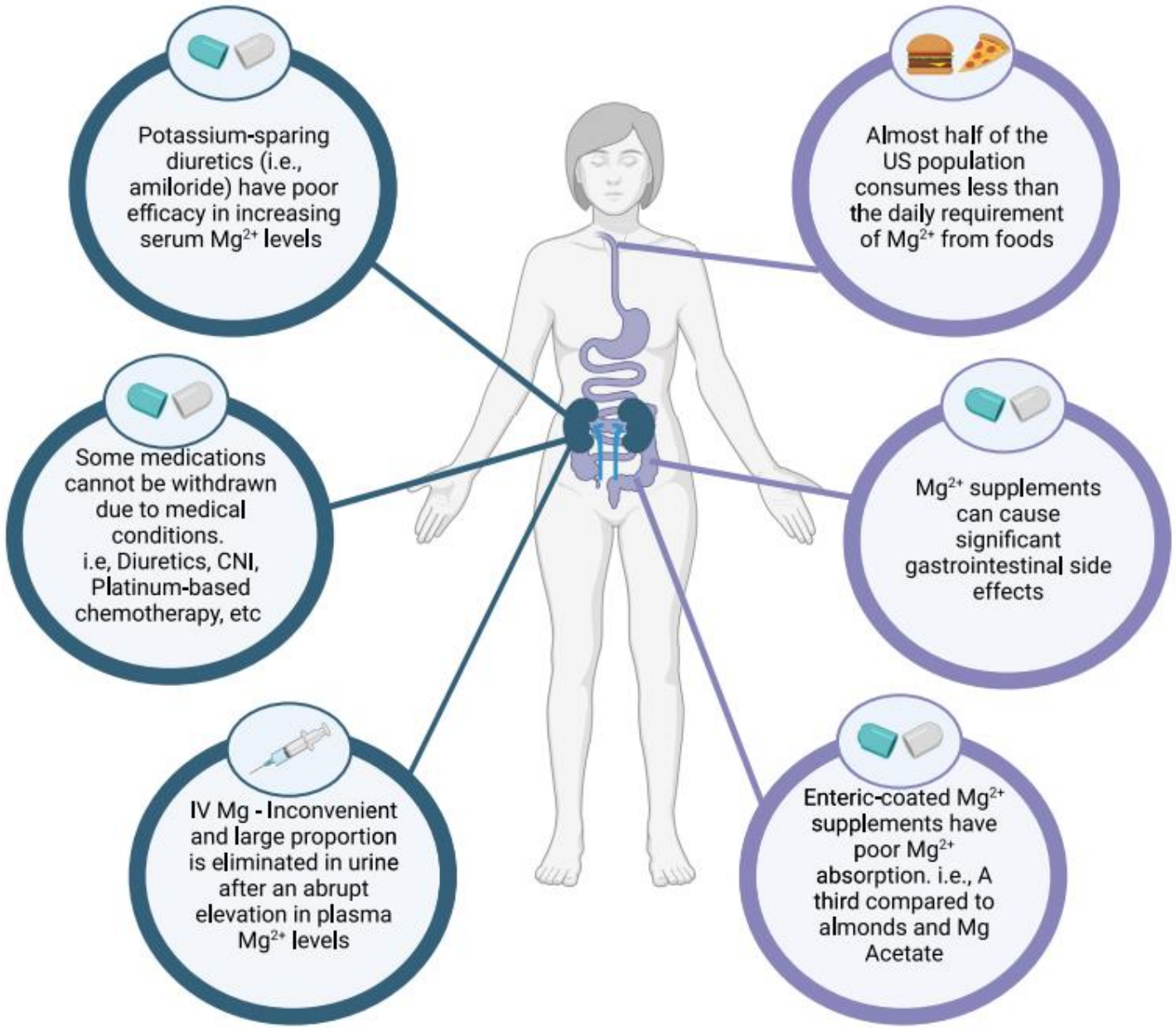
SYSTEMATIC REVIEW Open Access

The impact of sodium-glucose co-transporter-2 inhibitors on serum sodium and potassium in patients with Heart Failure: a systematic review and meta-analysis

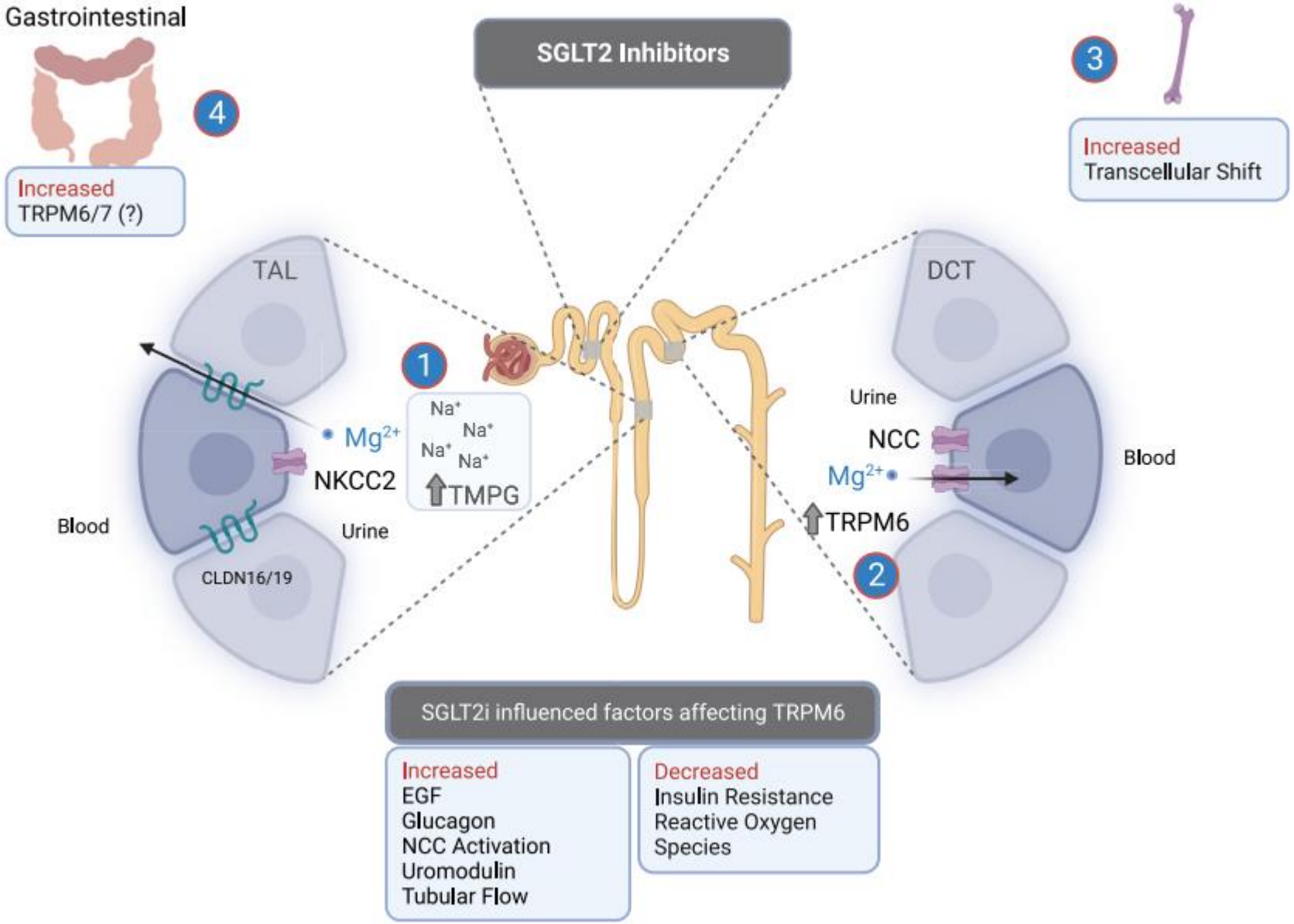
Conclusion SGLT2 inhibitors did not significantly change serum sodium levels in patients with acute and chronic HF. Similarly, regarding serum potassium levels, no clinically significant effect of SGLT2 inhibitors in either acute or chronic HF patients.

Magnesium

Hypomagnesemia Dilemma



- Hypomagnesemia is common, incidence being 25% in T2DM, 14.7% in CKD, and 19–37% in heart failure
- Renal magnesium wasting-induced hypomagnesemia is associated with diabetes
- Due to reduced transient receptor potential ion channel 6 (TRPM6) activity in the distal convoluted tubules, related to insulin resistance
- Associated with a more rapid decline of renal function, a predictor of end-stage renal disease
- Higher rates of cardiovascular disease
- Increased risk of all-cause mortality
- SGLT2i have been shown to increase serum magnesium in patients with T2D (0.08–0.2 mEq/ L in individuals without chronic kidney disease), which contributes to the cardiovascular benefits



Effect of SGLT2 inhibitors on Mg2+ homeostasis.

CLDN 16/19, claudin 16 and 19; EGF, epidermal growth factor; TMPG, transmembrane potential gradient; TRPM6, transient receptor potential cation channel subfamily M member

Observational Study › Clin Exp Nephrol. 2025 Apr;29(4):452-459.
doi: 10.1007/s10157-024-02590-8. Epub 2024 Nov 16.

SGLT2 inhibitors increase low serum magnesium levels in patients with chronic kidney disease immediately after treatment

Treatment with SGLT2 inhibitors significantly increased serum Mg^{2+} levels immediately from 1 month after treatment compared with those at baseline and persisted over 6 months, with an overall mean change of 0.13 mg/dL from baseline to 6 months.
Conclusions: SGLT2 inhibitors increased serum Mg^{2+} levels in patients with CKD, particularly those with lower baseline Mg^{2+} levels, potentially improving their prognosis.

SGLT2is affect serum electrolyte levels in T2D patients

Kidney360

Electronic databases

Pubmed
Embase
Cochrane Central
ClinicalTrials.gov

Up to January 2021

3 independent reviewers

RCTs of at least 24 weeks' duration that compared SGLT2is to placebo

N = 330
Full-text articles screened

Findings

25
trials included

28,269
participants

Canagliflozin 11,936
Dapagliflozin 1,530
Empaglifozin 12,518
Ertuglifozin 1,588
Ipragliflozin 313
Bexagliflozin 384

Effects on electrolyte elevation (vs placebo)

12 Mg

0.07mmol/L
(95% CI,0.06, 0.08 mmol/L)

15 P

0.03 mmol/L
(95% CI, 0.02, 0.04 mmol/L)

No evidence of significantly superior efficacy of any specific SGLT2 inhibitor over the others

No statistically detectable differences among the effects of SGLT2is on serum levels of other electrolytes

Conclusions: This meta-analysis showed that SGLT2is significantly increased serum magnesium and phosphate levels, representing a class effect of SGLT2 inhibition.

Jingjing Zhang, Yonghong Huan, Mark Leibensperger, *et al.* ***Effect of SGLT2 inhibitors on electrolytes.*** *Kidney360.* DOI: 10.34067/KID.0006672021.
Visual Abstract by Omar Taco MD, MSc

Open Access Review
Article

DOI: 10.7759/cureus.60919

The Role of Sodium-Glucose Co-transporter 2 Inhibitors in Patients With Hypomagnesemia: A Systematic Review

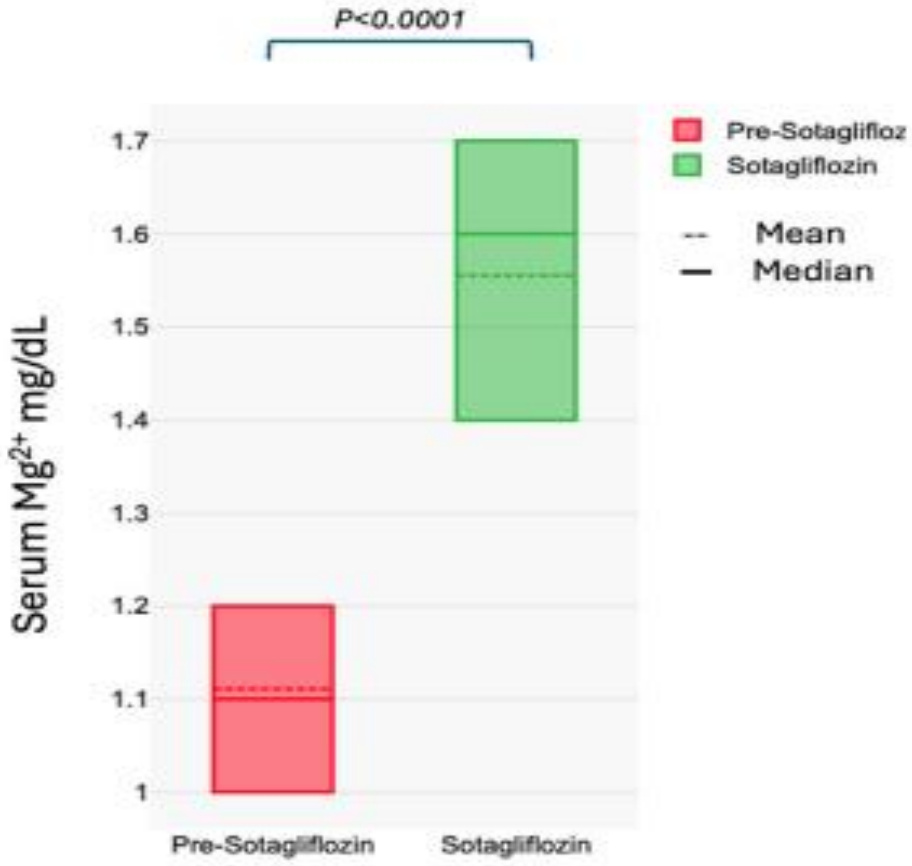
Conclusions

This systematic review highlights the potential effectiveness of SGLT2 inhibitors in addressing refractory hypomagnesemia, particularly in cases associated with urinary magnesium wasting. The findings from the included studies suggest that SGLT2 inhibitor therapy may lead to significant improvements in serum magnesium levels and correction of hypomagnesemia, even in patients with long-standing and treatment-resistant cases.

2024 Singh et al. Cureus 16(5): e60919. DOI 10.7759/cureus.60919

KI REPORTS
KIReports.org

Sotagliflozin in Refractory Hypomagnesemia



Duration	8 years	12 months
FEMg	6%	9%
Oral Elemental Mg (mg/day)	1200	360
IV $MgSO_4$	(+)	(-)

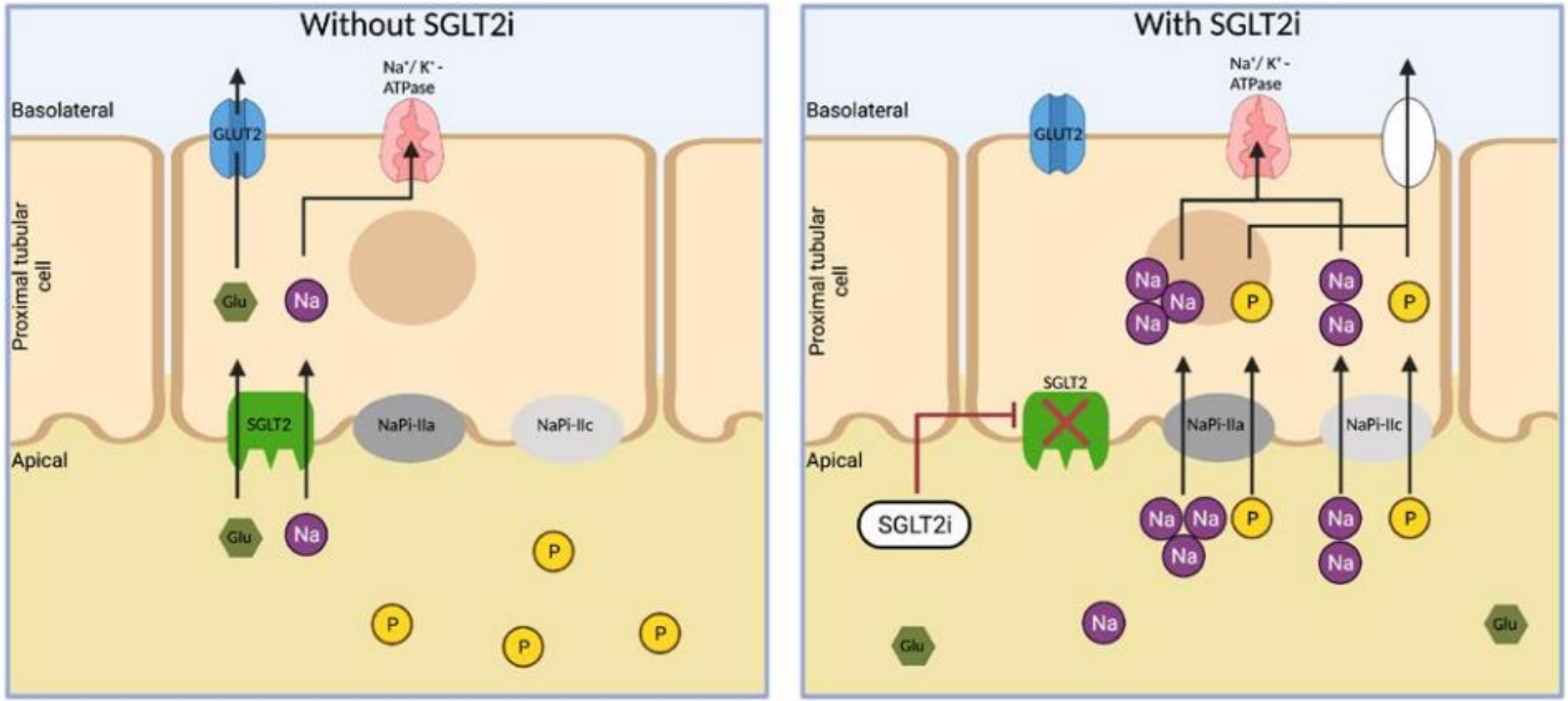
SGLT2i, Dapagliflozin: Improvement in hypomagnesemia, a reduction in fractional excretion of magnesium (FEMg)

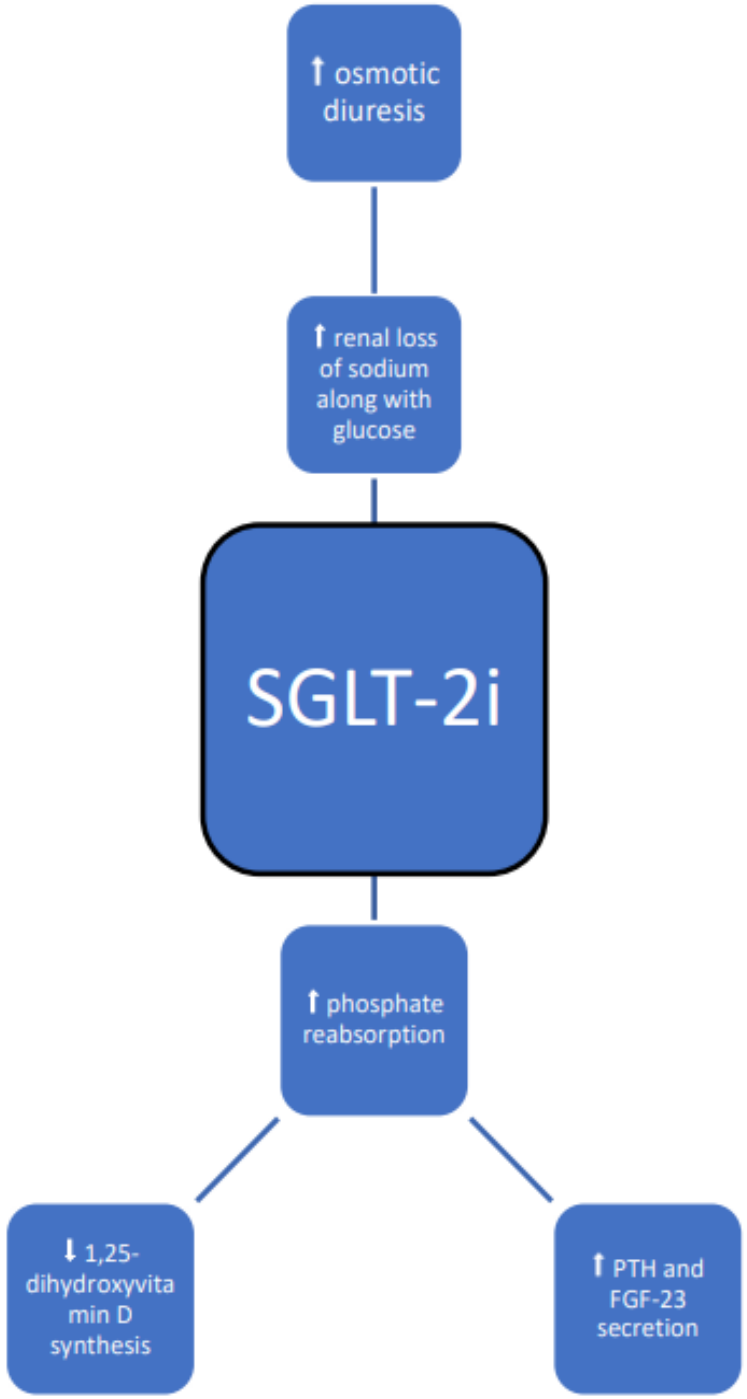
SGLT1 and SGLT2i, Sotaglifozin: a greater glycosuric effect and enhances glucagon secretion, a greater increase in serum mg level, not reducing FEMg, increased intestinal magnesium absorption through SGLT1 in the gastrointestinal tract

national Reports (2025) 10, 966–967

PHOSPHORUS AND CALCIUM

Visual representation of sodium–glucose co-transporter 2 inhibitors effects on phosphorous.

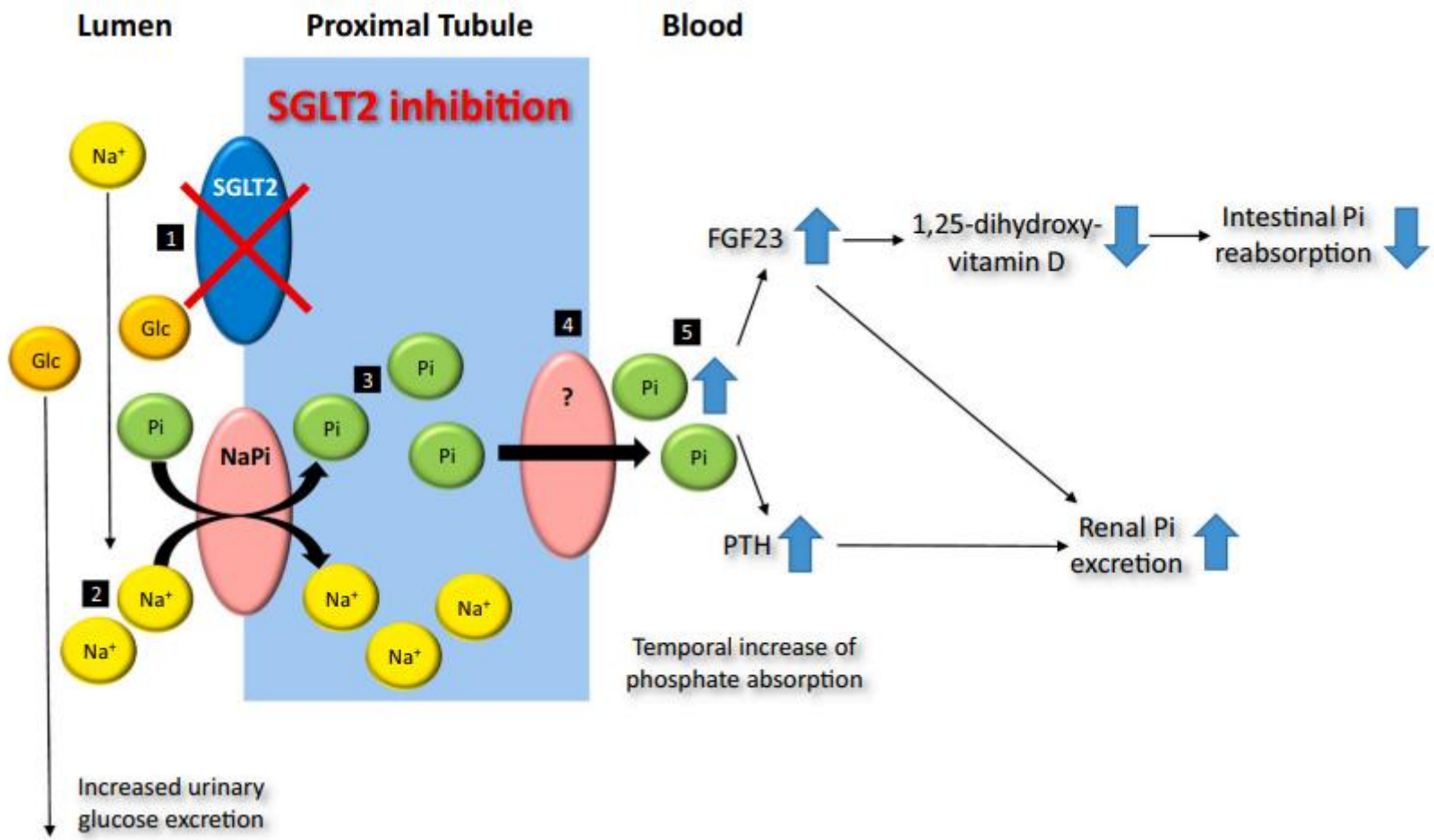




Hyperphosphatemia:
normalization in 3months
Increase in FGF23:
normalization in 6 months

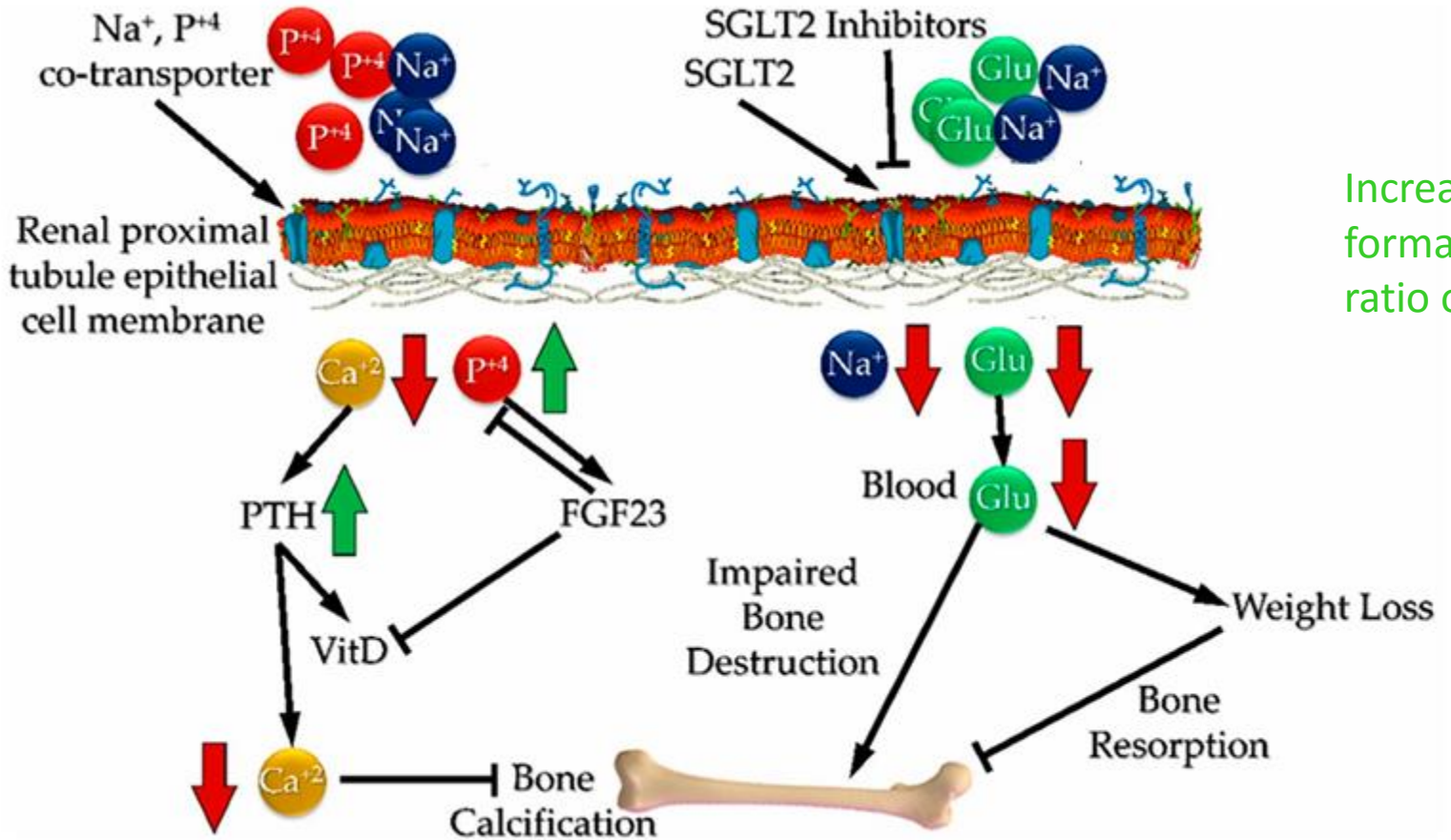
Possible impact of SGLT-2i on bone metabolism

Medicina 2024, 60, 393.
https://doi.org/10.3390/medicina60030393



Under SGLT2 inhibition

Bone Reports 16 (2022) 101175



Increased bone formation index, the ratio of P1NP to CTX

The potential mechanism of SGLT2 inhibitors on bone metabolism.

Effect of SGLT2 inhibitors on fractures, BMD, and bone metabolism markers in patients with type 2 diabetes mellitus: a systematic review and meta-analysis

Review | Published: 11 September 2023

Volume 34, pages 2013–2025, (2023) Cite this article

A total of 20 randomised controlled trials (RCTs) involving 12,764 patients

No significant association emerged between SGLT2 inhibitor use and elevated fracture risk

SGLT2 inhibitors exhibited no substantial effects on BMD changes

No notable impact of SGLT2 inhibitors on bone metabolism markers, including CTX, P1NP, PTH, calcium, and phosphate (Procollagen type 1 N-terminal propeptide (P1NP), a surrogate marker of bone formation, C-terminal telopeptide (CTX), a marker of bone resorption)

Original Investigation

Kidney360

Comparative Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Serum Electrolyte Levels in Patients with Type 2 Diabetes: A Pairwise and Network Meta-Analysis of Randomized Controlled Trials

Jingjing Zhang,[1] *Yonghong Huan*,[2] *Mark Leibensperger*,[3] *Bojung Seo*,[4] *and Yiqing Song*[4]

In this large meta-analysis of 25 RCTs involving 28,269 patients with T2D and six different SGLT2is, we found that SGLT2is significantly increased serum magnesium and phosphate levels, consistent with a class effect of SGLT2 inhibition. In contrast, there was no statistical evidence of differences in serum levels of other electrolytes produced by SGLT2is or specific SGLT2 inhibitor drugs.

KIDNEY360 3: 477–487, 2022

EJCRIM
European Journal
of Case Reports
in Internal Medicine

UNMASKING OF NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM AFTER SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITOR INITIATION

Christodoulos Dolapsakis, Emmanouil Karofylakis, Stamatios Chalvatzis

4th Department of Internal Medicine, National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have complex interactions with bone metabolism, including an increase in parathyroid hormone (PTH) levels. Although normocalcemic primary hyperparathyroidism is a rare entity, we propose obtaining a baseline PTH level before starting a SGLT2 inhibitor in patients with calcium levels in the upper limit of normal and normal total 25-hydroxyvitamin D levels, especially if they are under vitamin D supplementation. PTH should be rechecked in order to exclude overt primary hyperparathyroidism.

Kidney stone

Iran reports a prevalence of 21.1%,
SGLT2i may help reduce the risk of urolithiasis, particularly in patients with diabetes
The changes in urinary composition might also increase the risk of uric acid stone formation.
SGLT2 inhibitors specifically target CaOx stone formation and related renal inflammation
Their potential impact on other calcium-containing stones, such as calcium phosphate, remains promising.

CLINICAL RESEARCH: NEPHROLITHIASIS

The Impact of SGLT2 Inhibitors and GLP-1 Receptor Agonists on 24-hour Urine Parameters

A Retrospective Cohort Study

The cross-sectional cohort included 124 patients with a prescription fill for SGLT2i (and 620 matched controls)
Lower urine pH and higher sulfate, and uric acid were observed SGLT2is were associated with higher urine volume and citrate

Kidney360 :10.34067/KID.0000000728, February 07, 2025

Journal of
Clinical Medicine

MDPI

Review

SGLT2 Inhibitors and Their Effect on Urolithiasis: Current Evidence and Future Directions

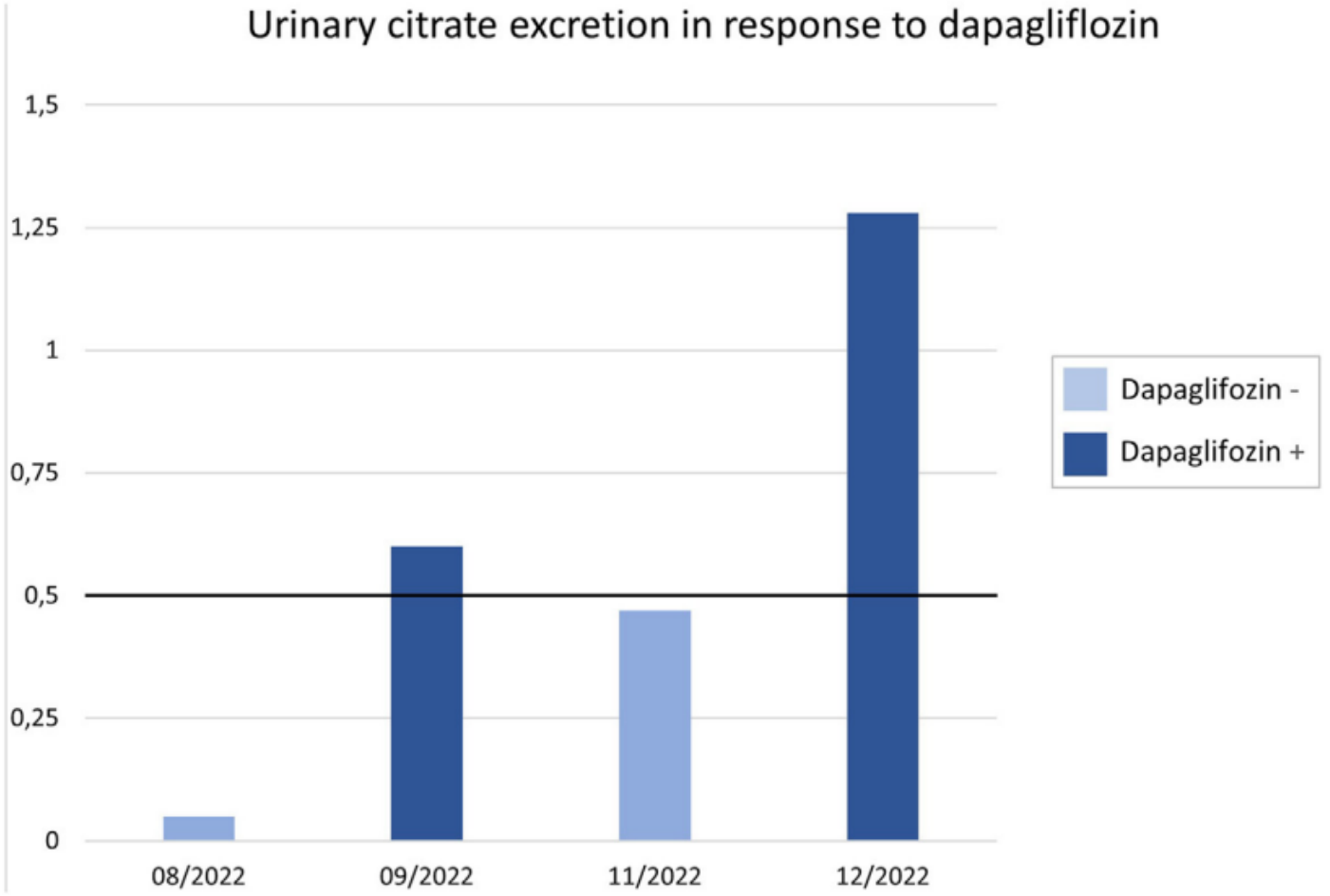
Živka Dika [1,2,*], Marijana Živko [2], Marina Kljajić [2] and Bojan Jelaković [1,2]

In conclusion, UL has become more common worldwide, partly due to rising rates of CRM diseases, which are bidirectionally related to stone formation. SGLT2 inhibitors may help reduce UL risk, particularly in patients with diabetes. However, these inhibitors also pose a potential risk for increased uric acid stone formation

Kidney Medicine

SGLT2 Inhibitor Use for Treatment of Hypocitraturia in a Distal Renal Tubular Acidosis

Stefan Scherr, Sara H. Ksiazek, Christoph Schwarz, and Marcus D. Säemann



Urinary citrate excretion corrected for body surface area (mmol/L/m2) in response to dapagliflozin. The lower reference value is indicated by a black line.

Kidney Med Vol 6 | Iss 7 | July 2024 | 100839

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).

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, electrolyte abnormalities, and glomerular diseases.