

In The Name Of GOD



The **19th**
International Congress of
**Nephrology, Dialysis
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(ICNDT)

12-15 December 2023
Homa Hotel, Tehran

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Use of SGLT2 Inhibitors in Nondiabetic Kidney Disease

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Outlines

- Introduction SGLT2 and SGLT2 inhibitors
- Renal protective pathways
- The latest RCT in this regard
- The nephrologist's guide
- Take home message

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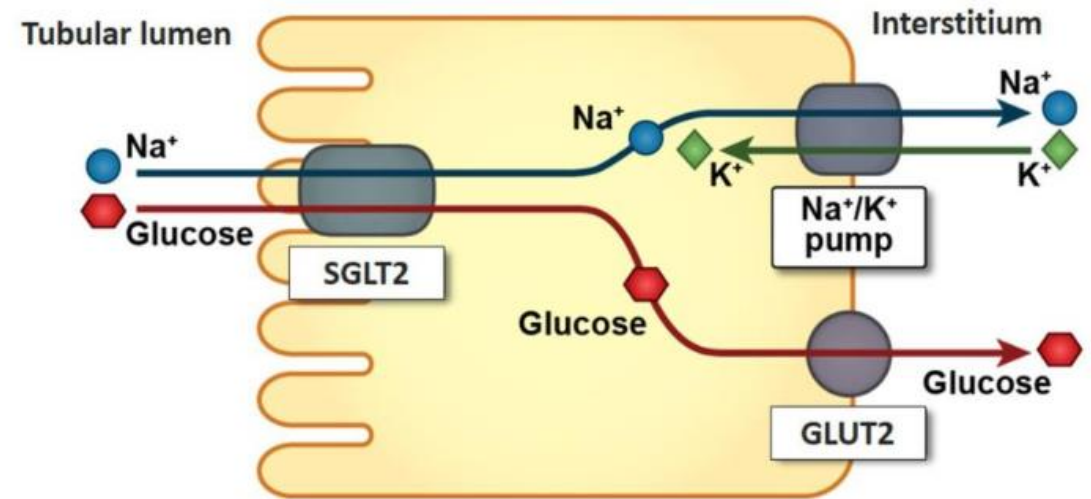
Introduction SGLT2

Sodium-Glucose Cotransporters

	SGLT1	SGLT2
Site	Mostly intestine with some kidney S2/S3	Almost exclusively kidney S1/S2 segments proximal tubules
Sugar specificity	Glucose or galactose	Glucose
Affinity for glucose	High Km = 0.4 mM	Low Km = 2 mM
Capacity for glucose transport	Low	High
Role	Dietary glucose absorption Renal glucose reabsorption	Renal glucose reabsorption

Lee YJ, et al. *Kidney Int Suppl.* 2007;S27-S35.^[5]

Active (SGLT2) and Passive (GLUT2) Glucose Transport in a Renal Proximal Tubule Cell



Nair S, Wilding JP. *J Clin Endocrinol Metab.* 2010;95:34-42.^[6]

SGLT2 inhibitors: **gliflozins**

- Originally developed to **improve glycemic control**,

Reduce blood glucose concentrations by:

- Inhibiting the main glucose transporter on the luminal surface of the
 - **proximal tubule**

- Suppress glucose reabsorption,
 - Resulting in glucosuria.

- the evidence from randomized clinical trials has shown a light on

- **Their efficacy** in
 - **Kidney and Heart Protection**
 - even **Without Diabetes.**

[Kidney Med.](#) 2023 Apr; 5(4): 100608.

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Renal Protective Pathways

SGLT2 inhibitors

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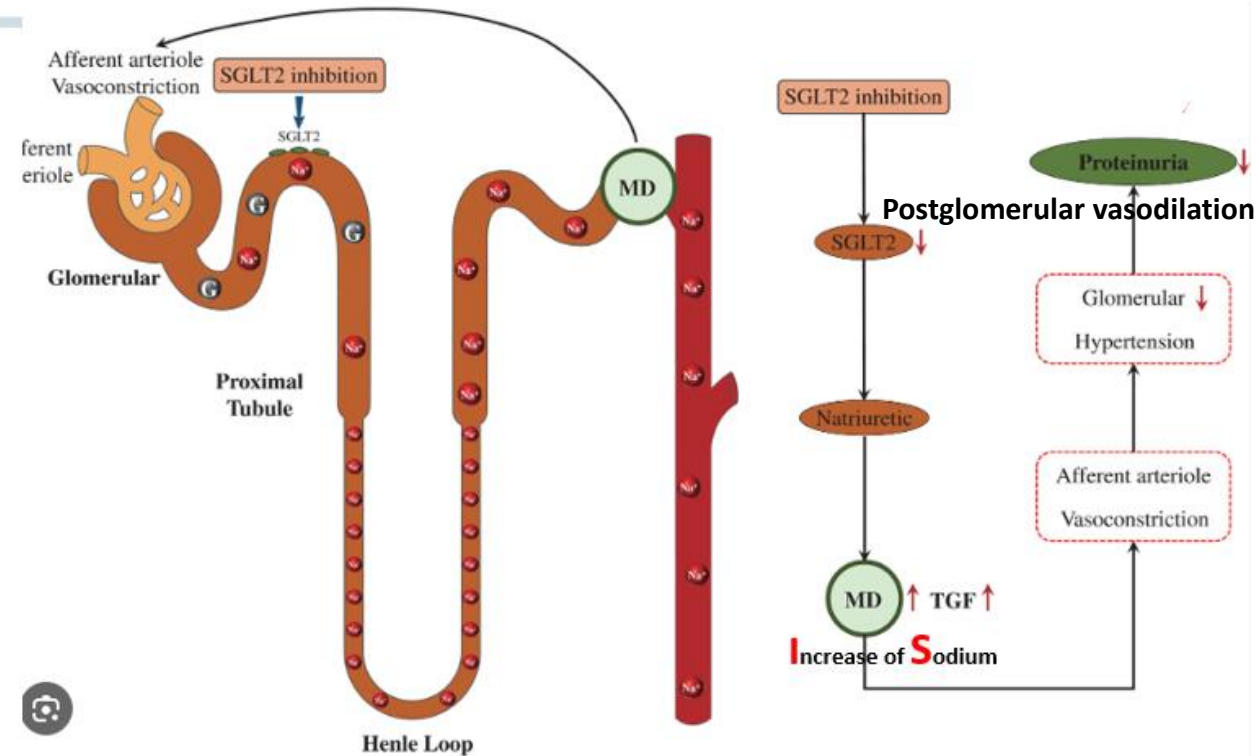
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Renal Protective Pathways

Direct renal benefits

- **F**irstly, **SGLT2i**, by
- **R**educing **S**odium **R**eabsorption at the proximal tubules,
- causes an **I**ncrease of **S**odium concentration at the
- **macula densa**,
- which in turn **E**nhances sodium entrance in the cell and therefore **E**nhances its osmolarity
- The net effect is an **I**ncrease in ATP's conversion to adenosine leading to
- **vasoconstriction of the afferent arterioles**—via the—**TubuloGlomerular Feedback**



Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation*. 2016;134(10):752–

Renal protective pathways

Direct renal benefits

SECONDLY SGLT2I Causing **Osmotic Diuresis**

- working in synergy with the other diuretics, in particular loop diuretics
- Indeed, it has been demonstrated that SGLT2i Primarily **Reduces Interstitial Volume**,
- with a minor effect on intravascular volume.

Griffin M, Rao VS, Ivey-Miranda J, Fleming J, Mahoney D, Maulion C, Suda N, Siwakoti K, Ahmad T, Jacoby D, Riello R, Bellumkonda L, Cox Z, Collins S, Jeon S, Turner JM, Wilson FP, Butler J, Inzucchi SE, Testani JM (2020) Empagliflozin in heart failure: diuretic and cardio-renal effects. Circulation. 10.1161/CIRCULATIONAHA.120.045691

Renal Protective Pathways

With Blocks of:

❖ proximal Sodium Reabsorption

❖ leading to **Natriuresis** (Figure 1).

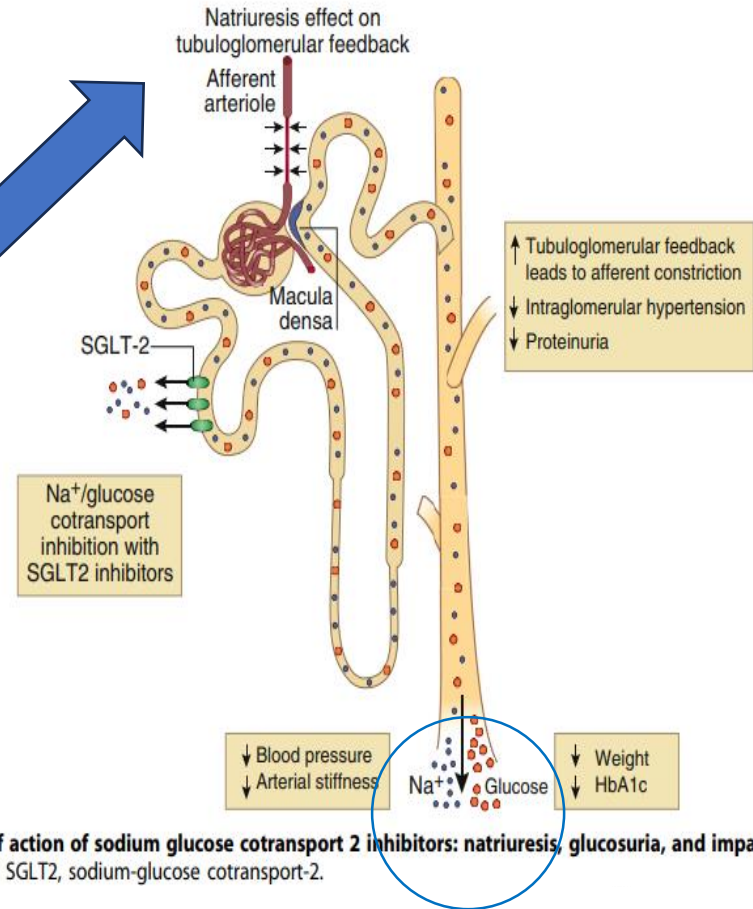


Figure 1 | Mechanism of action of sodium glucose cotransport 2 inhibitors: natriuresis, glucosuria, and impact on clinical parameters. HbA1c, hemoglobin A1c; SGLT2, sodium-glucose cotransport-2.

Renal Protective Pathways

- Treatment with the **SGLT1/2** inhibitor (**gliflozins**) improves :
- **Cortical Oxygen Tension**
- but at the expense of Medullary Hypoxia,
- possibly due to **increased distal solute delivery**,

• **Selective SGLT2 inhibition** may also **Reduce Renal Ischemic Injury.**



Renal Protective Pathways

Indirect renal benefits

Sympathetic nervous system

The cross-talk between :

the sympathetic nervous system and SGLT2

in animal models:

- it has been **demonstrated that chemical sympathetic denervation** in neurogenic hypertensive mice resulted in :
 - **Reduced Renal SGLT2 Expression**

➤ Dapagliflozin ^{-treated mice}

- showed a significant
- **Decrease** in the expression of markers of **sympathetic activity** and a **reduction in blood pressure**
- activates the **non-classic pathway of RAAS** by **Stimulating the type 2 angiotensin II receptor** with **vasodilatation and anti-inflammatory properties,**

Herat LY, Magno AL, Rudnicka C, Hricova J, Carnagarin R, Ward NC, et al. SGLT2 inhibitor–induced Sympathoinhibition a novel mechanism for cardiorenal protection. *JACC Basic Transl Sci.* 2020;5(2):169–179

Renal Protective Pathways

Indirect renal benefits

- **Weight Loss**
- **High body mass index (BMI) is one of the strongest risk factors for new-onset CKD.**
- **Metabolic effects induced by SGLT-2 inhibition** that seem to significantly contribute to weight loss.

Reduction	Increased
in visceral adipose tissue	urinary glucose excretion
insulin secretion,	lipolysis, and fat oxidation



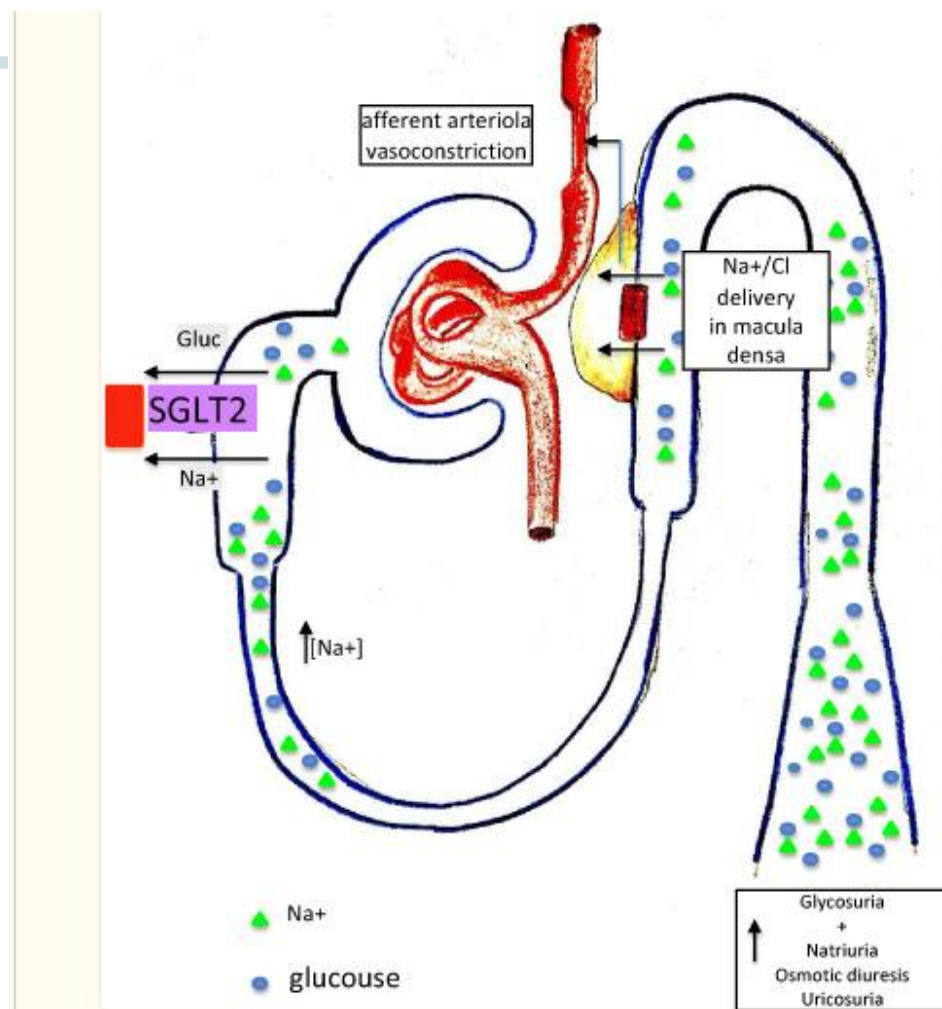
Effect of SGLT2i on Renal Uric Acid Handling

- **Hyperuricemia** is a common finding in CKD patients,
- and it has been **linked to tubulointerstitial fibrosis progression** through the **induction of**
 1. inflammation
 2. oxidative stress
 3. endothelial dysfunction
 4. and RAS activation.
- Therefore, **SGLT2 inhibition** may possibly **Indirectly** contribute to **renal tubular protection**
- by lowering serum uric acid levels

- significant **Reduction in the serum uric acid concentration**
 - through **Increased Uricosuria.**
 - Although the mechanism is not clearly understood,
 - **Changes the activity of GLUT-9 isoform b**
- **Reducing urate reabsorption .**

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Effects of SGLT2 inhibition on the kidney ,direct and indirect renal benefits



Direct Renal Effects

1. Osmotic diuresis—> intestinal pressure
2. Reduction of oxygen consumption
3. Reduction of oxidative stress and inflammation
4. Reduction of intraglomerular hypertension

Indirect Renal Effects

1. Reduction of blood pressure
2. Reduction of body fat and body weight
3. Reduction of oxidative stress and inflammation
4. Uricosuria
5. Reduction of plasma volume
6. Activation of AT2 type 2
7. Sympathetic system modulation

Mostly due to glycosuria

Mostly due to natriuresis

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Hediger MA, Rhoads DB. Molecular physiology of sodium-glucose cotransporters. *Physiol Rev.* 1994;74:993-1026.

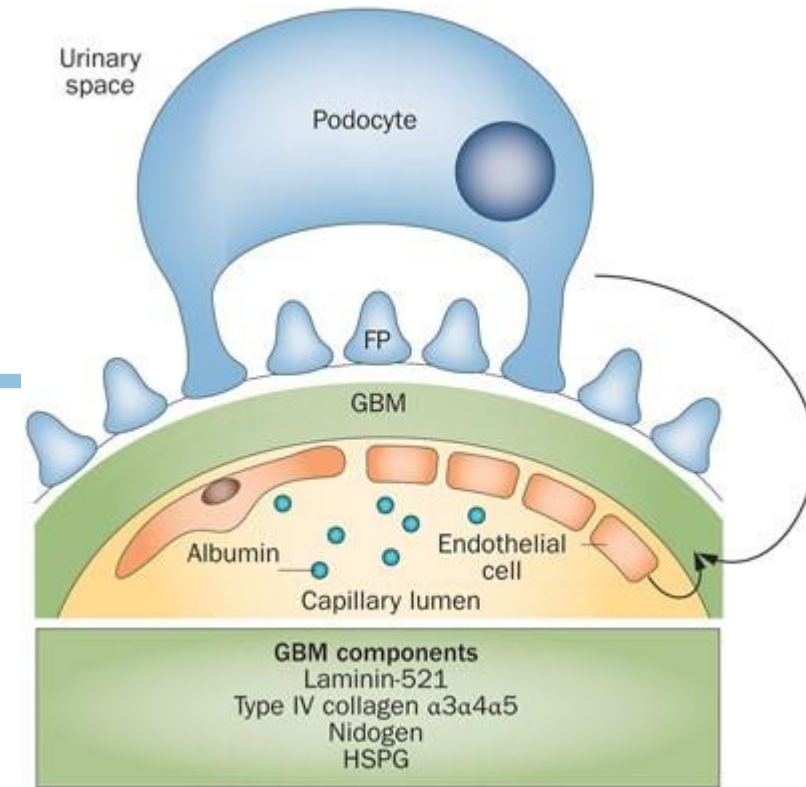
Renal Protective Pathways

AT THE LEVEL OF
The Glomerular Filtration Barrier

The Glomerular Filtration Barrier

consists of :

1. Glomerular Endothelial cells (**GECs**)
2. Glomerular Basement Membrane
3. Podocytes



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SGLT-2 Inhibitors in Nephrotic Range Proteinuria: Emerging Clinical Evidence

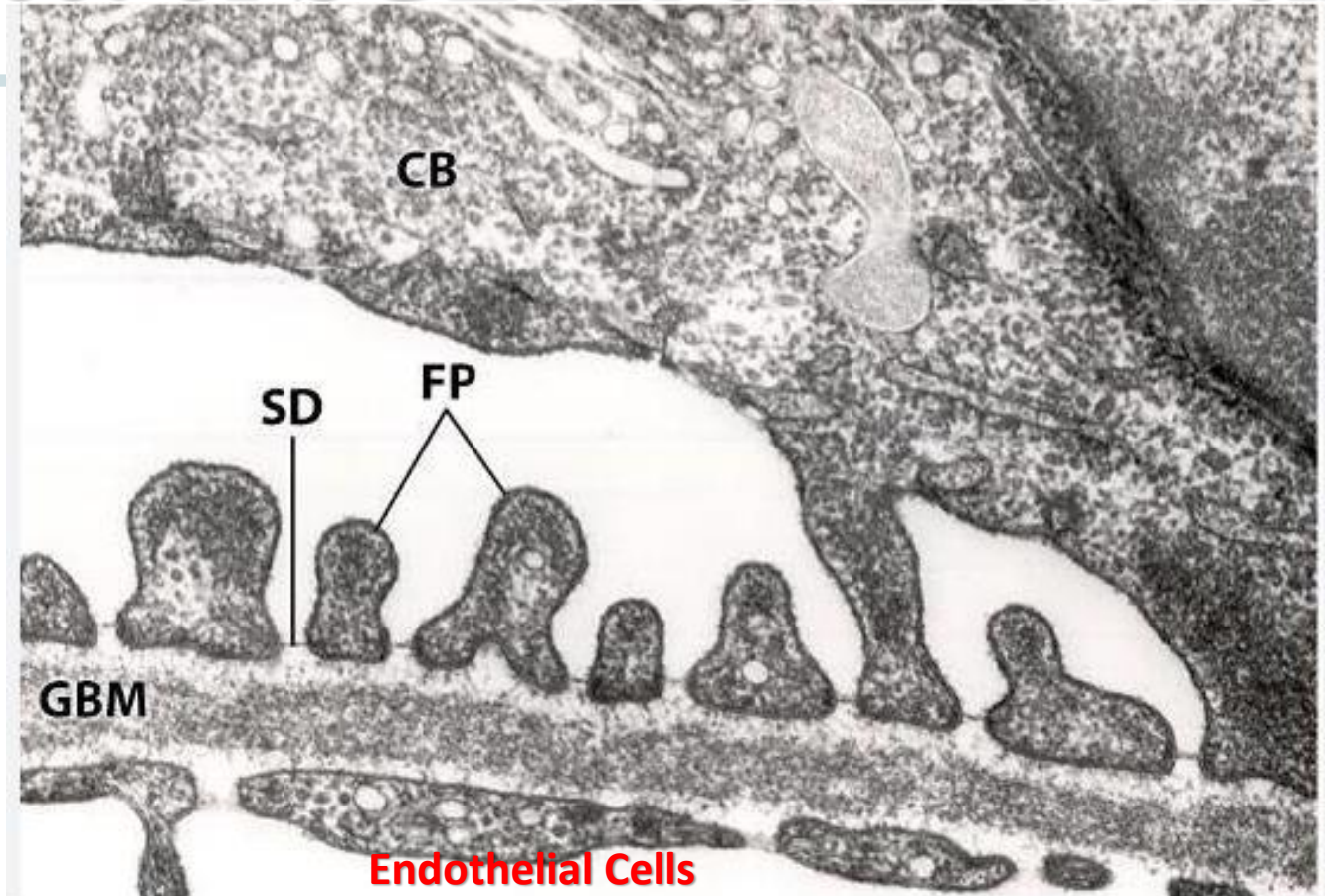
August 2022 · CKJ: Clinical Kidney Journal · 16(1)

DOI: [10.1093/ckj/sfac189](https://doi.org/10.1093/ckj/sfac189)

Beneficial role of SGLT-2 inhibitors in reducing proteinuria and delaying chronic kidney disease (CKD) progression in patients with nephrotic range proteinuria.

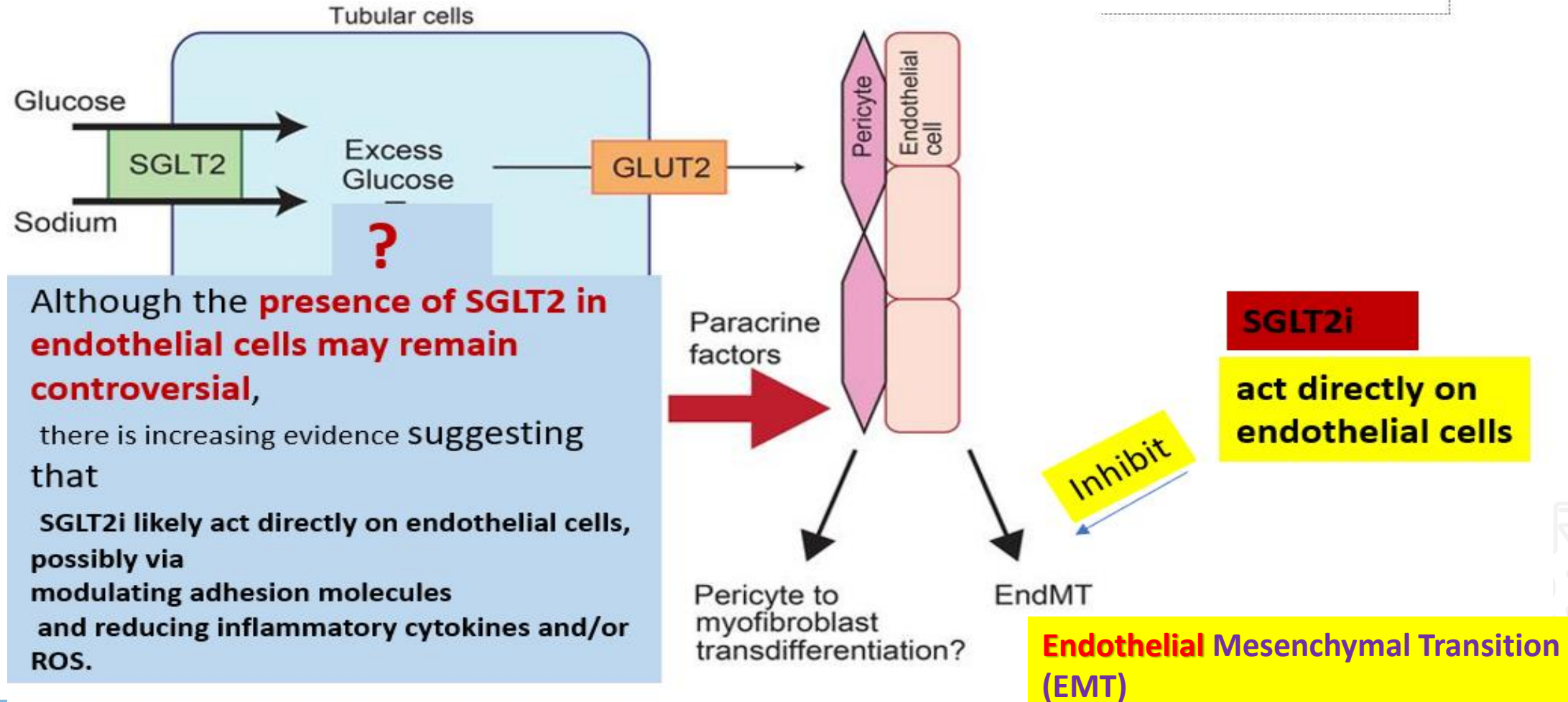
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Effect of SGLT2i on Endothelial Cells



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Effect of SGLT2i on Endothelial Cells



Effect of SGLT2i on Endothelial Cells

- **IN animal studies:** in the hearts of Dahl salt-sensitive rats

▪ Dapagliflozin

Decreased the overexpression of

1. **VCAM-1**
2. **E-selectin**

- and **Restored the downregulated eNOS levels**

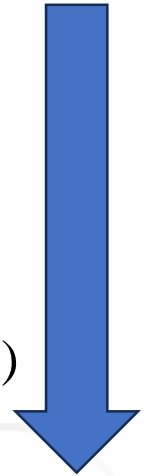


- In the atherosclerosis model of **Apo E knockout mice**,

▪ **E**mpagliflozin for 8 weeks **Lowered:**

circulating levels of:

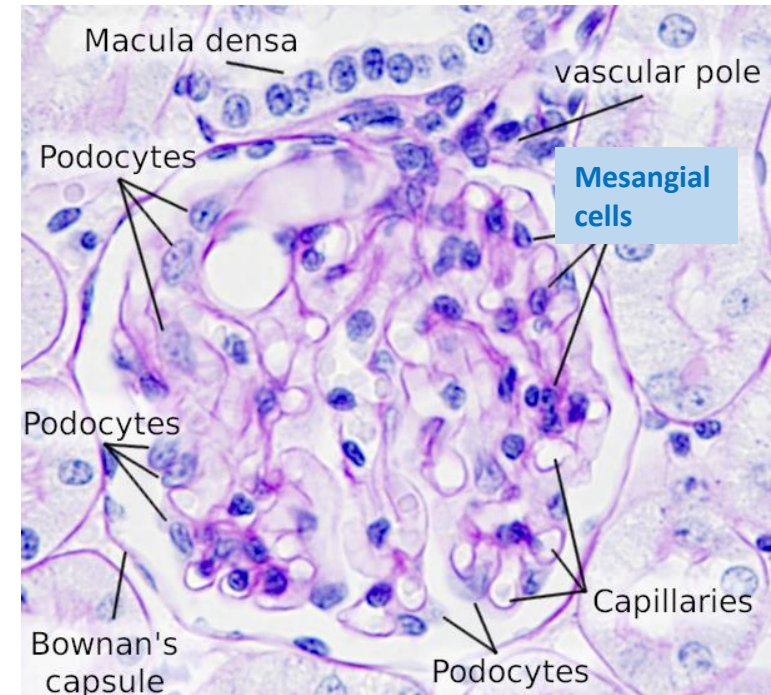
- Tumor necrosis factor alpha (**TNF α**)
- Interleukin-6 (**IL-6**)
- Monocyte chemoattractant protein 1 (**MCP-1**)
- high-sensitivity C-reactive protein . (**hs-CRP**)



- **Reducing Inflammation in Endothelial cells,**
➤ **Leading to: Improved Endothelial Function**

Effect of SGLT2i on Mesangial Cells

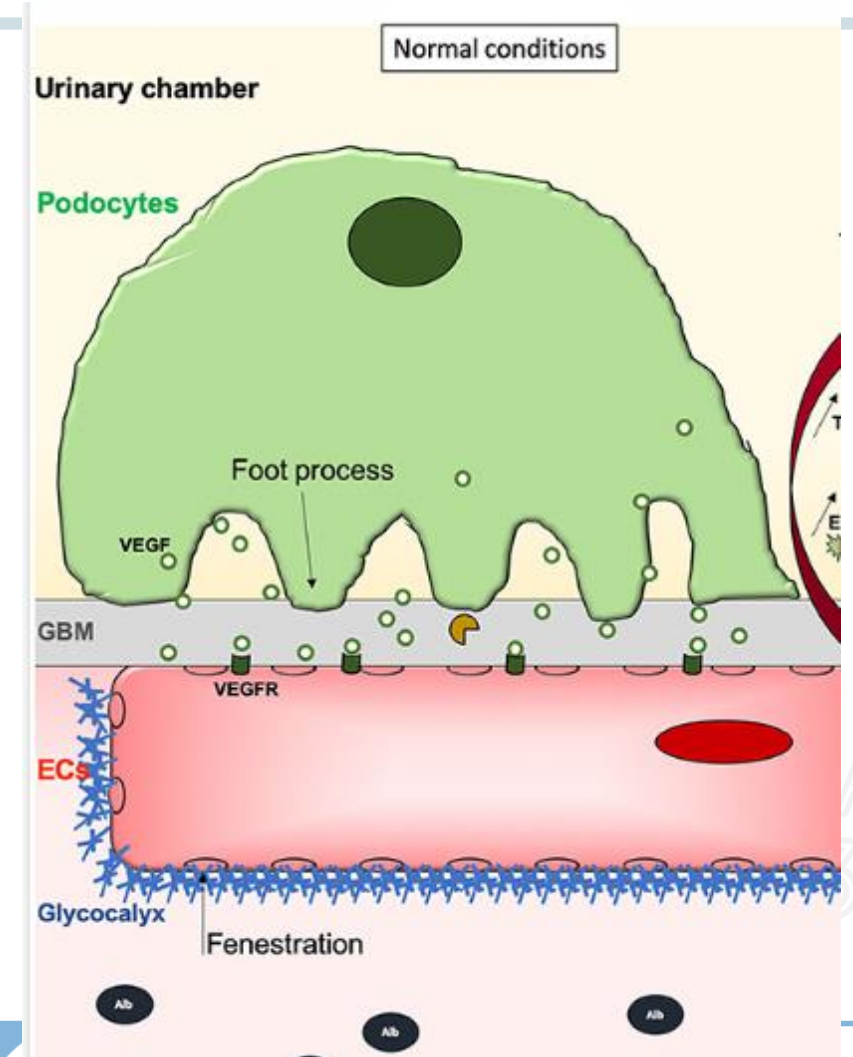
- **SGLT2 expression** has been reported to be present in mouse Mesangial cells.
 - Low-dose administration of **Canagliflozin, Improved:**
 - **Mesangial Expansion**
 - **Albuminuria**
- By Inhibitions of:**
- **Protein Kinase C activation(PKC)**
 - **ROS production**

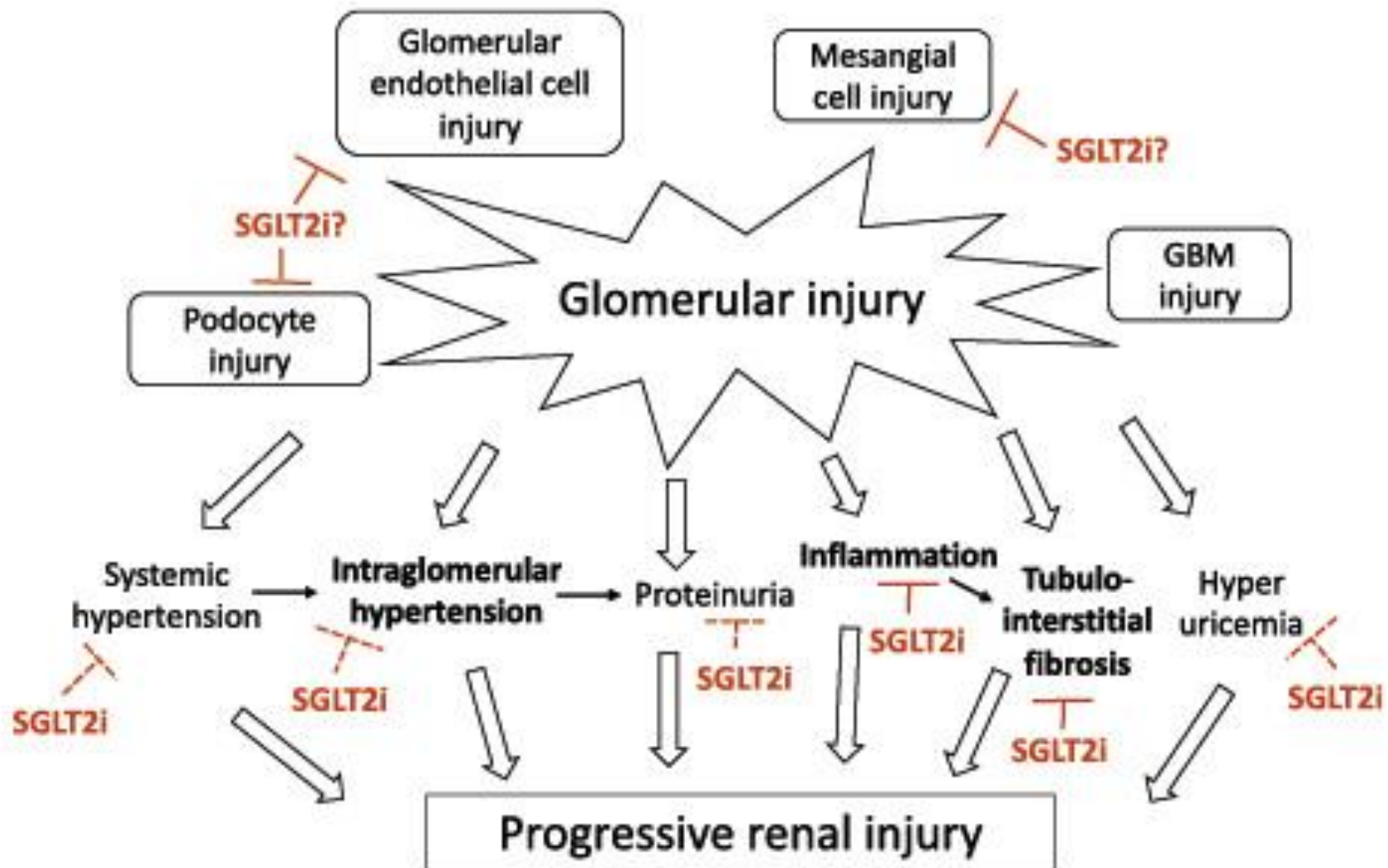


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Effect of SGLT2i on Podocytes

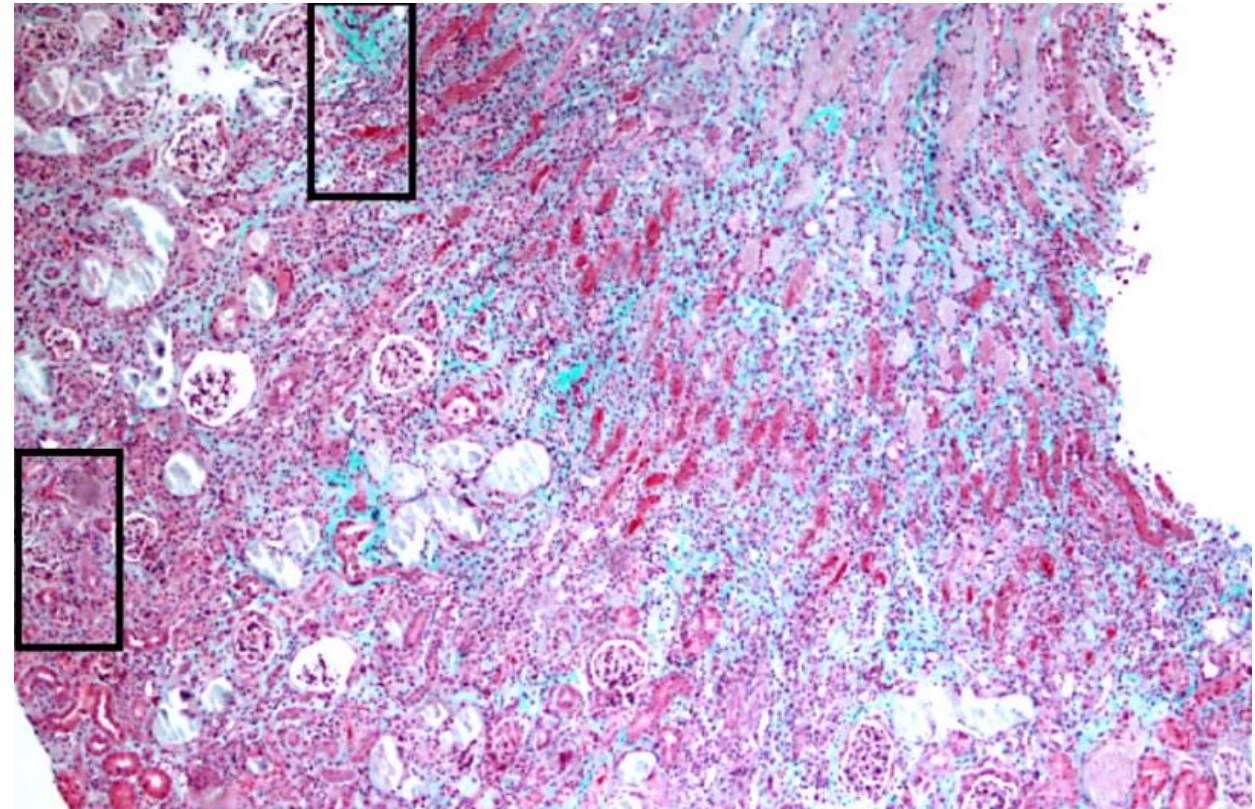
- Cassis et al. reported that
- SGLT2 is expressed in mouse and human Podocytes.
- Dapagliflozin Ameliorated
- Proteinuria
- Glomerular Lesions
- Foot process effacement .



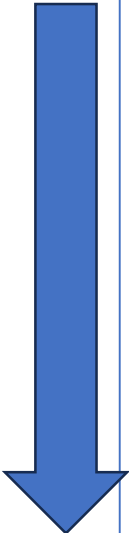


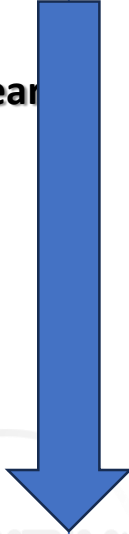
Effect of SGLT2i on Tubulointerstitial Fibrosis

- **Renal Fibrosis** IS THE LEADING CAUSE OF **ESRD/CKD**
- Even if the primary cause of CKD is glomerular injury,
- **The Best predictor of renal functional decline is actually the extent of interstitial fibrosis**



Effect of SGLT2i on Tubulointerstitial Fibrosis

- in the study by **Li et al.**
 - during the **2-year follow up**
 - **Empagliflozin** suppressed the **EMT** in the renal proximal tubules.
 - **Canagliflozin 300 mg/day**
Decreased plasma levels of
 - **TNF receptor 1 (TNFR1)**
 - **IL-6**
 - **Matrix Metalloproteinase 7(MMP7)**
 - **Fibronectin 1 (FN1)**
- 

- In human immortalized proximal tubular cells =
 - **Empagliflozin** attenuated
 - **Toll-like receptor-4 (TLR-4)** expression
 - **nuclear deoxyribonucleic acid binding for nuclear factor kappa B (NF-κB),**
 - **IL-6** secretion
 - **collagen IV** expression
 - **Dapagliflozin** also **reduced** :
 - **alpha smooth muscle actin (α-SMA)**
 - **STAT1**
 - **Transforming growth factor-β1 (TGF-β1)** expression
- 

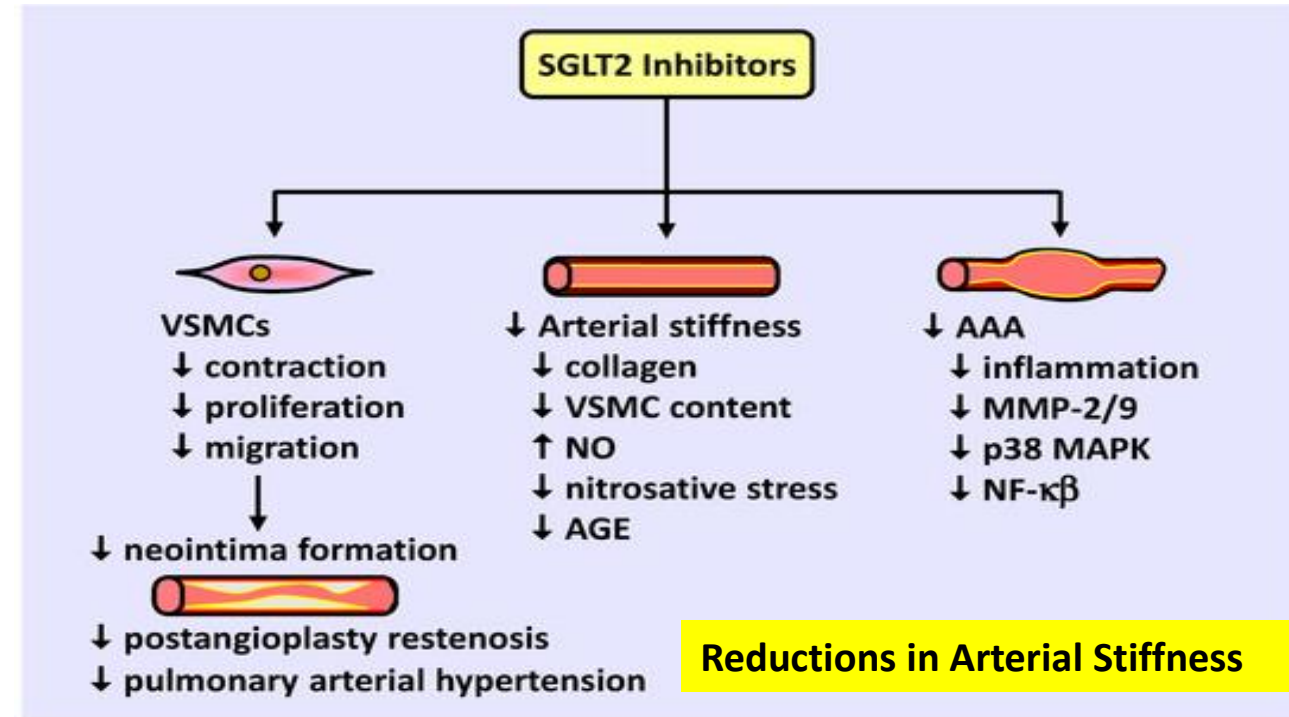
Renal Protective Pathways At the **structural** level

Antihypertensive effects of SGLT2 inhibitors

are also associated with Reductions in

• Arterial Stiffness,

• a marker of cardiovascular and renal risk.



Effects of Sodium-Glucose Co-Transporter 2 Inhibitors on Vascular Cell Function and Arterial Remodeling

by William Durante* and Ghazaleh Behnammanesh and Kelly J. Peyton

Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, MO 65212, USA

* Author to whom correspondence should be addressed.

Int. J. Mol. Sci. 2021, 22(16), 8786; <https://doi.org/10.3390/ijms22168786>

Renal Protective Pathways At the **structural** level

Hematocrit & SGLT2 inhibition

- ❑ Sano et al. : **Increase in Hematocrit** with SGLT2 inhibition **is due to Normalization of Renal Cortical Oxygenation,**
- ❑ thereby restoring **Normal cellular function** to erythropoietin-producing cells,



Renal Protective Pathways

SGLT2 inhibitors promote

- I. Anti-inflammatory**
- II. Antifibrotic pathways**
- III. Improve renal oxygenation**

➤ **Reduce** the state of Renal hypoxia

➤ **effects on reduced** :

- 1. Glomerular hypertension**
- 2. and Hyperfiltration.**

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Clinical Studies

Effects of SGLT2i on Renal Function in Clinical Studies in Patients with Nondiabetic CKD

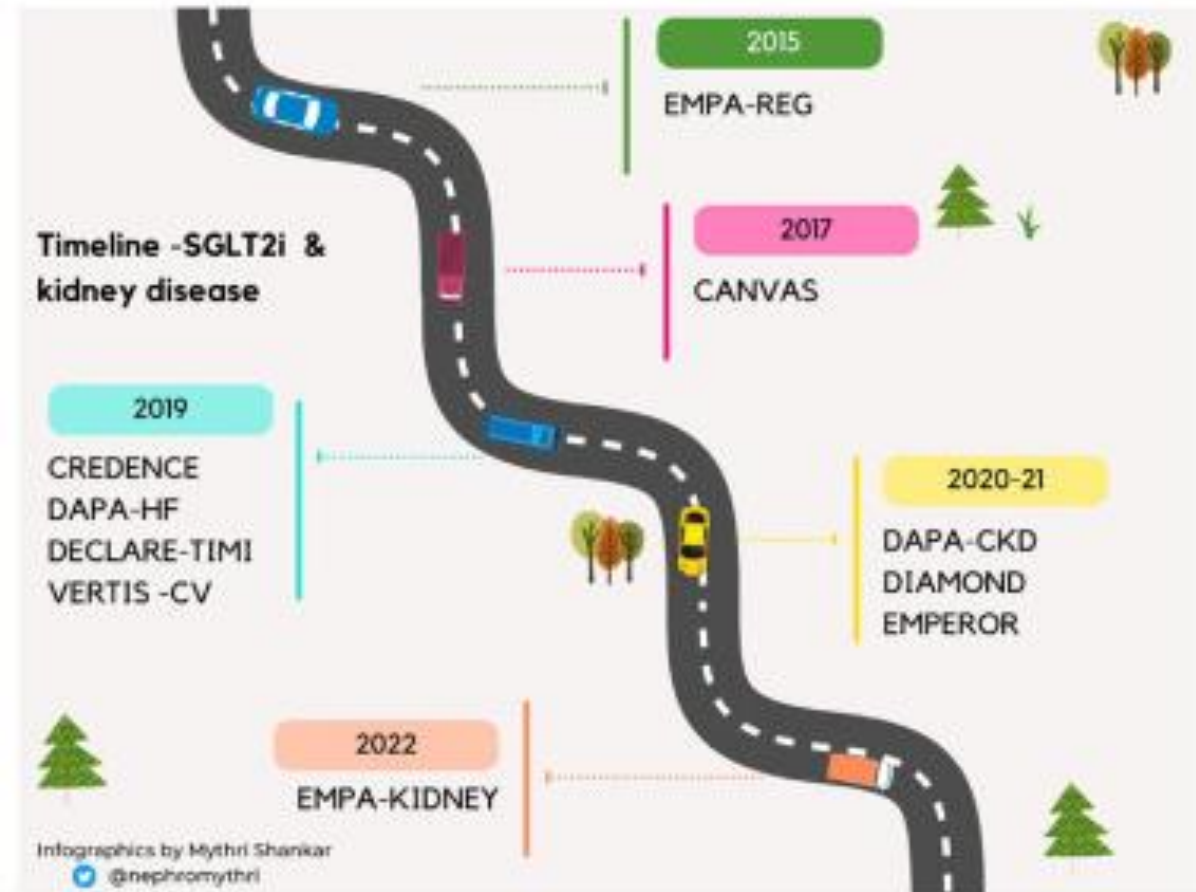
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Timeline of trials involving SGLT2 inhibitors

- SGLT2 inhibitors have **come a long way in a short period of time.**
- Drugs has **Revolutionized the management of:**
- **Chronic Kidney disease (CKD)**
- and **Heart Failure**, irrespective of the underlying diabetes status.



Pharmacologic SGLT2 inhibition

FDA-Approved and Investigational SGLT2 Inhibitors

FDA-Approved	Investigational
Canagliflozin	Ertugliflozin*
Dapagliflozin	Ipragliflozin*
Empagliflozin	Luseogliflozin*
	Tofogliflozin*

□ available in Japan

Limitations include

- Increased risk for genital mycotic infections
- Potential for polyuria
- Dose-related increase in LDL-C
- Risk for volume depletion/hypotension/dizziness

*The US FDA has not yet approved this medication for use.

- Ertugliflozin
- Sotagliflozin, a combined SGLT2 and SGLT1 inhibitor) currently under **investigation**.

Pharmacol., 01 June 2023
Sec. Translational Pharmacology
Volume 14 - 2023 | <https://doi.org/10.3389/fphar.2023.1142003>

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In the **DAPA-CKD 2020** study

- **4,304** patients,
- were randomized to receive **Dapagliflozin 10 mg/day or placebo**.
- “**overwhelming efficacy**” of dapagliflozin.
- Over a median **follow-up period of 2.4 years**,
- the **primary endpoint**
- a composite of **sustained decline in the eGFR of at least 50%**,
- **end-stage kidney disease**,
- **or death from renal**
- **or cardiovascular causes**)
- was significantly **attenuated by dapagliflozin**
- (hazard ratio, 0.61; 95% CI: 0.51–0.72; $p < 0.001$).

CKD in those without T2D were reported as

- **ischemic/hypertensive nephropathy [16%]**,
- **IgA nephropathy [6.3%]**
- **FSGS [2.7%]**
- **membranous nephropathy [1%]**
- **minimal change disease [0.3%]**
- **chronic pyelonephritis [1.6%]**
- **chronic interstitial nephritis [1.2%]**
- **obstructive nephropathy [0.6%]**
- **and others**

- **lupus nephritis,**
- **polycystic kidney disease,**
- **vasculitis**
- **were excluded.**



EMPA-KIDNEY

The study of heart and kidney protection
with empagliflozin

EMPA Kidney2022 (NCT03594110)

RCT with **E**mpagliflozinit

suggested that:

improvement of BP and proteinuria by SGLT2i may persist in advanced CKD .



the DIAMOND trial

- Rajasekeran et al. published the DIAMOND trial,
- the first randomized double-blind clinical study of SGLT2i on patients with nondiabetic CKD
 - on stable RAS blockers at baseline
 - with IgA nephropathy
 - FSGS
 - hypertensive nephropathy
- proteinuria was unchanged during the observation .
- These results suggest that:
- SGLT2i likely exert renal hemodynamic functional changes in humans who do not have diabetes.

2020 Jul;8(7):582-593. doi: 10.1016/S2213-8587(20)30162-5.



The nephrologist's guide

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The nephrologist's guide to adverse effects with SGLT2 inhibitors

physicians may

Start to treat high-risk cardiovascular patients

with an

eGFR between 30 and 60 ml/min per 1.73 m² with these agents.

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The nephrologist's guide to adverse effects with SGLT2 inhibitors

Volume Depletion

- Not associated with an increased risk of hypokalemia
- Do not induce hyponatremia

▪ Risk of hypoglycemia

- Do **N**ot **I**ncrease
- may be increased when combined with other agents such insulin or sulphonylureas

DKA

- mostly in **T1D** patients.

▪ Fralick et al. reported an 2-fold higher risk of DKA with SGLT2 inhibitor use versus DPP4 inhibitors in >70,000 patients in the United States.

The nephrologist's guide to adverse effects with SGLT2 inhibitors

- **patients undergoing procedures** with anticipated reductions in renal perfusion, including:
 - elective surgery**
 - i.v. contrast procedures,**
- may **Need to have their SGLT2 inhibitors held, for 24 to 48 hours before the procedure** in a similar way that RAAS inhibitors should be held in these situations.
- to minimize further volume shifts and the risk of peri surgical DKA.

adverse effects

Genital mycotic infections

- **C**andida vaginitis in women
- **B**alanitis in men.
- An increased risk of **u**rinary **t**ract **i**nfection .

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Take Home Messages

Kidney Medicine

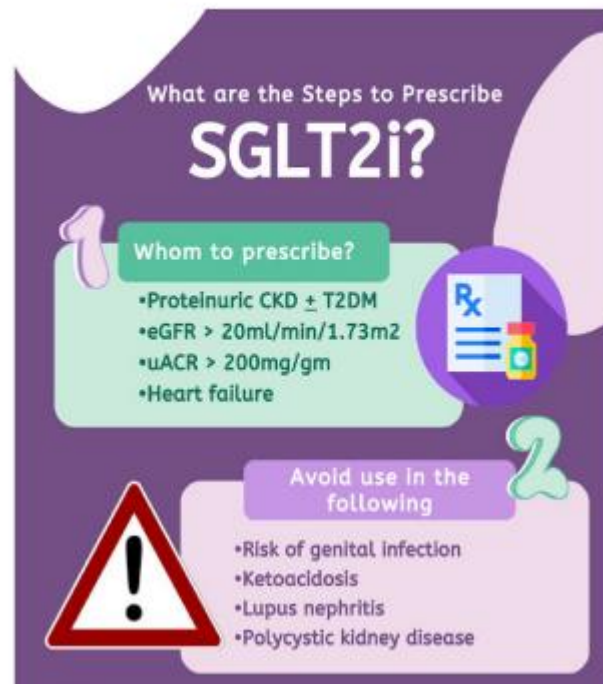
What are the Steps to Prescribe SGLT2i?

1 Whom to prescribe?

- Proteinuric CKD ± T2DM
- eGFR > 20ml/min/1.73m²
- uACR > 200mg/gm
- Heart failure

2 Avoid use in the following

- Risk of genital infection
- Ketoacidosis
- Lupus nephritis
- Polycystic kidney disease



3 How to prescribe?

Use one dose with proven benefit.

- Canagliflozin 100mg
- Dapagliflozin 10mg
- Empagliflozin 10mg

4 Educate patients about?

- Stop during any period of illness
- Stop during perioperative period
- Maintain foot care, avoid keto diet
- Maintain adequate hydration
- Watch for hypoglycemia



What to anticipate?

- Acute drop in eGFR
- Caution: If acute drop in eGFR >30%.
- Titrate Diuretics / Antihypertensives
- Titrate insulin & sulfonylurea agents in patients with low A1C

GlomCon^{edu}

Zoungas S, de Boer IH. Clin J Am Soc Nephrol. 2021. PMID: 33536241.
doi: 10.2215/CJN.18081220
Infographics by Mythri Shankar @nephromythri



Source: Zoungas S, de Boer IH.

Practical approach to prescribing SGLT2 inhibitors

THANK YOU



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