SGLT-2 inhibitors and AKI

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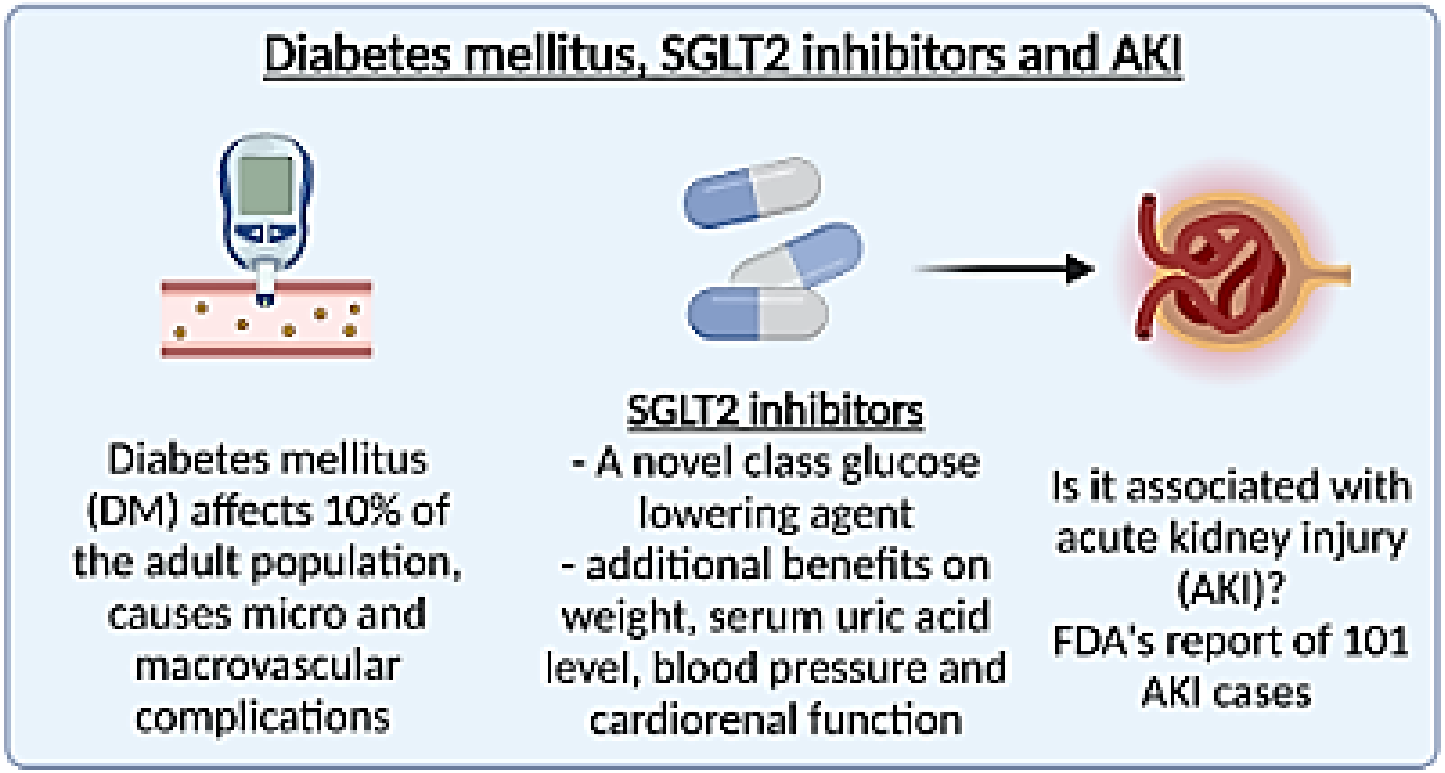
Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2is)



Journal of Nephrology 2023;36:31–43

Pharmacovigilance Reports

- **The proportion of reports with ARF among reports with SGLT2 inhibitor was almost three-fold higher compared to reports without these drugs (ROR 2.88, 95% CI 2.71–3.05, p < 0.001).**

Acute renal failure with sodium-glucose-cotransporter-2 inhibitors: Analysis of the FDA adverse event report system database. Nut Met Cardiovasc Dis 2017;27;1108-13

- **The reporting odds ratio (ROR) values of AKI events associated with all SGLT2is was 2.84 (95% CI 2.71−2.98) in patients with diabetes. When SGLT2is were combined with RAAS blockers, the corresponding ROR was even higher, reaching 4.05(3.66−4.48). Of note, these ROR values were slightly higher when SGLT2is were combined with diuretics (ROR 6.07, 5.27−7.00) or with NSAIDs (ROR 4.66, 3.79−5.74).**

Risks of acute kidney injury due to sodium glucose co-transporter 2 inhbitors: a study based on the related data in the US Food and Drug Administration Adverse Event Reporting System. Adverse Drug Reactions J 2019;21:190-7

- **The ROR for acute renal failure with SGLT2is versus other glucose-lowering drugs was calculated as 1.0 (95% CI 0.9−1.2).**

Acute renal failure, ketoacidosis, and urogenital tract infections with SGLT2 inhibitors: signal detection using a Japanese spontaneous reporting database. Clin Drug Invest 2020;40;645-52.

References	Design	SGLT2i users (*N*)	Results	Follow-up
Nadkarni et al. [15]	1:1 propensity matched retrospective cohort study (SGLT2is vs. non-SGLT2is)	1584	No increased AKI risk	15 months
Neal et al. [21]	Randomized single-blind placebo-controlled trial (SGLT2is vs. placebo)	5795	No increased AKI risk	44.5 months
Cahn et al. [14]	Retrospective cohort study (SGLT2is vs. DPP-4is)	6418	No increased AKI risk	6 months
Donnan et al. [23]	Meta-analysis (SGLT2is vs. placebo)	6864	No increased AKI risk	–
Gilbert and Thorpe [25]	Meta-analysis of cardiovascular outcome trial	17,599	Decreased AKI risk	52 months
Menne et al. [24]	Meta-analysis	68,159	Decreased AKI risk (36%)	–
Lin et al. [13]	Retrospective cohort study (SGLT2is vs. non-SGLT2is)	7624	Lower incidence of eGFR decrease and no increase in AKI risk	18 months
McMurray et al. [22]	Phase 3 placebo-controlled trial (SGLT2is vs. placebo)	2373	Significantly fewer serious renal adverse events compared to placebo	24 months
Miyoshi et al. [12]	Retrospective longitudinal cohort study (SGLT2is vs. non-SGLT2is)	1337	Lower incidence of eGFR decrease	24 months
Perkovic et al. [20]	Double-blind, randomized placebo-controlled trial (SGLT2is vs. placebo)	2202	No increased AKI risk	31.5 months
Heerspink et al. [17]	Randomized double-blind placebo-controlled multicenter clinical trial (SGLT2is vs. placebo)	2152	Decreased risk of ESRD HR 0.64 (0.5–0.82)	29 months
Cahn et al. [16]	Dapagliflozin Effect on Cardiovascular Events (DECLARE)–TIMI randomized double-blind placebo-controlled trial (SGLT2is vs. placebo)	8582	Decreased AKI risk	50 months
Katsuhara et al. [26]	Analysis of Japanese Adverse Drug Event Report database (JADER) (SGLT2is vs. non-SGLT2is)	4322	No increased AKI risk; increased risk of ketoacidosis and urogenital tract infections	–
Cannon et al. [18]	Multicenter double-blind randomized placebo-controlled event-driven non-inferiority trial (SGLT2is vs. placebo)	5499	No increased AKI risk	42 months
Bakris et al. [19]	Randomized double-blind placebo-controlled multicenter international trial (SGLT2is vs. placebo)	84	No increased AKI risk and even slowed progression of kidney failure	30.5 months
Pasternak et al. [11]	1:1 propensity matched retrospective cohort study (SGLT2is vs. DPP-4is)	29,887	Reduced risk of serious renal events	20 months
Iskander et al. [10]	Retrospective cohort study (SGLT2is vs. DPP-4is)	19,611	Decreased AKI risk	26 months
Rampersad et al. [9]	1:1 propensity matched retrospective cohort study (SGLT2is vs. oral glucose lowering drugs)	4778	No increased AKI risk	33 months
Alkabbani et al. [6]	Population-based retrospective cohort study (SGLT2is vs. DPP-4is)	9608 (7712 + 1896)	No increased AKI risk	15 months
Katsuhara et al. [27]	Analysis of United States Food and Drug Administration's Adverse Event Reporting System records (SGLT2is vs. non-SGLT2is)	29,204	Increased AKI risk in monotherapy; AKI incidence reduced with the concommitant use of ACEis or ARBs	–
Lee et al. [7]	Propensity score-matched retrospective cohort (SGLT2-is vs. DPP-4is)	3521	Decreased AKI risk ($P < 0.001$) and slowed eGFR decline compared to DPP-4is	24 months
Zhuo et al. [8]	1:1 matched population based retrospective cohort study (SGLT2is vs. DPP-4is or GLP-1RA)	68,130	Decreased AKI risk compared to the DPP-4i group (HR 0.71, 0.65–0.76) or GLP-1RA (HR 0.81, 0.75–0.87)	6 months

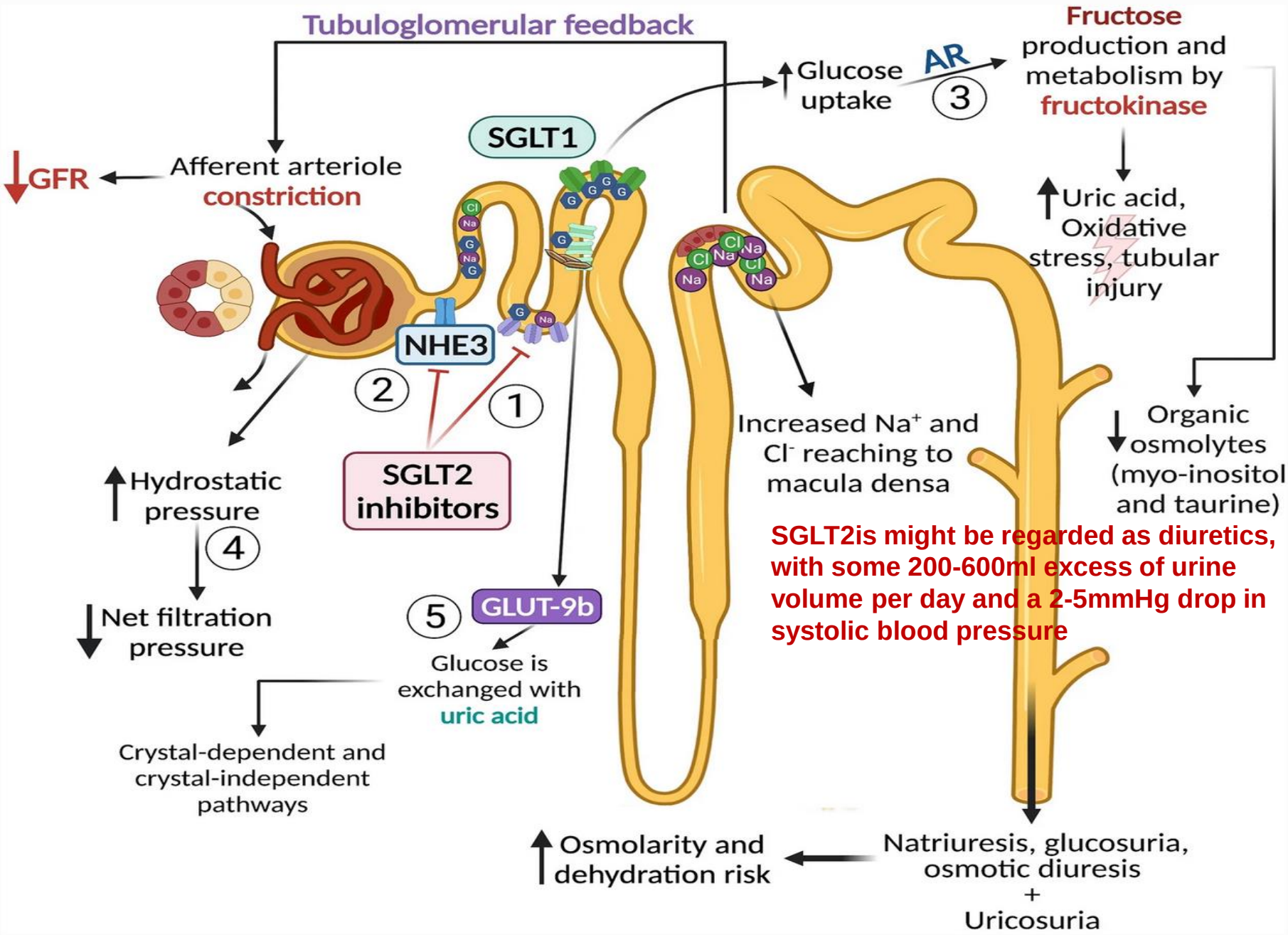
SGLT2is, sodium-glucose co-transporter type 2 inhibitors, *AKI*, acute kidney injury, *DPP-4is* dipeptidyl-peptidase-4 inhibitors, *GLP-1RA* GLP-1 receptor agonists, *HR* hazard ratio, *RAASis* renin angiotensin aldosterone inhibitors, *ACEis* angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *eGFR* estimated glomerular filtration rate

Acute kidney injury risk factors when using sodium-glucose co-transporter type 2 inhibitor

References	RAASis (ARBs and ACEis)	NSAIDs	Diuretics	Age group or patient group risk factors	Other mentioned risk factors
McMurray et al. [22]	N/A	N/A	N/A	Slight increase with age: < 65 years vs. ≥ 65 years: 15.7 vs. 16.7	N/A
Miyoshi et al. [12]	N/A	N/A	Significantly smaller initial decrease in eGFR in patients who discontinued diuretics compared with those who continued diuretics ($P = 0.004$)	N/A	N/A
Perkovic et al. [20]	N/A	N/A	N/A	UACR at baseline > 1000 1000 mg/g: SGLT2i protective; UACR at baseline ≤ 10,001,000 mg/g: SGLT2i no beneficial effect	N/A
Rampersad et al. [9]	No effect modification by RAASis ($P = 0.9$)	N/A	No effect modification by diuretics ($P = 0.8$)	N/A	N/A
Cahn et al. [16]	N/A	N/A	N/A	Higher rates of AKI with increasing age: incidence rates of 4.2, 5.4, and 9.3 cases per 1000 person-years in age-groups < 65, 65–75, and > 75 years, respectively ($P < 0.0001$)	N/A
Pasternak et al. [11]	No increased AKI risk with the concomitant use of RAASis	No increased AKI risk with the concomitant use of NSAIDs	No increased AKI risk with the concomitant use of diuretics	Protective in all groups	N/A
Heerspink et al. [17]	N/A	N/A	N/A	Protective in all groups	N/A
Iskander et al. [10]	Monotherapy with SGLT2is = 0.97; concomitant use of baseline ACEis or ARBs = 1.19	N/A	No baseline diuretic use = 0.85; any diuretic class = 2.01	Age < 80 (1.04) Age ≥ 80 (1.84)	N/A
Katsuhara et al. [27]	Reduced AKI risk with the concomitant use of ARBs or ACEis	N/A	N/A	N/A	N/A
Lee et al. [7]	no-ACEi use: 1.5 ACEi use: 2.2	N/A	No diuretic use: 1.4 Diuretic use: 6.6	N/A	A lower rate of AKI in females than in males (2.18 vs. 3.56%)

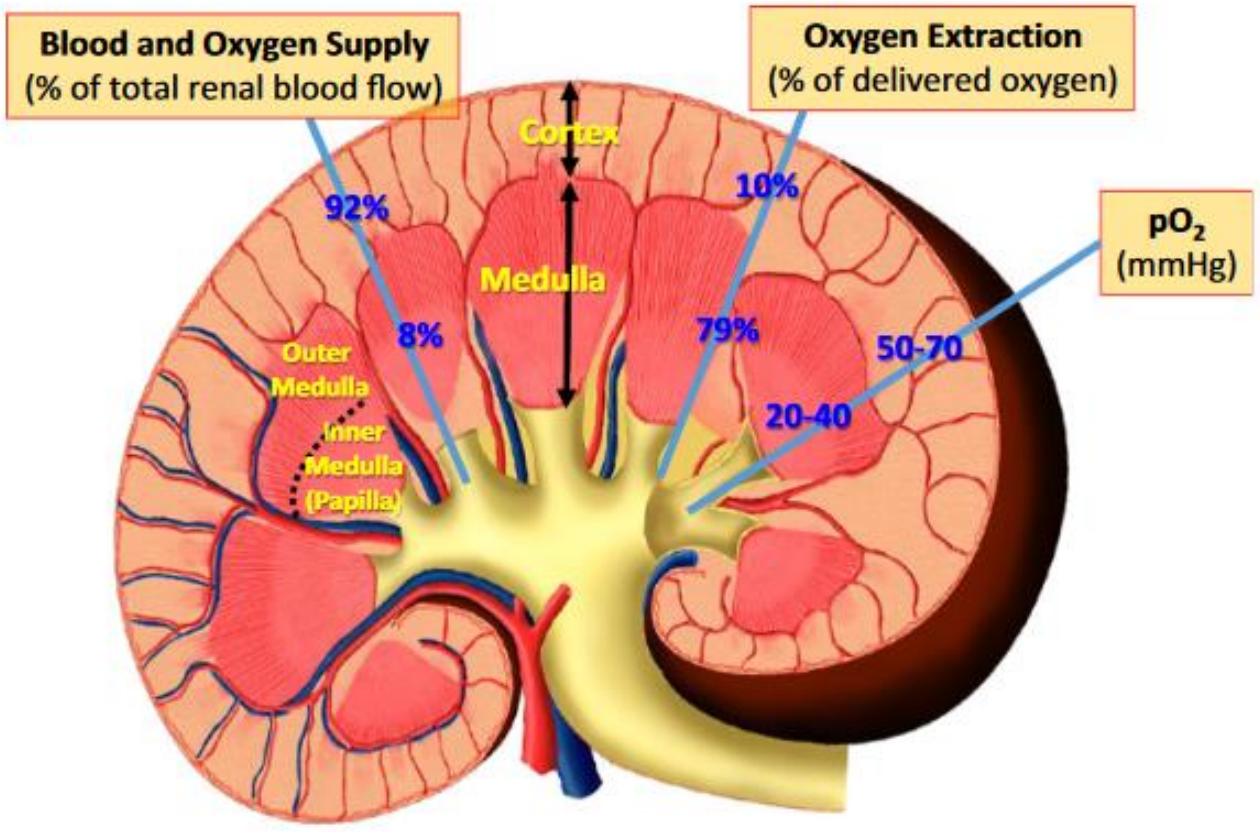
UACR urinary albumin-to-creatinine ratio, *N/A* not applicable, *RAASis* renin angiotensin aldosterone inhibitors, *ACEis* angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *AKI* acute kidney injury, *SGLT2is* sodium-glucose co-transporter type 2 inhibitors

Journal of Nephrology 2023;36:31–43



Journal of Nephrology 2023;36:31–43

Can SGLT2 Inhibitors Cause Acute Renal Failure? Plausible Role for Altered Glomerular Hemodynamics and Medullary Hypoxia

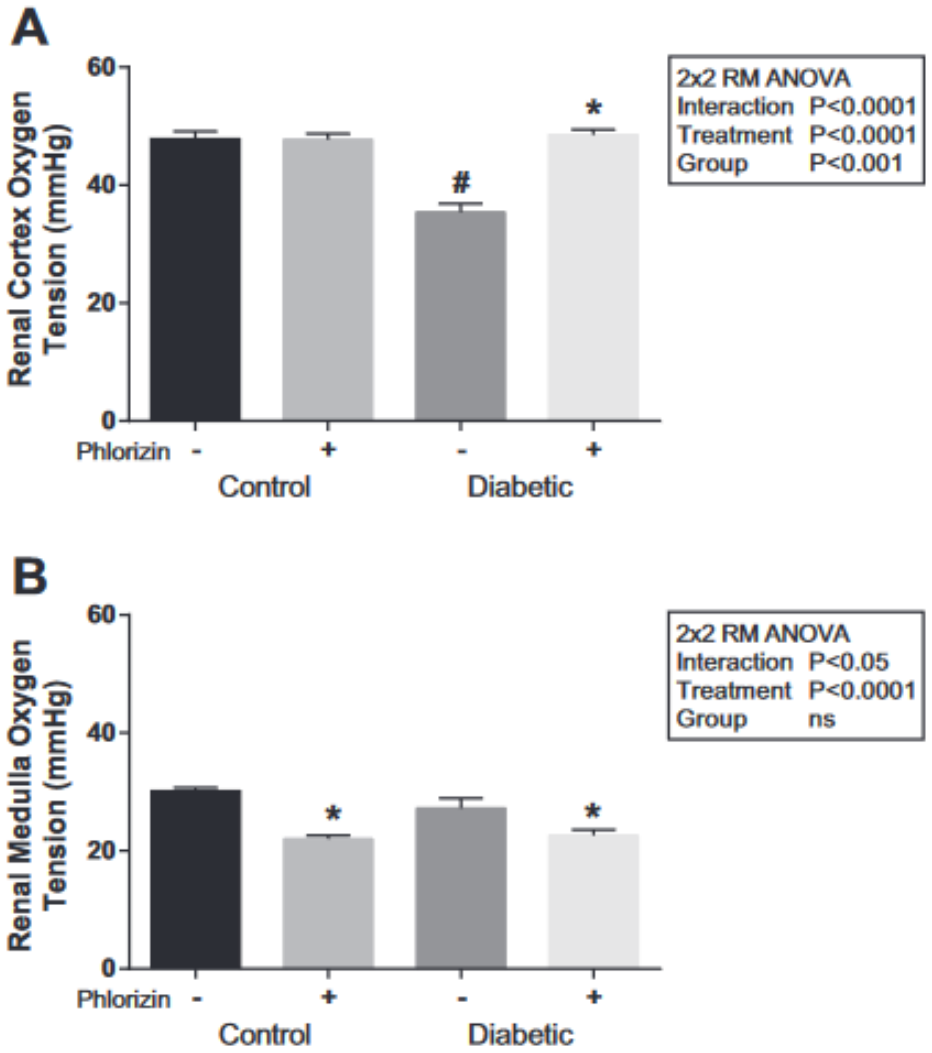


SGLT2is are not true tubulotoxic mediators but exert renal injury through the induction of hypoxic medullary injury.

Drug Saf 2018;41:239–252

SGLT2is: O_2 tension in the renal Cortex and Medulla

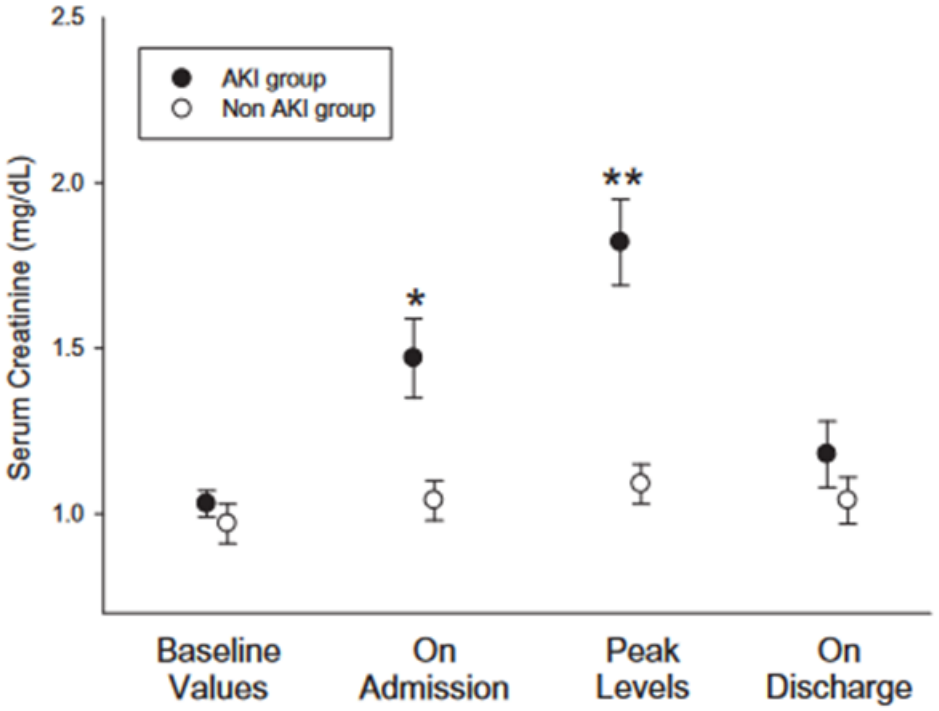
Acute SGLT inhibition normalizes O_2 tension in the renal cortex but causes hypoxia in the renal medulla in anaesthetized control (n=12) and diabetic rats (n=9)



Am J Physiol Renal Physiol 2015;309: F227–F234

Biomarker evidence for distal tubular damage but cortical sparing

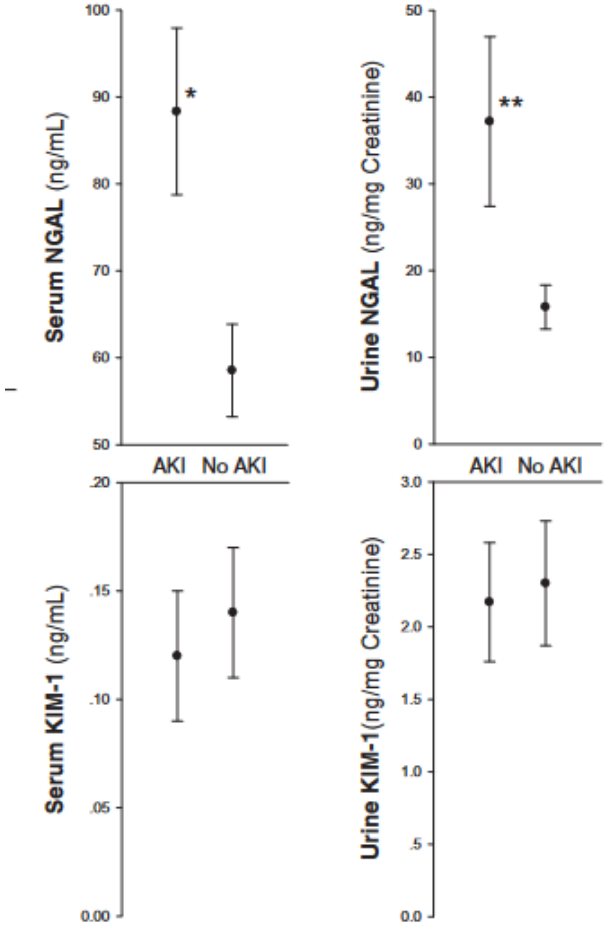
AKI Group= 21 pts
No AKI Group= 25 pts

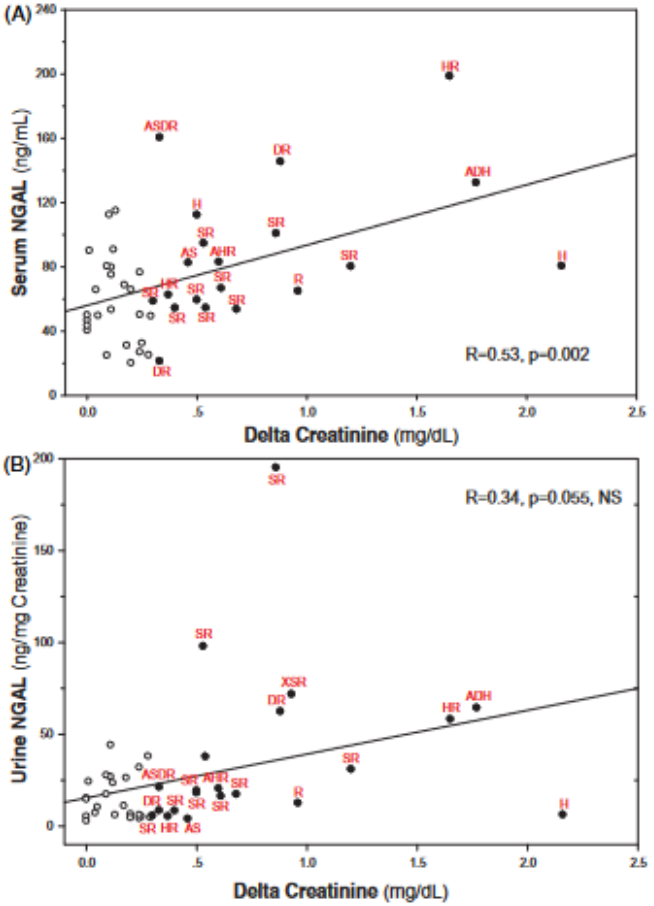


Serum creatinine in the AKI and non-AKI groups. While baseline (pre-hospital) levels are comparable, serum creatinine is significantly higher upon admission (* p = .002) and at peak levels during hospitalization (** p < .0001, means ± SEM, student t-test).

Renal Failure 2020;42(1): 836–844

Biomarker evidence for distal tubular damage but cortical sparing

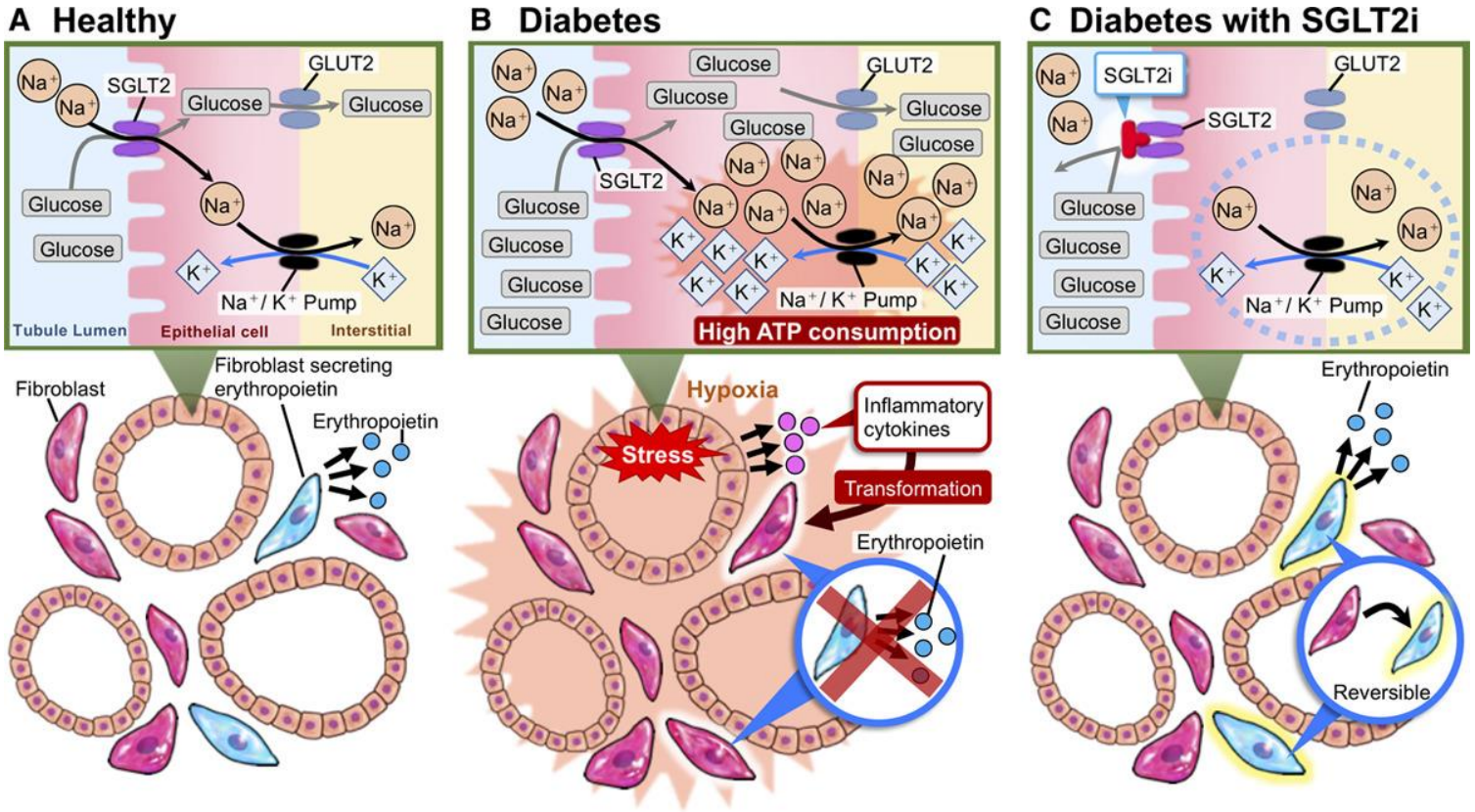




Serum and urine NGAL and KIM-1 in the AKI and non-AKI groups 21 and 25, respectively). While KIM-1 levels are comparable in the two groups, NGAL levels both in serum and urine samples are significantly higher in the AKI group (*p=.006 and **p = .032, respectively, means ± SEM, student t-test)

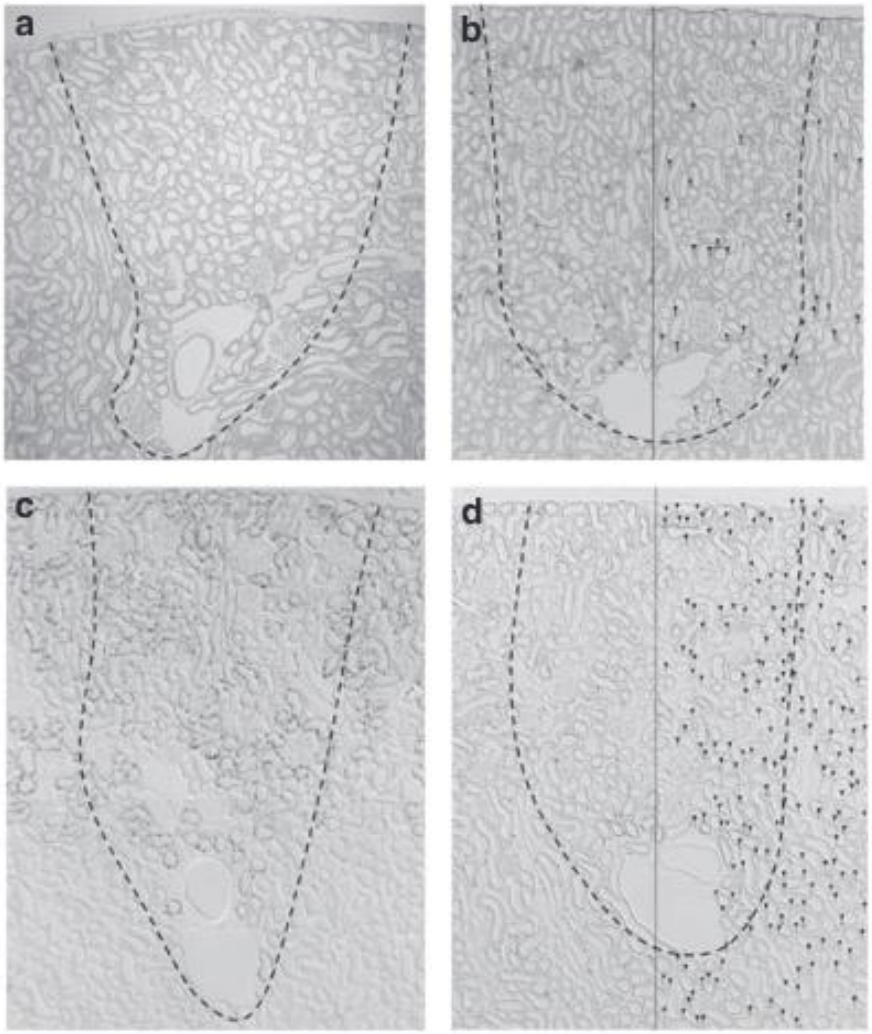
Renal Failure 2020;42(1): 836–844

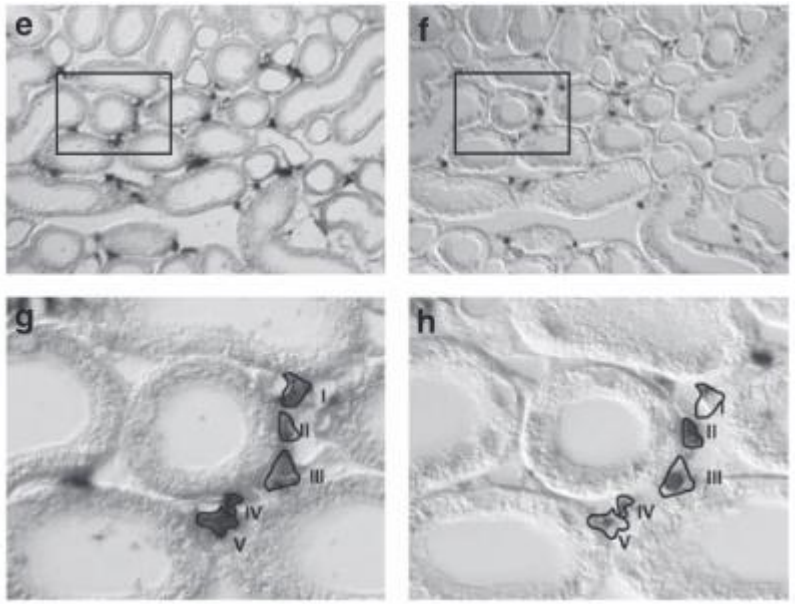
Possible Mechanism of Hematocrit Elevation by SGLT2is and Associated Beneficial Renal and Cardiovascular Effects



Circulation. 2019;139:1985–1987

SGLT2is Alter the Renal Oxygenation Profile

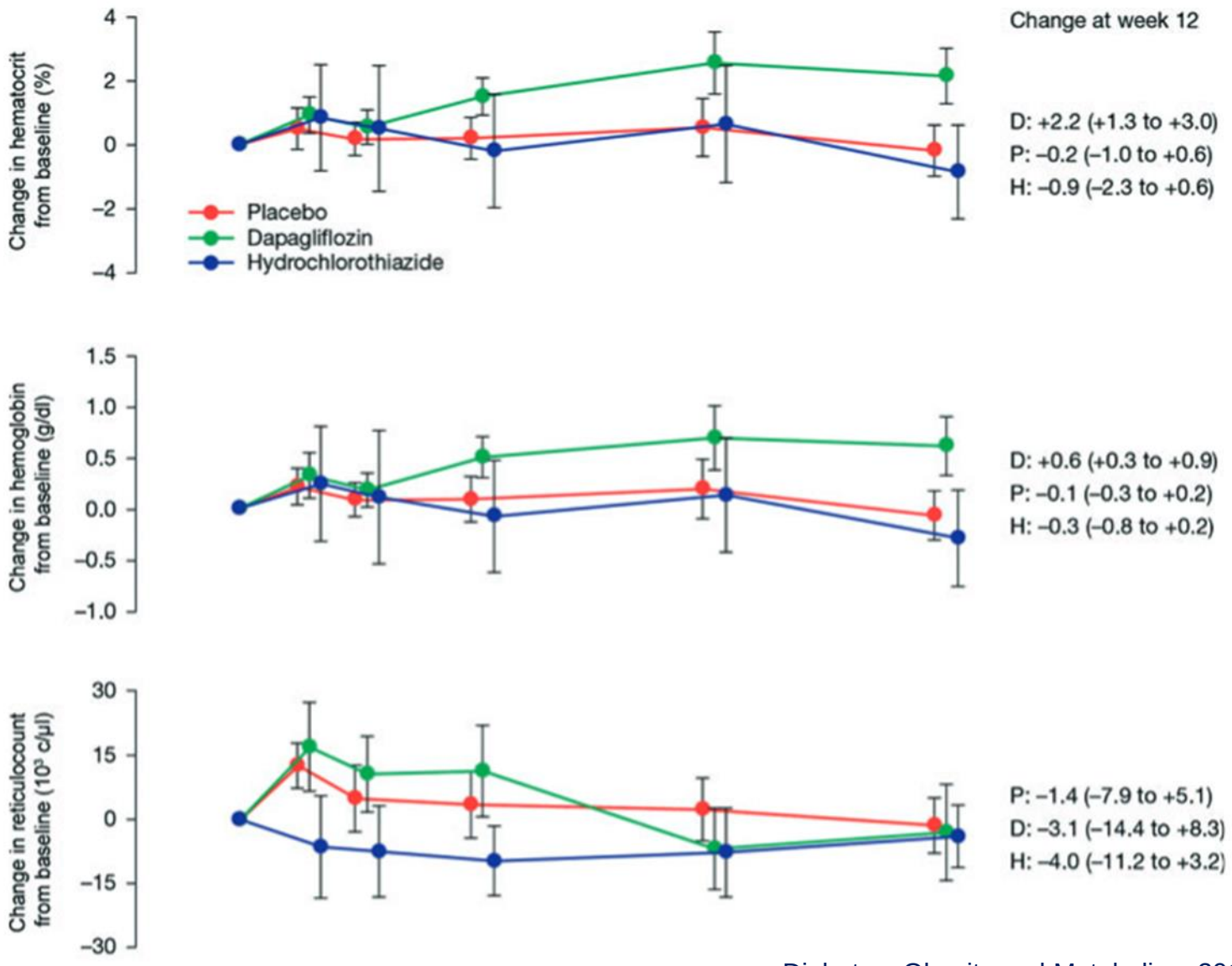




SGLT2is Alter the Renal Oxygenation Profile Hypoxia-inducible factor-2a-expressing interstitial fibroblasts are the only renal cells that express erythropoietin under hypoxia-inducible factor stabilization

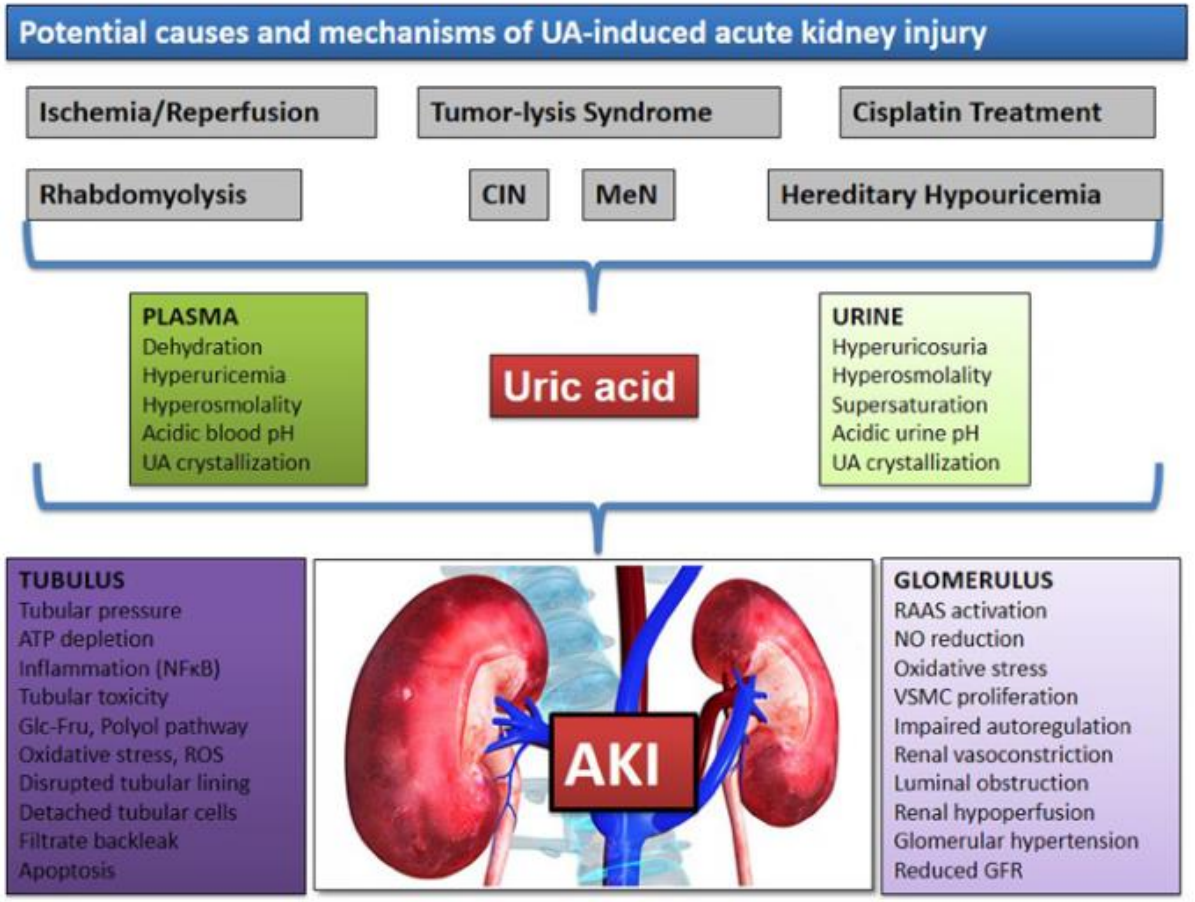
Kidney International 201077, 312–318

SGLT2is Alter the Renal Oxygenation Profile

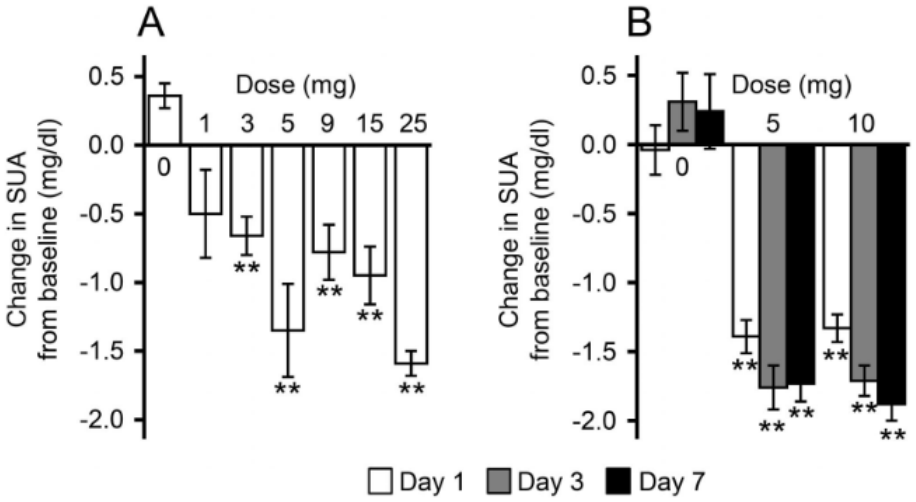


Diabetes, Obesity and Metabolism 2013;15: 853–862

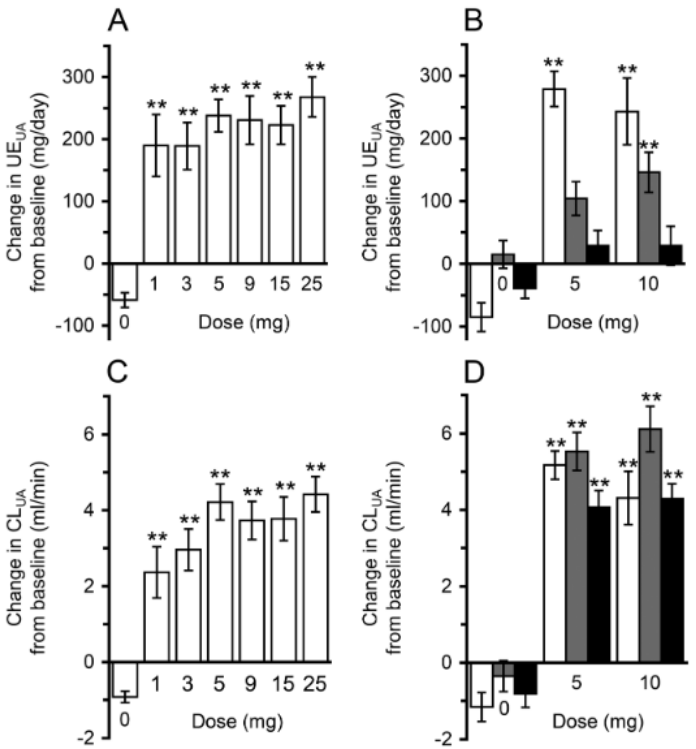
Additional Mechanisms that may predispose to SGLT2is-Related Renal Impairment



Journal of Advanced Research 2017;8:529–536



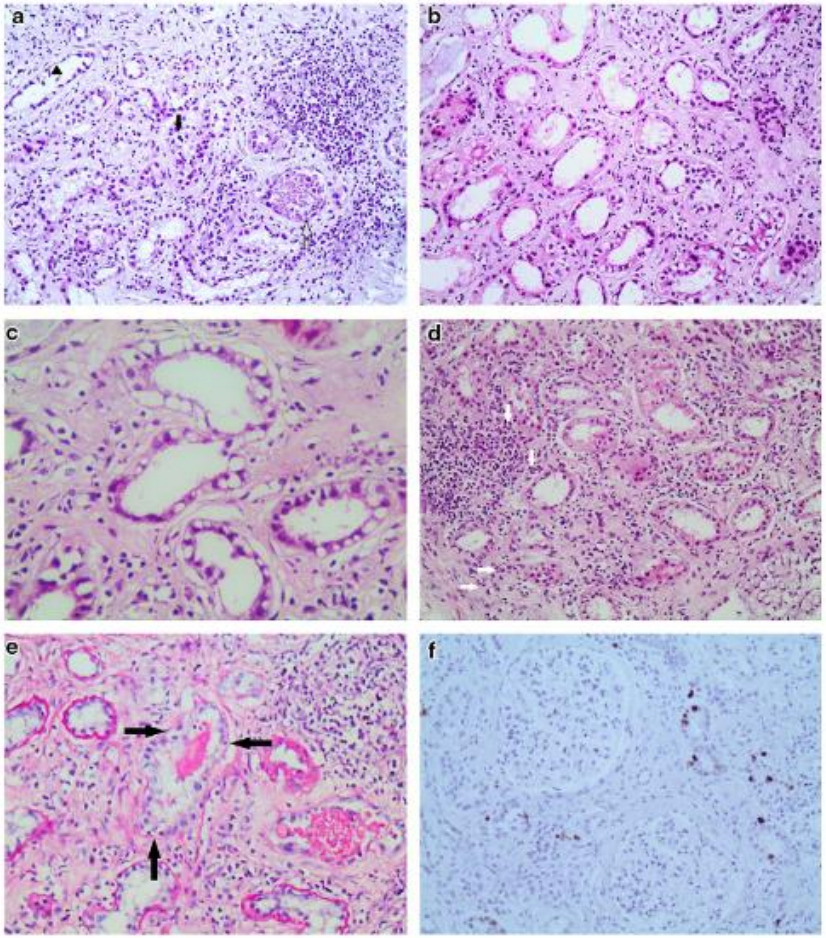
Effect of luseogliflozin on the serum uric acid (SUA) level. Changes in the SUA level from the baseline after a single dose (A, n = 3–14) and after multiple doses (B, n = 8) are shown. Data are mean ± SEM. **p < 0.01 vs placebo (0 mg) (Dunnett's test)



Effects of luseogliflozin on the urinary excretion rate (UEUA) and the renal clearance (CLUA) of uric acid. Changes in UEUA and CLUA from the baseline after a single dose (A and C, n = 3–14) and after multiple doses (B and D, n = 8) are shown. Data are mean ± SEM. **p < 0.01 vs placebo (0 mg) (Dunnett's test)

Biopharm. Drug Dispos. 2014;35: 391–404

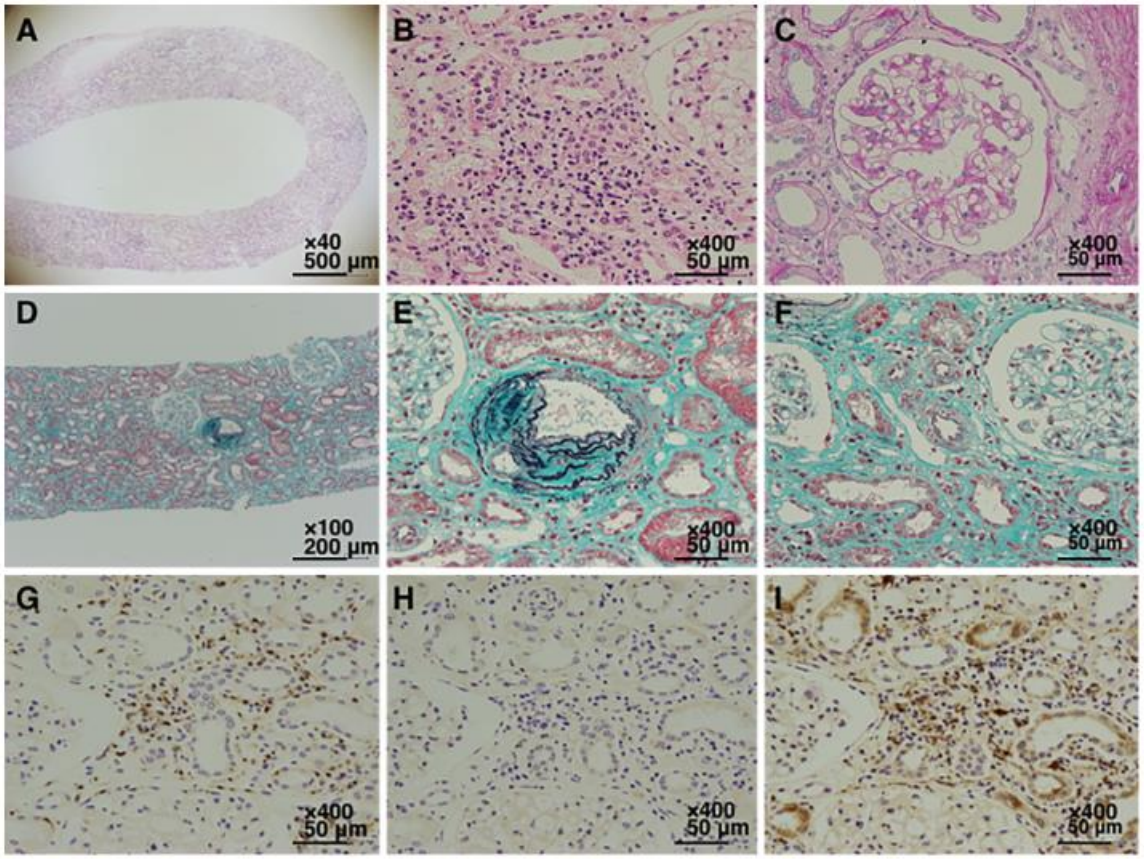
Dapagliflozin as a cause of acute tubular necrosis with heavy consequences: a case report



a Acute tubular injury with epithelial cell coarse vacuolization or flattened epithelium with detached cells leaving areas of tubular basement membrane covered by a thin layer of cytoplasm from adjacent cells (arrowhead). Necrotic luminal debris (transparent arrow). Regeneration with mitosis (black arrow). Interstitial mononuclear infiltration is also observed . b.Flattened tubular epithelium with diminishing or loss of brush borders and cytoplasmic vacuolization. c. Cytoplasmic vacuolization in higher magnification . d Among the interstitial inflammatory cells, some eosinophils are discerned (white arrows) . e Tubulitis in a non-atrophic tubule (black arrows)

CEN Case Rep 2018;7:17–20

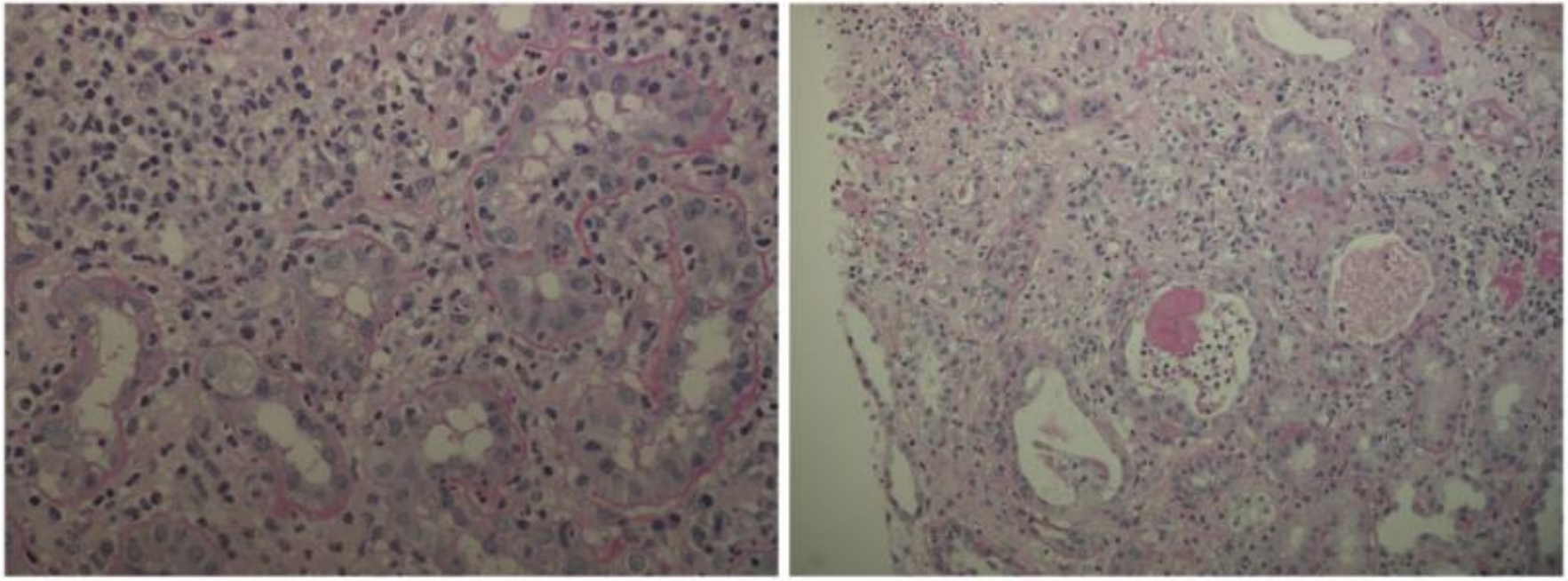
Tubulointerstitial Nephritis after Using a SGLT2i



Tubulointerstitial nephritis in the patient after empagliflozin use. (A, B, D) Tubular atrophy and interstitial fibrosis were observed diffusely in approximately 70% of the area. (A, B) Tubular interstitium showed infiltration mainly composed of lymphocytes and monocytes. (C) The glomerulus had slight mesangial matrix expansion without mesangial cell proliferation. (E) The small and medium-sized arteries showed moderate arteriosclerosis with fibroelastosis, (F) while arteriolar hyalinosis was not observed in the arterioles. (G: CD3, H: CD22, I: CD68) Immunostaining showed cells expressing CD3 (T cells) and CD68 (macrophages) but did not show cells expressing CD22 (B cells). Cells expressing CD3 and CD68 infiltrated more strongly around the tubular region than around the glomerulus.

Intern Med 2022; 61: 3239-3243

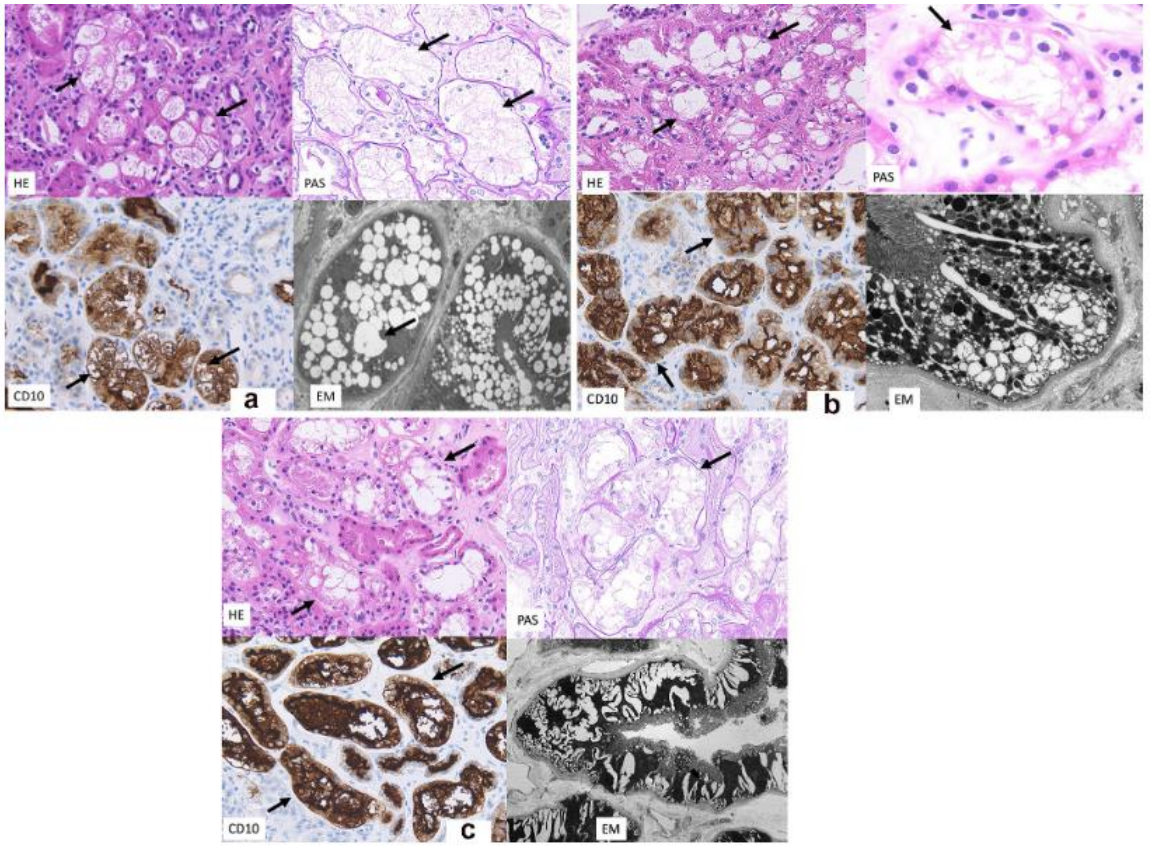
Acute interstitial nephritis due to SGLT2i Empagliflozin



Renal histology following native renal biopsy, showing marked acute tubulointerstitial nephritis with lymphocytic infiltrates and eosinophils in the interstitium and focal tubulitis. No granulomas are present and no significant fibrosis is seen. Background changes are suggestive of early diabetic nephropathy.

Clinical Kidney Journal 2021;14(3)1020–1022

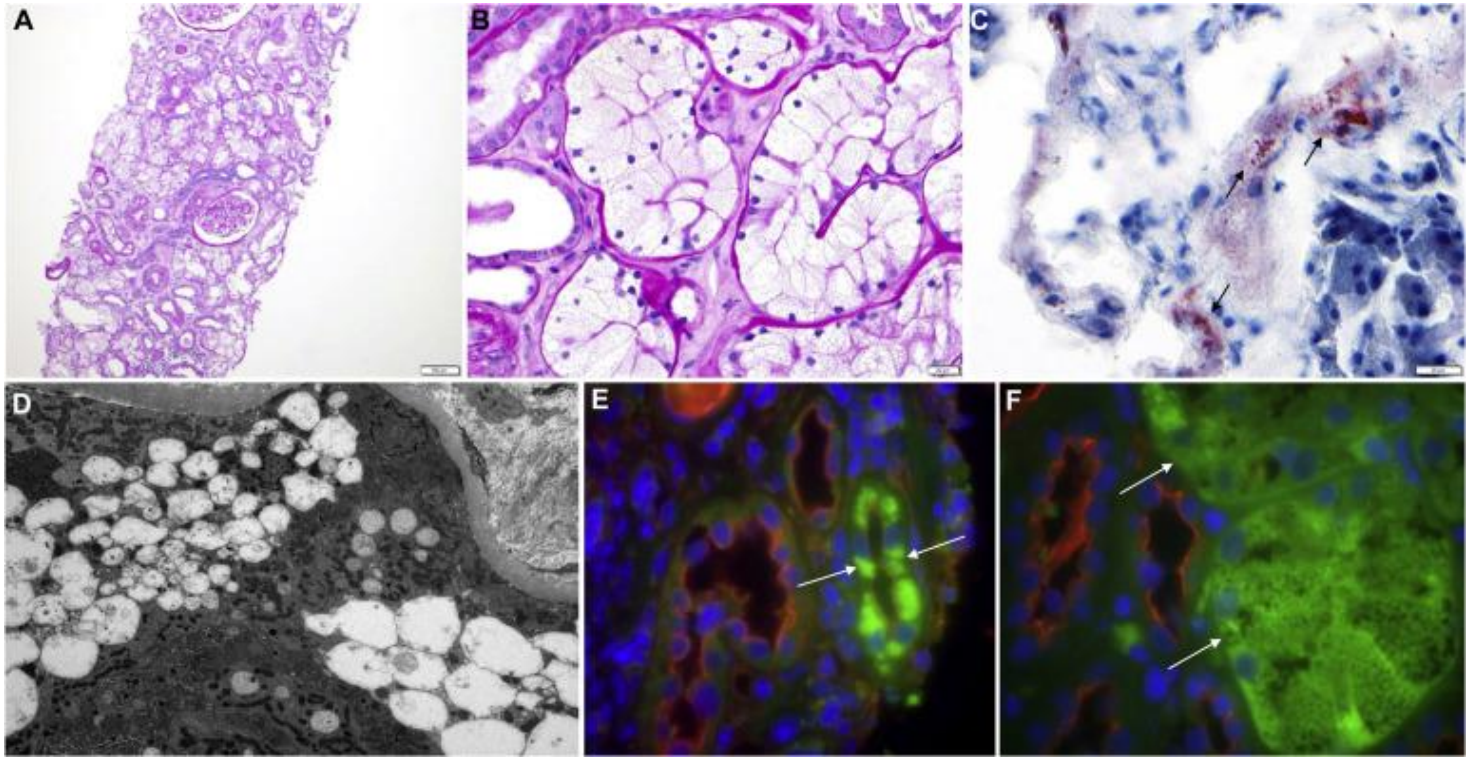
Development of osmotic vacuolization of proximal tubular epithelial cells following treatment with SGLT2is in type II DM patients-3 case reports



a) Case 1Proximal tubule is vacuolated (arrows) (Hematoxylin–Eosin stain, Periodic Acid Schiff stain and CD10 stain 400 ×). Brown color shows positivity for CD 10 stain, consistent with proximal tubule). EM analysis revealed round or elliptical vacuolization as confirmed on proximal tubules. b) Case 2 shows that proximal tubule is vacuolated (arrows) (Hematoxylin–Eosin stain, Periodic Acid Schiff stain and CD10 stain 400 ×). Brown color shows positivity for CD 10 stain, consistent with proximal tubule).EM analysis showed round or elliptical vacuolization as confirmed on proximal tubules. c) Case 3 showed that proximal tubule is vacuolated (arrows) (Hematoxylin–Eosin stain,, Periodic Acid Schiff stain and CD10 stain 400 ×). Brown color shows positivity for CD 10 stain, consistent with proximal tubule). EM analysis showed curved stripe-formed vacuolization as confirmed on proximal tubules

CEN Case Reports 2021;10:563–569

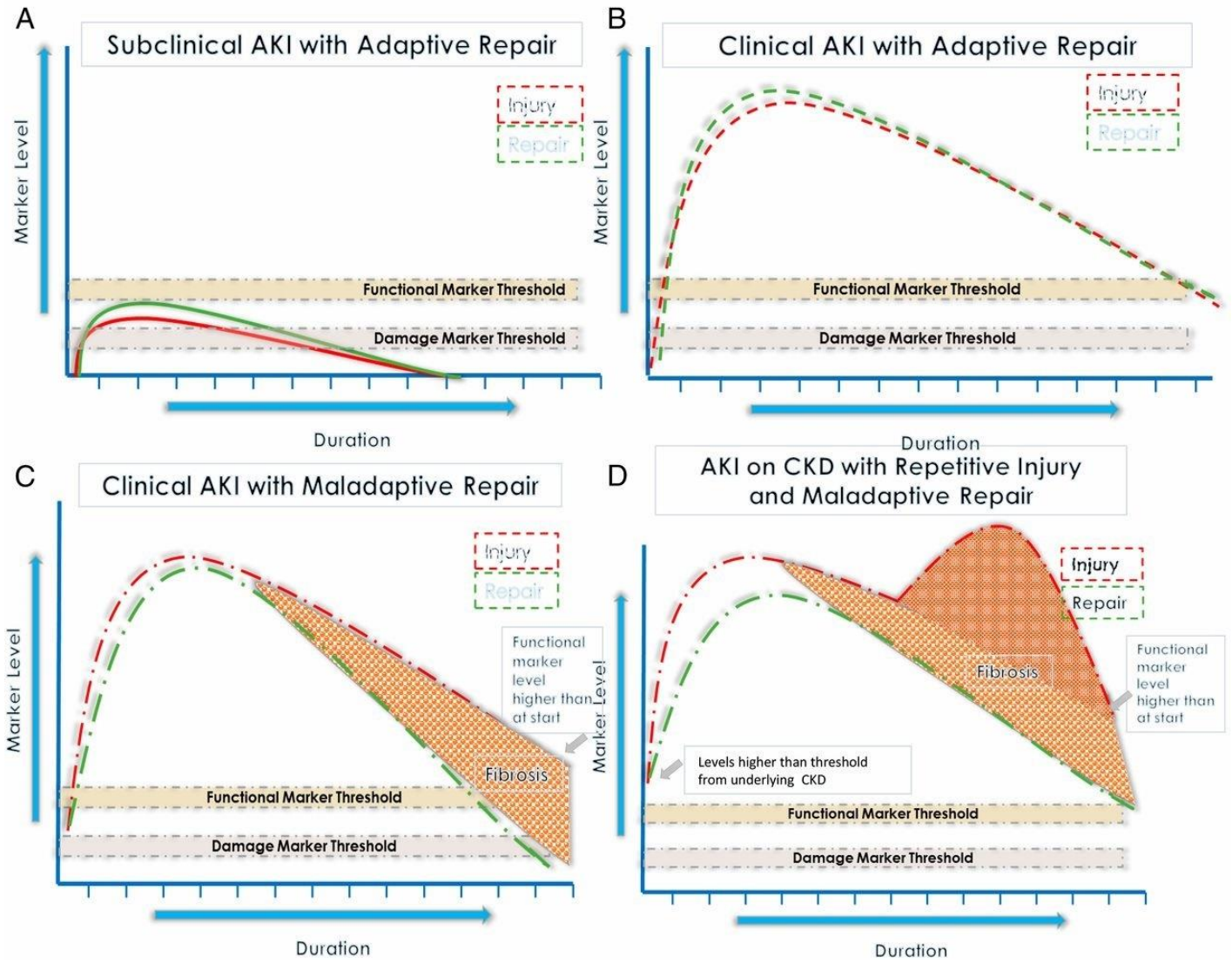
Osmotic Nephrosis and Acute Kidney Injury Associated With SGLT2i Use: A Case Report



Osmotic nephrosis in a patient with canagliflozin-mediated acute kidney injury. (A) Low- and (B) high-power view of proximal tubules with osmotic tubulopathy (periodic acid–Schiff stain; original magnification, A: ×10, B: ×40). (C) Oil Red O staining shows the presence of rare positive lipid deposits in some proximal tubules (arrows; original magnification, ×40). (D) Ultrastructural studies show clear vacuoles within the proximal tubules, arguing against lipid droplets. (E) Immunofluorescence of some proximal tubules for aldose reductase (white arrows; original magnification, ×40). (F) Immunofluorescence for fructokinase (white arrows; original magnification).

Am J Kidney Dis.2020;76(1):144-147

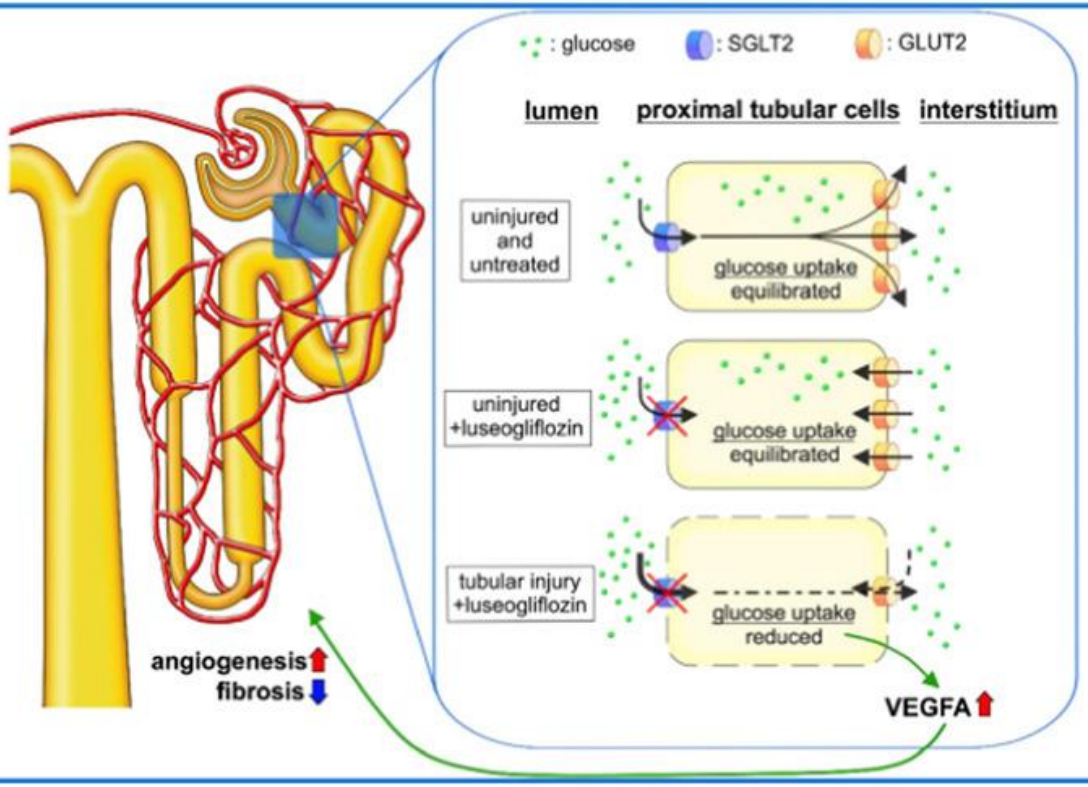
Progression after AKI: Understanding Maladaptive Repair Processes to Predict and Identify Therapeutic Treatments



Journal of the American Society of Nephrology 2016;27(3):687-697

A sodium-glucose cotransporter 2 inhibitor attenuates renal capillary injury and fibrosis by a vascular endothelial growth factor_dependent pathway after renal injury in mice

Working hypothesis for the SGLT2 inhibitor-induced depletion of glucose uptake in proximal tubules.



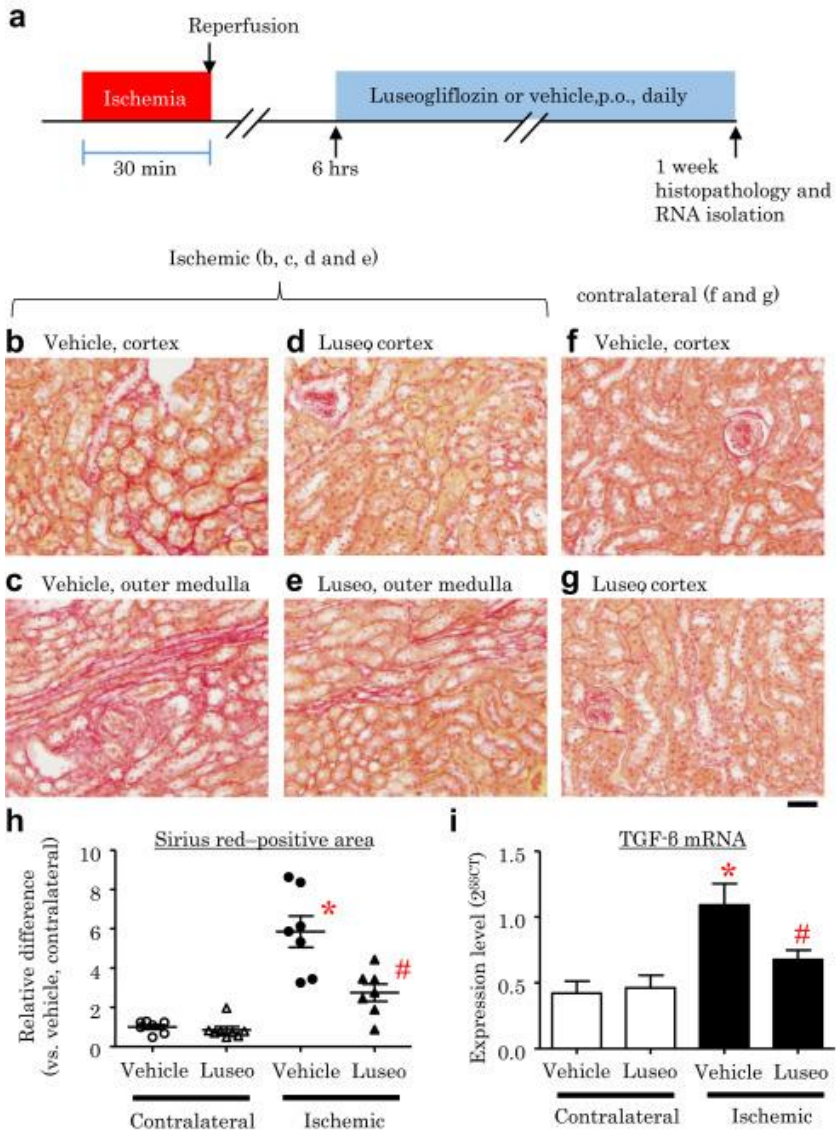
Conclusion

Luseogliflozin prevented endothelial rarefaction and subsequent renal fibrosis after renal I/R injury through a VEGF-dependent pathway, which was induced by the dysfunction of proximal tubular glucose uptake in tubules with injury-induced GLUT2 downregulation

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

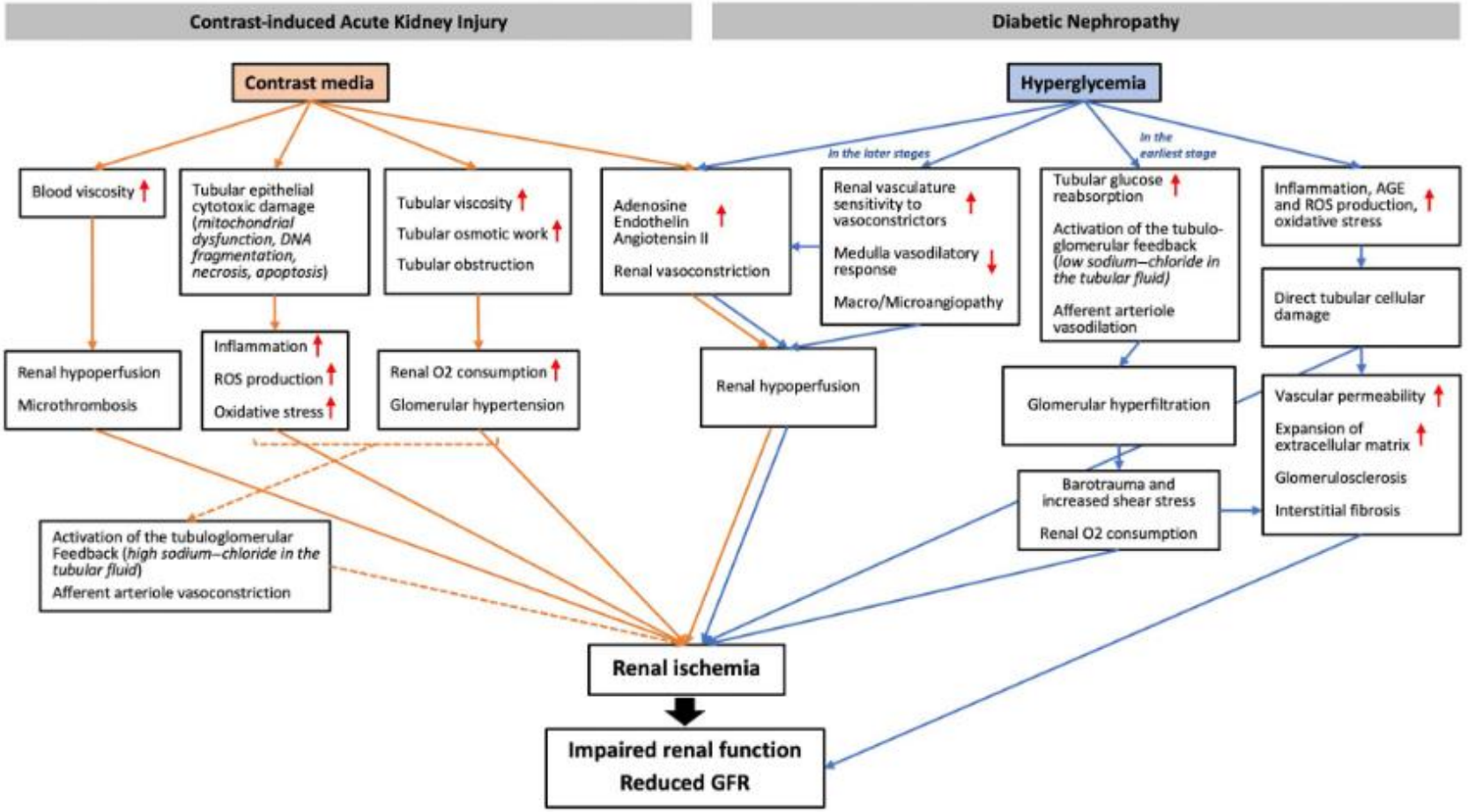
Kidney International 2018;94, 524–535

A sodium-glucose cotransporter 2 inhibitor attenuates renal capillary injury and fibrosis by a vascular endothelial growth factor–dependent pathway after renal injury in mice



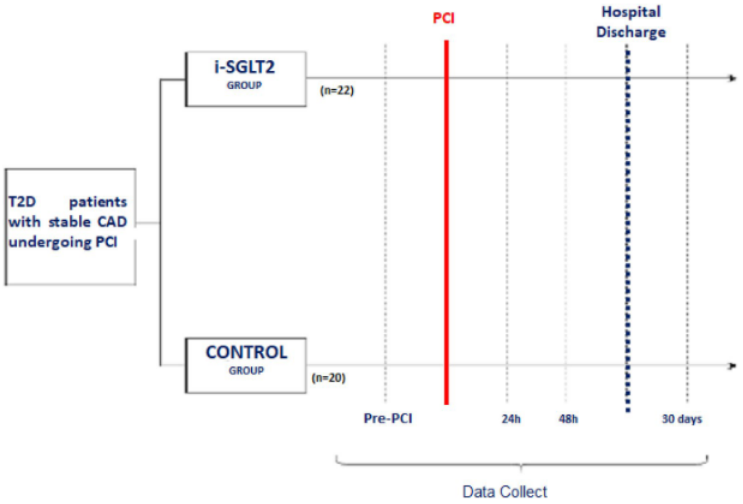
Kidney International 2018;94, 524–535

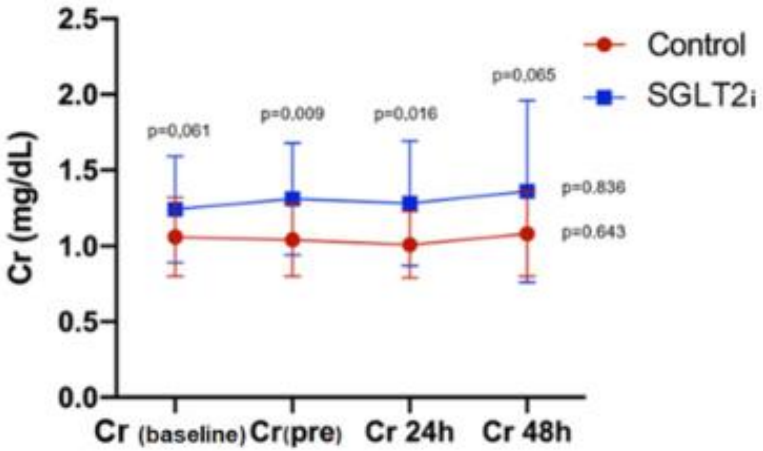
Contrast-induced Acute Kidney Injury in Diabetic Patients and SGLT-2 Inhibitors: A Preventive Opportunity or Promoting Element?

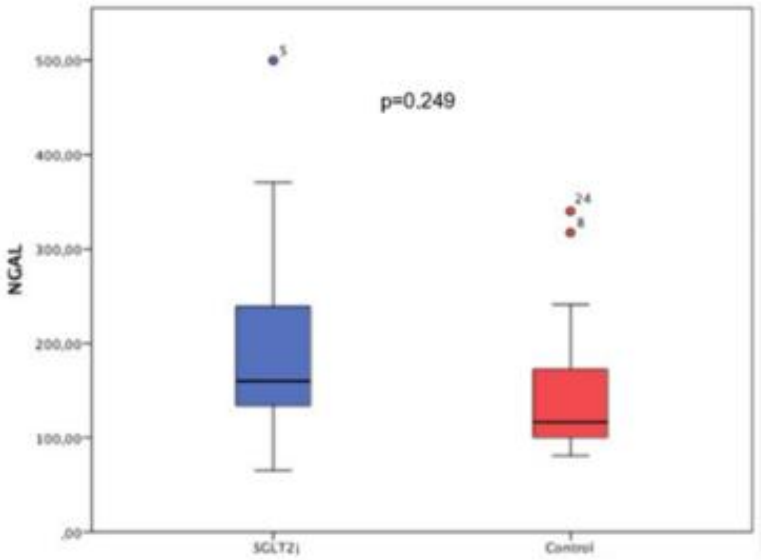


J Cardiovasc Pharmacol 2022;80:661–671

The safety of SGLT-2 inhibitors in diabetic patients submitted to elective percutaneous coronary intervention regarding kidney function: SAFE-PCI pilot study







NGAL value (ng/dL) 6 h after percutaneous coronary intervention. There was no difference in the primary endpoint of the study. Mean serum NGAL 6 h after PCI was 199 ng/dL in the SGLT2i group and 150 ng/dL in the control group (p = 0.249). *Test-t used to compare two different groups

Diabetology & Metabolic Syndrome 2023;15:138

Randomized controlled trials reporting an initial dip of eGFR

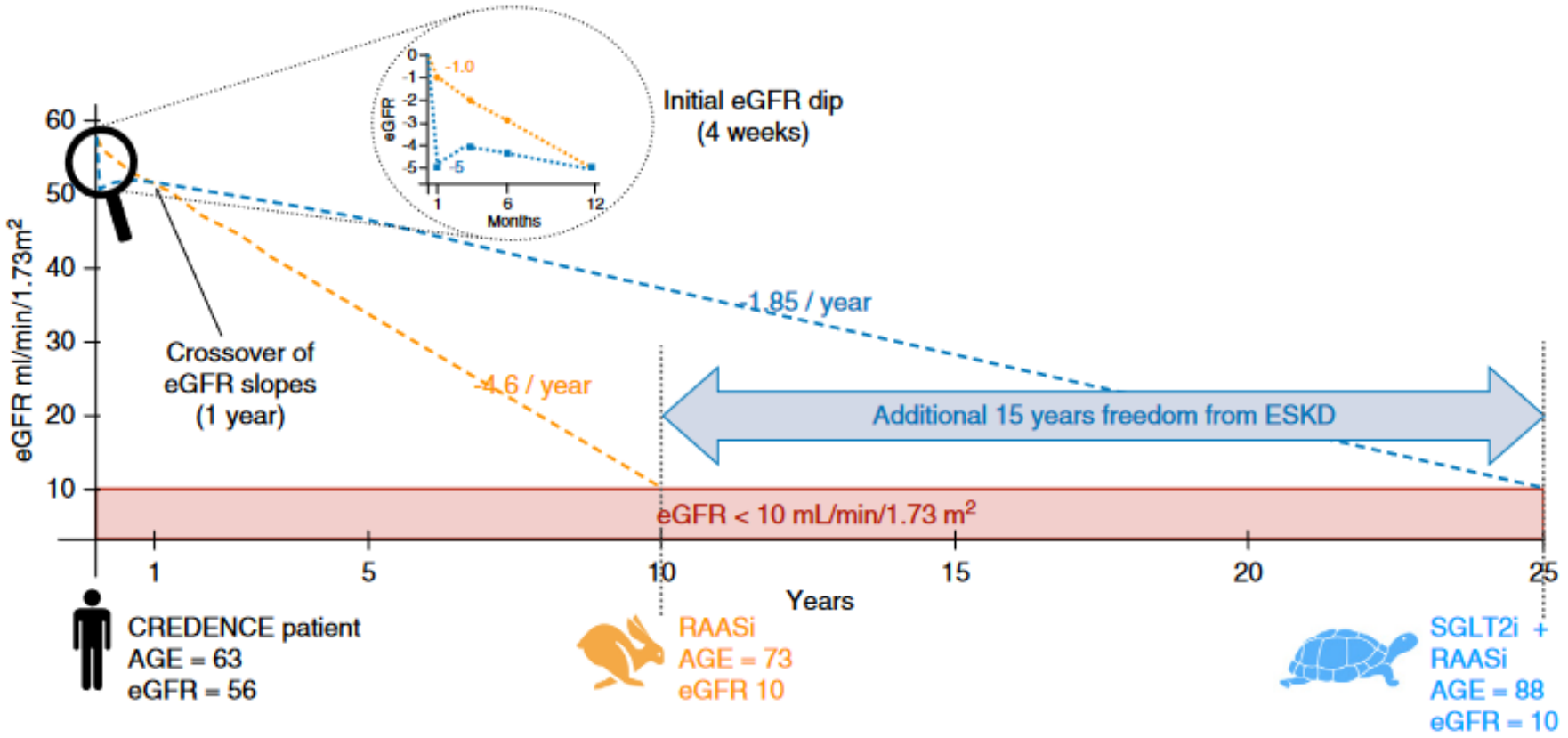
Trial Name	Agent Studied	Primary Outcomes	Observed Early Drop in eGFR
CREDENCE (8)	Canagliflozin	Reduction in the composite risk of ESKD, doubling serum creatinine level, or death from renal or cardiovascular causes (HR, 0.70; 95% CI, 0.59 to 0.82), compared with placebo.	5 ml/min per 1.73 m^2
DAPA-CKD (9)	Dapagliflozin	Reduction in the risk of 50% eGFR decline, ESKD, or death from renal or cardiovascular causes (HR, 0.61; 95% CI, 0.51 to 0.72), compared with placebo.	4 ml/min per 1.73 m^2
EMPEROR-Reduced (5)	Empagliflozin	Reduction of the risk of cardiovascular death or hospitalization for worsening heart failure (HR, 0.75; 95% CI, 0.65 to 0.86), compared with placebo.	4 ml/min per 1.73 m^2
EMPA-REG Outcome (11)	Empagliflozin	Canagliflozin decreased the risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (HR, 0.86; 95% CI, 0.74 to 0.99), compared with placebo.	3–4 ml/min per 1.73 m^2
CANTATA-SU (12)	Canagliflozin	Canagliflozin slowed the progression of kidney disease compared with glimepiride in patients with type 2 DM ($P<0.01$ for each canagliflozin group versus glimepiride).	3–6 ml/min per 1.73 m^2

CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; HR, hazard ratio; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in CKD; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPA-REG Outcome, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CANTATA-SU, Canagliflozin Treatment and Trial Analysis–Sulfonylurea; DM, diabetes mellitus.

Kidney360 2021;2: 1042–1047

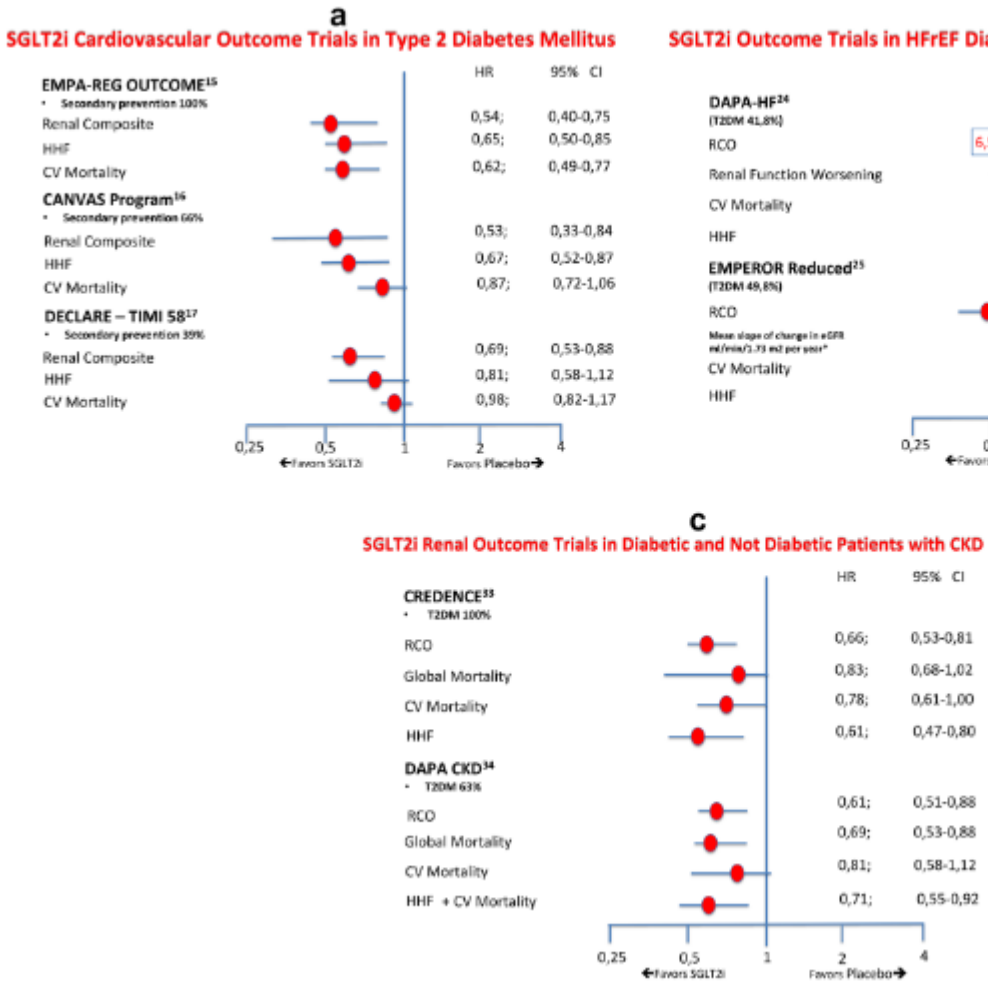
eGFR Decline after SGLT2 Inhibitor Initiation:

The Tortoise and the Hare Reimagined



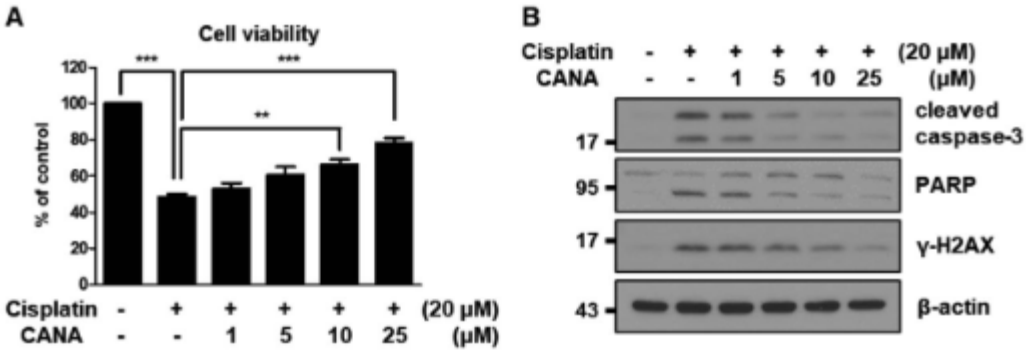
Kidney360 2021;2:1042–1047

Renal effects of SGLT2is in cardiovascular patients with and without chronic kidney disease: focus on heart failure and renal outcomes

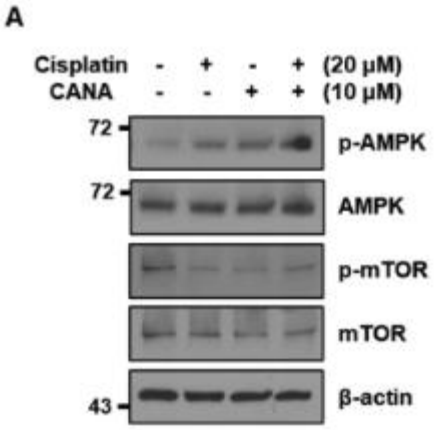


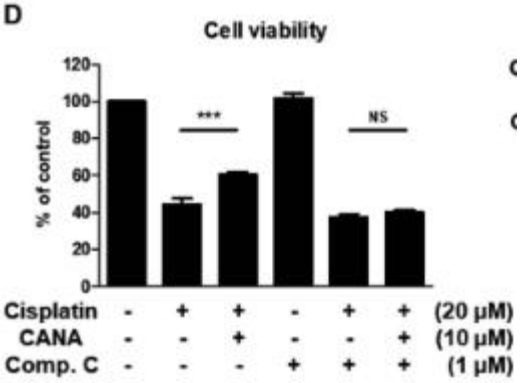
Heart Failure Reviews 2023; 28:723–732

Canagliflozin protects against cisplatin-induced acute kidney injury by AMPK-mediated autophagy in renal proximal tubular cells

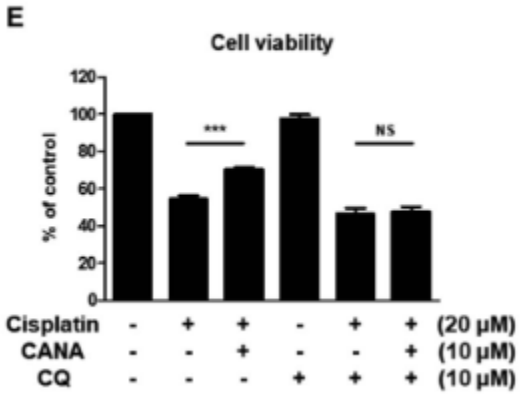


Canagliflozin protects HK-2 cells from cisplatin by inhibiting apoptosis





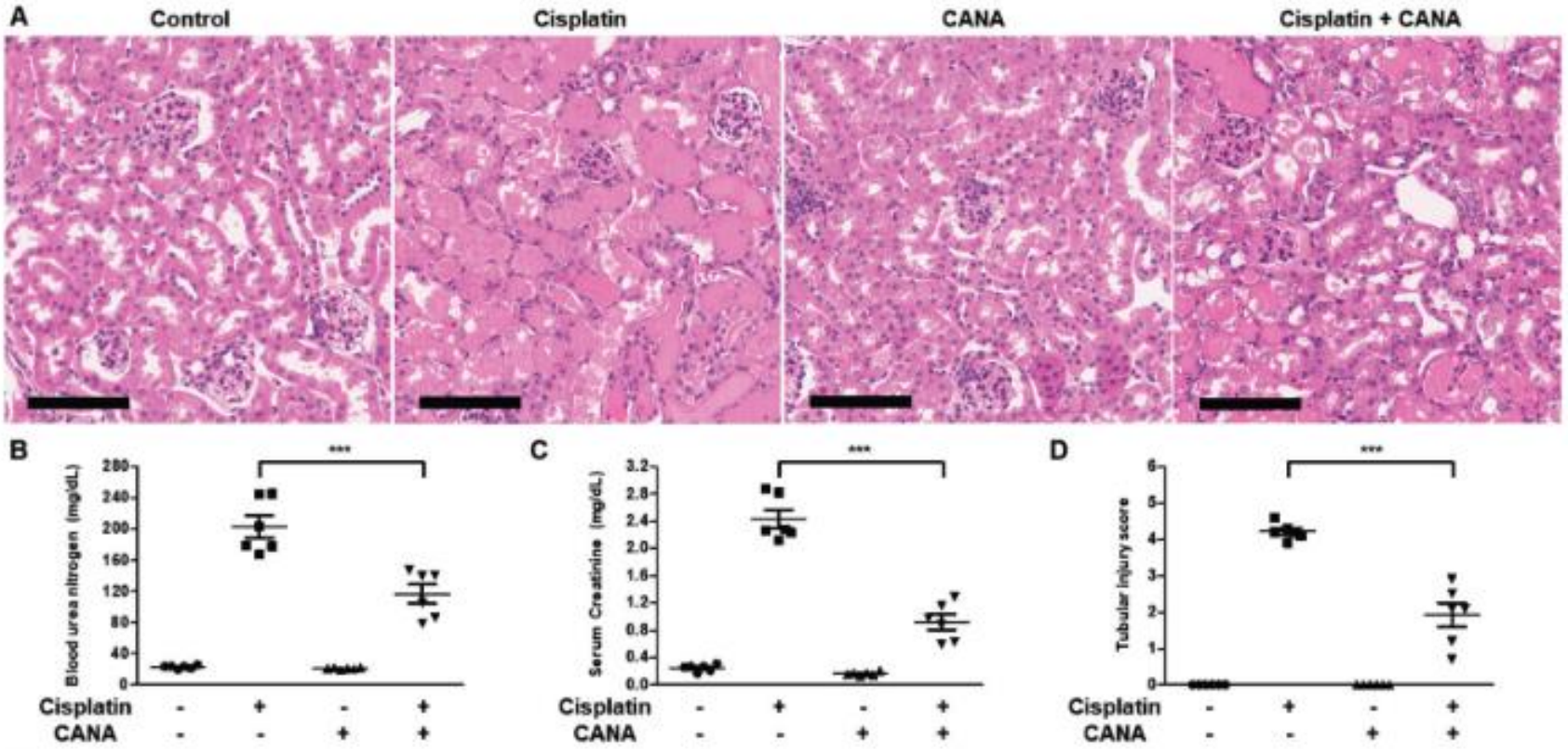
Canagliflozin activates AMPK and inhibits mTOR in HK-2 cells and protects HK-2 cells from cisplatin in an AMPK activation-dependent manner.



Canagliflozin induces autophagy in HK-2 cells and protects HK-2 cells from cisplatin in an autophagy-dependent manner

Cell Death Discovery 2022;8:12-23

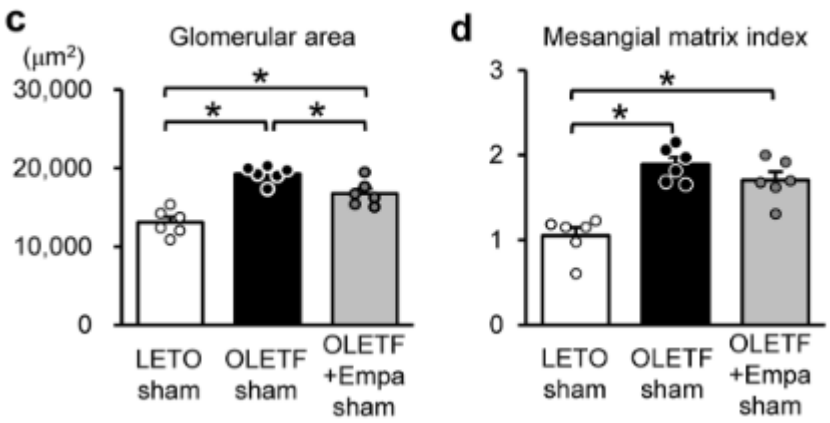
Canagliflozin protects against cisplatin-induced acute kidney injury by AMPK-mediated autophagy in renal proximal tubular cells



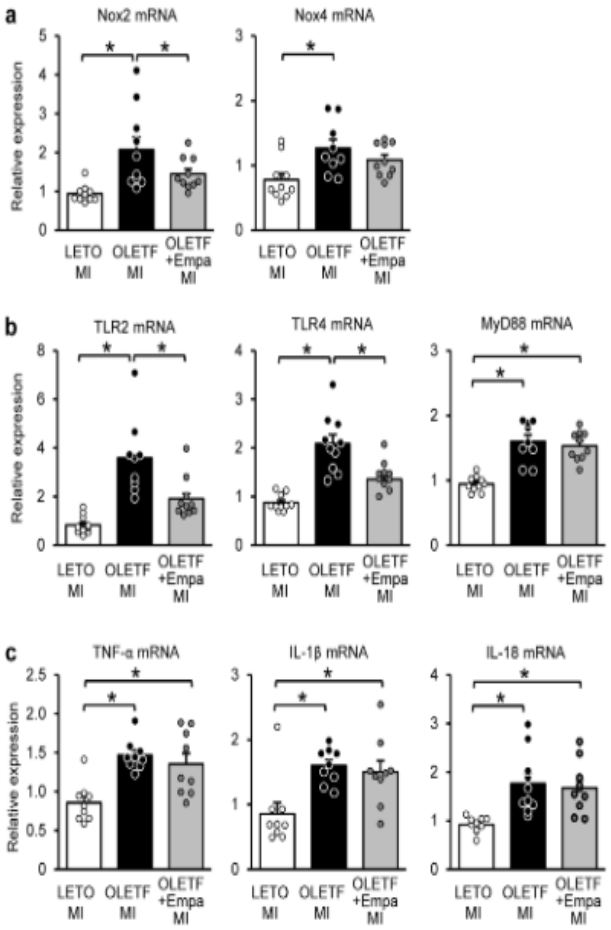
Canagliflozin attenuates cisplatin-induced AKI and increases autophagy in mice

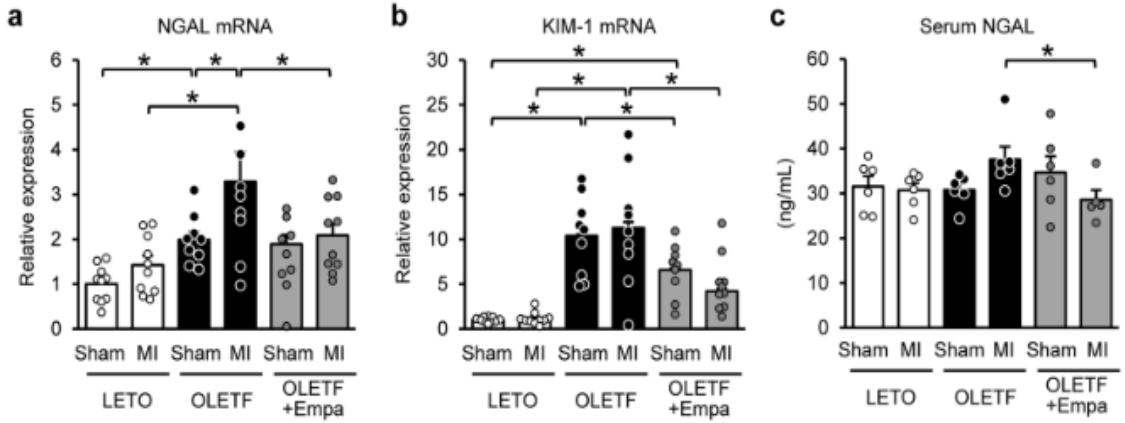
Cell Death Discovery 2022;8:12-23

Empagliflozin attenuates acute kidney injury after myocardial infarction in diabetic rats



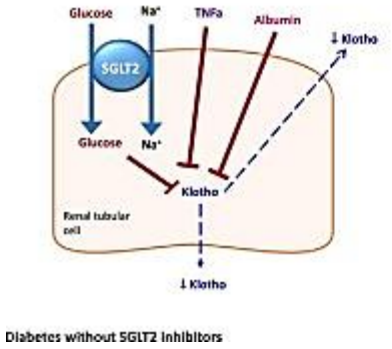
Enlargement of the glomerular area



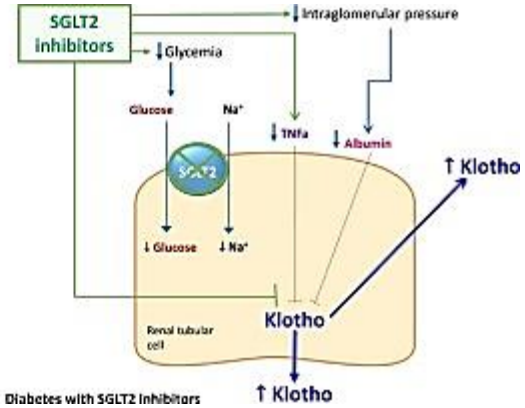


Sci Rep.2020;29;10(1):7238

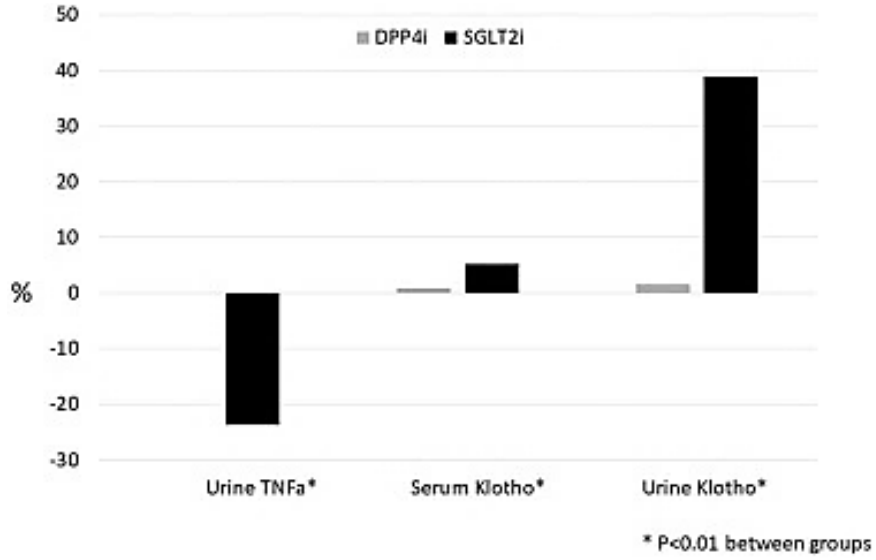
SGLT2is increase Klotho in patients with diabetic kidney disease: A clinical and experimental study



Diabetes without SGLT2 inhibitors



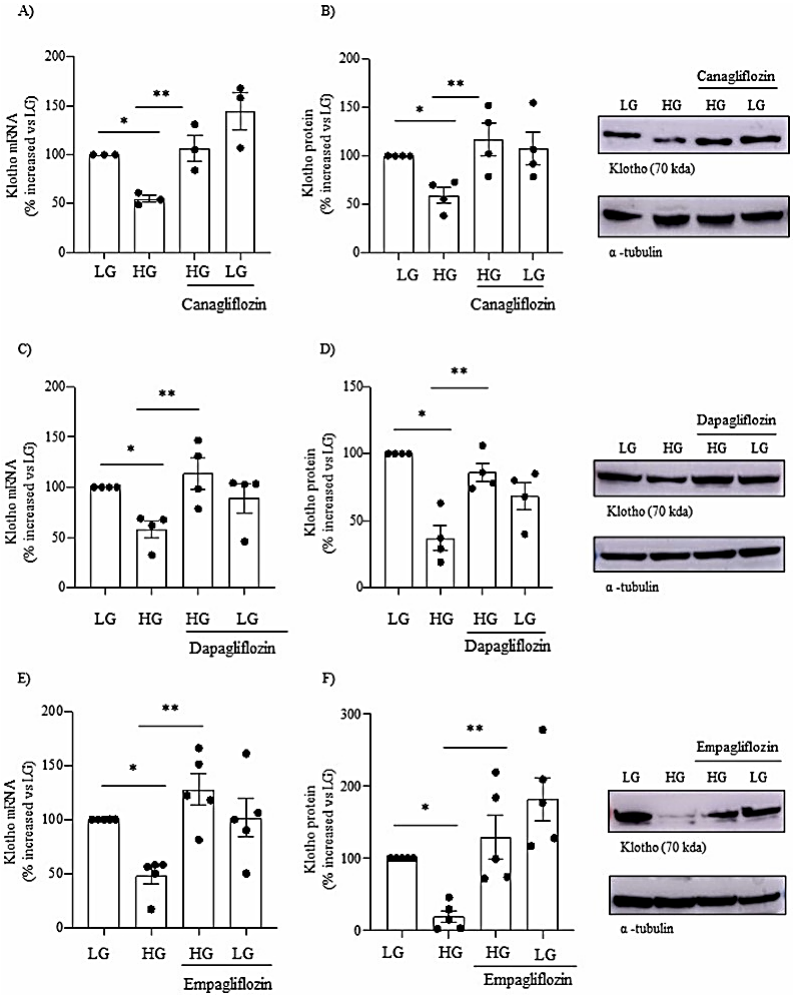
Diabetes with SGLT2 inhibitors

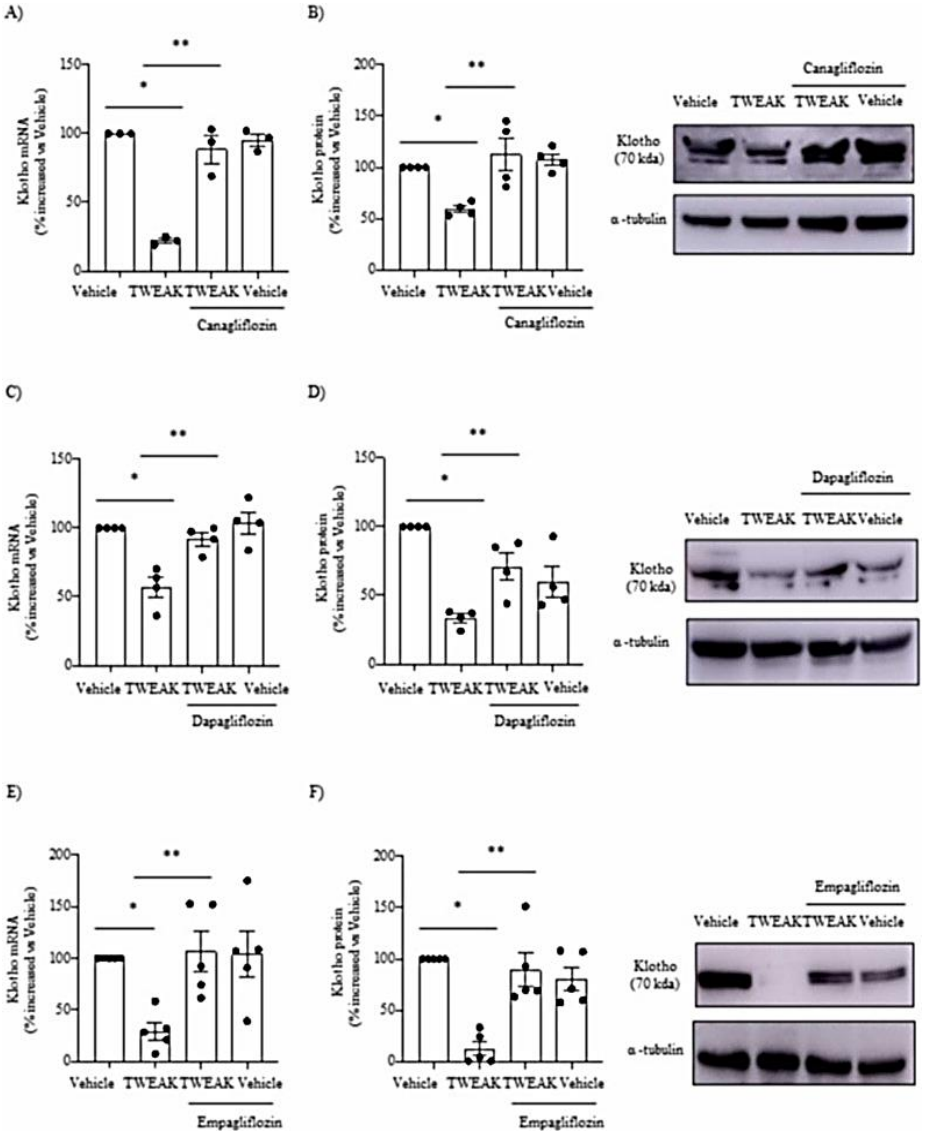


Percent reductions with respect to baseline in urine tumor necrosis factor-alpha (TNFa) and soluble (serum and urine) Klotho in patients treated with SGLT2i and DPP4i.

Biomedicine & Pharmacotherapy 2022;154:113677

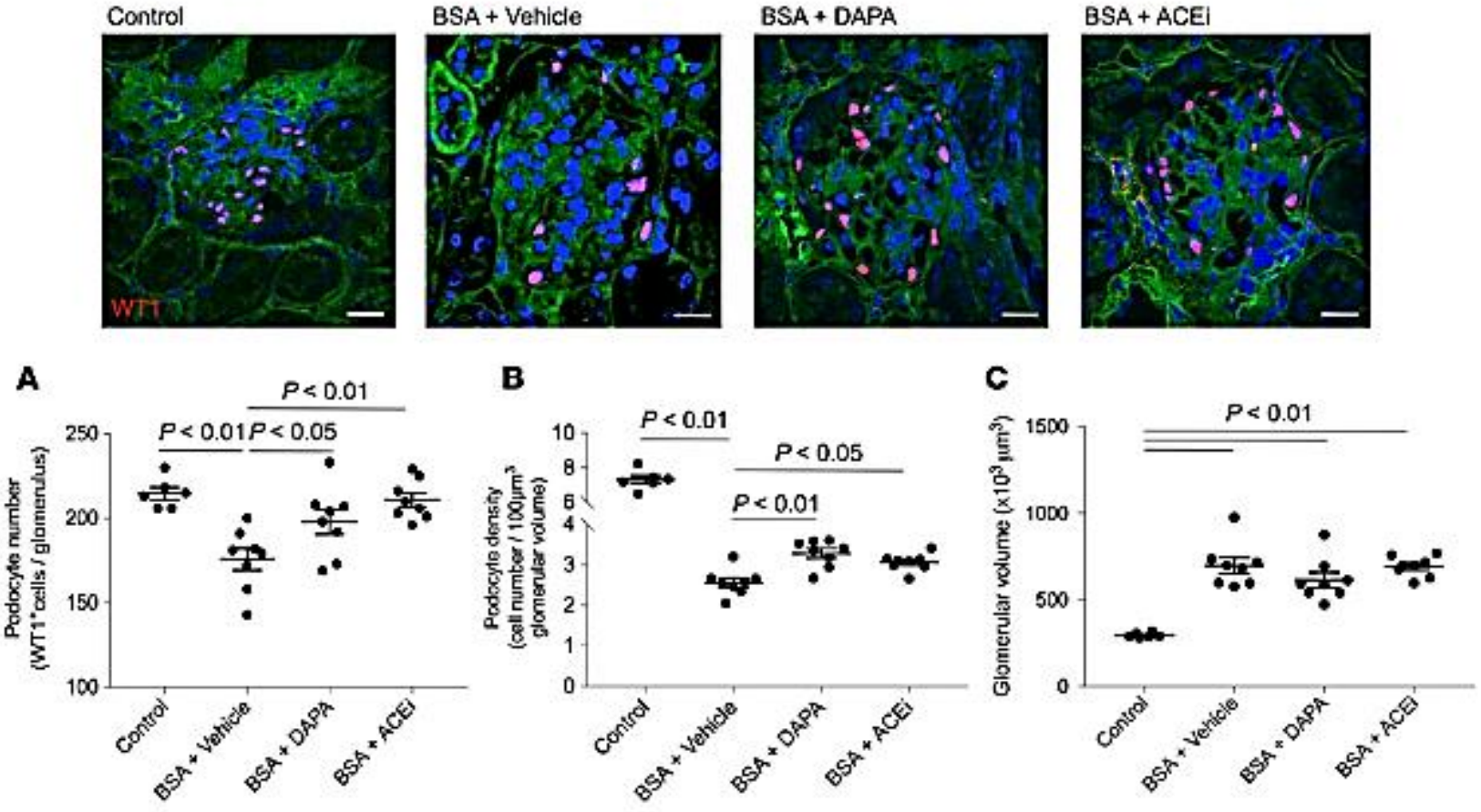
SGLT2is increase Klotho in patients with diabetic kidney disease: A clinical and experimental study





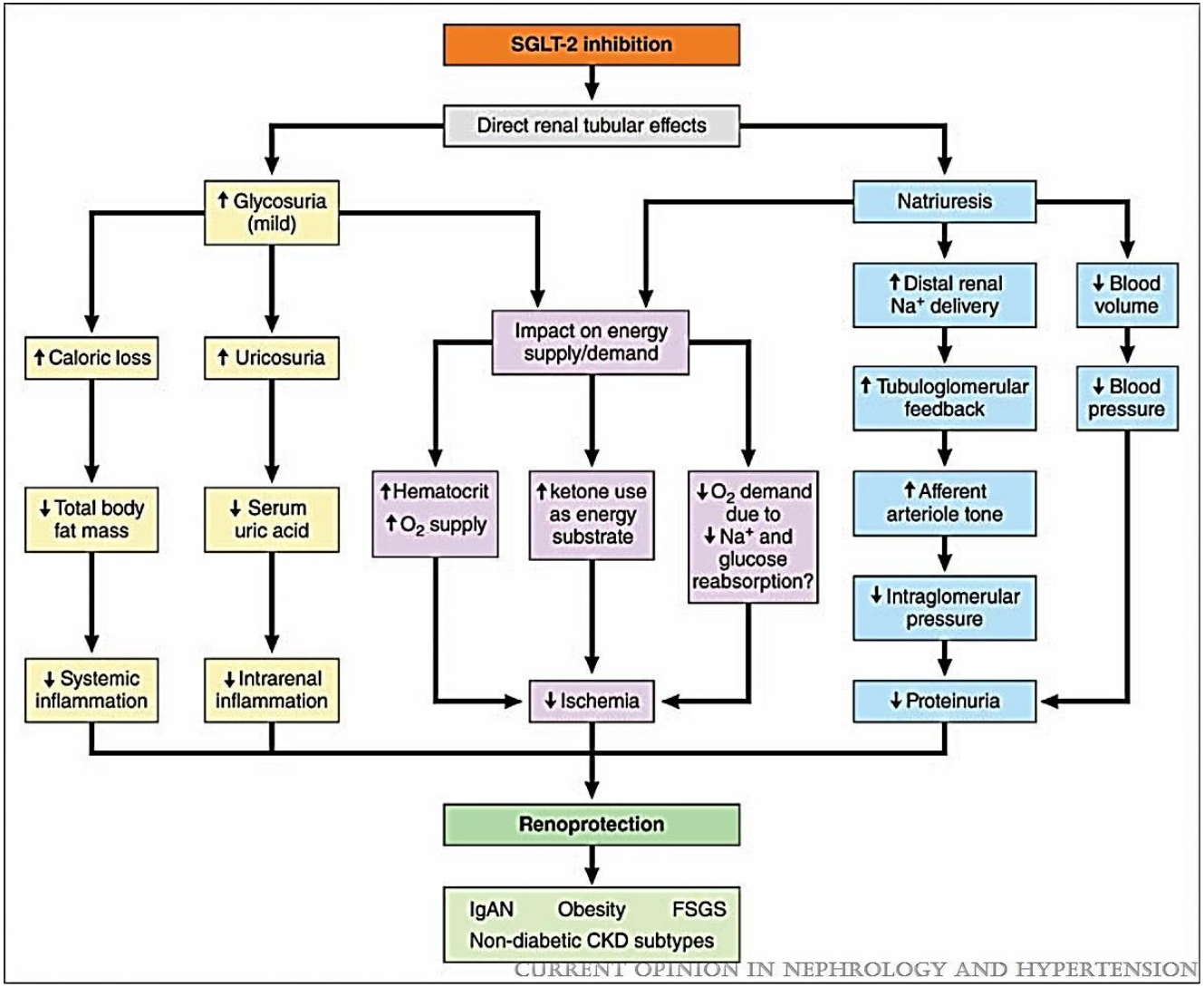
Biomedicine & Pharmacotherapy 2022;154:113677

SGLT2i Dapagliflozin limits podocyte damage in proteinuric nondiabetic nephropathy



JCI Insight. 2018;3(15):e98720

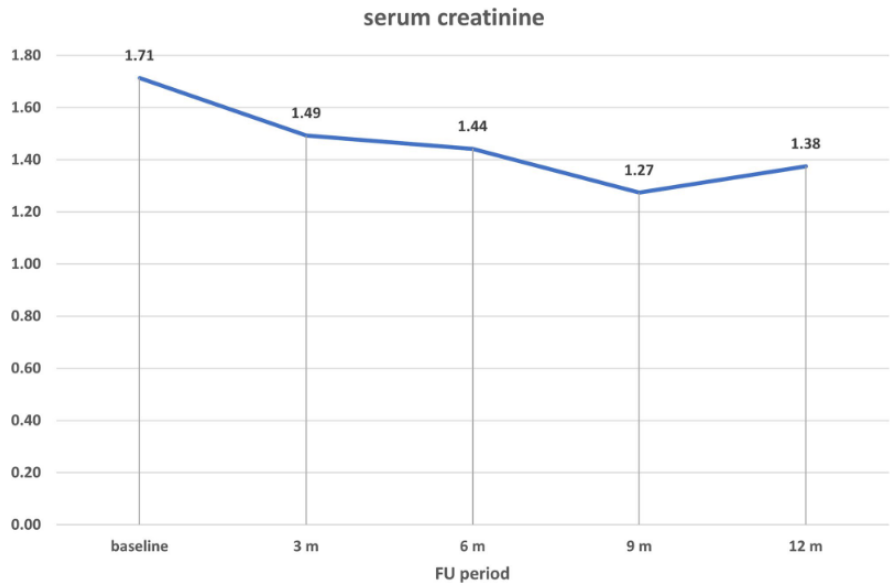
Potential use in non-Diabetic Kidney Disease



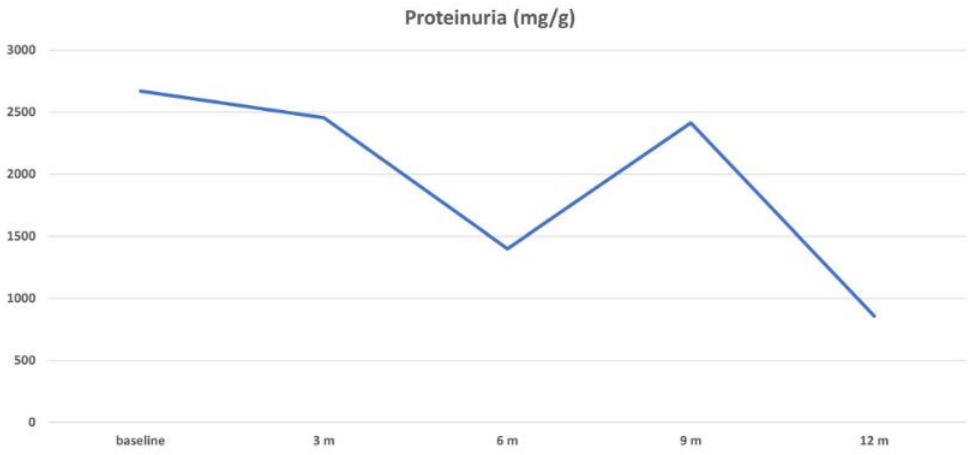
Current Opinion in Nephrology and Hypertension 2017;26(5):358-367

Safety of SGLT2 inhibitors in patients with different glomerular diseases treated with immunosuppressive therapies

	N (%)
Gender	
Male	11 (64.7%)
Female	6 (35.3%)
Age (mean ± SD)	46.7 ± 16.3
Primary kidney disease	
Focal segmental glomerulosclerosis	5 (29.4%)
Membranous nephropathy	4 (23.5%)
Lupus nephritis	1 (5.8%)
Minimal change disease	1 (5.8%)
Myeloma kidney	1 (5.8%)
Vasculitis	1 (5.8%)
Diabetic kidney disease (+ systemic sclerosis)	1 (5.8%)
Cholesterol vascular emboli	1 (5.8%)
Transplant glomerulopathy	1 (5.8%)
Unknown	1(5.8%)
Immunosuppressive treatment	
Corticosteroids	15 (88.2%)
Azathioprine	1 (5.8%)
Mycophenolic acid or mofetil	2 (11.7%)
Cyclosporine	4 (23.5%)
Cyclophosphamide	4 (23.5%)
Sirolimus	1 (5.8%)
Bortezomib	1 (5.8%)
Comorbidities	
Hypertension	13 (76.4%)
Diabetes mellitus	8 (47%)
Liver disease	2 (11.7%)
Rheumatological disease	3 (17.6%)
Ischemic heart disease	2 (11.7%)



Mean eGFR: 59.09±31.86 ➡ 62.89±31.59ml/min



Mean spot urinary ACR 2669 ➡ 858mg/g

European Journal of Clinical Pharmacology 2023;79:961–966

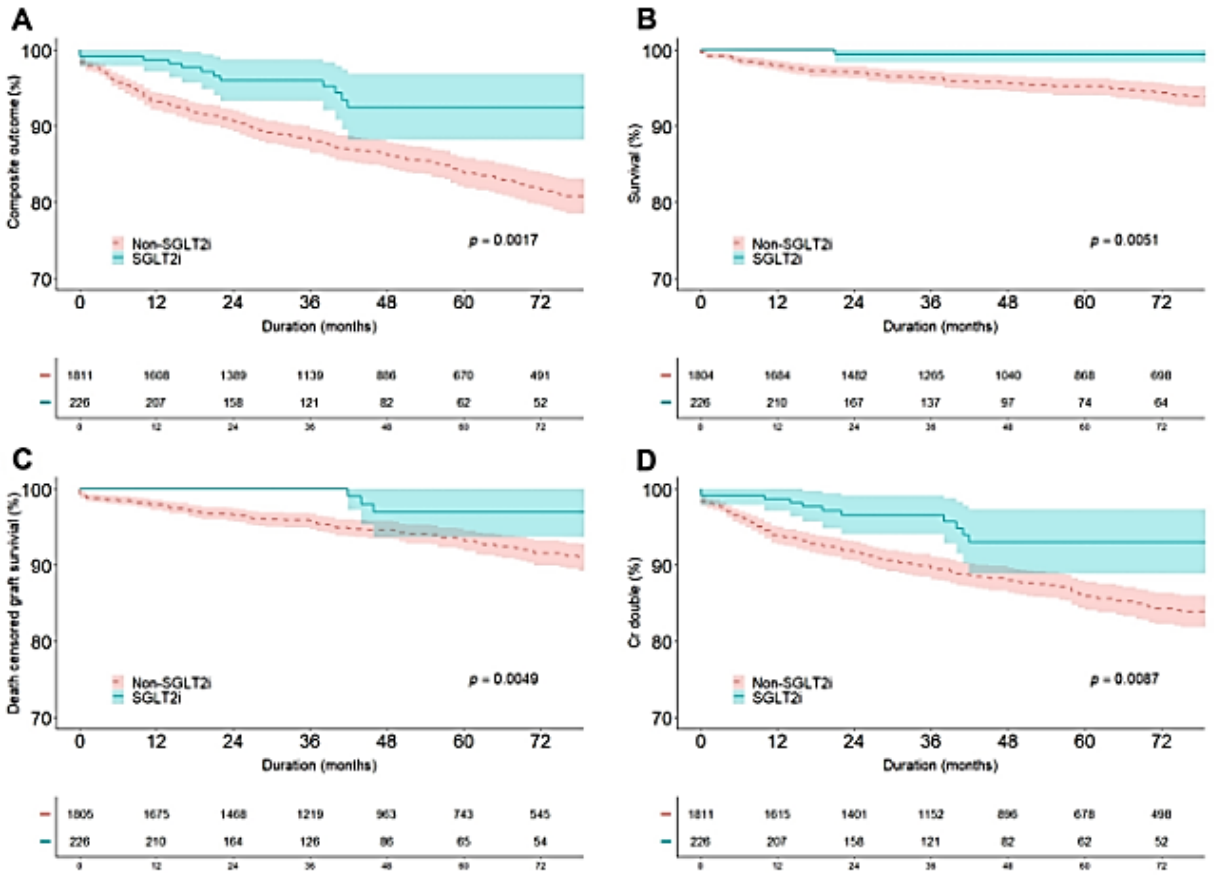
SGLT2i in kidney transplant recipients: what is the evidence?

Author, year	Study Type	N	Drug with dose (n)	Follow-up (months)	% DM prior to KT	Inclusion criteria	Exclusion criteria
Halden *et al.*, 2019[27]	RCT	Empaligflozin (n = 22) Placebo (n = 22)	Empagliflozin 10 mg	6	0%	1. Age ≥ 18 KT ≥ 1 year prior 2. Stable kidney function (<20% deviation in SCr in 2 months) 3. Stable IS therapy for 3 months	1. eGFR < 30 ml/min/1.73 m2 2. Pregnant or lactating women
Schwaiger *et al.*, 2019[30]	PS	14	Empagliflozin 10 mg	12	0%	1. Age ≥ 18 2. KT ≥ 6 months 3. eGFR ≥ 30 ml/min/1.73 m² 4. PTDM treated > 6 months	1. Insulin therapy ≥ 40 IU/day 2. HbA1c ≥ 8.5%
Mahling *et al.*, 2019[28]	CS	10	Empagliflozin	12	60%	1. Stable allograft function 2. eGFR > 45 ml/min/1.73 m² 3. No history of UTI	1. T1DM 2. History of UTI
Attallah and Yassine, 2019[26]	CS	8	Empagliflozin 25 mg/day	12	50%	–	–
Rajasekeran *et al.*, 2017[29]	CS	10	Canagliflozin	8	20%	1. Adult's s/p KT or KPT	–
Shah *et al.*, 2019[31]	PS	24	Canagliflozin 100 mg	6	83%	1. Age ≥ 18 years 2. Stable kidney function 3. Cr clearance > 60 ml/min HbA1c > 6.5%	1. Unstable Cr 2. Cr clearance < 60 ml/min 3. Total bilirubin > 1.5× normal 4. ALT > 2× normal 5. Recent UTI or genital mycosis
Kong *et al.*, 2019[33]	PS	42	Dapagliflozin 5 mg/day	12	67%	–	–
AlKindi *et al.*, 2020[25]	CS	8	Empagliflozin 10 mg/day (5), Empagliflozin 25 mg/day (1), Dapagliflozin 5 mg/day (2)	12	25%	–	–
Song *et al.*, 2021[32]	RS	50	Empagliflozin (43), Canagliflozin (6), Dapagliflozin (1)	6	80%	1. T2DM or PTDM 2. No AKI < 30 days prior 3. No UTIs < 6 months prior 4. eGFR ≥ 30 ml/min/1.73 m²	–

ALT, alanine transferase; CS, case series; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; KT kidney transplant; KPT, kidney and pancreas transplant; PS, prospective study; PTDM, posttransplant diabetes mellitus; RCT, randomized controlled trial; SCr, serum creatinine; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.

Ther Adv Endocrinol Metab 2022;13:1–14

The Efficacy and Safety of SGLT2 Inhibitor in Diabetic Kidney Transplant Recipients



N-202 SGLT2i users after propensity score matching
N=554 Non-SGLT2i users after propensity score matching

Transplantation 2022;106: e404–e412

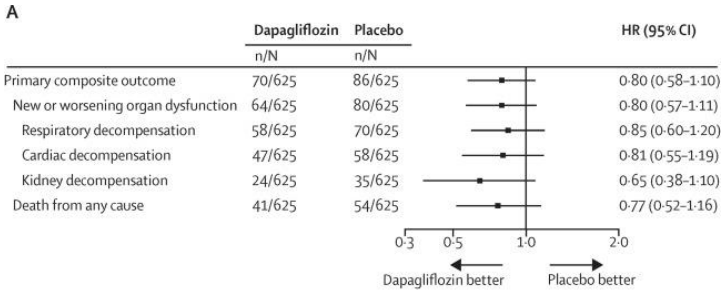
SGLT2i in kidney transplant recipients: what is the evidence?

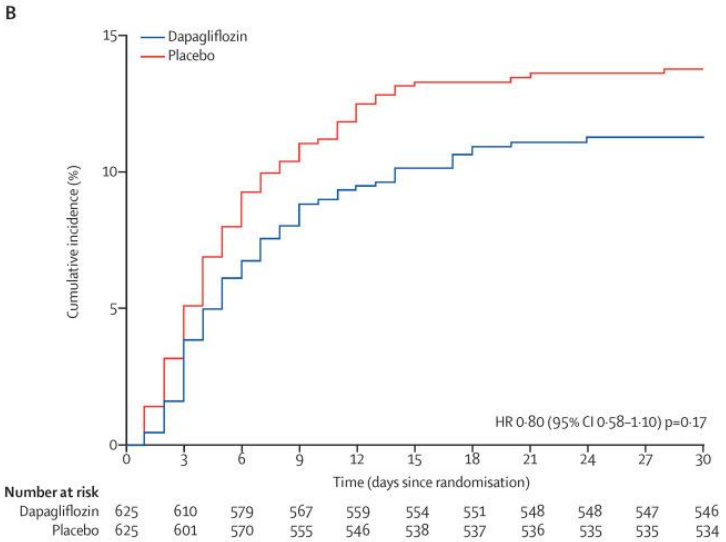
Author, year	Study Type	Change in baseline metabolic parameters		Change in baseline kidney parameters		Adverse effects in SGLT2i group	Dropped out from study
Halden et al., 2019[27]	RCT	Median (IQR) 1. ΔHgAlc −0.2 [−0.6 to −0.1] versus 0.1 [−0.1 to 0.4] 2. ΔFPG −0.65 [−1.2 to −0.13] versus 0.30 [−0.45 to 0.55] mmol 3. Δ2 h PG −1.75 [−3.7 to 0.93] versus −0.40 [−1.4 to 1.4] mmol/l. 4. ΔBody weight −2.5 [−4 to −0.05] versus 1.0 [0.0 to 2.0] kg	$p = 0.025$ $p = 0.272$ $p = 1.0$ $p = 0.014$	Median (IQR) 1. ΔeGFR −3 [−7 to 0] versus −1.0 [−2.8 to 0.75] 2. ΔSBP −5 [−12 to 1] versus 2 [−6 to 8] mmHg	$p = 1.0$ $p = 0.06$	UTI (n − 3) Genital yeast infection (n − 1)	Urosepsis (n − 1)
Schwaiger et al., 2019[28]	PS	Mean (± SD) 1. ΔHbA1c 6.7 [±0.7] inc. to 7.1 [±0.8]% 2. ΔFPG inc. to 144 ± 45 mg/dl 3. Δ2-h PG inc. to 273 ± 116 mg/dl 4. ΔBody weight 83.7 ± 7.6 to 78.7 ± 7.7 kg 5. ΔSBP 150 (26) to 145 (20), $p = 0.36$	$p = 0.03$ $p = 0.005$ $p = 0.06$ $p = 0.02$	Mean (± SD) 1. ΔeGFR 54.0 ± 23.8 to 53.5 ± 13.3 Median (IQR) 1. ΔUPCR 206 (84–901) to 348 (147–555) mg/g	$p = 0.93$ $p = 1.0$	UTI (n − 5) Balanitis (n − 1) Pneumonia (n − 1)	
Mahling et al., 2019[26]	CS	Median (IQR) 1. ΔHbA1c 7.3 (6.4–7.8) to 7.1 (6.6–7.5) 2. ΔBody weight −1 [−1.9 to −0.2] kg 3. ΔSBP −3[−36 to 1] mmHg	-	Urine protein not recorded	-	UTI (n − 2) AKI (n − 1) Diabetic ulcer (n − 1)	Tiredness(n − 1) AKI(n − 1)
Attallah and Yassine, 2019[24]	CS	Mean 1. ΔHbA1c −0.85 g/dl 2. ΔBodyweight −2.4 kg/year 3. ΔSBP −4.2 mmHg	-	Mean ΔUrine protein −0.6 g/day	-	UTI (n − 2) Nausea (n − 2)	
Rajasekeran et al., 2017[29]	CS	Mean (± SD) 1. ΔHbA1c −0.84 ± 1.2% 2. ΔBody weight −2.14 ± 2.8 kg	$p = 0.07$ $p = 0.07$	Mean (± SD) 1. ΔeGFR −4.3 ± 12.2	$p = 0.3$	Cellulitis (n − 1) Hypoglycemia (n − 1)	
Shah et al., 2019[31]	PS	Mean (± SD) 1. ΔHbA1c 8.5 ± 1.5% to 7.6 ± 1% 2. ΔBody weight 78.6 ± 12.1 kg to 76.1 ± 11.2 kg 3. ΔBP 142 ± 21 and 81 ± 9 to 134 ± 17 and 79 ± 8 mmHg 4. ΔTacrolimus level 6.7 ± 3.7 ng/ml to 6.1 ± 2 ng/ml	$p < 0.05$ $p < 0.05$ (SBP)	Mean (± SD) 1. ΔSCr 1.1 ± 0.2 before and 1.1 ± 0.3 after	-	None reported	Rise in creatinine(n − 1)
Kong et al., 2019[32]	PS	Mean (± SD) 1. ΔHbA1c 7.5 ± 1.1% to 6.9 ± 0.8"% 2. ΔBody weight 69.6 ± 12.5 to 68.0 ± 14.0 kg	$p = 0.000$	Mean (± SD) 1. ΔeGFR 60.3 ± 17.0 to 59.3 ± 14.5 ml/min/1.73 m^2	-	Acute cystitis (n − 2)	UTI(n − 3) Weight loss (n − 2) Physician preference (n − 1)
AlKindi et al., 2020[25]	CS	Mean (± SD) 1. ΔHbA1c 7.41 ± 1.44 from 9.34 ± 1.36 2. ΔSBP 126.43 ± 11.46 from 135 ± 9.59 3. ΔBMI 27.4 ± 4.2 from 32.74 ± 7.2	$p < 0.05$ $p < 0.05$ $p < 0.05$	Mean (± SD) 1. ΔeGFR 69.88 ± 14.70 from 75.75 ± 13.38 ml/min/1.73 m^2	$p < 0.05$	UTI (n − 1)	
Song et al., 2021[33]	RS	Mean (± SD) 1. ΔHbA1c −0.53% [±1.79] 2. ΔWeight −2.95 kg [±3.54]	$p = 0.1189$ $p < 0.0001$	Mean (± SD) 1. ΔeGFR + 1 ml/min/1.73 m^2	$p = 0.1478$	UTI (n − 7) Genital mycosis (n − 1)	UTI (n − 5) Genital yeast infection (n − 1) Native disease recurrence (n − 1) Physician preference (n − 1) Resolution of PTDM (n − 1)

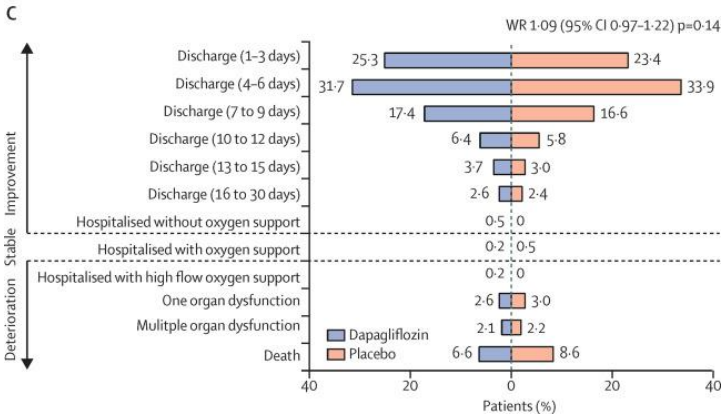
CS, case series; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; PG, plasma glucose; PS, prospective study; RCT, randomized controlled trial; SBP, systolic blood pressure; SCr, serum creatinine; UTI, urinary tract infection; UPCR, urine protein creatinine ratio.

Ther Adv Endocrinol Metab 2022;13: 1–14

Dapagliflozin in patients with cardiometabolic risk factors hospitalized with COVID-19 (DARE-19): a randomized, double-blind, placebo-controlled, phase 3 trial







Inhibition of glycolysis (a pathway that can be used by respiratory pathogens
Stimulation of lipolysis
Reduction of Oxidative Stress and Inflammation
Improved endothelial dysfunction
Improved Oxygen carrying capacity

Safety outcomes in the safety population

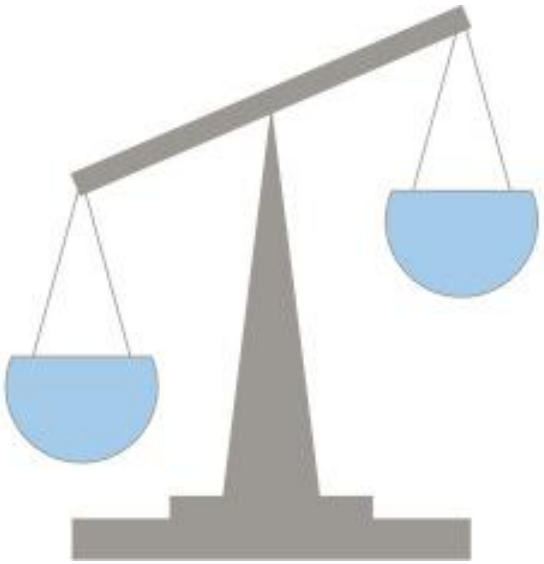
	Dapagliflozin (n=613)	Placebo (n=616)
Any serious adverse event, including death	65 (10·6%)	82 (13·3%)
Adverse event with the outcome of death	32 (5·2%)	48 (7·8%)
Discontinuation due to adverse event	44 (7·2%)	55 (8·9%)
Adverse events of interest		
Acute kidney injury	21 (3·4%)	34 (5·5%)
Diabetic ketoacidosis	2 (0·3%)	0

Data are n (%). Data show the number and proportion of patients with the listed outcome with an onset date on or after the date of the first dose and up to and including 2 days after the last dose of the study medication.

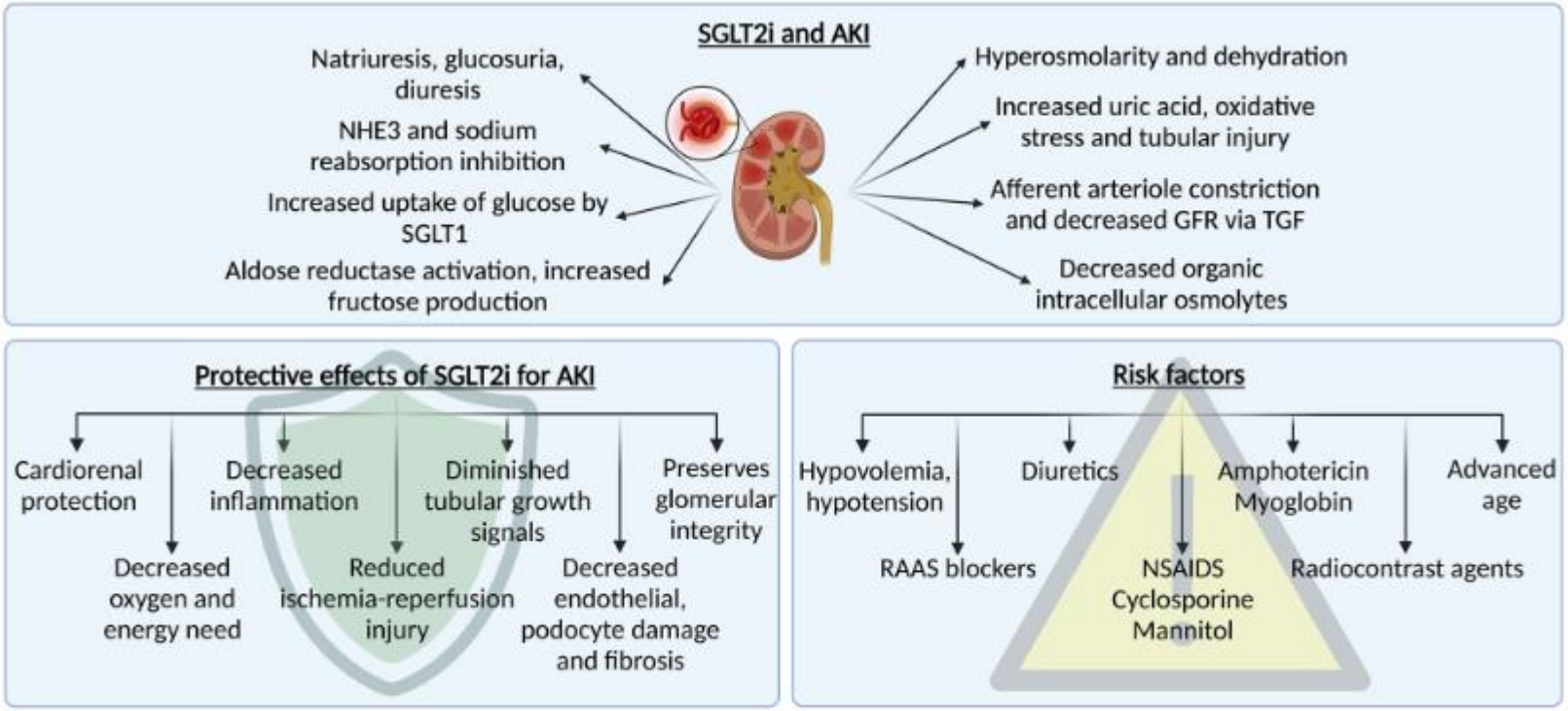
Lancet Diabetes Endocrinol 2021;9(9):586-594

Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes

Favorable effects
Reduction of pre-load (diuretic effects)
Reduction of afterload (blood pressure, arterial stiffness)
Improvement of mitochondrial efficiency
Delay of decline in eGFR
Delay of micro- and macroalbuminuria
Weight loss
Reduction in epicardial adipose tissue
Improvement in glycemia
Reduction in uric acid



Unfavorable effects
Amputations (in particular toe, metatarsal)
Volume depletion/Hypotension
Diabetic ketoacidosis
Fractures
Urinary and genital infections


SGLT2i and AKI
Natriuresis, glucosuria, diuresis
NHE3 and sodium reabsorption inhibition
Increased uptake of glucose by SGLT1
Aldose reductase activation, increased fructose production
Hyperosmolarity and dehydration
Increased uric acid, oxidative stress and tubular injury
Afferent arteriole constriction and decreased GFR via TGF
Decreased organic intracellular osmolytes
Protective effects of SGLT2i for AKI
Cardiorenal protection
Decreased inflammation
Diminished tubular growth signals
Preserves glomerular integrity
Decreased oxygen and energy need
Reduced ischemia-reperfusion injury
Decreased endothelial, podocyte damage and fibrosis
Risk factors
Hypovolemia, hypotension
Diuretics
Amphotericin Myoglobin
Advanced age
RAAS blockers
NSAIDS Cyclosporine Mannitol
Radiocontrast agents

Key points

- SGLT2is are approved for the treatment of hyperglycemia in patients with T2D.
- Owing the mechanism of their action, these agents provide cardio- and renal protection.
- Based on proximal tubular natriuretic effects, SGLT2is have therapeutic potential for use in nondiabetic patients.
- Should SGLT2is be withheld in the presence of high-risk clinical situations?

Thank you for your attention

Clinical Randomized Trials on SGLT2i and Renal Outcomes

Study	Drug	Key Inclusion Criteria	No. of Patients	Renal End Points	Main Results
CANVAS /CANVAS R[44]	Canagliflozin	T2DM, age ≥ 50 yr with high CV risk or age ≥ 30 yr with a history of CVD, eGFR ≥30 mL/min	10,142	Albuminuria progression Renal composite outcome (comprising a 40% reduction in eGFR, need for RRT, or death from renal causes)	Reduction in albuminuria progression (HR, 0.73; 95% CI, 0.67–0.79) Lower incidence of the composite outcome (HR, 0.60; 95% CI, 0.47–0.77)
CREDENCE[47]	Canagliflozin	Age ≥ 30 yr, T2DM, eGFR = 30–90 mL/min, UACR = 300–5000 mg/g, ACEi or ARB use	4401	Composite of ESRD (dialysis for at least 30 d, kidney transplantation, or an eGFR of <15 mL/min), doubling of the SCr level from baseline, or death from renal or CV disease *Secondary*: renal-specific composite of ESRD, doubling of the SCr level, or renal death	30% lower RR for the primary outcome (HR, 0.70; 95% CI, 0.59–0.82; $P = 0.00001$) 34% lower RR for the renal-specific composite of ESRD, a doubling of SCr level, or death from renal causes (HR, 0.66; 95% CI, 0.53–0.81; $P < 0.001$) 32% lower RR for ESRD (HR, 0.68; 95% CI, 0.54–0.86; $P = 0.002$)
DAPA-CKD[48]	Dapagliflozin	Age ≥ 18 yr, T2DM, eGFR = 25–75 mL/min, UACR = 200–5000 mg/g, ACEi or ARB use	4094	*Primary*: first occurrence of any of the following: ≥50% sustained decline in eGFR, the onset of ESRD, or death from renal or CV causes *Secondary*: composite kidney outcome of ≥50% sustained a decline in eGFR, ESRD, or death from renal causes	Reduction in primary end point occurrence (HR, 0.61; 95% CI, 0.51–0.72; $P < 0.001$). Lower incidence of the secondary end point (HR, 0.56; 95% CI, 0.45–0.68; $P < 0.001$)
DECLARE –TIMI 58[45]	Dapagliflozin	Age ≥ 40 yr, T2DM, eGFR ≥ 60 mL/min, high CV risk or established CVD	17,160	Renal composite (≥40% decrease in eGFR to <60 mL/min, new ESRD, or death from renal or CV causes) and death from any cause	Reduction in the renal end point (HR, 0.76; 95% CI, 0.67–0.87) and death from any cause (HR, 0.93; 95% CI, 0.82–1.04)
EMPA-REG OUTCOME[44]	Empagliflozin	Age ≥ 30 yr, T2DM, established CVD, eGFR ≥ 30 mL/min, UACR 5300–5000 mg/g, ACEi or ARB use	7020	Incident or worsening nephropathy (progression to macroalbuminuria, doubling of SCr level, initiation of RRT, or death from renal disease) and incident albuminuria	Reduction of incident or worsening nephropathy (HR, 0.61; 95% CI, 0.53–0.70; $P < 0.001$) No significant difference in incident albuminuria
VERTIS CV[46]	Ertugliflozin	Age ≥ 40 yr, T2DM, established atherosclerotic CVD	8246	A composite of death from renal causes, RRT, or doubling of the SCr level	No reduction in composite end point (HR, 0.81; 95.8% CI, 0.63–1.04)

CV, cardiovascular; CVD, cardiovascular disease; ESRD, end-stage renal disease; RR, relative risk; RRT, renal replacement therapy; T2DM, type-2 diabetes mellitus; UACR, urinary albumin–creatinine ratio.

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ACUTE KIDNEY INJURY

	Timing	Functional changes		Structural damage*
		Change	Threshold	
Acute kidney injury	≤7 days	Creatinine ≥1·5 times baseline (or increase of ≥0·3 mg/dL within any 48 h period)	Urine volume <0·5 mL/kg for ≥6 h	Undefined
Acute kidney disease	>7 days, <90 days	Creatinine ≥1·5 times baseline (or increase ≥0·3 mg/dL within any 48 h period)	eGFR <90 mL per min (with damage marker) eGFR mL per min per 1·73 m^2 <60 mL per min	Kidney damage
Chronic kidney disease	≥90 days	Not applicable	eGFR <90 mL per min (with damage marker) eGFR mL per min per 1·73 m^2 <60 mL per min	Kidney damage

Comparisons are in terms of timing, functional changes, and structural damage. eGFR=estimated glomerular filtration rate. *Kidney damage can be assessed by pathology, urine or blood markers, or imaging. Stuctural criteria are not included in the current definitions for acute kidney injury as none have yet been validated for this purpose.

Comparison of acute kidney injury, acute kidney disease, and chronic kidney disease

Lancet 2019; 394: 1949–64

ACUTE KIDNEY INJURY

Staging of acute kidney injury according to current Kidney Disease Improving Global Outcomes definition

Stage 1
Creatinine ≥1·5 times baseline or increase of ≥0·3 mg/dL within any 48 h period, or urine volume <0·5 mL/kg for 6–12 h

Stage 2
Creatinine ≥2·0 times baseline or urine volume <0·5 mL/kg for ≥12 h

Stage 3
Creatinine ≥3·0 times baseline or increase to ≥4·0 mg/dL or acute dialysis, or urine volume <0·3 mL/kg for ≥24 h

Lancet 2019; 394: 1949–64

Determinants of medullary oxygen balance: major factors affecting renal medullary oxygen consumption and expenditure for tubular transport activity

Improved medullary oxygenation	Reduced medullary oxygenation
Increased regional blood/oxygen supply	*Decreased regional blood/oxygen supply*
Prostaglandins (PGE2, PGI2)	Altered cyclo-oxygenase (NSAIDs, aging)
Nitric oxide	Altered nitrovasodilation (D, dyslipidemia, and other causes for enhanced ROS formation)
Adenosine (mediated by adenosine A_2 receptors)[a]	Hypotension with mean BP < 65 mmHg[b]
Endothelin (mediated by endothelin ETB receptors)[a]	Profound decline in total or medullary blood flow other than hypotension (endogenous or exogenous vasoconstrictors)
Angiotensin II (mediated by AT_2 receptors)[a]	Increased interstitial pressure (radiocontrast agents, urine outflow obstruction)
	Rarefaction of capillary meshwork in CKD (D)
	Anemia
Decreased medullary transport activity	*Increased medullary transport activity*
Pre-renal failure (S-mediated and other causes of dehydration, hypotension but with BP > 65 mmHg)[b]	Enhanced GFR or single-nephron GFR (D, high-protein diet, CKD with reduced number of nephrons, post-nephrectomy compensatory hypertrophy of remnant kidney, pregnancy)
Declining GFR due to other causes (S and other factors activating TGF, including AKI, RAAS blockade)	Reduced transport activity in proximal tubular segments (S)
Increased proximal tubular reabsorption (reduced GFR, dehydration)	Other causes of enhanced solute delivery to distal nephron segments (D, mannitol, radiocontrast agents)
Loop diuretics[c]	Dis-inhibition of Na/K/ATPase in mTALs (ROS, NSAIDs)

Plausible impacts of diabetes and sodium–glucose co-transporter-2 inhibitors (SGLT2i) are highlighted. The net effect of both diabetes and SGLT2i is a reduction in medullary partial pressure of oxygen by combined decline in regional blood flow and enhanced tubular transport and oxygen consumption

Drug Saf 2018;41:239–252

Drugs affecting medullary oxygenation

Drug	Effect on regional oxygen supply	Effect on regional oxygen demand	Comments	References
Reducing medullary pO_2				
NSAIDs	↓	↑		[47]
Cyclosporine (ciclosporin)	↓	?↓	Reduced medullary oxygen consumption in part due to reduced GFR and solute load to the distal nephron, yet vasoconstriction and reduced oxygen supply prevails	[55]
Amphotericin	↓	↑		[56]
Radiocontrast media	↓	↑		[47]
Mannitol	?↓	↑		[47]
ANP	?	↑		[91]
SGLTi	?↓	↑	Medullary hypoxia has been documented with non-selective SGLTi. It is anticipated that with SGLT2i this effect might be even more pronounced because of enhanced transport by S3 segments, located at the outer medulla [40]	[21]b
Increasing medullary pO_2				
Furosemide	↓	↓↓	Improved medullary oxygenation develops despite profound reduction in medullary blood flow, illustrating the major impact of reduced oxygen demand for tubular transport	[54]

ANP atrial natriuretic peptide, *GFR* glomerular filtration rate, *NSAIDs* non-steroidal anti-inflammatory drugs, pO_2 partial pressure of oxygen, *SGLT2i* sodium–glucose co-transporter-2 inhibitors, *SGLTi* sodium–glucose co-transporter inhibitors, ↓ indicates decrease, ↑ indicates increase, ? indicates unknown

Drug Saf 2018;41:239–252