"An Evidence-Based Approach to Proteinuric Kidney Disease in Native and Transplant Kidneys"

May 28, 2026

CME Learner Information

Wright State University Boonshoft School of Medicine (WSU BSOM) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to offer American Medical Association (AMA) Physician's Recognition Award (PRA). WSU BSOM is committed to ensure that accredited continuing education (1) presents learners with only accurate, balanced, scientifically justified recommendations, and (2) protects learners from promotion, marketing, and commercial bias.

Physicians

Wright State University Boonshoft School of Medicine designates this live activity for a maximum of 1 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure Summary

WSU BSOM policy ensures that those who have influenced the content of a CE activity (e.g. planners, faculty, authors, reviewers and others) disclose all financial relationships with any ineligible companies so that WSU BSOM may identify and mitigate any conflicts of interest prior to the activity. All educational programs sponsored by Wright State University Boonshoft School of Medicine must demonstrate balance, independence, objectivity, and scientific rigor.

There are no relevant financial relationship(s) with ineligible companies for anyone who was in control of the content of this activity, except: NONE

All of the relevant financial relationships listed for these individuals have been mitigated.

*An **ineligible company** is any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.*

For questions and concerns, please contact **WSU BSOM CME Office** at som_cme@wright.edu

"An Evidence-Based Approach to Proteinuric Kidney Disease in Native and Transplant Kidneys"

Artificial Intelligence (AI) Use Disclosure

CME Learner Information

In accordance with ACCME guidance on the Responsible Use of AI in Accredited Continuing Education, portions of this activity were developed with AI assistance.

AI Tool Information: NONE

Tool: [Name of AI tool]
Version: [Version, if applicable]
Date(s) of Use: [Month/Year]
Purpose: [e.g., drafting slides, organizing content, assessment question development]
Model/Source: [e.g., GPT-4, OpenAI]
Prompts/Outputs Stored Externally: [Yes/No]
System Security: Only secure, institution-approved AI systems were used.

Human Oversight and Review:

All AI-assisted or AI-generated content was reviewed, edited, and verified by [Name/Role of qualified reviewer], an experienced clinician, to ensure:

- Scientific and clinical accuracy, validity, and reliability
- Independence from commercial bias or influence
- Screening for bias, stereotyping, and AI "hallucinations"
- Compliance with ACCME Standards for Integrity and Independence

Review included **documented version control and traceability** indicating who reviewed content and when.

Reviewers had **No relevant financial relationships** with ineligible companies.

For questions and concerns, please contact **WSU BSOM CME Office** at som_cme@wright.edu

Boonshoft School of Medicine
WRIGHT STATE UNIVERSITY

"An Evidence-Based Approach to Proteinuric Kidney Disease in Native and Transplant Kidneys"

WRIGHT STATE UNIVERSITY

Artificial Intelligence (AI) Use Disclosure

CME Learner Information

Responsible Use Statement:

AI was **not used** to generate unverified clinical recommendations or provide assessment answers directly to learners.

No protected health information (PHI) or personally identifiable information (PII) was entered into AI systems.

Accountability:

Final responsibility for content accuracy, clinical recommendations, and independence rests with the faculty presenter.

The accredited provider maintains oversight, ensuring AI use aligns with ACCME standards and internal governance policies, including the use of approved AI tools and ongoing quality review.

Learner Transparency:

Learners are informed that AI tools were used to assist in content development, while all educational judgments were made by qualified human faculty.

ACCME AI Guidance Reference:
https://accme.org/resource/guidance-on-ai/

For questions and concerns, please contact **WSU BSOM CME Office** at som_cme@wright.edu

Activity Name

Text Attendance

Please text 5490 to 855-618-2034.

You have 60 minutes prior, during, and 120 minutes after the end of the activity to text in your attendance

The evaluation for this event will be sent once you text your attendance in. You must complete the evaluation to get your CME certificate.

Any questions please contact Amy DeVos, Medical Education Manager (adevos@premierhealth.com)

EVALUATION WILL CLOSE ON 5/31/26 and move to the library section on CloudCME

An Evidence-Based Approach to Proteinuric Kidney Disease in Native and Transplant Kidneys

Niralee Patel, MD, MEd, FASN

Associate Professor of Medicine

Nephrology Fellowship Program Director

Renal-Endocrine Systems Course Director

Division of Nephrology

University of Cincinnati

UNIVERSITY OF Cincinnati

Disclosures

No Disclosures

Objectives:

- Review the evidence for the four pharmacologic pillars for proteinuria reduction in chronic kidney disease and diabetic kidney disease.
- Evaluate initiation strategies for combination kidney-protective therapy.
- Identify clinical scenarios warranting avoidance, dose modification, or temporary discontinuation of antiproteinuric agents.
- Extrapolate the evidence — and its gaps — to the kidney transplant population.

Diabetes Estimates Around The World

Diabetic kidney disease develops in up to 40% of patients who have diabetes and is the leading cause of CKD worldwide.

IDF DIABETES ATLAS

Pathophysiology of Proteinuria: From Barrier Breach to Nephron Loss

Glomerular Barrier Failure

- Insult (hyperglycemia, HTN, immune) →
- podocyte effacement + GBM damage
- → albumin leak

Maladaptive Hemodynamics

- Nephron loss →
- hyperfiltration →
- ↑ AngII →
- ↑ intraglomerular pressure →
- → segmental sclerosis

Tubular Toxicity of Filtered Proteins

- Proximal tubule overwhelmed by protein reabsorption →
- inflammation (NF-κB), oxidative stress, complement activation →
- tubular cell injury and death →
- chemokine release recruits inflammatory cells

Fibrosis → Nephron Death

- Chronic tubular injury →
- fibroblast activation →
- interstitial fibrosis →
- capillary loss + hypoxia →
- self-amplifying nephron loss →
- ESKD

GFR categories (ml/min1.73 m²) Description and range			Persistent albuminuria categories Description and range		
			A1	A2	A3
			Normal to midly increased	Moderately increased	Severely increased
			<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
G1	Normal or high	≥90		Monitor	Refer*
G2	Midly decreased	60–89		Monitor	Refer*
G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
G3b	Moderately to severely decreased	30–44	Monitor	Monitor	Refer
G4	Severely decreased	15–29	Refer*	Refer*	Refer
G5	Kidney failure	<15	Refer	Refer	Refer

Proteinuria is not a bystander — it is a self-perpetuating injury loop.

Breaking the cycle is the rationale for aggressive pharmacologic intervention.

Why Proteinuric CKD Demands Attention

1. Predicts Progression

- Higher levels → faster eGFR decline
- Clear dose–response relationship

2. Drives Kidney Injury

- Tubular toxicity → inflammation → fibrosis
- Leads to irreversible nephron loss

3. Treatment Target

- ↓ Albuminuria → ↓ risk of kidney failure
- Strong surrogate endpoint in trials

4. Beyond the Kidney

- ↑ CV events and mortality—even at low levels

Albuminuria As A Valid Early Endpoint

Early Signal	• Changes seen within **6 months** • Precede measurable **GFR decline** • Enables faster trials & early decisions
Biological Link	• Proteinuria **drives injury** (not just a marker) • → Tubular damage → inflammation → fibrosis • Reduction **interrupts disease progression**
Consistent Evidence	• Strong association with **ESKD risk** • Valid across **populations & CKD types** • Confirmed in large meta-analyses

The Four Pharmacologic Pillars

RASI

ACEi / ARB

2001

Foundation
Max tolerated dose

SGLT2i

Empa · Dapa · Cana

2018–20

CKD benefit DM
& non-DM

Ns-MRA

Finerenone

2020

FIDELIO
FIGARO

GLP-1 RA

Semaglutide

2024

FLOW — first
dedicated KD trial

The Four Pharmacologic Pillars

RASI

ACEi / ARB

2001

Foundation
Max tolerated dose

SGLT2i

Empa · Dapa · Cana

2018–20

CKD benefit DM
& non-DM

Ns-MRA

Finerenone

2020

FIDELIO
FIGARO

GLP-1 RA

Semaglutide

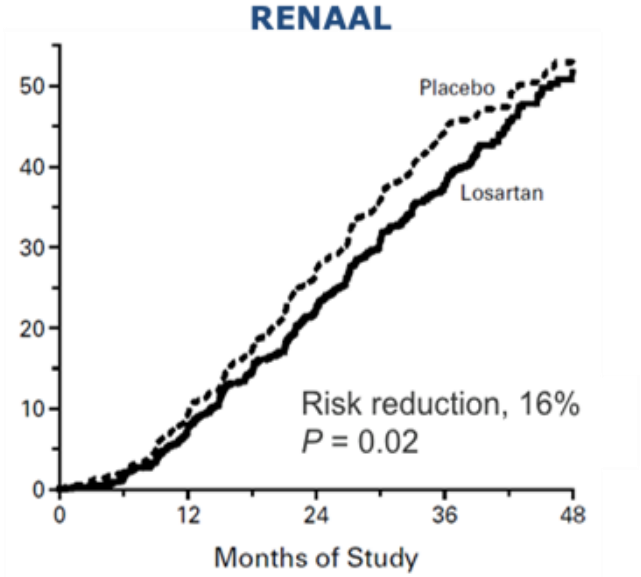
2024

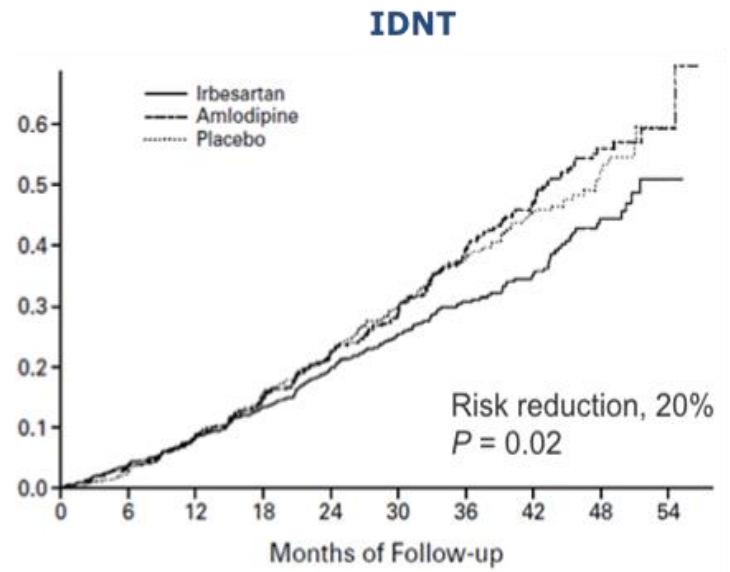
FLOW — first
dedicated KD trial

RASI: The Landmark Evidence

RENAAL & IDNT (NEJM 2001)

- Losartan (RENAAL): T2DM + macroalbuminuria → ↓ ESRD 28%, ↓ composite 16%
- Irbesartan (IDNT): T2DM + HTN + nephropathy → ↓ doubling sCr 33%
- Both trials: benefit independent of BP lowering
- All used maximum tolerated dose — dose matters



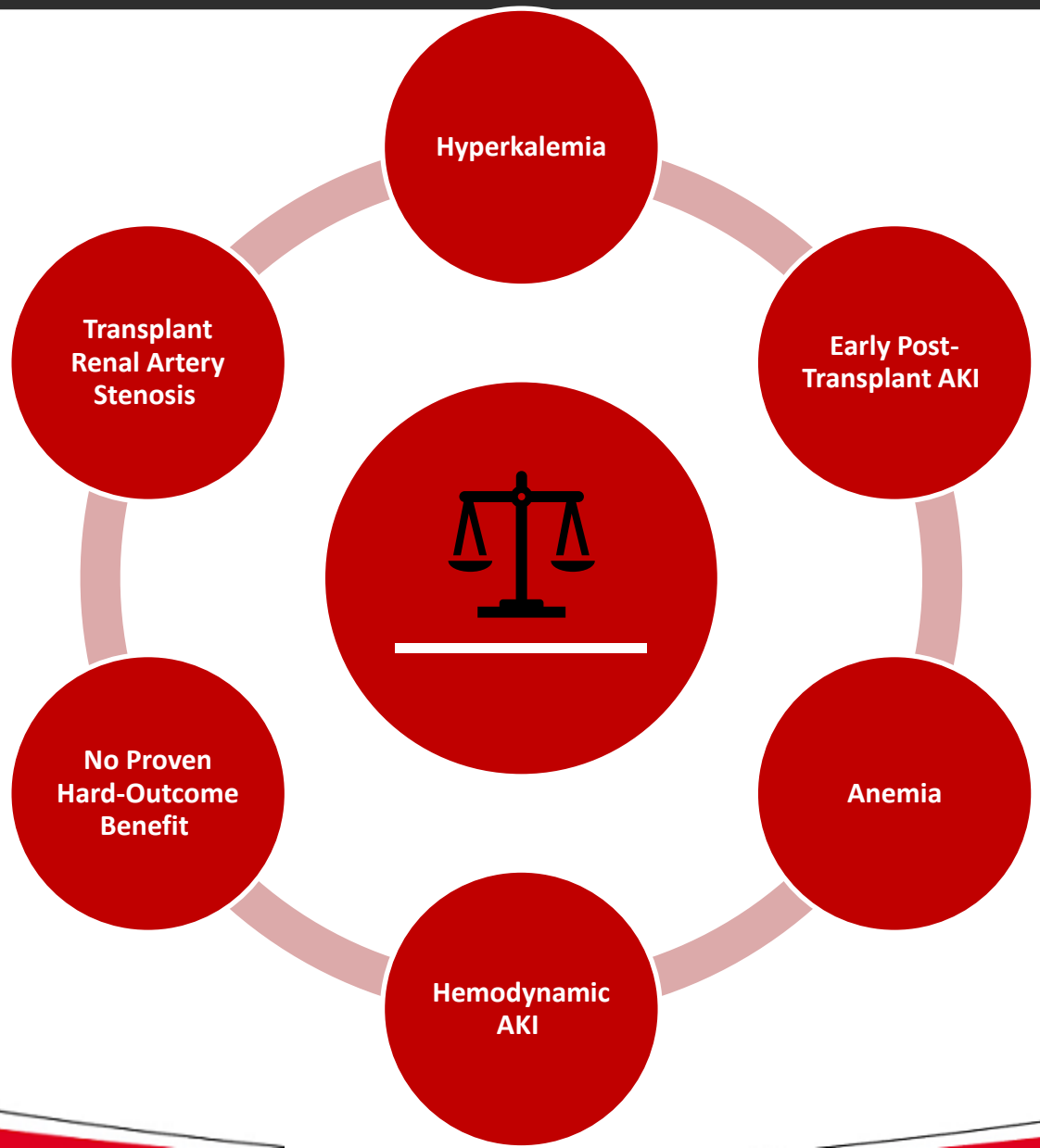


Practical Prescribing Rules

- Titrate to max tolerated dose — every trial did
- sCr rise ≤30% without hyperkalemia: expected, do NOT stop
- Never combine ACEi + ARB
- Check K^+ and sCr 2–4 weeks after start/dose change
- Continue at eGFR <30: mortality benefit still present

Patients who had RASI stopped and restarted (for AKI or hyperkalemia) had better outcomes long-term than those who never restarted

ACEi/ARB Cautions in Kidney Transplant



RASI in Kidney Transplant — Hesitation vs. Evidence

Why Clinicians Hesitate

- Hyperkalemia: additive with tacrolimus + TMP-SMX
- AKI risk in volume-depleted or borderline-perfused grafts
- Erythropoietin suppression → post-KT anemia
- Hypotension in patients with CNI-related volume sensitivity
- Fear of reducing allograft perfusion pressure

What the Evidence Actually Shows

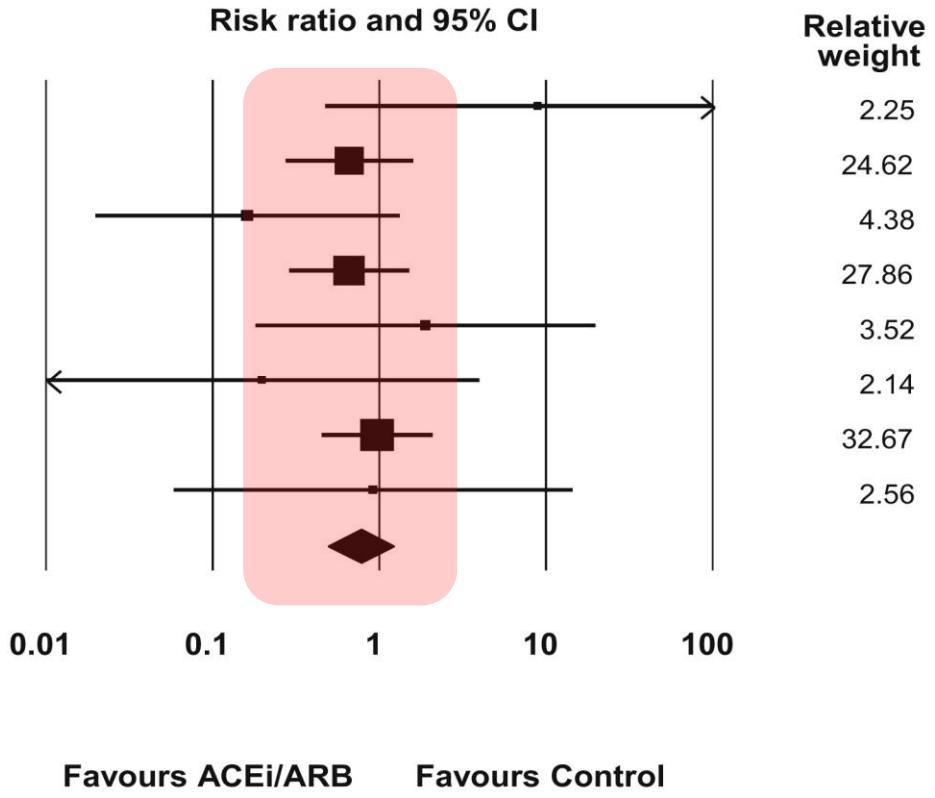
- Retrospective cohort (n=500, age ≥60): RASI within 1 year → ↓ graft loss (HR 0.62, p=0.047)
- RASI within 1 year post-KT associated with lower AKI rates
- Meta-analysis (Hiremath, AJKD 2017): trend to benefit, RR 0.76
- Most hesitation is expert opinion / tradition, not RCT evidence

Avoid RASI in first 4–8 weeks post-KT; consider at 1–3 months once eGFR stable — monitor K^+ closely with tacrolimus

RASI in Kidney Transplant: Meta-analysis of Graft Outcomes

Trial	Year	Risk ratio	95% CI		p	Graft failure / Total: RAS blockade	Control	Relative weight
Midtvedt	2001	8.91	0.47	168.87	0.2	3 / 54	0 / 69	2.25
Amara	2010	0.66	0.27	1.61	0.4	6 / 25	8 / 22	24.62
Philipp	2010	0.16	0.02	1.33	0.09	1 / 255	6 / 247	4.38
Ibrahim	2013	0.66	0.29	1.52	0.3	8 / 77	12 / 76	27.86
Paoletti	2013	1.89	0.18	19.89	0.6	2 / 36	1 / 34	3.52
Salzberg	2014	0.20	0.01	4.03	0.3	0 / 66	2 / 65	2.14
Knoll	2015	0.97	0.45	2.10	0.9	11 / 103	12 / 109	32.67
Mandelbrot	2015	0.91	0.06	14.44	0.9	1 / 138	1 / 126	2.56
Summary RR		**0.76**	**0.49**	**1.18**	**0.2**			

Q 6.7; p 0.46 I^2 = 0%



Summary RR 0.76 (95% CI 0.49–1.18) — trend to benefit; evidence limited but supports cautious use post-KT

Hiremath et al., AJKD 2017 — RAS blockade and long-term clinical outcomes in kidney transplant recipients (meta-analysis of RCTs)

Initiation of ACEI/ARB within one year of transplant is associated with lower risk of AKI and graft loss

ELSEVIER

The American Journal of the Medical Sciences

Volume 368, Issue 5, November 2024, Pages 432-437

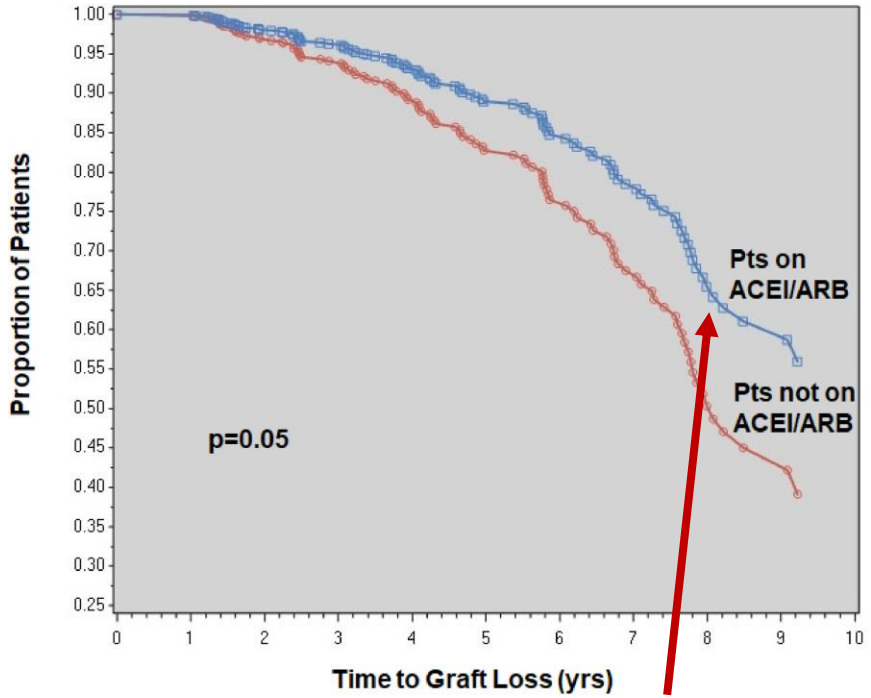
Clinical Investigation

ACEI/ARB use within one year of kidney transplant is associated with less AKI and graft loss in elderly recipients

A. Daoud MD [1 2], K. Soliman MD, PhD [1 2 3], D. Rodriguez MD [1], P. Amaechi MD [1], T. Fulop MD [1 3], D. Taber PharmD [2 4 5], MA Posadas Salas MD [1]

Retrospective, longitudinal, cohort study of 500 patients age ≥60 years

About half with CKD due to diabetes mellitus



Elderly pts with a KT on **ACEI/ARB within one year of transplant had lower risk of graft loss** compared to elderly kidney transplant recipients who were not on ACEI/ARB at one year post-transplant (HR=0.62, CI 0.38–0.99, *p* = 0.047).

UNIVERSITY OF Cincinnati

The Four Pharmacologic Pillars

RASI

ACEi / ARB

2001

SGLT2i

Empa · Dapa · Cana

2018–20

CKD benefit DM & non-DM

Ns-MRA

Finerenone

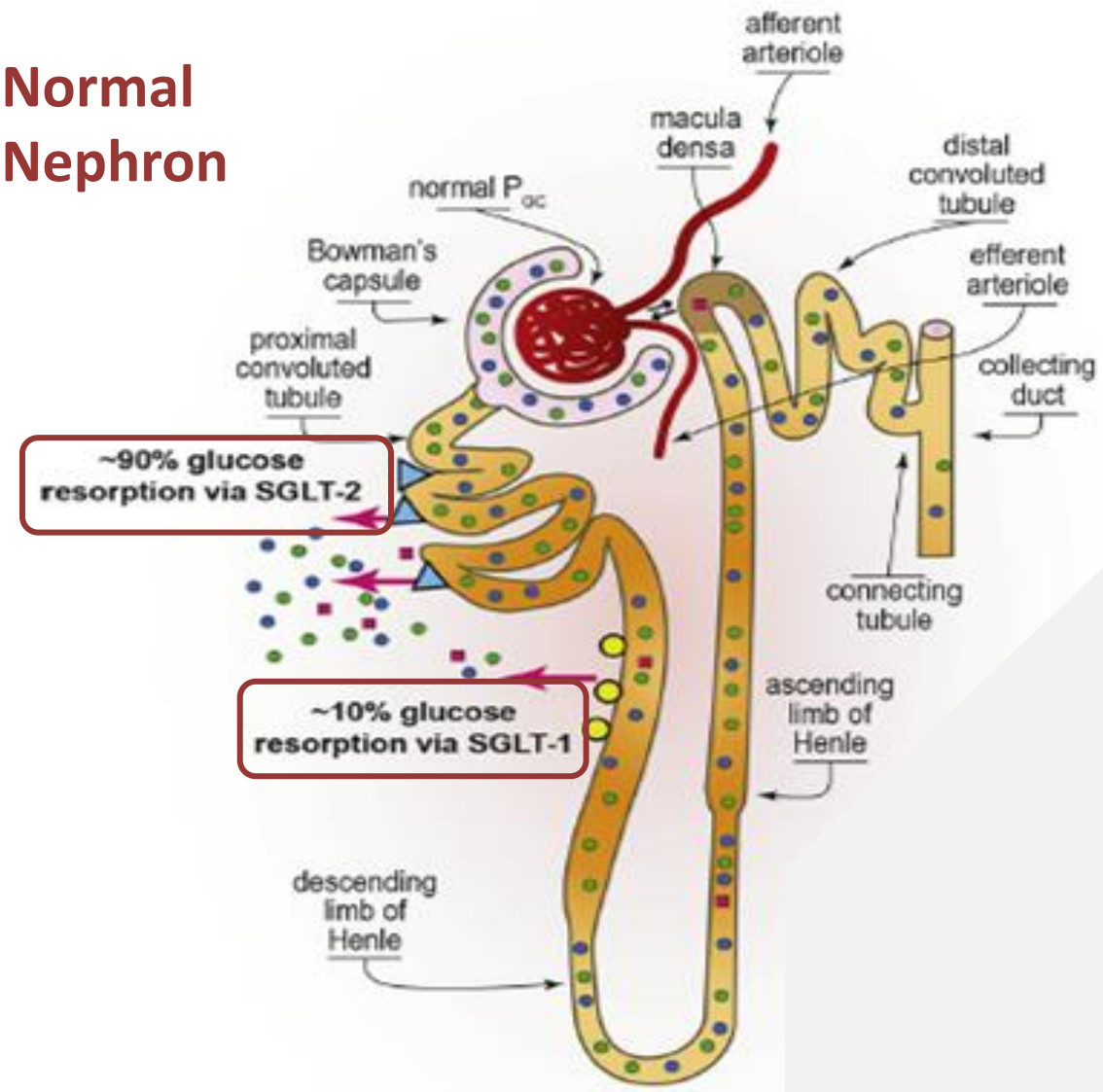
2020

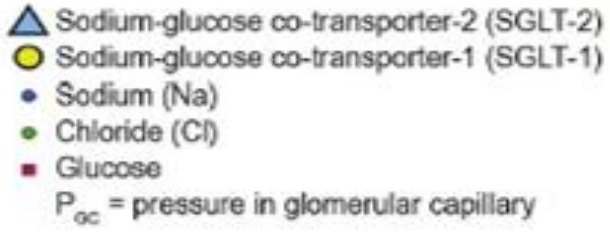
GLP-1 RA

Semaglutide

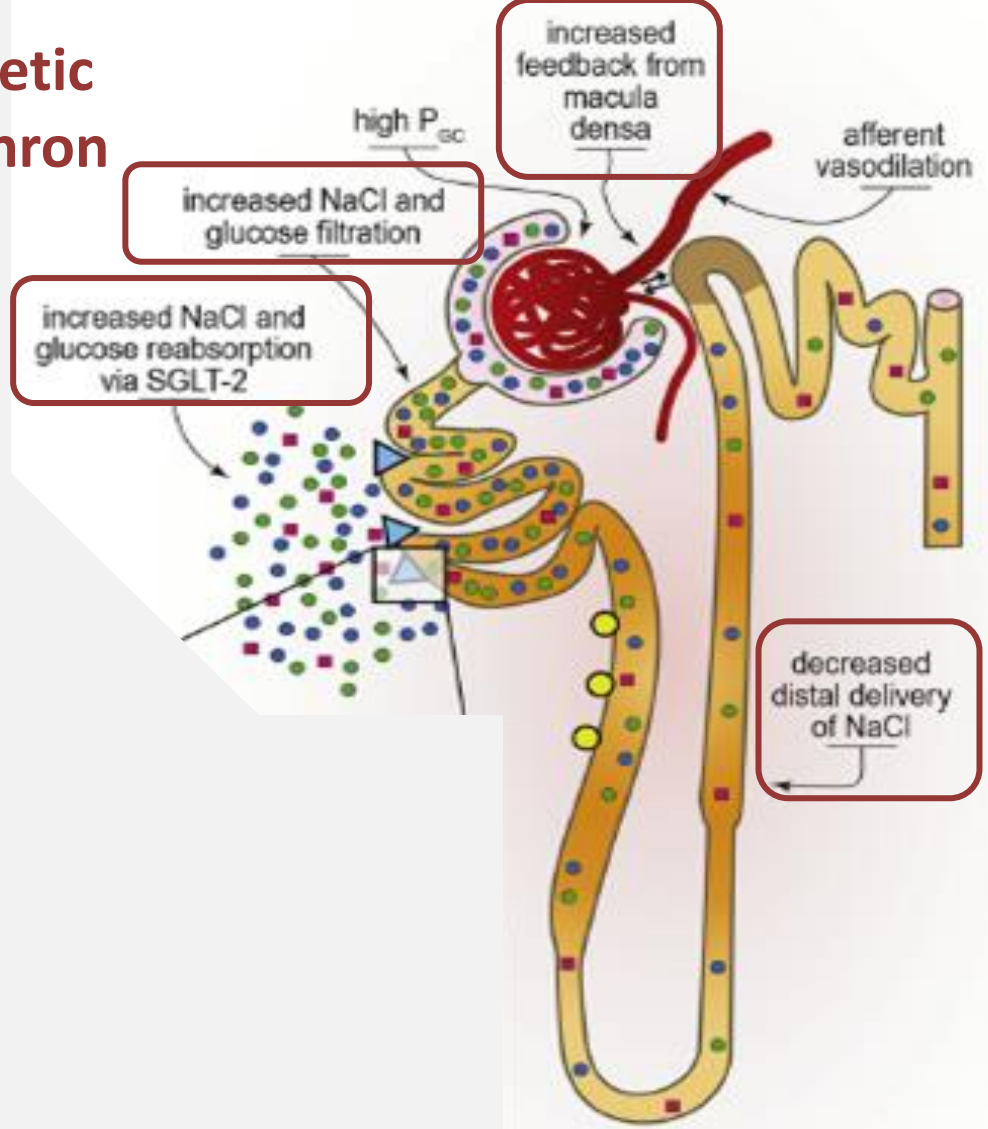
2024

Normal Nephron





Diabetic Nephron



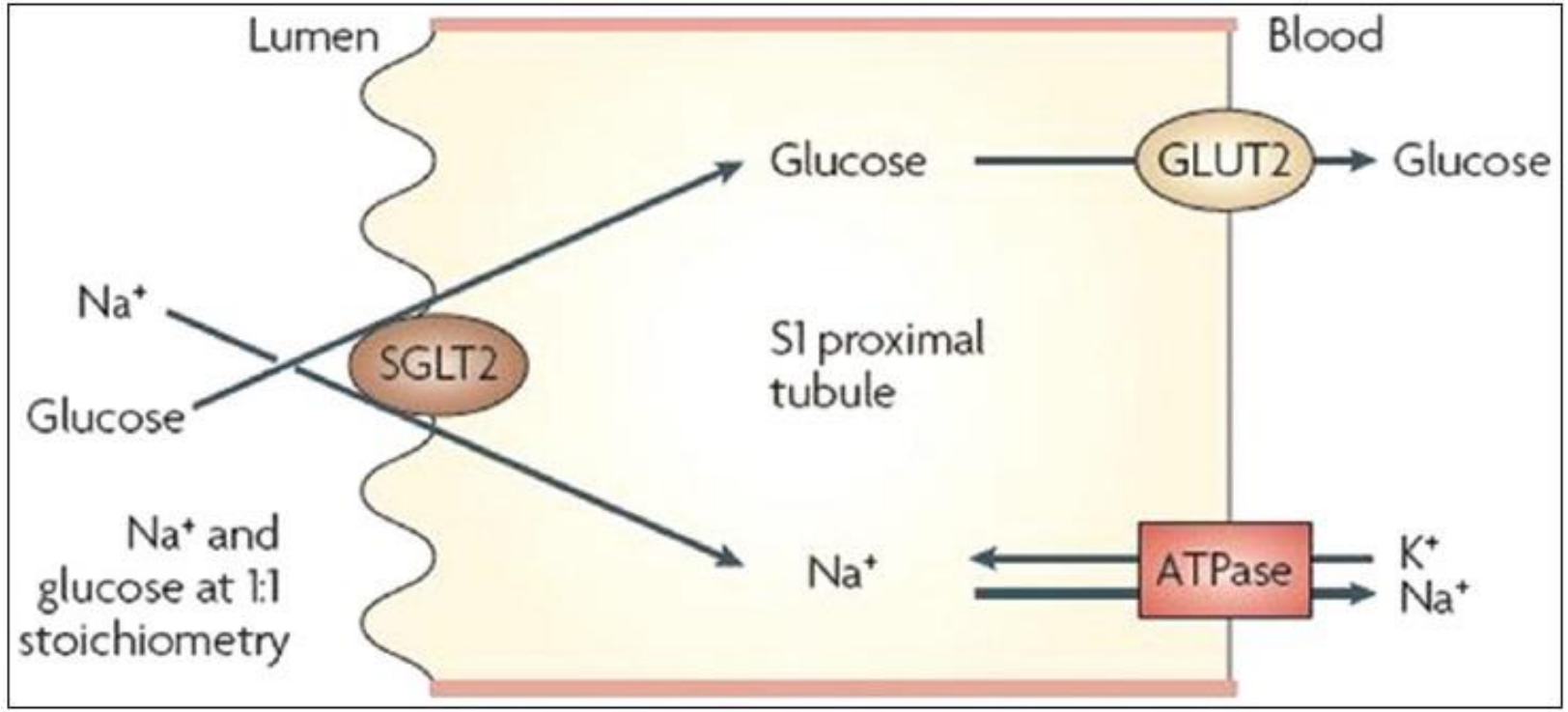
Alicic et al. AJKD 2018

Inhibition of Sodium-Glucose Co-Transporter-2

Inhibiting SGLT2 in the proximal renal tubules

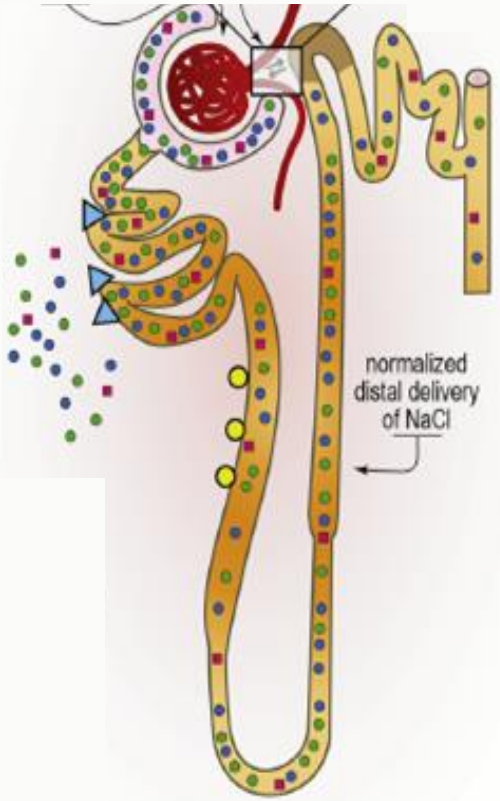
↓

Reduces reabsorption of filtered glucose from the tubular lumen



Alicic et al. AJKD 2018

Why SGLT2 Inhibitors Work in the Kidney



Tubuloglomerular feedback restoration

- ↑ Na^+ delivery to macula densa → reverses afferent dilation → ↓ intraglomerular pressure

Reduced proximal tubule glucotoxicity

- Less oxidative stress, less tubulointerstitial injury, less proximal cell hypertrophy

Natriuresis & volume effects

- Modest BP reduction, weight loss, ↓ sympathetic tone

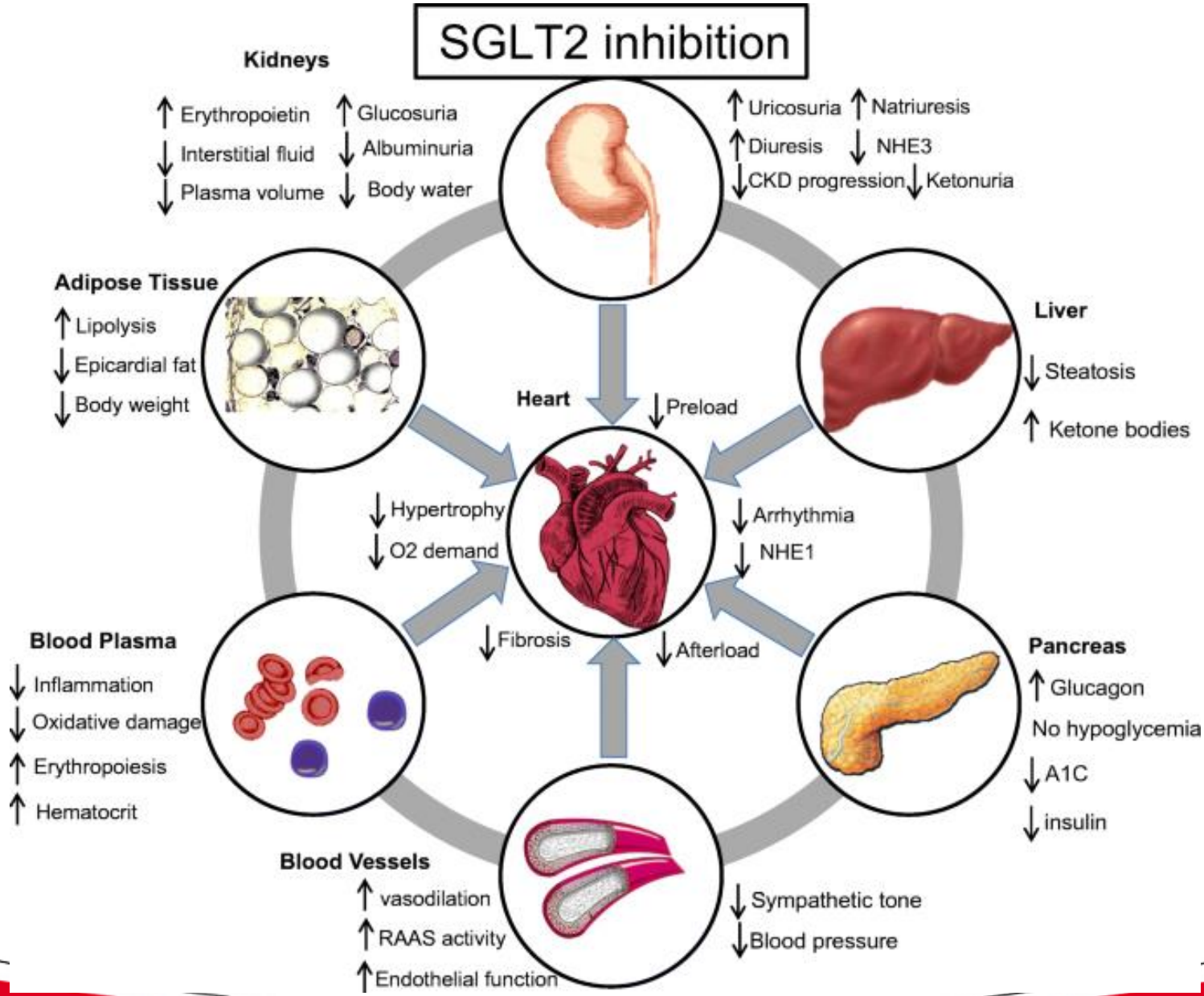
Metabolic & anti-inflammatory effects

- ↓ uric acid, anti-fibrotic signaling, possible mitochondrial protection

Net Effects

- ↓ **Albuminuria**
- ↓ **eGFR decline slope**
- ↓ ESRD risk
- ↓ CV death
- ↓ HF hospitalization
- ↓ Renal progression

Cardiovascular Mortality Benefits



Wojcik and Warden. Current Cariology Reports, 2019

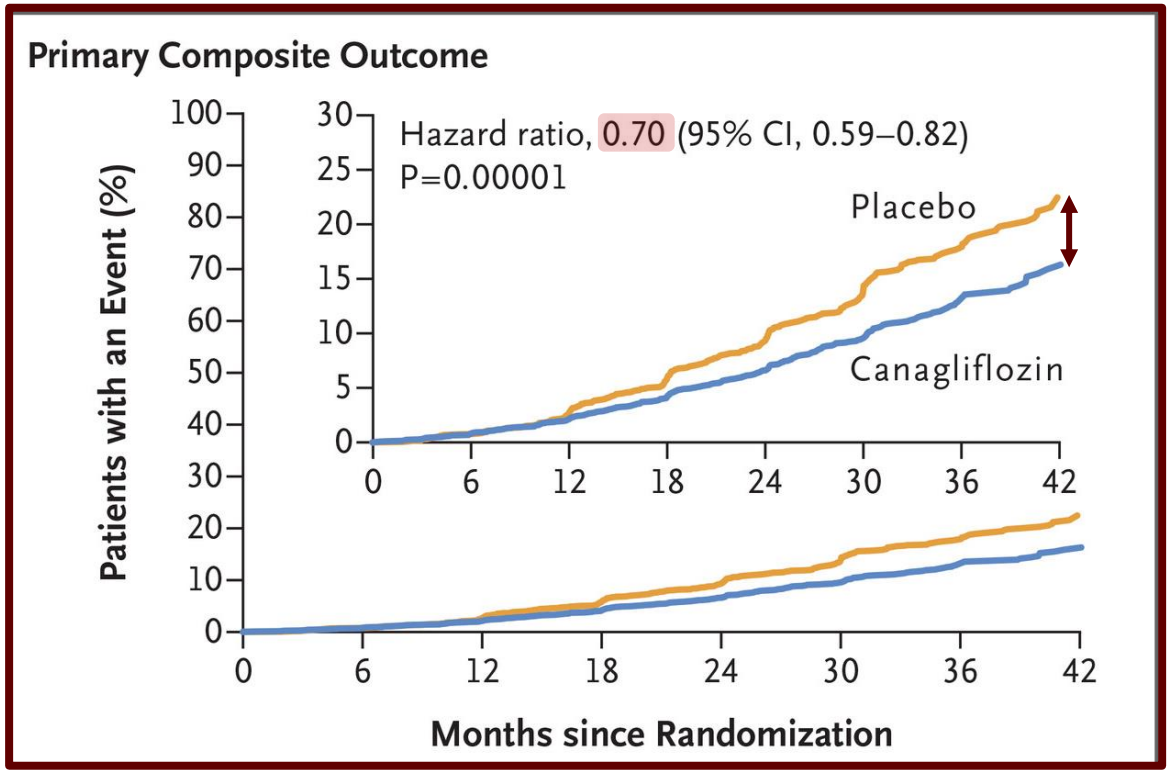
CREDENCE: First Dedicated CKD Trial for SGLT2i

T2DM, eGFR 30–90, UACR 300–5000 mg/g — all on max-tolerated ACEi or ARB | Canagliflozin 100 mg vs. placebo | N = 4,401 | 34 countries | Stopped early for overwhelming efficacy

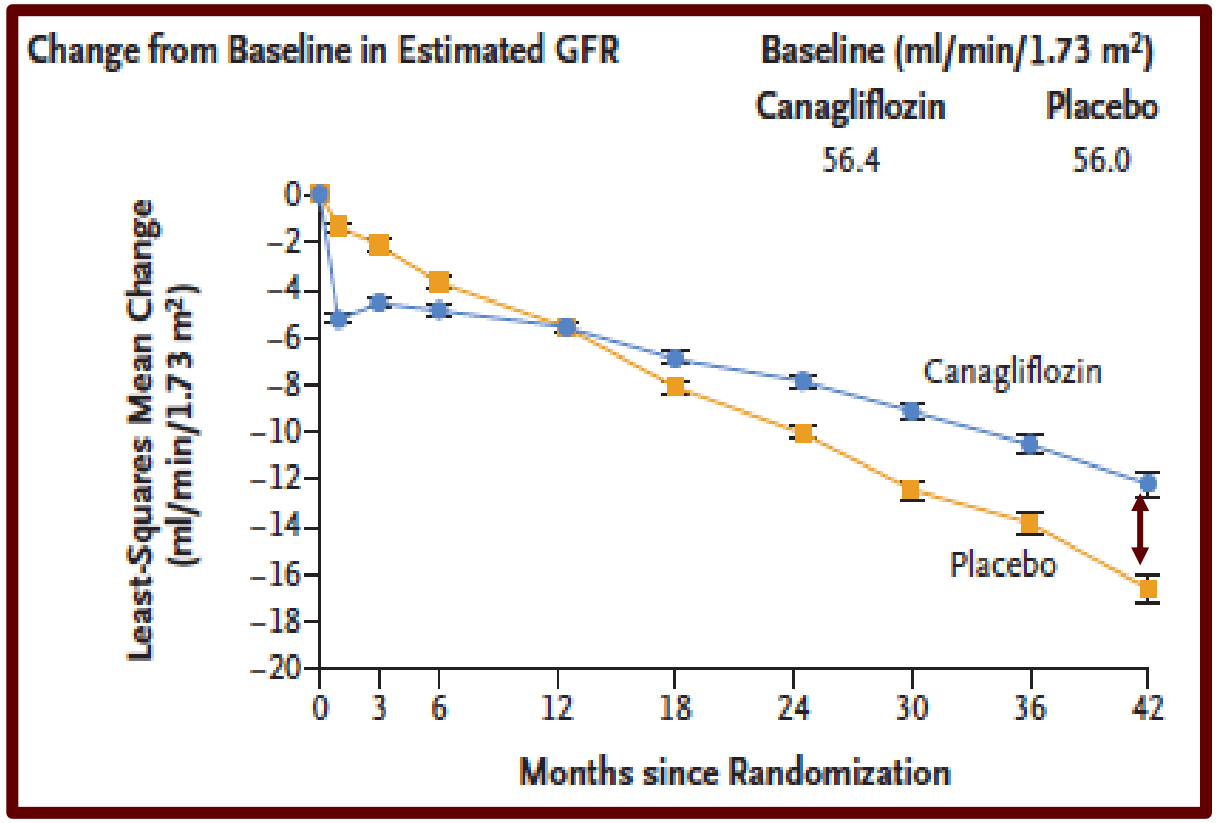
–30%
ESRD / 2× sCr / renal-CV death (primary composite)

–34%
ESRD / 2× sCr / renal death

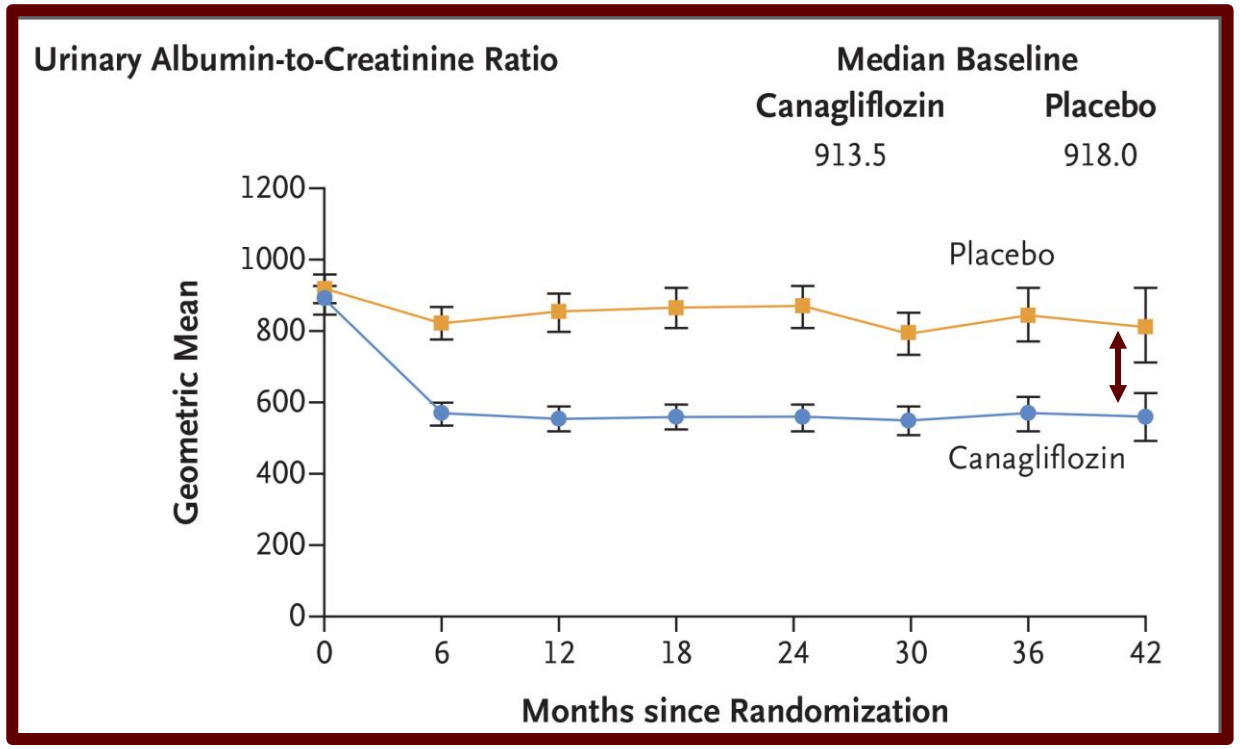
–32%
ESRD alone



CREDENCE: Kidney Outcomes — Canagliflozin vs. Placebo



- Canagliflozin preserved ~5 mL/min/1.73m² more than placebo by 42 months
- NNT ≈ 22 over ~2.6 years to prevent 1 primary event



- ~3–5 mL/min drop at start: hemodynamic, expected
- Significant and sustained UACR reduction from baseline throughout follow-up

SGLT2i: Kidney Outcome Trials at a Glance

Trial / Drug	Population	Key Kidney Result	RRR
EMPA-REG (Empagliflozin)	T2DM + ASCVD	↓ eGFR decline; ↓ new macroalbuminuria	~46% renal composite
CANVAS (Canagliflozin)	T2DM + high CV risk	↓ UACR; slower eGFR slope	~40% renal composite
CREDENCE (Canagliflozin)	T2DM, eGFR 30–90 UACR 300–5000	↓ ESRD, doubling sCr, renal death	30% (stopped early)
DAPA-CKD (Dapagliflozin)	CKD ± DM eGFR 25–75	Benefit in DM AND non-DM CKD; IgA Neph subgroup	39% (stopped early)
EMPA-KIDNEY (Empagliflozin)	CKD, eGFR ≥20 UACR ≥200	Broadest population; benefit regardless of DM	28%

SGLT2i Beyond Diabetes: DAPA-CKD & IgA Nephropathy

DAPA-CKD (NEJM 2020) — Key Points

- N=4,304 | eGFR 25–75 | UACR ≥200 mg/g | ~32% without T2DM
- ↓ 39% primary composite (≥50% eGFR decline, ESRD, CV/renal death)
- Benefit consistent: DM AND non-DM subgroups
- IgA nephropathy subgroup: significant benefit — now KDIGO 2024 guideline
- Trial stopped early for benefit

EMPA-KIDNEY (NEJM 2023)

- Broadest CKD population enrolled to date: eGFR ≥20
- 28% RRR in kidney progression or CV death regardless of diabetes status
- Even eGFR 20–45 subgroup: clear benefit
- No lower eGFR limit for kidney protection (efficacy ends <20, but don't stop arbitrarily)

DAPA-CKD visual abstract: 14.5% (placebo) vs. 9.2% (dapagliflozin) primary composite — NNT ≈ 19 over ~2.4 years

SGLT2i: Safety — What to Counsel and When to Stop

Generally Well-Tolerated

- UTI rates: similar to placebo in all major RCTs
- AKI rates: similar or lower than placebo
- Amputation signal (canagliflozin in CANVAS) — not replicated in CREDENCE
- Volume depletion: modest; mainly relevant if on diuretics
- Fournier's gangrene: ~12 cases on SGLT2i in trials vs. 1,500+/year population background

Counsel Every Patient About

- Genital mycotic infections — most consistent AE across all agents
- Hygiene counseling cuts risk: 4.8% vs. 40.8% without advice
- Euglycemic DKA — hold peri-operatively, during prolonged fasting, serious illness
- Sick-day rules: hold if vomiting, diarrhea, or unable to drink
- eGFR dip at start: hemodynamic, expected — do not stop

SGLT2i can be continued to eGFR 20 for kidney protection — efficacy ends below 20, but don't stop for eGFR drop alone

SGLT2i Post-Transplant: The Safety Picture

The core concern: UTIs are already prevalent post-KT

- 25% of KT recipients have a UTI by year 1 — even without SGLT2i
- Immunosuppression increases risk of ascending infection, atypical organisms, urosepsis

What the observational data show (18 studies, Bellos 2024; Halden RCT 2019)

- UTI incidence on SGLT2i post-KT: 6–20% — similar to background rates
- Genital infections: only 2–3 cases across all studies — lower than general DKD trials
- Drug discontinuation: 0–20%; most common reasons: cost, AKI, UTI — not genital infection
- eGFR and tacrolimus levels: stable in follow-up across studies

Halden 2019 (RCT, n=44, 24 weeks): safe; 3 UTIs, 1 genital infection, no urosepsis

Schwaiger 2019 (n=14): 5 UTIs in first 4 weeks — monitor closely early on

SGLT2i Post-Transplant: A Practical Approach

When to Consider

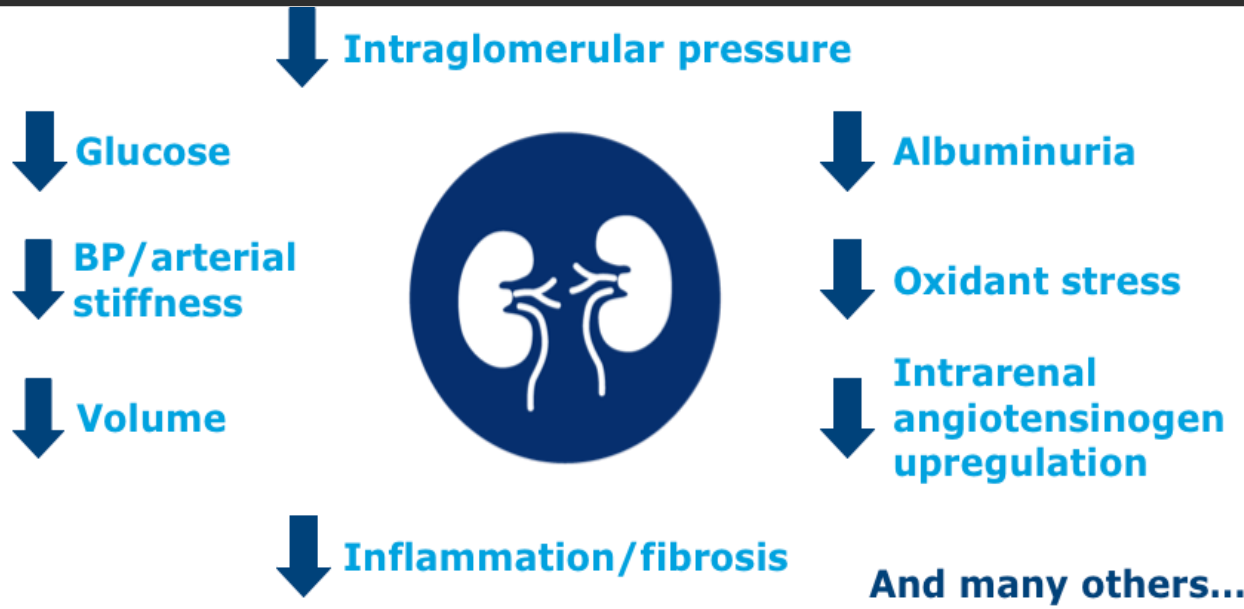
- Stable allograft function: eGFR ≥20, no AKI in past 4–8 weeks
- At least 3–6 months post-transplant — past early vulnerability window
- No active UTI, recent urosepsis, or recurrent candiduria
- PTDM or pre-existing T2DM with proteinuria
- Patient motivated and able to recognize sick-day symptoms

Counsel Every KT Patient On

- Genital hygiene — reduces infection risk dramatically
- Sick-day rules: hold if vomiting, dehydrated, AKI, fasting before procedure
- Signs of UTI: report early, don't self-treat
- Euglycemic DKA risk: especially with steroid taper or missed meals
- Volume depletion: may need diuretic dose reduction

No dose adjustment needed for immunosuppressants | No tacrolimus/mycophenolate PK interaction | Closest monitoring in first 4 weeks

Potential Mechanisms of SGLT2i Benefits



- Restoring tubuloglomerular feedback
  - Restoring solute delivery to the macula densa, reversal of afferent vasodilation.
- Mitigate hyperglycemia related tubulointerstitial injury
  - Decreased glucose uptake in proximal tubular cells
- Lower blood pressures and weight loss
  - Natiuretic effect

Adverse Events - Canagliflozin - Risk of Limb Amputation

WARNING: LOWER LIMB AMPUTATION RISK

- **In patients with type 2 diabetes who have established cardiovascular disease (CVD) or at risk for CVD, INVOKANA has been associated with lower limb amputations, most frequently of the toe and midfoot; some also involved the leg.**
- **Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving INVOKANA for infections or ulcers of the lower limbs, and discontinue if these occur.**

In the Credence study, regular foot exams were implemented

Pre-specified Analysis of the DAPA-CKD Trial: Effects of Dapagliflozin on IgA Nephropathy

DAPA-CKD cohort

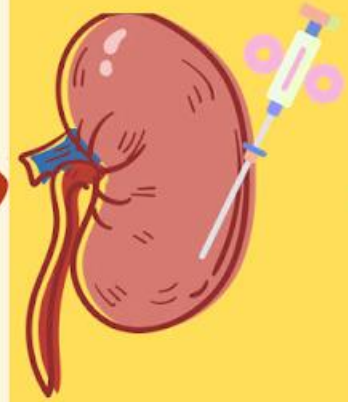
dapagliflozin 10 mg vs placebo

eGFR

25-75 ml/min/1.73m^2

Urinary ACR

200-5000 mg/g



IgA nephropathy

(n=270)

254 (94%)

Biopsy proven

Placebo

n=133

Dapagliflozin

n=137

Primary composite endpoint

Sustained decline in eGFR of ≥ 50%

ESKD

Death from a kidney disease-related or cardiovascular cause

Median

2.1 years

Results

Placebo

Dapagliflozin

Primary outcome n (%)

20 (15%)

6 (4%)

HR 0.29 (0.12-0.73) 95% CI

Mean eGFR decline (ml/min/1.73 m^2/year)

-4.7

-3.5

(- 0.12 to 2.51) 95% CI

Change in uACR

-26%

(-37% to -14%) 95% CI

Conclusion:

In participants with IgA nephropathy, dapagliflozin reduced the risk of chronic kidney disease progression with a favorable safety profile.

Wheeler DC, et al; DAPA-CKD Trial Committees & Investigators. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. Kidney Int. 2021 Jul;100(1):215-224. doi: 10.1016/j.kint.2021.03.033.

VA by @Dilushiwijay

Could dapagliflozin improve kidney and cardiovascular outcomes in patients with CKD?

#NephJC

Randomized
Double-blind
Placebo-controlled
Multicenter

386 sites in 21 countries

N= 4304

GFR 25-75 ml/min

67.5% diabetes type 2

ACR 200-5000mg/g

Outcomes

Kidney
- Decline in GFR at least 50%
- ESKD
- Death from renal causes

Cardiovascular
- Hospitalization for heart failure
- Death from cardiovascular causes

	Placebo N= 2152	Dapagliflozin 10mg/d N= 2152	
Primary composite outcome	14.5%	9.2%	P<0.001
Composite kidney outcome	11.3%	6.6%	P<0.001
Composite cardio-vascular outcome	6.4%	4.6%	P=0.009
Death from any cause	6.8%	4.7%	P=0.004

Conclusion: Among patients with chronic kidney disease, the risk of any composite kidney or cardiovascular outcomes or death was significantly lower with dapagliflozin than with placebo.

Reference: Heerspink HJL *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Sep 24. DOI: 10.1056/NEJMoa2024816.

Visual abstract: Denisse Arellano, MD @deniise_am

NEPHROLOGY EST 2015 SOCIAL MEDIA COLLECTIVE

Adverse Events - Canagliflozin - Risk of Fournier's Gangrene

FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes

Safety Announcement

[8-29-2018] The U.S. Food and Drug Administration (FDA) is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. We are requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patient Medication Guide.

12 cases on SGLT2i vs 6 REPORTED to FDA in those not on SGLT2i when there are **over 1500 cases per year of FG** in the US

Hygiene and Genital Infections

Poster Presentations: Clinical Diabetes/Therapeutics

1224-P: Improving Compliance with SGLT2 Inhibitors by Reducing the Risk of Genital Mycotic Infections: The Outcomes of Personal Hygiene Advice

SCOTT M. WILLIAMS **and** SYED HARIS AHMED

[+] Author Affiliations

Diabetes 2019 Jun; 68(Supplement 1): -.
https://doi.org/10.2337/db19-1224-P

Aims: To determine whether the provision of hygiene advice is beneficial in the prevention of genital mycotic infections in patients commenced on SGLT2 inhibitors.

Conclusion: Personal hygiene advice should be provided for all patients commenced on SGLT2 inhibitor therapy to improve compliance with this clinically beneficial treatment.

4.8% (advice)

vs.

40.8% (no advice)!!!

Giving advice on hygiene helps prevent genital mycotic infections!

Summary of the Adverse Events

Study/Drug	Increased Amputation Risk	Increased DKA Risk	Increased Genital Infection Risk	Increased UTI Risk
EMPA-REG - **Empagliflozin**	X	X	✓	X
CANVAS - **Canagliflozin**	✓	✓	✓	X
CREDENCE - **Canagliflozin**	X	✓	✓	X
DECLARE - TIMI - **Dapagliflozin**	X	✓	✓	X

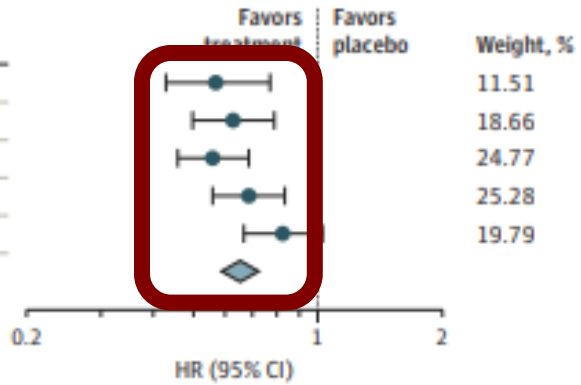
Identifying and Addressing Knowledge Gaps in Transplant Care

Is it safe to start SGLT2i?	When is it safe to start ACE or ARBs?	What to do with Immunosuppressive meds when a patient has an infection?	What to do with immunosuppression with cancer?
Is it safe to give GLP1-RA?	Changes in medicine from Covid	What vaccines should transplant patients receive?	What to do with immunosuppression once back on dialysis?

Effects of SGLT2 Inhibitors on Kidney-Related Outcomes

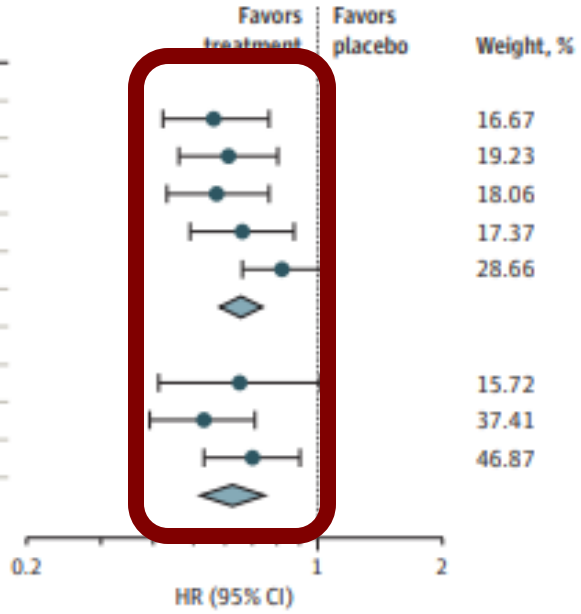
A Overall kidney outcomes

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 7.96; *df* = 4; *P* = .09; I^2 = 49.7%)					0.62 (0.56-0.70)



B Kidney outcomes by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 6.09; *df* = 4; *P* = .19; I^2 = 34.4%)					0.64 (0.56-0.72)
Patients without ASCVD					
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)
Fixed-effects model (Q = 1.86; *df* = 2; *P* = .40; I^2 = 0.0%)					0.60 (0.50-0.73)



Overall **positive kidney outcomes** throughout all large randomized clinical trials

---

However, previously limited data on patients with KT

McGuire,D. et al. *Jama Cardio* 2021

SGLT2 inhibitors: Benefits

Mechanism of action

Reduction in Intraglomerular pressure
↑ Afferent vasoconstriction
↓ Glomerular Hyperfiltration

Neurohormonal Improvement
↓Intrarenal RAAS activity
↓SNS activity

Reduction in Inflammation/Fibrosis
↓ Inflammation biomarkers
↓ Fibrosis biomarkers

Renal metabolism Hypoxia reduction
↓ Solute transport
↓ Oxygen demand

CLINICAL EFFECT

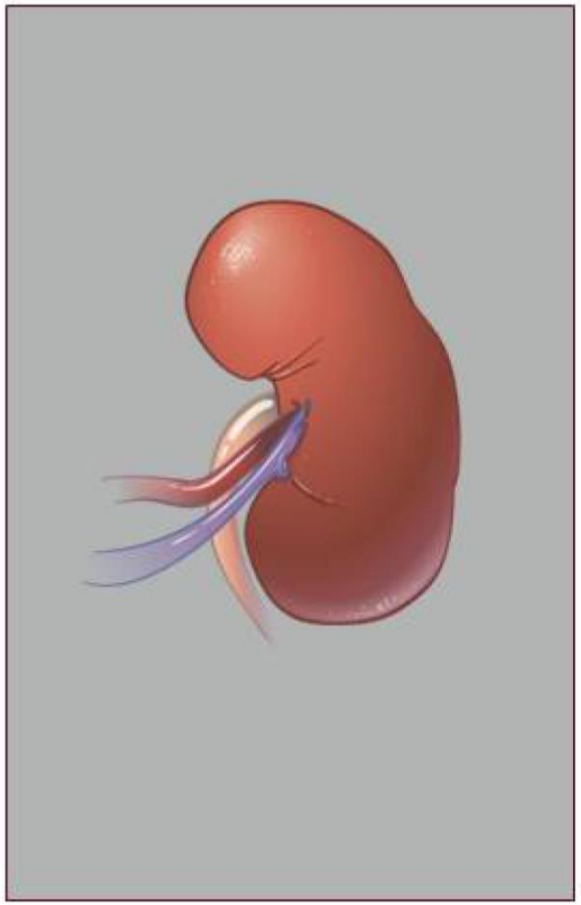
GFR preservation

↓Blood Pressure

↓ Tubular/ Glomerular damage
↓Albuminuria

↓ Ischemic Renal damage
↑ Hb/Hematocrit

RENAL PROTECTION



Leoncini,G. et al. Int. J. Mol. Sci. 2021

Adverse Events from Empa-Reg

Similar Rates of UTIs (18%)

Higher Rates of Genital Infections

No Diff. in Volume Depletion or AKI

Table 2. Adverse Events.*

Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
	number of patients (percent)			
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event§§	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture‖‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

UNIVERSITY OF Cincinnati

Adverse Events - CANVAS

Higher Rates of Amputation

Higher rates of Genital Infections in both males and females

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001

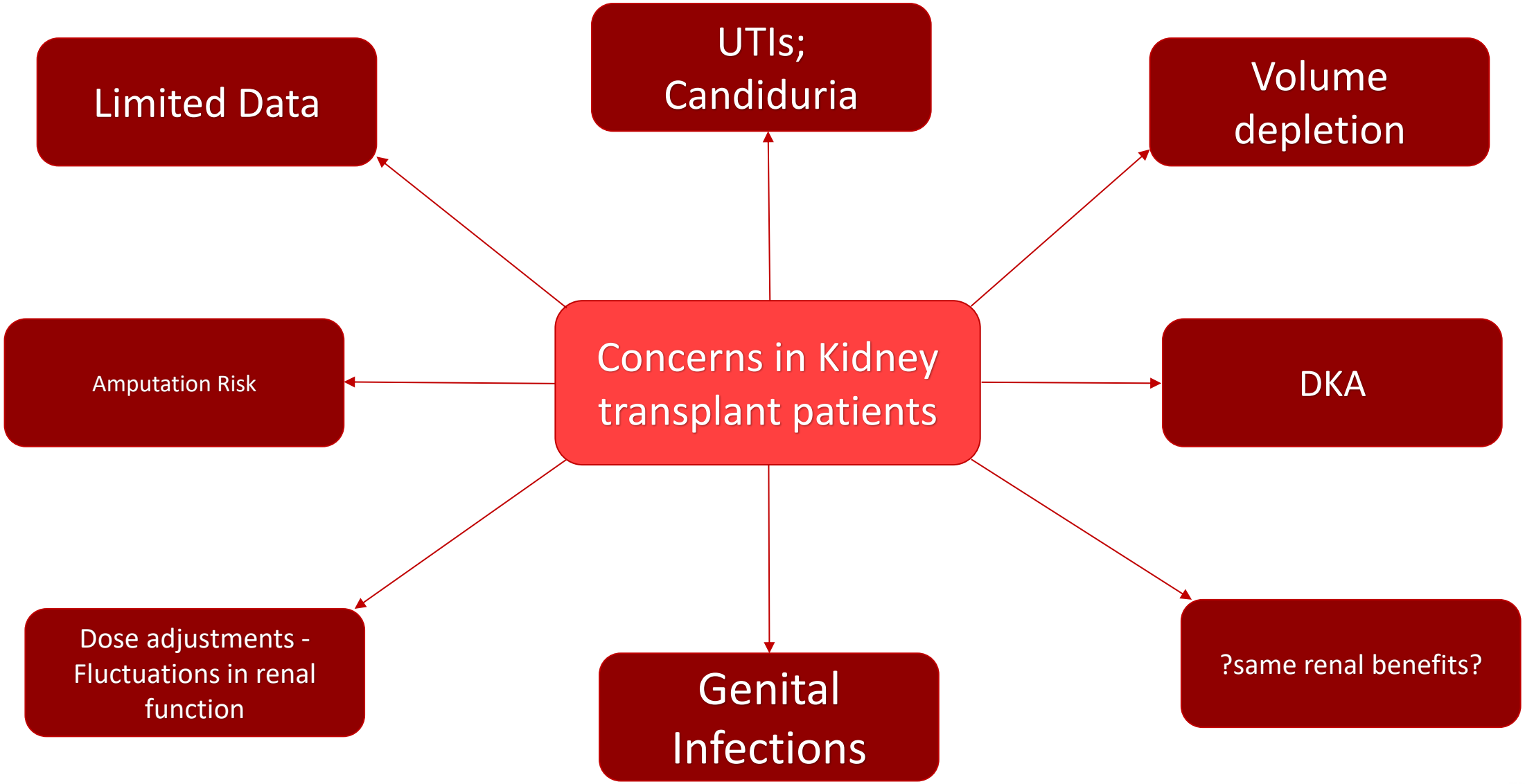
Similar Rates of UTI

Adverse Events - CREDENCE

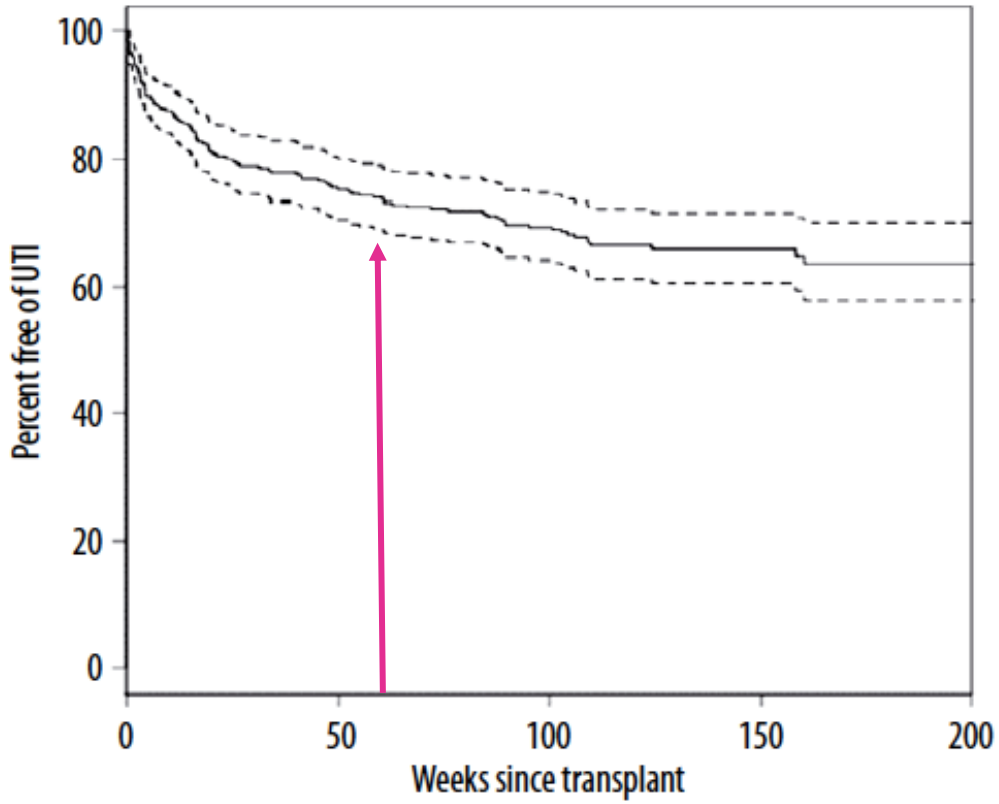
Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		*events/ 1000 patient-yr*			
Any adverse event	1784/2200	1860/2197	351.4	379.3	0.87 (0.82–0.93)	NA
Any serious adverse event	737/2200	806/2197	145.2	164.4	0.87 (0.79–0.97)	NA
Serious adverse event related to trial drug	62/2200	42/2197	12.2	8.6	1.45 (0.98–2.14)	NA
Amputation	70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)	NA
Diabetic ketoacidosis	11/2200	1/2197	2.2	0.2	10.80 (1.39–83.65)	NA
UTI	245/2200	221/2197	48	45	1.08 (0.90-1.29)	
Mycotic Infections						
Males	28/1439	3/1466	8.4	0.9	9.3 (2.8-30.6)	
Females	22/761	10/731	12.6	6.1	2.1 (1.00-4.45)	

Higher rates of Genital Infections in both males and females

Similar Rates of UTI


Concerns in Kidney transplant patients
Limited Data
UTIs; Candiduria
Volume depletion
Amputation Risk
DKA
Dose adjustments - Fluctuations in renal function
Genital Infections
?same renal benefits?

UTI Rate Post-Transplant



Clinical implication

- UTI fear should not reflexively preclude SGLT2i use post-KT
- Screen for active infection before starting; counsel on hygiene
- Stop temporarily for UTI; restart once resolved

Time to first UTI:
25% of transplant recipients had a UTI by the first year

Ariza-Heredia et al. Ann Transplant, 2013

Adverse Events in the First Few Major SGLT2i Trials

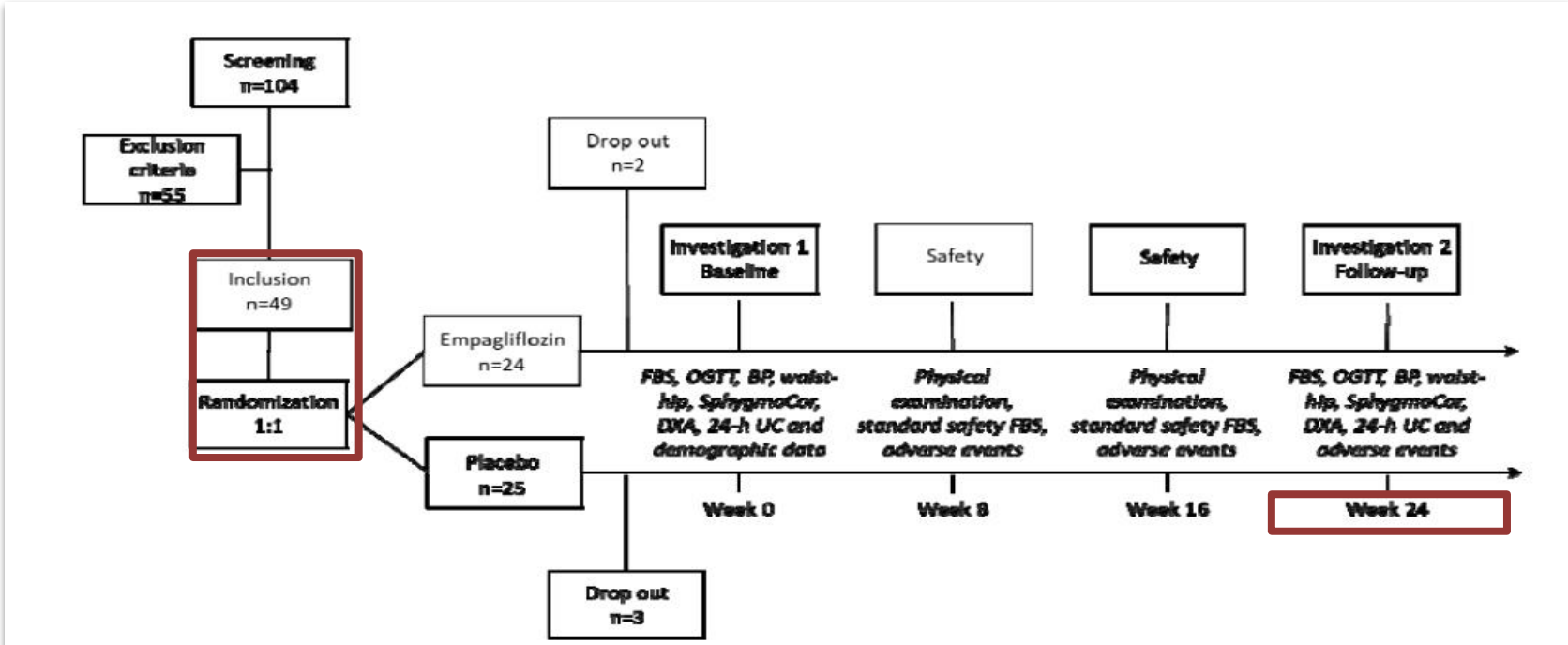
Study/Drug	Increased Genital Infection Risk	Increased UTI Risk
EMPA-REG - **Empagliflozin**	✓	X
CANVAS - **Canagliflozin**	✓	X
CREDENCE - **Canagliflozin**	✓	X
DECLARE - TIMI - **Dapagliflozin**	✓	X

Safety Of SGLT2i In Patients With A Kidney Transplant

Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus

Thea Anine Strøm Halden,[1] Kine Eide Kvitne,[2] Karsten Midtvedt,[1] Laavanyaah Rajakumar,[1] Ida Robertsen,[2] Jan Brox,[3] Jens Bollerslev,[4,5] Anders Hartmann,[1] Anders Åsberg,[1,2] and Trond Jenssen[1,4]

https://doi.org/10.2337/dc19-0093



Halden et al. Diabetes Care, 2019

Adverse events in all patients randomized

Adverse events	Empagliflozin n=24	Placebo n=25
Diarrhea	0	1
Dizziness	2	0
ESBL in urine	0	1
Facial swelling	1	0
Genital itching	1	0
Genital yeast infection	1	0
Gout	0	1
Hematuria	1	0
Herpes zoster	0	1
Obstipation	0	1
Urinary tract infection	3	3

Abbreviations: ESBL, "Extended Spectrum Beta Lactamase"

1 patient with genital infection

Similar events of UTI, 1 had urosepsis

Halden et al. Diabetes Care, 2019

Some more on kidney transplant patients

14 patients on SGLT2i -> followed for 1 year

BRIEF COMMUNICATION

AJT

Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety

Elisabeth Schwaiger[1] | Lukas Burghart[1] | Lorenzo Signorini[2] | Robin Ristl[3] | Chantal Kopecky[1] | Andrea Tura[4] | Giovanni Pacini[4] | Thomas Wrba[5] | Marlies Antlanger[1] | Sabine Schmaldienst[6] | Johannes Werzowa[7] | Marcus D. Säemann[1,8] | Manfred Hecking[1]

Bioimpedance spectroscopy revealed a **reduction** of approximately **1 L in extracellular and total body fluid volume by 4 weeks**, and a reduction in fat mass throughout the entire follow-up.
The fluid parameters, however, returned to baseline after 4 weeks.

2 patients dropped out due to recurrent UTIs

Bacterial UTIs occurred in **5** patients throughout follow-up; 3 in the first 4 weeks

1 patient with balanitis

Schwaiger. et al. Am J Transplant., 2019

Another Case series of 10 patients - Kidney and Kidney-Pancreas

Table 1—Baseline characteristics of study patients at the time of canagliflozin initiation and mean changes in hemodynamic and metabolic parameters over follow-up

Baseline characteristic	SPKTR ($N = 4$)	KTR ($N = 6$)
Age at time of canagliflozin initiation, years	49.4 ± 8.9	61.6 ± 12.6
Female sex	2 (50)	1 (17)
PTDM	4 (100)	4 (67)
Prior DM therapy	3 (75)	5 (83)
Time from transplant to canagliflozin treatment, years	3.5 ± 3.9	4.4 ± 3.3
Time on canagliflozin treatment, months	5.6 ± 3.4	10.1 ± 4.2
Hemoglobin A_{1c}, %	7.4 ± 1.1	8.6 ± 1.4
Hemoglobin A_{1c}, mmol/mol	57 ± 12.0	70 ± 15.3
eGFR, mL/min/1.73m^2	60 ± 14	78 ± 18.2
Serum creatinine, µmol/L	108.3 ± 21.6	90.2 ± 22.9

- Pts with good renal function
- NO UTIs
- NO mycotic infections
- No AKIs observed

Rajasekeran, et al. Diabetes Care, 2017

Many observational studies since 2019… 18 studies

UTIs ranging from 6-20%

Drug discontinuation from 0-20%
Most common reasons for SGLT2i discontinuation

1. Drug cost
2. AKI/CKD progression
3. Urinary tract infection

Only 2-3 mycotic/genital infections

Study	Urinary tract infection	Drug discontinuation
SGLT2-i		
2024; Lim	12/127 (9.4%)	18/129 (14.0%)
2024; Schork	2/22 (9.1%)	1/22 (4.5%)
2023; Mahmoud	15/98 (15.3%)	0/98 (0.0%)
2023; Fructuoso	48/323 (14.9%)	34/323 (10.5%)
2023; Demir	6/36 (16.7%)	1/36 (2.8%)
2023; Yeggalam	5/44 (11.4%)	NR
2022; Lemke	6/39 (15.4%)	17/39 (43.6%)
2022; Lim	12/202 (5.9%)	NR
2021; Hisadome	2/28 (7.1%)	0/28 (0.0%)
2020; Song	7/50 (14%)	9/50 (18%)
2019; Halden	3/22 (13.6%)	1/22 (4.5%)
2019; Mahling	2/10 (20%)	2/10 (20%)

Bellos, I, et al. *Clinical Medicine*, 2024

SGLT2i Post-Transplant: The Safety Picture

The core concern: UTIs are already prevalent post-KT

- 25% of KT recipients have a UTI by year 1 — even without SGLT2i
- Immunosuppression increases risk of ascending infection, atypical organisms, urosepsis

What the observational data show (18 studies, Bellos 2024; Halden RCT 2019)

- UTI incidence on SGLT2i post-KT: 6–20% — similar to background rates
- Genital infections: only 2–3 cases across all studies — lower than general DKD trials
- Drug discontinuation: 0–20%; most common reasons: cost, AKI, UTI — not genital infection
- eGFR and tacrolimus levels: stable in follow-up across studies

Halden 2019 (the only small RCT, n=44, 24 weeks): safe; 3 UTIs, 1 genital infection, no urosepsis

Schwaiger 2019 (n=14): 5 UTIs in first 4 weeks; 2 dropped out — monitor closely early on

SGLT2i Post-Transplant: A Practical Approach

When to Consider

- Stable allograft function: eGFR ≥20, no AKI in past 4–8 weeks
- At least 3–6 months post-transplant — past early vulnerability window
- No active UTI, recent urosepsis, or recurrent candiduria
- PTDM or pre-existing T2DM with proteinuria
- Patient motivated and able to recognize sick-day symptoms

Counsel Every KT Patient On

- Genital hygiene — reduces infection risk dramatically
- Sick-day rules: hold if vomiting, dehydrated, AKI, fasting before procedure
- Signs of UTI: report early, don't self-treat
- Euglycemic DKA risk: especially with steroid taper or missed meals
- Volume depletion: may need diuretic dose reduction

No dose adjustment needed for immunosuppressants | No known tacrolimus/mycophenolate PK interaction | Closest monitoring in first 4 weeks

Consider before prescribing SGLT2i

- 6-12 months after KT with stable kidney function
- No history of recurrent UTIs or genital infections and a 6 month UTI free period
- Caution in use with those with PVD
- Avoid in those with issues with hypotension and volume depletion

The Four Pharmacologic Pillars

RASI	SGLT2i	Ns-MRA	GLP-1 RA
ACEi / ARB	Empa · Dapa · Cana	Finerenone	Semaglutide
2001	2018–20	**2020**	2024
		FIDELIO *FIGARO*	

Finerenone: Evidence and Why It's Different from Spironolactone

FIDELIO-DKD & FIGARO-DKD

- FIDELIO: eGFR 25–75, UACR 300–5000 mg/g, T2DM, on max RASI → kidney composite ↓18%
- FIGARO: broader eGFR, UACR ≥30 → CV composite ↓13%; kidney progression ↓23%
- FIDELITY (pooled): ↓ composite kidney/CV outcomes, ↓ UACR ~31%
- All enrolled on background max RASI — designed as add-on therapy

Non-Steroidal Advantage

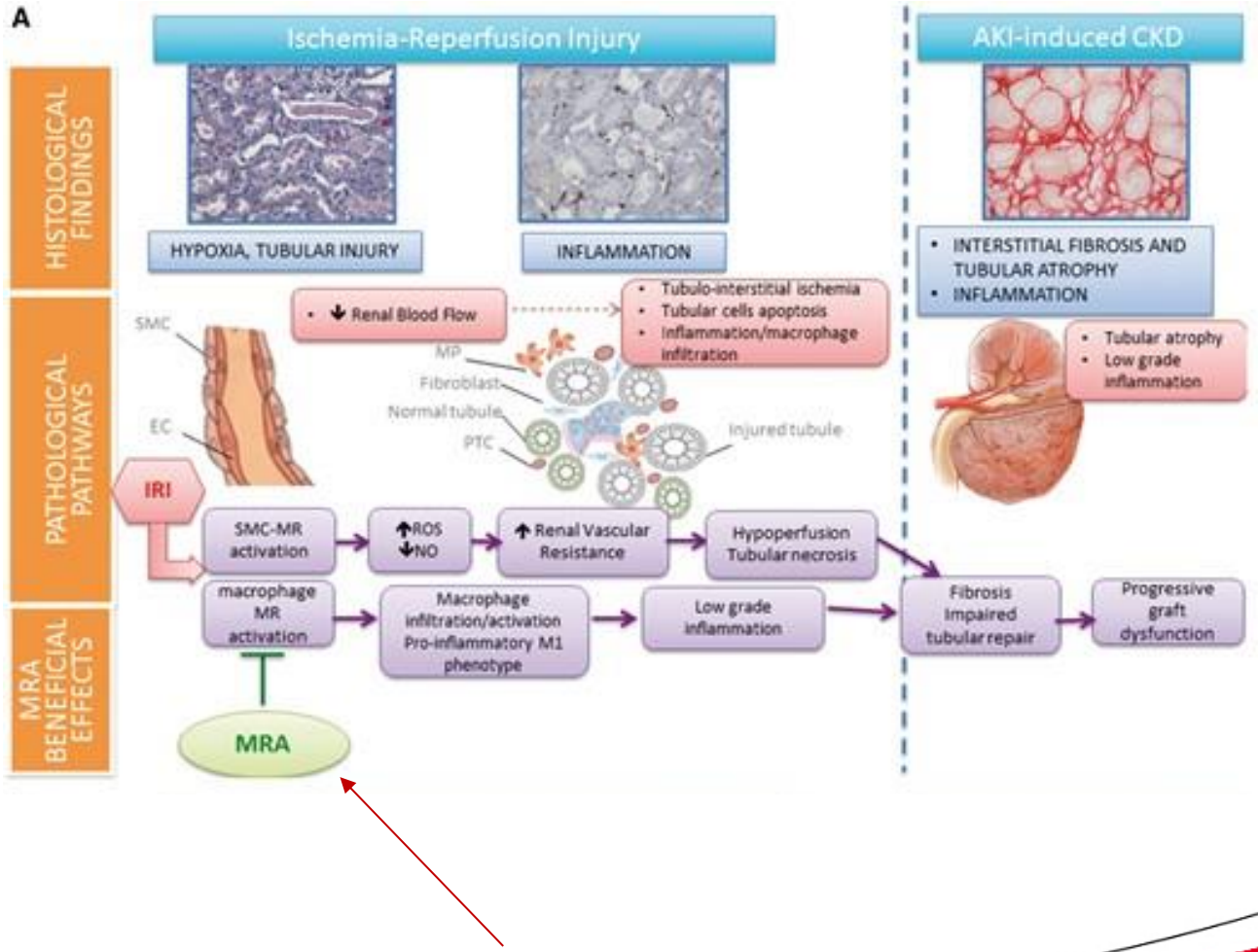
- High MR selectivity — no glucocorticoid, androgen, progesterone off-target effects
- Less gynecomastia vs. spironolactone; less erectile dysfunction
- Lower hyperkalemia rate than steroidal MRAs in comparable populations
- Different tissue distribution — strong cardiac and renal MR blockade

Finerenone adds benefit on top of RASI + SGLT2i — FIDELITY sub-analyses show complementary, not redundant, effect

Limited Data on Ns-MRAs in patients with KT

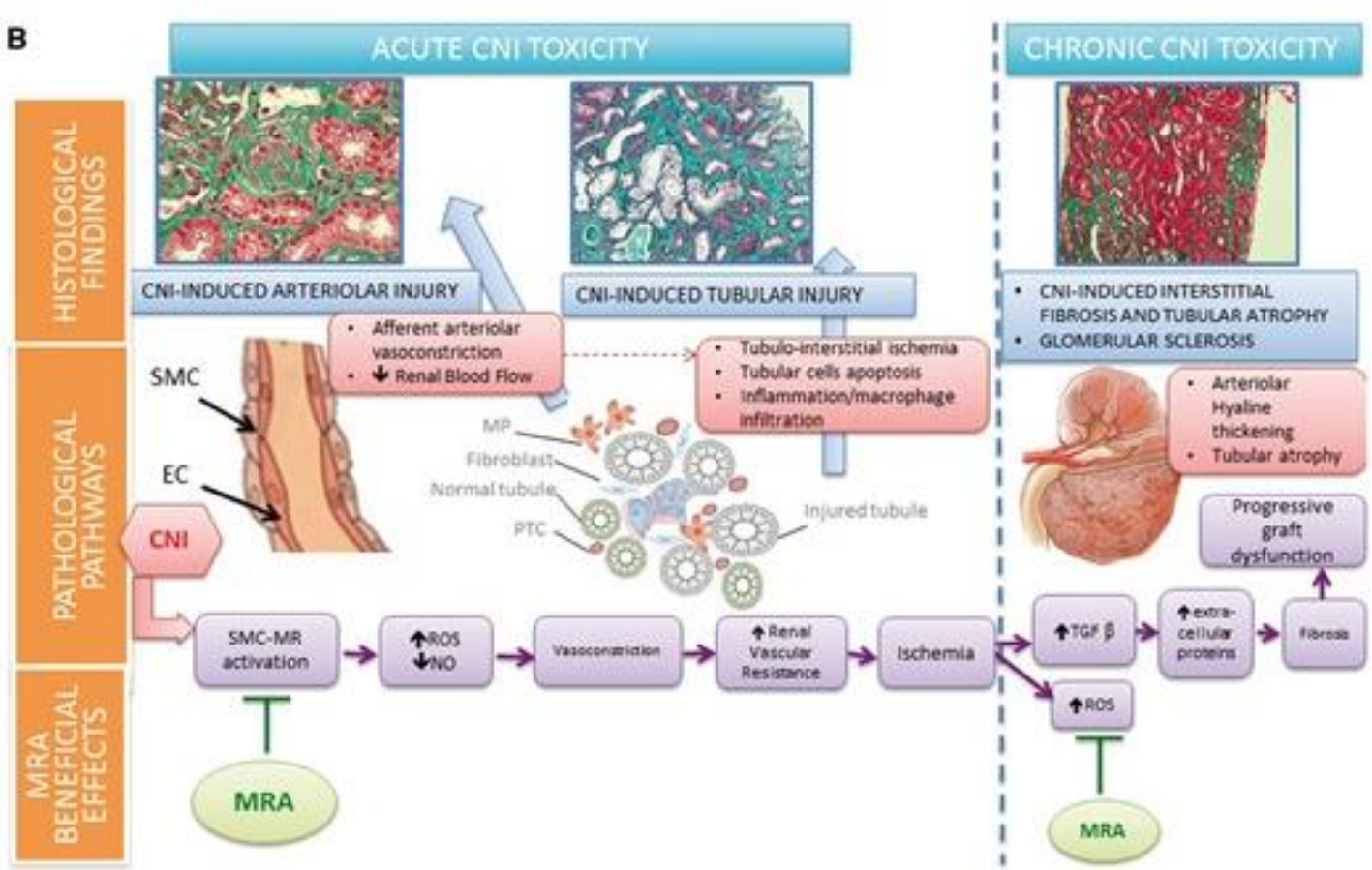
- Overall **MRAs** are underutilized in kidney transplant recipients; largely due to concerns with hyperkalemia and volume depletion!

- Lack of data of **NsMRAs** in this population
- No known interactions with immunosuppressive therapy
- Thought to have benefits in **the prevention of ischemia reperfusion injury and AKI-induced CKD**



Girierd,GS Jaisser, F. NDT. 2018

MRA benefits for CNI toxicity



MRA benefits in **prevention** of acute and chronic **CNI toxity: induced arteriolar injury and IFTA** in animal studies

Girierd,GS Jaisser, F. NDT. 2018

Spironolactone Use In Patients With Kidney Transplant: Safe But Limited Long-Term Benefit

CJASN
Clinical Journal of the American Society of Nephrology

SPIREN Trial:
Multi-center, randomized, placebo-controlled, double blind clinical trial
2018-2021

Prevalent kidney transplant recipients

On calcineurin inhibitor treatment
Proteinuria <3 g/d
Cr Cl ≥30 ml/min
K <5.5 meq/L

1-4 years post txp

3-year follow-up

1:1 randomization in blocks of four

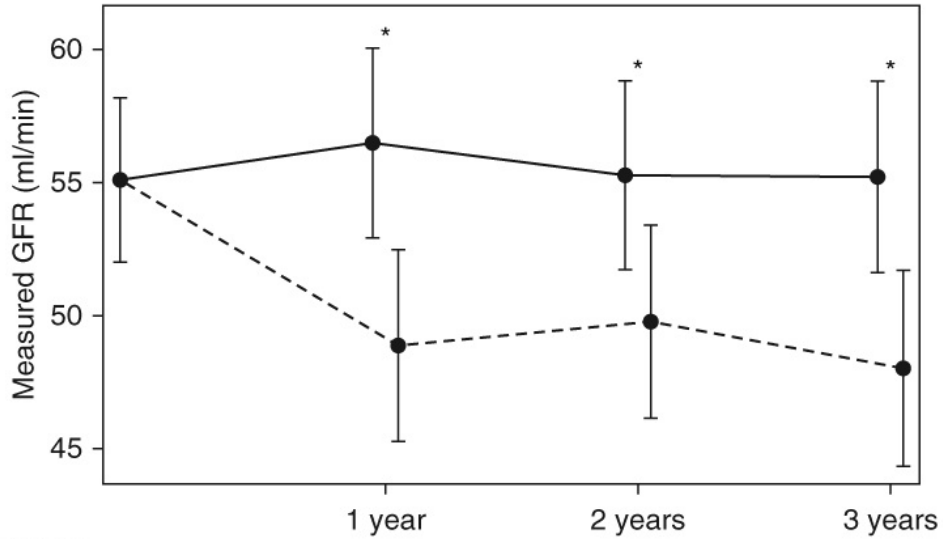
Spironolactone + standard therapy N=90

OR

Placebo + standard therapy N=90

No difference in chronic eGFR slope (6 mos-3 yrs)

No sustained proteinuria reduction at 2 and 3 yrs



		1 year	2 years	3 years
No. of patients				
Placebo	90	78	76	72
Spironolactone	88	74	68	63
Mean change from baseline				
Placebo	Ref.	1.4	0.2	0.1
Spironolactone	Ref.	-6.2	-5.3	-7.1
Diff. of change (95%CI)		-7.6 (-10.9;-4.3)	-5.5 (-8.9;-2.1)	-7.2 (-10.6;-3.7)

Mortensen,L. et al. *CJASN* 2024

UNIVERSITY OF Cincinnati

MRAs in Kidney Transplant — Underutilized for Good and Bad Reasons

Why They're Underused

- Hyperkalemia: tacrolimus + TMP-SMX + RASI already raises K^+
- Fear of volume depletion in patients with fragile graft hemodynamics
- Expert habit — not protocol-driven
- No RCT data in KT recipients for finerenone

What the Evidence Does Show

- Animal data: MRAs reduce CNI-mediated arteriolar injury and IFTA
- Spironolactone (CJASN 2024, Mortensen, n=500): safe 1–4 yrs post-KT; limited long-term benefit signal
- Finerenone: no known PK interaction with tacrolimus or mycophenolate
- Thought to be beneficial in preventing ischemia-reperfusion injury and AKI-induced CKD transitions

Finerenone post-KT: rational extrapolation — start 10 mg only if K^+ <5.0, eGFR stable; recheck K^+ at 4 weeks; avoid with other K-sparing agents

Finerenone: How to Start and What to Watch

Indication

- T2DM + CKD with eGFR ≥25 and UACR ≥30 mg/g on maximally tolerated RASI

Starting dose

- 10 mg/day if eGFR <60 or K^+ ≥4.8 mEq/L at initiation
- 20 mg/day if eGFR ≥60 and K^+ <4.8 mEq/L

Hyperkalemia monitoring

- Recheck K^+ at 4 weeks; hold if K^+ >5.5 mEq/L; titrate up if K^+ <4.8 and tolerated

Drug interactions

- Strong CYP3A4 inhibitors (ketoconazole, clarithromycin): avoid — markedly ↑ finerenone levels
- Do NOT combine with spironolactone, eplerenone, or other K^+-sparing diuretics

No known interaction with tacrolimus or mycophenolate

The Four Pharmacologic Pillars

RASI

ACEi / ARB

2001

SGLT2i

Empa · Dapa · Cana

2018–20

Ns-MRA

Finerenone

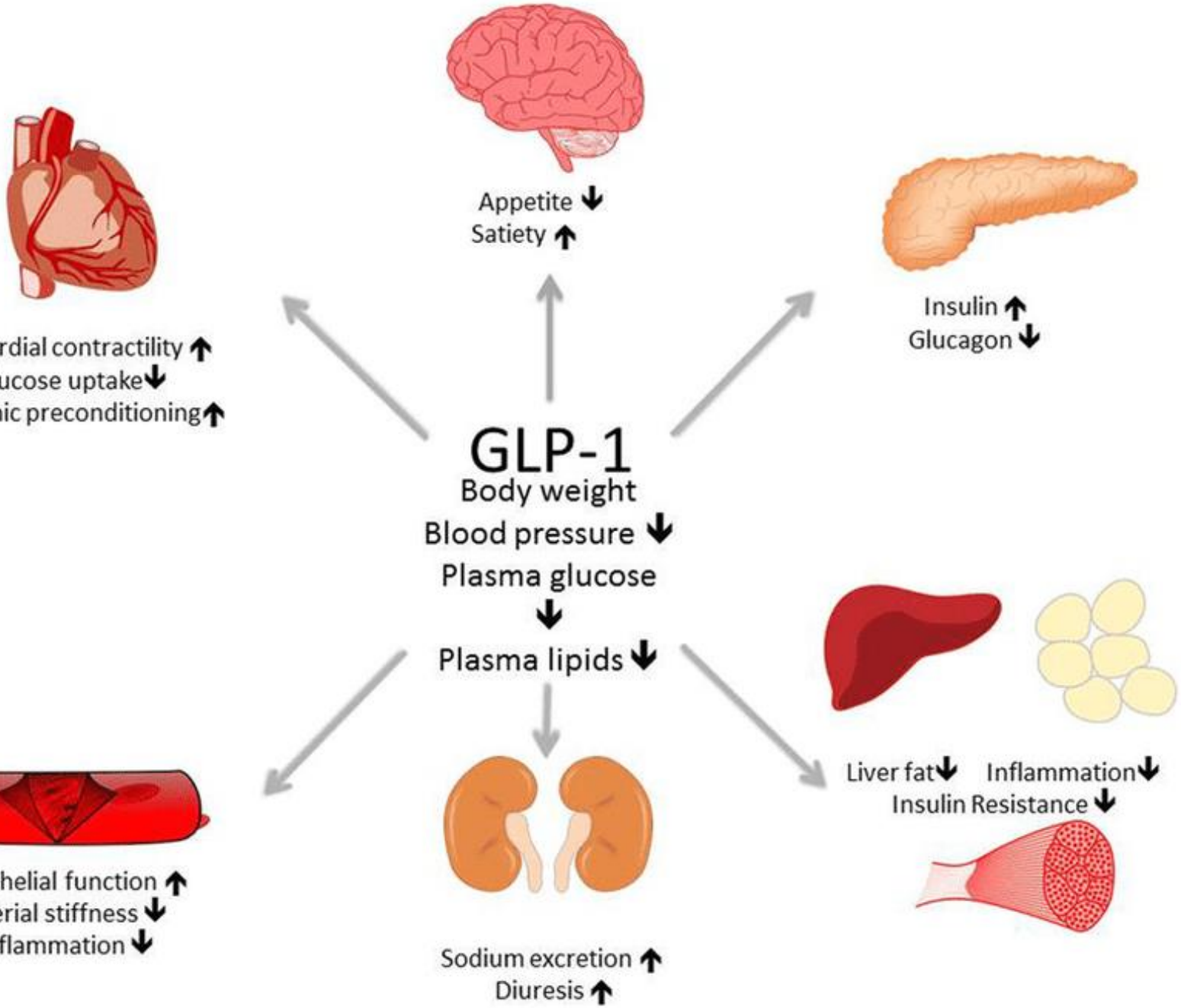
2020

GLP-1 RA

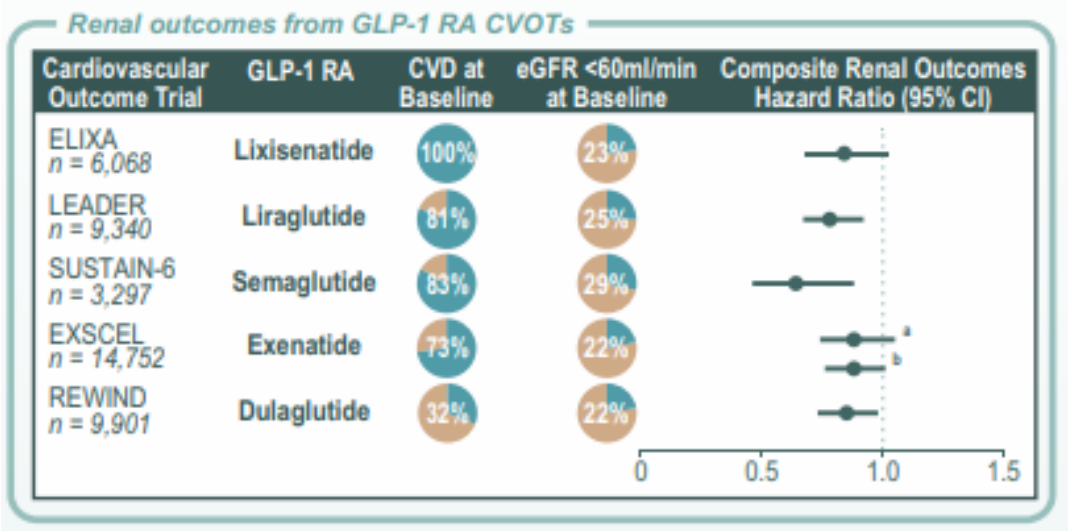
Semaglutide

2024

FLOW — first dedicated KD trial



Kidney Outcomes from Major CV Trials and then Came FLOW

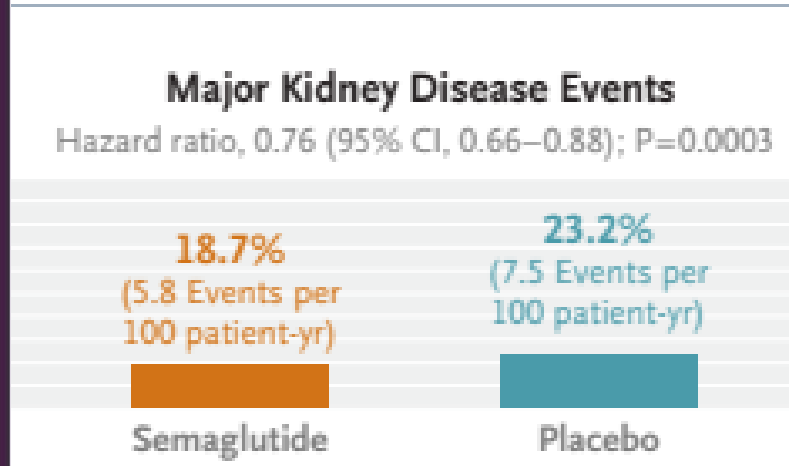


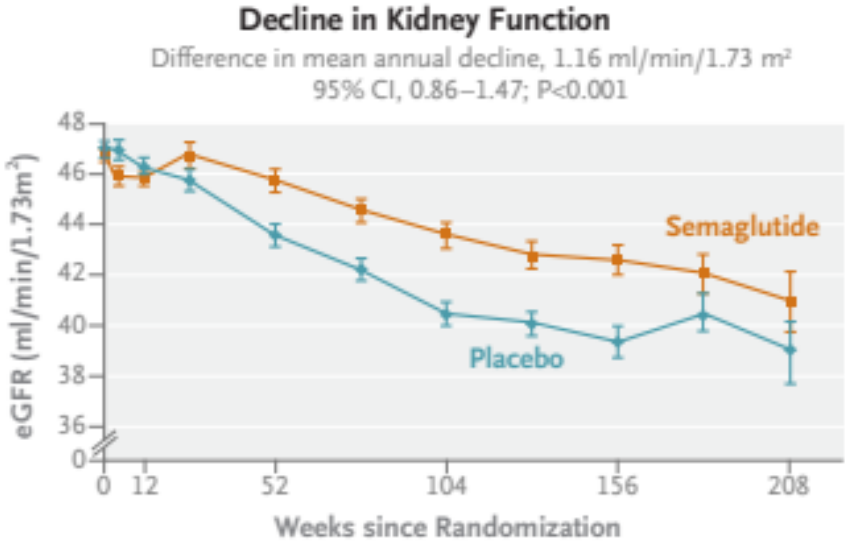
METHODS

International, double-blind, placebo-controlled
28 countries

Type 2 DM and CKD:
GFR 50-75 ml/min + ACR 300-5000 mg/g
or
GFR 25-<50 ml/min + ACR 100-5000 mg/g

Median follow-up, 3.4 years





Reference: Perkovic,V et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. NEJM, May 2024.

VA by Anjana Gopal @anjanagopal9

FLOW: Semaglutide in CKD (NEJM 2024)

Clinical Scenario

T2DM + CKD (eGFR 50–75 + UACR ≥300, or eGFR 25–<50 + UACR ≥100 mg/g) | Semaglutide 1 mg SC weekly vs. placebo | N = 3,533 | Median 3.4 yrs | First dedicated GLP-1 RA kidney outcomes trial | Stopped early for benefit

–24%

Major kidney disease events (primary composite)

–20%

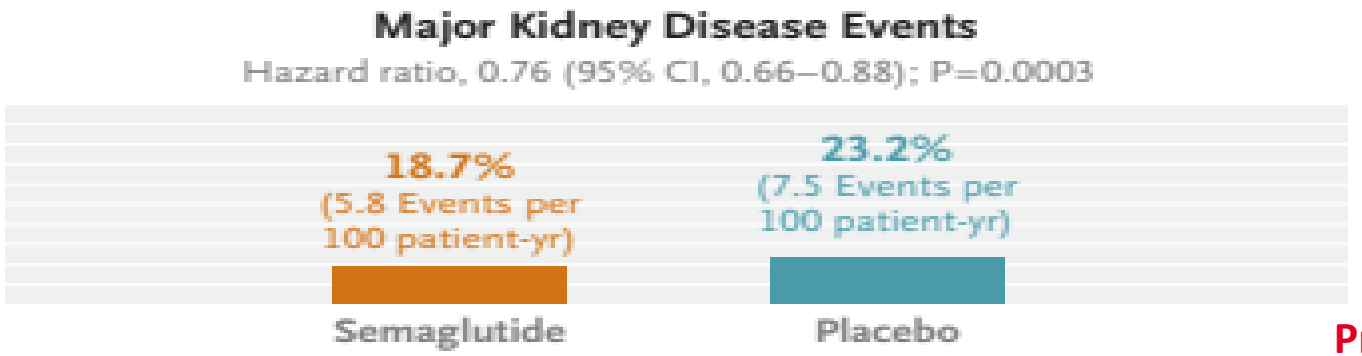
CV death or major adverse CV events

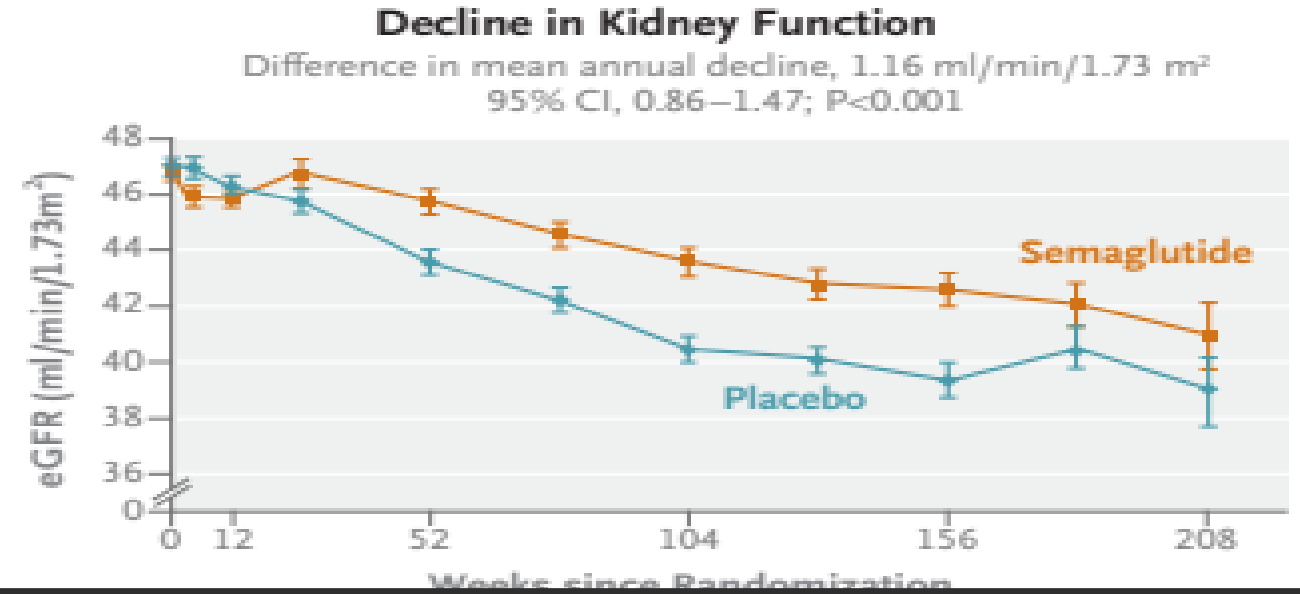
–47%

Rate of eGFR decline (slope benefit)

Semaglutide is the ONLY GLP-1 RA with an FDA indication for CKD risk reduction | Benefit consistent whether or not patients were also on an SGLT2i

FLOW: eGFR Trajectory and Event Rates





Primary composite events

- 18.7% semaglutide vs. 23.2% placebo
- 5.8 vs. 7.5 events per 100 patient-years

eGFR slope benefit

- Difference in mean annual decline: 1.16 mL/min/1.73m²
- Consistent whether or not patient on SGLT2i

Trial stopped early at interim — overwhelmingly positive

Perkovic et al., NEJM 2024 — FLOW trial. HR 0.76 (95% CI 0.66–0.88), P=0.0003 for primary composite. Difference in mean annual eGFR decline: 1.16 mL/min/1.73m² (95% CI 0.86–1.47, P<0.001)

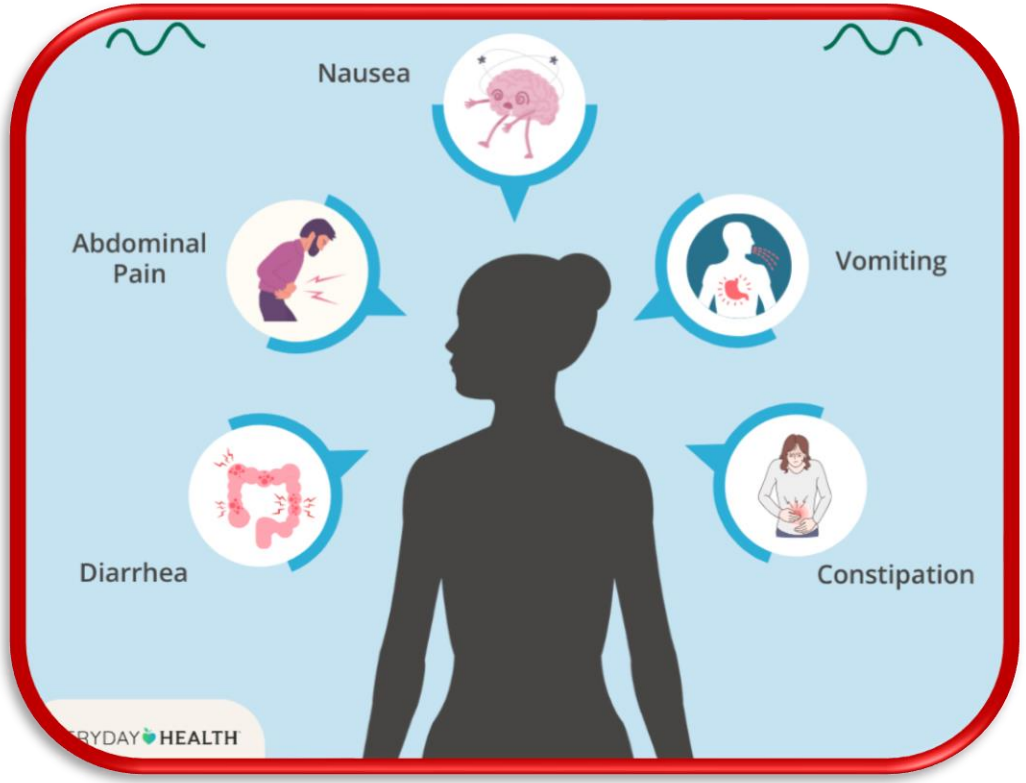
GLP-1 RA: Which Agent Has Kidney Data?

Agent	Key Trial	Kidney Evidence	Status
Semaglutide	FLOW (2024)	24% ↓ major kidney events; 47% ↓ eGFR slope	FDA CKD indication ✓
Liraglutide	LEADER (2016)	↓ new macroalbuminuria; ↓ UACR	No dedicated KD indication
Dulaglutide	REWIND (2019)	↓ UACR; ↓ progression to macroalbuminuria	No dedicated KD indication
Tirzepatide (dual GIP/GLP-1)	SURPASS-CVOT	Promising signals; no dedicated kidney trial yet	Await FLOW-equivalent trial
Exenatide / Lixisenatide	Various	No demonstrated kidney benefit	Avoid eGFR ≤30

GLP-1RA Use In Those With A Kidney Transplant

Adverse Effects that can be amplified in the transplant population?

Interactions with immunosuppression medications?



UNIVERSITY OF Cincinnati

GLP-1RA Data

10 retrospective studies that included KT recipients

Study	Study design	Treatment	Health status	Sample size	Kidney outcomes (primary vs secondary)	Results
Kidney transplant recipients						
HALLMARK (recruitment in progress)[52]	RCT	Combination Semaglutide and Dapagliflozin	With and without T2D	20	GFR, eGFR, urinary albumin excretion, incidence of AKI (Secondary)	Study ongoing
Krisanapan et al[53]	Meta-analysis	GLP-1RAs		338	eGFR, serum creatinine, UPCR (Primary)	• No change in eGFR (SMD −0.07 mL/min/1.73m^2, 95% CI −0.64, 0.50) or creatinine [SMD −0.08 mg/dL, 95% CI −0.44, 0.28). • Significant decrease in UPCR (SMD -0.47, 95% CI −0.77 to −0.18).
Mahmoud et al[54]	Retrospective Study	GLP-1RAs and SGLT2i	T2D Baseline eGFR ≥ 25 mL/min	GLP-1RA (n=41), SGLT2i (n=98), control (n=70)	eGFR, UACR (Primary)	• eGFR in SGLT2i and GLP-1RA not significantly different compared with control. • Sub-analysis by CKD stage showed improvement in eGFR ≥90 with SGLT2i, dip eGFR in SGLT2i at 1-3 months. Reduction in albuminuria in SLGT2i and GLP-1RA
Sato et al[55]	Retrospective Study	GLP-1RAs	T2D At least 2 years follow-up post-transplant	73 recipients on GLP-1RAs, 73 recipients not using GLP-1RAs	eGFR (sustained reduction of at least 40% from baseline for 4 months post-transplant) (Primary)	• 40% sustained eGFR reduction for 4 months post-transplant with GLP-1RAs (OR 0.105; 95% CI 0.012, 0.961; $p = .046$), • Recipients with sustained eGFR reduction of >40% for 4 months experienced graft loss.
Vigara et al[56]	Retrospective Study	GLP-1RAs	T2D	40 (follow-up of 6 months) and 26 (follow-up of 12 months)	eGFR, UACR (Primary)	• Improved eGFR by +3.5 mL/min/1.73m^2 at 12 months ($p = .03$) • Reduced proteinuria of -59.1 mg/g at 6 months ($P = .009$) and -48.5 mg/g at 12 months ($P = .021$)
Sweiss et al[57]	Retrospective Study	GLP-1RA with diabetes	SOT	118	Serum creatinine and eGFR (Secondary)	Significant change in serum creatinine (median change -0.0 [IQR -0.01, -0.23], $P < .0001$) and eGFR (median change 5 [IQR 0, 13], $P < .0001$)
Yugueros González[58]	Retrospective Study	GLP-1 analogues and/or SGLT2	With and without T2D	Diabetes (n=10), Obesity without Diabetes (n=5)	Serum creatinine and 24-hour proteinuria (Secondary)	No significant change in serum creatinine or proteinuria
Kukla et al[59]	Retrospective Study	GLP-1RAs	T2D	17	Change in serum creatinine and eGFR (Secondary)	eGFR and creatinine remained stable
Thangavelu et al[60]	Retrospective Study	GLP-1RA	SOT	19	eGFR (Unclear)	No changes in eGFR
Singh et al[61]	Retrospective Study	Dulaglutide and Liraglutide	SOT	Dulaglutide (n=63), Liraglutide (n=25)	All-cause graft failure (Primary), serum creatinine, and eGFR (Secondary)	• No difference in graft survival • 10% reduction in creatinine and 15% reduction in eGFR with dulaglutide • 7% increase in creatinine and 8% increase in eGFR with liraglutide
Singh et al[62]	Retrospective Study	Dulaglutide	SOT with diabetes	63	Serum creatinine, eGFR, all-cause graft failure (Secondary)	• No difference in creatinine or eGFR • No increased risk in graft failure
Liou et al[63]	Retrospective Study	Liraglutide	T2D	7	Serum creatinine, eGFR, UPCR (Secondary)	• Improved eGFR from initial 67.7 ± 18.7 to a nadir of 76.5 ± 18.7 mg/dL. • No significant change in UPCR

Riehl-Tonn,V. et al. *Canadian Journal of Kidney Health and Disease*, 2024

GLP-1RA Use: Adverse Effects

Overall, the discontinuation rate of GLP1-RAs due to any cause in patients with a KT based on observational data is ~ 10%.

Most common reported adverse events were nausea and vomiting (17.6%), diarrhea (7.6%) and injection site pain (5.4%)

Study	Drug discontinuation
GLP1-RA	
2024; Mahzari	2/39 (5.1%)
2023; Mallik	3/23 (13.0%)
2023; Mahmoud	0/41 (0.0%)
2022; Vigara	2/50 (4.0%)
2021; Kim	NR
2020; Kukla	5/17 (29.4%)

Bellos, I, et al. *Clinical Medicine*, 2024

Weight and BMI changes with GLP-1RA in KT Recipients

Overall a mean weight reduction of ~4Kg and BMI reduction of ~1.34kg/m²

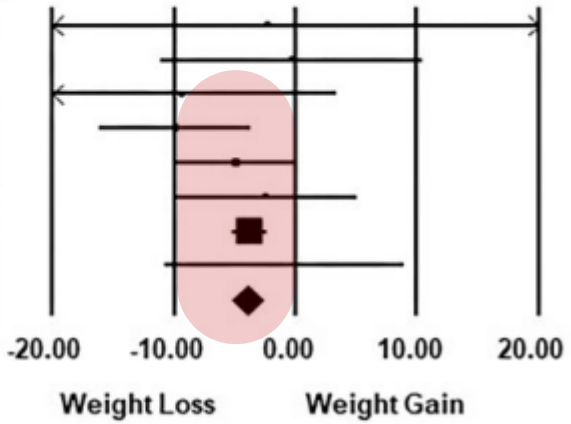
A. Weight

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Pinelli et al (2013)	-2.200	11.335	128.488	-24.417	20.017	-0.194	0.846
Liou et al (2018)	-0.300	5.505	30.304	-11.089	10.489	-0.054	0.957
Kukla et al (2020)	-9.400	6.506	42.332	-22.152	3.352	-1.445	0.149
Gonzalez et al (2021)	-9.900	3.177	10.092	-16.126	-3.674	-3.116	0.002
Kim et al (2021)	-4.900	2.628	6.907	-10.051	0.251	-1.864	0.062
Vigara et al (2022)	-2.400	3.836	14.716	-9.919	5.119	-0.626	0.532
Mallik et al (2023)	-3.800	0.709	0.503	-5.190	-2.410	-5.360	0.000
Campana et al (2023)	-0.900	5.022	25.221	-10.743	8.943	-0.179	0.858
	-4.032	0.645	0.416	-5.296	-2.768	-6.253	0.000

$I^2 = 0\%$

Statistics for each study

Difference in means and 95% CI



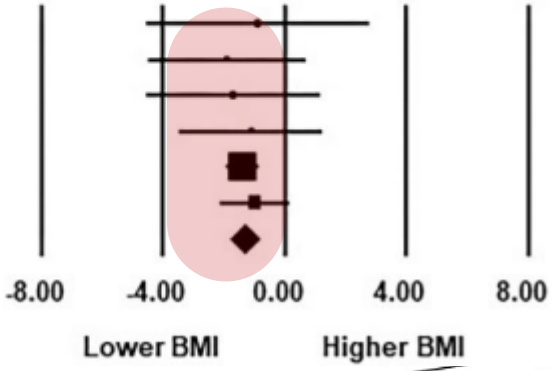
B. BMI

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Liou et al (2018)	-0.900	1.877	3.521	-4.578	2.778	-0.480	0.632
Kukla et al (2020)	-1.900	1.313	1.723	-4.473	0.673	-1.447	0.148
Gonzalez et al (2021)	-1.700	1.454	2.115	-4.550	1.150	-1.169	0.242
Vigara et al (2022)	-1.100	1.196	1.431	-3.445	1.245	-0.919	0.358
Mallik et al (2023)	-1.400	0.271	0.073	-1.931	-0.869	-5.165	0.000
Sato et al (2023)	-1.000	0.581	0.338	-2.140	0.140	-1.720	0.085
	-1.341	0.232	0.054	-1.795	-0.886	-5.783	0.000

$I^2 = 0\%$

Statistics for each study

Difference in means and 95% CI



Krisanapan, P. et al. *Clinical kidney Journal*, 2024

UNIVERSITY OF Cincinnati

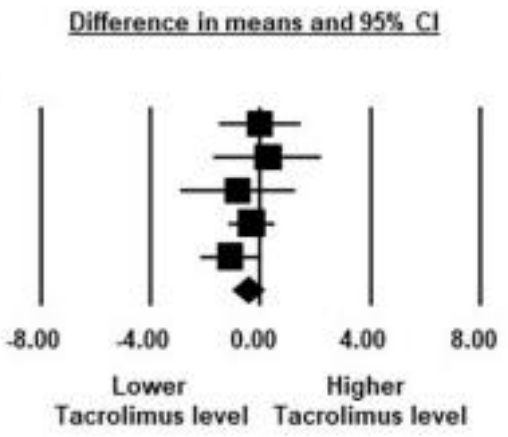
GLP-1RA Use: No Interactions with Immunosuppressive Medicines

No dose changes were required or concern about tacrolimus absorption

(despite theoretical concerns about reduced absorption due to GLPA1-RA-induced vomiting)

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Pinelli et al (2013)	0.000	0.760	0.578	-1.490	1.490	0.000	1.000
Liou et al (2018)	0.300	0.998	0.996	-1.656	2.256	0.301	0.764
Gonzalez et al (2021)	-0.800	1.062	1.127	-2.881	1.281	-0.754	0.451
Vigara et al (2022)	-0.300	0.425	0.181	-1.134	0.534	-0.705	0.481
Mallik et al (2023)	-1.050	0.569	0.324	-2.166	0.066	-1.845	0.065
	-0.434	0.286	0.082	-0.994	0.127	-1.517	0.129

$I^2 = 0\%$



Krisanapan, P. et al. *Clinical kidney Journal*, 2024

What's next to come?

Study	Study design	Treatment	Health status	Sample size	Kidney outcomes (primary vs secondary)	Results
Kidney transplant recipients						
HALLMARK (recruitment in progress)[52]	RCT	Combination Semaglutide and Dapagliflozin	With and without T2D	20	GFR, eGFR, urinary albumin excretion, incidence of AKI (Secondary)	Study ongoing
OK-TRANSPLANT 2 (upcoming)[65]	RCT	Semaglutide	Obesity, high-risk CKD/dialysis that are kidney transplant candidates	60	% Change in HbA_{1c}, change in 2-week fasting glucose, change in 2-week glycemic variability and time in rage in order to be eligible for kidney transplant	Not yet Recruiting, doing feasibility trail initially

Riehl-Tonn,V. et al. *Canadian Journal of Kidney Health and Disease*, 2024

GLP-1 RA in Kidney Transplant: Kidney Outcomes Summary

Reduction in the UACR

Study	Evaluation method	Baseline	End of follow-up	Individual difference	*P-value*
GLP1-RA					
2024; Mahzari	Albumin-to-creatinine ratio in mg/mmol	6.85 [3.55; 54.5]	5.60 [1.70; 40.18]	NR	0.093
2023; Mahmoud	Albumin-to-creatinine ratio in mg/mmol	4.1	4.0	NR	NR
2023; Mallik	Protein-to-creatinine ratio in mg/mmol	NR	NR	−3.14 [−14.18 to 0.76]	0.87
2022; Vigara	Albumin-to-creatinine ratio in mg/g	108.1 [25.6; 12.5]	59.6 [12.5, 88.2]	NR	**0.021**
2020; Kukla	24-h protein excretion in mg	150 [100; 185]	157 [75; 319]	24 [-8.5; 149]	0.1

No significant difference in UACR following GLP-1RA therapy in others

Evidence level: Low — all observational. Semaglutide data in KT specifically limited; HALLMARK trial (sema + dapa in KT) ongoing

Summary of GLP-1 RA studies in solid organ transplant recipients — kidney outcomes. Riehl-Tonn et al. 2024 systematic review.

Bellos, I, et al. *Clinical Medicine*, 2024

GLP-1 RAs in Kidney Transplant Recipients

Summary of observational evidence (10 retrospective studies, Riehl-Tonn 2024; Bellos 2024)

- Mean weight loss ~4 kg, BMI ↓ ~1.34 kg/m² across studies
- Discontinuation rate ~10%: nausea/vomiting 17.6%, diarrhea 7.6%, injection site pain 5.4%
- UACR: some studies show reduction; others no significant difference — heterogeneous populations

Critical question: does semaglutide-induced vomiting alter tacrolimus absorption?

- Multiple observational studies: no significant change in tacrolimus trough levels
- No dose adjustments required based on current evidence — monitor as with any change in GI motility

No known interactions between any GLP-1 RA and tacrolimus or mycophenolate

Practical use: PTDM + obesity + CV risk → start semaglutide, slow dose titration to minimize GI effects

- Avoid exenatide/lixisenatide at eGFR ≤30; semaglutide: no eGFR-based dose adjustment needed

The Four Pharmacologic Pillars

RASI

ACEi / ARB

2001

Foundation
Max tolerated dose

SGLT2i

Empa · Dapa · Cana

2018–20

CKD benefit DM
& non-DM

Ns-MRA

Finerenone

2020

FIDELIO
FIGARO

GLP-1 RA

Semaglutide

2024

FLOW — first
dedicated KD trial

Why Combination Therapy Makes Biological Sense

Each pillar attacks a different pathophysiologic pathway

- RASI: blocks angiotensin II–mediated efferent constriction and aldosterone-driven fibrosis
- SGLT2i: restores tubuloglomerular feedback, reduces proximal hypertrophy, natriuresis
- Finerenone: blocks aldosterone/MR–mediated inflammation and fibrosis — distinct from RASI
- GLP-1 RA: reduces glomerular hypertension, weight, BP, systemic inflammation

The trials were designed for combination — all required background RASI

- FLOW: benefit of semaglutide consistent in patients already on SGLT2i

KDIGO 2024 explicitly recommends RASI + SGLT2i as first-line combination in DKD

Simultaneous vs. Sequential: A Practical Framework

Start Together (Preferred)

- Every day without all active agents = lost kidney function
- No PK interactions between RASI, SGLT2i, or GLP-1 RA
- KDIGO 2024: RASI + SGLT2i together as standard first-line
- Finerenone sub-studies: no safety signal when added to SGLT2i
- Don't wait for one to 'stabilize' before adding the next — trials didn't

When Sequential Makes Sense

- Active contraindication to one agent (e.g., UTI → hold SGLT2i)
- Hyperkalemia concern: add finerenone once K^+ confirmed acceptable on RASI
- GI intolerance: titrate GLP-1 RA slowly rather than high dose from start
- Patient overwhelm: prioritize RASI + SGLT2i, plan finerenone at next visit
- eGFR instability: stabilize before adding finerenone

Framework: RASI + SGLT2i at initiation → finerenone 4+ weeks later if K^+ acceptable → GLP-1 RA if T2DM + CV/weight burden

When to Hold, Adjust, or Avoid Each Pillar

Drug	Hold / Avoid	Acceptable — Don't Stop	Dose Modify
RASI	K^+ >5.5; AKI; bilateral RAS; pregnancy	sCr rise ≤30%; eGFR <30 if tolerated	Reduce if sCr rises >30%; restart after AKI
SGLT2i	eGFR <20 (no efficacy); T1DM; surgery/fasting (DKA); candiduria/recurrent UTI	eGFR 20–45: continue; sCr rise at start is expected (hemodynamic)	Sick-day rule: hold if dehydrated or ill
Finerenone	K^+ >5.0 at start; strong CYP3A4 inhibitors; other K-sparing agents	K^+ 4.8–5.0: start at 10 mg and recheck in 4 weeks	Start 10 mg if eGFR <60; titrate to 20 mg if K^+ <4.8
GLP-1 RA	Personal/family hx MEN2 or MTC; severe gastroparesis; T1DM (relative)	Mild-moderate GI symptoms: slow titration, don't abandon	No eGFR-based dose adjustment for semaglutide

GLP-1RA Practical Considerations

GLP-1RAs may be safe and effective for managing glycemic control and weight loss in KTRs. They may also reduce insulin requirements.

Initiate when patient is stable post kidney transplant. Only 2 studies reported time of initiation (~7 months or a median of 24 months)

Start at low doses to minimize side effects.

Closely monitor for changes in renal function and gastrointestinal symptoms.

Overall, there is limited evidence but more yet to come

Studies are needed to determine if GLP-1RAs improve patient and allograft survival

Recap So Far

Drug Class	Immunosuppressant interaction?	Special Considerations
ARB/ACEi	No	Hyperkalemia, hypotension
SGLT2i	No	Volume depletion, UTI, genital infections
MRA	No	Hyperkalemia, hypotension
GLP-1 RA	No	GI tolerance, weight management

Initiating these medications should be **individualized**, ensuring patients are:

- **Consistently Hemodynamically Stable**
- **Free From UTIs**
- **With Stable Electrolytes**
- **Stable Weight**
- **Adequate Intake**
- **No Gastrointestinal Dysfunction**

Four Pillars Post-Kidney Transplant: Where Do We Stand?

Drug Class	IS Interaction	Main Concern Post-KT	When to Start	Evidence Level
RASI (ACEi/ARB)	None	Hyperkalemia, hypotension, anemia	1–3 months post-KT, stable eGFR	Moderate — retrospective cohorts
SGLT2i	None	UTI (high baseline), DKA, volume depletion	3–6 months post-KT, no active infection	Low — small RCTs + 18 observational studies
Ns-MRA (Finerenone)	None	Hyperkalemia — monitor at 4 weeks	After RASI/SGLT2i stable, K^+ <5.0	Very low — rational extrapolation only
GLP-1 RA (Semaglutide)	None (no tac level changes observed)	GI tolerance; weight/volume effects	PTDM + obesity; titrate slowly	Low — observational data only

Key Takeaways

1. Proteinuria is a mediator — treat it aggressively and early with all available tools
2. RASI remains the indispensable foundation; use maximum tolerated dose
3. SGLT2i: proven kidney benefit in DM and non-DM CKD — start early, continue to eGFR 20
4. Finerenone: complementary benefit on top of RASI + SGLT2i in DKD (FIDELIO/FIGARO/FIDELITY)
5. Semaglutide (FLOW 2024): only GLP-1 RA with FDA CKD indication; adds to SGLT2i benefit
6. Initiation: start RASI + SGLT2i together; add finerenone at 4+ weeks; GLP-1 RA for T2DM
7. Transplant: no IS interactions with any pillar; extrapolate evidence carefully — individualize timing and monitor closely

Key takeaways for the presentation:

•**Semaglutide** is the only GLP-1 RA with a dedicated FDA indication for CKD risk reduction, based on the FLOW trial's 24% reduction in major kidney disease events.

•**Liraglutide** and **dulaglutide** have demonstrated kidney and albuminuria benefits in their cardiovascular outcome trials (LEADER and REWIND, respectively), but these are not FDA-approved indications.

•**Tirzepatide** (a dual GIP/GLP-1 agonist) shows promising signals, but a dedicated kidney outcomes trial has not yet been completed.

•**Exenatide and lixisenatide** should be avoided in advanced CKD (eGFR ≤30) due to renal clearance and lack of demonstrated kidney benefit.

•Benefits of semaglutide appear consistent when used alongside **SGLT2 inhibitors** or **mineralocorticoid receptor antagonists**, supporting combination therapy in CKD.

University of CINCINNATI

Thank You