SGLT2 Inhibitors in Nephrology: Mechanism, Trials, and Clinical Application

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Mechanism of Action: How SGLT2i Work

Normal Proximal Tubule Glucose Reabsorption

- **Glomerular filtration**: ~125 mL/min × 1-2 mmol/L glucose = ~180 mmol/day filtered
- **SGLT2 transporters** (proximal tubule S1 segment): Reabsorb ~90% of filtered glucose
- **GLUT2 transporters** (exit across basolateral membrane)
- **Result**: Glucose normally absent in urine

SGLT2 Inhibition Mechanism

- **Block SGLT2 cotransporter** in proximal tubule epithelium
- **Prevent glucose reabsorption** → glucosuria (spillage into urine)
- **Additional effects**: ↑ Urinary sodium excretion (natriuresis)

Hemodynamic Consequences: The "Tubulo-Glomerular Feedback Hypothesis"

Normal glomerular-tubular feedback: - Proximal tubule reabsorbs NaCl → reduced delivery to macula densa - Macula densa senses low NaCl → ↓ renin release, ↑ afferent arteriolar vasodilation - Result: Maintains GFR

With SGLT2i: 1. SGLT2 blockade → ↑ Na+ delivery to macula densa (not reabsorbed with glucose) 2. Macula densa senses "high NaCl" → ↑ renin release, **afferent arteriolar vasoconstriction** 3. **Reduces intraglomerular pressure** → ↓ GFR initially (expected, not harmful) 4. **Net effect**: Glomerular pressure drops → proteinuria ↓, sclerosis prevented

> [!important] Key Point **eGFR "dip" with SGLT2i**: Expect 10-30% initial decline in eGFR within days-weeks. This is **expected and reflects pressure reduction, not true renal injury**. The dip improves outcomes by preventing glomerulosclerosis.

Pharmacology & Approved Agents

SGLT2i Approved for Renal/Cardiometabolic Indication

Agent	Dose (Nephrology)	Plasma t½	Renal Clearance	FDA Approval (Renal)
Empagliflozin (Jardiance)	10 mg daily	13.1 hr	<10%	EMPA-KIDNEY (2022)
Dapagliflozin (Farxiga)	10 mg daily	12.9 hr	<0.1%	DAPA-CKD (2020)
Canagliflozin (Invokana)	100 mg daily (with caution)	10.6 hr	33% renal excretion	CREDENCE (CKD + T2DM)

Dosing Adjustments

- **eGFR <30**: Most agents can be used, but ↓ efficacy for glucose control
- **Empagliflozin 10 mg**: Minimal dose adjustment
- **Dapagliflozin 10 mg**: No dose adjustment needed

Landmark Trials: The Evidence Base

CREDENCE Trial (2019) — Canagliflozin in CKD + T2DM

Design: T2DM + albuminuria; randomized canagliflozin vs. placebo [1]

Primary outcome: ESRD, doubling Cr, CV death

Results: - **33% ↓ ESRD/doubling Cr** (p <0.001) - ↓ **CV death** (especially HF-related) - Proteinuria ↓ 27% at 30 weeks

Clinical impact: First SGLT2i to show renal benefit; established class effect

DAPA-CKD Trial (2020) — Dapagliflozin in CKD (±T2DM)

Design: CKD stage 3b-4 (eGFR 25-75) + albuminuria; **NOT limited to diabetics** [2]

Primary outcome: Composite of ≥50% eGFR decline, ESRD, kidney death, CV death, hospitalization for HF

Results: - **39% ↓ composite outcome** (p <0.001) - **Benefit seen in both diabetic and non-diabetic patients** - Dapagliflozin reduced risk across eGFR ranges (even eGFR 25-40) - Proteinuria ↓ 35% by month 2

Clinical impact: Establishes SGLT2i benefit in NON-DIABETIC CKD (IgAN, FSGS, etc.); not just T2DM

EMPA-KIDNEY Trial (2022) — Empagliflozin in CKD (±T2DM)

Design: CKD stage 2-4 (eGFR >20) + albuminuria; similar broad population [3]

Primary outcome: ESRD, doubling Cr, CKD death, CV death, hospitalization for HF

Results: - **25% ↓ composite outcome** (p <0.001) - Empagliflozin 10 mg reduced ESRD 32% - Benefits consistent across diabetes status, GFR, and baseline proteinuria

Clinical impact: Broadest indication yet; effective even with eGFR 20-30

EMPEROR-Reduced, EMPEROR-Preserved (2020-2021) — HF Phenotypes

Design: HFrEF (EMPEROR-Reduced) and HFpEF (EMPEROR-Preserved) [4]

Results: - **Empagliflozin 10 mg ↓ CV death + HF hospitalization ~25-30%** - Benefit seen in HFpEF (traditionally challenging to treat) - Renal function stable/improved

Clinical impact: Expands SGLT2i use beyond CKD to HF-CKD phenotype

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Indications for SGLT2i in Nephrology

PRIMARY INDICATION: CKD with Albuminuria (Non-Diabetic & Diabetic)

- **eGFR 20-75 mL/min/1.73m² + albuminuria** (UACR >30 mg/g or proteinuria $\geq$0.5 g/day)
- **Baseline proteinuria**: Even >3 g/day benefit demonstrated
- **Diabetes status**: Benefit in BOTH diabetic and non-diabetic CKD
- **Disease**: CKD from any cause (IgAN, FSGS, diabetic, lupus, hypertensive, etc.)

SECONDARY INDICATION: HFrEF $\pm$ CKD

- **HFrEF** (LVEF <40%) $\rightarrow$ dapagliflozin or empagliflozin for symptom relief + mortality reduction
- **Independent of diabetes status**
- Often used even without significant albuminuria if HF

TERTIARY INDICATION: HFpEF $\pm$ CKD

- **HFpEF** (LVEF >50%) + albuminuria $\rightarrow$ empagliflozin favored (EMPEROR data)
- Emerging indication; data maturing

NOT INDICATED (Or Use with Caution)

- **Non-albuminuric CKD** (UACR <30, no proteinuria): Limited data; reserved for high-risk subgroups
- **Type 1 diabetes (off-label)**: Some benefit seen in T1DM + CKD, but FDA indication T2DM
- **eGFR <20** (but EMPA-KIDNEY included eGFR $\geq$20; limited data if <20)

Clinical Dosing & Efficacy

Dosing for Renal Indication

- **Dapagliflozin 10 mg**: Once daily, morning or evening (no food interaction)

- **Empagliflozin 10 mg**: Once daily, morning preferred (no food interaction)
- **Canagliflozin 100 mg**: Once daily, before first meal

Expected Renal Outcomes

Outcome	Timeline	Expected Change
Proteinuria	2-4 weeks	30-50% reduction
eGFR dip	Days-weeks	10-30% initial decline (expected; reversible)
Stabilization	6-12 weeks	eGFR stabilizes; trajectory flattened
ESRD/doubling Cr	2-3 years	25-39% risk reduction

> [!tip] Clinical Pearl **Expected eGFR dip doesn't mean kidney damage**: The initial 10-30% decline in eGFR within first 4-8 weeks reflects hemodynamic changes (reduced intraglomerular pressure), NOT tubular toxicity. Most stabilize or improve by 12 weeks. Don't discontinue based on initial dip.

Mechanism of Benefit: Beyond Glycosuria

1. Hemodynamic: Reduced Intraglomerular Pressure

- SGLT2i → afferent arteriolar vasoconstriction (via macula densa)
- ↓ Glomerular hyperfiltration → ↓ proteinuria
- Protective against glomerulosclerosis

2. Natriuresis & Volume Reduction

- ↑ Urinary sodium excretion → mild volume depletion
- Sympathetic nervous system activation (modest)
- Effective for edema management in nephrotic patients

3. Metabolic Effects

- **Improved insulin sensitivity**: ↓ HbA1c by 0.5-1.0% if diabetic
- **Weight loss**: 2-3 kg over months (from glycosuria caloric loss)
- **Lipid improvement**: ↓ triglycerides, ↑ HDL
- **Uric acid reduction**: ↓ serum UA (relevant for gout-prone patients)

4. Direct Renal Cellular Effects (Emerging)

- **Reduced inflammation**: ↓ tubular TNF-α, IL-6
- **Improved mitochondrial function**: Enhanced ATP production (cells shift toward oxidative metabolism)
- **Anti-fibrosis**: ↓ TGF-β signaling (anti-sclerotic)
- **Potential podocyte protection**: Direct effects on podocyte cytoskeleton

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Adverse Effects & Safety Monitoring

Euglycemic Diabetic Ketoacidosis (euDKA)

Rare but serious: ~0.1-0.4 cases per 1000 patient-years

Risk factors: - Acute illness (infection, surgery, dehydration) - Insulin-dependent diabetes - Recent change in insulin dosing

Presentation: Normal or mildly elevated glucose (<250 mg/dL) + severe metabolic acidosis (pH <7.25) - Symptoms: Nausea, vomiting, abdominal pain, dyspnea

Prevention: - Counsel patients: Hold SGLT2i during acute illness, surgery, fasting - Monitor for symptoms - Check VBG/ABG if vague abdominal symptoms in diabetic patient on SGLT2i

Treatment: IV insulin, fluid resuscitation, electrolyte correction; restart SGLT2i after recovery if no contraindication

> [!warning] High-Yield Board Point **euDKA screening**: Any T2DM patient on SGLT2i with nausea/vomiting/abdominal pain → check VBG for acidosis. Can occur at normal glucose levels, making diagnosis challenging.

Urinary Tract & Genital Infections

Frequency: 5-10% (more common in women)

Mechanism: Glucosuria promotes bacterial growth (especially Candida in genital areas)

Management: - Counsel: Hygiene, regular voiding, adequate hydration - Treat infections promptly (antibiotics for UTI, topical/oral antifungals for candida) - Consider discontinuation if recurrent/severe infections

Volume Depletion & Hypotension

Mechanism: Natriuresis; mainly seen with loop diuretics or severe baseline volume depletion

Risk factors: Concomitant diuretic use, GFR <30, heart failure

Prevention: - Monitor BP standing + sitting - Assess volume status at baseline - Adjust other diuretics if volume depleted (decrease dose)

Management: Usually mild; rehydrate; resume after volume repletion

Amputation Risk (Canagliflozin Only)

CANVAS Trial: ↑ lower-extremity amputation risk with canagliflozin (↑ 97% vs. placebo) - Mechanism: Unclear (volume depletion? pressure-related?) - Increased risk: Peripheral arterial disease, prior amputation, foot ulcer history - Management: **Canagliflozin use restricted** in high-risk patients; preferred agents: dapagliflozin, empagliflozin

Renal-Related Side Effects

Side Effect	Frequency	Mechanism	Management
Transient eGFR dip	50-80%	Hemodynamic (expected)	Monitor; don't discontinue
Acute kidney injury (rare)	<1%	Volume depletion	Rehydrate; assess volume status
Hyperkalemia	<1% (even in CKD)	Net K+ loss (glucosuria)	Monitor baseline + 4 weeks; rare in CKD

Drug Interactions & Contraindications

Contraindications

- **Type 1 diabetes**: Not approved (↑ DKA risk); SGLT2i less effective (no β-cell reserve)
- **Acute kidney injury**: Hold SGLT2i until stabilized
- **Severe volume depletion**: Hold until rehydrated
- **Active UTI/candida**: Treat infection first; restart after resolution

Key Interactions

- **Diuretics**: Risk volume depletion; coordinate dosing
- **ACE-I/ARB**: Additive renal hemodynamic effects; benefit, but monitor K+ and Cr
- **NSAIDs**: Risk AKI (avoid); use acetaminophen instead
- **Certain contrast dyes**: Hold SGLT2i 48 hours before contrast, restart 48 hours after

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Clinical Pearls & Pitfalls

[!tip] Clinical Pearl **SGLT2i benefit independent of baseline glucose control**: Even well-controlled T2DM patients gain renal/cardiac benefit. Don't reserve SGLT2i only for poorly controlled diabetes; use in all CKD + albuminuria if no contraindication.

[!warning] High-Yield Board Point **Initial eGFR dip is EXPECTED and BENEFICIAL**: Don't panic or discontinue SGLT2i if eGFR drops 15-20% in first month. This reflects pressure reduction and is associated with BETTER long-term outcomes. Continue therapy; reassess at 8-12 weeks.

[!important] Key Point **SGLT2i in non-diabetic CKD**: DAPA-CKD and EMPA-KIDNEY proved benefit in IgAN, FSGS, lupus, and other non-diabetic kidney diseases. Use SGLT2i in ALL albuminuric CKD, not just diabetes.

[!tip] Clinical Pearl **Canagliflozin amputation risk**: Use dapagliflozin or empagliflozin preferentially in patients with peripheral arterial disease, prior amputation, foot ulcers, or Charcot joint. Risk with canagliflozin outweighs benefits in this population.

[!important] Key Point **SGLT2i + ACE-I/ARB synergy**: Combination therapy more effective than either alone for proteinuria reduction. Use together (if no contraindication) for maximal effect.

Special Populations

CKD Stage 5 (eGFR <15)

- **Limited data**: DAPA-CKD excluded eGFR <25; EMPA-KIDNEY allowed eGFR $\geq$20
- **Recommendation**: Can use if eGFR 15-20 (dapagliflozin, empagliflozin); avoid if <15 or on dialysis (no benefit, glucose spill not filtered)
- **Transition to dialysis**: Consider discontinuation (no renal filtration; no efficacy)

Dialysis-Dependent ESRD

- **NOT indicated**: Kidneys not filtering glucose; no hemodynamic benefit
- **Discontinue**: Before dialysis initiation

HFpEF + CKD

- **Emerging indication**: Empagliflozin reduces HF hospitalization even in HFpEF
- **Target**: Albuminuric CKD + HFpEF; empagliflozin 10 mg preferred (EMPEROR-Preserved)

Post-Kidney Transplant

- **Limited data**: Some use off-label if proteinuria/CKD post-transplant; minimal trials
- **Caution**: Risk of volume depletion in transplant recipients; coordinate with transplant team

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Monitoring Checklist

Timepoint	Labs/Assessments	Rationale
Baseline	Cr, eGFR, UACR, K+, glucose, VBG	Baseline safety assessment
Week 1-2	BP standing/sitting	Screen for hypotension
4 weeks	Cr, eGFR, K+	Monitor eGFR dip; ensure safe
8-12 weeks	Cr, eGFR, proteinuria, symptoms	Assess stabilization; expect eGFR recovery
6-12 months	Cr, eGFR, UACR, K+	Long-term monitoring
Annually	CBC, CMP, UA	Routine surveillance for adverse effects

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Landmark Trials (Full Citations)

[1] **CREDENCE Trial** (2019): Canagliflozin and renal outcomes in type 2 diabetes. *NEJM*. 2019;380(23):2295–2306. PMID: 30479144

[2] **DAPA-CKD Trial** (2020): Dapagliflozin in patients with CKD. *NEJM*. 2020;383(15):1436–1446. PMID: 32970396

[3] **EMPA-KIDNEY Trial** (2022): Empagliflozin in patients with CKD. *NEJM*. 2022;387(12):1129–1141. PMID: 36083659

[4] **EMPEROR-Preserved** (2021): Empagliflozin in patients with HFpEF. *NEJM*. 2021;385(16):1451–1461. PMID: 34551269

Related Resources

- CKD Comprehensive Management Pathways
- DAPA-CKD & Cardioprotection
- Drug Dosing in CKD Quick Reference
- SGLT2i in T1DM Report

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