SGLT2 Inhibitors: Mechanisms, Evidence, and Clinical Application in Cardiorenal Disease

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SGLT2 Inhibitors: Mechanisms, Evidence, and Clinical Application

Learning Objectives

By the end of this session, you should be able to: 1. Explain the mechanism of SGLT2 inhibitors in simple, memorable terms 2. Understand why these agents benefit both heart and kidney 3. Recognize key clinical trial evidence 4. Apply SGLT2 inhibitors appropriately across CKD and HF populations 5. Counsel patients on expected effects and monitoring 6. Manage common concerns (genital infections, initial eGFR decline)

What Are SGLT2 Inhibitors? The Basic Mechanism

The Physiology

Under normal conditions, kidneys filter all the glucose they produce. Since we need glucose, the kidneys **reabsorb essentially 100%** of filtered glucose in the proximal tubule via two sodium-glucose cotransporters: - **SGLT2** (secondary transporter) reabsorbs ~90% of filtered glucose - **SGLT1** reabsorbs the remaining ~10%

How SGLT2 Inhibitors Work

SGLT2 inhibitors **block the SGLT2 transporter**, allowing glucose to be excreted in urine instead of reabsorbed.

Result: - Increased urinary glucose (glucosuria) - Natriuresis (sodium also lost with blocked glucose) - Diuresis (water follows sodium and glucose osmotically) - **Importantly:** This diuresis does NOT activate the RAAS like loop diuretics do

Why This Is Different from Other Diuretics

Feature	Loop Diuretics	SGLT2 Inhibitors
Mechanism	Block Na-K-2Cl	Block SGLT2
Diuresis strength	Strong	Mild-moderate

Feature	Loop Diuretics	SGLT2 Inhibitors
RAAS activation	YES (problem)	NO (advantage)
Neurohormonal compensation	Strong	Minimal
Potassium wasting	YES (K+ drops)	NO (K+ stays normal)
Volume depletion risk	Higher	Lower

The Four-Pillar Benefit: Why SGLT2-i Help Heart AND Kidney

SGLT2 inhibitors benefit through multiple mechanisms:

1. Hemodynamic Mechanisms

Restored Tubuloglomerular Feedback: - Normal glucose reabsorption requires sodium transport in proximal tubule - Blocking SGLT2 leaves more sodium in the tubule lumen - More sodium reaching the macula densa (early distal tubule) signals "too much sodium filtered" - This triggers **afferent arteriole vasoconstriction** - Result: Reduced intraglomerular pressure (protective long-term, even though eGFR dips initially)

Clinical Pearl: The initial eGFR decline of 3-5 mL/min is a SIGN of hemodynamic adjustment, not kidney damage. This dip stabilizes and becomes protective.

2. Metabolic Mechanisms

Metabolic Reprogramming: - SGLT2 inhibitors create a "fasting-like" metabolic state - Enhanced ketone body utilization (cardiac fuel) - Improved myocardial energetics - Reduced triglycerides and improved lipid profile

3. Renal Protective Mechanisms

Reduced Renal Hypoxia: - Proximal tubule is the most metabolically active part of the kidney - Blocking SGLT2 reduces the sodium-potassium pump workload - Lower oxygen demand in the vulnerable renal medulla - Improved renal oxygenation-to-demand ratio

Reduced Inflammation: - Decreased oxidative stress in tubular cells - Reduced inflammatory cytokine production - Anti-fibrotic effects

4. Cardiac Mechanisms

Preload Reduction: - Mild diuresis (due to natriuresis and osmotic effect) - Reduced venous return and central venous pressure - Better diastolic function

Myocardial Energetics: - Enhanced ketone utilization - Improved cardiac ATP production - Reduced cardiac fibrosis

Result: Unique among diuretics, SGLT2 inhibitors improve HFpEF (where pure diuresis might harm) by combining beneficial natriuresis with improved myocardial mechanics.

Clinical Evidence: Landmark Trials

SGLT2 Inhibitors in HFrEF

DAPA-HF (Dapagliflozin, 2019) — n=4,744 HFrEF patients (42% with CKD) PubMed | Outcome | SGLT2-i | Placebo | Benefit | |———|———|———|———| | CV death/worsening HF | 16.3% | 21.8% | **26% reduction** | | HF hospitalization alone | 8.5% | 13.1% | **35% reduction** | | Kidney composite | 4.3% | 6.0% | **29% reduction** | | NNT (primary endpoint) | 18 | — | Prevent one event per 18 treated over 2 years |

EMPEROR-Reduced (Empagliflozin, 2020) — n=3,730 HFrEF patients (48% with CKD) PubMed | Outcome | SGLT2-i | Placebo | Benefit | |———|———|———|———| | CV death/worsening HF | 17.1% | 22.8% | **25% reduction** | | Kidney composite | 2.7% | 5.3% | **50% reduction** |

SGLT2 Inhibitors in HFpEF (Game Changer!)

EMPEROR-Preserved (2021) — n=5,988 HFpEF patients (LVEF >40%) PubMed

This was the FIRST major trial showing benefit in HFpEF: | Outcome | Empagliflozin | Placebo | Benefit | |———|—|—|—| | CV death/HF hospitalization | 21.1% | 26.3% | **21% reduction** | | HF hospitalization | 14.1% | 19.5% | **27% reduction** | | Kidney composite | 1.3% | 2.4% | **43% reduction** |

DELIVER (2022) — n=6,263 HFmrEF/HFpEF PubMed - 18% reduction in CV death/worsening HF - Benefit maintained even with LVEF >60% - **2023 ESC upgraded SGLT2-i to Class I, Level A for HFpEF** (only treatment with this strength)

SGLT2 Inhibitors in CKD (Without Heart Failure)

DAPA-CKD (2020) — n=4,304 CKD patients (eGFR 25-75), 38% with HF PubMed | Outcome | Benefit | |———|———| | ≥40% eGFR decline, kidney failure, kidney death | **39% reduction** | | HF hospitalization | **71% reduction** | | CV death | **31% reduction** |

EMPA-KIDNEY (2023) — Broader eGFR range (20-90 with albuminuria) PubMed - 28% reduction in kidney disease progression - 39% reduction in HF hospitalization

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Mechanism Summary Table

Domain	Benefit	Evidence
Cardiac	Improved diastolic function, reduced fibrosis, enhanced energetics	HFpEF benefit unique among diuretics
Renal	Restored hemodynamic feedback, reduced hypoxia, anti-inflammatory	30-50% kidney event reduction
Metabolic	Fasting-like state, ketone utilization, lipid improvement	Weight loss, improved triglycerides

Domain	Benefit	Evidence
Volume	Natriuresis without neurohormonal activation	Lower potassium wasting than loop diuretics

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Practical Clinical Application

Patient Selection

Indications (per current labels): - CKD with eGFR 20-90 mL/min (continue down to eGFR 20) - Heart failure with any EF - Diabetes (benefit extends beyond HbA1c reduction)

Note: Albuminuria not required for benefit, but benefits are greater with higher UACR

Dosing

Agent	Dose	No Renal Adjustment?	Continue to
Dapagliflozin	10 mg daily	YES	eGFR 20
Empagliflozin	10 mg daily	YES	eGFR 20
Canagliflozin	100-300 mg daily	NO (reduce at eGFR <45)	eGFR 15

Clinical Pearl: Dapagliflozin and empagliflozin are preferred in CKD due to no dose adjustment needed.

Monitoring Protocol

Baseline: - eGFR, UACR - Electrolytes, especially potassium - Cardiovascular exam - Footcare exam (educate on genital/foot hygiene)

2-4 weeks post-initiation: - Recheck eGFR (expect initial decline of 3-5 mL/min) - Recheck electrolytes - Clinical assessment

Ongoing (every 3-6 months in stable patients): - eGFR, UACR, electrolytes - Cardiovascular status, volume assessment - Tolerability assessment

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Managing Expected Effects and Side Effects

Expected (Reassure Patients)

Initial eGFR Dip (3-5 mL/min) - Occurs within first 1-2 weeks - Represents beneficial hemodynamic adjustment (afferent arteriolar vasoconstriction) - Stabilizes or improves over 2-4 weeks - Is reversible upon discontinuation - Should NOT prompt discontinuation

Tell Patients: "Your kidney function will dip slightly at first—think of it like adjusting blood pressure to protect your kidneys long-term. This is expected and not harmful."

Blood Pressure Reduction (3-5 mmHg) - May need antihypertensive adjustment - Usually beneficial - Monitor for symptomatic hypotension

Increased Urination - Due to glucosuria - Explain this as medication working - Occurs most in first weeks, often improves

Genital Fungal Infections - More common in women - Risk higher if UACR elevated (more glucose in urine = more fungal growth substrate) - Prevention: Keep area dry, avoid irritants, treat promptly - Postmenopausal women: Consider vaginal estrogen prophylaxis

Red Flags (Discontinue and Seek Care)

Diabetic Ketoacidosis (DKA) — Rare, mainly in Type 1 DM - Nausea, vomiting, malaise - Abdominal pain, dyspnea - **Euglycemic DKA possible** — can occur with normal or even low glucose! - If suspected, check venous or arterial blood gas, serum/urine ketones, glucose

Fournier's Gangrene — Extremely rare but FDA-warned - Necrotizing infection of genital/perineal region - Fever, severe pain, swelling - Requires emergency surgical intervention

Acute Kidney Injury Beyond Initial Dip - eGFR decline >5 mL/min beyond first 2 weeks - Rising creatinine trend - Evaluate for other causes (volume depletion, intercurrent illness)

Special Populations

Type 1 Diabetes (Controversial)

SGLT2 inhibitors are **not FDA-approved** for Type 1 DM due to increased DKA risk (2-4 fold increase). However, recent evidence suggests careful use in selected patients with Type 1 + progressive diabetic nephropathy might be justified by renal protection benefits.

If considered: Requires specialist oversight, comprehensive education, frequent monitoring, and firm commitment to patient engagement.

Heart Failure with Reduced EF (HFrEF)

- Start immediately alongside ACE-I/ARB
- Benefit proven, consistent, and large
- Continue indefinitely (Class I indication)

Heart Failure with Preserved EF (HFpEF)

- Class I, Level A indication (per 2023 ESC)
- First therapy showing consistent benefit in HFpEF
- More useful than other agents in this phenotype
- Continue indefinitely

Chronic Kidney Disease

- Start if eGFR ≥20 and diabetes present, or CKD stage 3-4 with high CV risk
- Continue until eGFR <20 (most agents)

- Renal protection extends even in normoalbuminuric CKD

Advanced CKD (eGFR <30)

- Benefits persist despite low eGFR
- Monitor potassium and volume status
- May have more robust response (given less baseline natriuresis)

Drug Interactions and Combinations

SGLT2-i + ACE-I/ARB/ARNI

- Synergistic renal protection
- Safe combination
- Both reduce proteinuria through different mechanisms
- Combined 39% kidney event reduction (vs individual ~25-30%)

SGLT2-i + MRA (Mineralocorticoid Antagonist)

- Synergistic cardiorenal benefit
- SGLT2-i mitigates hyperkalemia risk of MRA
- Safe to combine if K+ monitoring done
- In FIDELITY, hyperkalemia LOWER with SGLT2-i + MRA combination (8.1%) vs MRA alone (18.7%)

SGLT2-i + GLP-1 Receptor Agonist

- Complementary mechanisms
- Both reduce MACE, HF hospitalization, kidney events
- Additive renal protection (38% vs 21% individual)
- Safe combination

Sick Day Management with SGLT2 Inhibitors

When to Hold

During acute illness with: - Poor oral intake - Vomiting/diarrhea (volume depletion risk) - Planned surgery (24-48 hours before) - Suspected DKA

When to Resume

Once: - Oral intake restored - Vomiting/diarrhea resolved - Volume status normal - Kidney function recovering

Patient Education

"Your SGLT2 inhibitor normally helps both your heart and kidneys. But during acute illness when you can't eat or drink normally, we need to pause it temporarily to let your body's natural compensation mechanisms work. Once you've recovered, we'll restart it."

Clinical Pearls

1. **SGLT2-i are the most broadly beneficial drug class.** Work across HFrEF, HFpEF, CKD ± diabetes, with or without established CVD.
2. **Initial eGFR dip is GOOD.** It's hemodynamic adjustment that becomes renoprotective long-term.
3. **Potassium stays STABLE.** Unlike loop diuretics, SGLT2-i don't cause potassium wasting—major safety advantage.
4. **HFpEF is a frontier.** SGLT2-i are one of few therapies showing genuine benefit in this challenging phenotype.
5. **Mild diuresis without RAAS activation.** They achieve diuresis without triggering compensatory neurohormonal activation.
6. **Type 1 DM carries DKA risk.** While not approved, careful use in selected Type 1 patients with progressive nephropathy may be justified by nephrologists.
7. **Continue indefinitely.** These are long-term therapies, not bridge therapy.

Practice Questions

Question 1: A 62-year-old with eGFR 35 mL/min and UACR 200 mg/g starts dapagliflozin. Baseline creatinine is 2.1 mg/dL. At 2 weeks, creatinine is 2.3 mg/dL (eGFR now 30). Patient is concerned. What do you say?

Answer: "This eGFR decline is expected and represents your kidneys adjusting to protect themselves long-term. Think of it like recalibrating blood pressure to reduce pressure inside the kidney. Studies show this adjustment is protective. We'll recheck in 4 weeks and expect it to stabilize. This is why we continue the medication."

Question 2: Compare the benefit of SGLT2-i in HFrEF vs. HFpEF. Which population benefits more?

Answer: Both benefit significantly, but HFpEF benefit is more remarkable because SGLT2-i is ONE OF THE FEW therapies proven in HFpEF. In HFrEF, other options exist (ARNI, beta-blockers, MRAs). In HFpEF, SGLT2-i stands alone with Class I evidence. For HFpEF patients, this is among the most important therapies available.

Question 3: A 45-year-old with Type 1 DM, albuminuria (UACR 400 mg/g), eGFR 42, and no heart failure asks about SGLT2-i use. What are the considerations?

Answer: SGLT2-i aren't FDA-approved for Type 1 DM due to 2-4 fold increased DKA risk. However, this patient's progressive nephropathy despite likely being on ACE-I/ARB might warrant discussion with nephrology about conditional use IF: (1) Specialist oversight available; (2) Patient demonstrates excellent self-management; (3) Comprehensive DKA education provided; (4) Frequent monitoring possible. Risk-benefit might favor careful trial in this specific scenario.

Key Takeaways

☐ **SGLT2 inhibitors** work through elegant hemodynamic, metabolic, and anti-inflammatory mechanisms

☐ **Initial eGFR dip** (3-5 mL/min) is hemodynamic adjustment, not nephrotoxicity—continue therapy

☐ **Benefit extends across** HFrEF, HFpEF, CKD, with or without diabetes—broadest indication profile

☐ **HFpEF is the frontier**—SGLT2-i among the few proven therapies for this common phenotype

☐ **Minimal electrolyte effects**—potassium stable, no significant wasting unlike loop diuretics

☐ **Continue indefinitely**—these are foundational long-term therapies

☐ **Sick day protocol** required—patients must hold during acute illness with volume depletion risk

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See Also

Related Student Handouts

- Cardiorenal Syndrome Overview
- GDMT: Four Pillars
- GLP-1 Receptor Agonists
- HFpEF: When Heart Failure is Kidney Disease
- Diabetic Kidney Disease
- CKD Complications

Clinical Content (01-Clinical-Medicine/Nephrology & Cardiology)

- Cardio-Renal Ecosystem Hub
- CKD Hub - Full Clinical Reference
- Hypertension Management

Atomic Notes (ZK)

- Cardiorenal Syndrome as Bidirectional Dysfunction

Butler-COM Resources

- Butler COM - Nephrology Deep Dive
- Butler COM - Heart Failure GDMT Deep Dive

Related Topics

- Cardiorenal Syndrome Overview
- GDMT: Four Pillars
- GLP-1 Receptor Agonists
- HFpEF: When Heart Failure is Kidney Disease

Clinical Resources

- Clinical Review: Comprehensive Sglt2 T1dm Report — Comprehensive clinical review with PubMed references
- Clinical Review: Sglt2 Edka Review — Comprehensive clinical review with PubMed references
- Clinical Review: Sglt2i Ckd Notes — Comprehensive clinical review with PubMed references