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<tr>
<th></th>
<th>Canagliflozin</th>
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<th>Empagliflozin</th>
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<td><strong>eGFR Cut-Off for Initiation</strong></td>
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SGLT“2” Good to be True?
Renal Outcomes of SGLT2 Inhibitors
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School of Pharmacy and Health Sciences

Disclosure
• The speaker has no conflicts of interest to disclose
• Non-FDA approved indications will be discussed

Learning Objectives
1. Outline current guidelines and the role of SGLT2 inhibitors in kidney disease
2. Review the literature regarding SGLT2 inhibitors and their place in patients with kidney disease
3. Define optimal patients to initiate on SGLT2 inhibitors

Chronic Kidney Disease
• Chronic kidney disease (CKD) defined as abnormalities of kidney structure or function for > 3 months
• Diabetes (DM) is the leading cause of kidney failure

SGLT2 Inhibitors
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Canagliflozin</th>
<th>Empagliflozin</th>
<th>Empagliotin*</th>
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<tbody>
<tr>
<td>HbA1c Reduction</td>
<td>0.5-1%</td>
<td>0.5-1%</td>
<td>0.5-1%</td>
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<tr>
<td>MDA</td>
<td>Inhibits SGLT2 in the proximal and renal tubules, thus reducing the reabsorption of filtered glucose</td>
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<tr>
<td>Side Effects</td>
<td>Risk of UTI, increased urination, dehydration</td>
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<tr>
<td>Notes</td>
<td>Previous FDA warning for canagliflozin which warned of higher risk of lower extremity amputations; Removed August 2020</td>
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Renal Protective Mechanism

- SGLT2 inhibitors reduce sodium reabsorption in the proximal tubule
- Causes afferent arteriole vasoconstriction
- Leads to a reduction in hyperfiltration

KDIGO 2020 Guideline for DM in CKD

- Most patients with type 2 diabetes, CKD, and eGFR > 30 ml/min/1.73m² would benefit from treatment with both metformin and an SGLT2 inhibitor
- Prioritize SGLT2 inhibitors with documented kidney or cardiovascular benefits
- A reversible decrease in eGFR with initiation of SGLT2 inhibitor treatment may occur and is not an indication to stop therapy
- It is reasonable to continue an SGLT2 inhibitor even if the eGFR falls below 30 ml/min/1.73m², unless renal replacement therapy is needed

Assessment Question #1

In patients with type 2 diabetes and CKD, the 2020 KDIGO guideline recommends:
A. starting an SGLT2 inhibitor in all patients regardless of eGFR
B. continuing an SGLT2 inhibitor even with a reversible decrease in eGFR
C. maintaining SGLT2 inhibitor therapy even if patients require dialysis
D. initiating any SGLT2 inhibitor for proposed renal benefits

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

| Inclusion | Type 2 diabetes and high cardiovascular risk, eGFR > 30 ml/min/1.73m² |
| Interventions | Canagliflozin 100 mg daily vs matching placebo |
| Renal Outcome(s) | - Progression of albuminuria |
| | - Composite renal outcome of 40% reduction in eGFR, need for renal replacement therapy (RRT), or death from renal causes |
| N | 10,142 |
| Results | - Less progression of albuminuria in canagliflozin group (HR 0.73, 95% CI 0.67-0.79) |
| | - Lower incidence of composite renal outcome in canagliflozin group (HR 0.60, 95% CI 0.47-0.77) |
| Conclusion | Patients treated with canagliflozin had a lower risk of progression of albuminuria and loss of kidney function versus placebo. Outcomes not viewed as significant on the basis of the prespecified testing sequence. |

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

| Objective | Assess the renal effects of canagliflozin in patients with type 2 diabetes |
| Design | Randomized, double-blind, placebo-controlled, multicenter trial |
| Inclusion | - Type 2 diabetes, CKD with eGFR 30 to 90 ml/min/1.73m² and albuminuria |
| | - Receiving angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) for >4 weeks |
| Intervention | Canagliflozin 100 mg daily vs matching placebo |
| N | 4,401 |
| Outcome(s) | Primary composite of end stage renal disease (ESRD), doubling of serum creatinine (SCr) from baseline, or death from renal or cardiovascular (CV) disease |

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

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| N | 4,401 |
| Outcome(s) | Primary composite of end stage renal disease (ESRD), doubling of serum creatinine (SCr) from baseline, or death from renal or cardiovascular (CV) disease |
Outcome Canagliflozin (N = 2202) Placebo (N = 2199) HR (95% CI)

Primary Composite, n 245 340 0.70 (0.59–0.82)
Doubling of SCr, n 118 188 0.60 (0.48–0.76)
ESRD, n 116 165 0.68 (0.54–0.86)
Renal Death, n 2 5 -

• Trial stopped early on a planned interim analysis
• 4,401 patients randomized with median follow-up 2.62 years
• Patients with type 2 diabetes and CKD who received canagliflozin had lower risk of primary composite outcome

Canagliflozin Dapagliflozin Empagliflozin

eGFR Cut-Off for Initiation ≥ 30
Dose 100 mg daily
Renal Benefits Lower risk of ESRD including need for HD, and increasing SCr
Use in Type 2 Diabetes Only? Yes

Dapagliflozin in Patients with Chronic Kidney Disease

Objective Assess the effect of dapagliflozin in patients with CKD, with or without type 2 diabetes
Design Randomized, double-blind, placebo-controlled, multicenter trial
Inclusion - Adults with or without type 2 diabetes and eGFR 25 to 75 ml/min/1.73m², and urine albumin-to-creatinine ratio of 200 to 5000 mg/g
- Receiving ACEI or ARB for >4 weeks
Intervention Dapagliflozin 10 mg daily vs matching placebo
N 4,304

Outcome(s) - Primary composite: first occurrence of 50% decline in eGFR, new ESRD, or death from renal or CV causes
- Secondary composite: same as primary composite sans death from CV causes

Primary Composite, n (N = 2152) Placebo, n (N = 2152) HR (95% CI)

197 (9.2) 312 (14.5) 0.61 (0.51–0.72)
142 (6.6) 243 (11.3) 0.56 (0.45–0.68)
100 (4.6) 138 (6.4) 0.71 (0.55–0.92)

• Event rates for all components of composite outcome favored dapagliflozin
• Number needed to treat for primary outcome = 19
DAPA-CKD

- Effect of dapagliflozin on primary outcome consistent across prespecified subgroups
- Renal benefit in CKD patients with or without type 2 diabetes
- Patients with CKD, regardless of type 2 diabetes, who received dapagliflozin had lower risk of primary composite outcome

<table>
<thead>
<tr>
<th>DAPA-CKD</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR Cut-Off for Initiation</td>
<td>≥ 30</td>
<td>≥ 25 (DAPA-CKD)</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>100 mg daily</td>
<td>10 mg daily</td>
<td></td>
</tr>
<tr>
<td>Renal Benefits</td>
<td>Lower risk of ESRD including need for HD and increasing SCr</td>
<td>Slower decline in eGFR, lower risk of new ESRD</td>
<td></td>
</tr>
<tr>
<td>Use in Type 2 Diabetes Only?</td>
<td>Yes</td>
<td>No (as per DAPA-CKD)</td>
<td></td>
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</table>

Literature

- Canagliflozin
- Dapagliflozin
- Empagliflozin

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

- Inclusion: Type 2 diabetes and established CV disease, eGFR ≥ 30 ml/min/1.73m²
- Intervention: Empagliflozin 10 mg or 25 mg daily vs matching placebo
- Outcome(s): Incident or worsening nephropathy (progression to macroalbuminuria, doubling of SCr and eGFR < 45, initiation of RRT, death from renal disease)
- N: 7,020
- Results:
  - Incident or worsening nephropathy: 12.7% empagliflozin vs 18.8% placebo (P < 0.001, HR 0.61, 95% CI 0.53–0.70)
- Conclusion: Patients with type 2 diabetes at high risk for CV events who received empagliflozin had a lower rate of incident or worsening nephropathy as compared to placebo. Various renal outcomes, including progression to macroalbuminuria, doubling of SCr, and initiation of RRT were also lower.

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

- Objective: Assess the effects of empagliflozin in patients with heart failure with reduced ejection fraction (HFrEF)
- Design: Randomized, double-blind, parallel-group, placebo-controlled trial
- Inclusion:
  - Heart failure with reduced ejection fraction and NYHA class II-IV on guideline directed medical therapy
  - Excluded if eGFR < 20 ml/min/1.73m²
- Intervention: Empagliflozin 10 mg daily vs matching placebo
- N: 3,730
- Outcome(s):
  - Decline in eGFR, ml/min/1.73m²
  - Renal Composite, n (%)
- Results:
  - Decline in eGFR: -0.55 ± 0.23 vs -2.28 ± 0.23 (P = 0.001, HR 1.73 (1.10–2.37))
  - Renal Composite: 30 (1.6%) vs 58 (3.1%) (P = 0.50 (0.32–0.77))
- Conclusion:
  - Empagliflozin slowed the rate of decline in the eGFR
  - Risk of composite renal outcome was lower in empagliflozin group
  - Not included in testing hierarchy
  - No prespecified subgroup analysis comparing diabetes vs no diabetes

- Empagliflozin (N = 1863)
- Placebo (N = 1867)
- HR (95% CI)
- Decline in eGFR, ml/min/1.73m²: -0.55 ± 0.23 vs -2.28 ± 0.23 (P = 0.001, HR 1.73 (1.10–2.37))
- Renal Composite, n (%): 30 (1.6%) vs 58 (3.1%) (P = 0.50 (0.32–0.77))

- Empagliflozin slowed the rate of decline in the eGFR
- Risk of composite renal outcome was lower in empagliflozin group
- Not included in testing hierarchy
- No prespecified subgroup analysis comparing diabetes vs no diabetes
Landmark trials regarding renal outcomes have demonstrated that all SGLT2 inhibitors:
A. Have the same eGFR cut off of ≥30 ml/min/1.73m²
B. Can be used in patients with or without type 2 diabetes
C. Have shown a slower decline in eGFR or doubling of Scr
D. Need to be titrated to their maximum and optimal dose

## Future Studies

### The Study of Heart and Kidney Protection with Empagliflozin

<table>
<thead>
<tr>
<th>EMPA-KIDNEY</th>
<th>REGROUP</th>
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<tbody>
<tr>
<td>Multicenter, international, randomized, double-blind, placebo-controlled trial</td>
<td>Single-center, prospective, placebo-controlled, double-blind, randomized, cross-over trial</td>
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<td>Objective: to assess cardio-renal outcomes in patients with CKD using empagliflozin once daily</td>
<td>Objective: to investigate the effect of empagliflozin on kidney function in people with preserved or impaired renal function with or without type 2 diabetes</td>
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<tr>
<td>Outcomes: measured eGFR</td>
<td>Outcomes: time to first occurrence of kidney disease progression or cardiovascular death</td>
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<td>Estimated study completion date: December 2022</td>
<td>Estimated study completion date: March 2022</td>
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### Renohemodynamic Effects Empagliflozin in Various Populations

- **EMPA-KIDNEY**
  - Multicenter, international, randomized, double-blind, placebo-controlled trial
  - Objective: to assess cardio-renal outcomes in patients with CKD using empagliflozin once daily
  - Outcomes: measured eGFR
  - Estimated study completion date: December 2022

- **REGROUP**
  - Single-center, prospective, placebo-controlled, double-blind, randomized, cross-over trial
  - Objective: to investigate the effect of empagliflozin on kidney function in people with preserved or impaired renal function with or without type 2 diabetes
  - Estimated study completion date: March 2022

### Assessment Question #2

#### Landmark trials regarding renal outcomes have demonstrated that all SGLT2 inhibitors:

- A. Have the same eGFR cut off of ≥30 ml/min/1.73m²
- B. Can be used in patients with or without type 2 diabetes
- C. Have shown a slower decline in eGFR or doubling of Scr
- D. Need to be titrated to their maximum and optimal dose

### FDA Approved Indications

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<td>• Type 2 DM with CV disease</td>
<td>• Type 2 DM</td>
</tr>
<tr>
<td>• Type 2 DM with CV disease</td>
<td>• Diabetic kidney disease</td>
<td>• Chronic kidney disease</td>
</tr>
<tr>
<td>• Diabetic kidney disease</td>
<td>• HFpEF</td>
<td>• HFrEF</td>
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### Who Should Receive an SGLT2 Inhibitor?

- **Assessment**
  - eGFR ≥ 60 ml/min/1.73m²
  - High priority features
    - UACR > 200 mg/dL
    - Heart failure
  - Potential Contraindications
    - Genital infection
    - Diabetic ketoacidosis
    - Foot ulcers
    - Immunosuppression

- **Intervention**
  - Low-dose SGLT2 inhibitor with proven benefits
    - Canagliflozin 100 mg
    - Dapagliflozin 10 mg
    - Empagliflozin 30 mg
  - Education
    - Sick day protocol
    - Perioperative care
    - Foot care

- **Follow-Up**
  - Assess adverse effects
  - Review knowledge
  - Anticipate an acute drop in eGFR, which is generally not a reason to stop the SGLT2 inhibitor

### Contraindications

- History of serious hypersensitivity reaction to drug
- Severe renal impairment, ESRD, or dialysis
- History of osteoporosis (canagliflozin)

### Citations

Hypoglycemia risk:
- Insulin or sulfonylurea
- History of severe hypoglycemia
- HbA1c at or below goal

Education:
- Hypoglycemia symptoms
- Glycemia monitoring
- Consider insulin/sulfonylurea dose reduction

Follow-Up:
- Ask about hypoglycemia
- Reduce sulfonylurea or insulin if needed

Volume depletion risk:
- Concurrent diuretic use
- Tenuous volume status
- History of acute kidney injury

Education:
- Volume depletion symptoms
- Consider diuretic dose reduction

Follow-Up:
- Re-assess volume
- Reduce concomitant diuretic if needed

Patient Case
A 69 YO M with PMH type 2 DM, HTN, HLD, OSA, and back pain was referred to your clinic for declining eGFR. He was diagnosed with DM 32 years prior to referral and developed retinopathy and nephropathy over time. Urine albumin-creatinine ratio initially elevated 10 years prior. eGFR has declined over the years.

Current Labs
- UACR 2291 mg/g
- eGFR 32 ml/min/1.73m²
- HbA1c 7.2%
- BP 132/68

Current Medications
- Metformin
- Losartan
- Glipizide
- Amlodipine
- Insulin
- HCTZ
- Spironolactone

Assessment Question #3
Should this patient be started on an SGLT2 inhibitor?
A. Yes, given their decline in eGFR and increase in UACR in the past years
B. No, their HbA1c is too close to goal which increases hypoglycemia risk
C. No, they take insulin and a sulfonylurea which increases hypoglycemia risk
D. No, their eGFR is too close to the guideline recommended cut off

Summary
Canagliflozin, dapagliflozin, and empagliflozin have shown renal benefit in patients with type 2 diabetes and CKD

Dapagliflozin has shown renal benefit in patients with CKD with or without type 2 diabetes

SGLT2 inhibitors should be started when eGFR > 30 ml/min/1.73m², and can be continued until patient requires renal replacement therapy

Monitor for hypoglycemia and volume depletion risk, especially if patient taking insulin, sulfonylurea, and/or diuretics concurrently

Special Acknowledgement:
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University of Chicago Medicine
Questions