SODIUM GLUCOSE CO-TRANSPORTER-2 INHIBITORS: RENAL HARM OR BENEFIT?

Chelsey Roscoe, PharmD
PGY2 Ambulatory Care Clinical Pharmacy Resident

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DISCLOSURES

- No conflicts of interest to disclose

OBJECTIVES

- Discuss Medication Use in T2DM
- Review Mechanism and Efficacy of SGLT-2 Inhibitors
- Understand Differences Between AKI, ATN, and CKD
- Evaluate Data Regarding Renal Effects of SGLT-2 Inhibitors
- Recite Patient Counseling Points for SGLT-2 Inhibitors

FDA WARNING REGARDING SGLT-2 INHIBITORS

- FDA received reports of 101 confirmable cases of acute kidney injury (AKI) from March 2013 – October 2015
- AKI occurred within 1 month of starting drug in 50% cases
- Some cases occurred in patients < 65 years of age
- Some patients dehydrated, low blood pressure, or taking other medications that can affect kidneys

FDA Recommendations: Before initiating canagliflozin or dapagliflozin, consider factors that may predispose patients to AKI

CASE REPORT: PLEROS, ET AL

50 y/o male with type 2 diabetes mellitus, hypertension, dyslipidemia
Presentation of fatigue, anorexia, nausea, non-oliguric AKI and anemia. Renal biopsy: ATN
Dialysis dependent for 4 weeks, currently CKD stage 3a

MEDICATION USE IN TYPE 2 DIABETES MELLITUS
**TYPE II DIABETES MELLITUS PATHOPHYSIOLOGY**

Hyperglycemia

- Insulin resistance
- Beta cell dysfunction
- Glucose production and release
- Peripheral glucose utilization

**TYPE II DIABETES MELLITUS MEDICATIONS**

**MECHANISM AND EFFICACY OF SGLT-2 INHIBITORS**

- SGLT-2 inhibitors decrease A1C by 0.5–1%
- SGLT-2 transporters reabsorb 90% of glucose in the body
- SGLT-1 transporters reabsorb 10% of the glucose
- Renal thresholds for glucosuria:
  - Normal, healthy: 180 mg/dL
  - Chronic hyperglycemia: 220–240 mg/dL
- SGLT2 transporters overexpressed in the kidney in patients with chronic hyperglycemia

**SODIUM GLUCOSE CO-TRANSPORTER UPREGULATION IN HYPERGLYCEMIA**

- SGLT2, a high-capacity, low-affinity ATP-dependent co-transporter located in the proximal renal tubular cells, reabsorbs 90% of glucose in the body
- SGLT1 co-transporters reabsorb 10% of the glucose
- Normal healthy: 180 mg/dL
- Chronic hyperglycemia: 220–240 mg/dL
- SGLT2 co-transporters overexpressed in the kidney in patients with chronic hyperglycemia

**SGLT-2 INHIBITORS DOSING RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Renal Dosing Recommendations</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>100mg-300mg once daily</td>
<td>eGFR 45-60: max dose 100mg once daily, eGFR 30-45: manufacturer dose not initiate</td>
<td>Hyperkalemia, gastrointestinal (GU) infections, AKI</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10-25mg once daily</td>
<td>eGFR 30-45: manufacturer recommends do not initiate therapy, may still have some benefit</td>
<td>Dyslipidemia, GU infections</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>5-10mg once daily</td>
<td>eGFR 30-45: manufacturer recommends do not initiate therapy</td>
<td>GU infection, increased urine output, dyslipidemia, AKI</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>5-15mg once daily</td>
<td>eGFR 30-45: do not initiate therapy or continue use</td>
<td>GU infection, headache, hypoglycemia, increased urine output</td>
</tr>
</tbody>
</table>
DISCUSS RENAL CONDITIONS

ACUTE KIDNEY INJURY (AKI) DEFINITION: KDIGO

Increase serum creatinine ≥ 0.3 mg/dL within 48 hours
Increase in serum creatinine by ≥ 1.5 times baseline in the prior 7 days

FACTORS THAT MAY PREDISPOSE PATIENTS TO AKI

- Hypovolemia
- Chronic renal insufficiency
- Congestive heart failure
- Concomitant medications - diuretics, ACE inhibitors, ARBs, NSAIDs
- Acute illness, decreased oral intake, or excessive heat exposure

SYMPTOMS OF AKI

- Oliguria or Anuria
- Edema
- Fatigue
- Shortness of Breath
- Confusion
- Nausea
- Chest Pain

ACUTE TUBULAR NECROSIS (ATN)

- Most common intrinsic (renal) cause of AKI
- Novel biomarkers: KIM-1, L-FABP, IL-18, urinary alpha one macroglobulin, beta-2 microglobulin

<table>
<thead>
<tr>
<th>Diagnostic Tests</th>
<th>Pre-renal AKI</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis</td>
<td>Normal, possible hyaline casts</td>
<td>Muddy brown casts or renal tubular epithelial cells</td>
</tr>
<tr>
<td>FENa</td>
<td>&lt; 1%</td>
<td>&gt; 2%</td>
</tr>
<tr>
<td>Urine Sodium Concentration</td>
<td>&lt; 20 mEq/L</td>
<td>40 – 50 mEq/L</td>
</tr>
</tbody>
</table>

CHRONIC KIDNEY DISEASE DEFINITION: KDIGO

- eGFR < 60 mL/min/1.73m² with duration > 3 months
- Markers of kidney damage: UACR ≥ 30, urine sediment or structural abnormalities

Markers of kidney damage: UACR ≥ 30, urine sediment or structural abnormalities
CLINICAL PEARLS FOR PATIENTS WITH CKD

- Type 2 diabetes with A1c > 7% can lead to progression of CKD
- Many medications are eliminated via renal route and may need dose adjustment based on CKD stage
- Counsel patients to contact clinic if acute illness
- Consider temporary discontinuation of potentially nephrotoxic drugs in patients with eGFR < 60 with serious intercurrent illness that increases AKI risk

DATA REGARDING RENAL EFFECTS OF SGLT-2 INHIBITORS

RENAL STUDIES REVIEW

AKI Risk w/ SGLT2 Inhibitors

- AKI in SGLT2 Inhibitors: Nadkarni, et al

CKD benefits in RCTs

- CREDENCE: Perkovic, et al
- DECLARE-TIMI 85: Wiviott, et al

AKI IN SGLT2 INHIBITORS: NADKARNI, ET AL

Table 3—AKI outcomes in the SGLT2 inhibitor user and nonuser groups in the Mount Sinai and Geisinger propensity-matched cohorts

<table>
<thead>
<tr>
<th></th>
<th>User</th>
<th>Nonuser</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI events</td>
<td>22 (5.4)</td>
<td>18 (4.3)</td>
<td>0.49</td>
</tr>
<tr>
<td>Change in serum creatinine during AKI</td>
<td>+0.08 (0.24)</td>
<td>+0.06 (0.20)</td>
<td>0.16</td>
</tr>
<tr>
<td>Need for acute dialysis</td>
<td>1 (2.3%)</td>
<td>0 (0.0%)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Conclusions

- No increased risk of AKI in real-life SGLT2 inhibitor use before and after propensity matching over 1 year of follow-up in two large health systems
- AKI severity not worse in SGLT2 inhibitor patients vs dapagliflozin/canagliflozin vs empagliflozin

Strengths/ Limitations

- Patients generally well-matched within cohort arms, sensitivity analysis verified results
- Retrospective study
- Small empagliflozin representation within cohort
**CREDENCE: PERKOVIC, ET AL**

**Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy: CREDENCE**

**Methods**
- Double-blind randomized controlled clinical trial, multicenter (495 sites, 34 countries)
- Intervention: canagliflozin 100mg vs placebo, randomized 1:1
- Inclusion: ≥ 30 years of age w/ T2DM, CKD w/ eGFR ≥ 30 to <90, UACR >300 – 5000 mg/g

**Objectives**
- Composite of ESKD, doubling Scr level from baseline for at least 30 days or death from renal or CVD
- Composite of ESKD, doubling Scr or renal death

**Baseline**
- Age ~ 63 y/o, duration diabetes ~ 16 years, eGFR ~ 56

**Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin n=2202</th>
<th>Placebo n=2199</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD, 2X Scr, renal/CVD death</td>
<td>43.2*</td>
<td>61.2*</td>
<td>0.7</td>
<td>0.59-0.82</td>
<td>0.00001</td>
</tr>
<tr>
<td>ESRD, 2X Scr renal death</td>
<td>27*</td>
<td>40.4*</td>
<td>0.66</td>
<td>0.53-0.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>29.7*</td>
<td>36.9*</td>
<td>0.8</td>
<td>0.65-1.01</td>
<td>N/A</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>16.9*</td>
<td>20*</td>
<td>0.85</td>
<td>0.64-1.13</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Events per 1000 patient years

**Conclusions**
- Patients treated with canagliflozin had lower risk of composite outcome of ESKD, doubling of Scr level, or death from renal or cardiovascular causes than those receiving placebo.

**Strengths/Limitations**
- Large, multicenter double-blind randomized trial, stratified based on eGFR, concomitant diabetes medication classes and comorbidities
- Included patients w/ pre-existing CKD and albuminuria at high risk for AKI
- No active comparator
- Unclear specific agents or dosing of concurrent diabetes drugs used within the study

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**DECLARE-TIMI 58: WIVIOTT, ET AL**

**Dapagliflozin and Cardiovacular Outcomes in Type 2 Diabetes: DECLARE-TIMI 58**

**Methods**
- Randomized double-blind placebo controlled phase 3 trial of dapagliflozin in patients with type 2 diabetes and ASCVD disease or multiple risk factors for ASCVD disease
- Included patients ≥ 40 years of age w/ type 2 diabetes, eGFR ≥ 60
- Dapagliflozin 10mg vs placebo, 1:1 ratio

**Objectives**
- Primary outcome: MACE
- Secondary outcomes: ≥ 40% decrease in eGFR to <60, ESRD or death from renal or cardiovascular cause

**Baseline**
- Mean duration diabetes ~ 11 years, mean eGFR 85, 10% patients had history of HF, similar ACEI/ARBs and diabetes classes between study arms

**Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin n=8582</th>
<th>Placebo n=8578</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>22.6*</td>
<td>24.2*</td>
<td>0.93</td>
<td>0.84 - 1.03</td>
<td>0.17</td>
</tr>
<tr>
<td>≥ 40% decrease in eGFR to &lt;60, ESRD or death from renal or CV cause</td>
<td>10.8*</td>
<td>14.1*</td>
<td>0.76</td>
<td>0.67 - 0.87</td>
<td>N/A</td>
</tr>
<tr>
<td>≥ 40% decrease in eGFR to &lt;45, ESRD or death from renal cause</td>
<td>3.7*</td>
<td>7.0*</td>
<td>0.53</td>
<td>0.43 - 0.66</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Events per 1000 patient years

**Conclusions**
- Dapagliflozin was non-inferior to placebo in primary safety outcome of MACE
- Findings support a possible lower rate of adverse renal outcomes

**Strengths/Limitations**
- Large randomized controlled trial
- Randomized based on alternative diabetes therapy presence of ACEI/ARB within study arm
- No active comparator
- Trial not powered to look at renal events
- Low event rate within groups likely due to short follow-up 4.2 years
SUMMARY OF STUDIES

- AKI in SGLT2 inhibitors: Nadkarni, et al
  - No increased risk of AKI with SGLT2 inhibitors in real world setting
- CREDENCE: Perkovic, et al
  - Lower risk of composite outcome of ESKD, doubling of Scr level, or death from renal or cardiovascular causes with canagliflozin vs placebo
  - Trend toward decreased risk AKI in canagliflozin vs placebo
- DECLARE-TIMI 58: Wiviott, et al
  - Possible lower rate of adverse renal outcomes with dapagliflozin vs placebo

FUTURE STUDIES FOR RENAL OUTCOMES WITH SGLT2 INHIBITORS

- DAPA – CKD (2020)
- EMPA – KIDNEY (2022)

RECIPE PATIENT COUNSELING POINTS FOR SGLT2 INHIBITORS

- Avoid SGLT2 Inhibitors in patients with eGFR < 30 – treatment likely ineffective
- Consider avoiding SGLT2 inhibitors in frail, elderly patients
- Counsel patients to stay hydrated during therapy, especially on initiation
- Counsel patients to contact clinic if acute illness
- Consider temporary discontinuation of SGLT2 inhibitors in patients w/ eGFR < 60 with serious intercurrent illness that increases AKI risk
- Educate on signs and symptoms of AKI with ER precautions

FDA WARNINGS REGARDING SGLT2 INHIBITORS

- FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)
- FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density
- FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections
- FDA Drug Safety Communication: FDA issues alert about potential link between SGLT2 inhibitors and diabetic acidosis

PREVENTION OF OTHER ADVERSE EFFECTS WITH SGLT2 INHIBITORS

- Consider avoiding use in patients with past history of:
  - Amputation from diabetes mellitus
  - Current diabetic foot ulcer
  - Osteoporosis or bone fracture
  - DKA
  - Frequent genitourinary infections
SGLT2 INHIBITOR COUNSELING

- Careful selection of patients will avoid many adverse events associated w/ SGLT2 Inhibitors
- Educate patients thoroughly regarding risks and benefits of treatment
- Benefits include possible delay/prevention of CKD, weight loss, blood pressure reduction, in addition to blood glucose lowering

PATIENT CASE 1, PART 1:

A 54 y/o Caucasian patient w/ PMH of T2DM, hypertension, smoking, and hyperlipidemia presents to your clinic on metformin ER 500mg – 4 tablets once daily, lisinopril 40mg daily. Patient does not want to start injectable therapy due to fear of needles. Lab values:

- Wt: 298 lbs (BMI 45)
- HgA1c: 8.5%
- eGFR 59
- BP: 145/89 (5 minute recheck 148/92)
- Last lipid panel: TC 145, LDL 89, HDL 35, Trig 146
- Calculated 10 yr ASCVD risk – 16.4%

What is the next step for therapy in this patient?

A. Exenatide ER inject 2mg weekly
B. Pioglitazone 15mg by mouth daily
C. Canagliflozin 100mg by mouth daily
D. Glimepiride 2mg by mouth daily

PATIENT CASE 1, PART 2:

The 54 y/o caucasian F patient from previous part 1 of question started canagliflozin at the last visit as instructed but misses your next clinical pharmacy appointment a month later due to N/V and diarrhea, reports she has not had an appetite. What would you tell this patient?

A. “How dare you miss my appointment?”
B. “Please stay hydrated and call to make another appointment when you are feeling better”
C. “Please make sure you take all of your medications since your blood sugars will be higher when you are sick, stay hydrated, and call to make an appointment when you are better”
D. “Please hold canagliflozin until you are able to eat again, check your sugars frequently if blood sugars >150 restart canagliflozin, stay hydrated, and call to make an appointment when you feel better”

ACKNOWLEDGEMENTS

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RESOURCES

- StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-

QUESTIONS?

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