Potential Protective Effects of SGLT2 Inhibitors on Kidney Function

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At the end of this presentation, pharmacy technicians should be able to:

1. Describe the role of kidneys in the regulation of glucose.
2. Explain the unique mechanism of action of SGLT2 inhibitors.
3. Recall safety and monitoring parameters (including contraindications) for SGLT2 inhibitors.
Pharmacist Objectives

At the end of this presentation, pharmacists should be able to:

1. Relate the potential benefits of SGLT2 inhibitors to their mechanism of action.

2. Discuss the potential benefits to using SGLT2 inhibitors in patients with impaired kidney function.

3. Differentiate between patients who would be likely to benefit from the use of SGLT2 inhibitors vs. those who would likely not.
DISCLOSURES:

▷ I have no conflicts of interest to disclose for this presentation.
SGLT2 Inhibitors: Place in Therapy

Let’s look at how well SGLT2 inhibitors work.
Diabetes and Glucose Homeostasis

- **Hypoglycemia**
  - Cognitive impairment
  - Arrhythmias
  - Seizures
  - Heart attack
  - Brain death

- **Hyperglycemia**
  - Cardiovascular disease
  - Retinopathy
  - Neuropathy
  - Nephropathy
  - Acidosis

- **Euglycemia**
Roles of the Kidney in Glucose Homeostasis

Production through gluconeogenesis

Utilization of circulating glucose

Reabsorption at proximal tubule

Movement of Glucose from Blood to Urine

In type 2 DM, increased reabsorption of glucose contributes to existing hyperglycemia.

SGLT2 is responsible for 90% of glucose reabsorption.

Inhibition of SGLT2 will attenuate glucose reabsorption and increase urinary excretion.
Potential Benefits and Risks of SGLT2 inhibitors

**Risks**
- Vaginitis, balanitis
- Hypovolemia symptoms
- Polyuria
- Hyperkalemia
- Increased LDL

**Benefits**
- Weight loss
- HbA$_{1c}$ lowering
- Improved beta cell function
- Reduced blood pressure
- Kidney protection?
The Stakes

Why do we want to expand the use of SGLT2 inhibitors?
Reduced Kidney Function Reduces Treatment Options

SGLT2 inhibitors – The Bad News

- Clinical trials noted risk of AKI under certain conditions
- A 2016 analysis of FAERS researched ≈19,000 cases over ≈3 ½ -years
- Associated with 1224 AKI events
- Proportion of AKI was ≈3x higher than patients who had not received SGLT2 inhibition

Rates of AKI:
- Canagliflozin (Invokana®): 7.3%
- Dapagliflozin (Farxiga®): 4.8%
- Empagliflozin (Jardiance®): 4.7%
“SGLT2 Inhibitors CAUSE Kidney Injury!”

Some unfortunate evidence.
“SGLT2 inhibitors CAUSE AKI!”

It’s true, SGLT2 inhibitors do:
• Increase diuresis
  o Can lead to volume depletion
• Decrease trans-glomerular pressure
  o Reduces glomerular filtration
• Increase oxygen consumption in renal medulla
  o Increases risk for hypoxia

June 14\textsuperscript{th}, 2016: the U.S. Food and Drug Administration strengthens existing AKI warnings for canagliflozin and dapagliflozin after an evaluation of cases from March 2013 through October 2015.
“SGLT2 inhibitors CAUSE AKI!”

1: Uric Acid Crystal Deposition
2: Uric Acid-Induced Pro-Inflammatory Effects and Oxidative Stress
3: Fructokinase-Induced Chemokines and Oxidative Stress
4: Medullary Hypoxia

Adapted from Saly, et al. Am J Physiol Renal Physiol. 2017;F952, Fig. 1.
“SGLT2 inhibitors CAUSE AKI?”

Urine Microscopy
- RBCs, RBC casts
  - Glomerular injury
- WBCs, Ø bacteria
  - Interstitial inflammation
- Crystals
  - Crystalline nephropathy

Novel Biomarkers
- KIM-1
- Albumin
- Total protein
- β2 microglobulin
- Cystatin C
- Clusterin
- Trefoil factor 3

Emerging Technology
- Kidney-on-a-chip
- Give an *in-vitro* model using harvested renal cells
- May help predict renal toxicity and the mechanism by which it occurs
Dr. Heyman, et al. published an article encouraging caution for SGLT2 inhibition in patients due to potential hypoxic renal injury

- Diabetes itself leads to renal medullary hypoxia.
- Medullary hypoxia evokes stress response which predisposes patients to tubular injury.
- Inhibition of SGLT2 transporter increases medullary hypoxia.
- Increased reticulocytosis and erythropoiesis in patients taking SGLT2 inhibitors indicates that renal oxygenation drops.
“SGLT2 Inhibitors PROTECT Kidneys!”

An examination of further evidence.
“SGLT2 inhibitors PROTECT the kidney!”

Cherney, Perkins, et al., Circulation (2014)

Aim:
Determine the effect of SGLT2 inhibition on renal hyperfiltration in subjects with type 1 diabetes mellitus, comparing empagliflozin 25 mg daily with placebo
“SGLT2 inhibitors PROTECT the kidney!”

Methods:

• Measured inulin
  • More accurate GFR measurement than creatinine

• Measured p-aminohippurate
  • Measures effective renal plasma flow

• Patients stratified
  • Known hyperfiltration (GFR ≥ 135 mL/min/1.73m², n=27)
  • Normal GFR (GFR 90–134 mL/min/1.73m², n=13)

• Renal function and circulating levels of RAAS mediators + NO were measured under euglycemic and hyperglycemic conditions
Results:

• Hyperfiltration arm: −33 mL/min/1.73m$^2$, p<0.01
  • Accompanied by declines in plasma NO and effective renal plasma flow and an increase in renal vascular resistance (all P<0.01).
• Normal GFR arm: GFR, other renal function parameters, and plasma NO were not altered
• Empagliflozin reduced hemoglobin A1c significantly in both groups, despite lower insulin doses in each group (P ≤ 0.04).

“SGLT2 inhibitors PROTECT the kidney!”
“SGLT2 inhibitors PROTECT the kidney!”

Conclusion:
Short-term treatment with empagliflozin attenuated renal hyperfiltration in subjects with T1D by affecting tubular-glomerular feedback mechanisms.

Diabetic nephropathy cannot be stopped once established – but progress can be slowed!


• Inconsistencies in kidney behavior after longer periods of SGLT2 inhibition
• SGLT2 transporter protein contributes to glomerular hyperfiltration
• Lower rates of CV events when on SGLT2 inhibitors, and lower rates of albuminuria in both type I and type II
“SGLT2 inhibitors PROTECT the kidney!”

Cherney, Perkins, et al., *Diabetologia*
SGLT2 inhibition reduces:

- HbA$_1c$
- Systolic BP
- Weight
- Renal Hyperfiltration

Hypothesis - lowering these factors is associated with anti-albuminuric effects in diabetes.

Therefore, **SGLT2 inhibition should lower the urine albumin/creatinine ratio (UACR)** to a clinically meaningful extent.
“SGLT2 inhibitors PROTECT the kidney!”
After controlling for clinical confounders (baseline UACR, HBA$_{1c}$, SBP, baseline GFR), treatment with empagliflozin reduced UACR in both sets of patients:

- Microalbuminuria (n=636): -32% vs. placebo
- Macroalbuminuria (n=215): -41% vs. placebo

“SGLT2 inhibitors PROTECT the kidney!”
“SGLT2 inhibitors PROTECT the kidney!”

In regression models, most of the UACR-lowering effect was not explained by SGLT2 inhibition-related improvements in $A_{1c}$, SBP or weight.
Summary

- Glucose and blood pressure control are both important in managing patients with diabetes - less than 20% of patients are in goal ranges for both.
- Decreasing glucose reuptake in the kidney is an effective mechanism for managing:
  - A$_{1c}$
  - Blood pressure
- Major adverse effect is increased risk of genital infection
- May protect already injured kidneys from further injury
References


References


Questions?