4-2019

Sodium Glucose Co-transporters Inhibition and Diabetic Kidney Disease

Radica Alicic
Providence St. Joseph Health, radica.alicic@providence.org

Follow this and additional works at: https://digitalcommons.psjhealth.org/other_pubs

Part of the Endocrinology, Diabetes, and Metabolism Commons

Recommended Citation
https://digitalcommons.psjhealth.org/other_pubs/86

This Presentation is brought to you for free and open access by Providence St. Joseph Health Digital Commons. It has been accepted for inclusion in Books, Presentations, Posters, Etc. by an authorized administrator of Providence St. Joseph Health Digital Commons. For more information, please contact digitalcommons@providence.org.
SGLT inhibition and Diabetic Kidney Disease
Radica Alicic, MD, FHM, FACP
Associated Professor of Medicine
University of Washington School of Medicine
Providence Health Care, Spokane, Washington
WADE Conference April 27, 2019

Disclosure to Participants

Notice of Requirements for Successful Completion: For successful completion, participants are required to be in attendance in the full activity and complete the program evaluation at the conclusion of the educational event.

Presenter Conflicts of Interest/Financial Relationships Disclosures:
No conflicts exist.

Disclosure of Relevant Financial Relationships and Mechanism to Identify and Resolve Conflicts of Interest:
No conflicts of interest.

Non-Endorsement of Products: Accredited status does not imply endorsement by AADE, ANCC, ACPE or CDR of any commercial products displayed in conjunction with this educational activity.

Off-label Use: Participants will be notified by speakers to any product used for a purpose other than that for which it was approved by the Food and Drug Administration.

Outline

• Diabetic kidney disease epidemiology
• Role of the kidney in glucose homeostasis
• Sodium glucose cotransporters (SGLT)
• Review of the kidney outcomes in Cardiovascular Outcomes Trials (CVOT)
• Overview of CREDENCE
• Field guide for use of SGLT-2 inhibitors circa mid-2019
• Future of SLGTs inhibitors
Diabetic Kidney Disease (DKD)

- A persistent elevated urinary albumin excretion (UAE) ≥30 mg/g, a persistent reduction in estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m², or both
- Epidemiological data show that about 30% of patients with DM 1, and about 40% of DM 2 patients have DKD
- Post-mortem human studies show that up to 60% of diabetic patients have structural changes of DKD
Diabetic Kidney Disease (DKD)

- World wide leading cause of ESKD (in US about 44% of all dialysis patients have diabetes)
- ESKD and need for KRT = death sentence in large part of the world
- The global number of deaths attributed to DKD rose by 94% between 1990-2012

Mortality and Morbidity of DKD Patients

- The prevalence of cardiovascular (CV) disease: 70% among patients aged 66 and older who have CKD compared with 35% among those who don’t have CKD
- Diabetic patients with ESKD have 10 to 100-fold higher mortality risk
- Most of the excess all-cause and CV death risk in diabetes is attributable to the presence of diabetic kidney disease

References:
- United States Renal Data System; www.usrds.org
Mortality Rates

Prevalence of Diabetic Kidney Disease is Increasing Despite Contemporary Management

Kidneys and Glucose Homeostasis

Physiologic conditions
- Gluconeogenesis (20%-25%)
- Reabsorption of glucose in the kidney (160-180 g/d)
- Uptake of glucose from the circulation (10%)

In diabetes
- ↑Postabsorptive gluconeogenesis
- ↓Reabsorption of glucose in the kidney
Renal Threshold for Glucose Excretion

- **RT** = renal threshold.
- Adapted from Alicic et al., Diabetes 2019; 68: 248-257.

---

**Sodium-glucose co-transporter-2 (SGL-T2)**
- Sodium-glucose co-transporter-1 (SGL-T1)
- Sodium (Na)
- Chloride (Cl)
- Glucose

**PGC** = pressure in glomerular capillary

Adapted from Alicic et al., Diabetes 2019; 68: 248-257.
Sodium Glucose Co-Transporters 1 and 2
SGLT-1 and SGLT-2

- Under normoglycemia the kidneys reabsorb all of the glucose from the glomerular filtrate
- Energy saving measure
- SGLT-2 is expressed in the proximal, SGLT-1 in the distal tubule

~ 90% of glucose is reabsorbed via SGLT-2
~ 10% via SGLT-1

U.S. Approved and Approval-Pending SGLT2 and SGLT1 And SGLT2 Inhibitors

- canagliflozin (Invokana) – March 2013
- dapagliflozin (Farxiga) – January 2014
- empagliflozin (Jardiance) – August 2014
- ertugliflozin (Steglatro) – 2017
- sotagliflozin (Zynquista) – pending

Metabolic Effects of SGLT-2 Inhibition

- Glucose loss of 70-80 g/day
- Weight loss
- Natriuresis and osmouresis with contraction of plasma volume and increase in hematocrit and albumin
- Reduction in BP
- Reduction in uric acid level
- Concerns of diabetic ketoacidosis
- Concerns of AKI and hyperkalemia


Mazidi M et al. J Am Heart Assoc. 2017;6:e004007
CardioVascular Outcomes (CVO) Trials

• Since December 2008, the U.S. FDA requires that the cardiovascular (CV) safety of all new drugs for diabetes be demonstrated to exclude an unacceptable increased relative CV risk
• Non-inferiority trials to extend minimum 2 years and enroll a more vulnerable population with DM2
• Higher CV risk are “patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment”

Hirshberg B et al., Diabetes Care 2011; 34: 101-106
**Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG)**

- 7,020 DM2 participants
- 10mg, 25 mg of empagliflozin or placebo (1:1:1 fashion)
- Mean age 63 yrs.
- Follow up: 3 years
- DM2 dx > 10 years
- H/O MI (high CV risk)
- eGFR > 30 ml/min/1.73m²

**Canagliflozin Cardiovascular Assessment Study (CANVAS) Program**

- 10,142 DM2 participants
- Canagliflozin vs. placebo
- Mean age 63 yrs.
- Follow-up: 2.4 years
- DM2 dx > 10 yrs.
- High CV risk
- eGFR > 30ml/min/1.73m²

---

**Cardiovascular Outcomes and Death from Any Cause**

**EMPA - REG**

**EMPA-REG Sub-group Analysis**

Kidney Outcomes in Patients with DKD

- 2,000 participant had DKD: 26% had an eGFR between 30-60 ml/min/1.73 m², and close to 40% of participants had albuminuria (29% with microalbuminuria and 11% with macroalbuminuria)
- Subgroup analyses of participants with eGFR <60 ml/min/1.73 m² or macroalbuminuria

---

Key Kidney Outcomes in EMPA-REG

- Doubling of SCR: 44% relative risk reduction (1.5% vs. 2.6%)  
- Progression to macroalbuminuria: 38% relative risk reduction
- Initiation of RRT: 55% relative risk reduction
- Slowing GFR decline: $0.19 \pm 0.11$ vs. $1.67 \pm 0.13$ ml/min/1.73 m² per year, $P < 0.001$)

Cardiovascular Outcomes in the Integrated CANVAS Program.

- Hospitalization for Heart Failure: 33% relative risk reduction
- Progression of albuminuria: 27% relative risk reduction
- Composite kidney outcome (40% reduction in eGFR, RRT, Death from kidney causes): 40% relative risk reduction

Effects of Canagliflozin on Cardiovascular, Kidney, Hospitalization, and Death Events in the Integrated CANVAS Program.