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

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# DISCLOSURES

- No conflicts of interest to disclose

# ABBREVIATIONS

- **T2DM**: Type 2 Diabetes Mellitus
- **SGLT-2 I**: Sodium Glucose Co-transporter-2 Inhibitors
- **GLP-1 Agonists** – Glucagon-like Peptide-1 Receptor Agonist
- **TZDs** – Thiazolidinediones
- **ACE** – Angiotensin-Converting Enzyme
- **ARB** – Angiotensin Receptor Blocker
- **NSAIDs** – Non-steroidal Anti-inflammatory
- **ER** – Emergency Room
- **ESKD** – End Stage Kidney Disease
- **ESRD** – End Stage Renal Disease
- **y/o** – Year-Old
- **Scr** – Serum Creatinine
- **s/s** – Signs/Symptoms
- **h/o** – History of
- **d/t** – Due to
- **MACE** – Major Adverse Cardiovascular Events
- **AKI** – Acute Kidney Injury
- **ATN** – Acute Tubular Necrosis
- **UACR** – Urine Albumin Creatinine Ratio
- **AA** – African American
- **eGFR** – Estimated Glomerular Filtration
- **CV** – Cardiovascular
- **PMH** – Past Medical History

# PHARMACIST OBJECTIVES

- Evaluate data regarding renal effects of sodium glucose transporter-2 (SGLT-2) inhibitors
- Identify high risk patient populations for acute kidney injury (AKI) on SGLT-2 inhibitors
- Assess patient populations that may benefit from addition of SGLT-2 inhibitors
- Recite patient counseling points for SGLT-2 inhibitors

# PHARMACY TECHNICIAN OBJECTIVES

- Give examples of medications within the SGLT-2 inhibitor drug class
- State the mechanism of action of SGLT-2 inhibitors
- Identify signs/symptoms of acute kidney injury (AKI)

# FDA WARNING REGARDING SGLT-2 INHIBITORS

**FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)**

- 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**



*www.fda.gov/drugs/drugs-safety-and-availability*

# 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



*CEN Case Rep. 2018; 7:17-20*

# MEDICATION USE IN TYPE 2 DIABETES MELLITUS

# TYPE II DIABETES MELLITUS PATHOPHYSIOLOGY

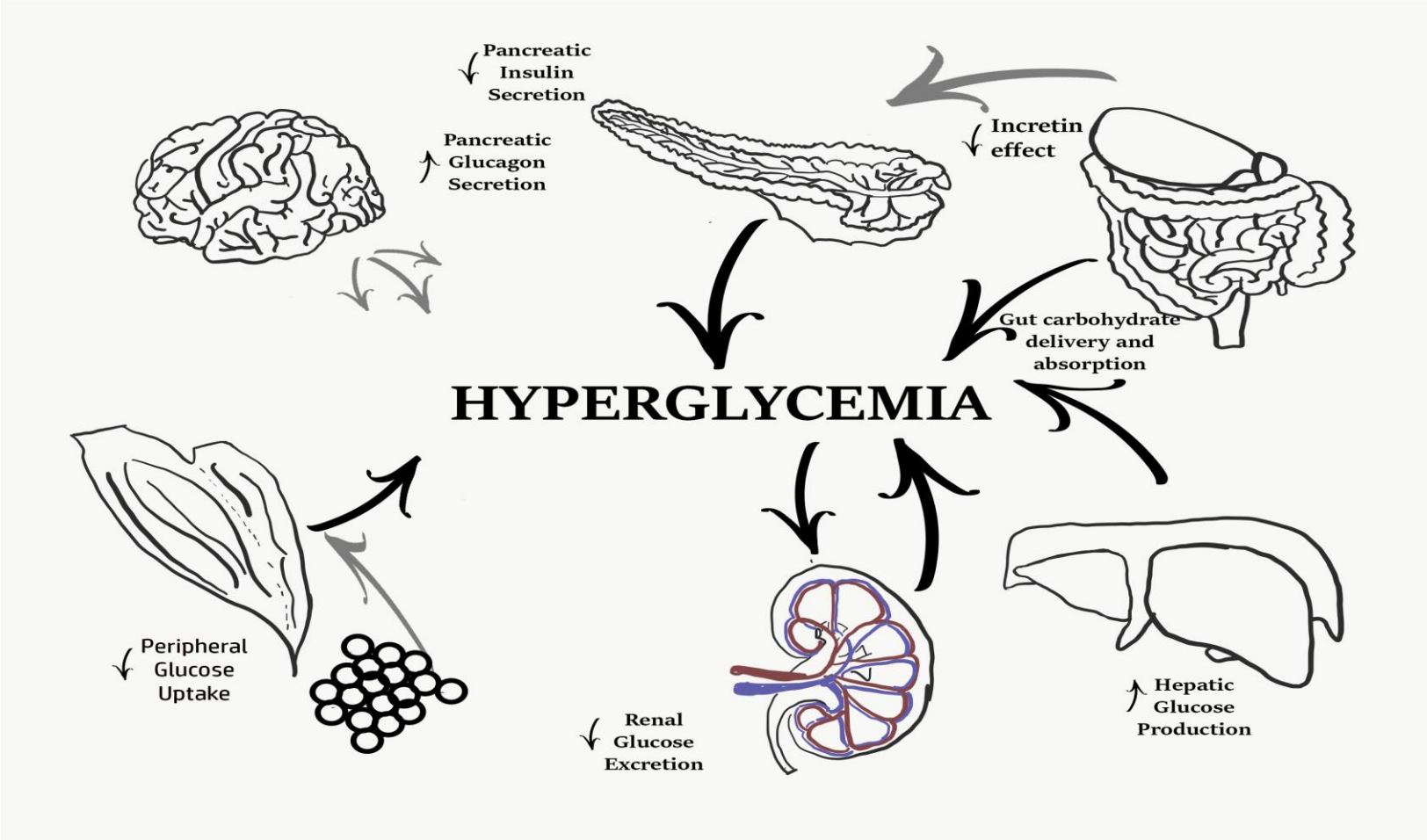





*Image by: Cassie Schornack, CPhT*

# TYPE II DIABETES MELLITUS PATHOPHYSIOLOGY

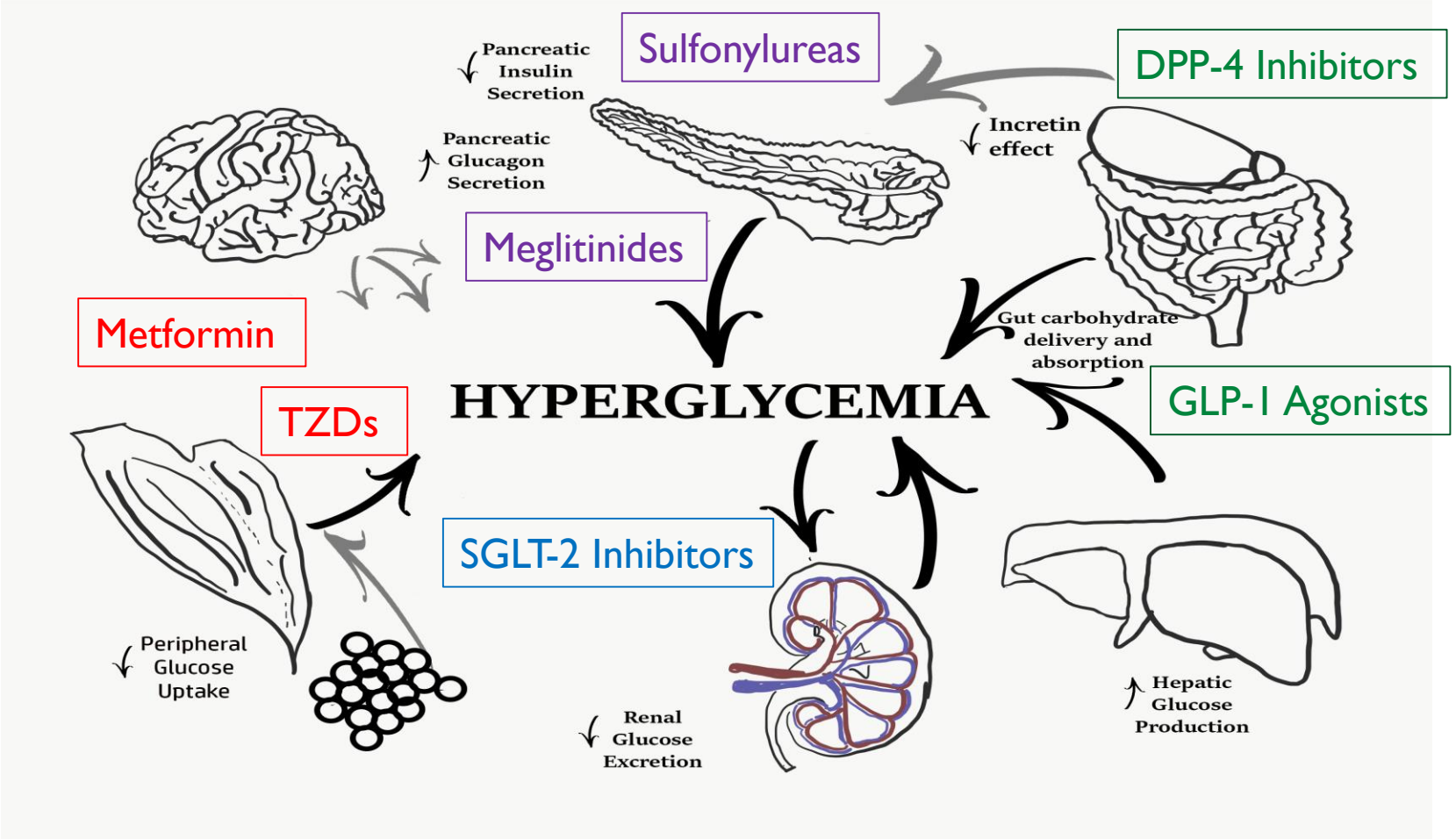


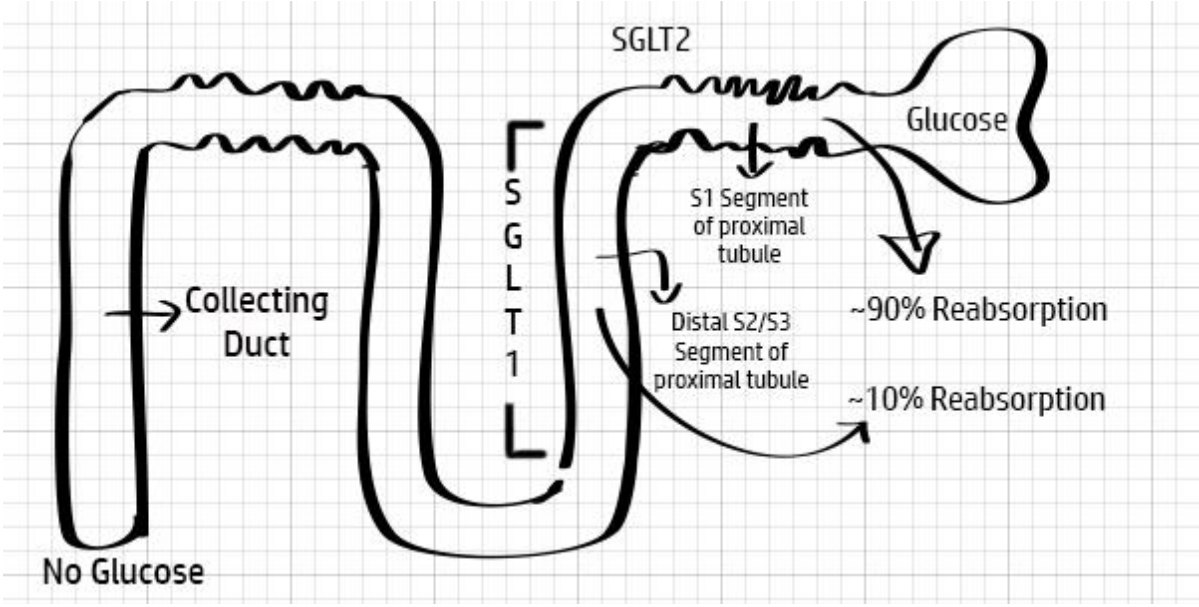



*Image by: Cassie Schornack, CPhT*

# MECHANISM AND EFFICACY OF SGLT-2 INHIBITORS

# SODIUM GLUCOSE CO-TRANSPORTER UPREGULATION IN HYPERGLYCEMIA

- SGLT-2, a high capacity, low affinity ATP-dependent co-transporter located in the proximal renal tubular cells, reabsorbs 90% glucose in body
- SGLT-1 co-transporters reabsorb 10% of the glucose
- Renal thresholds for glucosuria:
  - Normal, healthy – 180 mg/dL
  - Chronic hyperglycemia – 220-240 mg/dL
- SGLT2 co-transporters overexpressed in the kidney in patients with chronic hyperglycemia

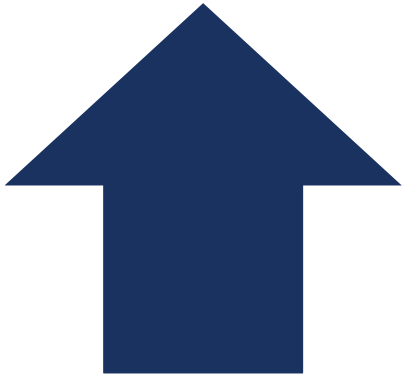





*Pharmacotherapy: A Pathophysiologic Approach, 10e* New York, NY: McGraw-Hill

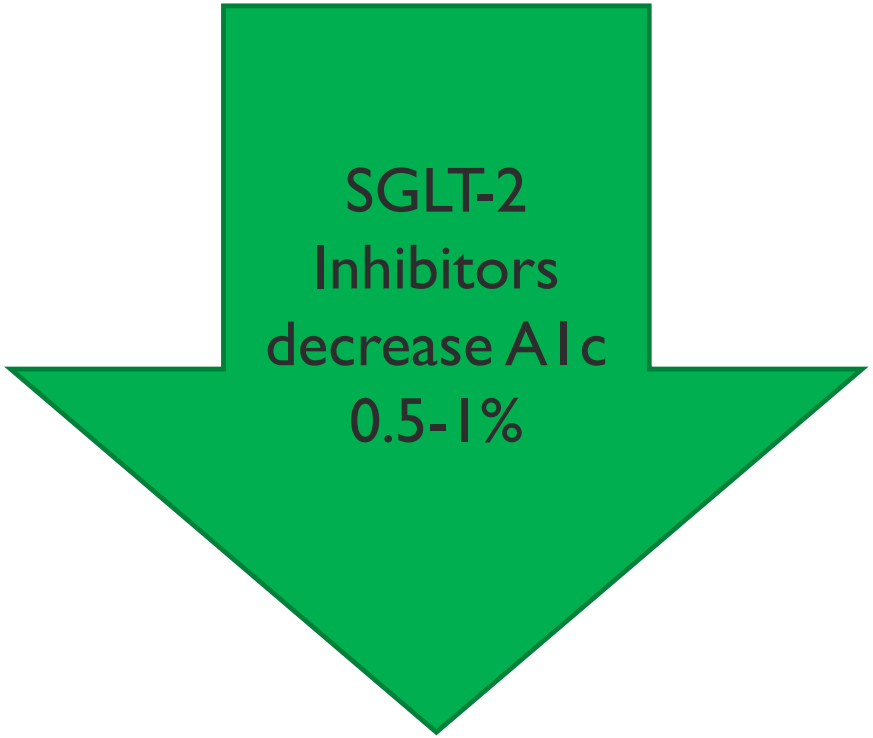
*Image by: Cassie Schornack, CPhT*

# MECHANISM AND EFFICACY OF SGLT2-INHIBITORS



SGLT-1 transporters reabsorb 30-40% glucose load

Inhibition of SGLT-2 co-transporters lowers the renal threshold for glucose reabsorption






*Pharmacotherapy: A Pathophysiologic Approach, 10e* New York, NY: McGraw-Hill

# SGLT-2 INHIBITORS DOSING RECOMMENDATIONS

| Agent | Dosing | Renal Dosing Recommendations | Adverse Effects |
|---|---|---|---|
| Canagliflozin | 100mg-300mg once daily | eGFR 45 - 60: max dose 100mg once daily<br>eGFR 30 - 45 manufacturer - do not initiate | Hyperkalemia, genitourinary (GU) infections, AKI |
| Empagliflozin | 10-25mg once daily | eGFR 30 – 45: manufacturer recommends do not initiate therapy, however may still have some benefit | Dyslipidemia, GU infections |
| Dapagliflozin | 5-10mg once daily | eGFR 30 – 45: do not initiate therapy | GU infection, increased urine output, dyslipidemia, AKI |
| Ertugliflozin | 5-15 mg once daily | eGFR 30 – 60: do not initiate therapy or continue use | GU infection, headache, hypoglycemia, increased urine output |



*(Lexi-Drugs). Wolters Kluwer Clinical Drug Information, Inc.; September 13, 2019.*

# 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



*Diabetes Care. 2017; 40: 1479-1485*

# 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



*www.fda.gov/drugs/drugs-safety-and-availability*

# SYMPTOMS OF AKI

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



*Diabetes Care. 2017; 40: 1479-1485*

# 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

| Diagnostic Tests | Pre-renal AKI | ATN |
|---|---|---|
| Urinalysis | Normal, possible hyaline casts | Muddy brown casts or renal tubular epithelial cells |
| FENa | < 1% | > 2% |
| Urine Sodium Concentration | < 20 mEq/L | 40 – 50 mEq/L |



*StatPearls Publishing; 2019 Jan*

# CHRONIC KIDNEY DISEASE DEFINITION: KDIGO

eGFR < 60 mL/min/1.73m$^2$ with duration > 3 months

Markers of kidney damage: UACR ≥ 30, urine sediment or structural abnormalities



*Kidney International Supplements. 2013; 3(1): 1-150.*

# 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 w/ serious intercurrent illness that increases AKI risk**



*Kidney International Supplements. 2013; 3(1): 1-150.*

# 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 SGLT-2 INHIBITORS: NADKARNI, ET AL

| Acute Kidney Injury in Patients on SGLT2 Inhibitors | |
|---|---|
| Methods | Retrospective, two large community-based cohorts, propensity-matched analysis<br><br>Included patients w/ eGFR < 60, diagnosis of T2DM, taking SGLT2 inhibitor (empagliflozin, dapagliflozin, canagliflozin)<br><br>N=377 SGLT2 inhibitor users<br>N=377 patients w/ T2DM non SGLT2 inhibitor users |
| Objective | First AKI event after index date detected in the inpatient setting |
| Baseline characteristics | Users: canagliflozin (71.8%), dapagliflozin (19.4%), empagliflozin (8.9%)<br><br>Users and nonusers well matched aside from race (AA 18.3% vs 29.6%) in users vs nonusers and A1c (8% vs 7.5%) in users vs nonusers |



*Diabetes Care. 2017; 40: 1479-1485*

# AKI IN SGLT-2 INHIBITORS: NADKARNI, ET AL

**Table 2—AKI outcomes in the SGLT2 inhibitor user and nonuser groups in the Mount Sinai and Geisinger propensity-matched cohorts**

| | Mount Sinai cohort | | | Geisinger cohort | | |
|---|---|---|---|---|---|---|
| | User ($n$ = 372) | Nonuser ($n$ = 372) | P1 | User ($n$ = 1,207) | Nonuser ($n$ = 1,207) | P2 |
| $AKI_{KDIGO}$–inpatient | 14 (3.8) | 36 (9.7) | 0.002 | 26 (2.2) | 55 (4.6) | 0.001 |
| $AKI_{ICD}$ | 22 (5.9) | 40 (10.8) | 0.02 | 15 (1.2) | 36 (3.0) | 0.003 |
| Peak creatinine in $AKI_{KDIGO}$ events | 1.6 (1.4–1.8) | 1.9 (1.6–2.4) | 0.02 | 1.7 (1.4–2.6) | 1.6 (1.3–2.4) | 0.91 |
| Change in serum creatinine during $AKI_{KDIGO}$ events | 0.5 (0.4–0.7) | 0.9 (0.8–1.3) | 0.004 | 0.6 (0.5–1.0) | 0.6 (0.4–1.2) | 0.80 |
| Need for acute dialysis | 1 (0.3) | 1 (0.3) | 1.00 | 0 (0.0) | 1 (0.1) | 0.317 |

P1 and P2 are *P* values for primary and secondary analyses, respectively.



*Diabetes Care. 2017; 40: 1479-1485*

# AKI IN SGLT-2 INHIBITORS: NADKARNI, ET AL

| Acute Kidney Injury in Patients on SGLT2 Inhibitors | |
|---|---|
| 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<br><br>AKI severity not worse in SGLT2 inhibitor patients or dapagliflozin/canagliflozin vs empagliflozin |
| Strengths/ Limitations | Patients generally well-matched within cohort arms, sensitivity analysis verified results<br><br>Retrospective study<br><br>Small empagliflozin representation within cohort |



*Diabetes Care. 2017; 40: 1479-1485*

# CREDENCE: PERKOVIC, ET AL

| Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy: CREDENCE | |
|---|---|
| Methods | Double-blind randomized controlled clinical trial, multicenter (690 sites, 34 countries)<br><br>Intervention: canagliflozin 100mg vs placebo, randomized 1:1<br><br>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<br><br>Composite of ESKD, doubling Scr or renal death |
| Baseline | Age ~ 63 y/o, duration diabetes ~ 16 years, eGFR ~ 56 |



*N Engl J Med. June 2019; 380(24):2295-2306*

# CREDENCE: PERKOVIC, ET AL

| Outcome | Canagliflozin n=2202 | Placebo n=2199 | HR | 95% CI | p value |
|---|---|---|---|---|---|
| ESRD, 2X Scr, renal/CV death | 43.2* | 61.2* | 0.7 | 0.59-0.82 | 0.00001 |
| ESRD, 2X Scr, renal death | 27* | 40.4* | 0.66 | 0.53-0.81 | <0.001 |
| Hyperkalemia | 29.7* | 36.9* | 0.8 | 0.65-1 | N/A |
| Acute Kidney Injury | 16.9* | 20* | 0.85 | 0.64-1.13 | N/A |

*Events per 1000 patient years



*N Engl J Med. June 2019; 380(24):2295-2306*

# CREDENCE: PERKOVIC, ET AL

| Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy: CREDENCE | |
|---|---|
| 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.<br><br>Safety outcomes indicate trend toward lower risk AKI in canagliflozin treated group |
| Strengths/ Limitations | Large, multicenter double-blind randomized trial, stratified based on eGFR, concomitant diabetes medication classes and comorbidities<br><br>Included patients w/ pre-existing CKD and albuminuria at high risk for AKI<br><br>No active comparator<br><br>Unclear specific agents or dosing of concurrent diabetes drugs used within the study |



*N Engl J Med. June 2019; 380(24):2295-2306*

# DECLARE-TIMI 58: WIVIOTT, ET AL

| Dapagliflozin and Cardiovascular 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<br><br>Included patients > 40 years of age w/ type 2 diabetes, eGFR ≥ 60<br><br>Dapagliflozin 10mg vs placebo, 1:1 ratio |
| Objectives | Primary outcome: MACE<br><br>Secondary outcomes: sustained decrease of 40% or more in eGFR, new ESRD, death from renal or cardiovascular causes |
| Baseline | Mean duration diabetes ~ 11 years, mean eGFR 85, 10% patients had history of HF, similar ACEI/ARBs and diabetes classes between study arms |



*N Engl J Med. Jan 2019; 380(4):347-357*

# DECLARE-TIMI 58: WIVIOTT, ET AL

| Outcome | Dapagliflozin n=8582 | Placebo n=8578 | HR | 95% CI | p value |
|---|---|---|---|---|---|
| **MACE** | 22.6* | 24.2* | 0.93 | 0.84 – 1.03 | 0.17 |
| **≥ 40% decrease in eGFR to <60, ESRD or death from renal or CV cause** | 10.8* | 14.1* | 0.76 | 0.67 – 0.87 | N/A |
| **≥ 40% decrease in eGFR to <60, ESRD or death from renal cause** | 3.7* | 7.0* | 0.53 | 0.43 – 0.66 | N/A |

*Events per 1000 patient years



*N Engl J Med. Jan 2019; 380(4):347-357*

# DECLARE-TIMI 58: WIVIOTT, ET AL

| Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes: DECLARE-TIMI 58 | |
|---|---|
| Conclusions | Dapagliflozin was non-inferior to placebo in primary safety outcome of MACE<br><br>Findings support a possible lower rate of adverse renal outcomes |
| Strengths/ Limitations | Large randomized controlled trial<br><br>Randomized based on alternative diabetes therapy, presence of ACEI/ARB within study arm<br><br>No active comparator<br><br>Trial not powered to look at renal events<br><br>Low event rate within groups likely due to short follow-up 4.2 years |



*N Engl J Med. Jan 2019; 380(4):347-357*

# SUMMARY OF STUDIES

- **Aki in SGLT2 inhibitors: Nadkarni, et al**
  - No increased risk of AKI with SGLT-2 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)

# RECITE PATIENT COUNSELING POINTS FOR SGLT-2 INHIBITORS

# PREVENTION OF AKI WITH SGLT-2 INHIBITORS

- Avoid SGLT-2 Inhibitors in patients with eGFR < 30 – treatment likely ineffective
- Consider avoiding SGLT-2 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 SGLT-2 Inhibitors in patients w/ eGFR < 60 with serious intercurrent illness that increases AKI risk
- Educate on signs and symptoms of AKI with ER precautions



*KDIGO 2012 Guidelines for CKD*

# FDA WARNINGS REGARDING SGLT-2 I

**FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes**

**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**



*www.fda.gov/drugs/drugs-safety-and-availability*

# PREVENTION OF OTHER ADVERSE EFFECTS W/ SGLT-2 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

# SGLT-2 INHIBITOR COUNSELING

- Careful selection of patients will avoid many adverse events associated w/ SGLT-2 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. Glimeperide 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 >250 restart canagliflozin, stay hydrated, and call to make an appointment when you feel better"

# RESOURCES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- Images Created by Cassie Schornack, with inspiration from images within Diabetes Care Jan 2015, 38 (1) 140-149 and Diabetesincontrol.com/sglt2-inhibitors-a-new-class-of-diabetes-medications/

# ACKNOWLEDGEMENTS

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# QUESTIONS?

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