SGLT2 Inhibitors: Renal Harm or Benefit?
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Objectives:
- Discuss Medication Use in Type 2 Diabetes Mellitus
- 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
Mechanisms of Hyperglycemia in Type 2 Diabetes Mellitus

- Decreased pancreatic insulin secretion
- Increased pancreatic glucagon secretion
- Gut carbohydrate delivery and absorption
- Decreased incretin effects
- Increased hepatic glucose production
- Decreased peripheral glucose uptake
- Decreased renal glucose excretion

Comparison of Medications Used in Type 2 Diabetes Mellitus

- **Metformin**
  - *A1c lowering* – 1.5 – 1.7%
  - Mechanism – decreases hepatic glucose production, increases peripheral glucose uptake
  - ADRs: diarrhea, nausea, vomiting
- **Thiazolidinediones**
  - *A1c lowering* – 0.6 – 1.3%
  - Mechanism – increases glucose utilization by periphery, decreases hepatic glucose output
  - ADRs: headache, weight gain, increased incidence bone fractures, HF worsening
- **Sulfonylureas**
  - *A1c lowering* – 1.7%
  - Mechanism – increases insulin secretion from the pancreas, reduces glucose output from the liver, increases insulin sensitivity at peripheral sites
  - ADRs: weight gain, hypoglycemia
- **Meglitinides**
  - *A1c lowering* 1.7%
  - Mechanism – increases insulin secretion from pancreas
  - ADRs: headache, hypoglycemia
- **Alpha-glucosidase inhibitors**
  - *A1c lowering* – 0.5 – 1%
  - Mechanism – slows absorption of complex carbohydrates in GI tract
  - ADRs: significant abdominal pain, diarrhea, flatulence
- **Amylin analogs**
  - *A1c lowering* 0.4 – 0.6%
  - Mechanism – inhibits glucagon secretion, increases satiety
  - ADRs: headache, nausea, vomiting, hypoglycemia
- **DPP-4 inhibitors**
  - *A1c lowering* – 0.5-0.9%
  - Mechanism – increase insulin synthesis, decrease hepatic glucose production
  - ADRs: headache, abdominal pain, pancreatitis
- **GLP1 receptor antagonists**
  - *A1c lowering* – 0.5 – 1% additional decrease w/ metformin
Mechanism – increases insulin secretion, increases beta cell growth/replications, slows gastric emptying, and decreases food intake
- ADRs: nausea, vomiting, diarrhea, pancreatitis

- **Bile Acid Sequestrant**
  - A1c lowering – 0.3-0.5%
  - Mechanism – reduces hepatic insulin resistance which reduces glucose production in liver, decreased intestinal glucose absorption
  - ADRs – constipation, headache, hypertriglyceridemia

- **Dopamine receptor antagonists**
  - A1c lowering – 0.5%
  - Mechanism – unknown
  - ADRs – nausea, fatigue, vomiting

### Mechanism of SGLT-2 Inhibitors

- 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 in the body
- Renal thresholds for glucosuria:
  - Normal, healthy – 180 mg/dL
  - Chronic hyperglycemia – 220-240 mg/dL
- In patient with chronic hyperglycemia, SGLT-2 co-transporters are overexpressed in the kidney

### Efficacy of SGLT-2 Inhibitors

- When SGLT-2 cotransporters are inhibited, SLGT-1 Inhibitors reabsorb 30-40% glucose load, thereby decreasing effectiveness of SGLT-2 Inhibitors
- Inhibition of SGLT-2 co-transporters lowers the renal threshold for glucose reabsorption
- SGLT-2 Inhibitors decrease A1c 0.5 – 1%

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Renal dosing recs</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, 30-45 manufacturer recommends do not initiate therapy, however CREDENCE trial suggests can use to 30</td>
<td>Increased serum potassium: genitourinary infections, renal insufficiency</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10 – 25mg once daily</td>
<td>eGFR 30 – 45: manufacturer recommends do not initiate therapy, however may still have some benefit</td>
<td>Dyslipidemia, genitourinary infections, increased hematocrit</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>5-10mg once daily</td>
<td>eGFR 30 – 45: manufacturer recommends do not initiate therapy</td>
<td>Genitourinary infection, increased urine output, dyslipidemia, renal insufficiency</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>5-15 mg once daily</td>
<td>eGFR 30 – 60: manufacturer recommends do not initiate therapy or continue use</td>
<td>Genitourinary infection, headache, hypoglycemia, increased urine output</td>
</tr>
</tbody>
</table>
Renal Conditions\textsuperscript{1,4-6}

Acute Kidney Injury (AKI)

AKI Definition: KDIGO

- Increase in serum creatinine $\geq 0.3$ mg/dL within 48 hours
- Increase in serum creatinine by $\geq 1.5$ 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

- The most common, intrinsic (renal) cause of AKI
- Novel biomarkers: KIM-1, L-FABP, IL-18, Urinary alpha one macroglobulin, Beta-2 microglobulin

*Differences between AKI and ATN: Table 2\textsuperscript{5}*

<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

**CKD Definition: KDIGO**

- eGFR < 60 mL/min/1.73m² with duration > 3 months
- Markers of kidney damage: albuminuria ACR ≥ 30, urine sediment or structural abnormalities, h/o kidney transplantation, electrolyte abnormalities d/t tubular disorder

**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 temporarily discontinuation of potentially nephrotoxic agents, such as SGLT-2 Inhibitors, ACE inhibitors, ARBs, metformin, digoxin, and lithium in patients w/ eGFR < 60 with serious intercurrent illness that increases risk of AKI

**Chronic Kidney Disease Staging: KDIGO**

<table>
<thead>
<tr>
<th>GFR categories in CKD</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>≥ 90 Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60-89 Mildly decreased*</td>
</tr>
<tr>
<td>G3a</td>
<td>45-59 Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30-44 Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15-39 Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt; 15 Kidney failure</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

<table>
<thead>
<tr>
<th>Albuminuria categories in CKD</th>
<th>AER (mg/24 hours)</th>
<th>ACR (approximate equivalent) (mg/mmol)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt; 30</td>
<td>&lt;3</td>
<td>&lt;30 Normal to mildly increased</td>
</tr>
<tr>
<td>A2</td>
<td>30-300</td>
<td>3-30</td>
<td>30-300 Moderately increased*</td>
</tr>
<tr>
<td>A3</td>
<td>&gt; 300</td>
<td>&gt;30</td>
<td>&gt;300 Severely increased**</td>
</tr>
</tbody>
</table>

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level
**Including nephrotic syndrome albumin excretion usually > 2200 mg/24 hours (ACR >2220 mg/g; >220 mg/mmol).
### Acute Kidney Injury in Patients on SGLT-2 Inhibitors

| **Purpose** | • Objective: To determine the real-world risk for AKI associated with initiating SGLT-2 Inhibitors in two large health care utilization cohorts of patients with T2DM, with and without baseline eGFR, using propensity-score matching |
| **Design** | • Retrospective, two large community based cohorts, propensity based analysis |
| **Patient Population** | • Inclusion:  
  o All cohorts: Diagnosis of T2DM  
  o Mount Sinai cohort: Patients within Mount Sinai Chronic Kidney Disease Registry (eGFR <60, ICD-CM 9/10 codes for CKD, or urinary albumin-to-creatinine-ratio (ACR) >30 mg/mg). Must have available serum creatinine ratio between January 1, 2014 and December 30, 2016  
  o Geisinger cohort: Patients who received primary care within Geisinger Health System. Must have available Scr between January 1, 2013 and February 10, 2017  
• Exclusion  
  o Missing data on eGFR prior to prescription |
| **Intervention** | • 1:1 match for SGLT-2 Inhibitor Users and Case Controls |
| **Outcomes** | • Primary outcome: First AKI event after the index date detected in the inpatient setting  
• Secondary endpoints:  
  o Severity of AKI  
  o Change in serum creatinine  
  o Need for acute dialysis during AKI episode |
| **Methods** | • All new users and nonusers of SGLT2 inhibitors were identified from EMR  
• SGLT2 inhibitor user follow-up period started on date of first prescription and ended on date of last outpatient encounter  
• AKI events defined according to KDIGO definitions  
• Utilized either single serum creatinine measurements or averaged creatinine measurements if multiple over past year before first episode  
• Severity of AKI measured by subtracting baseline serum creatinine from peak serum creatinine during AKI event |
| **Statistics** | • Case controls matched via propensity scores, calculated using logistic regression of SGLT2 inhibitor use on age, race, sex, year of prescription/creatinine measurement, prevalent heart failure or coronary artery disease, hypertension status, insulin use, antihypertensive medication use, nonsteroidal anti-inflammatory use, diuretic use, eGFR, and HbA1c  
• Differences in demographics, comorbidities, physiologic variables, laboratory values, and medication regimens compared using chi squared tests for categorical variables and Wilcoxon Rank-sum tests for continuous variables  
• Survival analyses was performed among case and control subjects using Cox proportional hazards regression from index date to the minimum of event date, death date, or end of follow-up.  
• Adjusted analysis was performed with additional adjustment for propensity score and covariates with significant differences among case and control subjects  
• Sensitivity analyses performed to analyze users of each type of SGLT-2 inhibitor and then in individuals not missing covariate data |
Results

N = 388 SGLT2 inhibitors, 12,316 patients with T2DM nonusers of SGLT2 Inhibitors prior to matching
N= 377 patients in both user and nonuser cohorts

Baseline Characteristics:

- 71.8% canagliflozin, 19.4% dapagliflozin, 8.9% empagliflozin

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MS user (n=372)</th>
<th>MS nonuser (n= 372)</th>
<th>G user (n = 1,207)</th>
<th>G nonuser (n=1,207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity – black</td>
<td>68 (18.3)</td>
<td>110 (29.6)</td>
<td>15 (1.2)</td>
<td>13 (1.1)</td>
</tr>
<tr>
<td>Smoker</td>
<td>36 (9.7)</td>
<td>93 (25)</td>
<td>666 (55.2)</td>
<td>666 (55.2)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.0 (7.3-9)</td>
<td>7.5 (6.7-8.8)</td>
<td>8.2 (7.4 – 8.8)</td>
<td>7.7 (6.7-8.3)</td>
</tr>
</tbody>
</table>

Table 2: Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MS user (n=372)</th>
<th>MS nonuser (n= 372)</th>
<th>G user (n = 1,207)</th>
<th>G nonuser (n=1,207)</th>
<th>(p value 1 and 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td>14 (3.8)</td>
<td>36 (9.7)</td>
<td>26 (2.2)</td>
<td>55(4.6)</td>
<td>(0.002, 0.001)</td>
</tr>
<tr>
<td>Peak Creatinine in AKI</td>
<td>1.6 (1.4-1.8)</td>
<td>1.9 (1.6 – 2.4)</td>
<td>1.7 (1.4 – 2.6)</td>
<td>1.6 (1.3 – 2.4)</td>
<td>(0.02, 0.91)</td>
</tr>
<tr>
<td>Change in Serum creatinine during AKI</td>
<td>0.5 (0.4 – 0.7)</td>
<td>0.9 (0.8 – 1.3)</td>
<td>0.6 (0.5 – 1)</td>
<td>0.6 (0.4 – 1.2)</td>
<td>(0.02, 0.8)</td>
</tr>
<tr>
<td>Need for acute dialysis</td>
<td>1(0.3)</td>
<td>1(0.3)</td>
<td>0</td>
<td>1(0.1)</td>
<td>(1, 0.317)</td>
</tr>
</tbody>
</table>

- No differential risk of AKI associated specifically with canagliflozin or dapagliflozin (sufficient data for empagliflozin not available in Geisinger cohort)

Strengths

- Patients relatively well-matched within cohort arms
- Reflect results of large RCT studies w/ SGLT-2 inhibitors, including EMPA-REG OUTCOME
- Results verified via sensitivity analyses
- Subgroup analysis of dapagliflozin/canagliflozin which verified results

Limitations

- Retrospective study
- Small empagliflozin representation
- Study design not created in manner to perform full comparison analysis
- Peak creatinine differed between Mount Sinai Cohort vs Geisinger Cohort

Conclusions

No increased risk of AKI in real-life SGLT2 Inhibitors before and after propensity matching over 1 year of follow-up in two large health systems. Trend toward decreased AKI in patients with SGLT2 inhibitor use over 1.5 year timeframe

AKI severity not worse in SGLT-2 inhibitor patients or dapagliflozin/canagliflozin vs empagliflozin
### Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy: CREDENCE Trial

#### Purpose
- **Objective:** To assess effects of canagliflozin on renal outcomes in patients with T2DM and albuminuric chronic kidney disease

#### Design
- Double-blind randomized controlled clinical trial, multicenter (690 sites, 34 countries)

#### Patient Population
- **Inclusion:**
  - ≥ 30 years of age with T2DM
  - A1c ≥ 6.5% to ≤ 12%
  - CKD with estimated eGFR ≥ 30 to < 90 mL/min/1.73 m² (60% with eGFR 30-60 mL/min/1.73 m²)
  - UACR > 300 mg/g to ≤ 5000 mg/g
- **Exclusion:**
  - History of DKA or T1DM
  - Patients able to become pregnant during study time period
  - Nondiabetic renal disease, renal transplant, dialysis
  - ASCVD event within 12 weeks before randomization
  - Current or history of HF class IV, HIV, uncontrolled hypertension
  - Known significant liver disease

#### Intervention
- Canagliflozin 100mg vs. placebo, randomized 1:1

#### Outcomes
- **Primary outcome:** composite of end-stage kidney disease, doubling of serum creatinine level from baseline for at least 30 days or death from renal or cardiovascular disease
- **Secondary endpoints:**
  - Composite of end-stage kidney disease, doubling of serum creatinine or renal death
  - Composite of cardiovascular death or hospitalization for heart failure
  - Composite of cardiovascular deaths, MI, or stroke
  - Hospitalization for heart failure
  - Cardiovascular death
  - Death from any cause
  - Composite of cardiovascular death, MI, stroke, or hospitalization for HF or unstable angina

#### Methods
- 2 week, single-blind, placebo run-in period with requirement of ≥ 80% compliance
- On stable maximum dose ACEI/ARB at least 4 weeks before randomization
- Visits conducted at 3, 13, then every 13 weeks thereafter for study duration
- Protocol amendment to examine patients' feet at each visit and disrupt therapy as needed

#### Statistics
- Intent-to-treat population
- 4200 patients, power 90% to detect 20% lower risk of prim outcome in canagliflozin grp, \( \alpha = 0.045 \)
- Single interim analysis after primary outcome occurrence in 405 patients with pre-specified criteria
- Stratified Cox proportional-hazards model for primary and secondary outcomes
- Mixed models for repeated measures to analyze changes in intermediate outcomes over time
- Slope analyses regarding estimated GFR for acute phase, chronic phase and total slope in appendix
- Calculated NNT to prevent one event during 2.5 years on basis of Kaplan-Meier curve
Results
12,900 screened, n=4401 patients, 2202 canagliflozin, 2199 placebo
Early trial discontinuation based on interim analysis data, trial duration 2.62 years
Baseline characteristics – similar between groups (including concurrent diabetes therapies)
• age = 63 y/o
• duration diabetes ~ 16 years
• BMI ~ 31
• Ethnicity ~ 67% white, 5% black, 20% Asian

Table 1: Primary and Secondary Outcomes:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin</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/CV 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>CV death or HF hospitalization</td>
<td>31.5*</td>
<td>45.4*</td>
<td>0.69</td>
<td>0.57-0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death, MI, stroke</td>
<td>38.7*</td>
<td>48.7*</td>
<td>0.8</td>
<td>0.67-0.95</td>
<td>0.01</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>15.7*</td>
<td>25.3*</td>
<td>0.61</td>
<td>0.47-0.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*events per 1000 patients years
- Death from any cause and CV death not statistically significantly different between groups

Table 2: Safety events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin</th>
<th>Placebo n=2199</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>12.3*</td>
<td>11.2*</td>
<td>1.11 (0.79-1.56)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4.1*</td>
<td>1.6*</td>
<td>2.59 (0.69-9.76)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>11*</td>
<td>1*</td>
<td>10.8 (1.39-83.65)</td>
</tr>
</tbody>
</table>

*events per 1000 patients years
- Similar results seen in sensitivity analysis and subgroup analysis
- HgA1C and BP were slightly lower in canagliflozin group compared to placebo
  - A1c least squares mean difference of -0.25%
  - BP least squares mean difference -3.3 mmHG/-0.95 mmHG

Strengths
- Large, multicenter double-blind randomized controlled trial
- Stratified based on eGFR, concomitant diabetes medication classes, and comorbidities
- Included patients w/ pre-existing CKD and albuminuria
- Sensitivity and subgroup analyses verified results
- All patients on stable dose maximally tolerated ACEI or ARB at least 4 weeks prior to randomization

Limitations
- Short follow-up time frame
- Protocol amendment interrupted treatment for patients with potential amputation conditions
- No active comparator
- Unable to determine effects in excluded patients
- Unclear specific agents or dosing of concurrent diabetes drug classes used within study

Conclusions
Results from primary and secondary outcome indicate canagliflozin may be an effective treatment for renal and cardiovascular protection in patients with type 2 diabetes and CKD. More data is needed to determine long-term effects, effects on populations not reviewed in the study, and overall comparison of canagliflozin to other SGLT2 Inhibitors and diabetes treatments. Given increased risk of amputations seen in CANVAS trial, would recommend patients be monitored closely while on canagliflozin for increased risk of amputating conditions, in addition to diabetic ketoacidosis.
| **Purpose** | Objective: To evaluate the effects of dapagliflozin on cardiovascular and renal outcomes in a broad population of patients who had or were at risk for atherosclerotic cardiovascular disease. |
| **Design** | Double-blind randomized placebo controlled clinical phase 3 trial |
| **Patient Population** | • Inclusion:  
  - >40 years of age w/ T2DM and established ASCVD or multiple risk factors for clinical ASCVD  
  - A1c 6.5% - < 12% at baseline  
  - CrCl ≥ 60 mL/min  
  • Exclusion:  
  - Current or previous TZDs use for 2 years or more  
  - Acute ASCVD <8 weeks prior to randomization  
  - SBP >180 or DBP >100 at randomization  
  - h/o malignancy, recurrent UTIs  
  - medication compliance <80% at randomization |
| **Intervention** | Dapagliflozin 10mg vs placebo 1:1 |
| **Outcomes** | • Primary outcome: MACE  
  • Secondary endpoints:  
  - Sustained decrease of 40% or more in eGFR  
  - New ESRD  
  - Death from renal or cardiovascular causes |
| **Methods** | • 4-to-8 week single-blind run-in period – all patients received placebo, blood & urine test  
  • Use of other glucose lowering agents at discretion of treating physician  
  • Patients returned for follow-up every 6 months until trial completion for lab and clinical assessment, contacted by phone every 3 months in between visits.  
  • Protocol adjusted after EMPA-REG Outcome trial showed greater benefit with respect to CV death and hospitalization for heart failure than with respect to MACE |
| **Statistics** | • Intention to treat analyses  
  • Safety assessed first for MACE – non-inferiority versus placebo shown if upper boundary of the two-sided 95% CI of the hazard ratio for MACE was less than 1.3 at a one-sided alpha level of 0.023 (after adjustment for two interim analyses)  
  • If non-inferiority confirmed, then two efficacy outcomes of MACE and composite of cardiovascular death or hospitalization for heart failure were to be tested in parallel at two sided alpha of 0.023  
  • Cox proportional hazards models used to determine time to event of primary outcome, stratified according to baseline ASCVD disease category and presence/absence of hematuria at baseline  
  • After initial safety analyses, other safety assessments were performed in a safety analysis population (received at least one dose of dapagliflozin) |
Results

Screened 17,160 patients. Dapagliflozin, N=8582 Placebo, N=8578

Baseline characteristics – similar between groups (including concurrent diabetes therapies and ACEI/ARB)

- age ≈ 63 y/o
- mean duration diabetes ~ 11 years
- mean eGFR 85
- 10% patients had HF

Table 1: Primary and Secondary Outcomes:

<table>
<thead>
<tr>
<th>Outcome</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>CV death or hospitalization for heart failure</td>
<td>12.2*</td>
<td>14.7*</td>
<td>0.83</td>
<td>0.73 – 0.95</td>
<td>0.005</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;60, ESRD or death from renal</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>

Table 2: Safety events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dapagliflozin n=8582</th>
<th>Placebo n=8578</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event</td>
<td>2925 (34.1%)</td>
<td>3100 (36.2%)</td>
<td>0.91 (0.87 – 0.96)</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>125 (1.5%)</td>
<td>175 (2.0%)</td>
<td>0.69 (0.55 – 0.87)</td>
</tr>
<tr>
<td>Genital Infection</td>
<td>76 (0.9%)</td>
<td>9 (0.1%)</td>
<td>8.36 (4.19 – 16.68)</td>
</tr>
<tr>
<td>Amputation</td>
<td>123 (1.4%)</td>
<td>113 (1.3%)</td>
<td>1.09 (0.84 – 1.4)</td>
</tr>
</tbody>
</table>

Strengths

- Large randomized controlled trial
- Randomized based on alternative diabetes therapy and presence of ACE-I/ARB within study arm to avoid confounding.

Limitations

- Trial not powered to look at renal events and high eGFR at baseline
- No active comparator
- Low event rate within groups likely due to short follow-up (4.2 years)
- Protocol adjusted after trial began

Conclusions

Dapagliflozin was non-inferior to placebo with respect to primary safety outcome of MACE. Findings support a possible lower rate of adverse renal outcomes but study was not powered for renal outcomes. AKI risk appears to be lower for dapagliflozin use compared to placebo within this study group.
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 SGLT-2 Inhibitors

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

Recite Patient Counseling Points for SGLT-2 Inhibitors

**Prevention of AKI**

- Avoid SGLT-2 Inhibitors in patients with CrCl < 30 mL/min – 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 SGLT-2 Inhibitors in patients w/ GFR < 60 with serious intercurrent illness that increases risk of AKI
- Educate on signs and symptoms of AKI with ER precautions

**Prevention of Other Adverse Effects with 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 Conclusions**

- Careful selection of patients to receive SGLT-2 Inhibitors will avoid many adverse events associated w/ SGLT-2 Inhibitors
- Educate patients thoroughly regarding risks and benefits of treatment
- Benefits include possible delay or prevention of CKD, weight loss, blood pressure reduction, in addition to blood glucose lowering effects
Appendix A:

Abbreviations

T2DM: Type 2 Diabetes Mellitus
SGLT-2 I: Sodium Glucose Co-transporter-2 Inhibitors
GLP-1R Agonists – Glucagon-like Peptide-1 Receptor Agonist
SUs – Sulfonylureas
AGI – Alpha-glucosidase Inhibitors
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
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
y/o – Year Old
ACEI – Angiotensin-Converting Enzyme Inhibitor
Appendix B:

Resources: