CARDIAC AND RENAL PROTECTIVE EFFECTS OF SGLT-2 INHIBITORS: BENEFITS BEYOND GLYCEMIC CONTROL

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OBJECTIVES

 Understand the role of the sodium-glucose co-transporter (SGLT) in glucose homeostasis in normoglycemic and hyperglycemic states
 Discuss pleiotropic effects observed with the use of SGLT-2 inhibitors and explore proposed pathophysiology
 Review clinical data studying renal and cardio protective endpoints related to SGLT2 inhibition
 Analyze the cardio and renal outcomes drawn from the EMPA-REG outcomes trial

ABBREVIATIONS
 A1c/HbA1c: hemoglobin A1c
 ACE-I = Ace inhibitor
 ADA = American Diabetes Association
 ARB = angiotensin receptor blocker
 ARF = acute renal failure
 CKD = chronic kidney disease
 CV = cardiovascular
 CVD = cardiovascular disease
 DCCT = diabetes control and complications trial
 DKD = diabetic kidney disease
 DN = diabetic nephropathy
 DPP = diabetes mellitus
 EDIC = epidemiology of diabetes interventions and complications
 ESRD = end stage renal disease
 mAlb/Cr = microalbumin to creatinine ratio
 MI = myocardial infarction
 PAD = peripheral artery disease
 RAAS = renin-angiotensin-aldosterone system
 SGLT = sodium glucose co-transporter
 T1DM/T2DM: Type 1/Type 2 DM
 TGF = tubuloglomerular feedback
 UA = unstable angina
 UKPDS = United Kingdom Prospective Diabetes Study
 UTI = urinary tract infection

DM & A MAJOR CAUSE FOR CONCERN

Macrovacular
- CV, MI, sudden cardiac death
- Microvascular
- Diabetic neuropathy
- Gastrointestinal/genitourinary dysfunction
- Diabetic nephropathy (DN)
- Leading cause of mortality and end stage renal disease
- Early predictors: enlarged kidney, hyperfiltration, microalbuminuria
- Every 5 minutes: 2 people die due to these complications

DIABETES RELATED COMPLICATIONS

DM: A MAJOR CAUSE FOR CONCERN

Major Causes of Mortality


DIABETES RELATED COMPLICATIONS


Abbreviation


Hallmark of diabetes: progressive insulin resistance or complete lack of insulin leading to hyperglycemia
- Goal: Achieve glycemic targets to reduce the risk of macrovascular and microvascular complications

Diabetes related complications:

- Macrovacular: CV, MI, sudden cardiac death
- Microvascular: Diabetic neuropathy, Gastrointestinal/genitourinary dysfunction, Diabetic nephropathy (DN)
- Leading cause of mortality and end stage renal disease
- Early predictors: enlarged kidney, hyperfiltration, microalbuminuria
- Every 5 minutes: 2 people die due to these complications
ADA RECOMMENDATIONS

- Control blood pressure
- Control blood glucose
- UKPDS and DCCT: Demonstrated microvascular benefit
- EDIC: Demonstrated macrovascular benefit
- Screen for development of complications
  - mAlb/Cr
  - Dilated eye exam
  - Monofilament foot exam
  - Dental exam

UKPDS and DCCT: Demonstrated microvascular benefit
EDIC: Demonstrated macrovascular benefit
Screen for development of complications
mAlb/Cr
Dilated eye exam
Monofilament foot exam
Dental exam

RAAS INHIBITION

- Slows progression to diabetic kidney disease
- ADA recommendations
  - Initiate ACE-I or ARB in patients with macroalbuminuria (mAlb/Cr > 300 mg/gm)
  - Initiate ACE-I or ARB in patients with microalbuminuria (mAlb/Cr 30-300 mg/gm)
  - Weak evidence: small trials in normotensive patients with microalbuminuria


INTRODUCING THE CONCEPT
SODIUM GLUCOSE CO-TRANSPORTERS (SGLT)

INTRODUCING SGLT

<table>
<thead>
<tr>
<th>Expression</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT1</td>
<td>High affinity, low capacity glucose transport</td>
</tr>
<tr>
<td>SGLT2</td>
<td>Low affinity, high capacity glucose transport</td>
</tr>
</tbody>
</table>


ROLE IN GLUCOSE HOMEOSTASIS

- Purpose: maintain consistent fasting glucose level
- Threshold for reabsorption: BG 180-200 mg/dl
- BG>200 mg/dl: glycosuria
- Prolonged hyperglycemia → maladaptive mechanism

PROLONGED HYPERGLYCEMIC STATE

↑ glucose filtered

SGLT-2 upregulation

Prolonged filtration

RAAS + SNS activation

Nitric oxide suppression

↑ BLOOD PRESSURE

↑ ARTERIAL STIFFNESS

TUBULOGLOMERULAR FEEDBACK

1. Adenosine maintains tone

2. Excess glucose reabsorbed

3. Decreases blood glucose

↑ 10-15% reduction in plasma uric acid

Increased levels associated with HTN, CVD and renal disease

Undeclared clinical relevance

WEIGHT LOSS AND URIC ACID

- Weight loss of 1-4.5 kg
  - Loss of calories from glycosuria and osmotic diuresis
  - Contributes to reduced insulin requirements
  - Maintained post initial time period

- Uric acid
  - 10-15% reduction in plasma uric acid
  - Increased levels associated with HTN, CVD and renal disease

SGLT2 INHIBITORS: AT A GLANCE

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Available dosing (mg)</th>
<th>Efficacy (A1c lowering)</th>
<th>ADEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invokana</td>
<td>canagliflozin</td>
<td>100-300</td>
<td>about 0.7%</td>
<td>DKA, ketosis, genital mycotic infections, UTI, slight ↑ LDL, bone fracture, bladder cancer</td>
</tr>
<tr>
<td>Farxiga</td>
<td>dapagliflozin</td>
<td>5-10</td>
<td>about 0.42%</td>
<td>DKA, ketosis, genital mycotic infections, UTI, slight ↑ LDL, bone fracture, bladder cancer</td>
</tr>
<tr>
<td>Jardiance</td>
<td>empagliflozin</td>
<td>10-25</td>
<td>about 0.4-0.6%</td>
<td>DKA, ketosis, genital mycotic infections, UTI, slight ↑ LDL, bone fracture, bladder cancer</td>
</tr>
<tr>
<td>Suglat</td>
<td>ipragliflozin</td>
<td>25-100</td>
<td>about 0.3-0.4%</td>
<td>DKA, ketosis, genital mycotic infections, UTI, slight ↑ LDL, bone fracture, bladder cancer</td>
</tr>
</tbody>
</table>


CARDIOVASCULAR EFFECTS

- Decrease in blood pressure without increase in orthostasis
  - SBP - 4 mmHg
  - DBP - 2 mmHg

- Decrease even in non-dippers

- Maintained in CKD patients

ARterial Stiffness

- Well established marker for CVD
- Improvements observed in studies for T1DM and T2DM
- Cherney and colleagues: 8 week open label prospective trial in T1DM
  - ↓ carotid-radial pulse wave velocity
- T2DM studies
  - ↓ pulse pressure and myocardial oxygen consumption

Proposed Pathophysiology

- Volume contraction
- ↓ Arterial stiffness
- Weight loss
- Neurohormonal changes
  - Differences observed in trials not as expected
  - ↑ vasoconstrictors
  - ↑ urinary ACE2 (vasodilator)

Renal Effects

- Decreased kidney weight and glomerular size
- Early decrease in eGFR
- Decreased occurrence of albuminuria
- Maintained in CKD independent of A1c reduction

Early Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>2013 Cefalu and colleagues</th>
<th>2014 ATIRMA trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject type (n)</td>
<td>T2DM (n=1450)</td>
<td>T2DM (n=600)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Canagliflozin 100 mg, 300 mg or glimepiride for 52 weeks</td>
<td>Empagliflozin 25 mg for 8 weeks</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Primary A1c reduction, eGFR as a safety measure</td>
<td>Change in eGFR in patients with normofiltration (N) or hyperfiltration (H)</td>
</tr>
<tr>
<td>eGFR</td>
<td>Week 4: greater ↓ in treatment group&lt;br&gt;Week 12: stabilized in Canagliflozin group vs steady decline in glimepiride group</td>
<td>Euglycemic conditions: -3.4 H vs -3.3 H&lt;br&gt;Hyperglycemic conditions: -3.4 H vs -4.4 H</td>
</tr>
</tbody>
</table>

Can SGLT2 inhibitors protect patients with Type 2 Diabetes from Renal and Cardiovascular Complications?

LITERATURE REVIEW
EFFICACY AND SAFETY OF EMPAGLIFLOZIN FOR TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

LIAKOS A, KARAGIANNIS T, ATHANASIADOU E, ET AL.

DIABETES, OBESITY AND METAB. 2014;16(10):984-993.

METHODS

- Objective: To utilize available studies to assess the safety and efficacy of empagliflozin compared with placebo or other antidiabetic agents in patients with type 2 diabetes
- Searched studies through publication date December 19, 2013 and abstracts presented at Endocrinology meetings between 2009 and 2013
- Inclusion:
  - RCTs comparing empagliflozin to placebo or other antidiabetics
  - T2DM
  - Duration ≥ 12 weeks

OUTCOMES

- Primary: Absolute change in HbA1c
- Secondary: Absolute change in weight, SBP, DBP; % patients achieving target A1c<7%
- Safety: hypoglycemia, change in eGFR, incidence of UTI/genital tract infections, volume depletion

RESULTS

- 10 studies with 6203 patients
- 8 with high bias: use of LOCF
- Duration 12-90 weeks
- Baseline A1c: 7.8% to 8.3%
- Background therapy:
  - 4 studies: none
  - 3 studies: metformin
  - 1: metformin + SU
  - 1: basal insulin
  - 1: any oral antidiabetic drug
  - 1: metformin + pioglitazone

<table>
<thead>
<tr>
<th>Measure (change in)</th>
<th>Empagliflozin v placebo</th>
<th>Empagliflozin v active agent</th>
<th>P (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg (10 mg)</td>
<td>-1.85 (-2.09, -1.66)</td>
<td>-2.15 (3.03, -1.27)</td>
<td>43/56</td>
</tr>
<tr>
<td>Weight, kg (25 mg)</td>
<td>-1.84 (-2.30, -1.38)</td>
<td>-2.16 (3.57, -1.55)</td>
<td>85/15</td>
</tr>
<tr>
<td>SBP mmHg (10 mg)</td>
<td>-3.49 (-4.32, -2.67)</td>
<td>-3.53 (-5.37, -1.69)</td>
<td>0.0</td>
</tr>
<tr>
<td>SBP mmHg (25 mg)</td>
<td>-4.19 (-5.17, -3.20)</td>
<td>-4.24 (-6.08, -2.41)</td>
<td>32/0</td>
</tr>
<tr>
<td>eGFR*** (10 mg)</td>
<td>-0.09 (-1.40, 0.96)</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>eGFR*** (25 mg)</td>
<td>-0.84 (-2.29, 0.62)</td>
<td>--</td>
<td>59</td>
</tr>
</tbody>
</table>

Values represented are mean changes and 95% confidence interval. CI is for percentage of empagliflozin vs placebo vs empagliflozin vs active agent. Heterogeneity was indicated by removing studies including CKD patients; ***ml/min/1.73m²

BIAS AND DATA ANALYSIS

- Bias assessments: key domains
  - Random sequence generation: allocation concealment and incomplete outcome data
  - Meta-regression analysis to adjust for publication type (abstract vs full text)
  - Type of comparator; dosage; intention to treat analysis
  - Continuous outcomes: weighted mean differences with inverse variance weighted random effects model
  - Dichotomous outcomes: odds ratio via Mantel-Haenzel formula assuming random effects model
  - Heterogeneity: Cochran’s Q test (p<0.10 and I² >50 = high)

RESULTS

- All cause mortality: 7 trials reported
  - Empagliflozin 5 deaths (n=2874)
  - Control 5 deaths (n=1704)
- None reported on hard cardiovascular outcomes

Author’s conclusion: Both doses of empagliflozin are effective at lowering blood glucose while providing benefits of weight loss and blood pressure reduction.

DISCUSSION

- Valuable summation of results from early trials of patients with T2DM and treated with empagliflozin.
- Introduces a potential treatment option in patients with moderate renal impairment.

METHODS

Objective: To determine the efficacy of dapagliflozin in lowering HbA1c, body weight and SBP in patients determined to be at high risk for CVD events.

Design:
- 24-week multinational randomized, double blind, placebo-controlled international phase 3 study with a 28-week extension period
- Funding: NIH grant and support from Bristol-Myers Squibb and AstraZeneca

Study Population

- Men ≥ 45 or women ≥ 50 years old
- T2DM with CVD* and HTN
- Stable antihyperglycemic therapy for 4 weeks
- HbA1c 7.2% to ≤ 10.5%
- T1DM
- On >3 oral antidiabetic medications
- FPG>270 mg/dl at screening
- h/o DKA
- CV event within 2 months
- SBP ≥ 165 mmHg, DBP ≥ 100 mmHg
- CHF NYHA class IV or unstable CHF
- Severe hepatic insufficiency

*CVD= prior documented CHD (history of MI, revascularization or documented coronary artery disease), coronary artery bypass graft, or documented cerebrovascular disease

Intervention

- Randomized 1:1 to Dapagliflozin 10 mg or placebo + existing stable background therapy
- If on insulin, ↓ insulin dose by 25%
### Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=459)</th>
<th>Dapagliflozin (n=455)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years ± SD)</strong></td>
<td>63 ± 7.7</td>
<td>62.8 ± 7.0</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>31.4</td>
<td>32.1</td>
</tr>
<tr>
<td><strong>White (%)</strong></td>
<td>85.2</td>
<td>82.6</td>
</tr>
<tr>
<td><strong>CV event (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVA/TIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c ± SD</strong></td>
<td>8.08 ± 0.8</td>
<td>8.18 ± 0.84</td>
</tr>
<tr>
<td><strong>ACEI/ARB</strong></td>
<td>98.3</td>
<td>98.9</td>
</tr>
<tr>
<td><strong>Lipid lowering medications</strong></td>
<td>88.5</td>
<td>84.1</td>
</tr>
</tbody>
</table>

### Outcomes

<table>
<thead>
<tr>
<th>End point</th>
<th>Placebo (n=459)</th>
<th>Dapagliflozin (n=455)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in HbA1c (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 item composite %</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight loss (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight loss (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI ≥ 27 and ≥ 5% weight loss</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Decreased eGFR at 52 weeks (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Deaths (%)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*resolved without discontinuation; **Deaths deemed to be unrelated to treatment.

### Conclusions

- Author’s conclusion: Dapagliflozin was found to be superior to placebo in reducing A1c and achieving a 3 item composite representing reduction in cardiovascular risk in a population with documented CVD.

- Demonstrates the durability of efficacy of dapagliflozin in patients with cardiovascular disease. However, these endpoints are only surrogate markers and may hint at cardiovascular benefits.

### Strengths

- Study design
- Large % of patients on standard therapy
- Long follow-up period

### Weaknesses

- Dual primary endpoints
- Use of surrogate markers
- Limited information on CHF patients
- Vague safety endpoints

### Outcomes

**EMPA-REG OUTCOMES TRIAL**


### Methods

**Objective:** To determine the cardiovascular-related outcomes of adjunctive empagliflozin therapy when added to standard of care in patients with T2DM and high cardiovascular risk.

**Study design:**
- Randomized, double-blind placebo-controlled, multinational and multicenter trial
- 7028 patients randomized from September 2010 to April 2013
- Median treatment duration 2.6 years
- Funding/oversight: Boehringer Ingelheim, Eli Lilly

**Inclusion:**
- ≥ 18 years old
- Uncontrolled T2DM
- BMI ≥ 35kg/m²
- eGFR ≥ 30 ml/min/1.73m²
- High risk for cardiovascular events
- On diet or exercise regimen and drug naïve or pre-treated with stable therapy for ≥12 weeks prior to randomization

**Exclusion:**
- Fasting blood sugar ≥ 240 mg/dl
- Active liver disease
- Planned cardiac surgery/angioplasty within 3 months
- eGFR < 30 ml/min/1.73m²
- Acute coronary syndrome, TIA or stroke within 2 months
- Cancer treatment within 5 years

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- eGFR < 30 ml/min/1.73m²
- Acute coronary syndrome, TIA or stroke within 2 months
- Cancer treatment within 5 years


INTERVENTION
- 2 week open label placebo run in
- Stable antihyperglycemic background therapy
- Randomized 1:1:1 to empagliflozin 10 mg, 25 mg or placebo for up to 204 weeks
- 1st 12 weeks: no changes to background therapy unless FPG >240 mg/dl
- After 12 weeks: free to adjust background therapy
- Free to adjust other therapies to meet standard of care

OUTCOMES
- Cardiovascular
  - Primary: MACE (CV death, non-fatal MI, non-fatal stroke)
  - Key secondary outcome: Composite of MACE + hospitalization for HF
- Renal
  - Incident or worsening nephropathy
  - Composite of incident or worsening nephropathy or death cardiovascular causes
  - Individual components of the composites
    - Incident albuminuria if previously normal baseline urinary albumin
    - Safety: AKI, hyperkalemia, mycotic infections, diabetic ketoacidosis

STATISTICAL ANALYSIS
- Primary outcome: Cox proportional hazards model
- Non-inferiority analysis followed by a 4 step hierarchical testing for superiority
- Power analysis: 691 events needed for 90% power with assumed hazard ratio of 1.0
- Between group differences and risk of an outcomes: Cox proportional hazards model
- Change in weight, HbA1c, waist circumference, heart rate, LDL, HDL, uric acid, eGFR from baseline repeated measures mixed model

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=2333)</th>
<th>Pooled empagliflozin (n=4687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ±SD)</td>
<td>63.2 ± 8.8</td>
<td>63.1 ± 8.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td>73</td>
<td>73.2</td>
</tr>
<tr>
<td>White race (%)</td>
<td>71.9</td>
<td>72.6</td>
</tr>
<tr>
<td>BMI (kg/m² ±SD)</td>
<td>30.7 ± 5.5</td>
<td>30.6 ± 5.3</td>
</tr>
<tr>
<td>AL (mg/dl)</td>
<td>0.09 ± 0.04</td>
<td>0.07 ± 0.06</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>75.6</td>
<td>75.4</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>10.5</td>
<td>11.4</td>
</tr>
<tr>
<td>SBP (mmHg ±SD)</td>
<td>135.8 ± 17.2</td>
<td>135.3 ± 16.9</td>
</tr>
<tr>
<td>GFR (ml/min/1.73m²)</td>
<td>60 to &lt;90</td>
<td>52.7</td>
</tr>
<tr>
<td>70-80</td>
<td>58.8</td>
<td>56.7</td>
</tr>
<tr>
<td>&lt;70</td>
<td>20.4</td>
<td>18.9</td>
</tr>
<tr>
<td>Urea albumin Cr &gt;300mg/dl (%)</td>
<td>11.1</td>
<td>12.9</td>
</tr>
<tr>
<td>Metabolic -insulin resistant therapy</td>
<td>40.9</td>
<td>41.9</td>
</tr>
<tr>
<td>Diabete</td>
<td>64.2</td>
<td>65.7</td>
</tr>
</tbody>
</table>

Cardiovascular Outcomes (n%)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Placebo (n=2333)</th>
<th>Pooled empagliflozin (n=4687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>282 (12.1)</td>
<td>490 (10.5)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.86 (0.74-0.99)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Key secondary outcome</td>
<td>333 (14.3)</td>
<td>599 (12.8)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.89 (0.78-1.01)</td>
<td>0.08**</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>194 (8.3)</td>
<td>269 (5.7)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.68 (0.57-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>137 (5.9)</td>
<td>172 (3.7)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.62 (0.49-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>95 (4.1)</td>
<td>126 (2.7)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.65 (0.50-0.85)</td>
<td>0.003</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>69 (2.9)</td>
<td>150 (3.2)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.26 (1.03-1.54)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>69 (2.9)</td>
<td>150 (3.2)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.26 (1.03-1.54)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*for superiority, Noninferiority, P<0.001; **0.08 for superiority, Noninferiority <0.001

### Renal Outcomes (%)

<table>
<thead>
<tr>
<th>Renal Outcomes</th>
<th>Empagliflozin (n=4124)</th>
<th>Placebo (n=2061)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy or death from cardiovascular causes</td>
<td>16.2</td>
<td>23.6</td>
<td>0.61 (0.55-0.69)</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>12.7</td>
<td>18.0</td>
<td>0.61 (0.53-0.70)</td>
</tr>
<tr>
<td>Progression to microalbuminuria</td>
<td>11.2</td>
<td>16.2</td>
<td>0.62 (0.54-0.72)</td>
</tr>
<tr>
<td>Doubling of Scr</td>
<td>1.5</td>
<td>2.6</td>
<td>0.56 (0.39-0.79)</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>0.3</td>
<td>0.6</td>
<td>0.45 (0.21-0.97)</td>
</tr>
<tr>
<td>Incident albuminuria</td>
<td>51.5</td>
<td>51.2</td>
<td>0.95 (0.87-1.04)</td>
</tr>
</tbody>
</table>


### CONCLUSIONS

- **Author’s Conclusions:** Patients with type 2 diabetes with high cardiovascular risk had significantly lower rates of cardiovascular related deaths and were noted to have a slower progression of kidney disease while on standard treatment.

#### Strengths

- Large sample population
- Well-designed outcomes study
- Large number of patients on standard of care
- Good distribution of baseline renal function
- Funding source

#### Weaknesses

- Cannot be extrapolated to patients with low CV risk
- Baseline BP and A1c near goal
- Renal outcomes as a secondary endpoint
- Funding source


---

### FUTURE STUDIES

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Study Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin (Invokana®)</td>
<td>CANVAS</td>
<td>T2DM with microalbuminuria and CVD • Primary: composite CV death, nonfatal MI, nonfatal stroke</td>
</tr>
<tr>
<td></td>
<td>CANVAS JR</td>
<td>Studying renal endpoints over 78-156 weeks To be completed April 2017</td>
</tr>
<tr>
<td></td>
<td>CREDENCE</td>
<td>T2DM with diabetic nephropathy • Primary: ESRD, doubling of Scr, renal or cardiovascular death</td>
</tr>
</tbody>
</table>


### SUMMARY

- SGLT’s role in glucose homeostasis presents an interesting target for not only glucose homeostasis, but also renal and cardiac protection.
- Pathophysiology is unclear, but appears to be multifactorial and related to reduction in arterial stiffness and renal damage.
- Benefits appear to be independent of SGLT2 dose or renal function and indicate class-wide modification of early endpoints of renal and cardiovascular disease.
- The DAPA-HELIX study demonstrated cardio-protective and renal-protective effects in diabetic patients with high cardiovascular risk factors.

### CONCLUSIONS

- In this group of patients with type 2 diabetes who are at high risk for cardiovascular events on standard of treatment, empagliflozin appears to be beneficial in secondary prevention of cardiovascular events and progression of renal damage.
- It remains to be seen if empagliflozin may be beneficial for primary prevention in a population initiated on therapy earlier in disease progression.
- Further studies are warranted to fully assess mechanisms behind these improvements, to clarify dosing effects in patients without cardiovascular disease and establish benefit as a class-wide effect.
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  - Michelle Nguyen, Pharm.D., BCACP

- Evaluator
  - Nile Barnes, Pharm.D., BCPS

CARDIAC AND RENAL PROTECTIVE EFFECTS OF SGLT-2 INHIBITORS: BENEFITS BEYOND GLYCEMIC CONTROL

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