SGLT2 inhibitors in the treatment of diabetic nephropathy

KCC staff education
Sept 26, 2019
Mike Bevilacqua
Disclosures

• I have accepted consultant, advisory, speakers honoraria and/or grants from:
  • AstraZeneca Canada
  • Boehringer Ingelheim Canada
  • Janssen Canada
  • Otsuka Pharmaceuticals Canada
  • Sanofi Canada

• Many of these slides/images were created as part of a slide set entitled “Renal Leap” with oversight from Drs. P MacFarlane and J Weinstein. They have been modified for this session
Outline

• Overview of diabetic nephropathy and its consequences
• The existing standard of care including RASB
• SGLT2 inhibitors, how they work
• Results of SGLT2 trials including CREDENCE
• Safety and use of SGLT2i in CKD
• Upcoming trials/future landscape of diabetic/CKD treatment
Causes of CKD in people with and without diabetes

Diabetic Nephropathy

1. Hyperfiltration
   - GFR significantly higher than normal
   - Identification of hyperfiltration is not currently clinically useful

2. Microalbuminuria
   - Small amounts of albumin in urine (30–300 mg/day; 2–20 mg/mmol)
   - Currently clinically useful
   - Detectable by dipstick urinalysis (>300 mg/day; >20 mg/mmol)

3. Macroalbuminuria (Overt nephropathy)
   - Rate of decline of renal function can accelerate (5–10 mL/min/1.73 m²/year)
   - >1000 mg/day; >67 mg/mmol

4. Late overt nephropathy

Followed by decline in kidney function, renal impairment, and ESRD

ESRD: End-stage renal disease, i.e. progression of kidney disease to failure requiring dialysis or transplant

- Progression can be accelerated by other comorbidities
- Many people with T2DM do not follow this “classical” progression
  - Over half of patients in United Kingdom Prospective Diabetes Study (UKPDS) cohort who developed eGFRs <60 mL/min/1.73 m² showed no preceding albuminuria
DKD prevalence and burden

- **40-50%** of people with diabetes will develop DKD\(^1,2\)
  - *CKD is more common than CVD* in patients with T2DM (24.1% vs 21.6%)\(^3\)
  - Co-prevalence of CKD + CVD rises 6-fold from age <65 years (3.0%) to ≥75 years (18.2%)\(^3\)
- Diabetes is the **leading cause of new cases of ESRD** in Canada\(^4\)
  - ~50% of adults **requiring dialysis or renal replacement** have ESRD attributable to diabetes\(^2\)
- **DKD can lead to complications**, including significant reductions in both length and quality of life\(^5\)
  - Between 1990 and 2012, number of **deaths due to DKD rose by 94%**\(^1\)
  - This rise is one of the highest observed for all reported chronic diseases

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\(^2\) Steele A. LMC Clinical Practice Update 2018 [in press].  
Over the last 20 years, Diabetes Canada (CDA) has advocated a three-pillared approach for patients with T2DM and renal impairment.

Grade A recommendations are supported by systematic overview or meta-analysis of high-quality randomized clinical trials (RCTs) or appropriately designed RCT(s) with adequate power to answer the question posed by the investigators.

CDA: Canadian Diabetes Association; T2D: type 2 diabetes; A1C: glycated hemoglobin; BP: blood pressure; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Despite these three strategies, there has been little improvement in the rate of ESRD

- Rates of the other major complications in diabetes have declined
- Rates of ESRD have actually increased among older adults

ESRD, end-stage renal disease; MI: myocardial infarction
DKD is Associated with Substantial Excess Risk of All-Cause Mortality

Ten-year standardized all-cause mortality by diabetes and kidney disease status (data from US NHANES III)

Incidence of mortality percentages indicate excess mortality above the reference group (individuals with no diabetes or kidney disease).

US, United States; NHANES III: Third National Health and Nutrition Examination Survey; eGFR, estimated glomerular filtration rate; ACR, albumin to creatinine ratio; Cr, creatinine.

Study included 15,046 participants aged >20 years who participated in a health examination and had available data on medications used, serum Cr and urine albumin and Cr concentrations and follow-up mortality data through 2006. Kidney disease was defined as urinary ACR ≥30 mg/g (≥3.4 mg/mmol) and/or eGFR <60 mL/min/1.73 m².

### Evidence behind ACEi or ARB: “Gold Standard” for DKD

<table>
<thead>
<tr>
<th>Study</th>
<th>Albuminuria</th>
<th>Baseline renal function</th>
<th>2xCr, ESRD, Renal Death – # of events</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDNT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Median 1900 mg/d (1000 – 3800 mg/d)</td>
<td>Mean Cr: 148 μmol/L</td>
<td>644</td>
<td>20% (p=0.006)</td>
</tr>
<tr>
<td>(irbesartan)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RENAAL&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Median ACR: ~1250</td>
<td>Mean Cr: 168 μmol/L</td>
<td>686</td>
<td>16% (p = 0.02)</td>
</tr>
<tr>
<td>(losartan)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi Collaborative study group&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Mean proteinuria: 2500 mg/d</td>
<td>Mean Cr: 115 μmol/L</td>
<td>2xCr: 68 Death or ESRD: 65</td>
<td>43% (p = 0.007) 46%</td>
</tr>
<tr>
<td>(captopril)</td>
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</tbody>
</table>

ACEi: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin receptor blocker

ACEi or ARB: “Gold Standard” for DKD

- Risk reduction associated with ACEi or ARB agents was an important development in primary care
- There is still a clear unmet need for new therapeutic interventions to improve the poor outcomes experienced in DKD

Note that this does not represent a head-to-head comparison or of ARB and ACEi effects in patients with DKD.

No new treatment for DKD since the advent of ACEi or ARB 17 years ago

ACEIs and ARBs

- **High blood pressure identified as risk factor for DKD**
- **1980s**
  - **β-blockers¹**
  - **Hydralazine²**
- **1990s**
  - **Captopril³**
    - **T1D**
- **2000s**
  - **IDNT⁴, IRMA ²⁵**
    - **Irbesartan**
      - **T2D**
  - **RENAAL⁶**
    - **Losartan**
      - **T2D**

No new specific treatments for DKD in the last 17 years

DKD, diabetic kidney disease; T1D, type 1 diabetes; T2D, type 2 diabetes; IDNT, Irbesartan Type 2 Diabetic Nephropathy Trial; RAAS, renin–angiotensin-aldosterone system; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan


Figure adapted from: Steele A. *LMC Clinical Practice Update* 2018 [in press].
Emerging evidence for a new intervention in DKD: SGLT2 inhibitors (SGLT2i)

“In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR >30 mL/min/1.73m², an SGLT2 inhibitor with proven renal benefit may be considered to reduce the risk of progression of nephropathy.”

– Diabetes Canada Guidelines, Chapter 29: Chronic Kidney Disease in Diabetes
The Normal Kidney

Renal handling of glucose in non-diabetic individuals

Glomerulus ~10% glucose reabsorbed
Facilitated by SGLT1

Proximal tubule ~90% glucose reabsorbed
Facilitated by SGLT2

Collecting duct No/minimal glucose excretion

Glucose filtration

Glucose reabsorption

SGLT = sodium glucose cotransporter

Renal handling of glucose in T2DM: increased glucose reabsorption

Excess glucose (≥240 g)

Glucose filtration

Glucose reabsorption

Increased expression of SGLT2 and SGLT1
  = more glucose filtered, more glucose absorbed

SGLT = sodium glucose cotransporter

Effect of ACEi and ARBs on intraglomerular pressure

**Pharmacological actions:**
ACEi or ARB

- Efferent dilation

**Hemodynamic effects and clinical implications:**

- More out = decreased pressure
- Decreased hyperfiltration
- Proven renal protection in clinical trials

**Diabetic Kidney**

- More in, less out = increased pressure
- Hyperfiltration, proteinuria, and renal cell damage

RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2; T1D-H, type 1 diabetes with hyperfiltration

Effect of SGLT2i on intraglomerular pressure

Pharmacological actions:
- Afferent constriction

Hemodynamic effects and clinical implications:
- Less in = decreased pressure
- Decreased hyperfiltration

Diabetic Kidney
- More in, less out = increased pressure
- Hyperfiltration, proteinuria, and renal cell damage

RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2; T1D-H, type 1 diabetes with hyperfiltration
Effect of SGLT2 inhibition and ACEi and ARBs on intraglomerular pressure

Diabetic Kidney

Afferent Dilated

Efferent Constricted

Pharmacological actions:
SGLT2 inhibition + ACEi or ARB

Hemodynamic effects and clinical implications:
- Potential for additive effect?
- Potential for long-term renal protection?

• More in, less out = increased pressure
• Hyperfiltration, proteinuria, and renal cell damage

RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2; T1D-H, type 1 diabetes with hyperfiltration
SGLT2 Inhibition

Exploratory data on Renal Efficacy & Safety from Large Cardiovascular Trials
CV Outcomes: EMPA-REG OUTCOME and LEADER

**EMPA-REG OUTCOME**
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

- HR 0.86 (95.02% CI, 0.74-0.99)
- P=0.04 for superiority

**LEADER**
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

- HR 0.87 (95% CI, 0.78-0.97)
- P<0.001 for noninferiority
- P=0.01 for superiority

CV Outcomes: CANVAS and DECLARE-TIMI 58

**CANVAS**
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

- HR 0.86 (95% CI, 0.75-0.97)
- P<0.001 for noninferiority
- P=0.02 for superiority

**DECLARE-TIMI 58**
Composite of death from cardiovascular death, myocardial infarction, or ischemic stroke

- Hazard ratio, 0.93 (95% CI, 0.84-1.03)
- P=0.17 for superiority

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In CV trials, eGFR initially drops and is stabilized over time

**EMPA-REG OUTCOME**
Change in eGFR* over 192 weeks

**CANVAS Program**
Change in eGFR over 6.5 years

*CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; CVOTs: cardiovascular outcome trials

In CV trials, SGLT2 inhibitors reduced the exploratory composite renal endpoints by ~45%

<table>
<thead>
<tr>
<th>Patients with event (%)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>26</td>
<td>52</td>
<td>78</td>
<td>104</td>
<td>130</td>
<td>156</td>
<td>182</td>
<td>208</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>22.2</td>
<td>22.2</td>
<td>21.4</td>
<td>20.4</td>
<td>17.1</td>
<td>12.9</td>
<td>10.7</td>
<td>6.8</td>
</tr>
</tbody>
</table>

**EMPA-REG OUTCOME**: (composite of doubling of SCr*, initiation of renal replacement therapy, or renal death)

Hazard ratio, 0.54 (95% CI, 0.40-0.75)
P=0.0002

**CANVAS Program**: (composite of doubling of SCr, ESRD, or renal death)

Hazard ratio, 0.53 (95% CI, 0.33-0.84)

No serious renal-related AEs, AKI, or hyperkalemia were observed in the CANVAS Program or EMPA-REG OUTCOME

~80% of patients were taking ARBs or ACE inhibitors

*C: Accompanied by eGFR ≤ 45 mL/min/1.73 m². Kaplan-Meier estimate. Treated set.

**CANA**: canagliflozin; SCr: serum creatinine; ESRD: end-stage kidney disease; PBO: placebo; HR: hazard ratio; CI: confidence interval

Putting DKD evidence into perspective

<table>
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<tr>
<td>REGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi Collaborative study group 3</td>
<td>Mean proteinuria: 2500 mg/d</td>
<td>Mean Cr: 115 μmol/L</td>
<td>68</td>
<td>43%</td>
</tr>
<tr>
<td>CANVAS Program 4, 5 (80% on RAASi)</td>
<td>Median UACR ~12 mg/g</td>
<td>Normal: ~70%</td>
<td>Micro: ~23%</td>
<td>Macro: ~7.5%</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME 7, 8 (81% on RAASi)</td>
<td>Median UACR ~17.7 mg/g</td>
<td>Micro: 29%</td>
<td>Macro: 11%</td>
<td>Mean eGFR: 74 mL/min/1.73 m²</td>
</tr>
<tr>
<td>DECLARE-TIMI 589, 10 (81% on RAASi)</td>
<td>&lt;30 mg/g: ~66%</td>
<td>30–300 mg/g: ~23.4%</td>
<td>&gt;300: ~6.8%</td>
<td>Mean eGFR: 86 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>

RAAS blockade trials were dedicated renal trials consisting of patients with advanced DKD and included primary renal endpoints.

CANVAS, EMPA-REG, and DECLARE-TIMI 58 were CVOTs consisting of patients with mild or no DKD and included exploratory or secondary renal outcomes.

*Kidney outcomes were not confirmed or adjudicated during the EMPA-REG OUTCOME trial5

CV outcomes trial results suggested possible attenuation of renal effects in patients with reduced kidney function

Composite of worsening of renal function, ESKD, or renal death

<table>
<thead>
<tr>
<th>eGFR &lt;60</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>DECLARE</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td><strong>0.67 (0.51–0.89)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eGFR 60–&lt;90</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>DECLARE</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td><strong>0.56 (0.46–0.70)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eGFR ≥90</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>DECLARE</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td><strong>0.44 (0.32–0.59)</strong></td>
</tr>
</tbody>
</table>

CREDENCE was designed specifically for renal outcomes in a higher risk renal population.

**CREDENCE**
T2DM + DKD
(N = 4,401; ~5.5 years follow-up)

**CANVAS-R**
T2DM + CVD risk/history
(N = 5,812; ~2 years follow-up)

**CANVAS**
T2DM + CVD risk/histroy
(N = 4,330; ~6 years follow-up)

**EMPA-REG OUTCOME**
T2DM + CVD history
(N = 7,020; ~3 years follow-up)

**CANVAS Program**
(N = 10,142; integrated analysis)

* Note that the patient populations in CANVAS and CANVAS-R are nearly identical to facilitate an integrated analysis of the data.

**Key inclusion criteria**

- ≥30 years of age
- T2DM and HbA1c 6.5–12.0%
- eGFR 30–90 mL/min/1.73 m²
- UACR 300–5000 mg/g (33.9–565 mg/mmol)
- Stable maximum tolerated or labelled dose of ACEi or ARB for ≥4 weeks

**Key exclusion criteria**

- ≥Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

Participants continued treatment if eGFR was <30 mL/min/1.73 m² until chronic dialysis was initiated or kidney transplant occurred.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; UACR, urinary albumin-to-creatinine ratio

In July 2018, after the planned interim analysis, the IDMC made the recommendation to stop the CREDENCE trial based on demonstration of efficacy.
**CREDENCE: Key baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (n = 4,401)</th>
<th>Proportion (n = 4,401)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant RAASi use</td>
<td>99.9%</td>
<td></td>
</tr>
<tr>
<td>CKD Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>(≥60 to &lt;90 mL/min/1.73 m²)</td>
<td>35%</td>
</tr>
<tr>
<td>Stage 3a</td>
<td>(≥45 to &lt;60 mL/min/1.73 m²)</td>
<td>29%</td>
</tr>
<tr>
<td>Stage 3b</td>
<td>(≥30 to &lt;45 mL/min/1.73 m²)</td>
<td>27%</td>
</tr>
</tbody>
</table>

- **Male Gender**: 2907 (66.1%)
- **Age, years**: 63.0±9.2
- **BMI, kg/m²**: 31.3±6.2
- **HbA1c, %**: 8.3±1.3
- **Duration of T2DM, years**: 15.8±8.7
- **eGFR, mL/min/1.73 m²**: 56.2±18.2
- **Median UACR, mg/mmol**: 105
- **Systolic BP, mmHg**: 140.0±15.6
- **Diastolic BP, mmHg**: 78.3±9.4
- **LDL-C, mmol/L**: 2.5±1.1
Primary Endpoint: Composite of ESKD, doubling of serum creatinine, and renal or CV death

Hazard ratio, 0.70 (95% CI, 0.59–0.82)
\( P = 0.00001 \)

No. at risk
- Placebo: 2199, 2178, 2132, 2047, 1725, 1129, 621, 170
- Canagliflozin: 2202, 2181, 2145, 2081, 1786, 1211, 646, 196

**Secondary Endpoint:** Composite of ESKD, doubling of serum creatinine, or renal death

Hazard ratio, 0.66 (95% CI, 0.53–0.81)
P < 0.001

Secondary Endpoint: End-stage kidney disease

Hazard ratio, 0.68 (95% CI, 0.54–0.86)  
P = 0.002

## Summary of key renal endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>0.70 (0.59–0.82)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Doubling of serum creatinine</td>
<td>0.60 (0.48–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESKD</td>
<td>0.68 (0.54–0.86)</td>
<td>0.002</td>
</tr>
<tr>
<td>eGFR &lt;15 mL/min/1.73 m²</td>
<td>0.60 (0.45–0.80)</td>
<td>–</td>
</tr>
<tr>
<td>Dialysis initiated or kidney transplantation</td>
<td>0.74 (0.55–1.00)</td>
<td>–</td>
</tr>
<tr>
<td>Renal death</td>
<td>0.39 (0.08–2.03)</td>
<td>–</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.61–1.00)</td>
<td>0.0502</td>
</tr>
<tr>
<td>ESKD, doubling of serum creatinine, or renal death</td>
<td>0.66 (0.53–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis, kidney transplantation, or renal death*</td>
<td>0.72 (0.54–0.97)</td>
<td>–</td>
</tr>
</tbody>
</table>

* Post-hoc analysis

Perkovic V. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-360.
Primary outcome by screening eGFR and albuminuria

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI)</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening eGFR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 to &lt;45 mL/min/1.73 m²</td>
<td>0.75 (0.59–0.95)</td>
<td>0.11</td>
</tr>
<tr>
<td>45 to &lt;60 mL/min/1.73 m²</td>
<td>0.52 (0.38–0.72)</td>
<td></td>
</tr>
<tr>
<td>60 to &lt;90 mL/min/1.73 m²</td>
<td>0.82 (0.60–1.12)</td>
<td></td>
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<tr>
<td><strong>Baseline UACR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1000 mg/g</td>
<td>0.76 (0.55–1.04)</td>
<td>0.49</td>
</tr>
<tr>
<td>&gt;1000 mg/g</td>
<td>0.67 (0.55–0.81)</td>
<td></td>
</tr>
</tbody>
</table>

Perkovic V. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-360.
Effects on eGFR

**Acute eGFR change (3 weeks)**
Placebo: –0.55 ml/min/1.73 m²
Canagliflozin: –3.72 ml/min/1.73 m²
Difference: –3.17
(95% CI, –3.87, –2.47)

**Chronic eGFR slope**
Difference: 2.74/year
(95% CI, 2.37–3.11)

<table>
<thead>
<tr>
<th>Months since randomization</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
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</tr>
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<tbody>
<tr>
<td>6</td>
<td>2178</td>
<td>2084</td>
<td>1985</td>
<td>1882</td>
<td>1720</td>
<td>1536</td>
<td>1006</td>
<td>583</td>
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<tr>
<td>12</td>
<td>2179</td>
<td>2074</td>
<td>2005</td>
<td>1919</td>
<td>1782</td>
<td>1648</td>
<td>1116</td>
<td>652</td>
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<tr>
<td>18</td>
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<td>24</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
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<td>36</td>
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<td>42</td>
<td></td>
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</tr>
</tbody>
</table>

Perkovic V. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-360.
Summary: Renal outcomes

• Canagliflozin **reduced the risk of the primary outcome** of ESKD, doubling of serum creatinine, or renal or CV death by **30%** (P = 0.00001)
  • The results were consistent across a broad range of prespecified subgroups

• Canagliflozin also **reduced the risk of the secondary outcome** of ESKD, doubling of serum creatinine, or renal death by **34%** (P <0.001)

• Similar risk reductions were seen for exploratory outcomes assessing components of the primary outcome
  • ESKD: **32%** lower
  • Doubling of serum creatinine: **40%** lower

• There is an expected initial drop in GFR

• Canagliflozin **attenuated the slope of chronic eGFR decline** by 2.7 mL/min/1.73 m²/year (−1.9 vs −4.6)
Risk reduction beyond ACE inhibitors and ARBs

• SGLT2 inhibitors reduce CV risk in patients with diabetes\(^1\)

• CREDENCE results demonstrate a reduction in hard renal outcomes associated with diabetes\(^2\)
  • Composite of ESKD, doubling of serum creatinine, and renal or cardiovascular death\(^3\)

• These benefits are on top of the standard of care of ACEi- or ARB-related risk reduction\(^2,3–5\)
  • ~80% of patients in EMPA-REG OUTCOME, CANVAS Program, and DECLARE TIMI 58 were taking ACEi or ARB with SGLT2i
  • 99.9% of patients in CREDENCE were taking ACEi or ARB

Secondary Endpoint: CV death or hospitalization for heart failure

Hazard ratio, 0.69 (95% CI, 0.57–0.83)  
P <0.001

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
Secondary Endpoint: CV Death, MI, or stroke (major adverse cardiovascular events, or 3-point MACE)

Hazard ratio, 0.80 (95% CI, 0.67–0.95)
P = 0.01

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
NNT for renal and CV outcomes over 2.5 years

- **Primary composite outcome**: 22
- **ESKD, doubling of serum creatinine, or renal death**: 28
- **ESKD**: 43
- **Hospitalization for heart failure**: 46
- **CV death, MI, or stroke**: 40
## Safety: AEs and serious AEs

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (N = 2200)</th>
<th>Placebo (N = 2197)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All AEs</strong></td>
<td>1784</td>
<td>1860</td>
<td>0.87 (0.82–0.93)</td>
</tr>
<tr>
<td><strong>All serious AEs</strong></td>
<td>737</td>
<td>806</td>
<td>0.87 (0.79–0.97)</td>
</tr>
</tbody>
</table>

Includes all treated participants through 30 days after last dose.

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
## Renal safety

<table>
<thead>
<tr>
<th>Number of participants with an event, n</th>
<th>Canagliflozin (N = 2200)</th>
<th>Placebo (N = 2197)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All renal-related AEs</td>
<td>290</td>
<td>388</td>
<td>0.71 (0.61–0.82)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>151</td>
<td>181</td>
<td>0.80 (0.65–1.00)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>86</td>
<td>98</td>
<td>0.85 (0.64–1.13)</td>
</tr>
</tbody>
</table>

Includes all treated participants through 30 days after last dose.

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
Concurrent SGLT2 inhibition and ACEi could have potential for additive drop in GFR

RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2; T1D-H, type 1 diabetes with hyperfiltration
A crucial safety mechanism in all of our patients, but especially when on combined treatments (like ACE/ARB and SGLT2i)
Effects on eGFR

![Graph showing the effects on eGFR with Placebo and Canagliflozin]

**Acute eGFR change (3 weeks)**
- Placebo: $-0.55$ ml/min/1.73 m$^2$
- Canagliflozin: $-3.72$ ml/min/1.73 m$^2$
- Difference: $-3.17$
  
  (95% CI, $-3.87$, $-2.47$)

**Chronic eGFR slope**
- Difference: 2.74/year
  
  (95% CI, 2.37–3.11)

Remember that an initial drop in GFR is expected.

Similar to starting ACEi/ARB

Especially in lower GFR patients, prudent to check after starting.

<table>
<thead>
<tr>
<th>Months since randomization</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2178</td>
<td>2084</td>
<td>1985</td>
<td>1882</td>
<td>1720</td>
<td>1536</td>
<td>1006</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>2179</td>
<td>2074</td>
<td>2005</td>
<td>1919</td>
<td>1782</td>
<td>1648</td>
<td>1116</td>
</tr>
</tbody>
</table>

Perkovic V. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-360.
Canagliflozin renal benefits are additive to ACEi and ARB

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Albuminuria</th>
<th>Baseline renal function</th>
<th>Median Follow-up</th>
<th>2xCr, ESKD, Renal Death # of events</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDNT¹</td>
<td>1715</td>
<td>Median: 1900 mg/d</td>
<td>Mean Cr: 148 μmol/L</td>
<td>2.6 years</td>
<td>644</td>
<td>20%</td>
</tr>
<tr>
<td>RENAAL²</td>
<td>1513</td>
<td>Median ACR: 140 mg/mmol</td>
<td>Mean Cr: 168 μmol/L</td>
<td>3.4 years</td>
<td>686</td>
<td>16%</td>
</tr>
<tr>
<td>ACEi Collaborative study group³</td>
<td>409</td>
<td>Mean proteinuria: 2500 mg/d</td>
<td>Mean Cr: 115 μmol/L</td>
<td>3.0 years</td>
<td>2xCrR: 68 Death or ESKD: 65</td>
<td>43%</td>
</tr>
<tr>
<td>CREDENCE*⁴,⁵ (99.9% on RAASI)</td>
<td>4401</td>
<td>Median UACR: 105 mg/mmol</td>
<td>Mean eGFR: 56.2 mL/min/1.73 m²</td>
<td>2.6 years</td>
<td>377</td>
<td>34%</td>
</tr>
</tbody>
</table>

*NOTE: All patients enrolled in CREDENCE were taking maximal labelled or tolerated daily dose of ACEi or ARB in addition to being treated to target for blood pressure and A1C as part of the standard of care⁴

---

**CREDENCE: Concomitant medications**

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (n = 2202)</th>
<th>Placebo (n = 2199)</th>
<th>Total (N = 4401)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose-lowering agents, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>66</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>Metformin</td>
<td>58</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>28</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Renal and CV protective agents, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAAS inhibitor</td>
<td>&gt;99.9</td>
<td>99.8</td>
<td>99.9</td>
</tr>
<tr>
<td>Statin</td>
<td>70</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>Antithrombotic</td>
<td>61</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Diuretic</td>
<td>47</td>
<td>47</td>
<td>47</td>
</tr>
</tbody>
</table>

Jardine MJ. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-359.
Does combination treatment alter treatment results or lead to AKI?

Analysis from the EMPA-REG OUTCOME® trial indicates empagliflozin may assist in preventing the progression of chronic kidney disease in patients with type 2 diabetes irrespective of medications that alter intrarenal hemodynamics

Gert J. Mayer¹, Christoph Wanner², Matthew R. Weir³, Silvio E. Inzucchi⁴, Audrey Koitka-Weber²,⁵,⁶, Stefan Hantel⁵, Maximilian von Eynatten⁵, Bernard Zinman⁷ and David Z.I. Cherney⁸

¹Department of Internal Medicine IV (Nephrology and Hypertension), Medical University, Innsbruck, Austria; ²Division of Nephrology, Würzburg University Clinic, Würzburg, Germany; ³Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA; ⁴Section of Endocrinology, Yale School of Medicine, New Haven, Connecticut, USA; ⁵Boehringer Ingelheim International GmbH, Ingelheim, Germany; ⁶Department of Diabetes, Central Clinical School, Monash University, Melbourne, Australia; ⁷Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Canada; and ⁸Department of Medicine and Department of Physiology, Division of Nephrology, University Health Network, University of Toronto, Canada
SGLTii combined with RASB, diuretic, CCB, NSAID

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Background medication use at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 2333)</td>
</tr>
<tr>
<td><strong>Background medication, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin receptor blocker</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1868 (80.1)</td>
</tr>
<tr>
<td>No</td>
<td>465 (19.9)</td>
</tr>
<tr>
<td>Any diuretic</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>988 (42.3)</td>
</tr>
<tr>
<td>No</td>
<td>1345 (57.7)</td>
</tr>
<tr>
<td>Thiazide</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>492 (21.1)</td>
</tr>
<tr>
<td>No</td>
<td>1841 (78.9)</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>364 (15.6)</td>
</tr>
<tr>
<td>No</td>
<td>1969 (84.4)</td>
</tr>
<tr>
<td>Potassium-sparing agent</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>139 (6.0)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>788 (33.8)</td>
</tr>
<tr>
<td>No</td>
<td>1545 (66.2)</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drug</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>188 (8.1)</td>
</tr>
<tr>
<td>No</td>
<td>2145 (91.9)</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme.

**Figure 2** | Doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease by background medication use at baseline. Serum creatinine accompanied by estimated glomerular filtration rate <45 ml/min per 1.73 m². Cox regression analysis in patients treated with ≥1 dose of study drug. Estimated glomerular filtration rate assessed by Modification of Diet in Renal Disease formula. ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug.
Higher initial drop in GFR (significant with RASB, diuretic, non-sig with CCB and NSAID)

Despite this
- No difference in treatment benefit at end of trial
- No difference in rate of AKI
- No difference in rate of drug discontinuation

Figure 5 | Change in estimated glomerular filtration rate values over prespecified periods by background medication use at baseline: (a) baseline to week 4; (b) week 4 to last value on treatment; and (continued)
Other AEs of interest

<table>
<thead>
<tr>
<th>Number of participants with an event, n</th>
<th>Canagliflozin (N = 2200)</th>
<th>Placebo (N = 2197)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male genital mycotic infections*</td>
<td>28</td>
<td>3</td>
<td>9.30 (2.83–30.60)</td>
</tr>
<tr>
<td>Female genital mycotic infections†</td>
<td>22</td>
<td>10</td>
<td>2.10 (1.00–4.45)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>245</td>
<td>221</td>
<td>1.08 (0.90–1.29)</td>
</tr>
<tr>
<td>Volume depletion–related AEs</td>
<td>144</td>
<td>115</td>
<td>1.25 (0.97–1.59)</td>
</tr>
<tr>
<td>Malignancies‡</td>
<td>98</td>
<td>99</td>
<td>0.98 (0.74–1.30)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>1</td>
<td>5</td>
<td>0.20 (0.02–1.68)</td>
</tr>
<tr>
<td>Breast†</td>
<td>8</td>
<td>3</td>
<td>2.59 (0.69–9.76)</td>
</tr>
<tr>
<td>Bladder</td>
<td>10</td>
<td>9</td>
<td>1.10 (0.45–2.72)</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>5</td>
<td>2</td>
<td>2.44 (0.47–12.59)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>11</td>
<td>1</td>
<td>10.80 (1.39–83.65)</td>
</tr>
</tbody>
</table>

Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.

*Includes male participants only (canagliflozin, n = 1439; placebo, n = 1466).
†Includes female participants only (canagliflozin, n = 761; placebo, n = 731).
‡Includes malignant tumors of unspecified type.
AEs: Fracture

Concern in prior SGLT2i trials, not seen in CREDENCE

Hazard ratio, 0.98 (95% CI, 0.70–1.37)

<table>
<thead>
<tr>
<th>Months since randomization</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>2197</td>
<td>2200</td>
</tr>
<tr>
<td>12</td>
<td>2166</td>
<td>2171</td>
</tr>
<tr>
<td>18</td>
<td>2128</td>
<td>2121</td>
</tr>
<tr>
<td>24</td>
<td>2061</td>
<td>2074</td>
</tr>
<tr>
<td>30</td>
<td>1769</td>
<td>1785</td>
</tr>
<tr>
<td>36</td>
<td>1178</td>
<td>1225</td>
</tr>
<tr>
<td>42</td>
<td>656</td>
<td>668</td>
</tr>
</tbody>
</table>

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
**AEs: Lower extremity amputation**

- **Hazard ratio, 1.11 (95% CI, 0.79–1.56)**

- **Participants with an event (%)**
  - Placebo: 6, 12, 18, 24, 30, 36, 42
  - Canagliflozin: 70 participants

- **70 participants**
- **63 participants**

- **No. at risk**
  - Placebo: 2197, 2169, 2131, 2065, 1766, 1177, 658, 182
  - Canagliflozin: 2200, 2163, 2118, 2071, 1788, 1228, 667, 202

---

Concern in prior SGLT2i trials, not seen in CREDENCE:
Routine foot checks were included in CREDENCE:
considered standard of care

---

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
### SGLT2i-Associated Side Effects

<table>
<thead>
<tr>
<th>COMMON</th>
<th>LESS COMMON</th>
<th>RARE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genital infections</strong></td>
<td><strong>Urinary tract infections</strong></td>
<td><strong>Diabetic ketoacidosis</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Osmotic diuresis,</strong></td>
<td><strong>Amputations</strong></td>
</tr>
<tr>
<td></td>
<td><strong>hypovolemia,</strong></td>
<td><strong>Possible increase in fractures</strong></td>
</tr>
<tr>
<td></td>
<td><strong>hypotension</strong></td>
<td><strong>Increase in bladder cancer</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Mild LDL-C increase</strong></td>
<td><strong>Pancreatitis</strong></td>
</tr>
</tbody>
</table>
Summary: Safety

• Similar rates of amputation and fracture observed with canagliflozin and placebo are reassuring and consistent with trials of other SGLT2 inhibitors
  • Reassuring and differ from the CANVAS program findings
• Overall safety profile is otherwise consistent with the known adverse effects associated with canagliflozin
Putting all together

• SGLT2i represent an additional mechanism for delaying decline in DKD
• The dedicated CREDENCE trial demonstrated impressive, clinically important benefits in renal outcomes
  • Effect on top of RASB
  • These medications are safe, including in combination treatment
  • Remember the ‘Sick Day’ medication list

• Not yet firmly recommended as standard of care, but that is likely coming – in the CREDENCE like population (GFR >30, ACR>30)
• Coverage can sometimes be an issue
Stay tuned: Update on Renal Outcomes Trials

<table>
<thead>
<tr>
<th>CREDECE$^{1,2}$</th>
<th>DAPA-CKD$^3$</th>
<th>EMPA-KIDNEY$^4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stopped early based on the achievement of pre-specified efficacy criteria</td>
<td>Ongoing, estimated completion Nov 2020</td>
<td>Ongoing, estimated completion June 2022</td>
</tr>
</tbody>
</table>

Will include:
- Lower ranges of GFR
- Lower ranges of protein
- *Non-diabetic* CKD

3. ClinicalTrials.gov Identifier: NCT03036150; 4 ClinicalTrials.gov Identifier: NCT03594110.
Questions/Discussion