**CREDENCE**: Canagliflozin (INVOKANA) & Renal Outcomes in T2DM with Nephropathy

**Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation**

**SUMMARY:**

- In individuals with T2DM and nephropathy (stage 2 or 3 CKD), canagliflozin compared to placebo:
  - **Benefit**: reduced the primary composite outcome of ESKD, doubling of Scr & renal or CV death (NNT= 23/2.6 yrs)
    - Components of the composite primary outcome:
      1. Doubling of Scr: NNT=33/2.6 yrs
      2. Composite ESKD (estimated eGFR <15 & need for dialysis or kidney transplant); → NNT=46/2.6 yrs: driven by ↓ in patients with eGFR <15 not by ↓ in dialysis or kidney transplant
      3. Cardiovascular death: NS
      4. Renal death: NS
  - **Harms**: increased the risk of DKA (HR 10.80; 95% CI 1.39-83.65, event rate 0.05% vs 0.5%, NNH = 223/2.6 yrs) and male genital mycotic infections (HR 9.30; 95% CI 2.83-30.60, event rate 0.2% vs 1.9%, NNH = 59/2.6 yrs) were numerically increased in the canagliflozin group. Overall, serious adverse events were similar between the two groups, including risk of amputation and fractures. These findings were different than the CANVAS trial which showed an increased risk of amputation (HR 1.97; 95% CI 1.41-2.75) and fractures (HR 1.26; 95% CI 1.04 to 1.52) over 3.6 years. However, CREDENCE had a lower dose (100mg) and shorter duration of trial (2.6 yrs).
  - All participants were required to be on a stable, maximum tolerated labeled daily dose of ACEi or ARB for renal protection at least 4 weeks prior to randomization. This may make it harder to show a difference with other interventions, however, this is representative of current best practice.
  - The majority of patients did not meet Diabetes Canada guideline recommendations for optimizing modifiable cardiovascular risk factors for patients with longstanding diabetes and chronic kidney disease complications (i.e. baseline characteristics included mean A1C 8.3%, BP 140/78 mmHg, LDL-C 2.5 mmol/L, 69% statin use, BMI 31.3, 14% current smokers). Physical activity was encouraged but not reported.

**BOTTOM LINE:**

Canagliflozin may be considered 2nd line for patients with longstanding T2DM and high risk of renal complications (i.e. Stage 2 or 3 CKD with nephropathy) to provide renal and cardiovascular protection in addition to using renoprotective medications (i.e. RAAS inhibitors). The renoprotective benefit should be weighed against the potential harms; rare ketoacidosis, amputation concerns CANVAS, genital infections, Fournier' gangrene and acute kidney injury. There is also limited long term safety data. Diabetes Canada recommends glycemic control (A1C <7%) for renal protection, however renal benefit was realized despite A1C not at target (mean A1C 8.3%, duration of DM 15.8 yrs ± 8.6, median ACR 105 mg/mmol (i.e. 927 mg/g)).

**BACKGROUND:**

- T2DM is the leading cause of CKD, previous CV trials of SGLT-2 inhibitors demonstrated CV protection and suggested a signal for potential kidney benefits results with exploratory outcomes for improving renal outcomes. EMPA-REG, CANVAS, DECLARE
- Canagliflozin INVOKANA is a sodium-glucose co-transporter 2 (SGLT-2) inhibitor approved in 2014 for the management of T2DM as monotherapy or add-on to metformin alone, sulfonylurea ± metformin, pioglitazone + metformin, sitagliptin + metformin, insulin ± metformin as adjunct to diet and exercise. HC
- Canagliflozin is also indicated as adjunct to diet, exercise and standard of care to ↓ MACE in adults with T2DM and established CVD.
- Canagliflozin benefits results with exploratory outcomes for improving renal outcomes.
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- In the CANVAS trial, patients were started on canagliflozin 100mg once daily dose with the option of titrating to 300mg once daily for those who needed more stringent glycemic control.
- At the time of print/publishing, Saskatchewan Health (EDS) and NIHB coverage currently cover for patients who are not controlled on metformin + SU and for whom insulin is not an option and not in combination with a DPP-4 inhibitor. EDS

**TRIAL SUMMARY**

**DESIGN:** Randomized (concealed allocation), multinational (690 sites, 34 countries), double-blind, placebo-controlled superiority trial with ITT analysis for efficacy, 2 week single-blind, placebo run-in phase. Enrollment: March 2014 – May 2017; Funding: Janssen (manufactures canagliflozin).

**INTERVENTION:** Canagliflozin 100mg once daily vs matching placebo, added to existing standard of care therapy based on local guidelines concluded with ITT analysis.

**INCLUSION:** T2DM, Age ≥ 30 years, A1C 6.5-12%, **Stage 2 or 3 CKD:** eGFR 30-90 mL/min (calculated using the CKD-EPI formula) & albuminuria 33.9-565 mg/mmol (i.e. 300-5000mg/g), established on max labeled/tolerated doses of ACEi or ARB for ≥ 4 weeks prior to randomization [calculated using the CKD-EPI (CKD Epidemiology Collaboration) formula]

**EXCLUSION:** T2DM or non-diabetic kidney disease; kidney disease treated with immunosuppressants; dialysis or kidney transplant; use of SGLT-2 inhibitor ≤ 12 weeks prior randomization; participation in prior canagliflozin study; dual treatment of ACEi, ARB, direct renin-inhibitor or MRA; CV event in prior 12 weeks; NYHA class IV HF; uncontrolled HTN (≥180/100mmHg); K+ >5.5 mmol/L; liver dx (ALT>2x ULN or total bilirubin >1.5x ULN); hx of malignancy in prior 5 yrs; HIV; major surgery in prior 12 weeks; hx of atrumatic amputation in prior 12 mos or active skin ulcer, osteomyelitis, gangrene or critical ischemia of the lower limb in prior 6 mos; pregnancy or breastfeeding; poor compliance during run-in period (<80%).

**POPULATION at baseline:**

- Age: 63 ± 9.2 yrs; %66% male; 26.9% North America (14.6% CAN, 59.8% US, 25.6% Mexico)
- A1C: Duration of DM; Median ACR: 8.3% ± 1.3; 15.8 years ± 8.6; 105 mg/mmol (i.e. 927 mg/g)
- Renal function (mL/min/1.73m²): eGFR <60 (4.8%), 60 to 89 (35.4%), 45 to 59 (28.8%), 30 to 44 (27.1%), 15 to 29 (3.9%), <14 (<0.1%)
- Race/Ethnicity:……………………………………………………………………………….White (66.6%); Black (5.1%); Asian (19.9%); Other (8.4%)
- Other Antihyperglycemics:………………………………………………………………….Insulin (65.5%); Metformin (57.8%); SU (28.8%); DPP-4 inhibitor (17.1%); GLP-1 agonist (4.2%)
- CV/Renal Therapies:…………………………………………………………………………….RAAS inhibitor (99.9%); Statin (69.0%); Antithrombotic (59.6%); Diuretic (46.7%); Beta-blocker (40.2%)
- Microvascular disease:…………………………………………………………………………….Nephropathy (100%); Neuropathy (48.8%); Retinopathy (42.8%)
- Cardiovascular disease:…………………………………………………………………………….ASCVD (coronary 29.8%, cerebrovascular 15.9%, PAD 23.8%); CVD (50.4%); HTN (96.8%); HF (14.8%)
- Modifiable Risk Factors:…………………………………………………………………………….SBP (140 ± 15.6mmHg); DBP (78.3 ± 9.4mmHg); smoker (14.5%); BMI (31.3 ± 6.2 kg/m²); LDL (2.5 ± 1.1 mmol/L)
### STRENGTHS, LIMITATIONS, & UNCERTAINTIES

**STRENGTHS:**

- This is the first trial to assess canagliflozin’s renal efficacy and safety as the primary outcomes in patients with high risk of progression of CKD. It also adds to the current literature on SGLT-2 inhibitor’s CV efficacy and safety.
- Intention to treat analysis and blinded adjudication was utilized for efficacy and safety endpoints.
- Rate of adherence to the trial regimen was 84%, therefore results are a good representation of the drug’s effect.
- No new adverse events uncovered; somewhat mitigates amputation concerns raised by CANVAS if lower dose is used for a shorter duration.

**LIMITATIONS:**

- Trial was stopped early for benefit (2.6 years) at a planned interim analysis limiting the power of secondary outcomes and the possibility of overestimating effect sizes when events rates were small (i.e. composite endpoint driven by surrogates). The trial length may have been too short to show long term adverse events (e.g. amputations, fractures).
- Not generalizable to certain populations. Patients were excluded who had very advanced kidney disease (eGFR<30), non/microalbuminuric kidney disease or other non diabetes related kidney disease.
- Subgroup analysis of the primary outcome showed the most renal protective effect benefit at eGFR 45-59ml/min but was seen as low as eGFR 30ml/min. 60% of the study population had an eGFR <60ml/min and was ultimately a driver for the positive renal outcomes.
- The type of heart failure, based on ejection fraction, was not reported, nor the type of beta-blocker used in these individuals. Only ~15% of patients has HF at baseline, but HF hospitalizations was one of the CV outcomes.
- Additional 2* outcomes: Difference in CV death was nonsignificant, therefore all other subsequent outcomes were not formally evaluated including all-cause death & the composite of CV Death, MI, stroke or hospitalization for HF or for unstable angina.

### TABLE 1: EFFICACY

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT</th>
<th>CANAGLIFLOZIN 100mg n = 2202</th>
<th>PLACEBO n = 2209</th>
<th>HR (95% CI)</th>
<th>P VALUE</th>
<th>ARR/ARI</th>
<th>NNT/NNH /2.6yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESKD, doubling of SCR, or death from renal or CV disease</td>
<td>11.1% (n=245)</td>
<td>15.5% (n=340)</td>
<td>0.70 (0.59-0.82)</td>
<td>0.00001</td>
<td>↓ 4.4%</td>
<td>23</td>
</tr>
<tr>
<td>COMPONENTS OF PRIMARY COMPOSITE ENDPOINTS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Double of SCR</td>
<td>5.4% (n=118)</td>
<td>8.5% (n=188)</td>
<td>0.60 (0.48-0.76)</td>
<td>&lt;0.001</td>
<td>↓ 3.1%</td>
<td>33</td>
</tr>
<tr>
<td>ESKD (eGFR &lt;15ml/min, dialysis or kidney transplant)</td>
<td>5.3% (n=116)</td>
<td>7.5% (n=165)</td>
<td>0.68 (0.54-0.86)</td>
<td>0.002</td>
<td>↓ 2.2%</td>
<td>46</td>
</tr>
<tr>
<td>Renal death</td>
<td>0.1% (n=2)</td>
<td>0.2% (n=5)</td>
<td>NS</td>
<td>*HR calculated for outcomes with &gt;10 events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>5.0% (n=110)</td>
<td>6.4% (n=140)</td>
<td>0.78 (0.61-1.00)</td>
<td></td>
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</tr>
<tr>
<td>All-cause mortality</td>
<td>7.6% (n=168)</td>
<td>9.1% (n=201)</td>
<td>0.83 (0.68-1.02)</td>
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</tr>
</tbody>
</table>

**SECONDARY ENDPOINTS**

- CV Death or HHF
- CV Death, MI or stroke
- Hospitalization for HF (HHF)
- ESKD, doubling of SCR, or renal death

End Stage Kidney Disease: estimated eGFR <15 ml/min for ≥ 30 days, dialysis initiated for ≥ 30 days or kidney transplant. Additional 2* outcomes: Difference in CV death was nonsignificant, therefore all other subsequent outcomes were not formally evaluated including all-cause death & the composite of CV Death, MI, stroke or hospitalization for HF or for unstable angina.

### TABLE 2: SAFETY RESULTS (ADVERSE EVENTS)

<table>
<thead>
<tr>
<th>CLINICAL ENDPOINTS</th>
<th>CANAGLIFLOZIN 100mg n = 2202</th>
<th>PLACEBO n = 2209</th>
<th>HR (95% CI)</th>
<th>P VALUE</th>
<th>NNT/NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event (AE)</td>
<td>81.8% (n=1814)</td>
<td>84.7% (n=1860)</td>
<td>0.87 (0.82-0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All serious AE</td>
<td>33.5% (n=737)</td>
<td>36.7% (n=806)</td>
<td>0.87 (0.79-0.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious AE (related to study drug)</td>
<td>2.8% (n=62)</td>
<td>1.9% (n=42)</td>
<td>1.45 (0.98-2.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputations</td>
<td>3.2% (n=70)</td>
<td>2.9% (n=63)</td>
<td>1.11 (0.79-1.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td>3.0% (n=67)</td>
<td>3.1% (n=68)</td>
<td>0.98 (0.70-1.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Pancreatitis</td>
<td>0.2% (n=5)</td>
<td>0.1% (n=2)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>3.9% (n=86)</td>
<td>4.5% (n=98)</td>
<td>0.85 (0.64-1.13)</td>
<td></td>
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</tr>
<tr>
<td>Diabetic Ketoacidosis (DKA)</td>
<td>0.5% (n=11)</td>
<td>0.05% (n=1)</td>
<td>10.80 (1.39-83.65), NNH = 222/2.6 yrs</td>
<td></td>
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</tr>
<tr>
<td>Hypoglycemia</td>
<td>10.2% (n=225)</td>
<td>10.9% (n=240)</td>
<td>0.92 (0.77-1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital Mycotic Infection (M)</td>
<td>1.9% (n=28)</td>
<td>0.2% (n=3)</td>
<td>9.30 (2.83-30.60), NNH = 59/2.6 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital Mycotic Infection (F)</td>
<td>2.9% (n=22)</td>
<td>1.4% (n=10)</td>
<td>2.10 (1.00-4.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal-related events (including AKI)</td>
<td>13.2% (n=290)</td>
<td>17.7% (n=388)</td>
<td>0.71 (0.61-0.82)</td>
<td></td>
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</tr>
</tbody>
</table>

Patients who discontinued from randomized treatment for any reason: Canagliflozin (24.7%) vs placebo (29.9%), with adverse events accounting for 12.0% (263 patients) in the canagliflozin group vs 13% (285 patients) in the placebo group.

Of note: 137 patients discontinued treatment due to an AE with a fatal outcome, however, it was not noted whether this was in the treatment or placebo group.

### SUMMARY

- **Endpoints:** Canagliflozin vs placebo
  - A1C ↓ 0.25%
  - SBP ↓ 3.3 mmHg
  - DBP ↓ 0.95 mmHg
  - Weight ↓ 0.80kg
  - ACR ↓ 31%
  - Change in eGFR slope ↓ 1.52ml/min/year

- **HARM**
  - *HR calculated for outcomes with >10 events
  - DKA: this result is limited by small number of outcomes

- **JUNE 2019:**
  - **Table 1: Efficacy**
  - **Table 2: Safety Results (Adverse Events)**

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recommended by Diabetes Canada were not met in this population at baseline or end of study.

- Findings are relevant to long standing diabetic patients (~15 yrs) with CKD (eGFR 30-90 ml/min), it is uncertain what the renal protective benefit would be in an earlier prevention strategy.

- Patients with a history of amputations were excluded from the trial in May 2016 after the signal of increased amputation risk arose from the publication of the CANVAS trial decreasing the event rate of this safety outcome.

 Uncertainties:

- The difference in amputation risk could be due to less patient drug exposure in CREDENCE vs CANVAS. In CREDENCE, the length of the trial was shorter (2.6 vs 3.6 years), there was a smaller population size (4,400 vs 10,142) and a lower daily dose of canagliflozin (100mg vs 100-300mg).

- Is renal protection a SGLT-2 class effect? Other trials are currently ongoing DAPA-CKD (estimated completion Nov 2020), EMPA-KIDNEY (estimated completion 2022).

- Does it help to prevent kidney damage in health diabetic patients? Unknown- this trial started people on the drug late in the course of their kidney damage.

- The rate of progression from normoalbuminuria to microalbuminuria, then to overt kidney disease, is usually slow, typically taking five years or longer to progress through each stage. SC A longer trial would have created more opportunity to see the significance rare events such as renal death.

- Patients were enrolled in the trial using only one ACR level, which is not in accordance with Diabetes Canada guidelines which states at least 2 out of 3 urine samples exhibiting elevations in urinary albumin levels over 3 months are required before it is considered to be abnormal. The severity of CKD could have been misrepresented and therefore affect measured outcomes.

- Roughly one-quarter (26.9%) of participants were from North America, but the percentage of individuals specifically from Canada was not reported.

- Trial did not report or publish the mean number of antihyperglycemic medications per patient at the end of trial.

- Exact mechanism of potential CV and renal benefits unknown.

References:


