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

Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation [1]

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=33/2.6yrs
      2. Composite ESKD {estimated eGFR <15 & need for dialysis or kidney transplant};
         → NNT=46/2.6yrs: driven by a ↓ in patients with eGFR <15 not by ↓ in dialysis or kidney transplant
      3. Cardiovascular death: NS
      4. Renal death: NS too small of an effect size to measure significance (2 vs 5 deaths with placebo), therefore driven by surrogate endpoints
  - **Harms**: increased the risk of DKA (HR 10.80; 95% CI 1.39-83.65; event rate 0.05% vs 0.5%, NNH = 222/2.6 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 another intervention, 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 long standing 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 reduction of 0.25%; baseline A1C=8.3%) as well as modest decreases in weight and blood pressure.

The DAPA-CKD (estimated completion Nov 2020) and EMPA-KIDNEY (estimated completion 2022) trials are currently underway to see if renal benefit extends to the whole class of SGLT-2 inhibitors.

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 ☎ ✆; ~ $325/100 days 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. CANVAS, HC 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 EDS, NIHB and for whom insulin is not an option and not in combination with a DPP-4 inhibitor. EDS

TRIAL SUMMARY [1, 2]

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

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: T1DM 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 previous 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 atraumatic 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: .....n=4,401; Age 63 ± 9.2 yrs; ~66% ♂; 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 yrs ± 8.6; 105 mg/mmol (i.e. 927 mg/g)
- Renal function (mL/min/1.73m^2).....eGFR ~56.2: ≥90 (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-1agonist (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 history:..... 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/m^2); LDL (2.5 ± 1.1 mmol/L)

RESULTS

follow-up: median 2.62 yrs

TABLE 1: EFFICACY

CLINICAL ENDPOINTS ITT ANALYSIS	CANAGLIFLOZIN 100MG n= 2202	PLACEBO n=2199	HR (95% CI)	P VALUE	ARR/ARI	NNT/NNH /2.6YRS	COMMENTS
PRIMARY ENDPOINT							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.
ESKD, doubling of SCr, or death from renal or CV disease	11.1% (n=245)	15.5% (n=340)	0.70 (0.59-0.82)	0.00001	↓ 4.4%	23	
COMPONENTS OF PRIMARY COMPOSITE ENDPOINTS							
Doubling of SCr	5.4% (n=118)	8.5% (n=188)	0.60 (0.48-0.76)	<0.001	↓ 3.1%	33	
ESKD (eGFR <15ml/min, dialysis or kidney transplant)	5.3% (n=116)	7.5% (n=165)	0.68 (0.54-0.86)	0.002	↓ 2.2%	46	
Renal death	0.1% (n=2)	0.2% (n=5)	NS *HR calculated for outcomes with >10 events				
Cardiovascular death	5.0% (n=110)	6.4% (n=140)	0.78 (0.61-1.00)	NS			
All-cause mortality	7.6% (n=168)	9.1% (n=201)	0.83 (0.68-1.02)	NS			
SECONDARY ENDPOINTS							**Mean difference in surrogate 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
CV Death or HHF	8.1% (n=179)	11.5% (n=253)	0.69 (0.57-0.83)	<0.001	↓ 3.4%	30	
CV Death, MI or stroke	9.9% (n=217)	12.2% (n=269)	0.80 (0.67-0.95)	0.01	↓ 2.3%	44	
Hospitalization for HF (HHF)	4.0% (n=89)	6.4% (n=141)	0.61 (0.47-0.80)	<0.001	↓ 2.4%	42	
ESKD, doubling of SCr, or renal death	6.9% (n=153)	10.2% (n=224)	0.66 (0.53-0.81)	<0.001	↓ 3.3%	31	

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)

CLINICAL ENDPOINTS	CANAGLIFLOZIN 100MG n= 2200	PLACEBO n=2197	HR (95% CI)	COMMENTS
Any adverse event (AE)	81.0% (n=1784)	84.7% (n=1860)	0.87 (0.82-0.93)	*HR calculated for outcomes with >10 events DKA: this result is limited by small number of outcomes
All serious AE	33.5% (n=737)	36.7% (n=806)	0.87 (0.79-0.97)	
Serious AE (related to study drug)	2.8% (n=62)	1.9% (n=42)	1.45 (0.98-2.14)	
Amputation	3.2% (n=70)	2.9% (n=63)	1.11 (0.79-1.56)	
Fracture	3.0% (n=67)	3.1% (n=68)	0.98 (0.70-1.37)	
Acute Pancreatitis	0.2% (n=5)	0.1% (n=2)	NA*	
Acute Kidney Injury	3.9% (n=86)	4.5% (n=98)	0.85 (0.64-1.13)	
Diabetic Ketoacidosis (DKA)	0.5% (n=11)	0.05% (n=1)	10.80 (1.39-83.65), NNH = 222/2.6 yrs	
Hypoglycemia	10.2% (n=225)	10.9% (n=240)	0.92 (0.77-1.11)	
Genital Mycotic Infection (M)	1.9% (n=28)	0.2% (n=3)	9.30 (2.83-30.60), NNH = 59/2.6 yrs	
Genital Mycotic Infection (F)	2.9% (n=22)	1.4% (n=10)	2.10 (1.00-4.45)	
Renal-related events (including AKI)	13.2% (n=290)	17.7% (n=388)	0.71 (0.61-0.82)	

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.

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.
- Intention to treat analysis was preformed; lost-to-follow-up was low (0.9%).
- Rate of adherence to the trial regimen was 84%, therefore results are a good representation of the drug's effect.
- Adds to the hypothesis that the benefit is independent of glucose levels and possibly due to decrease in intraglomerular pressure.
- 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.
- The primary composite outcome may have not been appropriate as individual components were not all renal related. (i.e. CV death was grouped in with renal outcomes)
- There were many composite outcomes measured, including the primary outcome, so it is difficult to know the clinical impact of the individual components. Although not powered for individual components of a composite endpoint, reviewing each individual endpoint can help.
- Individuals with HF were not allowed to be on the combination of an ACEi/ARB and MRA (e.g. spironolactone), despite the guideline recommendations for the mortality and morbidity benefits shown in this population. 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.
- Modifiable risk factors (i.e. A1C, lipids, BP targets, obesity and smoking) for decreasing renal disease progression as

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 a 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.

UNCERTAINITIES:

- 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.[DC] 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.

RxFILES RELATED LINKS

- RxFiles Diabetes Agents Outcome Table: https://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf
- RxFiles EMPA-REG trial summary: https://www.rxfiles.ca/rxfiles/uploads/documents/EMPA-REG%20Trial%20Summary.pdf
- Rxfiles DECLARE trial summary: https://www.rxfiles.ca/RxFiles/uploads/documents/DECLARE-trial%20summary-%20Dapagliflozin-%20FORXIGA.pdf

✗ = non-formulary in SK **⊗**= not covered by NIHB **℘**= Prior approval required by NIHB **☎**= Exceptional Drug Status in SK **♂**= male **♀**=female **A1C**=glycosylated hemoglobin **ACS**=acute coronary syndrome **ACEi**= angiotensin-converting enzyme inhibitor **AE**= adverse event **AKI**= acute kidney injury **ARB**= angiotensin receptor blocker **ARI**=absolute risk increase **ARR**=absolute risk reduction **ASCVD**=atherosclerotic cardiovascular disease **BMI**=body mass index **BP**=blood pressure **CI**=confidence interval **CKD**= chronic kidney disease **CKD-EPI**= CKD Epidemiology Collaboration **CV**= cardiovascular **CVD**=cardiovascular disease **DBP**=diastolic blood pressure **DC**= Diabetes Canada **D/C**=discontinue(d) **DKA**= diabetic ketoacidosis **DPP-4**=dipeptidyl peptidase-4 **DM**= diabetes mellitus **eGFR**=estimated glomerular filtration rate **ESKD**= end stage kidney disease **GLP-1**=glucagon-like peptide 1 **HC**= Health Canada **HF**=heart failure **HHF**= hospitalization for heart failure **HR**=hazard ratio **hx**=history **ITT**= intention to treat **MACE**= major adverse cardiac events **MI**=myocardial infarction **NNH**=number needed to harm **NNT**=number needed to treat **PAD**=peripheral artery disease **PP**=per protocol **pts**=patients **SBP**=systolic blood pressure **SGLT-2 Θ**= sodium-glucose transporter 2 inhibitor **sx**=symptom **T1DM**=type 1 diabetes mellitus **T2DM**=type 2 diabetes mellitus **TIA**=transient ischemic attack **TZD**=thiazolidinedione **UTI**=urinary tract infection

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