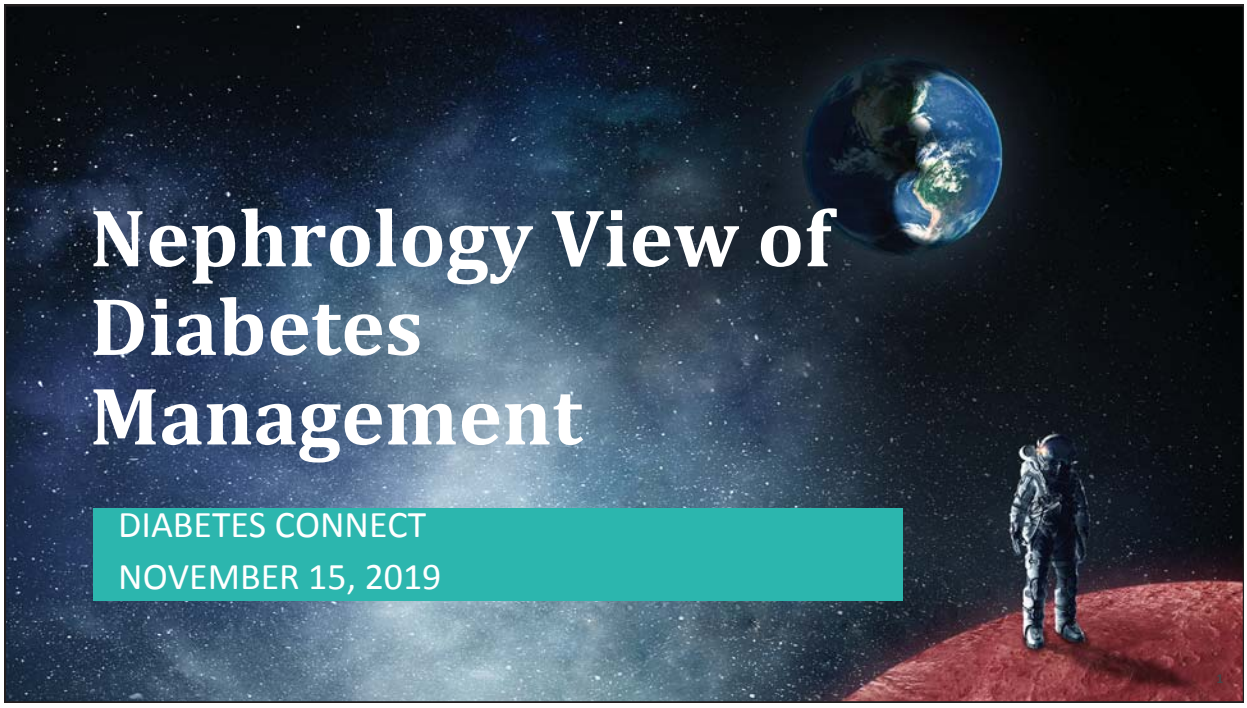


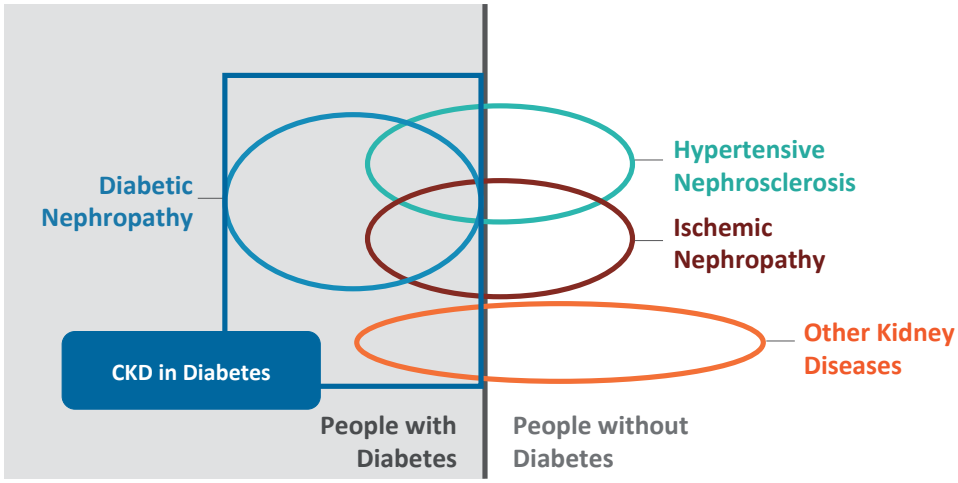
Learning Objectives

Upon completion of this program, participants will be better able to:

- Define chronic kidney disease (CKD) in diabetes and its prevalence
- Discuss current standards of care in the treatment of CKD in patients with diabetes and the need for new therapeutic interventions
- Apply evidence from recent clinical trials in patients with diabetes with renal outcomes

2

Causes of CKD in people with and without diabetes



Adapted from: Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42 :S201–209.

3

High prevalence and burden of CKD in diabetes

- **40-50%** of people with diabetes will develop CKD[1,2]
  - **CKD is more common than CVD** in patients with T2DM (24.1% vs 21.6%)[3]
- Diabetes is the **leading cause of new cases of ESKD** in Canada[4]
  - **~50%** of adults **requiring dialysis or renal replacement** have ESKD attributable to diabetes[2]
- **CKD in diabetes can lead to complications**, including significant reductions in both length and quality of life[5]
  - Between 1990 and 2012, number of **deaths due to CKD in patients with T2DM rose by 94%**[6]

ESKD, End-stage kidney disease; CKD: Chronic kidney disease; CVD: cardiovascular disease; T2DM: type 2 diabetes mellitus

1. Alicic et al. *Clin J Am Soc Nephrol* 2017;12:2032–45. 2. Steele A. *LMC Clinical Practice Update* 2018 [in press]; 3. Iglay et al. *Curr Med Res* Opin 2016;32(7):1243-52. 4. Public Health Agency of Canada. *Diabetes in* Canada: *Facts and figures from a public health perspective*. Ottawa, ON: 2011. 5. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42 :S201–209. 6. Lozano et al. *Lancet* 2012;380:2095–128.

4

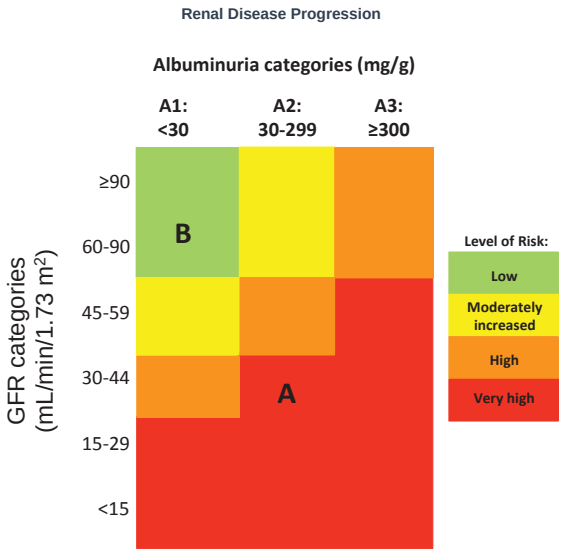
Screening kidney function in patients with T2DM

- Significant renal disease can be present at the time of T2DM diagnosis
- Screening should take place:
  - **Immediately upon diagnosis**
  - **Annually thereafter**
- Measurements of urinary albumin excretion and eGFR
  - Albumin: Random urine albumin to creatinine ratio (urine ACR)
  - eGFR: Based on serum creatinine

Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42:S201–209.

CKD Staging

- Serum creatinine is not a good measure of kidney function in people with diabetes
  - GFR usually will be **less than half of normal** before the serum creatinine exceeds the lab normal range
- Patient A has an increased risk of:
  - All-cause mortality
  - CV Mortality
  - ESRD
  - CKD Progression



Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42:S201–209.

Over the last 20 years, Diabetes Canada (CDA) has advocated a three-pillared approach for patients with T2DM and renal impairment

(Grade A)	(Grade A)	(Grade A)
Target ≤ 7.0%	Target < 130/80 mmHg	Treatment

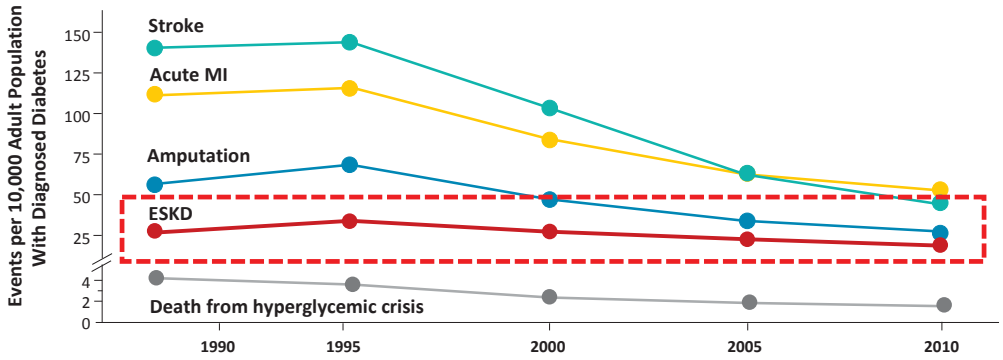
Grade A recommendations are supported by systematic overview or meta-analysis of high-quality randomized clinical trials (RCTs) or appropriately designed RCT(s) with adequate power to answer the question posed by the investigators

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

1. Meltzer S, et al. *CMAJ* 1998;159(Suppl 8):S1-29. 2. CDA Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2008;32(Suppl 1):S1-S201.
3. CDA Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2013;37: S129-136.
4. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42 :S201–209.

Despite these interventions, there has been little improvement in the rate of ESKD

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



ESKD, end-stage kidney disease; MI: myocardial infarction

Adapted from: Gregg EW, et al. *N Engl J Med* 2014;370:1514-23.

8

ACEi or ARB: "Gold standard" for CKD in diabetes

	N	Albuminuria	Baseline renal function	2xCr, ESKD, Renal Death – # of events	Relative Risk Reduction
IDNT[1] (irbesartan)	1715	Median 1900 mg/d (1000 – 3800 mg/d)	Mean Cr: 148 µmol/L	644	20% (p=0.006)
RENAAL[2] (losartan)	1513	Median ACR: ~140 mg/mmol	Mean Cr: 168 µmol/L	686	16% (p = 0.02)
ACEi Collaborative study group[3] (captopril)	409	Mean proteinuria: 2500 mg/d	Mean Cr: 115 µmol/L	2xCrR: 68 Death or ESKD: 65	43% (p = 0.007) 46%

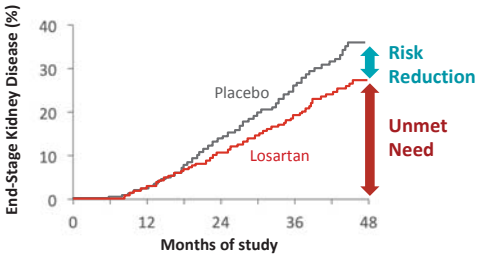
ACEi: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin receptor blocker

1. Lewis EJ, et al. *N Engl J Med* 2001;345:851-60. 2. Brenner BM et al *New Engl J Med* 2001;345:861-69. 3. Lewis EJ, et al. *N Engl J Med* 1993; 329:1456-1462

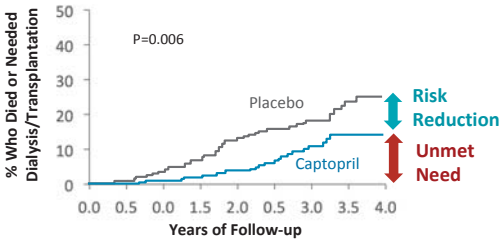
9

ACEi or ARB: "Gold standard" for CKD in diabetes

ARB[1]



ACE Inhibitor[2]



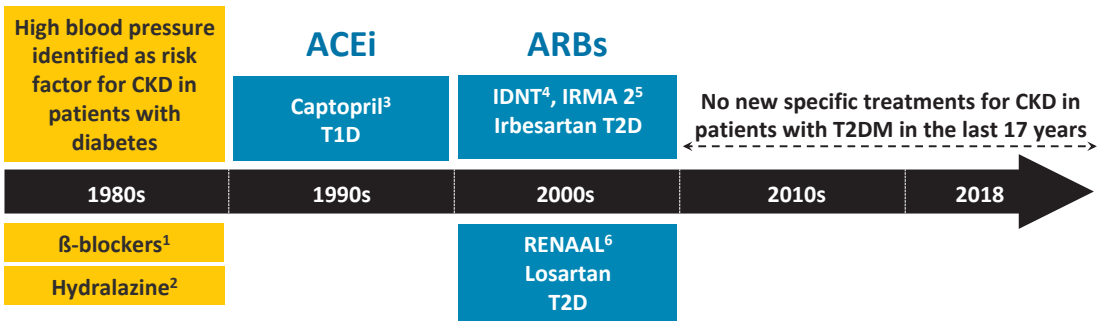
- **Risk reduction associated with ACEi or ARB agents was an important development in primary care**
- **There is still a clear unmet need for new therapeutic interventions**

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

1. Brenner BM, et al *New Engl J Med* 2001;345:861-69. 2. Lewis EJ, et al. *N Engl J Med*. 1993; 329:1456-1462.

10

No new treatment for CKD in diabetes since the advent of ACEis and ARBs 17 years ago



CKD, chronic 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

1. Mogensen CE, et al. *Br Med J* (Clin Res Ed)1982;285:685; 2. Parving HH, et al. *Lancet* 1983;1:1175; 3. Lewis EJ, et al. *N Engl J Med* 1993;329:1456; 4. Lewis EJ, et al. *N Engl J Med* 2001;345:851; 5. Parving HH, et al. *N Engl J Med* 2001;345:870; 6. Brenner BM, et al. *N Engl J Med* 2001;345:861.
Figure adapted from: Steele A. *LMC Clinical Practice Update* 2018 [in press].d

11

Newer Antihyperglycemic Agents in Patients with CKD and T2DM

DDP4-inhibitors in Patients with CKD and Diabetes

Advantages

- Safe in patients with renal impairment
- No increased CV risk

Disadvantages

- No demonstrated CV benefit
- No demonstrated benefit on hard renal outcomes (doubling sCreat, ESKD, renal death)

13

GLP1- RA in Patients with CKD and Diabetes

Advantages

- Benefit on composite renal outcome was driven by a reduction in new-onset macroalbuminuria
- Maintain A1C efficacy in renal impairment
- Some agents can be used to eGFR of 15 mL/min/1.73 m^2

Disadvantages

- No demonstrated benefit on hard renal outcomes
- Injectables

14

Emerging evidence supports a new intervention for CKD in diabetes: SGLT2 inhibitors (SGLT2i)

A1C Control

SGLT2i agents effectively lower A1C

BP Control

SGLT2i ↓ SBP by ≈4 mmHg and ↓ DBP by ≈2 mmHg

"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/1.73m^2, 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**

Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42:S88–103.
Baker WL, et al. *J Am Heart Assoc* 2017;6:e005686.

15

Potential Renal Protective Mechanisms with SGLT2 Inhibition

Indirect Effects	Direct Effects
• Improved glycemic control	• Prevent hyperfiltration
• Reduced insulin levels	• Renin angiotensin system (?)
• Improved insulin sensitivity	• Prevent tubular hypertrophy
• Weight loss	• Reduced tubular toxicity of glucose
• Reduced blood pressure	• Reduced nephrolithiasis?
• Reduced uric acid	

Clinical effect on renal outcomes examined in dedicated renal outcome trials

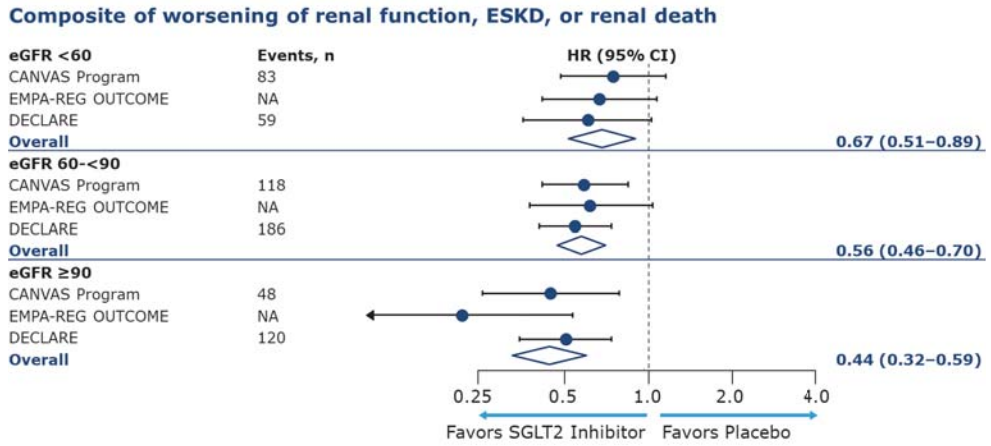
SGLT2: Sodium glucose co-transporter 2

Thomas MC. *Ther Adv Endo Metab* 2014;5:53–61; Gembardt F, et al. *Am J Physiol Renal Physiol* 2014;307:F317–25; Škrtić M, Cherney DZ. *Curr Opin Nephrol Hypertens* 2015;24:96–103; Lytvyn Y, et al. *Am J Physiol Renal Physiol* 2015;308:F77–83.

16

Why Is CREDENCE Important?

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



Adapted from: Zelniker, et al. *N Engl J Med* 2018; DOI: 10.1016/S0140-6736(18)32590-X

17

One trial of SGLT2i agents with primary renal outcomes has been completed

	CREDENCE[1,2]	DAPA-CKD[3]	EMPA-KIDNEY[4]
No. of patients	4401	4000	5000
Treatment arms	CANA 100 mg vs. PBO	DAPA (5, 10 mg) vs. PBO	EMPA vs. PBO
Patient population	CKD + T2D **Must** be taking max. labelled or tolerated ACEi/ARB	CKD ± T2D May be taking ACEi/ARB	CKD ± T2D May be taking ACEi/ARB
Kidney function inclusion criteria (eGFR units: mL/min/1.73 m²)	eGFR ≥30 to <90 **AND** UACR >33.9 mg/mmol 60% to have eGFR ≥30 to <60	eGFR ≥25 to <75 **AND** UACR ≥22.6 mg/mmol	eGFR ≥20 to <45 **OR** eGFR ≥45 to <90 with UACR ≥22.6 mg/mmol
Primary endpoint	Composite of ESKD, doubling of sCr, renal or CV death	Composite of ≥50% sustained decline in eGFR, ESKD, CV or renal death	Composite of CV death, kidney disease progression (ESKD, renal death or a sustained decline of ≥40% in eGFR)
Start	2014	2017	2018
Completion	**Complete**: Stopped early due to achievement of efficacy endpoint	2020	2022

1. Perkovic et al., N Engl J Med 2019, DOI: 10.1056/NEJMoa1811744; 2. Jardine MJ et al., *Am J Nephrol* 2017;46:462–472;
3. ClinicalTrials.gov Identifier: NCT03036150; 4. ClinicalTrials.gov Identifier: NCT03594110.

18

CREDENCE

Primary Renal Outcomes for SGLT2i in Patients with CKD and Diabetes

DISCLAIMER: Marketing authorization for the treatment of CKD in T2DM has not yet been established for SGLT2 inhibitors.

CREDENCE: Primary and secondary endpoints, additional exploratory analyses and AEs of special interest

Primary endpoint	• Composite of ESKD, doubling of sCr, or death from renal or CV disease
Secondary endpoints (Hierarchical)	• Composite of CV death or hospitalization for heart failure • Composite of CV death, MI, or stroke • Hospitalization for heart failure • Composite endpoint of ESKD, doubling of sCr, or renal death • CV death • All-cause death • CV composite endpoint of CV death, MI, stroke, hospitalization for HF or unstable angina

CREDENCE is powered to detect a 20% relative risk reduction in the primary renal endpoint, commensurate with the risk reductions seen in IDNT and RENAAL

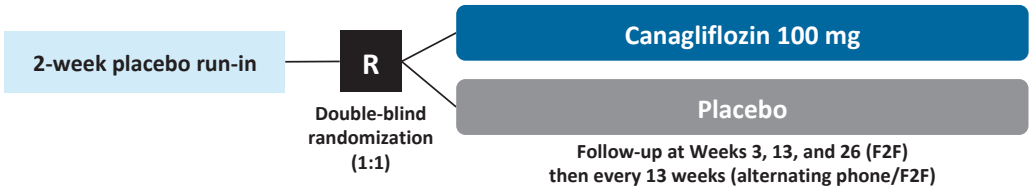
CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; ESKD, end-stage kidney disease; sCr, serum creatinine; CV: cardiovascular; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; AEs: adverse events

Jardine MJ, et al. *Am J Nephrol* 2017;46:462–72; Perkovic et al., N Engl J Med 2019, DOI: 10.1056/NEJMoa1811744.

CREDENCE: Study design

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5–12.0%
- eGFR 30–90 mL/min/1.73 m^2
- UACR 33.9–565 mg/mmol (300–5000 mg/g)
- 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 m^2 until chronic dialysis was initiated or kidney transplant occurred.

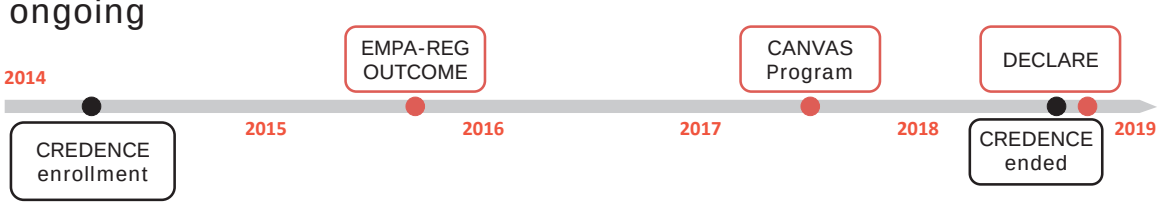
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; UACR, urinary albumin-to-creatinine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

Adapted from: Jardine MJ, et al. *Am J Nephrol* 2017;46:462–72.

21

Timeline of Major SGLT2 Inhibitor Trials

- CREDENCE began while SGLT2 inhibitor CV outcomes trials were ongoing



- Renal effects were not the primary focus of the CV outcomes trials

CREDENCE: Key baseline characteristics

Characteristic	Mean (n = 4,401)
Male Gender	2907 (66.1%)
Age, years	63.0±9.2
BMI, kg/m^2	31.3±6.2
HbA1c, %	8.3±1.3
Duration of T2DM, years	15.8±8.7
eGFR, mL/min/1.73 m^2	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
Median UACR (mg/mmol)	104.8

Characteristic	Proportion (n = 4,401)
Concomitant RAASi use	**99.9%**
CKD Stage	
Stage 2 (≥60 to <90 mL/min/1.73 m^2)	35%
Stage 3a (≥45 to <60 mL/min/1.73 m^2)	29%
Stage 3b (≥30 to <45 mL/min/1.73 m^2)	27%

Jardine MJ, et al. *Am J Nephrol* 2017;46:462–72; Jardine MJ, Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-359.

23

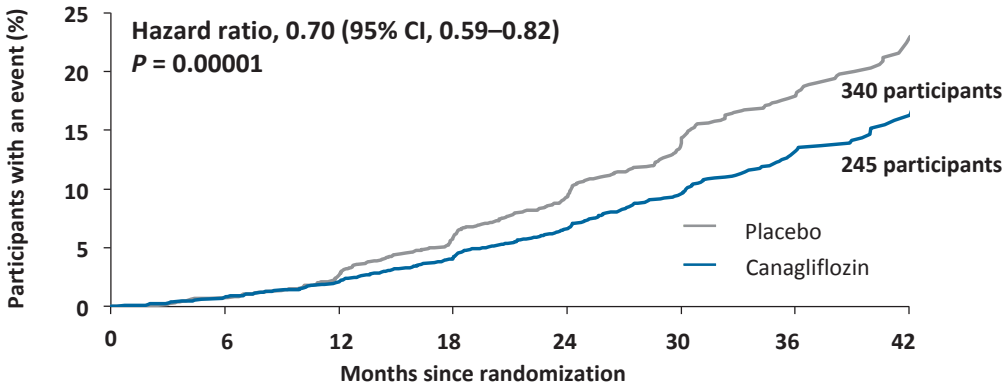
Disease History

Characteristic	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Hypertension, %	97	97	**97**
Heart failure (NYHA I-III), %	15	15	**15**
CV disease, %	51	50	**50**
Prior amputation, %	5	5	**5**

Jardine MJ, Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-359.

24

Primary Endpoint: Composite of ESKD, doubling of serum creatinine, and renal or CV death

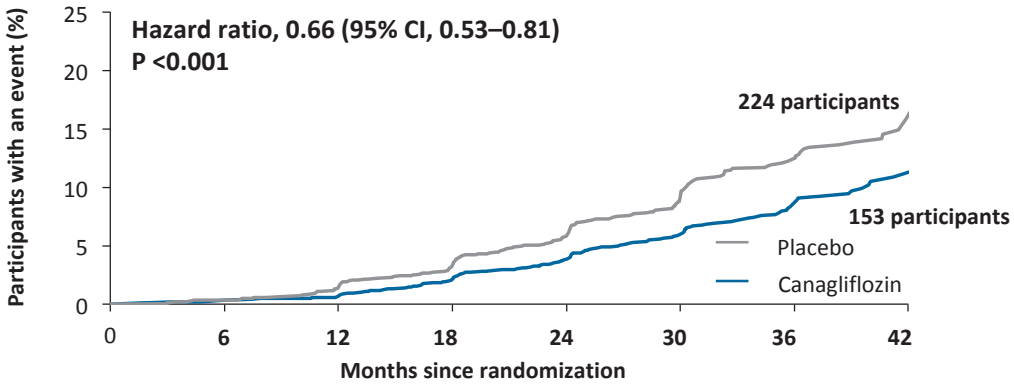


No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic et al., *N Engl J Med* 2019, DOI: 10.1056/NEJMoa1811744.

25

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

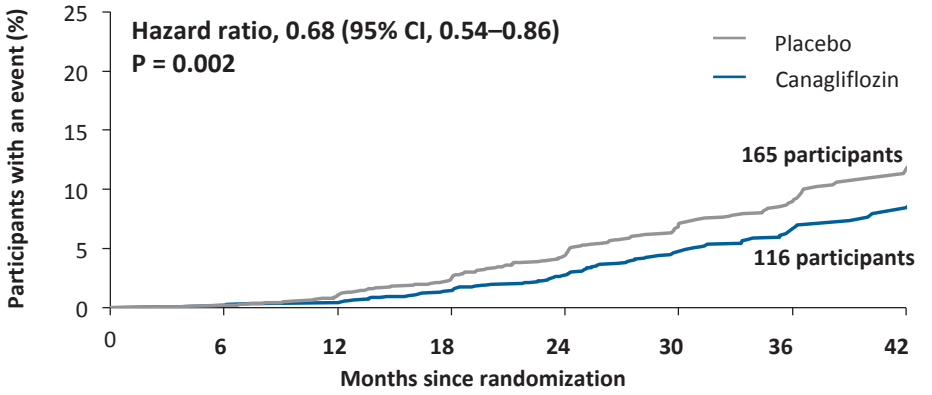


No. at risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

Perkovic et al., N Engl J Med 2019, DOI: 10.1056/NEJMoa1811744.

26

Secondary Endpoint: End-stage kidney disease



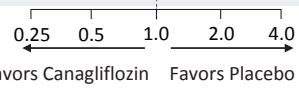
No. at risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

Perkovic et al., N Engl J Med 2019, DOI: 10.1056/NEJMoa1811744.

27

Summary of key renal endpoints

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



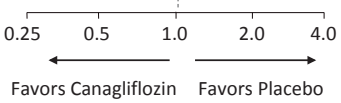
* Post-hoc analysis

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

28

Primary outcome by screening eGFR and albuminuria

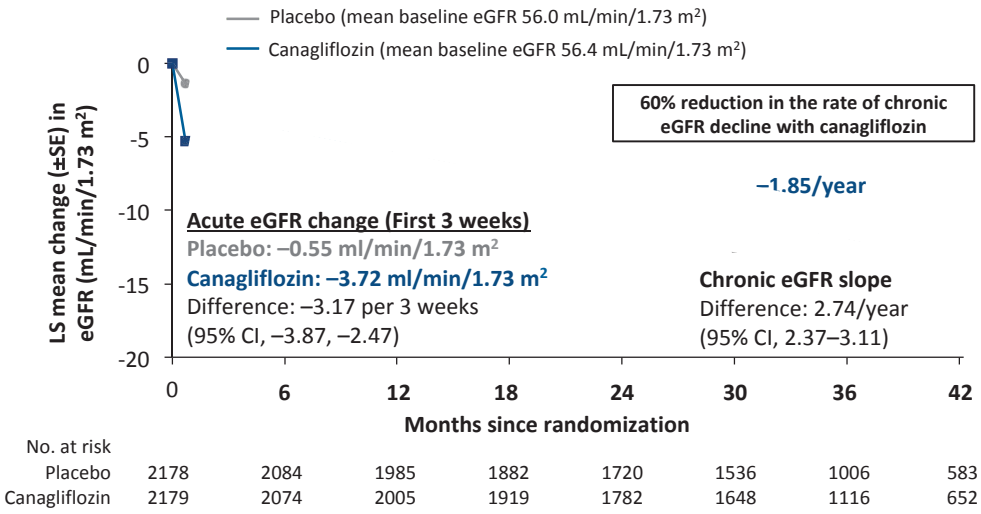
	Hazard ratio (95% CI)		Interaction P value
Screening eGFR			0.11
30 to <45 mL/min/1.73 m^2		0.75 (0.59–0.95)	
45 to <60 mL/min/1.73 m^2		0.52 (0.38–0.72)	
60 to <90 mL/min/1.73 m^2		0.82 (0.60–1.12)	
Baseline UACR			0.49
≤113 mg/mmol		0.76 (0.55–1.04)	
>113 mg/mmol		0.67 (0.55–0.81)	



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

29

Effects on eGFR

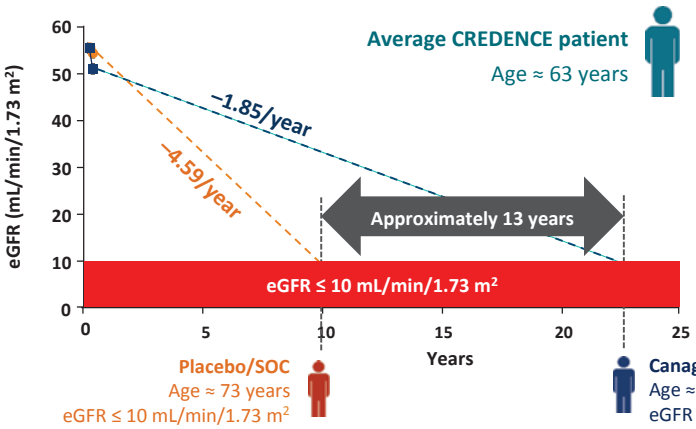


No. at risk								
Placebo	2178	2084	1985	1882	1720	1536	1006	583
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652

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

30

Hypothetical importance of chronic eGFR slope difference



Dialysis, kidney transplantation, or renal death (number of events)*	
Canagliflozin (n=2202)	Placebo (n=2199)
78	105
HR 0.72 (95% CI 0.54–0.97)	

*Post-hoc analysis

Projections are based on eGFR slopes from week 3 to end of treatment (chronic phase) and assume linear progression of eGFR decline
- Calculated as [(eGFR at start of chronic phase – 10 mL/min/1.73 m²) / chronic eGFR slope]

eGFR at start of chronic phase (3-week time point): Canagliflozin 100 mg/SOC 51.9 mL/min/1.73 m², Placebo/SOC 55.5 mL/min/1.73 m²

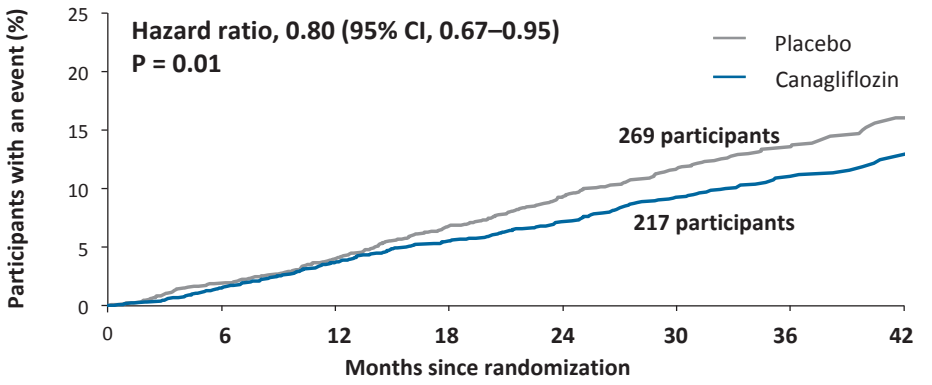
Adapted from: Perkovic et al., *N Engl J Med* 2019, DOI: 10.1056/NEJMoa1811744.
Rivara & Mehrotra, *Semin Nephrol*. 2017; 37(2): 181–193.

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**
- Canagliflozin **attenuated the slope of chronic eGFR decline** by 2.7 mL/min/1.73 m²/year (–1.9 vs –4.6)

32

Secondary Endpoint: CV Death, MI, or stroke (major adverse cardiovascular events, or 3-point MACE)

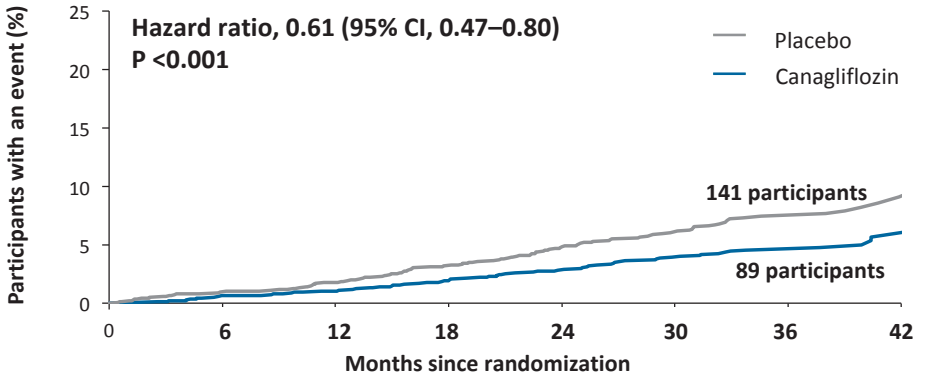


No. at risk								
Placebo	2199	2152	2100	2022	1717	1143	635	168
Canagliflozin	2202	2163	2106	2047	1756	1196	642	198

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

33

Secondary Endpoint: Hospitalization for heart failure

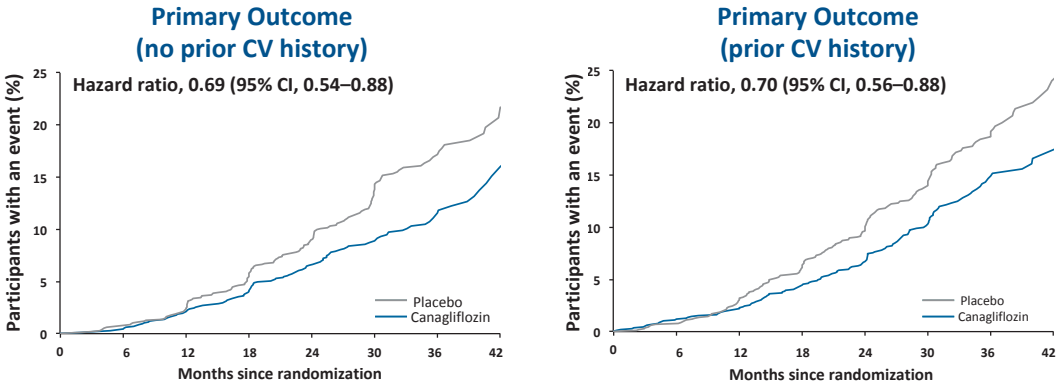


No. at risk								
Placebo	2199	2165	2122	2043	1735	1147	638	170
Canagliflozin	2202	2171	2131	2076	1789	1226	668	199

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

34

Primary Outcome (ESKD, doubling of serum creatinine, or renal or CV death) in patients with and without prior CV disease

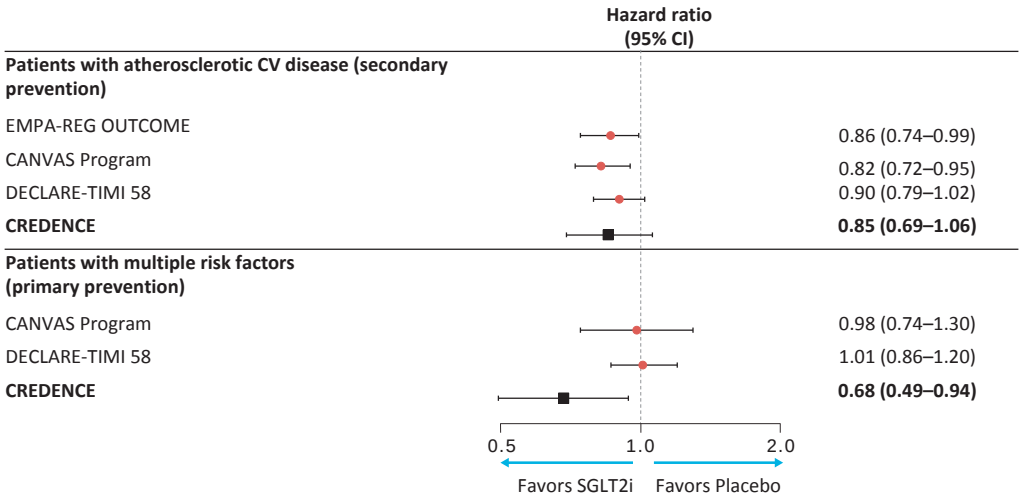


P interaction = 0.91

Presented at the 79th Scientific Sessions of the American Diabetes Association. June 11th 2019; San Francisco, CA.

35

CV Death, MI, or Stroke in SGLT2 Inhibitor Outcome Trials With and Without Prior CV Disease



Zelniker TA, et al. *Lancet*. 2019;393(10166):31-39.
Presented at the 79th Scientific Sessions of the American Diabetes Association. June 11th 2019; San Francisco, CA.

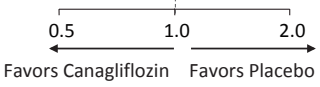
Reflection

- Which CV outcomes are most relevant to your practice?
- Which data do you consider to be most impactful? Why?

37

AEs and serious AEs

	Number of participants with an event, n			
	Canagliflozin (N = 2200)	Placebo (N = 2197)	Hazard ratio (95% CI)	
All AEs	1784	1860		0.87 (0.82–0.93)
All serious AEs	737	806		0.87 (0.79–0.97)



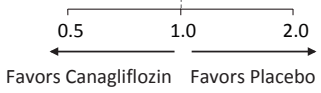
Includes all treated participants through 30 days after last dose.

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

38

Renal safety

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



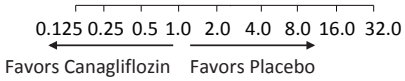
Includes all treated participants through 30 days after last dose.

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

39

Other AEs of interest

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



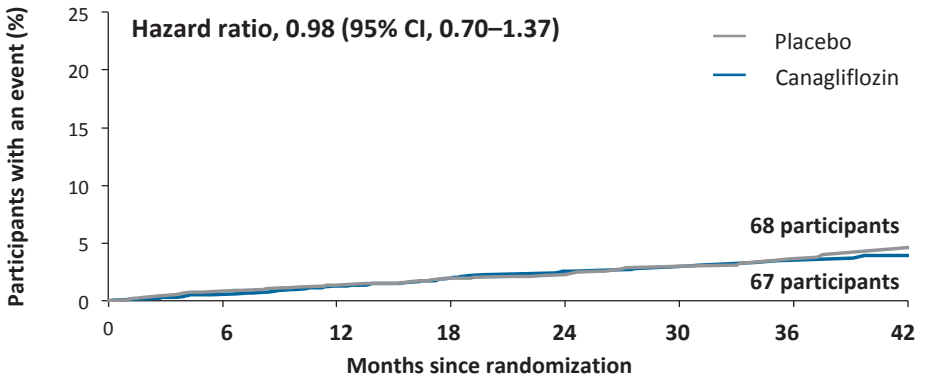
Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.

*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.

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

40

AEs: Fracture

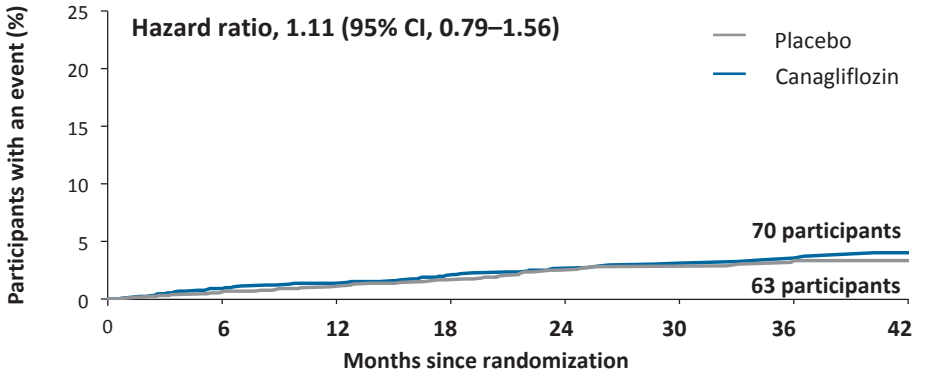


No. at risk								
Placebo	2197	2166	2128	2061	1769	1178	656	176
Canagliflozin	2200	2171	2121	2074	1785	1225	668	200

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

41

AEs: Lower extremity amputation



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

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

42

Summary: Safety

- Similar rates of amputation and fracture observed with canagliflozin and placebo are reassuring and consistent with trials of other SGLT2 inhibitors
  - Differ from the CANVAS Program findings
- Overall safety profile is otherwise consistent with the known adverse effects associated with canagliflozin

43

SGLT2i-associated side effects

COMMON	LESS COMMON	RARE
Genital infections	Urinary tract infections	Diabetic ketoacidosis*
	Osmotic diuresis, hypovolemia, hypotension	Increase in bladder cancer[§]
	Mild LDL-C increase	Pancreatitis

For the most current side effect information, please review each individual product monograph

* observed with all SGLT2 inhibitors; [†] avoid using canagliflozin in individuals with a history of lower extremity amputation(s); [‡] observed with canagliflozin; [§] dapagliflozin not to be used in patients with bladder cancer.

Adapted from Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018 Apr;42 (Suppl 1):S88-103.

44

Reflection

- What safety concerns about canagliflozin and other SGLT2i agents are most important to you?
- Do the data from CREDENCE address your concerns?

45

Canagliflozin renal benefits are additive to ACEi and ARB

	N	Albuminuria	Baseline renal function	Median Follow-up	2xCr, ESKD, Renal Death # of events	Relative risk reduction
IDNT[1]	1715	Median: 1900 mg/d	Mean Cr: 148 µmol/L	2.6 years	644	20%
RENAAL[2]	1513	Median ACR: 140 mg/mmol	Mean Cr: 168 µmol/L	3.4 years	686	16%
ACEi Collaborative study group[3]	409	Mean proteinuria: 2500 mg/d	Mean Cr: 115 µmol/L	3.0 years	2xCrR: 68 Death or ESKD: 65	43% 46%
CREDENCE*[4,5] (99.9% on RAASi)	4401	Median UACR: 105 mg/mmol	Mean eGFR: 56.2 mL/min/1.73 m^2	2.6 years	377	34%

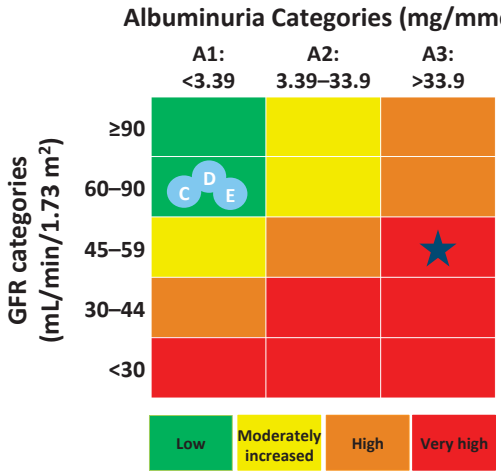
*NOTE: All patients enrolled in CREDENCE were taking maximal labelled or tolerated daily dose of ACEi or ARB in addition to being treated to target for blood pressure and A1C as part of the standard of care[4]

1. Lewis EJ, et al. *N Engl J Med* 2001;345:851-60. 2. Brenner BM et al *New Engl J Med* 2001;345:861-69. 3. Lewis EJ, et al. N Engl J Med 1993; 329:1456-1462
4. Jardine MJ, et al. *Am J Nephrol* 2017;46:462–72; 5. Perkovic et al., N Engl J Med 2019, DOI: 10.1056/NEJMoa1811744.

46

Putting Evidence into Perspective

Higher renal risk population in CREDENCE



Baseline renal function	Mean eGFR (mL/min/1.73 m²)	Median UACR (mg/mmol)
D DECLARE	85	1.47
C CANVAS Program	76	1.36
E EMPA-REG OUTCOME	74	2.03
★ CREDENCE	56	104.8

Sustained transplant or dialysis events	
DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11
CREDENCE	176

Wheeler DC. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-362.

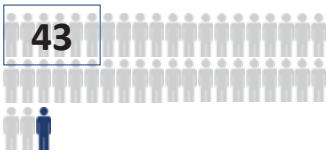
48

NNT for renal and CV outcomes over 2.5 years

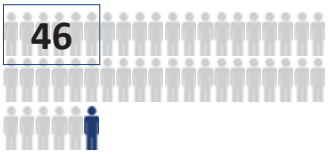
Primary composite outcome

ESKD, doubling of serum creatinine, or renal death

ESKD



Hospitalization for heart failure



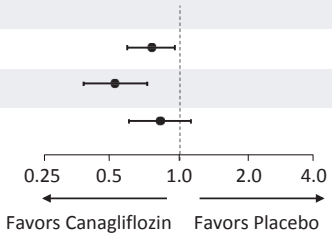
CV death, MI, or stroke

Wheeler DC. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-362.

49

Primary Outcome: Benefits in eGFR 30 to <45 subgroup

		Hazard ratio (95% CI)	Interaction P value
Screening eGFR			0.11
30 to <45 mL/min/1.73 m^2		0.75 (0.59–0.95)	
45 to <60 mL/min/1.73 m^2		0.52 (0.38–0.72)	
60 to <90 mL/min/1.73 m^2		0.82 (0.60–1.12)	



NNT in patients with eGFR 30 to <45 mL/min/1.73 m^2

Wheeler DC. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-362.

50

Discussion Question

How do the results from CREDENCE compare to those from trials of ACEis and ARBs in patients with diabetes and CKD?

What is the significance of demonstrating these benefits in patients who were already being treated with ACEis and ARBs?

ADA Standards of Care Updated With Renal Guidance Based on CREDENCE

- **Based on the Grade A evidence from the CREDENCE trial, the ADA *living guidelines* (updated on June 3, 2019)[2] propose the following:**
  - "For patients with type 2 diabetes and diabetic kidney disease, consider use of an SGLT2 inhibitor in patients with an eGFR ≥30 mL/min/1.73 m^2 and particularly in those with >33.9 mg/mmol albuminuria to reduce risk of CKD progression, cardiovascular events, or both."

1. American Diabetes Association. http://www.diabetes.org/newsroom/press-releases/2019/updates-standards-medical-care-diabetes.html. Accessed June 5, 2019.
2. American Diabetes Association. *Standards of Medical Care in Diabetes–2019*. http://care.diabetesjournals.org/content/42/Supplement_1. Last updated June 3, 2019. Accessed June 5, 2019.

Applying to Your Practice

Patient case

ROBERT

68-year-old male

- Retired sales associate
- New patient (Family Doctor retired)
- Generally feels well, came to you for med repeats

Personal History
Non-smoker
Type 2 diabetes x 10 years
Hypertension
BMI 30 kg/m^2

Current Medications
Metformin-Sitagliptin XR (1000 mg / 100 mg od)
Rosuvastatin 20 mg od
Indapamide 2.5 mg daily
Telmisartan 80 mg od

54

Discussion Question

What lab tests do we need to order for Robert?

55

Patient case

ROBERT

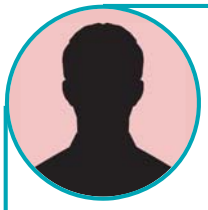
68-year-old male

- Retired sales associate
- New patient (Family Doctor retired)
- Generally feels well, came to you for med repeats

Current Medications	Physical Exam	Lab Results
Metformin-Sitagliptin XR (1000 mg / 100 mg od)	84 kg	A1C 6.5%
Rosuvastatin 20 mg od	BP 134/81	LDL 1.76 mmol/L
Indapamide 2.5 mg od	Pulse normal	eGFR 59 mL/min/1.73 m^2
Telmisartan 80 mg od	No peripheral edema	ACR 77 mg/mmol

56

Patient case



ROBERT

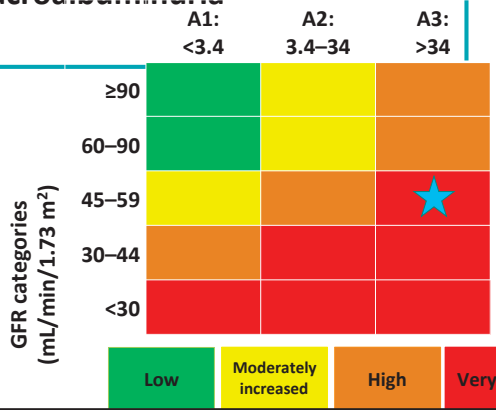
Unmet needs

- 68-year-old male with target A1c
- Full dose ARB
- Persistent Macroalbuminuria

Which agent would you consider adding?

1. Liraglutide once weekly
2. Canagliflozin 100 mg daily
3. Perindopril 4 mg daily

Would you consider adjusting any of his current medications?



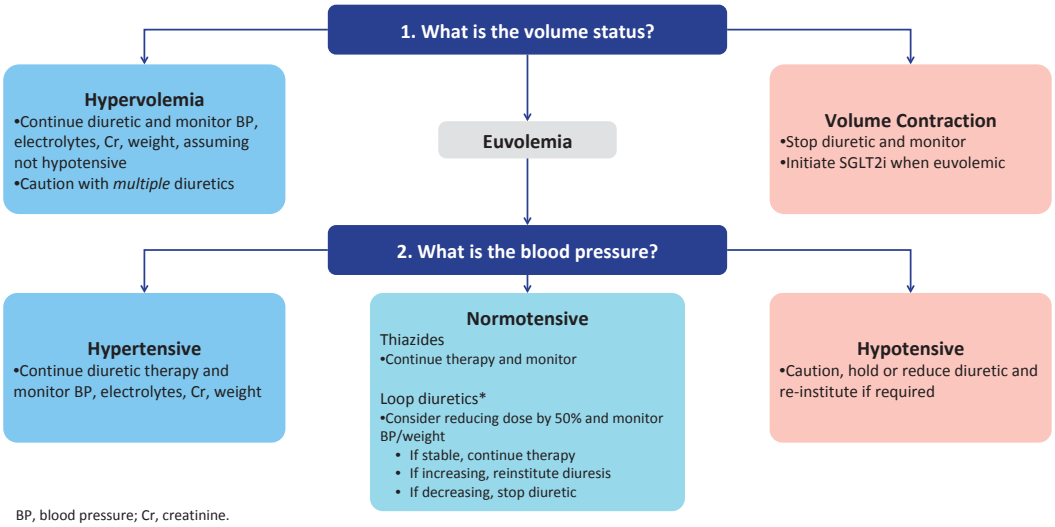
57

Discussion Question

In order to start Robert on an SGLT2 inhibitor, what medication adjustments should be considered?

58

An option for management of diuretics with SGLT2 inhibitors



BP, blood pressure; Cr, creatinine.
*Canagliflozin is not recommended for use in patients receiving loop diuretics.

Adapted from Cherney DZ, Udell JA. Circulation. 2016;134:1915-1917.

59

Patient case

ROBERT

Summary of diabetes/CKD management for Robert

High Renal Risk Patient with Persistent Macroalbuminuria and A1c at target

1. **Continue Indapamide 2.5 mg daily**
2. **Stop Metformin/Sitagliptin XR 1000/100 mg**
3. **Metformin XR 1000 mg daily**
4. **Add Canagliflozin 100 mg daily**

McFarlane P, et al. Chronic Kidney Disease in Diabetes, *Can J Diabetes* 2018. 42 (2018) S201–S209

60

Patient case

ROBERT

Summary of diabetes/CKD management for Robert

Assess blood pressure (target: <130/80 mmHg) and A1C (target: ≤7.0% or ≤6.5%)

Ensure patient is taking maximum tolerated dose of Acei or ARB

Add: Canagliflozin if eGFR 30-90 and ACR >30
OR
SGLT2i if A1c> target and eGFR >45-90

Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42:S201–209.
MacFarlane P, Weinstein J. Professional communication. 2019.

61

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**

1. Zelniker, et al. *N Engl J Med* 2018; DOI: 10.1016/S0140-6736(18)32590-X
2. Jardine et al., *Am J Nephrol* 2017;46:462–472.
3. Perkovic et al., *N Engl J Med* 2019, DOI: 10.1056/NEJMoa1811744.
4. Neal B, et al. *N Engl J Med*. 2017;377:644-57.
5. Zinman B, et al. *N Engl J Med* 2015;373:2117-28.
6. Raz I, et al. Diabetes Obes Metab. 2018;20:1102–1110.

62

Sick day medication list

S	Sulfonylureas
A	ACE inhibitors
D	Diuretics, direct renin inhibitors
M	Metformin
A	Angiotensin receptor blockers
N	Nonsteroidal anti-inflammatory
S	SGLT2 inhibitors

http://guidelines.diabetes.ca/docs/cpg/Appendix-8.pdf

63

Discussion Question

At what point should we refer Robert to a nephrologist?

64

Patient case

ROBERT

Summary of diabetes/CKD management for Robert

Diabetes Canada 2018 Guidelines Chapter 29, Recommendation #9

1. Chronic, progressive loss of kidney function
2. Urine ACR persistently >60 mg/mmol
3. eGFR <30 mL/min
4. Unable to remain on renal-protective therapies due to adverse effects, such as hyperkalemia or a >30% increase in serum creatinine within 3 months of starting an ACE inhibitor or ARB
5. Unable to achieve target BP.

McFarlane P, et al. Chronic Kidney Disease in Diabetes, *Can J Diabetes* 2018. 42 (2018) S201–S209

65

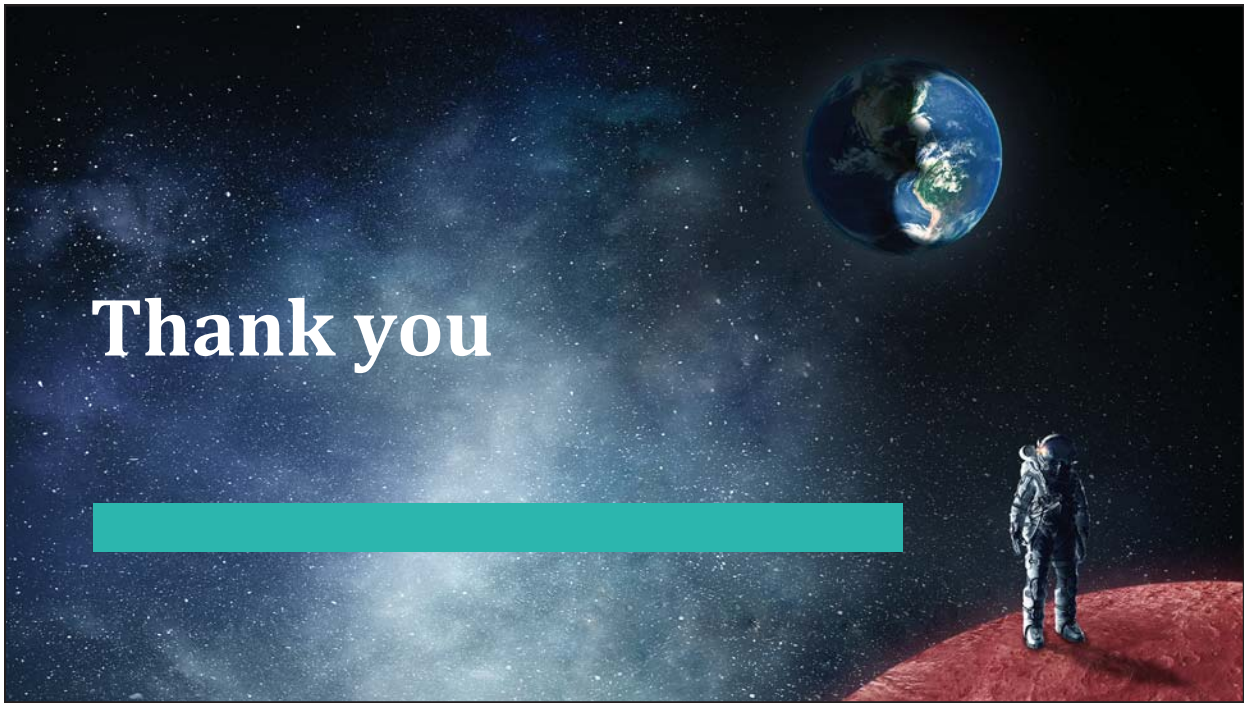
Summary & Key Take Aways

There is a significant unmet need in the treatment of CKD in patients with diabetes

Canagliflozin reduced the incidence of renal endpoints such as doubling of serum creatinine and progression to dialysis or transplantation

The CREDENCE results represent a leap forward with respect to reducing renal risk in patients with CKD and type 2 diabetes

66


Thank you