Canadian Society of Nephrology/
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DID YOU KNOW?

TAKING BACK DKD

Faculty

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Disclosure of Potential Conflicts of Interest

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Dr. Philip McFarlane	Educational grants for eLearning/ live program development and honoraria: Amgen, Astra-Zeneca, Bayer, BI, Janssen, Lilly, GSK, Novartis, Novo-Nordisk, Otsuka, IiV, Antibody Advisory board member and/or presenter: Amgen, Astra-Zeneca, Baxter, Bayer, BI, Janssen, Novartis, Otsuka, Sanofi Grants/research: Abbott, Bayer, BMS, BI, GSK, Merck, Novartis, Otsuka
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Dr. Louis-Philippe Girard	Honoraria for CME and educational slide development: Alexion, Bayer, BI-Lilly, Astra Zeneca, Janssen, Merck, Otsuka, Bausch Health Funded grants or clinical trials: Otsuka Other: Member of The CPD Network

Disclosure of Financial Support

Canadian Society of Nephrology/
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This program has received:

- Financial support from Janssen Inc. in the form of an educational grant

Potential for conflict(s) of interest:

- Janssen Inc. benefits from the sale of the following products that may be discussed in this program:
    - Canagliflozin

Learning Objectives

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After this program, participants will be better able to:

- Summarize renal benefits of SGLT2 inhibitors in patients with type 2 diabetes (T2D) and renal impairment
- Describe practical considerations around the use of SGLT2 inhibitors in patients with T2D and renal impairment
- Recognize knowledge gaps and construct a plan to integrate recent evidence into practice

Program Format

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- Please log into the platform with your email address using your mobile device in order to receive your Section 3 credit for this program
- Knowledge checks will be given at several intervals throughout the presentation, please respond by selecting one of the multiple-choice answers
- At the end of the presentation, there will be several questions asking you to reflect on the data presented and how it applies to your practice
- You will be asked to select components of an action plan for incorporating information from the program into your practice
- This action plan will be emailed to you at the address provided when you log into the platform

Test Question

What was the mass of the largest kidney stone ever recorded?

a) 780 g

b) 1120 g

c) 1540 g

d) 2260 g

DID YOU KNOW?
TAKING BACK DKD

Did you know…

Many nephrologists are using SGLT2 inhibitors as kidney drugs rather than diabetes drugs?

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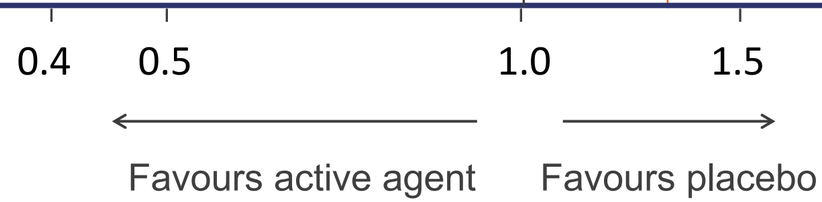
Dr. Silva

Data from SGLT2i CV Outcomes Trials (CVOTs) Suggested Renal Benefit in Patients with T2D

In a systematic review and meta-analysis of exploratory analyses of CVOT data, SGLT2 inhibitors protected against substantial loss of kidney function*, ESKD, or death due to cardiovascular or kidney disease

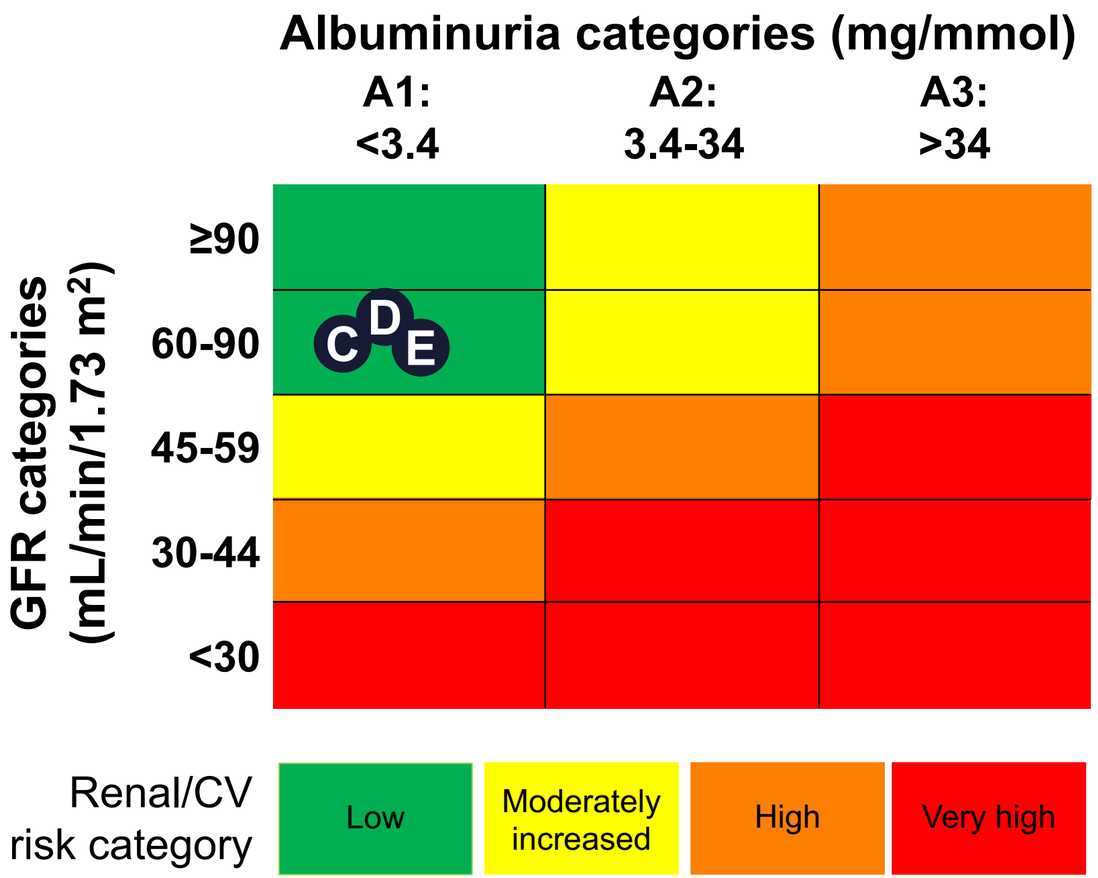
	Patients	Events	HR (95% CI)
EMPA-REG OUTCOME	6968	152	0.54 (0.40–0.66)
CANVAS Program	10142	249	0.60 (0.47–0.77)
DECLARE-TIMI 58	17160	365	0.53 (0.43–0.75)
Overall p < 0.001			0.55 (0.48–0.64)



*Defined as sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate

Zelnicker et al. Circulation. 2019;139:2022–2031.

Patients in SGLT2i CVOTs had preserved kidney function



		Mean eGFR (mL/min/ 1.73 m²)	Median UACR (mg/mmol)
C	CANVAS Program	76	1.36
D	DECLARE-TIMI 58	85	1.47
E	EMPA-REG OUTCOME	74	2.03

Sustained transplant or dialysis events	
CANVAS Program	18
DECLARE-TIMI 58	Not reported
EMPA-REG OUTCOME	11

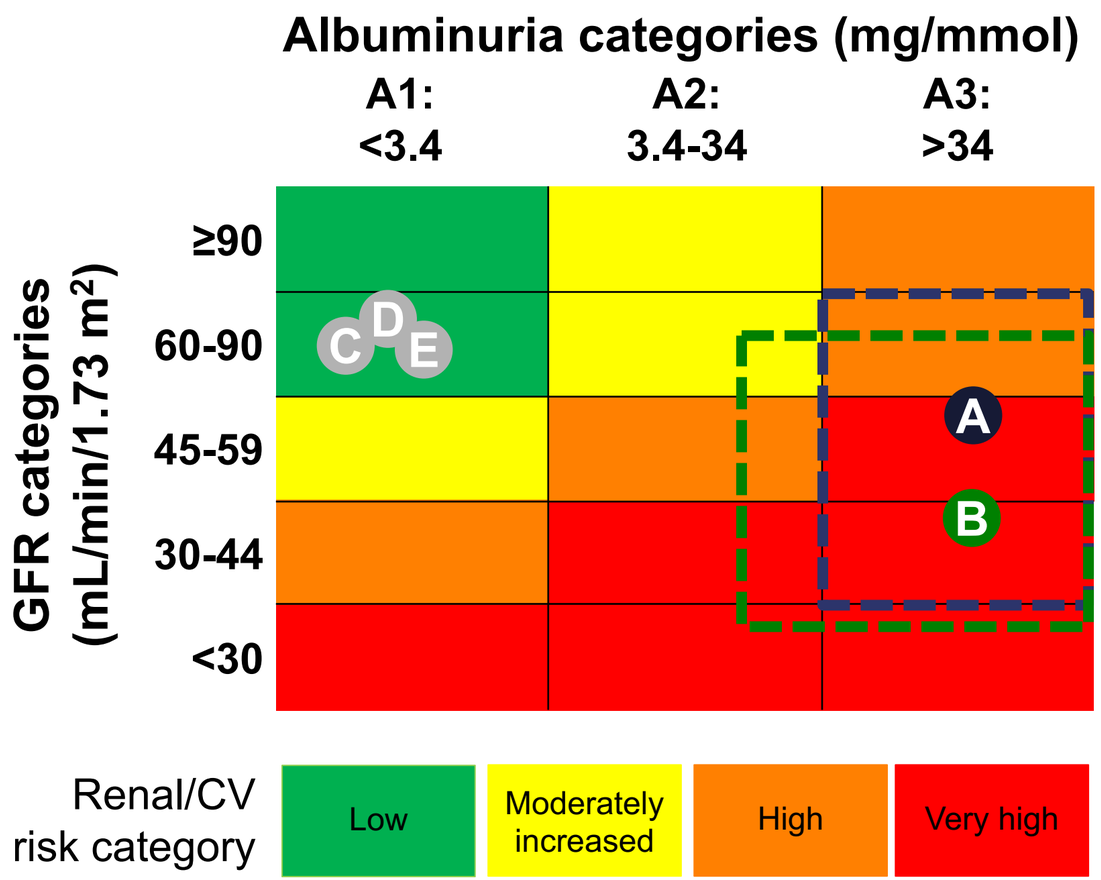
Jardine MJ, et al. Am J Nephrol. 2017;46(6):462-472.
Wheeler DC. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-362.

Dedicated trials of SGLT2 inhibitors in CKD

	CREDENCE[1,2]	DAPA-CKD[3,4]	EMPA-KIDNEY[5]
No. of patients	4401	4000	5000
Treatment arms	CANA 100 mg vs. PBO	DAPA 10 mg vs. PBO	EMPA vs. PBO
Patient population	CKD + T2D **Must** be taking max. tolerated ACEi/ARB	CKD ± T2D Max. tolerated/labeled ACEi/ARB unless contraindicated	CKD ± T2D Clinically appropriate doses of ACEi/ARB unless not tolerated/indicated
Kidney function inclusion criteria	Stage 2/3 CKD (eGFR ≥30 to <90 mL/min/1.73 m^2) AND UACR >300 mg/g (33.9 mg/mmol)	Stage 2-4 CKD (eGFR ≥25 to <75 mL/min/1.73 m^2 [CKD-EPI Formula]) AND UACR ≥200 mg/g (22.6 mg/mmol)	Stage 2-4 CKD (eGFR [CKD-EPI formula] ≥20 to <45, or ≥45 to <90 mL/min/1.73m^2 with UACR ≥200 mg/g [22.6 mg/mmol])
Primary endpoint	Composite of ESRD, doubling of sCr, renal or CV death	Composite of ≥50% sustained decline in eGFR or reaching ESRD or CV death or renal death	CV death or kidney disease progression (ESRD, sustained decline in eGFR to <10 mL/min/1.73m^2, renal death or a sustained decline of ≥40% in eGFR)
Start	2014	2017	2018
Completion	Stopped in 2018 due to achievement of efficacy endpoint	Stopped in 2020 due to achievement of efficacy endpoint	2022

1. ClinicalTrials.gov Identifier: NCT02065791; 2. Jardine MJ et al., Am J Nephrol 2017;46:462–472. 3. ClinicalTrials.gov Identifier: NCT03036150; Astra-Zeneca Press release. March 30, 2020. Available at: https://www.astrazeneca.com/media-centre/press-releases/2020/farxiga-phase-iii-dapa-ckd-trial-will-be-stopped-early-after-overwhelming-efficacy-in-patients-with-chronic-kidney-disease.html 5. ClinicalTrials.gov Identifier: NCT03594110.

Patients in Renal Outcome Trials Had More Advanced Kidney Impairment



		Mean eGFR (mL/min/ 1.73 m²)	Median UACR (mg/mmol)
C	CANVAS Program	76	1.36
D	DECLARE-TIMI 58	85	1.47
E	EMPA-REG OUTCOME	74	2.03
A	**CREDENCE**	**56**	**104.8**
B	**DAPA-CKD**	**43**	**107.3**

Sustained transplant or dialysis events	
CANVAS Program	18
DECLARE-TIMI 58	Not reported
EMPA-REG OUTCOME	11
CREDENCE	**176**
DAPA-CKD	**174**

Jardine MJ, et al. Am J Nephrol. 2017;46(6):462-472.
Wheeler DC. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-362.
Heerspink et al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282.

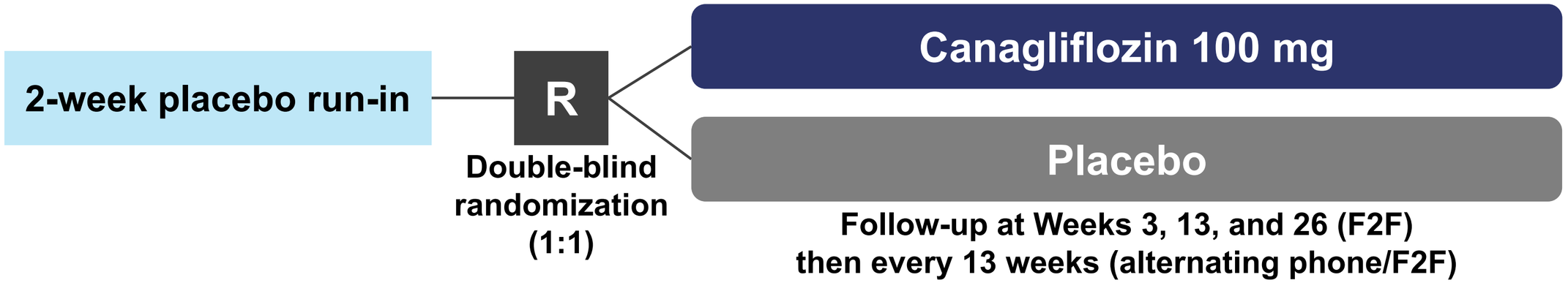
Patients in CREDENCE Were Receiving Standard of Care Treatment

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.

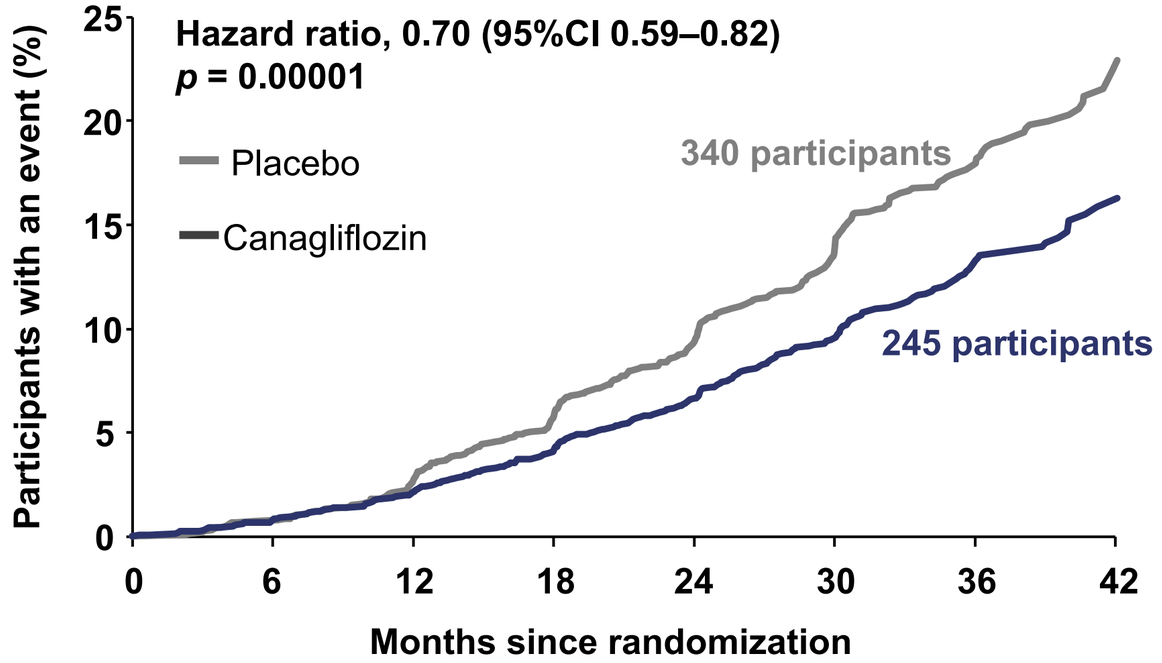
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; UACR, urinary albumin-to-creatinine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

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

Canagliflozin reduced renal events in a primary outcome trial

- Patients in CREDENCE received fixed-dose **canagliflozin 100 mg in addition to the standard of care**
  - Patients had T2D and CKD
- **Primary composite endpoint** of ESKD, doubling of serum creatinine, and renal/CV death was **reduced by 30%**[1]
- EMPA-KIDNEY is underway and will test the effect of empagliflozin on renal outcomes in patients with CKD +/- T2D[2]

CREDENCE primary endpoint: Composite of ESKD, doubling of serum creatinine, and renal or CV death[1]

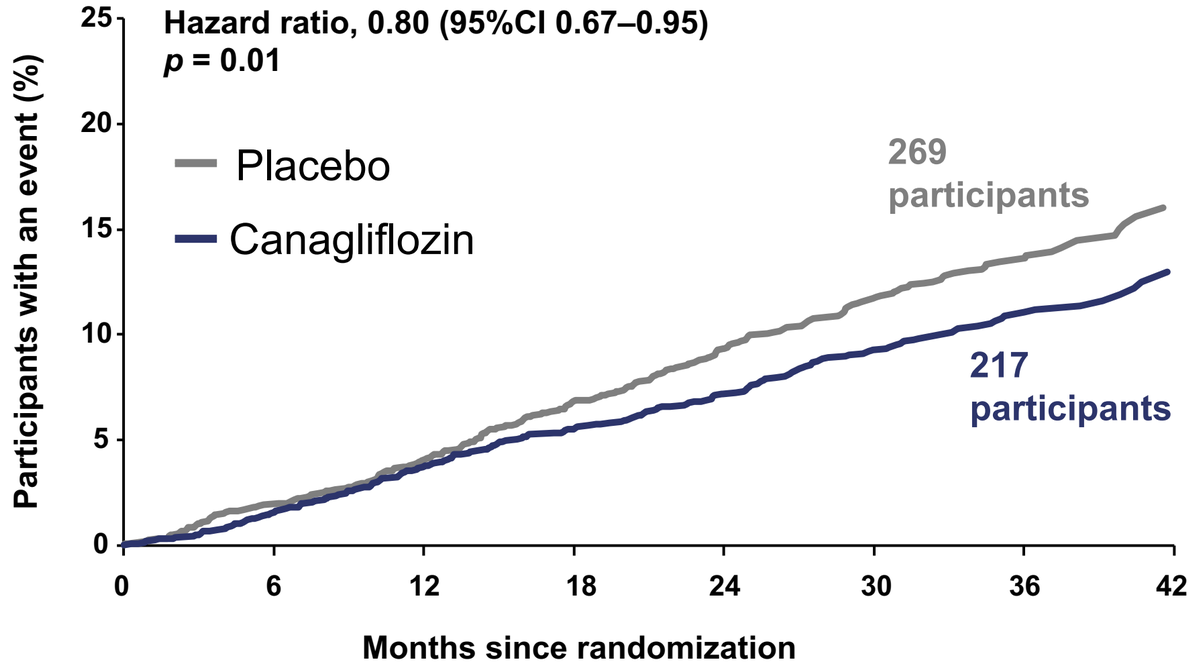


No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

1. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306.
2. ClinicalTrials.gov Identifier: NCT03594110

3-Point MACE Outcomes in CREDENCE (secondary endpoint)

- Risk of CV events was also decreased in patients taking canagliflozin 100 mg in the CREDENCE trial[1]
- Renal and CV benefits were consistent among patients:
  - Regardless of baseline eGFR[2]
  - With and without prior CV events[1]



No. at risk

Placebo	2199	2152	2100	2022	1717	1143	635	168
Canagliflozin	2202	2163	2106	2047	1756	1196	642	198

1. Mahaffey et al. *Circulation*. 2019;140:739–750.
2. Perkovic et al. *N Engl J Med.* 2019; 380(24):2295-2306.

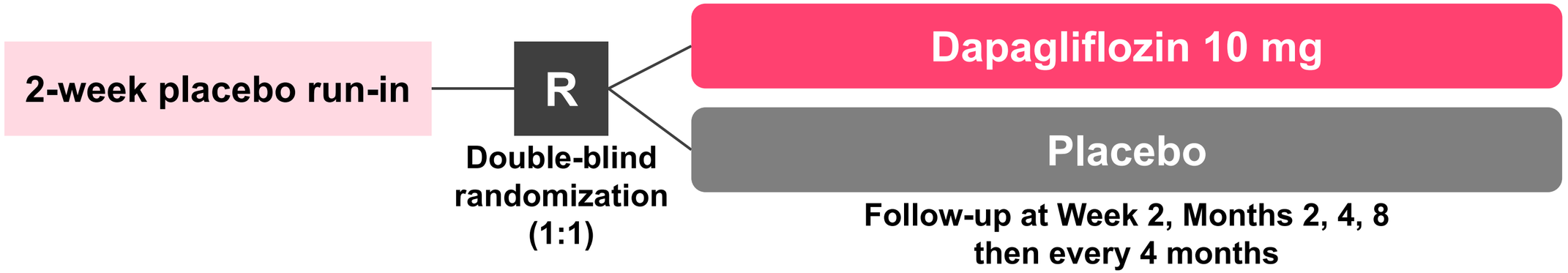
Patients in DAPA-CKD Also Received Standard of Care Treatment[1,2]

Key inclusion criteria

- ≥18 years of age
- **eGFR** 25–75 mL/min/1.73 m^2
- **UACR** 22.6–565 mg/mmol (200–5000 mg/g)
- **Stable maximum tolerated/labelled dose of ACEi or ARB for ≥4 weeks (if not contraindicated)**

Key exclusion criteria

- Type 1 diabetes
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy within 6 months prior to enrolment



Participants continued treatment if eGFR was <25 mL/min/1.73 m^2

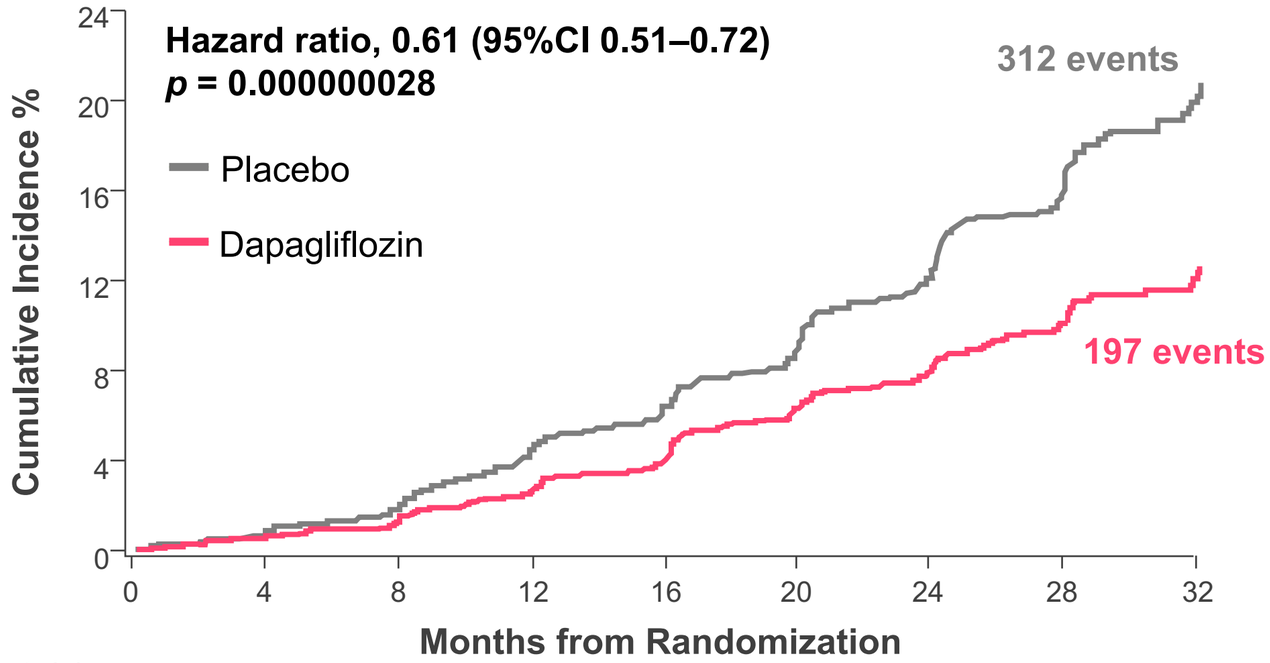
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; ANCA, Anti-Neutrophilic Cytoplasmic Autoantibodies

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282;
2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

Dapagliflozin reduced renal events in a primary outcome trial in patients with and without T2D

- Patients in DAPA-CKD received fixed-dose **dapagliflozin 10 mg in addition to the standard of care**[1]
  - CKD with and without T2D
  - 67.5% of patients had T2D[2]
- **Primary composite endpoint** of ESKD, sustained ≥50% eGFR decline, and renal/CV death was **reduced by 39%**[1]

DAPA-CKD primary endpoint: Composite of Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death



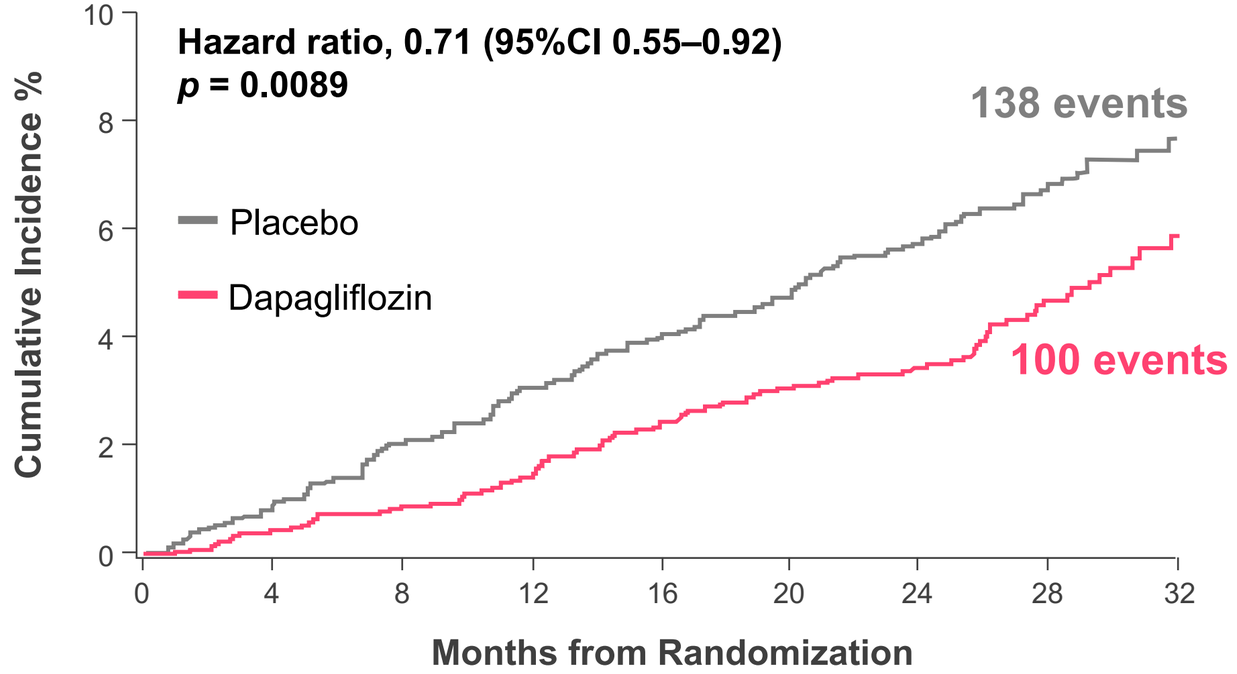
No. at risk									
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapa	2152	2001	1955	1898	1841	1701	1288	831	309

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282;
2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

Dapagliflozin reduced a composite endpoint of CV death and hospitalization for heart failure (HHF) among patients with CKD

- Treatment with dapagliflozin 10 mg was associated with a reduced occurrence of a composite endpoint of CV death and HHF
- All-cause mortality reduced by 31% (HR 0.69, 95% CI 0.53-0.88)
- Numerical reduction in incidence rate of CV death (HR 0.81, 95% CI 0.58-1.12)
- Data on 3-point MACE (exploratory outcome) yet to be reported

DAPA-CKD Secondary Outcome: Composite of CV Death or Hospitalization for Heart Failure (HHF)



No. at risk									
Placebo	2152	2023	1989	1957	1927	1853	1451	976	384
Dapa	2152	2035	2021	2003	1975	1895	1502	1003	384

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282;
2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

Commentary on SGLT2i Use in Nephrology

"After more than a century of research into the physiology of tubular glucose reabsorption, we are now entering a new era of kidney protection with proven effective therapeutic approaches that prevent clinically important outcomes in patients with type 2 diabetes. **It is now up to the nephrology community to implement these treatments in clinical practice**."

Hiddo J L Heerspink, Denis Fouque, Christoph Wanner (2020)[1]

"**Collaborative efforts from the nephrology community** and other stakeholders are now required to ensure that findings from randomized trials are translated into routine clinical practice."

Brendon L Neuen, Meg J Jardine, Vlado Perkovic (2020)[2]

1. Heespink et al. Nephrol Dial Transplant. 2020 Jan; 35(Suppl 1): i1–i2.
2. Neuen et al. Nephrol Dial Transplant. 2020 Jan; 35(Suppl 1): i48–i55.

Summary

- Exploratory data from SGLT2i CVOTs suggested a renal benefit of these medication in patients with T2D
- Primary outcome data confirm a renal benefit of SGLT2i on top of ACEi/ARB for patients with T2D and renal impairment including macroalbuminuria
  - Canagliflozin 100 mg (T2D), dapagliflozin 10 mg (+/- T2D)
- Secondary outcome measures from CREDENCE confirm a benefit of canagliflozin 100 mg on 3-point MACE outcomes
  - Reduction of 20%, vs 14% in the CANVAS Program and in EMPA-REG OUTCOME
- Secondary outcome measures from DAPA-CKD show a benefit of dapagliflozin 10 mg on all-cause mortality and a composite of CV death and hospitalization for heart failure
- Leaders in nephrology are calling on their colleagues to integrate SGLT2 inhibitors in their treatment of patients with T2D

Knowledge Check 1

Approximately what proportion of patients in CREDENCE were taking an ACE inhibitor or ARB medication?

a) 50%

b) 75%

c) 90%

d) >99%

DID YOU KNOW?
TAKING BACK DKD

Did you know…

SGLT2 inhibitors provide renal protection in a manner that is independent of A1C?

Canadian Society of Nephrology/
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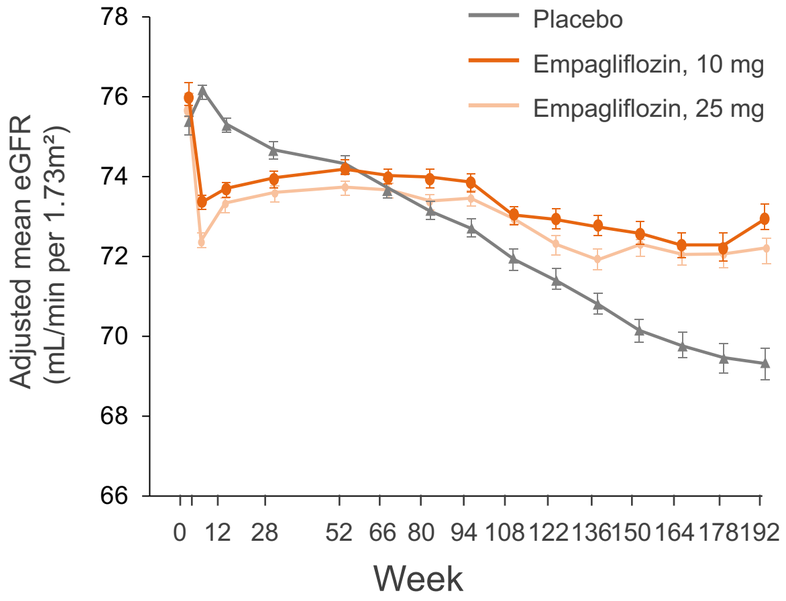
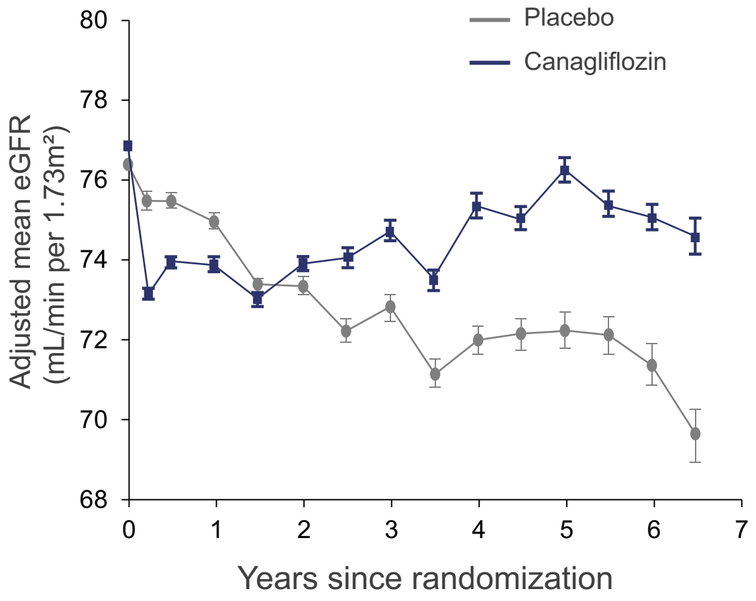
Dr. Cheng

Data from CVOTs Suggested SGLT2i Slow eGFR Decline

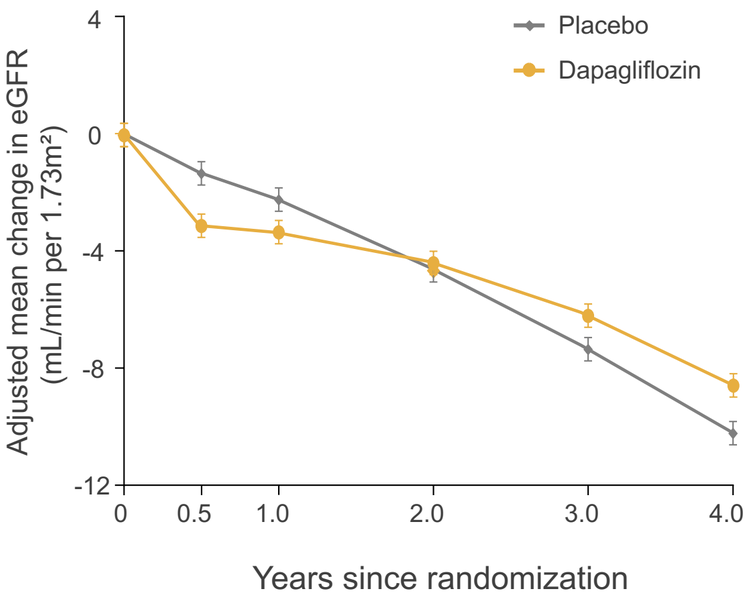
EMPA-REG OUTCOME
Change in eGFR over 192 weeks[1]



CANVAS Program
Change in eGFR over 6.5 years[2]



DECLARE-TIMI-58
Change in eGFR over 4 years[3]



1. Wanner C, et al. N Engl J Med 2016;375:323-34.
2. Perkovic V, et al. Lancet Diabetes Endocrinol 2018;6:691-704
3. Mozenson O, et al. Lancet Diabetes Endocrinol 2019; 7: 606–17

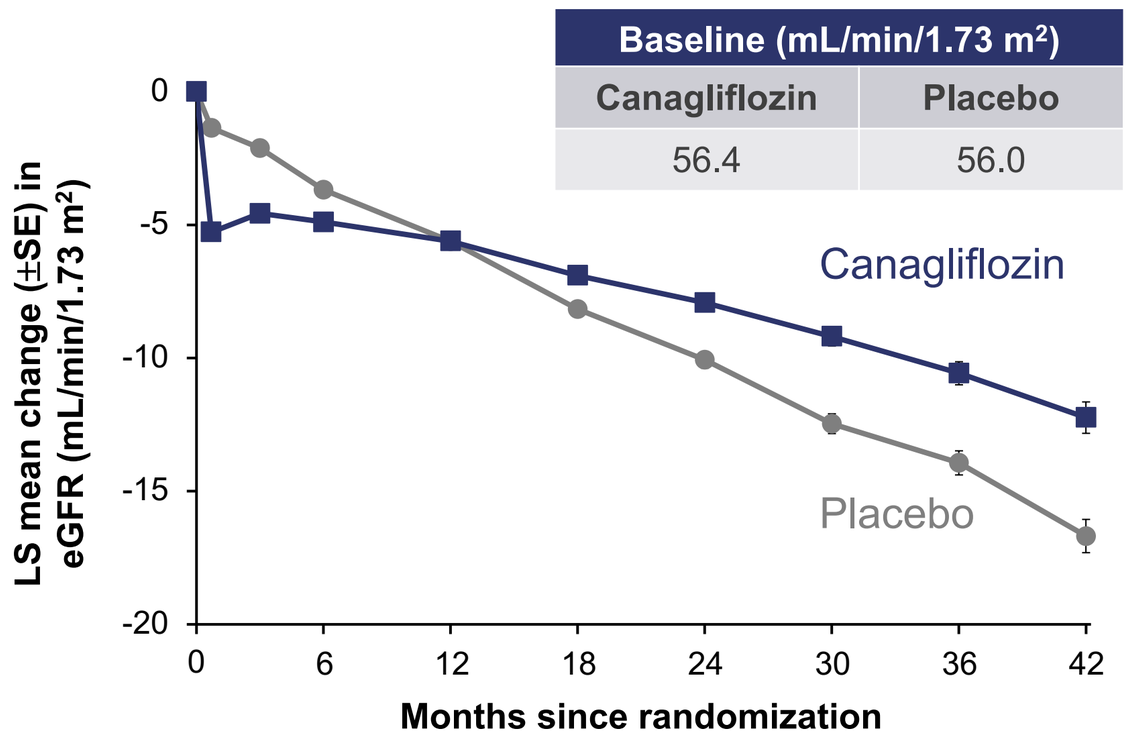
CREDENCE: Effect on eGFR decline

- In CREDENCE, canagliflozin was associated with a slower **long-term** decline in eGFR despite initial reversible hemodynamic drop[1]
- Placebo represents eGFR decline in modern standard of care (99.9% of patients taking ACEi/ARB)[1]
  - In IDNT, irbesartan slowed eGFR decline by roughly 1.2 mL/min/1.73 m^2 per year[2]

eGFR Changes in CREDENCE[1]

	First 3 weeks (mL/min/1.73 m^2)	Thereafter (mL/min/1.73 m^2 per year)
Placebo (±SD)	–0.55 ± 0.25	–4.59 ± 0.14
Canagliflozin (±SD)	–3.72 ± 0.25	–1.85 ± 0.13
Difference (95%CI)	–3.17 (–3.87 to –2.47)	2.74 (2.37 to 3.11)

eGFR Changes in CREDENCE[1]

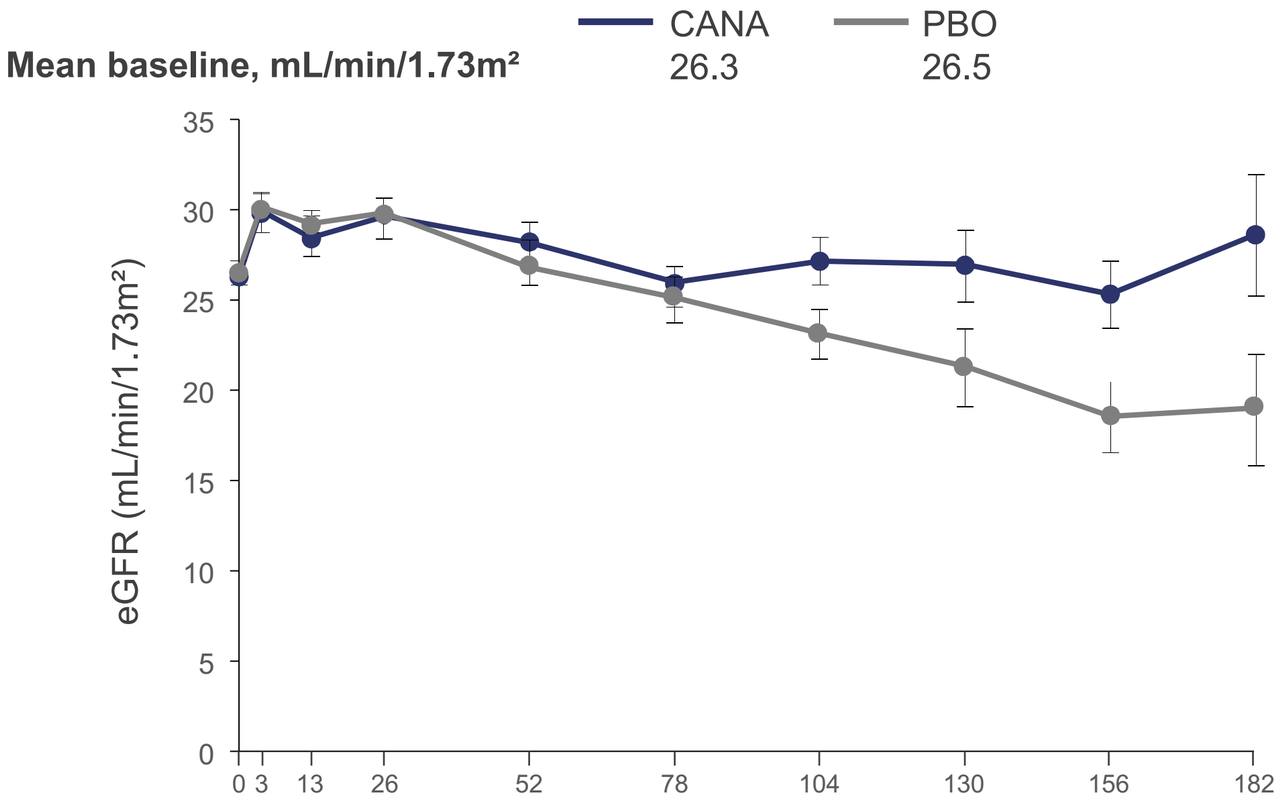


No. at risk								
Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

1. Perkovic et al. *N Engl J Med*. 2019 Jun 13;380(24):2295-230.
2. Evans et al. *Nephrol Dial Transplant*. 2012 Jun;27(6):2255-63.

Renal Efficacy of Canagliflozin in Patients with eGFR <30 mL/min/1.73 m²

- In the CREDENCE trial, some patients had eGFR values <30 mL/min/1.73 m² at treatment initiation
- In a sub-analysis, canagliflozin 100 mg was associated with a reduction in the rate of eGFR decline relative to placebo in these patients
- Effects on renal, CV, and mortality outcomes in participants were consistent with those seen in the overall population

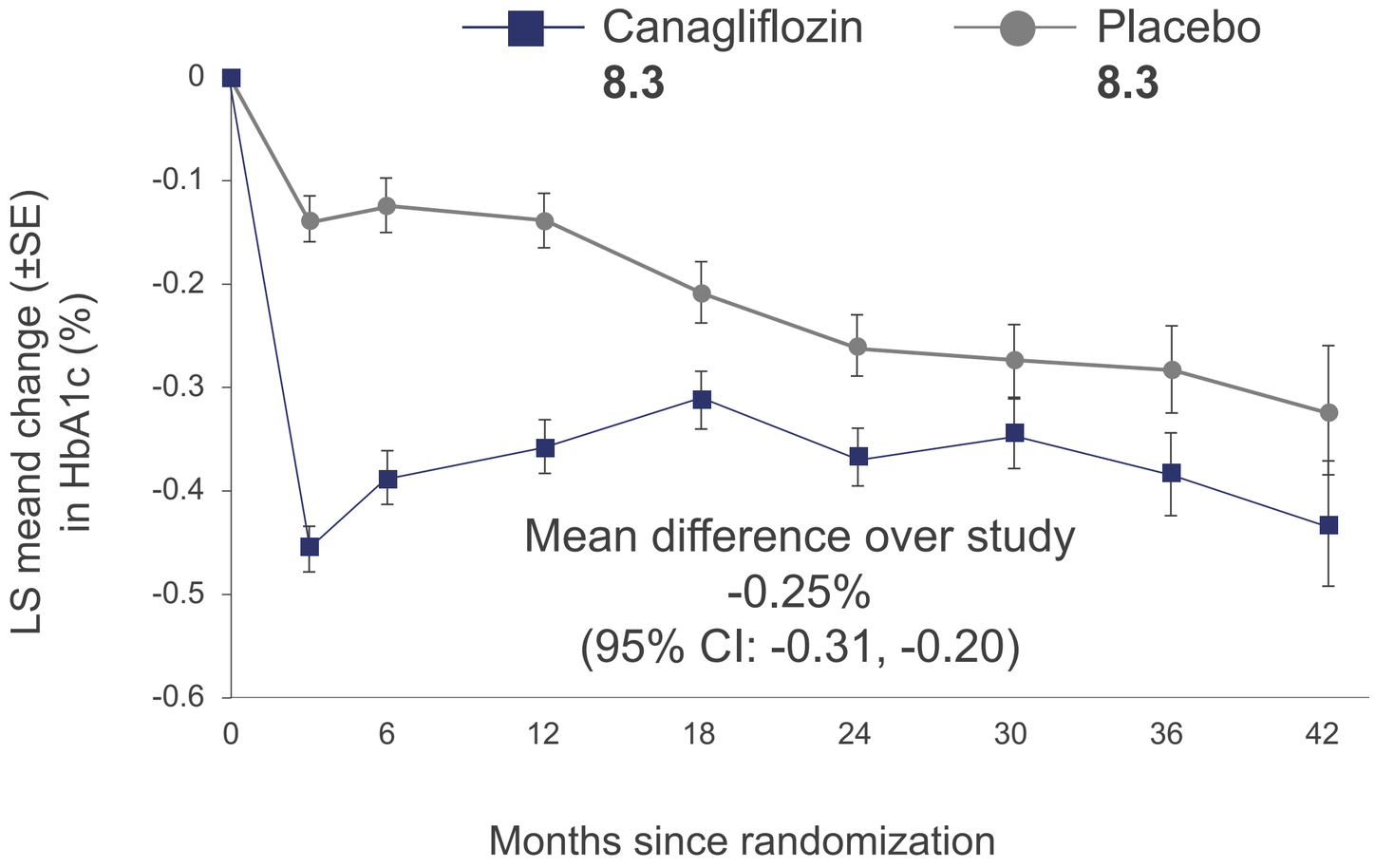


CANA, n	82	82	77	78	71	57	50	36	22	7
PBO, n	89	88	85	81	76	65	59	33	21	8

Bakris G, et al. Presented at the American Society of Nephrology (ASN) Kidney Week 2019 Annual Meeting; November 5-10; Washington, D.C. Abstract TH-PO1202

Minimal Change in A1C in CREDENCE

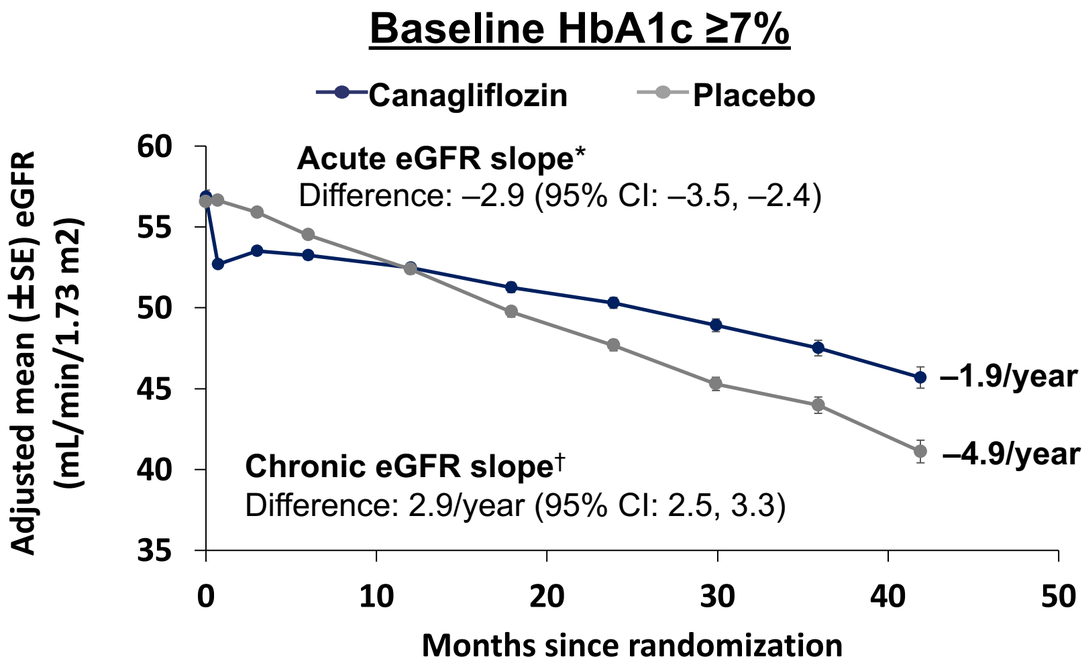
- A1C in CREDENCE was reduced by a mean of 0.25% over the duration of the study
- Suggests that renal protection and slowed eGFR decline are independent of glucose-lowering effect

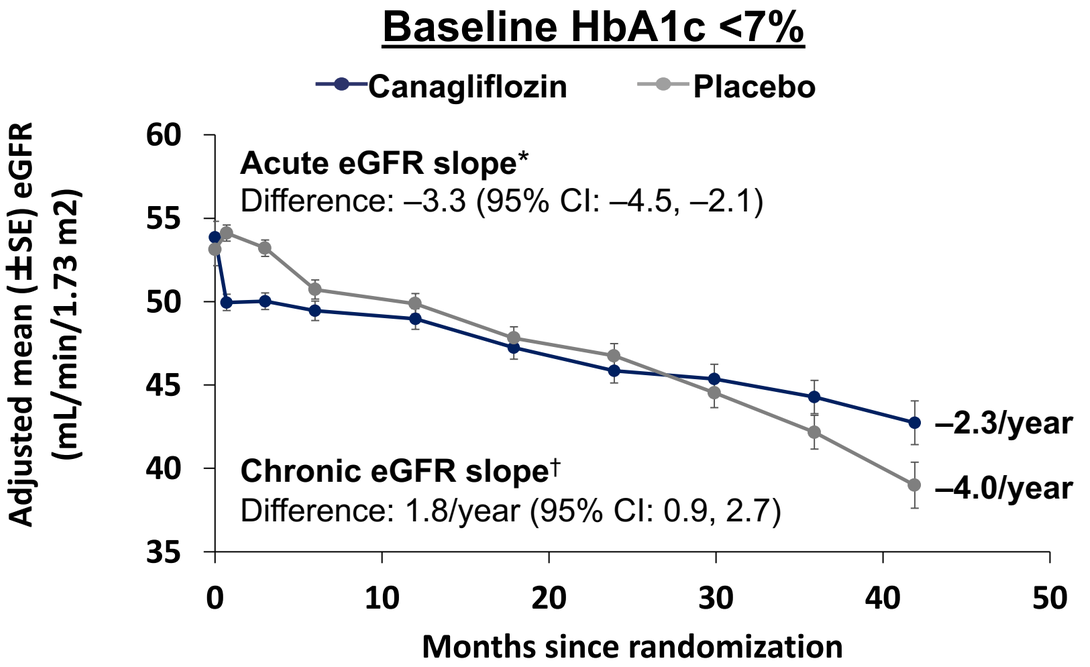


Perkovic et al. *N Engl J Med.* 2019; 380(24):2295-2306.

Canagliflozin Slowed eGFR Decline Among Patients Both Above and Below A1C Targets

In the CREDENCE trial, decline in eGFR over the chronic phase of the study was slowed among patients taking canagliflozin 100 mg even among patients with A1C at or below target

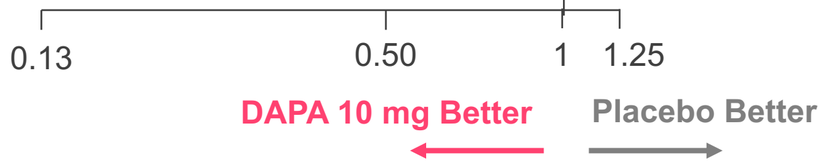




Jardine M , et al. Presented at the American Society of Nephrology (ASN) Kidney Week 2019 Annual Meeting; November 5-10; Washington, D.C. Abstract TH-PO1204

DAPA-CKD Primary Composite Outcome: Prespecified Subgroup Analyses

	Number of Events			
	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR (95% CI)	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death				
All Patients	197	312	0.61 (0.51, 0.72)	
T2D at Baseline				0.24
Yes	152	229	0.64 (0.52, 0.79)	
No	45	83	0.50 (0.35, 0.72)	
UACR (mg/g) at Baseline				0.52
≤1000	44	84	0.54 (0.37, 0.77)	
>1000	153	228	0.62 (0.50, 0.76)	
eGFR (mL/min/1.73m^2) at Baseline				0.22
<45	152	217	0.63 (0.51, 0.78)	
≥45	45	95	0.49 (0.34, 0.69)	



CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

Summary

- Evidence from CVOTs and renal outcomes trials demonstrates an association between SGLT2 inhibitor use and slowing of eGFR decline despite an initial reversible drop
- The A1C difference between groups in CREDENCE (0.25%) does not account for renal and CV benefit
- Slowing of eGFR decline by canagliflozin 100 mg was apparent in patients whether they had achieved A1C target or not
- Renal benefit of dapagliflozin 10 mg was consistent regardless of T2D status

Knowledge Check 2

Which patient group did not experience a slowing of eGFR decline when taking an SGLT2 inhibitor?

a) Patients with relatively small A1C reduction relative to placebo (<0.5%)

b) Patients below A1C target (≤7.0%)

c) Patients above A1C target (>7.0%)

d) None of the above (A1C-independent effect)

DID YOU KNOW?
TAKING BACK DKD

Did you know…

Renal-related adverse events, including incidence of AKI, are lower in patients taking SGLT2 inhibitors compared to placebo in clinical trials regardless of their initial eGFR?

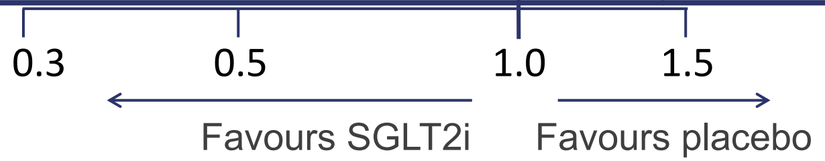
Canadian Society of Nephrology/
Société canadienne de néphrologie
CSN/SCN

Dr. Girard

SGLT2 Inhibitors and Acute Kidney Injury

In a systematic review and meta-analysis of exploratory analyses of SGLT2i trials, the overall incidence of acute kidney injury (AKI) was reduced

	Patients	Events	HR (95% CI)
CREDENCE	4397	184	0.85 (0.64–1.13)
DECLARE-TIMI 58	17143	300	0.69 (0.55–0.87)
CANVAS Program	10134	58	0.66 (0.39–1.11)
EMPA-REG OUTCOME	7010	401	0.76 (0.62–0.93)
Overall p < 0.0001 (I^2=0.0%; $p_{heterogeneity}$=0.68)			**0.75 (0.66–0.85)**



Neuen et al. *Lancet Diabetes Endocrinol*. 2019;7(11):845-854.

DAPA-CKD Safety Outcomes

Safety Outcomes[a], n (%)	Dapagliflozin 10 mg (N=2149)	Placebo (N=2149)
Discontinuation of study drug	274 (12.8)	309 (14.4)
Discontinuation due to adverse event	118 (5.5)	123 (5.7)
Any serious adverse event	633 (29.5)	729 (33.9)
Adverse events of interest		
Amputation[b]	35 (1.6)	39 (1.8)
Any definite or probable diabetic ketoacidosis	0	2 (0.1)
Fracture[c]	85 (4.0)	69 (3.2)
Renal-related adverse event[c]	155 (7.2)	188 (8.7)
Major hypoglycemia[d]	14 (0.7)	28 (1.3)
Volume depletion[c]	127 (5.9)	90 (4.2)
Serious adverse events of volume depletion	22 (1.0)	18 (0.8)

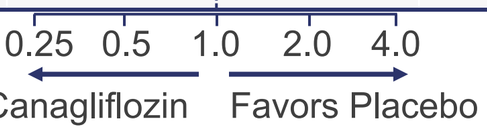
[a]Safety outcomes reported in participants on and off treatment; [b]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; [c]Based on pre-defined list of preferred terms; [d]Adverse events with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behavior, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

CREDENCE: Adverse Events in Patients with eGFR <30 mL/min/1.73 m^2

- Adverse event profiles in CREDENCE were similar for the overall population and for those with eGFR <30 mL/min/1.73 m^2

	Number of participants with an event		
	Canagliflozin	Placebo	HR (95% CI)
Any AE			
Overall	1784	1860	0.87 (0.82, 0.93)
eGFR <30mL/min/1.73m^2	77	81	1.08 (0.79, 1.47)
Any serious AE			
Overall	737	806	0.87 (0.79, 0.97)
eGFR <30mL/min/1.73m^2	37	40	1.03 (0.66, 1.61)
Hyperkalemia			
Overall	151	181	0.80 (0.65, 1.00)
eGFR <30mL/min/1.73m^2	14	13	1.33 (0.61, 2.87)
Any renal-related AE			
Overall	290	388	0.71 (0.61, 0.82)
eGFR <30mL/min/1.73m^2	31	34	1.11 (0.68, 1.80)
Acute kidney injury			
Overall	86	98	0.85 (0.64, 1.13)
eGFR <30mL/min/1.73m^2	9	10	1.04 (0.42, 2.57)



Bakris G, et al. Presented at the American Society of Nephrology (ASN) Kidney Week 2019 Annual Meeting; November 5-10; Washington, D.C. Abstract TH-PO1202

Diabetic Ketoacidosis (DKA)

- DKA is a rare complication of SGLT2 inhibitor use that is reported more commonly among patients who are taking insulin[1]
  - CREDENCE: 11/2200 patients taking canagliflozin[2]
  - DAPA-CKD: 0/2149 patients taking dapagliflozin[3]
- DKA results from insufficient insulin and excess glucagon[4]
  - SGLT2 inhibition can “mask” DKA, allowing it to occur at lower glucose levels than usual
- Use caution when reducing or discontinuing insulin therapy[1]
- Sick-day management strategies should be discussed before an SGLT2 inhibitor is initiated to help your patients avoid adverse events such as DKA[2]

Sick Day Medication List[5]

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

1. Woo et al. Can J Diabetes. 2018; 42:88–93
2. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306.
3. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.
4. Goldenberg et al. Clin Ther. 2016 Dec;38(12):2654-2664.e1.
5. Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes 20118. 42:S316.

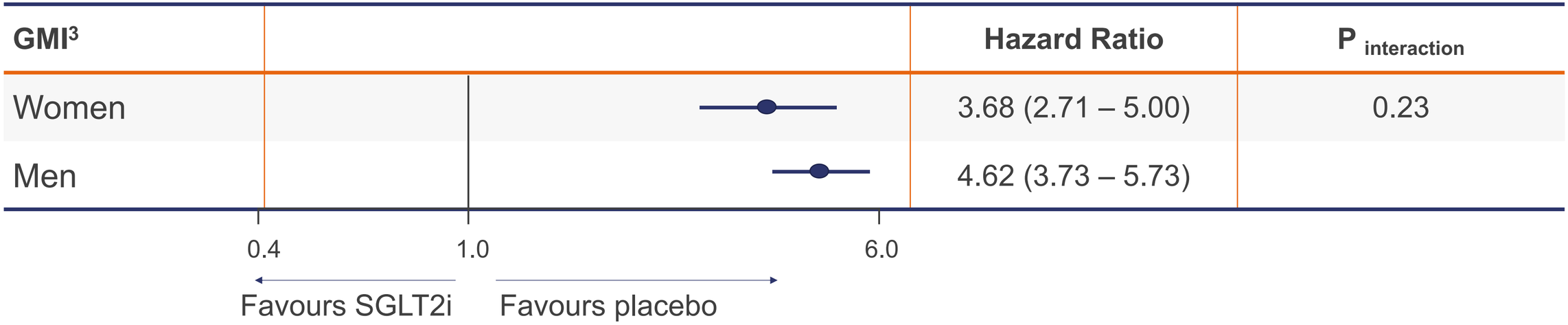
Foot Care is the Standard of Care

- An increased risk of lower-limb amputation (toes, feet, or legs) was observed with canagliflozin in the CANVAS Program[1,2]
  - This result was not seen in CVOTs of other SGLT2i medications[1]
  - Highest absolute risk of amputation occurred among patients who had a history of amputation or peripheral vascular disease[2]
  - Patients with T2DM and renal impairment did not have a higher rate of lower limb amputations when taking canagliflozin 100 mg in CREDENCE or dapagliflozin 10 mg in DAPA-CKD[3-5]
- Good foot care is the standard of care in patients with T2D[6]
  - In CREDENCE, canagliflozin was withheld if patients developed an active lesion and restarted upon its resolution[3,4]

1. Zelnicker et al. Lancet. 2019 Jan 5;393(10166):31-39.
2. Neal et al. N Engl J Med 2017;377:644-57.
3. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306.
4. Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
5. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.
6. Diabetes Canada Clinical Practice Guidelines Expert Committee. Chapter 32: Foot Care. *Can J Diabetes* 2018; 42(Suppl 1):S1–S325

Genital Mycotic Infection (GMI)

- Patients taking SGLT2i are at increased risk of genital mycotic infections (GMIs)[1]
- Remember to counsel patients on the increased risk of GMIs associated with SGLT2i agents and to wash frequently[2]
  - Patients can be counselled to to rinse the genital area with water after every void and before going to bed to reduce incidence of GMI



1. Zelnicker et al. Lancet. 2019 Jan 5;393(10166):31-39.
2. Williams & Ahmed. Diabetes 2019 Jun; 68(Supplement 1): https://doi.org/10.2337/db19-1224-P
3. Rådholm et al. Diabetes Obes Metab. 2020 Feb;22(2):263-266.

Summary

- Renal-related adverse events are lower in patients taking SGLT2 inhibitors relative to those taking placebo
- DKA is rare among patients taking SGLT2 inhibitors and usually results from a precipitating event
- Counsel patients taking SGLT2 inhibitors on genital hygiene
- Foot care is the standard of care in patients with T2D

Knowledge Check 3

Based on the CREDENCE sub-analysis, patients with a baseline eGFR of ≤30 mL/min/1.73 m^2 were:

a) At increased risk of AKI relative to the overall population

b) At decreased risk of AKI relative to the overall population

c) At equal risk of AKI relative to the overall population

DID YOU KNOW?
TAKING BACK DKD

Did you know…

One SGLT2 inhibitor is indicated for reducing renal events in patients with T2D and renal impairment with macroalbuminuria?

Canadian Society of Nephrology/
Société canadienne de néphrologie
CSN/SCN

Dr. Cheng

Current Canadian Indications for the SGLT2i Class

	Canagliflozin[1] (INVOKANA)	Dapagliflozin[2] (FORXIGA)	Empagliflozin[3] (JARDIANCE)
3-Point MACE reduction* **(nonfatal stroke, nonfatal MI, or CV death)**	Yes: 3-point MACE	No	Yes: CV death only
Hospitalization for heart failure in T2DM	No	Yes (with CV risk factors or established CV disease)	No
Heart Failure	No	Yes‡	No
Renal protection in primary outcome trial	Yes[4]	No	No
GFR guidelines	Initiate ≥30 mL/min/1.73 m^2 100 mg can be continued down to dialysis†	Initiate ≥45 mL/min/1.73 m^2 Contraindicated below 30 mL/min/1.73 m^2	Initiate ≥30 mL/min/1.73 m^2 Contraindicated below 30 mL/min/1.73 m^2

*in T2D and established CVD
†in patients with albuminuria >33.9 mg/mmol
‡indicated in adults, as an adjunct to standard of care therapy, for the treatment of heart failure with reduced ejection fraction (HFrEF) to reduce the risk of cardiovascular (CV) death, hospitalization for heart failure and urgent heart failure visit

1. INVOKANA Product Monograph. 23/01/2020. Janssen Inc.
2. FORXIGA Product Monograph. 01/04/2020. AstraZeneca Inc.
3. JARDIANCE Product Monograph. 15/04/2020. Boehringer Ingelheim (Canada) Ltd
4. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306.

SGLT2 Inhibitors: Practical Considerations

- Most SGLT2i agents are safe to initiate and use at normal dose in patients with renal impairment
  - Canagliflozin 100 mg is indicated for use until dialysis in patients with macroalbuminuria
- No dose adjustments are required for patients ≥65 years old
  - Risk of volume depletion should be taken into account
- Patients taking diuretics may be at increased risk for hypovolemia and hypotension

SGLT2i agent	eGFR (mL/min/1.73 m^2)		
	<30	≥30 to 45	>45 to 60
Canagliflozin[1]	Therapy may be continued*	100 mg/day	
Dapagliflozin[2]	Contraindicated	5-10 mg/day	
Empagliflozin[3]	Contraindicated	10-25 mg/day	

*In patients already initiated on canagliflozin therapy who meet the criterion of an eGFR <30 mL/min/1.73 m^2 with albuminuria >33.9 mg/mmol, therapy can be continued at 100 mg once daily and should be discontinued at the initiation of dialysis.

1. INVOKANA Product Monograph. 23/01/2020. Janssen Inc.
2. FORXIGA Product Monograph. 29/06/2020. AstraZeneca Inc
3. JARDIANCE Product Monograph. 15/04/2020. Boehringer Ingelheim (Canada) Ltd

SGLT2 Inhibitors: Practical Considerations

- Most SGLT2i agents are safe to use at normal dose in patients with renal impairment
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SGLT2i have reduced efficacy for lowering A1C and other glucosuric effects as GFR declines, but still provide CV and renal benefits in patients with renal impairment[4,5]

SGLT2i agent	eGFR (mL/min/1.73 m^2)		
			to 60
			y
			y
			ay

*In patients already initiated on canagliflozin therapy who meet the criterion of an eGFR <30 mL/min/1.73 m^2 with albuminuria >33.9 mg/mmol, therapy can be continued at 100 mg once daily and should be discontinued at the initiation of dialysis.

1. INVOKANA Product Monograph. 23/01/2020. Janssen Inc.
2. FORXIGA Product Monograph. 29/06/2020. AstraZeneca Inc
3. JARDIANCE Product Monograph. 15/04/2020. Boehringer Ingelheim (Canada) Ltd
4. Fioretto et al. Diabetes Care 2016;39(Suppl. 2):S165–S171.
5. Perkovic et al. *N Engl J Med*. 2019; 380(24):2295-2306.

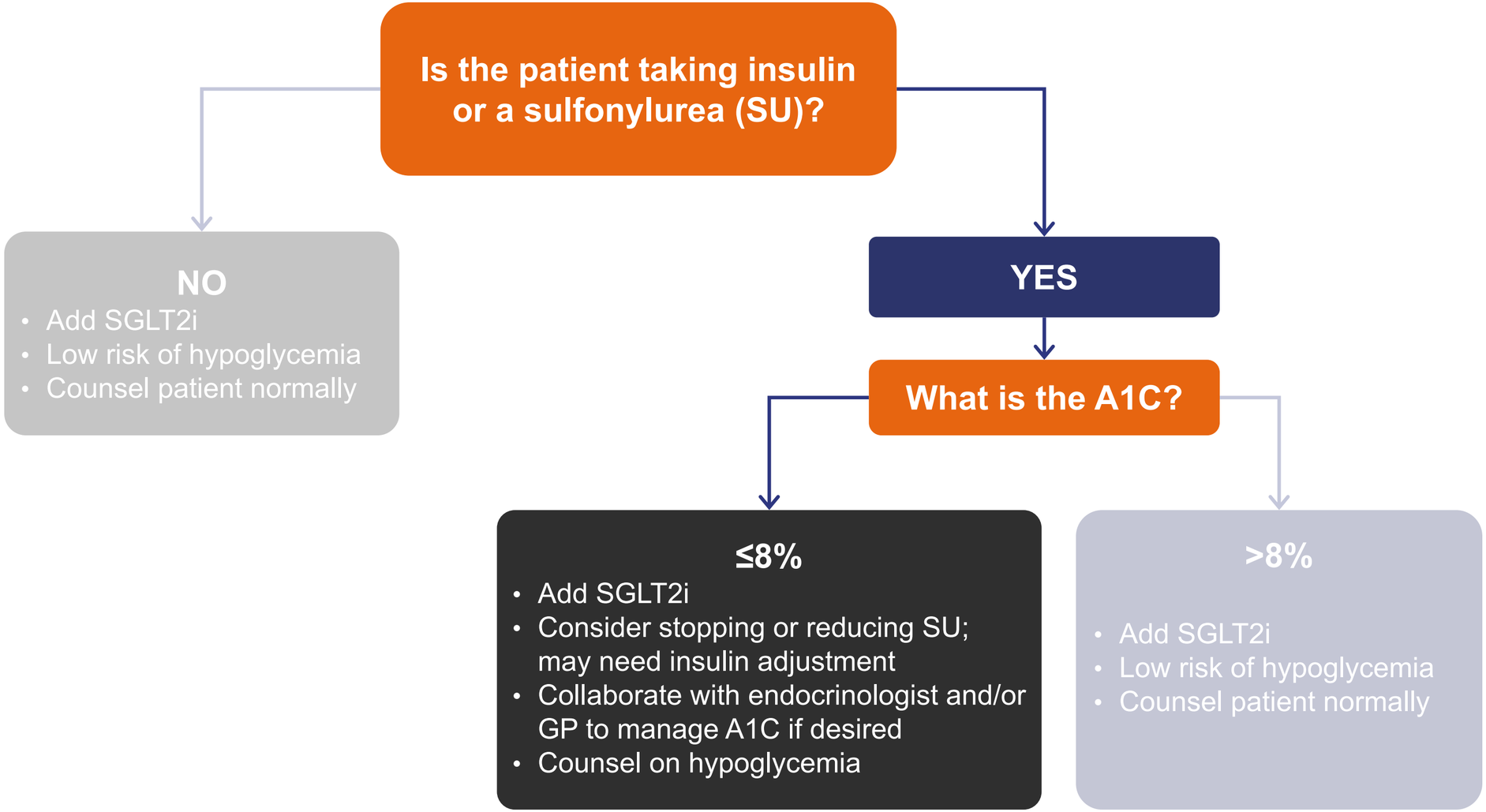
SGLT2 Inhibitors as Kidney Medications

- Initiate without adjustment of ACEi/ARB dose[1]
- Counsel patient on need to stay hydrated, risk of genital mycotic infection (GMI), and the sick day medication list[2,3]
- Some drop in eGFR is expected upon initiation[1,4]
  - Subanalysis of CREDENCE data suggests an acute drop in eGFR of <30% following canagliflozin initiation is not a safety concern

Initial eGFR (mL/min/1.73 m^2)	**Follow-up**[4,5]		
>60	Monitor normally as per relevant guidelines and physician discretion		
<60	Check eGFR decline after 3 weeks	<25%	Recheck after 3 months, then at physician discretion
		25–30%	Recheck within 7 days
		≥30%	Investigate pre-renal causes (e.g. diuretics, NSAIDs)

1. Perkovic et al. *N Engl J Med.* 2019; 380(24):2295-2306.
2. McGIll & Subramanian. Am J Cardiol. 2019 Dec 15;124 Suppl 1:S45-S52.
3. Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes 20118. 42:S316.
4. Oshima et al. Presented at the American Diabetes Association (ADA) 2020 Annual Meeting; June 12-16, 2020
5. Steering Committee Expert Consensus

Management of Antihyperglycemic Medications When Initiating SGLT2 inhibitors



Management of Diuretics in Patients Taking SGLT2i

When adding an SGLT2i, continue diuretic and monitor

An option for management of diuretics with SGLT2 inhibitors

1. What is the volume status?

Hypervolemia
- Continue diuretic and monitor BP, electrolytes, Cr, weight, assuming not hypotensive
- Caution with *multiple* diuretics

Euvolemia

Volume Contraction
- Stop diuretic and monitor
- Initiate SGLT2i when euvolemic

2. What is the blood pressure?

Hypertensive
- Continue diuretic therapy and monitor BP, electrolytes, Cr, weight

Normotensive

Thiazides
- Continue therapy and monitor

Loop diuretics
- Consider reducing dose by 50% and monitor BP/weight
  - If stable, continue therapy
  - If increasing, reinstitute diuresis
  - If decreasing, stop diuretic

Hypotensive
- Caution, hold or reduce diuretic and re-institute if required

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

Summary

- Canagliflozin 100 mg is indicated to reduce the risk of ESKD, doubling of serum creatinine, and CV death in adult patients with T2D and diabetic nephropathy with albuminuria >33.9 mg/mmol
- SGLT2i agents are safe to initiate and use at normal dose in patients with renal impairment; with canagliflozin 100 mg indicated for use until dialysis in patients with macroalbuminuria
- SGLT2 inhibitors can be initiated in patients with T2D and CKD without changing ACEi/ARB dose
  - Monitor volume status and adjust diuretic as needed
  - Consider collaborating with endocrinologist and/or GP for A1C management strategy in patients taking insulin and/or sulfonylurea

Knowledge Check 4

Based on what we know about SGLT2i, is there a renal or CV benefit for patients with kidney impairment if we use doses that provide higher glycemic efficacy (e.g. canagliflozin 300 mg vs 100 mg)?

A. No

B. Yes

C. No evidence

Overall Summary

- SGLT2 inhibitors can be thought of as kidney drugs that may also lower glucose
- SGLT2 inhibitors provide renal protection in a manner that is independent of A1C
- Renal-related adverse events, including incidence of AKI, are lower in patients taking SGLT2 inhibitors compared to placebo in clinical trials regardless of their initial eGFR
- One SGLT2 inhibitor is indicated for reducing renal events in patients with T2D and renal impairment with macroalbuminuria

DID YOU KNOW?

TAKING BACK DKD

Taking Action

Canadian Society of Nephrology/
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CSN/SCN

Dr. Girard

Reflection Questions

Are you likely to make changes to the way you manage patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) in your practice based on what you've learned today?

a) Yes, I plan to make changes in my practice

b) No, I will NOT be making any changes in my practice

Reflection Questions

If you answered YES, please share the change(s) or action(s) you intend to undertake (check all that apply):

a) Prioritize cardiorenal protective strategies in the management of my patients with type 2 diabetes (T2D) and chronic kidney disease (CKD)

b) Identify patients at high risk in whom cardiorenal protection is most important

c) Construct a plan to integrate recent evidence presented today into my practice

d) Optimize communication between my peers (multidisciplinary teams) to enhance the management of CKD and T2DM

Reflection Questions

If you answered NO to making changes, please tell us why? (check all that apply):

a) I am already successfully implementing the presented strategies into my practice

b) The topics presented did not apply to my patients and/or practice

c) I foresee barriers to implementing the presented strategies into my practice

Action Plan

Based on what you have seen today, what specific action(s) do you expect to take over the next 6 months?

- Read/re-read publications including the CREDENCE and DAPA-CKD clinical trials and the meta-analyses on CV and renal outcomes with SGLT2i agents
- Review my charts to determine if my patients with T2D and CKD would benefit from the latest evidence presented today
- Attend additional CHE events on the optimal management of this patient population
- Review the most current national/international guidelines to ensure my care of patients with T2D and CKD is up to date
- Discuss strategies with my colleagues to ensure systematic implementation of organ-protective care
- Schedule grand rounds or a journal club to review this data with my colleagues
- Engage with my allied health care colleagues to institute collaborative and optimal organ protection care

DID YOU KNOW?

TAKING BACK DKD

Questions and Discussion

Canadian Society of Nephrology/
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CSN/SCN

DID YOU KNOW?

TAKING BACK DKD

Thank you!

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CSN/SCN