Update on CKD and Diabetes: Treatment and mechanisms

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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 with renal outcomes

Unmet Needs: Chronic Kidney Disease in Diabetes

CKD in diabetes has high prevalence and burden

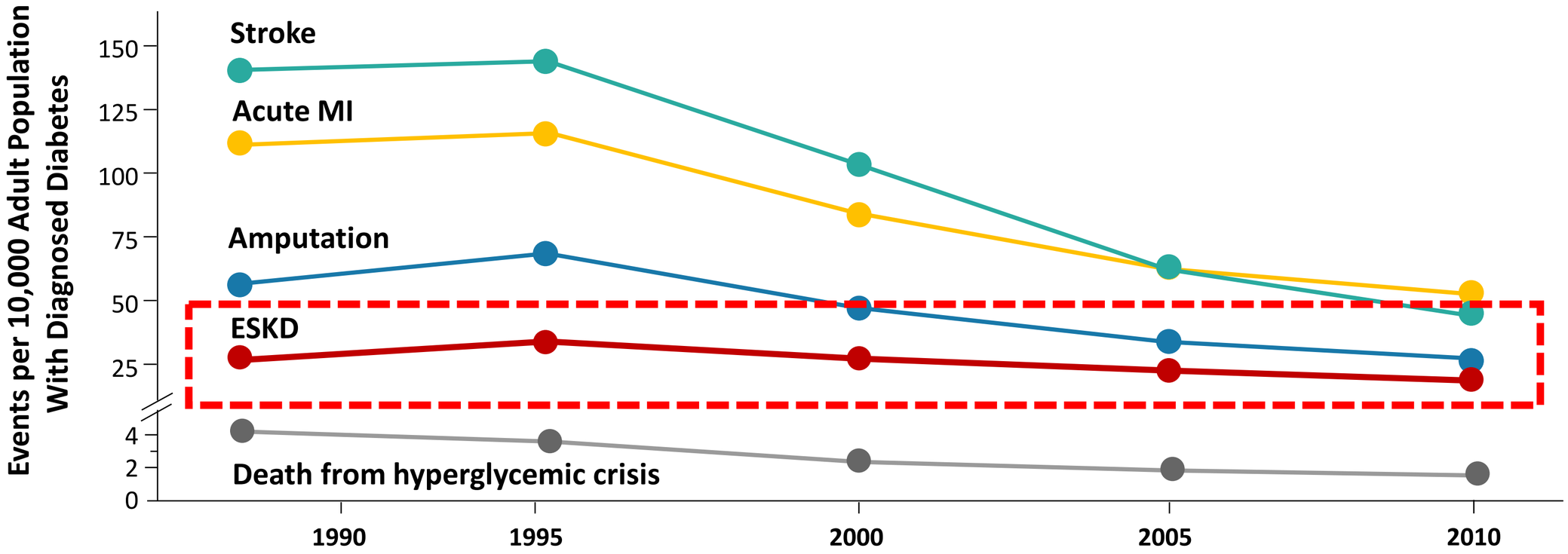
- **40-50%** of people with diabetes will develop CKD[1,2]
  - **CKD is more common than CVD** in patients with T2DM (24.1% vs 21.6%)[3]
- Diabetes is the **leading cause of new cases of ESKD** in Canada[4]
  - **~50%** of adults **requiring dialysis or renal replacement** have ESKD attributable to diabetes[2]
- **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%[1]**

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.

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.

Over the last 20 years, Diabetes Canada (DC) has advocated three key targets for patients with diabetes and renal impairment

A1C Control	BP Control	ACEi or ARB
≤ 7.0%	< 130/80 mmHg	Treatment
(Grade A)	(Grade A)	(Grade A)

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.

ACEi or ARB: “Gold standard” for CKD in diabetes

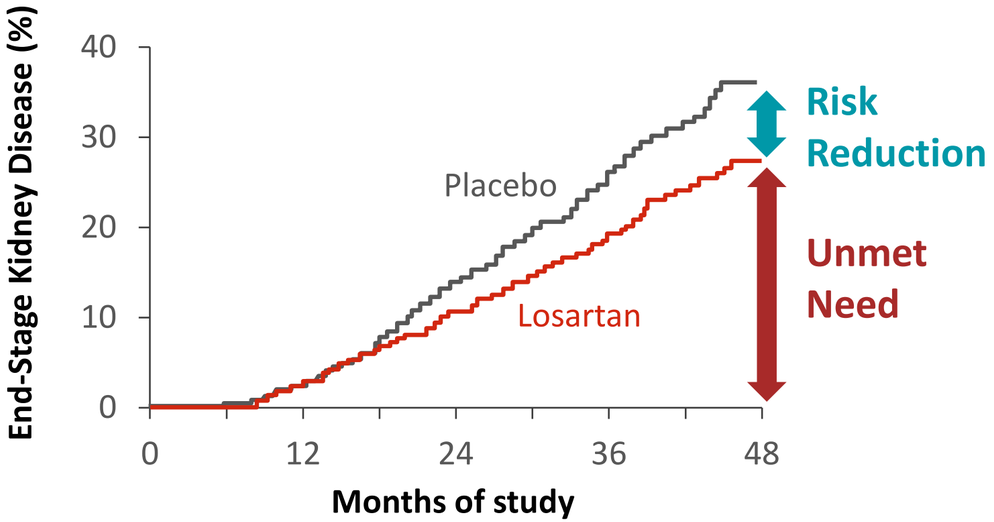
	N	Albuminuria	Baseline renal function	2xCr, ESKD, Renal Death – # of events	Relative Risk Reduction
IDNT[1] (irbesartan)	1715	Median 1900 mg/d (1000 – 3800 mg/d)	Mean Cr: 148 µmol/L	644	20% (p=0.006)
RENAAL[2] (losartan)	1513	Median ACR: ~140 mg/mmol	Mean Cr: 168 µmol/L	686	16% (p = 0.02)
ACEi Collaborative 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

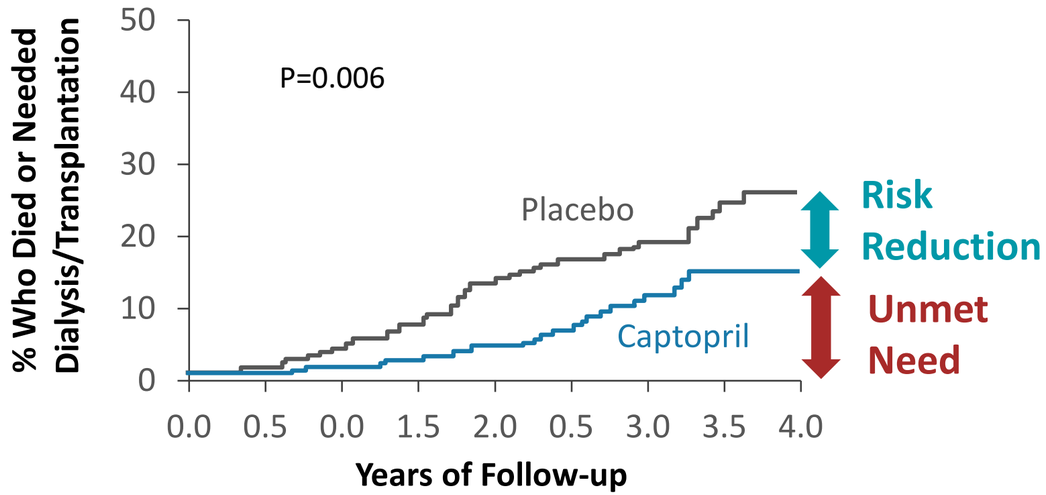
1. Lewis EJ, et al. *N Engl J Med* 2001;345:851-60. 2. Brenner BM et al *New Engl J Med* 2001;345:861-69. 3. Lewis EJ, et al. *N Engl J Med* 1993; 329:1456-1462

ACEi or ARB: “Gold standard” for CKD in diabetes

ARB[1]



ACE Inhibitor[2]

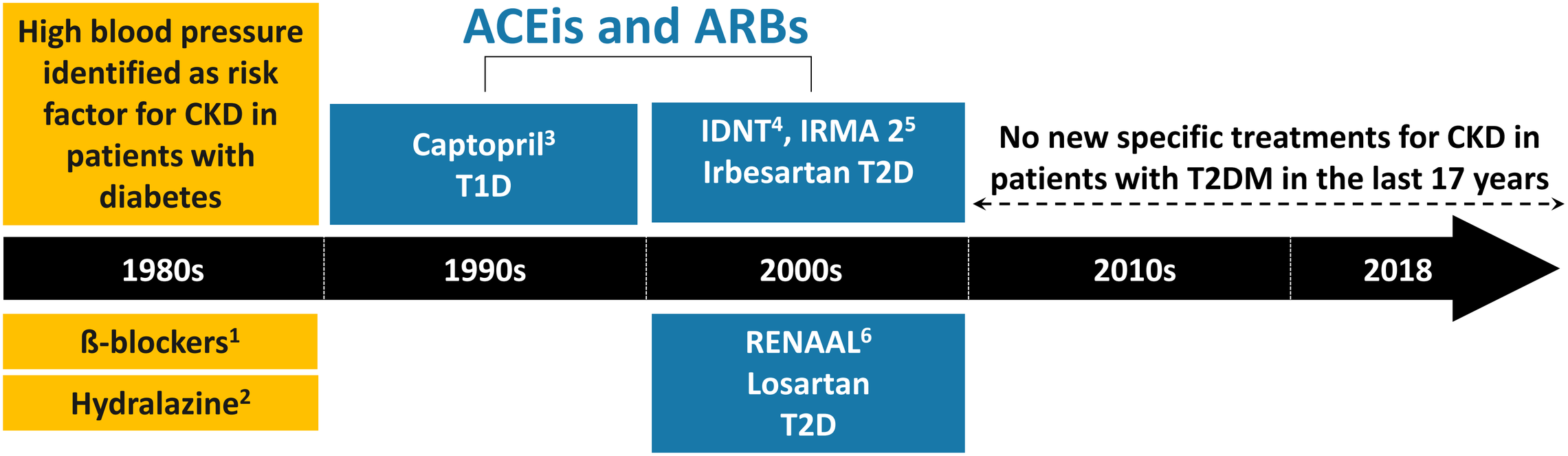


- **Risk reduction associated with ACEi or ARB agents was an important development in primary care**
- **There is still a clear unmet need for new therapeutic interventions**

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.

No new treatment for CKD in diabetes since the advent of ACEi or ARB 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

Turning Point:
EMPA-REG, CANVAS, DECLARE

SGLT2 inhibitors and cardiovascular disease: MACE

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	29·4	0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·4	0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·8	41·0	38·2	0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)							**0·86 (0·80–0·93)**
Patients with multiple risk factors							
CANVAS Program	2039	1447	215	15·8	15·5	25·9	0·98 (0·74–1·30)
DECLARE-TIMI 58	5108	5078	539	13·4	13·3	74·1	1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)							**1·00 (0·87–1·16)**

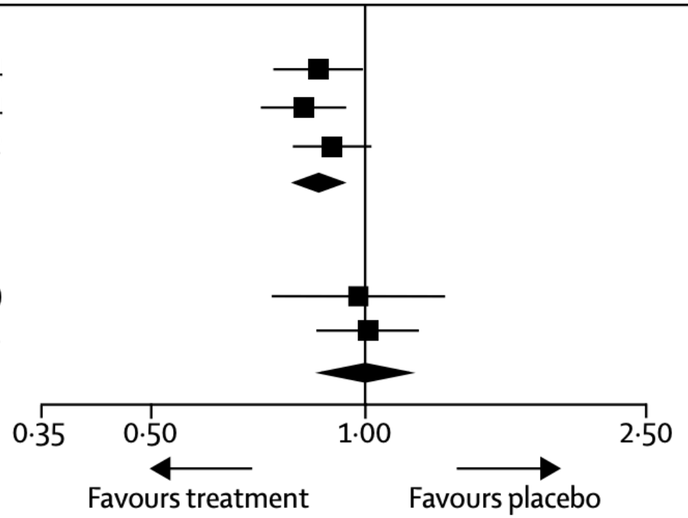


Figure 1: **Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease**

No heterogeneity was found in terms of between-study variance in the subgroups (atherosclerotic cardiovascular disease: Q statistic=0·94, p=0·63, I^2=0%; multiple risk factors: Q statistic=0·03, p=0·86, I^2=0%). Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. The p value for subgroup differences was 0·0501. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

SGLT2i-associated side effects

COMMON	LESS COMMON	RARE
Genital infections	Urinary tract infections	Diabetic ketoacidosis*
	Osmotic diuresis, hypovolemia, hypotension	Amputations†
	Mild LDL-C increase	Possible increase in fractures‡
		Increase in bladder cancer§
		Pancreatitis

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

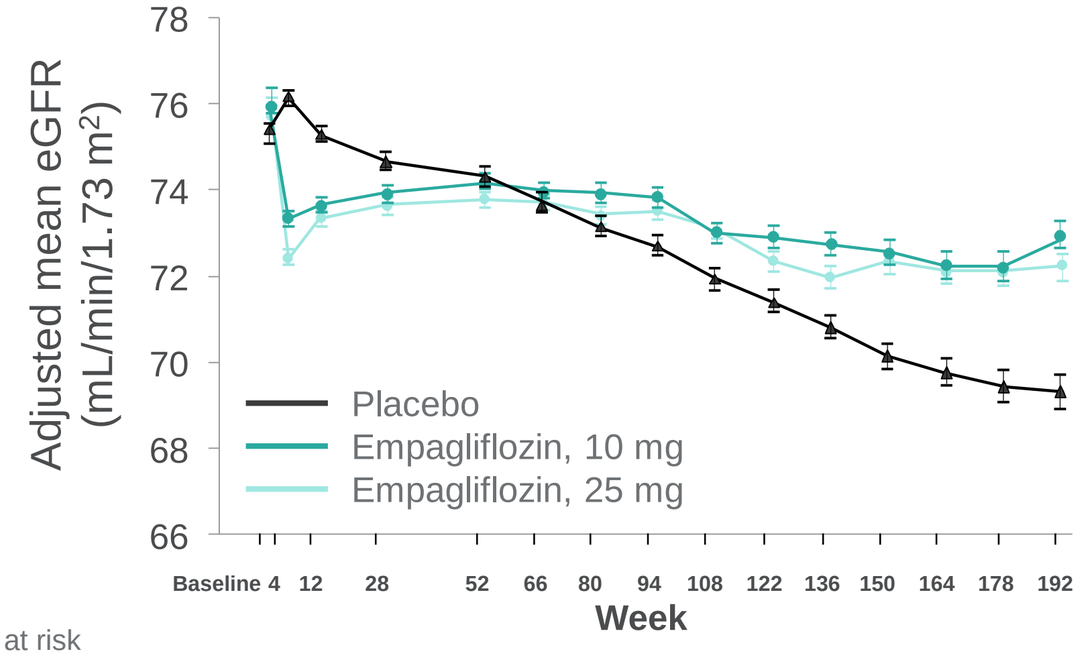
* observed with all SGLT2 inhibitors; † avoid using canagliflozin in individuals with a history of lower extremity amputation(s);
‡ observed with canagliflozin; § dapagliflozin not to be used in patients with bladder cancer.

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

Turning Point:
The Kidney

In CVOTs, eGFR initially drops and is stabilized over time

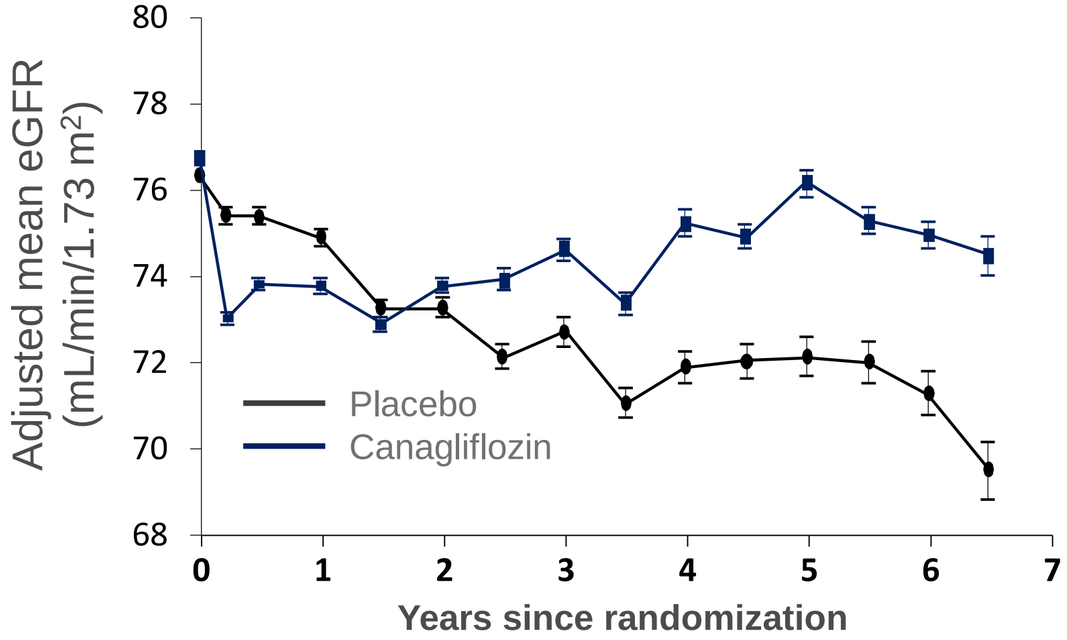
EMPA-REG OUTCOME
Change in eGFR* over 192 weeks[1]



No. at risk

	2323	**2295**	**2267**	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
EMPA, 10 mg	**2322**	**5590**	**2264**	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
EMPA, 25 mg	**2322**	**2288**	**2269**	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524

CANVAS Program
Change in eGFR over 6.5 years[2]



No. of patients

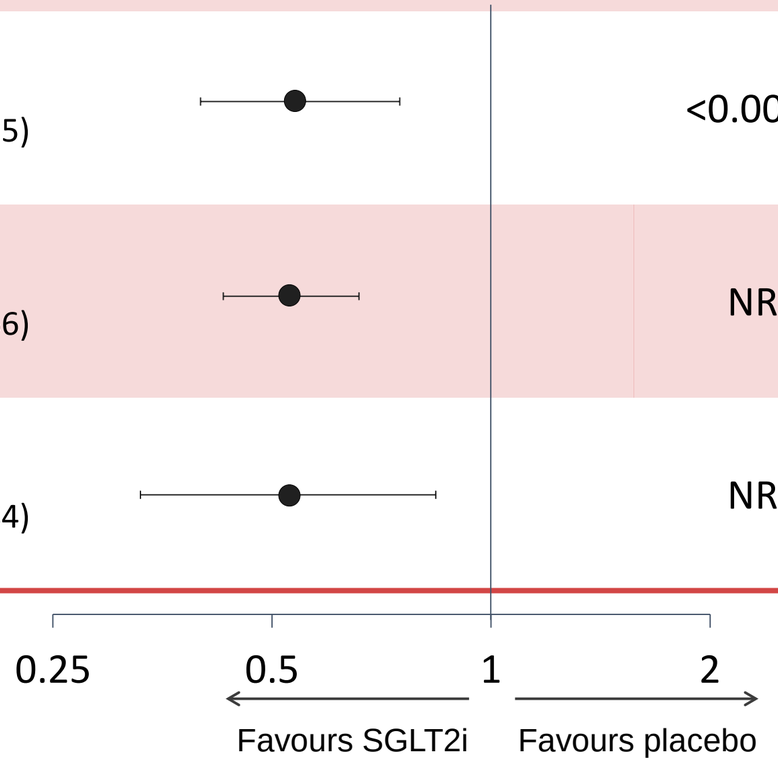
	4276	3867	3212	1030	899	809	694
CANA	5711	5212	4570	2230	2039	1895	1653

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

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

Kidney outcomes in SGLT2 inhibitor CV outcome trials

Trial	SGLT2i n event/N analysed (%)	SGLT2i Rate/ 1000 PY	Placebo n event/N analysed (%)	Placebo Rate/ 1000 PY	HR (95% CI)	p-value
Dedicated cardiovascular outcomes trials: exploratory analyses						
EMPA-REG OUTCOME[1] Doubling of serum creatinine,* RRT or death from kidney causes	81/4645	6.3	71/2323	11.5	0.54 (0.40, 0.75)	<0.001†
DECLARE-TIMI 58[2] ≥40% decrease in eGFR to <60 mL/min/1.73 m^2, new ESRD or death from kidney causes	127/8582	3.7	238/8578	7.0	0.53 (0.43, 0.66)	NR
CANVAS[3] Doubling of serum creatinine, ESKD or death from kidney causes	NR	1.5	NR	2.8	0.53 (0.33, 0.84)	NR



Comparisons of trials should be interpreted with caution due to differences in study design, populations and methodology

*Accompanied by eGFR ≤45 mL/min/1.73 m^2; †Nominal p-value. See slide notes for abbreviations

1. Wanner C et al. *N Engl J Med* 2016;375:323; 2. Wiviott SD et al. *N Engl J Med* 2019;380:347; 3. Perkovic V et al. *Lancet Diabetes Endocrinol* 2018;6:691;

Recommendation 10

2018

10. 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/1.73 m^2, a SGLT2 inhibitor with proven renal benefit may be considered to reduce the risk of progression of nephropathy [Grade B, Level 2 for empagliflozin; Grade C, Level 3 for canagliflozin]

CVD, cardiovascular disease; *eGFR,* estimated glomerular filtration rate

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.

CREDENCE

Primary Renal Outcomes for SGLT2i in Patients with CKD and Diabetes

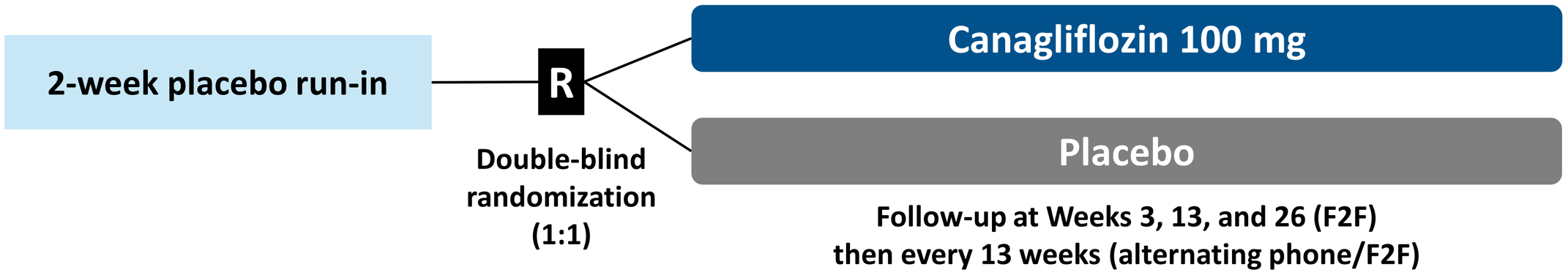
CREDENCE: Study design

Key inclusion criteria

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

Key exclusion criteria

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

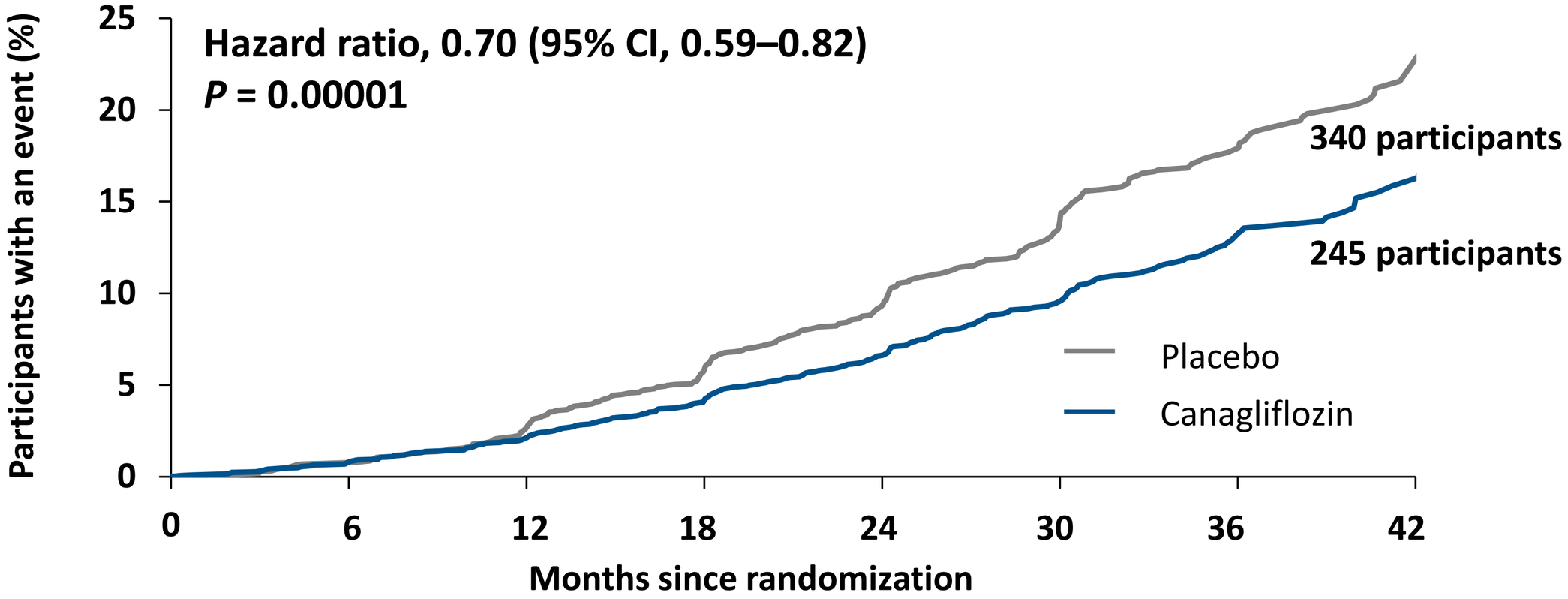


Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated or kidney transplant occurred.

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.

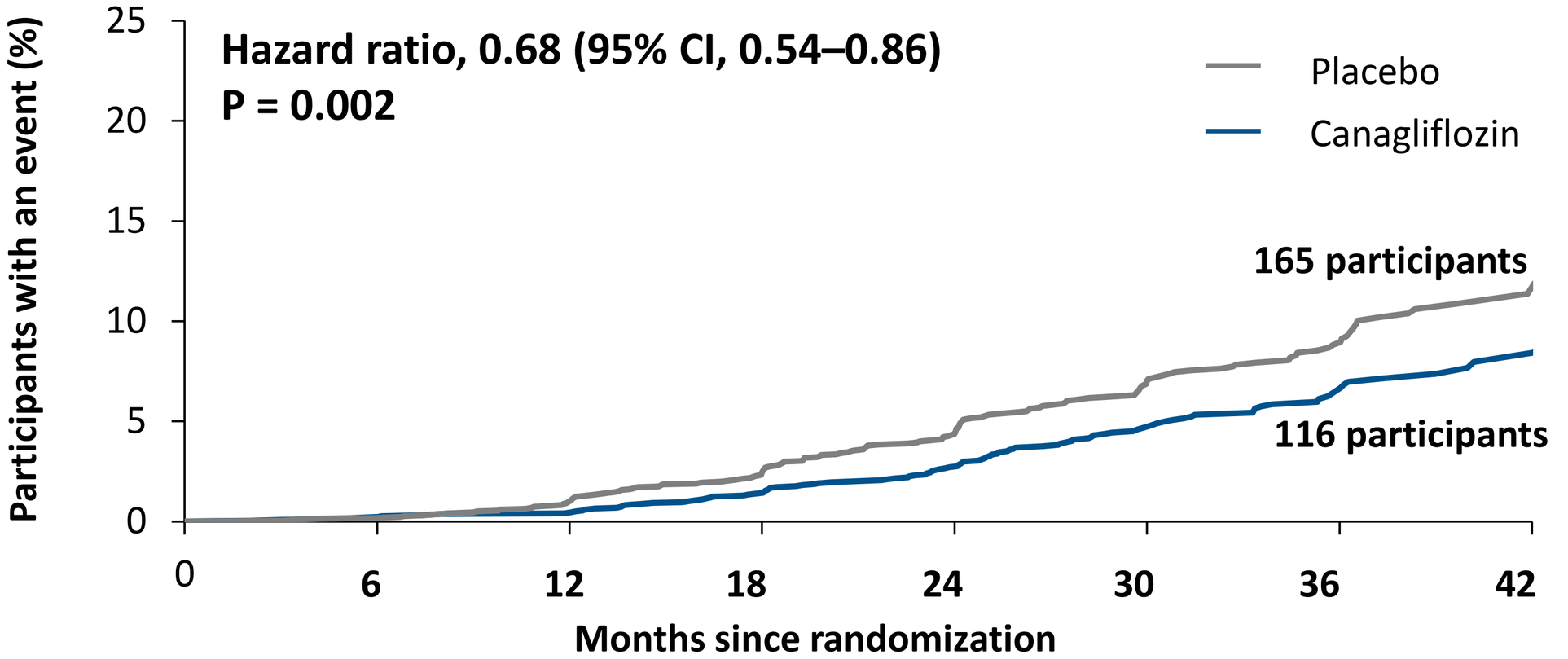
Primary Endpoint: Composite of ESKD, doubling of serum creatinine, and renal or CV death



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.

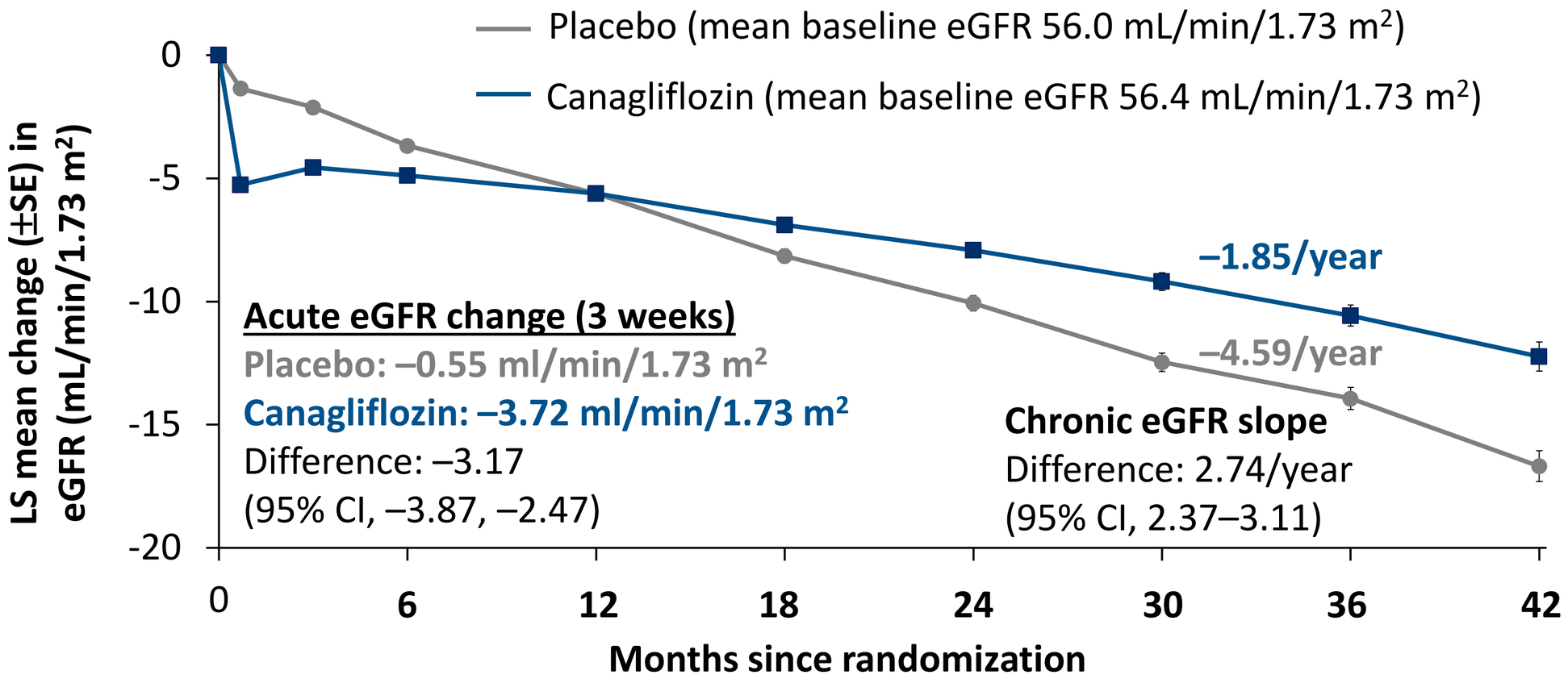
Secondary Endpoint: End-stage kidney disease



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.

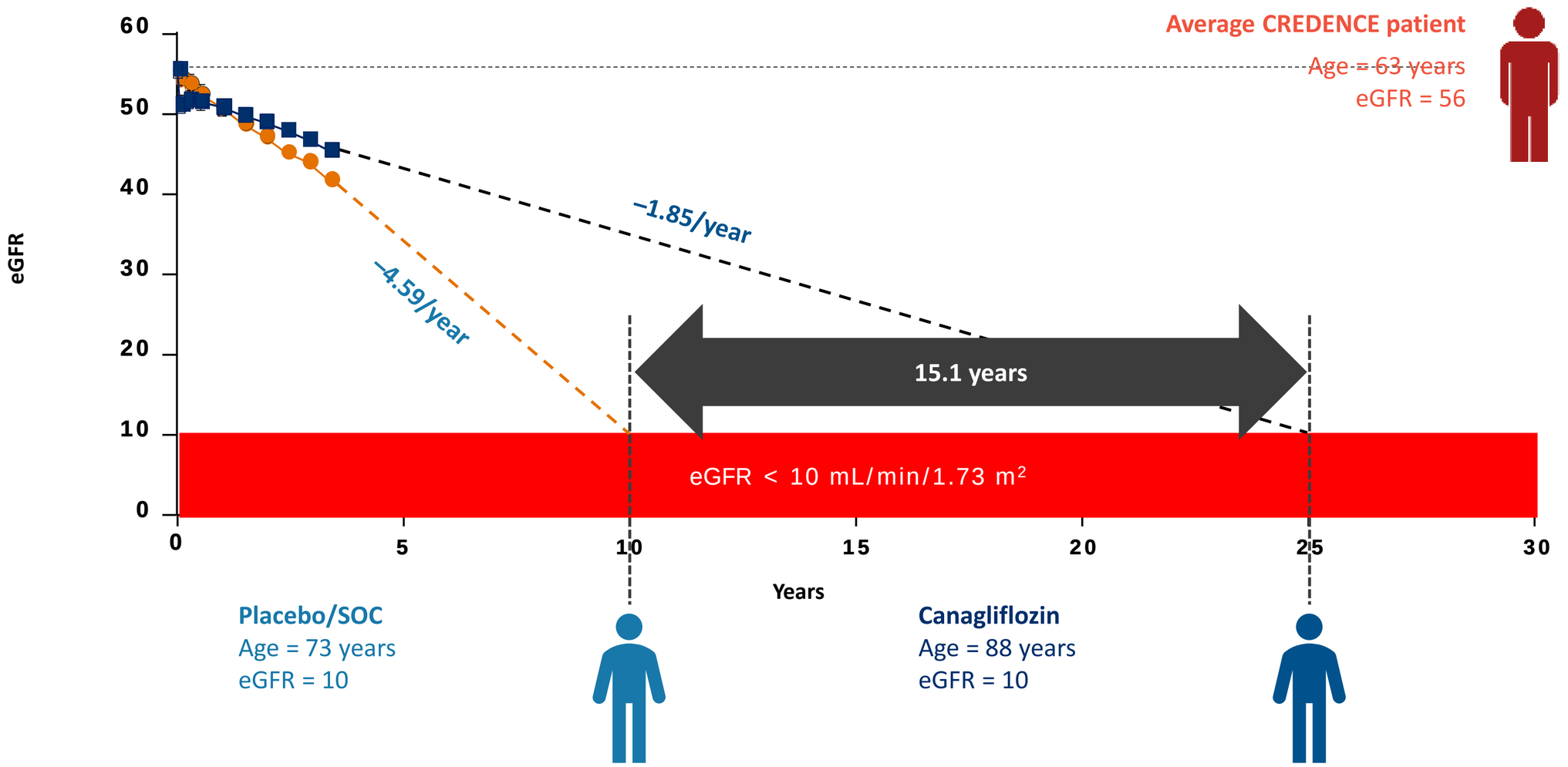
Effects on eGFR



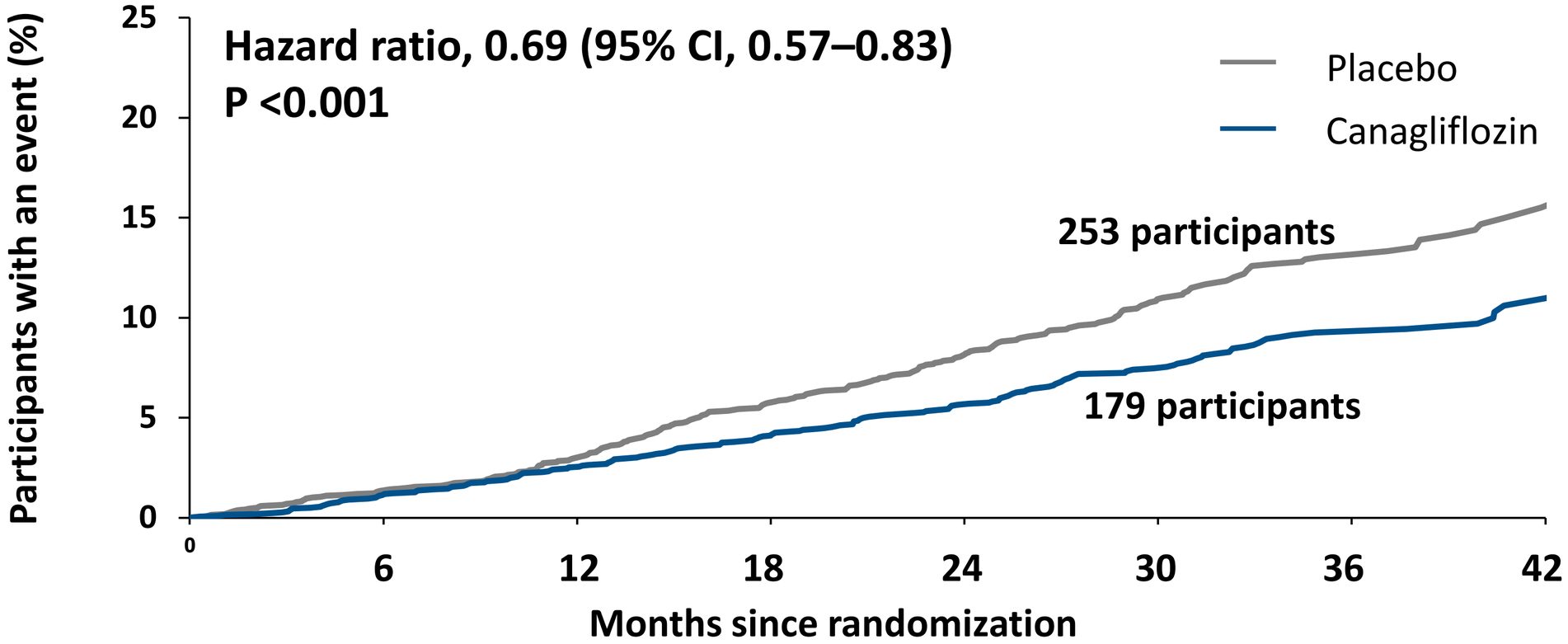
No. at risk								
Placebo	2178	2084	1985	1882	1720	1536	1006	583
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652

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

Projected Effects on eGFR



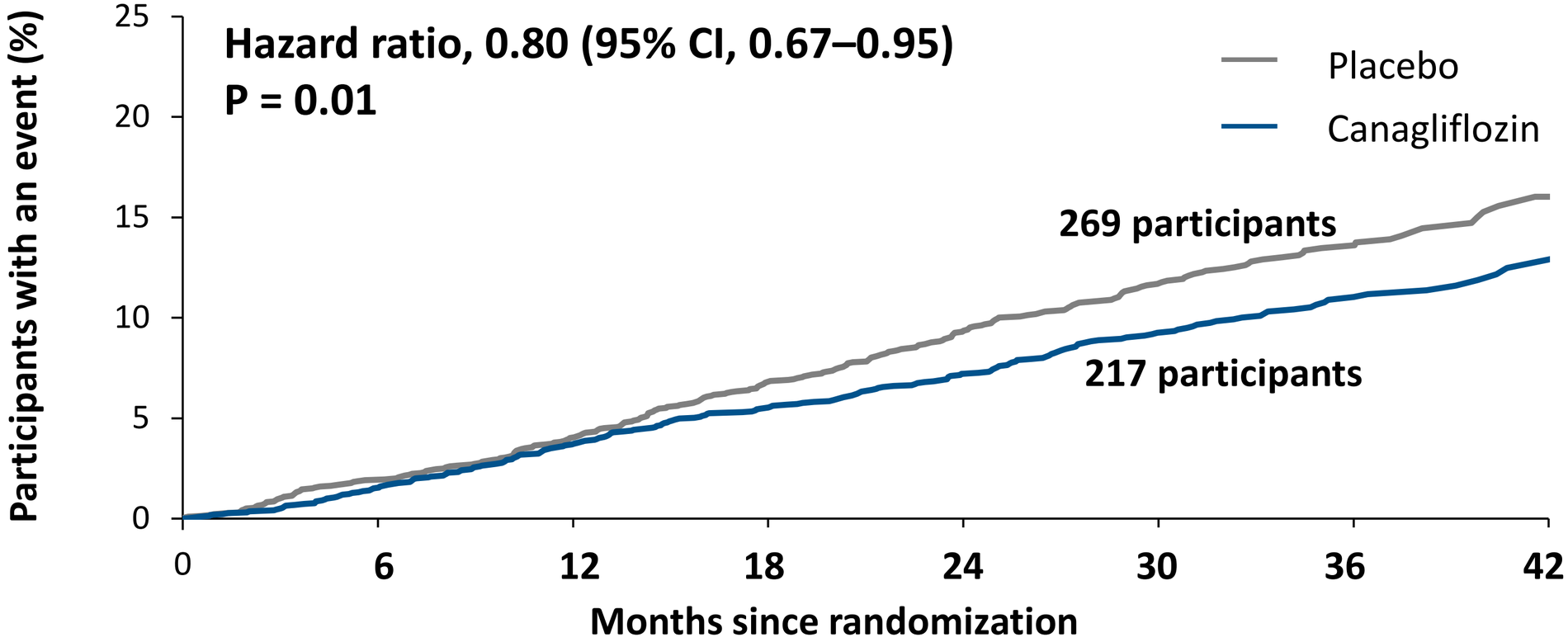
Secondary Endpoint: CV death or hospitalization for heart failure



No. at risk								
Placebo	2199	2165	2123	2044	1736	1147	638	170
Canagliflozin	2202	2171	2132	2077	1789	1226	668	199

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

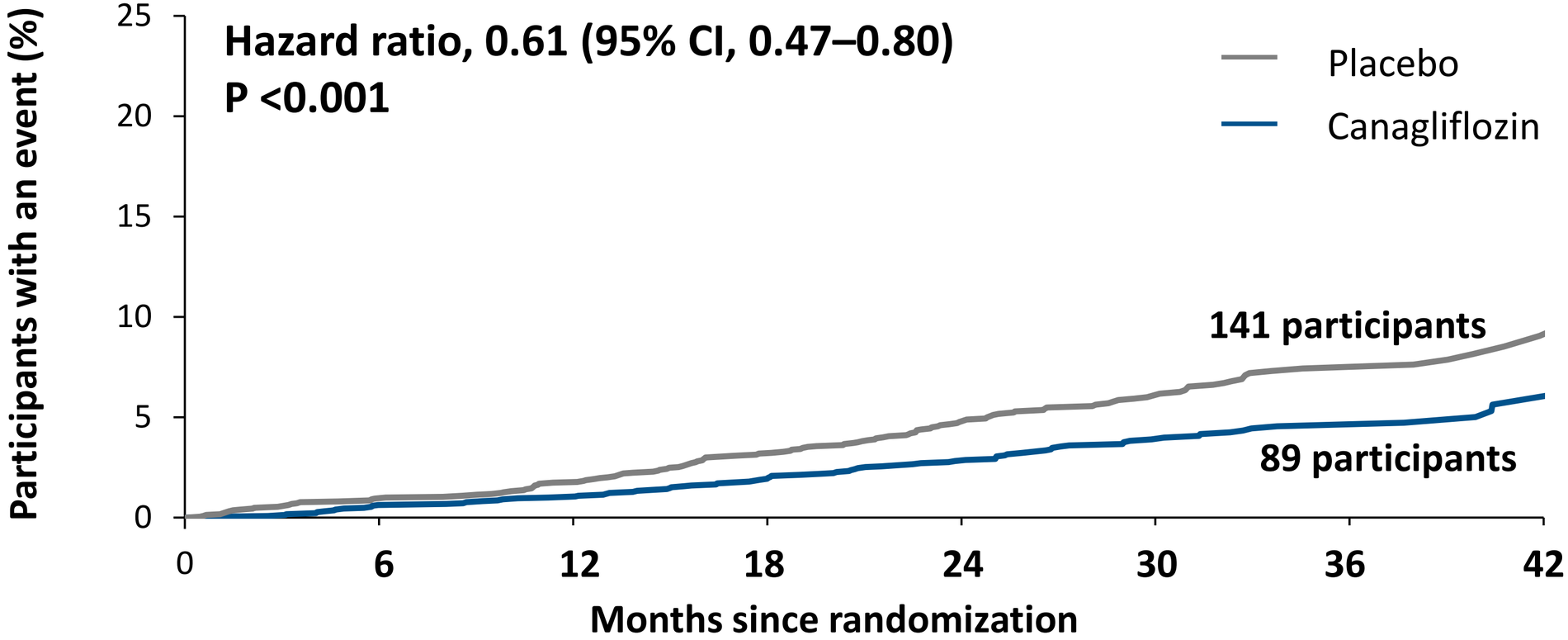
Secondary Endpoint: CV Death, MI, or stroke (major adverse cardiovascular events, or 3-point MACE)



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.

Secondary Endpoint: Hospitalization for heart failure

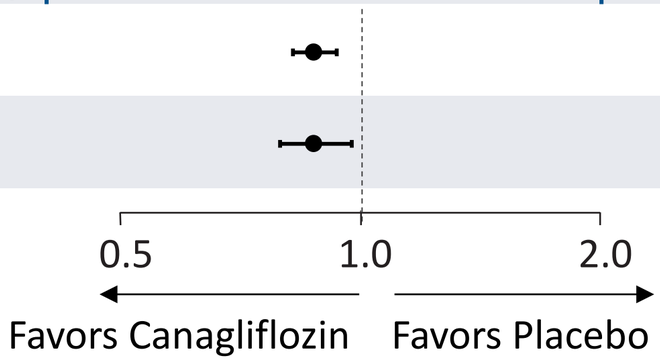


No. at risk								
Placebo	2199	2165	2122	2043	1735	1147	638	170
Canagliflozin	2202	2171	2131	2076	1789	1226	668	199

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

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)

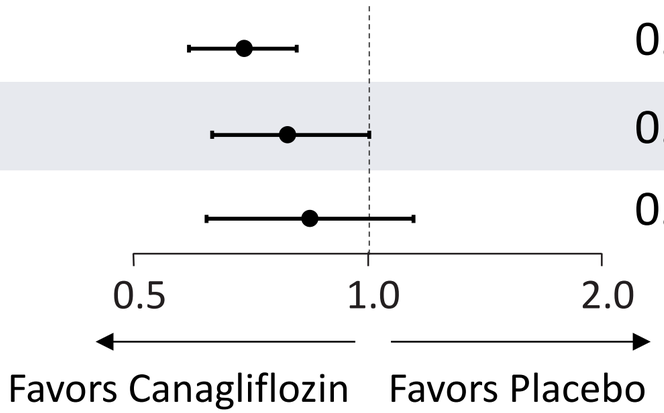


Includes all treated participants through 30 days after last dose.

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

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)

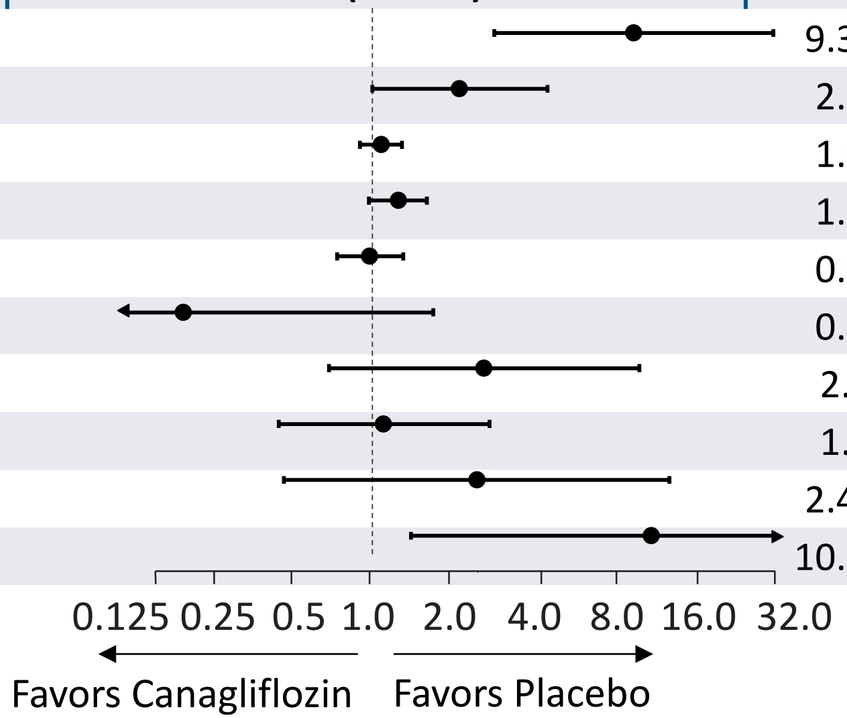


Includes all treated participants through 30 days after last dose.

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

Other AEs of interest

	Number of participants with an event, n		Hazard ratio (95% CI)
	Canagliflozin (N = 2200)	Placebo (N = 2197)	
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)

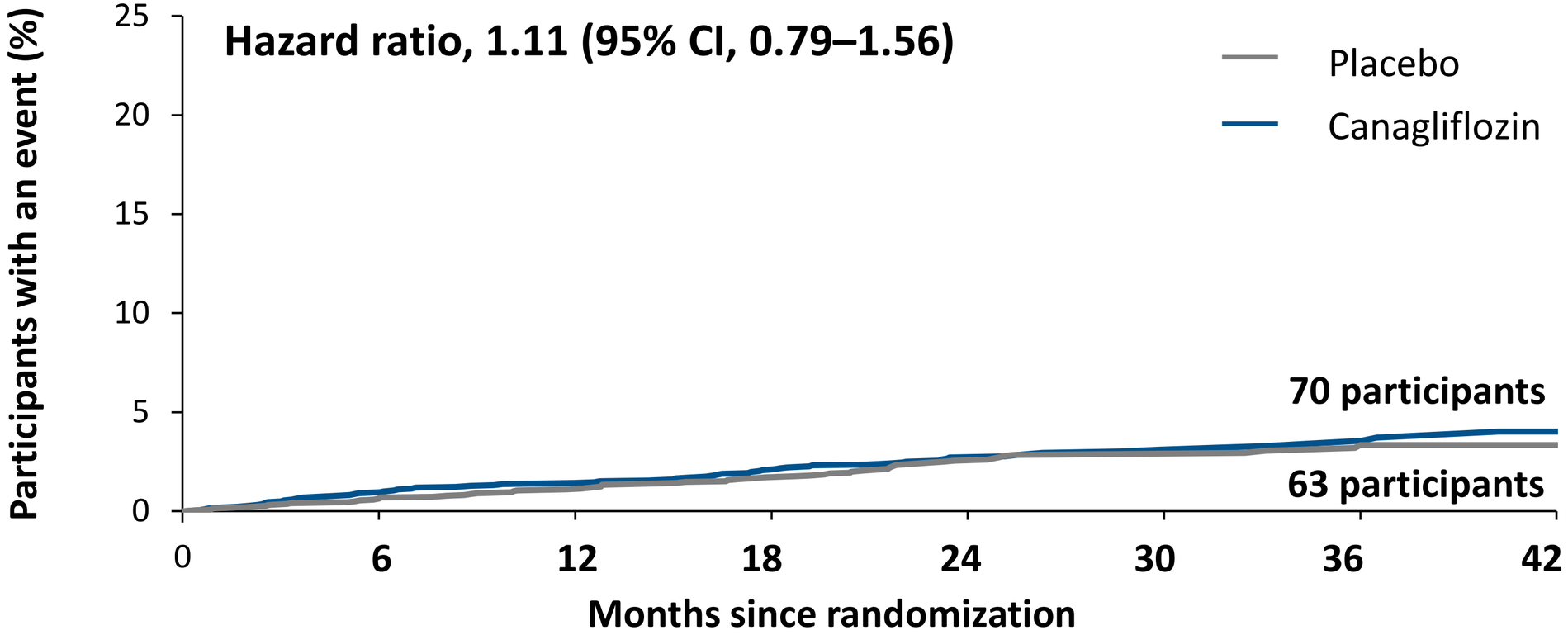


Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.

*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.

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.

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%

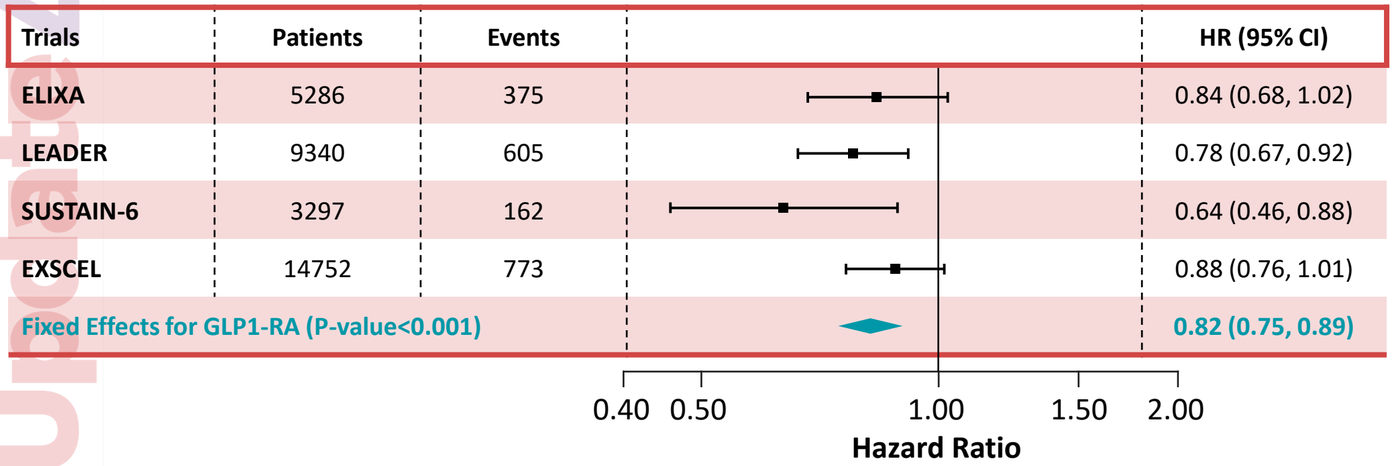
*NOTE: All patients enrolled in CREDENCE were taking maximal labelled or tolerated daily dose of ACEi or ARB in addition to being treated to target for blood pressure and A1C as part of the standard of care[4]

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.

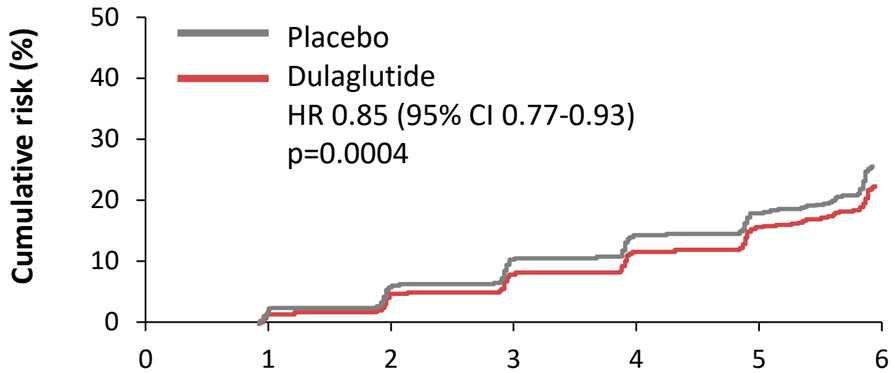
GLP-1RA effects on a composite renal endpoint in CVOTs

- Meta-analysis of GLP-1RA CVOTs on composite renal endpoint:
  - **New-onset macroalbuminuria**, sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or death of renal cause
- REWIND trial (dulaglutide CVOT)
  - New-onset macroalbuminuria, sustained decline in eGFR ≥30%, or new chronic renal replacement therapy

Meta-analysis



REWIND



No. at risk

Placebo	4952	4756	4475	4145	3887	3169	641
Dulaglutide	4949	4798	4571	4303	4045	3320	667

Zelnicker et al. *Circulation*. 2019;139:2022–2031.
Gerstein et al. *Lancet*. 2019. doi: 10.1016/S0140-6736(19)31150-X. [ePub ahead of print]

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 [illegible] labelled or [illegible]	CKD ± T2D May be [illegible]	CKD ± T2D May be taking ACEi/ARB
Kidney function inclusion criteria (eGFR units: mL/min/1.73 m²)	60% [illegible]	U[illegible]	eGFR ≥20 to <45 **OR** eGFR ≥45 to <90 with UACR ≥22.6 mg/mmol
Primary endpoint	Co[illegible], doubling of sCr, renal or CV death	Comp[illegible] 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

DONE

DONE*

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.

DAPA-CKD: Also stopped early…

"AstraZeneca has announced that the phase 3 DAPA-CKD trial for dapagliflozin (Farxiga) in patients with chronic kidney disease has been halted early because of overwhelming efficacy of the drug, at the recommendation of an independent data monitoring committee."

Time to update the guidelines

A1C Control	BP Control	ACEi or ARB	SGLT2i
≤ 7.0%	< 130/80 mmHg	Treatment	Treatment
(Grade A)	(Grade A)	(Grade A)	(Grade A)

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.

Time to update the guidelines

Canagliflozin indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of end-stage kidney disease, doubling of serum creatinine, and cardiovascular (CV) death in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria

A1C Control	BP Control	ACEi or ARB	SGLT2i
≤ 7.0%	< 130/80 mmHg	Treatment	Treatment
(Grade A)	(Grade A)	(Grade A)	(Grade A)

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

Where do we go from here

- General principles:
  - **Address atherosclerotic risk factors**
  - On top of ACEi or ARB, SGLT2i are profoundly cardio and nephroprotective, especially in high-risk patients
  - Perhaps the most potent single intervention we can offer diabetics
  - **Even in low-risk patients data support outcome benefits unseen in any other class – consider using SGLT2i as first add-on after metformin in all patients**
  - SGLT2i have side affects
    - Properly counseled, all side affects seem acceptable given the benefits

Where do we go from here?

- Does my patient have CKD (with or without proteinuria)?
  - If yes:
    - Ensure patient is taking an ACE or ARB
    - For all patients with GFR > 30 ml/min, consider an SGLT2i
    - Scrutinize any internal or external decision not to prescribe
      - Warn about adverse effects (esp: DKA, amputation, GMI, diuretic effects)
    - For patients with marginal BP, consider reducing or removing all meds that do not have Grade A evidence for organ protection
      - Consider reducing (not removing) dose of organ protecting drugs to accommodate SGLT2i

Where do we go from here?

- Recommend SGLT2i or start them myself?
  - Will depend on comfort level for modifying insulin or AHA
  - I will start SGLT2i in patients:
    - On AHA which do not cause hypoglycemia
    - On AHA which do cause hypoglycemia if A1C greater than 8, especially if patient self-monitors blood glucose +/- reduces SU

Where do we go from here?

- I will not start (but will recommend) SGLT2i:
  - In patients on MDI insulin +/- larger doses of basal insulin especially if A1C <8% and patients do not self-monitor blood glucose
  - Type 1 DM
  - +/- prior amputation
- Some uncertainty in patients with A1C at target
  - Start anyways?
  - Swap out AHA

Where do we go from here?

- For patients with residual proteinuria (ACR >50-70 mg/mmol)
  - Consider starting or recommending GLP1-RA
  - High dose ACEi/ARB
  - Consider MRA (Coming soon: Finerenone in diabetic CKD)

Where do we go from here

- Areas of further exploration:
  - SGLT2i in non-diabetes
  - MRA (finerenone) to improve renal outcomes
  - GLP-RA to improve renal outcomes
  - Endothelin antagonists to improve renal outcomes